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

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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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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

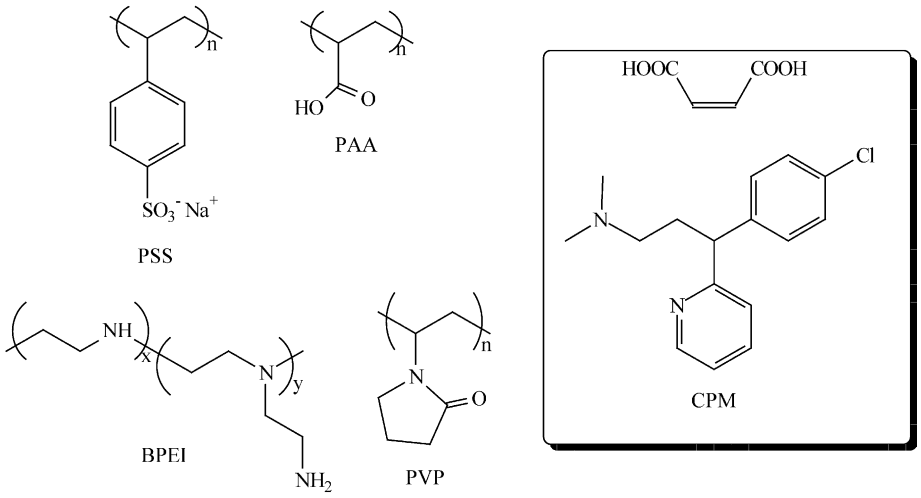

Fig. 1. Molecular structures.

the WSP or other diafiltration cell components, j and k^{m} are, respectively, the slopes of the plots of the $\ln\langle c_{\mathrm{drug}}^{\mathrm{filtrate}}\rangle$ versus the filtration factor (F) for the experiment in the presence of the WSP and the blank experiment, provided that $1 \geq k^{\mathrm{m}} \geq j$. $\langle c_{\mathrm{drug}}^{\mathrm{filtrate}}\rangle$ is the concentration of drug in the volume equivalent filtration fractions, and F is defined as the volume ratio of the filtrate versus the volume in the diafiltration cell. Higher $K_{\mathrm{drug}}^{\mathrm{diss}}$ indicates a weaker interaction between the WSP and the drug. It has been shown [19,20] that the drug equilibrium distribution is given by the following system:

$$c_{\mathrm{drug}}^{\mathrm{bound}} = (c_{\mathrm{drug}}^{\mathrm{bound}})_{\mathrm{irrev}} + (c_{\mathrm{drug}}^{\mathrm{bound}})_{\mathrm{rev}} = \frac{c_{\mathrm{drug}}^{\mathrm{cell-init}}}{k^{\mathrm{m}}}[k^{\mathrm{m}}u + (k^{\mathrm{m}} - j)v\exp(-jF)] \quad (2)$$

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

where $c_{\mathrm{drug}}^{\mathrm{cell-int}}$ is the initial concentration of the drug in the diafiltration cell, $(c_{\mathrm{drug}}^{\mathrm{bound}})_{\mathrm{irrev}}$ is the concentration of drug irreversibly bound to the WSP or other diafiltration cell

