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Coating of Pharmaceutical Powders by Fluidized Bed Process. II. Microcapsules Produced by Layering of Fine Powder on Coarse Particles and Subsequent Aqueous Enteric Coating

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The Wurster process (Glatt GPCG-1) could produce particles whose outer layer consisted of fine phenacetin particles (70% under 20 μm) adhering to or fixed on lactose particles (90 μm), when a mixture of both powders was fluidized and sprayed with a binder solution. The enteric coating of layered particles was performed with an aqueous methacrylic acid–ethylacrylate (MA-EA) copolymer suspension (Eudragit L30D-55).

The simple MA-EA microcapsules of coarse lactose crystals (120 μm) exhibited a delayed release characterized by a lag time in the JP XI disintegration 1st fluid (pH 1.2), as previously reported. The layered phenacetin and hydroxypropylcellulose used as the binder in this study had no significant effect on the delayed release of lactose. However, phenacetin was released according to biphasic zero-order kinetics, different from the case of directly coated coarse crystals (128 μm). The apparent dissolution rate increased after the first slow release. The formation of a fine phenacetin suspension within microcapsules after the dissolution of lactose accounted for such an enhanced release.

When polvinylpyrrolidone (PVP) was used as the binder, the lag times of the release of phenacetin and lactose were remarkably prolonged. The release rate of phenacetin after the lag time increased. The water intake into the microcapsules enhanced by PVP, which induced an extremely large expansion of the particles, and the reduction of viscosity accounted for these phenomena.

The results showed that when PVP was used as the binder, the enteric coating through the layering process was sufficiently protective against the release of both phenacetin and lactose at the 50% coating level.

Keywords——enteric coating; powder; fluidized bed; dissolution; lactose; phenacetin; microencapsulation; Wurster process; methacrylic acid–ethylacrylate copolymer; delayed release

A serious problem in the fluidized bed coating process is that a large amount of membrane material may be needed to encapsulate fine powders with a large specific surface area. The results reported in the previous paper showed that for the purpose of enteric coating, more than 60% membrane material (methacrylic acid–ethylacrylate copolymer) relative to core material was needed even with phenacetin particles of 128 μm.[1)]

The Wurster process can produce particles whose outer layer is composed of fine particles adhering to or fixed on a core particle, when a bicomponent mixture of fine and coarse powders is sprayed with a binder solution.[2)] In this study, this layering technique was applied to develop a method for enteric coating of fine particles.

Another feature of the previous study was the delayed release of lactose microcapsules.[1)] The effect of the binders used in the layering process on the dissolution behavior was studied to elucidate the mechanism of the delayed release.

Experimental

Materials——As a coarse core powder, the fraction of 145 to 200 mesh of lactose (DWV 200 M) was used. Phenacetin (JP X grade, industrial raw material, Kawasaki Kagaku Kogyo, Co., Ltd.) as a hydrophobic drug model was micronized by a hammer mill (Sample-Mill K-II-1, Fuji Paudal, Co., Ltd). A 3% aqueous solution of hydroxypropylcellulose (HPC, HPC-L, Nippon Soda Co., Ltd.) or polyvinylpyrrolidone (PVP, K-90, Wako Junyaku Co., Ltd.) was used as the binder in the layering process. The spray dispersion was an aqueous suspension (12.5% lacquer on a dry basis) of methacrylic acid–ethylacrylate copolymer (MA-EA, Eudragit L30D-55, Röhm Pharma) containing triacetin (TA, Nakarai Chemicals Co., Ltd.) as the plasticizer and talc (JP XI grade, Maruishi) as the spacing agent.

Coating——A Glatt GPCG-1 apparatus was used.

Dissolution——Dissolution tests were performed as previously reported.[1] For microcapsules produced through the layering process, the tests were performed for samples containing 0.15 g of phenacetin. For the undercoated microcapsules, dissolution samples contained 0.15 g of lactose or phenacetin.

Solubility——The JP XI disintegration 1st fluid (pH 1.2) was used as a solvent. A tightly capped 50 ml centrifuge tube, containing 30 ml of HPC or PVP solution of 0, 1, 2, 3 or 5% and 1 g of phenacetin, was shaken in a water bath at 37°C for 24 h and then centrifuged. The phenacetin concentration of the supernatant was determined by spectrophotometry at 245 nm.

Viscosity——For more than 5% polymer solutions, a falling-sphere viscometer was assembled. A glass tube of 35 mm inner diameter and 26 cm length with a stopcock at the bottom and stainles steel balls of 0.7 mm diameter were used. The solvent was the JP XI disintegration 1st fluid (pH 1.2). The viscosity was calculated according to the Stokes' law.[3] For less than 5% polymer solutions, an Ubbelohde viscometer was used. The density of polymer solutions was determined by using hydrometers.

Instrumentation——Sieve analysis, scanning electron microscopy (SEM) and polarizing microscopy were performed as previously reported.[1] The elongation of particle breadth measured by means of a polarizing microscope was defined as $(l_t - l_0)/l_0$, where l_0 was the original breadth and l_t the breadth at the time t after immersion of particles in the dissolution medium.

