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International Journal of Pharmaceutics 188 (1999) 71–80

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Controlled release of dual drug-loaded hydroxypropyl methylcellulose matrix tablet using drug-containing polymeric coatings

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Received 6 January 1999; received in revised form 1 June 1999; accepted 9 June 1999

Abstract

A dual drug-loaded hydroxypropylmethylcellulose (HPMC) matrix tablet simultaneously containing drug in inner tablet core and outer coated layer was formulated using drug-containing aqueous-based polymeric Eudragit® RS30D dispersions. Effects of coating levels, drug loadings in outer layers, amount and type of five plasticizers and talc concentration on the release characteristics were evaluated on the characteristics in simulated gastric fluid for 2 h followed by a study in intestinal fluids. Melatonin (MT) was selected as a model drug. The surface morphology of dual drug-loaded HPMC tablets using scanning electron microscope (SEM) was smooth, showing the distinct coated layer with about 75-μm coating thickness at the 15% coating level. Unlike the uncoated and conventionally coated HPMC tablet, the dual drug-loaded HPMC matrix tablet gave a biphasic linear release, showing a zero-order for 4 h (first) followed by another zero-order release when fitted using linear regression ($r^2 = 0.99$). As the coating levels (15, 25%) increased, the release rate was further decreased. The biphasic release profiles of dual drug-loaded HPMC matrix tablet was unchanged except when 25% coating level containing 0.5% drug concentration was applied. As the drug concentration in polymeric coating dispersion increased (0.25–1.0%), the amount of drug released increased. The time for the first linear release was also advanced. However, the biphasic release pattern was not changed. The biphasic release profiles of dual drug-loaded HPMC matrix tablet were highly modified, depending on the amount and type of five plasticizers. Talc (10–30%) in coating dispersion as an anti-sticking material did not affect the release profiles. The current dual drug-loaded HPMC matrix tablet, showing biphasic release profiles may provide an alternative to deliver drugs with circadian rhythmic behaviors in the body but needs to be further validated in future in human studies. The dual drug-loaded coating method is also interesting for the modified release of poorly water-soluble drugs because solubilizers and other additives can be added in drug-containing polymeric coating dispersions.

Keywords: HPMC matrix tablet; Drug-containing polymeric dispersions; Dual drug-loaded; Biphasic release

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0378-5173/99/$ - see front matter
PII: S0378-5173(99)00204-5

1. Introduction

Hydroxypropyl methylcellulose (HPMC) has been widely used for pharmaceutical applications because of its nontoxic property, ease of handling, small influence of processing parameters, and direct compressible manufacturing (Ford et al., 1987; Tahara et al., 1995). A swellable and hydrophilic property of HPMC has been paid considerable attention for the preparation of matrix tablet as sustained release formulations of various drugs (Ford et al., 1987; Lee et al., 1999). The release characteristics of HPMC matrix tablet are affected by various factors (Ford et al., 1987; Freely and Davis, 1988; Kurahashi et al., 1996; Lee et al., 1999). The coatings of HPMC matrix tablet can further modify the release profile (Gazzaniga et al., 1993; Lee et al., 1999).

Polymeric coating techniques using fluid-bed or pan coater have been widely recognized in the pharmaceutical industry for many reasons such as taste masking, protective barrier, stability improvement, but mostly controlled release of drugs (McGinity, 1989). In general, coating dispersions are applied on various drug-loaded cores such as nonpareil seed, pellet, bead, granule or tablet. However, it is interesting to prepare coated HPMC matrix tablets using drug-containing polymeric coating dispersions because conventionally, no drug is included in coating dispersions. Nobody systematically investigates release profiles of drug-loaded cores after application of drug-containing polymeric coating dispersions. We previously reported dual drug-loaded alginate beads containing ibuprofen as a model drug in inner and outer layer for the controlled delivery (Lee et al., 1998b). The drug-loaded alginate beads were dipped in sodium alginate solution and dropped in $CaCl_2$ solution again, resulting in dual drug-loaded alginate beads. No coating techniques were applied.

In this study, drug-containing polymeric dispersions were applied onto drug-loaded HPMC matrix tablet as a core, resulting in dual drug-loaded HPMC matrix tablet. The dual drug-loaded HPMC matrix tablet simultaneously contains drug in the inner core and outer-coated layer as depicted in Fig. 1. A commercially available Eudragit® RS30D polymeric dispersion was used for coatings. Eudragit® RS30D, a copolymer synthesized from acrylic and methacrylic acid esters with low content of quaternary ammonium group has been widely used for aqueous-based coatings of pharmaceutical preparations (McGinity, 1989; Wang et al., 1997; Lee et al., 1999).

The purpose of this study was to formulate dual drug-loaded HPMC matrix tablets using drug-containing aqueous-based polymeric coating dispersions. The release profiles and mechanism of dual drug-loaded HPMC matrix tablet were investigated in simulated gastric fluid for 2 h followed by a study in intestinal fluids, varying coating level, drug loading in outer layer, amount and type of five plasticizers, and talc concentration. The surface morphology and cross-sectional view of dual drug-loaded HPMC matrix tablet were also investigated using scanning electron microscopy (SEM). Melatonin (MT), an indole amide pineal hormone was selected as the model drug.

