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Salting-out taste-masking system generates lag time with subsequent immediate release

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ABSTRACT

Salting-out effects were utilized for developing a multiparticulate system balancing numbness masking and high bioavailability. A "salting-out taste-masking system" consisting of a drug core containing acetaminophen as a model drug, a salting-out layer containing sodium carbonate (Na_2CO_3) and hydroxypropylmethylcellulose (HPMC), and a water-penetration-control layer consisting of cetanol was designed and prepared. The system successfully generated a long lag time while achieving immediate drug release. In the system, the Na_2CO_3 release rate was slower and the lag time was longer than when the water-penetration-control layer was not present. During the release of Na_2CO_3 from the system, the release of HPMC and drug was suppressed. These results indicated that the water-penetration-control layer maintained a high concentration of Na_2CO_3, prevented HPMC's dissolution, and generated a long lag time of drug release. The system generated longer lag time and released drug more immediately than formulation containing the water-penetration-control layer of same thickness without the salting-out layers. These results indicated the salting-out layers were necessary for obtain a long lag time and subsequent immediate drug release. This novel taste-masking system has the potential to be a useful multiparticulate dosage form for effective, safe, and user-friendly drug therapy.

1. Introduction

Taste-masking technologies are important for obtaining high-patient compliance and drug therapy efficiency, since many oral-delivery drugs have unpleasant qualities such as bitterness, sourness, saltiness, or causing oral numbness (Kumazawa et al., 1988; Sugao et al., 1998; Hashimoto et al., 2002; Nanda et al., 2002; Keast and Breslin, 2005). Multiparticulate dosage forms (granules, powders, dry syrups, or suspensions) can not only be easily dose-adjusted for safe drug therapy, but also can be included in tablets, capsules, or oral disintegrating tablets. Therefore, taste-masking technologies are important for multiparticulate dosage forms to become effective, safe, and user-friendly drug therapies.

Many approaches have been reported for taste-masking multiparticulate dosage forms (Takahashi et al., 1988; Lu et al., 1991; Yajima et al., 1996; Sugao et al., 1998; Agarwal et al., 2000; Al-Omran et al., 2002; Hashimoto et al., 2002; Nanda et al., 2002; Sohi et al., 2004; Kajiyama et al., 2006). One general taste-masking method is the application of coating materials over the drug particles (Fukumori et al., 1987; Nanda et al., 2002; Sohi et al., 2004). Coated layers mask the unpleasant taste by generating a lag time before drug release. Approximately 1 min of lag time is sufficient because most formulations are swallowed within that time (Lagerlöf and Dawes, 1984; Crossner et al., 1991; Morita, 2003; Siqueira et al., 2005). After the drugs reach the gastrointestinal tract, it is desirable that drug release be immediate since slow drug dissolution has been reported to cause low bioavailability (Blume et al., 1993; Löbenberg et al., 2000). Several known taste-masking technologies can generate lag times of 0.5–1 min with subsequent immediate drug release (Nanda et al., 2002; Sohi et al., 2004). The ethylcellulose (EC) spray dried particles (Kajiyama et al., 2006) and the microcapsule containing the disintegrant and the coating layer of aminoalkyl methacrylate copolymer RS (Ueda et al., 1993) suppress bitter tastes of drugs in 15–30 s with subsequent 75–90% drug release in 20–30 min. The system containing core granule of drug and low-substituted hydroxypropylcellulose and coated film of EC and HPMC (Shirai et al., 1993), and another system coated with a layer containing polyvinyl acetate, dimethylaminoethyl methacrylate, and neutral methacrylic acid ester (Corbo et al., 2001) generate lag times of 0.5–1 min with subsequent 80–90% drug release in 30 min. A large portion of multiparticulate dosage forms are sent to the stomach instantly after administration. But a small portion

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of the dosage forms remains in the epiglottic vallecula or adheres to the epiglottis (Morita, 2003). It takes 1–2 min for that portion to gradually be carried to the stomach with the saliva (Helm et al., 1983; Oguchi et al., 2000). Since numbness caused by drugs affects both the oral cavity and the esophagus, at least 2 min of lag time is necessary to mask the numbness effect exerted by multiparticulate dosage forms.

The purpose of this study was to develop a novel multiparticulate system that generates a lag time of at least 2 min and releases drugs immediately afterwards. In this study, salting-out effects were utilized to develop such a system. Some water-soluble polymers are precipitated by adding salts to solutions of the water-soluble polymers; this is the so-called salting-out effect (Azorlosa and Martinelli, 1962; Harding and Rose, 1962; Nakano et al., 1999; Eeckman et al., 2001). Changes in the concentration of the salts induce changes in the physical phase of the water-soluble polymers in water. The change might achieve both lag time generation and immediate drug release. Na_2CO_3 is a strong salting-out agent (Azorlosa and Martinelli, 1962; Harding and Rose, 1962), and HPMC was easily precipitated by the salting-out effect (Nakano et al., 1999), therefore the two materials were used in this study. Acetaminophen has bitter taste, which was used as the model drug for this study. The *in vitro* dissolution rate of acetaminophe, the salt, and the water-soluble polymer were measured to estimate the roles of the components in the system.

