International Journal of Pharmaceutics 409 (2011) 9–18

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Suitability of κ-carrageenan pellets for the formulation of multiparticulate tablets with modified release

Dima Ghanam, Peter Kleinebudde*

Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Universitaetsstr. 1, 40225 Duesseldorf, Germany

ARTICLE INFO

Article history:
Received 18 October 2010
Received in revised form 7 January 2011
Accepted 9 February 2011
Available online 16 February 2011

Keywords:
Pellets
κ-Carrageenan
Microcrystalline cellulose
Enteric coating
Tablet
Sustained release

ABSTRACT

κ-Carrageenan is a novel pelletisation aid with high formulation robustness and quick disintegration leading to fast drug release unlike the matrix-like release from non-disintegrating microcrystalline cellulose pellets. Compression of pellets into tablets is cost effective. The feasibility of formulating multiparticulate tablets with coated κ-carrageenan pellets was investigated. Pellets containing a highly soluble drug in acid, namely bisacodyl and κ-carrageenan or MCC as pelletisation 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, type of 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 during 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. Moreover, sufficient prolonged release properties were obtained with κ-carrageenan pellets containing theophylline as a model drug and coated with Kollicoat® SR 30 D 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 pelletisation aid. The sustained release properties of both coated pellet formulations were maintained after compression at different compression pressures.

1. Introduction

Pellets as multiparticulate dosage forms are gaining increasing interest due to their several benefits over monolithic dosage forms. The more homogenous distribution of pellets in the gastro intestinal tract allows for better drug absorption and results in less variable plasma profiles along with reduced risks of local irritation and dose dumping encountered with single-unit dosage forms (Bechgaard and Hagermann, 1978; Gehbre-Sellassie, 1989; Krämer and Blume, 1994).

The formulation of pellets into multiparticulate tablets is particularly advantageous compared to their encapsulation due to the higher production speed associated with enhanced cost effectiveness as well as the markedly reduced stability problems compared to capsules. The feasibility of tablet scoring allowing greater therapeutic flexibility is another advantage of multiparticulate tablets over capsules and coated single-unit tablets (Celik, 1994; Bodmeier, 1997; Beckert et al., 1996).

The compression of pellets involves several formulation challenges. Pellet fragmentation or severe deformation under load should be avoided. Sufficient mechanical strength of the prepared tablets should be ensured along with a short disintegration time as an essential element in maintaining the multiparticulate function of the system. Last but not least, a particularly critical issue upon formulating pellets into tablets is to protect the coating layer when coated pellets are compressed and to deliver, as most as possible, an unchanged release profile compared to the original pellets (Bodmeier, 1997).

κ-Carrageenan is a novel pelletisation aid with high formulation and process robustness (Thommes and Kleinebudde, 2006a,b, 2007a). Pellets made with κ-carrageenan show the particular advantage of quick disintegration against microcrystalline cellulose (MCC) pellets known for their lack of disintegration. Fast disintegration of κ-carrageenan pellets was associated with rapid drug release especially in the case of poorly soluble active ingredients unlike the slow matrix-like release encountered with MCC pellets (Thommes and Kleinebudde, 2006a,b). Thus the fast drug release from κ-carrageenan pellets may be beneficial in formulating enteric coated pellets with this pelletisation aid which, after leaving the stomach, liberate their active ingredients quickly in the intestine.

* Corresponding author. Tel.: +40 211 8114220; fax: +49 211 8114251.
E-mail address: kleinebudde@uni-duesseldorf.de (P. Kleinebudde).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.02.016

In a previous work (Ghanam et al., 2010) the compression behavior of high and low drug strength pellets of the size range 500–800 μm prepared with κ-carrageenan as pelletisation-aid and using different model drugs and excipients with different compression behavior (plastic, brittle) was investigated. A deformation mechanism and minimal to absent fragmentation of all studied pellet formulations was established indicating that κ-carrageenan pellets are promising candidates for the formulation of multiparticulate tablets. Compression of the examined pellets with silicified microcrystalline cellulose HD 90 as embedding powder protected the pellets from severe deformation and resulted in tablets with sufficient mechanical strength, low friability and short disintegration time.

As a further step of the described work, the feasibility of formulating enteric-coated κ-carrageenan pellets into tablets was investigated. A drug of high solubility in acids and low dose, namely bisacodyl, was chosen as a "worse case" model drug in order to detect the smallest damages to the coating layer upon compression. Pellets with κ-carrageenan and MCC were produced, coated, compressed and compared.

On the other side 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 dosage form with sustained release properties. 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 second objective of this work was to investigate the suitability of pellets made with κ-carrageenan as pelletisation aid for the formulation of multiparticulate tablets with sufficient prolonged release properties.

2. Materials and methods

2.1. Materials

Bisacodyl (Bidachem, Fornovo San Giovanni, Italy), theophylline monohydrate (BASF, Ludwigshafen, Germany), α-lactose monohydrate (Granulac® 200, Meggle, Wasserburg, Germany), κ-carrageenan (Gelcarin® GP 911 NF, FMC, Philadelphia, USA), microcrystalline cellulose (MCC Sanaq® 102 G, Pharmatrans Sanaq AG, Basel, Switzerland), methacrylic acid–ethyl acrylate copolymer (Kollicoat® MAE 30 DP, BASF, Ludwigshafen, Germany), ethyl acrylate–methyl methacrylate copolymer (Eudragit® NE 30 D Evonik Röhm, Darmstadt, Germany), polyvinyl acetate (Kollicoat® SR 30 D, BASF, Ludwigshafen, Germany), triethyl citrate (Merck, Hohenbrunn, Germany), glycerol monostearate (Imwitor® 491, Sasol, Witten, Germany), polysorbate 80 (Caelo, Hilden, Germany), silicone antifoam emulsion (Silfoam® SE 6, Wacker, Nuechritz, Germany), high density silicified MCC (Prosolv® SMCC HD 90, J.R.S Pharma, Rosenberg, Germany), crospovidone (Kollidon® CL, BASF, Ludwigshafen, Germany), magnesium stearate (Baerlocher, Unterschleissheim, Germany), citric acid (Roth, Karlsruhe, Germany), sodium hydroxide (J.T. Backer, Deventer, Holland), deionised water.