2. Materials and methods

2.1. Materials

MT was purchased from Morepen (New Delhi,

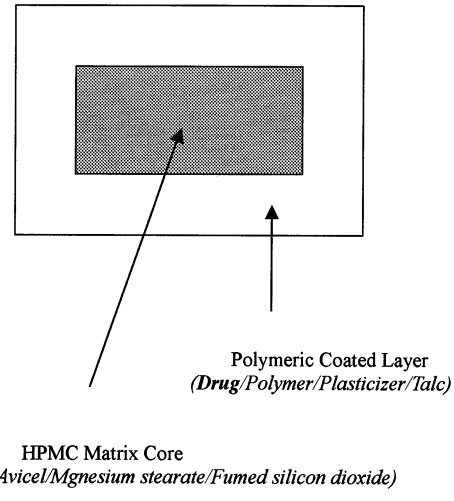

Fig. 1. Schematic diagram of dual drug-loaded HPMC matrix tablet.

India). The HPMC (100 000 cps, SR type) was provided by courtesy of Richwood (Seoul, South Korea). Eudragit® RS30D as an aqueous-based polymeric coating material was also provided by courtesy of Duc Woo (Seoul, South Korea). Microcrystalline cellulose (Avicel®) was kindly obtained from Chong Kung Dang (Seoul, South Korea). Magnesium stearate and talc were purchased from Katayama (Osaka, Japan) and Shin Jun (Seoul, South Korea), respectively. Cab-O-Sil®, a fumed silicon dioxide was kindly supplied from Cabot (Boston, MA). Dibutyl sebacic acid (DBS) was purchased from Sigma (St. Louis, MO). Triethyl citrate (TEC), acetyltriethyl citrate (ATEC), tributyl citrate (TBC) and acetyltributyl citrate (ATBC) were obtained from Morflex (Greensboro, NJ). Absolute alcohol (99.9%) was bought from Hayman (Witham, UK). All other chemicals were of reagent grade and used without further purification.

2.2. Preparation of HPMC matrix tablet

HPMC (92.4%), drug (1.6%) and Avicel® (4%) were thoroughly blended and then mixed with magnesium stearate (1%) and Cab-O-Sil® (1%) for 1 h according to the procedure of Lee et al. (1999). After passing through the 20 mesh sieve screen, the resulting powders were compressed into tablet using a single-punched tablet machine (Apex, UK) to prepare the flat-faced tablets, 6.35 mm diameter and 52.7 ± 2.0 mg average weight. The compaction pressure was 150 ± 20 N/mm^2.

2.3. Preparation of coated and dual drug-loaded HPMC matrix tablet

For the preparation of coated HPMC matrix tablet, aqueous-based polymeric Eudragit® RS 30D (about 30% solid contents) was diluted with distilled water (1:1 weight ratio). The talc (40% based on solid polymeric content) was added to the above polymeric dispersion and then completely stirred using an overhead stirrer for 4 h. Thereafter, the plasticizers (20% based on polymeric contents) were added and then stirred for 24 h to ensure sufficient plasticization of the polymer. The weight ratios of polymer dispersion, distilled water, talc and plasticizer (DBS) were 100:100:12:6, giving 48% of total solid contents. The coating dispersion was then applied to HPMC matrix tablets in a pan coater (Korea Machine, Seoul, South Korea) at 50°C.

On the other hand, for the preparation of dual drug-loaded matrix tablet, the drug was dissolved in alcoholic solution as a solubilizer and then added into the final coating dispersion (1:1 weight ratio), resulting in 0.25, 0.5 or 1.0% of drug concentration. The plasticizers (10–30%) and talc (10–30%) based on solid content of polymeric dispersion were also mixed as described previously. The resulting mixtures were further stirred for 4 h prior to initiation of coatings. Aqueous-based polymeric coating dispersion containing drug was then applied to drug-loaded HPMC matrix tablet, resulting in dual drug-loaded coatings of HPMC matrix tablet. The coated dual drug-loaded HPMC matrix tablets were further air-dried at room temperature for 24 h. The coated tablets were sampled occasionally until about 15 or 25% weight was gained. The coating levels were designated as percentage of weight gain when compared to uncoated tablet. The detailed compositions (g) of aqueous-based polymeric coating dispersion for the preparation of dual drug-loaded HPMC matrix tablet are shown in Table 1.

2.4. Scanning electron microscopy (SEM)

The surface morphology and cross-sectional view of dual drug-loaded HPMC matrix tablet were visualized using SEM. The dried matrix tablet was coated with gold using an Auto Coating Unit E5200 coater (London, UK) for about 2 min to obtain a coating thickness of 200 Å. The tablet was carefully cut in half with a scalpel blade to assess the coated layer. Micrographs were taken at an accelerating voltage of 15 kV with a Cambridge Stereo Scan 200 (London, UK).

