Available online at www.sciencedirect.com
SCIENCE DIRECT
International Journal of Pharmaceutics 307 (2006) 300–307
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Short-term delayed-release microcapsules spraycoated with acrylic terpolymers

Dongchun Liu [a,b], Hideki Ichikawa [a], Fude Cui [b], Yoshinobu Fukumori [a,*]

[a] *Faculty of Pharmaceutical Sciences and Life Science Center for Cooperative Research, Kobe Gakuin University, Arise 518, Ikawadani-cho, Nishi-ku, Kobe 651-2180, Japan*
[b] *Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, Wenhua-road 103, Shenhe, Shenyang 110016, China*

Received 23 May 2005; received in revised form 20 September 2005; accepted 18 October 2005
Available online 23 November 2005

Abstract

A series of poly(ethyl acrylate (EA)/methyl methacrylate (MMA)/2-hydroxyethyl methacrylate (HEMA)) lattices were synthesized to prepare short-term delayed-release microcapsules by employing the Wurster coating process. Latex with a HEMA molar fraction exceeding 60% could not be synthesized as an aqueous suspension due to latex particle precipitation. The effects of monomer composition on the particle size of latex and the water-uptake and glass transition temperature (T_g) of cast films were investigated. Lattices whose T_g ranged from 40 to 80 °C were used to prepare the microcapsules. Most of the lattices exhibited excellent process performance while coating particles that were smaller than 100 μm: the product yields were 85.1–90.6% and the mean particle sizes were 82–85 μm. However, since the lattices with high molar ratios of EA and HEMA were highly hydrophilic and strongly adhesive, the core particles in the coating were severely agglomerated. The microcapsules coated with lattices whose HEMA molar fractions were higher than 50% were unable to retard the release of carbazochrome sodium sulfonate, a water-soluble model drug, during the initial 0.5 min. Poly(EA/MMA/HEMA) with a molar ratio of 9:9:10 appeared to be suitable for the preparation of short-term delayed-release microcapsules by the Wurster coating process.

Keywords: Microcapsule; Controlled release; Acrylic polymer; Latex; Fluidized bed; Coating

1. Introduction

Due to the pioneering works by Pechmann and Röhm in the late 1930s, the industrial use of acrylic polymers has gained popularity (Diggen et al., 1997). Acrylic polymers can be synthesized using different combinations of monomers to achieve distinctive properties. The acrylic polymers such as Eudragit® and Carbopol® are currently being used worldwide in the pharmaceutical industry to control drug release, repel moisture, and develop special drug delivery systems.

Fukumori et al. (1988) and Ichikawa et al. (1993, 1994) developed poly(ethyl acrylate (EA)/methyl methacrylate (MMA)/2-hydroxyethyl methacrylate (HEMA)) lattices to coat fine particles by using a fluidized bed (the Wurster process) in order to produce controlled-release microcapsules with an average size smaller than 100 μm. Generally, the monomeric units of methacrylic derivatives contribute to the rigid, hard, and brittle nature of the polymers, while those of the acrylic derivatives contribute to their softness and flexibility (Diggen et al., 1997). The introduction of HEMA, which is a freely water-soluble monomer, into the polymers enhanced the water permeability of cast films due to the hydroxyl part of HEMA (Fukumori, 1994). By using poly(EA/MMA/HEMA) as the coating materials, even particles as fine as 32–44 μm could be discretely coated with a slight agglomeration of the core particles. Such small-sized microcapsules would be highly advantageous in the preparation of special formulations such as suspensions, rapidly disintegrating tablets that do not cause a gritty sensation during their administration (Shah and Chafetz, 1994; Shen, 1996; Ichikawa et al., 1997), and drug-targeting delivery systems (Kumar, 2000; Dai et al., 2005).

In this paper, we aimed to utilize the advantages of poly(EA/MMA/HEMA) in fine particle coating technology to produce fine microcapsules with short-term delayed-release

* Corresponding author. Tel.: + 81 78 974 4542; fax: +81 78 974 4542.
E-mail address: fukumori@pharm.kobegakuin.ac.jp (Y. Fukumori).

0378-5173/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2005.10.020

characteristics by employing the Wurster process. The mean diameter of the microcapsules was required to be smaller than 100 μm and the drug release was required to be as slow as possible in the initial short time (0.5 min) and as fast as possible after the short delay. These microcapsules could have potential applications in the formulations to mask any unpleasant taste. We synthesized a series of hydrophilic poly(EA/MMA/HEMA) lattices and investigated the characteristics of polymers including the latex particle size and the water-uptake and glass transition temperature (T_g) of the polymer films, which would affect the coating operation and drug release from the microcapsules. Carbazochrome sodium sulfonate (CCSS), a highly water-soluble drug, was selected as the model drug.

2. Materials and methods

2.1. Materials

The monomers, ethyl acrylate (EA), methyl methacrylate (MMA), and 2-hydroxyethyl methacrylate (HEMA), were used as purchased (Nakarai Tesque, Japan). Sodium dodecyl sulfate (SDS; Wako Junyaku, Japan) and ammonium peroxodisulfate (APS; Nakarai Tesque, Japan) were used as an emulsifier and a reaction initiator, respectively, in emulsion polymerization.

