Coating of Pharmaceutical Powders by Fluidized Bed Process. VI.[1] Microencapsulation Using Blend and Composite Latices of Copoly(Ethyl Acrylate–Methyl Methacrylate–2-Hydroxyethyl Methacrylate)

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An aqueous acrylic latex which could exhibit a low degree of agglomeration, low membrane permeation and high coating efficiency was developed using copoly(ethyl acrylate (EA)–methyl methacrylate (MMA)–2-hydroxyethyl methacrylate (HEMA)) whose molar ratio was 6:12:8 or 12:6:4. Blend latices composed of the hydrophilic 6:12:8 latex and the hydrophobic 12:6:4 latex exhibited a very low degree of agglomeration. However, the coating operation had problems with particle adhesion and cohesion due to the low softening temperature (26 °C) of the 12:6:4 copolymer. In addition, the release of lactose from the microcapsules coated with the substances, even if cured by heating, could not be sufficiently suppressed, with a fraction of fast releasing microcapsules remaining due to a variation of the membrane structure formed by the random packing of latex particles. Hence, composite latices composed of the low permeable 12:6:4 copolymer core and the nonadhesive 6:12:8 polymer shell were synthesized. A 6:4 (core:shell) composite latex formed a low permeable membrane by curing, so that the microcapsules of 53—63 μm lactose 40% coated with it released only 10% of its lactose at 3 h without an initial burst. Moreover, composite latices exhibited a very low degree of agglomeration, with the polymer yield remaining very high, and they did not induce any adhesive behavior. These properties were still effective even in the coating of corn starch as fine as 12 μm. At a 50% level of coating, the mass median diameter of the product was 16 μm and it contained only 3% agglomerates. These results showed that by using the composite latex, the particles of the order of 10 μm could be discretely coated as single-core microcapsules in the Wurster process, a kind of spouted bed process assisted with a draft tube.

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

The polymer latex will be an excellent candidate for use as a fine powder coating material, if it can be designed to compatibly exhibit a high coating efficiency, a very low degree of agglomeration and low permeability of the formed membrane. These properties of a membrane material are essential to the successful fluidized bed coating of fine particles with low inertia and a large specific surface area. In a previous study,[1] the latices of copoly(ethyl acrylate (EA)–methyl methacrylate (MMA)–2-hydroxyethyl methacrylate (HEMA)) showed a very low tendency for agglomeration in coating by the Wurster process when the softening temperature was higher than the inlet air temperature and the coating was performed under conditions where their film-formability was low. Their low tendency for agglomeration was achieved even in the coating of powder as fine as 32—44 μm. Since the coating efficiency was sufficiently high even under such conditions, the membranes could be made nonporous by curing. However, the cured membranes were too permeable for the practical prolongation of lactose release.

In the present study, an aqueous latex of copoly(EA–MMA–HEMA) which formed a nonadhesive and low permeable membrane along with high coating efficiency was developed.

Experimental

Materials All materials were used as purchased or supplied without any purification. As core materials, lactose (DMV 200M) and corn starch (12 μm, Nippon Shokuhin Kako Co., Ltd.) were used. The lactose powder was fractionized into 53—63 μm by sieving. Carbazochrome sodium sulfonate (CCSS, Kanebo Ltd.) was adhered on corn starch by mixing them in a ball mill for 10 h. Anhydrous silica (Aerosil #200, Nippon Aerosil Co., Ltd.) was used as an antiadherent, when microcapsules were heated for curing, and as a sieving aid in particle size analysis.

Preparation of Latex The acrylic copolymer latices, EA–MMA–HEMA, were synthesized as previously reported.[2] The molar ratio of EA, MMA and HEMA used was 12:6:4 or 6:12:8. The total weight of the monomer mixture was 433 g in each polymerization. In the synthesis of composite (core-shell) latices, 150 g of monomer mixture (12:6:4) was first emulsified in an aqueous surfactant solution, and the remainder was dropped into the reactor to prepare the cores. Thirty min after the dropping was completed, the other mixture (6:12:8) was dropped to prepare the shells. The ratio of core to shell was denoted as the weight ratio.

Particle Size and Density of Latex The particle size distribution of the latices used was determined by the photon correlation method (Zetaplus, Brookhaven Instruments Corp.). Mass median diameters of homogeneous 12:6:4 and 6:12:8 latices were 129 and 148 nm, respectively; that of the 6:4 core-shell latex was 138 nm.

For the density measurements, each of the latices were diluted with water to 5% concentration and then freeze-dried. The density of the freeze-dried materials was measured by an air comparison pycnometer (model 930, Beckman-Toshiba Co., Ltd.).

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 1.0 mm was used. A filter with a 5 μm opening and a laminated filter with about a 1 μm opening were set for lactose and for corn starch, respectively. The charged weight was 25 g for lactose and 300 g for corn starch. Spraying was performed up to polymer level of 40% (based on core weight) on a dry basis.

