DIPLOMARBEIT

"Hot-melt direct pelletisation in a fluid-bed rotor granulator based on a 3^2 full-factorial design - Challenging the process with Nimesulide"

Verfasserin

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ABSTRACT

Hot-melt direct pelletisation in a fluid-bed rotor granulator is characterised as an advanced process of manufacturing pellets. The convincing advantage is not only the save of time and manpower, but also the prevention of cross contaminations.

The main idea of the present study was to optimize the pelletisation process for the production of immediate drug release spheroids, based on experimental design as an efficient tool. Two variables at three different levels were investigated in the experiments. Additionally the process was challenged through utilizing an active pharmaceutical ingredient of low water solubility, namely nimesulide.

The recipe of the pellet formulation included not only microcrystalline cellulose (MC), lactose monohydrate and colloidal silicon dioxide, but also polyethylenglycole (PEG) 400 and 4000 as binding materials. The material variables, binder spraying amount and binder spraying rate, both at low, medium and high levels were studied by using a 3^2 full factorial design. The quality of the pellets was estimated consulting three different characteristics, namely geometric mean diameter, geometric standard deviation, the shape factors and the yield. For the evaluation of the nimesulide-pellets dissolution studies were investigated for assessing the optimization process.

From the response surfaces and the contour plot it was noticeable that the binder spraying amount had a significant influence on the geometric mean diameter, unlike the binder spraying rate. Though this fact it was observed that the factor of the binder spraying rate participated in an important interaction with the other factor. That means that increasing the binder quantity was linked to a continuous increase of the pellet size. Medium sizes of pellets could be obtained with binder quantities of the medium level of 400 grams.

For the geometric standard deviation a narrow range of sphericals has been received, showing an advantageous outcome in comparison with alternative methods for producing pellets. The same tendency was observed with regard to the shape of pellets, showing a narrow range in the sphericity.

Depicting the dissolution results of the nimesulide-containing pellets it was realized that the outcome at pH 8.2 was better than expected, which means that more than the half of the dose of Nimesulide was dissolved within the first 30 minutes.

In Conclusion, hot-melt direct pelletisation is a considerable approach and suitable technique of producing pellets in a single-step manufacturing process.

ABSTRACT (in german language)/ZUSAMMENFASSUNG:

Hot-melt (Heißschmelz) Pelletierung in einem Wirbelschicht Rotor Granulator zeichnet sich als ein fortgeschrittener Prozess aus, um Pellets zu produzieren. Der heausragende Vorteil zeigt sich nicht nur in der Minimierung von Arbeitszeit und Laborpersonal, sondern auch in dem Ausschluß von Kreuzkontaminationen.

Das Hauptziel der aktuellen Studie beinhaltete die Optimierung des Pelletierungsprozesses zur Herstellung von „immediate-release" Pellets, aufbauend auf „experimental design" als effizeinte Grundlage für die Experimente. Des weiteren wurde die Bedeutung des Herstellungsprozess durch das Miteinbeziehen von Nimesulid als aktiver pharmazeutischer Bestandteil, in Frage gestellt.

Die Pellet-Formulierung beinhaltete nicht nur mikrokristalline Zellulose (MC), Laktose Monohydrat und kolloidales Siliziumdioxid, sondern auch Polyethylenglycole (PEG) 400 und 4000 als Bindungsmittel. Die Material-Variablen, Menge an Bindungsmittel und Sprührate an Bindungmittel, wurden beide in ihren niederen, mittleren und hohen Level auf Basis eines 3^2 vollständig-faktoriellen Designs. Die Qualität der hervorgehenden Pellets wurden anhand drei unterschiedlicher Charakteristika abgeschätzt, als folgt, mittlerer geometrischer Durchmesser, geometrische Standardabweichung, die Formfaktoren und die Ausbeute. Für die anschließende Evaluierung der Nimesulid-Pellets wurden Dissolutionstests durchgeführt, um die Optimierung des Prozesses einzuschätzen.

Anhand des „response surfaces" und dem Niveauliniendiagramm war erkennbar, dass die Menge an Binder einen signifikanten Einfluß auf den mittleren geometrischen Durchmesser hatte, im Gegenteil zur Sprührate des Bindungsmittels. Trotz dieser Beobachtung stellte sich heraus, dass die Sprührate an Bindungsmittel an einer wichtigen Interaktion mit dem anderen, signifikanten Faktor teilnahm. Dies bedeutet, dass eine zunehmender Menge an Bindungsmittel mit zunehmender Pelletgröße korrelierte. Mittlere Größen an Pellets konnten mit einer Menge von 400 Gramm Bindungsmittel erreicht werden.

Im Bereich des geometrischen Standardabweichung konnten sehr enge Schwankungsbreite erzielt werden, welche sich als überlegenes Outcomes im Vergleich zu alternativen Methoden bestätigten. Ähnliche Tendenzen zeigten sich im

Bereich der Formfaktoren, wiederum enge Schwankungen in der Spherizität der Pellets.

In Bezugnahme auf die Dissolutions Ergebnisse der Nimesulid-hältigen Pellets wurde erkannt, dass das Outcome bei einem pH von 8.2 besser war, als erwartet. Dies bedeutet, dass mehr als die Hälfte der Dosis an Nimesulide innerhalb der ersten 30 Minuten gelöst war.

Ingesamt kann man die direkte Heißschmelz-Pelletierung durchaus als ein konkretes Konzept und geeignete Technik zur Herstellung von Pellets in einem Einstufenprozess bezeichnen.

1. THEORETICAL PART

A.1. PELLETS

A.1.1. Definition

Pellets are geometrically defined agglomerates that are built up from fine powders or granules of bulk drugs and the adequate excipients. They are described as small, free-flowing, spherical or semi-spherical solid bodies. In the pharmaceutical sector mostly used are pellets that have an average size between 0.5 until 1.5 mm, intended for oral administration [1].

Pellets are multiple-unit dosage forms, which show several advantages according to their safety and efficiency of the containing active ingredient over single-unit dosage forms, such as controllability of the gastric emptying, constant drug-absorption, predictable plasma levels and a reduced risk of locally higher concentrations, based on the fact that the drug dose is split over many elements. These formulations are even small enough to pass by the pyloric sphincter without causing complications [2, 3]. Even when pellets are defined as solid dosage forms with a modified drug release, they avoid objectionable dose-pumping in contrary to the drug-reservoir-type as a single-unit dosage form [1].

Hence they offer the benefit to be appropriate for further processing in order to modify their drug-release properties. In favour they have to be coated with polymers, so that different pellet-batches can be filled in capsules or compressed into tablets [4], which may be the most important cause of their popularity. Pellets compressed into tablets are defined as multi-unit dosage form.

Evidently pellets show a huge potency of developing new solid dosage forms or designs that exhibit a good reproducibility of the manufacturing [5, 6].

Historically seen the production of pharmaceutically used pellets is first described in the 1950s, actually as a response to the increasing need of sustained-release formulations. In the beginning rather utilized as pills that were filled in hard gelatine capsules in order to create the desired sustained-release oral dosage form. Nevertheless the manufacturing process implied intensive and hard labour work, described rather as an art than a science. As long as the quantity of pellets that could be filled into capsules remained small, the research for alternative techniques has continued. One of the most important findings on the way of developing sustained-release dosage forms has been taken place in 1949, when tiny candy seeds, produced for topping decoration

became a guide in the pharmaceutical industry. The description of their production through layering of powder and binder on sugar granules in a conventional coating pan reformed the pharmaceutical industry. Nonetheless alternative possibilities of producing pellets were in great demand, namely faster, more efficient and less expensive approaches. Not until 1964, pellets sized between 0.25 - 2.0 mm have been fabricated through spraying the drug as a dispersion or dissolution in a gas-chamber, comparable with a spray-dryer, in order to form the desired sphericals. Concurrently, the Marumerizer and Spheronizer as exponents for the extrusion-spheronization process have been designed, exalting the rank of pellets in pharmaceutical dosage form progress, thus including over 90% of the drug and keeping the physical and chemical characteristics at its highest level.

Since then this development of manufacturing pellets is the central point of excessive research [1].

The process of manufacturing pellets includes in general specific tools and technologies in order to transform the involved materials into those globular shaped units [6,7]. They can be prepared by various methods, usually notwithstanding by wet agglomeration processes in bolted granulating systems [1].

The following properties of a pellet should be fulfilled in order to show ideal behaviour during the production process [5]:

- for an optimal film coating process, a spherical appearance and a flat surface are required
- the particle size should be limited between 600 and 1000 µm, so that the size variety is kept as small as possible
- the active ingredient should be contained in pellets as high as reachable so that the final formulation is hold onto tolerable limits

Pelletisation can be seen as the effort of the particle size enlargement which is advantageous for the following motives [1, 8]:

- to avoid the build-up of co-agglomerated particles, followed by upgrading the conformity of the ingredients
- the safety during the production process is increased, thus powder formation is averted; these light powders can probably cause dangerous dust explosions

- achievement of a clear definition of the appearance
- amendment of the utilisation of the formulation due to their free-flowing properties
- owing to the optimal relation of the pellet face to its volume, the drug release characteristics can be influenced; moreover the shape is described as being appropriate for further coating processes

Disadvantages according pellets and their production are:
- in some cases only encapsulation instead of tabletting of pellets is possible due to their inflexibility
- Pelletisation often seems to be too inefficient from an financial viewpoint
- The production process itself demands for specific skills and experience according the different process variables

A.1.2. Principle of pellet formation and growth

❖ *Bonding forces:*

Agglomerates, like Pellets owe their solid properties to the major binding-mechanisms [5, 9]:

- ➢ *Solid bridges* – produced by increasing temperature and pressure or chemical reaction or partial melting it is possible in case of materials with a deep melting point in order to affect liquid bridges that harden after cooling down.
- ➢ *Adhesion and cohesion in binders with a high viscosity* [10] - this kind of binders act both through their adhesion-forces on the border solid/liquid and also through their cohesion-forces.
- ➢ *Particle interlocking* – due to the different appearance of the particles they can be fixed together under pressure or through shearing forces that are present during processing.
- ➢ *Liquid bridges* – this is the dominant mechanism according the agglomeration of solid materials. Before liquid addition the particles are held together only by bonds like "Van-der-Waals" forces, which are not very strong. Only by addition of a small liquid amount, weak liquid-bridges are built up (figure A.1a). With increasing liquid addition the bridges between the particles can be

enlarged in order to fill the space between the particles. As a result of capillary depression the particles are stacked together (figure A.1 b,c).

a   **b**   **c**
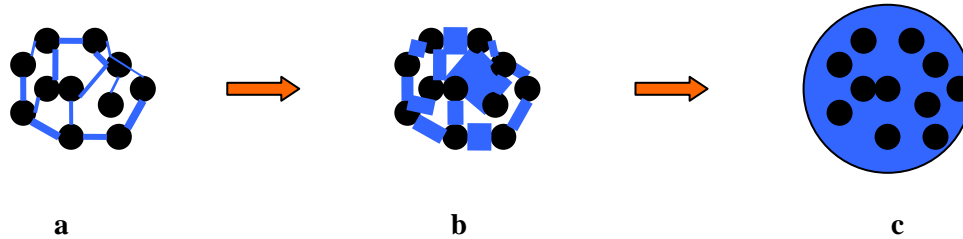
Figure A.1: Different stages of wetting particles for liquid bridges (black=solid, blue=liquid, white interspaces=air (modified from [11])

❖ *Growth mechanism*

The knowledge about the materialization of pellets is a fundamental step towards the optimization of the major process.

The most important input to the granulation growth was established by Sastry and Fürstenau in 1972 [11], who detailed the major mechanisms for granule growth, separated in nucleation, coalescence, layering and abrasion transfer.

➢ Nucleation (figure A.2a): first nuclei are built up from the fine particles, all including three phases, air-water-liquid. Mass and quantity of the pellets change as a function of time.

➢ Coalescence (figure A.2b): described as the creation of large-size particles through arbitrary impact of nuclei, provided that the surface is slightly moistly and that they are enough flexible. Mass remains the same, only the quantity is decreased.

➢ Layering (figure A.2c): dry or wet material is added/layered at the surface of the former modelled nuclei. Mass and size are changed to higher values, quantity remains unchanged.

➢ Abrasion Transfer (figure A.2d): is seen as the exchange of material from one to another particle, thus the mass and quantity remain the same, only the size changes.
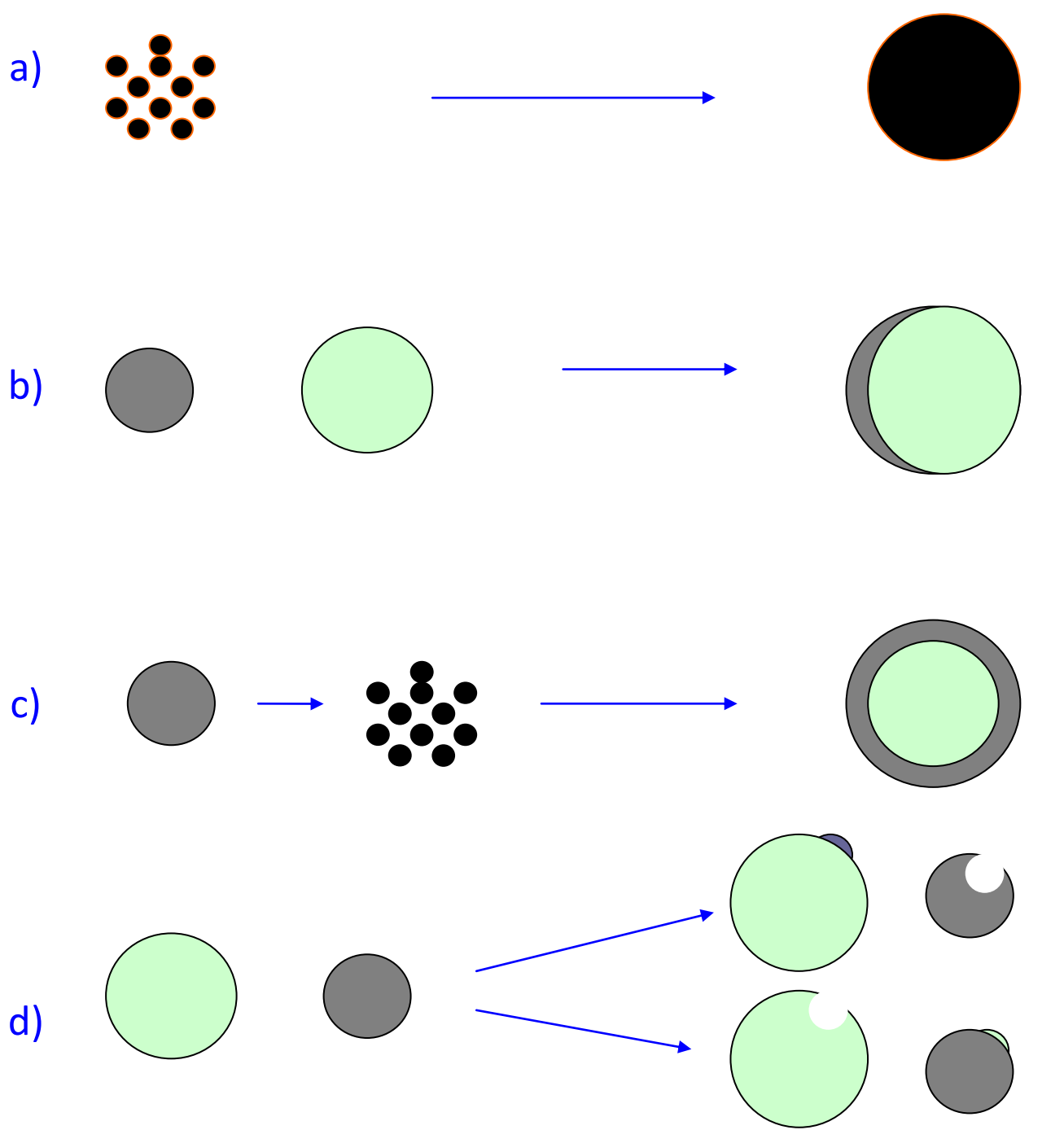
Figure A.2: Pellet formation and growth mechanism (modified after [12])
a) Nucleation
b) Coalescence
c) Layering
d) Abrasion transfer

However, destructive phases during the size reduction should be considered. This may occur at the manufacturing process and may be important for single growth mechanisms (layering). They are described as attrition, breakage and shatter [12]. The resulting small particles are important as they are part of the growth phenomenon, especially at the layering process.
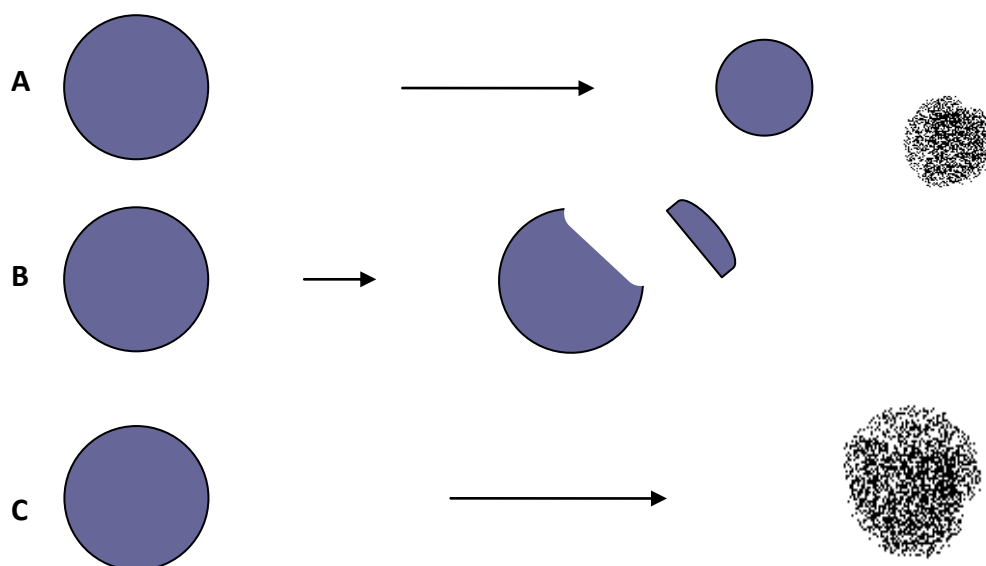
Figure A.3: Size decreasing: A = attrition, B = breakage, C = shatter

A.2. *Characterisation of pellets*

In order to value the reproducibility of a manufacturing process, pellets have to be characterised in terms of size distribution, surface area, hardness so that the quality of the pharmaceutical product can be ensured. Optimizing the variables of interest therefore cannot be neglected [13].

A.2.1 Size distribution

Particle size directly affects the surface area. The quantity of coating material, if a film over the pellets is desired, has to be calculated in order to reach uniformity. Hence the particle size distribution should be as narrow as possible. Also if pellets are filled in capsules or compressed into tablets, a wider size distribution is unwanted, thus

segregation may happen, and this would have a variation in the uniformity of the dosage.

The size distribution can be determined by several methods. The most common method is still the sieving [6, 14], due to the low cost, simplicity, low time consumption and little change among the operators. Nevertheless, sieve-loading, motion-type, intensity and length of agitation are serious variables. In addition, misleading could occur because of the inability of sieves to detect variations in the shape of the particles.

Another common method of determining the size distribution is the microscopy technique. It is typified as a direct method with the significant advantage that it measures the particle profile instead of only properties that depend on the size. The development of the optical microscopy reaches from calibrated filar micrometer or simple eyepiece grates up to the method of image analysis [15] or scanning electron analysis/SEM [16]. The last two mentioned methods are quite monotonous and time consuming, thus a higher amount of pellets has to be quantified individually in order to create a size-frequency distribution plot. Furthermore it should also be considered that different operators may cause variation among the received data. What is more in use is the laser diffraction method [17], which is mostly appropriate for spherical particles.

A.2.2. Shape and surface roughness

Pellets that are intended to be coated in order to create an optimal controlled-release product should exhibit a spherical shape. The outcome of this is good flow properties for a proper transfer of materials, and defined metering for processes like encapsulation [18].

Though several methods of measuring the shape and surface roughness exist, the most commonly used is the analysis of microscopic and non-microscopic pictures of the pellets. The combination of optical microscopy and image analysis is the most tolerated one [19, 20]. With the obtained shape factors, diversity between pellets of different batches can be determined.

The direct evaluation of the surface roughness by image analysis is not precise enough, thus fractional geometry (microscopy + image analysis) is consulted to measure the surface smoothness, which is important for flowability and packing characteristics [18].

For the visualization of additive qualitative and quantitative measurements, electron microscopy (SEM) is used as the technique of choice [16, 27].

A.2.3. Surface area

The surface area plays an important role not only for the coating process but also for uncoated pellets. If a film is considered in order to achieve sustained-release properties, the thickness of the film is the essential part according to the drug-release amount per time. In case of the uncoated pellets, it should be considered that the drug release is affected by the surface area that is available [22].

For measuring the surface area of pellets three techniques are generally used.

First of all it can be calculated through the knowledge of the diameter, thus the surface area of a sphere is equal to π x d^2. But this equation doesn't explain pellets with different morphologic properties, such as porosity or surface roughness [22]. The other two techniques, gas absorption and air permeability, calculate the surface area directly [13].

The method of gas absorption was developed by Brunauer, Emmett and Teller (BET Method) in 1937. The volume of nitrogen gas, absorbed by the substrate, which is in an evacuated glass bulb, is measured at various pressures. The results are plotted as $\rightarrow$ V. $(p_0 - p)$ vs. p/ p_0 in order to create a linear plot, where V = volume of gas in cm^3 that is absorbed per gram of substrate at pressure p. p_0 is the saturation vapour of pressure of liquefied nitrogen at the temperature of the experiment. The slope and intercept of the plot yield the values b and V_m, so that the specific surface (S_w) of the pellets is obtained by using the following equation: $S_w = 4,35$ x V_m [13].

Air permeability is known as a simple and fast method to determine the specific surface of pellets. Hence it is often in use in the pharmaceutical sector in order to check variations between different batches. It is defined as the principle resistance of a fluid

(air) that goes through compacted material. This method is not much accepted, thus the compression of the material affects the result [13].

A.2.4 Porosity

The porosity of pellets plays an important role when they are coated afterwards, but also the release rate of the drug could be changed, justified by the effect of the porosity on the capillarity action of the dissolved drug [13].

On the one hand the porosity is qualified through scanning electron microscopy = SEM [21], on the other hand quantified by mercury porosimetry [22,23,24].

A.2.5. Density

The density of pellets may be influenced by changes in the formulation or the process. This should be considered if pellets are designed for being filled into capsules, being coated or if mixing different batches with each other. A variation of density from batch to batch changes the potency of the final product, such as the capsule or the tablet or causes problems during the coating process and segregation during mixing processes [13].

In addition, the bulk density has an effect on the packing properties of the particles, affected by the diameter and the size distribution of the pellets [13].

A.2.6. Friability

A low abrasion is implied for pellets. They should withstand mechanical influences, such as handling, shipping or subsequent processes like coating. Higher abrasion amounts could affect the drug release of coated pellets, thus the incorporation of small particles in the film [13].

For determination of abrasion a friabilator is proposed, the same principle as it is valid for tablets. Friability is defined as the loss of weight expressed as the percentage according the total mass of the tested subject. In case of new tablet formulations, an

initial weight loss of 0.08% is permitted, until sufficient packaging data are obtained to extend the limit to a targeted value of 1% [24].

A.3. *Pelletisation techniques*

Manufacturing pellets can be carried out through various methods based on different principles. Processes can be divided among the type of binder used, such as aqueous, organic or melted materials. But they can also be distinguished according to the growth mechanism of the pellets. Figure A.4 depicts a rough classification, from which single parts will be immerged on the following pages.
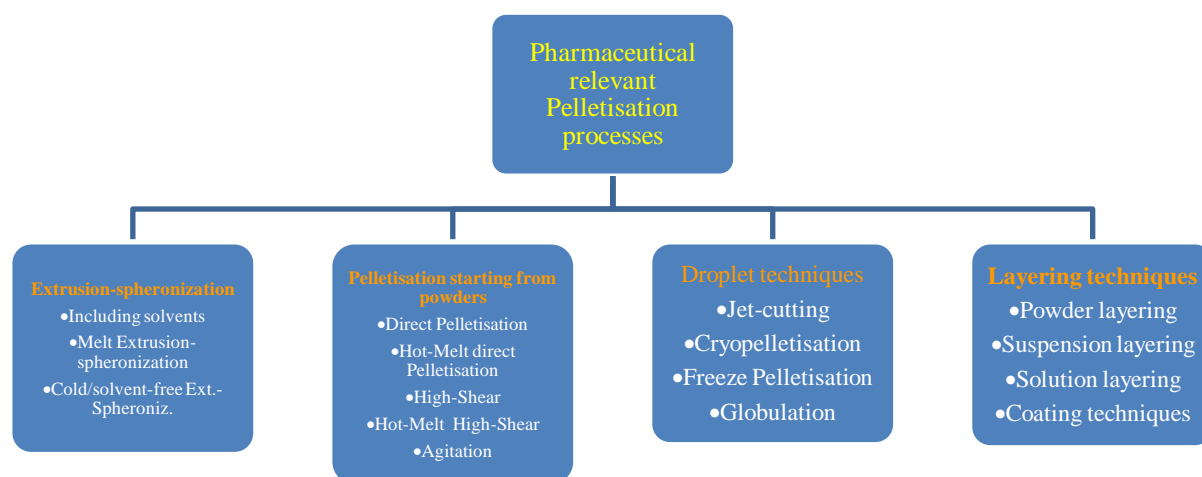
Figure A.4: Flow chart representing the most important pelletisation processes in the pharmaceutical sector (modified from [25]).

