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Pharmaceutical powder compressibility – a science-based approach

Inauguraldissertation
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Philosophisch-Naturwissenschaftlichen Fakultät
der Universität Basel

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Basel, den 21. Februar 2012

Prof. Dr. Martin Spiess

Dekan

Αφιερωμενο στους γονεις μου

με πολυ αγαπη, εκτιμηση και σεβασμο

Dedicated to my parents

with love, appreciation and respect

ἓν οἶδα ὅτι οὐδὲν οἶδα

Σωκράτης

469 π.Χ. – 399 π.Χ.

“I know one thing, that I know nothing”

Socrates

c. 469 BC – 399 BC

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List of Original Publications

This PhD thesis is based on the following publications:

1. **Nicolaos D. Gentis, Gabriele Betz**. Compressibility of binary powder formulations: Investigation and evaluation with compaction equations. *J Pharm Sci.* 2012, 101 (2), S. 777-793

2. **Nicolaos D. Gentis, Branko Z. Vranic, Gabriele Betz**. Assessing compressibility and compactibility of powder formulations with Near-Infrared Spectroscopy. *Pharm Dev Technol*. under review

List of Abbreviations

API	Active pharmaceutical ingredient
BET	surface area measurement method (abbr. of the scientists initials Brunauer, Emmett, and Teller)
$CaHPO_4$	Calcium hydrogen phosphate
FT	Fourier transformation
GIT	gastrointestinal tract
HCl	Hydrogen chloride
InGaAs	Indium-Galium-Arsenide
IR	Infrared
JRS	Pharmaceutical company name (JRS Pharma)
LVDT	Linear variable differential transformer
MCC	Microcrystalline Cellulose
NaOH	Sodium hydroxide
ncl	Normalization by closure
NIR	Near-Infrared Spectroscopy
NIRCal	Near-Infrared Spectroscopy software
NIRWare	Near-Infrared Spectroscopy software
NSAID	Non-steroidal anti-inflammatory drug
PC	Personal Computer
PLS	Partial least square
PVC	Polyvinyl chloride
R&D	Research & Development
SMCC	Silicified microcrystalline cellulose

SMCC-HD	Silicified microcrystalline cellulose with high density
SNV	Standard normal variate
UICEL	University of Iowa Cellulose
UV-VIS	Ultraviolet-visible

Thesis Abstract

Background

The compressibility is a crucial property of powder formulations. For being able to compress a powder mixture to tablets with satisfactory pharmacocinetical behaviour, its compressibility has to be within a certain range.

Especially nowadays, where powder formulations for tablets can contain a big number of different compounds, a reliable determination and monitoring of the compressibility is very important.

Objective

Investigation of three methods to determine powder compressibility (Heckel-Plot, modified Heckel-Plot, Leuenberger equation) with focus on their scientific reliability and their ability to show the influence of small composition adjustments to the compressibility of the formulation. Development of a method to determine and monitor powder compressibility and additional quality aspects by scanning the final tablet with Near-Infrared Spectroscopy.

Materials and Methods

Binary mixtures of poorly compressible API and well-compressible excipient were compressed to tablets within a range of relative densities. The compaction pressure, the relative density of the tablet and its tensile strength were used to calculate the compressibility value of the formulation. In a second step, the API of the formulation was increased to detect and investigate the change of the compressibility values.

An investigation with compaction and analysis of the final compacts was performed with 12 different powder formulations. Relative density and tensile strength were the main investigation targets since these elements are used to establish the powder compressibility with the chosen approaches.

One part of the final compacts was tested for relative density and tensile strength with the

traditional method, while another part of the tablet collection was investigated with Near-Infrared Spectroscopy. These research steps led to a development of a method for compressibility determination with Near-Infrared Spectroscopy.

Results and Discussion

The results of the investigated binary mixtures showed the values for compressibility to be really individual for the three different approaches. Additionally, it could be shown that the change of the compressibility value with increase of the poorly-compressible API led to individually different changes in compressibility values for the three different plots.

The developed NIR-method showed really similar results in comparison to the traditional method for the compressibility values, calculated with the Heckel-Plot and the modified Heckel-Plot. Additionally the values of relative density and tensile strength could be detected in a reliable way with the established method.

Conclusion

The importance of a reliable compressibility determination and all the challenges associated with it could be shown clearly with the research work of this thesis. Especially the sensitivity of the chosen method to small variations within the formulation could be identified and shown.

The developed NIR-method showed promising results and underlined its usability for online monitoring of the tablet production and of the final compact quality.

Theoretical background

Material

Cellulose

Cellulose ($C_6H_{10}O_5$) is a chemical compound consisting of a long-chain polymeric polysaccharide of beta-1,4-linked polyanhydroglucopyranose (Sonnenberg, 2008).

Cellulose is mainly found in the primary cell walls of green plants and some forms of algae. It is actually the most common organic compound on Earth.

A high percentage of the industrially manufactured cellulose originates from cotton and several types of wood. Raw cotton contains 85 – 90 % of cellulose while 40-60 % of cellulose can be found in wood (Malcolm Brown, et al., 2007).

For potential use in the pharmaceutical field, Cellulose is usually dispersed in a 17.5 % sodium hydroxide solution. While the non-dissolved α-cellulose is removed, the white residue is washed and mechanically pulverized. The resulting compound of this treatment chain is Cellulose powder with low crystallinity and a wide range of polymerization degree (between 100 and 1300) (Blaschek, 1990; Sullivan, 1997; Mueller, 2008).

In a further step, a treatment of this Cellulose powder with an HCl-solution (aq) is needed for the production of Microcrystalline Cellulose (MCC). This additional treatment leads to a partial chemical hydrolysis of the cellulose, which increases its crystallinity and mainly lowers the degree of polymerization to around 200-300.

A lot of different adjustments of this method for the production of Cellulose derivates have been developed in the last decades. The result is a big variety of Cellulose and Microcrystalline cellulose subtypes (S.Wei et al., 1996).

Depending on the starting cellulose source and processing variables used during their manufacture, the cellulose products vary in physicochemical properties and consequently in

their usability as direct compression excipients (E. Doelker et al., 1987; R.C. Roberts et al., 1987).

The country of origin (Landin, et al., 1993), the biological source of the starting material (Landin, et al., 1993) and the production method (Parker, et al., 1988) influence crucially the quality and properties of the final product.

A nice example of an innovative production method for cellulose is the choice of a mercerization step for the production of so called UICEL (University of Iowa Cellulose). Different raw material, like e.g. α-cellulose, cotton linter and pulp are treated with a NaOH (aq) –solution to produce a gel, which is purified with water and dried. The final compound shows lower crystallinity and polymerization degree in comparison to MCC (Kumar, et al., 2002; Reus-Medina, et al., 2004; Kumar, 2002; Lanz, 2006; Mueller, 2008). The production and application of further Cellulose modifications are described in the works of Reus Medina and Kumar (Reus Medina, et al., 2007; Kumar, et al., 2002) and Kumar et al. (Kumar, et al., 2002). A basic research focus was set here to the improvement of the binder characteristics with keeping the fast disintegration nature of produced tablets. The main approach was the cross-link step of Cellulose with glutaraldehyde.

The described different ways and options for the production of cellulose-based excipients show clearly the polymorphic nature of this compound.

In general, polymorphism is found in excipients and also active pharmaceutical ingredients.

Polymorphic compounds have the ability to crystallize in different crystalline phases with specific molecular arrangements and conformations within the crystal lattice.

Polymorphs can build different crystalline forms of the same pure chemical compound (Sehic, 2008; Grant, 1989).

Solvates represent a crucial subcategory of polymorphic compounds. They contain an amount of a solvent incorporated within the crystal structure. In many cases, the incorporated solvent is water. These very important solvates are commonly known as hydrates (Grant, 1989).

Also a non-crystalline – amorphous – form can exist for numerous pharmaceutical solids.

Such solids show disordered arrangements of molecules and do not exhibit a crystal lattice. Consequently, they have zero crystallinity.

Since the stabilizing lattice energy is absent for amorphous compounds, the molar enthalpy is higher than for the stable crystalline state (Grant, 1989; Sehic, 2008).

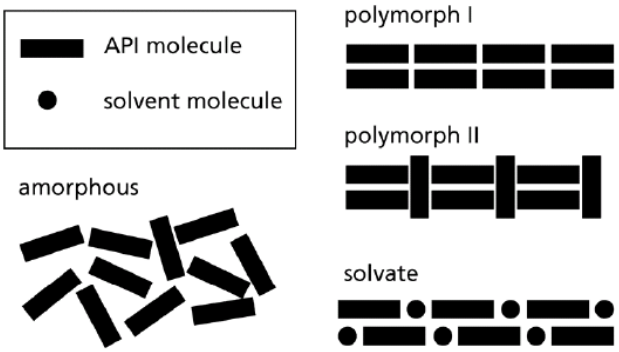


Fig. 1: The different types of solid forms (taken from: (Hilfiker, et al., 2006; Sehic, 2008)

By taken into consideration the different arrangements of the molecules in the several polymorphic forms of a compound, an essential difference in the exhibition of the chemical and physical properties can be expected. Actually, such differences are shown on the melting point, the chemical reactivity, the dissolution rate, the mechanical properties and many other properties.

For a successful application of a polymorphic powder compound in tablet production, the potential differences between the polymorphic forms in the mechanical properties like e.g. hardness, tensile strength, compressibility, flowability and blending should be considered.

For example, the difference in particle size can influence the powder flowability and compressibility, whereas the melting point plays an important role in the occurrence of sticking and picking during powder compression.

Mc Crone (McCrone, 1965; Sehic, 2008) stated that every compound has different polymorphic forms with the number of known forms for a compound being proportional to the money and time spent for research in the field of that compound.

Since about one third of the organic compounds and approximately 80% of all marketed pharmaceutical drugs show polymorphism under experimentally accessible conditions (Hilfiker, 2006) and these polymorphic forms can vary a lot on terms of mechanical

properties, the choice of the most ideal polymorphic form is crucial for a successful tablet production.

Microcrystalline Cellulose: Polymorphism and its influence on the compaction

In industrial production, Microcrystalline Cellulose is manufactured by acid hydrolysis. An essential influence of the conditions during hydrolysis for the particle morphology, the molecular weight and the crystallinity of the resulting Microcrystalline Cellulose has been reported some researchers in this field (Iida, et al., 1997; Wu, et al., 2001).

Pesonen and Paronen (Pesonen, et al., 1990) claimed that the remaining amorphous phase of MCC molecules after hydrolysis could have a positive influence on the compressibility of a powder, since in their research project the most amorphous cellulose batches showed the greatest tendency to both total and plastic deformation. Nevertheless, also the ability of agglomerated cellulose powder to fragmentate at small compressional pressure into smaller plastically deforming particles was shown to be an additional advance for the tablet formation.

Moisture content and particle size showed to be crucial parameters for the compaction nature of MCC (Wu, et al., 2001). Additionally, the mechanical interlocking between irregularly shaped MCC - particles shows to influence in a positive way the compaction step (Nyström, et al., 1993). An irregular shape of a particle indicates a bigger surface area, which on its part can be seen as bigger area of contact for interfering with other particles during the compaction process.

The ability of microcrystalline cellulose to deform in a plastic way is well reported (Roberts, et al., 1987; Roberts, et al., 1987).

The presence of slip planes and dislocations on microscale and the ability of the cellulose aggregate to deform on macroscale, make microcrystalline cellulose powder extremely compressible (Pesonen, et al., 1990).

The high compressibility of microcrystalline cellulose is a main reason why this material is seen as attractive choice for a good powder compact excipient. Nevertheless,

microcrystalline cellulose is a main subcategory of cellulose products, containing of a big number of different kinds of microcrystalline cellulose (MCC 101L, MCC 102G, UICEL, etc.) with varying physical and pharmaceutical properties.

Therefore, the choice of the most suitable microcrystalline cellulose product should be made carefully to prevent undesirable troubles during compaction, disintegration, dissolution or final drug effect.

Paracetamol

Paracetamol is an analgesic and antipyretic compound, which is used widely for the relief of minor pains, headaches and side-symptoms of cold and flu. It is sold over the counter in the most countries worldwide.

Its major advantages over non-steroidal anti-inflammatory drugs (NSAIDs) are the safe administration to patients with a history of peptic ulcers or asthma and its crucial lack of interference with the function of the platelets (Hyllested, et al., 2002). The efficacy of oral paracetamol for the treatment of acute pain could be confirmed by reviewing systematically randomized controlled trials (Perrot, et al., 2004; Toms, et al., 2008).

1g of Paracetamol achieved a pain release of 50% in one of four patients (Hyllested, et al., 2002; McNicol, et al., 2011).

Three polymorphic forms of Paracetamol can be found in the literature (Di Martino, et al., 1997). In addition to this, several molecular solvates and hydrates have been identified (Oswald, et al., 2002; McGregor, et al., 2002).

The monoclinic form I is the most used and marketed polymorphic form of Paracetamol. Back in 1974, Haisa et al. (Haisa, et al., 1974) could obtain a new crystalline form by ethanolic solution. This new form was identified as orthorhombic form (Di Martino, et al., 1997) and is validated by research works of further scientists (Al Zoubi, et al., 2002).

A third polymorphic form (Form III) was recrystallized but was too unstable for further investigation of its crystalline structure (Peterson, et al., 2002).

There is a wide industrial interest to further investigate metastable forms of Paracetamol

since the commercial form I shows a poor compressibility and needs additional binders to be compacted in a commercial tablet.

Fachaux et al. (Fachaux, et al., 1995) could reach an improvement in compressibility of Paracetamol by varying the crystallite habits of the compound. The orthorhombic form II of Paracetamol shows slip planes, which allow plastic deformation (Nichols, et al., 1998). Nevertheless, this process step has a main challenge: The elimination of solvent residues (Beyer, et al., 2001).

In the current available literature, there are several methods reported for the crystallization of orthorhombic paracetamol from solution (Kachrimanis, et al., 2008). Some of them can even be implemented for industrial use. Seeding of ethanol solutions with melt-grown form II crystals (Nichols, et al., 1998) and high-pressure crystallization (Fabbiani, et al., 2004) are just two of the numerous recommended ways.

Up to date, the only reproducible method is the seeding technique (Kachrimanis, et al., 2008; Nichols, et al., 1998). The extensive study (Al Zoubi, et al., 2002; Al Zoubi, et al., 2002; Al Zoubi, et al., 2003) of this method showed the harvesting and drying process steps to be very critical for affecting polymorphic purity. The main reason is the induction of transformation to form I after prolonged contact with the solvent.

A basic issue and challenge for the use of orthorhombic paracetamol is the long-term polymorphic stability of the crystals. Concerning this, conflicting data can be found in the literature (Kachrimanis, et al., 2008). In dependence of the used method, the produced orthorhombic crystals show different stability. Crystals obtained from ethanol solutions show to be stable at dry atmosphere, when their moisture content is properly low, while crystals from water solutions have been reported to transform easy to form I in all the range of investigated storage conditions (Kachrimanis, et al., 2008; Nichols, et al., 1998). Quiet stable orthorhombic paracetamol crystals were obtained by melt crystallization (Di Martino, et al., 1996). Without special storage conditions they showed a satisfying stability over 11 months.

Even though, the industrial importance of the orthorhombic form of Paracetamol is very essential, there are crucial scaling up problems in combination with the controversial data outcomes concerning the transformation to form I during storage or compaction which make this form not to be ready yet for industrial production.

Paracetamol is often used in scientific research projects as model drug with a main property being its low compressibility and brittle deformation mechanism. A main challenge is the combination of Paracetamol with excipients, to design a well-compressible formulation with satisfying pharmacocinetical and pharmacodynamical properties.

Mefenamic acid

N-(2,3-xylyl)anthranilic acid, also known as mefenamic acid, is a non-steroidal anti-inflammatory drug (NSAID) which is used often for treating pain of dysmenorrhoea as well as mild up to moderate pain (including toothache, headache and postoperative pain) (Moll, et al., 2011). Similar to other NSAIDS, mefenamic acid shows analgesic, anti-inflammatory and antipyretic activities. It inhibits the prostaglandin synthetase, which is responsible for the synthesis of prostaglandins and leads that way to its pharmacological effect.

Prostaglandins show numerous physiological functions in the human body such as the regulation of the renal blood flow and the maintenance of gastricomucosal barrier (Hawkey, et al., 1998). Since prostaglandins have an important role in nociceptive and inflammatory processes, the inhibition of their production can lead to the pharmacological effect of the NSAIDs. It has to be underlined, that the amount of knowledge concerning additional mechanisms of action of NSAIDs beside the described one is very little.

The pharmacokinetic behaviour of mefenamic acid shows a rapid absorption after oral administration and its half-life is of about two hours (Moll, et al., 2011).

From a pharmacokinetic perspective it shows a poor solubility in water and aqueous media (Romero, et al., 1999). On the basis of the biopharmaceutical classification system (Amidon, et al., 1995) it is classified as class II (Kimura, et al., 2007).

Mefenamic acid powder is not easy to be handled for compaction since it has a high tendency to stick to any kind of surface (Adam, et al., 2000). The powder formulation for mefenamic acid tablets is usually developed as a high-dose immediate release formulation with active drug content of 500 mg and higher (Adam, et al., 2000). Having such a starting position in powder formulation development the choice of a granulation step before final compaction can be seen as warmly recommended.

Also mefenamic acid, like many other pharmaceutical compounds, show some polymorphism and can have an essential batch – to – batch deviation in basic properties (Romero, et al., 1999). Therefore, if numerous different batches are used for commercial tablet production or research studies, the similarity of the powder properties between the batches should be verified.

The different polymorphic forms and the variation in crystallinity of mefenamic acid can also influence the dissolution behaviour of the compound. Aguiar and Zelmer (Aguiar, et al., 1969) evaluated the dissolution behaviour of different polymorphic forms. A variation in solubility and even a convertion between the polymorphic forms during dissolution could be shown.

The crystal habit of mefenamic acid can also affect its compressibility. Halelian (Halelian, 1975) underlined in his research work, that the compressibility and the problematic nature of mefenamic acid powders with different crystal habit can vary significantly, even when the melting point and the X-ray pattern between the formulations is similar.

For the research work of this PhD – thesis, a mefenamic acid powder with really poor compressibility and a really high tendency for sticking was chosen. In the designed powder formulations the mefenamic acid was mainly playing the role of a brittle, poorly compressible compound, being mixed with a well-compressible, plastic excipient (microcrystalline cellulose).

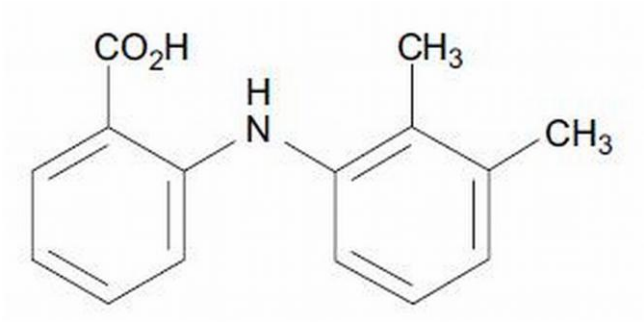


Fig. 2: Chemical structure of Mefenamic acid

Starch

Starch is a carbohydrate, belonging to the group of the so-called polysaccharides. The term polysaccharide has a greek origin and is an assembled word of the expressions poly (greek: πολυ; many) and saccharide (derived from the greek word σακχαρον; sugar) referring to the structure of polysaccharides, being a chain of carbohydrate or sugar groups.

Starch consists of two principal components, which are both polymers of glucose: Amylopectin, a highly branched molecule and amylose, which has an essentially linear molecular structure (Ellis, et al., 1998). Starch usually occurs as granules in the chloroplasts of green leaves and in the amyloplasts of storage organs, like for example seeds or tubers (Preiss, J, 2004).

Much has been written during the last decades concerning the structure of starch, its properties and its biosynthesis (Tester, et al., 2004). The level of analytical understanding of the starch structure development and how functional properties are connected with it is quiet evident from the developing literature base. With the available molecular biology tools the process of starch biosynthesis with all its subcategories, numerous cascades and processes involved could be explored in depth (Tester, et al., 2004).

The amyloplasts in starch is deposited over a period of days or weeks and stored till the germination of the seeds and the sprouting of tubers arrives, where this amyloplast is re-mobilised. On the other hand, a rapid turnover of starch can be found in chloroplasts (Ellis, et al., 1998).

Being an ingredient of many natural and processed food products, starch is the most important carbohydrate source in human nutrition (Belitz, et al., 2009). Starch and its

derivatives are also products of choice for a lot of different industries, e.g. the textile and paper industry.

Starches play an important role as excipients in tablet manufacturing. They are used as filler, disintegrating agent and as a binder in form of starch paste during moist granulation (Muzikova, et al., 2011). Even though natural starches show good compacting properties, the bad powder flowability in combination with a high lubricant sensitivity leads to a low choice attractivity of natural starches for powder formulation design, since they are not suitable to serve as dry binders for direct compression. The compressibility of starches depends strongly on the air humidity of the storage environment (Muzikova, et al., 2011). Absorbed water inside starch particles can influence significantly properties of a compact by changing its viscoelasticity (Malamataris, et al., 1993; Muzikova, et al., 2011). This can have also an impact on the sensitivity of starch powder to lubricants, which should in general never be neglected.

An increased attention has been given by pharmaceutical researches to the extraction, development and potential use of different starch in powder dosage forms (Alebiowu, et al., 2002). For improving the usability of starches in powder formulations for tablet production a wide range of modified starches have been developed by chemical treatment. These steps have lead to starch being the most commonly employed adjuvant in tablet formulations in the beginning of the 1990s (Garr, et al., 1991).

Pregelatinization and granulation are two of two most prominent methods for receiving starch products with satisfying compaction properties.

Granulation of rice starch could show improved flowing properties but this improvement could not be reached with other starches (Muzikova, et al., 2011). On the other hand, pregelatinization is applied to increase the densification tendency of starch particles during matrix filing and at low compression forces. Additionally, the tendency to deform plastically after application of a compression force is increased (Alebiowu, et al., 2002).

During the gelatinization process, the intermolecular bonds of starch molecules are broken down. By using heat and water, the chemical active side-groups of the starch start to interact

with the water-molecules, which leads to a final dissolvation of the starch granule (Donald, 2004). The crystallinity of the particle changes essentially. More and more amorphous forms are build up and a swelling effect can be noticed. The viscosity of the liquid mixture increases and the rheology is changed essentially. This effect is also used in cooking and pastry science, e.g. for preparation of thick liquids and sweet desserts.

After drying, a huge variety of powder products can be reached out of this gelatinization products. Some of them show good flow and compaction properties.

Starch 1500 is one of those attractive pregelatinized starch products. Is is widely regarded as next choice excipient after lactose and microcrystalline cellulose (Jivraj, et al., 2000). Starch 1500 was designed with aim to have higher compressibility and flowability. It appears as odourless, white to off-white powder of moderately coarse-to-fine nature. A distinctive taste of the powder has been reported (Wade, et al., 1994).

For receiving a Starch 1500 with good compaction quality, some of the hydrogen bondings between amylose and amlopection have to be ruptured partially so that the final product will contain about 80% of unmodified starch, 5% of free amylose and 15% of amylopectin (Jivraj, et al., 2000). The free amylopectin is mainly responsible for the cold water solubility and the desired binding properties of the excipient, while the free amylose is mainly responsible for the positive disintegration properties (Bolhuis, et al., 2006).

A main property of Starch 1500 is its extreme sensitivity to alkaline stearate lubricants, mainly because of a tablet softening effect by this interaction (Shangraw, et al., 1981). A reliable way to prevent this interaction is to avoid the use of magnesium stearate for powder formulations with Starch 1500 or to keep the concentration level below 0.5% (m/m). Higher concentrations may influence the tablet strength and dissolution in a negative way (Bolhuis, et al., 1973; Jivraj, et al., 2000). Therefore, stearic acid is usually the chosen lubricant with pregelatinized starch.

Even though, starch showed very attractive properties to be used as disintegrant, friablity problems could occur in a long-term. Additionally, at higher compression forces, the mechanism of deformation takes place in an elastic way, which lead to a high elastic

recovery during ejection. With high percentages of elastic recovery, tablet capping can be induced (Rees, et al., 1978; Jivraj, et al., 2000).

Nevertheless, the attractivity of Starch 1500 as filler and tablet excipient is indisputable, since a high percentage of marketed tablet products contain Starch 1500 as part of the total formulation mixture.

Calciumhydrogenphosphate

Calcium phosphates, like e.g. dibasic calcium phosphate or calcium hydrogen phosphate have gained importance in pharmaceutical and nutritional formulations (Carstensen, et al., 1990). The reason for this gain in importance can be found in their high calcium content, which makes these compound really attractive for dietary supplements and in their low manufacturing cost. By using skillful manufacture techniques, also satisfying flow and compressibility characteristics can be reached.

The chemical nomenclature of Calciumhydrogenphosphate is $CaHPO_4$. There are numerous synonymes for this chemical compound like Calciumhydrogenphosphate, Anhydrous dibasic calcium phosphate, Calcium monohydrogen phosphate and Dicalcium orthophosphate (JRS Pharma, 1995). Commercial brands of this compound are A-Tab (Sanofi-Aventis,France), Dicaphos (Budenheim, Germany) and Emcompress anhydrous (JRS Pharma,Germany).

In our research project, Emcompress anhydrous was used for compaction experiments with the Presster-simulator.

JRS Pharma markets basically two compounds for their Emcompress branch:

Emcompress (Calciumhydrogenphosphate dihydrate) and Emcompress anhydrous (Calciumhydrogenphosphate) (Joshi, et al., 2003). Both compounds are used in solid dosage forms as tablet binder, for enhancing formulation flow or as a capsule diluent (JRS Pharma, 1995). The excellent flow properties and deformation characteristics make the Emcompress products to be an excellent choice for solid powder formulations.

The deformation mechanism of Emcompress and Emcompress anhydrous is a brittle particle fraction, where the compound particles fragment into smaller particles (JRS Pharma, 1995).

This way, less lubricant surface is exposed to the particles what improves the tablet binding. It was shown (JRS Pharma, 1995) that Magnesium Stearate has almost no influence on the hardness and dissolution times of powder formulations with Emcompress and Emcompress anhydrous.

The compaction behaviour of Calciumhydrogenphosphate showed also that its low capping tendency and also a reduced sensitivity to compaction speed. In some ways a similar compaction behaviour to lactose was observed, which makes it an attractive solution for powder formulations being applied to patients with lactose intolerance (JRS Pharma, 1995).

Pharmaceutical powder: Analytical investigation

Powder is a bulky material consisting of a larger number of fine particles. This type of material shows a unique and very interesting behaviour. The question raises, in what state of matter a powder can be categorized. On a first sight, powder is assumed to be a solid material. Even though, the powder particles themselves are small units of solid material, a pile of these particles together show some behaviour elements, which are non-typical for a solid body.

In the PhD – Thesis of Michael Lanz (Lanz, 2006), powder was described as 4th state of matter, since it shows some behaviour as solid (reversibel and irreversibel deformation), some as liquid (flowing abilities) and some gaseous behaviour (extend compressibility).

In a further step, the attempt was made to compare the nature of a single particle with the natural behaviour of a molecule in a liquid or gaseous environment. This attempt failed due to two reasons: i.) No random Brownian movements are shown by powder particles ii.) the thermal energy can be neglected, since powder particles show a significant potential energy, due to their much higher mass in comparison to single chemical molecules.

The biggest part of the pharmaceutical raw materials are available in form of powders. This fact underlines the importance of this material form for the pharmaceutical industry.

Even though, a lot of scientific research work has been performed in the field of pharmaceutical powder technology in the last decades, the daily implementation and handling of powders in industry and academia is still executed in a way, which can be considered more as an art than a science (Leuenberger, et al., 2002).

Bringing the powder technology from a level of handling and operating experience to Science still remains a big challenge, basically due to two reasons: 1. A powder formulation is a really complex system, which is influenced by a big number of parameters, 2. The large amount of poorly understood processes in tablet manufacturing. Still today, the development of a powder formulation is based on traditional “trial and error” experiments, which then results often in a non-robust final tablet product (Lanz, 2006). Developing a robust powder

formulation by application of a wide range of scientific knowledge is able to reduce the R&D costs in a crucial way.

Even though, many concepts, like e.g. percolation theory, force-distance compaction curves and dissolution formulas are already at our disposal, there is still a long road for us to walk to reach the stage of a completely science based pharmaceutical powder technology.

Powder sampling (Allen, 2003; Lohr, 2010)

If a powder batch consist of a big amount of powder, just a small part of it can be characterized in a physical and chemical way, basically because of logistic reasons. A complete characterization of a big powder quantity can not be performed in its entirety. Therefore, a collection of smaller powder amounts is performed for receiving a representative sample assortment of the total powder bulk.

This can be seen as the big challenge of the whole powder analysis concept: When a powder is analyzed with focus on chemical or physical aspects, the quality of the final results depend crucially on the representativeness of the chosen bulk samples. When a sample of a few miligrams is taken from a bulk of several tonnes, the chances of having chosen a non-representative sample is really considerable.

The total error of a result in sample analysis can be seen as a combination of the primar sample choice and the analysis itself. Usually a non-ideal sampling shows analysis results which differ significantly between the single samples taken, expressed by a high standard deviation of the final analysis results.

Segregation is a common problem in powder technology because it can generate a high quality deviation between powder fractions within the same bulk batch. This phenomenon can be minimized by a suitable mixing of the powder and by taking a representative number of increments for analysis from the bulk material.

Statistical errors are the second main factor for analysis deviations in sampling. This factor is difficult to be prevented since even in an ideal mixture the quantitative distribution of the particles within the samples is seen as subject to random fluctuations.

Pycnometry

An important factor in the field of solid dosage forms for the scientific investigation of powder formulations is a correct qualitative determination of the involved powder particles and their dimensions. The dimension measurement of a material with simple geometry can be performed really easy (Myers, 2006). However, the measurement of a particle volume with an irregular shape is challenging.

Powder usually consists of a high number of small solid particles with an irregular shape and in many cases the presence of open and closed pores further complicates the scientific measurement of its dimensions values (specific surface, true density, etc.).

Archimedes of Syracuse (greek: Αρχιμηδης; 287 B.C. – 212 B.C.) faced such a problem with the crown of King Hiero II (Boudon, 2002). The king of Syracusa requested the help of Archimedes in resolving a problem: According to Marcus Vitruvius Pollio, an arbitrarily shaped crown was made by a goldsmith from pure gold. The raw gold was supplied for this reason by King Hiero himself. However, the suspicion was in the air that the goldsmith worked in a dishonest way, substituting an amount of gold with cheaper silver.

Archimedes from his side had to determine if the crown consisted of pure gold or not. An easy solution for this problem would have been the melting of the crown into a regularly shaped form with following classical density measurement over the dimensions of the form (Angelo, et al., 2008). But Archmiedes had to act scientifically without causing any damage to the artfully made crown. While at the local baths, upon immersing himself into the bathtub, Archimedes could see how the tub water overflowed. This phenomenon led to the solution of the big problem. Archimedes could put a mass of gold equal to the mass off the crown into a container filled to the top with water. The amount of overflow from this teld could then be compared to the amount of water being overflown by placing the crown in the container. An equal amount of overflowing water with the two methods would allow Archimedes to conclude that the crown was made with pure gold. A smaller water amount overflowing with the placing of the crown in the container in comparison to the calibrated gold mass would

proof the unpure nature of the crown metal (Myers, 2006). With this applied method, the density of the crown was determined in an indirect way, by dividing the mass of the crown by the volume of the displaced water. In a following step the density of the crown could be compared with the density of pure gold.

Archimedes was so happy and excited about his genious idea, that forgotten to get dressed, he started running through the streets naked and shouting Eureka! (greek: ευρηκα! ,"I have found it!"). At the end, the test was performed in a successful way, proving the existence of silver in the metal alloy of the crown (Hidetaka, 2010).

The principle applied by Archimedes is still today known as Law of Buoyancy and is a basic element in pycnometry. The technique of pycnometry is very appropriate for nonporous and porous objects. The displaced medium may be a gas, a liquid or even a fine powder for bigger macroscopic objects.

The pycnometry method with a liquid displaced medium can be applied with a Wadon-type pycnometer, as seen in Fig. 3 (Kousaka, et al., 2006). This vessel has a constant volume. As first step, the different numbers of involved masses and factors have to be calculated and defined, namely the mass of the empty pycnometer m_0, the mass of the pycnometer containing liquid m_l, the mass of the pycnometer including sample particles m_{sl} and the density of the applied liquid ρ_l. With these factors, the density of the particles can be calculated with the following equation 1:

$$\rho_p = \frac{\rho_l \cdot (m_s - m_O)}{(m_l - m_O) - (m_{sl} - m_s)}$$

Equation 1

The right choice of liquid is very important since the particles should be wetted and completely unsoluted.

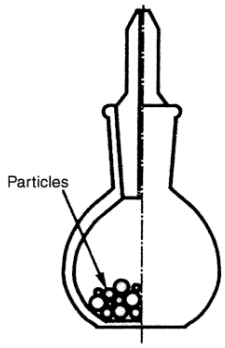


Fig. 3: Wadson-type Pycnometer

Another really usual measurement method for the true density of a powder is the constant gas voulme method. The basic principle of this method is shown in Fig 4.

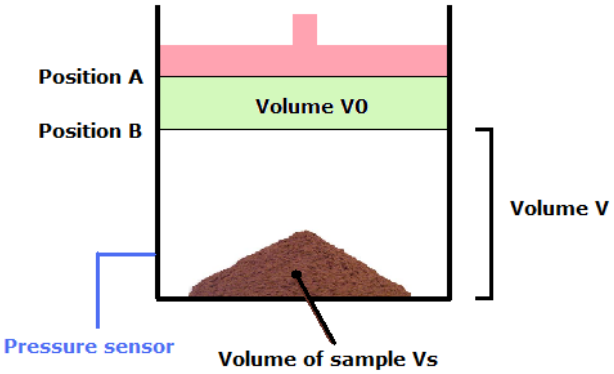


Fig. 4: Pycnometer for constant gas volume methode

In a first step, the volume and pressure values of the empty vessel are calbirated by moving the piston from position A to B and the changes in pressure and volume are measured as follows:

$$V + v_0 \rightarrow V$$
$$P_a \rightarrow P_a + \Delta P_l$$

Equation 2

Where V is the volume of the vessel between position B and the bottom, and v_0 is the vessel volume between the positions A and B.

