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Suppression of agglomeration in fluidized bed coating. IV. Effects of sodium citrate concentration on the suppression of particle agglomeration and the physical properties of HPMC film

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Abstract

We previously reported that sodium citrate (Na citrate), which is a high order salt in the Hofmeister's series, greatly suppressed particle agglomeration in fluidized bed coating (Pharm. Res., 16 (1999), 1616–1620). In this paper, we studied the effects of Na citrate concentration on the particle agglomeration in fluidized bed coating and on the structure of coated film on the particles. Spherical granules made of crystalline cellulose (Celphere®) containing phenacetin were coated in a fluidized bed with the aqueous coating solution of hydroxypropylmethyl cellulose (HPMC) containing Na citrate at various concentrations. The particle diameter and drug release profile of coated particles, and the physical properties, i.e. tensile strength, elongation percentage at break, porosity and pore size distribution, of the HPMC cast film were investigated. The particle agglomeration was suppressed with the increasing Na citrate concentration. It is considered that the increase in the suppression effect was caused by the salting-out effect of the increased Na citrate. In the HPMC cast film system, the tensile strength and elongation percentage decreased and the porosity and cumulative pore volume increased with an increase in Na citrate concentration. It is considered that the increase in the porosity by adding Na citrate resulted from a phase separation due to the salting-out during the film forming process. The drug release rate from coated particles also increased with the increasing Na citrate concentration. It can be concluded that the increase in the release rate was due to the increase in porosity of the HPMC coated film caused by the increased Na citrate concentration.

Keywords: Fluidized bed coating; Agglomeration; Hydroxypropylmethylcellulose; Sodium citrate; Salting-out; Phase separation

1. Introduction

Film coating of pharmaceuticals with polymeric materials is useful to prevent their denaturation

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and deterioration due to moisture adsorption and oxidation, to mask their bitter taste and offensive smell, and also to control the release rate of an active agent (Ghebre-Sellassie, 1994; McGinity, 1997). A fluidized bed apparatus has been widely used for film coating in the pharmaceutical industry (Fukumori et al., 1987, 1991, 1992; Jones, 1994; Watano et al., 1994; Horio and Mori, 1999). In the coating process with this apparatus, however, agglomeration of core particles is liable to happen due to the slow current of particles caused by the properties of the apparatus. Particularly in coating fine particles, agglomeration happens very frequently (Fukumori et al., 1991, 1992, 1993; Jones, 1994; Kage et al., 1998).

Fukumori et al. reported that particle agglomeration was reduced by adding NaCl to the hydroxypropyl cellulose aqueous coating solution in fine particle coating through the Wurster process (Fukumori et al., 1993). We studied the effect of NaCl concentration on the suppression of particle agglomeration, and found that the suppression was due to a reduction in the viscosity of the coating solution caused by the salting-out of the polymeric membrane materials (Yuasa et al., 1997, 1999). In our previous paper, we clarified the relationship between the suppressive effect of salts in the Hofmeister's series (Schott, 1980; Voelkel, 1981) and the order of their consistent ions in the series, and found that the suppressive effect of a salt on particle agglomeration depended on the salting-out power of the salt (Nakano et al., 1999).

In the present study, Na citrate, which is a high order salt in the Hofmeister's series, was used as an additive to suppress particle agglomeration in fluidized bed coating because it is widely used as a food or pharmaceutical additive and its safety has been well confirmed (American Pharm. Association and The Royal Pharmaceutical Society of Great Britain, 1986; Fujiwara and Aibara, 1992). The effects of Na citrate concentration in HPMC aqueous coating solution on the suppression of particle agglomeration in fluidized bed coating and the structure of the HPMC coating film were examined. The drug release profile of the coated particles was also studied.

2. Materials and methods

2.1. Materials

Phenacetin (PHE) (Tsukishima Pharmaceutical, Japan) was used as a model drug. Spherical granules made of crystalline cellulose (CP) (Celphere™, CP203, the mean particle diameter is 210 μm. Asahi Chemical Industry, Japan) were used as the core material to prepare drug-loaded core particles. HPMC (TC-5R, the density is 1.29 g/cm^3, the kinematic viscosity of its 2% aqueous solution at 20°C amounts up to 6 mm^2/s, Shin-Etsu Chemical, Japan) was used as the coating material. Sodium citrate (Na citrate) (the density is 1.19 g/cm^3, analytical grade, Wako Pure Chemical Industries, Japan) was used as the additive.