Lactose (DMV 200) was used as the core material after it was fractionated to 63–75 μm particles by sieving. CCSS (Kanebo Ltd., Japan) was selected as a water-soluble model drug. Methylcellulose (Metolose; SM-4, Shinetsu Chemical Co. Ltd., Japan) was selected as a binder for drug layering. Anhydrous silica (Aerosil 200; Nippon Aerosil Co. Ltd., Japan) was used as a sieving aid for particle size analysis and as an antiadherent for curing the microcapsules by heating. All the materials were used as purchased or supplied without any purification.

2.2. Synthesis of lattices

The acrylic polymer lattices were synthesized by emulsion polymerization as previously reported by Fukumori et al. (1988). A monomer mixture of 100 g was used for each polymerization reaction. A part – 34.6 g – of the monomer mixture was poured into distilled water (300 g) containing SDS (0.92 g) and emulsified using a homomixer (4C; Tokushu Kika Kogyo Co. Ltd., Japan). The emulsion was maintained at 80 °C in the presence of nitrogen gas, and 0.25 ml of the APS solution (1 g/25 ml) was introduced to initiate the polymerization. The remainder of the monomer mixture was slowly dropped into the reactor over a period of 1 h. The reaction was continued further for 2 h. During the 3 h reaction, 0.25 ml of APS was added every 30 min. After the reaction was completed, the latex was filtered through a stainless steel sieve (53 μm). The precipitates of latex particles on the sieve were collected and dried for 24–48 h at 80 °C and then for 3 h at 120 °C. The dried precipitates of the latex particles were accurately weighed to evaluate the production loss. The formulations of the synthesized lattices are listed in Table 1.

In order to remove the residual monomers and water-soluble impurities, all the lattices prepared were dialyzed in distilled water for 5 days using a cellulose tube (UC 1-7/8; Sanko Junyaku Co. Ltd., Japan). The water was replaced with fresh water at 12 h intervals.

Table 1
Synthesis and characteristics of poly(EA/MMA/HEMA) lattices

Batch no.	Polymeric latex composition				Loss as precipitates (w/w, %)	Particle size (μm)	T_g (°C)
	EA:MMA:HEMA (molar ratio)	X_1[a]	X_2[a]	X_3[a]			
1	6:12:10	0.214	0.429	0.357	1.34	0.0684	81.44
2	6:12:14	0.188	0.375	0.438	1.77	0.0839	85.86
3	6:12:18	0.167	0.333	0.500	1.00	0.1631	89.01
4	6:12:22	0.150	0.300	0.550	1.82	0.2028	90.11
5	6:12:27	0.133	0.267	0.600	5.97	0.2571	92.06
6	9:9:10	0.321	0.321	0.357	1.43	0.0834	64.91
7	9:914	0.281	0.281	0.438	0.97	0.1417	69.86
8	9:9:18	0.250	0.250	0.500	1.43	0.2761	76.25
9	9:9:22	0.225	0.225	0.550	2.07	0.2896	81.52
10	10.8:7.2:10	0.386	0.257	0.357	0.63	0.0780	49.57
11	10.8:7.2:14	0.338	0.225	0.438	0.83	0.0835	57.50
12	10.8:7.2:18	0.300	0.200	0.500	2.11	0.3083	68.40
13	10.8:7.2:22	0.270	0.180	0.550	2.50	0.3109	72.87
14	12:6:10	0.429	0.214	0.357	1.60	0.0891	41.47
15	12:6:14	0.375	0.188	0.438	0.86	0.1084	50.92
16	12:6:18	0.333	0.167	0.500	1.30	0.2009	64.01
17	12:6:22	0.300	0.150	0.550	2.53	0.2697	71.23
18	14:4:10	0.500	0.143	0.357	1.84	0.0864	33.50
19	14:4:14	0.438	0.125	0.438	0.85	0.1248	42.98
20	14:4:18	0.389	0.111	0.500	1.13	0.2163	53.29
21	14:4:22	0.350	0.100	0.550	1.89	0.2256	60.69
22	14:4:27	0.311	0.089	0.600	3.23	0.2831	66.10

[a] X_1, X_2, and X_3 represent the molar fractions of EA, MMA, and HEMA in the latex composition, respectively; $X_1 + X_2 + X_3 = 1$.

2.3. Latex particle size analysis

The mean particle diameter of the latex particles was measured at 25 °C using a Horiba LB-500 dynamic light scattering particle size analyzer (Horiba, Japan).

2.4. Preparation of polymer films

Approximately 3 g of the polymer latex suspensions (10%, w/w) were poured in a shallow dish (2.5 cm × 2.5 cm) and heated at 80 °C in an oven for 48 h to form transparent films. Prior to the water-uptake study, the films were cut into 2 cm × 1 cm strips and stored in a desiccator at 75% RH at 25 °C or in a vacuum desiccator for 3 weeks for measuring T_g.

