Coating Performance of Aqueous Composite Latices with *N*-Isopropylacrylamide Shell and Thermosensitive Permeation Properties of Their Microcapsule Membranes

Hideki ICHIKAWA,* Shuji KANEKO, and Yoshinobu FUKUMORI

Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Arise, Ikawadani-cho, Nishi-ku, Kobe 651–21, Japan.
Received August 8, 1995; accepted September 20, 1995

An aqueous composite latex which suppressed particle adhesion by electrostatic charge and agglomeration in coating and had self-film-formability in dissolution was developed as a coating material for subsieve-sized particles using the Wurster process. This composite latex was composed of a poly(ethyl acrylate (EA)/methyl methacrylate (MMA)/2-hydroxyethyl methacrylate (HEMA)) core and a thermosensitive poly(*N*-isopropylacrylamide (NIPAAm)) shell. The polymer yield in coating of 53—63 μm lactose with homogeneous latices without poly(NIPAAm) shell exhibited a remarkable particle size dependency because of particle adhesion arising from the electrostatic charge. On the contrary, composite latices reduced the production of poorly coated particles and the particle size dependency of polymer yield, when the coating operation was done at temperatures where poly(NIPAAm) shells were swellable, *i.e.*, below the lower critical solution temperature (LCST; 32 °C) of poly(NIPAAm). Agglomeration tendency strongly depended on the hardness of the poly(EA/MMA/HEMA) cores. Microcapsules coated with composite latices exhibited a temperature-sensitive release of water-soluble lactose, while with homogeneous latices the release was simply enhanced with rise in temperature. When the microcapsules coated with composite latices were exposed to a critical temperature around LCST during the dissolution process, the lactose release from them was most suppressed, suggesting that shrinkage of the dehydrated poly(NIPAAm) shells in the coat of the microcapsules at the critical temperature would contribute to formation of a compact film which could strongly suppress water- and lactose-permeation.

Key words coating; composite latex; *N*-isopropylacrylamide; spouted bed; microcapsule; controlled release

Our studies on microencapsulation of pharmaceutical powders by means of a spouted bed coating process with a draft tube (the Wurster process) have been focused on how to reduce the product size and how to gain a variety of useful functions of microcapsules. For such purposes, in our previous studies, various membrane materials and formulations, including organic solvent-based polymeric solution systems,[1] water-based polymeric solution systems[2] and aqueous dispersion systems,[3] were developed and their performances in coating of fine particles in a subsieve region were evaluated. Most recently, an aqueous polymeric latex with composite structure of poly(ethyl acrylate (EA)/methyl methacrylate (MMA)/2-hydroxyethyl methacrylate (HEMA)) was synthesized.[4] This composite latex was composed of a low water-permeable poly(EA/MMA/HEMA) core and a nonadhesive poly(EA/MMA/HEMA) shell. When its core-shell weight ratio was 6 : 4, it formed a low permeable membrane by curing. For example, when 40% coated with the latex, the microcapsules composed of a 53—63 μm lactose core released only 10% of lactose at 3 h without any initial burst. In addition, the composite latex induced no adhesive behavior during the coating operation, leading to production of microcapsules with a low degree of agglomeration and a high polymer yield. These properties were still effective even in the coating of corn starch as fine as 12 μm. This indicated that particles of the order of 10 μm could be discretely coated as single-core microcapsules in the Wurster process. However, there still remained two serious problems.

First, surfaces of the coated corn starch were too rough and porous to be cured by heating, though the product had a high polymer yield. Since the inertia of fine particles of the order of 10 μm was very small, the membrane could not be smoothed by mechanical force such as the collision of particles to the inner surface of the draft tube. This indicated that enhancement of film-formation by some additional function of latices would first be required for the production of prolonged release microcapsules of 10 μm.

Meanwhile, to avoid agglomeration of core particles in a spray coating process, a spray liquid flow generally has to be adjusted to a low rate. In fact, the previously synthesized 6 : 4 composite latex of poly(EA/MMA/HEMA) induced a significant agglomeration when the liquid flow rate was above 2.6 ml/min.[4] However, an operation under low humidity frequently results in particle adhesion to the chamber wall due to electrostatic charge, leading to interparticle variation of product properties such as release behavior and drug content.[1a] Thus, the ability to suppress this electrostatic charge, even though the coating is performed under low humidity, was the second requisite for membrane materials.

Various polymeric hydrogels have increasingly been utilized to provide a variety of functions such as bioerosion, stimuli-sensitive drug release and so on to devices for drug delivery.[5] Environmentally sensitive hydrogels have particularly received much attention.[6] They display sharp phase transition in swelling in an aqueous solvent in response to such environmental stimuli as temperature,[6a] pH,[6b–d] electrical field,[6e–g] and light ray.[6h,i]

In the present study, to develop an aqueous latex which could regulate water content on the microcapsule surface during coating operation and would have self-film-formability in the dissolution process in an aqueous

* To whom correspondence should be addressed.

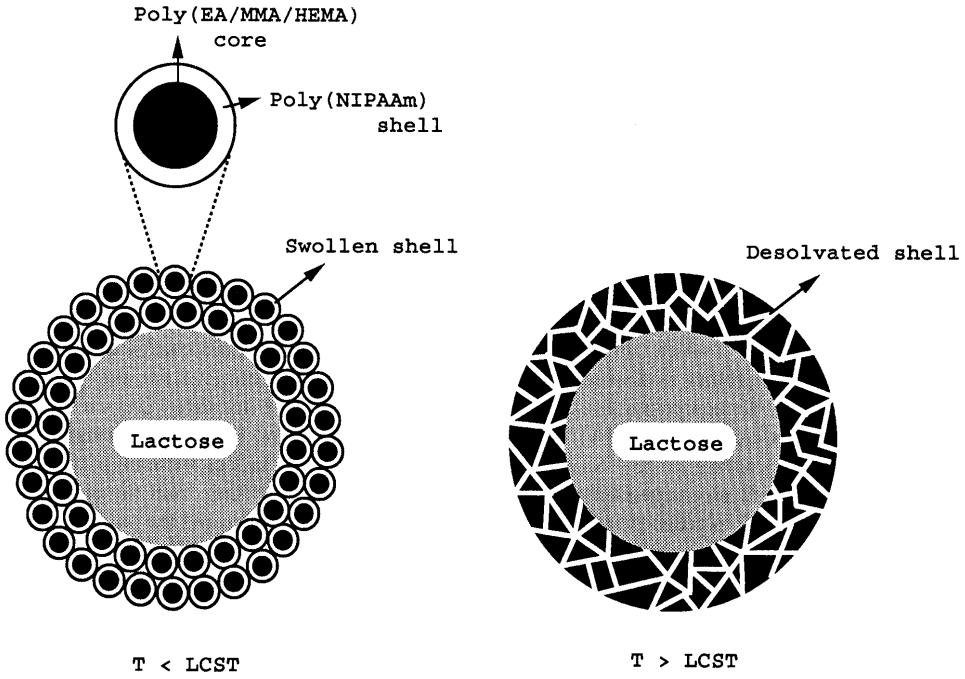

Fig. 1. Schematic Diagram of an Aqueous Composite Latex Particle with Hydrogel Shell and a Lactose Particle with Its Coating Layer

medium, stimulus-sensitive hydrogel was introduced on the surface of latex particles of poly(EA/MMA/HEMA). A schematic illustration of the aqueous composite latex with a hydrogel shell and a lactose particle coated with the latices is shown in Fig. 1. *N*-Isopropylacrylamide (NIPAAm) was selected to be the hydrogel shell of the latex particle. Poly(NIPAAm) gel has a negative temperature dependency of swelling behavior in an aqueous solvent,[7] so that it has been applied as a functional material in several fields of controlled drug release,[8] extraction[9] and enzyme activity control technologies.[10] In this study, its thermally sensitive swelling/shrinking property was utilized to provide the above functions to the latex particles. The coating performances of the synthesized latices and release properties of the lactose particles coated with them were evaluated.

