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European Journal of Pharmaceutics and Biopharmaceutics 63 (2006) 59–67
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

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

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Received 29 April 2005; accepted in revised form 6 October 2005
Available online 2 December 2005

Abstract

Microcrystalline cellulose (MCC) is commonly used as an excipient in extrusion/spheronisation process. However, MCC owns several disadvantages as lack of disintegration and drug adsorption. Therefore, κ-carrageenan was investigated to substitute MCC in pelletising processes. Formulations with 20% of pelletisation aid (κ-carrageenan or MCC) and acetaminophen as a model drug have been produced. Different fillers (lactose, mannitol, maize starch and dicalciumphosphate dihydrate) at fractions of 0, 20, 40 and 80% were evaluated and the properties of the resulted pellets were determined (e.g. yield, aspect ratio, mean Feret diameter, 10% interval fraction, tensile strength and release profile). κ-Carrageenan has proven to be a suitable substitute as pellets with sufficient quality were produced. The pellet batches of different formulations were characterised by high yield, spherical pellet shape and narrow pellet size distribution. The distinguished behaviour between κ-carrageenan and MCC pellets was the lower tensile strength and the faster release of κ-carrageenan pellets. For the various types and fractions of fillers only minor effects to the pelletisation process and pellet properties were noticed. From the practical view these effects are neglectable indicating a robust formulation and process.

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

1. Introduction

Recently, pellets gained more attention in the development of modified release dosage forms. Because of their regular shape and size [1] they are suitable for coating and encapsulation processes. In addition, pellets may sometimes improve the bioavailability, reduce the risk of dose dumping and decrease local irritations in the gastrointestinal tract [1].

There are several techniques to produce pellets e.g. layering in fluid bed equipment or direct pelletisation in high shear mixers and rotary processors. The pelletisation by extrusion/spheronisation is an established technique to produce pellets of a high density and narrow size distribution. This technique includes two steps using specific apparatuses. The first step is the extrusion: a paste is pressed through dies of defined diameters resulting in cylindrical extrudates. In the second step these extrudates are transferred to a spheroniser and formed to beads [2,3]. Special rheological properties of the paste are required for a successful spheronisation process. These properties e.g. a suitable relation between brittleness and plasticity in spheronising are achieved by the formulation [3]. Commonly used MCC allows spheronisation in fractions below 20% of the formulations. However, formulations based on MCC as pelletisation aids have some shortcomings. The first disadvantage is the lack of disintegration [4] which results in a prolonged matrix type drug release [5]. For low soluble drugs the time for complete release might be slower than the gastrointestinal passage time resulting in decreased bioavailability. The second disadvantage is an adsorption of some drugs to MCC [6–8] that can affect the drug release. Also, a decomposition of some drugs e.g. ranitidine in the presence of MCC could be observed [9]. Therefore, alternatives to the commonly used pelletisation aid MCC were searched. An aqueous solution of hydroxypropylcellulose as binder was used by Otsuka et al. [10] resulting in pellets with less spherical shape. Scheler et al. [11] also evaluated a combination of povidon and ethanol as granulation liquid. In a preliminary study, Tho et al. [12] used pectinic acid in a wide range of fractions from 20 to 99%. The aspect ratio of the chosen formulations varied between 1.11 and 1.21. The release differed in 0.1 N HCl and phosphate buffer pH 6.8. Further

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doi:10.1016/j.ejpb.2005.10.002

optimisation is important for pectinic acid as pelletisation aid. Pure chitosan was pelletised using acetic acid by Steckel et al. [13]. Data with drugs are not available. Agrawal [14] combined chitosan with hydroxypropylcellulose as a binder. Spherical beads without MCC with good mechanical properties were manufactured using water as granulation liquid. Using caffeine as model drug the chitosan pellets showed a similar drug release compared to MCC pellets. A substitution of MCC by glycerol monostearate was investigated [15]. Four different model drugs were incorporated in a fraction of 10%. Diclofenac could only be pelletised without MCC, whereas the other three model drugs required 30% MCC. Thus, glycerol monostearate did not display the universality of MCC as a pelletisation aid. Other approaches improved the pellet properties by combining super disintegrants like sodium starch glycolate with organic granulation liquids [4] or high contents of special additives like waxy corn starch [16]. Up to date, there is no suitable alternative to substitute MCC. Therefore, κ-carrageenan was evaluated as a substitute for MCC.