2.2. Methods

2.2.1. Preparation of pellets by extrusion/spheronisation

Four pellet formulations were prepared by extrusion/spheronisation (Table 1).

The powders were mixed in a laboratory scale blender (LM 40, Bohle, Ennigerloh, Germany) for 20 min at 35 rpm then wetted with deionized water (48%, 32%, 52% and 36% for pellet formulations A, B, C and D, respectively) using a high shear granulator (Mini-MGT, Bayer, Leverkusen, Germany) for 5 min at 420 rpm.

Table 1
Prepared pellet formulations and amount of water used for extrusion/spheronisation based on the weight of solids.

Ingredient	A	B	C	D
Bisacodyl (%)	10	10		
Theophylline monohydrate (%)			80	80
α-Lactose monohydrate (%)	70	70		
κ-Carrageenan (%)	20		20	
Microcrystalline cellulose (%)		20		20
Deionized water (%)	48	32	52	36

The wetted mass was supplied to a flat die press 14-175 (Amandus, Kahl, Germany) and extruded at a roller speed of 30 rpm through a flat plate with dies of 0.6 mm diameter. The distance between the die plate and knife was adjusted to 2.5 mm.

Collected extrudate batches of approximately 300 g were transferred into a spheroniser (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) and were spheronised for 6 min at 1500 rpm and 25 °C. The resulting pellets were then transferred to a fluid bed dryer (GCPG1, Glatt, Dresden, Germany) and dried for 20 min at 60 °C inlet air temperature.

The size fraction 500–800 μm obtained by sieving (Retsch, Haan, Germany) was used for characterization and throughout the coating and compression studies. The yield of this size fraction was 88.4, 89.1, 79.2 and 84.6% for formulations A, B, C and D, respectively.

2.2.2. Characterization of the uncoated pellets

2.2.2.1. Pellet size and shape. The particle size, particle size distribution and the shape of the prepared pellets 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 300 F, Cambridge, UK), and an image-analysing software (Qwin, Leica, Cambridge, UK). Five hundred pellets of the chosen size fraction of each pellet formulation were analysed at a suitable magnification (1 pixel = 7 μm). For each pellet 64 Feret diameters and the projected area (A) were measured. The equivalent diameter was quoted as:

$$d_{eq} = \sqrt{\frac{4A}{\pi}} \quad (1)$$

The 10% interval was calculated as the percentage of pellets with a dimensionless diameter d_d between 0.9 and 1.1 (Thommes and Kleinebudde, 2006a).

$$d_d = \frac{d_{eq}}{d_{eq50}} \quad (2)$$

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

2.2.2.2. 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 made of plexiglass with 21 mm inner length and 10 mm inner diameter and equipped with 355 μm sieves on the upper and lower faces. The compartments were then placed in the disintegration apparatus, fixed using metal cylinders of appropriate size and tested in deionized water at 37 °C and 30 lifts/min. The disintegration time of each sample was determined and the average disintegration time and the standard deviation were calculated.

2.2.3. Coating of the pellets

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

Table 2
Formulation of enteric coating dispersion.

Ingredient	Percentage (%)
Kollicoat® MAE 30 DP/Eudragit® NE 30 D 60:40 mixture	50
Triethyl citrate	3
Glycerol monostearate	0.75
Polysorbate 80	0.3
Silicon anti foam emulsion	q.s.
Deionized water	Up to 100%

Pellet formulations A and B were enteric coated. The formulation of the enteric coating dispersion is summarized in Table 2.

The enteric coating dispersions were prepared by emulsifying glycerol monostearate in hot water (40% of the total water amount, 70–75 °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 (using citric acid solution 20% or sodium hydroxide solution 2%) under light stirring using a magnetic stirrer to avoid polymer agglomeration.

Formulation A (κ-carrageenan based pellets) was coated with two coating levels: 2.7 and 4.2 mg Kollicoat® MAE and Eudragit® NE/cm^2 (AC1 and AC2, respectively) whereas formulation B (MCC based pellets) was coated with 4.3 mg polymers/cm^2 (BC).

Formulations C and D were coated with Kollicoat® SR 30 D. The formulation of the coating dispersion is shown in Table 3.

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

The coating level was 3.1 or 6.1 mg Kollicoat® SR/cm^2 for κ-carrageenan-based pellets (CC1 and CC2, respectively) and 1.9 mg Kollicoat® SR/cm^2 for MCC based pellets coated with the formulation containing 25% Kollicoat® IR (based on the dry weight of Kollicoat® SR) as pore former (DC1) 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 (DC2).

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

2.2.4. Compression of the pellets

2.2.4.1. Compression of enteric coated pellets. The enteric coated pellets were compressed into tablets containing 20 mg bisacodyl using a rotary tableting machine (IMA Pressima, Kilian, Germany) equipped with a single biconvex oblong punch (16.2 mm × 7.6 mm) at the compression forces 5, 7, 10 and 15 kN and a turret speed of 25 rpm. The tablets prepared consisted of 50% coated pellets, 48.95% silicified microcrystalline cellulose SMCC HD 90, 1% Kollidon® CL as disintegrant and 0.05% magnesium stearate as lubricant. Before compression the pellets were mixed with Kollidon® CL and SMCC HD 90 at for 20 min in a turbula mixer at 42 rpm and then for 5 min with magnesium stearate at the same speed.

Table 3
Formulation of coating dispersion for sustained drug release.

Ingredient	Percentage (%)
Kollicoat® SR 30 D	50
Kollicoat® IR	3.75 or 6
Triethyl citrate	1.5
Glycerol monostearate	0.75
Polysorbate 80	0.3
Silicon anti foam emulsion	q.s.
Deinonized water	Up to 100%

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 biconvex round punches with 12 mm diameter and 15 mm curvature radius at the pressures corresponding to the compression forces used for the oblong punches.