2. Materials and methods

2.1. Materials

Na_2CO_3, potassium dihydrogen phosphate, sodium hydroxide, methanol, and dichloromethane were purchased from Kanto Chemical Co. Inc. (Japan). HPMC (TC-5E) was kindly provided by Shin-Etsu Chemical Co. Ltd. (Japan). Sucrose spheres (Nonparail 103 24-32) were purchased from Freund Co. (Japan), and acetaminophen was supplied by Yoshitomi Fine Chemicals Ltd. (Japan). Cetanol (cetyl alcohol, Kalcol 6098) was generously provided by Kao Corporation (Japan).

2.2. Effects of sodium carbonate concentrations on the salting-out of hydroxypropylmethylcellulose

Ten milliliters of aqueous Na_2CO_3 solution (2–200 mg/mL) were added dropwise to 10 mL of vigorously stirring aqueous HPMC solution (200 mg/mL) at 37 °C. Final Na_2CO_3 concentration in the mixture was 1–100 mg/mL. Precipitated solids were separated from the mixed solutions by vacuum filtration through quantitative filter papers (No. 3, Advantec Toyo Kaisha Ltd., Japan). The solids on the filter papers were weighed after drying at 40 °C for 24 h.

2.3. Quantification of sodium carbonate in the solids precipitated by the salting-out effects

The solids precipitated by mixing the Na_2CO_3 solutions and the HPMC solutions (which were prepared in Section 2.2) were dissolved in 500 mL of purified water at 37 °C. The conductance of each solution was measured using a conductance meter (CM-60V, TOA Electronics, Japan). The concentrations of Na_2CO_3 in the solutions were determined by plotting the conductance values on calibration curves. Measuring the conductance of 0, 20, 40, 60, 80, and 100 μg/mL Na_2CO_3 solutions yielded the following calibration curve:

$$\text{Concentration of } Na_2CO_3 \text{ (mg/mL)} = 0.00287\kappa + 0.00018 \quad (1)$$

where κ is the conductance (mS/m) and the correlation coefficient was 0.998. The precision of this quantification ($n = 5$), expressed as the % relative standard deviation (R.S.D.), was 1.9% and 1.1% at 20, and 60 μg/mL, respectively. The intra- and inter-day accuracy ($n = 5$, respectively), as indicated by the relative error (R.E.), ranged from −2.2 to 2.4%. The amount of Na_2CO_3 (mg) in the solids was calculated by multiplying the concentrations of Na_2CO_3 (mg/mL) by 500 (mL). The amount of HPMC in the solids was calculated by subtracting the amount of Na_2CO_3 from the total weight of the precipitated solids. Recovery as precipitated solid (%) was obtained by dividing the weights of Na_2CO_3 or HPMC in the precipitated solids by the weights of the Na_2CO_3 or HPMC that had been dissolved in the solutions.

2.4. Dissolution of the solid precipitated by the salting-out effect

Ten milliliters of 200-mg/mL Na_2CO_3 solution was added dropwise to 10 mL of vigorously stirring 200 mg/mL HPMC solution. The precipitated solid was separated and dried as described in Section 2.2. The solid was dissolved in 500 mL of purified water at 37 °C. The paddle rotation speed was 100 rpm. Dissolution of the solid was microscopically observed.

2.5. Preparation of drug cores

Acetaminophen and HPMC were dissolved in methanol–dichloromethane (54:46, w/w) to yield final concentrations of 13.6% (wt) and 1.36% (wt). A 750-g batch of sucrose spheres was fluidized in a fluidized-bed granulator (GPCG-1, Okawara Mfg. Co. Ltd., Japan). This solution was pumped at a flow rate of 20 g/min and sprayed on the spheres from the side of the granulator. The drying air outlet temperature was 30 °C. The pneumatic spraying pressure was 2.5 kg/cm^2.

2.6. Coating of salting-out layers

HPMC was dissolved in methanol–dichloromethane (70:30, w/w) to yield a final concentration of 2.50% (wt). Na_2CO_3 was pulverized in a jet mill (Spiral Jet Mill 50AS, Hosokawa Micron Co., Japan), and dispersed in the HPMC solution. The ratio of Na_2CO_3 to HPMC was 5:1 (w/w) in all salting-out layers, because the previous study showed that the longest lag time was generated when the ratio was 5:1 (w/w) (Yoshida et al., in press). A 450-g batch of the drug cores was fluidized in the fluidized-bed granulator. This dispersion was pumped at a flow rate of 15–20 g/min and sprayed on the drug cores from the side of the granulator. The drying air outlet temperature was 30–32 °C, and the pneumatic spraying pressure was 3.5–4.5 kg/cm^2.

2.7. Coating of water-penetration-control layers

Cetanol was dissolved in dichloromethane to yield a final concentration of 2.50% (wt). A 350-g batch of beads was fluidized in the fluidized-bed granulator. This solution was pumped at a flow rate of 8.5 g/min and sprayed on the beads from the side of the granulator. The drying air outlet temperature was 39 °C, and the pneumatic spraying pressure was 3.0 kg/cm^2.