Results and Discussion

Layering of Fine Phenacetin Powder on Lactose

In the previous study,[1] phenacetin powder (500 g with 128 μm mean diameter) was directly coated with MA-EA copolymer. The weight, W_{core}, of lactose powder which has the same particle number as this phenacetin powder and the mean diameter of d (μm) can be estimated by means of Eq. 1.

$$W_{core} = 500 \times d^3 \rho_l / (128^3 \rho_p) \quad (1)$$

where ρ_l (1.54 g/cm^3) and ρ_p (1.24 g/cm^3) are the densities of lactose and phenacetin crystals, respectively. The lactose powder prepared in this study had a mean diameter of 90 μm, obtained as the arithmetic mean of the sieve openings. The calculated value of W_{core} was 216 g.

The weight W_{layer} of fine phenacetin needed for producing the powder with the mean diameter of 128 μm could be estimated from Eq. 2.

$$W_{layer}/W_{core} = g(\rho_p/\rho_l)\{(128/d)^3 - 1\} \quad (2)$$

where g is the packing fraction of phenacetin in the layer formed on the above lactose particles (the mean diameter of d). In the closest packing of monodispersed spheres where g is 0.740, W_{layer} could be calculated as 241 g. In anticipation of some loss of fine powder in the layering process, 250 g of phenacetin was used in this study.

Table I lists the materials and the operating conditions in the layering process. HPC or PVP (48 g on a dry basis) was used as a binder. Talc powder (50 g) was included as necessary in the coating chamber as an antiadherent. The filter was changed to one with a smaller opening (5 μm) in this study, because very fine phenacetin powder was used. The inlet air temperature was elevated to 80°C. The conditions was set so as to keep the powder wet,

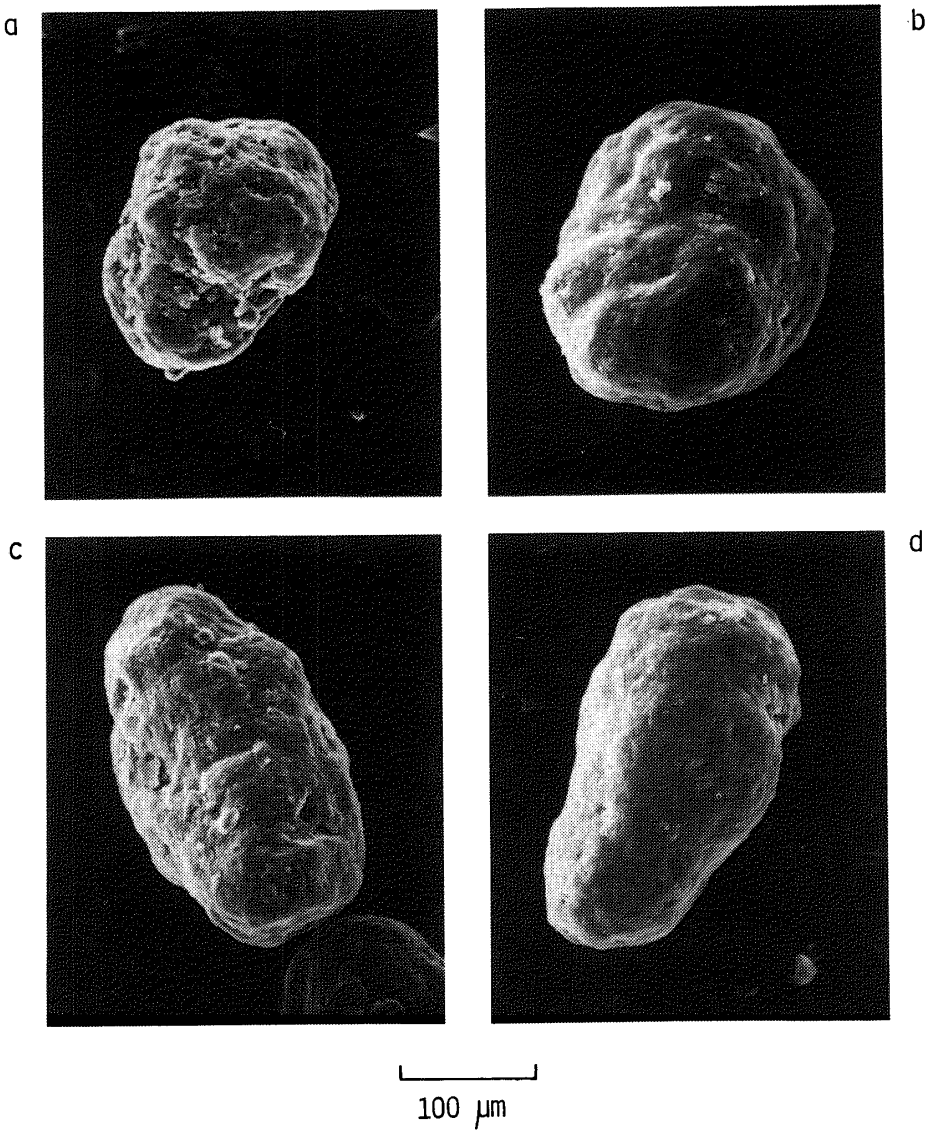

Fig. 1. Photographs (SEM) of Layered and Coated Particles (× 300)

a) After layering with HPC. b) After enteric-coating of the particles layered with HPC. c) After layering with PVP. d) After enteric-coating of the particles layered with PVP.

accelerate the adhesion of fine phenacetin powder to coarse lactose particles and prevent the ejection of fine particles to the filter. Even under such moderate, wet conditions, the coarse particles were not markedly agglomerated, since in the presence of a large amount of fine powder, layering occurred prior to agglomeration of coarse particles. When PVP was used as the binder, the powder was kept drier by reducing the spray rate and by increasing the flow rate (output air flap) because of its agglomerability.

