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Suppression of Agglomeration in Fluidized Bed Coating. III. Hofmeister Series in Suppression of Particle Agglomeration

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Purpose. Fourteen kinds of salts consisting of various cations and anions in the Hofmeister series were used as additives for suppression of particle agglomeration in the fluidized bed coating. We attempted to clarify the relationship between the suppression effect of the salts and the Hofmeister series of their consistent ions.

Methods. Fluidized bed coating was carried out with hydroxypropylmethyl cellulose (HPMC) aqueous coating solution containing the salts and Celphere® as core particles. To elucidate the salting-out power of the salts for HPMC, the transmittance of the coating solutions at 600 nm was measured at various temperatures and the phase separation temperature (T_{PS}) was determined from the values at 50% transmittance.

Results. A high suppression effect was observed when the salts including high order ions in the Hofmeister series were added to the coating solution. T_{PS} decreased in the presence of the salts except for sodium iodide and sodium thiocyanate and lowered with the higher order ion in the Hofmeister series. The particle agglomeration was suppressed with decrease in T_{PS} of the HPMC aqueous coating solution.

Conclusions. It has been suggested that the suppression effect of a salt on the particle agglomeration depended on the salting-out power of the salt. We regard sodium citrate and potassium citrate as very useful pharmaceutical additives for the suppression of particle agglomeration in actual pharmaceutical coating.

KEY WORDS: fluidized bed coating; Hofmeister series; agglomeration suppression; salting-out; phase separation temperature; hydroxypropylmethyl cellulose.

INTRODUCTION

Film-coating of pharmaceuticals with polymeric materials are useful to prevent their denaturation and deterioration due to moisture adsorption and oxidation, and to mask their bitter taste and offensive smell (1,2). The fluidized bed apparatus has been widely used for film-coating. 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 property of the apparatus. Particularly in coating fine particles, agglomeration happens very frequently (3–7).

Fukumori *et al.* reported that particle agglomeration was reduced by adding NaCl to the hydroxypropyl cellulose aqueous coating solution in fine particle coating by the Wurster process (5). We previously studied the effect of NaCl concentration in the coating solution 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 salting-out of the polymeric membrane materials, that is, the phase separation of the aqueous coating solution (8,9).

The order of the salting-out power is generally known as the Hofmeister (lyotropic) series. It governs many colloidal phenomena, including the salting-out of hydrophilic colloids, and the effect of salts on the temperature of gelation, the swelling of hydrogels and the viscosity of hydrosols (10–13). For cations bounded with chloride anion, the series is generally

$$Ba^{2+} > Sr^{2+} > Ca^{2+} > K^{+} > Na^{+}$$

where the salting-out power of cation increases from the right to the left side of the series (14,15). Similarly, for anions bounded with the same cation, the series is generally

$$\text{citrate}^{3-} > SO_4^{2-} > \text{acetate}^{-} > Cl^{-} > Br^{-} > I^{-} > SCN^{-}$$

(10–15). Addition of NaCl to the aqueous coating solution suppresses particle agglomeration as stated above. Therefore, salts other than NaCl must suppress particle agglomeration and the order of the suppression effect of the salts must follow the order of the salting-out power, that is, the Hofmeister series.

In the present study, 14 kinds of salts consisting of various cations and anions in the Hofmeister series were used as additives for the suppression of particle agglomeration. The relationship between the order in the Hofmeister series and the suppression effect of the salts was studied. The effect of salt addition on the phase separation temperature (T_{PS}) (lower critical solution temperature, LCST) of hydroxypropylmethyl cellulose (HPMC) aqueous coating solution and the relationship between T_{PS} and the degree of suppression of particle agglomeration were also studied. Further, considering the Hofmeister series, we selected the effective salts that are food and/or pharmaceutical additives for the suppression of particle agglomeration.

MATERIALS AND METHODS

Materials

As core particles, spherical granules made of crystalline cellulose (CP) (Celphere™, CP203, Asahi Chemical Industry, Japan) were used. HPMC (TC-5R, the kinematic viscosity of a 2% aqueous solution at 20°C amounts up to 6 mm^2/s, Shin-Etsu Chemical, Japan) was used as coating material. Fourteen kinds of salts (all of analytical grade, Wako Pure Chemical Industries, Japan) were used as additives.

The cation system (the chlorides with various cations) consisted of barium chloride ($BaCl_2$), strontium chloride ($SrCl_2$), calcium chloride ($CaCl_2$), potassium chloride (KCl) and sodium chloride (NaCl).

