DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(2), 271-280 (1991)

INTERACTION BETWEEN CALCIUM, A MODEL DIVALENT CATION, AND A RANGE OF POLY(ACRYLIC ACID) RESINS AS A FUNCTION OF SOLUTION pH[1]

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ABSTRACT

The interaction between calcium, a small divalent cation, and selected polyacrylic acid polymers has been studied. The addition of calcium chloride to dispersions of the polymer reduced the maximal viscosity through an interaction which was not dependent upon physical entrapment of the cation by the viscous medium. The binding interaction between the cation and the polymer was pH dependent and apparently

[1]This work was presented, in-part, at the Second Annual Meeting of the American Association of Pharmaceutical Scientists held in Boston, MA, June 1987.

related to an ionic interaction with the ionized carboxylate groups in the polymer. The pH dependency of the calcium binding was more closely related to the intrinsic pKa (4.3) of the acrylic acid residues in the polymer rather than the apparent pKa (6.8) of the polymeric species.

INTRODUCTION

The Carbopol® range of polyacrylic acids find application in the pharmaceutical and cosmetic industries as thickening and suspending agents and are often utilized to stabilize the interfacial properties of selected liquid/liquid systems[1]. These resins are hydrophilic in nature and their rheological properties, which are pH dependent, follow the ionization profile of the carboxylic acid functional groups present in the polymer. The resins offer good temperature stability profiles and they are resistant to bacterial degradation. Various forms of the resins are commercially available and are differentiated in terms of molecular weight (range of approx. 4.5×10^5 - 4.0×10^6 daltons) and the degree of cross-linking present in the backbone of the polymer.

Carbopol® 934P is the only resin currently approved for oral human pharmaceutical applications. The interaction between Carbopol® 934P and a number of drugs has been studied. Graf et al.[2] studied the interaction of diphenhydramine HCl and dextrochlorpheniramine maleate with Carbopol® 934P as a function of polymer concentration and solution pH. Infra-red analysis indicated that the interaction was predominantly physical (i.e. viscosity based) in nature and unlikely to occur through a specific chemical interaction between the drug and the ionized carboxyl groups of the polyacrylic acid. Elgindy[3] investigated the utility of Carbopol® 934P for controlling the release of selected cationic drugs and found that the entrapment of drug, although pH dependent, appeared to be a consequence of the pH induced viscosity profile of the Carbopol® system.

Monovalent and divalent salts are often utilized as excipients in topical and oral formulations which contain Carbopol®. Although the

TABLE 1

Structural Characteristics of Selected Carbopol® Polymers[4]

Resin Type	Approx. Mol. Wt.	Structure
907	4.5×10^5	Nearly linear
910	7.5×10^5	Low degree of cross linking
941	1.25×10^6	Branched, low degree of cross linking
934P	3×10^6	Highly branched, high degree of cross linking
940	4×10^6	Highly branched, medium degree of cross linking

addition of electrolyte is known to decrease the solution viscosity of such formulations, the mechanism of the pH dependency of the interaction has not been fully evaluated. Furthermore, the relative contribution of either physical entrapment (due to viscosity effects) or chemical interaction with the polyacrylic acid polymer has not been characterized. The purpose of this study was to evaluate the pH and concentration dependent interaction between Carbopol® 934P and calcium, a model divalent cation, and to determine whether the interaction was consistent with either a physical (viscosity) or chemical based phenomena.

MATERIALS AND METHODS

The Carbopol® resins employed in this study were kindly donated by B.F. Goodrich Chemical Company (Ohio, USA). The relationship between molecular weight and the structure of the five different resins is shown in Table 1. All solvents and chemicals were of analytical reagent grade.

Viscosity Measurements

Aqueous dispersions of Carbopol® 934P (0.2% w/v) were prepared with a rotary mixer using a high shear rate stainless steel unipellar and were allowed to stand for at least 12 hours to ensure complete hydration of the polymer. This was followed by addition of either calcium chloride or sodium hydroxide to the hydrated Carbopol® dispersions. In this study, an equivalence of calcium ion (assuming a 1:2 interaction between a calcium ion and two ionized carboxylate groups) was defined in terms of molar quantities of the resin based on an apparent molecular weight of 76 daltons for the monomeric acrylic acid residues present in the polymer. Viscosity measurements were performed on a Brookfield viscometer (Mass., USA) with spindle number 3 operated at a rotational speed of 10 rpm. The temperature of the system was controlled at 25 ± 1 °C with a jacketed beaker apparatus.

Titration Of Carbopol® Solutions

For the determination of apparent pKa values of the different polyacrylic acid polymers, the hydrated resins (0.05% w/v) were potentiometrically titrated against a standardized 0.05 N sodium hydroxide solution. The sodium hydroxide solution was added in 0.5 ml increments at two minute intervals to the Carbopol® dispersion to ensure equilibrium. The pH meter was a Beckman Model 71 (Beckman Products, CA, USA) and all titrations were performed at 25 ± 1 °C. The apparent pKa values of the different Carbopol® resins were estimated from a plot of the first derivative of pH (i.e. d(pH)/d(volume)) versus volume of added sodium hydroxide solution.

