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SCIENCE DIRECT
Polymer 46 (2005) 7240–7245
polymer
www.elsevier.com/locate/polymer

Comparison between the binding of chlorpheniramine maleate to poly(sodium 4-styrenesulfonate) and the binding to other polyelectrolytes

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Received 5 January 2005; received in revised form 26 May 2005; accepted 13 June 2005
Available online 19 July 2005

Abstract

The interactions of the antihistaminic drug chlorpheniramine maleate (CPM) with the negatively charged polyelectrolytes poly(sodium 4-styrenesulfonate) (PSS) and poly(acrylic acid) (PAA) are studied by the washing method of the diafiltration technique at conditions simulating those of the small intestine such as pH 7.5 and 0.13 M NaCl. The results are compared with those already reported involving other pharmacologically important polyelectrolytes such as alginic acid (ALG), carboxymethylcellulose (CMC), and κ- and ι-carrageenan (κ- and ι-CAR). As in the case of ALG, CMC, and CAR, interactions of CPM with PAA appear to be electrostatic and are cleaved in the presence of 0.13 M NaCl. On the contrary, apart from electrostatic interactions, additional interactions are found with PSS and residual interactions are kept in the presence of 0.13 M NaCl, a fact that may be attributed to π–π interactions and hydrophobic forces. The effect of the addition of 4 M urea, branched poly(ethyleneimine) (BPEI), and poly(vinylpyrrolidone) (PVP) is also studied. The addition of urea 4 M or 0.001 M BPEI produces a decrease on the amounts of counterions bound to PSS at infinite elution, while the addition of PVP does not produce any change on the diafiltration profiles.

Keywords: Chlorpheniramine maleate; Ultrafiltration-diafiltration; Water-soluble polymers

1. Introduction

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery systems because of their ability to obtain desirable drug release profiles, cost-effectiveness, and broad regulatory acceptance [1–12]. The release of the drug from a pharmaceutical form is mediated by the ability of the matrix to hydrate, swell and erode, as well as by diffusion of the water-soluble drug through the hydrophilic gel network thus formed. Neutral hydrophilic polymers are widely used in the formulation of drug delivery matrices as non-ionic cellulose derivatives (methylcellulose (MC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), etc.). They are biologically compatible and nontoxic, easily compressible, and hydrate rapidly at body temperature. They accommodate a large percentage of the drug with negligible influence of the processing variables on the release rates.

Specific interactions between the drug and the excipients including the hydrophilic polymers may be important in the diffusion of the drug through the gel [10]. In this context, negatively charged macromolecules produce interactions with positively charged drugs that may be crucial in the kinetics of the drug release. Moreover, the use of these anionic polyelectrolytes in drug delivery systems may provide mucoadhesivity, by means of chemical interactions with the mucus in mucous membranes. Measurements of the drug binding capacities of some polyelectrolytes were related to the release profiles of matrix tablets containing the same drug—polyelectrolyte system [10]. In a previous paper [13] we have described that the respective strengths of the interactions (relative to the number of charges) of some

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0032-3861/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.polymer.2005.06.033

natural water-soluble polymers (WSP) as alginic acid (ALG), and κ- and ι-carrageenan (κ- and ι-CAR) or the semisynthetic carboxymethylcellulose (CMC) with chlorpheniramine maleate (CPM) at pH 7.5 are very similar. It was also found that the respective interactions were cleaved in the presence of 0.13 M of NaCl. These facts give account of electrostatic interactions, which are nonspecific towards the nature of the WSP, but dependent on the total number of charges, and very sensitive to changes on the ionic strength.

