PAT Implementation in Pharmaceutical Manufacturing and its Economical Impact

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Héðinn Valþórsson

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Prof. Dr. Hans Leuenberger
Dr. Ajaz Hussain
Dr. Urs Flury

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Dekan Prof. Dr. Hans-Peter Hauri

To my parents

Baldvina and Valþór

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Summary

The overall aim of this thesis was to evaluate the feasibility of implementing Process analytical Technology (PAT) into pharmaceutical manufacturing. First of all the implementation of PAT was looked at from a bird perspective, taking all unit operations into account. This task was divided into two parts, the first one developing a PAT strategy that could result in a real time release in tablet manufacturing for one product, identifying the critical variables in the manufacturing process and selecting the analytical techniques to measure these critical variables. The second part of the bird perspective determined the economical feasibility of the PAT implementation based on the strategy formed in part one for three products. After determining the overall feasibility of the PAT implementation a closer look was given to special technologies which contribute to the PAT philosophy in ways of product efficiency, manufacturing flexibility, process understanding and building quality into the products instead of testing quality into products.

Critical process variables were determined by analysis of validation data, discussion with plant operators and literature analysis of the fundamental operation of each process step. The critical process variables were determined to be moisture content, identity, and particle size distribution of the raw materials, blend homogeneity of the mixing steps, particle size distribution after granulation, content uniformity of the drug substance and hardness of tablets, coating thickness, final tablet moisture content, droplet size distribution of coating solution, identity of material packaged and package integrity.

Analytical techniques to measure each of the critical variables were chosen based on a literature search to evaluate what techniques are available and further narrowed based on availability of equipment. Diffuse reflectance near infrared spectroscopy (DR-NIR) is recommended for determining component identity, moisture content, blend homogeneity, hardness, coating thickness, and material identity. Transmittance NIR (T-NIR) is recommended for determining content uniformity. Laser light diffraction (LLD) is recommended for determining particle size distribution. The PAT strategy that combines process monitoring and product characterization will hopefully

eliminate or at least reduce the need for Quality Assurance / Quality Control (QA / QC) laboratory testing.

The first technologies to be implemented should be the ones that are easiest to implement and least expensive. Full adoption of the PAT philosophy will require an alteration of the method used to develop pharmaceuticals. A better scientific understanding of the process and materials will be required so as to result in a process that is fully understood, has a process model and produces materials with built-in quality assurance for real time release.

The two areas where PAT can provide the greatest savings were found to be: (1) reduction in Quality Control (QC) testing, leading to real time release and (2) improvement of product yield from better process control. The financial analysis is sensitive to the time when these benefits begin to take effect. Since there is some uncertainty as to when real time release will be approved, two scenarios were created for implementation of PAT. The first scenario (base case) assumes that QC savings start accruing after the installation and qualification of analytical instruments, at the end of the first year. The second scenario is a conservative case in which it is assumed that the QC savings begin in the third year, after correlations have been developed for tablet friability, disintegration time and dissolution time.

PAT implementation is envisioned to occur in three stages. The first phase involves the installation of on-line analytical equipment and results in benefits related to savings in QC costs, reduced time for investigations, and reduced throughput time. During the first phase of PAT implementation, correlations will be developed for process understanding and to replace current analytical tests such as disintegration, dissolution and friability. The second phase is the implementation of process control systems which results in savings due to fewer Food and Drug Administration (FDA) audits, fewer investigations, fewer batch rejections, shorter throughput times, and increased product yield. The third phase is the integration of PAT into the development process of a new product, resulting in quality by design. The third phase was not addressed within this project as PAT implementation was only evaluated for products already on the market and so concentrating on the production side. In order to investigate the impact of PAT on the development process of a new drug product a separate dissertation work would be necessary.

For the first scenario (QC savings after the first year), the results of the economic analysis indicate that the implementation of PAT for solid tablet manufacturing is very cost-effective. The Return on Investment (ROI) for implementation of PAT after phase I is 69% for Product X, 49% for Product Z and 46% for Product Y. The Return on Investment for implementation of PAT in phase II is 147% for Product X, 92% for Product Z and 60% for Product Y.

For the second scenario (no QC savings in phase I), the Return on Investment drops to 130% for Product X, 81% for Product Z and 49% for Product Y. Thus, PAT implementation is cost-effective even in the conservative case.

Companies tend to move ahead with a project when the Return on Investment is at least 25% and these results demonstrate that PAT should be implemented. The Return on Investment results indicate that the installation of on-line analytical equipment creates great savings for companies while implementation of control systems is even more cost effective.

In matters of new manufacturing technology, the Glatt Multicell®was evaluated as an innovative approach for granulation. The Multicell®, being a semi-continuous granulator producing small sub-batches of approximately 7kg, is able to circumvent the unpleasant practice of scale-up as it is capable of producing one sub-batch or just as many as required. The capacity of the Multicell® was compared to the capacity of conventional granulation equipments. It did not only show that it could hold up with the conventional granulation but also increased capacity dramatically and at the same time reducing the needed personnel or Full Time Equivalents (FTE) from 18 down too 7, bringing in yearly savings of approximately 1100kCHF.

Another technology which contributes to process understanding and building quality into the product is the MCC Presster®. The Presster® is a rotary press simulator which is capable of replicating different rotary presses by utilizing the same compression tooling and using the same dwell time as the original rotary press with only one pair of punches. This allows the comparison of different rotary presses with only one machine and very little powder formulation. In this study the Presster® was used to replicate the results of three different rotary presses. Two commercial product

formulations were run on all three rotary presses with different dwell times. The two product formulations were chosen considering their flowing properties, one product having bad flowing properties and the other very good flowing properties. It was shown that the Presster® was capable of simulating the effects of a full scale tableting machine if the Presster® is equipped with the corresponding compression tooling. Further it was shown that prolonged pre-compression dwell time due to pneumatic compensation leads to tablets with higher crushing strength than regular pre-compression rolls.

Last but not least a Near Infrared (NIR) Spectrometer was evaluated for implementation on a packaging line. This technology also contributes to the proposed PAT philosophy by enhancing process understanding and enabling 100% real time analysis of the product being packed. For this study a packaging line simulator was used with an integrated NIR spectrometer system from Visiotec called VisioNIR®. The products used for this study were all strengths of Sandimmun Neoral® which are in soft gelatin capsules and different tablet products for mix-up studies. The aim of this study was to estimate which product flaws the VisioNIR could detect within the soft gelatin capsules, such as capsules without content, capsules with wrong content and product mix-ups. It was shown that the VisioNIR was capable of distinguishing empty capsules, excessively smudged capsules and capsule mix-ups from the Sandimmun Neoral® capsules for all strengths. It became apparent that Sandimmun Neoral® strengths which were grey were harder to analyze as the lighter soft gelatin capsules as the halogen light did not penetrate deep enough into the capsule shell.

Abbreviations

AOTF	**A**cousto **O**ptical **T**unable **F**ilters
API	**A**ctive **P**harmaceutical **I**ngredient
BU	**B**lend **U**niformity
CHF	Swiss Franks
CMC	**C**hemistry/**M**anufacturing/**C**ontrols
CU	**C**ontent **U**niformity
DT	**D**well **T**ime
EBIT	**E**arning **B**efore **I**nterest and **T**axes
ECM	**E**xchangeable **C**ompression **M**odule
FDA	**F**ood and **D**rug **A**dministration
FTE	**F**ull **T**ime **E**quivalent
HPLC	**H**igh **P**ressure **L**iquid **C**hromatographie
ICH	**I**nternational **C**onference on **H**armonization
IPC	**I**n **P**rocess **C**ontrol
IRR	**I**nternal **R**ate of **R**eturn
LIF	**L**aser **I**nduced **F**luorescence
LLD	**L**aser **L**ight **D**iffraction
LOD	**L**oss **o**n **D**rying
MSC	**M**ultiplicative **S**catter **C**orrection
MVDA	**M**ulti**v**ariate **D**ata **A**nalysis
NIR	**N**ear **I**nfra**r**ed
NIRA	**N**ear **I**nfra**r**ed **A**nalysis
NPV	**N**et **P**resent **V**alue
OOS	**O**ut **o**f **S**pecification
P&ID	**P**rocess and **I**nstrumentation **D**iagram
PAT	**P**rocess **A**nalytical **T**echnology
PCA	**P**rincipal **C**omponent **A**nalysis
PFD	**P**rocess **F**low **D**esign
PLC	**P**artial **L**east **S**quares
PSD	**P**article **S**ize **D**istribution
QA / QC	**Q**uality **A**ssurance / **Q**uality **C**ontrol
ROI	**R**eturn **o**n **I**nvestment

SCM	**S**upply **C**hain **M**anagement
SD	**S**tandard **D**eviation
SGC	**S**oft **G**elatin **C**apsules
SNV	**S**tandard **N**ormal **V**ariant
SREL	**Rel**ative **S**tandard Deviation
USP	**U**nited **S**tates **P**harmacopoeia
UV	**U**ltra **V**iolet

1. Preface

1.1. Introduction

The pharmaceutical industry is exposed to an increasing pressure from the authorities and health insurance companies today, to reduce their prices. At the same time however, the costs of the development of new drugs rise. Thus, the development of a new medicine takes on the average 12 – 13 years and costs around 800 – 900 million $US. In order to amortize these investments by the sales of the medicine again, the development companies have seven too eight years time, until the patent protection runs out. Afterwards the generics manufacturers can bring a generic on the market, which is substantially cheaper. In order to be able to profit for as long as possible from the exclusive position by the patent protection on the market, the time up to the introduction on the market of the new medicine must be kept as short as possible. In order to shorten this "Time-to-Market", new technologies must be integrated into the conventional production process.

In the last years the Food and Drug Administration (FDA) has been rather reserved in the cases of new technology implementation, in order to uphold the safety of the patient. Their focus was rather much more that the drugs were supposed to be produced exactly according to specification with proven and established devices. Recently a change in this situation has appeared. The FDA is now pushing the pharmaceutical industry to improve their quality standards and implement innovative manufacturing methods. Therefore the FDA published a guideline, which describes new technological concepts to quality control, which are summarized under the name PAT (Process Analytical Technology)

The core of this thesis is PAT. As can be seen in figure one below, it is tried in this thesis to take on all of the recommendations of the FDA in their PAT guidance. At first a PAT implementation strategy will be presented with an adjacent economic analysis of the PAT implementation. Then in order to address terms as "Process Understanding" and "Quality by Design" a semi-continuous granulation machine was looked at and a rotary press simulator. Finally, the most common PAT technology

was tested on a packaging line. The PAT strategy and the economic analysis will be presented in a separate chapter as well as all the different technologies.

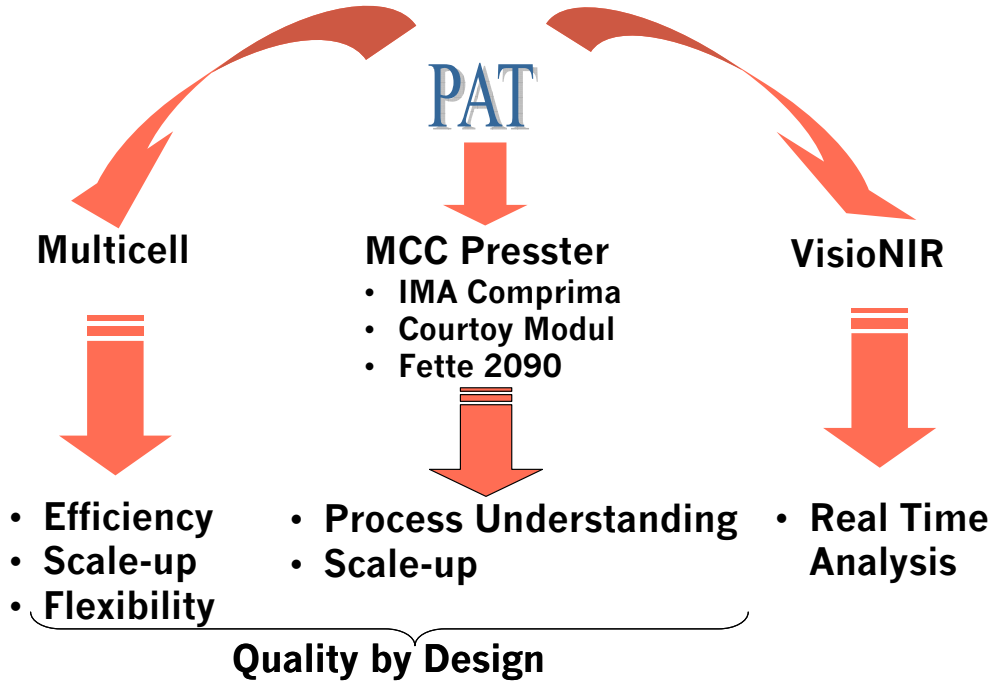

Figure 1: An overview of the thesis scope.

2. PAT implementation strategy and PAT's economic impact

2.1. Introduction

The pharmaceutical industry faces a unique set of challenges in the manufacture of its products. Due to the nature of the products, governments exercise a significant degree of regulatory control over the manufacturing process. In order to ensure the safety of drug products to consumers, the manufacturing process must be validated extensively. Any deviation in the process requires a time-consuming and expensive approval process. As in many other industries, the advantage of being first to market with a new product is enormous. Additionally, delays in the rollout of a new product result in lost sales. As a result, there is a great deal of pressure to develop and validate the manufacturing process for new drugs as quickly as possible. The confluence of these two factors, desire for speed to market and rigid regulatory control, results in manufacturing processes which are frozen into place before optimal conditions can be determined.

There are a number of disadvantages to manufacturing drugs in this way. Quality assurance is performed after the product has been made, so products are sequestered for as much as a month after production while testing of samples is completed. If irregularities are found, it is too late to adjust the process parameters, and the irregularities must be identified and explained in a time-consuming investigation, or the out-of-specification material must be thrown away or re-worked. The difficulties associated with changing the process also mean that improvements in manufacturing technology which evolve during the life of the product cannot be easily applied. The final result of this situation is that the pharmaceutical industry is lagging behind other related industries in implementing new manufacturing technologies which have the potential to improve product consistency, reduce delays in product release, and cut overall manufacturing costs.

In recent years the US Food and Drug Administration (FDA) in cooperation with leading pharmaceutical manufactures is looking into the method of Process Analytical Technology to improve production efficiency and reduce costs. The FDA has defined PAT as a system for

designing, analyzing, and controlling manufacturing through timely on-line measurements of critical quality and performance attributes of raw materials and in-process materials with the goal of ensuring final product quality. The FDA has also stated that the goal of PAT is to develop a basic understanding of the manufacturing process and control it accordingly. Quality cannot be tested into the products; it should be by design. Through a better understanding of the manufacturing process, the critical variables can be determined and the quality of the product can be determined by on-line measurements or correlation of measured variables to other product attributes. Electronic records of the process parameters can then replace post-process testing for quality control and assurance. The philosophy of PAT is appealing to the pharmaceutical industry as it will aid in the ease of product manufacturing, but the true economic benefit is yet to be determined.

2.2. Background

At present, pharmaceutical companies manufacture solid tablet drugs with a process which entails a significant number of manual steps. Quality control is accomplished through offline laboratory testing both during and after the completion of the manufacturing process. This leads to long periods (20-30 days) during which the final product is warehoused while the QA tests are completed. A more automated system of process and quality control will allow for speedier release of product to consumers.

A solid tablet production facility is to serve as the starting point for part one, for the effort to develop a PAT implementation strategy. A high volume product (which will be called product X from now on) process has been chosen because the impact would be more noticeable. Presented below are two flow sheets. Figure 1 gives a rough overview of the general solid tableting process, while figure 2 gives specific details concerning the production of product X.

For part two, the economic analysis of the PAT implementation in a solid tablet production facility was the focus. Table 1 illustrates the most frequently produced drugs at the production facility. Evaluation of the costs and benefits of implementing PAT for the production of Product X, Product Y, and Product Z was selected for this project.

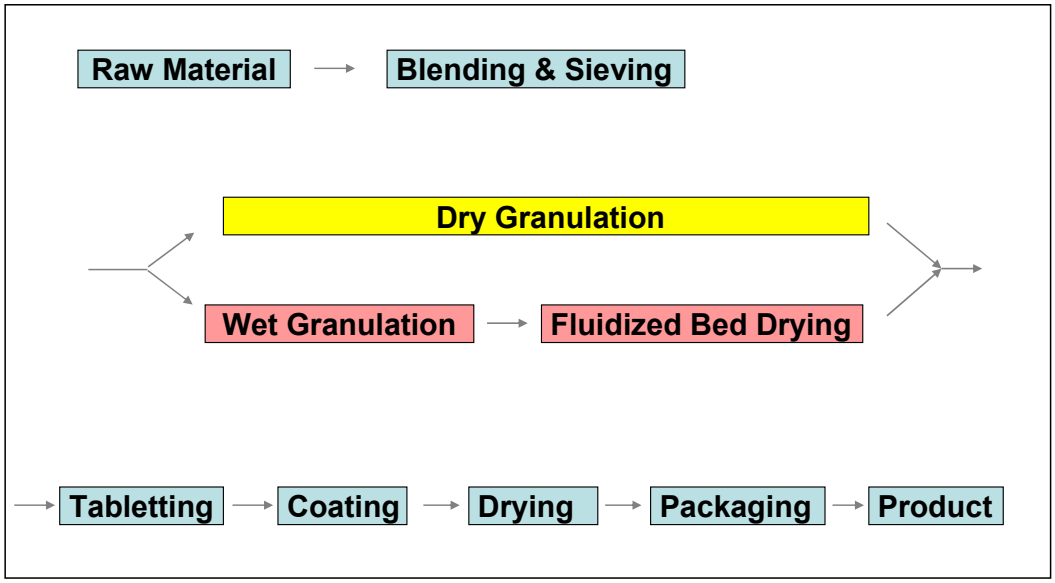

Figure 1: General Tableting Process

The specific steps in the tableting process are as follows:

- The first step is the weighing out of the various raw materials, which include both active ingredients and excipients, into small bins.

- The separate powders are transferred into a single large container and mixed for a set length of time, then sieved. The mixer rotates the container as a whole, as opposed to agitating the powder inside the container.

- Following the initial mixing step, the mixture undergoes one of two granulations steps.

- In wet granulation, a set quantity of water is added to the powder to agglomerate the particles. The wet granulate is then dried in a fluidized bed drier. The mixture is then sieved again as described above.

- In dry granulation, the powder is compacted by a pair of rollers into flat ribbons. The ribbons are then milled and sieved.

- After granulation, a lubricant is added and the container is mixed once again. Generally, magnesium stearate is used as a lubricant to ensure release of the tablets from the die in the tableting step that follows.

- Following granulation, the powder is transferred to an automatic rotary press which forms tablets by compressing the powder in a die. The rotary press currently has a feedback control system that manipulates the tablet volume in order to control the tablet mass.

- Tablets are coated with a liquid which is sprayed at a low flow rate onto the tablets in a rotating drum. The process relies on a tumbling action of the tablets as the drum rotates to ensure even coating.

- After coating, the tablets are fed into an automatic packaging line and inserted in blister packs.

Figure 2 is a flow sheet of the specific procedure for the product X. The individual steps are as described previously. The A and B referenced in the flow sheet refer to sub-batches of identical materials that are processed in series as a result of volumetric limitations on some of the processing equipment.

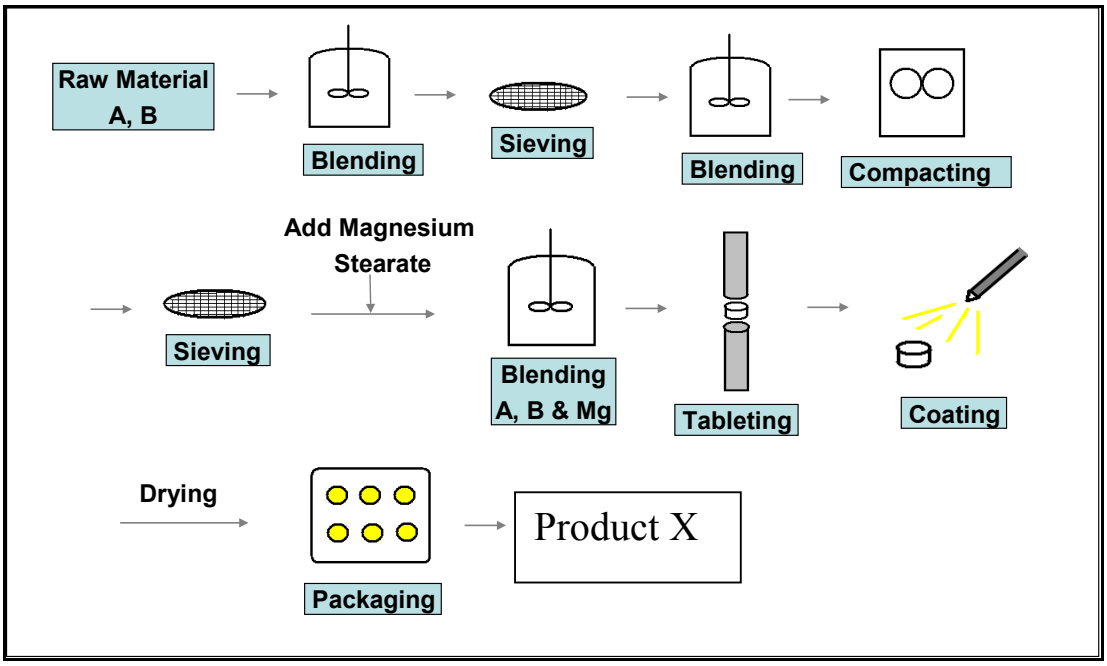

Figure 2: Flow sheet for manufacture of product X.

	Formulation	Batches 2002	Batches 2003	Projected Batches 2004
Product X	Dry Granulation	859	900	856
Product Z	Wet Granulation	556	656	400
Product Y	Wet Granulation	478	490	195
q	Dry Granulation	331	469	518
w	Capsule	362	402	389
e	Wet Granulation	310	300	214
r	Dry Mixing	48	72	213

Table 1: The volume of the most commonly manufactured drugs at the site.

2.3. Objectives for part one

The final and overarching goal of this chapter is to put the manufacturer in a position to move from a post-process quality control system to one which operates at the same time as and interacts with the manufacturing process in real time. This system will allow the manufacturer to achieve real time release, which means that the company can release the product to consumers as soon as the manufacturing process is over. The quality assurance system is to be built directly into the process control system. To this end, a number of specific objectives have been defined.

1. Evaluate the current manufacturing process for solid tablets from raw materials to packaging with a focus on product X, looking for opportunities to implement PAT.

2. Identify critical variables that affect the quality and consistency of the final product.

One key goal of PAT is to be able to predict key quality attributes of the product based on monitoring and control of the critical variables. A high degree of confidence in the

relationship between the final product attributes and the controlled variables is necessary if post-production testing is to be eliminated.

3. Suggest automated manufacturing processes to eliminate human error and reduce processing variability.

Increasing the level of automation goes hand in hand with improving the consistency of the final product. Additionally, manual tasks do not produce the type of electronic records which are needed to state with confidence that the manufacturing procedure has been followed precisely. Automation should be investigated to the extent that it contributes specifically to the goal of real-time release with PAT.

4. Identify specific technology to monitor and control critical variables on-line.

This objective involves finding and selecting specific vendors and models as well as identifying the general analytical techniques that are most appropriate for the implementation of PAT.

5. Suggest a central control structure that is able to interface with the individual monitoring and control devices.

This objective seeks to tie together the separate analytical and control devices which are to be suggested. The system should be capable of compiling a "batch report" which contains the important details of each stage of the manufacturing process. This report will essentially replace the current QA report which is generated during production and after a batch has been completed.

2.4. Method of approach

The final result of this project is to develop a PAT strategy for solid tablet manufacturing. The project focused specifically on solid tablet manufacturing so that the time could be spent researching PAT technologies and developing a PAT strategy which is more in-depth, rather than spending a large amount of time learning about different manufacturing processes

for all varieties of pharmaceutical products. The project focused on the manufacture of one solid tablet product, product X, so that there is a specific example for which a PAT strategy is developed.

2.5. PAT for the solid dosage manufacturing process

Within this section, the solid dosage manufacturing process is broken down by unit operation. The outline follows the manufacturing process for Product X, but the unit operation evaluations should be taken as general for all solid dosage products. In each subsection, a short description of the unit operation itself, along with the relevant physical phenomena involved, is presented. A distinction is made between critical variables and process parameters, both of which will be identified. The term *variable* will refer to quantities which describe the condition of the process material, such as particle size distribution, moisture content, or tablet hardness. In contrast, *process parameters* refer to those quantities that are directly controllable such as the compaction force or inlet air temperature. Once the critical variables have been identified, a summary of analytical methods will be given, along with a recommendation of one technology. Finally, a list of suitable vendors of each technology type will be presented.

2.5.1. Dispensation of raw materials

The first step in the production process is the weighing out of the raw materials from bulk storage into individual bins. For the Product X process, the batch is split into two identical halves, denoted ***A*** and ***B*** which are processed separately until the final blending step. For each half-batch, the individual powders are transferred to small bins and weighed by hand.

There are several opportunities for improved monitoring in the dispensation step, and they are best illustrated by a description of failure modes for the step. Currently, there is no electronic record-keeping of the material weights which are actually placed in the bins. While there is extensive manual checking and sign-offs, an additional electronic record of the

material weight would allow for more confidence that the correct proportions of raw materials were used if questions arise later. A second possible failure mode is that the wrong powder might end up in the bin. This could be due to mislabeling of the bulk storage hopper or simple human error during the weighing step. Analytical confirmation of the identity of the powder being weighed will increase the degree of confidence that the correct raw material has been distributed. The last potential failure mode will be addressed is the possibility that the raw material in question may be out of specifications. The two variables that have the greatest effect on the downstream process are the particle size distribution and moisture content on the roller compaction and mixing steps, respectively [1-3]. As there is a possibility that these properties can change over time and within a bulk shipment, it is recommended that these measurements be made during the dispensing step, rather than (or as well as) on a bulk scale when raw materials arrive.

To address the question of electronic record keeping for the weights, the recommendation is two-fold: a scale which can report the measured weight should be coupled with a bar-coding system. It is recommended that each bin have a bar-code tag that would be linked to a computer file containing the specifics of the bin such as capacity and empty weight. After the bin has been loaded, the operator would scan the bar-code, and an electronic record would be kept concerning the bin, as well as the weight of powder added.

For purposes of material identification, a host of analytical techniques are available, so the choice was based primarily on ease of use. One does not wish simply to transfer an analytical laboratory out onto the production floor. For this reason, Diffuse Reflectance Near Infrared (DR-NIR) spectroscopy is the best choice. As opposed to HPLC or UV spectroscopy, DR-NIR does not require any sample preparation, so the identification can be performed simply by inserting a handheld probe into the powder and taking a spectrum. Diffuse reflectance NIR works by measuring the reflectance spectrum of the material being assayed over the wavelength range of 1100 – 2500 nm. This range contains overtones and combinations of the vibrational modes chiefly for bonds involving hydrogen such as C-H, O-H, and N-H. Due to the lower absorption at these wavelengths, no dilution of the sample is required [1]. Raw material spectra can be taken and compared to calibration spectra performed earlier to give

the operator a "yes or no" answer on the identity of the powder. One significant advantage of using DR-NIR to determine raw material identity is that the same equipment can also be used to monitor moisture content. Water has two strong absorption bands in the near infrared, at approximately 1450 and 1940 nm. By comparing the relative height of these peaks to other peaks in the spectrum which are unaffected by the presence of water, it is possible to determine moisture content [1, 4-6].

Particle size distribution (PSD) is a fairly complicated metric to measure, as particle size itself can have a number of meanings. Presently, particle size of raw materials is only measured by pharmaceutical companies when the vendor is selected during development. There are several methods that can be used to measure particle size – sieving, image analysis [7-9], and laser light diffraction [7-11]. Sieving is the method most commonly used to determine particle size distribution, but requires operators to perform several sieving steps and weight measurements. The image analysis method involves taking a photograph of a sample and determining the particle size distribution by analysis of a gray scale image [7]. This method is the most accurate for measurements that involve irregularly shaped particles, but can be very time consuming because large samples ~1,000,000 particles must be measured to get an accurate representation of the distribution [7]. Laser light diffraction measures the intensity of light scattered by a particle, which is a function of wavelength, particle diameter, and relative refractive index [11]. Particles are illuminated with a parallel beam of monochromatic light and the light patterns are measured on a photo detector. Laser light diffraction is the recommended method to determine the particle size distribution of the raw materials because it can give a more detailed particle size distribution than the sieve analysis with simpler data analysis than image analysis. Laser light diffraction measurements can be taken of solids suspended in air, thereby simplifying the sample preparation process. The solids are suspended in air by the measurement instrument by the flow of an air stream through the sample. (E.g. see Malvern Instruments Mastersizer).

2.5.2. Pre-blending

The pre-blending unit operation as it is evaluated here is actually composed of three separate steps. Currently, the raw materials are combined in a large container and mixed in a tumble blender for 30 minutes at a low speed of 10 rpm. The mixture is then run through a Frewitt

sieve mill in order to remove any lumps which may have formed and/or remain after the first blending step. Finally, the powder mixture is blended again under the same conditions for an additional eight minutes. It has been assumed that the powder does not experience forces which are likely to lead to significant changes in the PSD during the first sieving step, so it is ignored in the PAT strategy. This assumption could be tested fairly easily by measuring the PSD for a batch before and after the first sieving step. This subsection thus focuses on the question of successful blending.

Achieving a uniform powder blend is a key step in the production of solid tablets. It is essential that the active drug compound be dispersed evenly in the powder so that tablets will contain the correct dosage of active substance. This, however, is not a sufficient condition to guarantee successful blending, as the excipients each have a specific and important role to play in the formation of acceptable tablets. For example, insufficient dispersion of glidant can result in difficulties during roll coating, as the ribbon will have a tendency to adhere to the roller.

Powder blending is a combination of *convection*, in which large groups of particles move relative to each other, *diffusion*, in which individual particles move relative to each other, and *shear*, which is the change of configuration of particles due to slipping of layers[12, 13]. Unfortunately, the complicated process of powder blending is very specific to the material being mixed, so there has been little success in using theory to predict mixing behavior.

> *A complete, validated theoretical description of blending different powders does not exist. The majority of theoretical descriptions of powder blending involve the mixing of materials that differ only in color and do not account for any cohesion or interaction between the components being mixed. The theory derived from such studies is not useful for describing practical pharmaceutical powders and, as a result, most powder mixing science in use in the pharmaceutical industry is empirical.*
>
> *Professor Charles L. Cooney [14]*
> *Massachusetts Institute of Technology*
> *Department of Chemical Engineering*

The determination of blend uniformity in powder blends has historically been an expensive and time consuming process that is frequently criticized as inaccurate[13, 15]. Traditionally, a thief probe is inserted into a number of positions within the mixing vessel, and the small (order 1 gram) sample is analyzed using traditional laboratory methods (HPLC or UV Spectroscopy) to determine the content of active drug substance. In 1993, the Barr decision (United States vs. Barr Laboratories) established 90% -110% of the theoretical active composition in a sample limited to three times the dosage weight as the criteria for establishing uniform blending [16]. This standard does not take into account the uniformity of the other excipients, upon which critical tablet parameters depend.

The traditional thief probe method for monitoring blend uniformity has been shown to introduce errors in the blending measurements due to disturbance of the powder bed as the probe is inserted. Differences in the flowability of the blend components can also affect the rate at which powders flow into the sampling cavity, so that free-flowing powders are preferentially sampled[17, 18]. This is not an issue for methods that do not involve disturbing the powder bed. Non-invasive spectroscopic monitoring methods such as DR-NIR and Light Induced Fluorescence (LIF) thus carry an additional advantage of accuracy over the traditional measurement method apart from the immediately apparent savings in process time and cost that are afforded by an on-line measurement.

The most mature, well studied, and commercially available technology for online determination of blend uniformity is Diffuse Reflectance Near Infrared Spectroscopy (DR-NIR). The determination of blending uniformity involves comparing consecutive spectra taken of the powder mixture as the mixing progresses. When the variation in the spectra as a function of time decreases to a minimum, this signals that blending is complete [15, 19]. One key advantage to NIR spectroscopy is that it monitors the dispersion of both the active drug substance as well as the excipients. Below are the individual DR-NIR spectra for the components of a model pharmaceutical blend, followed by the blend spectra taken over the course of a 25 minute mixing cycle from Sekulic et al.[13].

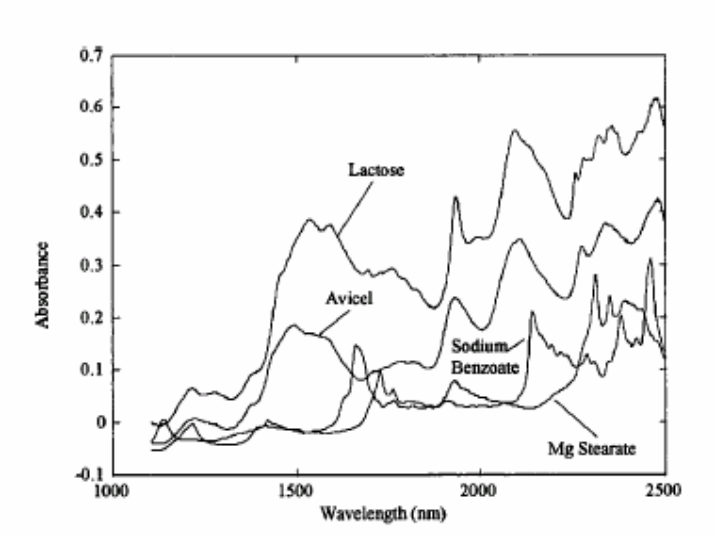

Figure 3: DR-NIR spectra of pure blend components from Sekulic et al. (1996)

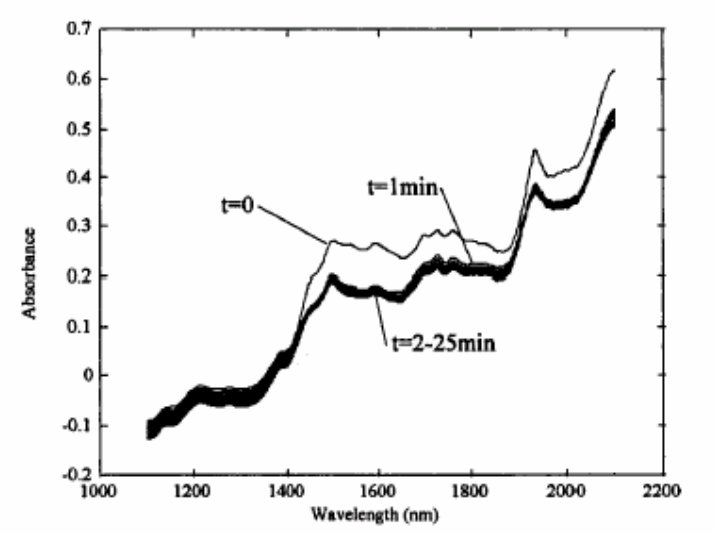

Figure 4: Typical DR-NIR spectra collected for an entire mixing rung from Sekulic et al. (1996)

As is apparent from figure 4, the spectra begin to look very similar to each other almost immediately, so a quantitative analysis of the spectra is required to glean a clear picture of the progress of blending. This is currently accomplished by one of several statistical strategies. In many cases, the spectra are first pretreated by multiplicative scatter correction (MSC), principle component analysis (PCA), or second derivative, standard normal variant (SNV). This will be handled thoroughly in chapter 5. Figure 5 shows the second derivative

spectra calculated from the absorbance spectra in figure 4. Statistical pattern recognition software is then used to determine the endpoint of blending. Figure 6 is the standard deviation of a moving block standard deviation of the spectra shown in figure 5. The uptick in the standard deviation at the end of the mixing time in figure 6 is due to an addition of Mg stearate at the 20-minute mark in the experiment, and should be ignored.

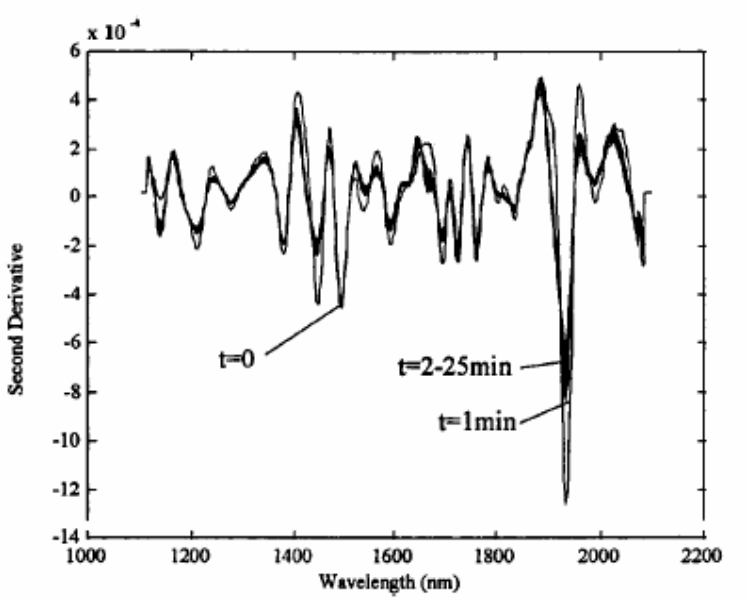

Figure 5: Second derivative of DR-NIR spectra from Sekulic et al. (1996)

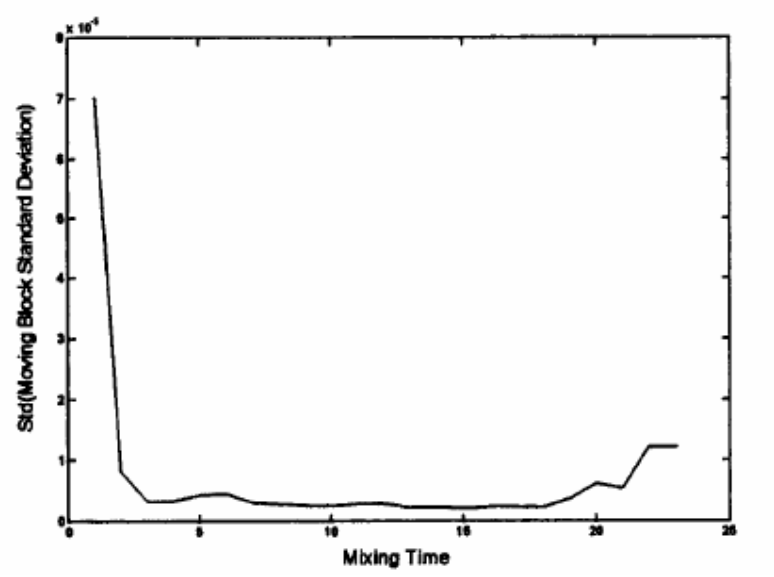

Figure 6: Final mixing metric (Sekulic et al. 1996)

Other non-invasive techniques that were considered include NIR imaging (NIR-I), in which images of the top of the powder bed are collected using bandpass filters consistent with absorption bands for the powder components. The individual pixels of the images are analyzed to determine the level of variation in the concentration of each powder component. NIR-I is able to sample a larger quantity of material than NIR spectroscopy, which allows for greater statistical confidence in the results. While this appears to be a promising technology, it has yet to be studied as extensively as DR-NIR spectroscopy, particularly with regard to monitoring powder blending. The technique is also limited to the top surface of the powder bed, so it may be more useful in concert with another technology as a check [18].

Light Induced Fluorescence (LIF) is another emerging analytical technique which is being applied to the monitoring of powder blending [20]. This technique takes advantage of the fact that many drug substances fluoresce when excited by the correct wavelength of laser light. The emission spectra from the powder mix can then be analyzed to determine the uniformity of the drug substance. LIF has an advantage over DR-NIR spectroscopy in that it is quite a bit more sensitive, and might be a good replacement for DR-NIR in cases in which the concentration of the drug substance is too low to detect by DR-NIR. However, there are several limitations to LIF as well. First, not all drug substances fluoresce. Lai and Cooney report that over 60% of the top 200 pharmaceutical molecules fluoresce [21]. Second, the technique is limited to monitoring the active drug substance, so excipient dispersion is ignored. Finally, the technology is currently in the development stage, and few commercial systems for monitoring powder blending are currently available. While this technique is not yet ready for application in the manufacturing setting, it is worthwhile to keep abreast of its development, as it may be very useful for specific monitoring needs in the future.

Several practical issues concerning the use of DR-NIR spectroscopy for this purpose merit discussion. The first is the question of how to attach probes to the mixing vessel. Currently, interchangeable containers are attached to the mixer, and are tumbled whole during the mixing step. This creates a difficulty in terms of probe attachment that may require some creativity to overcome. First, one must determine whether to dedicate one container to mixing, or if it is more advantageous to outfit all containers to allow for NIR monitoring. Secondly, a fiber optic wire is generally required to transmit spectra to the spectrometer. The tumbling motion of the container will require that a bearing of some sort be coupled to the

probe in order to avoid twisting the fiber optic cable. This difficulty is further aggravated by the fact that a single probe is insufficient for an accurate measurement, so probes positioned in different places around the container are necessary[18]. Wire twisting then becomes a significant barrier. In a number of studies, investigators have inserted probes through the axle on V-blenders, however, that is not an option for the current mixer configuration. The development of wireless probes will go far to ameliorate this difficulty.

2.5.3. Dry granulation

The dry granulation process consists of two discrete sub-processes which are best analyzed separately. The first step, roller compaction, serves to compress the powder into ribbons of agglomerated material. These ribbons are subsequently milled into particles in the second step, sieving.

The physical principle behind roller compaction is to agglomerate smaller particles into a large ribbon by deforming them beyond their region of elastic deformation [22]. The deformation characteristics of the product ribbon are affected by three key process parameters: feed rate, roller speed, and gap width. Together, these determine the compaction force experienced by the powder as it is compressed. The porosity of the exiting ribbon is closely tied to the compaction force. The purpose of the dry compaction step is to create denser, larger, and better flowing particles [23]. A balancing act must be performed, however. The mechanism that allows dry granulation to work, namely the irreversible plastic deformation of the particles, is the same mechanism at work in the tableting process, and the particles have a limited total deformation. Thus, if the particles are compacted too tightly during compaction, the tablets produced will have significantly greater friability [22]. On the other hand, too little compaction force can result in incomplete agglomeration, in which case the percentage of fines will increase. There is currently a control system in place on the roller compactor which varies the powder feed rate in order to maintain a set compaction force. As the current control system allows for control over the operation of the roller compactor, no additional instrumentation is recommended. The force vs. time data needs to be recorded and included in the electronic batch file so that it can be included in any multivariate analysis that is performed on the data captured by the PAT devices.

The second step in the dry compaction process is the sieving step, in which the ribbon produced during roller compaction is milled against a sieve plate to produce granules of a certain size range. The particle size distribution of the granules, which is the key output variable for the sieving process, is largely dependant on the size and layout of holes on the sieve plate. The mechanism for breaking up the ribbon is partially due to the forcing of material through the holes in the sieve plate, and partially due to the shearing action of the oscillating arm against the top surface of the plate. As it is known to have a significant effect on both the flow and tableting properties of the blend, the particle size distribution is the key variable to be measured during the sieving step. It is recommended that this measurement be made for purposes of understanding the phenomenon involved and verification that the process is within specifications. It is not recommended that the PSD be used for feedback control. As the sieve plate dimensions are set during the development phase, this parameter is not a good candidate for feedback control. The oscillation rate of the shearing arm may be varied, but a significant correlation between PSD and oscillation rate would first have to be established.

The granulate PSD can be measured using laser light diffraction on-line. This method was chosen using the same rationale as that for PSD measurements of the raw materials. Additionally, since the PSD measurement at this point in the process needs to be an on-line measurement, the only technique that has commercially available on-line equipment is laser light diffraction.

Granule bulk density is an important factor in setting the die volume to achieve the correct tablet weight, and is currently measured during validation. While this is not a quantity which is easily measured on-line, it is recommended that an effort be made at the development level to establish a correlation between incoming raw material particle size, compaction force, and the granule bulk density.

2.5.4. Final blending

The final blending step is somewhat more complicated than the pre-blending steps described previously. The purpose of the final blending step is to disperse the portion of magnesium stearate that is added after the granulation step. The magnesium stearate is weighed and

added manually through a hand sieve into the container that holds the granulate. The purpose of the magnesium stearate which is added at this point is to serve as a lubricant during the tableting process. Specifically, it aids in the release of the tablet from the die after compression. The lubricant extends the life of the punch set significantly. There is, however, a balance to be reached between even dispersion and over-mixing. If the magnesium stearate is mixed with the granulate for too long, a hydrophobic film will form over the granules. This can lead to a number of problems with the tablets including decreased tablet strength, and increased disintegration and dissolution times.

This mixing step is performed on the same mixer as the first blending step, and it would be advantageous to use the same analytical equipment to monitor both steps. Fortunately, this is indeed the case. DR-NIR is the most appropriate candidate for monitoring the dispersion of magnesium stearate, for the same reasons that it is the best choice for monitoring the pre-blending. Thus, the hardware used to monitor the two blending operations should be the same, although a separate spectrum analysis routine will need to be created that is specifically sensitive to the presence of magnesium stearate [24]. From a model-building perspective, it would be instructive to monitor the force required to eject tablets from the die in the tableting step. This metric would provide insight into the effectiveness of the lubricant.

2.5.5. Tableting

Viewed from a macroscopic perspective, the tableting step is the heart of the solid dosage production process. It is in this step that the powder is finally transformed into discrete tablets. As a result, a significant portion of the quality concerns for the process are focused on this step. One must monitor tablet mass, hardness, friability, drug content, and several other output quantities in order to insure that the process is proceeding satisfactorily. In contrast to the complexity associated with ensuring that the process is producing satisfactory tablets, the mechanics of the tablet forming process are less complicated. There are two primary events that occur during this step: the filling of the die with granules, and the compression, which proceeds in two steps within the die. In the die-filling portion, granules flow into the die cavity, then are leveled off mechanically so that, as long as the die has filled completely, a consistent volume of granulate will be pressed into a tablet. In order to achieve a consistent tablet mass, the die must fill completely, and the granules must be of a consistent bulk

density. Once the die has been filled, the only parameters that affect the condition of the tablets are the compression force and the time over which the force is imparted, the dwell time. The punch gap is set on the rotary press resulting in higher compression force the closer the punch tips are to each other, while the dwell time is a direct result of the speed the machine is run at. The compression is mechanistically similar to what happens during roller compaction in the dry granulation stage.

Unlike some of the other unit operations, the tablets that are produced must meet a number of criteria. In light of this, two points are important. First, the condition of the incoming granulate plays an important part in the quality of the tablets produced. Second, there is not a simple relationship between the operating parameters and any of the tablet properties. With this fact in mind, any special relationships will not be suggested (i.e. if hardness varies upward, adjust the compression force downward) for use in controlling the unit operation.

2.5.5.1.Tablet mass

The mass of tablets produced is obviously important for achieving the correct dosage level in each tablet. Compression force is monitored during manufacturing and this measurement is actually a very good example of a PAT implementation. As soon as the monitored compression force exceeds the given tolerances it indicates that the amount of granulate in the die is not correct. This information is then fed into a control loop and the dosing of the granulate into the die will be corrected. There is currently online monitoring of tablet mass by sampling tablets in the Checkmaster system (roughly 60-80 out of every 120,000, or 0.05%). This is sufficient to replace the current post-production testing from a regulatory standpoint; however, the data should be fed to a centralized "batch report" and incorporated into a larger empirical model relating the granulate properties recorded previously to the die volume that is filled before compression.

2.5.5.2.Tablet hardness

In the current process, tablet hardness is measured by placing the tablet between two metal plates, and then recording the force required to crush the tablet. There are several disadvantages to this method. It is destructive, so there is a limit to the number of tablets that

can be tested. It is also off-line and time-consuming for plant personnel. As an alternative to crush-testing, several researchers have attempted to show a linear dependence between the logarithm of the hardness and the density of a tablet. Unfortunately, this relation does not appear to be valid over a significant range of densities, so other avenues must be pursued for monitoring tablet hardness [25].

A great deal of attention has been paid in the last decade to the use of DR-NIR spectra taken on intact tablets to predict hardness [26, 27]. For tablets of identical composition but varying hardness, the diffuse reflectance NIR spectra show an increase in baseline absorption with increasing hardness. Figure 7 illustrates this trend [28].

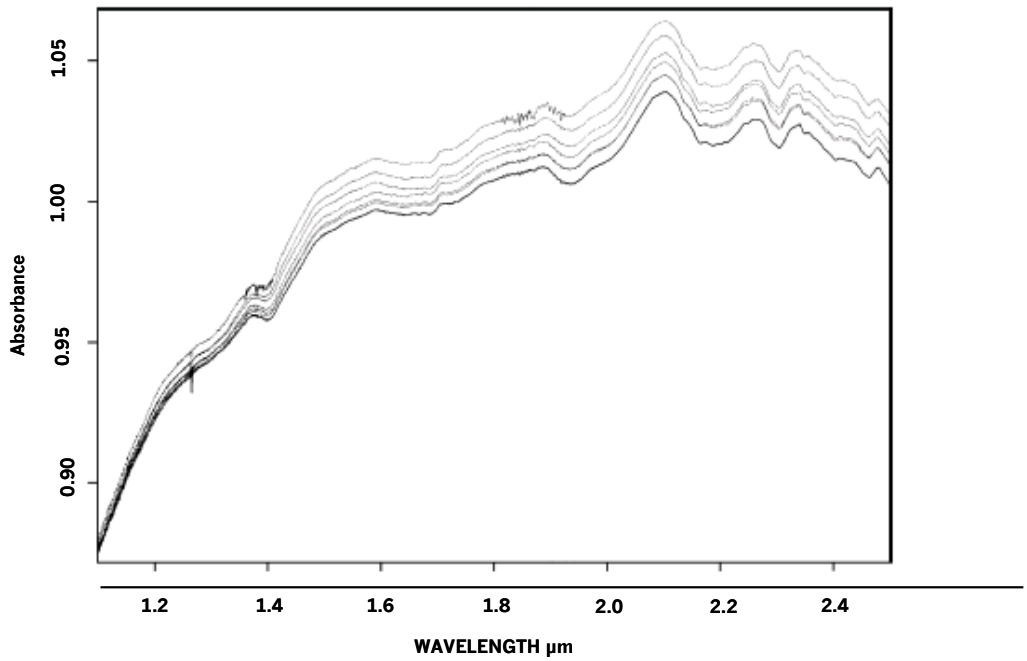

Figure 7: DR-NIR spectra for 20% theophylline tablets at seven hardness levels ranging from 2.87 – 17.2 Kp.

This baseline can be affected by both the tablet hardness and the position of the tablet being sampled, so steps must be taken to confirm that the tablet to be tested is oriented correctly. Various calibration methods have been proposed, either taking a best-fit regression of the entire spectrum, or else using a few specific wavelengths to quantify the baseline shift as compared to a standard. Both methods have been demonstrated to be as accurate as the crush test described previously [29].

2.5.5.3.Dissolution time and disintegration time

The question of finding an online replacement for dissolution and disintegration time testing is a difficult one for a number of reasons. Both phenomena are the result of a number of mechanical and chemical features of the tablet, and can be affected by changes in any of them. As opposed to hardness, there is not a singular physical property of the tablet that can be measured that can accurately predict these quantities. We are thus forced to retreat to a position that has been unthinkable in the past, but is a centerpiece of the PAT philosophy. A multivariate predictive model should be built in order to elucidate the most important powder and tablet characteristics that effect dissolution and disintegration times. The ability of water to reach and be absorbed by the crospovidone or other disintegrant is a major factor in the rate of disintegration, and consequently dissolution. Over-compressing a tablet can have the effect of sealing the surface of the tablet, slowing the absorbance of water into the interior of the tablet. Another possibly important factor is the extent of final blending. As described previously, too much mixing with mg stearate can cause a hydrophobic film to form over the surfaces of the granulates. In this case, the entire tablet may be made hydrophobic, which will surely slow the rate of dissolution. These and other contributing factors must all be considered and incorporated into an empirical model. It is recommended that parameters (and variables from upstream unit operations) to be considered for such a model include: compression force both in the roller compactor and the rotary press, rotary press speed, granule bulk density, granule PSD, extent of dispersion of Mg stearate, distribution of disintegrant, and moisture content of granulate.

2.5.5.4.Content uniformity of the drug substance

Unlike a number of the other tablet properties that have been discussed, the content uniformity is set as soon as the granulate in question has flowed into the die. The compression has no effect on the content of drug in the tablet. As a result, there is an opportunity to make an easier analytic measurement that will be equivalent to its more difficult cousin. By measuring the proportion of active substance in the granulate as it is fed into the rotary press, one can, in concert with tablet mass, deduce the drug content of each tablet. The advantage to this approach lies in the fact that it is much easier to monitor the chemical makeup of a (relatively) physically homogeneous powder mix than it is to measure

with the same degree of accuracy the drug content in a shaped tablet because the orientation of the tablet must be tightly controlled to achieve accurate analyses in the latter case.

Measuring the content uniformity of bulk powder is essentially the same process as measuring blend uniformity, so it naturally follows that the best analytical technique remains DR-NIR spectroscopy. It is recommended to install an NIR device to monitor the drug content in the granulate just as it flows into the rotary press feeding mechanism. While this equipment will be making the same measurement that was made in the previous blending step, the additional measurement point will serve as a final check of mixing efficacy, and will allow for a better understanding of the effect fines segregation has on content uniformity. This will lead to a better understanding of the acceptable limits of the particle size distribution of the granulate emerging from the dry granulation step.

If for any reason companies would be more comfortable measuring the content uniformity of the tablets after they have been formed, two spectroscopic techniques that are capable of doing so in an on-line manner are transmittance near-infrared (T-NIR) and DR-NIR spectroscopy [30, 31]. Each technique has advantages over the other, but many vendors offer spectrometers that can operate in either mode. In both cases, measurements are dependent on other tablet properties: hardness, porosity, particle size, tablet size, and imprints on the surface; thus, each requires chemometrics that eliminate these variations. Reflectance is faster than transmittance, however transmittance tends to be more accurate than reflectance [30, 32, 33]. This may be due to the fact that transmittance measures whole tablet while reflectance only looks at the surface and requires a uniform distribution throughout. In both modes, sample presentation is absolutely essential to accurate measurements, so care must be taken to orient the tablet properly.

2.5.6. Coating

Coating is the final processing step before the completed tablets are packaged. In the case of Product X, the coating is non-functional, which means it is applied for aesthetic purposes as well as to aid in swallowing and taste masking. Once in the body, however, the coating quickly dissolves and does not affect the bioavailability of the tablet. In the coating step, the cores are rotated in a revolving pan while a coating solution in an adequate dispersion is

sprayed on the bed of cores [34]. As droplets hit the cores, they spread out, forming an even coating. The coating is then dried by warm air which is constantly flowing through the coater.

There are a large number of formulation and processing parameters that can influence the quality of the final film, but they all in one way or another boil down to the condition of droplets as they land on the tablets [35, 36]. The inlet air temperature, flow rate, and humidity all have an effect on the degree that the droplets dry in the air before they reach the tablets, as well as the time it takes for the water to be driven off of the surface of the tablets after the droplets land [35]. The viscosity (and by extension, temperature) of the coating solution, the atomizing air pressure, and the solution flow rate all affect the size of the droplets as they leave the nozzle [36]. Rather than to monitor these parameters only to ensure that they remain within specified bounds, companies should record parameter values for incorporation into a modeling effort.

In terms of a control strategy, the best process variables to monitor are the size and moisture content of the droplets just before they reach the bed of tablets. While no specific technologies have been identified that are intended for this specific task, it may be worth the company's time to discuss with NIR vendors the possibility of using reflectance NIR to monitor the moisture content and mean particle size of the falling droplets. The specific situation of a disperse field of falling liquid droplets does not appear in the literature, but in principle, water content and mean particle size are both quantities people have claimed to measure with reflectance NIR spectroscopy [37].

In terms of quality control, a more direct measurement of tablet coating quality is needed. To determine coating thickness, reflectance NIR spectroscopy appears to be the only viable on-line analytical technique [38-40]. Much like content uniformity and hardness testing, this will require tight control on the orientation of the tablet.

2.5.7. Packaging

Potential failures in the packaging line are identified below:

- Broken tablets in the feed.

- Incorrect tablet in the feed.
- Pin holes or cracks in the packaging foil.
- Missing or surplus of tablets in a blister.
- Misalignment of the packaging foil.
- Leakage of sealed blisters.
- Impurities in the blister pack.
- Incorrect printing on the blister foil lid.
- Missing leaflet.
- Missing or surplus of blister layers in the box.
- Incorrect printing on the carton box.

VisioTec is proposing a strict step-by-step control on the packaging line to avoid errors caused in any packaging step. According to their proposal, non-transparent forming materials can be inspected by the VisioScan system. The correct size, color, shape, position, and drug content of the product can be checked by the VisioNIR system. The misalignment of the foil lid and the printing errors can be picked up by the VisioRead HR system. The impurities in the blister pack can be detected by the VisioChrom HR system. The VisioCount system can check that there are the correct number of blister layers and the existence of a leaflet in a closed carton box. VisioTec also recently introduced their new system which is able to detect blister leakage online during packaging.

2.5.8. Wet granulation

The wet granulation step does not appear in the Product X process, but it is an important step in the production of most solid dosage forms, so it is being presented out of order here. Within the wet granulation step, there are three key variables that should be priorities for monitoring; the extent of mixing during the wet massing stage, the moisture content of the powder during the drying phase, and the final particle size distribution (PSD) of the granulate produced. The online measurement of PSD is reviewed in sections 2.5.1 and 2.5.3, so that analysis will not be repeated in this section.

2.5.8.1. Wet massing

In the wetting step, the individual particles are agglomerated into larger particles by the formation of liquid bridges connecting the particles. It is the key that the wet massing step be ended at the correct time. Faure et al. write:

> *"In high-shear granulation, the fast dispersion of the binder is taken for granted. The spraying conditions are therefore not critical. The coalescence into granules is mainly affected by the mixing conditions and the proportion of liquid used [41]."*

> *"The principle difficulty with wet granulation in high-shear mixers is to decide 'when to stop': hence, the importance of control of the end-point [41]."*

Presented below is a diagram of the stages of agglomeration experienced by a powder as more binder liquid is incorporated into the agglomerates. The transition between states is not strictly linear. The formation of liquid bridges between agglomerates often begins before the transition between the funicular and capillary states has been completed. The phase behavior of the moist powder is governed by the amount of water present as well as the energy imparted to the mixture by the agitator. As a rule, in the production of solid dosage forms, the quantity of water to be added to the powder during the wet granulation stage is fixed during the development stage. As a result of this, the key parameter which must be controlled during the process is the length of time over which agitation occurs, or "when to stop".

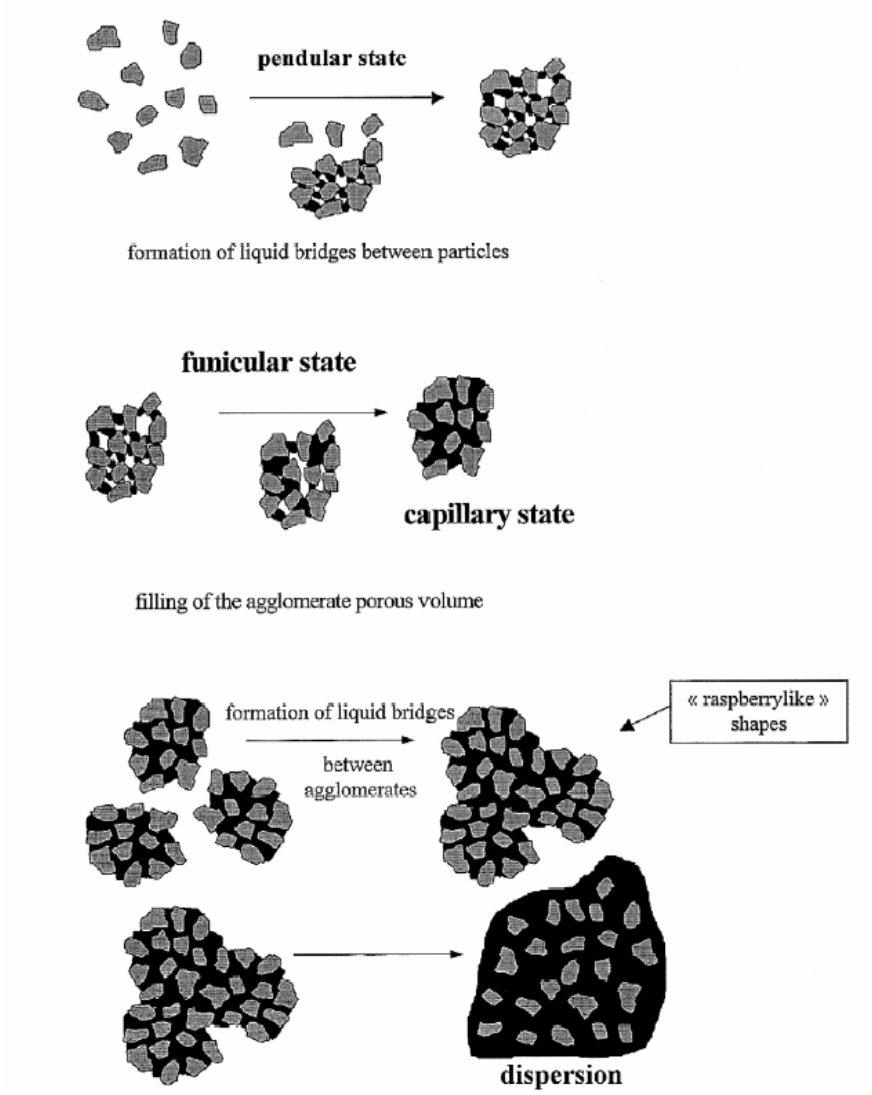

Figure 8: Stages of wet agglomeration from Goldszal and Bousquet [42].

The most widely studied method for determining the end-point for the wet massing step is to monitor the power consumption of the agitator motor. The method was first proposed in 1979 by Bier et al. [43], but it is by no means a mature technique. Research on the analysis of power consumption profiles during the wet massing stage of wet granulation continues at present [44].

While the power consumption profile varies significantly with equipment model and with the specific particle properties of the powder to be agglomerated, most powder mixtures exhibit several distinct regions of power consumption. These can be related to the various stages of

agglomeration described above. Empirical modeling will be required to determine the correlation between wet massing and the power consumption curve for each drug formulation [42].

Several other methods have been studied for determining the endpoint of the wet massing step. Closely related to monitoring power consumption is the method of monitoring the viscosity of the mixture with a torque rheometer [41]. Other researchers have investigated the use of vibration probe to determine the level of densification of particles. Finally, a number of techniques have been proposed to monitor the moisture level of the powder including NIR, capacitance sensors, and conductivity probes [41].

Power consumption monitoring is presented as the preferred method for controlling the wet massing step. None of the alternate methods mentioned above have been shown to be superior to the more mature technology of power consumption measurement [44].

2.5.8.2.Wet granulation: Drying

During the drying phase of the wet granulation process, the water which served to agglomerate the particles in the wet massing stage is driven off, resulting in particles which are larger than the original powder. The key parameters that control the drying process are inlet air temperature, and the drying time [4, 45]. The air temperature is generally set just below the melting point of the lowest melting material in the powder mix, normally not below 50 – 60°C. The current practice is to dry for a set time then test the granulate moisture content off-line by Loss on Drying (LOD), at which point the material is dried further if necessary. In the case that the powder is over-dried, the entire step may be repeated.

There are two drying regimes that occur during the process, which are rate limited by different phenomena. In the first drying stage, water is driven off by the heat introduced with the air. During this stage, the drying is evaporation-limited. The air generally leaves the fluid bed at a relatively constant temperature throughout this stage. Eventually, all the readily available water is driven off, at which point the drying becomes diffusion limited. As the evaporation rate drops off, the exit temperature of the air increases markedly, approaching the entry temperature [4].

Historically, fluid bed drying has been monitored using temperature probes to measure the air temperature at both the inlet and outlet. At the transition point between the two drying stages, a sharp increase in the outlet air temperature signals the end of evaporative drying. The moisture level can then be correlated to the exit air temperature as it approaches the inlet air temperature. Unfortunately, this method is limited in its accuracy [4]. Diffuse reflectance NIR spectroscopy represents an alternative non-intrusive online analytical tool for monitoring the progress of the drying step [5]. NIR is attractive as an analytical technique for moisture measurement for a number of reasons. First, NIR measures the overtones and combinations of vibrational modes for bonds involving hydrogen. As opposed to IR spectroscopy, the lower absorptivities of the NIR radiation allows spectra to be taken without any sample preparation. Coupled with the fact that glass does not absorb NIR radiation, the method is ideally suited to serve as an on-line monitoring tool.

The absorption spectrum of water shows strong absorption bands near 1940 nm and 1450 nm. Commercial NIR systems generally use these two peaks, as well as other reference wavelengths that are less affected by the presence of water, to quantify the level of moisture in the fluid bed [1].

NIR monitoring of moisture has the potential to replace the current process control method, which is to subject the dried granulate to a loss on drying (LOD) test in an off-line laboratory. In addition to saving processing time and laboratory costs, on-line monitoring will eliminate the need for remunerative steps to be taken when the granulate is either too wet or too dry, both of which contribute to uncertainty concerning the final condition of the granulate product.

As a final point to be considered, the tight control on the drying process made possible by NIR opens the door to time-saving techniques which would be too risky to implement using the traditional control methods. The drying step can be sped up by increasing the inlet air temperature, which speeds up evaporative drying. Air temperature is limited by the lowest melting point among the substances that make up the powder mixture. For drug substances with low melting points, this limitation can lead to significant drying times. During the evaporative portion of the drying step, the phase change of the water absorbs energy as fast

as the air can supply it. As a result, the granules never "see" the inlet air temperature until evaporation rate becomes diffusion-limited. Recent research has shown that the inlet air can be supplied well in excess of the melting temperature during the evaporative region without any ill-effects on the granules, as long as the temperature is reduced before the system crosses over into the diffusion regime. In this way, drying times can be cut by as much as 50%. Using NIR spectroscopy, it is possible to accurately monitor the moisture content and thus predict the transition point, making this time-saving method possible without the risk of exceeding the material melting point [4].

2.6. PAT methods to replace current quality assurance testing

Current Quality Assurance/Quality Control (QA/QC) testing of Product X tablets takes 12-15 days. If an investigation is required, an additional 3 days or more may be required. The average batch time for Product X production is 70 days, from the weighing of materials at dispensation until the final product leaves the company. One of the goals of PAT and this project was to reduce the holding time for laboratory testing of samples. This testing holds up the production process and requires products to be held after production is completed. The remainder of this section will detail what QA/QC testing is currently done and how the proposed PAT strategy can eliminate many of the laboratory tests with on-line or at-line measurements.

The PAT strategy encompasses two types of approaches to eliminating end product testing. The first is to replace a measurement currently made in the lab with one that can be done in-line or at-line by an automated process. The second approach involves correlating process characteristics to final product characteristics, which will not be possible until the process is better understood and monitored. Table 1 is a summary of the quality tests currently performed during solid tablet manufacturing and how they will be replaced in the proposed PAT strategy.

	Measurement	Current Method	Proposed Method
Cores	Aspect	IPC Lab	IPC Lab
	Thickness	IPC Lab - Checkmaster	At-Line Checkmaster
	Hardness	Compression Test	NIR
	Friability	Tumble Tablets	Correlation from Controlled Process
	Disintegration Rate	At-Line Checkmaster	Correlation from Controlled Process
	Average Mass	At-Line Checkmaster	At-Line Checkmaster
	Content Uniformity	HPLC	NIR
	Assay	SD of Content Uniformity	SD of Content Uniformity
Tablets	Appearance	IPC Lab	IPC Lab
	Aspect	IPC Lab	IPC Lab
	Shape	IPC Lab	IPC Lab
	Code	IPC Lab	IPC Lab
	Dimensions	IPC Lab Checkmaster	NIR - Coating Thickness, At-Line Check Master
	Disintegration Rate	Time to Dissintegrate Tablet	Correlation from Controlled Process
	Average Mass	IPC Lab Checkmaster	At-Line Checkmaster
	Humidity	Loss on Drying	NIR
	Identity	TLC & HPLC	NIR
	Degradation Products	HPLC	NIR (?)
	Dissolution Rate	Time to Dissolve AI	Correlation from Controlled Process
Packaging	Package Integrity	Blue Liquid Test	At-Line Package Monitoring
	Dates	QA Lab	At-Line Package Monitoring

Table 2: Quality assurance tests.

2.6.1. Quality assurance of core tablets

2.6.1.1.Aspect

Tablet cores are analyzed in the In-Process Control (IPC) laboratory to evaluate the quality of the tablet by visual inspection. The analysis insures that tablets are smooth, have the specified shape of the product, and are blemish free and intact. This analysis will continue to be performed by IPC laboratory personnel or operators within the PAT strategy because it is not time-consuming, and much more difficult to accomplish automatically.

2.6.1.2.Thickness

Certain tablet dimensions are currently measured by the Checkmaster in the IPC laboratory. The Checkmaster is an at-line piece of analytical equipment that can measure mass, hardness and tablet dimensions. There are Checkmasters attached to the rotary press for at-line testing and in the IPC lab. The only measurement that is done at-line is the tablet mass. It is recommended that the PAT strategy make full use of the Checkmaster's capabilities and

perform the measurements of all dimensions of the tablet core at-line, on a portion of tablet cores, as they exit the rotary press.

2.6.1.3.Hardness

Tablet hardness is currently measured by a compression test in the IPC lab. A tablet is compressed between two metal plates until it is crushed and the force required to crush the tablet is measured. Drawbacks of this method are that it is destructive to the tablets and requires an operator to take the measurements. The PAT strategy will replace the current testing method with a DR-NIR measurement on selected tablets after they have exited the tableting machine.

2.6.1.4.Friability

Tablet friability is measured in the IPC lab by tumbling tablets for 20 minutes. This measurement determines tablet brittleness. There is a specified amount of weight that the tablets can lose during the test. In the PAT strategy, friability will be predicted based on correlations with other process parameters such as granulation compression force, tableting compression force and tablet hardness.

2.6.1.5.Disintegration time

The disintegration time of a tablet is measured in the IPC lab by determining the amount of time that the tablet takes to break up in an aqueous environment. A given drug formulation has a specified time over which the tablet should break up in order to make the drug available to the patient. The disintegration time depends on the tablet hardness and the distribution of excipients throughout the tablet. Certain excipients expand when contacted with water to break up the tablet. In the PAT strategy the disintegration time will have to be predicted from the correlation of several process variables such as tablet hardness and distribution of the excipients throughout the tablet. Further study will be required to determine the exact relationship between tablet hardness and excipient distribution that predicts tablet disintegration time.

2.6.1.6.Average mass

The mass of 20 tablet cores (approximately 0.05%) exiting the rotary press are measured at-line by the Checkmaster through an automatic sampling mechanism at 10 different time points throughout the tableting process for feedback control to the tableter. The tablet mass is determined for a second time in the IPC lab using the Checkmaster. This at-line mass measurement made by the Checkmaster will be utilized in the PAT strategy without repeating the test in the IPC lab.

2.6.1.7.Content uniformity of the drug substance

The content uniformity of tablets is currently measured by selecting ten tablets or cores, produced throughout the tableting process, to test the amount of active drug substance in each by HPLC in the QA lab. HPLC is a very accurate method, but it is a time consuming test to perform and it is destructive to the tablet. The PAT strategy will replace HPLC testing of content uniformity with a DR-NIR measurement of the powder flowing into the tableter or a T-NIR measurement on selected tablets as they exit the rotary press.

2.6.1.8.Assay

The average amount of active drug substance is measured in several tablets by averaging the content uniformity results. This procedure will be continued within the PAT strategy.

2.6.2. Film coated tablets

2.6.2.1.Appearance

The appearance of film coated tablets is analyzed to ensure that the tablets have been coated with the appropriate color coating solution. This test will continue to be performed by IPC lab personnel or operators within the PAT strategy.

