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A novel approach to sustained pseudoephedrine release: Differentially coated mini-tablets in HPMC capsules

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ABSTRACT

We developed and optimized a novel pseudoephedrine hydrochloride (PSE) sustained-release dosage form. The system comprises immediate-release mini-tablets (IRMT) and sustained-release mini-tablets (SRMT) contained in a hydroxypropyl methylcellulose (HPMC) capsule. The IRMT contained PSE, excipients and low-substituted hydroxypropyl cellulose (a disintegrant), and the tablets were coated with HPMC, a water-soluble polymer. IRMT prepared with varying amounts of low-substituted hydroxypropyl cellulose all dissolved completely within the first 60 min, so low-substituted hydroxypropyl cellulose content does not greatly influence PSE release. The SRMT contained only PSE and excipients, and were coated with a mixture of HPMC and the water-insoluble polymer ethylcellulose. The PSE release profile for the SRMT could be controlled by varying the thickness of the coat, and the lag time could be controlled by varying the amount of ethylcellulose present in the polymer coat. PSE was released immediately from our encapsulated mini-tablet system and release was sustained over an extended period of time: the PSE in the IRMT dissolved within 60 min, whereas the PSE in the SRMT was released over 8–10 h. This system can be modified to yield various extended drug-release profiles, thereby harnessing the benefits of both SRMT and IRMT.

1. Introduction

Pseudoephedrine hydrochloride (PSE) is a drug found in both over-the-counter and prescription pharmaceuticals for the treatment of nasal and sinus congestion caused by the common cold, sinusitis, hay fever, and other respiratory allergies (Jawad and Eccles, 1998; Eccles et al., 2005). PSE is now more likely than phenylpropanolamine to be used for treating the common cold and nasal problems, given a recommendation in a Public Health Advisory issued by the US Food and Drug Administration in 2000 (Caravati, 2005). PSE acts as a stimulant, so pseudoephedrine concentrations in pharmaceutical formulations must be less than 10%. And because such formulations contain many excipients, the PSE content must be further reduced, especially in over-the-counter products. In conventional dosage forms, PSE is rapidly and efficiently absorbed, with maximum plasma concentrations occurring within 0.5–2 h (Kanfer et al., 1993). PSE is then rapidly excreted in the urine (Kanfer et al., 1993). These characteristics make PSE a candidate for incorporation in a sustained-release dosage form. Many oral sustained-release formulations have been developed, including polymer-coated preparations, matrix systems, osmotically driven systems, floating systems, and bioadhesive systems (Tanaka et al., 2005). These can be classified into multiple-unit dosage forms such as granules, pellets and mini-tablets (MT), and single-unit dosage forms such as tablets and capsules. Multiple-unit dosage forms offer several well-established advantages over conventional single-unit dosage forms, including a higher degree of dispersion in the gastrointestinal tract, a reduced risk of systemic toxicity due to dose dumping, and a reduced risk of high local concentrations (Bechgaard and Nielsen, 1978; Follonier and Doelker, 1992).

MT are good substitutes for granules and pellets because they can be manufactured relatively easily, and are amenable to coating in order to sustain drug release. In addition, dosage forms containing MT can be smaller than those containing granules and pellets. So the development of MT for controlling drug release is an important focus of research into oral controlled-release solid dosage forms. Many approaches have been trialled, and matrix MT have been developed based on hydroxypropyl methylcellulose (HPMC), ethylcellulose (Lopes et al., 2006), polyvinylacetate/polyvinylpyrrolidone (Kranz et al., 2005), calcium alginate (Østberg et al., 1994), HPMC/guar gum (Mukesh and Manhapra, 2002), polyvinylacetate, cellulose acetate propionate (Colombo et al., 1985), xanthan gum, karaya gum (Sujja-areevath et al., 1998; Cox et al., 1999) and starch/microcrystalline wax (De Brabander et al., 2000). Coated oral sustained-release forms of drugs are widely used to improve drug tolerance or to yield a dos-

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ing regimen that is easier to manage for patients (Waterman and Fergione, 2003). However, little published information is available on sustained-release systems using coated MT. In particular, it has proven challenging to develop one dosage form with sustained and immediate-release properties. However, production of a sustained dosage form that would maintain an effective plasma PSE concentration would improve patient compliance.

