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RESEARCH PAPER

Matrix Tablets of Carrageenans. I. A Compaction Study*

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ABSTRACT

Carrageenans can be used as excipients for controlled-release tablets. The aim of this study was to determine their compaction and consolidation behavior to prove their usefulness for tableting. The Carr indices of the three carrageenans, two κ-carrageenans (Gelcarin® GP-812 NF and GP-911 NF) and one ι-carrageenan (Gelcarin GP-379 NF), indicate that the materials are free flowing. They are polymers in the rubbery state. Their glass transition-temperature is about 0°C analyzed by differential scanning calorimetry (DSC). The powders were analyzed regarding their compression behavior using an eccentric tableting machine. From data obtained during one compaction cycle, porosity-pressure and pressure-time plots were made. Compaction behavior is evaluated by fitting the pressure-time function to the pressure-time plot and by fitting the Heckel function to the porosity-pressure plot. The polymers show ''viscoelastic'' tableting behavior. Several additional tableting parameters were analyzed for strengthening the results obtained, namely, maximum work, maximum power, and the time between maximum upper punch force and maximum displacement of the upper punch. The crushing strength of the tablets is high; therefore, the carrageenans are able to form strong compacts. However, they remain in the rubbery state, as shown by thermomechanical analysis. In addition, elastic recovery is regarded at several times after ejection. Finally, after 10 days, it is about 30% as determined from the minimum of tablet height during the compression cycle. These results indicate that the carrageenans are suitable tableting excipients for controlled-release tablets. They show good compactibility and good consolidation behavior. Strong compacts with a high elastic recovery are formed; this means

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* Dedicated to Professor Dr. Habil Zessin on the occasion of his 65th birthday.

that the materials are able to embed drugs softly. Only a little stress and strain remains in the tablet. All three carrageenans show similar tableting behavior, and a flexible dosage form design is possible.

INTRODUCTION

Polymers are widely used to control drug release from tablets. Generally, synthetic or modified natural polymers are used for this purpose, such as hydroxypropyl methylcellulose (HPMC). Until recently, there were only a few natural gums that could be used to sustain drug release because there was a problem with standardization. The raw material showed different compositions depending on harvesting (1). Carrageenans are natural polysaccharides extracted from seaweed. Today, these seaweeds can be cultivated; therefore, the raw material is much more homogeneous. To now, the carrageenans were mainly used as gelling and thickening agents. Only a few studies examined their use as potential drug delivery excipients (2–6), but these studies deal only with drug delivery from tablets fabricated on a hydraulic press or from tablets that contain the carrageenans in a mixture with other excipients. In a recently published study, the carrageenans have shown their ability to sustain drug release (7). For analyzing the release behavior, they were tableted on a reciprocating tableting machine in a mixture with a model drug. Tablets from the pure material were never manufactured on a tableting machine like that used in production, and until now there has been no study dealing with the compaction and consolidation behavior of the carrageenans. (See Note Added in Proof.)

Carrageenans are marine hydrocolloids obtained by extraction from some members of the class Rhodophyceae. The most important members of this class are *Chondrus crispus* and *Gigartina stellata*. These natural polysaccharides have only been used since 1945 because a substitute for agar was needed after World War II. There are three different types of carrageenan κ-, ι-, and λ-carrageenan. All consist chiefly of the sulfate esters of galactose and 3,6-anhydrogalactose copolymers, linked α-1,3 and β-1,4 in the polymer (8). The λ-carrageenan does not contain 3,6-anhydrogalactose and is highly sulfated. It does not gel and is only used as a thickening agent. The κ- and ι-carrageenan are very similar, except ι-carrageenan is sulfated at carbon 2. Both polymers swell and form gels. The κ-carrageenan forms strong, rigid, and brittle gels. A very small amount of potassium ions is essential for this. The ι-carrageenan forms elastic gels that show thixotropy, mainly in the presence of calcium salts (9,10). In the present study, two different κ-carrageenans (Gelcarin® GP-812 NF and GP-911 NF) and one ι-carrageenan (Gelcarin GP-379 NF) were investigated. The GP-812 NF contains a small amount of potassium chloride (11% w/w) (11), which is left over from production.

