EVALUATION OF BIOPOLYMERS AND NOVEL PELLETIZATION PROCESSES FOR ORAL DOSAGE FORMS

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To my family
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1 Introduction

1.1 Pellets

In pharmaceutical applications, pellets are defined as spherical and isometric agglomerates with a narrow size distribution in the range 0.5 mm - 2 mm and low intra-agglomerate porosity (Kleinebudde, 2003). Because of their multiparticulate nature, pellets are classified as multiple unit dosage forms (MUDFs). MUDFs contain a number of subunits (granules, pellets, mini tablets, etc.) that can be incorporated in capsules or tablets. In contrast, single unit formulations contain the active ingredient within a single tablet or capsule (Vergote et al., 2002). Although similar drug release profiles can be achieved with both dosage forms, MUDFs have several advantages. Gastric emptying is influenced by the nature of the dosage form, i.e. multiparticulates such as pellets pass through the gastric system even when the stomach is in digestive mode, whereas single units remain in the stomach for prolonged periods depending on the size of the meal (Davis et al., 1986; Follonier, Doelker, 1992; Weitschies, 2001). Bioavailability variations caused by food effects are therefore reduced when using multiple units. Multiparticulates spread uniformly throughout the gastrointestinal tract. Better distribution of multiparticulates in the gastrointestinal tract could improve bioavailability, making it possible to reduce the required dose and potential side effects. Moreover, multiparticulate drug delivery systems can significantly reduce the risk of dose dumping (Bechgaard, Nielsen, 1978). A further advantage of MUDFs is that variable drug release profiles can be obtained by mixing pellets with different release characteristics or incompatible drugs can easily be separated (Dashevsky et al., 2004a).

Among the various types of MUDFs such as mini tablets or granules, pellets have attracted the most attention due to advantages such as spherical shape, smooth surface morphology, low friability and narrow size distribution, which is important for coating processes. Finally, these advantages can lead to improved patient compliance.
1.2 Conventional pelletization methods

Several methods are used for pelletization. Solution/suspension layering, powder layering and extrusion/spheronization are standard pelletization methods. These methods are explained in the following sections.

1.2.1 Solution/suspension layering

Solution/suspension layering involves the application of a drug/binder solution or suspension onto solid cores, which can be inert materials such as nonpareils (sugars). The droplets of the sprayed formulation are spread on the starter seeds. After evaporation, the dissolved or dispersed substances crystallize. On further evaporation of the liquid, the crystals approach each other by capillary forces. This process leads to the formation of solid bridges between particles. The solution/suspension layering process is normally used to prepare pellets with a low drug load. Typically, solution/suspension layering is performed in fluidized bed coaters or drum/pan coaters (Ghebre-Sellasse, 2002).

1.2.2 Powder layering

Powder layering involves the deposition of successive layers of dry powder (drug and excipients) onto inert materials in combination with binding liquid. During powder layering, the binding solution and a milled powder are added simultaneously to starter seeds. First, the drug particles are bound to the starter seeds by liquid bridges. These liquid bridges are replaced by solid bridges, which consist of the binder or any excipients including the drug substance. The pelletization process continues until the desired pellet size is reached. Typically, the equipment used for this process is a rotor tangential spray fluid bed, although drum/pan coaters have also been used in the past (Ghebre-Sellasse, 2002; Rashid et al., 2001).
1.2.3 Extrusion/spheronization

Pellets with a high drug load can be prepared by extrusion/spheronization. The pellets manufactured by the extrusion/spheronization method are characterized by a high yield, narrow size distribution, good sphericity and low friability. However, the extrusion/spheronization process involves several steps using different items of equipment:

The first step of the extrusion/spheronization process consists of dry powder mixing and granulation. During granulation, the blended powder mass is wetted. Powder mixing and granulation are usually performed using planetary mixers, high shear mixers or continuous granulators (Gandhi et al., 1999; Vervaet et al., 1995).

The second step in the extrusion/spheronization process is shaping of the wet mass into long rods. Several extruder types are used: screw, sieve and basket, plus roll and ram extruders. A screw extruder utilizes the screw to develop the necessary pressure for pressing the wetted powder mass through the uniform openings. In the sieve and basket extruders, the wetted powder mass is fed by a screw or by gravity into the extrusion chamber in which a rotating or oscillating device pushes the plastic mass through a screen on the bottom of the extrusion chamber (sieve extruder) or through a vertical screen (basket extruder). The third class of extruders are the roll extruders, of which two types are available. The first type of roll extruder is equipped with two counter-rotating wheels, one or both of which are perforated. The second type of roll extruder has a perforated cylinder that rotates around one or more rollers which presses the wet mass out of the cylinder. Another type of extruder is the ram extruder, which is mainly used as an experimental device. In the ram extruder, a piston pushes the wet mass through the screen.

The third step is the spheronization process. The extrudate is placed in the spinning plate of the spheronizer, which is called the friction plate. The friction plate has a grooved surface to increase the frictional forces. There are two types of groove geometry: cross hatch geometry in which the grooves intersect each other at 90 ° angles, or a radial pattern, in which grooves radiate from the centre like the
spokes of a bicycle wheel (Ghebre-Sellassie, 2002). In the spheronizer, the extrudate is broken down into spherical pellets.

The fourth and final step of the extrusion/spheronization process is drying of the pellets. Pellets can be dried at room temperature, in a fluidized bed or in an oven.

All process steps of the extrusion/spheronization process are dependent on each other and are influenced by the number of individual process variables (Umprayn et al., 1999).

1.3 Alternative pelletization methods

Modern powder technologies provide alternative methods for pellet preparation, e.g. high shear granulation or ionotropic gelation methods. In particular, pelletization using high shear mixers allows spherical particles to be prepared in a single step. The main advantage of this technique compared to the extrusion/spheronization method is that they provide savings of time, energy and equipment costs. The ionotropic gelation method is also a rapid process. This method can produce pellets on a small lab scale, but is not well established. In addition, the mechanical stability and drug load of pellets prepared by the ionotropic gelation method are often lower than those of pellets prepared with extrusion/spheronization or high shear granulation.

1.3.1 High shear granulation

1.3.1.1 The high shear granulation process

The production of pellets in a high shear granulator involves several steps, namely homogenization of powders, granulation and then usually drying. All steps can be performed in a high shear granulator. After mixing, a binder solution is added to the powder mix which results in particle size enlargement through the formation of liquid bridges between primary particles (Giry et al., 2006). After granulation, the drying process is performed to obtain a suitable moisture content.
Generally, a high shear mixer consists of an impeller and a chopper (Figure 1.1). The impeller is used to apply high shear forces to the powder particles, which results in breakage, growth and densification. The purpose of the chopper is to disrupt the flow pattern of the powder mass, break granules and control granule distribution.

![Vertical shaft high shear granulator](image1)

**Figure 1.1** Vertical shaft high shear granulator (Giry et al., 2006)

Various high shear granulators are available. A distinction is drawn between vertical high shear mixers and horizontal high shear mixers fitted with a vertical shaft or...
horizontal shaft (Figure 1.1 and Figure 1.2). When the shaft is vertical, the influence of the gravity force on the powder bed is greater. The apparatus for high shear granulation can also be classified into single pot apparatus and multiphase granulation apparatus. In the single pot process, the granulation stage and drying stage take place inside the high shear mixer whereas in the multiphase process the drying step is done separately. The single pot process can be performed in lab quantities of 100 g as well as in larger machines with the capacity to handle production scales of 1-3 kg or pilot scales of 20-25 kg (Figure 1.3). The application of a vacuum inside the bowl of the single pot apparatus allows drying of pharmaceutical compounds at low temperature. The movement of the powder mass in the bowl as well as the liquid distribution and the contact surface area of the heated inner wall can all be influenced by using a spherical bowl, swinging bowl, gas stripping or microwaves. In contrast to a single pot process, the multiphase granulation process comprises only the mixing and granulation steps. The drying step is often performed in a fluid bed dryer or in a hot air oven. When the two processes are compared, the single pot apparatus is seen to offer several advantages as it makes for easier handling while reducing the risk of cross contamination.

Figure 1.3 Single pot in lab scale (left) and production/pilot scale (right)
For a better understanding of the high shear granulation process, the granulation phase will now be described in more detail.

Granulation generally takes place in three different steps: (i) wetting and nucleation, (ii) consolidation and coalescence and (iii) attrition and breakage (Figure 1.4).

Wetting and nucleation comprise the distribution of granulation liquid into the powder mass and the nuclei formation.

Consolidation and coalescence make up the second stage of the wet granulation process. In this stage, growth and compaction occur due to the plastic collisions of the nuclei. The agglomerate growth can be described using the granule deformation number and the maximum pore saturation. Iveson and Lister developed a growth regime map, which is shown in Figure 1.5 (Iveson, Lister, 1998; Iveson et al., 2001b). In this map, the maximum pore saturation, i.e. the amount of liquid present in the pores inside the granules as a fraction of the total pore volume, is shown on the x axis. The granule deformation, reported as a Stokes deformation number, is shown on the y-
The Stokes deformation number is calculated in Eq. (1) using the variables density \((\rho_g)\), collision velocity \((v_c)\) and granule strength \((\sigma)\).

\[
St_{def} = \frac{\rho_g v_c^2}{2\sigma}
\]

Bouwman et al. (2006) investigated three different mechanisms of material exchange during the equilibrium phase of granulation i.e. the disintegration mechanism, the deformation mechanism and the distribution mechanism and combined these material exchange mechanisms in the growth regime map (Figure 1.5). These mechanisms are presented schematically in Figure 1.6. The disintegration mechanism occurs when granules are crushed to fragments and new granules are formed during the process. This is a rapid process and typically leads to a bimodal size distribution. A rough surface is also a characteristic of the disintegration mechanism. The deformation mechanism occurs when the granules show abrasion or deformation upon impaction and shearing. The abraded parts can coalesce with other granules, followed by rearrangement into a sphere. No fragments are visible because the process is very rapid. The distribution mechanism occurs when granules cannot deform fast enough, resulting in an insufficient amount of granulation liquid for growth. All granules remain unchanged for a specific period of time. When the granules are sufficiently densified, ball shapes can develop. The disintegration mechanism is typical of materials and conditions showing the nongranular "crump behaviour". This "crump behaviour" is either an extremely weak system or non-growth of nuclei. "Steady growth" defines the deformation mechanism, while the distribution mechanism contains both "nucleation only" and "induction growth" regimes. When pore saturation is too high, the material is too wet and a "slurry" is obtained.
Attrition and breakage is the third stage of the wet granulation process. If the nuclei are not strong enough, granules may break off (attrition) or the agglomerate may break
into pieces (breakage). The broken parts can be layered around existing granules or may be coalesced. Vonk et al. (1997) defined the endpoint of the granulation process as equilibrium between growth and breakage or attrition.

1.3.2 Variables in the high shear granulation process

The granulation process is influenced by changes in the equipment, process and formulation variables (Holm, 1987; Knight et al., 2000). The influence of these parameters on the granulation process is explained in the following section.

1.3.2.1 Equipment parameters

It was observed that the particle characteristics such as the particle size distribution, growth mechanism and porosity are dependent on the distribution of the binder solution in the vessel. Inhomogeneous binder distribution resulted in a wider size distribution of the granules or pellets (Plank et al., 2003; Reynolds et al., 2004).

Bowman et al. (2004) studied the effect of the vessel material on the liquid distribution within the powder mass. A vessel made of low contact angle material for water, such as glass or stainless steel, created a liquid layer on the vessel wall that was not involved in the granulation process. This resulted in a wide particle size distribution. In contrast, vessel materials such as polymethyl methacrylate or polytetrafluoroethylene which are characterized by a high contact angle material for water yielded a narrow particle size distribution. Furthermore, a "slow imbibing" filler such as lactose is more influenced by the type of vessel material than microcrystalline cellulose, which is a "fast imbibing" powder. Faure et al. (1999) demonstrated that the effect of materials on the liquid distribution was lower when larger equipment was used.

The effect of the impeller (design and blade angle) on the granule density can be described in terms of the relative volume of powder swept out by the impeller, i.e. the volume swept out by the impeller blades per second divided by the volume of the bowl. Holm et al. (1987) concluded that a highly swept volume resulted in a high densification of the agglomerates and a narrow granule size distribution. He also
demonstrated that the chopper size and rotation rate had no effect on the granule size distribution.

1.3.2.2 Process parameters
An important process parameter is the method used to add the binder to the powder mass. Some authors found that atomizing the binder liquid improved the liquid distribution within the powder bed, whereas adding liquid without atomization led to inhomogeneous liquid distribution when using low impeller speeds (Fu et al., 2004; Kristensen, Schaefer, 1987; Scott et al., 2000). Litster et al. (2001) found that the size distribution and shape of pellets were dependent on the spray flux. Agglomerate formation and growth are dependent on the ratio between the initial particle size and the droplet size (Schaefer, Mathiesen, 1996). When the binder droplet size is smaller than the initial particle size, a distribution mechanism results, whereas a higher droplet size leads to the immersion mechanism. With the distribution mechanism, the binder particles are distributed on the surface of the solid particles, leading to increased agglomerate formation due to the coalescence of wetted particles. The subsequent coalescence of initial agglomerates results in agglomerate growth. With the immersion mechanism, the solid particles adhere to the surface of the binder particles and coalesce by immersion (Serno et al., 2007).

Further process parameters that influence the particle characteristics are the impeller speed and the granulation time. When the impeller speed increases, the distribution of the granulation liquid in the powder mix is improved. Therefore, smaller amounts of granulation liquid are required to obtain pellets. Higher impeller speeds resulted in smaller particles. In contrast, lower impeller speeds produced an inhomogeneous liquid distribution and consequently a broad particle size distribution. Knight et al. (2000) also described the impeller speed on the shape of the particles. Granules prepared with a high impeller speed and/or short granulation time were less spherical when compared to granules prepared with a low impeller speed and/or long granulation time. The porosity of granules prepared with high impeller speed and/or short granulation time was low due to higher densification of the granule mass (Oulahna et al., 2003).
1.3.2.3 Formulation parameters

Another important parameter is the composition of the powder mass. The wet powder mass must offer the optimal rigidity/plasticity ratio to form spheres. The commonly used pelletization excipient microcrystalline cellulose is well known for its ability to form spherical particles. Therefore, microcrystalline cellulose is an important excipient for producing spherical granules in the high shear granulation process. Several authors have prepared pellets by the high shear granulation process using microcrystalline cellulose as an excipient (Davay et al., 2006; Vojnovic et al., 1995; Ye et al., 2007).

To overcome the disadvantages of MCC, such as the lack of disintegration, several authors studied alternative pelletization aids to MCC (as described in Section 1.3) for the extrusion/spheronization process. However, no literature articles that have studied other possible excipients in the high shear granulation process are available at present.

The influence of fillers on pellet properties was also evaluated. When the filler is soluble in the granulation liquid, granulation requires a lower solvent volume. The water soluble filler lactose dissolves in the granulation liquid and subsequently recrystallizes. The resulting granules are therefore characterized by higher strength and lower porosity and friability (Faure et al., 1999).

The amount of the binder solution can also influence the properties of the granules. An influence of the binder concentration on the sphericity of the granules was demonstrated by Fu et al. (2004). When the concentration of the binder liquid is too low or too high, the granule sphericity decreases. In addition, Knight et al. (1998) observed that a large amount of granulation liquid resulted in lower granule porosity. The granule size is also dependent on the amount of granulation liquid. Larger amounts of granulation liquid lead to an increase in particle sizes during the granulation process.

1.3.3 Ionotropic gelation method

The ionotropic gelation method is a process for ionic crosslinking of polymers such as chitosan, pectin, alginate or carrageenan with monovalent or multivalent ions (Ca$^{2+}$, K$^+$, Na$^+$ etc.). This crosslinking process is used in the preparation of beads, in which
drugs are encapsulated. A more detailed description of the crosslinking process for alginites is given in Section 1.5. For the preparation of beads, the drug is dissolved or suspended in an aqueous polymer solution, which is then dropped into a monovalent or multivalent counter-ion solution (Figure 1.7). The resulting beads then have to be separated from the solution, filtered, washed and dried to obtain the desired mechanical stability. The usual particle size of beads is about 1.5 mm.

Figure 1.7  General procedure for preparation of beads

1.4  Excipients for pelletization

1.4.1  Microcrystalline cellulose as standard excipient

Microcrystalline cellulose (MCC) is a widely used pelletization aid in the pharmaceutical industry. MCC is a purified, partially depolymerized cellulose prepared by treating alpha cellulose (obtained as a pulp from fibrous plant material) with mineral acids (USP 31, 2008). MCC possesses a large surface area and high internal porosity allowing it to absorb and store great quantities of water, thus enhancing the plasticity of the wetted mass and improving spheronization. Dukic et al. (2009) and Kleinebudde (2003) reported that the properties mentioned resulted in
pellets with good sphericity, low friability and high density when produced by the extrusion/spheronization process.

The behaviour of MCC during the extrusion/spheronization process was determined using two model concepts which are explained in the following sections.

1.4.1.1 The sponge model

In the first model, MCC is described as a molecular sponge (Ek, Newton, 1988; Fielden et al., 1988). The MCC particles are able to bind water in a manner similar to a sponge. Each single particle behaves like a porous sponge that can absorb great amounts of water. Some of the water is absorbed by the pores inside the cellulose fibres and amorphous regions of MCC, while the rest is retained between the fibres, causing blockage and hydration of the fibres. During extrusion, some of the water enclosed inside the pores is squeezed out and acts as a lubricant for the extrusion process. After the extrusion process, water can be absorbed again, causing the sponges to expand. These sponges are dry and brittle and facilitate breakdown of the extrudates during the initial phase of the spheronization process. During spheronization, the particles are densified when collision occurs between particles and the spheronization plate and wall. Water also promotes the deformation and spheronization of the particles since it is instantaneously forced towards the sponge surface at sites of collision.

The sponge model may explain many experimental features but fails to explain the shrinking of the pellets during the drying process and the unsuitability of powdered cellulose as an excipient for the extrusion/spheronization process. Powdered cellulose is quite similar to microcrystalline cellulose. It can immobilize even more water but is not suitable for pelletization.

