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Research paper

Use of κ-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronisation. II. Influence of drug and filler type

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Abstract

The extrusion/spheronisation process is an established technique to produce pellets for pharmaceutical applications. Microcrystalline cellulose (MCC) is being usually used as a pelletisation excipient in the extrusion process. However, MCC has some disadvantages, e.g. lack of disintegration and prolonged drug dissolution. Therefore, κ-carrageenan was investigated as a substitute for MCC to overcome such disadvantages. A fixed ratio of κ-carrageenan (20%) was combined with different fillers (lactose, mannitol, maize starch and dicalciumphosphate dihydrate) and different drugs (acetaminophen, theophylline, mesalamine and hydrochlorothiazide) in several formulations. Some pellet properties (yield, aspect ratio, mean Feret diameter, 10% interval fraction, tensile strength and dissolution profile) were determined. Most formulations resulted in pellets of a sufficient quality with respect to size, size distribution and shape independent of the incorporated fillers and drugs. In contrast to MCC pellets, the release profile of κ-carrageenan pellets was much less affected by the solubility of the drug. Generally, κ-carrageenan pellets owned fast disintegration and fast drug release in contrast to MCC pellets.

Keywords: Pellets; Extrusion/spheronisation; Pelletisation aid; Carrageenan; Microcrystalline cellulose; Dissolution; Tensile strength

1. Introduction

The extrusion/spheronisation process can be used for manufacturing large pellet batches with reproducible pellet properties. Usually, a pelletisation aid is required for the successful production of pellets by this method. The small range of the suitable materials in use of this technique limits the applicability [1]. Most of the pellet formulations for the extrusion/spheronisation include microcrystalline cellulose as pelletisation aid, which possesses suitable rheological properties of the extrudates during spheronisation [2]. Preliminary investigations using κ-carrageenan as alternative pelletisation aid were reported by Bornhöft et al. [3]. In a previous part of the current study, the use of κ-carrageenan was evaluated [4]. Formulations containing 20% of κ-carrageenan were compared with the same formulations containing 20% of MCC. The type and fraction of the filler was varied. κ-Carrageenan was found to be a suitable pelletisation aid and a possible substitute for MCC. In the former part of the study, paracetamol was used as model drug. In the present part of the study more model drugs with different water solubility are included in order to prove the results of the first part regarding the fast dissolution of the drug. Moreover, the model drugs are combined with fillers of different solubility.

2. Materials and methods

2.1. Materials

The following materials were used as received, acetaminophen (BASF, Ludwigshafen, Germany), κ-carrageenan (Gelcarin® GP 911 NF, FMC, Philadelphia, PA, USA), dicalcium phosphate dihydrate (C92-14, Chemische Fabrik Budenheim, Budenheim, Germany), hydrochlorothiazide (Midas Pharmachemie, Ingelheim, Germany), α-lactose monohydrate (Granulac® 200, Meggle, Germany), maize starch (Emsland-Stärke, Emlichheim, Germany), mannitol (Mannitol 60, Roquette, Lestrem, France), mesalamin (5-aminosalicylic acid, Syntese, Hvidovre, Denmark), microcrystalline cellulose (MCC Sanaq 102 G, Phamatrans Sanaq, Basel, Switzerland) and theophylline monohydrate (BASF, Ludwigshafen, Germany).

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Table 1
Formulations of the powder mixture

Abbreviation	Acetaminophen (%)	Theophylline (%)	Mesalamine (%)	Hydrochlorothiazide (%)	Lactose (%)	Mannitol (%)	Starch (%)	Dicalciumphosphate (%)	κ-Carrageenan (%)	MCC 102 G (%)
Ace	80								20	
AceMCC	80									20
AceLac40	40				40				20	
AceMan40	40					40			20	
AceSta40	40						40		20	
AceCal40	40							40	20	
The		80							20	
TheMCC		80								20
TheLac		40			40				20	
TheMan		40				40			20	
TheSta		40					40		20	
TheCal		40						40	20	
Mes			80						20	
MesMCC			80							20
MesLac			40		40				20	
MesMan			40			40			20	
MesSta			40				40		20	
MesCal			40					40	20	
Hyd				80					20	
HydMCC				80						20
HydLac				40	40				20	
HydMan				40		40			20	
HydSta				40			40		20	
HydCal				40				40	20	

2.2. Methods

2.2.1. Experimental plan

The formulations used in this part of the study are given in Table 1. The different formulations are abbreviated according to the first column in Table 1. The content of the pelletisation aid was fixed at 20% in all formulations. Using κ-carrageenan as pelletisation aid four different actives in fractions of 40 and 80% were investigated. In case of formulations containing 40% active the remaining 40% were constituted of one of four different fillers. Pellets with MCC as pelletisation aid were produced with 80% active without fillers.