A.3.1. *Extrusion-spheronization*

If uniformly sized particles are desired, extrusion-spheronization is the most frequently practiced process of producing pellets [3, 25, 26, 27]. Comparing this to other pelletisation processes, which are mentioned later in this chapter, it is a multiple step compaction process, including several steps:

- Dry mixing:

First step in order to achieve a homogeneous dispersion of the ingredients, obtained through different types of mixers [3].

- Wet massing:

Through addition of a liquid binder a plastic mass for the extrusion step is produced. This step is quite similar to a standard wet granulation, without reaching the granulation endpoint. The optimal moisture of the mass is an important criterion, so that later produced extrudates have enough plasticity to deform, but not being overwetted and then adhering to other particles during the spheronization process [3].

- Extrusion:

Under the application of pressure the moistened mass is forced through an extrusion screen, receiving cylindrical formed extrudates, which show a high density. The extrusion is performed in an axial as well as in a radial movement. During this manufacturing step the temperature of the production chamber is controlled, so that masses including molten binders can also be extruded [4].

- Spheronization:

Providing, that the extrudates show enough cohesiveness, stability and plasticity, they are rounded into spherical particles on a fast-rotating friction plate. This step is divided into several subsequent stages (Figure A.5), including the breaking up of the cylindrical fragments, followed by agglomeration (smaller fragments are picked up by larger ones during smoothing) with the final phase, where the fragments are smoothed through the rational motion around their axis [3].
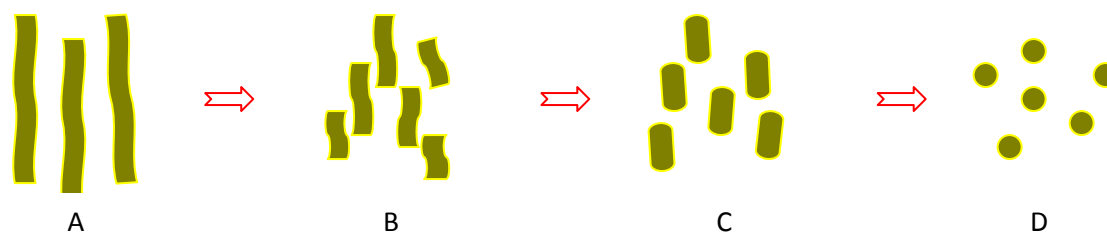
Figure A.5: Extrusion spheronization
A: extruded product
B: breaking up
C: spheronising
D: Pellets

A.3.1.1. *Cold extrusion-spheronization*

Cold-mass extrusion-spheronization is characterised by the usage of not-high temperatures. This consists of mixing the active ingredient with a composition of lipid binders, followed by cold extruding and subsequent spheronization of the cylindrical fragments [25]. This special kind of pelletisation has also been established to produce controlled-release matrix pellets, with an eroding matrix or release retarding agents. If water is used as a binder during the process, long drying-phases are required and therefore higher production and energy costs should be expected [28].

A.3.1.2. *Hot-melt extrusion-spheronization (figure A.6)*

Hot-melt extrusion is not only invented for the plastics industry, but has also been emphasised as a viable method in the pharmaceutical industry for producing different kinds of dosage forms and drug delivery systems. Hot-melt extrusion is the process of applying heat to the material in order to control its plasticity, followed by pressing the mass through the die. Molten binders are in use instead of water in order to achieve a product of uniform shape and reducing the number of production steps and time during drying [27]. In addition, extensive mixing and agitation during the manufacturing process affect a suspension of the active ingredient in the molten binder, so that a higher spreading of the fine particles is achieved [28]. Furthermore, the purpose of using hot melt in extrusion-spheronization process is [29]:

- Increasing the dissolution rate and the bioavailability of the active ingredient by creating finally a solid dispersion or solid solution

- Improving the release rate of the drug

- Hiding bad flavours of the active ingredients

Figure A.6: Schematic overview of the hot-melt pelletisation process (modified from [26])
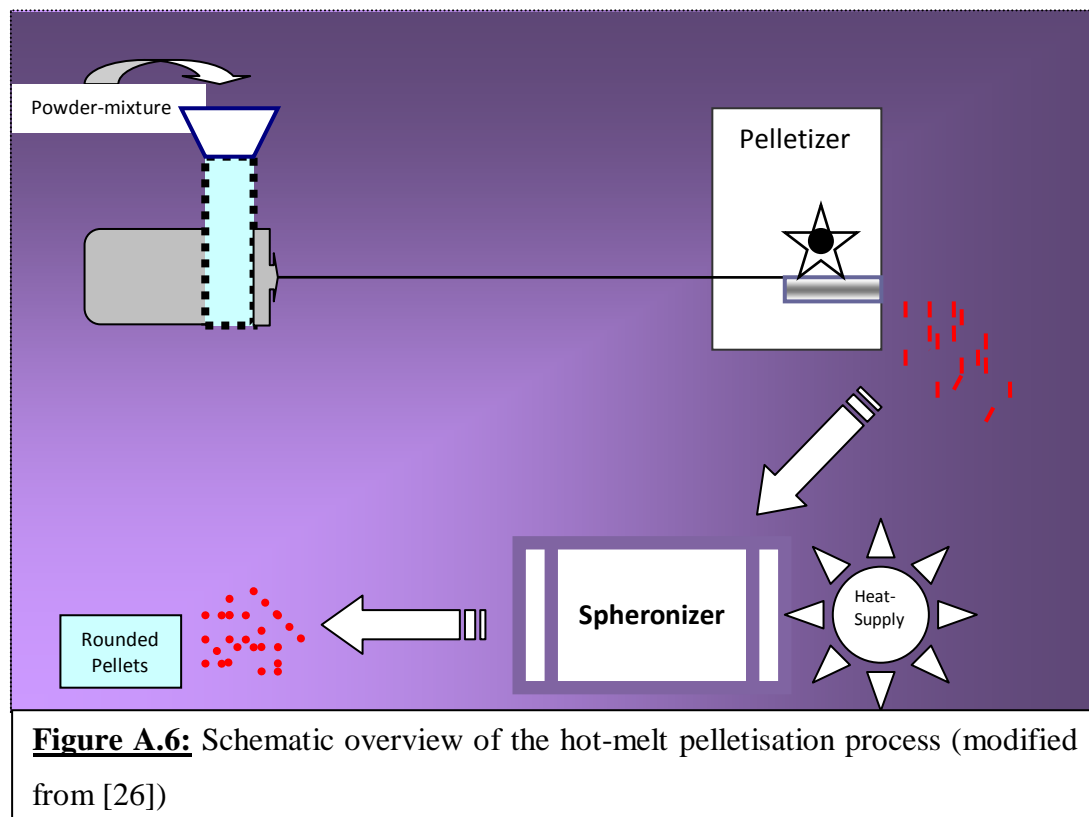
In addition, extrusion-spheronization is an adequate process of producing dense particles with high drug-contents for modified drug-release dosage forms using a minimum amount of excipients [3]. Due to the multistep procedure, as manufacturing time, costs and possible cross-contamination are drawbacks [25].

A.3.2. *Layering-techniques*

The Layering in pelletisation provides the successive apply of layers of material, such as solution, suspension or dry powder on inert cores or starter seeds (built of sugar or microcrystalline cellulose). The ingredients used for the layering process may be similar, yet is the powder layering [30] different from its mechanism to the suspension layering [32] (figure A.7).

- ❖ *Suspension /solution layering*: based on spraying a suspended/solved active ingredient onto the non-pareil (neutral starting core), utilising common coating techniques. Once the droplets reach the core's surface, they spread out, already followed by evaporation in order to create a solid layer. This process is repeated several times, until the desired drug quantity is sprayed onto the particles. Further steps provide coating with polymer film materials [32].

- ❖ *Powder – layering:* generally, a binder solution, followed by dry powder addition, is spread onto the neutral cores until the desired pellet size and consequently the exact amount of drug are obtained. During drying, the binder, when the binder crystallises out, solid bridges mostly take the place of the former build liquid bridges [12].

A.3.3. *Pelletisation from powders*

A.3.3.1. *Direct pelletisation*

It is described as the production of spheroids from powder mixture, using centrifugal rotary processing. Furthermore it is one of the most recently created techniques [6], and may be a good alternative to the extrusion-spheronization process. Direct pelletisation combines several production steps, such as agglomeration, drying and even coating, fulfilled in only one equipment. As a consequence of this advantage, dust problems and contamination risks can be prevented in order to save time, further equipment and space, energy and manpower [22]. All in all it comprises a single-step process that produces pellets with the same quality properties compared to a conventional extrusion-spheronization process [33]. Nevertheless the experimenter should be

conscious of the complexity of this process, thus a huge understanding and experience of the critical parameters are obliged in order to receive an expectable process [25].

A.3.3.2. *Melt pelletisation*

In some way melt pelletisation can be compared with wet pelletisation processes that require the usage of a molten binder or a solid binder that moltens during the production step [14]. Therefore it has the advantage of avoiding the application of solvents, thus no problems according in-process hydrolysis and removal of toxic and flammable of organic solvents [34]. In contrary melt pelletisation exerts binders like fatty acids, polyethylen glycols or waxes, and in addition, materials that are also stable over the melting point of the involved binder [14]. In general, the melting point of typically used binders reaches up to 50-80°C. Lower values imply the risk of melting or softening of the binder during handling or storage [35]. The exact hold of the production temperature is required in order to control the viscosity of the molten binder that leads to agglomerate growth [14].

In general, for melt agglomeration two different growth mechanisms are proposed, depending whether the meltable material is evenly spread on the surface of the solid (figure A.7a) or the solid is incorporated in the droplets of the melted binder (figure A.7b). The occurrence of one or the other mechanism is actually reliant on the size of the solid compared with the liquid melt droplets, the binder viscosity and the shear forces [37]. It should be distinguished between distribution and immersion.

Distribution (figure A.7a) happens when wetted nuclei coalesce in order to form agglomerates, solely because the molten binder is spread over the initial particles. It will only be dominant, if binder droplets are smaller than the solid particles or at least from the same size [35]. In the case of layering (Fig. 7 C), the binder is pressed, through capillary forces, to distribute itself outwards the agglomerate, resulting in a sticky shell, on which more initial particles are layered on, with finally forming a space inside the agglomerate [36]. The immersion mode is defined through the absorption of primary particles on the surface of the binder droplets, providing that the molten binder droplets are larger than the single solid particles. Immersion mostly occurs, when high

viscosity-binders are involved, whereas distribution is typical for low viscosity-binders [35].

Figure A.7: Mechanisms of melt-agglomeration (modified from [36, 37])
A = Distribution
B = Immersion
C = Layering
Grey particles = solid material
Red Particles = meltable binding material
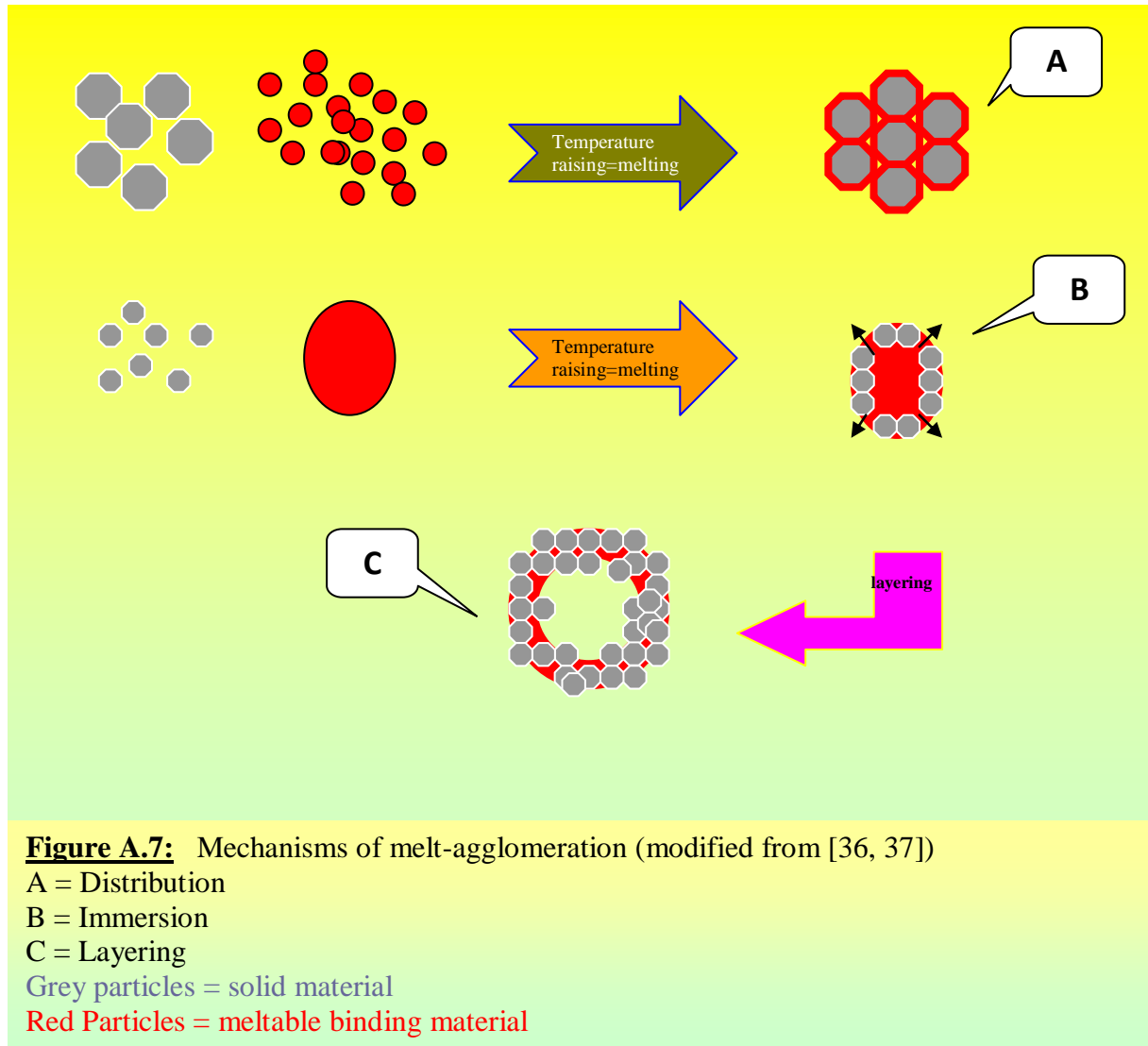
Melt pelletisation is considered as an uncomplicated and fast process that can be performed in only one step, advantageous over the conventional wet pelletisation, where drying of the mass is required afterwards. Labour time, advanced equipment, manpower and possible cross contaminations are prevented successfully, respectively [34].

A.3.3.2.1. *Hot-melt direct pelletisation*

It is described as a process of direct pelletisation, when meltable materials as binders are used. One advantageous criterion is certainly the higher temperature control in the product chamber. Heat comes not only from the binder itself, but also from the inlet air, in comparison to those processes, where the temperature mostly derives from the friction of the materials with the moving parts of the equipment, such as melt extrusion or high-shear melt pelletisation [25].

Two different types of single-pot apparatus are available for pellet production [15]:

- High-shear Mixers

- Fluid-Bed rotary processors

Although both are appropriate equipment for melt pelletisation, the major mechanisms of agglomerate growth is not the same [38].

A.3.4. *High-shear mixer* (fig.8)

High-shear mixers are distinguished through high shearing forces produced during the manufacturing process, starting with loading the binder into the product chamber in form of flakes or powder [38], also called "in situ"-method; in contrary to "spray-on", when molten binder material is spread onto the powder by the spraying nozzle [37]. Increasing the temperature over the binder's melting point is reached either by a heating jacket or by the heat of the friction caused through the impeller blades at a specific high velocity [39].

Figure 8: schematic description of a high-shear mixer (modified from [28])
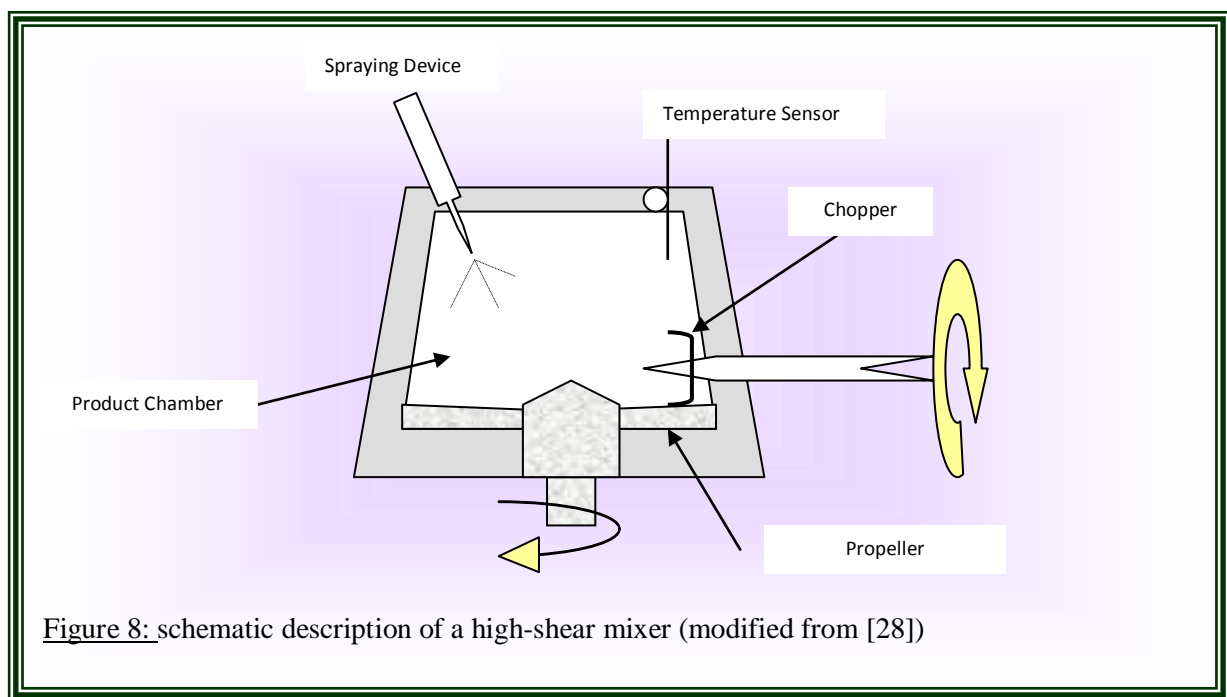
During processing in the high-shear the mass-flow is introduced through the movement of the propeller-blades, thus its name – high shear mixer [23]. Considerable parameters during manufacturing process are consequently propeller velocity, jacket temperature and kneading time [37].

A.4. *Fluid bed granulation*

A convincing argument for utilizing a fluid-bed granulator is the fact that various production steps are combined in only one equipment [15]. Hence manufacturing time and handling with the involved material is generally reduced [8].

A.4.1. *Rotary processors*

Producing spheroids in a rotary processor is one of the most recently developed methods, thus it offers several operation procedures in a single apparatus, such as spheronization, drying and coating [40]. Involving additionally a molten binder can increase both the dissolution properties of poorly soluble drugs and the bioavailability [41].

Figure 9: Schematic design of a rotary processor (modified from [14,25,40])
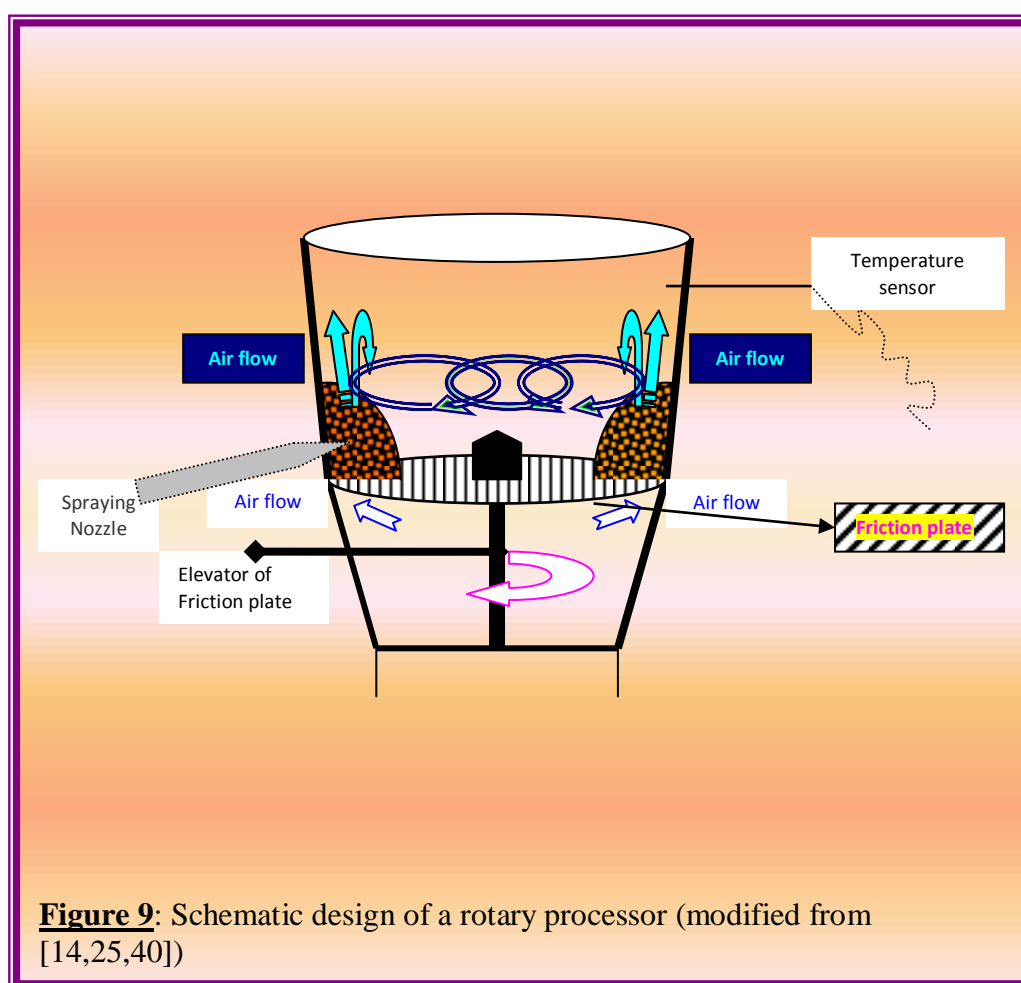
Actually, a rotary processor is modified from a conventional fluidized bed granulator. Different terms exist to describe this system; in case of the well-known manufacturer Glatt® Air Technique it is the rotor-granulator, varying in its basic designs to models produced by other manufacturers [40].

In general, rotary processing consists of three major stages: addition of the binder, tumbling and drying [40]. The molten binder is sprayed continuously onto the powder mass, during it moves on the friction plate (in contrary to high-shear, where the binder is generally added at once shortly before or during the process) [14].

The friction plate's surface is considered to have a significant influence on the properties and the yield of the pellets. Through varying the surface of the plate in order to meet specific applications means also to change the involved shearing forces. Thus a smooth plate decreases and a longitudinal (figure A.9), or even a crosshatched, increase the shearing forces observably [14]. On the one hand the smooth surface type is mostly used for neutral core spheroids that show better flow properties anyway. On the other hand the ripped surface type is generally utilised for the production of spheroids, where higher shearing forces are required, but probably effecting material adhesion [40].

Three major forces are involved into rotary processing: centrifugal - , gravitational- and fluidizing force. Centrifugal forces come from the rotation of the friction plate, causing that the material to be pressed towards the board of the chamber. In addition, incoming air, coming between the friction plate and the board, affects the ascending movement of the powder. On a specific point, when the lifting force decreases with the distance, the material is falling down and inwards as a result of gravitational force. The combination of these three forces affects a "rope-like" motion of the moistening material on the friction plate (shown in figure A.9). Consequently mechanical forces are basically low, thus particles are suspended in the air, instead of mixed through an impeller, like seen at high-shear mixers [39]. The position of the spraying nozzle, when it is set tangential, causes the sprayed binder and the material to have a simultaneous orbit [40].

