Effect of Additives on Agglomeration in Aqueous Coating with Hydroxypropyl Cellulose

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Water-soluble hydroxypropyl cellulose (HPC) was applied to fine lactose powder (53—63 μm) by the Wurster process. The effects of various additives on agglomeration were studied by the binding strength of membrane materials, the droplet size and the surface morphology of coated particles. The agglomeration was also computer-simulated by a previously reported model.

Methyl cellulose (MC) and sodium alginate (ALG) increased the mass median diameter of droplets at 10% addition to HPC, while the other additives exhibited no significant effect on the droplet size distribution. The production of coarse droplets induced by MC and ALG led to the agglomeration of 76 and 87% cores, respectively, though they reduced the binding strength of HPC. Polyethyleneglycol (PEG) reduced the agglomeration by weakening the binding strength of HPC in particular. NaCl, which was incompatible with HPC, reduced agglomeration by hindering HPC from forming homogeneous film. The computer simulation indicated that the smallest sizes of droplets causing the agglomeration were 44—71 μm. With MC and ALG the weight fraction of coarse droplets causing the agglomeration reached 5.7 and 4.4%, respectively; however, it was less than 1% with the other additives. Such a minor quantity of droplets caused the agglomeration of cores of 18% (PEG and NaCl) to 69% (polyvinyl alcohol). It was suggested that the agglomeration enhancing factor, *K*, might well reflect the state of fluidization.

Keywords coating; agglomeration; droplet size distribution; computer simulation; hydroxypropyl cellulose; pharmaceutical additive

Water-soluble polymers have been widely used as binders in granulation of pharmaceutical powders. Their films do not function as any practically effective permeation barriers for sustained release from fine microcapsules. However, they are useful as binders to fixing or layering of drugs on cores in preparation of multi-layered particles,[1] in addition to film-coating for a taste-masking or moistureproofing. While the polymers have to exhibit a sufficient binding strength for layering, an excessive binding strength unavoidably leads to agglomeration during coating operation. Therefore, it is practically useful to evaluate the agglomeration in the coating of fine powder with the water-soluble polymers.

A previous paper[2] studied the agglomeration in the coating of sharply fractionized lactose powders of 32—75 μm with hydroxypropyl cellulose (HPC). The computer simulation indicated that the smallest size of droplets, D_m, causing the agglomeration was 37.1—49.0 μm and the weight fractions larger than D_m were only 0.5—2.7%. These minor quantities of coarse droplets led to the agglomeration of 52—96% of the primary particles. When a pneumatic spray nozzle was used, such a minor quantity of coarse droplets seemed to be unavoidably produced. Therefore, it was suggested that the binding strength of membrane material had to be lowered to suppress agglomeration.

In this study, additives were sought which could suppress the agglomeration induced by spraying aqueous HPC solution in the Wurster process. The effects of additives on the fraction and size distribution of produced agglomerates, the droplet size and the binding strength of membrane were evaluated. The relation between the droplet size distribution and the agglomeration was studied by computer simulation to elucidate the mechanism of agglomeration in the coating process.[2]

Experimental

Materials All materials were used as purchased or supplied without any purification. Lactose (DMV 200M) of 53—63 μm was used as the core material and HPC (HPC-L, Nippon Soda Co., Ltd.) as membrane material.

As additives to HPC, polyethyleneglycol 6000 (PEG), sodium chloride (NaCl), saccharose (SAC), di-2-ethylhexyl sodium sulfosuccinate (AS, Aerosol OT), polysorbate 80 (PS80), benzethonium chloride (BC), propylene glycol (PG), polyvinyl alcohol (PVA, the degree of polymerization: about 500) and sodium alginate (ALG, 300 cP) were used as purchased from Nacalai Tesque Co., Ltd. Talc (No. 9 dust for industrial testing, Association of Powder Process Industry and Engineering, Japan), hydroxypropyl methyl cellulose (HPMC, TC-5R, Shin-Etsu Chemical Co., Ltd.), sodium carboxymethyl cellulose (CMC-Na, FT-1, a grade with specially low viscosity, Gotoku Pharmaceutical Co., Ltd.) and methyl cellulose (MC, 4000 cP, Wako Pure Chemical Ind., Ltd.) were also used as additives to HPC. An anhydrous silica (Aerosil #200, Nippon Aerosil Co., Ltd.) and sodium hexametaphosphate (GR grade, Nacalai Tesque Co., Ltd.) were used as a sieving aid and a dispersing agent in particle size analysis, respectively. Carbazochrome sodium sulfonate (CCSS), a drug model, was supplied by Kanebo, Ltd.