Carrageenans are a group of acid polysaccharides which are isolated from cell walls of red seaweeds of the genera Gigartinales [17]. The chemical structure of carrageenan bases on repetition of a disaccharide sequence of galactose and 3,6-anhydrogalactose which are alternately linked to α-1,3 and β-1,4 in the polymer (Fig. 1). Furthermore, there are sulfate ester groups in the molecule which are combined with potassium, sodium, calcium, magnesium and ammonium as counterions [18]. κ-Carrageenan contains one sulfate group per dimer in position 4 of the galactose [19]. In the presence of water κ-carrageenan forms brittle, strong and rigid gels in dependence of the presence of counterions.

In the food industry carrageenans are often used as a thickener, binder and stabiliser [19]. Recently, the carrageenans became important in pharmaceutical development. Carrageenans were used to reduce the amount of polymorphic transformation in tabletting [20], to produce controlled release matrix tablets [21–23], to achieve interactions with drugs for modified release systems [24,25] and as a part of composite films [26] and gels [27]. Garcia and Ghaly [28] used carrageenan in extrusion/spheronisation for preparing bioadhesive glipizide spheres. In contrast to the present study, the carrageenan was used additional to microcrystalline cellulose to achieve the bioadhesive properties and not as a substitute.

Recently, κ-carrageenan was suggested as a new pelletisation aid for the substitution of MCC in extrusion/spheronisation [29]. Preliminary results have shown that nearly spherical particles can be produced in a wide range of κ-carrageenan fractions from 5 to 98%. Further investigations showed that a fraction of 20% of pelletisation aid was found to be suitable. The quality e.g. pellet shape could be improved by means of using a higher content of pelletisation aid. However, systematic investigations on the use of κ-carrageenan are still lacking. The intent of this study was to use a low fraction of pelletisation aid to investigate the influence of the other ingredients and to allow a high load of the drug. Thus, all formulations are based on the use of 20% pelletisation aid, i.e. MCC or κ-carrageenan.

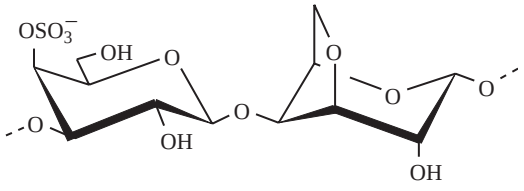

Fig. 1. Dimeric repeating sequence of κ-carrageenan.

This study is divided into two parts evaluating the use of κ-carrageenan as alternative pelletisation aid compared to MCC: In the first part the type and fraction of different fillers on pellet properties is investigated and in the second part the influence of drugs of different solubility is studied [30].

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), α-lactose monohydrate (Granulac® 200, Meggle, Wasserburg, Germany), maize starch (Emsland-Stärke, Emlichheim, Germany), mannitol (Mannitol 60, Roquette, Lestrem, France) and microcrystalline cellulose (MCC Sanaq 102 G, Phamatrans Sanaq, Basel, Switzerland).

3. Methods

3.1. Experimental plan

The formulations used in this part of the study are given in Table 1. Throughout the text the different formulations are abbreviated according to the first column in this table. The content of pelletisation aid was fixed at 20% in all formulations. Using κ-carrageenan as pelletisation aid fractions of 0, 20, 40 and 60% of each filler were investigated. Pellets with MCC as pelletisation aid were produced with 0 and 40% of the different fillers. The content of acetaminophen as model drug in the formulations was determined by the contents of the filler and the pelletisation aid.

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 suitable and was used for further characterisations. 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.

3.2. Extrusion and spheronisation

After weighing, the dry powders were blended for 10 min in a laboratory scale blender (LM 20 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

Table 1
Formulations of the powder mixture

Abbreviation	Acetaminophen (%)	Lactose (%)	Mannitol (%)	Starch (%)	Dicalciumphosphate (%)	κ-Carrageenan (%)	MCC 102 (%)
Ace	80					20	
AceMCC	80						20
AceLac20	60	20				20	
AceLac40	40	40				20	
AceLac60	20	60				20	
AceLacMCC	40	40					20
AceMan20	60		20			20	
AceMan40	40		40			20	
AceMan60	20		60			20	
AceManMCC	40		40				20
AceSta20	60			20		20	
AceSta40	40			40		20	
AceSta60	20			60		20	
AceStaMCC	40			40			20
AceCal20	60				20	20	
AceCal40	40				40	20	
AceCal60	20				60	20	
AceCalMCC	40				40		20

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.

3.3. 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.

3.4. 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 stereo microscope (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.

The dimensionless particle size was calculated from Eq. (1):

$$d = \frac{d_F}{d_{F50}} \tag{1}$$

with dimensionless diameter (d), mean Feret diameter (d_F) and median of all mean Feret diameters (d_{F50}). The distribution of the particle size is characterised by the fraction of the particles in the interval $0.9 < d < 1.1$. The size distribution is characterised as good, if the fraction of the 10% interval exceeds 50% and as excellent, if it exceeds 75%.

