Search for Technological Reasons to develop a Capsule or a Tablet Formulation

Inauguraldissertation

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

von

Johannes Caspar von Orelli
aus Basel, Zürich und Locarno

Basel, 2005

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät
auf Antrag von

Professor Dr. H. Leuenberger

und

PD Dr. P. van Hoogevest

Basel, den 21. September 2005

Professor Dr. H.-J. Wirz
Dekan

To Claudia

Acknowledgements

I wish to express my deepest gratitude to my supervisor Professor Dr. H. Leuenberger for giving me the opportunity to perform this thesis and for his trust and great support during the work.

Sincere thanks go to PD Dr. P. van Hoogevest who accepted assuming the co-reference of this work.

I deeply thank Novartis Pharma AG for providing me diclofenac sodium for my studies.

Many thanks go to my colleagues at the Institute of Pharamceutical Technology for creating such a great atmosphere. In this respect I am especially grateful to Dr. M. Lanz, Mr. H. Nalenz, Mr. M. Plitzko, Mr. D. Blaser, Dr. M. Puchkov, Dr. S. Reitbauer, Mr. D. Daneshvari, Dr. T. Kuny, Mr. M. Schneider, Mr. T. Meyer, Dr. A. Schiffmann and Mrs. S. Reutlinger. A very special thank goes to Mr. S. Winzap for his extraordinary friendly and helpful presence. I am also very grateful to Mrs. C. Erb for supporting me typing the manuscript.

My warmest thanks go to my family for their support, encouragement and love during my study. In this respect I am deeply grateful to my Fiancé Claudia Leber, my parents, François and Elsbeth von Orelli, my sister and her husband, Noemi and Stefan von Orelli, to Erika, Roberto and Nadja Leber.

Symbols and Abbreviations

[ ]	concentration
FDA	Food and Drug Administration
GIT	Gastro-intestinal tract
HPMC	Hydroxypropylmethylcellulose
IPT	Institute of Pharmaceutical Technology, University of Basel
LogD	distribution coefficient D = $[Unionised]_{(organic)}/\{[Unionised]_{(aqueous)} + [Ionised]_{(aqueous)}\}$
logP	partition coefficient P = [Octanole]/[water]
PAT	Process Analytical Technology
PVP	Polyvinylpyrrolidone
RSD (%)	Relative standard deviation (%)
SD	Standard deviation
s	Second(s)
v/v	Percent by volume
w/w	Percent by weight

1. Summary

The following work should be understood as an approval to the FDA's new concept of quality assurance in the 21st century, i.e. to understand the process and the formulation, to build in and not to test in quality.

There are a number of reasons from the economic and marketing point of view to prefer a capsule or a tablet formulation. The aim of this work, however, was to find specific technological reasons to develop a robust capsule or tablet formulation with special respect to physical properties of model drugs and excipients such as wettability, solubility as well as compressibility and compactibility.

Formulations nowadays are usually developed under high-time pressure on the basis of "trial and error" experiments. They are complex, variable systems consisting not only of an active substance but also of a number of excipients. An in-depth and science based knowledge, whether to formulate a drug as a robust capsule or tablet formulation, would help to shorten the developing process and as a consequence, time and money could be saved.

In early clinical trials for example when the dose is increased in order to find the optimal therapeutic effect with a minimum of side effects, the whole amount of drug should be released at the same time independently of the drug load. No decrease of the bioavailability has then to be expected from a technological point of view. In such a case, however, normally there is at first a capsule formulation because the developing time is in most cases not as complex as for a tablet formulation: a powder mixture can be filled directly into a capsule shell without a granulation and a compression process (Leuenberger et al., 2005).

In the case of the well soluble and well wettable model drug caffeine such an approach would have been successful. The standard capsule formulation consisting of caffeine, lactose and magnesiumstearate turned out to be entirely robust in the dissolution test independently of the drug load. The poorly soluble and poorly wettable model drug proquazone, however, showed a dramatically prolonged release in the dissolution test when it was found in high concentrations. It became clear that proquazone needs to be formulated as a granulate or a tablet to achieve a robust formulation regarding dissolution. With the poorly soluble but well wettable model drug diclofenac sodium neither the capsule nor the corresponding tablet formulation turned out to be robust.

It was therefore decided to introduce a novel excipient as all formulations mentioned above had all the same compositions. This excipient, UICEL, was developed at the University of Iowa. It is said to have excellent direct compressing properties, which could also be confirmed in this work. Furthermore it turned out to be a very good excipient in the capsule filling process leading to fast dissolution rates in combination with all model drugs because of its excellent wetting and disintegration properties. After a direct compression of all model drugs in combination with UICEL it also caused fast dissolution rates with the model drugs caffeine and proquazone. In combination with the model drug diclofenac sodium, however, no fast releases could be achieved.

When the disintegration of all formulation was investigated, in the case of the model drug proquazone no correlation between dissolution behaviour and the disintegration time has been observed. When

the different systems were evaluated from the point of view of sorption of water, which indicates the wettability behaviour of the different systems, a clear difference between the formulations could be observed having a correlation with the results found in the dissolution experiment. It is therefore strongly recommended for preformulation studies to include water sorption experiments, especially in the case of a high drug content.

As a good compressibility and compactibility of different system are important in the production of tablet formulations in contrast to capsule formulations where the powder or granulate can be filled directly into the capsule shell without any compression, it was decided to find a fast but science based screening approach to discriminate between systems with poor compression properties that could be candidates for a capsule filling approach and systems with good compression properties that could be compressed to tablets. Therefore the physical model of powder compression proposed by Leuenberger (1980), which connects the parameters compressibility and compactibility, was chosen. In contrast to earlier studies, just five different compression forces for each sample were applied and the crushing strength was determined with a common tablet tester. This approach turned out to be very useful giving a clear discrimination between the different systems.

It was found for a future continuation of this work that the wettability as a physical property for the decision whether to formulate a drug as a capsule or a tablet should be investigated in-depth and more specifically. Formulations with other excipients or other poorly wettable model drugs should be analysed at the same time than the sorption of water. The future compressibility or compactibility studies could be carried out with the Presster™ compaction simulator and with other model drugs having very poor compressibilities and compactibilities.

2. Introduction

In the course of the 19th century, the discovery of substances in powder form like the alkaloids suddenly opened new therapeutic possibilities. With the new substances, new dosage forms were created (like in 1834 the hard gelatine capsule invented by Mothes and in 1843 the tablet invented by Brockedown). The chance to process powders on a large scale with a prolonged stability compared to liquid or semi solid dosage forms opened all possibilities of industrial production.

Nowadays, solid dosage forms are still very popular because they have a high metering accuracy, the application of them is very easy and comfortable and their stability is very good.

On the one hand, a capsule has a number of advantages compared to a tablet: developing a capsule formulation is in most cases not as complex as for a tablet formulation. A powder mixture can be filled directly into a capsule shell without a granulation and a compression process. For this reason, a capsule formulation often is the first dosage form for early clinical studies in the industry and the filling of capsules by hand is a common practice in pharmacies for an individual medication. For blinding purposes an active ingredient can be easily encapsulated (Desai et al., 1996). Once the shell is soaked and dissolved in the stomach the active may in some cases be available in a loose, dispersed and, for this reason, in an early dissolvable and well absorbable state if the permeability through a biomembrane is given. Different colours of the capsule shells allow the patients to distinguish their medications (Mallory et al., 1977). A bad taste of a substance can be covered by a capsule shell (e.g. chloramphenicole, tetracycline). When a small sized capsule has to be administered the swallowing may in certain cases be more comfortable because after contact with the saliva it gets more slippery than a tablet.

On the other hand, if a big amount of a compound has to be administered, the size of the capsule can easily get too big compared to the same amount compressed to an oblong tablet. Some highly efflorescent and hygroscopic materials should not be filled into capsule shells because efflorescent materials may cause the capsules to soften, whereas hygroscopic powders may dry the capsule shell to excessive brittleness. A major disadvantage of the capsule, however, is the fact that producing a capsule formulation is more expensive compared to a tablet formulation because the capsule shell has to be bought additionally. Furthermore, a tablet rotary press is able to produce up to one million tablets per hour whereas the maximum production speed of a dosating disk capsule filler reaches about 200’000 capsules per hour. Thus, there are a number of reasons from the economic and marketing point of view to prefer a capsule or tablet formulation.

In this work, technological formulation properties are studied as a rational basis for the development of a capsule or tablet formulation. Special importance was attached to the physical properties of a drug such as its solubility and wettability. Furthermore, the compactional behaviour of the different formulations, granulates, drugs and excipients was investigated. The fact that a powder does not show good compression properties and it is not possible to make a granulation could be a technological reason to chose the capsule approach.

Nowadays, formulations are usually developed under high-time pressure on the basis of “trial and error” experiments (Leuenberger et al., 2005). They are complex, variable systems consisting not only of an active substance but also of a number of excipients, which contribute to a great extend that the active is at the right time at the right place in the patient with the right effect. The average cost to develop a new drug has grown to about 800 million US-Dollars. Of 500 to 10’000 screened compounds only about 250 enter pre-clinical testing where just one compound is approved. It takes an average time of 12 to 13 years of development from the discovery of the active substance to its commercialisation as a dosage form on the market.

The knowledge, whether to formulate a drug as capsule or tablet, would certainly help to shorten the developing process and as a consequence, time and money could be saved.

Nowadays, the FDA favours the attempt to base manufacturing processes on scientific based knowledge than on empirical standards. The FDA addresses the pharmaceutical industry by the recommendation to introduce the concept of the PAT-initiative (PAT: Process Analytical Technology) for manufacturing processes and quality assurance.

The aim of the PAT-Initiative is the voluntary development and implementation of innovative, pharmaceutical production processes and quality assurance concepts. A guideline published by the FDA (FDA, 2004) concerning the PAT-initiative presents a framework with two components: (1) A set of scientific principles and tools supporting innovation and (2) a strategy for regulatory implementation that will accommodate innovation. The basic idea is not to test quality into products but to build it in or to design it. The FDA emphasizes that the PAT-initiative is a recommendation to the pharmaceutical industry not a compulsory regulation.

The PAT-initiative was introduced because conventional manufacturing is generally accomplished by using batch processing with laboratory testing conducted on collected samples in order to evaluate quality. With this concept pharmaceutical products can be provided to the public, but nowadays, significant time and money saving opportunities exist for improving pharmaceutical development, process analysis, manufacturing and quality assurance through innovation. In other words: the actual drug discovery activity is a high tech business but the means or methods are still low tech. Many pharmaceutical processes are poorly understood, which causes a bad or unpredictable process.

Generally, the performance of a manufacturing process can be described with its Six Sigma Value. The champion is the chip industry with a Six Sigma Value, i.e. having an amount of defective samples ≤ 2ppb which is a prerequisite to guarantee the functioning of our computer hardware. Surprisingly, the pharmaceutical manufacturing performance is only about Two Sigma, which corresponds to 4.6% defectives creating high costs (Leuenberger et al., 2005).

The benefits claimed by the FDA for the industry introducing the PAT-concept are a better understanding of the process, an introduction of real time release, a reduction of cycle times, less batch failure, a better management of change controls and regulatory relief.

The impact of the academia is the possibility to perform basic research without time pressure. Possible reasons for various phenomena can be investigated in detail. At the Institute of Pharmaceutical Technology of Basel a lot of science-based work has been done or is still in process in order to build quality in pharmaceutical processes. The article “Pharmaceutical powder technology-

from art to science: the challange of the FDA's Process Analytical Technology Initiative" by Leuenberger et al., 2005, gives an overview for further reading.

3. Theoretical section

3.1. Solubility of solids

The term solubility (mol/l) is given by the concentration of a dissolved solid in a saturated solution at a certain temperature and atmospheric pressure. Solutions are homogeneous mixtures of different components. For the development of solid dosage forms, mixtures of solids in an aqueous media are of special importance, as the tablet or the capsule has to be dissolved in the GIT first. Preparations where a solid is solubilised in a liquid are molecular disperse systems where the particle size of the solid is < 1nm, i.e. which corresponds to a molecular dispersion.

The molecular lattice of a solid has to be loosened during its dissolution by an amount of energy, which exceeds the internal energy of the crystalline solid (heat entalpy). In this ideal case, the molecules of the lattice are found isolated from each other in the solvent. Mostly, however, this ideal behaviour of dissolving is not dominant. Thus, in real solutions, intramolecular and intermolecular interactions, which are given by the structural body of the molecules, the dipoles and charge location in the molecules, play the key role what the dissolving of the solid in the liquid is concerned. Some non-electrolytes for example, which are capable of building hydrogen bonds in an aqueous solvent, hardly dissolve in an apolar media. When a substance is dissolved there is a difference between lattice and solvation energy. Depending on the magnitude of both terms the dissolving process is exotherm (the solution is warmed up) or endotherm (the solution is cooled down).

From this it follows that the dissolving is depending on temperature. As shown in figure 3.1., a higher or a deeper temperature can lead to an enhanced or a degraded solubility.

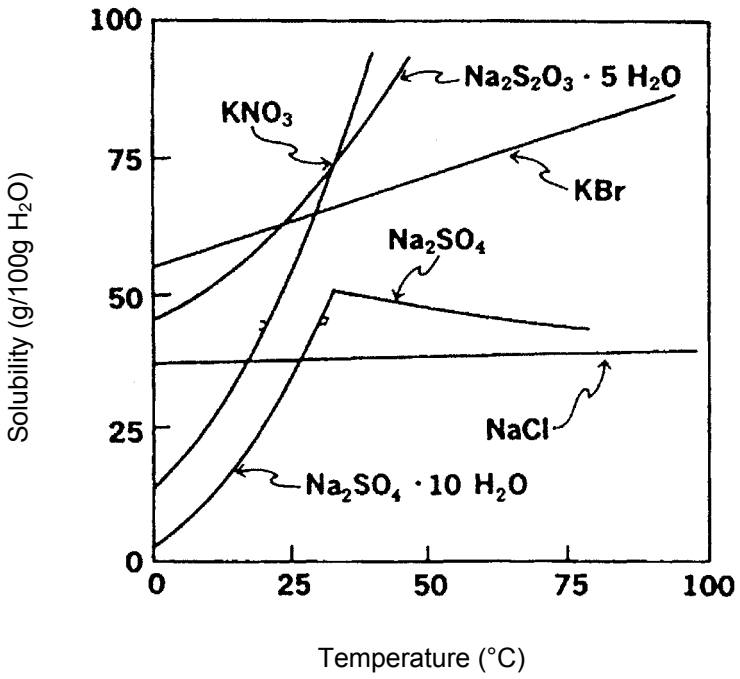


Figure 3.1.: The dependence of solubility on temperature.

Another factor, which has an impact on the solubility of a compound, is the pH of the dissolution media. As most pharmaceutics are either acidic or basic, the degree of ionisation and therefore the solubility depends on the pH of the medium.

There are different possibilities, however, to describe solubility. For practical handling the USP XXIV indicates the approximate solubilities of the different substances by descriptive terms as shown in table 3.1.

Table 3.1.: USP XXIV indicates the solubilities of the different substances in descriptive terms.

Descriptive Term	Parts of solvent required (v/v) for 1 part of solute (w/w)
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10'000
Practically insoluble or insoluble	Greater than or equal to 10'000

Another possibility to describe the solubility behaviour of different compounds is given by the Hansen parameter group contribution.

3.1.1. Hansen parameter group contribution

A substance is hold together by its cohesive energy. It is a direct measure of the attraction, which atoms and molecules have for one another. Cohesive energy is given by Van der Waals interactions, covalent bonds, hydrogen bonds, electrostatic interactions, induced and permanent dipole interactions. The cohesive energy determines many critical pysico-chemical properties of a drug or excipient such as melting point, mechanical force, solubility and so on (Hancock et al., 1997). The cohesive energy of a material can be quantified by the use of the solubility parameters. The theory of solubility parameters was developed by Hildbrand (Hildbrand et al., 1950) based on the following approach (see equation 1).

$$\Delta H = V_T \left\{ \left(\frac{\Delta E_{V1}}{V_{m1}} \right)^{0.5} - \left(\frac{\Delta E_{V2}}{V_{m2}} \right)^{0.5} \right\}^2 \cdot \phi_1 \cdot \phi_2 \qquad \text{Equation 1}$$

where ΔH is the heat of mixing, V_T the total volume, ΔE_V the energy of vaporisation, V_m the molar volume, ϕ the volume fraction, and 1 and 2 refer to the solvent and solutes components, respectively. The solubility parameter, δ, (also known as the Hildebrand solubility parameter or total solubility parameter) of each component is defined as the root of its cohesive energy density measured as the energy of vaporisation per unit volume (see equation 2).

$$\delta = \left(\frac{\Delta E_V}{V_m} \right)^{0.5} \qquad \text{Equation 2}$$

When the solubility parameters of two materials are similar, they will be mutually soluble. Hansen, 1967a,b, has subdivided the total solubility parameter into components, which express the interatomic/intermolecular forces (partial solubility parameters), i.e. a partial parameter for dispersion, δ_d, polar ,δ_p, and hydrogen bond interaction ,δ_h. (Barton, 2000) (see equation 3).

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \qquad \text{Equation 3}$$

The partial solubility parameters can be calculated on the basis of the molecular structure of the compound. Several group contribution methods have been developed for calculating solubility parameters (van Krevelen et al., 1976; Rowe et al., 1988). Barton (2000) gives an overview where the polar and non-polar contributions as well as the contributions of the hydrogen bonds for each atom or functional group to the total solubility parameter found by different authors are listed. By using such a summary the total solubility parameter can easily be calculated according to equation 3.

This approach can especially be useful in the pre-formulation process as it allows a first characterisation of the material, when there may not be sufficient available for experimental determinations (Hancock et al., 1997).

3.2. Wettability of solids

Wetting is the actual process when a liquid spreads on (wets) a solid substrate. The degree of wetting (wettability) can be derived from the experimental measurable contact angel *θ*, which is determined by the total surface free energy of the solid and the liquid (Luangtana-Anan et al, 1988 on the base of Buckton et al., 1985). A contact angle of 0° denotes a complete wetting, i.e. a complete spreading of the liquid over the solid's surface. The bigger the contact angle gets, the worse the wetting of the surface is (see figure 3.2.). A contact angle exceeding 90° denotes a poor wettability.

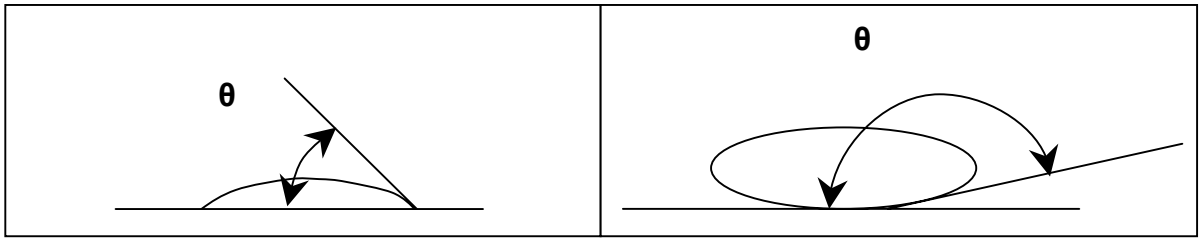


Figure 3.2.: The wettability of a solid with a liquid is given by the contact angle θ. On the left side a good wettability θ < 90° can be expected whereas the solid surface on the right hand side shows a poor wettability, θ > 90°.

Molecules inside a liquid/solid are in every direction affected by equal attraction forces, whereas the molecules at the surface lack a neighbour towards the air phase and therefore have larger attraction forces towards the liquid/solid than towards air. This leads to a situation where the interface has excess free energy. This excess free energy is characteristic for any liquid or solid. Generally, a system tends to get a minimum of potential energy by minimising its phase interphace. Consequently, for liquids a spontaneous contraction of the surface will take place. The surface tension of a liquid is a direct measure of the surface free energy. In an agravic environment a liquid would adopt the shape of a perfect sphere, which is the smallest surface for every given volume. In other words, the total surface free energy can be defined as reversible work, which has to be employed on condition that the temperature remains constant, to expand the surface of the liquid. In the case of a solid, there is no visible contraction but still the surface tension of the solid, called total surface free energy, is present at the surface of the solid. This implicates that the knowledge of the properties of the outmost layer of a solid is very important as due to the unbalance of forces at the surface/interface the structure and composition of the surface/interface of the solid is different than those of the bulk.

The total surface free energy of a solid can be expressed by the summation of polar and non-polar / dispersive interaction energies between the molecules. The polar contributions of the molecule, which are given by special functional groups within the molecule, are composed of dipole-dipole interactions, interactions caused by H –bonds and Lewis acid/base interactions. The non-polar contributions of the molecule are given by dispersion or London forces. It is possible for every molecule or atom to interact with other molecules by London forces, in contrast to the polar forces, which depend on specific functional groups.

The knowledge of the wettability and surface free energy of pharmaceutical solids is very important in the design of pharmaceutical formulations. A poor wettability of a compound limits the contact between the solid and a liquid, and thus reduces the available surface area. A poor wettability of a compound can be regarded as indication for a possible dissolution problem (von Orelli et al, 2004), by slowing it down dramatically. Powders are often formulated as granulates with binding agents. An important determinant for the optimum granulation is the wetting of the substrate by the binder, i.e. the spreading of the binder over the substrate, binder-substrate adhesion and binder-substrate cohesion (Krycer et al., 1983). Some properties such as the friability of a granulate for instance can be used as indicator for an improved granulation. Planisek et al., 2000, found a correlation between the friability and the spreading coefficient of different binders. Lower work of cohesion of the binders PVP and HPMC is considered to be responsible for a higher friability. Furthermore binder cohesions can be correlated with the tablet strength and tablet capping (Rowe, 1989).

3.2.1. Determination of the total surface free energy of solids

While the surface tension of liquids can directly be measured using for example the Du Noüy Ring method (Maijgren et al., 1982) or the Wilhelmy Plate method (Rame, 1997), the determination of the total surface free energy of a solid has to be done indirectly by measuring the contact angle with different liquids placed on the surface of the solid (Zilles, 2003 and Lechner, 2003).
A base for the calculation of the total surface free energy is the equation of Young (see equation 4).

$$\cos\theta = \frac{\sigma_S - \sigma_{LS}}{\sigma_L} \qquad \text{Equation 4}$$

where σ_L is the surface tension of the liquid, σ_S the total surface free energy of the solid and σ_{LS} the interface energy between liquid and solid. The Young equation can be combined with the equation describing the work of adhesion, the work that is necessary to overcome the attraction of unequal molecules (see equation 5).

$$W_a = \sigma_L + \sigma_S - \sigma_{LS} \qquad \text{Equation 5}$$

Equation 5 shows that the work of adhesion, W_a, is equal to the sum of the surface tension of the liquid, σ_L, and the total surface free energy of the solid, σ_S, shortened by the amount of the interface energy between liquid and solid, σ_{LS}.
The combination of equation 4 and 5 leads to equation 6.

$$W_a = \sigma_L(1+\cos\theta) \qquad \text{Equation 6}$$

Equation 6 is advantageous in so far that the difficult measurable total surface free energy of the solid, σ_S, and interface energy between liquid and solid, σ_{LS}, can be expressed by the more easily determinable contact angle θ and the direct measurable surface tension of the liquid, σ_L.

Fowkes (1964) managed to describe the work of adhesion, W_a, by the summation of the different components within the molecules, which interact. He made a difference between a non-polar (dispersive) and a polar force. The dispersive force is within all atoms and molecules and is generated by temporary and assymetrical charge distributions that appear around the atomic nucleus and the centre of the molecule. The polar force is only found in certain molecules and is a consequence of induced and permanent dipoles. According to Fowkes, the polar contribution is caused by different electronegativities of the atoms within the molecule. Owens, Wendt, Rabel and Kaelble postulated the existence of a polar contribution to the complete surface free energy (Owens et al., 1969). The total surface free energy of a solid or a liquid, σ, could then be formulated as the summation of dispersive and polar interactions (see equation 7).

$$\sigma = \sigma_{dispersive} + \sigma_{polar} \qquad \text{Equation 7}$$

When a solid is wetted only the interactions between the solid and the liquid along the interface are of importance. In other words, there is just an interaction along the phase interface between the polar and the dispersive components of the liquid and the solid, respectively. If one of the two phases, which are in contact, is completely non-polar, just dispersive interactions are possible. This matter can be used to determine polar and dispersive contributions of a solid.
According to Owens, Wendt, Rabel and Kaelble the contact angle is determined as an angle of progress in order to determine the total surface free energy of the solid. In conclusion the following relation is given (see equation 8).

$$\sigma_{LS} = \sigma_S + \sigma_L - 2\sqrt{\sigma_L^d \sigma_S^d} - 2\sqrt{\sigma_S^p \sigma_L^p} \qquad \text{Equation 8}$$

Where the work of adhesion is expressed as a geometric mean. The parameters σ_L^p and σ_L^d represent the polar and the dispersive contributions of the liquid to its total surface free energy, respectively, and σ_S^p and σ_S^p the polar and the dispersive contributions of the solid to its total surface free energy. The above equation 8 can be combined with the Young equation (equation 4) for the contact angle. The combination can be expressed in a linear function, $y=mx+q$, with $x = \sqrt{\frac{\sigma_L^p}{\sigma_L^d}}$, $y = \frac{1+\cos\theta}{2} \cdot \frac{\sigma_L}{\sqrt{\sigma_L^d}}$, $q = \sqrt{\sigma_S^d}$ and $m = \sqrt{\sigma_S^p}$. When the values of the total surface free energy of at least two liquids with its polar and dispersive contribution and the contact angle with the solid surface are known, the polar and dispersive contribution of the solid to its total surface free energy can be determined. Then, m corresponds to the square root of the amount of the polar contribution and q to the square root of the dispersive contribution of the solid to the total surface free energy (see figure 3.3.).

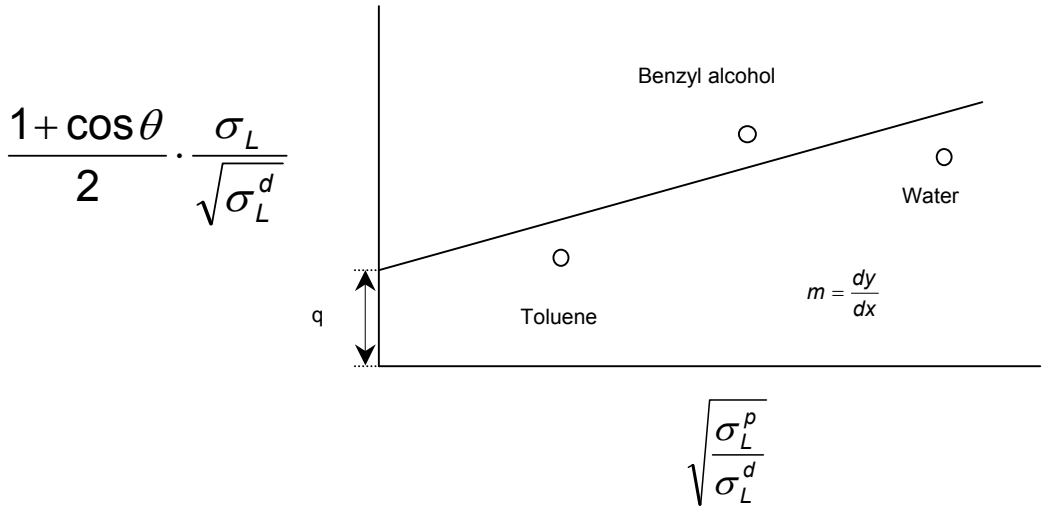


Figure 3.3.: If the total surface free energy of a liquid with its polar and dispersive contribution and the contact angle with the solid are known, the total surface free energy of the solid can be determined with to the slope *m* and the axis intercept *q*.

Owens and Wendt and also Kaelble used two test liquids. Rabel expanded the measurement to several test liquids and used the regression line (Rabel, 1971).
Another method to determine the surface free energy is the method of Wu (Wu, 1971). In this procedure the polar and dispersive contribution are also calculated. The work of adhesion, however, is expressed by the harmonic mean. In the procedure of van Oss, Good and Chaudry (van Oss et al., 1988) the polar contribution of the total surface free energy is divided further on into acceptor/donor or Lexis acid/Lewis base interactions, respectively.

3.2.2. Contact angle and the total surface free energy of solids

3.2.2.1. The capillary rise method

The wettability of a powder or a granulate can be best quantified with the capillary rise method (Lechner, 2003). By detecting the increase in weight as a function of time and by applying the modified Washburn equation the wettability of a solid can be determined.
The powder sample is placed initially in a glass tube with a porous glass base. The tube is fixed to an electronic balance, which is integrated in the test arrangement and brought into the test-liquid. The speed of capillary rise, i.e. the increase in weight in the sample can be measured in relation to time. The test arrangement is shown schematically in figure 3.4.

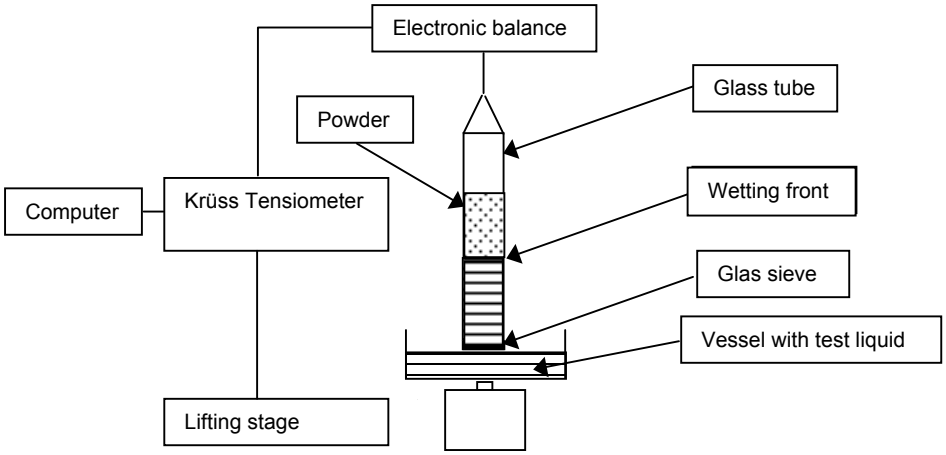


Figure 3.4.: Instrument for determining the contact angle and the total surface free energy, respectively on powders with the capillary rise method.

As already mentioned, the contact angle is determined according to the equation of Washburn (Washburn, 1921), which defines the flow of a liquid through a capillary (see equation 9)

$$\frac{l^2}{t} = \frac{\sigma_L \, r \cos\theta}{2\eta} \qquad \text{Equation 9}$$

where η denotes the viscosity of the test liquid and σ_L the surface tension of the liquid penetrating the bulk, r represents the radius of the capillary, θ is the contact angle between powder and liquid and l the height of the wetting front. The powder that has been packed in a tube can be described as a bundle of capillaries with a mean radius $\bar{r}$. The Washburn equation then becomes (see equation 10)

$$\frac{l^2}{t} = \frac{\sigma_L (\tau \bar{r}) \cos\theta}{2\eta} \qquad \text{Equation 10}$$

where τ represents a constant to approximate the tortuosity of the capillaries. The height of the wetting front can be replaced by the weight m due to the penetration of the liquid through a bundle of n capillaries. The Washburn equation then becomes (see equation 11).

$$\frac{m^2}{t} = \frac{\pi^2 (\tau \bar{r}) n^2 \rho^2 \sigma_L \cos\theta}{2\eta} \qquad \text{Equation 11}$$

Equation 11 can be expressed more simply (see equation 12),

$$\cos\theta = \frac{m^2}{t} \frac{\eta}{\rho^2 \sigma_L} c \qquad \text{Equation 12}$$

with the capillary constant c (see equation 13)

$$c = \frac{1}{2} \pi^2 (\tau \bar{r}) \, n^5 \qquad \text{Equation 13}$$

Where *m* is the mass of the absorbed liquid, ρ is the density of the liquid and *n* the number of capillaries. The capillary constant *c* is an empirical constant. It corresponds to the porosity and the tortuosity of the capillaries dependent of the particle size and the degree of packing.
The capillary constant *c* can be experimentally determined with a liquid that wets the sample completely, i.e. with a very small surface tension (e.g. hexane, xylol). The contact angle θ then becomes 0. The parameter *c* can then be estimated and substituted in the Washburn equation.
With the value of the capillary constant, contact angles of solids with other test liquids can be determined, when the total surface free energy (polar and dispersive contributions) the viscosity and density of the liquid are known.
The different values can for instance be plotted according to Owens, Wendt, Rabel and Kaelble in order to determine the total surface free energy of the solid.

3.2.2.2. Other methods

The sessile drop method

The sessile drop method is an optical procedure. A drop of a liquid with a known surface tension is placed on the solid's surface with a syringe. The diameter of the drop should be between 2-6mm, because in this range the contact angel is independent of the diameter. By using a goniometer, a tangent can be applied and the contact angle can be determined. Because of sedimentation effects, evaporation and etching the surface of the solid, this static measurement is dependent on time and a clear reproducibility is sometimes not possible. This static method, however, is useful to describe the time dependent changes of surfaces, e.g. when a lacquer is dried.
The negative effects described above can be overcome by measuring the contact angle dynamically using the sessile drop method. When the syringe remains in the droplet the volume of the liquid can be continually increased. The drop starts to move over the surface and an angle of progress can be measured automatically. As an opposite procedure the angle of receding is determined when the liquid is soaked up in the syringe. This angle is mostly very small (5-20°). It procides information about the roughness of the surface of the solid.

Wilhelmy method

The Wilhelmy method is named after Wilhelmy (1812-1864) and was originally used to determine the surface tension of liquids, but it can also be used for solids. The Wilhelmy method can be carried out like the sessile drop method as a static measurement. When the outline of a solid, L_w, as well as the surface tension of the liquid, $\sigma_{L,}$ is known, the force, $\vec{F}$, is measured with which the solid is drawn into the liquid as a consequence of the surface tension of the liquid. Having the value of the force, cos θ can be derived (see equation 14).

$$\cos\theta = \frac{\left|\vec{F}\right|}{L_w \cdot \sigma_L}$$ Equation 14

The measurement can also be carried out in a dynamic way. The solid is dipped into the liquid and the angle of progress or receding can be determined. The force that is measured consists of the vectorial summation of the buoyant force and the wetting force, $\vec{F}$.

3.3. In-vitro dissolution

A key property of a capsule or a tablet formulation is the release of the drug substance. The most widely used in-vitro test available to determine the release rate of drug products is the in-vitro dissolution test (Norry et al., 2000). Before a drug is absorbed from the gastrointestinal tract (GIT), it has to be released and dissolved first. 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 simplicity, their low costs and because they are easy to validate and standardise.

3.3.1. The dissolution process

Some basic principles of the dissolution process of a solid dosage form are given by the film theory (Nernst, 1904).
A solid is given in an agitated liquid and can dissolve. The dissolution media will pass the solid with a certain velocity. It is assumed, that the solid is surrounded by a layer of liquid with a certain thickness, *h*. This layer is stagnant, it does not move. At the solid's surface, the concentration of dissolved solid is equal to its saturation concentration, *S*. The concentration, *c*, is the concentration of the dissolved solid in the agitated dissolution media. If there is a steady state, Fick's first law can be employed as shown in equation 15.

$$J = -D\frac{\partial c}{\partial x}$$ Equation 15

where *J* is the diffusion current, defined as the amount of substance passing per time vertically through a unit surface area. *D* is the diffusion coefficient and $\partial c/\partial x$ the concentration gradient. It is considered constant, i.e. there is a linear gradient to form the surface of the solid to the dissolution media, where $\partial c/\partial x$ is the slope of the line, which is given by the term (*C-S)/h* (see figure 3.5.).

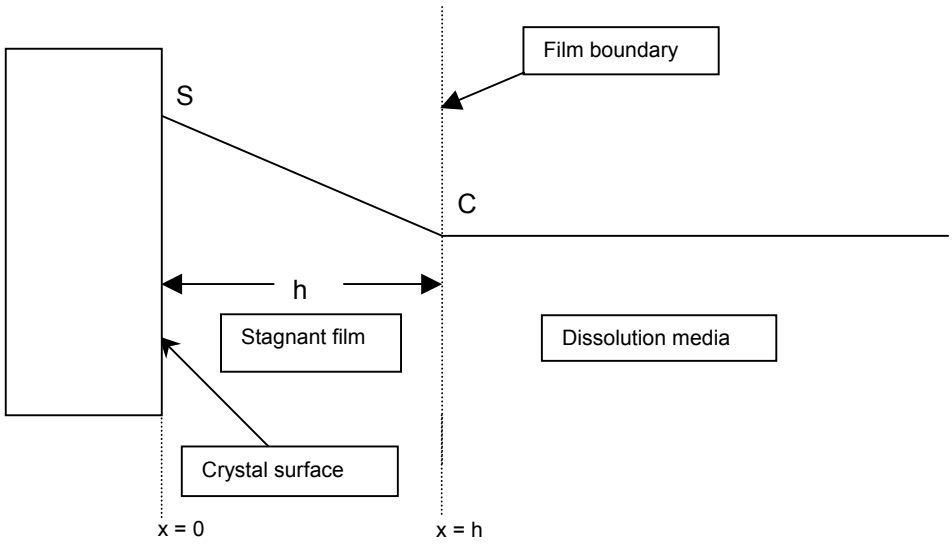


Figure 3.5.: Some basic principles of the dissolution are given by the application of Fick's first law.

In consideration of the dissolved mass, *m*, and the surface area, *O*, of the dissolving solid another presentation of equation 15 is given according to Noyes Whitney (Noyes et al., 1897) (see equation 16).

$$\frac{dm}{dt} = \frac{OD}{h}(S - c) \qquad \text{Equation 16}$$

Both sides of equation 16 can be divided through the volume, *V*, of the dissolution media (see equation 17).

$$\frac{dc}{dt} = \frac{OD}{hV}(S - c) \qquad \text{Equation 17}$$

For the diffusion constant, *D*, the relation of Einstein can be applied if the middle distance between the discussed molecules is negligibly short in contrast to the diameter of the molecules (see equation 18).

$$D = \frac{RT}{N_A 6\pi\eta r} = \frac{kT}{6\pi\eta r} \qquad \text{Equation 18}$$

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 media and *r* for the radius of the molecule. It becomes obvious that the molecular mass of a certain compound in a molecular-disperse solution does not have a big influence on the diffusion coefficient, *D*, because the radius of a spherical particle corresponds approximately with the third root of its molecular mass.

Beside the film theory, for the sake of completeness, the surface renewal theory or penetration theory (Higbie, 1935; Dankwerts, 1951) or the combinations of it with the film theory have to be mentioned

(Toor et al., 1958). In the surface renewal theory it is discussed that there is in fact no stagnant, laminar layer *h*. The surface is continually replaced by fresh liquid. Toor and Marchello, however have pointed out that film and penetration theory are not separate unrelated concepts.

Equation 16 and 17 show, which parameters pharmaceutical technology can influence, i.e. on the surface of a compound and on the saturation concentration, *S*, or on both in order to enhance the speed of the drug release, the solubility or wettability of a compound.

Practically the following steps can be done in order to take an influence on dissolution.

- Complexation (e.g. Cyclodextrines, PVP, HPMC (El-Zein et al., 1998; Nakamura et al., 2003; Badawi et al., 1980)),
- Salt formation of the active (O'Connor et al., 2001)
- Use of wetting agents (Tween® 20 (polysorbate), Corpol® (Dioctylnatriumsulfo-succinate) (Kassem et al., 1973)
- Crushing/Milling
- Use of disintegrants (Cellulose derivatives, starch, PVP (crosslinked)) (Lopez-Solis, et al., 2001)
- Use of hydrophilic fillers
- Granulation (covering of the poorly soluble/wettable substance with hydrophilic components) (von Orelli et al., 2004)
- Solid dispersions (e.g. griseofulvine). Active is dispersed in a molecular dispersed form in a hydrophilic matrix (e.g. PEG)
- …

However, it has to be pointed out that the mathematical explanations mentioned above describe an “ideal case” of the drug release. In reality variations of the “ideal” drug liberation curve occur, sometimes even at a large extend. First of all, a dosage form is a complex variable system consisting of the active(s) and a number of excipients, which could have completely different dissolution and/or disintergration characteristics. As a consequence, different time dependent dissolution processes could be overlapping causing for instance a slow or fast primary dissolution. The surface, *O*, is normally changing dramatically during the dissolution process for example when pores are built in the dosage form or a rapid disintegration takes place. Furthermore, a coating film or a capsule shell could cause a lag-time to a greater or lesser extent. Thus, there may be a lot of other reasons explaining the deviation of the “ideal case”. In fact, other functions explaining the dissolution process have to be introduced for practical handling.

3.3.2. Mathematical description of the dissolution process

Koch (1984) gives an overview of the different mathematical models existing for describing the dissolution process:

3.3.2.1. The “RRSW” or Weibull function

Different dissolution processes can be described, with a single equation, the "RRSW"- or “Weibull”-equation (see equation 19). (Thawatchai et al., 2000; Kachrimanis et al., 2000).

$$M = M_0\left[1 - e^{-\frac{(t-T)^b}{a}}\right] \qquad \text{Equation 19}$$

In this equation, *M* is the amount of drug dissolved as a function of time *t*. M_0 is total amount of drug being released. *T* accounts for the lag time measured as a result of the dissolution process. Parameter *a* denotes a scale parameter that describes the time dependence, while *b* describes the shape of the dissolution curve progression. For *b* = 1, the shape of the curve corresponds exactly to the shape of an exponential profile with the constant $k = 1/a$ (see equation 20).

$$M = M_0\left(1 - e^{-k\cdot(t-T)}\right) \qquad \text{Equation 20}$$

If *b* has a higher value than 1, the shape of the curve gets sigmoidal with a turning point, whereas the shape of the curve with *b* lower than 1 would show a steeper increase than the one with *b* = 1.

3.3.2.2. Cube root law

The cube root law refers to the mass of a given solid (Hixson et al., 1931) to describe its dissolution (see equation 21). The Cube root law (Hixson-Crowell equation) postulates that the decrease in mass is proportional to the third root of the mass of the solid during the dissolution process.

$$W_0^{1/3} - W^{1/3} = K \cdot t \qquad \text{Equation 21}$$

where W_0 is the known initial mass M_0 at the beginning of the dissolution and *W* the difference of the initial mass M_0 and the dissolved mass *M* at the time *t*. The equation can the be formulated as follows (see equation 22):

$$M = M_0 - (M_0^{1/3} - K \cdot t) \qquad \text{Equation 22}$$

The constant *K* includes different parameters such as density of the solid, the diffusion coefficient, particle number, geometry of the particles and so on.

The Cube Root law is valid for all solids with a defined surface area, i.e. regular geometric solid bodies and bulks of powder, which could be also multiparticular, however, with regular particle size distribution.
The solid can change its characteristic dimension during dissolution in a way that the Cube Root law in its original form cannot be applied anymore. This is the case when the dosage form consists of material with different dissolution characteristics. Another reason could be an irregular particle size distribution
Thus, a lot of attempts have been done to modify the equation and to accommodate it with the different dissolution scenarios. Niederball et al. (1963) modified the Hixson-Crowell equation by introducing a factor considering the number of particles (see equation 23)

$$W_0^{1/3} - W^{1/3} = K \cdot N^{1/3} \cdot t \qquad \text{Equation 23}$$

where *N* is the number of particles. It turned out that the equation, however, does not correlate very well with the measurements. The experimental data can be described in a better way with a square root equation (see equation 24).

$$W_0^{1/2} - W^{1/2} = K \cdot N^{1/2} \cdot t \qquad \text{Equation 24}$$

Higuchi et al. (1963a and 1963b), deviated another, modified equation for the dissolution of log normal variable powders. In its simplest form the equation can be written as follows (see equation 25):

$$W_0^{1/2} - W^{1/2} = K \cdot t^3 \qquad \text{Equation 25}$$

The equations 7-11 can be expressed according to Pedersen et al. (1976) in a more general way (see equation 26).

$$W = (W_0^{1/m} - K \cdot t)^m \qquad \text{Equation 26}$$

3.3.2.3. Examples for other equations

While the Weibull equation and the Cube root law are equations with a common validity for a majority of dissolution processes, the following equations can be applied in special cases. In the following sections a few examples are given.
The real dissolution time of a drug substance (intrinsic dissolution rate) undergoes a zero order reaction, if its surface is kept temporally constant (see chapter 3.3.1). It can be described with the following function (see equation 27) (Wood et al., 1965).

$$M = {}^0K \cdot t \qquad \text{Equation 27}$$

where ${}^{0}K$ is a dissolution constant of zero order. The drug release is independent of the absolute amount of drug M_0 (no term for M_0). The function also can be applied for systems with a constant surface, e.g. systems, which are osmotically controlled (OROS) and systems with a transport of the active through a barrier with a constant thickness, e.g. some polymeric coated dosage forms or special geometry (Hsieh et al., 1983). It has to be emphasised that the equation is just valid for strongly diluted solutions, thus for description of the drug releases under sink conditions.

For the diffusion-controlled dissolution of a non disintegrating formulation (Higuchi, 1961), the following famous equation can be formulated (see equation 28).

$$M = K \cdot \sqrt{t} \qquad \text{Equation 28}$$

Equation 28 indicates that the speed of the diffusion out of the non-disintegrating dosage form in the surrounding dissolution media is directly proportional to the square root of time. This equation originally was formulated for ointment bases containing drugs in suspensions and is valid up to about 60% of the total amount of drug released.

A lot of other mathematical models exist, describing the drug release under different conditions. The following list should give an overview of the literature for further reading:

- Modifications of the cube root equation (Desai et al., 1965; Touitou et al., 1982)
- Dissolution of a dispersed active from different matrix systems (Bamba et al., 1979; Higuchi, 1974; Higuchi, 1962; Hopfenberg, 1976)
- Modification of the real drug release by taking irregular disintegration, sink and non sink conditions into account (Pedersen et al., 1978)
- Biexponential dissolution (El-Yazigi, 1981)

Some examples for graphic representations of different dissolution profiles are given in the figures 3.6., 3.7. and 3.8. (according to Koch, 1984).

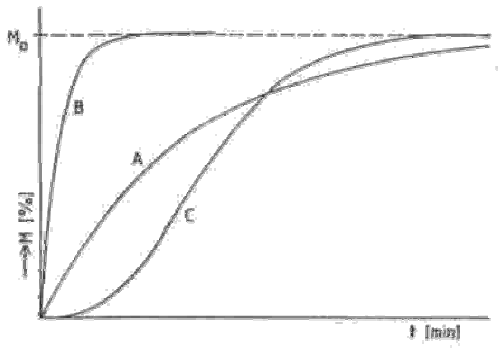


Figure 3.6.: Cumulative dissolution curve with a normal (A), biphasical (B) and sigmoidal progression (C).

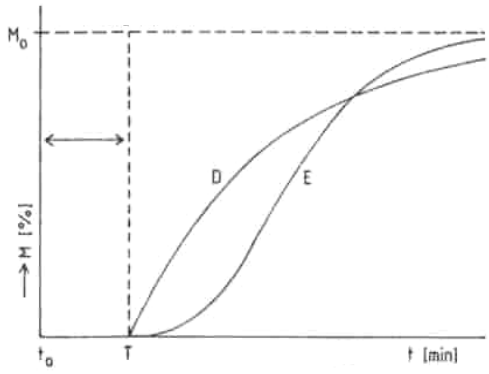


Figure 3.7.: (D) and (E): Examples for dissolution with a lag time.

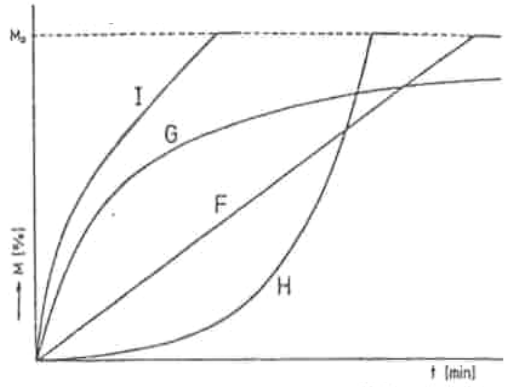


Figure 3.8.: Dissolution profiles with a kinetic of zero order (F), second order (G), with a release according to an exponential (H) and a square root function (I).

3.3.2.4. Dissolution Methodology

An official description of a dissolution apparatus with a rotating basket (apparatus I) and one with a paddle (apparatus II) can be found in USP XXIV as well as in the Ph. Eur. 2002 with the exact specifications.

