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Factorial Analysis of the Influence of Dissolution Medium on Drug Release From Carrageenan-Diltiazem Complexes

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Maria Cristina Bonferoni, Silvia Rossi, Franca Ferrari, Evy Stavik, Angelina Pena-Romero, Carla Caramella*

Department of Pharmaceutical Chemistry, University of Pavia, Viale Taramelli 12, 27100 Pavia, Italy

ABSTRACT This research studied the influence of buffer composition, pH, and ionic strength on the release of diltiazem hydrochloride from a complex of the drug with lambda carrageenan. Two viscosity grades of carrageenan were also compared. A factorial analysis was used to evaluate the influence of individual variables and their interactions. Both the complex solubility, measured as the drug concentration in equilibrium with the solid complex, and the drug release rate from constant surface area were considered. The increase of ionic strength significantly increased complex solubility in all the buffer systems. A significant effect of polymer grade on complex solubility was evidenced only in phosphate buffer with a pH of 6.8, indicating lower solubility of the complex when higher polymer molecular weight was involved. In most cases, drug release rate decreased when high polymer grade was involved in the complex. Ionic strength did not always have a significant effect on drug release rate and was quantitatively less important than for solubility. Ionic strength especially affected the drug release profiles. At higher ionic strength drug release was no longer constant, but decreased with time, probably because of lower polymer solubility.

KEYWORDS: lambda carrageenan; Drug-polymer complex; Diltiazem HCl; Dissolution medium pH and ionic strength; Factorial analysis

*)Corresponding author: Carla Caramella, Professor, The University of Pavia, Department of Pharmaceutical Chemistry, Viale Taramelli 12, 27100 Pavia, Italy; tel. +39-382-507385; Caramella@chifar.unipv.it

INTRODUCTION

The ionic interaction between oppositely charged drug and polymer has been proposed as a basis for controlled-release formulations [1-3]. More recently, the interaction between soluble basic drugs and lambda carrageenan, an anionic polysaccharide from algae, has been exploited for oral controlled-release matrix systems [4-6]. Release of the drug from these systems is supposed to follow a combination of matrix erosion and drug displacement due to the medium's pH or ionic strength. Carrageenan's strong acidic character , caused by the presence of sulphuric ester moieties, is probably responsible for its observed limited effect of pH on drug displacement. Theoretically then, good control of the release could also be obtained at low pH values typical of the gastric environment. However, evidence shows that the medium can affect the erosion of carrageenan matrices, which was faster in simulated gastric fluid at a pH of 1.2 than in 0.5 M of phosphate buffer with a pH of 6.8 [4]. To make the matrix tablet less sensitive to this difference, an optimized mixture of carrageenan and hydroxypropylmethylcellulose has been used for a controlled-release tablet matrix of chlorpheniramine maleate [5,6].

Another approach to the exploitation of drug-polymer interactions is based on the use of previously prepared and isolated complexes of carrageenan and the drug. Diltiazem hydrochloride (HCl), for example, reacts with lambda carrageenan in distilled water to give a slightly soluble complex. This complex has been characterized in a previous study by means of DSC (Differential scanning calorimetry) and X-ray analysis, both of which showed a significant interaction and loss of drug

crystallinity. Dialysis equilibria were also performed to quantify the binding capacity of λ carrageenan for diltiazem in water. Dialysis equilibria performed in buffered media showed no statistical difference in the amount of drug bound to the polymer with pH between 1.8 and 6.8. Instead, interaction decreased when buffer ionic strength increased, in line with the hypothesis of the prevalent ionic character of the bonds between oppositely charged polymer and drug [7].

By tabletting the diltiazem-carrageenan complex, either by direct compression or after wet granulation, it was possible to obtain controlled-release formulations compatible with once-a-day and twice-a-day administration [8].

Oral controlled-release formulations must face different pH values along the gastrointestinal tract. Ionic strength in the stomach has been estimated at about 0.11 in the unfed state, while a variability can be expected after a meal, depending on food composition. In the jejunum, the ion concentration is maintained at a constant level, probably by means of water and ions secretion; the ionic strength in the intestinal tract has been estimated at about 0.14 [9]. Therefore, it seems important to investigate the perfomance of oral controlled-release formulations under different pH and ionic strength conditions at the early stages of their development. This is particularly true when the formulation is based on an ionic complex potentially sensitive to pH and ionic strength variations.