Particle Size Distribution The sieve analysis was performed, as previously reported.[3] Particle size distribution of corn starch was measured in a 0.02% sodium dodecyl sulfate aqueous solution by a Horiba CAPA-300 particle analyzer. The theoretical diameter of the microcapsules, D_t, was estimated by the following equation.

$$D_t = D_c(1 + V_m/V_c)^{1/3}$$

where D_c is the diameter of the lactose cores (58 μm), defined as an arithmetic mean of sieve openings used for fractionization, and V_m and V_c are the volume of membrane materials and lactose cores used to prepare the microcapsules, respectively.

Dissolution Dissolution tests were performed by the JP XII paddle method at 200 rpm and 37 °C in the JP XII disintegration 2nd fluid, as previously reported.[2] Curing was performed by mixing microcapsules with anhydrous silica of 2% and then by heating them at 80 °C for 12 h in an air stream oven. The lactose content of the microcapsules was determined by the amount released in 24 h from unheated samples.

Scanning Electron Microscopy (SEM) A JEOL JSM-5300LV scanning electron microscope was used.

Results and Discussion

Coating with Blend Copolymer Latices The previous study showed that the molar ratio of 8:10:8 with EA–MMA–HEMA copolymer latices was a limit for the coating to proceed under a low agglomeration.[1] However, the agglomeration was gradually increased by changing EA : MMA from 6 : 12 to 8 : 10. A preliminary experiment showed that since the softening temperature (62 °C) of the 8 : 10 : 8 copolymer was very near the inlet air temperature (60 °C), the fluctuation of temperature sometimes induced significant agglomeration. Hence, the 6 : 12 : 8 copolymer whose softening temperature was 78 °C was used below as a model of nonadhesive coating materials.

The release of lactose from the 6 : 12 : 8 copoly(EA–MMA–HEMA) microcapsules of 64 μm was prolonged only a little at the 40% coating level,[1] so these were not practical as controlled release pharmaceuticals. On the other hand, among the copoly(EA–MMA–HEMA) latices synthesized in our previous study, the 12 : 6 : 4 copolymer exhibited the lowest permeability.[2] However, due to its low softening temperature (26 °C), coating could be performed at the inlet air temperature of 40 °C only with the assistance of an antiadherent inserted into the chamber.

To improve the film-formation and/or the membrane permeability, blend copolymer latices have been used. For example, Eudragit NE30D has been blended with RS30D to lower the softening temperature and to reduce the membrane permeability.[4] In this study, the 12 : 6 : 4 latex was blended with 6 : 12 : 8 latex to reduce the lactose permeability.

The operating conditions and the properties of products are shown in Table I. In blend latices, the yield of microcapsules produced was around 90%. This indicated that the polymer particles efficiently adhered to the lactose cores. The production of agglomerates was suppressed to less than 2% within the range of the present study. However, the coating operation was difficult due to particle adhesion to the chamber wall and particle deposition on the bottom plate. This was because the softening of the 12 : 6 : 4 copolymer particles could not be avoided due to its low softening temperature (26 °C), far lower than the inlet air temperature (60 °C). Although the particles barely circulated during the coating at a 12 : 6 : 4 copolymer content of 60% or less, the coating operation could not be performed above 60% due to the remarkable melting of the membrane and consequent particle adhesion and cohesion.

The dissolution profiles are shown in Fig. 1 for the microcapsules dried only in a vacuum and for those subsequently cured by heating. Microcapsules were cured at 80 °C for 12 h to permit film-formation to be completed at a temperature slightly higher than the softening temperature of the 6 : 12 : 8 copolymer (78 °C); excessively higher temperatures led to a blocking of the microcapsules. Clearly, the lactose permeability was further decreased the more the low permeable 12 : 6 : 4 copolymer latex was blended, but the film-formation during the coating process was not completed, since the dissolution was remarkably reduced by heating the microcapsules. Although the release was remakably prolonged when the 12 : 6 : 4 copolymer content was 50% or more, there was a fraction of microcapsules from which lactose had been released within 1 h.

