[Chem. Pharm. Bull. 36(12)4927—4932(1988)]

Coating of Pharmaceutical Powders by Fluidized Bed Process. IV.[1] Softening Temperature of Acrylic Copolymers and Its Relation to Film-Formation in Aqueous Coating

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(Received May 6, 1988)

The softening temperature (T_s) of films of commercially available and newly developed acrylic copolymers for aqueous coating was measured by thermomechanical analysis. The results are discussed in relation to the film-formation of their latices in the Wurster process.

Methacrylic acid (MA)–ethyl acrylate (EA) (1 : 1) copolymer dispersion (Eudragit L30D-55) containing 10% triacetin exhibited excellent film-forming ability in coating at a temperature (31 °C) far lower than its T_s (91 °C). The product exhibited no stickiness during drying at 60 °C. The dissolution properties were little changed by heating at 60 °C.

On the other hand, the copolymer dispersion consisting of hydrophobic acrylic esters and minor quaternary ammonium esters (Eudragit RS30D, $T_s = 83$ °C) did not form a film under the same coating conditions in spite of its T_s being lowered to 49 °C by the addition of 10% triacetin. The product was sticky during drying at 60 °C. The copolymer consisting of only hydrophobic esters (Eudragit E30D) had a good film-forming ability due to its low T_s (18 °C), but the product was too sticky to be discrete particles even at room temperature.

With the aqueous dispersion of EA–methyl methacrylate (MMA)–2-hydroxyethyl methacrylate (HEMA) copolymer, newly developed in the previous study, the hydrophilic HEMA enhanced the film-formation. In particular, the EA–MMA–HEMA (6 : 12 : 8) copolymer exhibited excellent film-formation in spite of its high T_s (78 °C), and the prolonged release characteristic of the product was not changed by heating it at 60 °C.

These results suggested that hydrophilic residues such as carboxyl and hydroxyl contribute to film-formation of the latices.

Keywords——coating; dissolution; lactose; microcapsule; Wurster process; acrylic copolymer; ethyl acrylate–methyl methacrylate–2-hydroxyethyl methacrylate copolymer; polymer softening temperature; latex

Three kinds of acrylic copolymers used for aqueous coating are commercially available at present.[2] Methacrylic acid (MA)–ethyl acrylate (EA) (1 : 1) copolymer latex (Eudragit L30D-55) has widely been used as an enteric coating material. The others, Eudragit E30D and RS/RL30D, are coating materials for prolonged release, and are pH-independently water-insoluble. They mainly consist of hydrophobic esters such as EA and methyl methacrylate (MMA), though RS/RL30D contains a small amount of quaternary ammonium ester.

As is well known, L30D-55 has an excellent film-forming ability in practical coating operations.[3] However, RS/RL30D sometimes requires addition of a plasticizer. Products with plasticized films tend to exhibit changes in drug release properties and interparticulate adhesion during storage. E30D has a good film-forming ability, but produces very sticky particles which can easily agglomerate or fuse into a solid mass even at room temperature.

The stickiness of E30D and plasticized RS/RL30D films should clearly be related to their

softening temperature. Since the product may sometimes be exposed to temperatures higher than 60 °C during storage and transportation, the softening temperature should preferably be higher than 60 °C.

On the other hand, the coating is usually performed at 25 to 40 °C. Therefore, the latices of coating materials should show a good film-forming ability at temperatures far lower than their softening temperatures. Such a property of the latex for aqueous coating will be very important, because softening of the product during preservation may not only bring about difficulty in handling, but also lead to variation in drug release characteristics.

In this study, the commercially available acrylic copolymer and the new acrylic copolymer latices developed in the previous study[1] were evaluated on the film-forming ability in Wurster process in relation to the softening temperatures of their films.

Experimental

Materials——As a core material, lactose (DMV 50 M), whose mean diameter was 328 μm on sieve analysis, was used. Eudragit L30D-55, E30D and RS30D (Röhm Pharma) were used as purchased. Triacetin (TA, Nakarai Chemicals), triethyl citrate (TEC, Citroflex 2, Pfizer) and polyethylene glycol 6000 (PEG, Nakarai Chemicals) were used as plasticizers. Talc (JP XI grade, Maruishi) was used as a spacing agent or an antiadherent.

