

Improvement of Drug Release Rate from Carbopol 934P Formulation

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Carbopol 934P (CP) is a mucoadhesive polymer which has been investigated as a useful adjuvant for bioadhesive drug delivery system. However, since the drug release rate from the solid formulation of CP is slow, it is difficult to take advantage of the polymer's mucoadhesive property in oral administration of fast-acting drugs. In this study, we prepared freeze-dried sodium salt of CP (FNaCP) in order to improve drug release from the formulation of CP. The drug release rate from the formulation of FNaCP was much faster than that of CP: the rate from the formulation of CP in JP XIII 1st fluid (pH 1.2) was faster than in JP XIII 2nd fluid (pH 6.8). To determine the cause of rapid drug release from FNaCP capsules, the change of CP gel properties with pH and ionic strength was investigated. Experimental results indicated that CP forms a swollen gel layer, a drug release barrier between the formulation of CP and the bulk release media. FNaCP was also thought to disperse rapidly in the 1st and 2nd fluids without formation of the swollen gel layer. In conclusion, since FNaCP improves the drug release rate from the solid CP formulation, it could be a useful adjuvant of an oral bioadhesive drug delivery system.

Key words Carbopol 934P; drug release rate; Carbopol 934P sodium salt; capsule; pH; ionic strength

Bioadhesive drug delivery is a very desirable system of oral peptide delivery.¹⁾ The main reason is that mucoadhesive polymers in the system have the possibilities of prolongation of residence time in gastrointestinal tract and increase contact time with absorbing mucosa, resulting in the enhancement of drug absorption. Carbopol 934P (CP) is a mucoadhesive polymer and has been investigated extensively by the pharmaceutical industry because of its high viscosity at low concentration and low toxicity. CP is a polyacrylic acid polymer, crosslinked with allyl sucrose. This acidic carboxyl group partially dissociates in aqueous solution, producing a flexible coil structure. Gel formation of CP depends on the electrostatic repulsion between the anionic carboxyl groups.²⁾ The gel behavior of CP has the following properties in aqueous solution: 1) the formation of gel consists of closely packed swollen particles^{3,4)}; 2) the formation of a thick gel layer inhibits water penetration,⁵⁾ resulting in slow drug release from the CP gel. Such properties of CP are disadvantageous for oral drug delivery, in which fast action is expected from a solid formulation. Thus we prepared freeze-dried sodium salt of CP (FNaCP) to improve drug release from the CP formulation. The ability of FNaCP to improve drug release from tablets including CP and the effect of freeze-drying on this release from tablets were reported earlier.⁶⁾

The purpose of this study had the following two goals: 1) to compare the drug release rates between FNaCP and CP capsules; and 2) to examine differences in the properties between FNaCP and CP gels affecting these release rates.

Experimental

Materials Carbopol 934P (CP) was generously donated by BF Goodrich Co., Cleveland, OH, U.S.A. Sodium salt of CP (FNaCP) was prepared by freeze-drying an aqueous dispersion of 0.5% CP which was neutralized with 10M NaOH to pH 7.0. Fluorescein-isothiocyanate dextran (average molecular weight 40500, FD-40) was purchased from Sigma Chemical Co., St Louis, MO, U.S.A. Hard gelatin capsules (size 9) were purchased from Japan Elanco Company Co., Nara, Japan. All other reagents were of analytical grade or better.

Preparation of Capsules and Their Release Tests Three kinds of capsules containing FD-40 (1 mg) as a model drug with FNaCP, CP or

lactose (6–8 mg) were prepared. Lactose was used as a representative excipient. Release tests of the capsules were performed in 900 ml release media at 37°C using the JPXIII rotating basket method at a speed of 50 rpm. For the release media, JPXIII 1st fluid (pH 1.2) and JPXIII 2nd fluid (pH 6.8) were used. The release rate of FD-40 was determined by measuring its fluorescence intensity in the release media (Hitachi spectrophotometer model F-3000).

Titration Experiments Potentiometric titrations were performed for CP solution by titrating CP solutions with standardized 0.1N NaOH (Horiba pH meter, F-21).

The degree of ionization, α , was calculated by

$$\alpha = \{[\text{Na}^+] + [\text{H}^+] - [\text{OH}^-]\} / \{[\text{PCOOH}] + [\text{PCOO}^-]\}$$

where $[\text{Na}^+]$ is the concentration of sodium ions due to the addition of NaCl used to adjust ionic strength, and $[\text{H}^+]$ and $[\text{OH}^-]$ are the concentrations of the hydrogen and hydroxyl ions determined from the pH value, respectively. The sum of $[\text{PCOOH}]$ and $[\text{PCOO}^-]$ is the total polymer concentration in terms of monomeric units. The $\text{p}K_a$ value, the pH value at $\alpha = 0.5$, was determined by linear regression analysis of the titration curve for values of α ranging from 0.2 to 0.8 according to the Henderson–Hasselbach relationship.

$$\text{pH} = \text{p}K_a - \ln(1 - \alpha) / \alpha$$

Results

Release Tests Figure 1 shows the FD-40 release profiles from three kinds of capsules in JPXIII 1st fluid (pH 1.2). The release rate of FD-40 from the FNaCP capsule was more rapid than that CP and was equal to the control capsule including lactose. The FD-40 release profile in the 2nd fluid (pH 6.8) was similar to that in the 1st fluid (Fig. 2), so that the release from the FNaCP capsule was more rapid in both the 1st fluid and 2nd fluids. The release rate of FD-40 from the CP capsule in the 2nd fluid, in contrast, was slower than that in the 1st fluid.