2.6.2.2.Aspect

The aspect of film coated tablets are analyzed by IPC lab personnel to ensure that the tablets have been fully coated, the tablet is free of particles or blemishes, that the tablets have remained intact, that the tablet coating is intact, and that the coating is smooth. This is a procedure that will continue to be done by IPC lab personnel or operators after the film coating process in the PAT strategy.

2.6.2.3.Shape

The tablet shape is assessed after the tablets have been film-coated by IPC laboratory personnel. This test is done to ensure that the tablets were formed using the correct die. This is a procedure that will continue to be done by IPC lab personnel after the film-coating process in the PAT strategy.

2.6.2.4.Code

The drug type is imprinted into the tablet during the tableting step. IPC laboratory personnel visually inspect the tablet to ensure that the proper code has been imprinted. This is a procedure that will continue to be done by IPC lab personnel after the film coating process in the PAT strategy.

2.6.2.5.Dimensions

The film coated tablet dimensions are measured in the IPC laboratory by the Checkmaster. This measurement is done to analyze the thickness of the film coating and check that the tablet has the proper dimensions. The PAT strategy will change this current method of testing so that the coating thickness, of a fraction of tablets, is measured by diffuse reflectance NIR and the film-coated tablet dimensions are measured by a Checkmaster in the coating area or within the IPC lab.

2.6.2.6.Disintegration time

The disintegration time of film coated tablets is measured using the same method as described above, for tablet cores, in the IPC laboratory. The PAT strategy will involve a

correlation of process parameters to disintegration time to determine if the tablet will meet the FDA specifications.

2.6.2.7.Average mass

The average mass of the film-coated tablets is measured in the IPC lab using the Checkmaster. The PAT strategy proposes that this measurement be done at-line as the tablets are being transferred out of the coating vessel by the Checkmaster.

2.6.2.8.Moisture content (Loss on Drying)

The water content of film-coated tablets is measured in the IPC laboratory by a loss-on-drying (LOD) test. This test is performed to measure the amount of water that the tablet absorbed during the film coating process as water can be detrimental to tablet stability. The PAT strategy will measure the water content of film coated tablets using DR-NIR spectroscopy at the same time coating thickness measurements are taken

2.6.2.9.Identity

The identity of the drug substance is currently determined by two different methods in the QA lab, TLC (thin layer chromatography) and HPLC. DR-NIR spectroscopy will be used in the PAT strategy to confirm the identity of the drug substance.

2.6.2.10. Degradation products

The concentration of drug substance degradation products are currently measured in the QA lab by HPLC. The FDA has set specifications on the levels of the different degradation products that can be contained in the final tablet. NIR may be used in the PAT strategy to measure the amount of degradation products in film coated tablets, but it is very doubtful that NIR has the sensitivity to differentiate degradation products from the active drug substance. An alternative option after the PAT strategy has been implemented is to correlate processing conditions to degradation of drug substance.

2.6.2.11. Dissolution time

The dissolution time of drug substance is measured by placing six tablets in a stirred tank at physiological pH and checking to ensure that a desired amount of drug substance has been solubilized in a given amount of time. The concentration of drug substance is measured by HPLC. The dissolution time should be able to be predicted after the implementation of PAT as more information about the process is known and variables that effect dissolution time are measured such as content uniformity and tablet hardness.

2.6.3. Packaging

2.6.3.1.Package integrity

The tablet packaging integrity is currently tested at-line by immersing that package in blue liquid. The package passes if no blue liquid is seen with in the package blisters. The PAT strategy would like to replace the off-line blue ink test with an on-line leakage test to detect problems in the packaging, like the newly offered VisioLeak from VisioTec.

2.6.3.2.Expiration date verification

The expiration date on the tablet packaging is verified by the QA lab. The PAT strategy proposes to include on-line video system for print verification in the packaging line to ensure the correct expiration date was printed on the package.

2.7. Recommended changes in development process

The philosophy of PAT needs to be integrated into the drug development process. In the future, the PAT strategy needs to be in place by the time drug manufacturing begins so that it is a part of the initially validated process. The PAT philosophy requires that a deeper understanding of the process needs to be achieved [46]. There is an opportunity to develop this greater understanding during the development process through the experiments that are performed to determine the formulation and operating parameters. Development needs to be steered towards determining cause and effect relationships, determining critical variables, always performing physical characterization of materials used, and in doing so will avoid

process problems [47]. Current development methods are empirical and operating parameters are determined by trial and error until they result in tablets that fall within specification. PAT requires that the process is understood, more mechanistically, and this requires that a scientific approach be taken to process development.

One aspect of this ultimate goal is gaining a deeper understanding of the operation of each process step in the solid tableting line. Each unit operation needs to first be studied in general terms and then with respect to each material that is processed. Only when the unit operations are fully understood, especially with respect to the role of each parameter, can the critical process variables be determined.

Steps that should be taken in the beginning of the drug development process are to first understand the material properties of the drug substance. The dominant mixing mechanism, and consequently the overall performance of the blender, depends greatly upon the physical properties of the mixing materials, the type of geometry of the blender as well as the operation conditions [24]. Additionally, only when the final blend has desirable flow characteristics are uniform mass and content possible in the final tablets. Useful properties to know include flowability, moisture absorption isotherms, and particle size distribution. Other useful informations that should be determined during development are the desired particle size distribution of the final blend and the real relationship between dissolution and hardness.

At first the development process may take longer while the critical variables are determined for each unit operation as it is specific to each product. In time, a large scientific knowledge base of how particular properties affect the granulation and tableting process will be amassed. Therefore, in the future, the development process will be faster as fewer tests are needed to determine operating conditions because they will instead be set by previously documented scientific understanding.

2.8. Conclusions

There has been developed a PAT strategy to monitor the Product X tableting process that is general to the solid tablet manufacturing process. The critical variables were determined

based on scientific understanding of each unit operation. In summary the critical variables are as follows.

- The particle size distribution of the granulate leaving the sieve, that follows the roller compaction process, can be measured. The measurements will be taken by an on-line laser diffraction particle size analyzer.

- Blend homogeneity is the critical variable in all three blending steps. DR-NIR can be used to monitor the blending process and to determine the process end point. In the blending step before granulation the moisture content can also be measured by DR-NIR because it is critical in roller compaction.

- The content uniformity and hardness of the tablets can be measured at the tableting machine. Content uniformity will be measured either by analyzing the powder entering the tableting machine or of the tablets that exit the tableting machine by NIR spectroscopy. Tablet hardness will be measured at-line by DR- NIR.

- The critical process variable for coating is the droplet size distribution of the coating solution prior to contacting the tablets. The critical product variables of the tablet are coating thickness and tablet moisture content. The tablet's coating thickness and moisture content can be measured by DR-NIR.

- Moisture content, material identity and the particle size distribution of the raw materials needs to be determined in dispensation. The moisture content and material identity can be measured by DR-NIR. The particle size distribution can be measured by laser light scattering.

- The critical attributes to monitor in the packaging line are identity and packaging integrity. Product identity measurements can be determined by NIR.

- PAT has the potential to reduce manufacturing times significantly for Product X as well as other products. Due to the reduction of in-process testing delays and

elimination of the 12-15 day post-production waiting period there an approximate 20% reduction in throughput time.

2.9. Recommendations after part one

The first PAT technology to be developed should be the one that is the fastest and cheapest so that the success of PAT can be established. A first success will demonstrate the benefits of PAT and pave the way for the implementation of more PAT technologies. The priority of each PAT technology implementation will need to be evaluated based on the benefit and cost of implementation.

Therefore, the next step to take with this project is to determine the cost associated with implementation of each technique. The implementation cost will be a function of the cost of the equipment, labor costs of setting up the equipment and amount of production time that is lost as a result. The benefit will be a function of the time saved on quality assurance and quality control testing, the increased process efficiency, and the increased process yield due to fewer tablets out of specification from better process control.

It is recommended that PAT be implemented at the development level. PAT requires process understanding and quality by design, and process understanding must begin in the development phase. Only when the process is fully understood can an effective PAT strategy be defined.

2.10. Economic analysis of PAT (part two)

The next step for this project was to critically evaluate and complete the strategy proposed in the first part. Then the cost of PAT implementation, time savings and cost savings were evaluated to determine if implementation of PAT is economically advantageous for pharmaceutical companies.

2.10.1. Lean Manufacturing

An accurate economic evaluation requires a good estimate of the base case for the manufacturing processes of Product X, Product Y and Product Z. Therefore it was needed to estimate the current production timeline and the projects being planned to improve upon that timeline. 'Lean Manufacturing' is currently being implemented in different companies. Lean manufacturing aims at reducing the time spent in non-value-added steps during the manufacturing process such as waiting times between different unit operations and holding times in the warehouse. The main objectives of Lean Manufacturing can be broadly summarized as follows:

- Increase productivity and capacity
- Improve customer service
- Reduce throughput times
- Reduce inventory hold-ups
- Reduce problems in manufacturing.

Some of the key attributes of the Lean manufacturing thinking for achieving those goals are:

- All processes should be driven by demand rather than forecast. Coordination between Country Pharma Organizations (CPOs), Global Supply Chain Management (GSCM) and Pharmaceutical Operations needs to be improved.

- Business process integration within the manufacturing site involving Supply Chain Management (SCM), production, and QA/QC needs to be improved to reduce time delays. This integration is illustrated in figure 9.

- Organization should be aligned and focused to satisfy the customer.

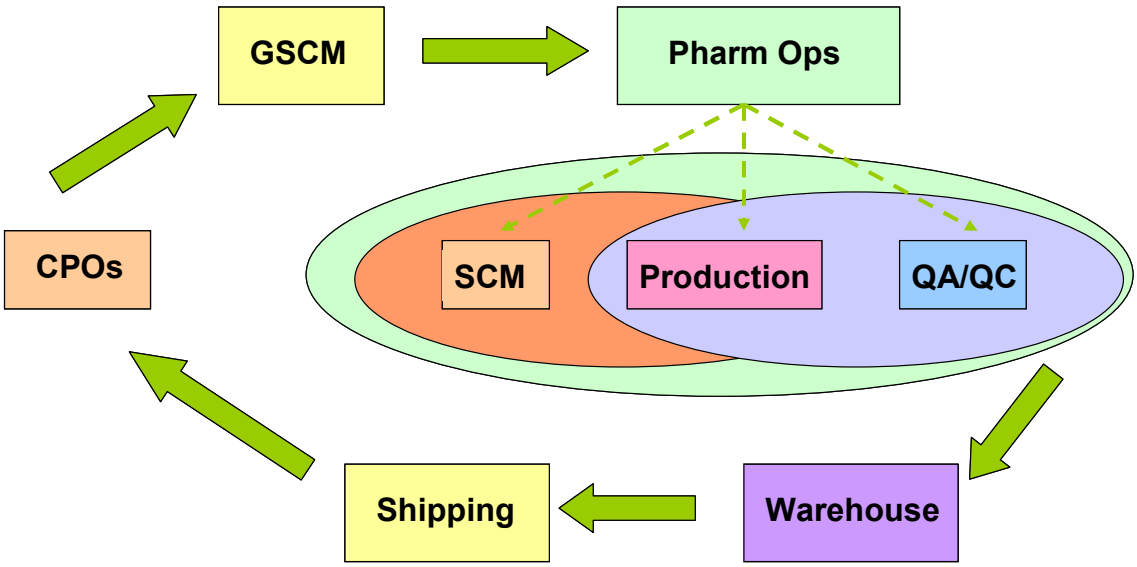

Figure 9: Business process integration in Lean manufacturing.

- Processes should be well defined and well documented. Processes should be linked together in a continuous flow so that production moves forward via downstream signals.

- Inventory hold-ups should be reduced considerably. The essence of lean manufacturing is to have an efficient and optimized manufacturing process that produces rapidly on-demand rather than have large inventory hold-ups to prevent stock-out risks.

- Problems should not be allowed to linger unresolved and should not be passed downstream. This leads to further increases in throughput time and inventory hold-ups.

Lean manufacturing projects have yielded positive results. Lean manufacturing is currently in the planning stages at the site in question and is expected to be implemented for some

important products later this year. Based on this information, it was decided that for the economic analysis of PAT, it will be assumed that lean manufacturing has been implemented in. Cost and time benefits of implementing PAT on a lean manufacturing process were determined. Details about current processing times and lean targets are presented in section 2.13.

2.11. Objectives

The objective of this project was to weigh the costs and benefits of employing a process analytical technology (PAT) strategy at a pharmaceutical production facility. The evaluation studied the use of PAT to monitor solid tablet formulations made by both wet and dry granulation, focusing on Product X, Product Y, and Product Z. To meet the objective of PAT economic analysis, several sub-objectives were established:

1. Continuation of the first part to verify critical variable lists and PAT methods to control them, selecting certain products as examples. These products are expected to be the focus for the first implementation of PAT.

2. Identification of parts of the process that offer the greatest potential for time and cost savings by implementation of PAT.

3. Proposal of preliminary PAT process designs, with modified process flow diagrams (PFD), as well as process and instrumentation diagrams (P&ID).

4. Determination of the times associated with each processing step, to allow for the determination of where PAT will aid in reduction of overall batch time.

5. Identification of costs associated with production of one batch, for both the current situation and after the installation of PAT. These costs include those incurred by capital equipment as well as operating expenses.

6. Comparison of the current and proposed designs using total batch costs, as well as savings gained by reducing delays from QA/QC and investigations.

7. Performance of a sensitivity analysis to determine which production costs have the greatest impact on the economic benefits of PAT.

Lean manufacturing throughput time was chosen as the base case for batch evaluation instead of the current throughput time. This decision was reached because during 2004 lean manufacturing will be implemented at the site for Product X, Product Y and Product Z. Additionally, PAT will only be implemented on lean manufacturing processes where the time savings of eliminating laboratory tests will have the greatest impact.

2.12. Method of approach

To approach the project objectives, the costs and timing of the current process were calculated or estimated from records at the site. In addition, records from investigations identified process areas that would benefit the most from PAT. An iterative approach was attempted to acquire the data needed for the cost-benefit analysis. General process data were requested, analyzed, and used to form preliminary conclusions. From these conclusions, key areas of the process were identified and more detailed information was requested. With more in depth information, final, definitive, conclusions were formed on the cost-benefit analysis of PAT implementation. The modified process flow diagrams and P&IDs were proposed, and the design's economics were calculated. The project focused on the manufacturing process from dispensation to the release of the product by quality assurance. The packaging line was not considered as the time spent after QA release depends solely on purchase orders received for the product and cannot be influenced by PAT.

The calculation strategy assumes that PAT will be implemented in three stages. Phase I will be the installation of on-line analytical equipment with computer archiving of data and multivariate data analysis (MVDA). "Quick wins" for Phase I of PAT implementation, which were benefits that were included in the economic analysis in the first years after implementation, are as follows:

- Faster release of products will be possible after installation of analytical equipment and correlation development because tests previously done in the QC and IPC labs will be replaced by tests performed during processing.

- QC time and cost will be greatly reduced because most tests previously done in these labs will be performed during processing.

- Investigations time will be reduced due to easier access to process data provided by electronic records. MVDA will also aid in identifying the root cause of an investigation.

- Inventory levels will be reduced due to shorter throughput times associated with the reduction in QC testing.

The FDA has stated that they will approve a process for real time release when on-line analytical measurements are shown to be equivalent to current laboratory testing. A company must demonstrate that each on-line test is an alternative analytical procedure and real time release will occur when equivalence for all laboratory testing has been demonstrated for every test. Before real time release can be realized testing that is to be replaced by correlations with other measured variables will have to be developed.

> *The combined process analytical measurements and other test data gathered during the manufacturing process can serve the basis for real time release of the final product and would demonstrate that each batch conforms to established regulatory quality attributes.*
>
> FDA Guideline
> PAT-A framework for Innovative
> Pharmaceutical Manufacturing
> and Quality Assurance

ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) is a group that represents the regulatory agencies of the US, Europe and Japan and pharmaceutical companies and is currently in the process of drafting a guideline to support PAT. This indicates that European regulatory agencies are likely to support PAT initiatives of pharmaceutical companies.

Phase II of PAT implementation involves the installation of process control systems for each critical variable and will have the following midterm benefits:

- Visual batch sorting will be reduced because control systems will correct problems as they occur resulting in only the production of tablets with the desired level of quality.

- IPC lab costs for PAT products will be completely eliminated due to on-line analytical tests and correlations that have been developed.

- Production yields for each batch will be increased as the control systems will carefully steer the process to its desired end point eliminating material losses.

- The number of batch rejections will be reduced as processing problems will be corrected as they occur.

- The FDA has stated that there will be fewer audits of PAT processes. The FDA believes that a PAT-approved process is being continually monitored by the company and does not need as much regulatory intervention.

- Inventory levels will be further reduced after implementation of control systems because the process will be more stable and have a lower associated risk of failed batches.

Phase III of PAT implementation involves integration of PAT in the development phase of new products. Integration of PAT into the development phase involves costs associated with increasing the understanding of each unit operation in solid tablet manufacturing and determining the critical variables associated with each unit operation for a particular product during development. These long term benefits and costs were not addressed in this project as the focus was only on products currently on the market. The benefits associated with PAT implementation in development are as follows:

- The time and cost associated with the process development of solid tablets will be reduced when there is a deeper understanding of each process step. However there

will need to be a significant effort within development to first acquire a deeper understanding of process steps.

- Increased understanding of solid tablet unit operations will allow for the best formulations and process to be applied to a particular product. This approach to process development addresses a major goal of PAT which is quality by design

2.13. The site's production data

2.13.1. Process flow diagram

Throughput time for a batch is defined as the duration of time from dispensation until QA release of the batch. The scope of this project does not include looking into time durations or delays from the release of raw material by QA to dispensation and from packaging to shipping. The flow diagram for this process is shown in figure 10.

2.13.2. Current manufacturing times

From figure 11, it can be observed that the total time of value adding steps in the process is a very small portion of the throughput time. There are a lot of waiting steps in the current process where there is no value addition, which leads to losses due to the financial cost of inventory. In the current manufacturing scenario, after coating, the product waits five weeks in the warehouse for packaging orders. The QC analytical testing is time consuming, around three weeks, but since it is done during the waiting time period it is not currently a bottleneck

2.13.3. Implementation of lean manufacturing

As mentioned in section 2.10.1, planning has begun for lean manufacturing in the site and is expected to be implemented soon. The target throughput time for lean manufactured products is projected to be around 20 days and the average throughput time for all solid tablet products in the site is expected to be around 35 days. Hence,

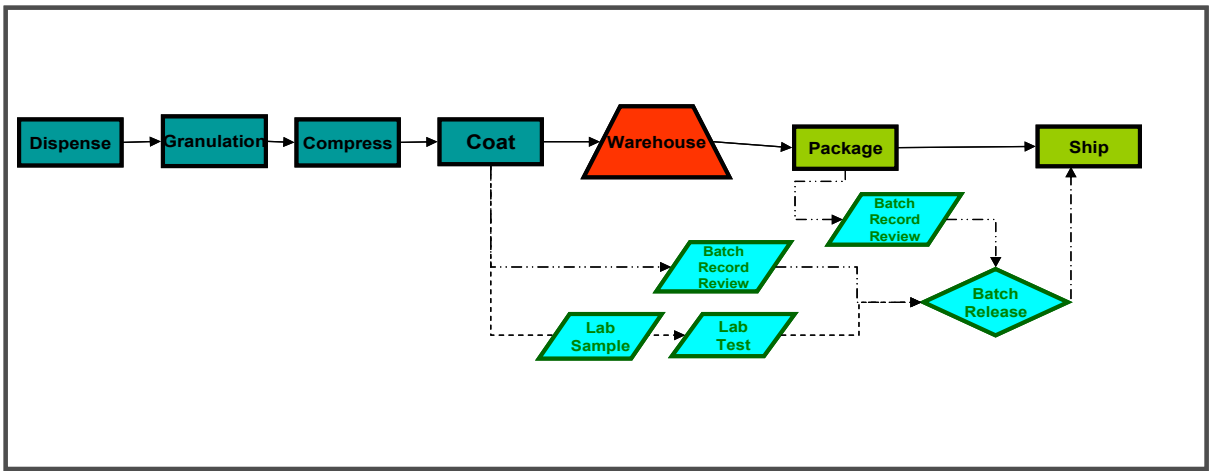

Figure 10: Process flow diagram for solid tablet manufacturing

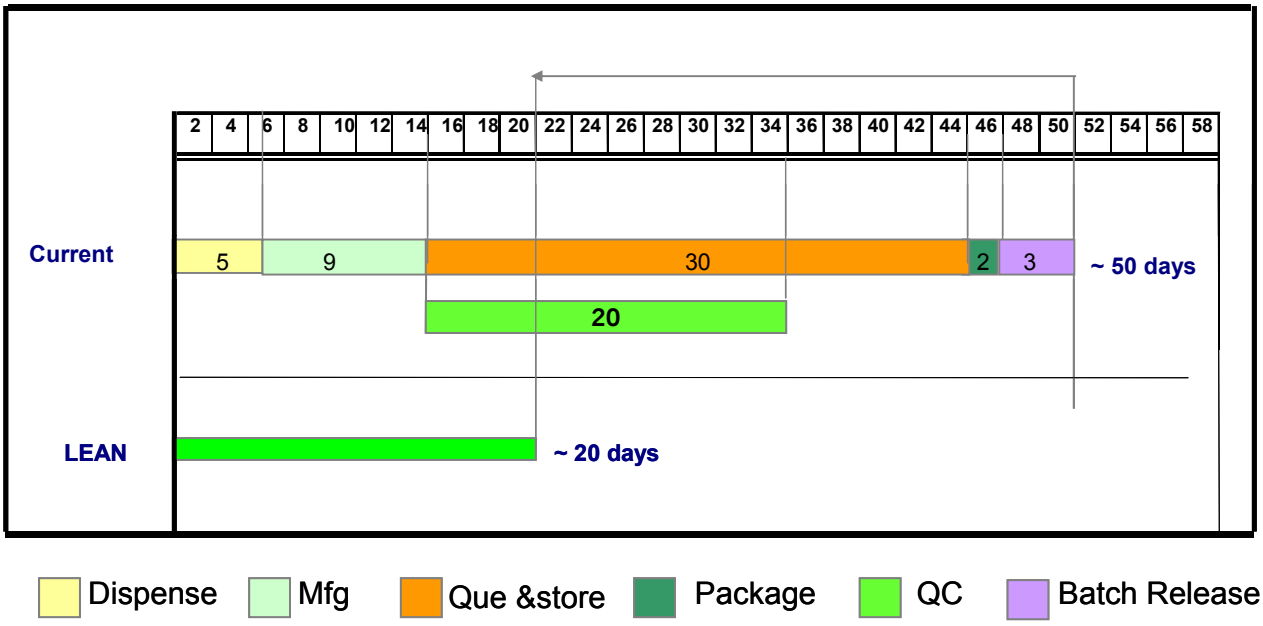

Figure 11: Current manufacturing and waiting time.

this project will use 20 days as the baseline throughput time for making cost and time benefit analyses. After implementation of lean manufacturing, QC analysis is expected to become a bottleneck, due to the long time required for analysis and resource constraints in QC. PAT

will prove to be most beneficial in lean manufacturing processes. According to estimates from, after implementation of lean, PAT can further help to reduce throughput time by five days by replacing QC testing. This five day reduction will result in savings of the financial cost of bulk product in the warehouse due to faster QA release of the batch.

2.14. Batch costs

The following section summarizes the production costs for batches of Product X, Product Y and Product Z.

The active ingredient cost was on average 85% of the ideal Product X batch cost. An ideal batch is one in which there were no manufacturing problems or investigations. The cost breakdown of an average, ideal Product X batch, excluding the cost of active ingredient is shown in figure 12, below:

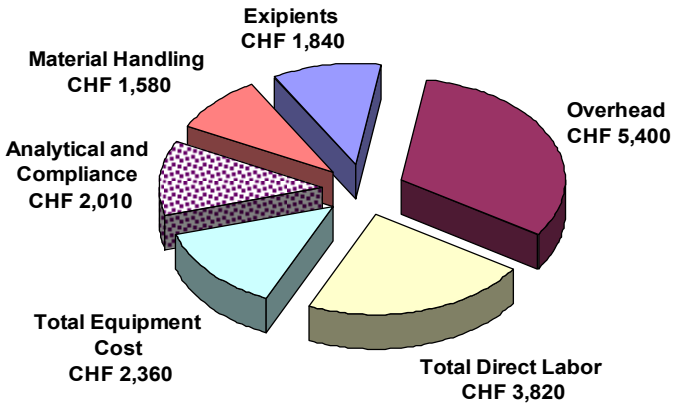

Figure 12: Cost breakdown, excluding active ingredient for an ideal product X batch.

For Product Z, the production costs were acquired. The cost breakdown is shown below.

The active ingredient cost is 88% of the average ideal Product Z batch cost. The production price per batch, excluding the cost of the active ingredient, is shown in figure 13, below:

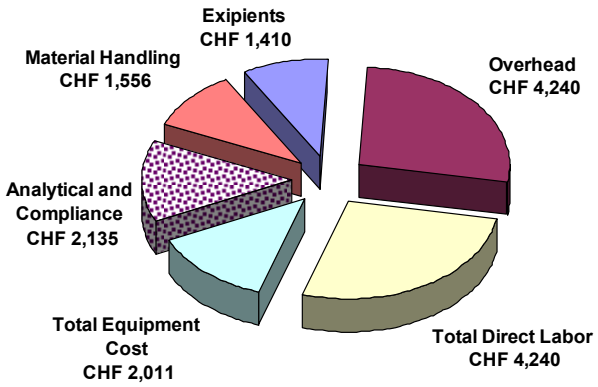

Figure 13: Cost breakdown, excluding active ingredient for an ideal product Z batch.

There is only one formulation of Product Y produced. With only one set of production cost no average was used to assess the cost of a Product Y batch.

The active ingredient cost is 75.6% of the average ideal cost of a Product Y batch. Other (non-active ingredient) costs are compared in figure 14.

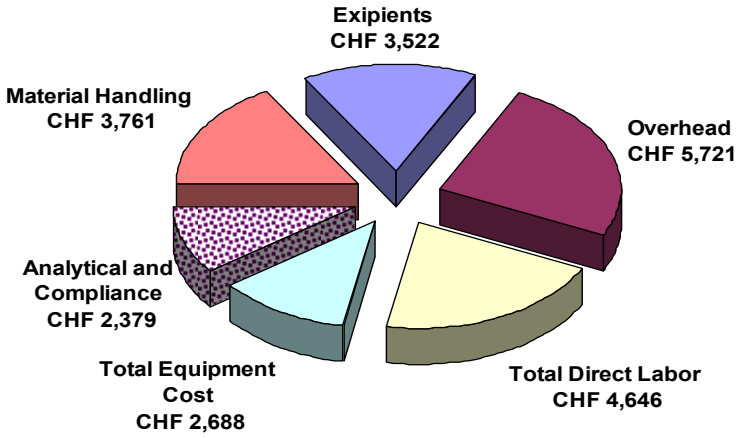

Figure 14: Cost breakdown, excluding active ingredient for an ideal product Y batch.

2.15. The site's compliance data

2.15.1. Standard testing

2.15.1.1. QC data

The following data from the Quality Control (QC) department were provided for the purposes of quantifying the time and cost of standard testing and QC investigations. Table 3 contains an overview of the total testing and investigations in one year for each of the three products evaluated.

	Product X	Product Z	Product Y
Analysis time (minutes) per Batch	510	440	550
Number of Batches Analyzed	752	634	533
Human Resources Needed (FTE)	3.6	2.6	2.8
Number of Out-Of-Spec. Due to Product Failure	1	0	0
Time for QC Investigation (hours)	1	0	0
Number of Out-Of-Spec. Due to Analytical Error	1	5	2
Time for QC Investigation (hours)	2	158	7

Table 3: Quality control analytical testing and investigations.

Table 4 is a summary of the equipment used by the QC department, the number in use, the equipment life and the annual depreciated value.

Type of Equipment	Cost of new equipment [CHF]	Number in use	Life (yrs)	Depreciated value/year
HPLC	65000	22	10	143000
Dissolution Tester	17000	9	15	10200
Balance	15000	9	12	11250
Shaking Machine	4000	25	7	14285
Ultrasonic Bath	8000	3	10	2400
UV Spectrophotometer	40000	3	10	12000
IR Spectrophotometer	55000	1	20	2750
Halogen Dryer	12000	2	10	2400
Potentiometric Titration	20000	1	10	2000

Table 4: Quality control equipment list

2.15.1.2. IPC lab data

The following data for the IPC lab tests and testing times summarized and is shown in the table below

Test	no. of Tablets	Testing time (min)
After Tableting		
Aspect		
Thickness	10	5
Hardness	10	10
Average weight	20	
Std. dev. Weight	20	
Friability	20	25
Disintegration	6	2-10 min
After Coating		
Aspect,shape,code		5
Length,diameter	1	1
Width	1	1
Thickness	10	10
Average weight	20	
Std dev weight	20	
Disintegration	6	2-10min
Loss on drying	10g	10

Table 5: IPC lab tests and testing time.

The IPC lab has 8 FTE's (over 3 shifts) working year round. After the IPC and the QC testing, the results are compiled and sent to the QA department. Batch records are reviewed by QA. If all the test results are within specifications and the batch records conform to the regulations, the batch is released by QA. This takes anywhere between 1-3 days. However, if

the testing results or batch records do not conform to specification, then an investigation is carried out to find the cause of the problem.

2.15.2. Investigations, rejections, resorting and audit data

2.15.2.1. Investigation data

Investigations can be classified into a number of different categories such as: production investigations, QC investigations, QA investigations, and packaging investigations. Implementation of PAT will impact production and QC investigations but not necessarily QA investigations. QA investigations might be due to issues that PAT cannot address such as human errors in paper batch records. Packaging is not included in the list of the project objectives and this report does not analyze packaging investigations.

The following data for investigations were summarized.

	Product X	**Product Z**	**Product Y**
Total no. of Investigations	**48**	**35**	**14**
Production Investigations	29	19	12
QC Investigations	1	5	2
Others	18	11	0

Table 6: Investigation data

The times for QC investigations were provided and were given previously in table 3. The times required for production investigations vary significantly depending on the nature of the problem and accurate records are not kept, making it extremely difficult to get accurate estimates. After discussion of investigation times with QA it was decided that a production investigation lasts an average of 10 days. In extreme cases, the investigation time (and batch quarantine time) may extend up to 90 days. The labor costs associated with investigations

was also hard to quantify as investigations are carried out by different people and vary considerably in terms of their complexity and man-hours required. After discussions with manufacturing, it was decided to approximate the labor cost for investigations by assuming that 2 full-time equivalents (FTEs) of labor (1 FTE in production and 1 FTE in QA) are involved full-time in dealing with investigations.

2.15.2.2. Batch rejection data

The QA department receives investigation reports and then must determine to release or reject the entire batch. Batch rejection leads to significant write-off costs and losses. The following data on Batch rejections was provided by QA.

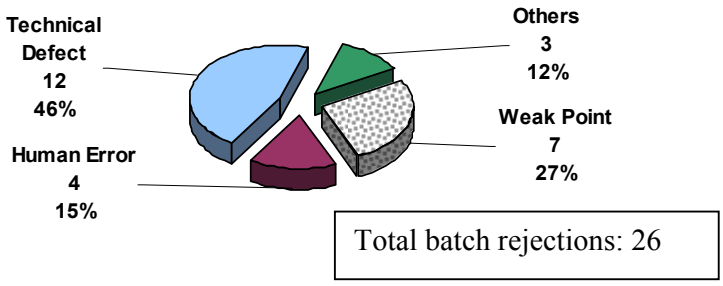

Figure 15: Breakdown of batch rejections for all products

Implementation of on-line analytical equipment and installation of programmable logical controllers (PLC's) with feedback control loops is expected to significantly reduce the batch rejections due to technical defects, human errors, and weak point rejections. For the three products of interest (Product X, Product Y and Product Z), the following data on batch rejections were provided by QA.

Product	No. of rejected batches	Origin of the problem
Product X	2 (0.2%)	Composition of tablet not in accordance with requirements; excess weight of 5.35 kg in one of the compounding steps
		Underside of tablet was flat instead of convex due to wrong punch
Product Z	3 (0.4%)	Aspects of most tablets doesn't comply- rough and porous surface
		Too low hardness and friability of tablet core
		Aspects of most tablets doesn't comply- residue of dust in break notch and badly readable embossing
Product Y	0	

Table 7: Batch rejection data for product X, Y and Z during one year.

2.15.2.3. Resorting data

The data for resorting Product X, Product Y and Product Z during one year were provided by QA and is presented in table 8.

Currently, resorting is performed manually by two operators sorting out the defected tablets. The time spent on resorting varies greatly and depends on what proportion of the batch has been affected. The costs for manual resorting were provided by manufacturing. For a resorted batch, it was assumed that 20% of the batch was sorted manually by 2 workers (at 89

CHF/h) over 4 days using a sorting machine that costs 7 CHF/h. The remaining 80% was sorted using an automatic sorting machine, over 1.5 days at a rate of 184 CHF/h. The automatic sorting machine requires only one FTE while in use.

Product	No. of resorted batches	Reasons
Product X	**31**	
	17	Oversized tablets due rotary press malfunction
	4	Rough surface, white spots
	1	Broken off edges, damaged edges
	1	damaged tablets
	4	damaged edges, rough surface, cavities
	3	damaged edges, cracks, bubbles, bonding surface
	1	Broken off edges
Product Z	**6**	
	4	broken off edges, pimples, rough surface
	1	cavities, rough surface
	1	broken off edges
Product Y	**1**	bonding surface, rough surface

Table 8: Resorting data for product X, Y and Z during one year.

The implementation of on-line analytical equipment alone is however not expected to significantly reduce the number of batches affected by cosmetic defects that need resorting. The installation of control systems with feedback control loops along with all the on-line analytical tools should significantly decrease the number of batches with cosmetic defects and the labor for resorting.

2.15.2.4. Audit inspection data

The following data regarding audits and inspections were provided

Year	FDA	RFS	EMEA	Others
1997	3	1	1	0
1998	4	8	2	1 (Canada)
1999	0	0	0	2 (Mexico+Bosnia)
2000	2	2	1	0
2001	4	0	2	0
2002	1	1	0	0
2003	2	2	0	1 (Brazil)
Total: 41	**16**	**15**	**6**	**4**

Table 9: Inspections performed at the site by different regulatory authorities.

It is quite difficult to quantify the exact cost of an FDA audit. This is because an FDA audit places additional responsibility on the compliance and production personnel, making it difficult to determine an audit's financial impact. The number of FTE's involved and the number of man-hours spent on an FDA audit varies from audit to audit. There were some average numbers provided for man-hours for an FDA audit which are presented in table 10.

Task	FTEs	No. of Days
Audit Preparation	4 – 5	15-20
Spy Inspection	20	3 - 4
Replying and Follow-up	10 – 15	1 - 2

Table 10: Labor personnel and man-hours required for an FDA autit.

The numbers in table 9 show that there have been 16 FDA audits in the last 8 yrs (approximately 2 FDA audits per year). The number of FDA audits depends on the FDA's confidence about the process. The essence of PAT is to develop a basic understanding of the process, implement complete control to ensure quality by design and manufacturing right the first time. Hence, implementation of on-line analytical equipment along with control systems is expected to increase FDA's confidence of the company's manufacturing process and quality control, and thereby reduce the number of FDA audits.

2.16. PAT implementation costs

2.16.1. Overview of PAT strategy

Above the proposed PAT strategy for solid dosage manufacturing was described. After further research and economic evaluations of costs associated with implementing PAT for solid tablets, several modifications were made to the proposed PAT strategy.

- Dispensation currently utilizes a computer system to monitor the weighing of raw materials for solid tablet production. A bar coding system is used to identify the materials that are received from the warehouse. The operator is then told by the computer the amount of material to be transferred by hand and is only allowed to finish when the mass is within +/- 0.5% of the specified amount. This is the same strategy that was proposed in part one to ensure that the proper amount of material is added to each batch. DR-NIR equipment and LLD equipment need to be purchased to identify the raw material, determine the moisture content and the particle size distribution.

- The content uniformity of tablets, instead of powder flowing into the rotary press, will be measured in order to reduce the number of NIR spectrometers that need to be purchased and the number of NIR measurements taken. An NIR spectrometer is

to be placed at the exit to the rotary press to sample a portion of tablets to measure tablet hardness. Therefore, with one measurement, and separate data analysis of the resulting spectrum, content uniformity and hardness can be determined. It is desired to limit the number of NIR spectrometers as equipment and validation costs are high.

- The change in temperature of the fluidized bed throughout drying during wet granulation is proposed as the method to control the drying time instead of DR-NIR. Descriptions of both types of measurements are in part one. This change is suggested because thermocouples are much less expensive than NIR spectrometers. The company has prior experience in monitoring the operation of the fluidized bed dryer by the change in temperature of the fluidized bed and has found this method satisfactory. There is also no equipment investment required to monitor the change in temperature. Temperature measurements are currently made to guide the operation of the fluidized dryers by operators but there is no feedback control system implemented at the site.

- The In Process Control (IPC) lab will be eliminated. Part one report recommended that aspect, appearance, shape and code continue to be analyzed by IPC lab personnel. It is now recommended that these tests be performed by operators to eliminate all labor costs in the IPC laboratory.

Figures 16, 17 and 18 contain process flow diagrams (PFD) for Product X, Product Y and Product Z, respectively. The PFD's indicate all unit operations involved in the manufacture of these products. The proposed PAT strategy is described by indicating all critical variables and the corresponding analytical methods proposed to monitor the critical variables.

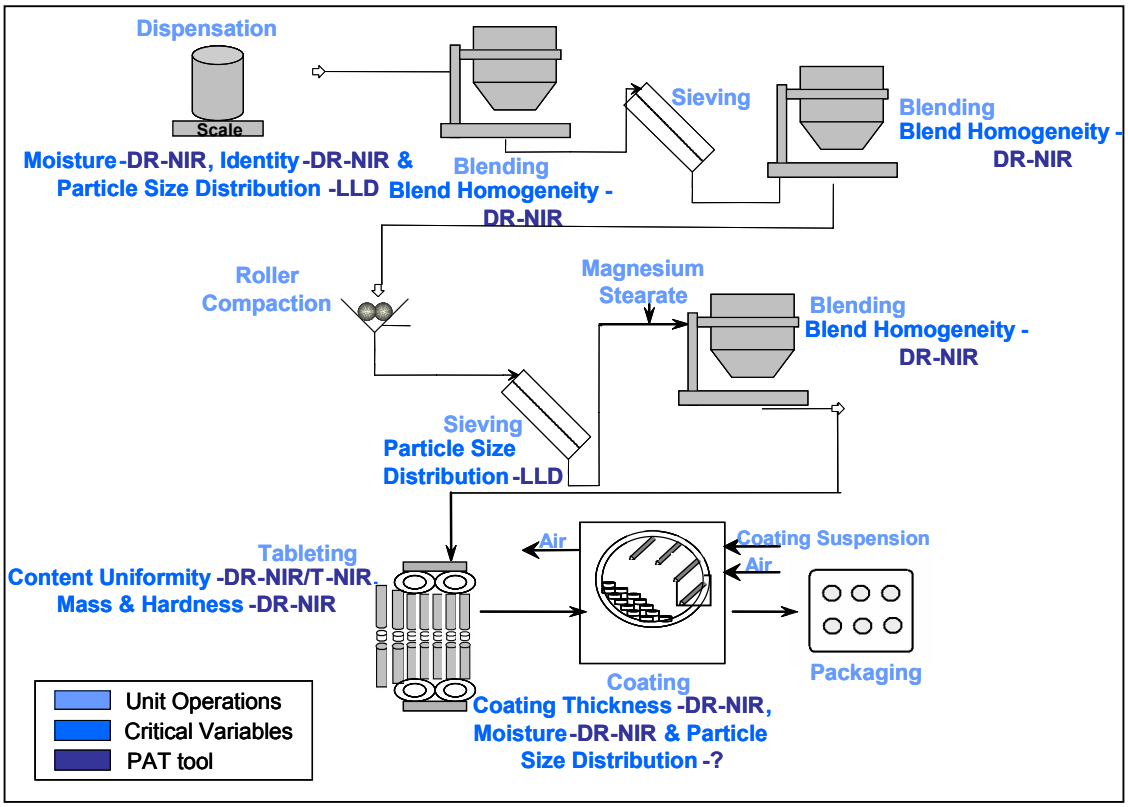

Figure 16: Product X process flow diagram

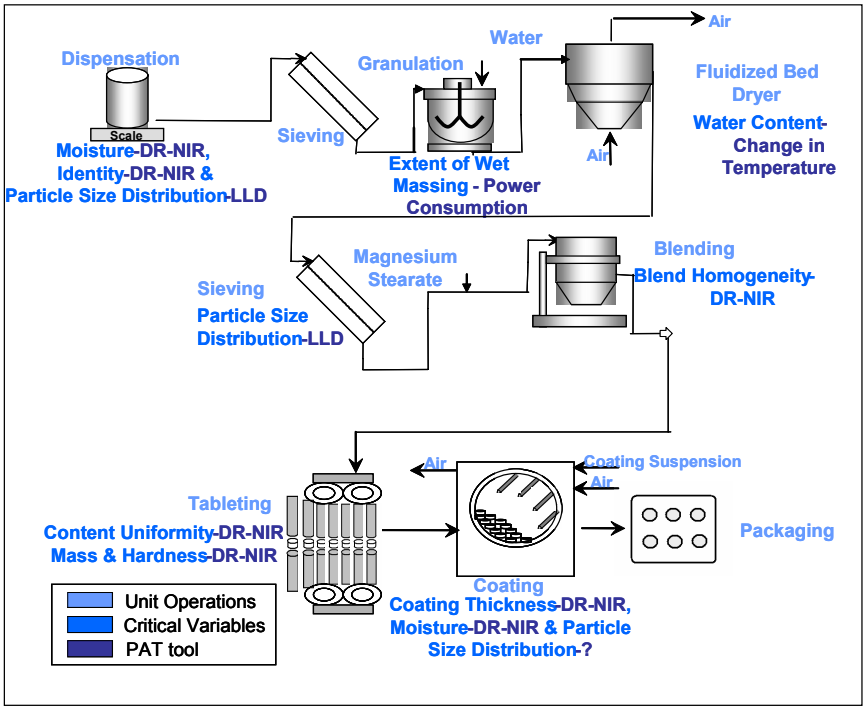

Figure 17: Product Y process flow diagram

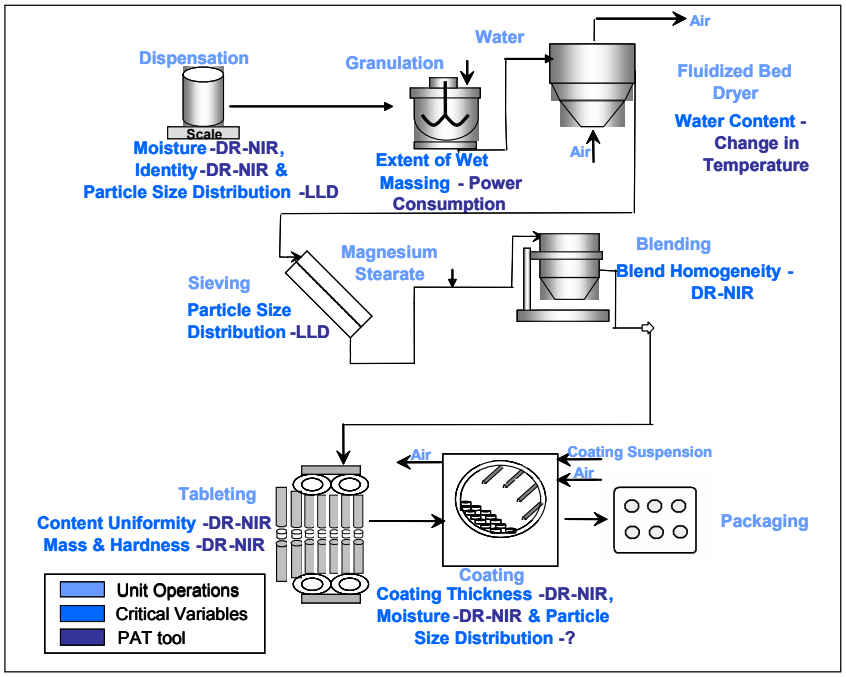

Figure 18: Product Z process flow diagram.

2.16.2. Equipment selection and costs

The production of Product X, Product Y and Product Z were analyzed to determine the number of analytical instruments required to implement the proposed PAT strategy. The results are summarized in table 11.

- Dispensation requires a total of 3 NIR spectrometers and 3 LLD systems one for each of the three dispensation booths used for the dispensing of solid tablet raw materials.

- One NIR spectrometer is required for the blender that is used by all solid tablet products. NIR probes must be attached to the container to monitor blending. The Bruker Optics Matrix-I NIR spectrometer can be adapted for use with a tumbling blender with wired probes. Bruker is currently developing an NIR system for blending that will involve wireless probes and it is expected to be on the market in 3-6 months. It is recommended that companies look into using a wireless NIR system for monitoring blending. The equipment quote obtained from Bruker (See References) for blending is for the Matrix-I instrument and would be an aggressive estimate for the new wireless system.

- A total of 11 tandem NIR units are required. There is one unit required for each of the eight rotary presses and one unit required for each of the three spray coaters that are all used in production of the three products of interest. The tandem NIR units have the capability to sample and perform NIR measurements on tablets, a scale to measure tablet mass, and the ability to determine tablet dimensions.

- Four on-line LLD particle size analyzers are required for four different sieves used in the different granulation processes. There is one sieve used in Product Y production and one sieve used in Product Z production following drying. There are two different Product X granulation rooms and both require an on-line particle size analyzer to monitor the particle size distribution of the material exiting the sieve that follows the roller compactor. The particle size analyzer will be placed on-line as the materials exit the sieve before entering the powder storage container.

- Thermocouples to detect the temperature in the fluidized bed dryer and power consumption meters for the high shear wet granulation mixtures do not need to be purchased as the equipment is currently equipped with these types of sensors.

The analytical equipment purchased for the unit operations, other than those involved in granulation, are shared amongst the three products. Analytical equipment changes will not be required when production process changeovers occur, but instrument cleaning will be required. The cost of PAT equipment attributed to one product is therefore reduced by implementing PAT for multiple products simultaneously. In the future when PAT is implemented for other solid tablet products the total equipment cost will be reduced as much of the required equipment will already be in place.

Equipment vendors were contacted to determine budgetary cost estimates for PAT equipment.
Individual equipment costs are contained in table 11along with the total equipment cost, 5.9M CHF, for the implementation of PAT equipment for Product X, Product Y and Product Z. The equipment cost attributed to each product is approximately one third of the total PAT equipment cost.

Equipment Type	Model	Vendor	Measurements	Location	Total Number	Unit Equipment Cost (CHF)	Total Equipment Cost (CHF)	Reference
NIR	MPA	Bruker Optics	Identity, Moisture Content	Dispensation	3	96,000	288,000	Bruker
NIR	Matrix	Bruker Optics	Blend Homogeneity	Blender	1	86,000	86,000	Bruker
NIR	Tandem	Bruker Optics	Content Uniformity, Hardness, Coating Thickness, Moisture Content	Tabletting, Coating	11	396,000	4,356,000	Bruker
LLD	Helos	Sympatec	Particle Size Distribution	Dispensation	3	160,000	480,000	Sympatec
LLD	TWISTER & MYTOS	Sympatec	Particle Size Distribution	Granulation	4	179,000	716,000	Sympatec
							5,926,000	Total

Table 11: PAT equipment costs.

2.16.3. Chemometric development time and cost

Chemometrics must be developed for each type of NIR measurement that is desired and for each product. Chemometrics are data analysis methods to extract the desired information from an NIR spectrum. The development of chemometrics is time consuming and expensive process for NIR spectrometers. The total cost of chemometric development, 1.9M CHF, is over 40% of the NIR spectrometer cost, see table 12.

Type of Measurement	Material Costs (CHF)	Chemometric Devlopment Cost (CHF)	Number of Products	Total Cost (CHF)	Reference
Identity	0	40'500	1	40'500	Solvias
Moisture Content	0	40'500	3	121'500	Solvias
Blending	0	27'000	3	81'000	Solvias
Content Uniformity	54'000	94'500	2	297'000	Company experience
Hardness	54'000	94'500	3	445'500	Company experience
Coating Thickness	54'000	94'500	3	445'500	Company experience
Tablet Moisture Content	54'000	94'500	3	445'500	Company experience
				1'876'500	Total

Table 12: Chemometric development cost.

Estimates for chemometric development were received from Solvias AG (See References) and from a cost estimate that has been proposed for the PAT pilot project currently underway at another site, to replace content uniformity measurements by HPLC with DR-NIR. Solvias AG is a company that performs NIR spectrometer qualification and chemometric development. The pilot PAT project will develop chemometrics for content uniformity of Product X tablets and therefore this cost is not included. It was assumed that chemometric development for other tablet properties will be similar to that for content uniformity. Chemometric development for solid tablet measurements has additional material costs as tablets need to be produced that range in the variable of interest. The additional tablets are usually produced by development. As an example, chemometric development for content uniformity tablets must be performed by measuring tablets with 80%, 100%, and 120% of the specified amount of drug substance. It is recommended that chemometric development be outsourced to Solvias AG rather than performed by personnel within the companies as there is seldom a group within companies that specializes in chemometric development. Solvias

has proposed that chemometric development, qualification, and training could be completed within six months. Calculations were performed assuming that by working on all products and all instruments simultaneously, chemometric development and equipment qualification could be completed within one year.

2.16.4. Equipment qualification cost

All equipment must be qualified and calibrated before being utilized in production. NIR equipment qualification costs were estimated by discussions with Solvias AG. The NIR instruments must be calibrated for each type of measurement that is to be performed and for each product that it will be used to analyze. The cost to qualify a second instrument for the same measurements may be reduced. Solvias AG recommended that only in certain cases will the qualification costs be reduced and therefore it is estimated that the NIR spectrometers used in dispensation and blending will each need to be fully qualified. It was suggested that the qualification of additional content uniformity measurements would be reduced to only the steps for the execution of the protocol. Therefore, all tandem NIR qualifications are assumed to be reduced for multiple pieces of equipment. Estimates for the qualification of LLD particle analysis systems were received from Sympatec Switzerland. It is recommended that the equipment vendors perform equipment qualification. The overall cost of equipment qualification is about 30% of the cost of the equipment. Equipment qualification costs are contained in table 13 below.

Equipment Type	Model	Vendor	Location	Number of Measurements	Total Number	Number of Processes	Initial Qualification Cost (CHF)	Secondary Instrument Qualification Cost (CHF)	Total Qualification Cost (CHF)	Reference
NIR	MPA	Bruker Optics	Dispensation	2	3	1	81'000	81'000	243'000	Solvias
NIR	Matrix	Bruker Optics	Blender	1	1	3	54'000	0	162'000	Solvias
NIR	Tandem	Bruker Optics	Tabletting	3	8	3	128'000	18'000	762'000	Company experience
NIR	Tandem	Bruker Optics	Coating	3	3	3	128'000	18'000	492'000	Company experience
LLD	HELOS	Sympatec	Dispensation	1	3	1	2'700	2'700	8'100	Sympatec
LLD	TWISTER & MYTOS	Sympatec	Granulation	1	4	1	3'200	3'200	12'800	Sympatec
									1'679'900	Total

Table 13: PAT equipment qualification costs.

2.16.5. Yearly maintenance costs

The equipment vendors were contacted to determine the cost associated with full maintenance contracts for the PAT equipment. The NIR maintenance contracts include the cost of personnel from Solvias AG to recalibrate equipment on site. The LLD maintenance contracts with Sympatec include all travel related expenses, unlimited visits per year and spare parts for the equipment. The exact costs of the maintenance contracts are shown in the table below and total 280,000 CHF per year.

Equipment Type	Model	Total Number	Maintenance Cost (CHF)	Reference
NIR	MPA	3	12,000	Bruker
NIR	Matrix	1	4,000	Bruker
NIR	Tandem	11	44,000	Bruker
LLD	Helos	3	88,908	Sympatec
LLD	TWISTER & MYTOS	4	123,979	Sympatec
			272,887	Total

Table 14: PAT yearly maintenance costs.

2.16.6. Multivariate data analysis

Multivariate data analysis (MVDA) tools need to be implemented when the PAT analytical equipment is installed to aid in data collection, data analysis, and the building of empirical correlations. Empirical correlations need to be developed so that analytical lab tests for dissolution, disintegration, and friability can be replaced with correlations to variables measured on-line. Correlation development is required in order to create models for control systems. The MVDA system consists of SIMCA Batch On-Line software by Umetrics for real time connectivity to various data sources. The cost for equipment, software and validation for each of the three products will be 360,000 CHF.

2.16.7. Correlation development cost

The cost associated with developing correlations for friability, disintegration, and dissolution was attributed to the labor of three engineers for one year. The cost for these three engineers was approximated to be approximately one and half times the yearly labor cost of an operator. The cost for correlation development occurs in-between PAT equipment installation and implementation of control systems. Savings from laboratory testing associated with friability, disintegration and dissolution testing will not be realized until after correlations have been developed which was predicted to coincide with control system implementation.

2.16.8. Control system costs

Phase II of PAT implementation is the installation of control systems to steer the process and prevent manufacturing problems. MVDA will allow for model building and greater process understanding which will lead to the ability to implement control systems. The P&ID diagrams for Product X, Product Y and Product Z in the appendix contain suggestions for control strategies based on the current understanding of the parameters that effect critical variables. The P&ID diagrams indicate where PAT tools are to be installed to monitor critical process and product variables along with proposed feedback control loops. The strategies may need to be altered when a better process understanding is realized.

The main costs associated with control implementation are the cost to program PLC controllers, the central PC and software associated with the PLC controller. The equipment cost is minimal (~2700 CHF). The cost to program the controllers was estimated from a budgetary quote received from Panacea Technologies to program four controllers for wet granulation. The assumption was made that there would be similar costs for programming each of the controllers required for the PAT strategy. The estimate for control system costs should be further refined by companies when the exact control strategy is determined after better process understanding is achieved. There are a total of 21 control systems required to

control the manufacture of all three products, and it was assumed that the same control system could be used on the same piece of equipment for multiple products. There are reduced costs associated with programming multiple controllers for the same application. The charge for the first controller is 160,000 CHF and the charge for each additional controller is 40,000 CHF. The costs of control systems for each unit operation are summarized in table 15.

Process Step	Number Process Instruments	Cost (CHF)
Blending	1	167'192
Compression Force	8	429'524
Coating Droplet Size	3	242'144
Product Z Wet Granulation	1	167'192
Product Z Drying	2	204'668
Product Y Wet Granulation	3	242'144
Procuct Y Drying	3	242'144
Total	21	1'695'008

Table 15: PAT control system costs.

2.16.9. Process change requests costs

Change requests must be filed with regulatory agencies for approval of any changes to the manufacturing process. The project team discussed the cost of such requests to the FDA with the CMC Regulatory Department of the company. It was advised that re-registration of the process would not be required for PAT implementation. There are two types of reports that can be filed: (1) prior approval requests for 8,000 CHF and (2) all other change requests for 1,500 CHF. The FDA does not charge a company for filing change requests and these costs are charged by the CMC Regulatory Department for preparation of the reports. Multiple changes can be requested in the same report without affecting the cost. As an aggressive estimate all requests were assumed to be prior approval requests. The assumption was made that all change requests for the same piece of equipment will be filed together. Change requests will be required for changes in analytical testing methods, implementation of on-line analytical tools and implementation of control systems. The assumption was made that a change request would not need to be filed to include additional analytical testing in dispensation (material identity, PSD, and moisture content); as they do not alter the current

production process, these changes will be reported in the annual report. The total cost (100,000 CHF) for change requests to the FDA are summarized in table 16.

	PAT Equipment Cost (CHF)	Control Systems Cost (CHF)	Total Cost (CHF)
Product X	10'667	8'000	18'667
Product Z	16'000	24'000	40'000
Product Y	16'000	24'000	40'000
Total	42'667	56'000	98'667

Table 16: Change request costs.

Change requests for European Union countries are more expensive as multiple countries are involved and the number of countries that the change request must be filed with will vary. Companies will need to further determine the exact strategy for filing these requests because the costs may turn out to be quite significant. The costs for particular changes are summarized below.

	Product X	Product Z	Product Y
Minor	0	73'000	73'000
Major	90'000	150'000	150'000

Table 17: Costs for change requests for EU (CHF).

2.16.10. Summary of implementation costs

A summary of the implementation costs attributed to each of the three products studied herein is given in the table below.

	Product X	Product Z	Product Y
Equipment	2,417,000	2,238,000	2,238,000
Chemometrics	527,000	675,000	675,000
Qualification	598,000	595,000	595,000
Training	41,000	41,000	41,000
Change Requests PAT Equipment	9,500	82,500	82,500
Phase I Implementation Cost	3,592,500	3,631,500	3,631,500
Control	272,000	627,000	740,000
Change Requests Control & Correlations	99,500	232,500	232,500
Total Implementation Cost	3,964,000	4,491,000	4,604,000
Maintenance (per year)	109,000	82,000	82,000

Table 18: PAT implementation costs.

2.17. Cost-Benefit analysis

A preliminary analysis of savings indicated that two areas where PAT can provide the greatest benefits are: (1) reduction in QC testing, leading to real time release and (2) improvement of product yield from better process control. The financial analysis was found to be sensitive to the time when these benefits begin to take effect. Since there is some uncertainty as to when real time release will be approved, two timelines were evaluated for the financial analysis (see figure 19). The first scenario assumes that QC savings start accruing after the installation and qualification of analytical instruments, at the end of the first year. The second scenario is a conservative case in which it is assumed that the QC savings begin in the third year, after correlations have been developed for tablet friability, disintegration time and dissolution time. The first scenario is treated as the base case in sections 2.17.1 through 2.17.3. The second scenario is treated in the sensitivity analysis on Section 2.17.3.4.

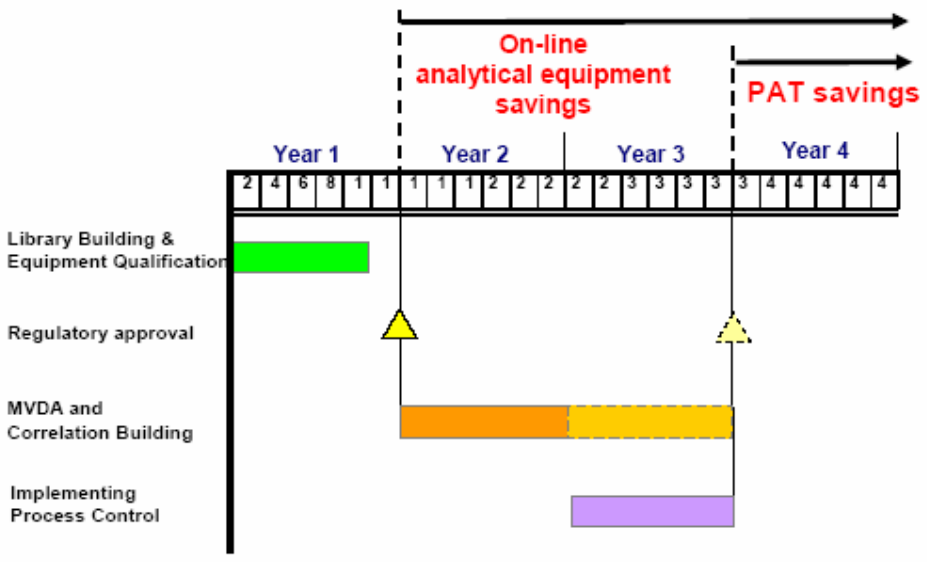

Figure 19: Implementation timelines.

2.17.1. Calculations used in Cost-Benefit Analysis.

There are several types of calculations used in assessing the benefits of installing new equipment in a production line. The simplest method is the earnings before tax and interest calculation (EBIT). EBIT for year *i* is calculated by adding the savings for each year, S_i, to the cost in year *i*, C_i, and depreciation of the invested capital per year,Dep_{IC}. Equation 1 shows the calculation for EBIT.

Equation 1

$$\text{EBIT}_\text{i} = S_i - C_i - Dep_{IC}$$

The net cash flow for year *i*, CF_i, is calculated by equation 2:

Equation 2

$$CF_i = S_i - C_i$$

Here, S_i is the money saved by the investment in year *i*. Likewise, C_i represents any extra costs of the installed equipment in year *i*. These extra costs are primarily maintenance, as well as any other expenses.

Calculating the net present value (NPV) of an investment is another tool used in estimating the return of an investment. Like EBIT, NPV is a sum of cash flows. Unlike EBIT, NPV uses a discount rate, *DR*, to reduce the value of future costs. The NPV of an investment is calculated by equation 3.

Equation 3

$$\text{NPV} = \sum_{year=0}^{N} \frac{CF_i}{(1+DR)^{year}}$$

Another method of evaluating financial benefit is internal rate of return (IRR); the discount rate that would make the net present value of all cash flow equal to zero. The equation used to calculate IRR is equation 4, below:

Equation 4

$$\text{NPV} = 0 = \sum_{year=0}^{N} \frac{CF_i}{(1+\text{IRR})^{year}}$$

This equation must be solved numerically to find IRR. Most software used in financial calculations, such as Microsoft Excel, has built-in functions to calculate IRR.

For situations where new process equipment must be purchased, a key indicator of economic efficacy is the return on investment (ROI). The calculation of ROI weighs the average EBIT of the investment versus the average depreciating investment cost for year *i*, (DIC_i=IC*(1-*i*/Life)). Equation 5 is the definition of ROI.

Equation 5

$$\text{ROI} = \frac{\text{AVERAGE(EBIT)}}{\text{AVERAGE(DIC)}}$$

Organizations consider the risk of a new venture to be acceptable when the ROI is greater than a certain percentage, typically 25%.

With equipment investments, there is a period of time before there are net profits. This payback time is often considered when evaluating a project's economic impact. The payback time, $T_{payback}$, is simply defined as the time when the NPV is zero, as shown in equation 6.

Equation 6

$$\text{NPV} = 0 = \sum_{year=0}^{T_{payback}} \frac{CF_i}{(1+DR)^{year}}$$

To solve for $T_{payback}$ in equation 6, interpolation is typically used over the year that profits are first realized. Payback time is useful for estimating how long it will take for an investment to begin to make returns.

These five financial calculations: EBIT, NPV, IRR, ROI, and payback time were used to evaluate the cost savings of implementing PAT at the company's production facility. In order to make these calculations, however, several assumptions and approximations must be made about the benefits of PAT.

The sensitivity of the financial calculations to process parameters must also be performed to identify the most sensitive parameters. To accomplish this, the derivative of the financial calculation is approximated by varying a single process parameter. Equation 7 shows how the sensitivity of IRR ($Sens_{IRR}$) is calculated with respect to arbitrary process parameter, P, using a parameter variance X. For the purposes of this report, X is assumed to vary from 1% to 30%.

Equation 7

$$Sens_{IRR} = \frac{\mathrm{IRR}(\ldots, P\cdot(1+X),\ldots) - \mathrm{IRR}(\ldots, P\cdot(1-X),\ldots)}{2\cdot X\cdot \mathrm{IRR}(\ldots, P,\ldots)}$$

2.17.2. Assumed savings used in financial calculations

To evaluate the benefits of on-line analytical measurements with and without feedback control, the savings of each must be estimated. Several assumptions were made regarding the implementation of PAT. An outline of the assumptions made for both on-line analytical testing as well as with feedback control is shown in table 19.

	On-line Testing	Control
Audit Labor Reduction	0%	50%
Investigation Labor Reductions	50%	95%
QC Analytical Time Reduction	90%	99%
Batch Rejection Reduction	0%	75%
TPT Reduction (days)	4	6
Yield Improvement	0	+1%
Reduction in IPC Labor per Product	35%	99%
Investigation Holding Time (days)	4	1

Table 19: Assumed benefits of PAT.

These savings are applied to the existing production costs proportional to each of the drug products examined. By applying these assumptions, annual savings from on-line analytical

testing and PAT can be calculated. The benefits from on-line analytical testing alone are termed short-term benefits, the benefits of implementing the control strategy is classified as mid-term benefits. A breakdown of the annual savings possible by on-line analytical testing alone is shown in table 20 and in figure 20. It is clear that the majority of the short-term benefits from PAT will be from the reduced analytical time needed per batch. Secondary cost reductions stem from reduced investigations and reduced IPC labor.

	Product X		Product Z		Product Y	
	kCHF	% of Total	kCHF	% of Total	kCHF	% of Total
Savings From Reduced Audits	0	0%	0	0%	0	0%
Savings From Investigations	83	7%	43	5%	33	4%
Savings from Quality Control	907	76%	679	77%	700	83%
Savings from Batch Writeoffs	0	0%	0	0%	0	0%
Savings from Batch Resorting	0	0%	0	0%	0	0%
Financial Cost of Inventory	87	7%	73	8%	49	6%
Savings from Improved Yield	0	0%	0	0%	0	0%
Reduction in IPC Labor	112	9%	83	9%	62	7%
Savings from Reduced Holding Time	8	1%	6	1%	2	0%
Total Savings	1197	100%	883	100%	846	100%

Table 20: Break down of short-term PAT benefits.

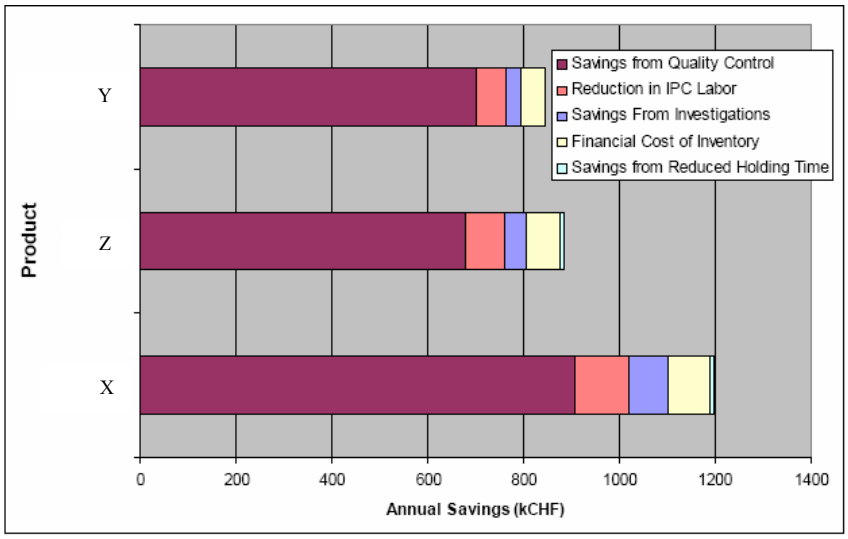

Figure 20: Quick wins.

The breakdown of the annual savings possible with both on-line analytical testing and control system is outlined in table 21 and figure 21, below.

	Product X		Product Z		Product Y	
	kCHF	% of Total	kCHF	% of Total	kCHF	% of Total
Savings From Reduced Audits	21	1%	18	1%	17	1%
Savings From Investigations	170	6%	91	4%	66	4%
Savings from Quality Control	968	32%	717	32%	741	47%
Savings from Batch Writeoffs	171	6%	253	11%	0	0%
Savings from Batch Resorting	413	14%	80	4%	13	1%
Financial Cost of Inventory	127	4%	105	5%	72	5%
Savings from Improved Yield	856	28%	712	32%	485	31%
Reduction in IPC Labor	319	10%	236	11%	177	11%
Savings from Reduced Holding Time	12	0%	9	0%	3	0%
Total Savings	3057	100%	2222	100%	1572	100%

Table 21: Breakdown of mid-term PAT benefits.

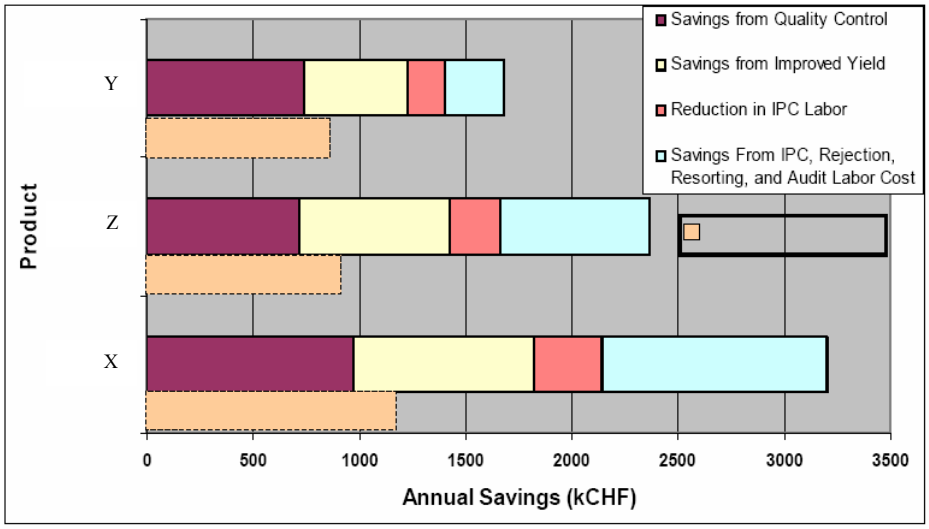

Figure 21: Mid-terms savings.

From table 21 and figure 21, it is apparent that, as with on-line analytical testing alone, the largest benefit from including a control system will be the reduced analytical time needed per batch. The second largest cost reductions in this case are from reduced investigations and the assumption of an improved product yield. Comparing the values in table 21 with the PAT implementation estimates in section 2.16, the most significant costs and most significant savings can be identified. Table 22 summarizes the three most significant costs and three most significant savings when PAT with feedback control is implemented.

		Product X		Product Z		Product Y	
		kCHF	% of Total	kCHF	% of Total	kCHF	% of Total
Savings	**Savings from Quality Control**	8.6	36%	6.4	37%	7.6	60%
	Savings from Improved Yield	6.0	25%	5.0	29%	3.4	27%
	Reduction in IPC Labor	2.5	11%	1.8	11%	1.4	11%
	Total Savings	23.8	100%	17.3	100%	12.7	100%
Costs	**PAT Cost**	2.4	47%	2.2	42%	2.2	39%
	Maintenance Cost for 10 years	1.1	21%	0.8	15%	1.1	19%
	Qualification, Approval, and Training	0.7	13%	0.7	13%	0.7	13%
	Total Costs	5.1	100%	5.3	100%	5.7	100%
	Net Total	18.7		12.1		7.0	

Table 22: Major savings and costs for PAT implementation.

2.17.3. Financial calculation results

2.17.3.1. Short-term PAT implementation

As mentioned in section 2.12, implementing PAT has several short term benefits. Most notable of these is the reduction or elimination of the analysis work needed to release a batch. Other benefits include the reduction of the number of investigations, and their associated labor. The reduction in batch release time will reduce the inventory time associated with QA/QC delays. The short term phase of PAT benefits begins with the qualification of the PAT equipment as on-line analytical tools to replace QC testing.

The short term analysis was made using a 10 year life for all of the PAT equipment. The first year is spent building a database of spectra to characterize the process, followed by training personnel and qualifying the equipment. During this year it is assumed that there are no cost benefits realized by the PAT system. After qualification, there is a reduction in the QC and investigation expenses. The financial calculations were determined over the life of the PAT equipment. Table 20 suggests there are some benefits of implementing the analytical technology alone. Based on the data, the costs of implementing PAT will be paid back as

soon as the middle of the fifth year; four years after the equipment is qualified. Figure 22 shows the discounted cumulative cash flow for the new process when the PAT equipment is qualified at the beginning of year 2.