3.5. Tensile strength

The mechanical characteristics of pellets were investigated 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. (2)) [31].

$$\sigma = \frac{1.6F}{\pi d^2} \tag{2}$$

3.6. Drug release

The tests were performed according to the monographs 'acetaminophen tablets' in USP 26 with a paddle apparatus at 50 rpm. Six dried samples (105 °C, 24 h) of each pellet batch were tested in randomized order. The concentration of acetaminophen in the release medium was determined each minute by a UV-photometer (Lambda 2, Perkin-Elmer, Überlingen, Germany) up to 90 min.

3.7. 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 per minute.

3.8. Water sorption

The sorption/desorption isotherms of MCC and κ-carrageenan were determined automatically by a SPS 11 sorption test system (Projekt Messtechnik, Ulm, Germany). Samples of approximately 2 g were exposed to different humidities between 0% and 90% r.H. at 25 °C. After equilibration (< 0.01% weight change/30 min) the weights were noticed automatically before the next programmed humidity was adjusted. Each pelletisation aid was evaluated in triplicate.

3.9. Gas pycnometric density

The gas pycnometric density (ρ_g) of dry extrudates and dry pellets were determined by a helium pycnometer (AccuPyc, Micromeritics, Moenchengladbach, Germany). For each tested extrudate or pellet batch three samples were analysed.

3.10. Mercury porosimeter density

The apparent density of the same extrudates (ρ_e) and pellets (ρ_p), which were used for the determination of the gas pycnometric density, were evaluated by a mercury porosimeter (Pascal 140, Thermo Finnigan, Milan, Italy).

3.11. Decrease of porosity in drying

Formulations Ace and AceMCC were used to determine a possible decrease in porosity. From the gas pycnometric density and the mercury porosimeter density the porosity of the extrudate or pellet can be calculated according to Eqs. (3) and (4):

$$\varepsilon_e = \left(1 - \frac{\rho_e}{\rho_g}\right) \quad (3)$$

$$\varepsilon_p = \left(1 - \frac{\rho_p}{\rho_g}\right) \quad (4)$$

The shrinking of the extruded mass during the drying process was calculated from the porosity of freeze dried (Lyovac, Amsco/Finn-Aqua, Huerth,Germany) extrudate (ε_e) and the porosity of the corresponding fluid-bed dried pellets (ε_p).

The decrease of the porosity (DP) during drying was calculated (Eq. (5)).

$$DP = \left(1 - \frac{\varepsilon_p}{\varepsilon_e}\right) 100\% \quad (5)$$

4. Results and discussion

Preliminary studies proposed κ-carrageenan as a novel pelletisation aid to substitute the commonly used MCC [29]. The current study pursues the suitability of κ-carrageenan as a pelletisation aid in combination with different fillers and different model drugs. κ-Carrageenan pellets should be compared with pellets produced with the standard pelletisation aid, namely MCC. Both pellet types were similarly produced but it was necessary to adapt the water content to the individual formulation. In the present study only three levels of water content could be tested. A thoroughly optimisation of the water content would require more test levels. Thus, the results of this study do not represent the optimal water content for each formulation. The differences between the κ-carrageenan and MCC pellets were only caused by the pelletisation aid and the different water content. Therefore, the pellet properties could directly be compared. Suitable process parameters were also evaluated in pre-tests to achieve pellets of an adequate quality. In this study the process parameters of extrusion and spheronisation were not adapted to each formulation in order to attain a better comparison of properties of different pellet batches.

The first part of this study focused on the influence of type and fraction of fillers on the properties of the pelletisation process and the pellet properties. Since the filler solubility was expected to affect the extrusion/spheronisation process and the pellet properties, fillers with different solubility were chosen. The following fillers were investigated: 1- lactose (soluble), 2- mannitol (soluble), 3-starch (swellable), and 4- dicalciumphosphate (insoluble) (Table 1). Acetaminophen was chosen as a model drug, which owns a high solubility, a low toxicity and a suitable UV-absorption for analytical purposes.