Coating A GPCG-1 Wurster (Glatt) was used throughout all experiments with a spray nozzle of 0.8 mm diameter and a filter with an opening of about 5 μm opening.[3]

Particle Size Distribution of Powders Sieve analysis of microcapsules was performed as previously reported.[4] The mass median diameter of talc powder was 7.7 μm, as measured in 1% (w/v) sodium hexametaphosphate aqueous solution using a Horiba CAPA-300 particle analyzer.

Viscosity An Ubbelohde viscometer (U-0519-20, TOP) was used. Specific gravities of solutions were determined by a pycnometer (TOP). Both measurements were performed at 30 °C.

Moisture Absorption A sample of 0.4 g was dried in a vacuum at room temperature for 1 d and then let stand in an atmosphere of relative humidity (RH) 75% and 37 °C for 4 d. The weight gain was defined as moisture absorption.

Tablet Hardness Three softly compressed tablets of 200 mg each with 29.0% porosity, 11.0 mm diameter and 2.10 mm thickness were prepared with HPC microcapsules of 63—75 μm. The tablets were allowed to absorb water vapor in the atmosphere of RH 75% and 37 °C for 3 d and then dried in a vacuum for 12 h. Hardness of the dried tablets was determined on a Kiya Hardness Tester (Kiya Seisakusho, Ltd.).

Droplet Size Distribution and Number of Primary Core Particles Composing an Agglomerate Both measurements were performed as previ-

ously reported.[2)]

Scanning Electron Microscopy (SEM) A Hitachi S430 was used.

Results and Discussion

Effect of Additives on Agglomeration Similar to the organic solvent systems previously reported,[4)] coatings were applied with aqueous HPC solutions containing various additives. The operating conditions are shown in Table I. The model drug (carbazochrome sodium sulfonate) suspended in a 2% (w/v) HPC solution was first fixed on 53—63 μm lactose powder and then the coating solution (2.5% (w/v) as HPC) containing an additive of 10% relative to HPC (1% in the surfactants, AS, PS80 and BC) was sprayed up to 40% coating level as HPC. The coating performance is shown in Table II. The coating efficiency (yield) of HPC was high, ranging from 83 to 99%.

When the density of membrane was assumed to be equal to that of HPC (1.22 g/cm^3), the diameter of microcapsules produced with 58 μm lactose cores was calculated to be 70.0 μm (68.4 μm with surfactants) and the membrane thickness 6 μm (5.2 μm). Although there were a few cases where the measured mass median diameter of microcapsules was smaller than the theoretical diameter of 70.0 μm (68.4 μm), this might have been due to an incorrectly estimated density of the membrane, incomplete coating efficiency and/or the fracture of particles during drug fixing and coating.[3)]

Table I. Operating Conditions in the Preparation of HPC Microcapsules

Core (lactose 53—63 μm):			25 g
Fixing of drug		HPC	2 g
		CCSS	2 g
		Water	added
		Total	100 ml
Coating		HPC	10 g
		Additive	1 g[a)]
		Water	added
		Total	400 ml
Operating conditions			
Inlet air temperature	(°C)		80
Outlet air temperature	(°C)		28—35
Spray pressure	(atm)		2.3
Spray rate	(ml/min)		3.5—3.8
Inlet air rate	(m^3/min)		0.5—0.8
Nozzle diameter	(mm)		0.8

a) 0.1 g for AS, PS80 and BC.

Microscopic observation revealed that particles larger than 75 μm were clearly agglomerates. A fraction larger than 75 μm is shown in Table II for all cases studied here. Even with NaCl and PEG, which most reduced agglomeration, 18% of the product was agglomerates. The agglomeration was enhanced by ALG and MC, while other polymeric additives, CMC-Na, HPMC and PVA, affected the agglomeration only slightly. Talc, a solid additive often used as a membrane diluent or antiadherant, somewhat enhanced agglomeration. The surfactants, AS, PS80 and BC, reduced the mass median diameter by about 10 μm in spite of their lower rate of addition (1%). PEG and NaCl reduced the mass median diameter by 21 μm and SAC by 15 μm.

