Film Formation with Coating Systems of Aqueous Suspensions and Latex Dispersions of Ethylcellulose[1)]

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We examined the film formation of an aqueous suspension system using micronized ethylcellulose (EC) in comparison with an EC latex system. The minimum film-forming temperatures (MFT) of the two systems and the glass transition temperature (T_g) of EC were measured with a micro melting point apparatus and a differential scanning calorimeter, respectively. Replicas of the free films prepared from the two systems were examined under a transmission electron microscope. The release of theophylline from granules coated with the two systems was compared to investigate the effect of curing, in which the coated granules were heated for an hour at 80 °C. MFT and T_g decreased as the amount of triethyl citrate used as a plasticizer increased in both systems. MFT of the suspension system was higher than T_g, while that of the latex system was lower than T_g. A replica of the free film from the suspension system showed no shapes of the EC particles used; in contrast, that from the latex system showed the shape of individual latex spheres in coalescence. Curing had no effect on the release behavior of the suspension-coated granules, whereas it remarkably delayed release from the latex-coated granules. The replica method revealed that the coalescence of latex particles was more complete after curing than before. These results demonstrate that the mechanisms of film formation of these two systems are different, and that this difference results in different properties of films prepared by the two systems.

Keywords aqueous coating; ethylcellulose; curing; suspension; latex; plasticizer

Coating with water insoluble polymers is an important technique in the controlled release formulation and taste-masking of drugs. Coating systems can be classified into three types. First is the organic solvent system, in which a water-insoluble polymer is dissolved in the molecular state. However, this method involves problems of environmental pollution and toxicity of the residual solvent. Most film coatings are therefore made with water-based coatings, as described later. Second is the latex dispersion system. This system involves latex dispersions prepared by emulsion polymerization of a monomer, or by emulsification of a preformed polymer. In this system, polymers are in colloidal dispersion. The latex dispersion system has the disadvantage of weakness to several stresses, such as electrolytes, pH change, storage temperature, and high shearing forces. These stresses must be avoided to prevent the system from breaking down into coagulation. Third is the aqueous suspension system. This system, newly developed by the authors, is free from the above problems. In this system, polymers are suspended in a solid state. The coating solution is prepared by dispersing a micronized water-insoluble polymer into water containing a small amount of plasticizer. The composition and method of preparation of this system has been patented.[2)]

Although many papers have been published concerning the latex system, only a few fundamental studies have investigated the aqueous suspension system. We previously reported that the aqueous suspension system needs more plasticizer for film formation than the latex system.[3)] This result is probably due to the fact that the film formation mechanism is different between the aqueous suspension and latex systems.

The purpose of the present study is to examine the mechanism of film formation in the aqueous suspension system, using ethylcellulose (EC) as a model polymer. We measured the minimum film-forming temperatures (MFT) of the two systems and the glass transition temperature (T_g) of EC. We also examined the surface topography of free films and granules with an electron microscope, as well as the release of a drug (theophylline) from coated granules prepared from the two systems.

Experimental

Materials The materials described below were obtained from commercial suppliers. Micronized EC (N-10F, Shin Etsu Chemical Co., Ltd.) and EC latex (Aquacoat, Asahi Chemical Industry Co., Ltd.) were used as water-insoluble polymers. Both polymers are Dow Standard Premium 10 cP viscosity grade EC. Triethyl citrate (TEC) (Tokyo Chemical Industry Co., Ltd.) was used as a plasticizer, and nonpareil (32—42 mesh, NP-103, Freund Co., Ltd.) as a seed for granulation. Theophylline (Shiratori Seiyaku Co., Ltd.) used as a model drug was pulverized with a sample mill (K II-1, Fuji Electronic Industry Co., Ltd.) under the following conditions: number of hammers, six; speed rate, high; and size of screen openings, 0.5 mm. Hydroxypropyl cellulose (HPC-L, Nippon Soda Co., Ltd.) was used as a binder for granulation.

Preparation of Coating Dispersion of the EC Latex System A 5% TEC solution was prepared with water. EC latex dispersion was then added to the TEC solution, and further water was added to adjust polymer concentrations.

Preparation of Coating Dispersion of the EC Suspension System The micronized EC was dispersed in a small amount of water. 5% TEC solution was then added, followed by the addition of more water to adjust the polymer concentrations.