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

2.2.4.2. Compression of pellets with sustained release coating. The coated pellets were compressed into tablets containing 200 mg theophylline using a rotary tableting machine (IMA Pressima, Kilian, Germany) equipped with a single oblong punch (19 mm × 9 mm) at the compression forces 5, 7, 10 and 15 kN and a turret speed of 25 rpm. The tablets formulation consisted of 50% coated pellets, 49.2% silicified microcrystalline cellulose SMCC HD 90, 0.75% Kollidon® CL as disintegrant and 0.05% magnesium stearate as lubricant. The amount of Kollidon® CL used was lowered compared to the formulation of tablets prepared from the enteric coated formulation because the tablets prepared using this formulation showed a very short disintegration time. Before compression the pellets were mixed with the other components as described in Section 2.2.4.1. The tablets were stored at 20 °C and 45% relative humidity for one week at least before characterization.

2.2.5. Characterization of the prepared tablets

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

2.2.5.2. 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 lifts/min. Disks of 20.7 mm diameter and 9.6 mm thickness with 5 orifices of 2 mm diameter were used to prevent the tablets from floating during the test.

2.2.5.3. Release studies. The drug release from the enteric coated pellets and their tablets was determined according to the method A for delayed release dosage forms of the United States Pharmacopeia USP 32 (2009) at 37 °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 reacidified to pH = 1 using hydrochloric acid 1 N as described by Beckert et al. (1996) and the samples were taken after one 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 37 °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 nm (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 Eq. (3) suggested by Moore and Flanner (1996).

$$f_2 = 50 \ \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{n=1}^{n}(R_t - T_t)^{-0.5}\right] \times 100\right\} \quad (3)$$

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. A similarity factor above 50% means that the dissolution curves are similar (less

Table 4
Mean Feret diameter, mean equivalent diameter, 10% interval and aspect ratio of the chosen size fraction (500–800 μm) of the prepared pellets formulations ($n = 500$).

Formulation	Feret diameter		Equivalent diameter		10% interval	Aspect ratio	
	Mean (μm)	CV[a] (%)	Mean (μm)	CV[a] (%)		Median	Interquartile range
A	682	11.2	666	11.1	58.6	1.12	0.098
B	735	9.6	722	9.5	71.0	1.11	0.095
C	660	11.3	655	11.2	60.2	1.12	0.090
D	671	9.0	660	8.9	70.4	1.09	0.079

[a] Coefficient of variation.

than 10% difference in the cumulative percentage of drug dissolved at each time point).

2.2.5.4. Scanning electron microscopy. In order to monitor the damages in the film coat after the compression of pellets scanning electron micrographs of the tablet upper surfaces and their fracture surfaces after the crushing strength test were made (LEO VP 1430, Carl Zeiss, Jena, Germany). Before scanning, the dried samples were sputter-coated with gold for 180 s under Argon (Agar Manual Sputter Coater B7340, Agar Scientific, Stansted, UK).

3. Results and discussion

3.1. Characterization of the uncoated pellets

Table 4 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 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 diameter above 50%, Thommes and Kleinebudde, 2006a). The pellets prepared using κ-carrageenan as pelletisation aid exhibited short disintegration times of few minutes (221 ± 5 s for bisacodyl pellets and 233 ± 23 s for theophylline pellets) as expected whereas those made using MCC did not disintegrate after 24 h in the disintegration apparatus.

3.2. Compression of enteric coated pellets

3.2.1. Model and choice of polymers

For the study with enteric-coated pellets the model drug bisacodyl was chosen as a "worst case" due to its high solubility in the acidic medium and its low dose as suggested by Beckert et al. (1996) and Schmid and Picker-Freyer (2009). Additionally the studied formulations contained 70% lactose monohydrate as 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. Since most enteric polymers are brittle in nature even in the presence of plasticizers more elongable polymers are usually added to the coating formulation to impart sufficient mechanical 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 this work a combination of the widely used and brittle enteric polymer Kollicoat® MAE (methacrylic acid–ethyl acrylate copolymer) with the highly elongable 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 effects of the film thickness, compression force, punch configurations and pellet core were investigated.

3.2.2. Drug release from the coated pellets

The three enteric coated pellet formulations showed sufficient resistance in the acidic medium (drug release after 2 h in HCl 0.1 N was 0.1 ± 0.02, 0.5 ± 0.3 and 0% for coated pellets AC1, AC2 and BC, respectively). However, while κ-carrageenan pellets coated with a thin or thick film layer (coating level 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 (percentage drug release 89 ± 1.1% and 84 ± 1.8% for coated formulations AC1 and AC2, respectively) enteric coated MCC pellets (BC) released only 18.9 ± 4.8% and, therefore, did not meet the specifications of the United States Pharmacopeia USP 32 (2009) for delayed release dosage forms. The poor release in case of MCC based pellets can be attributed to their lack of disintegration leading to a matrix-type release behavior of the active ingredient.

3.2.3. Characterization of the tablets prepared by compression of the enteric coated pellets with SMCC HD 90 as embedding powder

3.2.3.1. Mechanical resistance. The tablets prepared from coated pellets of all three formulations showed sufficient mechanical properties for any further handling (Table 5) at the compression pressures used. This can be attributed to the excellent plasticity and high binding ability of silicified microcrystalline cellulose which is able to ensure adequate binding forces within the tablet even at relatively low pressures. Muzikova and Novakova (2007) reported high tensile strength of tablets upon compression of pure SMCC HD 90 at low compression pressures (the tensile strength of tablets of 0.5 g weight prepared using flat faced round punches of 13 mm diameter was 0.8, 1 and 1.2 MPa at compression forces of 3, 3.5 and 4 kN, respectively). Moreover, in a previous work (Ghanam et al., 2010) it was found that decreasing the percentage of pellets (having a similar composition to those used in the current study with 10% hydrochlorothiazide, 70% lactose and 20% κ-carrageenan) and consequently increasing the percentage of SMCC HD 90 in the κ-carrageenan pellets/SMCC HD 90 mixture leads to tablets with higher tensile strength.

