International Journal of Pharmaceutics 376 (2009) 13–21

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Effects of physicochemical properties of salting-out layer components on drug release

Hiroaki Tasaki[a,*], Takayuki Yoshida[a], Atsushi Maeda[a], Masataka Katsuma[b], Kazuhiro Sako[a]

[a] Drug Delivery, Pharmaceutical Research and Technology Labs, Astellas Pharma Inc., 180 Ozumi, Yaizu, Shizuoka 425-0072, Japan
[b] Pharmaceutical Planning, Pharmaceutical Research and Technology Labs, Astellas Pharma Inc., 180 Ozumi, Yaizu, Shizuoka 425-0072, Japan

ARTICLE INFO

Article history:
Received 27 December 2008
Received in revised form 3 April 2009
Accepted 5 April 2009
Available online 11 April 2009

Keywords:
Salting-out effect
Taste-masking
Numbness
Lag time
Immediate drug release
Multiparticulate dosage form

ABSTRACT

A "Salting-out Taste-masking System" generates a long lag time for numbness and bitterness masking, with subsequent immediate drug release to exert pharmacological effects. In this study, the effects of physicochemical properties of salting-out agents and water-soluble polymers in the salting-out layer on the dissolution behaviors of acetaminophen were investigated and predominant factors for lag time generation (Lag time index, hereafter LI) and subsequent drug release (Rapid release index, hereafter RI) were discussed. Each prepared formulation showed a different dissolution profile of acetaminophen with a lag time and subsequent immediate release. Significant correlations between both LI and RI and ΔCST (the salting-out power of salting-out agents) (r^2 = 0.90, 0.67, respectively) and between both LI and RI and CST_1 (the sensitivity of water-soluble polymers to a salting-out effect) (r^2 = 0.98, 0.71, respectively) were shown. These results suggest that the components showing a strong salting-out effect inside the beads lead to extended lag times and slow drug releases after the lag times. Results further suggest the use of CST_1 to evaluate suitable combinations of salting-out agents and water-soluble polymers in this system.

1. Introduction

Drugs with unpleasant tastes, namely numbness and bitterness, occasionally reduce patients' compliance for medicine intake. When multiparticulate dosage forms are taken by patients, a small portion of the dosage forms remains in the epiglottic vallecula or adheres to the epiglottis for 1–2 min (Morita, 2003; Helm et al., 1983; Oguchi et al., 2000). Taste-masking is therefore an important technology for multiparticulate dosage forms containing such drugs. To mask numbness and bitterness, a lag time of at least 2 min would be necessary. Simultaneously, to exert pharmacological effects, immediate drug release in the gastrointestinal tract is desirable (Löbenberg et al., 2000; Blume et al., 1993).

To achieve the above goals, we have previously designed a "Salting-out Taste-masking System" that generates an extended lag time with subsequent immediate drug release (Yoshida et al., 2008a, b). This system utilizes the salting-out effect of water-soluble polymers (Nakano et al., 1999; Eeckman et al., 2001; Azorlosa and Martinelli, 1962; Harding and Rose, 1962). When salts are added to a solution of a non-ionic water-soluble polymer, dissociated ions remove the water molecules hydrating the polymer chains. This dehydration leads to the precipitation or the gelation of the polymer caused by the association of hydrophobic groups on the polymer chains. A non-ionic water-soluble polymer is known to have a lower critical solution temperature (LCST, hereafter CST) in water (Eeckman et al., 2001), and is therefore soluble at temperatures lower than the CST, as well as becomes insoluble at the CST due to phase-separation (Mitchell et al., 1990; Mitchell et al., 1993; Nakano et al., 1999; Iwanami Physics and Chemical Dictionary 4th edition, 1987; Liu et al., 2007; Li et al., 2002). CST is decreased by the addition of various types of salts. This reduction order in CST is generally known as the Hoffmeister series, reflecting the salting-out power of various salts (Eeckman et al., 2001; Mitchell et al., 1990, 1993; Nakano et al., 1999).

Various techniques available for masking bitterness of drugs are currently used including formation of inclusion-complexes with cyclodextrins, formation of ionic-complex such as ion-exchange resins, spray congealing with lipids, and beads or pellets coating with membranes of water-insoluble or poorly water-soluble materials which act as a physical barrier to inside drugs (Nanda et al., 2002; Sugao et al., 1998; Hashimoto et al., 2002; Kajiyama et al., 2006; Sohi et al., 2004; Yajima et al., 1996; Al-Omran et al., 2002; Agarwal et al., 2000; Lu et al., 1991; Takahashi et al., 1988). Considerable research has been performed on taste-masking using a coating technique due to the simplicity and the feasibility of the technique (Sohi et al., 2004; Pollinger et al., 1997; Shirai et al., 1992; Gupte et al., 2002; Kurimoto et al., 2005). Although the effects of salts on drug release rates from tablets have ever been reported

* Corresponding author. Tel.: +81 54 627 6879; fax: +81 54 627 9918.
E-mail address: hiroaki.tasaki@jp.astellas.com (H. Tasaki).

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doi:10.1016/j.ijpharm.2009.04.003

