Soft tabletting of MCC 102 and UICEL-A/102 pellets into Multiple Unit Pellet Systems

Inauguraldissertation

zur
Erlangung der Würde eines Doktors der Philosophie
vorgelegt der
Philosophisch-Naturwissenschaftlichen Fakultät
der Universität Basel

von

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aus Manfredonia (Italien)

Basel, 2009

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät
auf Antrag von

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und
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Basel, den 5. Februar 2008

Professor Dr. H-P Hauri
Dekan

Ai miei genitori, Raffaele Balzano e Addolorata De Cristofaro

Danksagung

Die vorliegende Dissertation entstand unter der Leitung von Prof. Dr. Hans Leuenberger und Dr. Gabriele Betz an der Universität Basel, im Departement für Pharmazeutische Wissenschaften, Industrial Pharmacy Lab.

In erster Linie möchte ich meinem Doktorvater, Prof. Dr. Hans Leuenberger, für die einmalige Gelegenheit solch einer spannenden Dissertation herzlich danken. Seine anregende Einstellung zu meiner Arbeit sowie die grosse Hilfe bei der Konzipierung und Planung der Experimente waren absolut entscheidend. Meiner Dissertationsleiterin, Frau Dr. Betz, danke ich sowohl für das heitere, angenehme und frei denkende Klima, das im Labor herrschte, als auch für die Unterstützung bei der Durchführung der Experimente. Auch in den schwierigsten Momenten konnte sie mich durch ihren unermüdlichen Glauben an mich und anhand ihres goldenen Humors wieder aufmuntern.
Herzlich danke ich PD Dr. Peter Van Hoogevest für das Korreferat dieser Dissertation.

Mein herzlicher Dank gilt der Mepha Pharma AG für die finanzielle Unterstützung.

Ein grosser Dank gebührt allen Arbeitskollegen des Industrial Pharmacy Labs: Dr. K. Chansanroj , E. Hadzovic, G. Kimura, Dr. E. Krausbauer, H. Myojo, M. Pašić, Dr. M. Puchkov, M. Rumman, M. Saeed, S. Šehić, H. Yamaguchi. Die menschliche und berufliche Interaktion mit verschiedenen Sprachen, Kulturen, Religionen und Weltanschauungen galt mir als grosses Erlebnis.
Dankend erwähne ich die Mitassistenten des Praktikums fester Arzeneiformen: Dr. K. Chansanroj, Dr. M. Lanz, T. Meyer, F. Müller, Dr. M. Plitzko, Dr. S. Reitbauer, M. Saeed, S. Sehic.
Zu grossem Dank bin ich gegenüber den von mir betreuten Masterstudent(innen)en N. Gentis, A. Guerra und S. Eisenhardt verpflichtet, die mit ihrer Begeisterung und Motivation meine Arbeit massgeblich bereichert sowie entlastet haben.

Un particolare ringraziamento va agli amici che mi hanno sostenuto nei momenti più difficili: A. Carlucci, D. Ghisetti, N. Panday, G. Spennacchio. Ringrazio infine di cuore i miei genitori, Raffaele Balzano e Addolorata De Cristofaro, mia sorella Mariapia, mio fratello Paolo e tutti i miei nipoti per la stima, la fiducia e l'affetto incondizionati.

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Abbreviations

AI:	Active Ingredient
API:	Active Pharmaceutical Ingredient
BCS:	Biopharmaceutical Classification System
BET:	Equation of Brunauer, Emmet and Teller
CLSM:	Confocal Laser Scanning Microscopy
CRT:	Cathode-Ray Tube
DP:	Degree of polimerization
FDA:	Food and Drug Administration
GAP	Distance between upper and lower punch (Presster™ Compaction Simulator)
GIT:	Gastro-intestinal tract
HR:	Hausner Ratio
MC:	Moisture Content
MCC:	Microcrystalline Cellulose
MCC pellets:	MCC 102 pellets
MFT:	Minimum Film-forming Temperature
MUPS:	Multiple Unit Pellet Systems
Mw:	Molecular weight
n.a.:	not applicable
PVP:	Polyvinylpirrolidone
rpm:	rounds per minute
SD:	Sodium Diclofenac
sd:	standard deviation
SEM:	Scanning Electron Microscopy
STAVEX:	STAtistische Versuchsplanung mit EXpertensystem
TEC:	Triethyl citrate
UICEL:	University of Iowa Cellulose (in the whole work UICEL synonym of UICEL-A/102)
USP:	United States Pharmacopoeia
v/v %	Percentage by volume
w/w %	Percentage by weight

0. Abstract

Multiple Unit Pellet Systems, widely known as MUPS, are tablets consisting of spherical, granular subunits (pellets). Thanks to their prompt disintegration into the single subunits immediately after administration, they transit shortly in stomach and promptly disperse across the huge surface area of the small intestine stabilizing the overall bioavailability and reducing the risk of dose dumping and local irritations. If until two decades ago pellets were exclusively filled into hard gelatine capsules, they represent nowadays the ideal subunits for multiparticulate tablets. In fact, MUPS present all the advantages of the production of tablets compared to capsules: lower production costs, higher production rates, reduced risk of tampering, lower tendency of adhering to oesophagus during swallowing and better patient compliance. Despite this, the compaction of pellets into tablets is a complex technology: MUPS must be robust enough but still disintegrate into their subunits within short time, and, not less importantly, they should retain the dissolution profile of the original subunits. At this scope, the pellets should undergo a soft compaction, without breakage of the pellet coating layer nor formation of matrix tablets. Such ideal MUPS may be strived optimizing the proportions between three crucial factors: the pellet cores, the coating materials and the embedding excipients. Not many studies have focused so far on the simultaneous optimization of these three variables.

Cellulose, and in particular microcrystalline cellulose, is one of the major excipients in solid dosage formulations. It presents four polymorphic forms, out of which the form I and II have pharmaceutical relevance. The form I, which behaves plastically when compressed, is extremely widespread as a filler-binder for MUPS. Unfortunately, it does not possess prevalent disintegration properties, so that a disintegrant must be added if prompt disintegration is strived. Kumar et al. developed a new Cellulose II pharmaceutical aid named UICEL-A/102 through alkali treatment of Avicel PH 102 and successive hydrolysis with ethanol and oven dry. So far, UICEL-A/102 has been extensively studied as potential multifunctional excipients (filler and disintegrant) in tablet formulations, whereas its employing as a multifunctional excipient in MUPS has been not yet investigated.

The aim of this study was on the one hand the multifactorial investigation of crucial parameters involved in the compaction of pellets into MUPS, on the other hand the evaluation of the suitability of UICEL-A/102 as filler in two different kind of pellets formulations for MUPS (homogeeous pellets from direct pelletization, inhomogeneous pellets from dry powder layering). In the end, a robust technology for UICEL-A/102 MUPS production was suggested and discussed.

To this scope, MCC 102 (Cellulose I) and UICEL-A/102 (Cellulose II) were compared as pellet filler and embedding excipients in MUPS for controlled release. In the first part of the study, MCC 102 and UICEL-A/102 were separately mixed with Sodium Diclofenac, directly pelletized, coated with Kollicoat® SR 30 D to 20% w/w weigth gain and compacted into MUPS. In the second part of the study, a binary mixture of MCC 102 or UICEL-A/102 and Sodium Diclofenac was layered on neutral cores (Suglets® or Cellets®), in order to produce inhomogeneous pellets by means of dry powder layering technology. These pellets were then coated and compacted into MUPS according to the same procedure employed for the previous pellet batches.

In the case of homogeneous pellets of either MCC 102 or UICEL-A/102, the MUPS formulations overcame compaction deformed rather than ruptured, as proved by comparison between the dissolution profiles and the SEM and CLSM images before and after compaction. Both MCC 102 and UICEL-A/102 MUPS resulted to be mechanically robust (crushing strength of 70-100 N), fast disintegrating in water (≤ 3 min) and maintained the same release profile and almost the same superficial and inner morphology of their uncompressed subunits.
Compared with MCC pellets, UICEL-A/102 pellets proved to be generally less spherical and more porous. Nonetheless, they could be homogenously coated and also retained their dissolution profile after compaction into MUPS. The fact that UICEL-A/102 pellets and MUPS presented shorter dissolution times than their MCC counterparts is to ascribe to the prevalent swelling properties of UICEL-A/102. In fact, UICEL-A/102 contained in pellets sped up their dissolution independently of the amount and homogeneity of their coating layer.
The multifactorial evaluation of selected parameters (drug loading amount in pellets, type and quantity of filler in pellets, type of disintegrant in MUPS) on response variables (disintegration and dissolution time) brought to an interesting conclusion: UICEL-A/102 was on the one hand favourable filler and disintegrant for immediate disintegration, on the other hand it proved to be unsuited as filler in pellets for extended release. MCC 102 MUPS, conversely, were appropriately delayed formulations, mainly due to retention of their subunits characteristics.

In the case of inhomogeneous pellets, only UICEL-A/102 pellets proved to be favourable subunits; in fact, MUPS made of UICEL-A/102 pellet featured pretty good robustness (crushing strength of 90-120 N) and rapid disintegration (disintegration time ≤ 12 min), whereas MUPS made of MCC 102 were too compact (200-300 N) and did not disintegrate before 50 min. This dichotomy was put in relation with the fact that UICEL-A/102 coated and uncoated pellets were less compact and more porous than their MCC 102 counterparts. In addition, the choice of Cellets® rather than Suglets® as basic neutral cores in dry powder layering had a significant impact on the characteristics of UICEL-A/102 MUPS. In fact, UICEL-A/102 MUPS whose

subunits had Cellets® cores retained the release profile of their uncompressed subunits more then their counterparts having Suglets® as subunit cores. This suggests that subunits with a MCC core contributed significantly to the softness of the compaction, this difference being associable with a plastic behaviour of Cellets® in contrast with the rather elastic behaviour of Suglets® during compaction.

On the one hand, it can be claimed that dry powder layering produced UICEL-A/102 pellets with less prevalent disintegration properties, which were therefore more suitable for controlled release MUPS. On the other hand, the presence of a hard core in those pellets favored the partial rupture of their coating layer during compaction, resulting in a faster drug release after compaction, especially in the case of Suglets® as non pareils.

Actually, the pellets produced via dry powder layering contained proportionally less UICEL-A/102 than their homologous prepared via direct pelletization (20% vs. 60% w/w). This means that the use of UICEL-A/102 as unique multifunctional excipients is rather suggested in pellets and MUPS for immediate release, while its employing as layering excipients on neutral core is very promising in the development of MUPS for extended release.

1. Introduction

MUPS (Multiple Unit Pellet Systems) are multiparticulate pellet formulations that, easily administered as tablets, disintegrate into their subunits directly after swallowing, so as to disperse into their subunits across the stomach and the small intestine. This behaviour accounts for a more constant bioavailability and contributes to the minimization of dose-dumping and local irritation risks.

Until two decades ago pellets used to be filled into hard gelatine capsules. Since 1990, Beloc-Zok®, Antra*mups*®, Nexium® and many others Multiple-Unit-Tablets have been flooding the pharmaceutical market, due to their low production cost and high production rate, reduced risk of tampering (Celik, 1994), low tendency of adhering to oesophagus during swallowing and high patient compliance (Davis et al., 1984), (Gebre-Sellassie, 1994).

Although they represent nowadays a first choice formulation, MUPS do not really constitute a straightforward option. In fact, the compaction of coated pellets into MUPS is a complex process, in which the subunits undergo structural deformation or even ruptures (Kuehl et al., 2002). This may profoundly modify the drug release profile of the subunits and/or circumvent the tablet disintegration because of enhanced cohesion between pellets (Schmidt et al., 2001), (Wagner et al., 1999b), (Béchard et al., 1992). Briefly, on the one hand pellet compacts need to have a certain crushing strength to withstand the mechanical shocks encountered in their production, packaging and dispensing; on the other hand, the tabletting process must be soft enough to enable the compacts to disintegrate promptly in their subunits after administration maintaining the drug release profiles of the subunits (Kuny, 2004), (Sawicki, 2005).

Such an ideal compromise should be strived optimizing the proportions between three crucial factors: the pellet cores, the coating materials and the embedding excipients.

The pellet cores, produced either through wet granulation of an homogenous mixture of active-filler or through dry powder layering of a mixture active-filler on MCC or sugar starter cores (Riedel, 2005), should feature a sufficiently high crushing strength so as not to get deformed or ruptured during compaction (Beckert, 1996). Also the coating agents have been extensively studied in recent years. Ethyl cellulose coated pellets were claimed not to be flexible enough to withstand compaction undamaged (Bodmeier et al., 1994); Lehman et al. achieved compaction of pellets coated with different types of Eudragit® (acrylic polymers) without significant damage (Lehmann, 1994); Dashevsky et al. asserted that pellets coated with Kollicoat® SR 30D are significantly softer than those coated with Kollicoat® MAE 30 DP and Kollicoat® EMM 30 D (Dashevsky, 2004), (Dashevsky, 2005), (Johansson, 1995a).

The embedding excipients, however, should be more deformable than the core excipients, as they should cushion the pellets by absorbing the mechanical stress during compaction (Lundqvist, 1998), (Bodmeier, 1997), (Santos, 2005). Furthermore, they should build a supporting structure in which the subunits may be homogeneously dispersed (Wagner et al., 1999a) providing the final tablets with appropriate mechanical strength and rush disintegration properties (Aulton et al., 1994b).

As the main component of cell walls in higher plants (wheat straw, wood, cotton, flax, hemp, jute, ramie) and one component of bacteria, fungi and algae, Cellulose is the most prevalent biopolymer in the world. Being renewable, biodegradable and biocompatible, cellulose represents the ideal excipient in solid pharmaceutical formulations. It exists in four major polymorphic modifications (cellulose I, II, III, IV), which can mutually interconvert by specific chemical and thermal treatments (Kono et al., 2004). The transition from lattice I to lattice II is realized by mercerisation of Cellulose I (soaking in highly concentrated NaOH followed by recrystallisation upon washing). Most of the experts convey that this transition is irreversible and that cellulose II is the thermodynamically more stable form (Lanz, 2005).
The polymorphs I and II are the most important forms. The crystalline structure of cellulose I and II vary in two main characteristics: The unit cell dimension and the polarity of the chains (Gardner et al., 1974), (Kolpak et al., 1976). This accounts for different wettability and disintegration properties of cellulose I and II excipients.
In particular, microcrystalline cellulose (MCC), cellulose I powder, is the most widely used filler-binder for direct compression. Unfortunately, it does not possess prevalent disintegration properties, so that a disintegrant must be added if an immediate release formulation is strived.
Kumar et al. developed a new Cellulose II pharmaceutical aid named UICEL-A/102 (synonym UICEL PH 102) through alkali treatment of Avicel PH 102 and successive hydrolysis with ethanol and oven dry (Kumar, 2002). Furthermore, UICEL-XL was produced by incorporation of glutaraldehyde, polyaldehyde, or polycarboxylic acid as a cross-linking agent into UICEL-A/102. Reus- Medina et al. compared the compression properties of UICEL-A/102 and UICEL-XL in the perspective of their employment as multifunctional excipients (filler and disintegrant) in tablet formulations (Reus-Medina, 2004), (Reus-Medina, 2005). These studies also suggest UICEL-A/102 as a potential aid in the manufacturing of MUPS (Reus-Medina et al., 2006).

2. Theoretical section

2.1 Cellulose I and Cellulose II excipients

"Used the longest, known the least": this statement is extremely appropriate for cellulose (Kryszewski, 2002). Cellulose is the most abundant biopolymer as the main component of cell walls in higher plants (wheat straw, wood, cotton, flax, hemp, jute, ramie) and one component of bacteria, fungi and algae. Being renewable, biodegradable and biocompatible, it is the ideal excipient in solid pharmaceutical formulations. The structure of cellulose can be divided into three levels (Klemm, 1998): i) the molecular level, ii) the supramulecular level and iii) the morphological level.

Figure 2.1: From wood to cellulose

2.1.1 The molecular structure of cellulose

In 1838, the French botanist Anselme Payen (Payen, 1838) isolated for the first time cellulose from wood, but no sooner than one century afterwards Freudenberg and Haworth managed to reveal independently the structure of cellulose on a molecular level (Freudenberg, 1928a), (Freudenberg, 1928b), (Haworth, 1928).

Cellulose is an unbranched, linear syndiotactic (e.g. A-A'-A-A') homopolymer composed of D-anhydroglucopyranose (A) units, which are linked together by β(1-4)-glycosidic bonds. The dimer cellobiose (C) is the basic unit, thus cellulose may be considered as an isotactic polymer of cellobiose (C-C-C). n stands for the total number of anhydroglucose units in the molecular structure of cellulose (see Figure 2.2) and corresponds to the degree of polymerisation (DP). Native cellulose has degrees of polymerisation higher than 10'000 (Gralen, 1943). Isolated and processed celluloses have degrees of polymerization around 200 for microcrystalline cellulose and between 700 and 1000 for powdered cellulose (Doelker, 1993), (Doelker, 1987), (Schurz, 1976).

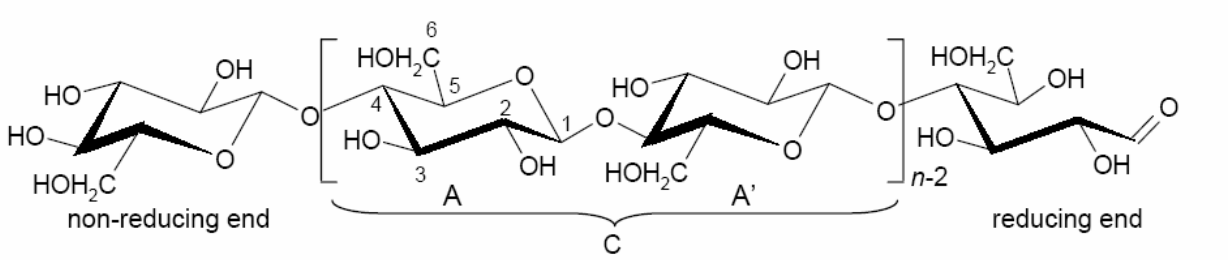


Figure 2.2: Molecular structure of cellulose. C: cellobiose; A, A': anhydroglucose unit [1].

2.1.2 The supramolecular structure of cellulose

Before the molecular structure of cellulose was elucidated, Nägeli presumed that the cell walls consisted of crystalline particles (micelles) embedded in an intermicellar substance (see Figure 2.3) (Hearle, 1963). Staudinger disproved this assumption by measuring the viscosity of different polymer solutions: the molecular weight of cellulose was higher than expected according to Nägeli's calculations (Staudinger, 1936). Staudinger's studies suggested that polymers constituted continuous crystals distorted in their ends (see Figure 2.3 B) (Staudinger, 1932). A harmonisation of these two contrasting models led to the fringed-micelles theory: The cellulose structure was divided into crystalline and non-crystalline regions, each single molecule being short enough to pass through both regions (see Figure 2.3 C). Hearle proposed a variation of this theory called fringed-fibrils. He considered the crystalline regions as fringed fibrils with various ramifications along their length (see Figure 2.3 D). The interlinked fibrillar network of fringed fibrils was referred to as microfibrils reaching an approximate length of few micrometers. This model, corroborated by photographs obtained by scanning electron microscopy (SEM) and X-Ray measurements, corresponds to the generally accepted theory. As a result, the concept of microfibrils might be considered as basic level of the structural organisation of cellulose.

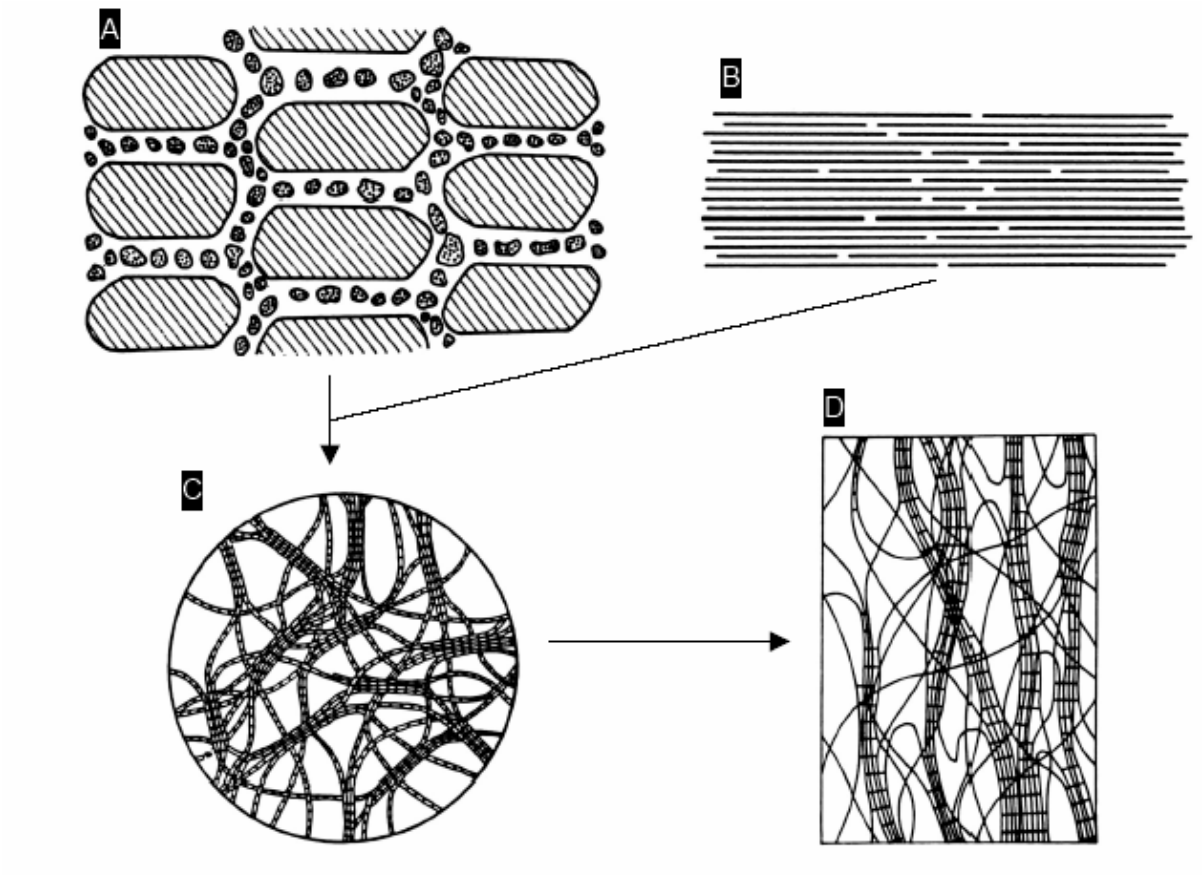


Figure 2.3: Various models for the supramolecular structure. A: micelle structure according to Nägeli; B: continous structure of crystalline structure according to staudinger; C: fringed.micelles; D: fringed-fibrils according to Hearle [1].

2.1.3 Relevance of Polymorphism

It is well known that about 50% of all drug substances show polymorphism, which is the tendency of a substance to exist in more than one crystalline form. As different polymorphic forms display diverse physicochemical properties (solubility, wettability, melting point etc.), the polymorphic form can play a role in the quality of a drug product (bioavailability and stability, shelf life). In contrast with the attention paid to the polymorphism of drug substances (e.g. carbamazepine, spieperone, tamoxifen citrate, etc.), hardly any studies investigated the polymorphism of excipients, despite the impact of this variable on the quality of the drug product. This can be illustrated by a few examples: i) α-lactose monohydrate is reported to be suitable for wet granulation, while the anhydrous α and β forms are preferably used for direct compression (Concheiro, 1987),(Giron, 1990),(Fell, 1970);

ii) D-mannitol exists in three polymorphic forms (α, β and γ) (Botez, 2003) presenting different compressibility and compactibility (Burger, 2000). No plolymorphic transition could be observed under pressure (Debord, 1987). However, a moisture-induced polymorphic transition from δ to β can occur during a wet granulation process (Yoshinari, 2002), (Yoshinari, 2003).

2.1.4 Polymorphism of the crystalline regions in cellulose

Extracted mainly from wood pulp, cellulose is the most common organic polymer and it is widely used as a raw material to prepare a large number of excipients. It is an extensive, linear-chain homopolymer generated from repeating 1, 4-linked β-D-glucose molecules.

Cellulose exists in four major crystal modifications, cellulose I, II, III, IV. The polymorphic forms can be interconverted according to Figure 2.4 mostly by certain chemical and thermal treatments (Kono, 2004).

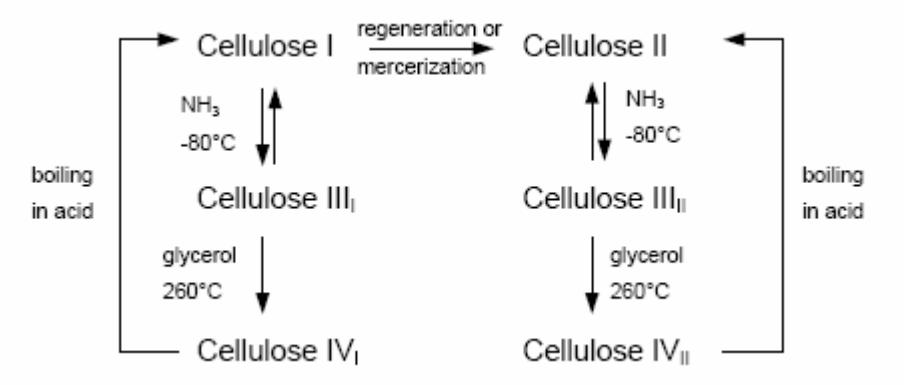


Figure 2.4: Interconversion of cellulose polymorphs [1].

As excipients in pharmaceutical dosage formulations, Cellulose I and II are the most important polymorphs. Cellulose I, also called native cellulose, is the most prevalent polymorph and paradoxally also the thermodynamically least stable. It exists as a mixture of I_α and I_β forms (Atalla, 1984), their mutual ratio depending on the origin of cellulose; in fact, the phase I_α mainly characterizes the cellulose from primitive organisms (bacteria, algae etc.), whereas the phase I_β is more prevalent in the cellulose from higher plants (wood, cotton, ramie etc.) (VanderHart, 1984). Cellulose II, on the other hand, is the most stable structure of technical relevance; it is produced by a mutant strain of glucanoacetobacter xylinum or by mercerization or regeneration from cellulose I (Reus-Medina, 2004),(Klemm, 2005).

Mercerization involves soaking of cellulose I in highly concentrated NaOH to form Na-Cellulose, followed by recrystallisation of cellulose II upon washing. Regeneration consists in dissolving cellulose in an appropriate solvent and reprecipitating it in water. The lattice transition from cellulose I to cellulose II starts using NaOH > 10% and is complete when employing NaOH > 15%, which accounts for the crucial role of the base strength. Most of the experts convey that this transition is irreversible and that cellulose II is the thermodynamically more stable form (O'Sullivan, 1997), (Langan, 2001). It has been recently reported that cellulose II can be produced by the *Acetobacter xylinum* at low temperatures (Hirai, 1997), and by the alga Halicystis (Sisson, 1938).

The crystalline structure of cellulose I and II varies in three main characteristics: The unit cell dimension, the hydrogen bond network and the polarity of the chains. The elucidation of the unit cell dimensions proposed by Meyer, Mark and Misch for cellulose I and by Andress (Andress, 1929) for cellulose II are the most widely accepted. The two unit cells are depicted in Figure 2.5.

polymorphic form	author	*a* [nm]	*b* (fibre axis) [nm]	*c* [nm]	*β*
cellulose I	Meyer, Mark, Misch	0.835	1.03	0.79	84°
cellulose I	Andress	0.823	1.03	0.784	84°
cellulose II	Andress	0.814	1.03	0.914	62°

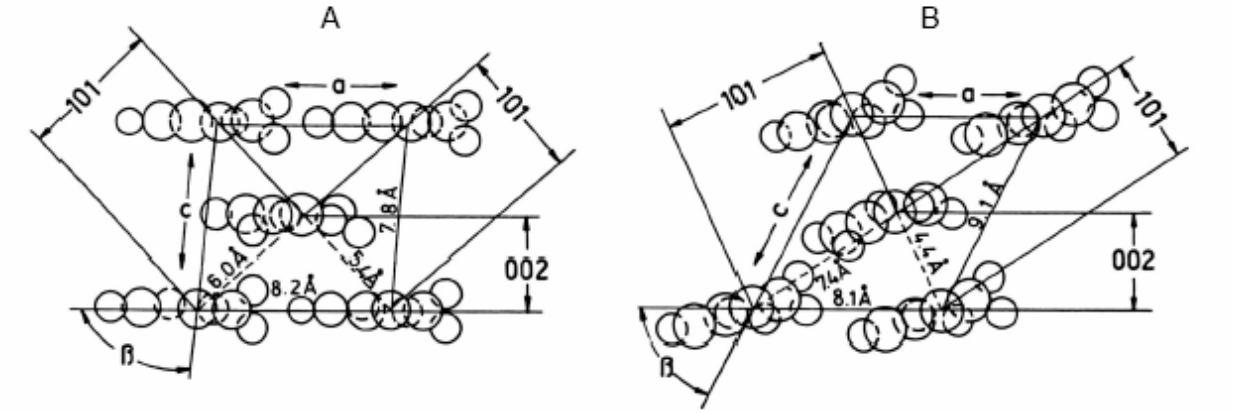


Figure 2.5: The unit cells of cellulose I (A) and cellulose II (B) in projection along the fibre axis b according to Andress with their dimensions [1].

As one cellulose molecule, also one cellulose chain can have either reducing or non reducing end. If all chains are packed homogenously, i.e. with the reducing ends on the same side, their arrangement is referred to as parallel, otherwise they are packed antiparallely. If the parallel arrangement of cellulose I is widely accepted (Sarko, 1974), (Gardner, 1974), the question whether the arrangement of cellulose II be parallel (Maurer, 1992), (Kroon-Batenburg, 1996), antiparallel (Langan, 2001), (Sarko, 1974), (Kolpak, 1976) or mixed is still open for discussion. Most scientists convey anyway that Cellulose II features antiparallel packing, which accounts also for its higher wettability and disintegration properties.

At a macromolecular level, the main differences in the chains arrangement in Cellulose I and II are shown in Figure 2.6. The differences in cell unit and chain polarity produce a totally different hydrogen bonding network, which could be observed with the advent of X-Ray diffraction (under 0.25 nm). Blackwell et al. suggested that cellulose II be tighter packed than cellulose I (Blackwell, 1977). In fact, the average length of the hydrogen bonds is shorter in cellulose II (0.272 nm) than in cellulose I (0.280 nm). Molecular modeling simulations have recently proved that cellulose II present more intermolecular hydrogen bonds than cellulose I, while cellulose I possess more intramolecular hydrogen bonds than cellulose II.

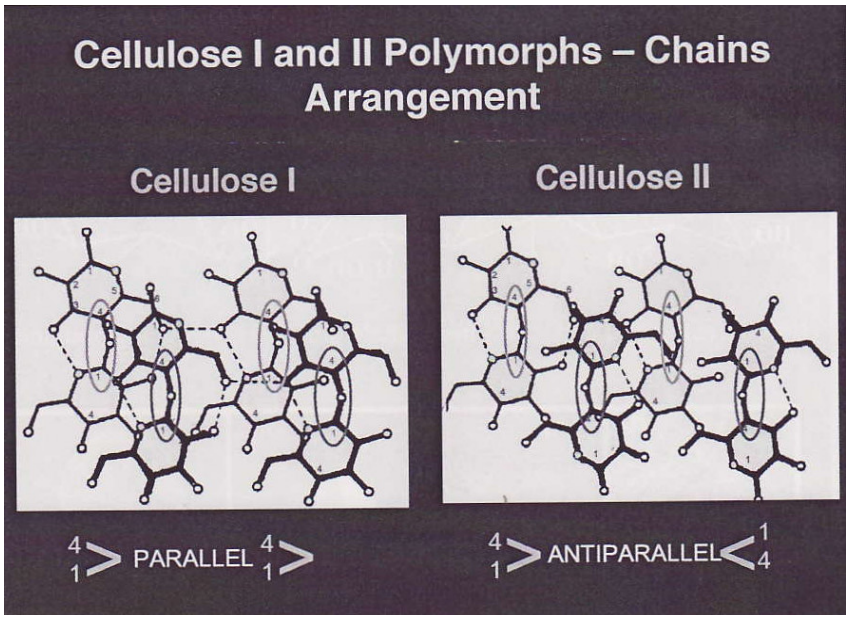


Figure 2.6: Chains arrangements in Cellulose I and II [2].

2.2 Microcrystalline cellulose

Cellulose derivatives are important pharmaceutical excipients and they are produced from wood by washing, bleaching, purifying, and drying. Microcrystalline cellulose (MCC), the most widespread filler for direct compaction, is manufactured by acid hydrolysis of native α-cellulose with subsequent neutralization and removal of amorphous regions and impurities. It shows the cellulose I polymorphic form, and it possesses accordingly a higher degree of crystallinity.
MCC is primarily used as a binder/diluent in oral tablet and capsule formulations, either as powder or in granulated form; its additional lubricant and disintegrant properties make it a versatile tabletting aid. MCC constitutes also the most important excipient in extrusion processes (Wallace, 1991),(Newton, 2002).

The fist commercial MCC came onto the market in 1964 under the brand name Avicel® PH by FMC Corporation (Philadelphia, PA). MCC is in the meanwhile available from different vendors under various trade names; however, Avicel® PH, which is available in nine grades depending on the moisture content and the mean particle size distribution, is still the most diffused (Table 2.1), (Friedler, 2002).

Table 2.1: Nine grades of Avicel® with respective moisture content and mean particle size [3]

Avicel®	**PH 101**	**PH 102**	**PH 102 SCG**	**PH 103**	**PH 105**	**PH 112**	**PH 200**	**PH 301**	**PH 302**
Moisture content [%]	< 5	< 5	< 5	< 3	< 5	< 1.5	< 5	< 5	< 5
Mean particle size [µm]	50	100	130	50	20	100	190	50	100

2.3 UICEL

Recently, the preparation and characterization of a new cellulose-based pharmaceutical aid has been reported and patented (Kumar et al., 2004). This new cellulose - named UICEL after the University of Iowa where it was developed - was obtained treating cellulose I powder (Avicel® PH 102) with an aqueous solution of sodium hydroxide (conc. ≥ 5N) and subsequently precipitating it with ethyl alcohol (Kumar, 2002). Four type of UICEL were isolated so far: UICEL-PH by oven dry, UICEL-XL by incorporation of glutaraldehyde as cross-linking agent, UICEL colloid by water-homogenization and UICEL beads by spray-dry (see Figure 2.7).

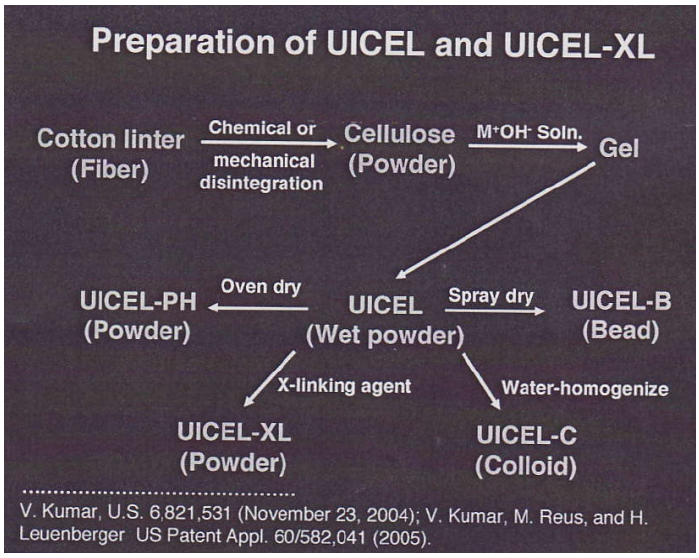


Figure 2.7: Mutual transformation of cellulose polymorphs [2].

Compared with Avicel® 102, all UICEL types feature lower crystallinity degree, higher water affinity, higher true density and accordingly lower porosity and specific surface area, and not the least prevalent disintegration properties (http://www.freepatentsonline.com/20050287208.html). UICEL is therefore suitable as a binder, filler and/or disintegrant in the development of solid dosage forms.

2.3.1 Characteristics of Avicel® PH 102 (MCC 102) and UICEL-A/102

Kumar et al. compared the technological characteristics of Avicel® PH 102 and UICEL-A/102 in terms of powder, tabletting and disintegration properties (Kumar, 2002). According to its scanning electron microscopy images, UICEL-A/102 appears as mixture of aggregated and non-aggregated fibres, whereas Avicel® PH 102 shows an aggregated structure with coalesced boundaries. In addition, UICEL-A/102 particle size distribution is slightly lower than Avicel® PH 102. These differences in morphology and particle size are to ascribe to the different manufacturing conditions: Avicel® PH 102 is prepared by spray drying, UICEL-A/102 by chemical hydrolysis.

The two cellulose excipients also differ in the degree of crystallinity: UICEL-A/102 shows a crystallinity of 47-57%, while Avicel® PH 102 crystallinity amounts to about 77%. This is due again to a different arrangement of the cellulose chains: in UICEL-A/102 the cellulose chains are arranged in an anti-parallel manner, in Avicel® PH 102 in a parallel manner, which leads to different interchain and intrachain hydrogen bonding networks, and consequently, to a different degree of crystallinity.

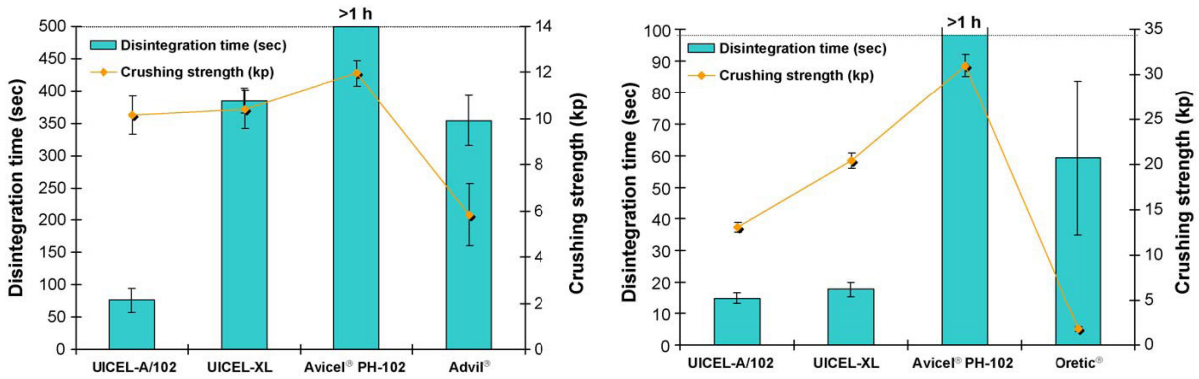
Accordingly with its non-aggregated structure, UICEL-A/102 is less porous and shows higher bulk and tap densities compared to Avicel® PH 102. Furthermore, its lower degree of crystallinity causes more hydroxyl groups to be freely accessible to water molecules and enhances its moisture content. The same phenomenon can also be advocated to explain the far lower disintegration time of UICEL tablets (15 s) in comparison to Avicel® PH 102 tablets (12 hours) (Kumar, 2002).

Regarding the flowability, UICEL-A/102 is slightly less flowable than Avicel® PH 102, because of its fibrous structure, which facilitates particle entanglements. The former is also less ductile and less plastic than the latter, as it has a higher tendency to elastic recover after compaction. As a result, UICEL-A/102 tablets are thicker than Avicel® PH 102 tablets at constant compaction force.

2.3.2 Technological properties of Avicel® PH 102, UICEL-A/102 and -XL

Reus-Medina et al. investigated the technological characteristics of Avicel® 102, UICEL-A/102 and UICEL-XL tablets loaded with two model drugs (hydrochlorothiazide, HCTZ and ibuprofen, IBU) in comparison with analogous tablets available on the US market (Advil®, Oretic®) (Reus-Medina, 2006). The major results of this study are listed in Figure 2.8. The crushing strengths of HCTZ tablets decrease in the order Avicel® PH-102 > UICEL-XL, UICEL-A/102 > Oretic® and of IBU tablets in the order Avicel® PH-102 ≥ UICEL-XL, UICEL-A/102 > Advil®. Oretic® tablets disintegrate in about 60 s, while Avicel® PH-102 tablets remain intact during 1 h test period. On the other hand, the IBU tablets make using UICEL-A/102 disintegrated the fastest, UICEL-XL and Advil® tablets the next, and Avicel® PH-102 tablets remained intact. These results, together with the results of friability and drug release, conclusively show that UICEL-A/102 and UICEL-XL have the potential to be used as filler, binder and disintegrant - all-in-one - in the design of tablets containing either low dose or high dose drug by the direct compression method.

So far, no investigations about the potential employement of these new pharmaceutical aids in granulation/pelletization and tabletting were carried out.



Compositions of model hydrochlorothiazide and ibuprofen tablet formulations

Ingredients	HCTZ formulation	IBU formulation
Drug (mg)	25	300
Cellulose excipient[a] (mg)	272	195
Stearic acid (mg)	3	5
Tablet weight (mg)	300[b]	500[c]

[a] UICEL-A/102, UICEL-XL and Avicel® PH-102.
[b] Tablet diameter was 11 mm.
[c] Tablet diameter was 13 mm.

Figure 2.8: Technological properties of UICEL-A/102 and UICEL-XL [4].

2.4 Pellets

In pure theory, tablets can be produced through direct compaction of powder mixtures of AI and appropriate excipients. Nonetheless, if very high drug contents are targeted, but the active is not sufficiently plastically deformable, an intermediate granulation is advisable. Granules, in fact, show better flowability as well as better tabletting properties than powders; an intermediate granulation minimizes therefore segregation, enhances dosing precision and contributes to increase the compactibility of any powder mass.

Pellets are a special form of granulates, characterized by a very regular, round shape, low porosity, smooth surface and a typical size range of 0.2-2mm. The definition can be expanded, however, to include all forms of multiparticulates, like drug-containing granules, drug crystals and minitablets (Porter et al., 2000). They can be obtained by direct size enlargement of primary particles, or size reduction from dry compacted material.

Depending on the drug distribution inside the pellets, they can be divided into homogeneous and inhomogeneous pellets. The former have the same composition in any part of their interior structure, whereas the latter typically present a MCC or sugar core on which one or more drugs are layered (“onion structure”, Figure 2.9).

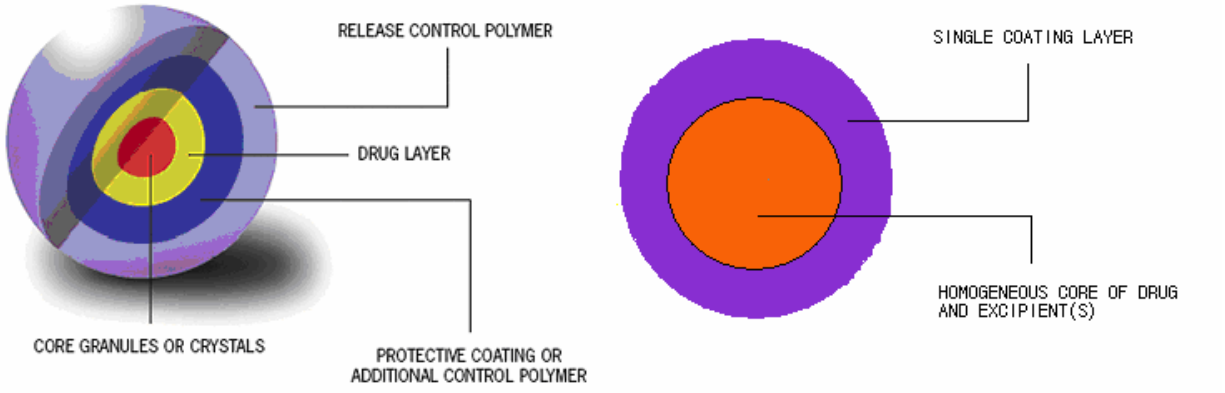


Figure 2.9: Section of an inhomogeneous (left) and a homogenous (right) coated pellet [5].