The aim of the study was to analyze the compaction and consolidation behavior of these substances and to estimate their value as functional tableting excipients for controlled-release tablets. Properties of the materials like glass transition temperature, particle size, and true, bulk, and tap densities were determined; the compaction and consolidation behaviors during one compaction cycle was analyzed; and the tablets obtained were mechanically characterized by analyzing their elastic recovery, their crushing strength, and their behavior during thermomechanical analysis. Another goal of the study was to generate data useful to formulators working with carrageenans.

EXPERIMENTAL

Materials

Three kinds of carrageenan (FMC Corporation, Newark, NJ) were used as tableting materials: Gelcarin GP-812 NF (lot no. ZB502), Gelcarin GP-911 NF (lot no. ZC502), and Gelcarin GP-379 NF (lot no. ZA502). The materials were sieved (Retsch sieving machine, K. Retsch GmbH, Haan, Germany), and only particles less than 125 μm were used for tableting.

Methods

Glass Transition Temperature

Differential scanning calorimetry (DSC; Netzsch Gerätebau, Selb, Germany) analysis was performed between −70°C and 150°C with the dried polymers to avoid the influence of humidity; a heating rate of 10 K min^{-1} was used. Drying was performed in desiccators over phosphorous pentoxide (0% RH) until a constant weight was attained. In a preliminary experiment, it was shown that no glass transition occurred at a temperature higher than 150°C. At about 200°C, decomposition of the material starts. The samples were heated twice at this temperature range, and the second heating was analyzed. The glass transition temperature was determined by the half-height method. All experiments were made in triplicate, and the means and standard deviations were calculated.

Particle Evaluation

Particle size distribution was measured by laser diffractometry (Sympatec Rodos 12 SR, Sympatec, Remlingen, Germany) with two repetitions. The mean particle size distribution was calculated. The pressure was 4 bar; the injector beneath pressure was 60 mbar; the focal distance was 200 mm; and the measuring time was 25–35 sec. The particle shape was analyzed using a light microscope (MC 80, Axiolab, Carl Zeiss, Jena, Germany).

Densities and Consolidation Behavior

The true densities of the substances needed for tableting were determined by a difference pressure pycnometer (Accupyc 1330, Micromeritics, Norcross, GA) using helium (12).

Bulk and tap densities were determined in triplicate in a weighed 50-ml cylinder using a volumeter (Erweka Apparatebau, Heusenstamm, Germany). From bulk and tap densities, Carr index [%] = tap density − bulk density/tap density * 100 [%] was calculated to estimate consolidation behavior (13).

Compaction

Tablets were produced on an instrumented eccentric tableting 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 five different maximum relative densities of the tablets $\rho_{rel,max}$: 0.750, 0.800, 0.850, 0.900, and 0.950 (precision 0.001).

$$\rho_{rel,max} = \rho_{max}/\rho_{true} \tag{1}$$

with $\rho_{\mathrm{rel,max}}$ the maximum relative density, ρ_{max} the density at minimum height of the tablet under load, and ρ_{true} the true density.

The tablet height, and therefore the volume, at maximum densification under load was held constant at 3.000 ± 0.001 mm (corrected for elastic deformation of the punches) (14). The depth of filling was held constant at 13 mm, and the compression rate was 10 rpm. Forces were measured by the calibrated strain gauges, and displacement of the punch faces was measured using an inductive transducer (W 20 TK, Hottinger Baldwin Meßtechnik, Darmstadt, Germany). The amount of material necessary for each tablet with a given maximum relative density and always the same apparent density was calculated. The powder was manually filled into the die, and one compaction cycle was performed (14). At each condition, 15 single tablets were produced.

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 greater than 1 MPa were used. Five compression cycles always were analyzed. The pressure-time function (Eq. 2) was fitted to the pressure-time plot using Origin 4.00 software. From the pressure-function, the parameters β and γ were obtained. Both low β and γ indicate high plasticity, and therefore judging them in combination is a tool to determine tableting properties (14,15).

$$\rho(t) = \rho_{u,\,max}\left[\frac{t_{end} - t}{\beta}\right]^{\gamma} \cdot e^{1-\left[\frac{t_{end} - t}{\beta}\right]^{\gamma}} \tag{2}$$

with $\rho(t)$ the pressure at time t, $\rho_{u,max}$ the maximum upper punch pressure, t_{end} the time at the end of one compression cycle, t the time, and β and γ constants.

The Heckel function (16) was fitted to the Heckel plot. The Heckel slope was judged in combination with recovery of the tablet up to the point at which the upper punch left the surface of the tablet.