(Bajwa et al., 2006; Kajiyama et al., 2008; Eeckman et al., 2002; Talukdar et al., 1998; Mitchell et al., 1990), no studies have investigated coating-based taste-masking systems using the salting-out effect for dissolution control. Our taste-masking system is a multiparticulate dosage form composed of a drug core, a salting-out layer comprising salting-out agents (salts) and water-soluble polymers, and a water-penetration-control layer comprising poorly water-soluble materials. The water-penetration-control layer regulates the saliva penetration rate while the dosage form is in the mouth. The salting-out agent dissolved in the saliva prevents the water-soluble polymer from dissolving due to the salting-out effect. The insolubilized water-soluble polymer suppresses drug release and masks numbness and bitterness. In the gastrointestinal tract, most of the salting-out agent dissolves and eliminated by the system and the water-soluble polymer then hydrates and dissolves, leading to immediate drug release. We have previously reported the formulation, which generate a lag time of 2 min or longer with a subsequent immediate drug release. The beads containing both 53 wt% salting-out layer and 8 wt% water-penetration-control layer showed a lag time of 5.4 min and a $T_{85\%}$ (the time for 85% of the drug to be released) of 26 min. On the contrary, the beads containing only 53 wt% salting-out layer showed no lag times (0.1 min), and the beads containing only 10 wt% water-penetration-control layer showed a sustained release with a $T_{85\%}$ of 92 min. These results suggests 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, and the salting-out layer plays both roles of generating a long lag time and an immediate drug release. Both the salting-out layer and the water-penetration-control layer are crucial (Yoshida et al., 2008a). Further we have described the mechanism behind the change in drug release from the early to late stage of the dissolution test. The phase-change of the water-soluble polymer in the salting-out layer induces the changes in the drug release rate. Insolubilization of the water-soluble polymer in high salt concentrations generates a lag time, and subsequent hydration of the water-soluble polymer in low salt concentrations causes an immediate drug release (Yoshida et al., 2008b). However, the physicochemical properties of salting-out layer components affecting drug dissolution behavior remain unclear.

Here we clarify the predominant physicochemical properties of salting-out agents and water-soluble polymers for lag time generation and subsequent drug release. The formulations containing various types of salting-out agents and water-soluble polymers were prepared. The correlations between the dissolution of the model drug acetaminophen from the prepared formulations and the physicochemical properties of the materials were investigated.

2. Materials and methods

2.1. Materials

Sodium carbonate (hereafter, Na_2CO_3), sodium chloride (hereafter, NaCl), sodium dihydrogenphosphate dihydrate (hereafter, NaH_2PO_4), glycine, trisodium citrate dihydrate (hereafter, sodium citrate), sucrose, disodium hydrogenphosphate (hereafter, Na_2HPO_4), potassium hydrogencarbonate (hereafter, $KHCO_3$), methanol, and dichloromethane were purchased from Kanto Chemical (Japan). Hydroxypropylmethylcellulose (TC-5E) (hereafter, HPMC) and methylcellulose (Metolose SM-4) (hereafter, MC) were purchased from Shin-Etsu Chemical Co. (Japan). Hydroxypropylcellulose (HPC-SL) (hereafter, HPC) was purchased from Nippon soda Co. Ltd. (Japan). Polyethylene glycol 6000 (Macrogol 6000) (hereafter, PEG6000) was purchased from Sanyo Chemical Industries Ltd. (Japan). Two grades of polyvinylpyrrolidone (hereafter, PVP-K90, PVP-K30) were purchased from Wako Pure Chemical Industries Ltd. (Japan). Copolyvidone (Kollidon VA64) was purchased from BASF Japan (Japan). Purified sucrose spheres (Nonparail 103, 500–710 μm) were purchased from Freund Co. (Japan) and used as core materials. Acetaminophen was purchased from Yoshitomi Fine Chemicals (Japan) and used as a model drug. Cetanol (cetyl alcohol, Kalcol 6098) was generously provided by Kao Corporation (Japan).

2.2. Preparation of taste-masked beads

Several formulations of taste-masked beads were prepared according to the method described in the previous studies (Yoshida et al., 2008a,b), and briefly described here. All coating operations were carried out using a fluidized-bed granulator (GPCG-1, Okawara Mfg. Co., Ltd., Japan). Mixtures of methanol–dichloromethane were used for drug layer and salting-out layer coating because methanol–dichloromethane with ratios ranging from 60:40 to 10:90 (w/w) are known to be good solvents for HPMC (Metolose product's brochure, 2004; TC-5 product's brochure, 2002). HPMC acts as a binder for acetaminophen in the drug layer, and as a water-soluble polymer for lag time generation as well as a binder for various kinds of salts. First, a solution of acetaminophen and HPMC in methanol–dichloromethane (54:46, w/w) was sprayed on sucrose spheres (drug core beads). Second, a dispersion containing a water-soluble polymer and salting-out agent pulverized by a jet mill (Spiral Jet Mill 50AS, Hosokawa Micron Co., Japan) in methanol–dichloromethane (70:30, w/w) was sprayed on the drug core beads. In methanol–dichloromethane (70:30, w/w), PVP-K30, PVP-K90, copolyvidone, and PEG6000 were well dissolved. Finally, a solution of cetanol in dichloromethane was sprayed on the prepared salting-out layer-coated beads. A small portion of each formulation was withdrawn at the amount of cetanol coating of 2, 4, 6, 8, and 10 wt% based on the salting-out layer-coated beads.

2.3. Drug dissolution

Drug dissolution tests were conducted using the prepared formulations containing 10 mg of acetaminophen. The tests were performed in accordance with Dissolution Test Method 2 (paddle method), as cited in the Japanese Pharmacopeia (14th edition), using an automatic 6-series dissolution testing device (Toyama Sangyo Co., Ltd., Japan) with a UV–visible spectrophotometer (Shimadzu Co., Japan). The test conditions are identical to those of previous studies (Yoshida et al., 2008a,b).

2.4. Analysis of drug dissolution profiles

Lag times, the times for 1% of the drug to be released, were assessed for the prepared formulations by linear regression calculations between the two measured time points lying on either side of the 1% drug release period (Yoshida et al., 2008a,b).

The times when the drug release reached 5% and 85% were also calculated by linear regression as mentioned above. The time taken from 5% to 85% of the drug release was shown as $T_{5-85\%}$, and assessed among formulations.

2.5. CST_1 and ΔCST measurement

This method was designed to measure the salting-out effect occurring inside the beads in the initial dissolution phase. Saturated aqueous solutions of salting-out agents were prepared according to the reported solubility data (Encyclopedia CHIMICA, 1987; Kagaku Binran II, 1993) and the solutions were diluted 2-fold (half saturated solution). A total of 25 g of each half saturated solution was added drop wise to 25 g of solutions containing a 0.3 wt% water-soluble polymer. Once drop wise addition was completed, the solutions

Table 1
Formulations prepared in this study.

