Binding of Chlorpheniramine Maleate to Pharmacologically Important Alginic Acid, Carboxymethylcellulose, κ-Carageenan, and ι-Carrageenan as Studied by Diafiltration

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Received 1 October 2004; accepted 30 January 2005
DOI 10.1002/app.22056
Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: The binding of cationic chlorpheniramine maleate (CPM) to the anionic water-soluble polymers (WSPs) alginic acid, carboxymethylcellulose, κ-carageenan, and ι-carageenan was evaluated by diafiltration at pH 7.5 and in the absence and presence of 0.13*M* NaCl. CPM interacted with all of the WSPs when no NaCl was present in the solution, with charge-related formation constants of around 700 M^{-1} for all of the polymers, whereas the interactions were cleaved in the presence of 0.13*M* NaCl, indicating interactions of an electrostatic nature screened by the single electrolyte. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 98: 598–602, 2005

Key words: water-soluble polymers; drug delivery systems; polysaccharides; membranes

INTRODUCTION

Chlorpheniramine maleate (CPM) is an antihistaminic drug that is effective in the clinical treatment of several kinds of allergies. The drug time effect is 4–6 h, and the usual oral dosage regime is 2–4 mg every 6–8 h in adults and 1–2 mg every 6–8 h in children. To reduce the frequency of administration, reduce the side effects, and improve patient compliance, a sustained-release formulation of CPM is desirable.[1–6] The drug is freely soluble in water, and hence, the judicious selection of release-retarding excipients is necessary to achieve a constant *in vivo* input rate of the drug. One of the most effective and commonly used methods of modulating the release of a drug is to include it in a matrix system. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery, the delivery of drugs into and through the skin, and controlled bioadhesion. The hydrophilic polymers, in contact with the dissolution medium, may swell and make a continuous gel layer, erode, or undergo a combination of these two processes. The extent of polymer swelling, relative mobility of dissolution medium and drug, and matrix erosion dictate the kinetics and mechanism of drug release. The release of a water-soluble drug from a hydrated matrix is regulated by drug diffusion through the gel network. Neutral hydrophilic polymers may be used in the formulation of drug delivery matrices, such as nonionic cellulose derivatives (e.g., methylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose), and charged polymers.

Negatively charged polymers will interact with positively charged drugs, and this interaction may be crucial in the kinetics of drug release. The measurements of the drug-binding capacities of some polyelectrolytes have been related to the release profiles of matrix tablets containing the same drug–polyelectrolyte system.[7]

Diafiltration has emerged as a useful technique to detect and quantify interactions between water-soluble polymers (WSPs) and metal ions[8–11] or, more recently, with low-molecular-weight substances.[12] This technique is based on the separation of particles with sizes greater than the diafiltration membrane pores (e.g., WSPs) from smaller molecules (e.g., drugs). The rate of filtration of the drugs under the washing method (analogous to a batch method[9–11]) is strongly influenced by their interactions with the WSP.

In this study, the washing method of the diafiltration technique was used to evaluate the binding of CPM to the negatively charged polyelectrolytes car-

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Contract grant sponsor: Fondecyt; contract grant numbers: 1020198 and 1030669.
Contract grant sponsor: Dirección de Investigación, Universidad Austral de Chile; contract grant number: S-200126.