In the Wurster process, particles blown up from a draft tube have to fall down gravimetrically. Therefore, heavier and/or larger particles are more steadily fluidized and, consequently, these particles would receive a thicker film. In fact, Wesdyk *et al.*[5] reported that the larger and heavier beads within a batch coated by the Wurster method received a thicker film and therefore displayed a significantly low rate of dissolution when compared to smaller and lighter beads. As also previously reported,[6] smaller particles tended to retard from particles steadily circulating in the coating chamber due to their adhesion

TABLE I. Properties of Microcapsules Coated with Blend or Composite Latices of Copoly (EA–MMA–HEMA)[a]

Composition of latex[b] (12:6:4):(6:12:8)	Blend 3:7	4:6	5:5	6:4	Composite 5:5	6:4	7:3
Yield of product (%)	92	88	93	92	90	92	89
Mass median diameter (μm)[c]	63	63	63	63	61	61	62
Agglomerates (%)[d]	0.6	1.5	1.4	1.3	0.5	0.9	1.3
Particle adhesion to wall[e]	+	+	+	+	−	−	+
Particle deposition to bottom[e]	−	+	+	+	−	−	−

a) Core, 25 g lactose of 53—63 μm. Operating conditions of NQ-GM: inlet air temperature, 60 °C; outlet air temperature, 26—29 °C; spray pressure, 1.9 atm; spray rate, 1.4—1.7 ml/min; inlet air rate, 0.8 m^3/min. *b*) Spray dispersion: 10 g of dry lacquer in 100 ml. *c*) Theoretical diameter was 66 μm. The density of copoly (EA–MMA–HEMA): 12 : 6 : 4, 1.21 g/cm^3; 6 : 12 : 8, 1.32 g/cm^3; 6 : 4 core-shell, 1.26 g/cm^3. *d*) Fractions larger than 75 μm, which was observed to be the smallest limit of agglomerates on microscopy of the sieved fractions. *e*) Symbol: +, occured; −, not occured.

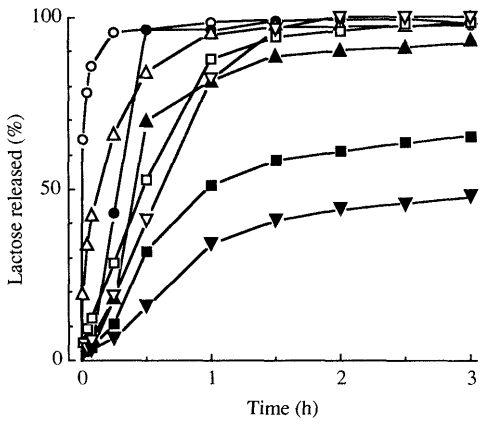

Fig. 1. Release of Lactose from Microcapsules 40% Coated with Blend Latices of Copoly (EA–MMA–HEMA) in the JP XII Disintegration 2nd Fluid

Weight ratio of 12 : 6 : 4 copolymer and 6 : 12 : 8 copolymer: ○●, 3 : 7; △▲, 4 : 6; □■, 5 : 5; ▽▼, 6 : 4. Pretreatment: open symbols, only dried in a vacuum at room temperature; closed, heated at 80 °C for 12 h.

to the wall by electrostatic charge and, consequently, they exhibited a faster release. Such a size dependency in the dissolution properties of microcapsules might lead to a biphasic release with blend latices, as seen in Fig. 1.

To elucidate the role of particle size dependency in drug release, the dissolution tests were performed for each of the fractionized microcapsules. The results are shown in Fig. 2 for the microcapsules coated with the 6:4 blend latex. As expected, the finer microcapsules exhibited a faster release of lactose. However, their contribution to the release profile for the unfractionized microcapsules was minor, since the fine fractions (below 53 μm) which exhibited the faster release accounted for only 8% of the product. The biphasic release profile was observed even in the main fractions (53—63 and 63—75 μm) which should be sufficiently coated. When these microcapsules were immersed in the dissolution medium and microscopically observed at 37 °C, some particles exhibited a marked expansion by osmotic pressure arising from the dissolution of lactose, indicating a suppressed release of lactose, whereas the others only slightly expanded at 3 h after immersion due to leakage of the dissolved lactose. This implied that both rapid and slow releasing microcapsules coexisted within the same fraction.

The percolation theory has been used by many authors to explain critical phenomena. In pharmaceutical technology, for example, it was used to explain the mechanical properties of a tablet[7] or the dissolution kinetics of a matrix controlled release system.[8] The probability at which a cluster of one component in a particle mixture just percolates the system is termed the percolation threshold. Bonny and Leuenberger[8a] reported that there were two percolation thresholds in matrix-type controlled release tablets prepared by the compression of binary mixtures of a soluble brittle model drug (caffeine) and a plastic matrix substance (ethyl cellulose). In their study, a morphological change in matrix components in the tablet and consequent changes in the dissolution kinetics as a function of drug concentration was described as follows. At low drug concentrations, most of the drug particles will be enclosed with the plastic matrix and only the few drug particles connected with the tablet surface can be dissolved. Therefore, the release will be incomplete. In the region where the drug concentration corresponds to the lower percolation threshold p_{c1}, the drug particles begin to form a connective network that spans the matrix tablet. Between p_{c1} and the upper percolation threshold p_{c2} the particles of drug and matrix substance form a bicoherent system, *i.e.*, both clusters of drug and matrix substance span the tablet, and the drug release obeys the square-root-of-time law of Higuchi. At p_{c2}, the particles which form the matrix start to become isolated within the drug particles and the tablet will disintegrate.

