Optimization of Salting-Out Taste-Masking System for Micro-Beads Containing Drugs with High Solubility

Takayuki YOSHIDA,*[,a] Hiroaki TASAKI,[a] Atsushi MAEDA,[a] Masataka KATSUMA,[b] Kazuhiro SAKO,[a] and Takahiro UCHIDA[c]

[a] *Drug Delivery, Pharmaceutical Research and Development Labs, Astellas Pharma Inc.;* [b] *Pharmaceutical Planning, Pharmaceutical Research and Development Labs, Astellas Pharma Inc.; 180 Ozumi, Yaizu, Shizuoka 425–0072, Japan: and* [c] *School of Pharmaceutical Sciences, Mukogawa Women's University; 11–68 Koshien 9-Bancho, Nishinomiya, Hyogo 663–8179, Japan.* Received July 18, 2008; accepted September 9, 2008; published online September 10, 2008

The salting-out taste-masking system is a multiparticulate system consisting of a drug core, a salting-out layer containing salts and water-soluble polymers, and a water-penetration control layer containing water-insoluble materials. The system generates a long lag time (time when released drug is less than 1%) for numbness masking, and a subsequent immediate drug release for high bioavailability. Aiming to contain the system and drugs that cause numbness in oral disintegrating tablets, the system was optimized to reduce the particle size and contain drugs with high water solubility in this study. The amount of coating on the layers, the coating solvent, and the positioning of the components were also optimized. The findings in this study will lead to the provision of numbness-masked oral disintegrating tablets to patients.

Key words salting-out taste-masking system; particle size; solubility; lag time; release

The oral disintegrating tablet is a user-friendly dosage form in that can be swallowed as easily as a liquid while retaining a tablet's ease of handling.[1—6] However, when oral disintegrating tablets are administered without water, it takes at least 3 min for the drug to pass through the esophagus because a small portion remains in the epiglottic vallecula or adheres to the epiglottis for 1—2 min even after administering drugs with water.[7—9] On the other hand, many drugs cause numbness in both the oral cavity and the esophagus. Therefore, formulations of oral disintegrating tablets containing drugs that cause numbness should generate at least 3 min of lag time (time when released drug is less than 1%) before drug release. It is also important to maintain bioequivalence between oral disintegrating tablets and other commercial dosage forms in order to retain the pharmacological effects.[10—12]

The salting-out taste-masking system has been designed to generate long lag times with subsequent immediate drug release.[13] This multiparticulate dosage form consists of a drug core, a salting-out layer containing salts and water-soluble polymers, and a water-penetration-control layer containing water-insoluble materials. In the salting-out layer, the salts insolubilize the water-soluble polymer by the salting-out effect, which generates a long lag time. After most of the salt has been released, the water-soluble polymer dissolves and the drug is released immediately. The previous study revealed that the above mechanism controlled drug release from the system.[13] The system prepared in the previous study had mean particle sizes of approximately 760 μm, and contained acetaminophen. The particle size was so large to cause the oral disintegrating tablet to have a rough texture.[14,15] Water solubility of acetaminophen is 22 mg/ml[16]; however, most drugs causing numbness have a high water solubility. For example, imipramine hydrochloride causes numbness and has solubility of 500 mg/ml.[17] It is generally difficult to generate long lag times with subsequent immediate drug release from small particle size of multiparticulate dosage forms containing a drug with high water solubility.[18—21] The purpose of this study is optimizing the salting-out taste-masking system in order to reduce particle size, and contain drugs with high water solubility. The amount of coating on the layers, the coating solvent for the salting-out layer, and the positioning of the components in the salting-out layer were optimized.

Experimental

Materials Sucrose spheres (Nonpareil 103 24-32) were purchased from Freund Co. (Japan). Microcrystalline cellulose spheres (CP-102) were purchased from Asahi Kasei Chemicals Co. (Japan). Acetaminophen was obtained from Yoshitomi Fine Chemicals Ltd. (Japan). Imipramine hydrochloride (Imipramine hereinafter) was supplied from Man Mill Chemicals Pvt., Ltd. (India). Sodium carbonate (Na_2CO_3), potassium dihydrogen phosphate, sodium hydroxide, methanol, and dichloromethane were purchased from Kanto Chemical Co., Inc. (Japan). Hydroxypropylmethylcellulose 2910 (HPMC, TC-5E) was kindly supplied by Shin-Etsu Chemical Co., Ltd. (Japan). Povidone (Povidone K30) was obtained from BASF Japan, Ltd. (Japan). Cetanol (Kalcol 6098) was provided by Kao Corporation (Japan). Triethyl citrate (Citroflex 2 SC-60, TEC hereinafter) was purchased from Pfizer, Inc. (U.S.A.). Aminoalkyl methacrylate copolymer RS (Eudragit RS100) was kindly supplied by Degussa Japan Co., Ltd. (Japan). Talc was purchased from Kihara Kasei Co., Ltd. (Japan).

