Multiparticulate tablets with uncoated and coated κ-carrageenan pellets

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List of abbreviations

Abbreviation	Meaning
A	projected area
ar	aspect ratio
C.V.	coefficient of variation
cm^2	square centimeter
ºC	degree Celsius
Conf.lev.	confidence level
d	diameter
DCP	dicalcium phosphate
d_{eq}	equivalent diameter
d_{max}	maximal Feret diameter
F	crushing force
f_2	similarity factor
g	gram
h	hour
κ	kappa
kN	kilo Newton
kg	kilogram
µm	micrometer
MCC	microcrystalline cellulose
mg	milligram
min	minute
ml	milliliter
mm	millimeter
MPa	mega Pascal
N	Netwon
n	sample size
p.a.	pharmaceutical quality: for analysis
Ph.Eur.	European pharmacopoeia
Q^2	prediction factor
R^2_{adj}	adjusted coefficient of determination
rpm	revolutions per minute

s	second
S.D.	standard deviation
SMCC HD	high density silicified microcrystalline cellulose
USP	United States Pharmacopoeia
UV	ultraviolet

1 Introduction

1.1 Pellets as a multiparticulate dosage form

Pharmaceutical pellets can be defined as isometric agglomerates having a narrow size distribution and a smooth surface structure (Knop, 1991). Typical mean diameter for pellets produced in the pharmaceutical industry varies in the range between 300 µm and 2 mm.

As a well established multiparticulate dosage form pellets are gaining increased interest in the pharmaceutical field due to their several benefits over monolithic dosage forms.

Multiparticulate dosage forms distribute more homogenously in the gastro-intestinal tract leading to maximized drug absorption and minimized irritation of mucosa resulting from high local concentration of some active ingredients encountered in case of monolithic dosage forms (Bechgaard and Hagermann, 1978; Ghebre-Sellassie, 1989; Krämer and Blume, 1994). The more uniform and to some extent more predictable gastric emptying of small particles compared to large monolithic dosage forms was associated with minimal influence on the transit time in the upper intestine and lowered inter- and intra-subject variability of drug plasma concentration (Davis et al., 1984; Follonier and Doelker, 1992; Digenis et al., 1990; Krämer and Blume, 1994; Decheshe and Delattre, 1996; Collett and Moreton, 2001). Coated multiparticulate systems exhibit a reduced or eliminated risk of dose dumping compared to coated monolithic systems.

Furthermore, the feasibility of producing dosage forms with different drug strengths starting from the same pellet batch by simply varying the capsule fill weight (Ghebre-Sellassie and Knoch 2002) and the possibility of combining several incompatible active ingredients in one product make these systems an attractive choice for pharmaceutical formulators. The possibility of mixing pellets with different release properties to achieve a desired liberation profile allows high therapeutic flexibility. The excellent flow properties of pellets are also quite beneficial for a reproducible die or capsule filling leading to a uniform drug content (Erkoboni, 2003). Compared to irregular-shaped granules pellets show the big advantage of spherical shape and smooth

surface, which are key factors for a simple and efficient film coating with lower amount of the coating agent needed (Ghebre-Sellassie, 1989).

1.2 Production of pellets

1.2.1 Overview

Various methods are used to produce pellets such as direct pelletization, spray layering, spray congealing, tableting and extrusion/spheronization (Ghebre-Sellassie and Knoch, 2002; Kleinebudde and Knop, 2007; Jones, 1989; Goodhart and Jan, 1989; Hincal and Kas, 1994; Lennartz and Mielck, 1998; Rouge et al., 1997; Lopes et al., 2006; Vervaet et al., 1995; Newton, 2002; Trivedi el al., 2007).

In the current work the preparation of pellets was performed only using extrusion/spheronization.

1.2.2 Extrusion/spheronization

1.2.2.1 Principle, advantages and challenges

The production of pellets via extrusion/spheronization is a well established technique in the pharmaceutical industry. The extrusion technique is based on forcing a plasticized mass (prepared by wet massing, melting or softening) through orifices with defined diameter and length to diameter ratio. The formed extrudates are then cut to small cylindrical pieces or transformed into spherical entities in a spheronizer. The latter consists normally of a static cylindrical jacket and a rotating ground plate.

The extrusion/ spheronization is particularly advantageous over most other methods for pellet production in terms of robustness, low costs, good reproducibility, feasible high drug loading up to 95% (Thommes, 2006). In particular the extrusion/ spheronization technique leads to pellets with high density and narrow size distribution which are desirable properties for capsule or die filling and coating processes. Moreover the continuous nature of the extrusion process is particularly profitable for high throughput when coupled with multiple spheronizers operating in parallel (Erkoboni, 2003; Dukic-Ott et al., 2009).

The main challenge encountered in the production of pellets by extrusion/spheronization compared to the other methods is to ensure sufficient sphericity of the prepared pellets especially in case of those intended for a subsequent coating. A balance between a sufficient degree of brittleness of the extrudates to break to smaller cylinders and adequate plasticity to deliver the needed deformation into spherical particles together with sufficient cohesiveness and low adhesiveness of the extrudates are key elements for a high yield of pellets with spherical shape (Conine and Hadley, 1970; Bornhöft, 2005). Optimization of the amount of liquid added, percentage of the pelletization aid used, extrusion parameters (feeding rate and extrusion speed), spheronization conditions (loading, time, speed and temperature) as well as the size and shape of active and inactive ingredients in some cases are required to achieve high pellet sphericity.

1.2.2.2 Equipments available for extrusion

Extruders are generally classified according to the way the pressure is applied to force the plasticized mass through the extrusion channels into: screw extruders, sieve- or basket-type extruders, roll extruders and ram extruders.

Whereas ram extruders as the simplest form of extrusion equipments are only used for early development phases and for the examination of rheological properties of plasticized masses on a laboratory scale (Chohan and Newton 1996), the three other types represent the main categories of large scale equipment available for the production of pharmaceutical extrudates.

Screw extruders (figure 1-1) use screws to force the plasticized mass through the dies. The combination of two steps (wet granulation and extrusion) in the twin screw extruder is a great advantage of this equipment especially in case of volatile granulation liquids. The granulation process can be optimized and adapted to the worked material through the use of different mixing and kneading elements in the screw configurations. A high level of energy is brought to the product, which can be positive in terms of robustness against the particle size in comparison to basket-type extruders in which much lower shearing of the worked mass takes place (Schmidt et al., 1997).

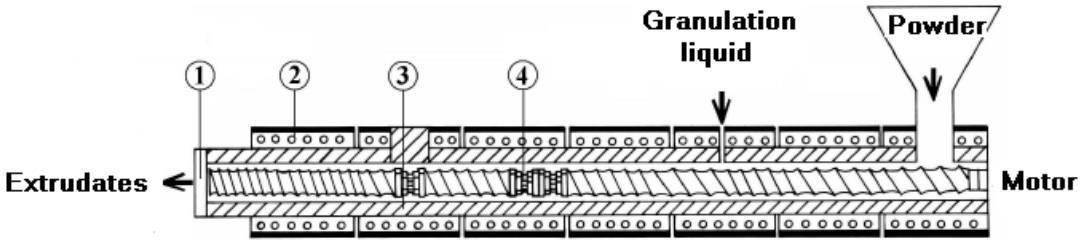


Figure 1-1: Schematic drawing of the twin screw extruder: (1) die plate (2) heating elements (3) barrel (4) screw (according to Thommes, 2006).

However, the high mechanical stress applied to the worked mass in screw extruders may not be desirable for shear sensitive substances. For such substances changes in the crystal modification leading to significant undesirable changes in the properties of the active ingredients may occur as a result of the high mechanical stress applied in this type of equipment.

The Nica extruder (figure 1-2) is an example of **basket-type extruders**. In this type of equipment the plasticized mass is forced through a horizontal ring-shaped screen with a high number of dies by means of one or two impellers located inside the perforated ring.

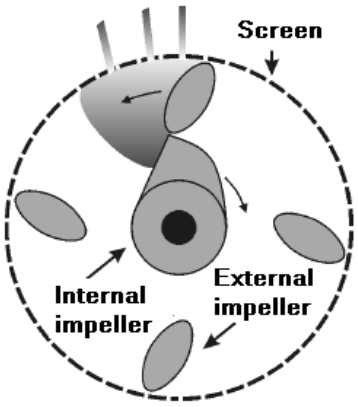


Figure 1-2: Schematic draw of the Nica extruder (according to Goebel, 2004).

Basket-type extruders have the advantage of short transport path and low shearing applied to the material subject to extrusion as a result of the short timed pressure building. The low pressure is associated with reduced work input and is ideal for substances which can be damaged by the intensive conditions encountered in screw extruders. The changes in water distribution in the wetted mass associated with the building of high pressure which may occur in screw extruders is avoided in such systems. The high number of dies

in the screen of basket extruders leads to high throughput and the feeding system is much simpler than that of the two screw extruder. However, the low extrusion pressure generated in such system may be a disadvantage for materials requiring high pressures for plasticization and densification into extrudates. The die length in basket-type extruders is shorter compared to that in roll extruders (Vervaet et al., 1994).

The monitoring of temperature and pressure in basket-type extruders is more complicated compared to screw extruders.

Roll extruders consist of a jacket or a plate with a high number of dies through which the plasticized mass is forced by means of rollers. Several designs of roll extruders are commercially available and differ in the location of the roller/rollers and the extrusion screen. The three main types are the ring die press, the rotary cylinder extruder and the flat die press (Schmidt et al., 1997; Schmidt and Kleinebudde, 1998; Fielden et al., 1992; Vervaet et al., 1994; Thoma and Ziegler, 1998; Sternowsky, 2007; Chen et al., 2008).

In both ring die press and rotary cylinder extruder the die cylinder rotates and has the form of a ring or a roller respectively (figure 1-3). In the ring die press (figure 1-3.I) the press roller is located inside the die ring and both roller and ring rotate in the same direction. The granulated mass is fed into the die cylinder and compressed to the outside.

In the rotary cylinder extruder the press roller is located outside the die roller and the material is fed into the space between the two rollers which rotate in opposite directions. The material is then extruded inside the die roller (figure 1-3.II).

The main advantage of roll extruders is like in the basket- type extruders the high throughput due to the high numbers of orifices available in the system. The low level of energy brought to the material mass is beneficial for shear sensitive substances which are damaged in screw extruders.

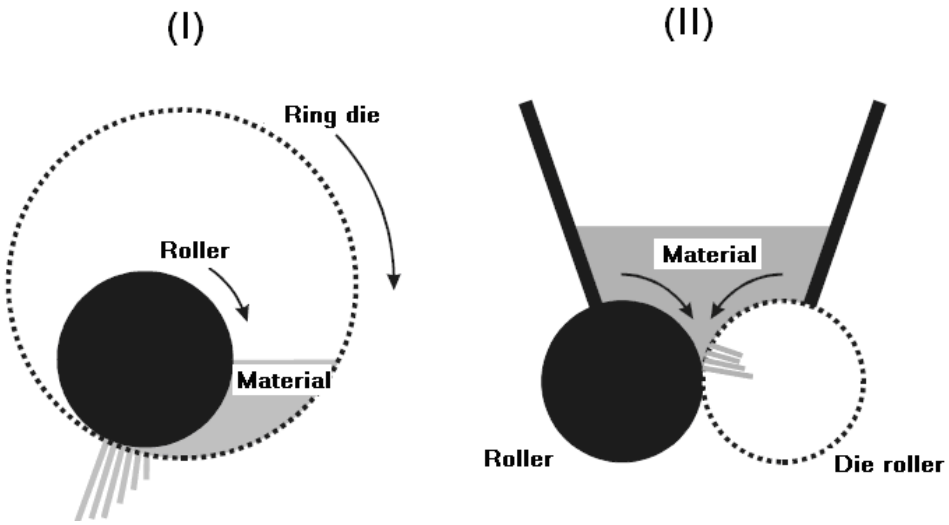


Figure 1-3: Schematic drawings of a (I) ring-die press (II) rotary cylinder extruder (according to Goebel, 2004).

Flat die presses fall in the category of roll extruders and are commonly used in the food, plastic, chemical and recycling industries for the compaction and pelletization of wood, fertilizers, feeding stuff, chemicals as well as the production of substitute refuse-derived fuel.

The operating principle of flat-die presses lies in forcing a bulk product through a flat die plate with orifices of defined diameter by means of a rotating roller. The resulting extrudates are then cut with a simultaneously rotating knife to the desired length.

Figure 1-4: A drawing of the a wood pelleting press (according to Amandus Kahl, 2008)

Flat die presses combine the advantages of low shearing and high throughput through the high numbers of dies (several thousands). The production capacity can be dramatically increased through the size and design of equipment and the use of several rollers. Wood pelleting presses (figure 1-4) with a range of capacities between 300 and 8000 kg/h are commercially available (Amandus Kahl, 2008).

Due to their high production capacities, reduced costs and limited place requirements flat die presses represent attractive alternatives for conventional extruders. Preliminary studies using specially designed plates with small die openings revealed the potential use of the flat die press 14-175 for preparing pharmaceutical extrudates (Chen et al., 2008; Mehraghdam, 2008). In this work the feasibility of using the mentioned flat die press for the preparation of small pharmaceutical pellets by wet extrusion/ spheronization was investigated.

1.2.2.3 κ-carrageenan as a pelletization aid

Microcrystalline cellulose MCC has been the most important pelletization excipient used to prepare pellets for pharmaceutical applications by the extrusion/spheronization technique (Ghebre-Sellassie, 1989; Dukic-Ott et al., 2009). The lack of disintegration (Kleinebudde, 1994) leading to a slow matrix-like drug release from MCC pellets (Zimm et al., 1996) as well as the absorption of some active pharmaceutical ingredients onto MCC fibres (Okada et al., 1987; Rivera and Ghodbane, 1994; Al-Nimry et al., 1997) emphasized the need for pelletization aids which can overcome these problems.

κ-carrageenan is a natural acidic polysaccharide taken from the cell walls of red seaweeds, particularly of the Gigartinales species. The linear backbone of κ-carrageenan is based on the repetition of disaccharide sequences of sulfate esters of β-1,3-linked galactose and α-1,4-linked 3,6- anhydrogalactose (figure 1-5).

Carrageenans are generally recognized as safe (GRAS) and are mainly used as thickening, suspending or gelling agents (Voragen, 2001) in food

applications (known as E407, a food additive) (Bundesministerium für Gesundheit, 2006).

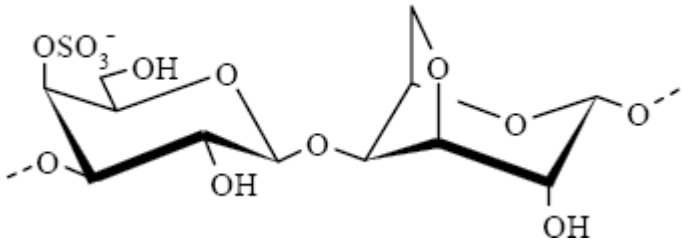


Figure 1-5: Ideal repeating dimer unit of κ-carrageenan.

κ-carrageenan forms gels through the development of double helices which associate to more complicated structures (Hänsel et al., 1999). The helical structure is generated and stabilized by conformation of polymer molecules through intermolecular hydrogen bounds (Stortz und Cerezo, 2003). The gels formed from κ-carrageenan exhibit a rheodestructive behavior as a result of the huge size of helices leading to low mobility of the chains.

κ-carrageenan has shown to be a promising alternative pelletization aid to microcrystalline cellulose. Recent studies indicate that pellets prepared using κ-carrageenan are of high quality (Bornhöft et al., 2005) and exhibit lower tensile strength, faster disintegration and faster drug release compared to MCC pellets (Thommes and Kleinebudde, 2006a). Moreover, the influence of drug solubility on its release profile from κ-carrageenan pellets is much less pronounced than that from MCC pellets. κ-carrageenan pellets also possess a considerably high formulation robustness allowing the use of a wide spectrum of fillers and active ingredients at largely variable fractions (Thommes and Kleinebudde, 2006b). Therefore κ-carrageenan seems to be particularly advantageous for the formulation of enteric coated pellets containing poorly water soluble drugs which, after leaving the stomach, release the active ingredient quickly in the small intestine.

The mechanism of pellet formation using κ-carrageenan is still not definitively determined. Preliminary investigations (Thommes, 2006) lead to the hypothesis that the associated helical structure plays the key role in the pelletization process. Due to their low mobility the helical entities are not lost during preparation and remain available in the powder product after drying of

the gels. A gel is formed again when the powder is wetted by absorption of water outside the helices. The hydrogen bonds between the helices impart firmness to the system but can be broken by shearing leading to a certain degree of plasticity.

The compression of κ-carrageenan powder has been the subject of a few studies (Picker, 1999; Schmidt et al., 2003). However, pellets show different consolidation and deformation mechanisms during tableting to those of powders, due to their significantly lower surface to volume ratio resulting in a smaller contact area between the particles upon compression. Different compaction properties and tensile strengths of tablets prepared from microcrystalline cellulose powder and pellets were reported (Maganti and Celik, 1993). Thus, further work should be done to assess the compression behavior and the properties of the tablets prepared from κ-carrageenan pellets.

1.3 Compression of pellets

1.3.1 Advantages of multiparticulate tablets

Pellets for oral use are generally presented in the form of capsules or tablets. The development of multiparticulate dosage formulations in the form of tablets is more cost-effective (Celik, 1994) due to the much higher production speed of the industrially available tableting machines compared to capsules filling machines and the absence of the of the costly control step of capsules integrity after filling. Multiparticulate tablets can be divisible (Beckert et al., 1996) thus allowing greater therapeutic flexibility in terms of the applied dose of a controlled drug delivery system, which is not achievable in the case of encapsulated pellets. Last but not least tablets show reduced liability to tampering compared to capsules (Abdul et al., 2010).

1.3.2 Challenges involved in the compression of pellets

The development of multiparticulate dosage formulations in the form of tablets is a challenging area. The main focus of such development is to obtain an unchanged or very slightly changed release profile after compression. Therefore breakage and/or severe damage of pellets under load should be avoided.

Compression of sole pellets results in severe deformation and some fragmentation (Maganti and Celik, 1993; Johansson et al., 1995, 1998; Johansson and Alderborn 1996; Nicklasson et al., 1999a,b), great damage to the coating layer (Maganti and Celik, 1994) and the formation of non-disintegrating tablets (Santos et al., 2004).

Compression of pellets with a cushioning filler (powder, granules or pellets) has been used to reduce the damage or the deformation degree of pellets and their coating as well as to prevent the formation of a retarding (non-disintegrating) matrix upon contact with water. However, de-mixing problems can also occur, leading to altered homogeneity of content of the resulting tablets. The careful choice of the cushioning filler in terms of particle size and density, the optimization of the pellet/cushioning filler ratio in the mixture (Beckert et al, 1998; Tirkkonen and Paronen, 1993; Wagner et al., 1999), the choice of tableting speed and the type of feeder used (Wagner et al., 2000) are important factors to ensure the desired homogeneity of content. The protective filler used should also possess a high binding ability due to the lower surface available for bonding in pellet-containing systems.

The protection of coating layer upon compression is also a key issue in the formulation of coated pellets into multiparticulate tablets. Although several studies approached the protective effect of type of cushioning filler on the compressed pellets, it has been established, that sufficient mechanical properties of the film and the compression speed rather than the type of protective bed are the most important elements for maintaining the integrity of coating upon compression (Lehmann et al., 1993; Torrado and Augsburger, 1994; Beckert et al., 1996; Wagner et al., 2000; Braun, 2003; Abdul, 2010).

1.3.3 Compression of uncoated pellets

The compression of microcrystalline cellulose pellets has been extensively investigated by the work group of Alderborn to derive information about the compression mechanisms of agglomerated substances and their contribution to the compact strength taking the spherical shape as simplification factor (Johansson and Alderborn, 1995, 1996, 2001; Johansson et al., 1995, 1998; Nicklasson and Alderborn 1999; Nicklasson et al. 1999 a,b). Although such

simplification may be constraining in terms of general conclusions on granulated material the work done by this group provides useful knowledge and assessment tools which are beneficial for the formulation of multiparticulate tablets in terms of studying the compression behavior of pellets and most precisely the extent of fragmentation occurring under the compression conditions.

Wickberg and Alderborn (1990) pointed out the deficiency of the conventional tablet volume reduction-compression pressure or porosity reduction-pressure relationships used normally to study the densification behavior of porous and non porous particles in providing a powerful and conclusive evaluation of the behavior of porous granules and pellets under load. Instead the Alderborn group used scanning electron microscopy to monitor the fracture surfaces of tablets after diametrical breaking as a powerful qualitative tool for the assessment of liability of pellets to fragment or deform under the compression conditions. Comparison of the size distribution, porosity and resistance to fracture of the uncompressed pellets with those retrieved after compression of lubricated pellets were also successfully used by the mentioned work group as a quantitative measure of deformation, fragmentation and the formation of significant flaws in the pellets upon compression. Other work groups used later the same methodology for other pellet formulations such as xanthan gum pellets (Santos et al., 2004).

In addition to the investigation of compression mechanism the studies performed in the field of the compression of uncoated pellets addressed the influence of pellet porosity, mechanical strength, size and the incorporation of other substances with different densification behavior on the mechanism, degree of deformation/fragmentation of pellets and the strength of resulting tablets.

Increased porosity of MCC pellets resulted in increased degree of deformation of the pellets leading to higher intergranular contact and resulting in higher strength of compacts prepared from sole pellets (Johansson et al., 1995; Johansson and Alderborn, 1996, 2001; Nicklasson et al. 1999 a,b).

The mechanical strength of the starting pellets was of secondary importance to their compression behavior and correlated to the degree of deformation through the parallel relationship for pellet porosity (Johansson et al., 1995).

More flattening of large-sized (1250-1400 μm) than small-sized (425-500 μm) MCC pellets was observed (Johansson et al., 1998) and was attributed to the fact that by increasing the pellet size less interparticulate contact points are available through which the stress applied to the pellet bed is transmitted. Consequently more stress is concentrated at these points rather than that in case of smaller pellets leading together with the larger spaces between the large-sized pellets to higher degree of deformation upon size increasing. The degree of densification of the individual pellets (indicated by the decrease of intragranular pellet porosity) did not differ between the two size fractions.

The incorporation of a brittle substance, dicalcium phosphate dihydrate (DCP), into MCC pellets at a ratio of (4:1) resulted in different mode of deformation from that of the original pellets towards a higher surface deformation of the pellets rather than bulk deformation but did not result in higher fragmentation (Nicklasson et al., 1999a). The higher surface deformation was attributed to the rigid nature of DCP leading to higher stress needed to cause deformation by flow of primary particles in the pellets. Increased deformation propensity in general and more readiness to local deformation of the pellets was also observed upon incorporation of polyethylene glycol as a ductile material into MCC pellets (Nicklasson and Alderborn, 1999).

However all mentioned factors showed no influence on the general compression mechanism of pellets and in all cases the fragmentation of pellets was limited and their deformation was the dominating mode of compression in addition to a certain degree of densification (contraction indicated by a decrease of the intragranular porosity) for both MCC and xanthan gum pellets. Changes in the mode or degree of deformation, induced by changes of porosity or size or by the incorporation of other substances in the pellet formulation, are important for the strength of compacts made of sole pellets but have lower relevance when pellets are cushioned by an embedding mixture to form a multiparticulate system.

1.3.4 Compression of coated pellets

1.3.4.1 Compression of enteric coated pellets

The formulation of enteric coated pellets into multiparticulate tablets is quite problematic since most available enteric polymers dissolving at a pH lower than 7 are brittle in nature (Lehmann, 1997).

The elongation at break (elongation recorded at the moment of rupture of a film of defined thickness and subjected to defined stress conditions, often expressed as a percentage of the original film length) of films made of these polymers is enhanced upon the addition of plasticizers (figure 1-6) but only to an extent, which is sufficient for coated pellets intended for encapsulation but still insufficient for those intended for compression. Lehmann et al. (1993) reported a minimum elongation at break value of 75% of the coating film to maintain the release properties of the pellets after compression. Ruptures of the coating layer leading to loss of enteric properties (defined as less than 10% drug release after 2 h in hydrochloric acid 0.1 N pH= 1 and more than 80% after 45 min in phosphate buffer pH = 6.8, USP 32 NF 27, 2009a) upon compression of pellets coated with methacrylic acid-ethyl acrylate copolymer (commercially available as Eudragit® L or Kollicoat® MAE) was reported by many authors (Beckert et al., 1996; Schmid and Picker-Freyer, 2009; Dreu et al., 2010).

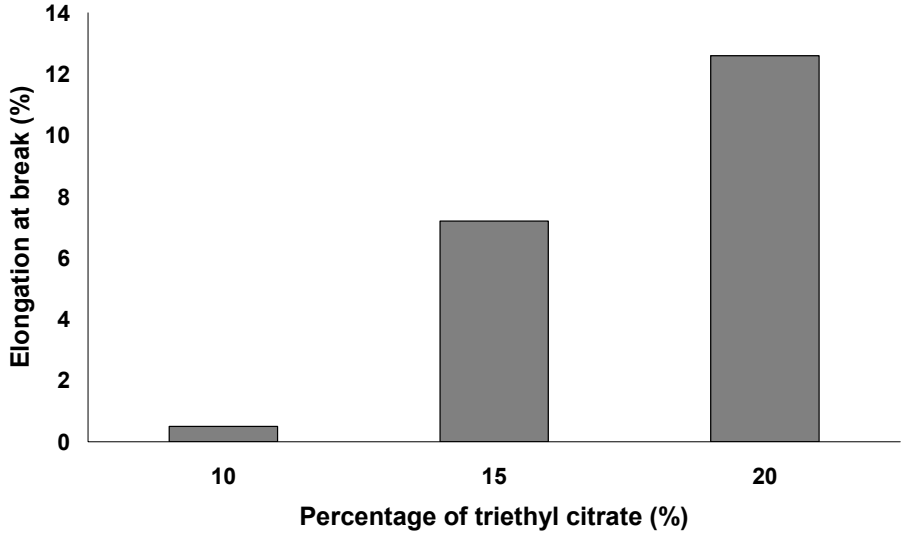


Figure 1-6: Elongation at break of Kollicoat® MAE (methacrylic acid- ethyl acrylate copolymer) as a function of the concentration of the plasticizer triethyl citrate (according to Bühler, 2007).

The elongation at break of enteric polymers is often enhanced by the addition of other polymers with higher elongation at break to the coating formulation so that the resulting films are able to withstand the compression pressures and give multiparticulate tablets with sufficient enteric properties i.e. less than 10% drug release after 2 h in the acidic medium (pH=1) and more than 80% after 45 min in phosphate buffer pH = 6.8 (USP 32 NF 27, 2009a).

Several studies suggested the use of Eudragit® FS, an anionic copolymer based on methyl acrylate, methyl methacrylate and methacrylic acid, which has an elongation at break of 300% (Lehmann, 1997) and dissolves at a pH above 7 in order to enhance the properties of coating formulations including the widely used enteric methacrylic acid-ethyl acrylate copolymer (commercially available as Eudragit® L or Kollicoat® MAE) which dissolves at pH= 5.5. Debunne et al. (2002) reported less than 1% release after 2 hours in HCl 0.1 N of piroxicam from multiparticulate tablets containing drug pellets prepared by extrusion/spheronization and coated with a 6:4 mixture of Eudragit® L and Eudragit® FS plasticized with 20% triethyl citrate and compressed with soft placebo wax beads as cushioning agents and 10% crospovidone as disintegrant (percentage of pellets in the tablet 40%). However the crushing strength of the tablets was low due to the poor bonding ability of the wax pellets. On the other hand Dreu et al. (2010) mentioned a high release of 9 ±1.76 % of the model substance tartarazine from tablets prepared from layered sugar pellets coated with a 6:4 mixture of the Eudragit® L and Eudragit® FS plasticized with 17.8% triethyl citrate (percentage weight gain 25%), overcoated with a protective film of Kollidon® VA 64 (vinylpyrrolidone-vinyl acetate copolymer) and Pharmacoat® 606 (hydroxypropyl methyl cellulose) at 25% percentage weight gain and compressed with Avicel® PH 101 (MCC PH 101) and Kollidon® VA 64 as embedding mixture (percentage of pellets in the tablet 40%).

The enteric properties of pellets coated with methacrylic acid-ethyl acrylate copolymer (Eudragit® L, Kollicoat® MAE) are better maintained after compression upon the addition of ethyl acrylate-methyl methacrylate copolymer (commercially available as Kollicoat® EMM or Eudragit® NE, elongation at break of about 600%, Lehmann, 1997), used normally for

prolongation of drug release, to the coating formulation (Lehmann, 1993; Beckert et al., 1996; Dashevsky et al., 2004). The mentioned polymer seems therefore more efficient than Eudragit® FS in providing sufficient resistance in the acidic medium for compressed pellets. The ratio of the two polymers in the mixture and the coating level should be carefully adjusted to avoid retardation of drug release in the neutral medium (Beckert et al., 1996).

1.3.4.2 Compression of pellets with sustained release coating

The formulation of pellets coated with a release sustaining film into multiparticulate tablets is less problematic than those with enteric coating. The elongation at break of most polymeric films intended for release prolongation can be dramatically increased by the addition of plasticizers and no additional polymers are required when the pellets are intended for compression. However, careful choice of the release modifying polymer is needed.