SEM photographs of layered particles are shown in Figs. 1a and 1c. The fine particles are fixed on the surface and coated with HPC or PVP. However, large pores are observed. PVP forms a smoother surface than HPC (Fig. 1c). This seemed to be related to the adhesive character of PVP, which more readily induced agglomeration than HPC.

Coating Process

The coating dispersion, the operating conditions and the mean diameter and final yield of the products are shown in Table II. The conditions could not be adjusted similarly to those in the previous study,[1)] due to the difference in the opening of the filter used. The layering with

Table I. Operating Conditions in Layering Process

Core material	Lactose	145—200 mesh (90 μm)	216 g
Layering powder	Phenacetin	70% under 20 μm	250 g
Binder	HPC or PVP	3% aqueous solution	1600 g
Antiadherent	Talc	Inserted as powder into the operating chamber	50 g

	HPC	PVP
Inlet air temperature (°C)	80	80
Material temperature (°C)	36	33
Outlet air temperature (°C)	32	30
Output air flap (%)	45	50
Spray rate (ml/min)	8.8	6.2
Spray pressure (atm)	2.5	2.5
Diameter of spray nozzle (mm)	0.8	0.8
Bag filter opening (μm)	5	5
Drying conditions	40 °C, 10 min	

Table II. Operating Conditions in Enteric Coating of Phenacetin Powder Layered on Lactose

Membrane material	MA-EA dispersion	1000 g
Plasticizer	TA	30 g
Spacing agent	Talc	90 g
Water		added
	Total	2400 ml
	Total solid	420 g (84%)
	MA-EA dry lacquer	300 g (60%)

Inlet air temperature (°C)	60	60
Material temperature (°C)	29	30
Outlet air temperature (°C)	26	27
Output air flap (%)	52	50
Spray rate (ml/min)	7.1	7.3
Spray pressure (atm)	2.5	2.5
Diameter of spray nozzle (mm)	0.8	0.8
Bag filter opening (μm)	5	5
Drying conditions	40 °C, 10 min	
Mean diameter of product (μm)	158	190
Yield (%)	95	97

PVP was performed under more severe conditions (higher air flow rate and lower spray rate) because of the more adhesive character of PVP.

Photographs of particles coated with 60% MA-EA lacquer on a dry basis are shown in Figs. 1b and 1d. The photographs show a smooth membrane formed on layered particles.

In this study, for example, the term "60%" means an amount of MA-EA corresponding to the 60% level in the direct coating of lactose or phenacetin crystals previously reported.[1] Hence, for coating at the 60% level, 300 g of MA-EA lacquer on a dry basis was used (Table II).

The particle size distributions of the raw materials and the produced microcapsules (60% coated) are shown in Fig. 2. The 50%diameter of the product was 158μm with HPC (Fig. 2b) and 190 μm with PVP (Fig. 2c). The larger particle size with PVP resulted from its more adhesive character which induced more agglomeration in the layering process. Particles

smaller than 74 μm could not be detected on sieve analysis (Figs. 2b and c). Although the fractions of 74 to 149 μm apparently consisted of single core particles, the fraction of 149—177 μm consisted partly of agglomerates of two particles. The powder of 177—250 μm consisted of agglomerates of 2—3 particles. The particles larger than 250 μm contained agglomerates of more than three particles. Although in some cases such agglomeration would be a problem, no further attempt to produce perfectly discrete particles was made in this study.

Release from Microcapsules Prepared through the Layering Technique by Using HPC

The release of layered phenacetin from MA-EA microcapsules prepared by using HPC as the binder is shown in Fig. 3a. The release was unchanged at more than 40% coating. The microcapsules coated with more than 20% lacquer on a dry basis exhibited biphasic dissolution profiles. The dissolution began at a slow rate and subsequently showed a zero-order release at a higher rate.

The release of lactose used as the core from the same microcapsules is shown in Fig. 3b. The results seem to be similar to those in the case of the directly coated lactose crystals previously reported.[1] Although the release of phenacetin is unchanged by more than 40% MA-EA coating (Fig. 3a), the release of lactose is restrained correspondingly to the coating applied (Fig. 3b). This result suggests that the membrane has been formed at the thickness corresponding to the coating material applied and that the unchanged release of phenacetin at the high coating level would be related to other factors.

Figure 4 shows the particle expansion in the dissolution medium observed on the polarizing microscope stage at 37 °C. The particles were expanded by water take-up after a

