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RESEARCH PAPER

Matrix Tablets of Carrageenans. II. Release Behavior and Effect of Added Cations

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ABSTRACT

Carrageenans are hydrocolloids in the rubbery state at standard conditions. They are useful excipients for controlled-release tablets. Three carrageenans, two κ-carrageenans (Gelcarin® GP-812 NF and GP-911 NF) and one ι-carrageenan (Gelcarin GP-379 NF), are analyzed regarding their release behavior in combination with sorption, swelling, and rheology. The ι-carrageenan has a higher substitution by sulfate groups. The κ-carrageenan Gelcarin GP-812 NF contains a small amount of potassium chloride left over from processing. Water sorption of the pure materials was studied gravimetrically, and the rheology of different solutions (2% and 5% w/w) was studied by cup-cylinder rotation viscosimetry. Swelling was determined as the vertical expansion of the tablets with a specially designed swelling apparatus. Drug release from the tablets was performed by the USP paddle method for 8 hr. The data indicate that drug release increases when water sorption and swelling extent decrease and as viscosity increases. The order of release is nearly zero-order kinetics for theophylline monohydrate, a nonionic drug. Diffusion of the anionic drug diclofenac sodium is anomalous. In addition, the influence of the added salts potassium and calcium chloride on swelling and release was studied. Before tableting, physical mixtures of these salts with and without theophylline monohydrate were prepared. Swelling and release change in the same order, but this is only valid when the ionic interactions responsible for this are strong enough. Besides this, physical mixing of salts with the carrageenans can result in an increased release of drug caused by decreased cohesion of the matrix during drug release, mainly for calcium chloride.

INTRODUCTION

Hydrocolloids can be used to sustain drug release from matrix tablets. Synthetic or partially synthetic polymers and also natural gums can be used for this purpose. Natural gums have been mainly used in food industries and not in the pharmaceutical industry because there was a problem with standardization (1,2).

Carrageenans are polysaccharides extracted from red seaweed. Today, the seaweeds can be cultivated, and thus the raw material is more homogeneous (1). Three basic types of carrageenan exist: κ-, ι-, and λ-carrageenan. Because of their ability to form stable gels at room temperature, κ- and ι-carrageenan are useful excipients to sustain drug release. They consist chiefly of the sulfate esters of galactose and 3,6-anhydrogalactose joined by alternating α-1,3 and β-1,4 glycosidic linkages. The ι-carrageenan is also sulfated at carbon 2, contrary to κ-carrageenan (2–4). The highly sulfated λ-carrageenan can only be used as a thickening agent. Therefore, it is not a useful main excipient to control drug release from tablets. Two kinds of κ-carrageenan and one kind of ι-carrageenan were used for this study. One of the κ-carrageenans contains a small amount of potassium chloride (5) left over from processing.

Until now (6), only a few studies have dealt with carrageenans for controlled-release tablets (7–11), but either a hydraulic press was used or the carrageenans were only used as modifying additives. There is no study analyzing drug release from matrix tablets of carrageenans produced on a tableting machine. (See Note Added in Proof.) Because these machines are normally used in production, it is of importance for dosage form development to study the drug release from these directly compressed matrices. Therefore, the main aim of this study was a systematic approach to analyze this field of application. Because it is difficult to estimate their value as excipients for controlled-release tablets without comparison, studies were performed using the well-studied cellulose ether hydroxypropyl methylcellulose. Model drugs used were theophylline monohydrate and diclofenac sodium, widely prescribed therapeutic agents with good solubility. Using these drugs, the influence of an ionic and a nonionic drug can be studied.

In addition, the influence of potassium and calcium ions on swelling and release behavior was investigated (12). These ions are able to change the gelling properties of gels made with these substances. Therefore, an influence on drug release is probable. Their influence on the viscosity of gels has been studied in polymer literature (12), but nothing is known about their influence on drug release from tablets. The evaluation of this was another aim of the study.