Preparation of Polymer Dispersion——The latices of EA–MMA–2-hydroxyethyl methacrylate (HEMA) (6 : 12 : X, X=4, 7 and 8) copolymers were synthesized as reported in the previous paper.[1]

Particle Size of Latex——The particle size distributions of the latices used were determined by means of a Photal LPA-3100 laser particle analyzer with an LPA-3000 photon correlator (Otsuka Electronics).

Coating——A Glatt GPCG-1 Wurster apparatus was used for coating. The lactose cores were directly coated with the copolymers, without undercoating or overcoating. The products were lubricated with 1% talc powder.

Dissolution——Dissolution tests were performed as previously reported.[3] The JP XI disintegration 1st fluid (pH 1.2) was used for the microcapsules coated with Eudragit L30D-55 and the 2nd fluid (pH 6.8) for those coated with the other polymer latices. The samples containing 0.1 g of lactose were usually tested after being dried in a vacuum at room temperature for 12 h or dried at 60 °C for 12 h.

Thermomechanical Analysis (TMA)——This was performed as previously reported.[1] The test films were prepared without the spacing agent, talc, though some spray dispersions used in coating contained it. The film-forming method was altered in this study.[1] A dispersion (5 g) containing 15% polymer on a dry basis, and the prescribed percent of plasticizer, was dried on a thinly Teflon-coated glass dish at 60 C for 12—48 h until a transparent film was formed. Thereafter, the film was stripped from the glass dish and again dried in a vacuum at room temperature for 12 h.

Results and Discussion

Effect of Plasticizers on the Softening Temperature of Eudragit L30D-55 and RS30D Films

The softening temperatures (T_s) are shown in Fig. 1 for Eudragit L30D-55 and RS30D plasticized by TA, TEC or PEG. In every case, T_s decreases monotonously.

In the previous study,[3] L30D-55 plasticized by 10% TA clearly exhibited an excellent film-forming property in coating at the outlet air temperatures of 31—35 °C. Figure 1 shows that the film has a far higher T_s (91 °C) than the operating temperatures of 31 to 60 °C. These properties of L30D-55 are very important in that microcapsules prepared with L30D-55 membrane would not soften at temperatures up to 91 °C: pharmaceuticals might be exposed to temperatures as high as 60 °C during storage and transportation.

RS30D exhibited a lower T_s than L30D-55, as shown in Fig. 1. To avoid softening of the film and the consequent adhesion of particles during storage and transportation, RS30D ought to be used with less than 10% of plasticizer.

The softening temperature of E30D film was 18 °C. This is lower than usual operating temperatures. Therefore, E30D film on cores will be always softened during coating. This will cause problems in the coating operation.

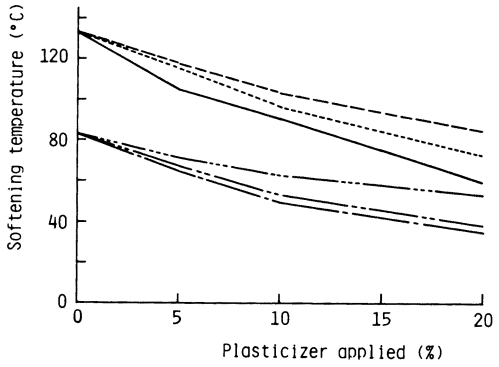

Fig. 1. Effects of Plasticizers on the Softening Temperature, T_s, of Eudragit L30D-55 or RS30D Films

Eudragit type (plasticizer): ——, L30D-55 (TA); – – – –, L30D-55 (TEC); ------, L30D-55 (PEG); — · —, RS30D (TA); — – —, RS30D (TEC); — · · —, RS30D (PEG).

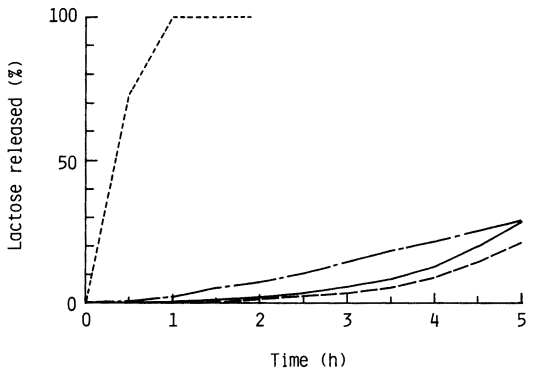

Fig. 2. Release of Lactose from Microcapsules 60% Coated with Eudragit L30D-55 or RS30D Plasticized by TA in the JP XI Disintegration Fluid

Percent of TA relative to dry copolymer weight: 10. ——, L30D-55 dried in vacuum at room temperature for 12 h (in the 1st fluid); – – – –, L30D-55 dried at 60 °C for 12 h (in the 1st fluid); ------, RS30D dried in vacuum at room temperature for 12 h (in the 2nd fluid); — · —, RS30D dried at 60 °C for 12 h (in the 2nd fluid).