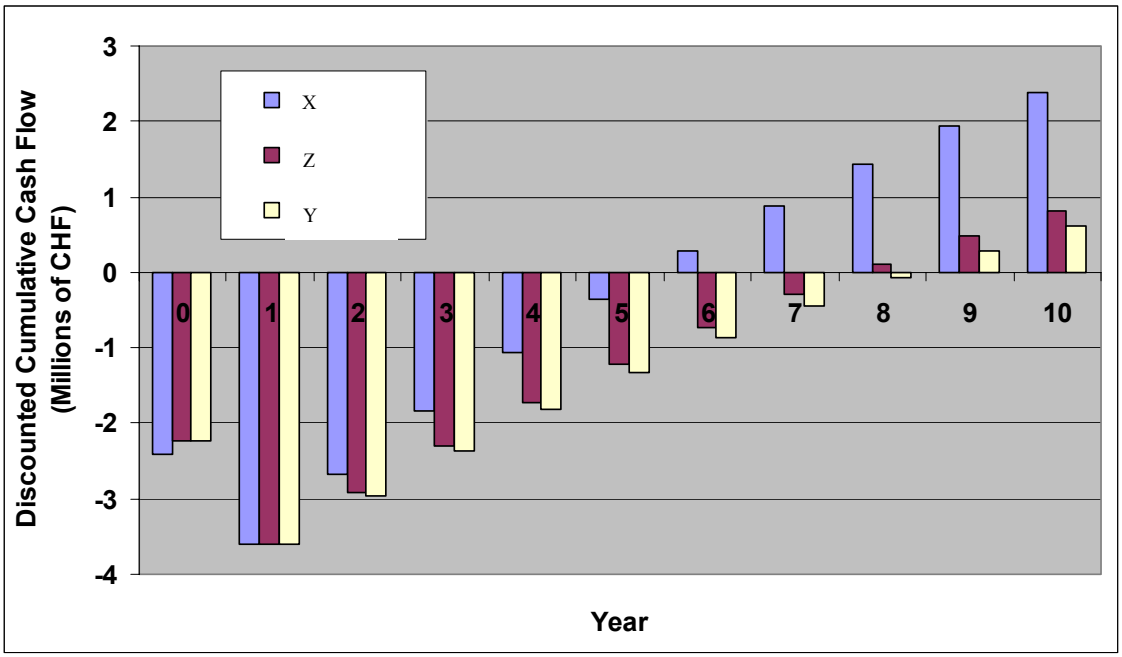

Figure 22: Discounted cumulative cash flow for on-line equipment.

As indicated by figure 22, the product with the greatest returns is Product X. This is due to several factors:

- Product X is produced in greater quantities per year, allowing more analysis time to be saved with on-line analytical equipment.
- Product X has disproportionately large investigation and resorting labor costs.
- Product X has the largest production levels so that when plant-wide savings (e.g. reduced audits) were divided among the products, Product X receives the greatest fraction of the savings.

For the PAT equipment, the total annual cost, including discounted annualized cost per year as calculated using straight-line depreciation plus maintenance costs. Phase I of PAT implementation requires the largest investment during the first year; when chemometrics, training and equipment qualification take place. However, the total savings calculated in table 20 illustrates the enormous economic benefit of Phase I. The results of these calculations are shown in table 23, below:

	Product X	Product Z	Product Y
10 yr NPV (Millions CHF)	4.8	3.0	2.8
IRR	20%	10%	10%
ROI	69%	49%	46%
Payback Time (years)	5.6	7.7	8.2

Table 23: Effects of phase I PAT implementation.

2.17.3.2. Mid-tem benefits of PAT

The inclusion of a feedback control system after implementation of on-line analytical equipment is the beginning of phase II of PAT implementation. For the purposes of this evaluation, the control system was assumed to be fully functional in the third year after the PAT equipment was installed. The cost-benefit analysis was performed in an identical fashion as in section 2.17.3.1, with the only difference of additional costs and benefits applied in the third year. With these additional factors, the 10-year analysis was repeated. The benefits of applying a control strategy far outweigh the costs associated with implementing it. Figure 23 plots the discounted cumulative cash flow at the end of each year over the life of the PAT equipment.

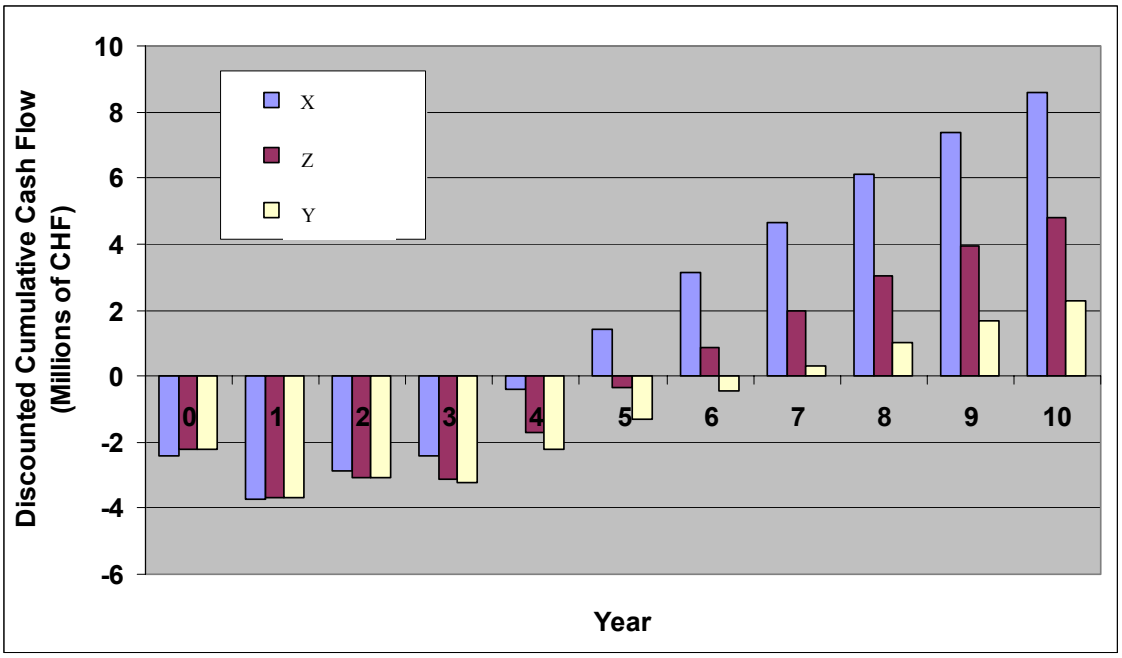

Figure 23: Discounted cumulative cash flow for PAT.

Before year 3, the discounted cumulative cash flow for PAT is identical to the on-line analytical equipment alone. However, after the third year, the implementation of the control system increases the rate of return for the process. This is despite the fact that the annual cost with the control system is greater than when PAT equipment is used by itself. As shown in table 18, the cost of control implementation is slightly greater than on-line analytical equipment alone. Yet, the savings possible by using feedback control are quite significant, as shown in table 21. Therefore, the savings from employing a control and on-line analytical system is greater than the savings possible by on-line analytical system alone. The results of this analysis are shown in table 24.

	Product X	Product Z	Product Y
10 yr NPV (Millions CHF)	8.6	4.8	2.3
IRR	40%	30%	20%
ROI	147%	92%	60%
Payback Time (years)	4.2	5.3	6.6

Table 24: Effects of mit-term PAT implementation.

2.17.3.3. Benefits of PAT for other products and other production facilities.

After the PAT systems are installed, other products produced at the same site would have the benefit of PAT monitoring without the expense of PAT. To examine this effect without acquiring production data for other products, the calculations in the above section were repeated with the control system and PAT installation costs set to zero. Chemometrics costs, equipment qualification costs, and maintenance costs were assumed to be identical as before. This evaluation also assumes that the new products will have very similar production and QA/QC costs. The results of this calculation are shown in the table below:

	Product X	Product Z	Product Y
10 yr NPV (Millions CHF)	11.0	7.1	4.5
IRR	100%	60%	50%
ROI	441%	270%	200%
Payback Time (years)	3.0	3.6	4.0

Table 25: Benefits of Zero equipment cost.

Because the equipment installation cost constitutes the largest portion of the PAT implementation cost, the return on investment is now about three times greater. Another benefit from PAT is that the chemometrics developed for one product can be used for the same product at other production plants. To study how this would translate into financial benefits, the calculations in section 2.17.3.2 were performed again with the chemometrics cost and time set to zero. All other expenses (installation cost, library building cost, maintenance costs) were not changed. This calculation will be most relevant for other facilities that are similar to the pilot site with respect to both production, as well as QA/QC costs. The results of evaluating zero chemometrics time and cost are shown in the table below:

	Product X	Product Z	Product Y
10 yr NPV (Millions CHF)	9.6	5.8	3.3
IRR	40%	30%	30%
ROI	151%	95%	63%
Payback Time (years)	3.7	4.5	5.3

Table 26: Benefits of Zero chemometrics time and cost.

The financial calculations improve somewhat; however, the chemometrics cost is only about 10% of the PAT implementation cost. Consequently, the ten-year EBIT and NPV increase only slightly. The most significant benefit is from the reduction of payback time by a factor greater than the chemometrics time. A comparison of tables 26 and 24 show that the payback time for Product X shifts from 4.2 years to 3.7 years, Product Z goes from 5.3 to 4.5 years, and Product Y is reduced from 6.6 years to 5.3 years. These changes are mostly due to the additional six months of PAT savings.

2.17.3.4. Benefits of PAT for delayed regulatory approval

It is possible that the regulatory approval of on-line analytical testing to replace current QC testing would be delayed. For this situation it is important that an evaluation be performed to determine if on-line analytical measurements with control is financially sound. Keeping all other values constant and assuming PAT savings only accrue after the third year, the financial calculations were performed again. The results of these calculations are shown in the table below:

	Product X	Product Z	Product Y
10 yr EBIT (Millions CHF)	22	14	8
10 yr NPV (Millions CHF)	13	8	4
IRR	60%	50%	30%
ROI	360%	210%	220%
Payback Time (years)	3.9	4.4	5.2

Table 27: Benefits of PAT with savings after year three.

Comparing table 27 to table 24, it is evident that increasing the time before PAT Savings are realized causes a drop in the overall profitability. However, the returns continue to be sufficiently high to indicate that PAT implementation is financially feasible.

2.17.3.5. Long-term costs and benefits of PAT implementation

Eventually PAT will begin to be used in the development of new production processes for a "quality by design" approach. Given the impossibility of quantifying this approach, no attempt was made to calculate the savings and costs associated with PAT when it is used in production development. This section will qualitatively discuss some of the benefits and costs of using process analytical technology in the development of new pharmaceutical products. The advantages of implementing PAT in development, as highlighted before, include a fundamental understanding of each unit operation in the solid tableting process. This understanding will reduce or eliminate the experimental design needed for process development. Optimal formulations will be found quickly when development is supported by process understanding – 'Quality by Design'. The savings in cost and time will translate into

large benefits, as shortened development times and early launches are absolutely vital to a new product's success.

The cost of using PAT in development is much more difficult to quantify than the benefits. The introduction of PAT to new process development will require additional workers to perform both conventional and PAT-enhanced development as quickly as before. For several years, the development staff will have to perform two product developments for each product in the same amount of time. This can be a obstruction for the PAT implementation for many companies, as the utilization of more personnel is combined with more costs.

2.17.4. Sensitivity analysis results

A sensitivity analysis for PAT was performed on the parameters used in the financial calculation. Percent variations in the parameters of interest were determined in accordance with the level of uncertainty to be 5%, 10%, 20% or 30%. The effects on the financial calculations were measured and normalized according to the parameter deviation. Large, positive values indicate that the parameter has a positive effect on the outcome of the calculation. Sensitivity values near zero mean that the parameter has little effect on the calculation. When the sensitivity values are much less than zero, the parameter will have a large negative influence on the calculation. The sensitivities of various process parameters on IRR were evaluated using equation 7 and are tabulated in table 28. For the instances where the sensitivity was greater than 0.5 or less than -0.5, the cell has been highlighted**.**

	% Change	Product X	Product Z	Product Y
Number of Batches per Year	10	0.62	0.80	1.26
Investigations per Year	30	0.01	0.01	0.01
Investigation Labor per Year	20	0.05	0.05	0.06
Discount Rate for Inventory	5	0.05	0.07	0.08
Rejected Batches per Year	30	0.04	0.10	0.00
Resorted Batches per Year	20	0.09	0.03	0.01
Production Salary	5	0.01	0.01	0.01
Investigator Salary	5	0.15	0.18	0.23
Analysis Cost	10	0.39	0.46	0.83
Production Cost per Batch	10	0.27	0.45	0.43
Audit Labor Savings	30	0.00	0.01	0.01
Investigation Labor Reductions	20	0.04	0.04	0.05
QC Time Saved	20	0.21	0.28	0.54
Batch Rejection Savings	20	0.04	0.10	0.00
Batch Resorting Savings	20	0.09	0.03	0.01
TPT Reduction	20	0.03	0.04	0.05
Reduction in IPC Labor	20	0.09	0.12	0.16
New Yield With PAT	20	0.18	0.28	0.35
PAT Installation Cost	30	-0.56	-0.59	-0.74
Control Costs	30	-0.04	-0.11	-0.19
Years to Automatic Control	30	-0.70	-0.64	-0.46
Annual Maintenance Cost	20	-0.11	-0.09	-0.12
Chemometrics Cost	30	-0.09	-0.14	-0.19
Chemometrics Time	30	-0.21	-0.27	-0.37
Equipment Qualification Cost	30	-0.11	-0.15	-0.20
Equipment Qualification Time	30	-0.21	-0.27	-0.37

Table 28: Sensitivity of IRR to various process parameters.

From the table above, the most significant factors are the time to start automatic control, the number of batches per year, and the installation cost of the PAT equipment. Other important values are the cost and time of quality control measurements, the improvement in process yield, and the time to develop chemometrics.

2.18. Conclusions

- Implementing on-line analytical measurements will have significant economic benefits, with a return on investment greater than 60%, and an IRR greater than 20% for Product X.
- Implementing on-line analytical measurements will cost 4.0 to 4.6 Million CHF, for each of the products studied.
- Installing a control system to complement the PAT equipment will increase the IRR to above 35%, and is estimated to cost from 280 to 760 kCHF for each of the products studied.
- Product X production will benefit most from PAT implementation, followed by Product Z, and Product Y. The large production levels of Product X present the most significant potential savings due to analytical time and expense of each batch.
- From a sensitivity analysis, the parameters that have the greatest effect on PAT profitability are the time to start automatic control, the number of batches per year, and the installation cost of the PAT equipment.
- The long term costs and benefits of PAT in development were not quantified, but are expected to provide wide-reaching fundamental benefits to the entire process, from early development to full production.

2.19. Recommendations

- It is highly recommended that companies implement Process Analytical Technology (PAT) by purchasing sensors discussed above.

- Chemometric development and equipment qualification for all the PAT equipment should be outsourced to experienced external vendors. Most pharmaceutical companies lack the human resources and specialized expertise to accomplish these tasks in-house.

- The sensitivity analysis indicates that chemometric development and equipment qualification time are very sensitive parameters. Hence all chemometric development

and equipment qualification should be done simultaneously for all PAT equipment by outside vendors to help implement PAT faster and lead to greater returns.

- Once the on-line analytical equipment is installed, computer archiving should be done to monitor and record all critical variables. This will reduce investigation times significantly. In addition to this, alarm systems should be installed with all the PAT equipment, until the control systems are in place. The alarm systems will inform the operator to take corrective actions whenever any critical variable goes out of specifications.

- Multivariate data analysis (MVDA) tools need to be implemented when the PAT analytical equipment is installed to aid in data collection, data analysis, and the building of empirical correlations. Empirical correlations need to be developed product specific so that analytical lab tests for dissolution, disintegration, and friability can be replaced with correlations to variables measured on-line. Correlation development will also be required in order to identify critical parameters and create models for control systems.

- After MVDA tools have been implemented and product specific empirical correlations have been developed, control systems should be implemented to steer the process and prevent any manufacturing problems. PLC's should be installed with feedback control loops to completely automate the control of the manufacturing process. The implementation of control systems should be done as soon as correlations have been developed because of the high sensitivity of mid-point benefits to implementation time

- Along with implementation of PAT, extra efforts should be made to provide operator training and educate them about good manufacturing practices to help increase process yields.

- It is recommended to implement PAT for other high volume, expensive, or important products to attain greater benefits. There will be significant cost savings in PAT equipment installation as a number of common machines will already have PAT equipment installed. There will be additional costs for chemometric development and equipment qualification.

- It is also recommended to consider implementing PAT at other plants manufacturing the same products as in the pilot, in other countries. There will be savings in chemometric development costs for PAT equipment.

- After the implementation of PAT for Product X, Product Y and Product Z, it should be looked into implementing PAT for the launch of a new product. PAT along with control systems can eliminate the need for running validation batches as there will be complete understanding of the process. This can eliminate the costly errors during the early phase of the production of a new drug and can provide tremendous cost savings

- Finally and most importantly, a PAT implementation strategy for development should be created. In order to achieve the goal of 'Quality by Design' and to develop a complete understanding of the process it is essential to implement PAT in development. Development is the place where the biggest cost and time savings will be realized by implementing PAT and control systems. Implementation of PAT is essential to accomplish the long cherished vision of the pharmaceutical industry and FDA of 'being right the first time'.

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Appendix

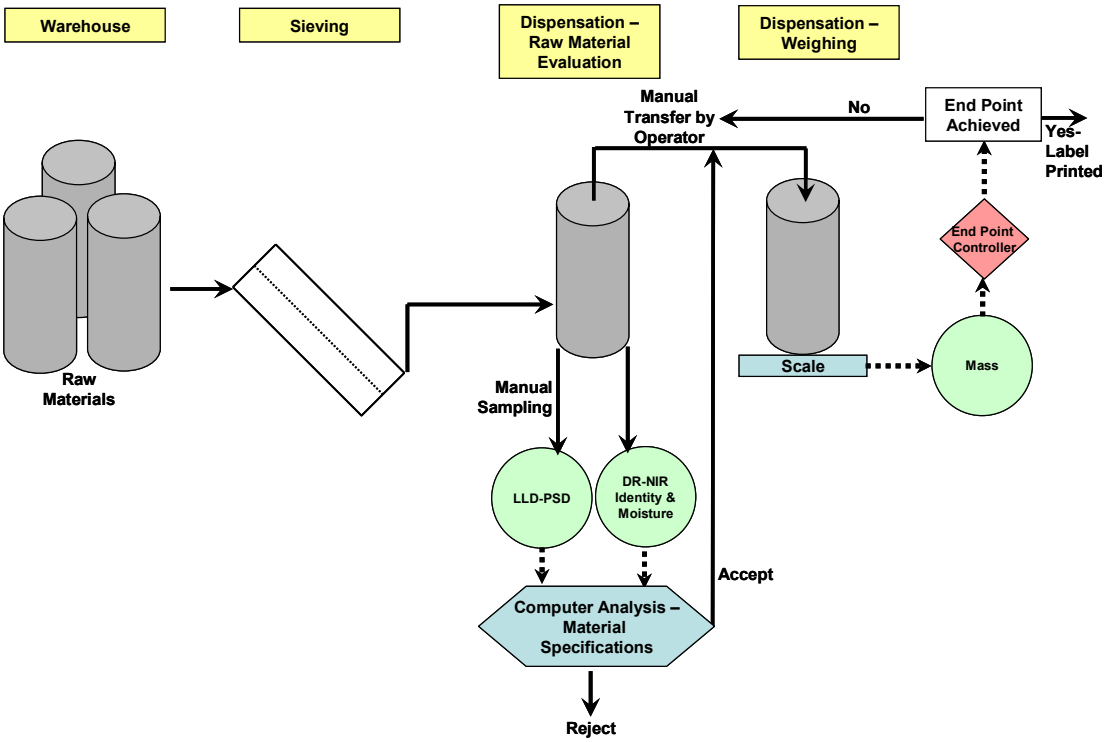


Figure 24: Product X P&ID part I

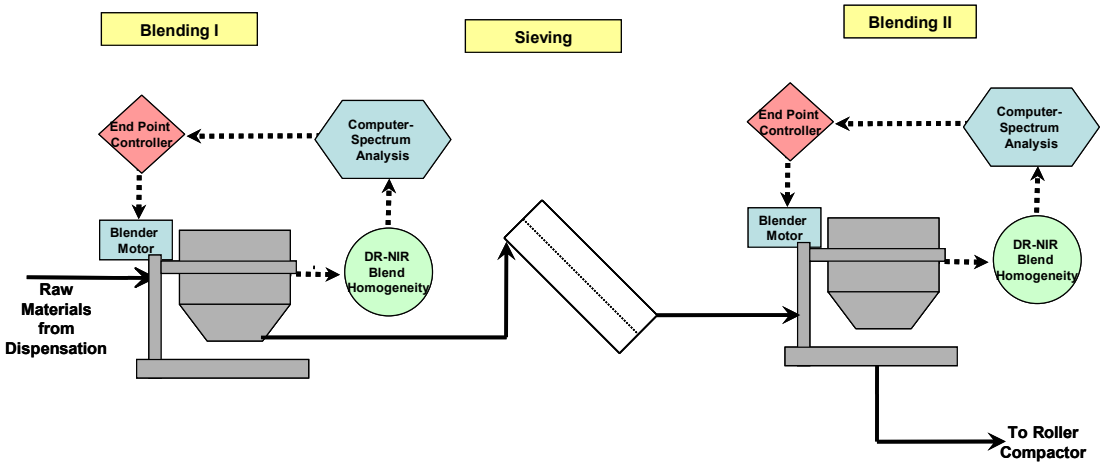


Figure 25: Product X P&ID part II.

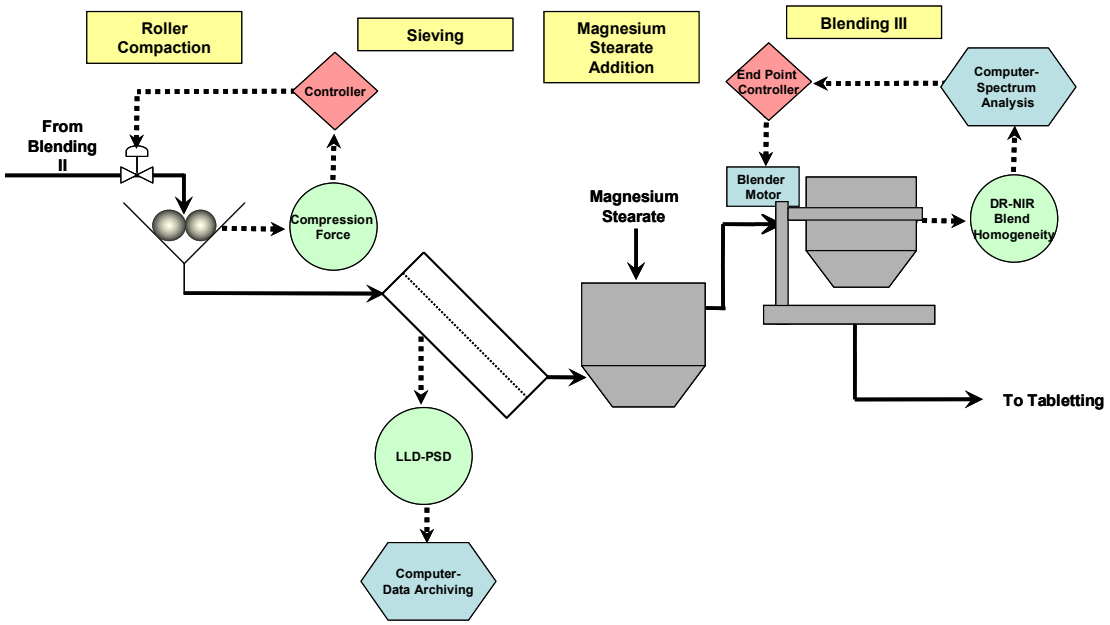


Figure 26: Product X P&ID part III.

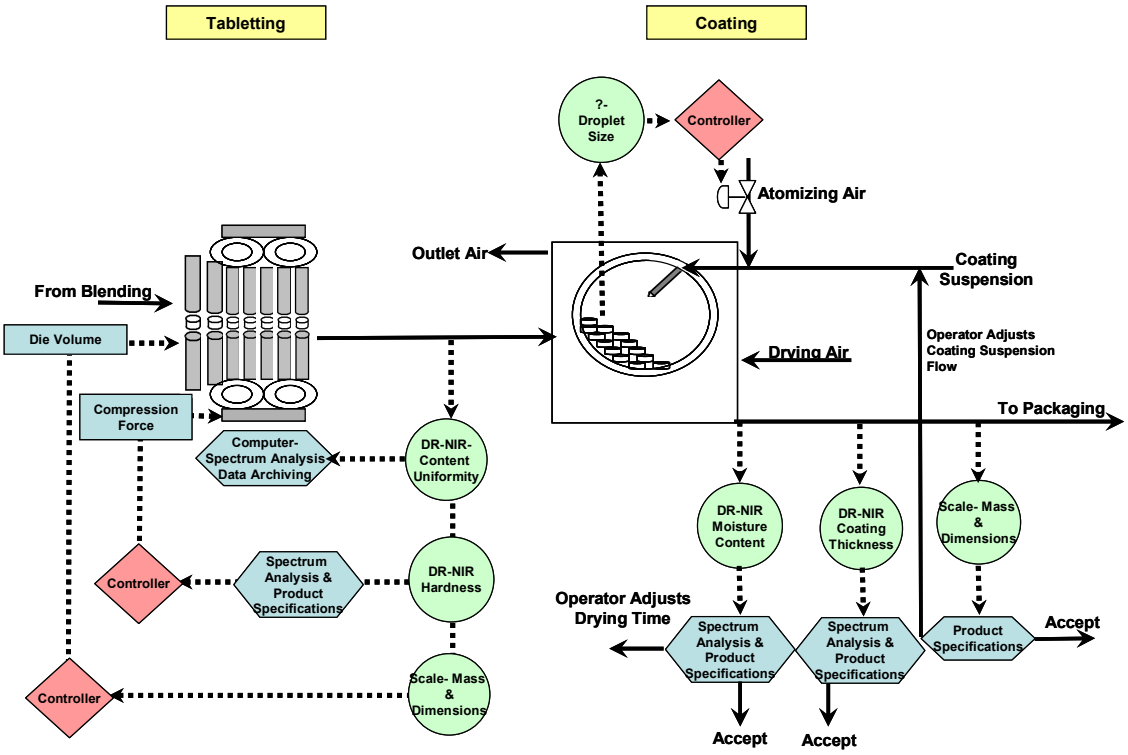


Figure 27: Product X P&ID part IV.

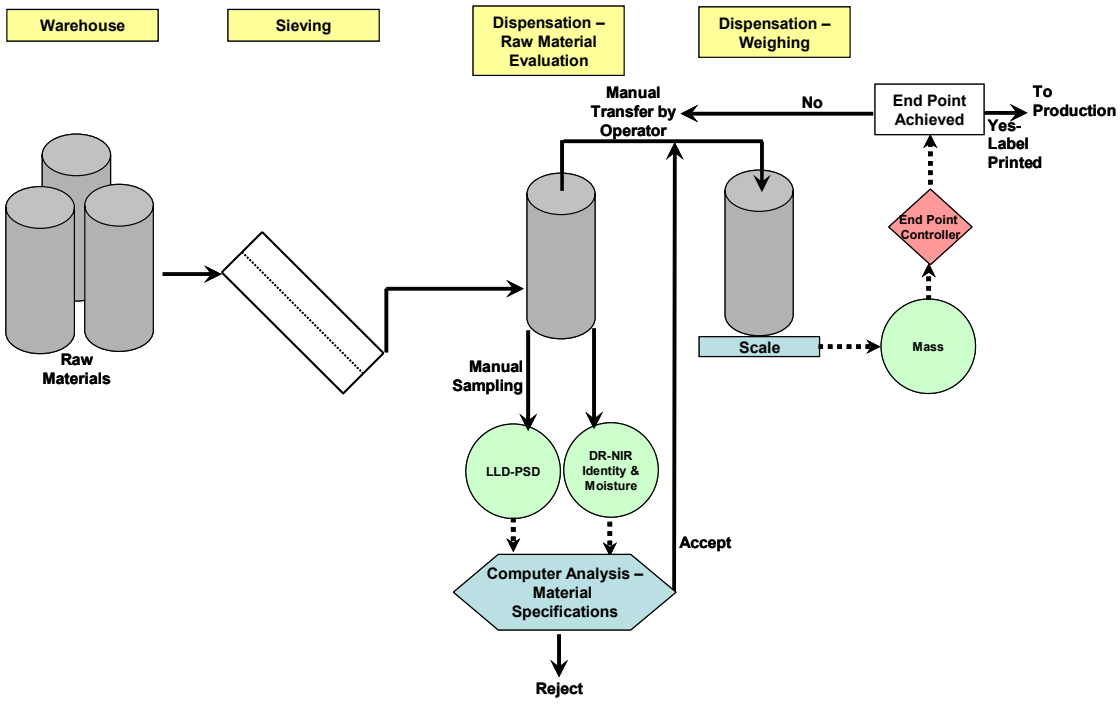


Figure 28: Product Y P&ID part I.

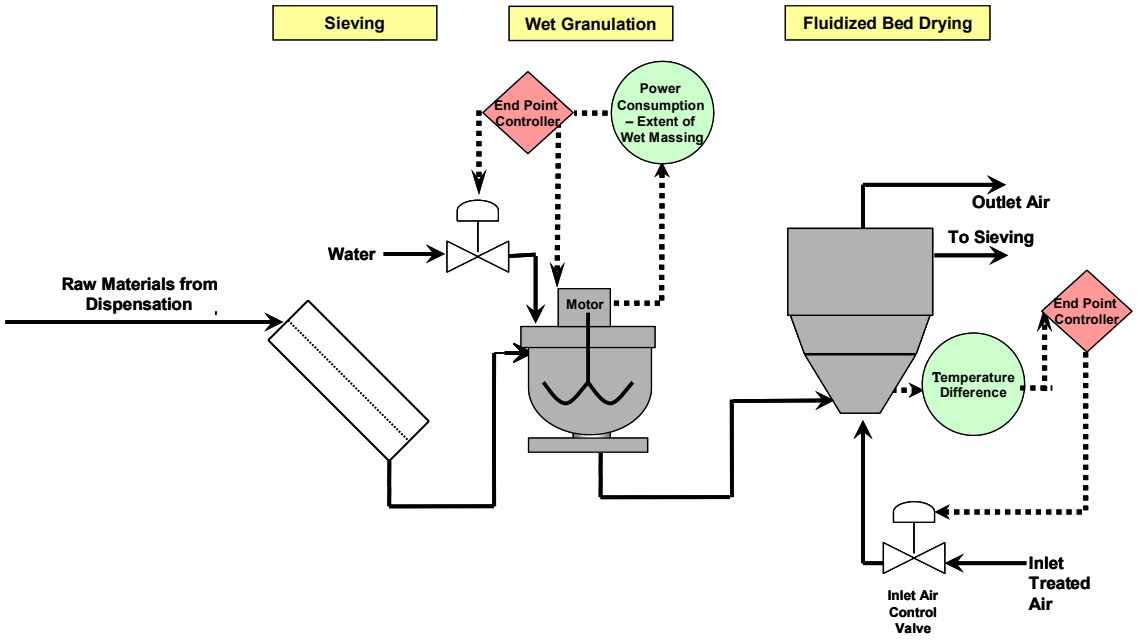


Figure 29: Product Y P&ID part II.

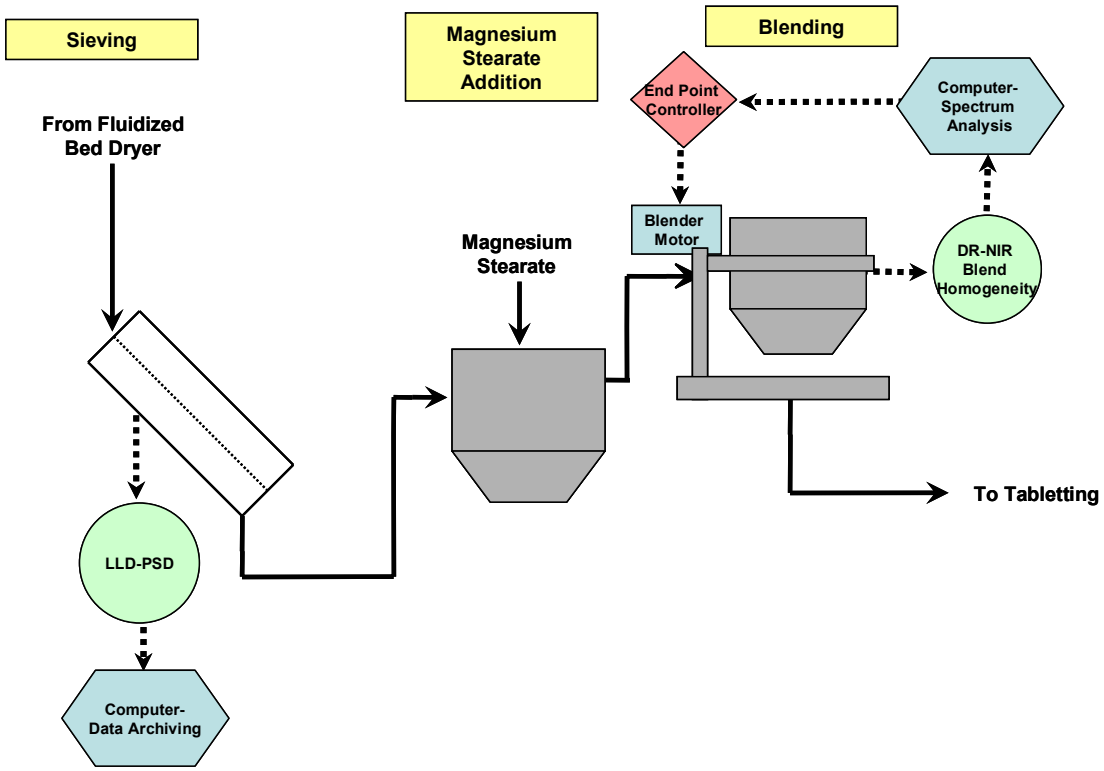


Figure 30: Product Y P&ID part III.

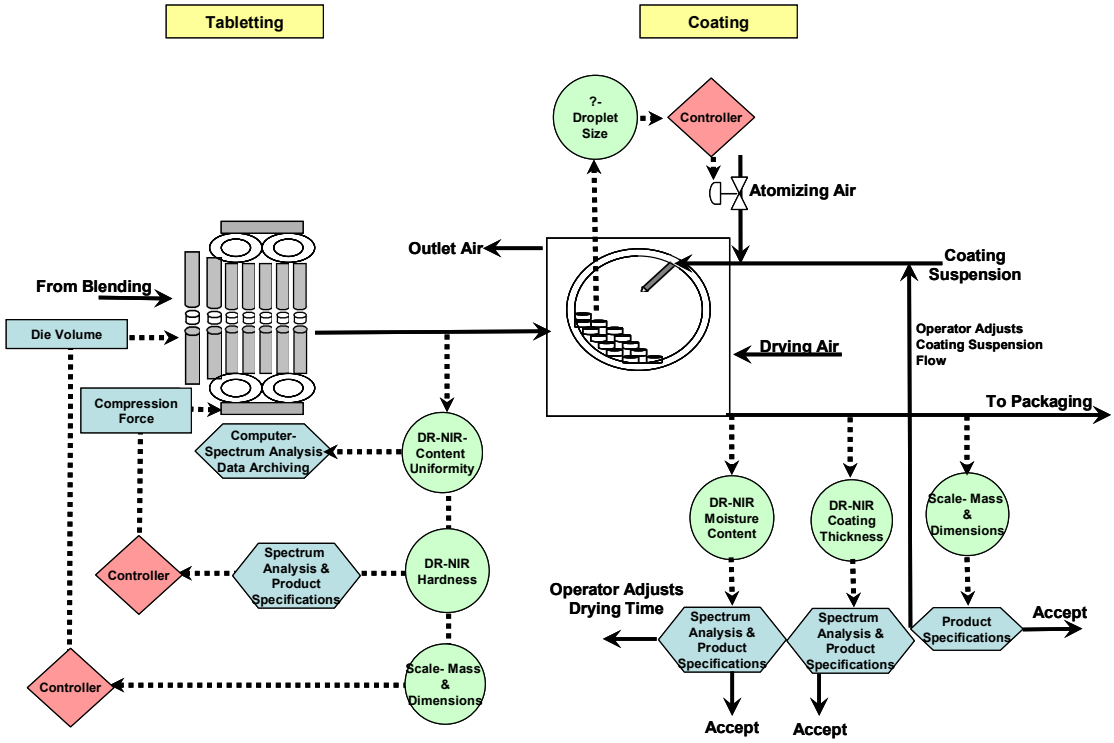


Figure 31: Product Y P&ID part IV.

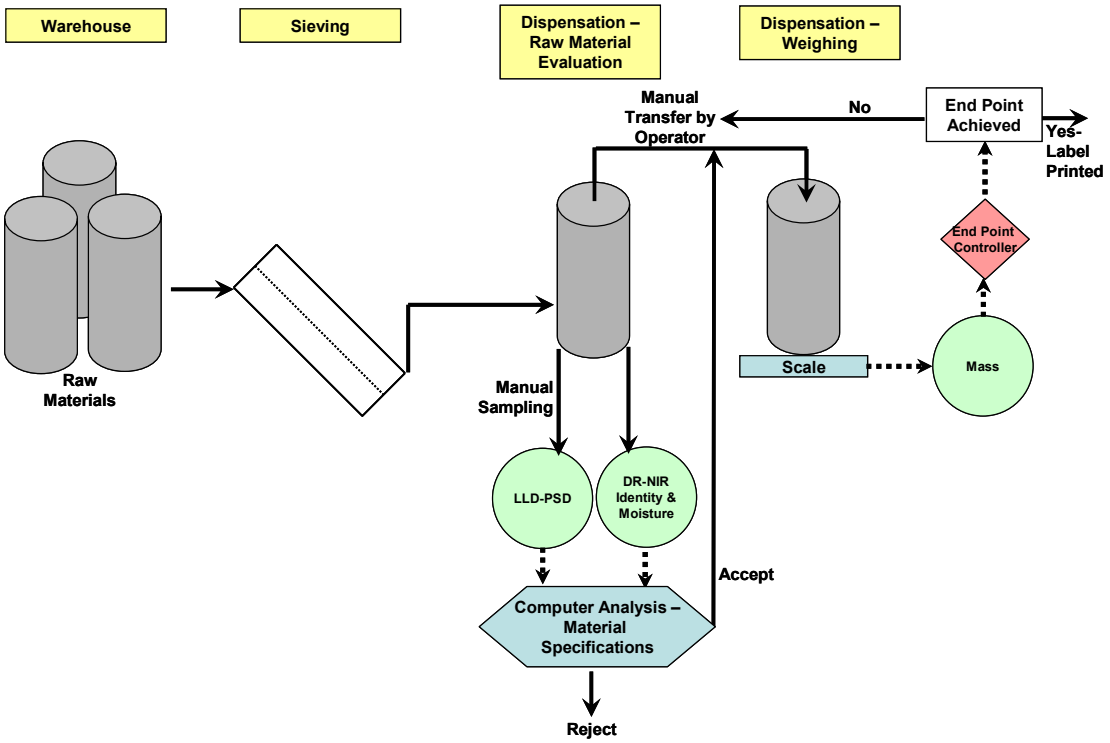


Figure 32: Product Z P&ID part I.

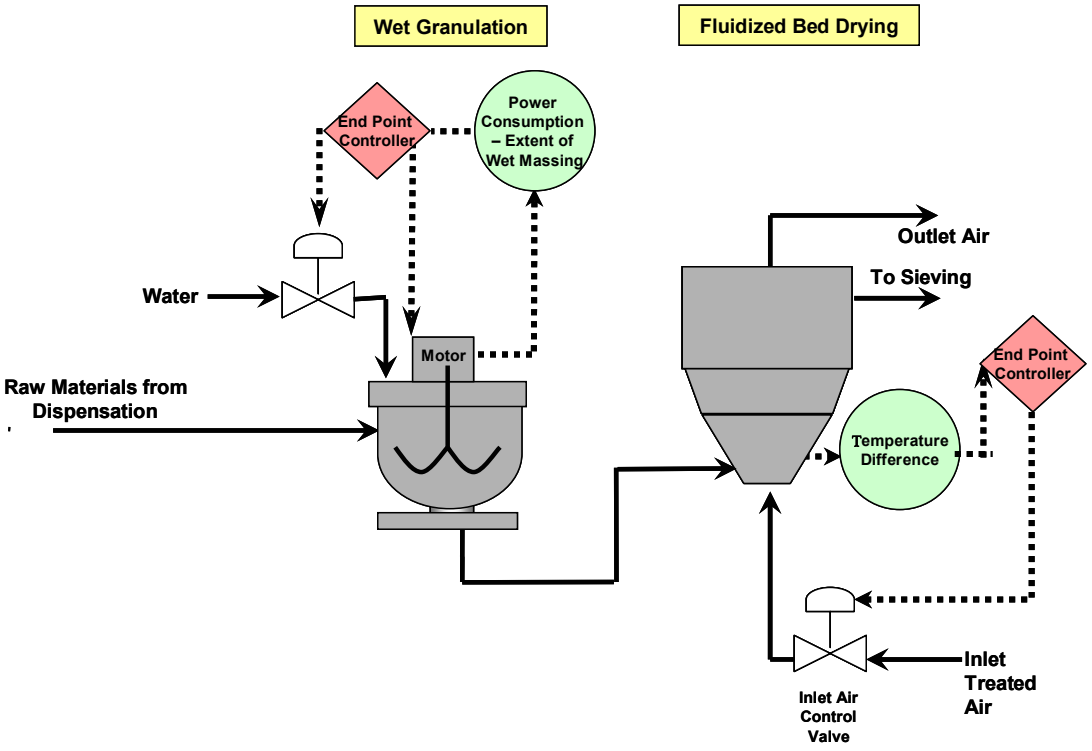


Figure 33: Product Z P&ID part II

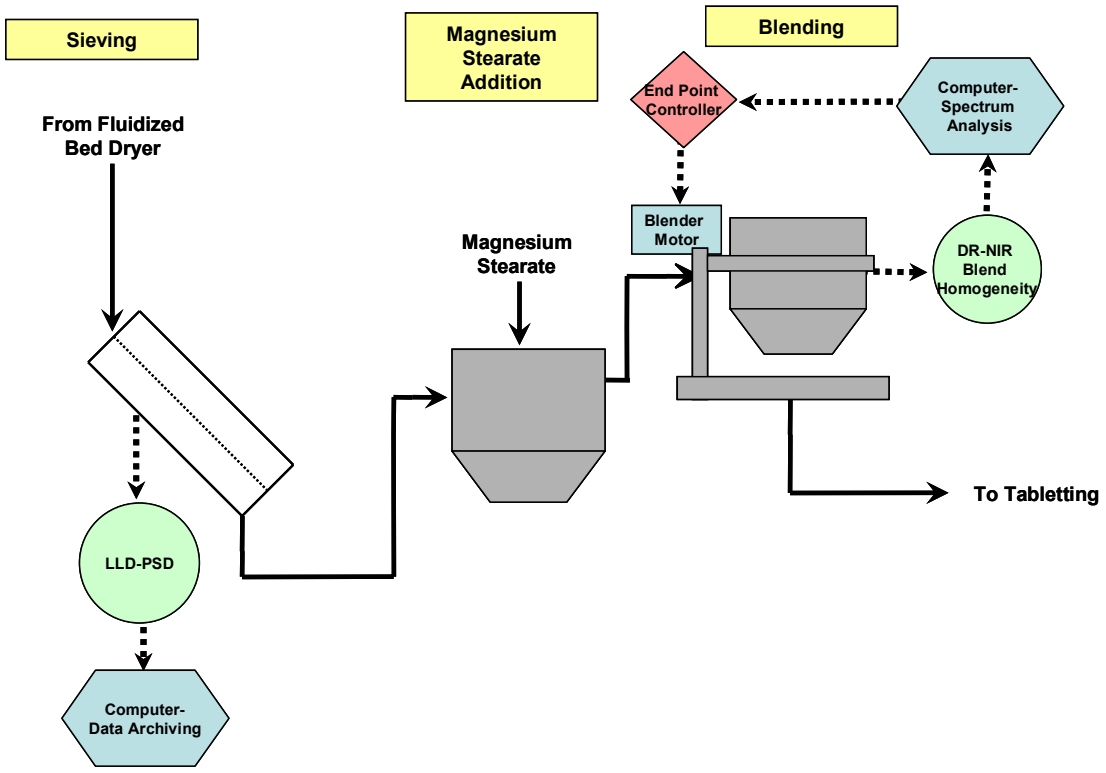


Figure 34: Product Z P&ID part III.

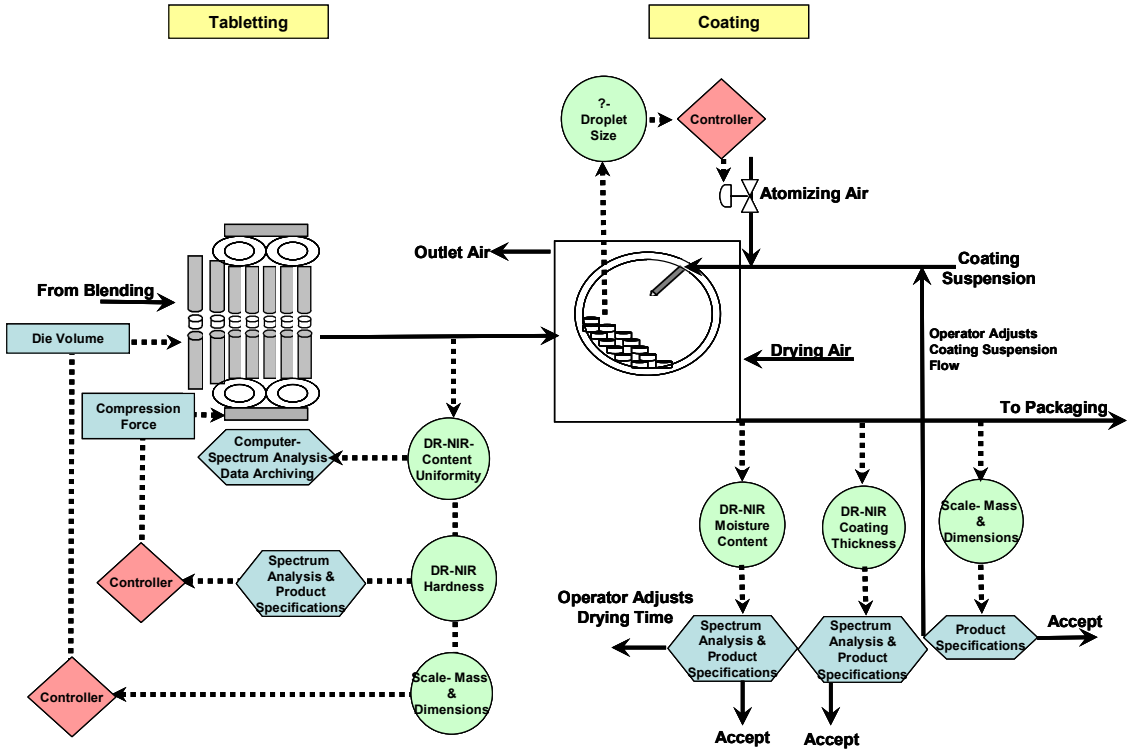


Figure 35: Product Z P&ID part IV.

3. The implementation of semi-continuous granulation and its economical influence.

3.1. Theory

3.1.1. Granulation in general

Granulation has the purpose of changing fine powder particles into bigger agglomerates by the formation of liquid bridges connecting the particles.

There are many reasons for the creation of granulate agglomerates:

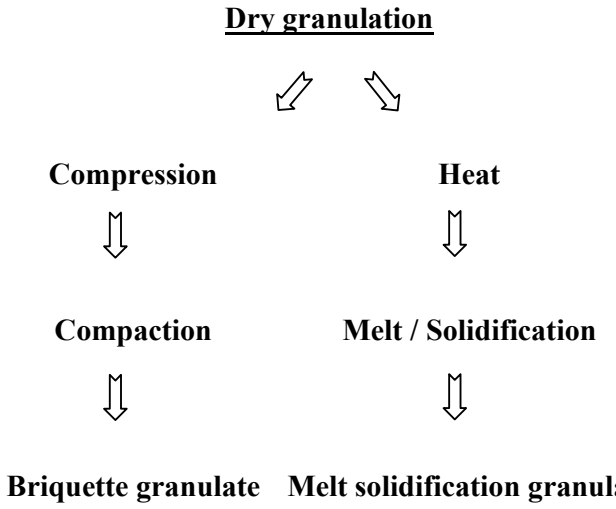
- A certain Particle Size Distribution (PSD) of the granulate particles is essential.
- The flowing properties and therewith the dosing accuracy are improved.
- The dust formation is reduced.
- Adhesive forces are reduced.
- Segregation tendency of the product blend is avoided.
- Raw material powders can not always be compressed to tablets as the cohesion forces are too weak for stable tablets.
- The surface texture, the wettability, the porosity, the solubility and the disintegration time regarding the bioavailability can be optimized.

Regardless of the granulation method, the following requirements are set for a high quality granulate:

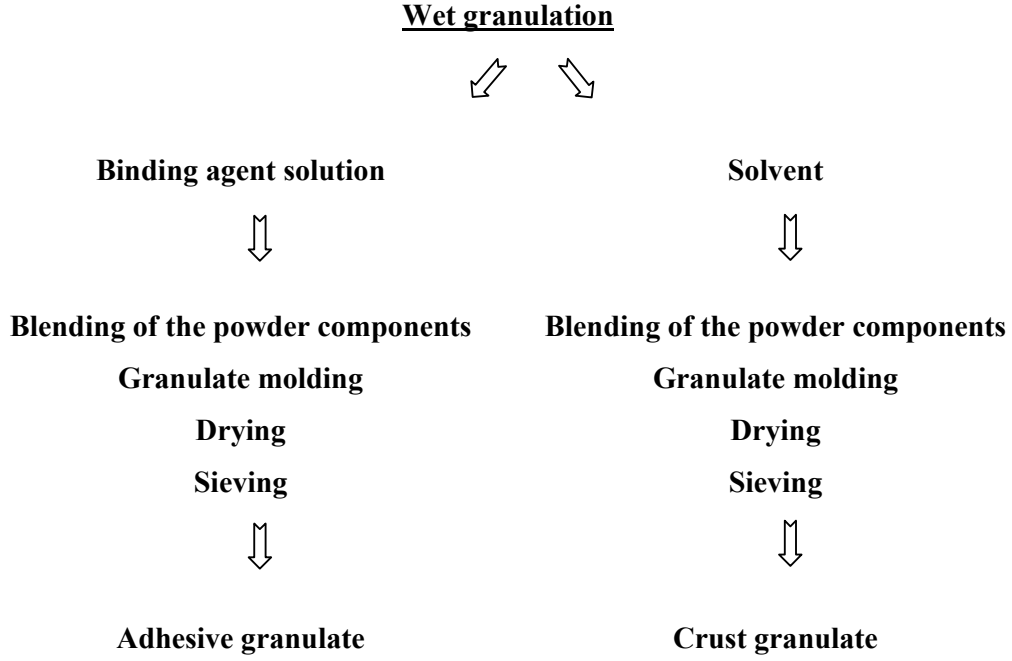
- It should be as consistent as possible regarding shape and color.
- Good flowing properties and lump formation should be avoided; good flowing properties are achieved with a particle size of 100µm or bigger.
- The particle size distribution should be uniform and narrow, whereas the median particle size should be adapted corresponding to the intended tablet size.
- The fines proportion in the granulate should not exceed 10% if possible.

- The granulate has to contain a certain amount of moisture, i.e. three too five percent, depending on the formulation and the raw materials, in order to prevent the produced tablets from sticking or capping.
- It has to exhibit enough mechanical cohesiveness in order not to crumble into powder again.
- The disintegration in water or other solvents should happen fast or controlled.

The types of granulates and the manufacturing methods are very versatile. There are the methods of dry granulation whereas briquette – or melt solidification granulate is produced with the help of compression respectively heat.



Other methods include the wet granulation. With binding agents adhesive granulate is produced and with solvents crust granulate is produced. Thereby the small powder particles are bound together to bigger agglomerates (constructive granulation) and partly those are milled to a certain particle size (retrenching granulation).



The most common granulation method is the wet granulation which is also used in the Multicell® (2).

3.1.2. Conventional discontinuous granulation methods

The classical wet granulation starts with an intensive dry blending of the active ingredient and the excipients in a mixer, dampening and dispersing follows in a slow moving kneader and ends with the sieving through a sieve. The long lasting, multiple-stage process results in favorable granulate properties concerning flowing – and tableting properties, but takes a long time and much effort. The strict rules of GMP can only be fulfilled with high efforts.

Special vertical or horizontal mixing systems equipped with extra milling heads make it possible to perform an intensive dry blending, damping and granulation in one operation. By choosing the correct amount of binding agents and controlling the granulation with a power consumption measurement, reproducible and immediate dryable granulate can be produced.

It is also often possible to dry the granulate in the mixer (e.g. Moritz® - Technology), particularly if the container has a heating jacket and a vacuum pump and possibly also

a microwave – or inert gas support (e.g. Bohle® - Technology). These methods are useful for crust granulation which are produced with the help of volatile organic solvents.

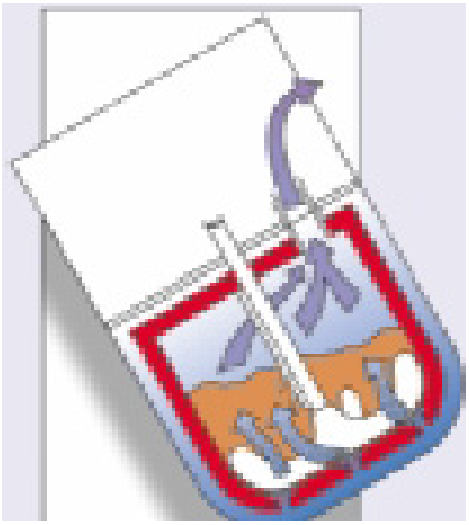


Figure 1: Collette Gral drying with the support of inert gas.

During Fluid Bed Granulation the powder is twirled into the air instead of being mechanically moved. Due to the intensive flow process the granulation binding agent can be adsorbed by the powder particles and simultaneously the created wet agglomerates can be dried in the warm flowing air (one-unit operation). The following sieving is done in order to prevent bigger agglomerates.

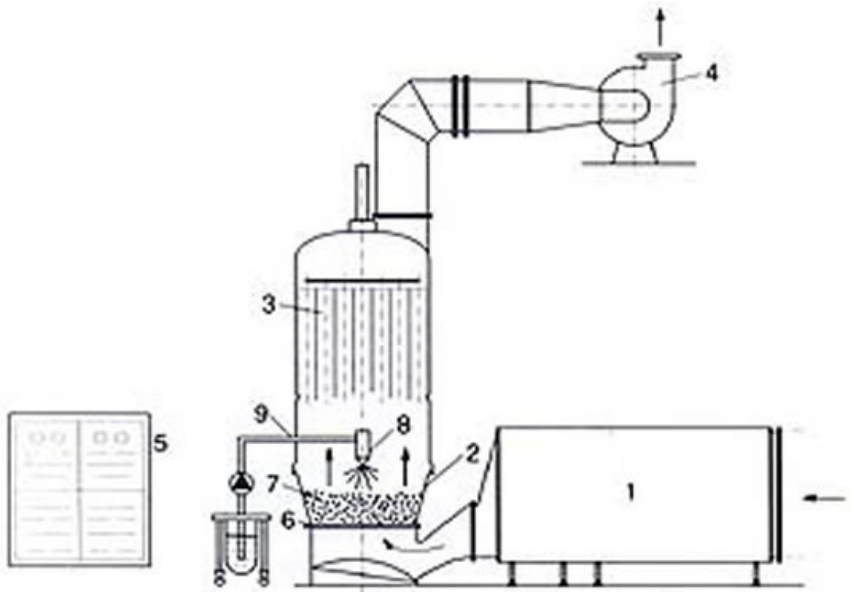


Figure 2: A typical fluid bed dryer system, 1 = air preparation unit; 2 = product container; 3 = exhaust filter; 4 = exhaust blower; 5 = control panel; 6 = air distribution plate; 7 = product; 8 = spray nozzle; 9 = solution deliver.

The most efficient way to manufacture a compactable product is making direct compactable blends, whereas the compaction ability of the blend into tablets is dependent on particle structure of the raw materials. This is true for e.g. acetylsalicylic acid which is compactable without prior granulation and also some of the benzodiazepines together with adequate excipients.

3.1.3. Discontinuous granulation in a vertical granulator.

In order to be able to compare the semi-continuous granulation method to the other conventional methods, the vertical granulation method will be described below:

The processing of the raw materials into a compactable granulate usually takes place in a batch production. One batch is the amount of a drug which is manufactured during one manufacturing cycle.

The batch size depends on the bulk density of the mixed raw materials. Usual batch sizes range from about 400kg up to 600kg. The size of the granulate batches can be adapted to the volume of the mixer or to the volume of the container which holds the

final blend for tableting. In the case of the latter, one batch can consist of multiple sub-batches.

The raw materials (active ingredients, excipients and binding agent) are filled either manually or with the help of a pneumatic pump into the mixer. There the powder will be mixed until it is homogeneous. The powder particles are centrifugally accelerated, resulting in a fluidized powder ring. Research results have shown that the desired homogeneity has been reached after 15 seconds and that longer mixing time do not show any improvement.

After the pre-blending of the raw materials the needed amount of binding agent solution will be added, manually or with the help of a pump. The easiest case is where it is enough to add water to the powder mixture, whereas a well water soluble binding agent has already been added as powder.

The addition of the binding agent solution should occur directly onto the milling heads. The high-speed turning milling heads have the following task:
It distributes and divides the binding agent and simultaneously densifies the powder formulation. Furthermore it disrupts the rising powder ring and leads the product back into the vertical route. Thereby a frequent passage between the mixing blades and the milling heads of the powder particles is secured. Bigger agglomerates will be chopped down and if the milling heads are positioned correctly it also assists during depletion.

During granulation the particle size distribution and the cohesiveness of the granulate particles can be controlled by the milling heads. The slower the binding agent is added, the better distribution is achieved. From the power consumption measurement of the mixer blades motor, the point in time can be estimated where the granulate formation and the granulate liquid amount have reached the optimum point.

The depletion of the wet granulate occurs straight into a fluid bed dryer tray, whereas production tests have shown that the quality of the granulate increases if the granulate is first sieved, regarding the homogeneity of drying, the sieve analysis and the

compression force / Hardness profile. Also the amount of granulate fitting into the fluid bed dryer tray is increased and so improving productivity.

After drying in the fluid bed dryer to the correct absolute humidity, the dry sieving follows. This step is done in order to prevent secondary granulation which occurs in the fluid bed dryer during the starting phase and transshipping. Also the essential particle size is achieved. Before tableting lubricant and disintegrator are added to the granulate.

3.1.4. The disadvantages of discontinuous granulation

1) There are many single equipment essential which are expensive and take a lot of space:

This is especially crucial when different mixers and dryers with dissimilar dimensions are needed for different batch sizes.

In older manufacturing sites for solid dosage forms there are often equipment which have been installed individually, i.e. not as a closed equipment network.

2) The granulation process is still associated with a lot of handwork, especially in older factories:

- Filling of the raw materials into the mixer.
- Making of binding agent solution in a planetary mixer or in a tank with an agitator.
- Pouring the binding agent solution onto the granulate.

For older equipment the following handwork might be needed:

- Shoveling the depleted wet granulate through a sieve into the fluid bed drier tray.
- It might be needed to manually sieve the granulate through a dry sieve.

- If there is no feeding system between the dry sieving and the final container carrying the final mixture, then the granulate must be sieved into bins and these will then be emptied into the container.

With modern equipment many manual steps can be erased and the system can be contained:

- There can be pumps installed for conveying the powder and liquids.
- During deployment out of the mixer, sieves can be used to assist or the deployment and wet sieving can occur by gravitation directly into the fluid bed dryer.
- After the drying of the granulate it could be pneumatically conveyed through a sieve into the final container.

3) Reproducibility cannot be guaranteed with batch production / discontinuous granulation.

- If the granulate is not conveyed automatically to the next process step, then the granulate intermediate stages might stand around for a different amount of time and so be changed physically (mainly in humid condition).
- Sieves can give different particle size distributions depending on the sieved mass. This could lead to different compaction properties.

4) The manufacturing process can be very complicated, depending on the product, and therefore high personnel effort needed and high costs.

These will have to be simplified with the appropriate technology – i.e. combining process steps and connecting the systems with e.g. a combination of a mixer deployment / wet sieving / loading of the fluid bed drier tray (e.g. Collette® Gral with Quadro Comil®) or even higher automation like pneumatic conveying systems.

5) The batch size is dependent on the equipment size used at the production site and not flexible regarding the market demand when entering the market.

For different batch sizes, different equipment for granulation will have to be used. Hence, very expensive scale-up exercises will have to be performed in order to adapt the batch size to different production dimensions. The launch of a new product specialty starts in a kilogram scale. Here it is basically about the decision of a definite drug application. For the clinical studies bigger batches will be needed. At last the process must be handed over to the production site and adapted to their dimensions.

6) There is a higher production risk:

As the whole batch is manufactured at once, it is at risk if a failure occurs or the equipment should brake down for some reason at all. Under circumstances the whole batch will have to be discarded (1).

3.1.5. Continuous granulation in the pharmaceutical industry

In the following paragraphs some different continuous granulation technologies will be introduced.

3.1.5.1.Fluid bed agglomeration

The most widespread continuous fluid bed agglomerators are horizontal moving bed granulators/driers (e.g. Glatt GF series, Niro Vibro-Fluidizer, Heinen Drying Technologies) (see figure below),

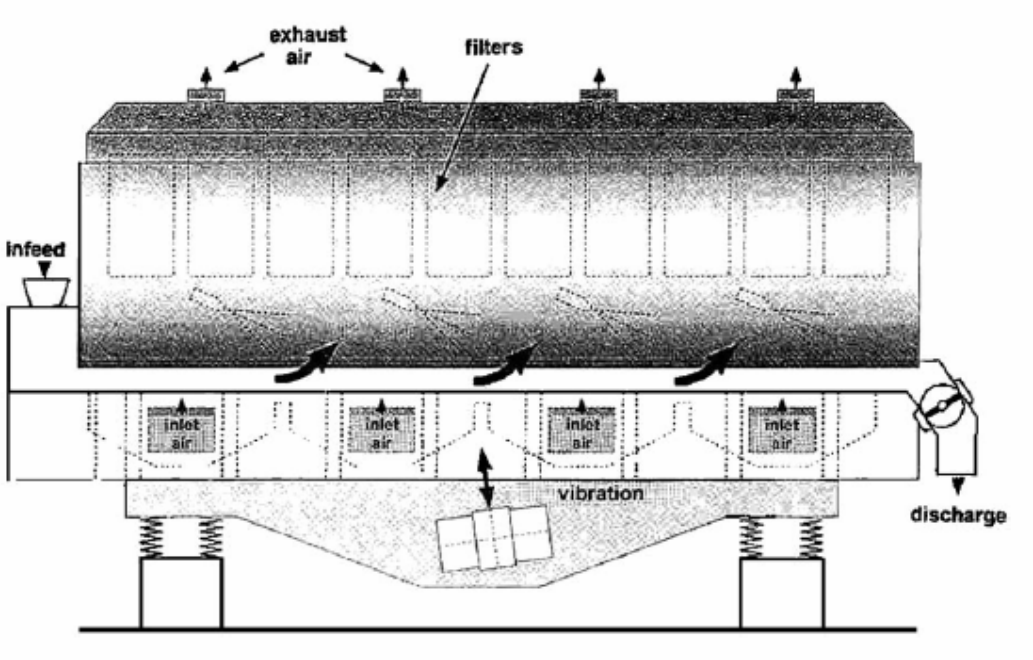


Figure 3: Heinen continuous fluid bed granulator.

they are mainly used in the chemical, dairy and food industry (e.g. for the production of instant products) and these systems were not specifically designed for pharmaceutical use. Inside the granulation chamber several processes are accomplished as the chamber is divided into different functional sections which are not mechanically separated from each other. After dosing the raw materials into the fluid bed at the feed zone and initial heating of the powders, a liquid is sprayed on the fluidized particles to induce agglomeration. As the materials are further transported down the processing chamber, solid bridges between individual particles are formed during drying, consolidating the agglomerates. In the final section the material is cooled to allow further processing after discharge of the product from the fluid bed. The different functionalities along the chamber originate from the presence of the spray nozzles at the agglomeration zone and from the introduction of air having different velocities and temperatures in the different sections. Controlled movement of material (mainly plug flow) inside the granulation chamber is essential and is due to mechanically vibrating the processing chamber (resulting in a shallow powder bed height) or controlling the air flow using specific air distributor plates at the bottom of the fluid bed, thus ensuring that the fluidized particles are constantly transported from the inlet zone to the discharge area while continuously being agglomerated and dried.

A more stringent control of the agglomerate particle size is possible by recirculation of the fines into the fluidized bed, the fines being separated from the agglomerated material during discharge of the material, e.g. using a zigzag sifter separating fines by means of elutriation.

Based on the same principle as the standard moving fluid bed Glatt developed the spouted bed systems (ProCell® series). In these systems the air does not enter the fluid bed through a rectangular bottom sieve but through a longitudinal slit, a design claimed by the manufacturer capable of processing difficult-to-fluidize materials due to the high air speed at the point of entry.

Although the concept of continuous moving bed agglomerators can be used within the pharmaceutical industry, there are hardly any applications of them for the production of solid dosage forms, mainly because they are ideally suited for high-volume products: production capacities typically range from 20 kg up to several tons per hour. These systems are unable to operate at the lower capacities required during drug development when the limited availability of the drug might impose some restrictions. Hence, during the development stage another granulation technique is chosen, mainly batch-wise as these granulation processes can be downscaled to as low as 50 g per batch. When at a later stage higher volumes must be processed (full-scale production) the pharmaceutical industry often sticks to the agglomeration technique initially selected and does not go for a technology transfer, even if the required production capacity would be within the range of these moving bed granulators.

To be able to cover a range of production rates (from lab-scale to full-scale production) with the same continuous fluid bed technique, Glatt developed a fluid bed (AGTseries) where the material is confined to an enclosed space (similar to batch fluid bed processors), but able to continuously discharge agglomerated material through an outlet at the bottom of the screen (round-shaped) (see figure below).

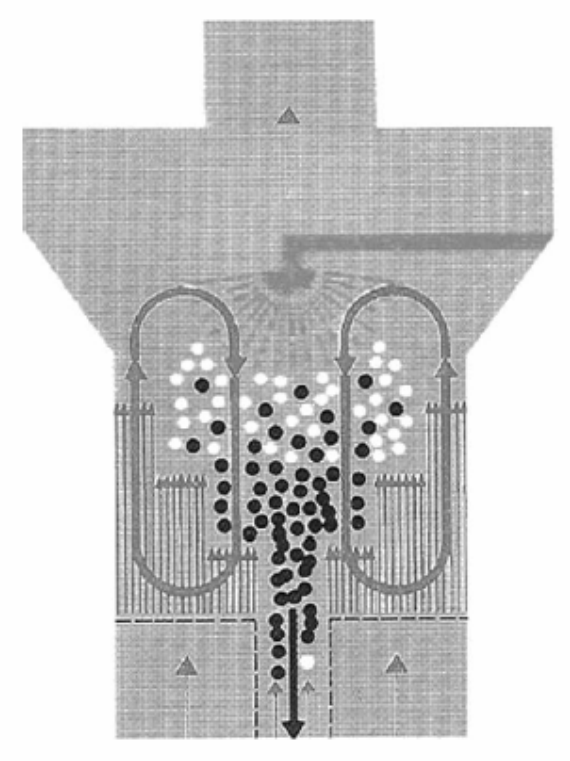


Figure 4: Glatt AGT® continuous fluid bed granulator.

A counter current air flow through the pipe positioned at the centre of the bottom plate ensures that only agglomerated particles are discharged. Only larger particles are able to overcome the air velocity, whereas the counter current airflow carries undersized particles back into the processing chamber until they are sufficiently agglomerated. This allows manufacturing an essentially dust-free product, the velocity of the counter airflow determining the particle size of the end product. This technique can be used for spray-granulation (spraying the raw material and building the agglomerates layer by layer) as well as conventional granulation (spraying a granulation liquid and possibly a binder onto individual particles in order to induce agglomeration). The latter method requires a powder dosing unit to continuously replace the solids being discharged from the fluid bed, in order to keep the solid/liquid ratio inside the processing chamber constant, an important parameter during a wet granulation process. This technique has a large dynamic range towards production rate as a lab-scale model for feasibility studies (throughput: 1 to 2 kg/h) as well as pilot-scale (50 kg/h) and full-scale production equipment is available.

3.1.5.2.Spray-drying

Although conventional one-stage spray-drying can be considered a continuous process, the materials obtained using this technique are in most cases not suited for tableting purposes without further treatment. Often a product with poor flow properties is obtained, consisting of non-agglomerated single particles or—at the best—of loosely bound agglomerates. Therefore, if one wants to incorporate a spray-dryer into a fully continuous tablet production line, the spray drying technique has to be combined with another agglomeration technique in order to produce a free flowing product in agglomerated form. Multi-stage (two or three) systems, combining a spray-drier with an externally or internally mounted fluid bed, allow manufacturing products meeting these specifications. When a spray dryer is linked to an external fluid bed the outlet temperature of the drying air is lowered to discharge a moister product (compared to
single-stage spray-drying) from the drying chamber into the fluid bed. The moist surfaces of the particles cause them to stick together, agglomerating the individual particles. The fluid bed, which is an in-line moving bed to allow continuous processing, can be used to further agglomerate the powders by spraying additional liquid onto the fluidized particles and/or to dry the agglomerates to the moisture content required for the down-stream processes.

Another design integrated the fluid bed inside the spray-dryer (see figure below) where the spray dryed but still moist particles are collected in a fluid bed at the bottom of the spray chamber.

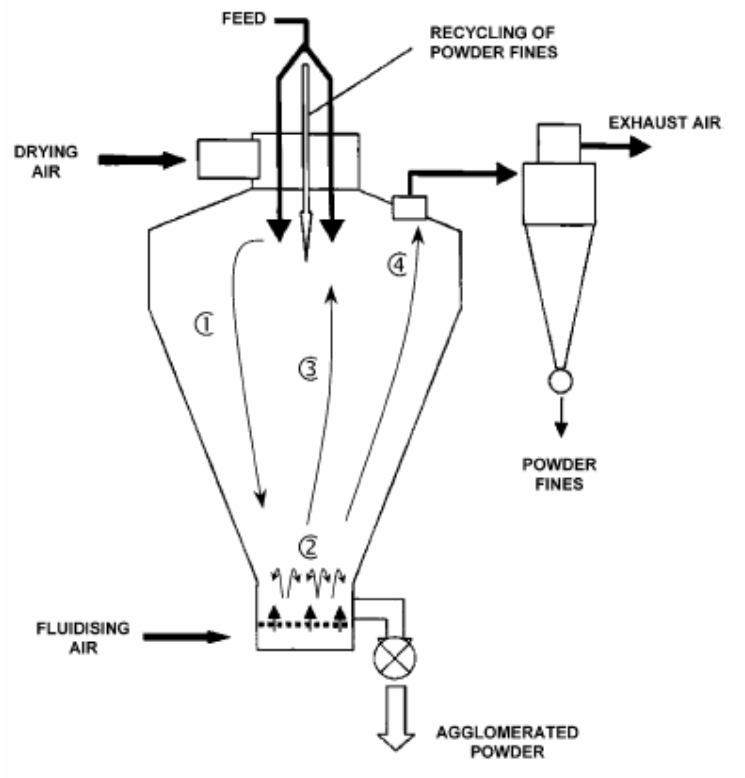


Figure 5: Spray-dryer with integrated fluid bed. 1. atomization and drying of droplets, 2. fluidization: coalescence of moist granules + interception of dry particles by moist granules, 3. collision of smaller particles and atomized droplets, 4. exhaust of non-agglomerated material from drying chamber.

