[Chem. Pharm. Bull. 36(8)3070—3078(1988)]

Coating of Pharmaceutical Powders by Fluidized Bed Process. III.[1] Aqueous Coating with Ethyl Acrylate–Methyl Methacrylate–2-Hydroxyethyl Methacrylate Copolymer and the Dissolution Properties of the Products

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(Received January 8, 1988)

Aqueous dispersions of ethyl acrylate (EA)–methyl methacrylate (MMA)–2-hydroxyethyl methacrylate (HEMA) copolymers were developed to produce microcapsules with a pH-independently water-insoluble membrane by the Wurster process. The dispersions were prepared by an emulsion polymerization technique. The resin dry weight content of the dispersion was 21—23%. Lactose (328 μm) and phenacetin were used as drug models.

The mole ratios of EA, MMA and HEMA used were 12 : 6 : X, 9 : 9 : X and 6 : 12 : X (X=4, 6, 8). An increase in MMA content raised the softening temperature of the membrane. HEMA affected it far less than MMA, but remarkably enhanced the release of lactose in JP XI disintegration 2nd fluid (pH 6.8).

The delayed release of lactose, characterized by a lag time and subsequent rapid release, was observed most clearly for the microcapsules prepared with EA–MMA–HEMA (9 : 9 : 4) copolymer. When the lactose microcapsules contained phenacetin and polyvinylpyrrolidone (PVP), PVP did not affect the lag time, but remarkably enhanced the release of lactose after the lag time. Phenacetin was also released in a similar manner.

From the expansion of the particles in the dissolution fluid, it was estimated that the lag time corresponded to the time needed for the membrane to be hydrated, and the subsequent rapid release resulted from the permeability change caused by hydration and the reduction in membrane thickness due to the particle expansion by taken-up water. Polyvinylpyrrolidone contained within microcapsules enhanced the water intake, which induced bursting of the membrane.

Keywords——coating; dissolution; lactose; phenacetin; polyvinylpyrrolidone; microcapsule; Wurster process; ethyl acrylate–methyl methacrylate–2-hydroxyethyl methacrylate copolymer; delayed release; polymer softening temperature

Lactose microcapsules coated with methacrylic acid–ethyl acrylate (1 : 1) copolymer were reported in the previous papers.[1,2] Their dissolution profiles in the acidic medium were characterized by a lag time, increasing with the amount of coating material applied, and subsequent rapid release. A membrane with such a dissolution profile should be useful as an oral drug delivery system with a controllable lag time.[3]

The membrane previously reported was soluble in the intestinal juice. In this study, we attempted to synthesize new membrane materials that would be pH-independently insoluble in usual gastro-intestinal fluids. The copolymer characteristics from practical point of view were as follows: (1) it could be synthesized at high yield in a stable aqueous dispersion by emulsion polymerization, (2) it could easily form a membrane on the core material in the Wurster process, and (3) the drug- and water-permeability of formed membrane could be controlled as

desired. Ethyl acrylate, methyl methacrylate and 2-hydroxyethyl methacrylate were selected as monomers. By using a series of copolymers composed of various mole ratios of the above three monomers, the effect of monomer composition on the softening temperature of the polymer and on the dissolution properties was studied.

Experimental

Materials——As a water-soluble drug model, lactose (DMV 50 M) having a mean diameter of 328 μm in sieve analysis was used. The monomers, ethyl acrylate (EA), methyl methacrylate (MMA) and 2-hydroxyethyl methacrylate (HEMA), were used as purchased (Nakarai Chemicals). Sodium dodecyl sulfate (SDS, Wako Jyunyaku) and ammonium peroxodisulfate (APS, Nakarai Chemicals) were used as an emulsifier and a reaction initiator, respectively, in emulsion polymerization. Triacetin (TA, Nakarai Chemicals) was used as a plasticizer in coating. Talc (JP XI grade, Maruishi), an antiadherent, was used as purchased.

As a sparingly water-soluble drug model, phenacetin (Kawasaki Kagaku Kogyo Co., Ltd.) was used. The fine phenacetin powder (70% under 20 μm) was dispersed in 3% polyvinylpyrrolidone (PVP, K-90, Wako Jyunyaku) aqueous solution and sprayed on lactose.