MFT The MFT of the EC aqueous suspension and EC latex dispersion were measured with a Micro Melting Point Apparatus (Yanagimoto-Seisakusyo Co., Ltd.) under the following conditions: two drops of each coating dispersion containing 10% EC were taken by Pasteur Pipets (7095B-9, Corning Inc., New York) and placed on the cover glass at a constant temperature; the temperature at which a transparent film was formed was determined as the MFT.

T_g The T_g was determined by differential scanning calorimetry (DSC) (DuPont 9900TA) according to the following conditions. The micronized EC was dissolved in anhydrous ethanol with or without TEC; further anhydrous ethanol was added to bring the EC concentration to 5%.

These EC solutions were cast in petri dishes and dried at 40 °C for 24 h. The free films thus obtained were dried further at 80 °C for 1 h. A small amount of these films was placed in an aluminum sealed pan and heated at the rate of 20 °C/min to 160 °C under a nitrogen atmosphere.

Observation of Replicas of Free Films Replicas of the free films were examined under a transmission electron microscope (TEM). A thin Pt film of 100—150 Å thickness was deposited onto the free film by vacuum evaporation, followed by additional carbon film as a reinforcement. Replicas of these films were examined with a TEM (Hitachi, H-800).

Preparation of Core Granules and Coated Granules of Theophylline The formulation and the granulation conditions of core granules are shown in Table I. The core granules were produced with a centrifugal granulator (Freund Co., Ltd., CF-360EX).

The formulation and coating conditions of theophylline granules are shown in Table II. The coated granules were produced with a top-spray fluidized-bed granulator (Freund Co., Ltd./Okawara Co., Ltd., FLO-MINI) and were passed through a 24-mesh sieve. The coating applied ranged from 10% to 30% of the core granule weight.

TABLE I. Granulating Conditions of Theophylline Core Granules

Formula of granulation	
Ingredient	Charged weight (g)
Nonpareil	637
Theophylline	160
Hydroxypropyl cellulose (HPC)	3
Total	800

Operating conditions	
Machine	CF-Granulator
Inlet air temperature	50—55 °C
Granule bed temperature	28—32 °C
Spray rate	8 ml/min
Atomizing pressure	0.6 kg/cm^2
Slit air flow	380—400 Nl/min
Rotating speed	125 rpm
Powder (theophylline) feed	12 g/min
Quantity of spray solution[a)]	100 g
Drying time	5 min

a) Concentration of spray solution: 3% HPC.

TABLE II. Coating Conditions of Theophylline Granules

Formula of coating solutions	Charged weight (g)	
	EC latex system	EC suspension system
EC latex dispersion	191.5	—
Micronized EC	—	50
TEC	7.5	30
Water	q.s.	q.s.
Total	1000	1000

Operating conditions	
Machine	FLO-MINI
Inlet air temperature	85—93 °C
Outlet air temperature	40—42 °C
Granule bed temperature	38—40 °C
Spray rate	4—4.4 g/min
Atomizing pressure	1—1.1 kg/cm^2
Inlet air flow	190—260 Nl/min
Shaking/interval	6 s/30 s
Charge of theophylline granules	200 g
Quantity of coating	10%, 15%, 20%, 25%, 30%
Drying temperature	40 °C
Drying time	20 min

Dissolution Test of Coated Granules Dissolution testing of the coated granules was performed by the JP XII rotating paddle method at 100 rpm in 900 ml of a JP 1st fluid (pH 1.2) at 37 °C. Theophylline was assayed spectrophotometrically (272 nm). The amount of granules used was equivalent to 500 mg of theophylline.

Observation of Theophylline Core Granules and Coated Granules The surface of the theophylline core granules and coated granules was examined with a scanning electron microscope (SEM) (JEOL, JSM-T20).

Results and Discussion

Properties of Free Films Prepared from the EC Latex System and EC Suspension System 1. Influence of TEC Content on MFT and T_g The MFT is the limiting temperature above which a continuous film can be formed from dispersions. The effect of the amount of TEC on the MFT was examined using EC coating dispersions. The EC latex system without TEC showed an MFT between 65 and 70 °C (Fig. 1), while the EC suspension system without TEC showed no MFT on heating up to 150 °C, which is near the decomposition temperature (180 °C) of EC. These results indicate that the film-formation mechanism of the latex system is different from that of the aqueous suspension system. MFT decreased as the amount of TEC increased in both systems. The MFT of the latex was lower than that of the EC suspension.