Preparation of Acetaminophen Drug Cores A solution of acetaminophen and HPMC in methanol–dichloromethane was sprayed on sucrose spheres fluidized in a fluidized-bed granulator (GPCG-1, Okawara Mfg. Co., Ltd., Japan). The manufacturing conditions were the same as those in the previous study.[13]

Coating with Salting-Out Layer of Methanol–Dichloromethane Na_2CO_3 was pulverized with a jet mill (Spiral Jet Mill 50AS, Hosokawa Micron Co., Japan), and dispersed in an HPMC solution in methanol–dichloromethane (ratio of Na_2CO_3 to HPMC in the salting-out layer: 83 : 17). This dispersion was sprayed on fluidized drug cores. The manufacturing conditions were the same as those in the previous study.[13]

Coating with Water-Penetration-Control Layer of Cetanol A solution of cetanol in dichloromethane was sprayed on the fluidized beads. The manufacturing conditions were the same as those in the previous study.[13]

Preparation of Imipramine Drug Cores Imipramine and HPMC were dissolved in methanol–water (60 : 40) to yield final concentrations of 18.2% and 1.82%. A 476.2-g batch of microcrystalline cellulose spheres was fluidized in the fluidized-bed granulator. This solution was pumped at a flow rate of 12.4 g/min and sprayed on the spheres from the side of the granulator. The drying air outlet temperature was 35 °C, and the pneumatic spraying pressure was 3.5 kg/cm^2.

Coating with Hydroxypropylmethylcellulose Layer A 5% solution of

* To whom correspondence should be addressed. e-mail: takayuki.yoshida@jp.astellas.com
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HPMC mixed with methanol–water (50 : 50) was pumped at a flow rate of 10.8 g/min and sprayed on fluidized beads (275 g). The drying air outlet temperature was 43 °C, and the pneumatic spraying pressure was 3.5 kg/cm^2.

Coating with Povidone Layer A 5% solution of povidone in methanol–water (50 : 50) was pumped at a flow rate of 8.6 g/min and sprayed on fluidized beads (270 g). The drying air outlet temperature was 45 °C, and the pneumatic spraying pressure was 3.0 kg/cm^2.

Coating with Salting-Out Layers Using Water An aqueous solution containing Na_2CO_3 at 3.33% and HPMC at 0.67% was pumped at a flow rate of 12.2 g/min and sprayed on fluidized beads (340 g). The drying air outlet temperature was 35 °C, and the pneumatic spraying pressure was 3.0 kg/cm^2.

Coating with Layer Containing Sodium Carbonate and Povidone A 5% and 1% solution of Na_2CO_3 and povidone in purified water was pumped at a flow rate of 13.6 g/min and sprayed on fluidized beads (271 g). The drying air outlet temperature was 40 °C, and the pneumatic spraying pressure was 3.0 kg/cm^2.

Coating with Water-Penetration-Control Layer Containing Aminoalkyl Methacrylate Copolymer RS, Triethyl Citrate, and Talc Eudragit RS100 and TEC were dissolved in dichloromethane, and talc was dispersed in this mixture to give the final concentrations of 3.13%, 0.313%, and 1.56% respectively. The suspension was pumped at a flow rate of 8.2 g/min and sprayed on fluidized beads (271 g). The drying air outlet temperature was 35 °C, and the pneumatic spraying pressure was 3.0 kg/cm^2.

Definition of Formulation Codes The formulation names were coded as follows: D, S, and W stand for the drug core, the salting-out layer, and the water-penetration-control layer, respectively. Use of the subscripts A or I with D indicates that the drug core contains acetaminophen or imipramine, respectively. Use of a subscript with S indicates the salting-out-layer's amount (weight %) of the amount of the drug core. Use of the subscripts C or RS with W indicates that the water-penetration-control layer is cetanol, or Eudragit RS/TEC/talc=10.0/1.0/5.0, respectively. Use of a number with C or RS indicates the water-penetration-control-layer's amount (weight %) of the amount of beads containing the drug core and the salting-out layer. For example, a formulation labeled $D_AS_{53}W_{C8}$ consists of a drug core containing acetaminophen, a salting-out layer whose amount is 53% of the amount of the drug core, and a cetanol water-penetration-control layer whose amount is 8% of the amount of beads containing the drug core and the salting-out layer.

