Coating of Pharmaceutical Powders by Fluidized Bed Process. V.[1] Agglomeration and Efficiency in the Coating with Aqueous Latices of Copoly(Ethyl Acrylate–Methyl Methacrylate–2-Hydroxyethyl Methacrylate)

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The latices of copoly(ethyl acrylate–methyl methacrylate–2-hydroxyethyl methacrylate) exhibited a very low degree of agglomeration in the Wurster coating process, when the softening temperatures of their films were higher than inlet air temperature. This low agglomeration was due to their poor film-formability and, consequently, their low binding strength. Although this led to a low fixing efficiency of cosuspended solid particles, the coating efficiency of polymer itself remained high (about 90%). This low tendency of agglomeration was confirmed even in a coating of as fine a powder as 32—44 μm.

Keywords coating; agglomeration; latex; spouted bed; copoly(ethyl acrylate–methyl methacrylate–2-hydroxyethyl methacrylate)

In previous studies,[1–4] the aqueous latices of acrylic copolymers were evaluated as coating materials and applied to controlled release pharmaceuticals. Especially, newly synthesized latices of copoly(ethyl acrylate (EA)–methyl methacrylate (MMA)–2-hydroxyethyl methacrylate (HEMA)) were studied as regards film-formation, softening temperature and membrane permeation of water and drugs. These copolymers were characterized by the following properties: (1) water-permeation was enhanced by MMA and HEMA; (2) softening temperature, T_s, was increased with MMA content, but only slightly by HEMA; (3) film-formation was enhanced by HEMA in the coating at an inlet air temperature below T_s. Microcapsules characterized by pH-independent, long delayed release were prepared using these copolymers.

The Wurster process is characterized by fine particle coating. Our most recent studies have focused on how fine microcapsules could be produced using the Wurster process and what kinds of additional properties would be required for the coating materials to produce fine microcapsules.

For the coating in an organic solvent system, calcium carbonate of 32—44 μm was successfully microencapsulated with a 2 : 1 : 0.03 mixture of ethyl cellulose (EC), cholesterol (CH) and stearyltrimethylammonium chloride (STAC).[5] The produced microcapsules had a mass median diameter of 56 μm. The coating of finer phenacetin powder, 11 μm, was then performed with EC–CH–STAC (1 : 1 : 0.06).[6] By previously microgranulating the fine powder, fine microcapsules with a mass median diameter of 31 μm were prepared.[6] In organic solvent solution systems, various additives were effective in overcoming serious problems encountered in fine powder coating such as drug-permeability, agglomeration and particle adhesion due to electrostatic charging. Similar techniques were applicable to the coating with aqueous solution systems of hydroxypropyl cellulose, a water-soluble polymer.[7,8]

For the latices, since soluble additives could possibly coagulate the latex particles, their use was believed to be limited. Thus, an attempt was made to vary the monomer compositions to adjust the properties of polymer latices to fine powder coating. The aqueous latices of copoly(EA–MMA–HEMA) were used again in the present study, since their properties had been well characterized previously.[1,4]

Experimental

Materials All materials were used as purchased or supplied without any purification. As a core material, lactose (DMV 200M) was used. The lactose powder was fractionized into 32—44, 44—53, 53—63 and 63—75 μm by sieving. Hydroxypropyl cellulose (HPC, HPC-L, Nippon Soda Co., Ltd.) was used as a water-soluble polymer. The aqueous latices of copoly(ethyl acrylate (EA)–methyl methacrylate (MMA)–2-hydroxyethyl methacrylate (HEMA)) were synthesized as previously reported.[4] Mass median diameter of latex particles increased with molar ratio of HEMA; that of 6 : 12 : 8 copoly(EA–MMA–HEMA) latex was 148 nm.[1]

As a tracer in polymer dispersions, the water-insoluble food yellow No. 4 aluminum lake (Y4-AL, Tokyo Kasei Co., Ltd.) was used. 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. The anhydrous silica was used as an antiadherent when microcapsules were heated for curing.