In summary, a rotary processor fulfils the qualifications by good regulation of the process temperature, combined with higher shearing forces, when using a ripped surface plate, and the ability of controlling the endpoint of the process. So it is considered to be an adequate and easy way of manufacturing, especially when melt pelletisation is required [14].

A.4.2. *Fluid bed equipment*

Fluid-bed processes have initially taken place in Europe long time ago. Afterwards they also reached the U.S.A., at the beginning with fluid-bed dryers. Their construction was quite simple, though they attracted huge interest from manufacturing companies, thus they indicated several advantages over conventional drying ovens. Only by addition of a spraying nozzle and an expansion area the first possibility for fluid bed agglomeration was born, which was an attractive alternative to low-shear mixers. Their ability for coating and spheronization even magnified their process-efficiency in the pharmaceutical sector, especially according the solid dosage forms. Furthermore, due to the fluid bed industry, CGMPs (current good manufacturing processes) and explosion protection have been innovated [42].

A.4.2.1. *Air-handling unit*

It should be considered that one big advantage of a fluid-bed processor over a conventional high-shear mixer is the exact control of the process temperature [14]. Therefore the knowledge about the air-handling unit is essential for temperature control, resulting in a better reproducibility [42].

A: bird screen
B: pre-filter
C: dehumidifier
D: pre-heater
E: humidifier
F: face and bypass
G: final heater
H: H.E.P.A. filters

Figure A.10: Air-handling unit (modified from [42])
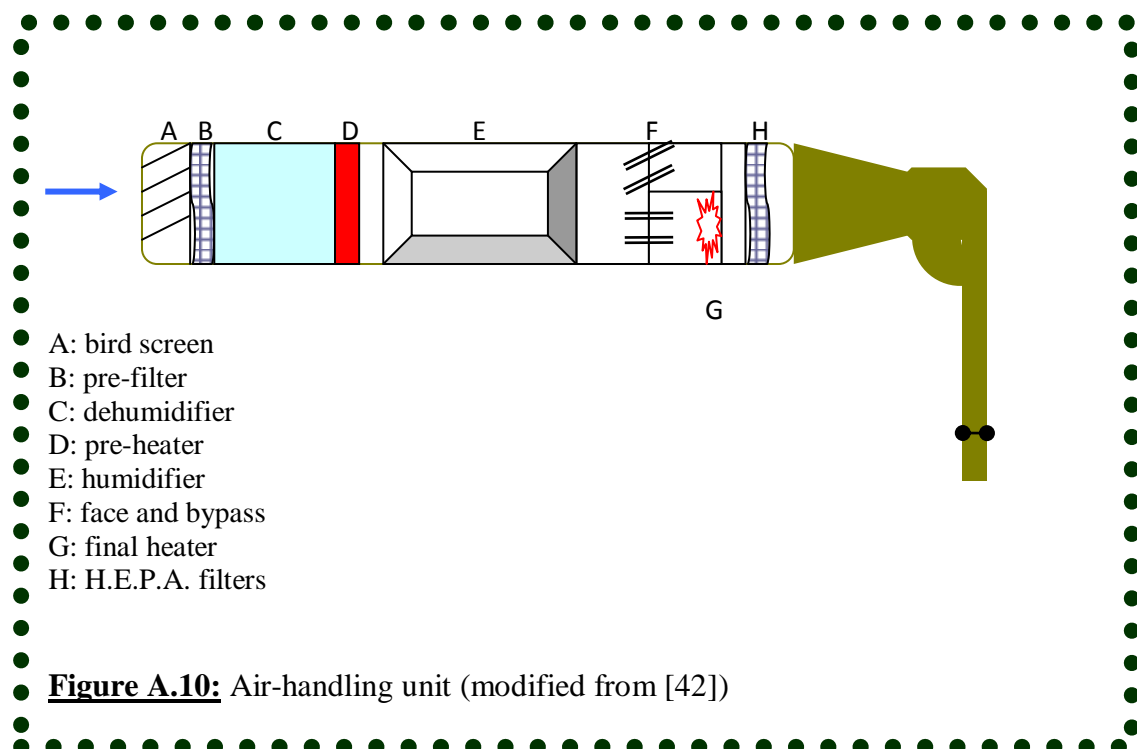
A.4.2.1.1. *Face and bypass system (figure A.10)*

For controlling the air temperature it represents the newer alternative to a steam valve, thus it is characterised through several regulators, which allow the mixing of heated air with the bypass-air. This enables to fast temperature changes and constant hold of the present temperature value within ±1°C [42].

A.4.2.1.2. *Dehumidification and humidification (figure A.10)*

On the one hand moisture is condensed out of the process air and removed from the system; on the other hand humidity can be adjusted in times of cold and dry weather, connected with a heater in order to increase the air temperature to the desired level.

Combining the humidifier and the dehumidifier results in perfect adjustment of the dew point of the production airstream [42].

A.4.2.2. *Product-dependent processing components*

Based on the design of a fluid bed dryer that consists in its product handling unit from the following major parts:

Product chamber: holds more than the full volume of the product

Expansion area: the product may be fluidized into this space, which is above the product chamber that is limited through the filter system

Filter system: separates the fine particles from the product air stream

As long as fluid bed dryers only have the function to remove moisture from the wetted mass, the expansion area does not have to be as huge as defined for a fluid bed granulator. Their product containers are characterised through relatively steep walls in comparison to the system described in the next paragraphs [42].

A.4.2.3. *Fluid-bed Granulator (figure A.11)*

First of all it is defined through an increased expansion area and a spraying nozzle. Its position depends on the special requirements of the process. Thus the binder can be sprayed onto the fluidized material in a controlled way. The product chamber is narrower and higher in order to assure an organized movement of the particles. Through small windows in the product chamber as well as in the expansion chamber the process can be supervised. More technical facilities are temperature sensor and a sample collection port tracking for further developing of the process [42].

A.4.2.3.1. *Top-spraying technique (figure A.11)*

Although it is not the system of choice for pelletisation, however for coating with a suspension or dispersion, aqueous or organic, it is necessarily a possibility. The spraying nozzle is in a position that allows spraying of the binder material when the

particles are moving with high velocity. In addition, the expansion chamber is quite huge and formed more conical than right circular. It is also very important that the filter system is equipped with multiple filters which allow a continuous process in spite of the automatic filter shaking as a cleaning solution [42].

When describing the movement of the material in the fluid bed, it is initially lifted from the process air flow before being sprayed and reaching the relief area. The velocity of the particles decreases thus the product container becomes lager from its diameter, so that they fall back into the border zone. During coating with organic solutions it is a fact that the liquid evaporates before the particles are actually coated and only the solid is left behind (= spray drying). While agglomeration is unwanted in coating, at granulation or pelletization it is the major behaviour of controlled particle growth [42].

Figure A.11: Fluid bed granulator – Top spraying technique (modified from [42])
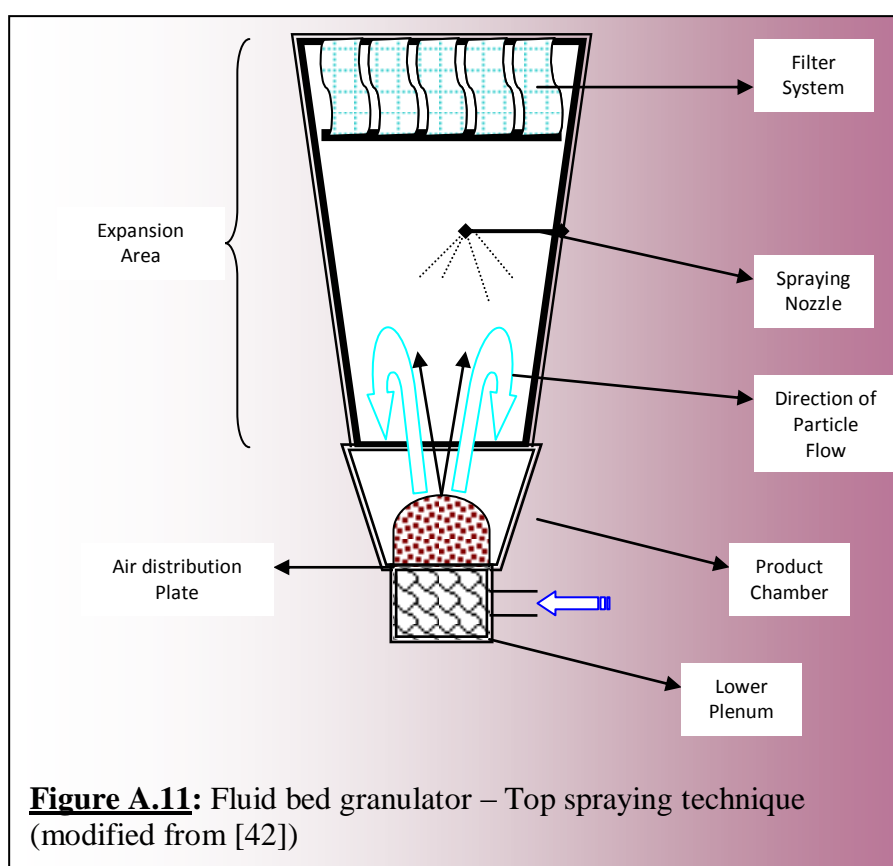
A.4.2.3.2. *Bottom-spray technique (figure A.12)*

It is a well-known and accepted process of spray-coating since a long period of time. At first view it is demonstrative that this equipment consists of two cylindrical chambers, the inner one is opened on both ends and allows the directional movement of the material. Another fact for the directional movement is the perforated plate, which is characterised through smaller holes around the perimeter and larger ones in the centre, where the position of the spraying nozzle is also defined. Consequently the material is sprayed when moving rapidly upwards through the inner cylinder, followed by falling down slowly in the outer cylinder. Wurster coaters can be used for coating tablets, pellets or granulates. Depending on which material is going to be involved, the size of the expansion area varies. The smaller the single particle, the larger is the relief zone in order to create a deceleration zone [42,43].

Figure A.12: Bottom-spray system (modified from [42])
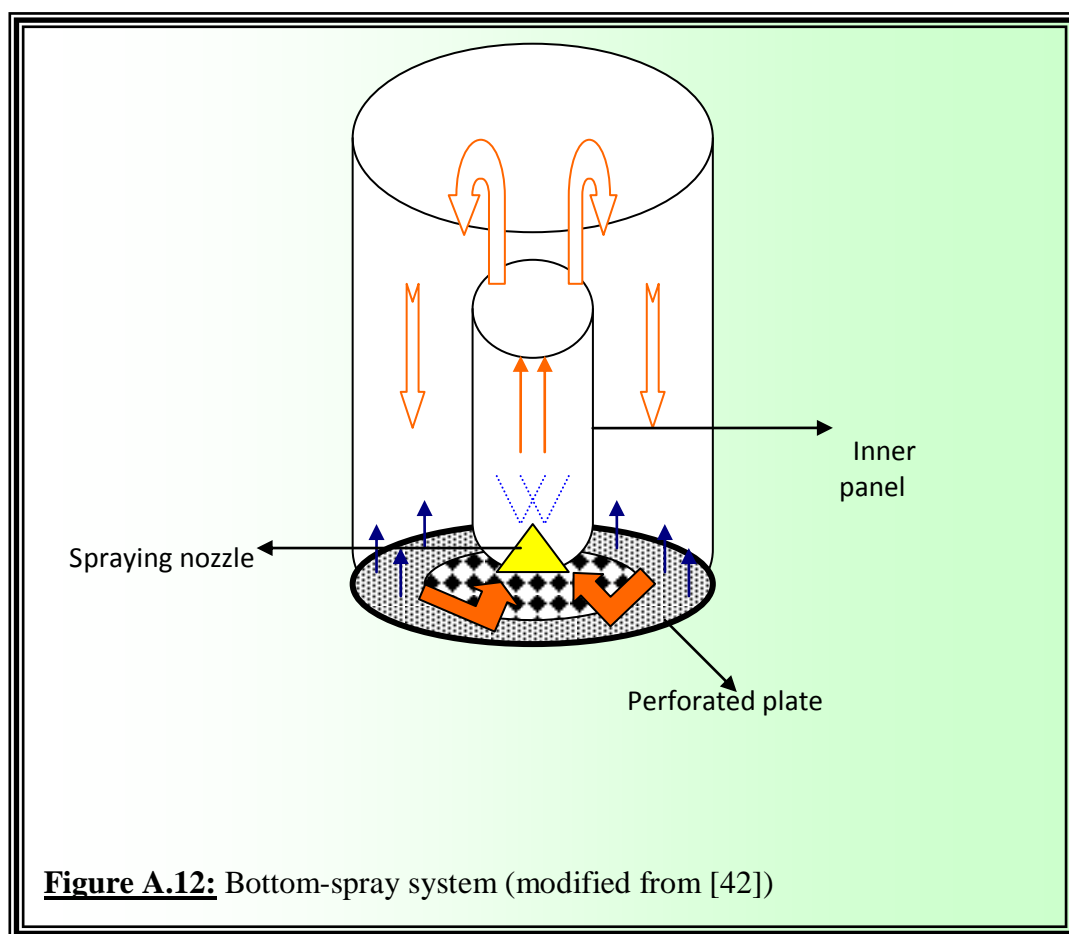
A.4.2.3.3. *Tangential spraying*

Better known as the "rotor-technique" it is suitable for granulating, pelletizing, layering and coating. Differences are shown in the tangential positioned spraying nozzle, the adjustable gap between the wall and the friction plate (in order to control the inlet air) as well as the more or less frictioned rotor disc (compare with A.4.1).

5. *Ingredients of Pellets*

Excipients that are used during the pelletisation process not only create desirable delivery characteristics or facilitate the manufacturing process, but have a great effect on the pellets' growth mechanism. Therefore, hardness, friability, pellet size and shape are contingent to a big part on the right choice of the specific excipients. The experimenter should be aware that a sufficient understanding of the physicochemical properties of the formulation aids is as important as the acknowledgement of the properties of the included drug, such as solubility or particle size. If the pharmaceutical ingredient possesses the proper characteristics for the direct production of the dosage form, there would be no need for additive excipients. But unfortunately they mostly do not show the necessary properties. Subsequently, the pellet manufacturing process takes more than one excipients in order to fulfil various functions [44].

In the case of orally administered pellets, the formulation aids used in pelletisation are quite the same as involved in tablet or capsule formulations [44]. The variety of formulation aids is huge, thus it is difficult to classify them in exact groups as long as a some of them fulfil different functions. In general, excipients should be indifferent, odourless and tasteless and probably colourless [4].

A.5.1. *Formulation aids* [4,44]

Fillers: they should be chemically and physiologically inert and digested easily thus their amount in the formulation can vary from 1% up to 99%. Fillers are mainly added to increase the bulk's density and should therefore be selected on the desired overall characteristic of the pellets.

➔ Lactose, microcrystalline cellulose, mannitol, starch, sucrose

Binders: they are mainly used to bind the powders in a particle together and keep the resistivity of the pellets, regardless which manufacturing process is going to be used. The concentration ranges between 2% and 10% and should be optimized in order to achieve durability instead of high friability.

➔ Polyvinylpyrrolidone (PVP), gelatine, hydroxypropyl- (HPC), hydroxypropylmethylcellulose (HPMC), polyethylene glycols (PEG)

Lubricants: they can be solids or liquids adhering different physicochemical characteristics. Lubricants decrease the friction between particles and processing equipment or inhibit the adhesion of the pellets to parts of the processing chamber.
➔Magnesium stearate, calcium stearate, glycerine, propylene glycol, polyethylene glycol.

Disintegrants: they support the disaggregation of a solid dosage form into the primary particles that were initially agglomerated, and producing finally a larger surface area for subsequent dissolution. In fact, the disintegrant is the adversary to the binder, characterised by absorptive and swelling performances. In pelletisation processes they are mostly used in compaction and spheronistion.
➔Alginates, croscaramellose sodium, crospovidone (a PVP).

pH-adjusters: they are added to protect or regulate the pellet formulation of the environment, such as acid-labile ingredients in the gastrointestinal tract (coating).
➔Citrates, phosphates.

Surfactants: they affect the wettability and increase the dissolution rates of poorly water-soluble ingredients and hydrophobic agents.
➔Sodium lauryl sulphate, polysorbates.

Spheronization enhancers: they simplify the pelletisation process by giving plasticity and passing on binding characteristics to the formulation.
➔Microcrystalline cellulose (MCC), sodium carboxymethyl cellulose.

Glidants: in order to give satisfactory powder flow characteristics, the addition of glidants in compression and powder layering is urgent, and require an exact powder-feeding rate.

→Talc, Starch, colloidal silicon dioxide, magnesium stearate.

Release modifiers: they are used for the preparation of pellets with a special release profile in a single step, only by incorporating ingredients, which change the release of the pharmaceutical ingredient to the medium.

→Ethylcellulose, carnuba wax, shellac.

Separating agents: especially when working with viscous binders, it is urgent to use these agents too in order to avoid the adhesion of the pellets to the rotating plate or the wall of the chamber during processing.

→Talcum, silicon dioxide, kaolin.

A.5.2. *Ingredients used during pelletisation process*

A.5.2.1. Microcrystalline cellulose PH 101(MICROCEL[®])

MCC is described as a white, odourless, tasteless, free-flowing or crystalline powder that is actually unsolvable in water and organic diluents. It is a product which is available on market in various particle sizes and moisture grades, linked therefore with different characteristics and applications, such as bulking agent, extender, texturizer, desintegrant or drying agent [4,45,46]. Thus its special and widespread properties it is used as excipient in pharmaceuticals (and cosmetics), also when producing pellets through wet granulation in a rotary processor or during extrusion/spheronization processes [33].

o **Physicochemical properties** [45,46]

Chemical family: Carbohydrates

Synonyms: Avicel PH, Celex, cellulose gel, E460, Emocel, Pharmacel, Tabulose, Vivapur, Microcel

Empirical formula: $(C_6H_{10}O_5)_n$, where n~220

Molecular weight: 36 000 g/mol

Structural formula:
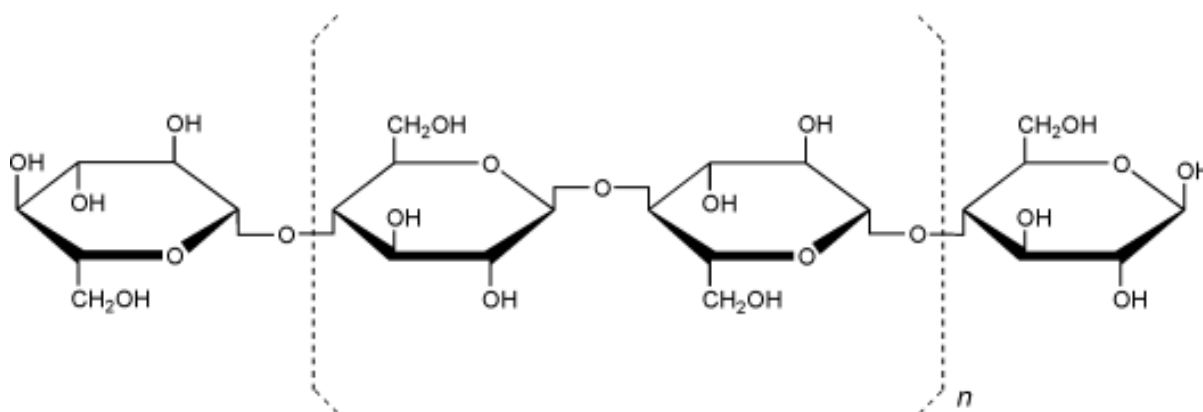
Functional category: adsorbent, suspending agent, diluent, disintegrant

Particle size distribution: varies from 20 to 200 µm, due to the different grades that have a different nominal mean particle size (for Avicel Ph-101it is 50 µm)

Density (tapped): 0.45 g/cm^3 for Avicel Ph-101

Density (true): 1,512-1,668 g/cm^3

Melting point: 260-270ºC

Solubility: about 5%w/v of MCC is slightly solvable in NaOH-solution; practically insoluble in water, diluted acids or organic solvents

Incompatibility: incompatible with stronger oxidizing agents

Safety: recognised as GRAS

Synthesis of MCC:

MCC is received through controlled hydrolysis with dilute mineral acid solutions of α-cellulose. The mean polymerisation grade decreases to 200-300, thus mostly undergraduated parts of the structure are hydrolysed, whereby the index of crystallisation increases. During hydrolysis, the hydrocellulose is purified by subsequent filtration and the aqueous mass is dried through spray-drying, forming finally particles with a high porosity and a broad size distribution.

Essential considerations:

In spite of the higher crystalline quantities of MCC compared with average cellulose powder, it shows better plasticity due to its specific structure, which is received through the fast drying process resulting dislocations in the molecule[4].

In the case of Microcel MCC 101, it is suggested as an indispensable excipient not only for compression and compaction, but also for wet and dry granulation of pellets, active absorption direct compression technologies [45].

A.5.2.2. Lactose [46,47,48]

Lactose is described as a natural disaccharide, consisting of glucose and galactose, which are linked through β-1, 4-glycosidic bonds. There are two existing anomers, the alpha- and the beta-form. In the pharmaceutical sector mostly used is alpha-Lactose monohydrate, but also the anhydrite form. Lactose is a white, crystalline and odourless powder, slightly sweet-tasting and slightly soluble in water under slow conditions.

o **Physicochemical properties (alpha-lactose)**

Chemical name:

O- β-D-Galactopyranosyl-(1, 4)-α-D-glucopyranose anhydrous [63-42-3]

O- β-D-Galactopyranosyl-(1, 4)-α-D-glucopyranose monohydrate [64044-51-5]
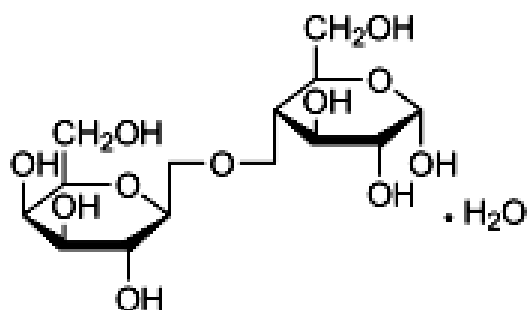
Synonyms: Lactochem, Microtose, milk sugar, Pharmatose, saccharum lactis, Tablettose, Zeparox.
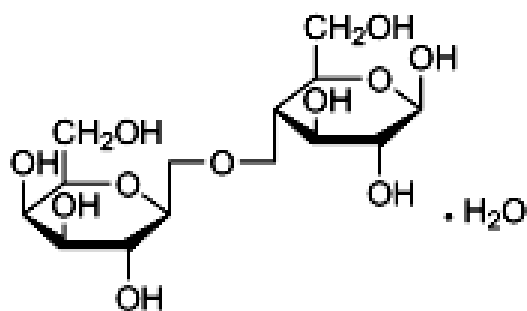
Empirical formula/molecular weight:

$C_{12}H_{22}O_{11}$ (anhydrous) →342.3

$C_{12}H_{22}O_{11}$. H_2O (monohydrate) →360.31

Structural formula:

α-Lactose monohydrate

β-Lactose monohydrate

Functional category: Lactose is used as diluent, binder, binding agent

The different grades of lactose that are commercially available exhibit various physical properties, such as particle size distribution or flow characteristics. The finer grades of lactose are widely used for wet-granulation processes, thus a better mixing behaviour with other ingredients is achieved. In addition, it is also utilized as a carrier for inhalation products or in lyophilized formulations in order to increase cohesion. Generally amounts between 65%-85% in formulation are common.

Melting point:
201-202°C (for alpha-lactose monohydrate)
223°C (for the anhydrous form)
Moisture content: 5 % w/w for the lactose monohydrate
Stability: if relative humidity of 80% is overdone, lactose can get a brown coloration on storage, while the colour stabilities of the different lactose types vary.
Incompatibilities: following the Maillard-type condensation, lactose reacts with primary amine groups, forming brown or yellow-brown products
Manufacturing methods:
Lactose is produced from the sweet whey of the cow's milk, which generally possesses about 4.5% lactose. After separating the albumin at pH 6.2, under heating and subsequent neutralisation and concentration, it is received by crystallization under vacuum. α-lactose monohydrate is then obtained under a temperature of 93,5°C.

Technological consideration:
In the case of Lactochem[®] [48], belonging to the milled lactoses, it is from fine particle size, and therefore exhibits ideal binding properties, which are advantageous not only for wet granulation, but also for pelletisation.

A.5.2.3. Colloidal silicon dioxide (Aerosil[®]) [46,49,50]

Colloidal silicon dioxide is purified, amorphous silicon dioxide that shows (dependent on the silanol-groups, which bind the water-molecules among hydrogen-bridges) diverse water-contents. In addition it is described as a submicroscopic fine, bluish-white coloured, non-crystalline, amorphous powder without taste or odour.

o **Physicochemical properties**

Synonyms: Aerosil, Cab-O-Sil, colloidal silica, fumed silica, Wacker HDK

Chemical name: Silica [CAS-Nr.: 7631-86-9]

Empirical formula/molecular weight: SiO_2 / M_r=60.08

Functional category: adsorbent, anti-caking and suspending agent, glidant, disintegrant, viscosity-increasing agent

Different grades of colloidal silicon dioxide exist on the market, which are received through modelling the production process. These modifications do not only influence properties, such as the silica content or the chemical structure, but also the particle size, density and surface areas are affected.