Drug release from hydrocolloid matrices is dependent on their gel-forming properties and their swelling behavior and, in combination, on the sorption tendency of the polymers (13–15). The viscosity of the gel layer formed by expansion of the tablets during swelling influences the mobility of the drug molecules in the tablet and thus the drug release. Therefore, first, the properties of the different types of carrageenans like sorption behavior, rheology, and swelling behavior were analyzed. Then, tablets manufactured with the carrageenans were studied for their ability to sustain drug release. The results obtained by all methods were compared. The results of a previous study (16) showed that, at standard conditions, all these carrageenans are polymers in the rubbery state. This property may be of importance for release behavior. A theory was developed to connect sorption, rheology, and swelling behavior and, finally, drug release of these viscoelastic substances.

EXPERIMENTAL

Materials

Three kinds of carrageenan (FMC Corporation, Newark, NJ) were used for manufacturing controlled-release tablets. Gelcarin® GP-812 NF (lot no. ZB502) and Gelcarin GP-911 NF (lot no. ZC502) are κ-carrageenans. Gelcarin GP-812 NF contains 11% (w/w) (5) potassium chloride left over from processing. Gelcarin GP-379 NF (lot no. ZA502) is a ι-carrageenan. Compared to κ-carrageenan, it contains additional sulfate groups at carbon 2. In addition, hydroxypropyl methylcellulose (HPMC 15.000) (Metolose 90 SH, lot no. 506825, Shin-Etsu, Tokyo, Japan) was used for comparison. Theophylline monohydrate (lot no. 4072.2, Roth GmbH, Karlsruhe, Germany) and diclofenac sodium (lot no. 35855.030A6, Wasserfuhr GmbH, Bonn, Germany) were used as model drugs. For all materials, only particles less than 125 μm were used for tableting. Larger particles were removed by sieving (Retsch sieving machine, K. Retsch GmbH, Haan, Germany).

Methods

Sorption Isotherms

Sorption isotherms were determined gravimetrically in duplicate. About 1 g of material was equilibrated at different constant relative humidities above saturated salt solutions (relative humidity percentages of 11, 22, 32, 43, 52, 57, 69, 75, and 80) (17) in desiccators. Then, the samples were dried above phosphorous pentoxide to constant weight. No drying before starting sorption was done

to avoid the influence of drying on sorption behavior. The content of water was calculated in percentage of the dry material.

Rheological Behavior

The rheological behavior of the carrageenan solutions (2% and 5% w/w) was measured by cup-cylinder rotation viscosimetry (Physica MC 1, Paar Physica, Graz, Austria). All determinations were done in triplicate, and the means and standard deviations were calculated.

Compaction

Physical mixtures of equal true volumes of drug and excipient containing 20% (v/v) drug were manufactured using a cubic mixer with fixed wide-necked bottles (250 ml, 15 min, 30 rpm; AR 400, Erweka GmbH, Heusenstamm, Germany). Using the same method, 5% (w/w) potassium or sodium chloride was added.

Tablets of these mixtures were produced on an instrumented rotary tableting machine (PH 103/DMS, no. 1.0021.82, Korsch GmbH, Berlin, Germany) with faceted punches of 11.0-mm diameter. Equal true volumes of the substances (0.242 cm^3) were tableted to a fixed upper punch force of 7.5 kN. The depth of filling was held constant at 13 mm, and the compression was done manually. Forces were measured by the calibrated strain gauges. At each condition, 10 single tablets were produced. Resulting apparent densities of the final tablets were 0.70 $\pm$ 0.05.

Swelling

The rate and extent of swelling of the tablets were determined using a special swelling apparatus (18). The tablets are 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) are responsible for the influx of water. On the tablet, a punch with a constant weight of 100.0 g controls swelling. The movement of this punch is transduced in voltages, and the resulting values are digitized and stored on a personal computer using the program Quell (Martin-Luther-University Halle-Wittenberg). For 8 hr, the movement of the punch is recorded in micrometers according to calibration and rate and extent of swelling result.