During release tests, it was observed that CP was hydrated with both the 1st and 2nd fluids, forming a gel layer around the capsule, and this layer was thicker than in the second fluid. However, FNaCP was dispersed rapidly in both media without formation of the gel layer.

Potentiometric Titrations of CP Figure 3 showed the degree of ionization of CP with increase in pH and ionic strength (μ). Ionization of CP starts near pH 4 and ends at over pH 8. The $\text{p}K_a$ values obtained as the pH values

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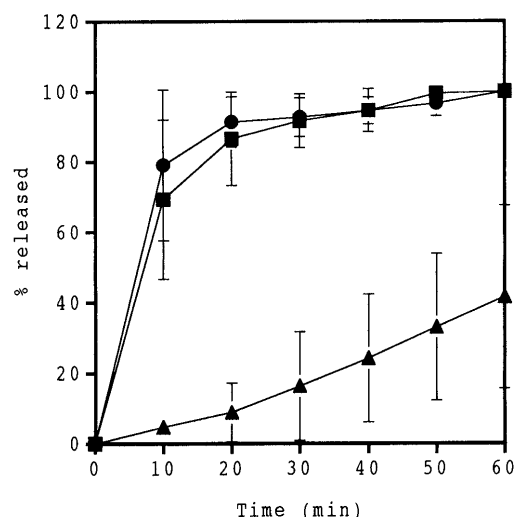


Fig. 1. *In Vitro* Time Profiles of FD-40 Release from Capsules in JPXIII 1st Fluid by Rotating Basket Method at 50 rpm

●, FNaCP; ▲, CP; ■, lactose. Values represent the mean \pm S.D. ($n=4$).

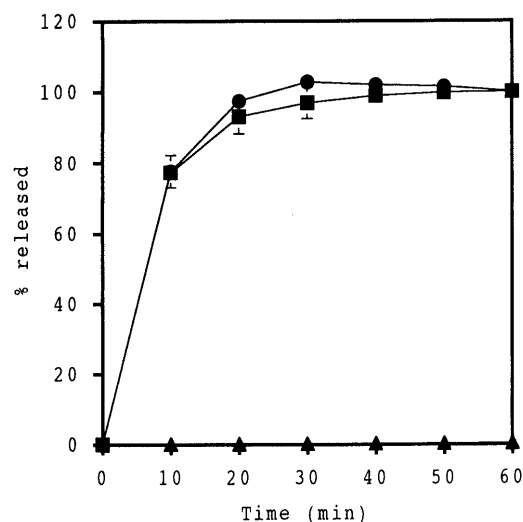


Fig. 2. *In Vitro* Time Profiles of FD-40 Release from Capsules in JPXIII 2nd Fluid by Rotating Basket Method at 50 rpm

●, FNaCP; ▲, CP; ■, lactose. Values represent the mean \pm S.D. ($n=4$).

at half ionization are listed for three μ values of 0, 0.05 and 0.1 in Table 1. The greater the ionic strength was, the smaller was the pK_a value. These results showed that ionization of CP depends on pH and μ .

Discussion

As the carboxyl groups of CP dissociate highly in an alkaline environment (Fig. 3), electrostatic repulsion between the negatively charged carboxyl groups causes uncoiling and expansion of the molecules, resulting in swelling of the polymer and gel formation.²⁾ The gel is composed of closely packed swollen particles,^{3,4)} whose swelling increases with the increase in pH, thus forming a thicker and more rigid gel layer. In this study, the swollen gel layer could be observed by the naked eye at the boundary between capsules of CP and the bulk release medium, and it became thicker with the increase in pH. Such pH-dependent swelling of CP corresponded to the fact that the release rate of FD-40 from the CP capsules

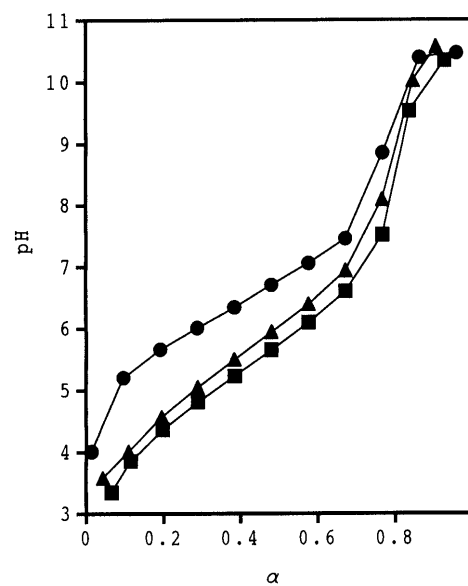


Fig. 3. Potentiometric Titration Profiles of CP 0.05% (w/v) as a Function of Ionic Strength (μ)

α is the degree of ionization of the polymer. ●, $\mu=0$; ▲, $\mu=0.05$; ■, $\mu=0.1$. Values represent the mean ($n=3$).