Proposals to improve dissolution testing were repeatedly made according to the different scientific questions (e.g. Saeed et al., 2003, Tempio et al., 1980). The various possibilities of experimental settings for the determination of the dissolution rates are not discussed further on, but figure 3.9. gives a short overview over the different apparatus and experimental settings for dissolution testing.

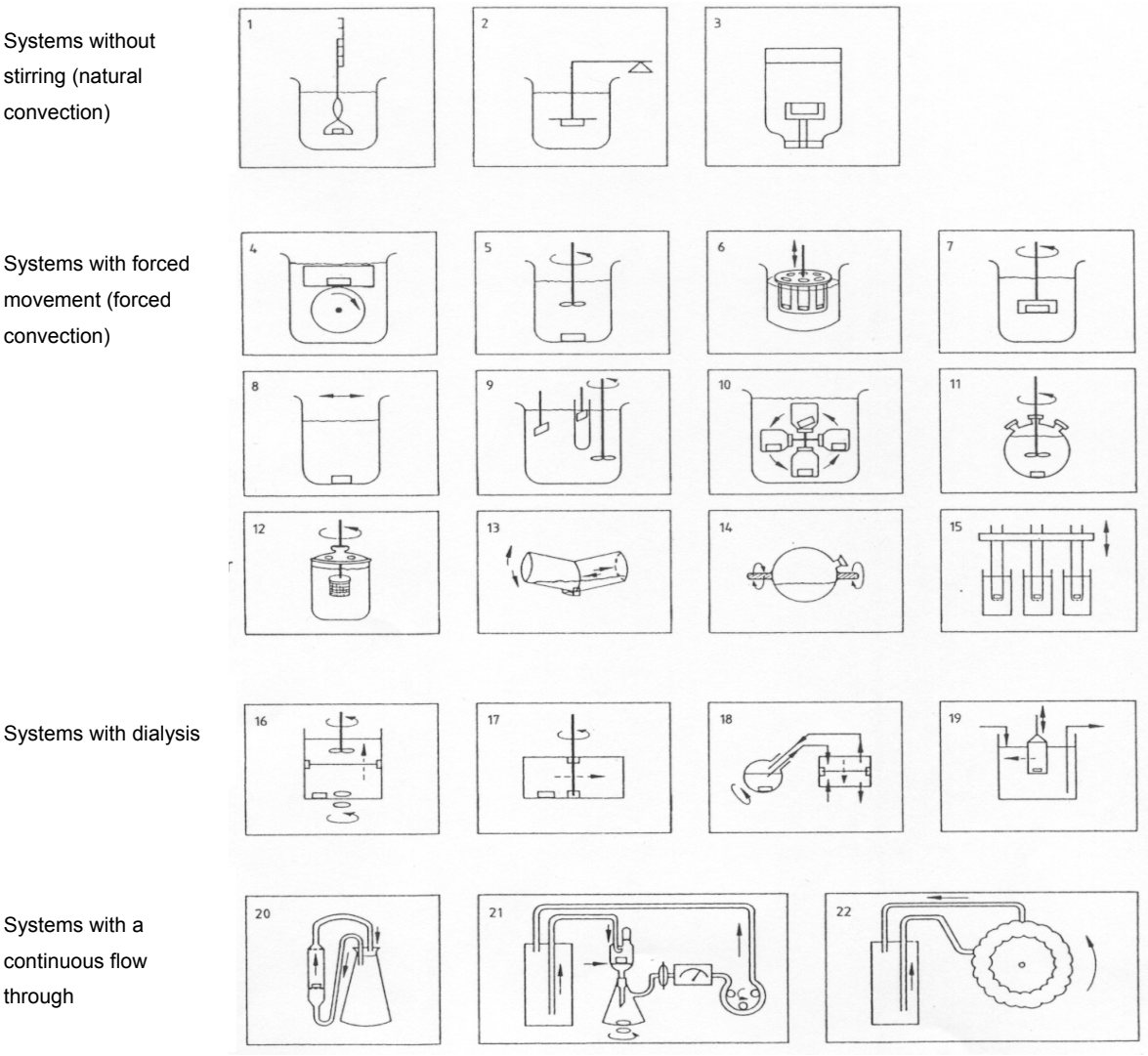


Figure 3.9.: Different system, methods and apparatus can be used for dissolution testing (according Ritschel et al., 2002).

3.3.2.5. Rotating basket method/apparatus I

The fact, that the sample can have a direct contact with the dissolution media without a holder or a mechanical stirring can be advantageous. The agitation of the liquid is just caused by the movement of the basket itself. On the other hand, especially when a rapid drug release occurs, the drug is not fast enough continuously distributed in the dissolution media.

The basket method is suitable especially for capsules. Hard gelatine capsules sometimes tend to swim at the surface because of the air, which is included in the capsule shell. Using the basket method, they are kept into the liquid.

3.3.2.6. Experimental setting

There are a number of experimental factors such as the volume of the dissolution media, its pH, the use of organic solvents, the usage of surface-active or wetting agents, the temperature and the agitation of the media, which can have a direct impact on the dissolution of a sample and which can influence the release dramatically.

The container with the dissolution medium in which the drug is dissolved should be adapted to the GIT with respect to its volume. Up to 1 l of solvent is acceptable (Koch, 1984). When a drug with a poor solubility is released, the volume has to be adapted in order to have sink conditions. Sink conditions can be defined as follows: the total concentration of the model drugs dissolved should not be significantly higher than 10% of their saturated concentration (Gibaldi et al., 1967). According to Koch (1984), a solution with a drug concentration up to 25% of its saturated concentration is still acceptable to conduct a dissolution experiment. It is implicated that poorly soluble drugs need large volumes of dissolution medium. Koch describes a case, where 20 l medium were used for dissolution, which is no longer physiological. Instead of using a large volume of dissolution medium at once, the drug release can be carried out by giving the media a constant supply of fresh liquid. In such a case the same amount of the old media is removed at the same time. The problem hereby is, especially when the drug is continuously removed in a fast way, that the GIT is not a percolator that extracts the drug continuously (Koch, 1982).

With every approach-and this is the challenge-compromises have to be made, i.e. maintaining conditions as physiological as possible and being able to perform the experiment under sink conditions at the same time.

The pH of the media is another important parameter. The majority of the drugs are compounds with acidic or alkaline character. Their pK_a-value and the pH of the dissolution media determine their ionisation and thereby their apparent solubility. It goes without saying that the pH of the dissolution media has a significant influence on the drug release. Table 3.2. gives an overview of the different pH values in the body.

Table 3.2.: Different pH-values in different sections of the GIT.

Body fluid	pH
Saliva	5.7-7.3
Gastric juice	0.9-3.2
Duodenum	6.5-7.6
Jejunum	6.3-7.3
Ileum	7.6
Colon	7.9 –8.0

By the choice of the right pH-value of the media, the dissolution can be enhanced. On the other hand the pH of the dissolution media should correspond to the place of application. The range of the different pH of the different dissolution media suggested by the USP XXIV goes from 1.0 up to 8.0.

To improve the dissolution, co-solvents such as alcohol are used. It is also proposed to combine an organic phase, which is not mixable with the aqueous phase (Gibaldi, 1967). The dissolved drug is extracted by the organic phase similar to the conditions in the GIT, where the drug permeates the intestinal wall.

The juice of the stomach and the intestine contains a lot of surface active substances such as enzymes (pepsine, pancreatine), ions, bile salts and so on. Synthetic and natural wetting agents such as polysorbate 20 or 80, sodiumlaurylsulfate, dicoltylesodiumsulfosuccinate, lysolecithine, bile acids and so on can be used in order to simulate a physiological environment.

The temperature of dissolution media should be equal to 37°C corresponding to the temperature in the human body.

Another task is the choice of the speed of agitation of the dissolution medium. On the one hand the same concentration of drug should be at each time in every part of the container on the other hand the agitation should correspond to the peristaltic movement. Levy (1963) reported that the peristaltic movement is very smooth and slow and corresponds approximately to a stirring speed of 50 rpm in a vessel with a volume of 500 ml.

3.4. Estimation of the drug permeation

Log P and Log D

The absorption process of drugs administered orally as solids consist of two consecutive processes: the process of dissolution, followed by the transport of the material across gastrointestinal membranes into the systemic circulation. The rate of permeation of a drug is dependent on size, relative aqueous and lipid solubility and the ionic charge of the molecules. The lipid solubility of a drug is an important factor in the assessment of its adsorption potential, because the gastrointestinal membranes are lipoidal in character. Lipids occurring in living are difficult to obtain. An indication of the relative lipid solubility, however, can by obtained by determining how a drug substance distributes itself between water and an immiscible organic solvent. The ratio of the drug substance between the two components is known as distribution or partition coefficient. The partition coefficient, log P, is a constant. It is defined as the ratio of concentration of a compound in an aqueous phase to the concentration in the immiscible solvent, which is mostly octanol. Other organic solvents are ether, amyl acetate, isopropyl myrstat and so on. Substances with a log P between 1 and 5 are expected to be likely to permeate the biomembrane. The distribution coefficient, log D, is the log distribution coefficient at a particular pH. This value, of course, is not constant and will vary according to the protogenic nature of the molecule. Log D at a pH of 7.4 is often quoted to give an indication of the lipophilicity of a drug at the pH of blood plasma. (LogP partition coefficient P = [Octanole]/[water], where [ ] = concentration ; LogD, distribution coefficient D = $[\text{Unionised}]_{(\text{organic})}$/ {$[\text{Unionised}]_{(\text{aqueous})}$ + $[\text{Ionised}]_{(\text{aqueous})}$}).

The usefulness of partition coefficients to assess the absorption of potential drugs is exemplified by the data of Schlanker (1959) where a correlation between the absorption of barbituric acids in a rat

colon and the partition coefficient is shown. However, the correlation with the partition coefficient is not universal. The absorption process in the body is too complex and can not be imitated just by means of an organic solvent. Nevertheless, the partition coefficient can be useful.

Lipinski rules of five

The Lipinski rules of five (Lipinski et al., 2001) predict that a poor absorption or permeation is more likely when there are more than five fused rings, more than 5 H-bond acceptors, more than 5 H –bond donors, the molecular weight is greater than 500 and the calculated Log P is greater than 5. Substance classes that are substrates for biological transports are exceptions of the rule.
The Lipinski rules of five are a first step to estimate a drug's behaviour in terms of permeability considering its chemical structure. Compounds have to be examined, however, from a chemical point of view, which exceeds the Lipinski rules of five (Bonnie, 2002).

3.5. Biopharmaceutical Classification System (BCS)

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. On the one hand, however, in vitro-dissolution may be relevant under certain conditions to the prediction of in vivo performance of a drug (Munday et al., 1995), on the other hand, there are a number of examples of unsuccessful correlation of dissolution characteristics to bioavailability (Meyer et al., 1998).
Such results can be explained on the basis of the Biopharmaceutical Classification System (BCS) as described further on in this chapter (see table 3.3.) (Löbenberg et al., 2000).

Table 3.3.: The Biopharmaceutical Classification system (BCS)

Biopharmaceutical Classification System (BCS)	
Class I	High Solubility –High Permeability
Class II	Low Solubility-High Permeability
Class III	High Solubility-Low Permeability
Class IV	Low Solubility-Low Permeability

The solubility for a classification in the BCS is defined as follows (FDA, 2000): A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of an aqueous media over a pH-range of 1-7.5.
A substance is considered highly permeable when the extent of absorption is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous dose.
According to the FDA, the permeability class can be determined across humans, across animal models (e.g. rat), across in-vitro permeation studies with human or animal excised tissue or by the use of cultured cell models (e.g. Caco-II-cells = adeno carcinoma cells). In pre clinical trials, however, the

Caco-II-cell approach is the method of choice. It is confirmed, that the cell lines show much similarity with the human intestine in terms of functionality and metabolism (Rubas et al., 1993). The Caco-cells grow together forming an epithelial monolayer. In this stage the cells are connected by tight junctions and consequently imitate the barrier of the GIT. In addition, the model possesses efflux pumps, all known carrier systems of the GIT and some of the phase-I-and phase–II-enzymes. A disadvantage, however, is the fact that the model cannot be perfused, there is no mucous membrane and no hormones are secreted, factors, which in-vivo all have a direct impact on the permeation of a drug. Furthermore Caco-II-cells are colon not small intestine cells imitating the absorption in the small intestine.
In the following sections the different BCS-classes (I-IV) are discussed (Amidon et al., 1995; Loftsson et al., 2004)

Class I

Class-I-substances usually show a good bioavailability if there is no important first pass effect. The FDA opens up the possibility for Class-I-substances that no bioavailability and bioequivalence-testing is needed when the following conditions are fulfilled:

- The substance must have an uncritical therapeutic range and the excipients used in the dosage form have to be unproblematic from a biopharmaceutical point of view.
- The drug must have a proven stability under physiological conditions.
- The finished product is investigated concerning its bioavailability in the clinical phase 1, 2 and 3.
- The in-vitro release is ≥ 85% within 15 min
- The profile of the solubility of the test formulation is comparable with the original.

Generally can be said that drugs belonging to Class I are frequently lipophilic with a molecular weight of less than about 500 Daltons and an aqueous solubility about or greater than 1 mg/ml.
Some examples for substances of class-I are: acetaminophene (paracetamol), piroxicam, propanolol, theophylline, salbutamole, digoxine, doxycycline, Lecodopa and so on.

Class II

If a substance has a high permeability and a low solubility, i.e a Class-II-compound, it can be expected that its solubility and dissolution, respectively, are the rate-limiting steps for its absorption in the body. The majority of the drugs are compounds with acidic or alkaline character. Their pK_a-value and the pH of the dissolution medium determine their ionisation and thereby their apparent solubility. The dissolution profile of a class-II-compound as a function over a certain pH range can play an important role what its bioavailability is concerned.
When the quality of a product is changed, a remarkable influence of its bioavailability can be expected. The challenge of the formulator is to “move” such a drug from class II to class I without changing the intrinsic ability of the drug molecules to permeate biomembranes.

Substances belonging to class II are mostly lipophilic and water insoluble drugs. Their saturated concentration is usually about 0.1 mg/l or smaller. Some examples for substances of class II include carbamazepine, cinnarizine, glibenclamide, ibuprofene, nifedipine and so on.

Class III

It can be assumed that the absorbtion of drugs with high solubility and low permeability is not given by physical properties of the substance or the dosage form. The rate-limiting step of the absorption of the drug is the permeability. The bioavailability of the substance is controlled by biological factors such as metabolism, motility of the intestine and permeability of the membrane. The inclusion of adsorption enhancing excipients in the formulation can enhance their bioavailability. Some examples for drugs in class III are acyclovir, atenolol, ranitidine, captopril and so on.

Class IV

Class IV substances consist of water insoluble drugs, which when dissolved do not really penetrate biomembranes. The prediction of the behaviour of such a substances is a difficult task. Those substances need extensive investigations in order to find out which process, the dissolution or the permeation or both, have an impact on the bioavailability. It goes without saying that these drugs can be very difficult to formulate. Some examples for this group of substances are cyclosporin A, furosemide, ritonavir and so on.

3.6. Preparation of capsules

There are mainly two different types of capsules, hard and soft gelatine capsules. Soft gelatine capsules manufactured according to the method of Scherer are above all the dosage forms the method of choice for the processing of oily liquids and pastes. Soft gelatine capsules are produced by filling the liquid in a gap of two endless ribbons of gelatine, which are wedged between two die rolls. The capsules are simultaneously shaped, hermetically sealed and cut of from ribbon. For further reading it is referred to the literature.

A hard gelatine capsule, however, is composed of a hard gelatine capsule shell, which is manufactured separately and has to be bought additionally, and usually a blend of powder, of granulates or pellets, which is filled in by a capsule filling machine. Beside blends, also tablets or smaller capsules as well as a number of liquid substances such as lipophilic liquid vehicles (sesame oil, soybean oil, olive oil) or emulsifying agents (Cremophor RH 40,Tween 80) can be filled into hard gelatine capsule shells. In pharmacies, the hand-filling of hard gelatine capsule shells is the method of choice for administration of a drug in powdery form. There are several types of capsule filling equipment, each with its own mode of operation. The widely used capsule filling equipment in industrial production make use of the dosator tube principle or are based on a tamping mechanism into a dosating disk. In the first, the dosator consists of a tube open at one end, inside of which is a

movable piston. The dosator is plunged into a bed of particulate solid contained in a hopper. Powder can then enter the open end of the dosator and is densified by a downward movement of the piston. A plug is formed which is taken by the withdrawing dosator and is positioned above the body of the capsule shell. The piston moves downwards, the plug is ejected into the capsule body and the upper part of the shell is then fitted. The powder has to be not too free flowing as no plug can be formed, on the other hand a too cohesive powder would prevent to maintain an uniform depth of the powder bed.
The other type of filling equipment is the dosating disk machine, which in some ways resembles most the tablet press. The dosating disk has a number of holes bored through it, which are all closed by a stop plate with the exception of the last hole. Powder flows into the first hole and is compressed with a tamping finger. The hole is then moved in position two where further powder flows in and is tamped again. This is repeated until the last hole is reached. After excess powder is wiped off at the transfer station, the plug is positioned over the capsule body and ejected by a piston. The capsule body is then closed by the upper part of the capsule shell. The overall arrangement can be compared to a die of a tablet press, where the material is compressed several times. The forces in the capsule filling equipment, however, do not exceed tens of Newtons, whereas the forces in a tablet press easily reach kilo-Newtons (see figure 3.10.).

Dosating disk equipement

Cross sectional view (schematically) Top view

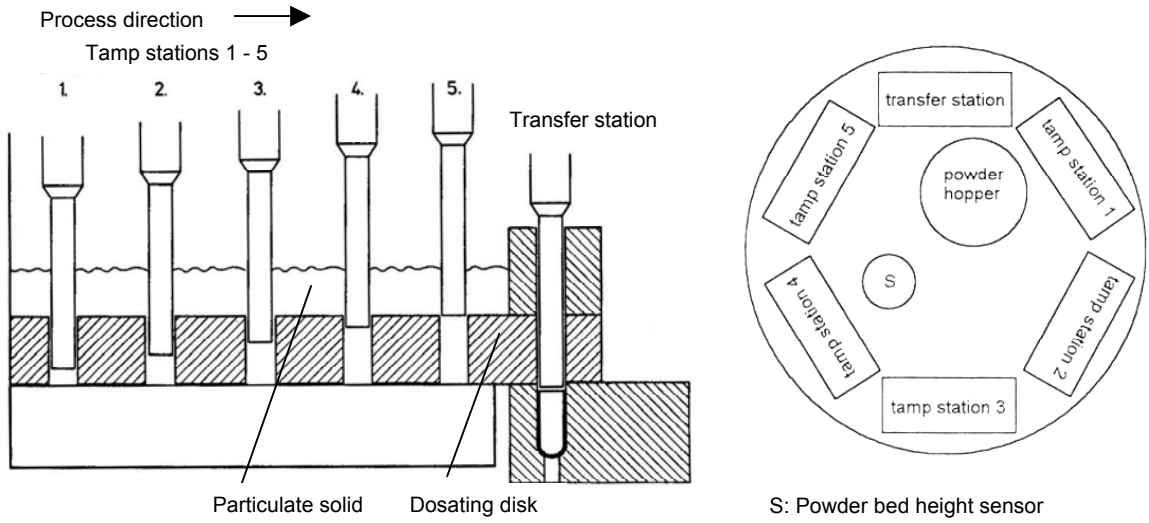


Figure 3.10.: Basic principle of a dosating disk capsule machine containing five tamp stations.

3.7. Granulation

Granulation is any process of size enlargement, whereby small particles are gathered together into larger permanent aggregates in a size range between 100-2000 µm. They have an irregular geometrical shape, which is in most cases approximately spherical, cylindrical or bacillary. Granulates often possess a rough and uneven surface and show a more or less high porosity.
The reason why a granulation process is often the method of choice in a pharmaceutical manufacturing process is, that powder systems due to their physical properties are often not suitable for direct processing. Applying a granulation process, the actual state of a given powder mixture can be fixed comparable to a freezing process what leads to several advantages: The consistent particle size distribution of a granulate minimises the tendency of unmixing. After a granulation process, a powder mixture usually shows a better flowability, what leads to a more accurate dosing, e.g. when the formulation is filled into a capsule shell or into the die. This matter can be explained by the smaller surface of the granulate, which offers less contact area for interparticular adhesion forces than the total surface of the same formulation in powder form would do.
In the compression process the rough and serrated surface of the granulate additionally contributes to an increased tablet strength by an interlocking of the granulate material creating more surface area for mutual adhesion.
The drug liberation can be different from a tablet made of a granulate as opposed to a tablet made of a powder due to another porosity, wettability and disintegration.
Another advantage of a granulation, which is important for the employees and the environment especially when highly potent substances are processed, is the fact that the fraction of fines is reduced (Monney, 2000).
As all granulates in this work were made in a wet granulation process with a high shear mixer, the following chapter especially deals with the wet granulation process.

3.7.1. Wet granulation

Wet granulation is a process in which a liquid is added to a powder in a vessel with any type of agitation that will produce agglomeration or granules. It is the oldest and most conventional method of making granulates. Although wet granulation is an expensive and laborious procedure, it persists because of its versatility, i. e. that almost every powder can be processed. In addition, the physical properties of a drug substance can often be improved in this unit operation to such an extend that better tablet properties are achieved, even if most of the dosage form consists of the drug.
All components involved in the wet granulation process form a three phase system made of the disperse solid (powder or powder blend), the granulation liquid and the air.
The addition of the granulation liquid to a mass of powder can be described in a series of four stages. When the powder particles are wetted during the initial state, liquid films will be formed on their surfaces. Discrete liquid bridges are then built at points of contact. The surface tension and the capillary force provide the cohesive force called pendular state at this stage. The air is still a coherent

phase and the powder bed still has low mechanical strength. As the liquid content increases it starts to coalesce. The strength of the blend increases at a modest extent. In this so-called funicular state the air does not build a coherent phase anymore. With a further increase of the water the whole amount of the interparticlar voids are filled. Inside the agglomerates a negative capillary pressure is generated, which holds all particles together as well as interfacial forces at the granule's surface. At this state, the capillary state, the granulate has its maximum strength. In a wet granulation process this is the state to be achieved. The addition of further liquid leads to the last state, the droplet state, where the solid particles are completely surrounded by liquid. A phase reversal has taken place, and the solid material is dispersed in the liquid. At this stage, the system consists of two phases. (see figure 3.11.).

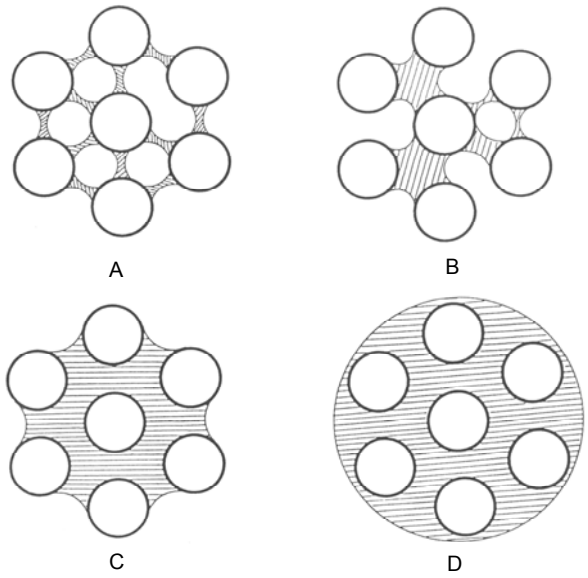


Figure 3.11.: Stages in the development of moist granulates when the liquid is increased: pendular (A), funicular (B), capillary (C), and droplet state (D).

When the granulation process is finished the liquid is removed by drying. After that, the granule is still kept together by different binding mechanisms. There is a general overview given the work of Rumpf (1958) which differs between five different binding mechanisms. Based on this classification, Pietsch (1972) distinguishes between bonds with and without material bridges (see figure 3.12.).

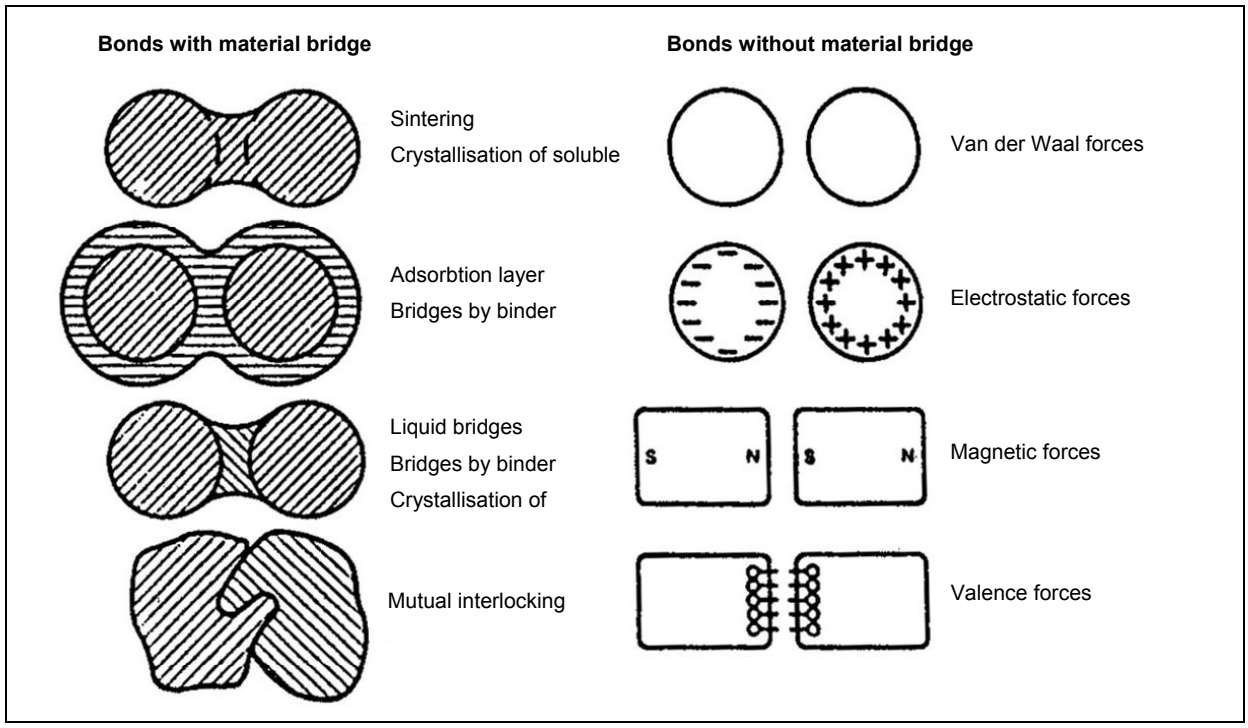


Figure 3.12.: Schematic representation of the binding mechanisms interacting in an agglomerate (Pietsch, 1972).

The coherence of a granulate manufactured in a wet granulation process, however, is mainly given by material bridges after the drying process (Stricker, 1989). Those material bridges are on the one hand mediated through excipients such as binders, which at first are mostly dissolved in the granulation liquid, then spread over the particles during granulation and finally stick all particles together after their re-crystallization in the drying process. On the other hand, the granulation liquid can etch parts of soluble particles during the granulation process and after drying the solid bridges between particles are directly built without any binder.

The strength and the quality of the forces, which hold the agglomerates together is also depending on the drying rate and the manufacturing process itself. High drying temperatures generally give hard granules. When a granulate is manufactured in a fluidised bed process it is usually softer and more porous than the adequate mixture processed in a high shear mixer, which is additionally densified by the movement of the agitator. The more granulation liquid is added the denser, the harder and the less porous the agglomerates get, i.e. it matters whether the granulation process is stopped at the beginning or at the end of the capillary state. All those circumstances, of course, can be used to control future tablet properties.

3.8. Preparation of Tablets

3.8.1. The compression process

Basic statements about the compression process are in general valid for powders, powder-mixtures and granulates, too. A powder in a die can in a way be considered as a solid dispersion in a gaseous media. The particles, however, in contrast to an aerosole are not isolated, but are kept in contact in the bulk material.
The compaction of tablets is a 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 compressed core with a definite shape.
According to Train (1956) the compression process can be described in four different stages:

Stage I

Before the compression process takes place, the particulate solid is filled into the die. Its volume corresponds to a volume between bulk and tapped density. The volume, which the powder adopts, is defined by different properties of the material such as particle size distribution, particle shape, surface properties and flowability, furthermore by technical reasons like the movement of the hopper or centrifugal forces in the production process. The punch touches the material and the particles start to overcome the friction force and to slide past each other to energetically convenient positions. The process is limited by reaching the densest packing because the particles become immobile in relation to one another. When this densest packing is achieved the bulk density corresponds approximately to the tapped density.

Stage II

With an increasing pressure and due to the immobility of the particles, temporary columns, struts and vaults are formed which surround protected voids within the bulk. When the system is highly cohesive, this reduction of interparticular separation may yield a compact of adequate strength for transfer into a capsule shell without any major particle deformation. However, the inherent cohesive properties of most drugs and excipients are unlikely to be sufficient to form tablets with adequate strength for subsequent handling (Leuenberger et al., 1986).

Stage III

A higher pressure causes a destruction of the structure built in stage II. As a consequence a deformation of the particles occurs. At the beginning of stage III, the contact surface of the particles is small compared to the total surface. There are just point and line contacts between the rough surfaces of the particles, where the applied stress is transmitted. The material is caused to fail, which leads to

the formation of new surfaces. The result is a more homogenous stress distribution with new interparticular bonds.

The deformation is dependent on the properties of the substance and is especially determined by the crystal characteristics of the substance. Three different stages can be distinguished regarding a plastic 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 result. The transition between reversible an 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 (see figure 3.13.).

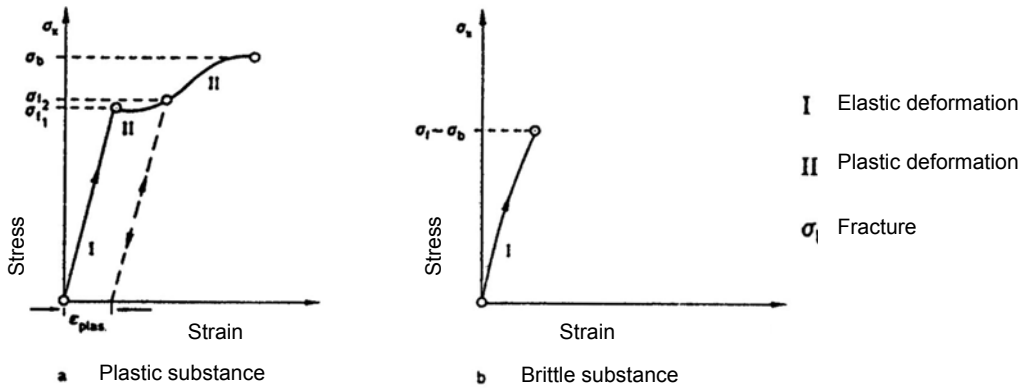


Figure 3.13.: Stress-strain diagram (Sucker et al., 1991).

Stage IV

When the formed structure is strong enough to support the imposed load, 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 such as capping and lamination and, in specific cases, in work softening (Leuenberger et al., 1986).

An elastic re-extension results, when the force is taken off the system after compression. The degree of re-extension is dependent on the character of the substances.

Finally, it has to be pointed out that the course of the above described compression process described above is strongly dependent on the substance. The extend of the four different stages and the dominant mechanisms are determined by the characteristics of the material. Furthermore, the phenomena are not sequential but overlapping.

3.8.2. Bonding in tablets

The strength of a compact after compression can be explained on the base of adhesive forces. These forces develop, when the particles get closer. At the same time the number of contacts between particles are increasing, which has an additional positive effect concerning the strengthening of adhesion. There are three types of interparticular adhesion that are of significance in tablet formation (Nyström et al., 1993):

- Intermolecular forces
- Mechanical interlocking
- Material bridges

The intermolecular forces are considered most important for the mechanical strength in the tablet. Intermolecular forces denote a collective term of bonding forces, such as van der Waal forces, electrostatic forces and hydrogen bonding (Israelachvili, 1985) that act between surfaces separated by some distance. The van der Waal forces again include three different forces between atoms and molecules, i.e. dipol-dipole interactions (Keesom interaction), dipole-induced dipole interaction (Debye interaction) and the dispersion forces (London interaction). The London interaction is an electrostatic force that affects all molecules including non-polar molecules. When a tablet mainly consists of a component, which is mostly hydrophobic, the London interaction accounts for 75%-100% to the overall cohesivity, i.e. the strength of the tablet (Wray, 1992). A tablet consisting of a high amount of a hydrophilic component, e.g. the excipient lactose (around 80% (w/w)), all types of van der Waal forces contribute to the tablet strength.

Mechanical interlocking is dependent on the shape and the surface of the particles and their deformation during the compression process. This mechanism is not founded on atomic interaction forces and therefore plays a minor role (Shotton et al., 1976).

Material bridges result from recrystallisation or melting and solidification. These phenomena can only appear in special cases, e.g. a partial melting or dissolution in adsorbed water.

Furthermore liquid bridges, which arise from capillary condensation of water or from residual moisture after wet granulation, have a significant impact on the compression behaviour of the solid. In general, moisture increases the compact strength (Nokhodchi, 2005).

3.8.3. Equipment for tabletting studies

The basic unit of any tablet press is a set of tooling consisting of two punches and a die, which is called station. The punches, upper and lower come together in the die that contains the tablet formulation to from the tablet. Principally, two different types of machines are used, the excentric and the rotary press. The excentric 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.

The excentric press is widely used in an early developing stage, because the tabletting machine and the tooling are cheap, it can be easily instrumented, little amounts of material is needed, the setting, the servicing, the cleaning and the changeover of the machine are easy. During the manufacturing process the tabletting mixture is dosed by a hopper into the die. The position of the lower punch defines the volume of the subsequent tablet mass. The compression force is given by the position of the upper punch, which defines its immersion depth into the die and the reagent force that is built up during the densification of the material. The ejection of the compressed tablet is done by the lower punch.

During the compression process on an excentric press, there are other pressure ratios at the upper and lower punch, respectively. The pressure at the upper punch is usually higher than the pressure at the lower punch. A part of the pressure is lost in the material and in the resulting radial friction force against the die wall during the compression. The relation between the pressure at the upper punch and the lower punch, respectively, can be described with the following equation (Unckel, 1945; Toor et al., 1956) (see equation 29).

$$\frac{P_l}{P_u} = e^{-\left(\frac{4\mu\upsilon h}{d}\right)} \qquad \text{Equation 29}$$

where P_l the pressure at the lower punch, P_u is the pressure at the upper punch, μ is the dynamic friction between the tabletting mass and the die, υ is the Poisson ratio (ratio of axial to radial stress), h the thickness of the tablet and d the diameter of the tablet. When the concentration of lubricant is adequate, the ratio P_U / P_l becomes approximately 1, because there is hardly any dynamic friction.

On a rotary press the filling of the die and the following compression process is done at the same time at different stations. The compression is carried out in the most simple case with two rolls touching the upper and lower punch and compressing the powder mixture. In contrast to the excentric press the upper and the lower punch exert pressure on the tabletting mixture from both sides at the same time. Tablets compressed on a rotary press generally show a more consistent hardness, when the upper and lower sides of the tablets are compared, where the upper side of tablets compressed on an excentric press is usually harder than their lower side (Ritschel et al., 2002). Figure 3.14. schematically illustrates the difference in the compression profiles of the upper and lower punch, respectively, and the punch movement with a fictitious rotary and excentric press.

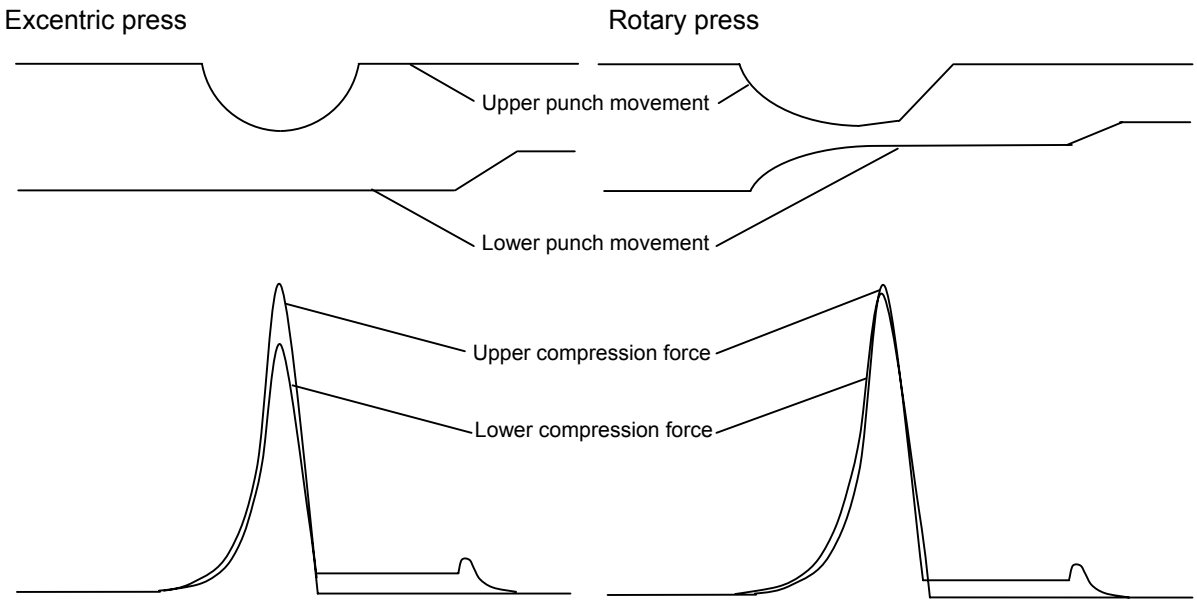


Figure 3.14.: The punch movements and the compression profiles of the upper and lower punch, respectively, of a rotary and an excentric press.

Another reason, why tablets compressed on a rotary press compared to tablets compressed on an excentric press may show different properties is the dwell time, which is usually shorter on a rotary press.

Rotary presses sometimes have two pairs of compression rolls. A pre-compression with the additional compression can then take place and the absolute dwell time can be prolonged. In other words, there are numerous different tablet presses with various possibilities to carry out the compression process. For further reading it is referred to the technical literature.

The problem, that a direct correlation between the results of an excentric press with a rotary press cannot always be drawn and the fact that there are a lot of different tablet presses with different settings and possibilities can be overcome by using a compaction simulator in an early developing stage. An advantage of such a simulator is its versatility, i. e. all types of presses can be simulated with small amounts of solid. 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. In table 3.4., a comparison between an excentric press, rotary press, a single punch and die set and a compaction simulator is listed according to Celik et al., 1989.

Table 3.4.:Comparison of the equipment for tabletting studies.

Feature	Excentric Press	Rotary Press	Punch and die set	Simulator
Mimic production conditions	No	Yes	Maybe	Yes
Mimic cycles of many presses	No	No	Maybe	Yes
Require small amount of material	Yes	No	Yes	Yes
Easy to instrument	Yes	No	Yes	Yes
Equipement inexpensive	Yes	No	Maybe	No
Easy to set up	Yes	No	Maybe	Maybe
Data base in literature	No	Yes	Some	No

3.9. Crushing strength

Strength is the resistance of a material against deformation such as fracture or deformation. It is dependent on the atomic structure of the starting material (Ilschner, 1982).
When a force is applied on a tablet, at a certain point the tablet fractures. This force is indicated as the crushing strength (F_B) of the material. The force can affect the compact axial or radial and it can be a matter of tensile or compression stress. There are a number of different apparatus on the market in order to determine the crushing strength of solid dosage forms with different functional principles (Bauer et al., 2002).

3.9.1. Determination of the radial crushing strength (tensile strength)

The detection of the radial crushing strength is a widely used method for characterisation. Thereby a force is diametrically applied on the compact.
The tensile strength of a cylindric tablet can be calculated according to equation 30 where the geometry of the tablet is also considered.

$$\sigma_T = \frac{2 \cdot F_B}{\pi \cdot D_T \cdot h_T} \qquad \text{Equation 30}$$

where σ_T denotes the radial crushing strength, F_B the crushing strength, D_T the diameter of the tablet and h_T the thickness of the tablet. Equation 30 can be used when the tablet breaks properly into two equal parts. Only under those conditions the stress ratio in the tablet was the way the application of the equation is valid (see figure 3.15.)

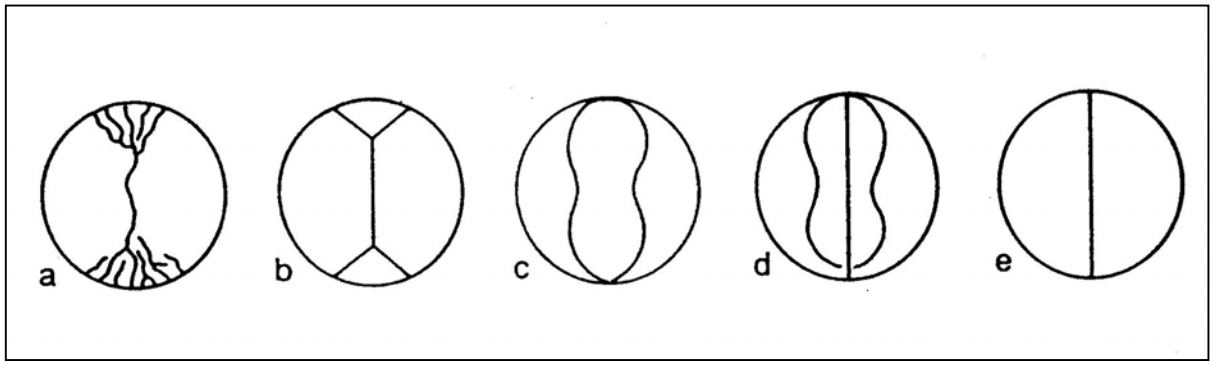


Figure 3.15.: Different types of fractures of a compact by applying a diametrical force. Equation 29 cannot be used for the types a)-d), whereas e) shows an ideal fracture.

3.10. Compressibility and compactility according to Leuenberger

The physical model of powder compression proposed by Leuenberger (1980) connects the parameters compressibility and compactibility.

When the model is derived, a cross sectional area of a compact is investigated. It is assumed that the cross sectional area of a cylindric compact consists of binding and non-binding points between particles. It is postulated that there is proportionality between the mechanical strength and the number of binding points. The relative decrease in non-binding points is proportional to the increase in pressure and the change in relative density. Some more detailed information can be found in Leuenberger, 1980; Leuenberger et al. (1981) and Leu et al. (1993).

The crushing strength/tensile strength can be considered as the strength of a compact. The following equation can then be formulated (see equation 31).

$$\sigma_T = \sigma_{T\max} \cdot \left(1 - e^{-\gamma \sigma_c \rho_r}\right) \qquad \text{Equation 31}$$

where σ_T denotes the radial crushing strength at a certain forming pressure σ_c, σ_{Tmax} the maximum crushing strength, γ the compression susceptibility parameter and ρ_r the relative density. The equation can be used for a single substance as well as for powder mixtures or granulate mixtures, respectively.

The equation also allows to use the deformation (Brinell) hardness instead of the crushing strength. In the following study, however, it was tried to establish a screening program for different powder systems. Therefore, easily accessible and measurable parameters such as the crushing strength were used.

According to Jetzer et al. (1983) the parameters σ_{Tmax} and γ allow a characterisation of the different raw materials: The maximum crushing strength, σ_{Tmax}, represents compactibility, i.e. the ability of the material to build a compact with a sufficient strength under pressure, that cannot be exceeded even if an infinite high forming pressure, σ_c, is applied. The compression susceptibility parameter γ is a constant specific for the compressibility of the material, i.e. the ability of the material to decrease its

volume under pressure. A substance with a high value of γ reaches the maximum crushing strength σ_{Tmax} very fast with an increasing forming pressure σ_c.

The compressibility of a raw material can be characterised according to the parameters σ_{Tmax} and γ as shown in table 3.5.

Table 3.5.: Values of σ_{Tmax} and γ classified according to the type of deformation (Jetzer et al., 1983).

Parameter	Type of deformation under stress	
	Plastic	Brittle
Compactibility σ_{Tmax} (MPa)	Small $0\text{-}10^2$	Large $10^2\text{-}10^3$
Compressibility γ $(MPa)^{-1}$	Large 10^{-2}	Small 10^{-3}

The compactibility of a raw material can be characterised according to the parameters σ_{Tmax} and γ as shown in table 3.6.

Table 3.6.: System for evaluation of the bonding properties of a substance with the parameters σ_{Tmax} and γ (Jetzer et al., 1983).

Compactibility parameter σ_{Tmax} (MPa)	Compression susceptibility γ $(MPa)^{-1}$	Bonding properties
Low ($1\text{-}10^2$)	Low (10^{-3})	Poor to very poor
High ($10^2\text{-}10^3$)	Low (10^{-3})	Moderate
Low ($1\text{-}10^2$)	High (10^{-2})	Good
High ($10^2\text{-}10^3$)	High (10^{-2})	Very good

4. Materials and Method

4.1. Materials

(Martindale, 1982; Hunnius, 1993; Fiedler, 2002)

Solubilty Log D, logP and pKa of the drug substances were calculated using Advanced Chemistry Development (ACD) Software Solaris V4.67 (© 1994-2003 ACD)

The following materials were used as received from the suppliers:

4.1.1. Drug substances

Caffeine anhydrous (Boehringer Ingleheim, Lotnr: 638, Ingelheim, Germany)
(see figure 4.1.)

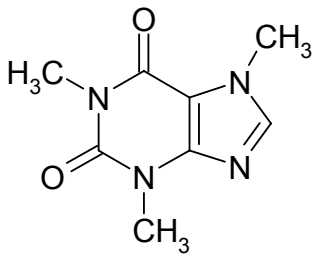


Figure 4.1.: Chemical formula of caffeine

Empirical formula:	$C_6H_{10}N_4O_2$
Appearance:	Silky white crystals, usually matted together, or a white crystalline powder, bitter taste
Molecular weight:	194.2 g/mol
Melting point:	234 - 236 °C
Solubility (pH 1-10):	soluble
pKa:	1.39
logP:	-0.08
logD (pH 1):	-0.62

Diclofenac sodium (Novartis AG, Lotnr.: 1030072000, Basel, Switzerland)
(See figure 4.2.)

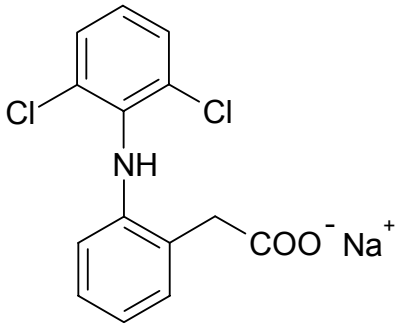


Figure 4.2.: Chemical formula of diclofenac sodium

Empirical formula:	$C_{14}H_{10}Cl_2NNaO_2$
Appearance:	white to slightly yellowish or light beige powder
Molecular weight:	318.1 g/mol
Melting point:	283 - 285°C
Solubility (pH 1-4):	sparingly soluble
pH 7:	slightly soluble
pH 8-10:	soluble
pKa:	4.18
logP:	3.284 ± 0.361
logD (pH 7):	0.48

Proquazone (Sandoz AG, Lotnr.: 87327, Basel, Switzerland)
(See figure 4.3.)

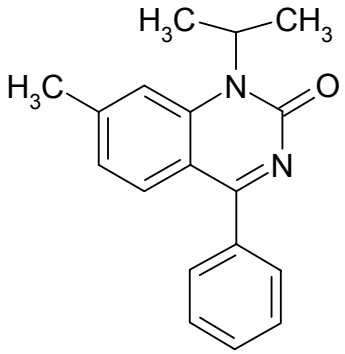


Figure 4.3.: Chemical formula of proquazone

Empirical formula:	$C_{18}H_{18}N_2O$
Appearance:	yellow, crystalline powder, inodorous or weak characteristic odour

Molecular weight:	280.4 g/mol
Melting point:	140.0 - 144.0°C
Solubility (pH 1-10):	sparingly soluble
logP:	3.129 ± 0.265
log D (pH 1):	3.02

4.1.2. Characterisation of the drug substances

Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio, respectively are shown in table 4.1.

Table 4.1.: Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio of the drug substances.