Drug Dissolution Drug dissolution tests were conducted using formulations containing 10 mg of acetaminophen or 20 mg of imipramine and an automatic 6-series dissolution testing device (Toyama Sangyo Co., Ltd., Japan) equipped with a UV–visible spectrophotometer (Shimadzu Co., Japan). The tests were performed in accordance with Dissolution Test Method 2 (paddle method), as described in the fourteenth edition of the Japanese Pharmacopeia (JP 14th ed.). The test fluid was phosphate buffer with a pH of 6.8 (2nd fluid, described in the Disintegration Test in the JP 14th ed.). No effects of the volume of the fluid, and the paddle rotation speed on the drug release from the formulations were preliminarily checked. Therefore, in this study, the volume of test fluid was 500 ml, and the paddle rotation speed was 100 revolutions per minute. The wavelength used to detect the drugs was 254 nm for acetaminophen and 250 nm for imipramine. The absorbance of the solutions was measured every 2 min from 1 to 181 min after starting the dissolution tests. All results are presented as the mean±S.D. (n=3).

Lag times (times when released drug is less than 1%) were calculated by regressing linearly between two time points when the released drug was closest to 1%, less than 1%, and more than 1%. In this study, the time at which drug release reached 85% ($T_{85\%}$) was obtained for comparison with the drug release rate after the lag time. $T_{85\%}$ was calculated by regressing linearly between two time points when the released drug was the closest to 85%, less than 85%, and more than 85%.

Dissolution of Sodium Carbonate Formulations containing 10 mg of acetaminophen were weighed and added to 500 ml of purified water at 37 °C with a paddle rotation speed of 100 rpm. The conductance of each solution was measured using a conductance meter (CM-60V, TOA Electronics, Japan). A calibration curve was obtained by measuring the conductance of several solutions of known Na_2CO_3 concentration, as described in the previous study.[6] The concentrations of Na_2CO_3 in the sample solutions were then determined by plotting the conductance values on this calibration curve. The amounts of Na_2CO_3 (mg) released were calculated by multiplying the concentrations of Na_2CO_3 (mg/ml) by 500 (ml). The remaining Na_2CO_3 (mg) in the formulations at a given time point were calculated by subtracting the amount of Na_2CO_3 that had been released at that time point from the theoretical Na_2CO_3 amount.

Mean Particle Size Particle distribution was determined by measuring the size of beads in the formulation (5 g) using the sieve method (Robot Sifter, Seishin Enterprise Co., Ltd., Japan). Screens with openings of 180, 250, 300, 355, 500, 710, 850, and 1400 μm were used to separate each fraction. The average particle size was estimated (median diameter) from the weight of the fraction based on the cumulative percentage curves.

Results and Discussion

Effects of Salting-Out Layer Coating Amount on Drug Dissolution Formulations containing different amounts of the salting-out layer and the same amount of the water-penetration-control layer were prepared. The D_AW_{C5}, $D_AS_{23}W_{C5}$, $D_AS_{40}W_{C5}$, $D_AS_{53}W_{C5}$, and $D_AS_{72}W_{C5}$ formulations contained the salting-out layer of 0, 23, 40, 53, and 72%, respectively (Table 1). Large amount of the salting-out layer generated long lag time (Fig. 1a). The large amount of the layer proba-

Table 1. Micro-Beads Formulations[a)]

	D_AW_{C5}	$D_AS_{23}W_{C5}$	$D_AS_{40}W_{C5}$	$D_AS_{53}W_{C5}$	$D_AS_{72}W_{C5}$	D_AS_{53}
Sucrose spheres	45.5	45.5	45.5	45.5	45.5	45.5
Acetaminophen	13.6	13.6	13.6	13.6	13.6	13.6
HPMC	1.4	1.4	1.4	1.4	1.4	1.4
Na_2CO_3	—	11.6	20.2	26.7	36.3	26.7
HPMC	—	2.3	4.0	5.3	7.3	5.3
Cetanol	3.0	3.7	4.2	4.6	5.2	—
Total	63.5	78.1	88.9	97.2	109.3	92.6