2.2. Preparation of PHE loaded CP (PCP)

PHE-loaded CP (PCP) was prepared as follows. Twenty-five grams of PHE was dissolved in 500 ml of ethanol in a 2 l beaker at room temperature, and 500 g of CP was suspended into the solution and stirred with a magnetic stirrer for 24 h. This mixture was filtered off with filter paper and air-dried at room temperature, and the fraction below 150 μm was removed by sieving. The PHE content in PCP obtained was 2.5%.

2.3. Coating operation

The coating operation was carried out using a fluidized bed (MP-01, Powrex, Japan) with top spraying. The formulation and the conditions for coating are listed in Tables 1 and 2, respectively.

2.4. Measurement of particle diameter

The particle diameters of PCP and coated particles were measured by the image analysis method using an image-analyzing package (WinROOF, Mitani, Japan). The number-basis median diameter of the particles (D_{50}) and its number-basis geometric standard deviation (SD_g, $D_{50}/D_{15.8}$) were determined from about 1000 particle diameters.

Table 1
Formulation in fluidized bed coating

	Concentration of sodium citrate (mol/l)				
	0	0.001	0.005	0.010	0.030
Core partricle					
PCP (g)	500	←	←	←	←
Coating solution					
HPMC (g)	100	←	←	←	←
Sodium citrate (g)	–	0.85	4.26	8.52	25.55
Water (ml)	3300	←	←	←	←

2.5. Preparation of cast film

The HPMC cast films with or without Na citrate were prepared from aqueous solutions having the concentration five times as high as that of the coating solution. Three grams of the solution was cast on a Teflon petri dish of 7.5 cm diameter and dried at 40°C for 8 h. The water content of the cast films obtained was about 1.5% in all cases.

2.6. Tensile test of cast film

The tensile test of the cast film was carried out using a universal testing machine (TCM-5000C, Minebea, Japan) with a load cell (U3B1-20K-B, Minebea, Japan) to measure the tensile stress, and the chucks (CH-200N, Minebea, Japan) to hold the sample. The extension speed was 10 mm/min. The stress–strain curve was recorded for each sample with an analysis recorder (AR-1200, Yokogawa Electric, Japan).

The tensile strength Eq. (1) and the elongation percentage at break Eq. (2) of the cast film were calculated by the following equations. (Narisawa et al., 1994a; Macleod et al., 1997)

$$\text{Tensile strength} = F/A_0 \tag{1}$$

$$\text{Elongation \% at break} = \Delta L/L \times 1/A_0 \times 100, \tag{2}$$

where L and A_0 are the length and cross sectional area of the cast film before the test, respectively, ΔL and F are the elongation and stress at break of the film, respectively.

2.7. Measurement of film porosity

The porosity of the films was calculated from the apparent film volume and the theoretical value of the true film volume. The film thickness was measured by using a micrometer (Dial Thickness Gage, Mitsutoyo, Japan) and evaluated from the average thickness of nine different positions in the film cut in a circular shape of 6.6 cm diameter. The true film volume (V_{th}) was calculated by the following Eq. (3)

$$V_{th} = W_f\ R_{HPMC}/\rho_{HPMC} + W_f\ R_{NAC}/\rho_{NAC}, \tag{3}$$

where W_f is the film weight, R_{HPMC} and R_{NAC} are the weight ratios of HPMC and Na citrate to the solid weight in the cast film preparation solution, respectively, and ρ_{HPMC} and ρ_{NAC} are the true densities of HPMC and Na citrate calculated from the volumes measured with an air comparison pycnometer (Beckman®, Model 930, Beckman Instruments, USA), respectively.