The purpose of this study was to optimize a sustained-release PSE dosage form using an encapsulated mini-tablet (EMT) system. We aimed to reduce the size of the PSE tablet such that it could be enclosed in a capsule, then deploy tablets with different release properties within the one EMT, which to the best of our knowledge has not been achieved previously. Our EMT system comprises immediate-release mini-tablets (IRMT) and sustained-release mini-tablets (SRMT) in a capsule made from HPMC, a water-soluble polymer (Fig. 1). Several MT can be placed into each HPMC capsule, which later disintegrates and releases these subunits. Because several MT can be placed into each capsule, tablets with different content, dose and release characteristics can be included. Inclusion of IRMT permits the development of rapid-acting EMT dosage forms with optimal pharmacokinetic profiles for fast action. EMT systems can be designed to yield various sustained drug-release profiles by combining different types or quantities of MT, and can include combinations of different drugs, thereby improving patient compliance.

To ensure immediate release, the IRMT contained low-substituted hydroxypropyl cellulose as a disintegrant, and were prepared simply by coating MT with HPMC. HPMC is a non-ionic, non-toxic, water-soluble substance that is easy to handle, relatively easy to manufacture, and has a minimal influence on processing parameters. In contrast, the SRMT were coated with a mixture of ethylcellulose (a water-insoluble polymer) and HPMC. Mixtures of two polymers are often used in controlled release drug delivery systems (Nagai et al., 1989; Tan et al., 1999) to allow pore-mediated diffusion through the polymer film. In the present study, for the IRMT we investigated the influence of disintegrant content on the immediate PSE release profile, and for the SRMT we investigated the influence of coating parameters (e.g. the ratio of ethylcellulose to HPMC in the mixed polymer coat and the thickness of the polymer film) on the PSE release profile. We thus aimed to develop a better understanding of the factors that can regulate PSE release from IRMT and SRMT. Our goal was to produce a dosage form that would maintain an effective plasma PSE concentration for 8–10 h after administration, which would permit a treatment regimen of two doses per day.

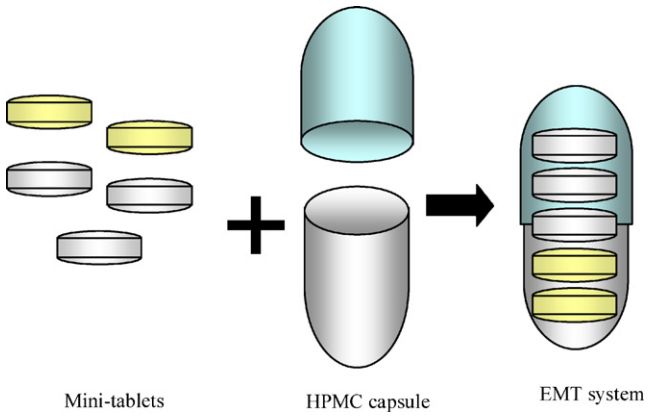

Fig. 1. Schematic diagram of the EMT system. During manufacture, two IRMT are placed within one half of the capsule, then three SRMT are added, and the other half of the capsule is pressed into place.

2. Materials and methods

2.1. Materials

PSE (ALPS Pharmaceutical Co., Japan) was used in both the IRMT and the SRMT. Belladonna alkaloids and dipotassium glycyrrhizinate (ALPS Pharmaceutical Co., Japan), D-chlorpheniramine maleate (Kongo Pharmaceutical Co., Japan) and anhydrous caffeine (Shiratori Pharmaceutical Co., Japan) were included in the IRMT only. Anhydrous dibasic calcium phosphate (Taihei Chemical Industrial Co., Japan), light anhydrous silicic acid (Aerozil®; Nippon Aerosil Co., Japan), D-mannitol (Touwa Chemical Industrial Co., Japan), polyethyleneglycol (PEG6000; Sanyo Chemical Industries, Japan), HPMC (TC-5R®; Shinetsu Chemicals Co., Japan), low-substituted hydroxypropyl cellulose (LH-31; Shinetsu Chemicals Co., Japan), hydroxypropyl cellulose (HPC-L; Nisso Co., Japan), ethyl alcohol (Japan Alcohol Co., Japan), ethylcellulose (Ethocel®, Dow Chemical, USA), talc (Matsumura Industrial Co., Japan), magnesium stearate (Taihei Chemical Industrial Co., Japan), HPMC capsules (Qualicaps Co., Japan) and other pharmaceutical excipients were of Japanese pharmaceutical excipient grade. All other chemicals were of analytical grade and were used without further purification.

2.2. Preparation of IRMT

The IRMT containing 11.8% (wt/wt) PSE (10%, wt/wt pseudoephedrine) were prepared using the wet granulation method. First, PSE was mixed with 18.4% (wt/wt) other active components, 58.8–68.8% (wt/wt) excipients and 0–10% (wt/wt) low-substituted hydroxypropyl cellulose, a disintegrant, in proportions varying according to the experimental design (Table 1). Then this powder was granulated using an agitation granulator (FM-VG-25 vertical granulator; Powrex Co., Japan). The resulting granules were dried using a fluidized bed granulator (FLO-5B; Freund Co., Japan) with heated air (75 °C). The drying cycle was terminated when the outlet air temperature reached 45 °C, indicating that the granules had dried sufficiently. After the drying cycle, the collected granules were passed through a 16–30 mesh. The prepared granules were blended with 1.0% magnesium stearate (wt/wt), then MT (weighing 64 mg each) were produced by compression using 5 mm diameter convex punches in a rotary tablet machine (AP-15SS; Hata Iron Works Co., Japan).