Preparation of Polymer Dispersion——The method of Molday *et al.*[4] was modified. A monomer mixture (433 g in total) was used in each polymerization. The mole ratio of EA, MMA and HEMA used was 12 : 6 : X, 9 : 9 : X and 6 : 12 : X (X=4, 6 and 8). The monomer mixture (150 g) was poured into distilled water (1300 g) containing SDS (4 g) and emulsified in a Homo Mixer (4C, Tokushu Kika Kogyo Co., Ltd.). The emulsion was kept at 80 °C in the presence of nitrogen gas and 1 ml of APS aqueous solution (2 g/30 ml) was introduced to initiate polymerization. The remainder of the monomer mixture was slowly dropped into the reactor over 3 h. The reaction was further continued for 2 h. During the 5 h reaction 1 ml of APS solution was introduced every 30 min.

The reaction product was passed through an 80 mesh sieve to remove coarse solid masses and used for coating. A known weight of dispersion was dried at 110 °C to constant weight. The yield was almost 100% as total polymer and 88—97% as dispersed polymer. The resin dry weight content of the dispersion was 21—23%.

Coating——A Glatt GPCG-1 Wurster apparatus was used for coating. Directly coated lactose microcapsules (DC-L mc) were prepared by using undiluted dispersions of EA–MMA–HEMA copolymers as they were. Lactose microcapsules containing phenacetin and PVP (P–PVP–L mc) was prepared by spraying the phenacetin suspension in 3% PVP aqueous solution onto lactose (328 μm) and thereafter by coating with EA–MMA–HEMA copolymer. When a plasticizer was needed, triacetin was used (10% relative to EA–MMA–HEMA copolymer on a dry basis).

Dissolution——The dissolution tests and the determination of released lactose and phenacetin were performed as previously reported.[2] The dissolution medium was JP XI disintegration 2nd fluid (pH 6.8). The test samples, containing 0.1 g of lactose, were previously dried in vacuum at room temperature for 12 h.

Particle Expansion in the Dissolution Fluid——This was observed as previously reported.[1,2]

Thermomechanical Analysis——The thermomechanical analysis (TMA) was performed on a Shimadzu DT-30-TM-30 thermal analyzer. The softening temperature (T_s) of EA–MMA–HEMA copolymer film was determined by means of the penetration test. The operating conditions were as follows: load of 50 g; range of 100 μm; heating rate of 1 °/min; nitrogen of 20 ml/min; chart speed of 2.5 mm/min. The test film was prepared by heating 5 ml of dispersion on a flat plastic dish (BIO-BIK, Bio Plastics Co., Ltd., T_s=107 °C) at 60 °C for 12 h, further drying it in vacuum for 12 h at room temperature and stripping a small piece of film with a smooth surface. When the film could not be stripped from the dish, a piece remaining attached to the dish was cut off and used in the test.

Results and Discussion

Effect of Monomer Composition on the Softening Temperature

An example of a TMA chart is shown in Fig. 1. The softening temperature was defined as the intersection between the extrapolated base line and the linear extrapolation of the plot of penetration of the needle into the film.

The softening temperature T_s of copolymers is shown in Fig. 2. Within the range of compositions studied here, an increase in MMA content remarkably elevated T_s, as expected from the literature,[5] but HEMA only slightly elevated T_s. With EA : MMA : HEMA = 12 : 6 : X (X=4, 6, 8), T_s had already reached the lowest limit for the coating operation to be successfully performed under ordinary conditions. On the other hand, T_s for the 6 : 12 : X (X=4, 6, 8) copolymers seemed to be too high for formation of a nonporous membrane by spraying in the coating process.

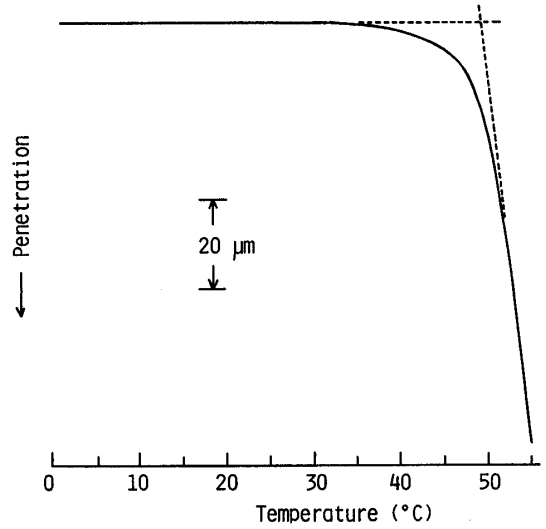

Fig. 1. An Example of Thermomechanical Analysis of EA–MMA–HEMA Copolymer Membrane

EA : MMA : HEMA = 9 : 9 : 6.