Primary hot air is entering at the top and is used to dry the atomized particles, in addition a secondary air flow is introduced at the bottom of the system to fluidize the agglomerate particles. Different agglomeration processes can be distinguished in this concept. The main agglomeration mechanism (forming the strongest granules) occurs in the fluidization zone and relies on the moist surface of particles to coalesce or to intercept dry particles. This is the primary agglomeration mechanism as the residence time of particles in this zone is the longest. As smaller particles are propelled high into the chamber due to the fluidizing air, there is the possibility of these fine particles colliding with each other (especially just above the fluid bed where they are still moist and particle density is the highest) or with atomized droplets, both enlargement phenomena. A third agglomeration mechanism (limited to the atomization zone) occurs when individual droplets merge. Non-agglomerated material being exhausted from the spray-drying chamber is collected in the cyclone and these fines are recycled into the spray-drier. Size and characteristics of particles produced using this

technique depend on parameters such as drying air temperature and spray characteristics, e.g. agglomerate size grows using a coarser spray and lower temperature as in that case particles dry slower and have a higher moisture content, enhancing agglomeration tendency. If required an additional external fluid bed can be added to the system (3-stage) in which the agglomerates are discharged for final drying to the required residual moisture content.

3.1.5.3.Extrusion

Extrusion, the most studied continuous granulation technique for pharmaceutical applications, employs one (single) or two (twin) screws rotating inside a barrel to continuously transport, mix, and agglomerated wetted particles, the energy required for agglomeration provided by shear and/or material densification. Depending on the degree of densification inside the barrel the material discharged from the extruder can immediately be used, e.g. extrusion process run without die block or requires an additional milling or chopping stage to reduce the dense extrudate to granules having an acceptable particle size range.

Although pharmaceutical applications of this technique have already been described about two decades ago by various sources for effervescent and paracetamol granules, in recent years several research groups have contributed to the body of knowledge about extrusion as a tool for continuous pharmaceutical granulation. Recently, the Warner-Lambert Company filed a patent application for a continuous granulation/dryer system using a twin-screw granulator/chopper device for the granulation of active ingredients and additives. Schroeder and Steffens (2002) developed a planetary roller consisting of a central screw (spindle) around which several intermeshing planetary screws are positioned (see figure below).

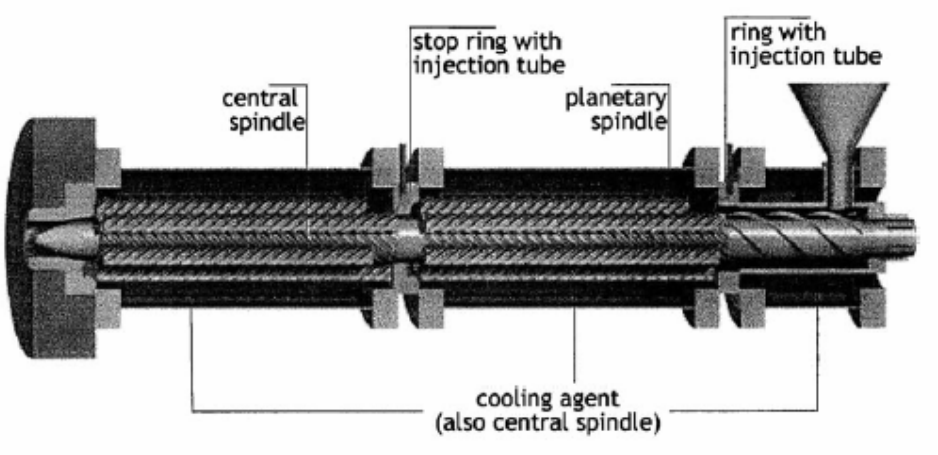


Figure 6: Planetary roller.

This design allows the introduction of nitrogen under pressure, inducing a foaming effect at ambient pressure and yielding a porous agglomerate, thus influencing the tableting properties of the material. Keleb et al. (2002) reported on the use of a laboratory scale co-rotating twin-screw extruder, running the process without a die block as in that case the limited densification allowed the immediate production of granules having the proper size, thus eliminating an additional milling step. Interestingly, Keleb et al. (2004) also provided actual data of an extrusion process continuously run over an 8-hour period. Sampling at regular intervals showed that the particle size, friability and tableting properties of placebo granules (α-lactose monohydrate containing 2.5% polyvinylpyrrolidone) were not significantly different as a function of time.

A major advantage of the extrusion technique seems the flexibility in output capacity, allowing development work as well as production on the same apparatus: (a) Keleb et al. (2004) were able to cover a range in capacity from 5.6 to 18.5 kg/h using the same extruder, (b) Schroeder (2004) claimed that a specific type of planetary roller (BCG10) can process 0.5 kg as well as 100 kg, simply by extending the run time of the equipment (i.e. 3 min and 10 h, respectively). Obviously the small batch can only be processed if the granulation process reaches steady-state extremely fast after start-up.

Contrary to agglomeration techniques using a fluid bed, granulation by extrusion yields wet granules, hence these systems must be linked to a continuous drier (e.g. fluid bed or microwave). The Bohle Company developed an integrated granulating and drying system consisting of the planetary roller combined with a microwave drier. To avoid the drying step, one could run a melt granulation process in the extruder using a molten binder (e.g. wax, polyethyleneglycol) for particle agglomeration. Upon discharging the granules into an atmosphere of ambient temperature the binder solidifies to consolidate the granule. A similar process is possible in a fluid bed, spraying a molten binder onto the fluidized particles. Using the melt granulation process, it is essential to determine the effect of the binder on the dissolution properties of the granules.

The quality of granules produced by extrusion depends on several parameters: extrusion temperature, design of the screws (i.e. the number of (back) mixing and densification zones), accuracy of powder and liquid dosing unit.

Processes which can be classified in a similar category as extruders are ploughshare mixers (Lödige) and horizontal high-shear mixer (HEC, Niro), however the commercially available systems have too large production capacities to be useful within the pharmaceutical industry.

3.1.5.4.Instant agglomerators

A few systems rely on high-speed mechanical agitation to continuously mix powder and liquid, thus ensuring instant formation of agglomerates. A special feature characterizing these granulators is the very short residence time (seconds), as a consequence product hold-up (i.e. material being processed in the equipment at a given time) is limited, reducing waste at the end of the production cycle. These systems are capable of high production capacities, but (theoretically) also allow processing limited quantities of material due to the small product hold-up. However, if one is to use these systems to process small quantities it is essential to rigorously determine the equilibrium time as at start-up one possibly has to discard a too large amount of product before granules of constant quality are obtained.

The Nica M6 mixer/granulator (see figure below) (Ivarson mixer)

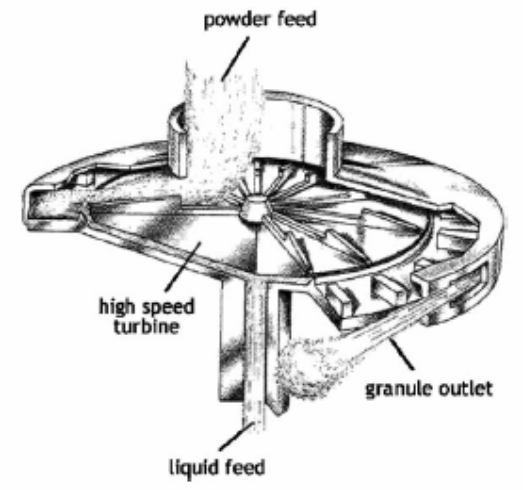


Figure 7: Nica M6 Mixer/Granulator.

uses a high-speed turbine to instantly mix the solids with the granulation liquid, whereas the Schugi Flexomix (Hosokawa) (see figure below) is equipped with blades rotating at high speed inside the processing chamber to generate sufficient mixing intensity and accomplish instant agglomeration.

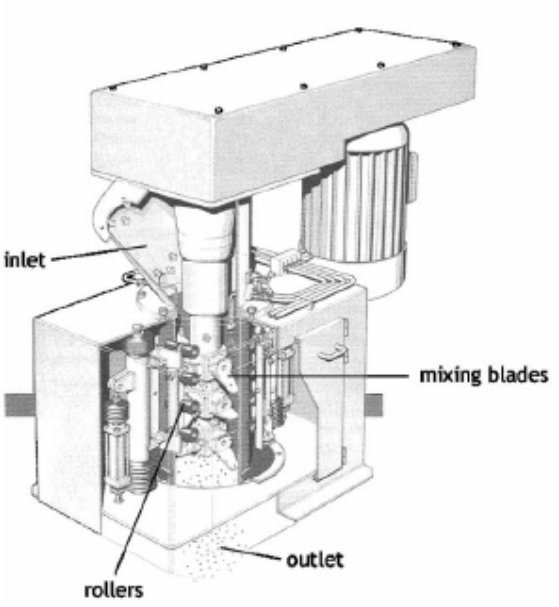


Figure 8: Schugi Flexomix instant agglomerator.

Similar to the granulation process by extrusion, the above-mentioned equipment produce wet granules, hence they must be linked to a continuous drying system (e.g. fluid bed). Due to the short residence time inside the mixing chamber the accuracy of the powder and liquid dosing units is essential to ensure an end-product of constant quality. Whereas the Nica mixer/granulator must be fed with a pre-blended powder, the Schugi Flexomix is also capable of mixing the powder components in the system and is already used in applications for bulk pharmaceuticals, although it has not specifically been designed for pharmaceutical purposes.

As these processes should run without interruption, an essential feature needed is that the systems has to be self-cleaning: no scale should form on e.g. the mixer wall or blades as this compacted material could break off and mix with other less-dense granules, creating a non-homogeneous end product. To avoid this, the Schugi Flexomix is equipped with an interesting feature: the process chamber is fitted with external rollers flexing the elastomeric mixing chamber to prevent build-up of material on the inside.

3.1.5.5.Roller compaction

Roller compaction (see figure below) can be used as a continuous dry granulation process, a technique which does not require a drying phase, hence high production capacities can be obtained using relatively small equipment.

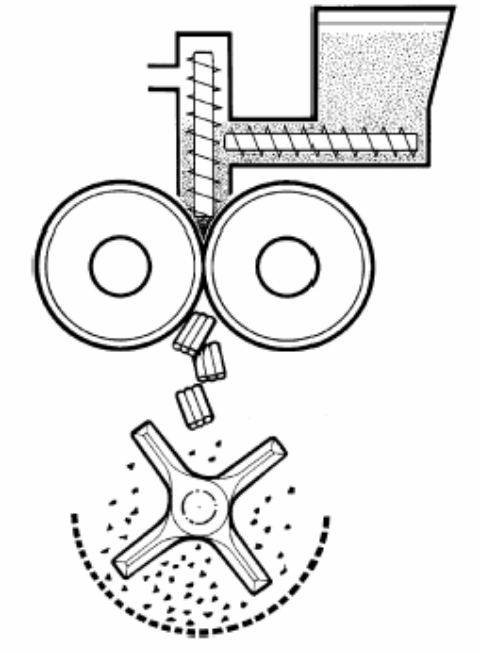


Figure 9: Flow diagram of roller compaction.

However, the absence of water also causes roller compaction's main problem: granule formation is strictly related to the compactibility of the material (under high compaction forces) as—contrary to wet granulation—capillary forces do not contribute to the binding mechanism. As a result a large amount of fines is formed during milling of the compacts to their appropriate agglomerate size. Although roller compactors can be equipped with a recycling unit for fines, a possible negative influence of recycling fines on drug uniformity has been reported. By controlled wetting of the powder formulation in a continuous fluid bed before roller compaction Inghelbrecht and Remon (1998) were able to dramatically reduce the amount of fines formed after milling and even improve the quality of the resulting tablets. However this approach eliminated the main advantage of roller compaction (a dry process, not requiring a drying phase), hence one should balance the added value of this approach against this disadvantage for each specific application.

3.1.5.6.Semi-continuous granulation

Combining two well established techniques, the high-shear granulation and fluid bed drying resulted in a semi-continuous agglomerator, the Multicell®.

The entire equipment train includes:

- A feeding and dosing system.
- A horizontal 30-liter high speed plough shear mixer with an airless spray system.
- A rotary high speed sieving machine for wet sieving.
- Three sequential fluid bed dryers.
- A rotary high speed sieving machine for dry sieving.
- Final product container.

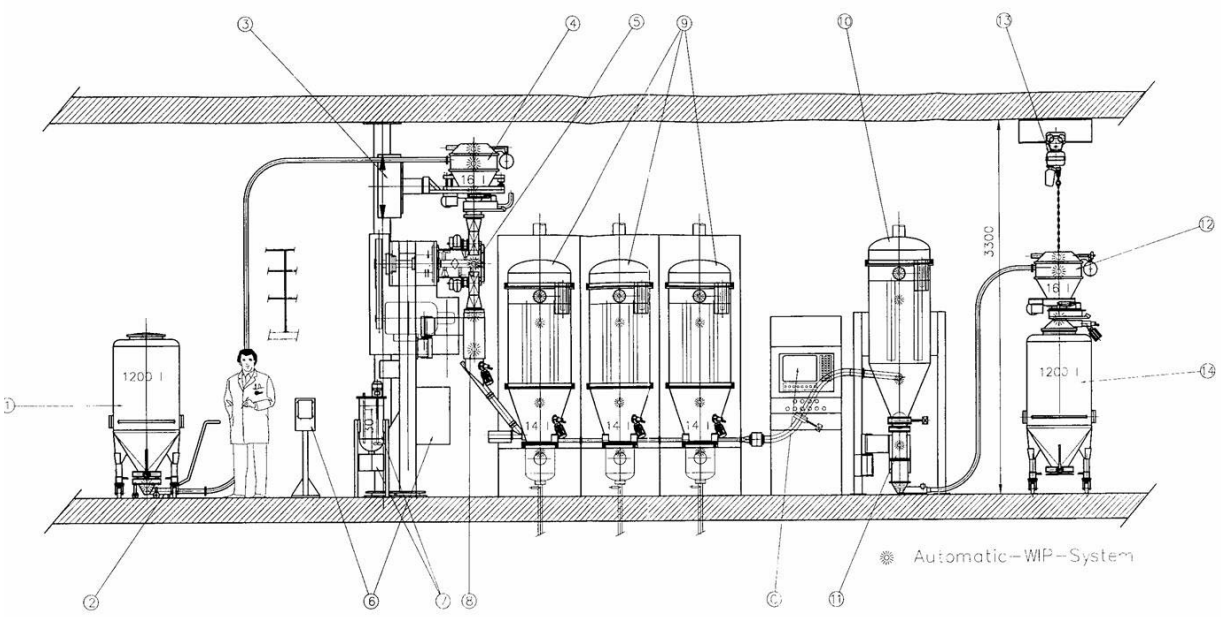


Figure 10: The Multicell®, 1. Master batch, 2. Flexible docking station, suction shoe of the IPC, 3. Post hoist for the IPC, 4. IPC, hopper, filter system, waging and discharging unit, 5. High shear mixer/granulator, 6. Airless high pressure dosing pump for the binder solution, 7. Solution tank, 8. Wet sieve, 9. Fluid bed dryers, 10. Product separator, 11. Dry sieve, 12. Conveying system with metal filters, 13. Lifting device, 14. Final product IBC.

Figure 11: The Multicell® at Pfizer / Goedecke, Freiburg, Germany.

The principle of the operation is simple. The first portion of the powder blend, which weighs about 8kg (+/- 2kg) is metered into the high shear mixer and moistened with an aqueous binder solution or with water if the binder is part of the pre-blend. After the granulation process is finished this first portion is transferred through a high speed rotation sieving machine into the first chamber of the sequential fluid bed dryers. The second portion of the powder blend is metered into the high shear mixer while the first one is pre-dryed. The first pre-dryed portion is then transferred to the second chamber, the second portion into the first drying chamber, and the third portion is metered into the high shear mixer. The process is continued until all the required portions which define the variable batch size have passed the equipment train. The output of the equipment train is regulated by the slowest step of the process which is normally the drying process. Typically the sequence is five minutes, providing an output of 96kg/hour (4).

3.1.5.7.The acceptance of continuous granulation processes

The utilization of continuous granulation processes in the pharmaceutical industry has not been widely spread, and this has various reasons.

The implementation of a continuous granulation process, resembling the food industry, only pays off for high volume products. The volumes produced in the pharmaceutical industry are very small compared to the food industry.

Regarding most of the continuous granulation processes, these mostly do not stand up to the high regulatory requirements made on the granulate. The raw materials will have to be pre-blended in a batch mixer, before starting the continuous process, thereby loosing the advantages of a continuous process.

One of the characteristics of continuous processes is the fact that the dwell period of the product is not really known inside the equipment. There is only an average dwell period known for the product, whereas parts of the product clearly fall below that average time or exceed it. This can have major influence on the quality of the product.

For continuous processes the start-up and shutdown of the process often prove themselves to be problematic regarding product quality. During start-up, equilibrium often does not kick in right away, therefore a certain amount of product will have to be discarded. The same goes for the shutdown, a part of the product will have to be discarded. Also the question will have to be raised, what happens with the product inside the equipment if the system shuts down due to a system failure (6).

Continuous processes always come with the advantage of higher automation level, leading to reduction in personnel. But this also means that the remaining personnel will have to be trained more.

3.1.5.8.The Multicell® approach

Semi-continuous processes are capable of using the advantages of continuous processes and at the same time avoiding the disadvantages mentioned above.

The biggest disadvantage of continuous processes is that the dwell period of the product in the equipment is not definable, as they are not divided into compartments whereas the product would be quantitatively moved from one compartment to another. Also the quality of the start-up and shutdown material cannot be verified and therefore will have to be discarded.

That is where the advantages of the semi-continuous processes come clear. The processing of the raw materials is divided into definite compartments, which do not only represent process steps but also partial steps. The product is quantitatively moved from one compartment to another and therefore the dwell period of the product is known in the equipment and can be controlled.

It is evident that a batch is now manufactured as many small sub-batches. The batch size is now flexible as the granulate quality parameters are now dependent on each and every subunit. Now the batch size depends on the number of sub-batches produced, and not on the size of the equipment. The quality of the sub-batches is reproducible, meaning that the quality of the first sub-batch corresponds to the quality of the last sub-batch. Therefore no part of the batch will have to be discarded after starting up the equipment or during shutdown (5).

3.1.6. Granulation scale-up process

Scale-up is normally identified with an incremental increase in batch size until a desired level of production is obtained.

The scale-up from the laboratory equipment to production-sized units is dependent on equipment design, which may or may not have been scalable as far as its dimensional feature or components selection is concerned. The importance of scalability is well understood and accepted by the manufacturers of fluid bed processors. Various sizes in their product line are logically designated and manufactured (3).

3.2. Introduction

It has been shown in many different publications that the implementation of the Multicell® could bring many advantages into the pharmaceutical industry.

- It contributes to the principles of Time-to-Market as it shortens the development time of the market image form.
- Opportunity to optimize process at a small scale and avoids scale-up (pilot scale = commercial scale).
- Provides stability results from the commercial equipment at an early development stage
- Avoids the need for multiple biostudies.
- It contributes to on of the ultimate principles of a lean manufacturing philosophy; Demand-driven production.
- Higher product output.
- Less floor space.
- Better process control due to smaller scale.

Also very a very important fact about the Multicell® is that this approach fits the needs of the new concepts of the FDA concerning risk-based management of critical processes such as the problem of scale-up and fulfills needs of FDA's PAT initiative (4, 7, 8, 9).

In the following approach it will be attempted to translate some of these statements made about the Multicell® into cash ("money talks…") to make it more interesting for upper management.

3.2.1. Economical evaluation of semi-continuous granulation

One of the reasons why the Multicell® is not yet more used in the pharmaceutical industry is the silo management structure prevailing today. Talking to people from marketing they would immediately be turned on by the idea of having a continuous process in manufacturing, leading to less personnel and higher automation. The same

goes with Research & Development people, they would be very interested in having equipment which would save them a few scale-up steps and finally production would be thrilled to have a process which would ease the transfer of the formulation from R&D to production.

"…Companies tend to operate in silos – R&D, manufacturing and marketing. This is a very proprietary culture. Knowledge and information sharing is the basis to overcome inefficiencies…" (10)

But the reality shows us that there is little communication between the silos. Up to now the Multicell® has only been implemented in production. In order tap the full potential of the Multicell® it would also have to be implemented in R&D. That way not only the obvious production advantages appear, but also the previously mentioned "Time-to-Market" advantage and the avoidance of the scale-up exercise.

Let us look at what that implementation in production brings along.

3.2.1.1.Comparison of discontinuous granulation and the semi-continuous

Werani et al. recently presented an interesting comparison between the traditional batch granulation and the Multicell®:

Technology	Lödige 900/WSG 300	Multicell	Difference
Process	Batch process	Semi-continuous	
Batch size	fixed to equipment capacity	flexible depending on process time	
Mode of operation	manual-driven and monitored	almost lights-out-operated	
Floor space	130m^2	100m^2	**- 23%**
Investment	1.6 Mio US$	2.0 Mio US$	**+ 25%**
Equipment volume	900 l (270 +/- 50kg)	30 l (8 +/- 2kg)	
Output	55kg/h	96kg/h	**+ 75%**
Overall output	10kg/24h/m^2	20kg/24h/m^2	**+ 100%**

Table 1: Comparison between classical batch and semi-continuous granulation process. (4)

Based on these information a comparison was performed on the volume of an average production site with 44 different products produced in 3 granulation rooms. Each granulation room has roughly the same equipment volume which is mentioned in the table above. The batch sizes vary from 76.8kg up to 456kg.

We will start by showing the results of the granulation rooms A, B and C for one year of production. In the table below there is an overview for granulation room A.

Products A	Batches/ year	Batches/ Campaign	Batch Size [kg]	Total amount [kg]	Gran. Duration / Batch [h]	Total Gran Duration [h]	Change - overs
aaa	24	5	229.9	5'517.6	2.6	63.4	5
bbb	3	3	220.0	660.0	9.0	27.0	1
ccc	5	5	231.8	1'158.8	6.5	32.5	1
ddd	451	12	243.8	109'931.3	6.5	2'931.5	38
eee	6	7	204.6	1'227.6	5.0	30.0	1
fff	13	7	207.0	2'691.0	4.5	58.5	2
ggg	59	8	210.0	12'390.0	3.9	230.1	8
hhh	1	1	200.0	200.0	4.0	4.0	1
iii	116	10	253.3	29'378.2	4.0	464.0	12
jjj	3	3	204.0	612.0	3.0	9.0	1
kkk	27	7	235.0	6'345.0	2.6	70.7	4
lll	7	7	240.0	1'680.0	3.4	23.9	1
mmm	6	3	290.0	1'740.0	5.8	34.5	2
nnn	19	5	290.0	5'510.0	5.2	99.0	4
ooo	10	5	286.0	2'860.0	5.6	56.3	2
ppp	111	10	144.0	15'984.0	5.9	650.5	12
Total	**861**			**197'885.5**		**4'784.9**	**95**

Table 2: Granulation room A production volume for one year.

A change-over from one product to another has an average duration of eight hours (one shift) resulting in a total change-over time during one year of 760 hours. This leads to a total occupancy time of the equipment of 5’544.9 hour per year. Granulation rooms B and C are shown below.

Products B	Batches/ year	Batches/ Campaign	Batch Size [kg]	Total amount [kg]	Gran. Duration / Batch [h]	Total Gran Duration [h]	Change - overs
qqq	7	4	200.0	1400.0	4.0	28.0	2
rrr	1	1	150.0	150.0	3.8	3.8	1
sss	2	2	250.0	500.0	1.8	3.5	1
aaa	30	5	229.9	6897.0	2.6	79.2	6
ttt	8	4	344.4	2755.2	8.0	64.0	2
uuu	61	8	208.0	12688.0	3.5	213.5	8
vvv	47	8	230.0	10810.0	2.5	117.5	6
www	2	2	217.0	434.0	4.0	8.0	1
xxx	3	3	247.8	743.4	3.5	10.5	1
yyy	1	1	210.0	210.0	3.5	3.5	1
ddd	27	5	243.8	6581.3	6.8	183.6	6
eee	1	1	204.6	204.6	4.0	4.0	1
fff	3	3	207.0	621.0	4.5	13.5	1
zzz	7	4	200.0	1400.0	3.9	27.3	2
abb	2	2	210.0	420.0	6.0	12.0	1
acc	2	2	200.0	400.0	7.5	15.0	1
ggg	40	8	210.0	8400.0	3.9	156.0	5
hhh	18	6	200.0	3600.0	4.0	72.0	3
iii	154	10	253.3	39002.0	4.1	628.3	16
add	2	2	300.0	600.0	5.3	10.5	1
aee	1	1	200.0	200.0	7.0	7.0	1
aff	56	8	76.8	4300.8	4.3	239.7	7
mmm	18	6	290.0	5220.0	5.8	103.5	3
nnn	21	4	290.0	6090.0	5.2	109.4	6
ooo	6	3	286.0	1716.0	5.6	33.8	2
ppp	97	10	144.0	13968.0	5.9	568.4	10
Total	**617**			**129311.3**		**2715.5**	**95**

Table 3: Granulation room B production volume for one year.

Granulation room B also has 95 change-overs during one year which sums up to 760 hours. The total occupation time of the equipment is 3’475.5 hours.

Products C	Batches/ year	Batches/ Campaign	Batch Size [kg]	Total amount [kg]	Gran. Duration / Batch [h]	Total Gran Duration [h]	Change - overs
agg	19	7	340.0	6460.0	4.5	85.5	3
ahh	53	7	345.0	18285.0	4.7	247.0	8
ajj	179	10	331.3	59297.3	5.0	895.0	18
akk	4	4	165.6	662.5	5.0	20.0	1
all	32	8	261.6	8371.2	3.8	121.6	4
amm	1	1	310.0	310.0	18.5	18.5	1
ann	5	5	456.0	2280.0	7.0	35.0	1
aoo	26	6	246.0	6396.0	7.4	192.4	5
app	1	1	228.0	228.0	5.5	5.5	1
aqq	43	8	300.0	12900.0	2.8	121.7	6
arr	502	10	330.0	165660.0	3.5	1757.0	51
ass	3	3	340.0	1020.0	15.0	45.0	1
Total	**868**			**281870**		**3544.2**	**100**

Table 4: Granulation room C production volume for one year.

Granulation room C has 100 change-overs during one year which sums up to 800 hours. This leads to a total occupation time of 4'344.2 hours.

Granulation rooms A, B and C are all run in five days and two shift with three FTE's (Full Time Equivalent) working on each shift. Let us summarize:

	Gran A	Gran B	Gran C
Batches	861	617	868
Granulate [kg]	197'855.5	129'311.3	281'870.1
Production time [h]	4'784.9	2'715.5	3'544.2
Change-over [h]	760	760	800
Total occupation [h]	5'544.9	3'475.5	4'344.2
FTE / shift	3	3	3
Shifts	2	2	2

Table 5: Summarization of the conventional granulation output.

As Dörr tested with his work (7) 28 products out of 30 market formulations could be transferred directly onto the Multicell® without any formulation changes.

Now if we assume the best case and suppose that all existing products can be transferred without problems from the conventional granulation onto the Multicell® and basically replace granulation room number one and number three, the following can be observed for step 1.

	Multicell® A	**Gran B**	**Multicell® C**
Batches	(861)	617	(868)
Granulate [kg]	197'855.5	129'311.3	281'870.1
Production time [h]	2061.3	2'715.5	2'936.1
Change-over [h]	1520	760	1600
Total occupation [h]	3'581.3	3'475.5	4'536.1
FTE / shift	1	3	1
Shifts	2	2	2

Table 6: An overview on the production after replacing two conventional granulation rooms with the Multicell®.

It can be observed that overall the change-over duration doubled itself compared to the conventional granulation. This is due to the fact that although the Multicell® is equipped with a WIP (Washing in Place) system which has a duration of approximately 200 minutes there are still some spots which will have to be cleaned manually as e.g. the gaskets of the dosing system, the mixer, the sieving machine, the fluid bed dryers and of the strainer. Also the sieves of the sieving machine will have to be cleaned manually as well as the intakes of the temperature probes in the fluid bed dryers. As this comparison should not be made too optimistic, a change-over duration of 16 hours will be estimated.

As the production time makes up about 80% of the total occupation time this does not have too much impact on the total occupation time. The output of the Multicell® reduces the production time of 57% and at the same time it doubles the change-over time for room A. This leads to a new total occupation time of 3'581.3, a total decrease of 1963.6 hours. The production time in room C is reduced of 17% but the

change-over time is also doubled leading to a slight increase in total occupation time of 191.9 hours.

So what has happened just be replacing the conventional granulation with the Multicell® is that we can see that the Multicell® is capable of handling the number of products and volume of an average production site, with only one FTE per shift instead of three. The reason why all rooms where not replaced is simply because that it has to be expected that some products will not be transferable onto the Multicell® and due to the long change-over times, low volume products should not be produced semi-continuously.

That leads us to step 2 of our comparison. It could be observed in tables 2 and 3 above that these rooms shared some of the products. There are 11 products produced in room B which are also produced in room A. As there has already been capacity gain in room A these products should all be produced in room A.

Products Multicell A	Batches/ year	Batches/ Campaign	Batch Size [kg]	Total amount [kg]	Total Multicell Duration[h]	Change – over Duration
aaa+	54	5	229.9	12'414.6	129.3	176.0
bbb	3	3	220.0	660.0	6.9	16.0
ccc	5	5	231.8	1'158.8	12.1	16.0
ddd+	478	12	243.8	116'512.5	1'213.7	640.0
eee+	7	7	204.6	1'432.2	14.9	16.0
fff+	16	7	207.0	3'312.0	34.5	48.0
ggg+	99	8	210.0	20'790.0	216.6	208.0
hhh+	19	6	200.0	3'800.0	39.6	64.0
iii+	270	10	253.3	68'380.2	712.3	432.0
jjj	3	3	204.0	612.0	6.4	16.0
kkk	27	7	235.0	6'345.0	66.1	64.0
lll	7	7	240.0	1'680.0	17.5	16.0
mmm+	24	3	290.0	6'960.0	72.5	128.0
nnn+	40	5	290.0	11'600.0	120.8	128.0
ooo+	16	5	286.0	4'576.0	47.7	64.0
ppp+	208	10	144.0	29'952.0	312.0	336.0
Total	**1'276**			**290'185.3**	**3'022.9**	**2'368**

Table 7: Room A after implementation of the Multicell® and the addition of the mutual products from room B (product names in bold with +).

Room B then looks like this:

Products B	Batches/ year	Batches/ Campaign	Batch Size [kg]	Total amount [kg]	Gran. Duration / Batch [h]	Total Gran Duration [h]	Change - overs
qqq	7	4	200.0	1400.0	4.0	28.0	2
rrr	1	1	150.0	150.0	3.8	3.8	1
sss	2	2	250.0	500.0	1.8	3.5	1
ttt	8	4	344.4	2755.2	8.0	64.0	2
uuu	61	8	208.0	12688.0	3.5	213.5	8
vvv	47	8	230.0	10810.0	2.5	117.5	6
www	2	2	217.0	434.0	4.0	8.0	1
xxx	3	3	247.8	743.4	3.5	10.5	1
yyy	1	1	210.0	210.0	3.5	3.5	1
zzz	7	4	200.0	1400.0	3.9	27.3	2
abb	2	2	210.0	420.0	6.0	12.0	1
acc	2	2	200.0	400.0	7.5	15.0	1
add	2	2	300.0	600.0	5.3	10.5	1
aee	1	1	200.0	200.0	7.0	7.0	1
aff	56	8	76.8	4300.8	4.3	239.7	7
Total	**202**			**37011.4**		**763.8**	**36**

Table 8: Room B after loosing all mutual products to room A.

Room C stayed just like it was after step 1. Let us have an overview of what is happening.

	Multicell® A	Gran B	Multicell® C
Batches	(1’276)	202	(868)
Granulate [kg]	290’185.3	37’011.4	281'870.1
Production time [h]	3’022.8	763.7	2’936.1
Change-over [h]	2’368.0	288.0	1600
Total occupation [h]	5390.8	1’051.7	4’536.1
FTE / shift	1	3	1
Shifts	2	1	2

Table 9: An overview of the status in the three rooms after step 2.

It can be observed that the total occupation time in room A has reached the approximate occupation time which it had with the conventional granulation equipment, but this time with only 1 FTE per shift instead of 3 FTE’s per shift. Room B has decreased its total occupation time down to 1052 hours from 3475 hours. This way it is enough to run that room with one shift instead of two. Room C is still unchanged.

Now the won capacity in room B should be exploited with other products in order to keep the low volume products away from the semi-continuous equipment which have longer change-over times.

Products B	Batches/ year	Batches/ Campaign	Batch Size [kg]	Total amount [kg]	Gran. Duration / Batch [h]	Total Gran Duration [h]	Change - overs
qqq	7	4	200.0	1400.0	4.0	28.0	2
rrr	1	1	150.0	150.0	3.8	3.8	1
sss	2	2	250.0	500.0	1.8	3.5	1
ttt	8	4	344.4	2755.2	8.0	64.0	2
uuu	61	8	208.0	12688.0	3.5	213.5	8
vvv	47	8	230.0	10810.0	2.5	117.5	6
www	2	2	217.0	434.0	4.0	8.0	1
xxx	3	3	247.8	743.4	3.5	10.5	1
yyy	1	1	210.0	210.0	3.5	3.5	1
eee	7	1	204.6	1432.2	4.0	28.0	7
zzz	7	4	200.0	1400.0	3.9	27.3	2
abb	2	2	210.0	420.0	6.0	12.0	1
acc	2	2	200.0	400.0	7.5	15.0	1
add	2	2	300.0	600.0	5.3	10.5	1
aee	1	1	200.0	200.0	7.0	7.0	1
aff	56	8	76.8	4300.8	4.3	239.7	7
amm+	1	1	310.0	310.0	18.5	18.5	1
app+	1	1	228.0	228.0	5.5	5.5	1
ass+	3	3	340.0	1020.0	15.0	45.0	1
akk+	4	4	165.6	662.5	5.0	20.0	1
ann+	5	5	456.0	2280.0	7.0	35.0	1
bbb+	3	3	220.0	660.0	9.0	27.0	1
ccc+	5	5	231.8	1158.8	6.5	32.5	1
jjj+	3	3	204.0	612.0	3.0	9.0	1
lll+	7	7	240.0	1680.0	3.4	23.9	1
Total	**241**			**47054.9**		**1'008.2**	**52**

Table 10: Room B after receiving all low volume products from rooms A and C.

Products Multicell A	Batches/ year	Batches/ Campaign	Batch Size [kg]	Total amount [kg]	Total Multicell Duration[h]	Change – over Duration
aaa	54	5	229.9	12'414.6	129.3	176.0
ddd	478	12	243.8	116'512.5	1'213.7	640.0
fff	16	7	207.0	3'312.0	34.5	48.0
ggg	99	8	210.0	20'790.0	216.6	208.0
hhh	19	6	200.0	3'800.0	39.6	64.0
iii	270	10	253.3	68'380.2	712.3	432.0
kkk	27	7	235.0	6'345.0	66.1	64.0
mmm	24	3	290.0	6'960.0	72.5	128.0
nnn	40	5	290.0	11'600.0	120.8	128.0
ooo	16	5	286.0	4'576.0	47.7	64.0
ppp	208	10	144.0	29'952.0	312.0	336.0
Total	**1251**			**284'642.3**	**2'965.1**	**2288**

Table 11: Room A after moving all low volume products to room B.

Products Multicell C	Batches/ year	Batches/ Campaign	Batch Size [kg]	Total amount [kg]	Total Multicell Duration[h]	Change – over Duration
agg	19	7	340.0	6460.0	67.3	48.0
ahh	53	7	345.0	18285.0	190.5	128.0
ajj	179	10	331.3	59297.3	617.7	288.0
all	32	8	261.6	8371.2	87.2	64.0
aoo	26	6	246.0	6396.0	66.6	80.0
aqq	43	8	300.0	12900.0	134.4	96.0
arr	502	10	330.0	165660.0	1725.6	816.0
Total	**854**			**277369.5**	**2889.3**	**1520**

Table 12: Room C after moving all low volume products to room B

Now let's have an overview of the status after step 3, after moving all low volume products into room B.

	Multicell® A	Gran B	Multicell® C
Batches	(1’251)	241	(854)
Granulate [kg]	284'642.3	47’054.9	277’369.5
Production time [h]	2'965.0	1’008.2	2’889.3
Change-over [h]	2'288.0	416	1’520
Total occupation [h]	5253.0	1’424.2	4’409.3
FTE / shift	1	3	1
Shifts	2	1	2

Table 13: Final status after step 3.

It has been shown that by replacing the conventional granulation rooms with the Multicell® a radical decrease in production time could be achieved and altogether the total occupation time could be decreased creating extra capacities for production. Thereby the shifts could be reduced from two down to one for conventional granulation, saving three FTE’s already. By running the two Multicell® on two shifts with only one FTE per shift another 8 FTE’s could be saved, still having some free capacities in room B.

In order to try to feature the savings in cash flow the costs of implementation will have to be considered. For this case it will be assumed that not only the Multicell® costs will have impact on the cash flow. There will probably have to be done some HVAC (Heating, Ventilation and Air Conditioning) upgrading and the costs for qualification and validation could also be considered. Here is a summarization of the costs (HVAC and Qualification / Validation based on rough estimations) and savings.

Costs [kCHF]	Multicell A	Multicell C	Total
Equipment	2630	2630	5260
HVAC	150	150	300
Qual. / Val.	50	50	100
Total	**2830**	**2830**	**5660**

Table 14: Total costs of Multicell® implementation in thousands of dollars.

The average costs of one FTE in Switzerland for pharmaceutical sites are approximately 100'000CHF per year. As mentioned above the implementation of the Multicell® saved FTE's by easing the operation of the equipment and reducing shifts.

	Room A	Room B	Room C	Total
FTE	4	3	4	11
Value [kCHF]	400	300	400	1100
Total				**1100**

Table 15: Savings based on reduced personnel.

Assuming that all investments and implementation work will be performed in the first year and the FTE savings will start in the second year, the cash flow will look something like this:

What has not been incorporated into these calculations is for example the possible costs of the change-requests which might have to be submitted.

Also not included into these considerations are the possible savings due to reduced floor space and shorter throughput time. The FTE savings are also conservative as the operation of the Multicell® could even be controlled by 0.5 FTE (12), which would mean that one person could theoretically run both Multicell® granulation rooms during one shift, saving two more FTE's.

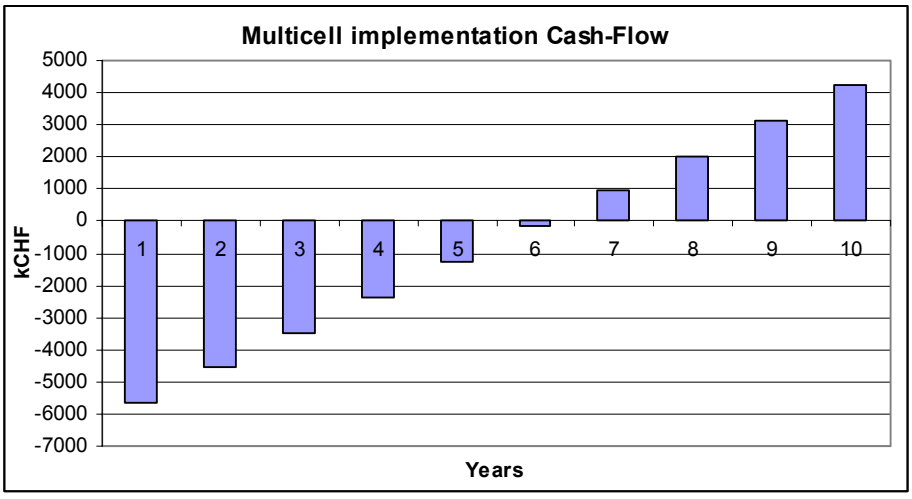


Figure 12: Cash-flow with a breakeven point of about 6 years.

As can be seen in the above figure the breakeven point will be reached around five years and an EBIT of approximately 4 Million CHF after 10 years after implementing the Multicell® in this case study.

These results show that the introduction of semi-continuous processes into the pharmaceutical industry does not only support lean manufacturing but also brings high saving potentials with it. But it should be made clear that the implementation of the Multicell® in the production only, does not exploit the possible savings which can be achieved with it. Additionally to that there will only be one validation of the process if the Multicell® is implemented in development, bringing in extra savings due to validation costs. The FTE savings is just a piece of the possible savings achievable by being faster on the market.

3.2.1.2.Time to market

In order to achieve the main advantage of the Multicell® the silos operation, prevailing in the pharmaceutical industry today, will have to be broken down (13). The interfaces between development and production is often extremely stiff, the researchers hardly communicate with the manufacturers and just deliver their formulation to the launch site and don't want to have anything more to do with it. The manufacturer will then have to try to run the formulation on the production equipment and often this procedure takes a long time. In order to easy these restrictions the researchers should accompany their formulation into manufacturing and not leave until the formulation runs on production equipment (14). This procedure would be so much easier if both departments had the same equipment. In order to achieve this, R&D should also purchase a Multicell® for their use.

That way a pharmaceutical formulation can be optimized in early development on the Multicell®, thereby providing stability results from the commercial equipment at an early development stage. Thereby the need for multiple biostudies is also avoided. By optimizing the formulation at such an early stage and having the Multicell® in R&D and at the production site, there will be no need for troublesome scale-up exercises (4).

Altogether this will have an impact on the development duration and hence "Time-to-Market". But what does that high investment for R&D bring in for a researching company?

The average costs to develop a new drug have reached an average of 802 million US$ in the year 2000 and the average time which goes by from the discovery of the active substance until market commercialization is 12 – 13 years (13). The development of the drug product is only a small part of the total time. Basically the pharmaceutical development only has time from the first delivery of active substance until the beginning of phase II clinical studies to develop the market formulation, including scale-up (which will not be necessary with the Multicell®). This time is in average just about ¾ of a year (15).

So it is clear that in that time, every day counts. The time savings potential has been well-investigated by Ewers, Küppers and Weinmann in their book "Pharma Supply Chain". There they also propose the implementation of the Multicell® and furthermore other improvements in the chemical production in order to speed up the delivery of the active substance. With all improvements which are suggested they see a "Time-to-Market" improvement of about one too one and a half year (16).

The "Time-to-Market" savings reachable with the Multicell® roughly sum up to 5 – 10 weeks (16). It is difficult to say how much that is worth, but there are some very good examples worth mentioning.

Assuming that a product has an on-patent life of five years and during these five years there are 600 – 1200 manufacturing days of that product per site. Depending on product they have different sales volume and so different values. In the table below there are some examples of what one manufacturing day brings in to the company.

Sales volume	Cash delivery
2 Billion drug	$1.6 million per day
1 Billion drug	$830'000 per day
0.5 Billion drug	$417'000 per day
0.175 Billion drug	$150'000 per day

Table 16: Drug manufacturing revenues (17).

The blockbuster product Lipitor from Pfizer e.g. delivers at least 5.7 million US$ per manufacturing day to Pfizer (17).

This makes it clear that every day counts when trying to get a product on the market. A delay of only a week could cost the company revenues up to 11.2 million US$, which easily pays up the implementation costs of the Multicell®.

Another example to emphasize the need to get fast to the market is a research which shows that on average, for every month a product is late to market it will lose 10% of its gross profit potential (18).

The implementation of the Multicell® does not only apply to the researching industry. Generics companies thrive on the fact of being first on the market after a drug patent expires. A generic company can be sure that they are not alone when a patent on a blockbuster drug is running out, but it is a cruel world and only the fastest generic companies win. The drug developer earns 50% of the available revenue on the drug in their patent life. But as soon the patent runs out the generics appear on the market and the first one gets 25% of the available revenue. The second generic company on the market only gets 15% and all the other generics makers coming to the market divide the remaining 10%.

3.2.1.3.The line of the future

If one considers continuous and semi-continuous processes for the pharmaceutical industry, tableting and packaging are the processes which are already continuous. A

connection between the rotary press and a packaging line is possible, i.e. if the tablets will not have to be coated. Granulation and coating are the processes which are, up to now almost always run in batch mode, making it necessary to run tableting in batch mode also. Now when we have shown that the implementation of a semi-continuous granulation process is lucrative, the possibility of a direct connection between the granulation process and tableting is possible. The discharged sub-batches from the Multicell® could be dispatched directly into a depot over the rotary press and the tablets from the rotary press could also be transported directly onto the packaging line, making the whole process continuous.

But what about coating? Another semi-continuous production system exists which is called the Bohle concept. The production line consists of an automatic dispensing system dosing the materials into a container, from where the materials are vacuum transported into the bowl of a high-shear mixer. This single pot system combines agglomeration and drying (vacuum, possibly accelerated by microwave or gas stripping). Next the dry product is milled and sieved on-line and after final blending fet into the compression machine. Tablets discharged from the press fall on a conveying belt and are transported to a holding container, before being fed into a continuous coating system, consisting of two independent coating drums. This is designed as a semi-continuous production process as the next dispensing process into the holding container can be started as soon as the initial sub-batch is introduced in the high-shear mixer. Granulation of the second sub-batch is initiated as soon as the granulating bowl is cleaned, again creating a process where sub-batches pass sequentially through the system.

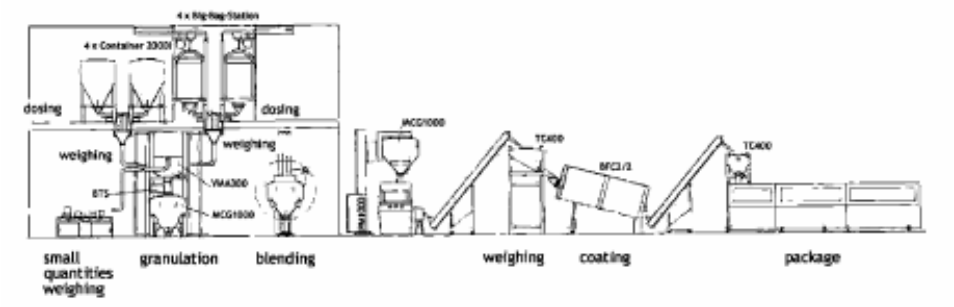


Figure 13: Semi-continuous production line (Bohle concept) (2).

As we can see from the Bohle concept, such an automated dispensing system could be set up in front of the Multicell®, dosing the needed raw materials into the high-shear mixer. After the granulate is tableted, the tablets could then be dispatched into a continuous coater called LeQtracoat® (Phoqus, Kings Hill, England). The benefits of the LeQtracoat® is the fact that there is no drying needed for the coated tablets, as the technique is a dry powder electrostatic tablet coating. The coated tablets could then be transported directly onto the packaging line. As this process is continuous then there is also no coating scale-up needed. The current capacity of the LeQtracoat® is at 75'000 tablets per hour but according to Phoqus, the next generation is in development and should be able to handle 200'000 tablets per hour, which is enough to keep up with most rotary presses (19).

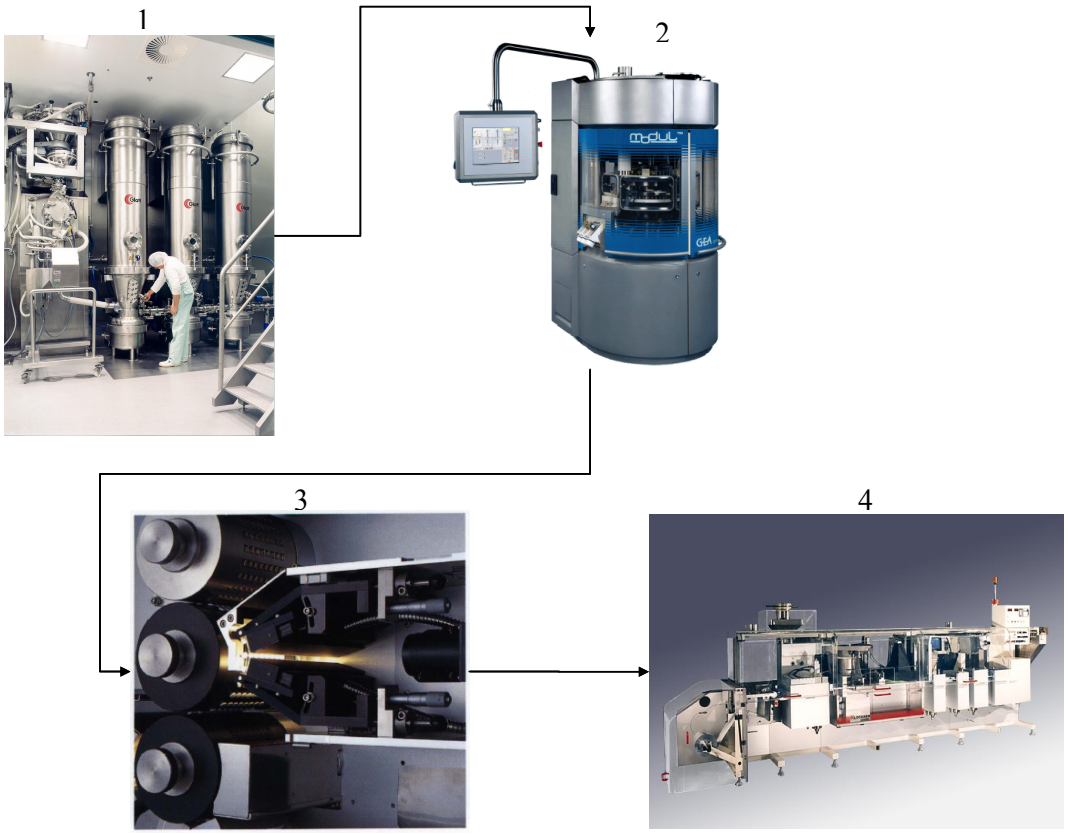


Figure 14: The possible "Line of the Future", featuring 1. the Glatt Multicell®, 2. the Courtoy Modul®, 3. LeQtracoat® and 4. a Klöckner packaging machine.

The line of the future is of course fully controlled by PAT. For the Multicell® one could implement NIR spectrometers on the fluid bed dryers, controlling the moisture

of the drying granulate making sure that the granulate always contains a predefined moisture.

3.3. Conclusion

Above it has been shown that there are many different possibilities for the implementation of continuous granulation but the aspect of a semi-continuous granulation process is the most profitable one as it does not possess the many disadvantages of continuous processes.

The reason why the Multicell® has not established itself yet in the pharmaceutical manufacturing and R&D is the fact that the silo thinking is still prevailing and that the couple of machines which have already been implemented, were only implemented in manufacturing, not taking advantage of the saving potential included in shorter "Time-to-Market". An interesting Stelex survey was published in Pharmaceutical Technology showing that 62% of the respondents believed that PAT could facilitate the implementation of continuous processes into pharmaceutical manufacturing (20). This shows that the awareness for the need of continuous and semi-continuous processes is very high.

It is clear that the new manufacturing process will bring high savings due to a shorter "Time-to-Market" and the ability of tailoring batch sizes to the demands of the marketplace ("just in time" manufacturing) reducing stock. Also this new manufacturing process fulfills ideally the prerequisites of a drug quality system for the twenty-first century and the Food and Drug Administration's Process Analytical Technlogy initiative (21)

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4. Comparison of Rotary Presses and their Simulation by MCC Presster™

4.1. Theory

4.1.1. Definition of a tablet

The word tablet originates from the Latin word tabuletta, a diminutive of tabula which means a board or even a cover of a book. This term, being aimed at the shape, was used for different solid dosage forms such as pills, pastilles and trochisci. The derivated word from Latin does not really fit to the solid dosage forms today as they are mostly cylindrical (1).

Tablets are solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated.
The particles consist of one or more active substances with or without excipients such as diluents, binders, disintegrating agents, glidants, lubricants, substances capable of modifying the behaviour of the preparation in the digestive tract, colouring matter authorised by the competent authority and flavouring substances.
Tablets are usually right, circular solid cylinders, the end surfaces of which are flat or convex and the edges of which may be bevelled. They may have lines or break-marks and may bear a symbol or other markings. Tablets may be coated (2).

4.1.2. History

The undisputed forerunners of the tablet are the pills, pastilles, rotuli, trochisci, morsels, pellets, boli and other shaped dosage forms which were intended for peroral application. The ancient Greece made beadlets called “katapotia” out of bad tasting drugs and the ancient romans made “pilulae”. Later these pills were coated with silver or even gold to cover the bad taste of some drugs which were the forerunners of the dragée. The first tablet came when William Brockedon patented the first manual tablet press. This press compressed with impact without any binders and was dosed

volumetrically. This machine should change the market of solid dosage drugs but this change was very slow. It took a few more decades until the first tableting machine patents were issued in America. 1874 McFerran obtained a patent for machines to produce compressed tablets, 1875 Remington and 1876 Dunton. From the year 1877 the American medical fraternity prescribed tablets more frequently to their patients and the tablet manufacturing started in an industrial manner (3). The advantages of the tablet are such as:

- Possible to manufacture in immense volumes.
- Exact dosing achievable
- Comfortable and safe administration
- As a dry medicament it has a long shelf life
- Easy to store and to transport
- Most of the solid active ingredients can be processed into a tablet
- Controllable release of drug effects
- Taste masking

4.1.3. Compression

During tableting a powder formulation is filled into a die volumetrically and then compressed with the help of punches which immerse into the die. During compression the particles inside the die experience different deformation stages between the tips of the upper- and lower punch tip. The precompression has come to an end when the particles in the die cannot glide past one another any more. During the further immersion of the punches into the die the next stage is reached, i.e. the deformation of the particles. The deformation of the particles starts off as an elastic deformation which is reversible. It increases the force which the punches will have to overcome to immerse further into the die. As the elastic deformation energy barrier has been exceeded by the punches, the irreversible deformation takes place. This point is called the yield pressure, i.e. the force which the material in the die needs to reach plastic deformation. The plastic deformation phase does not increase the needed force for further immersion of the punches into the die. Some brittle materials fracture when this much force is applied therefore brittle material should be avoided

for tablet formulations. Just as highly elastic materials should be avoided as the yield pressure would have to be very high to reach plastic deformation. Cohesive- and adhesive force, solid bond bridges and mechanical clasping are responsible for holding the tablet together after compaction. In order to enable these bonds the contact area of the granulate particles has to be enlarged. During compression the particles are pressed together and so decreasing the porosity of the powder therefore increasing the contact area. The bigger the contact area is, the more bonding points will evolve between the particles.

Crystalline materials show an ordered inner structure in the shape of a crystal lattice. These lattices mostly include some defects which weaken the structure bringing forth a favorable gliding plane. In these gliding planes the particle bonds are formed. Amorphous materials on the other hand do not feature any favorable gliding planes. Therefore their deformation evolves more homogeneous.

Thus it is obvious that the chemical properties of the powder particles are not the only important parameters but also the crystalline structure of the particles. Also very important for the deformation process is the plastic deformation. The plastic deformation is time dependent leading to the conclusion that the compression force will have to hold the pressure for a certain time before the plastic deformation yield pressure has been achieved. Otherwise the deformation will remain elastic and the powder will stay powder instead of turning into a tablet. This means that the tableting process cannot be run as fast as some would like. The production capacity limit is therefore not only determined by the machine capacity but also by the minimal dwell time needed to reach plastic deformation (4).

4.1.4. The Traditional Rotary Press

The compaction on a rotary press takes place with an upper and a lower punch which are respectively pressed towards each other with the help of compression rolls. These punch pairs are placed in a rotating turret along with the dies whereas during one rotation of the turret one pair of punches produce one tablet. The raising and lowering

of the upper and lower punches are mainly done by cams. An additional lowering cam supports tough movements of the upper punches in front of the compression rolls and a lifting cam after the tablet ejection. According to this one rotation of the turret produces as many tablets as the number of punch pairs placed in the turret. This number can vary from one punch up to 73 punch pairs.

The operating method of a traditional rotary press can be described as follows. The turret is turned horizontally and counterclockwise with the help of a gear or a spiral. The upper and lower punches are placed in the guiding cams and are lifted and lowered with their help. The lower punches slide on the lower punch guiding cam until reaching the filling cam where it will be pulled down and the free space in the die will be filled with powder. Moving further the lower punch will be pushed upwards by the adjustable dosing cam and the spare powder will then be scraped off. The lower punch will then be lowered again. During the filling of the die, the upper punch was gliding above the filling station and will now be guided downwards according to the guiding cam and eventually will be pressed into the die by the lowering cam. Both punches will then be moved under the compression rolls and where the punches will be pressed towards each other and make a tablet.

The precompression roll is mostly smaller than the main compression roll or has the same size depending on the type of rotary press. In many cases the precompression roll is beneficial as the powder will be de-aerated and big particle crystals will break, making it easier to consolidate during plastic deformation. One can imagine that a relief of the strain between the pre- and main compression roll and then anew compression under the main compression roll should have positive influence on the crushing strength of the tablets. Generally it can be said that the effect of a precompression roll is highly dependent on the powder formulation.

The upper punch will then be lifted up by the guiding cam removing itself from the tablet in the die. The lower punch will be pushed up by the ejection cam and will eject the tablet upwards. The tablet will then be scraped off the die table by the tablet scraper and slides down from the die table across a chute into a container. The upper punch will then be lifted further until it reaches its highest position and reaches the

filling station. At the same time the lower punch will be pulled down by the guiding cam and will reaches the filling station and the cycle starts again.

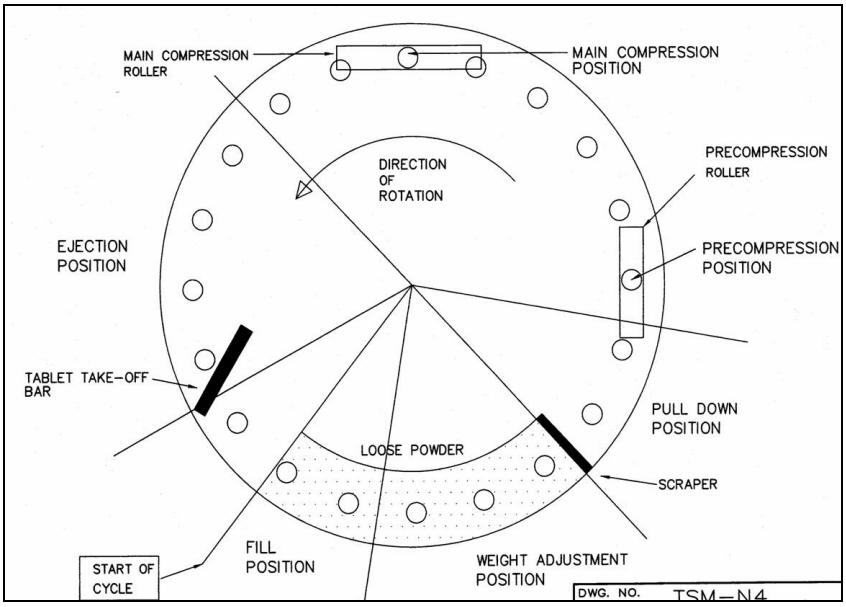


Figure 1: Top view of a tablet press cycle

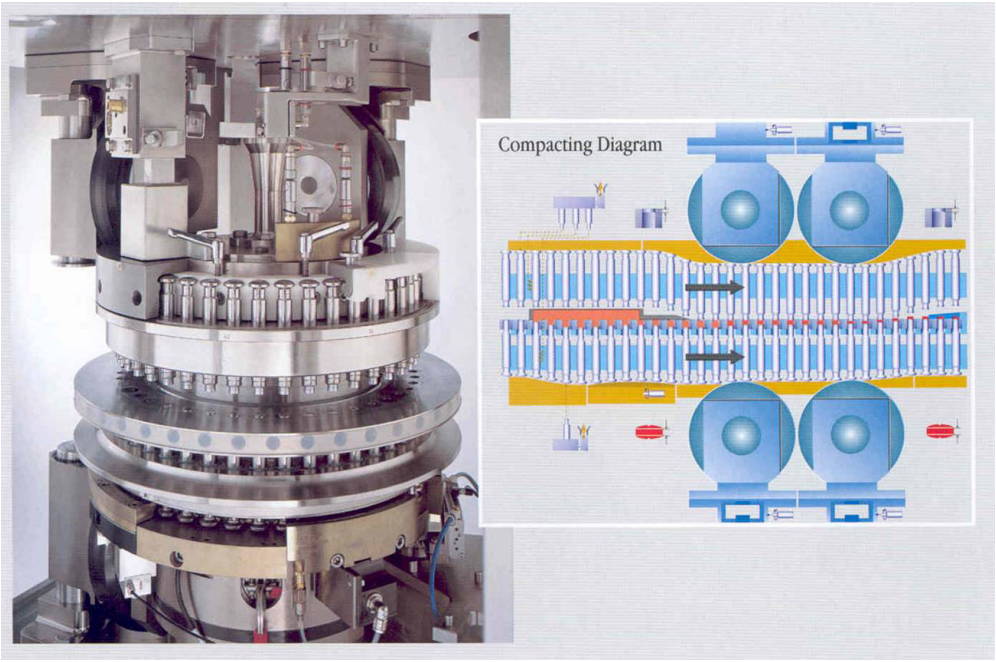


Figure 2: The turret of a Fette 2090® and a schematic illustration of the function of a rotary press.

4.1.5. Tablet Press Instrumentation

In order to monitor and control a rotary press, certain sensors must be placed at certain locations on the machine. These sensors are called transducers. A Transducer is a device that converts signals from one form to another. Rotary press transducers typically measure applied force, turret speed, or punch position. In order to be able to use the signals coming from the transducers they will have to be amplified and then converted to digital form in order to be processed by a data acquisition system.

Nowadays the preferred way of instrumenting rotary presses is with strain gages. Strain gages are foil, wire, or semiconductor devices which convert pressure or force into electrical voltage. When a thin wire is applied with stress it will become longer and thinner. These two factors lead to a higher electrical resistance. If an electrical current is sent through this wire, it will be affected by the change in the resistance of the conduit. This principle is used in strain gage-based transducers. Foil gages, known for robust application range, useful nominal resistance and reliable sensitivity control are most commonly used for instrumentation of compression, precompression and ejection forces. Semi-conductor-based strain gages are inherently more sensitive but suffer from high electrical noise and temperature sensitivity. Such gages are not commonly used in tablet press instrumentation except for measurements of die-wall pressure and take-off forces.

In order to ensure signal balancing of the strain gages the strain gages are arranged in a special way which is called a Wheatstone bridge. The “full” bridge is composed of two pairs of resistors in a circle with two parallel branches used for input ant two for signal output. By applying the so-called excitation voltage, which is typically 10V DC, to the bridge input and changing the resistance of different “legs” of the bridge by adding special resistors, we can make sure tat there is a zero output voltage when no load is applied to the transducers. This is called zero balance.

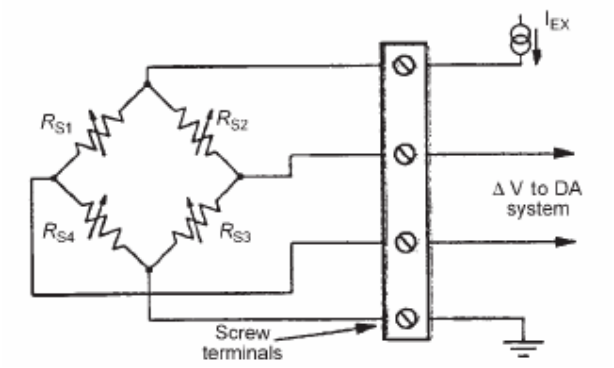


Figure 3: A typical Wheatstone bridge arrangement of strain gages.

Once the bridge is balanced, a small perturbation in the resistance of any "leg" of the bridge results in a nonzero signal output. The output of the Wheatstone bridge is normally expressed in millivolts per volt of excitation per unit of applied force. E.g. the a sensitivity of 0.2mV/V/kN means that applying 10kN force and 10V excitation will produce 20mV output. To utilize such output it usually needs to be amplified several hundred times to reach units of volts.

Another important function of the Wheatstone bridge is balancing of temperature effects. Although individual strain gages are sensitive to temperature fluctuations, the Wheatstone bridge arrangement provides for temperature sensitivity compensation, so that the resulting transducer is no longer changing its output to any significant degree when it heats up.

In a typical bending beam application (such as compression roll transducer), one side of the beam experiences tension while the other side undergoes compression. By mounting two gages on each side the sensitivity of the transducer can be doubled.

During research and development the measured compression force is usually compared to the actual position of the punch in the die. For these purposes the Linear Variable Differential Transformer (LVDT) can be used. LVDT is a device that produces voltage proportional to the position of a core rod inside a cylinder body. It measures displacement or a position of an object relative to some predefined zero location. On tablet presses, LVDT's are used to measure punch displacement and in-die thickness. They generally have very high precision and accuracy.

Figure 4: Linear Variable Differential Transformer (LVDT).

In a production environment, typical tablet weight control mechanism is driven by signals that are coming from a compression force transducer. Strain gages may be installed on a column connecting the upper and lower compression wheel assemblies. This transducer measures what is generally known as main compression, i.e. a diluted average of the forces acting on the upper and lower punches.

As described above, the punches are guided under the pre- and main compression rolls. As the positions of the rolls are fixed during compression, the force measured during compression depends on the amount of powder in the die. The more powder in the die the higher the compression force measured. This fact is utilized for the tablet weight controls during production.

With the help of the measured force at each position of the punches a force versus time diagram can be created. In these diagrams the dwell time can be determined by measuring the length of time in which the force curve is above 90% of the peak force.

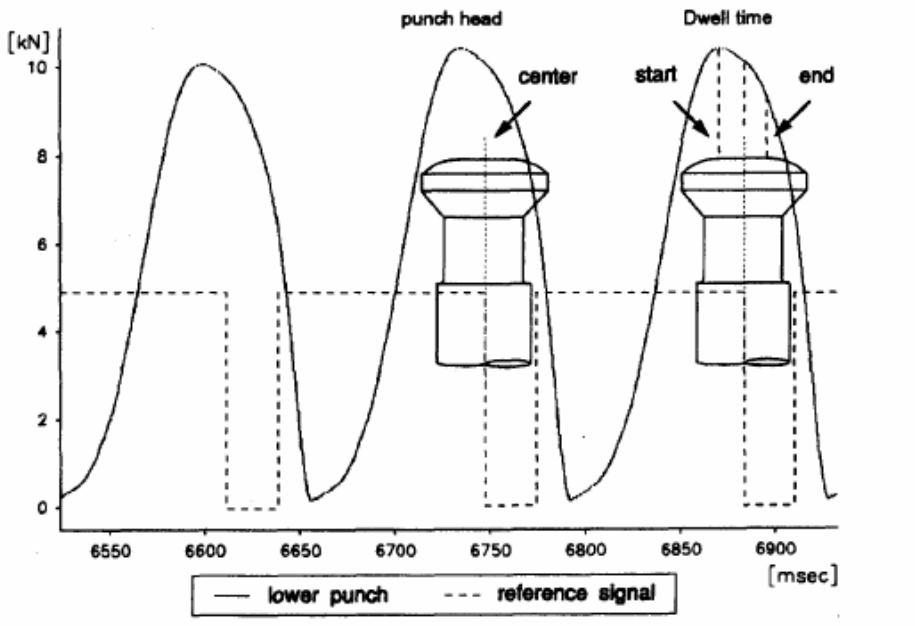


Figure 5: Force signal of the lower punch and reference signal indicating the mid of the punch head under the compression roller. The Dwell time is shown on the right side of the figure (5).

4.1.6. Displacement (Courtoy)

Tablet weight control using "displacement" is based on the measurement of thickness variations under constant force and is measured at precompression. This measurement is possible when using the so-called "pneumatic compensator".

The displacement-tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system's sensitivity does not depend on the operating point on the graph (i.e. it does not depend on the tablet weight) but depends on the applied precompression force. In fact, the lower the precompression force, the more sensitive the monitoring/control system.

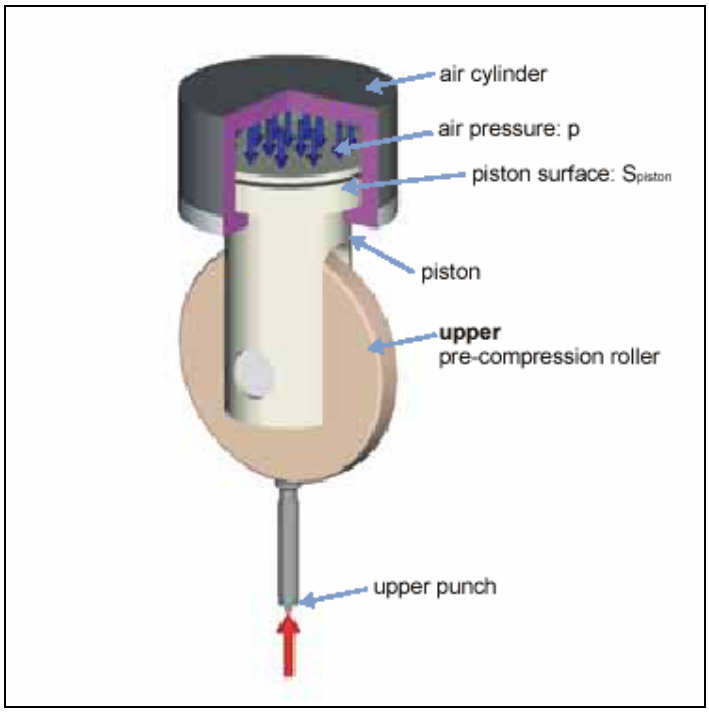


Figure 6: The pneumatic compensator

As indicated in the above drawing, the upper precompression roller is attached to an air-piston, which can move up/down in an air-cylinder. The air pressure [p] in the cylinder is set as a product parameter at initial product set-up and is kept at a constant value by the machine's control system. This pressure [p] multiplied by the piston surface [S_{piston}] is the constant force at which the piston – and consequently the roller – is pushed downwards against a fixed stop. The lower precompression roller is mounted on a yoke and its vertical position can be adjusted through the control system by means of a servomotor. The position of the lower precompression roller determines the precompression height. At every precompression, the upper punch hits the upper roller and is initially pushed downwards into the die. As the lower punch is pushed upwards by the lower roller, the powder is being compressed, while the exerted compression force increases. At a certain point (depending on set air pressure, precompression height and powder characteristics) the reaction force exerted by the powder on the upper punch equals the force exerted by the air pressure on the piston. The punch has to continue its way under the roller, because the turret is spinning. As the piston/roller precompression assembly cannot exert a force above

Equation 1

$$F_{\max} = p \times S_{piston}$$

no further compression of powder is possible. The upper punch will push the upper precompression roller assembly up and continue its way under the roller. In fact, the top punch, powder slug between punches and bottom punch will move together, following the bottom precompression roller. During this movement, there is no further compression and the top precompression roller will move up and back down. During the time the upper roller makes this up/down movement, the compression force on the punch – and therefore on the powder – remains constant and is equal to F_{max}. An LVDT position sensor accurately measures the movement of the upper roller assembly. This vertical movement will reach its maximum value when the punch is right under the centre of the roller. This maximum value is registered by the control system and is called the "displacement". The displacement is measured and recorded at the precompression section of the Courtoy.

It is easy to understand that

Equation 2

$$W = \rho \times S \times [height\_of\_the\_precompressed\_slug]$$

Equation 3

$$W = \rho \times S \times [PCH + (2 \times EqAr) + d)]$$

- W is the weight of the pre-compressed powder slug, and therefore also the first layer/final tablet weight
- ρ is the density of the pre-compressed powder slug (i.e. NOT the powder bulk density and not the final tablet density, but the density of the slug after pre-compression and prior to main compression)
- S is the surface area of the die opening

- PCH is the Precompression height measured as the distance between the 2 extreme tips of upper and lower punch when the punches are right under the centre of the rollers and the upper-roller is in its lowest position
- EqAr is the "equivalent arrow", a correction factor taking into account the concave part of the punch tips
- d is the displacement.

This can be re-formulated as follows:

Equation 4

$$W = \rho \times S \times \left[PCH + \left(2 \times EqAr\right)\right] + \rho \times S \times d$$

where the following conditions apply:

- ρ is constant from tablet to tablet as the pre-compression force on each slug is the same: F_{max}. All powder slugs are pre-compressed to the same density, thanks to the use of the air compensator.
- S is constant, depending only on tablet size
- The precompression height PCH is constant as long as the lower pre-compression roller is not moved
- EqAr is constant as it depends only on the punch tip shape

resulting in

Equation 5

$$W = A + B \times d$$

Equation 6

$$A = \rho \times S \times \left[PCH + \left(2 \times EqAr\right)\right] = Const.$$

Equation 7

$$B = \rho \times S = Const.$$

The relation between what is measured (the displacement) and what needs to be controlled (tablet weight) is a linear relationship. This linear relationship makes the control algorithm very simple. Yet at the same time very accurate.