4.1. Water content of extrudate

The wet-extrusion/spheronisation process was robust and easy to carry out for all investigated formulations as shown previously by Bornhöft et al. [29]. All formulations produced pellets with a high yield except the formulations containing MCC (Table 2). The formulations containing MCC as pelletisation aid owned a lower content of pellets in the

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	–
AceLac20	85.2±2.31	1.33±0.13	0.78±0.11	94	70
AceLac40	74.0±1.37	1.37±0.15	0.76±0.11	97	63
AceLac60	81.2±2.75	1.35±0.18	0.82±0.23	96	58
AceLacMCC	48.4±0.25	1.23±0.12	2.33±0.34	86	–
AceMan20	72.0±0.73	1.34±0.15	0.96±0.19	96	64
AceMan40	71.5±0.73	1.34±0.16	0.84±0.11	97	61
AceMan60	72.2±1.04	1.34±0.15	0.85±0.12	97	64
AceManMCC	44.2±0.12	1.26±0.09	2.44±0.44	86	–
AceSta20	97.0±0.76	1.31±0.13	0.53±0.08	94	73
AceSta40	112±2.09	1.27±0.13	0.68±0.13	94	68
AceSta60	110±0.54	1.32±0.14	0.90±0.16	96	61
AceStaMCC	82.0±0.57	1.26±0.12	2.80±0.69	87	–
AceCal20	81.8±0.41	1.33±0.15	0.69±0.13	96	59
AceCal40	92.3±0.96	1.33±0.14	0.81±0.13	98	67
AceCal60	110±3.25	1.27±0.12	0.49±0.15	96	68
AceCalMCC	58.9±1.66	1.16±0.11	1.82±0.32	57	–

range of 1.0–1.6 mm. The chosen sieve fraction was most suitable for κ-carrageenan pellets. MCC pellets were smaller resulting in a lower yield.

The water content in wet-extrusion/spheronisation process affected the shape and size of the pellets [29]. Each investigated formulation owned specific water content to produce pellets with optimal quality. It was necessary to experimentally evaluate the specific water content for each formulation (Table 2). In comparison to MCC based formulations, those containing κ-carrageenan required a higher water content to achieve round pellets. This was also observed by Bonhöft et al. [29] in preliminary investigations of κ-carrageenan. This could be related to the higher water binding of κ-carrageenan, what can also be observed in sorption experiments (Fig. 2). κ-Carrageenan is able to form gels, which can immobilize more water than MCC.

For each pelletisation aid the formulations containing the soluble fillers lactose and mannitol showed similar water contents. The small differences in the three lactose formulations may be caused by imperfect optimisation of water content. Dicalciumphosphate as a completely insoluble filler needed a higher content of water than the soluble fillers [32]. Additionally, a linear correlation between the fraction of insoluble filler and the water content was noticed. Increasing the fraction of insoluble filler resulted in higher water content for successful pelletisation. Starch is insoluble but could swell in the presence of water. Compared to dicalciumphosphate the starch extrudates required even more water. This might be explained by the high water binding of the starch caused by the swelling process. However, a linear correlation between filler content and required water content of the extrudate was not observed. Probably, the extrudate water content of formulation AceSta60 was not adequate. This will be evaluated in further parts of the study. Generally, an influence of soluble fillers on the water requirement for pelletisation could not be observed in contrast to insoluble fillers.

4.2. Pellet shape

Pellets are dosage forms with a spherical shape. Therefore, it was necessary to characterise the pellet quality by spherical shape. A lot of parameters are used to describe this property [33]. The most common parameter is the aspect ratio which was also used in the following investigations (Fig. 3). A mean aspect ratio lower or equal to 1.1 was considered good for pharmaceutical pellets. Pellets of a mean aspect ratio above 1.2 were regarded insufficient [34]. Most of the produced pellets possessed a median aspect ratio lower than 1.1 because the water content in extrusion was adapted in the way that this parameter became a minimum. Only three formulations Ace, AceLac60 and AceSta did not reach suitable median aspect ratios. The highest median aspect ratio of 1.19 was found for AceSta60. In this case the extrudate water content seemed to be too low resulting in underwetted extrudate. This hypothesis is supported by the results of the water content shown in Fig. 2. A higher water content of approximately 127% might be expected as more sufficient water content, as increasing the starch fraction in AceSta20 and AceSta40 formulations required higher water content for successful pelletisation.

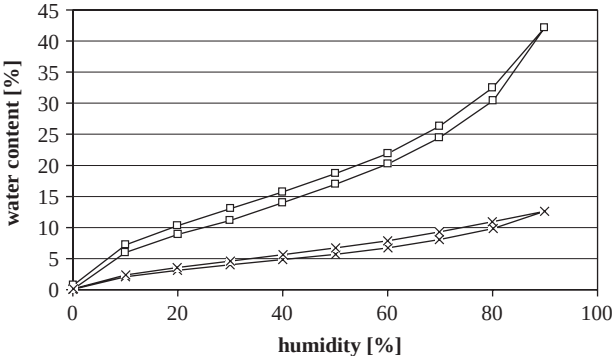

Fig. 2. Water adsorption of κ-carrageenan and MCC: Gelcarin GP 911 NF, MCC 102 G (arithmetic mean, $n=3$).