Effect of Additive on Droplet Size Agglomeration takes place through interparticulate bridging. The strength of the bridge is primarily dependent on the strength and amount of membrane material supplied to the interparticulate contact point. The amount of bridging material at each contact point is determined by the size of supplied droplets. Thus, droplet size is one of the key factors in the agglomeration process.

The droplet size distribution was determined with each spray solution. The mass median diameters of droplets are shown in Table II and the typical examples of droplet size distribution in Fig. 1. Increase in mass median diameter led to a broader droplet size distribution as typically shown with MC and ALG. The other additives exhibited no significant effect on this distribution; in the cases of the additives not shown in Fig. 1, the distributions were similar to that of HPC alone.

The mass median diameter of microcapsules is plotted in Fig. 2 against that of droplets. The remarkable agglomeration of HPC–MC and –ALG microcapsules clearly resulted

Table II. Effect of Additives on Properties of HPC Microcapsules and Droplet Size Distributions and Results of Simulation

Additives	None	PEG	NaCl	SAC	AS	PS80	BC	HPMC	CMC-Na	PG	PVA	Talc	ALG	MC
Product														
Yield (%)	83	83	83	84	81	86	86	84	88	84	88	86	85	85
Mass median diameter (μm)[a)]	88	67	67	73	75	78	79	83	83	85	87	91	95	110
Fraction larger than 75 μm (%)[b)]	69	18	18	43	50	56	58	61	62	66	69	74	76	87
Yield of HPC (%)	94	94	99	97	89	92	93	91	96	83	95	—	88	94
Moisture absorption (%)[c)]	3.3	3.6	6.4	4.1	3.3	3.2	3.3	3.3	3.8	3.2	3.3	—	3.8	3.5
Tablet hardness (kg)	6.8	0.8	6.2	4.4	4.2	3.0	5.4	4.8	6.2	6.6	6.2	6.3	5.1	3.8
Droplet														
Mass median diameter (μm)	17.1	16.4	17.3	17.4	17.9	16.2	16.6	16.8	17.0	17.4	19.6	18.6	21.2	25.5
$D_{84.1\%}$ (μm)	25.8	25.2	27.5	25.5	27.0	24.5	25.8	24.8	25.5	26.9	28.4	26.3	42.0	48.7
Relative viscosity	6.7	6.7	6.9	6.9	7.0	5.5	4.9	7.2	14.6	7.0	7.3	—	45.6	17.3
Simulation														
D_m (μm)	45.6	50.9	56.3	45.0	48.1	45.2	47.7	44.0	44.7	48.3	46.6	—	68.2	71.0
K	1.50	0.32	0.45	0.75	0.92	1.30	1.23	1.42	0.91	1.32	1.26	—	0.64	0.80
Fraction of agglomerates	0.74	0.28	0.26	0.54	0.56	0.60	0.60	0.65	0.70	0.68	0.73	—	0.83	0.91
Maximum of N_g	29	7	9	12	17	27	27	22	21	27	19	—	37	42
Droplet larger than D_m (%)	0.87	0.43	0.55	0.63	0.80	0.67	0.82	0.68	0.86	0.95	0.97	—	4.38	5.65

a) Theoretical (D_C), 70.0 μm; particle density, 1.407 g/cm^3. b) It was observed by microscopy that the fractions larger than 75 μm were composed of agglomerates. c) At RH 75% and 37 °C for 4 d.

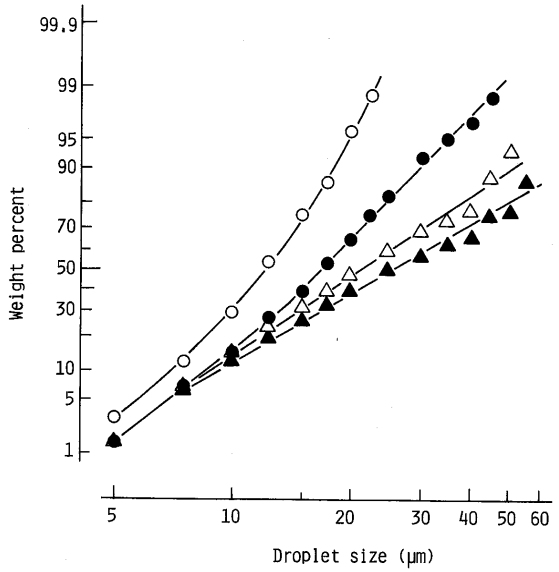

Fig. 1. Typical Examples of Cumulative Undersize Distribution of Droplets

Spray solution: ○, water; ●, HPC alone; ▲, MC; △, ALG. Spray conditions: see Table I.

