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# Physicochemical Properties of Calcium Polycarbophil, a Water-absorbing Polymer

TAKEHISA YAMADA, MASAKAZU KITAYAMA, MASAHIRO YAMAZAKI, OSAMU NAGATA, IKUMI TAMAI* AND AKIRA TSUJI*

*Research and Development Division, Hokuriku Seiyaku Co., Ltd, Katsuyama 911, and *Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa 920, Japan*

## Abstract

The physicochemical properties of calcium polycarbophil were examined.

Calcium polycarbophil was decalcified rapidly under acidic conditions, affording polycarbophil. Polycarbophil absorbed about 10 times its own weight of water under acidic conditions, but the swelling ratio markedly increased at above pH 4·0 and reached 70 times the initial weight under neutral conditions. The swelling of polycarbophil was not affected by non-ionic osmolarity, but was affected by ionic strength, showing a decrease with increase of ionic strength. Monovalent metal ions such as sodium and potassium ions in gastrointestinal fluid did not reduce the equilibrium swelling of polycarbophil, but divalent ions such as calcium and magnesium ions did. However, calcium ion only slightly reduced the equilibrium swelling under sodium-rich conditions. The viscosity (as an indicator of fluidity) of polycarbophil was larger than that of CMC-Na at every shear rate and polymer content examined.

Calcium polycarbophil, a water-absorbing polymer, is the calcium salt of polyacrylic acid cross-linked with divinylglycol. It has been developed as a treatment for constipation or diarrhoea associated with conditions such as irritable bowel syndrome. It releases calcium ions under acidic conditions and its pharmacological actions are due to the polycarbophil thus produced (Danhof 1982). The pharmacological efficacy of calcium polycarbophil has been proven in clinical trials (Winkelstein 1964; LaCorte et al 1982), although the mechanisms of the anti-constipation or anti-diarrhoeal action of calcium polycarbophil have not been clarified. Calcium polycarbophil and polycarbophil are chemically (Child et al 1955) and physiologically inert (Grossman et al 1957; Roth 1960), and are not absorbed from the gastrointestinal tract into the systemic circulation (Child et al 1955). Therefore, the physicochemical properties of these compounds must be important in generating the pharmacological effects in the gastrointestinal lumen. However, little investigation of the physicochemical properties of calcium polycarbophil have been reported, except for studies of the swelling ratios of polycarbophil at various pHs and at various ionic strengths (Ch'ng et al 1985; Park & Robinson 1985).

The purpose of this study was to investigate the physicochemical properties of calcium polycarbophil in order to throw light on the mechanisms of the anti-constipation and anti-diarrhoeal action of this polymer. In this study, we evaluated the decalcification of calcium polycarbophil, and the effects of various factors such as pH, ionic strength, osmolarity and metal ions in the gastrointestinal fluid on the equilibrium swelling and viscosity (as an indicator of fluidity) of polycarbophil.

Correspondence: T. Yamada, Research and Development Division, Hokuriku Seiyaku Co., Ltd, Inokuchi 37, Katsuyama 911, Japan.

## Materials and Methods

### *Materials*

Calcium polycarbophil was purchased from Lee Laboratories (USA) and polycarbophil was prepared in our laboratory from calcium polycarbophil according to the following procedure. Calcium polycarbophil was decalcified with 0·1 M HCl five times and washed with purified water five times, then the polycarbophil thus obtained was freeze-dried in-vacuo (0·4 torr) using a DF-05G freeze dryer (Nihon Shinkugijutsu Co., Ltd, Japan) at −20°C. The product was ground in an R-8 analytical grinder (Nihon Rikagakukikai Co., Ltd, Japan). Sodium carboxymethylcellulose (CMC-Na) was purchased from Maruishi Seiyaku Co., Ltd (Japan). Lanthanum chloride solution was of atomic absorption spectrochemical analytical grade. All other reagents were of analytical grade.

### *Measurement of calcium concentration*

Calcium concentrations were measured by atomic absorption spectrochemical analysis, using a model AA-860 atomic absorption spectrochemical analyser (Nippon Jarrel-Ash, Japan) equipped with an air-acetylene burner, at 423 nm.