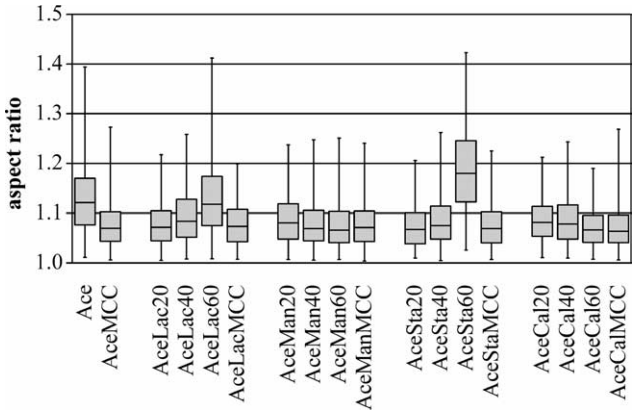

Fig. 3. Pellet shape of the different formulations (x_1, x_{10}, x_{50}, x_{90}, x_{99}, $n > 500$).

The median aspect ratio of AceSta60 might be optimised by increasing the extrudate water content. A possible optimisation of the water content of Ace and AceLac60 formulations might also result in spherical pellets.

Independent of the type and fraction of filler it is possible to produce spherical or at least pellets with sufficient shape.

4.3. Pellet size

Another important property of pellets is the small size distribution. Therefore, the pellet size and size distribution of the different formulations were evaluated (Table 2, Fig. 5). All formulations resulted in pellets with a mean average Feret diameter from 1.1 to 1.5 mm. However, all MCC pellets owned a smaller mean size than κ-carrageenan pellets but a similar standard deviation. There are three possible reasons for the higher mean Feret diameter of the κ-carrageenan pellets. The first reason might be an uncontrolled agglomeration during spheronisation known as snow balling. A second reason can be attributed to a different breaking behaviour in the first step of spheronisation. If κ-carrageenan breaks into longer extrudate cylinders, these pieces will result in larger pellets after spheronisation. A third reason might be the different shrinking behaviour during drying [35].

A snow balling was excluded, because for each batch a low amount of a fine fraction during the whole spheronisation process was observed. The fine particle fraction was observed for both pelletisation aids. The fine fraction of particles disappears in case of an uncontrolled agglomeration, because fine particles are fixed on the surface of larger particles upon colliding. κ-Carrageenan extrudates probably break into cylinders with higher length in the first step of spheronising. After 20 s of spheronisation the extrudate cylinders of Ace with κ-carrageenan were much longer than those of AceMCC (Fig. 4a and b). This might be one reason for the higher mean Feret diameter of the κ-carrageenan based pellets.

The porosity of freeze-dried extrudates made of Ace and Ace-MCC were $46.2 \pm 0.3\%$ and $49.8 \pm 0.4\%$, respectively. Pellets prepared from Ace and AceMCC showed porosities of $32.9 \pm 0.4\%$ and $17.5 \pm 0.8\%$, respectively. Freeze dried products showed no or only a minor shrinking whereas fluid-bed dried products tend to shrink during drying [35]. Based on these data, a decrease in porosity of 29% for Ace based on κ-carrageenan and of 65% for AceMCC pellets can be calculated. Thus, pellets based on MCC tend to shrink to a higher extent compared to pellets based on κ-carrageenan. Thus, the particle size of fluid-bed dried pellets based on MCC is lower, even if the size of wet pellets during spheronisation was the same.

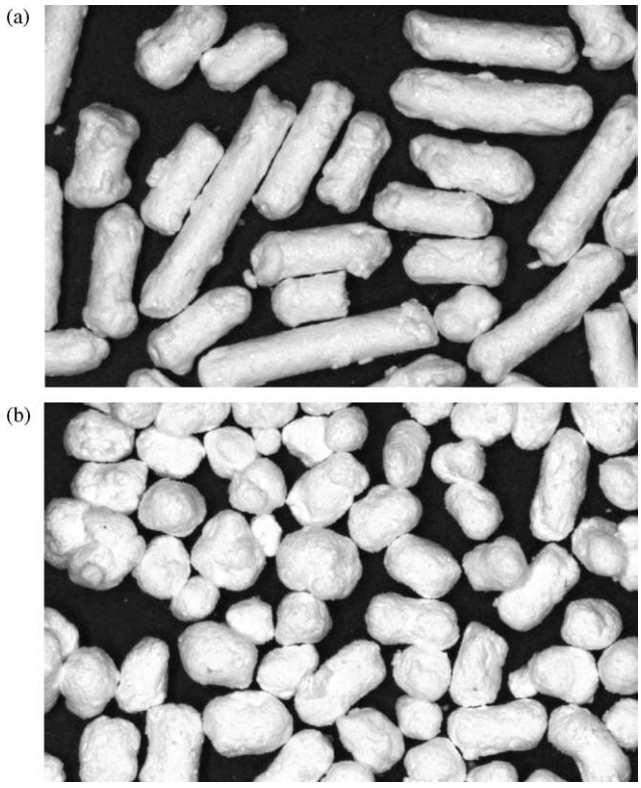

Fig. 4. (a=Ace and b=AceMCC) Extrudate cylinders after spheronising of 20 s.