The crushing force of tablets made with κ-carrageenan pellets was slightly higher than those made with 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 an increased compression force resulted in harder tablets in the range of pressures used.

3.2.3.2. Disintegration time. All prepared tablets disintegrated very rapidly (Table 5), 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-

Table 5
Crushing force and disintegration time of the tablets prepared from the enteric coated pellet formulations.

Designation	Pellet core	Polymer weight gain (mg/cm)	Type of punches	Compression pressure (MPa)	Crushing force (N)	Disintegration time (s)
AC1-Tab	Carrageenan pellets	2.7	Oblong	48.8	80.2 ± 7.1	14
				68.3	141.8 ± 7.0	30
				97.6	214 ± 4.7	161
				146.4	262.9 ± 9.6	>900
AC2-Tab	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
AC2-TabB	Carrageenan pellets	4.2	Round	48.8	77 ± 6.4	11
				68.3	139 ± 8.2	28
				97.6	213 ± 6.6	152
				146.4	251 ± 9.8	>900
BC2-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	>900

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® 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 mentioned by Malmataris (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 properties of the resulting tablets due to the prolonged mixing time with magnesium stearate.

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

3.2.3.3. Drug release.

3.2.3.3.1. Effect of coating level. The thickness of the coating layer influenced the amount released in the acidic medium for the compressed pellets (Fig. 1). A thin coat (coating level 2.7 mg polymers/cm^2) for κ-carrageenan pellets did not sufficiently withstand the compression conditions and led to more than 10% drug release 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% of the active ingredient released in the acidic medium. It seems, therefore, that a sufficient coating thickness is necessary to protect the film against the pressure occurring during the compression process. Scanning electron micrographs of the fracture surfaces and upper surface of the tablets (Fig. 2) show significant deformation of the coating layer for pellets close to the center 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/cm^2.

It is to be mentioned that the pellet formulation used in this study is quite challenging since the active 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 thin coat 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.

3.2.3.3.2. 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 polymers/cm^2 whereas no statistically significant difference was noticed in case of the pellets coated with the higher amount of polymer in the range of pressures used (ANOVA, confidence level 95%). It seems, therefore, that at sufficient film thickness no significant damage can occur to the coating of 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 the observations made above and related to SEM micrographs at the highest compression pressure leading to disintegrating tablets (Fig. 2). A thicker coat is thus robust against the compression pressure in the range of pressures used.

3.2.3.3.3. Effect of pellet core. The release in acidic and neutral medium form tablet prepared from κ-carrageenan pellets coated with 4.2 mg/cm^2 polymer and those prepared from coated MCC

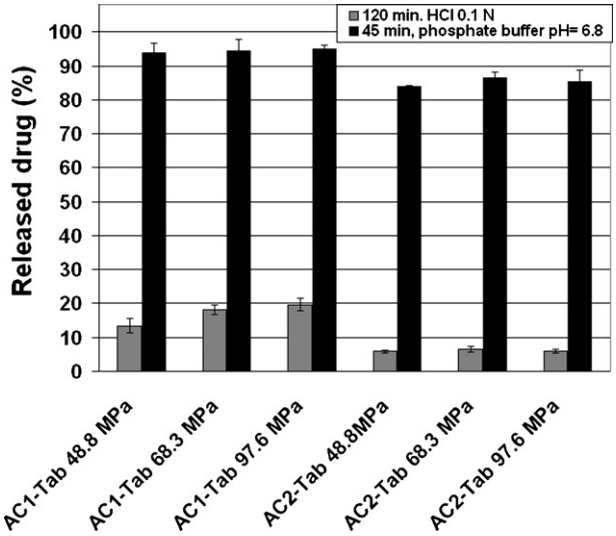

Fig. 1. Bisacodyl release from the tablets prepared from enteric coated κ-carrageenan pellets using SMCC HD 90 as embedding powder (percentage of pellets 50%): (AC1-Tab) tablets prepared from pellets coated with 2.7 mg polymer/cm^2, (AC2-Tab) tablets prepared from pellets coated with 4.2 mg polymer/cm^2.

