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Research paper

Controlled-release tablets from carrageenans: effect of formulation, storage and dissolution factors

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Abstract

The purpose of this study was to investigate the potential of two carrageenans, ι-carrageenan and λ-carrageenan for the preparation of controlled-release tablets. Tablets were compressed on a Carver press and the effect of formulation factors, moisture, and storage on the release of theophylline was studied. The effect of sodium chloride in the tablet formulation and a change in the ionic strength of the dissolution media was studied on the release of three model drugs. The release rate increased both with an increase in tablet diameter and increase in drug to carrageenan ratio in the tablets. The two lubricants studied had a negligible effect on the rate of drug release at their commonly used concentrations. Moisture content of carrageenans, storage of tablets at 37°C/75% RH for 3 months, and incorporation of 10% sodium chloride in the tablets did not have any significant effect on the release rate. The change in ionic strength of simulated gastric fluid altered the release rate whereas the ionic strength of simulated intestinal fluid did not have a significant effect on the release rate. Carrageenan tablets were relatively insensitive to small changes in formulation parameters and dissolution conditions.

Keywords: Controlled-release; Sustained-release; Zero-order; ι-Carrageenan; λ-carrageenan; Tablets

1. Introduction

Polymers that swell in an aqueous medium have been widely used to formulate controlled-release tablets [1–3]. Swellable polymers can be divided into two categories: water-insoluble polymers called hydrogels; and water-soluble hydrophilic polymers. The release of drugs from swellable controlled release systems is usually dependent on one or more of the following processes: wetting of the polymer matrix by the solvent, swelling of polymer, diffusion of drug through the hydrated polymer, dissolution of drug in the solvent and erosion/dissolution of polymer. A disadvantage of the use of hydrophilic polymers for controlled-release of very water soluble drugs is the rapid dissolution of the surface drug and quick diffusion of drug through the outer hydrated gel layer. This often causes initial rapid release followed by a period of slow release because of the increase in path length of diffusion of the drug through the polymer as the hydration and swelling of polymer matrix progresses [4]. Tablets made from mixtures of λ-carrageenan and sodium carboxymethylcellulose and λ-carrageenan and hydroxypropylmethylcellulose have been shown to release drug at a constant rate over a period of time [5]. It has also been shown that anionic polymers can control the early release of soluble basic drugs, probably through ionic interactions [6].

Carrageenans have long been commercially used in the food industry as viscosity building, gelling and stabilizing agents [7,8]. Due to their gelling and viscosity building properties and proven safety, there has been an interest in the use of carrageenans as sustained-release materials [9–11]. Carrageenans are naturally occurring polysaccharides extracted from red seaweed. They are high molecular weight polysaccharides made up of repeating units of galactose and 3,6 anhydrogalactose (3,6-AG). The units are joined by alternating alpha 1,4- and beta 1,4-glycosidic linkages. There are three main types of carrageenans available depending on the number and position of the ester sulfate groups. Lambda-carrageenan (λ-carrageenan) contains D-galactose-2-sulfate and D-galactose-2,6-disulfate as monomeric units; it dissolves to form viscous aqueous solutions. Iota-carrageenan (ι-carrageenan) is an alternating

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copolymer of D-galactose-4-sulfate and 3,6-anhydro-D-galactose-2-sulfate linked 1,3 and 1,4 which does not dissolve but forms gels in water [12].

Theophylline was selected as a model drug because it is nearly neutral and has a low aqueous solubility of 8.3 mg/ml in water [13]. Theophylline is an anti-asthmatic with a short half-life; hence there is a therapeutic rationale in formulating it for controlled-release applications. Sodium salicylate has an aqueous solubility of 1.11 g/ml and was chosen as a model soluble salt of an acidic compound [14]. Chlorpheniramine maleate has an aqueous solubility of 160 mg/ml and was chosen as a model salt of a basic drug [15].