Table 1
The compositions (g) of aqueous-based polymeric coating dispersion for the preparation of dual drug-loaded HPMC matrix tablets

Formulation	Drug	Ethanol	Eudragit® RS30D	Water	Plasticizer	Talc
#1	0	0	100	100	DBS (6)	12
#2	1.06	15	100	85	DBS (6)	6
#3	1.06	15	100	85	TBC (6)	6
#4	1.06	15	100	85	ATBC (6)	6
#5	1.06	15	100	85	TEC (6)	6
#6	1.06	15	100	85	ATEC (6)	6
#7	1.06	15	100	85	DBS (3)	6
#8	1.06	15	100	85	DBS (9)	6
#9	1.06	15	100	85	DBS (6)	3
#10	1.06	15	100	85	DBS (6)	9
#11	0.53	15	100	85	DBS (6)	6
#12	2.12	15	100	85	DBS (6)	6

2.5. In vitro release characteristics

The release characteristics of uncoated and coated HPMC matrix tablet were studied in triplicate using a dissolution apparatus type I basket method (Fine Scientific DST600A, Seoul, South Korea) with a stirring speed of 100 rev./min at 37 ± 0.5°C in 500 ml of simulated gastric fluid (pH 1.4 ± 0.1, NaCl–HCl buffer solution) for 2 h followed by study in simulated intestinal fluids (pH 7.4 ± 0.1, phosphate buffer solution) thereafter. The dissolution samples (1 ml) were collected at a given interval with replacement of equal volume of dissolution media, and were filtered through a Millipore membrane filter. The concentration of MT released as a function of time was determined using reverse phase HPLC as mentioned previously (Lee and Min, 1996).

3. Results and discussion

3.1. SEM of dual drug-loaded HPMC matrix tablet

The surface morphology and cross-sectional view of dual drug-loaded HPMC matrix tablet are shown in Fig. 2. The surface of coated dual drug-loaded HPMC tablets at 15% coatings was also smooth and poreless and had a similar morphology to conventionally coated HPMC matrix tablet (Lee et al., 1999) except intermittently concave spots. The cross-sectional view of dual drug-loaded HPMC matrix tablet showed a distinct coated layer with about 75 μm thickness at the 15% coating level. It was noted that the surface of the HPMC tablet could be further improved by increasing the coating levels.

3.2. Comparison of uncoated, conventionally coated and dual drug-loaded HPMC matrix tablet

The release characteristics of uncoated, conventionally coated and dual drug-loaded HPMC matrix tablet are compared in Fig. 3. The release profiles of MT were independent of pH in dissolution media because the drug released continuously increased when the gastric fluid was switched to intestinal fluid after 2 h. The Eudragit® RS30D is claimed by the manufacturer to be a pH-independent polymer. However, it should be noted that its pH-independent character could be pH-dependent in the case of poorly water-soluble ibuprofen because of drug solubility (Lee and Min, 1995). The conventional HPMC matrix tablet showed a zero-order release over 10 h. The release rate decreased as the coatings of conventional HPMC matrix tablet using Eudragit® RS30D polymer were applied. However, it was noted that the dual drug-loaded matrix tablet (formulation #2) gave a biphasic linear release, showing a zero-order for 4 h (first) followed by another zero-order release when fitted using linear regression ($r^2 = 0.99$). Un-

like the conventionally coated matrix tablet with stable core, the drug release characteristics from the dual drug-loaded HPMC matrix tablet depended on the swelling force of the core matrix and the mechanical properties of the coated film (Gazzaniga et al., 1993). It was assumed that at the first stage, the drug loaded in the coating layer was initially released through the polymeric films or through liquid-filled pores and channels. Thereafter, as the core HPMC matrix tablet was hydrated, the drug in the hydrophilic matrix core diffused out through the coated layer, resulting in biphasic release characteristics of dual drug-loaded HPMC matrix tablet. The detailed release mechanism using fabricated polymeric membranes is under investigation.