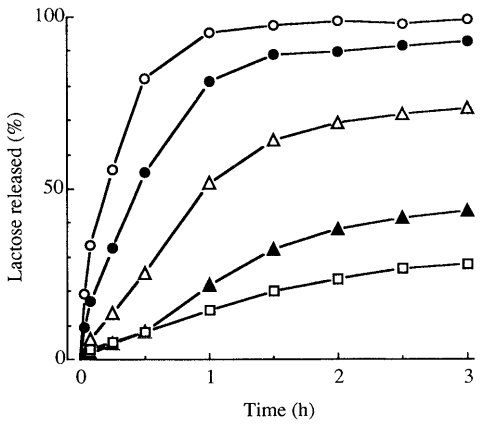

Fig. 2. Release of Lactose from Various Size Fractions of Microcapsules 40% Coated with 6:4 Blend Latex in the JP XII Disintegration 2nd Fluid

Size fraction (μm): ○, —44; ●, 44—53; △, 53—63; ▲, 63—75; □, 75—90. Microcapsules: heated at 80 °C for 12 h.

The intercept on the ordinate obtained by linearly extrapolating the latter portion (1.5—3 h) of the dissolution curve for cured microcapsules in Fig. 1 was regarded as representing the fraction of the microcapsules which exhibited a rapid release. The results are plotted in Fig. 3 as a function of 12:6:4 copolymer content. When the 12:6:4 copolymer content was less than 30%, there was no fraction of microcapsules exhibiting slow release. This indicated that there were only isolated clusters of low permeable 12:6:4 copolymer particles in the membrane. Hence, lactose was rapidly released through the connective network of high permeable 6:12:8 copolymer particles in the membrane. Above 30%, which might correspond to p_{c1}, the fraction of microcapsules exhibiting rapid release started to decrease with an increase in 12:6:4 copolymer content. This suggested that the clusters of 6:12:8 copolymer particles which spanned the membrane and rapidly released lactose would disappear in some microcapsules, whereas they would still exist in others. These may explain why the microcapsules coated with blend latices exhibited the biphasic release profile. In the present study, p_{c2} could not be estimated since the preparation of microcapsules coated with blend latices was limited to the case where the 12:6:4 copolymer content was below 60%.

Bonny and Leuenberger noted in their paper that the amount of drug released from a matrix tablet would be changed corresponding to the size and number of both the infinite (spanning) clusters of drug and matrix substance in the region where the drug concentration was from 30 to 70%.[8a] Unlike such an infinite system as tablet, in multi-unit systems with very thin shells, such as the microcapsules studied here, it would be difficult for the drug release to be controlled by the size and number of the spanning clusters because of the short distances of diffusion; each particle bursts by the formation of only one spanning cluster of the permeable sites (6:12:8 copolymer particles in the present study). In general, this makes the control of release from fine particulate systems very difficult.

To precisely estimate p_{c1}, the line connecting the data points at 40 and 50% of 12:6:4 copolymer content in Fig. 3 was extrapolated. The value estimated was 36% in weight percent and it corresponds to 38% in volume percent. The estimated p_{c1} of 38% was comparable with the theoretical value for the simple cubic lattice, which has a site percolation threshold of 31.2%.[9] Ma *et al.*[10] reported that latex particles tended to exhibit a face-centered-cubic arrangement in cast film. According to

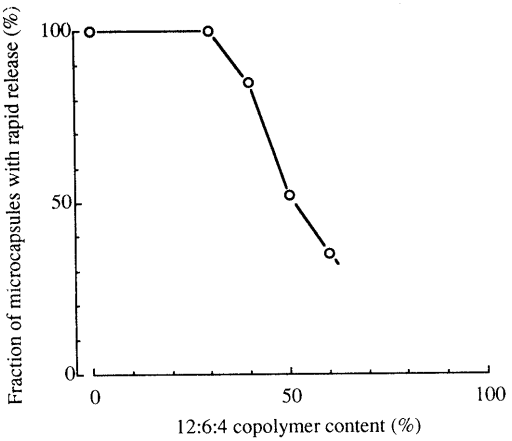

Fig. 3. Plots of Estimated Fraction of Rapid Releasing Microcapsules against 12:6:4 Copolymer Content

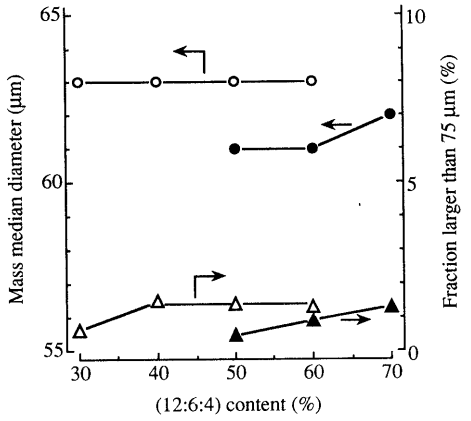

Fig. 4. Effect of 12:6:4 Copolymer Content in Blend and Composite Latices on Mass Median Diameter and Coarse Fraction of Microcapsules 40% Coated

Type of latex: open symbols, blend; closed, composite.