Drug Substances	Densities (n = 3)									
	True (g/cm^3)	RSD (%)	Poured $(g/ml)^2$	RSD (%)	ρ_p (rel)	Tapped $(g/ml)^2$	RSD (%)	ρ_t (rel)	Hausner ratio	RSD (%)
Caffeine	1.5335	0.04	0.277	1.6	0.181	0.506	1.4	0.330	1.83	1.0
Diclofenac sodium	1.5286	0.08	0.415	0.60	0.271	0.632	0.33	0.413	1.52	0.51
Proquazone	1.2556	0.03	0.267	2.8	0.212	0.494	2.6	0.393	1.85	0.20

All determinations were made according to the equipment specifications. Details in chapter 4.15. and 4.16.

Data for residual moisture content, the mean and median particle size is shown in table 4.2.

Table 4.2: Data for residual moisture content, mean particle size and median particle size of the drug substances

Drug Substances	Residual moisture content (n = 3)		Mean particle size (n = 5)		Median particle size (n = 5)	
	% (w/w)	RSD (%)	(µm)	RSD (%)	(µm)	RSD (%)
Caffeine	1.01	0.99	37.4	2.5	14.4	1.5
Diclofenac sodium	2.92	7.05	9.5	3.4	5.8	3.3
Proquazone	0.38	23.5	16.1	3.2	13.2	2.3

All determinations were made according to the equipment specifications. Details in chapter 4.6. and 4.8.

4.1.3. Excipients

α-Lactose monohydrate (200 mesh)
(Broculo Domo ingredients, Lotnr 3747, Zwolle, the Netherlands)
(See figure 4.4.)

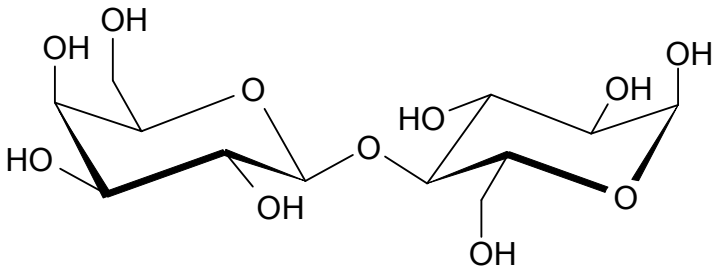


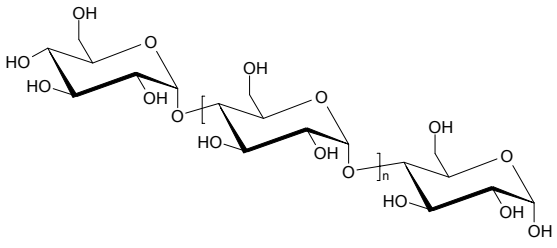
Figure 4.4.: Chemical formula of lactose

Empirical formula:	$C_{12}H_{22}O_{11}\cdot H_2O$
Appearance:	White crystalline or grainy powder, inodorous, with a sweet taste
Molecular weight:	360.3 g/mol
Melting point:	201 - 202 °C
Solubility:	very soluble (water)
Technological use:	Lactose is used as filler, binder and adsorbing agent in the tabletting and capsule filling processes. For direct tabletting, especially spray-dried lactose is suitable.

Corn starch (Maista® Agrana, Artnr: 21.000-50, Aschach, Germany)

Polysaccharide, α-glycosidically linked, composed of about 80% amylopectin and about 20% amylose (see figure 4.5.).

Amylose



Amylopectine

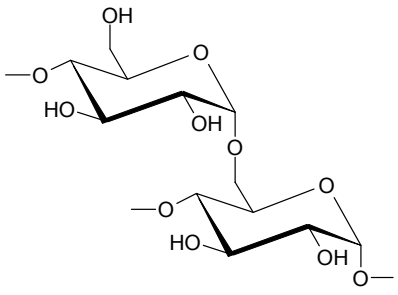


Figure 4.5.: Chemical formulas of Amylose and Amylopectine

Empirical formula:	$(C_6H_{10}O_5)_n$ with n = 300-1000
Appearance:	White matt-finished powder, odourless and tasteless

Molecular weight:	Amylose: 50’000-200’000 g/mol Amylopectine: 100’000-1’000’000 g/mol
Solubility:	insoluble (water)
Technological use:	Corn starch is used as binder for granulation. It can be used as filler, disintegrant and wetting agent for tabletting and capsule filling processes. For the encapsulation of powder it can also be used as lubricant.

PVP (Kollidon®, 29/30 BASF TXIII 08A, Minden, Germany)
(see figure 4.6.)

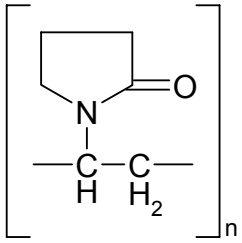


Figure 4.6.: Chemical formula of PVP

Empirical formula:	$(C_6H_9NO)_n$
Appearance:	Fine white or very slightly cream-coloured, tasteless, matt-finished powder, slightly sticky, with a weak characteristic flavour
Molecular weight:	40’000 g/mol
Solubility:	soluble (water)
Technological use:	In watery or organic solutions as binder for granulation and as binder (in a dry state) for direct tabletting. As binder or film former for coating and as wetting agent for hydrophobic substances.

Magnesiumstearate (Siegfried, Artnr: 968786, Zofingen, Switzerland)
(See figure 4.7.)

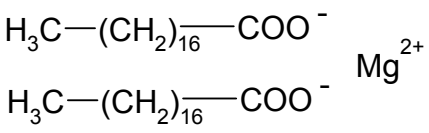


Figure 4.7.: Chemical formula of Magnesiumstearate

Empirical formula:	$C_{36}H_{70}O_4Mg$

Appearance:	Fine, white, bulky, impalpable, unctuous powder, tasteless, odourless or with a faint odour of stearic acid
Molecular Weight:	591.3 g/mol
Solubility:	insoluble (water)
Melting point:	120 – 140 °C
Technological use:	It is used as a dusting powder in skin diseases, and in cosmetics. It is widely used as lubricant in tabletting and encapsulation processes.

UICEL (Pharmaceutics Division, College of Pharmacy, The University of Iowa, Iowa City, USA) (see figure 4.8.)

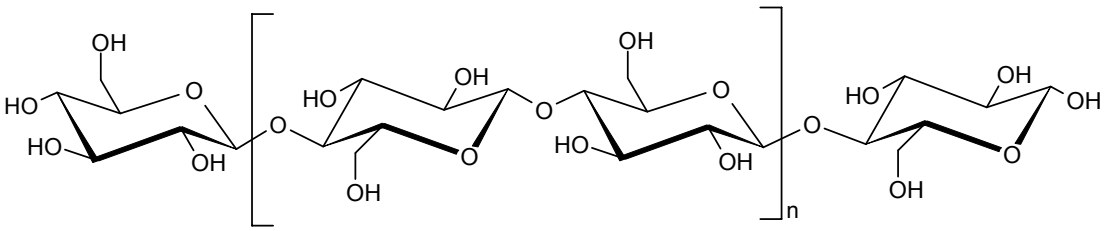


Figure 4.8.: Chemical formula of cellulose

UICEL (University of Iowa cellulose) is a new cellulose based tabletting excipient that has been developed at the University of Iowa (Kumar et al., 2002; Reus-Medina et al., 2004). Cellulose powder is treated with an aqueous solution of sodium hydroxide (5N) and precipitated with ethanol. It shows a cellulose-II-lattice and consists of a mixture of aggregated and non-aggregated fibres.
It can be compressed to a tablet without any binder. The resulting tablet shows an extremely rapid disintegration time (5-11 s) irrespective of its hardness. The ability to act as binder and as a highly effective disintegrant at the same time makes UICEL an interesting aid for direct compression.

4.1.4. Characterisation of the excipients

Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio, respectively are shown in table 4.3.

Table 4.3.: Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio of the excipients.

Excipients	Densities (n = 3)								Hausner ratio	RSD (%)
	True[1] (g/cm^3)	RSD (%)	Poured (g/ml)[2]	RSD (%)	ρ_p (rel)	Tapped (g/ml)[2]	RSD (%)	ρ_t (rel)		
Lactose	1.5397	0.05	0.524	1.6	0.340	0.830	0.99	0.539	1.59	1.4
Corn starch	1.5131	0.08	0.505	1.8	0.334	0.703	1.4	0.465	1.39	3.2
PVP	1.2249	0.09	0.312	1.1	0.254	0.410	1.5	0.335	1.32	1.2
Magnesiumstearate	1.0446	0.12	0.233	0.18	0.224	0.330	1.3	0.316	1.41	1.3
UICEL	1.5539	0.20	0.370	1.9	0.239	0.481	0.70	0.309	1.30	1.2

All determinations were made according to the equipment specifications. Details in chapter 4.15. and 4.16.

Data for residual moisture content, the mean and median particle size of the excipients is shown in table 4.4.

Table 4.4.: Data for residual moisture content, mean particle size and median particle size of the excipients.

Excipients	Residual moisture content (n = 3)[2]		Mean particle size (n = 5)[1]		Median paricle size (n = 5)[1]	
	% (w/w)	RSD (%)	(µm)	RSD (%)	(µm)	RSD (%)
Lactose	0.26	22.5	55.2	1.3	41.0	0.4
Corn starch	9.80	2.4	43.3	2.3	28.7	0.7
PVP	6.65	0.8	106.7	0.6	95.7	0.4
Magnesiumstearate	3.21	5.4	19.5	4.0	14.0	16.5
UICEL	9.17	2.1	137.7	2.2	131.6	2.1

All determinations were made according to the equipment specifications. Details in chapter 4.6. and 4.8.

4.2. Preparation of the capsule formulations

All capsule formulations were made from different powder mixtures. The mixtures were prepared as follows: each powder component was separately sieved through a screen of 250 µm. The different components were then brought together and mixed for 3 minutes in a Loedige M5 high-shear mixer with a volume of 5 litres (Loedige, Paderborn, Germany) at a constant impeller speed of 278 rpm. The total amount of blend for each capsule formulation was always 1 kg.

The powder mixtures were encapsulated in size no. 3 capsules hard gelatine capsule shells (Elanco Lok-Caps® Dr. Wander, Lotnr: 3 141 625, Bern, Switzerland) with a dosating disk capsule filler, Bosch GKF 602 (Robert Bosch Gmbh, Waiblingen, Germany), containing five tamp stations. The powder bed was kept continuously at a level of 1.5-2 cm during manufacturing. The position of the tamp stations was set differently for each formulation in order to encapsulate always the same amount of blend. Furthermore some of the powder mixtures were additionally filled by hand in size no. 2 hard gelatine capsule shells (Capsugel white 44.000/44.000, Bornem, Belgium).

4.2.1. Preparation of the capsules with caffeine

With the model drug caffeine the following capsule formulations containing 70% (w/w), 50% (w/w) and 10% (w/w) were prepared (see table 4.5.). The amount of filler (lactose) was varied.

Table 4.5.: The following capsule formulations were prepared with the model drug caffeine

Ingredient	Composition (w/w)		
	Machine filled (size no 3)		
Caffeine	70%	50%	10%
Lactose	29.5%	49.5%	89.5%
Magnesiumstearate	0.5%	0.5%	0.5%

4.2.2. Preparation of the capsules with diclofenac sodium

The following capsule formulations containing 70% (w/w), 50% (w/w), 33.1% (w/w) and 10% (w/w) were made with the model drug diclofenac sodium (see table 4.6.).

Table 4.6.: The following capsule formulations were prepared with the model drug diclofenac.

Ingredient	Composition (w/w)			
	Machine filled (size no 3)			
Diclofenac sodium	70%	50%	32.1%	10%
Lactose	29.5%	49.5%	67.4%	89.5%
Magnesiumstearate	0.5%	0.5%	0.5%	0.5%

4.2.3. Preparation of the capsules with proquazone

The following capsule formulations containing 70% (w/w), 50% (w/w) and 10% (w/w) of proquazone were prepared (see table 4.7.). Additionally, the capsule mixture containing 50% (w/w) of proquazone as well as the granulate containing 74.1% (w/w) of proquazone (see chapter 4.3.3.) were additionally filled by hand into size no. 2 capsule shells.

Table 4.7.: The following capsule formulations were prepared with the model drug porquazone.

Ingredient	Composition (w/w)				
	Machine filled (size no 3)			Handfilled (size no 2)	
Proquazone	70%	50%	10%	50%	-
Lactose	29.5%	49.5%	89.5%	49.5%	-
Magnesiumstearate	0.5%	0.5%	0.5%	0.5%	-
Proquazongranulate 74% (w/w)	-	-	-	-	100%

4.2.4. Preparation of the capsules with UICEL

The following capsule formulations were prepared with the excipient UICEL and the model drugs caffeine, diclofenac sodium and proquazone (see table 4.8.).

Table 4.8.: The following capsule formulations containing the excipient UICEL were prepared.

Ingredient	Composition (w/w)					
	Machine filled (size no 3)	Handfilled (size no 2)	Machine filled (size no 3)	Handfilled (size no 2)	Machine filled (size no 3)	Handfilled (size no 2)
Caffeine	70%	70%	-	-	-	-
Diclofenac sodium	-	-	70%	70%	-	-
Proquazone	-	-	-	-	70%	70%
UICEL	29.5%	29.5%	29.5%	29.5%	29.5%	29.5%
Magnesiumstearate	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%

4.3. Preparation of the granulates

The ingredients for each granulate were separately screened (mesh size: 250 μm) and brought together. For each preparation, the total amount of blend was 1 kg, which was then put into a Loedige M5 high-shear mixer with a volume of 5 litres (Loedige, Paderborn, Germany) and mixed for 5 minutes (278 rpm). The amount of PVP used for each granulation was always dissolved in the granulation liquid, which was always distilled water. The granulation was carried out by adding the mixture PVP/distilled water as granulating liquid with a constant speed of 18 g/min while the powder components inside the mixer were merged further on with a constant impeller speed of 278 rpm. All granulates were screened (mesh size: 2.2 mm) and dried in a dish dryer Hareus Typ UT 6200 (Sorvall®Heraus Instruments, Hanau, Germany) at a temperature of 40°C until their water content was reduced to about 10% (w/w), then they were sieved through a screen of 800 μm. The granulates were dried further until their moisture content was in equilibrium with 45% relative humidity at room temperature corresponding to the equilibrium moisture content of the original raw material (see chapter 4.6.)

4.3.1. Preparation of the granulates with caffeine

Three granulates with a mass of 1000 g containing 74.1% (w/w), 52.9% (w/w) and 10.6% (w/w) of caffeine were prepared. The amount of lactose was varied, while the amount of PVP and corn starch remained constant. Furthermore a “placebo”-granulate without any model drug was prepared (see table 4.9.).

The total amount of granulation liquid was 410 g for the granulate containing 74.1% (w/w) of caffeine, 284 g for the granulate containing 52.9% (w/w) of caffeine, 200 g for the granulate containing 10.6% (w/w) of caffeine and 210 g for the “placebo” -granulate.

Table 4.9.: Granulates containing 74.1% (w/w), 52.9% (w/w) and 10.6% (w/w) of caffeine and one “placebo”-granulate without any model drug were prepared

Ingredient	Composition (w/w)			
Caffeine	74.1%	52.9%	10.6	-
Lactose	5.82%	27.0%	69.3	79.9
Corn starch	15.9%	15.9%	15.9%	15.9%
PVP	4.23%	4.23	4.23%	4.23

4.3.2. Preparation of the granulates with diclofenac sodium

Four granulates with a mass of 1000 g with a content of 74.1% (w/w), 52.9% (w/w), 33.9% (w/w) and 10.6% (w/w) of diclofenac sodium were prepared. The amount of lactose was varied, while the amount of PVP and corn starch remained constant (see table 4.10.).

The amount of granulation liquid was 230 g for the granulate containing 74.1% (w/w) of diclofenac sodium, 263 g for the granulate containing 52.9% (w/w) of diclofenac sodium, 200 g for the granulate containing 33.9%% (w/w) of diclofenac sodium and 200 g for the granulate containing 10.6% (w/w) of diclofenac sodium.

Table 4.10.: Four granulates containing 74.1% (w/w), 52.9% (w/w), 33.9% (w/w) and 10.6% (w/w) of diclofenac sodium were prepared

Ingredient	Composition (w/w)			
Diclofenac sodium	74.1%	52.9%	33.9%	10.6%
Lactose	5.82%	27.0%	46.0%	69.3%
Corn starch	15.9%	15.9%	15.9%	15.9%
PVP	4.23%	4.23%	4.23%	4.23%

4.3.3. Preparation of the granulates with proquazone

Two granulates with a mass of 1000 g with 74.1% (w/w) and 52.9% (w/w) of proquazone were prepared. The amount of lactose was varied, while the amount of PVP and corn starch remained constant (see table 4.11.).

The amount of granulation liquid was 255 g for the granulate containing 74.1% (w/w) of proquazone and 200 g for the granulate containing 52.9% (w/w) of proquazone,

Table 4.11.: Two granulates containing 74.1% (w/w) and 52.9% (w/w) of diclofenac proquazone were prepared

Ingredient	Composition (w/w)	
Proquazone	74.1%	52.9%
Lactose	5.82%	27.0%
Corn starch	15.9%	15.9%
PVP	4.23%	4.23%

4.3.4. Preparation of the granulates with UICEL

Two granulates were prepared, where corn starch was replaced by UICEL. One granulate contained 20.1% (w/w) of UICEL and 70.4% of diclofenac sodium, while the other contained 15.9% of UICEL and 74.1% (w/w) of diclofenac sodium. The amount of lactose and PVP remained constant (see table 4.12.).

Table 4.12: Two granulates containing 20.1% (w/w) and 15.9% (w/w) of UICEL were prepared with the model drug diclofenac sodium.

Ingredient	Composition (w/w)	
UICEL	20.1%	15.9%
Diclofenac sodium	70.4%	74.1%
Lactose	5.82%	5.82%
PVP	4.23%	4.23%

4.4. Preparation of the tablet formulations

In the following three chapters (4.4.1., 4.4.2. and 4.4.3.), all tablets, made of a granulate or a granulate mixture, had the following compostion: 94.5% (w/w) of granulate or granulate mixture as internal phase and 5% (w/w) of corn starch and 0.5% (w/w) magnesiumstearate as external phase. The tabletting mixture was always prepared as follows: Each of the granulates were put into a turbula mixer Type T2C (Willy A Bachofen AG (WAB), Basel, Switzerland) with 5% (w/w) of screened (mesh size: 250 μm) corn starch and mixed for four minutes at a speed of 34 rpm. Then, 0.5% of screened (mesh size: 250 μm) magensiumstearate was added and the blend was mixed further on for another minute in the turbula mixer at the same speed. In the case of a granulate mixture, both granulates (together 94.5% (w/w) of the whole tablet mass) were put together with 5% (w/w) of corn starch into the turbula mixer and mixed for four minutes at a speed of 34 rpm. Then, also 0.5% (w/w) of magnesiumstearate was added and the mixing was continued for another minute at the same speed
For the preparation of all tablets, a pair of punches (flat face) and a die with a diameter of 7 mm were used. Tablets that showed a crushing strength of 50N ± 5N right after the compression were produced (n=10). The total weight of all tablets was within the limit of 155-157mg.

4.4.1. Preparation of the tablets with caffeine

Tablets with a content of 70% (w/w), 50% (w/w) and 10% (w/w), respectively, were made with the granulates containing 74.1% (w/w), 52.9% (w/w) and 10.6% (w/w) of caffeine (see chapter 4.3.1.). The three tabletting mixtures (see chapter 4.4.) were compressed into tablets with an excentric press (Korsch EKO 1.0021.87, Berlin, Germany) (see table 4.13.).
Two more tabletting mixtures containing 50% (w/w) and 10% (w/w) of caffeine, respectively, were additionally prepared from a blend with the “placebo”-granulate and the granulate containing 74.1%

(w/w) of caffeine (see chapter 4.3.1). For the mixture with totally 50% (w/w) of caffeine, 26.5% (w/w) of the “placebo”-granulate and 68.0% (w/w) of the granulate containing 74.1% (w/w) of caffeine was used. The tabletting mixture containing 10% (w/w) of caffeine consisted of 81.0% (w/w) “placebo”-granulate and 13.5% (w/w) granulate with 74.1% (w/w) of caffeine.

The tablet mixture with 50% (w/w) of caffeine consisting of the “placebo”-granulate and the granulate with 74.1% (w/w) of caffeine was first compressed into tablets with an excentric press (Korsch EKO 1.0021.87, Berlin, Germany).

In order to investigate the influence of another tablet press, the tabletting mixture with 70% (w/w) of caffeine and the two tabletting mixtures with 50% (w/w) and 10% (w/w), of caffeine, respectively, prepared from the “placebo”-granulate and the granulate with 74.1% (w/w) of caffeine, were compressed into tablets with a Presster™ compaction simulator (model 252 serial number 104, year of manufacture 2002, metropolitan computing corporation (MCC), East Hanover, NJ, USA). A rotary press KorschPH336 was simulated with a tabletting speed of 180’000 tablets/h. The following settings have been done, in order to get tablets having a crushing strength of 50N ± 5N right after the compression: dosing cam: 6.30mm; precompression: 3.60mm; compression: 2.58mm; ejection: 7.6deg. An amount of approximately 156 mg of tabletting mixture was filled for every tablet by hand into the die in order to get a tablet weight between 155-157 mg.

Table 4.13.: Different tablet formulations were prepared with the model drug caffeine.

Caffeine	Composition (w/w)						
Content of caffeine in the tablet:	70%	50%	10%	50%	70%	50%	10%
Tablet press:	excentric press	excentric press	excentric press	excentric press	Presster™	Presster™	Presster™
Granulate 74.1% (w/w)	94.5%	-	-	68.0%	94.5%	68.0%	13.5%
Granulate 52.9% (w/w)	-	94.5%	-	-	-	-	-
Granulate 10.6% (w/w)	-	-	94.5%	-	-	-	-
“Placebo”-Granulate	-	-	-	26.5%	-	26.5%	81.5%
Corn starch	5%	5%	5%	5%	5%	5%	5%
Magnesiumstearte	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%

4.4.2. Preparation of the tablets with diclofenac sodium

Tablets with a content of 70% (w/w), 50% (w/w), 32% (w/w) and 10% (w/w), respectively, were made with the granulates containing 74.1% (w/w) 52.9% (w/w), 33.9% (w/w) and 10.6% (w/w) of diclofenac sodium (see 4.3.2.). The four tabletting mixtures (see chapter 4.4.) were compressed into tablets with an excentric press (Korsch EKO 1.0021.87, Berlin, Germany) (see table 4.14.).

Table 4.14.: Different tablet formulations were prepared with the model drug diclofenac sodium

Diclofenac sodium	Composition (w/w)			
Content of diclofenac sodium in the tablet:	70%	50%	32%	10%
Tablet press:	excentric press	excentric press	excentric press	excentric press
Granulate 74.1% (w/w)	94.5%	-		-
Granulate 52.9% (w/w)	-	94.5%		-
Granulate 33.9% (w/w	-	-	94.5%	-
Granulate 10.6% (w/w)	-	-	-	94.5%
Corn starch	5%	5%		5%
Magnesiumstearte	0.5%	0.5%		0.5%

4.4.3. Preparation of the tablets with proquazone

Tablets with a content of 70% (w/w) and 50% (w/w) were made with the granulates containing 74.1% (w/w) and 52.9% (w/w) of proquazone (see chapter 4.3.3.). The two tableting mixtures (see 4.4.) were compressed into tablets with an excentric press (Korsch EKO 1.0021.87, Berlin, Germany) (see Table 4.15.).

In addition, the powder mixture that was used to prepare capsules with a content of 50% (w/w) of proquazon (see chapter 4.2.3.) was also compressed into tablets using a Zwick®1478 Universal Testing Instrument (Zwick GmbH, Ulm, Germany). Therefore, a compaction force of 6.9 kN was applied and the compression speed was set to the maximum of 25 mm/min, in order to receive tablets with a crushing strength of 50 $\pm$ 5 N.

Table 4.15.: Different tablet formulations were prepared with the model drug proquazone

Proquazone	Composition (w/w)		
Content of proquazone in the tablet:	70%	50%	50%
Tablet press:	excentric press	excentric press	Zwick®
Granulate 74.1% (w/w)	94.5%	-	-
Granulate 52.9% (w/w)	-	94.5%	-
Corn starch	5%	5%	-
Magnesiumstearte	0.5%	0.5%	-
Capsule mixture 50% (w/w)	-	-	100%

4.4.4. Preparation of the tablets with UICEL

The following tablet formulations were prepared containing the excipient UICEL (see table 4.16.).

The capsule mixtures containing 70% (w/w) of caffeine, diclofenac sodium and proquazone, respectively, each in combination with 29.5% (w/w) of UICEL, were compressed into tablets using a Zwick®1478 Universal Testing Instrument (Zwick GmbH, Ulm, Germany) (see chapter 4.2.4.). Different compression forces had to be applied for each mixture in order to always get a crushing strength of 50N ± 5N. The mixture containing 70% (w/w) of caffeine was compressed with 3.2 kN, the mixture containing 70% (w/w) of diclofenac sodium was compressed with 4.6 kN and the mixture containing

70% (w/w) of proquazone with 5.1 kN. The compression speed was in all cases set to the maximum of 25 mm/min.

In addition, two tabletting mixtures were prepared from two granulates (see chapter 4.3.4.). The whole amount of corn starch was replaced by UICEL. The first granulate contained 74.1% (w/w) of diclofenac sodium and 15.9% of UICEL. As external phase 5% of UICEL was added to the granulate and it was mixed at first four minutes in the turbula mixer and then another minute with 0.5% of magnesiumstearate exactly the same way as described in chapter 4.4. The second granulate contained 70.4% (w/w) of diclofenac sodium and 20.1% (w/w) of UICEL. As external phase only 0.5% (w/w) of magnesiumstearate were added and the blend was mixed for one minute exactly the same way as described in chapter 4.4. in the turbula mixer.

Two different formulation were received containing 70% (w/w) of diclofenac sodium, one with 15% (w/w) of UICEL in the internal phase and 5% (w/w) of UICEL in the external phase and the other with 20% of UICEL in the internal phase. They were compressed using an excentric press (Korsch EKO 1.0021.87, Berlin, Germany).

Table 4.16: Different tablet formulation were prepared with the excipient UICEL

UICEL	Composition (w/w)				
Content of UICEL in the tablet	29.5%	29.5%	29.5%	20%	20%
Tablet press:	Zwick®	Zwick®	Zwick®	excentric press	excentric press
Capsule mixture with 70% (w/w) of caffeine	100%	-	-	-	-
Capsule mixture with 70% (w/w) of diclofenac sodium	-	100%	-	-	-
Capsule mixture with 70% (w/w) of proquazone	-	-	100%	-	-
Granulate 70.4% (w/w) diclofenac sodium	-	-	-	99.5%	-
Granulate 74.1% (w/w) diclofenac sodium	-	-	-	-	94.5%
UICEL	-	-	-	-	5%
Magnesiumstearate	-	-	-	0.5%	0.5%

4.5. Flowability

The values of flowability were determined with a hopper made of plexiglass (centre angle: 37.5°, orifice diameter: 9 mm), which was connected to a balance (PC 8000 Mettler Toledo Gmbh, Greifensee, Switzerland). The increase in weight could be measured 375 times per minute. The data were transferred to a computer and automatically put in an excel sheet with the software Balance link (Mettler Toledo, Balance link V 3.01, Greifensee Switzerland). The flowability of all granulates as well as the flowability of UICEL were determined with approximately 100 g of sample. The other powders, however, did not show any flow. By division of the mass through the flowing time, the flowability of the different samples was calculated (see equation 34). The measurement was carried out 5 times for each sample.

$$flowability = \frac{mass}{flowing\ time} \qquad \text{Equation 32}$$

4.6. Determination of the 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 33).

$$M = \sum_{i=1}^{n} \frac{a_i \cdot w_i}{100} = \frac{a_1 \cdot w_1 + a_2 \cdot w_2 + \ldots + a_n \cdot w_n}{100} \qquad \text{Equation 33}$$

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 show 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 34 to values that refer to a dry state of the sample.

$$M_d = \frac{100 \cdot M_w}{100 - M_w} \qquad \text{Equation 34}$$

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

4.7. Particle size measurements

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 all granulates 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 had to be done. The average and median particle size of UICEL 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 two bar and the federate was set to level two.

The excipients lactose, PVP, corn starch and the model drug caffeine 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). For the different samples, different liquids were chosen, in order not to dissolve or swell the sample. For all samples, that have to be determined in a liquid the following settings has been done: 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 particle size of magnesiumstearate and diclofenac sodium was determined in Aceton. Proquazone was characterised in water. The mathematical model 2OFD was used (according to the recommendation of Malvern Instruments).

4.8. Mass and content uniformity

The mass uniformity of all dosage forms was determined by weighing 20 units that were randomly chosen (Ph. Eur. 4, 2002).

The content uniformity of each formulation was determined according to USP XXIV (n=10).

The samples were centrifugated (14000 rpm) and the amount of model drug was quantified by HPLC. The equipment consisted of a Hewlett Packard series 1050 pump (Hewlett Packard, Walbronn, Germany) connected to Hewlett Packard Series 1050 UV-detector model 79853A (Hewlett Packard, Walbronn, Germany), a Hewlett Packard series 1050 auto injector (Hewlett Packard, Walbronn, Germany) and a Macherey-Nagel (MN) Nucleosil reversed phase C8 ec 5 μm column (2 x 125 mm) (Macherey-Nagel AG, Oensingen, Switzerland).

As mobile phase, a mixture of bidistilled water and methanol was always used. The ratio methanol:water was 20:80 (v/v) for the model drug caffeine, 3:57 (v/v) for the model drug diclofenac sodium and 40:60 (v/v) for the model drug proquazone. The injected sample volume was 20 μl, the flow rate was set to 0.25 ml/min and the quantification was done at a wavelength of 276 nm for the model drug caffeine, at 230 nm for the model drug diclofenac sodium and at 275 nm for the model drug proquazone.

4.9. Solubility of the model drugs

To assure to work under sink conditions, saturated solutions of the model drugs were prepared at a temperature of 37°C and analysed (Sink conditions were defined as follows: the total concentration of the model drugs dissolved should not be significantly higher than 10% of their saturated concentration (Gibaldi et al., 1967)). Excess model drug to saturate the solvent was added to 500 ml of the medium. It was stirred with a paddle at a speed of 100 rpm. Samples were taken after regular intervals and quantified by HPLC with the same method described in chapter 4.9. The media for the model drugs caffeine and proquazone was a 0.1M HCl solution. The saturation concentration of diclofenac sodium was determined in 0.1M HCl and in a buffer solution (pH 6.8) according to Ph. Eur. 2002: Phosphat-Pufferlösung pH 6.8, R).

4.10. Contact angle and total surface free energy.

For the determination of the total surface free energy the capillary rise-or Washburn-method was used (Michel et al., 2001). The equipement consisted of a Krüss Processor Tensiometer K100 Mk2 (©Krüss GmbH, Hamburg, Germany) with the software LabDesk™ K100 Version 3.0, Artnr.: SW32 (©Krüss GmbH, Hamburg, Germany).

The powders were placed initially in a glass tube with a porous glass base. The mass and the volume of each sample in the glass tube were kept constant. The tube was fixed to the electronic balance, which was integrated in the tensiometer. The porous glass base was brought automatically in contact with a vessel containing the test-liquid. The speed of capillary rise, i.e. the increase in weight (m) in the sample, was measured in relation to time with the tensiometer.

The value m^2 was detemined by the tensiometer. It was plotted automatically against time by the tensiometer's software. The values of the viscosity and the different densities of the test liquids were provided in the program. The capillary constant c was always determined experimentally with hexane (Fluka Chemika, Artnr.: 52765, Buchs, Switzerland). The capillary constant c was estimated and substituted in the Washburn equation by the software (n = 3).

With the value of the capillary constant, contact angles with other test liquids could be determined. Three different contact angles of every powder were determined (n = 3 for each test liquid): For all powders with the exception of proquazone, diiodo-methane (Fluka Chemika, Artnr.: 66880, Buchs, Switzerland), formamide (Fluka Chemika, Artnr.: 47670, Buchs, Switzerland) and distilled water were used as test liquids. For proquazone, n-heptane (Riedel-de Haën, Artnr: 15677, Seelze, Germany), formamide (Fluka Chemika, Artnr.: 47670, Buchs, Switzerland) and a mixture of ethanol (Schweizerhall Chemie AG, Lotnr.: 82352-150, Basel, Switzerland) and distilled water in a ration of 10:90 (w/w) was used.

With the software LabDesk™ K100, the values of the different contact angles were plotted according to Owens, Wendt, Rabel and Kaelble. And a linear function was gained. Both, the value of the slope corresponding to the polar contribution of the total surface free energy of the solid and the y-axis

intercept, which corresponds to the non- polar or dispersive contribution of the total surface free energy of the solid could be determined (see chapter 3.2.1.).

4.11. Water absorption measurement

The sorption ability was determined in order to characterize the wetting behaviour of the different formulations (n=3) with a Krüss Processor Tensiometer K100 Mk2 (©Krüss GmbH, Hamburg, Germany) and the software LabDesk™ K100 Version 3.0, Artnr.: SW32 (©Krüss GmbH, Hamburg, Germany). All samples were put into a glass tube with a porous glass base and placed in contact with the test liquid, which was always distilled water.
The increase of mass squared of the samples (m^2) was monitored and plotted against time (t) [g^2/min] (see fig 4.9.) in order to get the slope K according to the modified Washburn-Equation (Luginbühl et al., 1994) (see equation 32).

$$M^2(t) = K \cdot t \qquad \text{Equation 35}$$

M is the absorbed mass of water at a certain time t. K stands for a velocity constant of the water uptake.

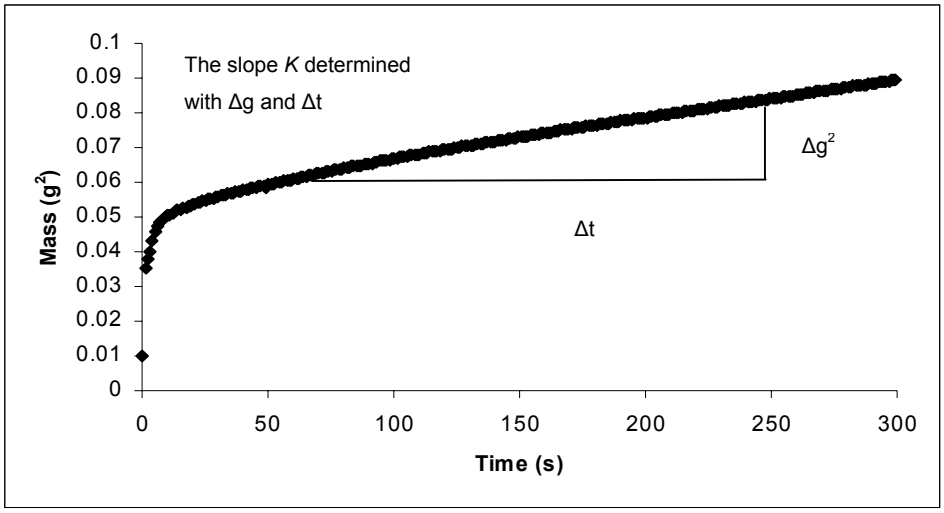


Figure 4.9.: The water sorption constant K can be determined by plotting the increase of mass against time.

The sorption of water was measured with all three model drugs and all dosage forms containing 70% (w/w) of the model drug caffeine, diclofenac sodium or proquazone, respectively. Furthermore the water uptake of the granulate containing 74.1% of proquazone was investigated.

4.12. Dissolution rate measurements and evaluation

Two dissolution apparatus were initially compared with the capsule formulation containing 70% (w/w) and 50% (w/w), respectively, of caffeine in combination with lactose (see chapter 4.2.).
One apparatus (Siegmund et al., 1998) was built and developed in the laboratories of Pharamceutical Technology at the University of Basel (see figure 4.10.).
The capsule formulations were released using a basket of stainless steel (mesh size: 0.381 mm) (n = 6 for each formulation). The rotation of the baskets was done with an electric engine (RW 18 IKA-Werk, Janke und Kunkel KG, Staufen i. Br., Germany). The rotation speed was set to 100 rpm. Additionally, in order to get a homogenous dissolution media, a magnet stirrer was placed at the bottom of the vessel containing 900 ml of 0.1M HCl at a temperature of 37 ± 0.5°C as dissolution media. It was driven by a stirring motor (1P 3218, Heto, Bikeröd, Denmark), a metal plate containing 6 stirring units, which was placed underneath the water bath (850 052, Termomix 1460, B. Braun Melsung AG, Germany). The speed of the magnet stirrer was set to level 5. The magnet stirrer was additionally covered with an insert made of stainless steel in order to prevent a turbulent current. Samples (10 ml) of dissolution medium were removed at regular time intervals. An equal volume of dissolution medium at 37°C was added to maintain a constant volume.

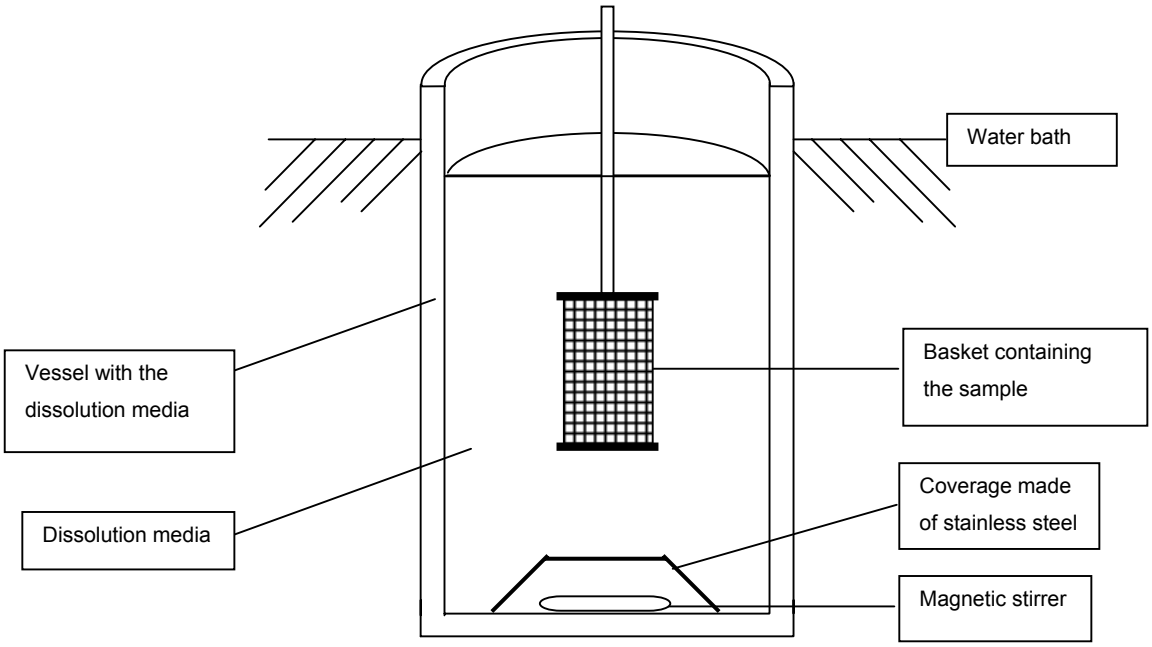


Figure 4.10.: Dissolution apparatus developed in the laboratories of Pharmaceutical Technology, University of Basel.

The other apparatus was a dissolution apparatus Sotax AT 7 (Sotax AT 7, Allschwil/Basel, Switzerland) according to the specifications of USP XXIV. It was decided to use this apparatus for all further experiments also using the basket method. The rotation speed of the baskets was set to 100

rpm (n=6). The volume of the dissolution medium was 900 ml 0.1 M HCl for caffeine and proquazone at a temperature of 37 ± 0.5°C. The dissolution tests with the model drug diclofenac sodium were performed in the same amount of a phosphate-citrate buffer at a pH of 6.8 (see chapter 4.10.) at the same temperature.

Samples (10 ml) of dissolution medium were removed at regular time intervals. An equal volume of dissolution medium at 37°C was added to maintain a constant volume.

All samples were prepared and the drug concentration quantified by HPLC as described in chapter 4.9. The data points were fitted with SYSTAT Version 7.0 for Windows® (SYSTAT inc., Evanston, IL, USA) using the Weibull equation (see equation 19, chapter 3.3.2.1.); *M* is the amount of drug released as a function of the time *t*, M_0 is the amount of drug in the formulation at the time zero. *T* is a parameter equivalent with the lag-time of the drug release; *a* denotes a scale parameter that describes the time dependence whereas *b* is a shape parameter (Koch 1984). The time, when 50% (w/w) and 90% (w/w) of drug being in each formulation was released, was calculated using the inverse function of the Weibull-equation (see equation 36).

$$t_{(50\%\ resp.\ 90\%\ dissolved)} = \left(-a \cdot \ln \frac{M_0 - M}{M_0} \right)^{\frac{1}{b}} + T \qquad \text{Equation 36}$$

i.e. with M = 0.5 M_0 and M = 0.9 M_0.

4.13. Disintegration time

The disintegration time of the different capsule and tablet formulations was determined with an apparatus according to the specifications of Ph. Eur. 2002 (Disintegration apparatus: Sotax DT 3, Allschwil/Basel, Switzerland). The disintegration media was distilled water at a temperature of 37°C (n=6). The disintegration time of each unit was checked separately by eye.

4.14. True density

The true density was determined with a an AccuPyc™ 1330 Helium Pycnometer (Micromeritics, Norcross, USA) with a known volume 12.0978 cm^3. The true density can be expressed as a quotient of mass and volume. The mass was calculated from the difference between the mass of the filled pycnometer and the mass of the empty pycnometer. The volume was determined by purging each sample 20 times with helium. In each run the volume of the sample could be deviated from the difference in volume of the full and the empty pycnometer. The first ten runs were considered as a equilibrating procedure, where the measurements were neither reproducible nor constant (see figure 4.11.). The average value of run 18, 19 and 20, however, gave the value for the true density by

dividing it through the previously determined mass. The procedure was carried out three times for each sample (see figure 4.11.).

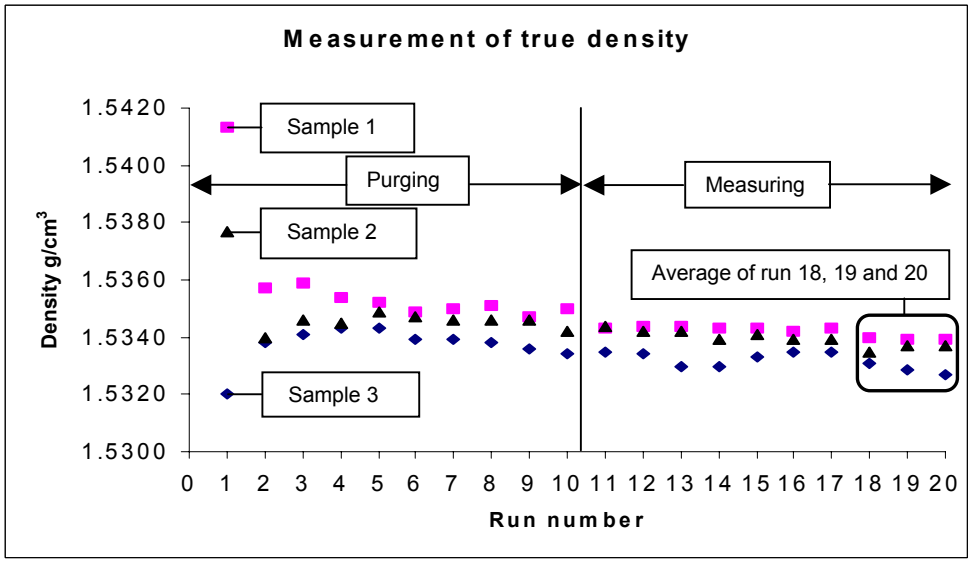


Figure 4.11.: The average value of run 18, 19 and 20 gave the value for the true density. The procedure was carried out three times for each sample.

4.15. Poured density, tapped density and Hausner ratio

At first the poured volume and the tapped volume were determined. The equipement consisted of a tapped density volumeter (StaV 2003, J. Engelsmann AG, Ludwigshafen, Germany). 100 g of sample or, if not possible, a mass of powder or granulate, respectively, giving a volume between 50 and 250 ml were prepared and poured into a glass cylinder which was fixed on the volumeter. The poured volume was given by the marks on the glass cylinder. Then, the sample was tapped 500 times and the volume was checked again. The sample was tapped further on 750 times giving the tapped volume (totally 1250 times). If the difference in volume between 500 times of tapping and 1250 times of tapping was > 2 ml, the sample was tapped further on 1250 times giving the tapped volume after 2500 times of tapping. The quotient of volume and weight of the sample gave the poured and the tapped density, respectively. The relative poured and tapped density was given by dividing the poured and tapped density, respectively, through the true density (see chapter 4.15.). The Hausner ratio (HF) was determined by the ratio of the poured and the tapped density (see equation 37).

$$HF = \frac{tapped\ density}{poured\ density}$$ Equation 37

4.16. Tablet geometry and relative density

The remaining dust on the surface of all tablets was removed by air pressure. Then, the mass was determined and the thickness of the tablets was measured with a thickness gauge (Digitcal, Tesa S.A., Renens, Switzerland). The difference in diameter, however, was so small that it could not be determined with the thickness gauge. Therefore, a diameter of 7 mm corresponding to the diameter of the die all tablets were made, was taken as value for the diameter of the tablets in all calculations.
With the tablet geometry (given by the value the thickness and the diameter) and the mass, the apparent density of the tablets was calculated. It was given by the quotient of the mass and the volume. The relative density was calculated from the quotient of the true density of the tabletting mixture (see chapter 4.15.) and the apparent density of the tablet (see equation 38).

$$relative\ density = \frac{apparent\ density}{true\ density}$$ Equation 38

4.17. Crushing strength

The crushing strength (average value of ten 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 during production of the tablets. After a storage time of approximately 2 weeks in a desiccator containing a saturated solution of potassium carbonate giving an air moisture of 45%, the crushing strength was investigated as well as the tablet geometry and relative density (see chapter 4.17.).

4.18. Compactibility and compressibility according to Leuenberger

Important characteristics of a substance are its compressibility, which is the ability to reduce its volume under pressure and its compactibility, which is the ability to build a compact with a sufficient mechanical strength (see chapter 3.10.).

4.18.1. Compression of the raw materials

All excipients, model drugs, ganulates, tabletting mixtures, the capsule mixtures containing 29.5% (w/w) of UICEL, additionally, the model drugs acetyl salicylic acid (Hänseler AG, Lotnr.: 6-0048-2, Herisau, Switzerland) as an example for a direct compressive agent and paracetamol (Mallinckrodt speciality chemicals co., Lotnr.: 103-90-2, Raleigh, North Carolina, USA) as an example for a substance with very bad compression properties were compressed on a Zwick®1478 Universal Testing Instrument (Zwick GmbH, Ulm, Germany) using a die and a punch flat face with a diameter of 7 mm. The compression speed was set to the maximum of 25 mm/min. Tablets of the samples were

made with five different compression forces except for magnesiumstearate where just four different compression forces were investigated. Five tablets were produced with each applied compression force. The weight of the prepared tablets was within the limits of 155-157 mg corresponding to the weight of the tablets and the capsules in chapter 4.2. and 4.4., respectively. The compression forces were always chosen the way that there was no visible capping of the tablets right after manufacturing and after the storage time of 24 h in a desiccator containing a saturated solution of potassium carbonate giving an air-moisture of 45%. The pressure of compression σ was calculated according to equation 40.

$$Compression\ pressure = \frac{Compression\ force}{\left(\pi \cdot \left(\frac{d}{2}\right)^2\right)} \qquad \text{Equation 39}$$

Where *d* is given by the value of the diameter of the punch and the die, respectively. When high compression forces were applied, except for the tabletting mixtures, the punch had to be treated with a minimal amount of magnesiumstearate, in order to prevent the compact from sticking too much in the die and being destroyed during ejection.

The following raw materials were compressed using a compression force of 2.5, 5, 10, 30 and 50 kN, respectively, corresponding to a compression pressure of 64.96, 129.92, 259.84, 779.53 and 1299.22 MPa, respectively:

Granulate with 74%, 53% and 10.6% (w/w) of caffeine and tabletting mixture containing 70%, 50% and 10% (w/w) of caffeine.

“Placebo-granulate” (see chapter 4.3.1.).