2.8. Drug dissolution

Drug dissolution tests were conducted using formulations containing 10 mg of acetaminophen. The tests were performed in accordance with Dissolution Test Method 2 (paddle method) (Japanese Pharmacopoeia XIV, 2001b), using an automatic 6-series dissolution testing device (Toyama Sangyo Co. Ltd., Japan) with a

UV–vis spectrophotometer (Shimazu Co., Japan). Since the pH of saliva was 6.8–7.0 (Azrak et al., 2003), a phosphate buffer with a pH of 6.8 (second fluid, identified in the Disintegration Test cited in Japanese Pharmacopoeia XIV, 2001a) was used as the test fluid. The volume of test fluid was 500 mL, and the paddle rotation speed was 100 rpm. The wavelength used to detect acetaminophen was 254 nm. To calculate precise lag time, the absorbance of the solutions was measured every 2 min from 1 to 181 min after starting the drug dissolution tests.

2.9. Analysis of drug dissolution profiles

For numbness to be masked, it was assumed that no drug should be released in either the oral cavity or the esophagus. Therefore, in this study, lag times of less than 1% were compared among the drug dissolution profiles of various formulations. The lag times 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 term, "immediate drug release," meant that a formulation released 85% of the drug within 30 min after starting the drug dissolution tests. The time at which drug release reached 85% was denoted as $T_{85\%}$; this was determined for each drug dissolution profile. The $T_{85\%}$ values were calculated by regressing linearly between two time points when the released drug was the closest to 85%, less than 85%, and more than 85%.

Differences in lag time, $T_{85\%}$, and drug release rate were statistically evaluated by the Student's *t*-test.

2.10. Dissolution of sodium carbonate

Formulations containing 10 mg of acetaminophen were weighed and dissolved in 500 mL of purified water at 37 °C. The paddle rotation speed was 100 rpm. The conductance of the solutions was measured as described in Section 2.3. The concentrations of Na_2CO_3 were calculated as the conductance using Eq. (1) (Section 2.3).

2.11. Dissolution of hydroxypropylmethylcellulose

The $DS_{53}W_8$ formulation containing 10 mg of acetaminophen were dissolved in 500 mL of purified water at 37 °C. The paddle rotation speed was 100 rpm. Amount of HPMC in the solution was determined using a gel filtration chromatography method and refractive index (RI) detection according to previously reported procedures (Lindstedt et al., 1991; Deshmukha et al., 2007). HPMC was separated on a column (TSKgel Super SW2000, TOSOH Corporation, Japan) using water as the mobile phase at 40 °C at a flow rate of 0.1 mL/min.

2.12. Mean particle size

Particle distribution was determined by measuring beads of 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 percentage cumulative curves. The thickness of each layer was calculated as half of the difference between the average particle size of the beads before and after coating.

3. Results and discussion

3.1. Design of a taste-masking system utilizing salting-out effects

HPMC solutions changed from transparent to turbid white by adding transparent Na_2CO_3 solutions in the Na_2CO_3 concentration range of 1–9 mg/mL (Fig. 1). White solids were precipitated from the turbid mixture solutions in the Na_2CO_3 concentration range of 10–100 mg/mL. The solids contained small amounts of Na_2CO_3, and the largest component was HPMC. These results demonstrated that the salting-out of HPMC was induced by Na_2CO_3, as was predicted in the literatures (Azorlosa and Martinelli, 1962; Harding and Rose, 1962; Nakano et al., 1999)

HPMC was precipitated, agglomerated, and recovered (66–93%), in the Na_2CO_3 concentration range of 40–100 mg/mL (Fig. 1). The efficient salting-out of HPMC might be used for efficient drug release suppression. However, precipitated HPMC wholly redissolved in purified water (Section 2.4). These results indicated that a change in the concentration of Na_2CO_3 induced a reversible change in the physical phase of HPMC in water. This reversible change might be utilized for balancing drug release suppression and immediate drug release.

We applied these phenomena to a "salting-out taste-masking system" in order to obtain a lag time of at least 2 min with subsequent immediate drug release. This system includes a multiparticulate dosage form consisting of a drug core, a salting-out layer, and a water-penetration-control layer (Fig. 2(a)). The salting-out layer contains salts and water-soluble polymers, and the water-penetration-control layer consists of water-insoluble materials. This system is thought to function as follows (Fig. 2(b) and (c)). In the mouth, saliva penetrates the system via the water-penetration-control layer. Since the salts have high-water-solubility and are located outside the drug substance, the salts dissolve in the saliva before the drugs start to dissolve. The water-soluble polymers in the salting-out layer are prevented from dissolving due to the high concentration of the salts in the system. The insolubilized water-soluble polymers suppress drug release, and mask the numbing effect of the drugs. To keep the high concentration of salts in the system for at least 2 min, the water-penetration-control layer controls the water intake rate and the salt dissolution rate. When the system passes through the pharynx and reaches the gastrointestinal tract, the large amount of digestive fluid causes most of the