For each powder formulation three batches with different water content were made. The batch resulting in pellets with the lowest aspect ratio was defined as optimum and was used for further characterisation. Thus, the presented results are based on one batch for each formulation. The standard deviations given in the text and figures are based on repetitive measurements for each method detailed below.

2.2.2. Extrusion and spheronisation

After weighing, the dry powders were blended for 10 min in a laboratory scale blender (LM20 or LM40, Bohle, Ennigerloh, Germany) and then transferred to the gravimetric powder feeder of the extruder. The twin-screw extruder (Mikro 27GL-28D, Leistritz, Nuremberg, Germany) was equipped with an axial screen with 23 dies of 1 mm diameter and 2.5 mm length. The extrusion took place at a constant screw speed of 100 rpm, a powder feed rate of 33 g/min and a suitable liquid feed rate. Deionised water was used as granulation liquid supplied by a membrane pump (Cerex EP-31, Bran and Luebbe, Norderstedt, Germany) with flow through metering device (Corimass MFC-081/K, Krohne, Duisburg, Germany). Batches of 300 g wet extrudate were collected and spheronised for 5 min at 750 rpm in a spheroniser (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) fitted with a cross-hatched rotor plate of 300 mm diameter. The drying step was carried out in a fluid bed apparatus (ST2, Aeromatic, Bubendorf, Switzerland or GPCG 1.1, Glatt, Dresden, Germany) for 20 min with an inlet air temperature of 60 °C.

2.2.3. Loss on drying

For each batch three samples of extrudate were taken during extrusion for the determination of the extrudate water content. The samples were dried at 105 °C for 24 h in a circulating air oven (Heraeus UT-6060 or UT-6120, Kendo, Hanau, Germany). The water of the extrudates was calculated based on dry mass.

2.2.4. Image analysis

Each batch was sieved from 1.0 to 1.6 mm defining this fraction as yield. Samples of suitable size from the yield fraction were obtained by using a rotary cone sample divider (Retschmühle PT, Retsch, Haan, Germany).

Image analysis was conducted using a system consisting of a stereomicroscope (SZX 9, Olympus, Hamburg, Germany), a ringlight with cold light source (Highlight 3001 with HL-VRL, Olympus, Hamburg, Germany), a digital camera (DIG1300C, Micromotion, Landshut, Germany), and a computer with data logging card and the software Image C (Imtronic, Berlin,

Germany). Images of at least 500 pellets of each sample at a suitable magnification (1 pixel = 15.2 μm) were translated into binary images. Contacting pellets were separated by a software algorithm. If the automatic separation failed, pellets were deleted manually. For each pellet, 36 Feret diameters were determined and used to calculate the mean Feret diameter. The ratio of the maximum Feret diameter and the Feret diameter perpendicular to the maximum Feret diameter is used as the aspect ratio. The pellet size and shape were characterised by mean Feret diameter and aspect ratio, respectively.

2.2.5. Tensile strength

The mechanical characteristics of pellets were investigated by using a texture analyser (TA.XT2i, Stable micro systems, Godalming, UK) after equilibrating the pellets at 20 °C and 60% r.H.). Therefore, the fracture force (F) of 50 pellets per batch at a loading rate of 0.1 mm/s was determined. To calculate the tensile strength (σ) the diameter (d) of each pellet in crushing direction was additionally considered (Eq. (1)) [5]:

$$\sigma = \frac{1.6F}{\pi d^2} \quad (1)$$

2.2.6. Dissolution

The tests were performed according to the monographs 'acetaminophen tablets', 'hydroclorothiazide tablets', 'mesalamine extended-release capsules' and 'theophylline tablets' in USP 26 with a paddle apparatus at 50 rpm. For the dissolution test of hydrochlorothiazide, a paddle apparatus was used in contrast to the monograph. Six dried samples (105 °C, 24 h) of each pellet batch were tested in randomised order. The concentrations of active in the dissolution medium were determined by a UV-photometer (Lambda 2, Perkin–Elmer, Überlingen, Germany) up to 90 min.