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 53—63 μm by sieving. Anhydrous silica (Aerosil #200, Nippon Aerosil Co., Ltd.) was used as an antiadherent when microcapsules were heated for curing. *N*-Isopropylacrylamide (NIPAAm) was the generous gift of Kojin Co., Ltd., and other materials were purchased from Nacalai Tesque, Inc.

Preparation of Latex The latices of poly(EA/MMA/HEMA) were synthesized as previously reported.[3b] The total weight of the monomer used was 433 g in each polymerization. Synthesis of composite latices was carried out as follows. One-hundred-and-fifty grams of a mixture of EA, MMA and HEMA was first emulsified in an aqueous surfactant solution and the remainder was dropped into a reactor to prepare the cores. Thirty min after the dropping was completed, 43 g of *N*-isopropylacrylamide dissolved in distilled water of 250 ml was further dropped into the reactor to prepare the shells. To remove unreacted monomers and water-soluble substances, all latices prepared were dialyzed using a cellulose-tube (UC 1-7/8, Sanko Junyaku Co., Ltd.) in distilled water for 5 d by replacing the water by a fresh water at 12-h intervals.

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 and a filter with an opening of about 5 μm were employed throughout all experiments. The charged weight of lactose cores was 25 g. Spraying was performed up to a polymer level of 100% (based on core weight) on a dry basis.

Particle Size Distribution The sieve analysis was performed as previously reported.[1a]

Yield of Polymer To extract lactose from microcapsules, exactly weighed 10 mg of microcapsules was dispersed in a glass tube containing 8 ml of hot water at 90 °C for 45 min. Then, the tube was centrifuged at 3000 rpm for 10 min and the supernatant was removed. After these procedures were repeated three times, the residual polymer was dried and exactly weighed. Polymer yield was obtained from the measured content of polymer in microcapsules multiplied by the total amount of produced microcapsules and divided by the charged amount of polymer.

Dissolution Dissolution tests were performed by a shaking method using an Erlenmeyer flask with 300 ml volume. The prepared microcapsules were dried in a vacuum at room temperature for 12 h. Microcapsules coated with homogeneous latices were cured by mixing with 2% anhydrous silica and then by heating for 12 h in an air stream oven at 60 °C for 12 : 6 : 4 poly(EA/MMA/HEMA) and 80 °C for 9 : 9 : 4. In order to eliminate the particle size dependency in lactose release, microcapsules sieved into 75—90 μm, which was the largest fraction of single-core microcapsules, were tested. A 0.9% saline solution (200 ml) was used as a dissolution fluid. Microcapsules containing 22 mg of lactose were placed in the flask and the flask was horizontally shaken at 120 times/min in a temperature-regulated water bath. The concentration of released lactose was monitored by taking an aliquot of 1 ml through a 0.22 μm filter (Micro Filter, FM-22, Fuji Photo Film Co., Ltd.) at specific time points, replacing the solution with a fresh dissolution fluid and determining lactose by the phenol–sulfuric acid method.[3b] When the dissolution temperature was below 10 °C, the dissolution fluid became turbid due to the separation of latex particles from the surface of microcapsules coated with composite latices whose cores consisted of 6 : 12 : 4 poly(EA/MMA/HEMA). In this case, a small amount of sodium chloride was added to an aliquot so that latex particles were removed by salting-out. After the aliquot was vortexed and centrifuged, the lactose concentration in the supernatant was determined.

Softening Temperature Thermomechanical analysis was performed as previously reported.[3b]

Elongation of Cast Films A dispersion (5 g) containing 10% polymer was cast on a thinly Teflon-coated glass dish and allowed to stand at room temperature and humidity until a transparent film was formed. Thereafter, the film was cut out so that it had a constant cross-sectional area (2.00 mm^2), hung in a glass bottle containing dissolution fluid of 37 °C and provided with a tensile load of 4.4 g. Elongation of the film was measured by a cathetometer (PIKA Seiko, Ltd.) with time. The

strain, L, was defined by $(L_t - L_0)/L_0 \times 100$, where L_t and L_0 are the length of the film at the time t and just after immersion in the dissolution fluid, respectively.

Polarizing Microscopy The change of particle breadth in dissolution fluid was measured as reported.[3d]

Results

Agglomeration and Coating Efficiency The coating conditions and the properties of products prepared using composite latices are shown in Table 1, compared with those for homogeneous latices. The softening temperature, Ts, of cast films of homogeneous poly(EA/MMA/HEMA) latices rose with increasing MMA content as previously reported.[3b] For the composite latices, Ts of their cast films also increased with MMA content in the core and were higher than those for the corresponding homogeneous latices. As also reported,[3a] agglomeration in the coating with aqueous latices was significantly suppressed when their Ts was higher than the inlet air temperature and, therefore, their film-formability was low. Thus, the inlet air temperature was adjusted to a temperature slightly lower than Ts of each latex (around 5 °C), except for 12:6:4 poly(EA/MMA/HEMA) whose Ts was too low to do so. There was no significant difference in Ts between homogeneous and composite latex whose molar ratio of poly(EA/MMA/HEMA) was 6:12:4, so that coating using these latices could be performed under the same conditions, except that the spray air flow rate and pressure in coating with homogeneous latex had to be slightly lowered to avoid its spray-drying. On the other hand, liquid flow rates in latices whose coating was done under an inlet air of less than 40 °C had to be lowered, because such a high rate as 2.4 ml/min in the case of 6:12:4 caused more remarkable agglomeration.

In coating with homogeneous latices, production of agglomerates (larger than 90 μm) was negligible when the molar ratio of poly(EA/MMA/HEMA) used was 9:9:4 or 6:12:4; with 12:6:4 poly(EA/MMA/HEMA), however, 7.4% of particles in the products were agglomerates. For the composite latices composed of the core of 9:9:4 or 6:12:4 poly(EA/MMA/HEMA), agglomerates were produced at only around 1%. Although the poly(NIPAAm) shells of composite latex having 12:6:4 poly(EA/MMA/HEMA) cores apparently raised Ts of its cast film, its agglomeration tendency could not be improved.