Specific surface area: 50-380 m^3/g (BET-Method)

Stability: though being hygroscopic, it is able to absorb big quantities of water without liquefying

Incompatibilities: with diethylstilbestrol preparations

Manufacturing process: vapour hydrolysis of silicon tetrachloride at a temperature of 1800°C, based on a hydrogen-oxygen flame. The resulting primary particles therefore have silanole- and siloxane-groups on their surface, which make the adsorption of water, due to hydrogen bridges and subsequent agglomeration, possible.

Technological considerations:

Colloidal silicon dioxide is, apart from cosmetics and food products, mostly utilized as excipient in the pharmaceutical sector. It owes its desirable properties to its small particle size and large surface area, resulting in preferable flow characteristics and therefore used for increasing this feature for dry powders in various manufacturing processes.

In the case of Aerosil fumed silica for solid drug forms an addition of 0.2-1% w/w is proposed in order to increase the packing and flow characteristics of powders. It also increases the bulk and tapped density of the powder mixture. As an adsorbent it is advantageous thus increasing the release properties of poorly soluble drugs.

A.5.2.4. <u>Polyethylene glycol (PEG400/4000)</u> [51,52,53]

Polyethylene glycols are mixtures of polymers, represented by the general formula H-$(OCH_2\text{-}CH_2)_n$-OH, where n stands for the amount of oxyethylene groups. The number following the name is equal to the average molecular weight of the polymer, where in case of typical polyethylene glycol polymers it goes from grade 200 to 8000.

o **Physicochemical properties**

Synonyms: Carbowax, Lipoxol, PEG, polyoxyethylenglycole, Macrogole

Chemical name: Poly(oxy-1,2-ethanediyl)

Structural formula:
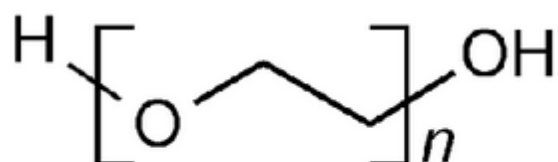
Functional category: base for ointments and suppositories, plasticizer, lubricant

Incompatibilities: phenol structure-molecules, diverse antibiotics, parabens, plastic packing materials (PE, PVC)

Stability: protected from light in tight containers, under a molecular weight of 2000 also hygroscopic

Synthesis: described as the condensation reaction of ethylene oxide and water under pressure, in presence of a catalyst

Specific properties:

→*PEG 400:* (in general 200-600) they are clear, colourless viscous liquids, which can me mixed with water or other PEGs in every proportion. Low viscosity PEGs are mostly used as lubricants for drugs in liquid dosage forms or for the adjustment of the viscosity of liquid and half solid dosage forms.

→PEG 4000: (in general >1000) they are defined as odourless substances that range from pasty consistence until waxy flakes. Mostly it is utilized as lubricant, glidant or

binder for solid active ingredients, especially when only slightly water-soluble drugs are involved.

Technological considerations: Apart from the fact that PEGs shows various incompatibilities, they have the advantage to enhance the solubility or dissolution characteristics of poorly water-soluble drugs when using the right polyethylene glycol. Plus they are able to give plasticity to granules/pellets, especially when using higher-molecular-weight polyethylene glycols.

A.6. **NIMESULIDE as API**

A.6.1. Description

Nimesulide, defined as 4-Nitro-2-phenoxymethane, refers to the NSAIDs, which are generally the most prescribed preparations against inflammatory diseases. Therefore it shows high analgesic, antipyretic and anti-inflammatory properties, in particular it is favourable by its selective inhibition of the isozyme cyclooxygenase-II [54,55].
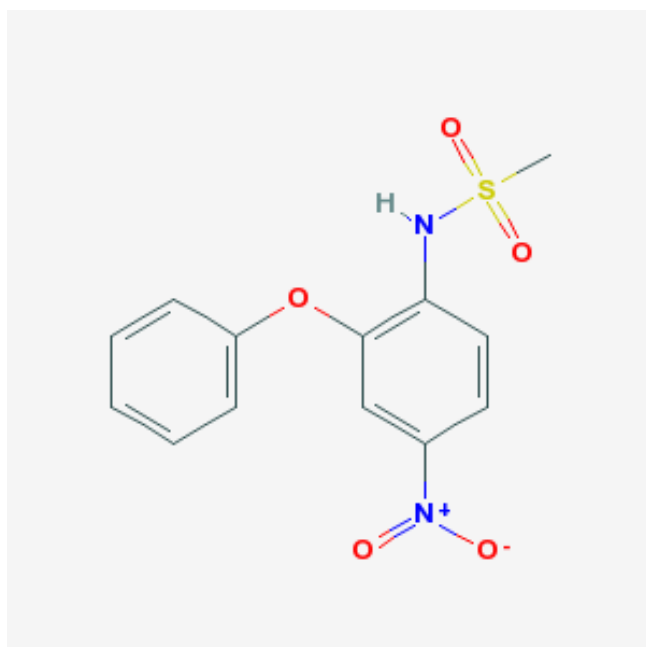
A.6.2. *Physicochemical properties:*[54,56]

Synonyms: 4-Nitro-2-phenoxymethane

Mesulide

Aulin

Fansidol

Cetrizine

CAS No. : 51803-78-2

Chemical formula: $C_{13}H_{12}N_2O_5S$

Molecular weight: 308.3 g/mol

Melting point: 140-146ºC

Appearance: yellow, needle-like crystalline powder

Solubility: practically insoluble in water (26.9 mg.l^{-1} at 25ºC), slightly solvable in ethanol, freely solvable in acetone

Stability: generally stable, but incompatible with strong oxidizing agents

Chemical synthesis [57]:
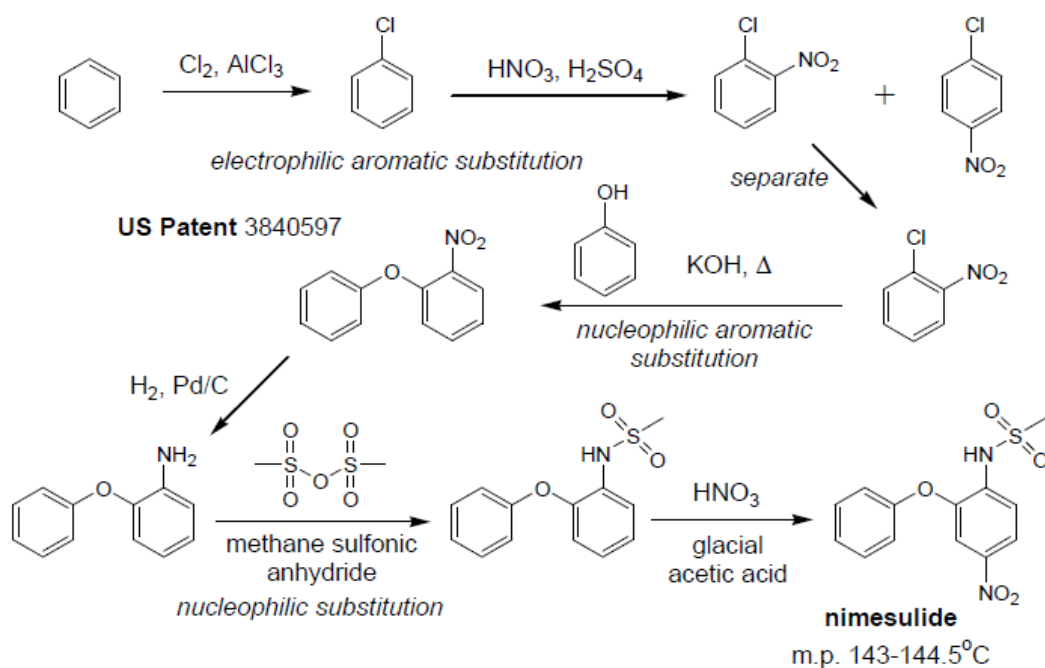
A.6.3. *Pharmacological properties* [55,58,59]

Nimesulide is a unique NSAID thus its key pharmacological property is shown by the selective inhibition of the isozyme cyclooxygenase-II while not affecting the cyclooxygenase-I. It is a peripheral affective inhibitor due to the reduction of inflammation-mediators such as prostaglandins and thromboxanes.

In comparison to other NSAIDs that also inhibit cyclooxygenase-I, nimesulide may cause less gastric and renal dysfunction by inhibiting only cyclooxygenase-II. Therefore it is one of the most commonly prescribed anti-inflammatory drugs, showing gastrointestinal tolerability and less problems in renal dysfunctions while having a high therapeutic index.

- Pharmacokinetic:

After nimesulide is orally administered, it shows a high desorption, whereas the plasmatic protein bond refers to 99%. The maximum plasmatic concentration is reached after 1.2 until 3.2 hours.

After the hepatic metabolism, which is hydroxylation, the excretion is mostly renal and over the stool. The plasmatic half-life is between 1.8 and 5.3 hours.

- Indications/dosage

Osteoarthritis
Pyrexia
Dysmenorrhoea
Painful
Rheumatoid arthritis
Painful swellings
Therapy of choice after operation or trauma

Adults receive a dosage of 100 to 200 mg twice a day, administered orally or rectal. Children receive 5 mg per kg weight in three single doses (children from 6 months until 8 years), rectal as 100 mg, up to four times a day when post operational pain or inflammation is given.

- Side effects

Like most drugs of the NSAID-category, nimesulide is often pulled together as being hepatotoxic [60] ; in rare but unpredictable cases that should be taken with care. Especially in the case of children the use of nimesulide should be carefully considered. Generally, the drug has several side-effects which are mostly reported as diarrhoea, vomiting, dizziness, stomach-pain or heartburn.

- Interactions:

When simultaneously other NSAIDs or calcium channel-inhibitors are prescribed, the risk of gastrointestinal bleeding is increased. Also at therapies with lithium-preparations, the plasma level should be controlled regularly, thus NSAIDs could higher the concentration of lithium to a toxic value.

A.6.4. *Technological considerations*

According to the BCS-system (biopharmaceutical classification system) nimesulide is a member of the class II-drugs, which are characterised by their low bioavailability, but high permeability if administered as a commercially oral dosage form. Obviously, it is practically insoluble in aqueous solutions, showing solubility from 0,01mg/ml [59]. In addition, a pK_a of 5.9 up to 6.8 was found, thus making it effectively a neutral molecule [58].

Therefore this fact gives rise to a challenge in the pharmaceutical technology to create a formulation, which adjusts the weak solubility of nimesulide in order to capitalise from its advantageous clinical characteristics.

Several studies have been carried out, trying to increase the aqueous solubility, such as using vacuum drying techniques [55] or utilising surfactants [61]. Nevertheless most trails include the complexation of nimesulide with a α-, β- or γ-cyclodextrin (CD), described as a "binary system" [62,63] .

A.7. *Experimental design*

A.7.1. *Definition and purpose*

Experimental design is defined as planning an experiment in order to achieve the desired information in the most effective and exact way [64]. Thus experimentation includes a specific amount of money, time, manpower and resources; it is obvious that the experimenter wants to decrease time and effort, nevertheless requiring the necessary information [65]. The experiment itself can be seen as a test or tests set in a row in which changes are intended according to the input variables in order determine the effects on the system in form of output variables [66] (fig. A.6.1).

Figure A.6.1: Model of an experimental process
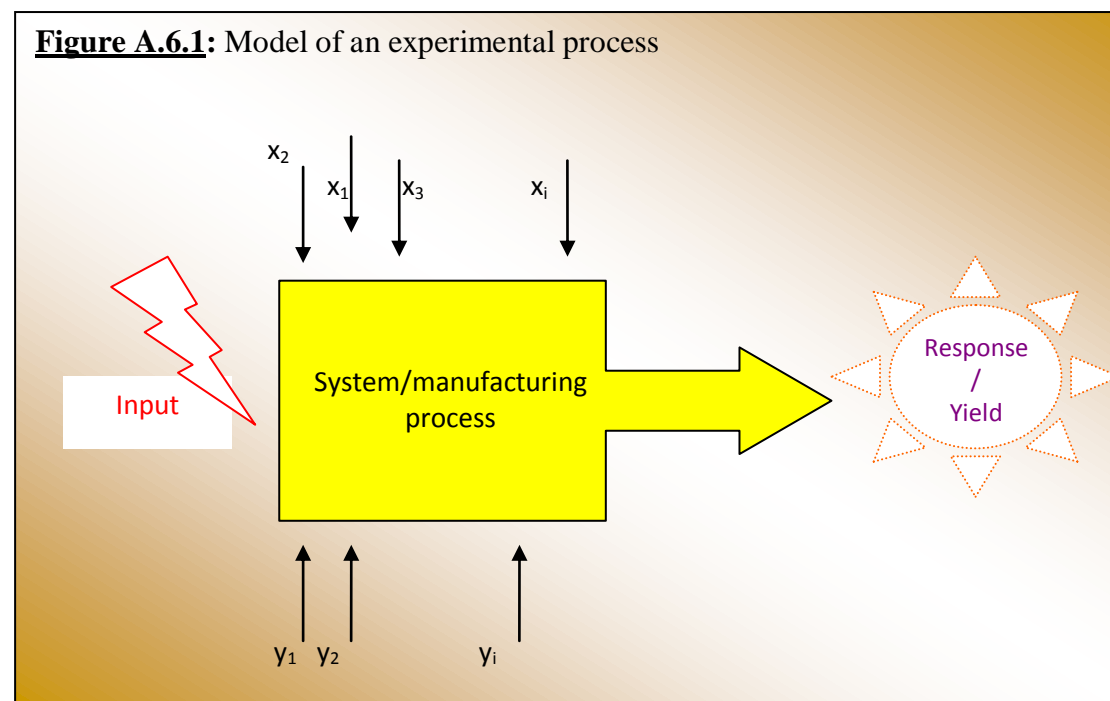
The process could be seen as a system, consisting of machines, methods, material and manpower, which transform the input in a product, that shows one or more responses. Some influencing variables are controllable (x_1, x_2 etc.) whereas others (y_1, y_2 etc.) can't be dominated.

Thus it is important to evaluate the following points [65]:

- Finding out the most effecting variables on the response

- Finding out which setting for the controlled factors is necessary to achieve the desired values of the response

- Finding out which setting for the controllable factors is necessary so that the variability of the response is as small as possible

- Finding out which setting for the controllable factors is necessary so that the influence of the uncontrollable factors is decreased

One strategy of evaluating the most influencing factors could be the "**one-factor-at-a-time**" approach, which means that one factor is changed while others are kept constant at a specific chosen level. Afterwards graphs are built up in order to understand which one of them has the greatest influence on the response. Although this strategy could give misleading results, thus it doesn't include possible interactions between the factors and therefore should be avoided [64].

Another considerable method for dealing with several factors is to vary all factors together, instead of one at a time, the so-called "**factorial**" experiment. Therefore we have at least two factors at two levels, each experiment is performed twice, which means that at least eight experiments have to be performed in order to study the factors' influence on the yield. The screening design is accepted for this problem, both to the aim and the limit. The factorial concept can be enlarged at any number of factors or levels, but experiments increase of course at the same time rapidly. This may be the right intention for a more complex design [64, 65].

6.2. *Starting the experimental design*

Before definitely choosing an experimental design, the experimenter should be aware of what is expected from the design. If he wants to determine which factors are affecting the response among a huge amount of factors, screening designs are the tool of choice. But if the most important factors are already identified, and only quantification of the factors' influence on the system and each other is required, a factor influence study is suggested,

generally including a factorial design. But if the experimenter wants to calculate a formulation or a process within the experimental domain, a design has to be found which establishes mathematical approaches for the responses. The right method to this problem is the "Response Surface Methodology" (RSM) [64].

A.7.2.1. *Important explanations* [64]

- Quantitative factors: factors, which affect a system, taking various values (like rate, amount, percent, time), mostly set within defined limits = continuous. A natural variable for a quantitative factor is written as U_i, where i is the level. Each factor can have different natural variables. With the natural variable there is also a "coded" variable linked. It is written as X_i, also known as normalization, where the limits are set as ±1, and 0 for the central value.

- Factor space: is defined through the coded variables X_i for the continuous quantitative factors that are involved. Only a small part of the factor space is of interest, the so called "experimental domain", limited through the high and low levels of the coded variables.

- Qualitative factors: can only take discrete values, like type of equipment or the kind of process. The factor space is defined through discrete points, a combination of the possible levels of all the factors. The levels of qualitative factors are written as numerical values, such as 1, 2, 3, but this doesn't bear any reference to the importance of the factors. The points in factor space are representing all combinations of the factors' levels. Multiplicating the levels together show the total point in the design space.

- Experimental run: is an experiment that is runs under clear terms, where factors are varied while others are kept constant, leading to a response that can be measured. Each point in the design space stands for the combination of the levels of the factors that are analysed in an experiment. On the one hand experiments may be carried out under changed settings, representing a separate point in the design space. On the other hand they may be replicated, carried out with the same settings. Nevertheless each of the experiments is autonomous according the other ones; the machine re-setted before each experiment.

- Response variable: are determined characteristics, such as the yield or the size, also expressed as "dependent variable", expressed in the equation as y_i for the response of the experiment.

- Mathematical model: shows the dependence of the dependent variables on the independent variables, expressed as coded variables. Generally, the models are polynomials of a certain order (first-order or second-order for two factors). Mostly used on this case they are linear models.

- Design of experiment: includes the experiments that are carried out in the design space, supported by the model and the purpose of the study.

- Experimental plan: is actually the experimental design, where the factors are expressed as real numbers.

A.7.2.2. *Arranging the project* [64]

Most of the time a single experimental design may not be sufficient enough, but information of a design may be useful in another stage of experimentation. The quality of a design is a question of the plan of the experiments in the factor space, and not dependent on the experimental results. The experimenter should consider before starting a project that it is essential to select a design that fits to the problem and not the other way round.

A perfect strategy to carry out a project may not be easily achieved. But it may be helpful to proceed like the following:

- ✓ Screening (can be omitted if information about the factors is already achieved from previous projects)

- ✓ Quantitative factor studies

- ✓ RSM (Response Surface Modelling) → explores the relationship between a response variable and several factors

- ✓ Optimization

- ✓ Validation

A.7.3. *The factorial design*

Factorial designs are useful if the experimenter wants to study two (2^k) or more factors (x^k) by combining their levels in every possible combination. If factors are represented as a factorial design, they are often called "crossed". If a factor has a significant effect, a difference in the response can be recognised when varying the level of this factor. These levels can be at their high levels, expressed with "+" or they are at their low level = "–" [67]. If each factor has the same amount of levels, they are called "symmetric", instead of "asymmetric" if the number of levels are not the same of the factors investigated [68].

A very important fact of factorial designs is their ability to register interactions between the factors investigated [69]. This means that the change in the response of a factor's level is different at the levels of the other factors [67]. It may be also defined as the "synergy between factors" [69].

The effect of an interaction can be illustrated graphically (fig.A.6.2), where the factors are plotted against each other at different levels. Though the lines in the graph are not parallel to each other, there is an interaction, respectively [67].
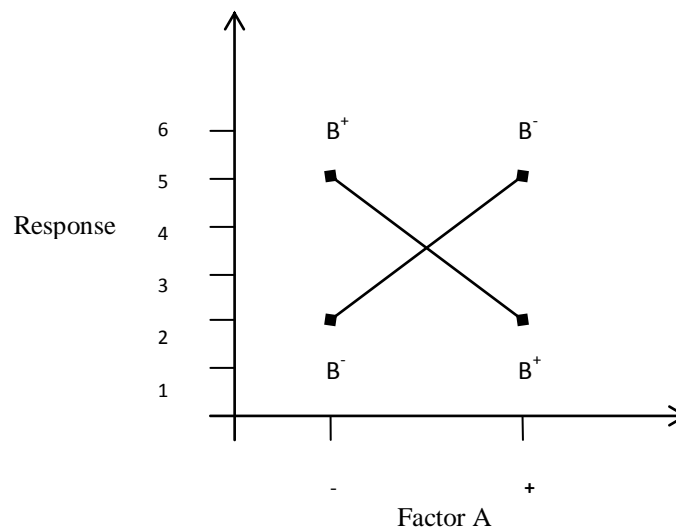

Figure A.6.2: Interaction between factor A and factor B at low and high levels

In addition, the interaction of two factors can also be represented as a *regression model* [69] :
$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + \varepsilon \quad (1)$$

β = parameter of the value that is established

x = variable for the factor

$x_1 x_2$ = interaction between the two factors

β_0 = average of all the response variables

ε = experimental error

For a further representation of this model it is suggested to use a *response surface plot* [69] (later discussed in detail). The yield is represented as surface figure as a result of the different combinations of the included factors (fig. A.6.3):
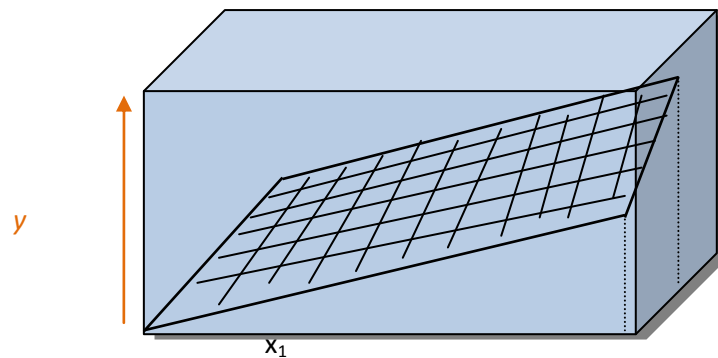
Figure A.6.3: Response surface

Actually the plane describes the response affected by the two factors x_1 and x_2 in three-dimensional form, whereas the contour plot gives the same information of a response surface in form of a plane. If there is an interaction between the two factors, the plane might be twisted, which means that interaction are given in a form of curvature according the response surface model. Thus RSM is an essential tool to design the experiment [67].

A.7.3.1. **The 2^k Design**

They are mostly used for screening designs and factor influence studies as the simplest form of orthogonal design → **two factors in two levels (2^2)**, each of them at their high (+) and low (-) levels, which is illustrated in a first-order model with a linear response. As in figure A.6.4 is depicted, each point represents an experiment, where the first

column (x^i) starts in general with 2^{i-1} repeats for the low level, to be followed by 2^{i-1} repeats for the high level [68].
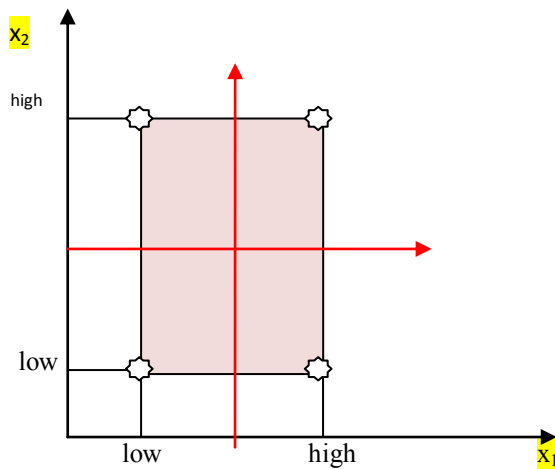
Figure A.6.4: 2^2 full factorial design

The *experimental plan* could therefore be [69]:

- 1) Defining the <u>experimental design</u> for two factors at two levels, written down in the standard order (all variables are -1 in the first experiment). All possible combinations of the factors at the two levels give four experiments.

Experiment	Factor x_1	Factor x_2	Response
A	+1	-1	y_1
B	-1	-1	y_2
C	+1	+1	y_3
D	-1	+1	y_4

- 2) Inserting the <u>mathematical model</u>:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \varepsilon \text{ (first order model/linear)(2)}$$

- 3) Calculating the <u>effect</u> of each factor on the response:

    Factor 1 : $b_1 = \frac{1}{2} \cdot (+y_1 - y_2 + y_3 - y_4)$

    Factor 2 : $b_2 = \frac{1}{4} \cdot (-y_1 - y_2 + y_3 + y_4)$

    ►b_1 and b_2 are the estimations of the main effects β_1 / β_2

- 4) Considering <u>interactions</u> between the two factors:

This could be estimated by calculating the partial effects of the factors:

! $b_{12} = \frac{1}{2} \cdot (b_1^{(+1)} - b_1^{(-1)})$ →only changing the level of fact.x_1; x2 constant $^{(+1/-1)}$

$= \frac{1}{2} \cdot [(\frac{1}{2} \cdot (-y_3 + y_4) - \frac{1}{2} \cdot (-y_1 + y_2)]$

$= \frac{1}{4} \cdot [+y_1 - y_2 - y_3 + y_4]$ *(3)*

Whether the result is positive or negative, this phenomenon is defined as synergism or antagonism. The mathematical model is described in equation *(1)*.