Cellulose based polymers such as ethyl cellulose (Surelease®, Aquacoat®) are very brittle even in the presence of high amounts of plasticizer and fail in withstanding the compression process leading to much accelerated drug release from the multiparticulate tablet compared to the coated pellets regardless of the type of embedding powder used (Bansal et al., 1993; Torrado and Augsburger, 1994; Dashevsky et al.; 2004).

Acrylic polymers intended for extended release result in films with higher elongation at break upon plasticization and are better suited for the formulation of multiparticulate tablets with coated pellets (Bodmeier and Paeratakul, 1994). Pellets coated with plasticized Eudragit® RS/RL or with the highly flexible Eudragit® NE could be successfully formulated into multiparticulate tablets with maintained extended release properties (Lehmann et al., 1993; Lehmann, 1997).

Polyvinyl acetate polymers (Kollicoat® SR) plasticized with 10% triethyl citrate have also shown to be beneficial as coating agent for pellets or granules intended for compression with unchanged release profile of the tablets compared to the coated pellets (Dashevsky et al., 2004; Sawicki and Lunio, 2005; Fini et al., 2008; Zeeshan and Bukhari, 2010).

1.3.5 Compression of pellets in an embedding filler

Compression of pellets in embedding filler helps protecting them from severe deformation and prevents the formation of a non-disintegration matrix tablet upon contact with water. The embedding filler should possess a high deformability to absorb the stress applied during compression and an excellent ability to form homogenous mixtures with the pellets in order to ensure the uniformity of content of the prepared tablets (Bodmeier, 1997). It should also exhibit a high dilution potential (carrying capacity) leading to a high amount of pellets in the tablet and small tablet size while maintaining sufficient mechanical properties. Most importantly the cushioning bed should ensure fast disintegration of the tablet into pellets after administration.

Different approaches were mentioned in the literature to cushion the pellets and to reduce the damages occurring during compression and most particularly to the film layer in the case where coated pellets were to be compressed. However, not all approaches were completely successful in terms of fulfilling the entire requirements for a multiparticulate system, namely, in addition to the protection of film from compression-induced damages, a disintegrating tablet with sufficient mechanical strength.

α-lactose monohydrate granules, microcrystalline cellulose pellets and different types of wax/starch beads were compared by Vergote et al. (2002) as cushioning agents during the compression of Diltiazem pellets coated with Eudragit® NE 30D known as a flexible release sustaining polymer (Lehmann et al., 1993, Lehman, 1997, El-Mahdi and Deasy, 2000). Both α-lactose monohydrate granules and microcrystalline cellulose pellets failed to protect the film layer upon compression. Vergote explained these finding by the fragmentation behavior of the former and the hard and dense nature of the latter reported by Maganti and Celik (1994) which could be improved in the mentioned study (Vergote et al., 2002) by incorporation of PEG 4000 as a ductile material but remained insufficient to maintain the dissolution behavior of the uncompressed pellets. Only wax beads cushioned the coating layer against damage. However tablets made using waxy maltodextrin/paraffinic wax placebo beads did not disintegrate (tablet core remained intact after 8 hours in the dissolution apparatus) resulting in slower drug release compared

to the original coated pellets and so did not maintain the multiparticulate function of the system. In the same study (Vergote et al., 2002), beads containing drum dried corn starch/Explotab® (sodium starch glycolate) /paraffinic wax at a percentage of 50% were suggested to provide disintegrating tablets with sufficient protection for the film upon compression. However, the tablets prepared using the latter type of beads had a disintegration time of 32 min when tested in a disintegration apparatus according to the USP 24 and 1 h upon visual inspection in the dissolution apparatus. Furthermore the mechanical resistance of the pellets was too low. Decreasing the percentage of these beads to 40% resulted in damages of the coating layer and faster drug release whereas increasing their percentage to 60% resulted in reduced dissolution rate compared to the original pellets since the higher content of wax lowered the wettability of the formulation.

Debunne et al. (2002) also used placebo wax pellets consisting of Paracera® P (microcrystalline wax)/drum dried corn starch/ Kollidon® CL (crospovidone) as cushioning agents for pellets prepared by extrusion/spheronization and containing MCC as a pelletization aid and piroxicam and coated with a mixture of Eudragit L® and Eudragit® FS (6:4). At a mixture of drug pellets/ cushioning pellets of 60: 40 the tablet maintained their enteric properties but did not disintegrate during the entire dissolution test. In the same study the addition of sodium croscarmellose and sodium carboxy methyl starch to the tablet formulation did not result in enhancement of tablet disintegration. Only by adding 7.5% or 10% Kollidon® CL as powder the disintegration time of the tablets was below 15 min and hence a multiparticulate behavior could be obtained. However, the obtained tablets exhibited again low mechanical strength.

In addition to all mentioned constraints and formulation issues associated with wax beads it should also be mentioned that the complexity of preparing such cushioning beads makes this approach unattractive.

A much simpler approach is to embed the pellets in a cushioning powder so that, in addition to the protection of release controlling membrane against severe damages, sufficient mechanical strength along with acceptable disintegration properties could be obtained. Torrado and Ausburger (1994)

correlated the damages to film layer caused by different powder excipients with their yield pressure upon examination of theophylline pellets coated with Eudragit® RS and reported the following order in terms of substances with the least damages to the film coating: polyethylene glycol < microcrystalline cellulose < crospovidone < lactose < dicalcium phosphate. At a low yield pressure of the embedding matrix high amount of the energy involved in the compression is absorbed by the matrix, which deforms itself thus protecting the embedded pellets and their coating. Moreover, high deformability of the matrix also results in strong tablets at low compression pressure and therefore there is no need to subject the pellets to high loads.

Schmid and Picker-Freyer (2009) investigated the potential use of alginate as a filler for soft tableting and reported a better level of protection for bisacodyl pellets coated with Eudragit® L as a pressure sensitive model pellets upon the use of excipients with high elasticity compared with some highly plastic excipients. However before the release studies the tablets made with alginate were cleaved in order to separate the pellets from the matrix and to exclude the retarding matrix effect caused by the alginate which makes this approach unrealistic.

Beckert et al. (1998) studied the effect of the particle size of embedding powder and pellet percentage in the tablet on the uniformity of content. Percolation of both components was found to be necessary for uniform content of the multiparticulate tablets as long as the filler has a sufficient particle size so that it does not slip through the percolating cluster of pellets.

1.3.6 High density silicified microcrystalline cellulose SMCC HD 90

High density silicified microcrystalline cellulose SMCC HD 90 is obtained by co-drying a suspension of high density microcrystalline cellulose MCC type 302 and colloidal silicon dioxide (Aerosil® 200). The dried co-processed substance contains 2% colloidal silicone dioxide. Upon silicification silicone dioxide adheres on the surface of MCC particles hence the particle size distribution, polymorphic properties, and the porosity remain unchanged but a rougher surface is obtained due to the large specific surface of silicon dioxide (Tobyn et al., 1998).

Enhanced flowability, better lubricity and higher compactibility upon silicification of MCC were reported by Hwang and Peck (2001). Increased compactibility upon silicification of MCC was attributed to the larger surface area available for bounding and the inter-surface interaction of SiO_2 with MCC.

SMCC HD posses a much higher ductility and 60% more toughness than MCC HD (high density microcrystalline cellulose type 302) hence exhibiting a much higher binding ability. The higher binding capability results in strong compacts at low compression force and high dilution potential (carrying capacity) and consequently reduced size and weight of the tablets which enhance patient compliance. Both mentioned advantages are of vital importance when compressing tablets containing pellets. First, the presence of pellets in the tablet significantly reduces the binding forces due to the low surface to volume ratio. Therefore a binder which results in strong tablets in the presence of high amount of pellets and preferably at low compression force to reduce the stress applied to the pellets is desirable. Second due to the issues related to the disintegration of multiparticulate tablets, protection of coating layer and uniformity of content the embedding powder should be available at a considerable amount in the tablet and hence an excipient which results in small tablets is beneficial.

In addition to its high tensile strength SMCC HD 90 exhibit also short disintegration times. Tablets made of unlubricated and lubricated sole SMCC HD 90 and those containing 50% acetyl salicylic or ascorbic acid as ductile and brittle active ingredients respectively and compressed at low compression forces (3-4 kN) had a high tensile strength and disintegrated within 1 min (Muzikova and Novakova, 2007).

2 Aim of the work

The two main goals of this work were to investigate the potential use of a flat die press for the production of pharmaceutical pellets by extrusion/spheronization and the feasibility of formulating coated and uncoated κ-carrageenan pellets into multiparticulate tablets with sufficient mechanical properties, fast disintegration and almost unchanged release properties. A systematic approach was used in the investigation as indicated by the specific objectives of the thesis, which can be summarized as following:

- Examination of the suitability of the flat-die press 14-175 for the preparation of small pharmaceutical pellets in the range between 400-1000 µm by extrusion/spheronization with acceptable sphericity and hence suitability for subsequent coating and compression.
- Gain of knowledge about the general compression mechanisms of κ-carrageenan pellets through the use of a model containing various active ingredients and fillers with different compression behaviors (plastic or brittle) and determination of the extent and relevance of undesirable fragmentation occurring during compression.
- Investigation of the suitability of high density silicified microcrystalline cellulose as a protective embedding powder for κ-carrageenan pellets and examination of the effect of percentage of pellets and the compression process parameters on the properties of the resulting tablets in terms of mechanical strength, friability and disintegration time along with the homogeneity of drug content.
- Exploration of the potential formulation of κ-carrageenan pellets into multiparticulate tablets with enteric release properties and the influence of various parameters (coating level, compression pressure and punch configurations) on the drug release from the resulting tablets.
- Investigation of the suitability of formulating κ-carrageenan pellets as multiparticulate tablets with sustained release and the effect of film properties and compression pressure on drug release.

3 Results and discussion

3.1 Production of pellets using the flat die press 14-175

3.1.1 Objective

Flat die presses represent an attractive choice for pharmaceutical purposes due to their large production capacities and low costs. The potential use of a flat die press (Pelleting Press 14-175, Amandus Kahl, Reinbek, Germany) for the production of pharmaceutical extrudates was established (Chen et al., 2008; Mehraghdam, 2008). As a further step the feasibility of using the mentioned flat die press for the preparation of small pharmaceutical pellets (400-1000 µm), suitable for subsequent coating and tableting, by means of wet extrusion/spheronization was investigated in the current work.

3.1.2 The flat die press 14-175

3.1.2.1 Description

The flat die press 14-175 (figure 3-1) is a laboratory pelleting press equipment for small production scale and research purposes. It consists of a feeding system (F), a processing area (P), a gearbox (G) and a control unit (C).

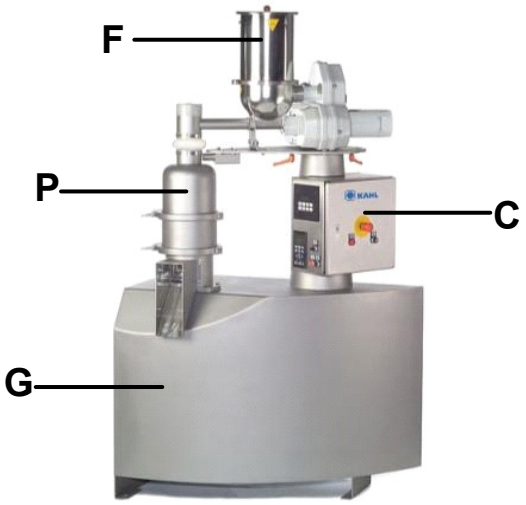


Figure 3-1: The flat die press 14-175: (F) feeding system, (P) processing area, (G) gearbox and (C) control unit (according to Amandus Kahl, 2005).

The feeding system is illustrated in figure 3-2 and consists of a reservoir tank (RT) from which the previously wetted mass is transferred to two feeding screws (FS). The reservoir tank contains a stirrer (ST) in order to avoid product bridging. The feeding screws and the stirrer are driven by the same

motor (M) and rotate simultaneously. The bulk material is fed volumetrically into the processing area.

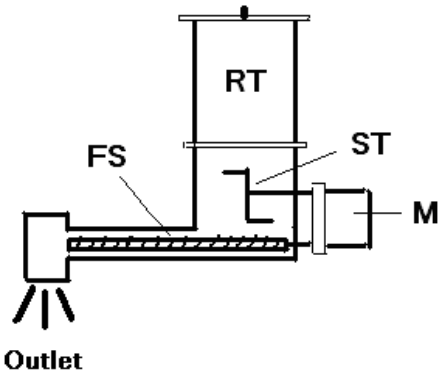


Figure 3-2: Schematic drawing of the feeding system of the flat die press 14-175: (RT) reservoir tank, (FS) feeding screws, (ST) stirrer, (M) motor (according to Chen, 2008)

The processing area (figure 3-3) includes two rollers (R) with a diameter of 130 mm and breadth of 29 mm and a die plate (DP) of a 175 mm diameter. The two rollers are fixed to the two sides of a roller head (H). The surface of the rollers is ribbed in order to avoid slippage and to ensure a proper material uptake. The roller head sits on an axis and is fixed to it using fitted keys. The roller head is driven by the axis thus inducing the rotation of the rollers over the die plate. The rollers can freely rotate. Two scrapers (S) are mounted on the roller head.

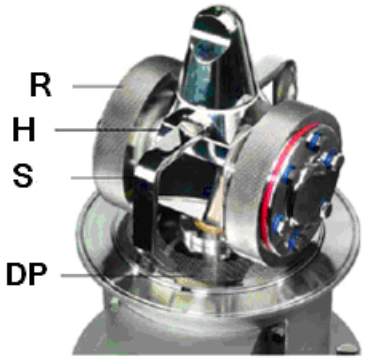


Figure 3-3: Processing area of the flat die press 14-175: (R) roller, (H) roller head, (S) scraper, (DP) die plate (according to Amandus Kahl, 2005).

The die plate is fixed to the casing and is located under the rollers. The die plates (figure 3-4.I) are made of a non-corrosive hard material to withstand the pressure and friction during processing. The die plate is changeable and

consists of a flat disk with a high number of dies (up to 9818 for a plate with 0.4 mm die diameter each).

The dies for all plates are cylindrical with a conical inlet. The outlets can be tiered to achieve the desired path length while maintaining a sufficient plate thickness to withstand work conditions (figure 3-4.II). The breadth of the die strip is 29 mm and corresponds to the breadth of the rollers.

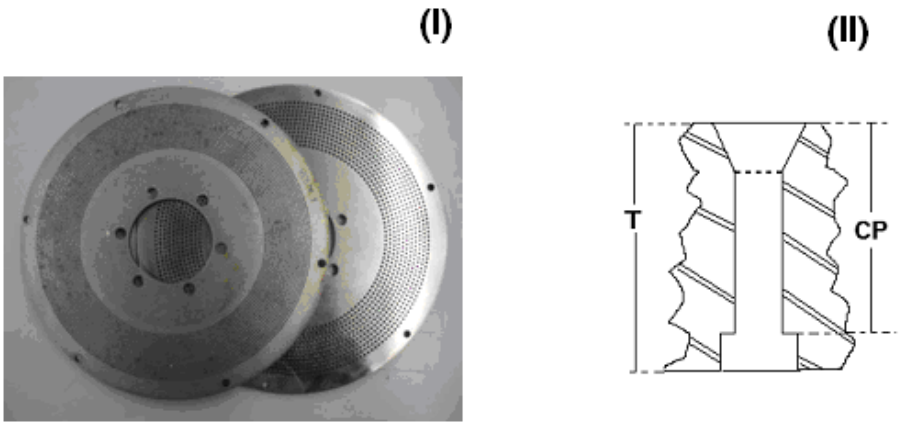


Figure 3-4: (I) Examples of the die plates supplied with the flat-die press 14-175 and (II) schematic drawing of a compression channel: (T) thickness of the plate and (CP) compression path (according to Chen, 2008).

The control unit consists of two control windows: One controls the feeding system allowing the variation of the rotational speed of the feeding screws. The other one controls the speed of the axle in the processing area and consequently that of roller and the knife.

3.1.2.2 Working principle

The bulk product is delivered from the feeding system through the discharge pipe to the processing area whereby a material layer is built. The rollers roll over the material layer compressing it and forcing it into the channels leading to the formation of strands. The formed extrudates are then cut upon leaving the lower side of the die plate to the desired length using a knife with adjustable distance to the plate through the addition of metal rings with different thicknesses. The distance between the rollers and the die plate is also adjustable. Larger space between the two compression elements (roller and die plate) leads to thicker product layer and hence higher pre-compression before passing through the dies.

The extrudates fall down onto a rotating dish and are driven by a centrifugal force to the outlet of the die press.

The mechanism of extrusion in the die press is illustrated in figure 3-5. After a material layer is built on the die plate the ribbed roller surface allows the entry of the material under the roller leading to a pre-compression followed by forcing the material into the dies where it is subjected to a friction force from the die walls. The process is continued until the compression force through the die becomes higher than the friction force and a strand is formed (Sternowsky, 2007). The friction force depends on the roughness of the dies, the friction coefficient between the plate and the compressed material, the side pressure working against the expansion of the extrudates and the surface area of the die.

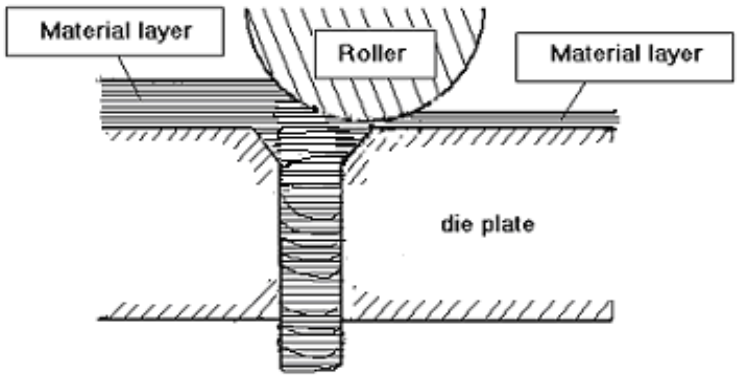


Figure 3-5: Schematic illustration of the extrusion process in the flat die press (according to Chen, 2008).

The extrusion process in the flat die press can be influenced by a number of factors such as the properties of the material subject to extrusion, the moisture content of the worked mass, the feeding rate, the distance between the rollers and the die plate, the distance between the rollers and knife, the length of the extrusion channels, the diameter of the dies, the metal type, the processing of the rollers and the die plate and the friction value of the press channel walls (Chen, 2008; Mehraghdam, 2008). In the current study the process parameters were kept constant and the versatility and formulation robustness of the flat die press were investigated.

3.1.3 Model and choice of formulations

Four pellet formulations with high drug strength (table 3-1) and twelve pellet formulations with low drug strength (table 3-2) were prepared by extrusion/spheronization using the flat die press 14-175 equipped with the die plate with dies of 0.6 mm diameter and 3:1 length to diameter ratio.

The studied formulations were chosen to cover a wide spectrum of different model drugs and excipients with different water solubility in order to assess the formulation robustness of the studied flat die press. Additionally, the formulation with 80% hydrochlorothiazide was produced in triplicate in order to examine batch conformity regarding the release properties.

The prepared pellets were assessed in terms of yield, size, size distribution, shape, mechanical resistance and drug release.

Table 3-1: Pellet formulations with high drug strength and amount of water used for extrusion/ spheronization based on the weight of solids.

	The	Par	Hyd	Hyd-b	Hyd-c	Fur
Theophylline (%)	**80**					
Paracetamol (%)		**80**				
Hydrochlorothiazide (%)			**80**	**80**	**80**	
Furosemide (%)						**80**
κ-Carrageenan (%)	**20**	**20**	**20**	**20**	**20**	**20**
Deionized water (%)	**52**	**50**	**52**	**52**	**52**	**54**

Table 3-2: Pellet formulations with low drug strength and amount of water used for extrusion/spheronization based on the weight of solids.

	TheLac	TheMan	TheCal	TheSta	HydLac	HydMan	HydCal	HydSta	FurLac	FurMan	FurCal	FurSta
Theophylline (%)	**10**	**10**	**10**	**10**								
Hydrochlorothiazide (%)					**10**	**10**	**10**	**10**				
Furosemide (%)									**10**	**10**	**10**	**10**
α-Lactose monohydrate (%)	**70**				**70**				**70**			
Mannitol (%)		**70**				**70**				**70**		
DCP dihydrate (%)			**70**				**70**				**70**	
Starch (%)				**70**				**70**				**70**
κ-Carrageenan (%)	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Deionized water (%)	**46**	**43**	**56**	**89**	**46**	**44**	**56**	**90**	**48**	**45**	**58**	**92**

3.1.4 Amount of water needed for extrusion/spheronization

Pellets were successfully obtained with all tested formulations at high and low drug strength. The amount of water needed for extrusion varied between the

different formulations and was as expected higher for the formulations containing poorly soluble ingredients (tables 3-1 and 3-2). Thus, high dose formulations containing the poorly soluble drugs hydrochlorothiazide and furosemide required a higher amount of water than that needed for the formulation with the more soluble paracetamol. The same applied for the formulations with low drug strength with less amount of water required for the extrusion of formulations containing lactose and mannitol as soluble fillers in comparison to those containing the insoluble DCP. Higher amount of water required for the extrusion of poorly soluble ingredients was reported by Baert et al. (1991) and was explained by the fact that soluble components dissolve in the liquid phase leading to an increased liquid/solid ratio and hence reduced amount of water needed to achieve the same degree of plasticity needed for extrusion.

The formulations prepared with starch as a filling agent required a considerably higher amount of water than all the other studied formulations due to the higher water binding ability of starch by swelling.

The extrusion time was less than 10 minutes for all formulations (batch size 500 g) which was expected due to the high number of extrusion channels in the die plate used (5049 dies). The throughput range varied hence in the range (3- 4 kg/h).

3.1.5 Characterization of the prepared pellet formulations

3.1.5.1 Yield of the pelletization process

All pellet formulations showed a high yield of the pelletization process (table 3-3). The yield varied in the range 86.5- 97%.

3.1.5.2 Size and size distribution

The median equivalent diameter was between 580-730 µm (figure 3-6) and a narrow size distribution was obtained for all prepared pellet formulations as indicated by the values of 10% interval of the dimensionless equivalent diameter exceeding 50 % (Thommes und Kleinebudde, 2006a) (table 3-3). Narrow pellet size distribution leads to a defined specific surface area, which is of vital importance for a reproducible dissolution pattern of the formulated active ingredients after coating (Kleinebudde, 1997).

Table 3-3: Yield of the pelletization process (size fraction between 400-1000 µm), mean and median Feret diameter, mean and median roundness factor and 10% interval of the dimensionless diameter for the prepared pellets formulations (n=500).

Formulation	Yield (%)	Feret diameter			Roundness factor		10% Interval (%)
		Mean (µm)	C.V.* (%)	Median (µm)	Mean	Median	
The	96.3	670	11.1	677	0.86	0.86	64.2
Par	97.3	702	10.8	704	0.86	0.87	60.8
Hyd	89.9	701	9.8	707	0.85	0.85	68.4
Fur	97.0	682	12.8	677	0.82	0.83	57.8
TheLac	93.2	692	10.3	695	0.86	0.86	65.4
TheMan	92.4	705	11.1	706	0.86	0.86	66.6
TheCal	95.8	638	10.6	637	0.85	0.85	65.2
TheSta	92.6	630	10.6	628	0.88	0.88	65.8
HydLac	86.5	717	9.8	719	0.85	0.85	68.8
HydMan	90.5	703	12.2	703	0.85	0.85	60.2
HydCal	87.0	648	9.9	652	0.85	0.85	70.6
HydSta	91.1	616	11.4	612	0.87	0.87	62.4
FurLac	95.5	732	10.1	734	0.85	0.85	64.0
FurMan	92.9	753	10.7	750	0.84	0.85	66.2
FurCal	97.0	674	11.8	680	0.84	0.84	63.0
FurSta	94.0	596	11.7	598	0.86	0.86	60.8

*Coefficient of variation.

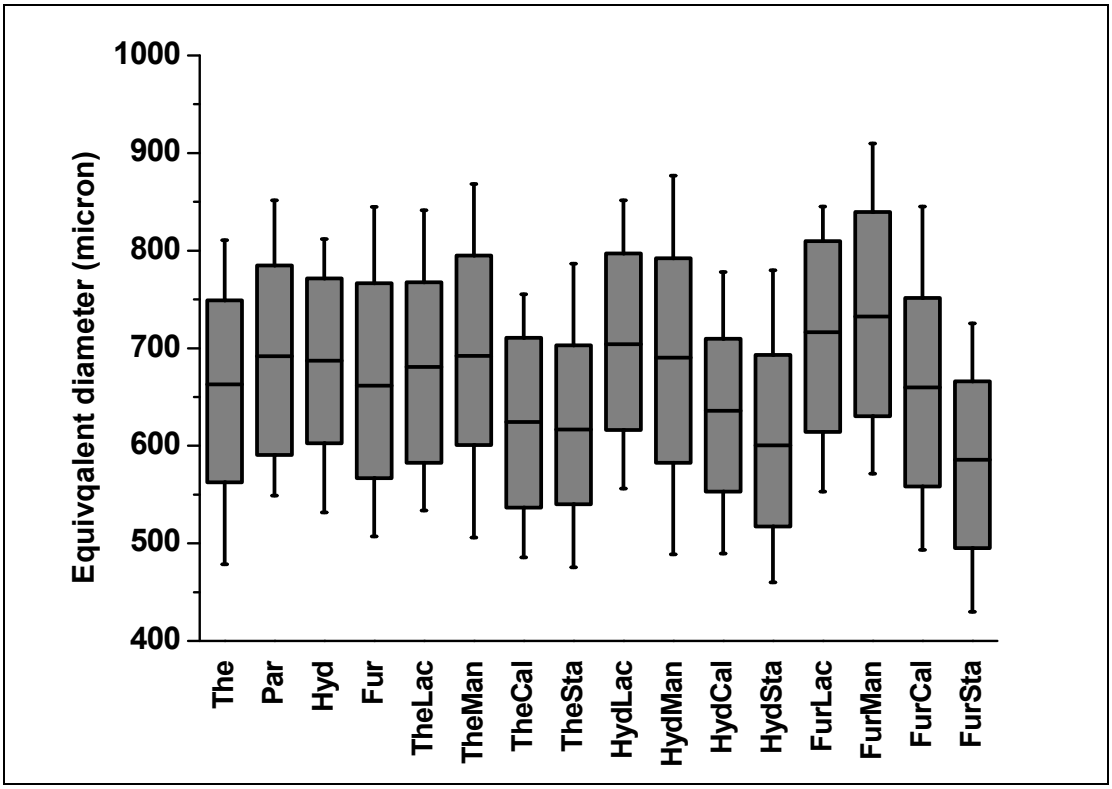


Figure 3-6: Equivalent diameter of the prepared pellet formulations (x_1, x_{10}, x_{50}, x_{90}, x_{99}, n=500).

3.1.5.3 Shape

The pellets were spheronized at a high spheronization speed (1500 rpm) for six minutes. Preliminary experiments with lower spheronization speeds resulted in dumbbell-shaped pellets. This may be explained as suggested by Thommes and Kleinebudde (2007a) by the fact that the extrusion through a high number of holes results in reduced speed of the extrudates through the dies and hence low shearing of the extruded mass. This leads in the case of using κ-carrageenan as pelletization aid to decreased plasticity of the produced extrudates since the water binding capacity of κ-carrageenan remains high at low shearing (rheo-destruction of κ-carraggenan gels being mentioned by Hänsel et al., 1999). Consequently less water is lost to the surface of the extrudates leading to reduced plastic deformability upon spheronization. Therefore higher level of energy is needed to ensure sufficient plastic deformation throughout the spheronization process.

Good sphericity of the pellets is a key factor for a successful subsequent coating and reduced amount of film forming agent needed to achieve a desired functionality (Kleinebudde, 1997). Several shape factors can be obtained from image analysis and used to assess the shape of pellets with both roundness factor and aspect ratio as the most powerful distinguishing tools (Hellen und Yliruusi, 1993). A roundness factor of 1 means a perfect round shape. The roundness factor of the prepared pellets varied in the range 0.83-0.87 (table 3-3). The aspect ratio is a simple parameter commonly used to evaluate the shape of pellets obtained by extrusion/spheronization (Bouwman et al., 2004). Generally pellets with a mean aspect ratio of less than 1.1 are classified as pellets with good sphericity whereas those with a mean aspect ratio higher than 1.2 are considered of poor sphericity (Kleinebudde 1995).

The pellets prepared in this study were of acceptable sphericity as expressed by the values of median aspect ratio lying around 1.1 except for those prepared with 80% furosemide (figure 3-7). The high aspect ratio of the latter could be probably attributed to the small sized needle-shaped active ingredient (figure 3-8). Small needles can interlock during processing resulting

in a decreased plasticity of the extrudates subject to spheronization (Thommes and Kleinebudde, 2006b).