Coating A spouted bed coater with a draft tube (NQ-GM, Fuji Paudal Co., Ltd.) was used. A pneumatic spray nozzle with a liquid outlet caliber of 0.8 mm and a filter with an opening of about 5 μm were set throughout all experiments.

Particle Size Distribution The sieve analysis was performed as previously reported.[5] The mass median diameter of Y4-AL was 2.9 μm, measured in 1% sodium hexametaphosphate aqueous solution by a Horiba CAPA-300 particle analyzer.

Dissolution Dissolution tests were performed by the JP XII paddle method at 200 rpm and 37 °C in the JP XII disintegration 2nd fluid.[1,2]

Yields of Tracer and Polymer The tracer, Y4-AL, was extracted from 500 mg microcapsules with 1 N HCl and determined at 432 nm by spectrophotometry (Shimadzu UV 190). After the soluble substance was washed out of the microcapsules coated with polymer latex with 1 N HCl, the residual polymer was dried and weighed. In HPC microcapsules, after HPC was extracted with ethanol, the extract was dried and weighed. The weight was corrected by the amount of additive dissolved in ethanol. The yields were obtained from the measured content of Y4-AL or polymer in microcapsules multiplied by the total amount of produced microcapsules and divided by the charged amount of Y4-AL or polymer.

Softening Temperature Thermomechanical analysis was performed as previously reported.[1,4]

Results and Discussion

Comparison among Various Coating Systems The coating performance with the synthesized 6 : 12 : 8 copoly(EA–MMA–HEMA)[1] was compared with the aqueous solution systems of plain HPC and 10 : 1 HPC–sodium carboxy-

Table I. Operating Conditions and Effect of Core Size on the Properties of Products

Membrane material	HPC		10:1 HPC–CMC–Na				EA–MMA–HEMA[a]		
Core weight (g): 32—44 μm			25				25		
44—53 μm				25				25	
53—63 μm	25				25				25
63—75 μm		25				25			
Operating conditions									
Inlet air temperature (°C)	80		80				60		
Outlet air temperature (°C)	30		26—31				25—29		
Inlet air rate (m^3/min)	0.7		0.35	0.5	0.7	0.7	0.7	0.8	0.9
Spray rate (ml/min)[b]	4.0		3.7	3.9	4.0	4.0	1.8		
Spray pressure (atm)	2.3		2.3				1.5		
Yield (%): Product	79	83	72	87	87	86	68	84	90
Y4-AL	—	—	—	—	—	—	52	55	62
Polymer	90	90	86	89	88	89	82	88	89
Mass median diameter (μm)	85	83	80	71	71	81	43	52	64
Theoretical[c]	66	79	44	56	67	80	43	55	66
Agglomerates (%): Observed	82	54	96	84	64	55	3.0	0.4	0.5
Estimated[d]			96	75	59	52			

a) 6:12:8 Copoly (EA–MMA–HEMA). *b)* Spray solution: 10 g of HPC (or plus 1 g of CMC–Na) in 400 ml water. Spray dispersion: 10 g of copoly (EA–MMA–HEMA) plus 0.2 g of Y4-AL in 100 ml water. *c)* The density of HPC membrane was assumed to be 1.22 g/cm^3. That of 6:12:8 copoly (EA–MMA–HEMA) was measured as 1.32 g/cm^3. *d)* From ref. 7.