In addition, maximum work and power during one compression cycle were analyzed (17). For further estimating plastoelastic behavior of the materials, the difference in time between the maximum of the upper punch force and the maximum displacement of the upper punch was calculated. All calculations were done for 10 compaction events.

Mechanical Characterization of the Tablets

Elastic recovery according to Armstrong and Haines-Nutt (18) was calculated directly after ejection and at 24 hr and 10 days after tableting for analyzing the complete recovery process (pair of calipers, Mitotuyo Corp., Tokyo, Japan).

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

The final tablets were analyzed in duplicate by thermomechanical analysis (TMA; Netzsch Gerätebau, Selb, Germany) to evaluate their viscoelastic behavior after compaction. The heating rate was about 5°C, and analysis was done between 20°C and 150°C.

RESULTS AND DISCUSSION

Powder Properties

Glass Transition Temperature

The DSC analysis for temperatures between −70°C and 150°C shows a glass transition temperature near 0°C

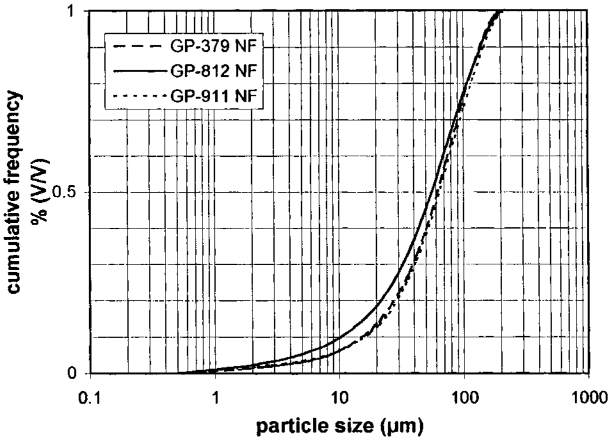

Figure 1. Particle size distribution of the carrageenans determined by laser diffractometry (mean of $n = 3$).

for all the analyzed polymers. The calculated means and standard deviations of the midpoint values are as follows: GP-812 NF, 2.7 ± 0.6°C; GP-911 NF, 2.5 ± 0.7°C; and GP-379 NF, 2.1 ± 0.4°C. Hence, there is no statistical difference between the ι-carrageenans and κ-carrageenans. The data indicate that the polymers are viscoelastic substances in the rubbery state at room temperature or during production. These results support the conclusions of Delalonde et al. (2), who found no glass transition temperature above room temperature.

Particle Evaluation

To remove the effects of particle size during tableting, all particles larger than 125 μm were removed. The remaining fractions of carrageenans showed very similar particle size distributions (Fig. 1). The most frequent particle size for all materials was about 80 μm. It may be assumed that the actual particle size was less than the measured size because the particles have a fibrous, anisometric form. From this point of view, a tableting behavior similar to other amorphous fibrous polymers like HPMC was expected.

Densities and Consolidation Behavior

The bulk, tap, and true densities of the carrageenans are given in Table 1. Both κ-carrageenans GP-812 NF and GP-911 NF show similar bulk, tap, and true densities. They are not identical, and the results are not in-between standard deviation, but the difference is only 1% for the true density, 9% for the tap density, and 5% for the bulk density. This difference is due to the amount of potassium chloride (11% w/w) left over from production of GP-812 NF. The densities of GP-812 NF always show higher values than those of GP-911 NF. The ι-carrageenan GP-379 NF shows a higher true density, and the bulk and tap densities are about 50% higher than with the κ-carrageenans. The additional sulfate ester at carbon 2 is responsible for this. The molecules are heavier even though their volume is bigger. The Carr indices calculated from tap and bulk densities are quite passable. The tapped volume reduction is about 30% less than bulk. This indicates that the material is free flowing. The Carr index of GP-379 NF indicates that this material should have better consolidation behavior. The materials have passable flow properties according to Wells (13).

Tableting Properties

Heckel Plots and Elastic Recovery

The results obtained indicate very special tableting behavior for the carrageenans (Fig. 2). The Heckel plots are

Table 1

True, Tap, and Bulk Densities and Carr Index of the Carrageenans

	GP-812 NF	GP-911 NF	GP-379 NF
True density (g/cm^3)	1.754	1.744	1.812
	(0.004)	(0.011)	(0.007)
Tap density (g/cm^3)	0.738	0.674	0.980
	(0.017)	(0.038)	(0.015)
Bulk density (g/cm^3)	0.465	0.444	0.710
	(0.001)	(0.008)	(0.005)
Carr index	36.95	33.93	27.51
	(1.48)	(2.65)	(1.36)

Mean for $n = 3$. Standard deviation in parentheses.