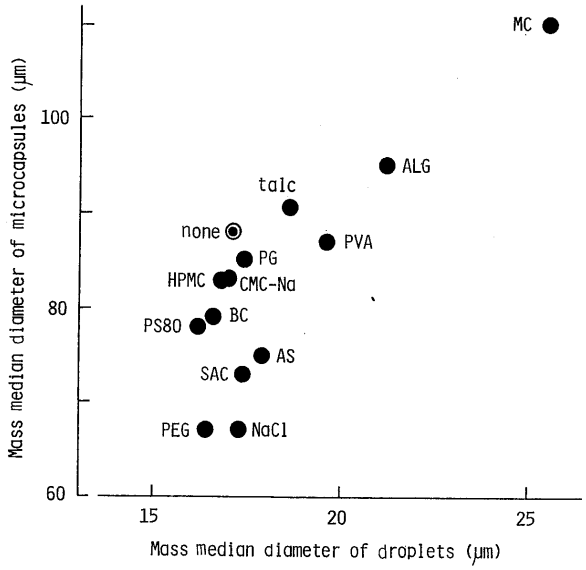

Fig. 2. Plots of Mass Median Diameter of Microcapsules against That of Droplets

from the large droplets produced.

One of the factors determining the droplet size is the viscosity of spray solution, as well known.[5] Three additives significantly increasing the viscosity were ALG, MC and CMC-Na (Table II); however, ALG whose addition led to the highest viscosity did not produce the largest droplets. CMC-Na which increased the relative viscosity of 6.7 in the HPC solution to 14.6 had no significant effect on droplet size. These are thus related to other properties of the spray solutions such as the non-Newtonian flow and/or the surface tension.[5]

Strength of Interparticulate Bridge Strength of bridging material relative to the agitation exerted on the agglomerates in the Wurster process determines whether they are disintegrated into discrete particles or remain agglomerated. The agitation was kept constant here, making useful for evaluating the binding strength of membrane material to elucidate the effect of additive in agglomeration.

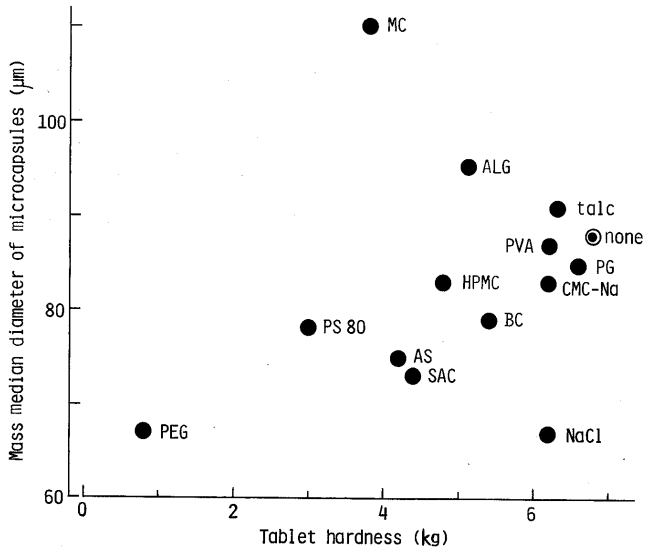

Fig. 3. Plots of Mass Median Diameter of Microcapsules against Tablet Hardness as a Measure of Binding Strength of Membrane

To conventionally evaluate the effect of additive on the interparticulate binding strength, the tablets were first prepared from unagglomerated microcapsules of 63—75 μm as described in the Experimental section, the interparticulate bridge was formed by moisture absorption and drying, and then the hardness of the tablets was determined. The softly compressed tablets with the porosity of 29.0% were easily disintegrated by a slight mechanical agitation before moisture absorption and drying. There should be little difference in their packing structure among the microcapsules produced with various additives, since sharply fractionized, unagglomerated microcapsules were used and the porosity in all was equal. Although the degree of moisture absorption might affect the extent of interparticulate bridging, there seemed to be no significant difference except the case of NaCl (Table II).