1.4.1.2 The crystallite-gel model

During granulation and extrusion, the powder particles of MCC are broken down into smaller units in the presence of water. Even single crystals of colloidal size (crystallites) can be obtained. With increasing shear forces and moisture content, dispersion into smaller particles becomes more complete. The resulting crystallites and porous particles form a coherent gel-like network and immobilize the granulation
liquid. As crystallites of powdered cellulose are linked via main valence bonds, it is not possible to obtain a dispersion equivalent to those with MCC. This is why it is impossible to produce a crystallite gel when powdered cellulose is used as the excipient for extrusion/spheronization. The shrinking properties of pellets during the drying process can also be explained by the crystallite-gel model. The gel network has to be deformable during extrusion or when subjected to other mechanical forces without losing its cohesion. If moisture is eliminated during the drying process, the gel matrix collapses. As drying continues, deformability decreases while the pressure on the capillaries increases due to the diminishing radius of the capillaries. This results in shrinkage of the pellets resulting in smaller particles with low porosity (Kleinebudde, 1997).

1.4.2 Alternative excipients for pelletization

MCC is usually added to formulations to increase the plasticity and binding properties of the powder mass for the pelletization process. In some cases, however, MCC has several limitations. One disadvantage of MCC is the non-disintegration of pellets, which results in a slow drug release rate of low soluble drug substances. A further disadvantage is that MCC fibres adsorb some drugs or that these or other drugs are chemically incompatible with MCC (Al Nimry et al., 1997; Basit, Sharma, 1999; Patel et al., 1988; Rivera, Ghodbane, 1994; Signoretti et al., 1986). For this reason, some alternative pelletization aids have recently been examined as an alternative to MCC. These are listed in the following section.

Bornhöft et al. (2005) studied the suitability of different types of carrageenan as pelletization aid. κ-carrageenan was found to be a promising pelletization substitute for MCC. Formulations containing κ-carrageenan require more water during extrusion/spheronization than MCC. Nevertheless, the resulting κ-carrageenan based pellets are less sensitive to variations in water content. Thommes and Kleinebudde (2006a, 2006b) also prepared κ-carrageenan based pellets containing four different drugs and four different fillers. All formulations resulted in pellets with good shape
and size characteristics. Drug release of κ-carrageenan based pellets was faster than the release from pellets prepared with MCC due to the swelling and erosion properties of κ-carrageenan. The rapid drug release of κ-carrageenan based pellets is an advantage when using poorly soluble drugs. The characteristics of pellets based on κ-carrageenan are influenced by the drying conditions and the presence or absence of cations in low concentrations. Thermal degradation over 70 °C leads to pellets with lower mechanical strength and increased rates of dissolution. In contrast, an increase in the cation concentration creates pellets of increased mechanical strength and decreased dissolution rate, which can be explained as due to ionic interactions occurring with the acidic sulphate ester groups of the κ-carrageenan (Thommes et al., 2007).

Kranz et al. (2009) studied drug release from MCC- and κ-carrageenan-based pellets. In this study the release of drugs with poor/low solubility from κ-carrageenan based pellets was rapid due to the porous pellet structure, resulting in rapid disintegration upon contact with the release media.

κ-carrageenan, as an alternative pelletization aid to MCC, can be used in several formulations and overcomes some of the deficits of MCC, such as the lack of disintegration and drug absorption. Two disadvantages are the lower mechanical stability and the possible occurrence of ionic interactions.

Several authors have studied the use of chitosan. Pellet production by extrusion-spheronization is possible either with a mixture of MCC and chitosan, or alternatively, with pure chitosan as a spheronization aid. Chitosan is a polycationic polymer consisting of the β-1,4-glycosidic linked monomers glucocamine and N-acetylglucosamine. Steckel (2004) used pure chitosan as a pelletization aid, and acetic acid or demineralized water as a binder for the production of spherical pellets. Jess and Steckel (2007) studied the influence of the degree of deacetylation of chitosan on the properties of pure chitosan pellets. Pellets of acceptable size, sphericity, low friability and good mechanical properties were obtained using chitosan with the highest degree of deacetylation and acetic acid as granulation liquid. Despite the aforementioned properties of the biopolymer chitosan, it cannot serve as an ideal pelletization aid since the granulation liquid used must have a certain pH and a second polymer like alginate is required. Alternatively, any binder similar to HPMC must be used to produce pellets.
of an acceptable quality (Dukic-Ott et al., 2009). Furthermore, the polycationic nature of chitosan means that ionic interactions may occur.

Dukic-Ott et al. (2009) reports on the unsuccessful attempts to produce pellets based on starch as main excipient. In other studies, it was found that the mixture of native starch and microcrystalline cellulose, with the addition of a surface-active agent like polysorbate 80, improved wetting and plasticity of the powder mass (Junnila et al., 2000). Using waxy maize starch, it was possible to obtain pellets with a 50 % maize starch ratio, 47.5 % microcrystalline cellulose and 2.5 % theophylline (Junnila et al., 2000). Unfortunately the aspect ratio of these pellets, which according to Kleinebudde (1995) should be between 1 and 1.2, was outside the acceptable limits. Compared to MCC, starch-based formulations are less robust and an additional binder has to be added to the formulation to obtain the appropriate wet mass consistency.

Pectinic acid is a gel-forming polysaccharide which is to some extent water soluble. A pectinic acid molecule consists of polygalacturonic acid leached from apple pomace or citrus peel. The chemical structure of pectinic acid is quite similar to the constitution of alginate which explains the possible crosslinking with Ca$^{2+}$ ions. Different substitution at position C6 results in free acids, methoxylated or amidated products differing degrees of methoxylation and amidation. However, most types of pectin are not suitable as a pelletization aid when using pure water as granulation liquid. This is due to the intense swelling and the adhesiveness of the extrudates. It was discovered that because of the cross-linking, the swelling and solubility of pectinic acid was reduced which in turn resulted in more spherical pellets. Tho et al. (2003) used a low soluble pectinic acid derivative (low methoxylated pectin), lactose, riboflavin as a model drug and water as the granulation liquid to produce pellets. The resulting pellets were not perfectly round, possibly because the spheronization step was not optimized. Nevertheless, they showed acceptable mechanical strength and partially disintegrated in dissolution studies which resulted in adequate drug release.

Pectinic acid possesses a large drug-loading capacity and can be used to produce disintegrating pellets. Pellets formed with pectinic acid allow the fast release of low water soluble drugs. Nevertheless, pectinic acid cannot be utilized to the same extent
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as the commonly used microcrystalline cellulose, as it is highly sensitive to the type
and quantity of the model drug (Tho et al., 2002).

Another alternative pelletization aid is powdered cellulose. Powdered cellulose differs
from microcrystalline cellulose in that the partial hydrolysis process based on the used
acids used is absent in the production of powdered cellulose. For this reason,
powdered cellulose shows a higher degree of polymerization and a lower crystallinity
index compared to MCC. Lindner and Kleinbudde (1994) studied the suitability of
powdered cellulose as pelletization aid. Pellets prepared with powdered cellulose are
characterized by higher porosities, a less spherical shape and faster dissolution rates
when compared with MCC based pellets.

Sodium alginate, a naturally occurring biopolymer, is a possible option as an
alternative pelletization excipient (Chatawalsaisin et al., 2005; Srijamornsak et al.,
2007). This substance was proposed as a promising polymer that could overcome the
disadvantages of MCC, such as its lack of disintegration during dissolution and its
inability to modify drug release. Sodium alginate is discussed in more detail in the
following section.

1.5 Alginites

1.5.1 General aspects

In recent years, the biomedical and pharmaceutical industries have shown increased
interest in the use of biopolymers, particularly alginites (Liew et al., 2006; Shilpa et
al., 2003). Extracted from brown seaweed, alginites are non toxic polymers that are
well established in the food and beverage industry. There are about 265 different types
of marine brown algae but currently only three different species are used for alginate
extraction. These are Macrocystin, which is mainly harvested along west coast of the
USA, and Laminaria and Scophyllum, which are raw materials commonly found in
Northern Europe and used in the production of alginites. These alginites are all
extracted from plants. Several attempts to cultivate brown algae for the alginate
industry have been made in China. It has also been discovered that several microbial sources (Acetobacter vinelandii, Pseudomonas aeruginosa etc.) produce alginates, but at present this ability is not utilized commercially.

Alginates present as mixed salts of different cations, such as Mg$^{2+}$, Sr$^{2+}$, Ba$^{2+}$ and Na$^+$. 1.5.2 Chemical structure

Alginates are water soluble, linear unbranched polysaccharides containing varying proportions of mannuronic (M) and guluronic acid (G) residues. The M and G monomers are 1, 4 linked by glycosidic bonds, forming homopolymeric MM or GG blocks, which are interspersed with heteropolymeric MG or GM blocks. The composition, sequence of polymer blocks and molecular weight are important factors when using alginates as controlled release matrices especially for controlled release of weakly basic drugs. Only minor differences exist in the structure of mannuronic and guluronic acid (G) residues (Figure 1.8).

Figure 1.8 The component monosaccharides of alginate: D-mannuronate (left) and L-guluronate (right)

These epimers adopt different chair conformations due to the energetically disposed equatorial position of the carboxyl group. This results in equatorial glycosidic bonds at position 1 and 4 in β-D-mannuronic acid but axial glycosidic bonds in α-L-guluronic acid in position 1 and 4. With regard to these characteristics, it can be expected that regions in which α-L-guluronic acid prevails form a buckled chain while those regions in which β-D-mannuronic acid predominates form an extended ribbon structure (Gacesa, 1988).
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Figure 1.9 Chain conformations of poly D-mannuronate (top) and poly L-guluronate (bottom).

Two G-block regions arranged side by side result in a hole with a diamond-like shape (Figure 1.9). This shape is ideal for the cooperative binding of polyvalent cations such as Ca$_{2+}$.

1.5.3 Gel formation

A valuable attribute of alginates is their ability to form gels in the presence of multivalent cations, especially Ca$_{2+}$ ions. The physical nature of these resulting gels is dependent on the ratio of mannuronic to guluronic acid. While alginates with a high content of $\alpha$-L-guluronic acid result in strong but brittle gels, a high percentage of $\beta$-D-mannuronic acid leads to gels of a more flexible but weaker nature. Secondly, the amount of cations utilized is important in determining the nature of the resulting gel. A minor quantity of Ca$_{2+}$ ions yields temporary, highly viscous thixotropic solutions whereas larger quantities of Ca$_{2+}$ ions produce stable gels (George, Abraham, 2006). The alginate gels can also be influenced by the type of divalent cations. Replacing calcium ions with other divalent ions with a higher affinity for alginate produces more stable gels.

Fortunately, the gelation of alginates can be performed under mild conditions and no toxic reactants are needed. One possible method of preparation is to extrude a solution of sodium alginate into the cross-linking solution containing the required polyvalent cation. Gelation and cross-linking of the polymers is mainly obtained when divalent
cations replace the Na\(^+\) ions within the guluronic acid residues. This replacement is followed by stacking of the guluronic acid groups to form a characteristic egg-box structure resulting in highly cooperative linkage between the L-guluronic acid blocks and the cations (Figure 1.10).

These maintaining junctions are kinetically stable against dissociation whereas the polymannuronic units show poly-electrolyte characteristics of cation binding (Figure 1.11). The result of these interactions is the formation of spherical beads.

![Figure 1.10  Egg-box junctions of Ca\(^{2+}\) ions in polyguluronate blocks](image)

1.5.4  pH sensitivity

In the development of oral delivery systems, it is important to consider the characteristics of alginates within a range of different pH values. The solubility of alginates is known to be pH-dependent: at low pH, as for example in the gastric
environment, sodium alginate precipitates in the form of a poorly soluble alginic acid and forms an insoluble gel layer. On passing into environments of higher pH, such as the intestinal tract, the alginic acid shell is converted into a sodium salt form, creating a viscous and soluble layer permeable for agents. As regards this pH-dependent behaviour, alginates appear to be an interesting excipient which are able to compensate the poor solubility of weakly basic drugs at high pH since the alginate matrix dissolves more rapidly at higher pH.

1.6 Extended release coating of pellets

A film coating process is one possible option for achieving sustained drug release from pellets. The film coating of pellets is usually based on organic polymer solutions or aqueous polymer dispersions (latices or pseudolatices). In contrast to organic polymer solutions, the use of aqueous polymer dispersions is generally less toxic. They also have the advantage of allowing the use of low viscosity levels, even with high solids contents (Lehmann, 1989). This reduces processing times when compared to the respective organic solvent based system.

Latices are prepared by emulsion polymerization where the monomers are induced to form polymer in the presence of an initiator. The resulting latices consist of fine polymer particles (< 200 µm) with a small size distribution and thus offering good film formation properties. Pseudolatices, on the other hand, are prepared by organic polymer solution emulsification in water followed by removal of organic solvent under vacuum. Various ready-for-use latex dispersions are commercially available, such as the polyacrylate dispersion Eudragit NE 30 D or the polyvinyl acetate dispersion Kollicoat SR 30 D. The ethyl cellulose dispersions Aquacoat ECD and Surelease or the polyacrylate dispersion Eudragit R 30 D belong to the pseudolatex dispersions.

The film formation of organic polymer solutions is a simple process. The organic solution must be sprayed onto the surface of the dosage form, then the polymer chains approach each other by evaporation of the organic solvent, finally resulting in the formation of a continuous homogeneous film (Lecomte et al., 2004).
In contrast, the film formation of aqueous polymer dispersions is a complex, multi-step process (Keddie et al., 1995). After spraying the aqueous polymer dispersion onto the surface of the pellets, the water starts to evaporate. Further up-concentration of the dispersion results in a closely packed array of particles. Continued loss of water causes in particle densification. Finally, the individual particles lose their identity, coalesce and form a continuous homogeneous film. Capillary forces have been identified as the mechanisms behind the particle deformation. The performance of the resulting film is greatly influenced by the temperature present during film formation. The temperature used must be higher than the minimum film formation temperature (MFT) of the polymer which is defined as the minimum temperature at which the polymer particles coalesce into a thin film (Bauer et al., 2002). In some cases, the addition of plasticizer is required to reduce the minimum film formation temperature, soften the polymer particles and promote their coalescence.

Film formation depends on the minimum formation temperature (MFT) of the aqueous dispersion. The coated dosage forms are often treated at elevated temperatures for short periods of time (curing) to complete film formation and therefore obtain stable release profiles. However, it is often difficult to achieve complete film formation even after curing. In these cases there is a risk of further coalescence during storage, resulting in denser film structures which reduce the release rates. These curing effects occur more frequently when using aqueous dispersions with relatively high minimum film formation temperatures, such as Eudragit RS 30 D or Aquacoat ECD. The minimum film formation temperatures of Eudragit RS 30 D and Aquacoat ECD are 47 °C and 81 °C. This phenomenon can be explained as resulting from insufficient polymer particle coalescence. In contrast, the aqueous polyvinyl acetate dispersion Kollicoat SR 30 D is an aqueous dispersion with a very low MFT of 18 °C, which means that curing effects are reduced. It is therefore interesting to use Kollicoat SR 30 D for coating experiments.
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1.7 pH-independent drug release

Many drugs are weak bases or their salts which show pH-dependent solubility, with good solubility at low pH but poor solubility at higher pH. The release of these compounds from controlled release formulations can therefore vary during dissolution at different pH values. These differences observed in in vitro studies are also critically important in vivo and can lead to inter- and intra-individual variations in plasma profiles and bioavailability (Hoerter, Dressmann, 1997). For this reason, several methods of overcoming the pH-dependent solubility of weakly basic drugs have been published. Most of these methods of achieving pH-independent release of weakly basic drugs from extended release dosage forms involve the addition of organic acids (e.g. fumaric or succinic acid) to tablet or pellet matrices in order to create a favourable pH microenvironment. Drug solubility and consequently dissolution of weakly basic drugs is enhanced at higher pH, thus leading to pH-independent drug release profiles. Streubel et al. (2000) achieved pH-independent release of verapamil hydrochloride from matrix tablets consisting of ethyl cellulose or HPMC by adding fumaric, sorbic or adipic acid. These investigators demonstrated that the addition of organic acids to both matrix formers maintained low pH values within the tablets during drug release in phosphate buffer pH 6.8, resulting in pH-independent drug release. Vinpocetine release from hydroxypropyl methyl cellulose (HPMC) matrices into phosphate buffer was greatly increased after addition of citric acid (Nie et al., 2004). Kranz et al. (2005) demonstrated pH-independent release of a weakly basic drug, ZK 811752, from polyvinyl acetate/polyvinylpyrrolidone matrix tablets in the presence of fumaric acid. Guthmann et al. (2007) showed pH-independent release of a weakly basic drug from polyvinyl acetate/polyvinylpyrrolidone coated pellets after addition of fumaric acid to the pellet core.

Another approach to achieving pH-independent drug release of weakly basic drugs was the addition of anionic polymers to dosage forms. Some authors used blends of enteric and extended release polymers as film coating materials (Amighi et al., 1998; Dashevsky et al., 2004b; Munday, 2003). The enteric polymer is insoluble at low pH whereas rapid dissolution of the polymer is observed at higher pH values. Due to the
dissolution of the enteric polymer at higher pH, the poor solubility of the active ingredient is compensated by the increased porosity of the film coat, thus leading to pH-independent drug release. Takka et al. (2001) incorporated the enteric polymer Eudragit L as pH-dependent soluble filler into hydroxypropyl methyl cellulose (HPMC) matrix tablets. At lower pH values the enteric polymers were part of the core matrix. In contrast, at higher pH values the enteric polymers dissolved and formed pores, thereby increasing drug release rates.

A matrix tablet containing both an anionic (sodium alginate) and a nonionic (HPMC) polymer has been patented by Howard and Timmins (1988). The resulting release profile of tablets containing both sodium alginate and HPMC was found to be pH-independent. Therefore, alginates seem to be an interesting polymer for achieving pH-dependent release of weakly basic drugs.

1.8 Research objectives

1.8.1 Strategies for overcoming the pH-independent solubility of weakly basic drugs by using different types of alginates

The objective of this study was to achieve pH-independent release of a weakly basic drug from tablets based on the natural occurring polymer sodium alginate. Three approaches to overcoming the pH-dependent solubility of the weakly basic model drug verapamil hydrochloride were investigated. Firstly, matrix tablets were prepared by direct compression of the drug substance with different types of sodium alginate. Secondly, pH modifiers were added to the drug/alginate matrix systems. Thirdly, press-coated tablets consisting of an inner pH modifier tablet core and an outer drug/sodium alginate coat were prepared.
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1.8.2 Immediate release pellets produced by the high shear granulation technique

The main aim in this phase was to develop a simple, one step pelletization method. The high shear granulation process normally used to produce granules was employed to prepare immediate release pellets in a single step. These pellets were then compared with pellets produced by the more common extrusion/spheronization process to determine pellet characteristics such as size, shape, mechanical properties and morphology. In order to create immediate-release pellets using the high shear granulation method, different polymers were used for the high shear granulation process, namely sodium alginate, carrageenan and MCC. A second focus of interest was to determine how the drug release rate of verapamil hydrochloride as well as vardenafil hydrochloride was influenced by these polymers.