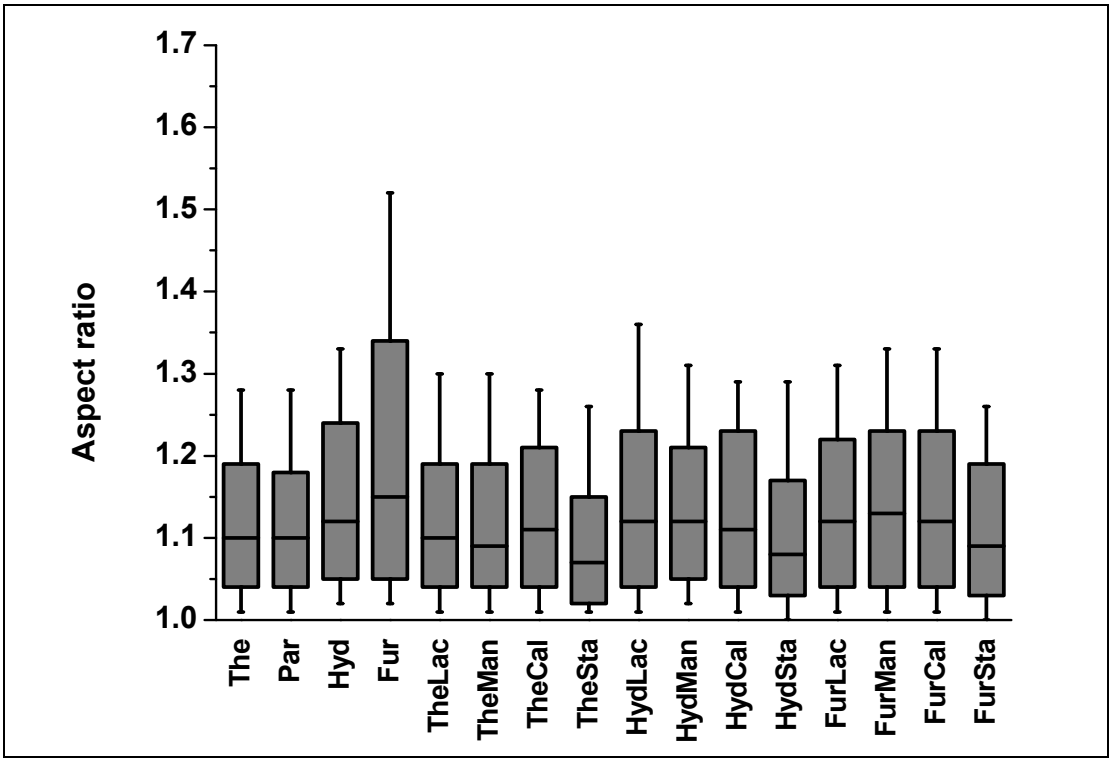
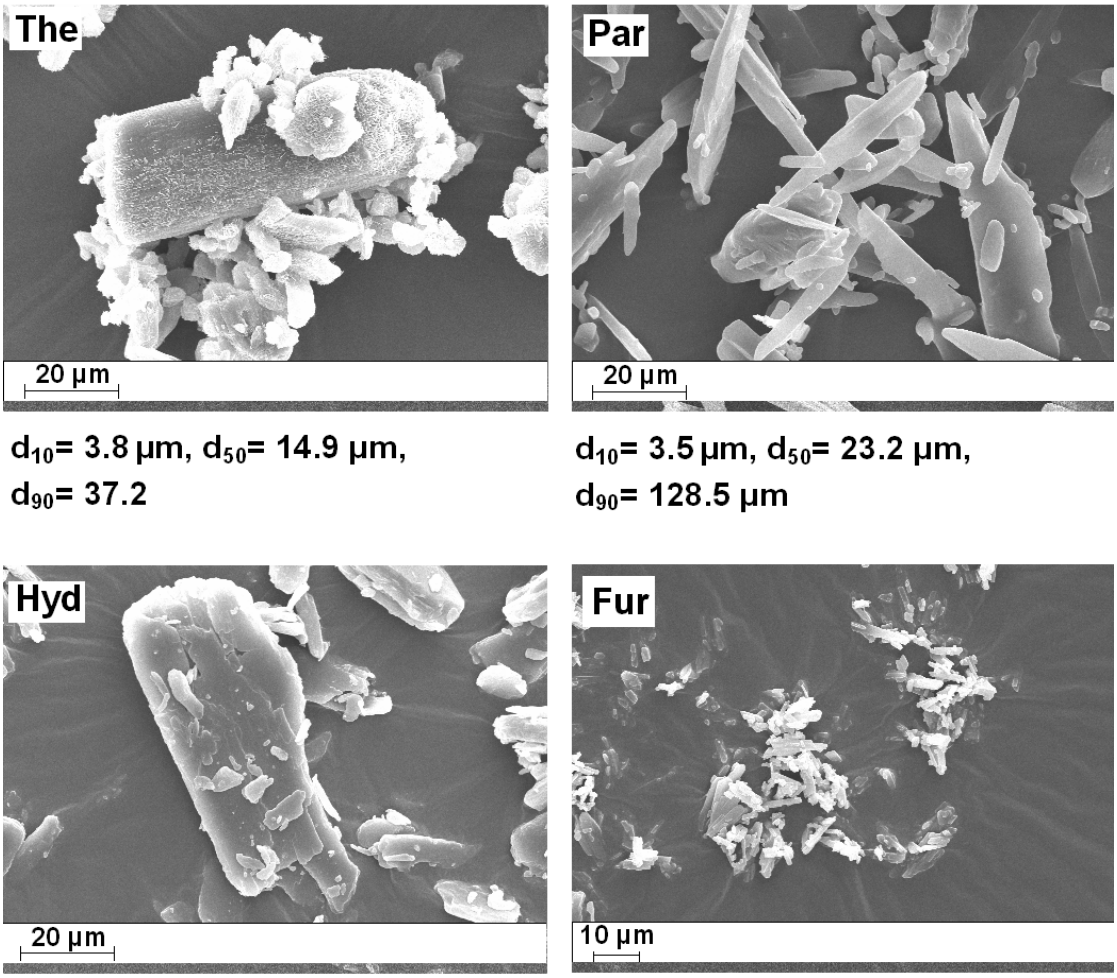


Figure 3-7: Aspect ratio of the prepared pellet formulations (x_1, x_{10}, x_{50}, x_{90}, x_{99}, n=500).

The pellets prepared with low drug loading of furosemide had markedly lower aspect ratio. Lower aspect ratio values of the high strength furosemide pellets could be probably expected upon using higher amounts of the pelletization aid or by milling of the active ingredient. The negative effect of the needle-shaped active ingredient was not observed in case of the large needle-shaped particles of paracetamol. The formulation with high dose of paracetamol possessed a good sphericity with a median aspect ratio of 1.1. It seems therefore that a significant particle interlocking is more likely associated with small needles rather than large ones.

The pellets produced with starch as filler showed particularly lower aspect ratio compared to the other formulations. This might be attributed to the higher water binding capacity of starch through swelling leading to higher plasticity of extruded mass und hence facilitated deformation during subsequent spheronization.



d_{10}= 3.8 µm, d_{50}= 14.9 µm, d_{90}= 37.2

d_{10}= 3.5 µm, d_{50}= 23.2 µm, d_{90}= 128.5 µm

d_{10}= 4.9 µm, d_{50}= 19.1 µm, d_{90}= 54.6 µm

d_{10}= 0.9 µm, d_{50}= 2.8 µm, d_{90}= 7.1 µm

Figure 3-8: Scanning electron micrographs and particle size of the active ingredients: (The) theophylline, (Par): paracetamol, (Hyd) hydrochlorothiazide and (Fur) furosemide.

3.1.5.4 Mechanical resistance

Sufficient mechanical strength of pellets is necessary for any further handling such as filling into capsules or coating processes as well as to avoid any loss during storage or transportation. The prepared pellets showed sufficient mechanical strength (figure 3-9). The type of filler used in the pellets with low drug strength had an influence on their mechanical resistance. The pellets containing the highly brittle DCP possessed a higher tensile strength compared to those containing lactose or mannitol. The same observation was made for the pellet prepared with starch as a filling agent.

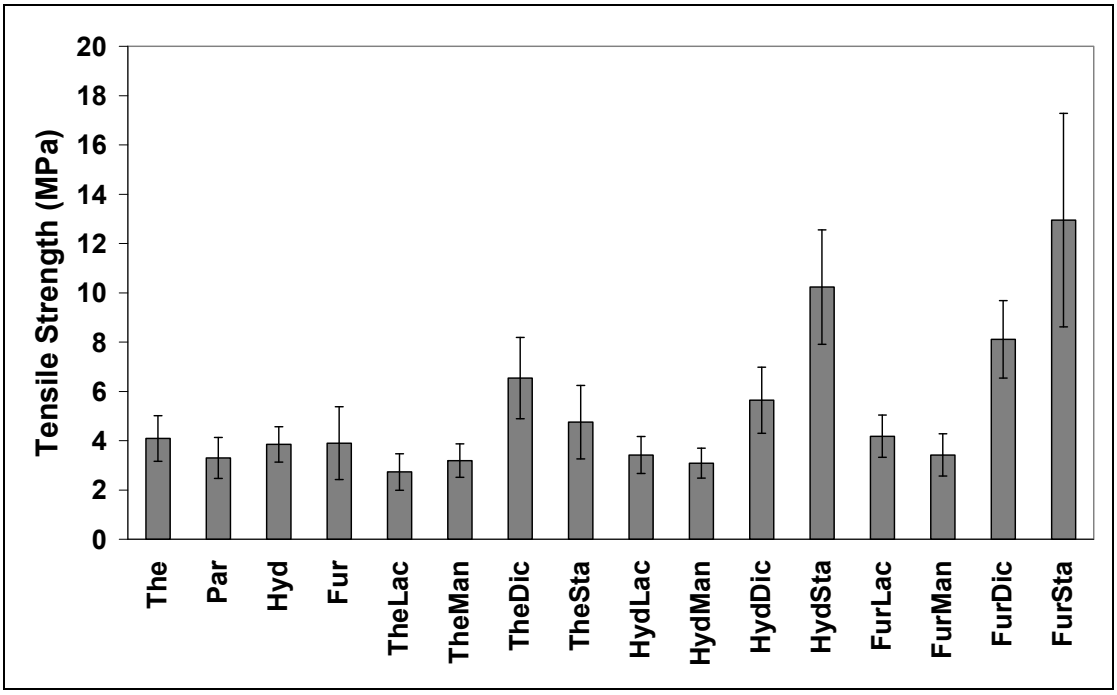


Figure 3-9: Tensile strength of the prepared pellet formulations (mean and standard deviation, n=55).

3.1.5.5 Drug release

Defined reproducible dissolution profile is crucial for a reproducible pharmaceutical bioavailability of the active ingredient being delivered. The dissolution profiles of high- and low dose pellet formulations are illustrated in figure 3-10.

All prepared pellet formulations released the drug rapidly, regardless of the solubility of their active ingredients as expected with pellets made using κ-carrageenan as pelletization aid in general. The standard deviation was low for most formulations indicating desirable batch uniformity.

The replicate experiments with the formulation with high strength of hydrochlorothiazide show also good batch conformity (figure 3-11).

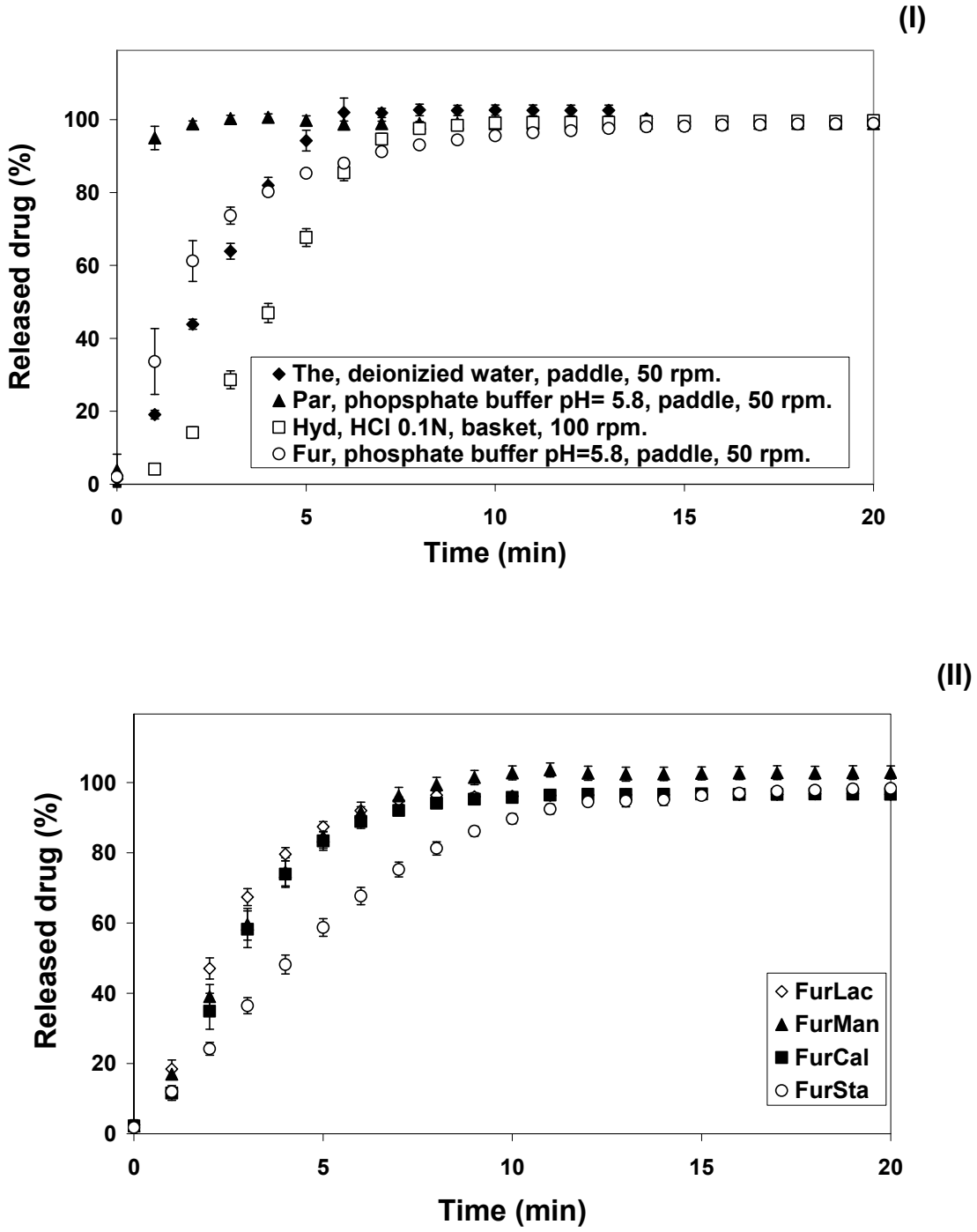


Figure 3-10: Release profiles of the pellets prepared using the flat die press 14-175: (I) high dose pellet formulations and (II) furosemide pellet formulations with low drug strength (n=6).

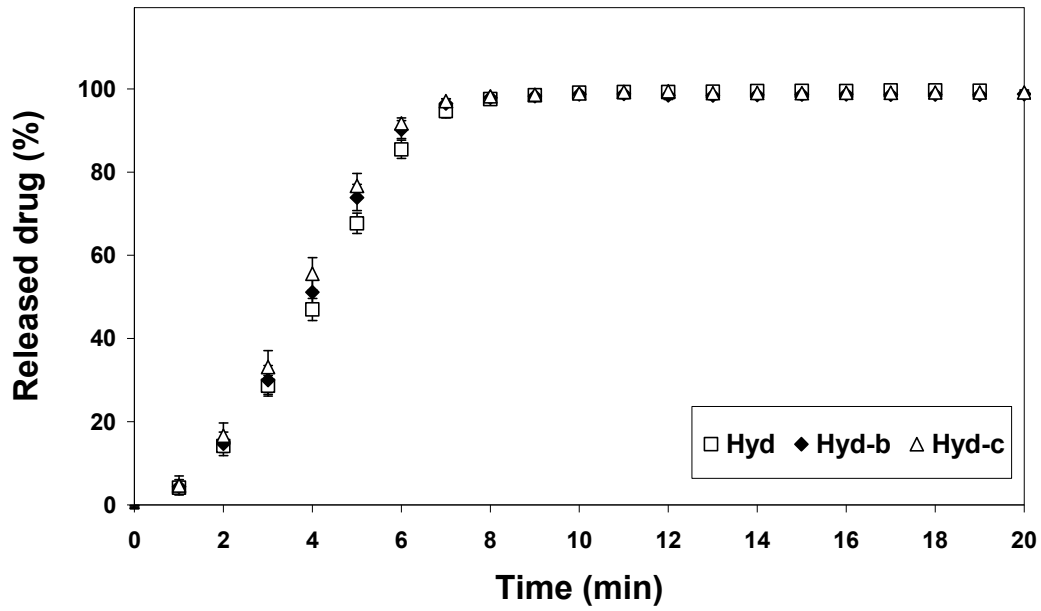


Figure 3-11: Release profiles of the three replicates of the pellet formulation containing 80% hydrochlorothiazide.

3.1.6 Summary of results and outlook

The flat die press is a promising choice for the production of pharmaceutical pellets by extrusion/spheronization with high formulation robustness. The pellets obtained in this work showed narrow size distribution, low aspect ratio and small variation in the release of their active ingredients.

In general flat die presses owing a high number of dies have a high throughput. Moreover, the simple working principle of the flat die press leads to a robust extrusion process. A main disadvantage of the flat die press is however the lack of an integrated wet massing, which is provided by the twin screw extruder. Therefore, when using a volatile granulation liquid it is preferable to use a twin screw extruder in order to minimize the possible liquid evaporation.

Optimization of the flat die press for pharmaceutical purposes is of particular importance. The dosing system should be particularly improved to avoid the accumulation of the wetted mass on the walls of the reservoir tank and of the cylinder surrounding the dosing screws in case of highly wetted materials. Furthermore, the mounting of the die press is laborious since the adjustment

of the distance between the die plate and the knife as well as that between the roller and die requires the addition of distance rings. Therefore variation of these distances in one experiment requires a dismantling and the removal of the rollers which is quite laborious. A temperature control of the process area is necessary for heat sensitive products as well as for any hot melt extrusion process intended to be done in this equipment. Further experiments should be done to assess the feasibility of producing extrudates with smaller diameter and their conversion into pellets (with die plate having channels with diameter below 0.5 mm).

Finally, instrumentation of the die press is desirable to monitor the power consumption as well as the pressure and temperature as a means to monitor the extrusion process.

3.2 Compression behavior of κ-carrageenan pellets

3.2.1 Objective, model and choice of formulations

As a first step in the systematic investigation of the suitability of κ-carrageenan based pellets for the formulation of multiparticulate tablets the compression behavior of these pellets was studied. In particular it was important to determine the significance of undesirable fragmentation occurring under load since pellets made with κ-carrageenan have in general a low tensile strength (Thommes 2006a,b; Yoo, 2008) and are therefore theoretically prone to breakage under compression conditions.

The great majority of compression studies on pellets were carried out using eccentric compression machines. A better approach would be to use rotary tableting machines, which ultimately mimic the work conditions encountered in the pharmaceutical industry. Therefore the compression mechanism of κ-carrageenan pellets was examined using a rotary tableting machine (Pressima, Kilian, Cologne, Germany).

In order to provide a realistic and comprehensive approach for studying the compression behavior of κ-carrageenan based pellets four pellet formulations were chosen of the those prepared in section 3.1 (designated in the current section with A, B, C and D for facilitation, table 3-4). The pellets were selected to represent both cases of high- (formulations A and B) and low drug strength (formulations C and D) as well as pellet components with different compression mechanisms in each category: 80% of the highly plastically deforming theophylline in formulation A against 80% of the highly fragmenting paracetamol known for its capping tendency in formulation B and 70% of the highly fragmenting brittle aggregates of dicalcium phosphate dihydrate in formulation C against 70% of the granular lactose, deforming by fragmentation but also to a certain extent by plastic deformation in formulation D.

The pellet size fraction 500-800 µm was chosen for the compression studies.

Table 3-4: Studied pellet formulations and amount of water used for extrusion/spheronization based on the weight of solids.

Ingredient	A	B	C	D
Theophylline (%)	80			
Paracetamol (%)		80		
Hydrochlorothiazide (%)			10	10
DCP dihydrate (%)			70	
Lactose (%)				70
κ-Carrageenan (%)	20	20	20	20
Deionized water (%)	52	50	56	46

In order to determine the effect of compression process parameters on the degree of pellet deformation the compression experiments were performed according to a 2^2 full factorial statistical design with three replicates of the central point taking compression force and turret speed as variables (Table 3-5). Unlubricated pellets of the formulation B (containing 80% paracetamol) and lubricated pellets (with added 0.5% magnesium stearate) from all pellet formulations were compressed. Lubrication of pellets with magnesium stearate was used by several authors (Johansson and Alderborn, 1996; Nicklasson et al., 1999; Santos et al., 2004) as a means to reduce the bonding forces during compression. The resulting tablets can then be easily de-aggregated by simple shaking in a petri dish allowing the retrieval of the compressed pellets for examination purposes. The experimental ranges were chosen in such a way that tablets could be formed at the lowest level of compression force used and are also not broken upon fast contact with the ejection finger at the highest turret speed used.

Table 3-5: Design of tableting experiments for lubricated (all formulations) and unlubricated pellets (formulation B).

Factor	-1	0	+1
Compression force (kN)	15	20	25
Turret speed (rpm)	10	25	40

3.2.2 Properties of the uncompressed pellets

Table 3-6 shows the size and shape factors, poured bulk density, tapped density, voidage and disintegration time of the chosen size fraction (500-800 µm) of the studied pellet formulations.

The prepared pellets exhibited short disintegration times of few minutes for all formulations as expected generally with pellets made using κ-carrageenan as pelletizing agent.

Table 3-6: Size and shape factors, poured bulk density, tapped density, voidage and disintegration time of the chosen size fraction (500-800 µm) of the studied pellet formulations.

Pellet formulation	Median of mean Feret diameter (µm)	10% Interval (%)	Median aspect ratio	Median roundness	Bulk density (g/ml)		Tapped density (g/ml)		Tapped voidage of pellet mass (%)	Disintegration time (s)	
					Mean	S.D.*	Mean	S.D.*		Mean	S.D.*
A	680	60.8	1.11	0.86	0.77	0.01	0.83	0.01	37.6	219	19
B	697	65.4	1.10	0.87	0.67	0.01	0.75	0.02	32.1	208	18
C	647	58.6	1.11	0.86	0.92	0.01	1.02	0.01	36.0	301	23
D	710	65.8	1.11	0.86	0.75	0.00	0.85	0.01	31.5	218	17

*Standard deviation

3.2.3 Scanning electron microscopy

Scanning electron micrographs of the uncompressed pellets and the pellets retrieved by de-aggregation of the tablets prepared of lubricated pellets from the four pellet formulations at the compression conditions of the central point (figure 3-12) indicate that, regardless of the compression behavior of the original pellet components, the pellets remained as coherent units after compression and did not fragment. Moreover, significant cracks on the surfaces of retrieved pellets are almost absent. It can be then suggested, that deformation is the dominating mechanism of compression.

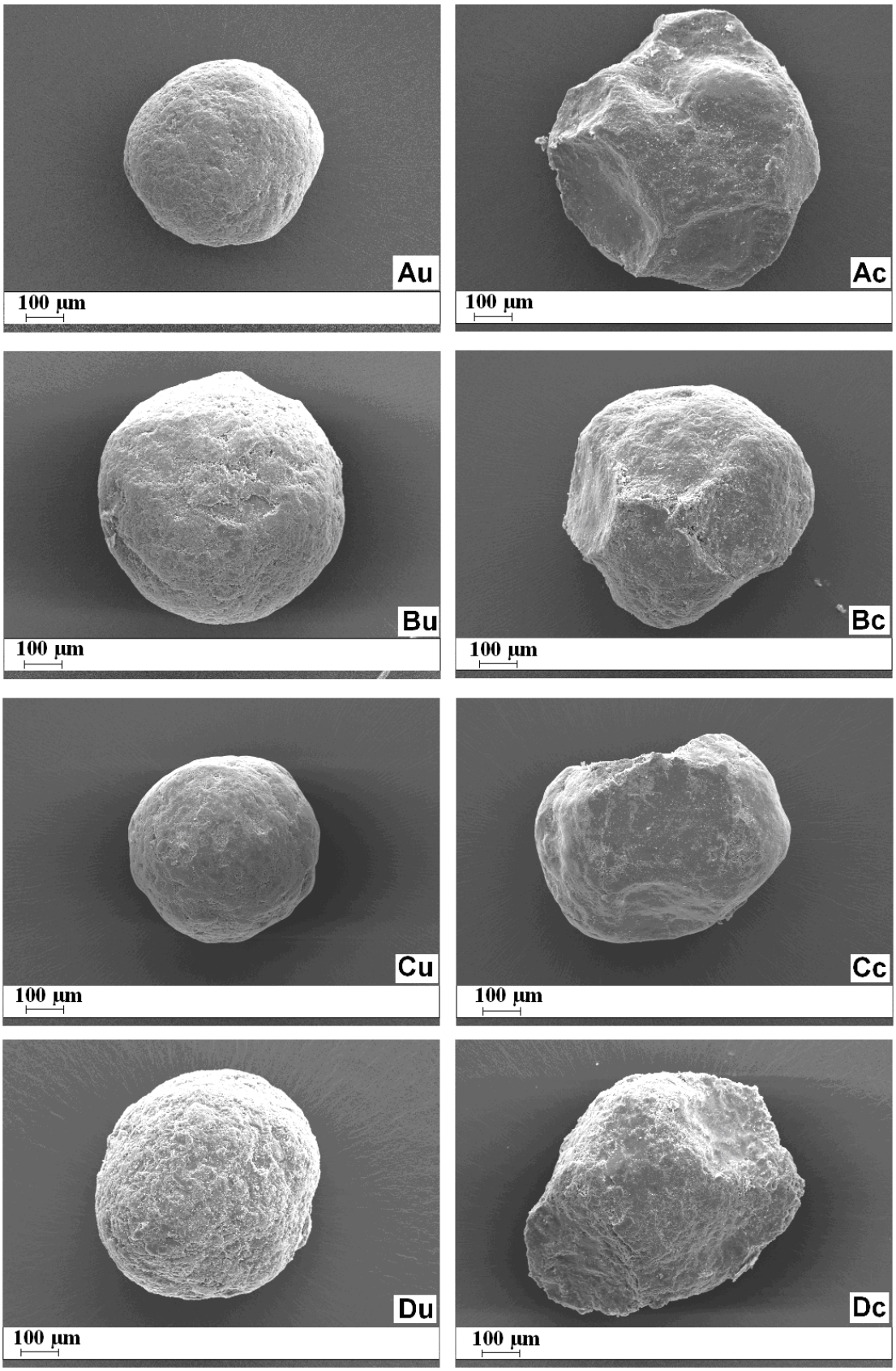


Figure 3-12 Scanning electron micrographs of uncompressed pellets (Au, Bu, Cu, Du) and pellets retrieved after compression (Ac, Bc, Cc, Dc) of the lubricated pellet formulations (20 kN, 25 rpm).

The retrieved pellets were readily obtained by gentle shaking of tablets in petri dishes and only a slight difficulty was encountered in the retrieval of compressed pellets D. The ability to easily de-aggregate the tablets prepared from lubricated pellets or in other words the low compactibility of lubricated pellets is an indirect indication of the domination of deformation and the absence of significant fragmentation and attrition. A high degree of attrition or fragmentation would otherwise rupture the magnesium stearate film surrounding the pellets thus creating new lubricant-free surfaces accompanied by increased bonding forces leading to the formation of stronger tablets which are difficult to de-aggregate (Johansson et al., 1995). It should be also noted, that the amount of magnesium stearate used to lubricate the pellets (0.5%) as well as the mixing time (5 min) in the current study were lower than those mentioned in the literature for MCC Pellets (2% for 100 min, Nicklasson et al. 1999 a, 0.5% for 100 min, Johansson et al. 1995) but still sufficient to de-aggregate the examined κ-carrageenan pellets.

Scanning electron micrographs of the fracture surface (after diametrical breakage in a hardness testing equipment) of the tablets prepared from unlubricated pellets of formulation B containing 80% of the highly fragmenting paracetamol (figure 3-13) support the previous findings whereby the fragmentation of pellets is negligible and their deformation seems be dominating.

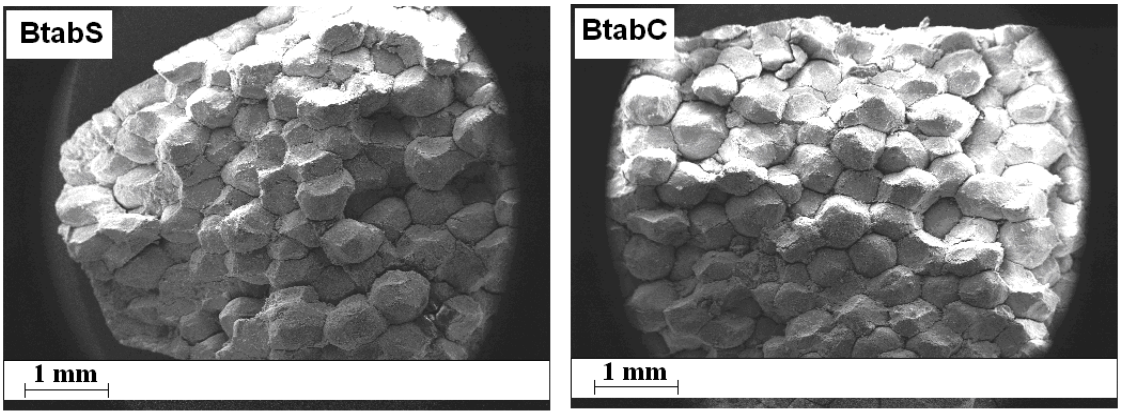


Figure 3-13: Scanning electron micrographs of the fracture surface of tablets prepared by compression of unlubricated pellet formulation B: (BtabS) side of the tablet and (BtabC) centre of the tablet (20 kN, 25 rpm).