The <u>model matrix</u> X for the complete full factorial design including interactions is explained as following:

X_0	X_1	X_2	$X_1 X_2$
+1	-1	-1	+1
+1	+1	-1	-1
+1	-1	+1	-1
+1	+1	+1	+1

X_0 = a "pseudo"-variable and equal to +1

A.7.3.2. **The 3^k design**

Factorial designs of a higher number of levels are mainly engaged in response surface optimization. These designs have the advantage that they are also able to identify and calculate possible nonlinear or quadratic effects, and allow a separation in calculation between main effects and interactions in an orthogonal way of design. On the other hand it should be considered that in higher level FF designs the number of experiments increases rapidly with the number of factors [68].

3^k designs include three levels for each factor. The factors and their levels will be written in capital letters, and the levels are described as low, intermediate and high level. There are different options for the notation of the levels, but it is advantageous to

use 0 and 1 in the 3^k designs instead of ±1 that is known from the 2^k design, which only facilitates the geometric view of the design in this case thus it is right appropriate for the regression model. Using -1, 0, +1 for the different levels simplifies the regression model fitting. In addition it gives the experimenter important information about possible curvature in the response function thus it can be demonstrated as a quadratic model [73].

In case of a 3^2 factorial design, as long as the factor A is shown as x_1 and factor B as x_2, each at three levels, the regression model would be written as:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \varepsilon \ (second\ order)\ (4)$$

Altogether we receive nine experimental runs, as shown in **figure A.6.5**:

Each point in the quadrate stands for an experiment at a specific level of a factor.
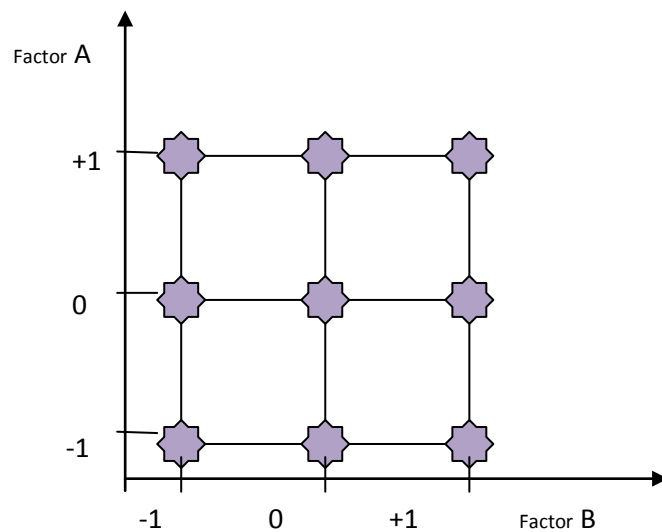
A 3^2 full factorial design, using coded values for the factors [68]:

Experimental Trail	Factor X_1	Factor X_2	Response Variable
1	-1	-1	y_1
2	-1	0	y_2
3	-1	+1	y_3
4	0	-1	y_4
5	0	0	y_5
6	0	+1	y_6
7	+1	-1	y_7
8	+1	0	y_8
9	+1	+1	y_9

A.7.4. *Regression analysis* [70,71]

Regression is the "tool" to construct quantitative relationships between a fundamental characteristic and one or more resultant characteristics. Linear regression describes the relationship between an independent variable *y* and the dependent one, *x*, resulting in a two-dimensional plot. Evidently more than two variables or levels are discussed, which would be case of multiple regression. It can be seen as an urgent section of the optimization techniques, being illustrated in three dimensions, which can only be visualized through an appropriate computer package for experimental design.

Some important terms that may occur during regression analysis:

- ♠ The standard error of the estimate: (*s*) expresses the difference between the predicted results from regression equation (y_{pred}) and the raw ones; often falsely called as standard deviation.

- ♠ The standard error of the coefficient: a high standard error indicates a low dependability of the coefficient and a low probability that the regression equation shows the raw data

- ♠ The F-value: presents the possibility that the equation shows the true relationship between the results

- ♠ The correlation coefficient: can lie between 0 and 1, but the greater it is, the higher the chance that x and y are related

A.7.5. *Optimization* [72]

The target of optimization is rather to find the optimum of a dependent variable/response than a maximum or a minimum. By selecting the values of the independent variables which is upon the experimenter, the dependent variables can be controlled indirectly. Thus the design of a pharmaceutical product is in most cases an agreement between two or more factors. In addition, every process includes limiting factors, such as time or finances. Therefore is should be first priority to receive the optimum outcome, comparably with the best possible compromise under specific conditions.

There are various approaches in order to aim the optimum response, such as sequential

and simultaneous methods. The latter is the most alternative. Mostly, experiments are set in a small number; in between the results are studied before the experimenter continues with performing the next trial.

Apart from which method is chosen, the experimenter gains an insight of the relationship between independent variables and the response, characterized by the response surface.

A.7.5.1. *Response surface methodology (RSM)* [73]

It is described as the assembly of mathematical and statistical methods for forming and analyzing difficulties according the response that is affected by the involved variables, aiming at the optimization of this response. If a response is plotted against the levels of the factors, it is usually represented as a response surface (fig. 6.5.). For visualizing its shape, a contour plot is used additionally. Each contour plot resembles to a specific type of response surface. First approaches in RSM are to find out the valid relationship between the response and the independent variables:
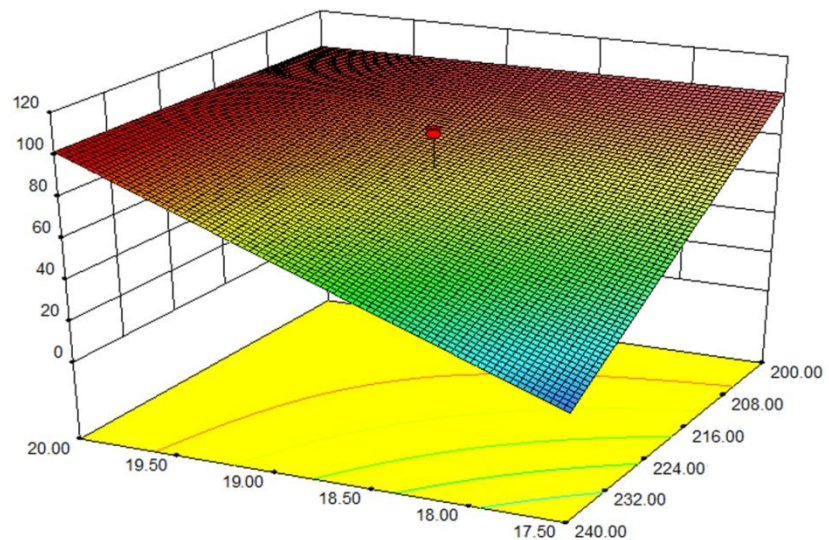

Figure B.5: Response surface /contour plot

➔ A low-order polynomial is used in the region of interest of the independent variables; if a linear function is efficient for modeling the response, a first-order model is being employed. If a curvature is found, it is advantageous to use a

second-order model. It is obvious that these models are only working for a limited region of interest.

➔ As further approximation to the region of the optimum, there are designs employed for *fitting the response surface*.

Simplifying the process of fitting and analyzing the response surface is primarily fulfilled by selecting an appropriate experimental design. When choosing a response surface design, the following properties should be achieved:

- ✓ Allowing an acceptable scattering of the data points over the area of interest
- ✓ Admitting a model that comprehends the lack of fit to be ascertained
- ✓ Admitting a sequential method of carrying out the experiments
- ✓ Also admitting designs of higher order to be developed sequentially
- ✓ Including an inner estimate of error
- ✓ Managing with a small number of experiments
- ✓ Involving a small number of levels of the independent variables
- ✓ Guarantees the facility for calculating the model parameters

A central-composite design (fig.A.6.7) is proposed for fitting the second-order model. It includes a 2^k factorial design with *n* runs, *2k* axial runs and center runs, n_c. It is supposed to be a very efficient tool, although two parameters should be identified, the distance α of axial runs from the center and the amount of center points.

A second-order response surface design is considered to be *rotatable*, which means that the variance of the predicted response is the same at all points x, lying on the same distance away from the center of the design. Thus a rotatable design provides the variance of the predicted value to be unaffected if the design is ratted about the center ➔*Rotability*. It is important to use a design that shows the same precision of the estimation in each direction of the design space.

Figure A.6.7: Face-centered central composite design for k=3
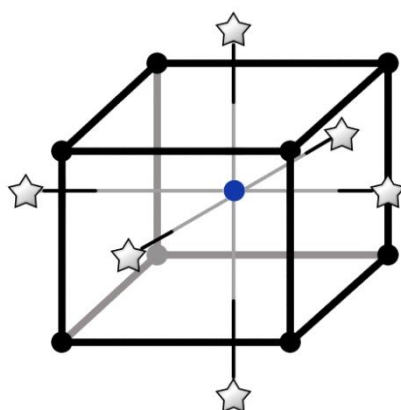
A *central composite design (CCD)* can be constructed in order to achieve rotability by the selection of α. The value for α relies on the amount of points in the factorial fraction, though the choice is influenced by the region of interest; if it is a shaped spherical, center points are required in order to achieve a constant variance of the predicted response. Basically, a CCD should adhere between three and five center points.

A.8. *AIM OF THE STUDY*

It should be considered that experimentation involves a large quantity of time, effort, manpower and money in order to receive satisfying results or outcomes to a complex question like in the case of nimesulide and its poor aqueous solubility. Obviously the aim is well-know, and presently there is no way around the finding of an acceptable formulation, while keeping the arrangements of time and materials as simple as possible.

First step therefore includes the finding of the significant variables and their interaction, followed by their influence on the outcome of the experiment. A reasonable choice would be the procedure of the factorial design (→A.7.3.), followed by response surface methods in order to receive a suitable model, where a minimum of experiments is requested. Over the optimization step, including FD and RSM, we have an efficient tool and a basic prerequisite for developing the optimal oral formulation for nimesulide.

2. PRACTICAL PART

B.1. *Scope*

The purpose of the present investigation was to characterize a novel direct pelletisation process for the production of immediate drug release spheroids. A composition of excipients was chosen that featured a low amount of effort, time and complexity. The settings of the rotor processor and the amount of the various excipients were already implied. Furthermore it was important to proof that through the optimum amount of binder material and its spraying rate pellets could be obtained that conform to certain requirements, namely geometric mean diameter, general standard deviation of size and the shape factor.

Moreover the application of a novel process was in focus, challenging its reproducibility through utilizing an active pharmaceutical ingredient of low water solubility.

B.2. *Materials and Instruments*

B.2.1. Substances

The following substances were used in the major experiments and the evaluation processes:

o Microcrystalline cellulose PH 101 (Microcel®, Blanver, Brazil, Lot 310/07) for the production of the spheroids

o Lactose monohydrate 150 M (Lactochem®, DOMO® Pharma - Friesland Foods Domo, the Netherlands, Lot 628815) for the production of the spheroids

o Colloidal silicon dioxide (Aerosil® 200 Pharma, Degussa, Germany, Lot 1302072) as glidant for the production of the spheroids

o Nimesulide (received from Aspire Pharma Ltd., United Kingdom, Lot 09000093) as the active ingredient in pellets

o Polyethylenglycole 4000 (PEG 4000, Clariant® Produkte GmbH, Switzerland, Lot 4000676) as binding material for the pellet production

o Polyethylenglycole 400 (PEG 400, Clariant® Produkte GmbH, Switzerland, Lot DEG146600) as binding material for the pellet production

o Potassium di-hydrogen phosphate, KH_2PO_4 (PRS-Panreac, Lot 0000208628) for the preparation of the phosphate-buffer for the dissolution tests

o Sodium chloride (NaCl, BDH® & Prolabo® – VWR, Lot 09G150016) for the preparation of the phosphate-buffer for the dissolution tests

o Sodium hydroxide (NaOH, BDH® & Prolabo® – VWR, Lot 09G300017) for the adjustment of the pH for the dissolution media

o Deionized Water (for laboratory usage) for the preparation of the dissolution media

o Acetone (Aldrich) as solvent for Nimesulide for the preparation of the mother-solution)

o Magnesium stearate, as lubricant which was added before loading the product chamber with the rotor-material

o Nimesulide tablets (Specilid tabs Nimesulide 100 mg, Batch 7196, Greece), used for the dissolution studies

B.2.2. Instruments and Tools

Subsequently the involved machines, instruments and special instrumental parts are listed:

o Glatt Powder Coater Granulator GPCG3 (Glatt GmbH, Binzen, Germany, Com.Nr. 6274) for the pelletisation process itself

o Rotation disc - with linear slots on the surface (part No. Z-22647-c, Glatt GmbH, Binzen, Germany)

o Spaying nozzle – operates with compressed air (part No. 9100804484, type: 941/7 – 1S38, Glatt GmbH, Binzen, Germany)

o Powder metering device – feeds the granulator with the MCC/Aerosil1%-mixture during the process (Serial-No. 280, SECUDOS G.&K. Fuchs GmbH, Wiehl, Germany)

o Peristaltic pump – for the transport of the binding material to the process chamber (Stahl® B8727/12-04-001, serial-No. 2066)

o Electric Steam Boiler – for heating up the air (FULTON® – T0BS1894 by Fulton Boiler Works, Great Britain)

- o Dissolution Test Instrument, semi-automated (type: PT-DT70, Pharmatest$^®$ Apparatebau GmbH, Germany)
- o Baskets, for holding the nimesulide samples (Art.No.311-2801, 309646)
- o UV/Vis spectrophotometer (type: T90+, PG$^®$ Instruments Ltd)
- o Quartz cells - for the evaluation of the absorption from the nimesulide-solution (size:1x1x4cm)
- o Vortex Heidolph − Germany, Type Relaxtop − for the homogeneous intermixing of the collected nimesulide sample from the dissolution test and the buffer, before being measured spectrophotometrically)
- o Filtration devices − (Whatman$^®$ 0,45μm nylon filter) − for the filtration of the samples before being measured spectrophotometrically
- o Magnetic plate − Heidolph, Germany
- o Electric stirrer − Stuart$^®$, stirrer SS10
- o pH-meter, HANNA Instruments, type: HI 9025 microcomputer ph Meter, for the adjustment of the buffer-solutions for the dissolution test
- o Powder Mixing Device, Erweka AR400, Nr 52995, Erweka$^®$ Apparatebau GmbH, Germany - for the homogenous premixing of the several powder mixtures
- o Sieving devices, Laboratory Test Sieve, Endecotts LTD., size of mesh: 1.4 & 2.0 mm − for the evaluation of the quantity of the yield, according to the size
- o Analytical Libra, Kern & Sohn GmbH (Albstadt, Germany)
- o Major balance, AND$^®$ HF - 2000
- o Another balance, Mettler$^®$ Toledo PB 5001
- o Microscope, LEICA$^®$ DMLM, for the pellet-measurements
- o Diverse computer stations

B.2.3. Software
- o Statistical Program, XLSTAT, Version 2009
- o Design Expert$^®$ Software
- o Microsoft Office, Excel Program
- o Image Analyzing System, Leica Qwin, Leica Imaging Systems Ltd., Cambridge, UK)

B.3. *Methodology*

B.3.1. GLATT

Image of a Glatt-GPCG 3

The Glatt can be used for small quantities of powders and other similar materials to be agglomerated, following a production in accordance with GMP (good manufacturing practice). Apart from the top-spraying and Wurster-technique as fluid-bed techniques, the rotor technique or tangential spraying (→ A.4.2.3.) is from main interest in the case of preparing the pellets.

B.3.1.1. Technical construction [43]
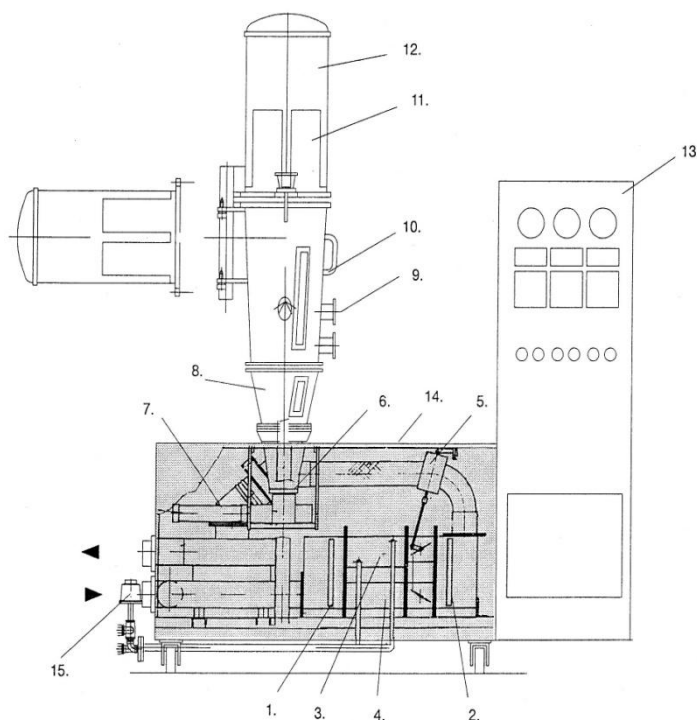
1. Prefilter 1
2. Prefilter 2
3. Warm air flap
4. Cool air flap
5. Bypass system
6. Pressing mechanism
7. Hydraulic cylinder
8. Product insert
9. Spraying nozzle insert
10. Expansion chamber
11. Filter system
12. Filter housing
13. Control box
14. Position for spray pump
15. Valve

Figure B.1: GPCG 3

The incoming process air, heated up through a steam boiler, is filtered by two prefilters (1. + 2.) and mixed in the face and bypass system (5.)(→ B.4.2.1.) in order to achieve the desired operating temperature via inlet air. The inlet air temperature is regulated by the flap (3. + 4.)that guarantees quick temperature changes. The whole flap consists of the cool and warm flaps that are controlled by a pneumatic control cylinder. After switching on the turbine, the mixing flap starts working and the pneumatic steam valve opens. The warm air flap therefore remains opened only until the desired temperature value is reached.

The product container (8.) is a removable part of the apparatus, conically shaped, equipped with a sampling port and temperature sensor port. It is lifted up and down during the process by a pneumatic pressing cylinder (7.).

The expansion chamber (10.) is also one of the removable parts of the Glatt and characterized through two nozzle ports and a temperature sensor port.

As a part of the filter housing (12.) the Glatt consists of a huge filter system (11.) that separates the process air from the fine particles. Through subsequent shaking at specific intervals, the particles are able to drop back into the process space, without disturbing the process itself.

If focusing on the spraying device, the spraying nozzle consists not only of the air spraying pipe but also of the liquid spraying pipe. These are connected with the pump by a heated hose.

For having a control over the temperature of the inlet air, exhaust air and the temperature of the product, which is essential for managing the pelletisation process, sensors for measuring the temperature are provided at specific positions of the Glatt apparatus.

The rotor insert (as mentioned above) that consists of the cylindrical process chamber (8.) (→Picture below) and the conical expansion chamber (10.) that is connected with the drive unit of the rotor through a flexible shaft.

Snapshot of the rotor's product chamber

The rotating disk is situated inside the production chamber and is adjustable in its height manually through a hand-wheel that is installed on the outside wall of the product container. The volume of the inlet air is therefore precisely contollable by creating a more or less wide slit between the rotor plate and the stator wall of the product chamber.

B.3.2. <u>The procedure of producing pellets</u>

B.3.2.1. Necessary preparations

The dry mixing of the solid materials was required before starting the main experimental part.

- *Material for the rotor*:

Microcrystalline cellulose: α-lactose monohydrate = 45:55

→ MCC 225.0g/ α-lactose m. ad 500.0g

Each batch was weighed in separately on a balance under the extractor hood, followed by mixing the solids for 15 minutes with 100 rpm on a cube-agitator. Afterwards the blend was sieved through a 1.0mm laboratory sieve in order to achieve a homogenous distribution.

- *Material for the powder feeder:*

Microcrystalline cellulose + 1% colloidal silicon dioxide

→Aerosil 0,2g/MCC ad 200.0g

The blends were prepared like mentioned above by following the GMP-rules. Especially in the case of the powder feeder it was essential to sieve the blend in order to avoid eventually appearing Aerosil-agglomerations.

- *Material for the liquid binder:*

Polyethylenglycole 400: polyethylenglycole 4000 = 53:47

The excipients were first weighed into a beaker glass and melted in a water quench over the melting point of the PEG 4000, which lies between 64-65ºC. Through stirring in regular intervals the homogeneity of the binder could be provided. Shortly before starting the experiment the adequate amount of the liquid was prepositioned next to the

Glatt apparatus. The amount required for the single experimental run was therefore taken from a heated glass-vessel and pumped over to the spraying nozzle.

B.3.2.2. The experimental design/plan

A 3^2 full factorial design ($\rightarrow$A.7.3.) study has been used in order to examine the physical characteristics of the obtained pellets, namely geometric mean diameter, geometric standard deviation and the shape factors ($\rightarrow$C.1).

This means handling with two variables at their three levels (figure B.1). The one dependant variable is a formulation variable, the amount of sprayed binder, whereas the other variable is a process variable, the spray rate of the pelletisation liquid.

The process parameters of this study are presented in table B.1 along with their respective operating limits.

Factors	low level (-1)	middle level (0)	high level (+1)
A: Binder Quantity (g)	360	400	440
B: Spray rate (g/ml)	35	40	45

Table B.1: considered factors and their levels

Therefore, using the full factorial design (figure B.3.), ten experiments were carried out, which corresponds to three levels for the two parameters. In addition, the design includes three center points.

Batch No.	Factor1 – A	Factor2 – B
1	-1	-1
2	0	-1
3	+1	-1
4	-1	0
5	0	0
6	+1	0
7	-1	+1
8	0	+1
9	+1	+1
10	0	0
11,12,13	0	0

Table B.2: Experimental design of 3^2 full factorial design.

From previous investigations of Paterakis et al. 2002[15] it was clear to use a mixture of microcrystalline cellulose and alpha-Lactose in a relation of 45:55 for the rotor. The other quantities can be withdrawn from table B.4.

Batch No.	1	2	3	4	5	6	7	8	9	10
MCC:Lactose	45/55	45/55	45/55	45/55	45/55	45/55	45/55	45/55	45/55	45/55
MCC	225	225	225	225	225	225	225	225	225	225
Lactose	275	275	275	275	275	275	275	275	275	275
Powder feeder	200	200	200	200	200	200	200	200	200	200
Material Rotor	500	500	500	500	500	500	500	500	500	500
Amount of Binder	360	400	440	360	400	440	360	400	440	400
Spray rate g/ml	35	35	35	40	40	40	45	45	45	40

Table B.3: Recipe for the production of pellets (3^2 design)

B.3.2.3. The actual manufacturing step

The adjustment of the Glatt-apparatus:

Hydraulic pressure (bar): 3.0

Spraying air pressure (bar): 2.5

Filters interval/shaking: 1/3

Flap (%air export opening fan): 30%

Disc velocity of rotor (rpm): 1200

Ingoing Air Temperature: 70ºC

Temperature of the Product: 52-56 ºC

Outgoing Air temperature: 52-54ºC

Duration of the process: ~16 min. ±2min.

Temperature during drying process: 40ºC

Duration of the drying: ~3min.

Table B.4: The major setting according the Glatt

Before starting any of the trails, the experimenter should be aware of the fact that each experiment was not only linked to an intensive preparation according the excipients, but also considerations and exact planning of the process step were necessary.

It was important to ensure that the electric steam boiler had been switched on previously in order to assure that enough power for the process was obtainable.

The adjustment of the Glatt had already been known on the one hand from the practical experience and the technical skills of the supervisor and on the other hand the final settings were (fig. B.4) in regard to the feasibility of the process.

Before loading the rotor material in the product chamber, the Glatt was switched on until the desired inlet air temperature was reached. In addition it was necessary to set the powder feeder of the MCC/Aerosil1%-mixture to 15g of addition per minute. After that the 500g-rotor material was loaded in as soon as possible in order to avoid the decrease of the temperature. Finally the bottoms for inlet air, binder pump and rotor were pressed simultaneously while manually adjusting the height of the rotor disc in order to reach an adequate gap between rotor and stator. This was also the start for the documentary and chronological supervision of the process. This means that in regular intervals both temperature values and the already sprayed quantity of binder were kept in records. The temperature of the inlet air was initially set at 70ºC, intending to hold a product temperature of 52-56ºC. For obtaining a better overview of the process, there was not only the observation window in the product chamber existing, but also a camera that sent pictures from inside the product chamber to a nearby situated screen. Therefore it could be noticed if changes in the desired "rope-like" movement ($\rightarrow$A.4.1.) of the mass were present. In this case manually temporary adjustments of the settings were necessary, such as increasing the air flow by raising the exhaust air flap for about 10% in order to get rid of sticking powder near the spraying nozzle so that fluidizing of the material could be guaranteed. Also increasing the inlet air temperature was essential if the desired product temperature was about to fall. In addition hammering against the outside wall of the chamber was a common practice to avoid the sticking of the powder on the inside surface instead of integrating in the process by forming spherical agglomerates. During the entire pelletisation process the exhaust air filters had been cleaned by controlled shaking intervals in order to prevent the filter from plugging up, and furthermore including the fine particles in the pelletisation process again, even without interrupting the spraying phase when it is set automatically. Because of the fact that mixing the materials had already been done as a

pre-experimental preparation, the process itself only consisted of the wet pelletisation step and the subsequent drying process. Dependent on the quantity of binder sprayed and the spray rate, the process of the liquid addition itself lasted between eight minutes (trial 7) and 12 minutes (trial 3), while the powder feeder ran for thirteen minutes. After the binder had been sprayed, the connection-hose was removed. From the point of "end of spraying" the temperature of the hot inlet air was decreased to 40ºC, heralding the drying phase which continued until the product temperature had also reached the value of 40ºC.