A coating suspension was prepared from HPMC, talc, plasticizer, ethyl alcohol and water. The talc was first dispersed in water, and

Table 1
Composition of IRMT containing different amounts of low-substituted hydroxypropyl cellulose

Ingredient	Amounts of low-substituted hydroxypropyl cellulose			
	0%	2.5%	5.0%	10.0%
PSE	11.7	11.7	11.7	11.7
Other active components	18.4	18.4	18.4	18.4
Low-substituted hydroxypropyl cellulose	0	2.5	5	10
D-Mannitol	27	24.5	22	17
Anhydrous dibasic calcium phosphate	35.9	35.9	35.9	35.9
Aerozil®	1	1	1	1
Hydroxypropyl cellulose	5	5	5	5
Magnesium stearate	1	1	1	1
Total (mg/Tab)	64	64	64	64

Other active components were belladonna alkaloids, dipotassium glycyrrhizinate, D-chlorpheniramine maleate and anhydrous caffeine. Values are percentages relative to the total weight of each core tablet (64 mg).

Table 2
Coating conditions used for preparation of the IRMT and SRMT in a pan-coating system

Batch size (g)	600
Rotation speed (rpm)	15
Spray air pressure (kg/cm)	1.5
Inlet air temperature (°C)	45–50
Exhaust air temperature (°C)	40–45
Spray rate (g/min)	7.5

The inlet air temperature was varied in order to maintain the exhaust air temperature at 40–45 °C.

the HPMC was first dispersed in an ethanol/water mixture. With gentle stirring, the talc suspension was added to the HPMC dispersion, and the aqueous ethanolic HPMC solution was plasticized with polyethyleneglycol. The mixture was stirred for 2 h to ensure sufficient plasticization of the polymer. The MT were coated with an aqueous ethanolic solution of HPMC using a pan-coating system (Hicoater-30; Freund Co., Japan) to yield a 4.8% increase in weight (as determined by weighing a sample of 100 tablets). Table 2 summarizes the conditions used for the coating process.

2.3. Preparation of SRMT

SRMT containing 11.8% (wt/wt) PSE were prepared using the same method as used for preparing the IRMT. However, the SRMT did not contain the other active components or low-substituted hydroxypropyl cellulose.

A coating suspension was prepared from HPMC, ethylcellulose, magnesium stearate, ethyl alcohol and water. We used magnesium stearate in the coating preparation to minimize friction between the surfaces of the mini-tablets, the mini-tablet-filling system and the HPMC capsules, and magnesium stearate is a more effective lubricant than talc at low concentrations. The coating preparation for the IRMT contained 28% talc, which was a high enough proportion to produce the needed lubrication. Since talc is a common ingredient used in the pharmaceutical industry, we used talc rather than magnesium stearate for the IRMT.

HPMC, ethylcellulose and magnesium stearate were dispersed in an ethanol/water mixture. Aqueous ethanolic solutions of HPMC and ethylcellulose were mixed at the desired ratios (15:85; 20:80; 25:75; and 35:65, respectively) based on the experimental design (Table 3). The MT were coated using a similar method to that used for coating the IRMT, using an aqueous ethanolic solution of HPMC and ethylcellulose to yield increases in weight ranging from 1.6 to 8% (as determined by weighing a sample of 100 tablets). A coating load of 4.8% was used to test the effect of the various ratios of HPMC and ethylcellulose.

2.4. Preparation of the EMT system

To prepare the EMT system, two IRMT and three SRMT were placed in each HPMC capsule using a MT-filling system (LIQFIL-super40; Qualicaps Co., Japan).

Table 3
Composition of the coating preparations for the SRMT

Ingredient	Ethylcellulose to HPMC ratio			
	65:35	75:25	80:20	85:15
Ethylcellulose	62.5	72.2	77.0	81.9
HPMC	33.7	24.0	19.2	14.3
Magnesium stearate	3.8	3.8	3.8	3.8
Coating load (%)	4.8	1.6–8	1.6–8	4.8

Values for ingredients are percentages relative to the total volume of each coating preparation. Values for coating load are percentages relative to the total weight of the core tablet.