Previous studies in our laboratory investigated the potential of two commercial carrageenans, Gelcarin GP-379 (ι-carrageenan) and Viscarin GP-209 (λ-carrageenan) for the preparation of controlled-release tablet matrices. Drug release from tablet formulations that contained equal amounts of the two carrageenans had near zero-order release profiles [16,17]. The aim of the present work was to further investigate Gelcarin GP-379 and Viscarin GP-209, for the preparation of controlled-release compressed tablets. The effect of drug to carrageenan ratio, diameter, lubricant level, moisture content of carrageenans and storage was studied on the release of theophylline. The effect of the incorporation of sodium chloride in the tablets and a change in the ionic strength of the dissolution media was studied on the release of theophylline, sodium salicylate and chlorpheniramine maleate. These three drugs provide a range of solubilities and pKa values and were hence chosen to get a better perspective of the ability of carrageenan matrices to control drug release.

2. Materials and methods

2.1. Materials

Theophylline anhydrous was a gift from Knoll AG, Ludwigshafen, Germany. Sodium salicylate and chlorpheniramine maleate were purchased from Sigma Chemical Company, St. Louis, MO. The two grades of carrageenans, Gelcarin GP-379 (ι-carrageenan) and Viscarin GP-209 (λ-carrageenan) and microcrystalline cellulose (Avicel PH 101) were gifts from FMC Corporation, Philadelphia, PA. Karl Fischer reagent was purchased from Fisher Scientific, Fair Lawn, NJ.

2.2. Formulation design

Tablets were made using *Formulation A* for all the experiments except for those investigating the effect of incorporation of sodium chloride in tablets for which *Formulation B* was used. The compositions of *Formulation A* and *Formulation B* are listed in Table 1.

Formulation B was used to investigate the effect of incorporation of sodium chloride in the tablet matrix at a level of 10% of tablet weight.

2.3. Tablet preparation

Tablets weighing 500 mg and measuring 1/2″ diameter were used for all the experiments except when studying the effect of drug to carrageenan ratio and tablet diameter on the release profile. Tablets of two different drug to carrageenan ratios - 13.5% (500 mg) and 16.9% (400 mg) - and two different diameters (3/8″ and 1/2″) were used to study the effect of drug to polymer ratio and tablet size on drug release. All the formulation ingredients were mixed in a 100-ml glass container and shaken by hand for 20 min. Tablets were compressed to either 105 MPa (1/2″ tablets) or 187 MPa (3/8″ tablets) on a Carver laboratory press (Model B, Fred S Carver Inc, Summit, NJ) fitted with flat faced 1/2″ or 3/8″ punch and die sets.

2.4. Moisture content studies

The initial moisture content of Gelcarin and Viscarin was determined by Karl–Fischer titration according to procedures outlined in the USP 24 [18] using sodium tartarate dihydrate as the standard.

To study the effect of moisture content of carrageenans (before tableting) on the drug release profile from tablets, Gelcarin and Viscarin were equilibrated in a constant humidity chamber (75% RH) and were used for tableting after they became saturated with moisture as evidenced by no further increase in their weight. The moisture content of equilibrated samples was determined by calculating the difference between the initial weight and the final weight of the equilibrated samples.

The initial moisture content of carrageenan tablets was calculated by Karl Fischer titration as described earlier, except that the sample was obtained by grinding not less than four tablets to a fine powder.

2.5. Storage studies

The tablets were placed flat on aluminium foil and stored in a constant humidity chamber at 37°C/75%H for 3 months. At the end of 3 months, tablets were taken out of the humidity chamber, weighed and tested for drug release profile. The moisture content of the tablets after storage was determined by calculating the difference between the initial

Table 1
Compositions of the two formulations used for studies[a,b]

Formulation	D	G	V	A	S	Total
A	10	37	37	16	–	100
B	10	37	37	6	10	100

[a] The numbers represent percentage of ingredients in the tablets. Unless otherwise stated, each tablet weighed 500 mg and was directly compressed in a 0.5″ die at 105 MPa.

[b] D, Drug; either theophylline, or sodium salicylate, or chlorpheniramine maleate; G, Gelcarin GP-379 (ι-carrageenan); V, Viscarin GP-209 (λ-carrageenan); A, Avicel PH 101 (microcrystalline cellulose); S, sodium chloride.

weight and the final weight of the tablets after storing at 37°C/75% RH for 3 months.