Table 2
Operating conditions for fluidized bed coating

Inlet air temperature (°C)	70
Outlet air temperature (°C)	38.0 ~ 42.0
Spray pressure (kgf/cm^2)	2
Spray rate (g/min)	13.0
Spray air volume (m^3/h)	1.9
Inlet air volume (m^3/h)	80 ~ 90

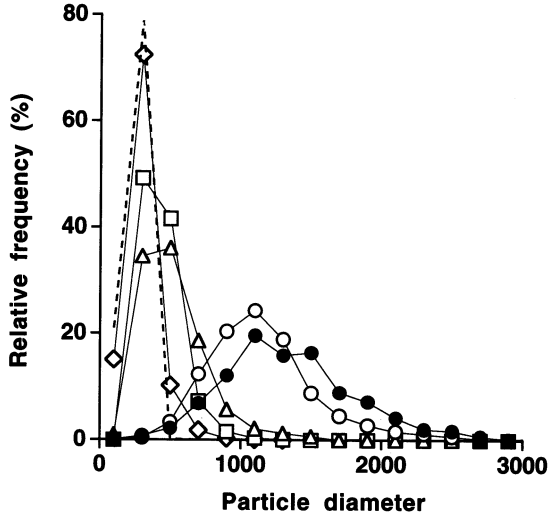

Fig. 1. Effect of Na citrate concentration on particle size distribution of coated particles. The dotted line represents PCP. Na citrate concentration (mol/l): (●) 0, (○) 0.001, (△) 0.005, (□) 0.01, (◇) 0.03.

2.8. Measurement of pore size distribution in the film

Pore size distribution in the HPMC cast film was measured by mercury intrusion porosimetry (Ozeki et al., 1995), employing a mercury porosimeter (AUTOSCAN-33, Quantachrome, USA). The contact angle of mercury with the samples and the surface tension of mercury were taken to be 140° and 480 dyn/cm, respectively (Ritter and Drake, 1945).

2.9. Scanning electron microscopy (SEM)

A scanning electron microscope (S-2250N, HITACHI, Japan) was used to observe the cross-section morphology of the HPMC cast films and the coated particles.

2.10. Release studies

The release profiles of PHE from PCP and coated particles (sieved at 150–425 μm) were studied with a dissolution tester (TR-5S3, Toyama Sangyo, Japan), according to the paddle method (JPXIII) at 150 rpm, using 900 ml of distilled water at 37 ± 0.5°C as the dissolution medium. The quantity of PHE was determined spectrophotometrically by measuring the absorbance at 243 nm.

3. Results and discussion

3.1. Effect of Na citrate concentration on particle size in fluidized bed coating

Fig. 1 shows the effect of Na citrate concentration on the particle size distribution of the coated particles that were collected after the coating was finished. D_{50} and SD_g of the particles are listed in Table 3. In the case of no Na citrate addition, a significant increase in particle diameter because of the agglomeration between the particles was observed. When Na citrate was added, the particle diameter decreased and the particle agglomeration was more suppressed with the increasing Na citrate concentration in the coating solution, in a manner similar to that with sodium chloride (Yuasa et al., 1997, 1999).

The coating efficiency in the fluidized bed coating is listed in Table 3. An increase in Na citrate concentration resulted in a greater coating effi-

Table 3
D_{50}, SD_g and coating efficiency of coated particles and PCP

	PCP	Concentration of sodium citrate (mol/l)				
		0	0.001	0.005	0.010	0.030
Median diameter (μm)	216	1270	1081	475	390	291
$SD_g(-)$	1.21	1.42	1.39	1.48	1.41	1.25
Coating efficiency (%)	–	61.4	64.1	69.9	71.2	89.8