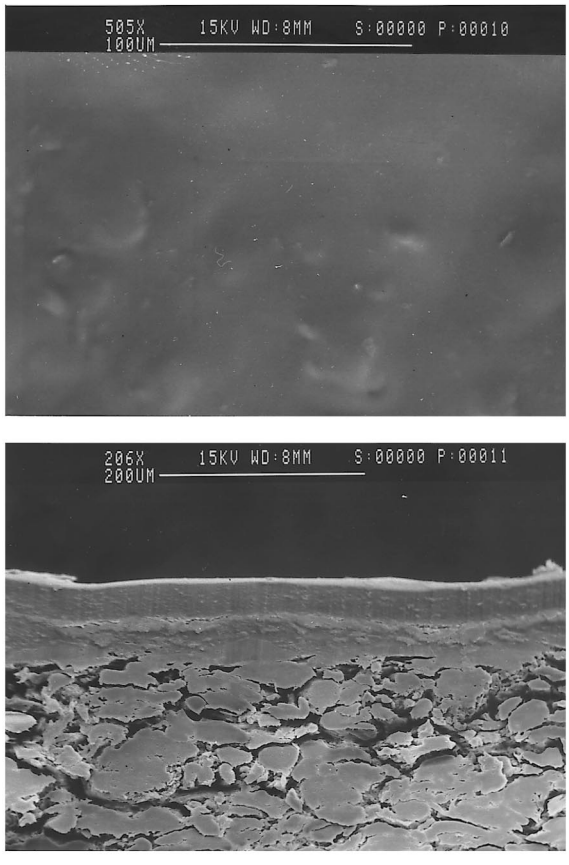

Fig. 2. Surface morphology (top) and cross-sectional view (bottom) of dual drug-loaded HPMC matrix tablet. The coating levels of dual drug-loaded HPMC matrix tablet were 15%, based on the weight gains when compared to uncoated tablet.

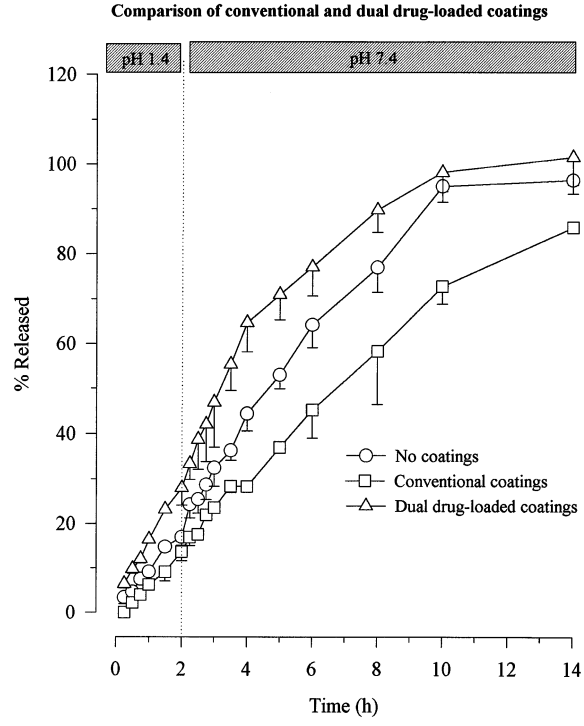

Fig. 3. Comparison of release characteristics of uncoated, conventionally coated and dual drug-loaded HPMC matrix tablet. The formulation # 2 was compared in the case of dual drug-loaded HPMC matrix tablet.

3.3. Effects of coatings

Effect of coating levels at two different outer drug concentrations (0.25 and 0.5%) on the release characteristics of dual drug-loaded HPMC matrix tablet is shown in Fig. 4. The release rate of drug from dual drug-loaded HPMC matrix tablet at 0.25 or 0.5% outer drug concentration was increased at 15% but decreased at 25% coating levels when compared to uncoated matrix tablet. As the coating levels increased, the release rate further decreased. The biphasic release profiles of dual drug-loaded HPMC matrix tablet was unchanged except at 25% coating level when 0.5% outer drug concentration in coating dispersion was applied. At 0.25% drug concentration in coating dispersion, the first linear release portion was advanced as coating levels increased (25%). The biphasic release profile was observed at 15% coating levels when 0.5% drug concentration in coat-

ing dispersion was applied. However, the biphasic release profiles gradually disappeared as the coatings of dual drug-loaded HPMC matrix tablet highly increased (data not shown). The release profiles of dual drug-loaded HPMC matrix tablet were dependent on swelling force of the core matrix and mechanical properties of the coated film. The core swelling was limited as long as the polymeric film adhered to the HPMC matrix tablet, resulting in change of the release profiles (Gazzaniga et al., 1993).

3.4. Effects of drug concentration in coating dispersion

In addition to coating thickness, the release characteristics can be varied by the amount of drug in inner and outer layers of the dual drug-loaded HPMC matrix tablet. The period of initial release from dual drug-loaded matrix tablet may also depend on the amount of drug loading in the coated layer. The effect of drug concentrations in coating dispersion on the release characteristics of dual drug-loaded HPMC matrix tablet is shown in Fig. 5. As the drug concentration in polymeric coating dispersion increased (0.25–1.0%), the amount of drug released increased. The time for the first linear release was also advanced. However, the biphasic release pattern was not changed. These results suggested that the amount of drug portion in inner and outer layers, and the coating levels are important factors (Fig. 4).