methyl cellulose (CMC–Na) studied earlier.[7] The operating conditions and the properties of products are shown in Table I. The spray solutions and dispersions were prepared in concentrations of 2.5% (w/v) HPC for the solution systems and 10% (w/v) for the latex, respectively. As a tracer, Y4-AL of 2.9 μm was suspended in the latex. Since there would be no practical reason for making the operating conditions and the concentration of spray solution inflexible, the conditions which best matched each system were adopted. The spray conditions, in particular, had to be allowed to vary between the two systems (Table I). The lower spray pressure used with the latex was chosen to prevent its easy spray-drying. The spray rate was adjusted so that particles could be fluidized without adhering to the chamber wall as a result of overwetting or electrostatic charging. Lactose cores of 25 g were coated up to 40% polymer level (based on core weight) on a dry basis and then the produced microcapsules were evaluated for the yields of Y4-AL and polymer and the size distribution of the microcapsules. The fractions of agglomerates were difficult to determine, but could be conveniently estimated from the broken points on the log-normal size distribution curves of microcapsules. The values of 10:1 HPC–CMC–Na estimated by computer simulation[7] are also shown in Table I.

As previously reported,[9] the water-soluble polymers, HPC and hydroxypropyl methyl cellulose, exhibited remarkable agglomeration and a high yield of Y4-AL which was added to the polymers when coatings were performed under the same conditions as those with the latex shown in Table I; the high yield of Y4-AL seemed to reflect a high yield of polymer. In the present study, the yield of polymer was confirmed to be equally high (about 90%). The strong binding strength of water-soluble polymers clearly led to these results.[7]

On the other hand, the latex exhibited a very low tendency of agglomeration and a low yield of Y4-AL particles; at least one third of the particles were lost, although little of the polymer itself was lost. Even with 32—44 μm cores, the yield of polymer was 82%, whereas the yield of product was decreased to 68% due to the leakage of particles through the bag filter used here. These findings indicated that the latex polymer had a low binding strength, leading to a low ability to fix solid particles on cores, but polymer particles themselves efficiently adhered to the cores. The low degree of agglomeration observed here is a desirable property for fine powder coating.

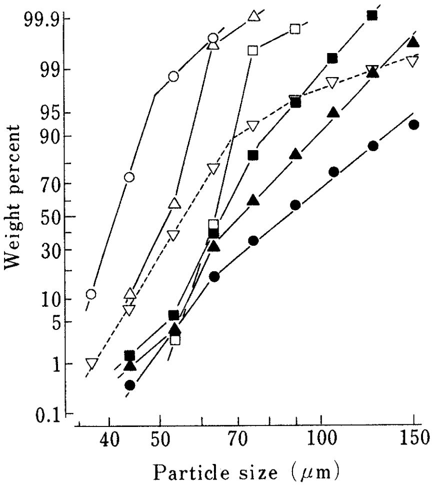

Fig. 1. Cumulative Undersize Distributions of Microcapsules Prepared with Various Coating Solutions and Dispersions

Membrane materials, core: ○, 6:12:8 copoly(EA–MMA–HEMA), 32—44 μm lactose; △, 6:12:8 copoly(EA–MMA–HEMA), 44—53 μm lactose; □, 6:12:8 copoly(EA–MMA–HEMA), 53—63 μm lactose; ●, HPC, 53—63 μm lactose; ▲, 10:1 HPC–CMC–Na, 53—63 μm lactose; ■, 10:1 HPC–NaCl, 53—63 μm lactose; ▽, 2:1:0.03 EC–CH–STAC, 32—44 μm calcium carbonate.

The size distributions of microcapsules prepared using the latex of 6:12:8 copoly(EA–MMA–HEMA) are shown in Fig. 1, compared with those for the aqueous solutions of HPC,[7,8] and the organic solvent solution of ethyl cellulose.[5] When the fraction of agglomerates was estimated from the broken point on the distribution curve in the figure, 12% of the primary cores were unavoidably agglomerated even in 10:1 HPC–NaCl and 2:1:0.03 EC–CH–STAC,