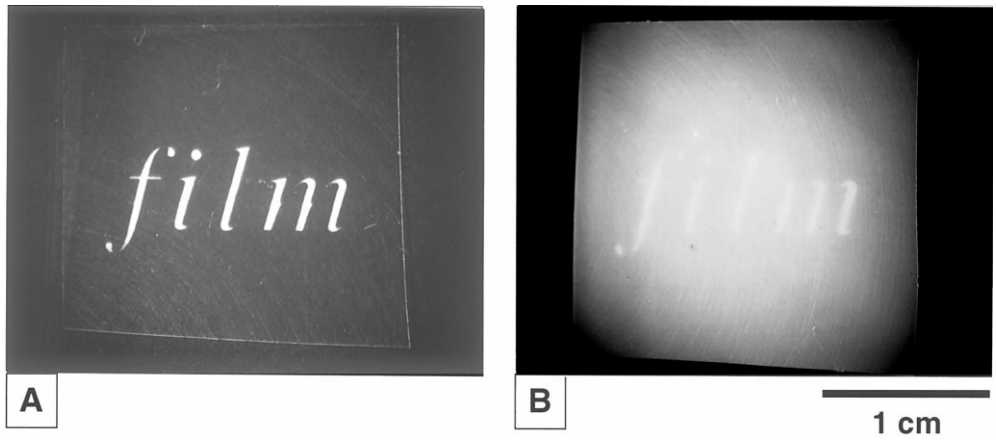

Fig. 2. Appearances of HPMC cast films with and without Na citrate. (A) without Na citrate; (B) 0.03 mol/l of Na citrate concentration.

ciency. This result was thought as follows. When the Na citrate concentration was high, a number of the particles with smaller particle diameters were fluidized in the spray zone in the vicinity of the spray nozzle because particle agglomeration was suppressed by the increased Na citrate concentration. Thus the interfacial surface area of the particles increased, and the collision probability between the spray mist and the core particles was also increased, causing an increase in the coating efficiency.

We previously reported the following mechanism for the suppression of particle agglomeration by adding salts (Yuasa et al., 1997 and 1999; Nakano et al., 1999). HPMC aqueous solution has a lower critical solution temperature (LCST), exhibiting a sol-to-gel phase transition on heating, and HPMC polymers precipitate from the aqueous solution (Klug, 1971; Sarkar, 1979; Mitchell et al., 1990). When salts like sodium chloride and Na citrate are added to the solution, the phase transition temperature is decreased by the salting-out effect of the salt, as the concentration of the salt gets higher (Klug, 1971; Sarkar, 1979; Mitchell et al., 1990; Nakano et al., 1999). During fluidized bed coating, the temperature of the coating solution containing the salt of a higher concentration easily reaches the phase transition temperature with a smaller rise than in the case of a lower salt concentration. In addition, the phase transition temperature is decreased by an increase in the salt concentration caused by water evaporation from the coating solution. Thus, the phase transition occurs earlier in the coating solution containing the salt of a higher concentration after the solution is sprayed. This transition results in a reduction in the viscosity of the liquid phase (supernatant fluid) because HPMC polymers precipitate and the structural viscosity is lost. As a result, particle agglomeration is more suppressed compared with the case of a lower salt concentration, because the binding force between the particles bridged by the viscous liquid is decreased by the reduction in viscosity.

When the phase transition occurs owing to the salting-out effect of the added salt, the HPMC polymer chains in the coating solution might aggregate because of dehydration of hydrated water and the hydrophobic interaction between the polymer chains (Sarkar, 1979 and 1995; Mitchell et al., 1990). It was thought that the aggregation of HPMC polymer chains might affect the structure of the HPMC coating film on the coated particles.

3.2. Effects of Na citrate concentration on physical properties of HPMC cast film

HPMC cast films were prepared to study the effects of Na citrate concentration on the HPMC coating films of the coated particles. Fig. 2 shows

the appearances of the cast films with and without Na citrate. The film without Na citrate was visibly transparent, whereas the film with Na citrate was visibly opaque.

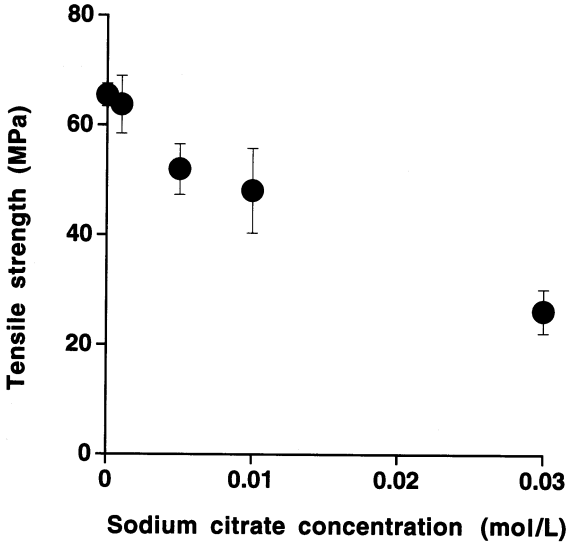

Fig. 3. Effect of Na citrate concentration on tensile strength of cast film. Each point represents the mean ± S.D. ($n = 5$).