As a medicinal form, pellets have been developed in the middle of the twentieth century, and their importance has been gradually increasing thanks to the manufacturing improvements and their wide therapeutic advantages. A couple of decades ago they used to be filled into hard gelatin capsules, whereas nowadays they are increasingly compacted into tablets (Bodmeier, 1997).

Because of their small size, pellets behave like liquids, reducing the variations in gastric emptying and intestinal transit time as well as inter- and intrapersonal variability.
Pellets are frequently developed as modified release dosage forms to appropriately steer the drug release and absorption in the gastrointestinal tract. Under these conditions, the risk of dose-dumping and side effects is enormously reduced, whereas the drug plasma profile is held constant over a long period of time.
Moreover, pellets with different active ingredients, or the same AI with different release properties, can represent a versatile single unit dosage form for better patient compliance.

2.4.1 Bonding forces in agglomerates

In granules, the primary powder particles are bound together by physical forces. The magnitude of such forces depend on granule characteristics as the particle size, the morphology, the moisture content, plus the surface tension of the granulating liquid used.
The bonding forces can be classified into five categories (Ausburger, 1997),(Ghebre-Sellassie, 1989):

- Adhesion and cohesion forces caused by the immobile liquid (binding bridges)
- Interfacial forces and capillary pressure at freely movable liquid surfaces
- Solid bridges
- Attractive forces between solid particles
- Form-closed bonds or interlocking bonds

Binding bridges

Once sufficient moisture content has been reached, a thin, immobile adsorption layer covers the surface of the solid particles. The liquid layer reduces the distance between the particles and enhances their contact area and accordingly the intermolecular attractive forces. Immobile films of highly viscous binder solutions can generate exceptionally strong bonds, which own a higher strength than the bonds produced by mobile liquid layers.
Additionally, viscous binders tend to harden during the agglomeration process leading to extremely solid bridges.

Interfacial forces and capillary pressure at freely movable liquid surfaces

By addition of further granulating liquid, the surface film increases from thin layer to mobile liquid film. Mobile liquid films form bridges wherein capillary pressure and interfacial forces create strong bonds, which are a prerequisite for the formation of solid bridges.

Four different stages can be defined, depending on the moisture content of the granulation mass:

- pendular state
- funicular state
- capillary state
- droplet state

The *pendular state* occurs by low moisture content (between 0 and 13.6% v/v). Under these conditions water forms lens-shaped rings at the position of contact of the particles; however, the ratio of the liquid to the void volume is low and air is still the continuous phase (Figure 2.10). Particles are held together by the hydrostatic suction pressure at the liquid bridges and by the surface tension at the solid-liquid-air interface. At this time granules are still non-spherical, they have still a dry surface and a low density.

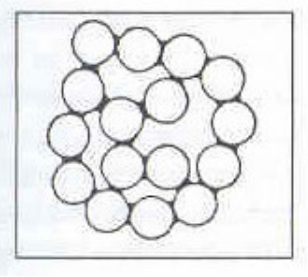


Figure 2.10: Pendular state

As the moisture content ranges between 13.6 and 100% v/v, the liquid becomes the continuous phase, in which pockets of air are still present. This state is known as *funicular state*. Granules become more spherical, the surface is still dry but the density is higher (Figure 2.11).

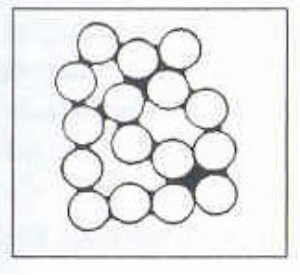


Figure 2.11: Funicular state

The *capillary regimen* shows spherical granules with a wet surface and a high density.
Every space between the particles is completely filled with liquid, which extends up to the edges of the pores at the surface forming a concave meniscus (Figure 2.12).

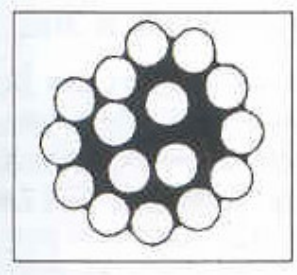


Figure 2.12: Capillary state

When the liquid completely envelopes the agglomerate, the *droplet state* is reached (Figure 2.13). A convex surface replaces the concave surface of the capillary state, the strength of the droplet is dependent only on the surface tension of the liquid phase, and there is no longer interparticle capillary bonding.

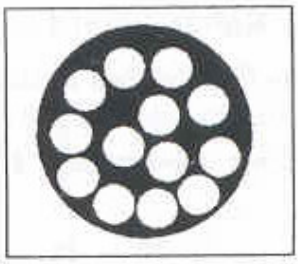


Figure 2.13: Droplet state

Solid bridges

Solid bridges between powder particles can occur as a result of different mechanisms: dissolved substances can crystallize out after the medium evaporation, binders can harden forming solid bridges, substances may melt out on the input of energy (by external source, from frictioning during agglomeration or from energy conversion) and solidify when cooled.
Solid bridges can also occur by sintering and chemical reaction, although these mechanisms are not common in the pharmaceutical industry.

Attractive forces between solid particles

Solid particles, when close enough, are attracted to each other by short range forces. These bonding forces do not play a crucial role in the building of the final product; despite this, they initially hold and orientate the particles in a contact region long enough for stronger forces to take over.

Attractive forces may be molecular (valence and Van der Waals), electrostatic or magnetic, where the former two are prevalent in pharmaceutical applications. Van der Waals dispersion forces are responsible for the adhesion occurring between particles less than 0.1 µm apart, so they are believed to make the most significant contribution to all intermolecular attractive effects.

Form-closed bonds

Mechanical interlocking might occur during the agitation and compression of fibrous, flat-shaped and bulky particles, leading to the formation of so-called form-closed bonds. Although they are a minor contributor to the pellet strength, they can anyway provide them with sufficient mechanical strength to put up with the mechanical stress caused by the elastic recovery following the compaction.

2.4.2 Pelletization technologies

Pelletization is the technical term describing the agglomeration of powder mixtures bulk drugs-excipients into pellets. The production of pellets can be realized using different technologies known as *layering, balling, compaction* and *globulation* (Ghebre-Sellassie, 1989).

Layering

Layering consists in the continuous addiction of powder particles on already preformed nuclei, such as nonpareil sugar seeds, MCC pellets, inter seeds, granules or crystals.

In *solution/suspension layering,* the binder liquid, in which powder particles are either dissolved or suspended, is atomized by a spray nozzle. After the droplets diffuse on the nuclei, the binder solution evaporates and the dissolved or suspended substance crystallize out forming a new layer (see Figure 2.14).

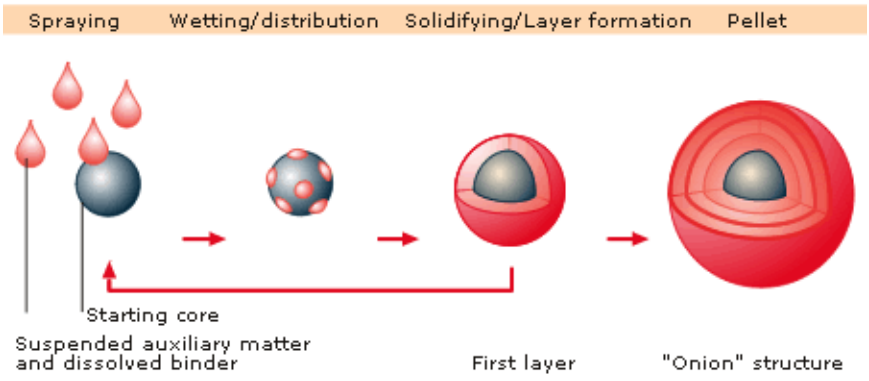


Figure 2.14: Principle of solution/suspension layering [6].

In dry powder layering, instead, the binder solution and the powder are added separately to the nuclei, in either intermittent or continuous way (Figure 2.15). An intermittent powder layering process is the result of several cycles: The layering solution is initially added until the bed is wet and tacky, and subsequently the powder is added till the bed is dry. The process continues until all the powder has been added.

In a continuous process, conversely, the layering solution and the powder particles are added simultaneously.

Since a smaller amount of binder solution is employed, the dry powder layering method requires lower processing times than the solution/suspension and it is particularly suited in case of water-sensitive or water-insoluble drugs or excipients.

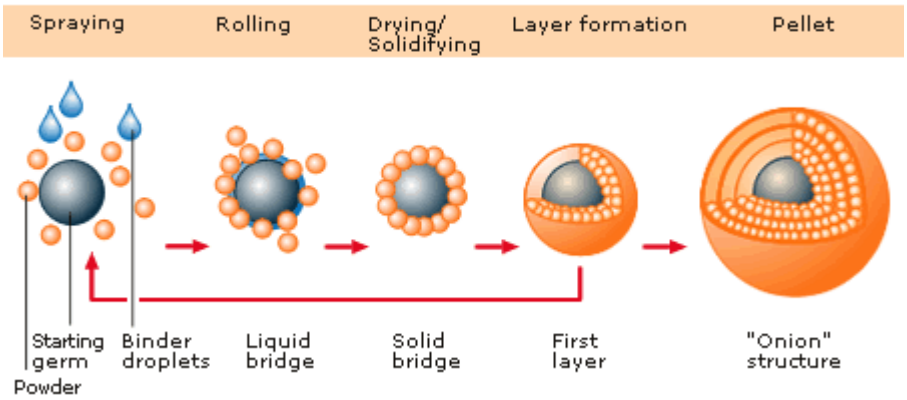


Figure 2.15: Principle of dry powder layering [6].

Balling

Pelletization by balling, widely known as direct pelletization, also involves binder solution spraying onto the powder particles. In this case the final pellet is obtained through nucleation, coalescence and layering of the starting powder particles. Nucleation describes the formation of liquid bridges between fine powder particles, leading to the formation of bigger particles (Figure 2.16); coalescence, on the other hand, is the formation of aggregates due to the random collision of already formed granules. This aggregation mechanism is facilitated by sufficient surface moisture and/or significant mechanical pressure.

The main disadvantage of this technology is the coexistence of different growth mechanisms, which makes it difficult to control the pellets growth. For this reason, pellets for pharmaceutical purposes are rarely produced by balling.

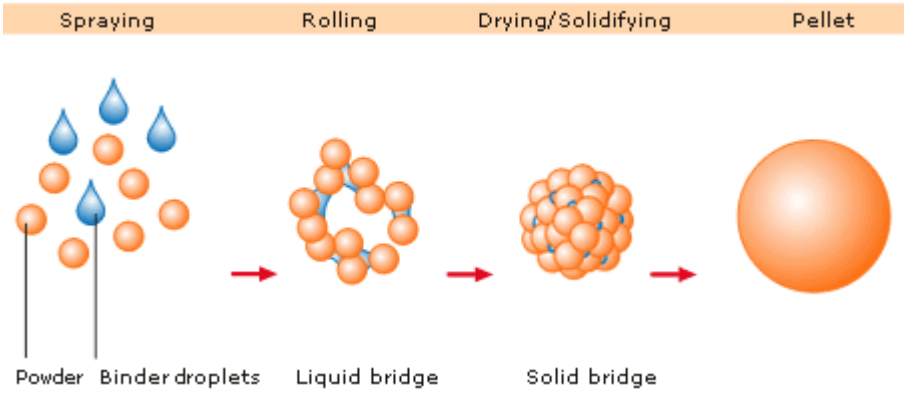


Figure 2.16: Principle of direct pelletizing method [6]

Compaction

Compaction is the general term for any pelletization technologies in which drug particles and excipients are forced together by a mechanical force.

Extrusion/spheronisation is one of the better known compaction technologies and is also referred to as Marumerizer® and Spheronizer® principle; it is a multiple step process, which leads to pellets with a typically narrow particle size distribution. The different steps are shown in Figure 2.17.

Initially, the binder solution is added to the powder mass until it reaches sufficient moisture to be pressed through a perforated roller compacter. The cylindrical extrudates fall directly onto a bowl equipped with a grooved rotating bottom plate. As a result of particles-to-particles and particles-to-equipment interactions, the extrudates break into smaller peaces and get subsequently smoothed and spheronized to pellets.

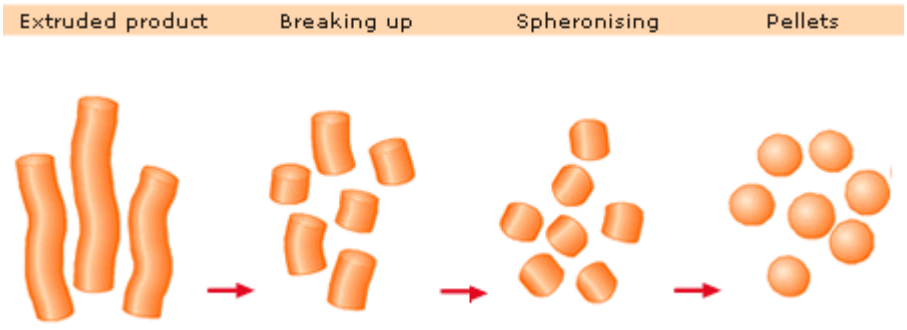


Figure 2.17: Principles of the extrusion/spheronisation method [6].

Globulation

The term globulation describes the process in which hot melts, solutions or suspensions are atomised to generate spherical pellets (Figure 2.18).

Pelletization by globulation can be achieved by either *spray drying* or *spray congealing*.

In the former method, the liquid evaporation from the atomised droplets is achieved by a hot gas stream, so that capillary forces in the droplet are gradually replaced by solid bridges; in the latter method, the atomised droplets are cooled below the melting point of the liquid, so that the congealed melts build solid bonds. As no liquid evaporation occurs, the pellets produced by spray congealing are generally more compact and less porous than those produced by spray drying.

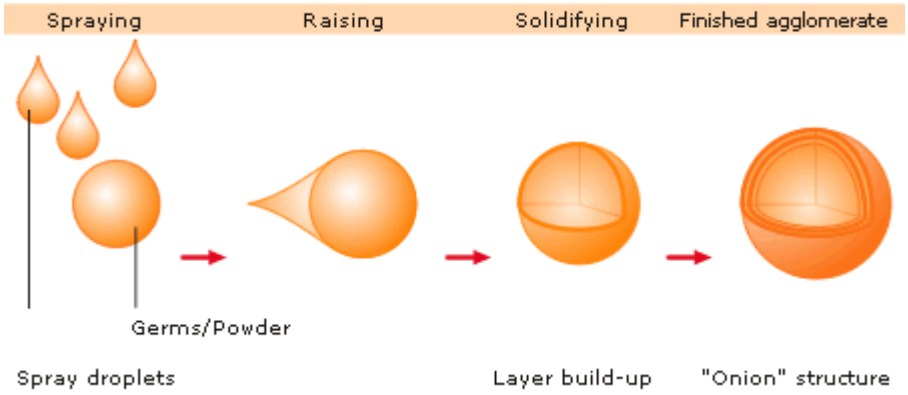


Figure 2.18: General principle of globulation[6].

2.4.3 Equipment for pelletization

This chapter focuses on the fluidized bed, which is also one of the equipments used in the practical section of this work.

2.4.3.1 Fluidized bed

Initially employed only for drying of fresh granules, the fluidized bed is nowadays extensively used for granulation (solution/suspension and dry powder layering).

The phenomenon of fluidization

When a packed bed of particles is subjected to a sufficient high upward flow of fluid (gas or liquid), the weight of the particles is supported by the drag force exerted by the fluid on the particles and the particles become freely suspended or fluidized. The behaviour of fluidized suspension is similar in many aspects to that of a pure liquid. Mass transfer and heat transfer rates between particles and submerged objects (e.g. heat exchanger tubes) is greatly enhanced in fluidized beds. In addition, rapid particle mixing allows uniformity in bed. As a result, fluidized bed are widely used for conducting gas solid reactions (coal combustion), gas solid catalytic reactions (catalytic cracking of petroleum), biotransformations (bioreactors) (Parikh et al., 1997), (Olsen, 1989).

In a liquid system, an increase in flow rate results in a smooth and progressive expansion on the bed. The particles are homogenously distributed through the bed, which state is called particulate fluidization or homogenous fluidization.

Gas-solid systems behave differently (Figure 2.19). Generally, an increase in flow rate beyond minimum fluidization (see next section) gives rise to large instabilities with bubbling and channeling of gas. Such agitation, which becomes more and more vigorous as the flow rate increases, is referred to as bubbling fluidization, since gas bubbles rise through the bed and increase in size due to coalescence. At further high flow rate, their terminal falling velocity can be exceeded, so that bubbles are no longer appreciable and the upper surface of the bed disappears. This state, referred to as turbulent fluidization, involves motion of solid clusters and voids of gas. With a further increase in the fluid flow rate, particles are carried out of the bed with the gas, giving the regime of lean-phase fluidization with solid transport.

The most important design parameters for such systems are: the minimum fluidization velocity, bed expansion of fluidization and pressure variation in the bed.

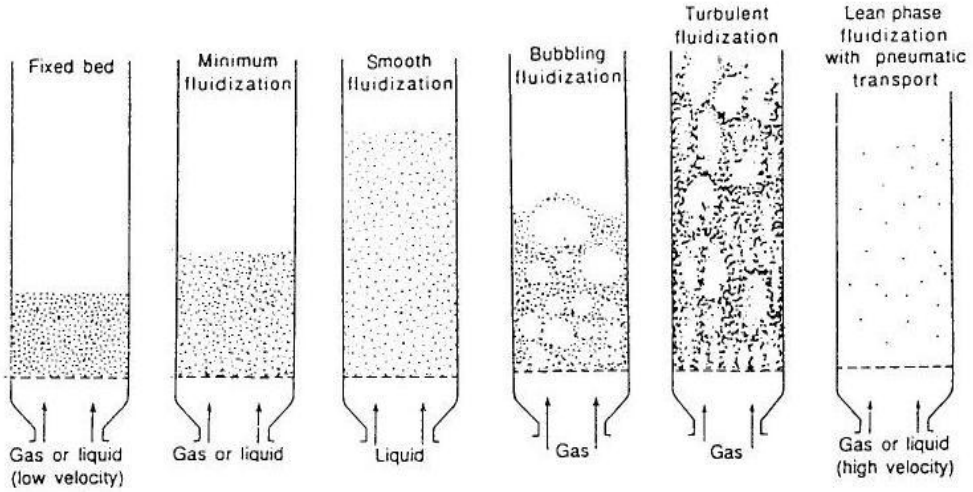


Figure 2.19: Minimum fluidization velocity [7]

Minimum fluidization velocity

At the so called incipient or minimum fluidization, the upward drag force exerted by the fluid on the particles counterbalances exactly the apparent particles weight in the bed; mathematically, this means that the pressure drop across the bed must be equal to the effective weight per unit area of the particles at the point of incipient fluidization, as expressed in Equation 2.1

$$Pressure\ Drop = \frac{weight\ of\ \ particles\ \ - upthrust\ on\ particles}{bed\ cross\ sectional\ area} \qquad \text{Equation 2.1}$$

which can also be expressed as:

$$\Delta p = \frac{HA\ (1-\varepsilon_{mf})(\rho_p - \rho_f)g}{A} = H\ (1-\varepsilon_{mf})(\rho_p - \rho_f)g \qquad \text{Equation 2.2}$$

Where

Δp	=	pressure drop
H	=	fluidized bed height
A	=	bed cross sectional area
ε	=	void space of the bed at minimum fluidization
ε_{mf}	=	porosity of the bed at minimum fluidization
ρ_p	=	particle density
ρ_f	=	fluid density
g	=	gravitational acceleration

At the same time, the estimated pressure drop in packet beds at minimum fluidization is best described by the Equation 2.3 (Ergun, 1952):

$$\frac{\Delta p}{H} = 150\frac{(1-\varepsilon_{mf})^2}{\varepsilon_{mf}^{\ 3}} \cdot \frac{\mu U_{mf}}{d^2} - 1.75\frac{(1-\varepsilon_{mf})}{\varepsilon_{mf}^{\ 3}} \cdot \frac{\rho U_{mf}^{\ 2}}{d} \qquad \text{Equation 2.3}$$

where:

μ = fluid viscosity

U_{mf} = minimum fluidization velocity

d = the particle diameter

The first summand in Equation 2.3 represents the laminar flow component, whereas the second one stands for the turbulent flow component. The minimum fluidization flow is reached when the

upward drag force exerted by the fluid on the particles is equal to the apparent weight of particles in the bed.

Substituting the value of Δp from Equation 2.2 in Equation 2.3 and multiplying by $-\left[\frac{\rho d^3}{\mu^2}(1-\varepsilon_{mf})\right]$, Equation 2.4 is obtained:

$$1.75\frac{1}{\varepsilon^3_{mf}}\cdot\frac{\rho^2 d^2}{\mu^2}U^2_{mf}-150\frac{(1-\varepsilon_{mf})^2}{\varepsilon^3_{mf}}\cdot\frac{\rho d}{\mu}U_{mf}-\frac{\rho d^3}{\mu^2}.(\rho_p-\rho_s)=0 \qquad \text{Equation 2.4}$$

This equation can be used to calculate the minimum fluidization velocity U_{mf} if the void fraction ε_{mf} is known. ε_{mf} depends on the form of the particles and it amounts to 0.40-0.45 in case of spherical particles (see Table 2.2) . To increase surface area and liquid-solid contact, many particle are often of irregular shape. In that case the particle is treated as a sphere by introducing a correcting factor called sphericity Φ_s to calculate the equivalent diameter.

$$\Phi_s=\frac{A_{sphere}}{A_{particle}}=\frac{6/D_p}{S_{particle}/V_{particle}} \qquad \text{Equation 2.5}$$

where D_p is the diameter of a sphere of the same volume as the particle (Haider, 1989)

Table 2.2: Void fraction at minimum fluidization [7]

Type of Particles	Particle size, D_p (mm)			
	0.06	0.10	0.20	0.40
	Void fraction, ε_{mf}			
Sharp sand (Φ_s = 0.67)	0.60	0.58	0.53	0.49
Round sand (Φ_s = 0.86)	0.53	0.48	0.43	0.42
Anthracite coal (Φ_s = 0.63)	0.68	0.60	0.56	0.52

Fluidized bed in agglomeration processes

The appropriate air velocity for initiating agglomeration should be about five-six times the minimum fluidization velocity, but never reach the so called entrainment velocity, at which the bed particles are carried away by the gas.

The bubbles of air rising through the powder bed, which are directly responsible for a good mixing of particles promoting their circulation, depend on bed geometry, distributor plate, type of particles and particles size and minimum fluidization velocity.

The bubbles can be formed through gas-solids contact near the distributor plate, which will lead to a highly expanded gas-solid dispersion. This is unstable and will divide into many little bubbles plus an emulsion phase.

Depending on the movement of air bubbles through the bed and their dimension/morphology, the fluidized bed can show up as (Figure 2.20):

- Slugging bed, in which the gas bubbles divide the powder bed in cross sections;
- boiling bed, where gas bubbles and powder particles have similar dimension;
- channeling bed, in which most of the air passes through gas channels in the bed;
- Spouting bed, where the gas forms a single opening through which some particles flow and fall on the outside.

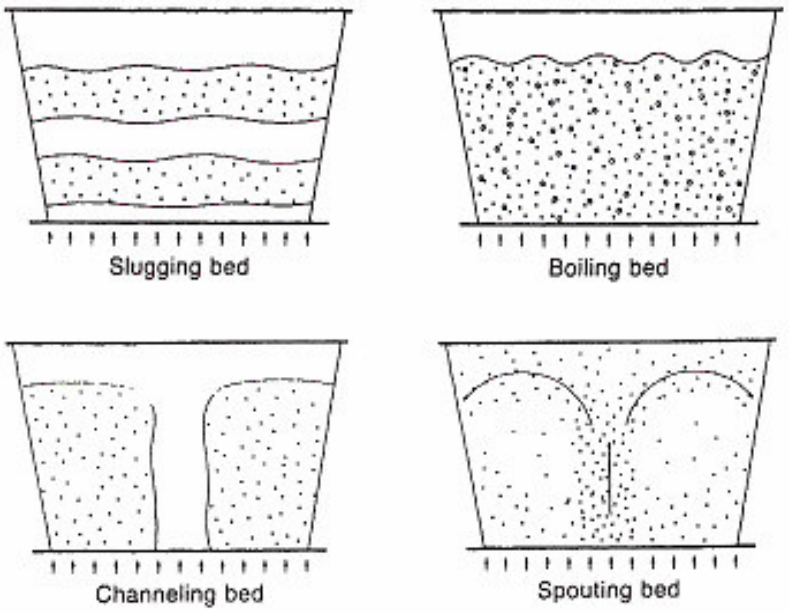


Figure 2.20: Various types of fluidized bed [7]

Description of the system

The fluidized bed processor consists of different components. The lower part of the processor is referred to as *air-handling unit* - typically composed of air filtering, air heating, air cooling and humidity removal sections. Before it is conveyed as make-up air to the heating and cooling sections, the external air is freed from dust and contaminants through coarse dust filters. Depending on the climate, re-humidification or dehumidification of the outside air becomes imperative to maintain a specific dew point. After the dehumidification and re-humidification step, the make-up air is heated/cooled to the desired process air temperature and sieved through a particulate air filter. The treated, conditioned and filtered air is transported via the inlet duct and introduced evenly at the bottom of the *product container,* so as to achieve a proper fluidization and mixing of the particles. To achieve this goal, the container volume must be filled between 35-40% and 90% of its total volume.

A fine sieve of 60-325 mesh, which separates the *air distributor* from the container, retains the product in the container.

The binder suspension is transported in a flexible pipe moved by a *peristaltic pump* into the granulation bed, where it is sprayed through an appropriate *nozzle*. The most commonly used nozzle is the two-fluid nozzle, also known as binary nozzle, in which the binder solution is delivered at low pressure through an orifice and atomized by compressed air.

Due to the pressure difference between the nozzle and the fluidized bed chamber, the suspension becomes a mass of discrete small drops, which spread onto the granules and initiate the agglomeration process.

Above the product container, the *disengagement area and the exhaust filters* are placed. They are involved in the separation of fine particles from the air flow once the air leaves the product bed. In the disengagement area, larger particles from the exhaust air lose momentum and fall back into the bed, whereas the filter system removes the smaller particles.

The filtered, exhaust air goes to the exhaust blower, a fan located on the outlet side of the system which keeps the system at lower pressure than the surrounding atmosphere. Just ahead or after the fan there is a damper or a valve which controls the airflow.

With regard to the location of the spray nozzle, a fluidized bed process can bear three different configurations: top spray, bottom spray and rotor tangential spray. In the conventional *top spray*, the nozzle, located in the expansion chamber, sprays the liquid against the air flow. This implies that the liquid is sprayed onto particles moving at a higher velocity, which minimizes surface wetting and agglomeration. Accordingly, this process is suited for drying, coating and spray granulation, but it is not the first choice process for pelletizing (Figure 2.21)

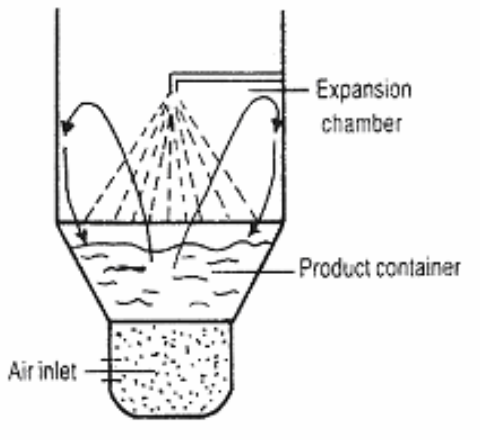


Figure 2.21: Conventional top spray [7]

In the *wurster bottom spray* processor, the product chamber contains an inner cylindrical partition, which is normally half the diameter of the outer container. At the base of the chamber there is a perforated plate, at whose middle an appropriate nozzle sprays the liquid in the same direction of the air flow (Figure 2.23). Due to the major perforation at the center of the plate, the air stream inside the partition has higher velocity than the air stream outside of it. This effect leads to a convective product flow with upward expansion through the chamber and falling outside the partition.

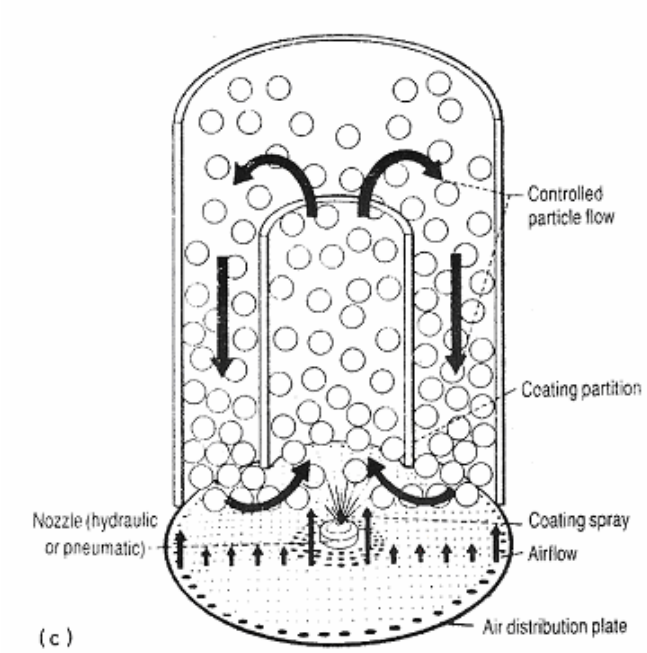


Figure 2.22: Wurster bottom spray [7]

Rotor tangential spray is particularly suited for solution/suspension and dry powder layering. The bottom of the product container is provided with a solid spinning disc adjustable in height and speed, and the spray nozzle is positioned just above the disc, tangential to the bowl wall (Figure 2.23). The product motion is produced by the three directional forces: a vertical upward movement, due to the fluidizing air passing through a gap between the disc and the container wall, and the centrifugal and centripetal forces, which pull the material, respectively, away from and back to the bowl center. The helicoidal movement of the product makes this process particularly advantageous for mixing, agglomeration and drying processes (Gu, 2004). In particular, the production of homogeneous pellets, which generally involves multi-step processing of mixing, wet granulation, spheronization and drying, can be dealt with in the rotor as a single processing unit, reducing processing time and material handling (Bouffard, 2007). Moreover, dry powder layering of neutral beads can be realized in the rotogranulator, in case the drug cannot be immersed in water or pellets with low density and perspectively rapid disintegration are required (Bouffard, 2007).

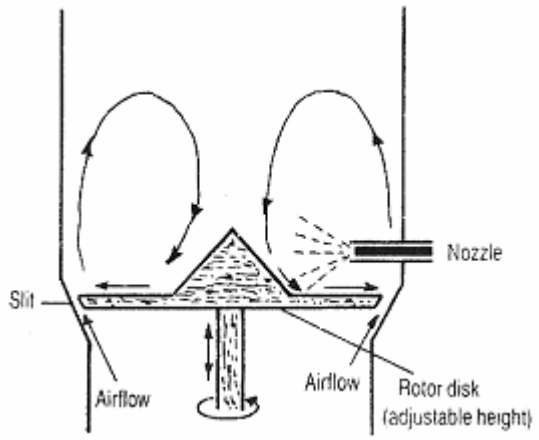


Figure 2.23: Tangential spray [7]

Pelletization variables

All factors affecting the fluidized bed granulation process fall into two broad categories (Parikh et al., 1997): formulation and process related variables, modifiable in dependence of the desired product characteristics, and equipment related variables, depending primarily on the machine design and typology. We will deal here solely with the first parameter category.

It can be claimed beyond any reasonable doubt that that the technological properties of the starting materials exert a crucial influence on the finals characteristic of pellets.

Among them we can mention loss on drying, particle size distribution, flowability, bulk and tap density, wettability and surface free energy, specific surface area, porosity, tendency to electrostatic charging (low cohesiveness and stickiness). In case of direct pelletization, the technological properties of active ingredient(s) and filler (different grades of mycrocristalline cellulose, lactose and corn starch) should be sufficiently comparable to allow a good mixing and thereupon an homogenous drug content uniformity in the final pellets. Not only: the binder (water suspension of poly-vinyl-pirrolidone, HPMC or MC) ought to cover the particles homogeneously in minimum quantity and in continuous layering, which requires again sufficiently diluted binder solutions and optimized spraying velocities (Tüske, 2005). In particular, the type of binder and its concentration can influence granules properties as friability, flowability, bulk density, porosity and particle size distribution. In case of dry powder layering of nuclei, the mean particle size ratio between neutral beads and applied powder should be at least 1:5, so that powder particles uniformly and continuously layer the core surface instead of aggregating between themselves.

Beside the above mentioned spray rate of the binder solution, other process related variables can steer the fluidization and therefore effect the product properties to a considerable extent. High inlet air temperatures as well as high fluidizing air flow enhance the solvent evaporation rate restraining the pellet growth and leading to accordingly smaller pellets. A relatively humid inlet air, on the other hand, reduces the solvent evaporation rate leading to bigger particles. Even the type of nozzle employed can play a role in the pellet size: e.g. a binary nozzle with low liquid flow rate atomizes the binding solution in very fine droplets, leading to an even powder wetting / layering and to accordingly smaller pellets (Figure 2.24).

Figure 2.24: Fluidized bed GPCG 1.1 with rotor insert (Glatt, Binzen)

2.4.3.2 Spouted bed

The company Glatt developed a technology, which enables also particularly fine or irregular powders or granules to be granulated and/or coated. The novel technology, called spouted bed technology, is shown in Figure 2.25a. The main change consists in making the air enter through a longitudinal slot instead of through the classical sieve bottom. This reduces considerably the process air speed due to a double expansion (in the process chamber and above the process chamber). As a result, not even fine particles are removed from the process. The process can also be stable in the case of products that are sticky or form lumps (Figure 2.25b).

(a) (b)

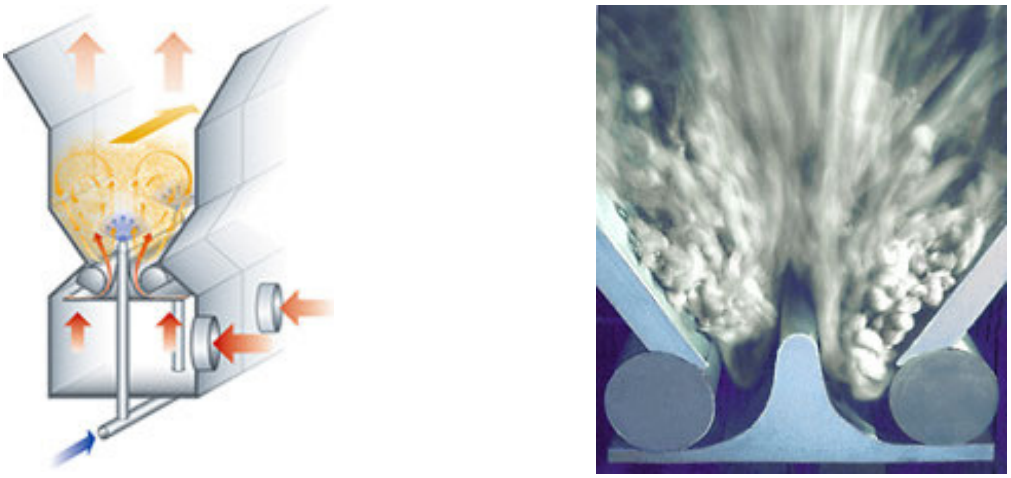


Figure 2.25: Spouted bed Pro Cell (Glatt, Binzen) [6]

2.5 Coating

Coating of solid oral dosage forms is a common technique in order to protect the active pharmaceutical ingredient against environmental impact and the body fluids or rather to protect the body against undesired effect of the API. Originally developed in order to cover foul-tasting tablets or capsules, coating of solid dosage forms is nowadays employed for diverse purposes. It can be applied to protect the active ingredient(s) against light, air and moisture (end-coating); it can avoid dissolution in stomach (enteric coating); it may control the drug release as appropriate (release control coating). Furthermore, coated tablets or capsules are better identifiable (drug safety requirements) and more robust, which is particularly important for their shipping and dispensing.

We can also differentiate between three different coating-types:

Sugar coats, primarily used to coat the first blanketed medicines having bitter taste, protect the active ingredient(s) against oxygen and water vapour as well. Due to the slow and complex coating process, such coats are nowadays of little importance. *Hot melt coats* are mainly employed to delay the active ingredient release. For this purpose, fats, fatty acid esters, fatty alcohols, magnesium or aluminium salts of fatty acids as well as various kind of waxes are used. Nevertheless, the most popular and versatile coating remains the *Film coating*.

2.5.1 Film coating

Compared to sugar or hot melt coatings, film coatings build up just a very thin layer around the solid dosage form, which is principally constituted of an appropriate polymer.
According to the final characteristics of the film tablets, the coats can be divided into different groups. Firstly, water-soluble cellulose ethers (methyl- and ethylcellulose) or polymethacrylates with amino groups (Eudragit® E) are appropriate for prompt disintegration tablets. Secondly, polymers with free acid groups (i.e. cellulose derivatives, polymethacrylates and polyvinyl acetate phthalates) are used as enteric coating agents, since they are insoluble in acid media but dissolve promptly above pH 5-6. The last group consists of ethylcellulose and polymethacrylates, which provide film for sustained release. They share the common characteristic of swelling (not dissolving) in digestive fluids, producing a constant, continuous release through their permeable membrane.

Being nowadays the use of organic solvents strictly forbidden due to their high toxicity and environmental pollution, also water-insoluble polymers must be dispersed in water.
The dispersed phase can be solid, liquid or any intermediate state, since the transition of polymers from solid to liquid takes place over a wide temperature range (Bauer, 1998).
The film coating process consists in spraying the coating suspension on the cores and drying them by air. These two steps can occur in an intermittent way, in which case small portions of coating are applied followed by a drying cycle, also known as curing step, or in a continuous way, in which the spraying and the drying steps occur simultaneously.

2.5.2 Film formation

The formation of polymer coatings is crucial with respect to the functionality such film layers should have (enteric resistance, modified release). The film formation of aqueous polymer dispersions is driven by the evaporation (Brown, 1956).

The coating solution or dispersion is atomized by the spray nozzle and, once in contact with the cores, it spreads on their surface. Initially, the dispersed particles are freely movable in the liquid film. During the drying step, the dispersing medium evaporates and the particles arrange themselves in the closest sphere packing; subsequently, they flow together squeezing out the remaining water and forming a water-insoluble, homogeneous film (Figure 2.26). The temperature at which the coating dispersion forms a clear, coherent film is known as *minimum film-formation temperature* (MFT). It depends mainly on the chemical properties of the polymer and its characteristic glass transition temperature T_g, but it can be utterly influenced by other excipients in the formulation as plasticizers or pore builders. To avoid the development of porous, friable films, it is important to keep the process temperature at least 10°C higher than the MFT.

In case of film-builders with a high MFT (over 40°C), the curing step at the end of the process is essential in order to complete the film formation, whereas it can be omitted in case of film-builders with a MFT lower than 30°C.

Two are the main driving forces carrying out the film formation process: first of all, the capillary pressure resulting from the evaporation of the dispersing medium; second of all, the gain in surface energy. Since the capillary pressure is inversely proportional to the droplets radius, smaller droplets lead to accordingly more homogeneous coating layers.

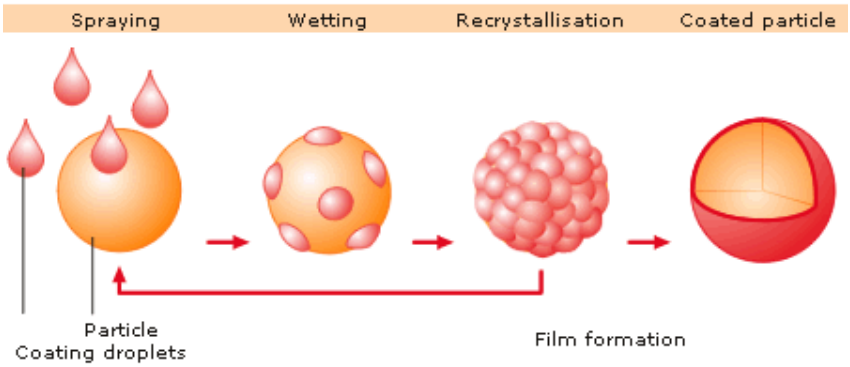


Figure 2.26: Formation of the film coating [8].

2.5.3 Delayed release polymers

For more than thousand years tablets have been coated in order to cover their bad taste. By developing the first synthetic drugs in the 19th century, it became imperative to protect the stomach against aggressive substances, and this was firstly realized through keratin, which is enzymatic digested in the ileum. Nowadays, the API contained in many pharmaceutical dosage forms irritate the stomach due to their chemical properties; others undergo chemical and enzymatic reactions which change their properties and make them less or even hardly effective. Thus, the obvious need for efficient enteric coating materials.

The material groups for enteric resistant coatings can be distinguished into three groups. The oldest one consists solely of shellac, which is of natural origin and has been used almost for hundred years for enteric coatings, taste masking as well as prolonged release. It consists of a mixture of polyesters, basically composed of shelloic and alleuritic acid, which account for its gastric resistant properties. However, as any product of natural origin, it is affected by batch-to-batch variation due to the purification process and the resulting content of wax, coloring material and other impurities (Hogan, 1995).

The second group was developed in the first half of the last century and is essentially based on cellulose. The partially synthetic derivates possess different acid functional groups as phthalates or acetates (Davis, 1986). Cellulose acetate phthalate (CAP) was the first semi-synthetic polymer catching on as a gastric resistant polymer. Other derivates based on cellulose acetate are cellulose acetate trimellitate (CAT) and cellulose acetate succinate (CAS). However, hydroxypropyl methylcellulose (HPMC) is preferred due to its low permeability in the gastric fluid and stability against hydrolysis.

Poly(meth)acrylate derivates build the third group of enteric coats. The backbone is based on a continuous carbon chain stabilized by methyl groups resulting in poly(methyl methacrylate) (PMMA). They are fully synthetic copolymers exhibiting free acidic carboxyl groups (–COOH), which are responsible for their resistance to acid hydrolisis in stomach. EUDRAGIT® L/S and Kollicoat® MAE, both methacrylic acid/ethyl acrylate copolymer (1:1), are the most widely diffused products on the market. The brand name Kollicoat comprises several other film forming agents, all produced by BASF, which are discussed in the next chapter.

2.5.4 Kollicoat® SR 30D

Kollicoat® products can be divided into four main groups, according to their chemical structure and their main application areas (see Table 2.3).

Table 2.3: Kollicoat product groups.

Product group	Basic chemical structure	Principal application areas
Kollicoat IR	Graft polymer, neutral	Water-soluble, protective coatings
Kollicoat MAE	Copolymer, ionic	Enteric coating for tablets, capsules and granules
Kollicoat SR	Homopolymer, neutral	Taste masking, sustained release coating for tablets, pellets
Kollicoat EMM	Copolymer, neutral	Sustained release coatings for pellets and tablets

Kollicoat SR 30D, the film-forming agent which was selected to coat the pellets in this study, is an aqueous dispersion of the homo-polymer polyvinyl acetate (Figure 2.27), with a solid content of 30%. The dispersion additionally contains the excipient povidone K30 and sodium lauryl sulphate in an amount of 2.7% and 0.3% respectively. These excipients prevent sedimentation of the polyvinyl acetate particles during storage; in addition, povidone increases Kollicoat SR 30D wettability in the gastric juice and intestinal fluid.

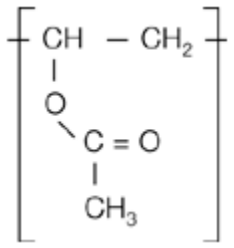


Figure 2.27: Chemical structure of polyvinyl acetate

Being insoluble in the gastro-intestinal fluid, Kollicoat SR 30D is used as sustained release polymer. It let the active ingredient be homogenously released over a certain period of time, depending on the film thickness and the eventual employment of pore builders.

The high plasticity of Kollicoat SR 30D makes plasticizers virtually redundant (Dashevsky, 2005). Nonetheless, in the case of MUPS (see § 2.7), it contributes to increase the film resistance of the coated pellets against the mechanical stress of the compaction.

Kollicoat SR 30D has a MFT of 18°C, which can be reduced even of 10°C or more by the addition of a plasticizer. The relative low MFT enables the performance of the coating process at room temperature, and makes the curing step after spraying unnecessary.