The apparent pKa values for the resins were also estimated in the presence of an added concentration of calcium chloride. Carbopol® resins (0.05% w/v) were prepared and 1.0 equivalent of calcium chloride was added and the dispersion stored for at least 12 hours to ensure equilibrium. These solutions were then potentiometrically titrated and the apparent pKa values determined as described.

Determination Of Calcium Ion Concentration

An ion specific electrode (Orion Research Inc., Mass, USA) was utilized to quantitate the free calcium ion concentration in the Carbopol® dispersions. Standard curves of E (mV) versus log calcium concentration were linear in the concentration range 0.0001 to 0.1 M calcium ion. The slope of the relationship, obtained by linear regression, was 28 ± 1.5 mV/log calcium concentration.

To measure the unbound concentration of calcium, the Carbopol® dispersions were separated in a temperature controlled ultracentrifuge (12,000 rpm for 30 minutes, Sorvall RC2B, Dupont Instruments) to yield a clear supernatant fraction. Quantitation of the concentration of calcium ion in the supernatant fraction was then performed potentiometrically with the ion specific electrode.

RESULTS AND DISCUSSION

Carbopol® polymers offer unique pH dependent properties which make them useful pharmaceutical excipients. They are polyacrylic acid polymers which differ in terms of molecular weight and the extent of cross-linking present in the polymer. The monomeric subunit of the polymers are acrylic acid moieties which, when ionized, lead to elongation of the polymer (due to electrostatic repulsion between the ionized carboxylate groups) and a consequent increase in the hydration of the polymer[1,5]. The ionization profile of the polyacrylic acid polymers is complex due to the inductive and steric interactions which occur between the large number of ionization sites present on the polymer[6,7]. Consequently, the rheological properties of formulations containing Carbopol® are highly pH dependent.

Figure 1 represents the effect of calcium chloride addition on the viscosity - pH profile of a 0.2% w/v dispersion of Carbopol® 934P. Similar profiles were observed with the other (Carbopol® 907 and 941) polyacrylic acids studied. The decrease in the maximal viscosity of the dispersions was apparent at calcium concentrations as low as 0.025 equivalents due to a

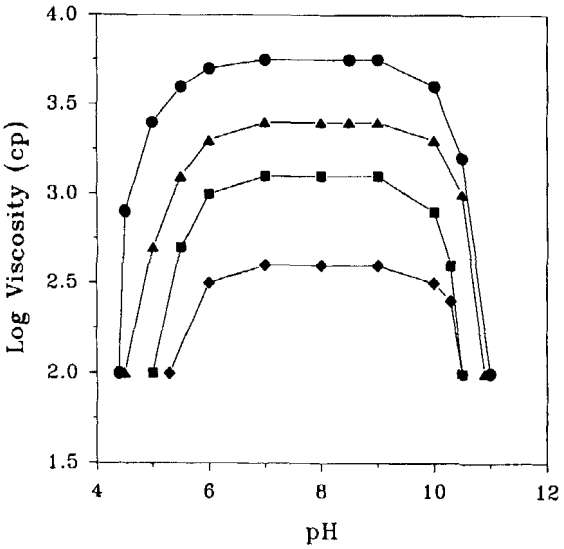

FIGURE 1

Effect of $CaCl_2$ on the viscosity profile of 0.2% w/v Carbopol® 934P (●-● 0 Eq. Ca; ▲-▲ 0.025 Eq. Ca; ■-■ 0.05 Eq. Ca; ♦-♦ 0.1 Eq. Ca)

decrease in the electrostatic repulsion and hydration of the polymer. Although the maximal viscosity of the Carbopol® dispersions decreased with increasing concentrations of calcium, the region of the profiles where the viscosity was largely independent of pH (6-9) remained constant. The decrease in the viscosity of Carbopol® dispersions at the high pH values is a function of the increased counter ion concentrations (which disturbs the electrostatic repulsion between the ionized carboxyl groups) and an overall decrease in the hydration of the polymer[1,5].

The binding interaction of calcium ions with the polymer, as a function of pH, was further studied by measuring the concentration of free calcium ion in solution. The free calcium ion concentration profiles, as a function of pH, are shown in Figure 2. The measured concentration of free calcium ion at pH values less than 2, corresponded with the mass of calcium chloride added to the dispersions, and indicated no significant