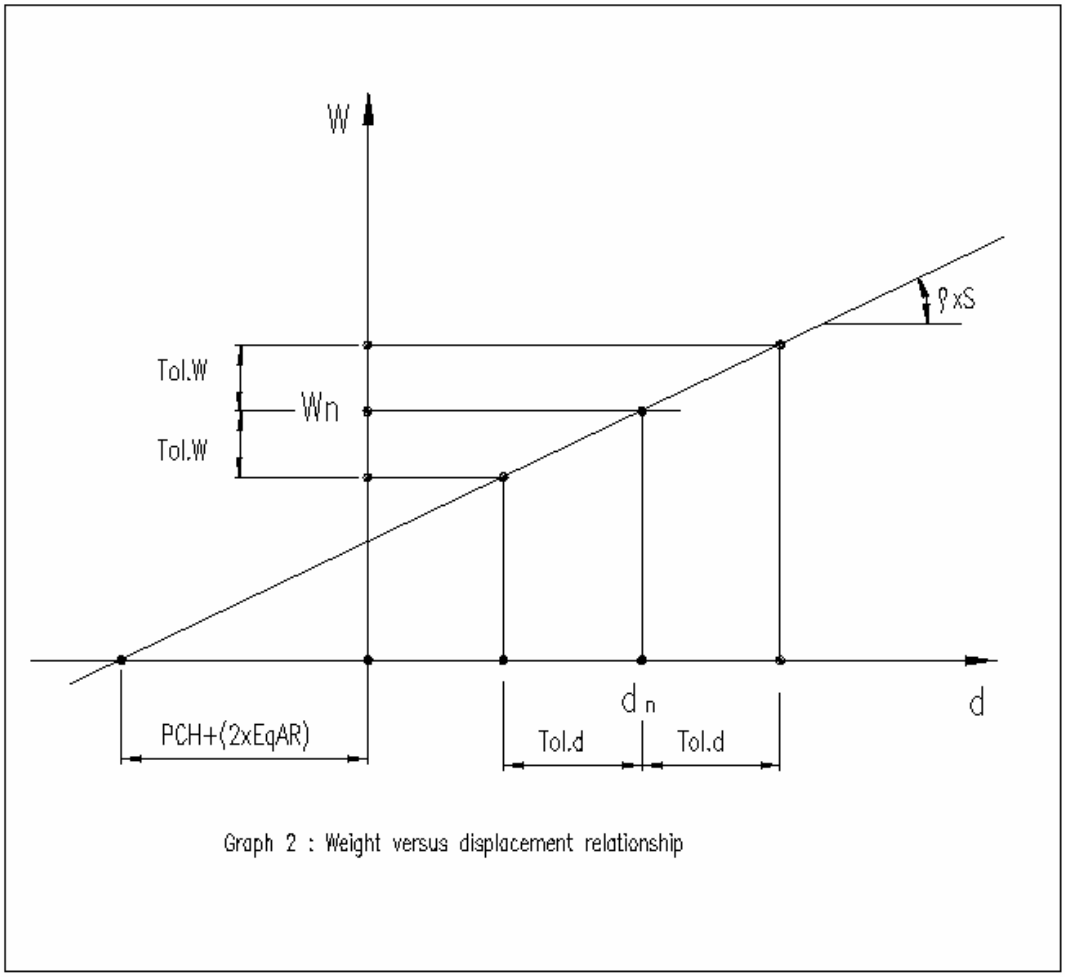


Figure 7: The linear weight versus displacement relationship.

The above graph clearly shows the relationship between W and d, but also clearly indicates the influence of the other parameters ρ, S, PCH and EqAr. One of the important advantages of the "displacement control" system is the automatic calculation of the tolerance. If the allowable tolerance on the weight is for example

3%, it will correspond to an allowable displacement tolerance of 3% on [PCH + (2 x EqAr) + d]. As PCH and EqAr are known at any moment, the tolerance on d can easily be calculated. Important to note is that the tolerance on the measured signal (being the displacement d) is independent from the operating point on the weight-versus-displacement graph. This is not the case with a compression force-controlled system, where the tolerance on the force varies with the working point on the graph. Moreover the upper and lower force tolerances are different, as can be seen from the graph below.

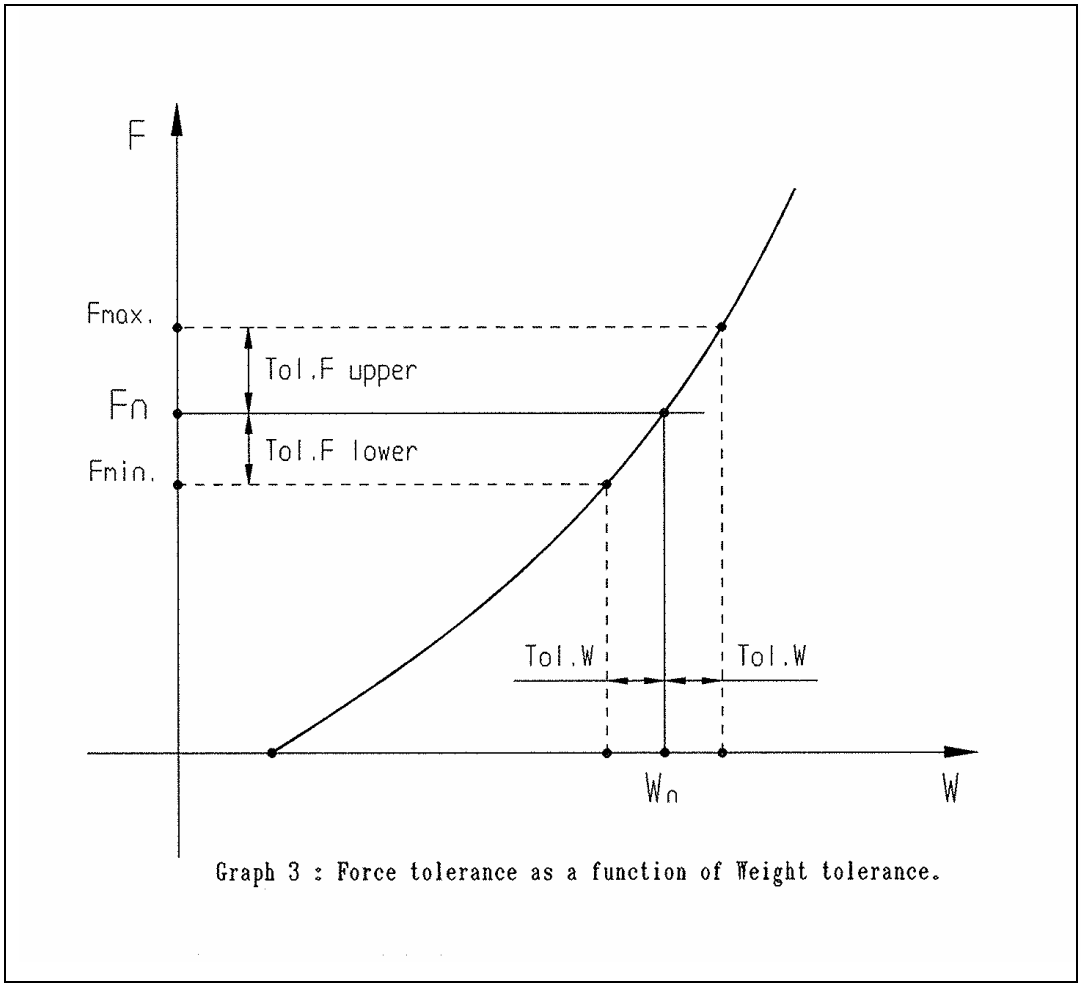


Figure 8: Force tolerance as a function of weight tolerance.

Another important advantage of the "displacement" control system is its independence from the machine's stiffness. As the displacement is measured at precompression under relatively low compression forces (typically between 1 and 3

kN), the deformation of the press is negligible. This is entirely different in case of a compression force control system, which measures the actual compression force at main compression, where forces can go up to 100 kN. As no 2 compression machines have the same stiffness (stiffness of individual parts and stiffness of joints can never be exactly the same), variations in the force-versus-weight characteristic of any 2 machines – even of the same model – are inevitable. The graph below illustrates that with the same compression force set point and same set distance between compression rollers, the weaker machine exhibits more deformation, resulting in a thicker (i.e. heavier) tablet. This means that for the same tablet weight and final compression height, the weaker machine will have to run at a lower compression force set point, resulting in tablets with lower crushing strength. Moreover, the variation in force / tablet weight varies with the rigidity of the complete system (i.e. tablet + tablet press), resulting in different force tolerance limits between various machines for the same tablet weight tolerance. It is clear that, in case of compression force control, simple transfer of force set point, force tolerance limits and compression height (i.e. distance between main compression rollers) is impossible, requiring parameter set-up per product and per machine.

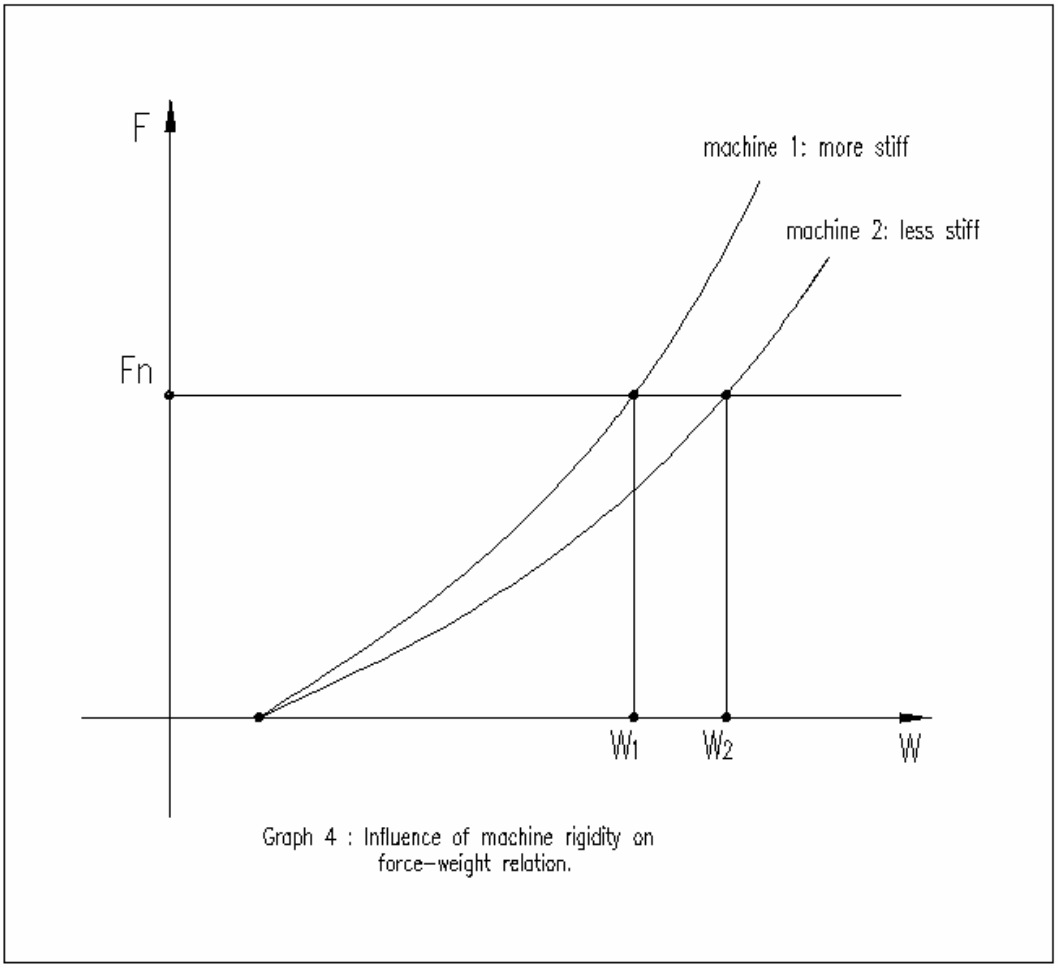


Figure 9: Influence of machine rigidity on force – weight relation.

The stiffness-independence of the "displacement" control system makes production exchange between displacement-controlled presses much easier, allows for more straightforward product scale-up, more flexible production, easier production transfer between different sites in case of a multinational pharmaceutical company.

The use of an air compensator has the additional and important advantage of an increased and controlled dwell time during precompression. In fact, during the up- and downward movement of the upper precompression roller, the compression force remains constant. As the dwell time is defined as the time during which compression force is above 90% of its peak value, the dwell time will be extended by the longer flat part in the compression profile shown in the graph below.

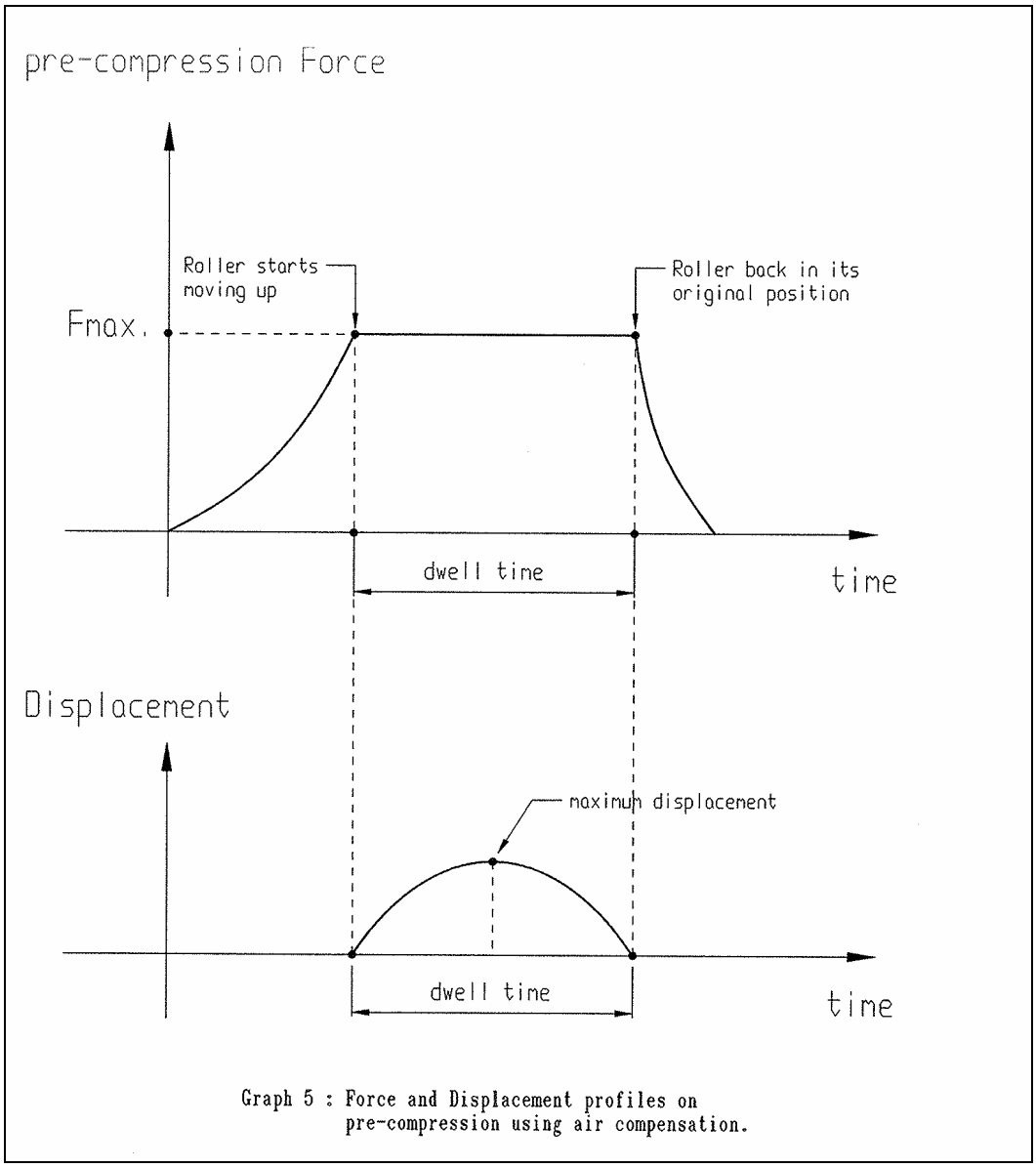


Figure 10: Force and displacement profiles on precompression using air compensation.

If the precompression height PCH is reduced by raising the lower compression roller, the point of initial contact and the point at which the upper roller starts moving up, will move to the left. This results in an increase in displacement, but also in a longer dwell time. A longer dwell time in turn improves the de-aeration of the powder and the re-arrangement of the granules in the die prior to the final compression. These two factors increase the crushing strength of the tablets considerably and prevent potential capping problems. The PCH and precompression force can be set up so as to offer

optimal dwell time. Once fixed, the control system automatically calculates and sets the tolerance on the displacement as a function of weight tolerance (6).

4.1.7. Scale-up in tableting

Scale-up is generally defined as the process of increasing the batch size. Scale-up of a process can also be viewed as a procedure for applying the same process to different output volumes. There is a subtle difference between these two definitions: batch size enlargement does not always translate into a size increase of the processing volume. E.g. for the tableting process, a scale-up simply means enlarging the output by increasing the speed.

In tableting applications, the process scale-up involves different speeds of production in what is essentially the same unit volume (die cavity in which the compaction takes place). However there are still kinematic and dynamic parameters that need to be investigated and matched for any process transfer. One of the main practical questions facing tablet formulators during development and scale-up is whether a particular formulation will sustain the required high rate of compression force application in a production press without lamination or capping. Usually, such questions are never answered with sufficient credibility, especially when only a small amount of material is available and any trial-and-error approach may result in costly mistakes along the scale-up path. As tablet formulations are moved from small-scale research presses to high speed machines, potential scale-u problems can be eliminated by simulation of production conditions in the formulation development lab. In any process transfer from one tablet press to another, one may aim to preserve mechanical properties of a tablet (density and, by extension, energy used to obtain it) as well as its bioavailability (e.g. dissolution that may be affected by porosity). A scientifically sound approach would be to use the results of the dimensional analysis to model a particular production environment. Studies done on a class of equipment generally known as compaction simulators or tablet press replicators can be designed to facilitate the scale-up of tableting process by matching several major factors, such as compression force and rate of its application (punch velocity and displacement), in their dimensionless equivalent form (7).

The only real test to determine that the scale-up batch will run well on the selected rotary press in production is a "use test", i.e. the batch must be run on the rotary press in question. The most important characteristics of the powder formulation to be compacted are particle size and particle size distribution, density and /or porosity, powder flow, cohesiveness and lubrication. The one consideration to keep in mind during scale-up is the speed of the press, which will directly affect the time available for the die filling to occur and the available time for plastic deformation. Only high-speed compaction simulators or other equipment that controls dwell time will give any indication of potential problems with high-speed rotary presses. The most important material properties to the compaction operation are elastic deformation behavior, plastic deformation behavior and viscoelastic properties which are the mechanisms of deformation. We remember, elastic deformation is a reversible process but plastic deformation and brittle fracture are not. More importantly, plastic deformation and viscoelastic behavior are kinetic phenomena, i.e. time is important and they can be affected by press speed.

The effect of the rotary press speed on the powder formulation is of primary concern in tableting scale-up. Whether the product development work was performed on a single-stroke press or a smaller rotary press, the objective in operation will be to increase efficiency, in this case the tablet output rate and thus the speed of the rotary press. For material that deforms exclusively by brittle fracture, there will be no concern. Materials that exhibit plastic deformation, which is a kinetic phenomenon, do exhibit speed sensitivity. The usual parameter indication is that target tablet crushing strength cannot be achieved at the faster rotary press speed. Sometimes slowing the rotary press down is the only option for the operator of the rotary press to correct the problem.

No matter what type of tablet press was used in research and development or in the pilot plant, there is no possible way to experience the phenomenon on a full-size batch and the associated time of the compaction run. There are several problems which can be expected such as build-up of heat due to the length of the operation of the press. This temperature increase could have effects on the stability of the active compound or even have softening effects on any low melting ingredients.

As explained above, the two major elements in the formation of a tablet are the forces applied to the blend and the length of time those forces are applied. This time is also called the dwell time and is the time in which the flat portion of the punch head is in contact with the compression roll. Dwell times significantly differ upon scale-up. Dwell times are also different between different manufacturing presses which could even be in the same production area. The dwell times on typical development presses run from 80 to 500msec. Manufacturing scale rotary presses reach dwell times down to 4msec per compaction event. So basically it is obvious that these differences between the development presses and the manufacturing presses can result in scale-up nightmares, leading to capping, lamination and die binding (8).

4.2. Introduction

There are many different kinds of rotary press manufacturers on the market today and all state that their presses produce the best available quality of tablets on the market. Most of the rotary presses on the market are based on the same concept, having a precompression- and a main compression roll. These rolls are generally monitored with a force control, controlling the weight of the tablets. The concept of filling the dies is also generally the same, having a feeding mechanism filling the dies from above, requiring the powder to have good flowing properties if the machine should run with high speed.

Three different rotary presses were tested on their performance with 2 different routine production formulations. The products to run on the different rotary presses were picked out according to their properties. There was one “trouble-free” product and one “worst case” product based on previous experience in manufacturing.

The three different rotary presses were selected, trying to keep them as different from each other as possible, concerning their tableting concept. The following three presses were selected.
The Fette 2090®, representing the usual concept of compression rolls monitoring and feeding mechanism,
the IMA Comprima 300®, representing a new concept of die feeding which feeds the dies sideways with the help of centrifugal force and the Courtoy Modul®, representing

a new concept for the compression rolls whereas the tablet weight is controlled using "displacement" of the pneumatic precompression roll and thereby prolonging the dwell time during precompression.

The results with these two products on the different presses were simulated on the MCC Presster™. The MCC Presster™ is a rotary press simulator which is able to simulate most rotary press type on the market based on compression force and dwell time. It is a high speed single station tablet press which replicates the rotary tablet presses linearly. Production press parameters and output speed are selected from a database and the appropriate tooling and compression rolls are installed into the MCC Presster™.

Based on the speed at which the different rotary presses were running on, during their performance trials, the MCC Presster™ was set up to simulate their respective dwell times and as close as possible to their production parameters. Most importantly the punch gap during precompression and main compression was simulated as it could be that the force measurements vary between presses. The tablets gained from these simulation runs were then inspected on crushing strength, disintegration and dissolution profile and these compared to the produced tablets on the respective rotary press.

The object of this work was to determine if the Presster™ is capable of preventing scale-up problems which occur when moving a formulation from lab scale or pilot scale onto manufacturing scale rotary presses.

4.3. Materials and Methods

As mentioned above, the formulations used for these comparison tests are routine production formulations. The ingredients are listed in Table 1.

	Product A, "trouble-free"	Product B, "worst case"
Excipients	**Hydroxypropyl-methyl-cellulose** **Poloxalkol** **Lactose monohydrate** **Polyvinylpolypyrrolidon** **Glyceryl monostearate** **Polyethylene glycol 4000**	**Avicel PH 102** **Polyvinylpolypyrrolidon** **Aerosil** **Magnesiumstearate**
Active Pharmaceutical Ingredient (API)	**a**	**b** **c**
Granulation	**Wet granulation**	**Dry granulation**

Table 1

4.3.1. Powder Evaluation

4.3.1.1.Particle Size Distribution

The particle size distribution is an important parameter for predicting the flowing properties and behavior of powders. Important parameters of the powder particles are the general size of the particles and their shape. Having a homogeneous particle size is very important as otherwise a segregation of the different powder ingredients is for sure, leading to a problem in content uniformity of the tablets. Another important parameter is the shape, as the particle size distribution can be homogeneous but with needle shaped particles, making the flowing properties poor (9).

The particle size and its distribution for the Presster™ powder samples were determined gravimetrically on a Retsch AS 200 Control (Retsch GmbH & Co. KG, Haan, Germany). Approximately 50g of powder was used for each measurement. The sieving duration was set at 5 minutes, the amplitude was set at 1mm and the vibration intervals lasted 10 seconds.

4.3.1.2.Density

The bulk and tap density of the two formulations was determined with a JEL STAV 2003 Stampfvolumeter (JEL Präzisionswerkzeuge, Stuttgart, Germany). Bulk density was determined after filling 100g of the powder formulation into a measuring cylinder and reading the volume of the powder from the cylinder. The bulk density represents the state in which the powder formulation is during powder flow. Generally the particles lie inordinate besides one another and do not show any preferred orientation. With mechanical vibration it is possible to carry enough energy onto the particles that they will overwhelm the inter-particular friction and settle into a higher orientation. With higher orientation of the particles, the powder cylinder will drop and indicate the tap density (10). Tap density was determined by tapping the measuring cylinder 1250 times two times in a row and determining the volume of the powder cylinder. If the volume of the powder cylinder did not sink more than $2cm^3$ after the second 1250 times the first value will be used. If the powder volume sank more than $2cm^3$ after the second 1250 times the measurement will have to be repeated. Having determined these parameters it is possible to calculate the Hausner ratio (HR) using

Equation 8

$$HR = \frac{Tap - density\left[g/ml\right]}{Bulk - density\left[g/ml\right]}$$

The Hausner ratio can be used to determine the compaction tendency of a powder formulation which is important for transportation and the tableting process. The Hausner ratio should not exceed 1,20 as the powder formulation tends to sink in volume and consolidate, thereby deteriorating the flowing properties of the powder formulation.

The true density of each powder formulation was determined with a helium pycnometer (AccuPyc 1330, Micrometitics Instrument Inc., Norcross, GA, USA). The experimental sample was accurately weighed and loaded into the sample cell. The sample volume was computed by measurements of the pressure observed by filling the sample chamber with ultra-high pure helium gas followed by discharging the gas into a second empty chamber. The measurements were repeated for 5 such cycles.

4.3.1.3.Flowing Properties

In order to determine the flowability of a granulate formulation a funnel was used according to the flowability test method 2.9.16 from the Ph. Eur. (11). The powder flow determination was repeated three times and the mean value of the results was determined.

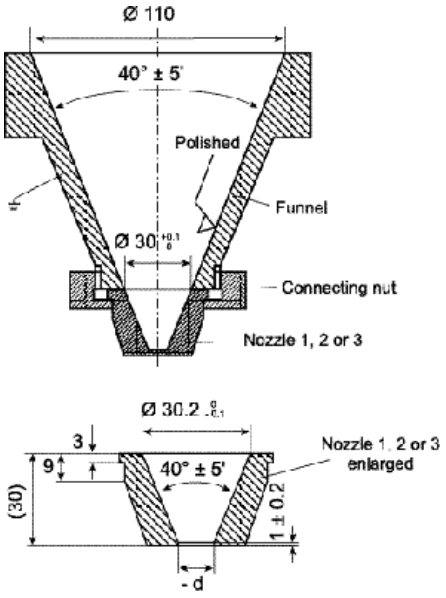


Figure 11: Flow funnel and nozzle. Dimensions are in millimeters.

4.3.2. Compact Preparation and Evaluation

4.3.2.1.Compression

The following three rotary presses were tested with the products A and B, whereas the Fette 2090® is used for routine production of these products, having the highest experience. The other two, IMA Comprima 300® and Courtoy Modul® were tested at their respective manufacturing site.

The tests were started at a slow speed, i.e. a long dwell time and gradually speeded up to a shorter dwell time. During production, samples were taken at each achieved dwell time and evenly throughout the test. These samples were then tested on

crushing strength, disintegration, content uniformity and dissolution rate (only Fette 2090®) as these parameters are the most common ones to change during a scale-up procedure or a transfer from one rotary press to another even though the production parameters are kept constant.

The dwell time was calculated using

Equation 9

$$Dwelltime\left[m\sec\right] = \frac{L \times NP \times 3600000}{\pi \times PCD \times TPH}$$

Whereas:
L = Flat portion of the punch head
NP = Number of Punches
π = 3.141
PCD = Pitch Circle Diameter
TBL/H = Tablets per Hour

These achieved dwell times were then set up on the MCC Presster™ along with all other parameters such as the size of the compression rolls, punch gap during maximum compression and the corresponding compression tooling.

Fette 2090®: As mentioned above, the Fette 2090® (Fette GmbH, Schwarzenbek, Germany) is used for routine production of products A and B. The Fette 2090® is a 43 station rotary tablet press equipped with EU B-Tooling for these tests. The punch gap during the production of the sampled batches is mentioned below.

Product A punch gap:	Pre Co. 2.3mm / Main Co. 1.9mm
Product B punch gap:	Pre Co. 2.5mm / Main Co. 1.1mm

Product A routine tooling: 7mm, round, flat, beveled edge.

Product B routine tooling: 10 x 5.2mm, oval, convex.

Product A tablet parameters: 128mg weight, 3mm thickness, 50N crushing strength

Product B tablet parameters: 150mg weight, 3.6mm thickness, 100N crushing strength

For the dwell time calculation, the following values are needed:

Flat portion of the punch head	= 9.65mm
Number of punches	= 43
Pitch circle diameter	= 410mm

The diameter of the Pre – and Main Compression rolls are both 250mm. In figure 1 the respective dwell times can be observed for the Fette 2090®.

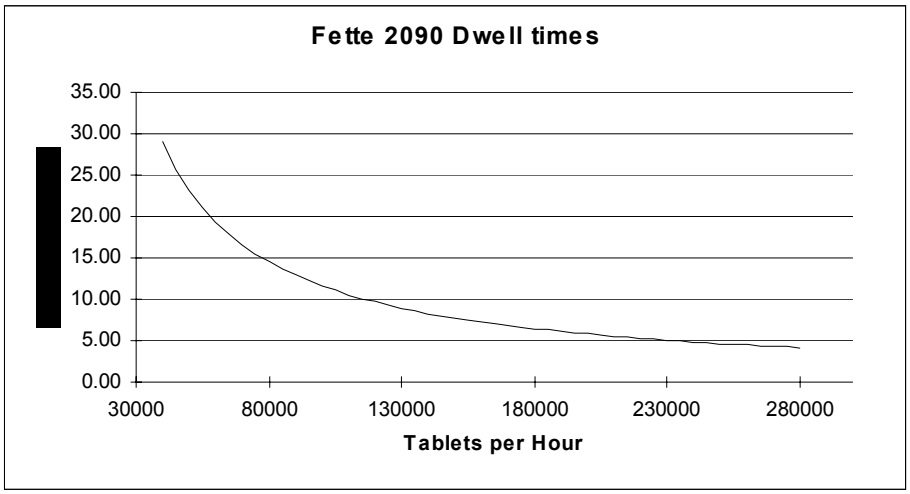


Figure 12: Showing the correlation between tableting speed and dwell time for the Fette 2090®.

IMA Comprima 300®: A performance test was done on the IMA Comprima 300® (IMA Industria Macchine Automatiche S.p.A, Bologna, Italy), a 36 station rotary tablet press equipped with special IMA compression tooling. This rotary press is representing a completely new tableting

technology principle. Filling of the dies by centrifugal force from inside the turret requires dies with a special lateral opening, as powder is located in the centre of a rotating die table and piped to dies through holes. Also the tablets are ejected downwards instead of upwards as is normal with the traditional rotary presses. There is a complete separation of lubrication and product area and an automatic Cleaning-In-Place (CIP) system. These are the most remarkable characteristics of the innovation tablet press IMA Comprima 300®.
Theoretically the filling of the dies should occur more accurately the faster the turret spins and so leading to lower standard deviations of tablet weight.
The CIP should enable a fully automatic cleaning during change-over with only one person in about 4 hours, instead of up to three persons for standard rotary presses (12).
Due to the innovative centrifugal die filling system the yield of the IMA Comprima® is exceptional. Where standard technology rotary presses loose a lot of powder due to the dust suction from the die table, the IMA Comprima® does not loose any powder due to the centrifugal filling.

The routine powder formulations were also transferred to the test site, 50kg respectively for product A and B. The IMA Comprima 300® is equipped with different kinds of punches than the usual EU B-Tooling. The IMA Comprima 300® punch shafts are permanently attached to the turret and only the punch tips are exchangeable. Therefore the standard tooling could not be installed and the punch tips available at IMA, which were the closest to the standard tooling, had to be used.

Product A punch gap: Pre Co. 2.0mm / Main Co. 1.4mm
Product B punch gap: Pre Co. 3.1mm / Main Co. 2.4mm

Product A alternative tooling: 7mm, round, convex.
Product B alternative tooling: 10 x 4mm, oval, convex.

Product A tablet parameters: 128mg weight, 3.5mm thickness, 50N crushing strength
Product B tablet parameters: 150mg weight, 4.1mm thickness, 100N crushing strength

For the dwell time calculation, the following values are needed:

Flat portion of the punch head	= 25mm
Number of punches	= 36
Pitch circle diameter	= 437mm

The diameter of the Pre – and Main Compression rolls are respectively 140mm and 300mm. In figure 2 the dwell times can be observed for IMA Comprima 300®.

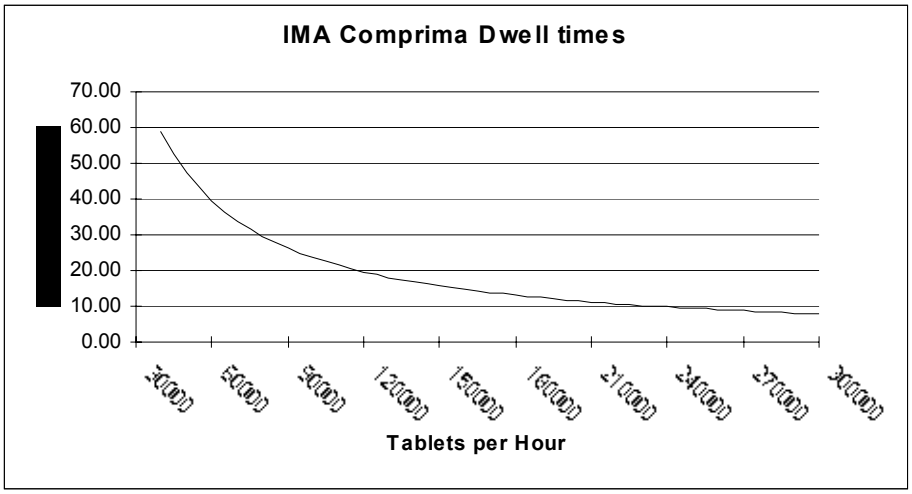


Figure 13: Showing the correlation between tableting speed and dwell time for the IMA Comprima 300®.

Courtoy Modul®: A performance test was done on the Courtoy Modul® (Courtoy nv, Halle, Belgium), a 38 station rotary tablet press equipped with EU B-Tooling. The Courtoy Modul® has, different to the standard rotary press, a displacement tablet weight control instead of the traditional compression force weight control. This approach is not dependent on the tablet weight but rather on the applied force. Another "irregularity" to the standard rotary press is the fast change-over concept which the Courtoy Modul® has to offer. This concept should enable a change-over in as little as one hour with one person. This is possible due to an Exchangeable dust-tight Compression Module (ECM) which can be built out of the manufacturing-press and a ready second module can be built in and production can

start again. This requires that the ECM will not be opened during production, otherwise the room will have to be cleaned as well.

The respective routine compression tooling for product A and B were installed into the Courtoy Modul®.

Product A punch gap:	Pre Co. 2.3mm / Main Co. 1.7mm
Product B punch gap:	Unknown

Product A routine tooling:	7mm, round, flat, beveled edge.
Product B routine tooling:	14 x 5.2mm, oval, convex.

The routine powder formulations were also transferred to the test site, 50kg respectively for product A and B. The Courtoy Modul® was set up according to the requested tablet parameters.

Product A tablet parameters:	128mg weight, 3mm thickness, 50N crushing strength
Product B tablet parameters:	150mg weight, 3.6mm thickness, 100N crushing strength

For the dwell time calculation, the following values are needed:

Flat portion of the punch head	= 9.65mm
Number of punches	= 38
Pitch circle diameter	= 425mm

The diameter of the Pre – and Main Compression rolls are both 240mm. In figure 3 the dwell times can be observed for Courtoy Modul®.

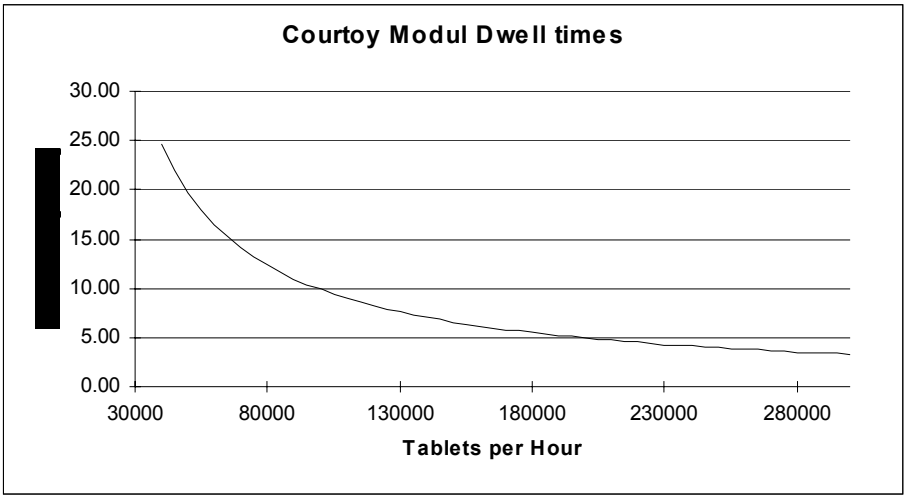


Figure 14: Showing the correlation between tableting speed and dwell time for the Courtoy Modul®.

MCC Presster™: A single-station development tablet press which reproduces the dwell time of manufacturing-scale tablet presses. The Presster™ (Metropolitian computing corporation, East Hanover NJ, USA) can be set up to match the rate, roll wheel configuration and tooling of many manufacturing-scale tablet presses. This enables developers to eliminate compaction rate as a variable upon scale-up. As described above, the three different manufacturing presses contain different pre- and main compression rolls. The corresponding roll sizes were installed previous to the simulations of the different manufacturing presses. Also the corresponding compression tooling for each of the routine production formulations were installed previous to simulation. After setting up the correct parameters and the corresponding rolls and compression tooling the simulation started with the longest dwell time used during the performance test of the manufacturing press. The granulate of the routine production formulation was filled by hand into the die, after weighing the correct amount. After producing thirty tablets for every dwell time, ten tablets were directly tested on crushing strength and thickness. The rest of the tablets were set aside for other tests such as disintegration and dissolution.

4.3.2.2.Crushing strength

The crushing strength is one of the most important tablet properties to be observed during development and scale-up. The crushing strength is a function of the

compaction force and is related to the disintegration and dissolution rate. The crushing strength is also dependent on the rotary press speed, i.e. the dwell time, which makes it very important to observe the effects of speed on the crushing strength of the tablet during development and eventually scale-up.

The crushing strength of the produced tablets was determined be compressing the tablet between two jaws which crushed the tablet. The machine measures the force which is applied to the tablet and detects when it fractures. For these crushing strength tests the Schleuniger Tablet Tester 8M (Dr. Schleuniger Pharmatron AG, Solothurn, Switzerland) was used.

4.3.2.3.F-Test and t-test

In order to evaluate the results of the comparison between the crushing strength of the tablets from the manufacturing presses and from the Presster™ an F-test and a t-test were performed.

The F-test tests if the difference between two different standard deviations from two independent data series is significant or just a coincidence. For the actual test the probability of error value α was chosen with 5%. I.e. hypothesis H_0 says with a probability of error of 5% that the standard deviations of the two data series differentiate coincidentally.

Equation 10

$$F_b = \frac{s_1^2}{s_2^2}$$
$$s_1^2 > s_2^2$$

s_1 and s_2 are the standard deviations from the two different crushing strength data series with n_1 and n_2 amount of samples. The degree of freedom f is then determined with

Equation 11 a / b

$$f_1 = n_1 - 1$$
$$f_2 = n_2 - 1$$

F-test H_0 is true if

Equation 12

$$F_b < F_t(\alpha, f_1, f_2)$$

Whereas F_b is the calculated F value, F_t is the value estimated from the table, depending on α, f_1 and f_2. H_0 is false if

Equation 13

$$F_b > F_t(\alpha, f_1, f_2)$$

If the compared standard deviations do not differentiate according to the F-test, then that is called a homogeneous variance. In that case it can be tested if the average values of the data series differentiate coincidentally or significantly. That is done with the t-test from Student. The t-test hypothesis H_0 says with a probability of error of 5% (α=5%) that the average values of two data series only differentiate coincidentally

Equation 14

$$t_b = \frac{\bar{x}_1 - \bar{x}_2}{s_d} \sqrt{\frac{n_1 n_2}{n_1 + n_2}}$$

where

Equation 15

$$s_d^2 = \frac{s_1^2(n_1 - 1) + s_2^2(n_2 - 1)}{n_1 + n_2 - 2}$$

The degree of freedom is determined with

Equation 16

$$f = n_1 + n_2 - 2$$

t-test H_0 is true if

Equation 17

$$t_b < t_t(2\alpha, f)$$

where t_b is the calculated value and t_t is the value estimated from the table, depending on 2α and f as the double sided t-test is used in this case. A one sided t-test can only be used if the trend of the values is known, e.g. during a stability test of pharmaceuticals whereas one can assume that the amount of active ingredient in the tablet will decrease with time and not increase.

4.3.2.4.Disintegration

The disintegration of a dosage form into its primary granules or particles is the first step toward the dissolution of the drug substance. Disintegration methods usually involve the submersion of the dosage form into the dissolution medium or in water at approximately 37°C. The time required for the dosage form to break down into its primary granules or particles is then recorded as the disintegration time. There have been done a whole lot of experiments in order to characterize the disintegration process itself. The disintegration time is related to the granule size of the tablet. With decreasing granule size the disintegration time of the tablet increases to a maximum. Also the decrease in disintegration time has been correlated to the capping propensity of the tablets, thereby supporting the theory that the mechanical integrity of the tablets played a role in the disintegration time (13). The viscosity, surface tension and penetration angle of the penetrating solution also influence the disintegration of the tablet accompanied with the mean diameter of the capillaries in the tablet, and as the

mean capillary diameter alters with different compression forces (14) it is clear that disintegration is a very important parameter to observe when changing tableting presses or scaling up.

The disintegrating time of the produced tablets was determined by a Sotax DT3 disintegrator (Sotax AG Basel, Allschwil, Switzerland) according to Ph. Eur. (15). Product A was disintegrated in 37°C water, whereas product B was disintegrated in 37°C gastric juice.

4.3.2.5.Dissolution Profile

The dissolution characteristic of a dosage form is one of the most important parameters to keep an eye on throughout development, scale-up and equipment and process changes. The dissolution of the drug substance can influence the bioavailability if the dissolution rate is the limiting factor for the absorption (16). For dissolution comparison between tablets made from two different manufacturing presses or during scale-up from research, clinical or bio-batches it is not sufficient to compare with a single point testing, i.e. saying that if both tablets are dissolved in e.g. 30 minutes they are "the same". In these cases there is a dissolution profile required and a determination of a difference factor (f_1) and a similarity factor (f_2) according to the SUPAC document for immediate-release dosage forms (17). With the following equation

Equation 18

$$f_1 = \left\{ \left[\sum_{t=1}^{n} |R_t - T_t| \right] / \left[\sum_{t=1}^{n} R_t \right] \right\} \times 100$$

the difference factor (f_1) is determined by subtracting the "postchange" from the "prechange" dissolution value, where n is the number of time points, R is the dissolution value of the reference (prechange) batch at time t, and T is the dissolution value of the test (postchange) batch at time t.

Equation 19

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0,5} \times 100\right\}$$

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.
For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test (postchange) and reference (prechange) products.

The dissolution profile was determined with a Sotax AT70 Smart (Sotax AG Basel, Allschwil, Switzerland) according to the Ph. Eur. 2.9.3. "Dissolution Test for Solid Dosage Forms" or USP<711>, "Dissolution" at a speed of 50 rpm and the samples were then manually quantified with an Uvikon XS UV (Szabo-Scandic HandelsGmbH und Co KG, Vienna, Austria) at the predetermined time intervals.

4.3.2.6.Content Uniformity of the drug substance

Content uniformity is dependent on the powder properties. It is clear that the content uniformity of the active substance in tablets is vital for the patient. As the feeding mechanism is known to be able to influence the segregation of the granulate formulation it is interesting to observe the content uniformity of the produced tablets from the three different rotary presses. An example is known from a tableting scale-up from an intermediate batch size to a manufacturing-size batch. There all previous scale-up steps were performed without problems until the dosing system was changed from hand scooping the powder into the hopper of the tablet press and using an overhead-feed duct. This overhead-feed duct acted as a classifier for the granulate formulation as the length and the angle of the ductwork fostered segregation (18). According to the Ph. Eur. the content uniformity test is performed on ten randomly selected tablets from a batch. Each tablet should be analyzed for amount of active ingredient with a suited analytical method. If all tablets are within 85% and 115% of

the average content and the standard deviation is under 6% they will meet expectations. The U.S.P. has a slightly different method. The ten randomly selected tablets must lie within 85% and 115% of the declared content. It did not make any sense to measure the content uniformity of the tablets made by the Presster™ as each and every tablet was hand weighed into the die.

The content uniformity was determined with an HPLC method on a TSP (Thermo Separation Products GmbH, 64291 Darmstadt, Germany).
For product A there was used a reversed phase RP-8 silica sphere-5 with a mean particle size of 5µm and 4,6mm internal diameter. A flow rate of 2ml/min was employed with UV wavelength detection at 220nm. The selected mobile phase was acetonitrile/ammonium carbamate (55:45). An isocratic HPLC method.
For product B there was used a Nucleosil C18,5µm column, 125mm long and an internal diameter of 3,0mm. A flow rate of 0,4ml/min was employed with UV wavelength detection at 265nm. The selected mobile phase A was Water/Acetonitrile/Trifluoroacetic acid (90:10:0,1) and mobile phase B was Water/Acetonitrile/Trifluoroacetic acid (10:90:0,1). A reversed phase HPLC method.

4.4. Results and Discussion

4.4.1. Powder Evaluation

4.4.1.1.Particle Size Distribution

Normally the particle size distribution is only homogeneous if all the particles have the same source. Powders made of more than one particle collective tend to have a flattened maximum or even more than one maximum if the particle size distributions are farther apart. That is what is seen in the particle size distribution of the products A and B, a flattened overall distribution with two maximums. Tables 2 and 3 contain the absolute values of the particle size distribution.

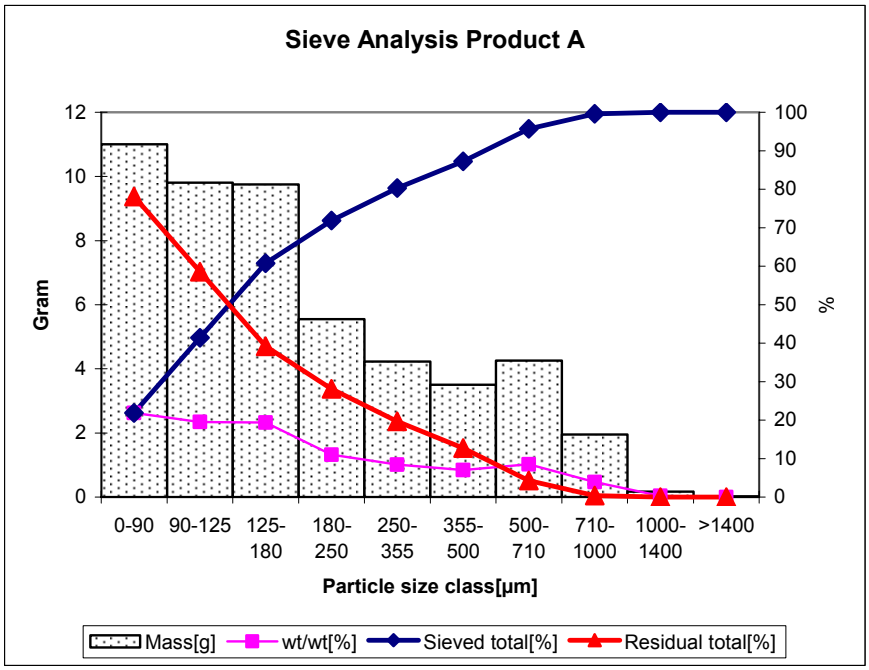


Figure 15: Particle size distribution of Product A with two flattened maximums

Particle size class Product A				
[µm]	Wt/wt [%]	Sieved total [%]	Residual total [%]	Mass [g]
0-90	21.9	21.9	78.1	11.01
90-125	19.5	41.4	58.6	9.81
125-180	19.4	60.8	39.2	9.75
180-250	11	71.9	28.1	5.55
250-355	8.4	80.3	19.7	4.23
355-500	7	87.3	12.7	3.51
500-710	8.5	95.7	4.3	4.26
710-1000	3.9	99.6	0.4	1.95
1000-1400	0.3	100	0	0.17
>1400	0	100	0	0.02

Table 2

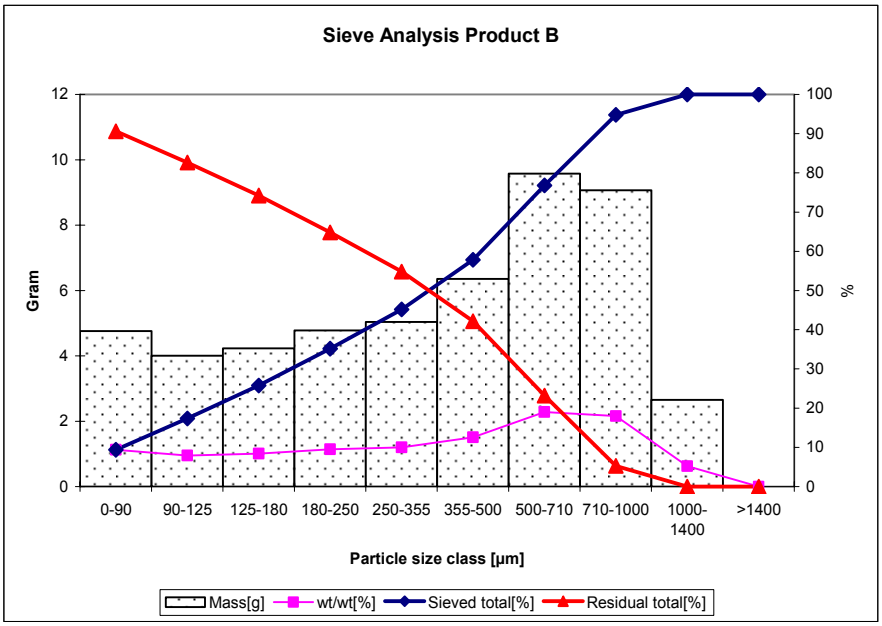


Figure 16: Particle size distribution of Product B with two flattened maximums

Particle size class Product B [µm]	Wt/wt [%]	Sieved total [%]	Residual total [%]	Mass [g]
0-90	9.4	9.4	90.6	4.76
90-125	7.9	17.4	82.6	4.01
125-180	8.4	25.8	74.2	4.23
180-250	9.5	35.2	64.8	4.78
250-355	10	45.2	54.8	5.04
355-500	12.6	57.8	42.2	6.36
500-710	19	76.8	23.2	9.58
710-1000	18	94.8	5.3	9.07
1000-1400	5.2	100	0	2.65
>1400	0	100	0	0

Table 3

4.4.1.2.Density

The following tables show the results of the density tests.

Product A density determination:

	ml	g	ml/g	g/ml
Bulk volume:	211	100	2.11	0.474
Tapped volume (1250 taps):	175	100	1.75	0.571
Tapped volume (2500 taps):	173	100	1.73	0.578
True density:			0.778	1.2861

Table 4

Product B density determination:

	ml	g	ml/g	g/ml
Bulk volume:	182	100	1.82	0.55
Tapped volume (1250 taps):	146	100	1.46	0.68
Tapped volume (2500 taps):	144	100	1.44	0.69
True density:			0.773	1.2936

Table 5

The resulting Hausner ratio from these results using equation 1:

Product A = 1,20

Product B = 1,24

According to the Hausner ratio, product B does not have ideal prerequisites for manufacturing as the Hausner ratio exceeds 1,20. When powder formulations exceed the Hausner ratio of 1,20 it can be expected that the powder densifies during transportation or during any applied vibration, e.g. during compression if the container is placed upon a rotary press. It is clear that if the powder formulation densifies during manufacturing the weight of the tablets might change, as the filling into the dies is volume controlled with the lower punch.

4.4.1.3.Flowing properties

Product A shows good flowing properties which are shown in the table below. Product B on the other hand shows poor flowing properties.

Product	Flowability [g/sec]
A	13.2
B	8.7

Table 6: Powder flow properties of products A and B.

4.4.2. Compact Preparation and Evaluation

4.4.2.1.Compression

Here the performance tests of the different manufacturing-presses will be described along with some "highlights" during the test, i.e. possible problems which came up during compression of the products A and B on other manufacturing-presses.

Fette 2090® routine manufacturing experience:

The samples used for the graphs below were taken out of routine manufacturing batches at different velocities.

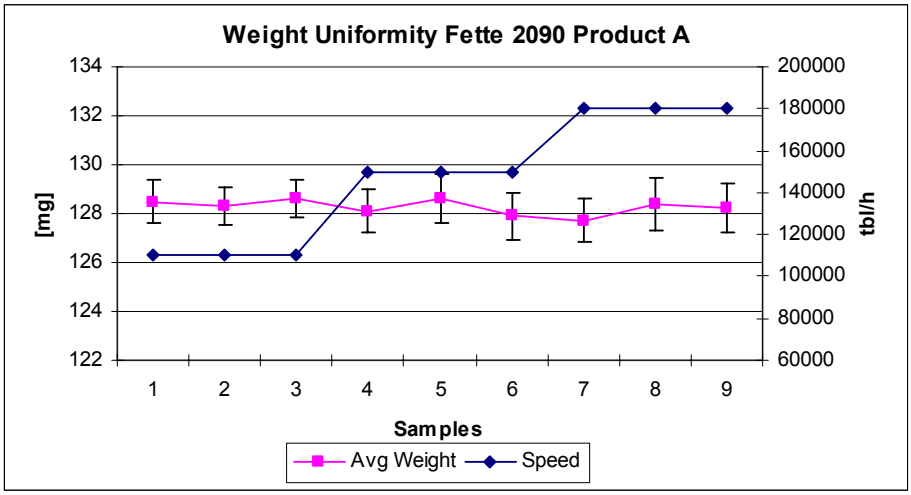


Figure 17: Weight Uniformity of Product A at 110, 150 and 180k tbl/h.

The good flowing properties of product A are easily observed in the above graph, whereas the weight standard deviation (illustrated with the error bars) only shows very little difference with increasing speed. Also the average weight of the tablets stays constant.

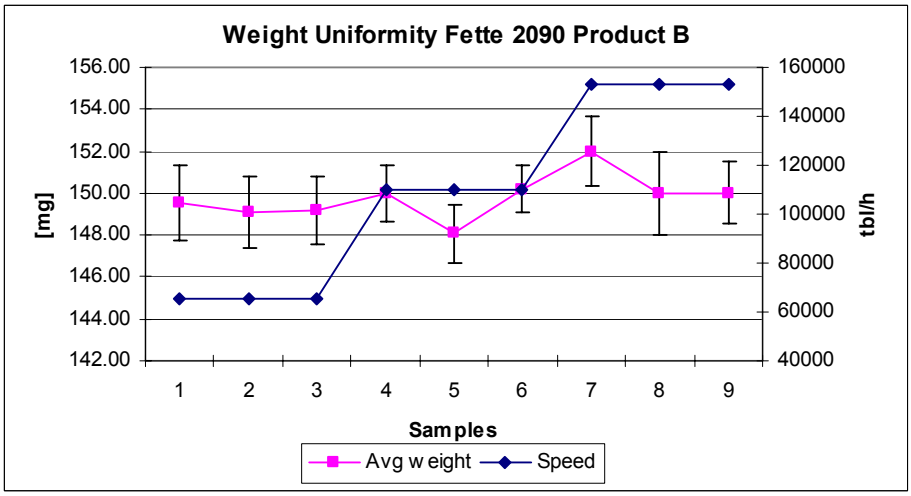


Figure 18: Weight Uniformity of Product B at 65.5, 110 and 153k tbl/h.

In the above graph it is clearly to be seen that product B possesses poorer flowing properties than product A. The weight standard deviations are higher and also increase with higher speed. Also the average weight of the tablets is not as constant.

IMA Comprima 300® test:

The granulate material for the performance tests was taken out of a produced commercial batch. Both test materials, product A and B, were sent to IMA by truck. Before the test-runs began, the barrels were rolled on the floor for 3 minutes, as the material had been standing for some while and shipped by truck which could have caused a pre-densification of the granulate material. For the test run, the material was shoveled into the turret by the operator. Each test started with the speed 250´000tbl/h. During the test-run, samples were taken regularly additionally to the automatic IPC of the IMA Comprima 300®.

The test-run of product A started off with 250'000tbl/h. Product A did not show any problems with the unusual die filling system of the IMA Comprima 300®. The granulate material is filled into the die sideways with help of centrifugal force. This way the standard deviation of the tablet weight should theoretically decrease as faster the manufacturing-press produces, in contrast to the force feeding of the die from above on the die table where the standard deviation of the weight increases with increasing production speed.

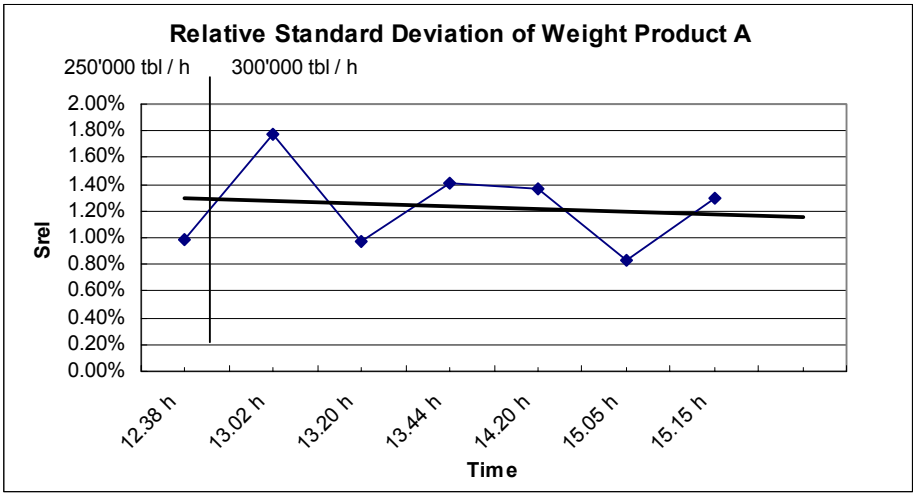


Figure 19: Relative standard deviation of tablet weight during the IMA Comprima 300® test-run, decreasing with increasing speed.

The relative standard deviation (Srel) of tablet weight from the manufacturing-press is shown in the above figures. As in theory, the relative standard deviation does decrease with higher tableting speed. It has been said that the IMA Comprima® can only process powder formulations which have good flowing properties as the feeding mechanism for the die is only the centrifugal force coming from the rotating turret and no force feeding is possible. Product B being a problematic product was then tested on the IMA. As expected, the compression did not run without problems. The relative standard deviation of the compression force of the punches was too high (13 – 15%), therefore the machine automatically stopped several times. The values of Srel of the compression force recommended in literature are 5 – 10%, which would lead to a weight Srel of about 0.7 – 1.5%. It was then suggested mounting rubber rings on the lower punches in order to increase the vacuum force in the die. This way the granulate did not only experience centrifugal powers on its way into the die, but was additionally being sucked into the die. This way, the Srel of the compression force was reduced (5 – 7%) and the machine was able to press the granulate. One stop occurred after the rings were mounted. One die opening seemed to be blocked, as the compression force measured on this punch was too low. After dismounting the die and cleaning the material out of the die channel the machine was running again. It was decided to increase the speed up to 3000'000tbl/h and after that the machine finished the material without further problems. This verifies the statements made on the IMA Comprima 300®, that as faster the machine runs, the better.

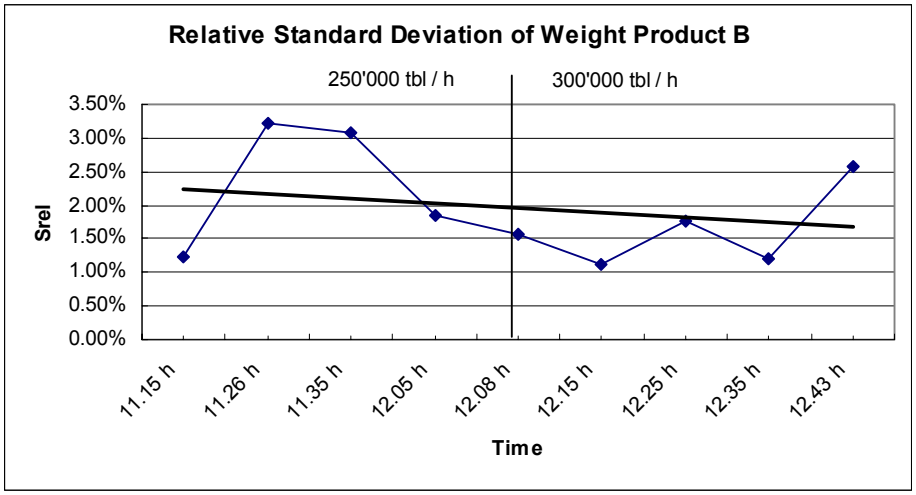


Figure 20: Relative standard deviation of tablet weight during the IMA Comprima 300® test-run, decreasing with increasing speed.

As can be seen in the figure above the Srel also decreased with increasing speed in this case. In this case, in spite of previous predictions, product B was possible to process on the IMA Comprima 300® after equipping the lower punches with rubber rings which created an additional vacuum force to the centrifugal force which helped the powder formulation to flow into the die. By using the IMA Comprima® the production output could at least be doubled with the products in question.

The yield of the IMA Comprima® was found to be very good. Where standard rotary presses show a yield loss of up to 2% it was measured to be about 0.3%. Regarding this from an economical point of view this could lead to massive savings, depending on the cost of the product being processed. Below is an example, based on information from IMA, Bologna.

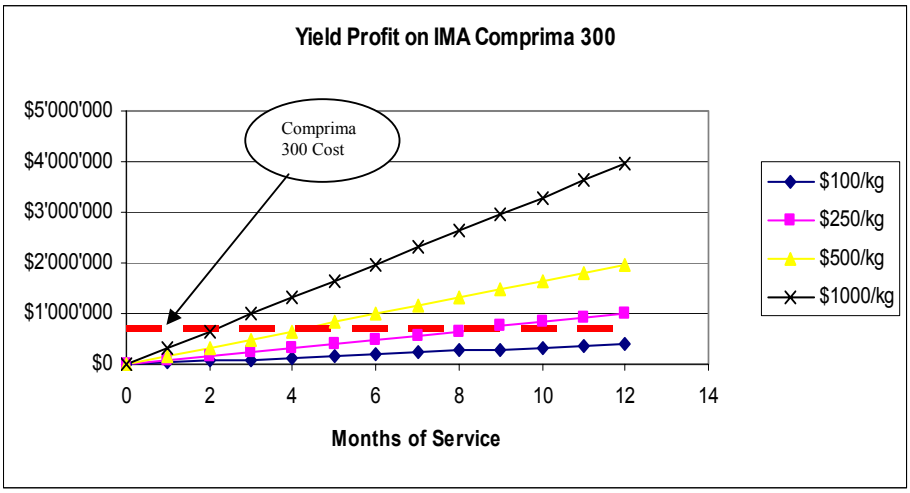


Figure 21: Based on the costs of product per kilogram, assuming 2% product loss for standard rotary press and 0,5% product loss for the IMA Comprima®. Further assumptions are a batch size of 2000kg and 11 batches per month.

The CIP system was tested with product B, which we remember, is the "worst case" product and it also happens to be a bastard to clean. The standard cleaning cycle consisted of 10 minutes pre-washing, 10 minutes washing with acid detergent, 10 minutes rinsing with deionized water and 2:30 hours of hot air drying making a total of 3 hours. Additionally to that time the removal of the compression tools takes about 30 minutes and the re-fitting another 30 minutes making a total of 4 hours change-over time between products.

With the standard cleaning procedure from IMA applied for product B the machine was not visually clean. There was still typical product B remains on the turret and in the processing area, which consist of a thin sticky layer of product. After the second cycle the processing area was visually clean. After having a look into the turret some more remains were found of product B which was gone after the third cleaning cycle. Additional product specific optimization is mandatory and might solve the problem. For example using 2 different detergents, acid and alkaline and longer phases. Even tripling each cleaning phase, excluding drying, a total change over time of about five hours could be reached which is still far beneath the change over time of standard rotary presses which can be done in about 6 hours with three persons instead of one for the IMA Comprima® (12).

Courtoy Modul® test:

The granulate material for the performance tests was taken out of a produced commercial batch. Both test materials, product A and B, were sent to Courtoy by truck. Before the test-runs began, the barrels were rolled on the floor for 3 minutes, as the material had been standing for some while and shipped by truck which could have caused a pre-densification of the granulate material. The granulate was then filled into a container and heaved onto the Courtoy Modul®.
The test run of product B was started first. Unfortunately this test had to be aborted as the lower punches kept getting stuck in the die due to the sticking properties of product B. Therefore there are no data on product B from the Courtoy Modul®, only product A. During this test it was shown that the dust-tight construction of the Exchangeable Compression Module (ECM) had to be opened in order to get to the punches. So in cases when something has to be done with the punches during production, such as polishing them once in a while during production, the ECM concept of change-over does not work. Dust will be released out of the dust-tight ECM and the room and the rest of the machine will have to be cleaned and so prolonging the change-over time.

Product A on the other hand performed very well on the rotary press. The weight regulation for the running-in process was very comfortable. The approximate dosing was set for 128mg and then a few tablets were produced and twenty tablets weighed. After giving the average weight into the computer the machine regulated itself on the basis of the average weight. One part of the test run was to increase the speed of the rotary press until the relative standard deviation (Srel) would exceed the tolerance limits of three percent. Starting from 224’000 tablets per hour the speed was gradually increased to 240’000tbl/h and then to 250’000tbl/h. At this speed the Srel of the displacement was about 1,5 – 2% (the relation of the Srel of displacement is linear to the Srel of the weight of the tablets).

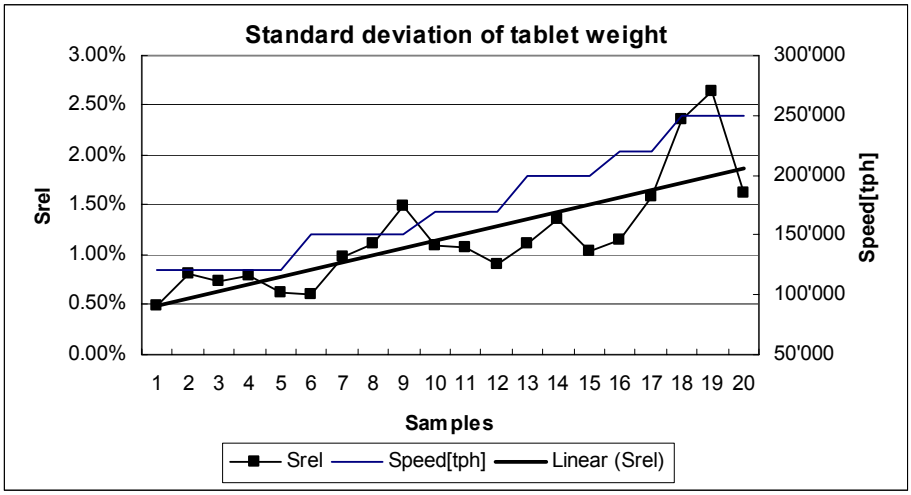


Figure 22: The relative standard deviation of weight during the test-run of product A.

In the above figure it can be seen that the Srel does increase with higher speed but does not exceed the three percent limit.

As mentioned before, the Courtoy Modul® offers the Exchangeable Compression Module (ECM) technology which enables a complete change-over to a new product in as little as one hour. This requires a double set of all periphery equipment and of the ECM. This way, one is able to remove the used ECM after production out of Courtoy Modul® and install the ready second ECM for the next product. All periphery equipment should be changed in the same manner. Due to the dust tight construction of the ECM there should be no cleaning necessary in the room. The removed ECM is then cleaned offline, along with all periphery equipment, and prepared for the next product. In order to verify this, a change-over was simulated before starting with product A. Starting the change-over test it was obvious that the whole construction of the press is very impressive. The mechanical handling is very simple and robust which makes the change-over very easy and possible with only one Allen-key. For the offline cleaning there are two features worth mentioning which make the cleaning easier and faster, the removable plates holding the punch scraper seals and the removable plates supporting the dies.

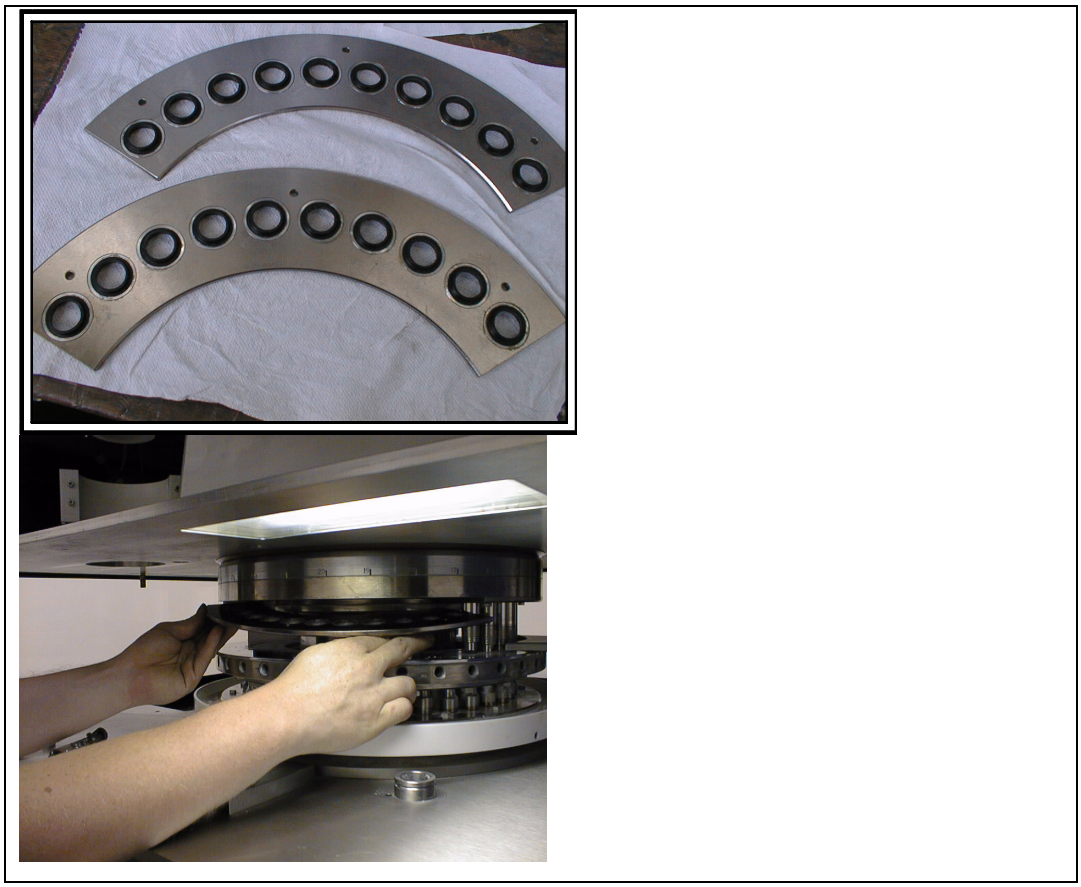


Figure 23: Plates with punch scraper

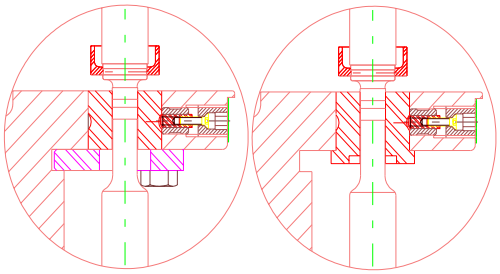


Figure 24: Plates supporting the dies

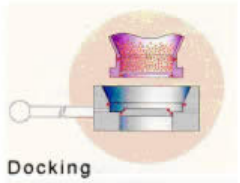
The offline cleaning of the ECM takes about three to four hours for one operator. This corresponds to the time needed cleaning conventional compression tooling.