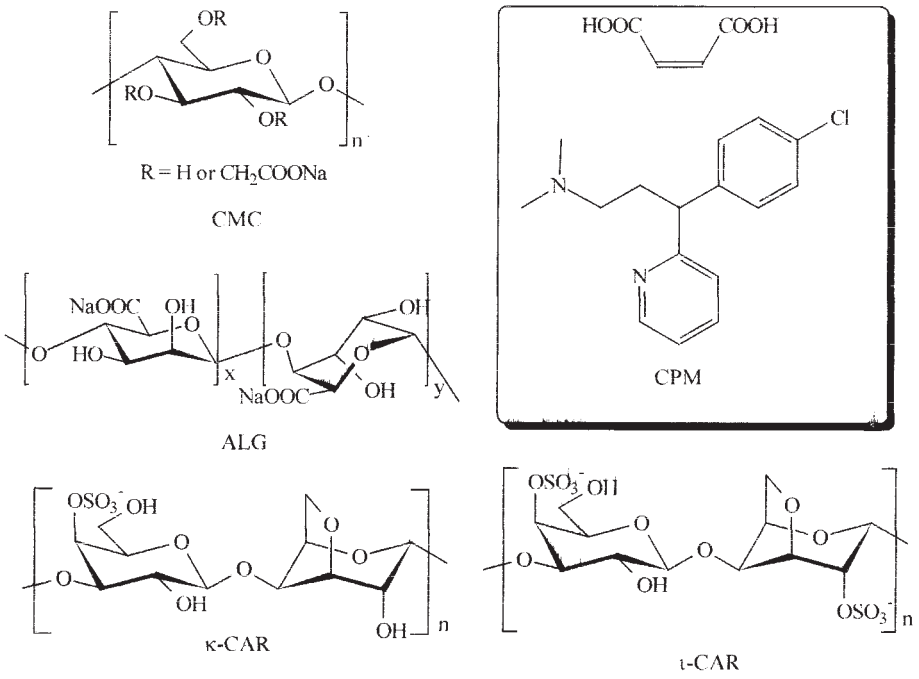

Figure 1 Molecular structures.

boxymethylcellulose (CMC), κ-carageenan (κ-CAR), ι-carageenan (ι-CAR), and alginic acid (ALG) at pH 7.5 in the absence and in the presence of 0.13*M* NaCl.

EXPERIMENTAL

Reagents

Commercially available ALG (Sigma, Santiago, Chile) and CMC (Munnich, Santiago, Chile) were fractionated by diafiltration over a membrane with a molecular weight cutoff (MWCO) of 100,000 Da (Biomax, Santiago, Chile; diameter = 63.5 mm), and the highest molecular weight fractions were selected and freeze-dried. κ-CAR and ι-CAR (Gelymar, Puerto Montt, Chile) were used without further fractionation. NaCl (Merck, Santiago, Chile) and CPM (Munnich, provided as a racemic mixture) were used to prepare the solutions. The structures of ALG, CMC, κ-CAR, ι-CAR, and CPM are shown in Figure 1. The pH was adjusted with NaOH and HCl (Merck).

Equipment

The unit used for the diafiltration studies consisted of a filtration cell (Amicon 8010, Santiago, Chile, 10-mL capacity) with a magnetic stirrer; a poly(ether sulfone) membrane with a MWCO of 5000, 10,000, or 100,000 Da (Biomax, 25 mm diameter); a reservoir; a selector; and a pressure source. The pH was controlled on a Quimis (Santiago, Chile) Q400M2 pH meter. Ultraviolet–visible (UV–vis) experiments and analyses were performed on a UNICAM (Santiago, Chile) UV5 spectrophotometer at 20°C and with a path length of 1 cm.

Procedure for diafiltration

The corresponding polymers (ALG, CMC, κ-CAR, and ι-CAR) were dissolved in twice-distilled and then deionized water together with NaCl and CPM to obtain the concentrations shown in Table I. The polymer concentrations (in monomeric units were calculated with the following molecular weights): ALG MW = 198, corresponding to a dehydroguluronic sodium salt analogue; CMC MW = 240, corresponding to a dehydromonomethylcarboxylated monosaccharide in its sodium salt form; κ-CAR MW = 408, corresponding to a dehydromonosulfated disaccharide; and ι-CAR MW = 510, corresponding to a dehydrodisulfated disaccharide. The solutions (10 mL) were placed into the diafiltration cell. The pH and the NaCl concentration in the aqueous solution contained in the reservoir were adjusted to the same value as in the cell solution. So no macromolecule was filtered, the filtration runs were carried out over a membrane with a MWCO of 5000 or 10,000 Da under a total pressure of 3 bar, with the solution volume in the cell kept constant by the creation of a continuous flux of liquid through the cell solution from the reservoir. Filtration fractions were collected (see Table I), and the drug concentrations were analyzed by UV–vis spectroscopy. The absence of CAR in the filtrate was checked by the