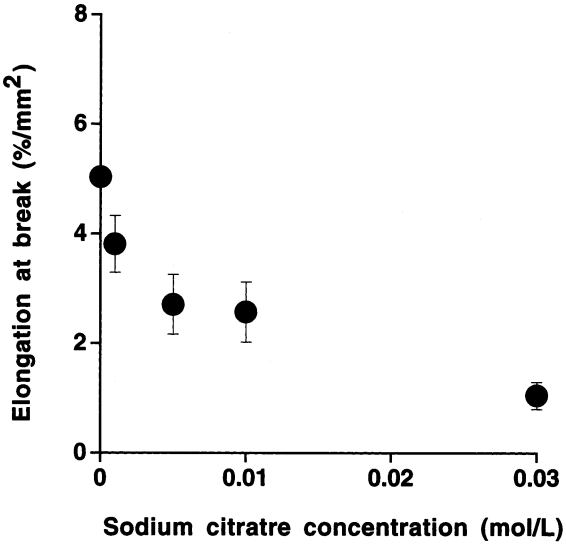

Fig. 4. Effect of Na citrate concentration on elongation percentage at break of cast film. Each point represents the mean ± S.D. ($n = 5$).

The mechanical properties of the cast films were examined by tensile testing. The effect of Na citrate concentration on the tensile strength (T_S) of the HPMC cast film is shown in Fig. 3. T_S decreased with an increase in the Na citrate concentration. Fig. 4 shows the elongation percentage at break of the HPMC cast film at various Na citrate concentrations. The percentage decreased with the increasing Na citrate concentration, indicating that the HPMC cast film becomes brittle due to the added Na citrate.

The internal structure of the films was investigated in order to clarify the reason for the lowering in the mechanical strength. The SEM photographs of the cross-sections of the HPMC cast films are shown in Fig. 5. The film without Na citrate was dense and homogeneous. When Na citrate was added, a number of micro-pores were observed in the films when the Na citrate concentration was high. From this fact, it is thought that the scattering of light from the pores formed in the films caused the opaqueness of the film with Na citrate, seen in Fig. 2.

Fig. 6 shows the effect of the Na citrate concentration on the pore size distribution in the HPMC cast film. The cumulative pore volume and the pore volume in the ranges of about 0.01–0.1 and 10–100 μm of pore diameter in the HPMC cast film increased with the increasing Na citrate concentration.

The effect of Na citrate concentration on the porosity (ε) of the HPMC cast film is shown in Fig. 7. The porosity increased with the increasing Na citrate concentration.

Regarding the relationship between the mechanical strength and the porosity of a porous material, Bal'shin et al. proposed the following empirical formula Eq. (4) (Kondou, 1986; Narisawa et al., 1994b)

$$\sigma_p = \sigma_o(1-\varepsilon)^{\alpha}, \tag{4}$$

where σ_p and σ_o are the mechanical strengths of a porous material and the corresponding nonporous material, respectively, and α is a constant. Fig. 8 shows the relationship between log T_S and log $(1-\varepsilon)$ A linear relationship was observed between these factors, showing that Bal'shin equation is suited for the mechanical strength of the