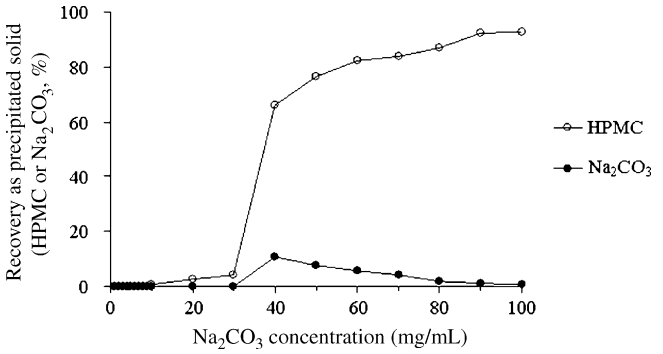

Fig. 1. Effects of Na_2CO_3 concentrations on substances recovered as precipitated solids. The solids precipitated after mixing the Na_2CO_3 solutions and HPMC solutions were separated and weighed after drying. The weights of Na_2CO_3 in the solids were obtained by dissolving the solids in water and measuring the conductance of the solutions. The weights of HPMC in the solids were calculated by subtracting the weights of Na_2CO_3 from the total weights of the solids. The rates of recovery as the precipitated solids (%) were obtained by dividing the weights of HPMC or Na_2CO_3 in the precipitated solids by the weights of whole HPMC or Na_2CO_3 that had been dissolved in the solutions.

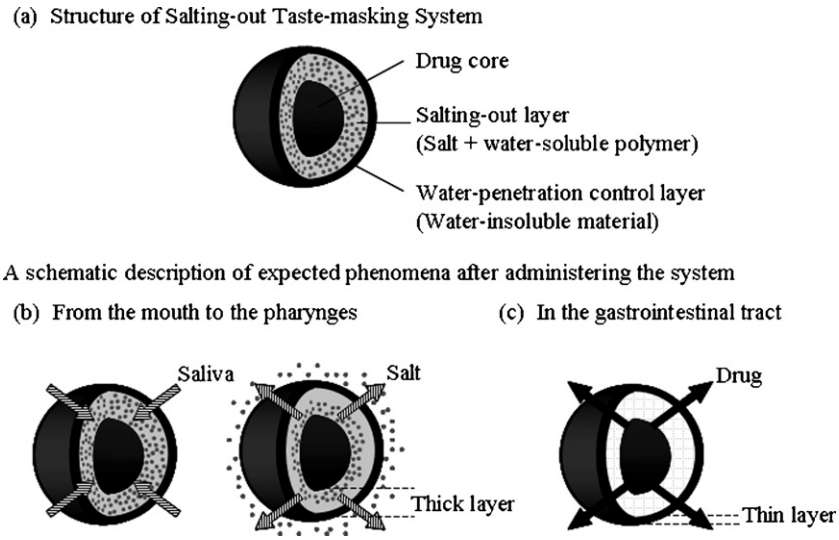

Fig. 2. Structure of the salting-out taste-masking system and a schematic description of expected phenomena after its administration. (a) Structure of the salting-out taste-masking system. (b) The water-penetration-control layer controls the saliva intake rate and salt dissolution rates from the mouth to the pharynx. Dissolved salts in the saliva prevent the water-soluble polymers from dissolving via the salting-out effect. The insolubilized water-soluble polymers suppress drug release and mask drug numbness. (c) In the gastrointestinal tract, most of the salts dissolve out from the system, the water-soluble polymers dissolve, therefore, drug release is immediate via the thin water-penetration-control layer.

salts dissolve out of the system, thereby decreasing the salt concentration, and dissolving the water-soluble polymers. Only the thin water-penetration-control layer remains around the drug core. This allows the drug to be released immediately in the gastrointestinal tract.

Fig. 1 shows that the salting-out taste-masking system containing Na_2CO_3 and HPMC functions as expected. Efficient salting-out of HPMC occurred at a Na_2CO_3 concentration threshold of 30–40 mg/mL or higher concentrations. In this system, the Na_2CO_3 solids are believed to maintain the saturated Na_2CO_3 concentration for a time after contacting water. Since the saturated concentration of Na_2CO_3, approximately 300 mg/mL at 25 °C (Robinson and Macaskill, 1979), is higher than the threshold, the salting-out of HPMC by Na_2CO_3 is expected to occur. Moreover, all of the Na_2CO_3 dissolves out, and the Na_2CO_3 concentration decreases due to dilution in the digestive fluids after the lag time. The volumes of gastric and intestinal water have been reported to be 500–1000 mL (Dressman et al., 1998). Assuming that a concentration of Na_2CO_3 in the digestive fluids is the threshold (30–40 mg/mL), 15–40 g of Na_2CO_3 should be administered to patients. This amount is too large to be taken at one time. In a normal dosing situation, the concentration of Na_2CO_3 in the digestive fluids is less than the threshold, HPMC dissolves in the digestive fluids, and the drug is released immediately after the lag time.