2.5.5 Coating technologies

Coating of solid dosage forms can be carried out in conventional coating pans, perforated pans as well as in fluidized-bed coaters. The former two are best suited for monolithic forms such as tablets and capsules, whereas the latter is rather appropriate for coating pellets, granules and other small particles.

Conventional coating pans ensure mixing of the core bed through their rotation on tilted axes. The particles are dried with hot air, which is blown into the pan and circulated over the surface of the tumbling bed. Perforated pans resemble conventional coating pans, with the only difference that the perimeter surface of the cylindrical drum is either entirely or partially riddled, so that the air flow can pass through the core bed ensuring an even drying up (Figure 2.28).

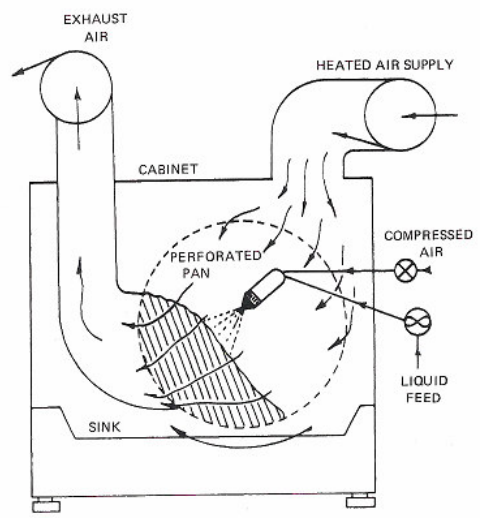


Figure 2.28: Perforated coating pan [9]

Coating of spherical beads can be conducted in diverse equipments. The very first industrial technology for pellet coating was the top spray fluidized bed (Figure 2.29 a); in this technology, the cores are fluidized by an heated air flow introduced into the product container via a base plate and at the same time coated through a nozzle spraying positioned against the air flow (countercurrent). Small droplets and low viscosity of the spray medium ensure that the distribution is uniform. Unfortunately, spherical granules coated through this technology generally exhibit low rigidity, which makes them inappropriate as subunits in MUPS (Knop, 1988).The bottom fluidized bed is the further development of the top spray fluidized bed (Figure 2.29 b).

The nozzle is fitted in the base plate and sprays in concurrent with the air feed. By using a Wurster cylinder and a base plate with perforations of different diameter, the cores ascend and descend in a convectional way: they move upwards while being sprayed, they dry and finally they fall back onto the lateral bed region to start another cycle (see spouting bed, Fig. 2.20). This produces an extremely even film. Using top and bottom spray fluidized beds, variations of the dry coating process have been performed. Obara et al. (Obara, 1999) remodelled a fluidized bed (top spray) by installing a separate powder feeder in addition to the liquid spray system. Furthermore, a fluidized bed with a Wurster insert can also be used to perform polymer powder coating (Pearnchob, 2003). The powder feeder is used with a conjunction to the coating chamber feeding the powder into the bed-up region. The major disadvantage of the equipment is that the powder is applied by a separate feeding system into the coating chamber, which leads to higher loss of the coating material.

(a) (b)

Figure 2.29: Top spray (a) and bottom spray (b) fluidized bed (Wurster) [6]

In contrast, in the rotor fluidized bed the powder and the liquid can be dosed together into the pellet bed by the three way nozzle (Figure 2.30). The pellets are set into a spiral motion by means of a rotating plate, where the air is introduced into the powder bed through the adjustable slit between the rotor plate and the product container. The spray nozzle is arranged tangentially to the rotor disc and also sprays concurrently into the powder bed. Since a bed of higher density completely covers the nozzle, the dry powder cannot easily follow the air flow and stick to the equipment; additionally, the intense movement cling the lack closer to the particles enhancing the layering.

Accordingly, very thick film layers can be applied by means of the rotor method, in contrast to the top and bottom spray.

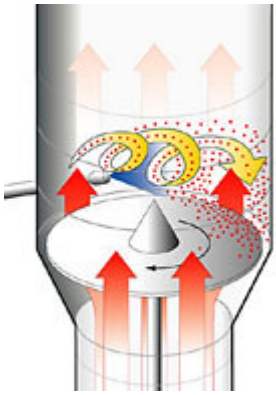


Figure 2.30: Rotor fluidized bed [6]

2.6 The compression/compaction process

Compression is the process of applying pressure to a material, whereas the consolidation of an appropriate volume of powder into a single matrix is more properly referred to as compaction. The tabletting mixture is normally put in a die cavity and compressed between an upper and a lower punch. This compact is then ejected from the die cavity as an intact tablet (Parrot, 1981). In line with the definition of compression and compaction, a similar distinction between the terms compressibility and compactibility can be made. Compressibility is the ability of a material to undergo a reduction in volume, while compactibility is defined as the ability of the material to produce tablets with sufficient strength under the effect of densification (Alderborn et al., 1996b; Jetzer et al., 1983). The compaction of tablets is an uniaxial compression. The free particles, which are filled into the die, get condensed by an applied force from an upper or a lower punch or both. The aim of this condensation is the formation of a compacted core with a definite shape. As in the whole study the compaction of pellets into MUPS is dealt with, the sole term compaction (and not compression) will be used.

According to Train, the compaction process can be described in four different stages which are in general the same for powders, powder mixtures and granulate (Train, 1956). These stages may be resumed as follow (Von Orelli, 2005):

Stage I:

Before any compaction process starts, the particulate solid must be filled into the die. The volume of the powder bed corresponds to a volume between bulk and tapped density. During stage I, the punch touches the material and the particles start to overcome the friction force and rearrange themselves by slippage into an energetically convenient position.

When particles are all in contact to each other, a dense packing is achieved and the bulk density corresponds approximately to the tapped density. The placement of the particles in the matrix depends on the flowability of the powder, on the physical properties of the particles (size, surface, shape, density, etc.), on the filling protocol (speed, movement of the hopper, centrifugal forces, vibrations) and on the press type (Woodhead et al., 1983; Zou et al., 1996).

Stage II:

Due to the immobility of the particles, an increase in pressure will lead to temporary columns, struts and vaults surrounding protected voids within the bulk. However, the inherent cohesive properties of most drugs and excipients are not sufficient to form tablets with adequate strength for subsequent handling (Leuenberger et al., 1986).

Stage III:

Increasing the stress on the material produces particle deformation. If the deformation disappears completely upon release of the stress (the moulding returns to the original shape), the speech is about an elastic deformation (Figure 2.31). A deformation that does not completely recover after release of the stress is a plastic deformation (Figure 2.31). The deformation is dependent on the properties of the substance and is especially determined by the crystal characteristics of the substance. Both plastic and elastic deformation may occur although one type predominates for a given material. At first, it undergoes an elastic deformation, the forming is reversible when the pressure is released and the solid regains its natural formation. Then, when the compression pressure is increased, the linear-elastic range is exceeded, an irreversible deformation will take place. The transition between reversible and irreversible deformation is called yield point. At last, when the pressure is increased further on, at a certain point the material breaks. Characteristic for brittle material, however, is the fact that the plastic range is extremely small or missing: the elastic deformation is followed by a breaking of the substance.

Stage IV:

In this stage a very strong structure is formed and the behavior of this compact under pressure depends on properties of the material. When the formed structure is strong, any further reduction in volume of the compact involves the normal compressibility of the solid material. In some cases, however, a further increase in stress may result in undesirable phenomena (see Figure 2.31) such as capping and lamination and, in specific cases, in work softening (Leuenberger et al., 1986). These phenomena result from an elastic re-extension of the material when the force is taken off the system after compaction.

It must be pointed out that the course of the above described compaction process is strongly dependent on the substance characteristics. Furthermore, the phenomena are not sequential but overlapping.

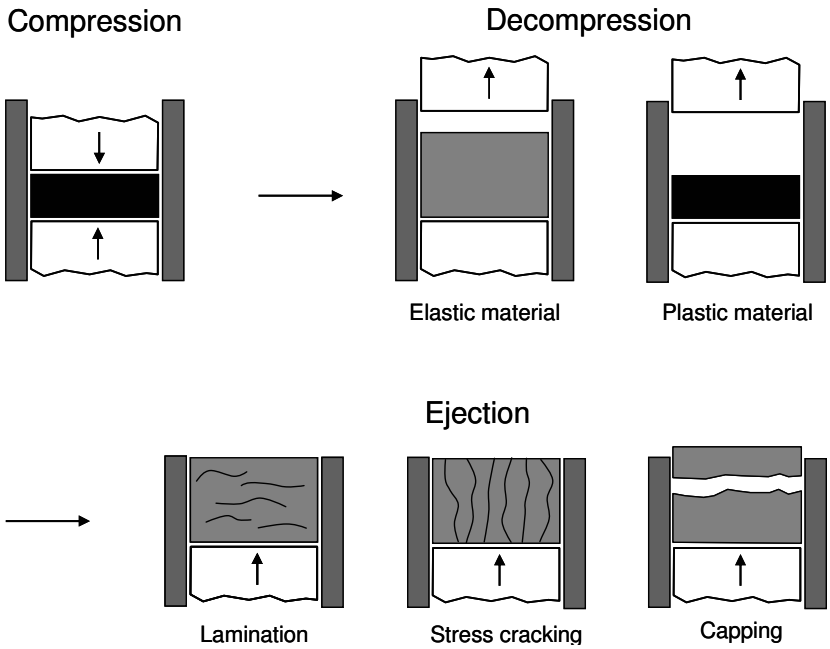


Figure 2.31: Problems appearing during compression [10].
- lamination: the compact cleaves in several parallel plans normal to the compression plan
- stress cracking: the side surface is damaged by sticking of the compact to the matrix walls
- capping: the upper part of the compact separating perpendicularly to the compression axis

2.6.1 Bonding in tablets

Bonding surface area

Bonding surface area is often defined as the effective surface area taking part in the interparticulate attraction (Alderborn et al., 1996a). In the case of solid bridges (see next section), the term corresponds to the true interparticulate contact area.

For intermolecular forces the term is more difficult to define (can be estimated from surface area measurements of the starting material). The internal surface area is small for dense crystalline solids (e.g. sodium chloride) but may be considerably greater than external surface area in case of porous bodies (e.g. microcrystalline cellulose). Thus the bonding surface area is a function of several secondary factors (Duberg et al., 1985). Table 2.4 illustrates the factors influencing the surface area of tablet particles and the bonding surface area in tablets.

Table 2.4: Factors influencing the surface area of tablet particles and the bonding surface area in tablets [11]

Tablet particle surface area		Bonding surface area	
Before compaction	After compaction	During compaction	After compaction
Particle size	Particle size	Particle size	Particle size
Particle shape	Particle shape	Particle shape	Particle shape
	Fragmentation	Fragmentation	Fragmentation
		Plastic deformation	Plastic deformation
		Elastic deformation	Elastic deformation
			Elastic recovery
			Friction properties
			Bond strength

Bonding mechanisms

During densification process, points and surfaces of contact between particles enable formation of bonding which ensure cohesion of the compact. Rumpf determined five types of possible attraction (Rumpf, 1962b):

1. Solid bridges (sintering, melting, crystallization, chemical reactions, and hardened binders)
2. Attractions between solid particles (molecular and electrostatic forces)
3. Shape-related bonding (mechanical interlocking)
4. Bonding due to movable liquids (capillary and surface tension forces)
5. Non freely movable binder bridges (viscous binders and adsorption layers)

This classification was widely accepted in literature but in case of compaction of dry, crystalline powders, it has been suggested that the dominating bonds between particles together be restricted to three types (Fürher, 1977):

1. Solid bridges (e.g. due to melting):
   They contribute to the overall compact strength and can be defined as areas of real contact, i.e., contact at tomic level between adjacent surfaces in the tablet. They appear when very high pressure is applied to the material during compaction.

Indeed, the pressure applied to a particulate system is transmitted through contact points between particles. This creates high friction zones where temperature increases. Different types of solid bridges have been proposed in the literature, such as solid bridges due to melting, self-diffusion of atoms between surfaces, and recrystallization of soluble materials in the compact (Ahlneck et al., 1989; Down et al., 1985; Mitchell et al., 1984; Rumpf, 1962a).

2. Distance attraction forces (intermolecular forces):
   Intermolecular are all bonding forces acting between surfaces separated by some distance. The term includes van der Waals forces, electrostatic forces, and hydrogen bonding (Israelachvili, 1985). The dominant interaction force between solid surfaces is the van der Waals force (Derjaguin, 1960; Derjaguin et al., 1956; Israelachvili et al., 1973). Hydrogen bonding is a prevalently electrostatic interaction and may occur either intramolecularly or intermolecularly (Israelachvili, 1985). Electrostatic forces arise during mixing and compaction due to triboelectric charging.
3. Mechanical interlocking (between irregularly shaped particles):
   This term is used to describe the hooking and twisting together of the packed material. This bonding mechanism depends on the shape and surface structure of the particles. The long needle-formed fibers and irregular particles have a higher tendency to hook and twist together during compaction compared with smooth spherical ones. This mechanism is not based on atomic interaction forces and therefore plays a minor role (Shotton et al., 1976).

2.6.2 Compaction equipments

Tabletting always follows three major steps:

- matrix filling with powder or granules
- compaction by displacement of punches
- ejection of the compact out of the matrix

The quality of the tablet obtained after compaction depends on different factors such as:

- the intrinsic properties of the tabletting material or mixture
- the type of equipment used
- the compaction speed
- punches displacements amplitude
- the pressure applied to the powder bed

However, it has to be stressed that the fine adjustment of crucial compaction parameters, if not accompanied by formulation optimization, is not sufficient to produce robust tablets. Conversely, the compaction parameters can in some cases give precious information on the defaults of a formulation.

Machine for compression

The production of tablets is performed using eccentric or rotary (simple or multi-stations) presses (Pietsch, 1991), (Pietsch, 2002).

The eccentric press produces about 40 to 120 tablets per minute. The rotary press has a multiplicity of stations arranged on a rotating table with the dies. A few or many thousands tablets can be produced per minute. There are numerous models of presses - manufactured by a number of companies - ranging in size, speed, and capacity. As their tabletting speed is rather low, eccentric presses are usually used only at the formulation step. This type of tabletting machines is equipped with an upper and a lower punch which operate in a single die. It can be further differentiated between *ejection* and *withdrawal presses.*

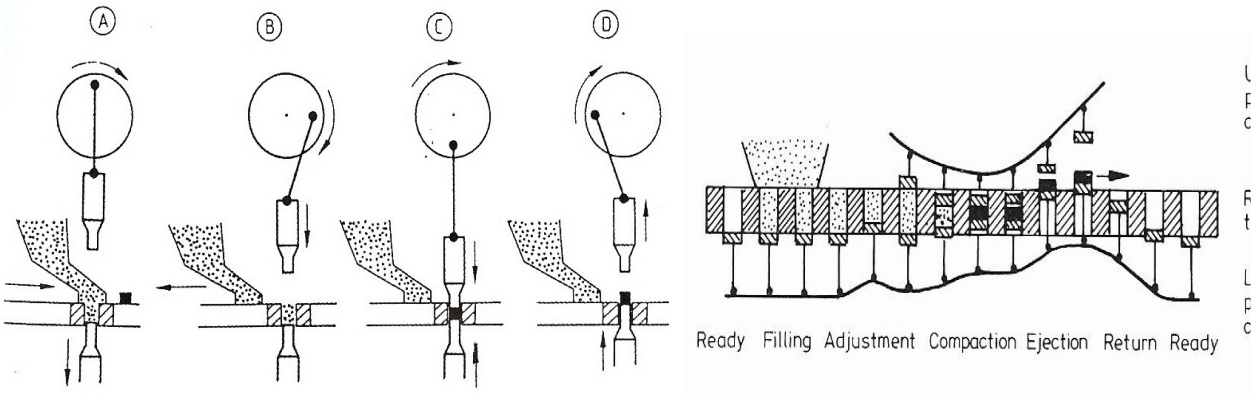
In the *ejection presses,* the two punches are mounted in a fixed press table, and the compression can be accomplished by the upper punch, which moves towards the stationary, lower one, or by both punches. The tabletting mass is charged into the die by a fill shoe and subsequently compressed between the upper and lower punches until a predetermined pressure. After the release of the pressure, the compact is ejected upward from the die, and the cycle begins again (Figure 2.32a). In this case, four phases are necessary to achieve the production of a compact with an eccentric press (see Figure 2.32a):

Phase I: the filling shoe, the upper and lower punches are in starting position and the matrix is filled with powder;

Phase II: the upper punch goes down into the die and compresses the powder bed;

Phase III: the upper punch is back at his initial position, while the lower punch pushes the tablet out of the matrix;

Phase IV: the filling shoe takes off the produced tablet and at the same time fills again the matrix with powder.



(a) (b)

Figure 2.32: Schema of the compression process with an eccentric press (a) and a rotary tablet press (compression station only). [12]

In the *withdrawal press*, compaction and ejection take place with a continuous downward movement of the upper punch and the die, whereas the lower punch remains stationary all the time. At the beginning, material is filled into the die, which is positioned on top of the lower punch, and it is compressed while both the upper punch and the die travel downward. At the end of the compression stroke, the upper punch is lifted up while the die continues to move down until the tablet is ejected, before returning to its start position again.

The simultaneous movement of the die and the punch minimizes the influence of wall friction on the structure of the tablet, leading to a highly uniform product density. As mentioned above, eccentric machines are suited when low output and/or high pressure are required.

Rotary tablet presses are employed for higher outputs, since they are equipped with more than one press station. The dies, each of them associated with a lower and an upper punch, are mounted onto a circular rotary train. Several punches pairs (upper and lower), independently moved by stationary cams, are mounted onto a circular rotary train. When the rotary train rotates, the pairs of punches are moved simultaneously up and down; the vertical position of a pair of punches depends on its position in the rotary train. When the bottom punch is located at the lowest position, the tabletting mass is loaded by a filling funnel/hopper in the die; immediately afterwards, the bottom punch rises up on an adjustable ramp to eject the powder excess. The compaction is accomplished by simultaneous approaching of upper and lower punch; the upper punch is then lifted from the die and the lower punch ejects the finished tablet (Figure 2.32b).

The phases of the compression process are in this case:

Phase I: filling of the matrix with powder when the upper punch is in its lower position.

Phase II: while the upper punch is in its lower position, the upper punch starts to go down guided by the curvature of the upper train (precompression).

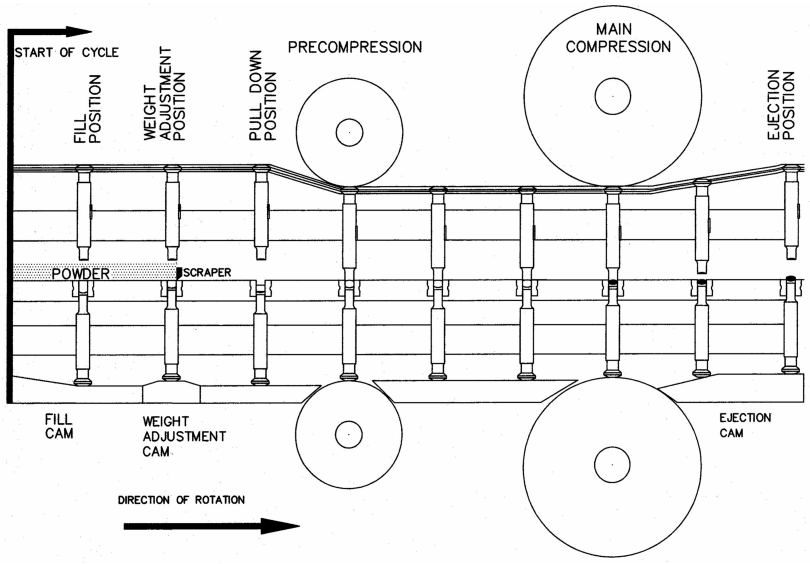
Phase III: the upper and lower punches are between rolls (main compaction).

Phase IV: the upper punch is in its highest position; the lower punch is guided up to eject the tablet.

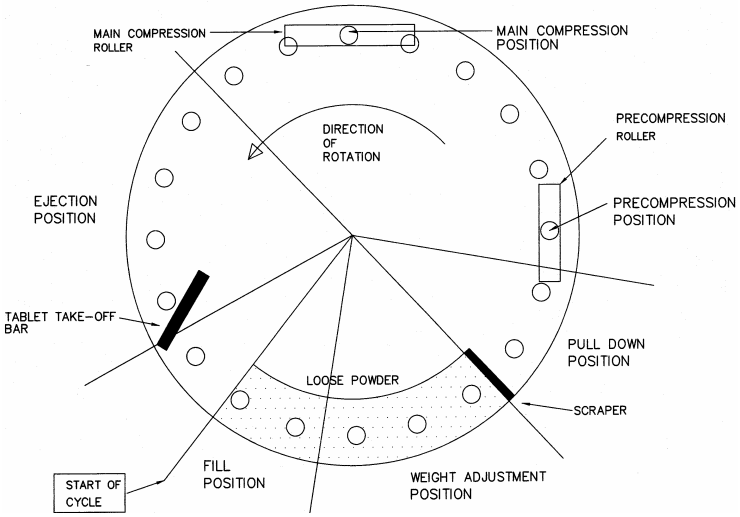
The actual multi station industrial rotary presses are usually equipped with a second pair of rolls for precompression (see Figure 2.33) which allow increasing the rotation speed of the machine while reducing the capping or laminating problems (often due to entrapped air in the die during compression).

Compaction simulators

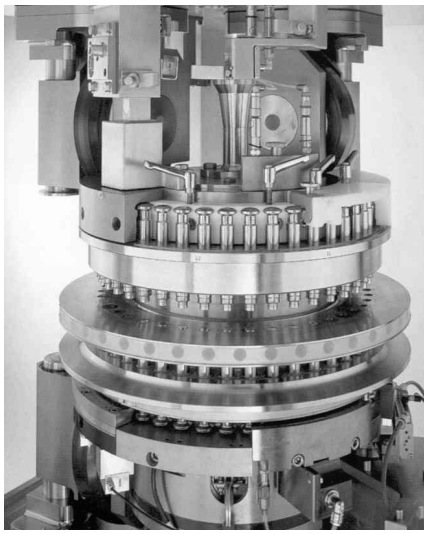
In the scale-up from development to production, tablets often show variability in crucial characteristics as disintegration time and crushing strength).



(a)



(b)



(c)

Figure 2.33: Multi stations rotary press with precompression and compression stations. (a): schema view from side (b) schema view from top, (c) picture of a Fette machine. [12]

This is due to the fact that different rotary tablet presses have diverse compression speeds and dwell times, which can heavily influence tablet properties. In order to overcome this scale up problem, so called linear compaction simulators have been designed (Celik, 1989).

Compression simulators are sophisticated tools that enable the reproduction of different compression parameters of any industrial machine (ex. compression speed, compression force, etc.). Published works encourage to use compaction simulators as research tools for robust formulations (Marshall, 1989; Muller et al., 1994; Nokhodchi et al., 1996; Yang et al., 1996).

The major problem, however, is the huge expense of such a simulator. At the Institute of Pharmaceutical Technology Basel, two kinds of simulators are in use: A Zwick® Universal testing Instrument, i.e. a punch and die set, and a Presster™ compaction simulator.

The Presster™ (see Figure 2.35) is a linear-type rotary tabletting machine replicator, which works with one single pair of punches and offers the possibility to simulate different rotary tabletting machines by mimicking the mechanics of these machines (Picker, 2003). Presster™ is instrumented with:

- Linear Variable Differential Transformers (LVDT) for upper and lower punch displacement measurement.
- Strain gauges for force measurement during compression and precompression.
- Strain gauges for die wall expansion measurement with instrumented die.
- Strain gauges for ejection force.
- Strain gauges for tablet take-off force.

The following set up can be installed before compression:

- Selection of an industrial machine model in a list
- Filling position of the lower punch before compression
- Minimal gap between the punches during precompression and compression by variation of the rolls positions
- Compression speed
- Ejection angle

Presster™ is a single station, linear compaction simulator, which can simulate any rotary tablet press by means of its specific dwell time, diameter of pre-compression and compression rolls, B / D tooling (different form and dimension of punches), and ejection angle (http://www.mcc-online.com/presster.htm), . Correspondingly, it is a very flexible investigation tool requiring just small amounts of material.

As shown in Figure 2.34 and Figure 2.35, the die is mounted on a fix table equipped with upper and lower punches, the tabletting mixture being filled into it either manually or through a feed shoe. The punches and the fix table move horizontally at an adjustable speed (between 0.055 and 2.2 m/s), whereas the vertical movement of the punches is controlled by an upper and a lower compression rolls, which can reach a compression force up to 50 kN. The machine is equipped with a precompression roll as well, which provide a first compaction of the powder mixture at low pressure (up to 10 kN), in order to eliminate the residual air before the main compression occurs. The produced tablet is then ejected from the die by an ejection cam, and important physical data as the compression, ejection, take-off and die wall forces can be investigated, as well as punch displacement and press speed.

A choice of interchangeable precompression and compression rolls, with a diameter varying from 60 to 305 mm and from 178 to 305 mm respectively, permits to simulate the loading pattern of any rotary machine .

Presster™ is connected to a computer, with which parameters like the depth of fill of the die (maximum 17.4 mm), the lower wheel position (to set the tablet thickness, maximum 8 mm) and the dwell time (between 5.8 and 230 ms) can be adjusted. It is also possible to calculate the tablet volume, elastic recovery, work of compaction and display, Heckel or stress vs. strain plots.

Figure 2.34: Presster™ Compaction Simulator

An important point is that for a given industrial machine model selected and for a given compression speed, the time during which one the flat portion of the punch head is in contact with the compression roll, called Dwell time (Figure 2.36) will be the same for any compression run. The tabletting process is scaled up on the base of the dwell time, which is the time of contact of the flat portion of the punch head with the compression roll (Equation 2.6):

$$DT = \frac{PHF \cdot NP \cdot 36 \times 10^5}{\pi \cdot PCD \cdot TPH} \qquad \text{Equation 2.6}$$

where:

DT: Dwell Time [msec]

PHF: Punch Head Flat of the TSM-B [mm]

NP: Number of stations

π: 3.141

PCD: Pitch Circle Diameter of the turret [mm]

TPH: Press speed in terms of Tablets Per Hour [Tabl/h]

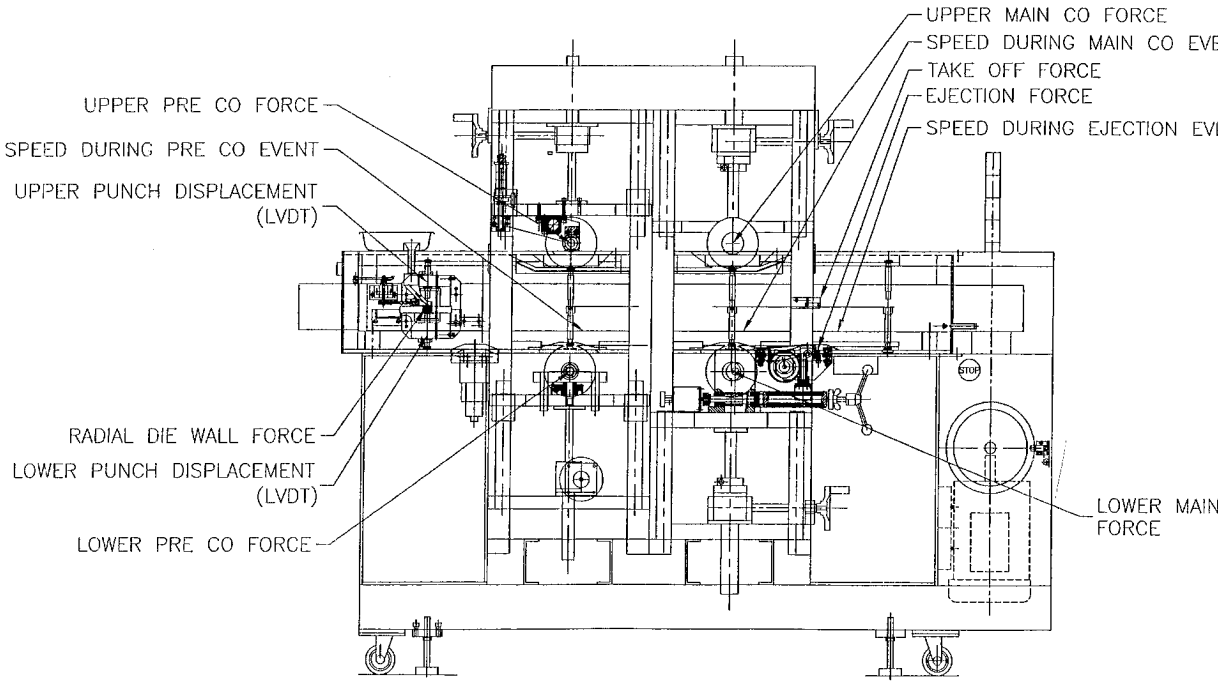


Figure 2.35: Presster™ instrumentation overview [12]

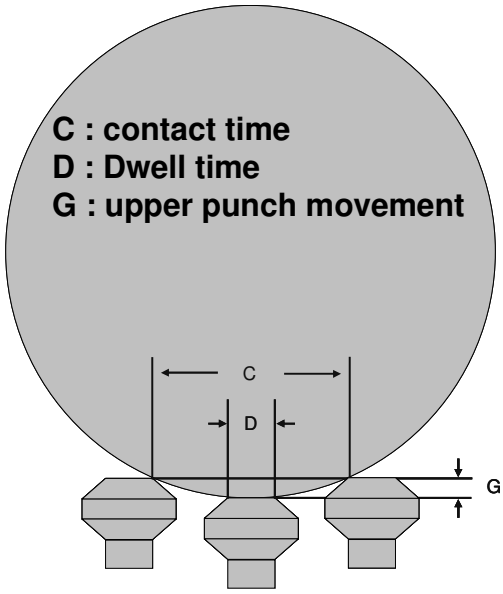


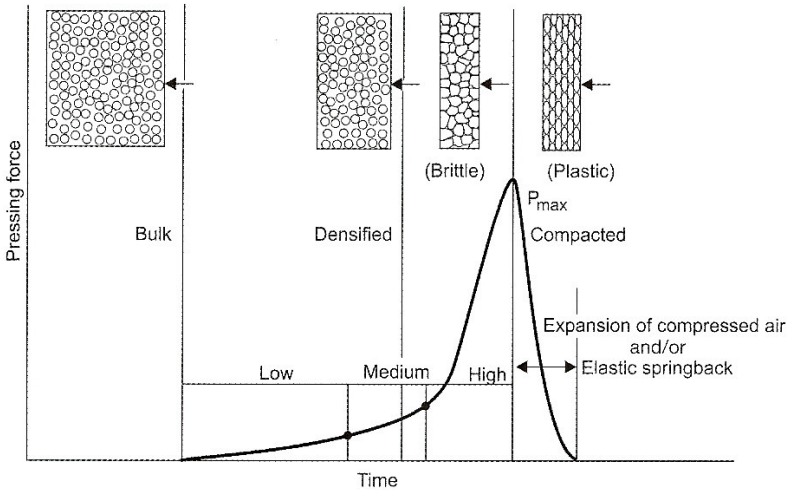
Figure 2.36: Schema of the lower punch position compared to the compression roll just before, at and just after Dwell time [12].

2.6.3 Description of densification cycle

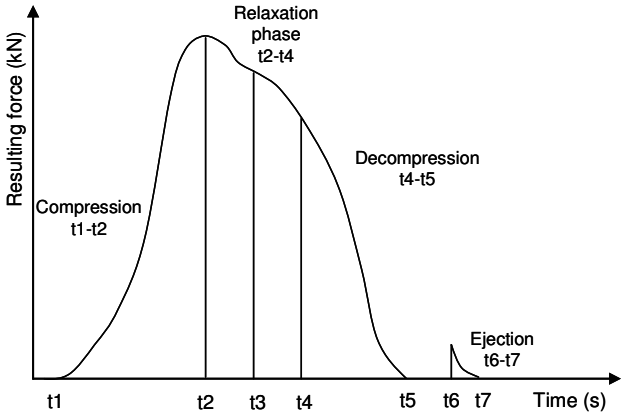
The punches pressure is recorded against time (Figure 2.37a,b) or against upper punch displacement (Figure 2.37c). According to Jones and Schmidt it is possible to distinguish four phases in a compression cycle (Schmidt et al., 1994):

1. Compression phase (t1-t2 or AB):
   The compression is the phase when the upper and the lower punches are brought together until the minimal distance or the maximal pressure.
2. Relaxation phase (t2-t4)
   Evolution of the pressure when the punches are maintained at their minimal distance. This phase expresses the viscoplastic properties of the material and increases the bonding possibilities. It was demonstrated (Masteau et al., 1998) that the increase of the Dwell time or the decrease of the compression speed is favorable to the formation of solid bonds and increases the mechanical quality of the resulting compact.
3. Decompression phase (t4-t5 or BC)
   This phase corresponds to the release of the stress when the punches go outside the matrix. An axial expansion of the compact occurs then in the matrix. This expansion can eventually destroy part of the bonds formed during compression and relaxation phases.
4. Ejection (t6-t7)

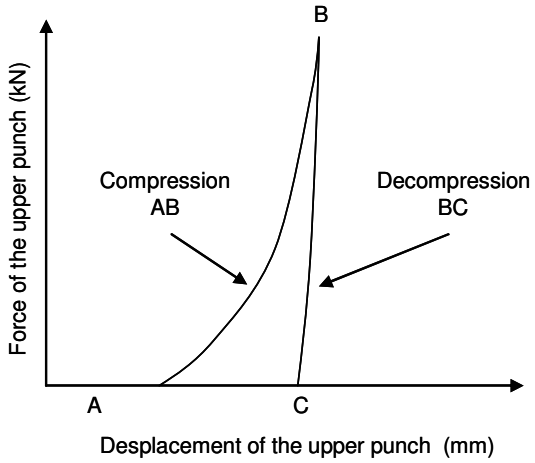
Ejection phase is the terminal phase of the cycle. This phase is also very important for the mechanical properties of the compacts. The efficiency of punches and die lubrication will counterbalance the sticking of the tablet to the matrix induced by the frictions tablet/die wall (Velasco et al., 1997). An insufficient lubrication can also induce lamination and capping effect.



(a) [14]



(b) [13]



(c) [13]

Figure 2.37: curve-type of pressure against time in general (a) and on a rotary tablet press (b); (c) curve-type pressure against upper punch displacement on a testing machine [12].

2.6.4 Energy and power occurring during compaction

De Blaey and Polderman identified five steps consuming energy during compression (Ragnarsson, 1996). They lead to:

1. Bring the particles close together.
2. Overcome interparticles frictions.
3. Overcome particle/matrix wall and particles/punches frictions.
4. Deform and create bonds.
5. Dissipate elasticity.

Energy consumption of the steps 1 and 2 is assumed to be negligible by comparison to the others. If the tooling is properly lubricated, the step 3 can be also neglected. If this is not the case, the work induced by these forces should be subtracted from the total compression work as this energy does not participate to the creation of bonds. In the same way, decompression enables stress release and thus expresses the elastic property of the material. If the elastic energy is also subtracted to the total compression work, the resulting true compression work corresponds to the deformation and to the creation of bonds (Figure 2.38).

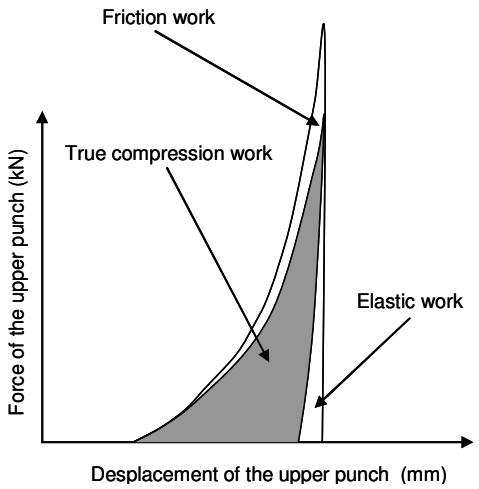


Figure 2.38: Energy occurring during compression [13]

Due to the possibility of high-speed manufacturing, low production costs and excellent patient compliance, tablets are the most extensively used pharmaceutical forms. Not only do they protect the active ingredient and hold it stable over a long period of time, but they can also drive its disintegration and dissolution as required.

2.7 MUPS (Multiple Unit Pellet Systems)

2.7.1 General description of multiunit tablets

Controlled release drug delivery systems for oral administration can be classified in single unit and multiple unit dosage forms. In multiple unit dosage forms, the active ingredient(s) are homogeneously distributed in their subunits, which can be granules, pellets or even micro-tablets. This characteristic make them highly advantageous in comparison to single unit forms (Bodmeier, 1997): once swallowed, they spread uniformly throughout the gastrointestinal tract independently of the nutrition state, reducing dose dumping, local irritation and toxicity risks.

Moreover, because of their small size, multiparticulates have a short stomach transit allowing a more rapid onset action and in some cases preventing drug degradation in the gastric gut.
Peroral controlled-release multiunit dosage forms (e.g., pellets, granules or microparticles) have conquered the pharmaceutical market over the last 3 decades to such an extent, that they nowadays represent a valid alternative to such classical single-unit dosage forms as tablets or capsules (Gebre-Sellassie, 1994). They present several advantages: they considerably reduce the risk of undesired drug release from a damaged single-unit tablet, as well as they minimize local irritations avoiding the attachment of monolithic dosage forms to the gastro-intestinal mucosa (Adriaens et al., 2002).

After prompt tablet disintegration in the stomach, single units, having diameter < 2 mm and density < 2.5 g/cm3, behave like a liquid: they have a short transit time through the stomach and avoid drug accumulation (Clarke et al., 1993),(Clarke et al., 1995). Moreover, small single units tend to disperse more homogeneously and reproducibly throughout the gastrointestinal tract reducing drug release fluctuations and improving the overall bioavailability. This also accounts for the decrease of the drug dose and side effects (Sandberg et al., 1988), (Sivenius et al., 1988), (Stefan et al., 1988), (May et al., 1989), (Follonier et al., 1992), (Abrahamsson et al., 1996), (Amighi et al., 1998), (Peh et al., 1997), (Hosny et al., 1998).
With regard to the final dosage form, multiparticulates can either be filled into hard gelatine capsules (Stegemann, 1999), (Chopra et al., 2002) or compressed into disintegrating tablets (Flament et al., 1994), (Maganti, 1994). The advantages of tabletting multiparticulates include less difficulty in oesophageal transport and thus a better patient compliance, lower production costs thanks to the higher production rate of tablet presses, no need for capsule integrity control after filling.
Nonetheless, several studies have reported that sustained-release multiunit tablets tend to release the AI faster than their uncompacted subunits. This is mainly due to pellet damage during compression, caused by interactions between the feeder, punches and the tablet press die or even between the components of the mixture. This complex issue can be tackled exclusively through robust manufacturing and appropriate formulation and fine optimization of coating and compaction parameters(Bodmeier, 1997), (López-Rodríguez et al., 1993), (Wagner et al., 2000b), (Wagner et al., 2000a).
Pellets are mixed with excipients before being compressed into multiunit tablets. The difference in form, size and density of the different mixing components are critical factors, which can influence the stability and segregation tendency of such mixtures.

Some authors recommend using filler-binders which are almost equal in size to the pellets used (Aulton et al., 1994a), (Çelik et al., 1994), (Flament et al., 1994), (Lundqvist, 1998), (Pinto et al., 1997), whereas others demonstrate a reduction of segregation using a fine microcrystalline cellulose as Avicel® PH 102 (Haubitz, 1996), (Wagner, 1999b). Homogeneous mixtures of pellets and filler-binders are crucial to obtain tablets of uniform weight and drug content, and thus to ensure a high reproducibility in production.

2.7.2 Multiunit Tablets Production

As explained in last paragraph, multiunit tablets are produced by compaction of single unit dosage form as granules, pellets or microtablets. The methods for preparing granules are based either on physical methods such as fluidized bed granulation, spray-drying, spray-congealing and solvent evaporation, on physicochemical methods such as coacervation, or on chemical methods such as interfacial polymerisation (Por Li, 1988). The production of pellets is a quite complex process, as it includes many steps such as moisturising, extruding, spheronising and drying (Flemming et al., 1995), (Kleinebudde, 1998). Moreover, pellets present the major disadvantage of being irregularly shaped particles (Munday, 1994). In this perspective, microtablets having a diameter equal to or smaller than 2 mm represent an interesting alternative to pellets (Flemming, 1995), (Flemming, 1996). This way, many steps of pellets production might be avoided, defined sizes and strengths might be easily achieved and the variability within a batch accordingly minimised (Butler, 1998), (Rey, 2000). Because of their uniform size, smooth surface, low porosity and high strength, micro-tablets can be better than usual pellets. (Vecchio, 2000). Moreover, it is possible to produce microtablets with higher drug contents than normal size tablets (Lennartz, 1998).

One way to achieve sustained-release multiunit tablets is to compress coated single units. The polymers used in the film-coating of solid dosage forms usually fall into two broad groups based on either cellulose or acrylic polymers (Bodmeier, 1997). Ethylcellulose is used frequently as coating material for the preparation of pellets. However, it forms quite brittle films which are not suitable for further tabletting (Béchard, 1992), (Tirkkonen, 1993), (Maganti, 1994). Polyacrylates are more qualified for this purpose, as they are more flexible (Beckert, 1996), (Lehmann, 1994) (Lehmann, 1995).

In order to control the drug release of multiunit tablets, the film coating has to withstand the applied compaction pressure without being ruptured. In fact, damages in the coating layer would result in a loss of the sustained release properties and dose dumping. Several studies have investigated into crucial parameters to obtain MUPS having consistent properties with their uncompressed coated units (Beckert, 1995), (Bodmeier, 1997), (Wagner, 1999a).

2.7.3 Mechanisms of compaction of pellets into tablets

Alderborn and Wikberg suggest a series of compression mechanisms for aggregates of irregular shape, namely reposition, deformation, densification, fragmentation and attrition (Alderborn, 1996). Studies on MCC pellets accomplished by Johansson et al. indicate that the relevant compaction mechanisms for pellets are permanent deformation (i.e. a change in shape of the individual pellets) and densification (i.e. a reduction of the pellets porosity), whereas fragmentation occurs to a minor extent. Pellet deformation seems to be related to the pellet porosity and size, as well as to the applied compression force, whereas the densification is related solely to the latter (Johansson, 1998), (Johansson, 1995b). Pellet porosity can be defined as the percentage volume of voids in pellets; the higher the amount of voids, the more porous the pellets. Johansson explains that moderately porous pellets get accordingly more deformed during compaction, due to the higher freedom degree of rearrangement of the powder particles within them. On the other hand, more compact pellets are more intensively buffered during compaction by powder particles, because they cannot widely rearrange. The pressure applied during compression also influences the degree of deformation in such a way that an increase in pressure leads to more elongated and flattened pellets.

Concerning the effect of the pellet size on the degree of their deformation, Johansson et al. propose three different explanations (Johansson, 1998).

The first is related to the force distribution in the pellets bed during compression. It is assumed that during the uniaxial compression of a particle assembly, the force applied is transmitted through the powder bed at the point of interparticular contact. According to this assumption, an increase in the particle size reduces the number of force transmission points, consequently increasing the contact force at each point and enhancing the pellet deformation.

Secondly, larger pellets are subject to higher degree of deformation due to reduced powder buffering. Finally, as the degree of deformation is directly proportional to the pellet porosity (see above), it's reasonable that larger pellets can more easily deform than small pellets.

In their research, Johansson et al. claim that pellet densification, which occurs during compression, seems to be influenced solely by the compression force, independently of the pellet size (Johansson, 1998).

Compared to the densification of the whole tabletting mixture, pellet densification is relatively low. Before compression, the amounts of air located in the intra- and intergranular pores are comparable, whereas during compression a densification of the tabletting mixture occurs, to the major detriment of the intergranular pores of pellets. In other words, the final porosity of the tablet directly depends on the residual pellets porosity after compaction.

2.7.4 MUPS compaction: key factors

Compaction of multiparticulates into tablets could either result in disintegrating tablets providing a multiparticulate system during gastrointestinal transit (ideal case) or in extremely hard tablets due to adhesion or partial fusion of the subunits in a larger compact (worst case) (Johansson, 1996).