### *Release of calcium ions from calcium polycarbophil*

Fifty milligrams of calcium polycarbophil was placed in 50 mL buffer at various pHs, shaken for 20 min and centrifuged. To 1 mL supernatant, 0·1 M HCl containing 0·5% lanthanum chloride was added up to 25 mL. Calcium concentration in the sample solution was measured by atomic absorption spectrochemical analysis. The calcium concentration which was achieved by using 0·1 M HCl instead of each buffer, in the same manner, was considered to represent complete decalcification (control). The buffer systems used were diluted hydrochloric acid (pH 1·2), 0·1 M phosphate buffer (pH 2·0, 3·0), 0·1 M acetate buffer (pH 4·0, 5·0) and 0·1 M imidazole-hydrochloric acid buffer (pH 6·0, 7·0, 8·0).

Ionic strength was adjusted to 0·12 with sodium chloride and osmolarity was maintained at 290 mOsm $kg^{-1}$ using mannitol.

*Measurement of equilibrium swelling*
Equilibrium swelling of polycarbophil and CMC-Na were measured by weighing the gel after centrifugation or by reading the meniscus at the interface between the fully hydrated polymer and the test solution. The equilibrium swelling of polycarbophil was calculated by dividing the gel volume or the gel weight by the weight of polycarbophil or calcium polycarbophil.

*Effect of pH on apparent volume of equilibrium swelling*
Water sorption of polycarbophil as a function of pH was determined as the apparent volume expansion of polycarbophil. Fifty milligrams of polycarbophil was placed in a beaker, 100 mL buffer solution was added, and the mixture was incubated at 37°C for 24 h. The polymer solution was periodically stirred to remove trapped air bubbles. After 24 h, the fully hydrated polymer was transferred to a 10-mL graduated cylinder after removal of the supernatant by decantation, and was allowed to stand for 24 h. The meniscus of the interface between the fully hydrated polymer and the test solution was read. The buffer systems were as described above. The pH of the supernatant was measured with a pH meter (Horiba, Japan).

*Osmotic difference between inside and outside of the hydrated gel*
Polycarbophil (50 mg) was shaken in 50 mL 1·5% sodium bicarbonate solution for 1 h, then the mixture was centrifuged. Sodium ion concentrations of the supernatant and 1·5% sodium bicarbonate solution were measured with a model 710 automatic electrolytes analyser (Hitachi, Japan). Sodium ion concentration of 1.5% sodium bicarbonate solution was 177·7 ± 0·3 mM. Sodium ion concentration in the gel was calculated as: $Na^+$ in 1·5% $NaHCO_3$ solution − $Na^+$ in supernatant/volume of gel

*Effect of ionic strength on equilibrium swelling*
Calcium polycarbophil (250 mg) was placed in a 50 mL glass tube, to which was added 35 mL 0·1 M HCl. The mixture was shaken to release calcium and centrifuged. The pellet was washed with purified water, then 35 mL Britton-Robinson buffer (pH 7·0) containing various concentrations of potassium chloride was added and the mixture was shaken five times. After standing overnight, the sample was centrifuged and the weight of the pellet was measured. The ionic strengths of the test solutions were 0·08, 0·10, 0·15, 0·20, 0·50, 1·0, 2·0 and 3·0.

*Effect of osmolarity on equilibrium swelling*
After decalcification of 250 mg calcium polycarbophil, 35 mL 1·5% sodium bicarbonate solution containing 0, 5·0 or 10·0% glucose was added and the mixture was allowed to stand overnight. After centrifugation, the weight of the pellet was measured.

*Effect of metal ions in gastrointestinal fluids on equilibrium swelling*
After decalcification of 250 mg calcium polycarbophil, the obtained polycarbophil was hydrated with 35 mL 1·5% sodium bicarbonate solution. Calcium chloride (1.25 mmol), magnesium chloride (1·25 mmol), sodium chloride (2·5 mmol) or potassium chloride (2·5 mmol) was added to the swelling gel with 35 mL purified water. After centrifugation, the pellet was weighed.

*Interaction between sodium ion and various calcium salts*
Two hundred milligrams of polycarbophil was placed in the glass tube, then 35 mL 1·5% sodium bicarbonate solution was added and the mixture was shaken for 1 h. After centrifugation, various calcium salts (equivalent to 50 mg calcium) as powder and 35 mL 1·5% sodium bicarbonate solution were added to the gel. The mixture was shaken for 1 h and allowed to stand overnight. After centrifugation, the weight of the obtained gel was measured.