3.5. Effects of plasticizers

Many pharmaceutical polymers exhibit brittle and fragile properties. Plasticizers are therefore incorporated into polymeric dispersions for film coatings. The plasticizers can modify the thermal and mechanical properties of polymers by decreasing tensile strength, lowering minimum film-forming temperature, and increasing elongation,

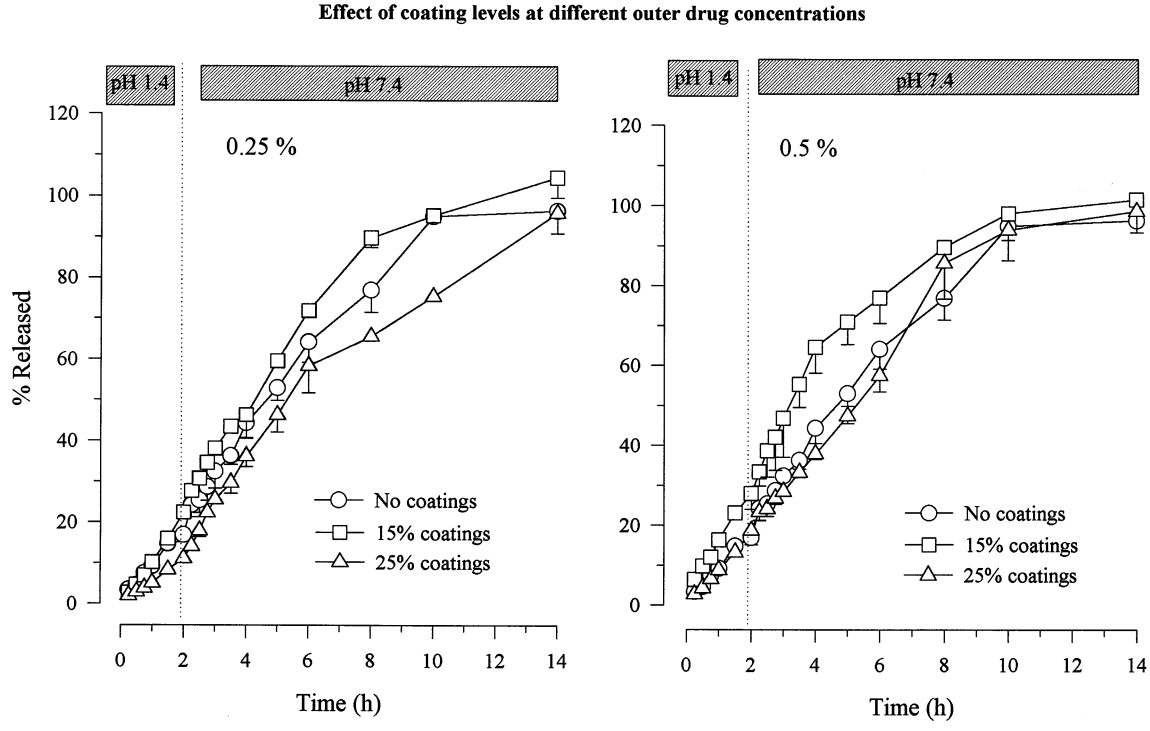

Fig. 4. Effect of coating levels at two different outer drug concentrations (0.25 and 0.5%) on the release characteristics of dual drug-loaded HPMC matrix tablet.

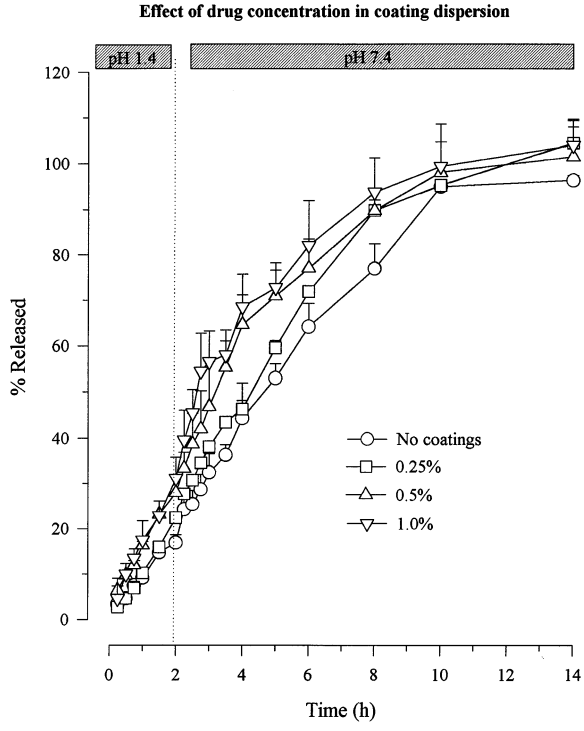

Fig. 5. Effect of drug concentrations in coating dispersion on the release characteristics of dual drug-loaded HPMC matrix tablet.

elasticity and flexibility of the films without cracking, edging, or splitting (Gutierrez-Rocca and McGinity, 1994; Wang et al., 1997). The mechanical properties of the polymeric film were significantly influenced by the concentration and type of hydrophilic and hydrophobic properties of the plasticizers, and the plasticization time before the coatings (Gutierrez-Rocca and McGinity, 1994; Bodmeier and Paeratakul, 1997; Wang et al., 1997). For these reasons, the use of plasticizers has been found to be imperative when brittle polymeric materials such as acrylic polymers are considered for coatings because the drug release from the pellets and tablet cores is largely affected.