The following raw materials were compressed using a compression force of 2.5, 5, 7.5, 15 and 40 kN, respectively, corresponding to a compression pressure of 64.96, 129.92, 194.88, 389.77 and 1039.4 MPa, respectively:

Granulate with 74%, 53%, 33.9% and 10.6% (w/w) of diclofenac sodium and tabletting mixture containing 70%, 50%, 32.6% and 10% (w/w) of diclofenac sodium.

Granulate with 74% and 53% (w/w) of proquazone and tabletting mixture containing 70% and 50% (w/w) of proquazone.

UICEL

Capsule mixture containing 29.5% (w/w) of UICEL with 70% (w/w) of the model drugs caffeine, diclofenac sodium and proquazone, respectively.

Granulate with 74% (w/w) of diclofenac sodium and 20% (w/w) of UICEL in internal phase and granulate with 74% (w/w) of diclofenac sodium, 15% (w/w) of UICEL in internal and 5% (w/w) in external phase.

Acetyl salicylic acid

The compression force of the following raw materials had to be chosen individually, because very different compression characteristics could be observed. The different compression forces applied and the corresponding pressures of compression are shown in table 4.17.

Table 4.17.: Tablets were made with different compression forces (kN). The applied pressure of compression is shown in Mpa.

Substance						
Caffeine	Compression force (kN)	2.5	5	8	9	10
	Compression pressure (MPa)	64.96	129.92	207.88	233.86	259.84
Diclofenac sodium	Compression force (N)	2.5	5	7.5	10	15
	Compression pressure (MPa)	64.96	129.92	194.88	259.84	389.76
Proquazone	Compression force (N)	2.5	5	7	9	10
	Compression pressare (MPa)	64.96	129.92	181.89	233.86	259.84
Paracetamol	Compression force (kN)	5	10	20	30	40
	Compression pressure (MPa)	129.91	259.84	519.69	779.53	1039.4
Lactose	Compression force (N)	2.5	5	10	20	30
	Compression pressure (MPa)	64.96	129.92	259.84	519.69	779.53
Corn starch	Compression force (N)	5	10	20	30	40
	Compression pressare (MPa)	129.92	259.84	519.69	779.53	1039.4
PVP	Compression force (N)	0.5	1	2	8.1	18.2
	Compression pressure (MPa)	12.99	25.98	51.97	210.47	472.92
Magnesiumstearate	Compression force (kN)	1	2.5	5	7.5	-
	Compression pressure (MPa)	25.98	64.96	129.92	181.89	-

4.18.2. Determination of the radial crushing strength

The resulting tablets were stored for 24 h in a desiccator containing a saturated solution of potassium carbonate giving an air-moisture of 45%. Then, their apparent density, relative density and crushing strength was determined (see chapter 4.17 and 4.18.).
The values of the crushing strength were transformed into values for radial crushing strength (MPa) according to Newton et al., 1971 (see chapter 3.9.1., equation 30).

4.18.3. Determination of the pressuceptibility γ and σ_{Tmax}

The values of the radial crushing strength (σ_T) were plotted against the product of the compression pressure and the relative density. The value of σ_{Tmax} and the pressuceptibility γ could be calculated using SYSTAT Version 7.0 for Windows® (SYSTAT inc., Evanston, IL, USA).

5. Results and Discussion

5.1. Solubility

The solubility of the model drugs caffeine and proquazone over a time of 37h and 30 h, respectively, are shown in table 5.1.

Table 5.1.: Solubility of caffeine and proquazone in 0.1M HCl at a temperature of 37°C.

0.1 M HCl (n = 3)	Solubility (g/l) ± RSD (%)	
Caffeine	37.2 ± 1.0 (16h)	37.3 ± 0.93 (37h)
Proquazone	1.25 ± 2.4 (16h)	1.28 ± 1.6 (30h)

The solubility of caffeine in 0.1M HCl was averaged 37.25 g/l at a temperature of 37°C. The solubility of proquazone accounted averaged 1.27 g/l under the same conditions. According to the solubilities, sink conditions were maintained in every dissolution experiment at each time. Sink conditions were defined in this work as follows: the total concentration of the drug dissolved should not be significantly higher than 10% of its saturated concentration (Gibaldi et al., 1967)).

It was tried to evaluate the saturation concentration of diclofenac sodium in 0.1 M HCl and in a phosphate-citrate buffer solution with a pH of 6.8 (Ph. Eur. 2002: Phosphat-Pufferlösung pH 6.8, R), (see table 5.2.).

Table 5.2.: The solubilities of diclofenac sodium in 0.1 M HCl and a phosphate buffer (pH 6.8) at a temperature of 37°C.

Diclofenac sodium	Solubility ± RSD (%) (time)			
0.1M HCl	1.86 mg/l ± 20.4 (12h)	1.39 mg/l ± 9.41 (36h)	1.61 mg/l ± 25.6 (60h)	1.27 mg/l ± 11.3 (84h)
pH 6.8	1.21 g/l ± 15.5 (12h)	1.02 g/l ± 5.8 (36h)	1.02 g/l ± 4.4 (60h)	1.04 g/l ± 5.0 (84h)

The saturation concentration of diclofenac sodium in 0.1M HCl was very low. It was averaged 1.53 mg/l at a temperature of 37°C. The concentration of diclofenac sodium in the buffer solution at a temperature of 37°C and a pH of 6.8 averaged 1.07 g/l. This result is not surprising as diclofenac sodium gets increasingly unionised at a deeper pH.

To maintain the same conditions as for the model drugs caffeine and proquazone it was tried to perform the dissolution experiment with capsules containing 10% (w/w) of diclofenac sodium in 0.1M HCl, too. It became obvious that sink conditions cannot be maintained at all (see figure 5.1.).

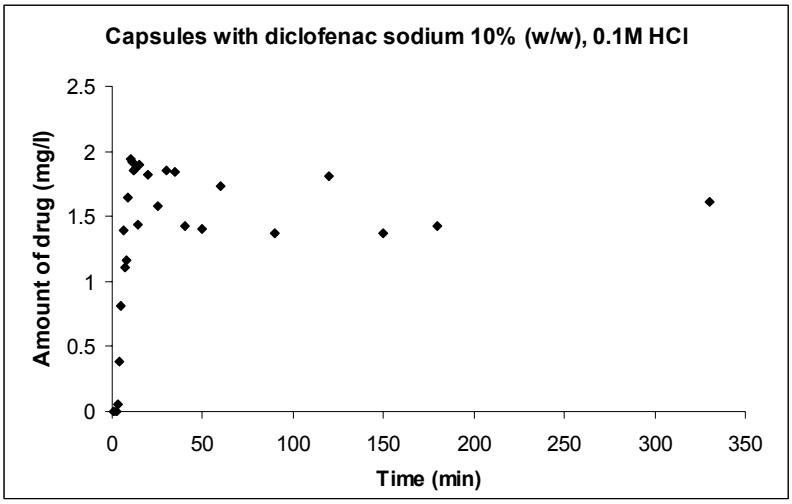


Figure 5.1.: Dissolution of a capsule containing diclofenac sodium 10% (w/w) in 0.1M HCl at a temperature of 37°C.

After approximately 3 minutes already 10% of the saturated concentration is realeased. In order to achieve reproducible results with formulations containing the same amount of model drug in percent than the formulations with caffeine and proquazone, it was decided to carry out the dissolution experiment with the model drug diclofenac sodium in a watery buffer solution at a pH of 6.8 at a temperature of 37°C.

To estimate the solubility of all model drugs in water, their solubility parameter were calculated according to the Hansen parameter group contribution method (see chapter 3.1.1.). The results are shown in table 5.3. According to this estimation, proquazone turned out to be the less soluble compound in water with an estimated solubility parameter of 22.22 $MPa^{0.5}$ followed by diclofenac sodium with 24.04 $MPa^{0.5}$ and caffeine with 25.53 $MPa^{0.5}$.

Table 5.3.: Solubility parameter of the model drugs calculated according to the Hansen parameter group contribution method.

	Solubility parameter $(MPa)^{0.5}$
Caffeine	25.53
Diclofenac sodium	24.04
Proquazone	22.22

5.2. Total surface free energy and wettability

The results of the determination of the contact angle with water and the total surface free energy with the polar and non-polar contributions of the model drugs and excipients are summerised in table 5.4.

Table 5.4.: The contact angle (water) and the total surface free energy with the polar and non polar contribution of the different starting materials (n=3).

Substance	Contact angle (water) (°) ± RSD %	Surface free energy (mN/m)		
		Polar contribution (mN/m)	Non polar contribution (mN/m)	Total surface free energy (mN/m)
Caffeine	66.4 ± 4.5	8.4	40.9	49.3
Diclofenac sodium	64.8 ± 3.7	20.4	22.1	42.5
Proquazone	> 90	3.7	17.3	21.0
Lactose	49.9 ± 7.7	16.8	42.3	59.1
Corn Starch	71.4 ± 3.0	9.8	31.0	40.8
PVP	78.1 ± 4.0	5.9	34.5	40.4
UICEL	41.1 ± 7.9	24.4	36.1	60.6

The values of the different contact angles of the solids with different test liquids are plotted according to the method of Owens, Wendt, Rabel and Kaelble in order to determine the total surface free energy of the solid (see chapter 3.2.1.). See figure 5.2. for the model drugs and figure 5.3. for the excipients.

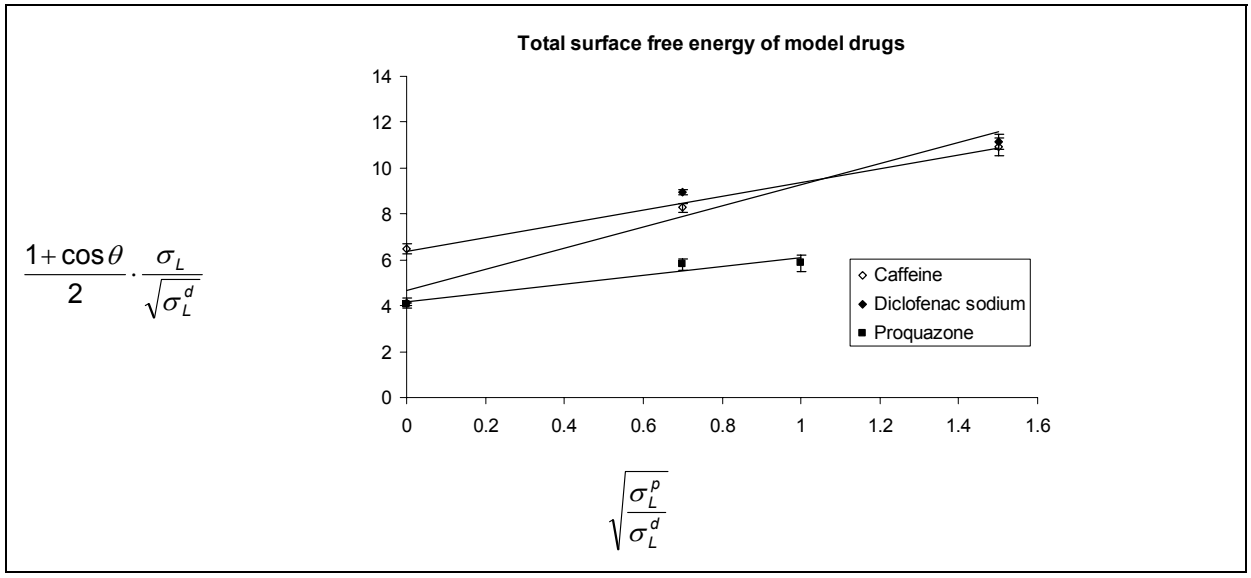


Figure 5.2.: The different contact angles of the three model drugs caffeine, diclofenac sodium and proquazone with different test liquid were plotted according to Owens, Wendt, Rabel and Kaelble in order to determine their total surface free energy with the polar and non-polar contribution.

Caffeine and diclofenac sodium form a similar contact angle with water. It accounts for 66.4° for caffeine and 64.8°for diclofenac sodium respectively. Caffeine seems to have a slightly better wettability (water) than diclofenac sodium. This assumption is also supported by the fact that the total

surface free energy of caffeine accounts for 49.3 mN/m, whereas it is equal to 42.5 mN/m for diclofenac sodium. Regarding the polar and non-polar contributions, caffeine seems to have a high non-polar contribution with a comparably low polar contribution in contrast to diclofenac sodium where the polar and non-polar contributions seem to be equal. The two model substance seem to be alike what the wettability in water is concerned. Proquazone, however, which has a total surface free energy of 21.0 mN/m with a polar contribution of 3.7 mN/m and a non-polar contribution of 17.3 mN/m seems to have a very poor wettability. The contact angle of proquazone could not be determined with water as the modified Washburn method does not allow to measure contact angles > 90°. To estimate the contact angle of proquazone with water, θ was deviated according to the plot of Owens, Wendt, Rabel and Kaelble by extrapolation. In this estimation θ accounted for 95.1°.

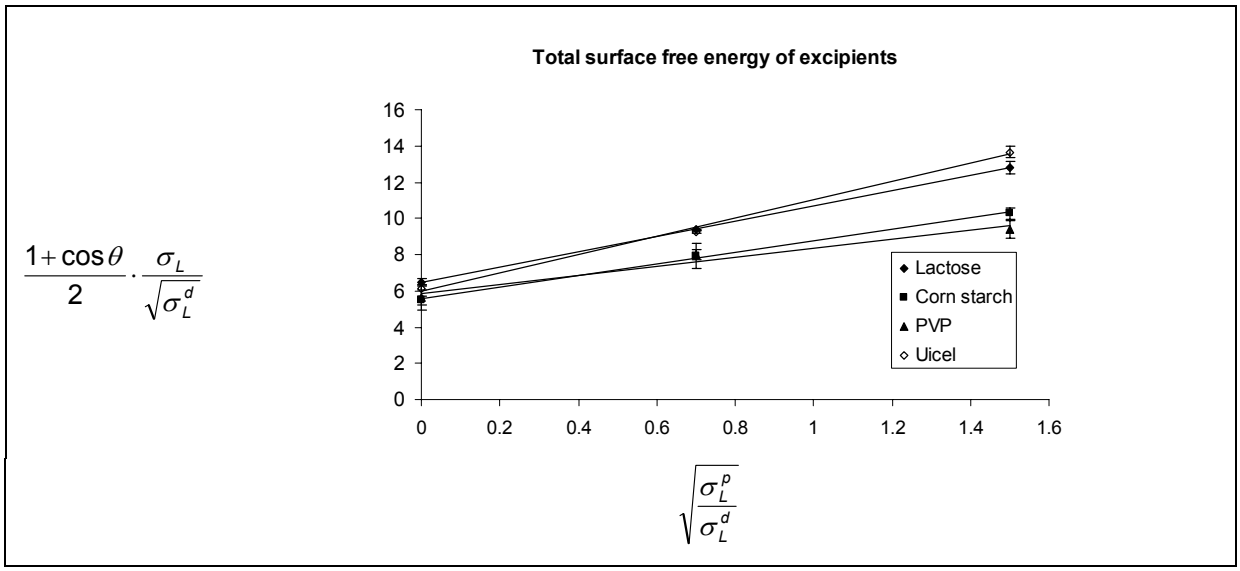


Figure 5.3.: The different contact angles of the four excipients lactose, corn starch, PVP and UICEL with different test liquid were plotted according to Owens, Wendt, Rabel and Kaelble in order to determine their total surface free energy with the polar and non-polar contribution.

The excipients can be roughly divided into two groups what their contact angles with water and their total surface free energy is concerned. PVP and corn starch show similarity as their contact angle with water is around 75°. They also have a similar total surface free energy of about 40 mN/m. The contact angle of lactose and UICEL accounts for about 46° and their total surface free energy for approximately 60 mN/m.

5.3. Dissolution

The weight of each tablet used in the dissolution test and the weight of the powder or the granulate in each capsule formulation was within the limits of 155.2 mg-156.6 mg (Mean value: 156.0 mg; Standard deviation: ± 0.3 mg; RSD (%)). To prevent the capsules from swimming at the surface, the basket method was used. In order to be able to compare all dissolution profiles, the basket method was also applied to all tablet formulations.

It became evident that the different dissolution behaviour can be related to the difference in the formulations. In order to describe the different dissolution processes in this work, a single equation the "RRSW"- or “Weibull”- equation was chosen (see chapter 3.3.2.1. equation 19).

In this equation, M is the amount of drug dissolved as a function of time t. M_0 is total amount of drug being released. Because the total amount of drug was released in each dissolution experiment, this value corresponds with the mean value determined in the content uniformity test according to USP XXIV (see chapter 4.9.). T accounts for the lag time measured as a result of the dissolution process. In case of the tablets the dissolution process started immediately and there was no lag time (T=0). For the capsules, however, the lag time, namely the dissolving of the capsule shells of both sizes (no 2 and 3), was 1 minute (T=1). In order to discuss the profiles more easily, the times $t_{50\%}$ and $t_{90\%}$ were calculated according to equation 36, chapter 4.12.

5.3.1. Dissolution of the model drug caffeine

The calculated variables M_0, T, a and b of the Weibull equation for all formulations containing caffeine (see chapter 3.3.2.1. equation 19), the correlation coefficient r as well as $t_{50\%}$ and $t_{90\%}$ (see chapter 4.12) are summerized in table 5.5.

Table 5.5.: The dissolution profiles of the formulations containing caffeine (n=6 for each formulation) can be described with the Weibull equation.

(n=6)	r	$t_{50\%}$ (min)	$t_{90\%}$ (min)	M_0 (%)	T (min)	a	b
Capsule 10% (w/w)	0.999	2.39	4.01	101.9	1	2.41	1.49
Capsule 50% (w/w)	0.998	3.76	6.62	101.9	1	7.78	1.63
Capsule 70% (w/w)	0.993	3.21	5.88	100.7	1	4.83	1.52
Capsule 10% (w/w), apparatus IPT	0.993	2.67	3.87	101.1	1	4.47	2.71
Capsule 70% (w/w), apparatus IPT	0.997	2.86	4.40	101.2	1	4.87	1.94
Tablet 10% (w/w), excenter	0.999	1.37	3.18	99.3	0	2.24	1.44
Tablet 50% (w/w), excenter	0.992	9.60	26.1	101.6	0	20.47	1.16
Tablet 70% (w/w), excenter	0.989	13.0	33.4	101.4	0	35.66	1.24
Tablet 10% (w/w), presster	0.999	2.25	4.45	104.5	0	5.74	1.63
Tablet 50% (w/w), presster	0.990	6.73	17.03	101.3	0	16.27	1.26
Tablet 70% (w/w), presster	0.993	12.1	31.6	100.2	0	31.84	1.24
Tablet 50% (w/w), mixture placebo and granulate 74% (w/w), excenter	0.987	6.23	15.8	101.0	0	14.69	1.26

M_0 (%) corresponds with the total amount of drug released. T describes the lag-time of the drug release, a describes the time dependence and b expresses the shape of the dissolution curve. The time when 50% and 90%, respectively, was released, was calculated according to the inverse function of the Weibull equation. r stands for the correlation coefficient.

5.3.1.1. Influenece of the dissolution apparatus on dissolution

In order to get an insight of the influence of the dissolution apparatus on dissolution, an apparatus, which was developed in the IPT (see chapter 4.13.) was investigated and compared to the USP apparatus. Capsules containing 10% (w/w) and 70% (w/w) of caffeine were released. The results are shown in figure 5.4. and figure 5.5.

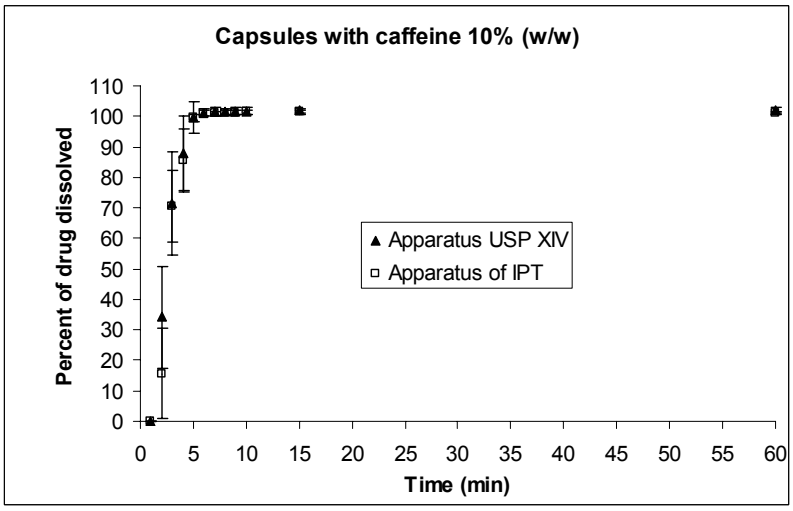


Figure 5.4.: The capsule formulation with 10% (w/w) of caffeine released on an apparatus built in the Institute of Pharmaceutical Technology (IPT) and the standard apparatus according to the specifications of USP XXIV. The bars represent the standard deviation of the mean (n=6).

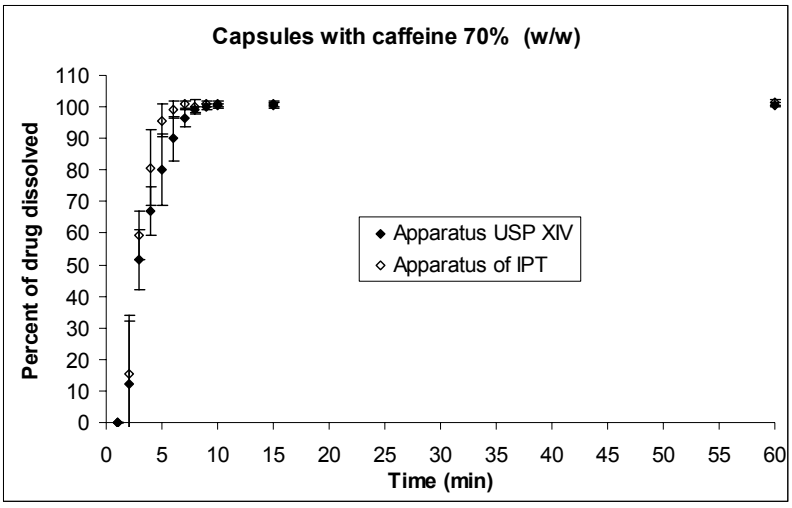


Figure 5.5.: The capsule formulation with 70% (w/w) of caffeine released on an apparatus built in the Institute of Pharmaceutical Technology (IPT) and the standard apparatus according to the specifications of USP XXIV. The bars represent the standard deviation of the mean (n=6).

The $t_{50\%}$ - and the $t_{90\%}$ - values of the capsules containing 10% (w/w) of caffeine accounted for approximately 2.5 minutes and for about 4 minutes, respectively, independently of the apparatus.

When both curves were investigated using a two sided t-test with a confidence interval of 5%, no significance could be found between the dissolution profiles although the *b* - and *a* - parameters differ. The profiles of the capsules containing 70% (w/w) of caffeine are significantly different after 5 minutes. At this stage, however, the capsules that were tested in the apparatus of the IPT have already released 95% (w/w) of caffeine, while the release of the other capsules tested in the apparatus according to the specifications of USP XXIV was just about 80% (w/w) of caffeine. The standard deviation of the two dissolution curves of the capsules released in the apparatus of the IPT are lower than the ones of the two capsules released in the apparatus according to the specifications of USP XXIV. This can be explained with the magnetic stirrer in the apparatus of the IPT, which additionally homogenizes the concentration in the dissolution media. On the other hand an additional stirring could lead to conditions that are less physiological, because the peristaltic movement, which is imitated, is in fact very smooth (Levy, 1963). Recapitulating it can be said that the apparatus of the IPT does not seem to have an outstanding advantage over the apparatus according to the specifications of USP XXIV. Furthermore, the work is meant to be close to an industrial setting. Therefore, the standard apparatus according to the specifications of USP XXIV was preferred for all further dissolution experiments.

5.3.1.2. Dissolution of the capsule formulation

The dissolution profiles of the capsule formulations containing caffeine are shown in figure 5.6.

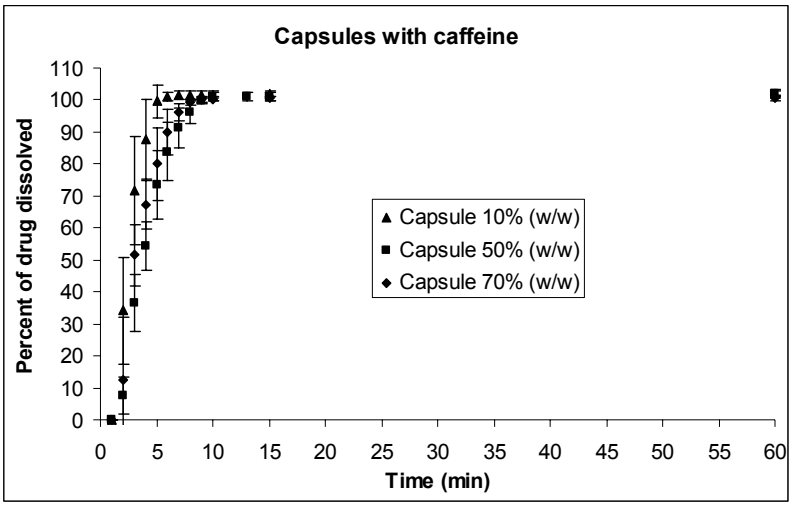


Figure 5.6.: The dissolution profiles of the capsules containing 10%, 50% and 70% (w/w), respectively, of the model substance caffeine. The bars represent the standard deviation of the mean (n=6).

The capsule formulations with 10%, 50% and 70% (w/w) of caffeine showed a similar dissolution profile. After approximately 3 min 50% of the drug was released and after approximately 6 min 90% (w/w) of the drug was released. The shapes of the dissolution curves are alike. They tend to describe a sigmoidal progression ($b \approx 1.5$ for all formulations). Generally, the capsule formulation can be considered to be robust, i.e. independently of the drug load, the drug is released more or less at the

same time. The difference in time between the $t_{90\%}$ - value of the slowest (Capsules 50% (w/w)) and the fastest release (Capsules 10% (w/w)) is just about 2.5 minutes. Such a formulation could be used in early clinical trials for the dosage finding: when the dose is increased in order to find the optimal therapeutic effect with a minimum of side effects the whole amount should be released at the same time independently of the drug load. In such a case, no decrease of the bioavailability has to be expected from a technological point of view.

The consistent release of caffeine can be explained by the fact that the powder components, which all have a good solubility and a good wettability are in a loose and disperse state. The water can penetrate and easily wet the large surface of the hardly compressed powder mixture and all components are solubilised immediately.

However, looking in detail at the different dissolution profiles, there are differences in the drug release of the different formulations. Those differences are marginal and they are assumed not to be relevant regarding bioavailability of the drug in the human body. Nevertheless they should briefly be discussed: the formulation containing 50% (w/w) shows in fact the slowest dissolution. This is also confirmed by the Weibull function. The *a*-parameter of 7.78 for the formulation 50% (w/w) indicates a slower dissolution than the *a*-parameter of 2.41 and 4.83, respectively, of the formulations containing 10% (w/w) and 70% (w/w) of caffeine, respectively. The matter was further investigated with a two-sided t-test with a confidence interval of 5%. At first the dissolution profiles of the capsule formulation containing 50% (w/w) and 70% (w/w) of caffeine, respectively, were compared. The two dissolution profiles differ significantly in the first four minutes of the release until 54% (w/w) is released from the capsules containing 50% (w/w) of caffeine and 67% (w/w) from the capsules containing 70% (w/w) of caffeine.

When the dissolution profiles of the capsules 10% (w/w) and the formulation 50% (w/w) are compared with a two-sided t-test, the formulations turn out to be significantly different but as mentioned before these findings are not relevant for practical application.

By comparing the dissolution profiles of the capsules 10% (w/w) and 70% (w/w), a significant difference could also be detected except for the first two minutes of the release until 34% (w/w) (capsule 10% (w/w)) and 12% (w/w) (capsule 70% (w/w)) of caffeine were dissolved.

5.3.1.3. Dissolution of the tablets (excentric press)

The dissolution profiles of the tablet formulations containing 10% (w/w), 50% (w/w) and 70% (w/w) compressed on an excentric press are shown in figure 5.7.

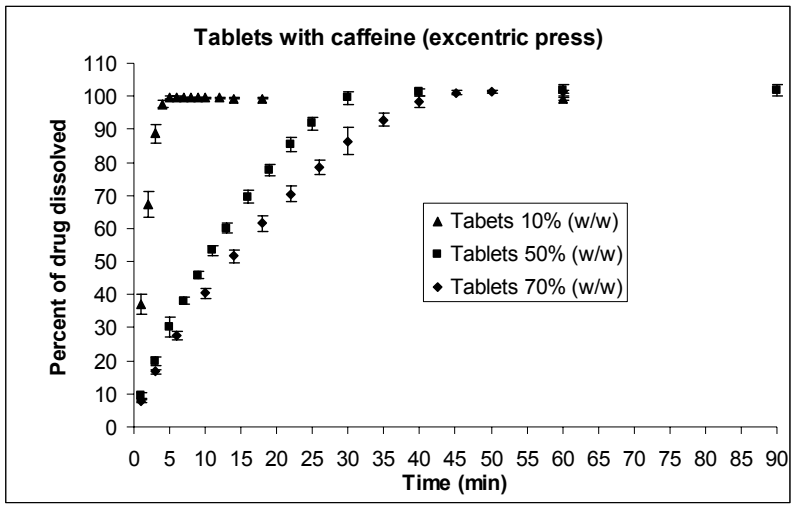


Figure 5.7.: The dissolution profiles of the tablets containing 10%, 50% and 70% (w/w), respectively, of the model substance caffeine. The bars represent the standard deviation of the mean (n=6).

The tablets 70% (w/w) showed the slowest release. 50% (w/w) of the caffeine was dissolved after 13.0 minutes and 90% (w/w) after 33.4 minutes. The speed of the release increased with a decreasing concentration of caffeine and an increasing concentration of lactose. Tablets with 50% (w/w) of caffeine released 50% (w/w) of their content after 9.60 minutes and 90% (w/w) after 26.1 minutes. The $t_{50\%}$ - and the $t_{90\%}$ - values for the tablets with 10% (w/w) of caffeine are equal to 1.37 and 3.18 minutes, respectively. When the releases of all tablets containing 10%, 50% and 70% (w/w) of caffeine were checked visually during the dissolution experiment, there was no visible disintegration of the tablet in the basket. All tablets remained compact. Therefore, a rapid extension of the tablets surface leading to a better dissolution can be excluded. The amount of excipients was constant in all formulations except for lactose. It is assumed that lactose having a contact angle (water) of 49.9°, which is lower than the one of all other excipients in this formulation and the one of caffeine (see chapter 5.2.), is wetted faster than the other components and finally wets caffeine and all other components by a kind of wicking. However, for this wetting effect the concentration of lactose has to be high enough. The caffeine has to be embedded in a continuous phase of lactose. With a sufficient amount of lactose the caffeine can easily be wetted and dissolved independently of the degree of compression. This is supported by the fact that the drug release of the tablet formulation 10% (w/w) resembles the release of the capsule formulation 10% (w/w). This becomes more obvious by comparing the *a*-and the *b*-parameters (*a*: Capsule 10% (w/w): 2.41, Tablet 10% (w/w): 2.24; *b*: Capsule 10% (w/w): 1.49, Tablet 10% (w/w): 1.44).

The percolation theory (Leuenberger et al., 1987) explains and quantifies such phenomena. In three dimensions there are two percolation thresholds, which describe three regions of the drug/excipient

system. Below the lower percolation threshold, the drug particles are embedded in a continuous phase of the excipients. Above the upper percolation threshold, the relatively low amount of excipients is embedded in a continuous phase of drug particles. Thus, in case of 10% (w/w) drug substance, it is expected that the excipients percolate the system and dominate its behaviour. In case of 70% (w/w) drug substance, it can be expected that the drug substance dominates the system. For the intermediate case of 50% (w/w) drug substance and 50% (w/w) excipients both components can percolate the system and it is difficult to give a prediction, which of the components will dominate.

For the tablets with 50% (w/w) the dissolution behaviour is more similar to the release of the tablets with 70% (w/w) of caffeine, than to the one of the tablets containing 10% (w/w) of caffeine. The fact that there is more similarity between the dissolution curves of the formulations containing 50% (w/w) and 70% (w/w) of caffeine is also supported by the *a*-parameters, which are equal to 20.47 and 35.66 for the formulations 50% (w/w) and 70% (w/w) and the *b*-parameters, which are equal to 1.16 for tablet 50% (w/w) and 1.24 for tablets 70% (w/w), as for the formulation containing 10% (w/w) of caffeine, *a* accounts for 2.24 and *b* for 1.44. In the case of the tablet formulation 50% (w/w) in contrast to the tablet formulation 10% (w/w) the critical amount of lactose is not yet reached to achieve a fast dissolution mediated through an improved wetting.

Despite the good wettability of caffeine and its high solubility there is a difference in the releases of the tablet formulations. Thus, this tablet formulation cannot be considered to be entirely robust in the range of 10% (w/w) to 70% (w/w) of drug load.

5.3.1.4. Dissolution of a mixture placebo and verum

To get a better insight in the dissolution behaviour of the tablet formulations and in the wetting effect of lactose in particular, the placebo granulate (placebo) was mixed with the granulate containing 74% (w/w) of caffeine (verum) in order to get a tablet with a content of 50% (w/w) of caffeine. The tablet consisting of the verum and the placebo showed a faster dissolution than the tablet made of the original granulate with 53% (w/w) of caffeine. After 6.23 minutes 50% (w/w) of the caffeine was released and after 15.8 minutes 90% (w/w) as opposed to the original formulation, where $t_{50\%}$ = 9.60 min and $t_{90\%}$ = 26.1 min (see figure 5.8.).

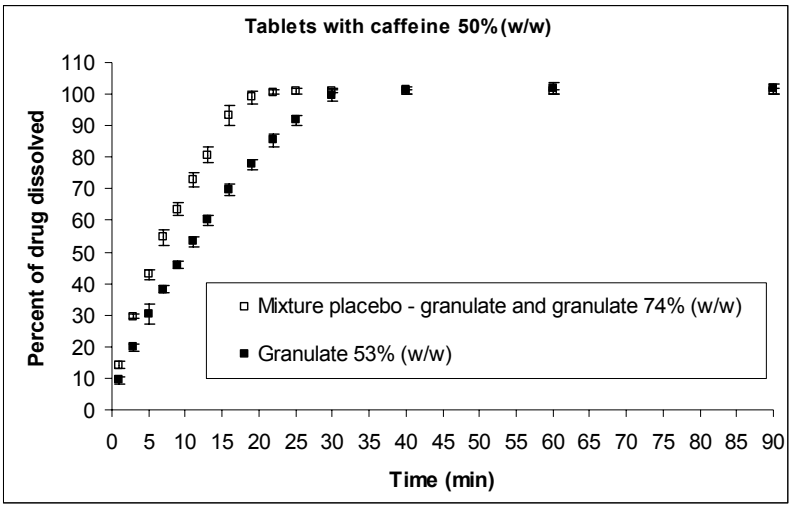


Figure 5.8.: The dissolution profiles of the two tablet formulations containing 50% (w/w) corresponding to a dose of 78.0 mg of caffeine. One formulation is made of a mixture (placebo-granulate and granulate with caffeine 74% (w/w)) the other is made of a granulate 53% (w/w). Both tablets are compressed on the same excentric press.

For both formulations no visible disintegration in the basket during the dissolution could be detected. As no visible disintegration occurred, the improved dissolution is improbably a result of a sudden enlargement of the surface but an improved wetting effect. It is assumed that for the tablets consisting of placebo and verum, the selectively higher concentration of lactose (mediated through the placebo) shows a better wicking effect than the same amount of equally dispersed lactose does in the tablets made of the original granulate with 53% (w/w) of caffeine. Obviously, the caffeine also having a partially higher concentration in the formulation consisting of verum and placebo is wetted more easily and a faster dissolution occurs. Astonishingly the effect mediated through a partial higher concentration of lactose is more dominant than the effect that could have been mediated through a partial higher concentration of caffeine, i.e. a delayed dissolution.

The shapes of both curves seem to be equal with a sigmoidal progression (*b* = 1.26 for verum and placebo); *b* = 1.16 for granulate 53% (w/w)). The difference in time of the release is expressed by the *a*-parameter, which is 14.69 for the formulation made of the placebo and verum and which is 20.47 for the formulation made of the granulte 53% (w/w) of caffeine.

5.3.1.5. Comparison Presster™ versus excentric press

The tablet formulation 70% (w/w), the formulation 50% (w/w) made of the placebo granulate (placebo) and the granulate with 74% (w/w) of caffeine (verum) and furthermore a new formulation of placebo and verum containing 10% (w/w) of caffeine were compressed on the Presster™ simulating a rotary press (Korsch PH 363). The dissolution profiles of the different formulations compressed on the Presster™ were compared to the ones of the tablets manufactured on the excentric press (see chapter 5.3.1.3.). They are shown in figure 5.9.

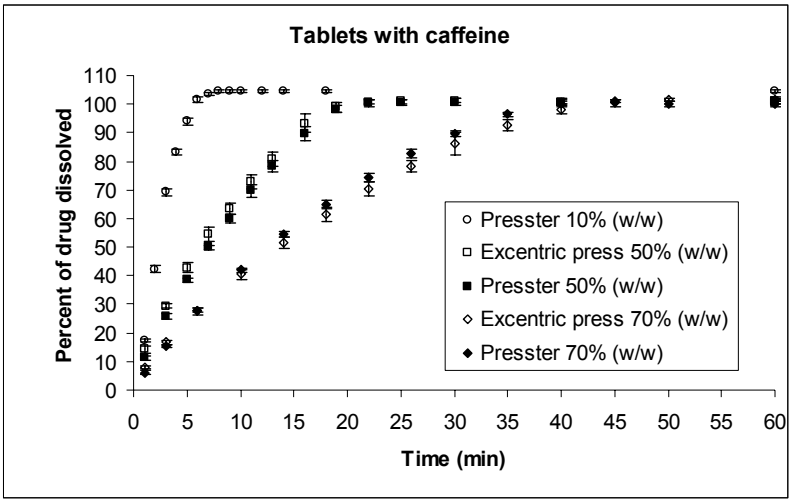


Figure 5.9.: The dissolution profiles of the capsules containing 10%, 50% and 70% (w/w), respectively, of the model substance caffeine compressed on a compaction simulator Presster™ and an excentric press. The bars represent the standard deviation of the mean (n=6).

The profiles of the formulations compressed on the Presster™ and the excentric press show the same sigmoidal progression. For the formulation 50% (w/w) *b* = 1.26 and for the formulation 70% (w/w) *b* = 1.24. A difference can be observed regarding the *a*-parameters. For the formulation 50% (w/w) *a* accounts for 14.69 (excentric press) and 16.27 (Presster™), where for the formulation 70% (w/w) *a* accounts for 35.66 (excentric press) and 31.84 (Presster™). For the formulation with 50% (w/w) compressed on the excentric press $t_{50\%}$ is equal to 9.60 min and $t_{90\%}$ is equal to 26.1 min, whereas for same formulation compressed on the Presster™ $t_{50\%}$ is equal to 6.73 min and $t_{90\%}$ is equal to 17.03 min. For the formulation containing 70% (w/w) of caffeine compressed on the excentric press, $t_{50\%}$ is equal to 13.0 min and $t_{90\%}$ is equal to 33.4 min whereas for same formulation compressed on the Presster™ $t_{50\%}$ is equal to 12.1 min and $t_{90\%}$ is equal to 31.6 min. The formulation 50% (w/w) compressed on the excentric press seems to have a slower release than the same formulation compressed on the Presster™, whereas the formulation 70% (w/w) compressed on the Presster™ seems to have a faster release than the same formulation compressed on the excentric press. There is no feasible reason why on the one hand the dissolution of the tablets with 50% (w/w) of caffeine is faster when the tablet is manufactured on the Presster™ whereas on the other hand the release of the tablet 70% (w/w) is faster when it is produced on the excentric press. Non-excludable experimental variations could be a possible reason.

In order to compare the dissolution curves a two-sided t-test was applied with a confidence interval of 5%. The dissolution profiles of the tablets with 50% (w/w) of caffeine turned out to be significantly different from one another. The profiles of the tablets with 70% (w/w) of caffeine differ significantly with the exception of the time between 6 and 10 minutes. Because a compression on a Presster™ is different than a compression on an excentric press (see chapter 3.8.3.), different physico-chemical properties of a compact and consequently other dissolution properties can be expected. The result can be considered as a hint for such a different behaviour although in this case there is no striking difference between the formulations at a first glance. Further experiments are needed with other model drugs or systems, which may be more sensitive to dissimilar manufacturing processes with respect to dissolution, if this matter is of further interest.

5.3.2. Dissolution of the model drug diclofenac sodium

The calculated variables M_0, T, a and b of the Weibull equation for all formulations containing caffeine (see chapter 3.3.2.1. equation 19), the correlation coefficient r as well as $t_{50\%}$ and $t_{90\%}$ (see chapter 4.12) are summerized in table 5.6.

Table 5.6.: The dissolution profiles of the formulations containing diclofenac sodium (n=6 for each formulation) can be described with the Weibull equation.

(n=6)	r	$t_{50\%}$ (min)	$t_{90\%}$ (min)	M_0 (%)	T (min)	a	B
Capsule 10% (w/w)	0.998	5.00	8.75	98.3	1	19.07	1.88
Capsule 32% (w/w)	0.999	10.3	19.4	100.6	1	68.47	1.73
Capsule 50% (w/w)	0.999	22.5	33.9	96.8	1	15595	3.04
Capsule 70% (w/w)	0.998	31.2	47.8	99.4	1	18817	2.78
Tablet 10% (w/w),	0.993	3.60	8.77	99.3	0	8.26	1.37
Tablet 32% (w/w)	0.997	6.55	15.7	100.6	0	18.73	1.36
Tablet 50% (w/w)	0.997	13.4	31.7	98.0	0	61.96	1.46
Tablet 70% (w/w)	0.997	20.1	45.4	100.3	0	118.8	1.47
Olfen	0.941	19.9	35.3	98.6	14	7.85	0.97

M_0 (%) corresponds with the total amount of drug released. T describes the lag-time of the drug release, a describes the time dependence and b expresses the shape of the dissolution curve. The time when 50% and 90%, respectively, was released, was calculated according to the inverse function of the Weibull equation. r stands for the correlation coefficient.

5.3.2.1. Dissolution of the capsule formulations

The dissolution profiles of the capsules with 10%, 32%, 50% and 70% (w/w) of diclofenac sodium are shown in figure 5.10.

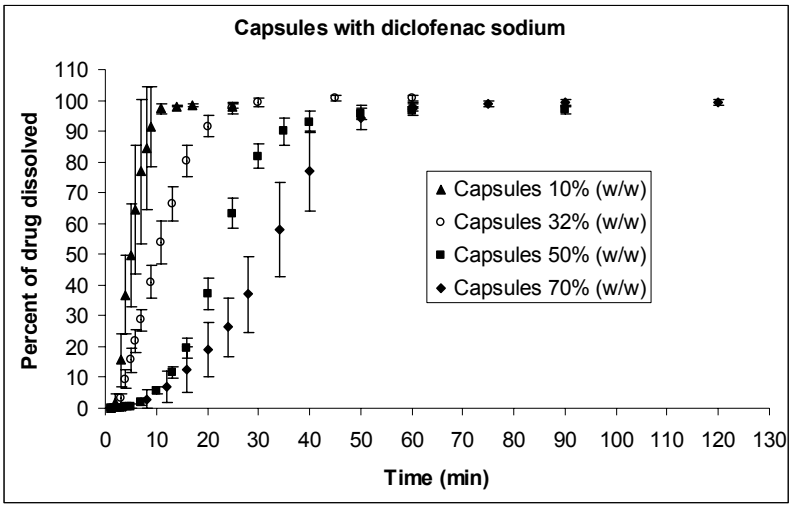


Figure 5.10.: The dissolution profiles of the capsules containing 10%, 32%, 50% and 70% (w/w), respectively, of the model substance diclofenac sodium. The bars represent the standard deviation of the mean (n=6).

Although the time, when 50% (w/w) and 90% (w/w), respectively, were released from the capsules containing 10% (w/w) and 32% (w/w) of diclofenac sodium, is different, the shape of the curves according to the *b*-parameter is quite similar as it is 1.88 for the capsule 10% (w/w) and 1.73 for the capsule 32% (w/w). When the dose is increased a change of the shape occurs. For the capsules 50% and 70% (w/w) *b* accounts for 3.04 and 2.78, respectively, which indicates that the progression of the dissolution curve gets more sigmoidal. The similarity of the two curves with the lower and the two with the higher concentration can also be observed regarding the *a*-parameters. For the capsules 10% (w/w) and 32% (w/w) it accounts for 19.07 and 68.47, respectively but for the capsules 50% (w/w) and 70% (w/w) *a* is equal to 15595 and 18817. This difference, however, between the two capsule formulations with the lower concentration and the two with the higher concentration can be explained with the percolation theory (see chapter 5.3.1.3.) as the concentration of diclofenac sodium increases determining the behaviour of the formulation as opposed to the formulation with a lower concentration where diclofenac sodium is likely to be embedded in a continuous phase of lactose.

The times when the drug is released is depending on the drug load. 50% (w/w) of the drug is released after 5.00, 10.3, 22.5 and 31.2 min and 90% (w/w) after 8.75, 19.4, 33.9 and 47.8 minutes with an increasing concentration of diclofenac sodium. The capsule formulation containing diclofenac sodium cannot be considered to be robust as the dissolution is depending on the drug load.

5.3.2.2. Dissolution of the tablet formulations

The dissolution profiles of the tablet formulations with 10%, 32%, 50% and 70% (w/w) of diclofenac sodium are shown in figure 5.11.

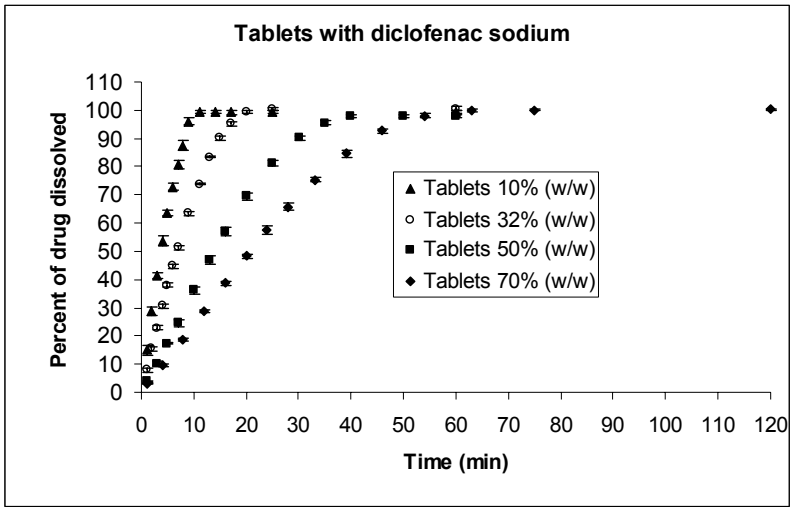


Figure 5.11.: The dissolution profiles of the tablets containing 10%, 32%, 50% and 70% (w/w), respectively, of the model substance diclofenac sodium. The bars represent the standard deviation of the mean (n=6).

The higher the amount of the drug released is, the more similar the dissolution times of the tablets with diclofenac sodium get to the dissolution times of the capsules containing the same amount of model drug: 50% (w/w) of diclofanc sodium is released after 3.60 min (tablet 10% (w/w)), 6.55 min (tablet 32% (w/w)), 13.4 min (tablet 50%(w/w)) and 20.1 min (tablet 70% (w/w)). Comparing those values to the values found for the capsule formulations, it becomes obvious that the release of the tablets is faster at the beginning. But then, regarding the time when 90% (w/w) of diclofenac sodium is released, there is more similarity to the capsule formulation: 90% (w/w) is released after 8.77 min (tablet 10% (w/w)), 15.7 min (tablet 32% (w/w)), 31.7 min (tablet 50% (w/w)) and 45.4 min (tablet 70% (w/w)). This difference between capsules and tablets is due to the different shapes of the dissolution curves. The dissolution profiles of the capsules tend to be more sigmoidal than the corresponding profiles of the tablets. This leads to a more delayed release of the capsules at the beginning of the dissolution.
For the tablet formulations containing 10% and 32% (w/w) of diclofenac sodium b = 1.37 and b = 1.36, respectively, as well as for a drug load of 50% and 70% (w/w), where b = 1.46 and b = 1.47. According to those numbers, a similarity of the two curves with the lower and the two with the higher concentration can also be observed as in case of the capsule formulations. This matter can also be explained with the percolation theory (see chapter 5.3.1.3.) as the concentration of diclofenac sodium increases determining the behaviour of the formulation as opposed to the formulation with a lower concentration where diclofenac sodium is likely to be embedded in a continuous phase of lactose. Regarding the values of $t_{50\%}$ and $t_{90\%}$ the difference in dissolution times of the two formulations having a lower concentration of diclofenac sodium is smaller (2.95 min regarding $t_{50\%}$ and 6.93 min regarding $t_{90\%}$) as well as the difference in dissolution times of the two formulations with the higher drug load (6.7

min regarding $t_{50\%}$ and 13.7 min regarding $t_{90\%}$) than the difference in dissolution time of the formulations with a drug load of 32% (w/w) and 50% (w/w), respectively (6.85 min regarding $t_{50\%}$ and 16 min regarding $t_{90\%}$).