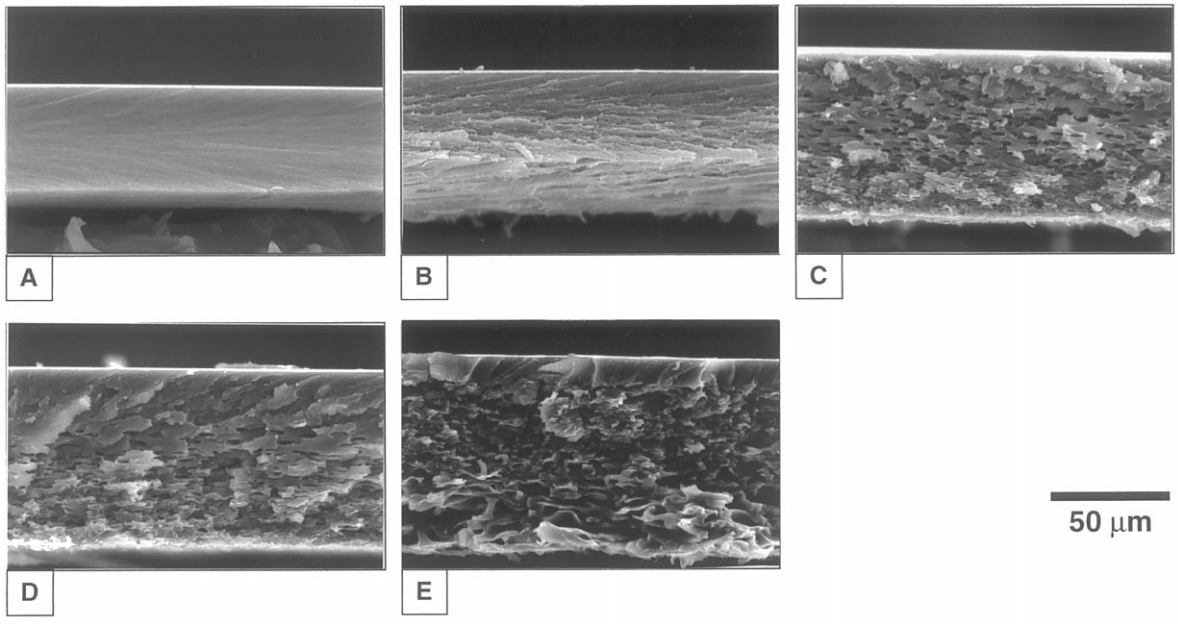

Fig. 5. SEM photographs of cross-section of HPMC cast films. Na citrate concentration (mol/l): (A) 0, (B) 0.001, (C) 0.005, (D) 0.01, (E) 0.03.

porous HPMC film in this study. Therefore, it is suggested that the decrease in T_S of the HPMC cast film with the increased Na citrate concentration resulted from the increase in the porosity (ε) of the film. The decreased in the elongation percentage was also due to the increase in the porosity.

Concerning the pore forming mechanism for porous polymer films, Lloyd et al. reported that microporous membranes were prepared through the thermally induced solid–liquid phase separation of polymer diluent mixtures (1990). Narisawa et al. reported that porous ethylcellulose (EC) films were formed from an EC–ethanol (a solvent)–water (a non-solvent) ternary mixture during the film forming on the basis of the micro-phase separation process (1993, 1994a, and 1994b). Park et al. reported porous PLLA (poly (L-lactide)) membranes generated from a three-component polymer solution (PLLA–methylene chloride–ethylacetate) by the phase inversion technique (1997). The porous HPMC films in this study may have been formed in a manner similar to that of these porous films, which is as follows. When the HPMC aqueous solution containing Na

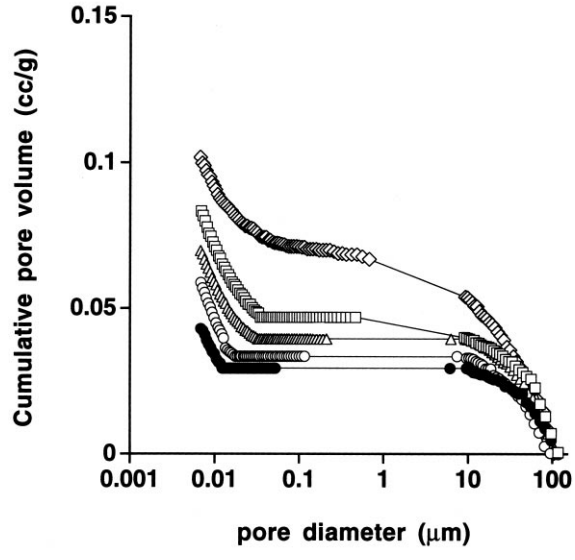

Fig. 6. Effect of Na citrate concentration on pore size distribution of HPMC cast film. Na citrate concentration (mol/l): (●) 0, (○) 0.001, (△) 0.005, (□) 0.01, (◇) 0.03.