2.6. Ionic strength studies

Simulated Gastric Fluid (SGF) and *Simulated Intestinal Fluid* (SIF) were prepared according to USP 24 [18] without enzymes. The *SGF Higher Ionic Strength* and *SIF Higher Ionic Strength* Fluids were prepared by adding additional 2 g/l of sodium chloride to SGF and SIF respectively. *SGF Lower Ionic Strength Fluid* was prepared by omitting sodium chloride (2 g/l) from SGF. The ionic strengths of various dissolution fluids are listed in Table 2.

2.7. Dissolution studies

Dissolution studies (six replicates for each experiment) were performed using the paddle method (USP 24), at 100 rev./min, 37°C, with 900 ml of dissolution fluid. Dissolution fluids used were SGF (three ionic strengths), SIF (two ionic strengths), water and a combination of SGF and SIF (3 h in SGF followed by SIF). The tablets were placed in spiral cages made of stainless steel wire to prevent adhesion of the tablet to the dissolution vessel. The amount of drug released was determined by withdrawing 3-ml samples at various time intervals and measuring the absorbance in an ultraviolet spectrophotometer (Spectronic 2000, Bausch and Lomb, USA). The carrageenans, in the concentrations formed in the dissolution media, did not absorb significantly at the analysis wavelengths. Equal amounts of dissolution media were replaced after withdrawal of each sample.

3. Results and discussion

3.1. Release kinetics

The results of dissolution studies of tablet formulations in terms of the 50% release time and release parameters determined from the Peppas and Korsmeyer model [19] are shown in Table 3. In this model, $M_t/M_\infty = kt^n$, where M_t/M_∞ is the fraction of the total drug released, k is the apparent release rate constant that incorporates the structural and geometric characteristics of the drug delivery device and n is the diffusional release exponent. The t_{50} is the time at which 50% of the drug was released from the tablet. The release exponent was determined by linear regression of initial 60% of the release data. If the value of n is 0.5, it indicates Fickian transport, a value of >0.5 and <1.0 suggests non-Fickian transport, and the values close to 1.0 indicate that the system is releasing drug in a zero-order manner regardless of the actual mechanism of release [16]. This type of analysis of release behavior is valuable to the formulator for comparative purposes [17]. Fickian release can be expected from an intact, insoluble, planar matrix in which edge effects are negligible. For all the formulations in this study, n values were between 0.5 and 1.0 suggesting non-Fickian release of drugs (Table 3). In the gel-forming matrices of this study, competing mechanisms of drug release occur simultaneously. At different stages of drug release, these mechanisms may include one or combination of hydration, dissolution, swelling, erosion, and diffusion.

Table 2
Ionic strengths of various dissolution media used

Dissolution medium	Ionic strength
Simulated gastric fluid (SGF)[a]	0.119
SGF higher ionic strength[b]	0.153
SGF lower ionic strength[c]	0.085
Simulated intestinal fluid (SIF)[d]	0.093
SIF higher ionic strength[b]	0.127

[a] pH of SGF was approximatley 1.2 and did not change with the addition or omission of 2g/L of sodium chloride.
[b] SGF higher ionic strength and SIF higher ionic strength solutions were prepared by adding additional 2g/L of sodium chloride to the solution.
[c] SGF lower ionic strength solution was prepared by omitting sodium chloride from SGF.
[d] pH of SIF was 7.5 ± 0.1 and did not change with the addition of 2g/L of sodium chloride.

Table 3
Release rates and diffusional constants for the release of theophylline from carrageenan tablets

Factors	t_{50} (hr)	n	k (h^{-1})	r^2
Theophylline tablets				
Drug to carrageenan ratio and diameter				
13.5% (500 mg), 1/2″	3.150	0.6932	0.2209	0.9970
13.5% (500 mg), 3/8″	4.550	0.7671	0.1555	0.9983
16.9% (400 mg), 1/2″	2.850	0.7879	0.2196	0.9966
16.9% (400 mg), 3/8″	4.325	0.7675	0.1651	0.9987
Lubricants				
No Lubricants	3.150	0.6932	0.2209	0.9970
0.5% Magnesium Stearate	3.150	0.7416	0.2205	0.9984
1% Magnesium Stearate	3.350	0.7163	0.2136	0.9925
1% Stearic Acid	3.175	0.7933	0.1977	0.9995
Moisture content of carrageenans				
Initial (Gelcarin 13.6%, Viscarin 15.3%)[a]	3.175	0.7160	0.2167	0.9982
Aged (Gelcarin 19.9%, Viscarin 21.3%)[b]	3.225	0.7275	0.2070	0.9958
Storage of tablets				
Initial (10.4%)	3.175	0.7160	0.2167	0.9982
Aged, 37°C/75%RH, 3 months (13.8%)	3.075	0.7231	0.2243	0.9993

[a] Carrageenans as received from the manufacturer.
[b] Carrageenans saturated with moisture after storage for 3 months at 37°C/75%RH.