Release Behavior

Drug delivery was analyzed using the paddle method according to USP XXIII in distilled water (900 ml, 37°c $\pm$ 0.5°C, 100 rpm) for 8 hr. Substitution by distilled water was made for 10-ml samples of medium. The resulting concentrations of drug in the release medium were determined spectrophotometrically (Spectronic 601, Milton Roy, Obertshausen, Germany). The content of drug was determined at peak maximum (theophylline monohydrate, 271 nm; diclofenac sodium, 276 nm). The release of 6 tablets was determined, and means and standard deviations were calculated.

RESULTS AND DISCUSSION

Sorption, Swelling, and Rheology

Sorption

The sorption behavior of the carrageenans is different from HPMC (Fig. 1). The carrageenans bind much more water than HPMC. At about 10% RH, HPMC contains 2% (w/w) water, and the carrageenans contain from 4% to 7% (w/w). At about 50% RH, HPMC contains about 7% (w/w), and the carrageenans contain from 14% to 17% (w/w). Therefore, the water content for the carrageenans is twice or three times as much as HPMC. This result is also valid for 80% RH.

However, sorption is different for several types. GP-911 NF, a κ-carrageenan, and GP-379 NF, a ι-carrageenan, sorb about 30% (w/w) at a relative humidity of 80%. This indicates that both κ- and ι-carrageenan are able to bind the same amount of water at that high relative humidity. But, the increase of the sorption isotherm at low relative humidities is higher for the ι-carrageenan GP-379 NF. This means that more water is tightly bound (19,20). The additional substitution by sulfate groups is responsible for this because water can be bound in solvate form. GP-812 NF, the κ-carrageenan containing potassium chloride, sorbs about 35% (w/w) water at a relative

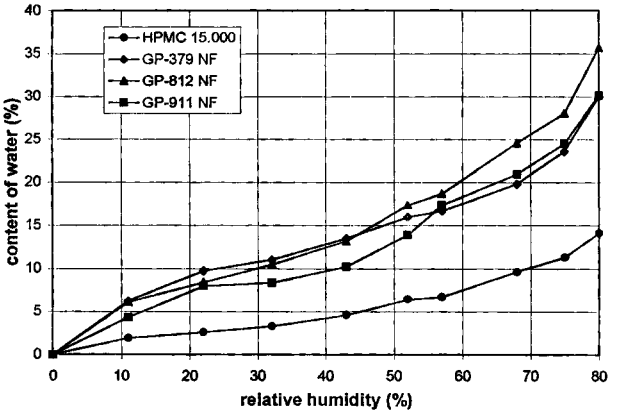

Figure 1. Sorption behavior of the carrageenans and HPMC determined gravimetrically (mean of $n = 2$).

humidity of 80%. At a low relative humidity of 10%, already 6% (w/w) is sorbed. These data indicate that GP-812 NF shows a higher attraction to water (19–21). The potassium chloride could be responsible for this behavior. Hence, the carrageenans represent a class of excipients with very high attraction to water. The responsibility for this may be that they rest in the rubbery state (16), allowing more mobility of the water molecules. The sorption tendency may be described as follows:

GP-812 NF > GP-911 NF > GP-379 NF > HPMC

(κ-carrageenan and KCl) > (κ-carrageenan)
> (ι-carrageenan)
> (cellulose ether)

Swelling

Looking at the swelling behavior of the tablets, first the carrageenans swell relatively fast—a steep increase in expansion is obvious—then swelling slows (Fig. 2). Contrary to HPMC, they show no lag time before swelling starts. However, the three carrageenans behave differently. The κ-carrageenans GP-911 NF and GP-812 NF swell faster and to a larger extent than the ι-carrageenan GP-379 NF. During the first 2 hr, the κ-carrageenans swell twice as much. Maybe at an infinite time the extent of swelling is the same, but this is not of importance for practical use. The responsibility for this behavior is the higher mobility of the water molecules between the polymer chains; they can penetrate more easily because there are fewer sulfate groups binding water tightly in solvate form at the chains. Looking at GP-812 NF, the κ-carrageenan containing a small amount of potassium chloride, the extent, but not the rate, of swelling was enlarged by potassium chloride. On the contrary, the readiness decreases. The potassium ions left from production of the material are able to bind water tightly, but they are mobile and not fixed at the chains like the sulfate substituents in ι-carrageenan. Thus, swelling is first slowed, but on the whole is increased. The extent of swelling may be described as follows:

GP-812 NF > GP-911 NF > GP-379 NF > HPMC

(κ-carrageenan and KCl) > (κ-carrageenan)
> (ι-carrageenan)
> (cellulose ether)

For analyzing the influence of added cations on swelling behavior only by physical mixing, tablets manufactured from the different carrageenans with added potassium or calcium chloride were studied. The results indicate (Fig. 3) that both the κ-carrageenans show enlarged swelling behavior for both salts. The physical addition by mixing increases swelling on the whole, and it is of no importance whether potassium chloride was left over from processing or not. There is no difference between GP-911 NF and GP-812 NF. On the contrary, swelling of ι-carrageenans is only enlarged by calcium chloride according to the literature (4,12). The reason for the increased swelling behavior is the fact that water is bound more tightly by the ions in the swelling tablet; thus, the attraction to water is greater. In the case of ι-carrageenan, only the calcium ions are able to do this. Their higher charge is responsible for swelling. Potassium shows no effect.

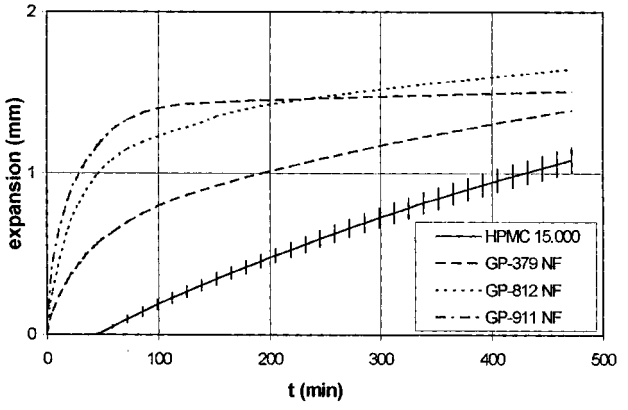

Figure 2. Swelling behavior of the carrageenans and HPMC (mean of $n = 3$, SD exemplary).

Rheology

Solutions of the three analyzed carrageenans show different rheological behavior (Fig. 4), but all of them show a faster decrease in viscosity than HPMC at high shear rates. The ι-carrageenan GP-379 NF shows the highest viscosity at low shear rates; at high shear rates, viscosity is nearly the same for all carrageenans. The chains of this highly sulfated carrageenan hinder the movement of each other during shear stress more than the chains of the κ-carrageenan with fewer substituents. This is the same for both a 2% (w/w) and a 5% (w/w) solution. The 2% (w/w) solution of GP-812 NF shows higher viscosity than GP-911 NF. The small amount of potassium ions added during production enlarges viscosity at low shear rates as described in the literature (4,12). The 5% (w/w) solutions of the κ-carrageenans show only a slight difference in thixotropy. GP-911 NF shows higher thixotropy than GP-812 NF, thus indicating that gel strength, but not thixotropy, is increased by potassium ions. The ι-carra-