Particle size distribution of microcapsules coated with homogeneous or composite latices and the polymer yield of the particles in each sieved fraction are shown in Fig. 2. The microcapsules (MCs) prepared using the homogeneous and the composite latices are denoted henceforth as HL MCs and CL MCs, respectively, and the molar ratio of poly(EA/MMA/HEMA) used will be represented as, for example, 12:6:4 CL MCs. The particle size distributions of CL MCs were sharper irrespective of the composition of poly(EA/MMA/HEMA) core, compared with the corresponding HL MCs. The fine fractions (53—63 and 63—75 μm) of CL MCs, which could be regarded as resulting from their adhesion to the chamber wall due to electrostatic charge, were lower in weight than those of HL MCs. As shown in Fig. 2, strong size dependency of polymer yield was observed in HL MCs; however, in CL MCs the size dependency was less.

Dissolution of Lactose from HL MCs Figure 3 shows release of lactose from 12:6:4 and 9:9:4 HL MCs at 100% coating level in a 0.9% saline solution at 37 °C and the corresponding particle expansion data. The effect of curing is also shown. The 12:6:4 HL MCs exhibited a delayed release profile with a lag time, when they were only dried in a vacuum (Fig. 3a). The curing at 60 °C did not essentially affect the release profile, though it slightly prolonged the lag time. When these microcapsules were immersed in a dissolution fluid and microscopically observed, particles were gradually expanded by osmotic pressure generated by lactose dissolved within the microcapsules. Their membranes were then ruptured at the time corresponding to the end of the lag (*ca.* 3 h). Clearly, this rupture of the membrane due to the osmotic pressure led to the subsequent rapid release of water-soluble lactose after the lag period.

Table 1. Operating Conditions in Coating and Properties of Products

	Molar ratio of poly(EA/MMA/HEMA)					
	12:6:4		9:9:4		6:12:4	
Type of latex	Homogeneous	Composite	Homogeneous	Composite	Homogeneous	Composite
Softening temperature of cast film (°C)	27	42	46	59	74	76
Operating conditions:						
Inlet air temperature (°C)	30	40	40	55	70	70
Outlet air temperature (°C)	23—24	26—27	23—25	26—27	29—31	29
Inlet air rate (m^3/min)	0.18—0.23	0.18—0.19	0.18—0.19	0.17—0.18	0.17—0.18	0.17—0.18
Spray air flow rate (l/min)	55	55	55	55	50—52	55
Spray air pressure (atm)	2.1	2.1	2.1	2.1	1.7—1.9	2.1
Liquid flow rate (ml/min)	0.6	1.9	1.5	2.3	2.4	2.4
Product:						
Yield (%)	85	87	88	91	88	88
Mass median diameter (μm)	76	79	76	77	75	75
Coarse fraction larger than 90 μm (%)	7.4	5.0	0.6	1.2	1.7	0.9
Fine fraction smaller than 63 μm (%)	7.6	4.5	10.2	8.9	11.7	5.3

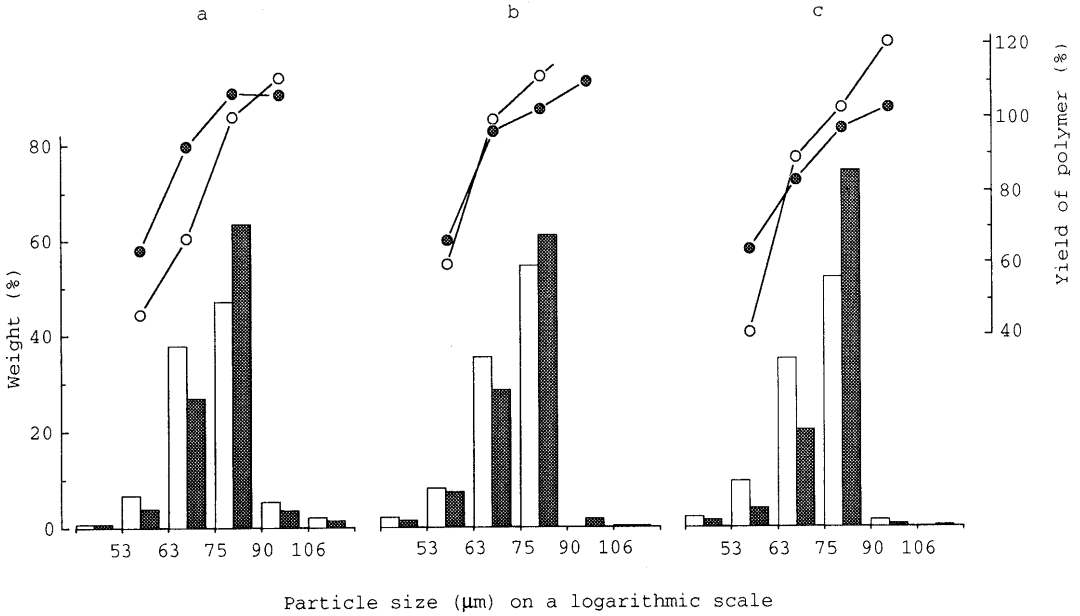

Fig. 2. Particle Size Distributions of HL and CL MCs and Polymer Yield of the Particles in Different Sieved Fractions

Type of latex: open symbols and bars, homogeneous; shaded, composite. Symbols and bars represent yield of polymer and particle size distribution, respectively. Molar ratio of poly(EA/MMA/HEMA): a, 12:6:4; b, 9:9:4; c, 6:12:4.

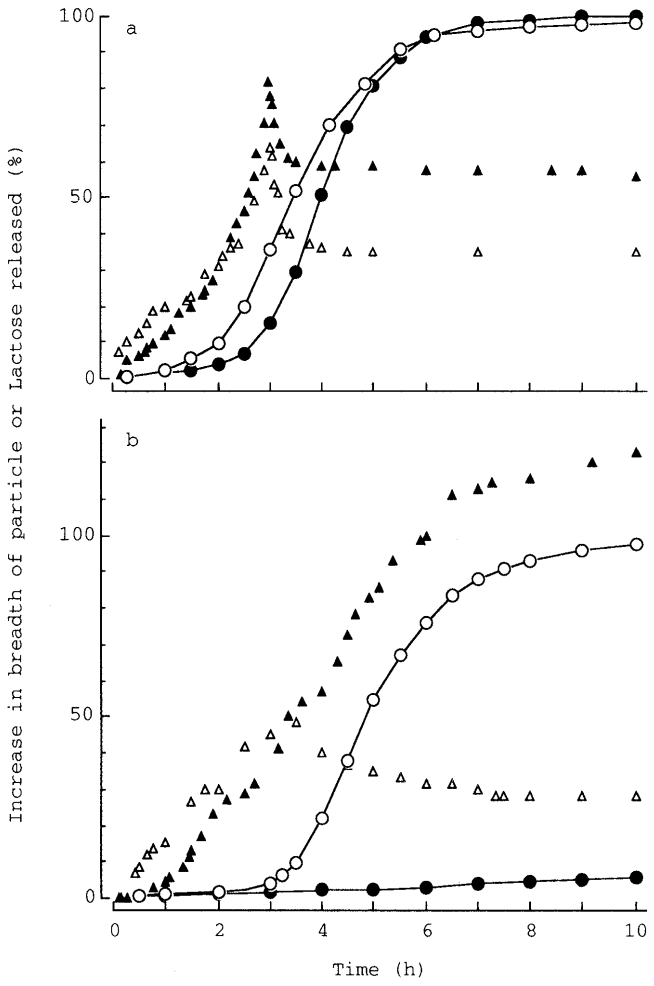

Fig. 3. Release of Lactose from HL MCs 100% Coated in a 0.9% Saline Solution at 37 °C and the Corresponding Expansion

○●, dissolution of lactose; △▲, particle expansion. Curing: open symbols, only dried in a vacuum at room temperature; closed, heated at 80 °C for 12 h. Molar ratio of poly(EA/MMA/HEMA): a, 12:6:4; b, 9:9:4.