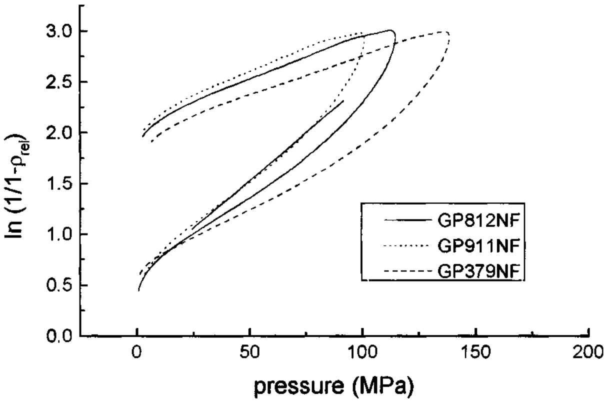

Figure 2. Porosity-pressure plot of the three carrageenans at a maximum relative density of 0.950. Fitting the Heckel-function exemplary.

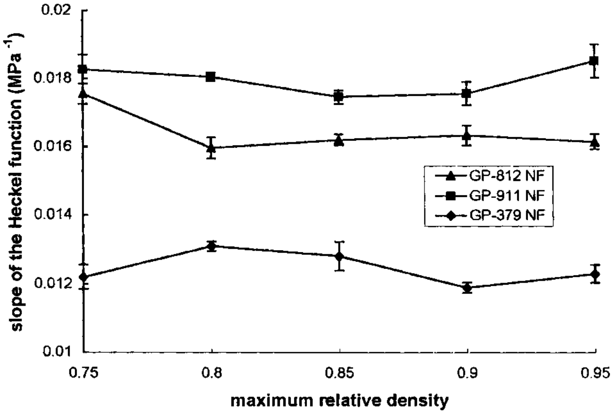

Figure 3. Slope of the Heckel function of the three carrageenans at different maximum relative densities (mean and SD of $n = 5$).

hard to linearize, and there is only a small linear part. Especially when reaching the maximum pressure, the plot is no longer linear, the porosity still increases, while pressure remains constant. This shows that, during the densification process, plastic and elastic deformation are occurring simultaneously, and at maximum densification, at the minimum height of the tablet, elastic recovery directly starts, indicated by decreasing $\ln(1/1 - \rho_{rel})$. This behavior is due to substances that show a lot of elasticity in addition to plasticity (19). Heckel plots of plastic materials can be linearized easily (20), and the decrease in $\ln(1/1 - \rho_{rel})$ is still small (19).

Fitting the Heckel function to these plots seems to be difficult. Nevertheless, general differences from other excipients can be shown, and the carrageenans can be compared to each other. Fitting the porosity-pressure plot with the well-known function of Heckel leads to the parameter slope of the Heckel function. Especially for GP-379 NF, this parameter is relatively low compared to other substances (20), indicating elastic behavior besides plastic deformation. It does not increase with increasing maximum relative density, but the three carrageenans show different values (Fig. 3). Indicated by the lower values for the Heckel-slope, GP-379 NF, the ι-carrageenan, deforms less than the κ-carrageenans GP-812 NF and GP-911 NF.

With the slope of the Heckel function, plastic and elastic deformation are described together, and therefore elastic recovery has to be described in addition (Fig. 4). Elastic recovery of the tablets is about 30% at the maximum (after 10 days) as measured from the height at maximum densification. That is little more than determined for HPMC (25%) (14,15), a well-established tableting excipient for controlled-release tablets. The ι-carrageenan GP-379 NF (Fig. 4c) shows increasing elastic recovery with increasing maximum relative density, and there seems to be a direct relationship between both parameters. It indicates that this material behaves elastically. The κ-carrageenans GP-812 NF (Fig. 4a) and GP-911 NF (Fig. 4b) show the highest elastic recovery at the lowest maximum relative density of 0.750. At higher maximum relative densities, elastic recovery decreases, indicating more plastic deformation of the two κ-carrageenans. Elastic recovery decreases more for GP-911 NF than for GP-812 NF, indicating less resistance to tableting. The κ-carrageenan GP-812 NF contains a small amount of potassium chloride left over from production, which is responsible for this behavior.