Component	A (mg)	B (mg)	C (mg)	D (mg)	E (mg)	F (mg)	G (mg)	H (mg)	I (mg)	J (mg)
Drug core										
Nonparail 103	33.3	33.3	33.3	33.3	33.3	33.3	33.3	33.3	33.3	33.3
Acetaminophen	10.0	10.0	10.0	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	1.0	1.0	1.0
Salting-out layer										
Salting-out agent										
Na_2CO_3	19.6	–	–	–	–	–	19.6	19.6	19.6	19.6
NaCl	–	19.6	–	–	–	–	–	–	–	–
Sucrose	–	–	19.6	–	–	–	–	–	–	–
Glycine	–	–	–	19.6	–	–	–	–	–	–
Sodium citrate	–	–	–	–	19.6	–	–	–	–	–
NaH_2PO_4	–	–	–			19.6	–	–	–	–
Water-soluble polymer										
HPMC	3.9	3.9	3.9	3.9	3.9	3.9	–	–	–	–
PVP-K30	–	–	–	–	–	–	3.9	–	–	–
PVP-K90	–	–	–	–	–	–	–	3.9	–	–
Copolyvidone	–	–	–	–	–	–	–	–	3.9	
PEG 6000	–	–	–	–	–	–	–	–	–	3.9
Water-penetration-control layer										
Cetanol[a]	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8
Total	74.6	74.6	74.6	74.6	74.6	74.6	74.6	74.6	74.6	74.6
Particle size (μm, mean ± S.D.)	846 ± 78	826 ± 36	851 ± 51	841 ± 65	811 ± 55	749 ± 57	847 ± 55	810 ± 56	832 ± 97	832 ± 71

[a] A small portion of each formulation was withdrawn at the amount of cetanol coating of 2, 4, 6, 8, and 10 wt% based on the salting-out layer-coated beads.

were cooled to −5 °C (sample solutions were not frozen due to freezing point depression) using a cooler (COOL ACE CA-1100, EYELA, ethylene glycol was used as a cooling agent), and then heated gradually in a water-bath. The temperature at which turbidity developed was named as CST_1.

ΔCST, defined as the difference between CST_0 and CST_1, measured using HPMC as a water-soluble polymer, was used as an indicator for the salting-out power of the salting-out agents in the system. CST_0 was the temperature at which the turbidity of a solution containing 0.15 wt% HPMC developed without salting-out agents. Greater ΔCST means stronger salting-out power. In contrast, CST_1, measured using Na_2CO_3 fixed as a salting-out agent, was used as an indicator for the sensitivity of water-soluble polymers to the salting-out effect in the system. Lower CST_1 means easier precipitation of water-soluble polymers.

2.6. Effect of Na_2CO_3 concentration on CST of HPMC

A saturated aqueous solution of Na_2CO_3 was diluted 4-fold, 8-fold, and 16-fold. A total of 25 g of each solution was added drop wise to 25 g of aqueous solutions containing 0.3 wt% HPMC. CST was measured using the same method as mentioned in Section 2.5.

2.7. Determination of osmolarities of saturated salting-out agent's solutions

The osmolarities of the saturated solutions of Na_2CO_3, NaCl, NaH_2PO_4, glycine, sodium citrate, and sucrose were determined using freezing point depression method (ARKRAY, Inc., OSMO STATION OM-6050).

2.8. Determination of ionic strength for saturated salting-out agent's solutions

The ionic strengths of the saturated solutions of Na_2CO_3, NaCl, NaH_2PO_4, glycine, sodium citrate, and sucrose were calculated using the following equation:

$$I = 0.5\ \Sigma(mz^2) \quad (1)$$

where "m" is molarity and "z" is valency of each ion. All the salting-out agents were treated as a strong electrolyte. The ionic strengths of non-ionic sucrose and zwitterionic glycine were ignored. It was reported that zwitterions did not contribute to the ionic strength of a solution (Stellwagen et al., 2008).

2.9. Measurement of viscosity of water-soluble polymers

The viscosities of aqueous solutions of HPMC, PEG6000, PVP K-30, PVP K-90, and copolyvidone (2 wt%) were measured using a vibro viscometer (A&D Company, Limited, Japan) at 20 °C.

2.10. Particle size analysis of prepared beads

The particle size of prepared beads with 8 wt% cetanol coating was determined using a microscopy. Microscopic techniques are one of the most accurate methods; particles are sized directly and individually (O'Conner et al., 1990). An arithmetic mean diameter was calculated using length (major axis) of a bead as a representative diameter (US Pharmacopeia XXXI, 2008) (n = 20) because the shapes of the obtained beads were almost spherical with mean length-to-width ratios ranging from 1.05 to 1.11 (n = 20, each data not shown).

3. Results and discussion

3.1. Dissolution behavior of prepared tasted-masking beads

A total of ten formulations of taste-masked beads were prepared: six formulations using Na_2CO_3 (Formulation-A), NaCl (Formulation-B), sucrose (Formulation-C), glycine (Formulation-D), sodium citrate (Formulation-E), and NaH_2PO_4 (Formulation-F) as salting-out agents and HPMC as a water-soluble polymer, and four formulations using PVP-K30 (Formulation-G), PVP-K90 (Formulation-H), copolyvidone (Formulation-I), PEG6000 (Formulation-J) as water-soluble polymers and Na_2CO_3 as a salting-out agent (Table 1). The effects of physicochemical properties of the salting-out agents on the dissolution profiles were investigated using Formulation-A, -B, -C, -D, -E, and -F. The effects of physicochemical properties of the water-soluble polymers on the dissolution profiles were investigated using Formulation-A, -G, -H, -I, and -J. To avoid the surface area of the beads affecting the dissolution behavior in each formulation, drug core beads with the same compositions were used and the coating amounts of the salting-out layer for all the formulations were set at 53% based on the drug core beads. The beads with a comparable mean particle diameter were obtained as shown in Table 1.