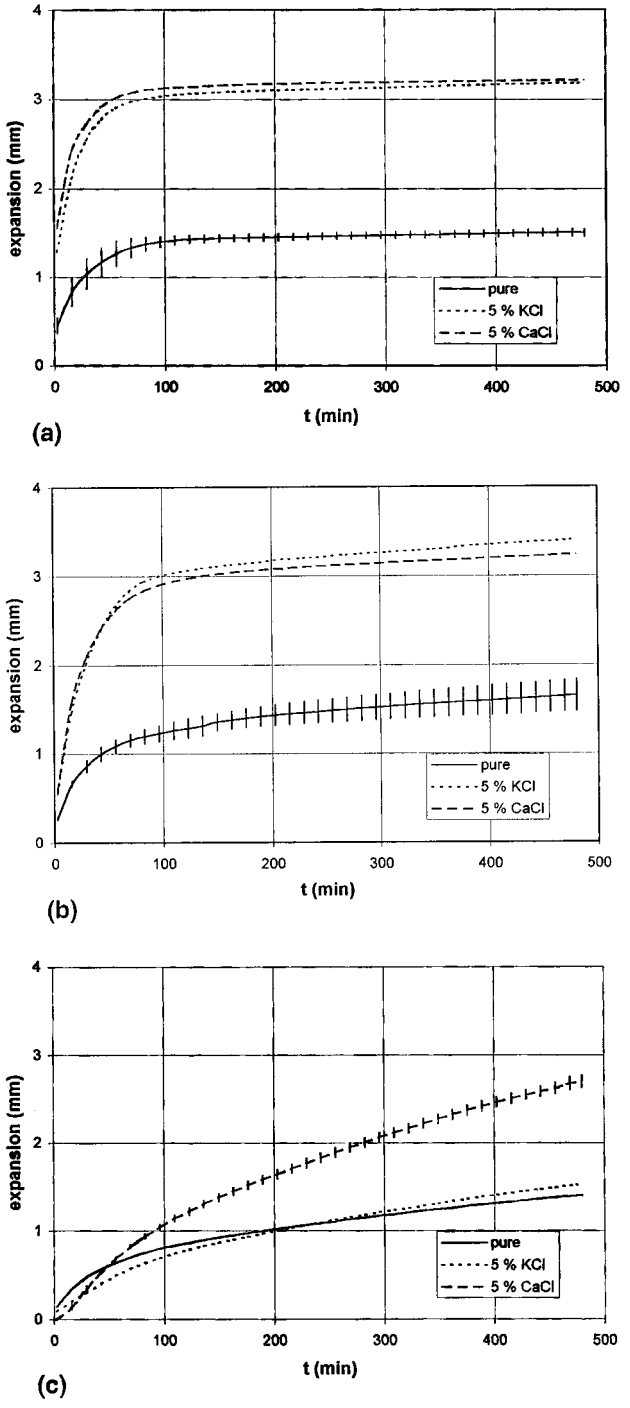

Figure 3. Swelling behavior of the carrageenans (a) GP-812 NF, (b) GP-911 NF, (c) GP-379 NF with and without added salts (mean of $n = 3$, SD exemplary).

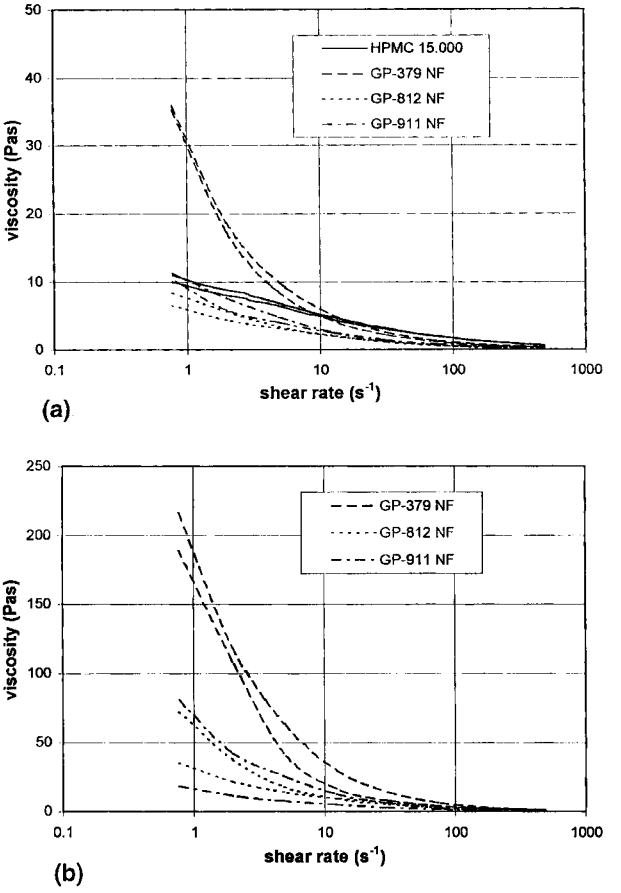

Figure 4. Rheological behavior of the carrageenans and HPMC at different concentrations of polymer (a) 2% (w/w) and (b) 5% (w/w) (mean of $n = 3$).