The mass median diameter of microcapsules is plotted in Fig. 3 against the hardness of the above tablets. A fairly good correlation was apparent except for MC, ALG and NaCl, though the plots were scattered to some extent. The high tablet hardness of HPC–NaCl microcapsules might be explained by especially high moisture absorption (Table II) forming a stronger interparticulate bridge. On the other hand, since the strength of HPC seemed to be decreased by MC and ALG (Fig. 3), the extremely high degree of agglomeration observed with HPC–MC and –ALG microcapsules must clearly result from the large sizes of produced droplets (Fig. 1). Figure 3 also indicated that the low degree of agglomeration with PEG might be due to its ability to lower the binding strength of HPC.

The HPC–NaCl microcapsules had a low tendency of agglomeration (Table II). This seemed to be related to the fact that among all the additives used here only NaCl hindered HPC from forming homogeneous, transparent film when the HPC–NaCl solution was cast at 60 °C. Fine crystals were really observed on the surface of HPC–NaCl

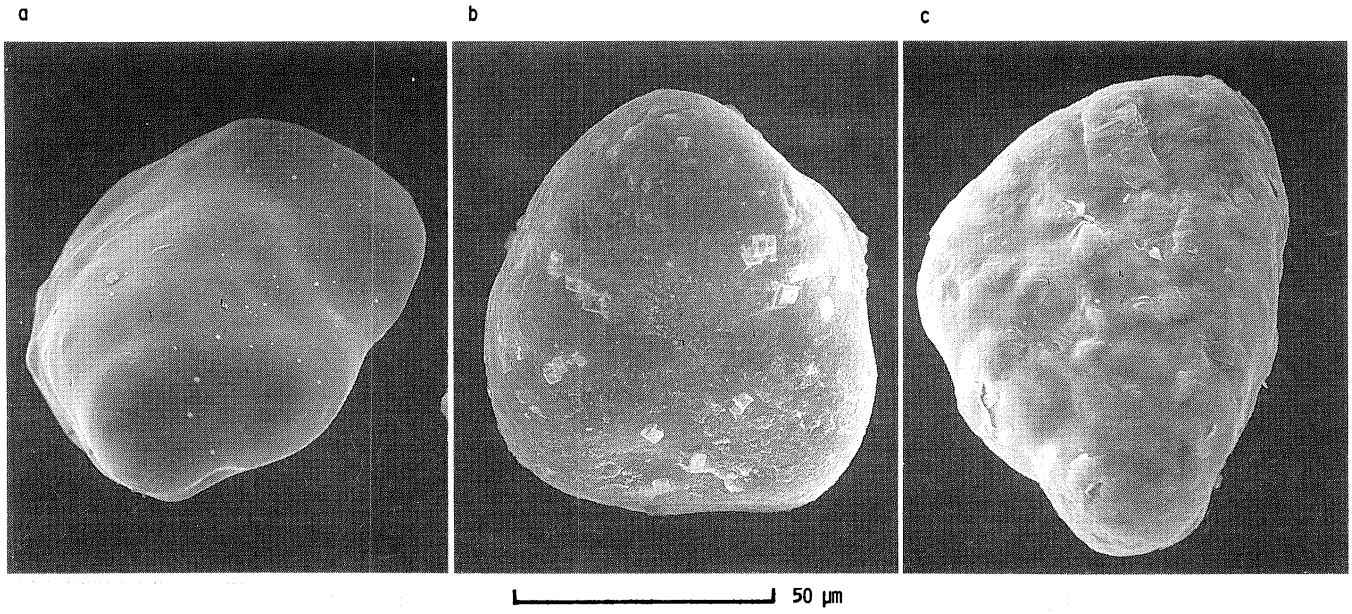

Fig. 4. Photographs of Microcapsules
Additive: a, none; b, NaCl (10%); c, talc (100%).

microcapsules by SEM, as shown in Fig. 4 where the photographs of typical microcapsules are compared. Similar recrystallization of the additive was observed in the previous study[4] where cholesterol was recrystallized in ethyl cellulose membrane. These results indicated that the formation of unhomogeneous film and/or rough surface could account for suppression of agglomeration.