3.2. Drug dissolution from the salting-out taste-masking system

A salting-out taste-masking system was prepared using drug cores containing acetaminophen, the salting-out layers containing Na_2CO_3 and HPMC, and the water-penetration-control layer consisting of cetanol. The $DS_{53}W_8$ formulation (Table 1) was prepared as follows: the drug core was coated with 53% (wt) salting-out layer, and subsequently coated with 8% (wt) water-penetration-control layer. The $DS_{53}W_8$ formulation generated a lag time of more than 2 min (5.4 min), and a $T_{85\%}$ of less than 30 min (26 min, Fig. 3(a)). Salting-out of HPMC in the presence of Na_2CO_3 might cause the long lag time, and dissolution of HPMC in the absence of Na_2CO_3 might induce the immediate drug release. The salting-out taste-masking system had the potential to combine numbness masking with high bioavailability.

3.3. Dissolution of sodium carbonate and hydroxypropylmethylcellulose from the salting-out taste-masking system

The dissolutions of Na_2CO_3 and HPMC were measured for the $DS_{53}W_8$ formulation. The release of Na_2CO_3 occurred sooner than that for the drug (Fig. 3(b)). Approximately 85% of the Na_2CO_3 had been released by 9 min after starting the dissolution test. In other words, at least 15% of the solid Na_2CO_3 remained in the salting-out layer, and the saturated concentration of Na_2CO_3 was probably maintained in the system for about 9 min. The release of HPMC was suppressed by 9 min, and then HPMC was released immediately (Fig. 3(b)). The drug release rates from the $DS_{53}W_8$ formulation also changed at around 9 min. The dissolution profile of drug and HPMC were similar. These corresponding results supported the assertion that the high concentration of Na_2CO_3 insolubilized HPMC, which suppressed drug release while the solid Na_2CO_3 remained in the system. Moreover these data indicated that immediate drug release after the lag time was caused by the immediate dissolution of HPMC, as designed.

Table 1
Formulations prepared in this study

Formulation[a]	Drug core (mg)	Salting-out layer (mg)	Water-penetration-control layer (mg)	Total (mg)
D	60.5	–	–	60.5
$DS_{53}W_8$	60.5	32.1	7.4	100.0
DS_{23}	60.5	14.1	–	74.6
DS_{40}	60.5	24.0	–	84.5
DS_{53}	60.5	32.1	–	92.6
DS_{72}	60.5	43.6	–	104.1
$DW_{2.5}$	60.5	–	1.5	62.0
DW_5	60.5	–	3.0	63.5
DW_{10}	60.5	–	6.1	66.6
DW_{15}	60.5	–	9.1	69.6

[a] D, S, W, and subscripts stand for the drug core, salting-out layer, water-penetration layer, and coating amount [% (wt)] of the layers, respectively.

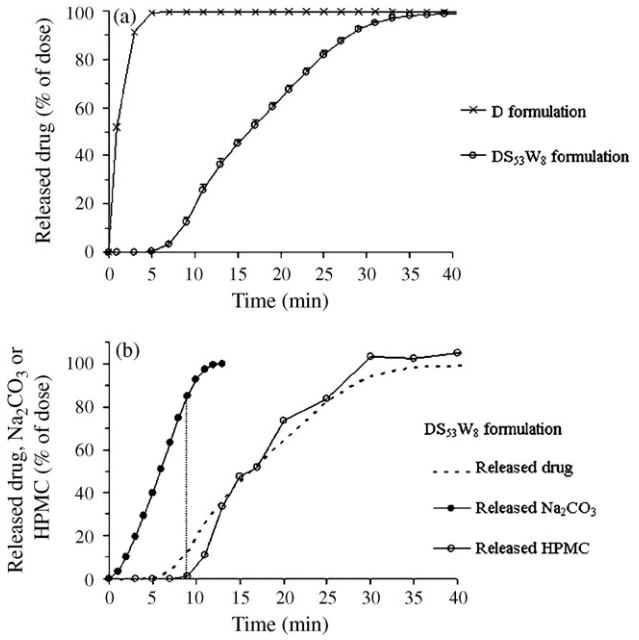

Fig. 3. Dissolution of drug and Na_2CO_3 from the $DS_{53}W_8$ formulation (salting-out taste-masking system). (a) Dissolution of drug from the D and $DS_{53}W_8$ formulation. The $DS_{53}W_8$ formulation contains the drug core, the salting-out layer [53% (wt)], and the water-penetration-control layer [8% (wt)]. Paddle method, 500 mL of phosphate buffer (pH 6.8), 100 rpm. Each result shows the mean ± S.D. (n = 3). (b) Dissolution of drug, Na_2CO_3, HPMC from the $DS_{53}W_8$ formulation. Paddle method, 500 mL of purified water, 100 rpm.