Pressure-Time Plot and Additional Parameters

The normalized pressure-time plot shows a very round shape at the maximum (Fig. 5), indicating that the interval between maximum pressure and maximum displacement is relatively high. This can be strengthened by the results obtained when calculating this interval (about 0.030 ms) (Table 2). Thus, the materials show ‘‘viscoelastic’’ behavior, and the results obtained by analysis of the porosity-pressure plot are strengthened.

Tableting shows a difference between κ-carrageenan and ι-carrageenan (Table 2). The ι-carrageenan GP-379 NF shows higher maximum pressures, and the normalized pressure-time plot has another shape (Fig. 5). The pressure increases faster, and the upper punch reaches

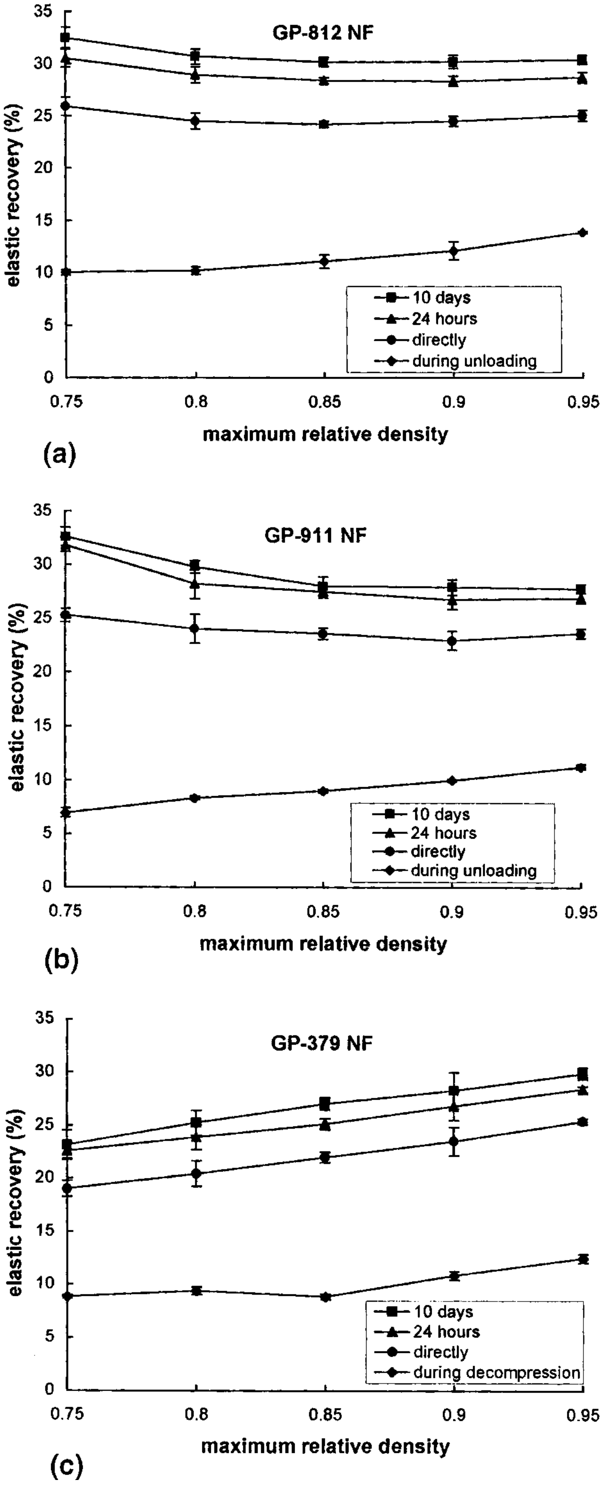

Figure 4. Elastic recovery of the carrageenans (a) GP-812 NF, (b) GP-911 NF, (c) GP-379 NF during compression, directly, 24 hr, and 10 days after ejection of tablets made at different maximum relative densities (mean and SD of $n = 15$).