3.2.4 Image analysis

The data acquired from image analysis (figure 3-14) of the uncompressed pellets and those retrieved after compression confirms the previously made statements about the mechanism of compression. For all tested pellet formulations there was no reduction of the pellet size upon compression, thus eliminating the occurrence of significant fragmentation. On the opposite an increase in the equivalent diameter was noticed in all cases (figure 3-14.I) hence confirming the flattening of pellets after compression since this size parameter is calculated based on the measured projected area of the particles. The minimal reduction in the equivalent diameter of pellet formulation D (in less than 10% of the measured particles) suggests a limited fragmentation.

The flattening of pellets after compression was further confirmed by the increase in the aspect ratio (figure 3-14.II) and the decrease of roundness (figure 3-13.III), two shape factors which are commonly used to assess the sphericity of pellets. In this work the roundness was quoted to provide another assessment tool in addition to the aspect ratio, since the latter is rather suitable for the description of sphericity of cylindrical to round particles and the retrieved pellets being examined exhibit an irregular shape. The worsening of these two shape factors in the retrieved pellets in comparison to the original pellets indicates the deformation of particles after being subjected to load.

Furthermore, all three measured parameters showed a considerably wider distribution in case of the retrieved pellets compared to the uncompressed pellets, caused most probably by the different deformation patterns undergone by the pellets due to differences in the stress distribution in the different areas of the tablet, i.e. in the centre or closer to the surfaces of the tablet.

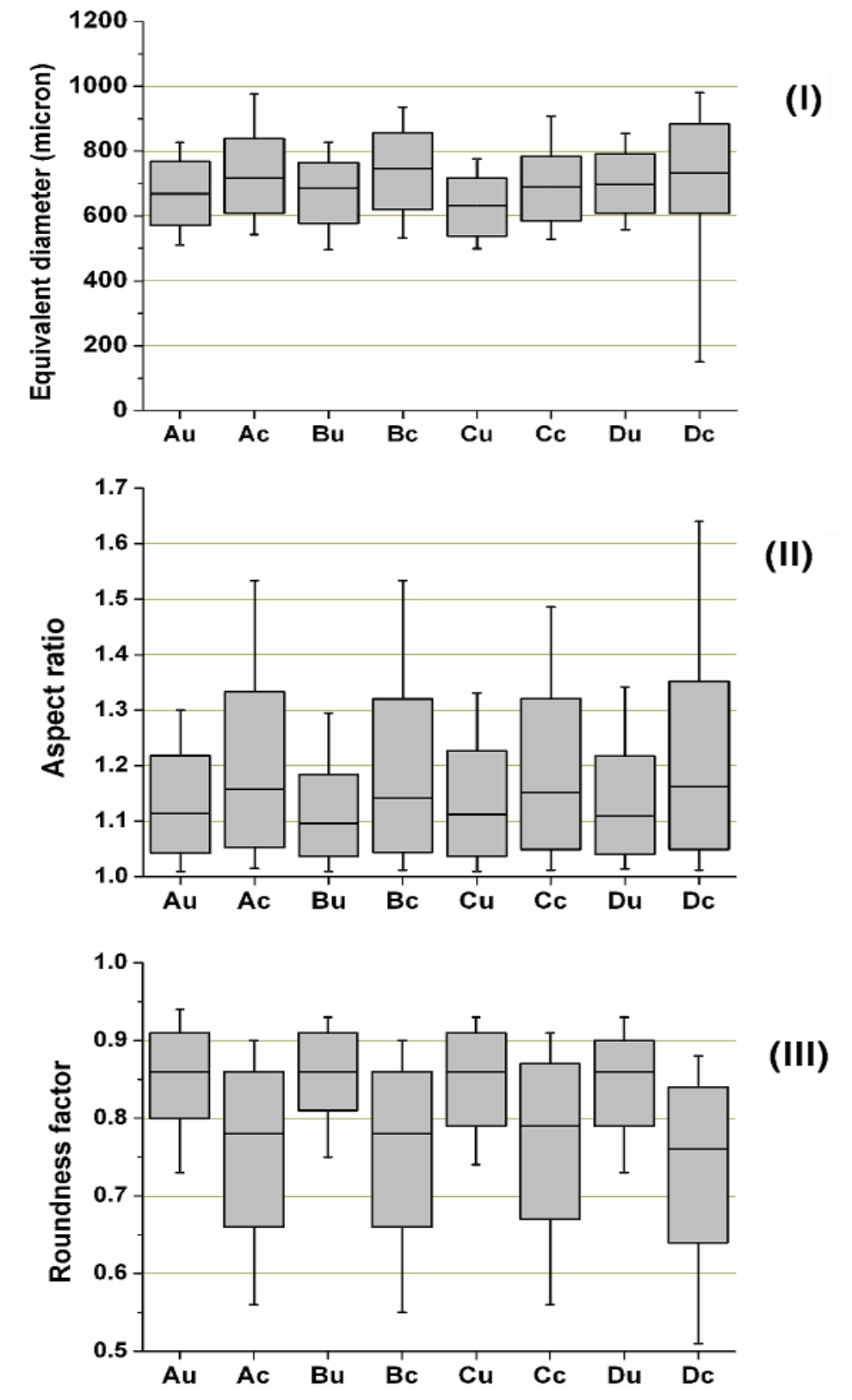


Figure 3-14: (I) Equivalent diameter, (II) aspect ratio and (III) roundness factor (x_1, x_{10}, x_{50}, x_{90}, x_{99}) of the uncompressed pellets (A_u, B_u, C_u, D_u) and the pellets retrieved after compression (A_c, B_c, C_c, D_c) (20 kN, 25 rpm).

3.2.5 Fracture force and porosity measurements

The fracture force of the uncompressed pellets and that of the pellets retrieved after compression were compared (Figure 3-15). A one-tailed t-test assuming unequal variances showed, at a confidence level of 95%, that the average fracture force of the retrieved pellets was significantly higher than that of the original pellets in case of pellet formulations A, B and D whereas no statistically significant difference was found in case of formulation C. These findings support the fact that the pellets remained as intact units and exclude the formation of significant cracks upon compression which would otherwise promote the breakage of pellets under lower loads than those for intact pellets.

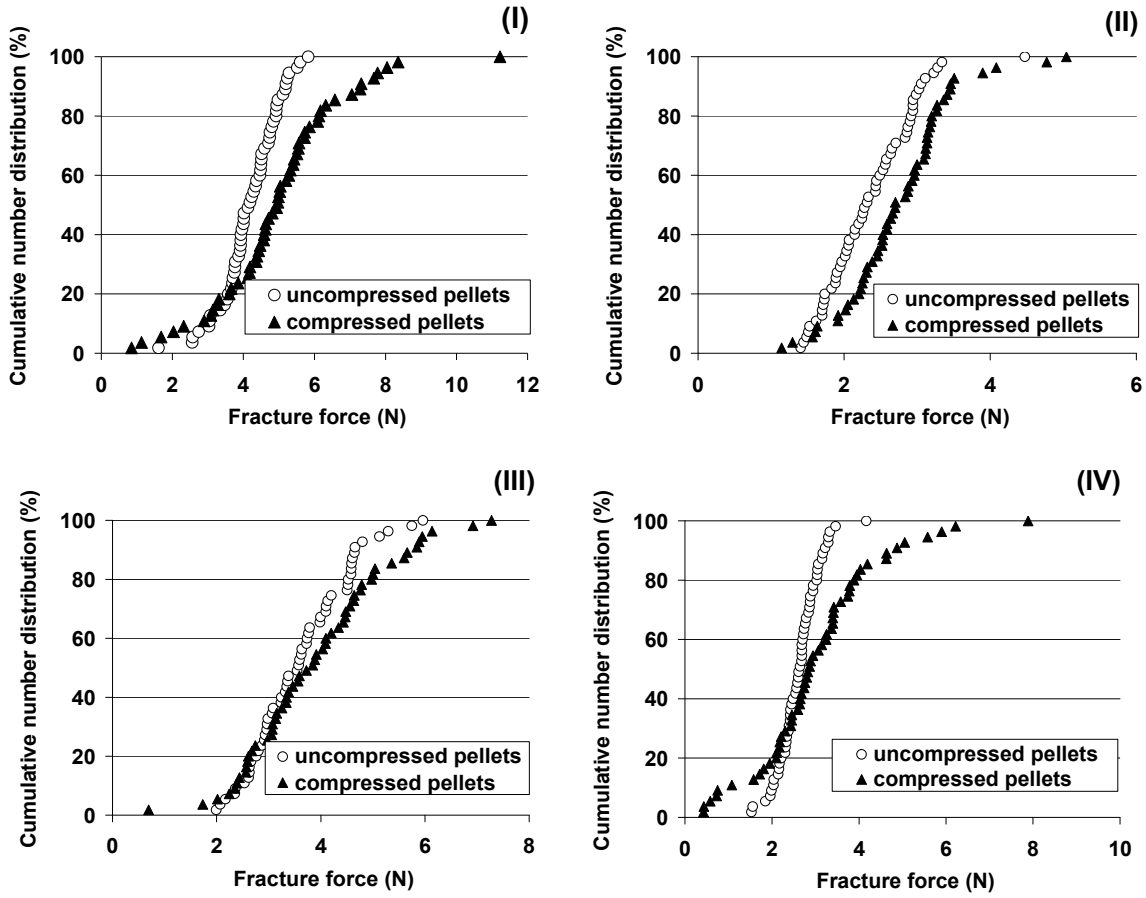


Figure 3-15: Cumulative number distribution of the fracture force of the uncompressed pellets and the pellets retrieved after compression: (I) pellets formulation A , (II) pellet formulation B, (III) pellet formulation C and (VI) pellet formulation D (20 kN, 25 rpm).

The unchanged fracture resistance in case of formulation C may be caused by the rigid character of DCP. Nicklasson et al. (1999a) suggested that

DCP/MCC pellets with a ratio of 4:1 exhibit lower densification when compared to MCC pellets and attributed the difference in the degree of densification to the properties of the primary particles and their readiness to reposition under load, which are limited in case of the rigid and non-deformable DCP. The mentioned authors reported a different mode of deformation between the two examined pellet formulations. The DCP/MCC pellets exhibited high surface deformation due to the concentration of stress at the contact areas between the pellets rather than across the pellets whereas MCC pellets underwent a bulk deformation under stress. The increase in the equivalent diameter and aspect ratio of retrieved pellets from formulation C in the current study without a significant change in the fracture force in comparison with the uncompressed pellets agrees with the statements made by Nicklasson et al. (1999a).

The few low values of fracture force for the retrieved pellets in all pellet formulations (figure 3-15) may be explained by the position of pellets under the texture analyzer probe during the analysis. When the edge of a deformed particle comes under the probe or oppositely lays in contact with the test plate the pellet can reorient itself during the measurement leading to a fall in the measured force, which is falsely interpreted by the system as a fracture force.

The higher fracture resistance of the retrieved pellets may be attributed to the lower porosity of the retrieved pellets in comparison to the original pellets (figure 3-16.I) thus indicating a densification of pellets under load. A decrease in the total porosity was also reported for pellet formulation C but the decrease was less pronounced compared to the other formulations, which is in accordance with the statistically non-significant increase in the fracture force of this formulation and the assumptions made about the higher resistance to densification of pellets containing DCP.

Moreover, the decrease of porosity was accompanied by a decrease of the median pore radius (figure 3-15.II), which supports the deformation of pellets by flow of primary particles in the free pores area as described by Johansson et al. (1995).

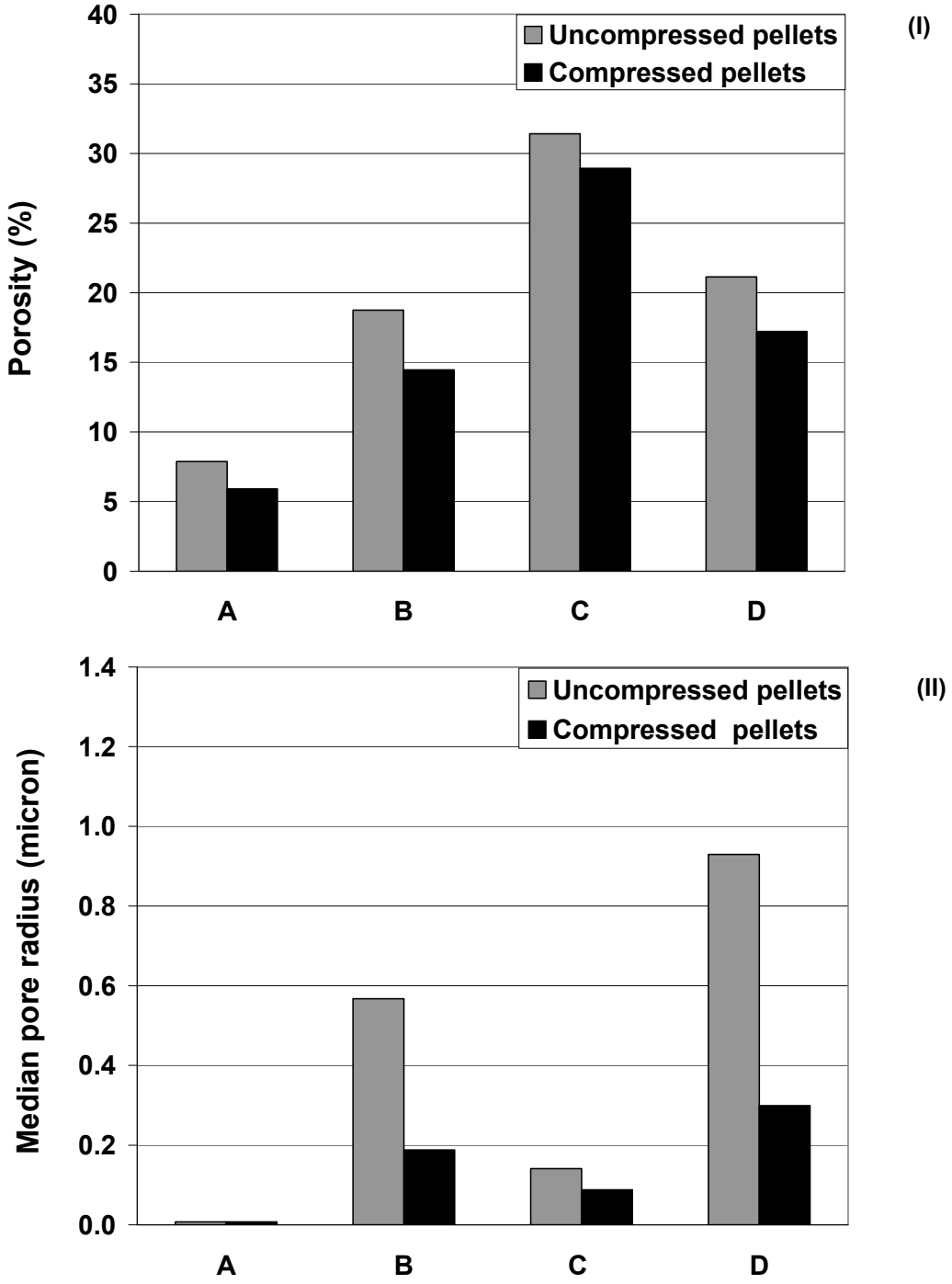


Figure 3-16: (I) Total porosity and (II) median pore radius of the uncompressed pellets (A_u, B_u, C_u, D_u) and the pellets retrieved after compression (A_c, B_c, C_c, D_c), (20 kN, 25 rpm).

Again pellet formulation C exhibited less pronounced decrease in the median pore radius compared to pellet formulations B and D. The unchanged median pore radius in case of pellet formulation A can be attributed to the poor reproducibility of porosity measurements performed on the retrieved pellets of

this formulation, probably caused by the very small pore size which lies close to the limits of sensitivity of the mercury porosimeter. Due to the high deviation between the results obtained with this formulation, a third measurement was carried out on these retrieved pellets. Two of the measured samples showed significantly smaller median pore radius (0.004 und 0.005 µm) in comparison to the uncompressed pellets (0.007 µm) whereas the remaining sample had a higher median pore radius (0.013 µm).

It is to also to be mentioned that another possible reason for the increased resistance to fracture of the studied pellets after compression is the flattening of pellets upon compression leading to higher stress distribution during the test for fracture resistance.

Key factors in the compression mechanics of aggregates are the porosity as well as the physical and mechanical properties of the primary particles contained in the compressed entities. The extent of fragmentation occurring during volume reduction of porous aggregates reported in the literature varies from a considerable level to very limited or non-existent based on the formulation used and other factors. Dominating deformation, some densification and limited fragmentation during compression was reported for xanthan gum pellets (Santos et al., 2004), MCC pellets (Johansson et al. 1995; Johansson and Alderborn 1996, 2001) and DCP/MCC pellets (Nicklasson 1999b) having different levels of porosity together with increased degree of deformation leading to a higher compactibility upon increasing the porosity of the original pellets. On the other hand, fracture of soft pellets containing MCC, barium sulfate and glycerol monostearate under low pressure and formation of cracks and flaws after a compression threshold of 9 MPa in hard pellets containing riboflavin, hydrous lactose and microcrystalline cellulose were reported by Salako et al. (1998). Elastic deformation and some fragmentation of pellets containing MCC, propranolol, and lactose or DCP as fillers were mentioned by Maganti and Celik (1993).

The fact that, despite the low tensile strength of the studied pellet formulations (as with pellets made with κ-carrageenan in general), the fragmentation of pellets under load was minimal to absent may disagree with the statements made by Wickberg and Alderborn (1992) who reported that a low mechanical

strength of the aggregates leads to high degree of fragmentation under compression and correlated the fragmentation of different lactose granule formulations to their lower tensile strength (varying between less than 1N to 4 N) compared to that of olsalazine sodium granules (fracture force between 3 and 4 N) which mainly deformed during tableting. It may be however argued that the spherical homogenous shape and the smooth surface of the pellets examined in the current work are quite different from the irregular rough surface of granules which were used in those studies. MCC pellet formulations with different levels of fracture forces varying from 2 N to around 13 N were all found to deform upon compression with no fragmentation (Johansson et al., 1995). In the same study it was suggested that the resistance to fracture of the individual pellets used is not a key factor in their behavior under load but may be of primary importance for pellets and granules exhibiting considerable fragmentation upon compression. Johansson attributed the minute fragmentation of the examined MCC pellets and the domination of deformation upon compression to the lower energy needed to cause particle repositioning within the pellets by a shearing process compared to that required to fragment the pellets and assigned this energy gap to the special pressure conditions of the sole pellets in the die whereby the pellets are simultaneously stressed from all directions and are thus not easily fractured. However, the same author did not exclude the role of the spherical shape and smooth surface of the compressed pellets as well as the plastic nature of the forming material. On the other hand, both MCC granules having irregular shape and MCC pellets with low, intermediate and high porosity deformed under load and did not fragment with only some attrition of the high porosity granules i.e. the shape did not influence the compression mechanisms for the agglomerates made from this substance although it influenced their degree of deformation (Johansson and Alderborn 2001). It seems therefore that also the role of the mechanical properties of the primary particles forming the pellets can not be omitted and is most probably of significant relevance. Compression studies on κ-carrageenan powder revealed a Heckel function of 0.0175 MPa^{-1}, high elasticity (elastic recovery up to 28% after 10 days) with mechanical interlocking of the particles (Picker, 1999). Unlubricated pure κ-carrageenan pellets were compressed in the

preliminary experiments of this work and no tablets could be obtained indicating that the high elasticity of this substance was maintained after wet extrusion/spheronization and subsequent drying. The low or absent fragmentation of the studied pellet formulations could be hence possibly partially related to this elastic behavior of κ-carrageenan. Force-displacement curves obtained from texture analysis of all studied pellets exhibit an initial curvature indicating an elastic component followed by plastic linear phase before the first drop of force corresponding to breakage. An elasto-plastic deformation pattern (initial non-linear part followed by a linear section in the pressure-strain curves of the individual granules) for different types of MCC pellets with different degrees of deformation propensity including high and low porosity pure MCC pellets as well as MCC pellets with lactose as a brittle material or polyethylene glycol as a soft component was also reported by Nordström et al. (2008). The same authors related the compression properties of pellets to the mechanical behavior of their single granules.

The limited fragmentation observed in the retrieved pellets in case of formulation D may be explained as suggested by Santos at al. (2004) by the re-crystallization of the water soluble lactose during drying of the wet pellets leading to increased interparticulate bonds within the pellets and resulting in less elastic and more brittle structure. Pellet formulation D exhibited also lower original porosity than that of pellet formulation C which is coherent with the suggested more closed pore structure. Limited fragmentation upon compression (small fragments in the voids between the pellets observed at the tablet fracture surface) and a more brittle nature for MCC lactose pellets compared to other types of MCC pellets were also observed by Nordström et al. (2008) along with the dominating deformation mechanisms for these granules. It is also to be mentioned, that the tablets prepared from lubricated pellets of formulation D were more difficult to de-aggregate than those prepared from the other three formulations, which suggests some fragmentation or attrition leading to increased lubricant-free bonding surfaces. It is also possible that this minute fragmentation occurred during the retrieval process. However, whether this limited fragmentation occurred during

compression or during retrieval of compressed pellets its extent is minimal and can be therefore neglected.

3.2.6 Effect of process parameters

3.2.6.1 Size and shape of compressed pellets

No significant effect of the process parameters (compression force and turret speed) on the size and shape of retrieved pellets could be established for all pellet formulations in the range of force and speed examined (tables 3-7 to 3-10). The variances between the measured responses were small and lower than that between the replicate experiments of the central point. It can then be argued, that the pellets show no significant difference in their degree of deformation inside the chosen ranges of the examined parameters.

Table 3-7: Factor levels and measured responses for the compression experiments with lubricated pellet formulation A.

Exp. Name	Compression force (kN)	Turret speed (rpm)	Median equivalent diameter (µm)	10% interval (%)	Median aspect ratio	Median roundness factor
N1	15	10	706	55.8	1.15	0.78
N2	25	10	755	62.2	1.14	0.77
N3	15	40	746	56.8	1.14	0.78
N4	25	40	691	54.6	1.15	0.78
N5	20	25	732	59.0	1.15	0.78
N6	20	25	713	55.0	1.15	0.78
N7	20	25	717	56.8	1.16	0.78

Table 3-8: Factor levels and measured responses for the compression experiments with lubricated pellet formulation B.

Exp. Name	Compression force (kN)	Turret speed (rpm)	Median equivalent diameter (µm)	10% interval (%)	Median aspect ratio	Median roundness factor
N1	15	10	753	61.4	1.14	0.77
N2	25	10	727	58.6	1.15	0.78
N3	15	40	710	62.2	1.14	0.77
N4	25	40	746	55.2	1.15	0.77
N5	20	25	746	56.0	1.14	0.78
N6	20	25	737	59.4	1.23	0.78
N7	20	25	652	59.8	1.14	0.78

Table 3-9: Factor levels and measured responses for the compression experiments with lubricated pellet formulation C.

Exp. Name	Compression force (kN)	Turret speed (rpm)	Median equivalent diameter (μm)	10% interval (%)	Median aspect ratio	Median roundness factor
N1	15	10	670	56.0	1.15	0.78
N2	25	10	675	63.6	1.15	0.78
N3	15	40	668	61.4	1.15	0.78
N4	25	40	672	64.8	1.16	0.79
N5	20	25	690	61.8	1.15	0.79
N6	20	25	671	58.4	1.14	0.79
N7	20	25	652	59.8	1.14	0.78

Table 3-10: Factor levels and measured responses for the compression experiments with lubricated pellet formulation D.

Exp. Name	Compression force (kN)	Turret speed (rpm)	Median equivalent diameter (μm)	10% interval (%)	Median aspect ratio	Median roundness factor
N1	15	10	731	51.0	1.15	0.77
N2	25	10	726	52.0	1.16	0.76
N3	15	40	710	52.4	1.15	0.77
N4	25	40	716	49.8	1.14	0.77
N5	20	25	733	50.4	1.16	0.76
N6	20	25	733	52.6	1.14	0.77
N7	20	25	718	54.6	1.14	0.73

The change of shape factors for MCC pellets with increased pressure reported by Johansson and Alderborn (1996) were minor and occurred in a pressure range far less than that used in this study (from 0-80 MPa), a range which corresponds to the deformation needed for the development of bonds between the pellets starting from uncompressed pellets to form a tablet. These changes are then in accordance with the previously made statements about equivalent diameter, aspect ratio and roundness factor for the compressed pellets. Changes in the degree of deformation of the studied pellets could be probably seen at lower compression pressure or upon examining a larger pressure range than the one applied. The variability of the replicate experiments of the central point could be attributed to the complicated deformation patterns of the pellets in a biconvex tablet due to differences in the stress distribution between the various areas of the compact.

3.2.6.2 Properties of tablets

The process parameters had a slight effect on the tensile strength of the tablets prepared from unlubricated pellets (figure 3-17). The tableting of sole pellets resulted in weak compacts caused most probably by the reduced bonding area in the compressed system due to the low surface area as well as the absence of attrition which would have resulted in new bonding points. Johansson and Alderborn (2001) highlighted the effect of shape on the compactibility of MCC aggregates whereby a more irregular shape of MCC granules corresponding to a lower poured bulk density resulted in stronger compact than those prepared from MCC pellets having a higher poured bulk density. The poured bulk densities of the studied pellets are presented in Table 3-6. An increase in the compression force led to only a slight increase in the tensile strength of the prepared tablets whereas no influence of the turret speed or the interaction of the two examined parameters on the tensile strength was detected in the studied range (figure 3-17). The slight increase in the tensile strength with increased compression force agrees with the insignificant change in the shape factors mentioned previously. However, during the preliminary experiments the compression of unlubricated pellet formulation B at 10 kN compression force did not result in coherent tablets indicating a low degree of pellet deformation which is under the limit required for the development of sufficient bonds to obtain a tablet. Hence, again, more significant changes in the tensile strength with increased compression force could be probably noticed at wider ranges of applied load.

Table 3-11: Factor levels and measured responses for the compression experiments with unlubricated pellet formulation B.

Exp. Name	Compression force (kN)	Turret speed (rpm)	Tensile strength (MPa)	Elastic recovery (%)
N1	**15**	**10**	**0.14**	**0.25**
N2	**25**	**10**	**0.26**	**0.31**
N3	**15**	**40**	**0.12**	**0.36**
N4	**25**	**40**	**0.23**	**0.37**
N5	**20**	**25**	**0.22**	**0.32**
N6	**20**	**25**	**0.18**	**0.34**
N7	**20**	**25**	**0.19**	**0.28**

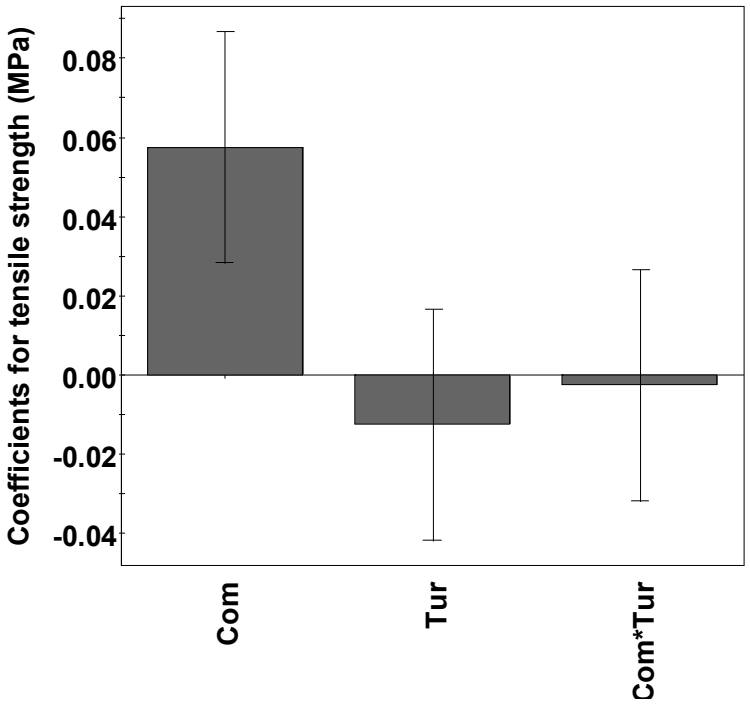


Figure 3-17: Coefficients plot for the tensile strength of tablets prepared from unlubricated pellet formulation B: (com) compression force, (tur) turret speed (R^2_{adj}= 0.846, Q^2=0.552, Conf.lev.=0.95).

The measured post-compressional elastic recovery of the tablets after 10 days was minimal (table 3-11) therefore the effect of process parameter on this response was not further investigated.

The tablets prepared form unlubricated pellets at the compression conditions of the central point did not disintegrate after 1h in the disintegration tester. The tablet remained as single unit with a surrounding gel layer and eroded slowly.

3.2.7 Summary of results

The compression behavior of high- and low drug strength pellets containing κ-carrageenan as pelletization aid was investigated. Model drugs and fillers with different compression mechanisms were used and the effects of compression force and turret speed were examined.