In the formulations containing various salting-out agents with 8 wt% cetanol coating, the drug release rates were initially suppressed for a fixed amount of time (lag time), followed by a drastic increase (Fig. 1a). For lag time, linear regression analysis for each formulation revealed a significant correlation between lag time length and the amount of cetanol coating ($r^2 > 0.90$, $P < 0.001$) (Fig. 1b). We denoted the slope value of the regression line "Lag time index (LI)" [generated lag time length (min) by 1% cetanol coating]. Greater LIs mean longer lag times. LIs for the salting-out agents were classified in decreasing order as follows: sodium citrate > Na_2CO_3 > NaH_2PO_4 > NaCl > glycine > sucrose (Table 2). For drug release after the lag time, linear regression analysis for each formulation also revealed a significant correlation between $T_{5-85\%}$ and the amount of cetanol coating ($R^2 > 0.96$, $P < 0.001$) (Fig. 1c). We denoted the value of the regression line's slope "Rapid release index (RI)" [increase of $T_{5-85\%}$ (min) by 1% cetanol coating]. Greater RIs mean slower drug release. RIs for

Table 2
Linear regression analysis between lag time and the coating amount of cetanol, and between $T_{5-85\%}$ and the coating amount of cetanol.

	Lag time vs. coating amount		$T_{5-85\%}$ vs. coating amount	
	Slope of regression line	r^2	Slope of regression line	r^2
Salting-out agent				
Na_2CO_3	0.67	0.98	2.50	0.99
NaCl	0.42	0.98	1.54	0.99
Sucrose	0.19	0.96	1.88	0.96
Glycine	0.33	0.90	1.87	0.99
Sodium citrate	0.76	0.99	2.90	0.99
NaH_2PO_4	0.52	0.97	2.58	1.00
Water-soluble polymer				
HPMC	0.67	0.98	2.50	0.99
PVP K-30	0.13	0.85	1.76	0.97
PVP K-90	0.48	0.86	2.59	0.89
Copolyvidone	0.32	0.93	2.12	1.00
PEG 6000	0.12	0.84	2.06	0.97

P values were <0.001 in all the cases.

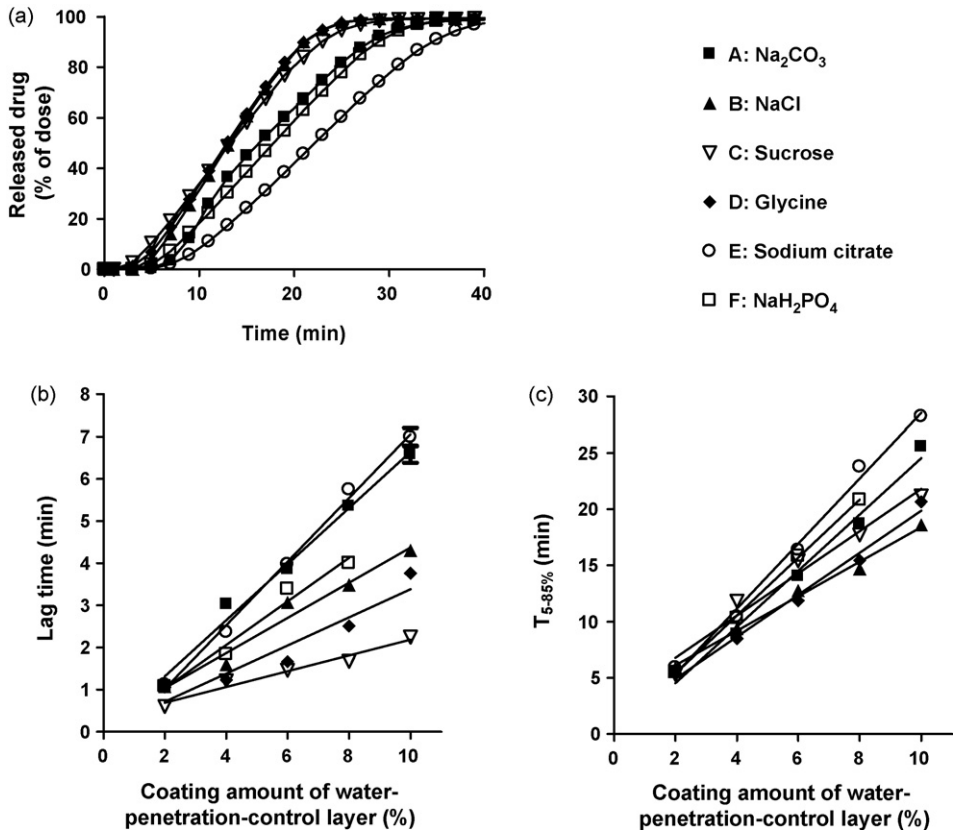

Fig. 1. Drug dissolution from prepared formulations (a) drug dissolution from Formulation-A, -B, -C, -D, -E, and -F. Paddle method, 500 mL of phosphate buffer (pH 6.8), 100 rpm. Each result shows mean ± S.D. ($n = 3$) and error bars are in the symbols. (b) The relationships between the coating amount of cetanol and lag time length in Formulation-A, -B, -C, -D, -E, and -F. (c) The relationships between the coating amount of cetanol and $T_{5-85\%}$ in Formulation-A, -B, -C, -D, -E, and -F.