2.5. Glass transition temperature (T_g) of polymers

We used a differential scanning calorimeter (DSC-50; Shimadzu, Japan) equipped with a refrigerated cooling accessory and thermal analysis data station. A 7–10 mg sample stored in the vacuum desiccator prior to the analysis was hermetically sealed in an aluminum pan. The samples were preheated up to 140 °C under dry nitrogen purge at 20 °C/min and rapidly cooled to approximately 0 °C using liquid nitrogen. They were reheated to 140 °C at 5 °C/min using an empty aluminum pan for reference. The value of T_g was determined from the resulting thermograms as the median point between the onset and endpoint temperature during the shift in the apparent specific heat due to the glass transition.

2.6. Water-uptake study

Water-uptake studies were performed by employing the equilibrium weight gain method. The film strips were accurately weighed and soaked in distilled water at 25 °C. The films were blotted with tissue paper to remove excess water, and reweighed at predetermined intervals (1, 3, 5, 10, 15, 20, 30, and 60 min) in triplicate measurements. The percentage of water uptake was calculated using Eq. (1):

$$\text{water uptake}\,(\%) = (W_t - W_0)/W_0 \times 100 \quad (1)$$

where W_0 represents the initial weight and W_t represents the weight of the film at time t.

2.7. Preparation of microcapsules

A fluidized bed coater with a draft tube (Wurster insert; Grow Max 140, Fuji Paudal Co. Ltd., Japan) was used. The processing parameters were: batch size, 25 g; inlet air temperature, 40–60 °C; outlet air temperature, 29–33 °C; air flow rate, 0.07–0.25 m^3/min; spray rate, 0.7–2.0 ml/min; atomizing air pressure, 2.3 bar; and spray nozzle diameter, 1.0 mm. The detailed formulations, operating conditions, and coating performance for typical cases are listed in Table 2.

2.8. Particle size distribution of microcapsules

A sieve analysis was performed using a row-tap shaker (Iida Seisakusho Co. Ltd., Japan). Twenty grams of the sam-

Table 2
Typical formulations, operating conditions, and performance during the preparation of the CCSS microcapsules

	Drug layering	Coatings (EA:MMA:HEMA)								
		6:12:10	6:12:14	9:9:10	9:9:14	9:9:18	9:9:22	10.8:7.2:10	12:6:14	12:6:22
Formulation										
Core: lactose (63–75 μm) (g)	250	25[a]	25[a]	25[a]	25[a]	25[a]	25[a]	25[a]	25[a]	25[a]
Carbazochrome sodium sulfonate (g)	25									
Methylcellulose (SM-4) (g)	5									
Latex suspension (dry weight) (g)		12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Water	ad	ad	ad	ad	ad	ad	ad	ad	ad	ad
Total (ml)	300	125	125	125	125	125	125	125	125	125
Operating conditions										
Inlet air temperature (°C)	60	60	60	50	60	60	60	40	40	50
Outlet air temperature (°C)	33	30	31	30	32	29	29	30	29	29
Inlet air flow rate (m^3/min)	0.07	0.14	0.14	0.12	0.18	0.25	0.25	0.29	0.25	0.29
Liquid flow rate (ml/min)	1.5–2.0	0.8–1.3	0.8–1.2	0.8–1.2	0.7–1.0	0.7–1.2	0.7–1.2	0.7–0.9	0.7–0.9	0.7–0.9
Spray air flow rate (l/min)	51	50	51	51	50	59	59	60	59	59
Spray pressure (atm)	2.3	2.3	2.3	2.3	2.3	2.9	2.9	2.9	2.9	2.9
Products										
Yield (%)	93.3	88.7	89.8	90.6	90.1	88.5	85.1	86.8	86.5	87.3
D_{50} (μm)[b]	78	82	84	82	83	82	82	85	85	86
D_{90} (μm)[b]	88	96	99	97	101	98	92	118	126	123
D_{10} (μm)[b]	60	69	75	68	72	67	68	69	67	68

[a] A fraction of 63–90 μm was obtained by sieving two batches of the drug-layered particles.
[b] D_{10}, D_{50}, and D_{90} represent the particle sizes at 10%, 50%, and 90%, respectively, in the cumulative undersize distribution.

ple was premixed with 0.5% anhydrous silica and then shaken for 10 min.

2.9. In vitro drug release studies

The in vitro drug release in 900 ml of 0.1 mol/l HCl was determined by the JP XIV rotating paddle method at 100 rpm and 37 °C, using a Toyama dissolution tester (NTRVS6P; Toyama-Sangyo Co. Ltd., Japan). After the microcapsules were dried for 12 h in the vacuum desiccator at room temperature, they were mixed with 2% (w/w) anhydrous silica and further heated for curing in an air stream oven for 12 h at T_g of the coated poly(EA/MMA/HEMA). The microcapsules containing approximately 9 mg of CCSS were accurately weighed and placed in the dissolution test flask. Ten milliliters of the solution was withdrawn, and an equal volume of fresh medium was immediately added at predetermined time intervals (0.5, 1, 5, 15, 30, and 60 min). The samples filtered through a 0.22 μm filter (Micro Filter; FM-22, Fuji Photo Film Co. Ltd., Japan) were assayed spectrophotometrically at 363 nm (Shimadzu UV-190, Japan).