2.5. PSE analysis

This dosage form (encapsulated mini-tablet system) contained SRMT and IRMT. Both the IRMT and SRMT contained PSE, and only the IRMT contained belladonna alkaloids, dipotassium glycyrrhizinate, D-chlorpheniramine maleate and anhydrous caffeine. Thus, the dissolution profile was measured based on PSE.

A reverse-phase HPLC system was used to measure PSE concentration at a wavelength of 215 nm. The HPLC system consisted of a pump (LC-10ADvp; Shimadzu Co., Japan), a UV spectrophotometric detector (SPD-M10Avp; Shimadzu Co., Japan), an auto sampler (SIL-HTc; Shimadzu Co., Japan), a degasser (DGU-14A; Shimadzu Co., Japan) and a reverse-phase column (ODS-A, 6.0 mm × 150 mm; YMC, Japan). A mobile phase consisting of a 40:60 mixture of phosphoric acid (containing 0.5% sodium lauryl sulfate) and acetonitrile was used at a flow rate of 1.0 mL/min. Ten microliters of the sample was injected into the HPLC system. The retention time of PSE was 5.0 min.

2.6. In vitro release test

PSE in vitro release tests were conducted using 900 mL of purified water at 37 °C, in accordance with the standard dissolution paddle test method of the Japanese Pharmacopoeia XIV (JPXIV). For all tests, the rotation speed of the paddle was 50 rpm. For the SRMT, the PSE release profile was obtained using UV absorption at 258 nm. For the IRMT and EMT, HPLC at 215 nm was used to obtain the PSE release profile, as described in the previous section. For all tests, 5-mL samples of the test medium were collected at set intervals (0.25, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h), and were replaced with an equal volume of purified water. The solution was then passed through a Millipore membrane filter before UV absorption or HPLC analysis. The lag time and $t_{80\%}$ (time to release 80% of the drug) were determined by extrapolation of the release profile (Table 4).

3. Results and discussion

PSE is rapidly absorbed and excreted in the urine, which makes it a candidate for incorporation in a sustained-release form. In order to develop an optimized sustained-release PSE dosage form, we tested EMT systems comprising differentially coated MT (IRMT and SRMT) in an HPMC capsule.

3.1. Influence of low-substituted hydroxypropyl cellulose on release of PSE from IRMT

IRMT containing PSE were coated with HPMC to achieve a 4.8% increase in weight. Low-substituted hydroxypropyl cellulose is commonly used as a disintegrant in tablets, and the degree to which it swells and takes up water is reportedly dependent on the degree of hydroxypropyloxy substitution and the particle size of the polymer (Nakagami and Nada, 1991; Kawashima et al., 1993). This suggests that these two properties may exert a strong influence on the disintegration time of the tablets. In order to assess the influence of disintegrant content on the release rate of PSE from IRMT, in vitro release tests were carried out for IRMT prepared with different amounts of low-substituted hydroxypropyl cellulose (0–10%). Fig. 2 shows the PSE release profiles of the various IRMT produced. As shown in Fig. 2, the dissolution profiles were very similar for IRMT containing different amounts of low-substituted hydroxypropyl cellulose, and there was no lag time prior to PSE release. The percentage drug released in the first 30 min differed somewhat among the four formulations. However, in all IRMT, 100% of the PSE was released within the first 60 min, and the low-substituted hydroxypropyl cellulose content of the tablet did not

Table 4
Lag time and $t_{80\%}$ for PSE release from SRMT coated with different preparations and coating loads

Coating load (%)	Ethylcellulose to HPMC ratio							
	65:35		75:25		80:20		85:15	
	Lag time (h)	$t_{80\%}$ (h)	Lag time (h)	$t_{80\%}$ (h)	Lag time (h)	$t_{80\%}$ (h)	Lag time (h)	$t_{80\%}$ (h)
1.6	–	–	0.17 ± 0.02	1.77 ± 0.12	1.16 ± 0.17	4.96 ± 0.80	–	–
3.2	–	–	0.86 ± 0.11	4.19 ± 0.30	2.15 ± 0.05	7.84 ± 0.71	–	–
4.8	0.00	0.56 ± 0.05	1.07 ± 0.09	5.62 ± 0.16	3.51 ± 0.02	11.07 ± 0.52	4.99 ± 0.09	16.03 ± 1.26
6.4	–	–	2.17 ± 0.18	6.69 ± 0.59	5.00 ± 0.27	14.04 ± 1.28	–	–
8.0	–	–	2.67 ± 0.13	7.94 ± 1.29	5.42 ± 0.25	18.67 ± 0.54	–	–

Each value represents the mean ± S.D. of three experiments.

greatly influence PSE release. There are a couple of possible reasons for this phenomenon. First, PSE is highly water soluble, with a solubility of 2 g/mL water (Makhija and Vavia, 2003), thus explaining its fast release. Second, low-substituted hydroxypropyl cellulose is used as a binder as well as a disintegrant in pharmaceutical industry. Thus, increasing the low-substituted hydroxypropyl cellulose content would theoretically strengthen interparticle binding in the IRMT, potentially decreasing the percentage of drug released in the first 30 min. However, we found no major influence of low-substituted hydroxypropyl cellulose, whereas use of HPMC in the IRMT coating preparation was very effective. We conclude that the low-substituted hydroxypropyl cellulose content of IRMT is not a critical factor in ensuring the immediate release of PSE.