2.2.7. Pellet disintegration

The pellet disintegration in water was evaluated by a tablet disintegration tester DT 2 (Sotax, Basel, Switzerland). Special transparent tubes of 10 mm diameter and 15 mm length were used. Sieves of 710 μm mesh size were at the top and the bottom of this tube. After filling 100 mg pellets in each tube they were inserted in the standard tablet disintegration tester. The disintegration time of six dried samples (105 °C, 24 h) at 37 °C was determined at a speed of 30 dips/min.

2.2.8. Particle size

The particle size of the powders was determined by a laser diffraction analyser (Helos/KF-Magic, Sympatec, Claustal-Zellerfeld, Germany) in use of a dry dispersing system (Rodos, Sympatec, Claustal-Zellerfeld, Germany). The measuring was carried out at an atomising pressure of 3.03 bar and with lens of 0.5/4.5…875 μm. Each powder was measured three times and the average of median, x_{10} quantile and x_{90} quantile was calculated.

2.2.9. Electron microscope

The powder particles of the drug were visualised by scanning electron microscope (Leo 1430 VP, Leo Electron Microscopy, Cambridge, UK). The samples were gold sputtered (Agar Manual Sputter Coater B7340, Agar Scientific, Stansted, UK).

2.2.10. Adsorption studies

The adsorption of hydrochlorothiazide to MCC was evaluated by addition of 0.4 g of MCC to 20 g hydrochlorothiazide solutions of different concentrations. After an equilibration time of 24 h the suspension was filtered through a membrane of 0.22 μm. The hydrochlorothiazide concentration was determined in the filtrate in using UV-photometer (Lambda 2, Perkin–Elmer, Überlingen, Germany). The difference between origin concentration and the concentration in the filtrate was used to calculate the adsorbed amount of hydrochlorothiazide. The results were plotted as a Freundlich Isotherm from which the n- and k-parameters were derived.

3. Results and discussion

The current study was divided into two parts. In the first part, the influence of fillers and their fraction on the pelletising process and pellet properties were examined [4]. In this part of the study, the results on the influence of different model drugs on the pelletising process are reported. Actives with different solubility were chosen since in the first part an influence of the filler solubility on the pellet properties was noticed. The different drugs were further combined with the different fillers used in part one. Thus, the results of the first part should be proven and the interactions between pelletisation aid, drug and filler should be evaluated.

All intended formulations resulted in pellets with a high yield in the range from 1.0 to 1.6 mm exceeding 90% (Table 2) using κ-carrageenan as pelletisation aid. The only exception was the formulation HydLac, which resulted in a yield of 89.1%. The formulations including MCC as pelletisation aid resulted in yields from 63.3 to 94.4%. The chosen sieve fraction was most suitable for κ-carrageenan pellets. MCC pellets were smaller with lower yield.

3.1. Water content of extrudate

The most suitable water content for pelletisation was evaluated by testing three different water contents for each powder formulation (Table 2). The water content of the batch with low aspect ratio was considered as the suitable water content. Formulations containing κ-carrageenan required always more water than the formulations containing MCC. This effect was previously observed in part 1 [4] of this study. It was supposed that the required water was mainly determined by water binding on the pelletisation aid.

However, the filler did also influence the water content. This influence is similar for each model drug. Soluble fillers like lactose and mannitol required lower water content during pelletisation compared to dicalciumphosphate. Insoluble filler is completely suspended and not dissolved in extrusion/spheronisation process resulting in higher water content [6]. Furthermore, dicalciumphosphate has the highest particle size

Table 2
Pellet and batch properties of different formulations (arithmetic mean, standard deviation)

Formulation	Loss on drying (%)	Mean Feret dia. (mm)	Tensile strength (MPa)	Yield 1.0–1.6 mm (%)	10% interval (%)
Ace	64.4±0.82	1.46±0.17	0.68±0.15	98	66
AceMCC	56.2±0.67	1.23±0.12	3.55±0.68	93	–
AceLac40	74.0±1.37	1.37±0.15	0.76±0.11	97	63
AceMan40	71.5±0.73	1.34±0.16	0.84±0.11	97	61
AceSta40	112±2.09	1.27±0.13	0.68±0.13	94	68
AceCal40	92.3±0.96	1.33±0.14	0.81±0.13	98	67
The	86.2±1.71	1.32±0.14	1.30±0.24	96	66
TheMCC	71.9±0.80	1.08±0.11	4.38±0.69	87	–
TheLac	83.0±0.33	1.31±0.13	1.27±0.17	96	66
TheMan	82.1±0.86	1.35±0.13	0.86±0.18	95	67
TheSta	98.9±0.98	1.29±0.12	1.28±0.33	90	78
TheCal	85.4±0.53	1.31±0.13	1.19±0.20	94	51
Mes	82.1±1.73	1.40±0.17	1.65±0.76	96	58
MesMCC	58.8±1.02	1.21±0.07	2.48±0.31	94	–
MesLac	80.7±0.18	1.32±0.14	1.05±0.19	97	62
MesMan	73.8±0.88	1.36±0.15	1.38±0.60	97	65
MesSta	125±3.66	1.36±0.16	0.68±0.15	98	73
MesCal	88.4±3.72	1.37±0.15	0.36±0.07	91	71
Hyd	82.7±0.77	1.34±0.15	0.68±0.12	94	64
HydMCC	56.1±5.24	1.42±0.08	3.71±0.65	98	–
HydLac	78.2±0.70	1.37±0.14	0.73±0.12	63	66
HydMan	79.0±0.30	1.31±0.14	0.84±0.13	89	62
HydSta	104±0.74	1.35±0.14	0.32±0.07	97	71
HydCal	94.4±3.57	1.29±0.14	0.91±0.15	92	66