3. Results and discussion

3.1. Effect of HEMA on size and precipitation of latex particles

The composition of the latex polymers was assumed to affect the size and stability of the latex suspensions. For the present polymers, the introduction of hydrophilic HEMA could possibly lead to the swelling of latex particles. In fact, the particle size of the lattices increased with the ratio of HEMA (Table 1 and Fig. 1). Increased precipitation of the latex particles was also observed with an increase in the ratio of HEMA, as shown in Fig. 1. When the molar fraction of HEMA exceeded 60%, polymeric latex could not be produced successfully due to the precipitation of latex.

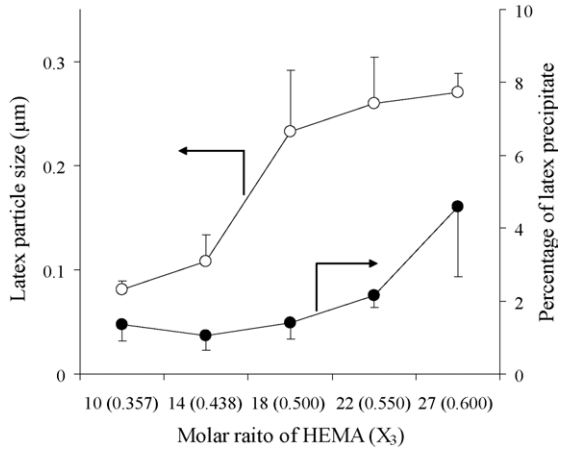

Fig. 1. Effect of HEMA on the particle size and percentage of the precipitate for the 6:12:*x* poly(EA/MMA/HEMA) lattices. Data represent mean ± standard deviation ($n = 3$).

Table 3
Statistical analysis of a second-order polynomial model for T_g

Coefficient	Estimated value	*P*
b_1	−52.00	<0.0001[a]
b_2	108.12	<0.0001[a]
b_3	122.69	<0.0001[a]
b_{12}	6.24	0.9275
b_{13}	86.82	0.2890
b_{23}	−50.01	0.5642

[a] Statistically significant when $P < 0.05$.

3.2. Glass transition temperature (T_g)

T_g is an extremely important factor in the coating process because it is closely related to film formation and core-particle agglomeration (Nakagami et al., 1991). In this study, T_g of the cast films of poly(EA/MMA/HEMA) was measured, and the relationship between T_g and the polymer composition was investigated by fitting the data to a statistical model. For data fitting, a second-order polynomial equation was adopted, although the traditional full linear model could not be predicted entirely due to a large number of terms. Scheffé (1958) recommended to (a) suppress the intercept, (b) include all the linear main-effect terms, (c) exclude all the square terms (such as X_1X_1), and (d) include all the cross terms (such as X_1X_2). Therefore, the model was expressed by the following equation:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 \quad (2)$$

where Y, X_1, X_2, and X_3 represent T_g (°C) and the molar fractions of EA, MMA, and HEMA respectively and b_1–b_{23} are the coefficients of the respective variables and their interaction parameters. The results of the statistical analysis are usually considered significant when their P values are less than 0.05.The statistical data were fitted to the model by using JMP® v5.0 statistical software (SAS Institute Inc.). Using the analysis results listed in Table 3, the model describing T_g of polymers can be written as follows:

$$Y = -52.00X_1 + 108.12X_2 + 122.69X_3 \quad (3)$$

In this model, $P < 0.0001$. The negative sign for the coefficient of X_1 (EA) indicated this factor reduced T_g, while both MMA and HEMA increased T_g due to the positive coefficients of X_2 (MMA) and X_3 (HEMA).

The estimated response surfaces of T_g are shown in Fig. 2. The T_g of the polymers whose molar fractions of EA were identical in the range from 0.133 to 0.500 was approximately equal, irrespective of the variation in the ratio of MMA/HEMA between 12/10 and 4/27 (Table 1). This indicated that the ability of MMA and HEMA to contribute to the T_g of the polymers was almost the same.

3.3. Water-uptake of polymers

The hydration or water-absorption behavior of the polymeric film coated on pellets or tablets plays an important role dur-

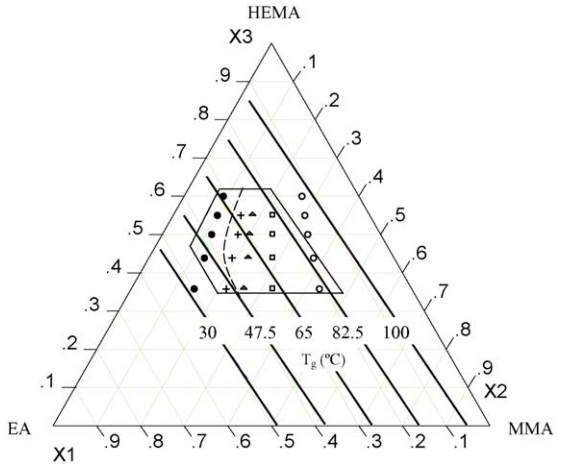

Fig. 2. Composition of the synthesized lattices and response surface of T_g in the ternary diagram. EA:MMA:HEMA (●) 14:4:10, 14, 18, 22, 27; (+) 12:6:10, 14, 18, 22; (▲) 10.8:7.2:10, 14, 18, 22; (□) 9:9:10, 14, 18, 22; (◯) 6:12:10, 14, 18, 22, 27. The pentagon represents the region in which the coating operation can proceed smoothly. Refer to text for details.