Table 1
Values of the experimental variables for diafiltration experiments

Experiment	PSS conc. (momom. units) (M)	PAA conc. (momom. units) (M)	BPEI conc. (momom. units) (M)	PVP conc. (momom. units) (M)	NaCl conc.[a] (M)	Urea conc.[a] (M)
Blank-01	–	–	–	–	–	–
Blank-02	–	–	–	–	0.13	–
Blank-03	–	–	–	–	–	4
Blank-04	–	–	–	–	0.13	4
PSS-01	0.002	–	–	–	–	–
PSS-02	0.002	–	–	–	0.13	–
PSS-03	0.002	–	–	–	–	4
PSS-04	0.002	–	–	–	0.13	4
PSS-05	0.002	–	0.001	–	–	–
PSS-06	0.002	–	0.001	–	0.13	–
PSS-07	0.002	–	–	0.001	–	–
PSS-08	0.002	–	–	0.001	0.13	–
PAA-01	–	0.002	–	–	–	–
PAA-02	–	0.002	–	–	0.13	–
PAA-03	–	0.002	0.001	–	–	–
PAA-04	–	0.002	0.001	–	0.13	–
PAA-05	–	0.002	–	0.001	–	–
PAA-06	–	0.002	–	0.001	0.13	–
BPEI-01	–	–	0.002	–	–	–
BPEI-02	–	–	0.002	–	0.13	–
PVP-01	–	–	–	0.002	–	–
PVP-02	–	–	–	0.002	0.13	–

Initial [CPM] is 0.001 M and the pH is 7.5 in all experiments.
[a] Values for both the cell solution and the reservoir solution.

Table 2
Calibration curves for UV–vis spectroscopic analyses: y=absorbance at 262 nm; x=[CPM]; R^2=linear regression factors were 1.00

NaCl conc. (M)	Urea conc. (M)	Calibration curve
–	–	$y=5040.3x$
0.13	–	$y=5200.8x$
–	4	$y=5340.0x$
0.13	4	$y=5254.4x$

The pH was 7.5. The CPM concentration range was $[2\times10^{-5}, 4\times10^{-4}]$ M.

components in every instant, u and v are constants that are also calculated from the plot of the $\ln\langle c_{\text{drug}}^{\text{filtrate}}\rangle$ versus F, and $u+v=1$.

The structures of the water-soluble polymers used in this study are shown in Fig. 1. PSS is a strong polyelectrolyte and is completely dissociated at pH 7.5. PAA is a weak polyelectrolyte, and around an 80% of the carboxylate groups are dissociated at pH 7.5 [23,24]. Electrostatic interactions between both polymers with CPM are expected. The diafiltration profiles of the drug in the presence of PSS and PAA are shown in Figs. 2 and 3, respectively. Filled symbols refer to experiments done in the absence of NaCl. By comparison with blank experiments the corresponding interactions may be quantified. From the j and k^{m} values found, the apparent dissociation constants are calculated following Eq. (1) as can be seen in Table 3 for the different experiments. Note that this constant is lower for PSS than for PAA. The respective isotherms are constructed in Fig. 4 applying Eqs. (2) and (3), and they clearly show that the binding fraction of CPM is much larger for PSS than for PAA. In order to compare the relative strength of the charged groups from different polymers to bind a counterion we have defined the charge related formation constant [21] of the corresponding complexes as

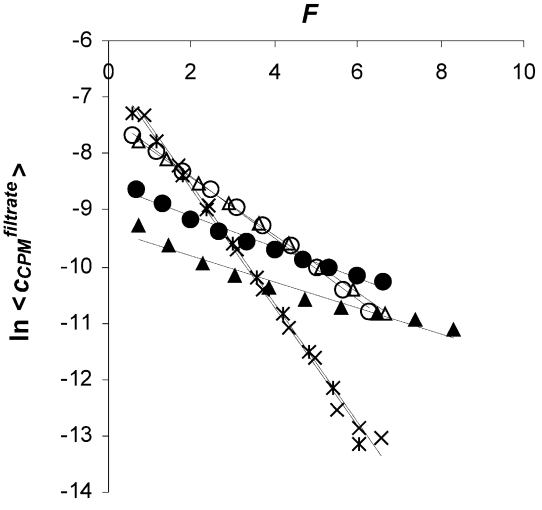

Fig. 2. Diafiltration graphs for experiments: (×) blank-01; (✳) blank-02; (▲) PSS-01; (△) PSS-02; (●) PSS-03; (○) PSS-04.