The Boyle-Marriotte law states that for a fixed amount of ideal gas at constant temperature the pressure and the volume show an inverse proportionality to each other (Windisch, 2008).

For the described pycnometry instrument, this law can be expressed mathematically as follows:

$$P_a \cdot (V + v_0) = (P_a + \Delta P_l) \cdot V$$
$$V = v_0 \cdot (\frac{P_a}{\Delta P_l})$$

Equation 3

When a known weight of powder sample is added into the vessel, the above described procedure is repeated. This way, the change in volume and pressure can be expressed as

$$V + v_0 - V_s \rightarrow V - V_s \qquad P_a \rightarrow P_a + \Delta P_2$$

Equation 4

The following equation can be formed by using this approach

$$V - V_s = v_0 (\frac{P_a}{\Delta P_2})$$

Equation 5

For calculating the desired final **particle volume V_s** of the added powder sample, the following equation can be used, which was formed by using the already mentioned equations:

$$\boxed{V_s = v_0 (\frac{P_a}{\Delta P_1} - \frac{P_a}{\Delta P_2})}$$

Equation 6

In the research projects of this PhD – thesis, the gas displacement method was used to measure the volume in an accurately way. The investigation was performed with a AccuPyc 1330 apparatus, as seen is the following Fig. 5.

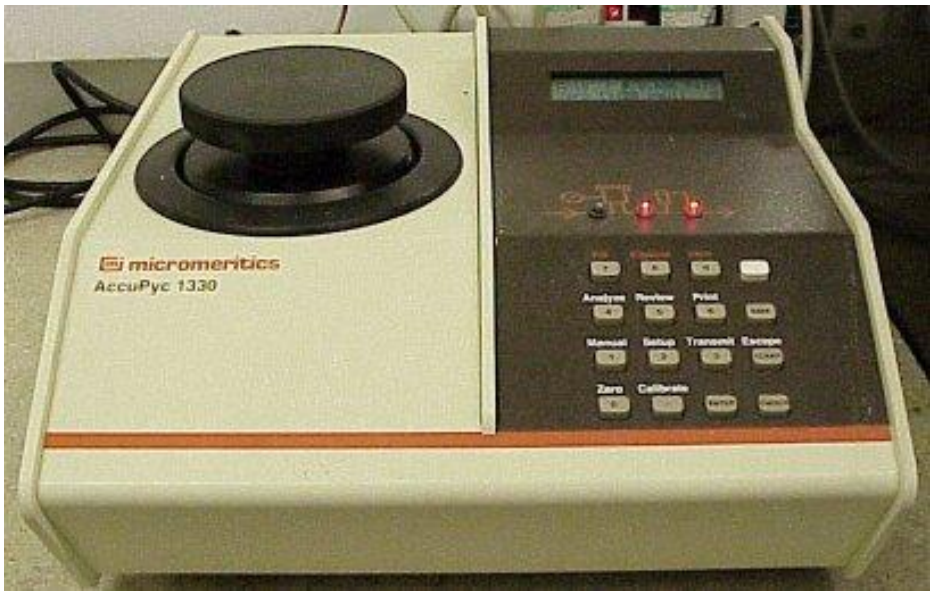


Fig. 5: AccuPyc 1330 (Micromeritics, USA)

The gas displacement method is a real advancement of the described constant gas volume method. Helium, as inert gas is used as the displacement medium. A powder sample is added in an instrument vessel of known volume. The vessel is sealed and helium is admitted before expanding into another precise internal volume. The vessel pressure before and after expansion is measured and the sample volume determined. By simply dividing the known sample mass by the measured sample volume, the gas displacement density (seen as true density) of the powder sample can be calculated (Micromeritics, 2011).

A schematic view of the working principles for the AccuPyc 1330 can be seen on the following figure.

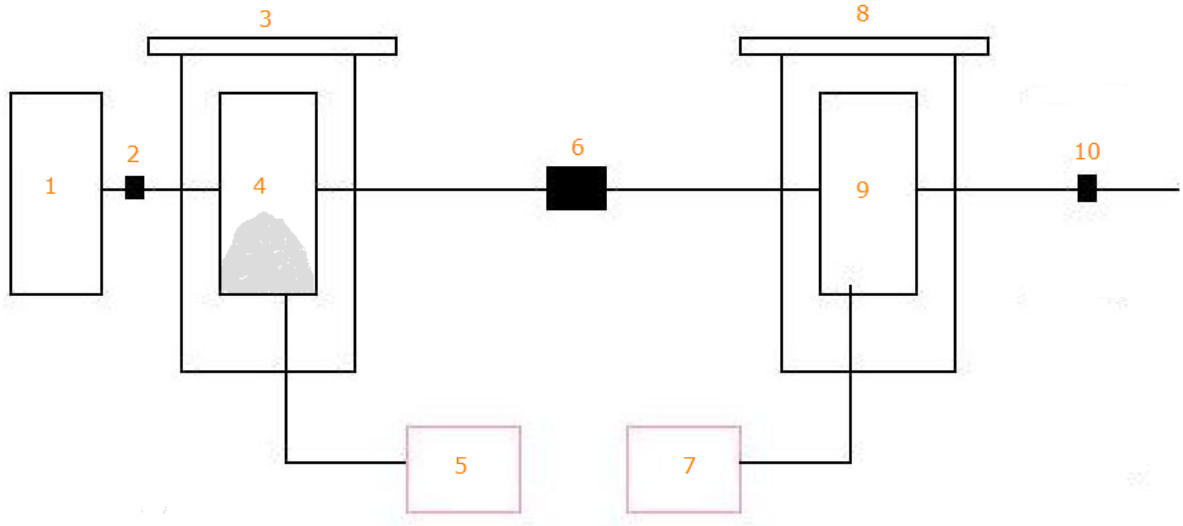


Fig. 6: Schematic view of the AccuPyc 1330 working device

The scheme shows the different parts of the pycnometer, where 1 is the helium gas tank, 2 is the fill valve, 3 is the sample chamber cap, 4 is the sample chamber, 5 is the sample chamber pressure transducer, 6 is the equilibration valve, 7 is the reference chamber pressure transducer, 8 and 9 are the internal reference chamber and 10 is the vent valve (Hintz, et al., 2009).

Particle size measurement

The size and shape of the investigated particles play an important in compaction studies since they affect directly the quality of the compaction process and the final tablet.

Therefore, an appropriate analysis of the particle size distribution of the powder compounds is crucial for the understanding of the powder behaviour under punch pressure (Thomas, et al., 1993).

There are numerous techniques available for the particle size measurement of a powder batch. Sieving, BET surface area measurement, electrozone sensing, sedimentation, aerodynamic techniques, image analysis are an assortment of the available methods for the particle size investigation.

Since the beginning of the 21st century, optical instruments based on the measurement of laser light scattered by particles in forward direction have become a standard and very popular technique for laboratory applications in powder characterization and analysis.

The use of the diffraction theory to accurately approximate the scattered light made this class of analysis devices to be named as “laser diffraction instruments”.

By comparison to other techniques for the determination of powder particle size, laser - diffraction shows advantages in term of good reliability, a high reproducibility and very high measurement speed with included detailed analysis (Ma, et al., 2000).

The scientist Mie investigated back in 1908 the behaviour of light waves on spherical particles. Mie formulated a theory which describes the scattering of a plane wave of light on spheres (van de Hulst, 1969). This theory is used to predict the electromagnetic field in space.

Lets take a light source which strikes a particle which is much larger than the wavelength of the incident light. By assuming the refractive index of the particle being much different from the surrounding medium, the biggest part of the light can be expected to scatter in the forward direction at small angles relative to the direction of the incident beam.

By taking into consideration the Fraunhofer diffraction theory, the scattering phenomena can be described for most applications (Ma, et al., 2000; Hecht, 1987). In a further step, this forward scattering pattern which is produced by any particle can be numerically calculated with Fourier transformation algorithms on a PC.

This subject contains a lot of detailed mathematical approaches and calculations. For not going into further details, we simply can keep in mind that the observed scattering angle of the light increases logarithmically with linear decrease of the investigated particle size. Also the observed scattering intensity depends on the particle size. The intensity value diminishes in relation to the particle cross-sectional area.

The measurement system usually consists of

(I) A laser source, which provides a coherent, intense light (fixed wavelength)

(II) A handling system, which is responsible for providing the laser beam with the powder under investigation as a homogenous particle stream

(III) Detectos for the reliable light pattern measurement

The following Fig. 7 shows the schematic organization of the laser diffraction system.

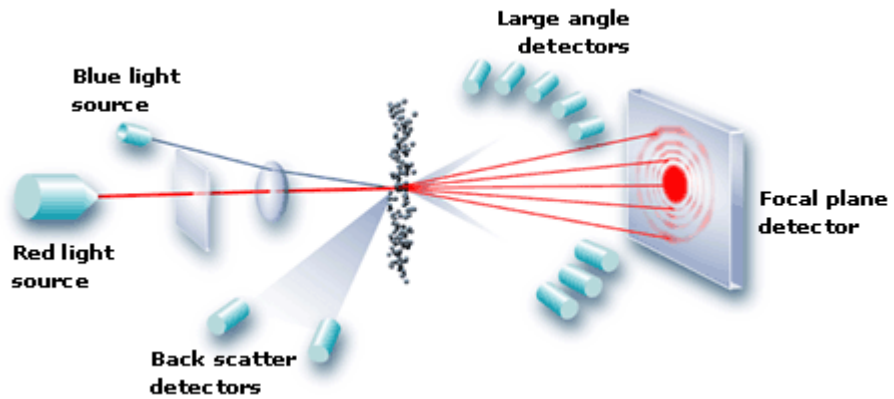


Fig. 7: Schematic laser diffraction system (Malvern)

The Mastersizer X was used for the particle size distribution investigation of this thesis. An example of this instrument can be seen on the following Fig. 8.

Fig. 8: Mastersizer X

Scientific term "density" (Litster, et al., 2004; Mueller, 2008)

The density of a powder formulation or a compressed tablet is a very important parameter for the understanding of the compound's behaviour during flowing, mixing, granulation, compaction, etc.

For solid bodies, the classic term "density" is known as mass divided by its volume, giving us a precise number for every object. Also in liquids and gases, the density can be measured and calculated. Since the behaviour of a powder shows similarities to a solid body (force resistance, elasticity, plastic deformation, etc.), to a liquid (e.g. flowing nature) and also shows similarities to a gas (certain compressibility), the term density needs some further developed and explained here.

i. *Bulk density (ρ_{bulk})* : This term is related to the volume which is occupied by the total bulk, including the void space.
ii. *Apparent particle density (ρ_{ap})*: This term is related to a single particle and precisely to the volume it occupies, including the internal porosity
iii. *True density (ρ_{true})*: this terms refers to the true solid density of the investigated material.

The following Figure 9 illustrates the terms in a schematic way.

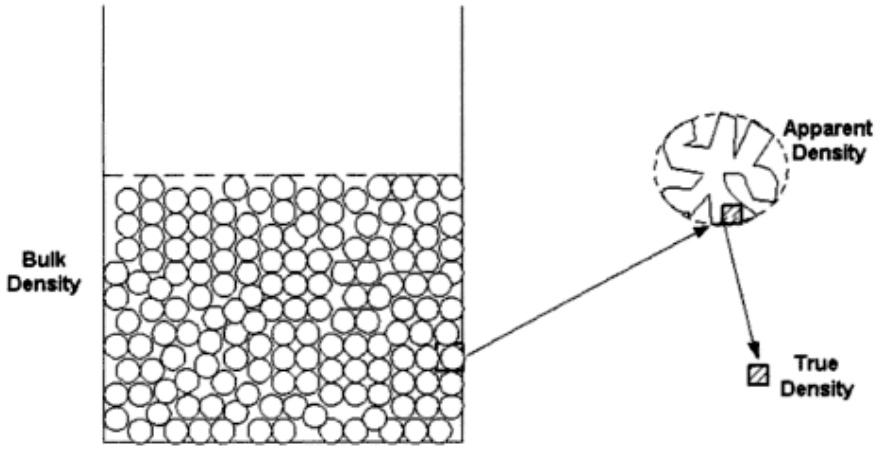


Fig. 9: Schematic illustration of the different powder densities

For compacts, we know mainly the apparent density ρ_{app} and the relative density ρ_r.

The apparent density ρ_{app} is defined as the density of the tablet including all pores and is calculated from the mass, the height and the radius of the compact. With the true density ρ_{true} (see paragraph above) we can calculate the relative density ρ_r.

$$\rho_r = \frac{\rho_{app}}{\rho_t} = \frac{m}{\rho_t \cdot h \cdot r^2 \cdot \pi}$$

Equation 7

where m is the compact mass and r is the compact radius.

The factor relative density is also used for determining the porosity of a compact, since the porosity ε is calculated with the following equation, having as main calculation factor the relative density ρ_r:

$$\varepsilon(\%) = (1 - \rho_r) \cdot 100$$

Equation 8

Powder compaction

Powder compaction is the conversion of a loose powder bed into a solid, compact body with usually a defined strength and shape. The success of a compaction is mainly dependent on four factors: The formulation, the tablet design, the compaction tooling and the chosen tableting process parameters.

The secret of successful industrial tablet manufacturing is mainly based on a wide scientific background knowledge and manufacturing experience of the staff involved in the set up of the process.

Since there is a big range of possible set up for every single of the above mentioned factors, the challenge is usually to choose correctly the levels of the numerous involved parameters.

The powder formulation itself should show a satisfactory compaction behavior, usually expressed as the powder *compressibility* and *compactibility*.

Compressibility is defined as the ability of a powder to decrease in volume under pressure, while compactibility is seen as the ability of a powder to be compressed into a tablet of specific strength (Leuenberger, 1982).

The raw formulation for tablet compaction is usually a granulation or a directly compressible powder formulation. The advantage of a directly compressible formulation is mainly the smaller number of production steps, which is connected to a smaller need for equipment, infrastructure, time and money.

On the other hand, the compaction of directly compressible shows also some limitations, since not all the powders have the necessary plastic deformation nature and also the mixture itself does not show always a stably compounds proportion for bigger batch volumes. Another important factor in tablet production are the total production costs. Well – compressible excipients are mostly expensive (Bolhuis, et al., 1996) while an introduction of a granulation step increases the production costs just slightly.

For producing tablets with satisfying properties, a chosen amount of a powder mixture or a granulation is usually filled in a matrice die of a tablet press. Then, a certain external force is applied by two punches (usually in a vertical way by upper and lower punch) for a defined time. After the force application, the produced tablet is ejected from the die by the lower punch and finally collected in a specific collection place of the tablet press.

The powder compaction process itself can be devided into four sequential steps (Rudnic, et al., 2005).

In a first phase, the applied force leads to an overcome of the friction between the powder particles. A first densification (packing) of the powder bed is reached by reduction of the apparent volume due to the interparticulate friction. In the second phase, the first physical force columns, chemical and physical particle bridges and reorganization of the particle molecules takes place. This leads to a first resistance of the powder bed to the applied force. The further application of an increased force leads to particle deformation, usually first in a reversible elastic manner followed by an irreversible plastic deformation or brittle fracture. This plastic and elastic powder behaviour is really dependant on the powder formulation and the nature (dwell time, punch shape, etc.) of the applied force.

In the last phase of the compaction process, a stable tablet is usually built, whose nature and properties depend also much on the different process and formulation parameters.

The described phases of the compaction process are shown as a schematic diagram of the powder bed / compact volume in dependence of the applied compaction force in the following Figure 10.

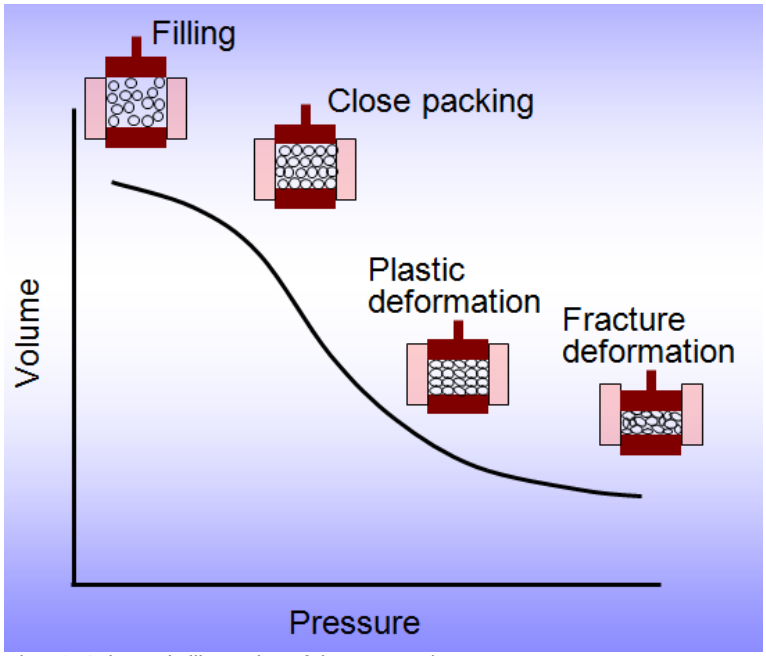


Fig. 10: Schematic illustration of the compaction process

For a better understanding of the compaction process, the general bonding mechanisms between the powder particles and the involved molecules have to be focused and taken into consideration.

The main involved bonding mechanisms are the following (Rumpf, 1958; Mueller, 2008):

- Molecular and electrostatical particle attraction forces
- Solid bridges (due to sintering, crystallization, melting, hardened binders and chemical reactions
- Movable liquid bonding (capillary forces and surface tension forces)
- Non freely movable binder bridges (adsorption layers, viscous binders)
- Mechanical interlocking (shape-related particle bonding)

In the research work of Fuehrer (Fuehrer, 1977; Mueller, 2008), the three main bonding mechanisms of a dry powder compaction were extracted. The following Table 1 lists further these mechanisms with corresponding dissociation energies and maximum attraction distances.

Table 1: Bonding mechanism specifications for compacted dry powders (Mueller, 2008)

Type	Dissociation energy [kcal/mol]	Maximum attraction distance [Å]
Solid bridges	50 – 200	< 10
Intermolecular forces	1 – 10	100 – 1000
Mechanical interlocking		

The intermolecular forces cover the different physical forces acting between different molecular surfaces over a small distance. Namely the van der Waals forces, the electrostatic forces and the hydrogen bondings are considered in this term.

Nyström et al. (Nyström, et al., 1993; Mueller, 2008) mainly focus on these intermolecular forces, describing them as being mainly responsible for the dominating bonding mechanism for pharmaceutical powder formulations.

The solid bridges between particles are seen as the areas of real contact at an atomic level. In comparison to the mentioned intermolecular bondings, the maximum attraction distance is much smaller for these bridges.

The mechanical interlocking between powder particles describes the twisting and hooking of the particles within the powder bed. This bonding mechanism can occur only when the

powder particle are in direct contact.

The exact nature and strength of the different involved bonding mechanisms are really individual for every different powder formulation. For producing tablets with a specific behaviour, e.g. during disintegration in the GIT, the predetermination and knowledge of these involved mechanisms for the handled formulation can be really important.

The microscopic influence of interaction between particles on the mechanical properties of particulate systems is described and evaluated in a detailed way in the research works of Forsyth et al. (Forsyth, et al., 2000) and Thornton et al. (Thornton, et al., 1998). Forsyth et al. focus especially on the van der Waals forces, since they are considered as the dominant interaction for dry particles.

The main understanding of these forces is crucial for many applications in industrial production of pharmaceutical dosage forms. For example, in challenges concerning powder mixing and flowability, the interaction nature between the powder particles become really crucial.

Also particle deformability influences a lot the nature of the interparticle van der Waals forces. During compression, soft particles undergo plastic deformation, which results in an increase of the van der Waals forces between the particles or between the particle and the die wall. Additionally, the high number of irregularly shaped particles with a high variation of particle size makes the scientific understanding of particle behaviour very tricky.

In general, the behaviour of interparticle forces is still far away from being well understood and an underestimation of these forces can have disastrous effects in powder technology.

The surface areas of the particles in intimidate contact as results of interparticulate bonds are referred as true areas of contact. To characterize the mechanical behaviour of compacts, a relationship between true contact area and the mechanical properties is attempted. The true contact area is difficult to be measured in real tablets. Therefore the approach through the relative density is used as indirect method to measure the contact area (Holman, et al., 1991).

Because of all the mentioned challenges in investigation of the particle behaviour on a

microscopic level in addition with the low number of particles taken into consideration, the focus has to be set on investigation made on a macroscopic level.

Powder behaviour under pressure and its predictabiliy

The behaviour prediction of a powder formulation after application of a compaction force is a main aim and challenge for the industrial tablet production. In the last decades, multiple predictive techniques have been developed what may benefits in reducing development time and research material. The focus on prediction techniques for the properties of solid dosage forms can be divided into three categories: Mechanical properties of raw material, physicochemical properties of raw material and process monitoring. Hardy et al. provides a detailed overview about the actual predictive and correlative techniques (Hardy, et al., 2003).

A model, or even a suitable fit of available data to a freshly designed multi-component powder formulation would be very valuable and appreciated to increase the efficiency of formulation design and so to reduce the number of time-consuming experiments.

The mechanisms and phenomena of the powder compaction have been the subject of numerous research investigations during the last six decades. There has been a wide variation of the compaction parameters and the used equipment (Celik, et al., 1989).

Today the number of mathematical equations proposed to characterize the compression is very high and many of them have been shown to have applicability only for a limited range of applied force and only for a limited number of materials. M. Celik gives a detailed and clear overview of the several data techniques (Celik, 1992).

Kolarik (Kolarik, 1994) proposes a model to predict the yield strength of binary blends of thermoplastics on the basis of the phase continuity acquired from the Hill model for the elastic properties of systems with two components. This model takes into consideration the bicontinuous structure of a binary mixture. With this model, van Veen et al. (van Veen, et al., 2004) developed a structure-dependent fit for a prediction of mechanical properties by taking into consideration the properties of the single materials and an interval of mixtures in which both components form a continuous structure in the compact. The developed equations

show a high validity for the investigated compounds (Sodium chloride and potato starch) but further enhancement with additional compounds and condition would be necessary to investigate the validity of this method for a global use.

Mechanical strength

The mechanical strength is a very important tablet property since it is responsible for many pharmacokinetical and pharmacodynamical behaviour of the resulting compact.

Tensile strength can be seen as one of the most important parameters for characterising the mechanical behaviour of tablets, as the compact must possess a minimum mechanical strength to substain potential loading during processing and handling (Wu, et al., 2005).

Belda et al. (Belda, et al., 2006) investigated the crushing strength of binary mixtures with adjusting the weight fraction of the components. They could observe a lowering of the tensile strength for non-extreme weight fractions. It was shown that a linear change of the crushing strength in dependence on the true volume fraction of the components could only be assumed if the single components deform to the same extent up to the point of fracture. This lead to the recommendation that as far as possible only components that deform equally during loading should be combined in tablets to avoid negative trends in the mechanical strength.

Compaction of binary mixtures

Researchers (e.g. Busignies, et al., 2006) have investigated the compaction of binary mixtures, whereas in most cases no simple relationship is found from the compaction properties of single materials and their proportions in the mixtures with the mechanical properties of the compressed tablets from binary mixtures. For the moment, there are a few papers available which propose a model for mechanical properties of compacted mixtures (Busignies, et al., 2006).

The mechanical strength of a tablet depends on processing and formulation parameters. The strength of tablets compressed from binary mixtures can not be predicted from the

compaction properties of the starting material alone for constant processing parameters, because interactions between the materials can occur during the compaction process (Vromans, et al., 1988).

Literature results for the compaction of binary mixtures show the complexity of the involved physical phenomena and the big challenge to define a single theory by e.g. designing an equation for explaining the tensile strength of binary tablets from the behaviour of individual components.

A main focus has been set to the compressibility of powder formulations. Busignies et al. investigated the compressibility of MCC, lactose and anhydrous calcium phosphate by designing binary formulations and further compaction. Compression cycles were investigated for the specific compaction energy, which showed a linear change with mass composition and the specific expansion energy which didn't show any linear behaviour. Additionally, a simple mixing rule with the porosity was designed to predict the mean yield pressure of a binary mixture by knowing the yield pressure of the single components. The experiment results with the used binary mixtures could validate this mixing rule.

Also the particle size of the substances in a powder formulation can have an important impact on the compactibility. Barra et al. (Barra, et al., 1999) show that the compactibility of a powder mixture depends mostly on the compactibility of the percolation material, whereas in case of no interaction between the materials, an intermediate compactibility of the powder can be found. An important outcome of the mentioned work is the possibility of formulation modification by sieving some the components, e.g. an increase of the API without loosing the compactibility of the formulation may be possible.

Michrafy et al. (Michrafy, et al., 2007) investigated the tensile strength of single component and binary tablets designed with lactose, MCC, and lactose with SMCC and SMCC-HD. The increase of the tensile strength with increasing relative density and with increasing MCC in the mixtures could be shown. A successful trial to predict the tensile strength of binary tablets from the characteristics of the single-component tablets with extensions of the Ryshkewitch-Duckworth model was performed. According to the authors, none of the designed model can

be considered as best one for tensile strength prediction of binary powders, since every model depends on multiple factors.

Kloefer et al. (Kloefer, et al., 2010) introduced a power law equation to predict tablet strength with compaction pressure. Different grades of MCC, lactose and mixtures thereof were used for investigation.

Basically, it showed good fitting for low pressure ranges, whereas for tablets produced with higher densities the model showed a significant deviation from the measured data.

Wu et al. (Wu, et al., 2006) showed the functional dependence of the tensile strength with the solid fraction or porosity of pharmaceutical excipients and of their binary, ternary and four-component mixtures at various concentrations. The logarithm of tensile strength was proportional to the solid fraction, which led to a model development on the basis of Ryshkewitch-Duckworth equation (Ryshkewitch, 1953).

The model validity could be shown from Wu et al. (Wu, et al., 2006) with experimental data.

Rasenack et al. (Rasenack, et al., 2002) describe a method for the tabletability by taking into consideration the final compact. Compression parameters like the total energy of compression, the plastic deformation and the local displacement were collected and combined in an equation for a calculation of tabletability. A challenging element in this method is the difficult transferability of this method to other machines because of the high sensitivity in deviation of these data.

Magnesium stearate in powder mixtures

The addition of Magnesium stearate on a tablet formulation normally decreases the tablet strength. An explanation for this phenomenon is provided by De Boer et al. (De Boer, et al., 1978) stating that the reduction of bonding force between particles occurs due to the presence of a magnesium stearate film on the particle surface.

A different approach is the explanation of relative decrease in tensile strength of a formulation due to the addition of magnesium stearate as a measure of particle fragmentation during compaction (Johansson, et al., 1995).

Van Veen et al. (van Veen, et al., 2005) show no significant influence of Magnesium Stearate on the compaction properties of MCC (Emcocel 90M). Nevertheless, for the projects of this PhD – thesis magnesium stearate was excluded from the powder compound and its use was decided to be just in a manual way after every compression by applying a small amount on the die wall and the punches with following cleaning by usage of compressed air.

Percolation theory

A very important subject in compression studies is the occurrence of the percolation phenomenon. Percolation is mainly responsible for the irregular change of powder formulations properties with adjustment of the quantity of one formulations' component. Binary mixtures can be seen as systems made of three phases: Two particle phases and the pore space. Numerous research papers describe in details the percolation phenomenon (eg. Van Veen, et al., 2000 ; Leuenberger, et al., 1997 ; Blattner, et al., 1990).

An important element of the percolation theory is the occurrence of the so called percolation thresholds. Let's take as example a binary mixture of components A and B. If the fraction B is small, the particles are isolated inclusions by forming a dispersed phase. Component A, as component with the higher proportion, forms a continuous phase. The presence of a dispersed phase usually changes the behaviour of the continuous phase due to the localization of tensions. By increasing the fraction B, these particles form aggregates.

By continuing the increase of compound B, a percolating B network occurs for a corresponding specific concentration of B. This concentration is called the percolation threshold,e.g p_{c1}. By further increasing of compound B, both compounds form a network up to the upper percolation threshold p_{c2}.

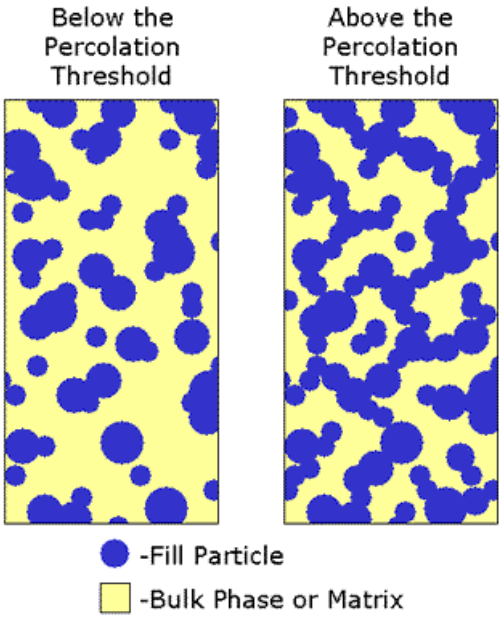


Fig. 11: Particle association below and above the percolation threshold (TDA)

Understanding the percolation phenomenon helps a lot for investigating and analysing elements of a specific powder formulation.

A further point to take into consideration is the occurrence of three kinds of interactions in a binary mixture of elements A and B:

(1) A binds preferentially with A / B binds preferentially with B;

(2) the affinity of A for A is the same as A for B, the same for B;

(3) A binds preferentially with B.

Compaction behaviour of binary mixtures

The percolation thresholds in a binary mixture compact depend on the relative concentrations and the relative bond-forming properties (Holman, 1991; Leuenberger, 1982; Busignies, et al., 2006).

Ramirez et al. (Ramirez, et al., 2004) show the usage of percolation theory and application to several tablet properties. They recommend avoidance of formulation design with mixing fraction close to the thresholds.

Busignies et al. (Busignies, et al., 2006) measured binary mixtures of lactose, MCC and calcium phosphate concerning inter alia tensile strength. No linearity could be noticed with regular change of compound load. More, a negative deviation from a proportional

relationship could be observed. Some compound concentration with very different tensile strength behaviour were related to the percolation threshold. Two statistical approaches are used here, which show some good fitting with the experimental data and the validity of these statistical approaches could be demonstrated for the used material.

M. Kuentz et al. (Kuentz, et al., 2000) investigated the compaction properties of Paracetamol and Avicel 101 as a binary mixture made with a well compressible and a poor compressible compound. The percolation theory was taken into consideration for the relationship of tensile strength vs. compaction pressure and the tensile strength vs. relative density. The validity of the percolation equation models could be shown for all measured pressure and fraction ratios. Additionally, the dilution capacity was introduced. The presented tools in this publication may be promising for being applied to mixtures of more than two substances, if only one compound is well compactable.

In the compression studies of van Veen et al. (Van Veen, et al., 2000) with no presence of mutual interactions on the individual densification behaviour of components, the mixtures' yield pressure could be calculated by linear interpolation of the yield pressure of the two materials involved.

For the change of the tensile strength with increasing quantity of Pregelatinised starch (with sodium chloride) the tensile strength of tablets with 100% pregelatinised starch is higher that of tablets containing 100% sodium chloride which indicates larger cohesive forces between pregelatinised starch particles as compared to sodium chloride particles (Van Veen, et al., 2000).

With increasing the % of pregelatinised starch the tensile strength initially decreases, which indicates the smaller adhesive forces of between sodium chloride particles and pregelatinised starch particles than the cohesive forces between the particles of the pure material.

Mathematical equations for prediction of powder compaction behaviour

Mathematical equations are really favoured for the measurement and possible prediction of compaction mechanisms and properties of the powder formulation and/or the final compact.

A compaction equation relates some compaction elements with the applied compaction pressure. The initial aim for fitting the data to an equation is to linearize the data and the corresponding plots. That way, comparisons can be applied easier between data sets. Also, the use of fitting parameters is really favoured for comparison reasons.

Till today, numerous equations have been proposed for analysis of compaction steps. While some seem to have a theoretical basis e.g. the Kawakita (Kawakita, et al., 1970) equation, many of them are purely empirical fits of specific limited data and can not claim any general validity (Denny, 2002).

For a reliable and satisfying application of compaction equation to investigate and compare compression of powder formulations, an equation should do more than only linearize the data (Denny, 2002). The parameters should somehow relate to basic physical and mechanical properties of the compacted material. Ideally the equation should apply to all materials, compacted the same way.

There are specific elements which should be considered during compaction and application of a compaction equation (Denny, 2002): (1): The method of die filling should be stated, (2): The use of internal lubricants should be minimized since they strongly affect the outcome of the result, (3): The satisfactory and detailed characterization of the primary material, (4): Minimization of die wall effects by choosing low die wall to thickness ratios, (5): Porosity measurement.

The porosity measurement and the corresponding measurement of true density and relative density is one of the most challenging step for the evaluation of compaction data. Small deviations on the true density measurement and/or the dimension measurement of the compact can lead to significant discrepancy of the outcome data (Celik, 1992).

After compaction, usually an elastic relaxation of the tablet occurs, which can be noticed by

an increase of the tablets height.

An increase of tablet height and volume after compression can be the result of two phenomena (Van Veen, et al., 2000): 1. decrease in material density and 2. increase in tablet porosity.

Van veen et al. show an independent increase of porosity for all investigated blends of sodium chloride and pregelatinised starch in the range of the applied compaction pressures.