3.2. Influence of ethylcellulose on release of PSE from SRMT

In order to evaluate the influence of the ethylcellulose content of the coat on the release rate of PSE from SRMT, in vitro release tests were carried out for SRMT coated with four different coating preparations: 65:35, 75:25, 80:20, and 85:15 mixtures of ethylcellulose and HPMC. The two polymers were mixed in order to achieve pore-mediated diffusion through the polymer film. To test the different coating preparations, SRMT containing PSE were coated to achieve a 4.8% increase in weight. Fig. 3 shows the PSE release profiles from SRMT coated with different ethylcellulose and HPMC preparations. For SRMT with a coating preparation comprising a 65:35 mixture of ethylcellulose and HPMC, almost 80% of the PSE had been released within the first 30 min; therefore, this preparation yields almost no extension of the release time relative to a coat comprising only HPMC. The lag time before PSE release from SRMT was 0 h for a 65:35 mixture of ethylcellulose and HPMC, 1.07 h for a 75:25 mixture, 3.51 h for a 80:20 mixture and 4.99 h for a 85:15 mixture. These lag times increased as the amount of ethylcellulose in the mixed polymer coat increased. Increases in the amount of ethylcellulose

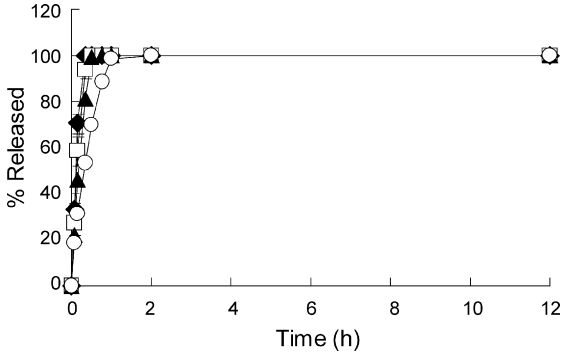

Fig. 2. Release profiles of PSE from IRMT (4.8% weight increase) containing different amounts of low-substituted hydroxypropyl cellulose [(♦) 0%; (□) 2.5%; (▲) 5%; (○) 10%]. The test was performed in water in accordance with the JPXIV paddle method. Each point is the mean ± S.D. (n = 3).

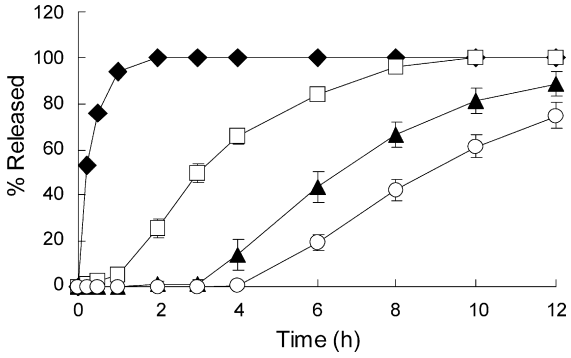

Fig. 3. Release profiles of PSE from SRMT (4.8% weight increase) with varying ethylcellulose to HPMC ratios [(♦) 65:35; (□) 75:25; (▲) 80:20; and (○) 85:15] in the coating preparation. The test was performed in water in accordance with the JPXIV paddle method. Each point is the mean ± S.D. (n = 3).

also yielded increases in the PSE release time: for tablets containing 75:25 and 80:20 mixtures of ethylcellulose and HPMC, approximately 100% and 80% of the PSE, respectively, was released within 10 h. This is because ethylcellulose and HPMC have different solubility properties, such that removal of the cosolvent mixture causes the two polymers to separate, leaving a dried film that is HPMC-rich on the surface (Sakellariou and Rowe, 1995). Sakellariou and Rowe (1995) suggested that having an HPMC-rich surface would increase the permeability of the ethylcellulose film. Fig. 4 shows the correlation between the amount of ethylcellulose in the mixed polymer coat and the $t_{80\%}$ value. The amount of ethylcellulose was calculated from the proportion of ethylcellulose in the 4.8% coating load. The coefficient of determination (R^2) was 0.9643. These results demonstrate that the drug-release rate is directly related to the amount of ethylcellulose present in the polymer coat, thus the release rate of PSE can be controlled by changing the ethylcellulose to HPMC ratio. The purpose of this study was to develop an EMT system in which 80% of the PSE would be released from the SRMT within 8 h