Ideally, the compacted single units should disintegrate rapidly into the individual subunits in the gastrointestinal gut rather than sticking together forming a non-disintegrating matrix (Chemtob, 1986), (Sveinsson, 1993). To this scope, various embedding excipients must be added to single units to assist the compaction process (López-Rodríguez et al., 1993), (Maganti, 1994). The ideal filler material used for the tableting of single units should dilute and buffer them acting as cushioning agent during compaction. In other words, compaction forces have to be absorbed mainly by the excipients so that the single units remain virtually intact. The protective effect of different tableting excipients on the compression of granules may be investigated directly via image analysis or indirect by means of dissolution studies (Torrado, 1994).

The amount of excipient used should be sufficient to separate and protect the units. Lehmann *et al*. report that an amount of filler and disintegrant between 30-50 % was necessary to reduce damage of coated pellets (Lehmann, 1990) (Lehmann, 1994). They conclude that when cushioning excipients (including disintegrant) account to approximately 30% of the tabletting mixture, the interspaces between the pellets are filled and the subunits are sufficiently separated. Hence, the tablets disintegrate rapidly and the pellet damage and change of release profiles may be reduced to an insignificant level. Moreover, the addition of excipients should produce hard and rapidly disintegrating tablets at relatively low compression forces. Flamment *et al.* (Flament et al., 1994) have shown that tablets containing active pellets alone lack the required hardness. On the contrary, inert granules may be added to facilitate the cohesion of the tablet.

According to the requirements of the current European Pharmacopoeia, the multiunit tablets have to liberate the subunits within 15 min; on the other hand, their crushing strength should be high enough to permit their packaging and dispensing, which means that the subunits have to result in a uniform blend with the excipients, avoiding segregation and therefore weight variation and poor drug content uniformity of the resulting tablets (Bodmeier, 1997).

All the advantages of MUPS are strictly linked to an important characteristic they must have: they have to disintegrate as rush as possible into their subunits (15 minutes at the most).

In that case, pellets of different compositions or diverse release profiles, or even pellets carrying mutually incompatible drugs, can be successfully embedded in MUPS.

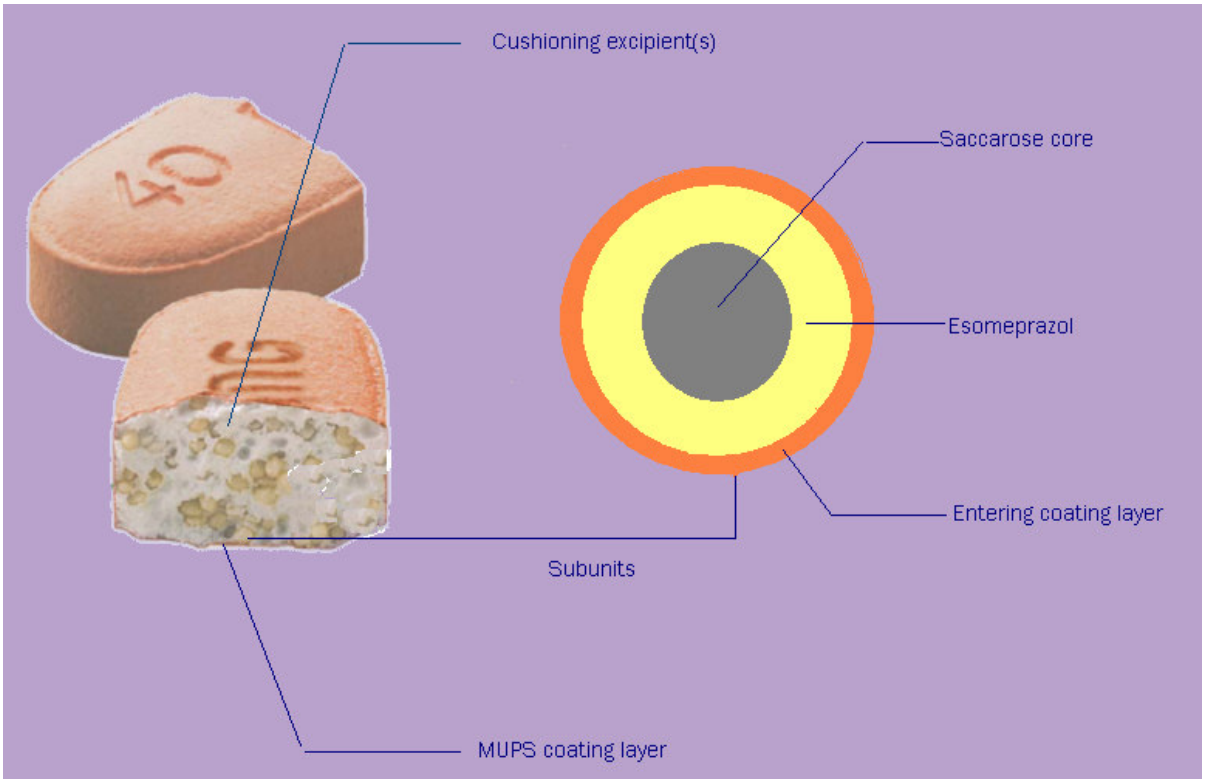


Figure 2.39: Structure and composition profile of Nexium MUPS

Figure 2.39 shows the structure of Esomeprazol MUPS, which consist of the following three functional units:

- Drug core (drug layered on a neutral core of saccarose)
- Film coating
- Embedding material

The active ingredient can be either homogeneously distributed within the pellet core or layered on the surface of inert sugar or MCC beads. The coating film, which can either steer the drug release from pellets or avoid their dissolution in the stomach, has in this case the additional function, along with the cushioning excipients(s), of cushioning the compaction stress. The embedding materials, which appropriately disperse the pellets in robust compact, also contribute to soften their compaction and are thus denominated cushioning excipients.

2.7.5 General requirements for MUPS

MUPS properties depend on the characteristics of the subunits (i.e. type of core, shape, porosity and size of the particles), on the type and amount of coating agent used, on the embedding excipients and not least on the compaction process (compression force exerted, compression velocity, type of tabletting machine employed).

The requirements that each component should meet to get MUPS with ideal characteristics have been investigated in several studies; despite this, the findings are partially discordant.

In case of inhomogeneous, coated pellets as subunits, Bodemeier et al. claim that the bead core should possess some degree of elasticity, in order to accommodate changes in shape and deformation during tabletting (Bodmeier, 1997). Conversely, Opitz asserts that cores should possess characteristics such as high crushing strength so as to overcome the compression neither deformed nor ruptured (Opitz, 2005). Similarly, Beckert et al. indicate that hard pellets coated with a thick film layer are better capable of withstanding the compression force than soft pellets, and that they tend to recover after compression without major damage of the coating layer (Beckert, 1996).

In addition to their thickness, the coating films should be elastic enough to deform during compression without rupturing and therefore maintaining the same drug release properties of the single particles. This implies, that the addition of plasticizers in the coating formulation need to be accurately optimized. Last but not least, under no circumstances should the coated pellets fuse into a non-disintegrating chewing-gum.

In literature, films from acrylic polymers were validated as more flexible than ethyl cellulose films and therefore more suitable for the compression of coated pellets (see § 2.5.3).

In particular, Kollicoat SR 30D has been reported as a very appropriate aqueous polymer for the coating of pellets, which must be subsequently compressed into tablets (Dashevsky, 2004, 2005). In fact, through the addition of a small amount of plasticizer, the film builder can reach high elasticity, preventing the drug cores from ruptures (see § 2.5.4).

Tabletting excipients should on the one hand disperse the subunits minimizing their reciprocal contact surface; on the other hand, they ought to cushion the compression stress preventing the subunits from damage. In order to fill the voids between densely packed spheres still avoiding matrix formation, the excipients should theoretically amount from 20 to 50% of the tablet weight (Opitz, 2005). A homogeneous pellets distribution in MUPS is strictly related to the goodness of the mixture between pellets and embedding excipients. The best mixing is achieved when the particles own more or less the same size; accordingly, to avoid segregation, pellets should be mixed with excipients with a comparable particle size or even with placebo pellets (Opitz, 2005), (Bodmeier, 1997).

Beckert et al. investigated the content and mass uniformity of MUPS (Beckert, 1998). In their study they provide support for the hypothesis that homogeneous MUPS can be obtained from tabletting mixtures containing 50-70% of pellets in case of fine excipients, 30-50% in case of excipients in form of granules or pellets.

In her comprehensive review about multiparticulate tablets, Opitz reports the effect of the compression force on the drug release from the MUPS. Increasing the compression force from

the minimum required to have a compact till a certain value, which differs for each formulation, film ruptures are enhanced and the dissolution velocity increased (Opitz, 2005).
Beyond this value, both disintegration and dissolution are delayed, which testifies the formation of undesired matrix tablets (Bodmeier, 1997).

2.7.5.1 Microcrystalline cellulose as filler/binder for multiunit tablets

Microcrystalline cellulose is certainly the most commonly used diluent for the compression of single units into tablets. In certain studies, microcrystalline cellulose was used directly as supplied by the manufacturer whereas in other studies, it was first mixed with other additives and then granulated or extruded into pellets. Torrado et al. have studied the protective effect of different excipients on the tabletting of theophylline granules coated with Eudragit RS (Torrado, 1994). Two excipients, namely polyethylene glycol 3350 and microcrystalline cellulose, were found to cause the lowest damages of the granules during tabletting. These results were explained with the yield pressure of the two excipients, which were lower than the pellet one. Therefore, the energy of compaction was absorbed by the outer excipients and these excipients were preferentially deformed. This protective effect of microcrystalline cellulose was confirmed in another study by Tunón and Alderborn (Tunón et al., 2001), in which the pellets after disintegration of the tablets were similar in size to the original pellets. A very few pellet fragments were obtained during disintegration. The compaction had only affected the shape of the individual pellets resulting in more irregular pellets. Moreover, Wagner *et al*. (Wagner et al., 2000a) observed that pellets compressed with the fine microcrystalline cellulose Avicel PH 101 (x50 = 50 µm) remained approximately spherical. The fine Avicel® PH 101 was able to fill the pores of the pellets lattice much more tightly than coarse Avicel granules (x50 = 194 µm). With regards to the physical properties of multiunit dosage forms, several studies showed that tablets of coated pellets containing microcrystalline cellulose presented a higher crushing strength than tablets of coated pellets without microcrystalline cellulose (López-Rodríguez et al., 1993), (Maganti et al., 1994). External excipients, being small and irregular particles, when added to the pellets, introduce new bounding sites, which lead to an increase in the number of potential cohesive and adhesive bonds, thereby producing relatively strong compacts.
Mixtures consisting of pellets and microcrystalline cellulose as external additive were found to be more compressible and produced stronger compacts than the tableting of pellets with pregelatinized starch or soy polysaccharide. Moreover, the size of microcrystalline cellulose had shown an effect on the crushing strength of tablets. Tablets compressed with Avicel PH 101 had demonstrated a significantly higher crushing strength than tablets produced with Avicel granules (Wagner et al., 1999b). Concerning the disintegration time, the use of microcrystalline cellulose

as external excipients has provided compacts that have disintegrated and regenerated the coated particles within less than 10 s as opposed to 7-10 min for other excipients such as spray dried lactose, spray dried sorbitol, compressible sucrose, polyethylene glycol 8000, pregelatinized starch (Béchard, 1992). In addition to the physical properties, multiunit tablets containing microcrystalline cellulose showed low friability with values below 1 %. In particular, compared to other excipients Avicel allowed the incorporation of a higher percentage (w/w) of single units without high tablet friability (Prapaitrakul et al., 1990), (Flament et al., 1994). An increase in the amount of single units has logically an effect on the other physical properties of the multi unit tablets. Increasing the single unit content decreases the tablet breaking load and the disintegration time. Pellets that are large and spherical in shape as compared to small, irregular powder particles, have a low surface to volume ratio, and this might result in a decreased area of contact between the particles as they consolidate (Lundqvist et al., 1997). Many studies determined the optimal amount of microcrystalline cellulose used to compress single units without serious degradation of tablet performance. López-Rodríguez *et al.* (1993), Prapaitrakul and Whitworth (1990) and Aulton *et al.* (1994), agree that it varies between 25 % and 40 % (w/w), corresponding to an amount of single units from 60 % to 75 % (w/w) (Aulton et al., 1994a; López-Rodríguez et al., 1993; Prapaitrakul et al., 1990). Moreover, Beckert *et al.* (1998) have observed that a pellet content in the range of 50-70 % (w/w) resulted in multiunit tablets that complied with the requirements for weight and content uniformity of European Pharmacopoeia. The explication was based on the percolation theory (Beckert et al., 1998).

Stauffer (Stauffer, 1985) used the term percolation to describe continuous structures (clusters) formed throughout the length, width and height of a system. When a binary system is considered, it depends on the concentration of each component, whether only one or both components percolate. The minimum concentration of a component at which a percolating cluster may be found is defined percolation threshold. Below this concentration only isolated clusters of one component can exist. Infinite clusters form above the percolation threshold. A bicoherent structure builds up if both components percolate. Becker et al. (Beckert, 1996) found that up to 50 % (w/w) of pellets, a percolating cluster of pellets that prevent segregation was ensured.

On the one hand, many authors agree that the particle size of external additives is a parameter of major importance in order to obtain a uniform mixture. Segregation is influenced by factors such as markedly differing particle size, density or shape. The difference in size distribution between powders and pellets is expected to lead to segregation, resulting in tabletting problems, such as weight variation and poor content uniformity. Therefore, the excipients should have a mean diameter close to that of the active single units to produce a stable mixture.

Consequently, it seems necessary to choose a large particle size of excipients or to prepare placebo pellets or granules (Aulton et al., 1994a), (Çelik et al., 1994), (Flament et al., 1994), (Beckert, 1996), (Pinto et al., 1997), (Lundqvist et al., 1997). On the other hand, Haubitz compressed mixtures consisting of 70 % (w/w) theophylline pellets (800-1250 µm) and the fine microcrystalline cellulose Avicel® PH 101 (x50 = 50 µm) and observed that in spite of the greater differences of particle sizes no distinct segregation occurred (Haubitz, 1996). In addition, Wagner investigated the pellet-distribution in single tablets via image analysis (Wagner, 1999a). The most homogeneous distribution of the pellets, particularly at intermediate and high machine speed was achieved with the fine Avicel PH 101. On the contrary to Avicel PH 101, coarser filler-binders led to segregation within the tablets at high machine speed. Avicel PH 101 has a large surface area and a fibrous surface texture, thus building a close percolating infinite cluster stabilising the pellets at their location in the mixture. A homogeneous distribution of the single units within the tablet presents also the advantage of divisible tablets.

2.8 Factorial Design

The successful management of a highly complex production process is strictly linked to the optimisation of the crucial parameters involved in any of its steps. Factor is meant to be any controllable parameter, which can be varied independently of other factors. It can be a quantitative (for example the amount of auxiliary substances, humidity or temperature), qualitative (such as different types of packing or auxiliary substances) or mixture factor. Mixture factors are two or more quantitative factors in relation between each other (i.e. they have to add up to some fixed value). Mixed factors are typical of formulation studies.

To assess the influence of the process factors (and their interactions) on one or more response variables, a certain number of experiments is needed. By changing one parameter per time, an exaggerated number of experiments would be needed, and yet no information would be gathered about the mutual interactions between the factors. On the contrary, factorial design permits to obtain a great deal of information by a minimal number of experiments (principle of the minimum).

Factorial design is applied to experiments in which two or more parameters or factors are involved, each of them having diverse values or "levels".

A designed factorial experiment takes into consideration all possible combinations of these levels across all factors, and it allows, therefore, studying the effect of each factor on the response variables, as well as the influence of interactions between factors on the response variables. If the number of experiments for a full factorial design is too high, a fractional factorial design may be carried out, in which some of the possible combinations are intentionally omitted.

The simplest factorial experiment contains two levels for each of two factors. Suppose a researcher wishes to study the effect on the drug release velocity from a tablet (response variable) using two different amounts of a disintegrant (variable A with two levels) and two different compression forces (variables B with two levels). The factorial experiment would consist of four experimental units: amounts of disintegrant A_1 and A_2 [mg], compression forces B_1 and B_2 [kN]. Each combination of a single level selected from every factor is present once.
This experiment is an example of a 2^2 (or 2x2) factorial experiment, so named because it considers two levels (the base) for each of two factors (the power or superscript), producing 2^2=4 factorial points. Similarly, a factorial design containing three levels for each factor will produce 2^3=8 factorial points (Figure 2.40).
In the end, the parameters of a factorial experiment are analyzed using regression analysis.

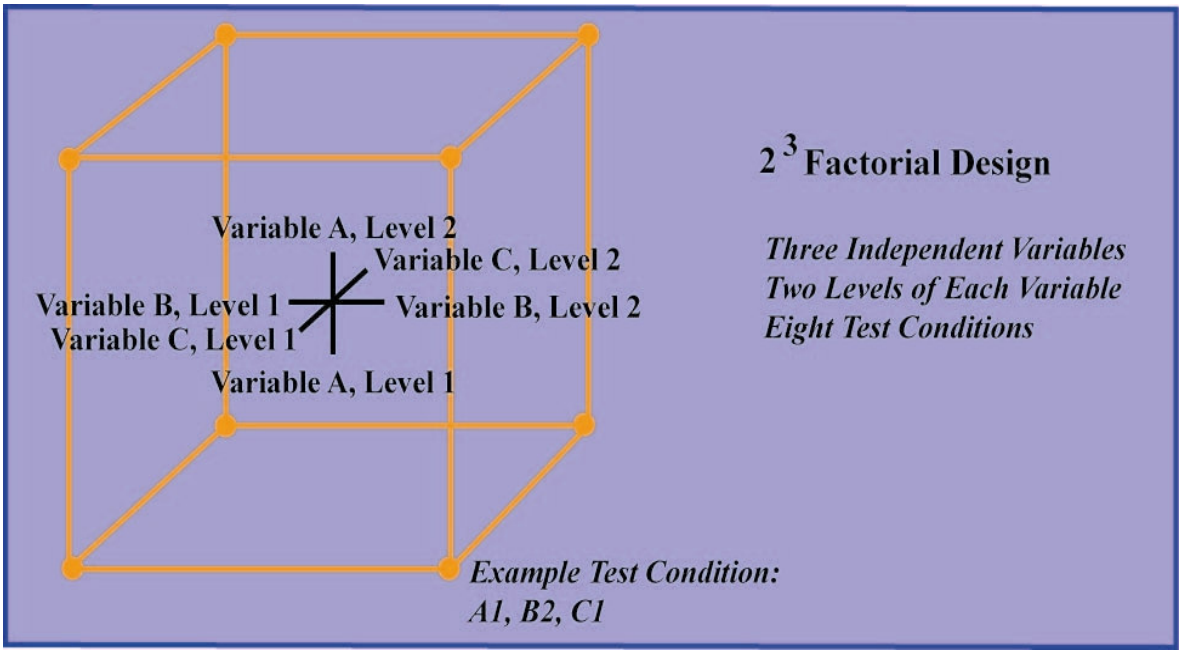


Figure 2.40: Factorial design with 2^3 factorial points [15]

2.8.1 STAVEX

STAVEX (STAtistische Versuchsplanung mit EXpertensystem) is a software for statistical design and evaluation of a series of experiments related e.g. to the process control, product optimisation or validation (Scheffler, 1997). It is an user-friendly PC-based software system enabling experimenters in research and development to apply statistical design and evaluation of experiments in their routine work independently of a statistician. It studies the relationship of

specified factors and responses. The ultimate goal is to find the optimal settings of all factors actually influencing the responses.

STAVEX helps to investigate process factors, like temperature or concentration, as well as mixture factors, which have to fulfill a summing-up condition typical for mixtures or formulations. STAVEX also supports the combination of responses in the form of a cost function assigning weights to the responses or a desirability function combining individual specification intervals. This way trade-offs been the responses can be studied. STAVEX supports sequential planning, it integrates statistical experimental design, statistical evaluation of results, and guidance to follow-up designs, i. e. the whole process of experimentation. This way, STAVEX typically runs through 3 stages of statistical experimental design: screening using linear models for factor reduction, modelling for further factor reduction using linear models with interactions, and optimisation for determining the optimal levels of the remaining factors.

For example, the plastic behaviour of a mixture of three additives can be investigated. In Figure 2.41, a 4-D plot has the % quantity of each additive on the three axes, whereas the colour scale represents the response value; this means the behaviour of the material ranges from brittle (red) to elastic (blue).

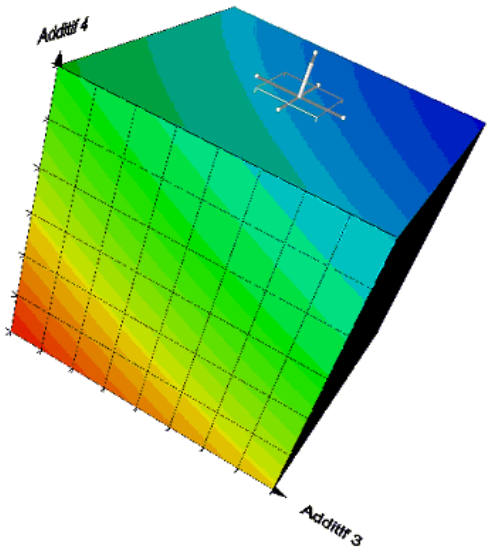


Figure 2.41: Example of the optimization of a material through a 4-D plot [16]

STAVEX is suited also for qualitative studies. Be a three component syrup (lemon, peach, and strawberry), the optimum component ratio providing an agreeable taste should be investigated. As the three components are mixed together, they have to add up to 100 % ("mixture factors"). The factors are depicted in a triangular coordinate system (Figure 2.42). 10 experiments were conducted (blue triangles). From the results for the response variable "taste", a quadratic model was fitted. The lines of constant value of the model function are ellipses (white); the best (highest) value for "taste" is attained at the blue encircled asterisk.

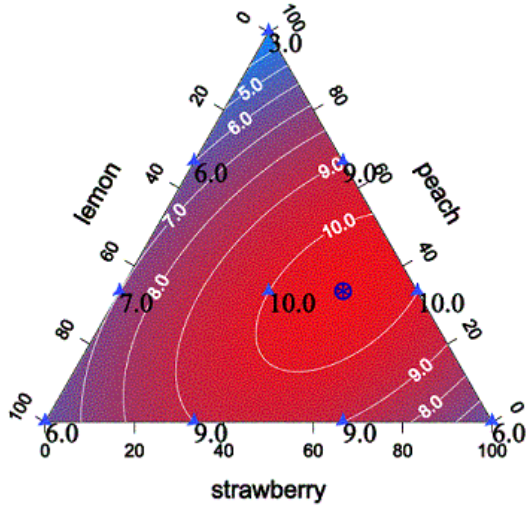


Figure 2.42: Example of a contour plot: taste variability of a three component syrup [16]

The program is organised in cycles, which consist of the data input, choice of the design, input of the results, analysis and acceptance of the analysis. After a cycle has been finished, the next cycle starts, with a possibly reduced set of factors, another design or other modifications from the previous cycle.The first step to start a statistical analysis is the specification of one or more response variable(s), which can be minimised, maximised or set at a target value. A first *screening* cycle (with normally more than 8 factors) might help to distinguish between crucial and neglectable factors. If the parameters are already on hand and they count between 4 and 8, a *modelling* cycle is more appropriate, whereas for less than 4 parameters an *optimisation* cycle can be directly executed.In all cycle types, the crucial (or thought to be such) factors are specified according to their type (qualitative, quantitative or mixture factors), their units, and eventually setting a value range. Modelling, and even more optimizing, permits to determine the optimal levels of all factors in order to get the previously targeted responses. Two different optima are determined, the “global” and the one lying in the “experimental area”. With the former, all quantitative factors can be freely varied, whereas with the latter, variations are possible only within the user-defined limits.

According to the response variables and the process factors chosen, STAVEX generates different possible factorial designs, among which the user may choose the most appropriate one. In this study, the factorial design “with D optimization” was chosen (where D stands for determinant of the results matrix), which fits particularly to investigate the perimeter and the central point of the experimental domain.

After having entered the results of the experiments, STAVEX proposes its analysis of the results: it determines the optimal settings of all factors to get the previously targeted responses, and suggests further factor settings for confirmatory experiments.

2.9 The dissolution process

2.9.1 In-vitro dissolution

The most widely used in-vitro test available to determine the release rate of drug products is the in-vitro dissolution test (Noory et al., 2000). Before a drug is absorbed from the gastrointestinal tract (GIT), it has to be released and dissolved first. Accordingly, the in-vitro dissolution test is a first important step to assess the quality of a certain compound and to guide development of new formulations. Such tests are extensively employed because of their low costs and accuracy (they can be standardized and validated).

2.9.2 The dissolution process

Some basic principles of the dissolution process of a solid dosage form are given by the film theory (Nernst, 1904). Be a solid immersed in an agitated liquid, surrounded by a stagnant liquid layer with a thickness h. At the solid's surface, the concentration of dissolved solid is equal to its saturation concentration S. Be c the concentration of the dissolved solid in the agitated dissolution medium. At the steady state, Fick's first law can be employed (see Equation 2.7)

$$J = -D\frac{\partial c}{\partial x} \qquad \text{Equation 2.7}$$

where *J* is the diffusion current, defined as the amount of substance passing vertically through an unit surface area per time. *D* stands for the diffusion coefficient, whereas *∂c/∂x* represents the constant concentration gradient corresponding to the slope (*C-S)/h* (see Figure 2.43). Considering the dissolved mass m and the surface area of the dissolving solid O, the Fick's law can be expressed according to Noyes Whitney (Noyes et al., 1897) (see Equation 2.8).

$$\frac{dm}{dt} = \frac{OD}{h}(S - c) \qquad \text{Equation 2.8}$$

Dividing both member of Equation 2.8 through the volume of the dissolution media *V,*
Equation 2.9 is obtained.

$$\frac{dc}{dt} = \frac{OD}{hV}(S - c) \qquad \text{Equation 2.9}$$

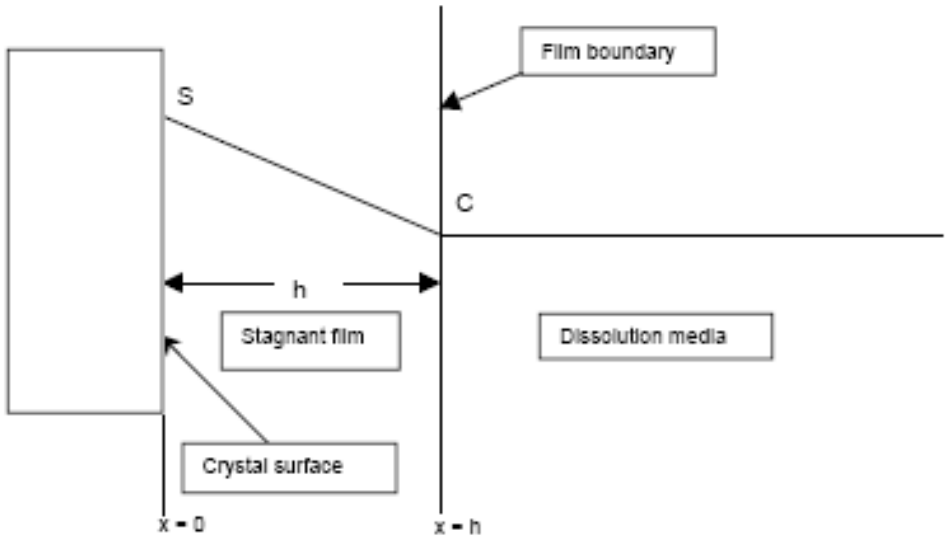


Figure 2.43: Fick's low graphic illustration [17]

If the middle distance between the discussed molecules is negligible compared to the diameter of the molecules, Einstein relation can be applied (see Equation 2.10).

$$D = \frac{RT}{N_a\ 6\pi\eta r} = \frac{kT}{6\pi\eta r} \qquad \text{Equation 2.10}$$

where N_A indicates the Avogadro number, R the universal gas constant, k the Boltzmann constant, T the temperature, η stands for the viscosity of the dissolution medium and r for the radius of the molecule. It is redundant to say that the molecular mass of a certain compound in a molecular-disperse solution does not have a big influence on the diffusion coefficient D, since the radius of a spherical particle corresponds approximately to the third root of its molecular mass. Another theory, called the surface renewal or penetration theory (Danckwerts, 1951), proposes the existence of a dynamic (and not stagnant) laminar layer h, meaning that the surface would be continually replaced by fresh liquid.

Mechanisms of release from coated pellets

Although MUPS are a kind of tablet, they dissolve into their subunits immediately after swallowing, which means that their dissolution is comparable to that of coated pellets.

In the case of release from coated pellets it can be distinguished between (Dressman et al., 1994) :

a. solution/diffusion through the continuous plasticized polymer phase;
b. solution/diffusion through plasticizer channels;
c. diffusion though aqueous pores.

The first mechanism assumes that the polymer forms a continuous phase in which the plasticizer and other additives are homogeneously dispersed. The diffusion of a solute molecule within an amorphous polymer phase is an activated process involving the cooperative movements of the penetrant (drug) and the polymer chain segments around it. It is by this stepwise process that hindered molecular diffusion occurs. Release by diffusion/solution through the plasticized polymer phase is depicted in Figure 2.44

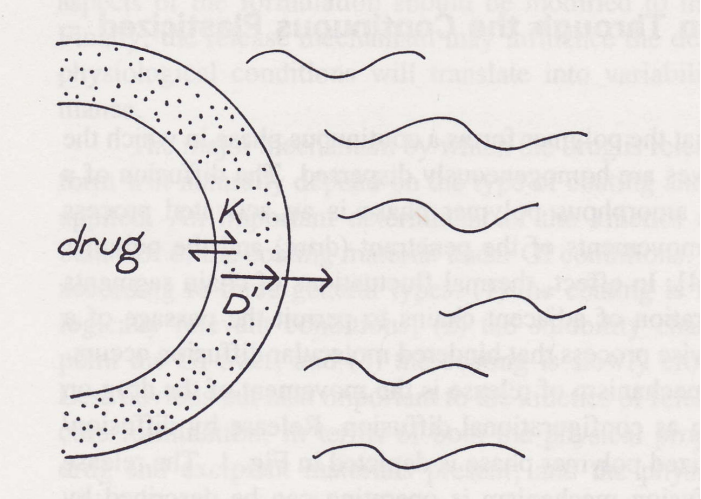


Figure 2.44: Drug release from coated pellets via solution/diffusion through the polymer film [18]

Based on the Fick's law (Equation 2.7), the release rate in presence of the above mentioned mechanism can be described by the Equation 2.11

$$J = \frac{P_m}{\delta}(C_s - C_b) \qquad \text{Equation 2.11}$$

Where J ist the flux (release rate per unit surface area of coating) C_s and C_b are the concentration of drug at the coating interface and the bulk, respectively, and δ is the coating thickness. The permeability coefficient of the coating polymer P_m can be written as

$$P_m = \frac{D\varepsilon}{\tau\beta} K = D'K \qquad \text{Equation 2.12}$$

where D ist the molecular diffusivity of the drug, K the distribution coefficient of the drug between the polymer membrane and fluid in the core (imbibed water), ε the volume fraction of the chain opening, β a chain immobilization factor and τ the tortuosity factor. The frequency with which a diffusion step occurs depends on the size and shape of the drug, tightness and bonds between adjacent polymer chains and the stiffness of the polymer chain. Generally speaking, the further below its glass transition temperature (T_g), the less permeable the polymer. Plasticizers lower the T_g, increase free volume and increase diffusivity. Accordingly, the solution/diffusion mechanism is dominant in continuous, flexible polymers.

The second mechanism intervenes when the plasticizer is not uniformly distributed in the coating polymer: it conceivably assumes the form of a continuous phase in form of patched channels. This mechanism, shown in Figure 2.45, can be described by the Equation 2.13, which derives from the Equation 2.12 replacing P_m, the permeability of the coating polymer, with P_{pl}, the permeability of the plasticizer.

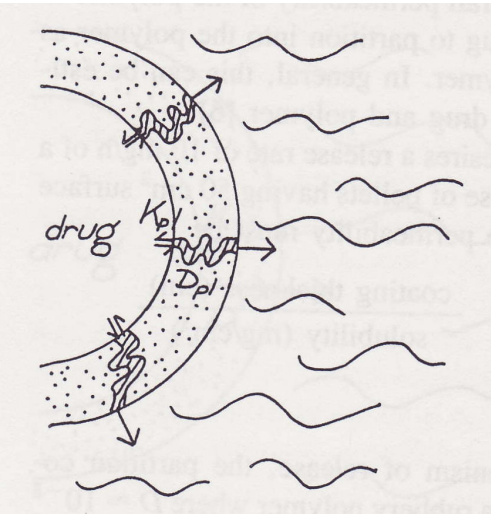


Figure 2.45: Drug release from coated pellets via solution/diffusion through plasticizer channels [18]

$$P_{pl} = \frac{D_{pl}\varepsilon_{pl}}{\tau_{pl}} K_{pl} \qquad \text{Equation 2.13}$$

In this case, K_{pl} is the distribution coefficient of the drug between plasticizer and the core fluid (imbibed water), τ_{pl} the tortuosity of the plasticizer channels, and ε_{pl} the volume fraction of plasticized channels. For this mechanism to be dominant, the following condition must be satisfied:

$$P_{pl} \approx 10^{-8} cm^2 / s = \frac{D_{pl}\varepsilon_{pl}}{\tau_{pl}} K_{pl}$$

Diffusivity in the plasticizer will generally be lower than in water since plasticizers tend to be relatively viscous. Assuming a $D_{pl} \approx 10^{-6}$ cm^2/s, a plasticizer load of 40% with half forming channels ($\varepsilon = 0.2$) and a low tortuosity ($\tau = 2$), the ability of the drug partition should be at least 0.1. In the reality, this mechanism was demonstrated to be too slow to explain the release rates observed.

The third model implies a continuous but inhomogeneous coating layer punctuated with pores. When the pellets come in contact with an aqueous medium, these pores fill with solution thus facilitating the diffusion of the drug, as illustrated in Figure 2.46.

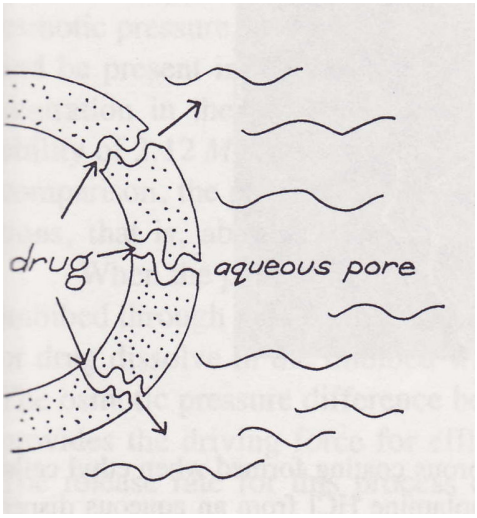


Figure 2.46: Drug release from coated pellets via diffusion through aqueous channels [18]

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This mechanism applies for coatings formed from aqueous dispersions of pseudolatexes rather than from organic solvents. During the coating and curing processes, the pseudolatex particles often do not fuse completely, thereby creating pores of about 1µm in the coating layer.
For diffusion through aqueous pores, the permeability coefficient P_p is given by

$$P_{pl} = \frac{D_p \varepsilon_p}{\tau_p} \qquad \text{Equation 2.14}$$

Where D_p is the aqueous diffusivity of the drug, ε_p the volume fraction of the auqueous channels, and τ_p their tortuosity. The partition coefficient K is the unity in this case.

For diffusion through aqueous pores to be the mechanism driving the release rate, P should be in the order of 10^{-8} cm^2/s. Considering $\tau = 10$, ε would amount to 0.02 (more than 2% of the surface area should consist of pores), whereas for $\tau = 2.5$, $\varepsilon = 0.005$ (more than 0.5% of the surface area should consist of pores). Therefore we can conclude that if SEM consistently indicates the presence of pores in the coating, it is likely that diffusion through the pores will contribute significantly to the overall release rate

.

3. Problem setting and Objective

UICEL PH/102 has been widely investigated as potential, bivalent excipient (filler/disintegrant) in direct compaction (see §2.3); surprisingly, so far has hardly any study focused on its perspective employment as filler/disintegrant in multiparticular formulations. Considering the limited number of appropriate cushioning excipients in MUPS formulations (see § 2.7.4), a novel "all-in-one" embedding material might represent a significant break-through in the search for more flexible and attractive multiparticular formulations. And this is also the scientific challenge this study faces.

As a matter of fact, MCC 102 is the most commonly used pelletization excipient in MUPS. Considering that UICEL is prepared starting from MCC 102, it becomes imperative to characterize and evaluate UICEL against MCC 102 as excipient in MUPS. To this scope, tabletting mixtures containing either UICEL-A/102 or MCC 102 pellets (loaded with sodium diclofenac and coated with Kollocoat SR 30D), appropriate cushioning excipients and disintegrants in different proportions will be prepared. Each tabletting mixture will be compressed into MUPS using a Presster™ Compaction Simulator under analogous parametric conditions. The resulting multiparticular tablets will be appropriately characterized, with a particular focus on their disintegration time and their dissolution profile. In fact, MUPS should ideally disintegrate immediately after administration and maintain the dissolution profile of their uncompressed subunits.

For the preparation of pellets, two different technologies will be employed and compared to each other: the direct pelletization and the dry powder layering on neutral cores. On the base of the properties of MUPS obtained from pellets produced with the former or the latter pelletization technology, a robust over-all production for MCC 102 / UICEL MUPS will be suggested.
This study aims also to compare MCC 102 (Cellulose I) and UICEL-A/102 (Cellulose II) as pellet filler and embedding excipients in MUPS for controlled release.

4. Materials and Methods

4.1 Materials

4.1.1 UICEL Production

Microcrystalline Cellulose SANAQ 102 L (Pharmatrans AG, LOT nr. MC230518, Basel, Switzerland; see Figure 4.1)

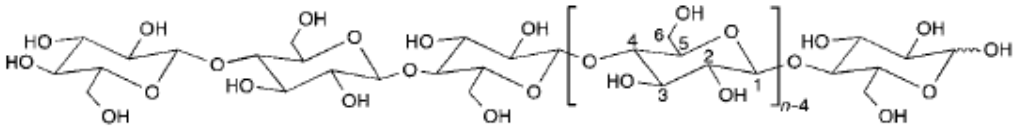

Figure 4.1: Chemical formula of cellulose

Empirical formula:	$(C_6H_{10}O_5)_n$
Manufacturing:	Powdered cellulose, manufactured by mechanical processing of α-cellulose pulp from fibrous plant materials.
Properties:	White, odourless, tasteless powder of various finesses, ranging from a free-flowing, dense powder to a coarse, fluffy, non-flowing material. Insoluble in water, dilute acids and most organic solvents.

Sodium Hydroxide, Hänseler AG, Switzerland

Ethanol 99%, Hänseler AG, Switzerland

4.1.2 Pelletization

Microcrystalline Cellulose SANAQ 102 L (Pharmatrans AG, LOT nr. MC230518, Basel, Switzerland; see Figure 4.1)

Sodium Diclofenac (Mepha AG, LOT nr. 346/126522, Aesch, Switzerland; see Figure 4.2)

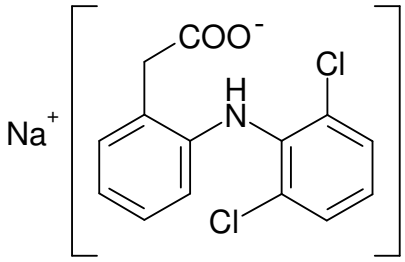

Figure 4.2: Chemical formula of sodium diclofenac

Empirical formula:	$C_{14}H_{10}Cl_2NNaO_2$
Molecular weight:	318.1 g/mol
Appearance:	white to slightly yellowish or light beige powder
Melting point:	283 - 285°C
Solubility pH 1-4:	sparingly soluble
pH 7:	slightly soluble
pH 8-10:	soluble

Plasdone® K-29-32 (LOT Nr. TX11108A, ISP AG Switzerland; see Figure 4.3)

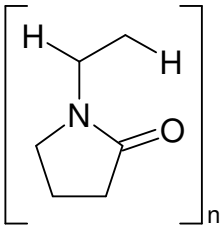

Figure 4.3: Chemical formula of polyvinylpirrolidone

Empirical formula:	$(C_6H_9NO)_n$
Molecular weight:	$(111.1)_n$ g/mol
Composition:	linear polymers of 1-ethenylpyrrolidin-2-one
Appearance:	white or light beige, highly igroscopic powder
Solubility pH 1-4:	freely soluble in water, ethanol and methanol, hardly soluble in acetone

Suglets® SANAQ 355 (LOT nr. 310 V, Pharmatrans-Sanaq AG, Basel, Switzerland)

Composition:	92 % of sucrose added of maize starch, hydrolyzed maize and colorants.
Appearance:	White spherical granules of sweet taste
Loss on drying:	1.8 %
Particle size:	98.7 % between 355 and 500 µm (0.4 % > 500 µm, 1.0 % < 355 µm)
Sphericity degree:	95%

Cellets® 350 (LOT nr. 04013505, Pharmatrans-Sanaq AG, Basel, Switzerland)

Composition:	100 % MCC 102.
Appearance:	White or nearly white or beige, hard and partially spherical particles
Loss on drying:	4.6 %
Particle size:	96.2 % between 355 and 500 µm
Sphericity degree:	96 %

4.1.3 Coating

Kollicoat® SR 30D (LOT nr. 0001235, BASF AG, Ludwigshafen, Germany; see Figure 4.4)

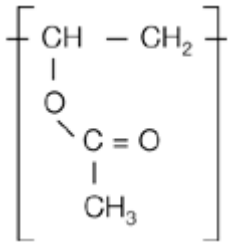

Figure 4.4: Chemical formula of polyvinyl acetate

Composition:	Aqueous dispersion of polyvinyl acetate (27% w/w), polyvinyl pyrrolidone (2.7 % w/w) and sodium lauryl sulfate (0.3% w/w).
Structural formula:	$(C_4H_6O_2)_n$
Approximate Mw:	450.000
Appearance:	Milky white-to-yellow, slight characteristic odour
Miscibility/ Solubility:	Miscible with water in any ratio, insoluble in dilute acids or bases
Viscosity:	100 mPa·s
MFT:	18°C
Monograph:	Ph.Eur. 5.8 Poly (Vinyl Acetate) dispersion 30 %

Triethylcitrate (TEC) (LOT nr. S26742-435, Sigma-Aldrich Chemie GmbH, Switzerland; see Figure 4.5)

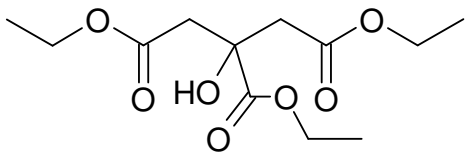

Figure 4.5: Chemical formula of triethylcitrate

Structural formula:	$C_{12}H_{20}O_7$
Mw:	276.29 g/mol
Composition:	> 99 % w/w of triethyl-2-hydroxypropane-1,2,3-tricarboxylat.
Properties:	Colourless, limpid, viscous, hygroscopic liquid; soluble in water, miscible with ethanol and ether, sparingly soluble in fat oils.

Riboflavin (Lot. Nr. 034k1323, Riboflavin-5'-Monophosphate Sodium Salt, Sigma-Aldrich Chemie, Steinheim, Germany; see Figure 4.6)

Structural formula:	$C_{17}H_{20}N_4NaO_9P$
Mw:	478.33 g/mol
Definition:	Riboflavin-5'-sodiummonohydrogenphosphate as main component added with other Riboflavin sodium phosphates; it contains 73.0 - 79.0 % of Riboflavin ($C_{17}H_{20}N_4O_6$; Mw 376,4) referred to the dry substance.
Properties:	Yellow-orange, crystalline, hygroscopic powder; soluble in water, hardly soluble in ethanol and practically insoluble in ether.