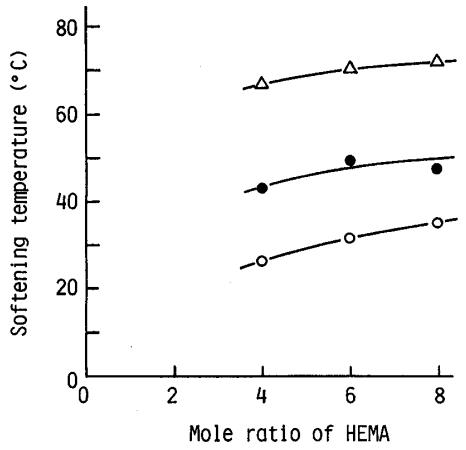

Fig. 2. Softening Temperature of EA–MMA–HEMA Membrane

Mole ratio of monomers (EA : MMA : HEMA): ○, 12 : 6 : *X*; ●, 9 : 9 : *X*; △, 6 : 12 : *X*.

TABLE I. Coating Conditions in the Preparation of Lactose Microcapsules Directly Coated with EA–MMA–HEMA Copolymer (DC-L mc) and Softening Temperature of Membrane

Core material	Lactose (DMV 50M)	500 g
Spray dispersion (undiluted)	EA–MMA–HEMA	300 g[b]
Plasticizer[a]	Triacetin	30 g
Antiadherent	Talc: inserted as powder	

Monomer	Mole ratio								
EA	12	12	12	9	9	9	6	6	6
MMA	6	6	6	9	9	9	12	12	12
HEMA	8	6	4	8	6	4	8	6	4
Inlet air temperature (°C)	40	40	40	60	55	45	60	56	56
Outlet air temperature (°C)	27	29	28	31	28	27	32	32	32
Output air flap (%)	50	52	50	48	48	50	48	48	48
Inlet air rate (m^3/min)	1.4	1.7	1.4	1.1	1.1	1.4	1.1	1.1	1.1
Spray rate (ml/min)	5.1	3.6	3.5	6.7	8.5	5.8	5.8	4.0	5.6
Spray pressure (atm)	2.1	2.4	2.1	2.1	2.1	2.1	2.2	2.1	2.2
Diameter of spray nozzle (mm)					0.8				
Bag filter opening (μm)					25				
Softening temperature (°C)	35	32	26	48	49	43	45[c]	42[c]	41[c]

a) Added only to EA–MMA–HEMA (6 : 12 : *X*) copolymers. *b*) On a dry basis. *c*) T_s of the film plasticized with triacetin.

Preparation of Lactose Microcapsules Directly Coated with EA–MMA–HEMA Copolymer (DC-L mc)

Coating conditions and softening temperature of membrane are listed in Table I. The dispersion of 6 : 12 : 4 copolymer did not formed a membrane on lactose crystals, because all the lactose was released during the first 30 min in a dissolution test in spite of the latex particles having adhered to the crystals in the coating process. Hence, DC-L mcs with the 6 : 12 : *X* copolymers were prepared by using 10% TA, relative to the membrane material on a

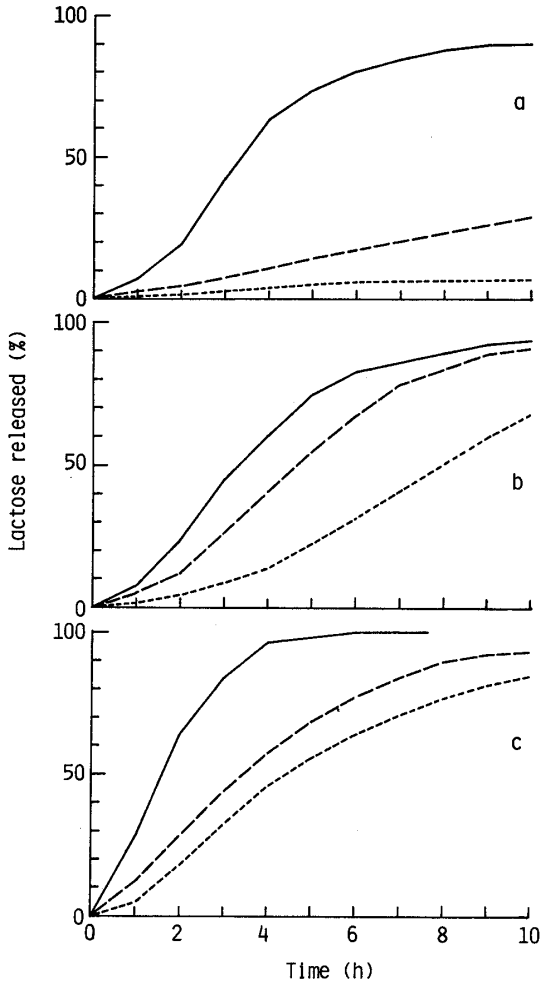

Fig. 3. Release of Lactose from Microcapsules (DC-L mc) Prepared with EA–MMA–HEMA Copolymers in JP XI Disintegration 2nd Fluid (pH 6.8)