The Heckel-Plot

The Heckel-equation can be seen as one of the most widely used mathematical tool for the evaluation of the tablet compressibility. In the method-section of the research project 1, the Heckel-Plot is mathematically described.

A detailed evaluation of this equation was performed and published by Denny (Denny, 2002) and also by Sonnergaard (Sonnergaard, 1999). There are some important points of criticism for this equation. There is the assumption of the isotropy of the compressed powder, which occurs also for a big number of compaction equations. This assumption is not ideal. Another point is the occurrence of a curved reason for low compaction pressures. In the past, this curved region was explained as phase of rearrangement. Research on this field shows in some cases brittle fracture in this region. A big point of criticism is the occurrence of strong deviations by comparing the published data for similar material by different authors. A possible reason for this deviation can be the already mentioned difficulty for a reliable measurement of true density, porosity and relative density. Since the Heckel-Plot follows a three steps transformation of the data, a small error can lead to tremendous effect.

Additionally, it seems unrealistic to look for a universal simple formula for the entire compression process, since it consists of several stages.

It can also be argued that materials which readily form strong interparticulate bonds will lead to tablets with higher tensile strength. Because of these strong interactions, there will be a greater compression resistance during the process.This is translated into greater energy requirement to make the tablets stronger.

Modified Heckel-Plot

Kuentz and Leuenberger (Kuentz, et al., 1999) designed a modified Heckel equation which takes into consideration a pressure susceptibility, defined as decrease of porosity under pressure. The detailed derivation for the modified Heckel equation can be found in the method-section of the Research projects 1 and 2.

The classical Heckel-equation assumes a constant pressure susceptibility while in this publication the susceptibility corresponds to the relative density and additionally, a term for the critical density has been introduced, which stands for the relative density where a rigidity between the punches starts to occur.

The compressibility of powder formulations was since a longer time ago a main target for scientific research with support of mathematical equations. The general principle can be seen as the analysis of quantitative data to a relation in pressure to volume reduction or pressure to porosity (Kawakita, et al., 1970). The aim of this data collection and fitting to equation is, as analysed in details a few paragraphs ago, the finding of linear behaviour and the comparison between powder formulations.

Leuenberger equation

An important approach in practice is the focus on the production of tablets with adequate strength. This ability of a powder formulation to be compressed into tablets with specified strength can be expressed as the formulations' compactibility. Leuenberger derivated an equation (Leuenberger, 1982), which includes one factor for compressibility and one factor for compactibility. The inclusion of a term for compactibility makes this equation, the so-called Leuenberger equation, an attractive tool for investigating powder formulations.

A detailed derivation and application proposals for this equation can be found in the method-section of the Research project 1.

The literature evaluation shows the attractivity of investigation for multiple-component tablets,

preferable binary mixtures with a well compressible and a poorly compressible compound.

What is usually the effect of a small compound quantity adjustment to the compressibility of a formulation? Is there a proportional behaviour of the compressibility to the quantity of a specific compounds' quantity?

An investigation of binary mixtures with adjustment of one compound or complete replacement of one compound by a comparable compound and following evaluation with different mathematical tools can show the behaviour of the formulation compressibility and the influence of adjusting the weight ratio of the used compounds. E.g. the use of the additivity rules for the Leuenberger equation can be investigated with this approach. Also a comparison of the fitted technical factors for the different equation can provide essential information for the usage and comparability of the methods.

This PhD-thesis and especially the research project 1 mainly focus on these questions and issues.

Instrumented tablet presses

The instrumented tablet presses are used in research and development of tablet formulations and also in the industrial manufacturing of compacts. The application focus of instrumented tablet presses in research & development is mainly set on the analytical measurement power (physical characterization of the compression properties) while in production their use is mainly focused on the ensurance of a constant tablet quality (Belda, et al., 1998).

The demands concerning precision and accuracy of the measurements can vary significantly in dependence on the aim and purpose for which the data are collected. While in many cases a specific instrument with constant settings for application in one and only repeatable process step may be sufficient, in other cases a high reproducibility is a main priority (for example for determining and monitoring the quality of the formulation and the final compact). The repeatability of the results plays an important role, namely the confidence, that same results can be achieved with different machines has to be reached.

An instrumentation of a tablet press turns the manufacturing machine into an analytical tool

which can support crucially the scaling up process of a new formulation and the tablet design from the stage of Research & Development to industrial production (Belda, et al., 1999). Instrumentation can be applied to eccentric presses, rotary presses and compaction simulators (Barra, et al., 1998; Ilkka, 1998; Abdel-Hamid, 2011).

The use of the tabletting press as an analytical instrument presumes a high precision and accuracy of the obtained results. This is a big challenge since the specifications of an instrumentation and data acquisition system after initial design and setup may change with installation of the device on the tablet press (Waring, et al., 1986; Steffens, 1978).

A tablet press is mainly designed for an optimal tablet production with a highest possible performance. The installation of a high-precise measurement instrument in such a press, within a given geometrical environment, may be very challenging and may influence crucially the characteristics and quality of the measuring system (Goodhart, et al., 1968; Lammens, et al., 1979; Belda, et al., 1999). Also some mechanical setups can have a negative impact on the response of the analytical instrument.

The sensor of the analytical instrument plays a key role in the data measurement for instrumented presses. The sensor in an instrumented press is a transducer device, which transforms a certain type of energy into another one (Bubb, 2008). A battery can be seen as a transducer, since it converse the chemical energy of the batterie parts into electrical energy. The sensors used in instrumented tablet presses convert a physical parameter into an electrical signal which is measurable and recordable. The following Fig. 12 shows the different ways of signal conversions which are executed by sensors in tablet presses.

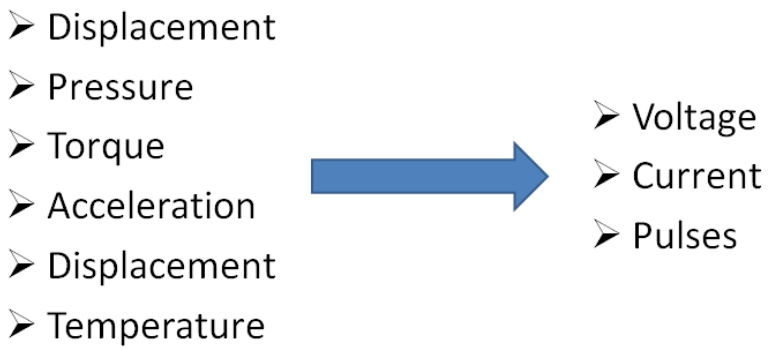


Fig. 12: Sensor signal conversions in tablet press

These challenges can be illustrated by the usual piezo-electric load washers, installed between the punch and punch holder for the measurement of the lower and upper punch force (Schmidt, et al., 1986; Lindberg, 1972; Belda, et al., 1998). Because of the direct connection of the load cells to the punch setup, an exchange of these punches is usually connected to a further reinstallation of the sensors. Since such a punch reinstallation changes the configuration and the location of the installed transducers, a recalibration of the instrumentation is unavoidable.

The calibration process for installed press instrumentation is a tricky point in this subject. An optimal established calibration process must be repeatable and should not influence at all the measurement outcomes. The question arises, how such a robust system can be created, since there will be a small variation in the compaction process of the tablet press, the installation of the press instrument will influence the whole process and the signal sensors on the press will also show some variation in the outcome signal. This chain of process parameters with individual small variations can lead to a final resulting process with a significant variation. Therefore, a reliable setup of the instrumented tablet press and the calibration process has to be planned.

Even though, the mentioned challenges have to be overcome, instrumented tablet presses are a very important support for the development of tablet formulations.

For the measurement of compression and ejection forces, there are piezoelectric and strain gauge-based sensors used. While piezoelectric sensors were favoured because of their small size and their high-frequency response, its usability only for dynamic events and signal changes because of small cable movements are a crucial issue. The strain – gauge based sensors show an advantage for static event measurement and do not show a signal decrease to zero within a few seconds even if a force is still applied (Bubb, 2008).

Piezoelectric force transducers are made with quartz or piezoceramic elements. The orientation of the cut quartz crystal to the axes is really precise in dependence to the application of the sensor (Cocolas, et al., 1993). When a change in load is applied on the crystal, an electric signal output is generated. This way, the piezoelectric load cells are an

attractive solution for dynamic events (Celik, 1992).

The strain gauge cell can be seen as a useful and common tool for the measurement of data in an instrumented tablet press. The strain gauge (or strain gage) is a tool device, which is used to measure the strain of an object. What is a strain? Strain is defined as the amount of a body deformation due to an applied force. From a mechanical point of view, the strain is seen as the fractional length change of the measured physical body, as illustrated in the following Figure and Equation.

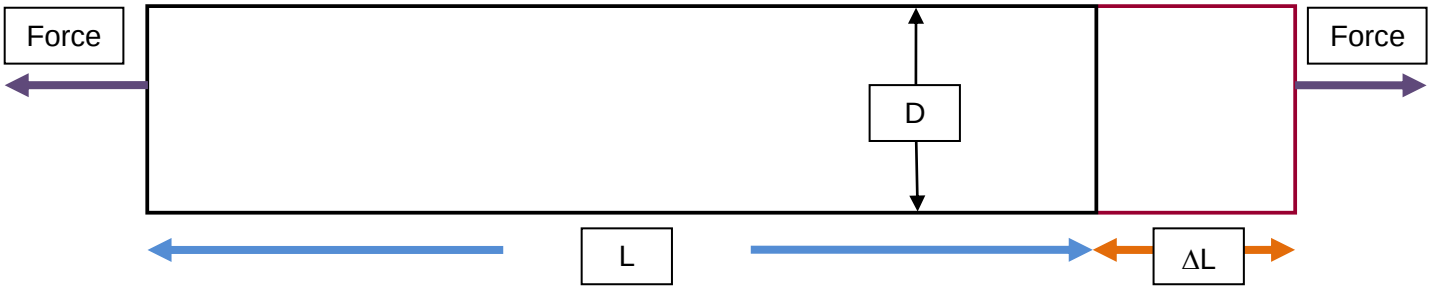


Fig. 13: Definiton of Strain (taken from: National Instruments)

$$\varepsilon = \frac{\Delta L}{L}$$

Equation 9: Physical Strain (taken from: National Instruments)

There is no clear picture about the exact discovery of the strain-induced resistance change in electrical wires. Lord Kelvin mentioned this effect already in the 19th century (Bubb, 2008). During the 1930s, Edward E. Simmons and Arthur C. Ruge developed the first real device with this technology. One of the most common strain gauge types is made of a flexible backing supporting a metallic foil pattern (Electronical source: http://www.omega.co.uk; 01.11.2011). This devices are then attached by an adhesive material, like e.g. cyanocacrylate (Electronical source: efunda.com; 01.11.2011), to the object to be measured. When the object is deformed or relocated, the foil is deformed, generating a change in its electrical resistance.

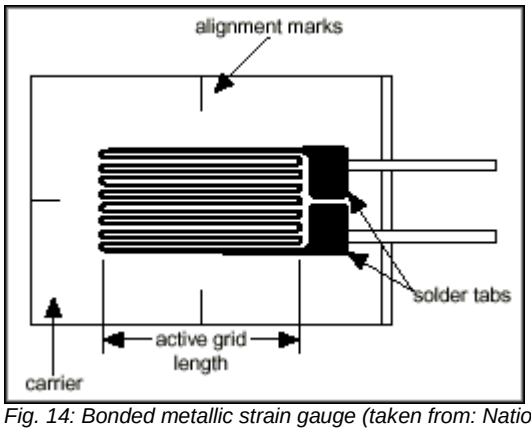


Fig. 14: Bonded metallic strain gauge (taken from: National Instruments)

The strain gauge has to be designed that way, that a proper instrument mounting can be made which is important for a reliable measurement. The following table shows the most important desired features, a stran gauge instrumentation should show (Chalmers, 1992):

- Small mass and size, with high resistance
- Satisfying stability, repeatability and linearity over a wide strain range
- Easy production in different sizes and configurations
- Reasonable sensitivity to strain
- A low production and handling cost
- Ability to control effects of environmental influences, like e.g. temperature
- Suitability for static and dynamic meausurements
- Ability of remote recording

The desired reasonable sensitivity to strain is a main challenge in the design of a strain gauge instrumentation, since in practice such a measurement has an outcome of a little bit more than a few millistrain. This way, the strain measurement recquires sensitivity to very small changes in resistance (National Instruments, 2011). The most accurate way for reaching this kind of sensitivity and meeting the requirements listed above the design and implementation of measurement systems like e.g. Wheatstone bridge or Quarter-Bridge Circuits are recommended and usually taken into consideration (Little, 1992; Kalsi, 2010; Bakshi, et al., 2007).

Compaction simulators

Apart of instrumented tablet presses, the use of compaction simulators can be seen as a promising approach for the investigation of the compaction process. There are several different compaction simulators on the market, which show a wide range of mechanical and technical properties. Basically, all compaction simulators have at least a load frame, a hydraulic unit and a data acquisition system (Bourland, et al., 2008; Abdel-Hamid, 2011). The use of the compaction simulator is the most common approach for dynamic compaction testing. The sophisticated control and monitoring of the compaction process with the simulator is an important reason for choosing this kind of machine for tests, since it provides an essential flexibility in compression conditions. For example the possibility of investigating compaction under constant velocity conditions for the compression and decompression phases is a big advantage of some compaction simulators towards instrumented tablet presses (Amidon, et al., 2009). There are many variables in a tablet press which can be simulated in a reliable way. Compaction forces, punch velocity, tableting speed, dwell time, relaxation and the influence of upper & lower compression rolls are main investigation targets, which can be reached by a simulator. On the other hand, the heat generation in the tablet press die after a longer batch run and the exact contact points and positions of the punch and the rolls during the compaction step are not easy to be simulated. Also, since there are usually small powder amounts applied in a simulator for investigation, the feeding setup of an industrial press differs crucially from the powder supply of a compaction simulator. By simulating similar dwell times like in a rotary press, the simulator instrument can be used for raw material evaluation concerning e.g. basic compaction mechanisms, study of process variables like compression force and speed, investigation of scale-up issues and industrial production and many more factors.

Presster

Also “linear” tablet press emulators, like the Presster have shown essential utility by offering many of the advantages of a conventional compaction simulator as the easy use and the flexibility. The Presster was developed by Metropolitan Computing Corporation Inc. NJ, USA in the late 1990s and has the crucial ability to simulate the globally available rotary tablet presses (MCC online, URL: http://www.mcc-online.com/presster.htm, 01.11.2011). A main special feature of the Presster is that compression rolls of the same dimensions as the simulated rotary press have to be installed. This way, the compression profiles are really similar to those of the simulated tablet press (Picker, 2003).

The design basically resembles a single station rotary press with all its parts, which are not arranged in a circular path but on a straight line. For being able to record exact measurement data, the sensoring system of this machine is based one pair of punches and one single die. A turret-analogue carriage with the tooling set is the central part of the machine. This carriage is driven horizontally through the machine. It passes the dosing cam, the upper and lower rollers of the pre-compaction, the roller set of the main compaction station, ending at the ejection cam and the take off bar. The punch tools, the dies, the precompaction and the compaction rolls are in the most cases the same, which are used in the rotary press (Neuhaus, 2007). For measuring the punch displacement, so called linear variable differential transformers (LVDTs) are used (Fig 15) (Abdel-Hamid, 2011).

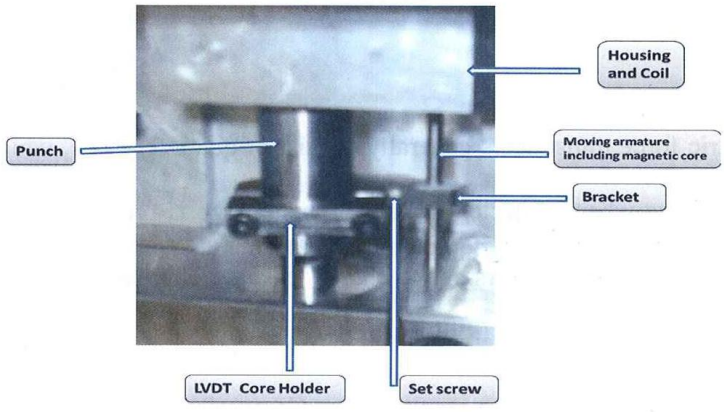


Fig. 15: Linear variable differential transformer for measuring punch displacement

These devices work by measuring the position of a core rode insinde the cylinder relative to a predefined zero position. The resulting voltage shows a proportionality to the object displacement. As seen in Fig 15, on the Presster both LVDTs are installed into the same carrier as the die. This way, the applied compaction force during the powder compaction has only a limited influence on the punch displacement measurement. Since different punch formats can be used and also compaction rollers with a wide range of diameters can be installed, practically all market available rotary presses can be simulated (Natoli, et al., 2009; Levin, et al., 2000).

Fig 16 illustrates the basic set up of the Presster with all the main elements (Neuhaus, 2007).

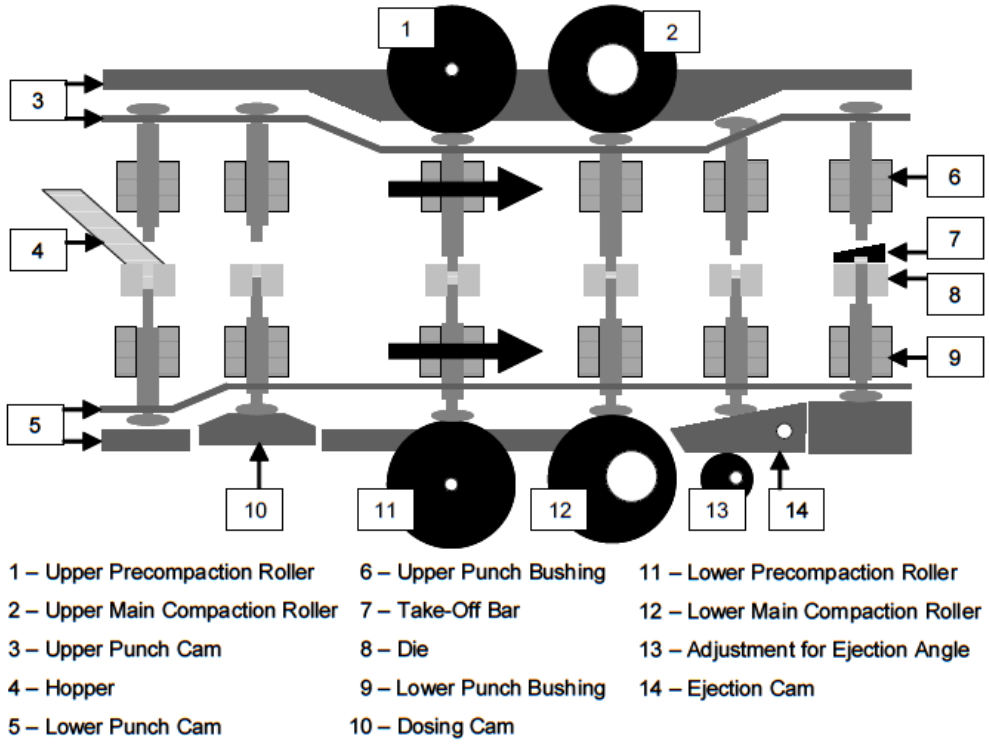


Fig. 16: Schematic view of the Presster instrument

The Presster compaction simulator is connected to an electronic data acquistion system and a software program, which allows all the technical experiment parameters to be set on a personal computer. Also the monitoring and the data outcome analysis is made on the IT system. This way, parameters, like e.g. gap, resulting compaction force, dwell time, ejection angle, can be chosen and also adjusted fast and easy, allowing the operator to investigate the influence of all these elements on the resulting tablet and the powder formulation

behaviour under pressure.

The following Fig 17 shows illustrative print screens of the Presster computer software program with its main screen, motor speed adjustment with calculation of dwell time and tooling selection.

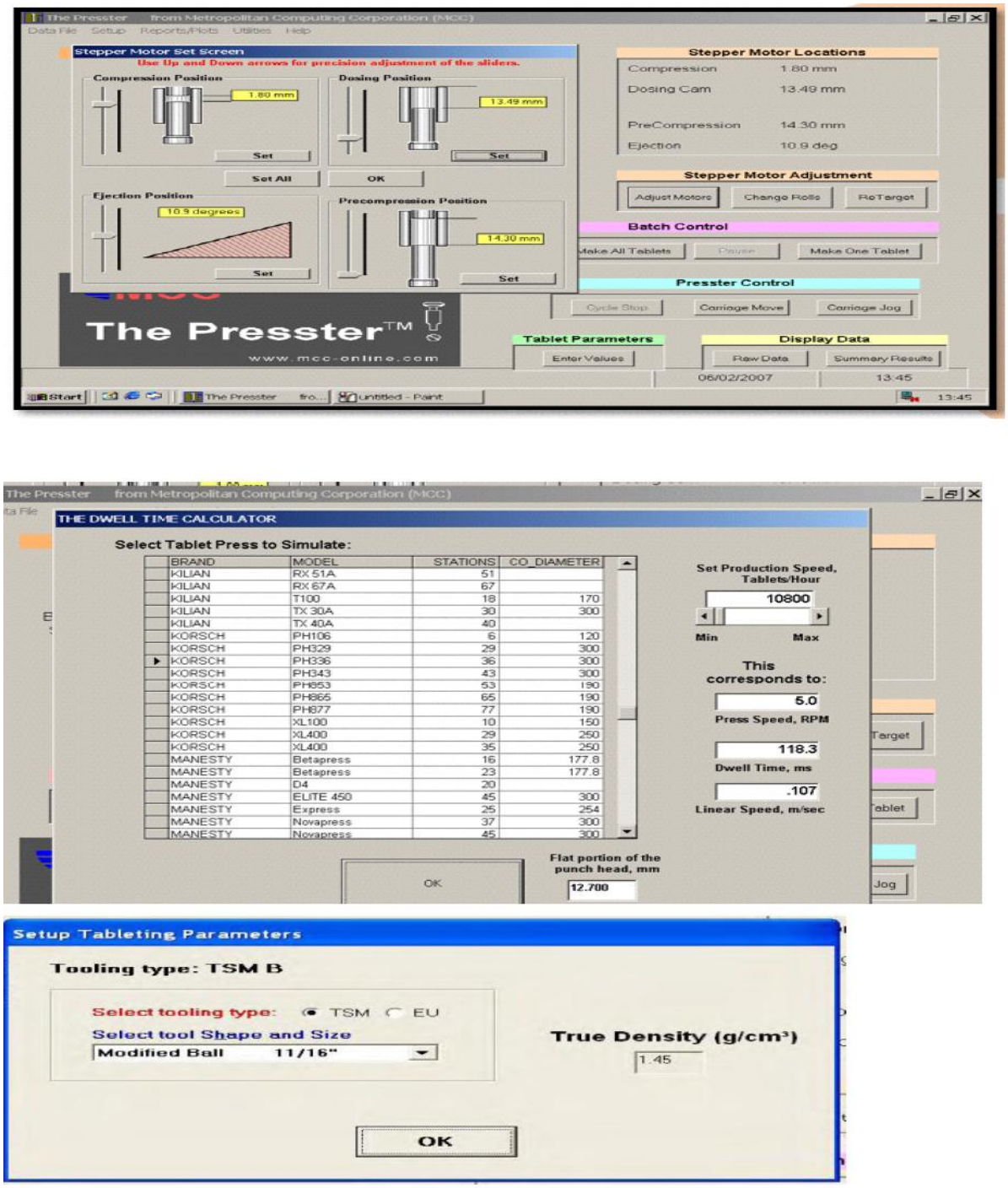
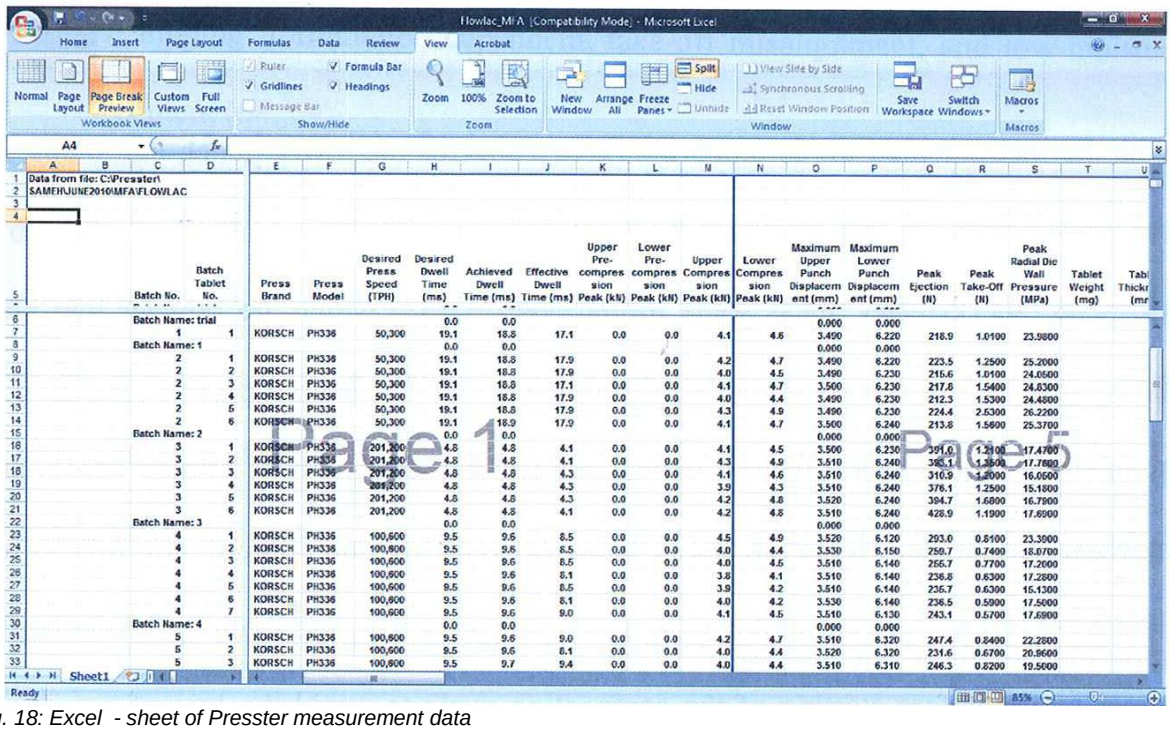


Fig. 17: *Presster software: main screen, motor speed adjustment with calculation of dwell time and tooling selection*

After completion of an experiment run, the measurement results of all sensors are collected by the Presster software and shown numerically and graphically. Examples of this

measurement can be seen in Fig 18 for numerical illustration in Microsoft Excel, compression curves and Ejection / Take – off force diagrams (Abdel-Hamid, 2011).



Howlac_MFA [Compatibility Mode] - Microsoft Excel

Data from file: C:\Presster\
SAMEH\JUNE2010\MFA\FLOWLAC

Batch No.	Batch Tablet No.	Press Brand	Press Model	Desired Press Speed (TPH)	Desired Dwell Time (ms)	Achieved Dwell Time (ms)	Effective Dwell Time (ms)	Upper Pre-compression Peak (kN)	Lower Pre-compression Peak (kN)	Upper Compression Peak (kN)	Lower Compression Peak (kN)	Maximum Upper Punch Displacement (mm)	Maximum Lower Punch Displacement (mm)	Peak Ejection (N)	Peak Take-Off (N)	Peak Radial Die Wall Pressure (MPa)	Tablet Weight (mg)	Tablet Thickness (mm)
Batch Name: trial					0.0	0.0						0.000	0.000					
1	1	KORSCH	PH336	50,300	19.1	18.8	17.1	0.0	0.0	4.1	4.6	3.490	6.220	218.9	1.0100	23.9800		
Batch Name: 1					0.0	0.0						0.000	0.000					
2	1	KORSCH	PH336	50,300	19.1	18.8	17.9	0.0	0.0	4.2	4.7	3.490	6.220	223.5	1.2500	25.2000		
2	2	KORSCH	PH336	50,300	19.1	18.8	17.9	0.0	0.0	4.0	4.5	3.490	6.230	215.6	1.0100	24.0500		
2	3	KORSCH	PH336	50,300	19.1	18.8	17.1	0.0	0.0	4.1	4.7	3.500	6.230	217.8	1.5400	24.8300		
2	4	KORSCH	PH336	50,300	19.1	18.8	17.9	0.0	0.0	4.0	4.4	3.490	6.230	212.3	1.5300	24.4800		
2	5	KORSCH	PH336	50,300	19.1	18.8	17.9	0.0	0.0	4.3	4.9	3.490	6.230	224.4	2.5300	26.2200		
2	6	KORSCH	PH336	50,300	19.1	18.9	17.9	0.0	0.0	4.1	4.7	3.500	6.240	213.8	1.5600	25.3700		
Batch Name: 2					0.0	0.0						0.000	0.000					
3	1	KORSCH	PH336	201,200	4.8	4.8	4.1	0.0	0.0	4.1	4.5	3.500	6.230	391.0	1.2300	17.4700		
3	2	KORSCH	PH336	201,200	4.8	4.8	4.1	0.0	0.0	4.3	4.9	3.510	6.240	383.1	1.1500	17.7600		
3	3	KORSCH	PH336	201,200	4.8	4.8	4.3	0.0	0.0	4.1	4.6	3.510	6.240	310.9	1.2000	16.0500		
3	4	KORSCH	PH336	201,200	4.8	4.8	4.3	0.0	0.0	3.9	4.3	3.510	6.240	376.1	1.2500	15.1800		
3	5	KORSCH	PH336	201,200	4.8	4.8	4.3	0.0	0.0	4.2	4.8	3.520	6.240	394.7	1.6800	16.7900		
3	6	KORSCH	PH336	201,200	4.8	4.8	4.1	0.0	0.0	4.2	4.8	3.510	6.240	428.9	1.1900	17.6900		
Batch Name: 3					0.0	0.0						0.000	0.000					
4	1	KORSCH	PH336	100,600	9.5	9.6	8.5	0.0	0.0	4.5	4.9	3.520	6.120	293.0	0.8100	23.3900		
4	2	KORSCH	PH336	100,800	9.5	9.6	8.5	0.0	0.0	4.0	4.4	3.530	6.150	259.7	0.7400	18.0700		
4	3	KORSCH	PH336	100,600	9.5	9.6	8.5	0.0	0.0	4.0	4.5	3.510	6.140	266.7	0.7700	17.2000		
4	4	KORSCH	PH336	100,600	9.5	9.6	8.1	0.0	0.0	3.8	4.1	3.510	6.140	236.8	0.6300	17.2800		
4	5	KORSCH	PH336	100,600	9.5	9.6	8.5	0.0	0.0	3.9	4.2	3.510	6.140	236.7	0.6300	15.1300		
4	6	KORSCH	PH336	100,800	9.5	9.6	8.1	0.0	0.0	4.0	4.2	3.530	6.140	236.5	0.5900	17.5000		
4	7	KORSCH	PH336	100,600	9.5	9.6	9.0	0.0	0.0	4.1	4.5	3.510	6.130	243.1	0.5700	17.6900		
Batch Name: 4					0.0	0.0						0.000	0.000					
5	1	KORSCH	PH336	100,600	9.5	9.6	9.0	0.0	0.0	4.2	4.7	3.510	6.320	247.4	0.8400	22.2800		
5	2	KORSCH	PH336	100,600	9.5	9.6	8.1	0.0	0.0	4.0	4.4	3.520	6.320	231.6	0.6700	20.9600		
5	3	KORSCH	PH336	100,600	9.5	9.7	9.4	0.0	0.0	4.0	4.4	3.510	6.310	246.3	0.8200	19.5000		

Fig. 18: Excel - sheet of Presster measurement data

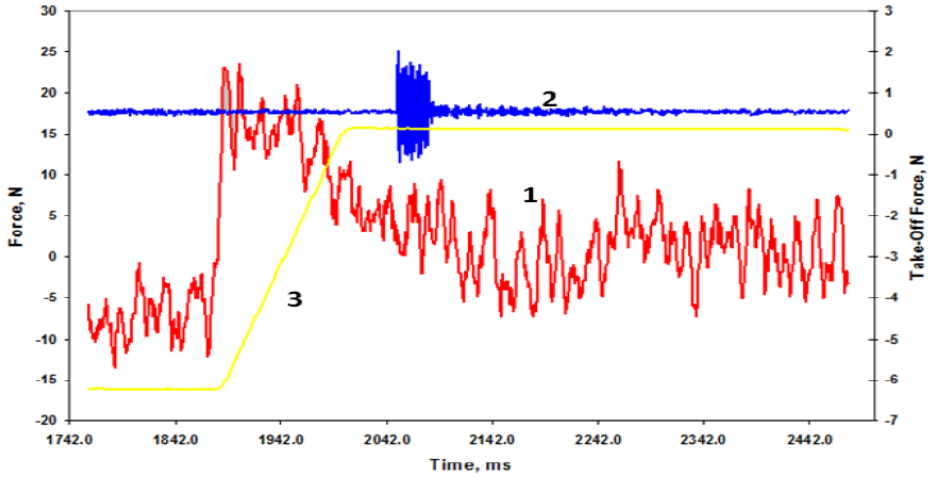


Fig. 19: Ejection force and take off force diagram: (1) Ejection force; (2) Take off force; (3) Lower punch displacement

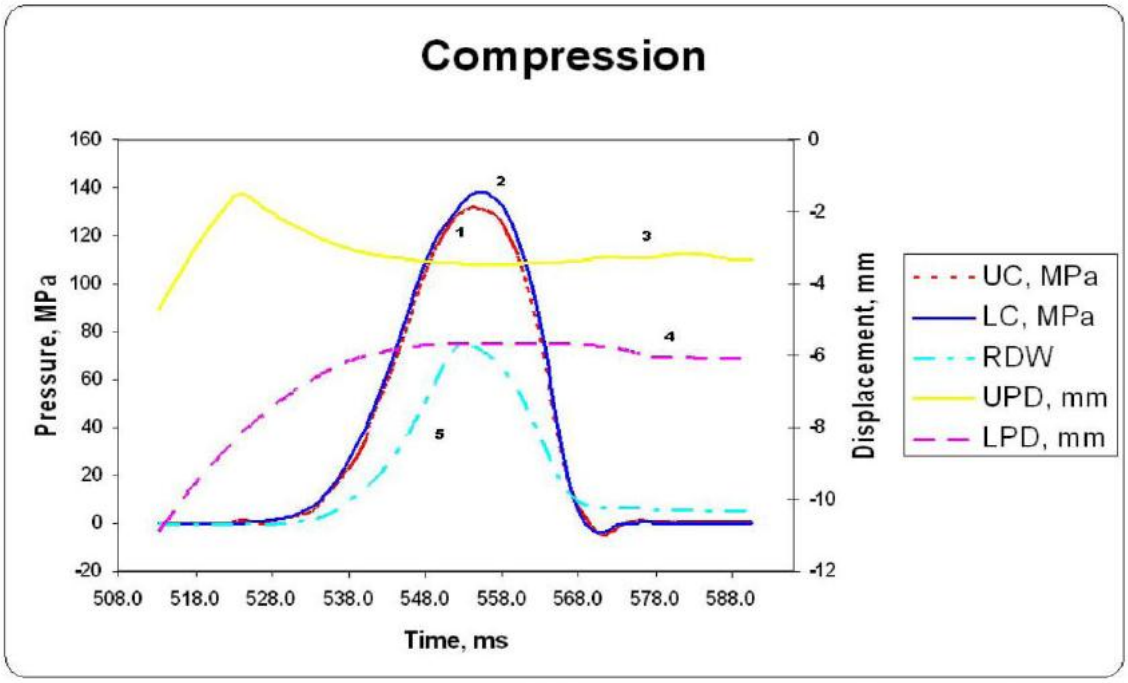


Fig. 20: Compression data diagram for pressures and displacements: (1) Compression force of upper punch; (2) Compression force of lower punch; (3) Upper punch displacement; (4) Lower punch displacement; (5) Radial die-wall pressure (not monitored in the research projects of this PhD thesis)

For very precise investigations of powder behaviour under punch pressure, precise measurement instruments from the field of mechanical engineering can be taken into consideration.