TABLE I
Values of the Experimental Variables for The Diafiltration Experiments and Linear Adjustments for the Corresponding Results

Experiment	NaCl concentration (M)[a]	Polymer monomeric unit concentration (M)	ΔF (mL)	Linear adjustments for the experimental data	R^2
Blank-01	—	—	0.71	$y = -1.055x - 6.4203$	0.9990
Blank-02	0.13	—	0.65	$y = -1.003x - 6.6243$	0.9992
ALG-01	—	0.002	0.73	$y = -0.4485x - 7.5066$	0.9924
ALG-02	0.13	0.002	0.74	$y = -1.0017x - 6.5561$	0.9998
CMC-01	—	0.002	0.82	$y = -0.4645x - 7.4768$	0.9984
CMC-02	0.13	0.002	0.53	$y = -1.0129x - 6.9356$	0.9982
κ-CAR-01	—	0.002	0.75	$y = -0.4327x - 7.6028$	0.9826
κ-CAR-02	0.13	0.002	0.65	$y = -0.9965x - 6.7097$	0.9929
ι-CAR-01	—	0.002	0.76	$y = -0.2776x - 8.3871$	0.9918
ι-CAR-02	0.13	0.002	0.55	$y = -0.9821x - 6.7652$	0.9919

$y = \ln \langle c_{CPM}^{filtrate} \rangle_i$, $x = F$; R^2 = linear regression factor. The initial CPM concentration was 0.001M for all of the experiments. The pH was 7.5 in both the cell and the reservoir solutions.
[a] Values for both the cell solution and the reservoir solution.

addition of methylene blue followed by UV–vis analysis.[13] Blank experiments were performed with the same procedure in the absence of the WSP (Table I). For CPM analyses, calibration curves were obtained at the conditions given in Table II.

RESULTS AND DISCUSSION

The WSPs used in this study showed different characteristics. ALG is a naturally occurring polymer bearing carboxylic groups in its structure. It is a linear polysaccharide containing diequatorially 1,4-linked β-D-mannuronic and diaxially 1,4-linked α-L-guluronic acid residues arranged in a nonregular, blockwise order around the chain. CMC is a carboxylated derivative of cellulose that presents its carboxylic groups separated from the main polysaccharide chain by a methylene group. The polyelectrolyte character of all of these polymers is sensitive to pH. Carageenan is a sulfated polymer and, therefore, has strong electrolyte character, so it is fully deprotonated in a wide range of pH values. The chemical repeat of ι-CAR may be written as →3)—A—(1→4)—B—(1→, where A and B represent β-D-Gal-4-SO_3^- and 3,6-anhydro-α- D-Gal-2-SO_3^-, respectively. κ-CAR also has the same sequence, except that its anhydride residue does not possess a sulfate moiety. It bears one sulfate group every dimeric repeat unit, whereas ι-CAR bears two. The interaction of CPM with these polymers was studied at pH 7.5, which is the pH of the small intestine. At this pH, most carboxylic units are deprotonated and so negatively charged, whereas CPM is positively charged due to its amino groups.

The diafiltration experiments showed an exponential decay of the CPM concentration in the filtrate when it was plotted versus the filtration factor (F). We measured the concentration of CPM in the i volume equivalent fractions of volume ΔV_i ($\langle c_{CPM}^{filtrate} \rangle_i$), which followed the equation

$$\langle c_{CPM}^{filtrate} \rangle_i = \langle c_{CPM}^{filtrate} \rangle^{init} \exp(-jF) \quad (1)$$

where F is defined as the ratio of the volume of the filtrate (V^f) versus the volume in the cell (V^{cell}; $V^f/V^{cell} = \Sigma \Delta V_i / V^{cell}$) and "init" refers to the initial values (at $F = 0$). Figure 2 shows the experimental profiles and the corresponding linear adjustments. The analytical expressions of these adjustments are given in Table I. The j parameter provides a measure of the system resistance to solute permeation.[11] If this resistance is only attributed to the membrane, this parameter is named the sieving coefficient (k^m). To obtain insight into the influence of the membrane on the system resistance to CPM permeation, we performed blank experiments (in the absence of the WSPs). Negligible