Applied EA–MMA–HEMA lacquer on a dry basis: 40%. Mole ratio of monomers (EA : MMA : HEMA): a, 12 : 6 : *X*; b, 9 : 9 : *X*; c, 6 : 12 : *X*; ——, $X=8$; – – – –, $X=6$; ------, $X=4$. c: containing 10% TA relative to EA–MMA–HEMA.

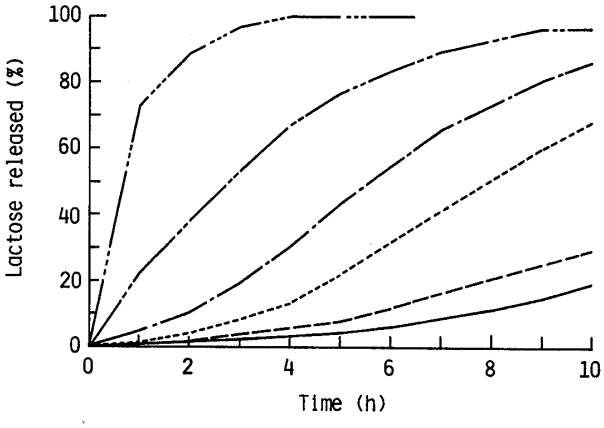

Fig. 4. Effect of the Amount of EA–MMA–HEMA (9 : 9 : 4) Copolymer Applied on the Profile of Lactose Release from Directly Coated Microcapsules (DC-L mc)

Applied EA–MMA–HEMA lacquer on a dry basis relative to the lactose core (%): ——·——, 10; ——··——, 20; ——–——, 30; ------, 40; – – – –, 50; ——, 60.

dry basis, as a plasticizer.

At the beginning of the coating operation, the inlet air temperature was set at 60 °C. However, this had to be lowered due to melting of the membrane and the subsequent formation of a solid mass. Consequently, the coating was performed at temperature ranges including T_s of each membrane except for the 12 : 6 : 4 copolymer (Table I). In the case of 12 : 6 : 4 copolymer, the softening temperature was lower than the outlet air temperature and therefore the fluidized particles were very cohesive. In that case, for successful operation, a large amount of talc powder, 50 g, had to be inserted into the coating chamber as an antiadherent during coating.[2)]

Release of Lactose from Directly Coated Microcapsules (DC-L mc)

As typical examples, the release profiles from DC-L mcs 40% coated with EA–MMA–HEMA copolymers are shown in Fig. 3. Most of the release profiles studied here were characterized by first-order release with or without a lag time. The most clearly delayed release profile was observed for the 9 : 9 : 4 copolymer. The release profiles from the DC-L mcs

