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Research paper

The use of carrageenan in mixture with microcrystalline cellulose and its functionality for making tablets

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Abstract

The modulation of tableting and release behavior of combinations of k-carrageenan Gelcarin® GP 911 NF and microcrystalline cellulose (MCC) Avicel® PH 101 has been evaluated. Graded binary mixtures were tableted to a maximum relative density of 0.850 at the maximum displacement of the upper punch. Additionally, ternary mixtures with the same ratios of k-carrageenan and MCC and a constant percentage of theophylline monohydrate (20% (v/v)) were tested for their release behavior. Tablets produced from pure k-carrageenan deformed more elastically than pure MCC, the tablets produced were stable but not at the same degree as those made from MCC. Scanning electron microscopy (SEM) pictures showed that for MCC a smooth surface of the tablets resulted, tablets made from k-carrageenan showed less 'fusion' and thus more mechanical interlocking is responsible for their stability. Binary mixtures showed a continuous change in compaction properties from plastic to elastic deformation. All ternary mixtures with theophylline deformed more plastically than the binary mixtures, the change in deformation properties remained the same. Theophylline reduced the crushing strength due to its different fracture properties. The ternary mixtures showed different release mechanisms: Fast release up to 20% (v/v) k-carrageenan, slower release starting from 30% (v/v). The kinetics of release tended at 70% (v/v) more clearly towards zero-order kinetics. This change in release is in accordance with a change in swelling of tablets made of the binary mixtures.

Keywords: Mixtures; Carrageenan; Microcrystalline cellulose; Tablets; Controlled release; Theophylline monohydrate

1. Introduction

The aim of using different excipients in tablet production is to enhance the tableting and release properties of the materials. The mixture of the excipients should have a better functionality in making tablets than the materials alone.

Although mixtures are frequently used there is a lack of studies on the analysis of mixtures [1–10]. Mixtures containing a combination of materials with dissimilar compaction mechanisms have been mainly analyzed [1,2,6,8,9]. In some cases it was possible to detect percolation thresholds [8,9] according to the percolation theory. In other analyses no relationship could be established. The percolation theory describes the interacting behavior of different substances. One of the materials, that with the lower concentration, is embedded in sole clusters in the other material. When the concentration increases, the clusters percolate and come to form a network. At a certain concentration, two interacting networks are formed and finally at high concentrations the other material forms clusters. The change from single clusters to network formation is usually characterized by a percolation threshold seen in a characteristic change in material properties. Normally a lower and a higher percolation threshold exists for binary mixtures. This has been shown for compaction properties and for drug release from inert matrices [11,12]. For hydrocolloid matrices, the cluster formation and penetration of the network changes during the release process and thus no direct correlation to the tableting properties is possible.

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Carrageenans are known to be used in controlled release technology [13–20]. They are natural polysaccharides extracted from algae of the class of Rhodophyceae and show hydrocolloidal properties. They consist of the sulfate esters of galactose and 3,6-anhydrogalactose copolymers, linked a-1,3 and b-1,4 in the polymer. The highly sulfated l-carrageenan does not gel, but both the other types, k- and i-carrageenan, are able to generate gels with different characteristics which can influence release behavior of mixtures [13,19]. The k-carrageenan showed controlled release for 8 h tending to zero-order kinetics. The material formed stable tablets deforming largely elastically [21].

Microcrystalline cellulose (MCC) is known to be one of the most compressible and compactible direct compression excipients [22]. It is able to form hard compacts at a low maximum punch pressure. MCC is described as a molecular sponge [23,24] and it is able to adsorb a high amount of water. Responsible for the mechanical strength of the compacts are strong hydrogen bondings [25] which ensure the cohesion between the polymer chains and the particles in the tablet. During the plastic deformation clean surfaces are formed which can form new hydrogen bonds by contact [22]. Therefore, MCC can be termed a binder/filler or a dry binder [26]. The hydrogen bonds in MCC are so strong that this material does not swell and thus the tablets disintegrate and immediate release results.

The combination of k-carrageenan with MCC can provide the possibility of obtaining a mixture with mixed tableting properties. The plastic deformation of MCC and the elasticity of the k-carrageenan can be a tool to modulate compaction properties. However, there may be the possibility to modulate release properties. The functionality of k-carrageenan in the mixtures and whether percolation theory is applicable or not will be evaluated, based on the description of the tableting and release behavior of these mixtures.

2. Materials and methods

2.1. Materials

The k-carrageenan Gelcarin® GP-911 NF (Lot. No. ZC502, FMC Corporation, USA) and the microcrystalline cellulose Avicel ® PH 101 (Lot. No. 14204, FMC Corporation, USA; distributed by Serva) were used as tableting excipients. Theophylline monohydrate (Lot. No. 4072.2, Roth GmbH, Karlsruhe, Germany) was used as the model drug. All the materials were sieved (Retsch sieving machine, K. Retsch GmbH, Haan, Germany) and only particles , 125 mm were used for tableting.

2.2. Methods

2.2.1. Particle size

A particle size analysis was performed using laser diffractometry in triplicate (Sympatec Rodos 12 SR, Sympatec, Remlingen, Germany; pressure: 4 bar, injector beneath pressure: 60 mbar, focal distance 200 mm and measuring time: 25–35 s.). The mean volume particle size distribution was calculated.

2.2.2. Density

The true density was determined by a difference pressure pycnometer using helium (Accupyc 1330, Micrometrics, Norcross, USA) in triplicate. Bulk and tap density were determined with two repetitions in a weighed 250 ml cylinder using a volumeter (Erweka GmbH, Heusenstamm, Germany). Determinations were performed according to Pharmacopoeia Europaea [27].