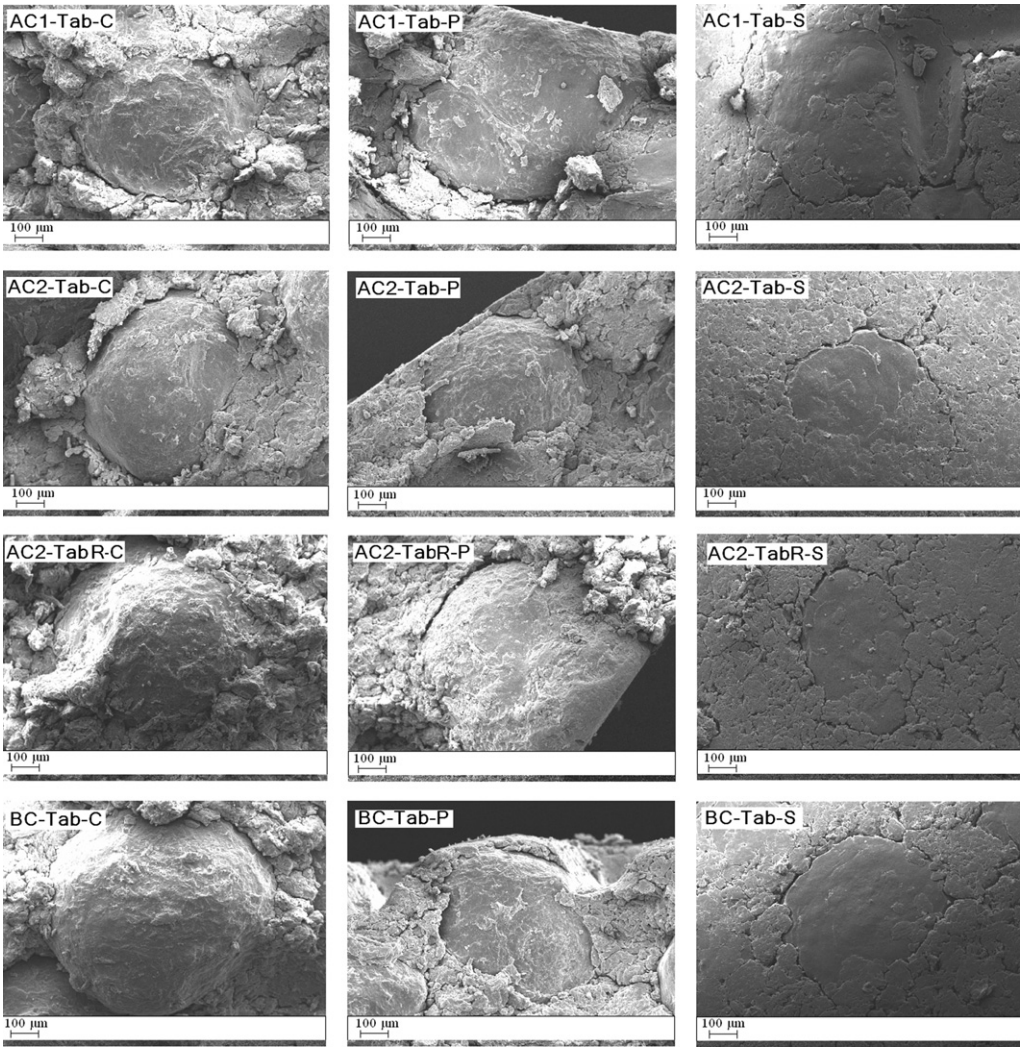

Fig. 2. SEM micrographs of the pellets close to the center (C), at the periphery (P) and at the surface (S) of the tablets prepared from the enteric pellet formulations. (AC1-Tab) tablets prepared from κ-carrageenan pellets coated with 2.7 mg polymer/cm^2, (AC2-Tab) tablets prepared from κ-carrageenan pellets coated with 4.2 mg polymer/cm^2 and compressed using biconvex oblong punches, (AC2-TabR) tablets prepared from κ-carrageenan pellets coated with 4.2 mg polymer/cm^2 and compressed using biconvex round punches, (BC-Tab) tablets prepared from MCC pellets coated with 4.3 mg polymer/cm^2 (percentage of pellets 50%, compression pressure 97.6 MPa).

pellets is illustrated in Fig. 3. The amount of drug released in HCl 0.1 N shows no pronounced differences between the tow tablets groups. Again the compression force did not influence the amount released in the acidic environment in case of the tablets prepared from coated MCC pellets (ANOVA, confidence level 95%). The percentage released in the neutral stage 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 then that the fast disintegration and of κ-carrageenan pellets is advantageous against the slow matrix-like drug release encountered in case of MCC pellets.

3.2.3.3.4. Effect of punch configurations. Both type of punches used led to multiparticulate tablets with sufficient mechanical strength and short disintegration time (Table 5). The type of punches used (biconvex oblong or biconvex round) did not significantly (ANOVA, confidence level 95%) influence the drug release from κ-carrageenan pellets coated with 4.2 mg polymers/cm^2 at the pressures applied in this study (Fig. 4). 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 coat (Fig. 2).

3.3. Compression of pellets coated with Kollicoat® SR

3.3.1. Model and choice of polymer

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 despite the short disintegration time and swelling behavior of the mentioned pellets. Kollicoat SR® 30 D (polyvinyl acetate) was chosen as a release modifying agent due to the fact that its plasticity can be significantly improved simply by the addition of 10% triethyl citrate. Dashevsky et al. (2004) reported an increase in the elongation at break of Kollicoat® SR 30 D 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® 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 a much faster drug release than that of the uncompressed

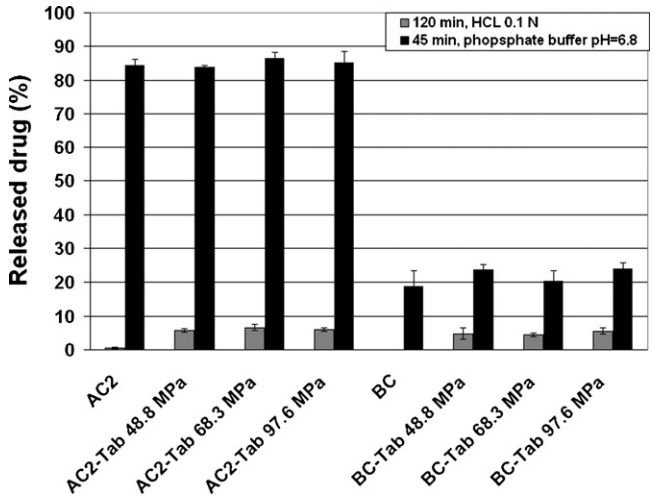

Fig. 3. Bisacodyl release from the tablets prepared from the enteric coated κ-carrageenan and MCC pellets using SMCC HD 90 as embedding powder (percentage of pellets 50%): (AC2-Tab) tablets prepared from κ-carrageenan pellets coated with 4.2 mg polymer/cm^2, (BC-Tab) tablets prepared from MCC pellets coated with 4.3 mg polymer/cm^2.

pellets. The release rate from the latter pellets also increased at higher compression forces and was attributed to the brittle nature and weak mechanical properties 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/spheronisation containing pseudoephedrine hydrochloride which were subsequently mixed with immediate release pellets containing loratadine 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.

Kollicoat® IR was added in the current study as a pore former to allow for drug release from the insoluble polymer film. The coating level and the amount of pore former were varied in order to achieve 80–100% drug release over about 10–12 h for κ-carrageenan- and MCC-based pellets. The coated pellets were then compressed into tablets.