geenan GP-379 NF shows a high extent of thixotropy, the highest of all analyzed polymers. The highly substituted chains hinder each other's movement. A mixture of 5% (w/w) HPMC was not measurable. On the whole, viscosity is lower for the carrageenans than for HPMC. The thixotropy can be described as follows:

$$\text{GP-812 NF} \leq \text{GP-911 NF} < \text{GP-379 NF} < \text{HPMC}$$

$$(\kappa\text{-carrageenan and KCl}) \leq (\kappa\text{-carrageenan}) < (\iota\text{-carrageenan}) < (\text{cellulose ether})$$

Combining the Results

The data indicate that rheological and swelling behavior are both dependent on the sorption tendency of the carrageenans. The order of changing different properties shows that substances having a high sorption tendency

swell more than those having a low sorption tendency. On the other hand, they showed less thixotropy. These properties are dependent either on the extent of substitution by sulfate groups or on the potassium ions left over from processing. The influence of both these ions is different because the sulfate group substituent is immobile, while the cations are mobile. At the least, there is a difference in swelling behavior of the tablets for physically added ions and ions left over from processing.

Drug Release

Influence of Drug Type

Tablets manufactured with the carrageenans were of good quality, as described in a previous study (16). Crushing strength, compressibility, and compactibility were satisfactory.

The analysis of drug release from tablets of carrageenans for both theophylline monohydrate and diclofenac sodium showed the same order of rate of release (Fig. 5). The HPMC tablets always showed the slowest rate of release; those made of the κ-carrageenan GP-911 NF showed the highest rate of release. Drug release from κ-carrageenans is reduced by potassium ions left over from manufacturing, as indicated by the tablets of GP-812 NF showing a slower release rate than those manufactured from GP-911 NF. The highly sulfated ι-carrageenan GP-379 NF tablets showed a release rate only a little faster than for HPMC tablets. Thus, the rate of drug release follows the order of swelling:

GP-911 NF ≥ GP-812 NF > GP-379 NF > HPMC

(κ-carrageenan) ≥ (κ-carrageenan and KCl)

> (ι-carrageenan)

> (cellulose ether)

The release curve corresponding to GP-911 NF was nearly linear for theophylline monohydrate using the model of Peppas (22) (Table 1; Fig. 5a). Drug release follows zero-order-kinetics. This release behavior is slowed and the order of release is changed for GP-812 NF by addition of potassium ions left over from the man-

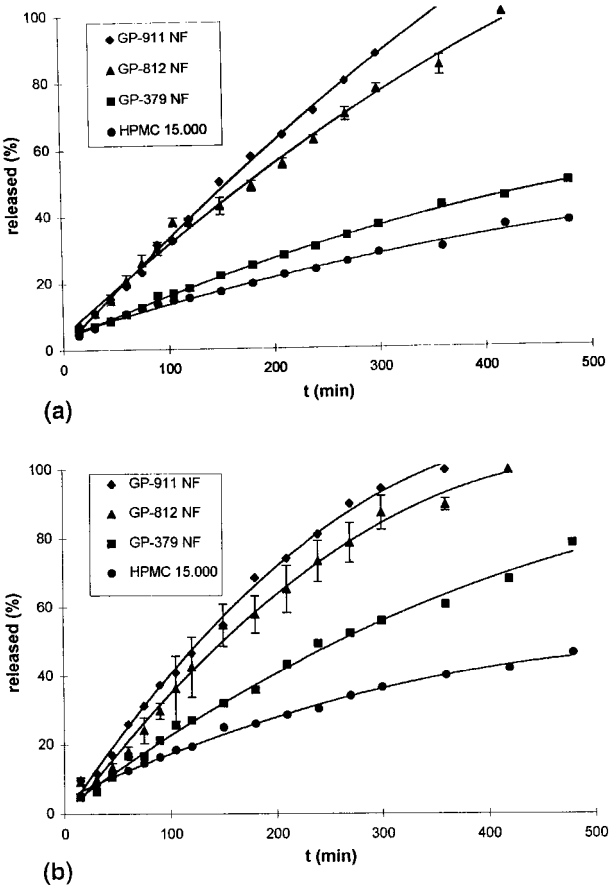

Figure 5. Drug release of the carrageenans and HPMC (a) theophylline monohydrate and (b) sodium diclofenac (mean of $n = 3$, SD exemplary).