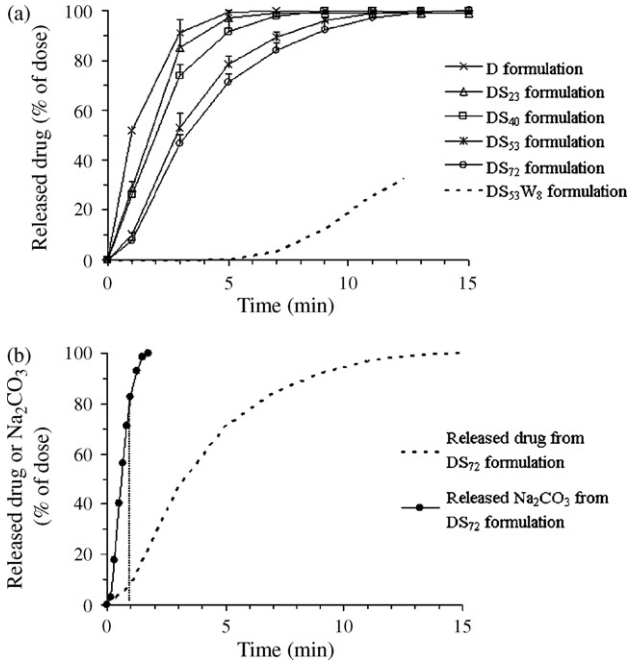

Fig. 4. Dissolution of drug and Na_2CO_3 from the DS_X formulations containing no water-penetration-control layers. (a) Dissolution of drug from the D, DS_X, and the $DS_{53}W_8$ formulations. The DS_X formulations contain the drug core and a salting-out layer [X% (wt)]. Paddle method, 500 mL of phosphate buffer (pH 6.8), 100 rpm. Each result shows the mean ± S.D. (n = 3). (b) Dissolution of drug and Na_2CO_3 from the DS_{72} formulation. Paddle method, 500 mL of purified water, 100 rpm.

3.4. Effects of water-penetration-control layers on drug dissolution profiles

During the investigation of water-penetration-control layer function, formulations containing no water-penetration-control layers were prepared as negative controls by coating the drug cores with the salting-out layers only (DS_X formulations). The DS_{23}, DS_{40}, DS_{53}, and DS_{72} formulations (Table 1) contained the drug core and, by weight, 23%, 40%, 53%, and 72% salting-out layers, respectively. The lag time of the $DS_{53}W_8$ formulation (5.4 min) was much longer (P < 0.05) than that of the DS_{53} formulation (0.1 min, Fig. 4(a)). This comparison proved that the water-penetration-control layer was necessary to generate the long lag time.

3.5. Dissolution of sodium carbonate from the salting-out taste-masking system without a water-penetration-control layer

The drug release profile from the DS_{72} formulation was well fitted in a first order release equation, except for a point of drug release of 0–1 min. The drug release rate of 0–1 min were separately calculated to be 0.080 min^{-1}, which was slower (P < 0.05) than 0.293 min^{-1} of that of 1–7 min (R^2 = 0.9995, Table 2). The salting-out layer decreased the drug release rate from the DS_{72} formulation for 1 min. Dissolution of Na_2CO_3 from the formulation was measured to investigate the functions of the salting-out layers. The release of Na_2CO_3 occurred sooner than that for the drug (Fig. 4(b)). Approximately 85% of the Na_2CO_3 was released 1 min after starting the dissolution test. The insolubilized HPMC might suppress drug release while the solid Na_2CO_3 remained in the DS_X formulation. For both the $DS_{53}W_8$ formulation (salting-out taste-masking system) and the DS_{72} formulation, approximately 10% of the drug was released when approximately 85% of the Na_2CO_3 was released (Figs. 3(b) and 4(b)). This correspondence supported that the insolubilized HPMC in the salting-out layer suppressed drug release.

The Na_2CO_3 release rate from the $DS_{53}W_8$ formulation was slower (P < 0.05) than that from the DS_{72} formulation (Figs. 3(b) and 4(b)). This comparison proved that the water-penetration-control layer suppressed the Na_2CO_3 release rate, as designed. The water-penetration-control layer was necessary to control the Na_2CO_3 release rate and generate the long lag time.

3.6. Effects of salting-out layers on drug dissolution profiles

To investigate the function of the salting-out layer, formulations containing no salting-out layer were prepared by coating the drug cores with only the water-penetration-control layer (DW_Y formulations). The $DW_{2.5}$, DW_5, DW_{10}, and DW_{15} formulations

Table 2
Correlation coefficients of fitting drug dissolution profiles (5–85%) to the first-order release model, the zero-order release model, and the Korsmeyer–Peppas equation

Formulation name	First-order release model		Zero-order release model		Korsmeyer–Peppas equation	
	Rate constant (min^{-1})	Correlation coefficient	Rate constant (% min^{-1})	Correlation coefficient	n	Correlation coefficient
DS_{72}	0.293	0.9995	12.66	0.9487	0.18	0.9985
$DS_{53}W_8$	0.098	0.9823	4.19	0.9940	0.43	0.9995
$DW_{2.5}$	0.188	0.9584	8.66	0.9986	1.02	0.9986
DW_5	0.055	0.9418	2.69	0.9969	1.17	0.9985
DW_{10}	0.013	0.9696	0.94	0.9887	1.25	0.9978