2.2.3. Water content

The content of water for the material used for tableting was determined by thermogravimetric analysis with two replicates (TG, Netzsch Gerätebau, Selb, Germany). Additionally, sorption isotherms were recorded gravimetrically after equilibration over saturated salt solutions [28] in triplicate. The powder was equilibrated at a specific relative humidity (r.h.) and after equilibration weighed and moved to the next higher r.h. This procedure started at 32% r.h. and was performed up to 90% r.h. Then the powder was weighed and after equilibration moved to the next lower r.h. up to 0% r.h. (phosphorous pentoxide).

2.2.4. Preparation of materials

The excipients, k-carrageenan and MCC, were physically mixed in a mixer with fixed wide-necked bottles (250 ml, 15 min., 30 rpm, AR 400, Erweka GmbH, Heusenstamm, Germany). The mixing ratios were calculated as true volumes (v/v). The ternary mixtures of the excipients and theophylline monohydrate were produced by adding theophylline monohydrate to the binary mixture using the same procedure as before.

2.2.5. Tableting

Tablets were produced on an instrumented single punch machine (EK0/DMS, No. 1.0083.92, Korsch GmbH, Berlin, Germany) with 11 mm diameter flat faced punches. Equal true volumes of the substances were tableted to a maximum relative density $\rho_{rel,\,max}$ of 0.850 (precision 0.001) with $\rho_{rel,\,max} = \rho_{max}/\rho_{true}$ ($\rho_{rel,\,max}$ = maximum relative density, ρ_{max} = density at minimum height of the tablet under load, ρ_{true} = true density).

The tablet height at maximum densification under load was held constant at 3.000 ± 0.001 mm (corrected for elastic deformation of the punches). The depth of filling was held constant at 13 mm and ten tablets per min were produced. Forces were measured by calibrated strain gages and displacement of the punch faces was measured using an inductive transducer (W 20 TK, Hottinger Baldwin Messtechnik, Darmstadt, Germany). The powder was manually filled into the die and one compaction cycle was performed. Fifteen single tablets were produced at each condition.

Force and distance signals were amplified and digitized with the DMC plus system (Hottinger Baldwin Meßtechnik, Darmstadt, Germany). Data were stored and analyzed by a Macintosh computer with BEAM Software (AMS, Flöha, Germany). For analyzing tableting data only data . 1 MPa were used. At each condition five compression cycles were analyzed. The pressure-time function [29], given below, was fitted to the pressure-time plot using the software Origin 4.00. From the pressure-time function the parameters b and g were obtained. Both b and g being low indicate high plasticity, b and g being high indicate high elasticity. The combined graphical presentation of b versus g can be used as a tool to analyze tableting properties.

$$P(t) = Pu_{\max}\left[\frac{t_{end}-t}{b}\right]^{g}\cdot e^{1-\left[\frac{t_{end}-t}{b}\right]^{g}} \quad (1)$$

with $P(t)$ = pressure at time t, Pu_{max} = maximum upper punch pressure and t_{end} = time at the lifting of the upper punch from the surface of the tablet.

Additionally, Heckel plots were analyzed as described previously [29]. The Heckel function [30] was fitted to the Heckel plot. The Heckel slope was judged in combination with elastic recovery of the tablet up to the point at which the upper punch leaves the surface of the tablet (fast elastic recovery). The maximum upper punch pressure and the time interval between maximum upper punch force and maximum displacement were always calculated for ten compaction events.

2.2.6. Mechanical characterization of the tablets

Elastic recovery according to Armstrong and Haines-Nutt [31] was calculated directly after ejection, 24 h and 10 days after tableting for analyzing the complete recovery process (micrometer screw, Mitotuyo, Tokyo, Japan) for ten tablets. Elastic recovery (ER) is defined as follows: ER (%) = ((height of the tablet (mm) − minimal height of the tablet under load (mm)) *100/minimal height of the tablet under load (mm).

Additionally, directly and 10 days after ejection, the diametrical crushing strength of three tablets was determined (Erweka crushing strength tester, Type TBH28, Erweka GmbH, D-Heusenstamm).

2.2.7. Scanning electron microscopy (SEM)

Vacuum oven dried samples of the powder as well as the tablets of the pure materials were mounted on a sample holder and coated with coal/gold/coal. The samples were examined with a scanning electron microscope (model JEOL 6400, Tokyo, Japan) at an accelerating voltage of 5 or 15 kV depending on the sample at different magnifications.

2.2.8. Swelling

The rate and extent of swelling of the tablets was determined using a special swelling apparatus [32]. In the following the method is explained. The tablets were put in a cylinder (11.1 mm width, 25.0 mm height). At the lower edge two rows of holes (1 mm diameter, 2.5 and 5.0 mm height) allowed the influx of water. A punch with constant weight of 100.0 g placed on the tablet controlled swelling. The movement of this punch is transduced in voltages and the resulting values are digitized and stored on a personal computer using a program called 'Quell' (Martin-Luther-University Halle-Wittenberg, Germany). For 8 h, the movement of the punch was recorded in micrometers according to calibration. The expansion of the tablet was measured and rate and extent of swelling resulted. The reproducibility of the method was proven for tablets made from the k-carrageenan by an analysis in triplicate. Then for tablets of the other conditions single experiments were performed.

2.2.9. Release

Drug release was analyzed using the paddle method according to USP XXIII in distilled water (900 ml, 37 ± 0.5°C, 100 rpm) for 8 h. Ten milliliter samples of medium were substituted by distilled water. The resulting concentrations of drug in the release medium were determined spectrophotometrically (Spectronic 601, Milton Roy, Obertshausen, Germany). The absorption of the released drug was determined at peak maximum (271 nm). The release of six tablets were determined and the means and standard deviations were calculated. The release data were fitted to the semi-empirical function of Peppas [33]: $x = k \times t^n$ with x = amount released, k = release constant, t = time and n = exponent giving the order of release ($n = 1$ zero order, $n = 0.5$ square root of time). This equation is approximately valid in the release range up to $x = 60\%$ released. By calculating n the mechanism of release will be analyzed. Additionally, a linear regression was performed for the release data in order to check zero-order kinetics.