among components (Table 3), which may also affect the required water amount for successful pelletisation. The most water requiring formulations were the four containing starch caused by the water binding effect due to swelling of the starch particles.

All investigated drugs required similar water content except acetaminophen, which shows the highest solubility. The water content of formulations containing 80% acetaminophen was comparable to formulations containing 40% acetaminophen and 40% of soluble fillers. Soluble components (drugs or fillers) are partly dissolved during extrusion, which affects the ratio of liquid to solid phase. Consequently, less water is required for pelletisation.

Generally, the amount of water for the pelletisation process was systematically influenced by the pelletisation aid, the filler and the drug.

Table 3
Particle size

Substance	x_{50}	x_{90}–x_{10}
Acetaminophen	16.2	66.5
Theophylline	11.1	31.8
Mesalamine	11.5	44.3
Hydrochlorothiazide	21.2	46.2
Lactose	26.1	82.5
Mannitol	83.2	239.8
Starch	15.0	24.4
Dicalciumphosphate	146.4	229.6
κ-Carrageenan	57.4	129.9
MCC 102 G	100.6	177.1

3.2. Pellet shape

Most formulations displayed a median aspect ratio below the demanded value of 1.1 [7] (Fig. 1). There were not insufficient formulations because all values for the median aspect ratio were below 1.2. This proves the suitability of κ-carrageenan as pelletisation aid. In comparison with the other drugs, mesalamine formulations were more difficult to spheronise when κ-carrageenan was used as pelletisation aid. The lack of plasticity during spheronising process may be related to the particle shape of mesalamine. Mesalamine powder consists of needle-like particles, whereas the other investigated drugs depicted a nearly isometric particle shape (Fig. 2(a)–(d)). The mesalamine needles may arrange during the spheronising process in a manner resulting in a reduced

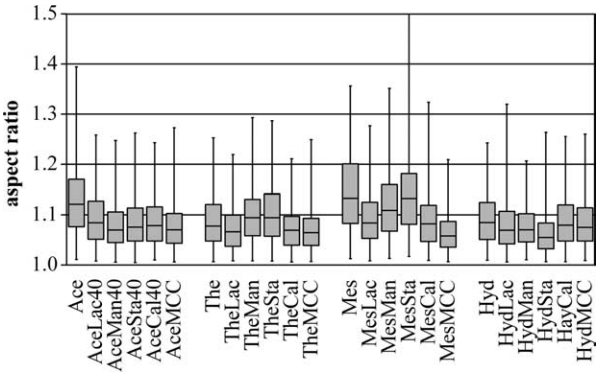

Fig. 1. Pellet shape of the different formulations (x_1, x_{10}, x_{50}, x_{90}, x_{99}, $n>500$).