TABLE I. Operating Conditions for Coating with Eudragit Copolymers by Means of GPCG-1

Core material: lactose (DMV 50M) (g)	300	300	300	300	500	300
Membrane material	L30D-55	RS30D	RS30D	RS30D	E30D	RS30D : E30D = 2 : 3
Weight on a dry basis (g)	180	180	180	180	150	180
Plasticizer	TA	TA	TEC	PEG	—	—
Weight applied (g)	18	18	18	18	—	—
Spacing agent (Talc, g)	90	90	90	90	75	90
Surfactant (Polysolvate 80) (g)	—	0.36	0.36	0.36	—	—
Total volume of spray dispersion (ml)	1500	1500	1500	1500	900	1500
Inlet air temperature (C)	60	60	60	90	27	60
Outlet air temperature (°C)	31	31	32	37	22	32
Inlet air rate (m^3/min)	1.1	1.1	1.2	1.2	1.6	1.2
Spray rate (ml/min)	5.7	5.6	6.8	7.9	2.6	5.4
Spray pressure (atm)	2.2	2.2	2.2	3.0	2.1	2.1
Mean particle size of latex (Standard deviation)[a] (nm)	89 (17)		158 (22)		168 (10)	
Softening temperature (C)	91	49	53	63	18	53

Diameter of spray nozzle: 0.8 mm. Bag filter opening: 25 μm. *a*) Number base.

Release of Lactose from Microcapsules Coated with Eudragit L30D-55, RS30D or E30D

Release from microcapsules 60% coated with L30D-55 plasticized by 10% TA is shown in Fig. 2. The results show that a tight membrane was formed under the coating conditions given in Table I. Since the softening temperature of the membrane was 91 °C (Fig. 1), this means that the latex film was formed at temperatures far lower than T_s. When the product was heated at 60 °C for 12 h, the particles exhibited no stickiness and, as shown in Fig. 2, the release profile was only a little changed. These characteristics are suitable for film-coated pharmaceuticals.

On the other hand, the microcapsules coated with RS30D exhibited no sustained release

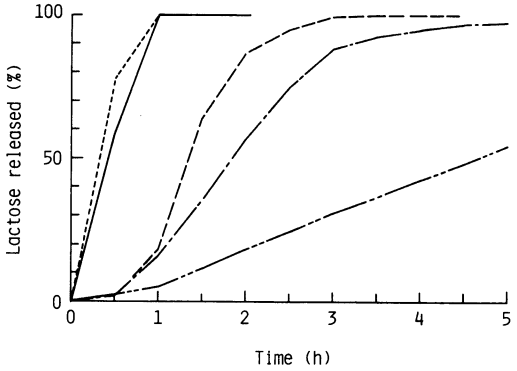

Fig. 3. Release of Lactose from Microcapsules 60% Coated with Eudragit RS30D, Plasticized by TEC or PEG, and 30% Coated with E30D, in the JP XI Disintegration 2nd Fluid (pH 6.8)

Eudragit type (plasticizer): ——, RS30D (TEC); ------, RS30D (PEG); — -- —, E30D; dried in vacuum at room temperature for 12 h: – – – –, RS30D (TEC); — · —, RS30D (PEG); dried at 60 °C for 12 h.