Table 1. pK_a values of CP 0.05% as a Function of Ionic Strength (μ)

μ	pK_a
0	6.78 ± 0.21
0.05	6.18 ± 0.01
0.1	5.82 ± 0.21

The concentration of CP was 0.05%. Ionic strength (μ) was adjusted with NaCl. Values represent the mean \pm S.D. ($n=4$).

was more rapid in the 1st fluid (pH 1.2) than in the 2nd fluid (pH 6.8) (Figs. 1 and 2). Accordingly, it is suggested that the swollen gel layer restricts drug diffusion from the solid CP formulation to the bulk release media (Fig. 4a, b).

The ionization of CP was influenced by an increase in ionic strength of CP gel. With greater ionic strength, the ionization profiles of CP shifted to lower pH, resulting in lower pK_a (Fig. 3, Table 1). Such shift was considered to be induced by more deprotonation of the polymer in the presence of Na^+ ions. Screening of the carboxyl groups by Na^+ ions at high μ value may possibly also influence the viscosity and swelling properties of CP as it does other polyelectrolyte gels.⁷⁾ The ionic strength of FNaCP is higher than CP since FNaCP was produced by addition of NaOH to CP. The release rate of FD-40 from the FNaCP capsules was more rapid than that of CP in both JPXIII 1st and 2nd solutions, independent of pH (Figs. 1 and 2). During the drug release from the FNaCP formulation, the swollen gel layer formed in CP was not observed (Fig. 4c). These results suggested that the ability of FNaCP to improve drug release from a solid formulation was attributable to the ionic strength. This difference in ionic strength between CP and FNaCP may influence the structure and the thickness of the gel layer which is a barrier to drug release from a solid formulation. Also, the difference in ionic strength between the gel and the bulk medium may determine the amount of water which

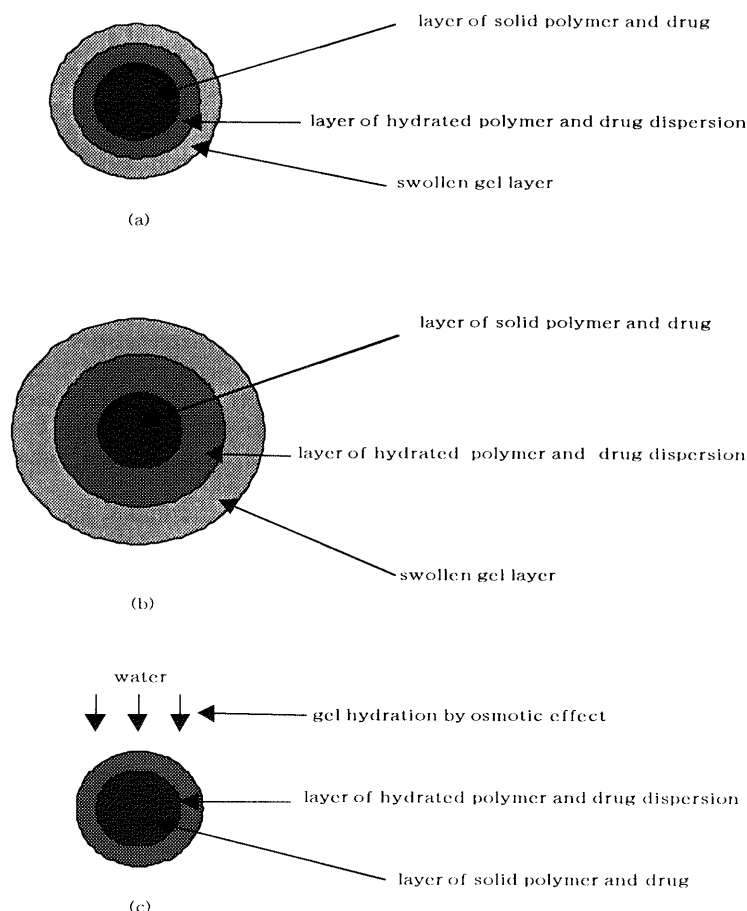


Fig. 4. Schematic Representation of Dissolution State of CP, FNaCP and Drug in Aqueous Solution of Low or High pH

(a) CP and drug in an acidic environment. (b) CP and drug in an alkaline environment. (c) FNaCP and drug in aqueous solution.

penetrates the formulation and swells the polymer.⁸⁾ The adhesive amount of FD-40 after the perfusion of the FNaCP solution on small intestinal mucosa of rats was almost equal to that in CP solution (data not shown). Thus, it is concluded that the difference in release rate of FD-40 from the solid formulation of these polymers is the most important factor in enhancement of drug absorption.

In summary, the barrier to the drug release from the CP capsule was the swollen and thick gel layer between the capsule and the bulk release medium. For the FNaCP capsule, no such firm barrier was formed and freeze-drying in the preparation of FNaCP made water penetration easier, resulting in an improvement in release of the drug.

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