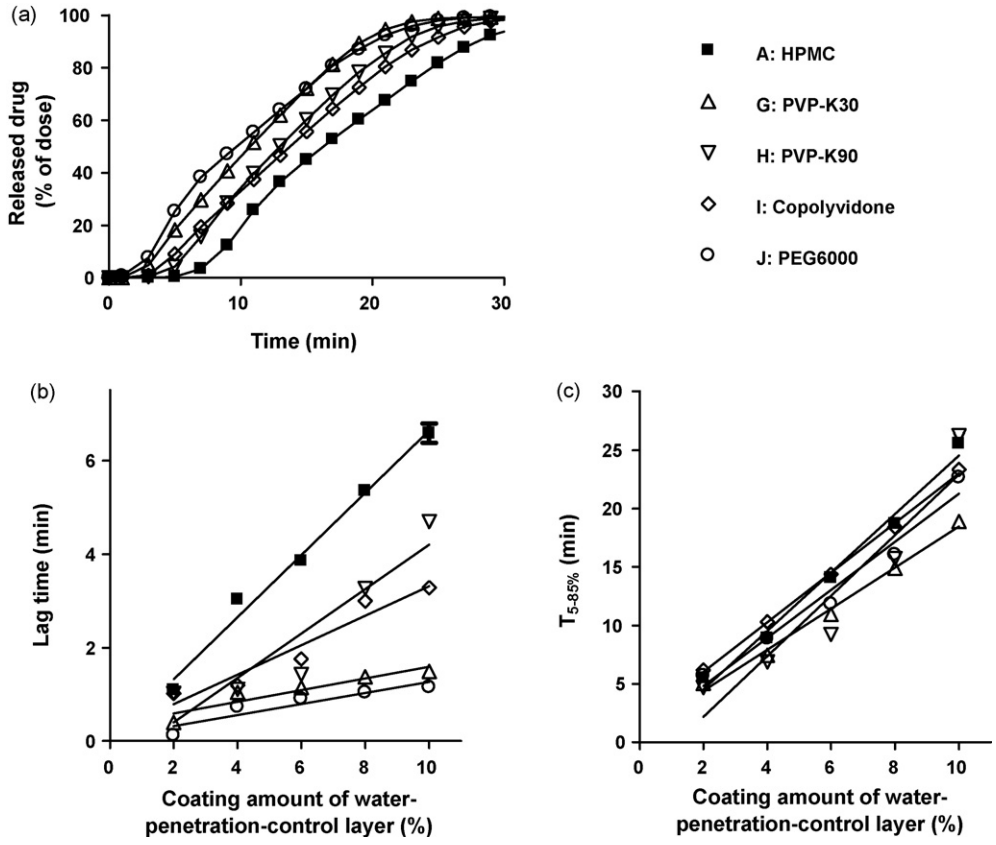

Fig. 2. Drug dissolution from prepared formulations (a) drug dissolution from Formulation-A, G, H, I, and J. Paddle method, 500 mL of phosphate buffer (pH 6.8), 100 rpm. Each result shows mean ± S.D. ($n = 3$) and error bars are in the symbols. (b) The relationships between the coating amount of cetanol and lag time length in Formulation-A, -G, -H, -I, and -J. (c) The relationships between the coating amount of cetanol and $T_{5-85\%}$ in Formulation-A, -G, -H, -I, and -J.

the salting-out agents were classified in decreasing order as follows: sodium citrate > NaH_2PO_4 > Na_2CO_3 > sucrose > glycine > NaCl (Table 2).

Formulation-A, -G to -J with 8% cetanol coating also demonstrated an initial suppression of the drug release, followed by a drastic increase of drug release rate (Fig. 2a). By linear regression analysis, LIs and RIs for water-soluble polymers were classified in decreasing order as follows, respectively: for LI, HPMC > PVP-K90 > copolyvidone > PVP-K30 > PEG 6000 (Fig. 2b, Table 2), and for RI, PVP-K90 > HPMC > copolyvidone > PEG 6000 > PVP-K30 (Fig. 2c, Table 2).

From the obtained results, it was found that the lag time length and the subsequent drug release were variable depending on the kinds of salting-out agents and water-soluble polymers in the salting-out layer.

3.2. Effects of physicochemical properties of salting-out agents on LI and RI

The effects of physicochemical properties of salting-out agents on LI and RI were investigated. ΔCST, molar solubility, molecular weight, ionic strength and osmolarity were used as physicochemical properties of the salting-out agents (Table 3).

Each physicochemical property of salting-out agents was plotted against LI and results were shown in Fig. 3. Statistically significant ($P < 0.01$) correlations were observed between LI and both ΔCST and ionic strength ($r^2 = 0.90$, 0.91, respectively) (Fig. 3a, and d), while molar solubility, molecular weight and osmolarity demonstrated low correlations with LI ($r^2 = 0.04$, 0.03, 0.07, respectively) (Fig. 3b, c, and e). The salting-out effect is known to be influenced by ionic strength. The CST of water-soluble polymers linearly decrease with

Table 3
Physicochemical properties of salting-out agents and water-soluble polymers.

Salting-out agent	CST_1 (°C)	ΔCST (°C)	Solubility (mol/L)	Molecular weight	Ionic strength	Osmolarity (Osm)
Na_2CO_3	0	65	2.7	106.1	8.0	5.8
NaCl	40	25	5.4	58.4	5.4	10.1
Sucrose	55	10	2.6	342.3	0	2.9
Glycine	45	20	2.9	75.1	0	2.9
Sodium citrate	10	55	1.8	294.1	11.0	4.8
NaH_2PO_4	20	45	5.3	156.0	5.3	7.1

Water-soluble polymer	CST_1 (°C)	Viscosity (2 wt%, 20 °C) (mPa s)
HPMC	0	3.1
PVP K-30	50	1.5
PVP K-90	20	5
Copolyvidone	40	1.4
PEG 6000	55	1.6