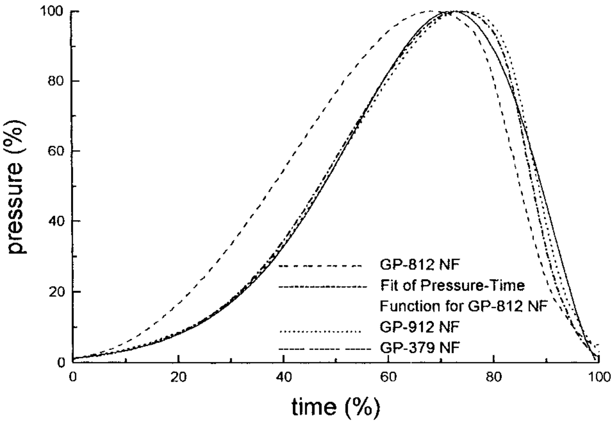

Figure 5. Pressure-time plot of the three carrageenans at a maximum relative density of 0.850. Fitting the pressure-time function exemplary.

the maximum pressure earlier. The decrease of pressure during unloading is slower, indicating that the elastic recovery during the compression cycle is higher. Maximum work and power needed for forming tablets of the same dimensions are higher, and the extent of increase with increasing maximum relative density is higher (Table 2). The GP-812 NF, the κ-carrageenan containing more potassium chloride, shows nearly the same tableting properties as GP-911 NF at low maximum relative densities. At high maximum relative densities, higher pressures occur, and more work resp. power is needed, indicating more resistance to tableting. The potassium chloride is responsible.

Again, it seems to be difficult to fit functions (here, the pressure-time function), but the parameters obtained (β and γ) are able to distinguish the compaction behavior from that of other excipients. The γ-β diagram (Fig. 6) indicates that these excipients are a little less plastic than others because β and γ show higher values than other excipients. The results of elastic recovery determinations strengthen this finding (Fig. 4). The γ-β diagram (Fig. 6) shows the most elastic behavior for the ι-carrageenan, and the elastic behavior decreases with increasing maximum relative density. The κ-carrageenan GP-812 NF shows the most plastic behavior.

A difference between the two types of carrageenan becomes obvious. The κ-carrageenan is less elastic than ι-carrageenan. The more elastic behavior of ι-carrageenan during tableting may be due to the additional sulfate group at carbon 2. Similar behavior was observed for cellulose ethers (14,15). Sodium carboxymethylcellulose showed the most elastic behavior at 38% RH. It was the

Table 2

Compressibility of the Carrageenans (GP-812 NF, GP-911 NF, and GP-379 NF) at Different Maximum Relative Densities $\rho_{\text{rel,max}}$

Material	$\rho_{rel,max}$	Maximum Upper Punch Force (MPa)	Interval Between Maximum Force and Maximum Displacement (ms)	Maximum Work (J)	Maximum Power (J sec^{-1})
GP-812 NF	0.750	41.24 (0.68)	0.0335 (0.0029)	4.17 (0.10)	13.53 (0.35)
	0.800	56.99 (0.68)	0.0317 (0.0019)	7.79 (0.24)	18.91 (0.65)
	0.850	72.51 (1.12)	0.0308 (0.0023)	9.01 (0.48)	24.69 (0.85)
	0.900	91.22 (0.49)	0.0290 (0.0025)	12.60 (0.51)	31.05 (0.54)
	0.950	113.44 (1.03)	0.0267 (0.0011)	16.84 (0.40)	38.33 (0.76)
GP-911 NF	0.750	41.44 (0.62)	0.0323 (0.0032)	4.44 (0.32)	11.38 (0.25)
	0.800	50.45 (0.71)	0.0317 (0.0016)	5.63 (0.13)	16.52 (0.32)
	0.850	66.23 (0.95)	0.0313 (0.0030)	8.27 (0.30)	21.91 (0.31)
	0.900	84.64 (1.51)	0.0247 (0.0100)	11.15 (0.33)	28.04 (0.56)
	0.950	104.52 (2.35)	0.0233 (0.0027)	14.80 (0.62)	33.46 (0.48)
GP-379 NF	0.750	51.48 (1.34)	0.0303 (0.0026)	3.77 (0.23)	15.99 (0.60)
	0.800	66.95 (1.21)	0.0308 (0.0023)	5.44 (0.59)	21.43 (1.42)
	0.850	87.48 (1.52)	0.0292 (0.0012)	8.43 (0.22)	29.36 (0.76)
	0.900	114.72 (0.80)	0.0262 (0.0020)	12.37 (1.13)	37.37 (3.20)
	0.950	139.19 (0.99)	0.0247 (0.0020)	17.78 (2.28)	46.90 (0.72)

Mean for $n = 10$. Standard deviation in parentheses.

substance with the biggest substituent compared to hydroxypropyl methylcellulose and hydroxyethyl methylcellulose. Maybe the polymer chains cannot come as close together if a big substituent is present, but this has to be proven generally.