The effect of DBS levels in coating dispersion on the release characteristics of dual drug-loaded HPMC matrix tablet is shown in Fig. 6. As the amount of DBS increased, the release rate slightly decreased but the biphasic release profiles was not significantly changed except at the 10% level. On the other hand, various types of hydrophilic and hydrophobic plasticizers were commonly used for the plasticization of Eudragit® RS30D polymer. The effect of plasticizers at 20% (w/w) levels in coating dispersion on the release characteristics of dual drug-loaded HPMC matrix tablet are also given in Fig. 7. It was evident that the release profiles greatly varied, depending on the type of plasticizers. The release rate greatly decreased in the case of ATEC and TEC. The release rate significantly increased in the order, ATEC, TEC, ATBC, TBC and DBS. There was no distinct correlation between hydrophilic and hydrophobic plasticizer on the release characteristics of dual drug-loaded HPMC matrix tablet. However, it was noted that the different release behavior could be attributable to the mechanical resistance of the film containing plasticizers or its diffusive properties. The plasticizers can also vary the film-forming property of the polymer and are distributed in the coated film.

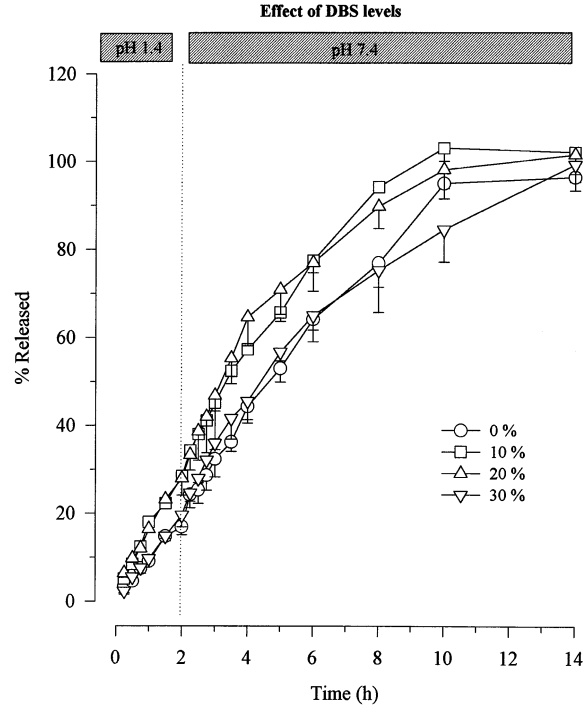

Fig. 6. Effect of DBS levels in coating dispersion on the release characteristics of dual drug-loaded HPMC matrix tablet.

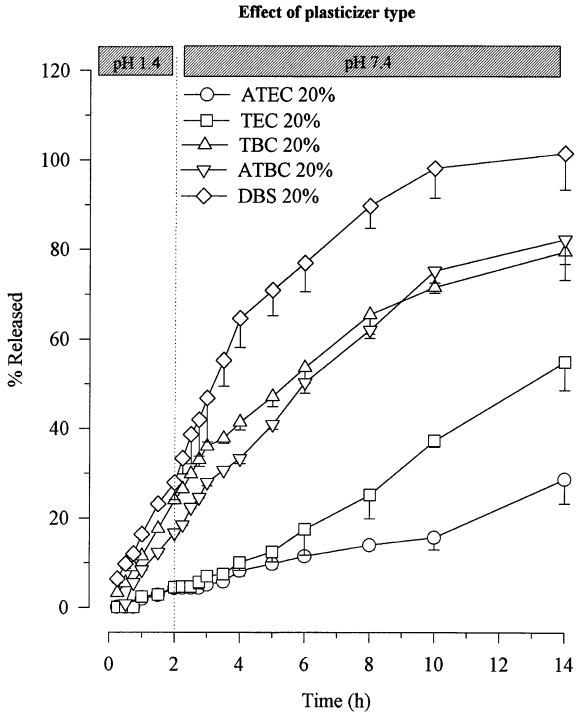

Fig. 7. Effect of plasticizers at 20% levels in coating dispersion on the release characteristics of dual drug-loaded HPMC matrix tablet.

3.6. Effects of talc

Due to the strong tackiness and adhesiveness of polymethacrylate polymers, addition of glidants such as talc is generally recommended. Talc avoids the tacky phase of the dispersion and agglomeration of the cores during coating processing, making a smoother film surface. The effect of talc levels on the release characteristics of dual drug-loaded HPMC matrix tablet is shown in Fig. 8. Talc did not affect the release rate of dual drug-loaded matrix tablet significantly.