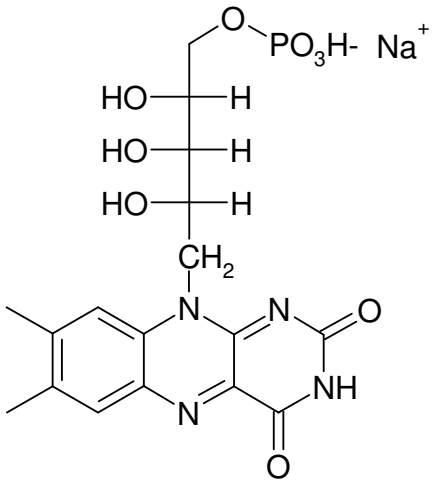

Figure 4.6: Chemical formula of Riboflavin-5'-Monophosphate Sodium Salt

Talcum powder (Talcum powder, Hänseler AG, Herisau, Switzerland)

Structural formula:	$Mg_3Si_4O_{10}(OH)_2$
Mw:	379.3 g/mol
Definition:	Pulverised, natural, magnesium silicate containing water. The substance can also contain different amounts of minerals as chlorite (aluminium and magnesium silicate), magnesite (magnesium carbonate), calcite (calcium carbonate), and dolomite (calcium and magnesium carbonate).
Properties:	Light, white powder; practically insoluble in water, ethanol, diluted acids and diluted alkali.

Sodium dihydrogen phosphate (Hänseler AG, Herisau, Switzerland; see Figure 4.7)

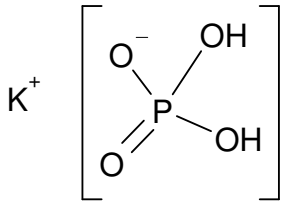

Figure 4.7: Chemical formula of Sodium dihydrogen phosphate

Structural formula:	KH_2PO_4
Mw:	136.1 g/mol
Definition:	Sodim dihydrogen phosphate contains between 98.0 and 100.5% of KH_2PO_4, calculated on the dried basis.
Properties:	White, crystalline powder or colourless crystals; easily soluble in water, insoluble in ethanol.

4.1.4 Tabletting

Partially pregelatinized maize starch Sta RX1500® (Lotnr. 811024, Dartford Kent, UK; see Figure 4.8).

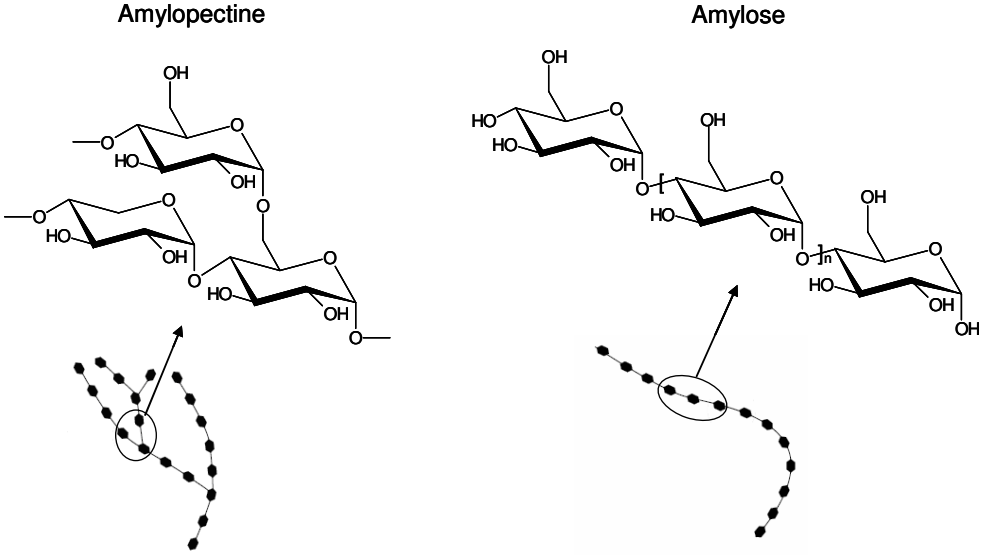

Figure 4.8: Chemical formula of maize starch

Definition:	Maize starch physically modified by compaction in presence of water. It contains undamaged maize grains and gelatinized starch particles, which swell considerably in contact with water bringing a certain hydrosolubility.
Properties:	White, tasteless and odourless powder; strong disintegrant

Magnesium stearate (Lot Nr. 1025336, Novartis Pharma AG, Basel, Switzerland; see Figure 4.9)

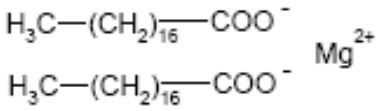

Figure 4.9: Chemical formula of Magnesium stearate

Definition: Magnesium stearate is a mixture of magnesium salts of several fatty acids, principally stearic acid ($[C_{17}H_{35}COO]_2$, molecular weight 591.27 g/mol) and palmitic acid ($[C_{15}H_{31}COO]_2$, molecular weight 535.1 g/mol).

Properties: White, very fine, light powder; insoluble in water and water free ethanol; prevalent lubricant properties.

4.2 Characterization of the materials

4.2.1 Characterization of MCC 102 and UICEL-A/102

The X-ray diffractogramm and and IR spectrum, plus the data for degree of cristallinity, loss on drying, bulk and tap density, porosity, Hausner Ratio, Carr's Index, particle size distribution, specific surface area for MCC 102 and UICEL-A/102 are presented and discussed in §5.1.

4.2.2 Characterization of the drug substance

Data for true density, poured and tapped density, relative poured density (ρ_p), relative tapped density (ρ_t), Hausner ratio, residual moisture content, mean and median particle size, respectively, are shown in Table 4.1.

Table 4.1.: Data for true, poured and tapped density, relative poured density (ρ_p), relative tapped density (ρ_t), Hausner ratio, residual moisture content, mean particle size and median particle size of Sodium Diclofenac

Diclofenac Sodium	(n=5)								
	True density [g/cm^3]	Poured density [g/ml]^2	Tapped density [g/ml]^2	ρ_p[rel]	ρ_t[rel]	Hausner ratio	Residual moisture content [% w/w]	Mean particle size [µm]	Median particle size [µm]
Mean Value	1.5296	0.274	0.582	0.261	0.397	1.48	3.21	20.5	16.5
RSD [%]	0.11	1.2	0.34			0.54	5.04	12.3	10.4

All determinations were made according to the equipment specifications. Details in § 4.3.2

4.2.3 Characterization of the excipients

SEM pictures of the main excipients are shown in Figure 4.10.

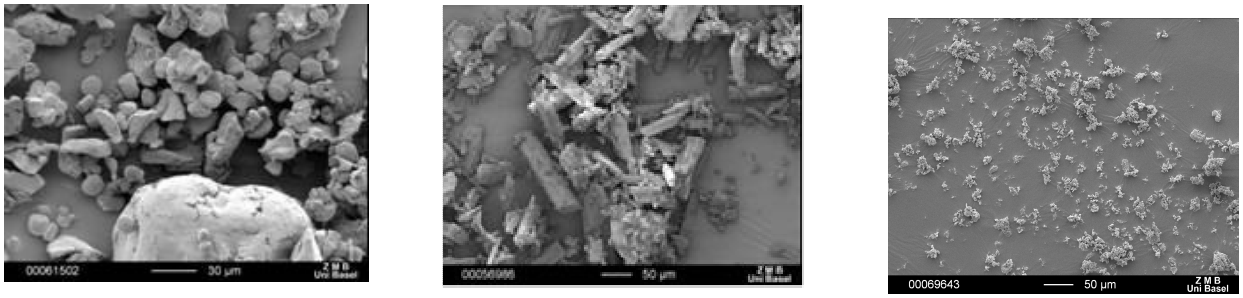

Figure 4.10: SEM images of, from left to right, STA RX 1500®, sodium Diclofenac and Plasdone® K-29-32

Data for true density, poured and tapped density, relative poured density (ρ_p), relative tapped density (ρ_t), Hausner ratio, residual moisture content, mean and median particle size, respectively, are shown in Table 4.2.

Table 4.2.: Data for true, poured and tapped density, relative poured density (ρ_p), relative tapped density (ρ_t), Hausner ratio, residual moisture content, mean particle size and median particle size of the used excipients

Excipients	(n=5)								
	True density [g/cm^3]	Poured density [g/ml]^2	Tapped density [g/ml]^2	ρ_p[rel]	ρ_t[rel]	Hausner ratio	Residual moisture content [% w/w]	Mean particle size [µm]	Median particle size [µm]
Plasdone® K-29-32									
Average	1.2356	0.324	0.410	0.276	0.335	1.32	6.56	106.7	95.7
RSD [%]	0.08	0.8	1.1			1.2	0.8	0.6	0.4
STA RX® 1500									
Average	1.498	0.312	0.410	0.254	0.335	1.32	9.80	49.8	29.5
RSD [%]	0.09	1.1	1.3			1.2	2.4	2.3	0.7
Mg-Stearate									
Average	1.0446	0.223	0.330	0.224	0.316	1.41	3.21	19.5	14.0
RSD [%]	0.12	0.18	1.3			1.3	5.4	4.0	16.5

All determinations were made according to the equipment specifications. Details in § 4.3.2

4.2.4 Characterization of the neutral cores

Data for true density, poured and tapped density, relative poured density (ρ_p), relative tapped density (ρ_t), Hausner ratio, residual moisture content, mean and median particle size, respectively, are shown in Table 4.3.

Table 4.3.: Data for true, bulk and tapped density, Hausner ratio, residual moisture content, mean particle size and median particle size of the used excipients

Cores	(n=5)							
	True density [g/cm^3]	Bulk density [g/cm^3]	Tapped density [g/ml]^2	Hausner ratio	Sphericity index	Residual moisture content [% w/w]	Mean particle size [µm]	Median particle size [µm]
Suglets® 355								
Mean Value	1.560	0.79	0.77	1.03	0.96	3.8	461.86	429.9
RSD [%]	2.5	2.2	2.4	1.5	6.5	1.2	10.5	12.8
Cellets® 355								
Mean Value	1.498	0.89	0.86	1.03	0.95	4.6	440.49	433.48
RSD [%]	3.1	3.2	1.5	2.1	5.2	0.8	16.8	18.9

All determinations were made according to the equipment specifications. Details in § 4.3.2

4.3 Methods

4.3.1 Production of UICEL-A/102

Figure 4.11 briefly schematizes the plant employed for the production. The vessel R 340, filled with 20 Kg of Microcrystalline Cellulose SANAQ 102 L, 24 Kg of Sodium Hydroxide particles and 116 Kg of distilled water, was cooled from 61°C to 28°C in 1 hour through an external cooling jacket. Afterwards, 120 l of ethanol were seeped from the vessels B 347 and B 348 into the reactor at the velocity of 10 l/min. The thus prepared cellulose gel was recovered 24 hours and later on filtered in three batches through an additional movable filter unit connected to the valve V 340.61. The product was then washed with distilled water until a neutral pH was reached, subsequently filtered and dried in a vacuum oven till it had residual moisture of 7%.

(a) (b)

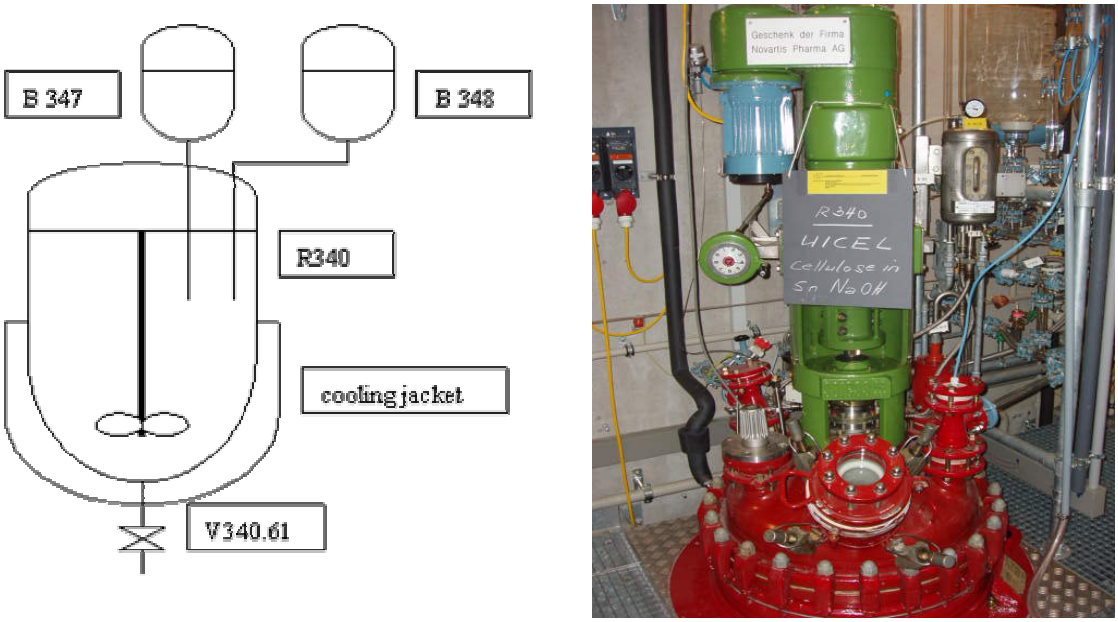

Figure 4.11: Multipurpose plant R340: (a) Schematic drawing; (b) Picture

4.3.2 Characterization of drugs, excipients and neutral cores

Residual moisture content

The residual moisture content was determined with an infrared balance Mettler Toledo Type LP 16M (Mettler Instruments, Nänikon-Uster, Switzerland). Samples of approximately 1 g were prepared. They were heated up for 20 min to 110°C giving the loss of moisture in percent by weight. The approximate theoretical moisture content of the granulates was determined by the sum of the moisture contents of the different starting materials in equilibrium with 45% relative humidity at room temperature (see Equation 4.1).

$$M = \sum_{i=1}^{n} \frac{a_i.w_i}{100} = \frac{a_1.w_1 + a_2.w_2 + ... + a_n.w_n}{100}$$ Equation 4.1

where *M* is the total amount of water in the sample, *a* denotes the part of weight of every component in percent by weight and *w* stands for the content of water of every part in the sample in percent by weight. All sorption isotherms present a hysteresis. Therefore the experimental values of the residual moisture content of the granulates coming from a wet state after granulation -in contrast to the residual moisture content of the starting materials coming from a dry state - were transformed according to Equation 4.2 to values that refer to a dry state of the sample.

$$M_d = \frac{100M_w}{100 - M_w}$$ Equation 4.2

M_d is the content of water referred to the dry sample, while M_w represents the content of water referred to the wet sample.

Particle size distribution

The average particle size was determined with a Malvern Mastersizer X (Malvern Instruments, Worcestershire, UK). The measurements were carried out 5 times for each sample. The average and the median particle size of the neutral cores and all pellet batches was measured using a MS 64-Dry powder feeder (Model MSX 64, Malvern Instruments, Worcestershire, UK). The following instrument settings had been done: The federate was set to level 5 and the air pressure to 1 bar. The number of sweeps was set to 30'000 in a time frame of 60 s. The active beam length was set to 10.0 mm with a range lens of 1000 mm. An obscuration value between 1-10% was got in all measurements. With the software (Malvern) the particle size distribution of the samples including mean and median particle size could be calculated from the raw data. The function "polydispers" was activated. The average particle sizes of all samples mentioned above were > 50 µm, therefore, the "Frauenhofer" model was chosen (according to the recommendation of Malvern). For the excipients in powdery form, different settings were used. The average and median particle size of UICEL-A/102 were measured with the dry powder feeder and the same lens as described above. The raw data were also evaluated with the "Frauenhofer"-model and the activated "polydispers"-function.

The pressure, however, had to be increased to 2 bar and the federate was set to level two. The excipients Plasdone® K-29-32 and Sta-RX 1500® could be characterized using the dry powder feeder. A lens of 300 mm was chosen, the federate was set to level 5 and the pressure was

increased to two bar. For the evalutation of the raw data, the mathematical model “2RAA” with the function “polydispers” was chosen (according to the recommendation of Malvern Instruments). It was not possible to determine the particle size distribution of the other powder samples with the dry powder feeder without generating artefacts: Huge powder clusters appeared (> 1000 µm), that could not been separated by increasing the air pressure or by changing the feedrate. Therefore, the particle size distribution had to be determined in a liquid with a MS-1-Small Volume presentation sample unit (Model: MS 519, Malvern Instruments, Worcestershire, UK). The particle size of magnesiumstearate and diclofenac sodium was determined in Aceton with the following settings: The number of sweeps was set to 2000 and the sample time to 60s. The active beam length was set to 2.4 mm using a lens of 300 mm. It was paid attention to get an obscuration value between 10-30% in all measurements. The polydispers function was activated. The mathematical model 2OFD was used (according to the recommendation of Malvern Instruments).

All pellet batches underwent a sieve analysis as well. A set of 8 sieves in a mesh size serie of √2 was used. The following mesh sizes (in micrometers) were selected: 1000, 710, 500, 355, 250, 180, 125, 90 and a receiving pan. The sieves were weighed and stacked on each other in ascending degrees of mesh size. 100g of the sample were placed on the top sieve and the tower was oscillated for 10 minutes (Oscillator Type Vibre, Rietsch, Germany). Afterwards, the substance amount on each sieve was weighed. The average particle size was arithmetically, the median graphically determined.

Flowability

The employed equipment consisted of a plastic hopper with an orifice of 0.9 cm diameter, a balance and a computer with the software “balance link”. 100g of the sample were firstly poured in a closed plastic hopper and then made flow into a plate. The mass on the plate got weighed every 0.16 s and the value automatically transferred in an excel sheet. The measurement was carried out in triplicate and expressed as a diagram mass vs. time. The average of the three diagram slopes represented the flowability in g/s.

Bulk and tapped density, Hausner Ratio

The equipment consisted of a tapped density volumeter (Jolting volumeter, Type EG80, J. Engelmann AG, Apparatebau, Ludwigshafen am Rhein, Germany). 100g of powder or granules were poured into a glass cylinder so as to read immediately their bulk volume (50-250ml), and then tapped 10, 500 and 1250 times, and if necessary further 1250 times, in order to check the respective tapped volume.

Both bulk and tapped density were calculated using the Equation 4.3:

$$\rho = \frac{m}{V}$$ Equation 4.3

where: ρ: Bulk or tapped density [g/ml]
m: Weight of the sample [g]
V: Bulk or tapped volume [ml]

The Hausner ratio (HR) was determined by the ratio of the poured and the tapped density:

$$HR = \frac{true\ density}{tapped\ density}$$ Equation 4.4

True density

The true density was measured using an AccuPyc 1330 helium pycnometer (Micrometrics, Norcross, USA) having a known volume 12.0978 cm^3. The apparatus determined the sample volume on the base of the displaced gas mass, and then it calculated the true density dividing the sample weight by the sample volume. The pycnometer repeated automatically the measurement five times for each sample, and the final true density was calculated as average of the five results.

Scanning Electron Microscopy

The SEM can plastically display surfaces like a light microscope, with the advantage that it scans the sample surface with an electron beam, instead of a light beam, leading to a resolving power of 1 nm and to a possible magnification of about 400'000x. The equipment consists of a cylindrical column supplied with an electron source, an anode plate, an electromagnetic lens, a specimen chamber, and a cathode-ray tube (CRT) (Figure 4.12). In order to obtain SEM images, extremely small quantities of UICEL-A/102 and MCC 102 samples were put on a double-sided carbon tape, sputtered with gold and then observed by means of a scanning electron microscope Philips SEM XL 30 FEG (Philips Electron Optics, Netherlands) at a voltage of 10 kV and 100x magnification.

4.3.3 Additional tests for the characterization of MCC 102 and UICEL-A/102

Powder X-ray diffraction (XRD) measurements were conducted over a 2-40° 2θ range on a Scintag Model XDS 2000 diffractometer (Cupertino, CA, USA), equipped with monochromatic Cu Kα X-Rays. The step width was 0.5° 2θ /min with a time constant of 0.5 s.

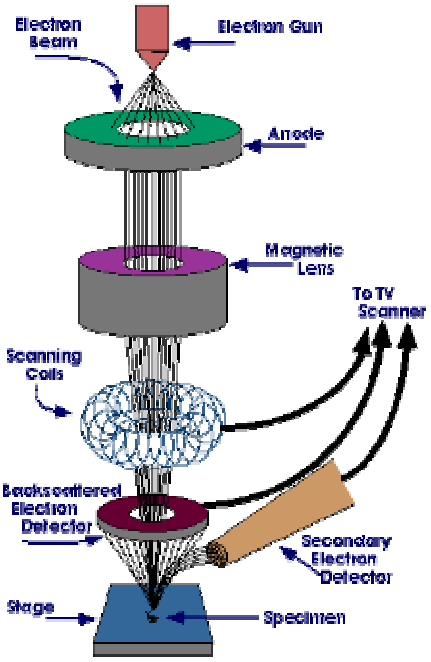

Figure 4.12: SEM Microscope [19]

Samples were degassed applying vacuum at room temperature during 24 h prior to the determination of the specific surface area. Three samples of about 1.5 g for each powder were analyzed; for each measure five experimental points were used for calculation (BET multipoint). According to the BET theory, gas molecules physically adsorb on a solid in layers infinitely, and there is no interaction between each adsorption layer, so that the Langmuir theory can be applied to each layer. The resulting BET equation is expressed by Equation 4.5 (Brunauer et al., 1938):

$$\frac{1}{v\left[\left(P/P_0\right)-1\right]} = \frac{C-1}{v_m C}\frac{P}{P_0} + \frac{1}{v_m C} \qquad \text{Equation 4.5}$$

where P and P_0 are the equilibrium and the saturation pressure of adsorbates at the temperature of adsorption, v is the adsorbed gas quantity (for example, in volume units), v_m is the monolayer adsorbed gas quantity and c is the BET constant.

4.3.4 Direct pelletization of MCC 102 and UICEL-A/102

First of all, homogeneous pellets, or pellets whose composition is the same in any point of their core and surface, were prepared (see Figure 2.9). A schematic representation of the machine and the technology employed are depicted in Figure 4.13. It consists of a metal pan in which the product is loaded, a fixed height rotary disc with adjustable slit, through which an appropriate

amount of fluidizing air flows, a tangentially oriented spray nozzle and a filter unit above all. By fine adjustment of such parameters as air flow, make-up air temperature, compressed air pressure, rotor velocity, diameter of the nozzle, spray rate, pellets with appropriate, reproducible characteristics may be produced.

(a) (b)

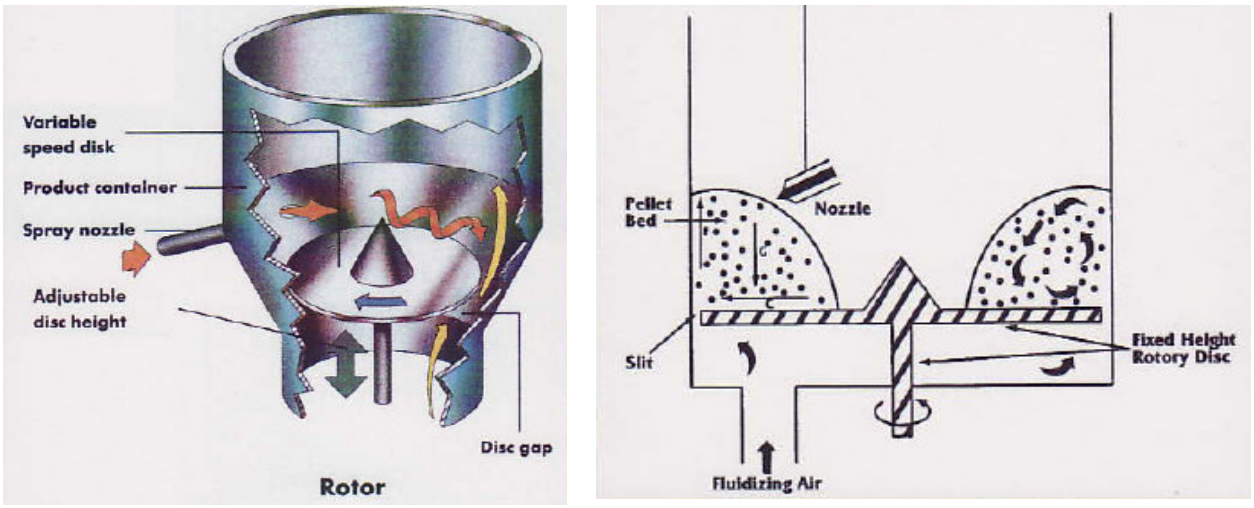

Figure 4.13: Schematic representation (a) and section (b) of a fluidized bed GPCG 1.1 [14]

Unfortunately, it was neither possible to provide the machine with a movable unit for powder consumption measurements, nor feasible to measure the torque. Accordingly, the end point of pelletization was determined by optimization, for each formulation, of the amount of granulating liquid leading to pellets with a mean diameter of 500 ± 300 nm. The process was monitored by pellets sampling in process.

The powder mixture of filler (MCC 102 or UICEL-A/102) and active ingredient (sodium diclofenac), each time in the appropriate ratio, was loaded into a fluidised bed GPCG 1.1 (Glatt, Binzen, Germany) equipped with a rotor insert and tangential spray for the binder solution. The optmimized process conditions were: batch size: 500 g; inlet temperature: 20°C; product temperature: 16°C; air flow: 1.2 bar; nozzle diameter: 0.8 mm; spray pressure: 3.0 bar; spray rate: 30-50 g/min; final drying: from 35 to 50°C over 20 min. The pellets were additionally dried in an oven at 50 °C till 5-8% residual moisture. The pelletization experiments were designed by means of a STAVEX full factorial design. The investigated factors were: type of filler in the tabletting mixture (MCC or UICEL-A/102), drug amount in the tabletting mixture (10-40% w/w), amount of sprayed granulating liquid (3-5% w/w). As response variables were chosen: the yield of the pelletization, defined as the mass of pellets within 500 ± 300 nm, and the proximity of the mean particle size of each run to the value 500 nm. In Table 4.4 the different runs carried out are listed.

Table 4.4: Batches of pellets produced

Run	SD [%]	PVP [%]	Filler
1	10	3	MCC 102
2	20	3	MCC 102
3	40	3	MCC 102
4	10	4	MCC 102
5	20	4	MCC 102
6	40	4	MCC 102
7	10	5	MCC 102
8	20	5	MCC 102
9	40	5	MCC 102
10	10	3	UICEL-A/102
11	20	3	UICEL-A/102
12	40	3	UICEL-A/102
13	10	4	UICEL-A/102
14	20	4	UICEL-A/102
15	40	4	UICEL-A/102
16	10	5	UICEL-A/102
17	20	5	UICEL-A/102
18	40	5	UICEL-A/102

4.3.5 Pelletization of MCC 102 and UICEL-A/102 by dry powder layering

Secondly, inhomogeneous pellets were prepared, i.e. pellets consisting of a neutral core layered with a mixture of excipient(s)/active ingredient(s). To produce such pellets, a novel pelletization technology known as dry powder layering was emplyoyed. The same machine used in §4.3.4 was equipped with the components for powder addition: an agitated feeder with hollow helix, a powder transfer funnel with frame for an air filter and a powder dosing sleeve which surrounds the immersed spray nozzle (see Figure 4.14). This made it possible to add the mixture excipients/active with a specified velocity into the main chamber, independently of the spray rate of the granulation liquid.

In the praxis, the main chamber of a fluidized bed GPCG 1.1 (Glatt, Binzen, Germany) was charged with 500 g of the starting cores (Suglets® 355 or Cellets® 350), whereas a powder mixture composed of 200 mg of filler (either MCC 102 powder or UICEL powder) and 200 mg of active ingredient (sodium diclofenac) was loaded into an appropriate box located over the main chamber. According to the dry powder layering method (see section 2.4.2), the cores were sprayed tangentially with the binder solution (5 % w/w water solution of PVP) and at the same time fed with the powder mixture.

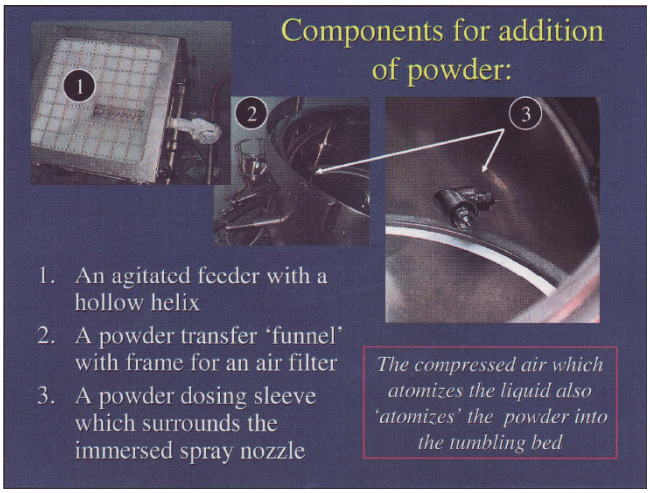

Figure 4.14: Components for powder addition in a fluidized bed GPCG 1.1 [14]

The optimized pelletizing conditions were: Batch size: 500 g; inlet temperature: 20°C; product temperature: 30°C; air flow: 100 m^2/h; nozzle diameter: 0.8 mm; spray pressure: 3.0 bar; spray rate: 14-20 g/min; powder feed rate: 10.4 g/min; rotor speed: 1120 rpm. According to this general procedure, the pellet batches shown in Table 4.5 were produced. In order to obtain a product mean size of about 0.5 mm, samples were regularly withdrawn until the targeted mean size had been reached. The pellets were then dried in an oven at 60 °C till 4-8% residual moisture and the yield (product fraction having a diameter of 0.2 - 0.8 mm for the MCC-pellets and 0.2 - 1mm for the UICEL- pellets) was calculated.

Table 4.5: Batches of pellets produced

Batch	Powder filler	Core
1	MCC 102	Suglets®
2	MCC 102	Cellets®
3	UICEL-A/102	Suglets®
4	UICEL-A/102	Cellets®

4.3.6 Pellet coating

Due to its retardation properties and its flexibility, the polyvinyl acetate Kollicoat® SR 30 D was selected as film builder (Dashevsky, 2004),(Guerra, 2006). The water suspension contained also the following components: Triethyl citrate (TEC) as a plasticizer, talk as a lubricant and riboflavin as a fluorescence marker (the riboflavin would act as marker in the integrity test of the film layer by means of CLSM). The complete coating formulation is listed in Table 4.6.

Table 4.6: Composition of the spray suspension

Substance	Mixture [% w/w]	Mixture on dry mass [% w/w]
Kollicoat® SR 30 D	80.0	75.5
TEC	3.6	11.3
Riboflavin	0.2	0.6
Water	14.2	-
Talc	2.0	12.6
Total	100	100

The suspension was prepared according to the following procedure. In a beaker put on a magnetic plate and furnished with a magnetic stirrer, Kollicoat® SR 30 D and TEC were mixed and agitated for 15 minutes. Then riboflavin was dissolved in water and added to the mixture, as well as talc passed through a sieve (mesh size 90 µm). Finally, the mixture was sieved (mesh size 125 µm) to dispose of solid particles due to premature polymerisation.
The coating formulation selected is normally employed for manufacturing sustained release pellets. What's more, it provides the pellets with a flexible film which avoids ruptures during their compaction into MUPS. The addition of ≈ 4% w/w plasticizer in the coating suspension plays a crucial role in the aimed soft compaction, as it enhances the elasticity of the final film. Talc, on the other hand, is added in order to prevent the adhesion of the pellets between each other and against the internal surface of the apparatus.

All four batches of pellets were coated in a fluidised bed, type Miniglatt (Glatt, Binzen, Germany), under the following optmimized parametric conditions: pellets 100 g, bottom spray, temperature of the inlet air 20°C, air flow pressure 0.5 bar, spray pressure 1.5 bar, nozzle diameter 0.8 mm, spray rate 1.3-1.5 g/min. According to the low MFT of Kollicoat® (18°C), no curing was necessary. The coated pellets were finally characterized and then stored in an exsiccator.

4.3.7 Pellet characterization

Homogeneous and inhomogeneous pellets (coated as well as uncoated) underwent the following characterization tests:

- Residual moisture
- Flowability
- Bulk and tapped density, Hausner Ratio
- Particle size distribution by means of sieve analysis

- Particle size distribution by means of Mastersizer
- True density
- Specific surface area
- Drug content
- Porosity
- Scanning electron microscopy (SEM)
- Confocal scanning laser microscopy CLSM (only for the coated batches)
- Drug release (only for the coated batches)

All methods, except drug content, porosity, CLSM and drug release, are extensively explained in § 4.3.2 and §4.3.3.

Drug content

The content of sodium diclofenac in pellets was measured by dissolving 100 mg of pellets in 100 ml phosphate buffer pH 7.4 and measuring the absorption of the solution at 276 nm in a Beckmann DU®530 Spectrophotometer. For every batch the measurement was carried out in triplicate and expressed as an average ± standard deviation.

Porosity

The porosity of the pellets was measured in a Mercury porosimeter PoreSizer 9320 System (Micromeritics, Norcross, GA, USA), Software V. 2.05. The experiment was carried out in triplicate on 200 mg of pellets.

Confocal laser scanning microscopy (CLSM)

The CLSM, which finds extensive application in natural sciences, is a light microscopy imaging technique capable of taking innumerable optical sections through a 3-dimensional fluorescent specimen along one specific plane. This is simply achieved by moving the focal plane of the instrument through the depth of the specimen, step by step.

To create the optical sections, a collimated, polarized laser beam is reflected by a beam splitter and focused onto the specimen. At each point of the specimen a certain fluorescent light is emitted and an image registered and reassembled by a computer. A pinhole positioned next to the detector serves as remover of any emitted light which does not come directly from the focal point (Figure 4.15).

Starting from different optical sections of a specimen, it is also possible to reconstruct its 3-dimensional image (Figure 4.16). This technique is especially suited for thick and opaque specimens, barely observable by conventional light microscopes.

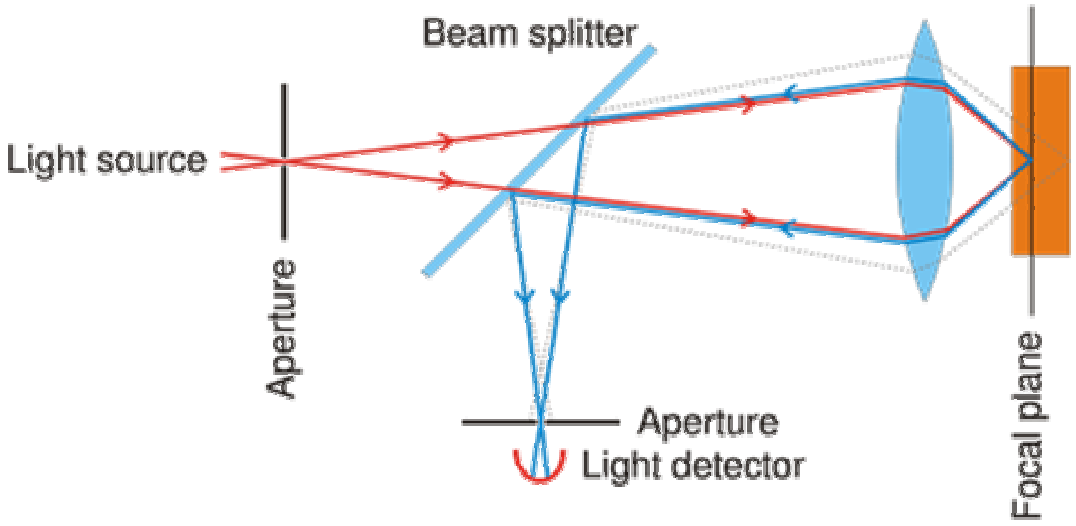

Figure 4.15: The principle of a confocal laser scanning microscope [20]

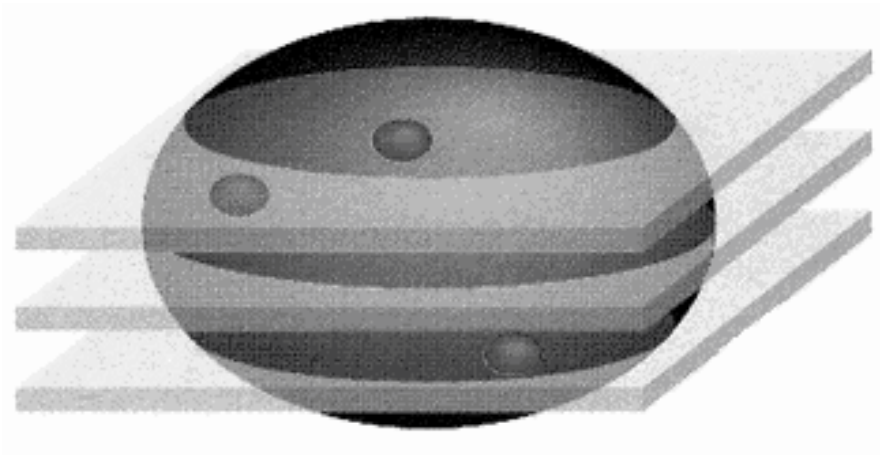

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Figure 4.16: Optical section of a sphere by confocal planes [21]

The uniformity of the pellet coating films was ascertained using a Leica TCS-SP5 (Leica Microsystems Heidelberg GmbH, Mannheim, Germany) confocal laser scanning microscope with an objective 10x 0.3 dry. Images were recorded in sections of 1 µm through the depth of the specimen, and evaluated using the software Leica Advanced Fluorescence 1.6.3 Build 1163.

Drug release from the coated pellets

The drug release test was performed in a dissolution apparatus Sotax AT 7 smart (Sotax AT 7, Allschwil/Basel, Switzerland) according to the general specifications of USP XXX; in particular, the dissolution conditions for sodium diclofenac solid dosage formulations were employed (USP XXX, NF XXV). 200 mg of each coated pellet batch were put into 900ml of phosphate buffer pH 7.4, the paddle rotating speed set was 50rpm and the temperature 37±1°C. Samples (10 ml) of dissolution medium were removed at regular time intervals, while an equal volume of dissolution medium held at the same temperature was added to maintain a constant volume. Sink conditions (the concentration of the active ingredient in the medium should be less than 10% of the concentration of a saturated solution) were maintained throughout the entire experiment. The drug liberated was measured using a Beckmann DU®530 Spectrophotometer and the values were plotted vs. time as an average with standard deviation.

To determine of the solubility of SD in phosphate buffer, and subsequently calculate the sink conditions, a saturated solution was prepared by adding an excess of SD to the phosphate buffer at pH 7.4 and 37°C. The concentration was then determined using the same spectrophotometer and calibration curve.

4.3.8 Tabletting

For the compaction of the coated pellets into MUPS, it was made a clear distinction between homogeneous and inhomogeneous pellets. The term “homogeneous” was here not referred to the homogeneity of the coating layer, but to the homogeneity in composition of the uncoated pellets. In other words, the homogeneous pellets were the ones obtained via direct pelletization (see §4.3.4), the inhomogeneous, on the other hand, those obtained by dry powder layering on neutral cores (see §0).

Homogeneous pellets

In order to restrict in advance potentially promising formulations, preliminary experiments were carried out. In the frame of such pre-experiments, the coated pellets were mixed with 5-15% w/w of disintegrant (UICEL-A/102 or STA-RX® 1500), 10-90% w/w of filler (MCC 102) and 0.5% w/w of lubricant (magnesium stearate) according to a preliminary STAVEX factorial design. Each tabletting mixture was compressed into MUPS using a Presster™ Compaction Simulator (Metropolitan Computing Corporation, East Hanover, USA) equipped with a D-tooling single-punch (diameter of 10 mm, flat surface). The distance between the punches (2.2 mm) and the linear velocity of the compression (0.108 m/s) were held constant.

The criteria for selection were the values of crushing strength and the disintegration time: only MUPS formulations with a crushing strength of 80-180 N and a disintegration time of < 15

minutes were processed further. The selected formulations were further investigated by means of STAVEX factorial design with quadratic external D-optimisation, with the aim of delimitating the experimental domain to its centre and a series of points at appropriate distance from the centre depending on the investigated factors.

The factor ranges varied according to the following scheme: the amount of coated pellets was set out at 40-60%, the amount of cushioning excipient at 30-50%, the disintegrant was held constant at 10%. In addition, the type of filler in pellets (MCC 102 or UICEL-A/102) and the type of disintegrant in MUPS (UICEL-A/102 or or STA-RX® 1500) were set out as quantitative factors with two levels each. The investigated response variables were: disintegration time and dissolution time of the tablets. The design is presented in

Table 4.7. For the coated pellet runs employed please refer to Table 4.4.

Table 4.7: Composition of the tabletting mixtures (homogeneous pellets)

Mixture	Type of filler in pellets	Loading amount of SD (%)	Run	Type of disintegrant in MUPS	Amount of pellets in MUPS (%)
1	MCC 102	10	1b	UICEL-A/102	40
2	MCC 102	10	1b	UICEL-A/102	60
3	MCC 102	40	3b	UICEL-A/102	40
4	MCC 102	40	3b	UICEL-A/102	60
5	MCC 102	10	1b	STA RX® 1500	40
6	MCC 102	10	1b	STA RX® 1500	60
7	MCC 102	40	3b	STA RX® 1500	40
8	MCC 102	40	3b	STA RX® 1500	60
9	UICEL-A/102	10	16b	UICEL-A/102	40
10	UICEL-A/102	10	16b	UICEL-A/102	60
11	UICEL-A/102	40	15b	UICEL-A/102	40
12	UICEL-A/102	40	15b	STA RX® 1500	60
13	UICEL-A/102	40	15b	UICEL-A/102	50
14	UICEL-A/102	20	17b	UICEL-A/102	60
15	UICEL-A/102	10	16b	STA RX® 1500	50
16	UICEL-A/102	20	17b	STA RX® 1500	40
17	MCC 102	20	2b	STA RX® 1500	50

For all 17 formulations in

Table 4.7, 25g mixtures were prepared. The coated pellets, the cushioning excipient and the disintegrant in the relevant proportions were first mixed 5-7 minutes in a turbula mixer (Willy A. Bachofen Maschinenfabrik, Basel, Switzerland), sieved (mesh size 800 µm) and then mixed 5 min more. Finally, 0.125 g (0.5 % of the total mixture) of magnesiumstearate were added and the mass was mixed for other 2 minutes.

The tabletting was performed in a Presster Compaction Simulator (Metropolitan Computing Corporation, East Hanover, USA) equipped with a single-punch (diameter of 10 mm, flat surface). 400 mg of each mixture were weighed, each time filled manually in the die, and compacted according to the same procedure and conditions mentioned above.

Inhomogeneous pellets

In analogy with the homogeneous pellets, several tabletting formulations of inhomogeneous pellets were also submitted to pre-experiments with the same procedure and criteria described above. The selected formulations underwent an analogous STAVEX factorial design with quadratic external D-optimisation (see Table 4.8), with the only difference that an additional factor was added, i.e. the neutral core type (Cellets® or Suglets®).

The tabletting mixtures were composed of: 20-80% of coated pellets with different cores (either Cellets® or Suglets®), MCC 102 powder as cushioning excipient and 10% of either UICEL or STA RX® 1500 as disintegrant.

In Table 4.8 all pre-formulations are listed; the number of pellet runs refer to Table 4.5, with the only difference that here the respective coated batches are meant. The rest of the formulation consist of 0.5% of Mg-Stearate, 10% of disintegrant and cushioning excipients (MCC 102) ad 100%.

Table 4.8: Composition of the tabletting mixtures (inhomogeneous pellets)

Mixture	Neutral cores		% pellets		Pellet Run	Type of disintegrant
	Cellets	Suglets	U. pellets	M. pellets		
1	x		40		4	UICEL-A/102
2	x		50		4	UICEL-A/102
3	x		60		4	UICEL-A/102
4		x	40		3	UICEL-A/102
5		x	50		3	UICEL-A/102
6		x	60		3	UICEL-A/102
7	x		40		4	STA RX® 1500
8	x		50		4	STA RX® 1500
9	x		60		4	STA RX® 1500
10		x	40		3	STA RX® 1500
11		x	50		3	STA RX® 1500
12		x	60		3	STA RX® 1500

8 g of each formulation were prepared. First of all, the coated pellets, along with the appropriate amount of filler and disintegrant, were mixed for 6 minutes in a turbula mixer (Bachofen Maschinenfabrik, Basel, Switzerland). The mixture was then sieved (mesh size 1.4 mm), mixed again for 4 minutes, added with 0.5% of magnesium stearate and finally mixed for 2 minutes more. Compaction was performed in a Presster™ Compaction Simulator (Metropolitan Computing Corporation, East Hanover, USA), equipped with a single punch with a diameter of 10 mm and a flat surface. The rotary tablet machine simulated was the Korsch 336, which is composed of 36 press stations, the precompression and compression rolls having a diameter of 110 and 330 mm respectively.
400 mg of each mixture were weighed and manually filled in the punch die. The tabletting parameters set for all formulations were: compression gap 2.20 mm, dosing position 17.40 mm, ejection position 10.9 degrees, precompression 14.30 mm.