3.2. Formulation factors

3.2.1. Effect of drug to carrageenan ratio and diameter of tablets

Tablets of two drug to carrageenan ratios - 16.9% (tablet

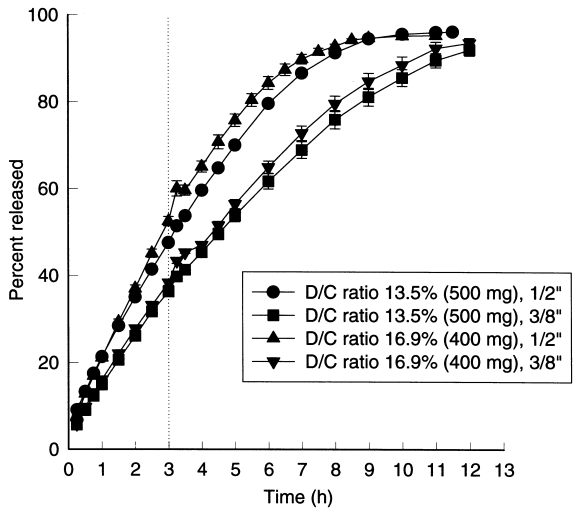

Fig. 1. Release profile of theophylline from tablets of different drug (D) to carrageenan (C) ratios and diameter for the first 3 h in SGF followed by SIF.

weight 400 mg) and 13.5% (tablet weight 500 mg) - and two diameters - 3/8″ and 0.5″, were used to study the effect of drug to carrageenan ratio and tablet size on drug release (Fig. 1). Dissolution was done in SGF for 3 h followed by SIF until approximately 90% of the drug was released. The rate of drug release increased with an increase in the drug to carrageenan ratio. Although the drug loading (50 mg) is the same in both, the total carrageenan present is higher in 500-mg tablets (370 mg) than in 400-mg tablets (296 mg). The larger quantity of carrageenans results in a longer path-length for the permeation of dissolution fluid into the tablet matrix and diffusion of drug through the gel.

The effect of tablet diameter was more pronounced than the effect of drug to carrageenan ratio. Tablets (500 mg) of 1/2″ diameter released drug faster (t_{50} 3.15 h) than 3/8″ diameter tablets (t_{50} 4.55 h). There could be two possible reasons for faster drug release from larger diameter tablets of the same weight. Although both 1/2″ and 3/8″ tablets were compressed at 3000 lb. force, the 3/8″ tablets (187 MPa) experienced more compression pressure as compared to 1/2″ tablets (105 MPa) because 3/8″ diameter tablets have smaller cross-sectional area. Higher compression pressure results in more dense tablets and could make it more difficult for the dissolution media to penetrate the tablet matrix and result in slower drug release. This reason can probably be ruled out because previous studies in our lab showed that variation of the compression pressure over a 70 to 175 MPa range had a negligible effect on the dissolution rate of drugs from carrageenan tablet matrices [16]. Faster drug release from 1/2″ diameter tablets as compared to 3/8″ tablets of the same weight can be attributed to the shorter initial diffusion distance and higher surface area to volume ratio of the 1/2″ tablets. Initial diffusion distance is the initial distance that has to be covered by the penetrating solvent front to wet the tablet matrix; which in this case can be simply calculated by halving the axial thickness of the tablet. Tablets (500 mg) of 1/2″ diameter have shorter initial diffusion distance (0.1537 cm) as compared to 3/8″ tablets (0.2601 cm); surface area to volume ratio for the 1/2″ tablets was 9.219 cm^{-1} while for the 3/8″ tablets it was 8.042 cm^{-1}. This results in faster penetration of the dissolution media in the tablet matrix and faster drug release. The values of initial diffusion distance, surface area, volume, and surface area to volume ratio of tablets of different weight, diameter, and drug to carrageenan ratio are listed in Table 4.