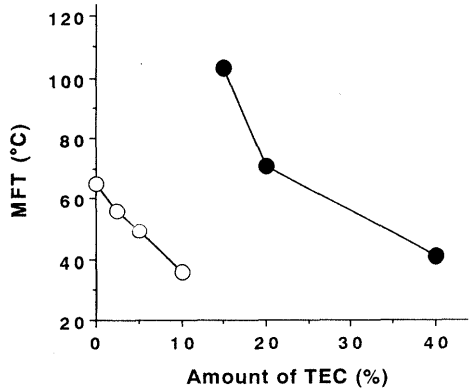

Fig. 1. MFT of the EC Latex System and EC Suspension System Containing Various Amounts of TEC

○, latex system; ●, suspension system.

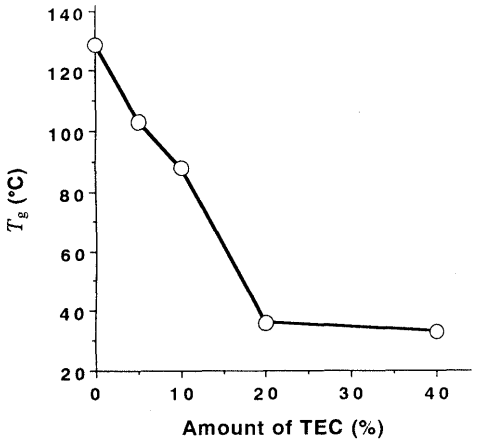

Fig. 2. Influence TEC Content on the T_g of EC

It is well known that a polymer is transformed from a glassy state, through a T_g, to a rubbery state as temperature increases, and that above T_g, the polymer is able to show micro-Brownian movement.[4] As water evaporates, latex particles become closely packed; above MFT, the particles are deformed, and fuse to form a continuous film.[5,6a] MFT exists at nearly T_g.[5] Thus, the effect of the amount of TEC on the T_g of EC was also examined using DSC. T_g, as well as MFT, decreased as the TEC concentration increased, as shown in Fig. 2. The curve of the MFT of EC latex was lower than that of T_g, while the curve of the MFT of the EC suspension was higher than that of T_g. These results indicate that the film-formation mechanism of the latex system is different from that of the aqueous suspension system.

The EC latex dispersion contains sodium lauryl sulfate and cetyl alcohol, at 4% and 9% respectively, of the level of EC in the formulation, as stabilizers to prevent the agglomeration of particles. These components probably act as plasticizers, so that the MFT curve of the latex is below that of T_g. Since the polymer chains of EC latex particles seem to be in a more pliable state than those of the micronized EC solid particles, it is probable that it is easier for TEC to diffuse into the polymer chains of EC latex, thus EC latex particles can be softened by a smaller amount of TEC than the micronized EC suspension particles.

2. Replicas of Free Films Prepared with the EC Latex System and EC Suspension System The surface of the free films was examined by the replica method[7] using TEM. A replica of the surface of free film prepared from an EC ethanol solution was also observed as a reference. The surface of the free film prepared from an organic solution was very smooth (Fig. 3A). The free film prepared with the EC latex system without TEC consisted of coalesced spheres, with an average diameter of individual spheres of 0.188 μm (Fig. 3B). This value corresponds to the previously reported 0.171 μm mean diameter of EC latex particles,[3] suggesting that the free film was made from the coalescence of closely packed latex particles. The spherical particles were still observed in free film prepared from a latex dispersion containing 10% TEC, as described later. In contrast, the surface of the free film prepared from the EC suspension system containing 50% TEC (Fig. 3C) showed no particulate shapes, and was a little more coarse than the film prepared using the organic solvent.

3. Film-Formation Mechanisms of the EC Latex System and Suspension System Judging from the above results, we considered the mechanism of film formation to be as follows. In the case of the latex system, film formation is probably carried out by the following driving forces: 1) dry sintering caused by interfacial tension between polymer and air, 2) capillary pressure caused by interfacial tension between water and air, 3) wet sintering caused by interfacial