ing the initial stage of drug release in the solid dosage forms (Golomb and Rahamim, 1990). Therefore, we investigated the water absorption behavior of the series of 6:12:*x* and 14:4:*x* poly(EA/MMA/HEMA) films as typical examples. The results shown in Fig. 3 demonstrated that with an increase in the ratio of HEMA, the water absorption of the polymers was quicker due to the hydrophilic character of HEMA. However, at the same ratio of HEMA, water absorption of the polymers with 14:4:*x* was quicker than that with 6:12:*x*. As shown in Fig. 2, an increase in the ratio of EA resulted in a decrease in T_g, which made the polymer soft and flexible. The intermolecular aggregation force in the soft and flexible polymers was weaker than that in the rigid and brittle ones (Salomon, 1970). The soft polymers required lesser energy for swelling as compared to the rigid ones. Consequently, the swelling proceeded more smoothly, resulting in faster water uptake. Other researchers have also observed that not only hydrophilic but also hydrophobic plasticizers could

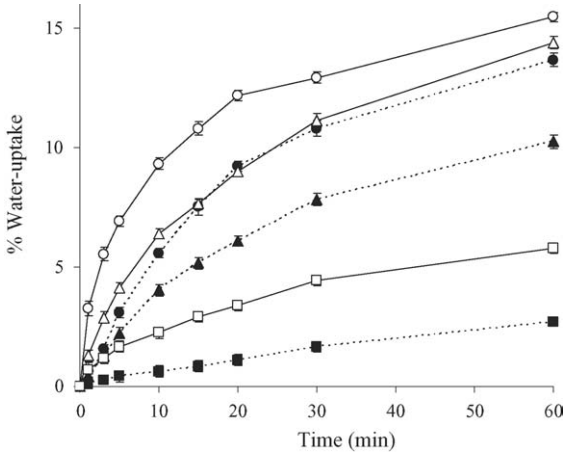

Fig. 3. Water uptake of poly(EA/MMA/HEMA) at 25 °C. EA:MMA:HEMA (◯) 14:4:27; (△) 14:4:22; (□) 14:4:10; (●) 6:12:27; (▲) 6:12:22; (■) 6:12:10. Data represent mean ± standard deviation (n = 3).

enhance the water uptake of hydrophilic acrylic polymers (Lee et al., 2000). This suggested that the softening of polymers might enhance water absorption.

3.4. Preparation of microcapsules

The formulations of the microcapsules and operating conditions of Grow Max (140) fluidized bed coater are listed in Table 2. In order to increase the drug release rate, highly water-soluble lactose was selected as the core material. It was expected that the lactose core would quickly introduce water into the microcapsules and the induced osmotic pressure could act as a driving force to release the drug rapidly. CCSS, which is the model drug, is yellow-colored and non-hygroscopic. It is highly soluble in water and can remain stable at 80 °C for 12 h. Thus, it is an ideal model drug for evaluating the performance of the Wurster process. In this study, water-soluble methylcellulose whose viscosity was very low was selected as a binder for drug layering. The high yields listed in Table 2 indicated that the drug adhered well onto the cores. D_{90} of the drug-layered particles was 88 μm, which indicated that the agglomeration was suppressed successfully. A fraction of the sieved particles with sizes ranging from 63 to 90 μm was used to study the subsequent coating process.

In order to coat the fine particles using aqueous polymeric lattices, T_g of the latex polymers was required to be neither too high nor too low. This is because when T_g was too high ($T_g > 80$ °C), post-curing had to be performed at high temperatures above T_g for completing the film formation thereby leading to possible causing chemical changes in the drugs. In contrast, when T_g was too low ($T_g < 40$ °C), low inlet air temperature had to be used in order to avoid the core-particle agglomeration caused by the softening of the polymeric membranes. This operation at low temperatures required a low spray liquid flow rate to avoid the wet agglomeration of the core particles due to the suppressed water evaporation, which led to a long operation time (Ichikawa et al., 1993). Thus, the lattices with T_g ranging approximately from 40 to 80 °C (enclosed within the pentagon in Fig. 2) were selected as candidates for the coating.