The particle size distribution based on the dimensionless diameter is shown in Fig. 5 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 distribution is not shown for MCC pellets, because for pellets based on MCC less than 90% of the pellets were within this range.

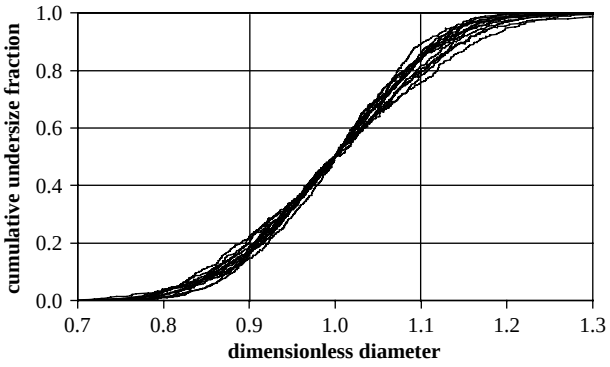

Fig. 5. Pellet size distribution for formulations containing κ-carrageenan as pelletisation aid.

The 10% interval is used to characterise the particle size distribution. It describes the fraction of pellets within the interval 0.9–1.1 of the dimensionless diameter. This fraction can be calculated for all products independent of the production method and it allows a comparison of different products. If the fraction in the 10% interval exceeds 50% the size distribution is rated as good and if the fraction exceeds 75% the size distribution is rated as excellent. For κ-carrageenan pellets the fraction in the 10% interval is only slightly overestimated due to the high yield in the fraction of 1.0–1.6 mm. Thus, the fraction would be highly overestimated.

The size distributions of κ-carrageenan pellets are self similar (Fig. 5), because they coincide more or less in the dimensionless representation. The fraction in the 10% interval was in the range 58–73%. Thus all, size distributions can be regarded as good.

An influence of type and amount of the filler on the pellet size and size distribution could not be observed in these investigations.

4.4. Mechanical properties

The tensile strength was used to characterise the mechanical properties of the pellets [4]. Pellets with low mechanical stability are unsuitable for further processing steps like coating and tabletting. The mechanical properties of the pellets were mainly determined by the kind of the pelletisation. Pellets produced with MCC as pelletisation aid showed a higher tensile strength than κ-carrageenan pellets (Table 2). The high mechanical stability of MCC pellets is caused by the strong binding forces of the MCC and the shrinking process during drying that reduces the porosity [35]. κ-Carrageenan pellets owned a higher porosity because they show a lower extent of shrinking during drying. Consequently, κ-carrageenan pellets had a lower tensile strength. However, for most batches the tensile strength was between 0.5 and 1.0 MPa which should be sufficient for further processing steps. The influence of the fraction of the filler on the tensile strength is marginal. Only for starch a systematic effect can be found, which might be explained by the elastic properties of this excipient.

4.5. Disintegration and drug release: type of filler

In all release tests κ-carrageenan pellets showed a very fast release of acetaminophen in contrast to the formulations including MCC (Fig. 6a–e). A fast disintegration and complete dissolving of pellets based on κ-carrageenan was observed in the release experiments. In contrast pellets based on MCC did not disintegrate or dissolve completely, even after 24 h. The lack of disintegration of MCC pellets resulted in a slower drug release following a matrix mechanism [5] (Fig. 7). Up to 60–80% of drug release a linear curve can be seen in the Higuchi plot.

In Fig. 6a the release profiles of different kinds of fillers with a fixed content of 40% are shown. For κ-carrageenan pellets the release is completed within 6 min for all types of fillers. For MCC pellets the insoluble fillers resulted in a slower drug release without a disintegration of the pellets. The soluble fillers dissolve during release resulting in a higher porosity, which allows a faster release of the incorporated drug.

However, the influence of different fillers on the release profile is very small. It was not possible to modulate the drug release substantially by the use of different fillers at a content of 40%.