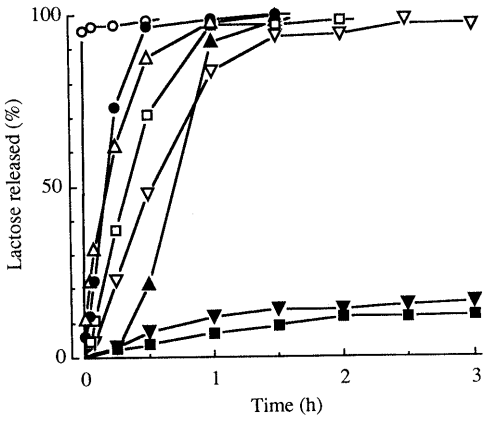

Fig. 5. Release of Lactose from Microcapsules 40% Coated with Composite Latices of Copoly(EA–MMA–HEMA) in the JP XII Disintegration 2nd Fluid

Weight ratio of 12:6:4 copolymer and 6:12:8 copolymer: ○●, 0:10; △▲, 5:5; □■, 6:4; ▽▼, 7:3. Pretreatment: open symbols, only dried in a vacuum at room temperature; closed, heated at 80 °C for 12 h.

Stauffer,[9] the face-centered-cubic lattice has a site percolation threshold of 19.8%. This value was far smaller than the p_{c1} estimated in this study. These suggest that latex paticles might be loosely deposited on core surfaces during coating, different from the static situation such as the formation of cast film, and/or the value of p_{c1} observed in this study might have a physical meaning different from the lower percolation threshold in the infinite systems.

Coating with Composite Latices With blend latices, the coating operation was not easy because the particles were adhesive due to the softening of the membrane and their electrostatic charging. These problems should result due to the properties of 12:6:4 latex particles. However, the low permeability of its film was very useful for coating fine particles whose specific surface area was large. Hence, we attempted to cover the 12:6:4 latex particles with the shells of a less adhesive or harder polymer (core-shell type of latex[11]; the term composite latex is used in this paper). As a shell copolymer, the 6:12:8 copoly(EA–MMA–HEMA), which was characterized by a low agglomeration tendency, high softening temperature and high coating efficiency,[1] was chosen.

The synthesized composite latices did not induce any adhesive behavior in coating when the content of the 12:6:4 copolymer (core) was 60% or less, although the circulating particles were adhesive at 70% of its content due to the electrostatic charging (Table I). These indicated that even if it would not form an ideal shell structure,[12] the 6:12:8 copolymer at least served as a "hard shell." The mass median diameter and the fraction of agglomerates in the produced microcapsules are shown in Fig. 4, compared with those for blend latices. The hard shell of 6:12:8 copolymer contributed to the reduction of agglomeration, though the degree of agglomeration was less than 2% in both latices.

Dissolution from the microcapsules prepared with composite latices is shown in Fig. 5. When compared with Fig. 1, the composite latices produced more permeable membranes than the blend latices in the cases where the microcapsules were only dried in a vacuum. This implied that the 12:6:4 latex particles blended at random worked as a permeation barrier. It was also possible that they worked as a low permeable binder during the coating operation because of its low softening temperature. On the other hand, all channels of the hard shells of composite latices should be spanning the films, leading to a faster release. With the microcapsules heated at 80 °C, the release was still slower in the blend latices, when the 12:6:4 copolymer content was 50% or less. When the fraction of the soft and low permeable 12:6:4 core reached 60%, the release was strongly suppressed in the composite latices.

Latex particles deposited on the surface of the core particle and the structure of the formed membrane are schematically shown in Fig. 6 for a blend latex whose weight ratio of 12:6:4 to 6:12:8 was 6:4. Figure 7 also shows that of the composite latex. The water channels formed by the clusters of 6:12:8 particles would be produced at random, since blend latex constructed a random packing structure (Fig. 6). The microcapsules whose membranes had spanning water channels would burst. On the other hand, the particles of composite latex should form a structure as shown in Fig. 7a. The thickness of the shells of the 6:4 composite latex was estimated to be about 10 nm. Figure 5 suggested that when the shell