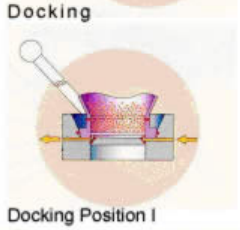
For the change-over test it was assumed that there was a ready second ECM unit set up for the next product along with a second set of periphery and a ready granulate container.

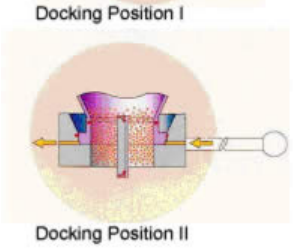
The ECM has to be removed out of the machine and out of the room without spilling any powder. That is why it has to be made sure that also the suction pipes and all other openings will be sealed. This is done with the help of lay-flat tubing parts. Every junction of the ECM to the Courtoy Modul® is sealed with lay-flat tubing parts. When the ECM is removed out of the press, the lay-flat tubing is unfolded, closed with two plastic clamps and then the tubing is cut with a head scissor between the clamps.

Figure 25: Unfolded lay-flat tubing closed with clamps.

This way any potential powder contamination is prevented. In 22 minutes the ECM was out of the press and in approximately 30 minutes all product specific equipment (granulate container / periphery) were removed. Assuming we had another ECM ready for installation, we used the same ECM we just removed and installed it again. Also the granulate container was dismounted and mounted again demonstrating the Buck docking system of containment. The Buck docking system consists of an active and a passive valve, which together seal two containers. The active valve operated manually or by an automated system, is mounted on the press,







while the passive valve is fitted on the mobile container. When docked, the two valves are interlocked for complete containment.

This complete change-over lasted 61 minutes and was done by one operator. The periphery was not attached to the press again, therefore is realistic to assume tat a change-over with double sets of equipment would be possible to realize in 60-90 minutes.

Apart from a small amount of powder trickling down from the active Buck valve when it was removed from the press during the change-over, the room and the press itself were optically clean.

MCC Presster™:

As the granulate of product A and B was weighed and filled into the die of the Presster™ by hand, it did not make any sense to inspect the achieved samples on content uniformity or weight uniformity. Worth mentioning about the weight control during the Presster™ tests is that the dosing cam was pulled down to its maximum, i.e. 17mm. This was done in order to prevent material leaving the die when the first yank of the press station carriage occurred for the tableting procedure.

The Presster™ is equipped with a strain gage on the ejection cam, measuring the peak ejection force. During the simulation of the different rotary presses it was eye-catching that as faster the press station was, the higher the ejection force.

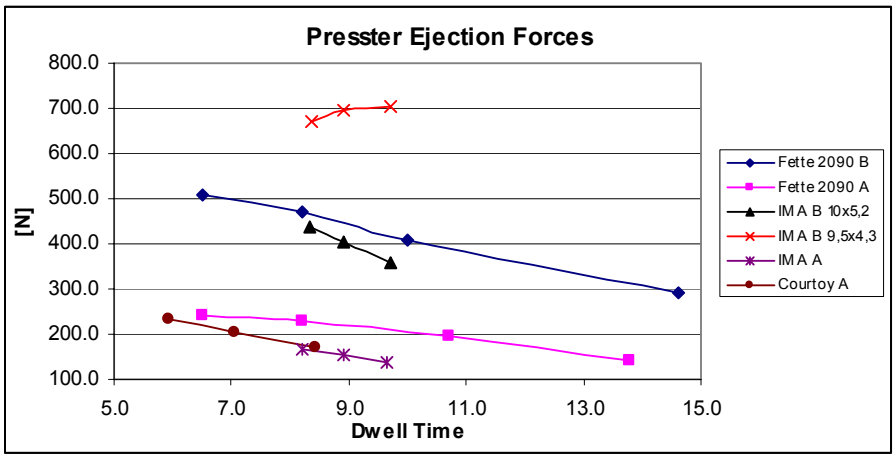


Figure 26: With higher speed (lower dwell time) the ejection force increased.

As can be seen in the above graph, the ejection force increases with higher speed. Also it is conspicuous that product B has much higher ejection forces than product A. Product B is known for its bad flowing properties and making the lower punches stick and hard of moving. Interestingly the ejection forces of the IMA simulation with the 9.5x4.3mm punches showed the highest ejection forces of all. These samples also had the highest crushing strength of all product B samples.

4.4.2.2.Crushing strength

All manufacturing-presses were tested with product A and B and these manufacturing-presses were then simulated on the Presster™ with the same products. The results are displayed in the graphs below.

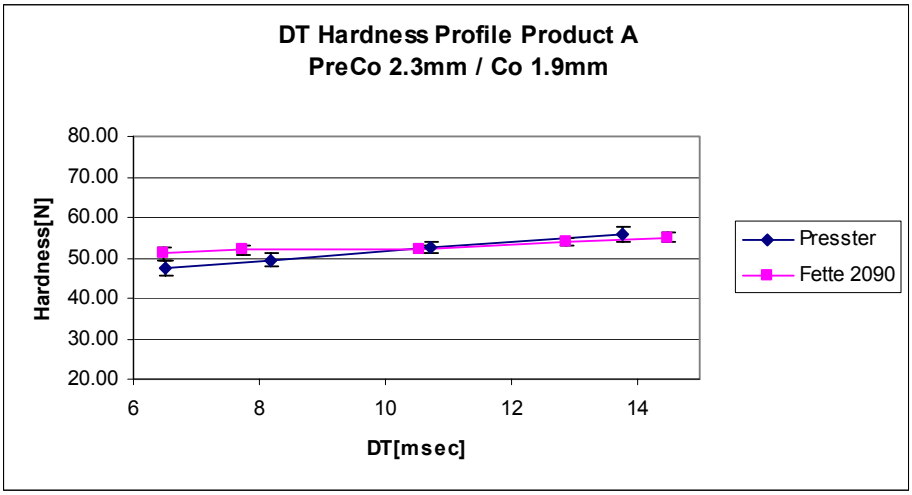


Figure 27: The crushing strength results of the Fette 2090® simulation compared to the actual manufacturing crushing strength results.

With product A the Presster™ shows very good crushing strength correlation to the Fette 2090® manufacturing-press results. The Presster™ graph shows a linear correlation between dwell time and crushing strength. The decrease of crushing strength with shorter dwell time is very well recognizable. The Fette 2090® graph also shows a decrease in crushing strength with shorter dwell time with a slight plateau between 10msec and 8msec.

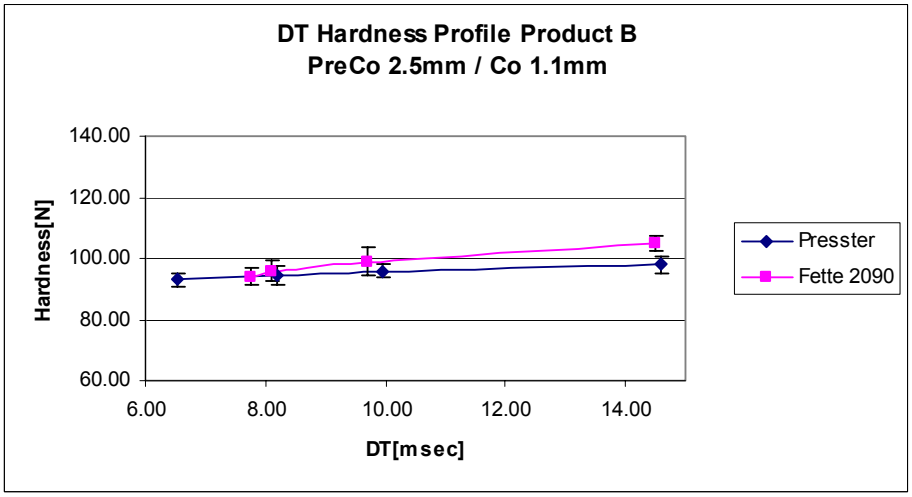


Figure 28: The crushing strength results of the Fette 2090® simulation compared to the actual manufacturing crushing strength results.

With product B the Presster™ shows very good crushing strength correlation to the Fette 2090® manufacturing-press results. The biggest difference between both graphs is at approximately 14,5msec where it reaches 7,1N. Again the Presster™ graph shows an excellent linear correlation between shorter dwell time and decreasing crushing strength. The Fette 2090® graph also shows decreasing crushing strength with shorter dwell times although somewhat steeper than the Presster™ graph between 10msec and 6msec.

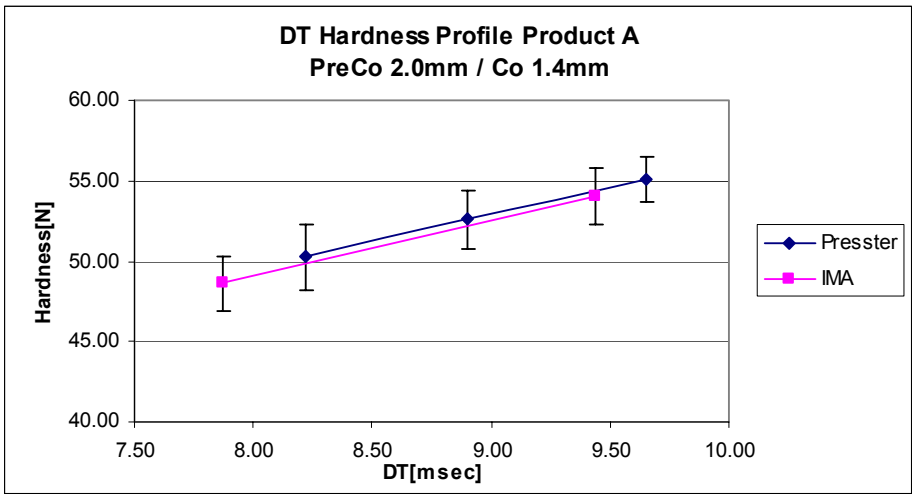


Figure 29: The crushing strength results of the IMA Comprima 300® simulation compared to the actual manufacturing-press results.

With product A the Presster™ shows excellent correlation to the manufacturing-press results of the IMA Comprima 300®. The Presster™ graph shows decreasing crushing strength with shorter dwell times just as well as the IMA Comprima 300® graph.

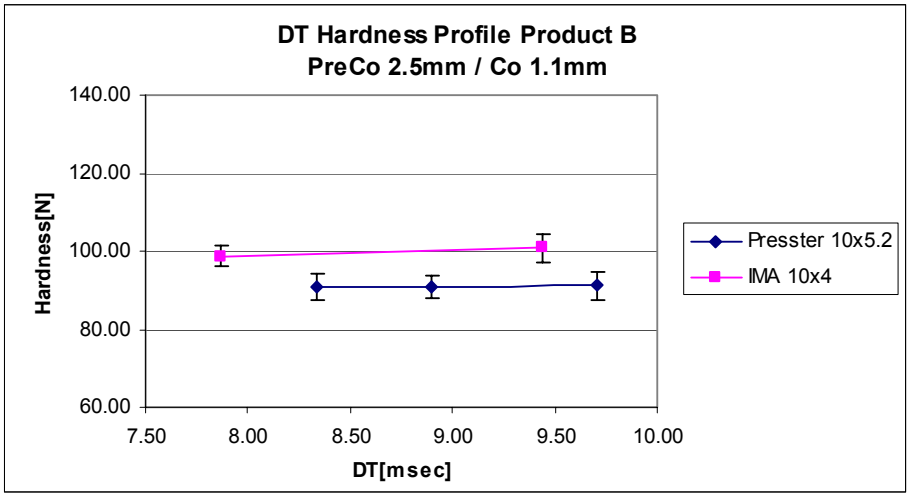


Figure 30: The crushing strength results of the IMA Comprima 300® simulation compared to the actual manufacturing-press results.

Product B on the Presster™ on the other hand does not compare as well to the IMA Comprima® manufacturing-press results. A slight decrease of the crushing strength is recognizable with shorter dwell times but the two graphs are parallel shifted. This was to expect, as the tooling used for this simulation did not equal the compression tooling used at IMA which were 10x4mm, oval and convex. The compression tooling used for the simulation above is the same as were used for the Fette 2090®, i.e. 10x5,2mm, oval and convex as well as the punch gap during pre- and main compression. As the tooling geometry was different (i.e. the punch tip surface was greater than the compression tools used at IMA) and has a significant effect on relative volume and total porosity (19) it could be expected that the crushing strength would not compare. The average main compression force applied on the tablets during this simulation on the Presster™ was 10,5kN.

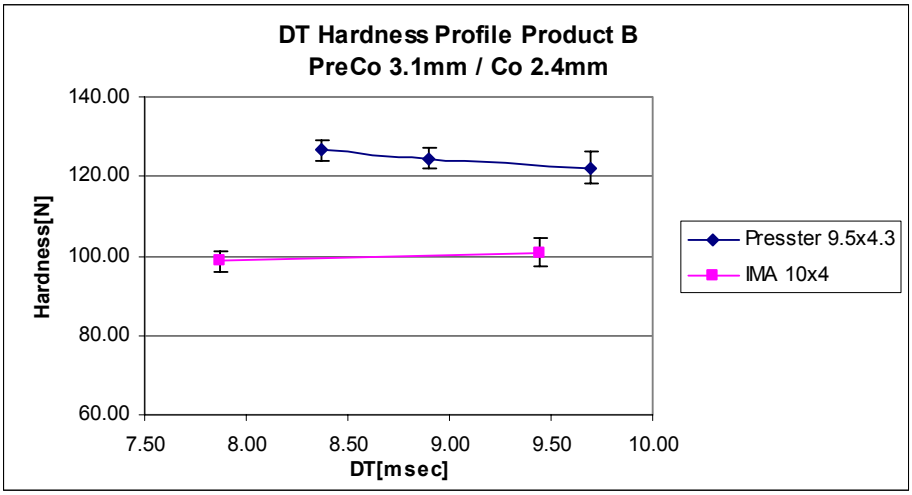


Figure 31: The crushing strength results of the IMA Comprima 300® simulation compared to the actual manufacturing-press results.

As the correct compression tooling which was used at IMA was not available for the Presster™, it was tried to use compression tooling with smaller punch tip surface. For this test a punch tip of 9,5x4,3mm was used which has a smaller punch tip surface than the compression tooling used at IMA. The punch gap used for this test was the same used for the IMA Comprima 300® manufacturing press, 3,1mm for precompression and 2,4mm for main compression. The results above show us that the IMA Comprima® manufacturing-press results have been contained by the two Presster™ results. Looking at the resulting average main compression force from the 9,5x4,3mm compression tooling of 14,1kN and the average main compression force from the 10x5,2mm compression tooling of 10,5kN it is obvious that the crushing strength increases. It is most probably due to the high compression force of the smaller punch tips which lead to the reversed graph of the Presster™, where the crushing strength increases with shorter dwell times. The average main compression force of the IMA Comprima® manufacturing-press was 9,55kN.

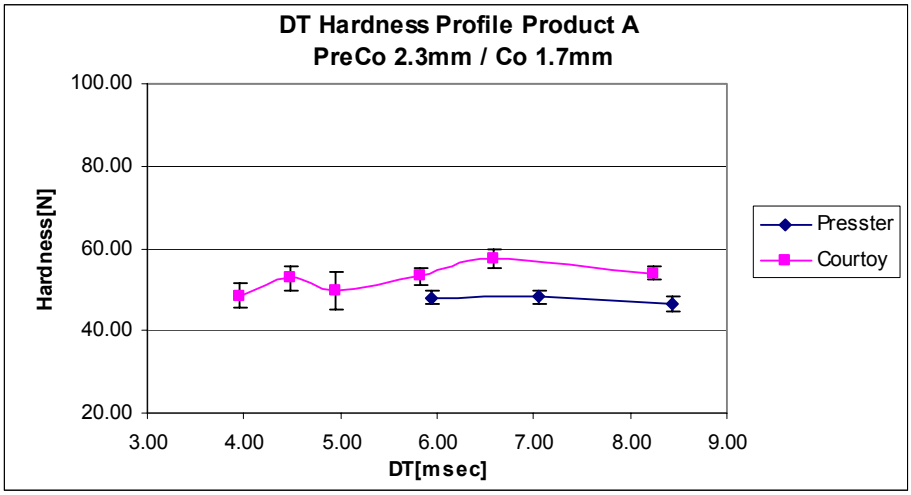


Figure 32: The crushing strength results of the Courtoy Modul® simulation compared to the actual manufacturing-press results.

The Courtoy Modul® crushing strength graph does not show the typical course as has been observed with the other two manufacturing-presses. From approximately 6,5msec down to 5msec it shows the typical decrease in crushing strength with shorter dwell times. But at 4,5msec there is a sudden crushing strength increase which then decreases rapidly again at 4msec. In addition there is a sudden decrease in crushing strength at approximately 8,2msec which actually acts in accordance with the Presster™ graph which also shows a decrease of crushing strength after 7msec. Otherwise the simulation graph from the Presster™ does not compare to the Courtoy Modul® results and it is parallel shifted of about 7N. This can be explained by the fact that the Courtoy is equipped with the pneumatic precompression roll and compresses to constant force, not to constant thickness as the other manufacturing-presses do. Also the pneumatic precompression roll prolongs the dwell time under the precompression roll and so providing an additional time for stress relaxation ad effectively increasing the tablet crushing strength. This effect could not be simulated by the Presster™ just by using the corresponding size of the compression rolls without the pneumatic precompression. A pneumatic precompression roll is available from MCC and every Presster™ can be equipped with one, but for these tests, this option was not available. The Presster™ setup of the punch gap was based on the Courtoy manufacturing-press settings and resulted in an average main compression force of 13,8kN.

These results show that with the corresponding compression tooling, the crushing strength behavior of a tablet can be predicted for different punch gap distances and different speeds with very little material for different manufacturing-presses as long as the compression technology matches the manufacturing-press in question. In the case of the Courtoy Modul® simulation the pneumatic precompression roll was not available and so the results did not correlate. Also in the case of the IMA Comprima 300® the corresponding tooling used for product B was not available for the Presster™ leading to similar crushing strength results but parallel shifted due to the different punch tip geometry.

4.4.2.3.F-test and t-test

In the following tables the results of the F-test and the t-test are given for each manufacturing-press, product and dwell time. In order to determine F_t for the F-test, a table is needed with the chosen probability of error α. In this case, having 10 values in each data series, the degree of freedom is 9 and the resulting value F_t then for α 5% is 3,18 and for α 1% is 5,35.
As can be seen, all F-tests except one are true for F_t α5%, i.e. they have a homogenous variance. One F-test for the Fette 2090® was not true for F_t α5%, but true for F_t α1% which means that the variance difference of the two data series might be systematical (20).

Based on these results, having a homogenous variance of the samples, the t-test could be performed. Similar to the F-test, a table is needed here in order to determine the t_t value. According to the chosen probability of error, in this case a double sided α 5% and f = 18 degree of freedom the value 2,10 was determined from the table. The results show that the difference of the average values of crushing strength between the Presster™ and the manufacturing presses are either only a coincidence or very significantly different.

Products	Presster DT's	s_1	s_2	F_b	F_t 5%	F_t 1%	t_b	t_t5%
A	6,52	1,84	1,70	1,17	3,18		4,42	2,10
	8,19	1,51	1,25	1,46	3,18		4,05	2,10
	10,71	1,35	0,94	2,05	3,18		1,18	2,10
	13,78	1,80	1,25	2,08	3,18		1,20	2,10
B	6,52	2,71	2,05	1,74	3,18		0,93	2,10
	8,20	3,59	2,99	1,44	3,18		1,01	2,10
	9,95	4,45	2,05	4,68	3,18	5,35	1,95	2,10
	14,58	2,69	2,40	1,24	3,18		6,25	2,10

Table 7: F-test and t-test results on Fette 2090® crushing strength values

Products	Presster DT's	s_1	s_2	F_b	F_t 5%	t_b	t_t5%
A	8,22	2,01	1,65	1,48	3,18	1,48	2,10
	8,90	1,84	/	/	3,18	/	2,10
	9,65	1,37	1,76	1,66	3,18	1,66	2,10
B 10x5,2	8,34	3,25	2,64	1,52	3,18	5,97	2,10
	8,92	2,87	/	/	3,18	/	2,10
	9,71	3,61	3,53	1,05	3,18	6,01	2,10
B 9,5x4,3	8,37	2,64	2,63	1,00	3,18	23,56	2,10
	8,90	2,59	/	/	3,18	/	2,10
	9,70	4,08	3,53	1,34	3,18	12,57	2,10

Table 8: F-test and t-test results on IMA Comprima® crushing strength values

As the IMA Comprima 300® was only run at two different speeds, there were no samples available for the comparison of 8,9msec.

Products	Presster DT's	s_1	s_2	F_b	F_t 5%	t_b	t_t5%
A	5,93	1,93	1,79	1.16	3,18	6,13	2,10
	7,06	2,31	1,48	2,45	3,18	10,49	2,10
	8,44	1,96	1,70	1,33	3,18	9,16	2,10

Table 9: F-test results on Courtoy Modul® crushing strength values

The significant difference calculated for the Courtoy Modul® with the t-test can be explained with the pneumatic precompression roll, which was not in place on the Presster™. Comparing the dwell time / crushing strength profiles graphs above it is noticeable that the values which do lie apart do have a significant difference of average crushing strength according to the t-test (20).

4.4.2.4.Disintegration

As described above under materials and methods, the tablet samples from the Presster™ and the manufacturing-presses were tested on disintegration. The results are displayed in the figures below.

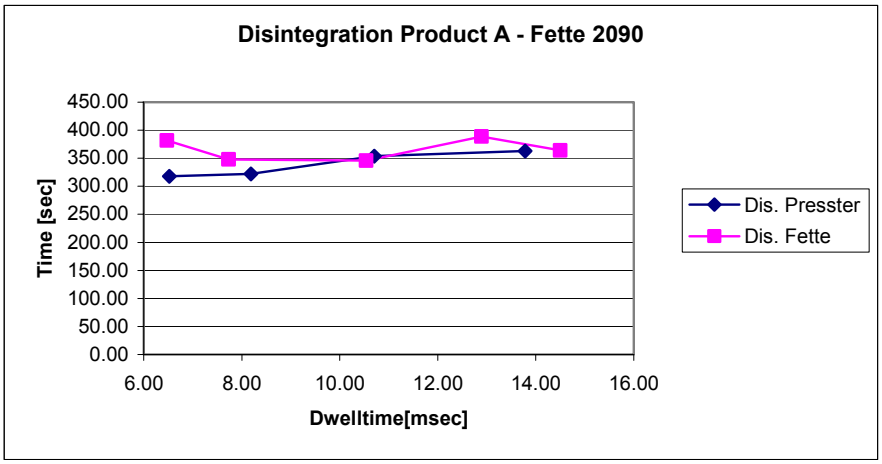


Figure 33: Disintegration results from Fette 2090® and the Presster™ simulation of Fette 2090®.

The disintegration results from the product A Fette 2090 samples could be predicted quite well with the corresponding dwell time samples from the Presster™. The biggest difference is to seen at approximately 6,5msec where it reaches 64 seconds which corresponds to a 16.8% deviation to the true disintegration time of the Fette tablets produced at this speed.

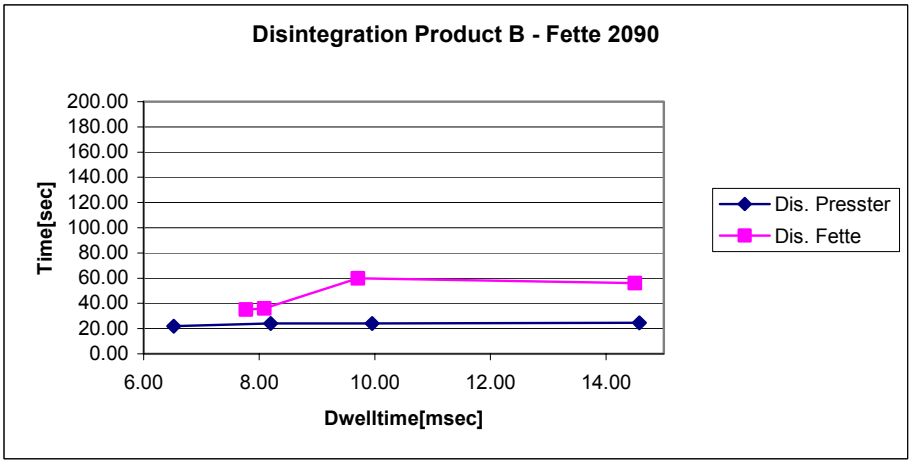


Figure 34: Disintegration results from Fette 2090® and the Presster™ simulation of Fette 2090®.

The disintegration time of product B could not be predicted quite as well with the Presster™ for Fette 2090®. There the biggest difference is to be seen at approximately at 9,8msec where it reaches 34 seconds. The Presster™ sample only needs 24 seconds to disintegrate whereas the Fette 2090® sample needs 60 seconds. This difference still is not essential for the tablet as the maximum disintegration time

is set at 10 minutes for this immediate release tablet and both samples are far beneath that value. Another factor which should also be mentioned is that the actual disintegration time determination is very difficult for this tablet as when it is put into gastric juice it macerates and disintegrates into large flakes which block the observation of the tablet. Therefore it is possible, that the actual disintegration time is dependent on the person doing the test.

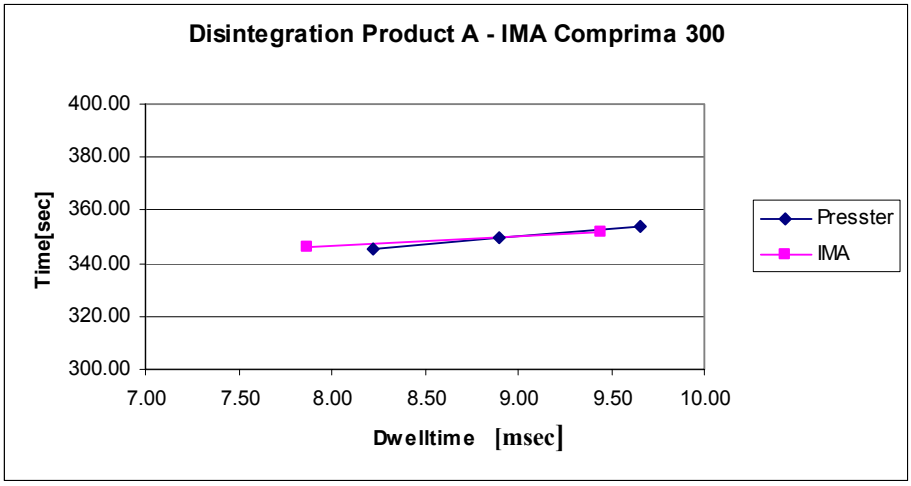


Figure 35: Disintegration results from IMA Comprima 300® and the Presster™ simulation of IMA Comprima®.

Simulating the IMA Comprima® manufacturing-press the Presster™ predicted the disintegration time of the IMA samples very well. The two graphs in the figure above show a maximum difference of two seconds.

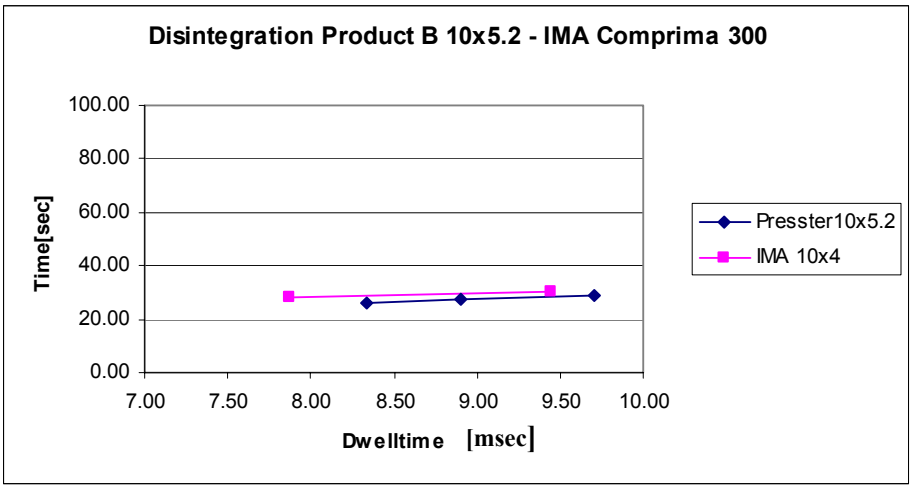


Figure 36: Disintegration results from IMA Comprima 300® and the Presster™ simulation of IMA Comprima®.

The disintegration results in the above figure correlate very well to the crushing strength results of the same samples. The crushing strength of the manufacturing-press samples were about eight to nine Newtons harder than the simulated tablets from the Presster™. Here the disintegration time of the simulated tablets is about 1,5 to 1,8 seconds shorter which is not significant but still shows a correlation of crushing strength (and density) to the disintegration time. This is again confirmed in the figure below.

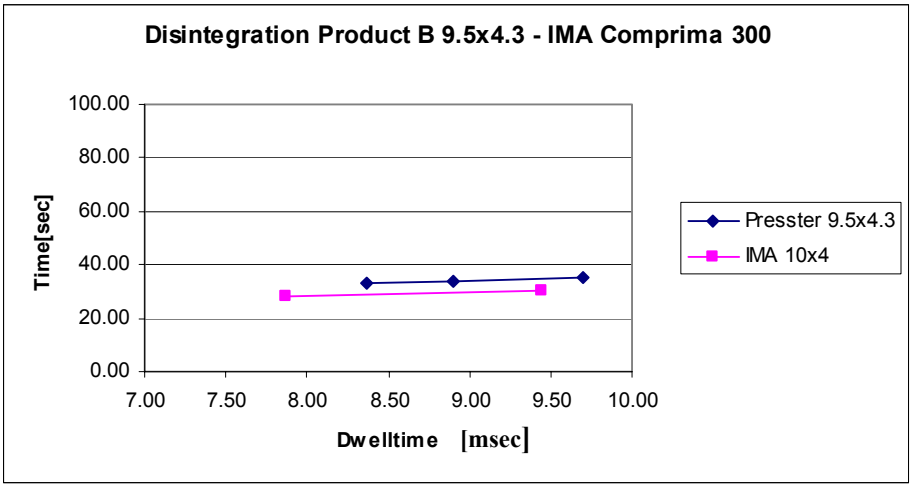


Figure 37: Disintegration results from IMA Comprima 300® and the Presster™ simulation of IMA Comprima®.

As mentioned above, the crushing strength shows a good correlation to the disintegration time. Here in the above figure the manufacturing-press samples from the IMA Comprima® are displayed with the simulated tablets with the 9,5x4,3mm compression tooling. As shown above the crushing strength of these Presster™ tablets exceeded the crushing strength of the manufacturing-press of about 22 to 28 Newtons and this corresponds to a disintegration time difference of about five seconds.

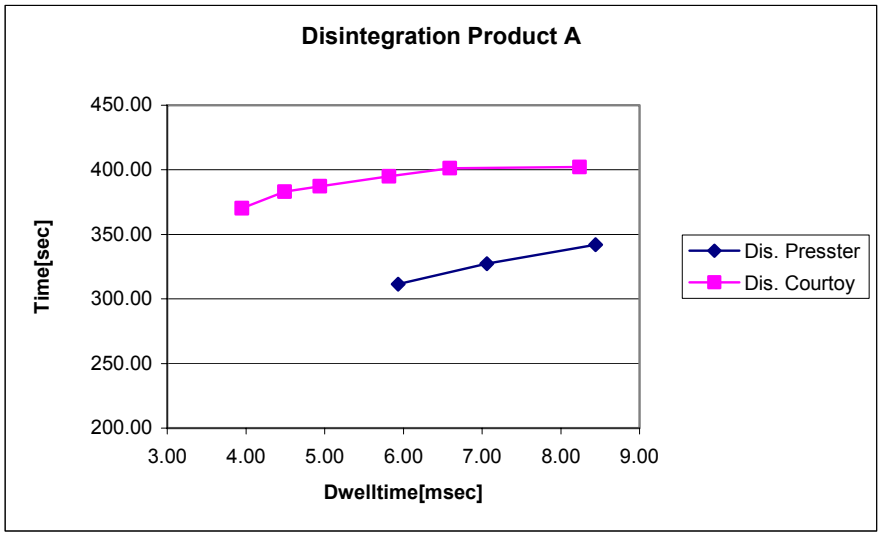


Figure 38: Disintegration results from Courtoy Modul® and the Presster™ simulation of Courtoy Modul®.

Corresponding to the crushing strength results of the Courtoy simulation the disintegration time also does not match. The manufacturing-press samples show an increased disintegration time compared to the Presster™ samples and also a higher consistency between dwell times. This supports the assumption that compressing with constant force results in more uniform tablets, even though it is only during precompression (19).

4.4.2.5.Dissolution Profile

The dissolution profiles of product A and B were unfortunately only available from Fette 2090® and from the Presster™. For the generation of the dissolution profiles, three routine manufacturing-batches were tested on dissolution with 12 tablets each and the different dwell times done on the Presster™ also with 12 tablets for each dwell time. The dissolution time points used for sampling were 10, 20, 30 and 40 minutes. The dissolution profiles are displayed in the following graphs.

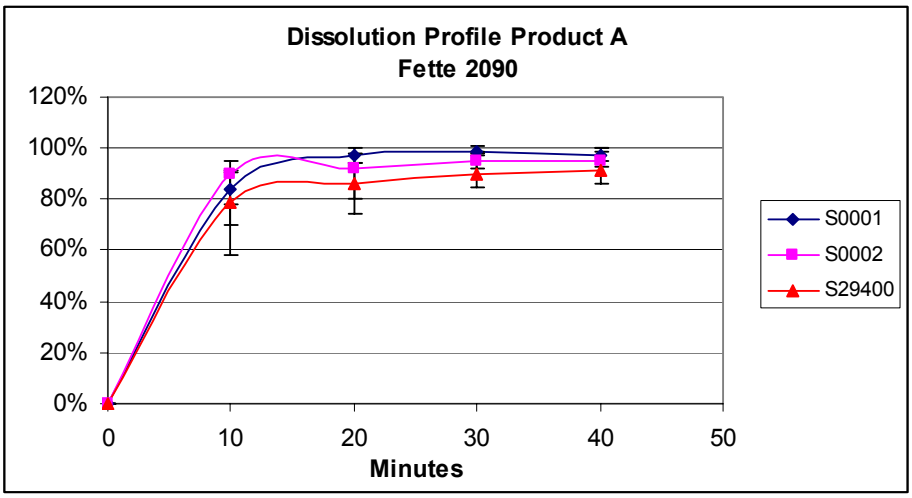


Figure 39: Dissolution profiles from routine manufacturing batches

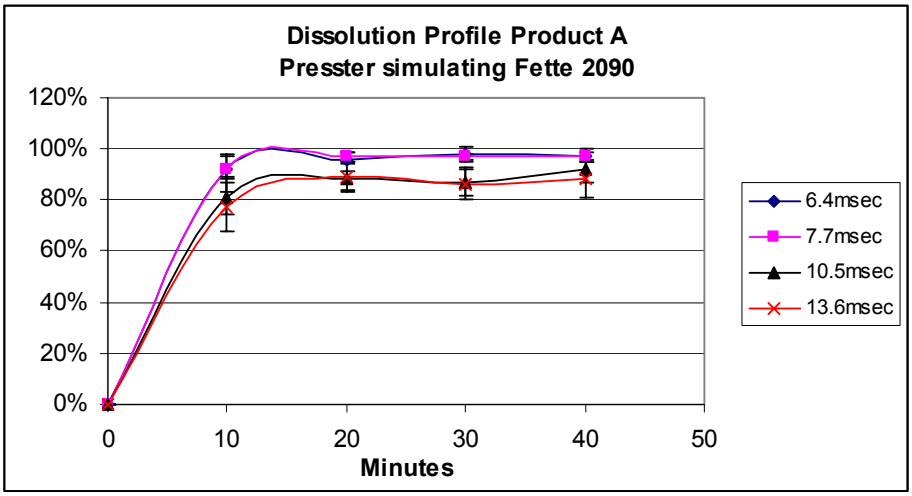


Figure 40: The dissolution profiles of the different dwell times from the Presster™

Product A seems to have a very similar dissolution profiles produced on the manufacturing-press Fette 2090® and on the Presster™. The difference in the dissolution rate between the different dwell times of the Presster™ samples can be seen very well in the above graph. The dissolution rate of the sample with the longest dwell time, i.e. 13.6msec also is the slowest one to liberate the active ingredient out of the tablet. As we could see very well comparing the crushing strength values was that the longer the dwell time the harder the tablets will get and so, the liberation of the active ingredient is slowed down. As the dwell time decreases so does the crushing strength and the liberation of the active ingredient is faster. The error bars on each

sampling point represent the minimum and the maximum concentration of the active ingredient from the 12 analyzed tablets. In order to double check our assumption, that the profiles are equivalent, the dissolution values of the Presster™ tablets were compared with the manufacturing batches using the difference factor f_1 and the similarity factor f_2 proposed be the SUPAC document for immediate release dosage forms (17). Every dwell time sample from the Presster™ was compared to all three routine manufacturing-batches, where the Presster™ samples were treated as the test values (postchange) and the Fette samples were treated as the reference values (prechange).

	6,4msec	**7,7msec**	**10,5msec**	**13,6msec**
f_1 to S0001	2,61%	2,61%	8,33%	11,82%
f_1 to S0002	2,87%	2,87%	6,61%	9,70%
f_1 to S29400	10,18%	9,66%	2,30%	3,64%
f_2 to S0001	68,92%	68,62%	54,55%	**49,81%**
f_2 to S0002	75,85%	73,72%	60,01%	52,70%
f_2 to S29400	**49,81%**	50,59%	81,49%	74,47%

Table 10: Difference factor and similarity factor for Product A

All estimated difference factors were under 15% which implies that the dissolution factors of the Fette 2090® and the Presster™ are not dissimilar. According to the similarity factor all dissolution rates of the Presster™ samples are equivalent to the Fette 2090® samples except two factors which missed the target of 50% by 0.19%. Considering that the hardest tablets from the Presster™ samples (dwell time of 13.6msec) did not compare to the fastest dissolving tablets from the manufacturing-batches (S0001) and that the slowest dissolving sample from the manufacturing-batches (S29400) did not compare to the fastest dissolving sample from the Presster™ samples, this difference is can be overlooked. According to this in-vitro test, the samples can be considered to be equivalent.

The same dissolution tests were performed on product B. The only difference this time is that product B contains two active ingredients a and b. Below the graphs are displayed with the corresponding dissolution profiles. Three routine manufacturing-

batches were tested and their batch numbers are listed in the legend of the below graphs with the corresponding active ingredient a or b noted behind the batch number.

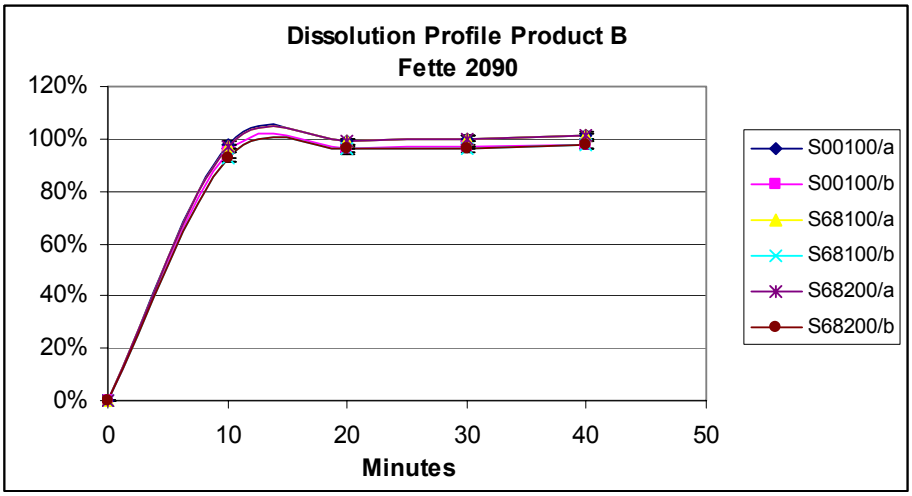


Figure 41: Dissolution profiles from routine manufacturing batches

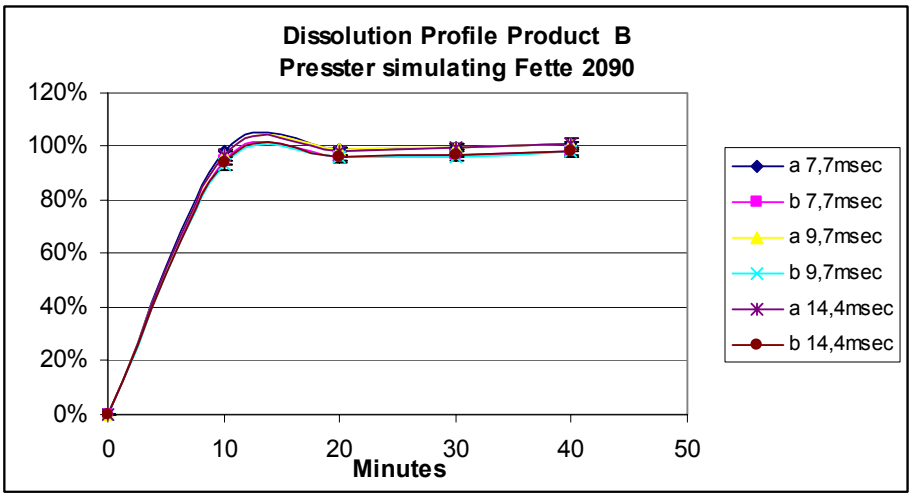


Figure 42: The dissolution profiles of the different dwell times from the Presster™

At first sight the dissolution profiles of the routine manufacturing-batches and the Presster™ samples look equivalent. Also very clearly to see is that the active ingredient a dissolves faster than b in both graphs. As done with product A, a double check was done with help from the difference factor f_1 and the similarity factor f_2. In this case, having two active ingredients, active a from all different dwell time

Presster™ samples was compared to active a from the three routine manufacturing-batches samples and the same with active b.

	7,7msec	**9,7msec**	**14,4msec**
f_{1a} **to S00100**	0,0%	0,25%	0,51%
f_{1a} **to S68100**	0,25%	0,0%	0,25%
f_{1a} **to S68200**	0,25%	0,0%	0,25%
f_{1b} **to S00100**	0,0%	0,78%	0,26%
f_{1b} **to S68100**	0,78%	0,0%	0,52%
f_{1b} **to S68200**	0,78%	0,0%	0,52%
f_{2a} **to S00100**	100,0%	97,58%	95,60%
f_{2a} **to S68100**	97,58%	100,0%	97,58%
f_{2a} **to S68200**	97,58%	100,0%	97,58%
f_{2b} **to S00100**	100,0%	91,20%	97,58%
f_{2b} **to S68100**	91,20%	100,0%	95,60%
f_{2b} **to S68200**	91,20%	100,0%	95,60%

Table 11

As can be seen in the above table all difference factors f_1 are far from being close to 15%, they are rather zero or slightly above. This means that there is almost no difference to be measured between the routine manufacturing-batches samples and the Presster™ samples. Further, the similarity factor f_2 above 90% in all cases, meaning

that the routine manufacturing-batches samples and the Presster™ samples are equivalent according to this in-vitro test.

According to these results, it is safe to say, that the most important parameter of the tablet for the patient could be predicted by the Presster™ simulating the Fette 2090® for products A and B.

4.4.2.6.Content Uniformity of the drug substance

The content uniformity (CU) of a tablet formulation should always be watched closely when transferring a product from rotary press A to rotary press B. What can happen is, as mentioned before, that different feeding mechanisms might facilitate powder segregation. This is of course very interesting to observe for tablet formulations which contain low doses of the active ingredient, e.g. product A in our case which only contains 4% active ingredient in one tablet. Product B contains over 50% of active ingredient and should not show any problems for CU.

In the graphs below, the CU of product A and B is shown on all three rotary presses, Fette 2090®, IMA Comprima 300® and the Courtoy Modul®. The standard deviation of the samples is illustrated with the error bars in the graph.

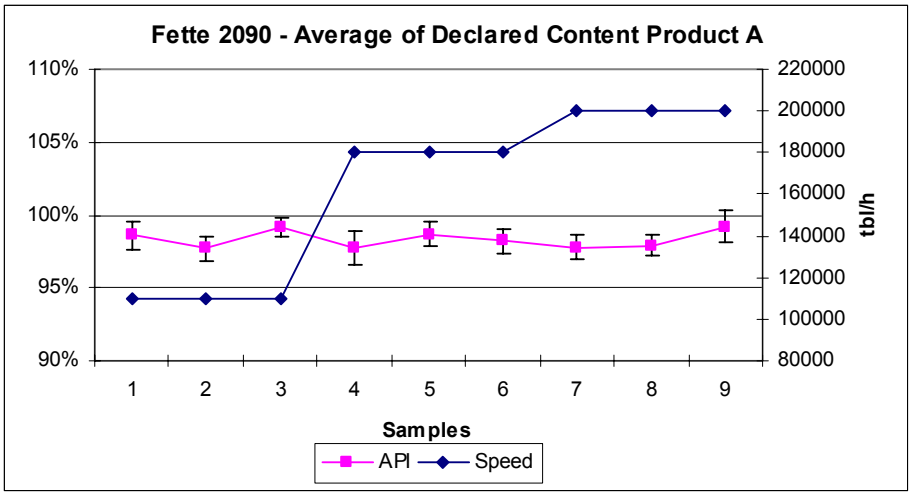


Figure 43: CU of Product A on the Fette 2090® along with the corresponding velocities, 110', 180' and 200'k tbl/h.

Product A seems to be totally unimpressed of the increasing speed of the Fette 2090®. It does not show an increasing standard deviation and the CU stays constant.

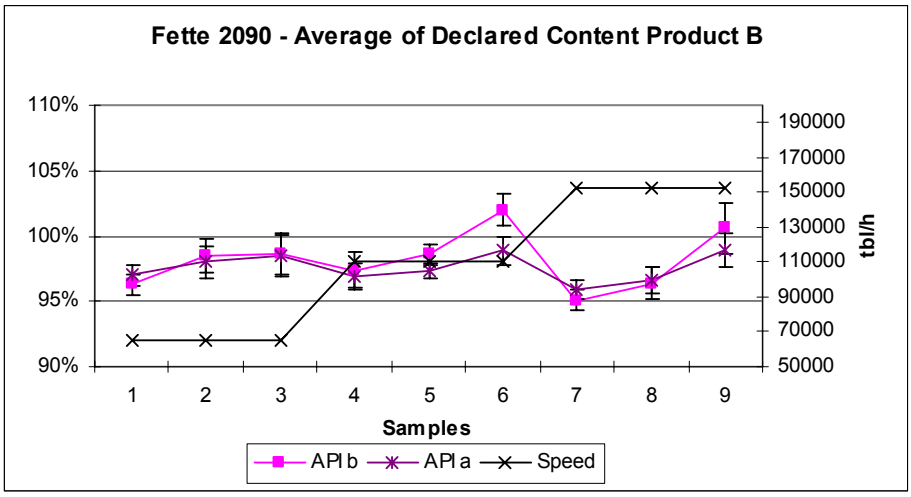


Figure 44: CU of Product B with both active ingredients, a and b. Sampling at 65.5', 110' and 153k tbl/h.

In the graph above it can be observed that the CU of product B is well within the limits of the Ph.Eur. and the USP. With increasing speed it seems that the standard deviation does increase which is completely normal as the weight uniformity also increases with higher speed.

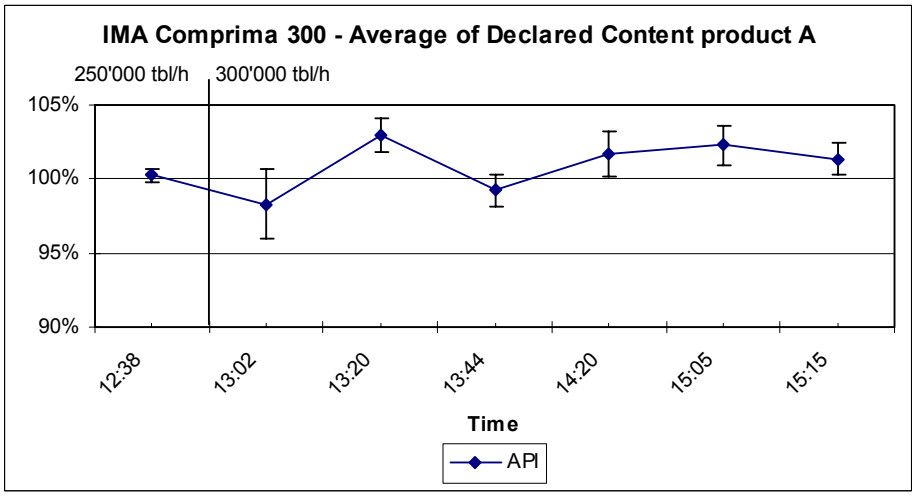


Figure 45: CU of Product A on the IMA Comprima®.

The IMA Comprima 300® already showed that the weight uniformity standard deviation decreased with higher speed. Here it is also clear that the standard deviation of CU of product A seems to decrease with higher speed. Also the CU is well within the limits of Ph.Eur. and USP.

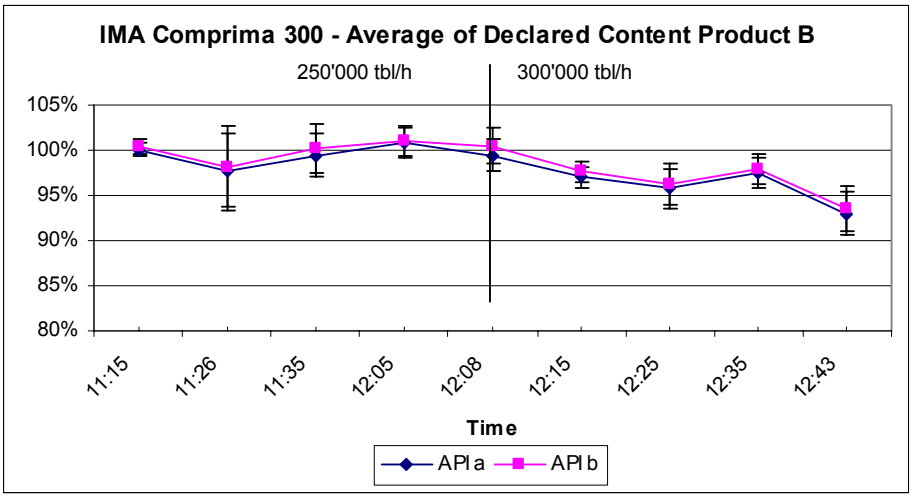


Figure 46: CU of Product A on the IMA Comprima®.

In the above graph it can be observed that the CU is also well within the limits for product B which has very poor flowing properties. Also the standard deviation decreases with higher speed.

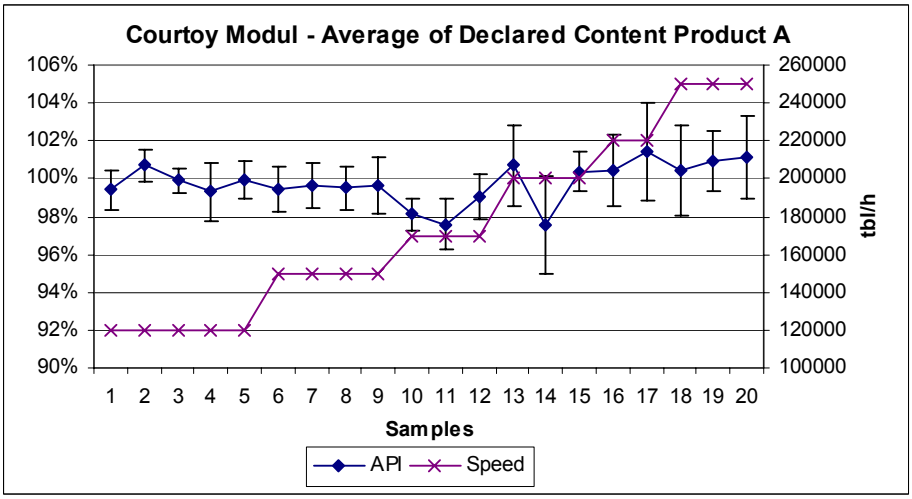


Figure 47: CU of Product A on the Courtoy Modul®.

Here it is very clear to see that the CU standard deviation of product A increases with higher speed. This is again what one would expect with a traditional die filling system, filling the dies from above.

Altogether it can be said that all three rotary presses produced tablets with CU within the limits of the Ph.Eur. and USP. According to expectations the standard deviation increased with higher speed on the traditional filling systems and decreased on the centrifugal die filling system.

4.5. Conclusion

From these results it is apparent that the compression behavior of a tablet formulation can be predicted for manufacturing scale rotary presses, provided that the Presster™ is equipped with the corresponding tooling such as punches and compression rolls. In our case the crushing strength behavior of the tablets could be predicted by setting up the corresponding punch gaps used on the manufacturing presses, on the Presster™. Disintegration, a parameter very dependent on the crushing strength, could also be predicted with the Presster™ but with the same variations as for the crushing strength. The most important parameter for the final appraisal of the samples is the dissolution rate of the tablets. We found out that the Presster™ was capable producing tablets with the same dissolution rate as the Fette 2090® for both products.

The only deviations were found to be with the IMA Comprima® / product B samples, where the corresponding tooling used for the IMA trials was not available for the Presster™, leading to a difference in crushing strength and disintegration due to the different punch tip geometry. Also in the case of the Courtoy Modul® simulation, the Presster™ could not be equipped with a pneumatic precompression roll and so, did not match the crushing strength and disintegration results obtained from the Courtoy Modul® trials, which is most probably due to the extended dwell time during precompression with the pneumatic precompression roll.

Regarding the content uniformity of the tablet samples obtained during the manufacturing press trials, it can be said that all three rotary presses produced tablets

well within the CU limits of the Ph. Eur. and the USP. According to expectations the standard deviation increased with higher speed on the traditional filling systems (Fette 2090® / Courtoy Modul®) and decreased on the centrifugal die filling system (IMA Comprima 300®).

Also worth mentioning is the observation made during the tests on the Presster™, that product B had very high ejection forces which increased with higher speed. This observation made during early development could have shown the sticking properties of the granulate material and so providing more time for the improvement.

The Presster™ with it's ability to simulate different rotary presses simply by implementing the corresponding compression rolls and tooling, clearly has an advantage over many other research tableting presses. But there are also some limitations which have to be mentioned.

- The Presster™ is not capable of simulating the feeding process of the manufacturing presses.
- The heating effect of tablets due to long run times at high speed cannot be simulated.
- The distance of the pre- and main compression rolls is not adjustable (56.2cm, whereas the Fette has 31.2cm).

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5. 100% control of soft gelatine capsules with a diode array NIR spectrometer - VisioNIR

5.1. Theory

5.1.1. NIR – historical review

In the year 1800 William Herschel discovered warming radiation beyond the visible red light, that he presented the Royal Society under the title 'Experiments on the Refrangibility of the invisible Rays of the Sun'. Today we know it must have been NIR, because the legendary telescope constructor used usual glass, which is not penetrable for longer wavelengths as infrared light. Hence the NIR area is also called 'Herschel-region'.

But it was necessary to wait until 1881 when Abney and Festing recorded the spectra of a couple of organic liquids realizing the importance of atomic groupings in the NIR spectrum and hydrogen bonding in particular. Coblentz identified the characteristics of CH-bonds in 1905 and postulated the bands could be part of a harmonic sequence.

The evolution of spectrographic instruments was underway, the diffraction grating (initially produced by winding a thin wire around a pair of fine threads) had been developed and the prism was well established. Christiansen and Rayleigh both produced relatively narrow-band optical filters, using index-matching and dyes. Just as Max Planck rounded off the 19th century with his radiation law, in 1891, Michelson published a paper describing the two-beam interferometer. Only one year later Rowland produced large ruled gratings and invented the concave diffraction grating, which became later the mainstay of spectrometer design.

Prior to the Second World War the near-infrared region was not considered to be particularly useful for the spectroscopy of organic compounds. It was observed that NIR bands are severely overlapped, difficult to resolve and to interpret. If samples were not dried before Near Infrared Analysis (NIRA) the changes in hydrogen bonding due to the effects of sample temperature, ionic strength and analyte concentration also would complicate the interpretation of mainly overlapping spectral

bands. Changes in hydrogen bonding produce real and apparent band shifts as well as flattening and broadening of band shapes. The molecular absorptions found within the NIR region have significantly lower intensity in comparison to the fundamental infrared absorptions. Thus, the changes in absorbance in the NIR region would be very small with regard to concentration changes. The relatively low extinction coefficients would place severe restrictions on the allowable noise levels and stability for any NIR instrument if quantitative work is carried out. Besides, sample presentation and the more or less obvious measurements by reflectance involve aspects which were not conceivable with the traditional infrared spectroscopy.

By the mid 1950s Karl Norris had drifted into the very near-infrared but was limited by detectors to < 1'000nm. At the U.S. Department of agriculture he demonstrated the potential value of this region for quantitative work by making measurements of agricultural products in the 1960s. The growing need to provide research facilities for fast, quantitative determination of moisture, protein, and oil provided the impetus for developing reliable calibrations.

The only commercially available instruments at that time were those developed to optimize measurements in the ultraviolet and visible regions, with the NIR capability only as an added feature. Adequate measurements without modifications were not possible, so that Norris decided to launch a new instrument specifically designed for recording NIR spectra. This instrument introduced tungsten halogen light sources, interference filters and uncooled lead sulfide detectors. The first operational unit was presented at the 1971 Illinois State Fair. Subsequently a first manufacturer designed a rotating filter grain quality analyzer. These instruments were non-user friendly dedicated systems with analog circuitry. The first dedicated on-line NIR analyzer appears to have been produced by Pier-Instrument in Germany in the late 1960s. It was vacuum tube based and employed two interference filters for the measurement of moisture. In the mid-1970s another manufacturer offered instruments for food analysis. This new instrument included features like dust-proof sealed optics and internal temperature control, thus improving the ruggedness and long term wavelength stability of the instrument. It also utilized the integrating sphere to give both reference reading and signal integration for each measurement. Many improvements of the commercially available instruments succeeded. The competition was initially

very intensive to win a large order for instrumentation from the U.S. Federal Grain Inspection Service which had adopted NIR initially as an approved method for analysis.

Obviously, the late 1960s and early 1970s saw the birth of what was to become the laboratory instrument sector of NIR analysis. By 1985, instruments had embedded microprocessors, memory was still expensive but there was a new versatility. Sets of calibrations could be stored, input data could be powerfully manipulated and results could be analyzed. Several new manufacturers appeared on the scene and a new group arose; the third party software vendors.

With personal computers rapidly dropping in price and massively increasing in performance, powerful data analysis software became available for data treatments, such as smoothing, curve fitting, regression etc. At last, principal components analysis and cluster analysis, with their origins in the 1930s, could be harnessed. Chemometrics, the name given to this expanding field by Svante Wold, had been born. Full wavelength instruments challenged wavelength pre-selection and the relative merits of the two methods have been the subject of much controversy. New optical techniques have also arisen with wavelength selection by non-linear optical crystals, acousto optical tunable filters (AOTF) and wavelength specific emitting diodes and laser diodes. The use of fiber-optical delivery means that in some applications a laboratory instrument can operate in the production environment or in hazardous areas. Over the last two decades, NIR technology has gained wide acceptance, deepening market penetration and maturity. The implementation of more powerful processors, better algorithms representing improved NIR modeling will lead to easier and more robust calibrations.

5.1.2. Spectral regions

Out of a spectroscopist's view NIR describes the transition between absorption of light energy due to transfer of electrons in the visible range (400 – 800nm or 25'000 – 12'500cm^{-1}) and absorption due to molecular vibration in the mid-range infrared region (2'500 – 5'000nm or 4'000 - 200cm^{-1}). In the area of NIR (780 – 2'500nm or 12'821 - 4000cm^{-1}) overtones and combinations of the vibration of CH, OH, SH and

NH bonds are mainly observed. All the absorption bands are the results of overtones or combinations of overtones originating in the fundamental mid-IR.

Due to absorption of light energy stretching and deformation of bonding angles are caused. The consequences are molecular vibrations. The difference between NIR and mid-IR is only the frequency of these vibrations. Whereas in mid-IR primarily fundamental vibrations are induced, the more powerful NIR provokes first, second or higher overtones. Partially combinations of fundamentals and overtones are resulting. They are due to strongly overlapping absorption bands.

5.1.3. Physical background

Vibrational spectroscopy is based on the concept that atom-to atom bonds within molecules vibrate with frequencies that may be described by the laws of physics. When these molecular vibrators absorb light of a particular frequency, they are excited to a higher energy level. At room temperature, most molecules are at their rest or zero energy levels. That is, they are vibrating at the least energetic state allowed by quantum mechanics. The lowest, or fundamental, frequencies of any two atoms connected by a chemical bond may be roughly calculated by assuming that the band energies arise from the vibration of a diatomic harmonic oscillator and obey Hooke's law.

Equation 1: Hookes law valid for ideal diatomic harmonic oscillator, with ν = vibrational frequency, k = classical force constant, μ = reduced mass of the two atoms.

$$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}}$$

This works fairly well for diatomic molecules and is not far from the average value of two-atom stretch within a polyatomic molecule. This approximation gives the average or center frequency of the band. Because the reduced masses of the involved atoms CH, OH and NH are 0.85, 0.89 and 0.87 respectively, the 'ideal' frequencies would be quite similar. But in actual molecules, the electron-withdrawing or donating properties of neighbors determine bond strength, length and thus frequency, so that an

average value is of little use in structural determinations. These differences underline the development of a real spectrum. The k values (bond strength) vary widely and create energy differences, which can both be calculated and used in spectral interpretation.

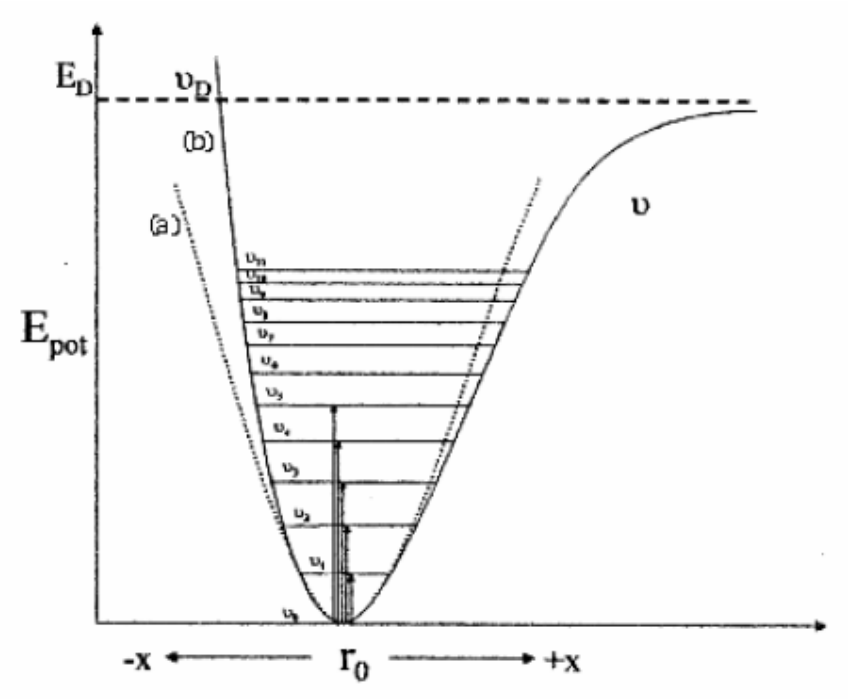

Figure 1: Potential energy diagram of vibrational mode calculated as (a) an ideal harmonic diatomic oscillator, and (b) an actual anharmonic diatomic oscillator (E_{pot} = potential energy, E_D = dissociation energy, r_0 = interatomic distance, ν_x = energy level).

Fundamental frequencies

Unlike the classical spring model for molecular vibrations, there is no infinite number of energy levels. Instead of a continuum of energies, there are discreet energy levels described by the quantum theory. The time independent Schroedinger equation is solved using the vibrational Hamiltonian for a diatomic molecule. Somewhat complicated values for the ground state ($\nu = 0$) and succeeding excited states are obtained upon solving the equation. Absorption of a photon of suitable energy can cause the molecule to change between vibrational energy levels. At room temperature only the ground state has a significant population, so that transitions due to absorption at these temperatures occur from the ground state.

A simplified version of these levels may be written for the energy levels of diatomic molecules, where the Hooke's law terms can be seen:

Equation 2: Valid for ν = 0, 1, 2, … and h = Planck's constant.

$$E_\nu = \left(\nu + \frac{1}{2}\right)\frac{h}{2\pi}\sqrt{\frac{k}{\mu}}$$

Rewritten using the quantum term hν, the equation reduces to

Equation 3: : Valid for ν = 0, 1, 2, … and h = Planck's constant.

$$E_\nu = \left(\nu + \frac{1}{2}\right)\cdot h\nu$$

In case of a non-linear molecule with N atoms, there are a considerable number of energy levels. Ideally, one can treat such a molecule as a series of diatomic, independent, harmonic oscillators and the above equation can be generalized to

Equation 4: Valid for $\nu_1, \nu_2, \nu_3, \ldots$ = 0, 1, 2, … and h = Planck's constant.

$$E\left(\nu_1, \nu_2, \nu_{3,\ldots}\right) = \sum_{i=1}^{3N-6}\left(\nu_i + \frac{1}{2}\right)\cdot h\nu_i$$

Transition between ground state and excited energy level one (ν = 1) gives the fundamental absorption if this leads to change in molecular dipole moment allowed by selection rules. Transitions between ground state and excited energy level two (ν = 2) or higher ones (ν > 2) give overtones. Transitions between multiple states can occur and give rise to combination bands. NIR spectra contain these overtones and combinations derived from the fundamental vibrations which appear in the mid-IR. From the selection rules viewpoint, overtones and combinations are not allowed, but appear as weak bands due to anharmonicity or Fermi resonance.

5.1.3.1.Anharmonicity and overtones

In practice the so-called ideal harmonic oscillator has limits. As the mass approaches the point at which the spring is attached to the ceiling, the real compression forces that counteract the bulk of the spring are often disregarded in calculations. As the spring stretches, it eventually reaches a point where it looses its shape and fails to return to its original coil. This ideal case is shown in part (a) of the potential energy diagram (figure 1). The barriers at each end of the cycle are approached in a smooth and orderly fashion. In molecules, likewise, the respective electron clouds of the two boundary atoms restrict the approach of the nuclei during the compression step, thus, creating an energy barrier. On extension of the stretch, the bond eventually breaks when the vibrational energy level reaches the dissociation energy. The barrier at smaller distances increases at a rapid rate, while at the far end of the stretch it slowly approaches zero (shown in part (b) of the potential energy diagram). The energy levels in the anharmonic oscillator are not equidistant, but slightly closer as the energy increases. This phenomenon is expressed by the following equation.

Equation 5: The anharmonic oscillator, where $\omega_e = (1/2\,\pi)(k_e / \mu)^{1/2}$ = vibrational frequency, x_e = anharmonicity constant, k_e = anharmonicity force constant, and μ = reduced mass of the two atoms.

$$E_\nu = \left(\nu + \frac{1}{2}\right) \cdot h\omega_e - \left(\nu + \frac{1}{2}\right)^2 \cdot h\omega_e x_e + higher\ terms$$

In practice, the anharmonicity constant is between 1 and 5%, thus, the first overtone wavelength of a fundamental of 3'500nm would be

Equation 6: Computation of the first overtone wavelength of an exemplary fundamental.

$$\lambda = \frac{3'500}{2}\left(1 + x_e + 3x_e^2 + ...\right)$$

Depending on structural or ambient conditions, the number may range from 1'768nm to 1'850nm for this example. However, it would generally appear at 1'750nm plus a relatively small shift to a longer wavelength. Due to forbidden transitions, the overtones are between 10 and 1'000 times weaker than the fundamental bands. Thus,

a vibration band would have to be in their third or fourth overtone to appear in the NIR region of the spectrum. For example, a fundamental carbonyl stretching vibration at 1'750cm^{-1} or 5'714nm would have a first overtone at about 3'000nm, a weaker second overtone at about 2'100nm and a third very weak one at about 1'700nm. The fourth overtone, at approximately 1'400nm could be left out. These are based on an example 5% anharmonicity constant.

As a rule, overtones occur at half and third of the fundamental absorption wavelength i.e. two and three times the fundamental frequency. Most overtones peaks arise from the stretching and bending modes because the dipole moment is high: OH, CH, SH and NH are strong NIR absorbers and form most NIR bands.

5.1.3.2.Combination bands

Another prominent feature of the near-infrared spectrum is the large number of combination bands. In addition to the ability of a band to be reproduced at twice or threefold the frequency of the fundamental, here is a tendency for two or more vibrations to combine (via addition or subtraction of the energies) to give a single band.

A simple system containing combinations bands is the gas sulfur dioxide (SO_2). From the simple theory of allowed bands there should be three absorption bands according to the following equation.

Equation 7: Calculation of the degrees of freedom.

$$Number\ of\ bands = 3 \cdot N - 6$$

These are the symmetric stretch (found at 1'151cm^{-1}), the asymmetric stretch (found at 1'361cm^{-1}) and the O-S-O bend (found at 519cm^{-1}). The tree bands mentioned are the allowed bands according to group theory. However, bands also appear at 606, 1'871, 2'305 and 2'4991cm^{-1}. As discussed earlier, it is impossible for the molecule characterized as a harmonic oscillator to acquire energy to be promoted from the ground state to a second level (second overtone) or higher. For the anharmonic

oscillator, although a first overtone of twice the frequency of the symmetric stretch is possible. This band occurs at 2'305 cm^{-1}, with the 3 cm^{-1} difference arising from an exact doubling of the frequency accounted for by the anharmonicity.

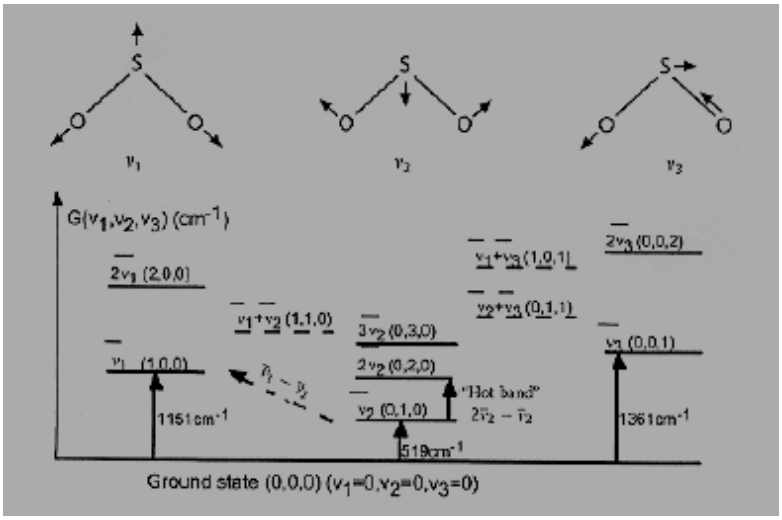

Figure 2: Illustration of the anharmonic vibrations of SO_2.

This still leaves three bands to be explained. If the possibility exists that two bands may combine as $\nu_a - \nu_b$ or $\nu_a + \nu_b$ to create a new band, then the remaining three bands are easy to assign arithmetically. The total bands for SO_2 can be assigned as seen in the table below. In the same manner, any unknown absorption band can, in theory, be deduced from first principles. When the bands in question are CH, NH and OH (4000 - 2500cm^{-1}), the overtones and combinations make up much of the NIR spectrum.