1.8.3 Ionotropic gelation as a further alternative manufacturing method for pellet production

The ionotropic gelation method was used as a different pelletization technique to study its suitability for the production of an oral pellet formulation. Particle characteristics such as pellet shape, hardness, drug load and encapsulation efficiency were studied.

1.8.4 Controlled release from alginate based pellets manufactured by the high shear granulation process

The interest of this section was to investigate how pellets manufactured by the high shear granulation process could be coated. Two different approaches to achieving sustained drug release from pellets prepared by the novel high shear granulation technique were investigated. The first approach examined a film coating formed from a slightly water soluble polymer that was used to create a diffusion layer, which in turn prolonged the rate of drug release. The aim of the second approach was to prepare a matrix formulation with an extended release profile of the drug used in pellets produced by the high shear granulation process.
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2.1 Materials

Model drugs
Verapamil hydrochloride (BASF, Ludwigshafen, Germany), vardenafil hydrochloride (Bayer Schering Pharma, Berlin, Germany), chlorpheniramine maleate (STADA GmbH, Bad Vilbel, Germany)

Polymers
Sodium alginate (Protanal LF 120 M, Protanal LF 200 M, Protanal LF 240 D, FMC Biopolymer, Drammen, Norway), κ-carrageenan (Gelcarin GP 911 NF, FMC, Philadelphia, PA, USA), aqueous dispersion of polyvinyl acetate (Kollicoat® SR 30 D, BASF, Ludwigshafen, Germany), polyvinyl acetate/povidone (Kollidon SR, BASF, Ludwigshafen, Germany), ethyl cellulose (Ethocel 45 Premium, Dow, Schwalbach, Germany), microcrystalline cellulose PH 101 (FMC Biopolymer, Drammen, Norway).

Other excipients
Lactose monohydrate (Granulac 200, Meggle Wasserburg GmbH), Cellets 350-500 µm (Syntapharm, Mühlheim an der Ruhr, Germany), 2-aminoheptane, acetic acid, potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, acetonitrile, fumaric acid (Merck, Darmstadt, Germany), calcium chloride (BASF, Ludwigshafen, Germany), calcium phosphate (Fluka, Buchs, Switzerland), colloidal silicon dioxide (Aerosil, Degussa, Frankfurt, Germany), magnesium stearate (Roquette, Lestrem, France), silicon dioxide (Syloid 244 FP, Merck, Darmstadt, Germany), barium chloride, magnesium chloride (Merck, Darmstadt, Germany), sodium lauryl sulphate (Sigma Aldrich, Taufkirchen, Germany), Polysorbate 20 (Tween 20, Serva Feinbiochemica GmbH & Co., Heidelberg, Germany).
2.2 Methods

2.2.1 Preparation of tablets

Tablets containing 1.5 % (w/w) magnesium stearate as lubricant and 1 % (w/w) colloidal silicon dioxide as flow promoter were prepared by direct compression unless otherwise stated. The respective powders (drug, polymer and additives) were passed through a 0.8 mm sieve (Haver and Böcker, Celle, Germany) and blended in a turbula mixer (W.A. Bachofen AG, Basel, Switzerland). The tablets were produced on a single punch tableting machine (EK0, Korsch, Berlin, Germany). The tablet hardness was kept constant at 80-100 N unless otherwise stated (Schleuniger hardness tester 6D, Schleuniger Pharmatron AG, Solothurn, Switzerland). For wet granulation, the blend was granulated in a planetary mixer (MTI, MTI-Mischtechnik Industrieanlagen GmbH, Lage, Germany) using distilled water.

2.2.2 Preparation of press-coated tablets

Core tablets consisting only of fumaric acid were prepared using a single punch tableting machine. The powder for the outer shell was prepared as described above and filled into the die to create a powder bed for the fumaric acid core. The core tablet was then carefully placed in the die and the equivalent amount of powder was spread over the core and the base. The tablet hardness was kept constant at 80-100 N.

2.2.3 Determination of the microenvironmental pH

After predetermined time intervals, the tablets were removed from the dissolution medium and immediately frozen. The height of each tablet was then measured separately in the frozen state using a calliper (Helios Messtechnik, Niedernhall, Germany). The tablets were fixed and cut into individual cryosections with a microtome in a cryostat at -10 °C. The microenvironmental pH (pHm) of the
cryosections was determined potentiometrically using a surface pH electrode (Metrohm AG, Switzerland) and plotted against the fractional distance \( f/f_0 \), where \( f_0 \) is the initial distance from the edge to the centre of the tablet and \( f \) the distance at the respective cryosection (\( f/f_0 = 1 \) represents the centre of the tablet, while \( f/f_0 = 0 \) indicates the edge of tablet).

2.2.4 Drug release studies on tablets

In vitro drug release was determined using the USP rotating paddle method (900 mL 0.1 N HCl or USP phosphate buffer pH 6.8; 37 °C; 50 rpm; \( n = 3 \); Distek Premiere 5100 Dissolution System, Distek Inc., North Brunswick, USA). At predetermined time intervals 10 mL samples were withdrawn (not replaced), filtered and assayed. The amount of verapamil hydrochloride released was measured on a Waters HPLC system (600 E Controller, 600 F pump, 717 plus Autosampler, 2487 Dual Absorbance Detector, Waters Corp., Milford, USA) according to the USP 31 (2008) method. The amount of chlorpheniramin maleate released was determined spectrophotometrically at the wavelength of 260 nm.

2.2.5 Fumaric acid release

Fumaric acid release was determined using the USP rotating paddle method (900 ml 0.1 N HCl or USP phosphate buffer pH 6.8; 37 °C; 50 rpm; \( n = 3 \); Distek Premiere 5100 Dissolution System, Distek Inc., North Brunswick, USA). At predetermined time intervals 10 ml samples were withdrawn, filtered and assayed. Afterwards the tablets were removed from the dissolution medium for water uptake and mass loss studies. The amount of fumaric acid released was measured with the above mentioned Waters-HPLC system. A 5 µl volume was injected onto a Hydrosphere C 18 column (YMC Europe GmbH, Schermbeck, Germany) using as the mobile phase a mixture of ammonium dihydrogen phosphate pH 2.0 (mobile phase A) and acetonitrile (mobile phase B) (gradient program: 100 % mobile phase A at time 0-6 min; 20 % mobile phase A at time > 6-13 min; 100 % mobile phase A at time
2 Materials and Methods

> 13–20 min); flow rate: 1.0 ml/min; UV-detection at 210 nm. Fumaric acid solutions of known concentrations were used to calculate the amount of fumaric acid released.

2.2.6 Solubility studies

An excess of verapamil hydrochloride was added to water and the pH was adjusted to different levels by adding HCl or NaOH (n = 3). After reaching equilibrium, the final pH of the medium was measured and the drug solubility in the supernatant was determined by HPLC as described above.

2.2.7 Water uptake and alginate mass loss

The water and alginate mass loss of the tablets was determined gravimetrically with a microbalance. Tablets were placed in 900 mL 0.1 N HCl or USP phosphate buffer pH 6.8 at 37 °C. At predetermined intervals, the drug and fumaric acid release was determined as described above. At each sampling interval the tablets were removed from the medium, blotted to remove surface medium, immediately weighed and then dried to constant weight. Three different tablets were measured at each sampling interval and fresh tablets were used for each individual time point. The % water uptake of the tablets was calculated according to the following equation:

\[
\% \text{ water uptake} = 100 \left( \frac{W_w - W_d}{W_d} \right)
\]

where \( W_w \) and \( W_d \) are the weights of wet and dry tablets measured at different time points.

The % of alginate mass loss was calculated by the following equation:

\[
\% \text{ alginate loss} = 100 \left( \frac{M_0 - (M_d + M_f)}{M_0} \right)
\]

where \( M_0 \) and \( M_d \) are the initial and the final dry mass after incubation in buffer medium at predetermined time intervals and \( M_f \) the mass of fumaric acid released at predetermined time intervals.
2.2.8 Preparation of pellets

Extrusion/spheronization
A dry powder mass of 20 % (w/w) active ingredient, 40 % (w/w) microcrystalline cellulose and 40 % (w/w) sodium alginate was combined in a L"{o}dige mixer, to which a granulation liquid of 3 % calcium chloride solution was added. The wet mass was then extruded through a screen, each hole having a diameter of 1.5 mm, at a feed rate of 35 rpm on a Nica™ (SP 300, Lejus, M"{o}lndal, Sweden) extruder. Finally, the extrudate was processed in a Nica™ spheronizer (SP 300, Lejus, M"{o}lndal, Sweden) fitted with a cross-hatched friction plate rotated at 800 rpm for 2-6 min. After spheronization, the pellets were dried in a hot air oven for 48 h at a temperature of 40 °C.

High shear granulation
Pellets containing 20 % (w/w) active ingredient, 49.5 % (w/w) microcrystalline cellulose and 30.5 % (w/w) sodium alginate (if no other composition is stated) were produced in a small scale laboratory high shear mixer (Pro-C-ept 4M8, Zelzate, Belgium) equipped with a glass bowl of 900 mL, a three blade impeller and a chopper. The respective powder was placed in the high shear mixer bowl and mixed (impeller rotation 1000 rpm, chopper rotation 1000 rpm) for 3 minutes. Granulation commenced with the addition of a calcium chloride solution as granulation liquid. A tube with an aperture of 1 mm was used to control the rate of liquid release with a dosing device (765 Dosimat, Metrohm Ltd., Hensau, Switzerland). The total amount of granulation liquid required for each formulation varied in a range of 86-128 mL and was dependent on the process variables (spraying rate and impeller speed). During granulation the chopper speed remained constant at 3000 rpm. After granulation, pellets were spheronized for 5 minutes at an impeller speed of 500 rpm (and no chopper). A hot air oven set to a temperature of 40 °C was used to dry the pellets over a period of 48 hours.
Ionotropic gelation method

Both the calcium solution and alginate solution were prepared by dissolving the appropriate amounts of crosslinking agent and sodium alginate (Protanal LF 120 M) in purified water. The calcium alginate beads were prepared by dropwise addition of 5 mL alginate solution (containing the active ingredient) to 20 mL of crosslinking solution (calcium chloride 0.1 M) through a fine 21 gauge stainless steel needle (Figure 2.1). The distance between the end of the needle and the surface of the crosslinking solution was 6 cm. During the crosslinking process the solution was stirred slowly. The beads that had formed were left in the gelation medium for a certain time period, then separated from the solution through a sieve, washed with water and subsequently dried for 72 hours before being used in further studies.

![Figure 2.1 Apparatus for preparation of beads](image)

2.2.9 Experimental plan

Two variables were evaluated in a high shear granulator for their influence on the total amount of granulation liquid. These variables were (1) impeller speed and (2) spraying rate. The two variables were altered during the granulation process and then screened with a sixteen run D-optimal-design (Design Expert 7.0, Stat-Ease Inc., Minneapolis,
USA). The range of the impeller speed was extended to 1100-1300 rpm, while the spraying rate was varied between 10-30 mL/min.

2.2.10 Sieve analysis

The size distribution of pellets prepared by a high shear granulation method and extrusion/spheronization was determined by sieve analysis (Retsch GmbH, Haan, Germany) using sieve apertures of 100, 250, 355, 630, 710, 800, 900, 1000, 1400 µm. The pellet size fraction between 355-630 µm was defined as the usable yield.

2.2.11 Image analysis

The sieve fractions of 355 to 630 µm (pellets prepared by the high shear granulation process) and 1000-1400 µm (pellets prepared by the extrusion/spheronization process) were used in the image analysis. The image analysis was performed using an optical microscope (Olympus BX 50, Olympus Deutschland GmbH, Hamburg, Germany) combined with a video camera (HV-T20, Hitachi Kokusai Electric Europe GmbH, Erkrath, Germany). For the pellet size and shape measurements, more than 500 pellets of each sample were prepared on a glass slide, which was scanned and imaged by the video camera. Digital image processing was performed with the software "analySIS FIVE" (Olympus Soft Imaging Solutions GmbH, Münster, Germany). For each pellet, 36 Feret diameters were determined and used to calculate the mean Feret diameter. The ratio of the maximum Feret diameter and the Feret diameter perpendicular to the maximum Feret diameter is used as the aspect ratio. The shape factor was calculated according to Eqs. (3)

\[
\text{Shape factor} = \frac{4\pi(area)}{\text{perimeter}^2} \quad (3)
\]
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2.2.12 Mechanical properties (crushing strength)

The crushing strength of 15 pellets was investigated with a texture analyzer (TAXT plus, Stable Micro Systems, Godalming, Surrey UK). Each pellet was placed between the flat plate and the upper punch with a diameter of 2 mm. The punch was then lowered at a rate of 0.1 mm/sec. The point at which the pellet fractured is shown on the force-time graph as the first peak. Force-time plots were recorded using the texture analyzer software Exponent. The arithmetic mean of the fracture force was used as the crushing strength.

2.2.13 Porosity

The porosity ($\varepsilon$) of the pellet can be calculated from the gas pycnometric density and the mercury porosimeter density according to Eqs. (4)

$$\varepsilon = \left(1 - \frac{\rho_p}{\rho_g}\right)$$

(4)

The gas pycnometric density ($\rho_g$) of the pellets was determined on a helium pycnometer (Ultrapyk 1000T, Quantachrome, Odelzhausen, Germany). The apparent density of the pellets ($\rho_p$) was evaluated with a mercury porosimeter (Pascal 140 & 440, Fisons-Carlo Erba, Valencia, USA). Three samples were analyzed for each tested pellet batch.

2.2.14 Scanning electron micrographs (SEM)

Pellets were coated for 60 s under an argon atmosphere with gold-palladium (MED 020, Bal-tec AG, Liechtenstein, Germany) and then observed under a scanning electron microscope (SEM) (DSM 982, Zeiss, Oberkochen, Germany).
2.2.15 Confocal laser scanning microscopy (CLSM)

The CLSM method was used to determine the surface roughness value (Ra value) of pellets said method is reported for example in Depypere et al. (2009).

2.2.16 Drug release studies of pellets

In vitro release of verapamil hydrochloride was determined using the 31 USP rotating paddle method (900 mL 0.1 N HCl or USP phosphate buffer pH 6.8; 37 °C; 75 rpm; n=3; Distek Premiere 5100 Dissolution System, Distek Inc., North Brunswick, USA). At predetermined time intervals 10 mL samples were withdrawn (not replaced), filtered and assayed. The amount of the active ingredient released was measured by HPLC according to the USP 31 method.

The dissolution of vardenafil hydrochloride was performed in 900 mL phosphate buffer pH 6.8 (10 %) with 0.1 % sodium lauryl sulphate using the 31 USP rotating paddle method at 75 rpm. At predetermined time intervals, 10 mL samples were withdrawn (not replaced), filtered and assayed. The amount of the active ingredient released was determined by HPLC with UV detection at a wavelength of 245 nm.

2.2.17 Determination of encapsulation efficiency and drug load of alginate beads

After preparing the alginate beads, the content of verapamil hydrochloride in the gelation medium (e.g. calcium chloride solution) was determined spectrophotometrically at a wavelength of 278 nm. The verapamil hydrochloride encapsulation efficiency was then estimated by the following formula:

\[
\text{Encapsulation efficiency} = \frac{M_i - M_d}{M_i} \times 100
\]  

where \(M_i\) is the initial mass of drug dissolved in the alginate solution and \(M_d\) is the mass of verapamil hydrochloride measured in the gelation medium immediately after preparation of the drug loaded beads.
The drug content in the beads was determined by pulverizing the alginate beads (130 mg) and then immersing them in 100 ml water for 12 h. After filtration through a 0.45 µm membrane filter, the drug concentration was determined spectrophotometrically at the wavelength of 278 nm.

After determination of the drug content, the drug load was calculated by the following equation:

\[
\text{Drug load (\%)} = \frac{M_a}{M_t} \times 100
\]

(6)

where \( M_t \) is the theoretical drug content after determination of the encapsulation efficiency and \( M_a \) is the actual drug content.

### 2.2.18 Coating of pellets

Pellets were coated with an aqueous polyvinyl acetate/polyvinyl pyrrolidone dispersion (Kollicoat SR 30 D, 15 % w/v solids content). For the coating process, fractions of 40 g of pellets were coated in a fluid bed coater (Midi-Glatt, Glatt, Binzen, Germany) using bottom spray and Wurster insert until a theoretical coating level of 20 % (w/w based on the core pellets) was reached. Coating conditions: batch size: 40.0 g, inlet temperature: 30-35 °C, nozzle diameter: 0.5 mm, spray pressure: 0.5 bar, spraying rate: 1 g/min and final drying at 35 °C for 5 min.
3 Results and discussion

3.1 Strategies for overcoming pH-dependent solubility of weakly basic drugs using different types of alginates

This study was conducted to evaluate the suitability of sodium alginate as a natural occurring polymer for creating an extended release formulation characterized by a pH-independent release profile for the weakly basic drug verapamil hydrochloride.

3.1.1 pH-dependent drug release from alginate (Protanal LF 120 M and 200 M) tablets

Alginates are known to have pH-dependent solubility. They dissolve more slowly at lower pH because alginate precipitates in the form of sparingly soluble alginic acid (Liew et al., 2006). They therefore appear to be a promising matrix former for tablets to overcome pH-dependent solubility of weakly basic drugs that show good solubility at lower pH but poor solubility at higher pH (drug solubility differences should be compensated by the inverse solubility of the polymer).