Further steps included switching off the inlet air and the rotor, whose electrical regulation was situated on the control box. Only until the disc velocity had nearly reached zero the rotor disc could be lowered to its starting position. Next step was to remove the product chamber from the processing unit, wearing protection gloves thus the metal walls still had saved residual heat.

First macroscopically impressions could have been made from the product, such as residual wetness, dryness, surplus powder feeder or agglomerated regions. Not until the final drying on wooden hordes at room temperature the pellets could be evaluated for their microscopically properties by utilizing an image analysis system ($\rightarrow$ B.3.3).

B.3.3. *Evaluation of the pellet properties*

The assigned purpose of the pelletisation process was to obtain spherical agglomerates showing a tolerable size, size distribution, standard deviation and shape. For the delivery of pellets either encapsulation or subsequent coating processes in order to change the release characteristics are reasonable approaches. Therefore it is obvious that the focused strategy of the research was to obtain desirable values within a specific range in order to guarantee ensuing production steps such as uniform filling in hard gelatin capsules or satisfying coating procedures.

The pellets were first fixed on an adhesive surface, which was laid underneath by a black sheet of paper with the intention to increase the contrast during the microscopic determination.

The actual measurements were carried out (→image beneath) using an image analyzer, consisting of an optical microscope (Leica DMLM), which was completed with a camera (JVC, Japan). An additional cold light source was utilized in pellets' position in order to illuminate the pellets against the black surface.

Necessary installation for the accomplishment of the measurement: left side →Leica image analyzer

About one hundred pellets from each batch were collected and analyzed. Before the data could have been sent to the computer (Excel, Microsoft Office, Windows XP) in order to fulfill the calculations, it was the experimenter's work to focus on those pellets, which should have been taken into calculation. That means that pellets were avoided, which had been probably sticking together. Moreover it was necessary to regulate the contrast of each image involved into calculation by changing the focus manually at the microscope on the one hand and regulating the camera's view by using the imaging processing and analyzing software (Leica Qwin, Cambridge, UK).

B.3.3.1. Determination of the size and the size distribution

From the image analyzing system the equivalent spheres diameter of the pellets was received. For determining their geometric mean diameter (d_g) and the geometric standard deviation (σ_g), a log-probability plot was utilized. The main analysis was carried out by statistical software, namely Design-Expert®.

B.3.3.2. Determination of the shape

For the actual determination of the shape of the pellets, a variety of factors have been taken into consideration, such as the circularity-, roundness-, roughness- and the e_R-factors. These shape parameters were calculated by utilizing the following equations:

1) $\text{Roundness} = \dfrac{\text{area}}{\pi.(d_{max}/2)^2}$

2) $e_R = \dfrac{\sqrt{2\pi r_e}}{pf} \quad [1-(\text{breadth}/\text{length})^2]^{1/2}$

   f = correction factor

The values of the area, the breadth, the length, the r_e (equivalent radius) and p (perimeter of the sphere) of the pellets and the elongation factor have been calculated directly by the image analysis software. The shape factor e_R consists not only from the geometrical shape but also from the surface behavior of the pellets.

B.3.3.3. Yield

The final yield was calculated from the total amount of the end product, expressed as a percentage of the amount of the starting materials.

Therefore each batch was sieved trough 1.4.mm and 2.0mm mesh, while possible agglomerates were separated from the material which had been taken into measurement.

B.3.4. *Pelletisation including nimesulide*

B.3.4.1. Motivation

The previous experiments were seen as a necessity for the single trial, where nimesulide has been involved as the pharmaceutical active ingredient. Thus the equipment, process and process variables to be investigated in the experiment and the range of these variables were selected on the basis of the results. Final motivation was to invent a simple and low-coast formulation of a poorly water-soluble drug, and achieving nonetheless satisfying dissolution-characteristics of the dosage form. Techniques, where superdesintegrants [55], surfactants [59] or cyclodextrins [63] are utilized in order to increase the solubility of nimesulide, were avoided. As a result, subsequent processing steps, costs and time could be saved.

The major pelletisation process was thus challenged with the production of Nimesulide pellets.

The following formulation (→table B.5.) was utilized, while the process was stopped when pellets of appropriate size came into sight. For the choice of the binder amount and the spraying rate, values that were lying in the experimental center were utilized.

Nimesulide	200g
Rotor material	300g
Powder feeder (MCC/L)	200g
Binder quantity	400g
Spraying rate (ml/min)	40g

Table B.5: Start-settings of the nimesulide-trial

B.3.4.2. Evaluation of nimesulide-pellets

For the evaluation of the dissolution properties of the produced pellets, in-vitro dissolution tests were performed at pH 6.8 and 8.2, using a USP Type II dissolution apparatus(referring to [63]. The samples were assayed by measuring the absorbance at 397 nm for nimesulide as target wavelength.

B.3.4.2.1. Preparation of the buffer-solutions

The buffer solutions were prepared in accordance to the USP/NF [74]. Therefore it is suggested to prepare the phosphate buffer by utilizing 6.8 grams of monobasic potassium phosphate as well as 5.5 grams of sodium chloride, and then adding water up to a volume of 1000 ml. Sodium Hydroxide solution 5N was applied to adjust the targeted pH of 6.8 and 8.2.

B.3.4.2.2. Dissolution studies

The main dissolution studies have been taken place in a semi-automated dissolution test apparatus (PharmaTest PT-DT70, Picture B.4a). The specific pHs (6.8, 8.2) and the sampling intervals were chosen in order to be similar to *Naluri et al.* [63] and in particular with the commercially available tablets containing nimesulide. As described in the USP [68], apparatus I with baskets (picture B.4b) was utilized for performing the studies. This means that the prior prepared buffer solutions were filled into the glass vessels, holding them at a constant temperature of 37°C ±0.5°. The samples were weighted (459,5mg) into dry baskets in accordance to be equal to a 100mg dose of nimesulide. A rotation speed of 50 rpm was chosen and samples of 5ml were withdrawn at specific time intervals (10'/20'/30'/45'/60'/90'/120'/180'/240'), while replacing them afterwards through fresh dissolution medium. Each sample was measured independently after filtering it through a 0,45μm membrane filter and diluting, if necessary.

The absorbance of the samples was measured using a UV/Vis spectrophotometer (PG[®] Instruments Ltd, T90+) with a target wavelength of about 397 nm for nimesulide. These dissolution experiments were conducted in sextets. The desired concentration to be measured was finally 0.1mg/ml, reflecting the complete dissolution of the commercially available dose of nimesulide in 1000ml of the dissolution medium.

Picture B.4a: Dissolution test apparatus
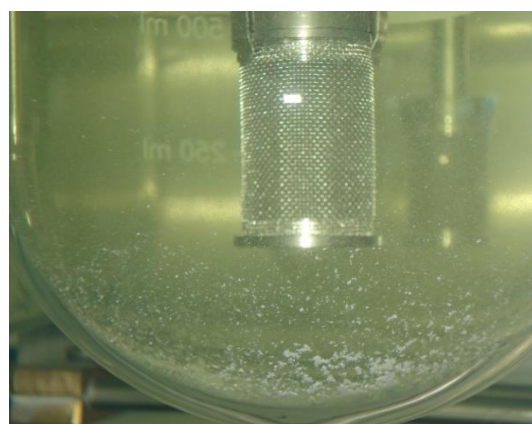
Picture B.4b: Pellets placed in the baskets (stage of disintegration of pellets)

3. RESULTS & DISCUSSION

C.1. Pellet size and size distribution

The size of the pellets was investigated by the geometric mean diameter (GMD) and the geometric standard deviation (GSD). The results of the experiment and the analysis of the pellet size distribution are shown in table C.1.

EXP	Quantity sprayed (g)	Spray rate (g/min)	Geometric Mean Diameter (GMD) (µm)	Geometric Standard Deviation (GSD)
1	360	35	522,6	1,22
2	400	35	555,2	1,18
3	440	35	566,7	1,13
4	360	40	456,7	1,13
5	400	40	565,7	1,20
6	440	40	612,0	1,19
7	360	45	412,4	1,20
8	400	45	554,8	1,19
9	440	45	643,2	1,23
10	400	40	580,7	1,21
11	400	40	569,0	1,20
12	400	40	574,0	1,21
13	400	40	578,0	1,20

Table C.1: **The results for the GMD/GSD**

C.1.1. GMD – The geometric mean diameter

For the design of the experiment for the GMD the model was selected including the following strategies:

a) The *Lack of Fit Tests* for different alternatives, starting from the simplest models and moving to high order models, if necessary. First of all it is essential that the model fits well to the data.

Table C.2: Lack of Fit Tests						
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob > F**	
Linear	12838,11	6	2139,68	55,65	0.0008	
2FI	4120,65	5	824,13	21,43	0.0055	
Quadratic	**479,77**	**3**	**159,92**	**4,16**	**0.1011**	**Suggested**
Cubic	284,24	1	284,24	7,39	0.0530	Aliased
Pure Error	153,80	4	38,45			

Considering that the F-value indicates the probability of the equation, representing a true relationship between the results, rather than coincidence, the quadratic model is the model of choice in this case.

b) In addition the summary indicates the best model to start with (Table C.3).
   A model reduction may be necessary in order to receive a model with different adjusted R-squared and predicted R-squared values.

Table C.3 Summary					
Source	Sequential p-value	Lack of Fit p-value	Adjusted R-Squared	Predicted R-Squared	
Linear	0.0022	0.0008	0,6461	0,2592	
2FI	0.0020	0.0055	0,8706	0,6689	
Quadratic	0.0013	0.1011	0,9753	0,9057	Suggested
Cubic	0.3975	0.0530	0,9761	0,2451	Aliased

According to the results which are illustrated in tables C.2 and C.3, the quadratic model is the most appropriate being used for describing the relationship between the factors and the response of GMD.

Taking advantage of the same software for providing the fitting of the model to the data, an ANOVA (analysis of the variance) table was generated. The variability can now be attributed to the different factors (table C.4).

Table C.4: ANOVA for Response Surface Quadratic Model						
Analysis of variance table [Partial sum of squares - Type III]						
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	**43414,91**	**5**	**8682,98**	**95,93**	**< 0.0001**	**significant**
A-QUANTITY BM	30863,19	1	30863,19	340,99	< 0.0001	
B-RATE BM	193,38	1	193,38	2,14	0.1872	
AB	8717,46	1	8717,46	96,32	< 0.0001	
A^2	2373,30	1	2373,30	26,22	0.0014	
B^2	206,20	1	206,20	2,28	0.1749	
Residual	633,57	7	90,51			
Lack of Fit	479,77	3	159,92	4,16	0.1011	not significant
Pure Error	153,80	4	38,45			
Cor Total	44048,47	12				

According the significance and the other statistics the model was found to be precise and appropriate enough in order to describe the design space, respectively.

Std. Dev.	9,51	R-Squared	0,9856
Mean	553,2	Adj R-Squared	0,9753
C.V. %	1,72	Pred R-Squared	0,9057
PRESS	4152,67	Adeq Precision	36,64

If considering the influence of the factors, it was observed that the second order interaction of factor B (B^2) does not have a significant influence. Therefore it was decided to exclude this parameter from the model in order to form a reduced model. A new ANOVA table was formed for the reduced model, representing the results in table C.5.

Table C.5: ANOVA for Response Surface Reduced Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	**43208,70**	**4**	**10802,18**	**102,91**	**< 0.0001**	**significant**
A-QUANTITY BM	30863,19	1	30863,19	294,02	< 0.0001	
B-RATE BM	193,38	1	193,38	1,84	0.2117	
AB	8717,46	1	8717,46	83,05	< 0.0001	
A^2	3434,68	1	3434,68	32,72	0.0004	
Residual	839,77	8	104,97			
Lack of Fit	685,97	4	171,49	4,46	0.0883	not significant
Pure Error	153,80	4	38,45			
Cor Total	44048,47	12				

Following the results of the analysis, the lack of fit still was not significant. Obviously the model statistics were excellent.

Std. Dev.	10,25	R-Squared	0,9809
Mean	553,2	Adj R-Squared	0,9714
C.V. %	1,85	Pred R-Squared	0,9436
PRESS	2484,58	Adeq Precision	37,27

When including the statistics, the following equation could be used in order to describe the relationship between the different factors and the response:

For the geometric mean diameter (GMD):

GMD = +370.6 + 8.76 x QUANTITY BM - 94.50 x RATE BM + 0.23 x

QUANTITY BM x RATE BM -0.02 x QUANTITY BM^2

C.1.2. Diagnostics:

C.1.2.1. Normal Probability:

The normal probability plot illustrates if the residuals (= calculated difference between the real value from the experiments and the calculated value from the model) follow a normal distribution. In this case the points would follow a straight line. On the other hand the presence of patterns, such as an "s-shaped" curve would indicate that a transformation of the response may result in a better analysis (figure C.1).
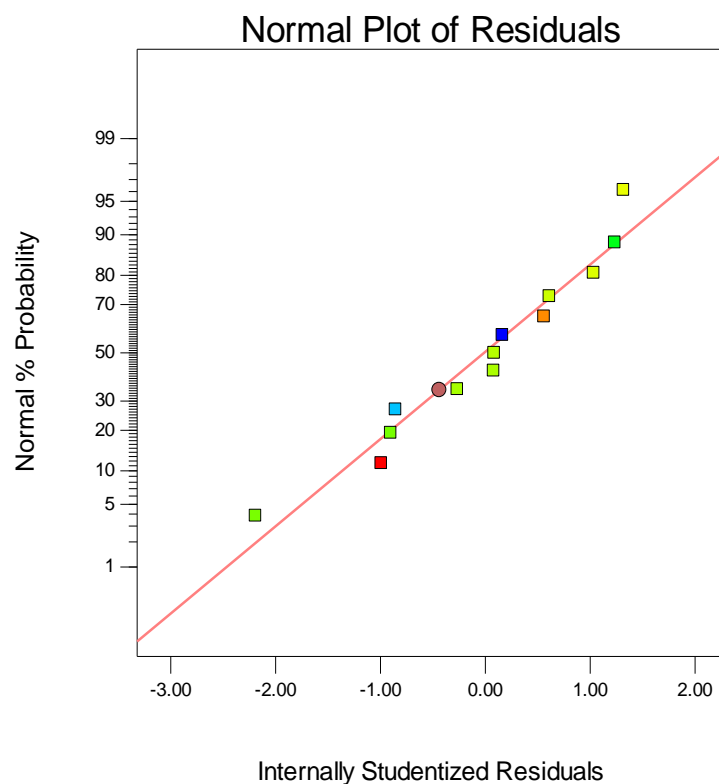

Figure C.1: The normal plot of the residuals

This means that insignificant effects should follow an approximately normal distribution, whereas significant effects are situated away from the straight line. Although this seems to be a subjective criterion, it is quite helpful for decisions according terms that should be kept in the model.

<u>C.1.2.2. Predicted vs. Actual Values:</u>

This plot shows the relationship between the predicted values and the actual response values in order to detect those values, or group of values, which are not easily predicted by the model (figure C.2). Notwithstanding these plots should be highly linear, fulfilling the rules of optimization technology.

In the following case the yellow spots in the plot represent the replicates in the model.
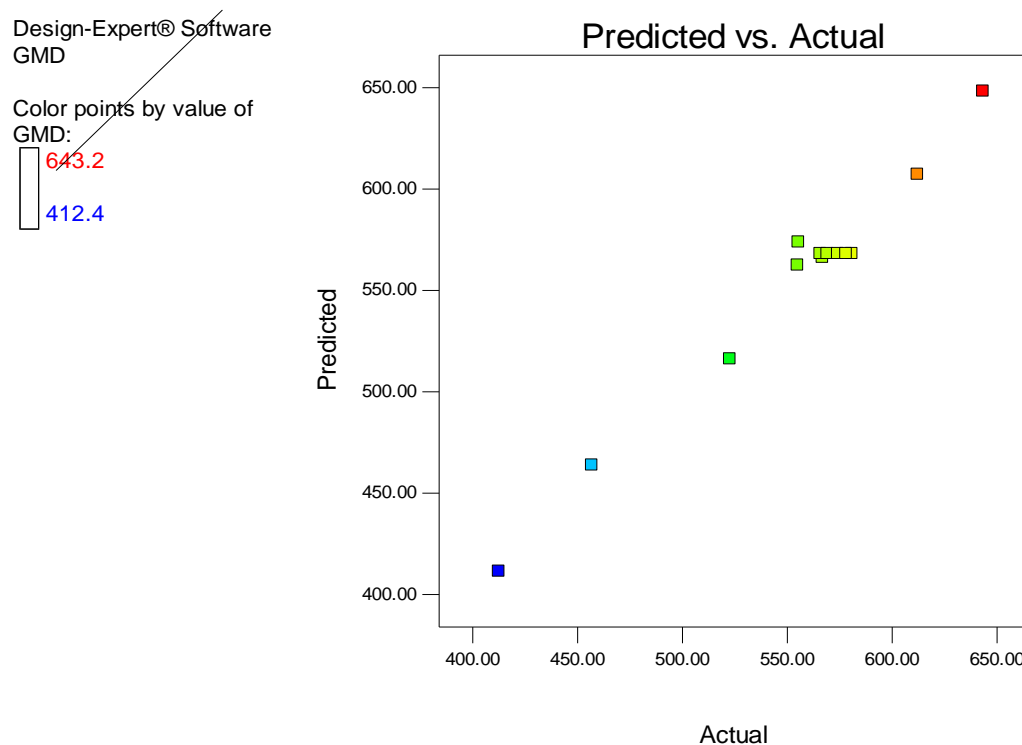

Figure C.2: Predicted vs. Actual Plot

<u>C.1.2.3. Box-Cox Plot for Power Transforms:</u>

In cases of non-normal distributions or a lack of fit of the chosen model, it is necessary to transform the experimental data. In order to make sure if this situation is occurring, the plot provides a guideline in selecting the correct power transformation for the response values. As recommending a transformation, this bases on the best lambda-

value that is found at the minimum point of the curve. This curve is created by the natural logarithm of the sum of squares of the residuals (figure C.3). If the 95%-confidence interval around the lambda-value includes 1, a specific power-transformation is not suggested.
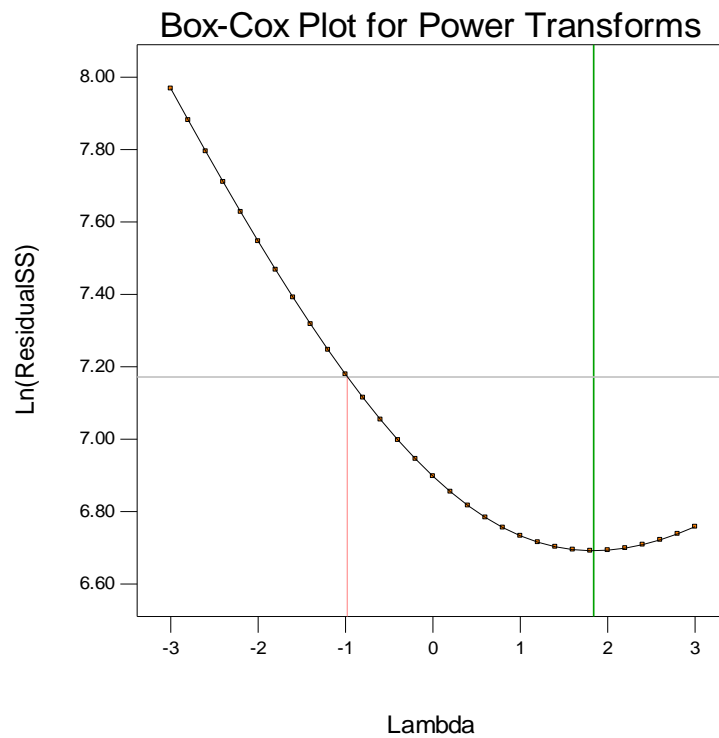

Figure C.3: The Box-Cox plot

C.1.3. Model Graphs:

C.1.3.1. The Contour Plot:

It includes the two-dimensional representation of the response for the selected factors.

Design-Expert® Software
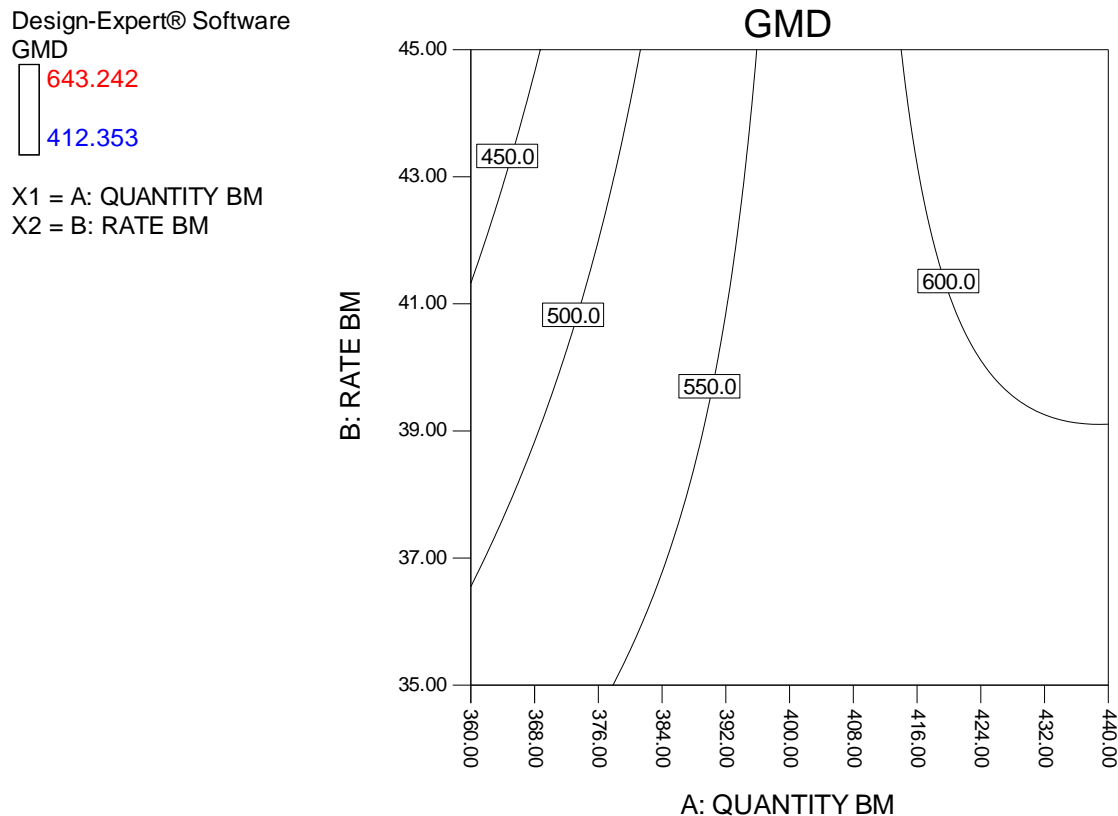GMD
643.242
412.353

X1 = A: QUANTITY BM
X2 = B: RATE BM

Figure C.4: Contour plot of the two factors

When following the tendency of the growth of pellets, it is obviously that increasing the binder quantity goes with a constant increase of the pellet size until 390-400 grams. In general the ascent of the lines in the graph is quite steep, each of them representing a group of GMDs in which pellets can be separated according the outcome.

After this there is a bigger step in the required amount of binder in order to receive the next larger series of pellets, seized around 600 μm. This response may also be linked to a spraying rate in medium or high levels in order to receive pellets of 600 μm and more. Only the combination of the factor A at its high level and factor B at its low

level gives pellet sizes under the 600 μm border. When considering the smaller GMDs of the pellets, it is rather factor A than factor B that influences the outcome.

This effect can also be seen in the GMD of pellets over 600μm, a size that can only be achieved with factor A at its high level (compare also with table C.1).