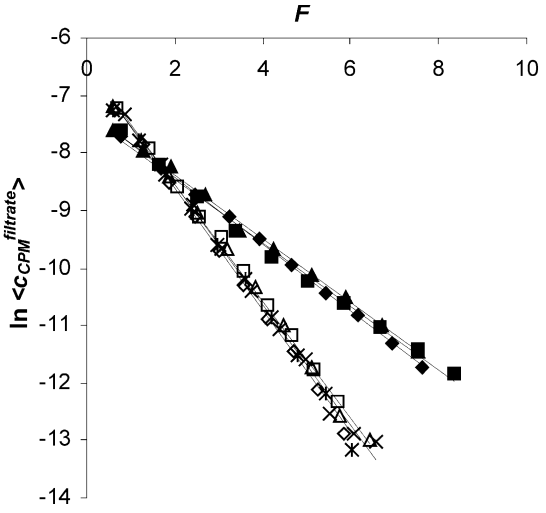

Fig. 3. Diafiltration graphs for experiments: (×) blank-01; (✳) blank-02; (▲) PAA-01; (△) PAA-02; (■) PAA-03; (□) PAA-04; (♦) PAA-05; (◇) PAA-06.

$$K_{\text{f}}^{\xi}=\frac{(c_{\text{drug}}^{\text{bound}})_{\text{rev}}}{[L^-]c_{\text{drug}}^{\text{free}}}=\frac{k^{\text{m}}-j}{[L^-]j}=\frac{k^{\text{m}}-j}{\alpha c^{\text{p}} j} \tag{4}$$

where $[L^-]$ corresponds to the effective concentration of charged functional groups in the solution, c^{p} is the polymer concentration in mole of monomeric units per liter, and thus α is the dissociation degree of the polyelectrolyte. In a previous work [13] we have described how the respective charge related formation constant of some water-soluble polyanions—CPM complexes at pH 7.5 are very similar, ranging between 636 and 719 M^{-1}. Assuming that for PAA α is 0.8, $K_{\text{f}}^{\xi}=560\ \text{M}^{-1}$, while for PSS α is 1 and then $K_{\text{f}}^{\xi}=1786\ \text{M}^{-1}$. These values are compared in Fig. 5. The high value of this constant for PSS, related with the high binding fraction of the drug to the polymer, may indicate some additional interactions apart from electrostatic interactions. In order to establish if hydrogen bonds are formed, urea is added up to a concentration of 4 M to both

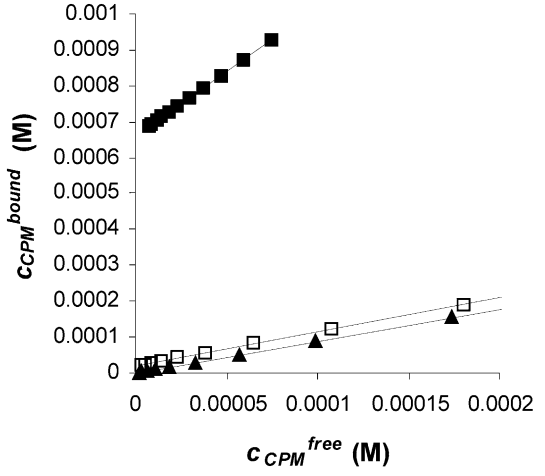

Fig. 4. Isotherms for experiments: (■) PSS-01; (□) PSS-02; (▲) PAA-01.

Table 3
Linear adjustments for the corresponding diafiltration results, experimental parameters, and apparent dissociation constants: $y = \ln\langle c_{CPM}^{filtrate}\rangle$; $x = F$; linear regression factors were higher than 0.95

