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RESEARCH PAPER

Formulation and Release Characteristics of Hydroxypropyl Methylcellulose Matrix Tablet Containing Melatonin

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ABSTRACT

A hydroxypropyl methylcellulose (HPMC) matrix tablet containing melatonin (MT) was formulated as a function of HPMC viscosity, drug loading, type and amount of disintegrant, lubricant and glidant, and aqueous polymeric coating level and was compared with two commercial products. The release characteristics of the HPMC matrix tablet were investigated in the gastric fluid for 2 hr followed by study in intestinal fluid. The surface morphology of an uncoated HPMC matrix tablet using scanning electron microscopy (SEM) was crude, showing aggregated particles and rough crystals or pores, but it became smoother as the coating levels increased. As the HPMC polymer viscosity increased, the release rate had a tendency to decrease. As the drug loadings increased, the release rate slightly decreased. When Polyplasdone®XL, Primojel®, and Ac-Di-Sol®, except Avicel®, were incorporated in the HPMC matrix tablet, the release rate was markedly increased. There was no significant difference in release profiles when a mixture of lubricants and glidants (magnesium stearate, talc, and Cab-O-Sil®), except for magnesium stearate alone, was incorporated into low and high viscosity grade HPMC matrix tablets. As the coating level increased, the release rate gradually decreased, giving an increased lag time. The sustained-release HPMC matrix tablet with optimizing formulations may provide an alternative for oral controlled delivery of MT and be helpful in the future treatment of circadian rhythmic disorders.

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INTRODUCTION

Hydrophilic matrix systems have been paid considerable attention as sustained-release formulations for various drugs (1,2). Hydroxypropyl methylcellulose (HPMC), a semisynthetic derivative of cellulose, has its popularity in the formulation of sustained-release dosage forms as a swellable and hydrophilic polymer because of its nontoxic property, ease of handling, minor influence on processing parameters, and relatively simple manufacturing technology (3,4).

On exposure to aqueous fluids, the tablet surface becomes wet and starts to hydrate to form a viscous gel layer. The release of drugs from the products can be governed by the diffusion through the hydrogel and by its subsequent erosion (1,4–6). It has been widely reported that drug release from HPMC matrices is affected by the physical character of the polymer, such as polymer viscosity, particle size, and drug/polymer ratio (2,4–9); by the physicochemical properties of drugs, such as solubility, particle size, and drug loading (1,6–9); and by manufacturing factors, such as compression force, tablet shape, hardness, formulation excipients, coatings, and processing techniques (1–6,10), as well as by the testing medium (9).

Melatonin (MT) was selected as a model drug in the formulation of a sustained-release HPMC matrix tablet. The MT may be helpful in the future in the treatment of such disorders as sleep syndrome, jet lag, seasonal affective disease, shift work syndrome, and other circadian rhythmic disorders (11). It was reported that the sustained-release MT treatment was more clinically useful to initiate and maintain sleep in elderly insomniacs compared with immediate-release or conventional therapy (12,13). For these reasons, the sustained-release dosage forms to deliver MT were widely investigated in our laboratory due to its short half-life (14–19). Currently, no commercial dosage forms of MT are available, although conventional tablets, solution, and tea have been marketed as a supplementary nutrient in the United States.

The purpose of this study was to prepare uncoated and coated HPMC matrix tablets and to evaluate release characteristics of MT as a function of HPMC viscosity, drug loading, type of disintegrants and lubricants/glidants, and aqueous polymeric coating levels in simulated gastric fluids, followed by assessment in intestinal fluids. The surface morphologies and cross-sectional views of uncoated and coated matrix tablets were also investigated using scanning electron microscopy (SEM).

MATERIALS AND METHODS

Materials

The MT was purchased from Morepen (New Delhi, India). Five viscosity grades of HPMC (100 cps, 400 cps, 4000 cps, 100,000 cps, 100,000 cps SR) with the same particle size (90SH type) were provided courtesy of Richwood (Seoul, Korea). The Eudragit® RS 30D, an aqueous-based polymeric coating material, was provided courtesy of Duc Woo (Seoul, Korea). Crospovidone (Polyplasdone®XL), microcrystalline cellulose (Avicel®), and crossed-linked carboxymethylcellulose sodium (Ac-Di-Sol®) were kindly obtained from Chong Kung Dang (Seoul, Korea). Sodium starch glycolate (Primojel®) was purchased from Avebe (Foxhol, Netherlands). Talc, a purified and hydrated magnesium silicate, was purchased from Shin Jun (Seoul, Korea). Magnesium stearate (Mg-stearate) was purchased from Katayama (Osaka, Japan). A fumed silicon dioxide (Cab-O-Sil®) was kindly supplied by Cabot (Tuscola, IL). Dibutyl sebacic acid (DBS) was purchased from Sigma (St. Louis, MO). All other chemicals were reagent grade and were used without further purification.