4.6. Disintegration and drug release: fraction of filler

In further experiments the influence of the filler amount on the release profile was investigated. The influence of the soluble fillers on the release profile is shown in Fig. 6b and c. The drug release of κ-carrageenan pellets was not determined by the content of the filler in contrast to the MCC formulations. Due to the small size of the pellets the different solubility of lactose, mannitol and acetaminophen did not effect the pellet disintegration. The drug release of the MCC pellets was determined by diffusion mechanism which correlated with the solubility of the ingredients of the matrix [32]. All three MCC formulations in Fig. 6b and c contained 20% MCC, 40% acetaminophen and 40% filler: lactose, mannitol and also acetaminophen in AceMCC. The solubilities of acetaminophen, mannitol and lactose are 160, 180 and 200 mg/ml, respectively [36], corresponding to the release of acetaminophen.

The release of acetaminophen in starch pellets (Fig. 6d) was influenced by the content of starch in the κ-carrageenan formulations. The formulation without starch showed a disintegration of about 8 min (Table 3) and a complete release after 3 min. The presence of starch resulted in a slightly slower drug release, which might be caused by the water binding and swelling properties of starch. In all cases the drug release was completed after 8 min. On the other hand the disintegration time decreased with increasing fraction of starch in the formulation to about 4 min (Table 3). The mechanical stress on the pellets in the disintegration test cannot be compared with mechanical forces in the release test.

The drug release from κ-carrageenan - dicalciumphosphate pellets was lower and depended on the concentration of dicalciumphosphate. Pellets with 60% of dicalciumphosphate required about 10 min for complete release. As for pellets with starch the disintegration time decreased with increasing fraction of dicalciumphosphate (Table 3). The release profile correlated as expected with the content of insoluble filler to the drug release. High content of filler hindered the fast infiltration of water into pellets and delayed the swelling and disintegration in release tests. Due to higher mechanical stress in the disintegration test pellets with a low tensile strength (AceCal60, Table 2) resulted in a comparable low disintegration time (Table 3).

However, κ-carrageenan pellets combined with all fillers in different contents resulted in a very fast drug release. Overall, there was only a small influence of the filler on the release