$\nu(cm^{-1})$	Assignment
519	ν_2
606	$\nu_1 - \nu_2$
1’151	ν_1
1’361	ν_3
1’871	$\nu_2 + \nu_3$
2’305	$2\ \nu_1$
2’499	$\nu_1 + \nu_3$

Table 1: Band assignments for the infrared spectrum of SO_2.

While readily apparent in the better-resolved mid-IR, these effects, like fundamentals, overtones and combinations of these two, is somewhat difficult to observe in the NIR region, often hidden under the broad, overlapping peaks associated with this region. Adding Fermi resonance to the overlapping combination and overtone bands already seen in the NIR, it is easy to understand why the region was dismissed for so many years as unusable. With current computers and chemometric software, however, these broad, undistinguished bands are merely non-esthetic while eminently usable. The NIR signal measured is a complex function of physical and chemical parameters that has to be resolved chemometrically.

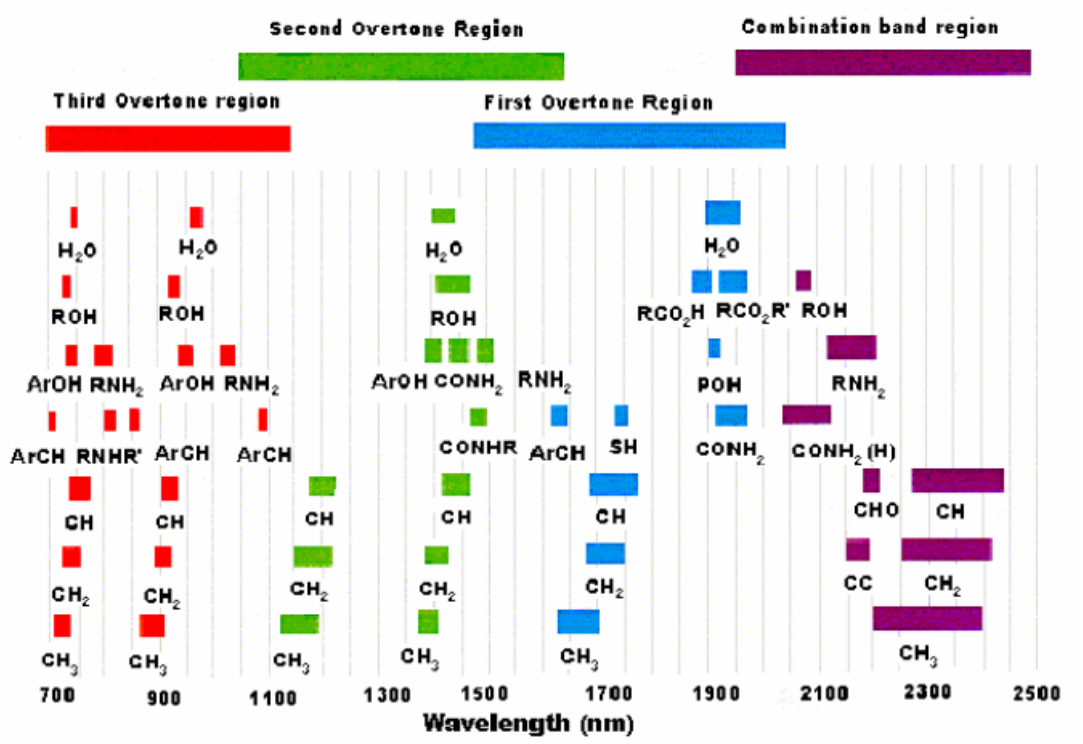

Figure 3: Table of near-infrared absorption bands of common functional chemical groups assigned to overtones and combinations.

5.1.4. NIR sampling modes

Different sampling techniques are leading to diverse results. Depending on the interest of information an adequate illumination mode has to be selected.

5.1.4.1.Transmittance

In case of liquids, solutions, goods in bulk, solids and tablets or capsules transmittance measurements are very common. The light source and the detector are positioned opposite of each other and the incident light has to cross the whole sample to be detected. Thus the spectrum contains a sum of information about surface and core of the sample. On the other hand this technique is only applicable if light intensity is high enough to penetrate the sample depending on the absorption coefficient and the sample thickness.

5.1.4.2.Diffuse reflectance

In contrast to the prior, the diffuse reflectance mode is used for solid substances and requires a different spectrometer configuration. Whereas source and detector are on the same side in an angle of 45° to each other, the light reaches the surface of the sample. Depending on its structure it penetrates some millimeters and the majority is absorbed. The rest is reflected but reaches only partially the detector. The deeper zones of the sample are not regarded. If the physical properties of the surface, like e.g. the particle size, vary a lot the corresponding spectrum may be dominated by these influences rather than the chemical information. If the surface is a 100% reflector like Spectralon virtually no absorbance will be recognized.

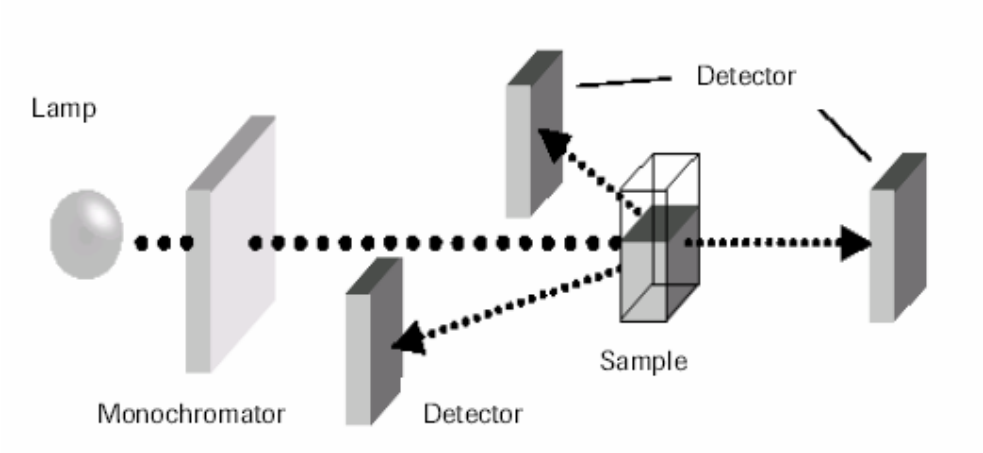

Figure 4: Illustration of NIR measurements in diffuse reflectance and transmittance mode.

5.1.4.3.Transflectance

Transflectance combines both transmittance and reflectance modes and can be used for both, solid and liquid substances. Behind the sample a mirror is installed to reflect the light back on the detector being on the same side as the source where diffusely reflected and transmitted light is detected in mean time. While the incident light has to cross the sample even twice, here the restrictions of transmittance measurements are especially relevant.

All of these sampling modes can be combined with, in some cases even, very long fiber optic probes out of quartz glass, guiding the incident light to the sampling zone or leading the reflected light back to the detector (1).

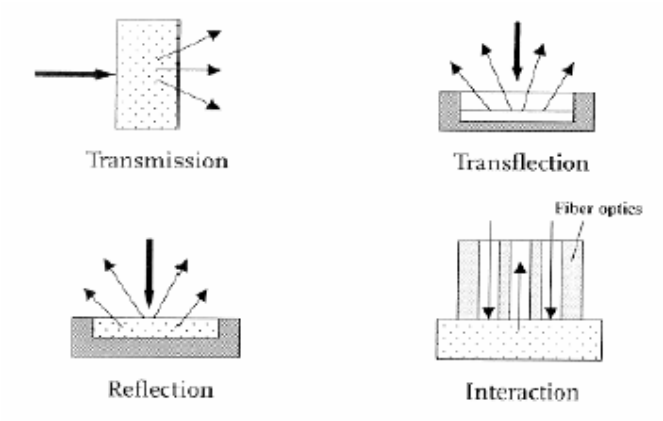

Figure 5: Overview of the different sampling modes that can also be combined (1).

5.1.5. Data transformation

There are many approaches, which describe the procedures during the diffuse reflectance mathematically. J. H. Lambert described this effect already in the year 1760 with the Lambert's cosine law. The experimental verification of this law by Pokrowski and Wright showed that the law is only valid with a small angle of incidence and a small observing angle. Gustav Mie developed a theory regarding the elemental single-scattering process. Theories about multiplicative scatter are given with the radiative transfer equation and with the Kubelka-Munk function. A detailed description of these theories can be found by Olinger et al. and Ploss HJ. Olinger and Janosch showed that the reflection measurements of analytes in a matrix gave poor results using the Kubelka-Munk function. The linearity between the concentration of the analytes and the intensity of the reflectance measurement was not sufficient. A new theory which described the diffuse reflectance for multiple layers was developed by Dahm in the year 1999. The best results are obtained if the intensity of the bands is described as the apparent absorption of the measurements with diffuse reflectance. If it is assumed that with diffuse reflectance on a sufficient layer thickness, a transmission barely takes place, then the apparent absorption is made up of the

scattered light and absorbed light. The calculation is done with the following equation

Equation 8

$$A' \approx -\log(R')$$

Equation 9: R' = Apparent absorption, A' = reflection, R_{Sample} = intensity of the measured sample, $R_{Reference}$ = intensity of the measured reference.

$$R' = \frac{R_{Sample}}{R_{Reference}}$$

By using log 1/R a nearly linear correlation between the analyte concentration and the apparent absorption is achieved.

5.1.5.1.Derivative spectroscopy

The most common data transformation method used in spectroscopy is the making of derivative spectra. Ph. Eur mentions the derivative spectroscopy along with the multiplicative scatter corrections (MSC) as an appropriate method of data pre-treatment. Works from Blanco et al. show that for quantifications the derivative spectroscopy is superior to other methods such as normalization or the multiplicative scatter corrections. As the NIR-spectra can not be described with a definite mathematical equation, the derivative has to be calculated with a special algorithm and techniques. A commonly used algorithm is the Savitzky-Golay algorithm, which is a box-car function. The spectrum is divided into many, equally big segments and these are then derived under consideration of the neighbor segment. A disadvantage of derivatives is that the signal to noise ratio gets worse with higher derivative factors. With the first derivative a basis line shift correction will be done on the spectra. The linear slope of the basis line following the wavelength is eliminated. Thus, basis line offsets occurring due to e.g. different particle size, can be eliminated with the first derivative. The second derivative describes the curvature of the spectra. By establishing the second derivative the spectra will be normalized to their extreme

values and border effects will be neglected for several bands. The signal to noise ratio increases by factor four with the second derivative.

5.1.5.2.Chemometrics

Based on the digital measurement technique a spectrum consists of multiple discrete measured values. However the measured values do not correspond to the real values as every measurement contains systematical and random errors. By carefully choosing the analyzing method and a thorough validation it is tried to minimize the systematical error, and keep it constant. The random error is eliminated by repeating the measurements. With the help of statistics the average value of the repeated measurements can be given as the measured value and the variance can be given as a measure of the precision of the analyzing method. As in most cases, the variance is not known and an exact calculation of the measured value is not possible. With empirical approximation calculation it is tried to describe the occurring phenomena mathematically, by taking relevant factors into account. For this there are sufficient amounts of measurements needed, the knowledge of the different factors and their influence on the measurements results. In order to be able to use multivariate data, chemometrics are put to use. Chemometrics is a relative young science, which tries to extract the relevant information out of a dataset with the help of mathematics and statistical methods. A chemometrical method for data analysis is the mathematical distinction and classification of different factors with the help of statistical approximation calculation. A precondition for these calculations is a dataset which was created by carefully planned experiments. The factors contained in the dataset must be linearly independent, in order to be able to calculate the single factors from the dataset. One of the most important methods for determining and weighing of the factors is the Principal Component Analysis (PCA).

5.1.5.3.Principal Component Analysis (PCA)

PCA forms the basis for multivariate data analysis. It goes back to the French mathematician Cauchy, but was first formulated in statistics by Pearson, who described the analysis as finding lines and planes of closest fit to systems of points in space. The most important use of PCA is to represent a multivariate data table as a

low dimensional space. Statistically, PCA finds lines, planes and hyper-planes in a K-dimensional space that approximate the data as well as possible in the least squares sense.

The starting point for PCA is a data matrix (X) with N rows (observations) and K columns (variables). The observations can be analytical samples with measured properties being reflected in the variables of spectral origin. Each X-variable defines a coordinate axis in a K-dimensional space. The principle of representing rows as points in a space makes it possible to convert a data table to graphical representation. All the observations of X are displayed in K-space as a swarm of points.

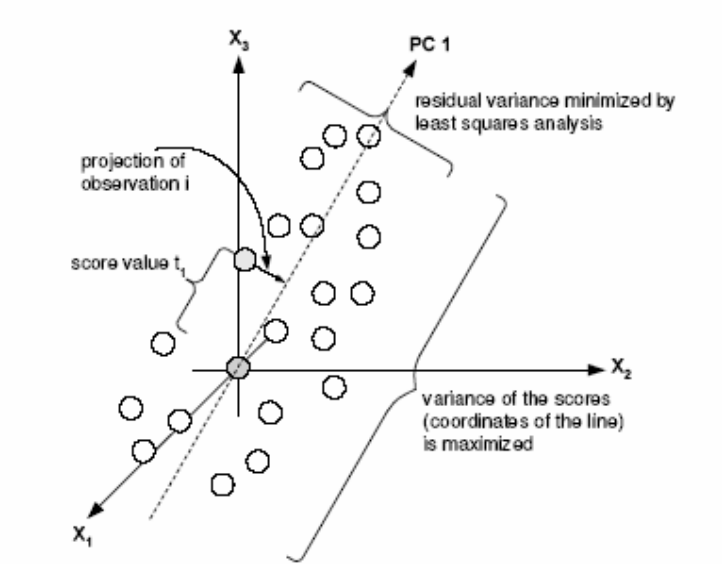

Figure 6: PCA derives a model that fits the data as well as possible in the least squares sense. Alternatively, PCA may be understood as maximizing the variance of the projection coordinates. Each observation is projected onto this line in order to get a coordinate value along the PC-line. This value is known as score.

After mean centering and scaling to unit variance, the data is set ready for computation of the first principal component (PC 1). This component is the line in the K-dimensional space that best approximates the data in the least squares sense. This line goes through the average point. Each observation may now be projected onto this line in order to get a coordinate value along the PC-line. This new coordinate value is known as a score.

Usually one component is insufficient to model the systematic variation of a data set. Thus, a second component (PC 2) is calculated. The second PC is also represented by a line in the K-dimensional variable space, which is orthogonal to the first PC. This line also passes through the average point and improves the approximation of the X-data as possible.

When two principal components have been derived they together define a plane, a window into the K-dimensional variable space. By projecting all the observations onto this low dimensional sub-space and plotting the results, it is possible to visualize the structure of the investigated data set. The coordinate values of the observations on this plane are called scores, and hence the plotting of such a projected configuration is known as a scores plot and represents a tool for geometric interpretation of the relationships of the variables.

The scores are accompanied by the corresponding loadings. Geometrically, the principal component loadings express the orientation of the model plane in the K-dimensional variable space. The direction of PC 1 in relation to the original variables is given by the cosine of the angles. These values indicate how the original variables load into, or contribute to the principal component. The loadings are used for interpreting the meaning of the scores.

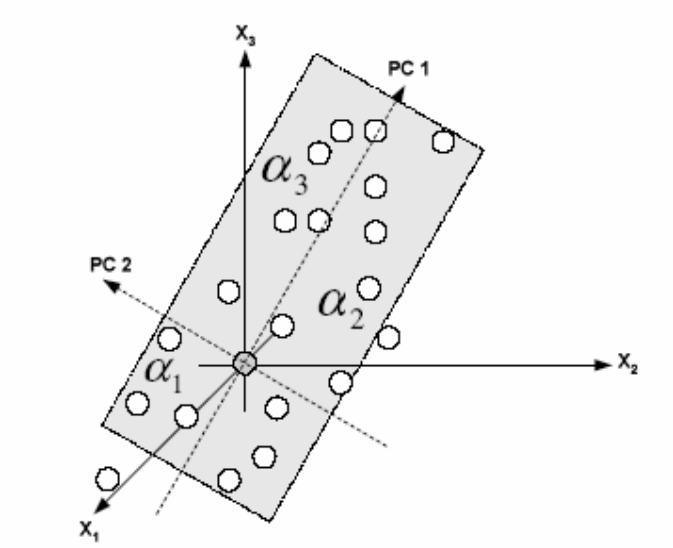

Figure 7: The principal component loadings uncover how the PC model plane is inserted in the variable space. The loadings are used for interpreting the meaning of the scores.

By using PCA a data table X is modeled as:

Equation 10: The first term represents the variable averages and originates from the preprocessing step. The second term is the matrix product and models the structure. The third term, the residual matrix *E*, contains the noise.

$$X = 1\overline{x'} + TP' + E$$

The principal component scores of the applied components ($t_1, t_2, t_3, \ldots$) are columns of the score matrix *T*. These scores are the coordinates of the observations in the model (hyper-) plane. Alternatively, these scores may be seen as new variables which summarize the old ones. In their derivation, the scores are sorted in descending importance.

The meaning of the scores is given by the loadings. The loadings of the components (PC 1, PC 2, PC 3, …) build up the loading matrix *P* (figure below). The loadings define the orientation of the PC plane with respect to the original x-variables. Algebraically the loadings inform how the variables are linearly combined to form the scores. The loadings unravel the magnitude (large or small correlation) and the

manner (positive or negative correlation) in which the measured variables contribute to the scores.

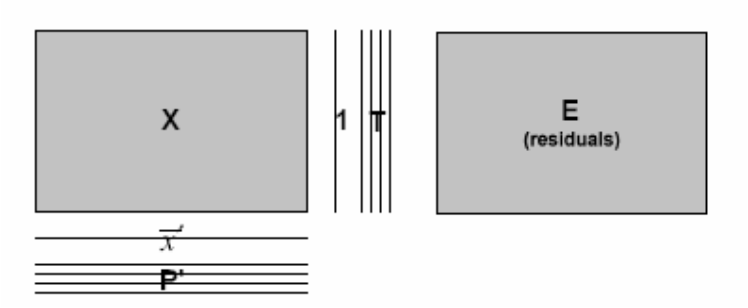

Figure 8: A matrix representation of how a data table X is modeled by PCA.

Loadings and scores are sufficient to give a satisfactory description of each of the variables in the K-dimensional space. If a high number of observations is involved but only few PCs necessary to lead to low residuals, a severe data reduction has taken place by the projection of the individual observations on the lines, planes or hyper-planes (2).

5.1.6. The VisioNIR pattern recognition method

The packaging lines of today run with a speed of up to 1200 blister per minute. For the analysis of each and every tablet or capsule, there is only approximately 5msec time available. Within this time, the measurement, the evaluation and the rejection of non compliant products must occur. The challenge was to develop mathematical algorithms and statistics, which are simple and fast enough, to take pace with the continuously incoming data every 2 ms of an online inspection system. The necessary steps of the evaluation algorithm are presented below (3).

5.1.6.1.Data pretreatment

First some data pretreatments are carried out to prepare data for comparison. For calibration correction the raw spectrum (figure below) data were standardized to a highly reflective spectralon standard and to the diode dark current by using the algorithm

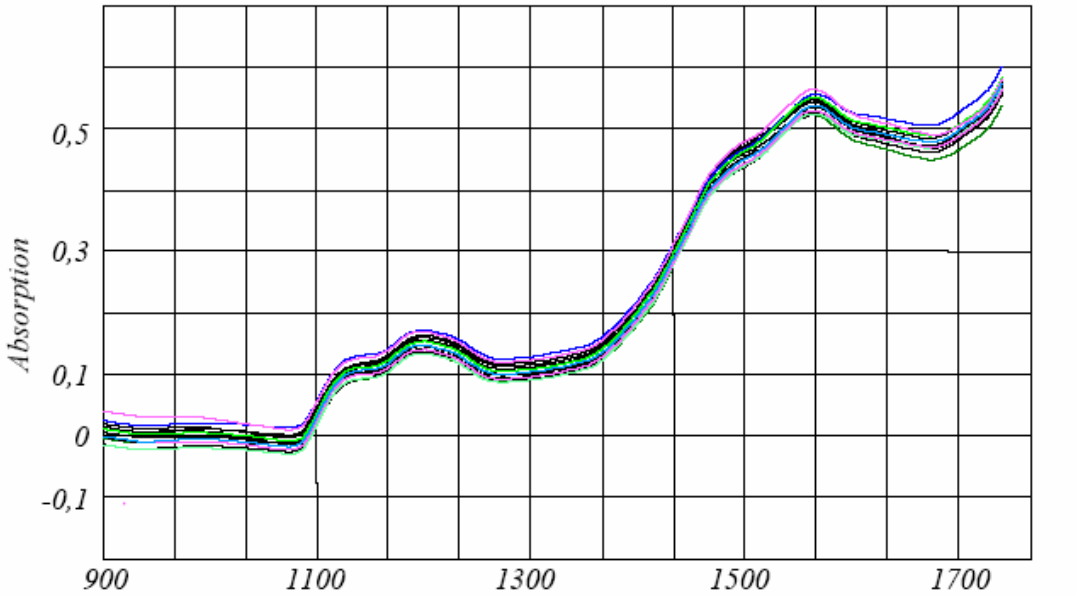

Figure 9: VisioNIR raw spectra

Equation 11

$$Ical_n = \frac{Iraw_n - Idark_n}{Iref_n}$$

where n is the wavelength number (corresponding from 900 to 1700 nm), $Ical_n$ is the calibrated intensity, $Iraw_n$ raw intensity value; $Idark_n$ is the intensity due to diode dark current; $Iref_n$ is the intensity of reference target (spectralon plate). This transformation includes the correction for odd, even pixel effects, if the intensity within the sample area is not uniform. Next a Gaussian weighting function over seven points is used to smooth the raw data (Ismoothed) and reduce the effects of noise. To

reduce the effects of different intensity values due to tablet orientation, the data is auto scaled (mean centered over the range of wavelengths).

Equation 12

$$Iscaled_n = \frac{Ismoothed_n - \overline{Ismoothed}}{\left[\sum_n \left(Ismoothed_n - \overline{Ismoothed}\right)^2\right]^{1/2}}$$

The first derivative of the data (Ideriv) is taken to highlight differences in the slope and position of spectral features between different samples. The first derivative data treatment removes additive offsets explicitly that are constant with wavelength. These data pre-treatments are carried out with every measured spectrum and the results are shown the figure below.

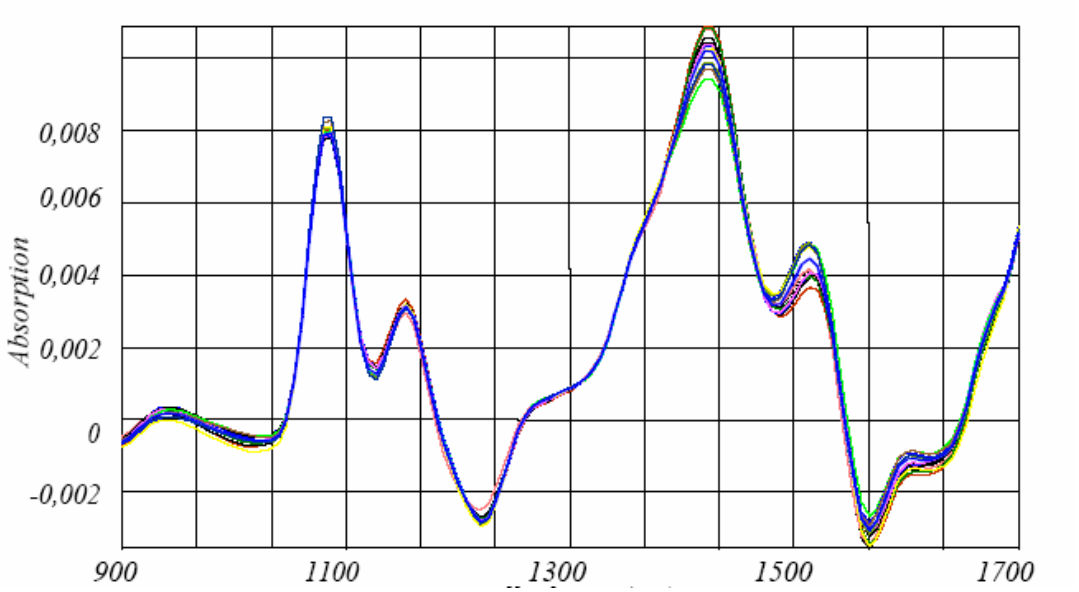

Figure 10: Pretreated VisioNIR spectra (1st derivative)

To decide whether a required spectrum and consequently the measured product meet the quality control demands a new kind of evaluation statistic was developed.

5.1.6.2.Evaluation statistics

A master model is created for each product. The spectrum of each measured product is compared with this master model and differences between them are calculated. A limit of differences is set to decide whether the sample can distinguish significantly from the master model or not. The master model for each product is created from the mean spectrum of the data measured for calibration.

Equation 13

$$Model_n = \frac{\sum_s Ideriv_{s,n}}{s}$$

where s is the range variable for all spectra acquired and S is the number of spectra. The figure below shows the master model spectrum of the interesting product and the spectrum of the nearest neighbor model. The spectra are nearly similar but differ in the intensity and slope. These differences are highlighted.

Figure 11: Master model spectrum and a faulty product spectrum (wavelength vs. intensity).

Some spectral features vary between samples of the same type, due to varying water content among or other factors. To increase the resolving power to distinguish between products that are very similar a weighting factor (WFn) is derived. This gives more emphasis to features that do not change between the product types.

Equation 14

$$DistModel_{s,n} = Ideriv_{s,n} - Model_n$$

Equation 15

$$SDModel_n = \sqrt{\frac{\sum_s \left(DistModel_{s,n} - \overline{DistModel}\right)^2}{S}}$$

Equation 16

$$WF_n = SDModel_n^3$$

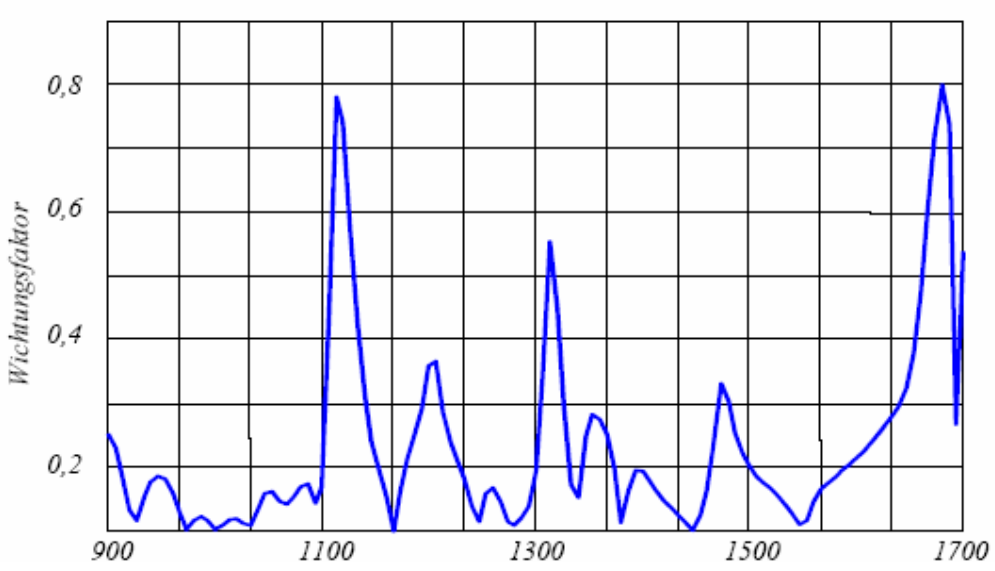

Figure 12: Weighting factor

A combined weighting factor is calculated taking the WFn and the differences between the master model spectrum and the spectrum of a measured product into

account (above figure). The combined weighting factor (cWFn) is used to calculate the Euclidean distance of each sample within the model.

Equation 17

$$EuclidDistModel_s = \sqrt{\sum_n \frac{(DistModel_n)^2}{cWF_n}}$$

The mean of this value is used to determine the standard deviation for the model (SD Model)

$$SDModel = \sqrt{\frac{\sum_s \left(EuclidDistModel_s - \overline{EuclidDistModel}\right)^2}{S}}$$

To enable an acceptable model SD the number of samples required for calibration may vary. The mean Euclidean distance (Model Difference Mean) for the model is expressed as a difference value in terms of the model standard deviation.

Equation 18

$$ModelDifferenceMean = \frac{\overline{EuclidDistModel}}{SDModel}$$

In the run mode the pre-treated spectrum for each product is compared against the master model spectrum. The Euclidean distance between the derived intensity at each wavelength and the corresponding intensity for the model is calculated, with the combined weighting factor at each wavelength applied.

Equation 19

$$SampleDist = \sqrt{\sum \frac{(Ideriv_n - Model_n)^2}{cWF_n}}$$

The `difference value' is calculated in a difference calculation from the distance values scaled in term of the model standard deviation.

Equation 20

$$SampleDifference = \frac{SampleDist}{SDModel}$$

A limit is set that is a number of standard deviations from the model difference value.

Equation 21

$$AcceptLimit = ModelDifferenceMean + LimitSD \times ModelSD$$

The Limit SD is the number of SDs away from the model difference mean that a sample difference value will be accepted as being the same as the same product as the model. A value for Limit SD of 5 gives an error rate of one error by 1.043×10^6 measurements based on the model data set. The products are rejected on NIR criteria if the Sample Difference is larger than the Accept Limit. Also products are accepted if the Sample Difference is smaller than the Accept Limit. In the figure below we can see a model in the middle and two different products on each side, which exceed the model limit of 5 SD (4).

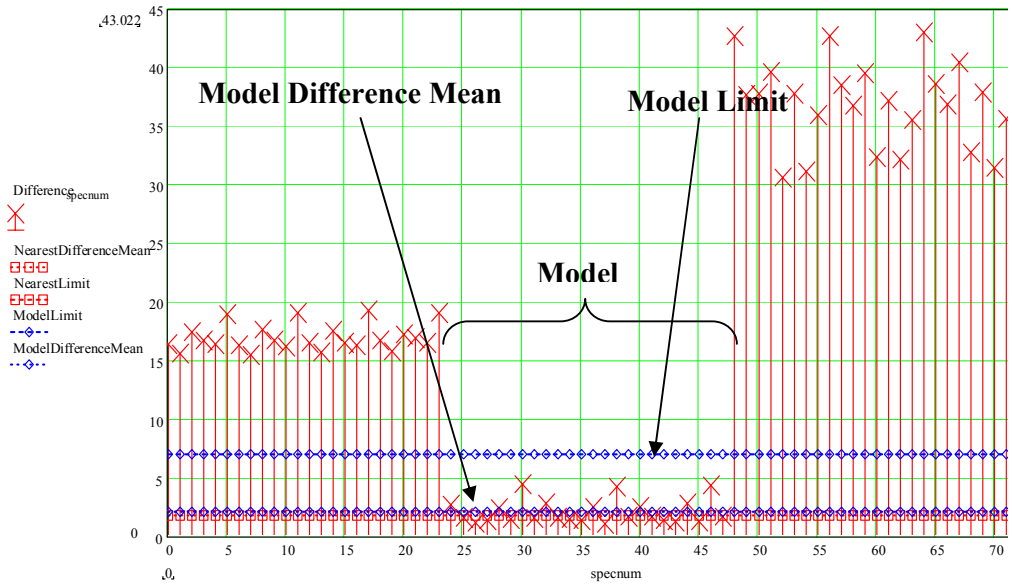

Figure 13: VisioNIR evaluation of spectral data, showing the model in the middle. On the left and on the right the measurements are shown which exceed the model limit.

The bigger the difference is, of the products being measured, the bigger the distance is on the graph.

5.2. Experimental part

5.2.1. *Introduction*

The packaging process is one of the most important process steps in the manufacturing of pharmaceutical products. Several studies reveal that, at least, a third of all drug recalls are due to packaging errors (5). If the packaging process is not fully under control, the quality of the product can not be guaranteed, as the blister might not be completely sealed and therefore not being able to uphold the expiry date, or the product might be damaged by some other means during packaging. In order to uphold quality, most packaging lines are equipped with different sensors at various positions on the line. The basic equipment on the line contains a filling control camera which controls the blister on the presence of the product or double filling of the blister-pockets. After the blisters are sealed, blisters will be taken out of the line regularly and put into a blue bath test to verify that the blisters are correctly and

tightly sealed. Usually there is also a print verification camera which will discard all blisters without clear printing on the head foil. After the blisters are put into the folding box, the box will be weighed to be sure that the right amount of blisters are in the box.

The present filling control cameras are able to verify if the blister-pockets do have a product or even if they are double filled. Many of the present cameras are black and white though, and therefore not able to detect the colour of the product, only shape and size. So during packaging, a mix-up with an equally sized and shaped product can not be excluded. Likewise, if the company has the luxury of a colour camera, a mix-up with an equally sized and shaped product, with the same or similar colour, can not be excluded as the camera is unable to detect the chemical integrity of the product.

Doing a blue bath test regularly will also not guarantee, that all the blisters are correctly sealed, as you only do the test on one cycle every two hours. All the blisters sealed in between the tests might be correctly sealed or might not.

In the case of Sandimmun Neoral soft gelatine capsules (referred to as SIM N from now on) there are 5 different types of soft gelatine capsules (SGC's) in different sizes and colours. There is a colour filling control camera present on the line which is supposed to detect whether the SGC´s are present or if a double filling has occurred. Also, if the capsules vary in colour, the camera will detect them as a foreign product. But as mentioned before, if there are SGC's which happen to have the same size and colour, these SGC's will be accepted as SIM N by the camera.

The company VisioTec has developed a quality control system called the VisioNIR®. VisioNIR® consists of a high resolution camera system, a NIR (Near Infrared Spectroscopy) spectrometer and a computer system for controlling the system. The camera system has 2 objectives. For one it performs an optical control on all products (shape, colour, size and fracture) and it locates the exact position of every single product for the NIR measurement. The products in the blister on the packaging line pass a zone of 300 × 300mm which is homogenous lighted up with halogen lamps. When passing this zone the blisters containing the products are exposed to halogen light in order to stimulate molecular vibrations. The reflected light impinges on a two-

axis mirror and is transferred into a monolithic diode spectrometer with a holographic grid via an optic fiber. Next, it is broken down into individual spectral ranges and digitized (see figure below).

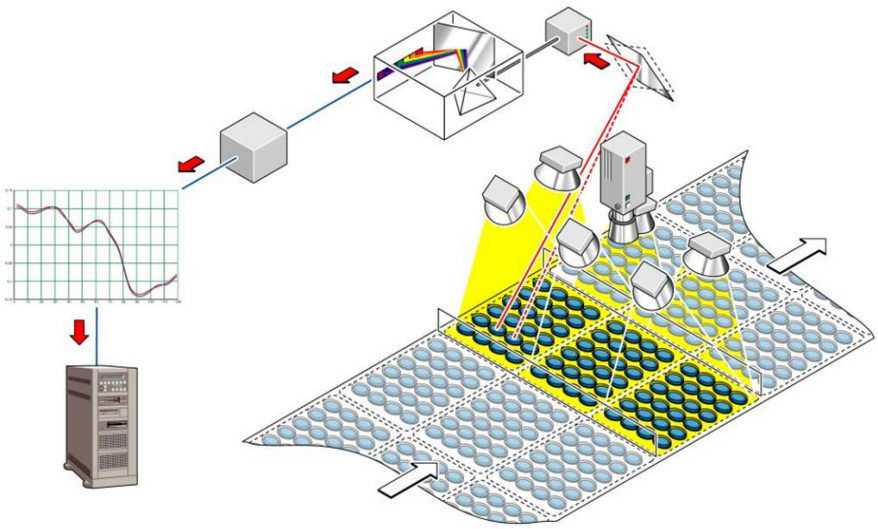

Figure 14: The setup of the VisioNIR® system. The halogen lamps stimulate molecular vibrations and the reflected light is transferred into the spectrometer via an optic fiber, broken down into its individual spectral ranges and digitized.

After the evaluation of the spectrum in the computer, the data obtained are compared to the stored set point spectrum, also referred to as the NIR-model. With this system the quality of all products, every tablet or capsule, being packed, independent of the batch size, will be determined by comparing the recorded spectra with an existing NIR-model of the product which complies to all quality specifications. If the recorded spectra show deviations above a certain limit to the NIR-model or the optical camera detects a flawed product, this blister will be discarded.

The VisioNIR system records a spectrum in the wavelength of 900 – 1700nm. The spectrum consists of 128 data points, which are equally spread over the spectral band.

5.2.2. *Objective*

The objective of this project was to determine, if the VisioNIR® system is capable of detecting different hidden flaws, not detectable by a solely optical system. The product chosen for the project was Sandimmun Neoral soft gelatine capsules in all strengths (10-, 25- grey, 25- yellow, 50- and 100mg) as this product is a life saving product and any product flaws could danger the lives of patients.

Figure 15: Different strengths and colors of SIM N. From left: 10-, 25- yellow, 25- grey, 50- and 100mg.

The following flaw types were examined by VisioNIR® and the spectra were then compared to a NIR-model of SIM N SGC's complying with all quality specifications (it should be mentioned, that the following flaws were decided based upon a brain storming session and not based upon experience from the manufacturer).

- **Empty capsule shell:**
  - Means that the shell is completely without content. This can happen via a hole in the shell. A hole in the shell could theoretically result due to improper sealing or due to a force impact on the SGC during packaging.
- **Half empty capsule shell:**
  - Part of the content of the SGC has leaked out of a hole in the shell.
- **Smudged capsules:**
  - An intact SGC which has been smudged with the content of a leaking SGC.
- **Low ethanol content:**

- When SGC are not stored properly in a sealed bag or blister, the ethanol content of the SGC quickly decreases and might influence the bioavailability of the active ingredient.

- **Mix-up:**
  - Some other product than the intended one is on the packaging line.
- **False content of SGC's:**
  - The SGC was filled with something else than the SIM N micro-emulsion. This could theoretically happen during the filling process.
- **Placebo:**
  - The SGC looks exactly the same and contains the same excipients but no active ingredient.

A further goal was also to determine if the VisioNIR® is capable of detecting mix-ups between other tablet products.

5.2.3. Project Design

VisioTec has designed simulation equipment consisting of the VisioNIR® system described above and an apparatus which moves the products in the blister under the VisioNIR®. The camera system for the locating of the products was not included. The VisioNIR® was mounted over a track and on this track there was an aluminium-slide which could easily be moved with compressed-air. The slide was capable of moving the blisters with the same speed under the VisioNIR® as they would be on a conventional packaging line. This way the recording of spectra of moving products was simulated. A folded foil (unsealed blister) was placed on the aluminium-slide and was stuck to it with a double faced adhesive tape.

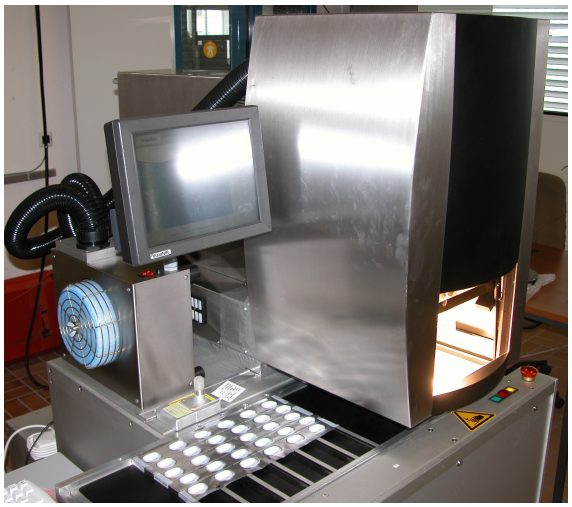

Figure 16: The VisioNIR® system and the packaging line simulator.

The locations of the blister-pockets at the time of measurement were manually entered into the controlling computer. The slide then triggered the measurement of the previously saved locations in the controlling computer when passing the light barrier placed on the side of the track. To measure the product it was placed in the blister pockets and slid under the VisioNIR® three times. Every time the slide passed the light barrier the measurement was triggered and the XY mirrors collected the reflected light at the previously saved locations. This way it was possible to record NIR-models of intact SGC's and then to place prepared SGC's on the blister (e.g. empty or smudged) and record their spectra. These spectra were then compared to the NIR-model spectra of the intact SGC's by transferring the data to an extern PC and there the data was analyzed with the software Mathcad11® (Mathsoft Inc., MS, USA). Mathcad11® compared the recorded spectra and calculated the deviation of the recorded spectra to the NIR-models. This deviation was then given as the number of standard deviations of the model-spectra or as the Euclidian distance from the model-spectra. If this distance exceeds a certain value, the Euclidian distance limit, which is the model mean difference + 5, the spectra will be rated as different and therefore the SGC belonging to the spectra not fulfilling the quality aspects.

5.2.4. Project Challenges

It is known that the content of SGC's is hard to detect with NIR, as the capsule shell contains high amounts of titanium dioxide and the grey capsules additionally contain black iron oxide, both substances making it very difficult to get light through the capsule shell thus generating molecular vibrations of the content. Therefore there had to be done some changes to the original system as the original halogen lamps did not suffice to reach the content of the grey SGC's (25mg and 100mg).

The strength of the halogen lamps was then increased to 800 watt which seemed to suffice to reach the content of the capsules. Having increased the strengths of the halogen lamps another problem was encountered. The 800W strong halogen lamps generated so much heat (>70°C), that the SGC's melted if the stayed too long under or close to the lamps. This concern was solved when the housing of the VisioNIR® system was mounted, as the housing is a closed box with a special NIR glass separating the lamps from the products. In this manner the heat was kept in the housing and transferred outside with an effective ventilation system.

In order to verify that the SGC's really were intact after being exposed to the halogen lamps some additional stability tests were done, as no stability data existed for this extreme temperature. Intact SGC's were put on the blister foil and then slid under the lamp, afterwards being examined on ethanol and propylene glycol content as these evaporate very fast. It is very important that the content of ethanol stays constant as ethanol keeps the active pharmaceutical ingredient from crystallizing. The active pharmaceutical ingredient is not bioavailable in crystalline state. One bulk of SGC's was exposed three times and one bulk for six times to the lamp. As a reference one unexposed bulk of SGC's was also examined on ethanol and propylene glycol content. Every bulk consisted of forty SGC's. These tests were done on grey SIM N 25mg as they should absorb the heat the most and therefore lose ethanol faster. All the used capsules came from the same lot. In the below figure, the results from these tests can be observed.

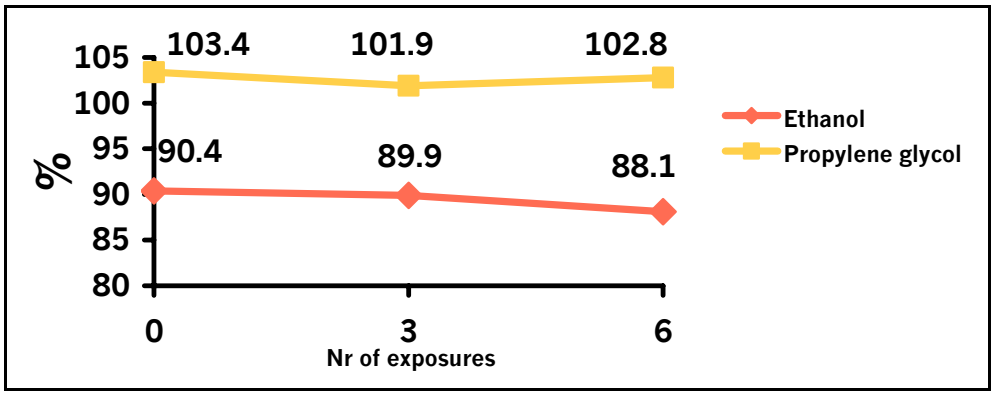

Figure 17: Stability of the exposed capsules, showing that the exposure to the hot halogen light does not affect the propylene glycol content and only slightly affects the ethanol content after six exposures.

Based on these results it is safe to say that one exposure to the lamp will not damage the SGC's in any way. It can be observed, that the ethanol content of the SGC's does decrease about 2.3% after six exposures to the lamp. The propylene glycol on the other hand does not seem to be impressed by the light exposure and stays constant after six rounds.

5.2.4.1.Making sure not to miss the target

As we could see above, the smaller SGC's (10- and 25mg) are in the shape of an American football. The blister cups of these capsules are very broad and the shape of the capsules lets them roll around in the cup during the yanking movements of the packaging line. This leads to the problem of collecting a measurement from the capsule and not from half the capsule and half the aluminum foil.

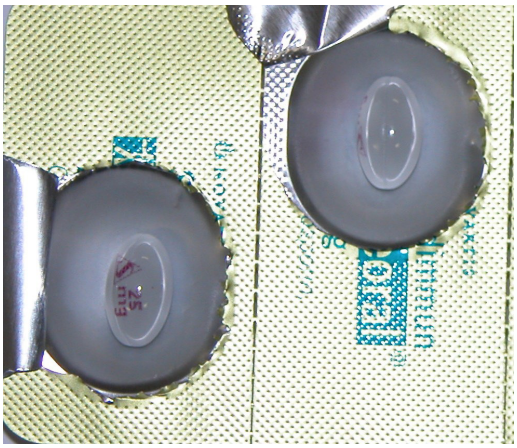

Figure 18: 25mg soft gelatin capsules with the typical American football shape in a blister.

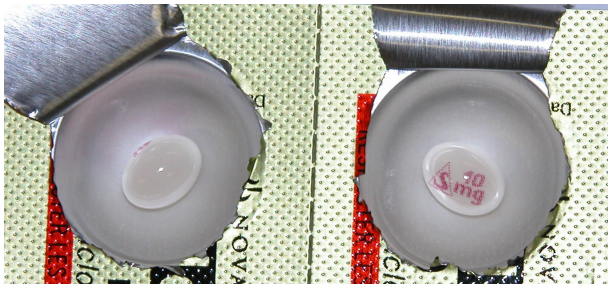

Figure 19: 10mg soft gelatin capsules with the typical American football shape in a blister.

As the visual camera detects the capsules they are sill in movement and come to a halt under the halogen lamp. Hence, due to the abrupt stop of the blister band, the capsules are set into movement and they roll around the blister cup. That is why the capsule might not be acquired with the spectrometer and so resulting to a wrong result.

The area which is measured with every movement of the mirrors was measured to be 11m in diameter. Due to that diameter of the blister cup of the 10mm capsules, it could be assumed (and the results showed later) that the measuring spot always detects the whole capsule and parts of the aluminum foil.

For the 25mg capsules it is another story. In order to be sure that the capsule was detected in the best possible way, there were made three measurements in the blister cup. One in the middle and one on the top and bottom

Figure 20: The three measuring spots in the 25mg blister cup.

These measurements were then all compared to the NIR-model and spectrum which is closest to the mean model spectrum is used for the final evaluation. For the measurements there were ten capsules measured whereas five capsules were prepared and five intact. These ten capsules were then measured three times and compared to a NIR-model recorded before.

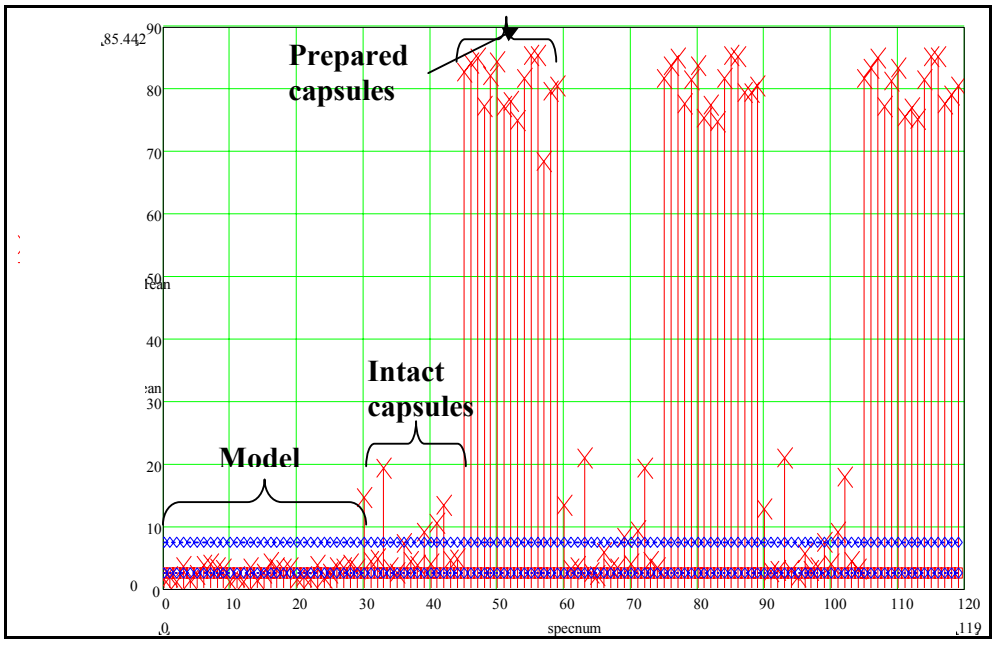

Figure 21: All spectra recorded compared to a NIR-model. The first thirty spectra represent the NIR-model and all spectra after that the test with the intact and prepared capsules.

In the figure above it can be observed that after the 29th spectrum (the first spectrum is number zero) the intact capsules are measured. It can be seen that some of the spectra exceed the model limit of five Euclidian distances, which only means that the measuring spot did not hit the capsule well. The first five capsules were measured with three spots on every capsule, which means that there are fifteen of them. The next fifteen spectra then belong to the prepared capsules. After the 59th spectrum the measurement is repeated.

Below the selection of the closest spectra to the NIR-model can be observed.

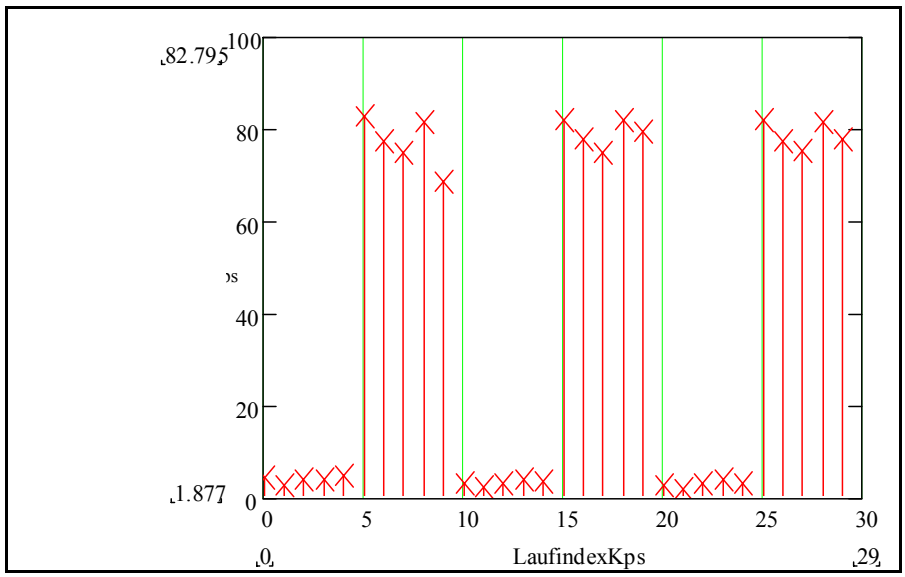

Figure 22: The five selected spectra from the 15 spectra respectively.

In the above figure the NIR-model is not depicted anymore, but the distinction of the prepared capsules to the intact capsules can be observed very well.

5.2.5. Experiments Description and Results

As mentioned above, there are NIR-models needed of the products which fulfil all required quality aspects. These were acquired by placing intact capsules on the blister and their spectra was then recorded and saved. These NIR-models were recorded in a standstill and made sure that the mirrors were completely centred on each and every

capsule. The NIR-model then consists of three spectra of every capsule placed on the blister.

All prepared capsules were then detected amongst intact capsules and the recorded data then transferred to the extern PC where it was evaluated with the help of MathCad11®. There the recorded spectra could be compared to the corresponding NIR-model and the Euclidian distance was calculated. The limit for the capsules having the same quality as the model capsules was five Euclidian distances added to the model mean difference.

The spectral range used for the evaluation of the measurements was cut down from 900 – 1700nm(all 128 diodes) to 1060 – 1460nm (diode numbers 27 – 96). This showed much better distinction of the prepared capsules as the relevant information seemed to be contained in that area. Towards the ends of the spectra there was also quite much noise.

5.2.5.1.Empty

The SGC's were emptied with a syringe, making a small hole on each end of the capsule and then blowing out the content by injecting air into the capsule. These freshly emptied capsules were then placed on a blister amongst intact capsules and then detected and evaluated as described above. They were detected fresh, otherwise the ethanol would have evaporated out of the capsule shell and so changing the composition of the capsule shell, making the deviation higher. By doing this, the possibility is being tested of detecting empty capsules which either got damaged in the packaging line, thus smudging other capsules, or already empty capsules which possibly got damaged shortly after production.

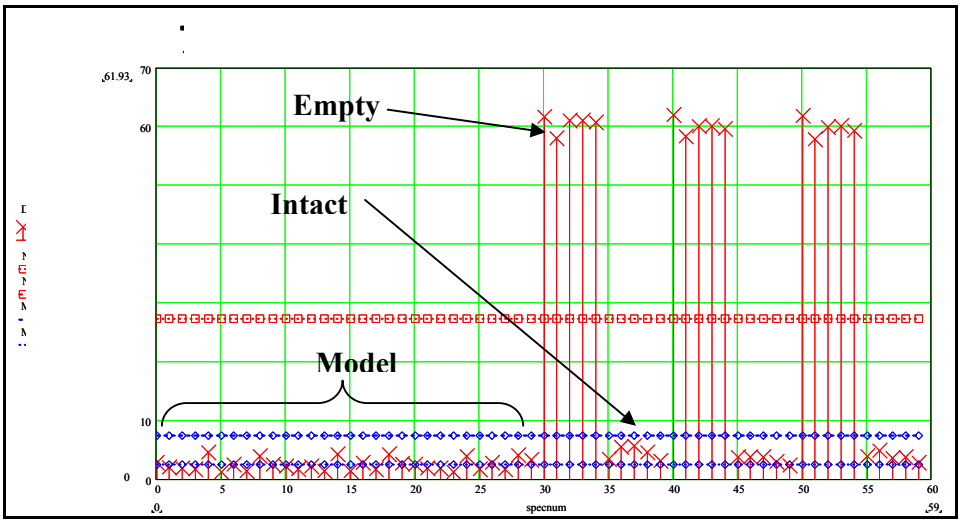

Figure 23: 10mg capsules empty. There is a clear distinction between the empty capsules and the intact capsules.

As explained above, a NIR-model is first scanned into the system and this model will then be compared to the prepared capsules. In the above figure, the model consists of ten intact 10mg SGC's which were recorded three times. These 30 spectra were then used as a model. Five of the prepared SGC's were then put onto the blister amongst five intact SGC's and then again measured three times. The above figure shows an excellent distinction between the intact capsules and the empty ones. Also the intact capsules were also recognized as good quality capsules.

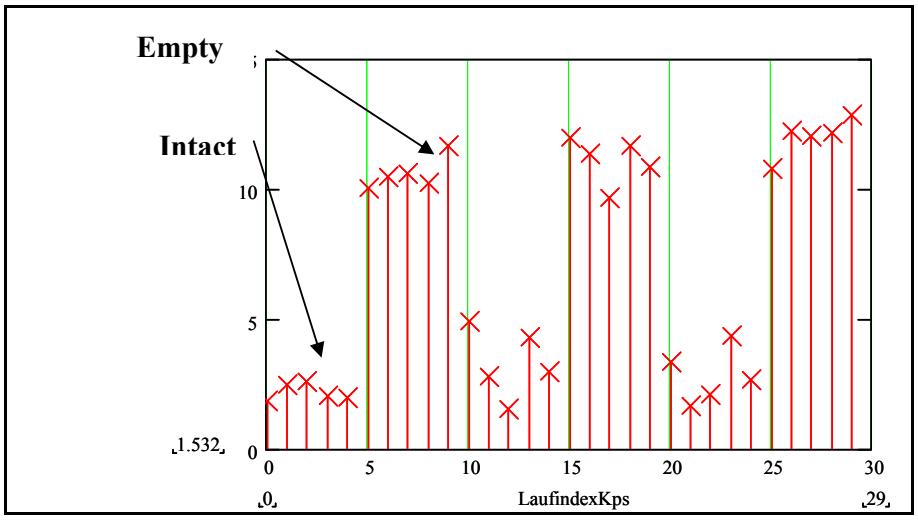

Figure 24: 25mg grey empty. A distinction of about 7 euclidian distances can be seen.

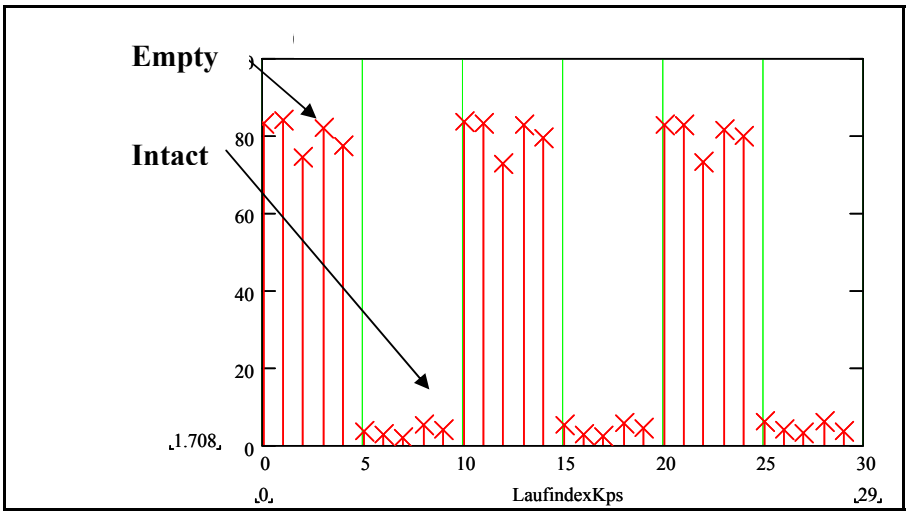

Figure 25: 25mg yellow empty. An excellent distinction between the empty capsules and the intact capsules.

As can be seen in the above figure, the multiple measuring methods were used, as the small 25mg SGC's could be situated anywhere in the blister pocked due to the yanking movement of the packaging line, or in this case, the simulator. From the three measurements made on each blister pocket the one measurement which is the closest to the NIR-model is sorted out and displayed in the above figure. We can see that the 25mg grey SGC's could be separated with at least five Euclidian distances and the 25mg yellow even with approximately 70 Euclidian distances.

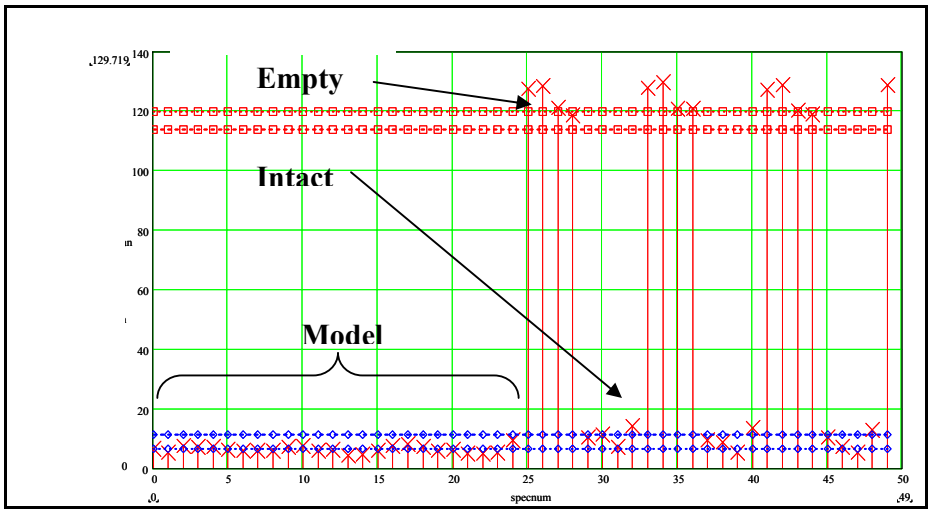

Figure 26: 50mg empty. An excellent distinction between the empty and the intact capsules.

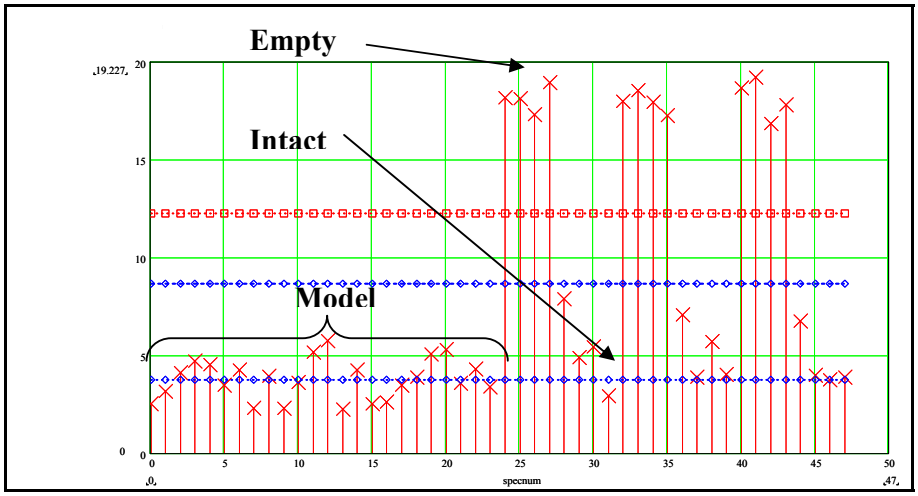

Figure 27: 100mg empty. A clear distinction between the empty and intact capsules.

It was possible to detect all empty capsules for all strengths and types. As we can see on the graphs above, the deviation is the smallest for the capsules which contain black iron oxide in the capsule shell (25- and 100mg, grey capsules), which leads to the conclusion, that the halogen light doesn't penetrate them as well as the others.

5.2.5.2.Half-full

These capsules were done the same way as the totally empty ones, except that only half of the content was retracted with the syringe. This simulates the detection of fresh damaged capsules which have only lost parts of their content. The 10mg capsules were left out of this experiment as they have so little content.

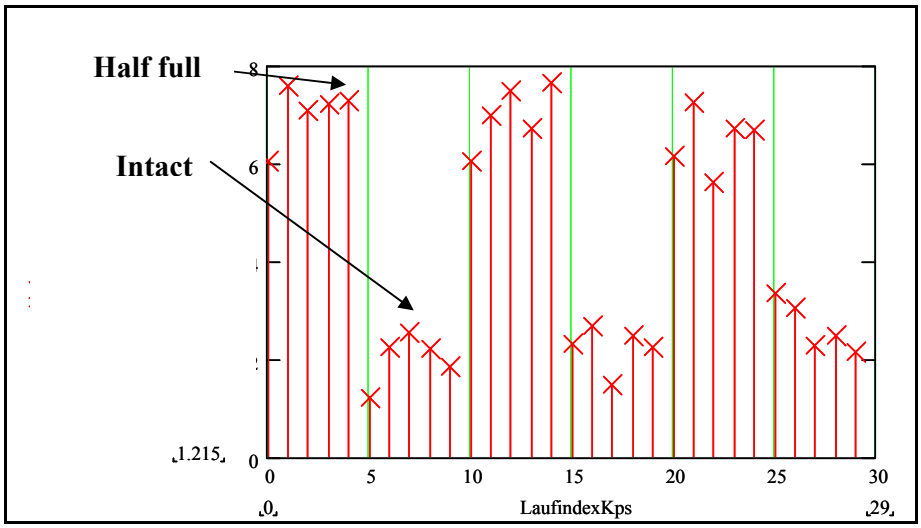

Figure 28: 25mg grey, half full. The distinction of the half full from the intact capsules is approximately 4 euclidian distances.

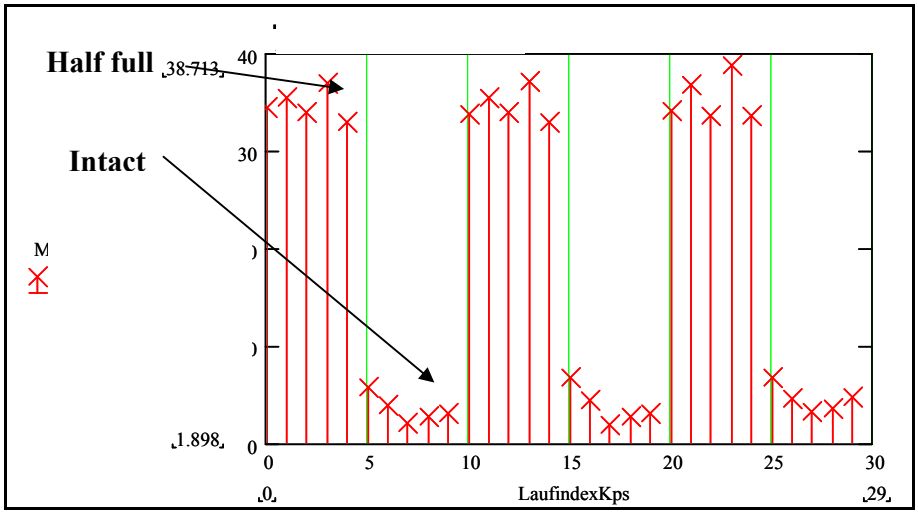

Figure 29: 25mg yellow, half full. A clear distinction between the half full and intact capsules.

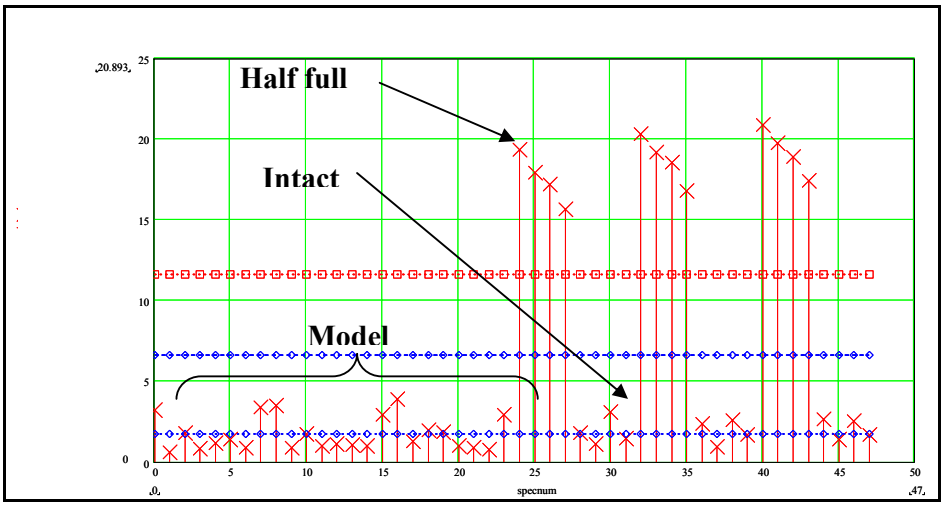

Figure 30: 50mg, half full. A clear distinction between the half full and the intact capsules.

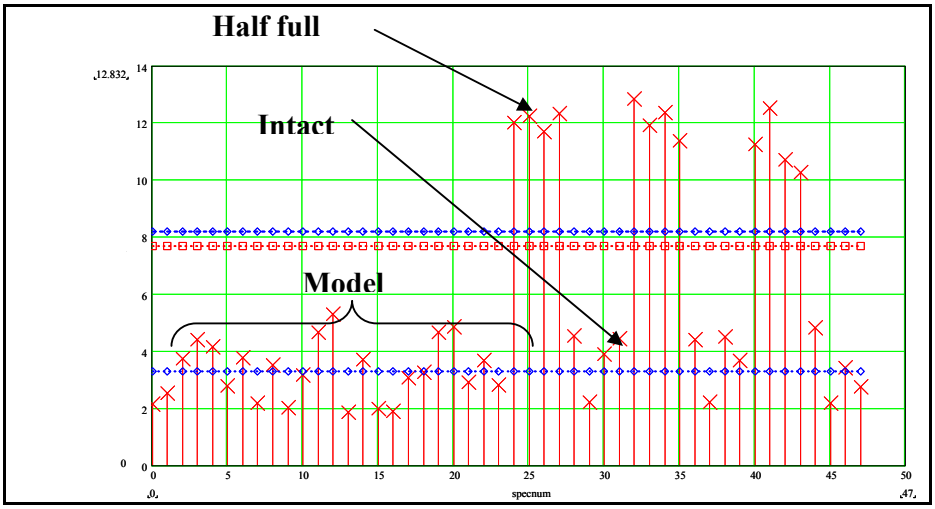

Figure 31: 100mg, half full. A clear distinction between the half full and intact capsules.

It was possible to detect all half-full capsules for all strengths and types. Again it is apparent, that the black iron oxide disturbed the detection of the content as the deviation wasn't as high for these as for the others.

5.2.5.3.Smudged (Lightly and excessive)

The micro emulsion of the SGC's was blown out with a syringe the same way as was done for the preparation of the empty capsules. The micro emulsion was collected and then used for the smudging of the capsules. The capsules were dipped into the

micro emulsion and then placed on the blister, having so much micro emulsion on it, that it created a small puddle in the blister cup, simulating an excessively smudged capsule. By doing this the possibility of detecting capsules which have been smudged by an open, damaged capsule is being simulated.

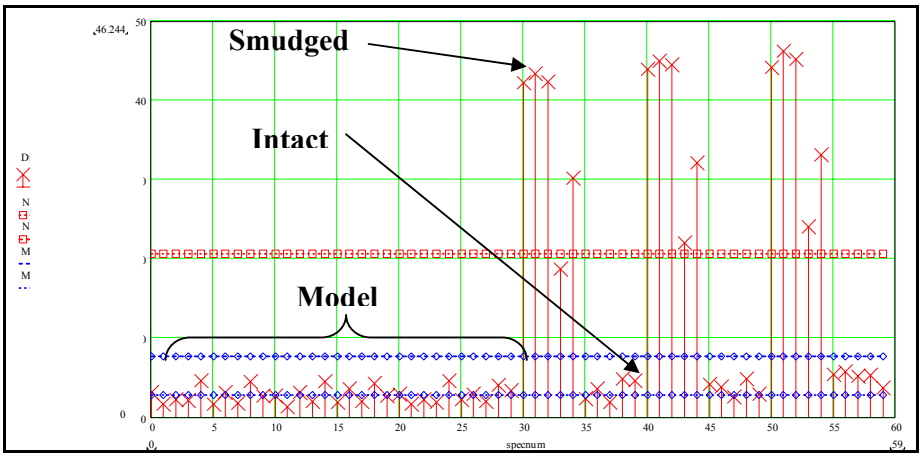

Figure 32: 10mg, excessively smudged. A clear distinction between the both.

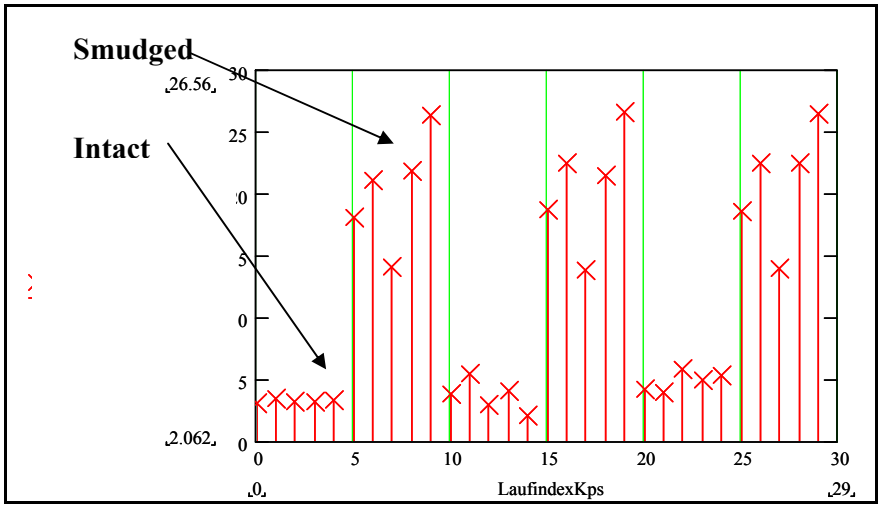

Figure 33: 25mg grey, excessively smudged. A clear distinction from the intact capsules.