*Viscosity*
Polycarbophil was emulsified with 1·5% sodium bicarbonate solution at various concentrations and allowed to stand overnight. Polycarbophil concentrations were 0·8, 1·0, 1·2, 1·4, 1·6 and 2·0%. Viscosity of the test solutions was measured with a rotational viscometer (Rotobisco RV12, Haake), using a shear rate of 1·5–30 $s^{-1}$, at 37°C. The viscosities of CMC-Na solutions of various concentrations were similarly measured, and the results were compared with those for polycarbophil.

## Results and Discussion

*Decalcification of calcium polycarbophil*
Calcium polycarbophil releases calcium ions under acidic conditions and polycarbophil thus obtained is efficacious in the treatment of constipation or diarrhoea associated with conditions such as irritable bowel syndrome (Danhof 1982). However, some patients may have low stomach acidity, so the decalcification ratio of calcium polycarbophil should be evaluated at various pHs. Our present results (Fig. 1) indicate that decalcification of calcium polycarbophil is complete at below pH 4·0, but decreases markedly above pH 4·0. This reflects the finding that the $pK_a$ value of polyacrylic acid is around 4·75 (Greenwald & Luskin 1980). As calcium ions are absorbed from the gastrointestinal tract (Bronner 1987), decalcification in vivo should be more efficient than would be predicted from the present in vitro study. When the time-course of decalcification ratios of calcium polycarbophil in artificial gastric

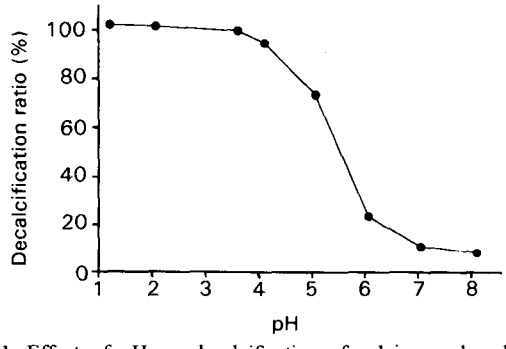


FIG. 1. Effect of pH on decalcification of calcium polycarbophil. Calcium concentration in the sample solution was measured by atomic absorption spectrochemical analysis. Each point represents the mean ± s.d. (n = 3). Standard deviations are smaller than the symbols.

juice was studied, decalcification was very fast and the decalcification ratio reached almost 100% after shaking for 2·5 min (data not shown). This implies that calcium polycarbophil would release calcium ions rapidly in the stomach to afford polycarbophil.

*Equilibrium swelling of polycarbophil*

The equilibrium swelling of polycarbophil in buffers of various pH values is shown in Fig. 2. Values of the equilibrium swelling under acidic conditions were small, corresponding to only about 10 times the initial weight, but, the equilibrium swelling increased markedly above pH 4·0, and the value was about 70 mL (g polycarbophil)$^{-1}$ at pH 7·0. Thus, the equilibrium swelling of polycarbophil was dependent on pH, and was 7 times larger at pH 7·0 than at pH 4·0. It is considered that the lower hydration of polycarbophil under acidic conditions is advantageous to minimize side effects such as distention of the upper gastrointestinal tract. The value of the equilibrium swelling of polycarbophil at pH 7·0 was about one half of the value reported by Ch'ng et al (1985). Generally, factors which influence the equilibrium swelling of a macromolecular water-absorbing polymer include the cross-linking ratio of the polymer and the osmotic difference between inside and outside the polymer gel (Flory 1953). To clarify the above discrepancy, polycarbophils containing various contents of the cross-linking agent, divinylglycol, were synthesized according to the method reported by Miskel et al (1967). The equilibrium swelling ratios of the synthesized polycarbophils changed drastically with change of the cross-linking ratio (data not shown). From these results, it is suggested that the difference of swelling ratios found by Ch'ng et al (1985) and us may have been due to a difference in the cross-linking ratio of the polycarbophils used.