3.2.2. Effect of lubricants

The effect of lubricants on drug release assumes significance because lubricants have been shown to increase the disintegration time of tablets and slow down the release of drugs from tablet matrices. Because of the hydrophobic nature of most tablet lubricants, they repel water and retard the wetting of the tablet components by the dissolution media. Magnesium stearate and stearic acid at levels of 0.5% (t_{50} 3.15 h) and 1% (t_{50} 3.175 h) respectively, did not significantly affect the release rate from carrageenan tablets. Magnesium stearate at the 1% level significantly slowed the release of theophylline after 4.5 h (Fig. 2).

3.3. Moisture and storage factors

3.3.1. Effect of moisture content of carrageenans

The effect of moisture present in carrageenans before tableting on the release rate of drug from the tablets was studied because many water-swellable controlled-release polymers including carrageenans, are highly hygroscopic. Absorbed moisture can potentially change the drug release profile because the controlled-release mechanism of carra-

Table 4
Values of initial diffusion distance, surface area, volume, and surface area to volume ratio for tablets of different weight, diameter, and drug to carrageenan ratio compressed at 3000 lb force

Tablets (weight, diameter, drug to carrageenan ratio)	Initial diffusion distance (cm)	Surface area (cm^2)	Volume (cm^3)	Surface area to volume ratio (cm^{-1})
500 mg, 1/2″, 13.5%	0.1536	3.852	0.4178	9.219
500 mg, 3/8″, 13.5%	0.2600	2.982	0.3708	8.042
400 mg, 1/2″, 16.9 %	0.1234	3.521	0.3131	11.24
400 mg, 3/8″, 16.9%	0.2085	2.671	0.2967	9.002

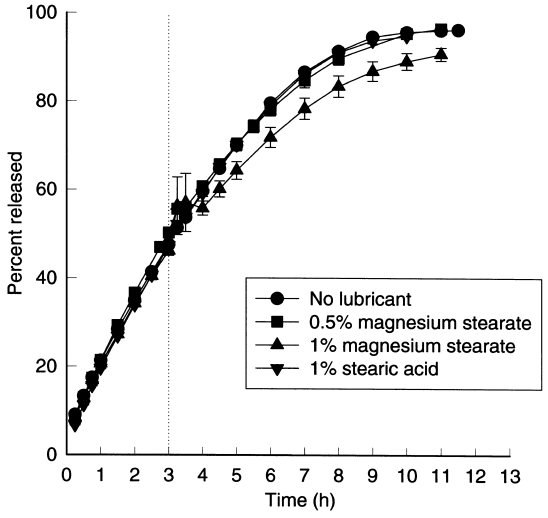

Fig. 2. Release profile of theophylline from carrageenan tablets containing different lubricants for the first 3 h in SGF followed by SIF.

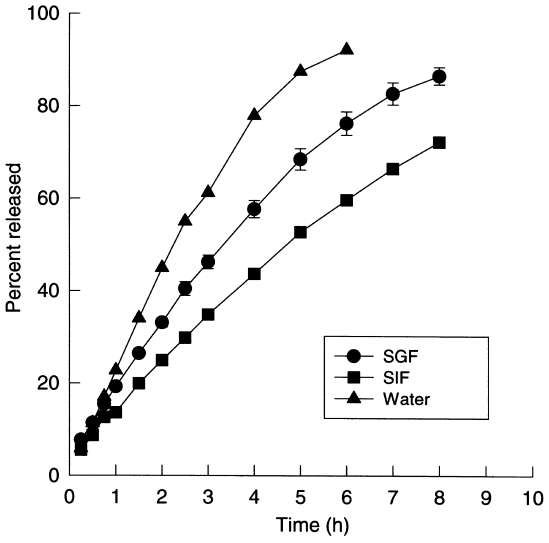

Fig. 4. Release profile of theophylline from carrageenan tablets in different dissolution media.

geenans involves gelling and swelling after they come in contact with the dissolution fluid.