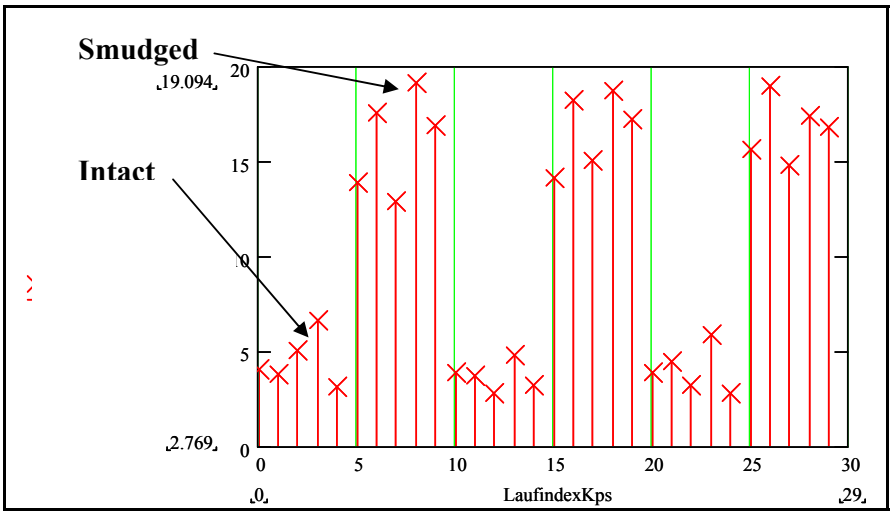

Figure 34: 25mg yellow, excessively smudged. A clear distinction from the intact capsules.

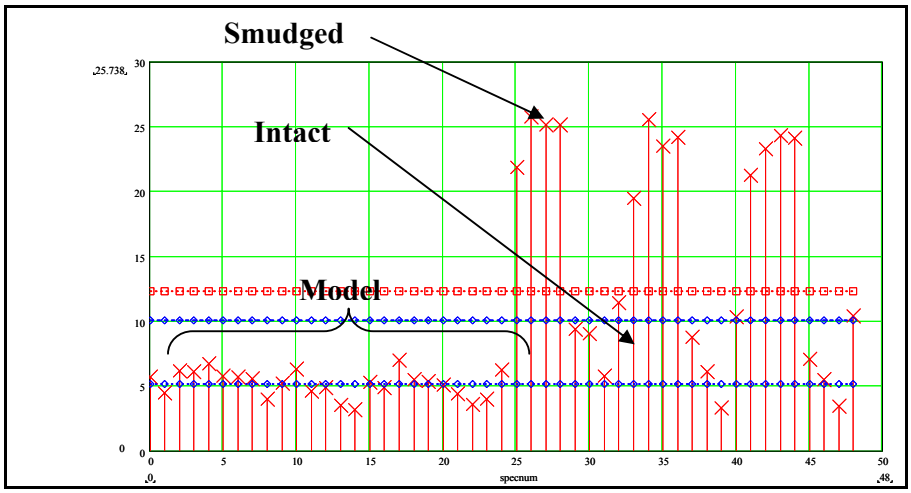

Figure 35: 50mg, excessively smudged. A clear distinction from the intact capsules.

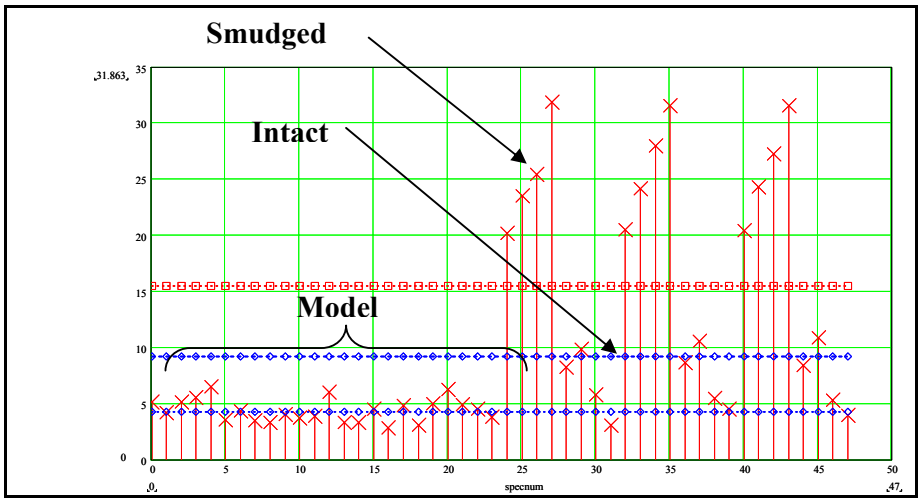

Figure 36: 100mg, excessively smudged. A clear distinction from the intact capsules.

The lightly smudged capsules on the other hand where prepared by emptying a few capsules into a glass with intact capsules and stir them around until the micro emulsion was evenly distributed onto the surface of the capsules.

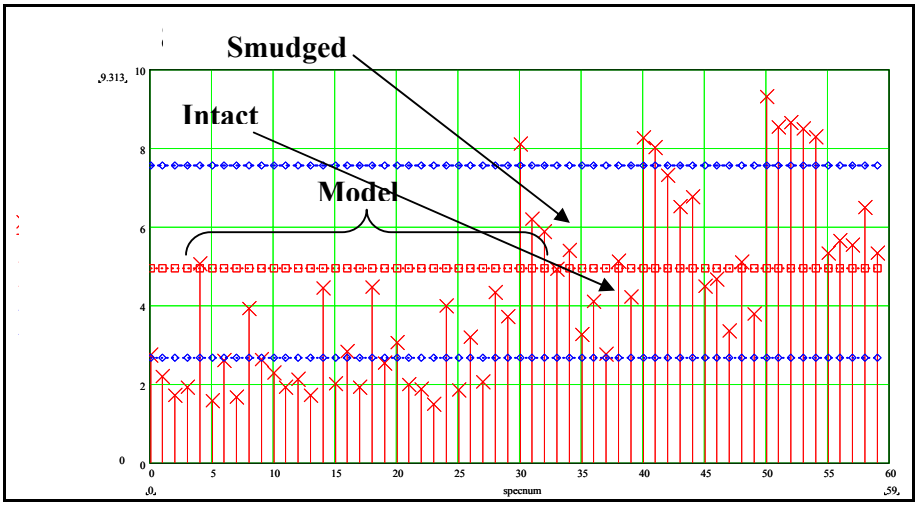

Figure 37: 10mg, lightly smudged (420mg content on 20 capsules). No distinction from the intact capsules.

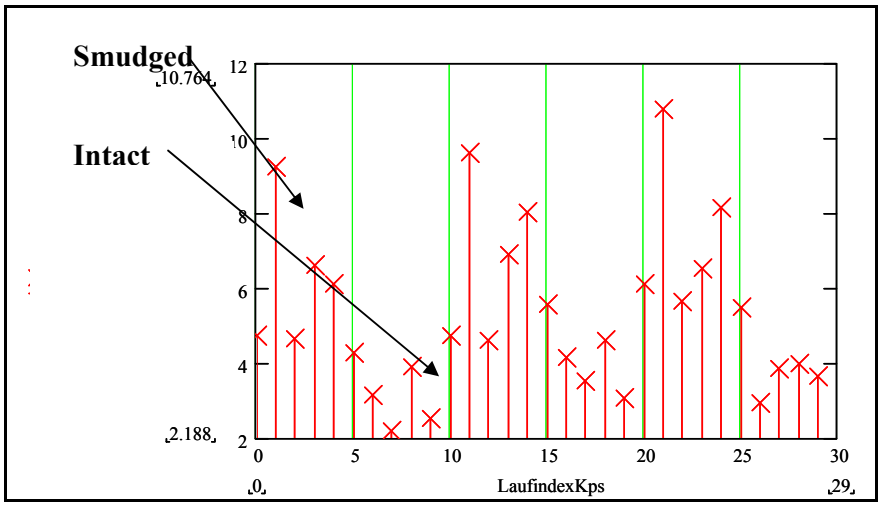

Figure 38: 25mg grey lightly smudged (787mg content on 20 capsules). No distinction from the intact capsules.

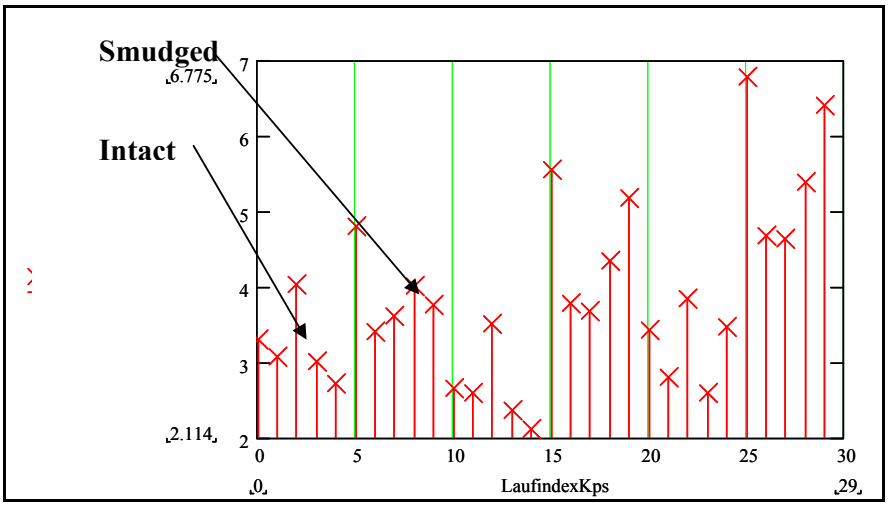

Figure 39: 25mg yellow lightly smudged (787mg content on 20 capsules). No distinction from the intact capsules.

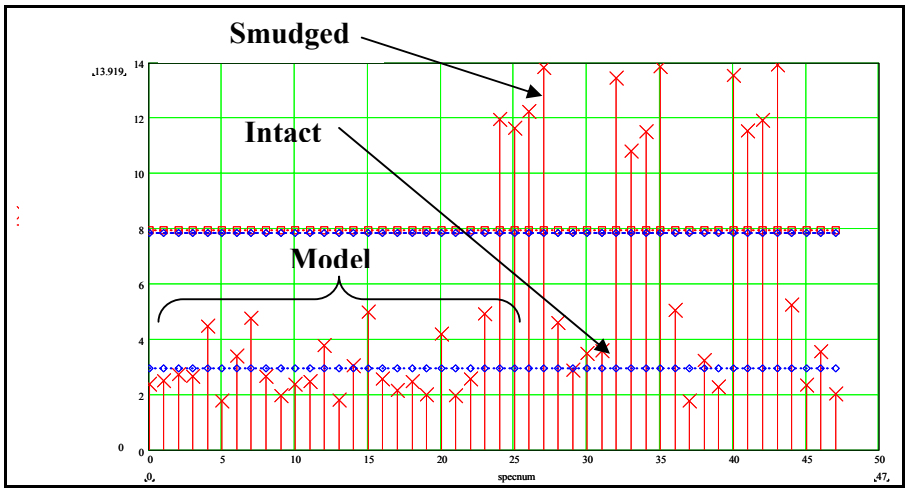

Figure 40: 50mg lightly smudged (1575mg content on 12 capsules). A distinction from the intact capsules is recognizable.

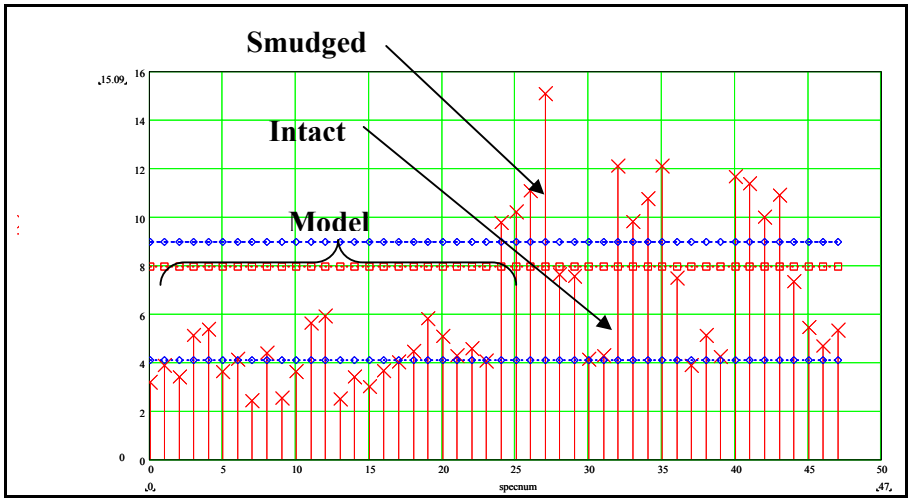

Figure 41: 100mg lightly smudged (3150mg content on 12 capsules). A slight distinction from the intact capsules.

The results show that the detection of an excessively smudged capsule is very clear whereas the detection of the lightly smudged only delivers a trend, except in the case of the 50 and 100mg. It was observed during the tests that as sooner the capsules were detected after being smudged, the higher the deviation the smudged capsules showed. This is most probably due to the evaporation of the ethanol from the micro-emulsion on the surface, leading to the conclusion that smudged capsules could only be detected if they get smudged just before being put under the spectrometer.

5.2.5.4.Low ethanol content

In order to prepare capsules with lowered ethanol content, the capsules were stored in open blisters at room conditions. This way the ethanol and propylene glycol evaporated from the capsules. The conditions were monitored during the tests and showed an average of 23.5°C and 44.6% relative humidity.

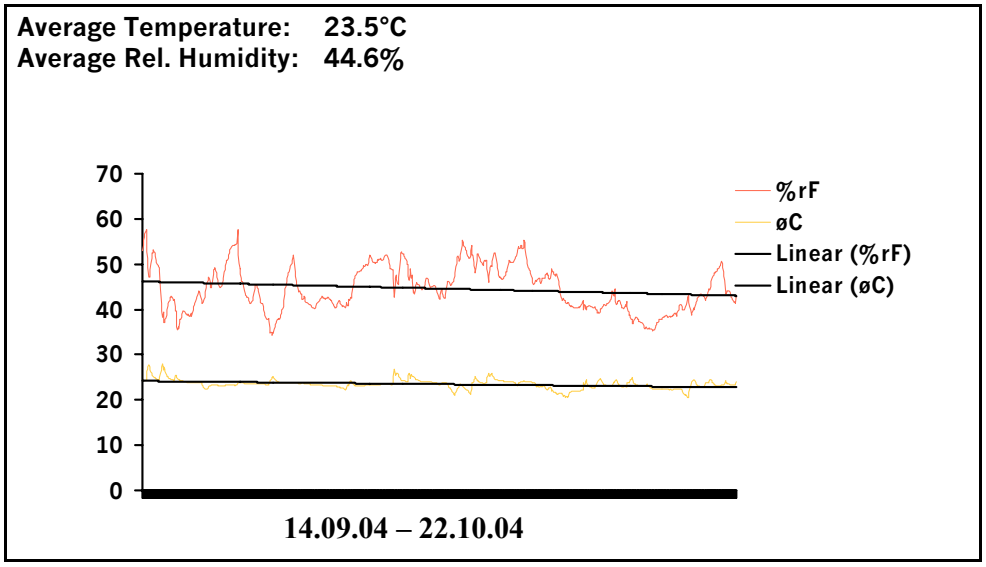

Figure 42: The test room conditions during the last 5 weeks of the tests. Measurements were made every hour.

According to stability report, the capsules loose ethanol very fast when they are stored openly. At the room conditions mentioned above the loss of ethanol should be slower than at the conditions used for the stability tests.

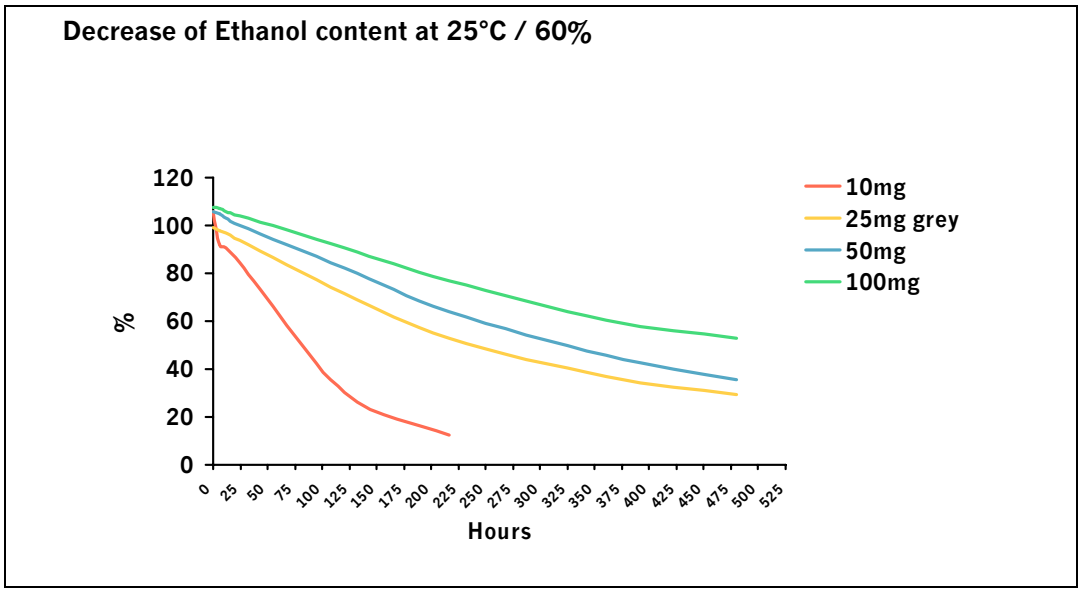

Figure 43: Stability of SIM Neoral SGC.

The limits of the ethanol content are 80 – 120%. As soon as the ethanol content falls below 80% it can not be assured that the active ingredient doesn't crystallize out of the micro-emulsion. In the crystalline state the active ingredient will not be absorbed so an improper storage of the capsules could be dangerous for the patients as the probability of an organ rejection rises if the patient does not receive his correct dose. By doing this test, the possibility of detecting capsules at the line which do not contain the required amount of ethanol is being tested.

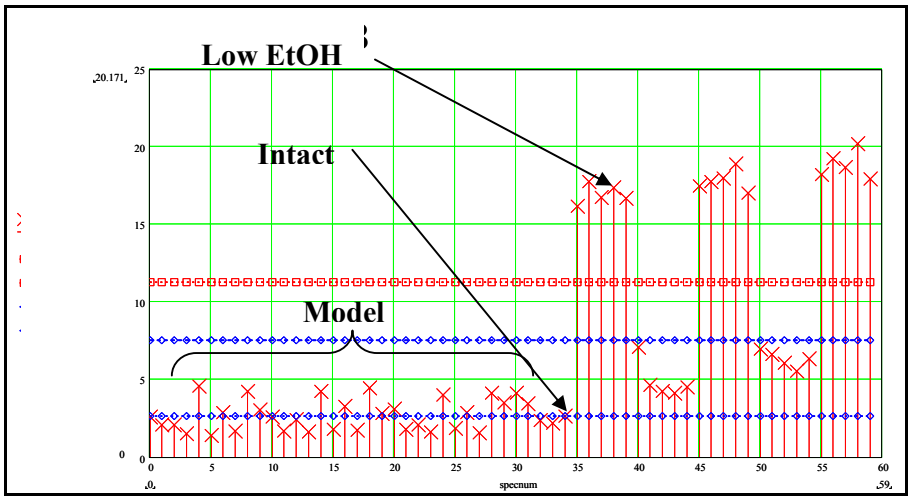

Figure 44: 10mg capsules after 24 hours storage without blister. A clear distinction from the intact capsules.

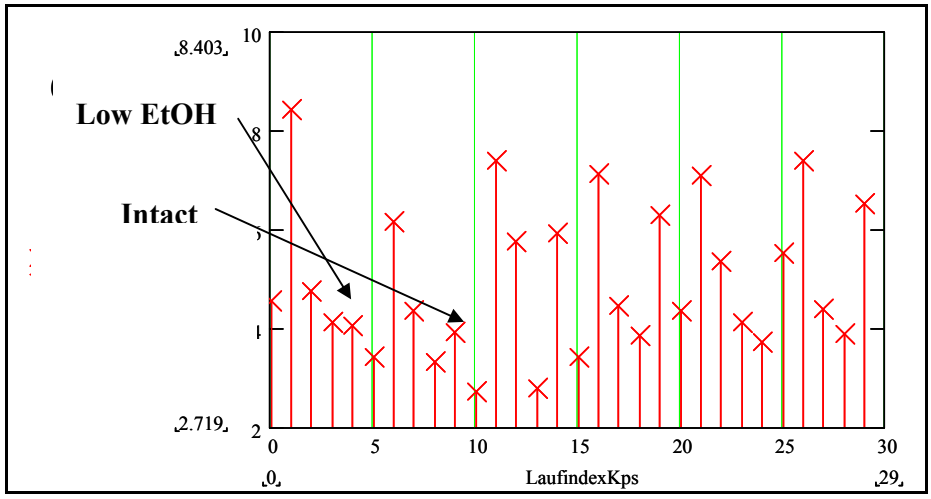

Figure 45: 25mg grey capsules after 144 hours storage without blister. No distinction at all.

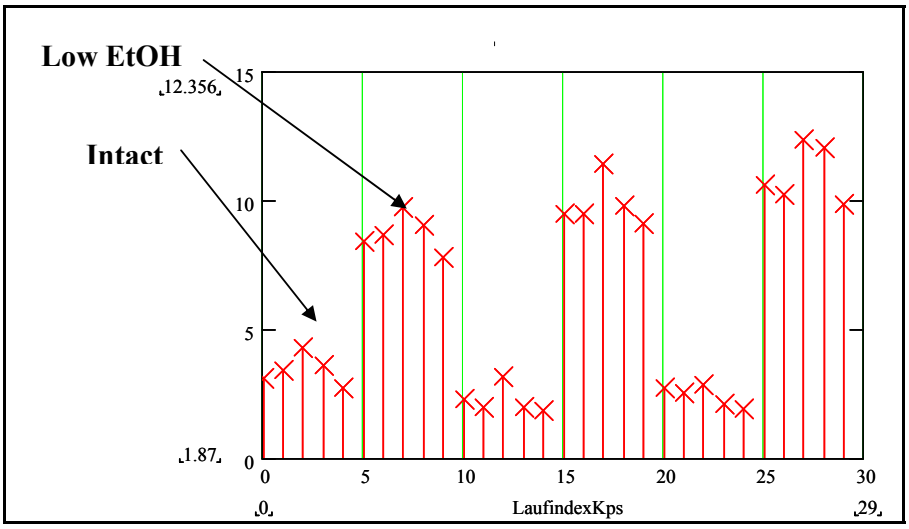

Figure 46: 25mg yellow capsules after 48 hours of storage without blister. A distinction from the intact capsules.

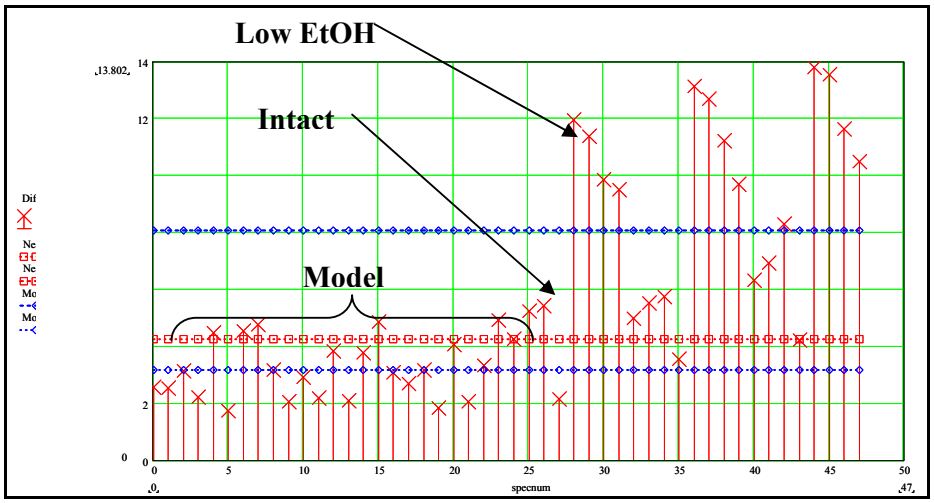

Figure 47: 50mg capsules after 144 hours of storage without blister. A distinction can be seen from the intact capsules of about 4 euclidian distances.

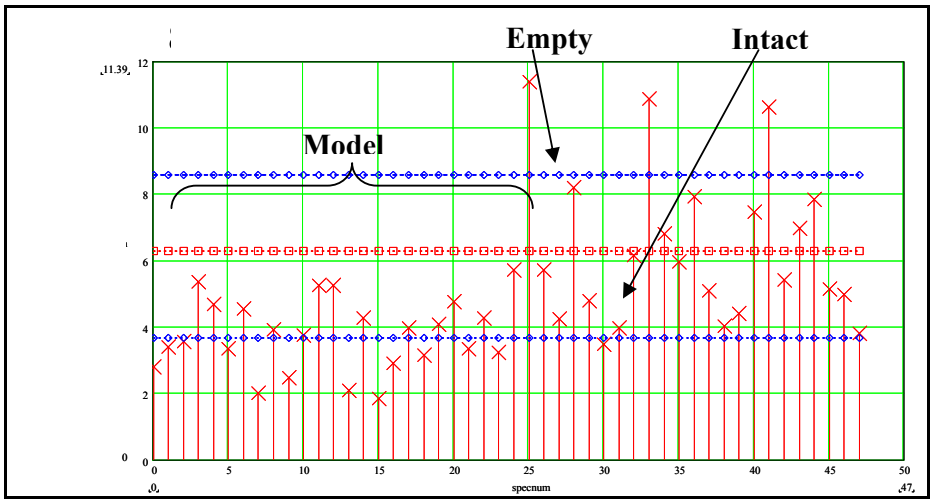

Figure 48: 100mg capsules after 216 hours of storage without blister. No distinction at all from the intact capsules.

From these results it is shown that the spectra of the capsules do change the longer they are stored. After only 24 hours the 10mg capsules showed deviation to the NIR-model, the 25mg yellow also after 48 hours and the 50mg showed deviations after 144 hours of storage. The 25mg grey and the 100mg did not show any clear distinction to the intact capsules after 144 hours and 216 hours respectively. After this time the ethanol concentration still is about 80% according to stability report, and the capsules still intact. It could also be that the grey capsule shell has some impact on the

detection, making the detection of ethanol less sensible. Unfortunately the time did not suffice to store the capsules long enough until they showed deviation to the NIR-model.

In order to be able to predict the actual ethanol content of the capsules at the time when detected by the VisioNIR®, samples were put in a climatic exposure test cabinet at the room conditions (23.5°C and 44.6% relative humidity) for the corresponding times. After storage the samples were used to determine the ethanol content.

	Ethanol content at t_0 [%]	**Stored for [h]**	**Ethanol content after storage [%]**
10mg	96.2	24	84.6
25mg yellow	89.5	48	79.5
25mg grey	91.61	144	43.6
50mg	98.0	144	60.0
100mg	105.3	216	62.3

Table 2: Ethanol content of the SGC's before and after open storage.

According to the results in the table above the SGC's lost their ethanol content faster than we should have expected, compared to the stability report. But it is clear that the integrity of the grey capsules is not confirmed as the ethanol content has fallen way beneath the allowed limit of 80%.

As a conclusion it can be said that a change in ethanol content of the SGC's does influence their NIR spectra. The grey capsules though, did not show much difference in the spectra and again proved that the analysis of the grey capsule shell is very difficult with NIR. All other capsules could be separated clearly from the intact SGC's with normal ethanol content.

5.2.5.5.*Mix-up*

By using Sandimmun Classic SGC's instead of SIM Neoral, a potential mix up was being simulated. The 10mg capsules were left out of this test as that dose does not exist for the SIM Classic. Also the grey 25mg capsules were left out of this experiment as the grey capsules are so different in colour from the SIM Classic 25mg, the yellow one is closer to it. SIM Classic contains the same active pharmaceutical ingredient but does not contain the same excipients as SIM N.

Figure 49: SIM Neoral lined up with SIM Classic.

These mix-ups would be possible to detect only based on their colour if there would be a colour optical camera placed on the line. But with NIR this detection is very fast and simple, as the contents of the capsule shell are different and therefore the deviations in the spectrum should be significant.

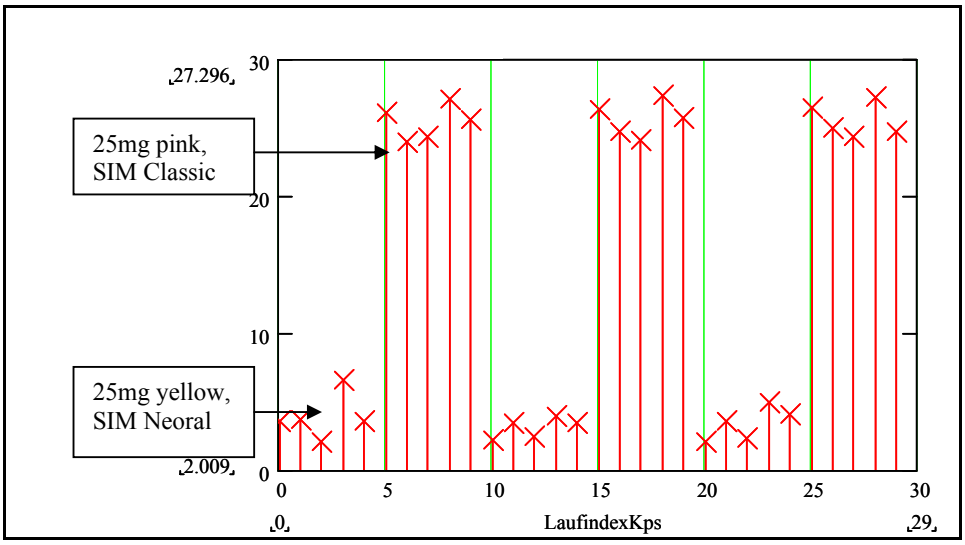

Figure 50: 25mg yellow SIM N, mixed with 25mg pink SIM Classic. A clear distinction from SIM Neoral.

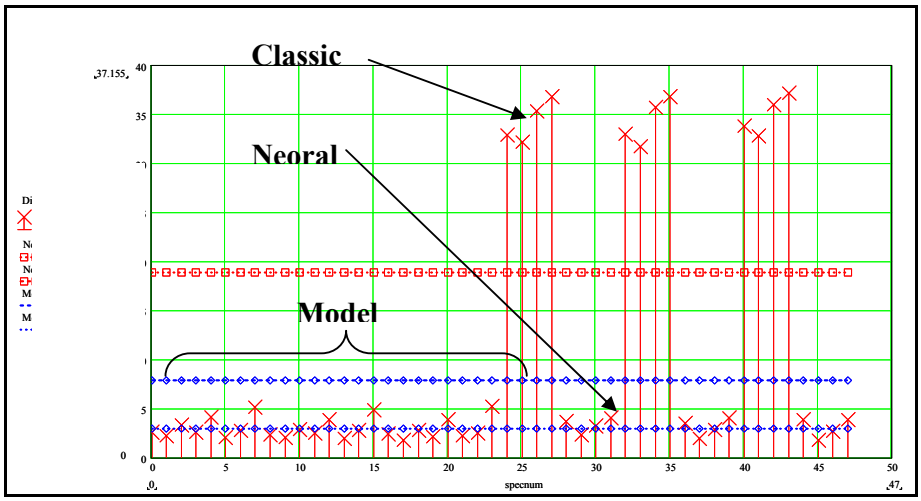

Figure 51: 50mg SIM N, mixed up with 50mg yellow SIM Classic.

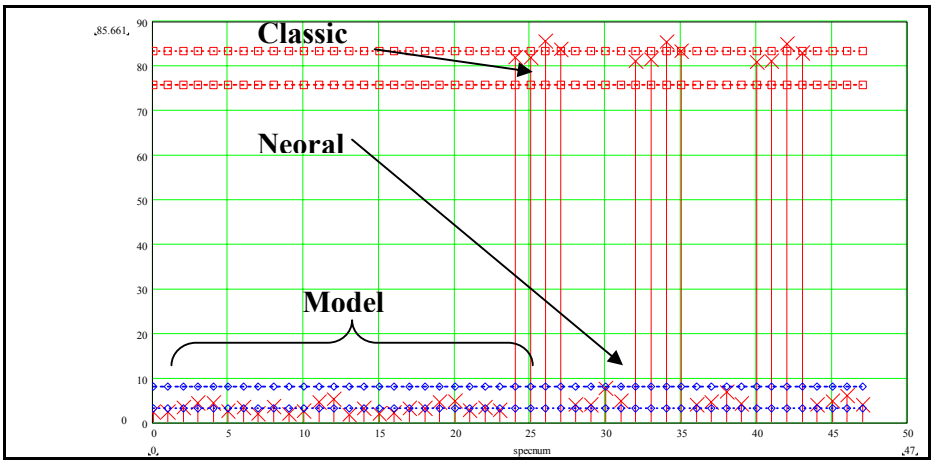

Figure 52: 100mg SIM N, mixed up with 100mg orange SIM Classic

The detection of a mix-up with VisioNIR® is, based on these results, very reliable.

5.2.5.6.Other Mix-ups

The VisioNIR® system was also tested for other mix-up possibilities and in this case for tablets. The choice for the products was based on their shape, size and colour. The tablets chosen may be separated from each other with an optical camera system but assuming there would be a black and white camera placed on the line, a mix-up would never be detected.

These tablets were placed in an aluminium blister and measured by the VisioNIR®. The recorded spectra were then compared in Matchcad11®.

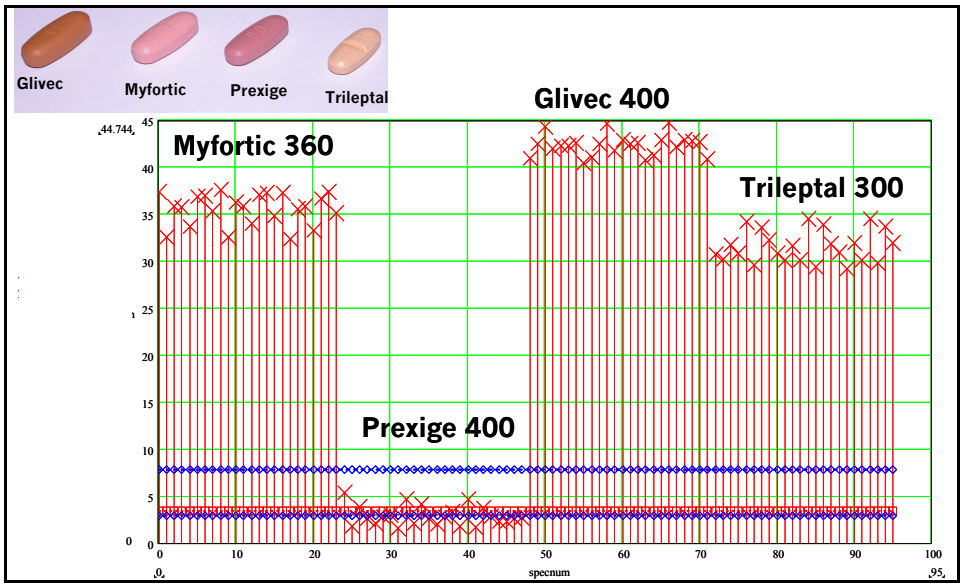

Figure 53: Four different products with similar shape compared on the basis of Prexige which is the NIR-model in this case.

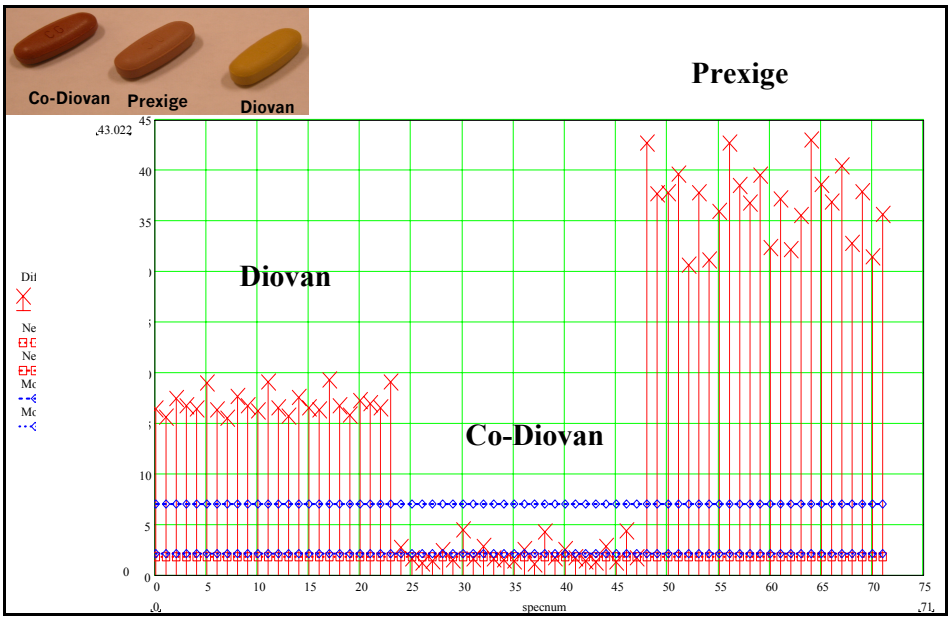

Figure 54: Three different products with similar shape and color compared on the basis of Co-Diovan, which is the NIR-model in this case.

As these results show, the distinction between the different tablets is very clear. The VisioNIR® would detect the mix-up as a product not meeting the required quality and discard the blister.

The possibility of a mix-up between strengths of one product does also exist, i.e. if the different strengths are produced with the same granulate and only differ in size. Than the spectrometer does not recognize any deviation from the NIR-model as the chemical composition is exactly the same.

5.2.5.7.False content of SGC's

The unlikely but possible situation could come up, that the capsule shells could be filled with the false content. E.g. that the capsule shell of SIM N could be filled with the content of SIM Classic, or even with the content of some completely different product. In order to simulate this possibility, the content of SIM N was removed with a syringe by blowing it out and then the empty shell was filled with the content of SIM Classic by injecting it into the shell. Measuring errors were avoided by emptying a SIM N capsule and filling it again with its content and then there was checked if these capsules differentiated themselves from the untouched ones. This was not the case as seen in the figure below.

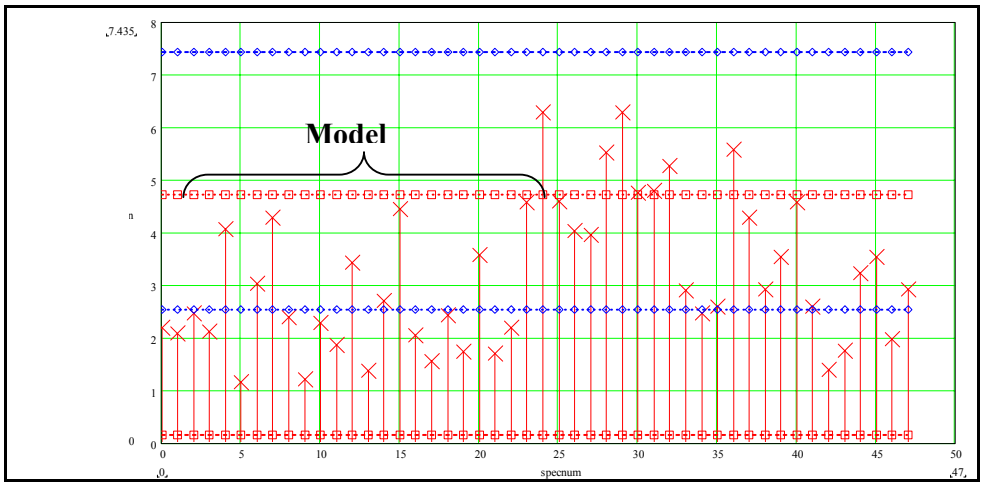

Figure 55: Measurement of intact 50mg capsules with refilled 50mg capsules. The NIR-model is represented with the first 24 spectra. After that there is no distinction to be observed.

After having shown that the preparation of the capsule shell does not influence the distinction of the falsely filled capsules, the measurements could take place.

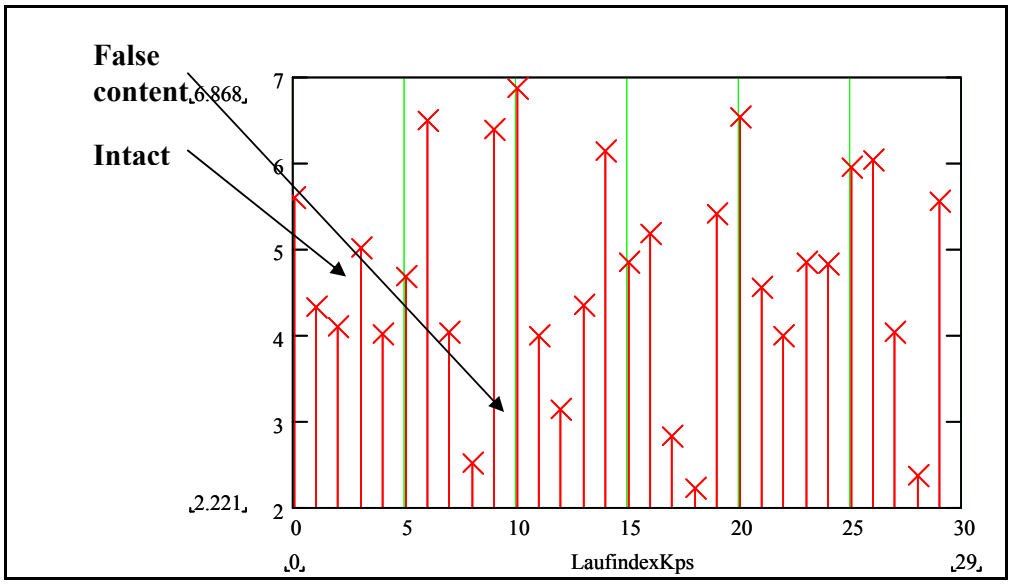

Figure 56: 25mg grey with false content. No distinction whatsoever.

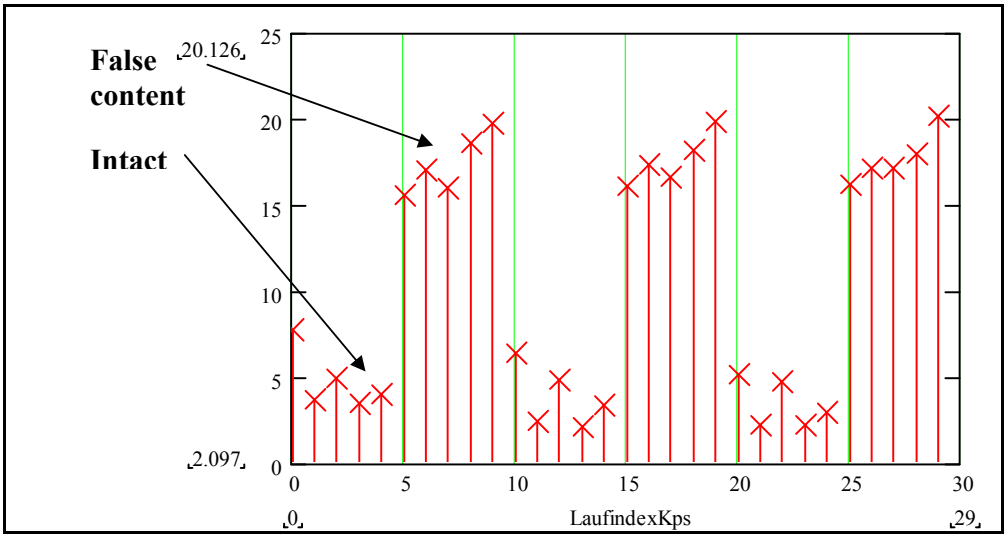

Figure 57: 25mg yellow with false content. A good distinction can be observed from the intact capsules.

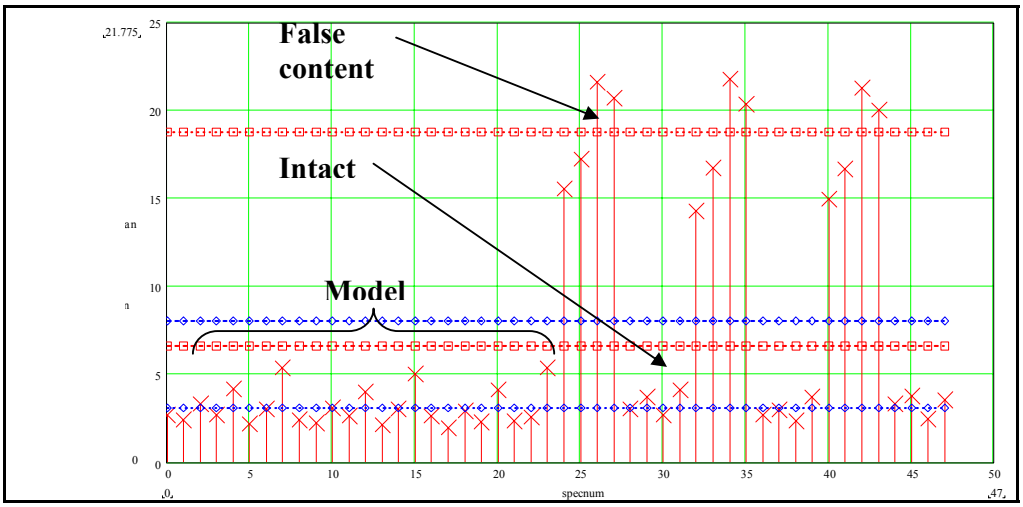

Figure 58: 50mg with false content. Excellent distinction from the intact capsules.

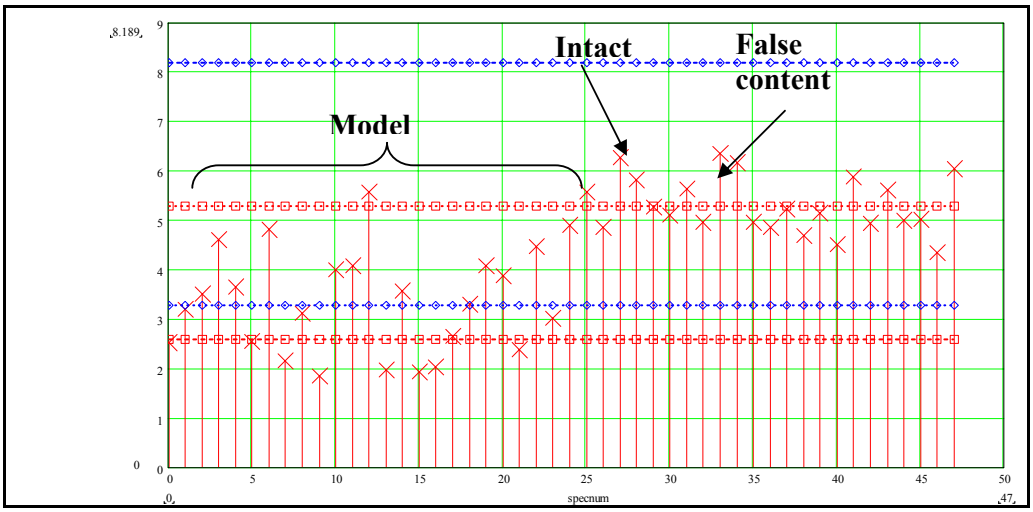

Figure 59: 100mg (grey) with false content. No distinction from the intact capsules.

Again it is conspicuous that the grey capsules (25mg grey and 100mg) with false content are not separable from the intact ones. The yellow 25mg and the white 50mg capsules with false content show high deviations compared to the intact ones. This supports the suspicion that the grey iron oxide in the capsule shell of the grey capsules doesn't let as much light through as the yellow and white ones.

5.2.5.8.Placebo detection

Detecting placebos would not be possible with any optical camera as the capsules look exactly the same because the patients are not supposed to notice any difference to the verum capsules. The only difference between placebo and verum is that the placebo does not contain any active pharmaceutical ingredient. So the only way to detect a placebo is to detect the active pharmaceutical ingredient in the capsule. Comparing the contents of a placebo SIM N to a verum SIM N there are some differences to be observed.

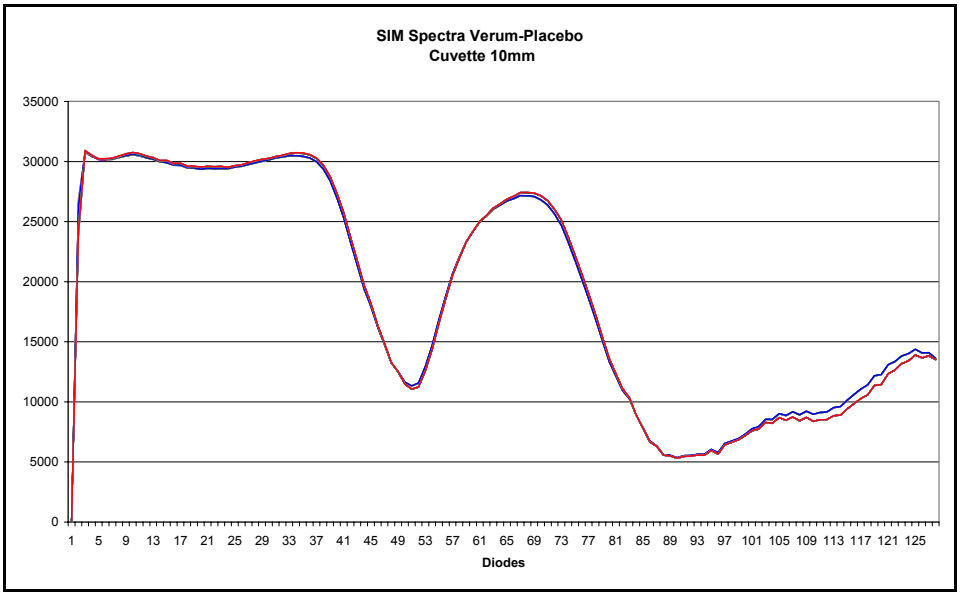

Figure 60: NIR spectra of the contents of SIM Neoral placebo and verum.

This application is very interesting for the clinical packaging as they pack blisters which partly contain placebo and verum in the same blister and a mix-up between blister-pockets could mean that a clinical study's results are partly or even completely falsified. These studies are mostly double-blind studies in order to achieve objective results. Therefore it is critical that the right capsules land in the right blister pocket. These tests were done by mixing placebo with intact verum capsules and then the data was treated with the same algorithms as for the other applications. Unfortunately there were no 25mg grey placebo capsules available for this test.

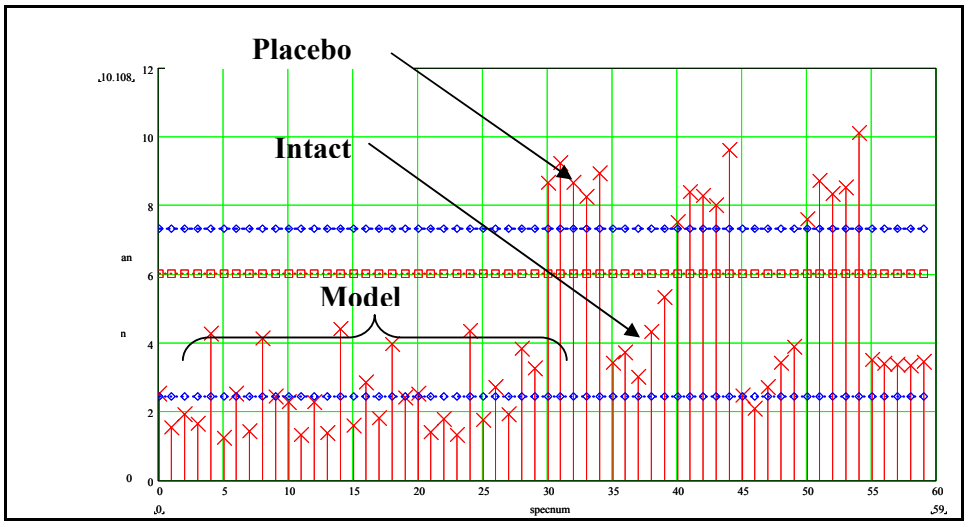

Figure 61: 10mg placebe / verum. There is a narrow distinction to be observed.

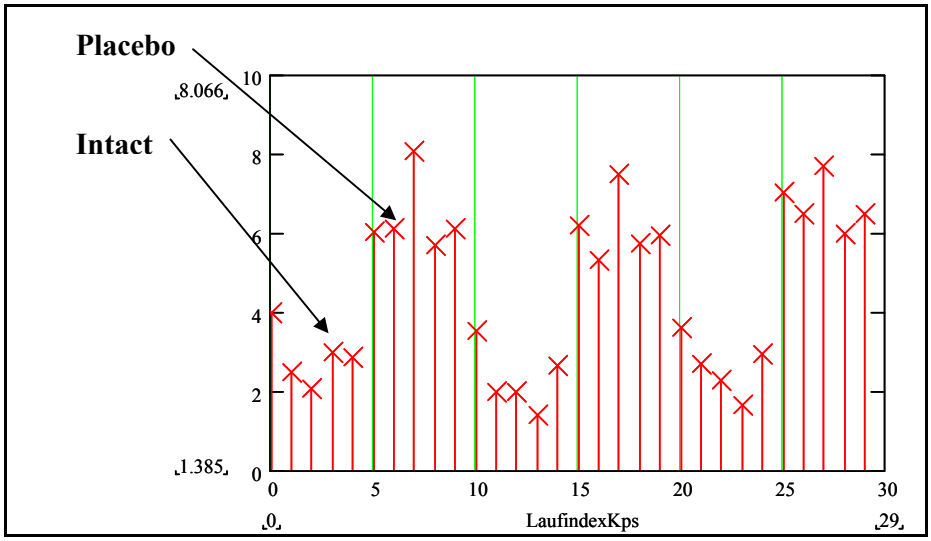

Figure 62: 25mg yellow placebo / verum. There is a narrow distinction to be observed.

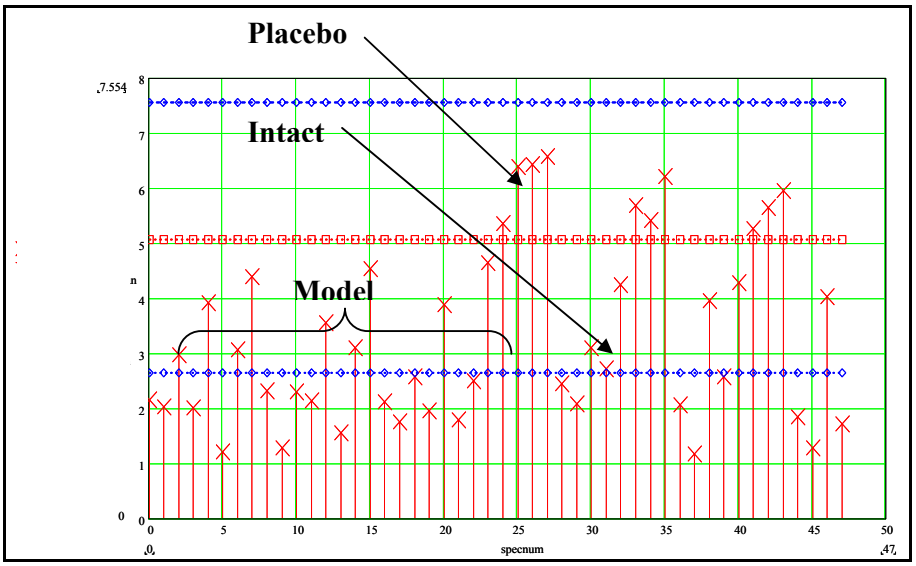

Figure 63: 50mg placebo / verum. There is no clear distinction to be observed, rather a trend.

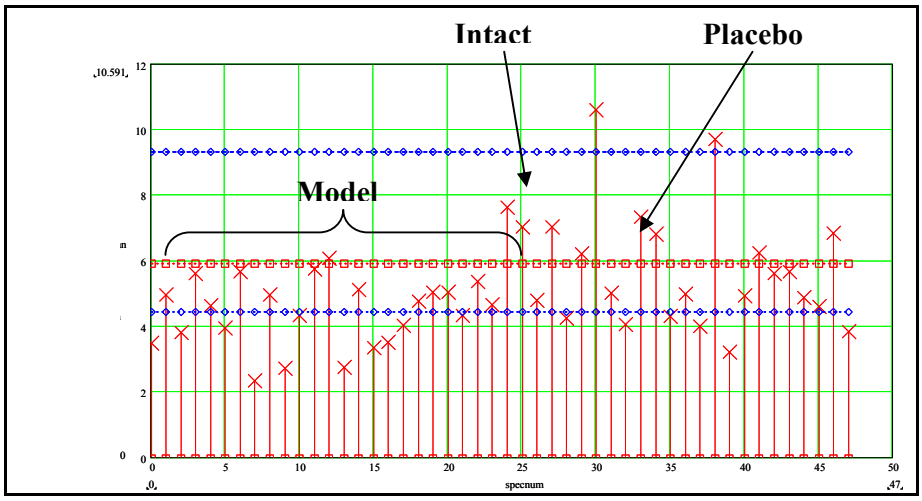

Figure 64: 100mg placebo / verum. There is no hint of a distinction to be observed, except for one capsule.

The detection of placebos is possible for the 10mg capsules. For the 25mg yellow capsules there is a definite trend for the recognition of placebos as they do show higher deviation to the NIR-model but still not exceeding the limits. The detection of 50mg placebos also shows a trend but still not high enough for a clear distinction from the verum. The 100mg show almost no difference to the verum capsules and the NIR-model. Again it is seen that a grey (100mg) shows the worst detection of all the

different capsules. It is to assume that the 25mg grey would also show a similar result.

It was very surprising that the detection of the 50mg placebo was not as clear, as the capsules were up to now the best ones to detect. The capsule shell is white and has been letting more light through the capsule shell than the darker capsules. In order to improve the detection of the placebo 50mg the data achieved from the measurement were put into a principal component analysis (PCA). For this the Unscrambler® (CAMO AS, Trondheim, Norway) was used. With PCA it was possible to identify the spectral band which gave the most information on the active pharmaceutical ingredient.

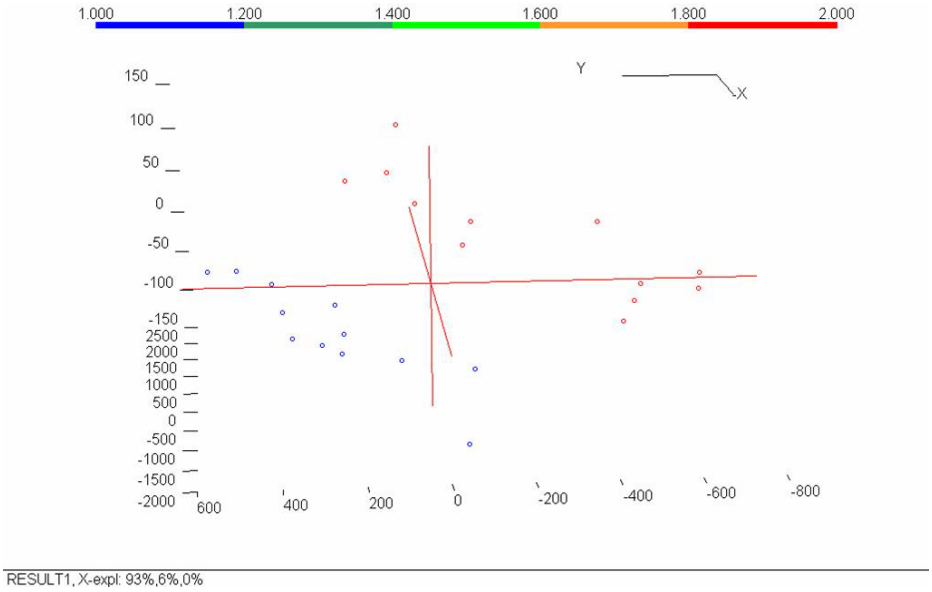

Figure 65: A clear distinction between SIM Neoral 50mg placebo and verum with the help of PCA.

The spectral band between 1080nm and 1210nm (diodes 30 – 50) contained the most information on the active pharmaceutical ingredient and using this band it was possible to separate the placebo from the verum capsules. Narrowing the spectral band down from 1060 – 1460nm to 1080 – 1210nm with the same data using Mathcad then brought a better result.

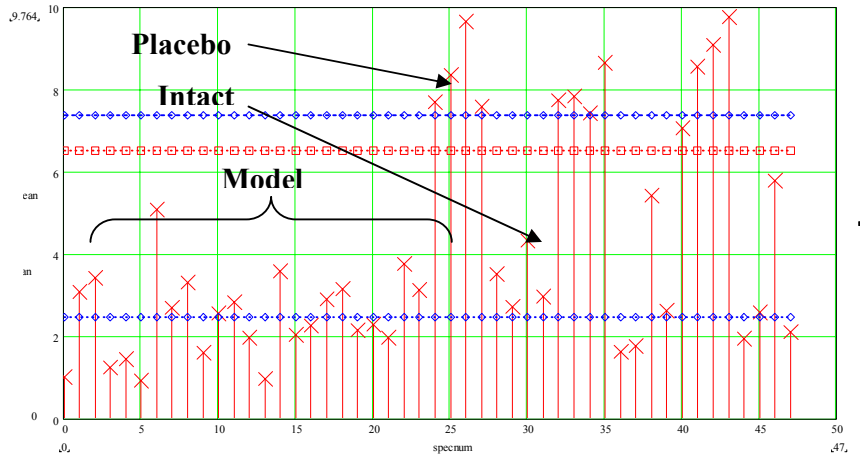

Figure 66: The distinction of 50mg placebo verum after modification of spectral bands.

This result shows that the distinction would be possible using this spectral band. But it has to be considered when using this spectral band the distinction of the other parameters could get worse as other physical or chemical parameters might reside in other spectral bands.

Considering the same situation for tablets, it was decided to see if the VisioNIR was able to separate placebo tablets from verum tablets. For these tests Glivec 400mg was used. The tablets have the same coating suspension and the same excipients.

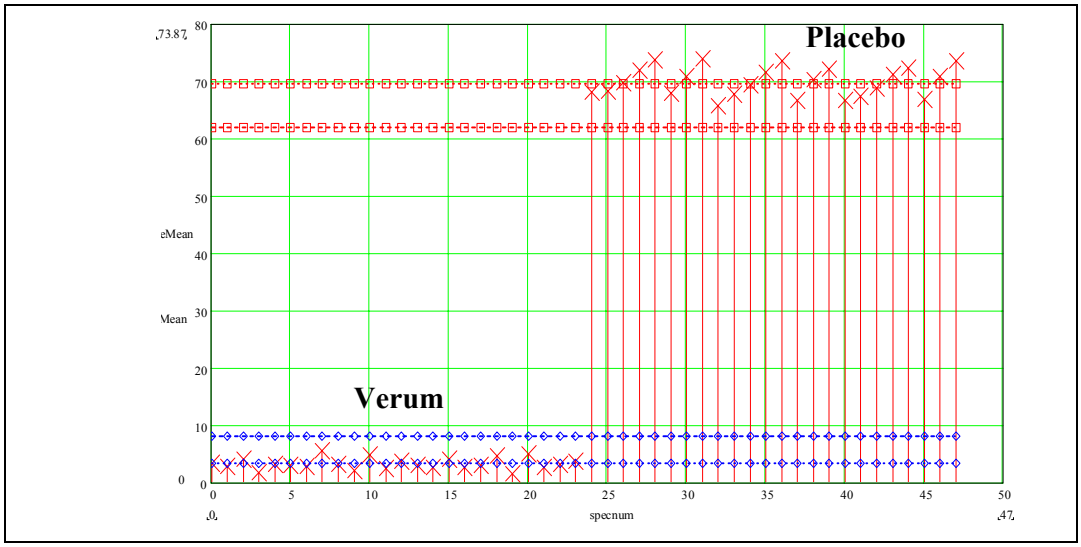

Figure 67: A clear distinction between tablet placebo and verum

It can be seen that the distinction is very clear. The distinction might get harder with lower concentrations of active ingredients in the tablets, but that would have to be tested for all individual tablets.

As a conclusion it can be summarized that VisioNIR would be a valuable sensor on the clinical packaging line for all SIM Neoral capsules excluding the grey ones. For tablets it would have to be checked, to what limits the distinction still works.

5.3. Conclusion

The following table summarizes the results for SIM N discussed above.

SIM N	10mg	25mg grey	25mg yel.	50mg	100mg
Full/empty	√	√	√	√	√
Half empty	**N/A**	√	√	√	√
Li. smudged	+/-	+/-	+/-	+/-	+/-
Exc. smudged	√	√	√	√	√
Low EtOH	√ **(24h)**	***1**	√ **(48h)**	√ **(144h)**	***2**
Plac./Verum	√	**N/A**	√	+/-	**X**
Mix-up	**N/A**	**N/A**	√	√	√
False content	**N/A**	**X**	√	√	**X**

Table 3: SIM Neoral results summarized.

*1: After 144 hours there was no detectable difference between the stored 25mg grey capsules and the fresh ones.

*2: After 216 hours there was no detectable difference between the stored 100mg grey capsules and the fresh ones.

It is conspicuous that when the prepared capsules where not separable that happened with the grey capsules, apart from the lightly smudged capsules and the 50mg placebo (which could be separated after optimization. This does lead to the conclusion that the grey capsule shell does not let as much light through the shell as the yellow or the white ones.

As the VisioNIR system measures with diffuse reflection, the spectrum of the capsule shell dominates the total spectra. The NIR spectra of the capsules consist of the spectra of the capsule shell and the spectra of the capsule content. When measuring with diffuse reflection one part of the stimulating light interacts with the capsule shell and another part with the content. The higher the intensity of the stimulating light, the deeper it penetrates the capsule and the interaction of the capsule content increases. Thus the apparent absorption of the capsule content increases with increasing light intensity. At the same time the apparent absorption of the capsule shell stays the same as the thickness of the shell stays constant (6).

The system would be a very valuable control system on the packaging line as the occurrences of empty capsules reaching the customer and even threatening his life by increasing the risk of an organ rejection, would be totally impossible. Detecting freshly smudged capsules on the line is very unlikely as the capsules do need some time to make it from the filling station to the camera system. In this time the lightly smudged capsules will not be detectible any more, but a damaged capsule with content spilled in the blister-cup will be detected. Also all mix-up's would be detected and excluded. The aspect of being able to differentiate between placebo and verum seemed very interesting for the clinical packaging. But as the results showed, it proved to be very difficult to separate the both from each other in the case of SIM Neoral. In the case of Glivec the distinction placebo and verum was very clear.

5.4. Outlook

In order to improve the distinction of the placebo capsules and possibly the grey scapegoat capsules the light intensity might be increased. This is on the other hand dangerous for SGC's as the heat might then be too much for the sensitive capsules.

Also, what was not considered in this work is the effect of such a strong light exposure on photo-sensible drugs. There are examples of active ingredients which decompose exposed to intensive daylight and others which darken. This would have to be considered before putting VisioNIR onto the packaging line.

References: 5. 100% Control of soft gelatine capsules with a diode array NIR spectrometer - VisioNIR

1. Sukowski L., NIR Based Process Analytical Technology: In-line Residual Moisture Determination for a Complete Batch Inspection of Lyophilized End-Products., 2003; p 56 – 66.
2. Sukowski L., NIR Based Process Analytical Technology: In-line Residual Moisture Determination for a Complete Batch Inspection of Lyophilized End-Products., 2003; p 77 – 80.
3. Herkert T. V., Evaluierung einer NIR-Methode zur on-line Qualitätssicherung von Pharmazeutika auf der Verpackungsstrasse., 2001; p 13
4. Herkert T.V., Prinz H., Kovar K-A., One hundred percent online identity check of pharmaceutical products by near-infrared spectroscopy on the packaging line., European Journal of Pharmaceutics and Biopharmaceutics, 51, 2001; p 9 – 16.
5. Visio|tec technology introduction guide.
6. Herkert T. V., Evaluierung einer NIR-Methode zur on-line Qualitätssicherung von Pharmazeutika auf der Verpackungsstrasse., 2001; p 36 – 37.

6. Overall conclusion

6.1. Discussions and conclusions

In this work, Process Analytical Technology has been looked at in terms of in which process steps the sensors should be implemented into manufacturing and consequently the expected costs were estimated and the anticipated revenue was determined.
It is clear that the implementation of PAT is very expensive, but it will pay off. In this case-study, an investment of about 4.5 million CHF for each product was needed and a break even point was reached after as little as 6 years. For this study, PAT applications were implemented as process controls and not as design help for development. It is essential to expand this study into drug development in order to study the impact of PAT onto quality of design.

NIR being the most common recommended PAT sensor, a NIR spectrometer was also investigated, for not such a frequent application, namely the packaging line. Using the VisioNIR on soft gelatin capsules, it was able to distinguish the intact capsules from empty-, half-empty-, excessively smudged- and mix-up capsules. Also mix-up and placebo detection amongst tablets was no problem on 100% of the product being packed.

Further, two different technologies which are recommended from the FDA in terms of product understanding and quality by design, were analyzed and the impact on current ways of doing development was looked at.

The Multicell®, being a semi-continuous granulation machine is capable of replacing the conventional granulation process and at the same time increasing manufacturing capacities with reduced personnel needed. By implementing the Multicell® into manufacturing and development a design of quality into granulate can be reached and dreadful scale-up exercises can be avoided leading to a faster time to market.

The Presster® was capable of predicting the compression behavior of two different tablet formulations on three different rotary presses, in terms of the most important

factors which are hardness and dissolution rate. This is only possible if the correct set of compression tools is available for the Presster®.

It is apparent that pharmaceutical companies will have to be innovative if they wish to survive the competition on the market today. From the point of view of the researching pharmaceutical companies, they will have to invest in innovation in order to get them selves as fast to the market as possible in order to prolong their window of exclusivity for a patented product. From the generics point of view, it is also essential to invest in innovative technology, as the generic company which comes first to the market, gets the biggest part of the cake.

In the end, the fact will be that when one company has decided to take the innovative road, the other companies will be forced to follow in their footsteps.

"…an economical benefit for a pharmaceutical company is a gun to its head"!
John E. Carroll
CfPA PAT course Amsterdam
(2004)

Curriculum Vitae

Personal information

Name	Hedinn Valthorsson
Date of Birth	April 2nd 1975
Place of Birth	Akureyri, Iceland
Parents	Baldvina Sigrun Sverrisdottir Sveinn Valthor Sigthorsson

Professional Experience

Since Jan 2006	Senior Scientist in Global PAT / GQO. Project manager in QbD / PAT pilot project at Novartis (East Hanover, USA).
Feb 2003 – Dec 2006	PhD Contract at Novartis (Stein AG, Switzerland), working on a PhD thesis in collaboration with the University of Basel, under the tutorial of Prof. Dr. Hans Leuenberger. During the PhD studies I also had the following functions at Novartis: • Stein Works Project Coordinator • PAT Stein Project Team Representative • GMP Training Supervisor • Think (Employee Suggestion System) Officer • MIT Project Leader • LEAN Trainer

Internships and Work Experience

Jun 2002 – Dec 2002	Internship in the Merlin Pharmacy in Cologne / Germany
Dec 2001 – Mai 2002	Internship at Novartis Stein / Switzerland
April 1999 – Dec 2001	QC laboratory assistant at Actavis / Iceland during semester breaks

Education

Feb 2006	Doctorate with highest honors (Summa cum Laude) in Pharmaceutical Technology from University of Basel
Dec 2002	Pharmacist (Staatsexamen) from Carolina-Wilhelmina Universität Braunschweig, Germany

School

Dec 1995	General Qualification for University Entrance (Studentsprof) from Flensborg, Hafnarfjördur / Iceland

Language Skills

English	fluent in written and spoken
German	fluent in written and spoken
Danish	fluent in written and spoken
Icelandic	mother tongue

Computer Literacy

MS Office, MathCad, SIMCA P+

Private Hobbies

Martial Arts