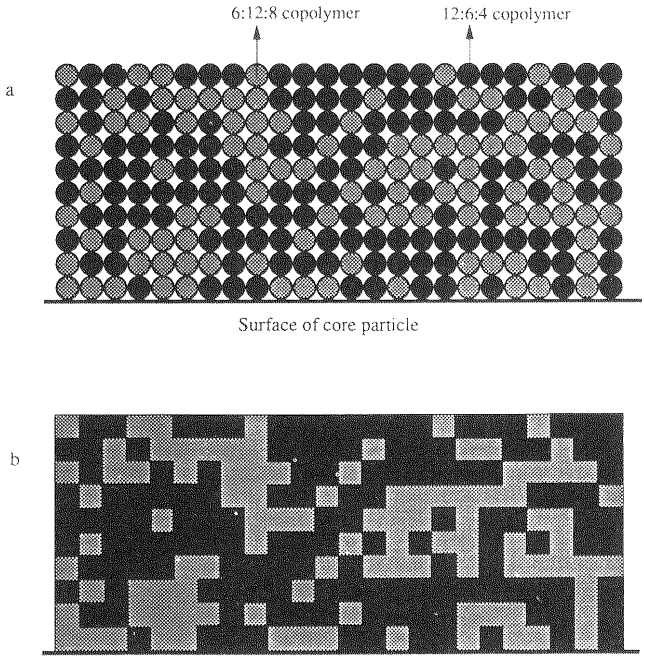

Fig. 6. Schematic Diagram of Blend Latex Deposited on the Surface of the Core Particle and Its Membrane Structure

a, before curing; b, after curing. The membrane structure was simulated by a two-dimensional model with ten particle-layers.

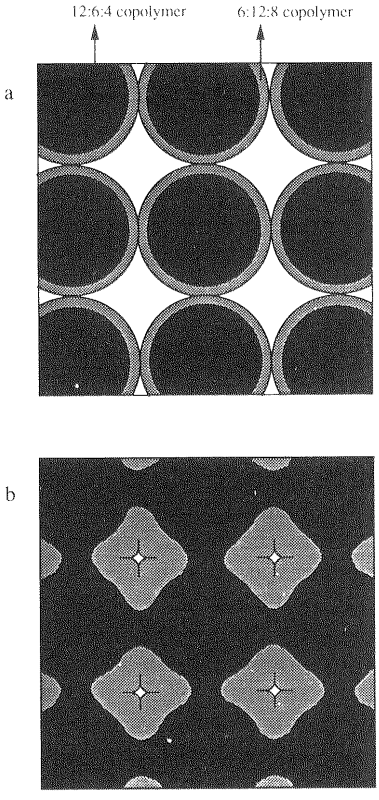

Fig. 7. Schematic Diagram of Composite Latex Deposited on the Surface of the Core Particle and Its Membrane Structure

a, before curing; b, after curing.

thickness was reduced to 10 nm and the microcapsules were cured at 80 °C, the interconnected network of melted 12 : 6 : 4 copolymer cores might be formed first, leading to isolation of the water channels formed by the more

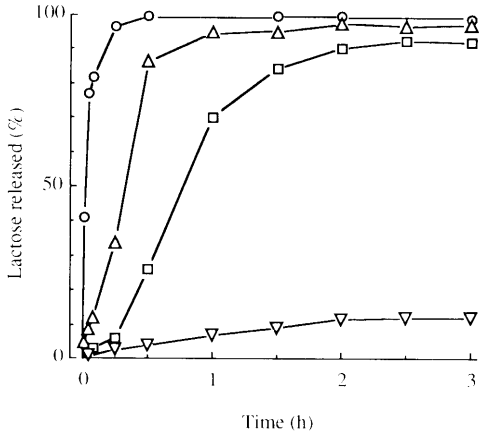

Fig. 8. Effect of Coating Level on the Release of Lactose from Microcapsules with a 6 : 4 Composite Latex of Copoly(EA MMA HEMA)

Coating level (%): ○, 10; △, 20; □, 30; ▽, 40.

Table II. Effect of Spray Rate and Charged Weight on Properties of Microcapsules Coated with 6 : 4 Composite Latex of Copoly(EA MMA HEMA)[a]

Charged weight of cores (g)	25				300
Spray rate (ml/min)[b]	1.6	2.2	2.6	3.7	6.2
Spray pressure (atm)	1.9				2.2–2.5
Yield of product (%)	92	92	91	91	97
Mass median diameter (μm)[c]	61	63	64	70	65
Agglomerates (%)[d]	0.9	1.5	8.3	38.8	6.7

a) Core, lactose of 53–63 μm. Operating conditions of NQ-GM: inlet air temperature, 60 °C; outlet air temperature, 24–29 °C; inlet air rate, 0.8 m³/min. *b*) Spray dispersion: 10 or 120 g of dry lacquer was dispersed in 100 or 1200 ml of water, respectively. *c*) Theoretical diameter was 66 μm. *d*) Fractions larger than 75 μm, which was observed to be the smallest limit of agglomerates on microscopy of the sieved fractions.

hydrophilic and water-permeable 6 : 12 : 8 copolymer (Fig. 7b). Moreover, it is reasonable to consider that the "ordered" structure formed from composite latex particles with the same structure simultaneously made the membranes of all microcapsules impermeable (Fig. 7b), different from the case of blend latex constructing a random packing structure (Fig. 6a).