Gelcarin and Viscarin were saturated with moisture by placing them in a constant humidity chamber at 75% humidity. There was no significant difference in the release profile of theophylline from the tablets made using moisture-saturated carrageenans (moisture content: Gelcarin 19.9%, Viscarin 21.43%) (t_{50} 3.22 h) and the tablets made using carrageenans as received from the manufacturer (moisture content: Gelcarin 13.6%, Viscarin 15.34%) (t_{50} 3.17 h).

3.3.2. Effect of storage

The sustained-release characteristics of carrageenans depend on the gel formed after swelling in the dissolution medium. Since the formation of gel might be affected by temperature and humidity, the effect of storage at 37°C/75%RH for 3 months was investigated on the release profile of theophylline. The moisture content of the initial and aged tablets (after 3 months at 37°C/75%RH) was 10.47 and 13.80% respectively. As shown in Fig. 3, there was no significant difference in the release profile of the initial tablets (before storage) and aged tablets (after storage).

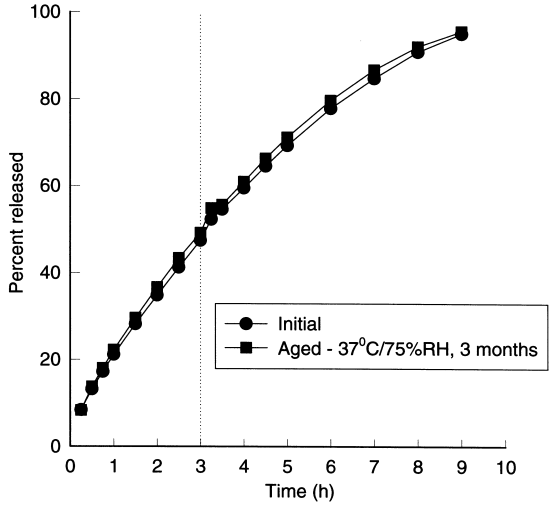

Fig. 3. Release profile of theophylline from carrageenan tablets before storage (Initial) and tablets after storage at 37°C/75%RH for 3 months (aged) for the first 3 h in SGF followed by SIF.

3.4. Dissolution factors

3.4.1. Effect of type and pH of dissolution media

The investigation of the effect of various dissolution media on the release profile of drug from the dosage form is important because the dosage form will encounter envir-

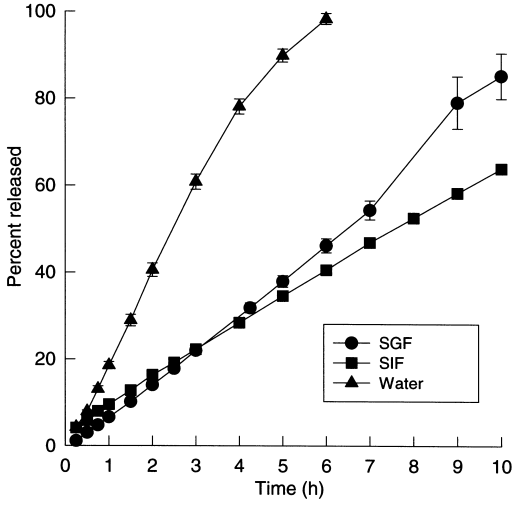

Fig. 5. Release profile of chlorpheniramine maleate from carrageenan tablets in different dissolution media.

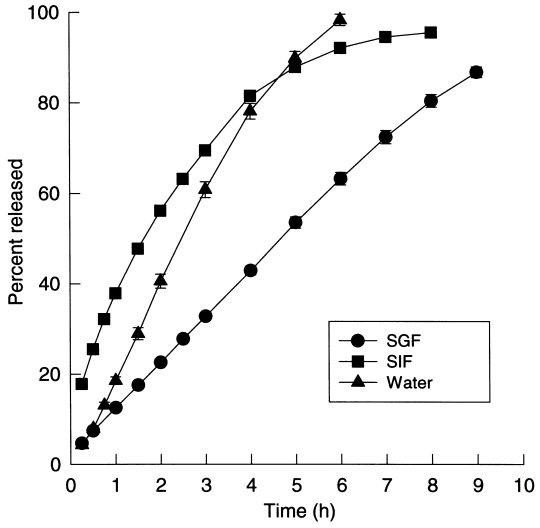

Fig. 6. Release profile of sodium salicylate from carrageenan tablets in different dissolution media.