The anion system (the sodium salts with various anions) consisted of sodium citrate (Na citrate), sodium sulfate (Na_2SO_4), sodium acetate (Na acetate), sodium chloride (NaCl), sodium bromide (NaBr), sodium iodide (NaI) and sodium thiocyanate (NaSCN).

Calcium sulfate ($CaSO_4$), potassium citrate (K citrate) and potassium sulfate (K_2SO_4) were also used.

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Coating Operation

The coating operation was carried out using the fluidized bed (MP-01, Powrex, Japan) with top spraying. Five hundred grams of CP were used as core materials. Aqueous solutions (1650 mL) of HPMC (3%) containing the salts were used as the coating solution. The salt concentrations were 0.01 or 0.08 mol/L. The operating conditions in this study were as follows: coating solution feed, 13 g/min; spray air pressure, 2 kgf/cm^2; spray air volume, 1.9 m^3/h; inlet air volume, 80 m^3/h; inlet air temperature, 70°C; and outlet air temperature, 38–40°C.

Five grams of the coated particles were collected every 30 minutes from the start of coating after preheating, and once more after the coating was finished.

Measurement of Particle Diameter

The particle diameters of CP and coated particles were calculated by the image analysis method using an image-analyzing package, WinROOF (Mitani, Japan), from about 1,000 particles. The mean of the horizontal Ferret diameters was regarded as the mean particle diameter by number basis.

Measurement of Transmittance and Determination of Phase Separation Temperature

The phase separation temperature (T_{PS}) of the HPMC aqueous coating solutions with or without salt was determined by measuring the transmittance at 600 nm and various temperatures (16–18), using a spectrophotometer (Ubest-30, Japan Spectroscopic, Japan). T_{PS} was defined at the temperature where 50% of the transmittance transition occurred (17,18).

RESULTS AND DISCUSSION

Effect of Salt Addition on Particle Diameter in Fluidized Bed Coating

The effects of the salts of the cation and anion systems on particle agglomeration in the fluidized bed coating are shown in Figs. 1 and 2, respectively. The concentration of the salt was set at 0. 08 mol/L where the suppression effect was observed for NaCl in our previous study (9). In the cation system (Fig. 1), all chlorides suppressed particle agglomeration and the suppression effect was larger with the higher order cation in the Hofmeister series. Particularly the effects of $BaCl_2$ and $SrCl_2$ were significant. In the anion system (Fig. 2), the sodium salts suppressed particle agglomeration except for NaI and NaSCN, and the suppression effect was larger with the higher order anion in the Hofmeister series, similarly to the cation system. Particularly the effects of Na citrate and Na_2SO_4 were remarkable.

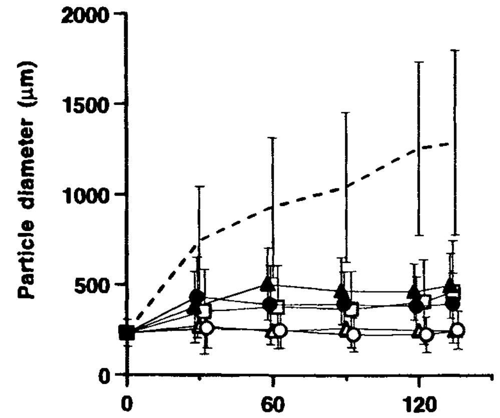

Fig. 1. Effect of addition of various chlorides at 0.08 mol/L concentration on particle diameter during fluidized bed coating. The dotted line represents the case of no salt addition. Chlorides: (○) $BaCl_2$, (△) $SrCl_2$, (□) $CaCl_2$, (●) KCl, (▲) NaCl. Each point represents the mean ± S.D. of about 1,000 particles.

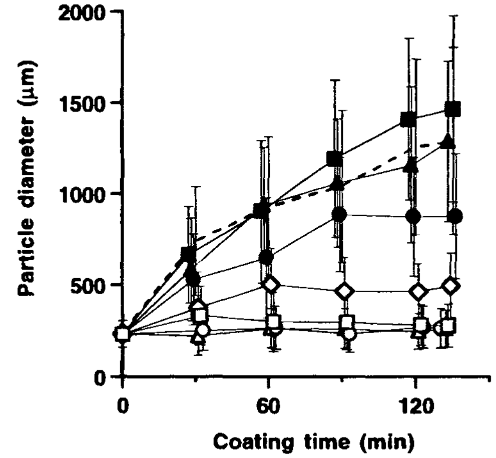

Fig. 2. Effect of addition of various sodium salts at 0.08 mol/L concentration on particle diameter during fluidized bed coating. The dotted line represents the case of no salt addition. Sodium salts: (○) Na citrate, (△) Na_2SO_4, (□) Na acetate, (◇) NaCl, (●) NaBr, (▲) NaI, (■) NaSCN. Each point represents the mean ± S.D. of about 1,000 particles.