Preparation of Matrix Tablets

The HPMC, drug, and disintegrants were thoroughly blended. Thereafter, the powders were mixed with lubricants and glidants. The resulting powder mixtures were directly compressed into tablets using a single-punched tablet machine (Apex, England) to prepare the flat-faced tablets, 6.35 mm diameter and 52.7 $\pm$ 2.0 mg average weight. The compaction pressure was 150 $\pm$ 20 N/mm^2. The detailed compositions of the HPMC matrix tablet formulations are given in Table 1.

Preparation of Coated Matrix Tablets

Aqueous-based polymeric Eudragit RS 30D (about 30% solid content) was diluted with water (1:1 w/w). The talc (40% based on polymeric contents) was added to the above solution and then completely dispersed using an overhead stirrer. Addition of talc reduces the tendency of the dispersion to stick during processing and makes a smoother film surface. Thereafter, the DBS (20% based on polymeric contents) was added as a plasticizer to improve film elasticity and minimum film-forming temperature. The weight ratios of polymer, water, talc, and DBS were 100:100:12:6, giving 48% total solid contents. The coating solution was then applied to matrix tablets in a

Table 1

Formulation Compositions of HPMC Matrix Tablet Expressed as Weight Percentages

Formulation	HPMC	Drug	Disintegrant	Lubricant/Glidant
1	96.4 (100 cps)	1.6	—	Mg-stearate (2)
2	96.4 (400 cps)	1.6	—	Mg-stearate (2)
3	96.4 (4000 cps)	1.6	—	Mg-stearate (2)
4	96.4 (100,000 cps)	1.6	—	Mg-stearate (2)
5	96.4 (100 cps)	1.6	Avicel (4)	Mg-stearate (2)
6	85.7 (100 cps)	8.3	Avicel (4)	Mg-stearate (2)
7	92.4 (100 cps)	1.6	Ac-Di-Sol (4)	Mg-stearate (2)
8	92.4 (100 cps)	1.6	Primojel (4)	Mg-stearate (2)
9	92.4 (100 cps)	1.6	Polyplasdone (4)	Mg-stearate (2)
10	96.4 (100 cps)	1.6	—	Talc (2)
11	96.4 (100 cps)	1.6	—	Cab-O-Sil (2)
12	96.4 (100 cps)	1.6	—	Mg-stearate (1)/Talc (1)
13	96.4 (100 cps)	1.6	—	Mg-stearate (1)/Cab-O-Sil (1)
14	96.4 (100 cps)	1.6	—	Talc (1)/Cab-O-sil (1)
15	96.4 (100,000 cps)	1.6	—	Mg-stearate (1)/Cab-O-Sil (1)
16	92.4 (100,000 cps)	1.6	Avicel (4)	Mg-stearate (1)/Cab-O-Sil (1)
17	92.4 (100,000 cps)	1.6	Avicel (4)	Mg-stearate (2)
18	92.4 (100,000 cps, SR)	1.6	Avicel (4)	Mg-stearate (1)/Cab-O-Sil (1)

pan coater (Korea Machine, Seoul, Korea) at 50°C and then further air dried. The amount of coating was designated as percentage of weight gain compared to an uncoated tablet.

Scanning Electron Microscopy

The dried samples were coated with gold using an Auto Coating Unit E5200 coater (London, England) for about 2 min to obtain about a coating thickness of about 200 Å. Surface morphologies and cross-sectional views of the uncoated and coated matrix tablets were characterized. Micrographs were taken at an accelerating voltage of 15 kV or 20 kV with a Cambridge Stereo Scan 200 (London, England).

In Vitro Release Characteristics

The release characteristics of uncoated and coated HPMC matrix tablets were studied in triplicate using a dissolution apparatus type I, basket method (Fine Scientific DST600A, Seoul, Korea), with a stirring speed of 100 rpm at 37°C ± 0.5°C in 500 ml of simulated gastric fluid (pH 1.4 ± 0.1, NaCl-HCl buffer solution) for 2 hr, followed by stirring in simulated intestinal fluids (pH 7.4 ± 0.1, phosphate buffer solution) thereafter. The dissolution samples (1 ml) were collected at a given interval, replaced with an equal volume of dissolution media, and filtered through a Millipore membrane filter. The concentration of MT released as a function of time was determined using reverse-phase high-performance liquid chromatography (HPLC) as mentioned previously (18).

RESULTS AND DISCUSSION

Scanning Electron Microscopy of Uncoated and Coated Hydroxypropyl Methylcellulose Matrix Tablets

The surface morphology and cross-sectional views of uncoated and coated HPMC matrix tablets are shown in Fig. 1. The surface morphology of the uncoated HPMC matrix tablet was crude and rough, showing aggregated particles and rough crystals or pores. The inner cores of the uncoated HPMC matrix tablet showed chasms and compressed lumps (Fig. 1A). For the coated HPMC matrix tablet, the surface morphology got smoother as the aqueous polymeric coating levels increased. The distinct and condensed coating layers were observed as viewed by the cross section of the coated tablet (Fig. 1B). The coating thickness increased as the coating level increased. For 15% and 25% of coating levels, designated as percentages of weight gain, the coating thicknesses were about 75 μm and 100 μm, respectively.