	$D_AS_{53}W_{C2}$	$D_AS_{53}W_{C4}$	$D_AS_{53}W_{C6}$	$D_AS_{53}W_{C8}$	$D_AS_{53}W_{C10}$
Sucrose spheres	45.5	45.5	45.5	45.5	45.5
Acetaminophen	13.6	13.6	13.6	13.6	13.6
HPMC	1.4	1.4	1.4	1.4	1.4
Na_2CO_3	26.7	26.7	26.7	26.7	26.7
HPMC	5.3	5.3	5.3	5.3	5.3
Cetanol	1.9	3.7	5.6	7.4	9.3
Total	94.4	96.3	98.1	100.0	101.9

	$D_IS_{150}W_{RS4}$	$D_IS_{50}W_{RS4}$	Type I	Type II	Type III	Type IV	Type V
CP-102	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Imipramine	10.0	10.0	10.0	10.0	10.0	10.0	10.0
HPMC	1.0	1.0	1.0	1.0	1.0	1.0	1.0
HPMC				2.1		1.1	
Povidone		2.1	2.1		2.1		2.1
Na_2CO_3	26.3	9.6	9.6	9.6	9.6		9.6
HPMC	5.3	1.9	1.9				
Povidone				1.9	1.9		1.9
HPMC					3.5		
Povidone		3.5	3.5	3.5			3.5
Eudragit RS	1.3	1.0	2.4	2.4	2.4	1.4	2.4
TEC	0.1	0.1	0.2	0.2	0.2	0.1	0.2
Talc	0.7	0.5	1.2	1.2	1.2	0.7	1.2
Total	54.6	39.6	41.9	41.9	41.9	24.3	41.9

a) D_A, D_I, S, W_C, and W_{RS} stand for acetaminophen drug core, imipramine drug core, salting-out layer, water-penetration-control layer of cetanol, and water-penetration-control layer of Eudragit RS/TEC/talc, respectively. Subscript number indicates the layer's amount (weight %) of the amount of beads in preceding process. The salting-out layer components are highlighted in gray.

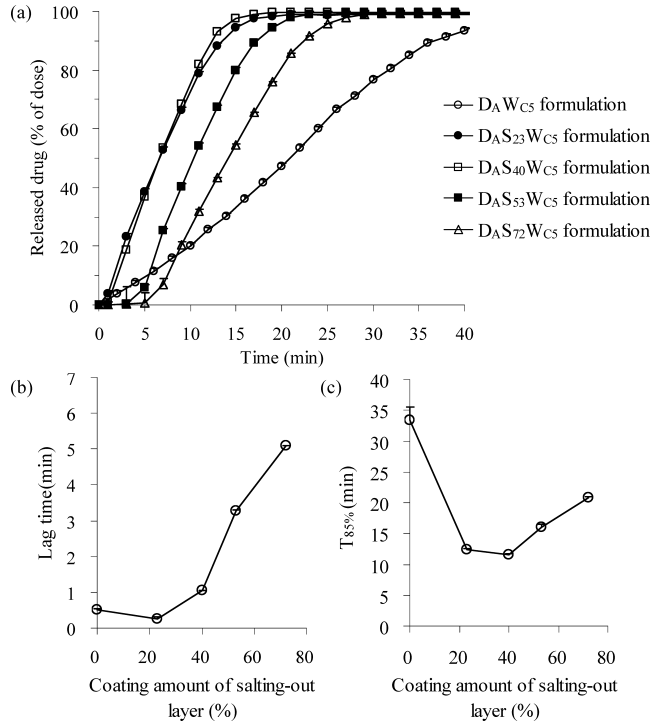

Fig. 1. Effects of Salting-Out Layer Coating Amount on Drug Dissolution

(a) Drug dissolution. (b) Effects of salting-out layer coating amount on the lag time. (c) Effects of salting-out layer coating amount on the $T_{85\%}$. Paddle method, 500 ml of phosphate buffer (pH 6.8), 100 rpm.