On the other hand, it was found that the 9:9:4 HL MCs did not complete the film-formation during the coating process, because the lactose permeability was decreased to a negligible level by heating the microcapsules at 80 °C (Fig. 3b), unlike the case of 12:6:4 HL MCs (Fig. 3a). As seen in Fig. 3b, the cured microcapsules did not exhibit any rupture of the membrane: they monotonously expanded for 6 h in dissolution fluid and thereafter maintained almost 10 times greater volume than the original particles; even at 24 h, the same state was retained.

Dissolution of Lactose from CL MCs Dissolution profiles of unheated samples in a 0.9% saline solution at various temperatures are shown in Fig. 4 for the microcapsules 100% coated with three kinds of composite latices with differing compositions of poly(EA/MMA/HEMA) core. In 6:12:4 CL MCs (Fig. 4c), microcapsules rapidly burst at every temperature studied here. In this case, increased turbidity of dissolution fluid was observed when the dissolution test was done below 10 °C, indicating the separation of latex particles from the microcapsule surfaces. In contrast, 12:6:4 and 9:9:4 CL MCs exhibited dissolution profiles responding to changes in dissolution temperature (Figs. 4a, 4b). In 12:6:4 CL MCs, most lactose burst at 20 °C or lower (Fig. 4a). As temperature was raised, the release of lactose was more prolonged, and at 28 °C it apparently exhibited the profile characterized by zero order-kinetics over the long period. As the temperature further increased beyond 28 °C, lactose release became gradually faster again. However, the dissolution of lactose at temperatures above 28 °C was controlled with a sigmoidal pattern, different from those below 28 °C. For 9:9:4 CL MCs, thermosensitive dissolution profiles similar to 12:6:4 CL MCs were obtained, except that the corresponding temperature became a little higher and the apparent zero-order release rate at the critical temperature became faster (Fig. 4b).

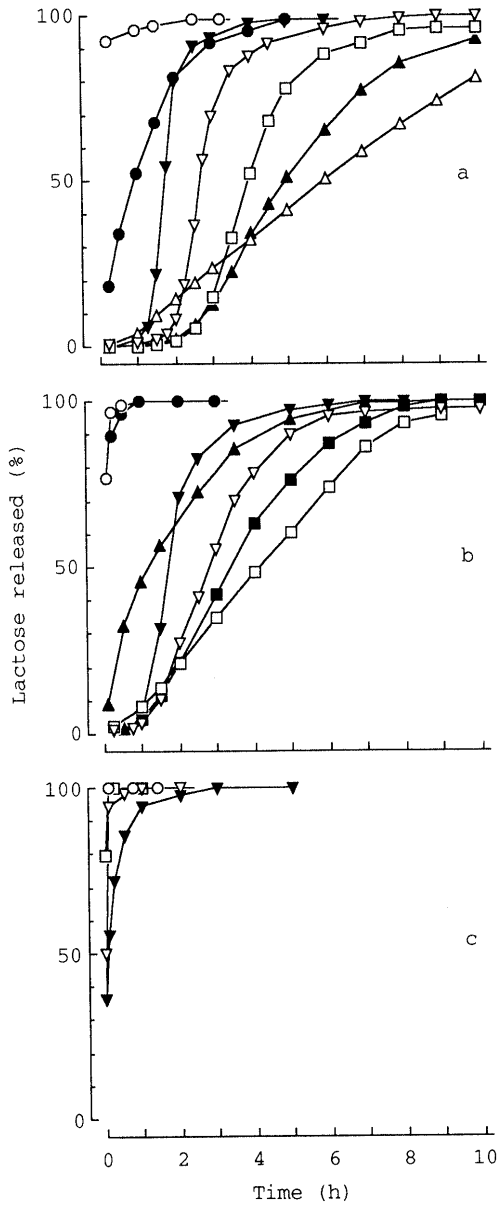

Fig. 4. Release of Lactose from CL MCs 100% Coated in a 0.9% Saline Solution at Various Temperatures

Molar ratio of poly(EA/MMA/HEMA): a, 12:6:4; b, 9:9:4; c, 6:12:4. Dissolution temperature (°C): ○, 20; ●, 25; △, 28; ▲, 30; □, 33; ■, 35; ▽, 37; ▼, 42.

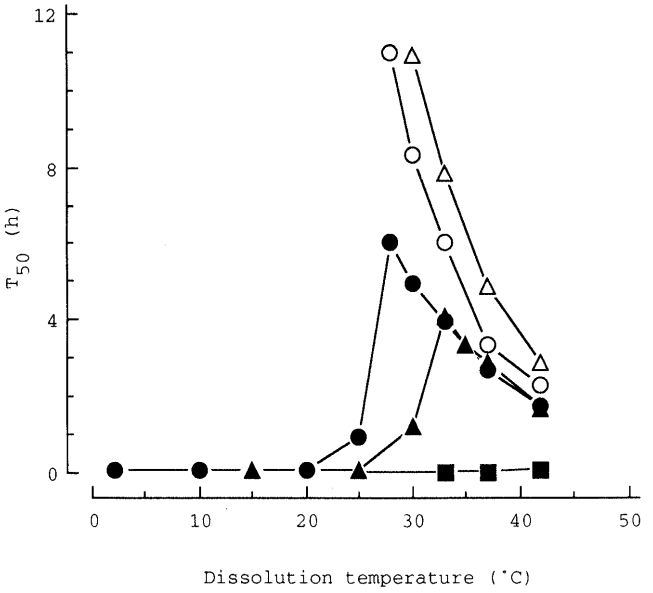

Fig. 5. Relationship between the Time for 50% Lactose Release, T_{50}, and Dissolution Temperature

Molar ratio of poly(EA/MMA/HEMA): ○●, 12:6:4; △▲, 9:9:4; ■, 6:12:4. Type of latex: open symbols, homogeneous; closed, composite.

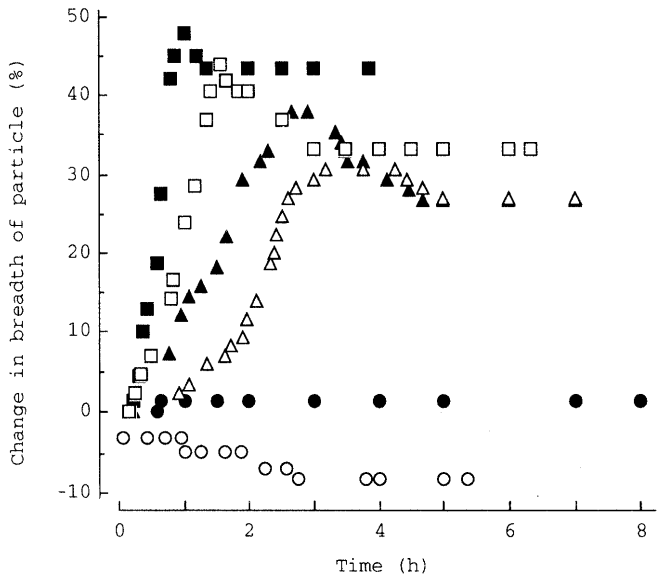

Fig. 6. Expansion of 12:6:4 CL MCs 100% Coated in 0.9% Saline Solution at Various Temperatures

Temperature (°C): ○, 13; ●, 28; △, 30; ▲, 33; □, 37; ■, 42.