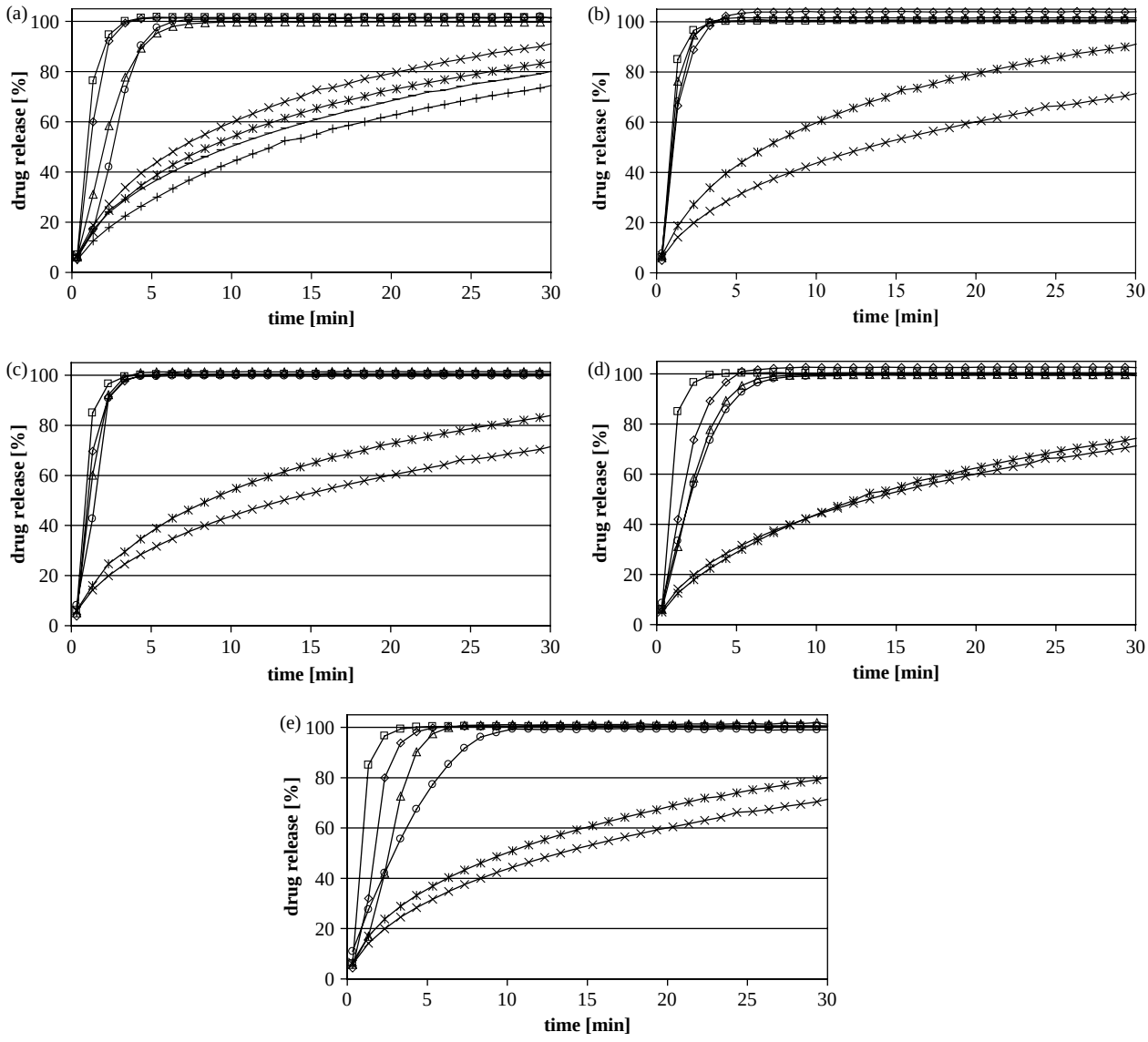

Fig. 6. (a) Release profiles of different fillers: □AceLac, ◇AceMan, △AceSta, ○AceCal, ×AceLacMCC, *AceManMCC, +AceStaMCC, −AceCalMCC (arithmetic mean, $n=6$). (b) Release profiles of lactose pellets: □Ace, ×AceMCC ◇AceLac20, △AceLac40, ○AceLac60, *AceLacMCC (arithmetic mean, $n=6$). (c) Release profiles of mannitol pellets: □Ace, ×AceMCC, ◇AceMan20, △AceMan40, ○AceMan60, *AceManMCC (arithmetic mean, $n=6$). (d) Release profiles of starch pellets: □Ace, ×AceMCC, ◇AceSta20, △AceSta40, ○AceSta60, *AceStaMCC (arithmetic mean, $n=6$). (e) Release profiles of dicalciumphosphate pellets: □Ace, ×AceMCC, ◇AceCal20, △AceCal40, ○AceCal60, *AceCalMCC (arithmetic mean, $n=6$)

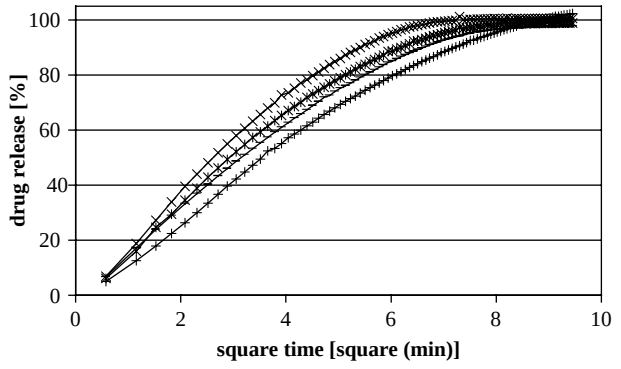

Fig. 7. Higuchi plot of MCC pellets: ×AceLacMCC, *AceManMCC, + AceStaMCC, −AceCalMCC (arithmetic mean, $n=6$)

profile. This showed the robustness of κ-carrageenan as a new pelletisation aid as the drug release was almost independent of the pellet composition. The release of pellets based on MCC is more sensitive to the composition, e.g. the filler solubility.

Table 3
Disintegration time of the pellets

Content of filler (%)	Disintegration time (min)	
	Starch	Dicalciumphosphate
0	7:53±0:15	
20	5:01±0:25	6:44±0:15
40	4:38±0:17	6:18±0:17
60	3:59±0:06	3:40±0:13

5. Conclusion

κ-Carrageenan is a suitable pelletisation excipient for extrusion/speronisation as pellets with sufficient quality were achieved for all formulations. The substitution of the commonly used MCC by κ-carrageenan was possible by the addition of 20% κ-carrageenan. κ-Carrageenan formulations always required higher water content during the pelletisation process. The low tensile strength of the κ-carrageenan pellets was explained by a high porosity. All κ-carrageenan pellets showed a fast disintegration of the pellet core resulting in a fast drug release. The different investigated fillers resulted in pellets of similar properties. The effects of the fillers and their contents on the pelletising process and the pellet properties were minimal. Therefore κ-carrageenan is a suitable pelletisation aid which increases the robustness of the process and it can be used as a sufficient substitute for the commonly used MCC.

Acknowledgements

The authors are grateful to BASF, Lehmann & Voss, Meggle and Pharmatrans Sanaq for the donation of materials.

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