In the present coating system, it was very difficult to use the 14:4:*x* (x = 10–27) series of lattices to coat the fine particles. At coating levels above 20%, the coating operations were not continued because most coated particles adhered to the Wurster insert column and chamber wall. This might be due to the low T_g and high hydrophilicity of the polymers that have a high molar ratio of EA and HEMA. Several reports had indicated that the absorbed water in the polymers decreased T_g since water is a potent plasticizer (Nakagami et al., 1991; Hancock and Zografi, 1994). Although T_g of the dry polymers was higher than the inlet air temperature during the coating process, moisture absorbed by HEMA in the polymers (Fig. 3) decreased T_g, which resulted in the softening of the polymers. This would cause severe agglomeration of the coated particles and thus failure of the coating. Since the wet-agglomeration in the coating chamber could not be avoided by increasing the inlet air temperature due to the low T_g, it was attempted to increase the inlet air flow rate. However, the high inlet air flow rate ruined the steady fluidization pattern

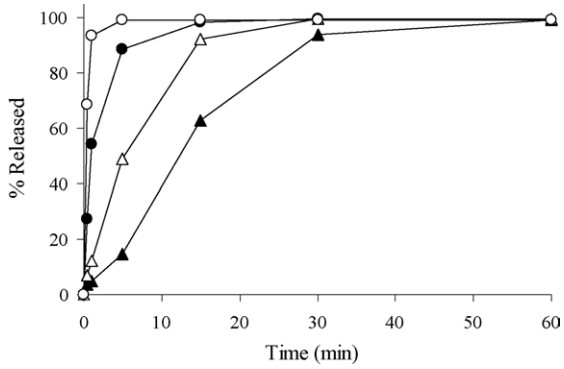

Fig. 4. Effect of HEMA on the release of CCSS from the microcapsules that were 50% coated with poly(EA/MMA/HEMA) in 0.1 mol/l HCl solution. EA:MMA:HEMA (◯) 9:9:22; (●) 9:9:18; (△) 9:9:14; (▲) 9:9:10. Curing: for 12 h at T_g.

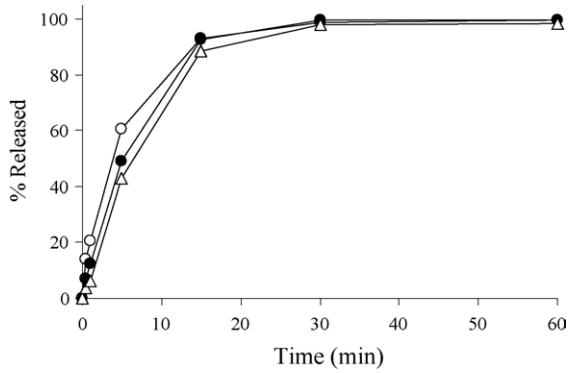

Fig. 5. Effect of EA/MA ratio on the release of CCSS from the microcapsules that were 50% coated with poly(EA/MMA/HEMA) in 0.1 mol/l HCl solution. EA:MMA:HEMA (◯) 12:6:14; (●) 9:9:14; (△) 6:12:14. Curing: for 12 h at T_g.

of the particles because the fine particles were blown toward the bag filter. This resulted in a low coating efficiency and low yield of the product.

For the 12:6:*x* (*x* = 10–22) and 10.8:7.2:*x* (*x* = 10–22) series of lattices, the attempt to coat using the 12:6:10 latex failed for the same reason as that for the 14:4:*x* series. Although the attempt to coat using the 12:6:14, 12:6:22, 10.8:7.2:10 lattices succeeded, approximately 15–20% agglomerates were produced. The fine particle coating with the 9:9:*x* (*x* = 10–22) and 6:12:*x* (*x* = 10–27) series lattices yielded satisfactory results. The yield was 85.1–90.6% with the mean particle sizes of 82–85 μm (Table 2), and the agglomerate fractions of the microcapsules were less than 10%. Thus, the lattices that could be used to coat fine particles are shown on the right of the dashed line in the pentagon in Fig. 2.

3.5. In vitro drug release studies

The effect of HEMA on the release of CCSS from the microcapsules that were 50% coated with poly(EA/MMA/HEMA) using a 0.1 mol/l HCl solution is shown in Fig. 4. The polymeric membrane with a higher molar ratio of HEMA exhibited a faster release of CCSS. This was because the introduction of HEMA with a hydrophilic hydroxyl group enhanced the water permeation through the membrane. In the case of 9:9:22 latex, CCSS was released almost completely from the microcapsules within 5 min only. Microscopic observations revealed that the microcapsules coated with 9:9:22 poly(EA/MMA/HEMA) still had complete films after the 1 h dissolution test. This implied that even when the polymeric membrane comprised 55% (22/40) HEMA, the polymer film of 9:9:22 could not be disaggregated in the dissolution fluid, while the water-soluble drug easily permeated through this polymeric membrane. In contrast, the dissolution profile of CCSS in the microcapsules that were 50% coated with the 9:9:10 polymer exhibited a marked suppression at the initial stage, approximately 3.7% and 4.9% at 0.5 and 1 min, respectively. After the short delay, rapid release of CCSS was observed: drug release exceeded 90% in 30 min. Evidently, osmotic pressure produced by the dissolved lactose could rapidly and thoroughly release the dissolved CCSS. Previous studies by Ichikawa et al. (1996) indicated that the dissolved lactose core caused the microcapsules to expand and even rupture. However, in the present study, the microcapsules films remained intact after the 1 h dissolution test. This might be due to the much higher water and lactose permeability of the present membranes.