When polycarbophil gel was allowed to swell in 1·5% sodium bicarbonate solution, sodium ion concentration (349·5 ± 8·6 mM, mean ± s.d., n = 3) inside the hydrated gel was found to be twice that (166·8 ± 0·6 mM) of the supernatant. Such a difference implies that the equilibrium swelling would be influenced by ionic osmolarity. The equilibrium swellings of polycarbophil in solutions of various ionic

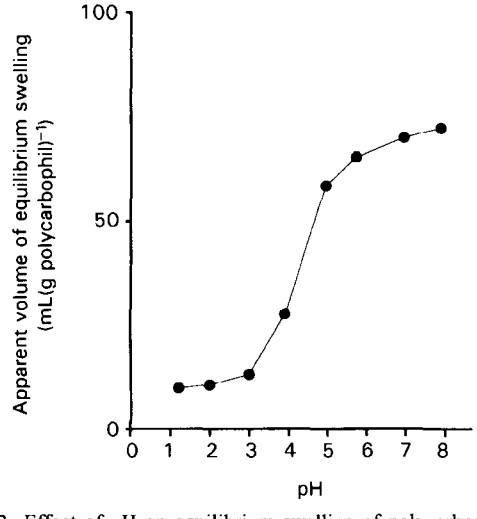


FIG. 2. Effect of pH on equilibrium swelling of polycarbophil. Each point represents the mean ± s.d. (n = 3). Standard deviations are smaller than the symbols.

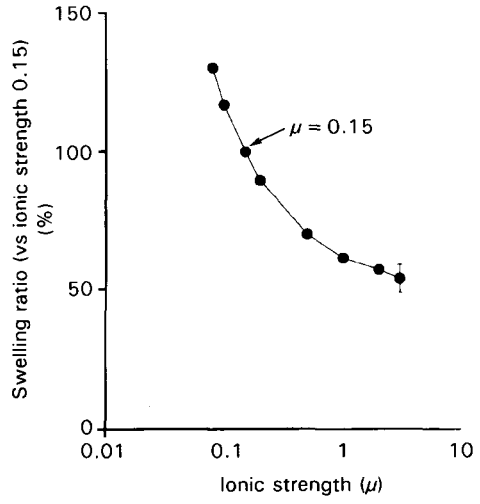


FIG. 3. Effect of ionic strength on equilibrium swelling of polycarbophil. Each point represents the mean ± s.d. (n = 3). Standard deviations are smaller than the symbols, except in one case.

strengths are shown in Fig. 3. The ratios of swelling at ionic strength 0·08 and 3·0 to that at 0·15 were 130 and 54%, respectively. Thus, the equilibrium swelling of polycarbophil decreased with increase of ionic strength. The effect of non-ionic osmolarity on the equilibrium swelling of polycarbophil was also examined by using various glucose concentrations. We found that the equilibrium swelling ratio (versus control) was 102·4 ± 1·0 or 104·6 ± 2·1 when the osmolarity of the test solution was increased by 2 or 3 times with glucose, respectively, indicating that the equilibrium swelling ratio of polycarbophil was unaffected by non-ionic osmolarity.

Consequently, it is considered that the equilibrium swelling of polycarbophil is mainly affected by the ionic strength. Since there are many metal ions, such as sodium, potassium, calcium and magnesium ions, in the gastrointestinal fluid, the effects of these ions on the equilibrium swelling of polycarbophil were studied. As shown in Table 1, the equilibrium swelling of polycarbophil was markedly reduced by addition of calcium or magnesium ions, whereas it was increased in the cases of sodium and potassium ions. Thus, it is considered that hydrated gel shrinks owing to release of retained water upon ionic binding of calcium or magnesium ions to the acrylic acid resin component of polycarbophil.

To determine the effects of calcium ion on the equilibrium swelling of polycarbophil in the presence of sodium ion, various calcium salts were used as additives. When the counter ions of the calcium ion differed, the equilibrium swelling of polycarbophil was also changed (Table 2). Calcium carbonate

Table 1. Effect of metal ions on the equilibrium swelling of polycarbophil.

| Metal ions | Metal ion concn (M) | Swelling ratio (%) |
|---|---|---|
| Calcium chloride | 0·03 | 10·2 ± 0·2 |
| Magnesium chloride | 0·03 | 12·8 ± 0·6 |
| Sodium chloride | 0·06 | 158·7 ± 8·6 |
| Potassium chloride | 0·06 | 134·4 ± 0·3 |

Each value represents the mean ± s.d. (n = 3).