3. Results and discussion

3.1. Powder and material properties

The particle size distributions of the k-carrageenan Gelcarin® GP 911 NF, in the following called k-carrageenan, and of the microcrystalline cellulose Avicel® PH 101, in the following called MCC (both materials , 125 mm) are similar. The mean particle size is 64.49 mm for k-carrageenan and 54.00 mm for MCC. There will be no influence of particle size on tableting behavior. Fig. 1a,b shows particles of k-carrageenan and of MCC. The particles of the k-carrageenan look smooth and long threads can be distinguished. The fibers of MCC look more rough and seem to be composed of a lot of small particles. However, both materials are fibrous polymers. The true density calculated by helium pycnometry (Table 1) is higher for the k-carrageenan than for MCC. This is due to the sulfate groups at the polymer chains. The monomers have a higher molecular weight. As the true

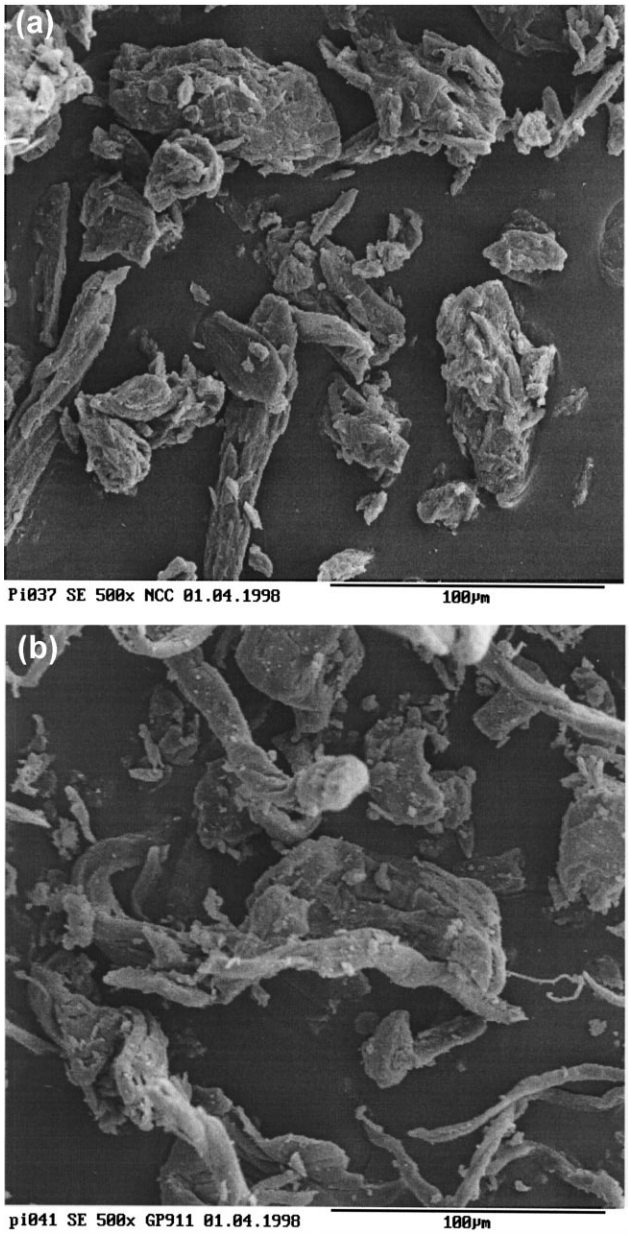

Fig. 1. Scanning electron micrographs of carrageenan (a) and MCC (b) particles (magnification 500×).

density of the k-carrageenan, its bulk and tap densities are higher, but the Carr index is only slightly higher (Table 1). This means that the volume reduction by tapping can be regarded as equivalent and thus the flow properties of both the materials are acceptable.

The compressed material contained different amounts of water as analyzed by TG: the k-carrageenan contained 12.50 ± 0.15% (w/w) and MCC 4.74 ± 0.04% (w/w). The materials contain these water contents when they are equilibrated at a relative humidity of 32% r.h. (Fig. 2). Thus, the materials were tableted at equal conditions. Further on, the sorption isotherms show that the k-carrageenan sorbs much more water than the MCC. This is due to its structure. The sulfate substituents cause a higher distance between the

Table 1
True, tap and bulk densities and Carr index of the excipients[a]

	Carrageenan	MCC
True density (g/cm^3)	1.744 (0.011)	1.580 (0.004)
Tap density (g/cm^3)	0.674 (0.038)	0.448 (0.004)
Bulk density (g/cm^3)	0.444 (0.008)	0.322 (0.004)
Carr index	33.93 (2.65)	28.48 (0.74)

[a]Mean for $n = 3$, SD given in parentheses.

polymer chains. In MCC the molecules are hold together by strong hydrogen bonds [25] which cannot be segregated easily.

Additionally, the different sorption behavior is due to the fact that the molecules of k-carrageenan are in the rubbery state [21]. In an amorphous rubbery material the polymer chains are much more mobile and thus they can interact with the water more easily. MCC is not in the rubbery state and it is to about 70% crystalline [34,35]. Accordingly, the interaction with water is much more restricted.