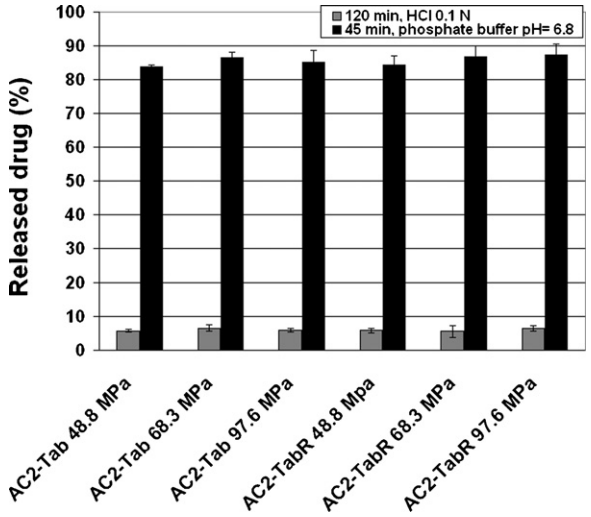

Fig. 4. Bisacodyl release from the tablets prepared from enteric-coated κ-carrageenan pellets (coating level 4.2 mg polymer/cm^2, SMCC HD 90 as embedding powder, percentage of pellets 50%): (AC2-Tab) tablets prepared using oblong punches, (AC2-Tab-R) tablets prepared using round punches.

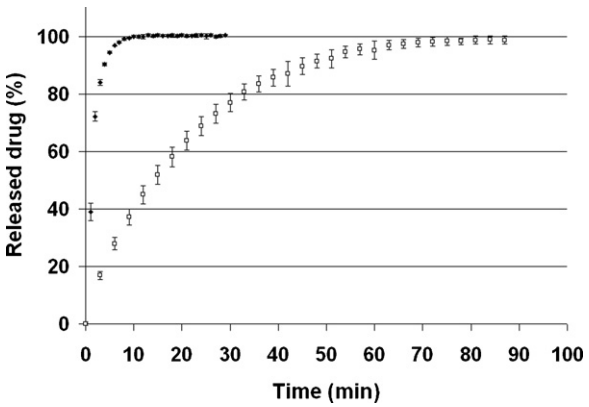

Fig. 5. Theophylline release from uncoated (♦) κ-carrageenan and (□) MCC pellets (phosphate buffer pH = 6.8, n = 6).

3.3.2. Drug release from uncoated pellets

The drug release from the uncoated pellets is illustrated in Fig. 5. It can be clearly seen that κ-carrageenan based pellets released their active ingredient within 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 matrix formation associated with the lack of disintegration of these pellets unlike the fast disintegration observed in case of κ-carrageenan based pellets.

3.3.3. Drug release from coated pellets

Fig. 6 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 (based on the dry weight of Kollicoat® SR). 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 3 h. Increasing the coating level to 6.1 mg polymer/cm^2 resulted in extended drug release over 10 h. A lag time of about 20 min 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 in order to 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 taking into consideration that Kollicoat® SR itself exhibit limited swelling properties (Wei et al., 2009). Swelling of κ-carrageenan may results in the formation of an outer gel layer surrounding the rest of pellet and slowing the drug release at the initial stage

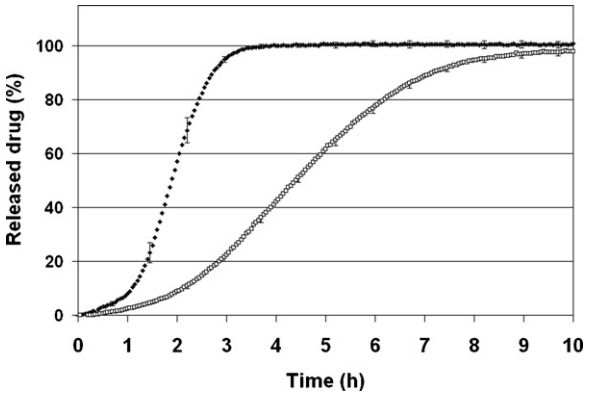

Fig. 6. Theophylline release from κ-carrageenan pellets coated with Kollicoat® SR at two coating levels: (♦) 3.1 mg/cm^2 and (□) 6.1 mg/cm^2 (25% pore former, phosphate buffer pH = 6.8, n = 6).

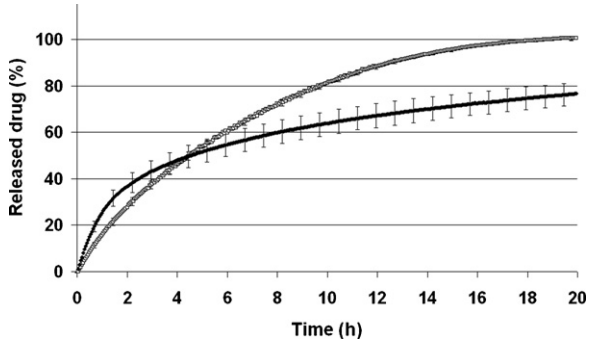

Fig. 7. Theophylline release from MCC pellets coated with Kollicoat® SR: (♦) 1.9 mg/cm², 25% pore former (□) 4 mg/cm², 40% pore former (phosphate buffer pH = 6.8, $n = 6$).

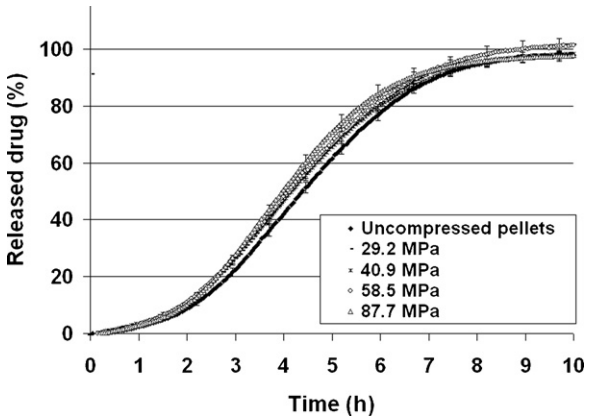

Fig. 8. Theophylline release from uncompressed and compressed κ-carrageenan pellets coated with Kollicoat® SR (coating level 6.1 mg/cm², 25% pore former, SMCC HD 90 as embedding powder, percentage of pellets 50%).