The purpose of the present work was to study the influence of medium variables, such as pH, ionic strength and buffer composition, on solubility of the diltiazem-carrageenan complex and on drug release. The influence of polymer viscosity grade was tested by preparing complexes between diltiazem and 2 grades of carrageenan. Factorial analysis was used to evaluate, the influence of individual variables and their interactions [10,11]. Dissolution media at 3 different pH values were used: pH of 1.2, pH of 6.8, and pH of 8.2; the last value was chosen because it is above the diltiazem pKa of 7.7). To test the effect of different buffer types, both HCl/NaCl and citrate buffers were used to obtain a pH of 1.2; both citrate and phosphate buffers were used to obtain a pH of 6.8. To study the influence of buffer ions, the buffers were prepared at 2 concentrations. NaCl was used to obtain an ionic strength of either 0.1 or 0.5.. Previous studies had already assessed the effect of different cations [1], so, in the present study, only sodium salts were used to prepare buffers; further, sodium is reported as the most common ion in the upper gastrointestinal tract [9]. A block experimental design was used, in which each block was a full factorial design. As response, both the complex solubility, measured as drug concentration in equilibrium with the solid, and the drug release rate from tablets at constant surface area were considered.

MATERIALS AND METHODS

Materials

Lambda Carrageenan Viscarin GP 209 (high viscosity grade) and Viscarin GP 109 (low viscosity grade) were used (Prodotti Gianni, Milan, I).Diltiazem HCl (DTZ HCl) was obtained from Profarmaco, Milan, I.

Preparation of the complex

Diltiazem HCl and carrageenan powders in the ratio 1.6:1 (wt/wt), corresponding to the maximum binding capacity as previously calculated from the interaction isotherm [7], were blended for 15 minutes in a turbula mixer (W.Bachofen, Basel, Switzerland). The minimum amount of distilled water necessary to obtain a paste was added, and kneading was effected at 37°C for about 20 minutes. The precipitate was washed a 2-3 times with distilled water, dried overnight in an oven at 45°C, and milled (RMO Retcsh GMbH miller, Haan, Germany). The following sieve fractions were obtained: <105 µm and <45 µm. The content in diltiazem was assayed spectrophotometrically (wavelength = 238 nm) after dissolution of the complex in HCl 0.1 M; it was 61.5 % (wt/wt) with GP 209 and 60.5 % (wt/wt) with GP 109.

Dissolution media

The following buffer systems were prepared: 0.1 M and 0.05 M HCl/NaCl with a pH of 1.2; 0.1 M and 0.05 M citrate buffer with a pH of 1.2 that was adjusted with HCl, and with a pH of 6.8 that was adjusted with NaOH; 0.066 M and 0.033 M NaH_2PO_4 / Na_2HPO_4 with a pH of 6.8 and a pH of 8.2. All media were prepared by using freshly prepared bidistilled water. The ionic strength was adjusted to either 0.1 or to 0.5 by adding NaCl.

Viscosity measurements

Viscosity of 2% (wt/wt) solutions of the 2 polymer grades was assessed at 37°C in all buffers of higher concentration. A CS Rheometer (Bohlin Instruments Division, Metric Group, Cirencester, UK) equipped with a C25 coaxial cylinder system was used. Polymers were dried to constant weight at 50°C followed by the preparation of solutions that were tested immediately after hydration. Apparent viscosity at 20 and 80 s-1 shear rates was measured.

Solubility measurements

The solubility of the complex at 37°C was assessed by measuring the drug concentration in equilibrium with the solid: 100 to150 mg of diltiazem-carrageenan complex < 105 µm were incubated for 24 hours at 37°C in 20 mL of dissolution medium. The samples were quickly filtered (0.45 µm Millipore filters) and the concentration of diltiazem HCl in solution was spectrophotometrically read (238 nm).

Preparation of the tablets

The sieve fraction < 45 µm of the complex was compressed in a Perkin Elmer hydraulic press for KBr tablets with flat 10 mm punches at 5 tons for 1 minute. All surfaces of the tablets except for 1 face (0.79 cm^2 area) were coated with cellulose acetate propionate 15% in acetone.