3.2. Tableting

3.2.1. Pure substances

Fig. 3 shows the Heckel plots of both the pure excipients k-carrageenan and MCC and of theophylline. The maximum punch pressure necessary for the same relative density is the same for both the excipients. Elastic recovery during decompression (fast elastic recovery, Table 2) and the shape of the plots are similar. However, MCC shows a higher slope of the Heckel plot. Thus the material shows more deformation. Since elastic recovery is lower, the material is more plastic than k-carrageenan. This material shows a lower slope of the Heckel function and more elastic recovery, even fast elastic recovery. Especially, its slow elastic

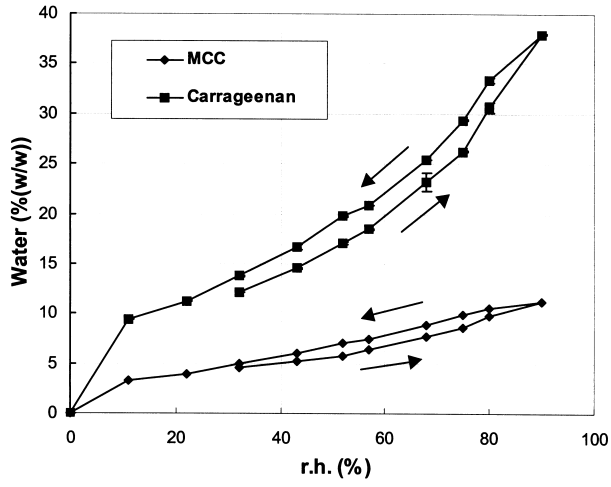

Fig. 2. Sorption isotherms of carrageenan and of MCC (mean, $n = 3$).

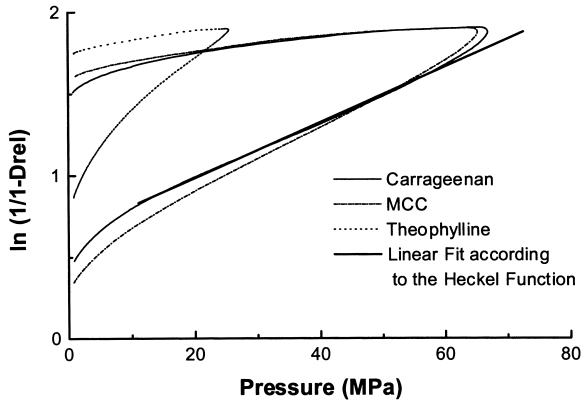

Fig. 3. Heckel plots the pure materials with a linear fit according to the Heckel function for carrageenan.

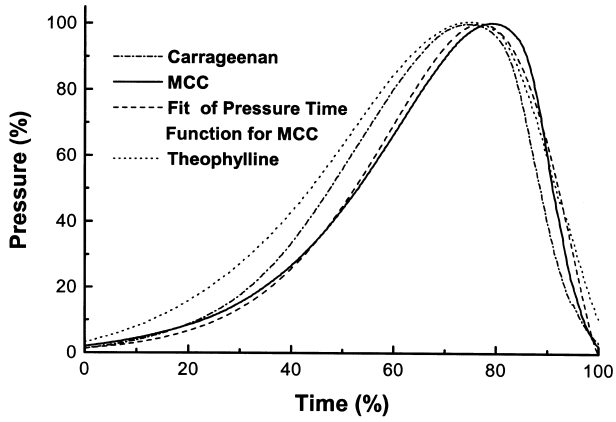

Fig. 4. Pressure time plot of the pure materials with a non-linear fit according to the pressure time function for MCC.

recovery is the double of that of k-carrageenan. Thus, a much more porous tablet is produced.

Theophylline is a plastically deforming substance. It shows at the same maximum relative density a higher slope of the Heckel function and it needs lower pressures for densification. Only half of the data of the compression part are able to fit the Heckel function (Fig. 3). Thus the material fractures before plastic deformation [36]. However, because of its plastic properties, the elastic recovery during decompression is much lower and after ejection the tablet height soon reaches a constant value (Table 2).

The pressure-time plot (Fig. 4, Table 2) shows a more round shape and the g-values are higher for the k-carrageenan than for MCC, indicating again that its elasticity is high. The plot of MCC shows the necessary maximum pressure at a relatively higher value of the time scale, the b-values are lower. Thus the deformation behavior is more plastic. Theophylline behaves differently when compared to the Heckel plot. The percentage of time of the elastic recovery during decompression is high compared with the excipients even when the amount of elastic recovery is low. This means that theophylline gives more resistance against deformation compared to both the excipients. This can indicate some fracturing. However, because of its low maximum pressures and its short contact time, it can be regarded as a mainly plastically deforming substance.

SEM pictures (Fig. 5) of tablets are used to complement the tableting results. Compacts made from MCC show a very plastically deformed structure on the surface of the tablets (Fig. 5a). Bonding between the particles occurs and the surface gets smooth. Contrary the k-carrageenan shows a more porous structure on the surface due to its high expansion (Fig. 5b). The fibers of the k-carrageenan can be distinguished and the surface is more rough than that of MCC due to its elasticity. Whether a material deforms more plastically or elastically can be interpreted from the SEM-picture in accordance with Alvarez et al. [37]. The higher elasticity of the k-carrageenan is in accordance with the higher elastic recovery of k-carrageenan. Therefore, mechanical interlocking of the particles will cause the strength and stability of these tablets, hydrogen bonding will be less important than for MCC.

Additionally, the crushing strength for both the excipients is different (Table 2). The k-carrageenan shows a lower crushing strength due to its different bonding. MCC shows a higher crushing strength due to the 'fusion' of its particles under pressure. According to Podczeck and Newton [38], MCC shows a rising crack resistance curve in fracture mechanics experiments. Thus there will be an unstable crack growth during diametral compression. k-carrageenan will have a more sudden fracturing due to its bonding. The different fracture mechanisms also contribute to the different values in crushing strength.