Fig. 5 shows the effect of the molar ratio of EA/MMA on the release of CCSS from the microcapsules that were 50% coated with poly(EA/MMA/HEMA) using 0.1 mol/l HCl solution. The membranes of these microcapsules were composed of equal ratios of HEMA (water permeable part). CCSS was released more rapidly from the microcapsules whose EA/MMA ratios were higher. The water-uptake study (Fig. 3) revealed that among the poly(EA/MMA/HEMA)s of the same ratio of HEMA, a lower value of T_g (higher ratio of EA/MMA) led to a faster absorption of water. Therefore, the membranes with a higher ratio of EA/MMA at an equal molar ratio of HEMA became more water permeable, thereby causing a rapid release of CCSS from the microcapsules.

As a typical example, the effect of the coating level on the release of CCSS from the microcapsules with the 9:9:10 polymer in the 0.1 mol/l HCl solution is shown in Fig. 6. For the cases of 20% and 30% coating levels, an initial burst release was observed due to the presence of incompletely coated microcapsules. As the coating level reached 40%, CCSS released initially in 0.5 min was successfully suppressed to less than 5%. As the coating level

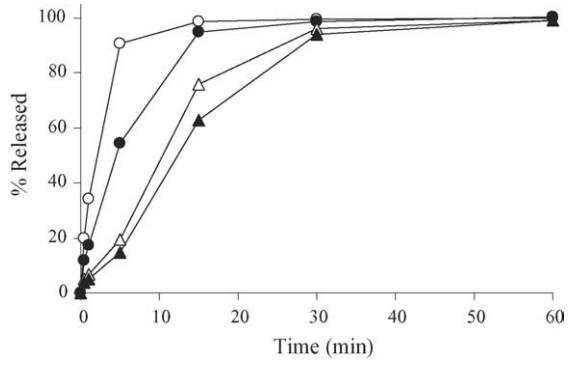

Fig. 6. Effect of coating level on the release of CCSS from the microcapsules that were coated with 9:9:10 poly(EA/MMA/HEMA) in 0.1 mol/l HCl solution. Coating level: (◯) 20%; (●) 30%; (△) 40%; (▲) 50%. Curing: for 12 h at T_g.

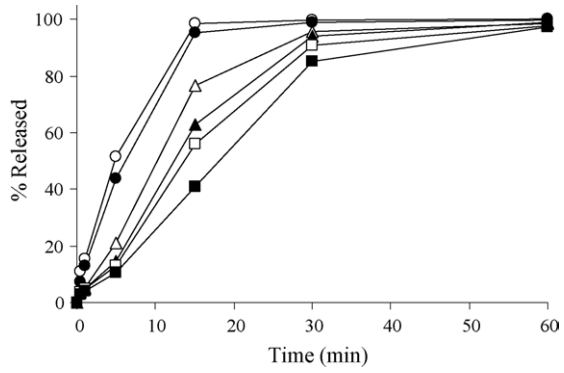

Fig. 7. Effect of curing temperatures on the release of CCSS from the microcapsules that were 50% coated with 9:9:10 poly(EA/MMA/HEMA) in 0.1 mol/l HCl solution. Curing temperature: (◯) uncured; (●) 50°C; (△) 60°C; (▲) 65°C; (□) 70°C; (■) 80°C. Curing time: 12 h.

increased further from 40% to 50%, there was no significant change in the initial drug release rate at 0.5. Although the drug release rate decreased after 5 min, CCSS was almost completely released after 30 min.

The microcapsules that were 50% coated with the 9:9:10 poly(EA/MMA/HEMA) were evaluated for the effect of the curing temperature on the drug release in the 0.1 mol/l HCl solution (Fig. 7). While approximately 15.4% CCSS was released from the uncured microcapsules after 1 min, its release was effectively suppressed in those cured at 65 °C or higher temperatures. The result was in good correspondence with the fact that T_g of the 9:9:10 polymer was 64.9 °C in Table 1.

The initial drug release in 0.5 min from the microcapsules with the 9:9:10 polymer cured at 65 °C for 12 h was 4.1% (Fig. 7). Such a small amount of initial burst release could sometimes result in the failure of taste masking. It was evident from the present studies that this burst resulted from the separation of a small amount of particles from the steady fluidization flow. Although these particles accounted for 4.1% of the total composition in the present operation at an extremely low charging rate of the particles in the processor, this would not pose a serious problem in normal operations.

4. Conclusions

A series of poly(EA/MMA/HEMA) lattices was synthesized in order to prepare short-term delayed-release microcapsules by employing the Wurster coating process. The mean particle sizes of latex increased with the HEMA ratio in the composition of the lattices. When the molar ratio of HEMA exceeded 60%, polymeric latex could not be synthesized due to solid mass precipitation. T_g of latex decreased with an increase in the EA content, whereas it was almost independent of the ratio of MMA to HEMA.