MT as a model drug is secreted in a circadian fashion, giving elevated blood concentrations of about 50–70 pg/ml during the night over 8 h but returned to the daytime baseline (<10 pg/ml) (Benes et al., 1997). It was reported that the sustained release MT treatment was more clinically useful to initiate and maintain sleep in the elderly insomniac (Garfinkel et al., 1995). For these reasons, various sustained release MT dosage forms have been published in our group (Lee et al., 1994, 1995, 1996, 1997, 1998, 1999; Konsil et al., 1995; Lee and Min, 1996; Benes et al., 1997) although conventional tablets, solutions and tea have been marketed as a supplementary nutrient in the United States. A capsule simultaneously containing immediate release and sustained release MT-loaded sugar spheres, transdermal and transmucosal preparations were previously investigated in human subjects to mimic endogenous plasma concentration profiles of MT (Lee et al., 1994, 1995, 1997; Benes et al., 1997). Benes et al. (1997) suggested that transmucosal administration of MT most closely mimicked the physiological nocturnal profile of MT while oral controlled release sugar spheres alone resulted in prolonged plasma concentration rather than square-wave characteristics. The transdermal preparation did not simulate the nocturnal plasma profile and showed a long delay in systemic absorption. The current dual drug-loaded HPMC matrix tablet, showing biphasic release profiles

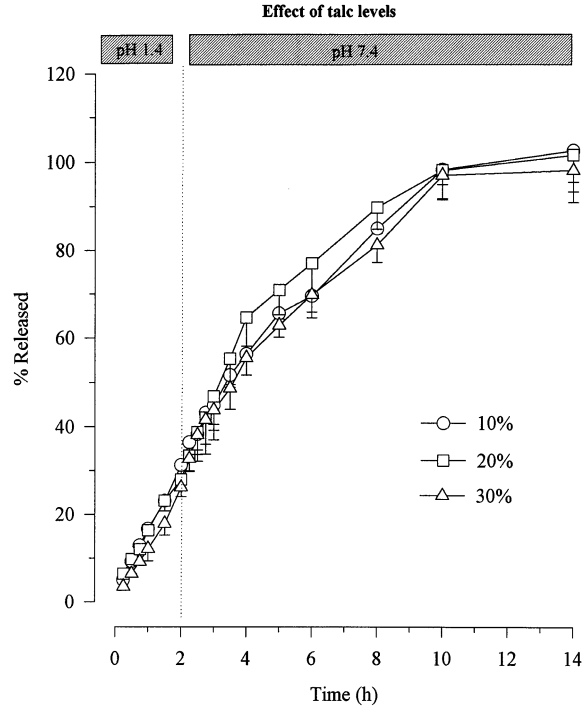

Fig. 8. Effect of talc levels on the release characteristics of dual drug-loaded HPMC matrix tablet.

may provide an alternative to deliver the drugs with circadian rhythmic behaviors in the body but needs to be validated in the future in human studies.

In addition, the biphasic or pulsatile release preparations can be helpful compared to sustained release because nearly all functions of the body, including pharmacokinetics and pharmacodynamics in clinical situations display significant daily variation and biological rhythms (Lemmer, 1991). A conventional zero-order release preparation is also found to be tolerant in the case of nitrates, antibiotics and steroids (Pozzi et al., 1994). For this reason, many pharmaceutical preparations, including sigmoidal release system, pulsatile release tablet, time-controlled explosion system, pulsincap, press tablet and dual drug-loaded alginate beads have been investigated for therapeutic needs or biological rhythms (Giunchedi et al., 1991; Maggi et al., 1993; Pozzi et al., 1994; Narisawa et al., 1995; Lee et al., 1998b). The dual drug-loaded HPMC matrix tablet can also be used for these purposes.

The current dual drug-loaded coating method is interesting for the modified release of poorly water-soluble drugs because solubilizers and other additives can be added in drug-containing polymeric coating dispersions. The controlled release of other cores such as alginate, sugar sphere or pellet coated using drug-containing polymeric dispersions is under further investigation. In addition, the release profile of cores having drug in only outer drug-containing polymeric coated layer is also of our continuous concern.

4. Conclusions

The dual drug-loaded HPMC matrix tablet was designed simultaneously containing drugs in inner core and outer coated layer using drug-containing aqueous-based polymeric coatings. Unlike the conventionally uncoated and coated HPMC matrix tablet, the dual drug-loaded matrix tablet had distinct biphasic release characteristics. However, the release characteristics of dual drug-loaded matrix tablet were highly dependent on coating levels, drug loading in coating dispersion, and the amount and type of plasticizers. Talc as an anti-tacking substance did not change the release profiles significantly. The current dual drug-loaded HPMC matrix tablet, showing biphasic release profiles may provide an alternative to deliver drugs with circadian rhythmic behaviors in the body but needs to be further validated in the future in human studies.

Acknowledgements

This work was in part supported by research grants from the Ministry of Health and Welfare (# HMP: 96-D-7-0049). Part of this research was also presented at the 1997 American Association of Pharmaceutical Scientists (AAPS) annual meeting held in Boston, MA, USA [Pharmaceutical Research, 14(11), S542 (1997)].

References

Benes, L., Claustrat, B., Horriere, F., Geoffriau, M., Konsil, J., Parrott, K.A., Degrande, G., McQuinn, R.L., Ayres, J.W., 1997. Transmucosal, oral controlled-release, and transdermal drug administration in human subjects: A crossover study with melatonin. J. Pharm. Sci. 86, 1115–1119.