To investigate the release of the weakly basic model drug verapamil hydrochloride from alginate matrix tablets, two grades of sodium alginate – Protanal LF 120 M and Protanal LF 200 M – were first studied (Table 1, formulation Nos. 1 and 2). Both polymers have similar mannuronic to guluronic acid ratios but different molecular weights (Table 2).
3 Results and discussion

Table 1: Composition of the investigated tablets (all quantities in milligrams)

<table>
<thead>
<tr>
<th>No.</th>
<th>Protanal LF 120M</th>
<th>Protanal LF 200M</th>
<th>Protanal LF 240D</th>
<th>Verapamil HCl</th>
<th>Chlorpheniramine maleate</th>
<th>Fumaric acid</th>
<th>Calcium phosphate</th>
<th>Lactose DIN 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>449.2</td>
<td>-</td>
<td>-</td>
<td>233.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>449.2</td>
<td>-</td>
<td>233.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
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<td>-</td>
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</tr>
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<td>6</td>
<td>682.5</td>
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<tr>
<td>9</td>
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<td>-</td>
<td>682.5</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>10</td>
<td>378</td>
<td>-</td>
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<td>233.3</td>
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<td>-</td>
<td>71.2</td>
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<td>11</td>
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<td>-</td>
<td>71.2</td>
<td>-</td>
</tr>
<tr>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13b</td>
<td>-</td>
<td>-</td>
<td>449.2</td>
<td>233.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

In addition, 10.5 mg magnesium stearate and 7.0 mg silica. All tablets manufactured by direct compression unless otherwise stated.

*a* Press-coated tablet

*b* Manufactured after wet granulation
Table 2: Physical-chemical properties of the studied alginates

<table>
<thead>
<tr>
<th>Alginate</th>
<th>Viscosity (mPa)a</th>
<th>M/G (%)a</th>
<th>Molecular weight (g/mol)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protanal LF 120 M</td>
<td>70-150</td>
<td>55-65/35-45</td>
<td>230,000-280,000</td>
</tr>
<tr>
<td>Protanal LF 240 D</td>
<td>70-150</td>
<td>65-70/30-35</td>
<td>230,000-280,000</td>
</tr>
<tr>
<td>Protanal LF 200 M</td>
<td>200-400</td>
<td>55-65/35-45</td>
<td>290,000-360,000</td>
</tr>
</tbody>
</table>

M: mannuronic acid; G: guluronic acid.
a from FMC Biopolymer (2003).

Verapamil hydrochloride release from alginate based matrix tablets consisting of Protanal LF 120 M and Protanal LF 200 M showed significant differences when measured in 0.1 N HCl and phosphate buffer pH 6.8 (Figure 3.1). Drug release at pH 6.8 was significantly slower compared to drug release at pH 1, which can be explained by the weakly basic nature of the compound. At pH < 6.4 the solubility of verapamil hydrochloride was higher than 100 mg/mL. The solubility decreased to approximately 50 mg/mL at pH 6.5 and even dropped to 3 mg/mL at pH 6.8. Drug release profiles therefore correlate well with the solubility of the weakly basic drug. Neither of the alginates (Protanal LF 120 M and Protanal LF 200 M) was able to compensate the pH-dependent solubility of the drug. Interestingly, at pH 1 no differences were observed in the release profiles of tablets prepared with alginates of different molecular weights. In contrast, at pH 6.8 drug release was faster from tablets prepared with alginates of lower molecular weight. These differences may be due to the different release mechanism at pH 1 compared to pH 6.8. It is well known that for alginates at pH 6.8, erosion is an important factor influencing drug release (Timmens et al., 1997). As higher molecular weight fractions dissolve more slowly, drug release at pH 6.8 was slower from the higher molecular weight Protanal LF 200 M. In contrast, at pH 1 diffusion of dissolved active agent through the polymer and water filled pores into the
release medium is the release limiting factor. Under these conditions, differences in the molecular weights appear to be negligible.

Figure 3.1  pH-dependent release of verapamil hydrochloride from alginate matrix tablets

3.1.2  Effect of addition of fumaric acid to alginate (Protanal LF 120 M) tablets

The usefulness of adding fumaric acid to the tablet matrix as a means of achieving pH-independent verapamil hydrochloride release was then investigated (Table 1, formulation Nos. 1, 3, and 4). Fumaric acid was chosen because of its high acidic strength ($pK_a1$ 3.03 and $pK_a2$ 4.54 (Merck, 2001) and relatively low solubility in 0.1 N HCl (7.79 mg/mL, from Streubel et al., 2000). Independently of the pH of the dissolution medium, the pH inside the matrix tablet was expected to be acidic and the solubility of verapamil hydrochloride therefore high. These studies were carried out only on Protanal LF 120 M formulations since similar results were expected for the higher molecular weight Protanal LF 200 M. Addition of 10 % or 15 % (w/w) fumaric acid resulted in pH-independent drug release when measured in 0.1 N HCl and phosphate buffer pH 6.8 (Figure 3.2). Regardless of the amount of fumaric acid added,
drug release from Protanal LF 120 M matrix tablets decreased at pH 1 compared to alginate tablets without fumaric acid (Figure 3.1). Surprisingly, almost identical release profiles were observed for tablets with and without fumaric acid at pH 6.8. The explanation for these observations might be as follows: Addition of fumaric acid to the tablet matrix resulted in an acidic microenvironmental matrix pH ($\text{pH}_m$) irrespective of the pH of the bulk medium. Therefore, at pH 6.8 the solubility of the drug within the tablet matrix was increased. However, as dissolution/erosion of alginate decreases with decreasing matrix pH, the increased solubility of verapamil hydrochloride was compensated by the reduced dissolution/erosion of the tablet. Hence, tablets prepared with and without fumaric acid showed similar release profiles at pH 6.8. At pH 1, drug release from alginate based tablets is mainly driven by diffusion of water into the tablet followed by diffusion of dissolved active agent through the polymer- and water-filled pores into the release medium. As fumaric acid is poorly soluble at pH 1, a less porous matrix tablet could be expected at low pH, thereby reducing drug release from tablets containing fumaric acid.
To prove the assumption that the matrices have different pH values, the pHₘ of tablets with and without fumaric acid was measured with a micro pH electrode (Figure 3.3). Tablets (Table 1, formulation Nos. 1 and 3) were exposed to buffer medium pH 6.8 for up to 8 hours. For alginate based matrix tablets without fumaric acid, a pHₘ of approximately 7 was measured throughout the entire tablet. In contrast, the pHₘ of tablets containing 10 % (w/w) fumaric acid was in the range of 4-5 for up to 8 hours. The pHₘ of these tablets increased slightly from the centre to the edge and with increasing time of exposure to the buffer medium pH 6.8. However, the data clearly demonstrate that the pHₘ of tablets containing fumaric acid was acidic throughout the entire dissolution period.
To explain these release phenomena, the water uptake and alginate mass loss of the tablets (Table 1, formulation Nos. 5 and 6) were investigated gravimetrically (Figure 3.4 and Figure 3.5). As expected, the water uptake and alginate mass loss were significantly faster for alginate based matrix tablets without fumaric acid at pH 6.8 compared to pH 1. These findings show good agreement with the above hypothesis that drug release at higher pH is mainly driven by erosion/degradation, whereas at low pH drug release is mainly driven by diffusion through the matrix and water filled pores. Furthermore, at pH 6.8 the addition of fumaric acid reduced water uptake and alginate mass loss, which is also consistent with the drug release studies. Lowering pHm increases the solubility of verapamil hydrochloride but also reduces water uptake and alginate erosion at pH 6.8. Consequently, almost identical drug release profiles were observed for tablets prepared with and without fumaric acid during dissolution studies in pH 6.8 buffer, as shown in Figure 3.1 and Figure 3.2. At pH 1, the mass erosion was reduced for tablets containing fumaric acid. This can be explained as follows. The pHm of tablets containing fumaric acid was reduced throughout the entire tablet and not only on the tablet shell due to imbibition of dissolution medium. The formation of less soluble alginic acid was therefore accelerated throughout the tablet,
thus reducing mass loss and consequently the formation of water filled pores. Hence, diffusion controlled drug release through water filled pores was reduced in tablets containing fumaric acid during release studies in 0.1 N HCl as shown in Figure 3.1 and Figure 3.2. In addition, the low solubility of fumaric acid at pH 1 also contributes to making the tablet less porous and reducing the release rate.

**Figure 3.4** Effect of adding 15 % (w/w) fumaric acid on water uptake of alginate (Protanal LF 120 M) matrix tablets stored up to 8 h in pH 6.8 buffer or 0.1 N HCl
3.1.3 Drug release from press-coated tablets

It has been reported in the literature that organic acids tend to leach from pellets and matrix tablets in release testing (Siepe et al., 2006). As a result, drug release became pH-dependent in the later stages of dissolution testing. As fumaric acid leaches mainly from the outer regions of the matrices, press-coated tablets with an inner core of fumaric acid and an outer shell of alginate were prepared (Table 1, formulation No. 7). However, drug release from these tablets was faster at pH 1 when compared to buffer medium pH 6.8 (Figure 3.6). Prior to wetting of the inner fumaric acid layer with dissolution medium, the verapamil hydrochloride release was evidently controlled by the alginate layer only. This results in pH-dependent drug release profiles that are almost identical to drug release from tablets prepared without fumaric acid (Figure 3.1). Further optimization of the press-coated tablets (e.g. addition of fumaric acid to the outer shell) was beyond the scope of this section, since it was intended to separate both (fumaric acid and drug) layers to minimize potential incompatibilities between
active ingredient and fumaric acid when using the press coating technology. It should be pointed out that fumaric acid did not change the pH of the dissolution medium in dissolution testing.

![Graph showing pH-dependent release of verapamil hydrochloride from press-coated tablets based on an inner fumaric acid core and an outer alginate:drug shell.](image)

**Figure 3.6** pH-dependent release of verapamil hydrochloride from press-coated tablets based on an inner fumaric acid core and an outer alginate: drug shell

3.1.4 pH-independent drug release from alginate (Protanal LF 240 D) tablets

Other types of alginates were studied for their usefulness in achieving pH-independent drug release regardless of the addition of an organic acid. Protanal LF 240 D was chosen because this type of alginate has a similar viscosity as Protanal LF 120 M but a different ratio of mannuronic to guluronic acid (Table 2). The ratio of mannuronic to guluronic acid in Protanal LF 240 D is higher than in Protanal LF 120 M. Verapamil hydrochloride release from Protanal LF 240 D matrix tablets (Table 1, formulation No. 8) was almost pH-independent in a range 1 to 6.8 (Figure 3.7). When compared to drug release from guluronic rich Protanal LF 120 M (Figure 3.1), drug release from the mannuronic-rich alginate was almost identical at pH 1 (after 8 hours 78.4 % and
74.1 % for Protanal LF 120 M and Protanal 240 D, respectively) but higher at pH 6.8 (after 8 hours 64.5 % and 78.8 % for Protanal LF 120 M and Protanal 240 D, respectively). Hence, drug release profiles at different pH almost overlapped when using the mannanuronic-rich alginate.

To improve understanding of these phenomena, the water uptake and mass loss of Protanal LF 240 D formulations were compared to Protanal LF 120 M formulations (Table 1, formulation Nos. 6 and 9). No significant differences in water uptake and mass loss were observed for any of the formulations at pH 1, showing good consistency with the almost identical drug release profiles at lower pH (Figure 3.8 and Figure 3.9). Distinct differences were observed at pH 6.8 (Figure 3.10 and Figure 3.11). Water uptake and consequently mass loss was faster for the mannanuronic-rich alginate Protanal LF 240 D when compared to guluronic rich Protanal LF 120 M. Since erosion of mannanuronic-rich alginates was faster at higher pH, the poor solubility of verapamil hydrochloride was compensated by the dissolution of the polymer matrix. As a result, drug release from Protanal LF 240 D was faster compared to Protanal LF 120 M when investigated at pH 6.8. These findings are in good agreement with those
of other studies (Liew et al., 2006). They found that the release of chlorpheniramine maleate from mannuronic-rich alginates was also faster compared to guluronic rich alginates when studied in phosphate buffer medium pH 6.8.

Figure 3.8 Effect of alginate type on water uptake of matrix tablets stored up to 8 h in pH 1.0.
Figure 3.9  Effect of alginate type on alginate mass loss of matrix tablets stored up to 8 h in pH 1.0.

Figure 3.10  Effect of alginate type on water uptake of matrix tablets stored up to 8 h in pH 6.8 buffer.
3.1.5 Effect of formulation and process variables on drug release at pH 6.8

The effect of different alginate concentrations in the tablet on drug release was studied at pH 6.8 (Table 1, formulation Nos. 1 and 10). As shown in Figure 3.12, drug release increased with decreasing polymer content resulting from the addition of the water soluble filler lactose.
Next, the influence of the nature of different excipients on the drug release of verapamil hydrochloride was studied in phosphate buffer pH 6.8 (Table 1, formulations Nos. 1, 10 and 11). The addition of lactose increased drug release more rapidly than pure alginate based tablets. This can be explained by the good water solubility of lactose. Upon contact with the release medium, the lactose diffused out of the matrix and created a porous network that increased drug release. In contrast, almost identical release profiles were observed for tablets containing calcium phosphate and for tablets based on Protanal LF 120 M only. This can be explained by the poor solubility of calcium phosphate.
To examine the effect of sodium alginate as matrix former on a highly water soluble drug, tablets were prepared with chlorpheniramine maleate (solubility; 584 g/L at pH 6.8, from Liew et al., 2006) (Table 1, formulation No. 12). Although chlorpheniramine maleate shows high solubility, the release profile was extended over a period of 8 hours (Figure 3.14). Alginate is thus also a suitable extended release polymer when using highly water soluble drugs.
Most of the research reported in the literature utilizes alginates as a directly compressible excipient for extended release matrices (Efentakis, Buckton, 2002; Hodson et al., 1995). The aim of this study was also to investigate drug release from mannuronic-rich alginate tablets (Table 1, formulations Nos. 8 and 13) prepared after wet granulation to improve the flow properties of the drug and matrix former during tableting, with the aim of minimizing potential difficulties during scale-up of the manufacturing process. In vitro release of verapamil hydrochloride from tablets prepared by direct compression or after wet granulation was similar when investigated in buffer medium pH 6.8 (Figure 3.15). The formation of a gel layer around the alginate tablets was observed immediately after the tablets were exposed to buffer medium. Hence, drug release is controlled primarily by the hydrated gel layer and erosion of this layer, which is independent of the dry alginate matrix. Different alginate particle sizes such as are obtained by direct compression or granulation techniques therefore have no influence on the drug release profiles.
3 Results and discussion

![Graph showing drug release over time for direct compression and granulation methods.]

Figure 3.15 Influence of manufacturing method (direct compression versus granulation) on release of verapamil hydrochloride from alginate (Protanal LF 240 D) matrix tablets in pH 6.8 buffer

In a robust tableting process, drug release from tablets should be relatively independent of the compression force and thus of the hardness of the tablets. The compression force during tableting of alginate matrix tablets was varied over a range of 10-15 kN, resulting in tablet hardness values of 80 N and 125 N. Drug release from matrix tablets (Table 1, formulation No. 8) was independent of the tablet hardness within the studied range when investigated in buffer pH 6.8 (Figure 3.16). Similar deliberations to those presented above are also applicable. Varying compression forces lead to different tablet hardnesses and different matrix porosities. Again, the formation of a gel layer around the alginate tablets was observed visually immediately after exposure of the tablets to buffer medium. Drug release from alginate based matrix tablets at pH 6.8 was therefore driven mainly by the hydrated gel layer and erosion of this layer and was independent of the porosity of the matrices in the dry state.
3.1.6 Effect of calcium ions on drug release in dissolution medium

Sodium alginate can be crosslinked with calcium ions to produce denser structures and consequently decreased drug release. As a result, drug release rates from alginate based tablets could be affected by the concentration of calcium ions in the release medium. This could create problems in the gastrointestinal tract if calcium is ingested with food.

It is therefore important to determine whether the presence of calcium ions in the dissolution medium influences the resulting drug release from alginate based tablets. The phosphate buffer dissolution medium could not be used for this investigation because of resulting precipitation of calcium phosphate. 0.1 N HCl was therefore used as dissolution medium (Table 1, formulation No. 8). As shown in Figure 3.17, the addition of calcium had no effect on the rate of verapamil hydrochloride release in 0.1 N HCl, regardless of whether the amount of calcium was equivalent to that present in blood (2.6 mmol) or a much higher concentration (25 mmol).
In conclusion, alginates were found to be a suitable matrix former for the preparation of tablets containing verapamil hydrochloride. pH-independent drug release of weakly basic drugs was achieved from drug/alginate based formulations when using selected alginates exhibiting pronounced erosion at higher pH. For other alginates, pH-independent drug release was achieved by adding pH modifiers to the matrices.
3.2 Immediate release achieved by different manufacturing techniques

Interest in the use of pellets as a dosage form has increased due to their pharmacological and technological advantages compared to single unit dosage forms such as tablets. Several methods are used for pellet preparation, which were discussed in more detail in the introduction. One popular method of manufacture is the extrusion/spheronization process.

3.2.1 Pellets produced by high shear granulation

A promising alternative method of pelletization is the high shear granulation process (e.g. using a Mi-Pro High Shear Mixer). High shear granulation, which is normally used to produce granules, offers more advantages when compared to the standard extrusion/spheronization process since this process is a one step, single pot process which can rapidly produce particles or granules.

3.2.1.1 Preparation and evaluation of conventional MCC based pellets using the high shear granulation method

The high shear granulation process was used to manufacture pellets. The influence of this novel method on the particle characteristics of the resulting pellets, such as size, shape, mechanical properties and morphology was studied. The drug release of pellets obtained by the high shear granulation process was also investigated in detail.

Composition of pellets and manufacturing process

In order to produce spherical pellets with an aspect ratio lower than 1.2, it was necessary to add MCC. MCC is commonly incorporated in pellets to obtain the optimal plasticity/rigidity ratio in the wetted powder mass, which is important for the spheronization process. Pellets were therefore prepared with 20 % verapamil hydrochloride, 60 % MCC and 20 % lactose monohydrate as filler. To improve the flow pattern in the vessel and the liquid distribution, the impeller speed must be higher than 1200 rpm. If the impeller speed was set too high, fine
particles were created as a result of mechanical stress. Based on these findings, the optimal impeller speed was chosen as 1300 rpm. The spraying rate of 10-30 mL/min had no effect on the total amount of granulation liquid. Pellets were produced using optimized process parameters. The total amount of the granulation liquid water was kept constant at 55 % (w/w, calculated with reference to the total powder mass).