Table 1

n *Obtained by Fitting Drug Release According to Peppas (22):* $x = k \cdot t^n$

	GP-812 NF	GP-911 NF	GP-379 NF	HPMC
Diclofenac sodium	0.779	0.770	0.775	0.616
	(0.040)	(0.034)	(0.022)	(0.013)
Theophylline monohydrate	0.786	0.912	0.716	0.635
	(0.019)	(0.012)	(0.014)	(0.015)
Theophylline monohydrate with 5% KCl	0.834	0.763	0.639	
	(0.044)	(0.019)	(0.018)	
Theophylline monohydrate with 5% CaCl	0.672	0.892	—	
	(0.025)	(0.021)		

Error of fitting given in parentheses.

ufacturing process of this material. Tablets with diclofenac sodium showed no release following zero-order-kinetics (Table 1; Fig. 5b). This anionic material shows less mobility in the swelling tablet. Interactions between ions and excipient might be responsible for this. The parameter *n* (Table 1), indicating the order of release of tablets of GP-911 NF and of GP-812 NF, was within standard deviation, but the rate of release was not. Tablets of GP-379 NF had the slowest release rate of all three carrageenans, but there still is no order following the square root of time. The release shown is anomalous and therefore case II (15). For GP-379 NF, drug release is less for theophylline monohydrate than for diclofenac sodium. Probably, drug release is increased by the anionic sulfate ions of the chains in the presence of an anionic drug.

Influence of Ions

Studying the influence of potassium or calcium ions (Fig. 6) in a concentration of 5% (w/w) shows that drug release is changed for both ι- and κ-carrageenan. But, the addition of these ions only by physical mixing does not always result in advantages for release. The addition of calcium chloride increases drug release. This corresponds to enhanced swelling behavior for all the carrageenans. Obviously, by the addition of this salt, a lower cohesion of the matrix during drug release results. This is most obvious for tablets of GP-379 NF. Two hours after starting release, the drug is dissolved; no sustained release results (Fig. 6c). In the case of the κ-carrageenan GP-911 NF (Fig. 6b), the rate, but not the order of release, is changed (Table 1). In the case of the κ-carrageenan GP-812 NF (Fig. 6a) containing a small amount of potassium chloride before mixing, the order, but not the amount totally released, after 8 hr is changed.

Physical addition of potassium chloride shows different effects. Release is slowed for the κ-carrageenan GP-911 NF (Fig. 6b), and the change is the same for GP-812 NF with 11% (w/w) potassium chloride left over from the manufacturing process (Fig. 5a). In the case of tablets made from GP-812 NF, after physical mixing, release is increased and tends more to zero-order kinetics. The most probable reason for this is that the matrix loses its cohesion during release by this high content of potassium chloride, on the whole about 16% (w/w). Thus, up to a certain amount of potassium chloride, drug release can be sustained; if this amount is exceeded, the matrix loses its cohesion. This influence cannot be shown for swelling behavior. The influence of ions on swelling behavior was the same for both the κ-carrageenans.

Drug release increases for tablets made of the ι-carrageenan GP-379 NF. Thus, the potency of the sulfate ions to slow drug release is diminished. This influence cannot be underlined by the data obtained for swelling behavior. The addition of potassium chloride showed no influence on the expansion of tablets. Obviously, ionic interactions that