TABLE II
Calibration Curves for the UV–Vis Spectroscopic Analyses

Molecule	NaCl concentration (M)	Calibration curve	R^2	pH	Concentration range (M)
CPM	—	$y = 5040.3x$	1.00	7.5	2×10^{-5} to 4×10^{-4}
CPM	0.13	$y = 5200.8x$	1.00	7.5	2×10^{-5} to 4×10^{-4}

y = absorbance; x = [CPM]; R^2 = linear regression factor at 262 nm.

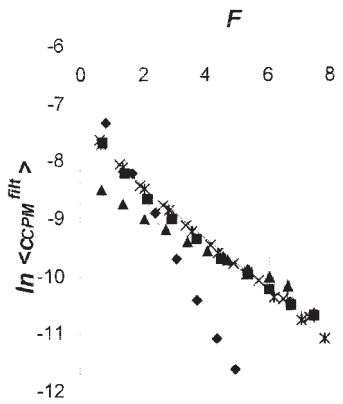

Figure 2 Elution profiles of CPM in the absence of NaCl: (♦) blank experiment, (■) κ-CAR, (▲) ι-CAR, (×) ALG, (*) CMC, and (—) linear tendencies. (See Table I for conditions and linear adjustments.)

interactions between the diafiltration system and CPM, both in the presence and in the absence of 0.13*M* NaCl, were found because the j values (or k^m values) were very close to 1 (see Tables I and III).

The WSP may be considered as another component of the diafiltration system. For the next of the discussion, some assumptions were made: (1) the diafiltration system was a steady-state, mixed-flow reactor; (2) the amount of drug bound to the membrane or other cell components, excluding the WSP, was negligible; and (3) the effect of the interaction of the WSP with the cell components was negligible so that k^m was constant whatever the solute concentration was and independently of the presence of the WSP for given conditions of pH and ionic strength. Under these assumptions, we defined the concentration of drug-free molecules in the solution ($c_{\text{CPM}}^{\text{free}}$) as the concentration of molecules that were able to pass through the diafiltration membrane and the instantaneous concentration of the drug bound to the WSP ($c_{\text{CPM}}^{\text{bound}}$) as the concentration of molecules that were attracted to the polymer with such a strength that would not pass through the diafiltration membrane. Considering then that $c_{\text{drug}}^{\text{cell}} = c_{\text{CPM}}^{\text{bound}} + c_{\text{CPM}}^{\text{free}}$, we obtained the distributions of CPM bound to the polymer or free in solution, respectively, by the following expressions:

$$c_{\text{CPM}}^{\text{bound}} = \frac{c_{\text{CPM}}^{\text{cell-init}}}{k^m}[k^m u + (k^m - j)v \exp(-jF)] \quad (2)$$

$$c_{\text{CPM}}^{\text{free}} = \frac{c_{\text{CPM}}^{\text{cell-init}}}{k^m} jv \exp(-jF) \quad (3)$$

where $c_{\text{CPM}}^{\text{cell-init}}$ is the feed concentration of CPM in the cell:

$$v = -\frac{\langle c_{\text{CPM}}^{\text{filtrate}}\rangle^{\text{init}} \Delta F}{c_{\text{CPM}}^{\text{cell-init}}[1 - \exp(j\,\Delta F)]} \quad (4)$$

$$u + v = 1 \text{ and } \Delta F = \Delta V_i / V^{\text{cell}}$$

The charge-related formation constant (K_f^{ξ}) of the CPM–polymer complex was defined[12] as

$$K_f^{\xi} = \frac{(c_{\text{CPM}}^{\text{bound}})_{\text{rev}}}{[\text{L}^-]c_{\text{CPM}}^{\text{free}}} = \frac{kj}{[\text{L}^-]j} \quad (5)$$

where $(c_{\text{CPM}}^{\text{bound}})_{\text{rev}} = c_{\text{CPM}}^{\text{bound}} - c_{\text{CPM}}^{\text{cell-init}} u$ and $[\text{L}^-]$ corresponds to the effective concentration of charged functional groups in the solution. This allowed us to calculate and compare the relative strength of the charged groups toward the binding of CPM.