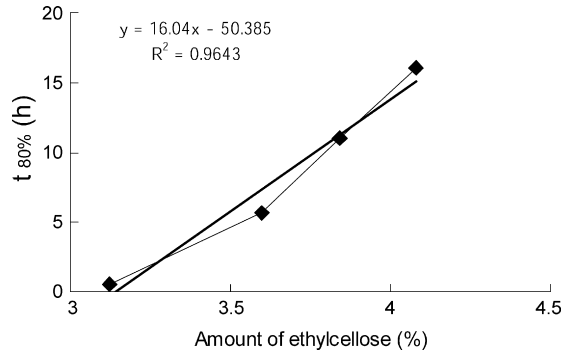

Fig. 4. Relationship between the amount of ethylcellulose in the mixed polymer coat of the SRMT and $t_{80\%}$.

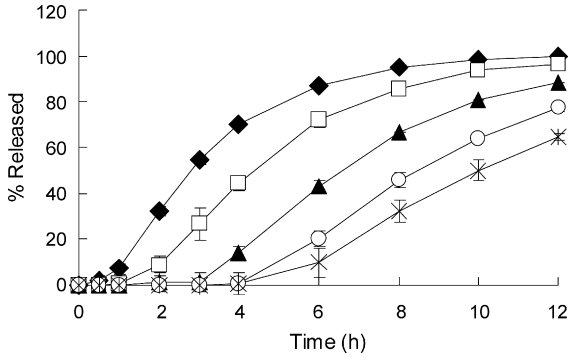

Fig. 5. Release profiles of PSE from SRMT with varying coating loads [(♦) 1.6%; (□) 3.2%; (▲) 4.8%; (○) 6.4%; (×) 8%] with an ethylcellulose to HPMC ratio of 80:20. The test was performed in water in accordance with the JPXIV paddle method. Each point is the mean ± S.D. ($n = 3$).

and 100% within 10 h, which would permit a treatment regimen of two times per day. We tested various ratios of ethylcellulose to HPMC to find the one most suitable for sustained drug delivery. As shown in Fig. 4, the $t_{80\%}$ was 0.65 h for the 65:35 mixture of ethylcellulose and HPMC, 5.62 h for the 75:25 mixture, 11.07 h for the 80:20 mixture and 16.03 h for the 85:15 mixture. The most suitable ratio of ethylcellulose to HPMC in the coating seems to be 75:25 or 80:20, as shown in Figs. 3 and 4. A further decrease in the ratio of ethylcellulose did not significantly hinder drug release relative to uncoated tablets.

3.3. Influence of coating load on release of PSE from SRMT

In order to evaluate the influence of coating load on the release of PSE from SRMT, in vitro release tests were carried out for SRMT. SRMT containing PSE were coated to achieve weight increases of 1.6–8%, using ethylcellulose to HPMC ratios in the coating preparation of 75:25 and 80:20, because these had been found to be the most suitable ratios in previous experiments (see previous section). Figs. 5 and 6 show the PSE release profiles for SRMT coated with 80:20 and 75:25 preparations of ethylcellulose and HPMC, respectively. For SRMT coated with a 80:20 mixture of ethylcellulose and HPMC, the lag time before PSE release from SRMT was 1.16 h for a 1.6% coating load, 2.15 h for a 3.2% coating load, 3.51 h for a 4.8% coating load, 5.00 h for a 6.4% coating load and 5.42 h for a 8.0% coating load. A coating load of 1.6% did not significantly hinder drug release. In contrast, a small increase (a few percent) to a 4.8% coating load yielded a PSE release rate of less than 80% at 8 h, and a further increase to a 6.4% coating load yielded a PSE release rate of less than 80% at 12 h. These results demonstrate that a small increase in coating load can have a large effect on PSE release when 80:20 mixtures of ethylcellulose to HPMC are used. Because it is difficult to control coating load in the manufacturing process with this level of precision, it may be difficult to control the release rate of PSE accurately.

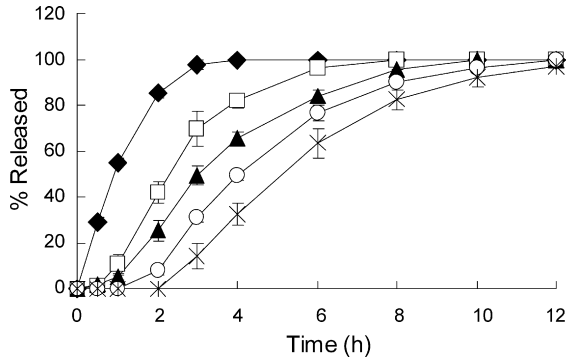

Fig. 6. Release profiles of PSE from SRMT with varying coating loads [(♦) 1.6%; (□) 3.2%; (▲) 4.8%; (○) 6.4%; (×) 8%] with an ethylcellulose to HPMC ratio of 75:25. The test was performed in water in accordance with the JPXIV paddle method. Each point is the mean ± S.D. ($n = 3$).