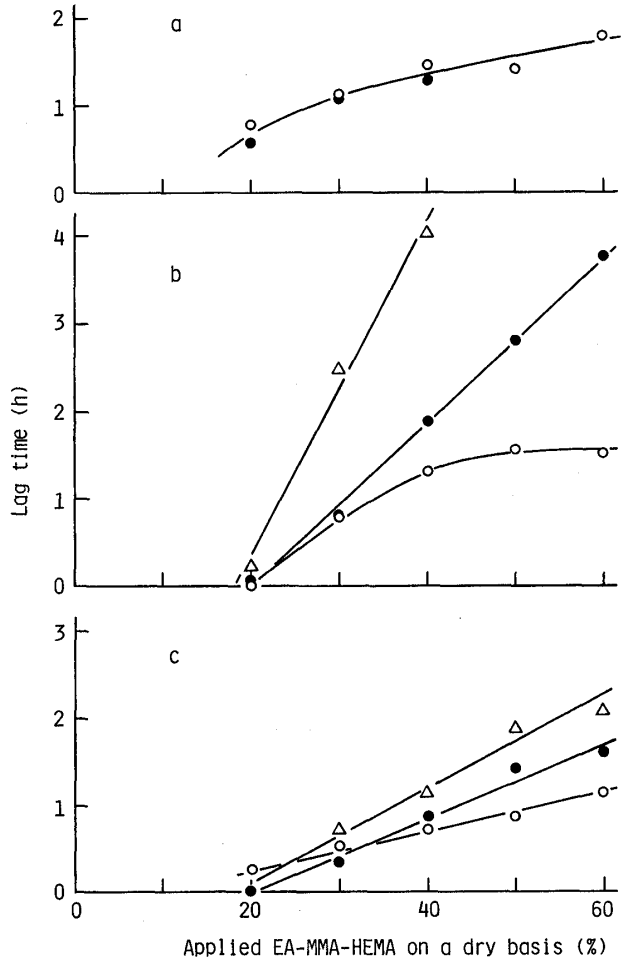

Fig. 5. Lag Time of Lactose Release from Microcapsules (DC-L mc) Prepared with EA–MMA–HEMA Copolymers

Mole ratio of monomers (EA : MMA : HEMA): a, 12 : 6 : *X*; b, 9 : 9 : *X*; c, 6 : 12 : *X*; ○, *X*=8; ●, *X*=6; △, *X*=4.

with various membrane thicknesses are shown in Fig. 4.

The lag time, estimated as in the previous study,[2] is shown in Fig. 5. In the cases where the plots are missing, the delayed release profile was not observed or could not be estimated from the data until 10 h. Except for 9 : 9 : 6 and 9 : 9 : 4 copolymers, the lag time was relatively short.

The apparent dissolution rate constant[2] is shown in Fig. 6. With 12 : 6 : 4 copolymer, the release at every coating level exhibited no lag time. In such a case, the apparent dissolution rate was strongly dependent on membrane thickness (Fig. 6a). With 12 : 6 : 8 and 12 : 6 : 6 copolymers, the dissolution rate is weakly dependent on membrane thickness at low levels of coating, where the delayed release profile was observed. At high coating levels, the dissolution rate is strongly dependent on membrane thickness again. In the cases of 9 : 9 : *X* and 6 : 12 : *X* copolymers (Figs. 6b and 6c) where the delayed release profile was observed, the disolution rate maintained a high value and was weakly dependent on membrane thickness. The higher values at 10% coating resulted from the cores not being fully covered by membrane.

The methacrylic acid (MA)–ethyl acrylate microcapsules of lactose exhibited typical delayed release profiles in JP XI disintegration 1st fluid (pH 1.2).[1,2] The particle expansion in the dissolution fluid suggested that the lag time resulted from the restriction of release due to the rapid water-intake, and bursting of the membrane seemed to account for the rapid release after the lag time.

The expansion of EA–MMA–HEMA microcapsules is shown in Fig. 7. When compared with MA–EA microcapsules prepared by using 120 μm cores,[1,2] the rate of expansion is much slower and the lag time is more prolonged. Clearly, the 7.5 times thicker membrane of DC-L