For the formulation containing 10% (w/w) of diclofenac sodium *a* = 8.26 and for the formulation containing 32 % (w/w) of diclofenac sodium *a* = 18.73, whereas *a* = 61.69 and 118.8 for the formulations containing 50% (w/w) and 70% (w/w) of diclofenac sodium. A sudden increase of the a-parameter can be observed between a drug load of 32% (w/w) and 50% (w/w) but also between 50% (w/w) and 70% (w/w). The a - parameters, however, do not discriminate clearly the two formulations with a lower drug load from the ones with a higher drug load.

The tablet formulation containing diclofenac sodium cannot be considered to be robust as the dissolution is depending on the drug load.

5.3.2.3. Comparison to market formulation

The tablet formulation 32% (w/w) contains 50 mg of diclofenac sodium. It was compared to the market formulation Olfen®-50 of the company Mepha (Aesch, Switzerland). The profiles of both releases are shown in figure 5.12.

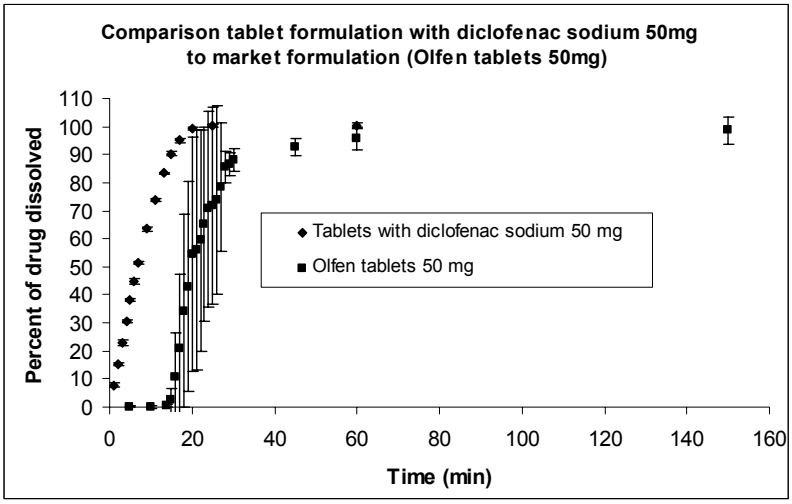


Figure 5.12.: The dissolution profile of Olfen®-tablets (50 mg) is compared to the one of the tablet formulation containing diclofenac sodium 32% (w/w) corresponding to a dose of 50 mg. The bars represent the standard deviation of the mean (n=6).

Most tablets containing diclofenac sodium on the market have an enteric coating, which explains the lag time of 14 minutes in contrast to tablet produced in the IPT, which was not coated.

When the lag-time is substracted, 50% (w/w) of the diclofenac sodium of the Olfen®- tablets is released after 5.9 min and 90% (w/w) after 21.4 min. The tablets produced in the IPT release 50% (w/w) after 6.55 min and 90% (w/w) after 15.7 min. At the beginning they seem to have the same speed of dissolution but the average speed of release of the Olfen®-formulation seems to be a little slower than the one of the formulation of the IPT. It was difficult to fit the dissolution profile of the

Olfen®- tablets properly because of the remarkable variability in the dissolution of the single Olfen®-tablets, which becomes manifest in the huge standard deviations and the comparatively bad correlation coefficient of 0.941. The shape, however, seems to a little steeper than a sigmoidal profile would be (*b* = 0.97). The formulation from the IPT turns out to be sigmoidal (*b* = 1.36). The parameter *a* accounts for 7.85 for Olfen® where it is 18.73 for the formulation of the IPT. The formulation of the IPT, however, seems to have an average release, which is faster than the one of the Olfen®-tablets although the amount of *a* is bigger. This clearly demonstrates that *a* and *b* always have to be interpreted together in relation to each other. If $b < 1$ a change of *a* would have a stronger effect what the steepness of the dissolution curve is concerned than it would have if *a* was changed by the same amount in a profile where $b > 1$. It is evident that that is no relevant difference in the dissolution behaviour if the lag time of Olfen® tablets is not taken into account.

5.3.3. Dissolution of the model drug proquazone

The calculated variables M_0, T, a and b of the Weibull equation for all formulations containing proquazone (see chapter 3.3.2.1. equation 19), the correlation coefficient r as well as $t_{50\%}$ and $t_{90\%}$ (see chapter 4.12) are summerized in table 5.7.

Table 5.7.: The dissolution profiles of the formulations containing proquazone (n=6 for each formulation) can be described with the Weibull equation.

(n=6)	r	$t_{50\%}$ (min)	$t_{90\%}$ (min)	M_0 (%)	T (min)	a	b
Capsule 10% (w/w)	0.991	3.33	6.17	99.9	1	5.18	1.51
Capsule 50% (w/w)	0.995	44.9	207	99.3	1	28.00	0.79
Capsule 70% (w/w)	0.997	308	849	101.5	1	1069	1.15
Tablet 50% (w/w)	0.997	2.35	5.27	99.9	0	5.15	1.49
Tablet 70% (w/w)	0.997	2.22	4.76	100	0	5.01	1.56
Capsule 50% (w/w), handfilled	0.999	43.1	130	98.7	1	57.34	1
Capsule filled with granulate 74% (w/w)	0.997	4.71	9.04	99.4	1	11.18	1.57
Capsule mixture 50% (w/w), compressed	0.998	439	1220	100	0	1787	1.17

M_0 (%) corresponds with the total amount of drug released. T describes the lag-time of the drug release, a describes the time dependence and b expresses the shape of the dissolution curve. The time when 50% and 90%, respectively, was released, was calculated according to the inverse function of the Weibull equation. r stands for the correlation coefficient.

5.3.3.1. Dissolution of the capsule formulations

The dissolution profiles of the capsules containing 10%, 50% and 70% (w/w) are shown in figure 5.13. and figure 5.14.

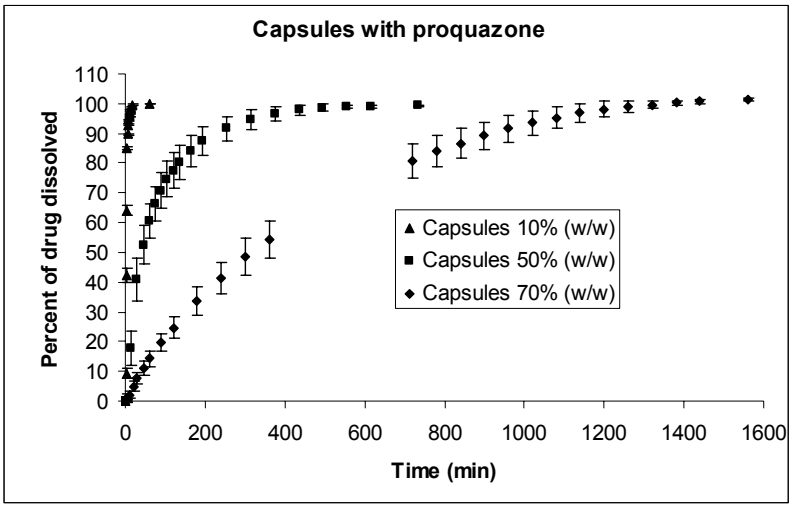


Figure 5.13.: The dissolution profiles of the capsules containing 10%, 50% and 70% (w/w), respectively, of the model substance porquazone. The bars represent the standard deviation of the mean (n=6).

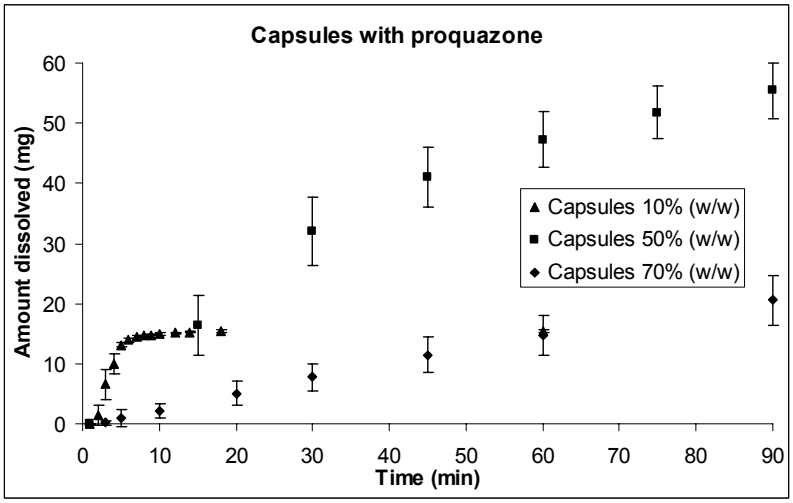


Figure 5.14.: The dissolution profiles of the capsules containing 10%, 50% and 70% (w/w), respectively, of the model substance porquazone corresponding to a dose of 15.6 mg, 50 mg, 78.0 mg and 109.2 mg. The bars represent the standard deviation of the mean (n=6).

The capsule containing 70% (w/w) of proquazone showed a very slow dissolution rate. After approximately 308 min 50% (w/w) and after about 849 min 90% (w/w) of the proquazone in the formulation was released. The capsule formulation containing 50% (w/w) of proquazone showed still a slow release compared to the formulation containing 10% (w/w) of proquazone: after 44.9 min 50% (w/w) and after 207 min 90% (w/w) of the drug in capsule 50% (w/w) was released, whereas the time

for a release of 50% (w/w) and 90% (w/w) of the model drug in capsule 10% (w/w) constituted about 3.33 and 6.17 min, respectively. The shapes of the dissolution profiles of capsule 70% (w/w) (*b* =1.15) and 10% (w/w) (*b* =1.51) tend to describe a sigmoidal progression, whereas the dissolution profile of capsule 50% (w/w) showed a steeper progression than the sigmoidal profiles (*b* = 0.79).
The fast drug release of capsule 10% (w/w) compared to the capsule 70% (w/w) can be explained with the percolation theory (see chapter 5.3.1.3.). In case of 70% (w/w) drug substance it can be expected that the drug substance dominates the system. For the intermediate case of 50% (w/w) drug substance and 50% (w/w) excipients both components percolate the system and it is difficult to give a prediction which of the components will dominate. The drug substance proquazone shows a low solubility and a poor wettability. It seems to be evident, that if the drug substance is embedded in a well soluble powder matrix of the excipients used, the dissolution rate of the drug substance can be increased. However, in case of a higher dose 78.2 mg (50% w/w) and 108.8 mg (70% w/w) respectively, the dissolution rate is not sufficient fast. It is evident that the basic capsule formulation is not a robust one as the dissolution rate depends significantly on the drug load.

5.3.3.2. Dissolution profiles of the tablet formulations

The dissolution profiles of the tablet formulations containing 50% and 70% (w/w) of proquazone, respectively, are summarised in figure 5.15.

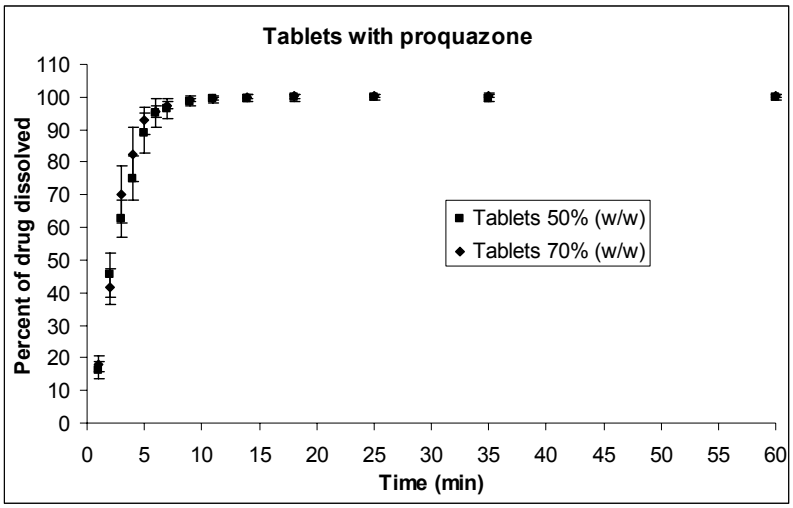


Figure 5.15.: The dissolution profiles of the tablets containing proquazone 50% and 70% (w/w), respectively. The bars represent the standard deviation of the mean (n=6).

The drug release of tablets produced from two granulates (granulate 53% (w/w) and 74% (w/w)) after wet granulation is much faster than in case of the capsule formulations. It could be observed that all tablets swelled and were disintegrated rapidly at the beginning of their dissolution process, offering more surface area available for dissolution. Tablet 50% (w/w) and 70% (w/w) were released after 2.35 min and 2.22 min, respectively, for 50% (w/w) and after 5.27 min and 4.76 min, respectively, for 90%

(w/w) of their content. When the values of the dissolution profiles of the tablets 50% (w/w) and 70% (w/w), respectively, were investigated with a two-sided t-test with a confidence interval of 5% no significance could be detected.

The difference in the dissolution behaviour is more than impressive compared to the capsule formulations with an equivalent amount of drug substance: the factor of dissolution enhancement for $t_{50\%}$ (min) corresponds in this comparison between 70% (w/w) drug load tablets versus capsules and 50% (w/w) drug load tablets versus capsules to 308/2.22 = 139 and to 44.9/2.35 = 19.1, respectively.

Surface properties of a system can be influenced by different excipients coating or embedding a drug or by various types of matrixes formed with different proportions of drug and excipients (Rowe, 1988b; Planinsek et al., 2000). It is evident that the improvement of the dissolution rate is a result of the wet granulation process, which coats the poorly wettable drug substance with the well wettable excipients. In the contrast of percolation theory the well wettable coating of the excipients forms a solvent matrix, i.e. a percolating phase. Thus the explanation is not in contradiction to the explanation given for the dissolution behaviour of the capsule formulation in chapter 5.3.3.1. It is also impressive that the basic tablet formulation is a robust one and the dissolution rate does not depend on the drug load in the range of 50% (w/w) to 70% (w/w).

5.3.3.3. Dissolution profile of additional formulations

In order to get a better insight of the difference in the dissolution behaviour of the capsule and tablet formulations studied, the following additional formulations were prepared (see figure 5.16.):

- preparation of a capsule formulation with the granulate 74% (w/w) used for the tablet formulations 70% (w/w). This formulation was prepared by hand filling.
- preparation of hand filled capsules with the powder mixture used for the preparation of capsule 50% (w/w).
- Preparation of tablets with the powder mixture used for the preparation of the capsule formulation 50% (w/w). These tablets were made with the Zwick®Universal Testing Instrument.

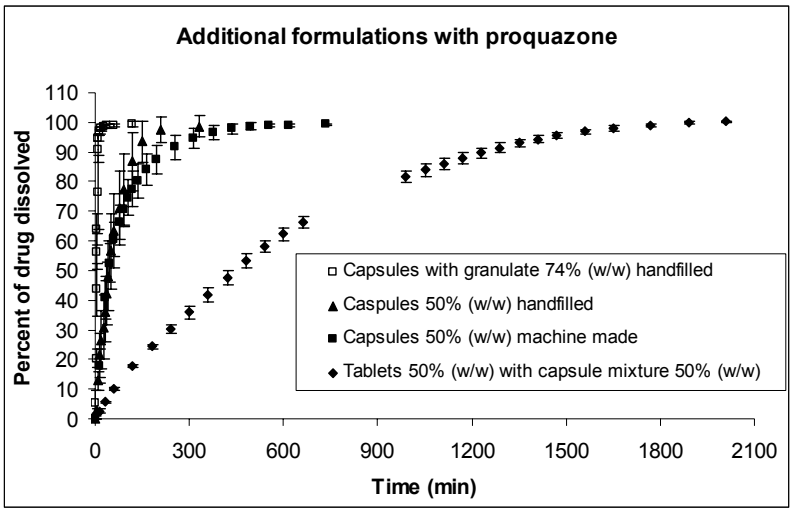


Figure 5.16.: Dissolution of the additional formulations. The bars represent the standard deviation of the mean (n=6).

It is evident, that the poor wettable drug exhibits a good dissolution rate if the drug is initially prepared as a granulate. The tablets 50% (w/w) prepared from the capsule mixture 50% (w/w) showed again an extremely slow dissolution. Thus, the granulation process is the unit operation of choice improving the dissolution rate dramatically.

5.3.3.4. Effect of compaction in case of the capsule formulation

To investigate the influence of pressure that may influence the release of proquazone, hand filled capsules were made. The same powder mixture as for capsule 50% (w/w) was used. It was not possible without applying a small pressure to fill the same amount of the powder mixture by hand into size no 3 capsule shells, used with the capsule filling machine. In order to fill the powder blend 50% (w/w) loosely into a capsule shell, size no 2 was chosen for the hand filled capsules resulting more surface area of the blend available for dissolution. The dissolution rate of those capsules was faster than the release of the corresponding machine-made capsules (capsule size 3): After 43.1 min, 50% (w/w) of the drug, and after about 130.5 min, 90% (w/w) of proquazone was released. If both capsule formulations, capsule 50% (w/w) (size 3, machine filled) and 50% (w/w) (size 2, handfilled), were compared, both curves after a drug release of 50% (w/w) looked likewise. For amounts > 50% (w/w) the two profiles differ. A possible explanation could be found when the capsules were opened. Some weak clusters of condensed powder sections could be found in the machine-made capsules in contrast to the hand filled capsules. The forming of variably condensed powder sections in a compressed core is described elsewhere (Adams, 1994). Although in a capsule filling process only little compression forces occur, as compared to the production of tablets where compression forces achieve easily several kN, those condensed sections, after the majority of the looser sections of powder had already been dissolved similarly to the powder mixture in the hand filled capsules, could have been responsible for a further delayed release. To confirm this assumption, tablets were made from the same powder mixture (tablet 50%* (w/w)). The dissolution rate of these tablets was much

slower than the one of both capsules. After 439 min only 50% (w/w) and after 1220 min only 90% (w/w) of proquazone was released. Thus, the wetting effect of 49.5 % (w/w) of the well water soluble lactose in this formulation did not help to improve the dissolution rate, (i.e. the effect of pressure is negative resulting in a low porosity of the tablet and in a lower specific surface of the poorly wettable drug substance). It has to be mentioned that this formulation as in the capsule formulation does not include a disintegrant. Thus, it is not surprising that the disintegration time is 125 min. Further studies include a "direct tabletting" formulation (see chapter 5.3.4.4.). However, it is important to notice that, as far as the tablets on the basis of the (tablet) granulate formulation are concerned, no negative effect of the compression force was observed. In fact, the fastest dissolution rate was observed with the tablets prepared on the basis of the granulate formulation. Thus, it is not surprising that one of the standard procedures in the pharmaceutical industry is first the wet agglomeration process to prepare granules as an intermediate product to manufacture tablets.

5.3.4. Dissolution with the excipient UICEL

5.3.4.1. Caffeine

The calculated variables M_0, T, a and b of the Weibull equation for all formulations containing caffeine (see chapter 3.3.2.1. equation 19), the correlation coefficient r as well as $t_{50\%}$ and $t_{90\%}$ (see chapter 4.12) are summerized in table 5.8.

Table 5.8.:The dissolution profiles of the formulations containing caffeine and the excipient UICEL (n=6 for each formulation) can be described with the Weibull equation.

(n=6)	r	$t_{50\%}$ (min)	$t_{90\%}$ (min)	M_0 (%)	T (min)	a	b
Capsule 70% (w/w), handfilled	0.997	2.46	4.43	100.8	1	2.47	1.39
Capsule 70% (w/w), machine filled	0.999	2.49	4.05	100.3	1	2.81	1.66
Capsule 70% (w/w), compressed to a tablet	0.999	0.49	0.73	101.2	0	0.175	3.05

M_0 (%) corresponds with the total amount of drug released. T describes the lag-time of the drug release, a describes the time dependence and b expresses the shape of the dissolution curve. The time when 50% and 90%, respectively, was released, was calculated according to the inverse function of the Weibull equation. r stands for the correlation coefficient.

The dissolution profiles of the formulations with the model drug caffeine and the excipient UICEL are shown in figure 5.9.

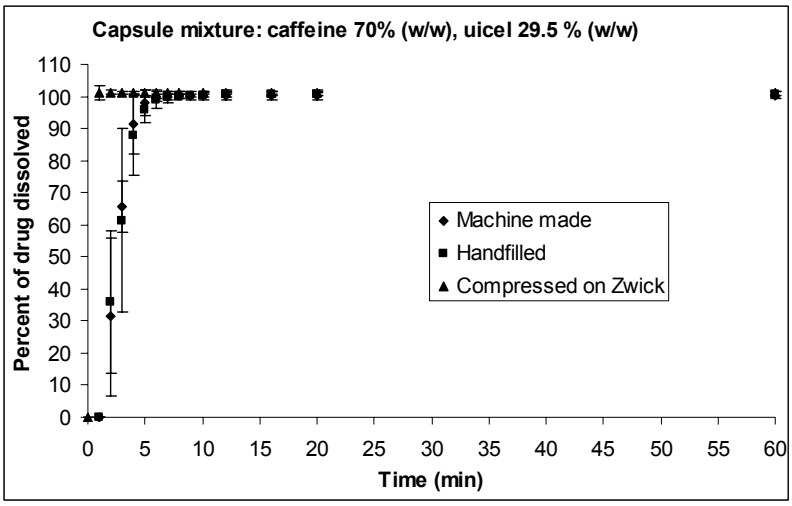


Table 5.9.: The dissolution of the capsule formulation containing 70% (w/w) of caffeine, 29.5% (w/w) of UICEL and 0.5% (w/w) of magnesiumstearte. It was filled into capsule shells by hand and by a capsule filler. Furthermore it was compressed. The bars represent the standard deviation of the mean (n=6).

The capsules 70% (w/w), handfilled, released 50% (w/w) of caffeine after 2.46 min and 90% (w/w) after 4.43 min. The same capsule mixture, which was filled with the capsule filling equipement into capsule shells, released 50% (w/w) of caffeine after 2.49 min and 90% (w/w) after 4.05 min. The shape of the curve is sigmoidal as *b* accounts for 1.39 for the handfilled formulation and 1.66 for the one produced on the capsule filler. The parameter *a*, which describes the time dependence of the dissolution process accounts 2.47 for the handfilled capsule and 2.81 for the one, which was machine filled. Although the machine-made capsules seemed to have a faster release than the handfilled ones no significance could be shown comparing the tow dissolution profiles applying a tow sided t-test with an interval of confidence of 5%. When the formulation is compared to the original machine-made capsule formulation with the excipient lactose (see chapter 5.3.1.2.) it is found that 50% (w/w) of the formulations containing 50% (w/w) or 70% (w/w) of caffeine is released on the average after about 3.5 min and 90% (w/w) after about 6 min. Just the formulation containing 10% (w/w) of caffeine, 89.5% of lactose and 0.5% (w/w) of magnesiumstearate shows about the same dissolution time than the formulation consisting of 70% (w/w) of caffeine, 29.5% (w/w) of UICEL and 0.5% (w/w) of magnesiumstearate. The difference in drug release can be explained by the fact that UICEL has a contact angle of 41.1° (water), while the contact angle of lactose accounts for 49.9° (water). It is evident that UICEL is able to achieve a better wetting of the model drug. Furthermore, UICEL shows very good disintegration properties in contrast to lactose that does not have a disintegrating effect. It could be shown that the disintegration properties of UICEL could develop further causing an accelerated release when the capsule mixture was compressed to tablets. After 0.49 min 50% (w/w) of the caffeine was released and after 0.73 min 90% (w/w). The profile got more sigmoidal compared to the one of the capsule formulations as *b* is equal to 3.05 and *a* accounts for 0.175. Additionally the release of the compressed formulation is faster than the one of the same formulation in a hard gelatine capsule shell. This could be due to the fact that a tablet does not have a capsule shell, which first has

to be dissolved and as long as the remains of the shell cover parts of the powder bulk the whole surface is not yet totally available for the dissolution media. In the case of the model drug caffeine in combination with UICEL, however, a compression of the formulation really seems to accelerate the dissolution dramatically.
UICEL turns out to be a suitable excipient not only for a direct compression but also as filler in a capsule formulation.

5.3.4.2. Diclofenac sodium

The calculated variables M_0, T, a and b of the Weibull equation for all formulations containing diclofenac sodium (see chapter 3.3.2.1. equation 19), the correlation coefficient r as well as $t_{50\%}$ and $t_{90\%}$ (see chapter 4.12) are summerized in table 5.10.

Table 5.10.: The dissolution profiles of the formulations containing diclofenac sodium and UICEL (n=6 for each formulation) can be described with the Weibull equation.

(n=6)	r	$t_{50\%}$ (min)	$t_{90\%}$ (min)	M_0 (%)	T (min)	a	b
Capsule 70% (w/w), handfilled	0.998	12.2	24.9	100.2	1	65.95	1.58
Capsule 70% (w/w), machine filled	0.999	10.0	19.5	99.9	1	53.95	1.65
Capsule 70% (w/w), compressed to a tablet	0.986	147	436	100.9	0	332.2	1.09
Tablets 70% (w/w), UICEL 20% (w/w) internal phase	0.997	20.8	46.4	99.8	0	135.7	1.50
Tablets 70% (w/w), UICEL 15% (w/w) internal phase, 5% (w/w) external phase	0.995	22.3	49.6	100.1	0	149.7	1.50

M_0 (%) corresponds with the total amount of drug released. T describes the lag-time of the drug release, a describes the time dependence and b expresses the shape of the dissolution curve. The time when 50% and 90%, respectively, was released, was calculated according to the inverse function of the Weibull equation. r stands for the correlation coefficient.

The capsule formulation 70% (w/w) that were filled by hand released 50% (w/w) of diclofenac sodium after 12.2 min and 90% (w/w) after 24.9 min. A similar profile is received looking at the capsules manufactured with the capsule filler. After 10.0 min 50% (w/w) and after 19.5 min 90% (w/w) of the diclofenac sodium were released. (see figure 5.17.).

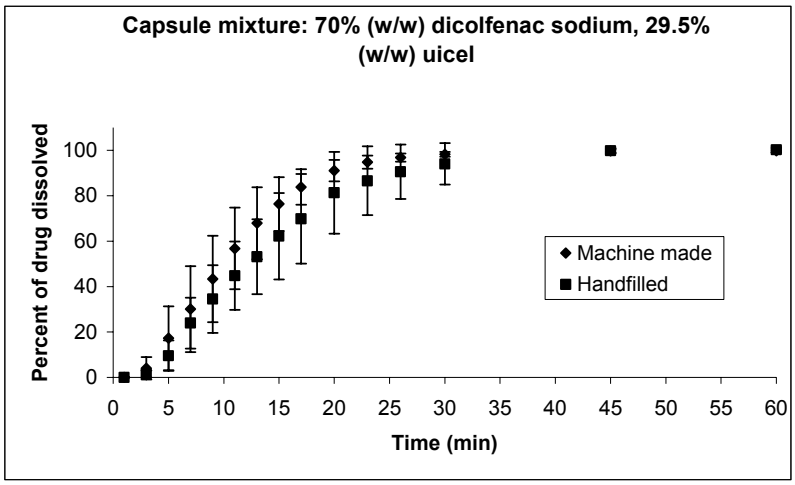


Figure 5.17.: The dissolution of the capsule formulation containing 70% (w/w) of diclofenac sodium, 29.5% (w/w) of UICEL and 0.5% (w/w) of magnesiumstearte. It was filled into capsule shells by hand and by a capsule filler. The bars represent the standard deviation of the mean (n=6).

Both dissolution profiles show a sigmoidal progression (*b* = 1.58 (capsule 70% (w/w), handfilled); *b* = 1.65 (capsule 70% (w/w)). Although *a* differs regarding the capsules manufactured by hand (*a* = 65.95) and by the capsule filler (*a* = 53.95), a two sided t-test with an interval of confidence of 5% showed no significance. However, when both capsule formulations are compared to the original capsule formulation containing 70% (w/w) diclofenac sodium and lactose (see chapter 5.3.2.1.) with $t_{50\%}$ = 31.2 min and $t_{90\%}$ = 47.8 min, it becomes obvious that in this case UICEL also develops a better wetting effect than lactose does as already shown in chapter 5.3.4.1. with the example of the model drug caffeine. Furthermore the additional disintegration effect of UICEL may help to accelerate the release of the drug from the capsule formulation as opposed to lactose, which does not help to disintegrate.

However, when the capsule formulation was compressed, the release was unexpectedly changing compared to the result with caffeine as model drug substance. The time when 50% (w/w) of the diclofenac sodium was released accounted for 147 min and the time when 90% (w/w) was released for 436 min. The shape was less sigmoidal (*b* = 1.09) than for the other formulations and *a* was equal to 332.2 (see figure 5.18.).

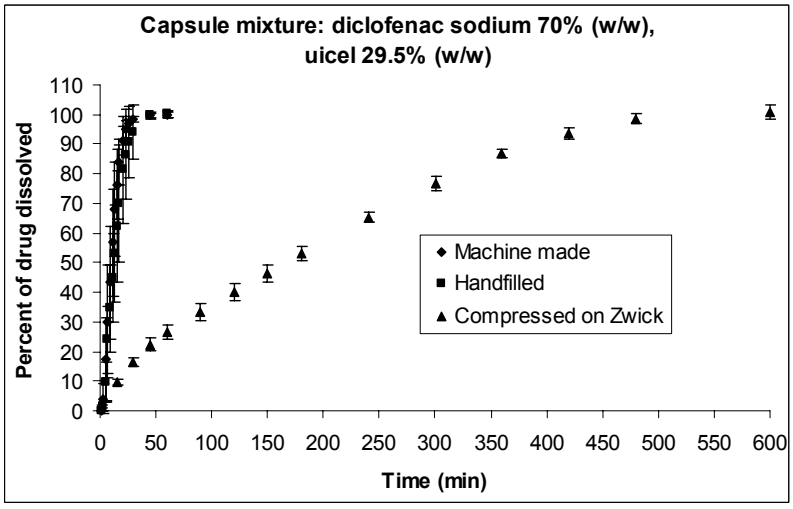


Figure 5.18.: The dissolution of the capsule mixture containing 70% (w/w) of diclofenac sodium, 29.5% (w/w) of UICEL and 0.5% (w/w) of magnesiumstearate. It was filled into capsule shells by hand and by a capsule filler. Furthermore it was compressed. The bars represent the standard deviation of the mean (n=6).

When the tablets were observed in the basket during the dissolution no rapid disintegration could be detected. In contrast to the previous formulation with caffeine (see chapter 5.3.4.1.) the tablets remained compact. The kinetic of the release of the capsule formulation compressed to a tablet was further investigated. When the values of the drug dissolved (%) were plotted against the square root of time, a straight line (y = mx+q) was received, where m = 4.76, q = -8.81 with a correlation coefficient r^2 = 0.9883. It appeared to be a $\sqrt{t}$ - kinetic and UICEL seemed to have formed a kind of matrix system.

The compaction, however, seemed to have a negative effect what the dissolution and disintegration is concerned and UICEL also seemed not to be able to wet the components in the particular formulation. The matter is discussed further in chapter 5.5.4. when the water uptake of the formulations is studied.

5.3.4.3. Granulation with UICEL

As the capsule formulation with diclofenac sodium compressed to a tablet showed a very slow dissolution (see chapter 5.3.4.2.) and since a wet granulation process is in many cases the unit operation of choice when a tablet formulation is developed, two formulations with UICEL were manufactured from two granulates (see chapter 4.3.4.). The dissolution profiles of both formulations is shown in figure 5.19.

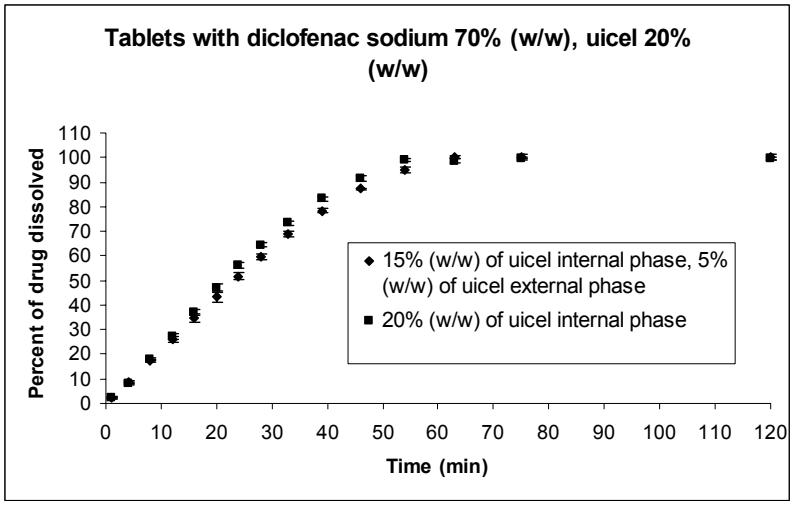


Figure 5.19.: The dissolution of the two tablet formulations of diclofenac sodium 70% (w/w) and UICEL 20% (w/w). In the first 20% (w/w) of UICEL was in the internal phase, in the second 15% (w/w) of UICEL was in the internal and 5% (w/w) of UICEL in the external phase. The bars represent the standard deviation of the mean (n=6).

From the first, where the internal phase consisted of 20% (w/w) UICEL, 50% (w/w) of the diclofenac sodium was released after 20.8 min and 90% (w/w) after 46.4 min. From the second formulation with 15% (w/w) of UICEL in the internal phase and 5% (w/w) of UICEL in the external phase 50% (w/w) of diclofenac sodium was released after 22.3 min and 90% (w/w) after 49.6 min. The sigmoidal shape of both curves seems to be alike as *b* is equal to 1.50 for both dissolution profiles. The little difference in dissolution time is expressed by *a*. For the formulation with 20% (w/w) of UICEL in the internal phase, *a* is equal to 135.7 while for the formulation with UICEL in the internal and external phase *a* is equal to 149.7. According to those results, UICEL in the external phase does not accelerate the release, in fact it seems to slow it down to a little extent. The dissolution of the formulation with 15% (w/w) of UICEL in the internal and 5% (w/w) in the external phase is compared to the corresponding original formulation (see chapter 5.3.2.2.) containing 15% (w/w) of corn starch in the internal phase and 5% (w/w) in the external phase. The release of the formulation containing corn starch is a little faster as $t_{50\%}$ = 20.1 min and $t_{90\%}$ = 45.4 min. In the case of the model drug diclofenac sodium, UICEL does not show an advantage as disintegrant after granulation compared to corn starch.

5.3.4.4. Proquazone

The calculated variables M_0, T, a and b of the Weibull equation for all formulations containing proquazone (see chapter 3.3.2.1. equation 19), the correlation coefficient r as well as $t_{50\%}$ and $t_{90\%}$ (see chapter 4.12) are summerized in table 5.11.

Table 5.11.: The dissolution profiles of the formulations containing proquazone and UICEL (n=6 for each formulation) can be described with the Weibull equation.

(n=6)	r	$t_{50\%}$ (min)	$t_{90\%}$ (min)	M_0 (%)	T (min)	a	b
Capsule 70% (w/w), handfilled	0.988	127	2268	101.8	1	10.28	0.40
Capsule 70% (w/w), machine filled	0.977	5.5	14.4	99.3	1	7.63	1.12
Capsule 70% (w/w), compressed to a tablet	0.996	2.1	17.6	101.3	0	2.19	0.55

M_0 (%) corresponds with the total amount of drug released. *T* describes the lag-time of the drug release, *a* describes the time dependence and *b* expresses the shape of the dissolution curve. The time when 50% and 90%, respectively, was released, was calculated according to the inverse function of the Weibull equation. *r* stands for the correlation coefficient.

The capsule that was handfilled released 50% (w/w) of the drug content after 127 min and 90% after 2268 min (see figure 5.20.).

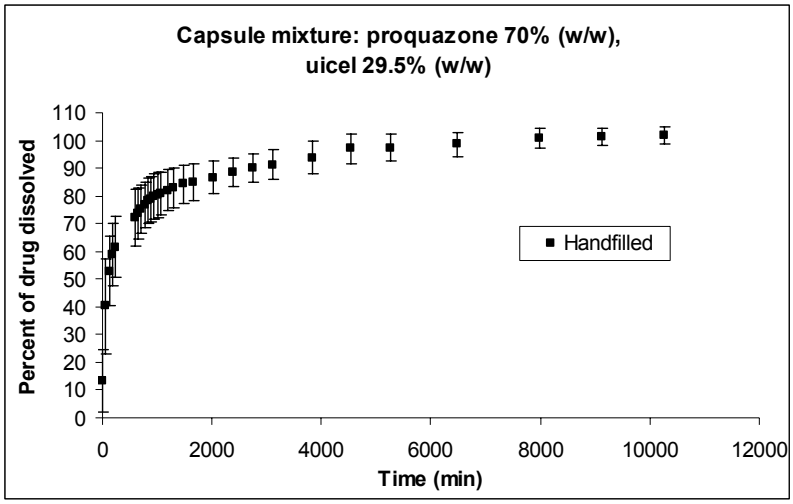


Figure 5.20.: The dissolution of the capsule formulation containing 70% (w/w) of proquazone, 29.5% (w/w) of UICEL and 0.5% (w/w) of magnesiumstearte. It was filled by hand into capsule shells. The bars represent the standard deviation of the mean (n=6). One has to keep in mind that there is no printing error in the time scale that a total release of ca. 100% was only achieved after 7.5 days.

The profile has a steep progression (*b* = 0.40). At first it could be observed that the powder bulk in the basket was slowly dissolving due to the wetting effect of UICEL as there was no disintegration at all. Then the powder mixtures started floating at the surface of the dissolution media to an increasing extent. According to the Noyes-Withney equation (chapter 3.3.1., equation 16) the dissolution is proportional to the surface area of the drug. It has to be considered that namely the effective surface area, the area that is available for the dissolution fluid, can decrease, if the drug is poorly wettable because of adsorbtion of air at the surface of the poorly wettable compound (Finholt et al., 1966). It is reported that the drug powder remains then partly floating at the surface of the medium during dissolution testing. As a consequence the area available for the dissolution media decreases and so does the dissolution rate although proquazone in this case had a larger total surface area compared to the proquazone that was encapsulated by a machine or compressed to a tablet.

The dissolution profiles of the formulation encapsulated by a capsule filling equipment and compressed to a tablet are shown in figure 5.21.

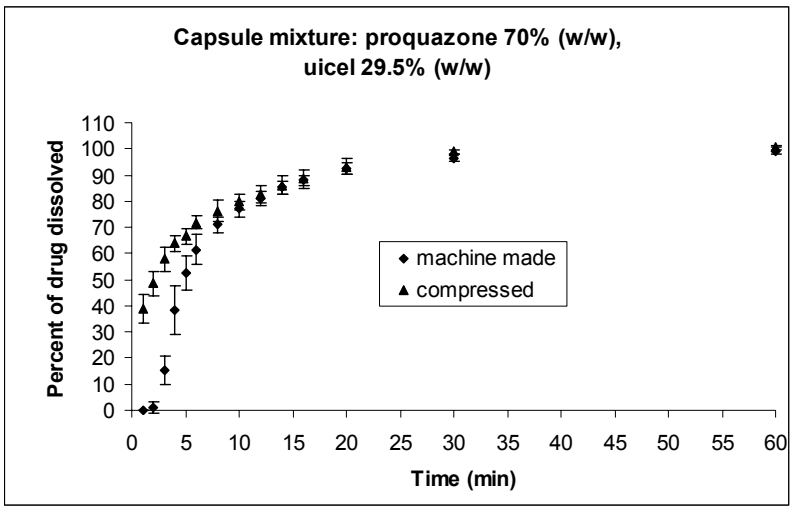


Figure 5.21.: The dissolution of the capsule formulation containing 70% (w/w) of proquazone, 29.5% (w/w) of UICEL and 0.5% (w/w) of magnesiumstearate. It was filled into capsule shells by a capsule filler and it was compressed to tablets. The bars represent the standard deviation of the mean (n=6).

The times when 50% (w/w) and 90% (w/w) were released from the capsules that were filled by the capsule filler and from the compressed powder mixture were 5.5 min and 2.1 min, respectively, and 14.4 min and 17.6 min, respectively. The fastest release can be observed when the powder mixture is compressed. The poorly wettable compound is wetted by UICEL and there is a distinct disintegration effect in the basket. The disintegrating effect cannot be observed that clearly when the machine-made capsules are released. Although in a capsule filling process only little compression forces occur, as compared to the production of tablets where compression forces achieve easily several kN, the poorly wettable particles of proquazone were brought close enough to the particles of UICEL. The absorbed air could be displaced to an extend that the model drug was wetted. The different mechanisms of dissolution can seen by regarding the shapes of the dissolution curves. The machine –made capsule formulation shows a sigmoidal profile (b = 1.12) and the capsule mixture compressed to a tablet a steeper progression (b = 0.55) than an exponential profile. The a-parameters of the three formulations can hardly be compared as the b-parameters really differ.

Comparing the capsule formulation to the original formulation with the filler lactose (see chapter 5.3.3.1.), UICEL seems to cause a far better wetting of proquazone.

5.4. Disintegration

In the following chapter the results of the disintegration experiments are discussed especially with respect to results found in the dissolution experiments.

5.4.1. Disintegration of the formulation with caffeine

The exact values of the disintegration of all formulations made with the model drug caffeine and the excipient lactose are shown in table 5.12.

Table 5.12.: The disintegration times of the formulations made of the model drug caffeine as well as their relative standard deviation are shown (n=6). The time when the last unit disintegrated is named maximum time.

Caffeine	Disintegration time (min) ± RSD (%)	Maximum time (min)
Capsules caffeine 10% (w/w)	2.1 ± 3.5	2.2
Capsules caffeine 50% (w/w)	2.3 ± 3.1	2.4
Capsules caffeine 70% (w/w)	2.4 ± 6.3	2.6
Tablets caffeine 10% (w/w), excentric press	3.8 ± 14.6	4.5
Tablets caffeine 50% (w/w), excentric press	13.3 ± 11.1	15.7
Tablets caffeine 70% (w/w), excentric press	15.3 ± 9.6	18.1
Tablets caffeine 10% (w/w), presster	3.7 ± 34.9	5.5
Tablets caffeine 50% (w/w), presster	9.3 ± 8.2	10.1
Tablets caffeine 70% (w/w), presster	14.7 ± 3.2	15.3
Tablets caffeine 50% (w/w), excentric press, mixture placebo granulate and granulate with caffeine 74% (w/w)	6.6 ± 11.3	7.7

All capsule formulations fulfilled the pharmacopeal requirements, what the disintegration is concerned (< 30min). The capsule formulations all disintegrated after approximately 2.5 minutes independently of the drug load. This result complies with the results found in the dissolution test as all capsules independently of the drug load were dissolved after approximately 6 minutes (see chapter 5.4.1.2.). The tablet formulation containing 50% (w/w) of caffeine compressed on the excentric press and the one with 70% (w/w) compressed on the excentric press and on the Presster™ did not fulfill the pharmaceutical requirements (< 15min) as the last tablets disintegrated after 15.7 min, 18.1 min and 15.3 min, respectively. In the case of the tablets containing the model drug caffeine the disintegration experiment can be taken as a hint for a prolonged dissolution with an increasing drug load. In addition even a correlation between the disintegration time and the dissolution of the tablets 50% (w/w) made of the granulate with 53% of caffeine and the tablets 50% (w/w) made of the mixture of the placebo-granulate and the granulate containing 74% (w/w) of caffeine can be observed as well. The tablets made of the mixture placebo-granulate 74% (w/w) show a disintegration time of 6.6 min, which is faster than the average disintegration time of the tablet made of the granulate 53% (w/w) that accounts for 13.3 min (compare chapter 5.3.1.4.).

In the case of the model drug caffeine the results of the disintegration experiment give an image of the results of the dissolution experiments. They could be used to give a prediction of the dissolution experiment.

5.4.2. Disintergration of the formulations with diclofenac sodium

The exact values of the disintegration of all formulations made with the model drug diclofenac sodium and the excipient lactose are shown in table 5.13.

Table 5.13.: The disintegration times of the formulations made of the model drug diclofenac sodium as well as their relative standard deviation are shown (n=6). The time when the last unit disintegrated is named maximum time.

Diclofenac sodium	Disintegration time (min) ± RSD (%)	Maximum time (min)
Caspules diclofenac sodium 10% (w/w)	3.1 ± 10.7	3.8
Caspules diclofenac sodium 32% (w/w)	4.1 ± 17.4	5.0
Caspules diclofenac sodium 50% (w/w)	12.3 ± 16.4	16.2
Caspules diclofenac sodium 70% (w/w)	12.7 ± 13.7	14.3
Tablets diclofenac sodium 10% (w/w)	4.0 ± 7.0	4.2
Tablets diclofenac sodium 32% (w/w)	13.6 ± 26.8	18.7
Tablets diclofenac sodium 50% (w/w)	16.3 ± 27.2	21.8
Tablets diclofenac sodium 70% (w/w)	21.4 ± 31.0	29.5

All capsule formulations fulfilled the pharmacopeal requirements, what the disintegration is concerned (< 30min). A difference between the two capsule formulations with the lower concentration of diclofenac sodium (10% (w/w) and 32 %(w/w)) and the ones with the higher concentrations of diclofenac sodium (50% (w/w) and 70% (w/w)) can be observed. The disintegration times are 3.1 and 4.1 minutes for the two lower and 12.3 and 12.7 minutes for the two upper concentrations. This fact corresponds to the results found in the dissolution experiment (compare chapter 5.4.2.1.).

The tablet formulations 32%, 50% and 70% (w/w) do not comply with the pharmacopeal requirements as the last unit disintegrates after 18.7, 21.8 and 29.5 minutes, respectively. According to the disintegration times the tendency for the dissolution experiment could be predicted, that the higher the drug content, the slower the release of 100% (w/w) of the drug load.

It can be concluded that in the case of the model drug diclofenac sodium the results of the disintegration experiment give an image of the results of the dissolution experiments.

5.4.3. Disintegration of the formulation with proquazone

The exact values of the disintegration of all formulations made with the model drug proquazone and the excipient lactose are shown in table 5.14.

Table 5.14.: The disintegration times of the formulations made of the model drug proquazone as well as their relative standard deviation are shown (n=6). The time when the last unit disintegrated is named maximum time.

Proquazone	Disintegration time (min) ± RSD (%)	Maximum time (min)
Capsules proquazone 10% (w/w)	4.0 ± 22.7	5.5
Capsules proquazone 50% (w/w)	4.7 ± 19.1	5.8
Capsules proquazone 70% (w/w)	9.7 ± 6.3	10.5
Capsules mixtersproquazone 50% (w/w) compressed to tablet	117 ± 5.2	125
Tablets proquazone 50% (w/w)	5.0 ± 10.6	6.0
Tablets proquazone 70% (w/w)	5.0 ± 11.9	6.5

With the exception of the capsule formulation 50% (w/w), which was compressed to a tablet, but did not contain a disintegrant, all formulations did comply with the pharmacopeal requirements (< 15 min for tablets; < 30 min for capsules). The average disintegration time of the capsule containing 10% (w/w), 50% (w/w) and 70% (w/w) accounted for 4.0, 4.7 and 9.7 min, respectively, while the tablets with 50% (w/w) and 70% (w/w) showed both a disintegration time of 5.0 min. Thus, with the exception of the capsule formulation compressed to a tablet 50% (w/w) with an average disintegration time of 117 minutes, no correlation between the dissolution behaviour and the disintegration time could be observed. This result confirms the superiority of the dissolution rate experiments compared to the disintegration time determination for a better discrimination between different formulations.

5.4.4. Disintegration of the formulation with UICEL

The exact values of the disintegration of all formulations made with the excipient UICEL are shown in table 5.15.