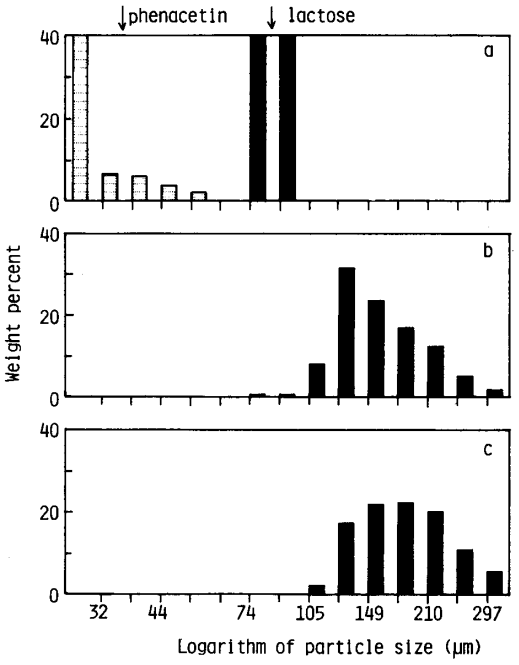

Fig. 2. Particle Size Distributions (Sieve Analysis) of Raw Materials and Enteric-Coated Powders with MA-EA Copolymer

a) Raw materials. Phenacetin: 82% under 32 μm, 70% under 20 μm. Lactose: 145—200 mesh (50% diameter 90 μm). b) Powder layered phenacetin with HPC on lactose, 60% enteric-coated (50% diameter 158 μm). c) Powder layered phenacetin with PVP on lactose, 60% enteric-coated (50% diameter 190 μm).

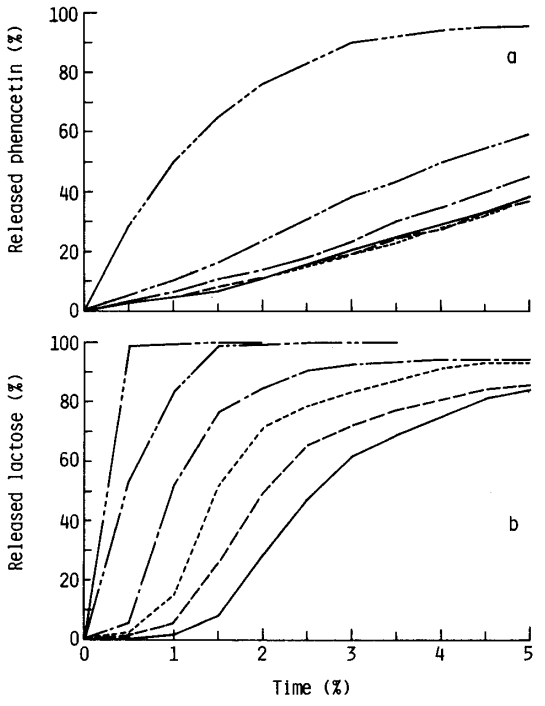

Fig. 3. Release of Phenacetin (a) and Lactose (b) from Microcapsules Layered with HPC as the Binder and Enteric-Coated with MA-EA Copolymer in JPXI Disintegration 1st Fluid (pH 1.2)

Applied MA-EA lacquer on a dry basis (%): —·—·—, 10; — — —, 20; — · —, 30; ------, 40; – – – –, 50; ——, 60.

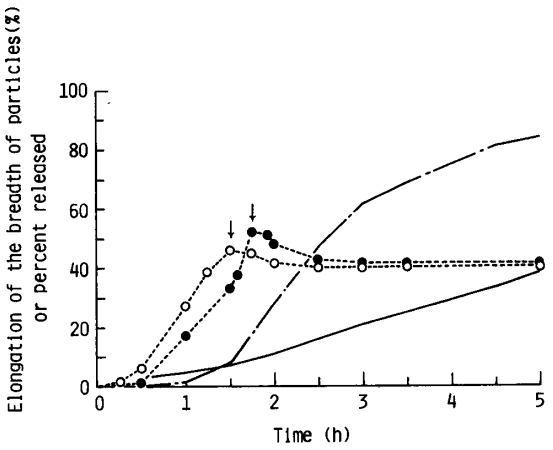

Fig. 4. Expansion of Microcapsules Layered with HPC as the Binder and Enteric-Coated with 60% MA-EA Copolymer in the JP XI Disintegration 1st Fluid (pH 1.2) at 37 °C and the Corresponding Dissolution Curves

○●, particle expansion (two measurements); ——, dissolution of phenacetin; — - —, dissolution of lactose. The arrow shows the disappearance of lactose crystals.

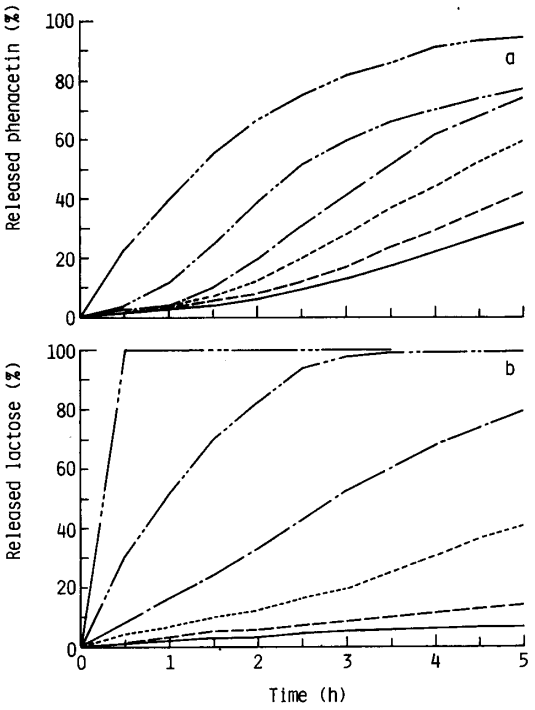

Fig. 5. Release of Phenacetin (a) and Lactose (b) from Microcapsules Layered with PVP as the Binder and Enteric-Coated with MA-EA Copolymer in JP XI Disintegration 1st Fluid (pH 1.2)

Applied MA-EA lacquer on a dry basis (%): — · · · —, 10; — · · —, 20; — · —, 30; ------, 40; – – –, 50; ——, 60.