Particle characterization

The high shear granulation process was found to be a suitable method of producing pellets with appropriate properties. The sphericity of the pellets, determined by the aspect ratio, and the mean Feret diameter are all illustrated in Table 3 (formulation No. 1). An aspect ratio of 1.0 indicates a perfect sphere. Aspect ratios lower than or equal to 1.2 are considered acceptable under pharmaceutical aspects. Pellets with a mean aspect ratio above 1.2 were regarded as unacceptable (Thommes, Kleinebudde, 2006a). The aspect ratio of pellets prepared by high shear granulation was 1.12, indicating good sphericity.

### Table 3 Particle characterization of pure MCC pellets

<table>
<thead>
<tr>
<th>Formulation number</th>
<th>Spraying rate (mL/min)</th>
<th>Yield (%)</th>
<th>Crushing strength (N)</th>
<th>Absolute amount binder (mL)</th>
<th>Mean Feret diameter (µm)</th>
<th>Aspect ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>75.3</td>
<td>3.5 ± 0.72</td>
<td>55</td>
<td>503.2 ± 0.05</td>
<td>1.12 ± 0.06</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>76.5</td>
<td>2.9 ± 0.68</td>
<td>53</td>
<td>515.2 ± 0.02</td>
<td>1.13 ± 0.03</td>
</tr>
</tbody>
</table>

Another important property is the size distribution of pellets which was measured along with the pellet size during this study. The particle size distribution was determined by performing a sieve analysis on the sieve fractions ranging from 100 to 1400 µm, whereas the mean Feret diameter was calculated by image analysis. The formulation resulted in pellets with a mean Feret diameter of 503.2 µm. The size
distribution was bimodal, which could be explained by the fact that some powder mass remained attached to the vessel wall during granulation. The stationary material on the wall of the bowl was wetted to a slight extent, resulting in over-wetting of the powder mass in motion. When a certain moisture content was reached, the stationary powder mass peeled off and combined with the powder mass in motion. This led to a non-uniform liquid distribution during granulation resulting in different particle sizes (Figure 3.18).

Another characteristic of a pellet is its crushing strength, which is used to determine the mechanical properties of the pellets. Pellets with inferior mechanical properties are unsuitable for the subsequent coating process. The mechanical properties of pellets are influenced mainly by the core formulation and by the method of manufacture. Previous scientific research has demonstrated that pellets produced by extrusion/spheronization and containing a certain amount of MCC densify to some extent during the drying process (Kleinebudde, 1994). In this study, high contents of microcrystalline cellulose were incorporated in the pellets. These pellets shrank during the drying process which resulted in denser pellets with a high crushing strength of 3.5 N (Table 3, formulation No. 1). Further densification of individual pellets occurred due to the high shear forces present inside the vessel, which also contributed to the increased crushing strength. Figure 3.19 shows the surface structure of pure MCC pellets which were characterized by a rough structure caused by the high shear granulation manufacturing technique. In contrast, pellets prepared by extrusion/spheronization often exhibit a smooth surface structure due to the frictional forces caused by the friction plate of the spheronizer during the spheronization process.
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![Graph showing bimodal size distribution of pure MCC pellets.](image)

**Figure 3.18**  Bimodal size distribution of pure MCC pellets.

![SEM micrographs of pure MCC pellets.](image)

**Figure 3.19**  SEM micrographs of pure MCC pellets prepared by high shear granulation. Water was used as granulation liquid and added at a spraying rate of 10 mL/min.

**Drug release**

An important finding is that verapamil hydrochloride release was slightly slower at pH 6.8 compared to drug release rates measured at pH 1, which can be explained by the weakly basic nature of the drug (Figure 3.20). At pH < 6.4, the solubility of...
verapamil hydrochloride was higher than 100 mg/mL. The solubility decreased to approximately 50 mg/mL at pH 6.5 and dropped even further to 3 mg/mL at pH 6.8. The relatively good dissolution of verapamil hydrochloride at high pH can be explained by the relatively good solubility of the drug at pH 6.8 compared to other weakly basic drugs. This property of high solubility meant that verapamil hydrochloride was released rapidly even from non-disintegrated MCC matrices. An extremely pH-dependent drug with a very low solubility at pH 6.8 was therefore used to demonstrate what occurs when drug release profiles are measured at different pH values. The drug used to demonstrate this was vardenafil hydrochloride (solubility in 0.1 N HCl 65 mg/mL, 0.87 mg/mL in phosphate buffer pH 4 and 0.03 mg/mL in phosphate buffer pH 7). Pellets prepared with vardenafil hydrochloride as model compound showed properties resembling those of pellets prepared with verapamil hydrochloride (Table 3, formulation No. 2). As demonstrated in Figure 3.21 drug release of vardenafil hydrochloride was much lower at pH 6.8 than drug release at pH 1. Vardenafil hydrochloride is poorly soluble at higher pH and drug release was therefore decreased. Drug release was reduced even further because of the non-disintegrated MCC used as pelletization aid in this formulation. This was demonstrated by the fact that only 20% drug had been released after 20 minutes at pH 6.8 when the drug was used in combination with the non-disintegrated MCC as pelletization aid. This lack of disintegration is a disadvantage at high pH when using poorly soluble drugs. Release of these drugs from pellets is prolonged, which means that the time required for complete release may be longer than is necessary for the drug to dissolve during gastrointestinal passage. This results in a decrease in bioavailability.
Figure 3.20  pH-dependent release of verapamil hydrochloride from MCC matrix pellets

Figure 3.21  Drug release of the extremely pH-dependent soluble drug vardenafil hydrochloride
3.2.1.2 Preparation and evaluation of alginate based pellets by the high shear granulation method

The standard pelletization excipient microcrystalline cellulose has some disadvantages such as lack of disintegration and inability to modify drug release. The inability to modify drug release is especially disadvantageous when using weakly basic drugs. To overcome these disadvantages, sodium alginate, a naturally occurring biopolymer, was investigated as an alternative excipient to MCC for the pelletization process.

Composition of pellets and manufacturing process

In an attempt to overcome the drawbacks of MCC, sodium alginate was examined as a substitute for MCC. For this study, one commercial type of sodium alginate was chosen, namely Protanal LF 120 M (M/G ratio of 55-65/35-45 %, high G alginate). However, the production of pellets was only successful when MCC was added to alginate because of its advantages in terms of pellet formation, such as water absorption and retaining characteristics and its plasticity properties allowing the formation of spheres. The need to use sodium alginate and MCC in combination is also confirmed by recent literature on the subject where pellets were prepared by extrusion/spheronization (Sriamornsak et al., 2007). Hence, the pellet formulation consisted of 20 % active ingredient (verapamil hydrochloride), 49.5 % MCC and 30.5 % sodium alginate. Due to unwanted accumulation of lumps (non spherical particles) in the high shear granulation process, the amount of sodium alginate was never more than 30.5 %. For the high shear granulation process, two different types of granulation liquid were investigated, in this case water and a calcium chloride solution. Due to its solubility in water, alginate turned into a sticky, swelling mass, which resulted in a large amount of lumps during the high shear granulation process. In order to reduce the solubility and swelling properties of sodium alginate, calcium chloride (3 %) was added to the granulation liquid. The guluronic acid residues of alginate can be crosslinked by means of calcium ions, resulting in a less swellable calcium alginate and a decrease in particle size and formation of spherical pellets during spheronization. It is thus likely that the crosslinking process is important for the ability of the moistening mass to form pellets. Generally, the formulation containing sodium
alginate as pelletization excipient needed a higher content of granulation liquid than pure MCC based pellets. This could be explained by the high water binding capacity of sodium alginate as examined in sorption experiments (Figure 3.22). Sodium alginate forms gels, which can immobilize more water than MCC.

![Water adsorption of MCC and sodium alginate](image)

**Figure 3.22** Water adsorption of MCC and sodium alginate

In contrast to pure MCC pellets, the total amount of granulation liquid (calcium chloride 3 %) used was modified due to the varying process parameters used in the high shear granulation process (e.g. impeller speed and spraying rate).

Firstly, a D-optimal design was used to investigate the effect of process variables in a high shear granulator on the total amount of granulation liquid (the amount of granulation liquid needed to create pellets) \( y \). This influence was investigated using alginate based pellets containing verapamil hydrochloride. Impeller speed \( x_1 \) and spraying rate \( x_2 \) were the same process variables as studied during the granulation process (Table 4, Figure 3.23). The result equations represent the significant effect of the process variable \( x_2 \) \((p < 0.05)\) on the total amount of granulation liquid \((R\text{-squared} = 0.9578)\).

\[
y = 101.1 + 1.445x_2 - 0.02x_2^2
\]
The effect of the process variable $x_1$ (impeller speed) in the investigated range of 1100-1300 rpm is not significant ($p > 0.05$). The studied variation in impeller speed was relatively low as sticking effects of powder and granules have been observed at impeller speeds $< 1100$ rpm. As demonstrated in Figure 3.23, the total amount of granulation liquid added was increased the higher the spraying rate. This could be explained as follows: Generally, two separate processes occur in the bowl during granulation, one being the crosslinking process between sodium alginate and calcium ions, and the other being the swelling of sodium alginate and MCC in contact with water. Sodium alginate swells in contact with water and prevents the calcium ions from crosslinking the guluronic acid residues of the alginate. When the crosslinking time is too short e.g. application of high spraying rates, the swelling process with increased water uptake is the dominant process, while the crosslinking process is reduced.
### 3 Results and discussion

#### Table 4  Matrix of the D-optimal design

<table>
<thead>
<tr>
<th>Trial</th>
<th>Impeller speed (rpm)</th>
<th>Spraying rate (mL/min)</th>
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<td>1.38</td>
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<tr>
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<td>30</td>
<td>125</td>
<td>8.7</td>
<td>1.30</td>
</tr>
<tr>
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<td>10</td>
<td>115</td>
<td>6.9</td>
<td>1.29</td>
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<tr>
<td>4</td>
<td>1100</td>
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<td>115</td>
<td>6.8</td>
<td>1.34</td>
</tr>
<tr>
<td>5</td>
<td>1300</td>
<td>20</td>
<td>122</td>
<td>7.9</td>
<td>1.36</td>
</tr>
<tr>
<td>6</td>
<td>1200</td>
<td>10</td>
<td>114</td>
<td>6.6</td>
<td>1.35</td>
</tr>
<tr>
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<td>1200</td>
<td>30</td>
<td>128</td>
<td>8.6</td>
<td>1.28</td>
</tr>
<tr>
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<td>1100</td>
<td>20</td>
<td>122</td>
<td>7.6</td>
<td>1.35</td>
</tr>
<tr>
<td>9</td>
<td>1300</td>
<td>10</td>
<td>112</td>
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<td>125</td>
<td>8.5</td>
<td>1.38</td>
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<td>8.9</td>
<td>1.39</td>
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<td>20</td>
<td>122</td>
<td>7.9</td>
<td>1.40</td>
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<tr>
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<td>10</td>
<td>112</td>
<td>2.4</td>
<td>1.29</td>
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<td>1150</td>
<td>25</td>
<td>124</td>
<td>7.2</td>
<td>1.28</td>
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<td>1250</td>
<td>25</td>
<td>126</td>
<td>7.4</td>
<td>1.31</td>
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</tbody>
</table>
To confirm this hypothesis, the influence of different calcium chloride concentrations (3, 5, 10 and 20 %) on the total amount of granulation liquid was investigated (Figure 3.24). As expected, for the formulations prepared with 5 % and 10 % calcium chloride solution, the total amount of granulation liquid was decreased when compared to formulations with 3 % calcium chloride in the granulation liquid (115 mL, 108 mL and 122 mL for formulations containing 5 %, 10 % and 3 % respectively). The spraying rate was kept constant at 20 mL/min. When a calcium chloride solution of 20 % was used, the total amount of granulation liquid decreased even further, resulting in a broader distribution in the range of pellet sizes. The increased amount of calcium chloride resulted in a more intense crosslinking process, which in turn reduced the swelling properties of the alginate. This meant that a lower amount of granulation liquid could be added to the system.
To investigate the ratio of crosslinking between guluronic acid residues of sodium alginate and calcium, FTIR measurements were used to compare formulations for their crosslinking efficiency. As demonstrated in Figure 3.25, differences between COO$^-$ peak shifts at ~ 1610 and 1420 cm$^{-1}$ (asymmetric and symmetric stretch, respectively) were observed for pellets prepared with calcium levels of 0 % (lumps, no pellets), 3 %, 5 % and 10 % ions. Both peaks demonstrated a shift to higher wavenumbers with increasing calcium content (no difference was observed in the wavenumbers for calcium ion percentage levels of 5 and 10 %) in the granulation liquid. This might be explained as follows: Calcium ions replace sodium ions during the crosslinking process and create a new environment around the COO$^-$ group. Due to the higher radius of calcium ions and the divalent cation structure, the electromagnetic energy needed for COO$^-$ vibrations was increased. That explains the shift to higher wavenumbers because of the increased crosslinking at higher calcium ion concentrations in the granulation liquid. This finding is in good agreement with other studies (Sartori et al., 1997).
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Figure 3.25 FTIR spectra of pellets, prepared with calcium levels of 0 %, 3 %, 5 %, 10 % ion concentrations (the spraying rate was constant at 20 mL/min).

Particle characterization

Figure 3.26 shows how the increase in the total amount of granulation liquid (the calcium chloride content of the granulation liquid was kept constant at 3 %) resulted in pellets with higher crushing strength. This is due to the greater plasticity of the material, resulting in denser pellets of lower porosity.

Figure 3.26 Effect of total amount of granulation liquid at 3 % calcium chloride concentration on crushing strength.
SEM images (Figure 3.27a) revealed pores and channels on the surface of pellets prepared with a small amount of granulation liquid. In contrast, pellets prepared with a large amount of granulation liquid exhibit no pores and channels (Figure 3.27b). The porosity values of the formulations manufactured with a small total amount of granulation liquid and a large total amount of granulation liquid were about 35 % and 11.5 %, respectively. This is in good agreement with the hypothesis that an increase in granulation liquid leads to denser pellets of lower porosity. Consequently, pellets with smaller total amounts of granulation liquid were characterized by lower crushing strength values (1.5 N - 2.3 N) when compared with commercially obtained pellets made of microcrystalline cellulose. For example, commercially available Cellets have crushing strength values of 3.8 N. However, the formulations prepared with larger total amounts of granulation liquid showed good hardness with crushing strength values above 7.4 N.

![Figure 3.27 SEM micrographs of pellets prepared with a spraying rate of 8 mL/min resulting in a small amount of granulation liquid (a); Pellets prepared with a spraying rate of 30 mL/min resulting in a large amount of granulation liquid (b).](image)

The pellet yield was in the range 58 % to 70 %. The size distribution also showed a bimodal character (Figure 3.28) which was caused by the inhomogeneous distribution of granulation liquid. During granulation, the moist powder mass adhered to the vessel wall. The stationary material on the wall of the bowl was wetted to a minor extent,
resulting in over-wetting of the powder mass in motion. When a certain moisture content was reached, the stationary powder mass peeled off and combined with the powder mass in motion. This resulted in a non-uniform liquid distribution during granulation. These findings are in good agreement to the literature (Holm, 1987, Knight et al., 2000).

![Figure 3.28 Bimodal size distribution of pellets prepared by high shear granulation at different spraying rates.](image)

The sphericity of the pellets, determined by the aspect ratio, and the mean Feret diameter are illustrated in Table 5 (formulation Nos. 3-8). The AR varied between 1.29 and 1.40 for pellets prepared with 3 % calcium chloride in the granulation liquid. In addition, the mean Feret diameter was in the range 546-669 µm for pellets prepared with 3 % calcium chloride in the granulation liquid.

Interestingly, the increase in calcium chloride concentration in the granulation liquid improved the pellet shape and reduced the undesirable content of lumps due to the lower adhesive properties of sodium alginate caused by the dominant crosslinking process. Pellets prepared with 5 % and 10 % calcium chloride in the granulation liquid were considered acceptable, because all values for the median aspect ratio were below 1.23 with a high yield of about 72.5-77.5 % (Table 5, formulation Nos. 9-18). The
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crushing strength varied between 4.7 N and 8.7 N, indicating good hardness of all formulations, irrespective of the spraying rate. Improved pellet hardness might be explained as due to the optimized crosslinking process between alginate and calcium ions.

**Table 5**  
**Particle characterization of different formulations**

<table>
<thead>
<tr>
<th>Formulation number</th>
<th>Calcium chloride (%)</th>
<th>Spraying rate (mL/min)</th>
<th>Yield (%)</th>
<th>Crushing strength (N)</th>
<th>Absolute amount binder (mL)</th>
<th>Mean Feret diameter (µm)</th>
<th>Aspect ratio</th>
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<tbody>
<tr>
<td>3</td>
<td>3</td>
<td>8</td>
<td>61.5</td>
<td>1.5 ± 0.7</td>
<td>106</td>
<td>668.7 ± 0.14</td>
<td>1.29 ± 0.04</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>10</td>
<td>67.5</td>
<td>2.3 ± 0.6</td>
<td>112</td>
<td>663.5 ± 0.14</td>
<td>1.38 ± 0.10</td>
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<tr>
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<td>67.5</td>
<td>7.4 ± 1.9</td>
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<td>1.35 ± 0.07</td>
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<tr>
<td>6</td>
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<td>61.5</td>
<td>7.9 ± 1.4</td>
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<td>553.4 ± 0.08</td>
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<tr>
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<td>116</td>
<td>537.4 ± 0.07</td>
<td>1.20 ± 0.02</td>
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## Results and discussion

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<tr>
<th>Formulation number</th>
<th>Calcium chloride (%</th>
<th>Spraying rate (mL/min)</th>
<th>Yield (%)</th>
<th>Crushing strength (N)</th>
<th>Absolute amount binder (mL)</th>
<th>Mean Feret diameter (µm)</th>
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<td>645.8 ± 0.01</td>
<td>1.17 ± 0.01</td>
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<td>10</td>
<td>74.3</td>
<td>4.7 ± 1.5</td>
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<td>109</td>
<td>529.1 ± 0.05</td>
<td>1.16 ± 0.02</td>
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</table>

* no pellets

Figure 3.29a,b displays the morphology of optimized pellets (5 %, 10 % calcium chloride in the granulation liquid) prepared by the high shear granulation process. The pellets are characterized by a relatively rough surface structure. The rough surface structure was confirmed by CLSM measurements exemplarily for pellets prepared with 10 % calcium chloride in the granulation liquid. The roughness values (Ra value) of 15.69 and 17.51 µm (measured at two different areas of the pellet) were relatively high (Figure 3.30). Consequently, pellets prepared by the high shear granulation method were characterized by a higher degree of roughness compared to pellets prepared by extrusion/spheronization, which exhibited a smooth surface area, as shown in Section 3.2.2. The smooth surface area of extrusion/spheronization pellets could be caused by frictional forces of the friction plate that occur during the spheronization process.
Pellets prepared with calcium chloride concentrations of 20 % showed cracks on the surface structure due to a non-optimized rigidity/plasticity ratio of the wet powder mass. A possible explanation might be the more rapid crosslinking process when using a granulation liquid containing 20 % calcium chloride. The increased crosslinking process reduced the swelling properties of the wet powder mass and consequently increased its rigidity fraction. As a result, pellets became unstable (Figure 3.29c). Therefore, only pellets prepared with 5 % and 10 % calcium chloride concentrations were considered to have optimal properties.