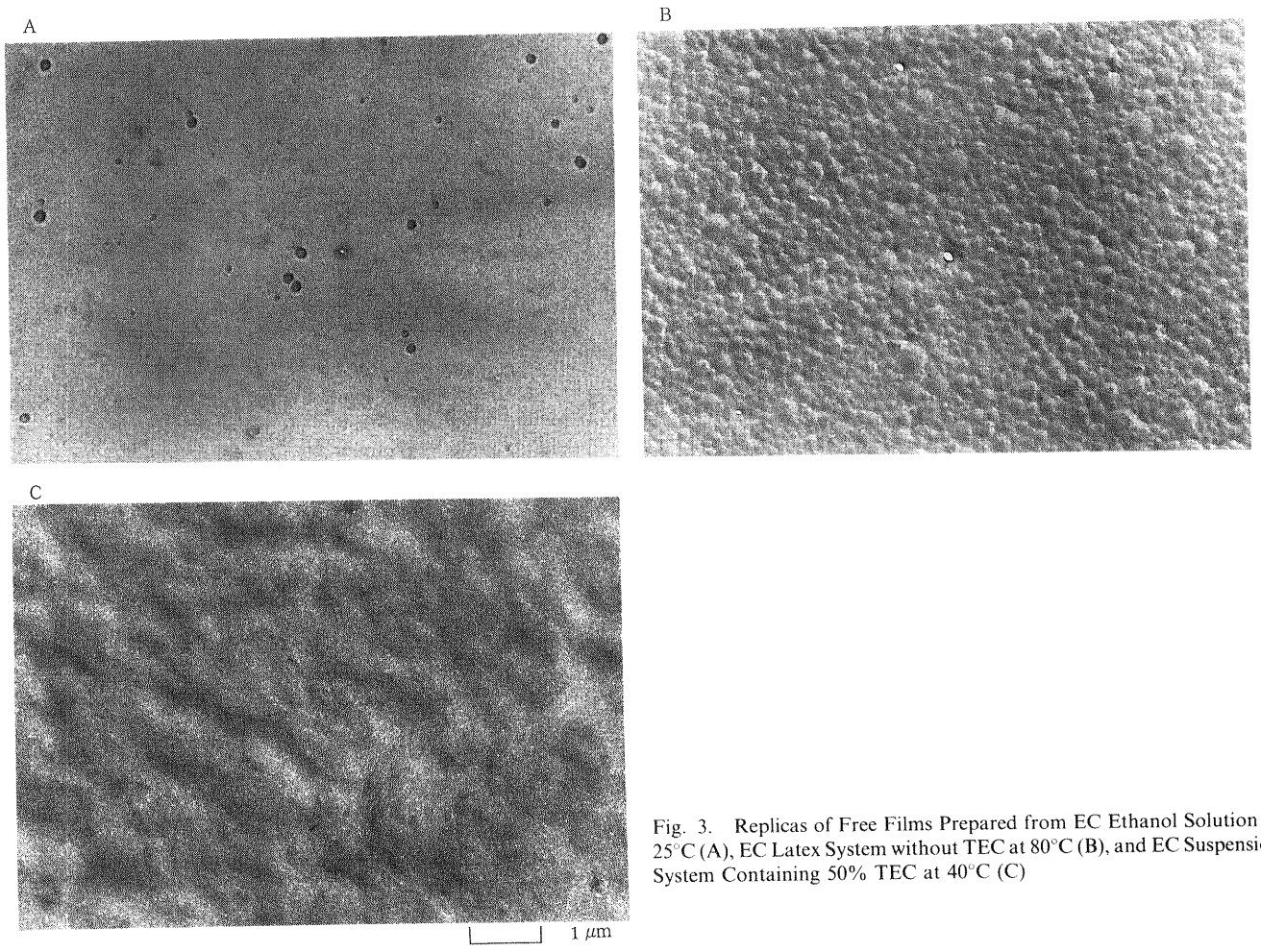

Fig. 3. Replicas of Free Films Prepared from EC Ethanol Solution at 25°C (A), EC Latex System without TEC at 80°C (B), and EC Suspension System Containing 50% TEC at 40°C (C)

tension between polymer and water, and 4) diffusion of water through the polymer.[5] Among these driving forces, the capillary pressure is reported as a main force in the film formation. The driving forces 1), 3) and 4) play a role in smoothing the film surface, in film-forming only in the initial stage, and in film-forming in the late stage after the surface film formation is completed, respectively.

Latex particles become closely packed as water evaporates and they come into contact with each other. The driving force exerted mainly by capillary action between particles overcomes repulsive forces between the closely packed particles, deforms the particles and causes the spheres to fuse, resulting in coalescence and the formation of a continuous film. The role of the plasticizer is to soften the particles of latex and to facilitate their deformation. As a result, the plasticizer lowers the MFT. However, TEM data showed that coalescing is not completed during the film formation and that particle boundaries still exist. Complete coalescence is probably obtained by curing, as shown later.