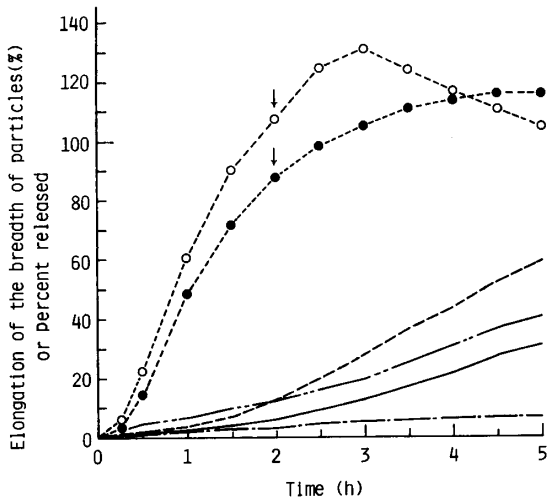

Fig. 6. Expansion of Microcapsules Layered with PVP as the Binder and 40 or 60% Enteric-Coated with MA-EA Copolymer in the JP XI Disintegration 1st Fluid (pH 1.2) at 37 °C and the Corresponding Dissolution Curves

Particle expansion: ---○---, 40%; ---●---, 60%. Dissolution of phenacetin: – – – –, 40%; ——, 60%. Dissolution of lactose: — – —, 40%; — · —, 60%. The arrow shows the disappearance of lactose crystals.

short lag time. At the maximum of expansion, which coincided with the lag time of lactose and phenacetin dissolution, the lactose crystals disappeared. Fine phenacetin crystals were observed through the polarizing microscope even after 5 h within the microcapsules coated with 60% MA-EA lacquer on a dry basis. This meant that a suspension of fine phenacetin crystals has been formed within the microcapsules.

Release from Microcapsules Prepared through the Layering Technique by Using PVP

The release of phenacetin is shown in Fig. 5a. When compared with Fig. 3a, the profiles more clearly exhibit delayed release characterized by lag time.

The release of lactose is shown in Fig. 5b. The profiles seem to follow zero-order kinetics. The characteristic delayed release of lactose seems to have disappeared in this case. However, Fig. 5 shows that PVP was more effective for the purpose of enteric coating, especially with such a water-soluble material as lactose, than HPC (Fig. 3).

TABLE III. Operating Conditions in Undercoating and Enteric Coating for Phenacetin and Lactose Powders

	Undercoating				Enteric coating			
Core material[a]	Lactose		Phenacetin		Lactose		Phenacetin	
Binder[b]	HPC	PVP	HPC	PVP	HPC	PVP	HPC	PVP
Inlet air temperature (°C)	65	60	65	60	60			
Outlet air temperature (°C)	36	38	37	38	33	32	33	37
Output air flap (%)	53	55	49	50	53			
Spray rate (ml/min)	7.5	6.6	5.8	5.2	8.0	7.0	7.6	5.4
Spray pressure (atm)	2.5	2.5	1.9	2.5	2.5			
Diameter of spray nozzle (mm)				0.8				
Bag filter opening (μm)				25				
Drying conditions				40 °C, 10 min				
Mean diameter of product (μm)					168	190	205	227
Yield (%)					96	96	95	94

a) Lactose, 100 mesh (120 μm); phenacetin, 80—250 mesh (128 μm). *b*) A 3% aqueous solution (1600 ml).

Figure 6 shows the expansion of the particles containing PVP in the dissolution medium. When compared with the case of HPC, the expansion was remarkably increased and the maximum was more than 115 and 130% with 60 and 40% coated micrcapsules, respectively. This means that the expanded particles have almost 10 and 12 times the volume of the original particles, respectively. This might result from the very strong attraction of water to PVP, which is far more wettable than HPC in the atmosphere, as is well known.[4] It is also possible that PVP affected membrane properties such as the water and/or drug permeability and the mechanical flexibility.

Microcapsules Undercoated with HPC or PVP

Lactose (120 μm) and phenacetin (128 μm) powders used in the previous study[1] were undercoated with HPC or PVP and the products were enteric-coated with MA-EA copolymer. It was expected that the release profiles from the simply undercoated microcapsules would throw light on the effects of PVP. The operating conditions in undercoating and enteric coating and the mean diameter and yield of the products are summarized in Table III. Since phenacetin is very fragile,[1] it was fluidized under relatively moderate conditions in undercoating (Table III). As a result, phenacetin was more easily agglomerated and the product had a larger diameter than in the case of lactose.

The release of phenacetin from the MA-EA microcapsules undercoated with HPC or PVP is shown in Fig. 7. The release, which followed zero-order kinetics, was markedly reduced, compared with the case of direct coating, particularly in the case of HPC.[1] For the purpose of enteric coating, the above undercoating technique should be very useful, though PVP induced a slightly larger release rate than HPC. The results show that when undercoated with HPC, the 20% coating of MA-EA is sufficient for enteric coating. However, the characteristic profiles with the lag time (Figs. 3a and 5a) have disappeared in these cases.