The coating was performed with the synthesized polymers at T_g ranging from 40 to 80 °C. The higher the fraction of HEMA in the composition of the polymeric membrane, the faster the CCSS release from the microcapsules. The microcapsules coated with latex whose HEMA molar fraction was higher than 50% in the composition could not retard the CCSS release during the initial 0.5 min. For the polymers whose ratios of HEMA were the same, those with lower T_g absorbed water faster, thereby resulting in a slightly faster drug release during the initial stage.

The microcapsules that were 40–50% coated with the 9:9:10 poly(EA/MMA/HEMA) latex were found to be a candidate for the short-term delayed-release dosage forms. They could be synthesized with an excellent process performance such as less than 10% agglomerates, 91% yield, and 82 μm mean particle size. Further studies are being conducted to mask the unpleasant taste of water-soluble drugs in fine particle dosage form by using poly(EA/MMA/HEMA).

Acknowledgements

This study was partially supported by the Nippon Foundation and a Grant-in-Aid for Science Research (C) (16590038) from the Japan Society for the Promotion of Science. Further, the authors also wish to thank Professor Keiji Yamamoto of the Graduate School of Pharmaceutical Sciences, Chiba University, for providing technical support during this work.

References

Diggen, M., Durrani, M., Lehmann, K., 1997. Acrylic polymers A review of pharmaceutical applications. S.T.P. Pharm. Sci. 7, 403–437.

Dai, C., Wang, B., Zhao, H., 2005. Microencapsulation peptide and protein drugs delivery system. Colloids Surf. B: Biointerf. 41, 117–120.

Fukumori, Y., Yamaoka, Y., Ichikawa, H., Takeuchi, T., Fukuda, T., Kanamori, R., 1988. Coating of pharmaceutical powders by fluidized bed process. III. Aqueous coating with ethyl acrylate-methyl methacrylate-2-hydroxyethyl methacrylate copolymer and the dissolution properties of the products. Chem. Pharm. Bull. 36, 3070–3078.

Fukumori, Y., 1994. Coating of multiparticulate using polymeric dispersion. In: Ghebre-Sellassie, I. (Ed.), Multiparticulate Oral Drug Delivery. Marcel Dekker Inc., New York, pp. 79–117.

Golomb, G., Rahamim, P.F., 1990. The relationship between drug release rate, particle size and swelling of silicon matrices. J. Contr. Release 12, 121–132.

Hancock, B.C., Zografi, G., 1994. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. Pharm. Res. 11, 471–477.

Ichikawa, H., Jono, K., Tokumitsu, H., Fukuda, T., Fukumori, Y., 1993. Coating of pharmaceutical powders by fluidized bed process. V. Agglomeration and efficiency in the coating with aqueous lattices of copoly(ethyl acrylate-methyl methacrylate-2-hydroxyethyl methacrylate). Chem. Pharm. Bull. 41, 1132–1136.

Ichikawa, H., Tokumitsu, H., Jono, K., Fukuda, T., Osako, Y., Fukumori, Y., 1994. Coating of pharmaceutical powders by fluidized bed process. VI. Microencapculation using blend an composite lattices of copoly(ethyl acrylate-methyl methacrylate-2-hydroxyethyl methacrylate). Chem. Pharm. Bull. 42, 1308–1314.

Ichikawa, H., Kaneko, S., Fukumori, Y., 1996. Coating performance of aqueous composite lattices with *N*-isopropy-lacrylamide shell and thermosensitive permeation properties of their microcapsule membranes. Chem. Pharm. Bull. 44, 383–391.

Ichikawa, H., Fukumori, Y., Adeyeye, C.M., 1997. Design of prolonged-release microcapsules containing diclofenac sodium for oral suspensions and their preparation by the Wurster process. Int. J. Pharm. 156, 39–48.

Kumar, M.N.V.R., 2000. Nano and microparticles as controlled drug delivery devices. J. Pharm. Pharm. Sci. 3, 234–258.

Lee, S.-Y., Chen, K.-S., Liang, R.-C., 2000. Organic esters of plasticizers affecting the water absorption, adhesive property, glass transition temperature and plasticizer permanence of Eudragit acrylic films. J. Contr. Release 68, 343–350.

Nakagami, H., Keshikawa, T., Matsumara, M., Tsukamoto, H., 1991. Application of aqueous suspensions and latex dispersions of water insoluble polymer for tablet and granule coating. Chem. Pharm. Bull. 39, 1837–1842.

Salomon, G., 1970. Adhesion. In: Houwin, R., Salomon, G. (Eds.), Adhesion and Adhesives, vol. I. Elsevier Publishers, New York, pp. 1–140.

Scheffé, H., 1958. Experiments with mixtures. J. Roy. Statist. Soc. B 20, 344–360.

Shah, K.P., Chafetz, L., 1994. Use of sparingly soluble salts to prepare oral sustained release suspensions. Int. J. Pharm. 109, 271–281.

Shen, R.W., 1996. Taste masking of ibuprofen by fluid bed coating. US Patent 5 552 152.