C.1.3.2. Perturbation Graph:

The perturbation plot is quite helpful for comparing the effect of all the factors at a particular point in the design space. The response is plotted by changing only one factor over its range while holding the other factor(s) constant at the same time → "one factor at the time" experimentation, which doesn't show the effects of interactions between the factors.
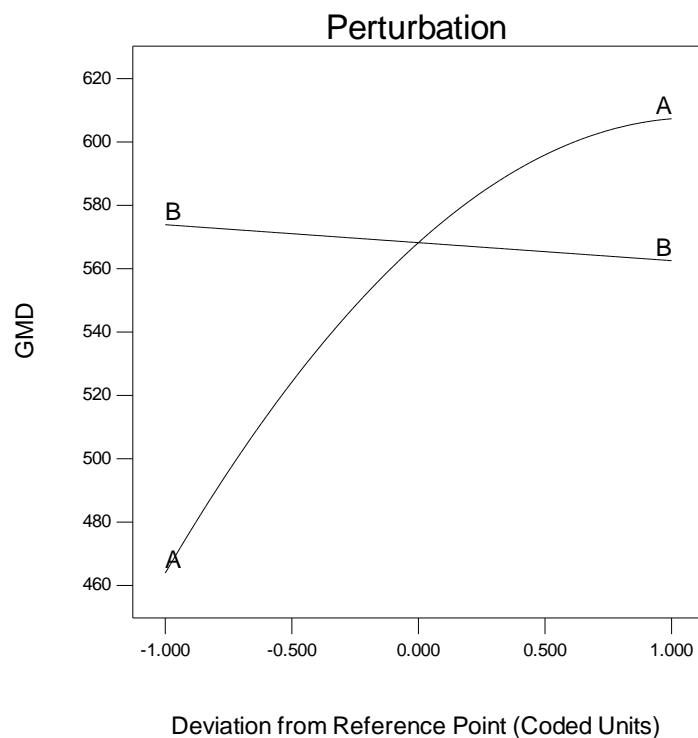

*Figure C.5:* Perturbation graph between the two factors

The reference point is set at the midpoint of all the factors, using coded units for the x-axes in order to show the position set relative to the coded (-1, 0, +1) scale.

Obviously a steep curvature for factor A is to denote, which goes continuously until the GMD over 600 μm, reaching then more or less, a saturated state. This shows again a significant sensitivity of the response to factor A, rather than to factor B. The flat line, representing the influence of factor B gives again raise to the conclusion that changing this factor at any level does not have a significant effect on the outcome of the GMD.

C.1.3.3. 3-Dimensional Surface (RSM)

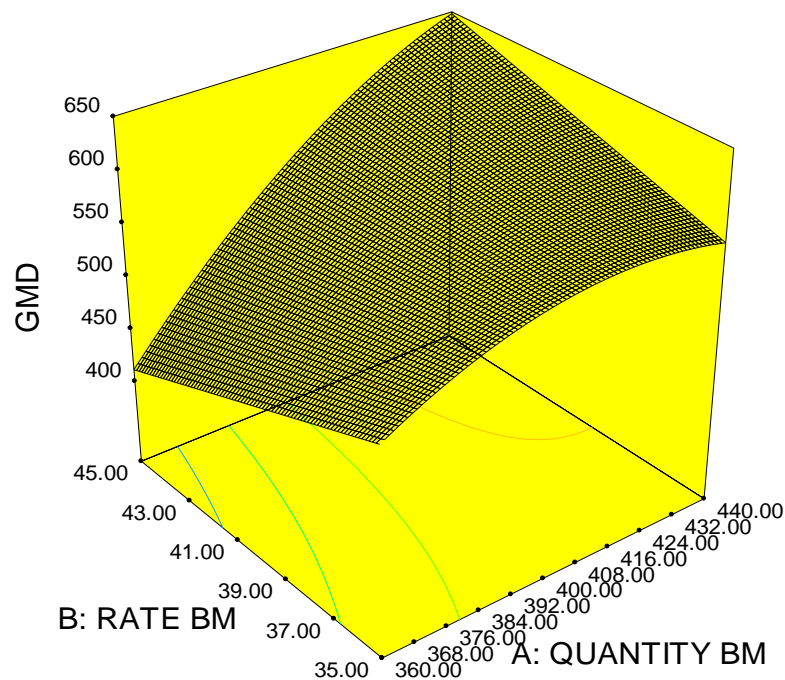Explanation of the procedure can be found in →A.7.5.1.
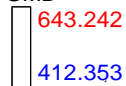
Figure C.6: RSM of the geometric mean diameter

The response surface illustrates the relationship between the amount of binder and the spraying rate over the experimental region (compare with figure C.4).

At low binder quantities, the pellets size remained low, regardless of a change in the spraying rate of the binder. The maximum GMD only occurs in a region where the binder quantity was amount to 440 grams. At a high spray rate the size of the pellets was found to be very low, in particular in combination with a low amount of binder material.

C.1.3.4. Interaction Graph:

From the ANOVA (table C.5) on the one hand and the following illustration of interactions it can be seen that there is a significant interaction between factor A and factor B, respectively.
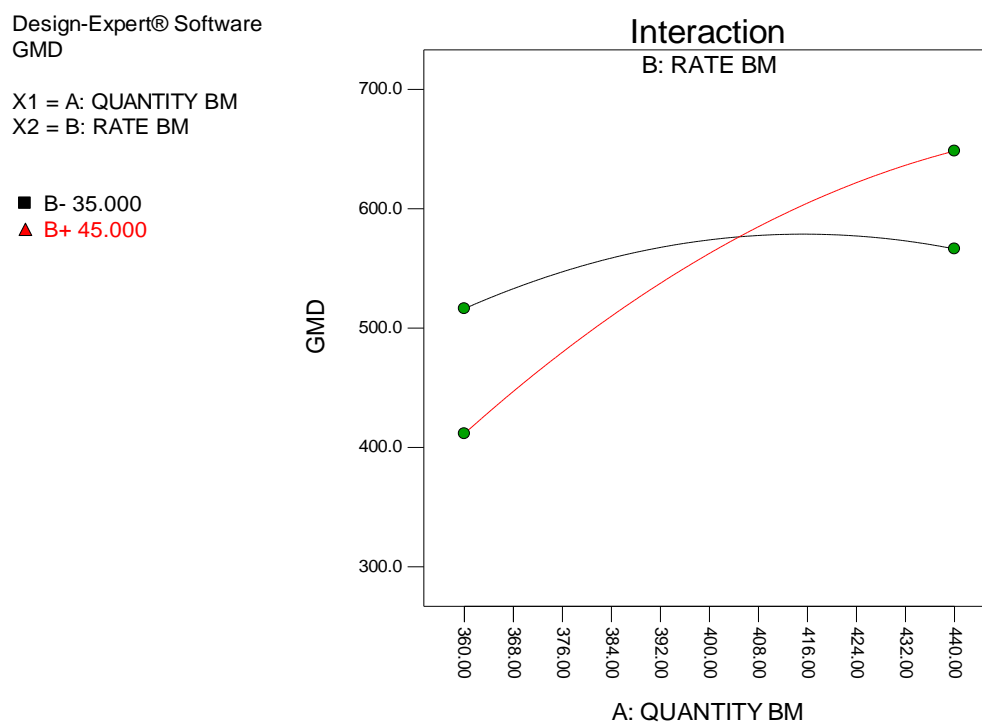

Figure C.7: Interaction Graph

The usage of a low quantity of binder in combination with medium or high spraying rates results in smaller particles, sized between 400 and 500 μm. In general it can be considered that the influence of factor A is maximized when factor B is at its higher levels, resulting in pellets sized over 600 μm.

C.1.4. Conclusions:

Summarizing all the results, evidently A (quantitiy of binder material) is the predominant main factor influencing the size of the pellets, in a quadratic way (see table C.4/C.5). The analysis of the variance illustrates clearly that factor A has a significant effect ($P < 0.05$) on the geometric mean diameter, either seen with the quadratic model or with the reduced model.

Increasing the binder quantity in the experiments is linked to a continuous increase of the pellet size. Larger pellets over 600 µm GMD can only be achieved when moving factor A to high levels, whereas the smaller sizes, ranged under 500 µm were reached using 360 grams of binder quantity. In addition, it should also be taken into account that the medium sizes of pellets, ranged between 500 and 600 µm, can be attained with binder quantities around the medium level of 400 grams (figure C.4 and C.6).

Though all this confirmation about the significance of the amount of the binder material, factor B (spraying rate) must not be excluded, even if it seems to be insignificant. In particular factor B participates in an important interaction with factor A. It is noticable not only from the ANOVA, but also from all the graphs that at high levels of factor B (spraying rate) the effect of factor A (quantity of binding material) is maximized (see also figure C.7). This means that high spraying rates pooled with low levels of binding material produce pellets from a small GMD, which could be explained through the drying out of the pellets when the binding material was sprayed in a short period of time. Not all the solid material could be integrated and loose material around the pellets as a consequence could be noticed (picture C.1.1). On the opposite the largest GMD of 643,2 µm could only be reached when setting both factors at their high levels. Thus pellets were achieved, being characterised though a smooth surface and no unbonded solid material around the agglomerates (picture C.2).

Also when considering the RSM graph and the contour plot, the maximum is obseved at the point where high spraying rates are combined with large quantities of binding materials, which is illustrated as red regions in the graphs (figure C.4 and C.6).

Finally it can be pointed out that holding the spraying rate at a constant high level while varying the amount of binder material yields in pellets from a tolerable size by giving better controllability over the result.
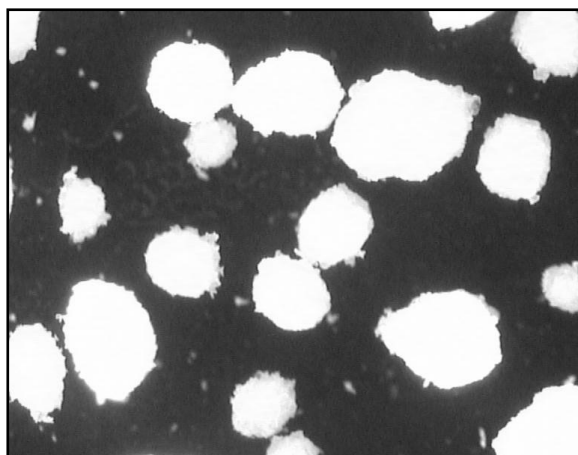
Picture C.1: Pellets (Lot.EXP4) from a small GMD and visible unboded solid materials around the agglomerates.
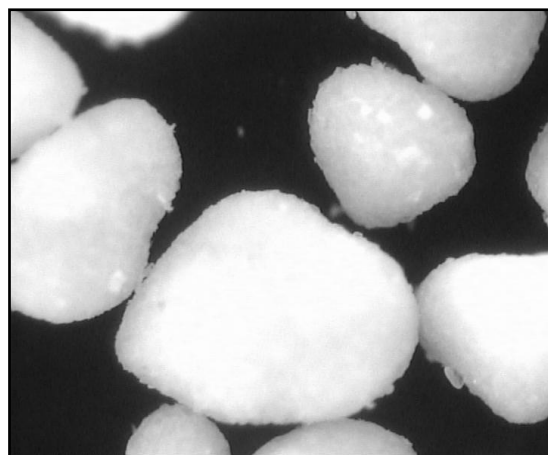
Picture C.2: Pellets (Lot.EXP9) of a large GMD, showing a smooth surface and no loose solid material around the objects.

C.2. GSD – The geometric standard deviation

The analysis of the GSD values showed that the mean is a better predictor than any of the models studied:

Figure C.7: Sequential Model Sum of Squares						
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Mean vs Total	**18,4414**	**1**	**18,4414**			**Suggested**
Linear vs Mean	0,0012	2	0,0006	0,6468	0.5443	
2FI vs Linear	0,0035	1	0,0035	5,7100	0.0406	Suggested
Quadratic vs 2FI	0,0008	2	0,0004	0,5746	0.5874	
Cubic vs Quadratic	0,0026	2	0,0013	3,0220	0.1379	Aliased
Residual	0,0021	5	0,0004			
Total	18,4515	13	1,4193			

In the Sequential Model Sum of Squares table (table C.7) it can be perceived how far the model fit is improved as terms are added. When focusing on the linear line, it shows the significance of the linear terms after accounting for the mean and block terms.

On the other hand the quadratic line indicates the significance of the addition of the quadratic terms to the linear, block and mean terms. None of the lines represents the complete model, but more the statistics for those additional terms. Terms with a P-value less than 0.1 should be considered for being included. Thus the highest-order model where the additional terms are significant should be chosen.

It is evident that in the case of the geometric standard deviation GSD a model cannot be estimated with the aim of relating the factors with the response. This might be probably due to the low values of the GSD throughout the design, ranging between 1.13 and 1.23.

Vilhelmsen et al (2004)[14] provided a comparison of the GSD values of pellets produced out of three alternative melting methods:

- Melt pelletization in a high shear mixer
- Pelletization by hot melt fluidized bed granulation
- Melt pelletization in a rotor processor

They came to the conclusion that the magnitude of the GSD for these three production processes follows roughly the order that fluid bed melt pelletization is preferred in front of melt rotogranulation, which is almost equal to the pelletization in high shear mixers. The fluid bed granulator has shown the best results according to a narrow size distribution of pellets. However, using powder feeder while spraying the melt material has not been taken into consideration in this comparing study, and therefore the GSD reaches values ranging between 1.3 and 2.08.

In the underlying study the utilization of spraying and addition of powder during the manufacturing process resulted in smaller GSD values in all the experiments of the design. Similar results were observed with preliminary works on the same subject (Paterakis and Rekkas, 2005) [76].
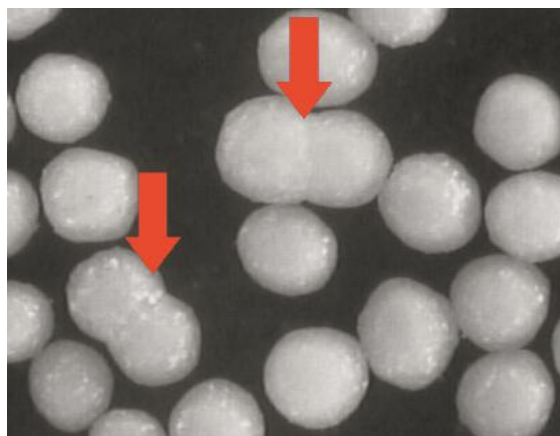
C.3. The Pellet Shape

Alternative methods for evaluating the shape of pellets have already been discussed in the theoretical and practical part of the thesis (A.2.2 and B.3.3.2).

During this project, the sphericity index e_r was used for the reason that it has on the one hand a high sensitivity, on the other hand the capability to assess the deviation of the pellets' shape from perfect spheres, as well as their elongation (Podczeck and Newton, 1994 & 1999) [19,77].

The values for the sphericity factor can range between 0 (for very elongated or rough particles) to 1 (for perfect spheres), like in case of a circle. Its estimation is not only highly dependent on the image analysis system, but also on the analyst. That means that the sphericity index can be utilized for evaluating different pellet populations in a relative way. Therefore, a reference to a standard of high sphericity or spherical starter seeds (inert cores) in general is desired.

For this case, "Leica Qwin" as image analysis system was in usage for the following evaluations:

- Inert spherical cores - e_r ranged between 0.428 and 0.526
- Coated pellets – they were produced from inert cores and tend to enclose smoother surface and spherical shape since the coating material reduces the roughness of the cores.

Picture C.3: Pellets produced through layering and coating process (LOT.RDOPI003). The arrows denote the agglomerated pellets during coating and deviate from the spherical shape.
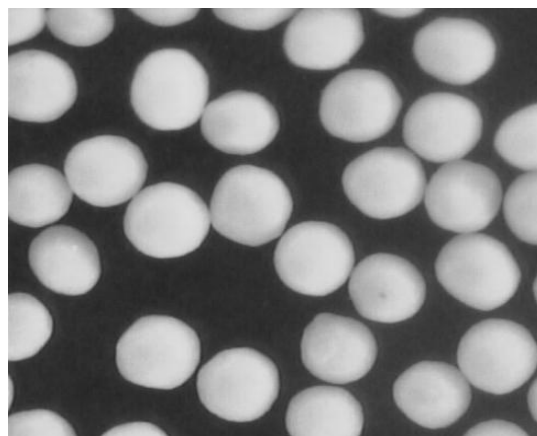
Picture C.4: Reference pellets of spherical shape (RPP109004).

The coated pellets of an acceptable shape as reference are presented above (picture C.3). Pellets that have been separated show a mean value of $e_r = 0.479$ (SD = 0.083). Other than this the shape factor for the agglomerated pellets is dramatically reduced ($e_r = 0.156$), showing that it can be used to distinguish from spherical particles.

The values of the shape factor for the pellets of picture C.4 range between 0.303 and 0.724. Obviously all these pellets have a spherical shape.
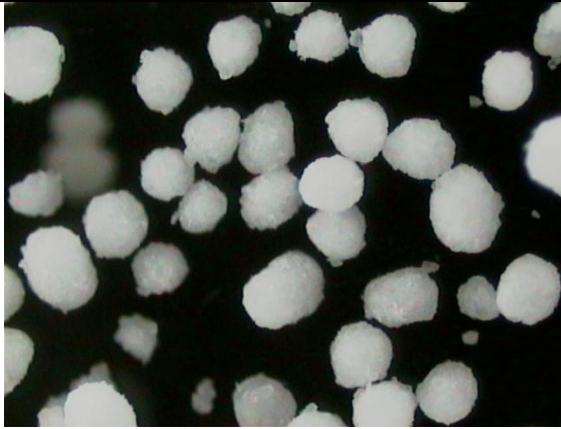
The results for the sphericity factors of the manufactured pellets were carried out by the design and studied. They are shown in the following table:

Exp.	Quant. Binder	Binder sprayed	e_r
Table C.8: The sphericity factors of produced pellets			
1	360	35	0,360
2	400	35	0,395
3	440	35	0,314
4	360	40	0,358
5	400	40	0,364
6	440	40	0,398
7	360	45	0,372
8	400	45	0,397
9	440	45	0,340
10	400	40	0,370
11	400	40	0,339
12	400	40	0,337
13	400	40	0,336

From these results it can be noticed that several batches consist of spherical pellets. Nevertheless, at the range studied, which was too narrow, no model could fit to the data obtained for the sphericity factor.

From the batches that have been pictured, some are illustrated on the next page. Four different batches were chosen, on which it can be seen that the produced pellets actually show a satisfying shape, without great variation of the surface.

Picture C.5: Manufactured pellets from different batches	
Picture C.5a: LOTEXP22	Picture C.5b: LOTEXP6
Picture C.5c: LOTEXP5	Picture C.5d: LOTEXP10
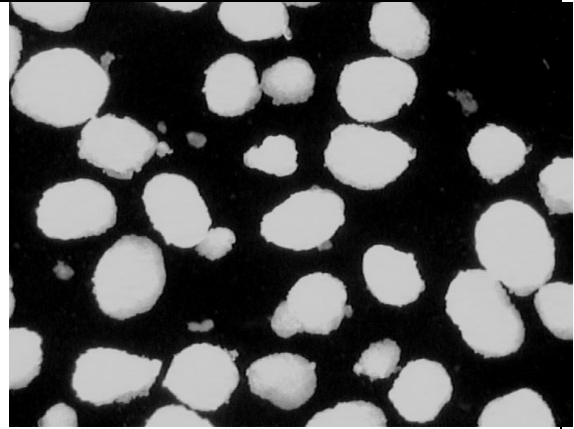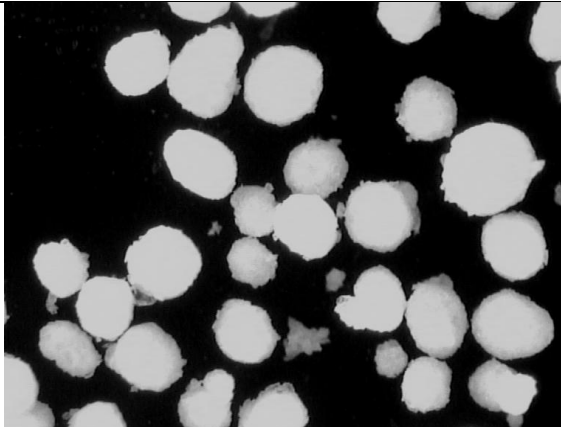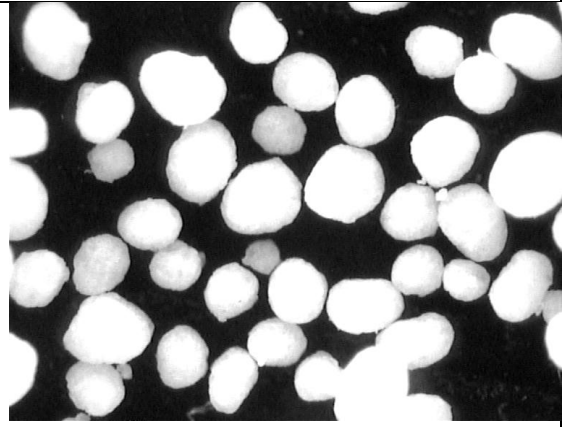
C.4.The Yield

The yield of the experiments was evaluated through sieve analysis (see B.3.3.3), using 1.4 and 2.0 mm mesh-sizes in order to remove potential agglomerates. The mass of the pellets is actual, showing high values. No undesired fines were produced during the whole process. Thus the yield was calculated as the % ratio of the mass of pellets produced against the amount of materials used during the whole manufacturing process. This includes rotor material, powder feeder and binding material.

As a conclusion it was found that the yield of pellets was satisfying (table C.9).

No	W<2.0 mm	W<1.4 mm	Q spr	W in rotor	W from PF	W theor	Yield <2.0 mm	Yield <1.4 mm
1	963,2	961,5	360,0	500,0	200,0	1060,0	90,9	90,7
2	1020,5	1005,0	400,0	500,0	200,0	1100,0	92,8	91,4
3	1045,6	1032,3	440,0	500,0	200,0	1140,0	91,7	90,6
4	979,0	971,2	360,0	500,0	200,0	1060,0	92,4	91,6
5	1050,3	1046,3	400,0	500,0	200,0	1100,0	95,5	95,1
6	1065,6	1048,9	440,0	500,0	200,0	1140,0	93,5	92,0
7	1003,2	996,3	360,0	500,0	200,0	1060,0	94,6	94,0
8	1018,2	1014,0	400,0	500,0	200,0	1100,0	92,6	92,2
9	1080,9	1071,9	440,0	500,0	200,0	1140,0	94,8	94,0
10	1040,3	1036,8	400,0	500,0	200,0	1100,0	94,6	94,3
11	1046,1	1040,6	400,0	500,0	200,0	1100,0	95,1	94,6
12	1042,8	1032,9	400,0	500,0	200,0	1100,0	94,8	93,9
13	1040,6	1035,1	400,0	500,0	200,0	1100,0	94,6	94,1

Table C.9: **The amount of materials used and the yield after sieving**

The quantity of material adhering on the rotor disk and the product chamber's wall was negligible (picture C.6).

__Picture C.6:__ Snapshot of the rotor's product chamber after the completion of the hot-melt pelletization process.

It should be considered that overwetting did not occur within the settings of the design space. The small differences in the yield-values may be credit to the different levels of material's adhesion on the surface of the rotor. Similar conclusions have been reported by Vilhelmsen et al (2004) [14], for processes with high yields throughout the design space.

C.5. Dissolution tests with nimesulide-containing pellets

C.5.1. The purpose of the experiment

For the reason that typical commercially available tablets of nimesulide comprise several excipients (table C.10) it was perceived as a challenge to produce nimesulide-pellets with less ingredients, nevertheless receiving a product with satisfying physicochemical properties and dissolution profiles.

Table C.10: Utilized excipients of a commercially available nimesulide tablet	
Excipient	*Role in the formulation*
Microcrystalline Cellulose	Diluent Disintegrant Binder
Lactose Monohydrate	Diluent
Carboxymethyl Cellulose Sodium	Disintegrant
Hydroxypropylmethylcellulose	Binder
Magnesium Stearate	Lubricant
Vegetable Hydrogenated Oil	Lubricant
Sodium Docusate	Wetting Agent Surfactant

Most formulations of this API are characterized by the presence of a primary surfactant, such as sodium docusate from the previous example.

It is needless to say that during manufacturing process of such formulations, additional process steps are necessary. In the case of sodium docusate, which is a waxy material, it cannot be added without prior preparations into the formulation. This means that either melting or dissolving is preliminary required before mixing it with the API or

other excipients. Consequently the manufacturing process of nimesulide tablets generally consists of the following steps:

1. Melting or dissolving of the surfactant

2. Addition of the API into the melt surfactant or the solution of the surfactant (in most cases ethanol is selected as organic solvent in order to achieve a fine dispersion of the API)

3. This melt material or the solvent including the surfactant and the API are used as granulating liquid.
   In the internal phase diluents, such as lactose monohydrate are used for wet granulation processes.

4. After the manufacturing process, the granules are cooled (if the binding mixture is a melt) or dried (if the binding material is a solution or dispersion in a solvent)

5. The granules are mixed with the external phase comprising the disintegrant, probably in combination with also quantities of the multipurpose used excipient MCC.