Drug release rate measurements

The partially coated tablets were tested for diltiazem release in a USP 23 apparatus 1 at 100 rpm, 37°C, in 500 mL fluid. UV detection was performed at 238 nm wavelength (Spectracomp 602, Advanced Products, Milan, Italy).

The drug release rate was calculated by linear fitting of the release data during the first 60 minutes. The overall release curves were also fitted by means of power law equation Mt/M =ktn (12); the n parameter was estimated by logarithmic linearization.

Experimental design

The experimental design used for the solubility test is illustrated in **Table 1.**

Table 1. Investigated Variables and Their Levels

Runs	Polymer Grade	Ionic strength	Buffer concentration (M) *	Buffer	pH	Block
1	109	0.1	0.1	HCl/NaCl	1.2	
2	209	0.1	0.1	HCl/NaCl	1.2	
3	109	0.5	0.1	HCl/NaCl	1.2	
4	209	0.5	0.1	HCl/NaCl	1.2	1
5	109	0.1	0.05	HCl/NaCl	1.2	
6	209	0.1	0.05	HCl/NaCl	1.2	
7	109	0.5	0.05	HCl/NaCl	1.2	
8	209	0.5	0.05	HCl/NaCl	1.2	
9	109	0.1	0.1	Citrate	1.2	
10	209	0.1	0.1	Citrate	1.2	
11	109	0.5	0.1	Citrate	1.2	
12	209	0.5	0.1	Citrate	1.2	2
13	109	0.1	0.05	Citrate	1.2	
14	209	0.1	0.05	Citrate	1.2	
15	109	0.5	0.05	Citrate	1.2	
16	209	0.5	0.05	Citrate	1.2	
17	109	0.1	0.1	Citrate	6.8	
18	209	0.1	0.1	Citrate	6.8	
19	109	0.5	0.1	Citrate	6.8	
20	209	0.5	0.1	Citrate	6.8	3
21	109	0.1	0.05	Citrate	6.8	
22	209	0.1	0.05	Citrate	6.8	
23	109	0.5	0.05	Citrate	6.8	
24	209	0.5	0.05	Citrate	6.8	
25	109	0.1	0.066	Phosphate	6.8	
26	209	0.1	0.066	Phosphate	6.8	
27	109	0.5	0.066	Phosphate	6.8	
28	209	0.5	0.066	Phosphate	6.8	4
29	109	0.1	0.033	Phosphate	6.8	
30	209	0.1	0.033	Phosphate	6.8	
31	109	0.5	0.033	Phosphate	6.8	
32	209	0.5	0.033	Phosphate	6.8	
33	109	0.1	0.066	Phosphate	8.2	
34	209	0.1	0.066	Phosphate	8.2	
35	109	0.5	0.066	Phosphate	8.2	
36	209	0.5	0.066	Phosphate	8.2	5
37	109	0.1	0.033	Phosphate	8.2	
38	209	0.1	0.033	Phosphate	8.2	
39	109	0.5	0.033	Phosphate	8.2	
40	209	0.5	0.033	Phosphate	8.2	

- Variable not considered in the experimental design for release rate measurements.

The experimental design for release rate was identical, but the buffer concentration was not considered as variable, and it was kept at the high level. All runs were performed in duplicate to estimate the error.

Each buffer-pH combination (block) represents a 2^3 full factorial design where the effects of polymer grade, ionic strength, and buffer concentration can be estimated ("within-blocks" analysis). In the case of HCl/NaCl pH 1.2 block, buffer concentration was not considered as a factor, because adjusting ionic strength brought about a change in buffer concentration.

Moreover, 2 blocks can be combined to give a 2^4 full factorial design in cases where additional effects of pH values and different buffers can be estimated ("between-blocks" analysis). By considering blocks 1 and 2 it was possible to estimate the effect of the buffer (HCl/NaCl or citrate) at pH 1.2; by considering blocks 2 and 3 it was possible to estimate the effect of pH (1.2 or 6.8) in citrate buffer; by considering blocks 3 and 4 it was possible to estimate the effect of the buffer (citrate or phosphate) at a pH of 6.8; by considering the blocks 4 and 5 it was possible to estimate the effect of pH (6.8 or 8.2) in phosphate buffer.

The results were evaluated with the analysis of variance (ANOVA) test, by means of STATGRAPHICS® Statistical Graphic System, 6.0 (Manugistic, Inc. and Statistical Graphics Corporation).