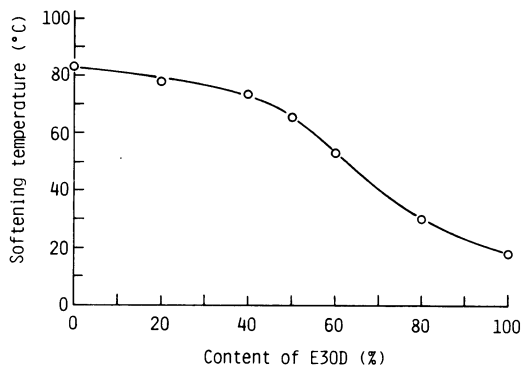

Fig. 4. Softening Temperature, T_s, of the Blend Copolymer Films of Eudragit RS30D and E30D

(Fig. 2), though T_s of the film was lowered to 49 °C (Fig. 1) by 10% TA and they were coated under the same conditions (Table I) as used with L30D-55. The microcapsules were sticky during heating at 60 °C. After the heating, the microcapsules exhibited sustained release, as shown in Fig. 2. This suggests that the film-formation in the coating process was incomplete, but was achieved during the heating at 60 °C. Identical results were observed in the cases where TEC or PEG was used as a plasticizer (Fig. 3). The microcapsules of RS30D plasticized with 10% PEG were sticky during heating at 60 °C, though T_s was 63 °C (Fig. 1). These results show that RS30D has poor film-forming ability, compared with L30D-55, and would be practically unsuitable in that the products would be sticky and their drug-release characteristics might change if they were exposed to a temperature of 60 °C.

Successful operation with E30D was very difficult on account of the low T_s of E30D; an example is given in Table II. Figure 3 shows the release profile for microcapsules 30% coated with E30D. The latex formed a film in the coating process, presenting a strong barrier against lactose release. However, the microcapsules were very adhesive even at room temperature, and would not be practically useful.

Softening Temperature of the Blend Copolymer Films of RS30D and E30D and Lactose Release from Their Microcapsules

Because of its low T_s, E30D has been used for the purpose of lowering T_s of other polymers. When E30D was mixed into RS30D, T_s was lowered. Figure 4 shows the softening temperatures of the blend copolymer films. It is clear that for practical purposes the content of E30D should be less than 60%.

Coating was tried at the 60% level of E30D content, where the value of T_s was 53 °C (Fig. 4). The coating conditions (Table I) were adjusted to those in the case of L30D-55 as closely as possible. The results of dissolution tests showed that the film-formation of the latices was insufficient, but could be achieved by heating at 60 °C (Fig. 5).

RS30D and E30D consist of hydrophobic esters such as EA and MMA, though RS30D contains a small amount of quaternary ammonium ester. On the other hand, L30D-55 contains 50% hydrophilic MA as the molar ratio of monomer. As is well known,[4] acetic acid is dissolved in carbon tetrachloride as the dimer, with two hydrogen bonds. These hydrogen bonds can easily be broken by water molecules in an aqueous medium. This suggests that

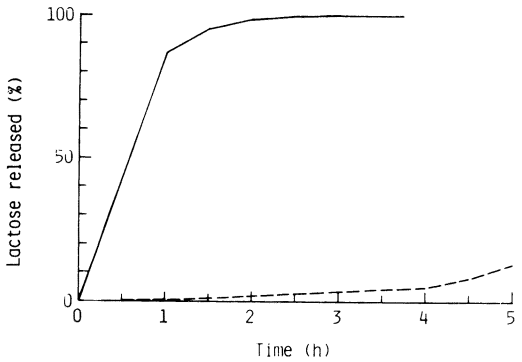

Fig. 5. Release of Lactose from Microcapsules 60% Coated with Eudragit RS30D : E30D = 2 : 3 Blend Copolymer in the JP XI Disintegration 2nd Fluid (pH 6.8)

——, dried in vacuum at room temperature for 12 h; – – – –, dried at 60 °C for 12 h.

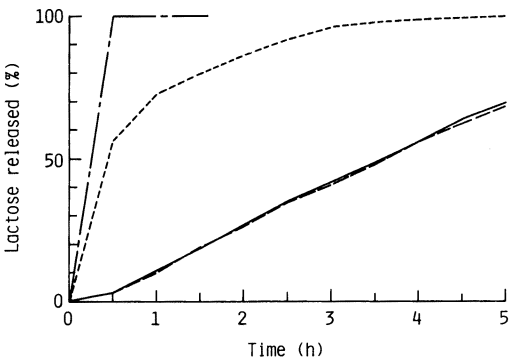

Fig. 6. Release of Lactose from Microcapsules 60% Coated with EA–MMA–HEMA Copolymers in the JP XI Disintegration 2nd Fluid (pH 6.8)

Molar ratio of monomers (EA : MMA : HEMA): ——, 6 : 12 : 8; ------, 6 : 12 : 7; — - —, 6 : 12 : 4, dried in vacuum at room temperature for 12 h. – – – –, 6 : 12 : 8, dried at 60 °C for 12 h.