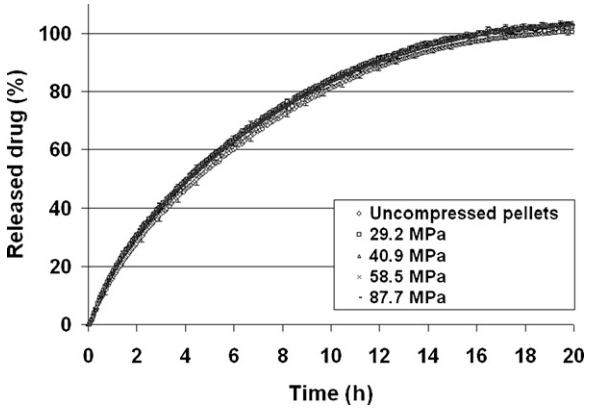

Fig. 9. Theophylline release from uncompressed and compressed MCC pellets coated with Kollicoat® SR (coating level 4 mg/cm², 40% pore former, SMCC HD 90 as embedding powder, percentage of pellets 50%).

after the lag time. Such swelling was not noticed in the case of uncoated pellets (Fig. 5) 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 the dissolution medium 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 the polymer relaxation after water absorption. The penetration of further amount of liquid in the system causes the erosion of the outer layer and a faster solely membrane-dependent drug release is expected which corresponds to the linear portion of the curves.

The drug release from coated MCC pellets is illustrated in Fig. 7. A thin coat (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/cm² 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 reason for the difference observed between the two types of pellets at the initial stage of drug release.

3.3.4. Characterization of the tablets prepared by compression of the pellets coated with Kollicoat® SR using SMCC HD 90 as embedding powder

Compression of both κ-carrageenan based pellets coated with 6.1 mg Kollicoat® SR/cm² with 25% Kollicoat® IR as pore former and MCC based pellets coated with 4 mg polymer/cm² and 40% Kollicoat® IR resulted in tablets with sufficient mechanical properties and short disintegration time at all compression pressures used (Table 6). The crushing force and the disintegration time of the tablets increased with increased compression pressure.

Table 6
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/cm)	Percentage of Kollicoat® IR	Compression pressure (MPa)	Crushing force (N)	Disintegration time (s)
CC2-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
DC2-Tab	MCC pellets	4	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

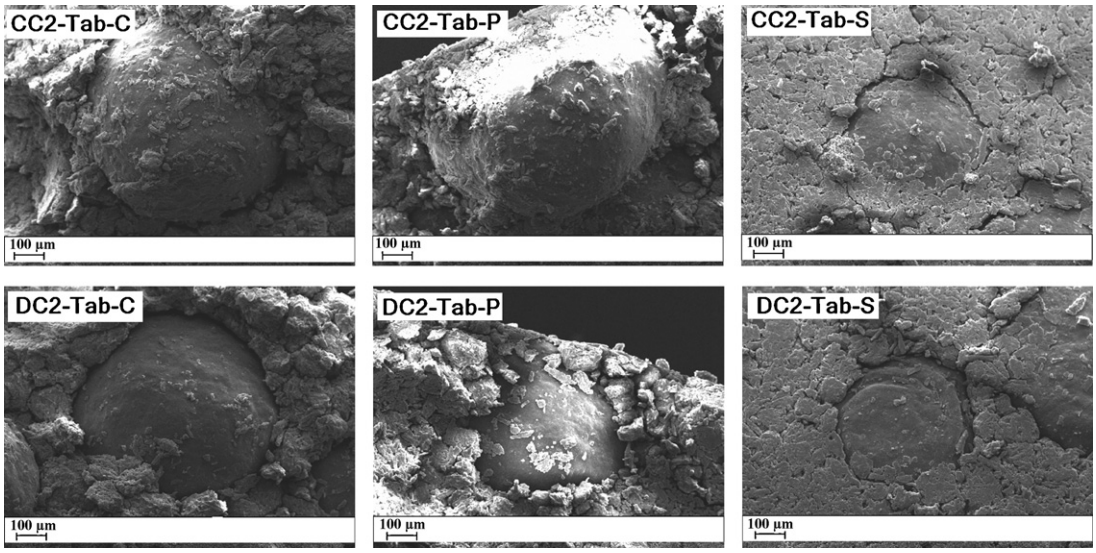

Fig. 10. SEM micrographs of the pellets close to the center (C), at the periphery (P) and at the surface (S) of the tablets prepared from the pellet formulations coated with Kollicoat® SR: (CC2-Tab) tablets prepared from κ-carrageenan pellets coated with 6.1 mg Kollicoat® mg/cm^2 with 25% pore former, (DC2-Tab) tablets prepared from MCC pellets coated with 4 mg Kollicoat® SR/cm^2 and 40% pore former (SMCC HD 90 as embedding powder, percentage of pellets 50%, compression pressure 87.7 MPa).

Table 7
Similarity factor for the dissolution curves of theophylline pellets coated with Kollicoat® SR and compressed at different compression pressures (SMCC HD 90 as embedding powder, percentage of pellets 50%) in comparison to the uncompressed pellets.

Designation	Compression pressure (MPa)	Similarity factor (%)
CC2-Tab	29.2	77.2
	40.9	72.4
	58.5	69.2
	87.7	64.5
DC2-Tab	29.2	76.8
	40.9	78.5
	58.5	77.4
	87.7	80.3

Both pellets formulations maintained their release properties after compression regardless of the compression pressure used (Figs. 8 and 9) the similarity factors of the dissolution curves with those of the uncompressed pellets are summarized in Table 7. 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. Coated MCC pellets were more robust at the highest compression pressure 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 polymer Kollicoat® IR (elongation at break of films made of Kollicoat® IR without plasticization is about 100%, Buehler, 2007) in the formulation and to the absence of swelling compared to κ-carrageenan pellets. Scanning electron micrographs (Fig. 10) show no cracks in the film coating for pellets at the center, close to the surface and wrinkles in the film layer for those at the upper surface tablets 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.