Table 2
Slope of the Heckel function, elastic recovery and g and b values of the pressure time function for the used materials[a]

	K (MPa^{-1})	Elastic fast	Recovery direct	(%) 24 h	10 days	g	b	Crushing strength after 24 h (*N*)
Carrageenan	0.0175	8.33	23.58	27.46	28.00	1.64	29.27	78.7
	(0.0001)	(0.17)	(0.55)	(0.56)	(0.85)	(0.03)	(0.67)	(3.2)
MCC	0.0200	7.32	11.80	13.12	13.58	1.36	22.34	198.4
	(0.0002)	(0.34)	(0.19)	(0.25)	(0.16)	(0.04)	(0.69)	(3.2)
Theophylline monohydrate	0.0308	2.19	5.01	5.22	5.24	1.47	29.8	22.0
	(0.0002)	(0.04)	(0.01)	(0.01)	(0.01)	(0.02)	(0.1)	(1.0)

[a]Mean for $n = 5$, SD given in parentheses.

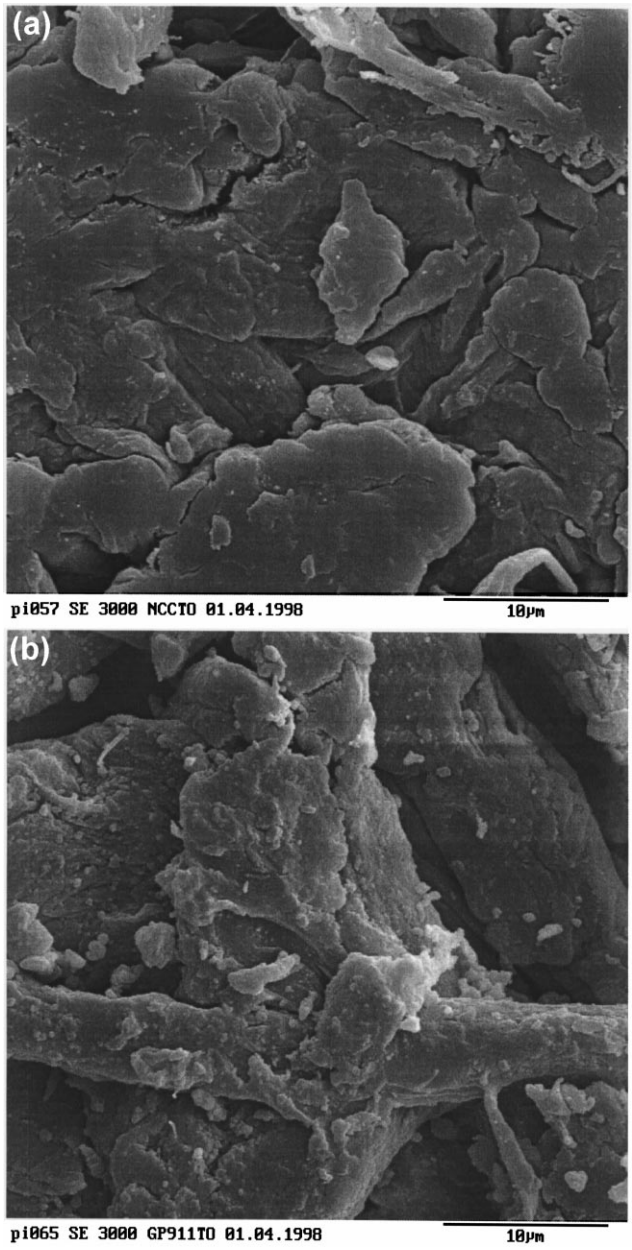

Fig. 5. Scanning electron micrographs of the surface of tablets made of carrageenan (a) and MCC (b) at a magnification of 3000×.

3.2.2. Mixtures

3.2.2.1. Binary mixtures. Graded mixtures of the k-carrageenan and of MCC were tableted to the same maximum relative density. Looking at the pressure-time plots (Fig. 6) a continuous change from plastic to more elastic deformation can be observed. With increasing amount of k-carrageenan, the maximum upper punch pressure occurs at a lower percentage of contact time and the interval between maximum upper punch pressure and maximum displacement (Table 3) increases with increase in concentration of k-carrageenan. Thus, the g/b-diagram (Fig. 7) of the binary mixtures shows a continuous change from more plastic to more elastic deformation with increase in concentration of k-carrageenan. Both the g and the b values are increasing. Small concentrations of k-carrageenan in MCC result in more change of g and b than small concentrations of MCC in k-carrageenan do. The mixture containing 10% (v/v) MCC behaves more elastically than the pure k-carrageenan.

In Table 3, a small but continuous decrease in the slope of the Heckel function can be observed in parallel with an increase in elastic recovery during decompression. Thus, the total deformation is decreasing and in combination with an increase in elastic recovery (Table 2), a change from plastic to elastic deformation can be interpreted in the case of the g/b-diagram. The pure substances have a higher slope of the Heckel function than the mixtures containing 10% (v/v) of the other excipient. Thus, they show more deformation than the mixtures. Elastic recovery (Fig. 8a) increases over time with increasing concentration of k-carrageenan and it reaches the double or even triple amount of that which occurs during decompression. A continuous change can be observed except for the mixture containing 10% (v/v) MCC. Here elastic recovery is higher than for the pure k-carrageenan. The pure material showed more deformation and in conclusion the tablet releases less deformation by elastic recovery.

With increasing concentration of k-carrageenan the crushing strength (Table 3) of the compacts decreases. It can be assumed that bonds between the particles of different materials can be segregated more easily and thus a more sudden crack growth results. Since during some time expansion (Fig. 8a) continues over the time and the particles rearrange, crushing strength slightly decreases during 10 days storage.