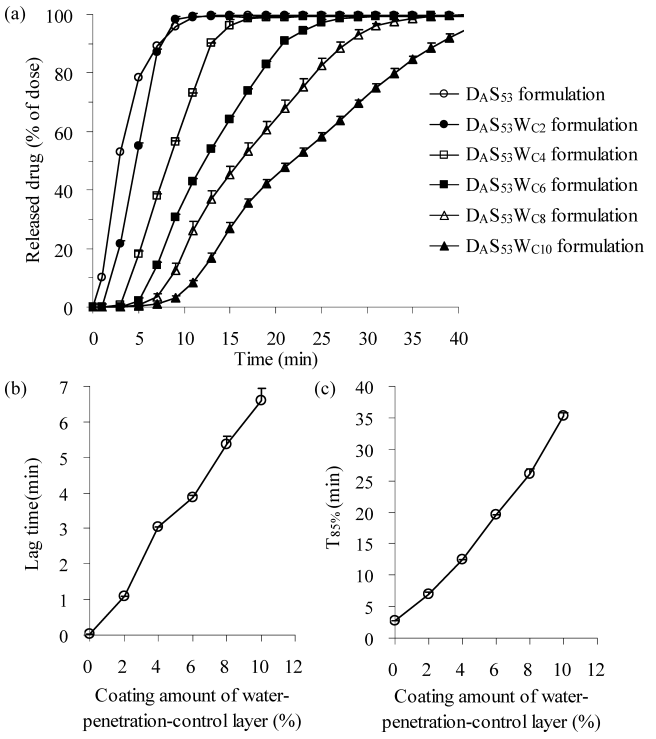

Fig. 2. Effects of Water-Penetration-Control Layer Coating Amount on Drug Dissolution

(a) Drug dissolution. (b) Effects of water-penetration-control layer coating amount on the lag times. (c) Effects of water-penetration-control layer coating amount on the $T_{85\%}$. Paddle method, 500 ml of phosphate buffer (pH 6.8), 100 rpm.

bly induced long-time insolubilization of HPMC in the salting-out layer, and long lag time of drug release. The rate of drug release from the $D_AS_{23}W_{C5}$, $D_AS_{40}W_{C5}$, $D_AS_{53}W_{C5}$, and $D_AS_{72}W_{C5}$ formulations after the lag time were similar, and all were faster than that of the D_AW_{C5} formulation (Fig. 1a). These results indicated that the presence of the salting-out layer increased the drug release rate regardless of the amount coated. The salts in the formulations induced an osmotic influx of water into the formulations,[22—25] which generated micropores in the water insoluble layers.[26,27] The water influx rates in all formulations containing Na_2CO_3 were probably constant regardless of the amount coated since they were determined by the solubility of Na_2CO_3. The four formulations contained the same amount of the water-penetration-control layer. Therefore, the effect of the micropores in the water-penetration-control layer, which increases the drug release rate, might be similar in the four formulations.

The lag time lengths were similar for salting-out layer coating amounts in the range of 0—40% (Fig. 1b). However, those accounting for more than 40% generated long lag times. The reason for these results is estimated as follows: the salting-out layers may have two effects on drug dissolution, one being an increase in the drug release rate during all stages of the drug dissolution tests due to the mechanisms described above; the other being the suppression of drug release in the early stage (our concept). Thus, a salting-out layer of more than 40% might be necessary to suppress drug release in the early stage.

Effects of Water-Penetration-Control Layer Coating Amount on Drug Dissolution Formulations containing the same amount of the salting-out layer and different amounts of the water-penetration-control layer were prepared. The D_AS_{53}, $D_AS_{53}W_{C2}$, $D_AS_{53}W_{C4}$, $D_AS_{53}W_{C6}$, $D_AS_{53}W_{C8}$, and $DS_{53}W_{C10}$ formulations contained the water-penetration-control layer of 0, 2, 4, 6, 8, and 10%, respectively. Long lag times and long $T_{85\%}$ were generated by large water-penetration-control layer coating amounts (Fig. 2), which also probably decreased the water influx rate significantly.

The information obtained by varying the coating amounts for these two layers is helpful for designing appropriate formulations for the salting-out taste-masking system. Lag time and $T_{85\%}$ were compared between formulations containing salting-out layer coating amounts of 40 and 72%, and water-penetration-control layer coating amounts of 2 and 8%. Both cases were similar in that they increased lag time by 4 min (Figs. 1b, 2b). However, changing the amount of the salting-out layer increased $T_{85\%}$ slightly more [9 min (Fig. 1c)] than changing the amount of the water-penetration-control layer [19 min (Fig. 2c)]. Therefore changing the amount of the salting-out layer offers more of an advantage when a longer lag time with subsequent immediate drug release is desired. On the other hand, changing the amount of the water-penetration-control layer also resulted in a 4-min increase in lag time, this could be the better choice for manufacturers, since it required only a small increase the amount of raw material (6% *vs.* 32% for the salting-out layer).