Zwick 1478 TM

The Zwick 1478 TM is a high-precision measurement instrument for engineering processes and material tests. The main design of this machine is a vertically movable platform, whose position and moving speed can be adjusted and monitored in a very precise way. Also the data outcome of the numerous installed sensors is really precise. This way, even the smallest deviation in a measurement process can be recognized immediately and corrective actions can be implemented. The Zwick 1478 is really recommended for exact, slow speed powder compaction, whereas industrial tablet production condition can not be simulated. A good example for the possible use of Zwick 1478 is the generation of force-time or force-displacement diagrams to investigate factors like compaction force and compaction speed to the compressibility of a powder formulation. The sensoring on the Zwick 1478 is mainly based on strain gauges, which is a satisfying choice for this kind of instrument, since strain

gauges can register in an exact way forces and displacements of a dynamic process.

Near-Infrared Spectroscopy

The choice of Near – Infrared Spectroscopy is a well received and reliable analytical approach for a wide range of different fields and industries like agrochemistry, food industry, cognitive neuroscience, medical diagnostics and also pharmaceutical technology.

The physical absorption band of Near-Infrared Spectroscopy is in the range of around 750 nm to 2500 nm (12,800 – 4000 cm^{-1}). The main source for the occurrence of the absorption bands is the overtones and combinations of fundamental mid-IR stretching and bending modes (Saeed, et al., 2009). X – H, X=C, N or O functional groups are the main chemical target groups in Near – Infrared Spectroscopy due to their absorption band intensity in the NIR – region. A crucial analytical factor here is the weak absorptivity of these band signals which allow, in combination with high scattering, the measurement of condensed-phased pharmaceutical powders, e.g. in form of thick tablets, without need of special sample preparation as for example the destruction of the powder compact (Saeed, et al., 2011). Also the possibility of measuring diffuse transmission and reflexion can be performed, due to the sensitivity of NIR on scattering effects (Siesler, et al., 2006).

Brief history of Near-Infrared Spectroscopy

Near-Infrared energy was discovered and first time investigated by Herschel in the 19th century. The time till the first industrial application was long. Actually, the first systematic application in the world industry began in the 1950s by introducing NIR measurement devices as add-on units to optical instrument which were focusing on the scientific measurement of visible, ultraviolet or mid-infrared light wavelengths (van de Hulst, 1969). In the 1980s the first single, stand-alone NIR instruments appeared on the industrial market. Their design and setup were basically concepted for an application in the field of chemical analysis. The development of light-fiber technique in the optic science and the introduction of monochromator-detectors lead to the design of NIR instruments with powerful application

ways in scientific research.

Basic characteristics of Near-Infrared Spectroscopy

A crucial characteristic of the near-infrared spectral region is its unique features, where for examples techniques and experience from IR spectroscopy can't be used. This led to a need of wide research & development for the handling of the photon energy and spectral light behaviour in the NIR region. Since the interaction between solid materials and NIR light is different than light photons in the IR or UV-VIS region, the choice of NIR spectrometry can open new ways of research and investigation in science.

Molecule atoms show always a certain movement, which is mainly dependent of the environmental temperature. The potential energy of the molecules is a crucial factor here. The binding potential of the present electrons and the repulsive force between atomic nuclei of two molecules play an important role for the final energy level between the molecules. The energy level between the molecules is mainly dependent of their room distance. Also the way of reaching the final distance between the molecules plays an important role. The displacement of molecules within the system leads to a change in the final potential energy level, with the absolute energy value change being non-proportionally different by displacing the molecules in a positive or negative direction (Saeed, 2011).

In an ideal harmonic potential system, the way of displacement plays no role for the bonding energy level between the molecules. The real anharmonic potential system shows effects which are significant for the NIR science. By overcoming more than one energy level after certain displacement of the molecules, a weak energy absorption can occur. Also the gap between the certain energy levels is no more constant in the anharmonic system. Pasquini (Pasquini, 2003) discusses in a detailed way the summarized phenomena of harmonic and anharmonic potential energy models. The understanding of the potential energy within a system and the awareness of the individual vibrational energy for every specific molecular system is really important for the usage ability of NIR in chemical and pharmaceutical sciences.

When a radiation is applied to a molecular system, the system responds in a selective way, since the final respond is dependent on the match of the radiation energy with the energy difference between the vibrational levels of the targeted system itself. The possible matching of the radiation frequency to the potential energy gaps of the system is determining the absorbance, partially absorbance or non-absorbance of the incoming frequency.

The incoming radiation energy can interact with a molecule system only if it can affect its energy level and changing its dipole moment. Polyatomic molecules can show transitions in two vibrational modes at once. In this case we talk about combination bands. They can have a significant impact in NIR. Very common is the influence of an NIR spectrum by absorptions of C-H, O-H and N-H functional groups in combination with bands from lower frequency as C-C and C=O. This effect can be useful in model development for quantitative analysis in the pharmaceutical field (Siesler, et al., 2006).

The interaction between the near-infrared radiation and the targeted solid particles leads usually to a weak absorbance and a high scattering. For solid compacts, the near- infrared radiation passes usually in the tablet interior part and even transmits it completely. This way, powders and compacts can be investigated by NIR without any sample preparation.

Two main measurement principles are applied in the NIR spectrophotometry for scientific investigation of pharmaceutical samples: Diffuse transmittance and diffuse reflectance.

A high number of scientific contributions on the two methods can be found in the available literature (e.g. Siesler, et al., 2006; Ciurczak, et al., 2002; Saeed, 2011). Since the diffuse transmittance approach was used in the research work of this PhD thesis, the focus in the follwoing paragraphs was set to this technique.

Diffuse transmittance in near-infrared spectroscopy

Diffuse transmittance can be measured in a reliable way only in the NIR region. Measurements in the UV and IR region have not shown comparable success up to now.

The transmittance T is defined as the ratio of light intensity transmitted through an empty system (I_0), for example a cuvette, and light intensity transmitted through the investigated

sample) (I_S). The Beer-Lambert equation is the basic approach for measuring and understanding the absorbance and transmittance of NIR radiation (Eq. 10)

$$A = \log(\frac{1}{T}) = \log(\frac{I_S}{I_0}) = a \times b \times c$$

Equation 10

where A: Beer-Lambert optical absorbance, T: transmittance ration, a=absorption coefficient, b=pathlength (sample thickness), c: concentration of absorbing species.

For the use of the Beer-Lambert relation with NIR spectroscopy in powder technology, we have to take a nonlinear deviation of the radiation transmittance into consideration (Owen-Reece, et al., 1999).

The Beer-Lambert equation assumes that the photons are either transmitted or absorbed. When NIR radiation hits a powder particle, also scattering and reflection of the photons in all possible directions can be noticed. This phenomenon is crucial for the application of diffuse transmission, since a photon, which is reflected on a particle in a powder bed will then hit a second powder particle, where again transmission, absorption, scattering and reflection can occur. It can be assumed, that during a measurement, the total pathlength of the photons within the powder bed can reach values within a wide range. If we assume the investigated powder bed or tablet to have a thickness T, the values of the total photon pathlengths will show a normal distribution on an average amount bigger than T (Saeed, 2011).

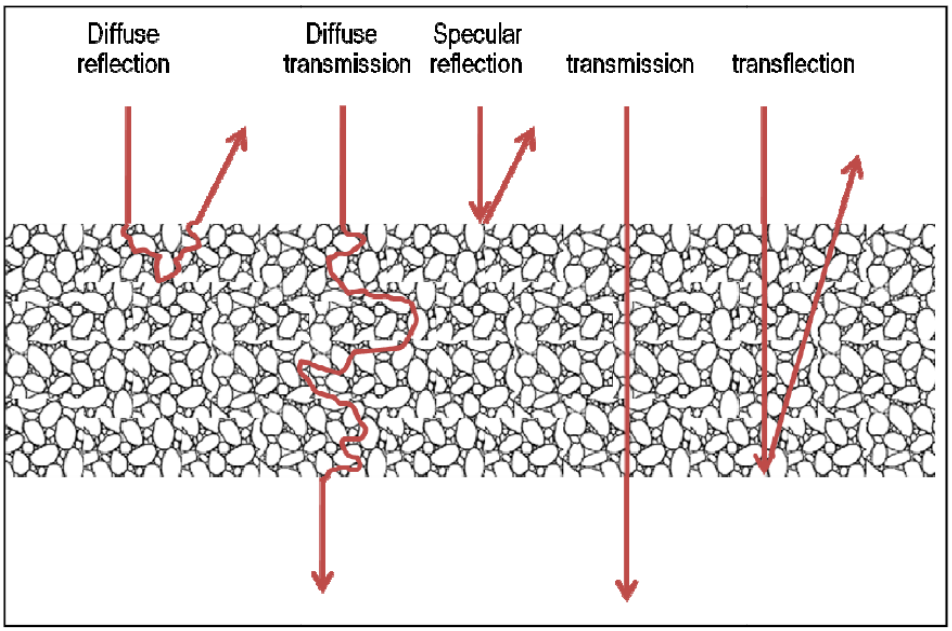


Fig. 21: Types of NIR radiation with solid powder systems, in practice, only diffuse transmission and reflection are seen (Saeed, 2011).

The mentioned phenomena (absorptivity, reflectance, scattering, way of transmission) may vary significantly between different investigated samples and powder formulations. Multiple material qualities, as e.g. particle morphology, particle size, bulk and true density play an important role here.

The expected total average wavelength and the nonlinear deviation of the sample relative to the Beer-Lambert relation are really difficult to be predicted in practise.

Near Infrared Spectroscopy Instrumentation

The near-infrared spectrometer consists of a light source, a detector and a dispersive element (like a prism or diffraction grating) for the control of the light wavelength. Additionally to this, interferometers are used for fourier transform NIR – spectrometers.

Measurement of near-infrared diffuse transmission and spectral analysis

The near-infrared diffuse transmission measurements can provide essential information on the investigated sample. With proper measurement settings of the near-infrared spectrophotometer and with a reliable mathematical model design for analyzing the spectra, significant physical or chemical characteristics of the sample can be measured.

The finding of the optimal measurement setup starts already at the choice of the most suitable spectrophotometer. There are numerous instrument types available on the market with a wide variation of properties and technical strengths (Siesler, et al., 2006).

The FT (Fourier transform) – NIR spectrometer applies the mathematical operations of function decomposition to separate the signals into frequency spectrums. There is a powerful application field for FT-NIR spectrometers and big advantage of these instruments can be seen towards other spectrometers.

FT-NIR spectrometers can be used when high-resolution capabilities are important or if many different kinds of sample interactions are needed. Also the constance of the spectral resolution across the whole spectral range and its adjustability make the FT-NIR an attractive instrument for reliable measurements (Saeed, 2011). All frequencies are detected simultaneously with this instrument and the accuracy of the wavelength is powerful.

The initial spectral signal is usually very confusing and spectral preprocessing methods have to be applied to find correlations between the spectral signal and the properties of the respective sample. The first step usually is the application of chemometric multivariate analysis. Since the nature environment is really multivariate, this is the only way to get enough correlation data by treating multiple measurements simultaneously. A high information collection in a relatively short time can be reached.

But there is an additional challenge we have to face in the finding of a reliable NIR – measurements system: The NIR spectral signal shows an uninformative variance which can occur by slight differences between the sample properties or by a variation in the operational parameters of the spectrometer.

The successful way to minimize these effects is the application of so called mathematical pretreatments to the spectra. There are many options for such pretreatments. Nevertheless, every of these pretreatments is applicable only for a certain range of products and conditions.

Standard Normal Variate (SNV) and Normalization by Closure (ncl) are two examples of mathematical pretreatments. In SNV, the spectra are treated with substraction of each

spectrum mean and normalization of the length to 1. Ncl is also used as spectral pretreatment, by reducing the baseline variations and smooth the signal in a mathematical way.

In a next step, vector geometry is usually introduced to detect the variable factor within the signals which correlate with a physical or chemical property of the powder system. For example, PLS (partial least square) algorithms can be used to construct a calibration model or also in a later step a reference model to measure and predict scientific powder properties in a future measurement of a comparable sample. In PLS, vector projections are designed with the spectral and also with referencing data. In the next step, these factor vectors are moved towards each other, till the linear fitting reaches a satisfying level. The final aim of PLS is to find the vector, which is the best compromise of the spectral factor and the reference factor.

For the final design of the calibration model, the design of the prediction model and the validation of these models there are a big number of statistic elements to take into consideration (Latent variables, predicted residual errors, BIAS, validation models, RMSEP, etc.). The detailed explanation of all these elements would go definitely beyond the scope of this PhD thesis and would very probably lead to an unnecessary confusion for the reader. Therefore, a reference is made here to the method section of research project 2 and the wide scientific literature in this field (e.g. Howard, et al., 2003; Naes, et al., 2010).

Research Project 1:
Compressibility of binary powder formulations: Investigation and evaluation with compaction equations

Abstract

The purpose of this work was to investigate and evaluate the powder compressibility of binary mixtures containing a well-compressible compound (microcrystalline cellulose) and a brittle active drug (paracetamol, mefenamic acid) and its progression after a drug load increase. Drug concentration range was 0 – 100% m/m with 10%-intervals. The powder formulations were compacted to several relative densities with the Zwick material tester.

The compaction force and tensile strength were fitted to several mathematical models to fitting that gives representative factors for the powder compressibility.

The factors K and C (Heckel and modified Heckel equation) showed mostly a non-linear correlation with increasing drug load. The biggest drop in both factors occurred at far regions and drug load ranges. This outcome is crucial, since in binary mixtures the drug load regions with higher changeover of plotted factors could be a hint for an existing percolation threshold.

The susceptibility value (Leuenberger equation) showed varying values for each formulation without the expected trend of decrease for higher drug loads.

The outcomes of this study showed the main challenges for good formulation design. Thus, we conclude that such mathematical plots are mandatory for a scientific evaluation and prediction of the powder compaction process.

Introduction

One of the most efficient processes for producing single dose medication is the compaction of pharmaceutical powder mixtures into tablets. Compacts are trusted by professionals and consumers worldwide. The easy administration for the patient and the simple handling of the active drug dose makes the tablet a very favoured dosage form (Natoli, et al., 2009).

For obtaining desired properties of compacts, the usage of powder formulations commonly consisting of one or more additives is preferred in the pharmaceutical and food industry. Whereas there are data available for single materials, in case of multi-component powder mixtures, numerous time-consuming experiments have to be performed to find appropriate formulations.

In the last years, there was an increasing pressure on pharmaceutical companies to reduce the time from drug discovery to marketed products, thus reducing costs and maximize the patent life of a drug. This need has initiated the development of predictive techniques that may have the benefit in reducing development time and research materials (Hardy, et al., 2003).

Even though some authors (Forsyth, et al., 2000; Thornton, et al., 1998) investigated and evaluated in a detailed manner the microscopic interaction forces between particles and their influence on the mechanical properties of particulate systems, the behaviour of interparticle forces is still far from being well understood and an underestimation of these forces can have tremendous effects in powder technology.

It is not easy to investigate directly the microscopic particle behaviour during compaction. Therefore, the investigation focus on a macroscopic level is gaining more importance.

The design of a powder formulation for industrial tablet production prerequisites a satisfactory compressibility of the powder and a tensile strength of the final compact in an acceptable range.

In the scientific field of pharmaceutical technology there is a distinction made between the terms compressibility and compactibility. Whereas the compressibility is defined as the

general ability of a powder to decrease in volume under pressure, the compactibility is seen as the ability of the powdered material to be compressed into a tablet of specific strength (Leuenberger, et al., 1982).

The mechanisms and phenomena of powder compaction have been the subject of numerous research investigations during the last six decades. There has been a wide variation of the compaction parameters and the used equipment (Celik, et al., 1989).

Many powder properties and also external factors have an impact on the quality of the final tablet (Barra, et al., 1999; Ryshkewitch, 1953; Rasenack, et al., 2002; Kawakita, et al., 1970; Ritschel, 2002; Nyström, et al., 1996; Ragnarsson, 1996). Therefore to date, numerous mathematical equations and approaches proposed to characterize the powder compaction exist. Many of these equations can be applied only to a restricted range of compaction force and only for a limited number of materials (Celik, 1992; Kolarik, 1994; van Veen, et al., 2004; Wu, et al., 2005).

Crucial tablet quality characteristics are the relative density and the mechanical strength. The surface areas of the particles in intimidate contact as a result of interparticulate bonds are referred as true areas of contact. Since the true contact area is difficult to measure in real tablets, the relative density is used as indirect method of measurement (Holman, et al., 1991). A big challenge for the relative density calculation of a powder is the scientific measurement of the true density (Paronen, et al., 1996). Several factors, like the bulk material, the chosen investigation method and the used analytical machines can have an impact on the determined true density value.

The pycnometric approach, especially helium pycnometry, is preferably used for true density measurements (Paronen, et al., 1996). One important issue to be taken into consideration here is the possible presence of impurities and even absorbed water, which could cause significant variations. Even during compression the particle density can change due to occurrence of polymorphic phase transitions.

An experimental error of the true density measurement can have a significant impact on compaction factors outcomes. Gabaude et al. (Gabaude, et al.) showed the fundamental

consequences of a true density experimental error on the data fitting to the Heckel-Plot. Paronen and Ilkka (Paronen, et al., 1996) underlined the importance of repeated measurement for a precise true density determination.

For such a reliable determination of the compact's relative density, the tablet dimensions play an important role. The height and diameter of a tablet can be measured basically with an "out of die"-approach, in the most cases with a digital calliper, or "in die" with the support of a precise compaction apparatus.

The measurement with a digital calliper does not take into consideration the elastic relaxation, occurring after the compaction step. Since this relaxation leads to an increase of the tablet height, it influences the factor values of the fitted plots (Celik, 1992). Celik and Marshall (Celik, et al., 1989) found a significant influence of the tablet dimension measurement method ("out of die" or "in die") for the final plotting of the Heckel equation. Also Denny (Denny, 2002) mentioned the challenge of different tablet dimension measurement. Both approaches can be chosen from a scientific point of view, but a clear statement of the chosen method should be made. Additionally, for a powerful comparison of two different data sets, the same choice of measurement parameters should be made for both sets.

Mechanical strength is another crucial tablet property since it is responsible for many physical, pharmacokinetic and pharmacodynamic aspects of the resulting compact. The strength depends on several processing and formulation parameters. It can be seen as one of the most important parameters for characterising the mechanical behaviour of tablets, as the compact must possess a minimum mechanical strength to sustain potential loading during processing and handling (Wu, et al., 2005; Belda, et al., 2006; Michrafy, et al., 2007; Kloefer, et al., 2010; Wu, et al., 2006; De Boer, et al., 1978; Johansson, et al., 1995).

The strength of tablets compressed from binary mixtures cannot be predicted from the compaction properties of the starting material alone because interactions between the materials can occur during the compaction process (Vromans, et al., 1988).

A very crucial parameter in compaction studies of binary mixtures is the percolation

phenomenon. Percolation is mainly responsible for the irregular change of powder formulations properties with quantity adjustment of a component. Binary mixtures can be seen as systems made of three phases: Two particle phases and the pore space. Numerous research papers describe in details the percolation phenomenon and the role of the percolation thresholds (Leuenberger, et al., 1997; Leu, et al., 1993; Blattner, et al., 1990; Holman, et al., 1991; Leuenberger, 1982; Krausbauer, et al., 2008). The percolation thresholds in a binary mixture compact depend on the relative concentrations and the relative bond-forming properties (Holman, 1991; Leuenberger, 1982; Busignies, et al., 2006).

Literature results (Barra, et al., 1999; Belda, et al., 2006; van Veen, et al., 2005; Van Veen, et al., 2000; Leueneberger, et al., 1985) for the compaction of binary mixtures show the complexity of the involved physical phenomena and the big challenge to define a universal equation, e.g. for predicting the tensile strength of binary tablets from the behaviour of individual components.

A representing example of this prediction difficulty is the work of Nokhodchi and Rubinstein (Nokhodchi, et al., 1998; Nokhodchi, et al., 2001; Nokhodchi, et al., 1998), where binary mixtures of ibuprofen and hydroxypropylmethylcellulose were investigated with focus on the compressibility and the tensile strength behaviour with different drug loads. A non-linear relation between the tensile strength and the drug load could be noticed for all compaction speeds applied. Also the influence of the moisture content, the compaction speed and the applied compaction force was investigated by this group and the importance of these factors on the compression nature could be shown.

A compaction equation relates some compaction elements with the applied compaction pressure. The initial aim for fitting the data to an equation is to have a linear relationship with the corresponding plots. With this approach, comparisons can be more easily applied between data sets. Additionally, the fitting parameters of the applied equations can be used for data comparison.

To date, numerous equations have been proposed for the analysis of compaction steps. While some seem to have a theoretical basis e.g. the Kawakita (Kawakita, et al., 1970)

equation, many of them are purely empirical fits of specific limited data and cannot claim any general validity (Denny, 2002).

A reliable compaction equation to investigate and compare powder formulations should achieve more than only linearizing the data (Denny, 2002). The equation parameters should somehow relate to basic physical and mechanical properties of the compacted material. Ideally the equation should apply to all materials, compacted in the same way.

The Heckel-equation can be seen as one of the most widely used mathematical tool for the evaluation of tablet compressibility. A detailed evaluation of this equation was performed and published by Denny (Denny, 2002) and also by Sonnergaard (Sonnergaard, 1999).

Celik and Marshall (Celik, et al., 1989) investigated numerous excipients by developing the corresponding Heckel-Plots. Nonlinearity was observed in many of these profiles, which were obtained under dynamic conditions.

Kuentz and Leuenberger (Kuentz, et al., 1999) designed a modified Heckel equation which takes into consideration a pressure susceptibility, defined as decrease of porosity under pressure. The classical Heckel-equation assumes a constant pressure susceptibility while in the modified Heckel equation the susceptibility corresponds to the relative density. Additionally, a term for the critical density has been introduced, which stands for the relative density where a rigidity between the punches starts to occur.

For a long time, the compressibility of powder formulations with support of mathematical equations has been the main target for scientific research. The general principle can be seen as the analysis of quantitative data to a relation in pressure to volume reduction or pressure to porosity (Kawakita, et al., 1970). The data collection and the fitting to the mathematical equations leads to an accurate evaluation of the equation parameters and to a scientifically reliable comparison between powder formulations.

An important approach in practice is the focus on the production of tablets with adequate strength. This ability of a powder formulation to be compressed into tablets with specified strength can be expressed as the formulations' compactibility. Leuenberger derived an equation (Leuenberger, 1982), which includes one factor for the compressibility and one for

the compactibility. The inclusion of a compactibility term makes this equation, the so-called Leuenberger equation, an attractive tool for investigating powder formulations.

The evaluation of the scientific literature (Ramirez, et al., 2004; Kuentz, et al., 2000; Fell, 1996; Leuenberger, 1985; Amin, et al., 2004) demonstrates the attractivity and need of multiple-component tablet investigation, preferable binary mixtures consisting of a well compressible and a poorly compressible compound.

Nevertheless, a simultaneous application of different plots (e.g. Heckel-Plot, Kawakita equation) to similar compacts with following scientific comparison of the factor values is still rarely found in the literature.

Research aim

In this study, the focus was set on the compressibility change of a binary mixture, consisting of a well compressible and a brittle, poorly compressible compound with stepwise increase of the brittle active drug.

To investigate this behaviour with model formulations, the challenge of the analytic capability of the powder compressibility was taken into consideration.

A way to describe the powder compressibility is the fitting of compaction data sets to specific mathematical equations. Such equations contain factors, which were described in the literature as representing the powder compressibility. The Heckel-Plot, the modified Heckel-Plot and the Leuenberger equation belong to this kind of equations.

By compacting one formulation and measuring the properties of the final compact (compaction force, thickness, porosity, tensile strength), the collected data set can be applied on the three mathematical equations for plotting the compressibility factors in a reliable way.

The comparison of these data can provide interesting outcomes concerning the validity of the investigated equations, since all the compressibility factors should have a similar behaviour with systematic change of binary mixture components.

As brittle, poorly compressible API, paracetamol and mefenamic acid were chosen in this study, since they have similar particle size. The basic difference between the two chosen

compounds is the significantly higher tendency of sticking for mefenamic acid (Bhadra, et al., 2004) (Kimura, et al., 2007). As ductile, well compressible excipents, the microcrystalline celluloses MCC 101L and MCC 102G were chosen, since they are both known for their high compressibility, since they differ in particle size (Picciochi, et al., 2010; Adam, et al., 2000; Kothari, et al., 2002; De la Luz Reus Medina, et al.).

Theoretical section

In this study, three mathematical equations have been chosen for the plotting of the compaction outcomes and the tablets properties.

1. The Heckel-Plot (Heckel, 1961; Heckel, 1961), 2. The modified Heckel-Plot (Kuentz, et al., 2000) and 3. The Leuenberger equation (Leuenberger, 1982) (Leuenberger, et al., 1984).

Heckel- Plot

The Heckel – Plot is still the most commonly used equation in the pharmaceutical compaction studies. It was developed by Heckel and published in 1961(Heckel, 1961; Heckel, 1961). The main approach in this equation is assuming similarity to a first-order chemical reaction. This approach was proposed earlier also by other research workers as e.g. Shapiro and Kolthoff (Shapiro, et al., 1947; Athy, 1930).

$$ln\frac{1}{1-D} = k \cdot P + A \quad \ln\frac{1}{1-D} = k \cdot P + A$$

Equation 11

where *D* is the relative density of a powder compact at pressure *P*. Constant *k* is a measure of the plasticity of a compressed material.

The Constant *A* is related to the die filling and particle rearrangement before deformation and to the bonding of the discrete particles.

In the early 1970s, the constant K was related to the mean yield pressure (P_y) by Hersey and Rees (Hersey, et al., 1970). The following equation shows the inverse relation of P_y to the ability of the material to deform plastically under pressure.

$K= (1/P_y)$

Equation 12

Modified Heckel- Plot

For a more holistic approach of the powder behaviour under pressure, the investigation focus of Kuentz and Leuenberger (Kuentz, et al., 2000) was set to the pressure susceptibility (χ_p). This parameter represents the decrease of porosity under pressure. Compacts obtained at very low pressures are of special interest in this approach, because of their transition state between a powder and a tablet. There is a range of limitation for the definition of the pressure susceptibility below some relative density and above the corresponding porosity, because no rigid structure exists in this pressure region.

The pressure susceptibility can be as a function of porosity and compression:

$$\chi_p \equiv -\frac{1}{\varepsilon} \cdot \frac{d\varepsilon}{d\sigma}$$

Equation 13

For a mathematical definition of the above described limitation range, a threshold value of the porosity ε_c and the corresponding relative density ρ_c were introduced. These factors define the values, where a rigidity starts to evolve.

These thresholds can be called *critical,* since they are crucial for the existence of the pressure susceptibility.

In the classical Heckel equation, the susceptibility χ_p equals to the constant K. With the new approach, the classical Heckel model needs to be replaced by an alternative equation, with a stronger focus on the susceptibility. The following equation was introduced:

$$\chi_p = \frac{C}{\varepsilon_c - \varepsilon} = \frac{C}{\rho - \rho_c}$$

Equation 14

The combination of equations (11) and (14) leads to a modified Heckel equation:

$$\sigma = \frac{1}{C} \cdot \left[\rho_c - \rho - (1-\rho_c) \cdot \ln\left(\frac{1-\rho}{1-\rho_c}\right) \right]$$

Equation 15

ρ is the relative density, σ is the pressure, ρ_c is the critical density and *C* is a parameter, claimed to represent the powder compressibility . For the description of material properties, the constant K from the Heckel equation and the constant C from the modified Heckel

equation can be determined. Ductile, highly compressible and soft powders have higher values for C and K than poorly compressible, brittle and hard powders.

The parameter ρ_c has been defined as the rigidity threshold. It represents the critical relative density, producing a negligible mechanical resistance between the punches. With a strict geometrical focus, this threshold represents the transition point between dispersed solid in air and voids in a solid matrix.

Leuenberger equation

The Leuenberger equation was introduced in the early 1980s by Leuenberger (Leuenberger, 1982; Leuenberger, et al., 1984).

It is based on the assumption that the cross-sectional area A of a cylindrical tablet contains a number N_+ of bonding contact points and a number N_- of non-bonding contact points. The following equation describes the contact points over the cross-sectional area

$$A = N_0 \cdot a = (N_+ + N_-) \cdot a \xrightarrow{with} N_0 = N_+ + N_-$$

Equation 16

where A is the cross-sectional area and *a* is the unit area per bonding point.

With the postulation of the hardness proportionality to the number of bonding points N_+ (λ: proportionality factor), Equation 17 was stated:

$$P = \lambda \cdot N_+ = \lambda \cdot (N_0 - N_-)$$

Equation 17

By taking into consideration that the relative decrease in the number of non-bonding points $\frac{dN_-}{N_-}$ has been assumed to change proportionally to the applied compression force and in connection with the relative density $d\rho_c$, the following equation can be proposed (γ: proportionality factor)

$$\frac{dN_-}{N_-} = -\gamma \cdot \sigma_c \cdot d\rho_r$$

Equation 18

After numerous mathematical steps and introduction of additional physicochemical powder technology rules the Leuenberger equation (Equation 19) is reached.

In a first phase, the Brinell hardness was used for this equation, but numerous authors, like Blattner (Blattner, et al., 1990) suggest the application with the tensile strength σ_t, the relative density ρ_r and the compaction pressure σ. This fitting allowed the determination of the maximum possible tensile strength σ_{tmax} at zero porosity and the pressure susceptibility γ_t.

$$\sigma_t = \sigma_{t\max} \cdot (1 - e^{-\gamma \cdot \sigma \cdot \rho_r})$$

Equation 19: Leuenberger equation

where σ_{tmax} is the tensile strength (kg/cm^2) when *P* (compression pressure) $\rightarrow \infty$, $\rho_r \rightarrow 1$, and *γ* is compression susceptibility. A main focus has been set to the factor γ, since it expresses the compressibility of the powder formulation. The compactibility, defined as the ability of the powder to be compressed to a tablet of specific strength, is represented by the maximal tensile strength σ_{tmax}.

Binary mixtures: compaction properties and percolation theory

Leuenberger (Leuenberger, 1985) proposed special additivity rules for the parameters P_{max} and γ of the Leuenberger equation (with Brinell hardness) for binary mixtures. A dependence of the initial conditions was mentioned for the specific choice of one of the three following equations (Leuenberger, 1985; Leuenberger, et al., 1985):

$$\ln P_{\max}(mixture) = x \cdot \ln P_{\max A} + (1-x) \cdot \ln P_{\max B} + \ln \frac{\gamma_A^x \cdot \gamma_B^{1-x}}{x \cdot \gamma_A + (1-x) \cdot \gamma_B}$$

Equation 20: Calculation of P_{max} for binary mixtures

$$\ln P_{\max}(mixture) = x \cdot \ln P_{\max A} + (1-x) \cdot \ln P_{\max B} + x \cdot (1-x) \cdot \ln P_{ww}$$

Equation 21: Calculation of P_{max} for binary mixtures

$$\ln P_{\max}(mixture) \cong \frac{1}{\frac{x}{P_{\max A}} + \frac{1-x}{P_{\max B}}}$$

Equation 22: Calculation of P_{max} for binary mixtures

with x as proportional load of one component in the binary mixture, $P_{(A,B \text{ or } max)}$ as Brinell hardness for the respective formulation and P_{ww} as interaction term, representing the ratio of adhesive to cohesive forces between unlike particles or molecules.