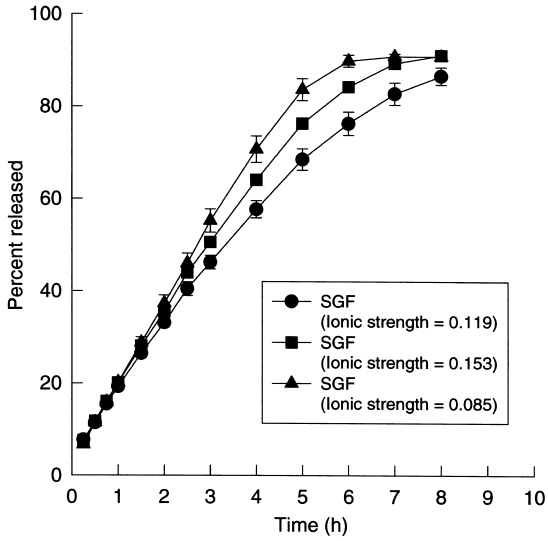

Fig. 8. Release profile of theophylline from carrageenan tablets in simulated gastric fluid (SGF) of different ionic strengths.

onments of differing pH during its transit in the gastrointestinal tract.

The release profiles of theophylline, sodium salicylate and chlorpheniramine maleate from carrageenan tablets was studied in three different dissolution media - SGF (pH 1.2), SIF (pH 7.5) and water. As shown in Fig. 4, the release rate of theophylline was highest in water (t_{50} 2.27 h) followed by SGF (t_{50} 3.35 h) and then SIF (t_{50} 4.73 h). The release rate was higher in SGF because theophylline acts as a base (pKb 13.5) at low pH (pH $<$ 2). Similarly, the release rate of chlorpheniramine maleate was highest in water (t_{50} 2.42 h) followed by SGF (t_{50} 6.45 h) and then SIF (t_{50} 7.52 h). The reason for the higher release rate in SGF compared to SIF is because of the basic nature (pKa 9.2) of the compound (Fig. 5). Conversely, the release rate of sodium salicylate was higher in SIF because of the higher solubility of salicylic acid in a solution of basic pH (Fig. 6).

Fig. 7 shows the comparative release profiles of the three drugs from carrageenan tablets for 3 hours in SGF followed by SIF. The release of theophylline and chlorpheniramine maleate was close to zero-order for approximately 70% of drug release. Theophylline has the lowest aqueous solubility among these three drugs (solubility at 37°C: theophylline - 8.3 mg/ml, sodium salicylate - 1110 mg/ml and chlorpheniramine maleate - 160 mg/ml), however, its release was faster (t_{50} 3.175 h) than both sodium salicylate (t_{50} 4.125 h) and chlorpheniramine maleate (t_{50} 6.125 h) for most of the dissolution time. Also, as expected, after a change in the dissolution media from SGF to SIF, the release of theophyl-

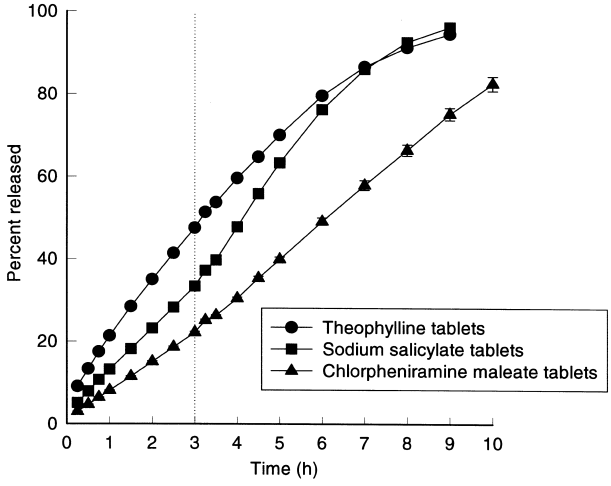

Fig. 7. Release profile of theophylline, sodium salicylate and chlorpheniramine maleate from carrageenan tablets for the first 3 h in SGF followed by SIF.