As a parameter of the dissolution properties of CL MCs, the time when the dissolution reached 50%, T_{50}, was estimated and plotted in Fig. 5 as a function of dissolution temperature, compared with those for unheated HL MCs. The T_{50} values of HL MCs markedly decreased with increase in dissolution temperature, while as expected from the dissolution data shown in Fig. 4, T_{50} of 12:6:4 and 9:9:4 CL MCs began to steeply increase at 25 °C and 30 °C, respectively. Thereafter, their T_{50} reached maximum at 28 °C for 12:6:4 CL MCs and 33 °C for 9:9:4, but it decreased again with further increase in temperature. T_{50} of CL MCs was lower than that of HL MCs at every dissolution temperature.

Expansion of 100% coated 12:6:4 CL MCs in 0.9% saline solution at various temperatures is shown in Fig. 6. At 13 °C, microcapsules shrank slightly, followed by rapid release of their contents (Fig. 4a). At 28 °C where the release profile characterized by zero order-kinetics was observed, there was no significant change in the particle size. Above 28 °C, microcapsules expanded by uptake of water and their membrane finally ruptured at the peak of expansion. The expansion became faster and greater with rise in temperature. These well corresponded to the dissolution properties above 28 °C shown in Fig. 4a.

Discussion

In this study, poly(EA/MMA/HEMA) was used as a core of composite latex (Fig. 1), since the properties had been well characterized previously.[3a,b] *N*-Isopropylacrylamide (NIPAAm) was selected as a monomer which could form a hydrogel shell on the latex particle of poly(EA/MMA/HEMA). As is well known, the crosslinked poly-

(NIPAAm) forms a thermosensitive hydrogel and its swelling properties in an aqueous medium markedly change at the phase transition temperature, the so-called lower critical solution temperature (LCST).[7] When an environmental temperature is raised to LCST, the hydrogels shrink due to dehydration arising from the hydrophobic interaction of polymer pendant (isopropyl group). Below LCST, hydrogels can uptake water because of hydration forces involved with dissociation of the polymer pendant by breaking of the hydrophobic interaction: the extent of swelling becomes larger with decrease in temperature. Poly(NIPAAm) has been shown to have an LCST around 32 °C in water.[7] In the coating process, therefore, it was expected that the waterish surface of a microcapsule formed by the swollen poly(NIPAAm) shell might lead to suppression of the particle adhesion due to electrostatic charge, provided the outlet air temperature was adjusted below the LCST. The hydrogel in the coat of the microcapsule, on the other hand, would be dehydrated during the dissolution process at 37 °C. Under such conditions, the strong shrinkage of poly(NIPAAm) chains on the latex particles, namely, a zipper effect,[11] was expected to lead to enhancement of the film-formation of these particles deposited on the lactose particles: this should be called self-film-formation.

In the Wurster spouted bed process, film thickness of coated particles varies with particle size within a batch, while a top or tangential spray fluidized bed rarely displays this variation.[12] This is ascribed to the fact that circulation of lighter and/or smaller particles takes more time because of the intrinsic particle flow pattern in the Wurster process. This tendency becomes more remarkable by the particle adhesion to the chamber wall arising from an electrostatic charge. As is well known, the electrostatic charge of particles circulating in the fluidized bed coating process is affected by their water content. The composite latices synthesized here allowed steadier circulation of particles in the coating chamber than the corresponding homogeneous latex as expected: their adhesive behavior due to the electrostatic charge occurred only slightly, when the flow pattern of particles was visually monitored through viewing ports located in the coating chamber. The observed steady circulation clearly led to less production of poorly coated particles and improvement of particle size dependency in polymer yield (Fig. 2). This clearly resulted from the suppression of electrostatic charge arising from the increased water content on microcapsule surfaces by the swollen poly(NIPAAm) shell.

In this study, the inlet air temperature was set to one slightly lower than Ts of each latex to avoid agglomeration, and the spray liquid flow rate was optimized so that particles could flow with as little adhesion as possible at the inlet air temperature employed (Table 1). Since the conditions in coating using the 12:6:4 and 9:9:4 composite latices were different from those in the corresponding homogeneous latices, it was difficult to quantitatively evaluate how much the water-holding of poly(NIPAAm) shells on those microcapsule surfaces contributed to improvement of the particle size dependency in polymer yield shown in Fig. 2. However, the results showed at least that with HL MCs further improvement in size dependency was impossible without generation of more agglomerates.

The enhancement of film-formation leads to the production of more agglomerates in general. For example, HEMA, a kind of hydrogel component,[13] enhanced the film-formation because of its hydrophilicity or strong hydration.[3c] Since composite latices had hydrogel layers, the extent of their hydration should be higher than that of homogeneous latices in the coating process. It was, however, fortunate that composite latices did not significantly enhance agglomeration (Table 1), possibly due to the very small amount of poly(NIPAAm) covering the latex particles. On the contrary, since the poly(NIPAAm) shells introduced onto the poly(EA/MMA/HEMA) apparently raised Ts of its cast film, agglomeration was expected to be reduced, especially in the case of 12:6:4 poly(EA/MMA/HEMA) whose Ts was lower than the employed inlet air temperature. However, these did not work as a hard shell which might effectively suppress agglomeration; this would be because the hydrated poly(NIPAAm) shells were soft just after spraying. Thus, the agglomeration tendency seemed to depend primarily on the deformability of latex cores.

Dissolution properties of lactose from microcapsules coated with homogeneous latices of poly(EA/MMA/HEMA) were reported previously in detail[3b]; large lactose cores of 328 μm were used there. It was demonstrated that the apparent rate constant of lactose release from 12:6:4 HL MCs was smaller than that from 9:9:4 HL MCs. In the present study, however, the lactose release through 12:6:4 and 9:9:4 poly(EA/MMA/HEMA) membranes had an inverse tendency (Fig. 3). This was because the rupture of microcapsule membranes by the osmotic pressure occurred in the 12:6:4 membrane. The membrane thickness[4] of the present microcapsules at 100% coating level was estimated to be about 9.1 μm. In addition, Ts of 12:6:4 poly(EA/MMA/HEMA) membrane was lower than the dissolution temperature (37 °C). The strength of this thin, soft film seemed too little to resist the expansion generated by the osmotic pressure; consequently, the rupture of membrane could not be avoided and it led to the rapid release of lactose. On the contrary, the cured membrane of 9:9:4 poly(EA/MMA/HEMA) did not rupture during the dissolution test for 10 h. In this case, only 5% of lactose was released during 10 h, although water had penetrated through the expanding membrane. This indicated that the lactose permeability of 9:9:4 poly(EA/MMA/HEMA) membrane was quite low. Kelbert and Bechard[14] also found that in the tablet coated with cellulose acetate (CA) latex containing a water soluble drug (propranolol HCl), no drug was released over 8 h, though tablet swelling, indicating water penetration through the CA membrane, was observed just as in the case of the microcapsules studied here. Considering that the lactose release from 12:6:4 HL MCs had been more suppressed than that from 9:9:4 HL MCs when their membrane was thick enough to resist the expansion,[3b] it is reasonable to consider that the 12:6:4 poly(EA/MMA/HEMA) membrane also had a very low lactose-permeability.