For the calculation of γ, the following equation was proposed by Leuenberger:

$$\gamma(mixture) = x \cdot \gamma_A + (1-x) \cdot \gamma_B$$

Equation 23: Calculation of γ for binary mixtures

Amin and Fell (Amin, et al., 2004) investigated binary mixtures containing excipients of plastic/brittle and plastic/plastic deformation properties. They mentioned the possible definition of lower and upper percolation thresholds for the compressibility of binary powder mixtures containing a well compressible and a poorly compressible compound, by gradual increase of one compound. These percolation thresholds correlate to the critical concentration of the two components. Close to the percolation threshold, a significant disruption in the compact's properties can be observed, either in a physical manner or through a noticeable change of the tablet strength. This effect is known as critical phenomenon.

Amin and Fell (Amin, et al., 2004) prepared mixtures with PVC/Eudragit, PVC/MCC and PVC / lactose. The binary mixtures were designed with PVC-loads of 0%, 20%, 40%, 60%, 80% and 100%.

Irregular progression of the P_{max} and γ could be noticed with increasing drug load and some significant changes were noticed at some drug loads. In general, specific critical drug loads were found, where the existence of a percolation threshold was strongly assumed. Even for binary combinations with of two plastic components, percolation thresholds could be found.

Leuenberger, Rohera and Haas (Leuenberger, et al., 1987) investigated powder formulations of caffeine with PEG 4000, Sodium stearate or magnesium stearate. A smooth linear decrease of the γ-value with increasing caffeine load could be noticed in their study. This linearity changed significantly at some specific drug loads. These drug loads were registered as percolation thresholds.

The focus of studies on binary mixtures found in the available literature sources is usually set to one specific mathematical equation.

Application of the same data set to different compressibility equations with following analysis of the outcomes is still very rarely found in the literature.

Materials and Methods

Materials

Paracetamol (Mallinckrodt, Batch 0048992565) and mefenamic acid (Sigma-Aldrich Inc., Batch 093K1608) were used as active ingredients.

Two kinds of microcrystalline cellulose (MCC 101 L, Pharmatrans Sanaq AG, Batch MC-160802) and MCC 102G (Pharmatrans Sanaq AG, Batch 140358) were chosen as excipients.

True density measurement of pure materials

A helium pycnometer (AccuPyc 1330,Micromeritics, USA) was used to measure the true density of the different powders. A repeated measurement design with three independent measurements was chosen to confine the experimental error.

Density calculation of powder mixtures

The true density of the produced powder mixtures was calculated using the obtained results of the true density measurements for all starting materials (see equation 24):

$$\rho_{true[mixture]} = \frac{C_{API[\%]} \times \rho_{true[API]} + C_{Excipient[\%]} \times \rho_{true[Excipient]}}{100}$$

Equation 24

where $C_{API[\%]}$ $C_{API\ [\%]}$ is the concentration of active ingredient, $C_{Excipient\ [\%]}$ is the concentration of the excipient, $\rho_{true[API]}$ and $\rho_{true[Excipient]}$ are the corresponding true densities.

In order to obtain tablets with a specific relative density, the corresponding tablet height was calculated using true density results of the powder mixtures.

Particle size measurement

Particle size in volume for all samples was measured by laser diffraction (Malvern Mastersizer X, Malvern, UK) using the dry method. For each compound, the average of three sample measurements (mass: 5g each) was taken.

Design of powder formulations

Each of the two active drugs (paracetamol or mefenamic acid) was mixed with one of the two excipients (MCC 101 or MCC 102). A drug concentration range of 0-100% (m/m) in 10%-intervals was chosen for the design of the formulations, as shown in Table 2:

Table 2: Investigated powder formulations

API	***Excipient***	***drug loads [%]***
Paracetamol	MCC 101	10 -100 10% - steps
Paracetamol	MCC 102	
Mefenamic acid	MCC 101	
Mefenamic acid	MCC 102	

The formulations were prepared as follows:

All powders were sieved (mesh size 355 μm) before weighing and mixing (Turbula mixer, Type T2A, Willy A. Bachofen AG Maschinenfabrik, Basel, CH) for 5 min. After the second sieving (mesh size 355 μm), the formulation was further mixed for 5 min.

Compaction

Tablets were prepared using a Zwick Universal Testing instrument (Type 1478TM, Zwick GmbH, Germany) with flat faced round punches of 11 mm diameter and a weight of 300 mg.

The designed formulations were compressed to relative densities of 0.75; 0.82; 0.8975, and 0.997.

The Zwick material tester provided the corresponding data concerning compaction force and ejection force for every single tablet.

For the determination of the linear part of Heckel-Plots, some compaction tests were performed using a compaction simulator (Presster, Metropolitan Computing Corporation, USA). The chosen formulations were investigated by simulating the Korsch PH336 rotary tablet machine with 36 stations. A powder mass of 300 mg was added manually into the die without feeder and then compacted with a 10 mm flat punch to a range of final gaps between

upper and lower punch from 1.6mm to 4.6mm. The corresponding compression force was between 0.1 and 20.0 kN.

The dimensions of the tablet were measured with a digital calliper immediately after the compression. The short time frame between compaction and dimension measurement did not allow the elastic recovery to reach a significant value. The tablet dimension was essential for calculating the relative density of the tablet.

Measurement of tablet tensile strength

The Tablet Tester 8M, Pharmaton, Switzerland was used to measure the breaking force of the tablet. The corresponding tensile strength was calculated according to equation 25.

$$TS = \frac{2 \cdot CS}{\pi \cdot D \cdot T} TS = \frac{2 \cdot CS}{\pi \cdot D \cdot T}$$

Equation 25

where TS is the tensile strength [N/mm^2], CS is the crushing force [N], D is the diameter [mm], and T is the thickness [mm] of the tablet. The diameter and thickness of tablets were measured with a three-button digital calliper.

Equations and concepts of Physics for the calculation of the outcomes

The obtained data were analyzed according to the equations of the Heckel-Plot, the modified Heckel-Plot and the Leuenberger equation by using Mathematica 7.0 (Wolfram Research Inc., USA), Excel (Microsoft, USA), GraphPad Prism (GraphPad Software Inc, USA) and OriginPro (OriginLab Corporation, USA).

In the theoretical section the scientific background of these equations is described in details.

Results and discussion

True density and particle size measurement

Table 3 shows the true density, the particle size average value and the median value of all powder compounds (incl. standard deviation between the three measurements). The true density of the excipients was found to be significantly higher than the true density of the investigated active drugs. With these data and Equation 24, the true density of the different powder mixtures was calculated. The average particle size was determined in the range of 74-83 µm, except for MCC 102, where it was around 120 µm.

Table 3: True density and particle size distribution of components

		Particle size distribution			
API	***True density [g/cm^3]***	**average [µm]**	**SD [µm]**	**median [µm]**	**SD [µm]**
Paracetamol	1.2211	82.8	5.79	51.4	1.08
Mefenamic acid	1.1641	74.1	6.05	38.4	1.83
MCC 101 L	1.4795	83.4	2.31	73.8	0.88
MCC 102 G	1.4345	119.7	0.15	114.1	0.53

Compaction force behaviour with increasing drug load

The behaviour of the compaction force with increasing drug load was investigated for the designed formulations.

All combinations of API and excipient showed a decrease of compaction force with increasing drug load, except for the compaction to the relative density of 0.997.

For the compaction to the relative density 0.75 a linear compaction force reduction with proportional increase of the drug load could be noticed for all investigated combinations of API and Excipient. For the combination of mefenamic acid and MCC 102 this linearity was shown for ρ_r 0.75, 0.82 and 0.8975.

An example of this linear behaviour is given in Fig. 22, with the combination of mefenamic

acid and MCC 101, compressed to a relative density of 0.75.

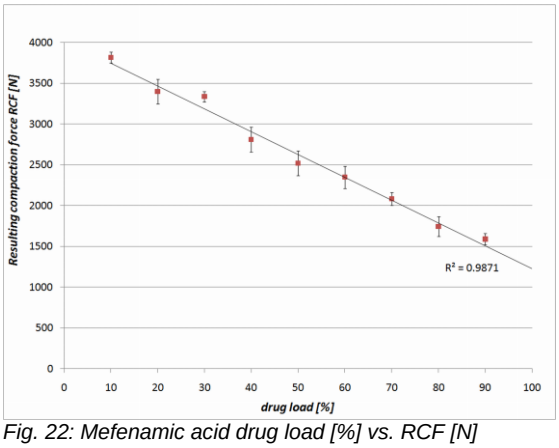


Fig. 22: Mefenamic acid drug load [%] vs. RCF [N]

As mentioned before, an exception here was the compaction to a relative density of 0.997. For these tablets, the resulting compaction force did not show any logical trend with increasing drug load. Additionally, the standard deviation for the compaction of the same formulation was very high. During the compaction of a powder formulation to very low porosities the expected plastic deformation of the particles is more and more replaced by a fracture deformation. This combined occurrence of plastic and fracture deformation lead to this very unpredictable behaviour of the powder bed after application of such high punch forces.

Outcomes of Tensile strength measurement

For being able to further investigate the compression properties of the formulations with taking into consideration the noticed compaction force decrease with increasing drug load, the quality of the final compacts, especially the tensile strength had to be investigated.

The tensile strength of the compacts decreased for all drug/excipient combinations with increasing drug load. The combinations of mefenamic acid / MCC 101 and mefenamic acid/MCC 102 showed a logarithmic decrease with increasing drug load. Fig. 23 shows the tensile strength results for the combination mefenamic acid / MCC 101. The behaviour of the tensile strength for the combination paracetamol/MCC 101 and paracetamol / MCC 102 showed a decrease with increasing drug load but not in a clear logarithmic way, except for the tablets with relative density 0.997.

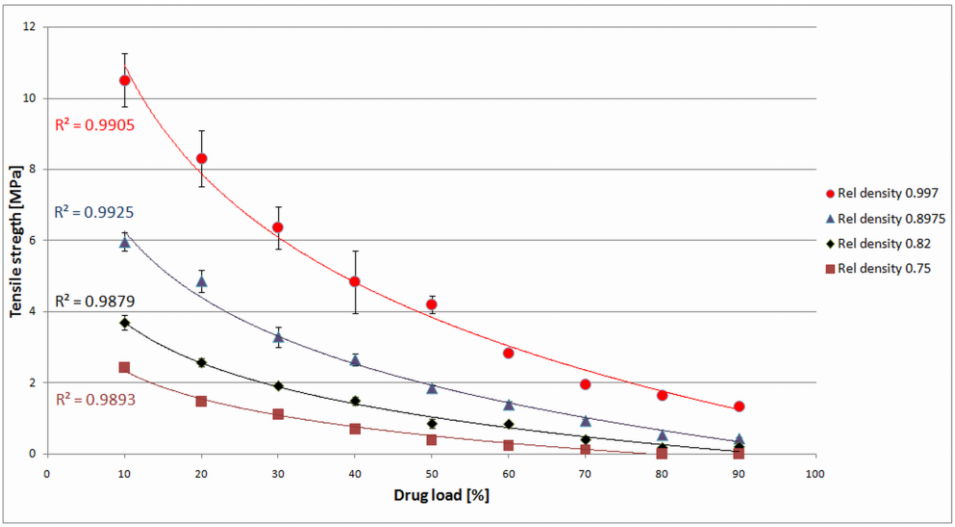


Fig. 23: Mefenamic acid / MCC 101: Tensile strength [MPa] vs. drug load [%]

Ejection force measurement

The ejection force showed linear increase with increasing drug load only for mefenamic acid/ MCC powder mixtures, compressed to high relative densities (ρ_r = 0.875;0.997). This confirmed the results of previous research work by Kimura et al. (Kimura, et al., 2007). For the other powder mixtures, there was no clear correlation between drug load and ejection force (data not shown).

Calculation and Evaluation of the technical factors

The collected compaction data allowed us to further investigate the formulations with support of mathematical tools in form of the Heckel-Plot, the modified Heckel-Plot and the Leuenberger equation.

With the plotted equation factors, the compressibility, i.e. the ability of a powder to decrease in volume under pressure (with Heckel- /modified Heckel-equation and Leuenberger equation) and the compactibility, i.e. the ability of the powdered material to be compressed into a tablet of specific strength (with Leuenberger equation), were investigated for the different formulations.

Since the investigated binary mixtures consisted of a poorly compressible active pharmaceutical ingredient and a well-compressible excipient, a compressibility decrease

could be expected with increase of the active pharmaceutical ingredient. The almost linear decrease of the resulting compaction force and the logarithmic decrease tensile strength for higher loads of active pharmaceutical ingredient were clear hints for this compressibility reduction with rising drug load in this study.

Compressibility parameters: factor K (Heckel-Plot), factor C (modified Heckel-Plot) and factor γ (Leuenberger equation)

The factor K of the Heckel equation, the factor C of the modified Heckel equation and the factor γ of the Leuenberger equation are mentioned in the literature as quantitative parameters for the determination of the compound's ductility and compressibility.

Therefore, it was assumed and expected, that the values of these factors as well as their change with increasing drug load would show some logical proportionality and follow corresponding profiles. For a scientific substantiation of this assumption, a comparison between these three factors was performed.

For a reliable calculation of the factor K, a determination of the Heckel - curve's linear part for the investigated formulations had to be established.

Therefore, some formulations, namely paracetamol 20% / MCC 101L 80% (m/m); paracetamol 40% / MCC 101L 60% (m/m) and mefenamic acid 20% / MCC 101L 80% (m/m) were compressed into tablets within a wide area of relative densities. Since this approach provided us a lot of measurement points on the whole range of the Heckel-curve, the linear part of the plot could be distinguished very clear. Fig. 24 shows an example for this approach and the distinction of the linear part. The area of linearity was really comparable for all investigated formulations.

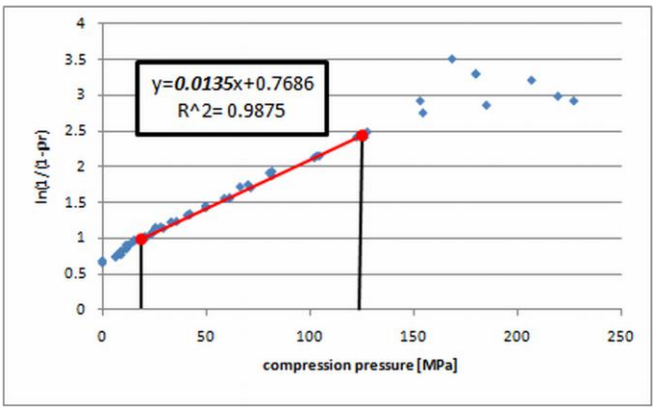


Fig. 24: Heckel-Plot for the determination of its linear part

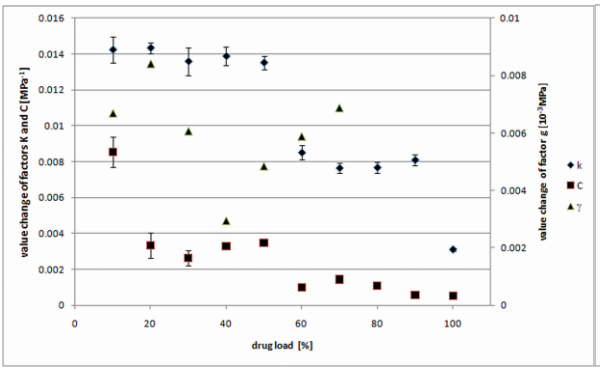
This finding allowed us a systematic evaluation and comparison of all calculated Heckel-Plots.

As a second step, the modified Heckel-equation and the Leuenberger equation were applied to the data set of the investigated powder formulations. This application allowed us to calculate the factors C and ρ_c from the modified Heckel-Plot and the factors γ and σ_{tmax} from the Leuenberger equation.

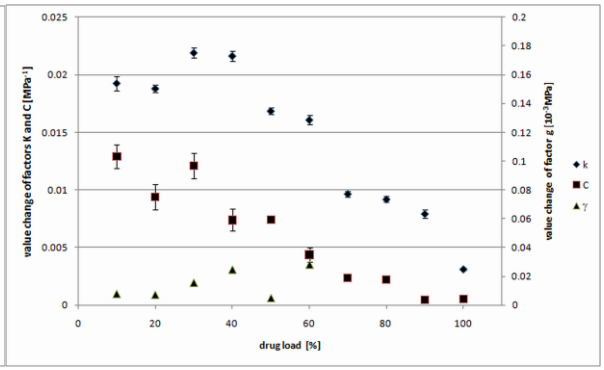
The result of these mathematical fitting steps is a numerical value of the different parameters for every formulation (see table 5, page 103).

For a reliable evaluation of the outcomes, the values for factors K, C and γ were plotted against the drug load for every combination of API and Excipient. The curve progression was investigation in details. The main focus was set on the decrease of the factor value with increasing drug load.

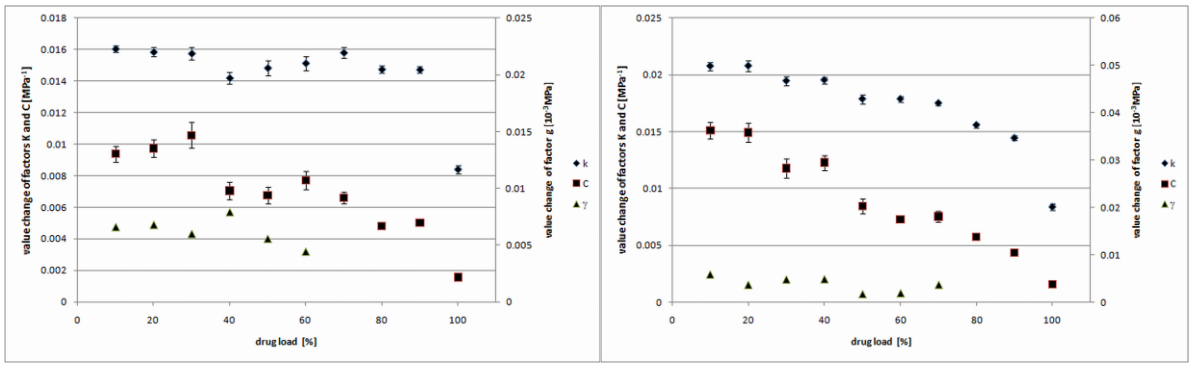
The Fig. 25a-d shows the values of factor K, C and γ for the investigated formulations and their progression with increasing drug load.



(a) Binary mixture Paracetamol / MCC 101



(b) Binary mixture Paracetamol / MCC 102



(c) Binary mixture Mefenamic acid / MCC 101 *(d) Binary mixture Mefenamic acid / MCC 102*

Fig. 25: parameter values (k, C, γ) vs. drug load [%]

Factors K and C

The calculated value results for factor C were all much smaller than the values for factor K. The grade of difference was found to be about a factor between 2 and 4. This outcome is in good agreement to the literature values (Kuentz, et al., 2000).

Further, the parameters K and C showed a decrease of the compressibility with increasing drug load (Fig. 25), which was in agreement with the theoretical expectation. The decrease was not linear but occurred stepwise. A main reason for this gradient is the percolation phenomenon, which plays a significant role here.

For low drug loads, the settings of the powder formulations are controlled by the excipient. With increasing drug quantity the settings are little by little controlled by the active drug. This transition of the formulation parameters to be more and more similar to the active drug is not occurring linearly but there are specific drug loads, where an extreme changeover can be observed. These critical drug loads are dependent on many compound settings and factors and are really specific for every powder formulation. The knowledge of these critical drug load regions is really relevant for a formulation design and can lead to a first screening of e.g. the ideal drug concentration in a powder mixture.

In the following section “Parameter value progression with increasing drug load” the regions of higher changeover, containing the assumable percolation threshold, could be identified by evaluating the numerical difference of the factor values between the formulations plotting them against the drug load – change steps.

For some combinations, even an increase of the values K or C could be noticed with higher drug load, like paracetamol 30% - 40% with MCC 102G (m/m) and mefenamic acid 30% - 70% with MCC 101L(m/m). For the same formulations a high standard error of the calculated values was noticed, e.g. for the combination of Paracetamol and MCC 102 G. Therefore it can be stated that this increase could have occurred due to external factors, which influenced the compaction process.

The outcomes showed the difficulty of compressibility comparison for two formulations with similar factor values of K or C.

Factor γ

The values of parameter γ (gamma) do not show any specific trend with increasing drug load. The data fitting faced a limitation for high drug loads. As mentioned in the paragraph "Outcomes of Tensile strength measurement", the tensile strength of the final compacts decreased very rapidly with increasing drug load, and also the resulting compaction force showed lower values for higher API-concentrations. After a certain drug load, these low values for resulting compaction force and tensile strength made a successfull plotting of the Leuenberger curve to the data points impossible. Therefore, no factor values could be determined for γ after a certain drug load.

Nevertheless, this plotting limitation could be seen also as a indicator of a formulation compressibility. A formulation which need to be compressed into tablets with very low porosity for reaching a sufficient hardness is the best example for a formulation with low compressibility.

Very interesting is the progression of value γ with rising drug load. Even though, there was a decrease expected, no trend could be recognized. The values were really individual for every formulation and only the plotting limitation was a hint for a compressibility reduction. As mentioned in the theoretical section an additivity rule (Equation 23) for the powder susceptibility γ was proposed by Leuenberger (Leuenberger, 1985). Since the progression of γ with increasing drug load did not show any linear behavior for the investigated formulations,

this additivity rule could not be verified in this study.

The irregular progression of the powder susceptibility value γ with increasing drug load matched well to the research outcomes of Amin and Fell (Amin, et al., 2004). In their study, irregular curve progressions with some drug load regions containing a noticeable changeover of value γ were found. Amin and Fell were suspicious that these regions contain a percolation threshold.

For all investigated combinations of brittle drug and well-compressible excipient, there was an abrupt changeover to an impossible fitting after a certain drug load. The highest drug loads of possible plotting measurement showed γ - values in a normal range and no systematic decrease could be noticed. As can be read in the following section "Leuenberger equation: σ_{tmax} (maximum tensile strength)", a tendency hint was provided only by the decrease of the σ_{tmax} –value for higher drugloads.

A very unique factor value progression could be noticed for the binary mixtures of paracetamol and MCC 102. The formulation with 50% drug load showed a much lower value (4.8×10^{-3} MPa) for the pressure susceptibility than the formulations with 40% and 60% drugload (24.68×10^{-3} MPa and 28.22×10^{-3} MPa respectively). The reason for this low outcome value for the formulation with 50% drugload can be found in the corresponding tensile strength values of the tablets compressed with this formulation. These tensile strength values were significantly lower than the values for the tablets of the 40% and 60% drug loads..

Even though, the susceptibility of every formulation was very specific without any big tendencies visible, this data point was very conspicuous. This special outcome could not be explained only with the percolation theory but maybe unknown external influences could have lead to this deviation. For the combination of paracetamol / MCC 101 an increase of the γ-value could be shown for drug loads between 40% and 70% . In the case of the mefenamic acid / MCC 102 – combination, a much smaller γ-value was shown for the 50%- and 60% - drug loads and a higher γ-value was evaluated for the 70% load. This characteristic increase

of the value occured due to the higher tensile strength values for this formulation.

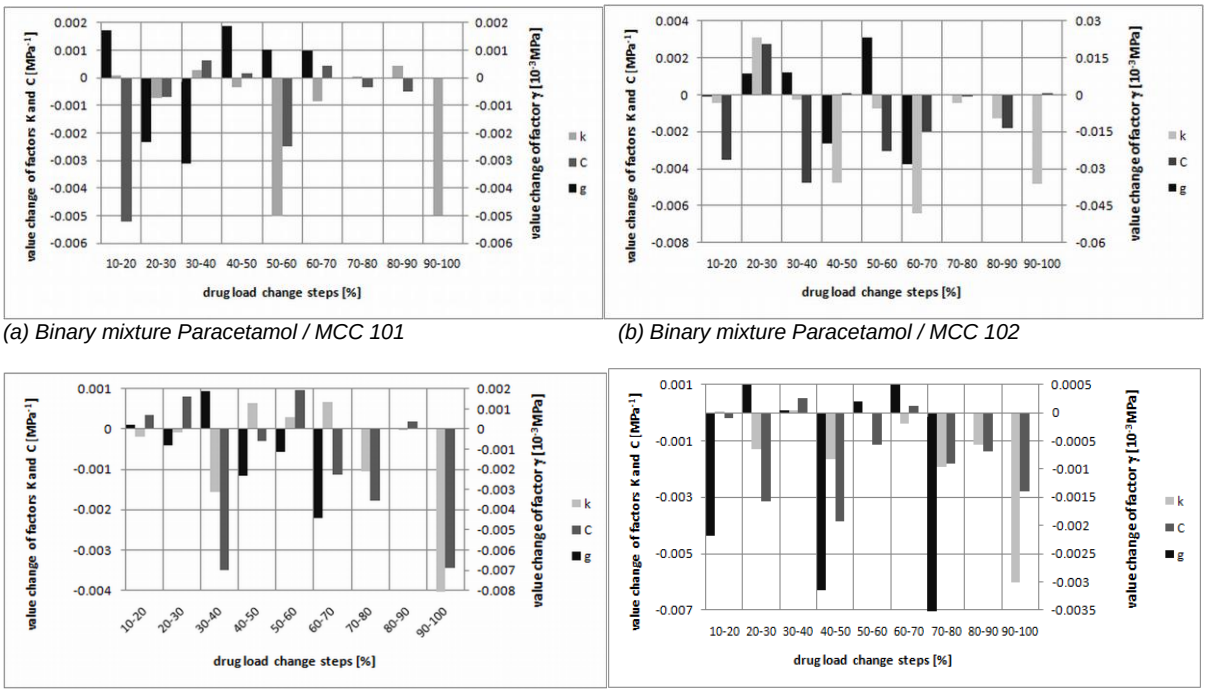
Effect of drug load on equation parameters

After evaluation of the factor values with increasing drug load for the different combinations of API and Microcrystalline Cellulose, the focus was set to the determination of the drug load regions with higher decrease of these factors.

This value decrease can be seen as powerful hint for the existence of a percolation threshold in this region.

For a clear observation and evaluation of these regions, the parameter value differences between the drug load regions were calculated and plotted graphically. This calculation was performed with all the three parameters and the results were plotted together on same diagrams.

The following figure illustrates these parameter differences graphically.



(a) Binary mixture Paracetamol / MCC 101

(b) Binary mixture Paracetamol / MCC 102

(c) Binary mixture Mefenamic acid / MCC 101

(d) Binary mixture Mefenamic acid / MCC 102

Fig. 26: Value differences between drug loads: factor K, C [MPa $^{-1}$] and factor γ [10^{-3} MPa $^{-1}$] vs. drug load [%]

Fig. 26 shows that in most cases the regions of higher value change did not match between the evaluated factors. Also the value decrease of the factors values did not occur in a parallel way. Nevertheless, there were some points recognized, where some parallel parameter

value change occurred. All drug load regions with higher factor value decrease are illustrated in the following table 4.

Table 4: drug load regions [%] with higher factor value decrease,
Matching between parameters: k-C italics; k-γ underlined; k-C- γ bold

		drug load region [%] with higher factor value decrease		
API	Excipient	k [MPa^{-1}]	C [MPa^{-1}]	γ [10^{-3} MPa^{-1}]
Paracetamol	MCC 101 L	*50-60* ; 90-100	10-20;*50-60*	20-30;30-40
Paracetamol	MCC 102 G	40-50;**60-70**;90-100	10-20;30-40;50-60; **60-70**	40-50;**60-70**
Mefenamic acid	MCC 101 L	*30-40;70-80;90-100*	*30-40;70-80;90-100*	40-50;60-70
Mefenamic acid	MCC 102 G	*20-30* ;**40-50**;**70-80**;*90-100*	*20-30* ;**40-50**;**70-80**;*90-100*	10-20;**40-50;70-80**

For the formulations with mefenamic acid as active drug, a correlation of the regions with higher factor value decrease could be noticed for the factors K and C. The drug load regions of 40-50% and 70-80% (m/m) mefenamic acid with MCC 102 G as excipient showed a strong correlation even between all the three factors.

For the binary mixtures of paracetamol with MCC 102G a correlation between the three factors could be found in the 60-70% (m/m) drug load region.

Nevertheless, this correlation of all three factors could not be noticed for any other drug load region.

The formulations with paracetamol as active ingredients show a correlation between K and C in regions 50-60% (m/m) of paracetamol with MCC 101 L. For the combination of paracetamol with MCC 102 G a stronger decrease of k and γ was noticed at the drug load region of 40% (m/m) and 50% (m/m) .

No consistency in the profile between the factors can be found for the other drug load regions with bigger drop in the factor values.

As main outcome of this evaluation, we can underline the small number of correlating drug load regions with bigger drop in the values between the three factors. Even though, the experiments were performed with four different combinations of API and excipient, only three drug load region could be found, where this correlation occurred.

For a systematic analysis of percolation threshold regions of binary mixtures, the outcomes may differ in dependence of the chosen fitting equation, at least for the investigated combinations of API and excipients.

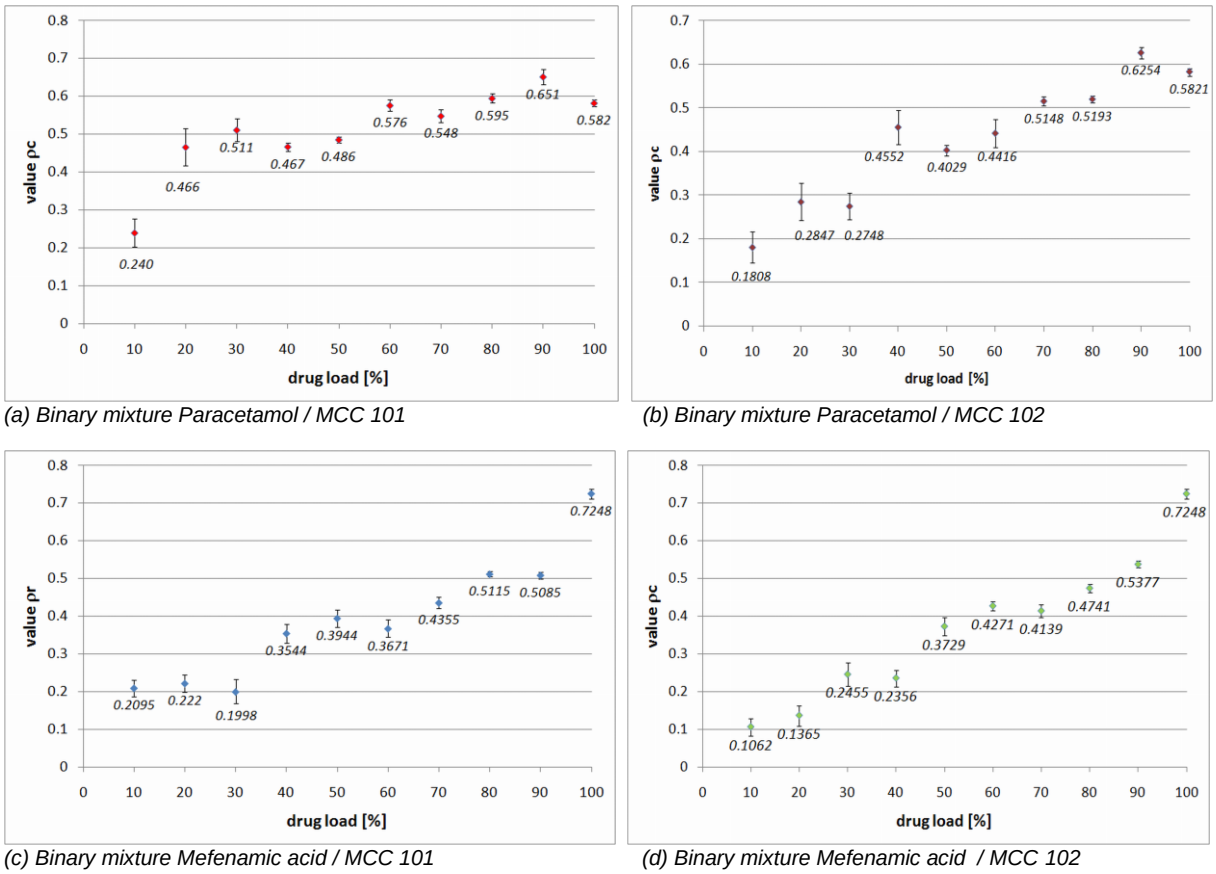
A possible explanation of the individual way of progression of the γ – value was the high sensitivity of the Leuenberger equation to small deviations in a data set.

The software fitting could demonstrate the crucial change of the factor values when a small deviation occurs in the data set.

Critical relative density ρ_c

Another important factor in the modified Heckel-equation is the critical relative density ρ_c. It represents the relative density where a rigidity starts to evolve and a negligible mechanical resistance between the punches can be registered. A detailed calculation and evaluation of the critical relative density is performed for all designed formulations.

The results are shown in Fig. 27.



(a) Binary mixture Paracetamol / MCC 101

(b) Binary mixture Paracetamol / MCC 102

(c) Binary mixture Mefenamic acid / MCC 101

(d) Binary mixture Mefenamic acid / MCC 102

Fig. 27: *Critical density $\rho_{critical}$ vs. drug load [%]:*
progression of the investigated binary mixtures with increasing drug load

According to Kuentz et al. (Kuentz, et al., 1999) the ρ_c is based on the powder's microstructure and for the most investigated powders, it is located between the bulk and the

tapped density. Since for our investigated formulations it showed a tendency of increase with increasing drug load, one can say that it somehow represents the brittleness of the investigated formulations.

An important finding here was a parrallel increase of the critical density with decrease of factor C.

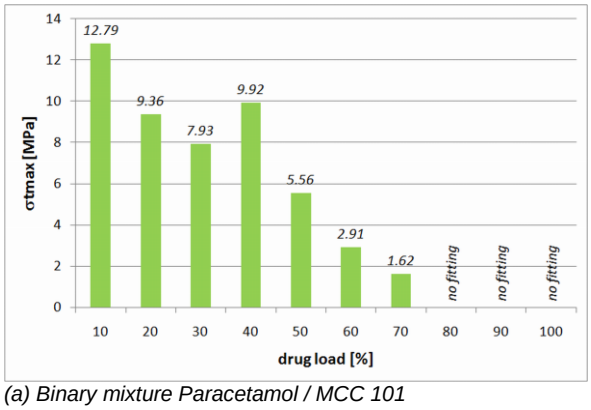
One main reason for the parallelism in the outcomes is the fact, that the factors C and ρ_c originate form the same equation. Since the equation was fitted to both factors, a kind of dependence between the factors within this equation could be expected.