In the case of the suspension system, in contrast, the diameter of the micronized particles is about thirty times greater than that of the latex, as reported previously[3]; considering that capillary force is in inverse proportion to the diameter of the particle, the capillary force here must have given little assistance to the coalescence of particles. Film formation here probably proceeds as follows. Micronized particles are closely packed as water evaporates, causing the plasticizer concentration between particles to increase. The plasticizer diffuses into the polymer particles and induces the polymer chain to expand, resulting in coalescence. Thus, plasticizers used for the suspension system should have the property of being a solvent for the polymer, as reported previously.[3] For this reason, the suspension system needs more plasticizer than the latex system. The free film of the suspension system showed no clear particle boundaries, as in the case of that of the organic system, in which the polymer exists in the colloidal solution. But the surface roughness of the free film of the suspension system was greater than that of the organic system, suggesting that polymer chain expansion is not sufficient to smooth the surface of closely packed particles. Poor diffusion of the polymer during film formation in the suspension system is probably ascribed to the high viscosity of a gel resulting from a polymer which can be solvated with a limited amount of plasticizer. In contrast, maximum solvation and polymer chain extension can be achieved by a sufficient amount of organic solvent in the organic system.

Release of Theophylline from Granules Coated with the EC Latex System and EC Suspension System The release of theophylline from granules coated with the EC latex system was compared with that of granules coated with the EC suspension system. Composition of the core granules and granulating conditions are shown in Table I. Nonpareil was used as a core material. Theophylline