Regardless the compression behavior of their starting components, all pellet formulations exhibited minimal to absent fragmentation and underwent compression by deformation, confirmed by increased equivalent diameter and aspect ratio and decreased roundness factor of the pellets retrieved after de-aggregation of tablets prepared from lubricated pellets. The retrieved pellets

showed also higher fracture resistance in three of the tested formulations and no statistically significant difference in the remaining one thus excluding significant crack formation. A densification mechanism was suggested based on decreased total porosity and reduced median pore radius of the compressed pellets compared to the uncompressed pellets. No significant effects of the process parameters on the degree of pellet deformation have been observed in the examined range. The tensile strength of the tablets prepared from unlubricated pellets increased slightly with increased compression force. The tablets made of sole pellets did not disintegrate to their original pellets and did not behave as a multiparticulate system.

3.3 SMCC HD 90 as embedding powder

3.3.1 Objective and model

Compression of pellets in a cushioning bed helps protecting them from severe deformation and prevents the formation of a non-disintegrating matrix tablet upon contact with water. The embedding medium should possess, in addition to the properties of directly compressible excipients, a high deformability and an excellent ability to form homogeneous mixtures with the pellets in order to ensure the uniformity of content of the prepared tablets. It should also exhibit a high dilution potential (carrying capacity) leading to high amount of pellets within the tablet while maintaining sufficient mechanical properties. Most importantly the cushioning bed should ensure fast disintegration of the tablet to its contained pellets (Bodmeier, 1997). In the current study the use of high density silicified microcrystalline cellulose SMCC HD 90 was investigated as a potential embedding medium for κ-carrageenan pellets. This excipient was chosen due to its high compactibility, ability to facilitate disintegration and high dilution potential allowing the formation of strong tablets with high amount of pellets containing the active ingredients at a smaller tablet size.

Pellets of the size fraction 500-800 µm from formulation D (see section 3.2.2.1, table 3-4), which showed a limited fragmentation upon compression, were mixed with 1% crospovidone and SMCC HD 90 at different ratios and the resulting mixtures were lubricated with 0.05% magnesium stearate. The prepared mixtures were compressed to tablets of 600 mg target weight according to a 2^{4-1} fractional factorial design (table 3-12) with three replicates of the central point taking the percentage of pellets, the pre-compression force, the compression force and the turret speed as variables.

Table 3-12: Design of compression experiments for pellet formulation D with SMCC HD 90 as embedding powder.

Factor	-1	0	+1
Percentage of pellets (%)	50	60	70
Pre-compression force (kN)	0	2.5	5
Compression force (kN)	15	20	25
Turret speed (rpm)	10	25	40

The prepared tablets were then characterized in terms of their tensile strength, elastic recovery, friability, disintegration time and uniformity of content.

Additionally, a highly lubricated pellet-powder mixture was prepared by separate lubrication of the pellets and SMCC HD 90 with magnesium stearate (0.5% for 5 min for the pellets and 2% for 24 h for SMCC HD 90 in a turbula mixer at 42 rpm), followed by mixing of the two components (percentage of pellets 60%). The highly lubricated mixture was then compressed under the compression conditions for the central point.

The cushioning effect of SMCC HD 90 was assessed by: 1. Comparison of the size and shape of uncompressed pellets with those retrieved after compression of the highly lubricated SMCC HD 90/pellet mixture and 2. Scanning electron micrographs of the retrieved pellets and of the fracture surface of the tablets prepared form the SMCC HD 90/ pellet mixture lubricated with 0.05 mg magnesium stearate and compressed at the conditions of the central point.

3.3.2 Characterization of tablets

3.3.2.1 Tensile strength

The results of the compression experiments carried out on pellet formulation D using SMCC HD 90 as an embedding powder are summarized in table 3-13.

A low amount of magnesium stearate (0.05% of the total tablet weight and 0.1-0.17 % of the powder weight depending on the percentage of pellets in the tablets) was used to lubricate these mixtures, due to the excellent flow properties of SMCC HD 90 consisting of a high density microcrystalline cellulose enriched with 2% colloidal silicone dioxide and the low surface area of the compressed system caused by the presence of pellets as big entities. The amount used resulted in good lubrication as shown by the low ejection force (220.6±14.5 N at the compression conditions for the central point, n=10).

Table 3-13: Factor levels and measured responses for the compression experiments carried out on pellet formulation D with SMCC HD 90 as embedding powder.

Exp. Name	Percentage of pellets (%)	Per-compression force (kN)	Compression force (kN)	Turret speed (rpm)	Tensile strength (MPa)	Elastic recovery (%)	Friability (%)	Disintegration time (s)	Coefficient of variation for tablet weight (%)	Acceptance value for the uniformity of content (%)
N01	50	0.0	15	10	1.27	0.05	0.01	48	1.2	13.0
N02	70	0.0	15	40	0.31	0.14	0.01	15	0.6	18.1
N03	50	5.0	15	40	1.06	0.06	0.02	37	0.5	7.6
N04	70	5.0	15	10	0.39	0.09	0.01	44	0.5	12.6
N05	50	0.0	25	40	1.87	0.04	0.01	470	0.7	7.2
N06	70	0.0	25	10	0.70	0.01	0.02	94	1.3	19.8
N07	50	5.0	25	10	1.66	0.04	0.01	349	0.8	12.4
N08	70	5.0	25	40	0.59	0.12	0.02	59	1.1	15.1
N09	60	2.5	20	25	0.82	0.06	0.02	89	0.6	11.1
N10	60	2.5	20	25	0.80	0.05	0.02	95	0.4	7.1
N11	60	2.5	20	25	0.83	0.06	0.02	99	0.7	7.7

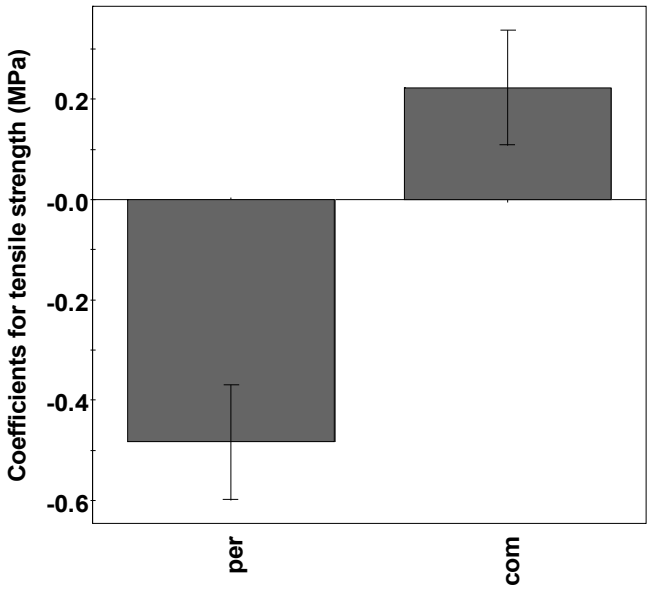


Figure 3-18: Coefficient plot for the tensile strength of tablets prepared from pellet formulation D with SMCC HD 90 as embedding powder: (per) percentage of pellet, (com) compression force (R^2_{adj}= 0.918, Q^2= 0.869, conf. lev.= 0.95).

The resulting tablets fall in the optimal range of tensile strength of 0.56 – 1.11 MPa mentioned by Muzikova and Novakova (2007) except those prepared with a high pellet content (70%) at a low compression force (15 kN) which

were below the lower limit and those with 50% pellet content prepared at high compression force which were higher than the defined range. A high percentage of pellets resulted in reduced bonding forces within the tablet due to the reduced contact area between the compressed entities (Figure 3-18). An increase in the compression force led to stronger tablets whereas no influence of the interaction of percentage of pellets and compression, the pre-compression force or the turret speed (excluded from the model upon backwards regression being insignificant) on the tensile strength could be noticed in the examined range (Figure 3-18).

3.3.2.2 Elastic recovery

All tablets showed low values of post-compressional elastic recovery after 10 days (table 3-13), which can be attributed to the high plasticity of SMCC HD 90. Due to the low values of the post-compressional elastic recovery the effect of percentage of pellets and compression process parameters on this response was not further discussed.

3.3.2.3 Friability

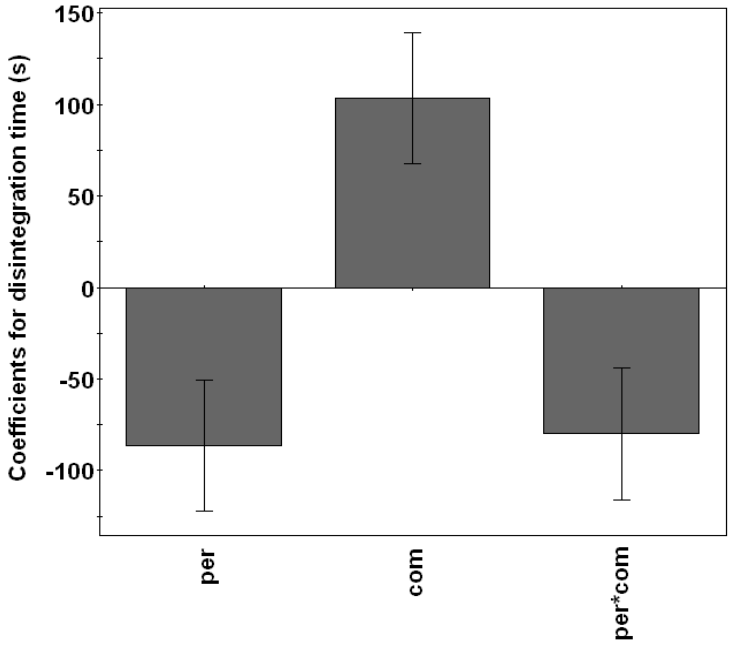
The prepared tablets showed minimal friability (table 3-13) at all compression conditions examined and met the requirements of the European Pharmacopeia 6th edition (2009) i.e. less than 1% loss of weight after the test for friability. The effect of percentage of pellets and compression process parameters on the friability was not further discussed because of the very low measured friability values.

3.3.2.4 Disintegration time

Most tablets disintegrated rapidly (less than 90 s). The disintegration time of the tablets containing 50% pellets and compressed at a high compression force (25 kN) was markedly higher than the rest of the prepared tablets, remained however within the acceptable range of less than 15 min as specified in monograph 2.9.1 "Disintegration of tablets and capsules" of the European Pharmacopoeia 6th edition, 2009. A multiparticulate behavior of the compressed system could be thus maintained in all studied cases. The coefficient plot for the disintegration time obtained after backwards regression (figure 3-19.I) suggests an increase in the disintegration time with increased

compression force whereas an increased pellet percentage and the interaction of pellet percentage and compression force results in decreased disintegration time.

(I)



(II)

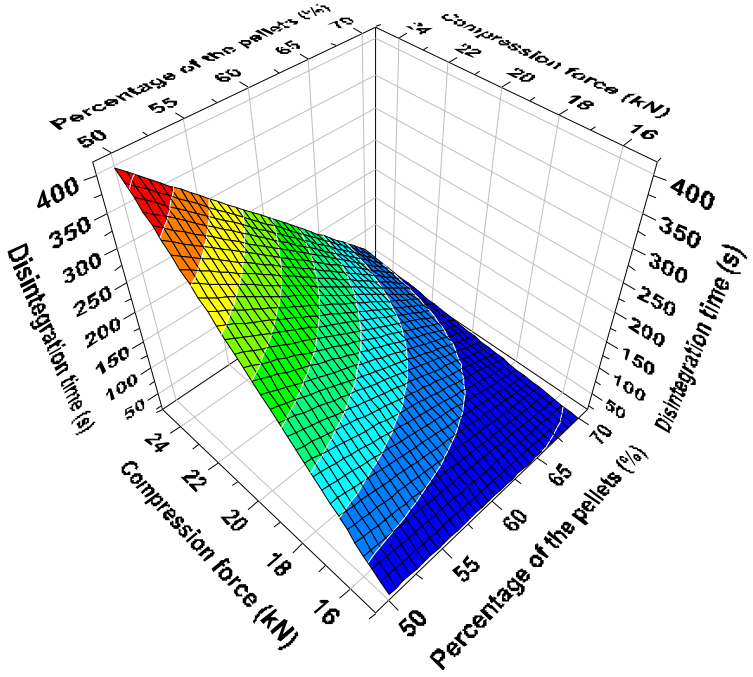


Figure 3-19: I. Coefficient plot and II. Response Surface plot for the disintegration time of tablets prepared from pellet formulation D with SMCC HD 90 as embedding powder: (per) percentage of pellets, (com) compression force (R^2_{adj}= 0.912, Q^2= 0.820, conf. lev.=0.95).

The response surface plot (figure 3-19.II) for disintegration time indicates that the effect of the compression force on the disintegration time is higher at low percentage of pellets in the tablet. At low percentage of pellets more powder (SMCC HD90) is available in the system leading to the development of higher bonding forces by increased compression force and therefore longer disintegration time. At high pellet percentage in the tablet the bonding forces in the tablet are low because of the lower number of contact points between the compressed entities. Therefore increasing the compression force will not contribute significantly to the strength of the tablet and consequently to the disintegration time.

Similarly, the effect of pellet percentage on the disintegration time is more pronounced at high compression forces.

The pre-compression force and the turret speed showed no significant influence on the disintegration time of the tablets and were therefore excluded from the model upon backwards regression.

3.3.2.5 Uniformity of content

Tablets containing 70% pellets showed poor uniformity of content (table 3-13). No variation of the tablet weight was observed and can be therefore exempted as a reason for the variation of content. The tablets prepared with 50 and 60% pellet percentage had a uniform drug content thus excluding any analytical mistake. Therefore, it could be assumed that the poor uniformity of content of tablets with 70% pellets is probably due to de-mixing caused by the low percolation of the powder at this ratio taking also a non ideal mixture into consideration. The particle size, bulk and tapped densities of SMCC HD 90 and pellet formulation D are shown in table 3-14.

Table 3-14: Particle size, poured bulk density and tapped density of SMCC HD 90 (according to manufacturer) and pellet formulation D.

	SMCC HD 90	Pellet formulation D
Particle size (µm)	**d_{10}=42, d_{50}=124, d_{90}=241 (using laser diffraction)**	**d_{eq10}= 608, d_{eq50}= 698 d_{eq90}= 792 (using image analysis)**
Poured bulk density (g/ml)	**0.46**	**0.75**
Tapped density (g/ ml)	**0.59**	**0.85**

3.3.3 Cushioning effect

The pellets retrieved after de-aggregation of tablets prepared from the highly lubricated pellet- powder mixture did not greatly differ in their equivalent diameter, aspect ratio and roundness (figure 3-20) from the uncompressed pellets. This may be explained by the good cushioning effect of the highly plastically deforming SMCC HD90, which absorbs a high part of the applied load and deforms itself, hence protecting the pellets from severe deformation upon compression.

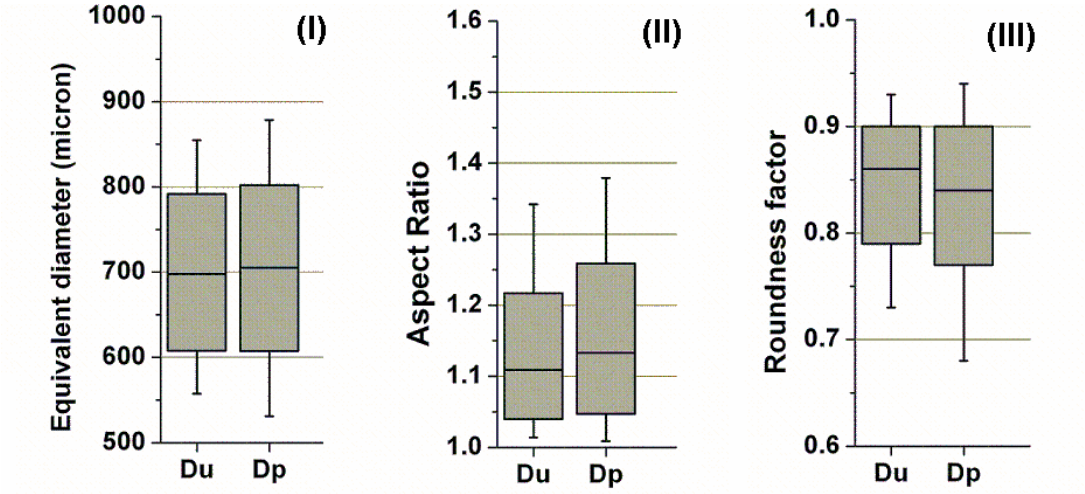


Figure 3-20: (I) Equivalent diameter, (II) aspect ratio and (III) roundness factor (x_1, x_{10}, x_{50}, x_{90}, x_{99}) of uncompressed pellet formulation D (D_u) and pellets retrieved after compression of a highly lubricated mixture of pellet formulation D with a powder bed of SMCC HD 90 (D_p) (20 kN , 25 rpm, percentage of pellets 60%).

SEM micrographs of the fracture surface of the tablets prepared under the compression conditions of the central point (figure 3-21.I) and the pellets retrieved after tableting of highly lubricated pellets-powder mixture (figure 3-21.II) confirm the above findings and indicate limited deformation of the compressed pellets, which remained spherical to a considerable extent in both cases.

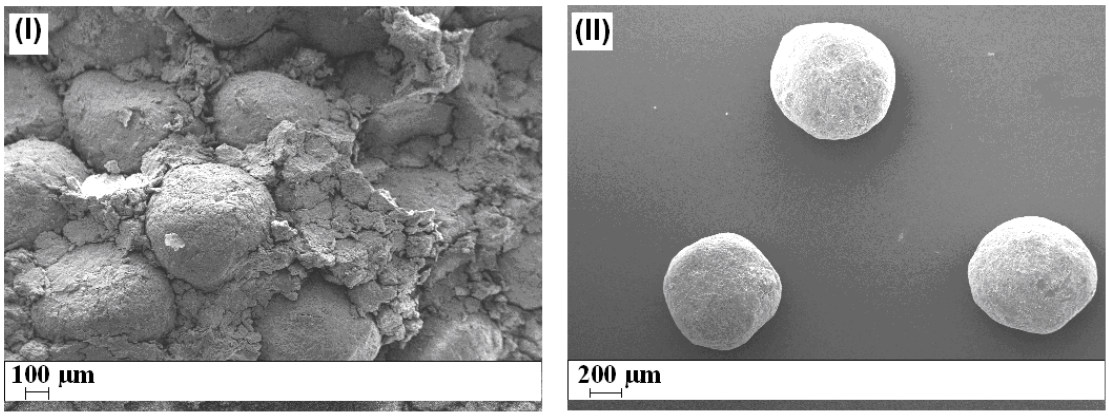


Figure 3-21: SEM micrographs of: (I) the fracture surface of tablets prepared from pellet formulation D with SMCC HD 90 as embedding powder and (II) pellets retrieved after compression of a highly lubricated mixture of pellet formulation D with SMCC HD 90 (20 kN, 25 rpm, percentage of pellets 60%).

3.3.4 Summary of results

Compression of κ-carrageenan pellets with SMCC HD 90 as embedding powder can markedly minimize their deformation under stress, results in tablets with sufficient mechanical strength and short disintegration time and helps maintaining a multiparticulate behavior of the tablet system. Optimization of the proportion of the powder bed is of vital importance.

3.4 Compression of enteric coated κ-carrageenan pellets

3.4.1 Model and choice of polymer and formulations

As a further step the feasibility of formulating enteric coated κ-carrageenan pellets into tablets was investigated. Bisacodyl, a drug which dissolves in diluted hydrochloric acid (Japanese pharmacopoeia JP XIV, 2001) and which is administrated in low doses, was chosen as a "worst case" model drug as suggested by Beckert et al. (1996), Wagner et al. (2000) and Schmid and Picker-Freyer (2009). Additionally, the studied formulations (table 3-15) contained α-lactose monohydrate as a soluble filler. Therefore minimal damages to the coating layer influencing the drug release properties in the acidic medium could be detected using the tested formulation. Pellets containing κ-carrageenan and microcrystalline cellulose as pelletization aids were prepared for comparison.

Table 3-15: Prepared pellet formulations and amount of water used for extrusion/spheronization based on the weight of solids.

Ingredient	BC	BM
Bisacodyl (%)	10	10
α-Lactose monohydrate (%)	70	70
κ-carrageenan (%)	20	
Microcrystalline cellulose (%)		20
Deionized water (%)	48	32

Since most enteric polymers dissolving below pH = 7 are remain brittle in the presence of plasticizers polymers with high elongation at break values are usually added to the coating formulation to enhance the properties to the film layer in order to withstand the compression conditions (Beckert et al., 1996; Dashevsky et al., 2004; Debunne et al., 2002; Dreu et al., 2010). In the current work a combination of the widely used and brittle enteric polymer Kollicoat® MAE (methacrylic acid - ethyl acrylate copolymer) with the highly flexible Eudragit® NE (ethyl acrylate - methyl methacrylate copolymer with an elongation at break of about 600% at room temperature, Lehmann 1997) was used to coat the pellets intended for compression. The two polymers were mixed at a ratio of 60:40 Kollicoat® MAE/ Eudragit® NE and plasticized with 20% triethyl citrate. Additionally the coating formulation contained glycerol monostearate as anti-tacking agent (5% based on the weight of dry polymers)

since this excipient can be used at low concentration compared to talc hence keeping a minimum influence on the mechanical properties of the film (Beckert et al., 1986, Bauer, 2004). κ-carrageenan based pellets were coated at two coating levels: 2.7 and 4.2 mg polymer/cm^2 whereas MCC based pellets were coated with 4.3 mg polymer/cm^2. The enteric coated κ-carrageenan and MCC based pellets were compressed to give tablets containing 20 mg bisacodyl (average tablet weight 503±6, 564±5 and 560±7 mg for κ-carrageenan based pellets coated with 2.7 and 4.2 mg polymer/cm^2 and MCC based pellets coated with 4.3 mg/ cm^2 respectively, n=20). The tablet formulation consisted of 50% pellets, 48.95% SMCC HD90, 1% crospovidone and 0.05% magnesium stearate. The effects of coating level, compression pressure, punch configurations and pellet core on drug release were investigated.

3.4.2 Characterization of the uncoated pellets

3.4.2.1 Size and shape

Table 3-16 shows the size and shape factors of the chosen size fraction (500-800 µm) of the prepared pellet formulations. The prepared κ-carrageenan and MCC pellets were approximately similar in size. All pellet formulations fulfilled the requirements for a successful subsequent coating in terms of sphericity (median aspect ratio approximately 1.1) and narrow particle size distribution (10% interval of the dimensionless diameter exceeded 50%, Thommes and Kleinebudde 2006a).

Table 3-16: Mean and median Feret diameter, 10% interval and aspect ratio of the chosen size fraction (500-800 µm) of the prepared pellets formulations (n=500).

Formulation	Feret diameter			10 % interval	Aspect ratio	
	Mean (µm)	C.V.* (%)	Median (µm)		Median	Interquartile range
BC	682	11.2	685	58.6	1.12	0.098
BM	735	9.6	744	71.0	1.11	0.095

*Coefficient of variation

3.4.2.2 Disintegration time

The pellets prepared using κ-carrageenan as pelletization aid exhibited a short disintegration time of few minutes (221± 5 s) as expected whereas those

made using MCC did not disintegrate after 24 h in the disintegration apparatus.

3.4.3 Drug release from the coated pellets

The release of bisacodyl from the coated pellets is illustrated in Figure 3-22. All coated pellet formulations showed sufficient resistance in the acidic medium. However, while κ-carrageenan pellets coated with 2.7 mg/cm^2 and 4.2 mg/cm^2 respectively released over 80% of their active ingredient after 45 min in the phosphate buffer stage enteric coated MCC pellets released only 20% and thus did not meet the specifications of the United States Pharmacopeia USP 32 (2009a) for delayed release dosage forms (defined as less than 10% drug release after 2 h in HCl 0.1 N pH=1 and more than 80% drug release after 45 min in phosphate buffer pH=6.8). The poor release in case of MCC pellets can be attributed to their lack of disintegration leading to a matrix-type slow release behavior.

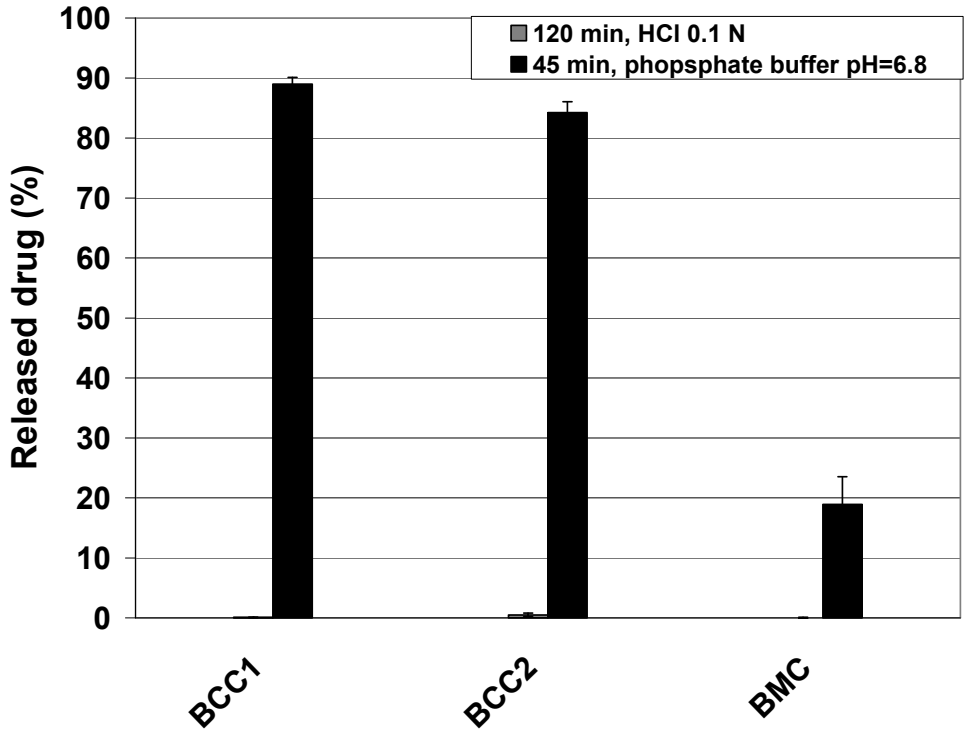


Figure 3-22: Bisacodyl release from κ-carrageenan and MCC pellets coated with 60:40 mixture of Kollicoat® MAE and Eudragit® NE plasticized with 20% triethyl citrate: (BCC1) κ-carrageenan pellets coated with 2.7 mg polymer/cm^2, (BCC2) κ-carrageenan pellets coated with 4.2 mg/cm^2 and (BMC) MCC pellets coated with 4.3 mg/cm^2 (37° C, paddle, 100 rpm).

3.4.4 Characterization of the tablets

3.4.4.1 Mechanical resistance

The tablets prepared from coated pellets of all three formulations showed sufficient mechanical resistance for any further handling (table 3-17) at the compression pressures used. This can be attributed to the high plasticity and binding ability of silicified microcrystalline cellulose which is able to ensure adequate binding forces within the tablet even at relatively low pressures.

Table 3-17 : Crushing force (n=10) and maximum disintegration time (n=6) of the tablets prepared from the enteric coated pellet formulations.

Designation	Pellet core	Polymer weight gain (mg/cm2)	Type of punches	Compression pressure (MPa)	Crushing force (N)		Disintegration time (s)
					Mean	S.D.*	
BCC1-Tab	κ-carrageenan pellets	2.7	Oblong	48.8	80.2	7.1	14
				68.3	141.8	7.0	30
				97.6	214.0	4.7	161
				146.4	262.9	9.6	> 900
BCC2-Tab	κ-carrageenan pellets	4.2	Oblong	48.8	84.8	5.1	12
				68.3	149.4	4.7	32
				97.6	217.6	6.8	170
				146.4	258.9	11.1	> 900
BCC2-TabR	κ-carrageenan pellets	4.2	Round	48.8	77.0	6.4	11
				68.3	139.0	8.2	28
				97.6	213.0	6.6	152
				146.4	251.0	9.8	> 900
BMC2-Tab	MCC pellets	4.3	Oblong	48.8	73.2	4.6	9
				68.3	130.7	6.6	27
				97.6	203.9	5.9	147
				146.4	245.3	14.0	> 900

*Standard deviation.

The crushing force of tablets prepared from κ-carrageenan pellets was slightly higher than those prepared from MCC pellets. This could be probably attributed to the higher resistance to densification of MCC pellets. Thommes and Kleinebudde (2006a) reported lower porosity of MCC pellets compared to κ-carrageenan pellets and attributed the difference to the higher shrinkage of MCC pellets during drying.

For all pellet formulations increasing the compression pressure resulted in tablets with higher crushing force in the range of pressures used.

3.4.4.2 Disintegration Time

All prepared tablets disintegrated rapidly (table 3-17), thus maintaining a multiparticulate behavior of the system except for those compressed at the highest compression pressure (146.4 MPa) where no complete disintegration of the tablets could be obtained within 15 min. Most probably the high volume reduction of the embedding powder at this highest pressure resulted in less effective percolation of the embedding medium and more contact between some of pellets in the tablet hence inducing local fusion of the coating layer taking also a non-ideal mixture in consideration. The same problem was reported by Beckert et al. (1996) for pellets coated with a 50:50 mixture of Eudragit® L and Eudragit® NE and compressed using cellactose® (spray dried excipient consisting of 75% α-lactose monohydrate and 25% cellulose powder) as powder bed (percentage of pellets 50%) at high compression forces. Beckert attributed this phenomenon to the formation of sinter bridges between the coated pellets proposed by Malamataris (1983). Pre-mixing of the pellets with magnesium stearate before subsequent mixing with the embedding powder in the mentioned study enabled faster disintegration of the tablets. This approach seemed not necessary in the current study since tablets with sufficient mechanical strength and short disintegration time were already formed at lower compression pressures with the embedding formulation used. Moreover, changing the mixing sequence may influence the mechanical resistance of the resulting tablets due to the prolonged mixing time with magnesium stearate.