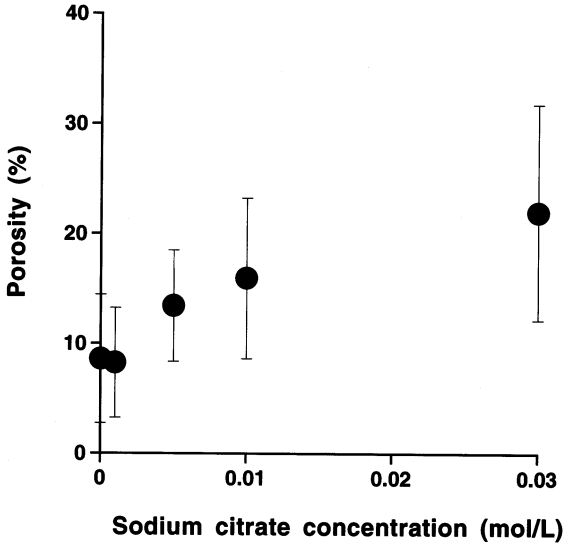

Fig. 7. Effect of Na citrate concentration on porosity of HPMC cast film. Each point represents the mean ± S.D. ($n = 10$).

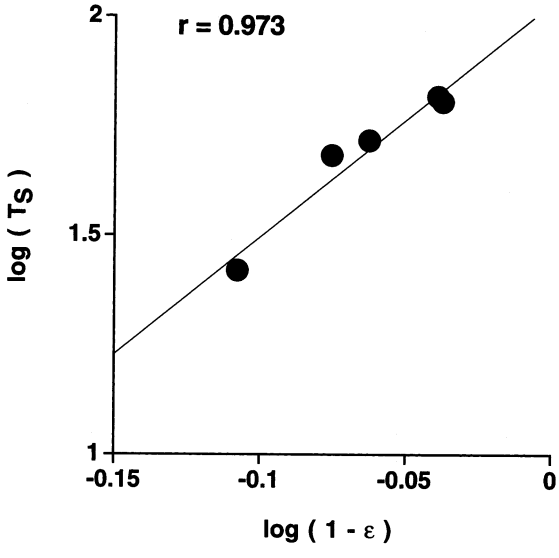

Fig. 8. Relationship between log T_S and log $(1 - \varepsilon)$.

citrate is cast, the solution is homogeneous and transparent. Since the Na citrate concentration increases due to the water evaporation, the phase transition of casting solution occurs owing to the salting-out effect of Na citrate, and HPMC polymers aggregate and form clusters. By further water evaporation, the HPMC clusters associate with each other and form the coagulation phase. Finally, micro-pores are formed through evaporation of the water remaining among the HPMC clusters. In addition, when the Na citrate concentration is higher, the phase separation occurs earlier in the film forming process. Therefore, the porosity and the number of micro-pores of larger size increase because more amounts of the clusters of larger sizes are formed.

3.3. Effect of sodium citrate concentration on the release profile of PCP

From above results, it has been shown that micro-pores were formed in the HPMC cast films by adding Na citrate, and that the number of micro-pores increased with the increasing Na citrate concentration. In the actual fluidized bed coating described in this study, the HPMC coating films must have been formed in the same manner as in the cast films. Hence, to evaluate the effect of Na citrate concentration on the coating film on the particles coated in the fluidized bed, the release profiles of coated particles obtained ware studied.

The release profiles of PHE from PCP and the coated particles are shown in Fig. 9 and the apparent PHE release rates for 2 min after lag time are listed in Table 4. The apparent PHE release rate increased when the Na citrate concentration was high.

The SEM photographs of the cross-sections of the coated particles with or without Na citrate are shown in Fig. 10. Similarly to the cast film, the HPMC coating film without Na citrate was dense and homogeneous, and the coating film with Na citrate was porous. Therefore, the increase in the PHE release rate from the coated particles might have resulted from the increase in the micro-pores in the HPMC coating film caused by an increase of Na citrate concentration. In addition, these results show that, when Na citrate was added to the coating solution, the phase separation caused by salting-out occurred during the film forming process in the actual fluidized bed coating.