RESULTS AND DISCUSSION

Polymer viscosity

The results of the viscosity test in different media are given in **Table 2.** As expected, the viscosity was higher for the 209 grade than for the 109 grade in all media. For each of the 2 grades, no difference could be seen between the values at pH 6.8 and 8.2. Lower viscosity values were observed at pH 1.2. No differences due to buffer type could be seen, neither between citrate and phosphate at pH 6.8, nor between HCl/NaCl and citrate at pH 1.2. At all pH values, and with all buffers, higher ionic strength corresponded to the highest viscosity.

Table 2. Viscosity Values of 2% Polymer Solutions (20 s-1 and 80 s-1 Shear Rates)

pH	Buffer	Ionic Strength	Polymer Grade	Viscosity $20s^{-1}$ (Pa.s)	Viscosity $80s^{-1}$ (Pa.s)
1.2	HCl/NaCl	0.1	109	0.205	0.139
1.2	HCl/NaCl	0.1	209	0.336	0.196
1.2	HCl/NaCl	0.5	109	0.397	0.220
1.2	HCl/NaCl	0.5	209	0.640	0.312
1.2	Citrate	0.1	109	0.227	0.150
1.2	Citrate	0.1	209	0.433	0.243
1.2	Citrate	0.5	109	0.446	0.236
1.2	Citrate	0.5	209	0.673	0.312
6.8	Citrate	0.1	109	0.612	0.369
6.8	Citrate	0.1	209	1.318	0.668
6.8	Citrate	0.5	109	1.144	0.580
6.8	Citrate	0.5	209	1.868	0.831
6.8	Phosphate	0.1	109	0.591	0.367
6.8	Phosphate	0.1	209	1.349	0.685
6.8	Phosphate	0.5	109	1.213	0.613
6.8	Phosphate	0.5	209	1.945	0.858
8.2	Phosphate	0.1	109	0.620	0.387
8.2	Phosphate	0.1	209	1.279	0.654
8.2	Phosphate	0.5	109	1.080	0.556
8.2	Phosphate	0.5	209	1.953	0.865

Solubility

Table 3 shows the effects of the considered variables on the complex solubility, expressed as diltiazem concentration in solution after 24 hours. **Table 3a** shows the analysis performed by considering the blocks one at a time ("within-blocks" analysis).

Table 3. Effects on Complex Solubility Expressed as DTZ Concentration at the Equilibrium (mg/mL)

a) Within-blocks analysis

	Average (mg/mL)	a: Polymer grade	b: Ionic strength	c:Buffer conc	Interactions
HCl/NaCl pH	2.96	Ns*	+ 1.22†		ns
Citrate pH 1.2	2.90	Ns	+ 1.153	ns	ns
Citrate pH 6.8	2.54	Ns	+ 1.01	ns	ns
Phosphate pH 6.8	2.73	- 0.389	+ 1.136	ns	ab= - 0.262
Phosphate pH 8.2	0.98	Ns	+ 0.215	- 0.453	ns

b) Between-blocks analysis

	Average (mg/mL)	A: Polymer Grade	B: Ionic strength	C: Buffer	D: pH	Interactions
pH 1.2	2.97	Ns	+ 1.26	ns		ns
Citrate buffer	2.72	Ns	+ 1.08		- 0.36	ns
pH 6.8	2.63	- 0.30	+ 1.09	+ 0.185		AB= - 0.213
Phosphate buffer	1.85	- 0.22	+ 0.69		- 1.74	AB= - 0.10 AD=+ 0.20 BD= - 0.48

† - sign means decrease in the response when the variable level changes from low to high.; + sign means increase in the response when the variable level changes from low to high.

In all cases a significant and positive effect of ionic strength can be observed. These effects were always quantitatively relevant, consisting of a variation of about 22% of the average value in the case of buffer pH 8.2 and of about 40% in all the other cases. However, it must be remembered that the ionic strength range considered here is quite large compared with the usual physiological values in the gastrointestinal tract (0.11-0.14). The positive sign of the effects due to ionic strength is in accordance with previous results [7] and with this study's assumption that more diltiazem is released when higher amounts of ions are present in the medium.