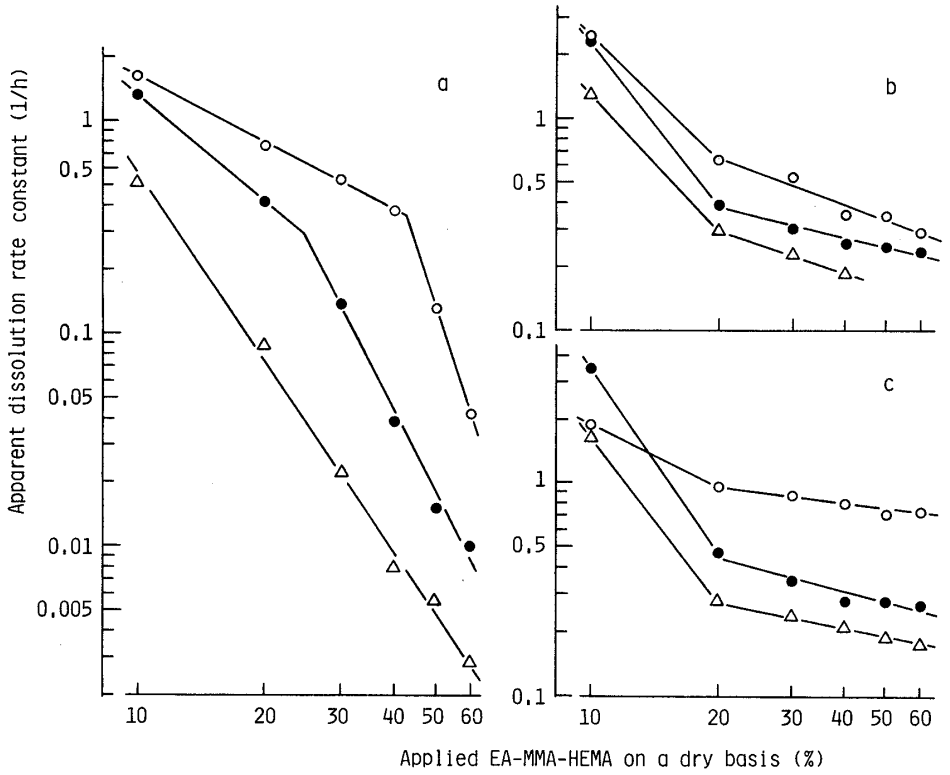

Fig. 6. Apparent Rate Constant of Lactose Release after the Lag Time from Microcapsules (DC-L mc) Prepared with EA–MMA–HEMA Copolymers

Mole ratio of monomers (EA : MMA : HEMA): a, 12:6:X; b, 9:9:X; c, 6:12:X; ○, X=8; ●, X=6; △, X=4.

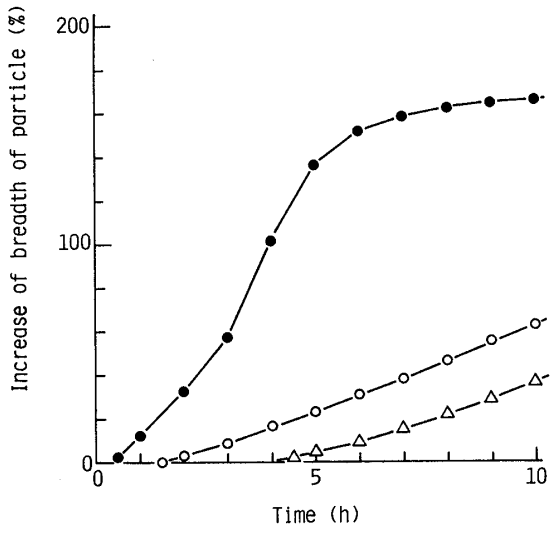

Fig. 7. Expansion of Lactose Microcapsule (DC-L mc) 40% Coated with EA–MMA–HEMA Copolymer in JP XI Disintegration 2nd Fluid (pH 6.8)

Mole ratio of monomers (EA : MMA : HEMA): ○, 9:9:4; ●, 9:9:8; △, 12:6:4.

mcs which had the larger cores (328 μm) accounts for this. The expansion of EA–MMA–HEMA microcapsules seemed to be followed by rapid release, and seemed to continue during the release (Fig. 3). In these cases, no membrane bursting was observed. Figure 7 also shows that HEMA and MMA enhance the expansion and therefore the water-permeation. These results suggest that the lag time corresponds to the time needed for the membrane to be hydrated and the subsequent rapid release is induced by the permeability change of the hydrated membrane and the expansion, which would have made the membrane thinner.

In Figs. 5 and 6, HEMA clearly makes the lag time short, which should result from the

enhanced hydration, and enhances the lactose release, as was expected from its higher hydrophilicity than the other monomers. For the design of delayed-release microcapsules with a long lag time, a lower content of HEMA may be preferable. However, one problem is that a lower content of HEMA results in a lower dissolution rate at the rapid release stage (Figs. 6b and 6c), because the lower rate of hydration usually results in slower water-permeation and particle expansion. As can be seen in Figs. 3a, 5a and 7, microcapsules prepared by using copolymers with extremely low water-permeability may no longer exhibit delayed release. Therefore, some other techniques were required to enhance the release after the lag time, if possible, independently of the lag time.

Preparation of Microcapsules Containing Lactose, Phenacetin and PVP (P–PVP–L mc)

In the previous study, PVP remarkably prolonged the lag time of lactose and phenacetin

TABLE II. Operating Conditions in the Preparation of PVP-Containing Microcapsules (P–PVP–L mc) Coated with EA–MMA–HEMA (9:9:4) Copolymer

Core material	Lactose (DMV 50M)	300 g
Layering powder	Phenacetin (70% under 20 μm)	30 g
Binder	3% PVP aqueous solution	30 g[a)]
Coating material	EA–MMA–HEMA (9:9:4)	360 g[a)]

	Layering	Coating
Inlet air temperature (°C)	55	60
Outlet air temperature (°C)	37	27
Output air flap (%)	53	48
Inlet air rate (m^3/min)	1.7	1.1
Spray rate (ml/min)	5.1	5.6
Spray pressure (atm)	3.5	3.2
Diameter of spray nozzle (mm)	0.8	
Bag filter opening (μm)	25	

a) On a dry basis.