In the release of lactose from the undercoated microcapsules, PVP remarkably prolonged the lag time (Fig. 8), while HPC caused no substantial change. The expansion of lactose particles undercoated by using PVP and subsequently enteric-coated is shown in Fig. 9. Most of the particles exhibited an expansion profile of the type shown by the closed circles, but some particles began to shrink after a short expansion period as shown by the open circles. This clearly accounted for the gradual release before the rapid dissolution in Fig. 8. Figure 9

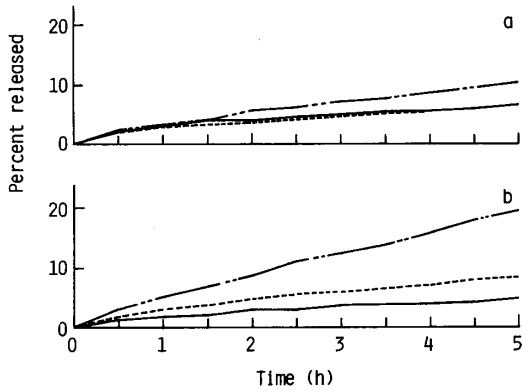

Fig. 7. Release of Phenacetin from Microcapsules of Coarse Crystals Undercoated with HPC (a) or PVP (b) and Enteric-Coated with MA-EA Copolymer in JP XI Disintegration 1st Fluid (pH 1.2)

Applied MA-EA lacquer on a dry basis relative to phenacetin (%): — - - —, 20; ------, 40; ——, 60.

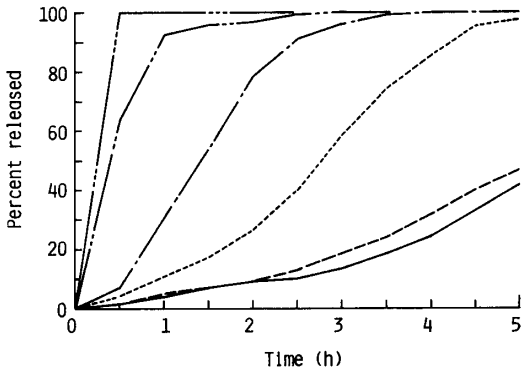

Fig. 8. Release of Lactose from Microcapsules of Coarse Crystals Undercoated with PVP and Enteric-Coated with MA-EA Copolymer in JP XI Disintegration 1st Fluid (pH 1.2)

Applied MA-EA lacquer on a dry basis relative to lactose (%): — - - —, 10; — - - —, 20; — - —, 30; ------, 40; - - - -, 50; ——, 60.

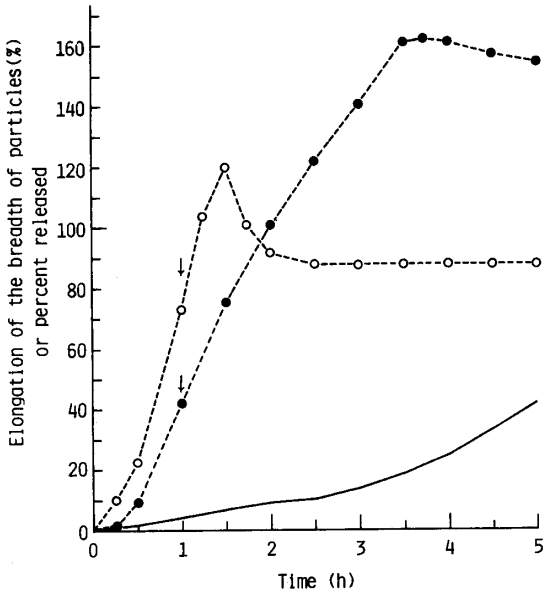

Fig. 9. Expansion of Lactose Microcapsules Undercoated with PVP and Enteric-Coated with 60% MA-EA Copolymer in the JP XI Disintegration 1st Fluid (pH 1.2) at 37 °C and the Corresponding Dissolution Curve

○●, particle expansion (two measurements); ——, dissolution of lactose. The arrow shows the disappearance of lactose crystals.

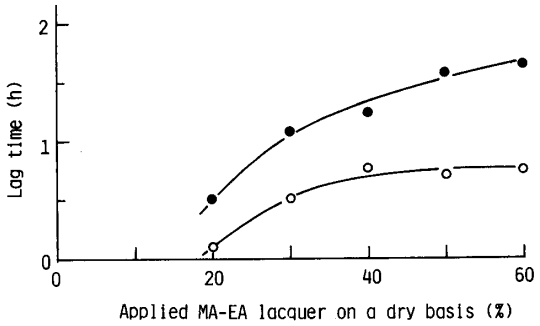

Fig. 10. Lag Time in the Dissolution of Phenacetin from MA-EA Microcapsules

○, phenacetin layered with HPC on lactose (90 μm); ●, phenacetin layered with PVP on lactose (90 μm).

shows that the particles undercoated with PVP were far more expandable than the other kind of particles (Figs. 4 and 6).