Also for the critical density the higher changeover between some drug loads could be seen as a hint for an existing percolation threshold. No special analysis was performed here since these regions were identical with the regions of the value C, due to the mentioned parralelism.

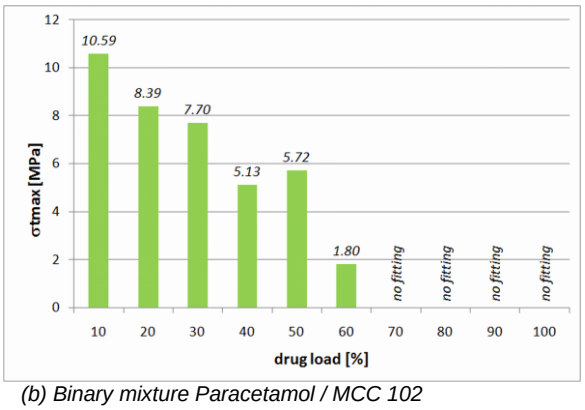
Leuenberger equation: σ_{tmax} (maximum tensile strength)

With the support of the Mathematica software, the curve fitting allowed us to evaluate also the maximum tensile strength σ_{tmax}. This factor can be seen as a numerical description of the formulation compactibility (Leuenberger, 1982; Leuenberger, et al., 1984), which is defined as the ability of the powder to be compressed to a tablet with a specific strength.

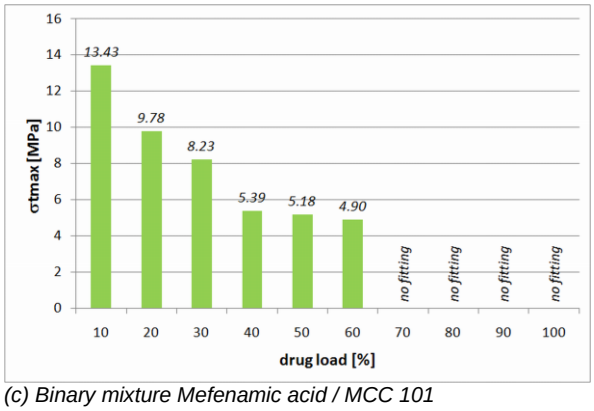
Fig. 28 shows the values of the maximum tensile strength for the investigated formulations.



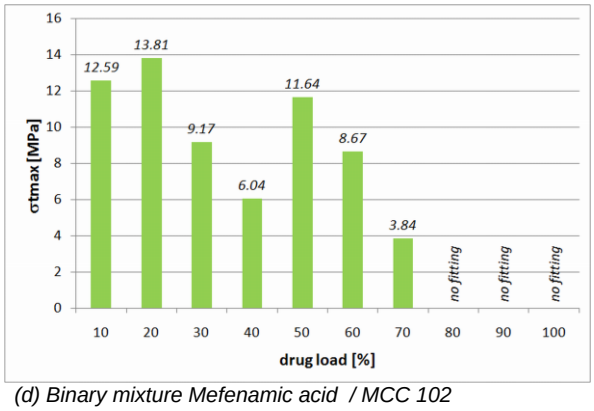
(a) Binary mixture Paracetamol / MCC 101



(b) Binary mixture Paracetamol / MCC 102



(c) Binary mixture Mefenamic acid / MCC 101



(d) Binary mixture Mefenamic acid / MCC 102

Fig. 28: *maximum tensile strength σ_{tmax} [MPa] vs. drug load [%]: progression of the investigated binary mixtures with increasing drug load*

A clear tendency of decrease with increasing drug load could be noticed for the investigated formulations apart from some single regions. The tendency could not be captured in a mathematical way since the slope of decrease was very individual for every combination of active drug and excipient. The combination of mefenamic acid and MCC 102 showed some changeover between 40% and 50% of drug load

Table 5: values of k [MPa^{-1}], C [MPa^{-1}], γ [10^{-3} MPa^{-1}]

API	Excipient
Paracetamol	MCC 101L

drug load [%]	k	SD (k)	C	SD	γ
10	0.01423	0.000710	0.008524	0.000837	0.006677
20	0.01433	0.000302	0.003332	0.000691	0.008395
30	0.01358	0.000768	0.002648	0.000419	0.006058
40	0.01387	0.000506	0.003287	0.000157	0.002950
50	0.01351	0.000373	0.003468	0.000127	0.004842
60	0.0085	0.000401	0.000981	0.000078	0.005877
70	0.00764	0.000283	0.001431	0.000128	0.006869
80	0.00767	0.000321	0.001074	0.000076	nfp
90	0.00809	0.000306	0.000583	0.000082	nfp
100	0.00311	0.000103	0.000539	0.000039	nfp

API	Excipient
Paracetamol	MCC 102G

drug load [%]	k	SD	C	SD	γ
10	0.01925	0.000629	0.01289	0.001046	0.007740
20	0.01879	0.000328	0.009379	0.001113	0.007048
30	0.0219	0.000465	0.01212	0.001105	0.015473
40	0.02162	0.000461	0.007383	0.000950	0.024679
50	0.01684	0.000301	0.00742	0.000319	0.004802
60	0.01607	0.000405	0.004361	0.000638	0.028216
70	0.00965	0.000280	0.002349	0.000153	nfp
80	0.00918	0.000259	0.002234	0.000117	nfp
90	0.00792	0.000373	0.000457	0.000053	nfp
100	0.00311	0.000103	0.000539	0.000039	nfp

API	Excipient
Mefenamic acid	MCC 101L

drug load [%]	k	SD	C	SD	γ
10	0.01604	0.000193	0.009392	0.000500	0.00657
20	0.01584	0.000289	0.009741	0.000565	0.006776
30	0.01575	0.000420	0.01056	0.000821	0.005979
40	0.01419	0.000376	0.007049	0.000553	0.007885
50	0.01483	0.000452	0.006744	0.000530	0.005553
60	0.01513	0.000457	0.007725	0.000584	0.004416
70	0.0158	0.000356	0.006585	0.000366	nfp
80	0.01474	0.000250	0.004813	0.000158	nfp
90	0.01472	0.000188	0.005014	0.000205	nfp
100	0.00839	0.000245	0.001573	0.000184	nfp

API	Excipient
Mefenamic acid	MCC 102G

drug load [%]	k	SD	C	SD	γ
10	0.02075	0.000383	0.01513	0.000724	0.00586
20	0.02077	0.000453	0.01494	0.000861	0.00368
30	0.01946	0.000389	0.01178	0.000864	0.004813
40	0.01953	0.000296	0.01229	0.000662	0.004862
50	0.01787	0.000392	0.008444	0.000663	0.001711
60	0.01787	0.000235	0.007301	0.000287	0.00191
70	0.0175	0.000205	0.007554	0.000473	0.003693
80	0.01558	0.000217	0.005754	0.000272	nfp
90	0.01444	0.000230	0.004382	0.000203	nfp
100	0.0084	0.000313	0.001573	0.000184	nfp

Evaluation of the mathematical equation factors

In this study, each of two brittle active pharmaceutical ingredients were blended with one of two ductile, well compressible excipients to binary mixtures within a wide range of drug loads (0% - 100%). In total, 38 different formulations were designed and compacted to tablets of a relative density between 0.75 and ~ 1. The resulting compaction pressure and the hardness of all the produced compacts were measured and registered.

The collected data were then evaluated with the Heckel-Plot, the modified Heckel-Plot and the Leuenberger equation. Each of these three equations contains a factor which is assumed to represent the compressibility of the investigated powder formulation. For a reliable compressibility determination and for the evaluation of these three equations, it was important to compare all the calculated factor values of the three equations individually for each formulation.

By analyzing the resulting compaction force and the tensile strength of the produced tablets, a reduced compressibility could be noticed with increasing drug load, which was supported by the occurrence of very weak and crumbly compacts for formulations with higher drug loads. Also the augmented powder sticking at the upper punch and the die wall at higher drug loads was a clear hint for a low compressibility. These findings lead to the conclusion that compressibility reduction with increasing drug load would result in lower equation factor values. The value outcomes for factor C and K could confirm this expectation in most cases. But in some single cases the factor values stayed constant or even showed slightly higher values after increasing of the drug load. This could be explained only by external factors influencing the compaction process. Some expected deviations (Paronen, et al., 1996) in the true density measurement could be a feasible reason for single unexplainable factor value progressions with increasing drug load.

On the other hand, the stepwise reduction of the factors K and C with increasing drug load instead of a linear reduction was already expected due to the percolation phenomenon. For every investigated combination of active pharmaceutical ingredient with excipient a higher

value change was expected in two drug load regions over the range of 0% to 100%. These regions are usually found close to the lower and upper percolation threshold. The evaluation of the results showed that the drug load regions with a higher changeover of the factor values did not always match between the two plots. Therefore a clear distinction of a lower and a higher threshold was not possible.

A crucial point in the analysis of these outcomes is the investigation of the possible external parameters, which could influence the measurement results. The correct tablet dimension measurement and the determination of the linear curve region in the Heckel-Plot were the two main sources of error in this study. Since the tablet dimensions were measured with an "out of die"- method, namely with a digital calliper, the elastic relaxation, occurring directly after the compaction step, was expecting to influence the factor values of the fitted plots (Celik, 1992; Celik, et al., 1989). In our study, this influence could be a seen as insignificant because the same measurement method was used for all the formulations (Denny, 2002). The tablet dimension measurement took place directly after the compaction, not allowing the tablet to relax elastically over time.

The second important parameter is the correct and reliable detection of the linear Heckel-plot region, as mentioned by Denny (Denny, 2002) and Sonnergaard (Sonnergaard, 1999). The determination of the linear curve region was successfully performed with support of the Presster-simulator. This step was in fact very crucial for our study. Without exclusion of tablets with very low and very high relative densities, very essential calculation deviations would occur for factor K.

The limitation of fitting the compaction data to the Leuenberger equation for higher drug loads was a clear indication of a compressibility decrease and its occurrence on the specific drug load region could be seen as a hint for the upper percolation threshold. In general, the progression of the powder susceptibility value γ with increasing drug load was not convincing for representing the powder compressibility, since a value decrease with higher drug loads could not be shown. Also the additivity rule (Equation 23) could not be verified. This irregular

progression of the powder susceptibility value γ with increasing drug load was also found in the research work of Amin and Fell (Amin, et al., 2004) with binary mixtures of plastic and brittle compounds.

On the other hand, the maximal tensile strength σ_{tmax} was shown to be a good and reliable outcome for the compactibility of the investigated powder formulation and it can be seen as a good hint for screening formulations which would lead to tablets with a desired hardness.

Conclusion

A scientific approach for the investigation and determination of a powder formulation's compressibility needs an evaluation with mathematical tools by taking into consideration the physical nature of the powder and its compaction. A numerical measurement of the powder compressibility would support the design of powder formulations and their qualitative improvement

In this study, binary mixtures, consisting of a well-compressible and a brittle substance, were evaluated with three different equations (Heckel-Plot, modified Heckel-Plot and the Leuenberger equation). All three plots contain a factor assumed to represent the powder compressibility. One main focus was set on the progress of the compressibility factor values with increase of the brittle drug in the binary mixture.

The assumed compressibility factors of the Heckel- and the modified Heckel-Plot could show the compressibility reduction after increasing the load of the brittle compound, but since the compressibility reduction profiles were not comparable between the factors, none of them could be determined as ideal representative of the powder compressibility. Especially the drug load ranges within the percolation thresholds were not in agreement between the plotting results of the two equations for all the investigated formulations.

The powder compressibility γ of the Leuenberger equation could not determine the compressibility reduction of the investigated formulations with increasing drug load but the limited plottability, especially for brittle formulations showed the usability of this equation for a general compressibility distinction of a formulation.

The outcome of this study could show clearly that with the current scientific knowledge the development of a classical numerical categorization for the powder compressibility is still a challenge. Especially for formulations with similar compaction nature, a mathematical comparison of compressibility faces a lot of difficulties.

By taking into consideration the numerous different compaction techniques and settings, the high probability of variation and deviation for the measurement of powder and tablet properties (true density, porosity, tablet volume, etc.) and the possible deviations in the raw material from batch to batch, the solution for an optimal investigation and prediction of a powder compressibility would be the choice of several mathematical equations for every designed formulation by considering all important process parameters.

The behaviour of powder formulations during compression is a very challenging issue in tablet manufacturing and an exact lab scale investigation of the blend before the industrial application is very essential to understand the formulation properties and compressibility limits for a robust tablet production.

Research Project 2: Assessing compressibility and compactibility of powder formulations with Near-Infrared Spectroscopy

Abstract

Context

The compressibility and compactibility of a powder formulation is usually determined by compaction and following destructive tensile strength and relative density measurement of the final compact.

Objective

In this study, a non-destructive method with Near-Infrared Spectroscopy was designed and evaluated for the measurement of powder compressibility and compactibility.

Materials and Methods

12 different formulations with a wide range of difference in properties were investigated by compaction and analysis of the resulting tablets. Two similar tablet batches were produced with every formulation. Relative density and tensile strength were measured with the traditional, destructive method on one tablet batch while a newly developed non-destructive chemometric Near-Infrared Spectroscopy method was applied for the second batch.

The outcomes of the two approaches were compared to validate the developed method.

All data sets were applied to three established mathematical equations to calculate equation factors, which are claimed to represent the formulation compressibility and compactibility.

The study focus was set on the equation factor value comparison between the traditional and the newly designed method.

Results & Discussion

The results showed a high similarity between the outcomes of the two methods. An essential difference was noticed for the outcomes of the equation factors after application to the

Leuenberger equation.

Conclusion

The approach with the Near-Infrared Spectroscopy is suggested as a promising tool for a reliable inline quality monitoring in the tablet manufacturing process.

Introduction

The most common dosage form on the pharmaceutical market is the tablet. The production of tablets should be as economical as possible and the production should only comprise a few working steps (Rasenack, et al., 2002).

Studies of tablet formation by direct compression are focused on single powders, powders with small percentage of binder and granulated powders.

Since it is a big challenge to predict the compaction properties of powder mixtures from the properties of the individual components, a main focus has been set to the development of prediction techniques for a successful design of reliable powder formulations (Michrafy, et al., 2007).

The main prerequisite for a reliable formulation is a satisfactory compressibility of the powder and tensile strength of the final compact in an acceptable range.

All the mechanisms and phenomena of powder compaction have been the subject of numerous research investigations and already a wide variation of compaction parameters and used equipment have been investigated (Celik, et al., 1989). Nevertheless, the compaction process is still far from being completely understood.

Multitudinous powder properties and external factors have an impact on the quality of the final tablet (Rasenack, et al., 2002; Barra, et al., 1999; Nyström, et al., 1996; Ragnarsson, 1996).

This led in the last decades to the choice of many different approaches for characterization of powder compaction along with the development of numerous mathematical equations.

The choice of the most preferable equation out of this wide collection is challenging because every equation can be applied only to a constricted range of compaction force and to a limited number of materials (Celik, 1992; van Veen, et al., 2004).

The relative density of a compact and its tensile strength can be seen as a basic and crucial tablet quality characteristic.

The relative density is assumed as the true area of contacts between particles as a result of

interparticulate bonds. It is usually calculated with the true density value of the powder (Holman, et al., 1991) and represents in an inverse way the porosity of the compact.

The mechanical strength is a very important tablet property since it has crucial impacts on itspharmacokinetical and pharmacodynamical behaviour. The strength depends on several processing and formulation parameters.

An essential focus is set on this parameter for characterising the mechanical behaviour of a compact, as the tablet must possess a minimum mechanical strength to sustain potential loading during processing and handling (Michrafy, et al., 2007; Wu, et al., 2005).

A compaction equation relates compaction elements with the applied compaction pressure. The initial step for fitting the data to an equation is to linearize the data and the corresponding plots. With this approach, comparisons between data sets are simplified and also the fitting parameters of the applied equations can be used for data comparison.

Till today, numerous equations have been proposed for the analysis of the compaction process. While some seem to have a theoretical basis e.g. the Kawakita (Kawakita, et al., 1970) equation, many of them are purely empirical fits of specific limited data and cannot claim any general validity (Denny, 2002).

For a reliable and satisfying application of compaction equation to investigate and compare compression of powder formulations, an equation should not only linearize the data (Denny, 2002).

The parameters should relate to basic physical and mechanical properties of the compacted material. Ideally the equation should be allowed to be applied to all materials which are compacted in the same way.

The compressibility measurement of powder formulations with support of mathematical equations has been since a longer time ago a main target for scientific research. The main principle is the analysis of quantitative data like a relation of pressure to volume reduction or the relation of the applied pressure to the corresponding porosity (Kawakita, et al., 1970). The aim of this calculation step is the determination of a linear relation and in a second step the comparison between powder formulations.

One of the most known mathematical approaches for the evaluation of tablet compressibility is the Heckel-equation. The detailed evaluation of the Heckel-equation was performed and published by J.M. Sonnergaard (Sonnergaard, 1999) and P.J. Denny (Denny, 2002).

Celik and Marshall (Celik, et al., 1989) investigated numerous excipients by developing the corresponding Heckel-Plots. Nonlinearity was observed in many of these profiles, which were obtained under dynamic conditions.

A modified Heckel equation was designed by Kuentz and Leuenberger (Kuentz, et al., 1999) which takes into consideration the pressure susceptibility, defined as decrease of porosity under pressure. The classical Heckel-equation assumes a constant pressure susceptibility while in the designed modified Heckel-equation the susceptibility corresponds to the relative density. Additionally, a term for the critical density has been introduced, which represents the specific relative density where a rigidity between the punches starts to occur.

The ability of a powder formulation to be compressed into tablets with specified strength can be expressed as the formulations' compactibility. Leuenberger developed an equation (Leuenberger, 1982), which includes one factor for the compressibility and one for the compactibility. This inclusion of the compactibility term makes this equation, the so-called Leuenberger equation, an attractive tool for investigating powder formulations.

Near-infrared spectroscopy (NIRS) is an analytical technique with various applications in the pharmaceutical field. Major advantages of NIR spectroscopy are its non-destructive nature, no need for sample preparation and immediate delivery of results. NIRS has proven its ability to analyze intact pharmaceutical dosage forms such as tablets.

Quantification and qualification of active pharmaceutical ingredients and other tablet constituents is well established (Cruz, et al., 2011; Dou, et al., 2005; Ito, et al., 2010; (Blanco, et al., 2000; Alvarenga, et al., 2008; Karande, et al., 2010). Tablet physical properties, e.g. relative density and tensile strength, contribute to high extent to NIR signal (Blanco, et al., 2010) and are usually considered as interferences. Various spectral preprocessing methods are applied to NIR spectra in order to minimize these effects (Heise, et al., 2002). Variations in compression force during tableting process have been reflected in

variable relative densities and tensile strengths of the tablets. This effect is observed in NIR spectra as baseline shift (Kirsch, et al., 1999; Blanco, et al., 2006). The spectral effect caused by varying relative density/tensile strength could be used to quantify these tablet parameters (Blanco, et al., 2010; Short, et al., 2009).

Theoretical section

For this study, the compaction outcomes have been plotted with the Heckel-Plot (Heckel, 1961; Heckel, 1961), the modified Heckel-Plot (Kuentz, et al., 2000) and the Leuenberger equation (Leuenberger, et al., 1984; Leuenberger, 1982).

Heckel- Plot

The Heckel – Plot is still one of the most commonly used equation in the pharmaceutical compaction studies. It was published by R.W. Heckel in 1961 (Heckel, 1961; Heckel, 1961). In this equation, the first-order kinetics type of reaction behaviour of the voidage reduction with applied pressure has been approached.

$$ln\frac{1}{1-D} = k \cdot P + A \qquad \ln\frac{1}{1-D} = k \cdot P + A$$

Equation 25

where *D* is the relative density of a powder compact at pressure *P*. Constant *k* is a measure of the plasticity of a compressed material.

The Constant *A* is related to the die filling and particle rearrangement before deformation and to the bonding of the discrete particles.

Modified Heckel- Plot

The pressure susceptibility (χ_p) is defined as the decrease of porosity under pressure. This term is assumed to be constant in the Heckel-Plot.

Kuentz and Leuenberger (Kuentz, et al., 2000) incorporated the pressure susceptibility (χ_p) in their calculation and developed a modified Heckel-Plot:

$$\sigma = \frac{1}{C} \cdot \left[\rho_c - \rho - (1-\rho_c) \cdot \ln\left(\frac{1-\rho}{1-\rho_c} \right) \right]$$

Equation 26

ρ is the relative density, σ is the pressure, ρ_c is the critical density and *C* is a constant, which is claimed to represent the compressibility of a powder.

For the compressibility calculation of powder formulations, the constant K from the Heckel equation and the constant C from the modified Heckel equation can be determined.

Well compressible, ductile and soft powders have higher values for C and K than poor compressible, brittle and hard powders.

The parameter ρ_c is defined as rigidity threshold. It represents the critical relative density, producing a negligible mechanical resistance between the punches. With a geometrical focus, this threshold represents the transition point between dispersed solid in air and voids in a solid matrix.

Leuenberger equation

This equation was developed and published in the early 1980s by H. Leuenberger (Leuenberger, et al., 1984; Leuenberger, 1982).

$$\sigma_t = \sigma_{t\max} \cdot (1 - e^{-\gamma \cdot \sigma \cdot \rho_r})$$

Equation 27

σ_{tmax} is the tensile strength (kg/cm^2) when *P* (compression pressure) → ∞ , $\rho_r \rightarrow 1$, and γ is compression susceptibility, expressing the compressibility of the powder formulation.

This equation allows the compressibility to be further determined and in a second step the compactibilty, defined as the ability of the powder to be compressed to a tablet of specific strength, can be evaluated by focusing on the maximum tensile strength σ_{tmax} .

Each of these three described equations contain a specific factor which is claimed to represent the compressibility of the formulation.

By fitting the measured and recorded compaction data to these three mathematical equations, those technical factors (k, C, γ) can be calculated and evaluated.

Since these factors represent the similar tablet quality parameter, the outcome values were

expected to show a certain proportionality between each other for the whole collection of formulations.

PLS regression for evaluation of the Near-Infrared Spectroscopy signals

Partial least squares regression (PLS regression) is a statistical method to create a linear regression model by projecting the predicted variables (y) and the observable variables (x) to a new space (Bastien, et al.). PLS finds the fundamental relations between the matrix of predictors (X matrix) and the matrix of responses (Y matrix), i.e. it can be seen as a latent variable approach to model the covariance structures in these two matrices. The goal of PLS regression is to predict Y from X and to describe their common structure. A PLS model to determine the multidimensional direction in the X space explains the maximum multidimensional variance direction in the Y space. PLS regression is particularly useful when the matrix of predictors has more variables than observations, and when there is multicollinearity among x values. It can analyze data with strongly collinear, correlated, noisy, and numerous x variables, and also simultaneously model several response variables.

Aim of the Study

In this paper the authors propose a NIRS method as an alternative to the conventional determination of tablet relative density and tensile strength. Multivariate prediction models for the respective tablet parameters were created. Every chosen formulation was compressed into tablets with different relative densities.

As next step, the tablet parameters of tensile strength and relative density were measured with NIR and also in the traditional way. The data set with the values received from the NIR spectras and also the data of the traditional method were fitted into mathematical equations used for the evaluation of powder compressibility and compactibility properties. The outcomes of the two data set evaluations were compared and tested for potential similarity.

With this approach, an alternative method for the assessment of compaction properties of powder formulations was established and evaluated.

Materials and Methods

Materials

For a reliable study of the compressibility measurement with the support of Near-Infrared Spectroscopy, favored excipients differing in mechanical properties (compressibility, ductile or brittle behaviour under pressure, disposition of sticking, etc.) were chosen to be investigated.

Also binary mixtures of a poorly compressible API and a well-compressible filler were investigated and evaluated in this study.

An overview list of all investigated formulations is given in the following table 6.

Table 6: List of investigated powder formulations

Formulation	**Drug load [%]**
Single powder	
MCC 101 L	
MCC 102 G	
Emcompress anhydrous	
Starch 1500	
Binary mixture	
Paracetamol / MCC 101 L	20
Paracetamol / MCC 101 L	40
Paracetamol / MCC 102 G	30
Mefenamic acid / MCC 101 L	20
Mefenamic acid / MCC 102 G	20
Mefenamic acid / MCC 102 G	40
Paracetamol / Parteck M 200	20
Paracetamol / Parteck M 300	20

Mefenamic acid (Sigma-Aldrich Inc., Batch 093K1608) and Paracetamol (Mallinckrodt, Batch 0048992565) were chosen as brittle, poorly compressible API. They have both a similar particle size distribution. Mefenamic acid (Picciochi, et al., 2010; Adam, et al., 2000) differs basically from Paracetamol because of its very high tendency to stick on the die wall and the punches.

The microcrystalline celluloses MCC 101 L (Pharmatrans Sanaq AG, Basel, Switzerland) and MCC 102G (Pharmatrans Sanaq AG, Basel, Switzerland) were chosen as ductile, well compressible excipients. Both are known for their high compressibility, even they differ in particle size (Kothari, et al., 2002; De la Luz Reus Medina, et al.; Abdel-Hamid, et al., 2011).

The directly compressible Mannitol products Parteck M200 and Parteck M300 (Merck KGaA, Darmstadt, Germany) show a plastic deformation behaviour during compaction (Abdel-Hamid, et al., 2011).

Anhydrous calcium hydrogen phosphate (Emcompress anhydrous, JRS Pharma, Rosenberg, Germany) can be used as excipient or as a calcium source in nutritional supplements. The predominant deformation mechanism for this powder is brittle fracture. This simplifies the scale-up to market production since the sensitivity to the strain-rate is reduced. However, at higher pressures, capping and lamination can occur. In this study, Emcompress anhydrous was chosen for investigating the influence of brittle deformation on the compressibility prediction with NIR. For the compaction of Emcompress, an external lubrification of the punch and die wall with Magnesium Stearate (Mg-stearate, Sandoz AG, Basel, Switzerland) was performed to keep the sticking tendency of the powder and the tablet ejection force on acceptable levels.

Pregelatinized starch (Sta-Rx 1500, Colorcon, Idstein, Germany) is a modified starch which is chosen in tablet production as binder, disintegrant and diluent. Its compressibility is not very satisfying, but a plastic behaviour under pressure is mentioned in the literature (Ilkka, et al., 1993).

A detailed overview of the individual deformation behaviour of the investigated compounds can be seen in the following table (information taken from Abdel-Hamid, et al., 2011).

Table 7: Deformation mechanisms of investigated powders

Material	Deformation mechanism
Paracetamol	Elastic, Brittle
Mefenamic acid	Brittle, sticky
Microcrystalline Cellulose powder MCC 101,102	Viscoelastic
Emcompress anhydrous powder	Brittle
Parteck M200, M300	Plastic
Sta-Rx 1500	Plastic

True density measurement

The true density of the investigated powders was measured with an AccuPyc 1330 helium pycnometer (Micrometrics, Norcross, GA, USA). Values were determined as the mean of three or five parallel measurements.

Design of binary powder mixtures

All powders were sieved (mesh size 355 μm) before weighting and mixing (Turbula mixer, Type T2A, Willy A. Bachofen AG Maschinenfabrik, Basel, CH) for 5 min. After the second sieving (mesh size 355 μm), the formulation was mixed for further 5 min.

Methods: Calculation of the true density for binary mixtures

The true density of the binary mixtures was calculated using the obtained results of the true density measurements for all starting materials (see equation 28):

$$\rho_{true[mixture]} = \frac{C_{API[\%]} \times \rho_{true[API]} + C_{Excipient[\%]} \times \rho_{true[Excipient]}}{100}$$

Equation 28

where $C_{API[\%]}$ $C_{API\ [\%]}$ is the concentration of active ingredient, $C_{Excipient\ [\%]}$ is the concentration of the excipient, $\rho_{true[API]}$ and $\rho_{true[Excipient]}$ are the corresponding true densities.

Partical size distribution

A Malvern Mastersizer X (Malvern Instruments, Worcestershire, UK) was applied to determine the average particle size by laser diffraction. 3 measurements were performed for each sample. The values of mean and median particle size, the span and the specific surface area were detected.

Powder compaction

The powder compaction was operated using a mechanical compaction simulator (Presster, Metropolitan Computing Corporation, New Jersey, USA). The tablet press Korsch PH336 with 36 stations was simulated. A flat-faced B-Tooling with 10mm of diameter was chosen for compacting tablets of 300 mg weight. The powder feeding was performed manually and an external lubrification was applied to prevent sticking of punches and tools during compaction.

In a first step, some preliminary experiments were performed to determine the maximal gap, where a robust tablet could be produced. Then, the gap was decreased continuously in small steps to receive resulting compaction forces from 0.5 kN to 20.0 kN.

For every formulation, two different compaction speeds were applied. One was corresponding to 100’000 tablets / hour (dwell time: 9.6 ms) and the second was corresponding to 216’000 tablets/hour (dwell time: 4.4 ms). A batch of around 40-80 tablets was produced with lower speed and one batch of around 40-80 tablets was produced with application of the higher speed. Every batch contained tablets with a uniformly distributed range of applied compaction force, from 0.5 kN to 20.0 kN. This compaction design led to a wide distribution of the final compacts’ relative density.

Measurement of tablet tensile strength

The breaking force of the produced tablets was measured with the Tablet Tester 8M (Dr. Schleuniger, Pharmaton, Switzerland). The tensile strength was calculated according to equation 29.

$$TS = \frac{2 \cdot CS}{\pi \cdot D \cdot T} TS = \frac{2 \cdot CS}{\pi \cdot D \cdot T}$$

Equation 29

where TS is the tensile strength [N/cm^2], CS is the crushing force [N], D is the diameter [cm], and T is the thickness [cm] of the tablet. The diameter and thickness of tablets were measured with a three-button digital calliper.

NIR measurements

Spectra were recorded in diffuse transmission measurement mode on a Fourier transform near infrared spectrometer NIRFlex N-500 (Büchi Labortechnik AG). A Diffuse Transmittance measurement module, mounted on a polarization interferometer, was equipped with tablet sample plate with ten iris apertures. Source of radiation was a Tungsten halogen lamp. Temperature controlled Indium-Galium-Arsenide (InGaAs) detector was positioned externally, above the sample holder. Each spectrum was an average of 64 scans at a resolution of 16cm^{-1}. Spectra were scanned over the spectral range of 11520 – 6000 cm^{-1} (870 – 1660nm). In total, 1381 data points were collected (Data point interval: 4, Apodisation for phase correction: Blackman, Photometric dynamic range: 2 AU, Wavelength accuracy: +- 0.2 cm^{-1}, Signal to noise ratio: 10000, Number of scans per second: 2-4, Analog-Digital-Changer: 24 Bit). 1203 tablet spectra from 22 batches were collected by NIRWare software (Büchi Labortechnik AG) and further analyzed by NIRCal 5.2 chemometrics software (Büchi Labortechnik AG). The NIR spectras were measured 48 hours after compression and storage of the compacts in a glass dessicator over white silica gel beads (1-3 milimeters layer).

Model development

Collected spectra from each batch were split into a calibration set, an internal and an external validation set in a proportion 25/25/50 %. Samples in all the sets were spanning the relative density range from 0.5 to 1.0 and tensile strength range from 0.1 to 9.4 MPa. Spectral preprocessing methods were applied to the raw spectra in order to reduce the excessive baseline variations and ordinate offsets caused by different physical properties of the samples and to group the spectra with similar values of analyzed tablet parameters. The light scattering information is correlated to the relative density and tensile strength of the compacts and enables the quantification of these parameters. Standard Normal Variate (SNV) and Normalization by Closure (ncl) were applied to reduce the scaling of the spectra due to very wide range of the compact porosity. Normalisation by Closure (ncl) spectral pretreatment is used to reduce the baseline variations due to different particle size or packing density differences (Martens, et al., 1989). It is a wavelength dependent pre-processing method. Savitsky - Golay first derivative (9 points) was used to correct for the baseline offsets and to minimize the noise by imposing the signal smoothing effect.

Calibration models for the prediction of relative density and tensile strength of the tablets were constructed using PLS algorithm. The number of significant latent variables (LVs) was chosen based on the value of sum of squares of the spectral residuals (X-PRESS) assuring adequate reconstruction of the spectra by the models and secondly, based on the calibration and validation predicted residual error sum of squares (C-set and V-set PRESS), as well as on the values of the root mean square error of prediction of an external validation set (RMSEP), validation set BIAS and coefficient of determination (r^2). The quality of the models was evaluated by calculating the root mean square error of calibration (RMSEC) and also the root mean square error of internal validation (RMSEV). The most important figures of merit were RMSEP of the external validation set and the r^2. Apart from the r^2, linearity was assessed by evaluating the slope and the intercept of the calibration line. The prediction residuals were tested for the normality. Durbin-Watson test was applied to the prediction

residuals to check if there are some evidences of serial correlations. Every model was tested for the outliers in both calibration and validation set by visual inspection of the scatter plots of the scores, Mahalanobis distances, spectral residuals and original vs. predicted property scatter plots. Obtained calibration models were fine-tuned by outlier exclusion and wavelength selection. Calibration wavelength regions were selected by observing the pretreated spectra, loadings and PLS regression coefficients.

Equations and concepts of Physics for the calculation of the outcomes

The obtained data sets of relative density, compaction pressure and tensile strength were analyzed and evaluated with the equations of the Heckel-Plot, the modified Heckel-Plot and the Leuenberger equation by using Mathematica 7.0 (Wolfram Research Inc., USA), Excel (Microsoft, USA), GraphPad Prism (GraphPad Software Inc, USA) and OriginPro (OriginLab Corporation, USA). For every formulation, there were two data sets evaluated, one of the traditional method application and a second data set obtained with the predicted method.