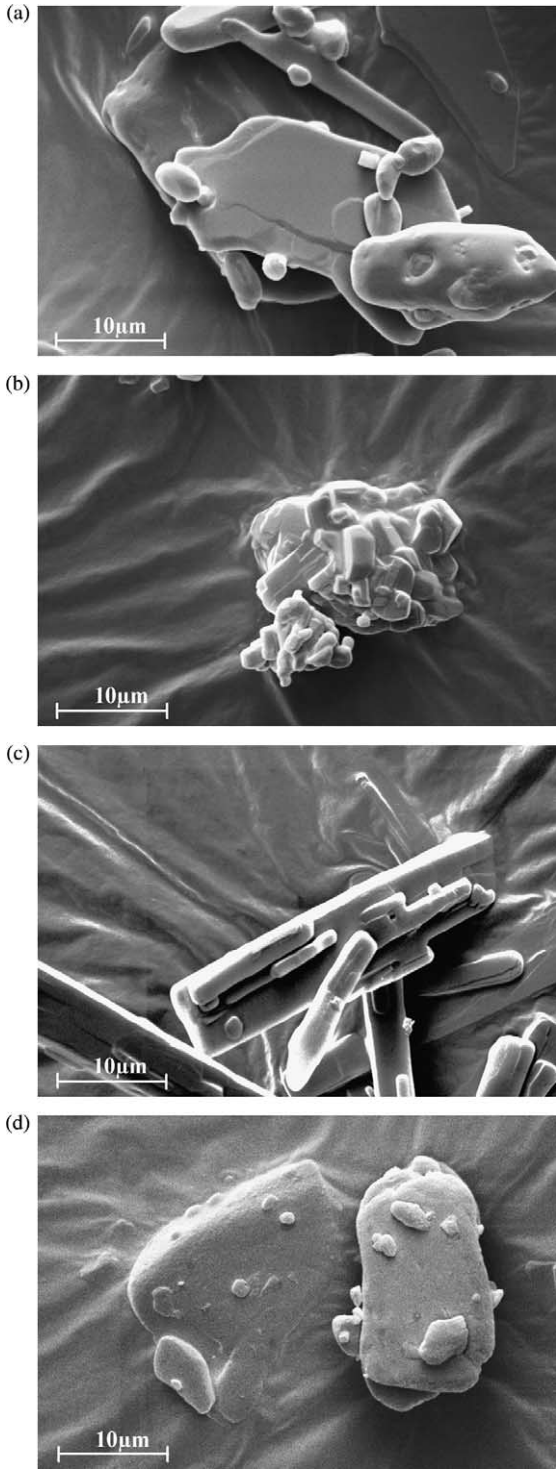

Fig. 2. SEM picture from the powder particles of the drugs. (a) Acetaminophen. (b) Theophylline. (c) Mesalamine. (d) Hydrochlorothiazide.

plasticity of the extrudate. Increasing the κ-carrageenan content or optimisation of the process parameters may improve the behaviour. The high value of median aspect ratio of Ace was possibly caused by an insufficient optimisation of the water content.

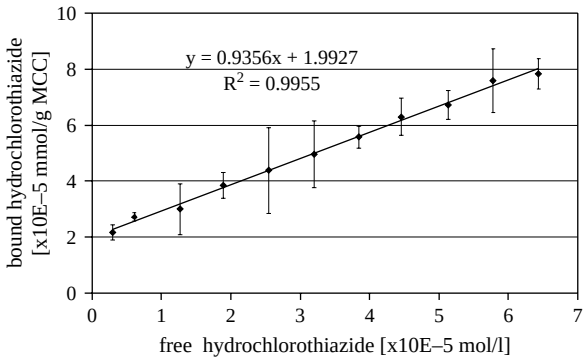

Fig. 3. Freundlich type adsorption of hydrochlorothiazide to MCC (arithmetic mean, standard deviation, $n=3$).

3.3. Pellet size

In contrast to MCC pellets, κ-carrageenan pellets showed higher mean pellet size (Table 2), which was previously determined in part one of this study [4]. This phenomenon was explained by the occurrence of longer extrudate cylinders in spheronisation and lower shrinking during drying in the presence κ-carrageenan as pelletisation aid. In contrast to these findings, the formulation HydMCC showed a larger particle size than most of the κ-carrageenan formulations. This fact might be explained by an adsorption of hydrochlorothiazide to MCC, which can affect the extrudate properties in the spheronising process. The interaction between drug and extrusion aid was further investigated by adsorption experiments. A Freundlich type adsorption was evaluated and the Freundlich parameters of $n=1$ and $k=0.94$ were determined (Fig. 3). The values described a small adsorption according to Okada [8].

The particle size distribution based on the dimensionless diameter is shown in Fig. 4 for pellets with κ-carrageenan as pelletisation aid. In the present study, image analysis was performed on the sieve fraction 1.0–1.6 mm. The size distributions are self-similar, because they coincide more or less in the dimensionless representation (Fig. 4). The fraction in

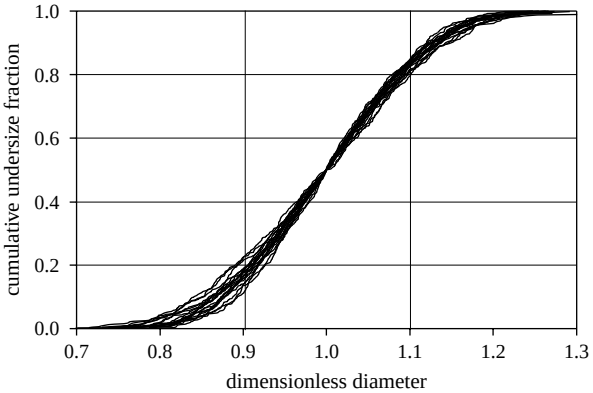

Fig. 4. Pellet size distribution for formulations containing κ-carrageenan as pelletisation aid.