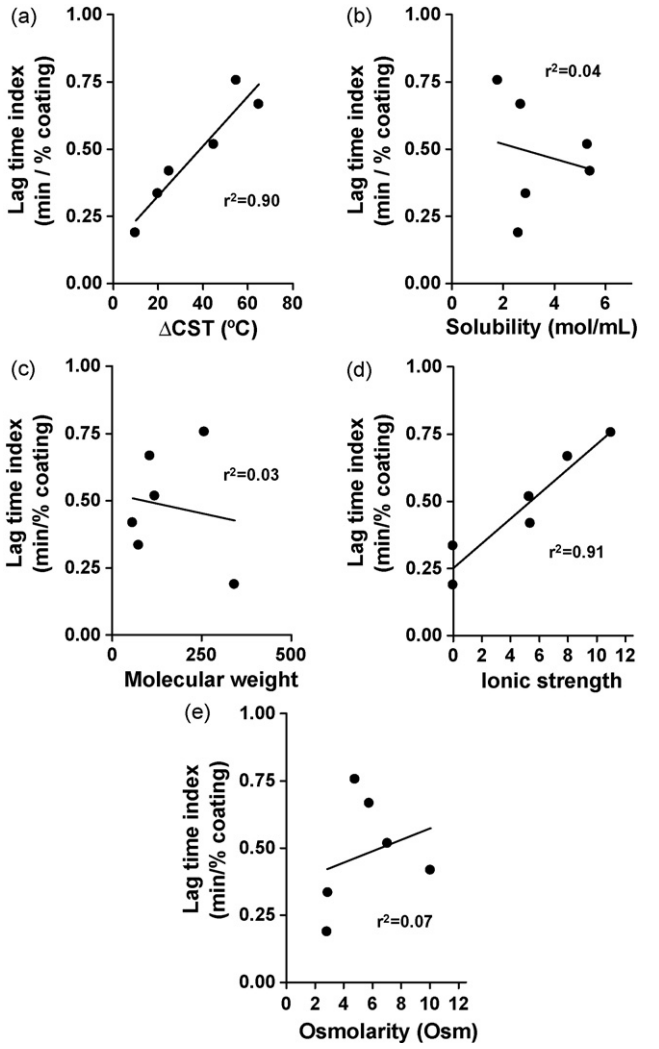

Fig. 3. Linear regression analysis between the lag time index and physicochemical properties of salting-out agents. (a) ΔCST, (b) solubility, (c) molecular weight, (d) ionic strength, and (e) osmolarity

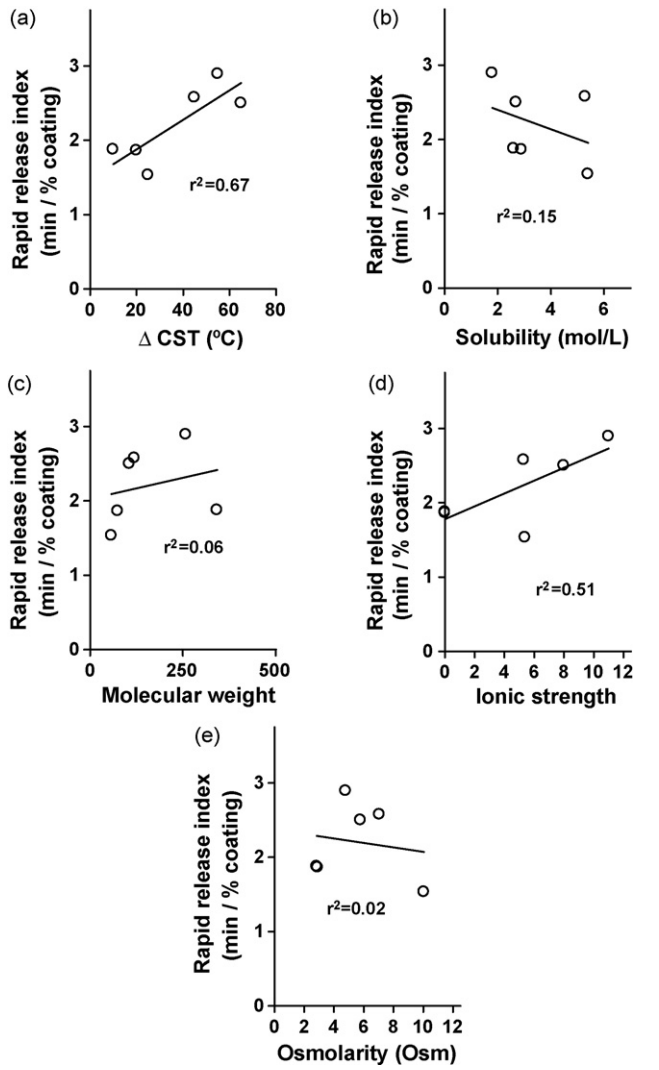

Fig. 4. Linear regression analysis between the rapid release index and physicochemical properties of salting-out agents. (a) ΔCST, (b) solubility, (c) molecular weight, (d) ionic strength, and (e) osmolarity

an increase in ionic strength (Mitchell et al., 1990). Significant correlations of not only ΔCST but also ionic strength with LI suggest that the salting-out effect contributes to lag time generation in the system. Each physicochemical property was also plotted against RI and results were shown in Fig. 4. ΔCST also showed a positive correlation with RI (r^2 = 0.67) (Fig. 4a), a little lower than that of LI. Molar solubility, molecular weight and osmolarity demonstrated low correlations with RI (r^2 = 0.15, 0.06, 0.02, respectively) (Fig.4b, c, and e). This result suggests that salting-out agents causing strong salting-out effect generate long lag times and decrease drug release rates after the lag times.

3.3. *Effects of physicochemical properties of water-soluble polymers on LI and RI*

The effects of physicochemical properties of water-soluble polymers on LI and RI were investigated. CST_1 and viscosity were used as physicochemical properties of the water-soluble polymers (Table 3). In particular, the CST_1 of copolyvidone exhibited 5 °C initially, and then increased to 40 °C a day later. This might be due to the ester-bond breakage by hydrolysis under strong basic condition caused by Na_2CO_3. Linear regression analysis resulted in statistically significant ($P < 0.05$) correlations between both LI and RI and CST_1 (r^2 = 0.98, 0.71, respectively) (Figs. 5a and 6a). This suggests that CST_1 is a predominant factor for lag time formation and subsequent drug release. Polymers with a low CST_1 show long lag times and slow drug releases after lag times. Moreover, a negative correlation between RI and viscosity (r^2 = 0.74) suggests that the viscosity of water-soluble polymers affects the subsequent drug release rate (Fig. 6b). Drug release rates after the lag times decrease with an increase in viscosity of a water-soluble polymer.