The effect of the coating level of the 6 : 4 composite latex on the release profiles is shown in Fig. 8 for the microcapsules heated at 80 °C for 12 h. When the coating level was below 30%, rapid release was observed. This clearly resulted from insufficient covering of lactose cores. At a 40% coating level, the release was strongly suppressed and no burst at the beginning was observed, different from the cases of the blend latices (Fig. 1). The thickness of the membrane at a 40% coating level was theoretically estimated to be 4.1 μm (see experimental section). It is important that the permeability of a membrane can be sufficiently suppressed in spite of such a thin film as 4.1 μm, because this leads to saving coating material, a large amount of which is required for the practically prolonged release of a fine powder with a large specific surface area; and it leads to the suppression of size enlargement due to an increase in membrane thickness. Thus, by coating with a composite latex and by subsequent heating, suppression of both drug release and agglomeration could be

compatibly achieved at only a 40% coating level even for such fine particles as 53—63 μm lactose.

It was desired from the practical point of view that a spray rate had better be as high as possible in order to save operation time. Therefore, the effect of the spray rate on the properties of microcapsules was examined. The results are shown in Table II. When the spray rate was below 2.2 ml/min, the production of agglomerates was suppressed to less than 2%. However, the degree of agglomeration greatly increased above 2.6 ml/min; agglomerates of 8.3 and 38.8% were produced when sprayed at 2.6 and 3.7 ml/min, respectively. When the spray rates were elevated under the constant inlet air temperature and air rate, the humidity in the coating chamber rose further and the water-evaporation rate was lowered. This clearly led to the enhancement of film-formation, as reported by Nakagami *et al.*[13] As also reported previously,[1] the enhanced film-formation consequently increased the degree of agglomeration. The probability that particle collisions lead to agglomeration by interparticulate bridging should also become larger at higher spray rates, which could produce more and larger droplets.[14] These clearly explained the increase in agglomeration at the high spray rates.

Table II also shows the effect of the charged weight of the cores on the properties of microcapsules. In the coating of 300 g of lactose cores, the spray rate had to be elevated to 6.2 ml/min, because particle adhesion to the chamber due to electrostatic charge was observed at lower spray rates, such as the case where the charged weight of cores was 25 g. In spite of the high spray rate of 6.2 ml/min, the fraction of agglomerates produced was only 6.7%. This may be a practically allowable level.

Coating of Corn Starch with Composite Latex The operating conditions are shown in Table III. The operation was characterized by a very low inlet air rate and a high spray pressure. As reported perviously,[3] a steady circulation of particles whose diameters were larger than 20 μm could be achieved under the usual conditions such as those shown in Table I. However, operation under such conditions was too strong for the corn starch used here to be steadily circulated, and led to a large loss due to leakage from the filter. Hence, the inlet air rate had to be lowered to 0.04 m^3/min. In contrast, the spray pressure was elevated to 4.5 atm so that the particles could be blown up from the draft tube by the suction of particles with the aid of spray air, even though the inlet air rate was very low.

TABLE III. Operating Conditions in Coating of Corn Starch

Core: Corn starch (12 μm)	300 g
CCSS	15 g
Spray dispersion: 6:4 composite latex	150 g[a]
Water	Added
Total	750 ml
Operating conditions of NQ-GM:	
Inlet air temperature (°C)	65
Outlet air temperature (°C)	30
Inlet air rate (m^3/min)	0.04
Spray rate (ml/min)	2.9
Spray pressure (atm)	4.5
Yield (%)	92
Mass median diameter (μm)	16

a) On a dry basis.

The mass median diameter of corn starch was 12 μm. Corn starch (300 g) was mixed with 15 g of CCSS (pass 20 μm) by a ball mill. This mixture was used as a core material. The 6:4 composite latex polymer of 40% relative to lactose core was needed to prolong the release of lactose of 53—63 μm (58 μm) (Fig. 8). Hence, it was not expected that the release of CCSS fixed on 12 μm particles might be prolonged at only a 50% coating level (Table III); in fact, the rapid leakage of CCSS was observed when the cured microcapsules were immersed in the dissolution fluid. In this experiment, therefore, operating conditions for coating the powder of the order of 10 μm without agglomeration were sought.