Table 5.15.: The disintegration times of the formulations made with the excipient UICEL as well as their relative standard deviation are shown (n=6). The time when the last unit disintegrated is named maximum time.

UICEL	Disintegration time (min) ± RSD (%)	Maximum time (min)
Capsules caffeine 70% (w/w), UICEL 29.5% (w/w), machine filled	2.4 ± 5.4	2.6
Capsules caffeine 70% (w/w), UICEL 29.5% (w/w), compressed	0.1 ± 6.0	0.1
Capsules diclofenac sodium 70% (w/w), UICEL 29.5% (w/w), machine filled	5.7 ± 21.8	7.6
Capsules diclofenac sodium 70% (w/w), UICEL 29.5% (w/w), compressed	29.2 ± 1.4	29.6
Tablets diclofenac 70% (w/w), UICEL 20% (w/w) internal phase	18.4 ± 5.2	20.2
Tablets diclofenac 70% (w/w), UICEL 15% (w/w) internal phase, 5% (w/w) external phase	18.4 ± 1.9	18.8
Capsules proquazone 70% (w/w), UICEL 29.5% (w/w), machine filled	2.4 ± 9.6	2.7
Capsules proquazone 70% (w/w), UICEL 29.5% (w/w), compressed	0.3 ± 13.7	0.4

The formulations with caffeine and proquazone in combination with UICEL showed all a disintegration, which complied with the pharmacopeal requirements (<15 min for tablets; < 30 min for capsules). The capsule mixture with the model drug caffeine, which was compressed, showed a faster dissolution than the same formulation encapsulated (see chapter 5.3.4.1.). This result can be considered as a consequence of the different disintegration times of 2.4 minutes for the capsule formulation and 0.1 minutes for the same formulation compressed. In the case of the tablet the well wettable and soluble caffeine is disintegrated as soon as it is wetted and dissolved and in the case of the capsule the capsule shell has to be entirely dissolved before a complete disintegration and dissolution can take place.

There is also a distinction in the disintegration times between the formulation containing the model drug proquazone either encapsulated or compressed, which is manifested at least at the beginning of the dissolution process (see chapter 5.3.4.4.). However, due to the poor wettability, which has to be overcome by both formulations after disintegration and which seems to be in this case the dissolution rate limiting step, the difference in the dissolution experiment is less obvious as it could be assumed according to the disintegration times of 0.3 minutes for the compressed formulation and 2.4 minutes for the same formulation encapsulated.

The formulations with diclofenac sodium that were compressed and encapsulated show a disintegration time of 29.2 min and 5.7 min, respectively. The dissolution experiment, however, allowed a clearer discrimination as the release of the same formulation compressed is prolonged to a big extent as opposed to the same formulation encapsulated (see chapter 5.3.4.2.). This circumstance can also be observed to a smaller extent regarding the disintegration times of both formulations, where UICEL was granulated. The disintegration time accounts for 18.4 min for both formulations.

Although both formulations released 50% (w/w) and 90% (w/w) of diclofenac sodium at approximately the same time, the dissolution experiments could show a difference between the two formulations regarding the *a* - parameters (see chapter 5.3.4.3.). This result also confirms a superiority of the dissolution rate experiments compared to the disintegration time determination for a better discrimination between different formulations.

5.5. Water uptake

In this chapter, it was tried to correlate the results of the dissolution experiments with the results found in the water uptake of the substances and the different formulations. The experimental determination of the contact angle and the total surface free energy is sometimes challenging. There are for instance big differences what the results are concerned by an apparently equal preparation of the same sample without any obvious reason. Another difficult task is the finding of the ideal test liquid as the sample should not swell or dissolve during the measurement. Especially when a system made of different components with, referring to this, different properties is analysed, the finding of suitable test liquids gets even more difficult. Another possible source of error is the determination of the capillary constant *c*. In the measurement it is assumed that the contact angle gets zero by using a test liquid with a very low surface free energy such as hexane or xylol, but there is a probability of no complete wetting when the surface energy of the solid is also very low. Furthermore a lot of parameters of the test liquid should be known such as its polar and non-polar contribution to the surface free energy, its viscosity and its density.

An aim of this work, however, was to find easily accessible and reproducible means of screening as it should contribute to the development of solid dosage forms in an industrial environment. Therefore the different systems are evaluated from the point of view of sorption of water, which can be regarded as a mean of the wettability of the different systems. In order to get a linear function in this procedure, the gain of mass squared was plotted against time (g^2/min) and the slope K was used as a degree of wettability of the different systems. The water uptake turned out to be a suitable mean for the investigation of the wettability. The water sorption constant K (g^2/min) of all investigated samples is shown in table 5.16.

Table 5.16.: The water sorption constant K [g^2/min] for all investigated systems as well as the standard deviation and the relative standard deviation are shown (n=3).

Sample	(K-values [g^2/min] ± SD)	RSD %
Caffeine	$(3.26 \pm 0.87) \cdot 10^{-1}$	26.8
Diclofenac sodium	$(7.64 \pm 0.49) \cdot 10^{-2}$	6.42
Proquazone	$(2.31 \pm 1.03) \cdot 10^{-4}$	44.5
Capsules with caffeine 70% (w/w)	$(1.42 \pm 0.35) \cdot 10^{-2}$	24.8
Tablets with caffeine 70% (w/w)	$(6.69 \pm 2.17) \cdot 10^{-3}$	32.5
Capsules with diclofenac sodium 70% (w/w)	$(5.30 \pm 0.57) \cdot 10^{-3}$	10.7
Tablets with diclofenac sodium 70% (w/w)	$(5.27 \pm 3.99) \cdot 10^{-3}$	75.7
Capsules with proquazone 70% (w/w)	$(7.10 \pm 4.97) \cdot 10^{-4}$	70.1
Tablets with proquazone 70% (w/w)	$(7.65 \pm 2.07) \cdot 10^{-3}$	27.0
Granulate with proquazone 74% (w/w)	$(4.47 \pm 0.99) \cdot 10^{-3}$	22.1
Capsules with caffeine 70% (w/w), UICEL 29.5% (w/w), machine filled	$(6.36 \pm 4.21) \cdot 10^{-2}$	66.3
Capsules with caffeine 70% (w/w), UICEL 29.5% (w/w), handfilled	$(3.54 \pm 0.31) \cdot 10^{-1}$	8.62
Caspules with caffeine 70% (w/w), UICEL 29.5% (w/w), compressed to tablet	$(9.01 \pm 2.48) \cdot 10^{-2}$	27.5
Caspules with dicolfenac sodium 70% (w/w), UICEL 29.5% (w/w), machine filled	$(1.42 \pm 0.26) \cdot 10^{-2}$	18.0
Caspules with dicolfenac sodium 70% (w/w), UICEL 29.5% (w/w), handfilled	$(6.06 \pm 0.21) \cdot 10^{-2}$	3.43
Caspules with dicolfenac sodium 70% (w/w), UICEL 29.5% (w/w), compressed to tablet	$(1.25 \pm 0.08) \cdot 10^{-3}$	6.52
Tablets diclofenac sodium 70% (w/w), UICEL 20% (w/w) internal phase	$(1.07 \pm 0.29) \cdot 10^{-3}$	19.5
Tablets diclofenac sodium 70% (w/w), UICEL 15% (w/w) internal phase and 5% (w/w) external phase	$(1.10 \pm 0.24) \cdot 10^{-3}$	21.9
Caspules with proquazone 70% (w/w), UICEL 29.5% (w/w), handfilled	$(3.26 \pm 0.61) \cdot 10^{-4}$	18.6
Capsules with proquazone 70% (w/w), UICEL 29.5 % (w/w), machine filled	$(6.75 \pm 1.26) \cdot 10^{-3}$	18.7
Capsule mixture proquazone 70% (w/w), UICEL 29.5% (w/w), compressed to tablet	$(2.20 \pm 0.53) \cdot 10^{-1}$	24.1

5.5.1. Water uptake of the model drugs

The water uptake of the model drugs caffeine, diclofenac sodium and proquazone are shown in figure 5.22.

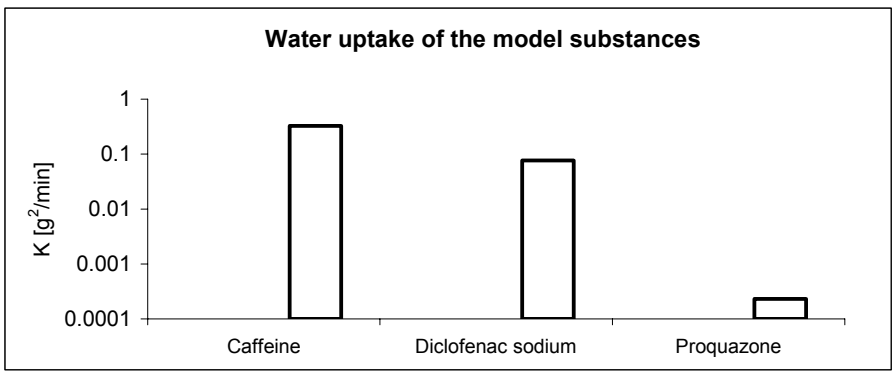


Figure 5.22.: The water sorption constant K (g^2/min) of the model drugs caffeine, diclofenac sodium and proquazone (n=3)

The K-values corresponded with the results found in the determination of the total surface free energy (see chapter 5.2.). The contact angle (water) of caffeine and diclofenac sodium is around 65°, whereas the contact angle (water) with proquazone was found to be > 90°. The water uptake of caffeine turned out to be higher than the one of diclofenac sodium as K was $3.26 \cdot 10^{-1}$ and $7.64 \cdot 10^{-2}$ g^2/min, respectively. There was, however, a remarkable difference regarding the sorption constant K of proquazone, which accounts for $2.31 \cdot 10^{-4}$ g^2/min. The K values support very well the fact that the model drug proquazone had the potential to have really prolonged releases due to its poor wettability (see chapter 5.3.) as all formulations with caffeine had comparably fast dissolution rates. However, beside the physico-chemical properties of the different starting materials most important is the water soprtion of the formulation itself determining the releases as shown in the following sections.

5.5.2. Water uptake of the formulations with caffeine and diclofenac sodium

The water sorption constant K (g^2/min) of the capsule formulations and tablet formulations 70% (w/w) with caffeine and diclofenac sodium, respectively are shown in figure 5.24.

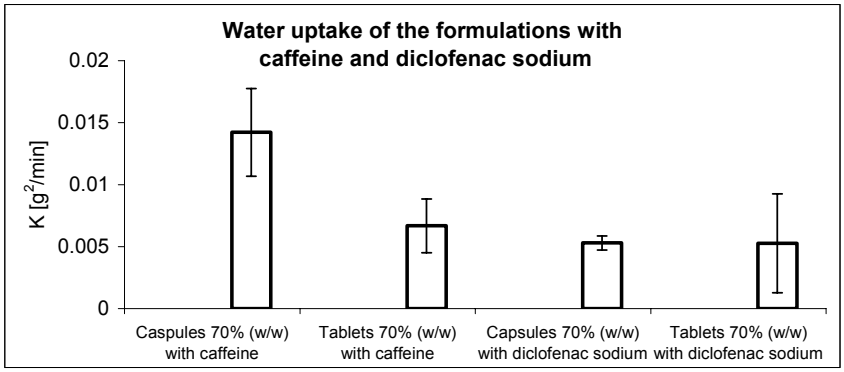


Figure 5.23.: The water sorption constant K (g^2/min) of the capsule formulations and tablet formulations 70% (w/w) with caffeine and diclofenac sodium, respectively (n=3).

The water sorption constant K of the capsules containing 70% (w/w) of caffeine accounted for $1.42 \cdot 10^{-2}$ g^2/min and the water sorption of the tablets with 70% (w/w) of caffeine compressed on the excentric press, the capsules with 70% (w/w) diclofenac sodium and the tablets with 70% (w/w) diclofenac sodium accounted all together for around $5.8 \cdot 10^{-3}$ g^2/min. Obviously, caffeine is much better wetted in the capsule than in the tablet formulation. Diclofenac sodium, however, is wetted equally independently of the formulation. The data comply with the results found in the dissolution experiments as 90% of the capsule with 70% (w/w) of caffeine was released after about 6 min and 90% of the other formulations after about 42 min. The values of the water sorption constant K were plotted against the $t_{90\%}$ - values of the dissolution experiments, and it was possible to detect a correlation between the dissolution behaviour and the water uptake of the formulations with r^2 ($t_{90\%}$) = 0.9670. The correlation when the values of the dissolution were plotted against $t_{50\%}$ was

r^2 ($t_{50\%}$) = 0.7063. The comparatively low correlation with $t_{50\%}$ and K indicates different dissolution characteristics. The dissolution profile of the capsule formulation containing 70% (w/w) of diclofenac sodium is highly sigmoidal and therefore as opposed to the other formulations shows a delayed release at the beginning (see chapter 5.3.2.1.). If $t_{50\%}$ of the capsule formulation 70% (w/w) is not taken into account, r^2 ($t_{50\%}$) is still equal to 0.9218.
In the case of the formulations containing 70% (w/w) of caffeine and diclofenac sodium, respectively, the results of the water sorption experiment give an image of the results of the dissolution experiments.

5.5.3. Water uptake of the formulations with proquazone

The water sorption constant K (g^2/min) of the capsule formulation 70% (w/w), the tablet formulation 70% (w/w) made of the granulate 74% (w/w), the granulate 74% (w/w) and proquazone powder is shown in figure 5.24.

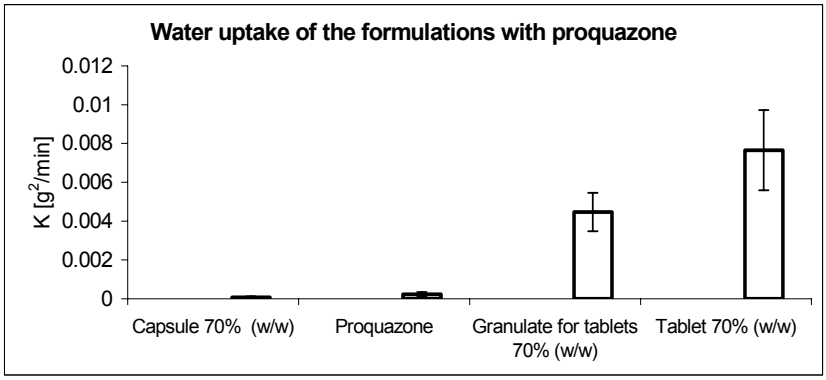


Figure 5.24.: The water sorption constant K (g^2/min) of the capsule formulation 70% (w/w), the tablet formulation 70% (w/w) made of the granulate 74% (w/w), the granulate 74% (w/w) and proquazone (n=3).

The following K-values were obtained: for granulate 74% (w/w) and tablet 70% (w/w) K = $4.47 \cdot 10^{-3}$ and $7.65 \cdot 10^{-3}$ g^2/min, respectively, while the sorption of water of the proquazone powder and the capsule 70% (w/w) came to K = $2.31 \cdot 10^{-4}$ and $7.10 \cdot 10^{-5}$ g^2/min, respectively. According to these differences, it could be seen that proquazone was much better wetted in this particular granulate or the tablet formulation. The results are very consistent with the results from the in-vitro dissolution experiments.
The K-values of tablet 70% (w/w), granulate 74% (w/w) (in the capsule formulation) and capsule 70% (w/w) were plotted against the $t_{50\%}$ - and the $t_{90\%}$ - values of the dissolution experiments, and it was possible to detect a correlation between the dissolution behaviour and the water uptake of the formulation with r^2 ($t_{50\%}$) = 0.8308 and r^2 ($t_{90\%}$) = 0.8288. In this case, it is evident that the formulation consisting of a granulate has lead to an improved wettability. However, it has to be checked in each

case whether such an approach is of advantage. In the case of proquazone the granulate containing a high amount of active ingredient could also be filled in capsule shells, i.e. for marketing reasons.

5.5.4. Water uptake of the formulations with UICEL

Caffeine

The water sorption constant K (g^2/min) of the capsule formulation 70% (w/w), handfilled, the capsule formulation 70% (w/w), machine filled and the capsules mixture 70% (w/w), compressed to a tablet, is shown in figure 5.25.

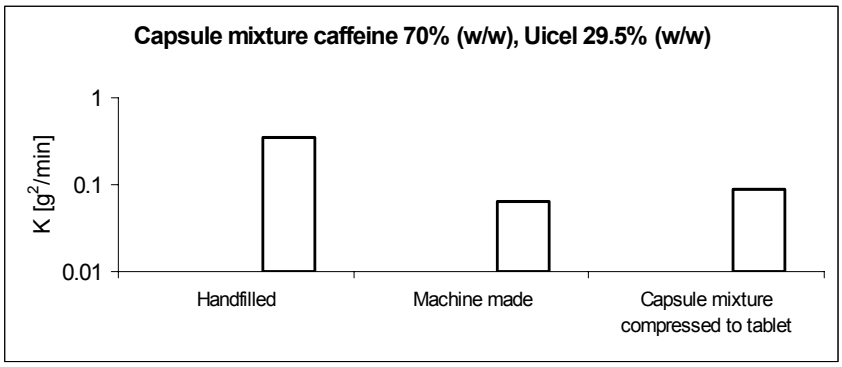


Figure 5.25.: The water sorption constant K (g^2/min) of the capsule formulation 70% (w/w), handfilled, the capsule formulation 70% (w/w), machine filled and the capsules mixture 70% (w/w), compressed to a tablet, (n=3).

When the mixture containing caffeine was analysed the highest water sorption constant was obtained when the handfilled mixture was investigated as K was equal to $3.54 \cdot 10^{-1}$ g^2/min. For the machine filled capsules K = $6.36 \cdot 10^{-2}$ g^2/min and for the same mixture compressed K = $9.01 \cdot 10^{-2}$ g^2/min. It is obvious that the mixture is capable to take up a comparably big amount of water no matter if it is compressed or loosely filled into the capsule shell. According to the K-values, a good wetting of the drug in all formulations can be expected. The dissolution experiment seems to be in contradiction to the values found in the water sorption experiment, because the mixture that was compressed with a K-value in between showed the fastest dissolution. The delayed release of the capsules can be explained by the previous dissolving of the capsule shells, which first has to be dissolved and as long as the remains of the shell cover parts of the powder bulk the surface is not yet totally available for the dissolution media. This circumstance seems to be the dissolution rate limiting step and cannot be detected by the water uptake measurement because in this procedure just the insight of the capsules is analysed. This fact also explains that no correlation was found with $t_{50\%}$ and $t_{90\%}$ of the dissolution experiments.

Diclofenac sodium

The water sorption constant K (g^2/min) of the capsule formulation 70% (w/w), handfilled, the capsule formulation 70% (w/w), machine filled, and the capsules mixture 70% (w/w), compressed to a tablet, is shown in figure 5.26.

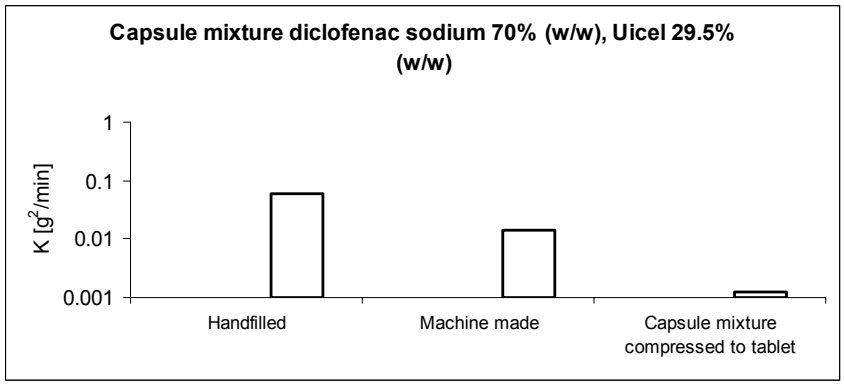


Figure 5.26.: The water sorption constant K (g^2/min) of the capsule formulation 70% (w/w), handfilled, the capsule formulation 70% (w/w), machine filled and the capsules mixture 70% (w/w), compressed to a tablet, (n=3).

The highest water sorption constant was obtained with the capsules mixture, which was filled by hand into capsule shells as K was equal to $6.06 \cdot 10^{-2}$ g^2/min followed by the water sorption constant of the powder mixture in the machine filled capsules, which was equal to $1.42 \cdot 10^{-2}$ g^2/min. K accounted for $1.25 \cdot 10^{-3}$ g^2/min for the capsule mixture, which was compressed to a tablet.

The values of the water sorption constant K were plotted against the $t_{50\%}$ - and $t_{90\%}$ - values of the dissolution experiments (see chapter 5.3.4.2.). There could not be found a linear correlation but one by using a power equation of the form $y = mx^{-q}$. The correlation r^2 ($t_{50\%}$) was then equal to 0.8114 and r^2 ($t_{90\%}$) to 0.8110. This result is demonstrating impressively that UICEL just needs small amounts of water to develop its ability to wet and to disintegrate and that there is a critical K-value for a formulation containing 70% (w/w) of diclofenac sodium and 29.5% (w/w) of UICEL between $1.42 \cdot 10^{-2}$ and $1.24 \cdot 10^{-3}$ g^2/min, where the amount of water penetrating the formulation is suddenly not enough any more to cause a sufficient wetting effect and a proper disintegration. This assumption is supported by the fact that in the case of the dissolution of the tablet formulation no disintegration in the basket was observed at all. The reason of the behaviour of the diclofenac sodium tablet can be explained by a possible low porosity of the tablet. It cannot be, however, excluded a possible interaction between the ionic drug substance and cellulose II within the tablet, as far the cohesion of cellulose hydrogen bonds play an important role.

The K-values for the formulation with the granulated UICEL were alike: $1.07 \cdot 10^{-3}$ g^2/min for the formulation with 20% (w/w) of UICEL in the internal phase and $1.10 \cdot 10^{-3}$ g^2/min for the formulation with 15% (w/w) of UICEL in the internal phase and 5% (w/w) of UICEL in the external phase. K accounted for $5.30 \cdot 10^{-3}$ g^2/min for the formulation with 15% (w/w) of corn starch in the internal and 5%

(w/w) in the external phase. According to the K-values there should be a similar dissolution behaviour of the three formulations. This assumption is confirmed as for all those formulations 50% (w/w) of the diclofenac sodium were released after about 21 min and 90% (w/w) after about 47 min (see chapter 5.3.4.3.).

Proquazone

The water sorption constant K (g^2/min) of the capsule formulation 70% (w/w), handfilled, the capsule formulation 70% (w/w), machine filled and the capsules mixture 70% (w/w), compressed to a tablet is shown in figure 5.27.

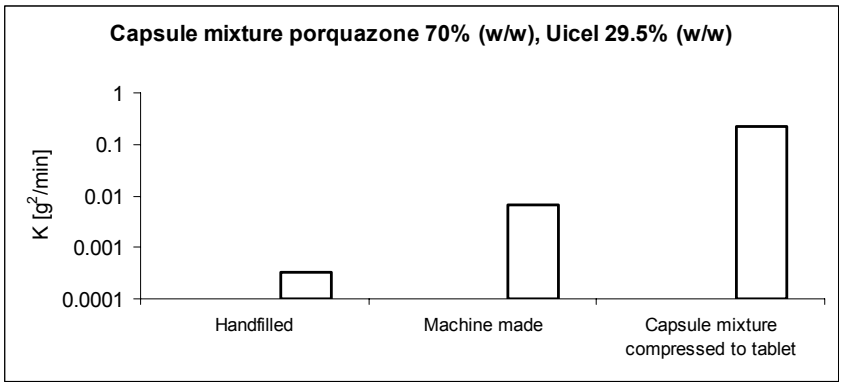


Figure 5.27.: The water sorption constant K (g^2/min) of the capsule formulation 70% (w/w), handfilled, the capsule formulation 70% (w/w), machine filled and the capsules mixture 70% (w/w), compressed to a tablet, (n=3).

The highest water sorption constant was obtained with the capsules mixture, which was compressed to a tablet as K was equal to $2.20 \pm 0.53 \cdot 10^{-1}$ g^2/min followed by the water sorption constant of the powder mixture in the machine filled capsules, which was equal to $6.75 \pm 1.26 \cdot 10^{-3}$ g^2/min. K accounted for $3.26 \cdot 10^{-4}$ g^2/min for the capsule mixture, which was filled by hand into capsule shells. The results also corresponds to the dissolution experiment as there was a wetting problem with the capsules that were filled by hand into capsule shells (see chapter 5.3.4.4.). Astonishingly the capsule that was machine filled as well as the powder mixture compressed to a tablet showed a more or less equal release although there was a difference between the K-values. The K-values were plotted against $t_{50\%}$ and $t_{90\%}$ and there was no linear correlation but one by using a power equation of the form $y = mx^{-q}$. The correlation r^2 ($t_{50\%}$) was then equal to 0.8904 and r^2 ($t_{90\%}$) to 0.5385. The results are a hint for the same phenomena as described with the model drug diclofenac sodium in combination with UICEL (see previous section). There is a critical value for K when UICEL is used as excipient where the amount of water penetrating the formulation is suddenly not enough any more to cause a sufficient wetting effect and a proper disintegration. As a consequence the dissolution rate goes down dramatically.

5.6. Compressibility and compactibility

An advantage of a capsule formulation is the fact that a powder, a powder mixture or a granulate can be easily encapsulated in a hard gelatine capsule shell without any compression process, as opposed to tablets where compacts with a sufficient mechanical strength must be manufactured. However, the physical property of the tabletting mixture should be the way that the tablets with the desired mechanical strength can be produced at the maximum speed of the tablet press with a relatively low compression force. The fact that a powder does not show good compression properties and it is not possible to make a granulation could be a technological reason to chose the capsule approach.
The physical model of powder compression proposed by Leuenberger (1980) connects the parameters compressibility and compactibility. In the following chapter it was tried to use this approach as a screening tool for the different starting materials as it was intended to have a fast and practical but scientific solution. Therefore, in contrast to earlier studies, just five different compression forces for each sample were applied and the crushing strength was determined with a common tablet tester (see chapter 4.17.).

5.6.1. Reference substances

The model drug acetyl salicylic acid is a compound, which can be directly compressed without a granulation process (e.g. Aspirin®Bayer). Paracetamol, however, is a compound with bad compression properties (Deodhar et al, 1988). The two model drugs should exemplify for a compound with good compression properties and for one with bad compression properties. Therefore, the radial crushing strength of compacts of both model drugs were plotted against the product of the pressure of compression and the relative density (see figure 5.28.).

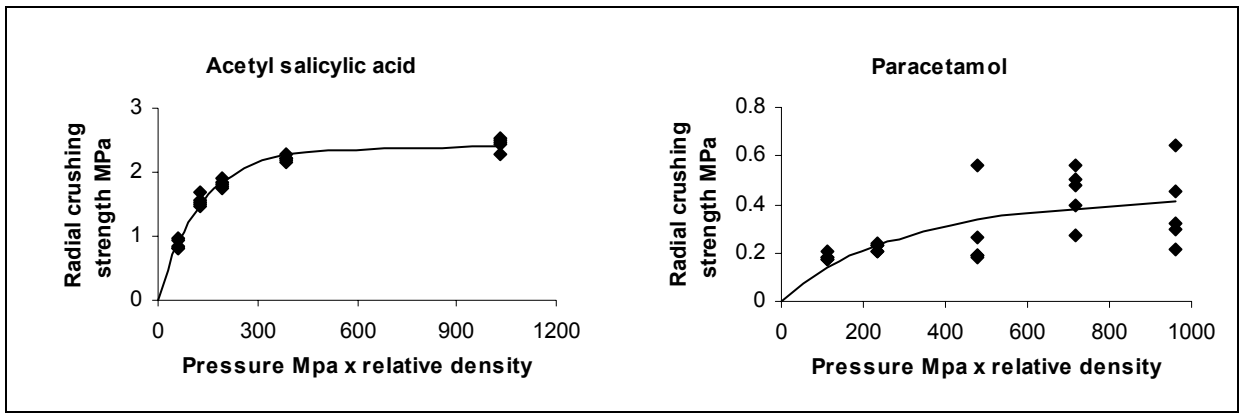


Figure 5.28.: The radial crushing strength was plotted against the product of the pressure of compression and the relative density. For every pressure of compression five compacts were investigated.

The average values of the radial crushing strength including the standard deviation and the corresponding pressure of compression, is shown in table 5.17.

Table 5.17.: The average values of the radial crushing strength including the standard deviation and the corresponding pressure of compression of the model drugs acetyl salicylic acid and paracetamol are shown.

Reference substance	(n = 5)					
	Compression pressure (MPa)	**64.96**	**129.92**	**194.88**	**389.77**	**1039.4**
Acetyl salicylic acid	Radial crushing strength (MPa)	0.872	1.55	1.82	2.21	2.44
	RSD (%)	9.09	5.48	2.75	2.04	4.07
	Compression pressure (MPa)	**129.91**	**259.84**	**519.69**	**779.53**	**1039.4**
Paracetamol	Radial crushing strength (MPa)	0.182	0.225	0.278	0.444	0.386
	RSD (%)	6.32	5.87	58.5	25.7	43.0

The determined values of the compression susceptibility parameter and the maximum crushing strength of the two model drugs are shown in table 5.18.

Table 5.18.: The compression susceptibility parameter, $\gamma \cdot 10^{-3}$ (MPa) $^{-1}$, and the maximum crushing strength, σ_{max} (MPa), of the different excipients are shown.

	$\gamma \cdot 10^{-3}$ (MPa^{-})^{1}	σ_{max} (MPa)	r
Acetyl salicylic acid	7.57	2.40	0.997
Paracetamol	3.57	0.415	0.921

The maximum crushing strength of acetyl salicylic acid accounts for 2.40 MPa and for 0.415 MPa for paracetamol. In the case of paracetamol, this value impressively demonstrates that even at a high pressure of compression, no sufficient strength in the tablet can be achieved. The compression susceptibility parameter, which accounts for 7.57 MPa^{-1} for acetyl salicylic acid indicates that the maximum crushing strength is reached faster at lower pressures of compression as opposed to paracetamol where γ is equal to 3.57 MPa^{-1}. In the case of paracetamol there is an increasing deviation of the different values for the radial crushing strength when a higher pressure of compression is applied whereas the crushing strength seem to remain constant independently of the increasing pressure of compression in the case of acetyl salicylic acid. This circumstance can be taken as a hint for a capping tendency as with an increasing compression pressure different internal tensions are generated, which can become differently manifest when the crushing strength is determined. This tendency could be confirmed by the fact that it was not possible to produce intact tablets at higher pressures of compression because of immediate capping in the die. The capping tendency of paracetamol is also described in literature (Fachaux et al, 1995).

5.6.2. Excipients

The radial crushing strength of compacts of the excipients was plotted against the product of the pressure of compression and the relative density (see figure 5.29.).

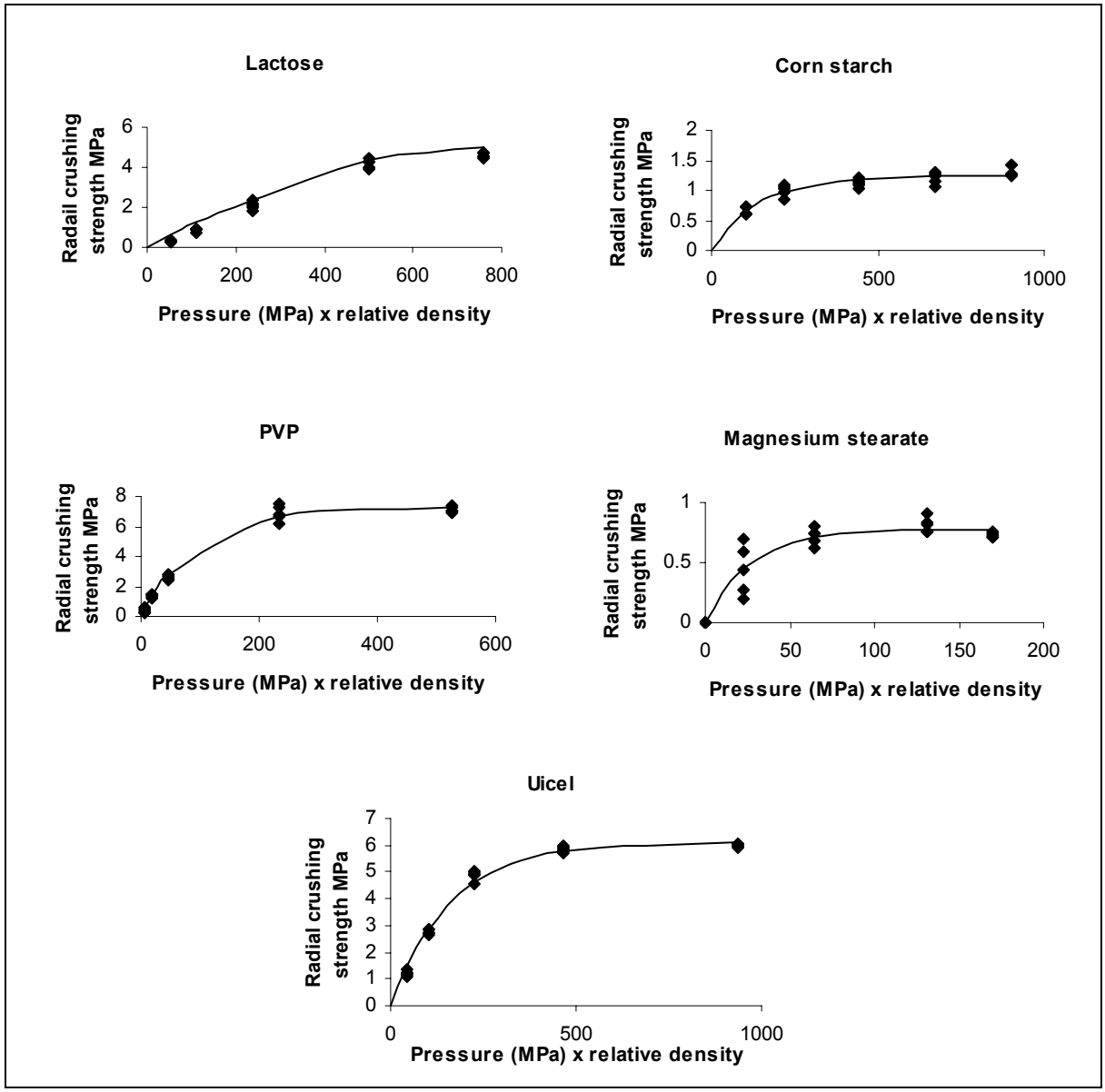


Figure 5.29.: The radial crushing strength of compacts of the excipients was plotted against the product of the pressure of compression and the relative density. For every pressure of compression five compacts were investigated.

The average values of the radial crushing strength including the standard deviation and the corresponding pressure of compression, is shown in table 5.19.

Table 5.19.: The average values of the radial crushing strength including the standard deviation and the corresponding pressure of compression of compacts of the excipients are shown.

Excipients	(n = 5)					
	Compression pressure (MPa)	**64.96**	**129.92**	**259.84**	**519.69**	**779.53**
Lactose	Radial crushing strength (MPa)	0.297	0.859	2.08	4.61	4.17
	RSD (%)	11.5	11.3	9.13	2.92	5.00
	Compression pressure (MPa)	**129.92**	**259.84**	**519.69**	**779.53**	**1039.4**
Corn starch	Radial crushing strength (MPa)	0.660	1.01	1.12	1.20	1.33
	RSD (%)	10.1	9.32	6.95	8.76	7.01
	Compression pressure (MPa)	**12.99**	**25.98**	**51.97**	**210.47**	**472.92**
PVP	Radial crushing strength (MPa)	0.389	1.38	2.63	6.88	7.15
	RSD (%)	34.9	9.58	6.38	7.13	3.04
	Compression pressure (MPa)	**25.98**	**64.96**	**129.92**	**181.89**	**-**
Magnesiumstearate	Radial crushing strength (MPa)	0.439	0.719	0.816	0.731	-
	RSD (%)	47.4	9.60	7.63	2.99	-
	Compression pressure (MPa)	**64.96**	**129.92**	**194.88**	**389.77**	**1039.4**
UICEL	Radial crushing strength (MPa)	1.22	2.75	4.86	5.85	5.99
	RSD (%)	7.34	3.11	3.73	1.67	0.626

The determined values of the compression susceptibility parameter and the maximum crushing strength of the different excipients are shown in table 5.20.

Table 5.20.: The compression susceptibility parameter, $\gamma \cdot 10^{-3}$ (MPa)$^{-1}$, and the maximum crushing strength, σ_{max} (MPa), of the different excipients are shown.

(n=5)	$\gamma \cdot 10^{-3}$ (MPa)$^{-1}$	σ_{max} (MPa)	r
Lactose	2.72	4.96	0.964
Corn starch	7.01	1.25	0.989
PVP	10.5	7.30	0.998
Magnesiumstearate	38.4	0.77	0.989
UICEL	6.17	6.12	0.995

PVP turns out to be the most plastic material with a relatively high compression susceptibility parameter of 10.5 MPa^{-1} and a really high maximum crushing strength of 7.30 MPa. It is followed by the UICEL, which also seems to be plastic with γ equal to 6.17 MPa^{-1} and σ_{max} equal to 6.12 MPa. There is hardly any deviation of σ_{max}, even when a high pressure is applied on UICEL, which indicates a very good compactibility. It can be confirmed that UICEL is a very suitable compound for direct tabletting as beside the good flowability, the very good disintegration and wetting property (see chapter 5.2., 5.4. and 5.5.), there is a good compression behaviour. (Furthermore UICEL is found to be very useful in the capsule filling process as shown in chapter 5.3.4.).

Lactose is widely used as a filler in the wet granulation process. Spray dried lactose can be used for direct compression. In this study, however, α-Lactose monohydrate (200 mesh) was utilized, which is described not to be directly compressible (Jivraj et al., 2000). The lack of flowability could be a main reason for that. A substance, whose σ_{max} is equal to 4.96 MPa and γ is equal to 2.72 MPa^{-1}, cannot be considered automatically as a inapplicable substance for direct compression as acetyl salicylic acid,

which is used for direct compression, was found to have a σ_{max} equal to 2.40 MPa indicating a far lower compactibility than lactose (see chapter 5.6.1.).
The maximum crushing strength of corn starch is smaller than the one of lactose as it accounts for 1.25 MPa but the maximum crushing strength is reached faster as γ is equal to 7.01 MPa^{-1}.
The compression profile of magnesiumstearate, however, resembles most the one of the model drug paracetamol (see chapter 5.7.1.) indicating a poor compressional behaviour, as σ_{max} is equal to 0.77 MPa and γ is equal to 38.4 MPa^{-1}.

5.6.3. Tablet formulations and granulates containing caffeine

The radial crushing strength of compacts of caffeine, all granulates with caffeine and the corresponding tabletting mixture was plotted against the product of the pressure of compression and the relative density (see figure 5.30.).

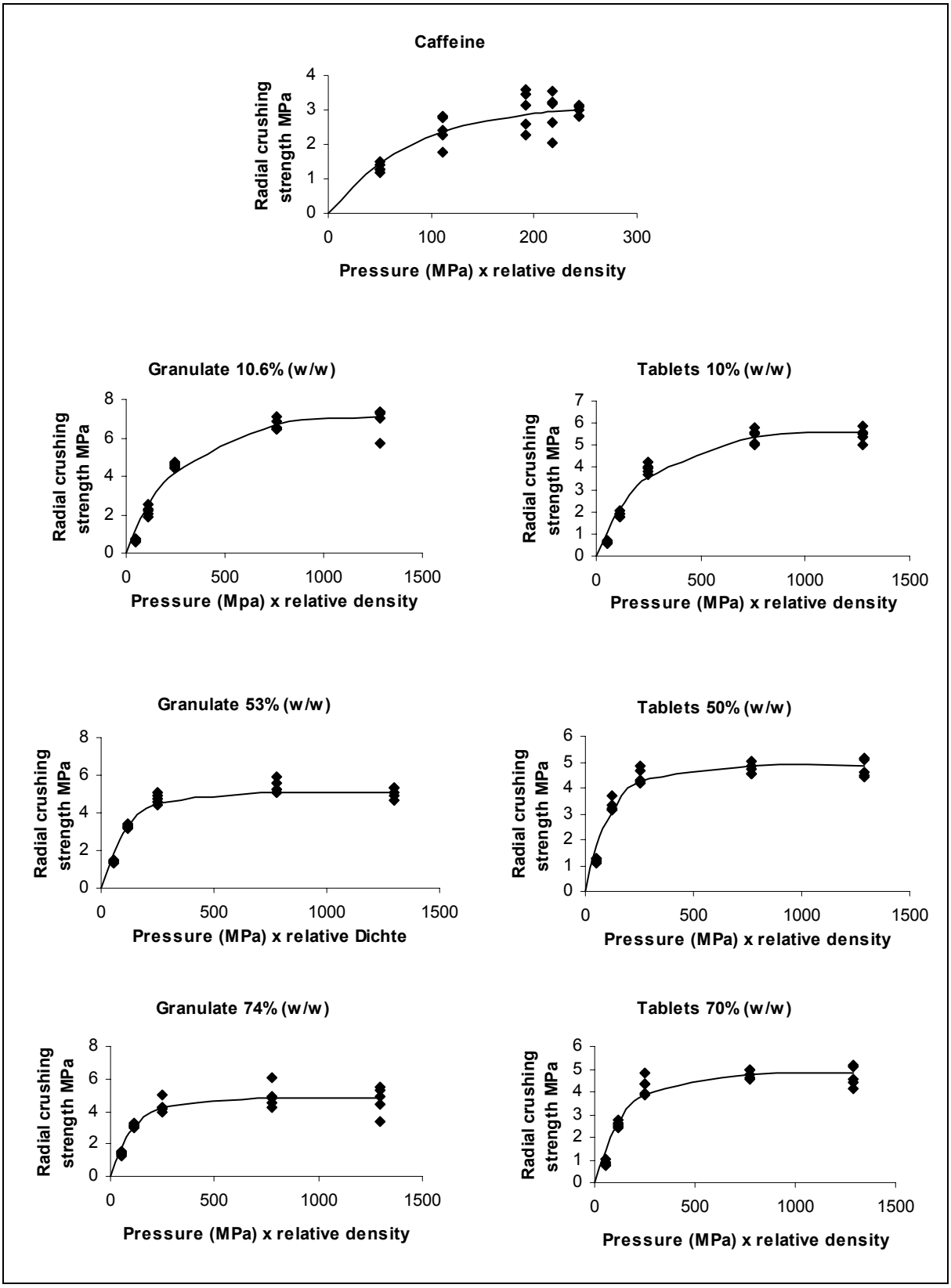


Figure 5.30.: The radial crushing strength of compacts of caffeine and of formulations containing caffeine was plotted against the product of the pressure of compression and the relative density. For every pressure of compression five compacts were investigated

The radial crushing strength of caffeine, of the “placebo”-granulate and the tabletting mixtures 10% (w/w) and 50% (w/w), respectively, made of the granulate 74% (w/w) and the “placebo”-granulate was plotted against the product of the pressure of compression and the relative density (see figure 5.31.).

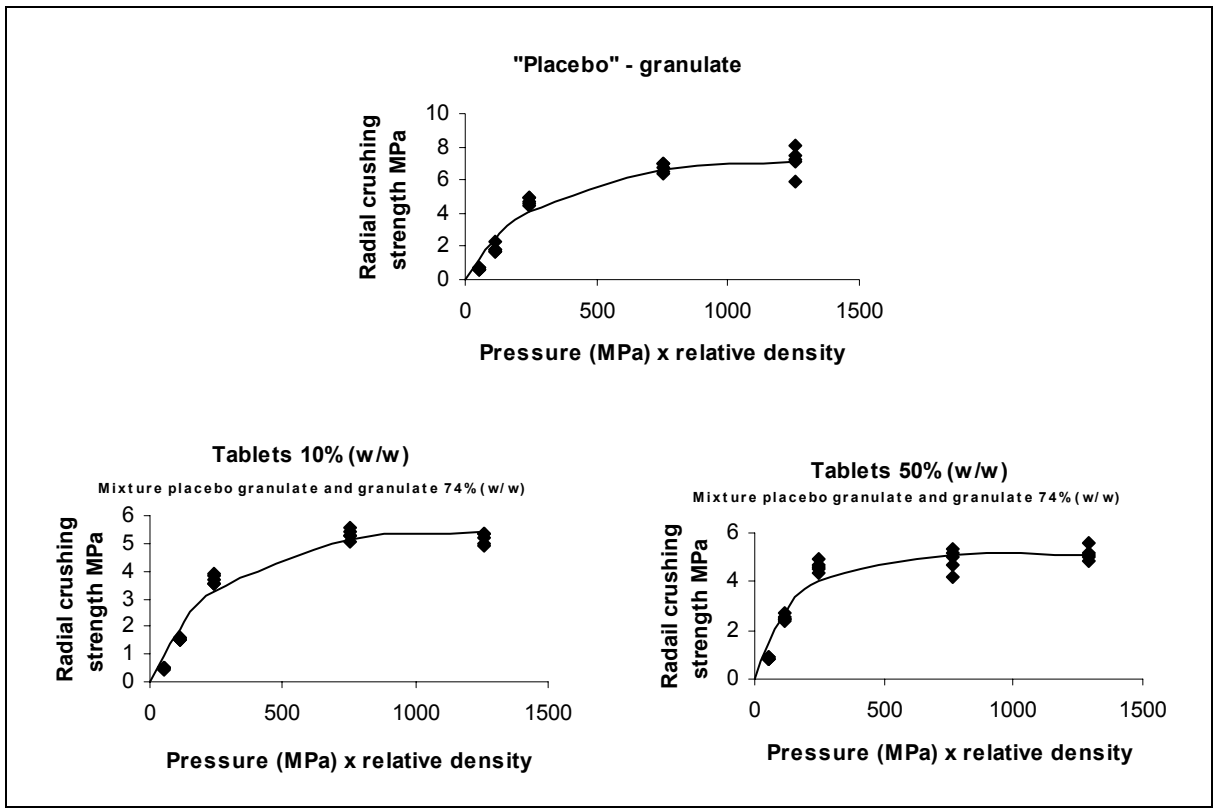


Figure 5.31.:The radial crushing strength of compacts of the placebo-granulate and of the formulations 10% and 50% (w/w) made of the placebo-granulate and the one containing 74% (w/w) of caffeine was plotted against the product of the pressure of compression and the relative density. For every pressure of compression five compacts were investigated.

The average values of the radial crushing strength including the standard deviation and the corresponding pressure of compression, is shown in table 5.21.

Table 5.21.: The average values of the radial crushing strength including the standard deviation and the corresponding pressure of compression of the model drug caffeine and all formulations with caffeine is shown.

Caffeine	(n=5)					
	Compression pressure (MPa)	**64.96**	**129.92**	**207.88**	**233.86**	**259.84**
Caffeine	Radial crushing strength (MPa)	1.33	2.40	3.02	2.92	2.98
	RSD (%)	8.27	18.3	18.5	19.9	5.03
	Compression pressure (MPa)	**64.96**	**129.92**	**259.84**	**779.53**	**1299.22**
Granulate 11% (w/w)	Radial crushing strength (MPa)	0.670	2.18	4.57	6.68	6.93
	RSD (%)	8.21	11.5	2.84	4.64	10.1
Tablet 10% (w/w)	Radial crushing strength (MPa)	0.634	1.89	3.92	5.40	5.49
	RSD (%)	8.20	5.29	5.36	6.11	5.46
Granulate 53% (w/w)	Radial crushing strength (MPa)	1.41	3.29	4.75	5.37	5.07
	RSD (%)	4.26	3.34	5.47	6.89	5.72
Tablet 50% (w/w)	Radial crushing strength (MPa)	1.20	3.30	4.45	4.74	4.76
	RSD (%)	5.83	6.98	6.74	4.43	7.14
Granulate 74% (w/w)	Radial crushing strength (MPa)	1.43	3.12	4.32	4.92	4.73
	RSD (%)	6.99	2.56	9.25	14.0	18.2
Tablet 70% (w/w)	Radial crushing strength (MPa)	0.85	2.57	4.27	4.77	4.67
	RSD (%)	12.9	4.67	8.67	3.56	9.85
"Placebo"-granulate	Radial crushing strength (MPa)	0.654	1.85	4.71	6.70	7.16
	RSD (%)	5.35	13.0	4.67	4.18	11.45
Tablet 10% (w/w) (Mixture placebo and granulate 74%)	Radial crushing strength (MPa)	0.49	1.55	3.69	5.32	5.18
	RSD (%)	4.08	2.58	4.07	3.38	3.67
Tablet 50% (w/w) (Mixture placebo and granulate 74%)	Radial crushing strength (MPa)	0.859	2.54	4.63	4.88	5.15
	RSD (%)	2.68	5.51	4.75	9.01	5.82

The determined values of the compression susceptibility parameter and the maximum crushing strength of the model drug caffeine and all formulations with caffeine are shown in table 5.22.