For SRMT coated with a 75:25 mixture of ethylcellulose and HPMC, the lag time before PSE release from SRMT was 0.17 h for a 1.6% coating load, 0.86 h for a 3.2% coating load, 1.07 h for a 4.8% coating load, 2.17 h for a 6.4% coating load, and 2.67 h for a 8.0% coating load. Almost 100% and 80% of PSE had dissolved within 4 h with coating loads of 1.6 and 3.2%, respectively. For a coating load of 4.8%, more than 80% of PSE was released within 6 h and almost 100% within 8 h. For coating loads of 6.4–8.0%, 80% of the PSE was released within 8 h and almost 100% within 10 h. Fig. 7 shows the correlation between the coating load and the $t_{80\%}$ value when 80:20 and 75:25 ethylcellulose to HPMC ratios are used (Fig. 7A and B). The coefficients of determination (R^2) for 80:20 and 75:25 mixtures of ethylcellulose to HPMC were 0.9911 and 0.9708, respectively. These results demonstrate that the drug-release rate is directly related to the coating load for each ratio. However, the influence of coating load on the release of PSE differed for the 75:25 and 80:20 preparations of ethylcellulose and HPMC. As shown in Figs. 6 and 7, SRMT coated with a 80:20 mixture of ethylcellulose to HPMC significantly hindered drug release, and had long lag times. In contrast, drug release after short lag time was decreased markedly by increasing the coating load of the 75:25 mixture of ethylcellulose to HPMC. Thus, considering that maximum plasma concentrations of PSE occur within 0.5–2 h and that PSE has a short plasma half-life of 5 h (Kanfer et al., 1993; Makhija and Vavia, 2003), it is necessary to have SRMT with a short lag time so that PSE is released in a timely fashion following the rapid onset of the effects of the PSE released from the IRMT. We therefore concluded that the most suitable ethylcellulose to HPMC ratio was 75:25, and that the most

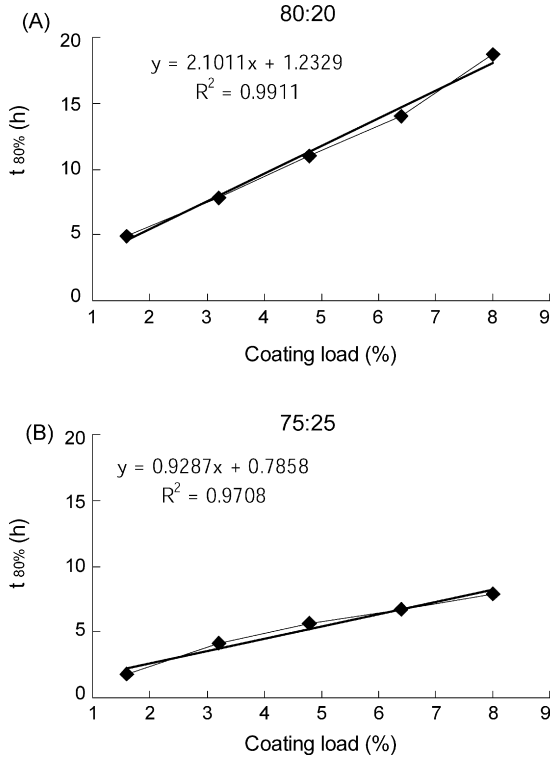

Fig. 7. Relationship between the coating load of SRMT and $t_{80\%}$: (A) Ethylcellulose to HPMC ratio of 80:20 and (B) ethylcellulose to HPMC ratio of 75:25.

suitable coating load was 6.4%. An SRMT so constituted would have a lag time before PSE release and a $t_{80\%}$ value of 2.17 h and 6.69 h, respectively. In the mixed polymer coat containing ethylcellulose and HPMC, HPMC allows pore formation in the polymer film, thus facilitating the release of PSE. The coating process involves a gradual building up of the film, so it is likely that the coat is incomplete at low coating load, with the uncovered areas rendering the coat porous. The lag time has a tendency to increase as a function of the amount of ethylcellulose present in the polymer coat and the PSE release rate most probably decreases with higher coating loads because of a reduction in the medium permeation rate through a thicker coating load and an increase in the mechanical strength of the polymer film.