Surface Roughness The HPC–NaCl microcapsules had a low tendency of agglomeration, possibly caused by the surface roughness which crystals had formed. To confirm this, a talc powder (7.7 μm) of 100% relative to HPC was added to a 2.5% (w/v) HPC spray solution and microcapsules were produced with the suspension. In this case, the theoretical diameter was 72 μm, when the talc particles with a density of 2.69 g/cm^3 were assumed to independently contribute to the membrane volume. The produced microcapsules, shown in Fig. 4, exhibited a rough surface as expected. But their mass median diameter was 87 μm and 74% were larger than 75 μm, which showed that the agglomeration tendency was higher than that with HPC alone (69%, Table II). The mass median diameter of the droplets formed from the HPC–talc (1 : 1) spray solution was 21 μm. Although the talc particles contained in the droplets were expected to weaken the interparticulate bridging by preventing tight contact between particle surfaces, they enlarged the droplet size, leading to the enhanced agglomeration. These results indicate that such a soluble, incompatible additive as NaCl is more effective to suppress agglomeration than solid additives which apparently make only the particle surface rough, but do not weaken the binding strength of polymer itself.

Simulation of Agglomeration The model of computer simulation for agglomeration was previously proposed.[2] In the coating of monodispersed cores with the size of D_c, it was first assumed that agglomerates could be produced only by droplets larger than a certain size (critical droplet size), D_m. This means that the strength of interparticulate bridge supplied by this critical droplet, whose volume is V_m, is balanced by the separation force exerted by fluidization on two primary particles or one primary particle and one agglomerate to be agglomerated. Secondarily, it was assumed in the simulation that the increase in droplet volume by $0.573\,V_m/K$ could induce the growth of agglomerates by one primary particle. K was a kind of agglomeration enhancing factor and also dependent on the separation force exerted by fluidization. D_m and K were properly dependent on the size of particles to be agglomerated because of particle size dependency of the separation force. In the present model, they were made constant at specified coating conditions for simplicity; therefore, they were estimated as averages in the computer simulation.

In the proposed model of computer simulation, the relation between the agglomerate size (D_g) and the number of primary cores composing the agglomerate (N_g) had to be determined experimentally.[2] Their relation under the experimental conditions (Table I) in the present study was determined. The results with plain HPC microcapsules are shown in Fig. 5. There was no significant effect of the additives on this relation.

Typical examples of measured and simulated size distributions of agglomerates are shown in Fig. 6. The values of D_m and K for each additive are shown in Table II with the related results. Only a minor amount of spray solution (less than 1% except for MC and ALG) caused the remarkable agglomeration. It was estimated with MC and ALG that 5.7 and 4.4% of spray solution might cause the agglomeration of 91 and 83% of the cores, respectively.

The estimated fraction of agglomerates is plotted against the fraction (F_a) of droplets larger than D_m (Table II) in Fig. 7, except the cases of ALG and MC which exhibited extremely different distributions of droplet size. The reference line in Fig. 7 was estimated by changing D_m at $K=1.5$ or 0.5 for the case of HPC alone. Figure 7 demonstrates that the fraction of agglomerates was primarily determined by F_a; the K-value only slightly

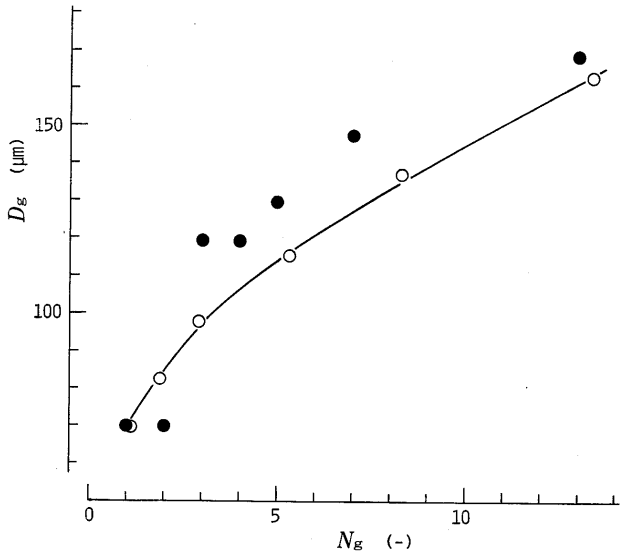

Fig. 5. Relation between the Number of Primary Cores Composing an Agglomerate, N_g and the Agglomerate Size, D_g

○, experimental; ●, estimated.[2)]