Figure 3.29  SEM micrographs of pellets prepared with 5 % calcium chloride in the granulation liquid (a); Pellets prepared with 10 % calcium chloride in the granulation liquid (b); Pellets prepared with 20 % calcium chloride in the granulation liquid (c) (spraying rate was kept constant at 20 mL/min).
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Figure 3.30  Surface measurements with the CLSM method of pellets prepared by high shear granulation.

The small round particles on the surface of pellets were due to a phenomenon that occurs during the granulation process. Wet powder mass sticks to the wall of the glass bowl during granulation, peels off during the subsequent spheronization step and then drops onto the surface of the spheronized pellets. Two different approaches to preventing this phenomenon have been studied. The first approach was to use a different vessel material (instead of glass), while the second approach was to heat the glass vessel wall during the granulation process. The choice of PTFE (polytetrafluoroethylene) as vessel material was based on the assumption that less adhesion would result during granulation since PTFE has a low friction coefficient. When water is present, friction is decreased even further (Borruto et al., 1998). However, experiments conducted with PTFE as a vessel material failed because
formulations tested in the vessel resulted in non-reproducible granule size distributions as well as irregularly shaped pellets. This could be explained by the fact that high shear forces are needed in the high shear granulation process. Shear forces are caused by the rotation of the impeller, granule-granule collisions and granule-wall collisions. All these variables are necessary to create spherical particles. The use of a PTFE vessel therefore removed one critical variable in the granulation process, namely the granule-wall collision factor. The friction coefficient was therefore too low to create reproducible granules. These findings are in good agreement with the literature (Bouwman et al., 2004). Secondly, the influence of the vessel temperature on the adhesion properties of the wet powder mass was studied. The two temperatures used in this experiment were 40 °C and 50 °C. Surprisingly, temperatures of 40 °C or 50 °C decreased the adhesive effect of the powder mass on the vessel wall. This could be due to the fact that water condensed on the vessel wall, forming a thin condensation film that reduced adhesion of the wet powder mass on the vessel wall. Therefore, small particles on the surface of the pellets were greatly reduced at vessel-wall temperatures of 40 °C or 50 °C (Figure 3.31). The internal structure of high shear granulation pellets revealed no cavity inside the pellets (Figure 3.32).
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Figure 3.31  SEM micrographs of pellets prepared in a vessel heated during the granulation/spheronization process; 40 °C (a), 50 °C (b) (the amount of calcium chloride in the granulation liquid was kept constant at 10 % and the spraying rate was constant at 10 mL/min)
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Figure 3.32 SEM micrographs of the internal structure of pellets prepared in a vessel heated during the granulation/spheronization process; 40 °C (a), 50 °C (b) (the amount of calcium chloride in the granulation liquid was constant at 10 % and the spraying rate was constant at 10 mL/min)

X-ray powder studies

Prior to drug release measurements, the compatibility between sodium alginate and verapamil hydrochloride in pellet formulation was investigated by x-ray powder diffraction. Theoretically, the positively charged verapamil hydrochloride could react with the negatively charged alginate to create a complex. However, the unchanged solid state of verapamil hydrochloride was detected in the pellets (Figure 3.33). This indicated that no significant complexation between sodium alginate and the drug substance occurred during pelletization. The deflection on the far right of the graph might be interpreted as follows: The peak could be caused by the crystalline substance calcium chloride which was part of the pellet structure. No such peak was evident when x-ray measurements of verapamil hydrochloride were carried out on the drug substance itself. Pellets were then treated with high relative humidity in sorption/desorption measurements to determine what peak shifts occur. When the pellets were then measured by x-ray powder diffraction, the peak on the far right of the graph had disappeared (Figure 3.34). This phenomenon could be explained by the fact that calcium chloride dissolves on contact with high humidity. It is then deposited as an amorphous film on the surface of the particles of other components in the pellet formulation. The peak can be assumed to be a calcium chloride peak, since it has
dissolved during the desorption process and is therefore no longer evident in the x-ray powder diffractogram.

**Figure 3.33**  x-ray powder diffractogram of alginate based pellets containing verapamil hydrochloride as drug substance and the reference diffractogram of verapamil hydrochloride

**Figure 3.34**  x-ray powder diffractogram of alginate based pellets containing verapamil hydrochloride as drug substance after sorption/desorption measurements
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**Drug release**

As can be seen in Figure 3.35, the calcium concentration in the granulation liquid affected drug release rates in phosphate buffer pH 6.8. When comparing the release profiles it is evident that the rate of drug release decreased with increasing calcium chloride concentration. The lower release rate could be a result of the increased restriction in the mobility of the polymeric chains due to increased crosslinking finally limiting the swelling of the pellets. These findings are in good agreement with Lin et al. (2005).

![Figure 3.35 Effect of calcium chloride concentration on release of verapamil hydrochloride in phosphate buffer pH 6.8.](image-url)
To confirm the effect of calcium ion concentration on drug release, the water uptake of pellets with different percentages of calcium chloride was measured. Pellets prepared with larger amounts of calcium chloride exhibit reduced water uptake as a result of the decreased swelling (Figure 3.36).

In contrast to pure MCC pellets, the release of verapamil hydrochloride from pellets containing both MCC and sodium alginate (Table 5, formulation No. 12) was almost pH-independent in a range 1.0 to 6.8 (Figure 3.37). The alginate (Protanal LF 120 M) was able to compensate the solubility differences of the drug due to its inverse solubility. Dissolution of sodium alginate at low pH is minor as alginate precipitates in the form of a poorly soluble alginic acid, which creates a diffusion barrier for verapamil hydrochloride. The faster drug release in the phosphate buffer at pH 6.8 could also be explained by the sodium ion exchange with the calcium ions resulting in a loose bead structure. This is in good agreement with Bajpai and Sharma (2004). To confirm the rate of calcium ion exchange with sodium ions, drug release studies from alginate based pellets were carried out in deionized water. Drug release in deionized water was slower compared to drug release in phosphate buffer pH 6.8 which can be explained as due to the absence of sodium ions (Figure 3.38).

Figure 3.36 Effect of calcium chloride concentration on percentage weight change in phosphate buffer pH 6.8.
Figure 3.37  pH-independent release of verapamil hydrochloride from alginate (Protanal LF 120 M) matrix pellets

Figure 3.38  Effect of the dissolution medium on drug release

Next, the influence of disintegration properties of sodium alginate on release of the extremely pH-dependent drug vardenafil hydrochloride was studied. Vardenafil
hydrochloride is sparingly soluble at pH 6.8 because solubility values are 0.03 mg/mL at pH 7. Pellets prepared with vardenafil hydrochloride as model compound were characterized by properties comparable to those of pellets prepared with verapamil hydrochloride (Table 5, formulation No. 21) in terms of its aspect ratio, crushing strength and particle size. As demonstrated in Figure 3.39, release of vardenafil hydrochloride from alginate based pellets was rapid at pH 6.8. Approximately 80% of the drug had been released after 20 min. In contrast, only 20% of vardenafil hydrochloride was released from pure MCC pellets over the same time period (Figure 3.21). Sodium alginate is more soluble in higher pH environments and it therefore increased the drug release of the sparingly soluble vardenafil hydrochloride in this environment. Sodium alginate is therefore a suitable pelletization aid which can increase the release of sparingly soluble drugs at higher pH values.

![Figure 3.39](image)

**Figure 3.39** Release of a highly pH-dependent soluble compound at pH 6.8 from alginate/MCC pellets compared to conventional MCC pellets

The particle characteristics of vardenafil hydrochloride pellets are comparable to those of verapamil hydrochloride pellets (Table 3, formulation Nos. 21 and 12). The surface structure of pellets containing vardenafil hydrochloride was also rough with small, round particles (Figure 3.40). These findings are in good agreement with pellets
produced with verapamil hydrochloride. Again, these findings can be explained in terms of the phenomenon that occurs during the granulation process. Wet powder mass sticks to the wall of the glass bowl during granulation, then peels off during the subsequent spheronization step and drops onto the surface of the spheronized pellets.

![SEM micrographs of vardenafil hydrochloride containing pellets prepared with a combination of sodium alginate and MCC (Figure 3.31 a); prepared with pure MCC (Figure 3.31 b).](image)

**Figure 3.40** SEM micrographs of vardenafil hydrochloride containing pellets prepared with a combination of sodium alginate and MCC (Figure 3.31 a); prepared with pure MCC (Figure 3.31 b).

### 3.2.1.3 Preparation and evaluation of κ-carrageenan pellets produced by the high shear granulation process

Several studies have investigated κ-carrageenan as an alternative pelletization aid to the commonly used MCC in the extrusion/spheronization process (Kranz et al., 2009; Thommes et al., 2007; Thommes, Kleinebudde, 2006; Thommes, Kleinebudde, 2007). In these studies, by κ-carrageenan is described as a suitable pelletization aid for the production of pellets by extrusion/spheronization. The pellet batches were characterized by a high yield, spherical pellet shape and narrow size distribution. In addition, κ-carrageenan pellets showed rapid release rates of poorly soluble drugs when compared to formulations containing MCC.

The following experiments evaluated the use of κ-carrageenan as a pelletization aid for the high shear granulation process. The properties of these pellets were compared with those of alginate based pellets.
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Composition of pellets and manufacturing process

The first part of this study focused on evaluating κ-carrageenan as a pelletization aid for the high shear granulation process. The process parameters used for pellet preparation were the same as those used for alginate or pure MCC based pellets. The high shear granulation process failed when using κ-carrageenan as the only excipient because of insufficient plasticity of the wet powder mass. The resulting pellets were irregular shaped after spheronization. To produce almost spherical pellets it is necessary to add MCC. An MCC content of higher than 30 % (w/w, based on the total powder mass) resulted in sufficient plastic formability, and the optimal plasticity/rigidity ratio of the moisture powder mass was obtained. The κ-carrageenan content was then varied in order to observe its effect on pellet properties. Pellets with 20 % - 50 % κ-carrageenan (w/w, based on the total powder mass) were produced. However, concentrations of more than 20 % κ-carrageenan in the powder mass resulted in lumps and particles then could not be spheronized. The content of κ-carrageenan was therefore kept constant at 20 %.

The amount of verapamil hydrochloride was varied between 20 % and 50 % throughout this study. Pellets were therefore prepared with 20 % verapamil hydrochloride, 60 % MCC and 20 % κ-carrageenan or 50 % verapamil hydrochloride, 30 % MCC and 20 % κ-carrageenan.

Water was used as granulation liquid. Each investigated formulation required a specific water content to produce pellets of almost optimal quality (Table 6). In comparison to alginate based pellets, the pellets containing κ-carrageenan required almost comparable contents of granulation liquid to form pellets. This is demonstrated by sorption measurements of κ-carrageenan (Figure 3.41) and sodium alginate (Figure 3.22; chapter 3.2.1.2). This means that both polymers can adsorb roughly the same amounts of water at a constant temperature of 25 °C.
Particle characterization

Pellets containing κ-carrageenan as a pelletization aid produced a lower yield of pellets with the desired pellet size of 355 µm - 710 µm (Table 6, formulation Nos. 25 and 26). The yield of pellets containing 20 % and 50 % verapamil hydrochloride was 51.2 % and 50.3 % respectively. The low yield could be explained by the non-optimized plasticity/rigidity ratio resulting in larger amounts of unwanted lumps. The aspect ratio of both formulations was > 1.2, indicating that further formulation and process optimization was required (Table 6, formulation Nos. 25 and 26).

Next, the influence of calcium chloride in the granulation liquid on the behaviour of the wet powder mass during pelletization and the resulting pellet properties were studied. Calcium is associated with the half-ester sulphate groups of carrageenan and is therefore able to alter the gelling properties of κ-carrageenan (Morris, Chilvers, 1983). However, a broad size distribution of particles was obtained with calcium chloride in the granulation liquid water. The yield of pellets in the range 355 µm - 710 µm was reduced even further (Table 6, formulation No. 28). Water was therefore used as granulation liquid in the further experiments.
The crushing strength of pellets prepared with κ-carrageenan as excipient was lower than that of alginate based pellets. The lower mechanical stability of κ-carrageenan pellets might be explained as follows: κ-carrageenan based pellets have been described as having high particle porosity due to the more limited shrinking process during drying (Kleinebudde, 1994; Thommes, Kleinebudde, 2006). The lower mechanical stability of κ-carrageenan pellets is disadvantageous for a subsequent coating process.

**Table 6: Particle characterization of κ-carrageenan based pellets**

<table>
<thead>
<tr>
<th>Formulation number</th>
<th>Calcium chloride ( %)</th>
<th>Spraying rate (mL/min)</th>
<th>Yield (%)</th>
<th>Crushing strength (N)</th>
<th>Absolute amount binder (mL)</th>
<th>Mean Feret diameter (µm)</th>
<th>Aspect ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>0</td>
<td>10</td>
<td>51.2</td>
<td>1.2 ± 0.72</td>
<td>105</td>
<td>524.1 ± 0.03</td>
<td>1.21 ± 0.02</td>
</tr>
<tr>
<td>26</td>
<td>0</td>
<td>10</td>
<td>50.3</td>
<td>1.2 ± 0.22</td>
<td>72</td>
<td>573.1 ± 0.05</td>
<td>1.24 ± 0.02</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>10</td>
<td>58.5</td>
<td>1.2 ± 0.68</td>
<td>108</td>
<td>598.7 ± 0.01</td>
<td>1.23 ± 0.06</td>
</tr>
<tr>
<td>28</td>
<td>5</td>
<td>10</td>
<td>41.3</td>
<td>-</td>
<td>89</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Drug release**

As shown in Figure 3.42, drug release from carrageenan based pellets increased the higher the drug content. This can be explained as due to the higher content of verapamil hydrochloride in the pellets.
Next, pellets were prepared with vardenafil hydrochloride as drug substance because of its relatively low solubility at higher pH values (0.03 mg/mL at pH 7). The properties of these pellets prepared with vardenafil hydrochloride were comparable to those of verapamil pellets (Table 6, formulation No. 27) in terms of its aspect ratio, crushing strength and particle size. Rapid disintegration and dissolution was observed for pellets containing κ-carrageenan. Consequently, drug release rates of vardenafil hydrochloride from κ-carrageenan-based pellets were faster compared to MCC pellets, which showed no disintegration (Figure 3.21 and Figure 3.43). Up to 80% of vardenafil hydrochloride was released after 30 minutes from carrageenan based pellets. Summarizing, it is possible to produce rapidly disintegrating pellets containing carrageenan in combination with MCC by high shear granulation with a high drug load of 50% and using demineralized water as granulation liquid. This is advantageous when compared to alginate based pellets, with which only a maximum drug load of 20% is possible. Nevertheless, it should be pointed out that carrageenan/MCC based pellets were characterized by lower yields and a poor aspect ratio when compared to pellets prepared with sodium alginate/MCC or pure MCC.

Figure 3.42  Effect of κ-carrageenan on drug release from pellets containing verapamil hydrochloride in concentrations of 20% and 50%
3.2.2 Comparison with the standard pelletization process extrusion/spheronization

The novel high shear granulation process was compared with the widely used pharmaceutical extrusion/spheronization process in terms of pellet size, shape, mechanical properties, morphology and drug release. During the high shear granulation process, the use of sodium alginate provided good properties (good hardness, high yield and spherical shape). Other pelletization aids, such as MCC and carrageenan, were also used during high shear granulation. The use of MCC resulted in pellets with a pH-dependent drug release profile of verapamil hydrochloride, while the use of carrageenan resulted in irregular shaped pellets. Sodium alginate was therefore chosen as pelletization aid for the standard pelletization process extrusion/spheronization, since the use of sodium alginate resulted in pellets with a pH-independent release profile of verapamil hydrochloride.

Pellets were made from the commercial type of sodium alginate (Protanal LF 120 M), microcrystalline cellulose (Avicel PH 101) and verapamil hydrochloride. Also in extrusion/spheronization, pellet production was only successful when MCC was added.
to alginate because of its advantages for pellet formation, such as water absorbing and retaining characteristics and plasticity properties allowing the formation of spheres. The need to use sodium alginate and MCC in combination is confirmed by relevant recent literature (Sriamornsak et al., 2007). For the pelletization process, different types of granulation liquid were investigated. Because of its water solubility, alginate turned into a sticky, swelling mass, resulting in long strands during the extrusion process. The long strands formed dumbbell shaped pellets during the spheronization process (Figure 3.44).

In order to reduce the solubility and swelling of sodium alginate, calcium chloride (3 %) was added to the granulation liquid. The guluronic acid residues of alginate can be crosslinked by means of calcium ions, resulting in a less swellable calcium alginate, which leads to a decrease in pellet size and the formation of spherical pellets during spheronization. It is therefore likely that the crosslinking process is important for the formation of spherical pellets. The investigated formulations are listed in Table 7 (formulation Nos. 29-31).

Optimized pellet formulations were obtained when using 20 % active ingredient (verapamil hydrochloride), 40 % MCC and 40 % sodium alginate (Table 7, formulation No. 29). In contrast to high shear granulation, the extrusion/spheronization method required a slightly lower content of microcrystalline cellulose as an additional
pelletization agent to prepare spherical pellets containing sodium alginate. The amount of granulation liquid (calcium chloride 3 %) used was kept constant at 113.5 % (w/w calculated with reference to the total pellet mass) of the powder mass for the extrusion/spheronization process.