The disintegration time of the prepared tablets increased with increased compression pressure. Only the disintegrating tablets were further investigated.

3.4.4.3 Drug release

3.4.4.3.1 Effect of coating level

The level of the coating influenced the amount of drug released in the acidic medium for the compressed pellets (figure 3-23). At a coating level of 2.7 mg

polymer/cm^2 for κ-carrageenan pellets the coating layer did not sufficiently withstand the compression conditions and led to more than 10% drug release after 2 h in the acidic medium at all compression pressures used. Increasing the coating level to 4.2 mg/cm^2 resulted in adequate resistance with less than 10% drug release after the acidic stage. It seems, therefore, that a sufficient coating thickness is necessary to protect the film against the pressure applied during the compression process.

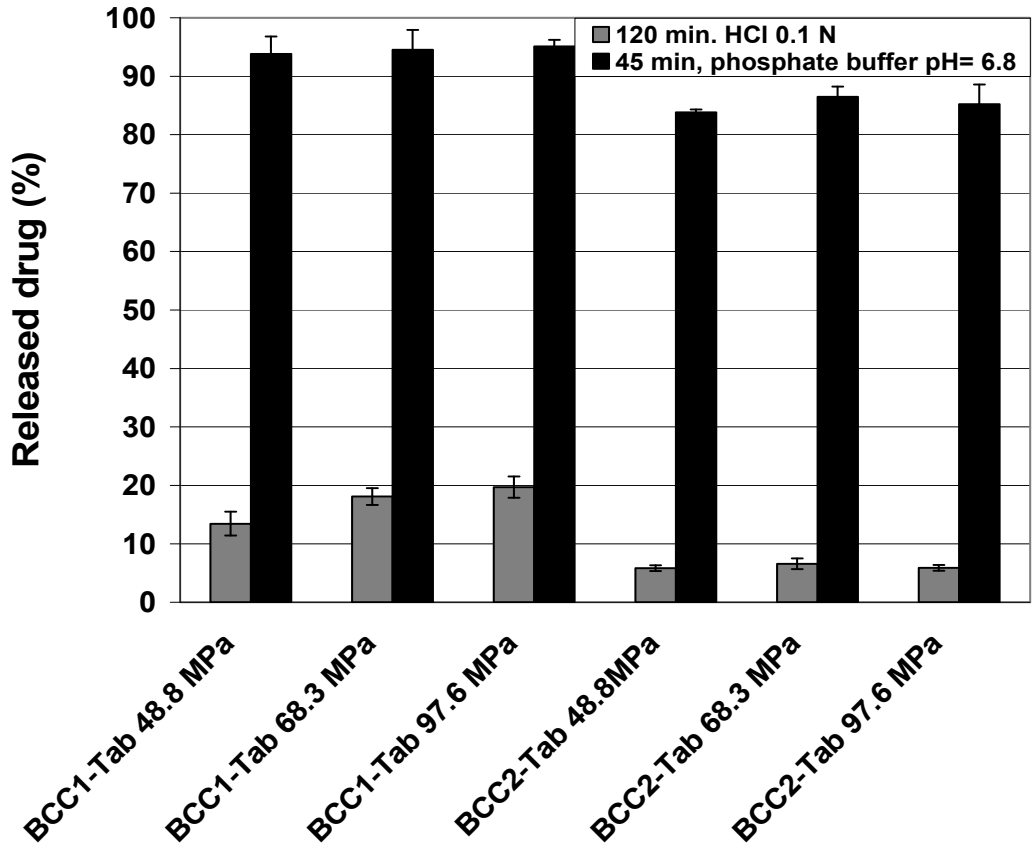


Figure 3-23: Bisacodyl release from the tablets prepared from enteric coated κ-carrageenan pellets using SMCC HD 90 as embedding powder (percentage of Pellets 50%): (BCC1-Tab) tablets prepared from pellets coated with 2.7 mg polymer/cm^2, (BCC2-Tab) tablets prepared from pellets coated with 4.2 mg polymer/cm^2 (37° C, paddle, 100 rpm).

Scanning electron micrographs of the fracture surfaces and upper surfaces of the tablets (figure 3-24) show significant deformation of the coating layer for pellets close to the centre of the tablet and the presence of some cracks in the film layer for pellets at the periphery and those at the upper surface of the tablet in case of tablets prepared starting from κ-carrageenan pellets coated with 2.7 mg polymer/cm^2. Less deformation, no significant cracks in the

coating layer in the pellets close to the surface of the tablets and deformation of the coating layer in the form of wrinkles for the pellets at the surface of the tablet were observed for the tablets prepared from the pellets coated with 4.2 mg polymer/cm^2.

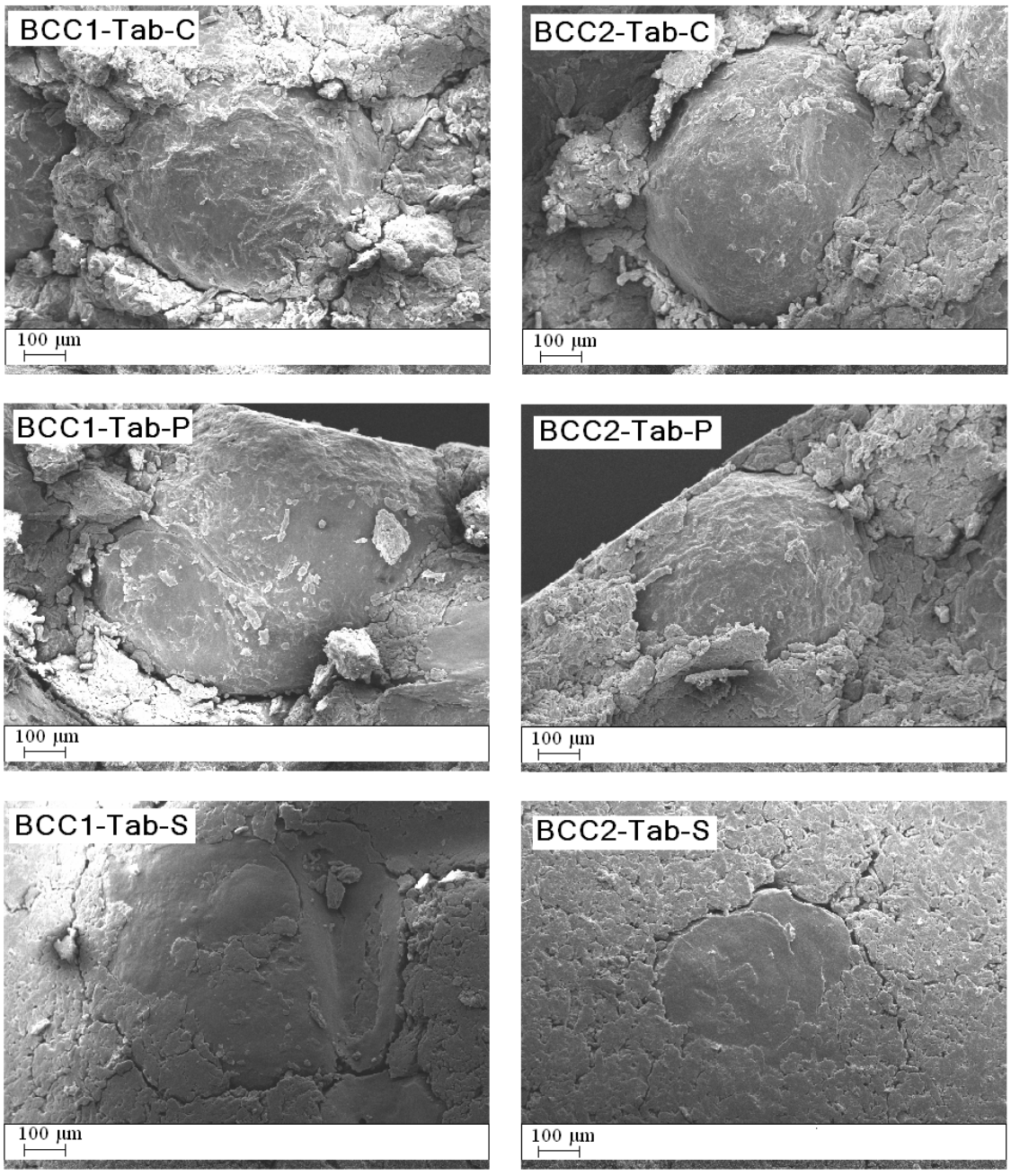


Figure 3-24: SEM micrographs of the pellets close to the center (C), at the periphery (P) and at the surface (S) of the tablets prepared from the enteric pellet formulations. (BCC1-Tab) tablets prepared from κ-carrageenan pellets coated with 2.7 mg polymer/cm^2, (BCC2-Tab) tablets prepared from κ-carrageenan pellets coated with 4.2 mg polymer/cm^2 (SMCC HD 90 as embedding powder, percentage of pellets 50%, compression pressure 97.6 MPa).

It is to be mentioned that the pellet formulation used in this study is quite challenging since the active ingredient is soluble in acidic pH and the filler used show also good solubility in HCl 0.1 N. For drugs with low solubility in acids a low coating level may be sufficient to protect the drug in the acidic medium as reported by Lehmann et al. (1993) for pellets containing indomethacin and acetylsalicylic acid coated with a 50:50 mixture of Eudragit® L and Eudragit® NE.

3.4.4.3.2 Effect of compression pressure

The compression pressure influenced the amount released in the acidic medium in case of κ-carrageenan pellets coated with 2.7 mg polymer/cm^2 whereas no statistically significant difference was noticed in case of the pellets coated with the higher amount of polymer (4.2 mg/cm^2) in the range of pressures used (Anova, 95% confidence level). It seems therefore that at this sufficient film thickness no damage can occur to the pellets inside the tablets at the compression pressures used whereas only the pellets at the surfaces of the tablets, i.e. those which are in contact with the punches and the die upon compression exhibit significant damages in their coating upon compression. This assumption is in good agreement with observations made previously related to scanning electron micrographs of the tablets compressed at the highest compression force leading to disintegrating pellets (figure 3-24). The thick coat is thus robust against the compression pressure in the range of pressures used.

3.4.4.3.3 Effect of pellet core

Bisacodyl release after the acidic and neutral stage form tablet prepared from κ-carrageenan pellets coated with 4.2 mg/cm^2 polymer and from those prepared from coated MCC pellets is illustrated in figure 3-25.

The amount of drug released in after 2 h HCl 0.1 N showed no pronounced difference between the two tablets groups. Again, the compression force did not influence the amount released in the acidic medium in case of the tablets prepared from coated MCC pellets.

The percentage of drug released after 45 min in phosphate buffer was, as observed in case of the pellets, much lower in case of the tablets made from

MCC pellets compared to the tablets made of κ-carrageenan pellets. It seems therefore that the fast disintegration of κ-carrageenan pellets is advantageous against the lack of disintegration of MCC pellets which leads to slow drug release.

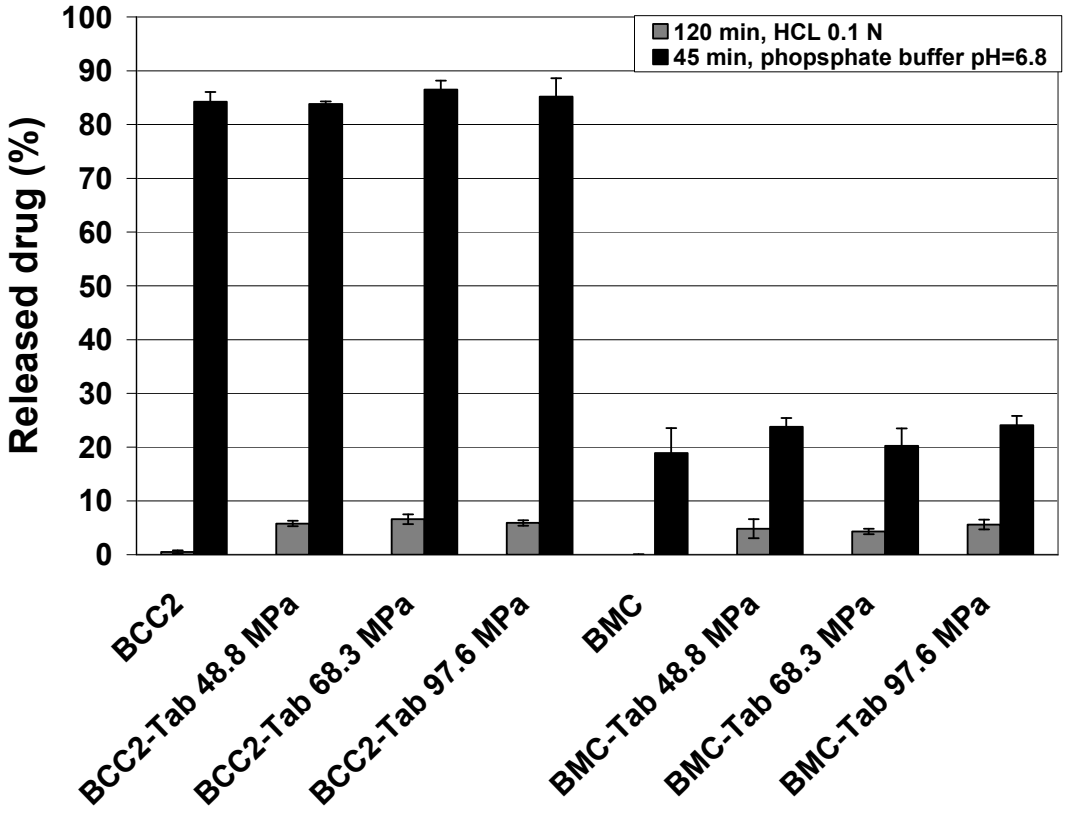


Figure 3-25: Bisacodyl release from the tablets prepared from the enteric coated κ-carrageenan and MCC pellets using SMCC HD 90 as embedding powder (percentage of Pellets 50%): (BCC2-Tab) tablets prepared from κ-carrageenan pellets coated with 4.2 mg polymer/cm^2, (BMC-Tab) tablets prepared from MCC pellets coated with 4.3 mg polymer/cm^2 (37° C, paddle, 100 rpm).

Scanning electron micrographs (figure 3-26) show no significant deformation or damage in the coating layer for the pellets at the center and periphery of tablets and some wrinkling of the coating film for tablets at the surface of the tablet for both types of pellets studied.

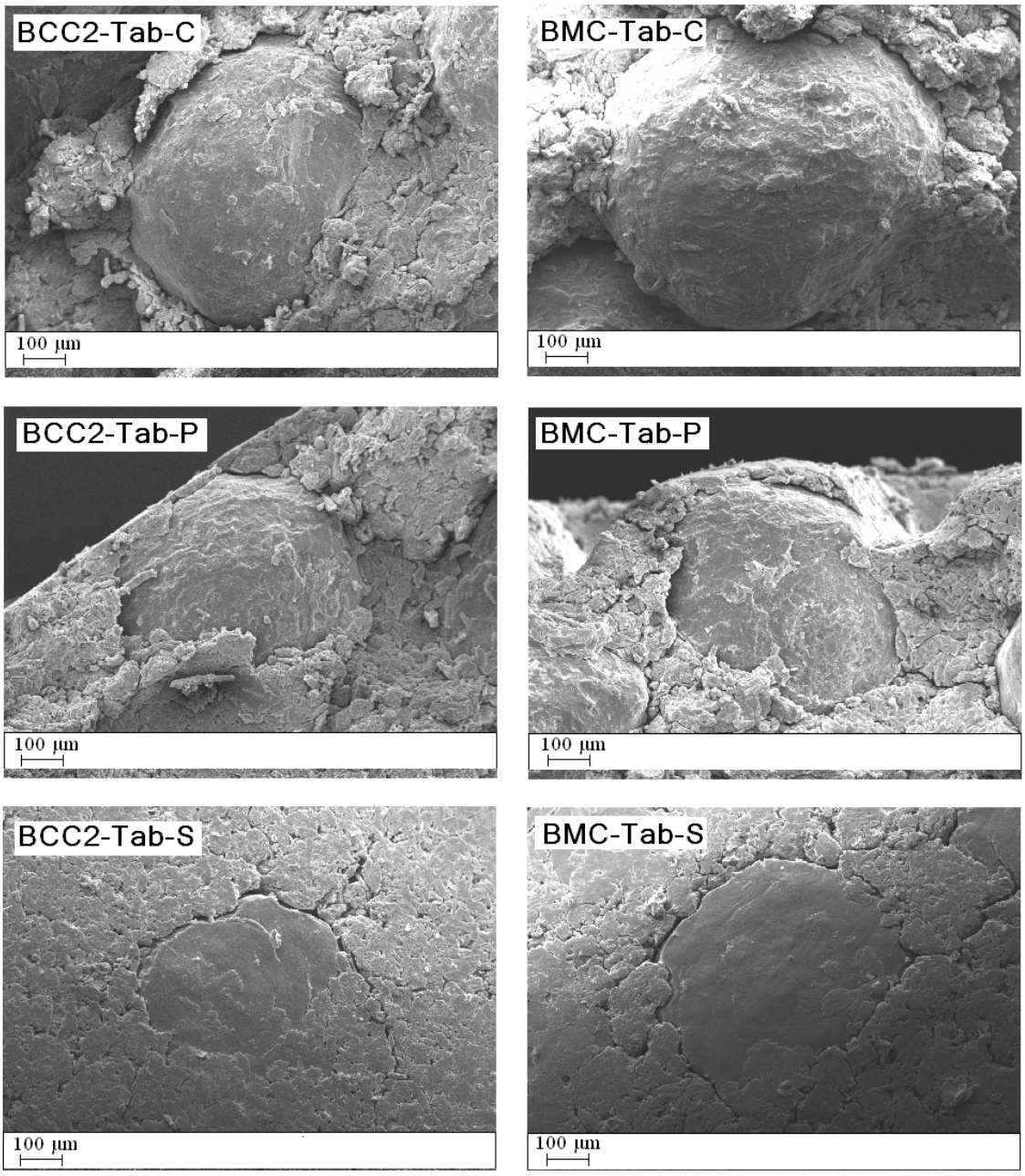


Figure 3-26: SEM micrographs of the pellets close to the center (C), at the periphery (P) and at the surface (S) of the tablets prepared from the enteric pellet formulations: (BCC2-Tab) tablets prepared from κ-carrageenan pellets coated with 4.2 mg polymer/cm^2, (BMC-Tab) tablets prepared from MCC pellets coated with 4.3 mg polymer/cm^2, (SMCC compression pressure 97.6 MPa).

3.4.4.3.4 Effect of punch configurations

Both types of punches used (oblong biconvex or round biconvex) led to multiparticulate tablets with sufficient crushing force and short disintegration time (table 3-17). The type of punches used did not significantly influence the drug release from κ-carrageenan pellets coated with 4.2 mg polymer/cm^2 at the range of pressures applied in this study (figure 3-27). Again no cracks in the film layer were noticed in the breakage surface of the tablets made using the round punches and the pellets on the outer surface of the tablets exhibited damages in the form of wrinkles in their coating (figure 3-28).

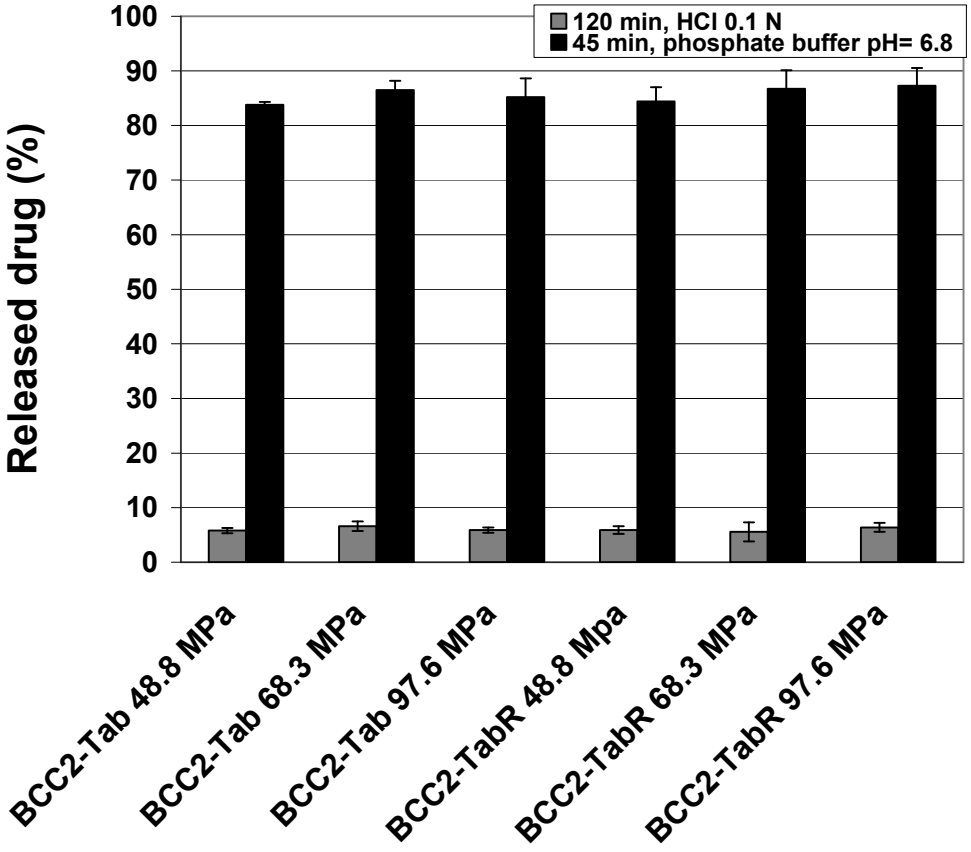


Figure 3-27: Bisacodyl release from the tablets prepared from enteric coated κ-carrageenan pellets (coating level 4.2 mg polymer/cm^2, SMCC HD 90 as embedding powder, percentage of Pellets 50%): (BCC2-Tab) tablets prepared using oblong punches. (BCC2-Tab-R) tablets prepared using round punches (37° C, paddle, 100 rpm).

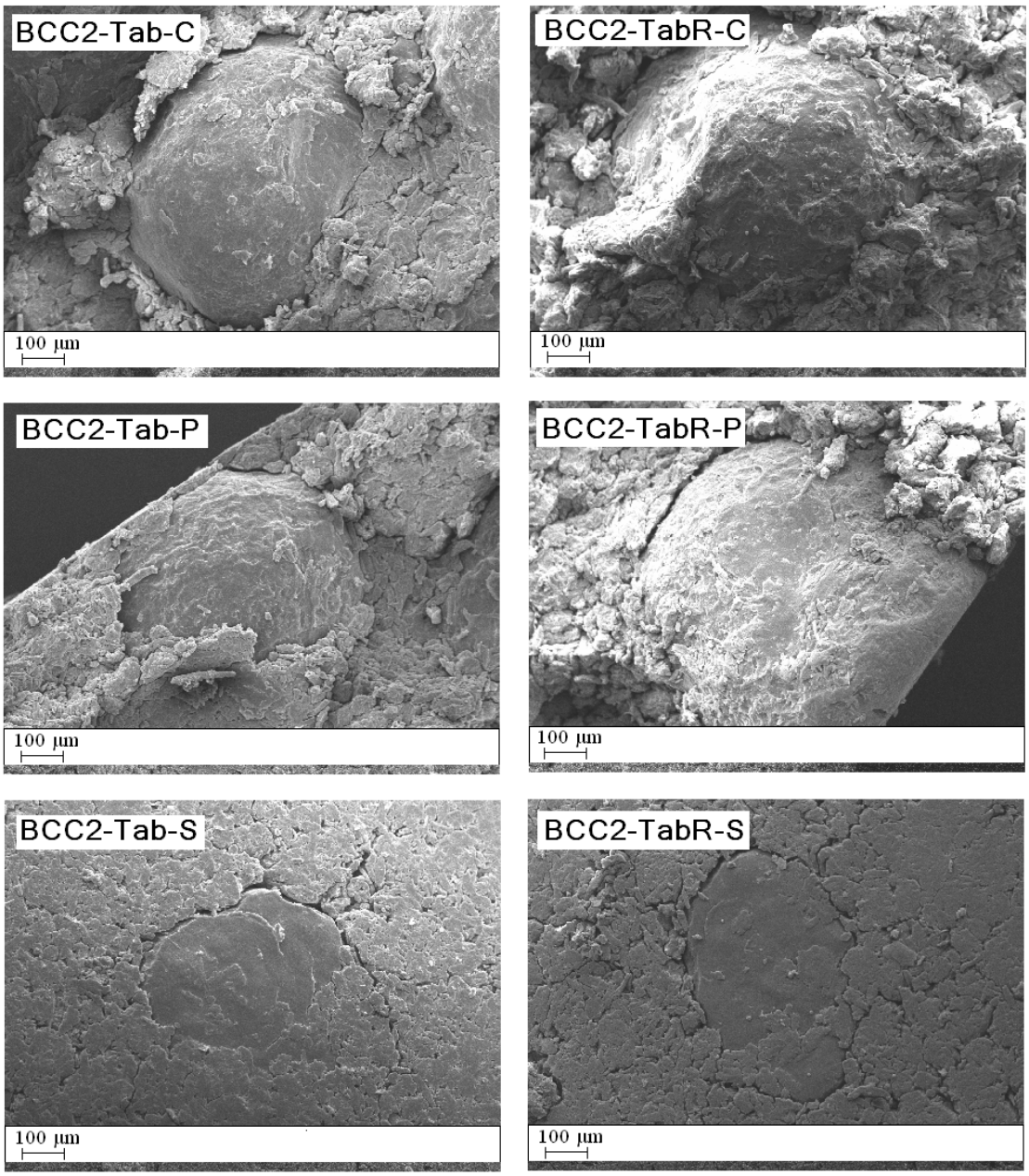


Figure 3-28: SEM micrographs of the pellets close to the center (C), at the periphery (P) and at the surface (S) of the tablets prepared from the enteric pellet formulations. (BCC2-Tab) tablets prepared from κ-carrageenan pellets coated with 4.2 mg polymer/cm2 and compressed using oblong punches, (BCC2-TabR) tablets prepared from κ-carrageenan pellets coated with 4.2 mg polymer/cm2 and compressed using round punches (SMCC HD 90 as embedding powder, percentage of pellets 50%, compression pressure 97.6 MPa).

3.4.5 Summary of results

κ-carrageenan pellets are advantageous over MCC pellets for the formulation of multiparticulate tablets with enteric properties. After passing the acidic stage the fast disintegration of κ-carrageenan pellets leads to adequate drug release in the neutral medium whereas poor release is observed for MCC pellets due to their lack of disintegration. An adequate coating level is necessary for sufficient enteric resistance of the multiparticulate tablets leading to a robust film against the compression pressure and the punch configurations.

3.5 Compression of κ-carrageenan pellets with sustained release coating

3.5.1 Objective and choice of polymer and formulations

The short disintegration time (only a few minutes) and the known swelling of κ-carrageenan (Thommes and Kleinebudde 2006a,b, 2007b) represent possible concerns when these pellets are to be presented in a coated sustained release dosage form. These concerns become even higher when the pellets with a sustained release coating are intended to be compressed into tablets due to the compression-induced changes in the surrounding film. A last objective of the current work was to investigate the suitability of pellets prepared with κ-carrageenan as a pelletization aid for the formulation of multiparticulate tablets with sufficient prolonged release properties.

Theophylline, a drug with good solubility in the release medium (phosphate buffer pH= 6.8) was chosen as a model drug in order to examine whether pellets prepared using κ-carrageenan are able to provide sufficient prolonged release properties which can be maintained after compression. Pellets containing MCC as pelletization aid were also prepared for comparison (table 3-18). The sieved size fraction (500-800 µm) was used in the study.

Table 3-18: Prepared pellet formulations and amount of water used for extrusion/spheronization based on the weight of solids.

Ingredient	TC	TM
Theophylline monohydrate (%)	80	80
κ-carrageenan (%)	20	
Microcrystalline cellulose (%)		20
Deionized water (%)	52	36

Kollicoat SR® 30 D (polyvinyl acetate) was chosen as a release modifying agent due to the fact that its plasticity can be significantly improved by the addition of 10% triethyl citrate. Dashevsky et al. (2004) reported an increase in the elongation at break of Kollicoat SR® 30 D casted films from less than 1% without plasticizer to up to 137% upon the addition of 10% triethyl citrate. In the same study sugar pellets layered with propranolol hydrochloride and coated with Kollicoat SR® 30 D plasticized with triethyl citrate were compressed into tablets using Avicel® PH 200 (MCC PH 200) as embedding

powder with maintained release profile at different compression forces, whereas compression of the same pellets after coating with Aquacoat® ECD 30 (ethyl cellulose polymer) plasticized with 25% triethyl citrate resulted in tablets exhibiting much faster drug release than that of the uncompressed pellets. Furthermore, the release rate from the latter pellets increased at higher compression forces and was attributed to the brittle nature of plasticized Aquacoat® film casts reported by Bodmeier and Paeratakul (1994). Zeeshan and Bukhari (2010) also used Kollicoat® SR plasticized with triethyl citrate to coat pellets prepared by extrusion/spheronization with MCC as pelletization aid and containing pseudoephedrine hydrochloride. The coated pellets were subsequently mixed with immediate release pellets containing loratidine and pseudoephedrine HCl and successfully compressed into multiparticulate tablets with a similar release profile to that from multiple-unit capsules containing the same pellet mixture.