carboxyl group in the dried L30D-55 membrane may be hydrogen-bonded to other carboxyl groups and, on hydration, these bonds may be broken by water. Conversely, in the film-forming process, such a hydrogen-bonding exchangeable among carboxyl groups and water molecules may account for the easy film-forming characteristics of L30D-55 at temperatures far lower than its T_s. This seems to be a case where intermolecular interaction is important in the film-forming process in addition to physical characteristics, such as the particle size, the surface tension, the capillary pressure and the viscosity or yield strength of polymer.[5]

Film-Formation of EA–MMA–HEMA (6 : 12 : *X*) Copolymer Suspensions in Coating Process

In the previous study, copolymers containing hydrophilic HEMA were synthesized. Based on the above discussion, HEMA may form a tight or hard membrane partly through its ability to hydrogen-bond to carbonyl groups and/or its higher degree of hydration than the hydrophobic esters.

Table II shows the coating conditions and T_s of EA–MMA–HEMA copolymer films used. HEMA only slightly hardens the film. This suggests that the hydroxy group of HEMA may not exhibit a strong hydrogen-bonding in dry membrane.

Figure 6 shows the dissolution profiles for the microcapsules coated with EA–MMA–HEMA (6 : 12 : *X*) copolymers under the conditions shown in Table II. In the previous study,[1] HEMA enhanced the lactose release. However, in this study the membrane could not restrain the lactose release, when the molar ratio of HEMA was lower than 7. This means that film-formation was inadequate in those cases. However, the microcapsules coated with EA–MMA–HEMA (6 : 12 : 8) copolymer showed a remarkably sustained release. These results clearly suggest that HEMA enhances the film-formation.

In general, the smaller the particles of latex are, the easier film-formation is.[5] As shown in Table II, the mean particle size of the 6 : 12 : 8 copolymer is rather larger than those of the 6 : 12 : 4 and 6 : 12 : 7 copolymers. This shows that the enhancement of film-formation by HEMA resulted from other factors such as its hydrophilicity or its easy hydration.

The EA–MMA–HEMA (6 : 12 : 8) microcapsules exhibited no stickiness during heating at 60 °C. Even after the heating, the lactose release characteristics were not changed (Fig. 6). This clearly resulted from the fact that the EA–MMA–HEMA (6 : 12 : 8) latex had excellent film-forming properties at temperatures considerably lower than T_s of its film. This shows the

TABLE II. Operating Conditions for Coating with EA–MMA–HEMA Copolymers by Means of GPCG-1

	Molar ratio		
EA	6	6	6
MMA	12	12	12
HEMA	4	7	8
Core material: lactose (DMV 50M) (g)	300	300	300
Membrane material			
Weight on a dry basis (g)	180	180	180
Total volume of spray dispersion (ml)	1500	1500	1500
Inlet air temperature (°C)	65	60	60
Outlet air temperature (°C)	27	27	28
Inlet air rate (m^3/min)	1.0	1.3	1.2
Spray rate (ml/min)	7.1	8.5	7.9
Spray pressure (atm)	2.5	2.2	2.2
Mean particle size of latex	58	134	148
(Standard deviation)[a] (nm)	(13)	(36)	(38)
Softening temperature (°C)	74	77	78

Diameter of spray nozzle: 0.8 mm. Bag filter opening: 25 μm. *a*) Number base.

practical usefulness of HEMA as a monomer component.

Conclusion

HEMA enhanced the film-formation of acrylic copolymer latices, though it hardly increased T_s. In particular, the EA–MMA–HEMA (6:12:8) latex exhibited excellent film-forming properties in the Wurster process at temperatures lower than its T_s. From a practical viewpoint, this latex should be most useful among the available pH-independently water-insoluble acrylic copylymer latices.

Eudragit RS30D (mainly composed of hydrophobic esters) exhibited only poor film-forming properties. E30D, which consisted only of hydrophobic esters and whose T_s was 18 °C, exhibited excellent film-forming properties, but, as in the case of RS30D, the product had a serious handling problem; it was sticky.

The mechanism of HEMA-enhanced film-formation has not been clearly elucidated in this study. The details should be investigated in the future.

Acknowledgement The authors would like to thank Prof. Y. Kawashima and Dr. H. Takeuchi of Gifu Pharmaceutical University for the particle size measurements.

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