Characteristic Parameters of Phenacetin Dissolution

The characteristic parameters of phenacetin release from the microcapsules prepared through layering were the lag time and the release rates after the lag time (Figs. 3a and 5a). Since a suspension of fine phenacetin crystals was formed within the microcapsules after the lag time, the concentration should be saturated, which would result in the zero-order kinetics

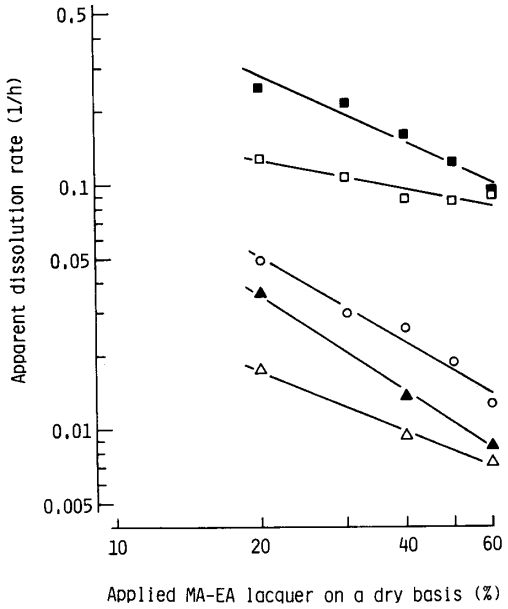

Fig. 11. Apparent Dissolution Rate of Phenacetin from MA-EA Microcapsules

○, directly coated on coarse crystals (128 μm); □, phenacetin layered with HPC on lactose (90 μm); ■, phenacetin layered with PVP on lactose (90 μm); △, undercoated with HPC on coarse crystals (128 μm); ▲, undercoated with PVP on coarse crystals (128 μm).

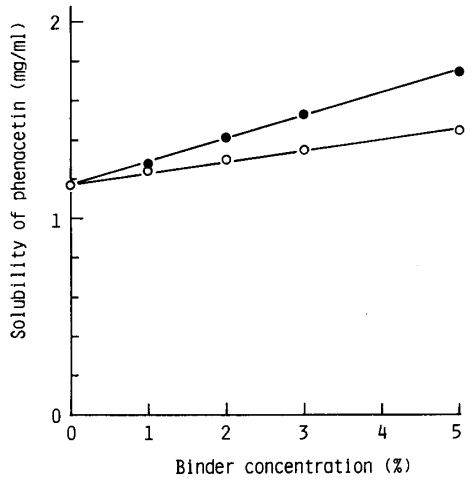

Fig. 12. Effect of Polymer on Phenacetin Solubility in JP XI Disintegration 1st Fluid (pH 1.2) at 37 °C

○, HPC; ●, PVP.

at less than 50% release (Figs. 3a and 5a).

The lag time estimated by linear extrapolation to the abscissa is shown in Fig. 10. PVP prolonged the lag time about twofold. The reason for the nonlinear profiles, different from the case of lactose,[1] is not clear at present.

The calculated dissolution rates for phenacetin are plotted in Fig. 11, compared with those in the case of direct coating previously reported.[1] Clearly, the apparent release rates are markedly increased by layering phenacetin as fine crystals. On the other hand, the microcapsules undercoated with the same amount of HPC or PVP as that used in layering exhibited a significantly lower release rate. These results show that the formation of a suspension of fine crystals in the microcapsules accounted for the enhanced release, and suggest that the phenacetin release from microcapsules prepared with coarse crystals (128 μm) would be rate-limited by the dissolution of phenacetin crystals and restrained by HPC or PVP, which could produce a viscous solution.

Figure 11 also shows that PVP induces faster dissolution than HPC. Sugimoto *et al.*[5] reported that nifedipine exhibited larger solubilities in aqueous PVP solutions than in HPC. The solubilities of phenacetin in the 1st fluid containing HPC or PVP at 37°C are shown in Fig. 12. The difference was not so large as that in the case of nifedipine. If the microcapsules were not expandable, the concentration of HPC or PVP in the microcapsules would be about 12% for a core size of 128 μm. With expanded particles, the concentration would be diluted to 4% for HPC and 1% for PVP. Figure 12 shows that phenacetin has similar solubility in both polymer solutions within microcapsules. Hence, the increase in solubility by PVP could not account for the enhanced release.

Figure 13 shows the viscosities of the 1st fluid containing polymer at 37°C. The viscosities within the microcapsules were estimated to be 13 cP with HPC and 3 cP with PVP. It is possible that the lowered viscosity with PVP would account for the higher release rate (Fig. 11).

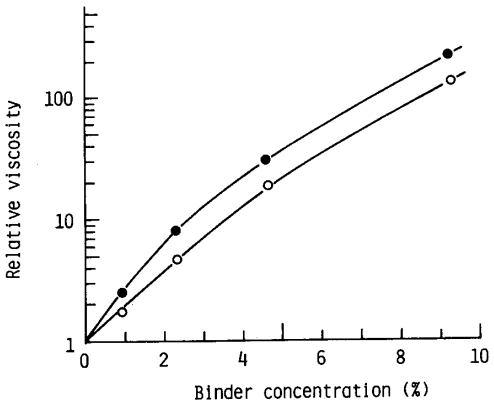

Fig. 13. Viscosity of JP XI Disintegration 1st Fluid (pH 1.2) Containing Polymer at 37 °C

○, HPC; ●, PVP.