Polymer grade seems less important for complex solubility: it is significant only in phosphate buffer with a pH of 6.8. In this case the negative sign shows a lower solubility of the complex involving the polymer of higher molecular weight. A significant interaction between polymer grade and ionic strength was noticed in phosphate buffer at a pH of 6.8, indicating that the effect of polymer grade is more pronounced at higher ionic strength.

The case of phosphate buffer with a pH of 8.2 is peculiar. Not only was the effect of ionic strength lower, as previously observed, but a significant negative effect of buffer concentration was also observed. These results are at least partially attributable to lower solubility of the drug above its pKa value.

The effects determined by the analysis of combined blocks (between-blocks analysis) are shown in **Table 3b.** At a pH of 6.8 the complex solubility was higher in phosphate than in citrate buffer, perhaps because of different solubilities of phosphate and citrate salts of the drug.

pH appears to be relevant to complex solubility both in the case of citrate buffer (pH of 1.2 vs pH of 6.8) and in the case of phosphate buffer (pH 6.8 vs pH 8.2). In both cases the higher pH values correspond to lower complex solubility. The much stronger effect observed in phosphate buffer (- 1.74 compared to - 0.36 in citrate) can be attributed to lower diltiazem solubility at pH 8.2.

The interactions observed in phosphate buffer confirm the results obtained from the within-blocks analysis: the effect of polymer grade is more pronounced at a pH of 6.8 than at a pH of 8.2 (AD=+0.20), and the increase in ionic strength brings about a stronger increase in complex solubility at a pH of 6.8 than at a pH of 8.2 (BD= -0.48).

Drug release rate

Table 4 shows the effects of the considered variables on drug release rate from tablets at constant surface area. **Table 4a** shows the results of analyses performed within each block, and **Table 4b** refers to analyses performed after combining 2 blocks.

Table 4. Effects of Considered variables on Complex Dissolution Rate Expressed as Percent diltiazem Released per Minute

a) Within-blocks analysis

	Average (%/min)	a: Polymer grade	b:Ionic strength	Interactions
HCl/NaCl pH 1.2	0.095	- 0.026*	ns†	ns
Citrate pH 1.2	0.092	ns	ns	ns
Citrate pH 6.8	0.081	- 0.015	$-7.05 \cdot 10^{-3}$	ns
Phosphate pH 6.8	0.079	ns	- 0.020	ns
Phosphate pH 8.2	0.072	ns	- 0.037	ns

b) Between-blocks analysis

	Average (%/min)	A: Polymer grade	B: Ionic strength	C: Buffer	D: pH	Interactions
pH 1.2	0.093	- 0.0143	ns	ns		AC= + 0.0115
Citrate buffer	0.086	$-(8.9) \cdot 10^{-3}$	$-(5.8) \cdot 10^{-3}$		-0.0115	$BD= -(6.1) \cdot 10^{-3}$
pH 6.8	0.080	- 0.0107	- 0.0137	ns		$BC= -(6.6) \cdot 10^{-3}$
Phosphate buffer	0.069	ns	ns		ns	ns

†ns = not significant ($P<0.05$). * - sign means decrease in the response when the variable level changes from low to high.; + sign means increase in the response when the variable level changes from low to high.

Some differences can be observed in the results of the solubility test. Polymer grade is significant in 2 buffers (HCl/NaCl pH 1.2 and citrate pH 6.8) and in three combined blocks (pH 1.2, citrate buffer, and pH 6.8). As expected, in all these cases the release rate decreases when high polymer grade is involved in the complex.

On the other hand, the effect of ionic strength is not always significant and is moreover quantitatively less important than in the solubility test. Quite surprisingly, the negative sign indicates that higher ionic strengths correspond to lower release rates. The pH is significant only in citrate buffer, in which release rate decreases when pH increases from 1.2 to 6.8; at a pH of 6.8 the negative effect of ionic strength on release rate is also more pronounced (interaction BD).