Yamamoto *et al.*[15] prepared rigid polystyrene latex

with a poly(NIPAAm) layer (a core-shell latex) by soap-free emulsion copolymerization and elucidated the local environmental change at the surfaces of the core-shell latex particles around LCST; they deposited the core-shell latex two-dimensionally on a flat substrate and observed it by environmental scanning electron microscopy. At 25 °C the core-shell latex particles on the substrate arranged themselves with a clearance corresponding to their size in a fully hydrated state (hydrodynamic size). The aggregation of the core-shell latex due to dehydration of the poly(NIPAAm) layer, in contrast, was observed when the environmental temperature was 45 °C. These results reported by Yamamoto *et al.* indicated that the poly(NIPAAm) layer of the core-shell latex above the LCST was strongly shrinkable to such an extent that latex particles were attracted by each other. To trigger a film-formation, however, it is also necessary that latex particles have to be yielded dynamically.[16] The membrane of 6:12:4 CL MCs was very porous and could not act as a permeation barrier throughout the dissolution temperatures studied here (Fig. 4c). Since 6:12:4 poly(EA/MMA/HEMA) cores of composite latex particles had a higher Ts than cores of 9:9:4 and 12:6:4 poly(EA/MMA/HEMA), they seemed too rigid to allow the fusion of discrete latex particles to make compact films by the shrinkage of poly(NIPAAm) layer at a temperature above the LCST. The results shown in Fig. 4 clearly demonstrated that it was difficult for the shrinkage of poly(NIPAAm) to enhance film-formation, unless the core of composite latex particles would be deformable during the dissolution process.

The dissolution profiles shown in Fig. 4a and 4b seemed to fall into three different mechanisms. In Fig. 4a, for instance, the lactose release at temperatures below 28 °C was very fast. At temperatures below the LCST, poly(NIPAAm) shells in the coat of microcapsules should easily swell as soon as they came in contact with the dissolution medium. Since few lactose molecules permeated through the core portions of composite latices as indicated in Fig. 3, they would be predominantly released through water-permeable channels formed by swollen poly(NIPAAm) shells. Unlike the monolithic matrix systems of hydrogels studied in many reports,[8,17] the membrane of CL MCs studied here was very thin. Therefore, the channels would no longer work as a permeation barrier to lactose because of the short diffusion distances. Next, at 28 °C an apparent zero-order release of lactose was achieved over 8 h and the release was most strongly suppressed. The lack of detectable change in the particle size of microcapsules at 28 °C indicated that water flow through the membrane was quite low (Fig. 6). In fact, it was found by microscopic observation that lactose crystals in the microcapsules were slowly dissolved and they disappeared at about 7 h. Such a reduced water-permeability of membrane would give rise to the zero-order release. It was suggested from these results that all thin poly(NIPAAm) layers in the coat of the microcapsules might be mutually attracted by each other at dissolution temperatures close to the LCST and, consequently, tight channels, which could suppress the permeation of water and lactose, might be formed. Finally, the release of lactose exhibited a sigmoidal profile at temperatures above 28 °C and again became faster than that at 28 °C. In these cases the microcapsules were rapidly expanded by taking up a great amount of water and their membranes finally ruptured as shown in Fig. 6, leading to the sigmoidal release profile. It is reasonable to consider that the enhanced water-permeation/diffusion at high temperatures accounted for these phenomena.

The effect of temperature change on the release of indomethacin (M.W. = 357.79) from thermoresponsive hydrogel microspheres composed of crosslinked poly(NIPAAm) containing a small amount of acrylamide as a comonomer was studied by D'Emanuele and Dinarvand.[17] It was demonstrated in their report that the release rate of indomethacin from the microspheres simply decreased as temperature increased in the range of 20 to 45 °C. In contrast to their results, there was a critical temperature at which lactose release had been most suppressed in the present microcapsules with composite latex membrane (Fig. 5). This was because the rupture of microcapsule membranes was induced by the expansion arising from osmotic pressure at higher temperatures, unlike the matrix system prepared by D'Emanuele and Dinarvand. Okahata *et al.*[18] reported a permeation study of NaCl and dyes (benzensulfonate and naphthalenedisulfonate) through an ultrathin nylon capsule membrane with a surface-grafted poly(NIPAAm) in water. The permeability of the large naphthalenedisulfonate molecules (M.W. = 332.28) was decreased 12—15 times above a critical clouding point (Cp; 35 °C) of poly(NIPAAm) compared with that below Cp. On the contrary, it was found that in the cases of small NaCl and benzenesulfonate (M.W. = 180.16) such a critical temperature as observed in this study existed near Cp; the permeation rate was decreased as the temperature was raised to Cp, but was gradually increased again as the temperature was raised beyond Cp. Okahata *et al.* discussed these phenomena as follows: the entangled, corked polymer covering the nylon capsules moved thermodynamically at high temperatures and the permeation of small molecules was little suppressed at temperatures beyond Cp. This seemed to suggest that the water-permeability through the shrunken poly(NIPAAm) layer at temperatures above LCST could be increased by thermally enhanced mobility of its entangled polymer chains.

The critical temperature depended on the composition of latex cores; it was 28 °C for 12:6:4 CL MCs and 33 °C for 9:9:4 CL MCs (Fig. 5). It is known that the LCST of poly(NIPAAm) in aqueous medium is affected by some electrolytes which coexist in the system.[7c,f,g,19,20] Saito[20] demonstrated that the LCST of crosslinked poly(NIPAAm) in a saline solution was decreased with increasing concentration of salt, although in water the LCST was 32 °C. According to his report, the LCST in 0.9% saline solution used as the dissolution medium in this study was estimated to be about 29 °C. This temperature of 29 °C was comparable to the critical temperature observed in 12:6:4 CL MCs (28 °C). However, it became 33 °C with 12:6:4 CL MCs whose core-shell ratio was increased to 8:2 (data not shown). The higher critical temperature observed for 9:9:4 CL