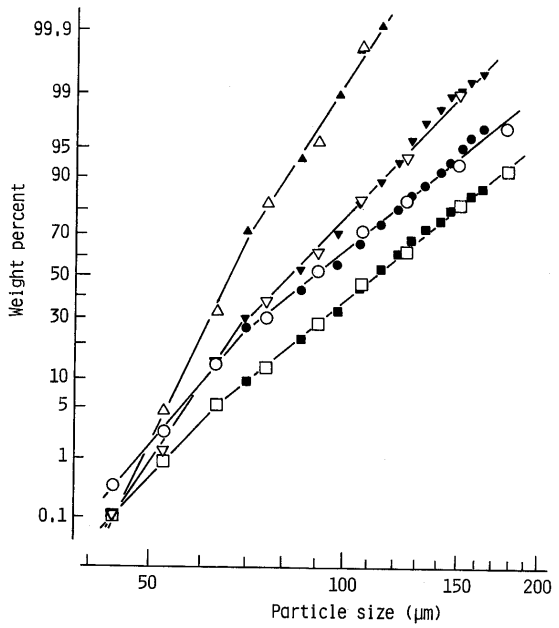

Fig. 6. Typical Examples of Cumulative Undersize Distribution of HPC Microcapsules

Additive: ○●, none; △▲, PEG; ▽▼, CMC-Na; □■, MC. Open symbols: from experiments; closed: from simulations.

affected the fraction of agglomerates.[2)] The figure also suggests that F_a had to be reduced to less than 0.1% to suppress the agglomeration to a practically allowable level (about 5%).

In the model of agglomeration previously proposed,[2)] D_m was related to the binding strength of membrane relative to the exerted separation force. In cases other than PEG, NaCl, ALG and MC, the values of D_m existed in the narrow range from 44 to 48 μm (Table II); therefore, no significant correlation with the tablet hardness was found there, because the differences were small. The large values of D_m with PEG and NaCl clearly reflected the low binding strength of HPC which contained them (Table II and Fig.

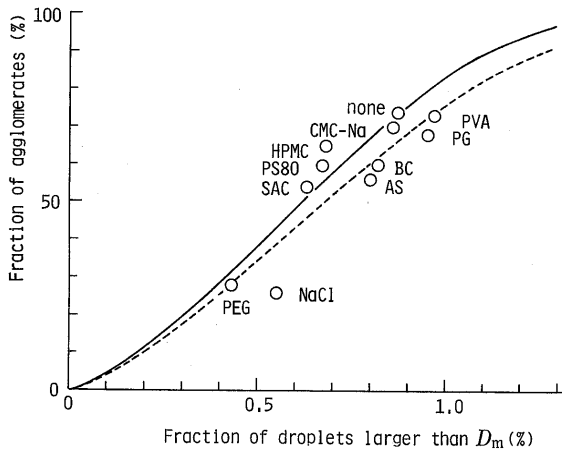

Fig. 7. Plots of Estimated Fraction of Agglomerates against That of Droplets Larger than D_m

The reference line was obtained from simulations by changing D_m at $K=1.5$ (——) or 0.5 (– – –) for HPC alone.

3). On the other hand, the values of D_m with ALG and MC seemed too large to be expected from the tablet hardness. This might partially be explained by the particle size dependency of D_m: as previously reported,[2)] D_m increased with the size of primary particles. This suggested that a more complicated model, where D_m and K were dependent on particle size, might be required to describe the case where a high degree of agglomeration occurred. However, such a complicated model should not be necessary, because only a low degree of agglomeration becomes a problem to solve in the coating technology for fine particles.

The values of K smaller than unity with PEG, NaCl, SAC, AS, CMC-Na, ALG and MC indicated that the production of coarse agglomerates was predominantly suppressed, possibly due to increase in separation force with particle size and/or change in the state of fluidization.[2)] For example, the slope of the agglomerate size distribution curve was larger with HPC–CMC-Na ($K=0.91$) than with HPC alone ($K=1.50$), while there was little difference in the fraction of agglomerates (Fig. 6). In both cases, there was also little difference in droplet size distribution (Table II) and the tablet hardness (Fig. 3). The only difference observed was that in the coating process the adhesion of particles to the chamber wall due to electrostatic charging was prevented by the addition of CMC-Na. It has often been experienced that such a particle adhesion affects the particle size distribution of a product; in many cases, this leads to enhanced production of coarse agglomerates.[6)] This is because the particle adhesion leads to overwetting of free-flowing coarse particles and consequent layering of small particles adhering to the chamber wall on their surfaces. This was the case not only with HPC alone, but also with the additives whose K-values were larger than unity.