Mathematical comparison of the technical factors

An essential part in this study was the scientific evaluation of the technical factor outcomes obtained with the two data sets (traditional measurement vs. NIR) for every formulation.

In a first step the obtained values of an equation factor were plotted on a two-dimensional diagram, where the x-axis represents the values calculated with the traditional method and the y-axis represents the predicted values for the different formulations.

The similarity between the outcomes of the two methods can be declared, if the data points on the diagram can be fitted with a high coefficient of determination (r^2) on a trendline on the form of the following equation 30, with values for λ preferably close to 1 and a value for ϕ close to 0.

$$TS = \frac{2 \cdot CS}{\pi \cdot D \cdot T} \quad y = \lambda \cdot x + \phi$$

Equation 30

Results

True density of components

The following table shows the true density values of all pharmaceutical powders used in the investigated formulations. Since a main criterion of the component choice was the similar range of true density, no big deviation can be noticed between the true density values of the chosen components. The only exception here is Emcompress anhydrous, whose true density was almost double.

Table 8: True density of components

Powder	***True density [g/cm^3]***	***SD [g/cm^3]***
Paracetamol	1.22	0.00
Mefenamic acid	1.16	0.00
MCC 101 L	1.48	0.01
MCC 102 G	1.43	0.00
Emcompress anhydrous	2.49	0.00
Parteck M 200	1.52	0.00
Parteck M 300	1.39	0.00
Pregelatinzed starch 1500	1.50	0.00

Particle size measurement

Since the influence of the particle size was a main investigation target in this study, a focus was set on the particle size distribution of the investigated material.

In the following table, the mean value and the median value (incl. standard deviation) of the handled compounds is shown.

The mean particle size between the investigated compounds showed a wide range from 74.13 µm for Mefenamic acid up to 248.70 µm for Parteck M 300.

Table 9: *Particle size distribution of investigated compounds*

Powder	***Mean [µm]***	***SD [µm]***		***Median [µm]***	***SD [µm]***
Paracetamol	82.78	5.79		51.35	1.08
Mefenamic acid	74.13	6.05		38.35	1.83
MCC 101 L	83.35	2.31		73.76	0.88
MCC 102 G	119.74	0.15		114.06	0.53
Emcompress anhydrous	188.02	2.90		181.71	3.02
Parteck M 200	149.22	2.55		131.15	1.99
Parteck M 300	248.70	5.49		179.04	5.38
Pregelatinzed starch 1500	94.90	0.03		86.51	0.16

Powder compaction: Technical factor outcomes

The relative density, compaction pressure and tensile strength were recorded for every single tablet. This data set was applied to the Heckel-Plot, the modified Heckel-Plot and the Leuenberger equation for fitting. With this approach, the technical factors of the plots were calculated.

Table 10 shows the values for the factors k (Heckel-Plot) and C (modified Heckel) of all investigated powder formulations.

The formulations Paracetamol / Parteck M200 (20% drug load) and Paracetamol Parteck M300 (20% drug load) could not be compacted successfully with the higher compaction speed since the distinctive sticking tendency of the formulations did not allow an application of a high compaction speed. Therefore, these formulations are skipped in the part (b) of the table.

Table 10: technical factors of the investigated formulations: (a) low speed; (b) high speed

(a)

	value k [Mpa^{-1}]			value C [Mpa^{-1}]	
	tra	SD		tra	SD
MCC 101 (100%)	0.01289	0.0001598		0.00886	0.0009103
Paracetamol / MCC 101 L (20%)	0.009729	0.0002309		0.002869	0.0001015
Paracetamol / MCC 101 L (40%)	0.0101	0.0001972		0.004342	0.0000955
Mefenamic acid / MCC 101 L (20%)	0.01352	0.0003581		0.006664	0.0002033
MCC 102 G (100%)	0.01623	0.0002451		0.01273	0.0004921
Mefenamic acid / MCC 102 G (20%)	0.01439	0.0003148		0.006273	0.000537
Mefenamic acid / MCC 102 G (40%)	0.01048	0.0003815		0.00507	0.0002348
Paracetamol / MCC 102 G (30%)	0.0128	0.0001163		0.007499	0.0002061
Paracetamol / Parteck M200 (20%)	0.005413	0.000332		0.002054	0.0001315
Paracetamol / Parteck M 300 (20%)	0.006301	0.0001224		0.002524	0.0000963
Emcompress (100%)	0.00162	0.0006309		0.000247	0.0000097
Starch 1500 (100%)	0.005043	0.0001389		0.001017	0.0000446

(b)

	value k [Mpa^{-1}]			value C [Mpa^{-1}]	
	tra	SD		tra	SD
MCC 101 (100%)	0.0126	0.0002089		0.0064	0.0001462
Paracetamol / MCC 101 L (20%)	0.009018	0.0002466		0.00526	0.0001813
Paracetamol / MCC 101 L (40%)	0.0107	0.0002046		0.00488	0.0001953
Mefenamic acid / MCC 101 L (20%)	0.01296	0.0004983		0.00466	0.000369
MCC 102 G (100%)	0.016	0.000709		0.01021	0.0009444
Mefenamic acid / MCC 102 G (20%)	0.01025	0.0004969		0.003378	0.0003149
Mefenamic acid / MCC 102 G (40%)	0.007095	0.0005402		0.002355	0.0003452
Paracetamol / MCC 102 G (30%)	0.01556	0.000161		0.009738	0.0004921
Emcompress (100%)	0.001657	0.0000608		0.000245	0.0000106
Starch 1500 (100%)	0.003842	0.0001623		0.001073	0.000216

For a more convenient analysis and comparison, the outcome values were plotted on a bar chart (see Fig 29).

At first sight, it could be noticed that the absolute values of k were higher than those of C for all investigated formulations. This was an expected outcome which fits to the literature (Kuentz, et al., 1999) because the mathematical structure of a plot mainly determines the absolute value of its factors.

Technical factors gain only explanatory power when they are systematically collected and the data sets of different formulations and batches are compared.

The value ratios between investigated formulations showed a parallel proportionality for the values C and values k.

Some deviations were noticed for the formulations with MCC 101 L, compacted with the higher speed. In these cases, the value C was decreasing with higher drug load. In the meantime, the value k showed higher values with increasing drug load.

For the formulations with MCC 102 G and all the other single compound formulations, the ratios showed the expected parallel value trends for the two compaction speeds.

In a further step, the evaluation focus was set to the factor value comparison between the formulations.

For this study, some single powders, like Emcompress, Starch 1500, and a number of binary mixtures with a poorly compressible active drug (Mefenamic acid and Paracetamol) and Microcrystalline Cellulose (MCC 101 L and MCC 102 G) as filler were investigated. The main scientific focus was the evaluation and comparison of the technical factor values for different drug loads and for different single powders.

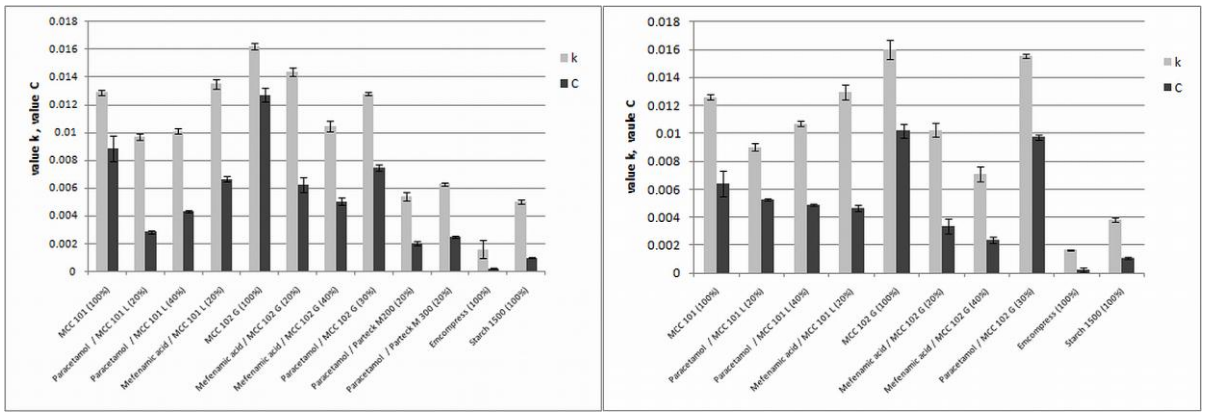
For the binary mixtures, a decrease of the compressibility with increasing drug load was expected and also noticed during handling. Since the investigated factors values k (Heckel-Plot) and C (modified Heckel-Plot) have been claimed (Heckel, 1961; Kuentz, et al., 2000; Leuenberger, et al., 1984; De Boer, et al., 1978) to represent the formulation compressibility, lower factor values were expected with increasing drug loads.

The pure MCC 102 G showed the highest factor values of all investigated formulations, followed by binary mixtures (20% drug load) of MCC 102 G with Paracetamol or Mefenamic acid.

Paracetamol (30%) / MCC 102 G showed higher factor values than Mefenamic acid (20%) / MCC 102 G. This outcome allowed us to assume a stronger negative influence of Mefenamic acid to the compressibility of a binary mixture than Paracetamol.

The binary mixtures with MCC 101 L showed a confusing outcome: For the formulation with 40% of Paracetamol some higher factor values were noticed than for the formulation with 20% of Paracetamol.

By assuming the factor values to represent compressibility, this outcome would show a better compressibility of a binary mixture after increasing the poorly compressible compound. Such a behaviour would not be realistic and could not be supported with literature findings. Also physical aspects, like the occurrence of percolation can not provide an explanation for such a behaviour.



(a) *(b)*

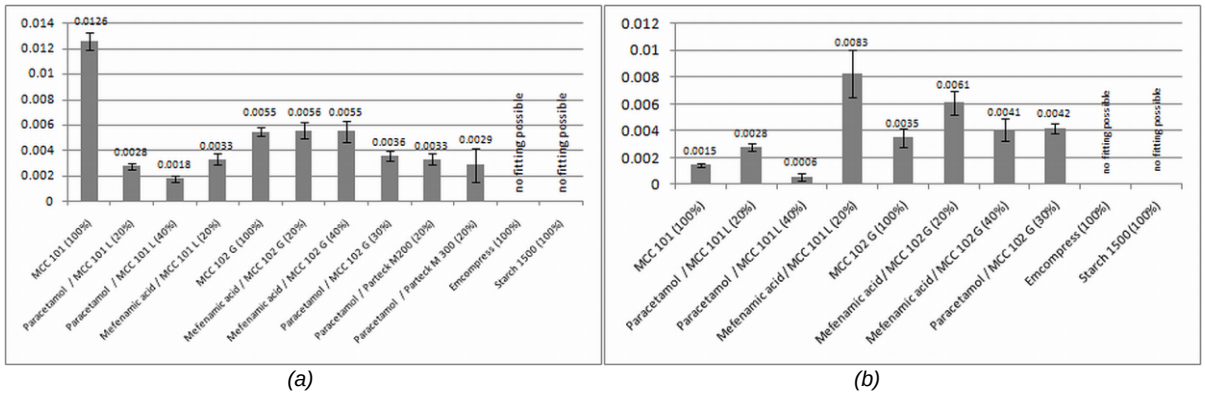
Fig. 29: values k and C of investigated formulations: (a) low speed; (b) high speed

Powder susceptibility γ

The data sets of all investigated formulations was fitted to the Leuenberger equation. Leuenberger et al. (Leuenberger, et al., 1984) claimed the parameter γ (powder susceptibility) of this equation to represent the compressibility of a formulation.

Therefore, the outcome values for γ were expected to be somehow proportional to the calculated values for factors k and C.

The powder susceptibility values for the investigated formulations are depicted in the following bar chart.



(a) *(b)*

Fig. 30: powder susceptibility γ: (a) low speed; (b) high speed

The factor calculation showed a high susceptibility for low speed compaction of single powder MCC 101 L and the high speed compaction of Mefenamic acid / MCC 101 L (20% drug load). For the other formulations their values were in a range between 0.0020 and 0.0060, whereas a quiet significant standard deviation was noticed for the most formulations.

Even though, the single compounds of Microcrystalline Cellulose are known for their high compressibility the fitting outcome values were in the same order of magnitude as the biggest part of the formulations.

A crucial finding was the fitting limitation for some formulations. The tensile strength values of the tablets compacted with these formulations showed significantly lower values than the tablets of the other formulations.

The occurence of this plotting limitation is a clear hint for an essentialy low compressibility. A formulation which need to be compressed into tablets with very low porosity for reaching a sufficient hardness is the best example for a formulation with low compressibility.

By comparing Fig. 29 with the bar charts of Fig. 30, no parallel value distribution for the parameter γ in relation to the factors k and C could be noticed.

A possible explanation for this outcome is the different structure of the Leuenberger equation in comparison to the Heckel and the modified Heckel equation.

Whereas the Heckel and modified Heckel equation have a two dimensional structure, the Leuenberger equation is based on a 3 –axis format.

The additional axis arised from the tensile strength values, which are a main part of the Leuenberger equation, while the Heckel Plot and the modified Heckel equation are only considering the compression pressure and the relative density of the produced compact.

The fitting of the data set to the Leuenberger equation uncovered a main element of this plot. As mentioned earlier, two compaction speeds were used in this project. For every formulation, one tablet batch was produced at lower speed and one batch at higher speed. Each batch contained around 40 to 80 tablets.

With a data set in this size, the value of every single tablet had an essential influence on the curve fitting. A small change in a data set for a single tablet can lead to a big change of the susceptibility value after fitting.

This could be a possible explanation for the deviation of the susceptibility values to the calculated numbers for the factors k and C.

The necessity of three variables per compacted tablet instead of two in combination with the

high sensitivity of the curve fitting on single variable value deviations made the application of the Leuenberger equation to the compressibility measurement being a challenging approach for this project.

Near – Infrared Spectroscopy measurement and model development

The construction of the calibration models in this paper is given on an example of the tablets composed of microcrystalline cellulose 102G, manufactured using low tableting speed. After the spectra were recorded, as shown in Figure 31, different spectral preprocessing methods were applied in order to enhance the spectral data relevant to the analysis and to exclude the excessive scattering effect.

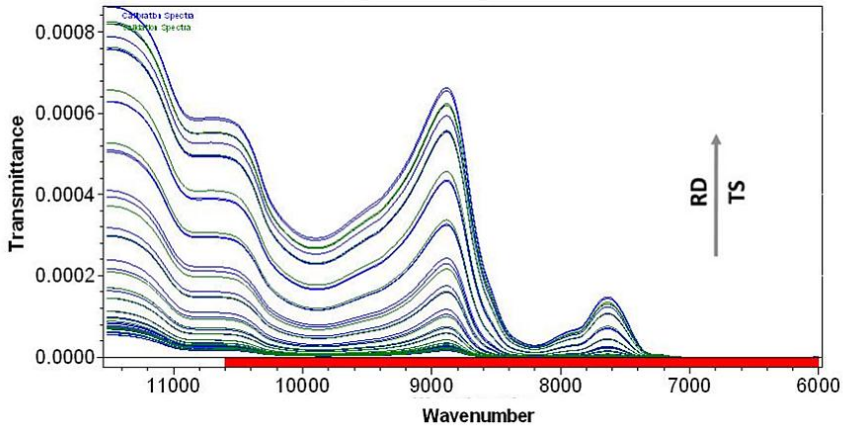


Fig. 31: Transmittance spectra of MCC 102G tablets with increasing tensile strength and relative density

Modeling the tablet relative density and tensile strength is based on a different degree of scattering between the samples but too high ordinate offsets and baseline shifts would impair the models. The criteria for the selection of the preprocessing method were the degree to which the preprocessed spectra are grouped according to the similar reference values and finally, the model performance (RMSEP). NIR transmittance values decreased regularly with an increase in the compression force applied to the powder bed as for an increase in the tensile strength and decrease in relative density of the tablets. Transmittance spectra were transformed to absorbance by Log 1/T function and it was noticed that the baselines are linearly shifted and no evidences of multiplicative effect were seen. The effect of the increasing compression force was seen as an overall spectral effect not related to the

specific wavelength since the tablet hardness does not have an analytical wavelength. Certain wavelength domains had higher correlation with the analyzed physical properties (r>0.90) and were selected for the construction of the calibration model.

Tablet relative density models (Figure *32*) gave the best performance when the Normalization by Closure (ncl) was applied, as seen in Figure 33.

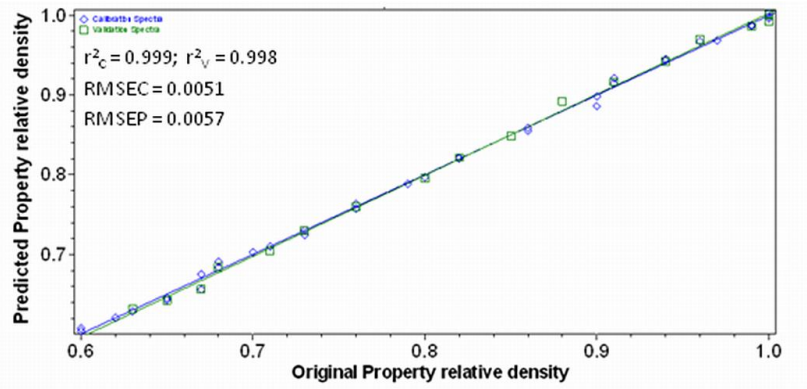


Fig. 32: *Calibration and internal validation reference vs. predicted property scatter plot of MCC 102G tablet RD prediction model; In the upper left corner are the figures of model merit*

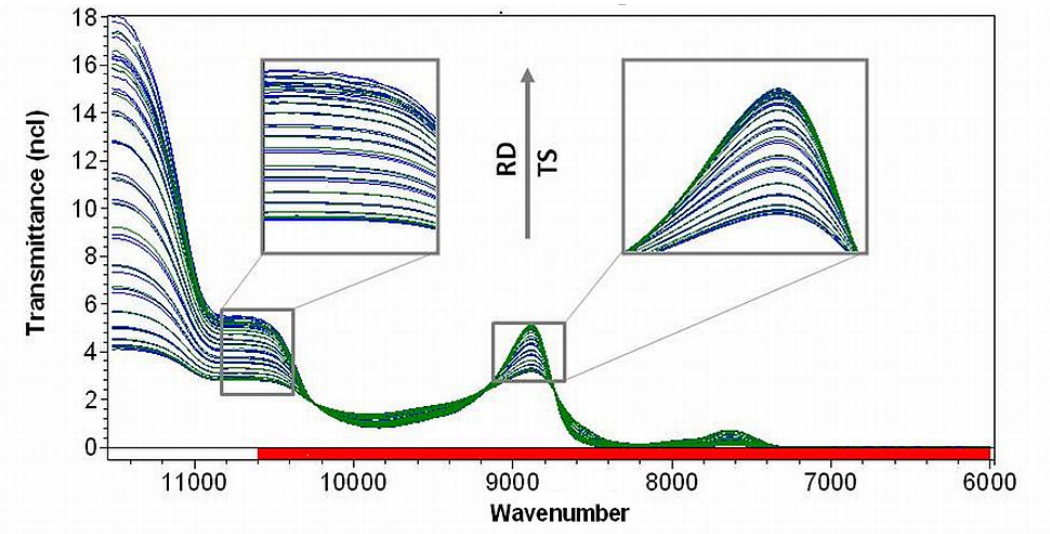


Fig. 33: Spectra of MCC 102G tablets pretreated with normalization by closure; The enlarged regions were used for calibration and show the grouping of the spectra according to RD.

The pretreated spectra were clearly grouped according to different relative density values. The calibration wave-number range was selected based on the observation of the first loading plot (see Figure *34*) and PLS regression coefficients.

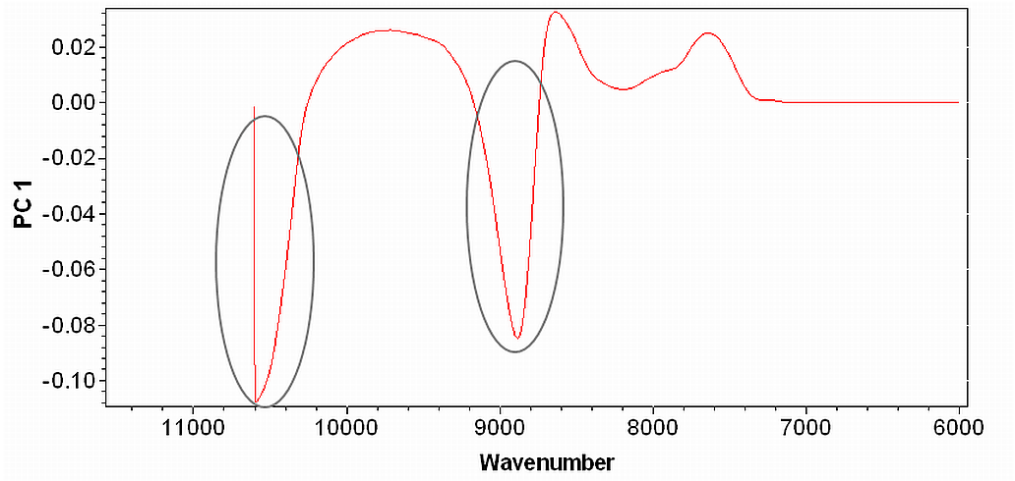


Fig. 34: The first loading vector of MCC 102G tablet RD prediction model;
The encircled regions carry the most spectral information and correspond to wave number regions used for calibration

The wave-number range from 10600 cm^{-1} to 11520 cm^{-1} was excluded due to high ordinate offset which ncl could not account for. The best tensile strength model was obtained when the Standard Normal Variate (SNV) pretreatment was applied to correct for the linear baseline shifts and subsequently Savitsky-Golay first derivative to correct for the ordinate offset which enabled the wave numbers from 10600 cm^{-1} to 11520 cm^{-1} to be included in the calibration (see Fig. *35*). The first loading vector was observed to check the wave number regions, i.e. variables that were modeled (see Fig. *36*).

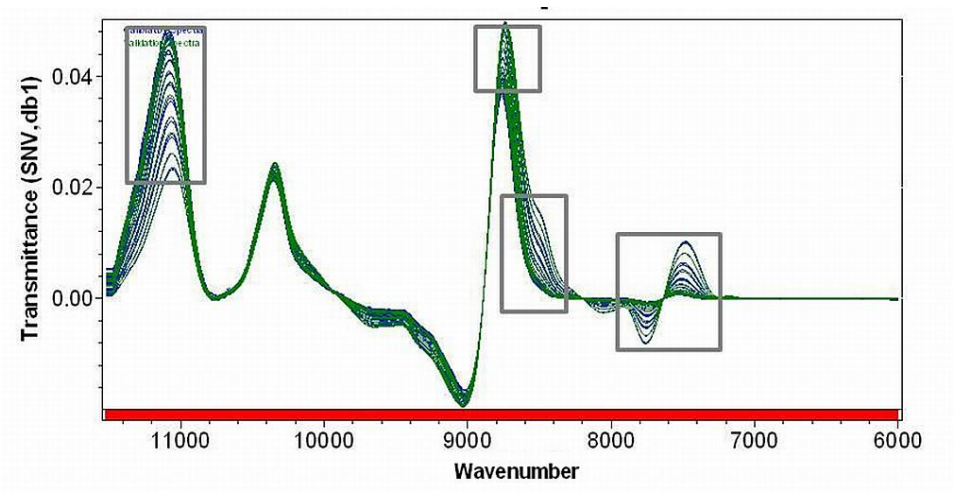


Fig. 35: Spectra of MCC 102G tablets pretreated with Standard Normal Variate and Savitsky-Golay first derivative;
The enlarged regions were used for calibration and show the grouping of the spectra according to TS.

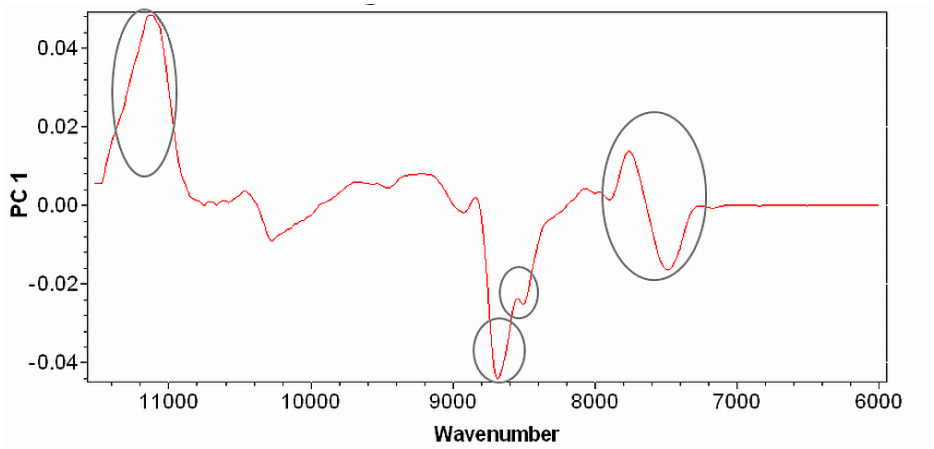


Fig. 36: The first loading vector of MCC 102G tablet TS prediction model;
The encircled regions carry the most spectral information and correspond to wave number regions used for calibration.

After the preprocessing of the data, the spectra and the measured relative density and tensile strength reference values were subjected to PLS regression. The overview of the figures of merit of the created calibration models for all the formulations is given in table *11.*

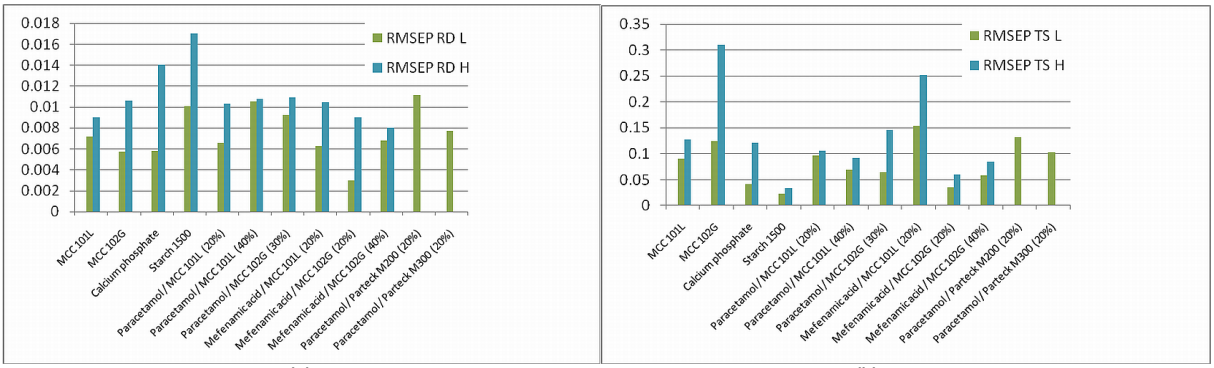
Table 11: Summary of the figures of merit obtained for the relative density and tensile strength calibration models

		relative density models				tensile strength models			
formulation		data pretreatment	LV	R^2	RMSEP	data pretreatment	LV	R^2	RMSEP
F1	LS	ncl	2	0.997	0.0072	SNV	3	0.997	0.0908
	HS	ncl	2	0.997	0.0090	ncl	2	0.998	0.1275
F2	LS	ncl	3	0.999	0.0057	SNV, 1 D	2	0.999	0.1242
	HS	ncl	3	0.993	0.0106	1 D	3	0.992	0.3099
F3	LS	SNV	5	0.982	0.0058	SNV	2	0.923	0.0415
	HS	SNV	5	0.992	0.0141	SNV	3	0.963	0.1211
F4	LS	ncl	2	0.984	0.0101	ncl	3	0.983	0.0229
	HS	ncl	5	0.973	0.0170	ncl	3	0.945	0.0336
F5	LS	ncl	2	0.998	0.0066	SNV	2	0.999	0.0970
	HS	ncl	4	0.995	0.0103	SNV	5	0.999	0.1062
F6	LS	ncl	3	0.996	0.0105	ncl	2	0.999	0.0695
	HS	ncl	4	0.997	0.0108	1 D	4	0.998	0.0917
F7	LS	SNV	3	0.989	0.0092	ncl	2	0.992	0.0650
	HS	SNV	3	0.981	0.0110	1 D	3	0.974	0.1461
F8	LS	ncl	2	0.997	0.0062	SNV, 1 D	2	0.983	0.1530
	HS	ncl	2	0.992	0.0104	SNV	4	0.988	0.2522
F9	LS	SNV	2	0.999	0.0030	ncl	2	0.997	0.0350
	HS	ncl	5	0.997	0.0090	ncl	5	0.988	0.0600
F10	LS	ncl	2	0.998	0.0068	SNV	2	0.996	0.0582
	HS	ncl	3	0.994	0.0080	SNV	4	0.985	0.0840
F11	LS	ncl	3	0.992	0.0111	SNV	5	0.983	0.1313
	HS	-	-	-	-	-	-	-	-
F12	LS	ncl	4	0.996	0.0077	SNV	4	0.996	0.1034
	HS	-	-	-	-	-	-	-	-

Created calibration models were compared in terms of performance (RMSEP) and it was noticed that all the models for the prediction of relative density and tensile strength of the tablets made by high tableting speed show worse performance (higher RMSEP) comparing

to low tableting speed models (Figure *37*). It was noticed that later models needed fewer latent variables to obtain the optimal model performance. This fact can be attributed to the poorer compaction reproducibility when the high tableting speed is applied to the powder bed since shorter dwell time gives less chances for particle bonding and the variations in compact density distribution are more pronounced (Tye, et al., 2005).

The numerous powder formulations showed really individual compaction properties in terms of compressibility which enhanced the differences in the models obtained for the low and high tableting speed tablets. The difference in prediction accuracy was observed between the MCC 101L and MCC 102G. The smaller mean particle size of MCC 101L comparing to MCC 102G contributed to the smaller difference between the relative density (RD) and tensile strength (TS) prediction accuracy of the tablets compacted under low and high tableting speed. Small particles have higher specific surface area and higher probability of particle bonding and thus, are less sensitive to dwell time i.e. tableting speed. A difference in predictions for high and low tableting speed was observed for dicalcium phosphate tablets, which is attributed to the tablet density inhomogenity, i.e. picking and cracking.



(a) *(b)*

Fig. 37: Comparison of the RMSEP values of the external validation set relative density (a) and tensile strength (b) predictions for all the studied formulations; L: low tableting speed, H: high tableting speed.

Comparison of numerical factors values, measured with traditional and predicted approach

Every single tablet of the produced batches was investigated with Near-Infrared-Spectroscopy. The measured data signal was then applied to the prediction model and the predicted values for relative density and tensile strength were determined and recorded.

In a second step, the diameter, height and hardness of the tablet were measured manually, which allowed us to calculate in the traditional way the relative density and the hardness of the tablets.

The two data sets (traditional method and prediction model) were applied on the Heckel-Plot, the modified Heckel- Plot and the Leuenberger equation. With this fitting step, a calculation of the technical factor values of the three applied equations could be performed.

A reliable evaluation of the designed prediction method for hardness and relative density with following determination of mathematical equation factor values (Heckel-Plot, modified Heckel-Plot and Leuenberger equation) prerequisited a scientific comparison of the final outcome values for the technical factors k, A, C, ρ_c, γ and σ_{tmax}.

Tables 12 and 13 gives an overview on the technical factor values for all investigated formulations. The outcomes are divided into one column for the traditional approach and one column for the NIR-approach.

A significant finding was the really small difference between the fitted values of the traditional method and the values, determined with the designed predictive method for the factors k of the Heckel-Plot and C of the modified Heckel-Plot.

The range of difference between the outcome values of the two methods was found to be within the standard deviation of both methods.

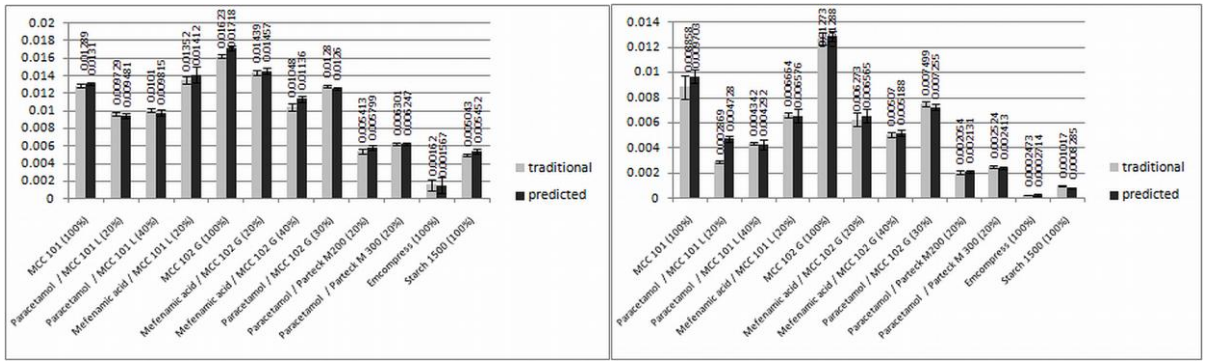
This outcome similarity between the two methods is illustrated graphically in Fig. 38 and Fig.39.

A similar outcome could be found for the factor critical density ρ_c of the modified Heckel-Plot. As shown in Fig. 40 the value difference between the ρ_c of the traditional method and the predictive method was also very small and was found to be in the standard deviation range of the data sets.

This outcome underlined the usability of the designed NIR - method for the reliable fitting of the used formulations to the Heckel-Plot and the modified Heckel-Plot. The particle size of the investigated powder did not show to influence the measurement in a negative way.