Glycerol monostearate was used again as an anti-tacking agent to keep a minimum influence on the mechanical properties of the coating film layer. Kollicoat® IR (polyvinyl alcohol-polyethylene glycol graft copolymer) was added as a pore former to allow for drug release from the insoluble polymer film. The coating level and amount of pore former were varied in order to achieve 80 -100% drug release over about 10-12 hours for κ-carrageenan- and MCC based pellets.

The coated pellets were compressed at different compression pressures to give tablets containing 200 mg theophylline. The tablet formulation consisted of 50% pellets, 49.2% SMCC HD90, 0.75% crospovidone and 0.05% magnesium stearate. The prepared tablets were then characterized in terms of mechanical resistance, disintegration time and drug release.

3.5.2 Characterization of the uncoated pellets

3.5.2.1 Size and shape

Table 3-19 shows the size and shape factors of the chosen size fraction (500-800 µm) of the prepared pellet formulations. The prepared κ-carrageenan and MCC pellets were approximately similar in size. The two pellet formulations met the required specifications for a successful subsequent coating in terms

of sphericity (median aspect ratio around 1.1) and narrow particle size distribution (10% interval of the dimensionless equivalent diameter exceeded 50%).

Table 3-19: Mean and median Feret diameter, 10% interval and aspect ratio of the chosen size fraction (500-800 µm) of the prepared pellet formulations (n=500).

Formulation	Feret diameter			10 % interval	Aspect ratio	
	Mean (µm)	CV* (%)	Median (µm)		Median	Interquartile range
TC	660	11.3	667	60.2	1.12	0.090
TM	671	9.0	672	70.4	1.09	0.079

3.5.2.2 Disintegration time

The pellets prepared using κ-carrageenan as pelletization aid exhibited a short disintegration time of few minutes (233± 23 s) for whereas MCC based pellets did not disintegrate after 24 h in the disintegration apparatus.

3.5.2.3 Drug release

The drug release from the uncoated pellet formulations is illustrated in figure 3-29.

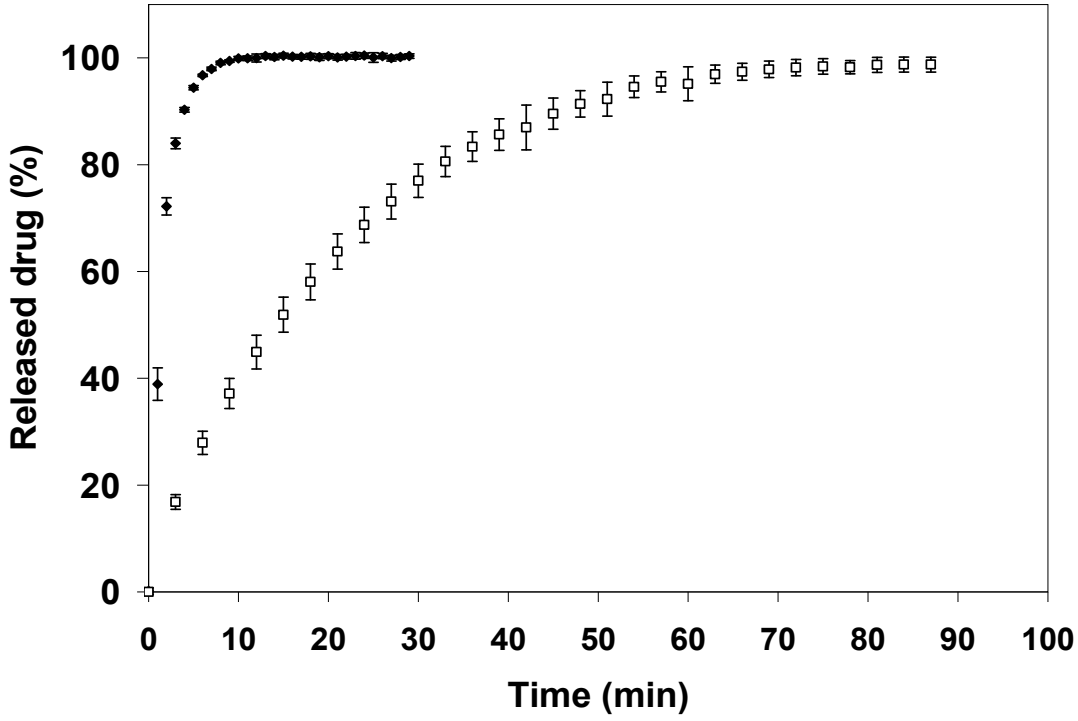


Figure 3-29: Theophylline release from uncoated (♦) κ-carrageenan and (□) MCC pellets (phosphate puffer pH=6.8, 37° C, paddle, 50 rpm, mean ± SD, n=6).

κ-carrageenan based pellets released their active ingredient within a few minutes whereas the release of theophylline from MCC pellets was much slower. The Higuchi kinetic observed for MCC based pellets is attributed to the formation of retarding matrix associated with the lack of disintegration of these pellets unlike the fast disintegration observed in case of κ-carrageenan based pellets.

3.5.3 Drug release from the coated pellets

Figure 3-30 shows the release of theophylline from κ-carrageenan based pellets coated with Kollicoat® SR at two coating levels using 25% Kollicoat IR as a pore former. A low coating level (3.1 mg Kollicoat SR®/ cm^2) was insufficient to obtain adequate prolongation of drug release and almost 100% theophylline was released within three hours. Increasing the coating level to 6.1 mg polymer/ cm^2 resulted in extended drug release over 10 hours. A lag time of about 20 minutes was observed for the pellets with high coating level and can be attributed to the time needed for the dissolution medium to penetrate the thick coat and dissolve the drug in the core. An initial slow release stage was noticed for both coating levels most probably due to the known swelling of κ-carrageenan pellets reported by Thommes and Kleinebudde (2007b) and observed in the dissolution apparatus. Swelling of κ-carrageenan may result in the formation of an outer gel layer surrounding the rest of pellets and slowing the drug release. Such swelling was not noticed in the case of uncoated pellets (figure 3-29) due to the fast erosion and disintegration of the studied small pellets upon complete contact with the release medium, which is a different condition from that for the coated pellets. Similar behavior and release profile to κ-carrageenan pellets coated in this study was reported by Schultz and Kleinebudde (1997) for MCC based pellets containing NaCl as osmotic active agent and coated with a semi-permeable cellulose acetate membrane whereby regardless of the coating level applied an initial lag time followed by a short phase of slow release then a main phase of faster zero order kinetic release (about 10-70%) of the drug were observed. Schultz pointed out a release rate which is controlled by the change of membrane structure induced by the osmotic active agent after the initial lag time corresponding to water penetration through the membrane

depending on the coating thickness. After a maximal osmotic pressure and consequently maximal swelling is achieved the semi- permeable membrane is converted to a porous membrane. For the studied coated κ-carrageenan pellets an initial lag time corresponds most probably to the time needed for water to penetrate through the pores formed after the dissolution of Kollicoat® IR in the thick coat. Upon first contact with the limited amount of dissolution medium reaching the pellet surface a gel layer could be formed which could be attributed to polymer relaxation after water absorption. The penetration of further amount of liquid in the system causes the erosion of the outer layer then that of the core and a faster solely membrane- dependent drug release is expected which corresponds to the linear portion of the curves.

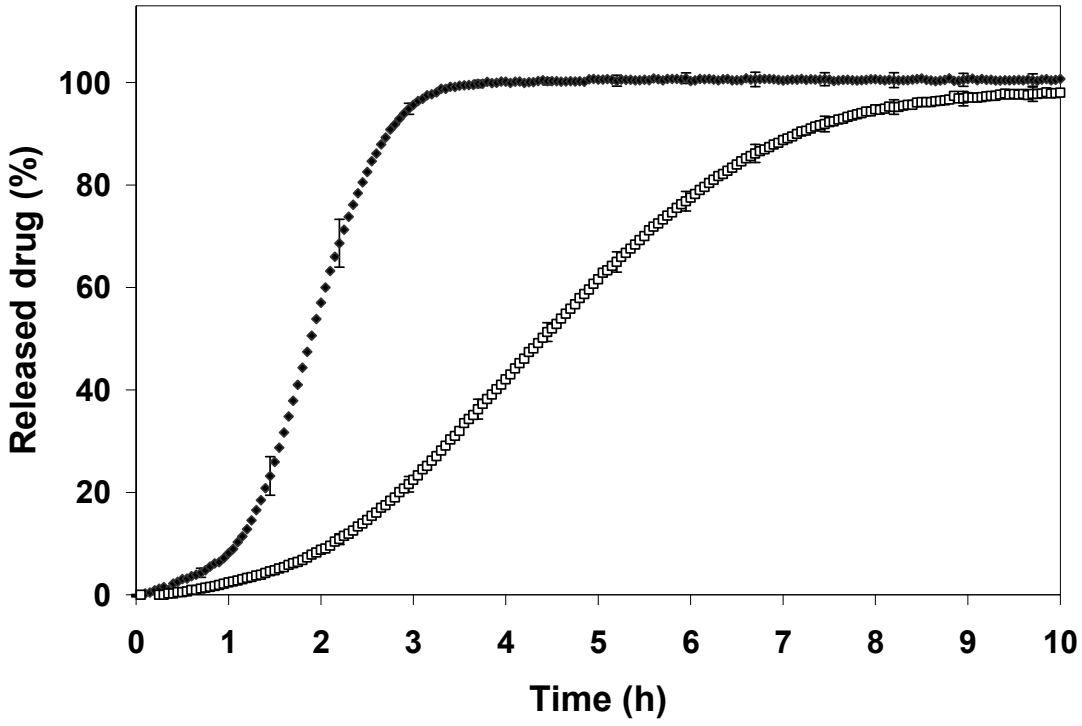


Figure 3-30: Theophylline release from κ-carrageenan pellets coated with Kollicoat® SR at two coating levels: (♦) 3.1 mg/cm² and (□) 6.1 mg/ cm² (25% pore former, phosphate puffer pH=6.8, 37° C, paddle, 50 rpm, mean ± SD, n=6).

The drug release from coated MCC pellets is illustrated in figure 3-31. A low coating level (1.9 mg Kollicoat SR®/ cm²) with the same percentage of pore former Kollicoat® IR (25% based on the dry weight of Kollicoat® SR) used for κ-carrageenan pellets resulted in a highly variable and a prolonged release

pattern with 80% of the active ingredient released over 20 h. Increasing the percentage of Kollicoat® IR to 40% and the coating level to 4 mg/cm^2 resulted in a more homogenous drug release with 80% of the active released over 10 h. Neither lag time nor slow initial release was observed for MCC based pellets in contrast to κ-carrageenan based pellets. The thinner coating layer, the higher amount of pore former and the non-swelling of MCC based pellets are possible reasons for the difference observed between the two types of pellets at the initial stage of drug release.

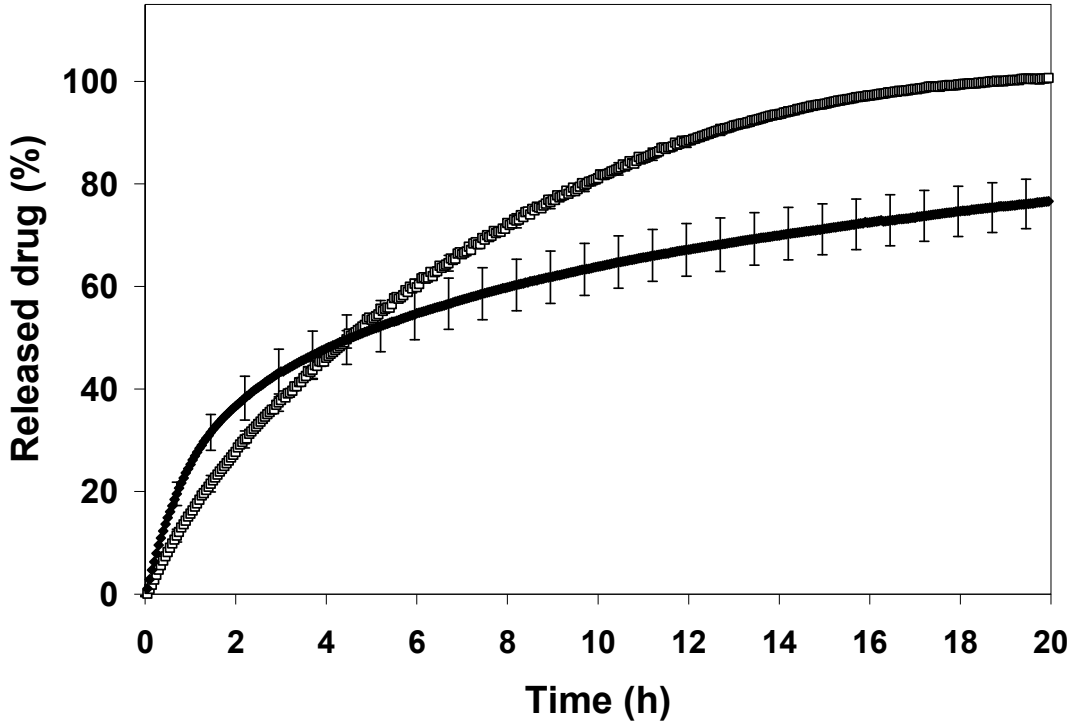


Figure 3-31: Theophylline release from MCC pellets coated with Kollicoat® SR: (♦)1.9 mg/cm^2, 25% pore former (□) 4 mg/ cm^2, 40% pore former (phosphate puffer pH=6.8, 37° C, paddle, 50 rpm, mean ± SD, n=6).

3.5.4 Characterization of tablets

3.5.4.1 Crushing force

Compression of both κ-carrageenan based pellets coated with 6.1 mg Kollicoat SR®/cm^2 with 25% Kollicoat® IR as pore former and MCC based pellets coated with 4 mg Kollicoat SR®/cm^2 and 40% Kollicoat® IR (average tablet weight 811±007 and 724±006 mg respectively, n=20) resulted in tablets with sufficient mechanical properties at all compression pressures used (Table

3-20). The crushing force of the tablets increased with increased compression pressure.

Table 3-20: Crushing force and disintegration time of the tablets prepared from the pellet formulations coated with Kollicoat® SR 30 D.

Designation	Pellet core	Weight gain (mg Kollicoat ®SR /cm2)	% of Kollicoat IR	Compression pressure (MPa)	Crushing force (N)		Disintegration time (s)
					Mean	S.D.*	
TCC2-Tab	κ-carrageenan pellets	6.1	25	29.2	73.9	4.2	35
				40.9	133.4	6.2	61
				58.5	156.9	4.9	72
				87.7	210.6	4.3	162
TMC2-Tab	MCC Pellets	4.0	40	29.2	46.5	4.5	19
				40.9	72.8	5.4	41
				58.5	137.7	5.0	50
				87.7	171.0	7.4	141

*Standard deviation

3.5.4.2 Disintegration time

The prepared tablets showed short disintegration time at all compression pressures used (table 3-20) thus maintaining a multiparticulate behavior of the system. The disintegration time increased with increased compression pressure.

3.5.4.3 Drug release

Both pellet formulations maintained their release properties after compression regardless of the compression pressure used (figures 3-32 and 3-33).

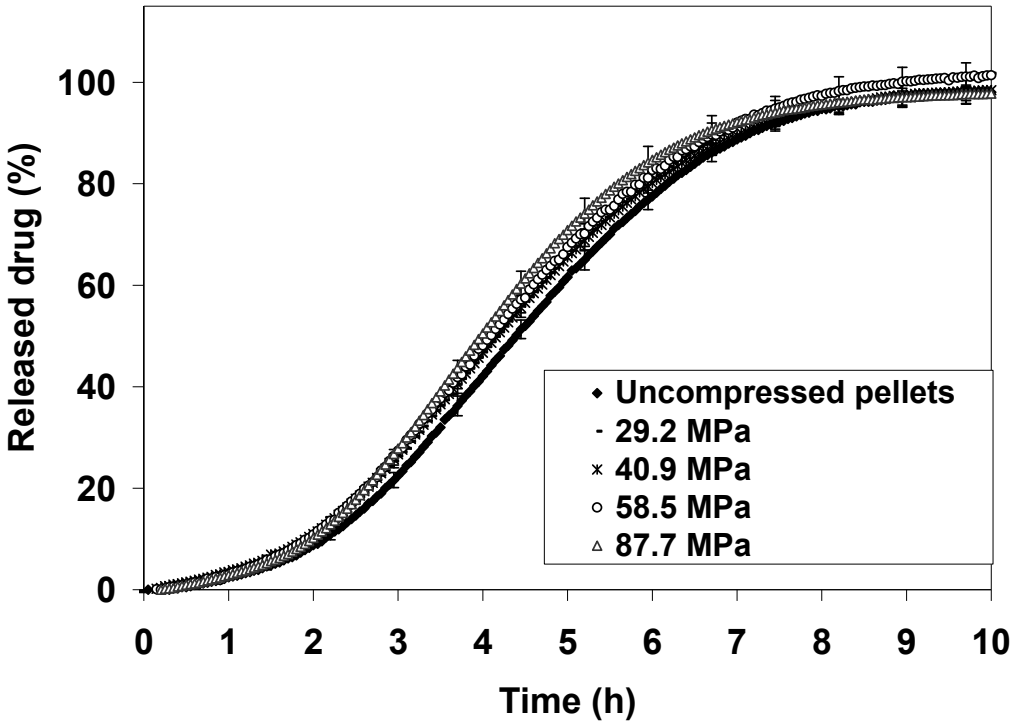


Figure 3-32: Theophylline release from uncompressed and compressed κ-carrageenan pellets coated with Kollicoat® SR (coating level 6.1 mg/cm², 25% pore former, SMCC HD 90 as embedding powder, percentage of pellets 50%).

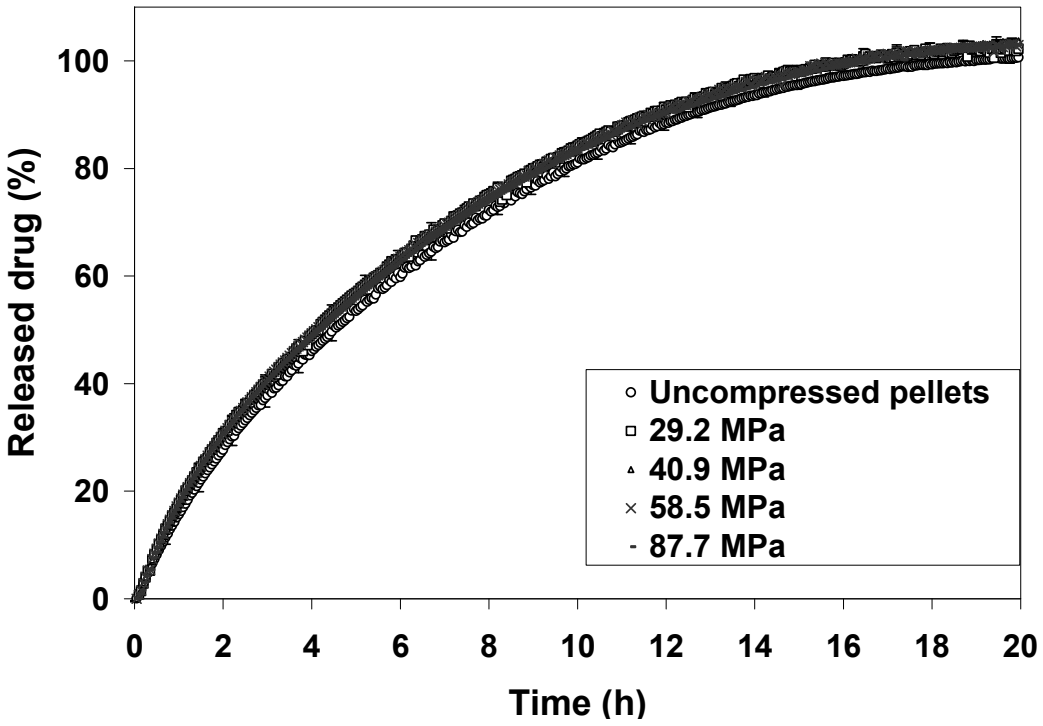


Figure 3-33: Theophylline release from uncompressed and compressed MCC pellets coated with Kollicoat® SR (coating level 4 mg/cm², 40% pore former, SMCC HD 90 as embedding powder, percentage of pellets 50%).

The similarity factors of the dissolution curves with those of the uncompressed pellets are summarized in table 3-20. The calculated similarity factors were all above 50% suggesting that the tablets formed at all compression pressures used are similar to those of their starting pellets (Moore and Flanner, 1996). Coated MCC pellets were more robust at the high compression pressures used compared to κ- carrageenan pellets, which could be attributed to both the more flexible nature of the film coating in case of MCC pellets due to the higher level of the polymer Kollicoat® IR (elongation at break about 100%, Bühler 2007) in the formulation and to the absence of swelling compared to κ-carrageenan pellets.

Table 3-21: Similarity factors for the dissolution curves of theophylline pellets coated with Kollicoat® SR and compressed at different compression pressures in comparison to the uncompressed pellets.

Designation	Compression pressure (MPa)	Similarity factor (%)
TCC2-Tab	29.2	77.2
	40.9	72.4
	58.5	69.2
	87.7	64.5
TMC2-Tab	29.2	76.8
	40.9	78.5
	58.5	77.4
	87.7	80.3

Scanning electron micrographs (figure 3-34) show no cracks in the film coating for pellets at the center, close to the surface and those at the upper surface at the highest compression pressure used for both MCC and κ-carrageenan pellets-based tablets. The small changes in the release profile could be attributed to the deformation and the thinning of the film coating of the pellets at some parts of the tablets.

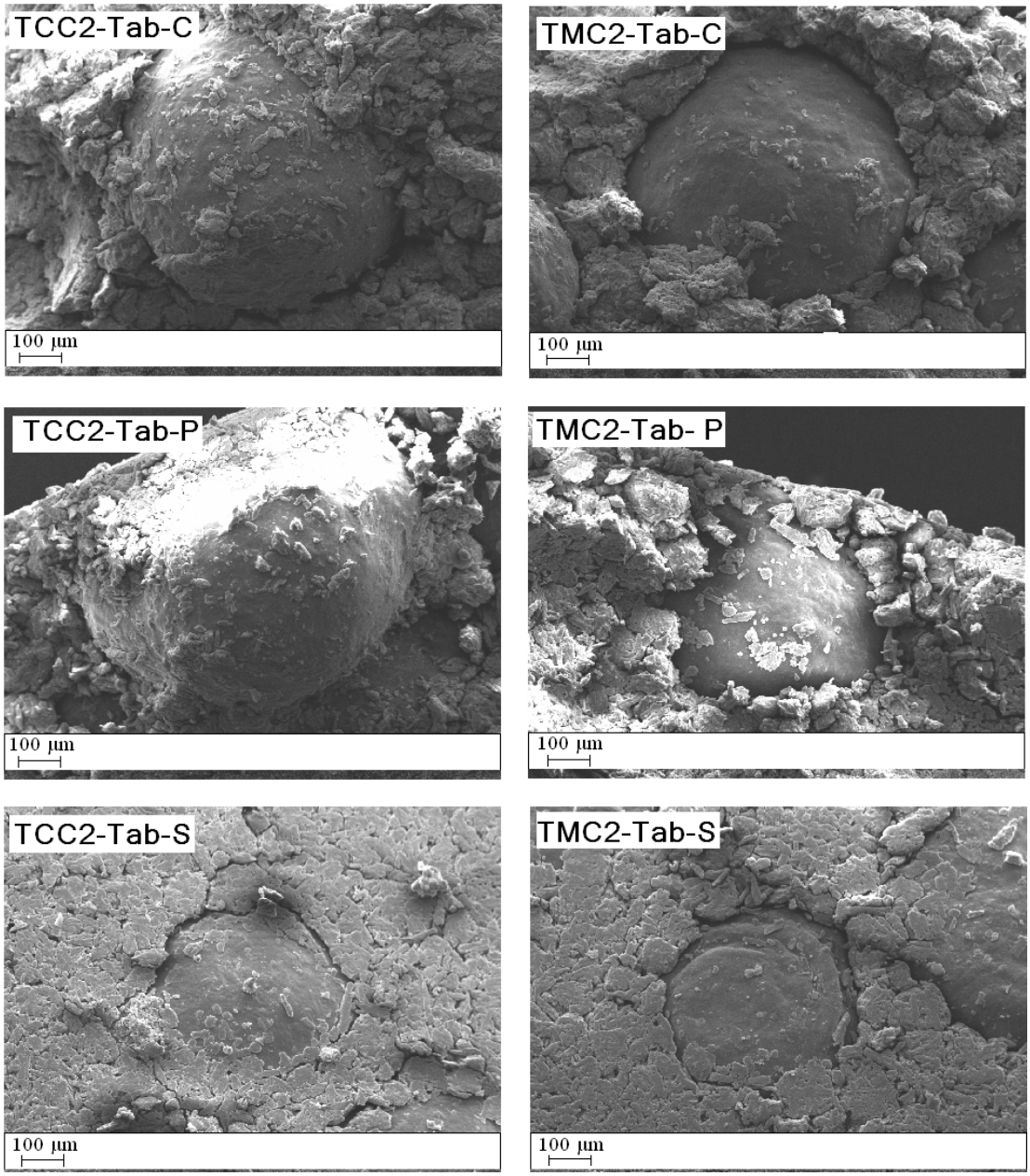


Figure 3-34: SEM micrographs of the pellets close to the centre (C), at the periphery (P) and at the surface (S) of the tablets prepared from the pellet formulations coated with Kollicoat® SR: (TCC2-Tab) tablets prepared from κ-carrageenan pellets coated with 6.1 mg Kollicoat® mg/cm² with 25% pore former, (TMC2-Tab) tablets prepared from MCC pellets coated with 4 mg Kollicoat® SR /cm² and 40% pore former (SMCC HD 90 as embedding powder, percentage of pellets 50%, compression pressure 87.7 MPa)

3.5.5 Summary of results

κ-carrageenan pellets can be successfully formulated into multiparticulate tablets with sustained release properties. For the mentioned pellets a higher coating level and lower amount of pore former are needed to achieve a certain release profile compared to MCC pellets. Pellets made using the two mentioned pelletization aids and coated with a sustained release film show different release mechanisms.

4 Summary of the work

The feasibility of using a flat die press for the manufacture of small pharmaceutical pellets (400-1000 µm) by extrusion/spheronization was investigated. Pellet formulations with high- and low drug strength containing different model drugs and excipients with different solubility were produced using κ-carrageenan as pelletization aid and a die plate with 0.6 mm die diameter. The prepared pellet formulations were assessed in terms of size distribution, shape and drug release properties. All formulations showed a high yield of the pelletization process and a narrow size distribution. The median aspect ratio was approximately 1.1 indicating acceptable sphericity with exception of high dose furosemide pellets due to the small-sized needle-shaped active. Drug release from the pellets showed good batch uniformity and conformity. The flat die press is a promising choice for the production of pellets by extrusion/spheronization with high formulation robustness.

κ-carrageenan is a novel pelletization aid with high process- and formulation robustness and quick disintegration leading to fast drug release unlike the matrix-like release from non-disintegrating microcrystalline cellulose based pellets. Compression of pellets into tablets is more cost effective compared to their encapsulation. The feasibility of formulating multiparticulate tablets with κ-carrageenan pellets was systematically investigated.

As a first step the compression behavior of high- and low drug strength pellets containing κ-carrageenan as pelletization aid was investigated. Model drugs and fillers with different compression mechanisms (plastic, brittle) were used and the effects of compression force and turret speed were examined. Regardless of the compression behavior of their starting components, all pellet formulations exhibited minimal to absent fragmentation and underwent compression by deformation, confirmed by increased equivalent diameter and aspect ratio and decreased roundness factor of the pellets retrieved after de-aggregation of tablets prepared from lubricated pellets. A densification mechanism was suggested based on increased fracture resistance and decreased total porosity and median pore radius of the compressed pellets.

As a second step the potential use of SMCC HD 90 as embedding powder for κ-carrageenan pellets was examined. SMCC HD 90 has shown to protect the pellets from severe deformation and resulted in tablets with sufficient tensile strength, minimal friability, negligible elastic recovery and short disintegration time. The percentage of the pellets and the compression force affected the tensile strength and the disintegration time of the prepared tablets.

Thirdly the feasibility of compressing enteric coated κ-carrageenan pellets was studied. Pellets containing a highly soluble drug in acid, namely bisacodyl and κ-carrageenan or MCC as pelletization aid were prepared, enteric coated with a mixture of Kollicoat MAE® 30 DP and Eudragit® NE 30 D and compressed using silicified microcrystalline cellulose as embedding powder. The effect of coating level, pellet core, compression force and punch configurations on drug release were studied. A sufficient coating thickness for κ-carrageenan pellets was necessary to obtain multiparticulate tablets with adequate resistance in the acid stage regardless of the compression pressure used. While κ-carrageenan pellets and their tablets released over 80% of the drug in the neutral stage only about 20-24% was released from MCC pellets and their tablets. The type of punches used (oblong or round) did not significantly influence the drug release from the prepared tablets.