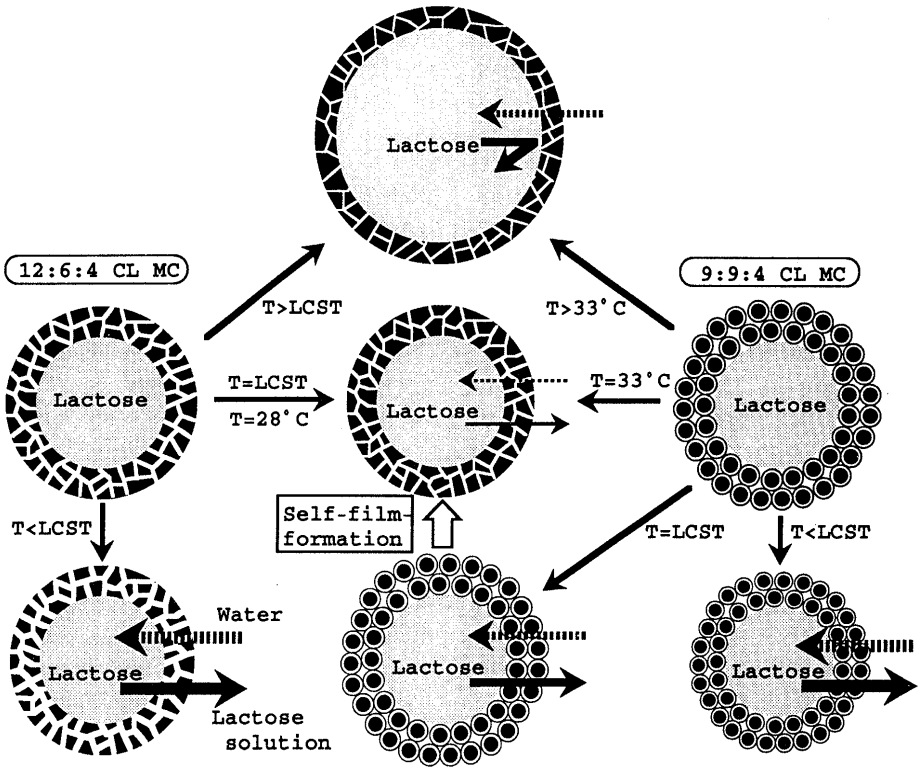

Fig. 7. Schematic Diagram of Estimated Release Mechanisms on 12:6:4 and 9:9:4 CL MCs

MCs with 9:1 core-shell ratio and 12:6:4 CL MCs with 8:2 core-shell ratio could not be explained by the thermodynamically enhanced water-permeation through poly(NIPAAm) layers at high temperatures. The dissolution data in Fig. 4 showed that, for example, the release from 9:9:4 CL MCs (Fig. 4b) was still very rapid at 28 °C where the release from 12:6:4 CL MCs (Fig. 4a) was the slowest. Since the permeation properties of poly(NIPAAm) layers were similar in the two cases, the faster release in 9:9:4 CL MCs could be explained only by their more porous membrane structure which would be formed during the coating process due to high Ts of 9:9:4 composite latex. In the case of 12:6:4 CL MCs with 8:2 core-shell ratio, particles held too much water to be steadily circulated during coating under the conditions used for the same latices with 9:1 ratio shown in Table 1. Therefore, the inlet air temperature was raised to 70 °C, leading to the outlet air temperature of 37 °C which was higher than LCST. Since Ts of 12:6:4 composite latex with 8:2 core-shell ratio was 60 °C, the membrane could be porous when coating was performed under the above dry conditions. These results indicated that the porous structure formed during coating due to a low deformability of latex particles accounted for the shift of critical point to higher temperature, and this higher temperature was required to eliminate the pores by the "zipper effect" of poly(NIPAAm). A schematic diagram of estimated release mechanisms is shown in Fig. 7.

At higher temperatures beyond LCST, 12:6:4 CL MCs exhibited a faster water-uptake and earlier membrane-rupture than 12:6:4 HL MCs (Fig. 3a and 6). This faster water-uptake could be explained by their membrane containing poly(NIPAAm) layers whose water-permeability should be higher than 12:6:4 poly(EA/MMA/HEMA). The earlier membrane-rupture suggested that the membrane of CL MCs was mechanically weaker than that of HL MCs. To confirm this, elongation of their cast films was evaluated in a 0.9% saline solution for the homogeneous and composite latices composed of 12:6:4 poly(EA/MMA/HEMA). The results are shown in Fig. 8. With the homogeneous latex, elongation was small even at 10 h, while with the composite latex the film was more rapidly elongated; at 3 h it was cracked and thereafter was finally torn. These results implied that in the dissolution medium at high temperatures the mechanical strength of the composite latex film was surely weaker than that of

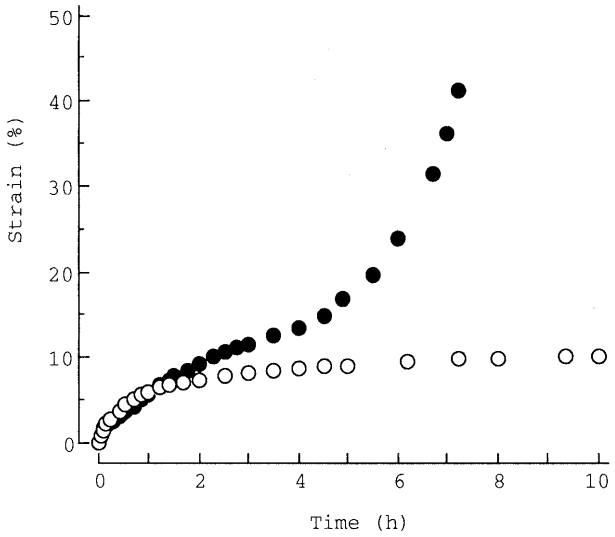

Fig. 8. Time Course of Elongation of Cast Film Immersed in 0.9% Saline Solution at 37 °C

○, homogeneous latex; ●, composite latex. Molar ratio of poly(EA/MMA/HEMA): 12:6:4.

the homogeneous latex film. Since the shrinkage of poly(NIPAAm) layers was driven by the hydrophobic interaction, they would make the membranes less tough, leading to easier rupture by the mechanical stress arising from osmotic pressure.

Conclusion

In this study, aqueous composite latices composed of a poly(EA/MMA/HEMA) core and a thermosensitive poly(NIPAAm) shell were synthesized for the first time. It was found that by using these composite latices the production of poorly coated particles and the particle size dependency of polymer yield arising from adhesion of circulating particles due to the electrostatic charging could be reduced, while the poly(NIPAAm) shells did not affect the agglomeration tendency. On the other hand, the lactose release from microcapsules coated with composite latices exhibited a thermosensitive profile with a critical temperature where lactose release had been most suppressed. The critical temperature varied in response to the hardness of composite latex particles. This was suggested to be due to the porous structure of membrane arising from a low deformability of the latex particles during coating. When the composite latex particles deposited on lactose surfaces sufficiently deformed during the dissolution process, the enhancement of film-formation by the shrinkage of poly(NIPAAm) shells around LCST, which could be called self-film-formation, was achieved at the critical temperature. This film-formation by the zipper effect of poly(NIPAAm) shells suppressed the permeation of water and water-soluble lactose.

The critical temperature was below the human body temperature of 37 °C and, therefore, the lactose release became faster when temperature was raised to 37 °C. This was ascribed to the fact that the rupture of microcapsule membranes by the osmotic pressure could not be avoided at temperatures higher than the critical temperature. However, the release seemed still sufficiently controlled and prolonged at 37 °C. If the core material will not generate such a high osmotic pressure as lactose does, a stronger suppression of release will be expected at 37 °C.