6. Lubrification of the granules follows by the addition of the lubricants (after sieving, adding the lubricants and mixing for an appropriate time)

For that reason it should be considered that the addition of the wetting agents results in a rather complicated multistep manufacturing process. This is not desired in the pharmaceutical industry, respectively. Further single step processes are esteemed, which take place in closed systems. Thus this is an advantage when not only production costs are effectively reduced, but also risks of cross contamination are lowered.

All these considerable facts gave rise to challenge the production process with nimesulide (see A.6). A formulation was used that is detailly described in B.3.4, and the process was stopped when pellets of an appropriate size were produced. For this reason samples were taken from the product chamber through the sampling port in regular time periods during manufacturing in order to supervise the development of the pelletization.

It must be noticed that the formation of pellets was faster than expected and experienced in general from the placebo experiments. Probably it was due to the fact that a lipophilic compound in form of the API was added and the percentage of MCC

that could absorb quantities of PEG was therefore reduced. Nevertheless the output of the process was satisfying for the outcome of the underlaying study.

C.5.2. Analytical Method

In general the analytical method for measuring the dissolution properties of nimesulide can be found in the European Pharmacopoeia [57]. The test is described for the commercially available form of tablets (compare with B.3.4.2.2). Thus it was necessary to modify the analytical method, referring also to Nalluri et al [63].

This means that the actual dissolution studies were performed with the USP dissolution apparatus I using baskets instead of paddles [75].

For the dissolution media, a solution of phosphate buffer, holding pH 6.8 and 8.2, was prepared (see B.3.4.2.1) in order to test once the dissolution at the physiological pH and once with higher pH. Thus eventual changes in the dissolution characteristics of nimesulide could be distinguished.

The analysis of nimesulide was performed at 390nm after diluting the samples appropriately to be comparable with a standard, which was prepared from a stock solution of nimesulide of 1mg/ml.

The determination of nimesulide was performed by a spectrophotometric method, which was developed by considering the following considerations:

- The *desired concentration* to be measured was 0.1 mg/ml, reflecting the commercially available dose of Nimesulide in 1000 ml of the dissolution medium.

- The *solubility of the API* in the dissolution medium. This was not an apprehension for the studies at pH 8.2 where sink-conditions were actually achieved.

- The *UV absorption* with the 0.1 mg/ml solution of nimesulide (only with dissolution medium of pH 8.2) shows very high values that lay outside the linearity range of the digital spectrophotometer used for the analysis. For this reason all the samples had to be diluted to a 10:1 ratio. Certainly the calibration curve was constructed taking this under consideration.
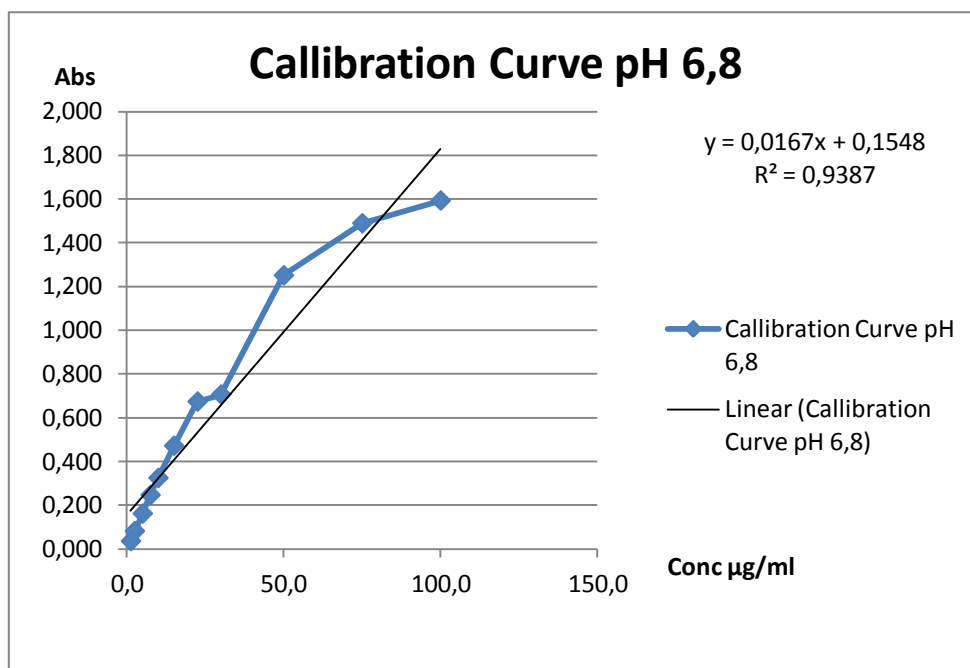
C.5.2.1. Calibration curve using a dissolution medium of pH 6.8 as solvent

All dilutions were prepared from a stock solution using acetone as a solvent, holding a concentration of 1 mg/ml. An appropriate scheme was planned in order to provide each of the solutions to be analyzed directly from this stock solution.

The spectrophotometric results of this analysis are presented in table C.11. Naturally , the analysis of each of the samples was performed one hour after its preparation, including subsequent filtering of the solution via 0.45µm syringe filter, in order to assure that only the dissolved quantity of the API was measured.

Table C.11: Absorbance vs sample concentration at pH=6.8		
Sample No	conc (µg/ml)	Abs :390nm
11	100,0	1,593
10	75,0	1,489
9	50,0	1,251
8	30,0	0,706
7	22,5	0,674
6	15,0	0,472
5	10,0	0,325
4	7,5	0,247
3	5,0	0,162
2	2,5	0,082
1	1,3	0,036

It was macroscopically noticed that samples with concentrations above 22.5µg/ml were blur, indicating saturated conditions and precipitation of the API. This was also obvious from the calibration curve presented in graph C.1.

Calibration Curve pH 6,8

y = 0,0167x + 0,1548
R² = 0,9387

Graph C.1: **Calibration curve at pH 6.8**

Obviously, this curve could not be utilized as a calibration curve. As a consequence it was decided to limit the range of the calibration curve below 20μg/ml, where it was expected for the API to reach a plateau during the dissolution test in this medium. The calibration curve for the reduced range is presented in graph C.2.

Calibration Curve pH 6,8

y = 0,0317x + 0,0025
R² = 0,9989
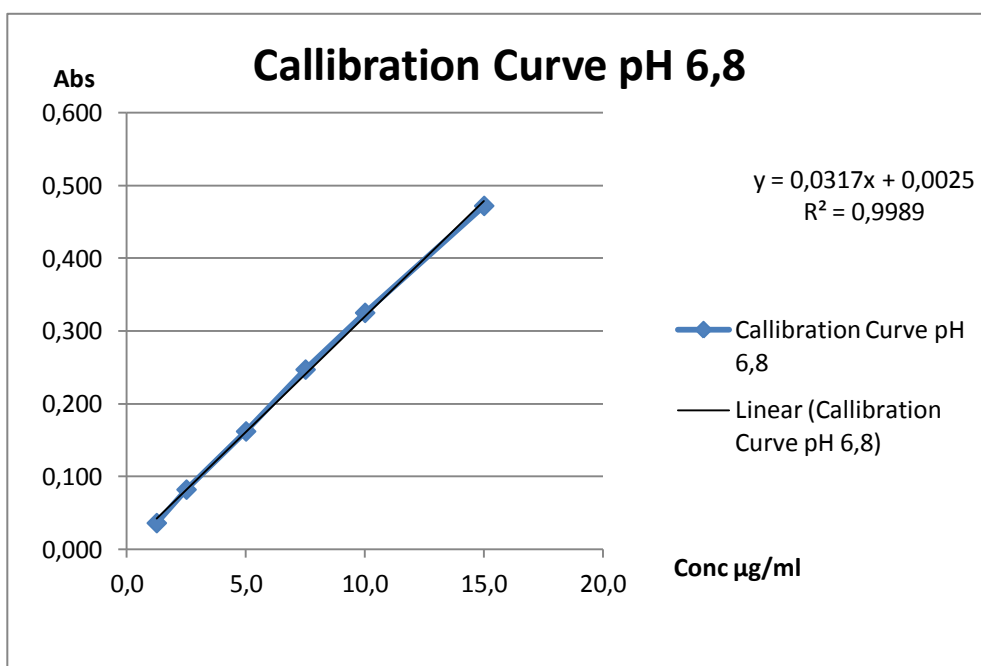
Graph C.2: **Calibration curve at pH 6.8 with limited range**

C.5.2.2. Calibration curve using a dissolution medium of pH 8.2 as solvent

The trails were treated in the same way as seen at pH 6.8. All dilutions were prepared from a stock solution using acetone as a solvent at a concentration of 1mg/ml. Further an appropriate dilution scheme was developed in order to provide an analysis of the solutions directly from the stock solution.

The spectrophotometric results of the analysis are illustrated in table C.12. Naturally, all solutions were initially filtered via 0.45µm syringe filter in order to assure that only the dissolved quantity of nimesulide would be measured.

Table C.12: Absorbance vs sample concentration at pH=8.2		
Sample No	conc (µg/ml)	Abs :390nm
6	12,5	0,591
5	10	0,481
4	7,5	0,366
3	5	0,246
2	2,5	0,118
1	1,25	0,056

It was macroscopically observed that all the samples within the above concentration range were clear (picture C.7), designating the complete dissolution of Nimesulide. Consequently it was reasonable to build up a calibration curve (graph C.3) using a medium of pH 8.2 as solvent.

Picture C.7: Complete dissolution of the API

Calibration Curve pH 8,2

y = 0,0477x + 0,0013
R² = 0,9992
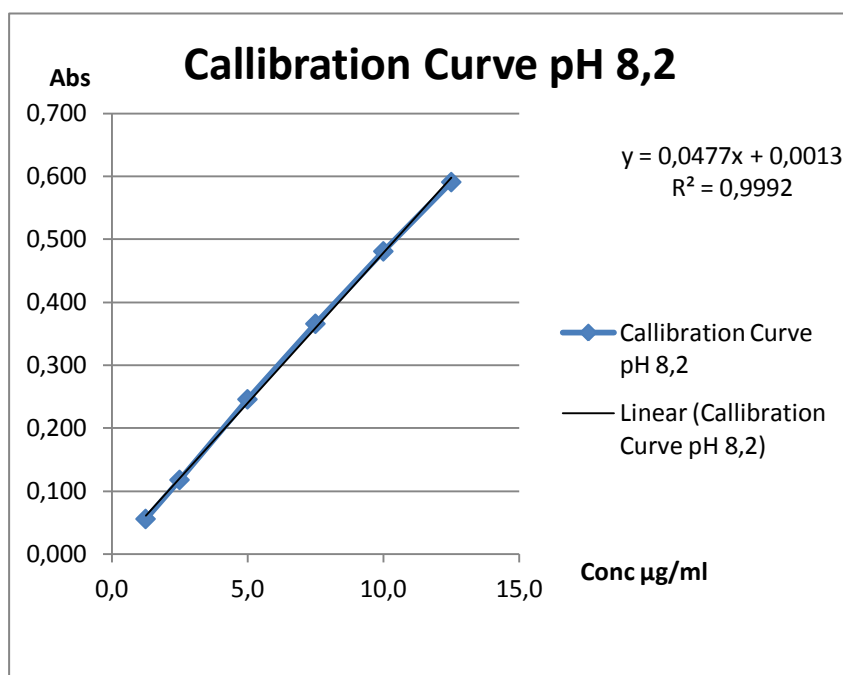
Graph C.3: **Calibration curve at pH 8.2**

In the case of pH 8.2 the limitation according the construction of the calibration curve were qualified through the poor solubility of the API in this specific medium. Reaching an absorbance of approximately 0.6 was reasonably considered as an appropriate range well within the region where the spectrophotometer could provide accurate measurements.

Thus a solution containing 125% of the API was prepared in order to ensure that the API is completely dissolved in this medium. The samples of this solution were filtered via 0.45µm syringe filter, in order to guarantee that only the dissolved quantity of nimesulide would pass through. This solution was then diluted with the same medium using a 1:10 ratio. The spectrophotometric analysis proved that Nimesulide was quantitatively diluted in the initial solution (where 125% of the commercially available dose of the API was dissolved in a volume equal to the one used for the dissolution test of the nimesulide-pellets).

C.5.3. Dissolution tests of nimesulide-pellets vs. commercially available nimesulide-tablets

The following results once show the dissolution profile of nimesulide of commercially available tablets (table C.13/C.14), and further the same procedure figured out for the nimesulide-pellets that were produced with the hot-melt pelletization process, both at pH 6.8 and 8.2.

<u>C.5.3.1. Study of commercially available tablets of nimesulide</u>

Results using dissolution medium of pH 6.8:

Table C.13: **% dissolved amount of nimesulide from commercially available tablets at pH=6.8**								
Sample	Time Interval (min)								
	10	20	30	45	60	90	120	180	240
S1	22,42	28,28	30,89	32,85	33,61	31,84	34,31	35,05	37,05
S2	21,74	28,56	30,56	33,41	34,12	32,85	34,40	34,89	37,57
S3	20,62	22,17	30,39	31,71	28,94	34,19	34,64	35,19	32,95
Average	**21,59**	**26,34**	**30,61**	**32,66**	**32,22**	**32,96**	**34,45**	**35,04**	**35,86**
StDev	0,91	3,61	0,25	0,87	2,85	1,18	0,17	0,15	2,53
%RSD	4,21	13,71	0,83	2,65	8,86	3,58	0,50	0,43	7,06

Results using dissolution medium pH 8.2:

Table C.14: **% dissolved amount of nimesulide from commercially available tablets at pH=8.2**					
Sample	Time Interval (min)				
	10	20	30	45	60
S4	66,62	72,30	76,78	84,95	88,21
S5	65,75	72,95	77,09	85,16	89,49
S6	65,15	72,44	77,05	85,46	89,87
Average	**65,84**	**72,57**	**76,97**	**85,19**	**89,19**
StDev	0,74	0,34	0,17	0,26	0,87
%RSD	1,12	0,47	0,22	0,30	0,97

Additionally the results are depicted in graph C.4, where the two dissolution curves are presented.
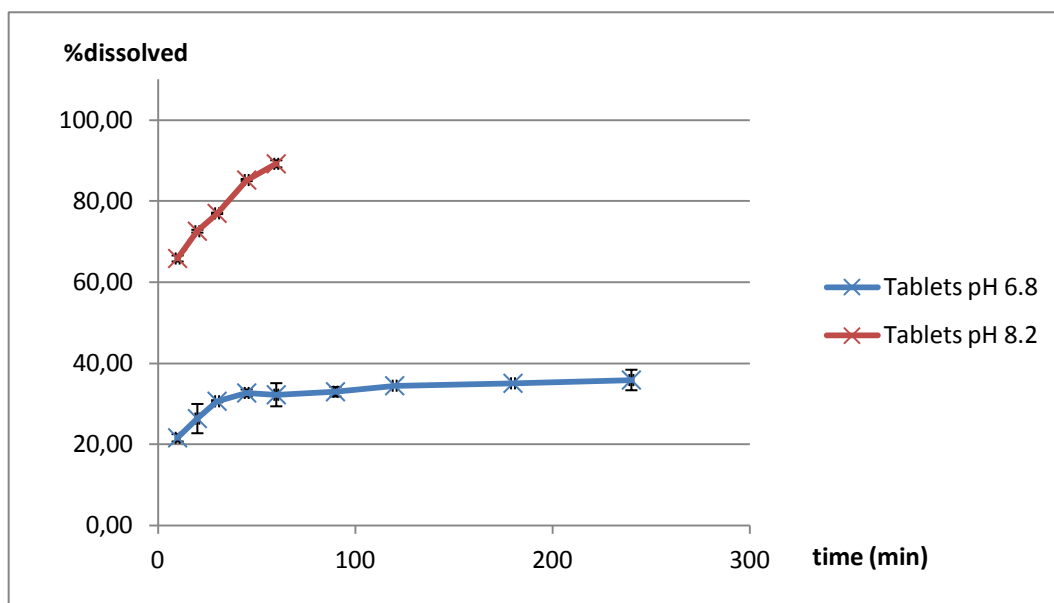
%dissolved

*Graph C.4***: Results of the liberation of the API out of tablets**

C.5.3.2. Study of pellets produced with the hot-melt approach

Dissolution medium with pH value of 6.8:

Sample	*Table C.15:* % dissolved amount of nimesulide from pellets produced when using the hot-melt technique at pH=6.8								
Sample	Time Interval (min)								
	10	20	30	45	60	90	120	180	240
S1	2,65	11,69	14,49	15,45	18,09	16,49	19,20	20,58	20,83
S2	7,45	12,98	16,12	18,18	19,29	19,88	17,38	20,92	22,77
S3	8,12	9,82	16,28	18,55	19,48	20,74	17,20	21,26	23,17
S4	11,38	10,95	13,48	16,06	17,23	19,54	17,75	19,75	20,89
S5	9,69	12,34	14,28	16,37	17,48	18,86	18,12	19,75	23,38
S6	10,15	12,49	13,75	15,45	16,46	17,85	17,75	19,20	23,88
Average	**8,24**	**11,71**	**14,73**	**16,68**	**18,01**	**18,89**	**17,90**	**20,25**	**22,49**
StDev	3,09	1,17	1,19	1,36	1,19	1,53	0,71	0,80	1,31
%RSD	37,44	9,95	8,10	8,18	6,61	8,08	3,98	3,94	5,82

Medium with pH value of 8.2:

Table C.16: **% dissolved amount of nimesulide from pellets prepared using the hot-melt method at pH=8.2**

Sample	Time Interval (min)								
	10	20	30	45	60	90	120	180	240
S1	11,87	41,07	63,38	74,06	73,83	80,71	85,70	93,77	92,58
S2	15,67	38,22	52,94	72,16	75,25	83,08	86,17	95,43	97,09
S3	11,63	25,16	49,61	54,60	64,57	74,30	83,80	87,36	96,14
S4	7,60	30,39	47,71	61,96	73,83	83,32	86,41	99,94	95,43
S5	10,44	28,25	45,58	61,24	73,59	76,44	82,13	111,81	94,48
S6	11,16	28,49	44,87	60,77	70,27	78,57	83,56	91,16	98,51
Average	**11,39**	**31,93**	**50,68**	**64,13**	**71,89**	**79,40**	**84,63**	**96,58**	**95,70**
StDev	2,60	6,27	6,87	7,46	3,95	3,64	1,72	8,57	2,07
%RSD	22,86	19,64	13,56	11,64	5,49	4,58	2,03	8,87	2,16

From the actual results of tables C.15 and C.16 it is validated that the dissolution of the API can be tested only at a medium with pH = 8.2, where sink-conditions were found. The results are presented in graph C.5, where both dissolution curves are described.
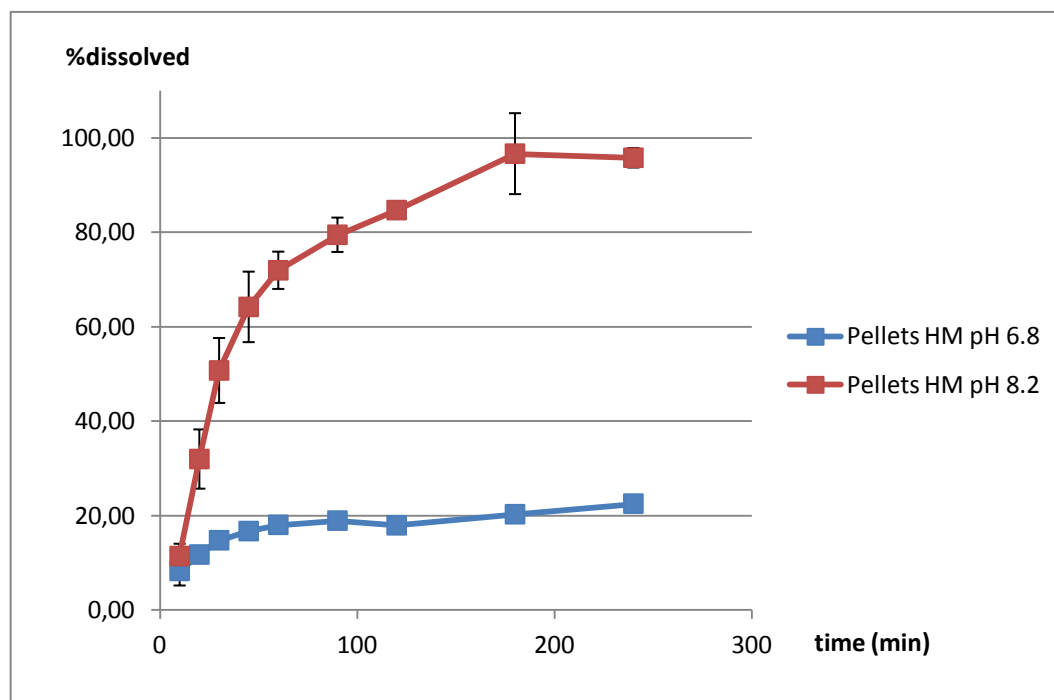
Graph C.5: **Results of liberation of nimesulide out of pellets**

A comparison of all the dissolution profiles is made in graph C.6:
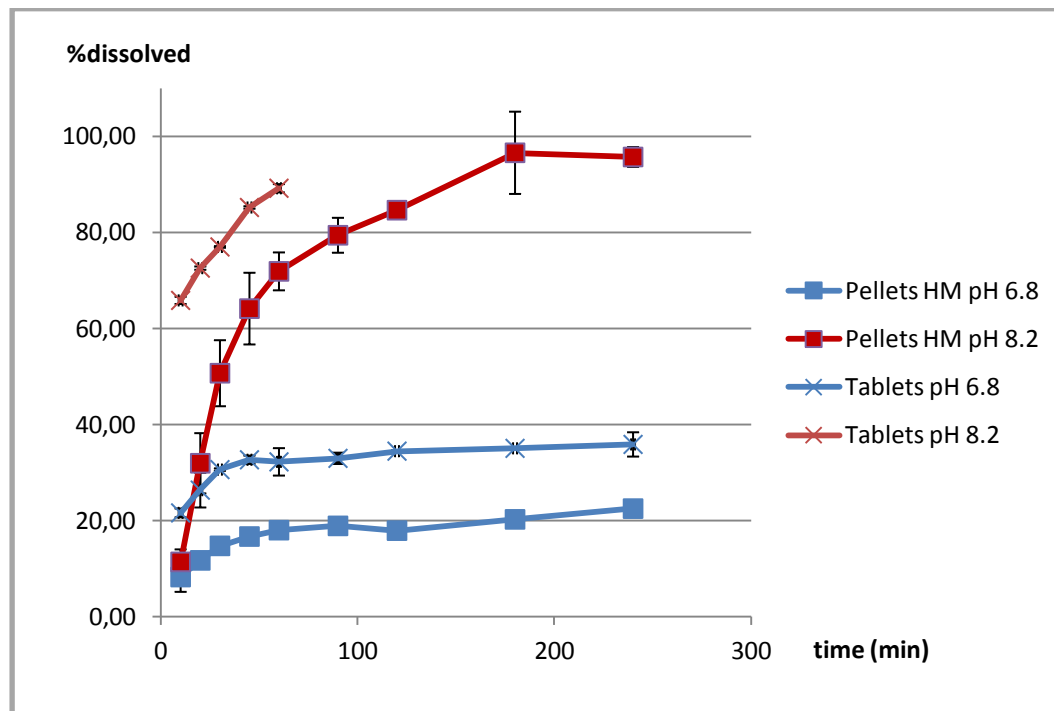
Graph C.6: **Comparison of results gained by dissolution tests**

C.5.4: Conclusion

The results of the dissolution tests revealed both for commercially available tablets and for the produced pellets that the dissolution of nimesulide at the pH of 6.8 (which alikes the physiological pH) was not satisfying concerning the average values reached after 30 to 45 minutes. That means no significant rise of the dissolution of nimesulide not only for the tablets but also for the pellets in between these time intervals.

Identifying the results of dissolution of the API at a pH of 8.2, the outcome was better than expected in the case of the pellets produced with the hot-melt technique, showing more than the half of the dose of nimesulide was dissolved after the first 30 minutes. Comparing this with the commercially available tablets of nimesulide at the same time, it is obvious that better dissolution profiles were obtained. Nevertheless it can be observed that the differences between the curves shown in graph C.6 are for both pHs quite the same, showing also similar sharpness characteristics.

Thus it is concluded that the hot-melt technique is a considerable approach and alternative procedure for the production of a solid dosage form. Also concerning the usage of less expensive adjuvants for the hot-melt pelletisation in comparison to other pelletisation techniques, justifies further development of this approach.

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Education

2004 →	**University of Vienna** Pharmacy
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Professional experience

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Technical skills

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AVS (Pharmaceutical Software)

Aseptically Work in Laminar Air-Flow (→Allerheiligen Apo)

Personal Interests and Hobbies

Riding, climbing, skiing, snowboarding, tennis, playing saxophone, baking, films