The search of more specific interactions is interesting in order to achieve a better control of drug release kinetics. These interactions may be expected to deal with hydrophobic interactions due to the hydrocarbon nature of drugs and water-soluble polyelectrolytes, hydrogen bond formation, or molecular stacking. Diafiltration has emerged as a useful technique to detect and quantify interactions between WSP and low molecular-weight molecules [14–20]. This technique is based on the separation of particles whose size is greater than the diafiltration membrane pores (as WSP) from smaller molecules (as drugs). The rate of filtration of the drug under the washing method (analogue to a batch method) is strongly influenced by its interactions with the WSP. We have previously described the mathematical paths to obtain a dissociation constant for the system drug-WSP (K_{drug}^{diss}) defined as the ratio between the concentration of the drug free in solution versus the concentration of the drug reversibly bound to the polymer [19,20]. By comparison with chromatography, we can name linear diafiltration the diafiltration process in which these two magnitudes keep proportional in a large concentration range (normally before polymer saturation). Using the diafiltration technique, attempts to elucidate the nature of the interaction have been made in order to distinguish electrostatic interactions from other interactions [21,22].

In this paper, the interactions of the antihistaminic drug chlorpheniramine maleate (CPM) with the negatively charged polyelectrolytes poly(sodium 4-styrenesulfonate) (PSS) and poly(acrylic acid) (PAA) are studied at pH 7.5 by the washing method of the diafiltration technique, and thus compared. The effect of the addition of 0.13 M NaCl, 0.4 M urea, branched poly(ethyleneimine) (BPEI), and poly(vinylpyrrolidone) (PVP) is also studied.

2. Experimental section

2.1. Reagents

Commercially available poly(sodium 4-styrenesulfonate) (PSS) (Aldrich, synthesized from the para-substituted monomer), poly(acrylic acid) (PAA) (Aldrich), branched poly(ethyleneimine) (BPEI) (Aldrich), and poly(vinylpyrrolidone) (PVP) (Merck) were purified and fractionated by diafiltration over a membrane of a molecular weight cut-off (MWCO) of 100,000 Da (Biomax, 63.5 mm diameter), first in the presence of 0.15 M $NaNO_3$ and then in the absence of the electrolyte. For each polymer, the highest molecular-weight fraction was selected and freeze-dried. $NaNO_3$ (Merck), NaCl (Merck), urea (Aldrich) and chlorpheniramine maleate (CPM) (Munnich, provided as a racemic mixture) were used to prepare the solutions without further purification. The structures of CPM and PSS, PAA, BPEI, and PVP are shown in Fig. 1. The pH was adjusted with NaOH and HCl.

2.2. Equipment

The unit used for diafiltration studies consisted of a filtration cell (Amicon 8010, 10 ml capacity) with a magnetic stirrer, a polyethersulfone membrane with a MWCO of 10,000 Da (Biomax, 25 mm diameter), a reservoir, a selector, and a pressure source. The pH was controlled with a Quimis Q400M2 pH meter. UV–vis experiments and analyses were performed in a Unicam UV 500 spectrophotometer at room temperature and 1 cm of path length.

2.3. Procedure for diafiltration

The corresponding fractionated polymers were dissolved in twice distilled and then deionized water together with NaCl, urea, and/or CPM to obtain the concentrations shown in Table 1. The solutions (10 ml) were placed into the diafiltration cell. The pH value and the urea and NaCl concentrations in the aqueous solution contained in the reservoir were adjusted to the same value as in the cell solution. In order no macromolecule is filtered, the filtration runs were carried out over a membrane with a molecular weight cut-off of 10,000 Da under a total pressure of 3 bar, keeping constant the solution volume in the cell by creating a continuous flux of liquid through the cell solution from the reservoir. Filtration fractions (ranging between 6.0 and 8.0 ml) were collected and the drug concentrations analyzed by UV–vis spectroscopy. Blank experiments were performed with the same procedure, in the absence of any WSP (Table 1). For CPM analyses, calibration curves were obtained at the conditions given in Table 2. Three replicates were done for every experiment.

3. Results and discussion

In order to study and compare the relative strength of the different WSP to bind a drug, the corresponding apparent dissociation constants [19,20] for the binding equilibrium may be calculated as

$$K_{drug}^{diss} = \frac{c_{drug}^{free}}{(c_{drug}^{bound})_{rev}} = \frac{j}{k^{m} - j} \quad (1)$$

where c_{drug}^{free} is the concentration of drug free in the solution, $(c_{drug}^{bound})_{rev}$ is the concentration of drug reversibly bound to