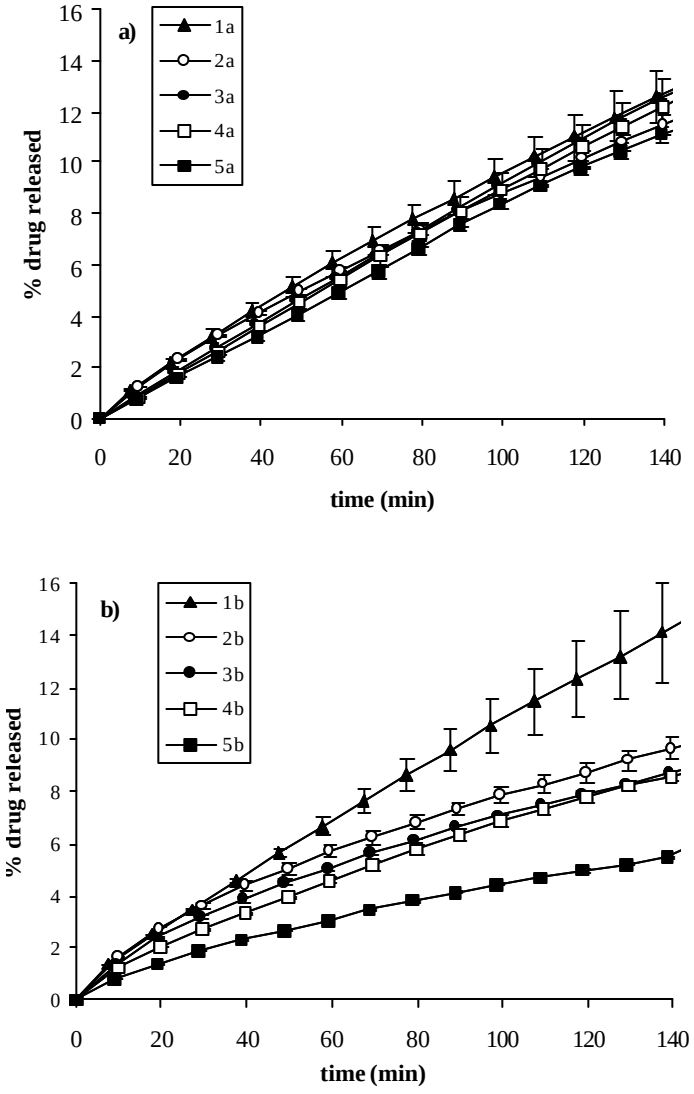

Figure 1. Drug release profiles from diltiazem-low viscosity carrageenan (GP 109) complex in different buffers at low (a) and high (b) ionic strength. HCl/NaCl 0.1 M pH 1.2 (1); citrate buffer 0.1 M pH 1.2 (2) and pH 6.8 (3); Na_2HPO_4/Na_2HPO_4 buffer 0.066 M pH 6.8 (4) and pH 8.2 (5).

These results are illustrated in **Figures 1** and **2**, which show the drug release profiles from diltiazem-carrageenan complexes (with GP 109 and GP 209, respectively) in all buffers considered. The results obtained at low (a) and high (b) ionic strength are illustrated separately. One can see that in both cases the release curves are shaped differently at the beginning of the release test, showing more pronounced curvatures at higher ionic strength. This was better quantified by interpreting the release profiles according to the power law and considering the parameter n. The results of the statistical analysis are given in **Table 5.**