4.3.9 Characterisation of MUPS

Both USP XXXI and European Pharmacopoeia 2002 do not make any difference between monolithic tablets and multiparticular tablets (MUPS) concerning their characterization. Accordingly, the MUPS were characterized by means of:

- Crushing strength
- Porosity
- True density
- Disintegration
- Drug release
- Scanning electron microscopy (§ 4.3.2)
- Confocal laser scanning microscopy (§ 4.3.7)
- Determination of pellet distance in MUPS

Crushing strength

The breaking load of the tablets was accomplished with a tablet tester Dr. Schleuniger model 8M (Dr. Schleuniger Pharmatron, Solothurn, Switzerland) with a crushing speed of 0.7 mm/s. The crushing strength was checked 24 hours after production of the tablets

Porosity

The porosity of the tablets was calculated according to the following equation:

$$\varepsilon = \left[1 - \frac{\rho_{app}}{\rho_{true}} \right] * 100$$ Equation 4.6

where: ε: porosity of the compact
ρ_{app}: apparent density of the compact [g/cm^3]
ρ_{true}: true density of the compact [g/cm^3]
$\rho_{app}/\ \rho_{true}$: relative density of the compact

The apparent density of the compact was calculated dividing the weight of the tablet by its volume:

$$\rho_{app} = \frac{m}{V}$$ Equation 4.7

where: m: weight of the tablet [g]
v: volume of the tablet [cm^3]

The weight, as well as the diameter and the thickness, which were used to calculate the volume, were determined using five tablets.

True density

The true density of the tablets was calculated by adding the true density of each component of the tablet multiplied by its fraction:

$$\rho_{true} = x_p \rho_p + x_{dis} \rho_{dis} + x_{MCC} \rho_{MCC}$$ Equation 4.8

where: x_n: fraction of the substance n in the tablet [w/w]
ρ_n: true density of the substance n [g/cm^3]
$_p$: pellets
$_{dis}$: disintegrant

Finally, replacing the Equation 4.7 and Equation 4.8 into Equation 4.6, the final equation is obtained:

$$\varepsilon = \left[1 - \frac{m}{V} \frac{1}{x_p \rho_p + x_{dis} \rho_{dis} + x_{MCC} \rho_{MCC}} \right] * 100$$ Equation 4.9

Disintegration

The disintegration time was determined in a disintegration apparatus Sotax ST2 (Sotax, Allschwil/Basel, Switzerland) with a basket-rack assembly. The disintegration medium used was distilled water set at the temperature of 37±1°C. The tablets were considered disintegrated when no residue of the units remained in the basket, except for fragments of the coating layer. For each formulation six tablets were tested and the time taken to complete the disintegration was recorded; the results were expressed as average of the six measurements.

Drug release

The drug release test was performed in a dissolution apparatus Sotax AT 7 smart (Sotax AT 7, Allschwil/Basel, Switzerland) according to the general specifications of USP XXX, monography NF XXV. For each formulations, 3 tablets (400 mg) were put into 900ml of a phosphate buffer at pH 7.4, the paddle rotating speed was set at 50rpm and the temperature at 37±1°C. Samples (10 ml) of dissolution medium were removed at regular time intervals, adding each time an equal volume of the same dissolution medium to maintain the volume constant. Sink conditions (the concentration of the active ingredient in the medium should be less than 10% of the concentration of a saturated solution) were maintained throughout the experiment. The absorbance of each sample at a specific wavelength (λ_{max} of sodium Diclofenac in the buffer = 276 nm) was measured by a Beckmann DU®530 UV-Spectrophotometer; through a calibration curve, from that absorbance value the amount of drug liberated at each time was calculated; in the end, the drug amount liberated was plotted as average with standard deviation [w/w %] in function of time.

For the determination of the solubility of SD in the phosphate buffer, and subsequently calculate the sink conditions, a saturated solution was prepared by adding an excess of SD to the phosphate buffer at pH 7.4 and 37°C. The concentration was then determined using the same spectrophotometer and calibration curve.

Determination of pellet distance in MUPS (Image J)

Image J is a public domain Java image processing program inspired by NIH Image for the Macintosh. In this study, it was downloaded directly from the internet (http://rsb.info.nih.gov/ij/) and employed to calculate the mutual distance between pellets in MUPS (see Figure 4.17). The standard deviation of this distance was defined as the segregation index of pellets in MUPS.

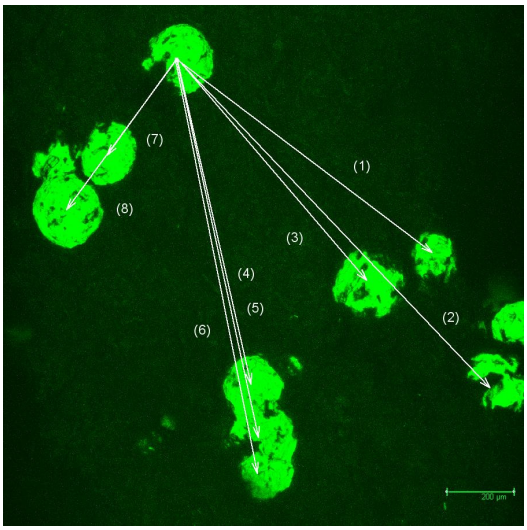


Figure 4.17: Determination of pellets distance by means of Image J

5. Results and Discussion

5.1 Characterization of MCC 102 and UICEL-A/102

Table 5.1.: Characterization data of MCC 102 and UICEL-A/102 (SD are given in parenthesis).

	MCC 102	UICEL-A/102
X-ray diffractogramm	Peaks at 15, 17, 23° 2θ (cellulose I lattice)	Peaks at 12, 20, 22° 2θ (cellulose II lattice)
Degree of cristallinity [%]	75.0	67.0
FT-IR spectra	- inter and intramolecular O-H stretching vibration band: 3440cm^{-1} - peaks at 1430 and 1320 cm^{-1} stronger	- inter and intramolecular O-H stretching vibration band: 3340cm^{-1} - peak at 900 cm^{-1}stronger
Loss on drying [%]	5.20 (0.03)	7.00 (0.05)
Bulk density [g/ml]	0.377 (0.001)	0.465 (0.006)
Tap density [g/ml]	0.425 (0.003)	0.526 (0.003)
True density [g/cm^3]	1.577 (0.003)	1.539 (0.004)
Porosity [%]	73.1	65.8
Hausner ratio	1.127 (0.02)	1.131(0.05)
Carr's Index [%]	11.29 (0.23)	11.60 (1.34)
Particle size distribution average [µm]	122.36 (2.45)	108.68 (3.57)
Specific surface area [m^2/g]	1.73 (0.05)	2.05 (0.10)

UICEL-A/102 showed a moderately higher loss on drying than MCC 102 (see 5.1); this difference is confirmed in literature (Kothari, 1998) and it is an indicator of the higher wettability of the former. The powder X-Ray diffractograms of MCC 102 and UICEL-A/102 are reported in Figure 5.1 and Figure 5.2. MCC 102 showed reflections that are characteristic for the cellulose I lattice; UICEL-A/102, in contrast, presented diffraction peaks at about 12, 20, and 22 ° 2θ (corresponding to 101, 101 and 002 reflections, respectively), which indicated the presence of the cellulose II lattice (Kothari, 1998). In addition, UICEL-A/102 exhibited a cristallinity degree of 67% (slightly higher than the results reported in literature (Kumar, 2002), whereas the degree of cristallinity of MCC 102 was about 75 % (Krassig, 1996).

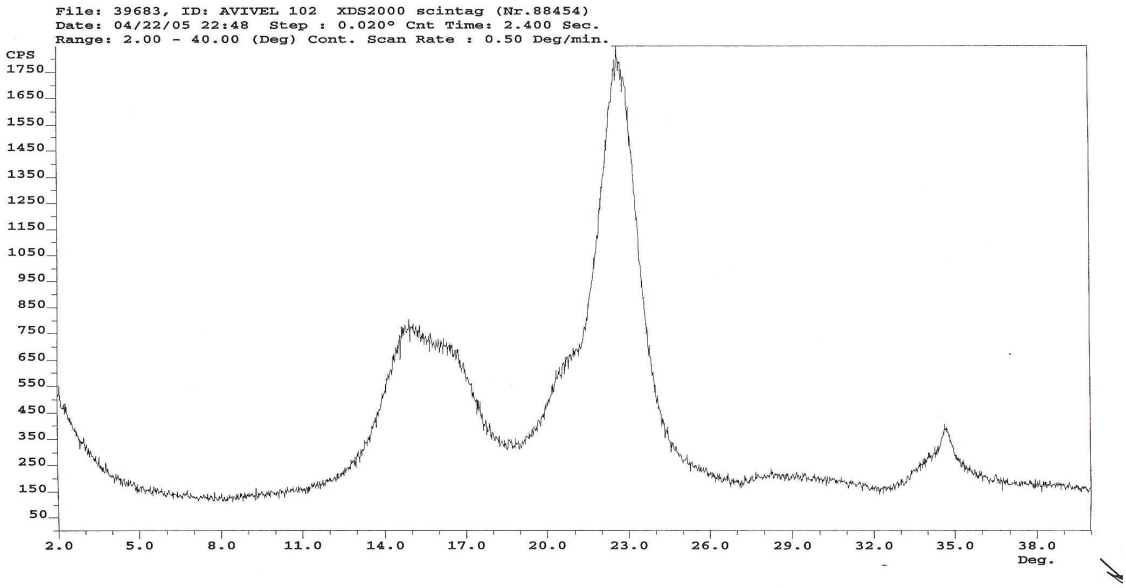


Figure 5.1: X-Ray diffractogramm of MCC 102

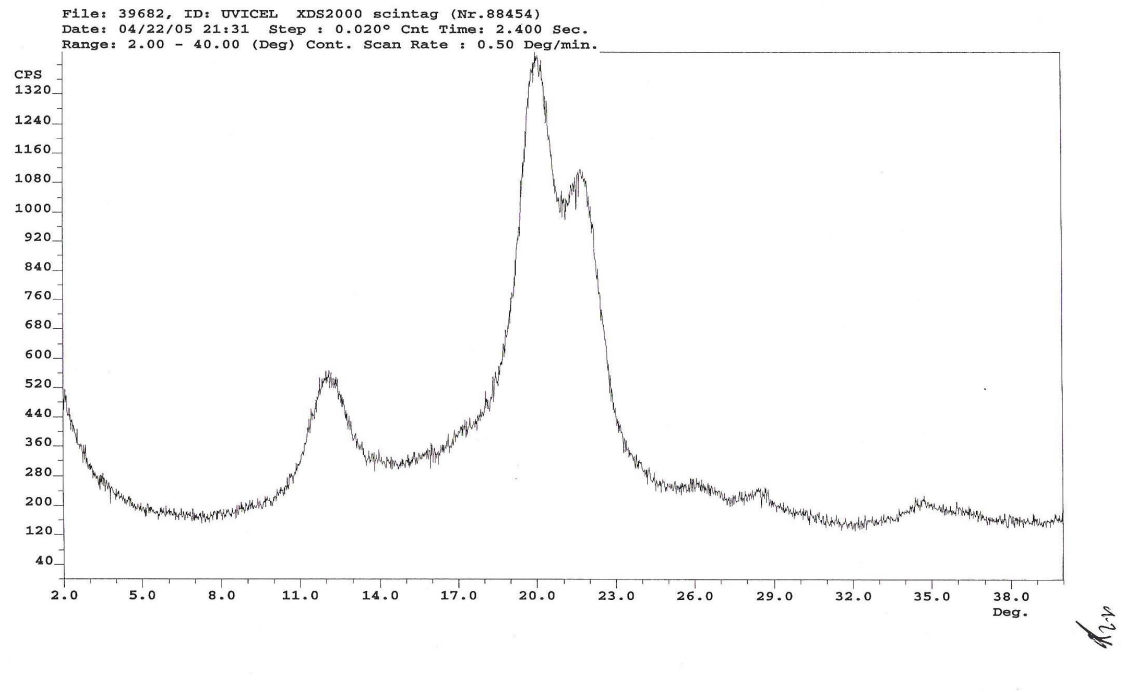


Figure 5.2: X-Ray diffractogramm of UICEL-A/102

This difference in crystallinity degree between UICEL-A/102 and MCC 102 can be attributed to the different crystal lattices present in the two materials: in cellulose I the chains are arranged in a parallel way, in cellulose II in an anti-parallel manner.
This leads to different interchain and intrachain hydrogen bonding networks, and, consequently, to a different degree of crystallinity. Studies show that cellulose II possesses additional hydrogen bonding between chains at the corners and the centres of the unit cells, and it is accordingly more stable than cellulose I (Krassig, 1996).
Figure 5.3 compares the SEM photographs of MCC 102 and UICEL-A/102. MCC 102 showed an aggregated structure composed of small fibres with coalesced boundaries, whereas UICEL-A/102 consisted of a mixture of aggregated and non-aggregated fibres.

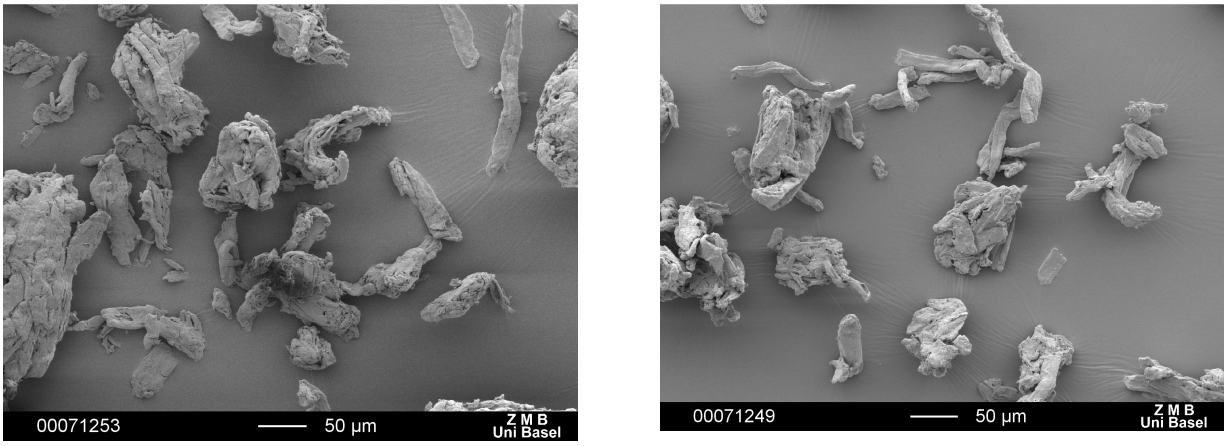


Figure 5.3: SEM pictures of MCC 102 (left) and UICEL-A/102 (right)

The FT–IR spectra of UICEL and MCC 102 are compared in Figure 5.4. The two spectra showed the following differences: firstly, the characteristic intermolecular and intramolecular O_H stretching vibration band in the spectrum of UICEL-A/102 appeared broader and showed the higher maximum intensity around 3440 cm^{-1}, whereas for MCC 102 this band was at about 3340 cm^{-1}; secondly, the peaks at 1430 and 1320 cm^{-1}, associated with the intramolecular hydrogen bonds at the C6 group and O_H in-plane bending vibration, respectively, were weaker in UICEL-A/102 than in MCC 102; thirdly, due to an enhanced antisymmetric out-of-phase stretching vibration, the absorption band at 900 cm^{-1} in the spectrum of UICEL-A/102 was relatively more intense than that in MCC 102. It has been reported that the intensity of this peak increases with a decrease in crystallinity of the cellulose sample and a change in the crystal lattice from cellulose I to cellulose II. The fact that UICEL-A/102 featured that peak more intensively compared with MCC 102 confirmed that the former was the low crystallinity material and contained the cellulose II lattice.

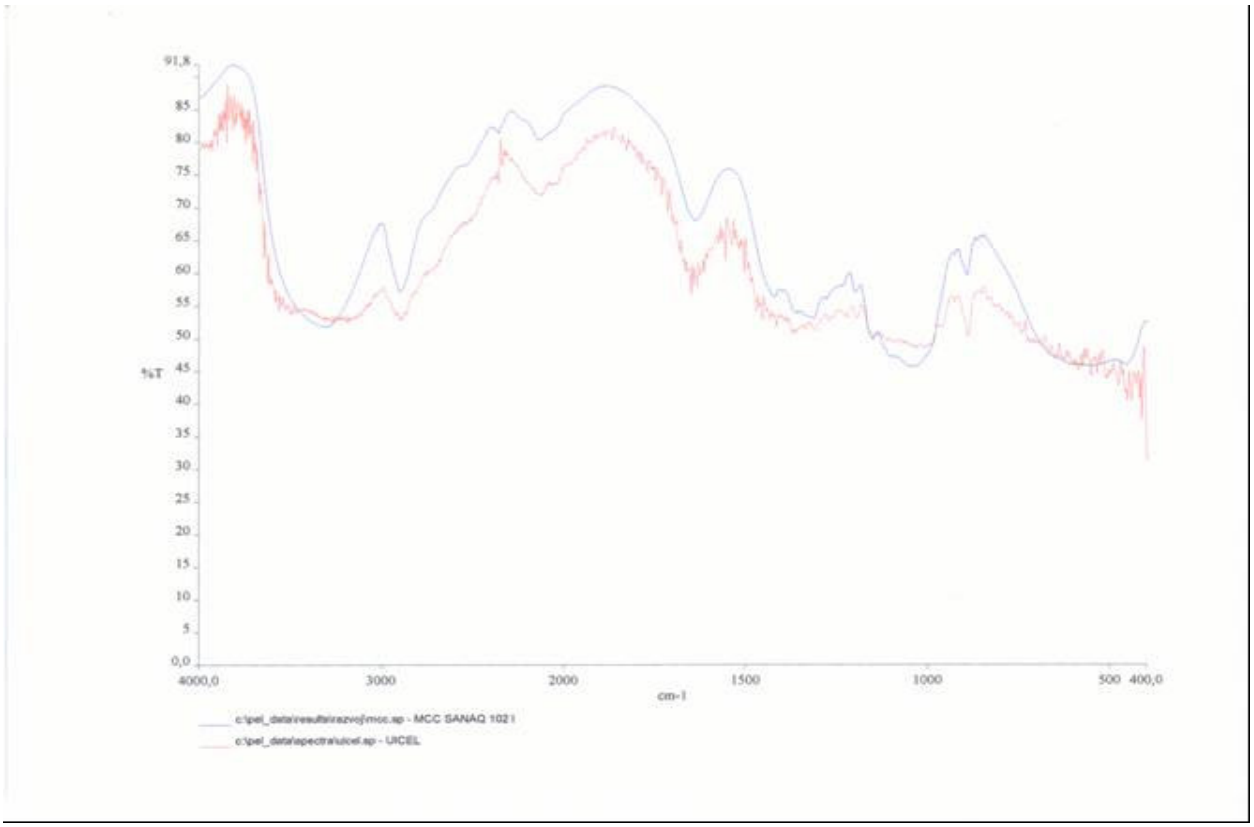


Figure 5.4: Comparative FT-IR of MCC 102 (blue) and UICEL (red)

UICEL-A/102 was proved to be more compact than MCC 102, as its lower true density and porosity indicated, which might pledge for less ductile and more elastic mechanical properties.

The Hausner ratio and the Carr index have been extensively used to evaluate the flow properties of powders. A Hausner ratio of less than 1.20 indicates good flowability of the material, whereas a value of 1.5 or higher suggests a poor flow (Wells, 1988). The Carr index values of 5-10, 12-16, 18-21, and 23-28 indicated, respectively, excellent, good, fair and poor flow properties of the material (Carr, 1965). The Hausner ratio and the Carr's index of UICEL-A/102 and MCC 102, which are listed in Figure 5.1, suggested that both powders possess fair good flow properties. The moderately higher Hausner ratio and Carr's index values of UICEL-A/102 were attributed to its fibrous structure, which easily aggregates and leads accordingly to moderately poorer flow properties.

As Kumar et al. suggest (Kumar, 2002), the relatively higher bulk and tap densities of UICEL-A/102 are advantageous in tabletting, because the volume of die-fill is correspondingly reduced. Both MCC 102 and UICEL-A/102 displayed a Gaussian particle size distribution, the former having a slightly higher particle size average than the latter (see Table 5.1). This difference may be attributed to the different production paths, spray-drying for the former, hydrolysis in alkali followed by drying at 45-50 °C for the latter.

5.2 Characterization of pellets by direct pelletization

5.2.1 Characterization of the coated vs. uncoated pellets

The characterization data of all homogeneous pellet batches, coated as well as uncoated, are summarized in Table 5.2. Runs “a” correspond to the uncoated pellet batches, whereas runs “b” refer to the respective coated batches.

Table 5.2: Pellet characterisation: a) uncoated pellets; b) coated pellets

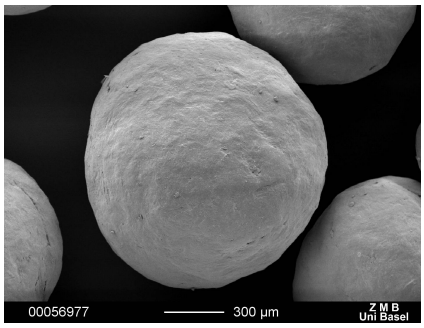
Run	AI [%]	Filler	Applied coating [%]	Loss on drying [%]	Porosity	HR	Mean particle size distribution [µm]		True density [g/cm^3]	Specific surface area [m^2/g]
							Sieve An.	Malvern		
1a	10	MCC	-	6	0.11	1.05	490.4	494.96	1.5949	0.6914
2a	20	MCC	-	6	0.13	1.04	624.8	610.25	1.6010	0.7364
3a	40	MCC	-	9	0.11	1.06	475.5	462.68	1.5973	0.6247
15a	10	UICEL	-	9	0.16	1.15	493.8	508.28	1.5750	1.1500
16a	20	UICEL	-	5	0.19	1.18	390.3	375.99	1.5410	0.8560
17a	20	UICEL	-	6	0.18	1.14	451.1	460.12	1.5530	0.9600
18a	40	UICEL	-	8	0.18	1.18	280.8	270.16	1.5592	0.8722
1b	8.1	MCC	22.2	5	0.10	1.08	589.7	628.02	1.5848	0.6500
2b	16.6	MCC	20.1	6	0.12	1.09	749.0	720.02	1.5996	0.6942
3b	33.8	MCC	18.2	8	0.10	1.10	570.0	555.02	1.5383	0.9824
15b	8.6	UICEL	16.5	8	0.18	1.16	591.6	600.02	1.5653	0.5964
16b	16.9	UICEL	18.6	4	0.17	1.20	558.6	564.19	1.5404	0.6247
17b	17.2	UICEL	16.0	5	0.16	1.16	578.0	591.65	1.5506	0.6345
18b	33.3	UICEL	19.8	7	0.15	1.22	284.0	305.31	1.5567	0.6475

MCC 102 uncoated as well as coated pellet batches displayed HR values between 1.04 and 1.10, showing therefore excellent flowability and perspective packing ability.

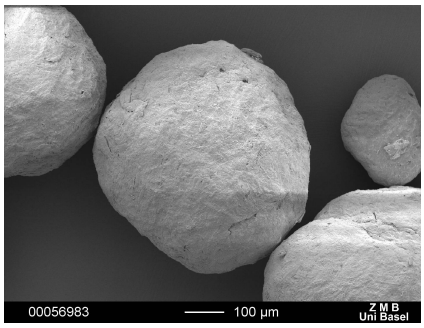
UICEL-A/102 uncoated and coated pellets, on the contrary, featured moderately higher HR values (1.14 - 1.22). This can be explained observing the pellet shape and surface morphology (Figure 5.4): UICEL-A/102 pellets appeared less spherical and smooth than MCC 102 pellets, which facilitated entanglement between them and sank their HR and flowability. Furthermore, MCC 102 pellets proved to have higher true densities and accordingly lower porosity and lower specific surface areas compared to their UICEL-A/102 counterparts. This was again supported by the SEM images of the uncoated and the CLSM images of the coated pellets (Figure 5.5).
In line with the production technology employed, all the uncoated pellet batches showed normal particle size distribution with average particle size around 500 μm; UICEL-A/102 pellets were generally smaller than MCC 102 pellets, as their SEM images confirmed. In particular, Run 18a featured significantly lower (275 μm) particle size average and was therefore no further processed. The enhancement in average size of the coated pellet batches generally reflected their 20% mass enhancement after the coating.
In analogy with the findings of previous studies, in which technological comparisons between UICEL-A/102 and MCC 102 as direct compaction excipients and their respective tablets were performed (Kumar, 2002), (Reus-Medina, 2006), the characterization results revealed a clear parallelism between the morpho-technological characteristics of MCC 102 and UICEL-A/102 and their respective pellets (see §5.1). This represents an important result, since no investigations have focused so far on the use of UICEL-A/102 as a pelletization excipient.

5.2.2 SEM and CLSM images

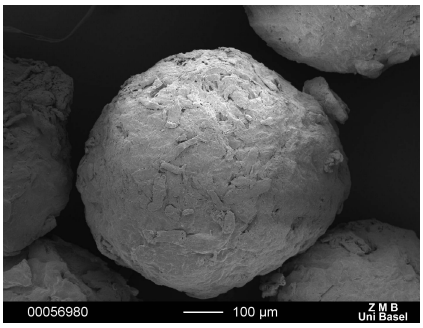
Figure 5.5 presents SEM images of uncoated pellets (a) and confocal images of coated pellets (b). The SEM images, along with the porosity results, indicated once more that MCC 102 pellets were generally more spherical and compact, and accordingly less porous, than UICEL-A/102 pellets, this discrepancy decreasing at enhancing amount of AI. The uncoated pellets generally retained their technological properties after coating: MCC 102 coated pellets proved to be slightly bigger and smoother than their UICEL-A/102 counterparts. Both MCC 102 and UICEL-A/102 coated pellets featured homogenous layers, as the CLSM images corroborated. In particular, UICEL-A/102 Runs proved to have enhanced sphericity after coating. This result is in contrast with literature, since two important studies reported that pellet sphericity coefficient is maintained after coating and that smoother pellets are consistently better and more homogeneously coatable than those featuring rough, irregular surface (Lehmann, 1994), (Beckert, 1996).



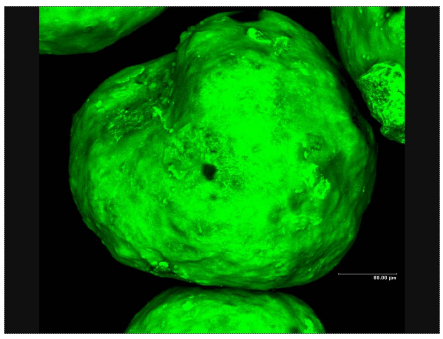
Run 1a



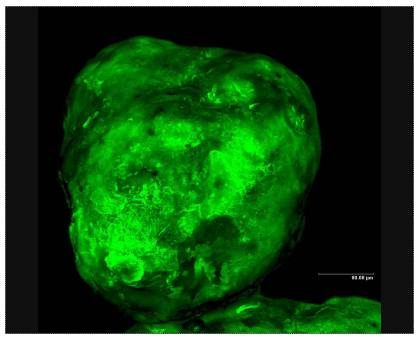
Run 2a



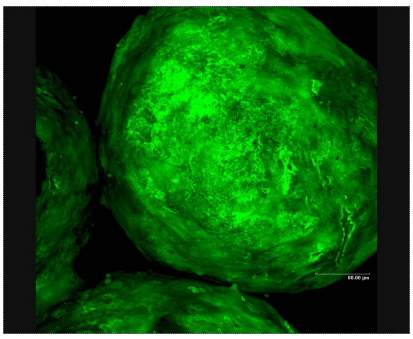
Run 3a



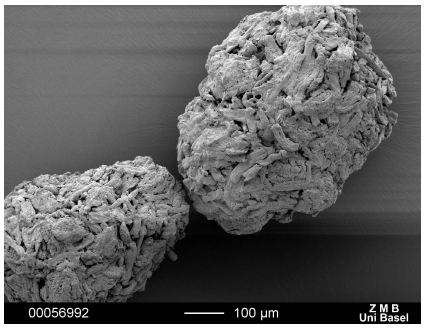
Run 1b



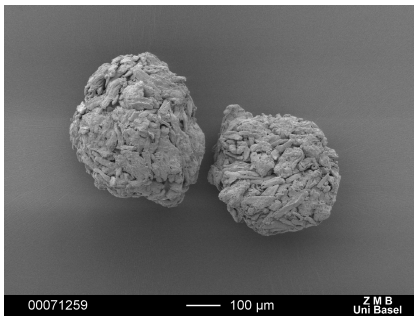
Run 2b



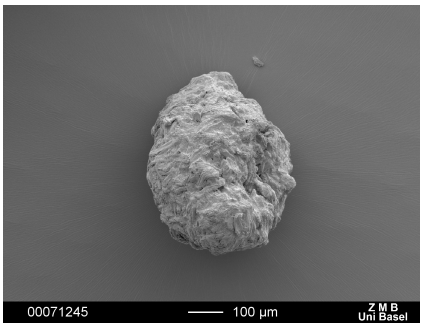
Run 3b



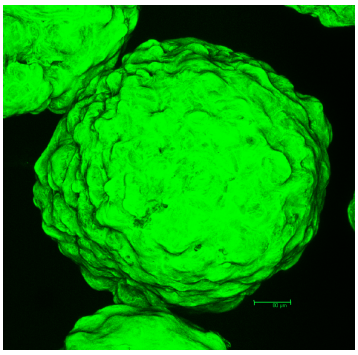
Run 15a



Run 16a



Run 17a



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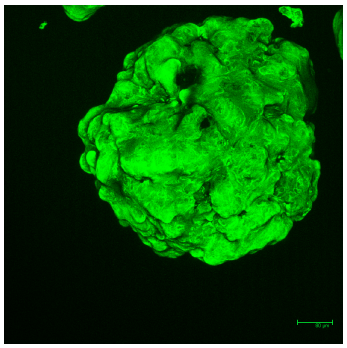
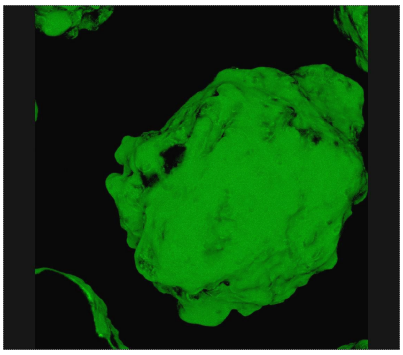


Run 16b



Run 17b

Figure 5.5: SEM images of uncoated pellets (grey) against CLSM images of coated pellets (green)

5.2.3 Dissolution from coated MCC 102 and UICEL-A/102 pellets

Figure 5.6 illustrates the drug release profile from diverse coated pellet formulations. If the coating film extended the AI dissolution from the MCC 102 pellets over about 2 hours, it failed to sustain the AI release from the UICEL-A/102 pellets (dissolution of around 20 min.).

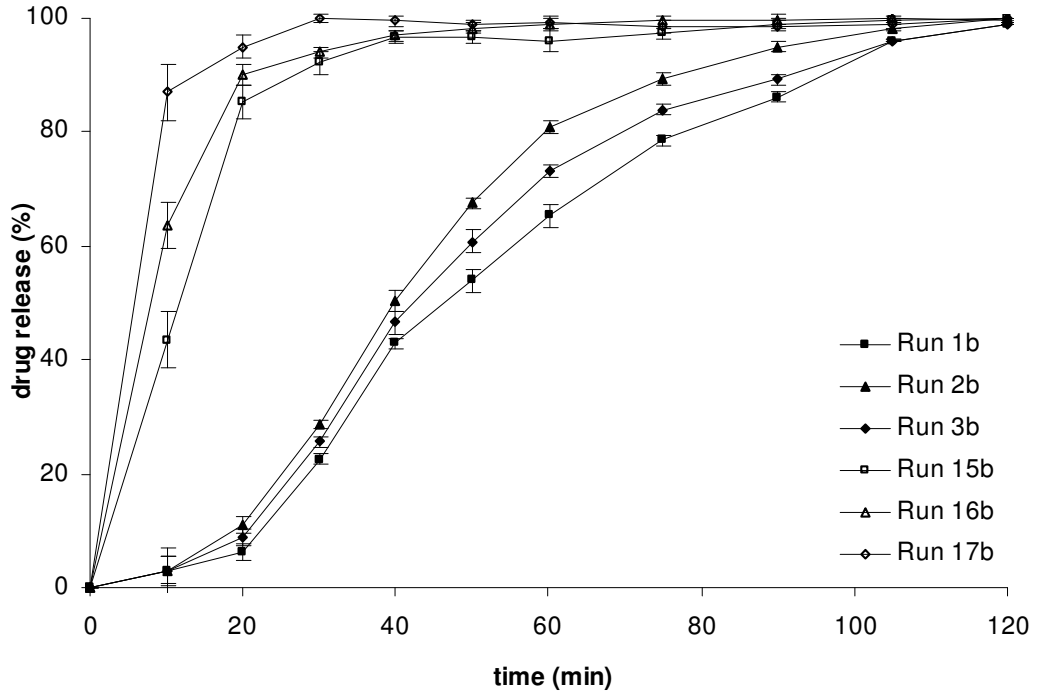


Figure 5.6: Drug release from diverse pellet formulations

Considering that the coating layers of all pellet batches were comparable in quantity and function, and that no pore maker was added into the coating suspension, this difference was attributed to the prevalent swelling properties of UICEL-A/102.

As discussed in §2.9.2, the release mechanism from pellets can occur via solution/diffusion through the polymer film, solution/diffusion through plasticizer channels or solution/diffusion through aqueous channels. Even if all these three mechanisms occur simultaneously, normally one of them steers the overall release. In our case, considering that Kollicoat® SR 30 D was suspendable (not soluble) in water, and that SEM consistently indicated the absence of any pores in the coating, it is likely that diffusion through the polymer film contributed significantly to the overall release rate in the case of MCC 102 coated pellets. On the contrary, in the case of UICEL-A/102 pellets, the solution/diffusion through aqueous channels was the driving mechanism due to the prevalent swelling properties of UICEL.

5.3 Characterization of pellets by dry powder layering

5.3.1 Characterization of uncoated MCC 102 and UICEL-A/102 pellets

The pellets compositions, calculated on the base of the PVP amounts actually employed, are listed in Table 5.3.

Table 5.3: Composition of each batch

Batch	Core		Filler		PVP	SD content	Eff. SD content
	Type	[%]	Type	[%]	[%]	[%]	[%]
1	Suglets®	63.2	MCC 102	16.8	3.2	16.8	18.2±0.3
2	Cellets®	66.4	MCC 102	15.3	3	15.3	16.5±1.1
3	Suglets®	60.8	UICEL-A/102	17.2	4.8	17.2	15.2±0.7
4	Cellets®	58.1	UICEL-A/102	18.6	4.7	18.6	16.1±0.6

The effective AI content of the four pellet batches was proved to slightly deviate from the theoretical one; it was moderately higher for the MCC 102 pellets and slightly lower for the UICEL-A/102 pellets. This difference could be explained by a more pronounced tendency of MCC 102 to stick to the equipment surface. Further results of the pellet characterisation are listed in Table 5.4.

Table 5.4: Characterization of uncoated pellets

Batch	Yield [%]	Residual moisture [%]	Flowability [g/min]	Hausner ratio	Mean particle size distribution [µm]		True density [g/cm^3]	Drug content [%]
					Sieve an.	Mastersizer		
1	84.2	3.5	435.54	1.07	602.5	569.75	1.455	18.2±0.3
2	94.5	2.8	518.56	1.03	596.1	550.92	1.444	16.5±1.1
3	85.1	5.0	463.51	1.03	656.8	671.87	1.400	15.2±0.7
4	96.5	6.5	444.14	1.03	636.5	649.74	1.411	16.1±0.6

Both batches of UICEL-A/102 pellets (3 and 4) showed higher mean particles size and residual moisture and lower true density than their MCC 102 counterparts. The same trend was observed in the homogeneous pellets produced via direct pelletization (§5.2.1).

The HR values being lower than 1.15 indicated that all batches owned very good flow properties. The however negligible discrepancy between the particle size determined with the sieve tower and with the Mastersizer is to explain considering that the sieve analysis provides a mass based particle size distribution, the laser analysis, on the other hand, a volume based particle size distribution. The slight difference in size between Suglets® and Cellets® batches was reflected in their pellets: batches 1 and 3 owned moderately bigger particle size than batches 2 and 4, respectively.

5.3.2 Characterization of coated vs. uncoated pellets

Table 5.5 schematically presents the characterisation results of coated and uncoated pellets. Compared with their MCC 102 counterparts, UICEL-A/102 uncoated pellets owned bigger particle size distribution (600 against 650 µm), higher residual moisture (5% against 3%), higher porosity (0.08 against 0.10), lower true density (1.400 against 1.450 g/cm^3), higher specific surface area (0.600 against 0.570). This trend, observable also in the coated batches, was put in correlation with the differences between MCC 102 and UICEL-A/102 (see §5.1). Nevertheless, all the over mentioned differences were comparably lower than in the pellet batches obtained by direct pelletization (see Table 5.2). In analogy with studies of Beckert and Lehmann, this discrepancy was attributed to the big neutral core reducing considerably the differences between the diverse pellet batches (Beckert et al., 1996), (Lehmann et al., 1995).

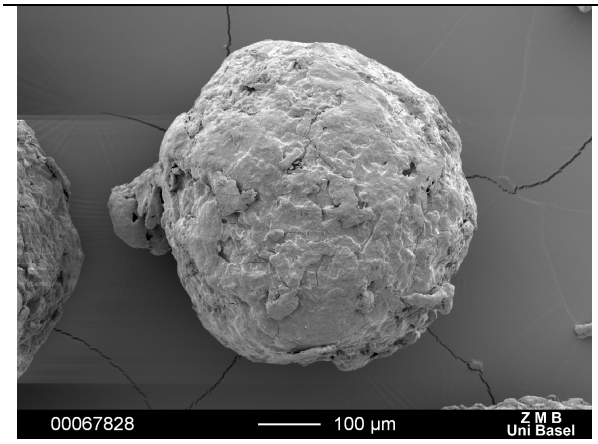
Table 5.5: Results of the uncoated and coated pellets characterization

Pellets		AI [%]	Applied coating [%]	Porosity	Loss on drying [%]	Mean particle size[(1)] [µm]	Mean particle size[(2)] [µm]	HR	True density [g/cm^3]	Specific surface area [m^2/g]
MCC 102	uncoated	18.2	-	0.081	3.5	602.5	569.75	1.07	1.455	0.551
Suglets®	coated	-	26	0.082	-	830.1	801.67	1.10	1.362	0.554
MCC 102	uncoated	16.5	-	0.073	2.8	596.1	550.92	1.03	1.444	0.584
Cellets®	coated	-	25.5	0.075	-	844.1	794.06	1.08	1.389	0.597
UICEL-A/102	uncoated	15.2	-	0.100	5.0	656.8	671.87	1.07	1.400	0.601
Suglets®	coated	-	25.6	0.090	-	907.2	892.55	1.12	1.335	0.610
UICEL-A/102	uncoated	16.1	-	0.110	5.5	636.5	649.74	1.03	1.411	0.620
Cellets®	coated	-	25.3	0.112	-	833.0	906.13	1.07	1.342	0.630

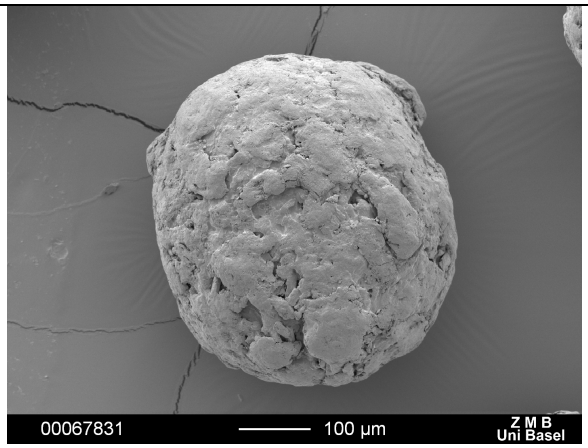
[(1)] particle distribution by means of sieve analysis; [(2)] particle distribution by means of laser analysis

5.3.3 SEM images

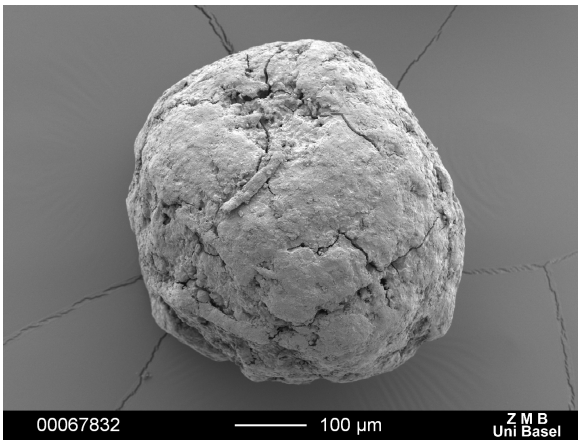
Figure 5.7 shows the SEM images of one pellet of each batch produced. Opposed to the pellets produced by direct pelletization (§5.2), no evident morphological differences could be identified between MCC 102 and UICEL-A/102 pellets. In fact, all pellet batches consisted of spherical pellets with smooth, homogeneous surface, as shown in Figure 5.7. In other words, the use of MCC 102 or UICEL-A/102 as filler in dry powder layering did not account for appreciable morphological differences in the final product. This result represented a big step forward compared to the simple fluidized bed pelletization, which delivered on the one hand almost spherical, homogenous and compact MCC 102 pellets, on the other hand porous, more irregularly shaped UICEL pellets (see Figure 5.5) (Guerra, 2006). Nonetheless, it must be signalized the presence of some protrusions, highly probably due to the impossibility of fine tuning of the powder addition into the main chamber of the fluidized bed. Considering their advantageous properties, we can reasonably assume that both MCC 102 and UICEL pellets produced with dry powder layering might represent homogeneously coatable cores (§5.3.4).



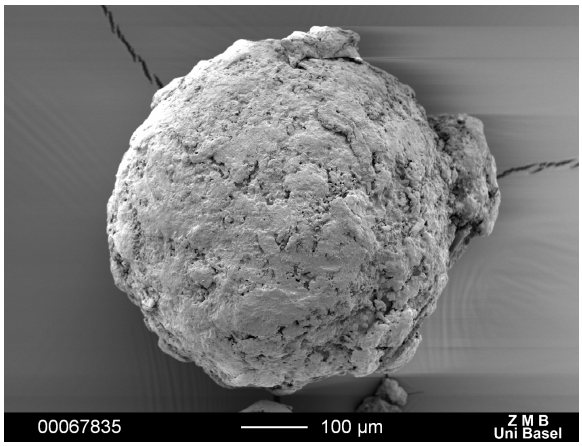
Batch 1: MCC 102 pellet with Suglets® cores



Batch 2: MCC 102 pellet with Cellets® cores



Batch 3: UICEL-A/102 pellet with Suglets® cores



Batch 4: UICEL-A/102 pellet with Cellets® cores

Figure 5.7: SEM images of the four pellet batches

5.3.4 SEM vs. CLSM images

SEM pictures of uncoated (grey, left) and coated (grey, middle) pellets plus CLSM pictures of the same coated pellets (green, right) are presented in Figure 5.8. According to the SEM pictures, all four pellet batches were covered with a homogeneous film layer without pores. The successful layering was to some extent due to coating technology employed, but more importantly to the favourable characteristics of pellet surface and morphology of the uncoated pellets. In other words, more compact and regularly shaped UICEL-A/102 pellets produced through dry powder layering on neutral beads eased the formation of a homogenous, coalesced film layer. This finding is in agreement with literature, as many publications asserted the advantages of dry powder layering on nuclei to get almost homogeneaously coated pellets (Beckert, 1995), (Bodmeier, 1997), (Wagner, 1999a), (Opitz, 2005).