Figure 9 shows the cumulative undersize distributions of the product and the related powders. Corn starch contained no particles larger than 17.5 μm when the particle size distribution was measured by the centrifugal

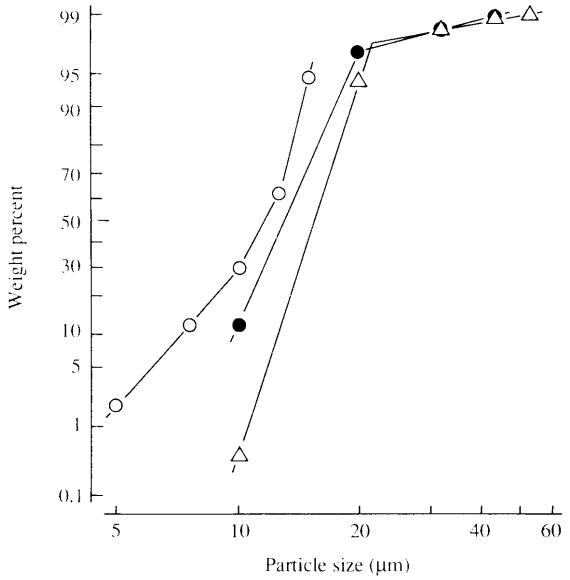

Fig. 9. Cumulative Undersize Distributions of Corn Starch Coated with 6:4 Composite Latex of Copoly(EA MMA HEMA) and the Related Powders

○, corn starch; ●, mixture of corn starch and CCSS; △, coated corn starch.

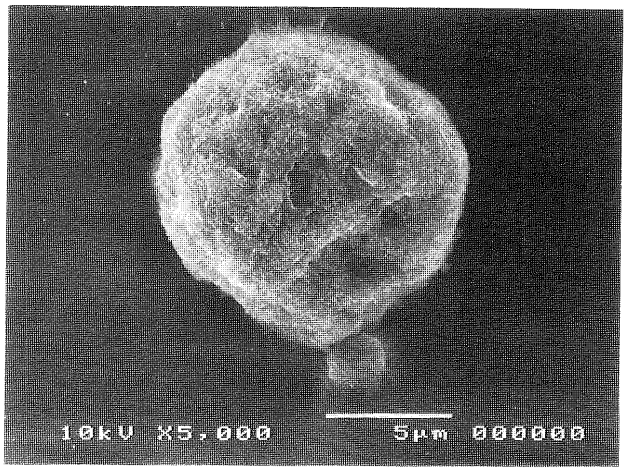

Fig. 10. SEM Photograph of Coated Corn Starch

sedimentation method. The mixture of corn starch and CCSS contained 3% agglomerates larger than 20 μm. After the mixture was coated, the amount of agglomerates estimated from a broken point at 21 μm of particle size was only 3%. Figure 9 also shows that no particles larger than 32 μm were newly produced during the coating process. The mass median diameter of the final product was 16 μm. These indicated that the particles of the order of 10 μm could be discretely coated as single-core microcapsules.

A SEM photograph is shown in Fig. 10. The particles were well coated, but their surfaces were very rough and porous. Although the coat formed using large particles such as Nonpareils® have exhibited a smooth-faced appearance,[15] the inertia of fine particles such as 12 μm corn starch used here was very small, so that the collision of particles to the inner surface of the draft tube would be insufficient for the membrane to be made smooth. These pores observed on the surface could not be eliminated, even if the microcapsules were heated at 80 °C. This indicated that some different film-formation mechanisms would be required for the production of prolonged release pharmaceuticals on the order of 10 μm.

Conclusion

Blend latices composed of the hydrophilic 6 : 12 : 8 latex and the hydrophobic 12 : 6 : 4 latex exhibited a very low degree of agglomeration. However, the coating operation was troubled by particle adhesion and cohesion due to the low softening temperature of the 12 : 6 : 4 copolymer. In addition, the release of lactose from the coated microcapsules, even if cured by heating, could not be sufficiently suppressed, with a fraction of fast releasing microcapsules remaining, due to a variation in the membrane structure formed by the random packing of latex particles.

On the other hand, composite latices composed of the 12 : 6 : 4 copolymer core and the 6 : 12 : 8 polymer shell could form a low permeable membrane by curing at a 6 : 4 core-shell weight ratio, so that the lactose release was strongly suppressed at the 40% coating level without an initial burst. Moreover, composite latices exhibited a low tendency for agglomeration, particle adhesion and cohesion, while the polymer yield remaining very high. These properties were still effective even when coating corn starch as fine as 12 μm. This showed that the particles of the order of 10 μm could be discretely coated as single-core microcapsules using the Wurster process.

However, there still remained a serious problem. Since the inertia of fine particles of the order of 10 μm was very small, smoothing the membrane by the collision of particles to the inner surface of the draft tube could not be achieved. Enhancement of film-formation by some additional function of the latices, for example, by the utilization of a physicochemical interaction such as hydrogen-bonding, hydrophobic interaction or so on, will be required to prolong the release of pharmaceuticals of the order of 10 μm.

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