The optimized process parameters of the extrusion/spheronization process resulted in spherical pellets (AR 1.08) with a high yield (85 %) as shown in Table 7 (formulation Nos. 29 and 30).

Table 7: Particle characterization of alginate based pellets prepared by extrusion/spheronization

<table>
<thead>
<tr>
<th>Formulation number</th>
<th>Alginate content (%</th>
<th>Calcium chloride (%</th>
<th>Yield (%)</th>
<th>Crushing strength (N)</th>
<th>Absolute amount binder (%)</th>
<th>Mean Feret diameter (µm)</th>
<th>Aspect ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>40</td>
<td>3</td>
<td>85.3</td>
<td>23.6 ± 0.9</td>
<td>113.5 ± 0.63</td>
<td>1062.3 ± 0.63</td>
<td>1.08</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>3</td>
<td>83.4</td>
<td>20.3 ± 0.3</td>
<td>100.0 ± 0.35</td>
<td>1002.1 ± 0.35</td>
<td>1.06</td>
</tr>
<tr>
<td>31</td>
<td>50*</td>
<td>3</td>
<td>-</td>
<td>25.1 ± 0.9</td>
<td>-</td>
<td>121.1</td>
<td>-</td>
</tr>
</tbody>
</table>

*irregular shaped

Because of the adhesive properties of the extruded mass of alginate based pellets, the diameter of the screen perforations was increased to 1500 µm, resulting in pellets with a larger particle size of about 1062.3 µm (Feret diameter). The porosity values of pellets were low (12 %) due to the high pressure to which the plastic mass was exposed during extrusion. The crushing strength was above 20 N.

As demonstrated in Figure 3.46, the extruded/spheronized pellets were characterized by a smooth surface. The relatively smooth surface was confirmed by measuring the surface roughness of pellets with the CLSM method. The mean roughness value (Ra value) of pellets prepared by the extrusion/spheronization method was relatively low, in this case 8.05 µm and 5.72 µm measured at two different areas of the pellet (Figure
3 Results and discussion

3.47) compared to the roughness values (15.89 µm and 17.51 µm) of pellets prepared by high shear granulation.

The disintegration of alginate based pellets prepared by extrusion/spheronization was rapid, resulting in fast drug release rates of verapamil hydrochloride (Figure 3.45).

![Figure 3.45](image)

**Figure 3.45** Drug release of verapamil hydrochloride from alginate based pellets at pH 6.8

Disadvantages of the extrusion/spheronization process were longer process times and greater process complexity.

In conclusion, the manufacture of pellets by the high shear granulation method is an easier process when using reduced process times, fewer manufacturing steps and lower cleaning complexity as compared to the extrusion/spheronization process. Both processes resulted in spherical pellets (AR < 1.2). Pellets with particle sizes below 600 µm were obtained with the high shear granulation method. In contrast, the particle size of pellets prepared by the extrusion/spheronization method was above the range of 1000 µm due to the required screen diameter of 1500 µm. The optimized process and formulation parameters of the high shear granulation process resulted in slightly lower pellet yields (72.5-77.5 %) compared to the high yield (85 %) of pellets prepared by extrusion/spheronization. Pellets produced by both manufacturing techniques exhibit
good mechanical properties. The rough particle surface of pellets manufactured by high shear granulation was also confirmed by CLSM measurements. The Ra value of pellets prepared by high shear granulation was higher than the Ra value of pellets prepared by extrusion/spheronization. The high Ra value indicates that pellets manufactured by high shear granulation feature a high degree of roughness compared to extrusion/spheronization pellets.

The combination of sodium alginate with MCC is a promising alternative to pure MCC for both processes – extrusion/spheronization and high shear granulation. Both methods resulted in pellets that can be used for subsequent coating processes.

Figure 3.46  SEM micrograph of pellets prepared by extrusion/spheronization
3.2.3 Pellets prepared by the ionotropic gelation method as a further alternative pelletization technique

The ionotropic gelation method is a process for ionic crosslinking of polymers such as chitosan, pectin, alginate or carrageenan with ionic counter-ions (Na\(^+\), Ca\(^{2+}\), K\(^+\) etc.). The ionotropic gelation method was used to produce alginate based pellets containing verapamil hydrochloride as a model compound. The effect of this alternative manufacturing method on the particle characteristics, drug load, encapsulation efficiency and drug release of alginate beads was observed.
Dripping of a sodium alginate solution into a calcium chloride solution resulted in spherical beads. A low content of sodium alginate (concentration below 1 %) produced flexible beads that were unstable, whereas high sodium alginate contents (concentrations above 4 %) resulted in a viscous solution which could not flow through a needle. As a consequence of the swelling process of sodium alginate in water, only 0.5 % (w/w) of verapamil hydrochloride could be dissolved in the sodium alginate solution. Adjusting this solution to different pH values, heating and the addition of surfactants were studied as ways of increasing the drug content. Only the addition of the solubilizer polysorbate 80 allowed the incorporation of 5 % verapamil hydrochloride into the alginate solution. Finally, the alginate solution contained 5 % verapamil hydrochloride, 15 % polysorbate 80, 1.5 % sodium alginate and 78.5 % water.

The encapsulation efficiency of the beads could be varied by changing the exposure time to the crosslinking agent. The encapsulation efficiency decreased with increasing exposure time to the crosslinking agent. This is due to a diffusion process of the relatively highly soluble drug verapamil hydrochloride from the dosage form. The crosslinking efficiency was higher than 80 % at exposure times of 5 min to the calcium chloride solution. The crosslinking efficiency decreased to 15 % after 24 h exposure to this solution. Using an ethanolic calcium chloride solution as crosslinking agent (where verapamil hydrochloride has a low solubility) or reducing the volume of the calcium chloride solution had no effect on the encapsulation efficiency.

Beads were characterized by a spherical shape and a mean Feret diameter of 1770 µm. As shown in Table 8 (formulation No. 1), the drug load of the wet and dried beads differed because a percentage of verapamil hydrochloride was lost during the drying process. The drug loss phenomenon might be explained as follows: The shrinking process led to a partial loss of water and a slight loss of the highly water soluble drug verapamil hydrochloride, i.e. the drug squeezed out of the pellets and remained on the bottom surface. As shown by SEMs of beads prepared with CaCl$_2$ as crosslinking agent, small crystals were visible on the particle surface (Figure 3.48). These crystals might also indicate that water was lost during the drying process, resulting in precipitation of the drug.
Different approaches were used in an attempt to prevent loss of drug content. First, the wet beads were treated with different agents such as ethanol 96 %, lactic acid (10 %), Na₂CO₃ (20 %), borate buffer pH 9 and sodium hydroxide (7.5 %) in order to stabilize the beads. The beads were then observed visually over a time period of 20 hours (Figure 3.49).
Table 8  Particle characterization of alginate based beads

<table>
<thead>
<tr>
<th>No</th>
<th>Cross-linking agent</th>
<th>After treatment</th>
<th>En-capsulation efficiency (%)</th>
<th>Drug load wet pellets (%)</th>
<th>Drug load dried pellets (%)</th>
<th>Crushing strength [N]</th>
<th>Mean Feret diameter (µm)</th>
<th>Shape factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CaCl₂ 0.1M</td>
<td>-</td>
<td>85.4</td>
<td>99.2</td>
<td>87.5</td>
<td>0.7 ± 0.07</td>
<td>1770 ± 0.02</td>
<td>0.89 ± 0.01</td>
</tr>
<tr>
<td>2</td>
<td>CaCl₂ 0.1M</td>
<td>Ethanol 96 %</td>
<td>85.4</td>
<td>98.9</td>
<td>86.2</td>
<td>0.687 ± 0.05</td>
<td>1180 ± 0.20</td>
<td>0.90 ± 0.01</td>
</tr>
<tr>
<td>3</td>
<td>CaCl₂ 0.1M</td>
<td>Lactic acid 10 %</td>
<td>85.4</td>
<td>99.2</td>
<td>85.2</td>
<td>0.598 ± 0.15</td>
<td>1480 ± 0.02</td>
<td>0.86 ± 0.02</td>
</tr>
<tr>
<td>4</td>
<td>CaCl₂ 0.1M</td>
<td>Na₂CO₃ (20 %)</td>
<td>85.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>CaCl₂ 0.1M</td>
<td>Borate buffer pH 9</td>
<td>85.4</td>
<td>99.1</td>
<td>84.6</td>
<td>0.613 ± 0.06</td>
<td>2180 ± 0.21</td>
<td>0.91 ± 0.01</td>
</tr>
<tr>
<td>6</td>
<td>CaCl₂ 0.1M</td>
<td>NaOH (7.5 %)</td>
<td>85.4</td>
<td>99.6</td>
<td>99.4</td>
<td>0.596 ± 0.07</td>
<td>2770 ± 0.02</td>
<td>0.88 ± 0.02</td>
</tr>
<tr>
<td>7</td>
<td>CaCl₂ 0.1M / MgCl₂ 0.05M (1:1)</td>
<td>-</td>
<td>80.2</td>
<td>95.6</td>
<td>95.6</td>
<td>1.154 ± 0.16</td>
<td>2100 ± 0.09</td>
<td>0.83 ± 0.01</td>
</tr>
<tr>
<td>8</td>
<td>BaCl₂ 0.5M</td>
<td>-</td>
<td>82.2</td>
<td>100.0</td>
<td>89.6</td>
<td>1.052 ± 0.07</td>
<td>1590 ± 0.13</td>
<td>0.85 ± 0.01</td>
</tr>
</tbody>
</table>
3 Results and discussion

a) Directly after preparation  
30 minutes after preparation  
20 hours after preparation

b) Directly after preparation  
30 minutes after preparation  
20 hours after preparation

c) Directly after preparation  
30 minutes after preparation  
20 hours after preparation
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Figure 3.49  Wet beads washed with water; b) washed with ethanol; c) washed with lactic acid; d) washed with Na$_2$CO$_3$; e) washed with borate buffer; f) washed with NaOH (1 graduation line = 0.059cm)
The beads remained spherical in shape except for those treated with Na$_2$CO$_3$. However, all the beads shrunk during drying. The shrinking process led to a partial loss of water and consequently, the highly water-soluble verapamil hydrochloride squeezed out of the pellets and deposited on the surface of the bottom. The particle characteristics of the beads are given in Table 8 (formulation Nos. 2-6). Treating the wet beads with NaOH after preparation successfully prevented loss of verapamil hydrochloride. This could be explained by the higher pH environment inside the dosage form resulting in partial precipitation of the weakly basic drug verapamil hydrochloride inside the beads. In addition, insoluble calcium hydroxide formed on the surface of the beads, when NaOH interacted with calcium ions. Drug release measurements in phosphate buffer pH 6.8 showed that only 60% of the drug had been released after 30 min. This could be explained as due to the insoluble calcium hydroxide layer on the surface of the beads and the lower solubility of the weakly basic drug at pH 6.8. In contrast, approximately 100% of the drug had been released after the same time period when measurements were performed in 0.1 N HCl. This could be due to the high solubility of verapamil hydrochloride at low pH values and the absence of the insoluble calcium hydroxide layer.

![Figure 3.50](image.png)

*Figure 3.50 Drug release of verapamil hydrochloride from alginate based beads treated with NaOH after preparation.*
3 Results and discussion

The use of sodium hydroxide failed due to the precipitation of the drug in the beads. Therefore, this approach was not investigated further in subsequent experiments. In order to stabilize the alginate beads without drug precipitation, calcium ions were replaced by barium ions. Smidsrod and Skjak-Braek (1990) found that alginate gels can be stabilized by replacing calcium ions with other divalent ions with a higher affinity for alginate. The affinity series for alginate is $\text{Pb}^{2+} > \text{Cu}^{2+} > \text{Cd}^{2+} > \text{Pb}^{2+} > \text{Ba}^{2+} > \text{Sr}^{2+} > \text{Ca}^{2+} > \text{Co}^{2+} = \text{Ni}^{2+} = \text{Zn}^{2+} > \text{Mn}^{2+}$. Both the rigidity and the mechanical strength of the alginate gels increased when the affinity of the divalent ions to alginate are increased. However, most of these ions are strictly limited in their use because of their toxicity. Only barium is commonly used in patients, e.g. radiolabelled $\text{BaSO}_4$ is given to patients to diagnose the presence of intestinal disorders. Its absence of toxicity is due to the fact that $\text{BaSO}_4$ is insoluble and is therefore eliminated from the body without dissolving. In this case, barium ions diffuse out of the beads slowly and can precipitate in the intestinal fluid as barium phosphate which is then easily eliminated from the body (Bajpai, Sharma, 2004). Even though barium was not the excipient of choice, investigational beads were prepared with barium ions as crosslinking agent (Figure 3.51). However, the use of barium ions failed to stabilize the beads. Although the mechanical strength increased, the beads lost a percentage of the drug (Table 8, formulation No. 8).
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![Figure 3.51 Alginate based beads prepared with barium chloride as crosslinking agent.](image)

Another approach to creating a bead formulation was to add ions, which potentially inhibit the gelation of alginate (e.g. magnesium chloride).

![Figure 3.52 Alginate based beads prepared with magnesium chloride/calcium chloride as crosslinking agent](image)

Surprisingly, the presence of MgCl$_2$ resulted in beads characterized by a high drug load (Table 8, formulation No. 7). This could be due to the fact that magnesium chloride worsened and slowed the conditions for the effective crosslinking process between alginate and calcium ions, resulting in a network of small defects. Hence, the use of salts such as magnesium chloride resulted in the formation of gels characterized by a homogeneous polymer network. This finding is in accordance with the scientific
literature (Skjak-Braek et al., 1989). Alginate beads produced with CaCl₂ and MgCl₂ had a spherical shape and low crushing strength values (Table 8, formulation No. 7). The particle surface of the pellets was examined by SEM (Figure 3.53). No crystals were visible on the surface of beads prepared with CaCl₂ and MgCl₂. In contrast, as shown by SEMs of beads prepared with CaCl₂ as crosslinking agent, small crystals were visible on the particle surface.

![SEM micrograph of pellets prepared with magnesium chloride/calcium chloride as crosslinking agent](image)

**Figure 3.53**  SEM micrograph of pellets prepared with magnesium chloride/calcium chloride as crosslinking agent

Drug release from beads prepared with MgCl₂/CaCl₂ as crosslinking agents is shown in Figure 3.54. The content of sodium alginate used was not able to compensate the pH-dependent solubility of verapamil hydrochloride. Consequently, drug release remained pH-dependent when drug release measurements were carried out at pH 6.8 and pH 1.0.
In conclusion, spherical pellets with a high drug load and encapsulation efficiency but low hardness values were prepared by the ionotropic gelation method. A further excipient such as MgCl₂ was necessary to produce pellets offering sufficient stability. Without these excipients, a considerable amount of drug loss takes place during the drying process.

Production by this kind of process is only possible in small volumes; producing pellets on larger scale using this method is therefore both too labour intensive and time consuming.

Overall, the ionotropic gelation method offers no advantage over the standard extrusion/spheronization process. However, this method might be interesting for encapsulation of highly sensitive but highly protective proteins.

### 3.3 Extended release of alginate based pellets prepared by high shear granulation

Coating of solid dosage forms with aqueous dispersions of ethyl cellulose or acrylate derivatives is often performed to obtain extended drug release characteristics. This
film coating creates a diffusion membrane to control the rate of drug release from pellets. The aqueous polymer dispersions offer the possibility of forming films from insoluble polymers in an aqueous environment without organic solvents. Two examples of aqueous dispersions containing ethyl cellulose or acrylate derivatives are Aquacoat ECD and Eudragit RS 30 D respectively. However, film formation from aqueous dispersions is a complex process. The film formation depends on the minimum formation temperature (MFT) of the aqueous dispersion. The coated dosage forms are often treated at elevated temperatures for short periods of time (curing) to complete the film formation process and obtain stable release profiles. However, it is often difficult to achieve complete film formation even after curing. In these cases there is a risk of further coalescence during storage, resulting in denser film structures which reduce the release rates. These curing effects occur more frequently when using aqueous dispersions with relatively high minimum film formation temperatures, such as Eudragit RS 30 D or Aquacoat ECD. The minimum film formation temperatures of Eudragit RS 30 D and Aquacoat ECD are 47 °C and 81 °C respectively. These phenomena can be explained as due to insufficient polymer particle coalescence.

Extended drug release from pellets can also be achieved by adding water insoluble polymers or lipophilic substances to the pellet core formulation. There is growing interest in the development of such matrix pellet formulations, because in practice polymeric coating is subject to problems such as film thickness variation, cracks in the film or ageing of the polymer coating. Drug release is controlled by diffusion through the matrix, erosion of the matrix or a combination of both diffusion and erosion. These matrix pellets can be prepared by extrusion/spheronization and high shear granulation or other pelletization methods.

Three separate objectives were investigated in this study: firstly, drug release from pellets coated with the aqueous polyvinyl acetate dispersion Kollicoat SR 30 D and prepared by high shear granulation was studied. Kollicoat SR 30 D is an aqueous dispersion with a very low MFT of 18 ºC, which means that curing effects are reduced. The dispersion contains polyvinyl acetate (27 %, w/v), polyvinyl pyrrolidone (2.5 %, w/v) sodium lauryl sulphate (0.3 % w/v) and water (70.2 % w/v). Secondly, to determine whether pellets prepared by high shear granulation can be coated.
In a third approach, the effect of adding water insoluble polymers or lipophilic substances to pellet cores prepared by high shear granulation on the particle properties and the drug release of verapamil hydrochloride was investigated.

3.3.1 Coating of alginate based pellets

Matrix pellets containing 30.5 % sodium alginate, 49.5 % MCC and 20 % verapamil hydrochloride were prepared by the novel high shear granulation method. To obtain optimal pellet properties for a subsequent coating process (i.e. good hardness and spherical shape), a 10 % calcium chloride solution was used as granulation liquid. Pellets were then coated with the aqueous polyvinyl acetate/polyvinyl pyrrolidone dispersion Kollicoat SR 30 D. A coating level of 20 % (w/w calculated with reference to the total pellet mass) was required in order to achieve homogeneous particle coating and extended drug release profiles. In order to avoid pellet adhesion following the coating process, silicon dioxide (Syloid 244 FP) was added to and mixed with the pellets before the curing stage.