4. Conclusion

κ-Carrageenan pellets are advantageous against MCC pellets for the formulation of multiparticulate tablets with enteric properties. An adequate coating thickness is necessary for sufficient enteric resistance and results in a robust film against the compression pressure used. κ-Carrageenan pellets can also be formulated into mutiparticulate tablets with sustained release properties. For the mentioned pellets a thicker coated and lower amount of pore former are needed to achieve a certain release profile compared to MCC pellets.

References

Bechgaard, H., Hagermann, N.G., 1978. Controlled-release multi-units and single unit doses. A literature review. Drug Dev. Ind. Pharm. 4, 53–67.
Beckert, T.E., Lehmann, K., Schmidt, P.C., 1996. Compression of enteric-coated pellets to disintegrating tablets. Int. J. Pharm. 143, 13–23.
Bodmeier, R., 1997. Review: tableting of coated pellets. Eur. J. Pharm. Biopharm. 43, 1–8.
Bodmeier, R., Paeratakul, O., 1994. Mechanical properties of dry and wet cellulosic and acrylic films prepared from aqueous colloidal polymer dispersions used in the coating of solid dosage forms. Pharm. Res. 11, 882–888.
Buehler, V., 2007. Kollicoat® Grades. Functional Polymers for the Pharmaceutical Industry. BASF Pharma Solutions, Ludwigshafen, Germany, p. 33.
Celik, M., 1994. Compaction of multiparticulate oral dosage forms. In: Ghebre-Sellassie, I. (Ed.), Multiparticulate Oral Drug Delivery. Marcel Dekker, New York, pp. 181–216.
Dashevsky, A., Kolter, K., Bodmeier, R., 2004. Compression of pellets coated with various aqueous polymer dispersions. Int. J. Pharm. 279, 19–26.
Debunne, A., Vervaet, C., Remon, J.P., 2002. Development and in vitro evaluation of an enteric-coated multiparticulate drug delivery system for the administration of piroxicam to dogs. Eur. J. Pharm. Biopharm. 54, 343–348.
Dreu, R., Ilić, I., Srčič, S., 2010. Development of a multiple-unit tablet containing enteric-coated pellet. Pharm. Dev. Technol., 1–9, early online 2010.
Gehbre-Sellassie, I., 1989. Pellets: a general overview. In: Ghebre-Sellassie, I. (Ed.), Pharmaceutical Pelletisation Technology. Marcel Dekker, New York, pp. 1–13.
Ghanam, D., Hassan, I., Kleinebudde, P., 2010. Compression behaviour of κ-carrageenan pellets. Int. J. Pharm. 390, 117–127.
Krämer, J., Blume, H., 1994. Biopharmaceutical aspects of multiparticulates. In: Ghebre-Sellassie, I. (Ed.), Multiparticulate oral Drug Delivery. Marcel Dekker, New York, Basel and Hong Kong, pp. 307–332.
Lehmann, K., Petereit, H.-U., Dreher, D., 1993. Schnellzerfallende Tabletten mit gesteuerter Wirkstoffabgabe. Pharm. Ind. 55, 940–947.
Lehmann, K.O.R., 1997. Chemistry and application properties of polymethacrylate coating systems. In: McGinity, J.W. (Ed.), Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. , 2nd ed. Marcel Dekker, New York, p. 161.
Malmataris, S., 1983. Tensile strength and compression of coated pharmaceutical powders: tablets. J. Pharm. Pharmacol. 35, 1–6.
Moore, J.W., Flanner, H.H., 1996. Mathematical comparison of curves with an emphasis on dissolution profiles. Pharm. Technol. 20, 64–74.
Muzikova, J., Novakova, P., 2007. A study of the properties of compacts from silicified microcrystalline celluloses. Drug Dev. Ind. Pharm. 33, 775–781.
Schmid, W., Picker-Freyer, K.M., 2009. Tableting and tablet properties of alginates: characterisation and potential for soft tableting. Eur. J. Pharm. Biopharm. 72, 165–172, 2009.

Schultz, P., Kleinebudde, P., 1997. A new multiparticulate delayed release system. Part I. Dissolution properties and release mechanism. J. Control. Release 47, 181–189.

Thommes, M., Kleinebudde, P., 2006a. Use of κ-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronisation. Part I. Influence of type and fraction of filler. Eur. J. Pharm. Biopharm. 63, 59–67.

Thommes, M., Kleinebudde, P., 2006b. Use of κ-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronisation. Part II. Influence of drug and filler type. Eur. J. Pharm. Biopharm. 63, 68–75.

Thommes, M., Kleinebudde, P., 2007a. Properties of pellets manufactured by wet extrusion/spheronization process using κ-carrageenan: effect of process parameters. AAPS Pharm. Sci. Technol. 8, article 95.

Thommes, M., Kleinebudde, P., 2007b. Effect of drying on extruded pellets based on κ-carrageenan. Eur. J. Pharm. Biopharm. 31, 112–118.

USP 32 NF27, 2009. Delayed release dosage forms. In: The United States Pharmacopeia Convention (Ed.), United States Pharmacopeia 32 National Formulary 27. Rockville, MD, p. 269.

Wei, H., Li-Fang, F., Bai, X., Chun-Lei, L., Qinga, X., Yong-Zhene, C., De-Ying, C., 2009. An investigation into the characteristics of chitosan/Kollicoat SR30D free films for colonic drug deliver. Eur. J. Pharm. Biopharm. 72, 266–275.

Zeeshan, F., Bukhari, N.I., 2010. Development and evaluation of a novel modified-release pellet-based tablet system for the delivery of loratadine and pseudoephedrine hydrochloride as model drugs. AAPS Pharm. Sci. Technol. 11, 910–916.