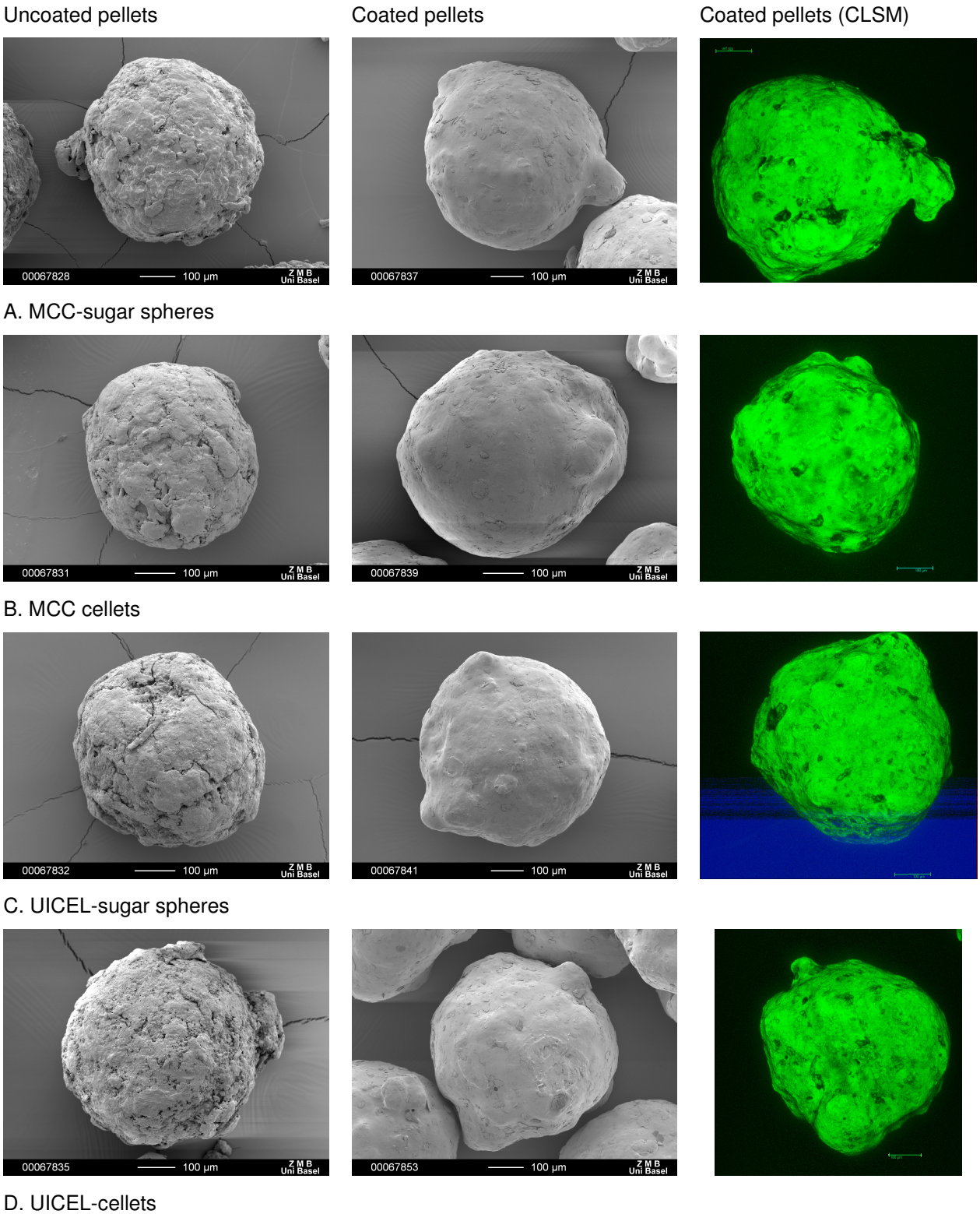


Figure 5.8: SEM and CLSM pictures of the four batches of pellets

5.3.5 Dissolution from coated MCC 102 and UICEL-A/102 pellets

Figure 5.9 shows the drug release profiles of the four batches of coated pellets. As expected, pellets loaded with UICEL-A/102 showed a faster release rate than those loaded with MCC 102. This was again ascribed to the swelling and disintegrating properties of UICEL-A/102. Conversely, neutral cores loaded with MCC 102 showed a relatively slower drug release, due to the less intense disintegration properties of MCC 102 (see §2.3.1).

The use of Cellets® or Suglets® as inert cores played a consistent role, since the pellets batches layered on the former were released slightly faster than their counterparts layered on the latter. This finding was associated with the starch content in Suglets® (4% w/w), which contributed to accelerate moderately the disintegration and dissolution processes.

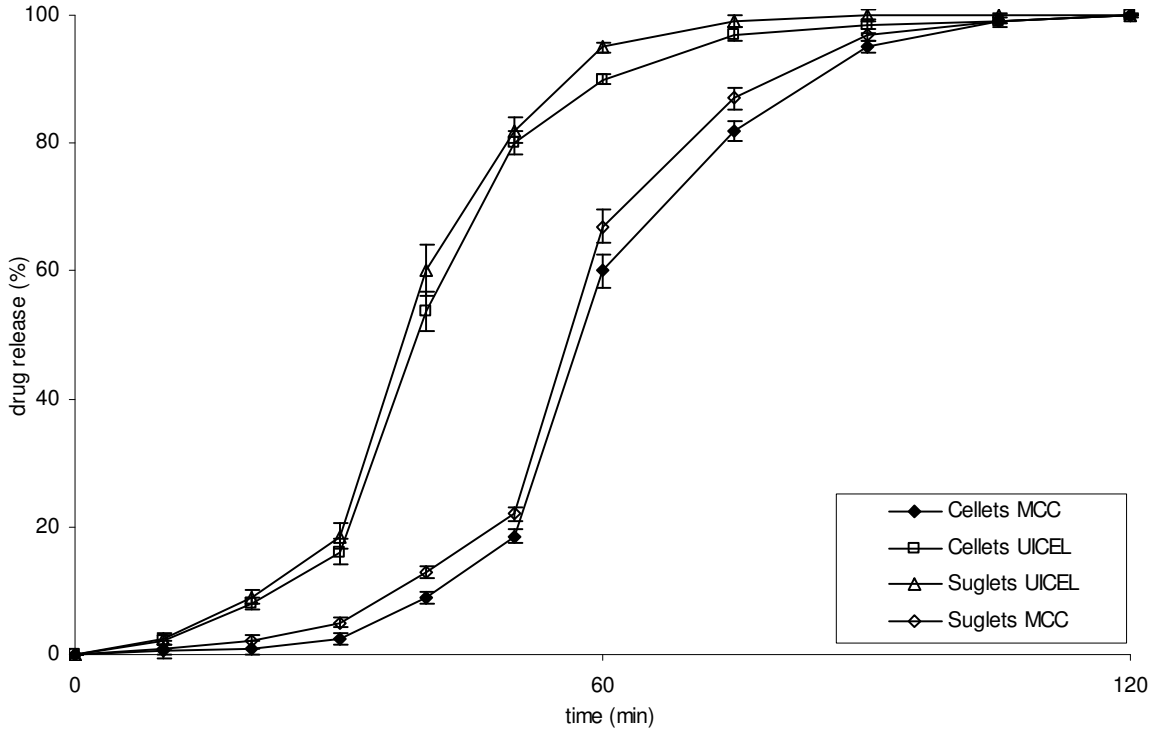


Figure 5.9: Dissolution behaviour of the coated pellets by dry powder layering (see

Table **5.5**)

In Figure 5.10, the release profile of one batch of MCC 102 and UICEL-A/102 coated pellets produced by dry powder layering are compared against their analogous produced by direct pelletization.

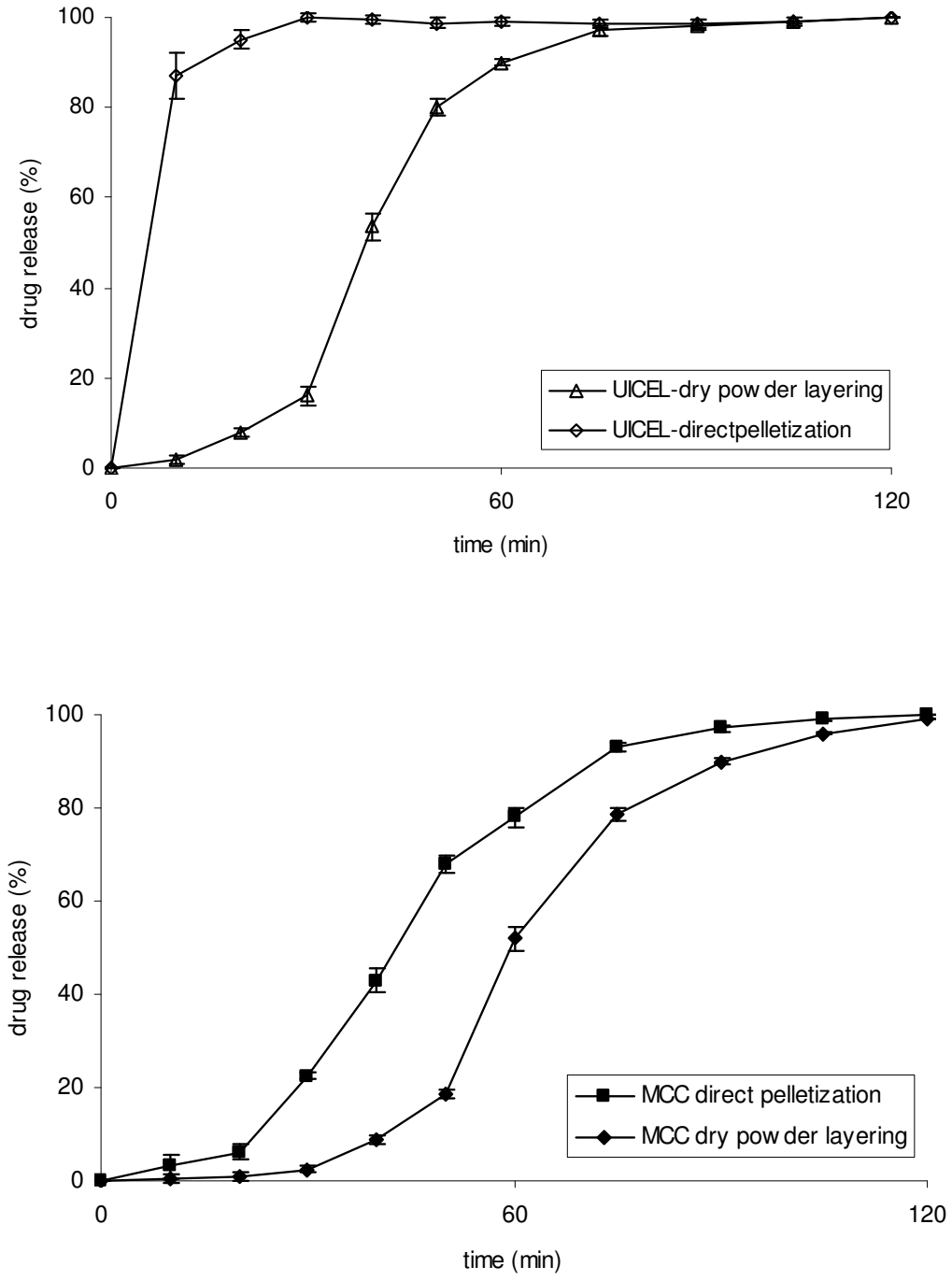


Figure 5.10: Dissolution behaviour of MCC and UICEL pellets produced with different techniques

In both cases, the pellets produced by drug powder layering underwent considerably slower dissolution than those manufactured through direct pelletization. This difference was attributed to the different composition of the two pellet types. In fact, homogenous pellets produced by direct pelletization had higher content of either MCC 102 or UICEL-A/102, if compared with their counterparts manufactured by dry powder layering. As a result, they disintegrated and dissolved proportionally faster. The fact that this trend was more remarkable in UICEL-A/102, far better disintegrant than MCC 102, corroborated the conclusion.

Regarding the dissolution mechanism, we concluded in §5.2.3 that homogeneous coated pellets underwent solution/diffusion through the polymer film and dissusion through aqueous channels simultaneously, with UICEL-A/102 pellets preferring the second release mechanism (see §2.9.2). Analogous conclusion can be drawn in the case of inhomogeneous coated pellets.

5.4 Multiple Unit Pellet Systems (MUPS)

5.4.1 Compaction of homogeneous pellets into MUPS

Preliminary experiments

The results of preliminary experiments for the compaction of homogeneous pellets are listed in Table 5.6. A noticeable correlation between the target properties and the amount of disintegrant could be easily observed. In fact, with respect to the targeted values of crushing strength (80-120 N) and disintegration time (less than 15 min.), the MUPS formulations containing 10% of disintegrant were indicated as the most suitable ones. In this favourable amount, no significant difference in the employment of UICEL-A/102 or STA RX® 1500 was observed.

Generally, the higher the percentage of pellets in the formulation, the lower the crushing strength of MUPS and the longer their disintegration into the subunits. In fact, MUPS containing 70-90% of pellets proved not to be robust enough and/or did not disintegrate into their subunits, but in inseparable agglomerates of fused pellets (n.a. in Table 5.6). This trend was attributed to the increasingly lower dilution effect of MCC 102, which caused the pellets to stick to each other building undesired aggregates. On the other hand, MUPS containing 10-30% of pellets showed too high crushing strength (>120 N), certainly due to the increasing amount of MCC 102 as embedding material, which made them behave as matrix tablets (Bodemeier, 1997).

Table 5.6: Values of crushing strength and disintegration time of different pre-formulations

Pellets in Tabletting Mixture [w/w %]	Disintegrant [5% w/w]	Crushing strength ±sd [N]	Dis. Time ±sd [min]
10%	UICEL-A/102	380±10	Not dis.
20%	UICEL-A/102	300±10	Not dis.
30%	UICEL-A/102	250±6	150
40%	UICEL-A/102	200±10	120±9
50%	UICEL-A/102	180±6	80±0.29
60%	UICEL-A/102	150±34	42±5
70%	UICEL-A/102	120±13	n.a.
80%	UICEL-A/102	130±5	n.a.
90%	UICEL-A/102	100±2	n.a.

Pellets in Tabletting Mix. [w/w %]	Disintegrant [5% w/w]	Crushing strength ±sd [N]	Dis. Time ±sd [min]
10%	STA RX® 1500	350±15	Not dis.
20%	STA RX® 1500	309±16	Not dis.
30%	STA RX® 1500	219±5	160
40%	STA RX® 1500	147±12	127±7
50%	STA RX® 1500	135±38	100±10
60%	STA RX® 1500	100±5	50±7
70%	STA RX® 1500	64±2	n.a.
80%	STA RX® 1500	28±2	n.a.
90%	STA RX® 1500	20±0	n.a.

Pellets in Tabletting Mixture [w/w %]	Disintegrant [10% w/w]	Crushing Strength ±sd [N]	Dis. Time ±sd [min]
10%	UICEL-A/102	280±15	180±15
20%	UICEL-A/102	206±11	120±9
30%	UICEL-A/102	150±6	30.5±3.5
40%	UICEL-A/102	121±10	12.1±2.1
50%	UICEL-A/102	110±6	5.6±1.3
60%	UICEL-A/102	91±3	3.9±0.8
70%	UICEL-A/102	67±13	n.a.
80%	UICEL-A/102	55±10	n.a.
90%	UICEL-A/102	35±2	n.a.

Pellets in Tabletting Mix. [w/w %]	Disintegrant [5% w/w]	Crushing strength ±sd [N]	Dis. Time ±sd [min]
10%	STA RX® 1500	350±15	200±11
20%	STA RX® 1500	250±16	125±5
30%	STA RX® 1500	180±5	29.7±3.5
40%	STA RX® 1500	119±12	19.2±2.8
50%	STA RX® 1500	110±38	8.7±1.8
60%	STA RX® 1500	100±5	4.9±0.7
70%	STA RX® 1500	64±2	n.a.
80%	STA RX® 1500	28±2	n.a.
90%	STA RX® 1500	20±0	n.a.

Pellets in Tabletting Mixture [w/w %]	Disintegrant [15% w/w]	Crushing Strength ±sd [N]	Dis. Time ±sd [min]
10%	UICEL-A/102	180±12	120±10
20%	UICEL-A/102	156±9	120±9
30%	UICEL-A/102	140±7	30.5±3.5
40%	UICEL-A/102	120±8	12.1±2.1
50%	UICEL-A/102	108±7	5.6±1.3
60%	UICEL-A/102	90±4	3.9±0.8
70%	UICEL-A/102	50±3	n.a.
80%	UICEL-A/102	45±10	n.a.
90%	UICEL-A/102	20±8	n.a.

Pellets in Tabletting Mix. [w/w %]	Disintegrant [5% w/w]	Crushing strength ±sd [N]	Dis. Time ±sd [min]
10%	STA RX® 1500	190±11	120±10
20%	STA RX® 1500	170±8	120±9
30%	STA RX® 1500	160±9	30.5±3.5
40%	STA RX® 1500	116±7	12.1±2.1
50%	STA RX® 1500	100±7	5.6±1.3
60%	STA RX® 1500	83±4	3.9±0.8
70%	STA RX® 1500	62±2	n.a.
80%	STA RX® 1500	51±3	n.a.
90%	STA RX® 1500	25±9	n.a.

Our results were in line with literature data. Lehmann *et al*. reported that an amount of filler and disintegrant between 30-50% is necessary to obtain rapidly disintegrating MUPS tablets (Lehmann, 1990) (Lehmann, 1994). Flamment *et al.* (Flament et al., 1994) showed that 30-50% of cushioning neutral pellets can reach the same goal also in the case of inert pellets as puffering means. It must be said, anyway, that our results furnished far better crushing strength values than using pellets as buffering excipients (70-130 N against 20-30 N with pellets as embedding material). Reguarding the disintegration time, our results reflected the technological differences between MCC 102 and UICEL-A/102, differences which have been extensively discussed in §2.3.1 and §2.3.2 (Kumar, 2002), (Reus-Medina, 2004), (Reus-Medina, 2005), (Reus-Medina et al., 2006). Accordingly, UICEL-A/102 MUPS had consistently higher disintegration times than their MCC 102 counterparts.

Main Experiments

In order to further investigate the chosen, favourable MUPS formulations, the compaction into MUPS was planned with a STAVEX external factorial design with quadratic D-optimisation (see §4.3.8). Table 5.7 reports the characterization results for MUPS.

Table 5.7: Results of MUPS characterization

MUPS	Pellet Runs(1)	Type of filler in pellets	Type of disintegrant in MUPS	Pellets in MUPS [%]	Crushing Strength [N]	Dis. time [sec]	Porosity	Pellet Distance [µm]
1	1b	MCC 102	UICEL-A/102	40	72.5	96.5	0.15	186±124
2	1b	MCC 102	UICEL-A/102	60	79.5	89	0.14	137±95
3	3b	MCC 102	UICEL-A/102	40	85	96	0.13	190±112
4	3b	MCC 102	UICEL-A/102	60	98	89.5	0.14	140±89
5	1b	MCC 102	STA RX® 1500	40	83.5	93	0.12	182±105
6	1b	MCC 102	STA RX® 1500	60	72.5	90	0.15	136±97
7	3b	MCC 102	STA RX® 1500	40	99.5	89.5	0.12	188±119
8	3b	MCC 102	STA RX® 1500	60	86	95	0.15	138±94
9	15b	UICEL-A/102	UICEL-A/102	40	93	60	0.22	190±122
10	15b	UICEL-A/102	UICEL-A/102	60	105	38.5	0.20	138±98
11	16b	UICEL-A/102	UICEL-A/102	40	73	50	0.21	186±112
12	16b	UICEL-A/102	STA RX® 1500	60	70.5	38	0.19	141±96
13	15b	UICEL-A/102	UICEL-A/102	50	86	52	0.21	158±107
14	17b	UICEL-A/102	UICEL-A/102	60	102.5	60	0.20	137±95
15	16b	UICEL-A/102	STA RX® 1500	50	82	47.5	0.23	151±99
16	17b	UICEL-A/102	STA RX® 1500	40	104	42.5	0.19	189±116
17	2b	MCC 102	STA RX® 1500	50	77.5	95	0.17	168±114

(1) For the pellets runs please refer to Table 5.2.

Compared with their MCC 102 counterparts, UICEL-A/102 MUPS were moderately more porous (0.13 versus 0.20). Being all other parameters fixed, this difference was put in relation with the diverse porosity of MCC 102 and UICEL-A/102 coated pellets (see Table 5.2). In fact, MUPS made of UICEL-A/102 pellets had half as long disintegration times as MUPS made of MCC 102. In contrast to this, no significant role was played by the type of disintegrant employed, meaning that employing of 10% w/w of either STA RX 1500® or UICEL-A/102 did not make a significant difference.

The mutual distance between pellets in MUPS proved to be inversely proportional to their percent loading amount in MUPS. The segregation index, which was defined in §4.3.9 as the standard deviation of the average distance between pellets, produced evidence of an increasing segregation decreasing the percentage of pellet in MUPS, as already asserted in several studies (see literature review in §2.7.4). In conclusion, in agreement with the findings of several previous studies, which have been reviewed by Opitz (Opitz, 2006) and Bodmeier (Bodmeier, 1997) and extensively discussed in § 2.7.4, the optimum loading amount of pellets in MUPS proved to be of 40-60% w/w. As a consequence, MUPS formulations containing 40-60% of pellets, 30-50% of MCC 102 and 10% of disintegrant were selected for the compaction into MUPS.

5.4.2 Factorial design: Analysis of the results

In the next pages, the analysis of the above mentioned STAVEX factorial design is presented. The influence of different factors on disintegration time and dissolution time is numerically expressed in Table 5.8, Table 5.9 and Table 5.10, respectively. These factors are: type of filler in pellets (PeI), loading amount of sodium diclofenac in pellets (SD), type of disintegrant in MUPS (dis.), amount of pellets in MUPS (% Pellets). In particular, in Table 5.8 the degree of influence of the mentioned factors on the disintegration time of MUPS is presented.

Table 5.8: Degree of influence of the factors on the disintegration time

	coded parameters			*uncoded parameters*	
parameter	*est*	*sd*	*p-value*	*est*	*sd*
intercept	4.5812	0.2322	*0.0000*	13.7400	4.6307
main effects:					
Pel[MCC]	0.0469	0.0635	*0.5011*	-0.6149	0.3608
Pel[UICE]	-0.0528	0.0714		0.6918	0.4059
SD	0.0179	0.0711	*0.8139*	0.1035	0.0545
Dis[UICE]	-0.1426	0.0643	*0.0906*	0.6723	0.3925
Dis[Star]	0.1605	0.0723		-0.7564	0.4416
%Pellets	0.1789	0.0724	*0.0688*	-0.4366	0.1910
quadrat./interact.:					
SD^2	-0.6253	0.2097	***0.0407***	-0.0028	0.0009
$\%Pellets^2$	0.4362	0.1906	*0.0840*	0.0044	0.0019
Pel[MCC]*SD	-0.0650	0.0682	*0.3947*	-0.0043	0.0045
Pel[UICE]*SD	0.0731	0.0768		0.0049	0.0051
Pel[MCC]*Dis[UICE]	-0.1031	0.0585		-0.1031	0.0585
Pel[MCC]*Dis[Star]	0.1160	0.0658	*0.1526*	0.1160	0.0658
Pel[UICE]*Dis[UICE]	0.1160	0.0658		0.1160	0.0658
Pel[UICE]*Dis[Star]	-0.1305	0.0740		-0.1305	0.0740
Pel[MCC]*%Pellets	0.1540	0.0697	*0.0917*	0.0154	0.0070
Pel[UICE]*%Pellets	-0.1733	0.0784		-0.0173	0.0078
SD*Dis[UICE]	0.0516	0.0779	*0.5441*	0.0034	0.0052
SD*Dis[Star]	-0.0580	0.0876		-0.0039	0.0058
SD*%Pellets	0.1099	0.0795	*0.2393*	0.0007	0.0005
Dis[UICE]*%Pellets	-0.1802	0.0757	*0.0760*	-0.0180	0.0076
Dis[Star]*%Pellets	0.2027	0.0852		0.0203	0.0085

In the left hand column are listed the factors and their mutual combinations. The p-value, which is calculated from the confidence interval of 95 %, indicates the relevance of each factor and its mutual correlations. P-values under 5% ($p<0.05$) are potentially significant, and in particular values < 0.01 are surely crucial. In the case of disintegration time, almost all p-values were <0.05, so that no main correlation was pointed out between the selected factors and the disintegration time. This was in agreement with the conclusions in §5.4.1 on the base of the characterization data of MUPS and it was attributed to the fact that a constant amount of disintegrant was used in the main experiments (10% w/w).

Only the quadratic interaction of SD proved to be <0.05. Despite this, no linear trend could be identified comparing the disintegration times of different MUPS formulations containing pellets with diverse SD loading amount (Table 5.7). Such discrepancy was neglected considering that the p-value was not significantly lower than 0.05 (0.0407).

Table 5.9: Degree of influence of the factors on the dissolution time 50%.

	coded parameters			*uncoded parameters*	
parameter	*Est*	*sd*	*p-value*	*Est*	*sd*
intercept	14.5557	0.8851	*0.0001*	44.7136	17.6483
main effects:					
Pel[MCC]	8.5090	0.2420	***0.0000***	23.5136	1.3752
Pel[UICE]	-9.5727	0.2722		-26.4528	1.5471
SD	-9.2283	0.2712	***0.0000***	-1.5178	0.2076
Dis[UICE]	-0.4247	0.2449	*0.1579*	-0.5666	1.4959
Dis[Star]	0.4778	0.2755		0.6374	1.6829
%Pellets	-0.0426	0.2759	*0.8847*	-0.1355	0.7278
quadrat./interact.:					
SD^2	4.2125	0.7992	***0.0062***	0.0187	0.0036
$\%Pellets^2$	0.1480	0.7266	*0.8485*	0.0015	0.0073
Pel[MCC]*SD	-9.6308	0.2601	***0.0000***	-0.6421	0.0173
Pel[UICE]*SD	10.8346	0.2926		0.7223	0.0195
Pel[MCC]*Dis[UICE]	0.1494	0.2229		0.1494	0.2229
Pel[MCC]*Dis[Star]	-0.1680	0.2508	*0.5395*	-0.1680	0.2508
Pel[UICE]*Dis[UICE]	-0.1680	0.2508		-0.1680	0.2508
Pel[UICE]*Dis[Star]	0.1890	0.2821		0.1890	0.2821
Pel[MCC]*%Pellets	0.2093	0.2658	*0.4749*	0.0209	0.0266
Pel[UICE]*%Pellets	-0.2355	0.2990		-0.0236	0.0299
SD*Dis[UICE]	-0.7176	0.2969	*0.0730*	-0.0478	0.0198
SD*Dis[Star]	0.8074	0.3340		0.0538	0.0223
SD*%Pellets	-0.1006	0.3031	*0.7567*	-0.0007	0.0020
Dis[UICE]*%Pellets	0.2676	0.2886	*0.4063*	0.0268	0.0289
Dis[Star]*%Pellets	-0.3011	0.3247		-0.0301	0.0325

Table 5.9 presents the degree of influence of the above mentioned factors on the time at which 50% of AI was dissolved. The type of filler in pellets and the amount of SD in pellets, which are actually mixtures factors, had a paramount effect of the dissolution time (both main and quadratic interactions were considerably less than 0.05). This is in full agreement with our observations, as MCC 102 MUPS showed twice or three times as long half disintegration times as UICEL-A/102 MUPS (see Table 5.12). Furthermore, the quadratic interection between disintegrant in MUPS and loading amount of pellets in MUPS was proved to be less than 0.05. This indicated that, even if the percentage of disintegrant in MUPS was held constant (10% w/w), its effect on disintegration and dissolution depended strongly on the loading amount of pellets in MUPS, or, in other words, on the percentage of embedding material in the tabletting mixture.

Table 5.10: Degree of influence of the factors on the dissolution time 90%.

	coded parameters			*uncoded parameters*	
parameter	*est*	*Sd*	*p-value*	*est*	*sd*
intercept	23.6023	2.3273	*0.0005*	146.7504	46.4046
main effects:					
Pel[MCC]	15.4457	0.6363	***0.0000***	47.6033	3.6160
Pel[UICE]	-17.3764	0.7158		-53.5537	4.0680
SD	-20.2162	0.7130	***0.0000***	-5.6303	0.5458
Dis[UICE]	-1.7086	0.6440	*0.0568*	-14.6565	3.9334
Dis[Star]	1.9222	0.7245		16.4885	4.4251
%Pellets	-1.3002	0.7255	*0.1476*	-1.3069	1.9137
quadrat./interact.:					
SD^2	18.3677	2.1014	***0.0009***	0.0816	0.0093
$\%Pellets^2$	1.0765	1.9105	*0.6032*	0.0108	0.0191
Pel[MCC]*SD	-15.2727	0.6839	***0.0000***	-1.0182	0.0456
Pel[UICE]*SD	17.1818	0.7694		1.1455	0.0513
Pel[MCC]*Dis[UICE]	-0.8586	0.5861		-0.8586	0.5861
Pel[MCC]*Dis[Star]	0.9659	0.6593	*0.2168*	0.9659	0.6593
Pel[UICE]*Dis[UICE]	0.9659	0.6593		0.9659	0.6593
Pel[UICE]*Dis[Star]	-1.0867	0.7418		-1.0867	0.7418
Pel[MCC]*%Pellets	-1.3406	0.6988	*0.1275*	-0.1341	0.0699
Pel[UICE]*%Pellets	1.5082	0.7861		0.1508	0.0786
SD*Dis[UICE]	0.7254	0.7807	*0.4054*	0.0484	0.0520
SD*Dis[Star]	-0.8161	0.8783		-0.0544	0.0586
SD*%Pellets	0.6024	0.7970	*0.4918*	0.0040	0.0053
Dis[UICE]*%Pellets	2.3478	0.7588	*0.0364*	0.2348	0.0759
Dis[Star]*%Pellets	-2.6413	0.8536		-0.2641	0.0854

As for the time needed to liberate 50% of the AI, the single type of filler and the amount of drug in the pellets had a high significance also for the time to 90% of the AI liberation (see Table 5.9). Table 5.11 represents a summary report of the factorial design analysis.

To sum up, UICEL-A/102 was on the one hand of comparable efficacy with the model superdisintegrant STA-RX 1500® as disintegrant in MUPS, on the other hand it proved to be less suited than MCC 102 as main filler in MUPS for extended release.

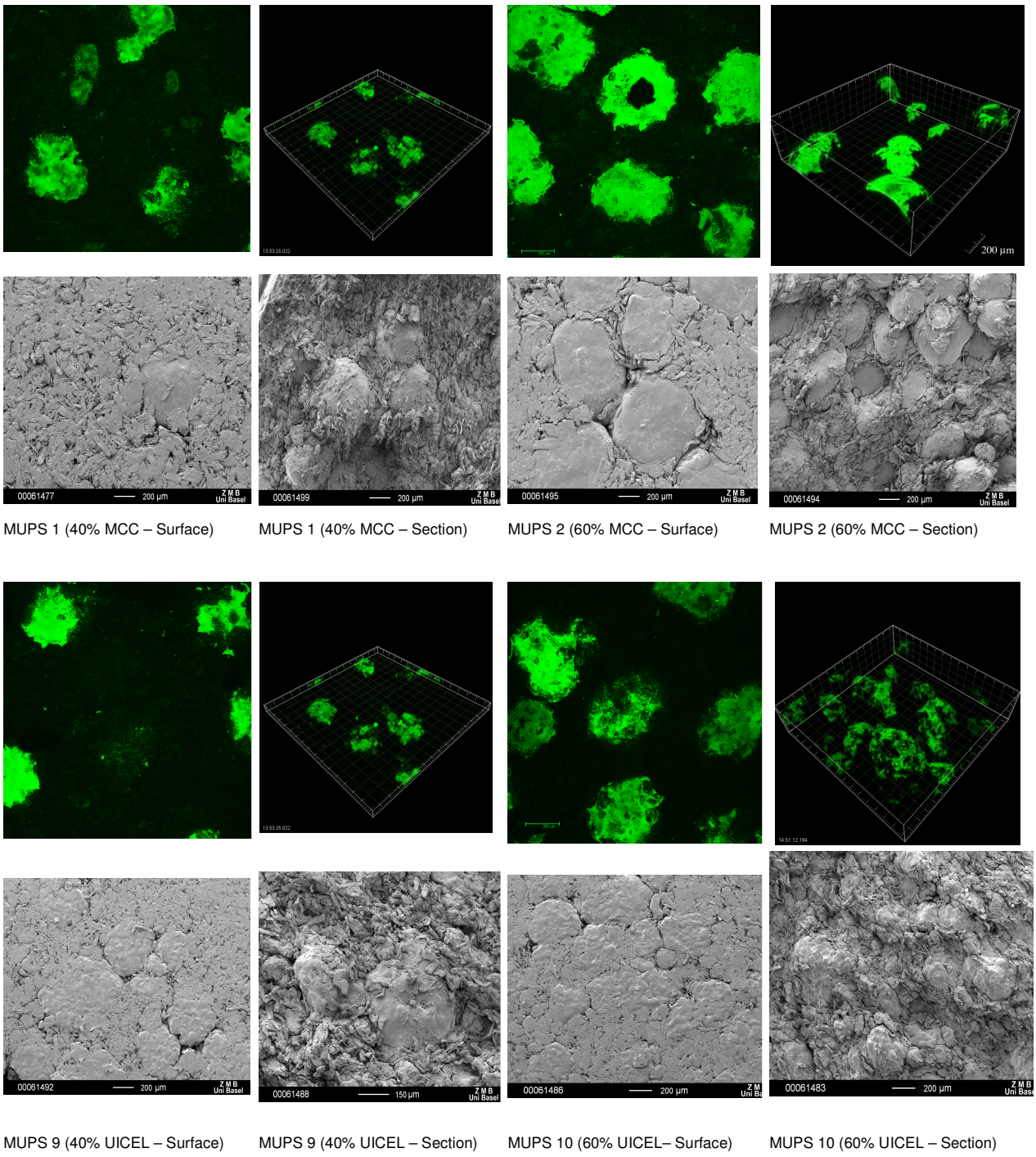
The first result confirmed the findings of previous studies, according to which UICEL-A/102 possesses peculiar swelling properties compared to MCC 102 formulations (Kumar, 2002), (Reus-Medina, 2004), (Reus-Medina, 2005), (Reus-Medina et al., 2006). The second result will be extensively discussed in §5.4.3.

Table 5.11: Summary of the analysis with the factorial design.

	Disintegration time	Dissolution time [50 % w/w]	Dissolution time [90 % w/w]
Type of filler in pellets	UICEL	MCC	MCC
Loading amount of SD in pellets [% w/w]	10.00	10.00	10.00
Type of disintegrant in MUPS	UICEL / STA RX® 1500	UICEL / STA RX® 1500	UICEL / STA RX® 1500
Amount of pellets in MUPS [% w/w]	50.00	60.00	40.00
Optimisation direction	min	max	max
(lower bound)	24.8	45.35	98.4
Optimum value	41.8	47.26	103.6
(upper bound)	70.6	49.18	108.7
Corr. goodness of fit	good	very good	pretty good

5.4.3 SEM/CLSM images of MUPS

Figure 5.11 compares CLSM and SEM images of the surface and section of six MUPS formulations. The composition of the six analysed batches (MUPS 1, 2, 9 and 10 as in Table 5.7) differed in the type of filler in pellets (either MCC 102 or UICEL-A/102) and the loading amount of pellets in MUPS (either 40% or 60%). Some black holes in the pictures were due to residues of cushioning excipients, which did not reflect at 488 nm. The pellets at the surface of both MUPS appeared to be flattened, but not ruptured. In contrast, the pellets inside the tablet were not appreciably deformed thanks to the cushioning effect of MCC 102.



MUPS 1 (40% MCC – Surface) MUPS 1 (40% MCC – Section) MUPS 2 (60% MCC – Surface) MUPS 2 (60% MCC – Section)

MUPS 9 (40% UICEL – Surface) MUPS 9 (40% UICEL – Section) MUPS 10 (60% UICEL– Surface) MUPS 10 (60% UICEL – Section)

Figure 5.11: CLSM images of MUPS 1, 2, 9, 12 (surface and break section)

5.4.4 Dissolution profiles from MUPS vs. uncompressed subunits

In Figure 5.12 the dissolution profiles of some pellet runs are compared to the corresponding MUPS having the same amount of cushioning excipient and either UICEL-A/102 or STA-RX® 1500 as disintegrant. Both MCC 102 MUPS (1 and 2) and UICEL-A/102 MUPS (9 and 10) consistently retained the dissolution profiles of the respective uncompressed pellets (see Figure 5.12). This suggests that no major damages in their film coating occurred, and that the choice of the disintegrant played a negligible role in the dissolution. On the contrary, both of them contributed to a rush disintegration of the MUPS into their subunits, so that the dissolution profiles of uncompressed pellets and MUPS were practically comparable. These results, supported with the SEM and CLSM images, confirmed the overall integrity of the pellet coating film after tabletting.

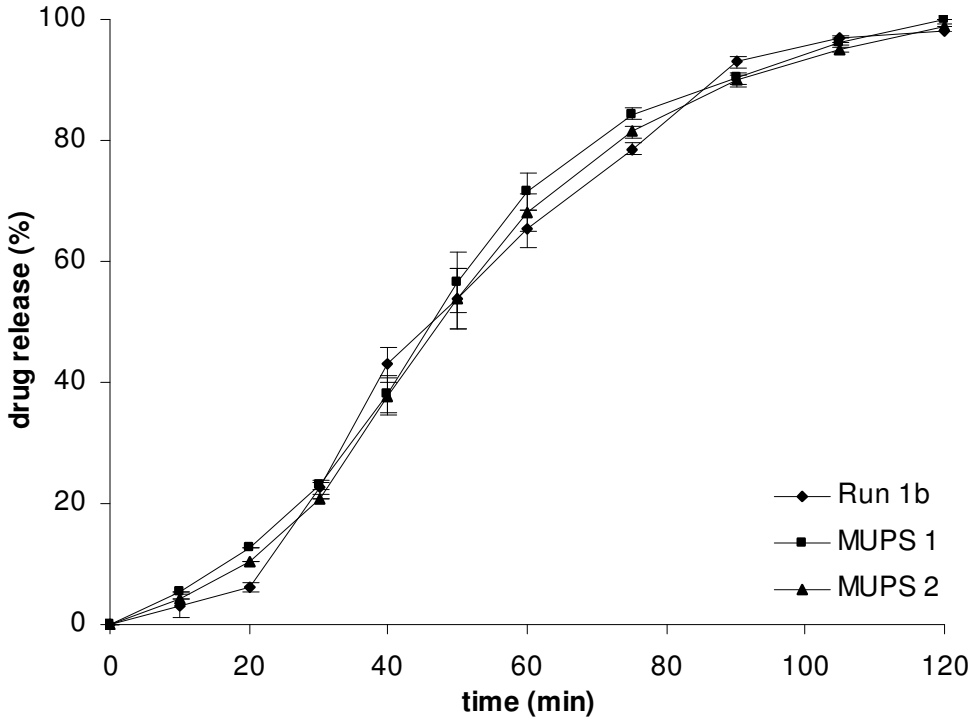
Furthermore, MUPS made of coated UICEL-A/102 pellets were released much faster than their MCC 102 counterparts, and this independently of the coating layer thickness (the same in all pellet formulation) and porosity (minimal due to the absence of a pore maker in the coating suspension). This implies that the drug release from UICEL-A/102 pellets was driven by the prevalent disintegration properties of their filler, rather than by their virtually delaying coating layer.

This result, corroborated by the CLSM images, indicates that both MCC 102 and UICEL-A/102 pellet formulations underwent soft compaction keeping the dissolution profiles of the uncompressed subunits. This is also in line with the findings of other studies (§ 2.7.5.1).

Picker compared the potential suitability for soft tabletting of Carrageenans, Chitosane, MCC, HPMC and Polyethylene oxides establishing the following ranking: Carrageenans < Chitosane < MCC < HPMC < Polyethylene oxides. Se also investigated the compaction of pellets (d=510-700 µm) loaded with diclofenac, coated with Eudragit L 30D and mixed with either carrageenan or MCC 102 or cellactose. In all three cases soft compaction without damage of the coating layer was reached, with carrageenan slightly better cushioning excipients than MCC 102 and Callactose, in accordance with its moderately higher plasticity (Picker, 2004). In Picker's studies, anyway, the role of the coating layer was not taken into account. Other studies provided evidence that sucrose pellets coated with Kollicoat® SR 30 D undergo soft compaction retaining the dissolution profile of the uncompacted subunits, which was in line with our findings about MCC 102 and UICEL-A/102 (Dashevsky, 2004), (Dashevsky, 2005), (Johansson, 1995a).

Comparing our results with Deshevsky's and Picker's findings, it might be concluded that employing a plastic cushioning excipient as MCC 102 together with a flexible coating layer as Kollicoat SR 30D is the best choice to reach conservative compaction. Anyway, also UICEL-A/102 coated pellets (sensibly more elastic than their MCC 102 counterparts) underwent soft

compaction, which made us conclude that the coating layer had a higher influence than the embedding material on the softness of the compaction.



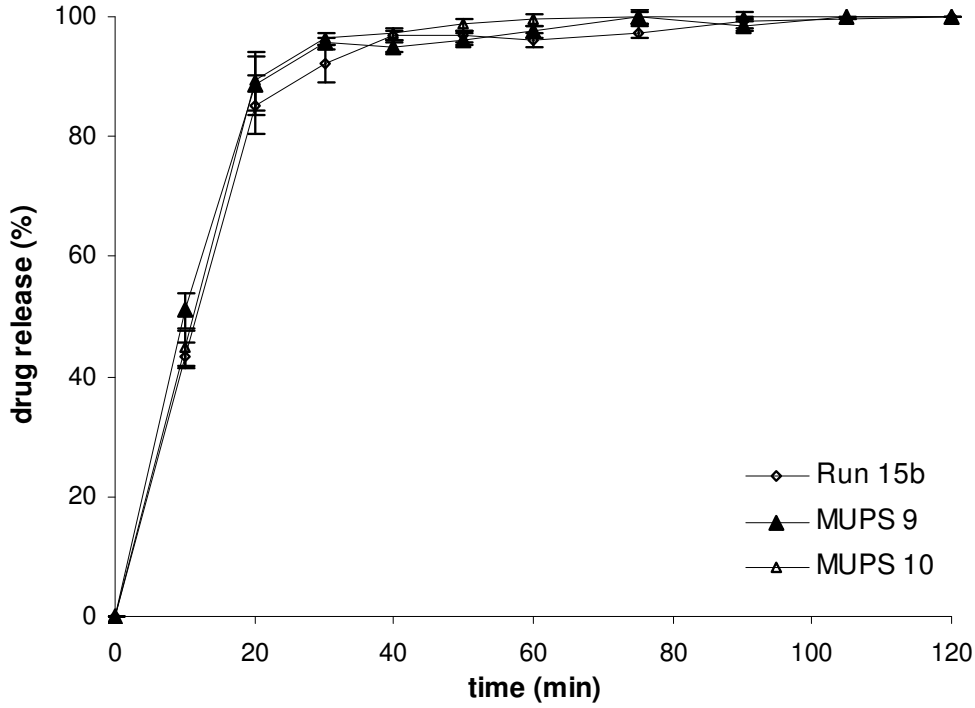


Figure 5.12: Drug release from diverse pellets formulations

5.4.5 MUPS from homogeneous pellets: summary of results

Homogenous pellets of either MCC 102 or UICEL-A/102 pellets loaded with 10-40% of sodium-diclofenac and coated with Kollicoat® SR 30 D to 20% w/w weight gain proved to be appropriate subunits for Multiparticulate Unit Pellet Systems. Mixed with 40-60% of MCC 102 powder, 10% of disintegrant (either UICEL-A/102 or STA RX®1500) and 0.5% of Mg-stearate, they were compacted into MUPS using a Presster™ Compaction Simulator (Metropolitan Computing Corporation, East Hanover, USA) equipped with a D-tooling single-punch (diameter of 10 mm, flat surface). The distance between the punches (2.2 mm) and the linear velocity of the compression (0.108 m/s) were held constant. All the MUPS formulations overcame compaction deformed rather than ruptured, as proved by comparison between the dissolution profiles and the SEM and CLSM images before and after compaction. Both MCC 102 and UICEL-A/102 MUPS resulted to be mechanically robust (crushing strength of 70-100 N), fast disintegrating in water (≤ 3 minutes) and maintained the same release profile and almost the same superficial and inner morphology of their uncompressed subunits.