By means of eqs. (1)–(5), K_f^{ξ}'s for the different CPM–WSP systems were calculated. As the sulfate groups of the CARs were strong electrolytes, the corresponding $[\text{L}^-]$ was given by the concentration in disaccharide units for κ-CAR (0.002*M*) and double for ι-CAR (0.004*M*). Assuming that at pH 7.5 all carboxylate groups were deprotonated so that the $[\text{L}^-]$ for ALG and CMC was 0.002*M*, it is shown in Table III that the calculated K_f^{ξ}'s were very similar when the different WSPs were compared when no NaCl was present in the solution. As the interaction seemed to be only dependent on the amount of charges on the polymer,

TABLE III
Diafiltration Experimental Parameters and Apparent K_f^{ξ} Values

Experiment	v	u	j	k^m	K_f^{ξ} (M^{-1})
Blank-01	1.04	−0.04	—	1.055	—
Blank-02	0.99	0.01	—	1.003	—
ALG-01	1.04	−0.04	0.449	1.055	676
ALG-02	0.96	0.04	1.002	1.003	→0
CMC-01	1.00	0.00	0.465	1.055	636
CMC-02	0.73	0.27	1.013	1.003	→0
CAR κ-01	0.98	0.02	0.433	1.055	719
CAR κ-02	0.87	0.13	0.997	1.003	→0
CAR *t*-01	0.74	0.26	0.278	1.055	700
CAR *t*-02	0.89	0.11	0.982	1.003	→0

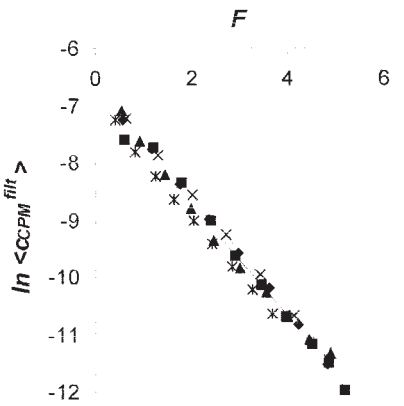

Figure 3 Elution profiles of CPM in the presence of 0.13*M* NaCl: (♦) blank experiment, (■) κ-CAR, (▲) ι-CAR, (×) ALG, (*) CMC, and (—) linear tendencies. (See Table I for conditions and linear adjustments.)

we inferred that the nature of the interaction was mainly electrostatic because additional attractive interactions should have yielded higher formation constants.

As electrostatic interactions are sensitive to the presence of other ions in solution, experiments were performed in the presence of an excess of NaCl. If Figure 3 and Table I are analyzed, one can see that the corresponding elution profiles were very similar to those of the blank experiments. Then, the interaction of CPM with all the WSPs was cleaved by the presence of 0.13*M* NaCl (which afforded an ionic strength comparable to that of the small intestine) due to screening effects and competition of the large excess of Na^+ to bind the polyelectrolyte surfaces.

CONCLUSIONS

The interactions of CPM with the negatively charged polyelectrolytes CMC, κ-CAR, ι-CAR, and ALG were studied at pH 7.5 in the absence and presence of 0.13*M* NaCl by the washing method of the diafiltration technique. If the effect of the interactions of the WSP with the diafiltration cell components was neglected, we found that CPM interacted with all the WSPs when no NaCl was present in the solution, with K_f^{ξ}'s of around 700 M^{-1} for all of the polymers. These interactions were cleaved in the presence of 0.13*M* NaCl. This fact and the similarity of the K_f^{ξ}'s, may indicate that the nature of the interaction was mainly electrostatic.

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