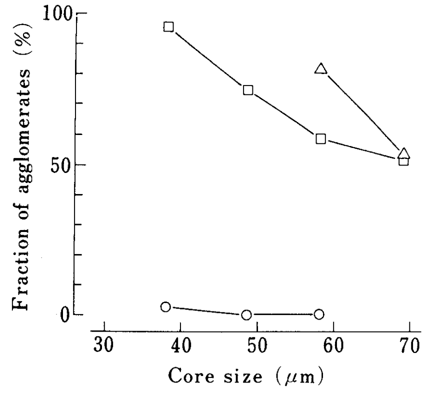

Fig. 2. Effect of Core Size on the Fraction of Agglomerates

○, 6:12:8 copoly(EA–MMA–HEMA); △, plain HPC; □, 10:1 HPC–CMC–Na (from computer simulation).[7]

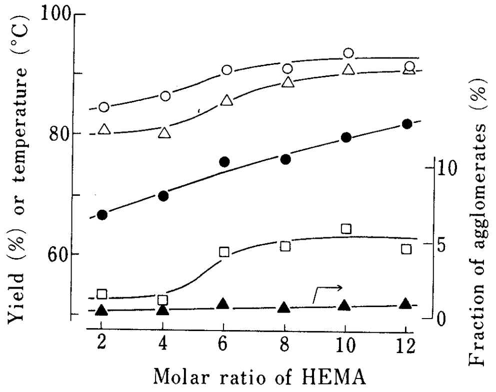

Fig. 3. Effect of Molar Ratio of HEMA on Agglomeration and Coating Efficiency with Latices of Copoly(EA–MMA–HEMA)

Fraction of agglomerates: ▲. Yield: ○, product; △, polymer; □, pigment. Softening temperature: ●. Molar ratio of EA–MMA was fixed to 6:12. Core: 25 g lactose of 53—63 μm. Spray dispersion, spray rate and operating conditions of NQ-GM are the same as those for 6:12:8 EA–MMA–HEMA in Table I.

which exhibited relatively low agglomeration among the solution systems previously studied. The agglomeration reached 82 and 64% in the coating of 53—63 μm cores with plain HPC and 10:1 HPC–CMC–Na, respectively. In contrast, with 6:12:8 copoly(EA–MMA–HEMA), the fraction of agglomerates was only 0.4—0.5% for cores larger than 44 μm; even for 32—44 μm cores, it was only 3.0%. Such a low degree of agglomeration as observed with the latex would be difficult to achieve in the coating with the solution systems.

The distinctively low degree of agglomeration in the latex system is well demonstrated in Fig. 2 where the observed agglomeration (Table I) is plotted against core size. In the coating with the two HPC systems, the fraction of agglomerates greatly increased with decrease in core size. The coating with plain HPC could no longer be performed with the cores smaller than 53 μm because they were too agglomerated to be fluidized. With 10:1 HPC–CMC–Na, the cores of 32—44 μm could be processed, but 96% of the microcapsules were agglomerates.

Agglomeration and Efficiency at Various Monomer Compositions of Copoly(EA–MMA–HEMA) Agglomeration is clearly related to the film-forming ability of a membrane materials. For example, agglomeration in the coating with HPC aqueous solution was suppressed by NaCl which was incompatible with HPC and hindered HPC from forming a homogeneous film.[8] The relation of agglomeration in aqueous latex systems to the film-formation was investigated in this study using the copoly(EA–MMA–HEMA).

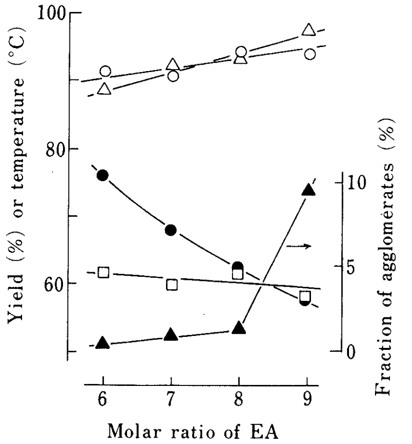

Fig. 4. Effect of Molar Ratio of EA–MMA on Agglomeration and Coating Efficiency with Latices of Copoly(EA–MMA–HEMA)

Fraction of agglomerates: ▲. Yield: ○, product; △, polymer; □, pigment. Softening temperature: ●. Molar ratio of EA–MMA–HEMA (X:Y:Z): $Z=8$, $X+Y=18$. Core: 25 g lactose of 53—63 μm. Spray dispersion, spray rate and operating conditions of NQ-GM are the same as those for 6:12:8 EA–MMA–HEMA in Table I.