Drug release

Verapamil hydrochloride release from pellets coated with polyvinyl acetate/polyvinyl pyrrolidone dispersion in 0.1 N HCl and phosphate buffer pH 6.8 at a 20 % coating level is illustrated in Figure 3.55 (curing 1d 40 °C). Drug release rates from coated pellets were found to be pH-independent. Again, the pH-independent release profile can be explained by the properties of sodium alginate. At low pH the alginate precipitates in the form of poorly soluble alginic acid, creating a diffusion barrier. At high pH, alginate converts to the sodium salt form, which is prone to erosion. Hence, alginates are able to compensate the pH-dependent solubility of weakly basic drugs which show good solubility at low pH and poor solubility at high pH.
In contrast, drug release from Kollicoat SR 30 D coated pellets containing 20% verapamil hydrochloride, 20% lactose monohydrate and 60% MCC was pH-dependent. This can be explained as due to the absence of sodium alginate (Figure 3.56). The coating level of 20% used for this formulation was comparable to the coating level for pellets containing sodium alginate described above.
Curing conditions

When using aqueous polymer dispersions as film coating, it is necessary to select the appropriate curing conditions. Film formation must be complete to avoid further polymer particle coalescence during long term storage, which would result in decreasing drug release rates.

The effects of different curing conditions on the release of verapamil hydrochloride from coated alginate/MCC pellets prepared by high shear granulation were therefore studied: 1 d curing at 40 °C with ambient relative humidity (ambient RH) and 1 d curing at 40 °C and 75 % relative humidity (RH) (followed by 5 d at 40 °C and 75 % RH) as well as 1 and 2 d curing at 60 °C with ambient RH. Clearly, the release rate significantly decreases in all cases with curing, indicating that the film formation is not fully completed immediately after the coating process (Figure 3.57). The reduced drug release rate could be explained by the physiochemical properties of the aqueous dispersion, as well as pellet core characteristics. Surprisingly, coated pellets without sodium alginate showed no significant curing effects, resulting in stable drug release profiles (Figure 3.58). This in turn indicates that the curing effects are mainly driven by the composition of the core pellets.
Pellets containing sodium alginate have a higher moisture content of 10.63 % compared to pure MCC pellets, which were characterized by a relatively low moisture content of 4.32 %. The higher moisture content of alginate based pellets might be explained by the presence of the calcium ions in the pellet core formulation. The calcium ions which are required to crosslink the sodium alginate are characterized by hygroscopicity, meaning that a liquid layer forms on the surface of the dosage form. To confirm the hypothesis that the moisture content in the dosage form was caused by calcium ions, pellets prepared with 0-20 % calcium ions in the granulation liquid were studied. Moisture measurements were then taken with a moisture analyzer and by NIR. Both studies demonstrated that pellets prepared with increasing levels of calcium ions resulted in pellets of increasing moisture content. Pellet batches prepared with 20 % calcium chloride in the granulation liquid had a total moisture content of 13.44 %, which falls to 5.22 % for pellets prepared without calcium chloride in the granulation liquid (Table 9). NIR measurements showed a peak shift to lower wavenumbers in the region of 5200 cm⁻¹ (water peak) when the calcium ion content increased in the granulation liquid (Figure 3.59). This also indicates that pellets containing different amounts of calcium are characterized by different moisture contents.

Table 9: Moisture measurements of pellets prepared with different percentages of calcium chloride in the granulation liquid

<table>
<thead>
<tr>
<th>Calcium chloride (%)</th>
<th>Moisture Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.22</td>
</tr>
<tr>
<td>3</td>
<td>6.52</td>
</tr>
<tr>
<td>5</td>
<td>8.28</td>
</tr>
<tr>
<td>10</td>
<td>10.63</td>
</tr>
<tr>
<td>20</td>
<td>13.44</td>
</tr>
</tbody>
</table>

For the coating process itself, only pellets containing 10 % calcium chloride in the granulation liquid were used. These pellets had a total moisture content of 10.63 %.
This relatively high moisture content could act as a plasticizer for the polymer, facilitating further polymer particle coalescence during curing, which in turn results in decreasing drug release rates of verapamil hydrochloride.

The RH also had an influence on the drug release profiles. Figure 3.57 shows drug release rates of coated pellets cured at 40 °C/ambient RH as well as at 40 °C/75 % RH. Verapamil hydrochloride release was slightly slower when curing was performed at 75 % RH instead of in ambient conditions. This can also be explained by the plasticizing properties of water facilitating further polymer particle coalescence and finally resulting in denser film coating. These findings are in good agreement with the literature (Siepmann et al., 2008; Siepmann et al., 2006).

The drug release of verapamil hydrochloride was significantly decreased after pellet curing for 1 d at 60 °C. But, no further decrease in the drug release rate was observed after curing for 2 d at 60 °C. This indicates that the release profile became stable, i.e. coalescence no longer occurred regardless of changes towards higher temperatures during further curing treatment.

The resulting release profile of verapamil hydrochloride remained pH-independent irrespective of the curing conditions (Figure 3.60).
Figure 3.57  Effect of curing on verapamil hydrochloride release in phosphate buffer pH 6.8 from coated pellets (coating level 20 %) consisting of sodium alginate/MCC.

Figure 3.58  Effect of curing on verapamil hydrochloride release in phosphate buffer pH 6.8 from coated pellets (coating level 20 %) consisting of MCC only.
3 Results and discussion

Figure 3.59  NIR measurements of pellets prepared with 0, 3, 5, 10, 20 % calcium chloride in the granulation liquid

Figure 3.60  pH-independent drug release of verapamil HCl from coated pellets (curing 1 d at 60 °C) consisting of sodium alginate/MCC.
Effect of calcium ions on drug release from coated pellets

Next, the effect of calcium ions in the dissolution medium on the release of verapamil hydrochloride from coated pellets was studied. The pellet core formulation consisted of MCC and sodium alginate. Calcium ions are known to influence the alginate structure due to further polymer crosslinking, resulting in denser structures and consequently decreasing drug release rates. It is therefore important to study drug release with addition of different calcium ion concentrations, especially since calcium is present in large amounts in the gastrointestinal tract. As described in Section 3.1.6, phosphate buffer pH 6.8 could not be used for this investigation because calcium phosphate precipitates in the buffer environment. Drug release studies were therefore performed in 0.1 N HCl. Figure 3.61 shows that verapamil hydrochloride release was unchanged when calcium ions in different concentrations were present in the dissolution medium.

![Figure 3.61](image-url)

Figure 3.61  Effect of calcium ion concentration in dissolution medium on verapamil hydrochloride release from coated pellets containing sodium alginate
3.3.2 Preparation of extended release core pellets by the high shear granulation method

Additional excipients such as extended release polymers or lipophilic substances were studied as a means of achieving sustained drug release rates of verapamil hydrochloride. In the present study, two different excipients – Kollidon SR and magnesium stearate – were tested in the high shear granulation process. The process parameters used for these formulations were the same as those described in Section 3.2.1. The first part of this study focused on the influence of Kollidon SR or magnesium stearate on the pellet properties. Kollidon SR is a polyvinyl acetate- and povidone-based matrix retarding agent. To demonstrate the drug release sustaining potential of Kollidon SR, matrix pellets were formulated using Kollidon SR and verapamil hydrochloride with microcrystalline cellulose as pelletization excipient. The preparation of pellets using high shear granulation was only successful when sodium alginate was added as a further pelletization excipient. The pellets were therefore composed of 20 % verapamil hydrochloride, 40 % MCC, 20 % Kollidon SR and 20 % sodium alginate.

Pellets containing magnesium stearate were also prepared by high shear granulation. In order to produce spherical pellets, sodium alginate must also be added when using magnesium stearate. The composition of the pellets was 20 % verapamil hydrochloride, 40 % MCC, 20 % magnesium stearate and 20 % sodium alginate. Due to the presence of sodium alginate in both formulations, a 3 % calcium chloride solution was required as granulation liquid.

Table 10 gives an overview of these particle characteristics. All pellets were characterized by good hardness values, spherical shape and a mean Feret diameter of 800 µm (formulation Nos. 1 and 2).

As shown in Figure 3.62, verapamil hydrochloride was rapidly released from formulations containing magnesium stearate and Kollidon SR which might be explained by the relatively high amount of sodium alginate within these pellets. Since both of the excipients studied failed to produce the desired result of extended release rates of verapamil hydrochloride, a third excipient – ethyl cellulose – was evaluated.
Again, the study focused on the ability of this water insoluble polymer to produce extended release matrix pellets in high shear granulation equipment. Pellets were prepared using ethanol 96 % as granulation liquid which allows the dissolution of ethyl cellulose. The addition of sodium alginate was no longer necessary since ethanol alone provides the desired rigidity and plasticity properties within the powder mass. The pellets therefore contained 20 % verapamil hydrochloride, 40 % ethyl cellulose and 40 % microcrystalline cellulose.

Figure 3.62 shows that pellets containing ethyl cellulose showed more prolonged release profiles than the aqueous granulated pellets comprising magnesium stearate or Kollidon SR. However, ethyl cellulose based pellets were characterized by a non-spherical shape, i.e. the aspect ratio was higher than 1.2, and a low yield of 50.2 % (Table 10, formulation No. 3).

This approach proved that ethyl cellulose might be an extended release matrix pellet formulation. However, further formulation and process optimization is required.

<table>
<thead>
<tr>
<th>No.</th>
<th>Matrix former</th>
<th>Calcium chloride (%)</th>
<th>Yield (%)</th>
<th>Crushing strength (N)</th>
<th>Absolute amount binder (%)</th>
<th>Mean Feret diameter (µm)</th>
<th>Aspect ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kollidon SR/ sodium alginate</td>
<td>3</td>
<td>67.3</td>
<td>6.4 ± 1.5</td>
<td>103.6</td>
<td>859 ± 0.45</td>
<td>1.10 ± 0.01</td>
</tr>
<tr>
<td>2</td>
<td>Magnesium stearate/ sodium alginate</td>
<td>3</td>
<td>74.4</td>
<td>5.2 ± 1.3</td>
<td>101.3</td>
<td>864 ± 0.35</td>
<td>1.17 ± 0.00</td>
</tr>
<tr>
<td>3</td>
<td>Ethyl cellulose</td>
<td>0</td>
<td>50.2</td>
<td>9.2 ± 1.7</td>
<td>65.1</td>
<td>921 ± 0.41</td>
<td>1.31 ± 0.01</td>
</tr>
</tbody>
</table>
Figure 3.62  Effect of addition of different matrix formers on drug release of verapamil hydrochloride from pellets prepared by high shear granulation.
4 Summary

4.1 pH-independent drug release

Weakly basic drugs show higher solubility at low pH, which often results in faster drug release at lower pH. The objective of the study was to achieve pH-independent release of weakly basic drugs from extended release formulations based on the natural occurring polymer sodium alginate. Alginates exhibit better solubility at higher pH, and are therefore able to compensate the poor solubility of weakly basic drugs at high pH.

Three approaches to overcoming the pH-dependent solubility of the weakly basic model drug verapamil hydrochloride were investigated. Firstly, matrix tablets were prepared by direct compression of drug substance with different types of sodium alginate only. Secondly, pH modifiers were added to the drug/alginate matrix systems. Thirdly, three-layer tablets consisting of an inner pH modifier layer and outer drug/sodium alginate layers were prepared.

pH-independent drug release was already achieved from matrix tablets consisting of selected alginates and drug substance only. This approach was successful when using alginates showing rapid hydration and erosion at higher pH. The approach failed for alginates with less pronounced erosion at high pH. The addition of fumaric acid to drug/alginate based matrix tablets reduced the microenvironmental pH within the tablets, thereby increasing the solubility of the weakly basic drug. Therefore, pH-independent drug release was achieved regardless of the type of alginate used. Drug release from three-layer tablets remained pH-dependent.
4.2 High shear granulation

The process of pelletization by extrusion/spheronization is widely used in the pharmaceutical industry. However, the extrusion/spheronization process involves several steps using different pieces of equipment. The high shear granulation method was chosen to achieve the goal of creating pellets in a simple one-step process, although this process is normally used to produce granules. Sodium alginate, carrageenan and microcrystalline cellulose (MCC) were evaluated as pelletization aids to produce immediate release pellets by the high shear granulation process. By optimizing the process parameters in this process, pellets with a low aspect ratio, a high yield and good mechanical properties were produced when MCC was used as the only pelletization aid in the pellet, and MCC was also used in combination with sodium alginate. The particle properties of these pellets were comparable to the properties of pellets produced by the more common extrusion/spheronization process. However, pellets containing only MCC were characterized by a lack of disintegration, resulting in very low drug release rates of the weakly basic drug vardenafil hydrochloride at pH 6.8. This was demonstrated by the fact that only 20 % of the drug had been released after 20 minutes at pH 6.8. In contrast to pellets containing MCC, pellets composed of alginate or carrageenan in combination with MCC showed rapid rates of disintegration and drug release in higher pH environments. Approximately 80 % of the weakly basic drug vardenafil hydrochloride had been released after 20 minutes at pH 6.8 when alginate and carrageenan combinations with MCC were employed.

4.3 Ionotropic gelation as a further alternative method for pellet production

The ionotropic gelation method is widely used for the encapsulation process of highly sensitive but highly protective proteins. The aim of this study was to investigate the suitability of this method for producing an oral pellet formulation containing verapamil hydrochloride as model drug.
Spherical beads with a high drug load and high encapsulation efficiency were prepared by dripping the drug in a sodium alginate solution into a calcium chloride solution. However, the beads shrank during the drying process due to partial loss of water. Slight loss (~10%) of the highly soluble drug verapamil hydrochloride also occurred because of the dehydration step during drying. To prevent this drug loss phenomenon, a special excipient such as magnesium chloride was necessary. The addition of magnesium chloride to the gelation medium resulted in the formation of a more homogeneous polymer network that successfully inhibited drug loss.

All beads/pellets were characterized by low hardness values which can be disadvantageous if the beads require subsequent coating. A further disadvantage is that production using this kind of process was only possible in small volumes. Producing pellets on a larger scale by this method is therefore both too labour intensive and time consuming.

Overall, the ionotropic gelation method offered no advantage over the standard extrusion/spheronization process.

4.4 Controlled release from pellets manufactured by the high shear granulation process

Two approaches to achieving sustained drug release from pellets manufactured by high shear granulation were studied. The first approach was based on the creation of a diffusion layer by film coating which in turn prolonged the rate of drug release, while the second approach focused on producing an extended release matrix pellet formulation. The first approach was successful in creating an extended release formulation for the weakly basic drug verapamil hydrochloride when the aqueous polyvinyl acetate dispersion Kollicoat SR 30 D was used at a coating level of 20% (w/w calculated with reference to the total pellet mass) and under optimized curing conditions (1 d, 60 °C). Since the pellet core contained sodium alginate, which exhibits inverse solubility compared to the weakly basic drug verapamil hydrochloride, the sodium alginate was able to compensate the pH-dependent solubility of verapamil hydrochloride. Consequently, the resulting release profile was
found to be pH-independent. The second approach demonstrated that ethyl cellulose might be an interesting polymer for creating extended release matrix pellets.
5 Zusammenfassung

5.1 Strategien zur Überwindung der pH abhängigen Löslichkeit schwach basischer Arzneistoffe durch die Verwendung verschiedener Alginat-Typen


5.2 Schnell freisetzende Pellets hergestellt durch High Shear Granulierung


Drei verschiedene Polymere, nämlich Alginat, Carrageenan und MCC, wurden eingesetzt, um eine schnell freisetzende Pelletformulierung für einen schwach basischen Arzneistoff auch bei höheren pH-Werten zu entwickeln.


5.3 Vertropfungsverfahren als eine weitere alternative Methode zur Pelletherstellung

Das Vertropfungsverfahren wird häufig eingesetzt für die Verkapselung von Proteinen. Das Ziel dieser Studie bestand darin, eine oral applizierbare Pelletformulierung mit


5.4 Verzögerte Arzneistofffreisetzung aus Pellets, die mittels High Shear Granulierung hergestellt wurden

Um die Arzneistofffreisetzung aus schnell freisetzenden Kernpellets, die mittels High-Shear-Granulierung hergestellt wurden, über mehrere Stunden zu retardieren, wurden zwei verschiedene Ansätze entwickelt. Der erste Ansatz basierte auf einem Polymer-Coating der Kernpellets, wohingegen der zweite Ansatz in der Entwicklung einer verzögert freisetzenden Matrix-Pelletformulierung bestand.

Durch einen wässrigen Polyvinylacetatüberzug (Kollicoat SR 30 D) von 20 % (w/w bezogen auf die Pelletkern-Gesamtmasse) gelang es, die Freisetzung von Verapamil Hydrochlorid aus den schnell freisetzenden Kernpellets, die mittels High-Shear-Granulierung hergestellt wurden, über mehrere Stunden zu retardieren.

Um eine Änderung der Wirkstofffreisetzung während der Lagerung zu verhindern, wurden die Kernpellets nach dem Überziehen mit Kollicoat SR 30 D für 1 Tag bei einer Temperatur von 60 °C thermisch nachbehandelt.
Das resultierende Freisetzungsprofil des schwach basischen Arzneistoffes Verapamil Hydrochlorid war während der gesamten Freisetzung pH-unabhängig. Die Begründung liegt darin, dass die Kernpellets Natriumalginat enthalten, welches eine umgekehrte Löslichkeit zu Verapamil Hydrochlorid besitzt und somit die pH-abhängige Löslichkeit des Arzneistoffes kompensieren kann.

Die Herstellung von Matrixpellets durch den Zusatz von schlechtlöschlichen Polymeren wie Ethlycellulose als eine weitere Möglichkeit, die Freisetzung von Verapamil Hydrochlorid aus den Kernpellets zu verzögern, ist ein viel versprechender Ansatz, der in nachfolgenden Studien noch optimiert werden könnte.
6 References


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6 References


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USP 31, 2008.


Publications

Poster presentations

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Gutsche S., Krause M., Kranz H., pH-independent release of weakly basic drugs from alginate based single unit drug delivery systems. *2007 AAPS Annual meeting and Exposition, American Association of Pharmaceutical Scientist, San Diego*

Gutsche S., Krause M., Kranz H., The use of sodium alginate as an alternative pelletization aid in a Mi-Pro High Shear Mixer. *2008 BSP Young Scientist’s Poster Session, Berlin*

Original Research Articles


Gutsche S., Krause M., Kranz H., The use of sodium alginate as an alternative to microcrystalline cellulose as a pelletisation aid in a Mi-Pro High Shear Mixer (in preparation).


Curriculum Vitae

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