Effects of Particle Size and Drug Solubility on Drug Dissolution Drug dissolution profiles of formulations which had different particle sizes and contained drugs with different water solubility were compared. The $D_AS_{53}W_{C8}$ formulation had a mean particle size of 760 μm (Fig. 3), and contained acetaminophen with a solubility of 22 mg/ml.[16] The $D_IS_{150}W_{RS4}$ formulation had a mean particle size of

267 μm (Fig. 3), and contained imipramine with a solubility of 500 mg/ml.[17] The $D_IS_{150}W_{RS4}$ formulation released drug in a manner very similar to that of the $D_AS_{53}W_{C8}$ formulation (Fig. 4). These results indicated that the salting-out taste-masking system can generate long lag times with subsequent immediate drug release from a small particle size system containing a drug with high water solubility.

Drug dissolution profile of the $D_AS_{53}W_{RS4}$ formulation was reported in the previous study.[13] The $D_AS_{53}W_{RS4}$ formulation contained the drug core and the salting-out layer which were same to the $D_AS_{53}W_{C8}$ formulation, and the water-penetration-control layer which was same to the $D_IS_{150}W_{RS4}$ formulation. Drug release control from the $D_AS_{53}W_{RS4}$ formulation by a 53% salting-out layer, was similar to that from the $D_IS_{150}W_{RS4}$ formulation by a 150% salting-out layer. These results imply that a large coating amount is necessary to control the release rate of a drug with high solubility from a small particle size system. A large concentration slope due to high solubility and a large surface area per weight of small particle resulted in immediate drug release; therefore, a large coating amount probably becomes necessary. Other drawbacks include the time required for manufacturing; coating the 150% salting-out layer on a 1-kg batch of drug cores required 9.5 h. In addition, methanol–dichloromethane is used as the solvent for coating the salting-out layer. Shortening the manufacturing time and using water as the solvent would improve the impact on the environment as well as cost effectiveness.

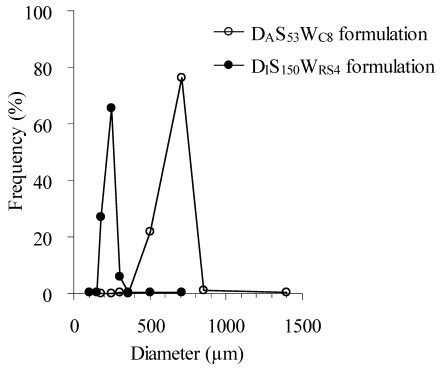

Fig. 3. Particle Size Distribution of the $D_AS_{53}W_{C8}$ and $D_IS_{150}W_{RS4}$ Formulations (Sieve Method)

Effects of Salting-Out Layer Coating Solvent on Drug Dissolution The salting-out layer was coated using water as a solvent. During the preparation of the $D_IS_{50}W_{RS4}$ formulation, micro-bead fluidization stopped when the aqueous solution of Na_2CO_3 and HPMC was sprayed on the imipramine drug core, and when the dispersion of Eudragit RS100, TEC, and talc was sprayed on the salting-out layer. The cause might be that, during coating, the aqueous solution, which contains a high Na_2CO_3 concentration, might convert the imipramine hydrochloride into a carbonate salt.[28] The Na_2CO_3 in the salting-out layer might also interact with the aminoalkyl group of the Eudragit RS100.[29] A thin shielding layer of povidone or HPMC between the drug core and the salting-out layer, and another between the salting-out layer and the water-penetration-control layer could resolve these problems.

The solvents used to coat the salting-out layer were methanol–dichloromethane for the $D_IS_{150}W_{RS4}$ formulation, and water for the $D_IS_{50}W_{RS4}$ formulation. The drug dissolution patterns for these two formulations were closely similar (Fig. 5). These results indicated that either solvent could be used for coating the salting-out layer. When the aqueous solution containing Na_2CO_3 and HPMC were sprayed, the pneumatic spraying pressure and evaporation of water increased the salt concentration, and caused HPMC to salt-out, which might prevent the agglomeration of beads[30] and prevent the drug from permeating the surface of the salting-out layer. The lag time for the $D_IS_{50}W_{RS4}$ formulation was a little less than that of the $D_IS_{150}W_{RS4}$ formulation, which was probably due to the difference in the amount of salting-out layer (50 *vs.* 150%).