3.2.2.2. Ternary mixtures. Graded mixtures of k-carrageenan and MCC with a constant concentration of 20% (v/v) theophylline monohydrate were tableted to the same maximum relative density as the binary mixtures. The

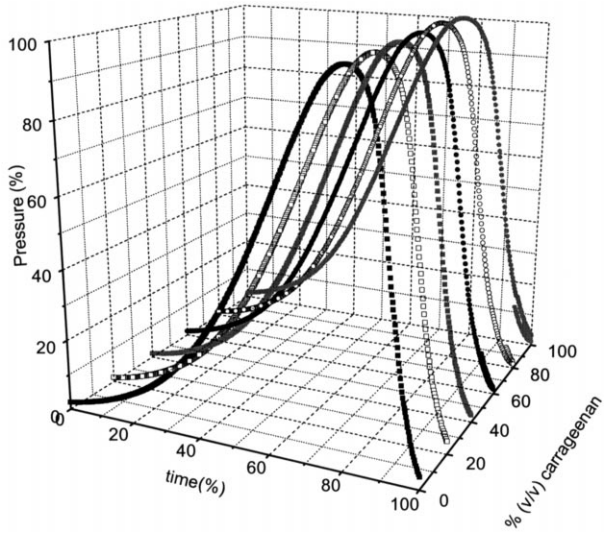

Fig. 6. Pressure-time plots of graded mixtures of carrageenan and MCC.

Table 3

Data of the compressibility of mixtures of carrageenan and MCC at maximum relative density of 0.850[a]

Carrageenan (% (v/v))	Maximum upper punch pressure (MPa)	Heckel slope (MPa^{-1})	Interval between maximum force and maximum displacement (ms)	Elastic recovery during decompression	Crushing strength after 24 h (*N*)	Crushing strength after 10 days (*N*)
0	66.65 (0.90)	0.0200 (0.0001)	0.0245 (0.0017)	7.32 (0.34)	272.7 (2.4)	239.7 (2.5)
10	67.91 (0.23)	0.0187 (0.0001)	0.0273 (0.0018)	7.67 (0.30)	217.7 (9.9)	205.0 (8.9)
20	67.84 (0.59)	0.0185 (0.0002)	0.0290 (0.0016)	7.22 (0.12)	220.3 (10.9)	196.0 (11.3)
30	68.60 (0.35)	0.0181 (0.0002)	0.0292 0.0014)	7.71 (0.08)	181.0 (1.0)	178.7 (8.3)
40	68.48 (0.45)	0.0181 (0.0001)	0.0285 (0.0025)	8.03 (0.34)	144.7 (6.7)	162.0 (2.0)
50	68.76 (0.79)	0.0176 (0.0001)	0.0290 (0.0020)	8.34 (0.18)	168.7 (5.9)	153.0 (3.6)
60	65.89 (1.41)	0.0184 (0.0001)	0.0220 (0.0025)	8.24 (0.24)	140.7 (8.5)	137.7 (1.2)
70	69.40 (0.50)	0.0174 (0.0001)	0.0303 (0.0022)	8.96 (0.12)	135.7 5.8)	131.3 (1.3)
80	70.04 (0.81)	0.0170 (0.0001)	0.0278 (0.0018)	9.48 (0.11)	124.7 (3.1)	109.7 (3.1)
90	69.51 (0.45)	0.0169 (0.0001)	0.0297 (0.0025)	9.99 (0.09)	101.0 (1.0)	86.7 (4.1)
100	66.23 (0.95)	0.0175 (0.0002)	0.0313 (0.0030)	8.33 (0.17)	100.0 (3.6)	94.3 (3.1)

[a]Mean, SD given in parentheses.

slope of the Heckel function (Table 4) is higher than for the binary mixtures. This means that theophylline changes the deformation behavior towards a more plastically type. However, the slope of the Heckel function also continuously decreases. The influence of the mixing proportions remains constant. Elastic recovery (Fig. 8b) increases after the ejection up to ten days afterwards. It increases with increase concentration of k-carrageenan. In the case of mixtures up to of 50% (v/v) k-carrageenen, a decrease in elastic recovery can be observed between elastic recovery (Fig. 8b) during decompression and directly after ejection. Here the material reorganizes [39]. The tablet expands and after expansion a more convenient arrangement inside the tablet is possible, thus it shrinks. This reorganization can not be observed for the mixtures containing more than 50% (v/v) k-carrageenan. However, since this reorganization occurs, the expansion is slowed down and the main part of the recovery takes place only between the first and the tenth day and not between decompression and ejection, as in the case of the binary mixtures.

Compared with the binary mixtures, the g/b-diagram (Fig. 7) of the ternary mixtures shows less differences

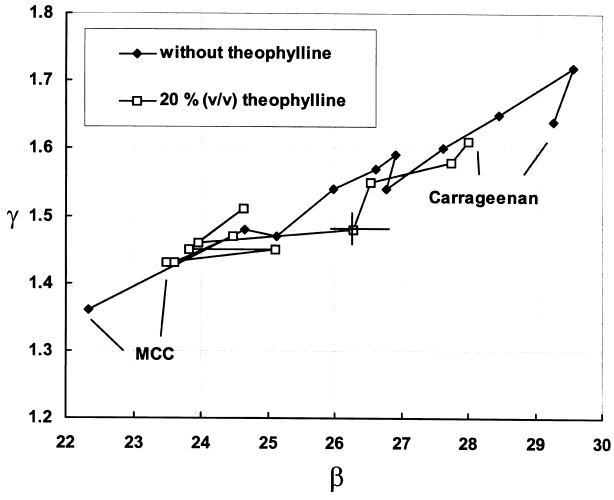

Fig. 7. g/b-diagram of graded binary and ternary mixtures of carrageenan and MCC (mean, $n = 5$; standard deviation(SD) given as an example).