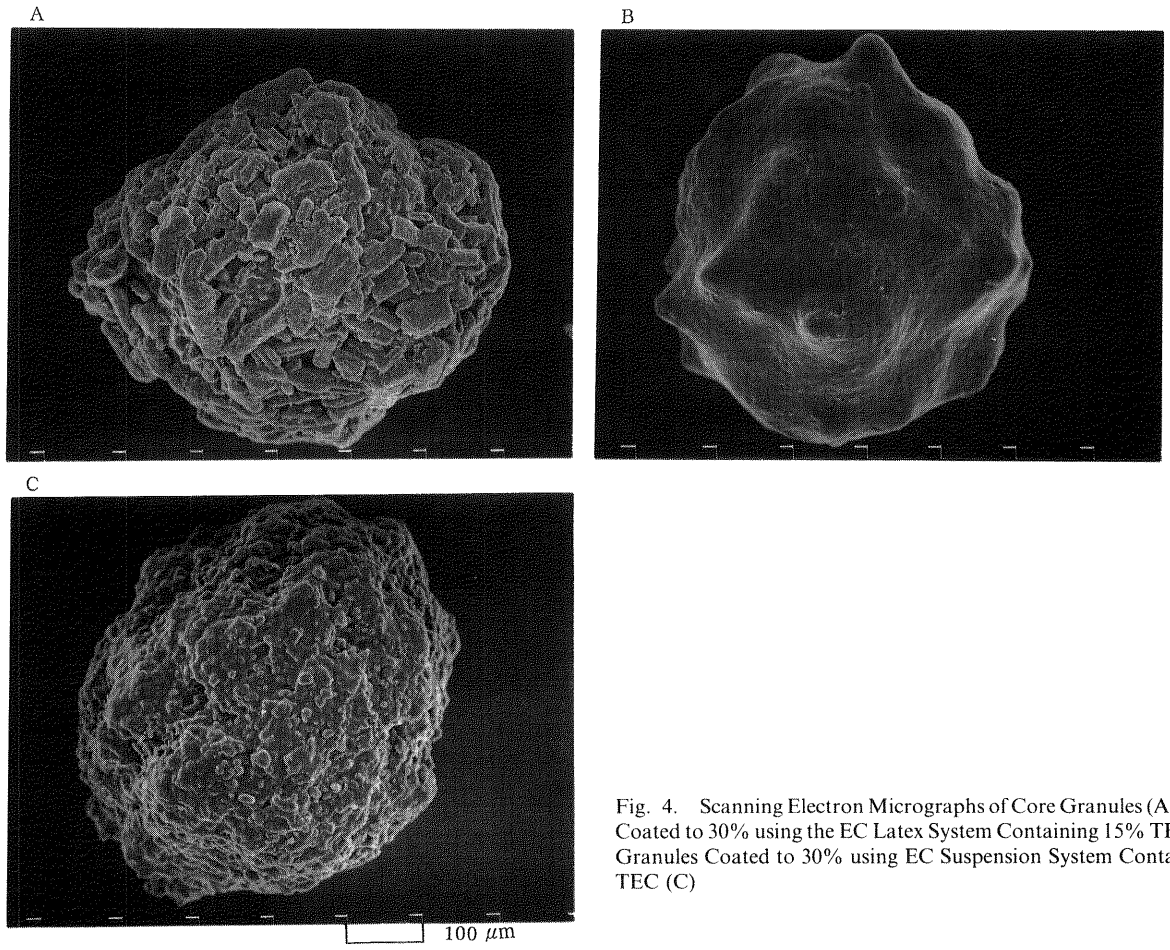

Fig. 4. Scanning Electron Micrographs of Core Granules (A), Granules Coated to 30% using the EC Latex System Containing 15% TEC (B), and Granules Coated to 30% using EC Suspension System Containing 60% TEC (C)

was coated onto nonpareil by the spraying of a hydroxypropyl cellulose solution in a centrifugal granulator. These core granules were further coated with dispersions in the EC latex or EC suspension system in a fluidized-bed granulator, as shown in Table II. The quantity of TEC was 15% of the polymer concentration in the latex system, and 60% in the EC suspension system. The polymer concentration was 5% in both coating dispersions. The same coating conditions were used for both systems. Granule bed temperatures were kept at 38—40 °C during the coating process, since the MFTs of these dispersions are about 35 °C.

1. SEM of Granules Coated with the EC Latex System and EC Suspension System SEM photographs of the theophylline core granules and coated granules using the EC latex system are shown in Figs. 4A and 4B. The core granules had an uneven surface and contained many particles of theophylline, whereas the coated granules had a smooth surface and no drug particles. The surface of the granules coated with the EC suspension system was less smooth than that of those coated with the latex, but was smoother than that of the core granules (Fig. 4C). A continuous film was also formed on the surface of the granules, as observed with latex coating.

2. Effect of Coating on the Release of Theophylline The effect of coating on the release of theophylline was examined in the EC latex and EC suspension systems. Core granules were coated to 10—30% with the two coating dispersions and the dissolution rate of theophylline was examined. In both systems, the dissolution rate gradually decreased as the amount of coating applied increased (Fig. 5). Although many studies have investigated sustained release using EC latex dispersion,[6a,8,9] only a few papers have examined the use of EC suspension coating. Kawashima[6b] *et al.* reported the sustained release of salicylamide, using a formula which contained 30—35% TEC in EC and/or hydroxypropyl methylcellulose acetate succinate and provided coating level of 39—41% based on the core granules. In the present paper, the granules were coated to 10—30% using a formula containing 60% TEC, this level being selected in consideration of MFT.

Comparison of the EC latex and EC suspension systems on the basis of equal coating clearly showed that granules coated with EC latex produced a slower release than those coated with EC suspension. Since the surface of the latex-coated granules was smoother than that of the suspension-coated granules (Fig. 4B) and thus had fewer pores, the latex system exhibited slower release than the suspension system. The latex and suspension systems contained 15% and 60% TEC, respectively. We consider this difference in the quantity of water-soluble TEC to be the reason for the slower release of the latex system.

3. Effect of Curing on the Release of Theophylline The film-formation mechanism of the latex dispersion involves

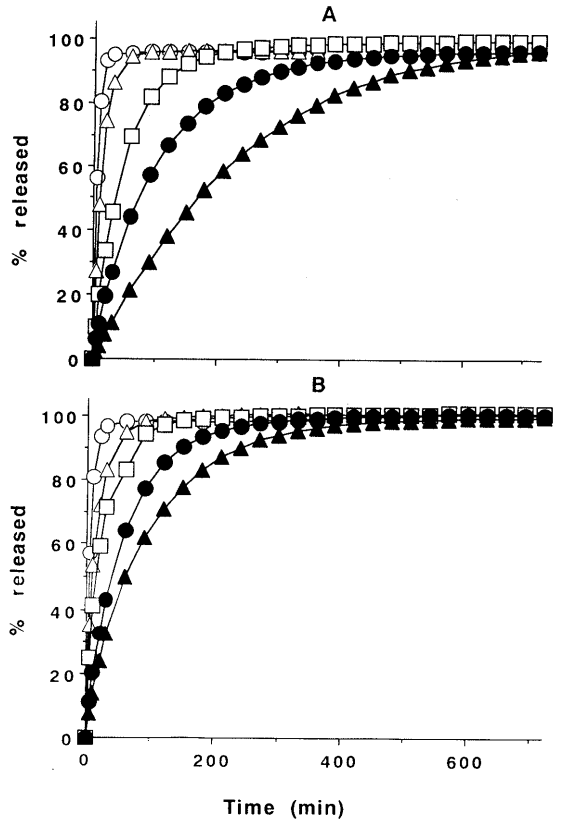

Fig. 5. Effect of Coating Applied on the Release of Theophylline from Granules Coated with the EC Latex System Containing 15% TEC (A), and EC Suspension System Containing 60% TEC (B)

○, 10% applied; △, 15% applied; □, 20% applied; ●, 25% applied; and ▲, 30% applied.