3.4. Release of PSE from EMT

The aim of this study was to develop an EMT system that would release 80–100% of the PSE within 8 h and 100% within 10 h. As shown in Fig. 1, each HPMC capsule was to be filled with five MT (each weighing 64 mg). Considering the above-mentioned data for PSE release from the IRMT and SRMT we tested in the present study, we would expect that EMT containing three or four IRMT would release 60 or 80% of the PSE within 0.5–1 h. Tablets that rapidly release PSE, however, have several disadvantages: they require a high dosing frequency, are associated with an increased incidence of adverse effects, and have a therapeutic effect of short duration. We therefore chose to use HPMC capsules each containing two IRMT and three SRMT for further study of our EMT system. Inclusion of two IRMT ensures rapid onset of the effects of PSE because the IRMT have optimal pharmacokinetic profiles for quick release, and the IRMT also contain other active ingredients (belladonna alkaloids, dipotassium glycyrrhizinate, D-chlorpheniramine maleate and anhydrous caffeine) for which sustained release is unnecessary. Inclusion of three SRMT ensures prolonged therapeutic efficacy of PSE. As shown in Section 3.1, we found that the low-substituted hydroxypropyl cellulose content of the IRMT was not a critical factor in determining the immediate release of PSE. One hundred percent of the PSE was released within the first 60 min, verifying that HPMC was adequate as an IRMT coating preparation. As shown in Sections 3.2 and 3.3, the lag time and the release rate of PSE could be controlled by varying the ethylcellulose to HPMC ratio and the coating load; we determined that the most suitable percentage of ethylcellulose in the SRMT coat was 75% and that the most suitable coating load was 6.4% (Fig. 6).

In order to assess the release rate of PSE from the EMT system, an in vitro release test was carried out for the EMT system. HPMC capsules have been found to dissolve rapidly, and for temperatures between 10 and 55 °C, there was found to be no difference in the time taken for dissolution (Chiwele et al., 2000). Therefore, HPMC capsules can be taken with cold or warm drinks (Chiwele et al., 2000). HPMC capsules have been used in many studies of oral dosage forms (Prasad et al., 2003; Ito et al., 2005), and are widely available commercially as an alternative to gelatin capsules.

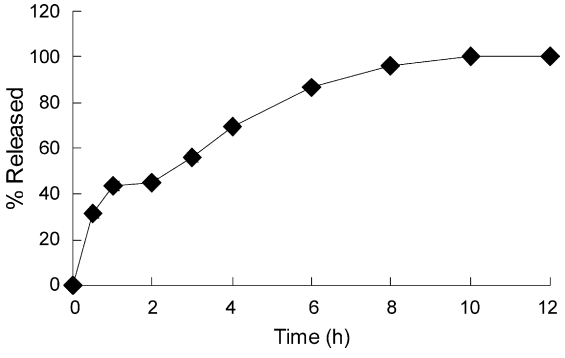

Fig. 8. Release profile of PSE from the optimized EMT system in water. The EMT system contained two IRMT and three SRMT in an HPMC capsule. The test was performed in accordance with the JPXIV paddle method. Each point is the mean ± S.D. ($n = 3$).

Fig. 8 shows the PSE release profile for the EMT system. The immediate-release PSE from the IRMT in the EMT system dissolved within the first 60 min, then the PSE in the SRMT began to be released more slowly, beginning within 2 h, without the polymer film dissolving. PSE release from the SRMT in the EMT system was sustained, with more than 80% of the PSE having been released within 8–10 h. Thus, the in vitro release profile of this EMT system coincided with the profile expected from the combination of two IRMT and three SRMT. The EMT system undergoes four processes as follows: (a) the HPMC capsule dissolves rapidly, and has no influence on the release rate of PSE from the EMT system; (b) once dissolved, the HPMC capsule releases the IRMT and SRMT subunits; (c) PSE is released rapidly from the IRMT; and (d) PSE is released from the SRMT over 8–10 h. Using different types of MT, the EMT system can be designed to yield the desired stable drug-release profiles, in addition to permitting different drugs to be combined, thereby improving patient compliance.

4. Conclusion

In conclusion, the results of testing both IRMT and SRMT indicate that the IRMT release PSE within the first 60 min, regardless of low-substituted hydroxypropyl cellulose content, and that the lag time and the drug-release rate of the SRMT can be controlled by varying the ethylcellulose to HPMC ratio and the coating load. Thus, this study adds to the body of knowledge in this area by showing that novel EMT systems can be designed to yield particular stable drug-release profiles by combining different types or quantities of PSE MT into one dosage form: the IRMT provide rapid-acting PSE, and the SRMT ensure prolonged therapeutic efficacy of PSE. Further studies are needed to establish the optimal dosage form, and develop a controlled-release tablet that has both sustained and immediate-release properties.

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