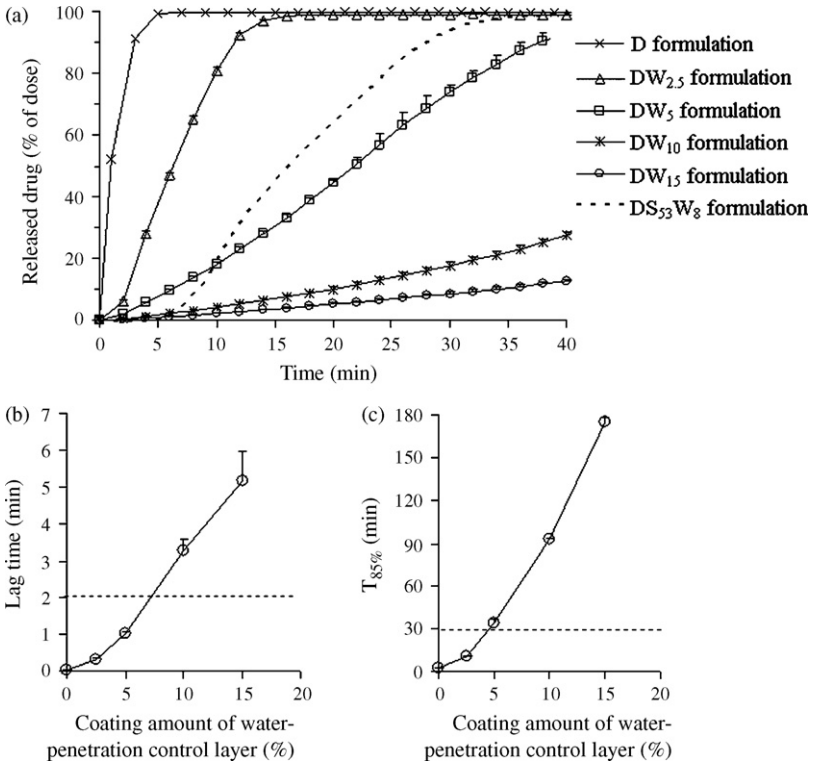

Fig. 5. Drug dissolution from the DW_Y formulations containing no salting-out layers. (a) Drug dissolution from the D, DW_Y, and $DS_{53}W_8$ formulations. The DW_Y formulations contain drug cores and *Y*% (wt) of the water-penetration-control layers. Paddle method, 500 mL of phosphate buffer (pH 6.8), 100 rpm. Each result shows the mean ± S.D. ($n = 3$). (b) Effects of the amount of coating of the water-penetration-control layers on lag times (times when released drug are less than 1%). (c) Effects of the amount of the water-penetration-control layer on $T_{85\%}$ (time at which 85% of the drug has been released).

(Table 1) contained the drug core and, by weight, 2.5%, 5%, 10%, and 15% water-penetration-control layer. The thicknesses of the water-penetration-control layers of the $DS_{53}W_8$ and DW_{10} formulations were similar (23 and 25 μm, respectively). The lag time of the $DS_{53}W_8$ formulation (5.4 min) was longer ($P < 0.05$) than that of the DW_{10} formulation (3.3 min, Fig. 5(b)). This indicated that the salting-out layer contributes to the long lag time.

The drug dissolution profiles from 5 to 85% were fitted in zero-order, first-order models, and Korsmeyer–Peppas equation (Ritger and Peppas, 1987) (Table 2). In the $DW_{2.5}$, DW_5, DW_{10}, and $DS_{53}W_8$ formulations, correlation coefficients for zero-order kinetics were higher than those of first-order kinetics, therefore the drug release was governed by zero-order release model. The order of zero-order drug release rate was DW_5 (2.69) < $DS_{53}W_8$ (4.19) < $DW_{2.5}$ (8.66) (all $P < 0.05$). In contrast, the lag time of the $DS_{53}W_8$ formulation (5.4 min) was much longer (all $P < 0.05$) than those of the $DW_{2.5}$ (0.3 min) and DW_5 (1.0 min, Fig. 5(b)) formulations. This indicated that the salting-out layer was important for obtaining a long lag time with subsequent immediate drug release.

The DW_{15} formulation generated 5.2 min of lag time (Fig. 5(b)), which was similar to that of the $DS_{53}W_8$ formulation (5.4 min); however, its $T_{85\%}$ of 170 min (Fig. 5(c)) was much longer ($P < 0.05$) than that of the $DS_{53}W_8$ formulation (26 min). The DW_5 formulation generated a $T_{85\%}$ of 32 min (Fig. 5(c)) similar to that of the $DS_{53}W_8$ formulation (26 min); however, its lag time was only 1.1 min (Fig. 5(b)), which was much shorter ($P < 0.05$) than that of the $DS_{53}W_8$ formulation (5.4 min). These results also indicated that the salting-out layer was a key component for obtaining a long lag time with subsequent immediate drug release.