Table 2. Effects of various calcium salts on the equilibrium swelling of polycarbophil.

| Applied source of calcium | Swelling ratio (%) |
|---|---|
| None | 100·0 ± 5·0 |
| Calcium chloride | 42·3 ± 4·0 |
| Calcium citrate | 64·0 ± 1·3 |
| Calcium hydroxide | 114·6 ± 1·0 |
| Calcium carbonate | 100·7 ± 0·7 |
| Calcium monohydrogen phosphate | 79·4 ± 0·8 |
| Calcium acetate | 55·1 ± 2·7 |

Each value represents the mean ± s.d. (n = 3). The amount of calcium applied (20%) was the same for all sources of calcium and corresponds to the amount in calcium polycarbophil.

and calcium hydroxide did not affect the equilibrium swelling of polycarbophil, but other calcium salts reduced it. We consider that this is related to the solubility of the calcium salts (calcium carbonate and hydroxide remained at the bottom of the tube). Even in the presence of both calcium ion (1·25 mmol) and sodium ion (6·3 mmol), the equilibrium swelling of polycarbophil was more than 42%. Calcium ion concentrations in gastrointestinal fluid are known to be below 10 mM (Thureborn 1961; Hunt & Wan 1967; Nakayaina & Van der Linden 1971) and the concentration was about 35 mM in the present study. We consider that the percentage reduction of the equilibrium swelling of polycarbophil would be less in the body. Since it is considered that calcium ion is present as the carbonate salt or monohydrogen phosphate salt in the intestine, the equilibrium swelling of polycarbophil in the presence of calcium salts in the intestine should be virtually the same as that in the absence of calcium salt. Thus, the equilibrium swelling should be sufficient to show the desired pharmacological effects.

*Viscosity*

In the diarrhoeal state, the water transport rate in the gastrointestinal tract is so fast that water can not be adequately absorbed (Sadik 1989). We therefore examined the viscosity, as an indicator of fluidity, of polycarbophil in comparison with that of CMC-Na. The viscosity of polycarbophil increased with increasing concentration, and was larger than that of CMC-Na at all concentrations examined (Fig. 4). A similar tendency was observed at all rates of shear examined (data not shown). As polycarbophil forms a gel, this gel could reduce the fluidity of the gastrointestinal contents and improve the looseness of stools in diarrhoea. Additionally, the reduction of fluidity would reduce the transport velocity of intestinal fluid, and so water would be better absorbed. That is, the anti-diarrhoeal action of polycarbophil is due to the gel formation and the reduction of fluidity arising from the increase of viscosity.

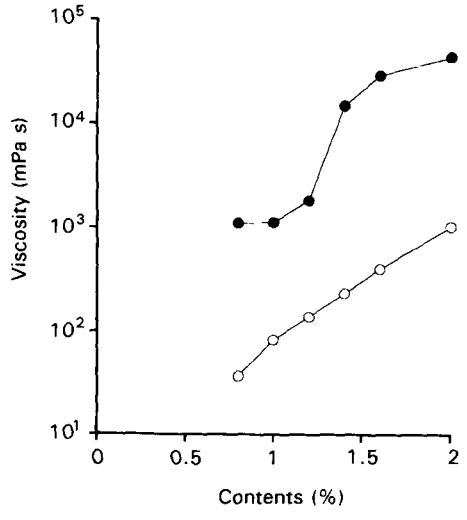


FIG. 4. Effect of polymer content on viscosity of polycarbophil (●) or CMC-Na (○). Viscosities were measured using a rotational viscometer at a shear rate of 10 $s^{-1}$. Each point represents the mean ± s.d. (n = 3). Standard deviations are smaller than the symbols.

In conclusion, calcium polycarbophil is decalcified under gastric acidic conditions, and the produced polycarbophil absorbs water to form a gel under intestinal neutral conditions. This gel retains water and endows the intestinal contents with high viscosity. These physicochemical properties of calcium polycarbophil account for its efficacy in the treatment of constipation and diarrhoea associated with conditions such as irritable bowel syndrome.

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