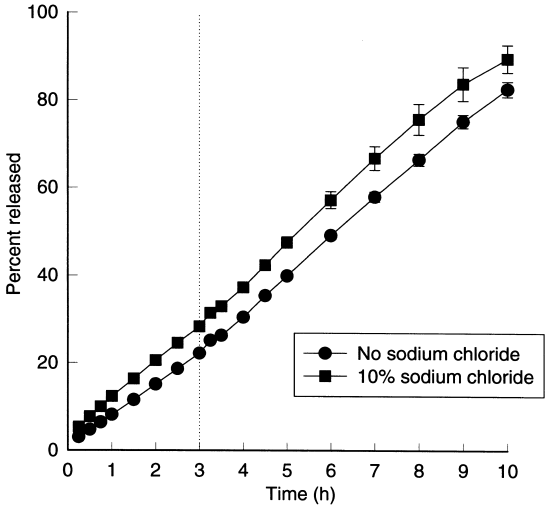

Fig. 9. Release profile of chlorpheniramine maleate from carrageenan tablets containing sodium chloride and from tablets that do not contain sodium chloride for the first 3 h in SGF followed by SIF.

line slowed and that of sodium salicylate became faster. As explained earlier, the reasons for the faster release of theophylline in SGF and sodium salicylate in SIF are because theophylline acts as a base at pH < 2 and sodium salicylate has a higher solubility in solutions of basic pH because it is in the ionized state.

At the end of 3 h, only about 22% of chlorpheniramine maleate was released from the carrageenan tablets as compared to 36% of sodium salicylate and 48% of theophylline. This unexpected slow release of chlorpheniramine maleate in SGF was also noticed by Bonferoni et al. [5,20]. The authors attributed this slow release to the possibility that λ-carrageenan, because of its strong acidic nature attributable to sulfate groups, might allow ionic polymer-drug interactions to occur in the gastric environment, especially in the case of basic drugs.

A number of competing phenomena can affect the release rate of drugs from these matrices. The solubility and basicity/acidity of the drug may confound simple effects of the pH of the dissolution media. For example the polymer is hydrolyzed at low pH values [12] and gel strength and rate of gel swelling are affected by the ionic strength of the dissolution media.

3.4.2. Effect of ionic strength of dissolution media

The effect of the ionic strength of dissolution media on drug release was studied because the extent of gelation and hence the drug release from carrageenan matrix might be affected by the concentration of ions present in the media. Fig. 8 shows the effect of ionic strength of SGF on the release of theophylline. Other experiments in our laboratory (data not shown) indicated that the release rate of all the three drugs increased with an increase in the ionic strength of SGF. The ionic strength of SIF did not have a significant effect on the release rate of either drug.

3.4.3. Effect of sodium chloride in the tablet matrix

Mono- and divalent ions like sodium and calcium have a high affinity for water molecules. The presence of the salts of these ions in controlled-release tablets could affect the gelation properties and hence the extent of drug release from the polymer. The effect of the incorporation of sodium chloride in the tablet matrix on the release of three model drugs representing neutral, acidic and basic characteristics was studied.

The effect of tablet matrix sodium chloride was significant on the release of chlorpheniramine maleate; the release rate was faster from the tablets containing sodium chloride in both SGF and SIF (Fig. 9). The reason for faster release could be because the strong electrolyte sodium chloride competes with and decreases the ionic interactions between chlorpheniramine maleate and λ-carrageenan. The effect of sodium chloride on the release rate of theophylline and sodium salicylate was negligible both in SGF and SIF.

4. Conclusion

Matrices containing carrageenan were found to be useful for tailoring the release of three model drugs for 8–12 h. Further, the release profiles approached zero-order kinetics which is usually desirable for sustained-release dosage forms. Factors such as tablet diameter, drug to carrageenan ratio, and ionic strength of the dissolution media appeared to play a role in the release of drugs from these matrices. These factors need to be taken into account when designing sustained-release dosage forms with carrageenans. The release rate increased both with tablet diameter and higher drug to carrageenan ratio. The two lubricants studied in commonly used concentrations did not affect the release rate. Drug release from theophylline and sodium salicylate tablets was insensitive to the moisture content of carrageenans, storage of tablets at 37°C/75% RH for 3 months, and incorporation of 10% sodium chloride in the tablets.

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