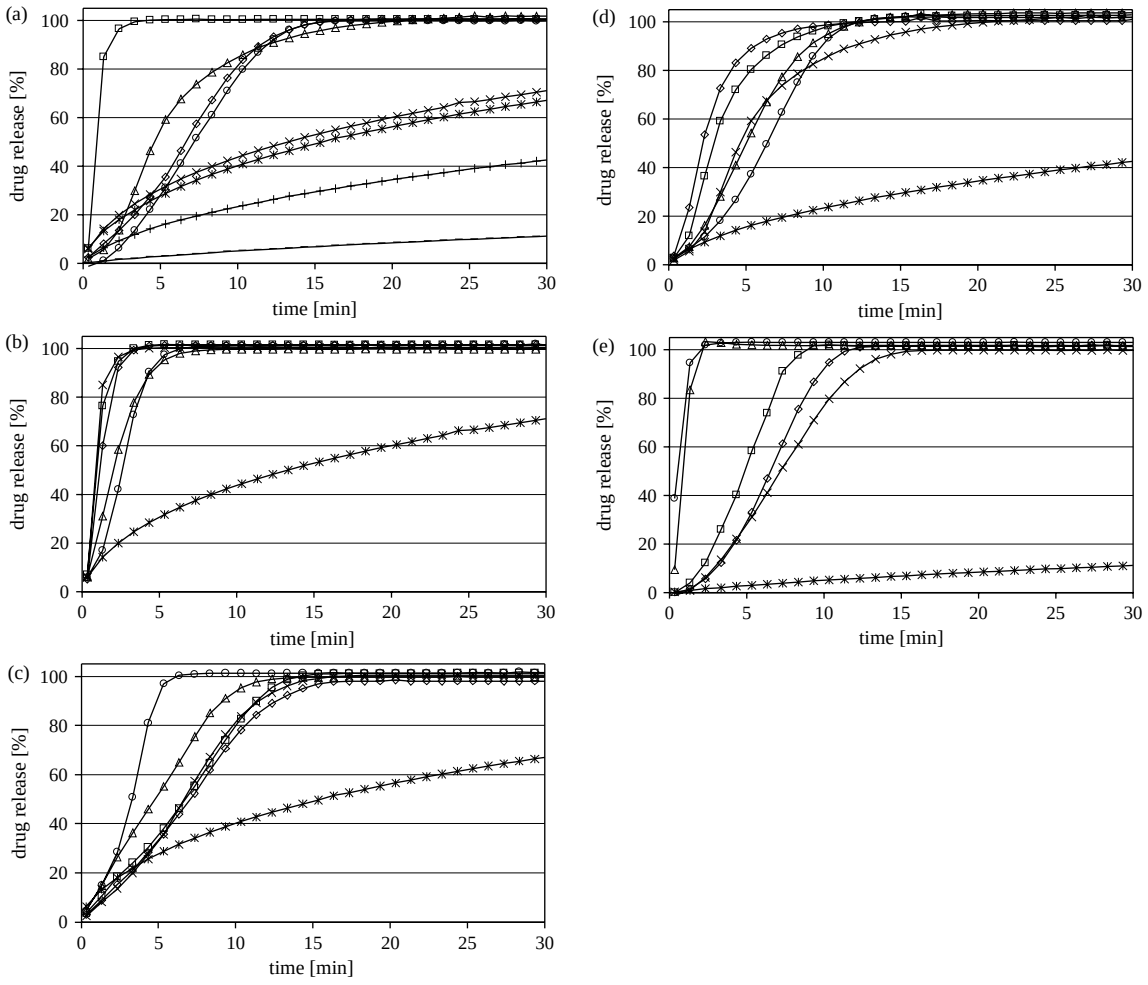

Fig. 5. (a) Release profiles of the different drugs: □, Ace; ◇, The; △, Mes; ○, Hyd; ×, AceMCC; ✳, TheMCC; +, MesMCC, −, HydMCC (arithmetic mean, $n=6$). (b) Release profiles of acetaminophen pellets: ×, Ace; □, AceLac40; ◇, AceMan40; △, AceSta40, ○, AceCal40; ✳, AceMCC (arithmetic mean, $n=6$). (c) Release profiles of theophylline pellets: ×, The; □, TheLac; ◇, TheMan; △, TheSta; ○, TheCal; ✳, TheMCC (arithmetic mean, $n=6$). (d) Release profiles of mesalamin pellets: ×, Mes; □, MesLac; ◇, MesMan; △, MesSta; ○, MesCal; ✳, MesMCC (arithmetic mean, $n=6$). (e) Release profiles of hydrochlorothiazide pellets: ×, Hyd; □, HydLac; ◇, HydMan; △, HydSta; ○, HydCal; ✳, HydMCC (arithmetic mean, $n=6$).

the 10% interval was in the range 51–78%. Thus, all size distributions can be regarded as good and the size distribution for the formulation TheSta is excellent. For all drugs, the formulations including starch as filler resulted in size distribution with the highest 10% interval fraction, i.e. the smallest size distribution. For MCC pellets, the size distribution is not shown as almost less than 90% of the pellets were within the sieve fraction of 1.0–1.6 mm resulting in biased results of image analysis.

3.4. Mechanical properties

In further investigations, the effect of the formulations on the mechanical properties of the pellets was evaluated (Table 2). The κ-carrageenan pellets showed a lower tensile strength than the MCC pellets due to the higher porosity caused by less shrinking of the pellets during drying [4].

The tensile strength of the different mesalamine pellet formulations showed high variation, which might be caused by the high variability in their shape (Fig. 1). A determination of the tensile strength of non-spherical pellets is difficult because the crushing surface is unknown and has to be evaluated for each pellet.

The tensile strength of theophylline pellets is slightly higher compared to similar formulations containing other drugs. That could be caused by the isometric and small theophylline particles (Table 3, Fig. 2(a)–(d)). Generally, there was a similar tensile strength of all κ-carrageenan pellets, which was not modulated by the filler.

Table 4
Solubility of drug in dissolution medium and MDT of MCC pellets

Formulation	Solubility of drug (g/100 ml)	MDT (min)