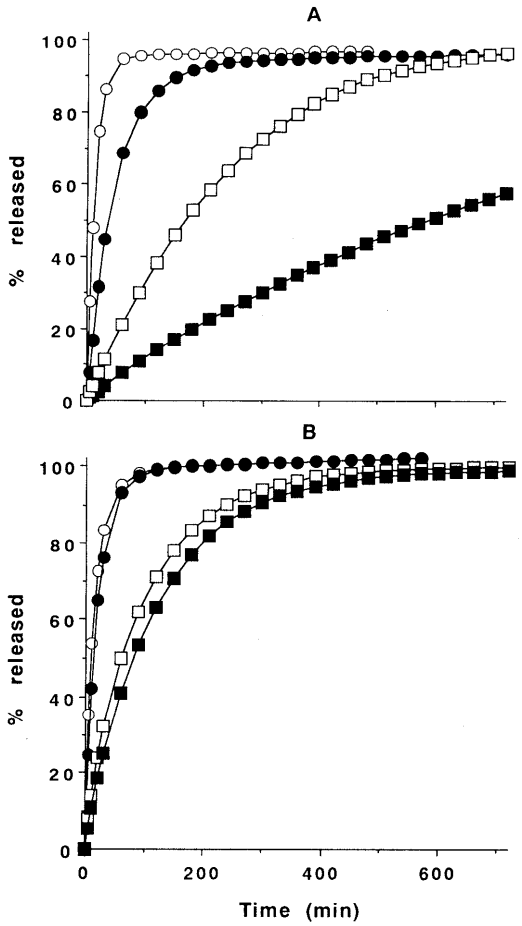

Fig. 6. Effect of Curing on the Release of Theophylline from Granules Coated with the EC Latex System (A), and EC Suspension System (B)

○, uncured, 15% applied; ●, cured (80°C, 1 h), 15% applied; □, uncured, 30% applied; and ■, cured (80°C, 1 h), 30% applied.