The difference between the κ-carrageenans depends only on the additional content of potassium chloride, as shown by the different tableting parameters. This crystalline material is responsible for the more plastic deformation during tableting.

Tablet Quality

The viscoelastic nature and the fact that the tablets remain in the rubbery state during and after compaction can be proved with the final tablets (22). Thermomechanical analysis of the tablets shows nearly no solving of internal stress. During analysis, tablet height mainly decreases instead of increasing (Fig. 7). This is strongly valid for GP-911 NF, the κ-carrageenan without additional potassium salt. For GP-812 NF and GP-379 NF, little solving of internal stress is shown. The ι-carrageenan GP-379 NF, more substituted by sulfate groups, and GP-812 NF, the κ-carrageenan with an additional content of potassium chloride, show some solving of stored internal stress during heating before drastic reduction of tablet height. The pure κ-carrageenan GP-812 NF directly loses height. Reduction of height is a distinguishing mark for viscoelastic materials (22). Therefore, GP-911 NF is the only one of viscoelastic nature, and the viscoelastic behavior of the other substances is hindered either by the substituent or by the addition of a crystalline material like potassium chloride.

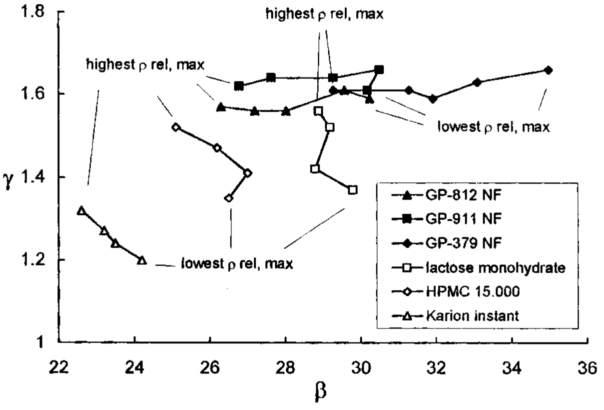

Figure 6. γ-β diagram of different excipients at different maximum relative densities (given in parentheses): GP-911 NF, GP-812 NF, GP-379 NF (0.75, 0.80, 0.85, 0.90, 0.95) (mean of $n = 5$, medium SD for β 0.71; medium SD for γ 0.03), lactose monohydrate (17), Karion instant (21) (0.77, 0.82, 0.87, 0.92), and HPMC 15.000 (0.80, 0.85, 0.90, 0.95) (15).

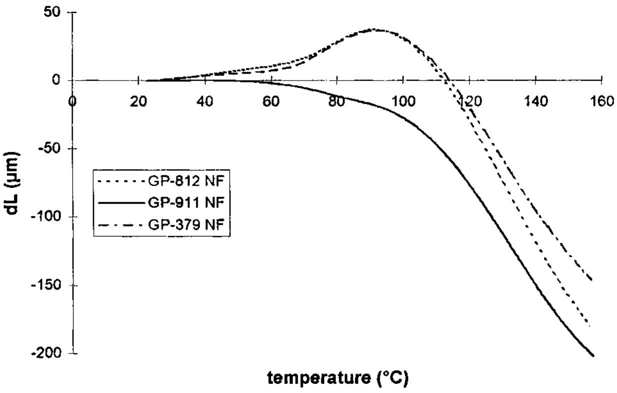

Figure 7. Thermomechanical analysis of tablets of the different carrageenans: (a) GP-812 NF; (b) GP-911 NF; (c) GP-379 NF (mean of $n = 3$).

The tensile strength of the tablets (Figs. 8a, 8b) increases for all carrageenans with increasing maximum relative density. In general, it is very high, and strong tablets of high robustness are formed. The tensile strength can reach values up to 215 N at the maximum relative density of 0.950. Strong interparticulate bridges are formed. Therefore, the tablets show good compaction behavior, and they are of high quality. The ι-carrageenan GP-379 NF shows the lowest tensile strength, and the pure κ-carrageenan GP-911 NF shows the highest. The difference is most obvious at the highest maximum relative density. This shows that, in GP-911 NF, more interparticulate bridges are formed and also in GP-812 NF more than in GP-379 NF. The formation of bridges occurs more often for more plastically deforming materials. The sulfate groups hinder the formation of bridges, and the potassium chloride content does the same because bridges between particles of the same kind of material are formed more easily. This result is strengthened by the fact that tablets made from GP-812 NF show a lower tensile strength 10 days after compaction. However, the differences in tensile strength between the different types of carrageenan are not of importance for tablet quality. In any case, tablet quality is high.