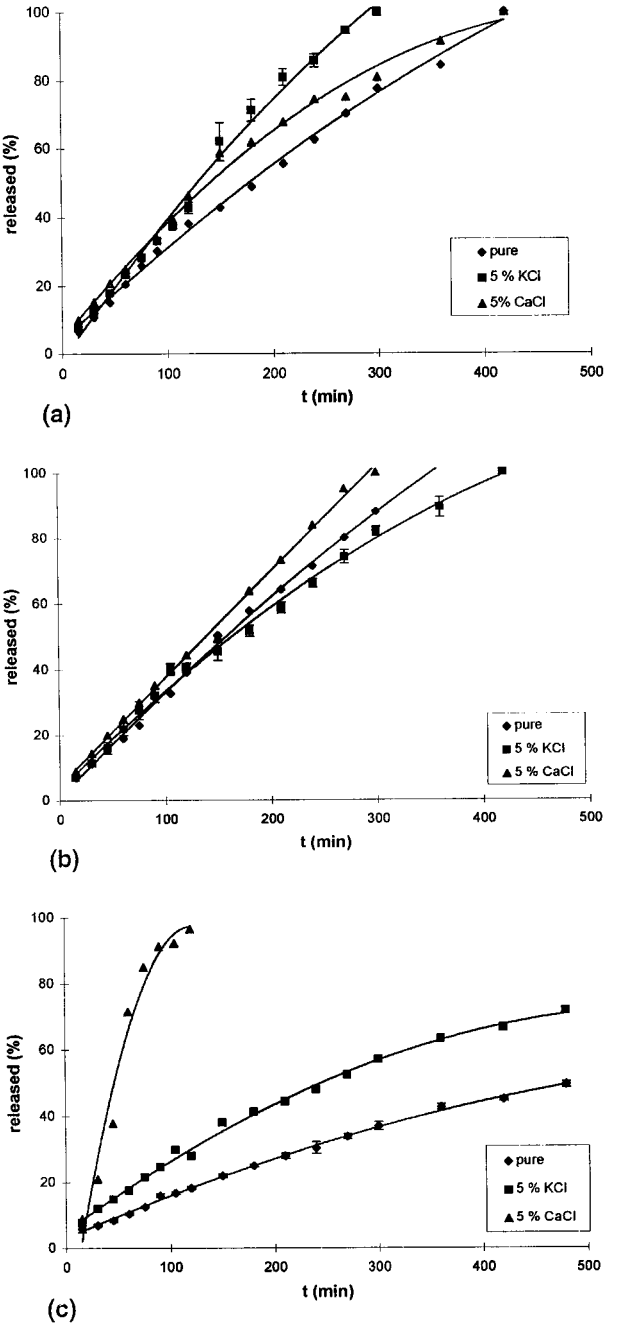

Figure 6. Drug release of the carrageenans (a) GP-812 NF, (b) GP-911 NF, and (c) GP-379 NF without and with added salts (mean of $n = 3$, SD exemplary).

have no statistically significant influence on swelling behavior here are responsible for the change in drug release.

On the whole, drug release can be influenced by cations left from processing or added during the manufacturing process of the tablets. Drug release is dependent on ionic interactions, and when the extent of these interactions exceeds a fixed amount, the ionic interactions are able to change swelling behavior. However, the change in swelling behavior is only partly responsible for sustained drug release.

CONCLUSIONS

In conclusion, the data indicate that drug release increases when water sorption and the extent of swelling decreases and when viscosity increases. These results are valid for all three carrageenans. The addition of salts by physical mixing with the carrageenans before tableting also shows a connection between swelling and drug release. However, this connection is more complicated. Up to a certain concentration of cations, drug release can be sustained; at higher concentrations, release increases due to a loss in the cohesion of the matrix. This is valid for the κ-carrageenans. For the ι-carrageenan, interactions with the anionic sulfate groups also have to be examined. Increased swelling can indicate sustained release for low concentrations of cations, but for high concentrations of cations, this is not valid. Interactions of cations and anions are not regarded.

In addition, a difference in drug release is shown for different types of drug, nonionic or anionic. The interaction of the drug with the charged polymers is of importance and can be used to model drug release. On the whole, both κ- and ι-carrageenan are useful excipients for controlling drug release, and drug release can be modeled using the cations potassium and calcium and using differently charged drugs. By doing so, many possibilities are offered to the formulator.

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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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