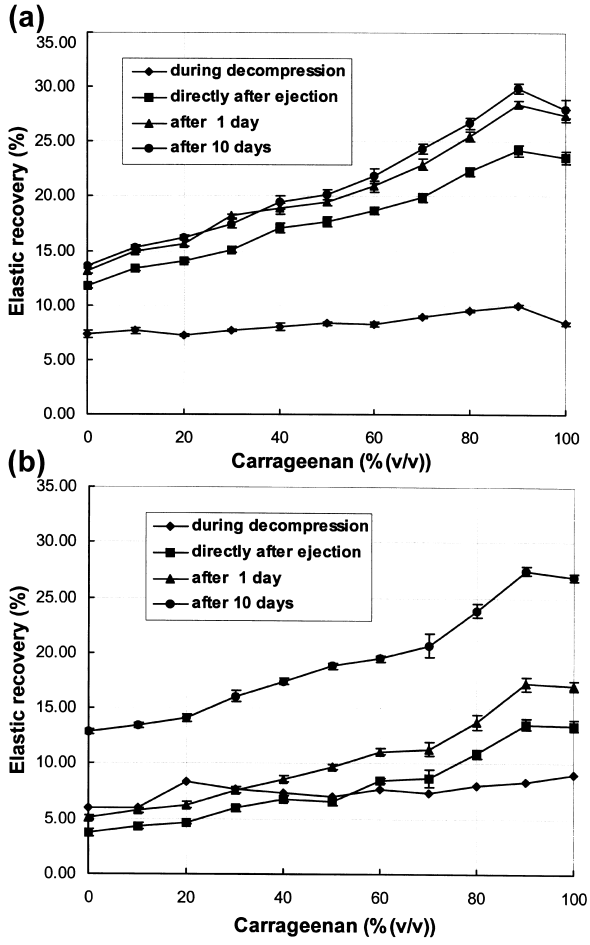

Fig. 8. Elastic recovery of graded binary (a) and ternary mixtures (b) of carrageenan and MCC at different times after compaction (mean and SD, $n = 10$).

Table 4
Data of the compressibility of mixtures of carrageenan and MCC with 20% theophylline monohydrate at a maximum relative density of 0.850[a]

Carrageenan (% (v/v))	Maximum upper punch pressure (MPa)	Heckel slope (MPa^{-1})	Interval between maximum force and maximum displacement (ms)	Elastic recovery during decompression	Crushing strength after 24 h (*N*)	Crushing strength after 10 days (*N*)
0	57.19 (1.65)	0.0215 (0.0001)	0.0215 (0.0013)	6.00 (0.15)	198.4 (3.2)	168.7 (10)
10	57.14 (0.44)	0.0224 (0.0003)	0.0267 (0.0028)	6.00 (0.30)	173.7 (6.4)	156.0 (8.5)
20	60.72 (0.45)	0.0208 (0.0001)	0.0230 (0.0014)	8.33 (0.24)	172.0 (11.8)	159.0 (12.1)
30	57.89 (0.38)	0.0213 (0.0001)	0.0263 (0.0023)	7.67 (0.06)	139.7 (3.1)	135.0 (3.0)
40	57.87 (0.26)	0.0209 (0.0001)	0.0287 (0.0027)	7.33 (0.30)	119.7 (2.1)	113.3 (6.1)
50	59.29 (0.32)	0.0203 (0.0001)	0.0278 (0.0026)	7.00 (0.18)	119.7 (2.2)	107.0 (9.1)
60	57.91 (0.43)	0.0204 (0.0003)	0.0278 (0.0021)	7.67 (0.15)	110.7 (3.5)	99.7 (0.5)
70	55.99 (0.79)	0.0208 (0.0001)	0.0268 (0.0021)	7.33 (0.30)	108.7 (6.0)	101.3 (6.1)
80	58.10 (0.93)	0.0197 (0.0001)	0.0258 (0.0020)	8.00 (0.30)	90.0 (3.6)	80.0 (5.2)
90	60.73 (0.56)	0.0188 (0.0002)	0.0265 (0.0020)	8.33 (0.18)	71.0 (1.0)	63.0 (1.2)
100	60.75 (0.51)	0.0186 (0.0001)	0.0278 (0.0016)	9.00 (0.24)	78.7 (3.2)	65.7 (2.5)
Theophylline monohydrate	25.30 (0.46)	0.0308 (0.0002)	0.0190 (0.0022)	2.18 (0.04)	22.0 (1.0)	26.7 (1.5)

[a]Mean, SD given in parentheses.

between the mixtures. The elastic behavior of the mixture is less than that of the pure k-carrageenan and its plastic behavior is reduced in comparison with pure MCC. The lowest g/b-values are higher and the highest g/b-values are lower for the binary mixtures than for the ternary mixtures. Up to a percentage of 60% (v/v) theophylline, the differences are difficult to distinguish. With increasing concentration of k-carrageenan, the mixtures become more elastic. Again the interval between maximum upper punch pressure (Table 4) and maximum displacement increases with increasing concentration of k-carrageenan. However, this increase is less than that for the binary mixtures due to the embedded theophylline which has a comparatively short time interval.

The crushing strength (Table 4) of the ternary mixtures ranges from 20 to 30% lower than for the corresponding binary mixtures. This may be due to theophylline. The crushing strength of theophylline tablets is very low. Thus these tablets can be easily fractured. The brittleness most probably reduces the crushing strength. This is in accordance with results from Sheikh-Salem and Fell [1].

3.2.3. Interpretation of tableting behavior

Binary mixtures of the two excipients are very different in deformation behavior; k-carrageenan and MCC show a continuous change in compaction properties from more elastic to more plastic. Thus a mixture with distinct tableting properties can be picked for formulation studies. MCC reacts like a dry binder in the tablets in order to improve stability. Carrageenan reacts as the elastic component which increases the expansion of the tablets. This expansion of the tablets might be useful in the case of pressure-labile drugs. The constant concentration of theophylline monohydrate changes tableting behavior of the mixtures to a more plastic one. However, the g/b-diagram of these ternary mixtures has shown that the plastic deformation of the mixtures containing a higher percentage of MCC is reduced and the values of g and b increase compared with the binary mixtures. Since a continuous change in deformation properties can still be observed for the ternary mixtures with a low concentration of drug, a mixture with distinct tableting properties can be chosen from the binary, as well as from the ternary mixtures. The results of the crushing strength measurements show that the combination of a plastic and a more elastic material produces tablets with mixed fracture properties. Thus both materials also contribute to this parameter. One might expect that percolation thresholds, according to percolation theory, can be distinguished. However, this is not the case. The existing percolation thresholds can exist at lower or higher percentages or the changes are so small that they do not become visible.