Experiment	Linear adjustments for the experimental data	v	u	j	k^m	K_{CPM}^{diss}
Blank-01	$Y = -1.06x - 6.42$	0.99	0.01	–	1.06	–
Blank-02	$y = -1.00x - 6.62$	0.94	0.06	–	1.00	–
Blank-03	$y = -0.99x - 6.46$	1.07	−0.07	–	0.99	–
Blank-04	$y = -1.01x - 6.61$	0.96	0.04	–	1.01	–
PSS-01	$y = -0.23x - 9.34$	0.34	0.66	0.23	1.06	0.28
PSS-02	$y = -0.51x - 7.40$	0.98	0.02	0.51	1.00	1.04
PSS-03	$y = -0.28x - 8.54$	0.48	0.52	0.28	0.99	0.39
PSS-04	$y = -0.55x - 7.30$	1.04	−0.04	0.55	1.01	1.17
PSS-05	$y = -0.29x - 8.90$	0.42	0.58	0.29	1.06	0.38
PSS-06	$y = -0.59x - 7.25$	0.95	0.05	0.59	1.00	1.42
PSS-07	$y = -0.25x - 9.30$	0.34	0.66	0.25	1.06	0.30
PSS-08	$y = -0.55x - 7.27$	0.90	0.1	0.55	1.00	1.21
PAA-01	$y = 0.56x - 7.26$	1.02	−0.02	0.56	1.06	1.12
PAA-02	$y = -1.00x - 6.54$	1.02	−0.02	1.00	1.00	→ ∞
PAA-03	$y = -0.56x - 7.33$	0.92	0.08	0.56	1.06	1.13
PAA-04	$y = -1.01x - 6.49$	1.1	−0.1	1.01	1.00	→ ∞
PAA-05	$y = -0.58x - 7.26$	0.95	0.05	0.58	1.06	1.22
PAA-06	$y = -1.07x - 6.49$	0.98	0.02	1.07	1.00	→ ∞
BPEI-01	$y = -0.79x - 6.89$	1.01	−0.01	0.79	1.06	2.91
BPEI-02	$y = -0.86x - 6.77$	0.98	0.02	0.86	1.00	6.13
PVP-01	$y = -1.04x - 6.53$	0.91	0.09	1.04	1.06	→ ∞
PVP-02	$y = -1.04x - 6.52$	0.99	0.01	1.04	1.00	→ ∞

the initial cell solution and the reservoir solution. As can be seen in Fig. 2, the effect of urea in the solution is noted as a decrease on the amount of CPM irreversibly bound to the polymer (reflected in an increase on the ordinate at the origin for the diafiltration profile), but not in a change on the equilibrium constant since the slope of the diafiltration profile remains practically unchanged.

Electrostatic interactions are easily screened by the presence of simple electrolytes. NaCl was added to both the initial cell solution and the reservoir reaching a 0.13 M concentration, a concentration similar to that of the 1/1 electrolytes in the small intestine. It can be seen in Fig. 3 (open symbols) that the interaction is completely screened in the case of PAA, but not in the case of PSS (Figs. 2 and 4). This constitutes another evidence of the existence of other interactions apart from electrostatic interactions in the case of PSS which is comparatively illustrated in Fig. 5. These additional interactions may be attributed to hydrophobic interactions in which the presence of the aromatic ring plays a crucial role. The possibility of π–π interactions and molecular stacking is pointed out. This finding may be useful in the design of modified release matrices.

On the other hand, positively charged polyelectrolytes may compete with CPM to bind anionic polyelectrolytes. BPEI was added to the initial solutions, preventing

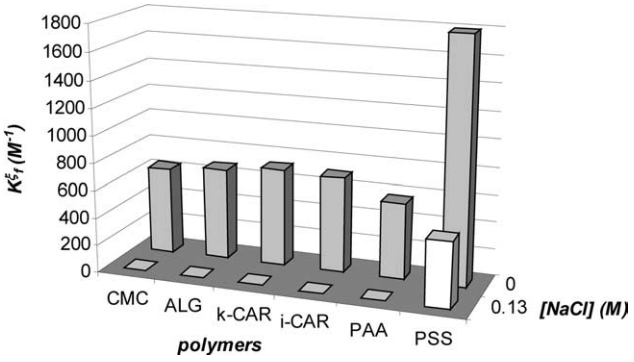

Fig. 5. Charge related formation constant for the different polymers in the presence and in the absence of 0.13 M NaCl.