AceMCC	16.12 ± 0.03	22.3 ± 0.72
TheMCC	7.43 ± 0.05	24.6 ± 0.63
MesMCC	1.23 ± 0.01	65.0 ± 1.93
HydMCC	0.45 ± 0.002	672 ± 33.6

Table 5
Disintegration time of the pellets

Formulation	Disintegration time (min)
Ace	7:53 ± 0:15
The	8:27 ± 0:18
Mes	4:01 ± 0:05
Hyd	9:49 ± 0:36

3.5. Disintegration and drug release

The influence of the two pelletisation aids and the different drugs on the release profile is shown in Fig. 5(a) for a drug loading of 80%. κ-Carrageenan pellets showed a fast disintegration during the dissolution test resulting in a fast dissolution of the drug. MCC pellets, which did not disintegrate [9], demonstrate a slower drug release. For MCC pellets, the drug release was related to the solubility of the drug (Table 4). The drug release of the HydMCC pellets was slower than expected from the solubility, which could be explained by the adsorption of the drug to the MCC pellet matrix (Fig. 3). The release of HydMCC was completed after 48 h (data not shown). The release from κ-carrageenan pellets is not directly related to the solubility of the drug as the release is completed within less than 20 min independent of the solubility of the drug. Thus, in all cases the release is much faster from κ-carrageenan pellets than from MCC pellets although the size of the κ-carrageenan pellets was larger. The very fast drug release of Ace can be explained by the high solubility of acetaminophen compared to the other drugs. The pellet batches The and Hyd owned a similar drug release which was mainly determined by the disintegration of the pellets (Table 5). The slightly faster release of Mes was caused by a rapid disintegration of the pellets. After disintegration, the release depends on the dissolution of the drug, which is also affected by the particle size.

Further investigations focused on the influence of different fillers on the release of different model drugs investigated. A systematic effect of the different fillers on the dissolution profile caused by the solubility, particle size or particle shape was not found (Fig. 5(b)–(e)). Independent of the filler, the drug release was always completed in less than 20 min. In the case of acetaminophen the addition of filler resulted in a slightly reduced release rate, whereas in the case of hydrochlorothiazide all fillers resulted in an increasing release rate.

