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Physicochemical Properties of Calcium Polycarbophil a Water-absorbing Polymer

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Abstract

The physicochemical properties of calcium polycarbophil were examined.

Calcium polycarbophil was decalcified rapidly under acidic conditions affording polycarbophi l. Polycarbo­

phil 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 magnesi n 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 po ner content examined.

Calcium polycarbophil a water-absorbing polymer is the calcium salt of polyacrylic acid cross-linked with divinylgly­ col. It has been developed as a treatrnent for constipation or

# *Materials*

Materials and Methods

diarrhoea associated with conditions such as irritable bowel S ldrome. It releases calcium ions under acidic conditions and

its pharmacological actions are due to the polycarbophil thus produced (Da lOf 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 om 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 physico­ chemical properties of calcium polycarbophil in order to throw light on the mechanisms of the anti-constipation and antì­ diarrhoeal action of this pol ηer. 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 poly­

carbophi l.

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Calcium polycarbophil was purchased from Lee Laboratories

(USA) and polycarbophil was prepared in our laboratory om calcium polycarbophil according to the following procedure. Calcium polycarbophil was decalcified with 0.1 M HCI five times and washed with purified water five times then the polycarbophil thus obtained was eeze-dried in-vacuo

(0-4 to using a DF-05G freeze yer (Nihon Shinkugijutsu

Co. Ltd Japan) at -20o C. The product was ground in an R-8

analytical grinder (Nihon Rikagakukikai Co. Ltd Japan).

Sodium carboxymethylcellulose (CMC-Na) was purchased om 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

absorptìon spectrochemical analyser (Nippon Jarrel-Ash

Japan) equipped with an air-acetylene bur at 423 nm.

# *Release of calcium ions m calcium polycarbophil*

Fi y milligrams of calcium polycarbophil was placed in 50 mL buffer at various pHs shaken for 20 min and cen­ trifuged. To 1 mL supematant 0.1 M HCI containing 0.5%

lanthanum chloride was added up to 25 mL. Calcium con­ centration in the sample solution was measured by atomic absorption spectrochemical analysis. The calcium concentra­

tion which was achieved by using 0.1 M HCI 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).

666 TAKEHISA YAMADA ET AL

Ionic strength was a justed to 0.12 with sodium chloride and osmolarity was maintained at 290 mOsm kg- I using mannito l.

*Measurement 01equilibrium 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 pol ner and the test solution. The equilibrium swelling of polycarbophil was calculated by dividing the gel volum or the gel weight by the weight of polycarbophil or

calcium polycarbophi l.

*Effect 01pH on apparent volume 01equilibrium swelling* Water sorption of polycarbophil as a function of pH was determined as the apparent volume expansion of poly­

carbophil. Fi y milligrams of polycarbophil was placed in a

beaker 100 mL buffer solution was added and the mixture was incubated at 370 C for 24 h. The polymer solution was

periodica lIy stirred to remove trapped air bubbles. After 24 h

the fuIly hydrated polymer was transferred to a 10-mL grad­

uated cylinder after removal of the supematant by decantation and was aIlowed to stand for 24 h. The meniscus of the interface between the fuIly hydrated polymer and the test

solution was read. The buffer systems were as described above. The pH of the supematant was measured with a pH meter (Horiba Japan)

*Osmotic difference between inside and outside 01the 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 ofthe supematant and 1.5% sodium bicarbonate solution were measured with a model 710 auto­ matic 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 cal­ culated as: Na+ in 1.5% NaHC03 solution - Na+ in super­ natant/volume of gel

*Effect 01ionic 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 HCI. The mixture was shaken to release calcium and centrifuged. The peIlet was

washed with purified water then 35 mL Britton-Robinson buffer (pH 7.0) containing various concentrations ofpotassium chloride was added and the mixture was shaken five times.

After standing ovemight the sample was centrifuged and the weight of the pellet was m asured. 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 olosmolari*η *on equilibrium swelling*

After decalcification of 250 mg calcium polycarbophil 35 mL

obtained polycarbophil was hydrated with 35 mL 1.5% sodiurn bicarbonate solution. Calcium chloride (1.25 mmol) magne\_ sium chloride (1.25 mmol) sodium chloride (2.5 mmol) or potassium chloride (2.5 mmol) was added to the sweIling gel

with 35 mL purified water. After centrifugation the peIIet was weighed.

*lnteraction between sodium ion and various calcium salts* Two hundred miJIigrams 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 centrifuga\_ tion 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 I h and allowed

to stand ovemight. After centrifugation the weight of the

obtained gel was measured.

Viscosity

*Polycarbophil was emulsified with 1.5% sodium bicarbonate solution at various concentrations and a*Il*owed to stand over­ nigh*t. *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 RVI2 Haake) using a shear*

*rate of 1.*5-*30 S-I at 37 0* C *The viscosities of CMC-Na*

*solutions of various concentrations were similarly measured and the resu*It*s were compared with those for polycarbophi* l.