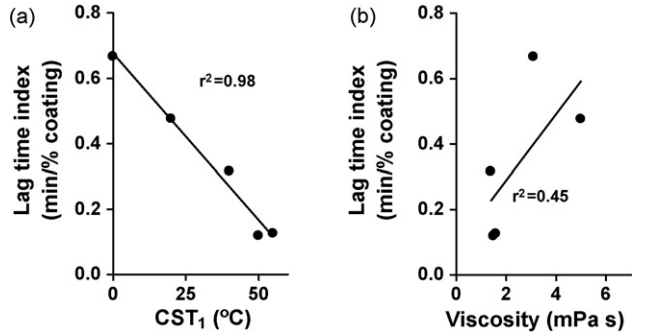

Fig. 5. Linear regression analysis between the lag time index and physicochemical properties of water-soluble polymers. (a) CST_1 and (b) viscosity

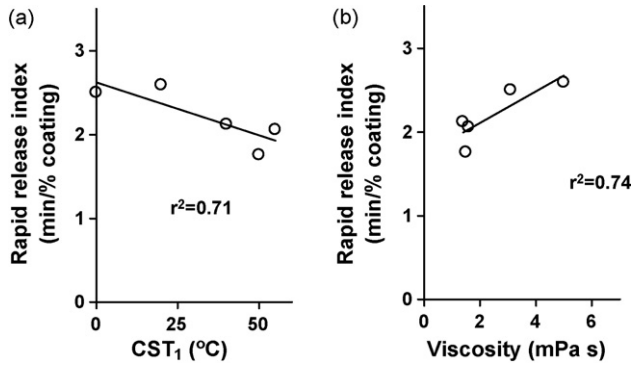

Fig. 6. Linear regression analysis between the rapid release index and physicochemical properties of water-soluble polymers. (a) CST_1 and (b) viscosity

3.4. Mechanism of lag time formation and subsequent drug release

It was found that both ΔCST for salting-out agents and CST_1 for water-soluble polymers were predominant factors for LI and RI. As explained in Section 2.5, ΔCST was defined as the difference between CST_0 (constant value) and CST_1. Essentially, CST_1 measured for the evaluation of the salting-out agents itself correlated with LI and RI, which would allow us to discuss the mechanism of lag time formation and subsequent drug release using CST_1. Schematic images of the CST changes inside the beads during lag time generation and subsequent drug release were illustrated in Fig. 8. Assuming that the temperature inside the oral cavity and the esophagus is approximately 37 °C, CST_1 should be less than 37 °C so that our taste-masking system could exert two functions of lag time generation and subsequent drug release as expected. When concentrations of the salting-out agents are high, water-soluble polymers would show CSTs lower than 37 °C and could not hydrate inside the beads (keep insolubilized state) (Fig. 8b). On the contrary, when the concentrations of the salting-out agents are low after the elimination from the system, water-soluble polymers would show CSTs higher than 37 °C and could hydrate inside the beads (change to solubilized state) (Fig. 8c). Formulation-A beads with 8 wt% cetanol coating were taken as representative model beads and the concentration of Na_2CO_3 inside the beads was calculated to be 308 mg/mL, higher than reported saturated Na_2CO_3 concentration of 280 mg/mL using the following data: the volume of 1 particle, 3.17×10^{-4} mL; total of 73.2 mg of the beads containing 19.6 mg of Na_2CO_3; the number of particles, 200 ($n = 3$, S.D. = 2.9). As shown in Fig. 7, the CSTs of HPMC decreased with increase in Na_2CO_3 concentration, which is in good agreement with several reported results (Liu et al., 2007; Mitchell et al., 1990). Furthermore, in our previous work, it was reported that 85% of Na_2CO_3 was released from the beads at the time when 10% of acetaminophen was released, and followed by drastic changes of dissolution rate (Yoshida et al., 2008a,b). These results would support the concept and the mechanism of our taste-masking system.

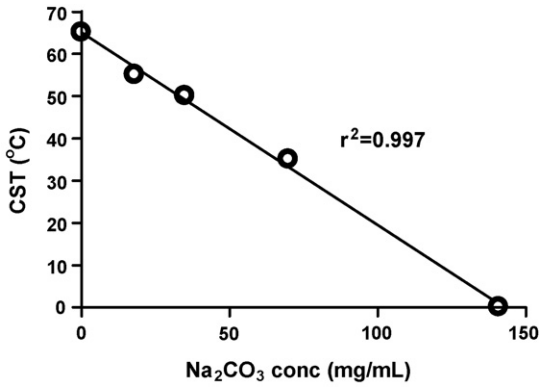

Fig. 7. Effects of Na_2CO_3 concentrations on CSTs of HPMC.

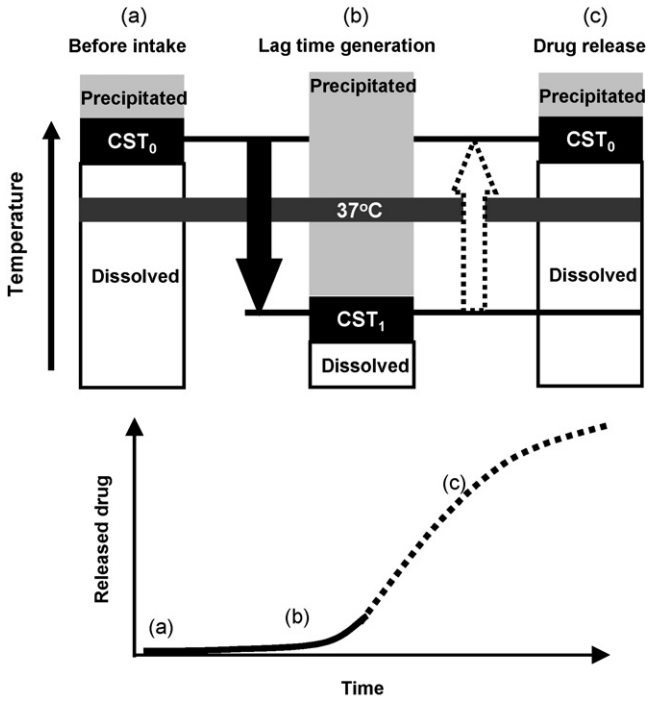

Fig. 8. Schematic images of the changes of the CST during lag time generation and subsequent drug release. (a) Before intake, (b) lag time generation and (c) drug release. The solid arrow and the dashed arrow express the decrease and the recovery of CST, respectively. The solid line and the dashed line mean lag time generation and subsequent rapid drug release, respectively.