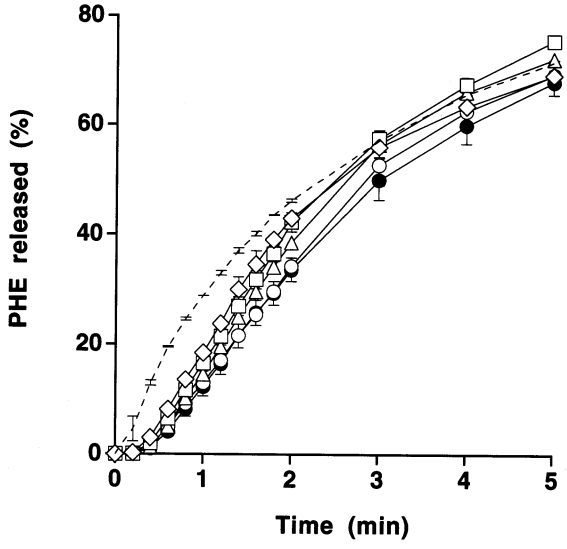

Fig. 9. Effect of Na citrate concentration on PHE release profile. The dotted line represents PCP. Na citrate concentration (mol/l): (●) 0, (○) 0.001, (△) 0.005, (□) 0.01, (◇) 0.03. Each point represents the mean ± S.D. ($n = 3$).

4. Conclusion

Particle agglomeration in fluidized bed coating was suppressed by adding Na citrate into the aqueous coating solution, and the suppression effect was dependent on the Na citrate concentration, similarly to the case with sodium chloride reported previously (Yuasa et al., 1997, 1999). In the cast film system, the porosity increased with the increasing Na citrate concentration, and it seems to be caused by the phase separation due to the salting-out and the aggregation of HPMC polymer chains. The drug release rate of HPMC coated particles increased with the increasing Na citrate concentration, indicating that the phase separation owing to the salting-out effect of Na citrate occurred in the actual fluidized bed coating. These results substantiate the propriety of the conjecture presented in our previous study on the mechanism for the suppression of particle agglomeration by adding salts.

Table 4
Apparent release rate of coated particles

Concentration of sodium citrate (mol/l)	Apparent release rate (%/min) [a]
0	20.91 ± 1.21
0.001	20.57 ± 0.17
0.005	23.82 ± 0.64
0.010	25.18 ± 0.76
0.030	25.54 ± 1.66

[a] The mean ± S.D. ($n = 3$).

Acknowledgements

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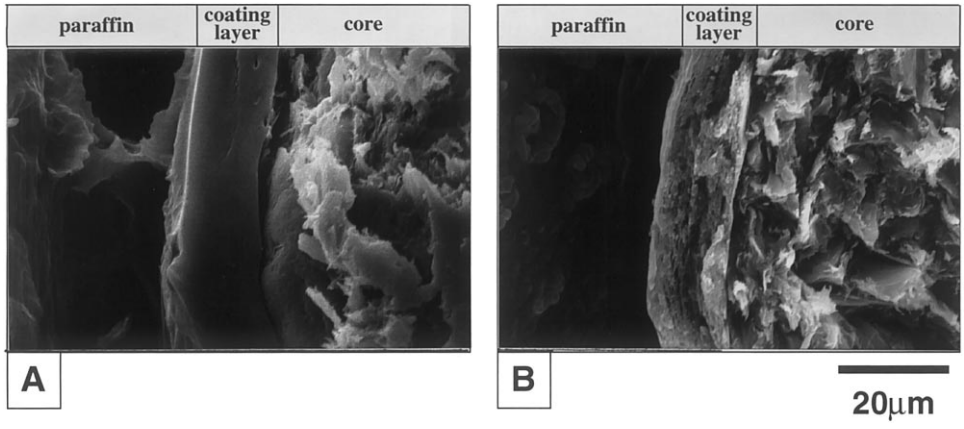

Fig. 10. SEM photographs of cross-section of coated particle with or without Na citrate. (A) without Na citrate; (B) 0.03 mol/l of Na citrate concentration.

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