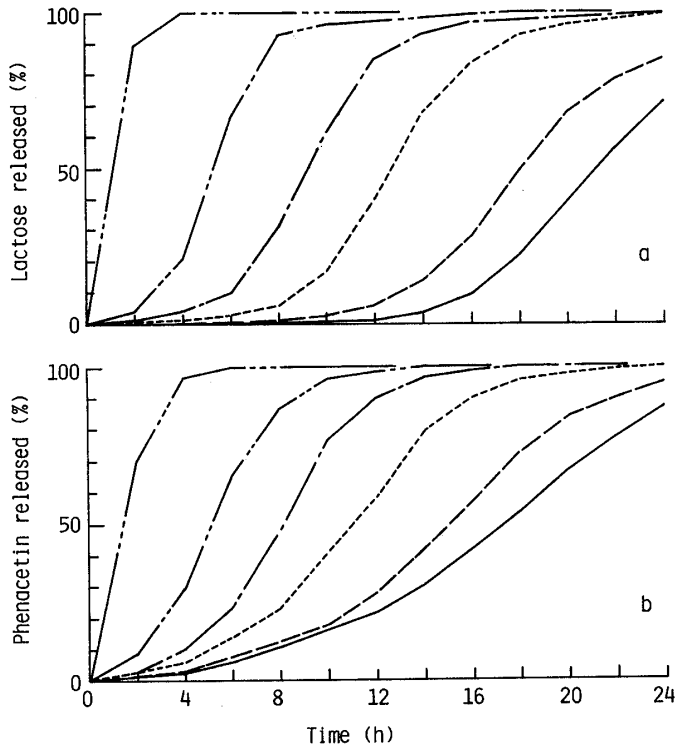

Fig. 8. Release of Lactose (a) and Phenacetin (b) from PVP-Containing Microcapsules (P–PVP–L mc) Coated with EA–MMA–HEMA (9:9:4) Copolymer in JP XI Disintegration 2nd Fluid (pH 6.8)

Applied EA–MMA–HEMA lacquer on a dry basis relative to the lactose core (%): —·—·—, 20; —··—, 40; —·—, 60; ------, 80; – – –, 100; ——, 120.

release from MA–EA microcapsules.[1] In this study, the effect of PVP on dissolution profile was examined again.

Table II shows the conditions for the preparation of P–PVP–L mc. As a membrane material, EA–MMA–HEMA (9:9:4) copolymer was used. Fine phenacetin crystals (70% under 20 μm) were fixed on coarse lactose crystals (DMV 50M) as a solid dispersion in PVP. The coating conditions in this layering process were based on those in the previous study.[1]

Release of Lactose and Phenacetin from Microcapsules Containing PVP (P–PVP–L mc)

The dissolution tests were performed for 24 h with microcapsules coated up to 120%. The release profiles are shown in Fig. 8. Typical delayed release profiles are observed, especially for lactose. When compared with Fig. 4, the lag time of lactose release seemed to be unchanged, but the rate of release after the lag time seemed to be enhanced by PVP.

From the data shown in Fig. 8, the lag time and the dissolution rate constant at the rapid release stage were estimated. The calculated results are shown in Fig. 9, in comparison with those from DC-L mc. The data for 10% coating are omitted because the membrane seemed not to cover the entire surface of the cores and the microcapsules exhibited extremely large release in the first 30 min. In both parameters, there is no significant difference between lactose and phenacetin. This suggests that the rapid dissolution results from some physical change in the membrane which could affect the permeability regardless of the chemical properties of the solutes. Such a change may be bursting of the membrane, reduction in membrane thickness or enlarged size of pores, which can be induced by membrane expansion owing to water-intake.

A noteworthy difference between the release profiles of lactose and phenacetin is the higher release rate of phenacetin during the lag time (Fig. 8). This might result from greater migration of phenacetin through the EA–MMA–HEMA membrane, or from the fact that phenacetin was layered outside the lactose cores.