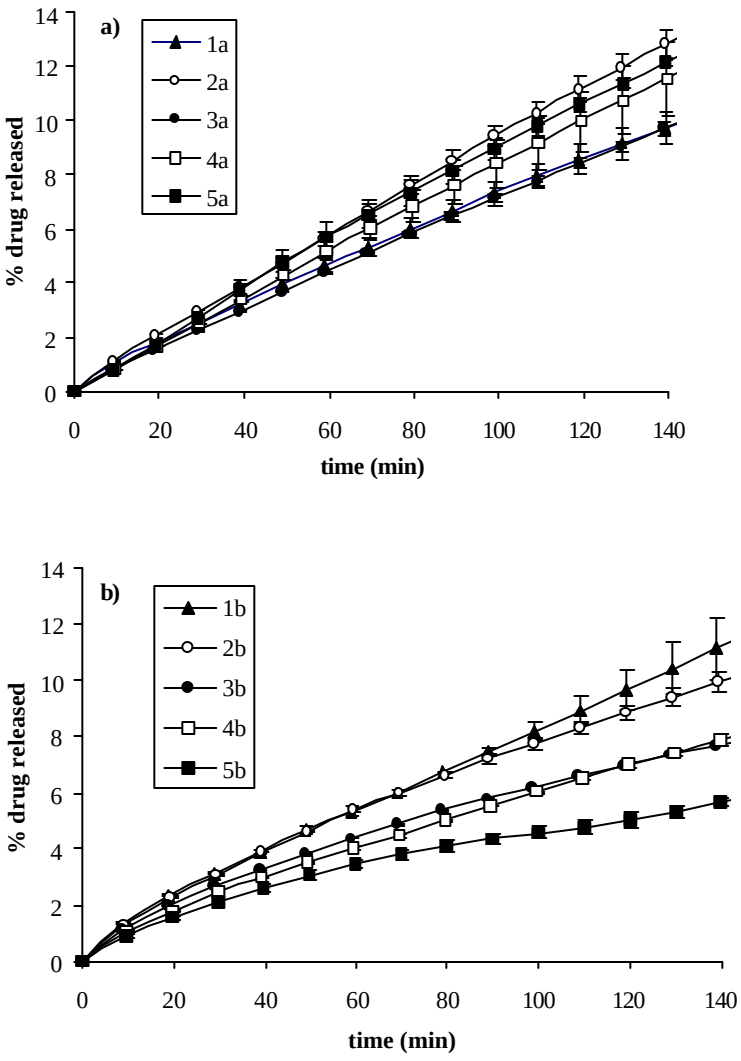

Figure 2. Drug release profiles from diltiazem-high viscosity carrageenan (GP 209) complex in different buffers at low (a) and high (b) ionic strength. HCl/NaCl 0.1 M pH 1.2 (1); citrate buffer 0.1 M pH 1.2 (2) and pH 6.8 (3); Na_2HPO_4/Na_2HPO_4 buffer 0.066 M pH 6.8 (4) and pH 8.2 (5).

Table 5: Effects on Diltiazem Release Profiles (n Exponent of the Power Law Equation)

a) Within-blocks analysis

	Average	a: Polymer grade	b: Ionic strength	Interactions
HCl/NaCl pH 1.2	0.82	ns*	ns	ns
Citrate pH 1.2	0.76	ns	ns	ns
Citrate pH 6.8	0.82	ns	- 0.274†	ns
Phosphate pH 6.8	0.88	ns	- 0.252	ns
Phosphate pH 8.2	0.85	ns	- 0.330	ns

b) Between-blocks analysis

	Average	A: Polymer grade	B: Ionic Strength	C: Buffer	D: PH	Interactions
PH 1.2	0.79	ns	ns	ns		ns
Citrate	0.79	ns	- 0.197		+ 0.053	BD= - 0.077
PH 6.8	0.85	ns	- 0.263	ns		ns
Phosphate	0.86	ns	- 0.291		Ns	ns

*ns = not significant (P<0.05).
† - sign means decrease in the response when the variable level changes from low to high.; + sign means increase in the response when the variable level changes from low to high.

The only statistically significant effect was ionic strength, where an increase reduces n parameter to values closer to those of diffusive behavior (n=0.5). It may be that the medium's ions cause a displacement of the drug yet simultaneously decrease the solubility of the polymer, which forms a diffusive layer at the tablet surface. This effect is in line with the observed higher viscosity of the polymer solutions in buffers that have high ionic strength. In these media, viscosity results suggest lower affinity of both the polymers for the hydration medium, increase in polymer-polymer interactions, and lower polymer solubility. The formation of this diffusive layer is probably impaired in acidic (pH 1.2) buffers, because, as observed in a previous paper [4], carrageenan tablets are more erodible in acidic than in neutral medium. This could explain why in the present study, the effect of ionic strength was not relevant at a pH of 1.2.

CONCLUSIONS

The solubility test shows that ionic strength is the most important factor in controlling the amount of diltiazem released at the equilibrium from its complexes with λ carrageenan. This result confirms the hypothesis that ionic interactions occur between λ carrageenan and the basic drug. However, from a quantitative point of view, it must be remembered that the range of ionic strength (0.1-0.5) considered here is quite wide in comparison with usual gastrointestinal variations.

When drug release rate is considered, the influence of polymer viscosity grade can also be observed. Ionic strength is relevant in this case, especially to diltiazem release profiles. At higher ionic strength, diltiazem release decreases with time, probably because of lower polymer solubility.

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