Bodmeier, R., Paeratakul, O., 1997. Plasticizer uptake by aqueous colloidal polymer dispersions used for the coating of solid dosage forms. Int. J. Pharm. 152, 17–26.

Ford, J.L., Rubinstein, M.H., McCaul, F., Hoagan, J.E., Edgar, P.J., 1987. Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. Int. J. Pharm. 40, 223–234.

Freely, L.C., Davis, S.S., 1988. Influence of polymeric excipients on drug release from hydroxypropylmethylcellulose matrices. Int. J. Pharm. 44, 131–139.

Garfinkel, D., Laudon, M., Dof, D., Zisapel, N., 1995. Improvement of sleep quality in elderly people by controlled-release melatonin. Lancet 346, 541–544.

Gazzaniga, A., Sangalli, M.E., Conte, U., Caramella, C., Colombo, P., La Manna, A., 1993. On the release mechanism from coated swellable minimatrices. Int. J. Pharm. 91, 167–171.

Giunchedi, P., Maggi, L., Conte, U., Caramella, C., 1991. Ketoprofen pulsatile absorption from 'multiple unit' hydrophilic matrices. Int. J. Pharm. 77, 177–181.

Gutierrez-Rocca, J.C., McGinity, J.W., 1994. Influence of water soluble and insoluble plasticizers on the physical mechanical properties of acrylic resin copolymers. Int. J. Pharm. 103, 293–301.

Konsil, J., Parrott, K.A., Ayres, J.W., Sack, R.L., 1995. Development of a transdermal delivery device for melatonin in vitro study. Drug Dev. Ind. Pharm. 21, 1377–1387.

Kurahashi, H., Kami, H., Sunada, H., 1996. Influence of physicochemical properties on drug release rate from hydroxypropyl methylcellulose matrix tablet. Chem. Pharm. Bull. 44, 829–832.

Lee, B.-J., Min, G.-H., 1995. Release characteristics of polymer-reinforced and coated alginate beads. Arch. Pharm. Res. 18, 183–188.

Lee, B.-J., Min, G.-H., 1996. Oral controlled release of melatonin using polymer-reinforced and coated alginate beads. Int. J. Pharm. 144, 37–46.

Lee, B.-J., Parrott, K.A., Ayres, J.W., Sack, R.L., 1994. Preliminary evaluation of transdermal delivery of melatonin in human subjects. Res. Commun. Mol. Pathol. Pharmacol. 85, 337–344.

Lee, B.-J., Parrott, K.A., Ayres, J.W., Sack, R.L., 1995. Design and evaluation of an oral controlled release delivery system for melatonin in human subjects. Int. J. Pharm. 124, 119–127.

Lee, B.-J., Parrott, K.A., Ayres, J.W., Sack, R.L., 1996. Development and characterization of an oral controlled release delivery system for melatonin. Drug Dev. Ind. Pharm. 22, 269–274.

Lee, B.-J., Ryu, S.-G., Choi, H.-G., Kim, C.-K., Parrott, K.A., Ayres, J.W., Sack, R.L., 1997. Batch variation and pharmacokinetics of oral sustained release melatonin-loaded sugar spheres in human subjects. Arch. Pharm. Res. 20 (6), 555–559.

Lee, B.-J., Cui, J.-H., Kim, T.-W., Heo, M.-Y., Kim, C.-K., 1998. Biphasic release characteristics of dual drug-loaded alginate beads. Arch. Pharm. Res. 21, 645–650.

Lee, B.-J., Ryu, S.-G., Cui, J.-H., 1999. Formulation and release characteristics of hydroxypropyl methylcellulose matrix tablet containing melatonin. Drug Dev. Ind. Pharm. 25, 493–501.

Lemmer, B., 1991. Circadian rhythm and drug delivery. J. Controlled Release 16, 63–74.

Maggi, L., Conte, U., Giunchedi, P., Colombo, P., 1993. Pressed coated tablets for the sequential pulsed administration of two different drugs. Int. J. Pharm. 99, 173–179.

McGinity, J.W. (Ed.), 1987. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. Marcel Dekker, New York.

Narisawa, S., Nagata, M., Ito, T., Yoshino, H., Hirakawa, Y., Noda, K., 1995. Drug release behavior in gastrointestinal tract of beagle dogs from multiple unit type rate-controlled or time-controlled release preparations coated with insoluble polymer-based film. J. Controlled Release 33, 253–260.

Pozzi, E., Furlani, P., Gazzaniga, A., Davis, S.S., Wilding, I.R., 1994. The time clock system: a new oral dosage form for fast and complete of drug after a predetermined lag time. J. Controlled Release 31, 99–108.

Tahara, K., Yamamoto, K., Nishihata, T., 1995. Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropylmethylcellulose 2910. J. Controlled Release 35, 59–66.

Wang, C., Zhang, G., Shah, N.H., Infeld, M.H., Malick, A.W., McGinity, J.W., 1997. Influence of plasticizers on the mechanical properties of pellets containing Eudragit RS 30D. Int. J. Pharm. 152, 153–163.