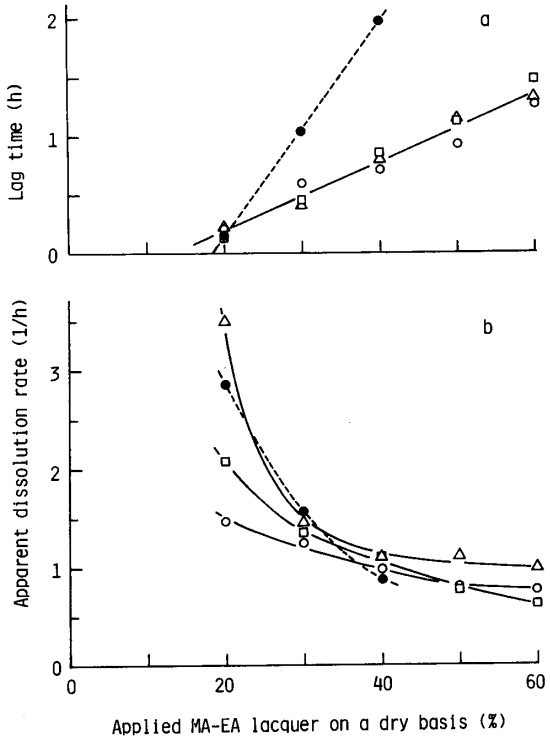

Fig. 14. Lag Time (a) and Apparent Rate (b) of Lactose Release from MA-EA Microcapsules Prepared by Using HPC or PVP

○, directly coated on coarse crystals (120 μm); □, phenacetin layered with HPC on lactose (90 μm); △, undercoated with HPC on coarse crystals (120 μm); ●, undercoated with PVP on coarse crystals (120 μm).

Characteristic Parameters of Lactose Dissolution

The characteristic parameters of lactose dissolution from the microcapsules containing HPC are shown in Fig. 14. The results are identical to those in the case of direct coating of lactose crystals.[1] The difference is in the higher release at low coating levels in the case of the microcapsules prepared through layering or undercoating, presumably resulting from the rough surface of core particles (Fig. 1a) and the agglomeration in the layering and the undercoating process (Fig. 2 and Table III). In particular, a large amount of coating material will be needed for the large inter-particle spaces or pores of agglomerates to be covered. In fact, the microcapsules (168 μm, Table III) prepared through undercoating exhibited a higher release rate at the beginning of coating (Fig. 14b), in spite of the smoothness of the surface of the crystals, than those prepared through layering (158 μm, Table II), which produced a rough surface (Fig. 1a).

The lag time and the apparent release rate after the lag time in the case of PVP, calculated from the data obtained with undercoated microcapsules (Fig. 8), are shown in Fig. 14. At high coating levels, data were not available.

The significant difference between the cases of HPC and PVP is in the lag time (Fig. 14a). It is clear that this is related to the larger expansion of the microcapsules containing PVP (Figs. 4, 6 and 9). PVP might interact with the membrane so as to make it more expandable and stronger.

In the case of microcapsules containing PVP, the release of lactose was remarkably prolonged, especially in those prepared through the layering technique (Figs. 5b and 8). The dissolution data for microcapsules prepared through layering (Fig. 5b) were superimposed

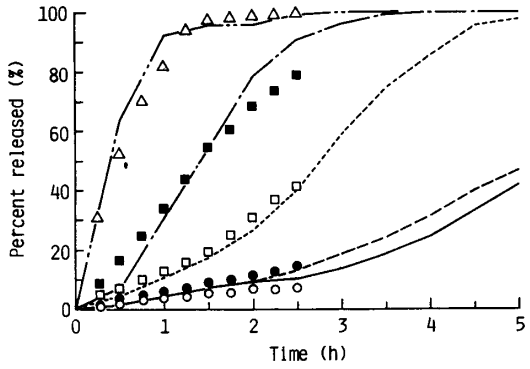

Fig. 15. Superimposition of Lactose Dissolution Curves of MA-EA Microcapsules Prepared by Using PVP

Plots: powder layered phenacetin with PVP on lactose (90 μm). Data were plotted on a half time-scale. Lines: undercoated with PVP on coarse crystals (120 μm).

Applied MA-EA lacquer on a dry basis (%): ——△, 20; —·—■, 30; ------□, 40; ----●, 50; ——○, 60.

with a half time scale on those for undercoated microcapsules (Fig. 8). The results (Fig. 15) agree well with one another. This might be related to the fact that the lactose core (120 μm) used in undercoating had 2.4 times the volume of that (90 μm) used in layering. The above results suggest that the smaller water intake into the microcapsules containing the smaller amount of lactose (Figs. 6 and 9) accounts for the more prolonged lag time.

Conclusion

The Wurster apparatus can process fine powders and, as a result, produce relatively small particles. Fine phenacetin powder with a large specific surface area was successfully enteric-coated after layering it on lactose cores, and particles with the mean diameter of 158—190 μm were produced in this study. This size would not be the smallest possible in the Wurster process. The produced particles were very sensitive to the aqueous medium due to their small size, their thin membrane and the fineness of the raw materials.

PVP used in the layering process induced a large particle expansion by take-up of water. The expansion diluted the PVP solution within the microcapsules to produce a fine phenacetin suspension with a low viscosity. Thus, the release of components was restrained by water influx druing more than 2 h and thereafter the components were rapidly released. The detailed mechanism of the effects of PVP is not clear at present. However, the results showed that when PVP was used as the binder, the enteric coating through the layering process was sufficiently protective against the release of both sparingly and readily water-soluble drugs.

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