Table 5.22.: The compression susceptibility parameter, $\gamma \cdot 10^{-3}$ (MPa)$^{-1}$, and the maximum crushing strength, σ_{max} (MPa), of the model drug caffeine and all formulations with caffeine.

(n=5)	$\gamma \cdot 10^{-3}$ (MPa)$^{-1}$	σ_{max} (MPa)	r
Caffeine	12.34	3.16	0.944
Granulate with caffeine 11% (w/w)	3.69	7.08	0.989
Granulate with caffeine 53% (w/w),	8.49	5.12	0.986
Granulate with caffeine 74% (w/w)	8.11	4.87	0.994
Tablets caffeine 10% (w/w)	4.08	5.62	0.987
Tablets caffeine 50% (w/w)	8.25	4.83	0.979
Tablets with caffeine 70% (w/w)	6.54	4.82	0.979
"Placebo" granulate	3.59	7.14	0.982
Tablets with caffeine 10% (w/w), mixture placebo and granulate with caffeine 74% (w/w)	3.81	5.42	0.978
Tablets with caffeine 50% (w/w), mixture placebo and granulate with caffeine 74% (w/w)	6.31	5.13	0.971

The average values of the compression properties of caffeine seem to be well as the maximum crushing strength accounts for 3.16 MPa. The high value of the compression susceptibility parameter, which is equal to 12.34 $(MPa)^{-1}$, is indicating that the comparatively high value of σ_{max} can be reached at low compression forces. However, it can be seen that the statistical spread for radial crushing strength increases at higher pressures of compression. Then, it accounts for about 20%. Although the reference substance acetyl salicylic acid has a lower value for σ_{max}, it keeps showing a regular distribution of the values of the radial crushing strength independently of the pressure of compression. Those deviations of the model drug caffeine could be a problem considering a direct compression. When caffeine is granulated, the statistical spread seems to be decreasing compared to the one of the pure model drug to about 10% at higher pressures of compression. The granulates show considerably high values for σ_{max} as they come to 7.08 MPa for granulate 11%, 5.12 MPa for the granulate 53% and 4.87 MPa for the granulate 74%. With an increasing load of lactose and a decreasing load of caffeine the compression susceptibility parameter decreases as it is equal to 3.69, 8.49 and 8.11 MPa^{-1} for the granulate 11, 53 and 74% (w/w). The values for σ_{max} and γ of the placebo-granulate account for 7.14 MPa and 3.59 MPa^{-1}, respectively. It corresponds most to the results found for the granulate containing 11% (w/w) of caffeine, which is not astonishing as their compositions are most likewise. When 5% (w/w) of corn starch is added to the external phase as it was the case for all tablet formulations, a decrease in the values for σ_{max} can be detected. It is equal to 5.62, 4.83 and 4.82 MPa for the mixture containing 10, 50 and 70% (w/w) of caffeine. The addition of corn starch to the external phase seems to cause a decreasing compactibility. The compression susceptibility parameter, however, seem to be comparable to the ones found for the granulates. They remained equal to 4.08, 8.25 and 6.54 MPa^{-1} for the mixtures 10%, 50% and 70% (w/w). Regarding the mixtures with 10% and 50% (w/w) of caffeine made of placebo granulate, the one containing 74% (w/w) of caffeine and 5% (w/w) of corn starch in the external phase, no clear difference in compactibility can be detected as σ_{max} is equal to 5.42 and 5.13 MPa for the mixture 10% and 50% (w/w), respectively. The compression susceptibility parameter seem to be lower to a certain extend indicating the need of a higher compression forces to reach the same strength of the tablet made of the granulate 53% and 11% (w/w) respectively (γ = 3.81 MPa^{-1} for the mixture 10% (w/w); γ = 6.13 MPa^{-1} for the mixture 50% (w/w)). To mix a “placebo”-granulate with another granulate containing a high drug load in this case does not seem advantageous regarding the compressional behaviour.

5.6.4. Tablet formulation and granulates containing diclofenac sodium

The radial crushing strength of compacts of diclofenac sodium was plotted against the product of the pressure of compression and the relative density (see figure 5.32.).

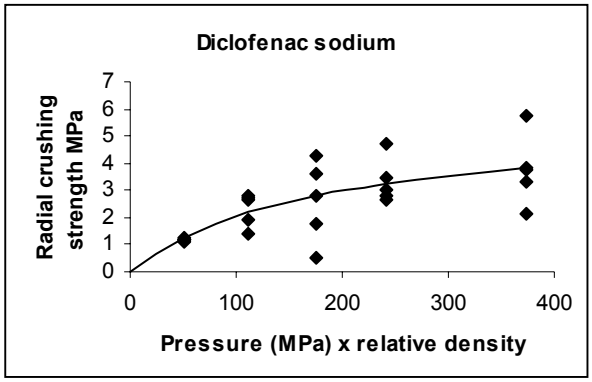


Figure 5.32.: The radial crushing strength of compacts was plotted against the product of the pressure of compression and the relative density. For every pressure of compression five compacts were investigated.

The radial crushing strength of compacts of all granulates containing diclofenac sodium and of the corresponding tabletting mixture was plotted against the product of the pressure of compression and the relative density (see figure 5.33.).

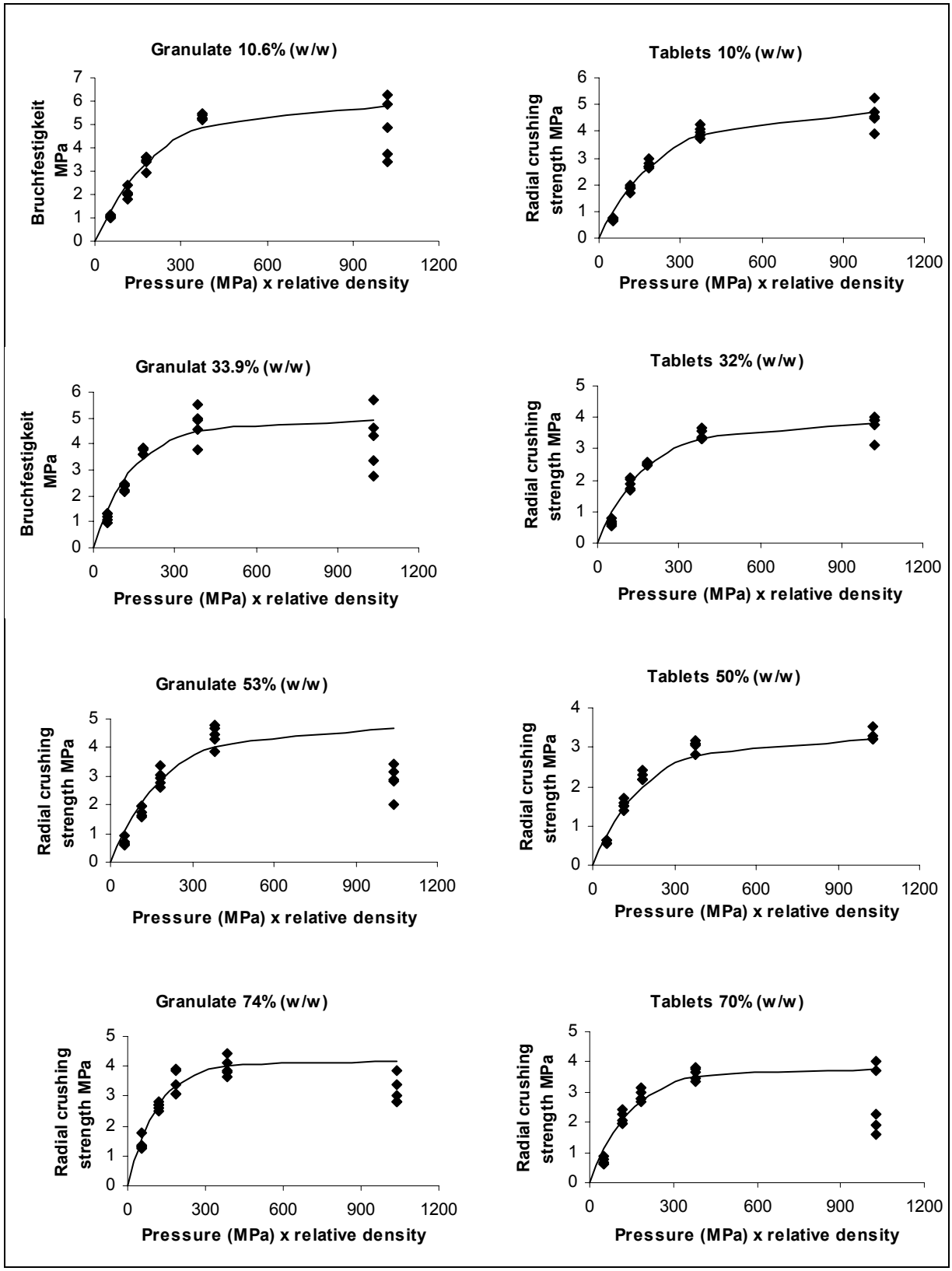


Figure 5.33.: The radial crushing strength of compacts was plotted against the product of the pressure of compression and the relative density. For every pressure of compression five compacts were investigated.

The average values of the radial crushing strength including the standard deviation and the corresponding pressure of compression, is shown in table 5.23.

Table 5.23.: The average values of the radial crushing strength including the standard deviation and the corresponding pressure of compression of the model drug caffeine and all formulations with caffeine is shown.

Diclofenac sodium	(n = 5)					
	Compression pressure (MPa)	**64.96**	**129.92**	**181.89**	**233.86**	**259.84**
Diclofenac sodium	Radial crushing strength (MPa)	1.18	2.30	3.12	3.34	3.76
	RSD (%)	5.29	26.5	34.0	24.6	34.6
	Compression pressure (MPa)	**64.96**	**129.92**	**194.88**	**389.77**	**1039.4**
Granulate 11% (w/w)	Radial crushing strength (MPa)	1.06	2.07	3.41	5.33	4.83
	RSD (%)	3.86	10.0	8.33	2.10	26.2
Tablets 10% (w/w)	Radial crushing strength (MPa)	0.711	1.86	2.75	3.97	4.58
	RSD (%)	5.97	4.98	5.12	4.97	10.6
Granulate 34% (w/w)	Radial crushing strength (MPa)	1.18	2.32	3.72	4.75	4.16
	RSD (%)	12.9	5.51	2.86	13.5	26.9
Tablets 33% (w/w)	Radial crushing strength (MPa)	0.652	1.87	2.52	3.44	3.73
	RSD (%)	13.4	9.07	1.75	4.66	9.46
Granulate 53% (w/w)	Radial crushing strength (MPa)	0.690	1.77	2.96	4.42	2.85
	RSD (%)	19.0	10.7	9.43	8.35	18.5
Tablets 50% (w/w)	Radial crushing strength (MPa)	0.462	1.39	2.10	2.88	3.12
	RSD (%)	8.49	8.65	4.86	5.03	4.21
Granulate 74% (w/w)	Radial crushing strength (MPa)	1.41	2.66	3.47	3.98	3.19
	RSD (%)	15.0	4.75	11.8	7.82	14.1
Tablets 70% (w/w)	Radial crushing strength (MPa)	0.714	2.13	2.87	3.61	2.71
	RSD (%)	13.0	9.82	6.39	5.47	40.3

The determined values of the compression susceptibility parameter and the maximum crushing strength of the different excipients are shown in table 5.24.

Table 5.24.: The compression susceptibility parameter, $\gamma \cdot 10^{-3}$ (MPa)$^{-1}$, and the maximum crushing strength, σ_{max} (MPa), of the different excipients are shown.

	$\gamma \cdot 10^3$	σ_{max}	r
Diclofenac sodium	8.81	3.76	0.992
Granulate with diclofenac sodium 11% (w/w),	4.81	5.81	0.976
Granulate with diclofenac sodium 34% (w/w)	6.49	4.90	0.984
Granulate with diclofenac sodium 53% (w/w)	5.03	4.68	0.970
Granulate with diclofenac sodium 74% (w/w),	8.70	4.16	0.996
Tablets with diclofenac sodium 10% (w/w)	4.57	4.70	0.993
Tablets with diclofenac sodium 32% (w/w)	5.52	3.80	0.989
Tablets with diclofenac sodium 50% (w/w)	5.14	3.23	0.980
Tablets with diclofenac sodium 70% (w/w)	6.91	3.76	0.977

The maximum crushing strength of diclofenac sodium is higher than the one of caffeine as it accounts for 3.76 MPa but the compression susceptibility parameter is lower as it is equal to 8.81 (MPa)$^{-1}$ (see chapter 5.6.3.). Diclofenac sodium seems to have a higher compactibility than caffeine. Regarding the

distribution of the single values of the radial crushing strength a higher spreading (RSD% ≈ 30%) can be observed at a higher pressure of compression indicating different internal tensions within the tablets and a higher tendency for capping than it is the case with the model drug caffeine. When diclofenac is granulated there is a tendency of a decreasing value of σ_{max}, which is also the case regarding the granulates made of the model drug caffeine. The maximum crushing strength crushing strength accounts for 5.81, 4.90, 4.68 and 4.16 MPa for the granulates containing 11%, 34%, 53% and 74% (w/w) of diclofenac sodium, respectively. It becomes obvious, that with the model drug caffeine within the formulations, higher values for σ_{max} can be achieved especially at low concentrations of the model drug as opposed to the formulations containing diclofenac sodium.
The higher the concentration of diclofenac sodium the higher the compression susceptibility parameter, which is 4.81, 6.49, 5.03 and 8.70 MPa^{-1} for the granulates containing 11%, 34%, 53% and 74% (w/w) of diclofenac sodium, respectively. This result can be explained by the different contents of lactose having a comparably low compression susceptibility parameter of 2.72 MPa^{-1} and the different contents of diclofenac sodium having a compression susceptibility parameter of 8.81 MPa^{-1}. With a decreasing concentration of lactose the behaviour of diclofenac sodium seems to get more dominant. The contrariwise phenomena can be observed with a decreasing concentration of diclofenac sodium.

In the case of the tabletting mixtures containing additionally 5% (w/w) of corn starch in the external phase σ_{max} is decreasing compared to σ_{max} of the corresponding granulates. For the tabletting mixture containing 10%, 32%, 50% and 70% (w/w) of diclofenac sodium, respectively, it accounts for 4.70, 3.80, 3.23 and 3.76 MPa. The same trend regarding σ_{max} could also be observed in the case of the model drug caffeine (see chapter 5.6.3.). A decrease in the compression susceptibility parameter can additionally be assessed as it accounts for 4.57, 5.52, 5.14 and 6.91 MPa^{-1} for the tabletting mixture containing 10%, 32%, 50% and 70% (w/w) of diclofenac sodium, respectively. Corn starch, however, seems to have a stabilising effect especially when higher pressures of compression are applied what can be seen regarding the values for the relative standard deviation in table 5.23. and figure 5.33.

5.6.5. Tablet formulation containing proquazone

The radial crushing strength of compacts of proquazone, of all granulates containing proquazone and of the corresponding tabletting mixture was plotted against the product of the pressure of compression and the relative density (see figure 5.34.).

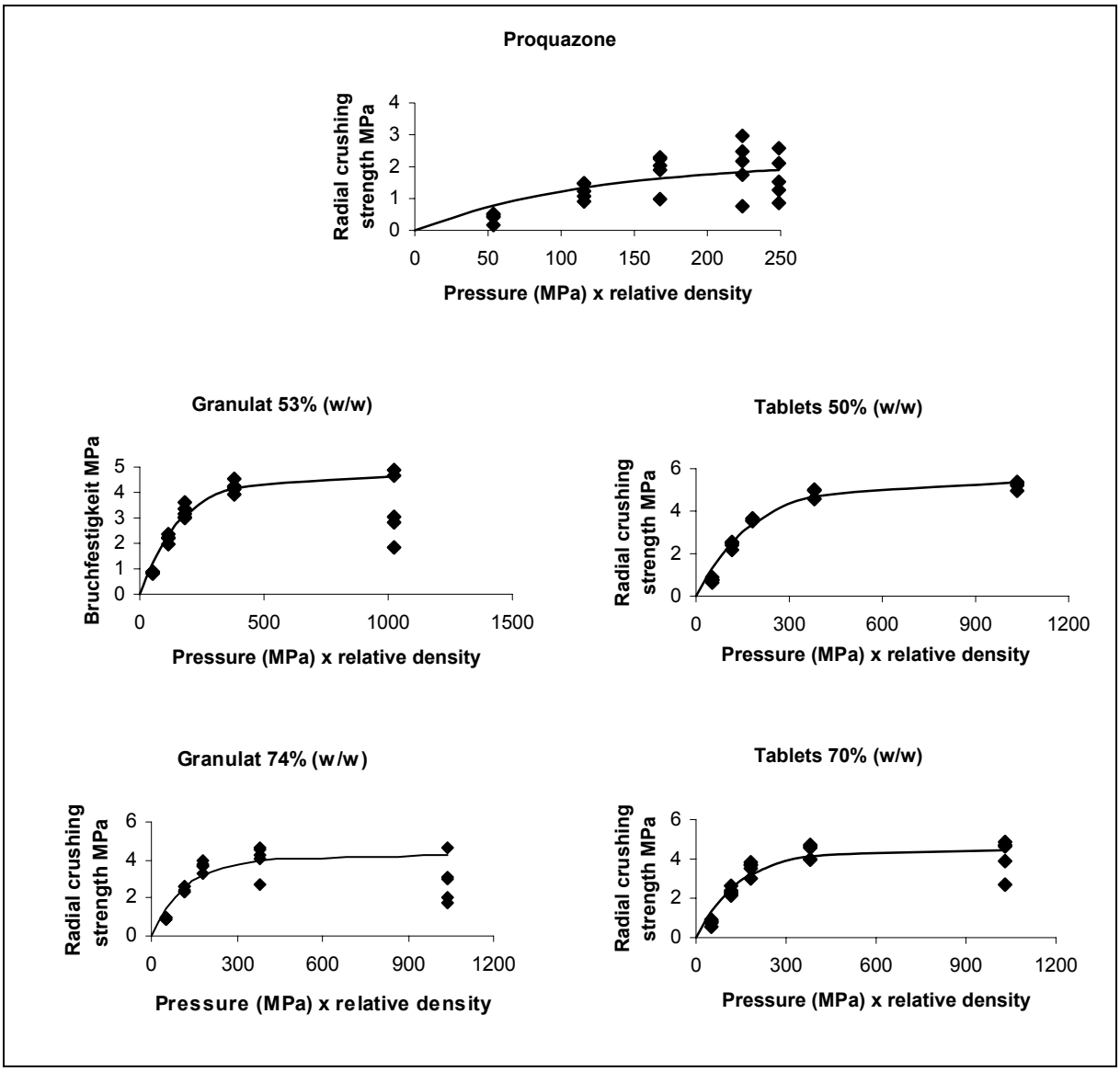


Figure 5.34.: The radial crushing strength of the different compacts was plotted against the product of the pressure of compression and the relative density. For every pressure of compression five compacts were investigated

The average values of the radial crushing strength of the compacts including the standard deviation and the corresponding pressure of compression, is shown in table 5.25.

Table 5.25.: The average values of the radial crushing strength including the standard deviation and the corresponding pressure of compression of the model drug proquazone and all formulations with proquazone is shown.

Proquazone	(n = 5)					
	Compression pressure (MPa)	**64.96**	**129.92**	**181.89**	**233.86**	**259.84**
Proquazone	Radial crushing strength (MPa)	0.404	1.23	1.89	2.03	1.67
	RSD (%)	34.5	20.1	28.3	41.3	40.9
	Compression pressure (MPa)	**64.96**	**129.92**	**194.88**	**389.77**	**1039.4**
Granulate 53% (w/w)	Radial crushing strength (MPa)	0.853	2.19	3.23	4.21	3.45
	RSD (%)	3.96	6.49	7.87	5.27	37.4
Tablets 50% (w/w)	Radial crushing strength (MPa)	0.760	2.42	3.59	4.83	5.24
	RSD (%)	11.8	6.23	1.43	4.59	3.18
Granulate 74% (w/w)	Radial crushing strength (MPa)	0.916	2.44	3.69	4.03	2.90
	RSD (%)	5.85	5.84	6.17	19.7	39.1
Tablets 70% (w/w)	Radial crushing strength (MPa)	0.773	2.34	3.55	4.37	4.16
	RSD (%)	17.6	7.98	9.15	8.44	21.6

The determined values of the compression susceptibility parameter and the maximum crushing strength of proquazone and the different formulations made with the model drug proquazone are shown in table 5.26.

Table 5.26.: The compression susceptibility parameter, $\gamma \cdot 10^{-3}$ $(MPa)^{-1}$, and the maximum crushing strength, σ_{max} (MPa), of proquazone and the different formulations made with the model drug proquazone are shown.

	$\gamma^{*}10^{3}$	σ_{max}	r
Proquazone	8.33	2.17	0.919
Granulate with proquazone 53% (w/w)	5.96	4.64	0.984
Granulate with proquazone 74% (w/w)	7.78	4.23	0.965
Tablets with proquazone 50% (w/w)	5.39	5.36	0.983
Tablets with proquazone 70% (w/w)	6.87	4.45	0.964

It can be assessed comparing proquazone to the model drugs caffeine and diclofenac sodium that the maximum crushing strength is lower as it accounts for 2.17 MPa. Proquazone turns out to have a maximum crushing strength similar to the one of the reference substance acetyl salicylic acid, which is equal to 2.40 MPa. The compression susceptibility parameter is equal to 8.33 MPa^{-1} and resembles most to the one of diclofenac sodium, which is equal to 8.81 MPa^{-1}. Regarding the distribution of the single values of the radial crushing strength, a higher spreading can be observed at higher pressures of compression as for diclofenac sodium. This can be taken as a hint for a stronger capping tendency than caffeine and diclofenac sodium may have.

In the case of proquazone the granulation process really improves compression properties. The maximum crushing strength gets equal to 4.64 and 4.23 MPa for the granulate containing 53% and 74% (w/w) of proquazone, respectively. With proquazone having a worse compressional behaviour than diclofenac sodium, granulates can be produced that seem to have a higher mechanical strength

than the granulates made of diclofenac sodium (see chapter 5.6.4.). Astonishingly, 5% (w/w) of corn starch in the external phase in any tablet formulation with proquazone do not seem to have a negative influence what the mechanical strength is concerned. The maximum crushing strength is higher than the one of the granulates (5.36 MPa for the tabletting mixture containing 50% (w/w); 4.45 MPa for the tabletting mixture containing 74% (w/w) of proquazone, respectively). Quite the opposite observations were made with the granulates and the corresponding formulations containing the model drugs caffeine and diclofenac sodium as σ_{max} seemed to be lower for the granultes then for the corresponding tablet formulations (see chapter 5.6.4. and 5.6.3.).

However, corn starch seems to have a stabilising effect what the spread of the values for the radial crushing strength is concerned especially when higher pressures of compression are applied (see table 5.24. and figure 5.34). The same stabilising effect could be seen in case of the model drugs caffeine and diclofenac sodium (see chapter 5.6.4. and 5.6.3.).

The compression susceptibility parameter seems to be lower for granulates than for the tablet formulations. For the granulate containing 53% (w/w) of proquazone and the corresponding formulation it is equal to 5.96 and 5.39 MPa^{-1}, respectively, and for the granulate containing 74% (w/w) of proquazone and the corresponding formulation it is equal to 7.78 and 6.87 MPa^{-1}, respectively.

5.6.6. Tablet formulation containing UICEL

The radial crushing strength of the compacts of all capsule formulations containing the excipient UICEL that were compressed to tablets simulating a direct compression was plotted against the product of the pressure of compression and the relative density (see figure 5.35.).

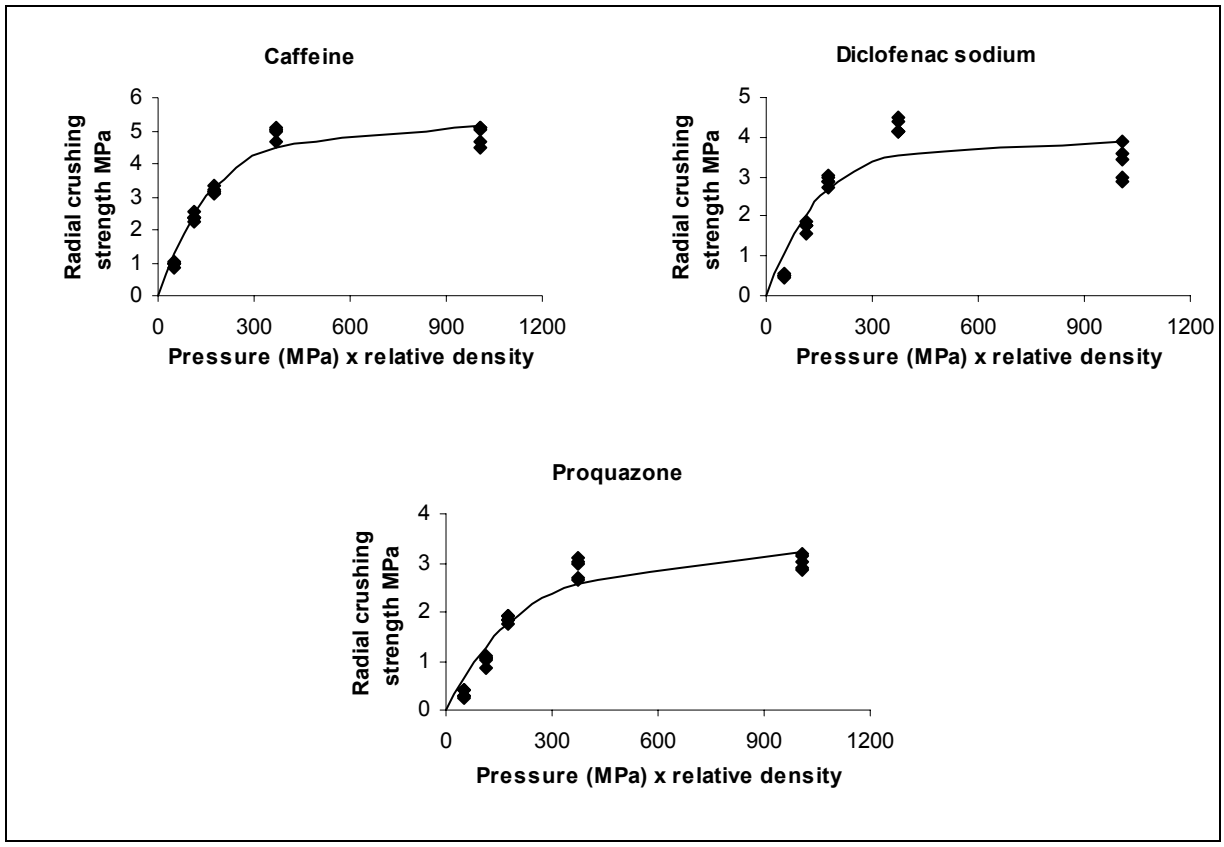


Figure 5.35.: The radial crushing strength of the compacts made of the capsule formulations containing the excipient UICEL and the model drugs caffeine, diclofenac sodium or proquazone, respectively, was plotted against the product of the pressure of compression and the relative density. For every pressure of compression five compacts were investigated

The radial crushing strength of the compacts of all granulates containing the excipient UICEL and the model drug diclofenac sodium as well as the one of the corresponding tabletting mixtures was plotted against the product of the pressure of compression and the relative density (see figure 5.36.).

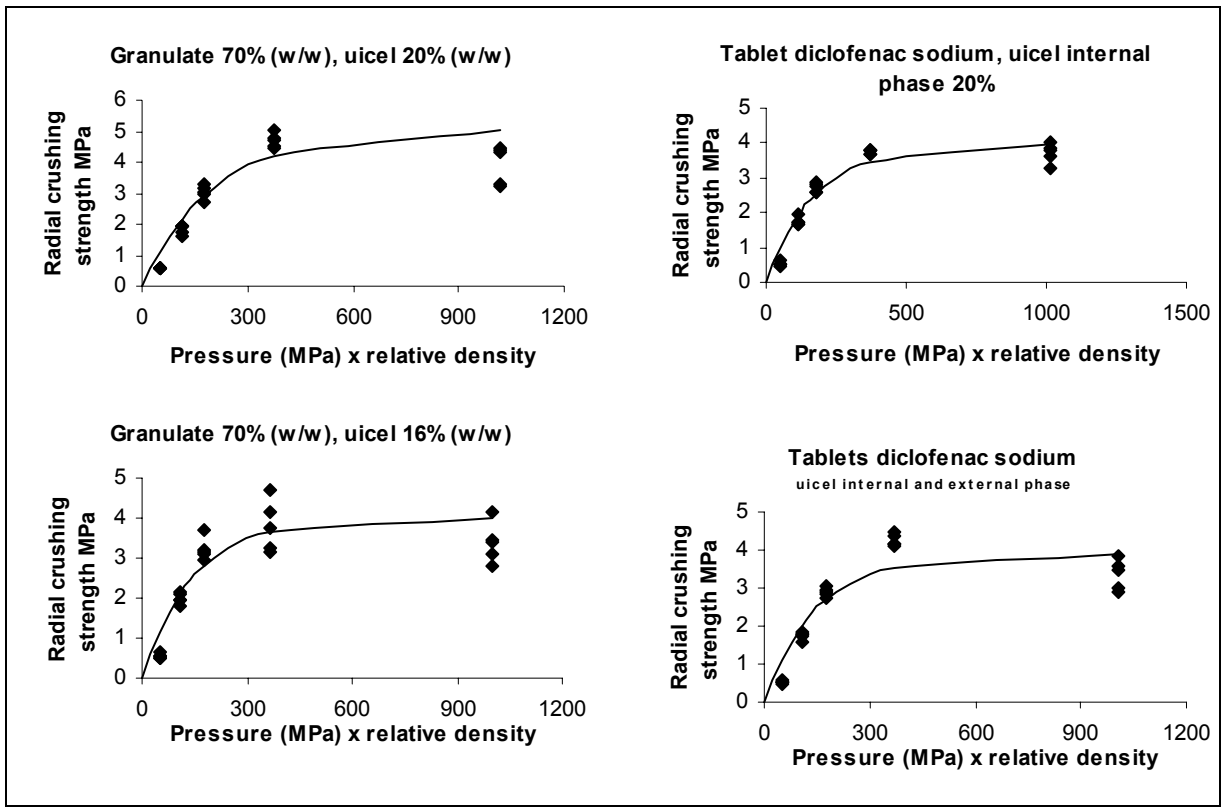


Figure 5.36.: The radial crushing strength was plotted against the product of the pressure of compression and the relative density. For every pressure of compression five compacts were investigated

The average values of the radial crushing strength including the standard deviation and the corresponding pressure of compression, is shown in table 5.27.

Table 5.27.: The average values of the radial crushing strength including the standard deviation and the corresponding pressure of compression of the compacts made of the capsule formulations containing the excipient UICEL and the model drugs caffeine, diclofenac sodium or proquazone, respectively, as well as the ones of all granulates containing the excipient UICEL and the model drug diclofenac sodium as well as the ones of the corresponding tabletting mixtures is shown.

Formulation with UICEL	(n = 5)					
	Compression pressure (MPa)	**64.96**	**129.92**	**194.88**	**389.77**	**1039.4**
Caffeine	Radial crushing strength (MPa)	0.960	2.38	3.18	4.95	4.86
	RSD (%)	5.62	4.22	2.70	3.12	5.55
Diclofenac sodium	Radial crushing strength (MPa)	0.379	1.49	2.59	4.02	3.32
	RSD (%)	14.7	10.1	8.76	5.58	16.1
Proquazone	Radial crushing strength (MPa)	0.333	1.02	1.85	2.89	3.01
	RSD (%)	23.1	8.96	3.24	7.17	4.87
Granulate diclofenac sodium 70% (w/w), UICEL 20% (w/w)	Radial crushing strength (MPa)	0.581	1.83	3.04	4.71	3.93
	RSD (%)	2.42	9.21	7.23	4.84	16.2
Tablet diclofenac sodium 70% UICEL 20% (w/w) internal phase	Radial crushing strength (MPa)	0.582	1.75	2.73	3.76	3.72
	RSD (%)	14.0	7.24	4.72	1.63	7.70
Granulate diclofenac sodium 74% (w/w), UICEL 16% (w/w)	Radial crushing strength (MPa)	0.544	1.98	3.22	3.80	3.38
	RSD (%)	12.6	7.19	8.94	16.7	14.9
Tablet diclofenac sodium 70% UICEL 25% (w/w) internal 5% (w/w) external phase	Radial crushing strength (MPa)	0.509	1.75	2.90	4.26	3.36
	RSD (%)	6.97	6.31	3.81	3.96	12.3

The determined values of the compression susceptibility parameter and the maximum crushing strength of the formulations with UICEL are shown in table 5.28.

Table 5.28.: The compression susceptibility parameter, $\gamma \cdot 10^{-3}$ (MPa)$^{-1}$, and the maximum crushing strength, σ_{max} (MPa), of the different granulates and formulations with the excipient UICEL are shown.

	$\gamma 10^3$	σ_{max}	r
Caffeine 70% (w/w), UICEL 29.5% (w/w)	5.73	5.12	0.982
Diclofenac sodium 70% (w/w), UICEL 29.5% (w/w)	5.32	4.06	0.929
Proquazone 70% (w/w), UICEL 29.5% (w/w)	4.40	3.20	0.965
Granulate diclofenac sodium 70% (w/w), UICEL 20% (w/w) internal phase	5.94	4.42	0.928
Tablets diclofenac sodium 70% (w/w), UICEL 20% (w/w) internal phase	5.70	3.94	0.967
Granulate diclofenac sodium 70% (w/w), UICEL 16% (w/w) internal phase	7.66	3.73	0.957
Tablets diclofenac sodium 70% (w/w), UICEL 15% (w/w) internal phase, 5% (w/w) external phase	6.64	3.88	0.934

It could be demonstrated in this study that the excipient UICEL has excellent properties as direct compression agent (see chapter 5.6.2.). The excipient was first mixed with the model drugs caffeine, diclofenac sodium and proquazone as a capsules mixture. This mixture was then compressed (see chapter 4.4.4.) simulating a direct compression. The resulting tablets show a remarkable strength. The maximum crushing strength accounts for 5.12 MPa for the tablets containing 70% (w/w) of caffeine, 4.06 MPa for the tablets containing 70% (w/w) of diclofenac sodium and 3.20 MPa for the tablets containing 70% (w/w) of proquazone. The values for σ_{max} of the corresponding tablet formulations with 70% (w/w) of model drug that were made of a granulate with no UICEL but corn starch are equal to 4.82 MPa for the formulation containing 70% (w/w) of caffeine (see chapter 5.6.3.), 3.76 MPa for the formulation containing 70% (w/w) of diclofenac sodium (see chapter 5.6.4.) and 4.45 MPa for the formulation containing 70% (w/w) of proquazone (see chapter 5.6.5.). In the case of the model drug caffeine and diclofenac sodium the resulting compactibility seems to be higher using the excipient UICEL than it is the case in the previously discussed formulations that were manufactured after a granulation step. Such an excipient can be an interesting candidate for direct compression. It would allow to leave out the granulation step. The strength of the tablets made with the model drug proquazone and UICEL seems to be weaker than the one of the formulations manufactured after a granulation step. According to the reference substance acetyl salicylic acid having a σ_{max} equal to 2.40 MPa and being a direct compressible substance (see chapter 5.6.1), a value for σ_{max} of 3.20 MPa for the formulation with the model drug proquazone and UICEL may still be sufficient to allow a direct compression. The compression susceptibility parameter of the formulations with UICEL account for 5.73 MPa^{-1} for the formulation containing 70% (w/w) of caffeine, 5.32 MPa^{-1} for the formulation containing 70% (w/w) of diclofenac sodium and 4.40 MPa^{-1} for the formulation containing 70% (w/w) of proquazone. The compression susceptibility parameter is lower than the one of previously discussed formulations that were manufactured after a granulation, which accounts for approximately 6.8 MPa^{-1}. (see chapter 5.6.3., 5.6.4. and 5.6.5.).

UICEL was also used in the granulation process in a way that corn starch was replaced by UICEL. For the granulate containing 20% (w/w) of UICEL and the corresponding tablet formulation with 20% (w/w) of UICEL in the internal phase σ_{max} is equal to 4.42 and 3.94 MPa. For the granulate containing 16% (w/w) of UICEL and the corresponding tablet formulation with 15% (w/w) of UICEL in the internal phase and 5% (w/w) in the external phase, σ_{max} is equal to 3.73 and 3.88 MPa. It follows that the maximum crushing strength seems to be higher when the total amount of UICEL is located in the internal phase. The formulation can be compared to the one where UICEL is replaced by corn starch where σ_{max} of the granulate is equal to 4.16 MPa and σ_{max} of the tablet formulation is equal to 3.76 MPa and the compression susceptibility parameter is equal to 8.70 and 9.91 MPa^{-1}, respectively, for the granulate and the corresponding tablet formulation (see chapter 5.6.4.). It becomes obvious that the values of σ_{max} are comparable to a certain extent. The higher compression susceptibility parameter, however, for the formulation with corn starch indicates that the same strength of a tablet is reached at lower compression forces than it would be the case for the formulation with UICEL. UICEL after granulation does not seem to have advantages over corn starch what its compressibility or compactibility is concerned.

5.7. Characterisation of the formulations

In the following chapter, important key data are shown and briefly discussed. They should give an in-depth characterisation of the different capsule and tablet formulations used in the dissolution test and the compactibility/compressibility investigation.

5.7.1. True, poured, tapped density and Hausner ratio

Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio, respectively, of all granulates and the capsule formulations made with the model drug caffeine are shown in table 5.29.

Table 5.29.: Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio all granulates and the capsule formulations made with the model drug caffeine.

Caffeine	Densities (n = 3)								Hausner ratio	RSD (%)
	True (g/cm^3)	RSD (%)	Poured $(g/ml)^2$	RSD (%)	ρ_p (rel)	Tapped $(g/ml)^2$	RSD (%)	ρ_t (rel)		
Granulate 10.6% (w/w)	1.5211	0.11	0.5442	1.5	0.358	0.687	1.3	0.451	1.26	1.1
Granulate 52.9% (w/w)	1.4691	0.04	0.571	2.2	0.389	0.725	1.2	0.493	1.27	2.7
Granulate 74.1% (w/w)	1.4404	0.14	0.589	1.3	0.409	0.725	0.43	0.725	1.23	1.2
"Placebo" granulate	1.5335	0.04	0.528	1.4	0.345	0.658	0.44	0.429	1.25	1.7
Capsule 10% (w/w)	1.5366*	-	0.458	0.70	0.298	0.710	1.6	0.462	1.55	1.2
Capsule 50% (w/w)	1.5341*	-	0.359	2.0	0.234	0.525	0.38	0.342	1.46	1.8
Capsule 70% (w/w)	1.5329*	-	0.336	0.98	0.219	0.480	1.1	0.313	1.43	1.5

*calculated according to the percentages of each component in the powder mixture (see chapter 4.1.2. and 4.1.3.)

All determinations were made according to the equipment specifications. Details in chapter 4.15. and 4.16.

Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio, respectively, of all granulates and the capsules formulations made with the model drug diclofenac sodium are shown in table 5.30.

Table 5.30.: .Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio of all granulates and the capsule formulations made with the model drug diclofenac sodium.

Diclofenac sodium	Densities (n = 3)								Hausner ratio	RSD (%)
	True (g/cm^3)	RSD (%)	Poured $(g/ml)^2$	RSD (%)	ρ_p (rel)	Tapped $(g/ml)^2$	RSD (%)	ρ_t (rel)		
Granulate 10.6% (w/w)	1.5259	0.09	0.512	4.4	0.335	0.823	1.5	0.539	1.24	0.14
Granulate 32.9% (w/w)	1.5003	0.04	0.672	1.7	0.449	0.8045	2.0	0.538	1.20	0.92
Granulate 52.9% (w/w)	1.4833	0.07	0.659	0.71	0.444	0.771	0.84	0.520	1.17	0.13
Granulate 74.1% (w/w)	1.4769	0.15	0.628	3.1	0.426	0.751	2.2	0.508	1.19	0.89
Capsule 10% (w/w)	1.5361*	-	0.512	4.4	0.512	0.822	1.53	0.537	1.60	2.8
Capsule 32% (w/w)	1.5337*	-	0.497	3.4	0.324	0.801	1.3	0.522	1.61	2.3
Capsule 50% (w/w)	1.5317*	-	0.483	1.1	0.316	0.754	1.9	0.492	1.56	2.5
Capsule 70% (w/w)	1.5295*	-	0.421	3.8	0.275	0.652	1.1	0.426	1.55	4.2

*calculated according to the percentages of each component in the powder mixture (see chapter 4.1.2. and 4.1.3.)

All determinations were made according to the equipment specifications. Details in chapter 4.15. and 4.16.

Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio, respectively, of all granulates and the capsule formulations made with the model drug proquazone are shown in table 5.31.

Table 5.31.: Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio of all granulates and the capsule formulations made with the model proquazone.

Proquazone	Densities (n = 3)								Hausner ratio	RSD (%)
	True (g/cm^3)	RSD (%)	Poured $(g/ml)^2$	RSD (%)	ρ_p (rel)	Tapped $(g/ml)^2$	RSD (%)	ρ_t (rel)		
Granulate 52.9% (w/w)	1.3727	0.13	0.465	1.1	0.338	0.586	0.91	0.427	1.26	1.9
Granulate 74.1% (w/w)	1.3204	0.12	0.449	1.2	0.340	0.564	0.72	0.428	1.26	0.90
Capsule 10% (w/w)	1.5088*	-	0.506	3.1	0.335	0.819	2.2	0.543	1.62	0.94
Capsule 50% (w/w)	1.3952*	-	0.370	3.8	0.265	0.661	1.5	0.474	1.79	4.3
Capsule 70% (w/w)	1.3384*	-	0.345	3.3	0.260	0.633	0.32	0.473	1.84	3.1

*calculated according to the percentages of each component in the powder mixture (see chapter 4.1.2. and 4.1.3.)

All determinations were made according to the equipment specifications. Details in chapter 4.15. and 4.16.

Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio, respectively, of all granulates and the capsule formulations made with the excipients UICEL are shown in table 5.32.

Table 5.32.: Data for true density, (relative) poured (ρ_p), (relative) tapped density (ρ_t) and the Hausner ratio all granulates and the capsule formulations made with the excipient UICEL.

UICEL	Densities (n = 3)								Hausner ratio	RSD (%)
	True (g/cm^3)	RSD (%)	Poured $(g/ml)^2$	RSD (%)	ρ_p (rel)	Tapped $(g/ml)^2$	RSD (%)	ρ_t (rel)		
Capsule mixture caffeine	1.4903	0.07	0.369	0.94	0.248	0.607	1.1	0.408	1.65	0.53
Capsule mixture diclofenac sodium	1.5244	0.08	0.489	1.6	0.320	0.751	0.56	0.492	1.54	2.1
Granulate diclofenac sodium, UICEL 20.1% (w/w)	1.4849	0.10	0.630	0.73	0.425	0.750	0.78	0.505	1.19	0.80
Granulate diclofenac sodium, UICEL 15.9% (w/w)	1.4911	0.07	0.592	0.47	0.397	0.737	0.51	0.494	1.25	0.68
Capsule mixture proquazone	1.3424	0.29	0.359	2.9	0.268	0.626	0.76	0.466	1.74	3.7

All determinations were made according to the equipment specifications. Details in chapter 4.15. and 4.16.

It can be concluded that all Hausner ratios of the granulates are around 1.2-1.3. The Hausner ratios of the capsule mixture always account for approximately 1.6. Wells, 1988, gives a correlation between Hausner ratio and flowability. According to him, all granulates show a flowability in a range of tolerable and good. The Hausner ratio of all capsule formulations indicates a very poor or even no flowability, which is confirmed by the flowability experiment (see chapter 5.7.2.).

5.7.2. Flowability and residual moisture content

The capsule formulations did not show flowability at all in the experimental setting described in chapter 4.5. The flowability of the different granulates used for all tablet formulation and their residual moisture content in percent by weight is shown in table 5.33.

Table 5.33.: The flowability (g/s) and the residual moisture content (%) as well as the corresponding relative standard deviation (%) (RSD) of the different granulates used for the tablet formulations are shown.

	Flowability (g/s) ± RSD (%) (n=5)	Residual moisture content (%)± RSD (%) (n=3)
Caffeine		
Granulate 10.6% (w/w)	5.65 ± 0.59	2.27 ± 19
Granulate 52.9% (w/w)	5.27 ± 3.5	2.49 ± 5.8
Granulate 74.1% (w/w)	5.11 ± 2.3	2.23 ± 8.6
"Placebo" granulate	5.69 ± 3.6	1.76 ± 19
Diclofenac sodium		
Granulate 10.6% (w/w)	6.19 ± 0.35	2.92 ± 7.0
Granulate 33.9% (w/w)	7.45 ± 1.2	2.93 ± 14
Granulate 52.9% (w/w)	6.94 ± 1.2	3.16 ± 5.0
Granulate 74.1% (w/w)	5.87 ± 3.4	2.90 ± 5.4
Granulate 74.1% (w/w), 20.1% (w/w) UICEL	6.72 ± 0.66	4.34 ± 6.7
Granulate 74.1% (w/w), 15.9% (w/w) UICEL	5.72 ± 1.9	3.70 ± 17
Proquazone		
Granulate 52.9% (w/w)	3.67 ± 2.2	2.14 ± 9.3
Granulate 74.1% (w/w)	3.07 ± 1.3	2.23 ± 2.6
UICEL	3.10 ± 3.5	9.17 ± 2.1

The granulates containing the model drug diclofenac sodium showed the fastest flow compared to the other granulates with the same drug loads followed by the granulates containing the model drug caffeine, which clearly flowed faster than the ones containing the model drug proquazone. During the experiment, it could be observed that all granulates showed a regular mass flow (first in first out).
The flowability of the excipient UICEL more or less corresponds to the flowability of the granulate 70% (w/w) made with the model drug proquazone as it accounts for 3.10 g/s.

5.7.3. Particle size of the granulates

The mean and the median particle size of all granulates used for the tablet formulations are summerised in table 5.34.

Table 5.34.: The mean and the median particle size as well as the relative standard deviation (%) of all granulates.

(n=5)	Mean particle size ± RSD (%)	Median particle size ± RSD (%)
Caffeine		
Granulate 10.6% (w/w)	552.1 ± 4.2	521.5 ± 4.0
Granulate 52.9% (w/w)	615.5 ± 0.26	605.0 ± 0.84
Granulate 74.1% (w/w)	484.8 ± 2.3	455.6 ± 3.3
"Placebo" granulate	489.5 ± 4.6	435.3 ± 6.0
Diclofenac sodium		
Granulate 10.6% (w/w)	546.2 ± 1.2	500.7 ± 6.1
Granulate 33.9% (w/w)	719.2 ± 8.2	684.4 ± 9.1
Granulate 52.9% (w/w)	738.6 ± 3.8	711.6 ± 4.0
Granulate 74.1% (w/w)	609.1 ± 3.3	578.0 ± 4.4
Granulate 74.1% (w/w), 20.1% (w/w) UICEL	621.0 ± 1.4	534.9 ± 2.2
Granulate 74.1% (w/w), 15.9% (w/w) UICEL	534.9 ± 2.2	438.4 ± 2.5
Proquazone		
Granulate 52.9% (w/w)	410.5 ± 3.8	339.8 ± 4.7
Granulate 74.1% (w/w)	404.2 ± 2.9	342.2 ± 6.5

5.7.4. Crushing strength, tablet height, apparent, true and relative density

The crushing strength right after the compression as well as the one after a storage time of 14 days in a desiccator containing a saturated solution of potassium carbonate giving an air moisture of 45%, the tablet height, the apparent, true and relative density of the tablets containing the model drug caffeine are shown in table 5.35. In the case of the formulations made with the model drug caffeine, no change in crushing strength could be detected after storage time of 14 days.

Table 5.35.: The crushing strength right after compression and after a storage time of 14 days, the tablet height, the apparent, true and relative density of the tablets conaining the model drug caffeine are shown.