Effects of Position of Salt and Water-Soluble Polymer in Salting-Out Layer on Drug Dissolution In order to obtain a long lag time with subsequent immediate drug release, the best position for the salt and water-soluble polymer was examined using three types of $D_IS_{50}W_{RS}$ formulations. It has been reported that the insolubilization of HPMC *via* the salting-out effect was much more efficient than that of povidone.[31,32] In this study, HPMC was used as an essential water-soluble polymer in the salting-out layer, and povidone was used as a binder or shielding material, since it is hardly insolubilized by Na_2CO_3 at all. Between the drug core and

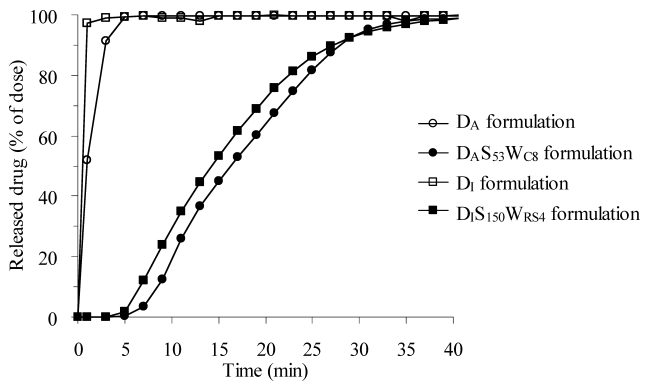

Fig. 4. Effects of Particle Size and Drug Solubility on Drug Dissolution

The $D_AS_{53}W_{C8}$ formulation (mean particle size: 760 μm) containing acetaminophen (solubility: 22 mg/ml). The $D_IS_{150}W_{RS4}$ formulation (mean particle size: 267 μm) containing imipramine hydrochloride (solubility: 500 mg/ml). Paddle method, 500 ml of phosphate buffer (pH 6.8), 100 rpm.

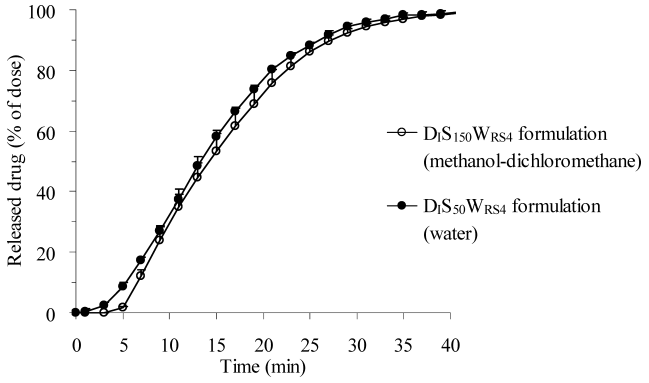

Fig. 5. Effects of the Solvent Used for Coating the Salting-Out Layer on Drug Dissolution

The solvents were methanol–dichloromethane ($D_IS_{150}W_{RS4}$ formulation) and water ($D_IS_{50}W_{RS4}$ formulation). Paddle method, 500 ml of phosphate buffer (pH 6.8), 100 rpm.

Table 2. Fitting Drug Dissolution Profiles (5—85%) to the First- and Zero-Order Release Model

Formulation name	First-order release model		Zero-order release model	
	Rate constant (min^{-1})	Correlation coefficient	Rate constant ($\%min^{-1}$)	Correlation coefficient
Type I (Na_2CO_3 and HPMC matrix)	0.0688	0.9351	2.3932	0.9881
Type II (Na_2CO_3 outside of HPMC)	0.0305	0.9904	0.7922	0.7973
Type III (Na_2CO_3 inside of HPMC)	0.0389	0.8632	1.3990	0.9898

the water-penetration-control layer, Na_2CO_3 formed a matrix layer with HPMC in the type I formulation, the Na_2CO_3 layer was outside of the HPMC layer in the type II formulation, and the Na_2CO_3 layer was inside of the HPMC layer in the type III formulation (Table 1). The type I salting-out layer (Na_2CO_3 and HPMC matrix layer) was the most effective for generating long lag times with subsequent immediate drug release (Fig. 6a).

The order for lag time was type II<type III=type I (Fig. 6a). The release rate order for 70% Na_2CO_3 was type II>type III=type I (Fig. 6b). These results indicated that slow Na_2CO_3 release caused a long lag time. Slow Na_2CO_3 release was probably caused by HPMC being in the matrix (type I) or outside the Na_2CO_3 layer (type III), which caused HPMC to become insolubilized for long periods of time.