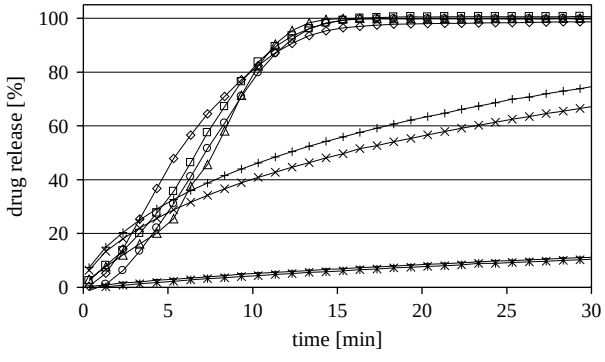

Fig. 6. Release profile depending on the dissolution medium: □, The in water; ◇, Hyd in water; △, The in 0.1 N HCl; ○, Hyd in 0.1 N HCl; ×, TheMCC in water; ✳, HydMCC in water; +, TheMCC in 0.1 N HCl; −, HydMCC in 0.1 N HCl (arithmetic mean, $n=6$).

Basically two effects determined the drug release. The first one is the dissolution of the drug and the filler. The second is the disintegration of the κ-carrageenan matrix. In most cases an interference of both effects might be expected. In all dissolution profiles, the κ-carrageenan pellets showed a fast drug release compared to MCC pellets caused by a fast disintegration.

κ-Carrageenan is an acid polysaccharide and could be hydrolysed in acids [10]. Therefore, it is necessary to evaluate the influence of the pH-value on the release profile. The formulations The, TheMCC, Hyd and HydMCC were tested in water and in 0.1 N hydrochloric acid (Fig. 6). There was no significant influence of the dissolution medium on the drug release of κ-carrageenan pellets. This may be due to the fast release of the drug and, therefore, the presence of pellets in acidic medium is very short. Hydrolysis of κ-carrageenan molecules requires higher temperature and longer time [10].

4. Conclusion

κ-Carrageenan was considered as a suitable pelletisation aid and a possible substitute for the commonly used MCC. The achieved κ-carrageenan pellets were characterised by a low tensile strength, fast disintegration and fast drug release. In contrast to MCC pellets, a fast release profile could be achieved independent of the solubility of the drug. Therefore, κ-carrageenan seems to be more suitable as excipient in pelletisation of slightly soluble drugs.

The effects of different fillers on the pelletisation process and the pellet properties were negligible. Also a systematic effect of the fillers on the dissolution profile was not found.

κ-Carrageenan is a promising excipient for pelletisation by extrusion/spheronisation. It shows significant advantages over MCC as disintegration and fast drug release.

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References

[1] P.J. Harrison, J.M. Newton, R.C. Rowe, The application of capillary rheometry to the extrusion of wet powder masses, Int. J. Pharm. 35 (1987) 235–242.
[2] A.D. Reynolds, A new technique for production of spherical particles, Manufact. Chem. Aerosol News 41 (1970) 40–43.
[3] M. Bornhöft, M. Thommes, P. Kleinebudde, Preliminary assessment of carrageenan as excipient for extrusion/spheronisation, Eur. J. Pharm. Biopharm. 59 (2005) 127–131.
[4] M.Thommes, P.Kleinebudde, Use of κ-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/ spheronisation I. Influence of type and fraction of filler, Eur. J. Pharm. Biopharm. (in press).
[5] P.H. Shipway, I.M. Hutchings, Fracture of brittle spheres under compression and impact loading. 1. Elastic stress distributions, Philos. Mag. A-Phys. Condensed Matter Struct. Defect. Mech. Properties 67 (1993) 1389–1404.

[6] L. Baert, D. Fanara, P. Debaets, J.P. Remon, Instrumentation of a gravity feed extruder and the influence of the composition of binary and ternary mixtures on the extrusion forces, J. Pharm. Pharmacol. 43 (1991) 745–749.
[7] P. Kleinebudde, Use of a power-consumption-controlled extruder in the development of pellet formulations, J. Pharm. Sci. 84 (1995) 1259–1264.
[8] S. Okada, H. Nakahara, H. Isaka, Adsorption of drugs on microcrystalline cellulose Suspended in Aqueous-Solutions, Chem. Pharm. Bull. 35 (1987) 761–768.
[9] M. Schröder, P. Kleinebudde, Development of disintegrating pellets obtained from extrusion/spheronisation, Pharm. Sci. (1995) 415–418.
[10] C. Rochas, A. Heyraud, Acid and enzymic-hydrolysis of κ-Carrageenan, Polym. Bull. 5 (1981) 81–86.