Compared with MCC 102 pellets, UICEL-A/102 pellets proved to be generally more irregular, porous and less spherical. Nonetheless, they could be rather homogenously coated and retained their dissolution profile also after compaction into MUPS.

The fact that UICEL-A/102 pellets and MUPS presented shorter dissolution times than their MCC counterparts is to ascribe solely to the prevalent swelling properties of UICEL-A/102 (Kumar, 2002). In fact, UICEL-A/102 contained in pellets eased their dissolution independently of the amount and homogeneity of their coating layer.

5.4.6 Compaction of inhomogeneous pellets into MUPS

Preliminary experiments

The results of the preliminary experiments are displayed in Table 5.12..

Table 5.12: Results of the preliminary experiments: above UICEL MUPS containing Suglets® (left) or Cellets® (right), below MCC 102 MUPS containing Suglets® (left) or Cellets® (right).

Pellets in Tabletting Mixture [w/w %]	Core / filler	Crushing strength ±sd [N]	Dis. Time ±sd [min]
20%	Suglets®/ UICEL-A/102	257±10	>30
30%	Suglets®/ UICEL-A/102	198±6	12.9±4.48
40%	Suglets®/ UICEL-A/102	116±10	12.1±2.1
50%	Suglets®/ UICEL-A/102	116±6	4.2±0.3
60%	Suglets®/ UICEL-A/102	109±34	2.9±1.33
70%	Suglets®/ UICEL-A/102	67±13	n.a.
80%	Suglets®/ UICEL-A/102	55±10	n.a.

Pellets in Tabletting Mix. [w/w %]	Core / filler	Crushing strength ±sd [N]	Dis. Time ±sd [min]
20%	Cellets®/ UICEL-A/102	309±16	Not dis.
30%	Cellets®/ UICEL-A/102	219±5	13.9±1.2
40%	Cellets®/ UICEL-A/102	121±12	10.8±1.5
50%	Cellets®/ UICEL-A/102	100±38	7.5±1.2
60%	Cellets®/ UICEL-A/102	90±5	5.3±0.5
70%	Cellets®/ UICEL-A/102	64±2	n.a.
80%	Cellets®/ UICEL-A/102	28±2	n.a.

Pellets in Tabletting Mixture [w/w %]	Core / filler	Crushing strength ±sd [N]	Dis. Time ±sd [min]
20%	Suglets®/ MCC 102	300±10	Not dis.
30%	Suglets®/ MCC 102	250±6	Not dis.
40%	Suglets®/ MCC 102	150±34	130±3.1
50%	Suglets®/ MCC 102	120±13	80±0.29
60%	Suglets®/ MCC 102	130±5	42±5
70%	Suglets®/ MCC 102	76±6	n.a.
80%	Suglets®/ MCC 102	48±2	n.a.

Pellets in Tabletting Mix. [w/w %]	Core / filler	Crushing strength ±sd [N]	Dis. Time ±sd [min]
20%	Cellets®/ MCC 102	297±10	Not dis.
30%	Cellets®/ MCC 102	247±5	Not dis.
40%	Cellets®/ MCC 102	147±12	127±7
50%	Cellets®/ MCC 102	135±38	100±10
60%	Cellets®/ MCC 102	100±5	50±7
70%	Cellets®/ MCC 102	64±2	n.a.
80%	Cellets®/ MCC 102	28±2	n.a.

On the base of the pre-experiments for homogeneous pellets, it was decided to restrict the filler content range to 20-80% and to carry out pre-experiments with only one disintegrant, i.e. UICEL A noticeable correlation between the crushing strength and the amount of pellets could be observed; in fact, the higher the percentage of pellets in the formulation, the lower the crushing strength of MUPS. As a result, MUPS containing 70% and 80% of pellets proved to be not robust (crushing strength < 70N) and did not disintegrate properly into the subunits. This trend could be attributed to the lower dilution effect of MCC 102, which caused the pellets to stick to each other building undesired pellet aggregates.

On the other hand, MUPS containing 20-30% of pellets showed too high crushing strength (>198 N). Thanks to UICEL-A/102 prevalent disintegrant properties, MUPS formulations containing 40, 50 and 60% of UICEL-A/102 coated pellets could still disintegrate within 15 minutes, which made us select them for further studies.

Our results were in line with literature data. Lehmann *et al*. reported that an amount of filler and disintegrant between 30-50% is necessary to obtain rapidly disintegrating MUPS tablets (Lehmann, 1990) (Lehmann, 1994). Flamment *et al.* (Flament et al., 1994) showed that 30-50% of cushioning neutral pellets can reach the same goal also in the case of inert pellets as puffering means. It must be said, anyway, that our results furnished far better crushing strength values than using pellets as buffering excipients.

Reguarding the disintegration time, our results reflected the technological differences between MCC 102 and UICEL-A/102, differences which have been extensively discussed in §2.3.1 and §2.3.2 (Kumar, 2002), (Reus-Medina, 2004), (Reus-Medina, 2005), (Reus-Medina et al., 2006). Accordingly, UICEL-A/102 MUPS had consistently lower disintegration times than their MCC 102 counterparts.

Main Experiments

The results of the main experiments are displayed in Table 5.13.

As already pointed out in the previous paragraph, the crushing strength was directly related to the amount of pellets and thereby to the amount of embedding material in MUPS. Additionally, it can be claimed that the type of disintegrant used did not have a significant influence on the disintegration time. Concerning the porosity, as expected, the higher the crushing strength was, the more compact the tablet and the lower its porosity was.

The mutual distance between pellets in MUPS proved to be inversely proportional to their percent loading amount in MUPS; the segregation index, which had been defined in §4.3.9 as the standard deviation of the average distance between pellets, produced evidence of an increasing segregation decreasing the percentage of pellets in MUPS. Both results were in line

with the ones emerged in the first type of MUPS (pellets from direct pelletization) and our expectations.

Table 5.13: Results of the MUPS characterisation

Mixture	Cellets®	Suglets®	% pellets in MUPS	Pellet run	Type of disintegrant	SD content [%]	Poro -sity [%]	Disint. time [min]	Pellet distance [min]
1	x		40	4	UICEL-A/102	4.8±0.2	9.00	10.8±1.5	189±116
2	x		50	4	UICEL-A/102	6.0±0.5	7.89	7.5±1.2	151±99
3	x		60	4	UICEL-A/102	7.2±0.7	7.27	5.3±0.5	137±95
4		x	40	3	UICEL-A/102	4.7±0.3	8.36	12.1±2.1	178±98
5		x	50	3	UICEL-A/102	5.9±0.2	7.54	4.2±0.3	145±86
6		x	60	3	UICEL-A/102	7.1±0.7	6.87	2.9±1.33	130±75
7	x		40	4	STA RX 1500	4.8±0.4	8.89	4.74±0.45	200±108
8	x		50	4	STA RX 1500	6.0±0.6	7.01	5.36±1.07	149±94
9	x		60	4	STA RX 1500	7.2±0.8	5.32	7.70±1.05	128±86
10		x	40	3	STA RX 1500	4.7±0.5	9.21	7.44±0.99	175±120
11		x	50	3	STA RX 1500	5.9±0.6	9.01	8.39±0.55	148±105
12		x	60	3	STA RX 1500	7.1±0.9	6.89	10.11±2.4	124±91

5.4.7 Factorial design: Analysis of the results

The STAVEX factorial design was employed to assess the influence of each variable on the characteristics of the MUPS as well as to determine the formulation which led to the best MUPS.

Disintegration time

Table 5.14 shows the results of the STAVEX analysis regarding the disintegration time.

In the left column, the single factors and their combinations are listed, whereas their influence on the response variables is expressed with the p-value. A p-value $\leq$ 0.05 indicates a probable effect of the factor on the analysed response variable, whereas p-values $\leq$ 0.01 indicates a sure correlation. No influence of the single factors investigated on the disintegration time could be identified. On the contrary, interactions between type of disintegrant and amount of pellets as well as between type of disintegrant and amount of MCC 102 were suggested as significant. This result could be associated with the following two different trends: the disintegration time of MUPS with UICEL-A/102 as disintegrant increases in order 60%<50%<40%, whereas it decreases in the same order in case of MUPS with STA RX 1500® as a disintegrant (see Table 5.13). It must be considered that any powder binary mixture, if compressed into a compact of a certain porosity, features different disintegration times at different compositions of that mixture.

Under the assumption that pellets have a minor impact on the disintegration time of MUPS than the binary mixture homogeneously distributed around them, the disintegration time of MUPS would be directly related to the disintegration time of that binary mixture (Krausbauer et al., 2007). Considering that the minimum disintegration time for the binary mixture MCC 102 / UICEL-A/102 is around 5% v/v and the one of MCC 102 / STA RX is around 15 % v/v, and observing that the ratios disintegrant/filler in MUPS are, respectively, 19.5, 24.3 and 32.2% v/v, we would have expected a similar trend in the disintegration times for both disintegrants. This result was interpreted as proof by contradiction of the approximation above; in other words, the UICEL-A/102 pellets highly probably played a non marginal role in the disintegration of MUPS.

Table 5.14: Degree of influence of all analysed factors on the disintegration time

	Coded parameters			*Uncoded parameters*	
Parameter	*est*	*sd*	*p-value*	*est*	*sd*
intercept	6.2725	0.6723	*0.0007*	6.2725	0.6723
main effects:					
D[UICE]	-0.0250	0.3881	*0.9517*	-0.0250	0.3881
D[St_1]	0.0250	0.3881		0.0250	0.3881
S[Sugl]	0.3617	0.3881	*0.4042*	0.3617	0.3881
S[Cell]	-0.3617	0.3881		-0.3617	0.3881
C	-4.0650	1.9015	*0.0993*	-0.0452	0.0211
E	5.0812	2.3768	*0.0993*	0.0565	0.0264
quadrat./interact.:					
C*E	-59.5500	32.9342	*0.1449*	-0.0074	0.0041
C^2	23.8200	13.1737	*0.1449*	0.0029	0.0016
E^2	37.2188	20.5839	*0.1449*	0.0046	0.0025
D[UICE]*S[Sugl]	-0.9950	0.3881	*0.0624*	-0.9950	0.3881
D[UICE]*S[Cell]	0.9950	0.3881		0.9950	0.3881
D[St_1]*S[Sugl]	0.9950	0.3881		0.9950	0.3881
D[St_1]*S[Cell]	-0.9950	0.3881		-0.9950	0.3881
D[UICE]*C	-9.6950	1.9015	***0.0070***	-0.1077	0.0211
D[St_1]*C	9.6950	1.9015		0.1077	0.0211
D[UICE]*E	12.1187	2.3768	***0.0070***	0.1347	0.0264
D[St_1]*E	-12.1187	2.3768		-0.1347	0.0264
S[Sugl]*C	-1.4850	1.9015	*0.4785*	-0.0165	0.0211
S[Cell]*C	1.4850	1.9015		0.0165	0.0211
S[Sugl]*E	1.8563	2.3768	*0.4785*	0.0206	0.0264
S[Cell]*E	-1.8563	2.3768		-0.0206	0.0264

Dissolution time

Table 5.15 and Table 5.16 show the results of the STAVEX analysis for the dissolution time.

The loading amount of coated pellets and cushioning excipients were indicated as crucial factors. The fact that 40% of pellets could be better diluited in a tabletting mixture and therefore puffered during compaction than in a mixture containing 60% of pellets was advocated to explain these findings.

Table 5.15: Degree of influence of all analysed factors on the dissolution time to 50%

	Coded parameters			*Uncoded parameters*	
Parameter	*est*	*sd*	*p-value*	*est*	*sd*
intercept	126.2500	7.8654	*0.0001*	126.2500	7.8654
main effects:					
D[UICE]	11.4167	4.5411	*0.0658*	11.4167	4.5411
D[St_1]	-11.4167	4.5411		-11.4167	4.5411
S[Sugl]	4.7500	4.5411	*0.3546*	4.7500	4.5411
S[Cell]	-4.7500	4.5411		-4.7500	4.5411
C	-118.0000	22.2467	***0.0061***	-1.3111	0.2472
E	147.5000	27.8084	***0.0061***	1.6389	0.3090
quadrat./interact.:					
C*E	-70.0000	385.3245	*0.8647*	-0.0086	0.0476
C^2	28.0000	154.1298	*0.8647*	0.0035	0.0190
E^2	43.7500	240.8278	*0.8647*	0.0054	0.0297
D[UICE]*C	-30.0000	22.2467	*0.2488*	-0.3333	0.2472
D[St_1]*C	30.0000	22.2467		0.3333	0.2472
D[UICE]*E	37.5000	27.8084	*0.2488*	0.4167	0.3090
D[St_1]*E	-37.5000	27.8084		-0.4167	0.3090
S[Sugl]*C	-6.0000	22.2467	*0.8007*	-0.0667	0.2472
S[Cell]*C	6.0000	22.2467		0.0667	0.2472
S[Sugl]*E	7.5000	27.8084	*0.8007*	0.0833	0.3090
S[Cell]*E	-7.5000	27.8084		-0.0833	0.3090

Table 5.16: degree of influence of all analysed factors on the dissolution time to 90%

	coded parameters			*uncoded parameters*	
parameter	*est*	*sd*	*p-value*	*est*	*sd*
intercept	7.5000	0.4082	*0.0001*	7.5000	0.4082
main effects:					
D[UICE]	-0.5000	0.2357	*0.1012*	-0.5000	0.2357
D[St_1]	0.5000	0.2357		0.5000	0.2357
S[Sugl]	0.1667	0.2357	*0.5185*	0.1667	0.2357
S[Cell]	-0.1667	0.2357		-0.1667	0.2357
C	-5.0000	1.1547	***0.0123***	-0.0556	0.0128
E	6.2500	1.4434	***0.0123***	0.0694	0.0160
quadrat./interact.:					
C*E	10.0000	20.0000	*0.6433*	0.0012	0.0025
C^2	-4.0000	8.0000	*0.6433*	-0.0005	0.0010
E^2	-6.2500	12.5000	*0.6433*	-0.0008	0.0015
D[UICE]*C	0.0000	1.1547	*1.0000*	0.0000	0.0128
D[St_1]*C	0.0000	1.1547		0.0000	0.0128
D[UICE]*E	0.0000	1.4434	*1.0000*	0.0000	0.0160
D[St_1]*E	0.0000	1.4434		0.0000	0.0160
S[Sugl]*C	0.0000	1.1547	*1.0000*	0.0000	0.0128
S[Cell]*C	0.0000	1.1547		0.0000	0.0128
S[Sugl]*E	0.0000	1.4434	*1.0000*	0.0000	0.0160
S[Cell]*E	0.0000	1.4434		0.0000	0.0160

Table 5.17 summarizes the formulations indicated by STAVEX as the most advantageous. With respect to the disintegration time, MUPS containing 60% of pellets with Cellets® as cores and UICEL-A/102 as disintegrant were the most favourable, as already pointed out in the MUPS characterization. Conversely, STAVEX suggested as ideal formulations in terms of dissolution time the MUPS containing 40% of pellets with Cellets®, and STA RX 1500® as disintegrant. The fact that 40% of pellets could be better diluited in a tabletting mixture and therefore puffered during compaction than in a mixture containing 60% of pellets created this trend.

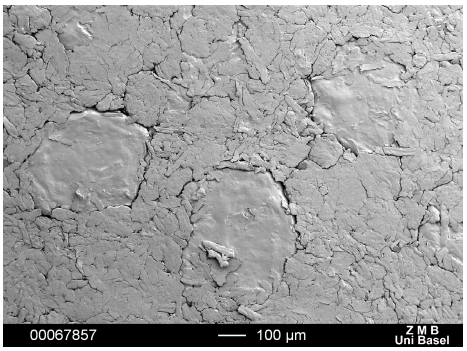
Table 5.17: Summary of the best formulations

Factor/Optimum	Response		
	Disintegration time	Dissolution 50%	Dissolution 90%
C:Coated Pellets	60	40	40
D:Disintegrant	UICEL	St_1500	St_1500
E:Embedding Material	30	50	50
S:Suglets or Cellets	Cellets®	Cellets®	Cellets®
Optimization direction (lower bound)	0.81	7.659	6.854
Optimization direction (upper bound)	5.77	10.674	9.987
Optimum value	3.29	9.167	9.056
Corr. goodness of fit	good	mediocre	mediocre

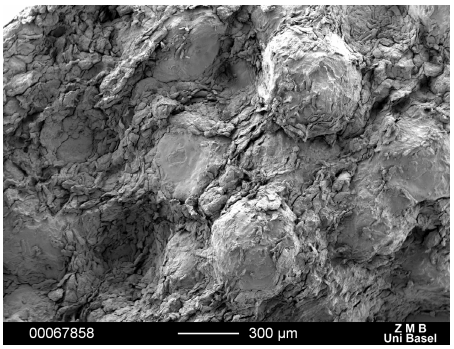
5.4.8 SEM/CLSM images of MUPS

Figure 5.13 shows the SEM images of the MUPS surfaces (on the left) and sections (on the right) for four different formulations. Mix 5 corresponds to MUPS with pellet loading of 50%, Suglets® cores and UICEL-A/102 as disintegrant; Mix 6 identifies MUPS with pellet loading of 60%, Suglets® cores and UICEL-A/102 as disintegrant; Mix 8 is related with MUPS with pellet loading of 50%, Cellets® cores and STA RX® 1500 as disintegrant; Mix 9 corresponds to MUPS with pellet loading of 60%, Cellets® cores and STA RX® 1500 as disintegrant.

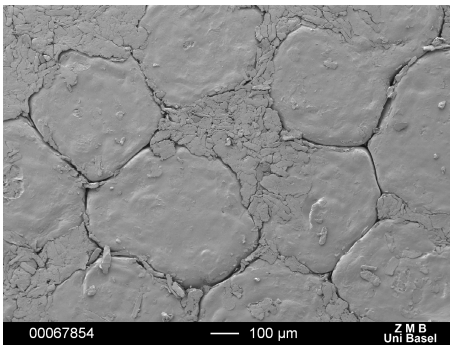
The four images of the MUPS surface revealed that the pellets underwent a deformation during the compaction. In particular, they were flattened because of the direct contact with the punch head, though they did not seem to be ruptured. On the contrary, pellets within the tablet seemed to retain their round shape or undergo just a small deformation. This suggests that the film coating was more damaged on the pellets located at the MUPS surface, whereas the pellets in the tablet remained almost intact, due to the cushioning effect of MCC 102.



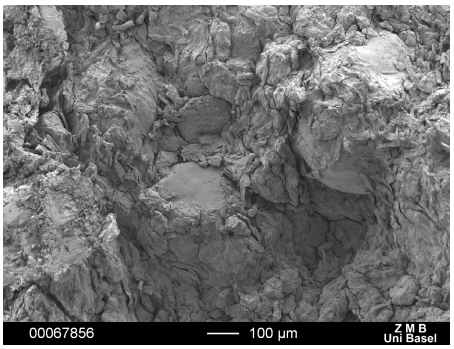
Mix 5, surface



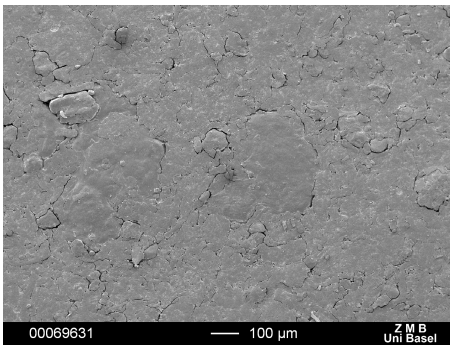
Mix 5, section



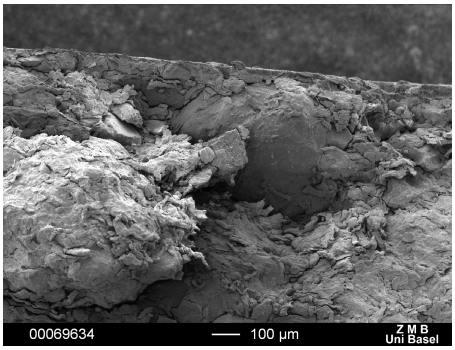
Mix 6, surface



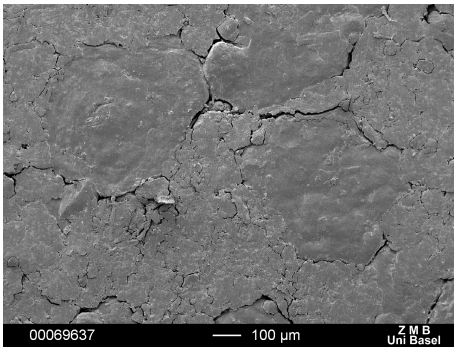
Mix 6, section



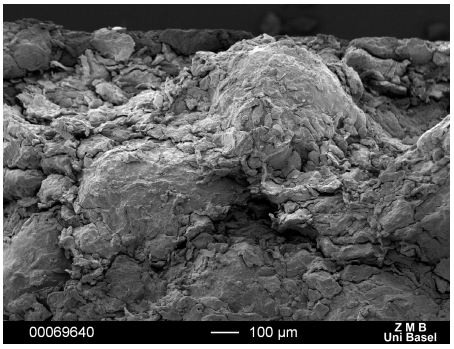
Mix 8, surface



Mix 8, section



Mix 9, surface

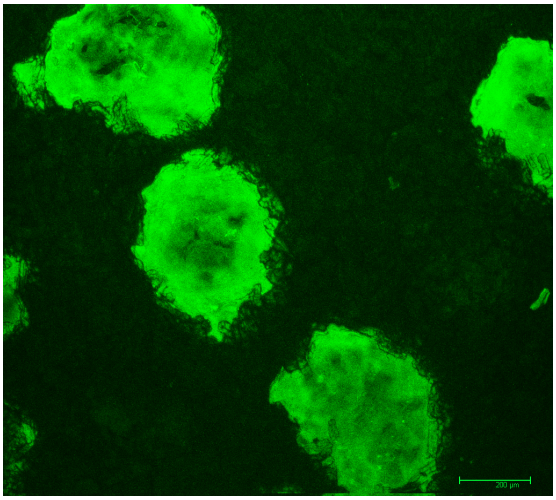


Mix 9, section

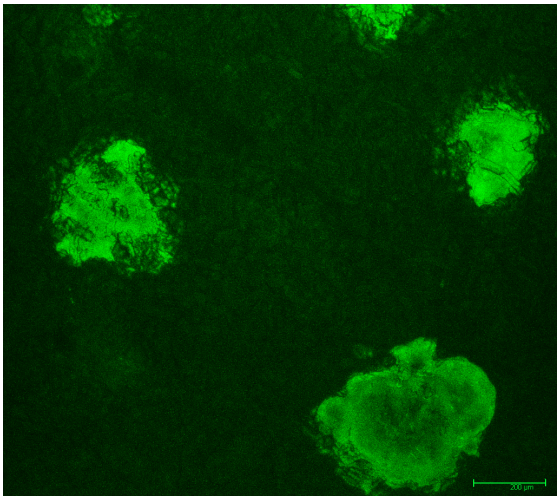
Figure 5.13: SEM images of MUPS (for the Mix composition please refer to Table 5.13)

The use of sugar Suglets® or Cellets® as cores did not seem to play a role in the compaction behaviour of the pellets; in fact, no significant differences in the degree of deformation could be detected from the images (see discussion about Figure 5.14**)**.

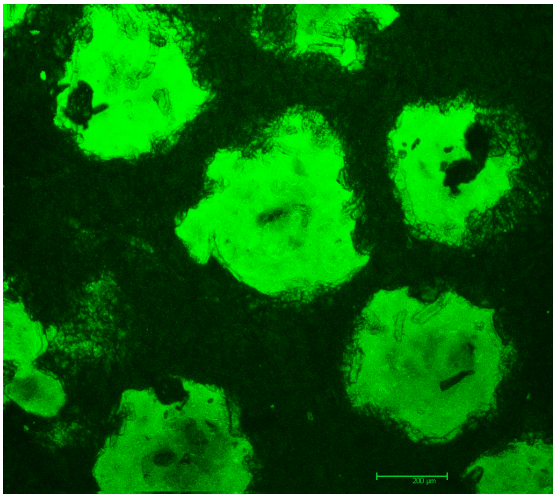
The segregation between powder and pellets, visible in particular in the images C and G, is to attribute to their different particle size. This was the result of a compromise between the induction of a soft compaction (cushioning powder) and the unavoidable segregation between powder and pellets.



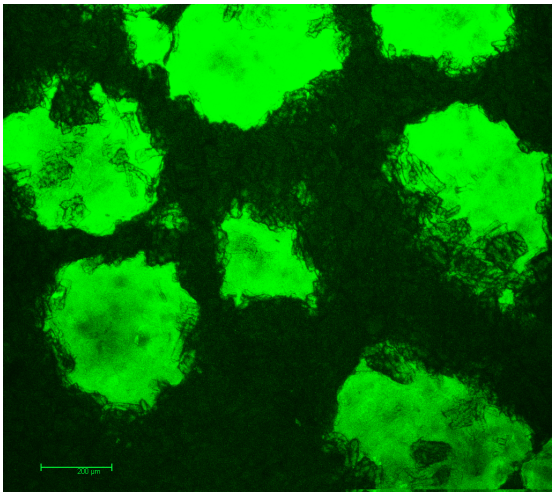
Mix 1 (Table 5.13)



Mix 3 (Table 5.13)



Mix 4 (Table 5.13)



Mix 6 (Table 5.13)

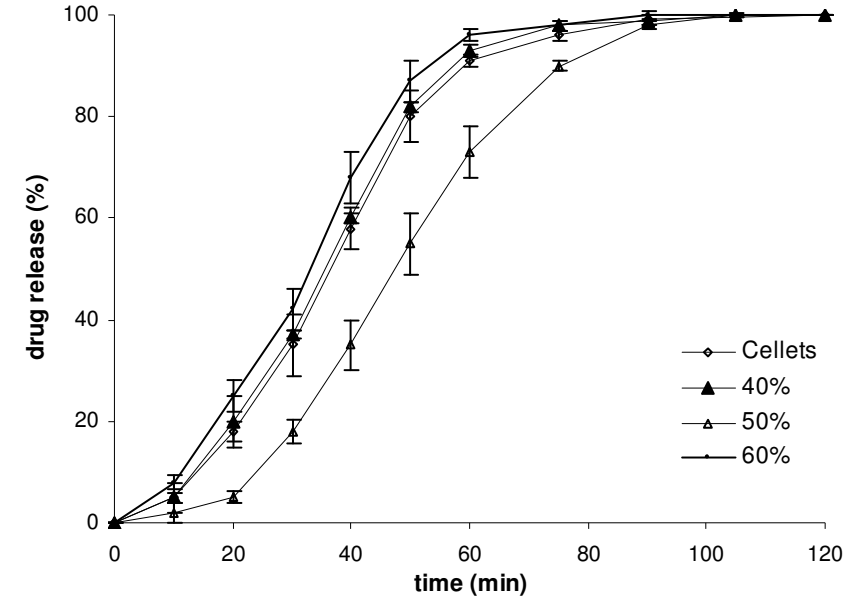
Figure 5.14: CLSM images of MUPS

In Figure 5.14, the coating layer of the pellets at the surface of the MUPS with 40% and 60% pellet content respectively are shown. In contrast to the SEM images, the CLSM pictures above showed black spots in the coating of some superficial pellets, suggesting that the compaction was not entirely conservative, especially for the pellets in direct contact with the punch head during compaction. This might have led to slightly faster half dissolution times of MUPS compared to their uncompressed subunits, especially in the MUPS with sugar spheres as subunits (see §5.4.9.

5.4.9 Dissolution profiles from MUPS vs. uncompressed subunits

In Figure 5.15 the AI dissolution profiles of six MUPS batches are compared with the dissolution profiles of their uncompressed subunits. In particular, each batch of UICEL coated pellets is compared with three MUPS formulations in which it was loaded (40, 50, 60% of coated pellets). In the first graph, the dissolution from UICEL-A/102 MUPS whose pellets were layered on Cellets® are plotted, whereas in the second graph the dissolution from UICEL-A/102 MUPS whose pellets were layered on Suglets® are reported.

In both cases, the drug release from MUPS was moderately faster than from the uncompressed subunits, suggesting that the coating layer had been slightly damaged during the compaction. Therefore, the employment of Cellets® rather than Suglets® as basic neutral cores in dry powder layering made a visible difference. In fact, MUPS whose cores were Cellets® underwent softer compaction than their counterparts having Suglets® as subunits. Being all other parameters unchanged, it can be asserted that Cellets® behaved plastically, while Suglets® behaved more elastically during compaction. This is in agreement with literature: hard pellets coated with a thick film layer are better capable of withstanding the compression force than soft pellets, and that they tend to recover after compression without major damage of the coating layer; elastic materials, accordingly, will produce proportionally bigger damage (Beckert, 1996), (Bodmeier, 1997), (Opitz, 2005).



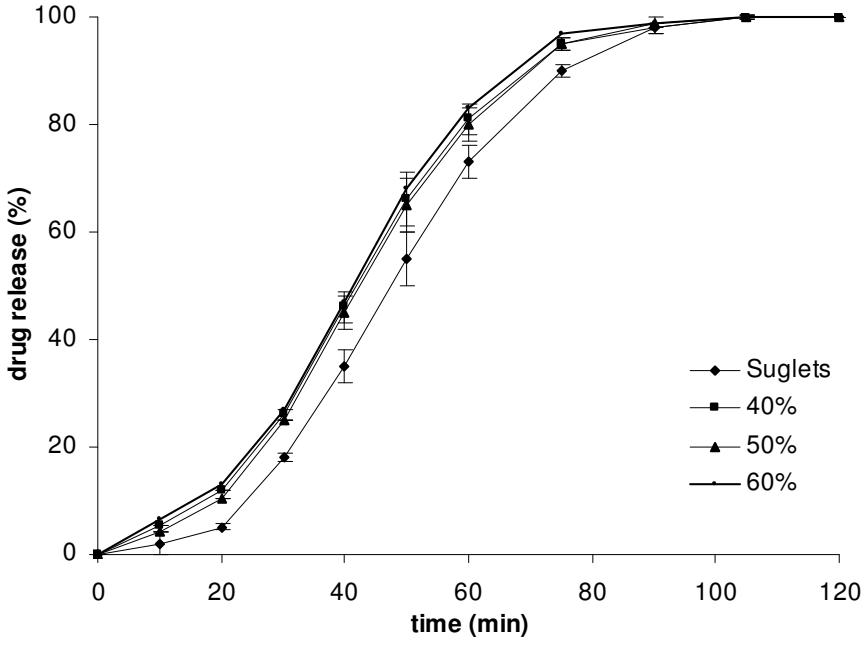


Figure 5.15: Drug release profiles from MUPS with Cellets® cores (above) and Suglets® cores (below).

5.4.10 MUPS from inhomogeneous pellets: summary of results

In this second part of this study, MUPS prepared by compaction of inhomogeneous pellets were investigated. These pellets, called inhomogeneous with reference to the inhomegenous composition of the uncoated core, were produced by layering a binary mixture 1:1 of UICEL and Sodium Diclofenac on neutral cores (either Suglets® or Cellets®) by means of dry powder layering technology. Afterwards, they were coated with Kollicoat® SR 30 D to 20% w/w weight gain, in full accordance with the coating methodology and parameters previously optimized.

Both UICEL-A/102 and MCC 102 pellets showed comparable characteritiscs, with exception of density, specific surface area and porosity. In fact, in line with the charactieristics of the starting materials, UICEL-A/102 coated and uncoated pellets were less compact and more porous than their MCC 102 counterparts. This had also a mojor impact on the characteristics of the MUPS.

Through preliminary experiments, the most favourable ranges of the loading amount of coated pellets, cushioning excipients and disintegrant in MUPS were identified. These ranges proved to be analogous with the ones previously selected for homogeneous pellets, i.e. 40-60 w/w % pellets, 30-50 w/w % cushioning excipients and 10 w/w % of disintegrant. The only difference regarded MCC 102 coated pellets, which on the base of pre-experiments did not result in favourable MUPS, highly probably due to the different characteristics of porosity of the subunits (see above).

Mixed with 40-60% of MCC 102 powder, 10% of disintegrant (either UICEL-A/102 or Sta-RX-1500) and 0.5% of Mg-Stearate, each tabletting mixture was compacted into MUPS using a Presster™ Compaction Simulator (Metropolitan Computing Corporation, East Hanover, USA) equipped with a D-tooling single-punch (diameter of 10 mm, flat surface). The distance between the punches (2.2 mm) and the linear velocity of the compression (0.108 m/s) were held constant. The so obtained MUPS resulted to be mechanically robust (crushing strength of 80-120 N), fast disintegrating in water (< 12 minutes) and maintained the release profile of their uncompressed subunits almost unchanged.

In particular, the choice of Cellets® rather than Suglets® as basic neutral cores in dry powder layering had a significant impact on the characteristics of MUPS. In fact, MUPS whose subunits had Cellets® cores retained the release profile of their uncompressed subunits more then their counterparts having Suglets® as cores. This suggests that subunits with a cellulosic core contributed significantly to the softness of the compaction, this difference being associable with the rather plastic behaviour of Cellets® against the rather elastic behaviour of Suglets® during compaction. All in all, the homogeneous pellets obtained by direct pelletization proved to retain more effectively the dissolution profiles of their subunits.

The MUPS characterisation along with the factorial design analysis (STAVEX) allowed to determine the effects of the chosen factors (type of cores, % amount of pellets and MCC 102, type of disintegrant) and their eventual mutual interactions on two key response variables (disintegration time and dissolution time).

Concerning the effect of the type of disintegrant on the disintegration time, the following trend could be figured out. The disintegration time of MUPS with UICEL-A/102 as disintegrant increases in order 60%<50%<40%, whereas it decreases in the same order in case of MUPS with Sta RX 1500® as a disintegrant. Finally, the CLSM images revealed that segregation between powder and pellets occurred, primarily because of the different particle size of the components in MUPS.

6. Conclusions and Outlook

MUPS (Multiple Unit Pellet Systems) are multiparticulate pellet formulations that, easily administered as tablets, disintegrate into their subunits directly after swallowing, so as to disperse into their subunits across the stomach and the small intestine. This behaviour accounts for a more constant bioavailability and contributes to the minimization of dose-dumping and local irritation risks. Although MUPS represent nowadays a formulation of first choice, they do not really represent a straightforward option. In fact, the compaction of coated pellets into MUPS is a complex process, in which the subunits undergo structural deformation or even rupture. This may profoundly modify the drug release profile of the subunits and/or circumvent the tablet disintegration because of enhanced cohesion between pellets. In other words, on the one hand pellet compacts need to have a certain crushing strength to withstand the mechanical shocks encountered in their production, packaging and dispensing; on the other hand, the tabletting process must be soft enough to enable the compacts to disintegrate promptly in their subunits after administration maintaining the drug release profiles of the subunits. Such an ideal compromise may be strived optimizing the proportions between three crucial factors: the pellet cores, the coating materials and the embedding excipients. Not many studies have focused so far on the simultaneous optimization of these three variables.

Cellulose, and in particular microcrystalline cellulose, is one of the major excipients in solid dosage formulations. It presents four polymorphic forms, out of them the form I and II have pharmaceutical relevance. The form I, which features a favourably plastic behaviour when compressed, is extremely widespread as a filler-binder for MUPS. Unfortunately, it does not possess prevalent disintegration properties, so that a disintegrant must be added if a prompt disintegration is strived. Kumar et al. developed a new Cellulose II pharmaceutical aid named UICEL-A/102 through alkali treatment of Avicel PH 102 and successive hydrolysis with ethanol and oven dry. So far, UICEL-A/102 has been studied just as potential multifunctional excipients (filler and disintegrant) in tablet formulations, whereas its employement as a multifunctional excipient in MUPS has not been investigated yet.

This study aimed to compare MCC 102 (Cellulose I) and UICEL-A/102 (Cellulose II) as pellet filler and embedding excipients in MUPS for controlled release. In the first part of the study, MCC 102 and UICEL-A/102 were separately mixed with Sodium Diclofenac, directly pelletized, coated with Kollicoat® SR 30 D to 20% w/w weigth gain and compacted into MUPS. In the second part of the study, a binary mixture of MCC 102 or UICEL-A/102 and Sodium Diclofenac was layered on neutral cores (Suglets® or Cellets®),

in order to produce inhomogeneous pellets by means of dry powder layering technology. These pellets were then coated and compacted into MUPS according to the same procedure employed for the previous pellet batches.
On the one hand, a multifactorial investigation of crucial parameters involved in the compaction of pellets into MUPS was strived; on the other hand, the suitability of UICEL-A/102 as filler in two different kind of pellets formulations for MUPS (homogeeous pellets from direct pelletization, inhomogeneous pellets from dry powder layering) was evaluated.

In the case of homogeneous pellets of either MCC 102 or UICEL-A/102, the MUPS formulations overcame compaction deformed rather than ruptured, as proved by comparison between the dissolution profiles and the SEM and CLSM images before and after compaction. Both MCC 102 and UICEL-A/102 MUPS resulted to be mechanically robust (crushing strength of 70-100 N), fast disintegrating in water (≤ 3 min) and maintained the same release profile and almost the same superficial and inner morphology of their uncompressed subunits. In literature, UICEL-A/102 has been validated to feature a higher elastic behaviour in comparison with MCC 102. Accordingly, we expected that UICEL-A/102 pellets and MUPS would undergo less soft compaction than their counterparts made of MCC 102. This unexpected finding suggests that also moderately elastic cores can be compacted without damage, provided they have been coated beforehand with a thick layer of a sufficiently flexible polymer.

In the case of inhomogeneous pellets, only UICEL-A/102 pellets proved to be favourable subunits; in fact, MUPS made of UICEL-A/102 pellet featured good robustness (crushing strength of 90-120 N) and almost rapid disintegration (disintegration time ≤ 12 min), whereas MUPS made of MCC 102 were too compact (200-300 N) and did not disintegrate before 50 min. Considering the diverse UICEL-A/102 pellets formulations, a common trend could be extrapolated: the choice of Cellets® rather than Suglets® as basic neutral cores in dry powder layering had a significant impact on the characteristics of MUPS. In fact, MUPS whose subunits had Cellets® cores retain the release profile of their uncompressed subunits more then their counterparts having Suglets® as subunits cores. This suggests that subunits with a cellulosic core contributed significantly to the softness of the compaction, this difference being associable with a plastic behaviour of Cellets® against the rather eleastic behaviour of Suglets® during compaction. It must be pointed out that this result is in contrast with some studies, in which sucrose cores loaded with Diclofenac and coated with Kollicoat® SR 30 D underwent compaction maintaining their own release profile (Dashevsky, 2004), (Dashevsky, 2005).

On the one hand, it can be claimed that dry powder layering produced UICEL-A/102 pellets with less prevalent disintegration properties, which were therefore more suitable for controlled release MUPS. On the other hand, the presence of a hard core in those pellets favored the partial rupture of their coating layer during compaction, resulting in a faster drug release after compaction, especially in the case of sugar spheres as non pareils.
Accordingly, the use of UICEL-A/102 as unique multifunctional excipients is rather suggested in pellets and MUPS for immediate release, while employing of UICEL_A/102 as layering excipient on neutral core is very promising in the development of MUPS for extended release.

In analogy with other parallel studies which are mentioned and discussed in §2.7.2, §2.7.3, §2.7.4 and §2.7.5, the perspective advantages of using smaller neutral cores, or embedding materials with a higher mean particle size distribution (Avicel® 200, Flow-lac®, Ludipress®) represent the further development of this study.

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01.05.1998 - 31.07.1998	Enviromental and managerial issues in the pharmaceutical industry Specialisation course, Università degli Studi, Milano, Italy
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01.05.1999 - 31.07.1999	Process research and scale-up in the pharmaceutical industry Specialisation course, "Università Statale degli Studi di Milano", Milano, Italy

Present position:

Since October 2004	Ph.D. in Pharmaceutical Technology under the supervision of Prof. Dr. H. Leuenberger and Dr. G. Betz at the University of Basel. Research field: MUPS as flexible carriers in solid dosage forms
Parallel duties	Assistantship in solid dosage forms practicals Tutorage of three master thesis regarding pellets and MUPS Tutorage of solid dosage forms seminars

Professional experience:

01.09.2002 - 31.05.2004	Validation Engineer at Pharmaplan AG (Fresenius Group), Basel, involved in the qualification of a new lyophilized production facility for Cilag AG, Schaffhausen
01.08.2000 - 31.07.2002	Validation Engineer at LSMW GmbH (Jenoptik Group), Stuttgart, involved in the validation and qualification of the following plants: Polpharma SA, Starogard Gdanskj (PL); Boehringer-Ingelheim, Wien (A); Haupt Pharma, Regensburg (D); Novartis, Huningue (F).
01.09.1999 - 31.07.2000	Quality Assurance at “Centro Tessile Cotoniero e Abbigliamento”, B. Arsizio (I)

Languages:

Italian	Mother tongue
English	Fluent (Certificate of Proficiency in English, 2000)
German	Fluent (Kleines Deutsches Sprachdiplom, 2005)
French	Fluent
Russian	Fluent

IT Knowledge:

Network and OS	DOS, Windows (2000/XP), UNIX, Linux, MAC OS

Conferences and Workshops:

20.04.2007 - 25.04.2007	Pharmaceutical Sciences World Congress, Amsterdam, Netherlands
12.03.2007 - 14.03.2007	Mixing, agglomeration and liquid separation technologies, VDI-GCV-FA-Workshops, Dresden, Germany
24.10.2006 - 05.12.2006	Factorial Design with STAVEX, AICOS Technology, Basel
27.03.2006 - 30.03.2006	APV Worldmeeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Geneva, Switzerland
12.06.2006 - 17.06.2006	Pharmaceutical Sciences Fair & Exhibition, Nice, France
18.10.2005 - 20.10.2005	Pelletizing techniques, TTC, Binzen, Germany
10.05.2005 - 12.05.2005	Granulation and tabletting, TTC, Binzen, Germany
08.03.2005 - 10.03.2005	Fluid bed drying, granulation and coating, TTC, Binzen, Germany
17.11.2004 - 19.11.2004	Practical Aspects of Aseptic Processing, PDA, University of Basel

Podium presentations:

"Development of new multiparticular formulations with UICEL (University of Iowa Cellulose II)"
Roche, 18 December 2006, Basel, Switzerland

"Preparation and compaction of modified release pellets using an innovative cellulose II excipient" VDI-GCV-FA-Sitzungen "Agglomerations und Schüttguttechnik" und „Mechanische Flüssigkeitsabtrennung", 12-14 March 2007, Dresden

Posters:

"Technological and Mechanical Properties of three Types of Microcrystalline Cellulose"
V. Balzano, N. D. Gentis, M. Puchkov, G. Betz, H. Leuenberger
APV Worldmeeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, March 2006, Geneva, Switzerland

"Soft compaction of MCC 102 and UICEL-A/102 pellets into MUPS"
V. Balzano, G. Betz, H. Leuenberger
Pharmaceutical Sciences World Congress, 20-21(Pre-Satellite), 22-25 (World congress) April 2007, Amsterdam, Netherlands

Companies visits:

15.05.2005	Pfizer, Freiburg in Breisgau, Germany
18.12.2006	Roche, Basel

Other activities and hobbies:

Italian teacher at "NSH Bildungszentrum", Basel

Listener in courses of German language, Deutsches Seminar, University of Basel

Listener in courses of French language, Romanisches Seminar, University of Basel

Listener in courses of Russian language, Slavistisches Seminar, University of Basel

Yoga, Pilates, Skiing, Music

Courses attended as a Ph.D. Student at the University of Basel were given by:

S. Althaus, G. Betz, P. Bret., E. Dangel-Pelloquin, J. Drewe, M. Egli, I. Endres, B. Ernst, T. Güntert, G. Imanidis, S. Krähenbühl, H. Leuenberger, S. Meyer, A. Prillard., A. Seelig, M. Shevrekuko, A. Vanoncini, H.P. Wessel.