The order for $T_{85\%}$ was type I<type II=type III (Fig. 6a). The rates of Na_2CO_3 release from the 70 and 100% formulations were faster for the type I (matrix) than those for the type III (Na_2CO_3 inside of HPMC). The outer HPMC layer probably induced the sustained release of Na_2CO_3, and slow drug release after the lag time. The drug dissolution profiles for the drug 5 to 85% formulations, were fitted to the zero- and first-order models, and their correlation coefficients were compared (Table 2). The results indicated that the types I (matrix) and III (Na_2CO_3 inside of HPMC) followed zero-order kinetics, and the type II (Na_2CO_3 outside of HPMC) followed first-order kinetics. The drug was released through the HPMC layer and the water-penetration-control layer, in all types. Effects of the HPMC layer were probably type II<type III=type I as the order for lag time. The drug release from the type II was mainly controlled by the water-penetration-control layer not the HPMC layer, therefore followed the first order. In contrast, the HPMC which had been insolubilized by Na_2CO_3 in the types I and III, probably dissolved gradually and decreased drug release rates at the early stage of the dissolution tests, which caused the zero-order kinetics.

Drug dissolution from control formulations supported this hypothesis. The type IV formulation, containing the drug core, HPMC layer, and water-penetration-control layer (in that order), generated no lag time, and achieved the drug dissolution profile overlapping that of the type II (Fig. 6a). This result might indicate that the HPMC layer in the type II was not insolubilized and did not affect the drug release rate. The type V formulation contained the drug core, a povidone layer, the Na_2CO_3 layer, another povidone layer, and the water-penetration-control layer (in that order). This formulation generated a short lag time and subsequent immediate drug release (Fig. 6a). This result indicated that the long lag times obtained with type I (matrix) and III (Na_2CO_3 inside of HPMC) were generated by Na_2CO_3 and HPMC.

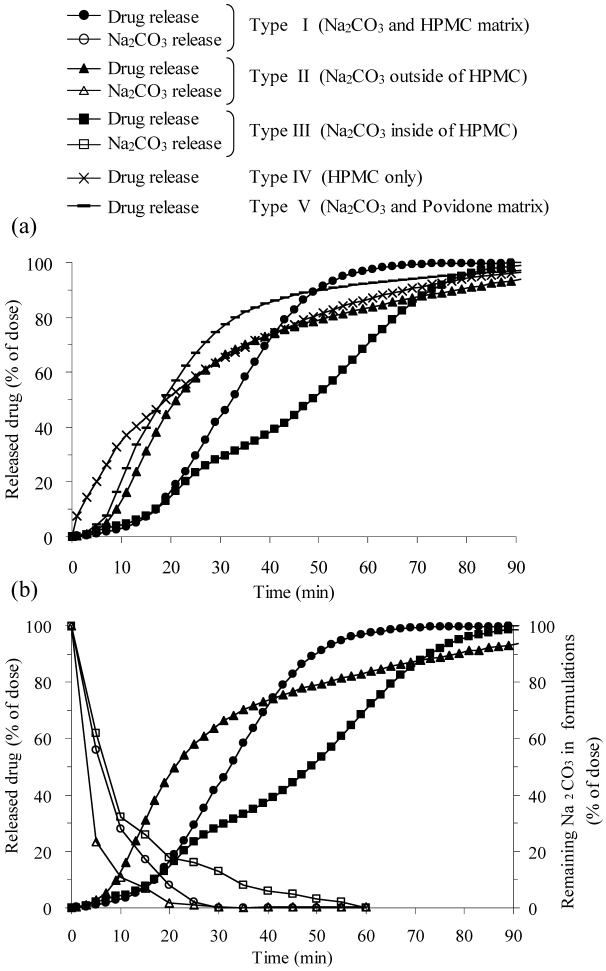

Fig. 6. Effects of the Positioning of the Salt and Water-Soluble Polymer in the Salting-Out Layer on Drug and Na_2CO_3 Dissolution

(a) Drug dissolution for formulation types I, II, III, IV, and V [paddle method, 500 ml of phosphate buffer (pH 6.8), 100 rpm]. (b) Drug dissolution and amount of Na_2CO_3 remaining in formulation types I, II, and III (paddle method, 500 ml of water, 100 rpm).

Conclusion

The salting-out taste-masking system could generate long lag times with subsequent immediate drug release from a small particle size system containing a drug with high water solubility. This study clarified the relationship between layer coating amount and drug dissolution profile. It was also

shown that the solvent for coating the salting-out layer could be changed from methanol–dichloromethane to water, a much more environmentally responsible and cost-effective option. In addition, the positions of the salt and water-soluble polymer in the salting-out layer were optimized. The findings in this study are useful in that they will lead to a more agreeable option for patients who must take drugs that cause numbness.

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