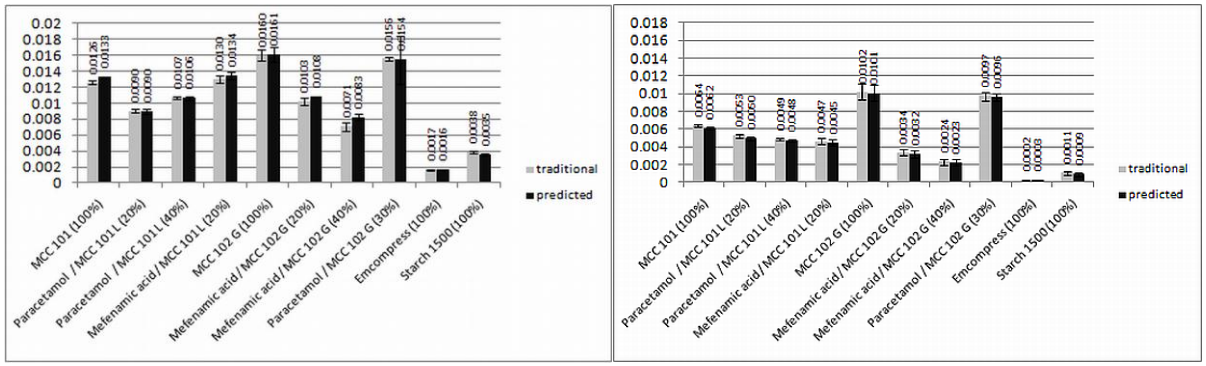
The comparison outcomes of the factors γ and σ_{tmax} in Fig. 41 and Fig. 42 show some bigger value differences between the fitting results of the traditional and the predicted approach. Even though, for some formulations the value differences between the methods are very low, other formulations showed an essential difference between the methods.

The reason for this difference can be explained with the three dimensional structure of the Leuenberger plot and also with the strong sensitivity of the fitting process to single data points.



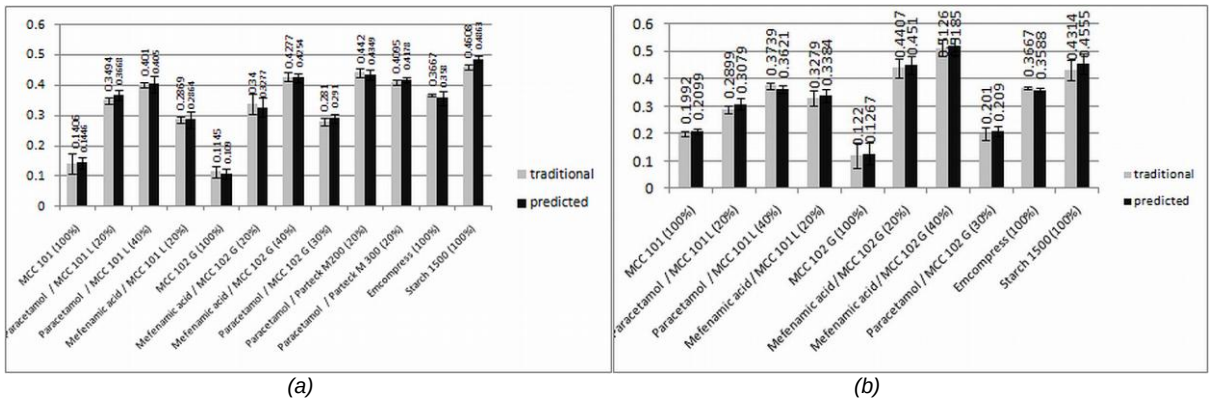
(a) *(b)*

Fig. 38: low speed batches: values k (a) and C (b) of investigated formulations



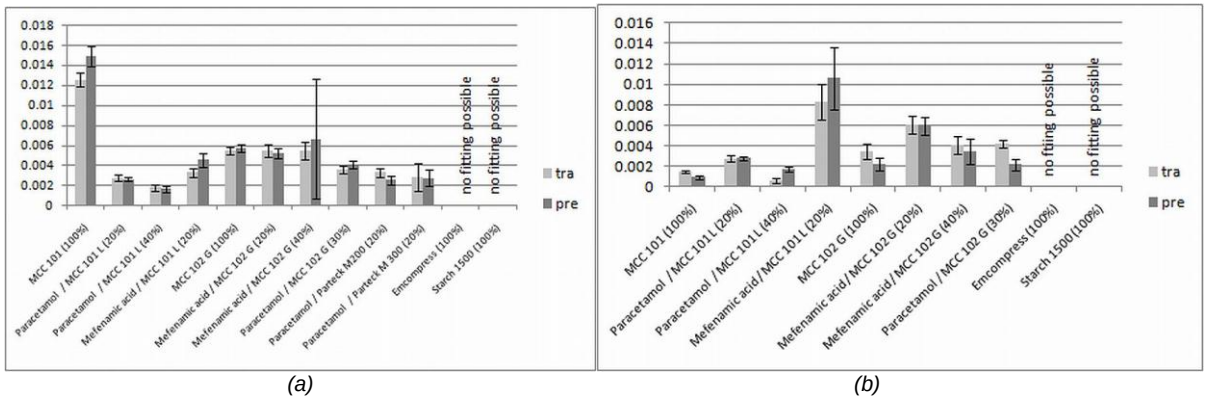
(a) *(b)*

Fig. 39: high speed batches: values k (a) and C (b) of investigated formulations



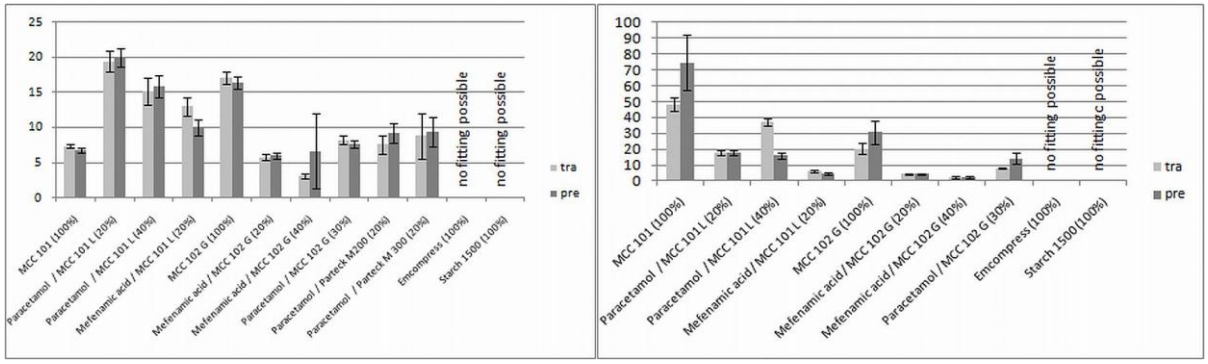
(a) *(b)*

Fig. 40: $\rho_{critical}$ *data comparison: (a) low speed batches; (b) high speed batches*



(a) *(b)*

Fig. 41: gamma data comparison: (a) low speed batches; (b) high speed batches



(a) *(b)*

Fig. 42: σ_{tmax} data comparison: (a) low speed batches; (b) high speed batches

Table 12: outcomes of factor values by using the traditional (tra) approach or the developed method (pre) for low speed batches

Low speed									
	Heckel equation								
	k					A			
	tra	SD	pre	SD		tra	SD	pre	SD
MCC 101 (100%)	0.0129	0.00016	0.0131	0.00018		0.6196	0.005686	0.6141	0.005827
Paracetamol / MCC 101 L (20%)	0.0097	0.00023	0.0095	0.00027		0.9515	0.02797	0.9674	0.03324
Paracetamol / MCC 101 L (40%)	0.0101	0.00020	0.0098	0.00033		0.9142	0.01833	0.935	0.03108
Mefenamic acid / MCC 101 L (20%)	0.0135	0.00036	0.0141	0.00090		0.7686	0.01219	0.739	0.02551
MCC 102 G (100%)	0.0162	0.00025	0.0172	0.00027		0.7778	0.01942	0.724	0.02128
Mefenamic acid / MCC 102 G (20%)	0.0144	0.00031	0.0146	0.00031		0.8257	0.02401	0.8103	0.02381
Mefenamic acid / MCC 102 G (40%)	0.0105	0.00038	0.0114	0.00032		1.205	0.04146	1.147	0.00349
Paracetamol / MCC 102 G (30%)	0.0128	0.00012	0.0126	0.00015		0.8302	0.01063	0.8371	0.014
Paracetamol / Parteck M200 (20%)	0.0054	0.00033	0.0058	0.00026		1.031	0.04882	0.9891	0.03756
Paracetamol / Parteck M 300 (20%)	0.0063	0.00012	0.0062	0.00019		0.9484	0.01348	0.9553	0.00219
Emcompress (100%)	0.0016	0.00063	0.0016	0.00088		0.5763	0.006201	0.5814	0.008541
Starch 1500 (100%)	0.0050	0.00014	0.0055	0.00025		0.8105	0.006846	0.7839	0.01287

Low speed									
	modified Heckel equation								
	C					rcritical			
	tra	SD	pre	SD		tra	SD	pre	SD
MCC 101 (100%)	0.008858	0.0009103	0.009703	0.0005259		0.1406	0.0344	0.1446	0.01911
Paracetamol / MCC 101 L (20%)	0.002869	0.0001015	0.004728	0.0002159		0.3494	0.01054	0.3668	0.01615
Paracetamol / MCC 101 L (40%)	0.004342	0.00009555	0.004292	0.0003808		0.401	0.007041	0.405	0.02799
Mefenamic acid / MCC 101 L (20%)	0.006664	0.0002033	0.006576	0.0005465		0.2869	0.009612	0.2864	0.02591
MCC 102 G (100%)	0.01273	0.0004921	0.01288	0.0004217		0.1145	0.02022	0.109	0.017
Mefenamic acid / MCC 102 G (20%)	0.006273	0.000537	0.006565	0.0005159		0.34	0.03353	0.3277	0.03165
Mefenamic acid / MCC 102 G (40%)	0.00507	0.0002348	0.005188	0.000234		0.4277	0.01526	0.4254	0.01502
Paracetamol / MCC 102 G (30%)	0.007499	0.0002061	0.007255	0.0002624		0.281	0.01209	0.291	0.01578
Paracetamol / Parteck M200 (20%)	0.002054	0.0001315	0.002131	0.0001315		0.442	0.01531	0.4349	0.01531
Paracetamol / Parteck M 300 (20%)	0.002524	0.00009627	0.002413	0.00009075		0.4095	0.009965	0.4178	0.009578
Emcompress (100%)	0.0002473	9.689E-06	0.0002714	0.00007271		0.3667	0.00358	0.358	0.02421
Starch 1500 (100%)	0.001017	0.00004457	0.0008285	0.00006119		0.4608	0.007228	0.4863	0.01083
Low speed									
	Leuenberger equation								
	gamma					stmax			
	tra	SD	pre	SD		tra	SD	pre	SD
MCC 101 (100%)	0.0125674	0.00068575	0.0149438	0.00100839		7.31092	0.26855	6.77104	0.305785
Paracetamol / MCC 101 L (20%)	**0.00277092**	0.00028592	**0.002664**	0.00022464		**19.3791**	1.46086	**19.9551**	1.33466
Paracetamol / MCC 101 L (40%)	**0.00180871**	0.00026463	**0.00172073**	0.00030494		**15.1827**	1.91932	**15.8972**	1.5243
Mefenamic acid / MCC 101 L (20%)	0.0033108	0.00044002	0.00457211	0.0007182		12.9792	1.35817	10.0376	1.14665
MCC 102 G (100%)	**0.00550401**	0.00036034	**0.00576584**	0.00036034		**17.0828**	0.842176	**16.438**	0.842176
Mefenamic acid / MCC 102 G (20%)	0.00556456	0.00062708	0.00523316	0.00053796		5.79902	0.425104	6.03112	0.411804
Mefenamic acid / MCC 102 G (40%)	0.00552612	0.00085903	0.00670111	0.00602235		3.10846	0.308401	6.64314	5.29407
Paracetamol / MCC 102 G (30%)	0.0036032	0.00037179	0.00415382	0.0003549		8.20486	0.623178	7.6377	0.449094
Paracetamol / Parteck M200 (20%)	0.00331118	0.00044002	0.00260538	0.00044002		7.58712	1.35817	9.18249	1.35817
Paracetamol / Parteck M 300 (20%)	0.00288876	0.00134468	0.00277918	0.00079557		8.84878	3.21327	9.4519	2.10216
Emcompress (100%)	no fitting		no fitting			no fitting		no fitting	
Starch 1500 (100%)	no fitting		no fitting			no fitting		no fitting	

Table 13: outcomes of factor values by using the traditional (tra) approach or the developed method (pre) for high speed batches

Highspeed									
	Heckel equation								
	k					A			
	tra	SD	pre	SD		tra	SD	pre	SD
MCC 101 (100%)	0.0126	0.00021	0.0133	0.00002		0.6038	0.006316	0.5788	0.00736
Paracetamol / MCC 101 L (20%)	0.0090	0.00025	0.0090	0.00031		0.8435	0.0323	0.8417	0.04055
Paracetamol / MCC 101 L (40%)	0.0107	0.00020	0.0106	0.00022		0.8573	0.01609	0.8569	0.01709
Mefenamic acid / MCC 101 L (20%)	0.0130	0.00050	0.0134	0.00050		0.687	0.02717	0.6694	0.02527
MCC 102 G (100%)	0.0160	0.00071	0.0161	0.00094		0.5824	0.07407	0.5832	0.06701
Mefenamic acid / MCC 102 G (20%)	0.0103	0.00050	0.0108	0.00005		0.9561	0.04252	0.9305	0.04685
Mefenamic acid / MCC 102 G (40%)	0.0071	0.00054	0.0083	0.00042		1.221	0.05801	1.126	0.04216
Paracetamol / MCC 102 G (30%)	0.0156	0.00016	0.0154	0.00030		0.7544	0.01147	0.7752	0.01631
Emcompress (100%)	0.0017	0.00006	0.0016	0.00006		0.5658	0.00589	0.5688	0.05731
Starch 1500 (100%)	0.0038	0.00016	0.0035	0.00017		0.8692	0.01423	0.894	0.01696

Highspeed									
	modified Heckel equation								
	C					rcritical			
	tra	SD	pre	SD		tra	SD	pre	SD
MCC 101 (100%)	0.006403	0.0001462	0.00618	0.0001238		0.1992	0.009304	0.2099	0.007997
Paracetamol / MCC 101 L (20%)	0.00526	0.0001813	0.004955	0.0002648		0.2899	0.01385	0.3079	0.02068
Paracetamol / MCC 101 L (40%)	0.00488	0.0001953	0.004752	0.0001761		0.3739	0.0137	0.3621	0.01176
Mefenamic acid / MCC 101 L (20%)	0.00466	0.000369	0.004514	0.0003011		0.3279	0.02752	0.3384	0.02274
MCC 102 G (100%)	0.01021	0.0009444	0.01007	0.0009158		0.122	0.04701	0.1267	0.03961
Mefenamic acid / MCC 102 G (20%)	0.003378	0.0003149	0.003211	0.0003774		0.4407	0.03456	0.451	0.03211
Mefenamic acid / MCC 102 G (40%)	0.002355	0.0003452	0.002278	0.0003239		0.5126	0.03159	0.5185	0.02997
Paracetamol / MCC 102 G (30%)	0.009738	0.0004921	0.009589	0.0004011		0.201	0.02412	0.209	0.01699
Emcompress (100%)	0.0002451	0.00001064	0.0002717	0.00001665		0.3667	0.003998	0.3588	0.005941
Starch 1500 (100%)	0.001073	0.000216	0.0009172	0.000208		0.4314	0.03572	0.4555	0.03657

Highspeed									
	Leuenberger equation								
	gamma					stmax			
	tra	SD	pre	SD		tra	SD	pre	SD
MCC 101 (100%)	0.00147601	0.00014339	0.00092792	0.00023049		48.0388	4.26322	74.6734	17.5723
Paracetamol / MCC 101 L (20%)	**0.00276639**	0.00028592	**0.00279528**	0.00022464		**18.019**	1.46086	**17.8554**	1.33466
Paracetamol / MCC 101 L (40%)	**0.0006**	0.00027668	**0.00172073**	0.00027668		**36.9461**	2.22764	**15.8972**	2.22764
Mefenamic acid / MCC 101 L (20%)	0.00831021	0.00176721	0.0106034	0.00306169		6.33417	0.664641	4.72677	0.694805
MCC 102 G (100%)	**0.00350423**	0.00071901	**0.00221382**	0.00060147		**20.3556**	3.36363	**30.7218**	7.33262
Mefenamic acid / MCC 102 G (20%)	0.00608481	0.00089901	0.00596524	0.00087723		4.46376	0.422988	4.54984	0.433131
Mefenamic acid / MCC 102 G (40%)	0.00410826	0.00085495	0.00350502	0.00125187		2.40258	1.04732	2.66629	0.754081
Paracetamol / MCC 102 G (30%)	0.00422058	0.00037612	0.00217636	0.00058681		8.03293	0.516722	14.1599	3.39755
Emcompress (100%)	no fitting		no fitting			no fitting		no fitting	
Starch 1500 (100%)	no fitting		no fitting			no fitting		no fitting	

For a further scientific substantiation of the found similarity of the equation factor outcomes between the traditional approach and the designed method with support of NIR, all the factor values were applied to a two – dimensional diagram. The data points were then fitted to the trendline according to Equation 30. An example for this fitting step is shown in Figure 43.

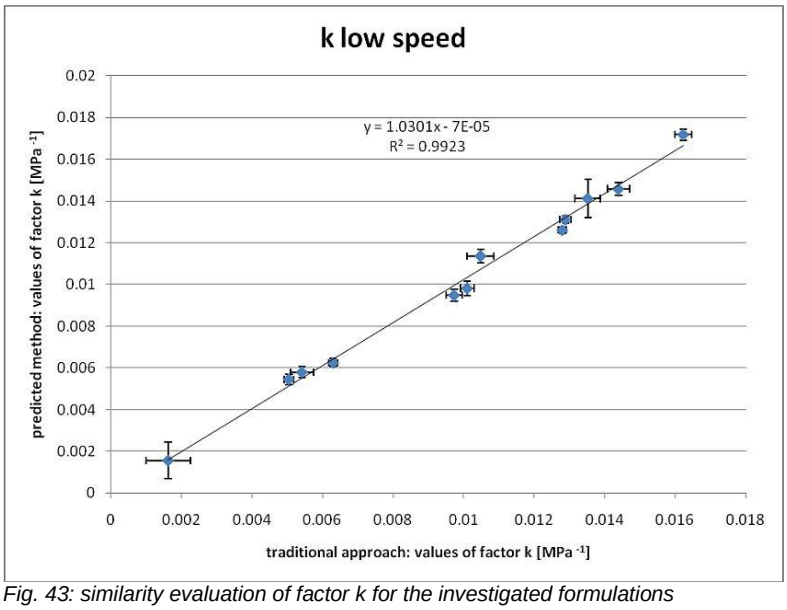


Fig. 43: similarity evaluation of factor k for the investigated formulations

In the following table 14 the values of λ and ϕ can be seen for all investigated technical factors. A similarity between two data sets can be shown when λ is close to 1, ϕ is close to 0 and especially the r^2 is higher than 0.95.

These conditions are fulfilled for the technical factors of the Heckel and the modified Heckel equation. The different particle size of the several chosen formulations did not show any influence on the reliability of the technical factor analysis with NIR.

The factors γ and σ_{tmax} of the Leuenberger equation showed a significant deviation from the conditions for similarity. Especially the r^2 – values have shown much lower values for these technical factors. This outcome underlines the non-similarity of the factor values for the Leuenberger equation between the traditional method and the approach with Near Infrared Spectroscopy.

Table 14: values of λ and ϕ for the technical factors

(a) low speed compaction

	λ	ϕ	r^2
k	1.0301	-0.00007	0.9923
A	0.95	0.0281	0.9757
C	1.0054	0.0002	0.9745
ρ_c	1.0213	-0.044	0.991
γ	1.2244	-0.0006	0.9727
σ_{tmax}	0.8516	1.9632	0.9009

(b) high speed compaction

	λ	ϕ	r^2
k	1.0076	0.0002	0.9908
A	0.8964	0.0707	0.9788
C	0.9892	-0.00009	0.9994
ρ_c	0.9997	0.0074	0.9925
γ	1.1682	-0.0008	0.8328
σ_{tmax}	1.1952	-0.9466	0.7014

Conclusion

For the investigated formulations, the designed NIR method for determining the factors of the Heckel-Plot and the modified Heckel-Plot showed reliable results and outcomes.

Essentially different outcome values were reached with the Near-Infrared Spectroscopy method for the factors of the Leuenberger equation (γ, σ_{tmax}).

In this range of tablet numbers, the mathematical fitting to the Leuenberger equation showed a high sensitivity to deviations of the relative density and tensile strength of some single tablets.

This sensitivity could be determined as essential reason of high outcome deviation between the traditional approach and the predicted method. The relatively high standard deviations of the calculated values for γ and σ_{tmax} are an additional hint for this sensitivity.

The choice of the formulations to be investigated in this study was made with the focus set on the different materials showing a widest possible range of particle size and a wide range of compression mechanisms. These factors showed not to influence the data outcomes of the designed method with Near-Infrared Spectroscopy.

The newly designed method is suggested as a promising approach for a non-destructive compressibility measurement of powder formulations. A potential usage of Near-Infrared Spectroscopy inline during tablet production could be underlined with this study in a remarkable way.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Overall discussion of thesis outcomes

The investigation of the pharmaceutical powder property “compressibility” in tablet formulation design and manufacturing has been the main aim of this thesis. Even though, in the scientific world the term is clearly defined as the ability of a powder to decrease in volume under pressure (Leuenberger, 1982), it has been and still continues to be a crucial challenge to express the compressibility of a powder as a mathematical value.

The numerical illustration of a material property, like e.g. the powder compressibility, is a crucial step in science, since it shows the complete understanding of this property and its interaction with other physical and mechanical factors. Additionally, the numerical expression of a material property allows scientists to further use it for research investigation of materials, tools, powder mixtures, mechanical devices and complex systems.

Multitudinous trials have been made by a big number of scientists and research groups in the past to find the ultimate approach for a mathematical definition of the pharmaceutical powder compressibility. A big disadvantage of the available research studies is the fact, that the developed mathematical formulations were applied only to a limited number of different formulations and only for a certain condition of the compaction setup.

Also the research outcomes on comparison between different mathematical approaches for powder compressibility determination are limited. Not to mention the gap in available literature for comparison of compressibility value change after slight adjustment of the investigated formulation between different approaches (e.g. Heckel Plot vs. Modified Heckel-Plot).

The research project of this thesis “Compressibility of binary powder formulations: Investigation and evaluation with compaction equations” was targeting exactly these open questions by investigating binary mixtures of poor compressible API and well-compressible excipient and showing the differences between the results of the compressibility factor value by applying three different approaches (Heckel-Plot, modified Heckel-Plot, Leuenberger equation). Additionally, the progression of these factor values with slight adjustment of the

investigated formulation was investigated. Two very important outcomes could be shown with this investigation step: First, by increasing the amount of the poorly compressible API, the factor value claiming to represent the powder compressibility showed an individual progression without the expected regular value decrease for the three different approaches. Second, the progression of the factor values did not show the expected parallelism between the three approaches.

In other words, it can be stated that the investigation of powder compressibility has to be planned, developed and performed in a careful way with clear definition of compaction method, compaction speed, choice of compressibility calculation approach, number of tested tablets and total batch size. Especially for the comparison of different formulations, the consistency of these investigation factors is really important.

In general, the research project could show that the application of the Heckel-Plot, the modified Heckel-Plot and the Leuenberger equation for an investigation of the compressibility value progression after slight adjustment of the formulation compounds is difficult to be recommended. The results of the factor values for the investigated formulations gave strong hints that the value differences between the formulations were not occurring only because of the physical and mechanical differences between the formulations but also because of some external factors which can never be kept 100% constant and also small differences of the physical particle nature within the same batch of the used compounds.

The relevance of a constant compaction method for comparing the powder behaviour under pressure between two individual formulations could be shown in the research project “Assessing compressibility and compactibility of powder formulations with Near-Infrared Spectroscopy” where the powder formulations were compressed with two different tableting speeds, generating two different tablet batches for every powder formulation. The followed analysis of the two batches and application of the data to the Heckel-Plot, modified Heckel-Plot and the Leuenberger equation showed the compressibility values to be crucially influenced by the tableting speed.

Even though, this outcome is significant and important for the scientific field of solid dosage

forms, the main outcome of the research project was the applicability of Near-Infrared Spectroscopy for the measurement and monitoring of the powder compressibility (with Heckel-Plot and modified Heckel-Plot).

The developed method allows the scientist to measure in a first step the relative density and the tensile strength of tablet without destroying the tablet. The designed method was applied to numerous powder formulations with a wide range of different compaction mechanisms. The results of the study showed the reliable applicability of the developed NIR-method for the investigated formulations.

In a second step, and as a main part of this project, the detected data for relative density and tensile strength was applied to the Heckel-Plot, the modified Heckel-Plot and the Leuenberger equation. The results were really promising, since the compressibility factors for the NIR data application data showed similar values for the Heckel- and the modified Heckel-Plot as the data collected with the traditional method.

This outcome showed clearly that the developed NIR-application has an essential future potential for being used in commercial tablet manufacturing, quality assurance and quality control as a fast and reliable method for online-monitoring of the bulk compressibility, relative density and tensile strength of the produced tablets. The developed NIR-method is a sensitive tool for detecting quality deviations occurring during tablet production which can occur e.g. due to demixing of the formulation, higher powder formulation quality within a batch and incidents which change the established gap between upper and lower compaction punch of the tableting machine.

A higher deviation of the relative density and the tensile strength of the tablets within a production batch can have a significant impact on the pharmacokinetical behaviour of the tablet within the patient’s GIT. Such an incident could lead in the last step to a pharmacodynamical effect of the active drug in the body being probably out of medical specification. This way, there is no guarantee that the level of the active drug in the body of the patient is within the therapeutical window and not too low or in the worst case too high, meaning toxic.

Such quality deviations can be prevented by guaranteeing a high quality of the raw material and by keeping the quality of every tablet manufacturing step on a highest possible level. Handling of the raw material, mixing and/or granulation, compaction, final packaging, logistic transportation and distribution: All these steps can have a crucial impact on the product quality.

After having compacted the powder to the final tablet, its quality should be measured and monitored. That way, deviations in the compressibility value (hint to stronger deviation in the quality of the used powder), tensile strength and relative density can be reliably detected. The developed detection method with support of Near-Infrared Spectroscopy can be a good and reliable way of guaranteeing the patient a drug product of high quality and satisfying effect on treating the combated disease.

Final conclusion of thesis outcomes and outlook

The powder compressibility is challenging to be precisely expressed since numerous different equations are available in the scientific literature, which claim to contain a factor representing the powder compressibility. The validity of these equations could be illustrated in the literature only for specific powder mixtures, compaction conditions and chosen tablet machine or compaction simulator.

With the research results of this PhD thesis, this challenge was clearly underlined. The different absolute and relative compressibility values by applying different equations and approaches could show clearly the difficulty in the choice of the appropriate mathematical equation for a compressibility determination. It can be strongly assumed, that by slightly adjusting the compaction settings in the project 1 of this thesis, like e.g. the compaction speed, the outcome values for the compressibility factors would be again deviating crucially from the value reached with the actual conditions. Nevertheless, the role and influence of the numerous compaction factors is still poorly understood.

There are still a lot of open questions, which need to be investigated and answered for a complete understanding and finding of a reliable mathematical approach for estimation of the powder compressibility.

The physical nature of the particles within a powder formulation, the compaction setup and the influence of external factors can be seen as important target points for future research in this field.

Even though, there has a crucial amount of research work been done in the field of powder compaction, the scientific knowledge is still in the fledgling state.

The developed measurement method with support of Near-Infrared Spectroscopy showed really promising results. It would be interesting to see, if it can be applied to additional compressibility plots available in the literature.

With the right research steps taken, one day there will be a huge number of different tablet properties and factors, which could be measured with support of Near-Infrared Spectroscopy.

This will support a lot the quality monitoring in tablet production, the optimization of the commercial tablet production and finally the complete understanding of the pharmaceutical powder compaction process.

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Curriculum vitae

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EDUCATIONAL BACKGROUND

- **Industrial Pharmacy Lab, University of Basel, Switzerland** **Feb 2009 – Jan 2012**
  PhD studies in powder compaction, solid dosage forms and compaction troubleshooting

- **University of Basel, Switzerland** **Aug 2005 – Aug 2006**
  Federal Diploma of Pharmacy
  Courses: Pharmacognosy, Drug Production, Law & Economy for Pharmacists, Health Care, Pharmaceutical Care II, Marketing

- **University of Basel, Switzerland** **Aug 2003 – Aug 2005**
  Master of Pharmaceutical Sciences
  Courses: Pharmaceutical Technology, Pharmaceutical Chemistry, Molecular Modeling, Biopharmacy, Pharmaceutical Biology, Pharmacology, Epidemiology, Public Health, Pharmacotherapy, Pathophysiology, Pharmaceutical Care I

- **University of Berne, Switzerland** **Aug 2001 – Aug 2003**
  Undergraduate Studies of Pharmaceutical Sciences
  Courses: Analytical Chemistry, Organic Chemistry, Cell Biology, Physics, Mathematics, Inorganic Chemistry, General Chemistry, Anatomy, Physiology, Pathophysiology, Microbiology

- **Gymnasium Koeniz** **Aug 1998 – Aug 2001**
  Swiss high school degree

LANGUAGE SKILLS

- German: native speaker
- Greek: native speaker
- Swiss: native speaker
- English: fluent
- French: fluent
- Spanish: beginner

WORK / RESEARCH EXPERIENCE

- **Natoli Engineering, Inc., Saint Charles, MO – University of Basel, Switzerland**
  Scientific Internship: Compaction troubleshooting and deeper understanding of the compaction process from the engineering side, especially issues concerning tooling.

  Jul 2011 – Nov 2011

- **Teaching Assistant, University of Basel, Switzerland**
  Teaching of Physical Chemistry classes for undergraduate students, supervision of graduate students for laboratory work in solid dosage forms

  Feb 2009 – Jul 2011

- **F. Hoffmann-La Roche Ltd (Basel / Kaiseraugst, Switzerland)**
  Working field: Quality and Complaint Management **Apr 2007 – Jan 2009**

- **Apotheke zur Waage (Basel, Switzerland)**
  Practical stage in local Pharmacy **Sep 2005 – Jul 2006**

- **Industrial Pharmacy Lab, University of Basel, Switzerland**
  Master thesis:
  "Microkristalline Celluose: An attractive excipient for solid dosage forms"
  supervision: PD Dr. Gabriele Betz and Dr. Vincenzo Balzano
  (Evaluation: best mark) **Apr 2005 – Sep 2005**

PRESENTATIONS AND POSTERS

Presentations:

- **Science based trouble shooting of the tableting process. Tablet defects. Root cause analysis**
  FIP Annual Congress (invited speaker), Hyderabad, India, September 2011

- **Scientific analysis of powder compaction: A physical process, described and evaluated with mathematical equations**
  EPSA Annual Congress 2011, Lisbon, April 2011

- **Mechanical and chemometric approach for the investigation of pharmaceutical powder formulations**
  2nd IPL Symposium, "The growing importance of Industrial Pharmacy", Riehen, September 2010

- **Powder compaction process: a physical and mathematical approach**
  Zurich-Geneva-Basel meeting: Annual Research Presentations, Geneva, June 2010

- **Physical and mathematical description of the powder compaction process – a new approach in pharmaceutical tablet production**
  EPSA Annual Congress 2010, Krakow, April 2010

- **After Graduation: Opportunities and Challenges**
  DIA Clinical Forum, Nice (F), October 2009

- **Quality aspects of marketed drugs, a big challenge for the Pharmaceutical Industry**
  EPSA Annual Congress, Serbia, April 2007

Posters:

- ***Compaction properties of binary mixtures – measured and monitored with Near-Infrared Spectroscopy***
  Nicolaos D. Gentis, Branko Vranic and Gabriele Betz (2011), Annual Research Meeting, Pharmazentrum, University of Basel, Switzerland, February 2011

- ***Compressibility and compactibility of powder formulations – investigation from a physico-mathematical perspective with introduction of Near-Infrared Spectroscopy***
  Nicolaos D. Gentis, Branko Vranic and Gabriele Betz (2010),
  FIP Pharmaceutical World Congress 2010, New Orleans (USA), November 2010

- ***Optimization of powder compaction – a challenge for industrial manufacturing science***
  Nicolaos D. Gentis and Gabriele Betz (2010), DIA Euromeeting, Monaco, March 2010

- ***Compaction behavior of powder mixtures with focus on the variation of the tablet relative density (advanced version)***
  Nicolaos D. Gentis, Branko Vranic and Gabriele Betz (2010), 7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Valetta, Malta, March 2010

- ***Compaction behavior of powder mixtures with focus on the variation of the tablet relative density (first edition)***
  Nicolaos D. Gentis and Gabriele Betz (2010) Annual Research Meeting, Pharmazentrum, University of Basel, Switzerland, January, 28th 2010

- ***Technological and Mechanical Properties of three types of microcrystalline cellulose***
  Vincenzo Balzano, Nicolaos D. Gentis, Maxim Puchkov, Gabriele Betz, Hans Leuenberger (2006) 5th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Geneva, Switzerland, March 27-30 2006.

ACTIVITIES IN PROFESSIONAL AND STUDENT ORGANIZATIONS

- FIP (International Pharmaceutical Federation) and YPG (Young Pharmacists Group)
- AAPS (American Association of Pharmaceutical Scientists)
- DIA (Drug Information Association)
- asep (Swiss Pharmaceutical Students Association): Active delegate 2001-2010
- EPSA (European Pharmaceutical Students Association):
  Parliamentarian and Liaison Secretary 2005-2010