Caffeine	Crushing strength (N) ± RSD (%) (n=10)		Height (mm) (n=10)	Densities (n=10)	(n=3)	
	After compression	After 14 days	± RSD (%)	Apparent (g/cm^3)	True (g/cm^3) ± RSD (%)	Relative
Tablets 10% (w/w), excentric press	50.6 ± 6.5	53.6 ± 6.1	3.10 ± 1.9	1.2906	1.5148 ± 0.04	0.8520
Tablets 50% (w/w), excentric press	49.4 ± 6.9	49.4 ± 4.2	3.14 ± 0.28	1.2831	1.4663 ± 0.09	0.8751
Tablets 70% (w/w), excentric press	48.4 ± 7.9	50.9 ± 5.7	3.24 ± 0.27	1.2483	1.4405 ± 0.03	0.8666
Tablets 10% (w/w), presster	49.9 ± 3.9	45.4 ± 11.4	3.19 ± 0.67	1.2703	1.5102 ± 0.12	0.8411
Tablets 50% (w/w), presster	50.4 ± 9.1	52.2 ± 10.0	3.22 ± 0.65	1.2595	1.4626 ± 0.08	0.8611
Tablets 70% (w/w), presster	50.3 ± 11.0	55.1 ± 10.0	3.23 ± 0.64	1.2546	1.4405 ± 0.03	0.8709
Tablets 50% (w/w), mixture placebo and granulate 74% (w/w), excentric press	49.0 ± 4.4	52.6 ± 7.3	3.17 ± 0.31	1.2769	1.4626 ± 0.08	0.8730

The crushing strength right after the compression as well as the one after a storage time of 14 days in a desiccator containing a saturated solution of potassium carbonate giving an air moisture of 45%, the tablet height, the apparent, true and relative density of the tablets containing the model drug diclofenac sodium are shown in table 5.36.

Table 5.36.: The crushing strength right after compression and after a storage time of 14 days, the tablet height, the apparent, true and relative density of the tablets containing the model drug diclofenac sodium are shown.

Diclofenac sodium	Crushing strength (N) ± RSD (%) (n=10)		Height (mm) (n=10)	Densities (n=10)	(n=3)	
	After compression	After 14 days	± RSD (%)	Apparent (g/cm^3)	True (g/cm^3) ± RSD (%)	Relative
Tablets 10% (w/w)	50.2 ± 5.8	47.2 ± 3.4	3.12 ± 0.01	1.3017	1.5181 ± 0.08	0.8575
Tablets, 32% (w/w)	50.2 ± 4.2	47.5 ± 7.4	3.01 ± 0.02	1.3456	1.4948 ± 0.03	0.9002
Tablets, 50% (w/w)	53.1 ± 6.1	50.8 ± 7.2	2.97 ± 0.32	1.3648	1.4833 ± 0.07	0.9201
Tablets, 70% (w/w)	53.8 ± 7.2	49.9 ± 9.8	3.12 ± 0.01	1.2951	1.4769 ± 0.15	0.8769

The crushing strength right after the compression as well as the one after a storage time of 14 days in a desiccator containing a saturated solution of potassium carbonate giving an air moisture of 45%, the tablet height, the apparent, true and relative density of the tablets containing the model drug caffeine are shown in table 5.37.

Table 5.37.: The crushing strength right after compression and after a storage time of 14 days, the tablet height, the apparent, true and relative density of the tablets containing the model drug proquazone are shown.

Proquazone	Crushing strength (N) ± RSD (%) (n=10)		Height (mm) (n=10)	Densities (n=10)	(n=3)	
	After compression	After 14 days	± RSD (%)	Apparent (g/cm^3)	True (g/cm^3) ± RSD (%)	Relative
Tablets 50% (w/w)	50.6 ± 2.7	50.1 ± 8.2	3.49 ± 0.31	1.1617	1.3774 ± 0.09	0.8434
Tablets 70% (w/w)	53.2 ± 7.1	45.7 ± 10.3	3.72 ± 0.29	1.0885	1.3254 ± 0.10	0.8213

The crushing strength right after the compression as well as the one after a storage time of 14 days in a desiccator containing a saturated solution of potassium carbonate giving an air moisture of 45%, the tablet height, the apparent, true and relative density of the tablets containing the excipients UICEL are shown in table 5.38.

Table 5.38.: The crushing strength right after compression and after a storage time of 14 days, the tablet height, the apparent, true and relative density of the tablets containing the excipient UICEL are shown.

UICEL	Crushing strength (N) ± RSD (%) (n=10)		Height (mm) (n=10)	Densities (n=10)	(n=3)	
	After compression	After 14 days	± RSD (%)	Apparent (g/cm^3)	True (g/cm^3) ± RSD (%)	Relative
Capsule mixture caffeine 70% (w/w) UICEL 29.5% (w/w) compressed to tablet	52.2 ± 3.5	47.3 ± 7.5	3.40 ± 0.24	1.1986	1.4903 ± 0.07	0.8043
Capsule mixture diclofenac sodium 70% (w/w) UICEL 29.5% (w/w) compressed to tablet	50.5 ± 7.5	44.7 ± 11.1	3.29 ± 0.03	1.2385	1.5244 ± 0.08	0.8125
Tablets with diclofenac sodium 70% (w/w), UICEL 20% (w/w)	48.4 ± 10.0	46.3 ± 8.1	3.17 ± 0.01	1.2848	1.4819 ± 0.05	0.8670
Tablets with diclofenac sodium 70% (w/w), UICEL 15% (w/w) internal phase, 5% (w/w) external phase	52.5 ± 8.1	49.6 ± 14.6	3.26 ± 0.01	1.2501	1.4903 ± 0.09	0.8388
Capsule mixture proquazone 70% (w/w) UICEL 29.5% (w/w) compressed to tablet	51.3 ± 7.3	47.9 ± 8.8	3.41 ± 0.01	1.1877	1.3424 ± 0.29	0.8848

5.7.5. Mass and content uniformity

The mass and content uniformity of all formulations fulfil the requirements of USP XIV. When the content uniformity of all capsule formulations was determined, the mass of an empty capsule shell with size number 3 was first subtracted. It accounted for 50.31 ± 2.36 mg (n=30).

The mass and content uniformity of all formulations with the model drug caffeine are shown in table 5.39.

Table 5.39.: The mass and content uniformity of all formulations with the model drug caffeine. The values of the content uniformity, *M* (mg) and *M* (%), as well as the mass uniformity, *M* (mg), and the relative standard deviation (%) (RSD) are shown.

Caffeine	Content uniformity (n=10)		Mass uniformity (n=20)
	M (mg) ± RSD (%)	*M* (%)	*M* (mg) ± RSD (%)
Capsules with caffeine 10% (w/w), machine filled	15.4 ± 1.6	9.98	205.5 ± 0.82
Capsules with caffeine 50% (w/w), machine filled	75.6 ± 2.0	48.8	206.2 ± 1.9
Capsules with caffeine 70% (w/w), machine filled	108.2 ± 3.9	69.6	206.4 ± 2.1
Tablets with caffeine 10% (w/w), excentric press	15.6 ± 0.50	9.94	156.0 ± 0.50
Tablets with caffeine 50% (w/w), excentric press	77.7 ± 0.60	49.9	155.4 ± 0.44
Tablets with caffeine 70% (w/w), excentric press	108.4 ± 0.67	69.4	155.8 ± 0.48
Tablets with caffeine 10% (w/w), presster	14.9 ± 4.9	9.59	156.1 ± 0.42
Tablets with caffeine 50% (w/w), presster	78.2 ± 2.0	50.3	156.1 ± 1.1
Tablets with caffeine 70% (w/w), presster	109.9 ± 1.6	70.7	155.7 ± 0.94
Tablets with caffeine 50% (w/w), mixture placebo and granulate with caffeine 74% (w/w), excentric press	78.1 ± 2.2	50.5	155.4 ± 0.01

The mass and content uniformity of all formulations with the model drug diclofenac sodium are shown in table 5.40.

Table 5.40.: The mass and content uniformity of all formulations with the model drug diclofenac sodium. The values of the content uniformity, *M* (mg) and *M* (%), as well as the mass uniformity, *M* (mg), and the relative standard deviation (%) (RSD) are shown.

Diclofenac sodium	Content uniformity (n=10)		Mass uniformity (n=20)
	M (mg) ± RSD (%)	*M* (%)	*M* (mg) ± RSD (%)
Capsule with diclofenac sodium 10% (w/w),	15.9 ± 4.6	10.3	207.0 ± 3.5
Capsules with diclofenac sodium 32% (w/w)	49.6 ± 3.3	31.7	203.8 ± 3.1
Capsules with diclofenac sodium 50% (w/w)	79.6 ± 3.9	50.4	207.8 ± 4.8
Capsules with diclofenac sodium 70% (w/w),	97.1 ± 3.4	69.7	184.6 ± 6.6
Tablets with diclofenac sodium, 10% (w/w)	15.2 ± 0.11	9.72	156.2 ± 0.54
Tablets with diclofenac sodium, 32% (w/w)	49.6 ± 3.4	31.7	156.0 ± 0.57
Tablets with diclofenac sodium, 50% (w/w)	76.9 ± 0.39	0.50	155.6 ± 0.52
Tablets with diclofenac sodium 70% (w/w)	107.4 ± 1.2	69.0	155.6 ± 0.71

The mass and content uniformity of all formulations with the model drug proquazone are shown in table 5.41.

Table 5.41.: The mass and content uniformity of all formulations with the model drug proquazone. The values of the content uniformity, *M* (mg) and *M* (%), as well as the mass uniformity, *M* (mg), and the relative standard deviation (%) (RSD) are shown.

Proquazone	Content uniformity (n=10)		Mass uniformity (n=20)
(n=10)	*M* (mg) ± RSD (%)	*M* (%)	*M* (mg) ± RSD (%)
Capsules with proquzazone 10% (w/w), machine filled	15.5 ± 1.6	9.92	203.7 ± 2.5
Capsules with proquazone 50% (w/w), machine filled	78.2 ± 1.7	50.2	198.2 ± 3.0
Capsules with proquazone 70% (w/w), machine filled	108.8 ± 5.3	70.1	203.4 ± 4.1
Capsule with 50% (w/w) proquazone, handfilled	78.2 ± 1.7	50.2	-
Tablets with proquazone 50% (w/w)	77.0 ± 0.52	49.4	155.9 ± 0.32
Tablets with proquazone 70% (w/w)	115.9 ± 0.62	69.7	155.9 ± 0.40
Capsules with granulate of proquazone 74% (w/w)	77.5 ± 1.7	74.3	-
Capsule mixture 50% (w/w) compressed	77.5 ± 0.28	49.8	155.7 ± 0.31

The mass and content uniformity of all formulations with the excipient UICEL are shown in table 5.42.

Table 5.42.: The mass and content uniformity of all formulations with the excipient UICEL. The values of the content uniformity, *M* (mg) and *M* (%), as well as the mass uniformity, *M* (mg), and the relative standard deviation (%) (RSD) are shown.

UICEL	Content uniformity (n=10)		Mass uniformity (n=20)
	M (mg) ± RSD (%)	*M* (%)	*M* (mg) ± RSD (%)
Capsules with caffeine 70% (w/w), UICEL 29.5% (w/w), machine filled	108.7 ± 2.4	70.0	204.0 ± 2.2
Capsule mixture caffeine 70% (w/w) UICEL 29.5% (w/w) compressed to tablet	-	-	156.4 ± 0.24
Capsules with diclofenac sodium 70% (w/w), UICEL 29.5% (w/w), machine filled	107.9 ± 2.3	69.16	205.9 ± 4.7
Capsule mixture diclofenac sodium 70% (w/w) UICEL 29.5% (w/w) compressed to tablet	-	-	156.4 ± 0.22
Tablets with diclofenac sodium 70% (w/w), UICEL 20% (w/w) internal phase	105.7 ± 1.2	67.6	156.5 ± 0.64
Tablets with diclofenac sodium 70% (w/w), UICEL 15% (w/w) internal phase, 5% (w/w) external phase	106.8 ± 0.73	68.3	156.4 ± 0.55
Capsules with proquazone 70% (w/w), UICEL 29.5% (w/w), machine filled	106.3 ± 1.7	68.5	185.8 ± 4.0
Capsule mixture proquazone 70% (w/w) UICEL 29.5% (w/w) compressed to tablet	-	-	155.9 ± 0.15

6. Conclusion

6.1. Dissolution, water uptake and disintegration

The intention of this work was to investigate technological reasons for the design and choice of an appropriate solid dosage form with the aim to build in and not to test in the quality according to FDA's new concept of quality assurance in the 21st century, i.e. to understand the process and the formulation. It should make a contribution towards formulation design. This task requires specific knowledge, often years of experience and is not yet completely documented. The work demonstrates that the choice of a capsule or tablet formulation needs to be related not only to marketing aspects but also to technological considerations. The choice to develop a drug as a capsule or a tablet formulation can play an important role. Special physico-chemical properties of the drugs and excipients that are normally determined in the preformulation stage should therefore serve as a base for the decision, whether to manufacture a tablet or a capsule formulation. Wettability and solubility are two physico-chemical properties that were investigated especially in context with dissolution, because from a technological point of view the drug dissolution test is a very suitable tool providing a lot of information about the formulation and to describe formulation properties also with certain respect to physiology.

There are various possibilities to analyse the solubility of a compound. In this study, however, it was determined with respect to the dissolution experiment in a saturated solution over a period of time at 37°C.

As a mean for the determination of the wettability, the contact angle with water and the total surface free energy using the modified Washburn method was chosen. Especially the determination of the total surface free energy of multi-component systems consisting of substances with completely different dissolving, disintegrating or swelling characteristics turned out to be very challenging, because at least two test liquids have to be found which do not cause a swelling or a dissolution with any of the components in the system. Another possibility to analyse the wettability of a system is the determination of the water uptake. This better accessible method helped to express the wettability of the different formulations by the water sorption constant and could be correlated with the results found in the dissolution experiments.

A standard tablet and a standard capsule formulation were manufactured with caffeine, a model drug found to be well soluble and well wettable. All capsule caffeine-formulations turned out to be robust in the dissolution experiment as the whole amount was released at the same time independently of the drug load. The consistent release of caffeine can be explained by the fact that the powder components, which all have a good solubility and a good wettability are in a loose and disperse state. As there was no disintegration in the basket the water is assumed to penetrate and to wet the large surface of the powder bulk in a way that all components are immediately dissolved. The hypothesis can be put forward that when a compound is found to be well wettable and well soluble the capsule approach leads to a robust formulation with a fast release. The dissolution of the tablet formulation, however,

turned out not to be robust, i.e. the caffeine dissolution rate was depending on the drug load. Tablets with a high concentration of lactose showed a fast dissolution but by an increasing drug load the drug release was decreasing. It can be concluded that when the model drug is embedded in a continuous phase of lactose there is a wetting effect leading to an accelerated dissolution in the tablet formulation. However, this wetting effect occurs when the concentration of lactose is proportionally high. In these cases the system can be considered as a drug in lactose formulation. If the amount of lactose is decreasing the less wettable drug percolates the tablet formulation, which results in a slow-down of the dissolution rate. If more lactose is added at the expense of drug, the formulation ends up in a lactose in drug system. In this respect one has to keep in mind the total different behaviour of an oil in water and a water in oil emulsion system, which is also related to the percolation phenomena of the two components involved. A different behaviour in disintegration between the tablet formulations was excluded as no disintegration could be observed in the basket during the dissolution experiment. The poorer wetting of the tablet formulation causing a delayed release and the missing disintegration is supported by the significant lower water uptake of the tablet formulation in contrast to the one of the capsule formulation.

To investigate the influence of another excipient on dissolution, lactose was replaced by UICEL in the capsule formulation with the highest drug load. Independently of the excipient the release of caffeine was comparably fast as it was the case with lactose as filler. As UICEL is said to be a direct compressible agent, the powder mixture was compressed to tablets. The speed of the dissolution of these tablets turned out to be as fast as the ones of the capsule formulations. The formulation containing UICEL showed beside its fast dissolution also a rapid disintegration in the basket. The disintegrant, however, which is developing its impact in the tablet, has to be wetted first. The wetting of a system being the first step in the dissolution process followed by solubilisation, disintegration or both can therefore be regarded fundamentally important and as indicator for a fast or a slow drug release of a system.

Diclofenac sodium was investigated having the same surface free energy than caffeine but a poorer solubility. The standard capsule and tablet formulations did not turn out to be robust as their release was depending on the drug load. Tablets and capsules with a high concentration of lactose showed a fast dissolution but by an increasing drug load the drug release was decreasing. None of the formulations showed a disintegration in the basket during the dissolution experiment. The same conclusion made with the model drug caffeine could be drawn in this example as well: when this particular model drug is embedded in a continuous phase of lactose there is a wetting effect leading to an accelerated dissolution in the tablet and the capsule formulation. However, this wetting effect occurs only when the concentration of lactose is proportionally high. Obviously, the powder mixture with a high concentration of diclofenac sodium in the capsule shell although being in a loose and porous state could not be satisfactory wetted followed by an immediate release of the drug as it was the case with the capsule formulation containing a high load of caffeine. This fact is supported by the water sorption constant. The water sorption of the capsule and the tablet formulation containing the highest drug content of diclofenac sodium turned out to be in the same range as the one of the corresponding tablet formulation containing caffeine.

When lactose was replaced by UICEL in the capsule formulation with the highest drug load, the release turned out to be faster. The water sorption constant was also higher compared to the formulation containing lactose. When the mixture was compressed to tablets a dramatic delayed release was observed. Interestingly, the kinetic of this dissolution turned out to be a $\sqrt{t}$-kinetic. UICEL seems to build a continuous phase around the drug diclofenac sodium. The water sorption of this formulation, however, turned out to be much lower than the one of the corresponding capsule formulation. The amount of water that was taken up was not enough for the excipient UICEL to develop its impact as a disintegrating and/or wetting agent. In this context the fact has to be mentioned that when the water sorption constant was plotted against the values found in the dissolution experiment no linear correlation as it was the case for all formulations without UICEL was found, but one by using a power equation of the form $y = mx^{-q}$. It can be concluded that this finding demonstrates impressively that UICEL just needs small amounts of water to develop its ability to wet and to disintegrate and that there is a critical value for the water, where the amount of water penetrating the formulation is suddenly not enough any more to cause a sufficient wetting effect and a proper disintegration. Another attempt was made to accelerate the dissolution by granulating the excipient UICEL. The amount of the previously used disintegrant, corn starch, was replaced by UICEL. The resulting tablets, however, did not show a faster release than the other tablets with corn starch. Again, the water sorption constant remained comparably low.

This result impressively shows that the choice of the "*right*" excipients in combination with the model drug plays a major role or even the major role no matter how the physical properties of the drug were at the beginning. In this context it is important to realize that diclofenac sodium is a ionic substance and that the system diclofenac sodium/cellulose II may show in the presence of ionic sodium a similar behaviour as Na-carboxymethylcellulose. However, to elucidate the exact reason further studies are necessary.

This assumption is confirmed with the example of the last model drug utilized in this study, proquazone. Proquazone is a poorly wettable and poorly soluble drug and in addition a neutral molecule. With the capsule formulation containing the model drug proquazone and lactose, there were really prolonged releases especially when the drug was found in high concentrations. When the same amount of proquazone was formulated as a tablet a fast dissolution could be achieved independently of the drug load. It became evident that the improvement of the dissolution rate was a result of the wet granulation process where the poorly wettable components were coated with the well wettable excipients. It can be concluded that a granulation process for poorly wettable compounds certainly is a possibility to receive a robust formulation. The measurement of the water sorption again correlated very well with the results found in the dissolution experiment.

When lactose was replaced by UICEL in the capsule formulation with the highest drug load, the release turned out to be as fast as the one of the corresponding tablet formulation with lactose. When the mixture was compressed to a tablet a comparably fast release could be observed. This result again is supported by the results found in the water sorption experiment.

It can be put forward the hypothesis that such a dissolution behaviour of proquazone could be characteristic for poorly wettable non-ionic drugs. However, to confirm this assumption further examples are needed.

As mentioned above, UICEL turned out to be an excellent filler in the capsule filling process leading to high dissolution rates. In a capsule filling process, however, only little compression forces occur as opposed to the tablet manufacturing where compression forces easily reach several kN. In order to totally exclude any compression of the powder mixture capsules were filled by hand. The releases of the model drugs caffeine and diclofenac sodium in combination with UICEL remained equal to the release of the capsule formulation manufactured with the capsule filling equipment. The dissolution of the model drug proquazone, again, slowed down dramatically. A dissolution of a drug is proportional to the surface area of the drug. It has to be considered that namely the effective surface area, the area that is available for the dissolution fluid, can decrease, if the drug is poorly wettable because of adsorption of air at the surface of the poorly wettable compound (Finholt et al., 1966). It is reported that the drug powder remains then partly floating on the surface of the medium during dissolution testing. As a consequence the area available for the dissolution media decreases and so does the dissolution rate although proquazone in this case had a larger surface area (towards air) compared to the proquazone that was encapsulated by a machine or compressed to a tablet. This is confirmed by the water sorption experiment as the water sorption constant decreased again to an amount comparable to the one found for the capsule formulation with proquazone and lactose mentioned above. It can be concluded that UICEL, to develop its impact as a wetting agent and as a disintegrant, must have a certain physical contact or closeness to the drug.

When the disintegration of the formulation was investigated according to Ph. Eur. 2002 for all formulations made of the model drugs caffeine and diclofenac sodium there was a correlation between the dissolution behaviour and the disintegration time. With the model drug proquazone, however, no correlation between the dissolution behaviour and the disintegration time could be observerd. This result confirms the superiority of the dissolution rate experiment as compared to the disintegration time determination for a better discrimination between the formulations. As a scientific tool, the disintegration time measurement must be considered controversial, as for example the “exact” disintegration time has to be determined by eye when the formulations seems to be disintegrated, which is in fact not really detectable during the experiment. Furthermore the mechanical stress caused by the disk made of plastic on the formulation can lead to false conclusions. The capsules mixture containing proquazone and lactose showing the slow dissolution rate was a loose powder bed. Due to the mechanical stress in the disintegration apparatus a disintegration time fulfilling the pharmacopeal requirements could be achieved. The results of the dissolution behaviour, however, showed quite the opposite.

In case of all model drugs the results of the water sorption experiments of the formulations contained a lot of information, which complied with the results found in the dissolution experiment. For preformulation studies of a new drug substance it is strongly recommended to include water sorption experiments especially in the case of a high drug content. Such an approval fits well into FDA’s new concept of quality assurance in the 21st century, i.e. to understand the process and the formulation, to build in and not to test in the quality.

6.2. Compressibility and compactibility

The physical model of powder compression proposed by Leuenberger (1980) connects the parameters compressibility and compactibility. In this work it was tried to use this approach as a screening tool for the different starting materials as it was intended to have a fast and practical, but scientific solution for an industrial environment. Therefore, in contrast to earlier studies, just five different compression forces for each sample were applied and the crushing strength was determined with a common tablet tester. The analysis of the different powders, formulations and granulates turned out to contain a lot of information about the properties of compression. According to the compression properties of the direct compressible reference substance acetyl salicylic acid and the direct compressible UICEL, three properties of a granulate or a substance should be analysed in order to find a compound to be well compressible or not. It is assumed that transitions are fluent and the interplay of several parameters effect whether a substance is poorly or well compressible. When their maximum crushing strength is compared to the one of the direct compressible reference substance acetyl salicylic acid it is found that this maximum tensile strength (extrapolated to infinite pressure) of 2.40 MPa is relatively low compared to the ones found for the granulates and the formulations, but this value for compactibility of acetyl salicylic acid seem to be enough for a direct compression. The compression susceptibility parameter, which describes volume reduction of the direct compressible UICEL and acetyl salicylic acid is between 6-7 MPa^{-1} indicating that at comparatively low pressures of compression a satisfactory mechanical strength can be achieved within a compact. This parameter, for some granulates is sometimes far lower around 4 MPa^{-1}. However, all formulations and granulates used in the study were easily compressible on the excentric press. The tabletting mixtures containing 10%, 50% and 70% (w/w) of caffeine could even be compressed on a Presster™ compaction simulator simulating a Korsch PH 336 with a speed of 180000 tablets per hour.

The direct compressible agents acetyl salicylic acid and UICEL do not show a large variation of the values for the maximum crushing strength even when high pressures of compression were applied. This is considered the third important property regarding compressibility and compactibility. Such a high variability and/or even a decrease in the crushing strength was found to be a sign for capping indicating internal tensions of the material in the compact. The lower the pressure of compression is causing those internal tensions, the poorer the adequacy of the material for compression. This is well confirmed by the reference substance paracetamol, having very poor compression properties: a low maximum crushing strength, a low compression susceptibility parameter and a huge spread of the values for the maximum crushing strength already at a low pressure of compression.

According to the two reference substances the compression properties of all formulations and granulates turned out to be well.

The granulation process was found to improve compactibility and there was no capping tendency, even at very high pressures of compression in contrast to the single model drugs compressed without excipients. When 5% (w/w) of corn starch was added to the external phase of the formulations, the maximum crushing strength seemed to be decreasing in the case of the model drugs caffeine and diclofenac sodium. In the case of the formulations and granulates made with the model drug proquazone such a decrease could not be observed. When the capsule formulation containing UICEL

were analysed, the addition of UICEL caused an impressive improvement of the compression properties demonstrating the suitability not only as disintegrant but as direct compressing agent. When UICEL was granulated comparable properties could be observed as for the granulates containing corn starch instead of UICEL.

As final comment the conclusion can be drawn that it is extremely important to design according to the FDA's new concept of quality insurance of the 21st century a science based and standardised preformulation study for every new drug, in order to measure the critical parameters, which need to include beside of disintegration time and dissolution tendency, the wettability of the drug, the water uptake capacity and in case of a tablet formulation the compactibility and compressibility, e.g. according to Leuenberger (1980).

6.3. Outlook

It is suggested that as a continuation of this study, a science based efficient technological screening program for drugs and excipients should be developed with the aim to facilitate a computer-aided design of dosage forms. In this context it is important to keep in mind the following comments:

The wettability of a pharmaceutical solid turned out to be a very important physical parameter. With a science based preformulation study it is important to explore possibilities to improve wettability of a compound. At first simple formulations with other commonly used excipients such as avicel or mannitol could be made and if not satisfactory the new excipient UICEL, i.e. cellulose II should be tested in order to avoid the use of surfactants which can in higher concentrations damage the biological membrane. Last but not least the manufacturing of a solid dispersion could be a further possible approach. A deepened investigation and quantification of the role of the particle size of a poorly wettable compound is another topic. The smaller the particle size of a poorly wettable compound gets the smaller the effective surface area available for dissolution gets in contrast to well wettable substances where there is an increasing dissolution rate with a decreasing particle size (Finholt et al., 1966).

Within a continuation of this work other poorly wettable compounds should be tested. According to Hugentobler et al., 1993, phenacetin shows a very poor wettability. The dissolution experiments could be carried out with this model drug again. The question of a ionic or non-ionic drug needs to be investigated in more detail especially in combination with excipients where hydrogen bonds play an important role.

The concept to use the water sorption constant as a tool for the decision whether to formulate a drug as a capsule or a tablet formulation is certainly worth to be deepened.

The compressibility and compactibility study that was carried out with the Zwick®1478 Universal Testing Instrument turned out to be very useful giving a clear discrimination between the different systems. An important question is the role of the compressibility parameter as a function of the compression speed: is it possible to achieve within the time of compression the necessary close contacts between the particles to form a tablet of adequate strength? Newly there is a Presster™ compaction simulator in the IPT, which is able to simulate different high-speed rotary presses. The screening procedure could be carried out with this simulator in the future. This would lead to conditions that are close to the ones in

the industry. In this respect substances or systems should be investigated with low compactibility and with low compression susceptibility parameters. The reference substance paracetamol was nearly incompressible. It would be of interest to produce different tablet formulations with this compound in high concentration and to investigate how compressibility or compactibility are changed using various excipients and different dwell times.

7. References

Adams, M., 1994. Agglomerate strength measurement using uniaxial confined compression. Powder Technol., 78, 5-13.

Amidon, G.L., Lennernäs, H., Shah, V.P., 1995. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res., 2, 413-420.

Badawi, A. A.; El-Sayed, A. A., 1980. Dissolution studies of povidone-sulfathiazole coacervated systems. J. Pharm. Sci. 69(5), 492-497.

Bamba, M., Puisieux, F., Marty, J. P., Carstensen, J. T., 1979. Release mechanisms in gelforming sustained release preparations. Int. J. Pharm. 2(5-6), 307-315.

Barton, A., 2000. Handbook of solubility parameters and other cohesion parameters. CRC press Inc. 8 and 177-185.

Bauer, K.H., Frömming, K.H., Führer, C., 2002. Pharmazeutische Technologie, Thieme Verlag, Stuttgart, 359.

Buckton, G., Newton, J. M., 1985. Assessment of the wettability and surface energy of a pharmaceutical powder by liquid penetration. Journal of pharmacy and pharmacology , 37(9), 605-609.

Celik, M., 1992. Overview of compaction data analysis techniques. Drug Devel. Ind. Pharm. 18(6 and 7), 767-810.

Celik, M., Marshall, K., 1989. Use of compaction simulator system in tabletting research. Drug Devel. Ind. Pharm. 15 (5), 759-800.

Danckwerts, P. V, 1951. Significance of liquid-film coefficients in gas absorption. Journal of Industrial and Engineering Chemistry, 43, 1460-1467.

Deodhar, U. P.; Paradkar, A. R.; Purohit, A. P. Preliminary evaluation of Leucaena leucocephala seed gum as a tablet binder. Drug Development and Industrial Pharmacy (1998), 24(6), 577-582.

Desai, D.S., Ranadive, S.A., Lozano, R., Varia, S.A., 1996. Dissolution instability of encapsulated market tablets. Int. J. Pharm., 144, 153-158.

Desai, S. J.; Simonelli, A. P., Higuchi, W. I., 1965. Investigation of factors influencing release of solid drug dispersed in inert matrices. J. Pharm. Sci. 54(10), 1459-1464.

El-Yazigi, A., 1981. Disintegration-dissolution analysis of percent dissolved-time data. J. Pharm. Sci. 70(5), 535-537.

El-Zein, H., Riad, L., El-Bary, A. A., 1998. Enhancement of carbamazepine dissolution: in vitro and in vivo evaluation. Int. J. of Pharm. 168(2), 209-220.

Fachaux, J. M., Guyot-Hermann, A. M., Guyot, J. C., Conflant, P., Drache, M., Veesler, S., Boistelle, R., 1995. Pure Paracetamol for direct compression Part I. Development of sintered-like crystals of Paracetamol. Powder Technology, 82(2), 123-128.

FDA, 2000. Guidance for industry. Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system.

FDA, 2004. Guidance for industry. PAT-A framework for innovative pharamceutical developement, manufacturing and quality assurance.

Fiedler Lexikon der Hilfsstoffe, 5. Auflage, (2002). Bearbeitet von Eva-Maria Hoepfner, Alwin Reng und Christian Schmidt, Editio Cantor Verlag Aulendorf.

Finholt, P., Kristiansen, H., Schmidt, O. C., Wold, K., 1966. Effect of different factors on the dissolution rate of drugs from powders, granules, and tablets. Meddelelser fra Norsk Farmaceutisk Selskap, 28(2;3), 17-30;31-47.

Fowkes, F. M., 1964. Attractive forces at interfaces. Industrial and engineering chemistry, 56 (12), 40-52.

Gibaldi, M., Feldman, S., 1967. Establishment of sink conditions in dissolution rate determinations. J. Pharm. Sci., 56 (1), 1238-1242.

Hancock, B.C., York, P., Rowe, R.C. 1997. The use of solubility parameters in pharmaceutical dosage form.

Hansen, C.M., 1967a The three dimesnional solubility parameter-key to paint component affinities, 1: solvents, plasticisers, polymers and resins. J. Paint Technol., 39, 104-117.

Hansen, C.M., 1967b The three dimesnional solubility parameter-key to paint component affinities, 2. Dyes, emulsifiers, mutual solubility and compatibility, and pigments. J. Paint Technol., 39, 505-510.

Higbie, R., 1935. The rate of absorption of a pure gas into a still liquid during short periods of exposure. Transactions of American Institute of Chemical Engineers, 31, 365-89.

Higuchi, T., 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. J. Pharm. Sci., 1961, 50, 874-875.

Higuchi, T., 1963. Mechanisme of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci., 52, 1145.-1149.

Higuchi, W. I., 1963. Analysis of data on the medicament release from ointments. J. Pharm. Sci. 51, 802-804.

Higuchi, W. I.; Hiestand, E. N., 1963a. Dissolution rates of finely divided drug powders. I. Effect of a distribution of particle sizes in a diffusion-controlled process. J. Pharm. Sci. 52, 67-71.

Higuchi, W. I.; Rowe, E. L.; Hiestand, E. N., 1963b. Dissolution rates of finely divided drug powders. II. Micronized methylprednisolone. J. Pharm Sci. 52, 162-164.

Hildebrand, J. H., Scott, R.L., 1950. The solubility of nonelectrolytes. Reinhold, New York.

Hildebrand, J. H., Scott, R.L., 1962. Regular Solutions. 180 pp. Publisher: (Prentice-Hall, New York)

Hixson, A. W., Crowell, J. H., 1931. Dependence of reaction velocity upon surface and agitation. I. Theoretical considerations. Ind. Engng. Chem., 23, 923-31, 1002-1009.

Hopfenberg, H., B., in Paul D., R., Harris, F. W., 1976. Controlled release polymeric formulations. Am. Chem. Soc. Washington, 26.

Hsieh D. S., Rhine, W. D., Langer R., 1983. Zero-order controlled-release polymer matrices for micro- and macromolecules. J. Pharm. Sci., 72(1), 17-22.

Hugentobler, A., 1993. Untersuchung zur Bindemittelauswahl bei verschiedenen Wirkstoffkompositionen. Dissertation, Basel,

Hunnius Pharmazeutisches Wörterbuch, 7. Auflage, (1993). Walter Burger and Helmut Wachter, Walter de Gruyter Berlin New York.

Ilschner, B., 1982. Werkstoffeigenschaften, Springer Verlag, Berlin, 102.

Israelachvili, J.N., 1985. Intermolecular and surface forces, with application to colloidal and biological systems. Academic Press, London.

Jetzer, W., Leuenberger, H., Sucker, H., 1983. The compressibility and compactibility of pharmaceutical powders. Pharm. Technol., 7, 33-39.

Jivraj, M., Martini, L. G., Thomson, C. 2000. An overview of the different excipients useful for direct compression of tablets. PSTT, 3, 58-63.

Kassem, A. A., Ghazy, F. S, 1973. Effect of surface active agents on the manufacture of diiodohydroxyquinoline tablets. Journal of Drug Research, 5 (2), 179-88.

Kachrimanis, K., Malamataris, S., 2000. Release of ibuprofen from spherical crystal agglomerates prepared using the solvent-change technique in the presence of Eudrogit polymers and from corresponding compacts. S.T.P. Pharma Science, 10 (5), 387-393.

Koch, H. P., 1982. The rotating flask method. Choice of an alternative methodology in dissolution testing. Pharm. Ind. 44(8), 838-842.

Koch, H.P., 1984. Die Technik der Dissolutionsbestimmung (Teil 2). Pharm. Acta Helv., 59 (4), 130-139.
Krycer, I., Pope, D.G., Hersey, J.A., 1983 An evaluation of tablet binding agents. Part I Solution binder. Powder Technol. 34, 39-51.

Kumar, V., Reus-Medina, M., Yang, D., 2001. Praparation, characterisation, and tabletting properties of new cellulose-based pharmaceutical aid. Int. J. Pharm. 235, 129-140.

Lechner, H., 2003. Krüss GMBH Seminarprogramm 14. Oktober 2003 Universität Zürich. Kontaktwinkelmessung: ein Verfahren zur Bestimmung der freien Grenzflächenenergie von Festkörpern, 1-23.

Luangtana-Anan, M., Fell, J. T., 1988. Surface energetics of powders before and after compaction. Int. J. Pharm. 41(3), 237-40.

Leu, R. U., Leuenberger, H., 1993. The application of percolation theory to the compaction of pharmaceutical powders. Int. J. Pharm., 90, 213-228.

Leuenberger, H., 1980. Zur Theorie der Pulverkompression, Habilitationsschrift, Basel.

Leuenberger, H., Hiestand, E. N., Sucker, H., 1981. Ein Beitrag zur Theorie der Pulverkompression. Chem. Ing. Tech., 53, 45-47.

Leuenberger, H., Lanz, M., 2005. Pharmaceutical powder technology-from art to science: the challange of the FDA's Process Analytical Technology Initiative. Advanced Powder Technology, 16, 3-25.

Leuenberger, H., Holman, L., Usteri, M., Winzap, S., 1987. Percolation theory - a novel approach to solid dosage form design. Int. J. Pharm., 38, 109-115.

Leuenbeger, H., Rohera, D.B., 1986. Fundamentals of powder compression. I. The compactibility and compressibility of pharmaceutical powders. Pharm. Res., 3(1), 12-22.

Levy, G., 1963. Effect of certain tablet formulation factors on dissolution rate of the active ingredient. I. Importance of using appropriate agitation intensities for in vitro dissolution rate measurements to reflect in vivo conditions. J. Pharm. Sci. 52(11), 1039-1146.

Liebermann, A.H., Lachmann, L., Schwartz, J.B., 1989, Pharmaceutical dosage forms, vol 1. Marcel Dekker Inc. New York Basel.

Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeny, P.J., 2001. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Delivery Rev., 46, 3-26.

Löbenberg, R., Amidon, G. L., 2000. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standarts. European Journal of Pharmaceutics and Biopharmaceutics. 50, 3-12.

Loftsson, T., Brewster, M.E., Masson, M. Role of cylcoldextrins in improving oral drug delivery. Am. J. Drug. Del. 2(4), 2-15.

Lopez-Solis, J., Villafuerte-Robles, L. 2001. Effect of disintegrants with different hygroscopicity on dissolution of norfloxacin/Pharmatose DCL 11 tablets. Int. J. Pharm, 216 (1-2), 127-135.

Luginbühl, R., Leuenberger, H., (1994). Use of percolation theory to interpret water uptake, disintegration time and intrinsic dissolution rate of tablets consisting of binary mixtures. Pharm. Acta Helv., 69, 127-134.

Maijgren, B., Oedberg, L., 1982. Surface tension data from slight deformations of the surface. The ring method. Journal of Colloid and Interface Science, 88(1), 197-203.

Mallory, A., Schaefer, J., 1977. Clinitest ingestion. British Medical Journal, 2 (6079), 105-107.

Meyer, M. C., Straughn, A.B., Mhatre, R.M., Shah, V.P., Williams, R.L., Lesko, L.J., 1998. Lack of in-vitro / in-vivo correlation of 50 mg and 250 mg primidote tablets. Pharm. Res., 15, 1085-1089.

Michel, J.-C., Rivière, L.-M., Bellon-Fontaine, M.-N., 2001. Measurement of the wettability of organic materials in relation to water content by the capillary rise method. European Journal of Soil Science, 52 (3), 459-467.

Monney, D., 2000. Ein Beitrag zur Porzessüberwachung bei der Wirbelschicht-granulierung. Philosophisch Naturwissenschaftliche Fakultät, Basel. 11-12.

Munday, D.L., Fassihi, A.R., 1995. In-vitro / in-vivo correlation studies on a novel controlled release theophylline delivery system and on Theo-Dur tablets. Int. J. Pharm., 118, 251-255.

Nakamura, K., Tokihiro, K., Motomura, Y., Nishide, S., Yokohama, S., 2003. Potential Use of Cyclodextrins to Enhance the Solubility of YM466 in Aqueous Solution. Drug Development and Industrial Pharmacy. 29(8), 903-908.

Nernst, W., 1904. Theory of reaction velocity in heterogenous systems. Zeitschrift für Physikalische Chemie, Stoechiometrie und Verwandtschaftslehre, 47, 52-55.

Niebergall, P. J., Goyan, J. E., 1963. Dissolution rate studies. I. Continuous recording technique for following rapid reaction in solution. J. Pharm. Sci., 52, 29-33.

Nokhodchi, A., 2005. Effect of moisture on compaction and compression. Pharm. Tech., 46-62.

Noory, C., Tran, N., Ouderkirk, L., Shah, V, 2000. Steps for development of a dissolution test for sparingly water-soluble drug products. Dissolution Technologies, 1-5.

Noyes, A. A., Whitney, W. R., 1897. The rate of solution of solid substances in their own solutions. J. Am. Chem. Soc., 19, 930-934.

O'Connor, K. M., Corrigan, O. I., 2001. Comparison of the physicochemical properties of the N-(2-hydroxyethyl) pyrrolidine, diethylamine and sodium salt forms of diclofenac. Int. J. Pharm. 222(2), 281-93.

Nyström, C., Alderborn, G., Duberg, M., Karehill, P.G., 1993. Bonding surface area and bonding mechanism-two important factors for the understanding of powder compactibility. Drug Dev. Ind. Pharm. 19 (17 and 18), 2143-2196.

Owens, D. K., Wendt, R. C., 1969. Estimation of the surface free energy of polymers. Journal of applied polymer science, 13 (8), 1741-1747.

Pedersen, P. V., Myrick, J. W., 1978. Versatile kinetic-approach to analysis of dissolution data. J. Pharm. Sci., 67(10), 1450-1455.

Pedersen, P. V; Brown K F., 1976. Experimental evaluation of three single-particle dissolution models. J. Pharm. Sci. 65(10), 1442-1447.

Pietsch, W., 1972. Granulieren durch Kornvergrösserung. CZ Chemie Technik, 1(3), 116-119.

Planinsek, O., Pisek, R., Trojak, A., Srcic, S., 2000. The utilization of free-energy parameters for the selection of a suitable binder in fluidised bed granulation. Int. J. Pham., 207, 77-88.

Rabel, W., 1971. Einige Aspekte der Benetzungstheorie und ihre Anwendung auf die Untersuchung und Veränderung der Oberflächeneigenschaften von Polymeren. Farbe und Lack. 77(10), 997-1005.

Rame, E., 1997. The interpretation of dynamic contact angles measured by the Wilhelmy plate method. Journal of Colloid and Interface Science, 185(1), 245-251.

Reus-Medina, M., Lanz, M., Kumar V., Leuenberger, H., 2004. Comparative evaluation of the powder properties and compression behaviour of a new cellulose-based direct compression excipient and Avicel PH - 112. Journal of Pharmacy and Pharmacology, 56, 1-6.

Ritschel, W. A., Bauer-Brandl, A., 2002. Die Tablette, Handbuch der Entwicklung, Herstellung und Qualitätssicherung. Editio Cantor Verlag Aulendorf, 505.

Schanker, L.S., 1959 Absorption of drugs from the rat colon. J. Pharmacol. Exp Ther. 126, 283-290.

Rowe, R.C., 1989. Correlation between predicted binder spreading coefficients and measured granula and tablet properties in the granulation process. Int. J. Pharm. 58(3), 209-213.

Rowe, R. C., 1988b. Surface free energy and polarity effects in the granulation of a model system. Int. J. Pharm., 53, 75-78.

Rowe, R.C., 1988a. Adhesion of film coatings to tablet surfaces - a theoretical approach based on solubility parameters. Int. J. Pharm., 41, 219-222.

Rubas, W., Jezyk, N., Grass, G., 1993. Comparison of the permeability characteristics of a human colonical epithelial (Caco-2) cell line to colon of rabbit, monkey, and dog intestine and human drug absorbtion. Pharm. Res. 10(1), 113-118.

Rumpf, H., 1958. Grundlagen und Methoden des Granulierens. Chemie - Ing. Tech., 30 (3), 144-158.

Shotton, E., Hersey, J.A., Wray, P.E., 1976. Compaction and compression, in “Theory and practice of industrial pharmacy”. Lachmann, L., Liebermann, H. A., Kanig, J. L., 2. edition, Lea and Felbiger, Philadelphia, 303-306.

Stricker, H., 1987. Physikalische Pharmazie. Wissenschaftliche Verlagsgesellschaft mbH Stuttgart.

Sucker, H., Fuchs, P., Speiser, P. 1991. Pharmazeutische Technologie, 2. Auflage, Thieme Verlag, Stuttgart.

Tempio, J. S., Caldwell, H. C., 1980 Improved capsule dissolution method. J. Pharm. Sci. 69 (3), IV.

Thawatchai, P., Tamotsu, K., Garnpimol, C.R., 2000. Chitosan citrate as film former: compatibility with water-soluble anionic dyes and drug dissolution from coated tablets. Int. J. Pharm., 198, 97-111.

Toor, H. L., Eagleton, S. D., 1956. Plug flow and lubrication of polymer particles. Ind. Eng. Chem. , 48, 1825-30.

Toor, H. L.; Marchello, J. M., 1958. Film-penetration model for mass and heat transfer. AIChE Journal, 4, 97-101.

Touitou, E., Donbrow, M., 1982. Drug release from non-disintegrating hydrophilic matrixes: sodium salicylate as a model drug. Int. J. Pharm. 11(4), 355-364.

Train, D., 1956. An investigation into the compaction of powders. J. Pharm. Pharmac. 8, 745-760.

Unckel, H. 1945 Processes during compression of metal powders. Archiv fuer das Eisenhuettenwesen. 18, 161-7.

Van Krevelen, D.W., Hoftyzer, P.J. , 1976. Properties of polymers: their estimation and correlation with chemical structur. Elsevier, Amsterdam.

Van Oss, C. J., Good, R. J., Chaudhury, M. K., 1988 Additive and nonadditive surface tension components and the interpretation of contact angles. Langmuir, 4(4), 884-91.

Von Orelli, J., Leuenberger, H. 2004. Search for technological reasons to develop a capsule or a tablet formulation with respect to wettability and dissolution. Int. J. Pharm., 287, 135-145.

Washburn, E. W., 1921. The dynamics of capillary flow. Physical review, 17, 273-283.

Wells, J. I. 1988. Pharmaceutical preformulation: the physico chemical properties of drug substances. Ellis Horwood, Chichester. 210.

Wood, J., Syarto, J., Letterman, H., 1965. Improved holder for intrinsic dissolution rate studies. J. Pharm. Sci. 54(7), 1068

Wray, P.E., 1992. The physics of tablet compaction revisited. Drug Dev. Ind. Pharm. 18 (6 and 7), 627-658.

Wu, S., 1971. Calculation of interfacial tension in polymer systems. J. Polym. Sci., 34, 19-30.

Zilles, J. U., 2003. Krüss GMBH Seminarprogramm 14. Oktober 2003 Universität Zürich. Tensiometer und Kontaktwinkelmessung, 1-12.

Curriculum Vitae

Name	Johannes Caspar von Orelli
Date of Birth	12th November, 1975
Place of Origin	Basel, Zürich and Locarno

Education

2002-2005	PhD study under the supervision of Prof. Dr. H. Leuenberger at the Institute of Pharmaceutical Technology, University of Basel Work as an assistant at the Institute of Pharmaceutical Technology teaching students in the subject of developing and producing liquid-sterile dosage forms
July 2002-2004	IT management at the Institute of Pharmaceutical Technology
March - November 2001	Swiss Federal Diploma in Pharmacy Diploma thesis entitled "Synthese eines Trisaccharides als Baustein eines stark vereinfachten GQ1ba -Mimetikums" under the supervision of Prof. Dr. B. Ernst and Dr. O. Schwardt at the Institute of Molecular Pharmacy, University of Basel.
1998-1999	Practical year at Pfauenapotheke, Basel
1996-2001	Pharmacy studies at the University of Basel
1995	Matura at Gymnasium Bäumlihof, Basel

Publication

Von Orelli, J., Leuenberger, H. 2004. Search for technological reasons to develop a capsule or tablet formulation with respect to wettability and dissolution. Int. J. Pharm., 287, pp 135 -145.

As a student and Ph.D. student I have attended lectures and courses given by:

As a student and PhD student I have attended lectures and courses given by

Aebi, U., Berger-Büter, K., Barras, J.P., Bruppacher, R., Drewe, J., Folkers, G., Giron, D., Erb, P., Ernst, B., Fahr, A., Güntert, T., Hädener, A., Hauser P., Heide, L., Hussain, A., Imanidis G., Kleinebudde, P., Krähenbühl S., Kress A., Leu R., Leuenberger H., Moroni C., Mühlebach, S., Oelhafen P., Plattner GR., Schaffner W., Schlienger R., Scholer A., Seelig, A., Séquin U., Siegel H., Spornitz U.M., Zuberbühler, A.