Results and Discussion Decalc 'cation 01calcium polycarbophil

*Calcium polycarbophil releases calcium ions under acidic*

*conditions and polycarbophil thus obtained is efficacious in the treatment of constípation or diarrhoea assocíated with condi­ tíons such as irritable bowel syndrome (Danhof 1982). How­ ever some patients may have low stomach acidi so the decalcification ratio of calcium polycarbophil should be eval­ uated at various pHs. Our present results (Fig. 1) indicate that decalcification of calcium polycarbophíl is complete at below pH 4.0 but decreases markedly above pH 4.0. This reflects the finding that the pKa value of polyacrylic acid ís around 4.75 (Greenwald & Luskin 1980). As calcíum ions are absorbed from the gastroíntestinal tract (Bronner 1987) decalcificatíon in vívo should be more efficient than would be predicted om the present in vitro study. When the tíme-course of decalcí­ fication ratíos of calcium polycarbophil ín artíficíal gastric*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 100 |  | | | | |
| 80 |  |  |  |  |  |
| 60 |  |  |  |  |  |
| 40 |  |  |  |  |  |
| 20 |  |  |  |  |  |



Hm

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+ud

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1.5% sodium bicarbonate solution containing 0 5.0 or 10.0% glucose was added and the mixture was allowed to stand

ovemight. After centrifugation the weight of the peIlet was

measured

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2 3 4 5 6 7 8

pH

*ct ( metal ions in gastrointestinal on equilibrium swelling*

After decalcification of 250 mg calcium polycarbophil the

FIG. 1. Effect of pH on d calcification of ca\cium 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 smal1er than the s nbols

PHYSICOCHEMICAL PROPERTIES OF CA-POL YCARBOPHIL

667

iuice was studied decalcification was very fast and the de­ alcification ratio reached almost 100% after shaking for

2.5 min (data not shown). This implies that calcium poly­

carbophil would release calcium ions rapidly in the stomach to afford polycarbophi l.

*Equilibrium swelling of polycarbophil*

The equilibrium swelling ofpo1ycarbophil in buffers ofvarious

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 marked1y above pH 4.0 and the value was about 70 mL (g polycarbophi1) -1 at pH 7.0. Thus the equi­ librium swelling of po1ycarbophil was dependent on pH and

was 7 times larger at pH 7.0 than at pH 4.0. It is considered

that the 10wer hydration of polycarbophil under acidic condi­ tions is advantageous to minimize side effects such as dis­ tention of the upper gastrointestinal act. The value of the

150

100

(JF)

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SFOZSEEau-coE )DEE

50

E=uz

0

0.01

/μ=0.15

0.1 1 10

lonic strength (μ)

equìlibrium swelling ofpolycarbophil at pH 7.0 was about one half of the value reported by Ch'ng et al (1985). Generally factors whìch ìnfluence the equilìbrium swellìng of a macro­ molecular water-absorbing polymer include the cross-linking ratio of the pol ner and the osmotic difference between inside and outside the po ner gel (Flory 1953). To clarify the above discrepancy polycarbophils containing various contents of the cross-linking agent divinylglycol were syn esized 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 ofswelling 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 super­ natant. Such a difference implies that the equilibrium swelling

would be influenced by ionic osmolarity. The equilibrium swellings of polycarbophil in solutions of various ionic

100

C--UE

'

F (=ZMDD

l

3ED--3

50

U -oa

FIG. 3. Effect of ionic strength on equilibrium swelling of po1ycarbo­ phi1. Each point represents the mean s.d. (n = 3). Standard devia­

tions are smaller than the symbols except in one case.

streng1hs are shown in Fig. 3. The ratios of swelling at ionic streng1h 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 1.0or 104.6 2.1 when the osmolarity of the test solution was increased by 2 or 3 times with glucose respec­ tively indicating that the equilibrium swelling ratio of poly­ carbophil 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 polycarbophi l.

To determine the effects of calcium ion on the equilibrium swe1ling of polycarbophil in the presence of sodium ion var­ ious calcium salts were used as additives. When the counter ions of the calcium ion differed the equilibrium swelling of polycarbophi1 was a1so changed (Table 2). Ca1cium carbonate

Table 1. Effect of metal ions on the equilibri n swelling of poly­ carbophi1

E)

23rHEE

Meta1 ions

' '

0

Metal ion concn

(M)

Swelling ratio

(%)

0 2 3 4 5

pH

6 7 8

Calcium chloride Magnesium chloride Sodium chloride Potassium chloride

0.03

0.03

0.06

0.06

10.2 0.2

12.8 0.6

158.7 8.6

134-4 0.3

F1G. 2. Effect of pH on equilibrium swelling of polycarbophi 1. Each

point represents the mean s.d. (n = 3). Standard deviations are smaller than the symbols

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

668

TAKEHISA YAMADA ET AL

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

indicator offluidity ofpolycarbophil in comparison with that ofCMC-Na. The viscosity ofpolycarbophil increased with

increasing concentration and was larger than that of CMC-Na

Applied source ofcalcium

Swellinl!: ratio

(%)

at all concentrations examined (Fig. 4). A similar tendency Was

observed at all rates of shear examined (data not shown). As

None

Calcium chloride Calcium citTate

Calcium hydroxide Calcium carbonate

Calcium monohydrogen phosphate Calcium acetate

100.0 5.0

42.3 4.0

64.0 1.3

114.6 1.0

100.7 0.7

794 0.8

55.1 2.7

polycarbophil forms a gel this gel could reduce the ftuidity 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

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

to the amount in calcium polyca 'phil.

and calcium hydroxide did not affect the equilibrium swelling of polycarbophil but other calcium salts reduced it. We con­

sider 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 sweIling of polycarbophil in the

presence of calcium salts in the intestine should be virtua Ily the same as that in the absence of calcium salt. Thus the equili­

brium sweIling should be sufficient to show the desired phar­

macological effects

Viscosity

*1n the diarrhoeal state the water transport rate in the gastro­ intestinal tract is so fast that water can not be adequately absorbed (Sadik 1989). We therefore examined the viscosity*

105

104

E) -gum-

(

103

102

10'

reduction of ftuidity arising from the increase of viscosity.

1n 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 condítions such as irritable bowel s drome.

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0 0.5

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FIG.4. Effect ofpolymer content on vi osity ofpolycarbophil (.) or CMC-Na (0). Viscosit i\_es were measured using a rotational viscometer at a shear rate of 10 s - • . Each point represents the mean s.d. (n =3). Standard deviations are smaller than the symbols.

63

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