Finally, despite the swelling and the short disintegration time of κ-carrageenan pellets, sufficient prolonged release properties were obtained with κ-carrageenan pellets containing theophylline as a model drug and coated with Kollicoat® SR 30 D as a sustained release agent using Kollicoat® IR as pore former. A lower coating level and higher amount of pore former were needed in case of theophylline pellets formulated with MCC as pelletization aid. The sustained release properties of both coated pellet formulations were maintained after compression at different compression pressures.

5 Materials and Methods

5.1 Materials

5.1.1 Pelletization aids

The main pelletization aid used in the current work is κ-carrageenan (table 5-1). Pellets with microcrystalline cellulose as pelletization aid were also produced for comparison (sections 3.4 and 3.5).

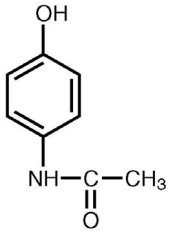
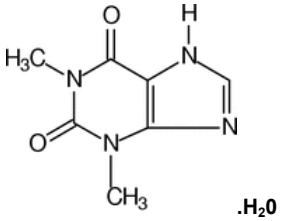
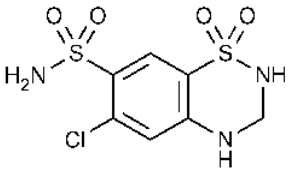
Table 5-1: Pelletization aids used.

Trade name	Type	Batch-No.	Manufacturer
Gelcarin® GP-911 NF	**κ-carrageenan**	**B20212160**	**FMC, Philadelphia, PA, USA**
MCC Sanaq® 102 G	**MCC PH 102**	**21207**	**Pharmatrans Sanaq AG, Basel, Switzerland**

5.1.2 Active ingredients

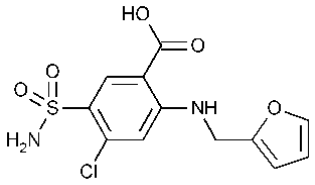
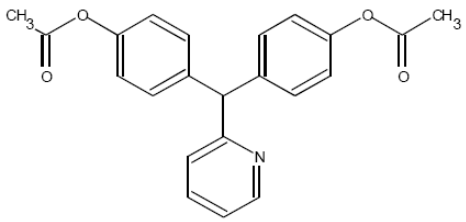
The active ingredients used in the work are presented in tables 5-2 and 5.3.

Table 5-2: Overview of the active ingredients used (I).

API	Paracetamol	Theophylline monohydrate	Hydrochlorothiazide
Quality	**Ph. Eur./USP**	**Ph. Eur./USP**	**Ph. Eur./USP**
Chemical structure			
Molecular weight [g/mol]	**151.2**	**198.2**	**297.7**
Solubility in water [g/l]	**14.3**[(1)]	**6.7**[(1)]	**0.6**[(1)]
BCS-class	**I**	**I**	**II**
Indication	**analgesic**	**bronchodilator**	**diuretic**
Batch-No.	**2703151**	**695361AX10**	**2070820010**
Manufacturer	**Atabay, Gebze, Turkey**	**BASF, Ludwigshafen, Germany**	**Unichem, Mumbai, India**

[(1)]AB Kommentar, 2006.

Table 5-3: Overview of the active ingredients used (II).

API	Furosemide	Bisacodyl
Quality	Ph. Eur.	Ph. Eur./USP/JP
Chemical structure		
Molecular weight [g/mol]	330.7	361.4
Solubility in water [g/l]	0.006[(2)]	0.003[(3)]
BCS-class	IV	IV
Indication	diuretic	laxative
Batch-No.	F-0805058	09030493
Manufacturer	Arandy, Hyderabad, India	Bidachem, Fornovo San Giovanni Italy

[(2)] Drug card for furosemide (DB00695), Drug bank, http://www.drugbank.ca/drugs/DB00695.
[(3)] Certificate of analysis. Boehringer-Ingelheim.

5.1.3 Fillers

The fillers used in the pellet formulations are summarized in table 5-4.

Table 5-4: Fillers used in the preparation of pellet formulations.

Name	Type	Solubility in water [g/l]	Batch- No.	Manufacturer
Granulac® 200[(4)]	Ph.Eur./USP	200[(5)]	L0523A4172	Meggle, Wasserburg, Germany
Mannitol 60	Ph.Eur./USP	80[(5)]	E10DC	Roquette, Lestrem, France
Meritena® 142[(6)]	Ph. Eur.	Insoluble	RV-G1984	Tate& Lyle, S. Nicaise, France
Dicafos® C92-14[(7)]	Ph.Eur./USP	insoluble	A68206	CFB, Budenheim, Germany

[(4)] α-Lactose monohydrate.
[(5)] Merck index, 1989.
[(6)] Corn Starch.
[(7)] Dicalcium phosphate dihydrate.

5.1.4 Coating excipients

The substances used for coating of the pellets are presented in table 5-5.

Table 5-5: Substances used for pellet coating.

Name	Quality	Batch- No.	Manufacturer
Kollicoat® MAE 30 DP[8]	**Pharma**	**66384788Q0**	**BASF, Ludwigshafen, Germany**
Kollicoat® SR 30 D[9]	**Pharma**	**12544024U5**	**BASF, Ludwigshafen, Germany**
Kollicoat® IR[10]	**Pharma**	**91449856P0**	**BASF, Ludwigshafen, Germany**
Eudragit® NE 30 D[11]	**USP/NF**	**B090112024**	**Evonik, Darmstadt, Germany**
Triethyl citrate	**Ph.Eur.**	**S4877051844**	**Merck, Darmstadt, Germany**
Silfoam® SE6[12]	**-**	**SE34190**	**Wacker, Nuechritz, Germany**
Polysorbate 80	**Ph.Eur.**	**53445106**	**Caelo, Hilden, Germany**
Glycerol monostearate	**Ph.Eur./ USP**	**607395E**	**Sasol, Witten, Germany**

[8] Methacrylic acid- ethyl acrylate copolymer.
[9] Polyvinyl acetate polymer.
[10] Polyvinyl alcohol-polyethylene glycol graft copolymer.
[11] Ethyl acrylate - methyl methacrylate copolymer.
[12] Silicone anti-foam emulsion.

5.1.5 Other substances

Table 5-6: Overview of excipients used for tablet preparation, dissolution and analytical methods.

Name	Quality	Batch- No.	Manufacturer
Prosolv® HD 90[13]	**USP/Ph. Eur**	**D9S8030**	**J.R.S. Pharma Rosenberg, Germany**
Kollidon® CL [14]	**Ph.Eur.**	**591641**	**BASF, Ludwigshafen, Germany**
Magnesium stearate	**Pharma**	**3043**	**Baerlocher, Unterschleissheim, Germany**
Sodium hydroxide	**Ph.Eur.**	**511903007**	**J.T. Baker, Deventer, Netherlands**
Citric acid anhydrous	**p.a.**	**120152429**	**Roth GmbH, Karlsruhe, Germany**
Potassium dihydrogen phosphate	**p.a.**	**18786828**	**Roth GmbH, Karlsruhe, Germany**
Hydrochloric acid 1N	**p.a.**	**several**	**Merck, Darmstadt, Germany**
Trisodium phosphate dodecahydrate	**p.a.**	**K36195872710**	**Merck, Darmstadt, Germany**

[13] Silicified microcrystalline cellulose.
[14] Crospovidone.

5.2 Methods

5.2.1 Characterization of the active ingredients

5.2.1.1 Laser diffraction

The particle size of the active ingredients (n=3) was determined using a laser diffraction system (Helos/ KF-Magic, Sympatec GmbH, Clausthal-Zellerfeld, Germany). The powder was applied on the Vibri feeder (Sympatec GmbH, Clausthal-Zellerfeld, Germany) which transported the powder to the dry dispersing system (Rodos T4.1, Sympatec GmbH, Clausthal-Zellerfeld, Germany). The feeding rate was 80% and the dispersion pressure 2 bar. The Measurements were conducted using the lens R_4 (range of measurement 0.5-350 µm). The data were analyzed using the corresponding analysis software (Helos, Sympatec GmbH, Clausthal-Zellerfeld, and Germany).

5.2.1.2 Particle morphology

The particle shape of the active ingredients (Chapter 3.1) was examined using scanning electron microscopy (LEO VP 1430, Carl Zeiss, Jena, Germany). Before scanning, samples were dried on silica gel then sputter-coated with gold for 180 s under Argon (Agar Manual Sputter Coater B7340, Agar Scientific, Stansted, UK). The measurements were operated with a voltage range of 20 to 21.16 kV.

5.2.2 Preparation of pellets by extrusion/spheronization

The dry powders were weighed (2 kg) and mixed in a laboratory-scale blender (LM, Bohle, Ennigerloh, Germany) for 30 min at 35 rpm then every 500 g were wetted with different amounts of deionized water for each formulation using a high shear mixer (Mini-MGT, Bohle, Ennigerloh, Germany) for 5 minutes at 420 rpm. The wetted mass was supplied to a flat die press (Pelleting Press 14-175, Amandus Kahl, Reinbek, Germany) at a feeding screw rate of 100 rpm and extruded at a roller speed of 30 rpm through a flat plate with 5049 dies of 0.6 mm diameter and 3:1 length to diameter ratio. The distance between the rollers and die plate was adjusted to 0.5 mm and that between the die plate and knife to 3 mm (section 3.1) or to 2.5 mm (sections 3.4 and 3.5). Collected extrudate batches of approximately 300 g were

transferred into a spheronizer (RM300, Schlueter, Neustadt /Ruebenberge, Germany) and were spheronized for 6 min at a temperature of 25º C and a spheronization speed of 1500 rpm. The resulting pellets were then transferred to a fluid bed dryer (GCPG1, Glatt, Dresden, Germany) and dried for 20 min at 60º C inlet air temperature. The amount of water leading to the roundest pellets for each formulation is given in tables 3-1, 3-2, 3-4, 3-15 and 3-18. The optimized pellet batches were used for further characterization.

The prepared pellets were then stored at 20˚C and 45% relative humidity at least three days before characterization.

5.2.3 Characterization of the pellets

5.2.3.1 Yield of the pelletization process

The yield of the pelletization process (the fraction of pellets with a diameter between 400- 1000 µm) was determined using a sieving system (Retsch, Haan, Germany) coupled with a vibration apparatus (AS200 control, Retsch, Haan, Germany) at an amplitude of 1.5 over three minutes.

Additionally, the size fraction 500- 800 µm was collected and used for characterization and throughout the compression studies of coated and uncoated pellets (sections 3.2, 3.3, 3.4 and 3.5).

Using a rotary cone sample divider, suitable samples from the yield fraction were obtained (Retschmuehle PT, Retsch, Haan, Germany).

5.2.3.2 Pellet size and shape

The particle size distribution (mean and median Feret diameters, median equivalent diameter and 10% interval) and shape factors (aspect ratio and roundness factor) were determined with the help of an image analysis system consisting of a stereo microscope (Leica MZ 75, Cambridge, UK), a ring light with cold light source (Leica KL 1500, Cambridge, UK), a digital camera (Leica CS 300F, Cambridge, UK), and an image-analyzing software (Qwin, Leica, Cambridge, UK). 500 pellets of the chosen size fraction of each pellet formulation (400-1000 µm in section 3.1 and 500-800 µm in the rest of the work) were analyzed at a suitable magnification (1 pixel= 5.47 or 7 µm). For each pellet 64 Feret diameters and the projected area (*A*) were measured.

The pellet size was described by the equivalent diameter (d_{eq}), as the diameter of a circle having the same area as the projected area A of the particle (Voigt, 2006).

$$d_{eq} = \sqrt{(4A/\pi)} \qquad \text{Equation 5-1}$$

The size distribution of the prepared pellet formulations was assessed by calculating the 10 % interval as the percentage of pellets with a dimensionless diameter d_d (equation 5-2) between 0.9 and 1.1 (Thommes and Kleinebudde, 2006a).

$$d_d = d_{eq} / d_{eq50} \qquad \text{Equation 5-2}$$

The aspect ratio was calculated as the ratio between the maximum Feret diameter and the Feret diameter perpendicular to it.

$$ar = d_{\max} / d_{90°} \qquad \text{Equation 5-3}$$

The roundness factor was quoted as the ratio of the particle area *A* to the area of a sphere with a diameter equal to the maximum Feret diameter d_{max} of the measured particle.

$$Roundness = A / \left[\pi \left(d_{\max} / 2\right)^2\right] \qquad \text{Equation 5-4}$$

5.2.3.3 Poured bulk density, tapped density

The poured bulk density and the tapped density of the pellets (n=3, sample mass= 150 g) were determined using a tap volumeter (J. Engelsmann A.G., Ludwigshafen, Germany) equipped with a 250 ml cylinder as described in the monograph 2.9.34 " Bulk density and tapped density of powders" of the European Pharmacopeia 6th edition (2009).

5.2.3.4 Helium density

The particle helium density of the prepared pellets was determined using helium pycnometry (AccuPyc 1330, Micromeritrics, Mönchengladbach, Germany) (n=3).

5.2.3.5 Mercury porosimetry and voidage

The apparent particle density (mercury density) and the median pore radius of the prepared pellets were determined using mercury porosimetry (Pascal 140,

Pascal 440, Thermo Electron, Milano, Italy) (n=2 for all formulations and n=3 for formulation A, section 3.2.1). After measurement of the helium density the same pellet sample was filled into a dilatometer type CD3P (Thermo Electron) and transferred to the low pressure mercury porosimeter Pascal 140. All samples were evacuated for 20 minutes at 0.01 kPa to ensure equal conditions for the addition of mercury. The pressure was increased at speed setting 5p up to 400 kP. After transfer to the high pressure porosimeter PASCAL 440, intrusion and extrusion curves were recorded from 0.1 to 400 MPa. Data were analyzed using the pascal software (Mercury contact angle: 140°, cylindrical pore model).

The total porosity was calculated as:

$$Porosity(\%) = \left[1 - \left(density_{mercury} / density_{helium}\right)\right] \times 100 \quad . \qquad \text{Equation 5-5}$$

The voidage of each bed of pellets was calculated from the tapped density and the mercury density.

$$Voidage(\%) = \left[1 - \left(density_{tapped} / density_{mercury}\right)\right] \times 100 \qquad \text{Equation 5-6}$$

5.2.3.6 Disintegration time

The disintegration time of the pellets was determined using a tablet disintegration tester (Erweka, Heusenstamm, Germany). 6 samples of 50 mg of each pellet formulation were filled into special cylindrical sample holders of plexiglass with 21 mm inner length and 10 mm inner diameter equipped with 355 µm sieves on the upper and lower faces. The compartments were then placed in the disintegration apparatus, fixed using metal cylinder and tested in deionized water at 37˚C and 30 shakes per minute.

5.2.3.7 Resistance to fracture

The mechanical properties of pellets were characterized using a texture analyzer (TA.XT2i, Stable Micro Systems, Godalming, UK) at a loading rate of 0.01 mm/s. The fracture force (*F*) of 55 pellets per formulation was determined as the first peak of the recorded force displacement curve. The diameter (*d*) of each pellet in the crushing direction was also determined. The tensile strength of the pellets was calculated after introducing the correction factor suggested by Shipway and Hutchings (1993) according to the formula:

$$\sigma = 1.6F/(\pi * d^2)$$ Equation 5-7

5.2.3.8 Morphology

The morphology of pellets was determined using scanning electron microscopy as described in section 5.2.1.2.

5.2.3.9 Drug release

Dissolution studies of the pellets in section 3.1 were carried out under sink conditions according to the monographs of the United States Pharmacopoeia 32 (2009b) at 37ºC ± 0.5º C using 900 ml of the appropriate medium and the appropriate apparatus (Sotax AT6, Sotax AG, Basel, Switzerland) for each substance (Table 5-1) (agitation speed 100 rpm for the basket method and 50 rpm for the paddle method). To determine the drug release and the concentration of active, each dissolution medium was calibrated by UV-absorption with 8 or 9 concentrations (A = 0.2-1.2).

Table 5-7: Test conditions used in the release studies of the prepared pellet formulations in chapter 3.1.

Active ingredient	Medium	Apparatus	Wavelength for UV detection
Theophylline	Deionized water	Paddle	272
Paracetamol	Phosphate buffer pH=5.8	Paddle	346
Hydrochlorothiazide	Hydrochloric acid 0.1 N	Basket	272
Furosemide	Phosphate buffer pH=5.8	Paddle	274

5.2.4 Compression of uncoated pellets

5.2.4.1 Compression of pellets without an embedding powder

Pellets of the chosen size fraction (500-800) µm were compressed using a rotary tableting machine (Pressima, Kilian, Cologne, Germany) equipped with a single convex punch with a diameter of 12 mm and a curvature radius of 15 mm, to give tablets of 550 mg target weight. Two sets of pellet formulations were used for compression studies: **I.** lubricated pellets (all pellet formulations), prepared by mixing the pellets with 0.5% magnesium stearate for 5 minutes at 42 rpm in a turbula mixer (T2C, Willy A. Bachofen, Basel, Switzerland), and **II.** unlubricated pellets (formulation B). In case of unlubricated pellets, the upper- and lower punch as well as the die walls were lubricated with a suspension of 1% magnesium stearate in ethanol 96%.

Compression of both lubricated and unlubricated pellets took place according to a 2^2 full factorial design with three replicates of the central point (chapter 3.2, Table 3-5). The prepared tablets were then stored at 20˚C and 40 % relative humidity for 7 days before characterization.

5.2.4.2 Retrieval and characterization of compressed lubricated pellets

Tablets prepared starting from lubricated pellets were gently shaken in Petri dishes to de-aggregate them and retrieve the original pellets.

Retrieved pellets were then subjected to the following tests: Morphology, size and shape, porosity and mechanical resistance as described in sections 5.2.1.2, 5.2.3.2, 5.2.3.5, 5.2.3.7 respectively.

5.2.4.3 Characterization of tablets prepared from unlubricated pellets

5.2.4.3.1 Resistance to fracture

The tensile strength of the tablets was determined using a tablet hardness tester (Sotax HT1, Basel, Switzerland) in the mode constant speed of 1 mm/s. The diametrical force needed to crush the tablets was measured and the tensile strength was calculated using the following formula for convex tablets according to Pitt et. Al (1988):

$$\sigma_t = \frac{10P}{\pi D^2}\left(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01\right)^{-1} \qquad \text{Equation 5-6}$$

Where *P* is fracture force, *D* is the tablet diameter, *t i*s the thickness of the cylindrical part of the tablet and *W* is the curvature radius.

5.2.4.3.2 Elastic recovery

The thickness of the produced tablets was measured immediately and 10 days after compression. The post-compressional elastic recovery was calculated as the percentage increase in tablet thickness.

5.2.4.3.3 Disintegration time

The disintegration time of 6 tablets per formulation was determined using a tablet disintegration tester (Erweka, Heusenstamm, Germany) in deionized water at 37˚C and 30 shakes per minute. Disks of appropriate size were used to prevent the tablets from floating during the test.

5.2.4.3.4 Morphology

The morphological changes in the compressed pellets in the tablet were monitored using scanning electron microscopy (as described in section 5.2.1.2) of the fracture surface of the tablets after diametrical breakage in a tablet hardness tester (Sotax HT1, Basel, Switzerland).

5.2.4.4 Compression of pellets with embedding powder

Pellets of the chosen size fraction 500-800 µm from formulation D were mixed with 1% crospovidone and SMCC HD 90 at different ratios for 20 minutes and the resulting mixtures were lubricated with 0.05% magnesium stearate in a turbula mixer for 5 minutes at 42 rpm. The prepared mixtures were compressed to give tablets of 600 mg weight according to a 2^{4-1} fractional factorial design (section 3.3, table 3-12) with three replicates of the central point.

Additionally a highly lubricated pellet-powder mixture was prepared by separate lubrication of the pellets and SMCC HD 90 with magnesium stearate (0.5% for 5 minutes for the pellets and 2% for 24 hours for SMCC HD 90 in a turbula mixer at 42 rpm), followed by mixing of the two components for 20 minutes (percentage of pellets 60%).

The highly lubricated mixture was then compressed under the compression conditions for the central point (section 3.3, Table 3-12).

The prepared tablets were then stored at 20˚C and 45 % relative humidity for 7 days before characterization.

5.2.4.5 Retrieval and characterization of embedded pellets

Tablets prepared from the highly lubricated pellets-powder mixture were gently shaken in Petri dishes to de-aggregate them, followed by sieving through a 500 µm sieve to remove the powder rests.

The particle size and shape factors of the retrieved pellets were then determined as described in section 5.2.3.2 and their morphology as described in section 5.2.1.2.

5.2.4.6 Characterization of tablets prepared from embedded pellets

5.2.4.6.1 Resistance to fracture

The tensile strength of the tablets was determined as described in section 5.2.4.3.1.

5.2.4.6.2 Elastic recovery

The post-compressional elastic recovery of the tablets after 10 days was determined as described in section 5.2.4.3.2.

5.2.4.6.3 Disintegration time

The disintegration time of the tablets was determined as described in section 5.2.4.3.3

5.2.4.6.4 Friability

The friability was determined using a friability tester (Erweka, Heusenstamm, Germany) according to the monograph 2.9.7 "friability of uncoated tablets" of the European Pharmacopeia 6th edition (2009). Samples of whole tablets corresponding to approximately 6.5 g were de-dusted prior to testing, weighed and placed in the drum, which was rotated 100 times. The tablets were then removed, de-dusted again and weighed. Friability was calculated as the percentage loss of weight.

5.2.4.6.5 Homogeneity of content

The homogeneity of content of the prepared tables was evaluated according to the monograph 2.9.40 "Uniformity of dosage units" of the European Pharmacopeia 6th edition (2009). 10 tablets were separately dissolved each in 1 liter of deionized water in an ultrasound bath for 30 minutes at room temperature. The resulting solutions were then filtered and diluted. The hydrochlorothiazide content was determined using UV spectroscopy at a wavelength of 272.

5.2.4.6.6 Cushioning effect

The morphological changes in the pellets compressed with SMCC HD 90 as embedding powder were detected using scanning electron microscopy (as described in section 5.2.1.2) of the fracture surface of the tablets after

diametrical breakage in a tablet hardness tester (Sotax HT1, Basel, Switzerland). Before breakage the tablets were frozen using nitrogen.

5.2.5 Coating of pellets

All pellet formulations in chapters 3.4 and 3.5 were coated in a fluid bed dryer (GCPG1, Glatt, Dresden, Germany) using the bottom spray technique (Wurster set-up).

Pellet Formulations BC and BM (section 3.4) were enteric coated. The coating dispersion consisted of a 60:40 mixture of Kollicoat MAE® 30 DP and Eudragit® NE 30 D (15% dry polymer substance of the final spray dispersion), both adjusted to pH 5 before mixing using a 20% w/w solution citric acid or a 2% w/w solution of sodium hydroxide. Triethyl citrate was used as plasticizer (20% of the dry polymer weight) and glycerol monostearate GMS as anti-tacking agent (5% of the dry polymer weight). Polysorbate 80% was used to emulsify GMS (40% based on GMS weight) and a silicone antifoam emulsion was added (q.s.).

Formulation BC (κ-carrageenan based pellets) was coated with tow coating levels: 2.7 and 4.2 mg Kollicoat® MAE and Eudragit® NE/cm^2 (BCC1 and BCC2 respectively) whereas formulation BM (MCC based pellets) was coated with 4.3 mg Kollicoat® MAE and Eudragit® NE /cm^2 (BMC).

The enteric coating dispersions were prepared by emulsifying glycerol monostearate in hot water (40% of the total water amount, 70-75º C) using polysorbate 80, an anti-foam agent and a rotor stator system (Ultra Turrax) for 10 min. The emulsion was cooled under conventional stirring to room temperature before the addition of the remaining water. The emulsion was then added to the two polymers previously adjusted to pH= 5 under light stirring using a magnetic stirrer to avoid polymer agglomeration.

Formulations TC and TM (Chapter 3-5) were coated with Kollicoat SR® 30 D (15% dry polymer substance of the final spray dispersion) with triethyl citrate as plasticizer (10% of the dry polymer weight) and glycerol monostearate GMS as anti-tacking agent (5% of the dry polymer weight). Again polysorbate 80% was used to emulsify GMS (40% based on GMS weight) and a silicone antifoam emulsion was added (q.s.). Kollicoat® IR was used as a pore former

(25% of the dry weight of Kollicoat® SR for κ- carrageenan based pellets and 25% or 40% for MCC based pellets).

The coating dispersions were prepared by slow addition of Kollicoat® IR to water on a magnetic stirrer until a clear yellow solution is obtained. Glycerol monostearate was emulsified as previously described. The dispersion of Kollicoat® IR and the cooled emulsion of glycerol monostearate were mixed with Kollicoat® SR on a magnetic stirrer.

The coating level was 3.1 or 6.1 mg Kollicoat® SR/cm^2 for κ- carrageenan-based pellets (TCC1 and TCC2 respectively) and 1.9 mg Kollicoat® SR /cm^2 for MCC based pellets coated with the formulation containing 25% Kollicoat® IR as pore former (TMC1) and 4 mg Kollicoat® SR /cm^2 for MCC based pellets coated with the formulation containing 40% Kollicoat® IR based on the dry weight of Kollicoat SR® (TMC2).

The coating conditions for all formulations were: batch size 0.5 kg, pre-heating time 10 min, product temperature 31-32º C, spraying nozzle diameter 0.8 mm, spray pressure 1.5 bar, spray rate 3-3.5 g/min.

5.2.6 Compression of coated pellets

The coated pellets were compressed into tablets containing 20 mg bisacodyl or 200 mg theophylline using a rotary tableting machine (IMA Pressima, Kilian, Germany) equipped with a single biconvex oblong punch (16.2 × 7.6 mm for bisacodyl pellets based tablets and 19 × 9 mm for theophylline pellet based tablets) at the compression forces 5, 7, 10 and 15 kN and a turret speed of 25 rpm. The tablets prepared from enteric coated pellets consisted of 50% coated pellets, 48.95% silicified microcrystalline cellulose SMCC HD 90, 1% Kollidon® CL as disintegrant and 0.05% magnesium stearate. The tablets prepared from pellets with sustained release coating had the same composition but contained lower amount of Kollidon® CL (0.75%).

In order to study the influence of punch geometry on the properties of the resulting tablets the enteric coated κ-carrageenan pellets were also compressed using a single round biconvex punch with 12 mm diameter and 15 mm curvature radius using the above mentioned formulation as a powder

bed at the pressures corresponding to the compression forces used for the oblong punches.

The tablets were stored at 20º C and 45% relative humidity for one week at least before characterization.

5.2.7 Characterization of the tablets prepared from coated pellets

5.2.7.1 Crushing force

The crushing force of the tablets was determined using a tablet hardness tester (Erweka, Heusenstamm, Germany, n=10).

5.2.7.2 Disintegration time

The disintegration time the tablets made of coated pellets (n=6) was determined as described in section 5.2.4.3.3.

5.2.8 Release studies from the coated pellets and their tablets

The drug release from the enteric coated pellets and their tablets was determined according to the method A of the United States pharmacopoeia USP 32 at 37º C using the paddle apparatus at 100 rpm (Pharma Test, Hainburg, Germany). Due to the very poor solubility of bisacodyl in neutral medium, after 45 min the medium was re-acidified to pH= 1 using hydrochloric acid 1N as described by Beckert et al. (1996) and the samples were taken after 1 more minute. The amount of bisacodyl was determined using UV spectroscopy (Lambda-2, Perkin-Elmer, Ueberlingen, Germany) at a wavelength of 264 nm.

The release studies of uncoated theophylline pellets and those coated with Kollicoat® SR and the corresponding tablets were performed at 37º C in phosphate buffer pH= 6.8 using the paddle apparatus (Pharma Test, Hainburg, Germany) at 50 rpm. The amount of theophylline was determined at a detection wavelength of 272 (Lambda-2, Perkin-Elmer, Ueberlingen, Germany).

The similarity factors f_2 for the dissolution curves of the tablets and that of the uncompressed pellets was calculated according to the formula suggested by Moore and Flanner (1996).

$$f_2 = 50 \cdot \log\left\{\left[1 + (1/n)\sum_{n=1}^{n}\left(R_t - T_t\right)^{-0.5}\right] \cdot 100\right\}$$ Equation 5-7

Where R_t and T_t are the cumulative percentage of drug dissolved at a certain time point *t* for the reference product (uncompressed pellets) and for the test product (tablets) respectively.

5.2.9 Damages of the film coating

The damages of the film coating were detected using scanning electron microscopy of the upper surface and fracture surface of the tablets after the diametrical breakage of tablets frozen in Nitrogen as described in section 5.2.1.2.

5.2.10 Statistical evaluation parameters of the design of experiments

The statistical analysis was performed using MODDE® software. The reliability of the regression models was assessed using the adjusted coefficient of determination and the prediction factor.

The coefficient of determination (R^2) provides a measure of the fraction of variation in the response variable explained by the model whereby an R^2 value of 1 indicates a perfect model. Adjusted R^2 (R^2_{adj}) was used instead of R^2 to adjust for the degrees of freedom (Equation 5-8):

$$R^2_{adj} = 1 - \frac{n-1}{n-p} * (1 - R^2)$$ Equation 5-8

where n is the sample size, p is the number of parameters in the model, and R^2 is the coefficient of determination.

The model predictability (the fraction of variation predicted by the model) is assessed by the goodness of prediction factor (Q^2) (Equation 5-9):

$$Q^2 = 1 - \frac{PRESS}{SS}$$ Equation 5-9

where *PRESS* is the prediction residual sum of squares and *SS* is the total sum of squares of Y corrected for the mean.

Values of $Q^2 > 0.5$ indicate good predictability and those > 0.9 an excellent one.

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