First, using the copolymers with various molar ratios of HEMA at the molar ratio of EA:MMA set at 6:12, coating was performed under the same operating conditions as those with 6:12:8 copoly(EA–MMA–HEMA) shown in Table I. The results are shown in Fig. 3. The softening tempeatures were higher than the inlet air temperature, 60 °C, throughout the range of HEMA molar ratio studied here. The yields of the product, polymer and pigment were all increased with HEMA content. This would possibly be explained by the enhancement of film-formation with increase in HEMA content.[1] However, the degree of agglomeration, fortunately, remained very low, suggesting that the film-formation was incomplete and consequently the binding strength of films did not become strong enough to induce the agglomeration.

In this manner, HEMA improved the coating efficiency, with very low agglomeration, but, as previously reported,[4] it enhanced the permeation of water and drug through copoly(EA–MMA–HEMA) membranes. This leads to increase in the quantity of coating material required for practical sustained release pharmaceuticals, which can be a fatal demerit in fine powder coating. As also reported previously,[4] EA suppressed the membrane permeation, in contrast to HEMA. However, EA lowered the softening temperature of copoly(EA–MMA–HEMA) membrane, possibly leading to enhanced agglomeration. From these reasons, using copoly(EA–MMA–HEMA) with various molar ratios of EA:MMA at a fixed HEMA ratio of 8, the coating was performed; the ratio, EA:MMA:HEMA = X:Y:Z, was varied at $Z=8$ and $X+Y=18$.

The results are shown in Fig. 4. The yields of the product and polymer increased with EA content, as expected. When the EA ratio was larger than 8.6, the softening temperature of the membrane became lower than the inlet air temperature of 60 °C, and the degree of agglomeration increased greatly above that ratio. Pigment yield, however, did not increase.

The temperature within the Wurster chamber ranges broadly between the inlet (60 °C) and outlet (25—29 °C) temperatures (Table I). The temperature in the partition where the aqueous dispersion was sprayed would be close to the outlet air temperature. The highest temperature would be found near the bottom plate which was directly exposed to inlet air. Therefore, the agglomeration caused by the lowering of softening temperature clearly resulted from the fusion of membrane near the bottom plate, and not from the formation of an interparticulate bridge by the polymer sprayed within the partition. This explained why the increase in the yield of pigment did not follow the enhanced agglomeration: the particles of Y4-AL would have been adhering more to the cores if the binding strength of sprayed polymer had become strong enough to induce more agglomeration just after spraying. In contrast, the increase of HEMA content led to an increase both in yield of Y4-AL particles and, although only slight, in agglomeration (Fig. 3), indicating that the formation of the interparticulate bridge within the partition was enhanced by HEMA.

Dissolution of Lactose from Copoly(EA–MMA–HEMA) Microcapsules Dissolution properties of lactose from copoly(EA–MMA–HEMA) microcapsules were reported previously in detail [3]; large lactose cores of 328 μm were used there. The core particles of 32—75 μm used in the present study had a specific surface area 4—10 times larger than the 328 μm cores. From the previous data, it was anticipated that too much coating material would be required for the microcapsules prepared in the present study to exhibit a practically useful sustained release.

The dissolution from the 6:12:8 copoly(EA–MMA–HEMA) microcapsules of 32—44 and 53—63 μm lactose cores were investigated here (Fig. 5). The results showed that the membrane of 6:12:8 copoly(EA–MMA–HEMA) was very porous and could not act as a permeation barrier, when subjected only to drying in a vacuum at room temperature after being prepared by the Wurster process. By mixing the microcapsules with anhydrous silica of 2% and then by heating them for 12 h at 80 °C, which was higher than the softening temperature, the microcapsules exhibited a sustained release. Thus, the film-formation of the latex had not been completed during the coating process.