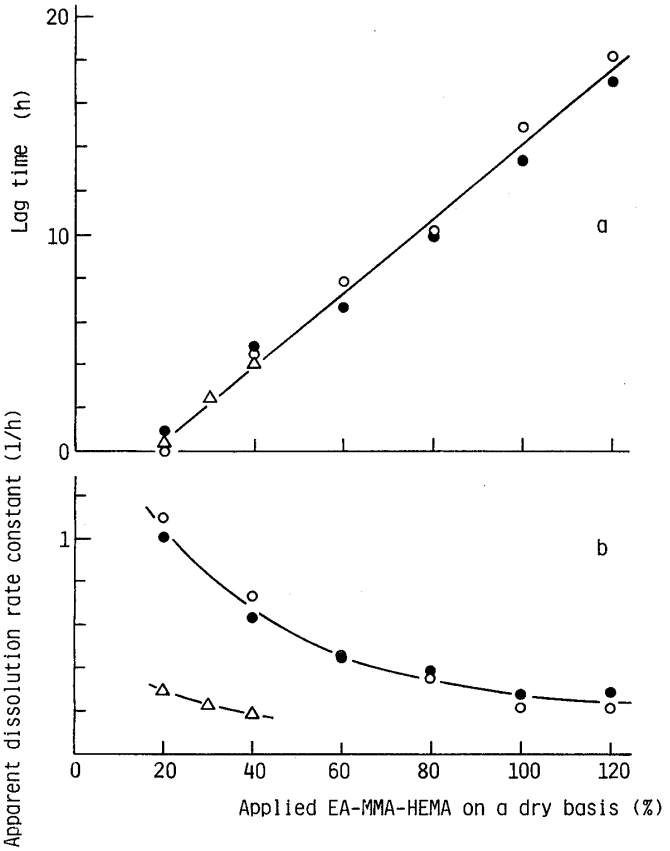

Fig. 9. Lag Time (a) and Apparent Rate Constant (b) of Lactose and Phenacetin Release from PVP-Containing Microcapsules (P–PVP–L mc) Coated with EA–MMA–HEMA (9:9:4) Copolymer in JP XI Disintegration 2nd Fluid (pH 6.8)

○, lactose from P–PVP–L mc; ●, phenacetin from P–PVP–L mc; △, lactose from DC–L mc.

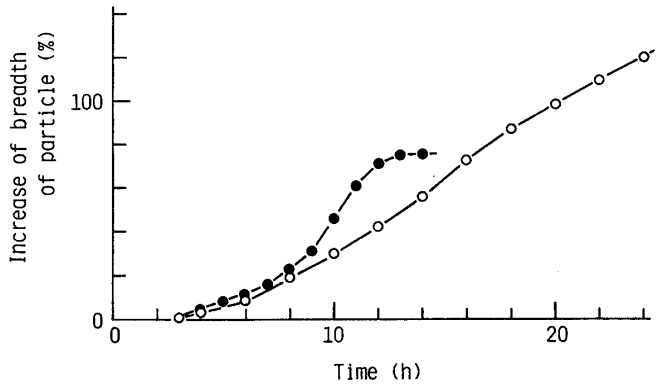

Fig. 10. Effect of PVP on the Expansion of Microcapsules 60% Coated with EA–MMA–HEMA (9:9:4) Copolymer in JP XI Disintegration 2nd Fluid (pH 6.8)

○, DC-L mc; ●, P-PVP-L mc.

When compared with DC-L mcs, P–PVP–L mcs exhibited a more rapid release, but their lag times were unchanged (Fig. 9). PVP acted as an enhancer only for the release after the lag time, different from the previous study on EA–MA microcapsules where PVP remarkably prolonged the lag time, but did not affect the rapid release rate.[1] This can be explained by assuming that PVP does not affect the hydration of the membrane and enhances only the particle expansion owing to its strong hydrophilicity. This is demonstrated by the particle expansion in the dissolution fluid (Fig. 10). The same expansion at the initial stage in both cases shows that the hydration has not been affected by PVP, while the subsequent larger expansion of P–PVP–L mc would induce faster release (Fig. 9). The small expansion of P–PVP–L mc terminated at 75% elongation (Fig. 10), implying that a large leakage of the contents of P–PVP–L mcs had occurred. Different from DC-L mcs, P–PVP–L mcs often exhibited bursting of the membrane, resulting in a sudden shrinkage of particles. This should account for the delayed release characteristics being independent of the chemical properties of the solutes (Fig. 9).

Conclusion

The EA–MMA–HEMA (9:9:4) copolymer provided effective delayed-release microcapsules of lactose, a water-soluble drug model, when they contained PVP. Polyvinylpyrrolidone did not affect the lag time, but acted only as an enhancer of the release after the lag time. The 9:9:4 copolymer could easily be synthesized in high yield as a stable aqueous dispersion and its film had a softening temperature suitable for coating operation by the Wurster process. A target for future research is to find a method for reducing the solute migration of hydrophobic drug such as phenacetin during the lag time without making the lag time shorter.

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