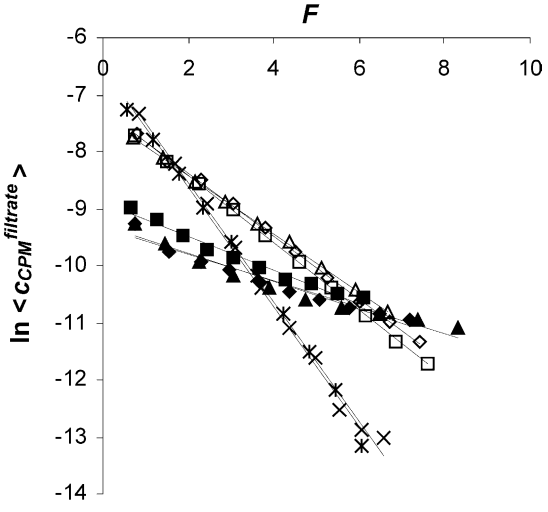

Fig. 6. Diafiltration graphs for experiments: (×) blank-01; (✳) blank-02; (▲) PSS-01; (△) PSS-02; (■) PSS-05; (□) PSS-06; (♦) PSS-07; (◇) PSS-08.

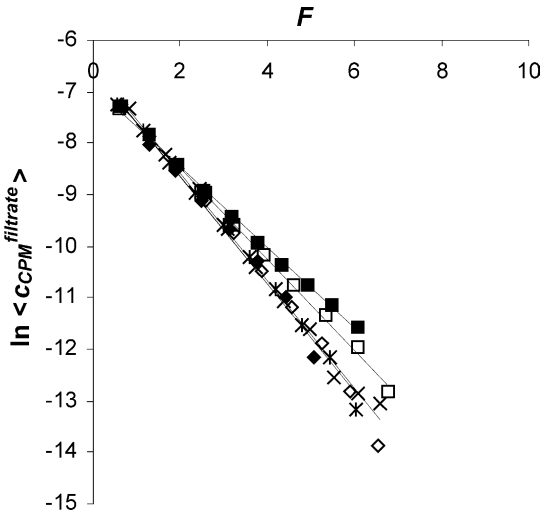

Fig. 7. Diafiltration graphs for experiments: (×) blank-01; (✳) blank-02; (■) BPEI-01; (□) BPEI-02; (♦) PVP-01; (◇) PVP-02.

precipitation of interpolymer complexes. The presence of this polymer at these experimental conditions did not change the elution profiles of CPM when diafiltered in the presence of PAA (Fig. 3). Only a slight decrease on the amount of CPM irreversibly bound to the polymer is found for PSS (Fig. 6). The influence of the neutral PVP did not change the interaction of the drug either with PAA or PSS, as can be seen in Figs. 3 and 6. The interactions of CPM with BPEI and PVP are evaluated and the corresponding elution profiles are shown in Fig. 7. They were found to be weak at these experimental conditions for BPEI and null for PVP.

4. Conclusions

The interaction of the antihistaminic drug chlorpheniramine maleate (CPM) with the negatively charged polyelectrolyte poly(sodium 4-styrenesulfonate) (PSS) at pH 7.5 showed to be stronger than the interaction with poly(acrylic acid) (PAA) and other anionic polyelectrolytes and the corresponding charge related formation constant was found to be 1786 M^{-1}. In the presence of 0.13 M NaCl, residual interactions are kept in the case of PSS, while they are cleaved in the case of PAA and the other polyelectrolytes. While interactions of CPM with PAA may be considered mainly electrostatic, hydrophobic and π–π interactions may contribute to the total interaction of CPM with PSS. The addition of urea 4 M, or 0.001 M BPEI, only produced a decrease on the amounts of counterions bound to PSS at infinite elution, while the addition of PVP did not produce any change on the diafiltration profiles.

Acknowledgements

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