Particle agglomeration was hardly observed with $BaCl_2$, $SrCl_2$, Na citrate and Na_2SO_4, and little difference was recognized in the suppression effect among them at 0.08 mol/L concentration. Accordingly, the coating operations were performed at 0.01 mol/L concentration. The results in the cation and anion systems are shown in Fig. 3 (A) and (B), respectively. All the salts suppressed particle agglomeration at even 0.01 mol/L concentration. The suppression effect of $BaCl_2$ was higher than that of $SrCl_2$ in the cation system (Fig. 3A). The suppression effect of Na citrate was higher than that of Na_2SO_4 in the anion system (Fig. 3B). Thus, in both the cation and anion systems, the order of suppression effect of the salt on particle agglomeration in the fluidized bed coating followed that in the Hofmeister series.

Effect of Salt Addition on Phase Separation Temperature of HPMC Aqueous Coating Solution

HPMC has a lower critical solution temperature (LCST), that is, the phase separation temperature (T_{PS}) in aqueous solution. The phase separation occurs through thermal gelation of HPMC while the aqueous solution is heated, and T_{PS} is altered in the presence of certain salts in the aqueous solution (19–21). Therefore, the effect of the salts on T_{PS} of HPMC aqueous coating solution was studied. The phase separation profiles of the solutions with various salts at 0.08 mol/L concentration in the cation and anion systems are shown in Figs. 4 and 5, respectively. The transmittance of the solution without salt

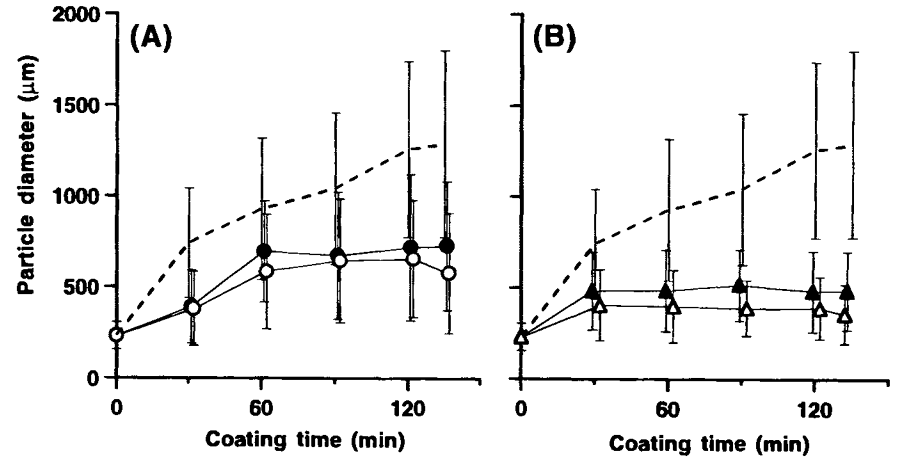

Fig. 3. Effect of addition of salts in the cation (A) and anion (B) systems at 0.01 mol/L concentration on particle diameter during fluidized bed coating. The dotted line represents the case of no salt addition. Salts: (○) $BaCl_2$, (●) $SrCl_2$, (○) Na citrate, (△) Na_2SO_4. Each point represents the mean ± S.D. of about 1,000 particles.

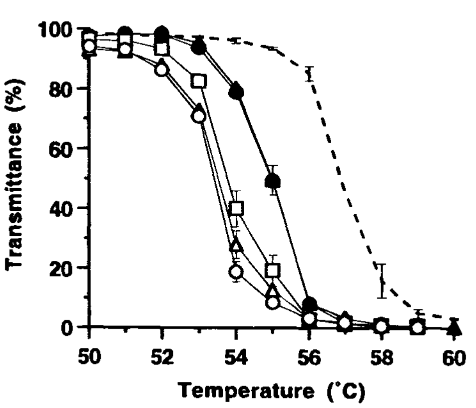

Fig. 4. Effect of temperature on transmittance of HPMC aqueous coating solutions with various chlorides at 0.08 mol/L concentration. The dotted line represents the case of no salt addition. Chlorides: (○) $BaCl_2$, (△) $SrCl_2$, (□) $CaCl_2$, (●) KCl, (▲) NaCl. Each point represents the mean ± S.D. (n = 3).