Acknowledgment This work was supported in part by a Grant-in-Aid for science research (05671798) from the Japanese Ministry of Education, Science and Culture and a Grant-in-Aid from the Hosokawa Powder Technology Foundation.

References

1) *a*) Fukumori Y., Ichikawa H., Yamaoka Y., Akaho E., Takeuchi Y., Fukuda T., Kanamori R., Osako Y., *Chem. Pharm. Bull.*, **39**, 164—169 (1991); *b*) *Idem, ibid.*, **39**, 1806—1812 (1991).
2) *a*) Fukumori Y., Ichikawa H., Jono K., Takeuchi Y., Fukuda T., *Chem. Pharm. Bull.*, **40**, 2159—2163 (1992); *b*) Fukumori Y., Ichikawa H., Jono K., Fukuda T., Osako Y., *ibid.*, **41**, 725—730 (1993).
3) *a*) Ichikawa H., Jono K., Tokumitsu H., Fukuda T., Fukumori Y., *Chem. Pharm. Bull.*, **41**, 1132—1136 (1993); *b*) Fukumori Y., Yamaoka Y., Ichikawa H., Takeuchi Y., Fukuda T., Osako Y., *ibid.*, **36**, 3070—3078 (1988); *c*) *Idem, ibid.*, **36**, 4927—4932 (1988); *d*) *Idem, ibid.*, **36**, 1491—1501 (1988).
4) Ichikawa H., Tokumitsu H., Jono K., Fukuda T., Osako Y., Fukumori Y., *Chem. Pharm. Bull.*, **42**, 1308—1314 (1994).
5) *a*) Park K., Shalaby W. S. W., Park H. (ed.), "Biodegradable Hydrogels for Drug Delivery," Technomic, Pennsylvania, 1993, pp. 1—12; *b*) Peppas N. A., Khare A. R., *Advanced Drug Delivery Reviews*, **11**, 1—35 (1993); *c*) Kim S. W., Bae Y. H., Okano T., *Pharm. Res.*, **9**, 283—290 (1992); *d*) Lee P. I., Kim C.-J., *J. Controlled Release*, **16**, 229—236 (1991).
6) *a*) Hoffman A. S., *MRS Bulletin*, **16**, 42—46 (1991); *b*) Kou J. H., Amidon G. L., Lee P. I., *Pharm. Res.*, **5**, 592—597 (1988); *c*) Peppas L. B., Peppas N. A., *J. Controlled Release*, **8**, 267—274 (1989); *d*) Peppas N. A., Klier J., *ibid.*, **16**, 203—214 (1991); *e*) Kwon I. C., Bae Y. H., Kim S. W., *Nature* (London), **354**, 291—293 (1991); *f*) Sawahata K., Hara M., Yasunaga H., Osada Y., *J. Controlled Release*, **14**, 253—262 (1990); *g*) Tomer R., Dimitrijevic D., Florence A. T., *J. Controlled Release*, **33**, 405—413 (1995); *h*) Tomer R., Florence A. T., *Int. J. Pharm.*, **99**, R5—R8 (1993); *i*) Irie M., "Advances in Polymer Science 94," ed. by Fujita H., Springer-Verlag, Berlin, 1990, pp. 28—67.
7) *a*) Heskins M., Guillet J. E., *J. Macromol. Sci. Chem.*, **A2(8)**, 1441—1455 (1968); *b*) Fujishige S., Kubota K., Ando I., *J. Phys. Chem.*, **93**, 3311—3313 (1989); *c*) Schild H. G., Tirrell D. A., *ibid.*, **94**, 4352—4356 (1990); *d*) Mukae K., Sakurai M., Sawamura S., Makino K., Kim S. W., Ueda I., Shirahama K., *ibid.*, **97**, 737—741 (1993); *e*) Wu X. S., Hoffman A. S., Yager P., *J. Polym. Sci.*, **30**, 2121—2129 (1992); *f*) Zhang Y. Q., Tanaka T., Shibayama M., *Nature* (London), **360**, 142—144 (1992); *g*) Kokufuta E., Zhang Y. Q., Tanaka T., Mamada A., *Macromolecules*, **26**, 1053—1059 (1993); *h*) Bae Y. H., Okano T., Kim S. W., *J. Polym. Sci.*, **28**, 923—936 (1990).
8) *a*) Hoffman A. S., "Advances in Drug Delivery Systems, 3," ed. by Anderson J. M., Kim S. W., Elsevier, Amsterdam, 1987, pp. 297—305; *b*) Okano T., Bae Y. H., Jacobs H., Kim S. W., "Advances in Drug Delivery Systems, 4," ed. by Anderson J. M., Kim S. W., Knutson K., Elsevier, Amsterdam, 1990, pp. 255—265; *c*) Yoshida R., Sakai K., Okano T., Sakurai Y., *Ind. Eng. Chem. Res.*, **31**, 2339—2345 (1992); *d*) Bae Y. H., Okano T., Kim S. W., *Pharm. Res.*, **8**, 531—537 (1991); *e*) *Idem, ibid.*, **8**, 624—628 (1991); *f*) Yoshida R., Okano T., Sakurai Y., Kaneko Y., Sakai K., *Drug Delivery System*, **10**, 31—35 (1995).
9) Freitas R. F. S., Cussler E.L., *Sep. Sci. Technol.*, **22**, 911—919 (1987).
10) *a*) Dong L. C., Hoffman A. S., *J. Controlled Release*, **4**, 223—227 (1986); *b*) Park T. G., Hoffman A. S., *Appl. Biochem. Biotechol.*, **19**, 1—9 (1988).
11) Katono H., Maruyama A., Sanui K., Ogata N., Okano T., Sakurai Y., *J. Controlled Release*, **16**, 215—228 (1991).
12) Wesdyk R., Joshi Y. M., De Vincentis J., Newman A. W., Jain N. B., *Int. J. Pharm.*, **93**, 101—109 (1993).
13) Refojo M. F., *J. Polym. Sci. A1*, **5**, 3103—3113 (1967).
14) Kelbert M., Bechard S. R., *Drug Dev. Ind. Pharm.*, **18**, 519—538 (1992).
15) Yamamoto S., Ojima R., Fujimoto K., Kawaguchi H., Preprints, 7th Polymeric Microspheres Symposium, Kobe, October 1992, p. 67.
16) *a*) Brodnyan J. G., Konen T., *J. Appl. Polym. Sci.*, **8**, 687—697 (1964); *b*) Vanderhoff J. W., Tarkowski H. L., Jenkins M. C., Bradford E. B., *J. Macromol. Chem.*, **1**, 361—397 (1966); *c*) Chevalier Y., Pichot C., Graillat C., Joanicot M., Wong K., Maquet J., Lindner P., Cabane B., *Colloid Polym. Sci.*, **270**, 806—821 (1992).
17) D'Emanuele A., Dinarvand R., *Int. J. Pharm.*, **118**, 237—242 (1995).
18) Okahata Y., Noguchi H., Seki T., *Macromolecules*, **19**, 494—496 (1986).
19) Technical reports No. 4, Kojin Co., Ltd., Tokyo, April 1991, p. 5.
20) Saito S., *Koubunshikakou*, **39**, 580—584 (1990).