The value of D_m was 44 μm at the minimum (Table II). It was expected from Fig. 7 that if the fraction of droplets larger than 44 μm could be reduced to less than 0.1%, the agglomeration would become less than 5% which would be practically allowable. As shown in Fig. 1, while the droplet size distribution was very broad with the 2.5% HPC solution, the distribution with water showed the production of droplets larger than 44 μm to be negligible. This suggest-

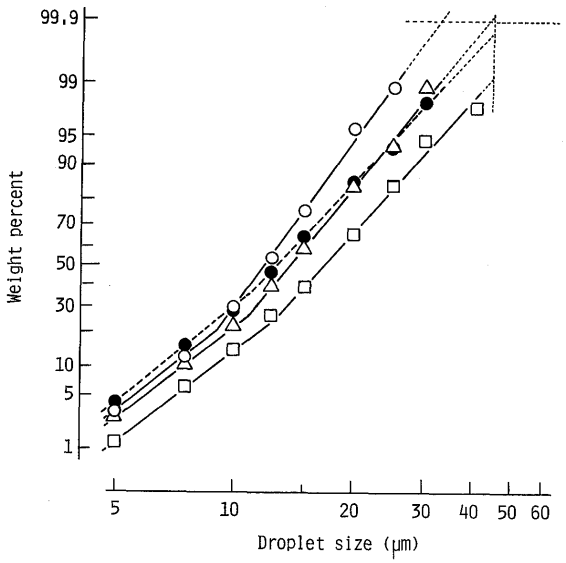

Fig. 8. Change of Cumulative Undersize Distribution of Droplets by Shifting Spray Conditions

Symbol	Spray solution	HPC concentration (w/v%)	Spray pressure (atm)
○	Water	0	2.3
△	HPC–CMC-Na (10:1)	1.25	2.3
□	HPC–CMC-Na (10:1)	2.5	2.3
●	HPC–CMC-Na (10:1)	2.5	3.0

For other spray conditions: see Table I.

ed that the agglomeration might be greatly reduced by changing spray conditions.

Among the spray conditions shown in Table I, changes in the spray rate were difficult because the rate controlled the water content of fluidized particles; therefore, it had to be adjusted so that the fluidization could be optimized. Although the droplet size would possibly decrease with spray rate, low spray rates would lead to greater particle adhesion to chamber wall due to electrostatic charging and consequently to enhanced agglomeration.[6]

The spray pressure and the concentration of spray solution were variable. In the spraying of HPC–CMC–Na (10:1) solution, an increase in spray pressure to 3.0 atm or a decrease in the concentration to 1.25% (w/v) led to reduction of the mass median diameter of droplets from 17.0 to 13.0 or 13.4 μm, respectively, as shown in Fig. 8. Increasing the pressure to above 3.0 atm no longer affected the droplet size distribution. Figure 8 shows that the disappearance of coarse droplets (larger than 44 μm) with increase in pressure stopped at about 0.2%. Generally, higher pressures make the agitation against particles in the partition of coating apparatus stronger, leading to even greater suppression of agglomeration. However, as previously reported,[3] spraying at pressure as high as 3.0 atm very often leads to fracture or abrasion of particles. On the other hand, preferential reduction of coarse droplets with decrease in the concentration than with increase in the pressure is observed in Fig. 8, since the profile of distribution approached that of water with decrease in the concentration. Consequently, the dilution of spray solution to 1.25% (w/v) or less seemed to make the agglomeration negligible. However, this was not practical because it required a very time-consuming process in the fine powder coating studied here.

Conclusion

In this study, the conditions of inlet air and spraying were kept constant to compare the effects of additives on agglomeration. Therefore, the degree of agglomeration should primarily be dependent on the droplet size distribution and the binding strength of membrane materials. It was found that PEG and NaCl could be candidates for suppressants of agglomeration in the coating of fine particles with HPC. Although neither PEG nor NaCl affected the droplet size distribution, NaCl was effective in reducing agglomeration by its hindering of the homogeneous film-formation and PEG by its weakening of the binding strength of HPC. The model of agglomeration proposed earlier[2] could well simulate the size distribution of agglomerates. It was demonstrated that the smallest sizes, D_m, of droplets causing the agglomeration were 44—71 μm, and the K-value, which was an agglomeration enhancing factor, might be used as a parameter well reflecting the state of fluidization. To suppress agglomeration to a practically allowable degree, the fraction of coarse droplets contributing to the agglomeration had to be reduced to less than 0.1%.

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