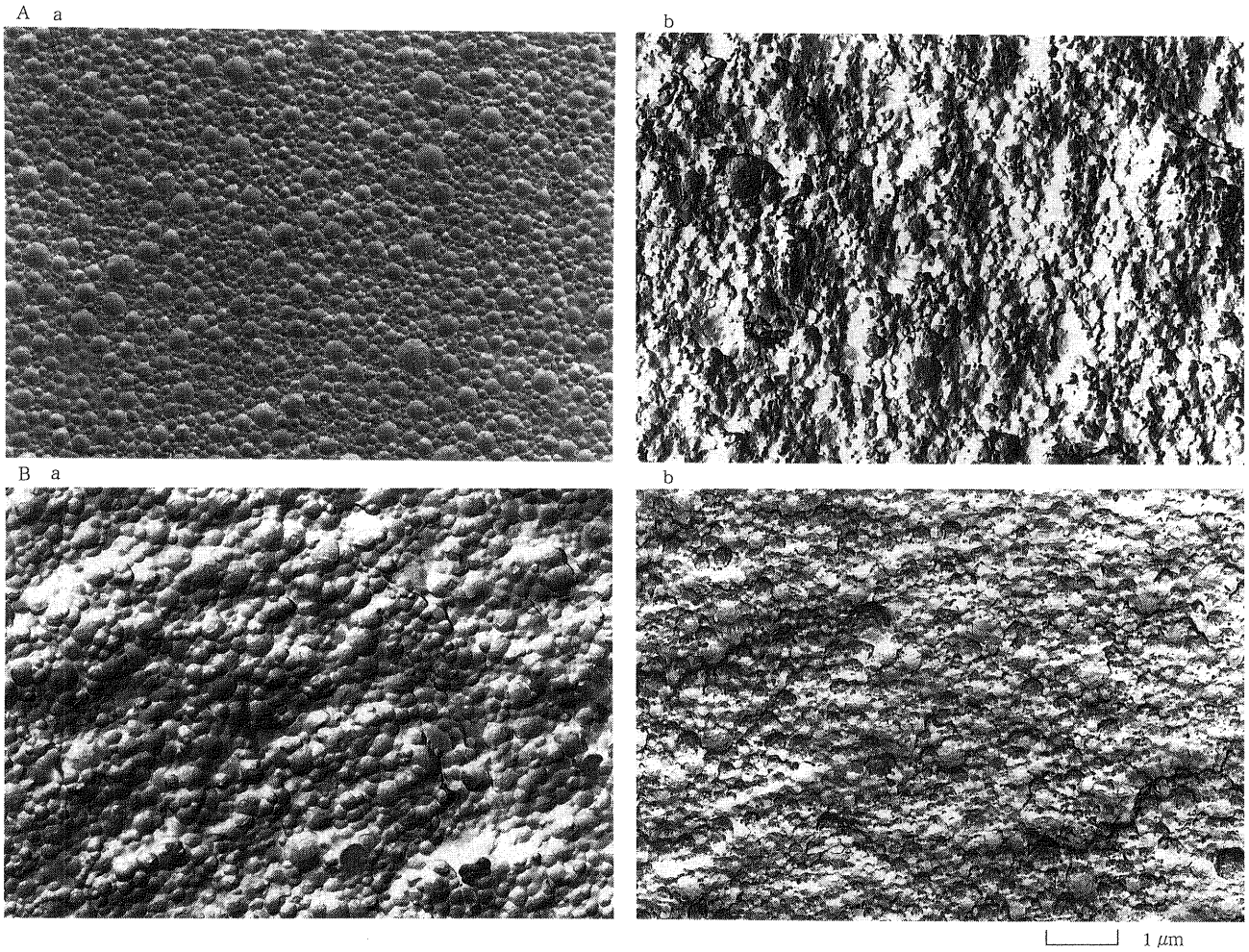

Fig. 7. Replica of Free Films Prepared from EC Latex Systems Containing 10% TEC at 40°C (A), and 5% TEC at 50°C (B)
a, uncured; b, cured (80°C, 1 h).

the evaporation of water followed by the coalescence of polymeric spheres. The coalescence process is aided by capillary forces. When this happens, the plasticizer softens and swells the polymeric spheres, thereby reducing their resistance to deformation.[5] Film formation from the fusing of latex particles during the coating operation depends on the manufacturing process, coating conditions, and formulation variables. Complete film formation is therefore not easily achieved, resulting instead in incomplete and inhomogeneous film formation. In the case of EC latex film, it is necessary to heat films to make them complete. The management of this heating is termed "Curing".[10] Granules coated using the EC latex and EC suspension systems were heated for 1 h at 80 °C, and the release of theophylline was examined. The results are shown in Fig. 6.

Theophylline release from granules coated to 15% and 30% using the latex system was remarkably delayed by curing. These results correspond with those reported by F. W. Goodhart *et al.*[11] In contrast, drug release from granules coated using the EC suspension system was not changed. These results indicate that curing changes the structure of EC latex film, but not of film formed by EC suspension.

To confirm this point, free films were prepared from latex dispersions containing 10% TEC and 5% TEC at 40 °C and 50 °C, respectively, and a portion of the obtained free film was heated at 80 °C for 1 h. The replicas of films before and after curing were examined with a TEM (Fig. 7).

In free film prepared from a dispersion containing 10% TEC at 40 °C, the spherical latex particles were recognizable, were closely packed before curing, and had an appearance similar to that in Fig. 3B. After curing, however, the latex particles were remarkably deformed, and their individual shapes could not be distinguished. In the case of free films prepared from a dispersion containing 5% TEC at 50 °C, in contrast, boundaries of particles were less clear compared to those of the film prepared with 10% TEC at 40 °C. This may be explained by assuming that the particles were more easily deformed during film formation at 50 °C than at 40 °C. After curing, moreover, no particle boundaries were observed in the film prepared at 50 °C.

These results show that, in the latex system, latex particles become closely packed as water evaporates and the film is formed by capillary forces, but coalescence of particles is incomplete at this stage. Curing, however, increases polymer chain entanglement and furthers the process of coalescence. As a result, coalescing is completed, and the release of a drug is thus delayed. In contrast,

coalescing in the suspension system is completed during the film formation, as in the case of the organic coating system. Curing, therefore, does not significantly affect the properties of this film.

References and Notes

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