Water-penetration-control layers of at least 7% (wt) were expected to generate lag times of at least 2 min (Fig. 5(b)), and those less than 5% (wt) were expected to generate a $T_{85\%}$ of less than 30 min (Fig. 5(c)). These two targets could not be reached with the DW_Y formulation no matter how thick the water-penetration-control layer was. This was probably because the water-penetration-control layer suppressed drug release in both the early and late stages of the dissolution tests. Other water-insoluble coating layers also suppressed drug release in both stages (Rowe, 1986; Ozturk et al., 1990; Narisawa et al., 1994). The rate of drug release through the water-insoluble coating layers is described using a square root of time or zero-order release model (Zhang et al., 1991). Therefore, it was reasonable that the DW_Y formulations were not able to achieve the target of long lag time with subsequent immediate drug release. In contrast, the $DS_{53}W_8$ formulation containing both the salting-out layer and the water-penetration-control layer allowed the target to be reached (Fig. 5(a)). The drug dissolution profiles of the $DS_{53}W_8$ and DW_5 formulations intersected at around 10 min. This result indicated that the drug release rates from the $DS_{53}W_8$ formulation changed significantly between the early and late stages of the dissolution test. The salting-out layer induced the change in drug release rate.

The thicknesses of the water-penetration-control layers of the $DS_{53}W_8$ and DW_{10} formulations were similar. Our hypothesis predicted that the drug release rates after the lag times were also similar for the two formulations, because, after almost all of the salting-out layer had dissolved, the drug release rates were controlled only by the water-penetration-control layer (Fig. 2(c)). However, the drug release rate after the lag time for the $DS_{53}W_8$ formulation ($T_{85\%}$ 26 min) was faster ($P < 0.05$) than that for the DW_{10} formulation ($T_{85\%}$ 92 min, Fig. 5(a)). This difference indicated that the salting-out layer increased the drug release rate after the lag time. The release rate of HPMC with high-molecular weight through 8% of the water-penetration-control layer (Fig. 3(b)) was faster ($P < 0.05$) than the release rate of the drug with low-molecular

weight through 5% of the water-penetration-control layer (Fig. 5). These results indicated that permeability of the water-penetration-control layer was changed by the salting-out layer (HPMC or Na_2CO_3), which probably caused the immediate drug release.

The order of the diffusional exponent values (n) was DS_{72} (0.18) < $DS_{53}W_8$ (0.43) < $DW_{2.5}$ (1.02) < DW_5 (1.17) < DW_{10} (1.25) (all $P < 0.05$, Table 2). The correlation coefficients and the diffusional exponent values indicated the model governing the drug release was the first-order release model in the DS_{72} formulation, the Fickian diffusion in the $DS_{53}W_8$ formulation (Ritger and Peppas, 1987), and the zero-order release model in the $DW_{2.5}$, DW_5, and DW_{10} formulations. These results probably show that both the salting-out and water-penetration-control layers contributed to the drug release from the $DS_{53}W_8$ formulation. The smaller diffusional exponent value of the $DS_{53}W_8$ formulation than that of the DW_Y formulations might be caused by that the salting-out layer increase the drug release rates soon after the lag time.

Swelling of a croscarmellose sodium layer was reported to rupture an outer water-insoluble layer and release drug immediately (Dashevsky et al., 2006). In the literature, macroscopical observation of the multiparticulate formulation in a dissolution test showed that the swelling caused to rupture the layer and release drug immediately. To confirm whether HPMC in the salting-out layer swelled, and ruptured the water-penetration-control layer, the $DS_{53}W_8$ formulation during the drug dissolution test was sampled, and macroscopically observed using an optical microscope (175× magnification). The results revealed that the formulation kept the spherical shape in the dissolution tests, and any rupture, clack, pore or hole of the water-penetration-control layer was not observed. It was indicated that rupture of the water-penetration-control layer due to HPMC swelling was not the reason for the immediate drug release. On the other hand, many literatures reported that salt in formulations induced osmotic influx of water into the formulations (Lindstedt et al., 1989; Schultz and Kleinebudde, 1997; Zhang et al., 2003; Heng et al., 2004). The water influx by high-osmotic pressure generated micropores in water insoluble layers in literatures (Taupin et al., 1975; Verma et al., 2000). Na_2CO_3 also induces the high-water influx, and probably generated the micropore in the water-penetration-control layer, which might induce the change of permeability of the water-penetration-control layer, and the increase of the drug release rate.

4. Conclusion

A salting-out taste-masking system consisting of a drug core, a salting-out layer (containing salts and water-soluble polymers), and a water-penetration-control layer (consisting of water-insoluble materials) has been designed. This study has shown that the water-penetration-control layer is effective to keep salting-out of a water-soluble polymer for a sufficient time, and generate a long lag time. The salting-out layer has been shown to play both roles of generating a long lag time and an immediate drug release. Both the salting-out layer and the water-penetration-control layer cooperated to obtain the target drug dissolution profile. This salting-out taste-masking system is expected to become a useful for effective, safe, and user-friendly drug therapy.

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