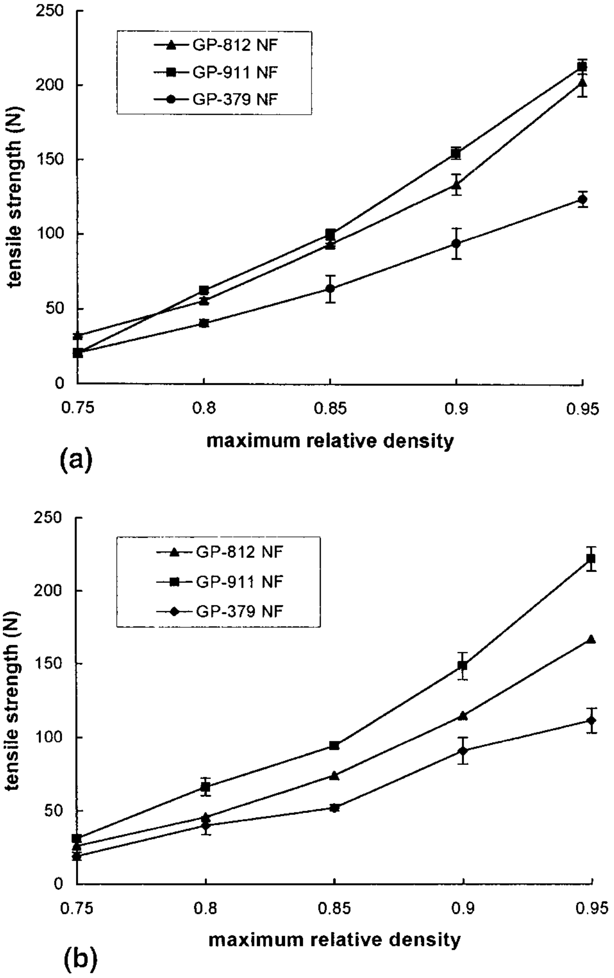

Figure 8. Tensile strength of tablets made of carrageenans (a) directly and (b) 10 days after compaction (mean and SD of $n = 3$).

CONCLUSIONS

The results indicate that the carrageenans are suitable tableting excipients for controlled-release tablets. As shown by Heckel plots and pressure-time plots, the compacts are easily formed, and the materials behave viscoelastically during compression. The resulting compacts are of high robustness, and they show good compactibility, indicated by a high tensile strength. Several types of carrageenans can be used for this purpose. Differences in substitution or addition of potassium chloride for influencing gelling behavior will only lead to minor changes in tableting properties and will offer a flexible formulation system.

In addition, the carrageenans represent a new class of tableting excipients with special properties. First, their elastic recovery seems to be a disadvantage for tableting. Generally, a lot of plastic deformation is expected for forming strong compacts. However, the formed compacts are strong, and the elasticity of the material does not influence the cohesion of the tablets. The viscoelastic nature of this material can be a prevailing advantage for special applications. Because of the directly occurring elastic recovery, drugs embedded in such tablets are not mechanically stressed. They are embedded very softly. Polymorphic transitions of drugs induced by mechanical stress can be minimized (23). Most useful for this purpose is the pure κ-carrageenan, which shows the most viscoelastic behavior.

Thus, tableting carrageenans as main tableting excipients for sustaining drug release has proved to be a useful, simple, and flexible method that offers new possibilities for solid dosage form design.

ACKNOWLEDGMENT

I would like to thank Prof. Leschonski and Dr. Legenhausen, Institute of Mechanical Engineering, Technical University Clausthal-Zellerfeld, Germany, for the possibility to use laser diffractometry and Lehmann and Voss GmbH, Hamburg, Germany, for generously providing the excipients.

Note Added in Proof

A paper has been published that deals with the tableting and release of carrageenans: M. Hariharan, T. A. Wheatley, and J. C. Price, Pharm. Dev. Technol., 2, 383–393 (1997). The work of Hariharan et al. was not available when this paper was submitted.

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