In particular, CST_1 showed a significant correlation with both LI and RI. The reason would be explained as follows. Concerning RI, our previous result regarding the dissolution of both acetaminophen and Na_2CO_3 and a significant correlation between RI and CST_1 make us speculate that a water-soluble polymer whose solubility was once suppressed by the salting-out effect would still continue to affect the drug release rate even after most of the salting-out agent was released. The phase-separation of non-ionic water-soluble polymers is known to occur by association of hydrophobic groups of polymer chains (Mitchell et al., 1993; Liu et al., 2007, 2008; Li et al., 2002). A water-soluble polymer with low CST_1 by a strong salting-out agent might have strong hydrophobic association and subsequent polymer chain compaction. The difficulty in disentanglement of aggregated polymer chains by hydrophobic association was reported in thermo-reversible sol–gel transition of hydrogels. Hydrogels of HPMC and MC are known to show thermal hysteresis of sol–gel transition between heating and cooling process, with different transition temperatures (higher transition temperature in cooling process than heating process). This phenomenon was considered to be due to the fact that the kinetic rate of degelation process was slower than that of the gelation process and the dissociation from a structured gel network was much difficult than the association of HPMC chains from aqueous solution (Li et al., 2002; Liu et al., 2007, 2008). Therefore strongly entangled polymer chains by a salting-out effect might lead to a longer hydration time, in other words, a long lag time and slow drug release, which would account for a significant correlation between both LI and RI and CST_1.

RI also exhibited a good correlation with viscosity of 2 wt% polymer solutions. Inside the beads, the viscosities of water-soluble

Table 4
CST_1s of various combinations of salting-out agents and water-soluble polymers.

	CST_1 (°C)							
	Na_2CO_3	Sodium citrate	NaH_2PO_4	Na_2HPO_4	$KHCO_4$	NaCl	Glycine	Sucrose
HPMC	0	10	20	28	40	40	45	55
MC	5	8	15	23	45	40	50	60
Copolyvidone	5(→40)	8	15	25	42	50	50	80
HPC	7	10	13	23	30	30	40	45
PVP-K90	20	40	70	55	80	n.d.	n.d.	n.d.
PVP-K30	50	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
PEG6000	55	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

n.d.: not determined (no change was observed). The measured CST_1s were aligned horizontally, from left to right, in decreasing order of the ΔCST determined using HPMC as a water-soluble polymer as well as aligned vertically in increasing order of the CST_1 determined using Na_2CO_3 as a salting-out agent.

polymers after hydration might retard the diffusion of the drug. After release of the most of the salting-out agent, HPMC would be hydrated and partially form hydrogel. Several literatures described the effect of the polymer viscosity on the drug release from the sustained release tablet and the beads (Ishikawa et al., 2000; Maggi et al., 2000; Ye et al., 2007). Maggi et al. reported that in three-layer tablet system, slow drug release rate from the core tablet was caused by high viscosity of the protective top and bottom layers comprising polyethylene oxide (PEO) or HPMC. Ye et al. reported that in reservoir type pellet coated with ethylcellulose and HPMC, slow drug permeability was obtained by high viscosity of HPMC in coated membrane. These reported phenomena correspond to our results and make us speculate that high viscous polymer would slow the drug release rates regardless of existing positions of polymers in dosage forms. On the contrary, a low correlation of viscosity with LI would be explained as follows. At the initial phase of the drug dissolution, the suppression of hydration of a water-soluble polymer by the strong salting-out effect would leave the polymer in solid state rather than in gelled (hydrated) state leading to the increase of viscosity.

3.5. CST_1 of various combinations of salting-out agents and water-soluble polymers

In the studies discussed above, it was suggested that CST_1 measured with either Na_2CO_3 as a salting-out agent or HPMC as a water-soluble polymer was a good indicator for lag times and subsequent drug releases after the lag time. CST_1s of other combinations were measured in order to find salting-out agents and water-soluble polymers applicable to this system, and sorted in increasing order of CST_1, measured using a fixed amount of Na_2CO_3 as a salting-out agent and HPMC as a water-soluble agent for polymers and salting-out agents, respectively (Table 4). Although there were a few exceptions, combinations with low CST_1 were generally positioned left upper. This result shows the generality of the salting-out powers of salting-out agents to various water-soluble polymers and the sensitivities of water-soluble polymers to various salting-out agents. Combinations of the components with CST_1s less 55 °C would become candidates for the salting-out layer with respect to lag time generation from the facts that Formulation-C, and -J with the salting-out layer comprising sucrose/HPMC with CST_1 of 55 °C and Na_2CO_3/PEG6000 with CST_1 of 55 °C generated short lag times. Above all, regarding water-soluble polymers, cellulosic polymers (HPMC, HPC, and MC) showing almost the same CST_1 with various salting-out agents would be preferable due to their inactivity, while copolyvidone might be hydrolyzed in the presence of basic and acidic salts, which might raise concerns about the changes of dissolution profiles during long periods of storage. Concerning salting-out agents, the strong salting-out agents positioned leftward in Table 4 would be preferable. Given that lag time length is adjustable by changing not only the coating amount of water-penetration-control layer but also the coating amount of salting-out layer (Yoshida et al., 2008c), combinations with lower CST_1 would be more effective and desirable for reducing the coating amount and shortening of manufacturing time.

4. Conclusion

Taste-masked beads using Salting-out Taste-masking System were prepared using various salting-out agents and water-soluble polymers, and then predominant physicochemical properties of the components in salting-out layer for LI and RI were investigated. Significant correlations between both LI and RI and ΔCST (the salting-out power of salting-out agents) and between both LI and RI and CST_1 (the sensitivity of water-soluble polymers to a salting-out effect) were shown. These results suggest that CST_1 is a predominating factor for LI and RI, in other words, salting-out effects occurring inside the beads lead to long lag times and slow drug releases after lag times. Furthermore, viscosity of water-soluble polymers is one of the predominant factors for RI. The use of CST_1 to evaluate suitable combinations of salting-out agents and water-soluble polymers in this system was also suggested.

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