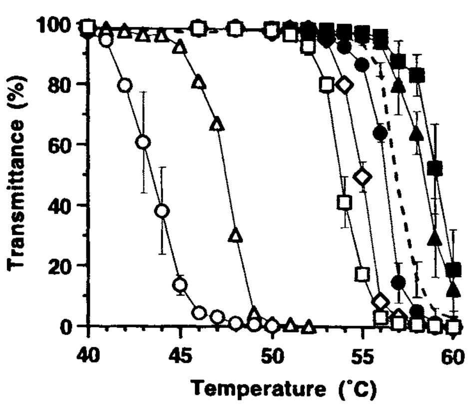

Fig. 5. Effect of temperature on transmittance of HPMC aqueous coating solutions with various sodium salts at 0.08 mol/L concentration. The dotted line represents the case of no salt addition. Sodium salts: (○) Na citrate, (△) Na_2SO_4, (□) Na acetate, (◇) NaCl, (●) NaBr, (▲) NaI, (■) NaSCN. Each point represents the mean ± S.D. (n = 3).

decreased at about 57°C owing to the thermal gelation of HPMC. In the cation system (Fig. 4), the phase separation occurred at a lower temperature than that of the solution with no addition. In the anion system (Fig. 5), the phase separation occurred at a lower temperature than that of the solution with no addition except for NaI and NaSCN. T_{PS} of HPMC aqueous coating solution in the cation and anion systems are listed in Table 1. The lowering effect of the chlorides on T_{PS} increased in the order of NaCl, KCl $<$ $CaCl_2$ $<$ $SrCl_2$ $\leqq$ $BaCl_2$, although the differences in T_{PS} by the cation species were smaller. In the anion system, the lowering effect of the sodium salts increased in the order of NaBr $<$ NaCl $<$ Na acetate $<$ Na_2SO_4 $<$ Na citrate. This order was consistent with the effects of those sodium salts on the phase separation of hydroxypropyl cellulose (19) and on the swelling and dissolution of poly(vinyl alcohol) (15). These results show that in the case of HPMC aqueous

Table 1. Phase Separation Temperature of HPMC Aqueous Coating Solution with Various Salts

	Salts	Salt concentration (mol/L)	T_{PS} (°C)[a]
	none	—	57.0 ± 0.4
Cation system	$BaCl_2$	0.08	53.4 ± 0.0
		0.01	56.2 ± 0.1
	$SrCl_2$	0.08	53.5 ± 0.0
		0.01	56.4 ± 0.0
	$CaCl_2$	0.08	53.8 ± 0.1
	KCl	0.08	55.0 ± 0.0
	NaCl	0.08	55.0 ± 0.1
Anion system	Na citrate	0.08	43.5 ± 0.6
		0.01	54.9 ± 0.2
	Na_2SO_4	0.08	47.5 ± 0.0
		0.01	55.5 ± 0.2
	Na acetate	0.08	53.8 ± 0.2
	NaCl	0.08	55.0 ± 0.1
	NaBr	0.08	56.3 ± 0.0
	NaI	0.08	58.5 ± 0.2
	NaSCN	0.08	59.1 ± 0.4

[a] The mean ± S.D. (n = 3).

solution the order of the lowering effect by salting-out follows that in the Hofmeister series. On the other hand, NaI and NaSCN raised T_{PS} of the HPMC aqueous coating solution. This result may be due to the salting-in effect of iodide and thiocyanate anions (12). These anions disrupt the water structure joined together by hydrogen-bonds, thereby raising the hydrogen-bonding ability of water available to the HPMC. This action raised T_{PS}, causing no suppression effect on the particle agglomeration in the cases of NaI and NaSCN as shown in Fig. 2.

Relationship Between Salting-out Effect of Salt and Suppression of Particle Agglomeration in Fluidized Bed Coating

Figure 6 shows the diameter of the coated particles collected after the coating was finished as a function of T_{PS} of the HPMC aqueous coating solution. When T_{PS} was lower than about 53°C, the increase in the particle diameter was hardly observed and the particle agglomeration was almost suppressed. When T_{PS} was higher than about 53°C, the particle diameters increased with the increase in T_{PS}. These results show that particle agglomeration was suppressed more effectively with the decreasing T_{PS} of the HPMC aqueous coating solution and that the suppression effect of the salt on particle agglomeration depended on the salting-out power of the salt added to the solution. These results substantiate the propriety of the conjecture in our previous study on the mechanism for suppression of particle agglomeration by adding salts, which is as follows.