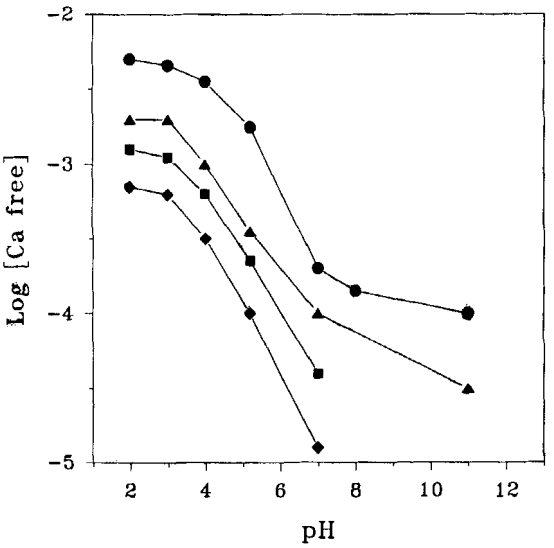

FIGURE 2

Logarithm of free calcium ion concentration as a function of pH and concentration in 0.2% w/v Carbopol® 934P. (●-● 0.5 Eq. Ca; ▲-▲ 0.2 Eq. Ca; ■-■ 0.1 Eq. Ca; ♦-♦ 0.05 Eq. Ca)

interaction or binding between the divalent ion and the polymer. As the pH of the dispersions was increased, the free concentration of calcium ion present in the supernatant fraction decreased markedly and appeared to approach a plateau at higher pH values. At pH values above 8, the concentration of free calcium ion present in the dispersions after the addition of 0.5 equivalents was approximately 1-5% of the initial added quantity. Unfortunately, the sensitivity of the calcium ion specific electrode assay precluded the analysis of the free concentration at the higher pH values where the added quantity of calcium was less than 0.25 equivalents.

The slope of the linear portion of the free calcium ion concentration profile was similar after addition of different concentrations (0.05 to 0.5 Eq.) of calcium chloride. At the higher pH values, the extent of the calcium interaction with the ionized polymer in the neutral pH range was greater than 95% as estimated from the concentration of free calcium ion in

solution. To extend these observations to the other homologous polymers, Carbopol® 907 and 941 were examined in this series of experiments. The profile of the calcium binding with these polymers was qualitatively similar to that observed with Carbopol® 934P, indicating that the mechanism of interaction was consistent within the polymer series.

The interaction between calcium and the polyacrylic acid predominantly occurred at pH values below the threshold for an increase in the viscosity of the Carbopol®/calcium dispersions. Analysis of the free calcium ion concentration data indicated that the interaction of calcium ions with the polyacrylic polymer appeared to be dependent upon ionization of functional groups within the polymer which began to occur below pH 5.

Carbopol® polymers are weak acids as reflected by the apparent pKa values which were estimated to range between 6.7 and 7.0 (table 2). These values are in agreement with reported values for the native polymer[4,6]. The pH dependent viscosity of Carbopol®, which is a function of the ionization of the polymeric species in solution, reflects the apparent pKa values. Titration of the polymers with sodium hydroxide solution, to determine the apparent pKa, yielded a relatively flat profile indicative of the complex intramolecular interactions within the polymer.

The intrinsic pKa of acrylic acid, the polymeric subunits of Carbopol®, is approximately 4.3[8]. Therefore, the acidity of the polymeric species is approximately 100 fold less than the monomeric form. The decrease in the apparent acidity of the polymeric species, relative to the monomer, is due primarily to the acid weakening inductive effects of ionized carboxylate residues affecting the ionization potential of neighboring groups. Therefore, the carboxylic functional groups within the polymer are not identical and the acidity of the polymer is a function of the degree of ionization.

The data in Table 2 indicate that the addition of calcium chloride to the Carbopol® dispersions decreased the observed pKa by approximately 2 units and that the effect was consistent between the different resins evaluated in this study. The decrease in the apparent pKa of the Carbopol® resins in the presence of added calcium chloride represented an increase

TABLE 2

Apparent pKa Values of Carbopol® Resins Determined in the Presence and Absence of 1.0 Equivalent of Calcium Chloride

Resin Type	Observed pKa Without $CaCl_2$	Observed pKa With $CaCl_2$
907	6.8	4.9
910	7.0	4.4
934P	6.7	4.5
940	6.8	4.5
941	6.8	4.1

in the apparent acidity of the carboxylic acid functional groups present in the polymer.

It appears that the binding interaction of calcium with ionized carboxylate sites in the polymer was sufficient to reduce the inductive effect that the ionization would otherwise have upon the acidity of a neighbouring carboxylic acid. Hence, the apparent pKa of the polyacrylic acid was significantly decreased in the presence of added calcium and approached the intrinsic pKa of monomeric acrylic acid.

The lower apparent pKa of the Carbopol® resin in the presence of added calcium (table 2) is consistent with the observed pH dependent binding profile of calcium shown in Figure 2. It appears that a consequence of the binding interaction between the divalent cation and the polyacrylic acid is that the interaction more closely follows the intrinsic pKa of the monomeric subunits rather than the apparent pKa of the polymer.

CONCLUSION

The data presented indicate that the binding interaction between calcium and Carbopol® polymers was dependent upon the pH of the

dispersion. The binding interaction was ionic in nature and dependent upon the ionization of the individual acrylic acid moieties present in the polymer. Unlike the interaction which has been observed for some drug molecules, the interaction between calcium and the polyacrylic acid polymers in this study was not dependent upon a physical entrapment phenomena. It is likely that the relative contribution of a physical or ionic process to the potential interaction between a drug/ion of interest will ultimately be dependent upon molecular size.

ACKNOWLEDGMENTS

The initial discussions with Dr. R.Y. Lockhead from B.F. Goodrich Chemical Company were appreciated.

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