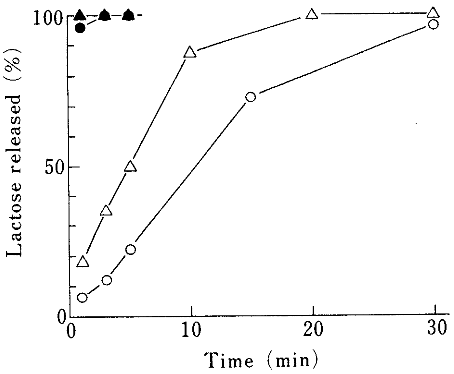

Fig. 5. Release of Lactose from 6:12:8 Copoly(EA–MMA–HEMA) Microcapsules

Size (μm) of lactose cores: ○●, 53—63; △▲, 32—44. Pretreatment: closed symbols, only dried in a vacuum at room temperature; open, heated at 80 °C for 12 h.

The 6:12:8 copolymer latex previously exhibited an excellent film-formation which was enhanced by HEMA.[1] The enhanced film-formation was clearly due to the high spray rate of 7.9 ml/min used in that study. This time the spray rate was reduced to 1.8 ml/min, because the charging of cores was decreased from the previous 300 to 25 g and smaller cores with higher coalescence probability[7] were used. Consequently, the humidity in the coating chamber was lowered and the water-evaporation rate was raised. Clearly, this led to the poor film-formation, a fact that has been shown before.[9-12]

Even with the microcapsules cured by heating, the dissolution was still too fast for them to be practically applicable to sustained release pharmaceuticals (Fig. 5). In addition, lactose burst at the beginning of dissolution (Fig. 5), at least 10% with the 6:12:8 copoly(EA–MMA–HEMA) microcapsules prepared with the 32—44 μm cores. The thickness of membrane in this case was estimated to be about 2.6 μm (Table I), while it was calculated as 22.3 μm in a 40% level coating with the 328 μm cores previously reported.[3] Clearly, such a thin 6:12:8 copoly(EA–MMA–HEMA) film as 2.6 μm could not fully cover the cores and its permeability was too high to sustain the release of lactose from fine microcapsules.

In the latex systems, the low film-formation clearly accounted for the low tendency of agglomeration. It is important that, in spite of its low film-formability, the coating efficiency be sufficiently high in these systems, for the curing after the coating process makes the film-formation possible.

Conclusion

When their film-formation was poor, latices exhibited a very low degree of agglomeration in the Wurster coating process, with the yield of polymer remaining very high. These properties were effective even in the coating of a powder as fine as 32—44 μm. However, the latices were not useful for fixing solid particles on cores, due to the low binding strength of their films. In addition, when the softening temperature of a polymer was lower than inlet air temperature, the latex displayed an enhanced agglomeration. Consequently, for suppression of agglomeration, the coating had to be adjusted so that the film-formation would not be completed. This produced such porous films that all lactose burst at the beginning of dissolution. Fortunately, the film-formation could be completed by curing, since the yield of polymer was high. These findings were important in the development of a coating technology for fine particles.

However, there still remained a serious problem. The membrane of microcapsules 40% coated with 6:12:8 copoly(EA–MMA–HEMA), which exhibited a low tendency of agglomeration as above, was, even if cured by heating, too permeable to practically sustain the release of lactose. Although the permeability could be suppressed by increasing the composition of EA, this lowered the softening temperature, leading to remarkable agglomeration. No monomer composition of copoly(EA–MMA–HEMA), which exhibited all of the low degree of agglomeration, the low permeability and the high yield of polymer, was found within the range of the present study. It will be reported in a later paper how these properties can be made compatible in the aqueous latex systems.

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