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

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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 epiglottis 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 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/ml16, 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 (Na2CO3), 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 (Kalcod 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 (GPGC-1, Okayawa 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 Na2CO3 was pulverized with a jet mill (Spiral Jet Mill 50AS, Hosokawa Micron Co., Japan), and dispersed in an HPMC solution 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 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-bed granulator. 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/cm2.

Coating with Hydroxypropylmethylcellulose Layer A 5% solution of

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Coating with Water-Penetration-Control Layer Containing Alkyl 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/cm².

Coating with Water-Penetration-Control Layer Containing Sodium Carbonate and Povidone

A 5% and 1% solution of Na₂CO₃ 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/cm².

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 (271 g). The drying air outlet temperature was 43 °C, and the pneumatic spraying pressure was 3.5 kg/cm².

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 D₆₅₅₅₅, D₆₅₃₅₃₅, D₆₅₁₅₅₃₅, and D₅₃₇₅₃₅ 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-
bly induced long-time insolubilization of HPMC in the salt-
ing-out layer, and long lag time of drug release. The rate of
drug release from the DAS23WC5, DAS40WC5, DAS53WC5, and
DAS72WC5 formulations after the lag time were similar, and
all were faster than that of the DAWC5 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 in-
flux of water into the formulations,22—25) which generated
micropores in the water insoluble layers.26,27) The water in-
flux rates in all formulations containing Na2CO3 were prob-
ably constant regardless of the amount coated since they were
determined by the solubility of Na2CO3. The four formula-
tions contained the same amount of the water-penetra-
tion-control layer. Therefore, the effect of the micropores in the
water-penetration-control layer, which increases the drug re-
lease 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 dissolu-
tion, 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 re-
lease 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
DAS53, DAS53WC2, DAS53WC4, DAS53WC6, DAS53WC8, and
DAS53WC10 formulations contained the water-penetration-con-
trol layer of 0, 2, 4, 6, 8, and 10%, respectively. Long lag
times and long T85% were generated by large water-penetra-
tion-control layer coating amounts (Fig. 2), which also prob-
ably decreased the water influx rate significantly.

The information obtained by varying the coating amounts
for these two layers is helpful for designing appropriate for-
mulations for the salting-out taste-masking system. Lag time
and T85% 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-
our layer increased T85% slightly more [9 min (Fig. 1c)]
then 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-pene-
tration-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 DAS53WC6 for-
mulation had a mean particle size of 760 µm (Fig. 3), and
contained acetaminophen with a solubility of 22 mg/ml.16)
The DSA150WRS4 formulation had a mean particle size of
267 µm (Fig. 3), and contained imipramine with a solubility of 500 mg/ml.\textsuperscript{17} The D\textsubscript{S150}W\textsubscript{RS4} formulation released drug in a manner very similar to that of the D\textsubscript{S30}W\textsubscript{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\textsubscript{S30}W\textsubscript{RS4} formulation was reported in the previous study.\textsuperscript{13} The D\textsubscript{S30}W\textsubscript{RS4} formulation contained the drug core and the salting-out layer which were same to the D\textsubscript{S30}W\textsubscript{C8} formulation, and the water-penetration-control layer which was same to the D\textsubscript{S150}W\textsubscript{RS4} formulation. Drug release control from the D\textsubscript{S30}W\textsubscript{RS4} formulation by a 53% salting-out layer, was similar to that from the D\textsubscript{S150}W\textsubscript{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.

**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\textsubscript{S30}W\textsubscript{RS4} formulation, micro-bead fluidization stopped when the aqueous solution of Na\textsubscript2}CO\textsubscript3 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\textsubscript2}CO\textsubscript3 concentration, might convert the imipramine hydrochloride into a carbonate salt.\textsuperscript{28} The Na\textsubscript2}CO\textsubscript3 in the salting-out layer might also interact with the aminoalkyl group of the Eudragit RS100.\textsuperscript{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\textsubscript{S150}W\textsubscript{RS4} formulation, and water for the D\textsubscript{S30}W\textsubscript{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\textsubscript2}CO\textsubscript3 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\textsuperscript{30} and prevent the drug from permeating the surface of the salting-out layer. The lag time for the D\textsubscript{S30}W\textsubscript{RS4} formulation was a little less than that of the D\textsubscript{S150}W\textsubscript{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\textsubscript{S30}W\textsubscript{RS} formulations. It has been reported that the insolubilization of HPMC via the salting-out effect was much more efficient than that of povidone.\textsuperscript{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\textsubscript2}CO\textsubscript3 at all. Between the drug core and
the water-penetration-control layer, Na₂CO₃ formed a matrix layer with HPMC in the type I formulation, the Na₂CO₃ layer was outside of the HPMC layer in the type II formulation, and the Na₂CO₃ layer was inside of the HPMC layer in the type III formulation (Table 1). The type I salting-out layer (Na₂CO₃ 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% Na₂CO₃ was type II<type III<type I (Fig. 6b). These results indicated that slow Na₂CO₃ release caused a long lag time. Slow Na₂CO₃ release was probably caused by HPMC being in the matrix (type I) or outside the Na₂CO₃ layer (type III), which caused HPMC to become insolubilized for long periods of time.

The order for T₈5% was type I<type II<type III (Fig. 6a). The rates of Na₂CO₃ release from the 70 and 100% formulations were faster for the type I (matrix) than those for the type III (Na₂CO₃ inside of HPMC). The outer HPMC layer probably induced the sustained release of Na₂CO₃, 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 (Na₂CO₃ inside of HPMC) followed zero-order kinetics, and the type II (Na₂CO₃ 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 Na₂CO₃ 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 Na₂CO₃ 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 (Na₂CO₃ inside of HPMC) were generated by Na₂CO₃ and HPMC.

**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

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

<table>
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<tr>
<th>Formulation name</th>
<th>Rate constant (min⁻¹)</th>
<th>Correlation coefficient</th>
<th>Rate constant (%min⁻¹)</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (Na₂CO₃ and HPMC matrix)</td>
<td>0.0688</td>
<td>0.9351</td>
<td>2.3932</td>
<td>0.9881</td>
</tr>
<tr>
<td>Type II (Na₂CO₃ outside of HPMC)</td>
<td>0.0305</td>
<td>0.9904</td>
<td>0.7922</td>
<td>0.7973</td>
</tr>
<tr>
<td>Type III (Na₂CO₃ inside of HPMC)</td>
<td>0.0389</td>
<td>0.8632</td>
<td>1.3990</td>
<td>0.9898</td>
</tr>
</tbody>
</table>

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Fig. 6. Effects of the Positioning of the Salt and Water-Soluble Polymer in the Salting-Out Layer on Drug and Na₂CO₃ 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 Na₂CO₃ remaining in formulation types I, II, and III (paddle method, 500 ml of water, 100 rpm).
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.

References