3.3. Release and swelling properties

Tablets made from the binary mixtures were used to study the swelling behavior of these tablets (Fig. 9), tablets of the

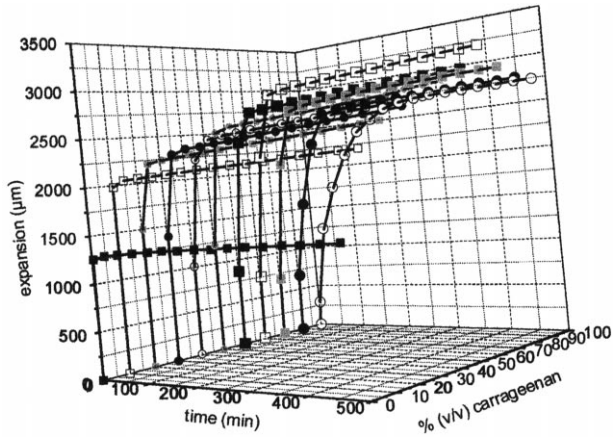

Fig. 9. Swelling behavior of tablets made of graded binary mixtures of carrageenan and MCC.

ternary mixtures were used to study release behavior (Fig. 10). The release of tablets made of ternary mixtures is continuously changing with increasing concentration of k-carrageenan. Different mechanisms of release can be seen. Tablets with up to 20% (v/v) k-carrageenan show fast release. These data are no further analyzed by fitting methods. Between 20 and 30% (v/v) a change in release properties can be observed. The release is slowed down. These data are fitted to the equation of Peppas [33] and additionally a linear regression is performed. The curve fitting according to Peppas shows that all higher percentages are more or less tending towards zero-order kinetics (Table 5). The exponent n is about 0.80 for release up to 60%. The linear regression of the data shows that starting with a concentration of 70% (v/v) the correlation coefficient is much better (. 0.99). This may indicate that for these concentrations release kinetics are tending more clearly towards zero-order kinetics. It follows that the concentrations of 30 and 70% (v/v) might be seen as thresholds for a change in release kinetics.

Release of theophylline has to be seen in combination with swelling of the tablets (Fig. 10). Up to a concentration of 20% (v/v) expansion happens suddenly. The extent of swelling is increasing. Starting with this concentration of k-carrageenan, the swelling is slowed down for the first 50 min. Most probably, the fibers of the k-carrageenan are now able to embed the particles of MCC in a continuous network. Starting with a concentration of 70% (v/v), the form of the swelling curve is changing and release is slowed down. Even the extent of swelling decreases now. This is due to a change in the mechanism of swelling. The k-carrageenan no longer only hinders disintegration by swelling, now it dominates swelling [13].

Release and swelling seem to change at about the same concentrations. When release is slowed down, swelling is sustained; when release tends more towards zero-order kinetics, the form of the swelling curve changes and swelling is reduced. Thus, a modulation of swelling and release kinetics should be possible with these mixtures. By changing the concentrations of the excipients, a mixture with distinct release and swelling properties can be selected.

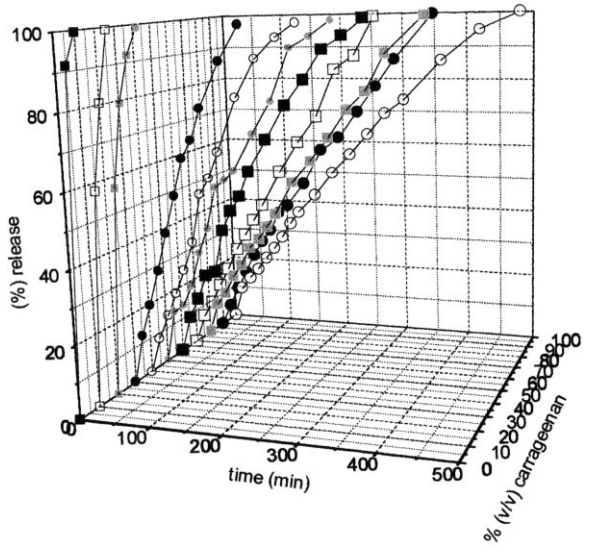

Fig. 10. Drug release from tablets made of graded ternary mixtures of carrageenan and MCC (mean, $n = 6$).

Table 5

Parameters of fitting according to the semiempirical function of Peppas [33] and the correlation coefficient R^2 of a linear regression

GP-911 NF (% (v/v))	k	*n*	SD	x^2	R^2
30	1.04	0.917	0.027	0.93	0.978
40	0.55	1.000	0.050	3.93	0.971
50	1.17	0.826	0.074	10.13	0.968
60	0.88	0.863	0.041	3.84	0.971
70	0.69	0.870	0.010	0.24	0.996
80	0.88	0.800	0.016	0.82	0.991
90	0.85	0.807	0.018	1.06	0.992
100	0.85	0.782	0.016	0.92	0.985

4. Conclusions

Tableting mixtures of k-carrageenan and MCC shows that these excipients complement each other in their compaction properties. A continuous change in tableting properties can be observed. Additionally, for the release and swelling properties, changes can be detected. These changes can be seen in combination with each other and the release behavior can be modulated very easily. Summarizing, k-carrageenan in mixture with MCC can be used to modulate tableting and release properties sensitively.

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