When salts were added to the HPMC aqueous coating solution, the salting-out occurred with a smaller rise in the temperature and a lower condensation by water evaporation from the coating solution than in the case of no salt addition, resulting in a reduction in the viscosity of the liquid phase (supernatant fluid). The binding force between the particles bridged by the viscous liquid decreased with a reduction in the viscosity. As a result, particle agglomeration was suppressed compared with the case of no salt addition (8,9).

Selection of Effective Salts for Suppression of Particle Agglomeration by Considering the Hofmeister Series and Their Safety

From the above results, the salts consisting of a high order cation and anion in the Hofmeister series must suppress particle agglomeration at lower additional concentration. It may be preferred here to use salts which have already been permitted as food and/or pharmaceutical additives (22,23) in view of the safety for the human body and the actual pharmaceutical design. Thus, by considering the Hofmeister series we selected $CaSO_4$, K citrate, K_2SO_4, Na citrate and Na_2SO_4 in use as food and/or pharmaceutical additives. Figure 7 shows the suppression effect of these salts on particle agglomeration at 0.01 mol/L concentration. Little suppression effect was observed with $CaSO_4$ at 0.01 mol/L concentration. Particle agglomeration was strongly suppressed by adding K citrate and K_2SO_4 as well as Na citrate and Na_2SO_4 which showed a high suppression effect in Fig. 3B. It was considered that, among the 4 kinds of salts, Na citrate and K citrate ware useful for actual pharmaceutical coating because they are widely used as food and pharmaceutical additives and their safety has been well confirmed (22,23).

CONCLUSIONS

Particle agglomeration was suppressed by adding various chlorides and sodium salts except for NaI and NaSCN. The suppression effect on particle agglomeration and the lowering effect on T_{PS} of the HPMC aqueous coating solution were larger when the salt with a higher order ion in the Hofmeister series was added. It was suggested that the suppression effect of the salt on particle agglomeration depended on the salting-out power. We selected a few greatly effective salts that are in use as food and/or pharmaceutical additives. In particular, Na citrate and K citrate, which are widely used as food and pharmaceutical additives (22,23), are considered to be very useful as pharmaceutical additives for the purpose of suppressing particle agglomeration in the fluidized bed coating.

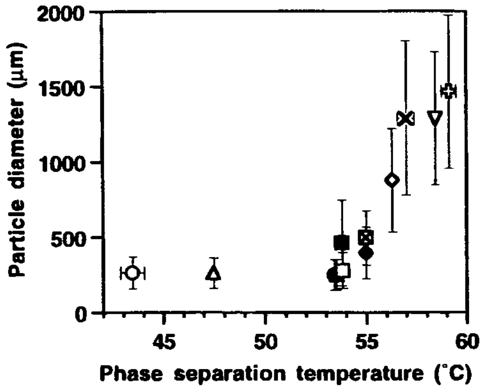

Fig. 6. Relationship between phase separation temperature (T_{PS}) of HPMC aqueous coating solution and coated particle diameter. Salts: (●) $BaCl_2$, (▲) $SrCl_2$, (■) $CaCl_2$, (◆) KCl, (☒) NaCl, (○) Na citrate, (△) Na_2SO_4, (□) Na acetate, (◇) NaBr, (▽) NaI, (✤) NaSCN, (X) no salt addition. The salt concentration is 0.08 mol/L. Each point represents the mean ± S.D. The horizontal and vertical error bars represent the S.D. of 3 measurements and about 1,000 particles, respectively.

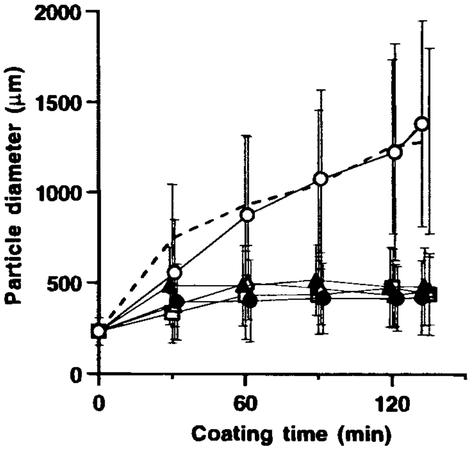

Fig. 7. Effect of addition of salts selected by considering the Hofmeister series at 0.01 mol/L concentration on particle diameter during fluidized bed coating. The dotted line represents the case of no salt addition. Salts: (○) $CaSO_4$, (△) K citrate, (□) K_2SO_4, (●) Na citrate, (▲) Na_2SO_4. Each point represents the mean ± S.D. of about 1,000 particles.

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