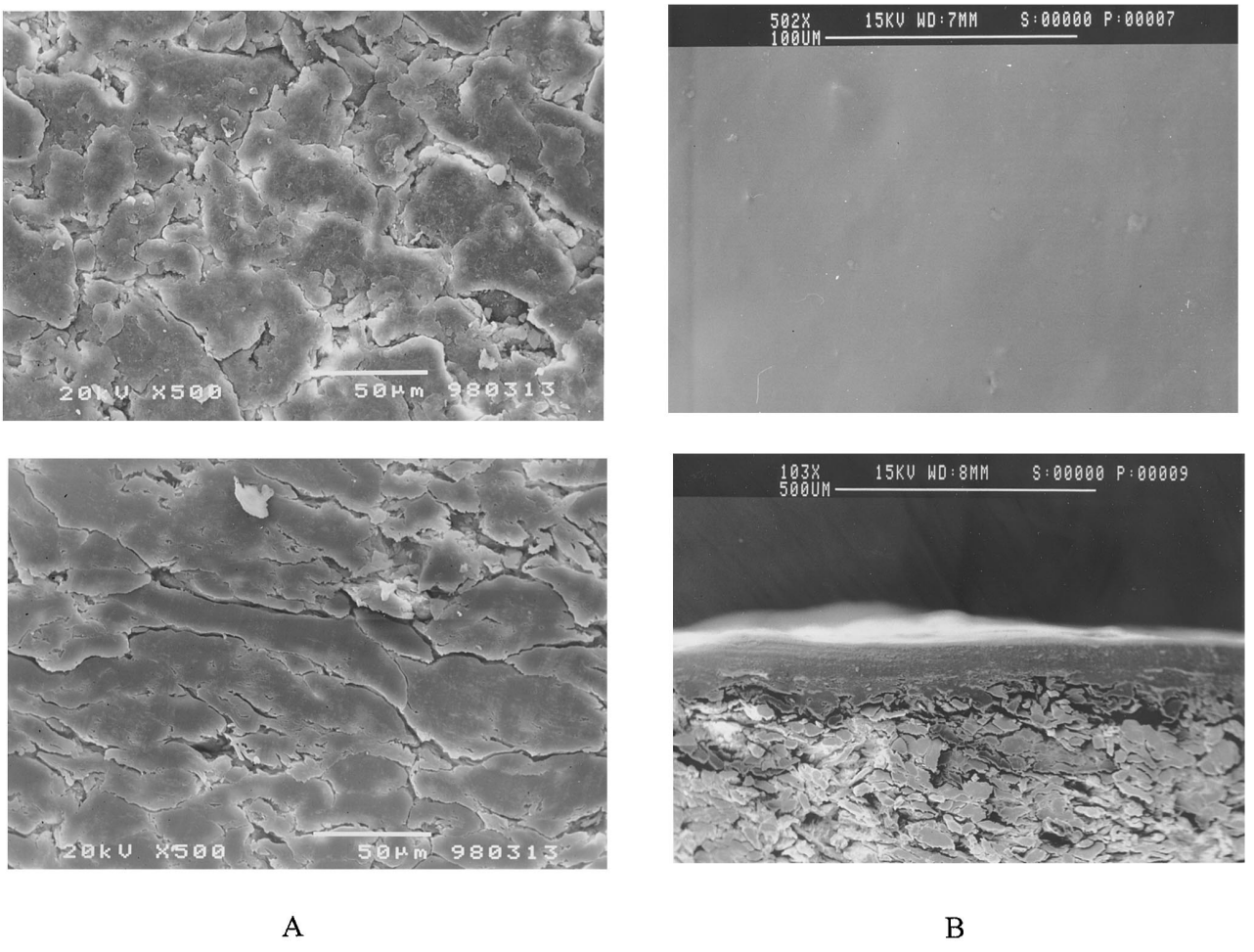

Figure 1. Surface morphology (top) and cross-sectional view (bottom) of (A) uncoated and (B) coated HPMC matrix tablet.

Effects of Hydroxypropyl Methylcellulose Viscosity

It is known that the release rate of an HPMC matrix-type tablet is highly dependent on the viscosity grades and particle size of HPMC polymer, which affect swelling and erosion of the tablet (2,4–8). The HPMC particles with high viscosity require a longer time (lag time) for dissolution to form a gel layer, resulting in a decreased release rate. However, it was noted that a viscosity of more than 4000 cps had little difference (8).

The effect of HPMC viscosity grade on the release profiles of the HPMC matrix tablet is shown in Fig. 2. As the viscosity of the HPMC polymer increased, the release rate had a tendency to decrease. The release rate of MT was independent of pH of the testing medium. The drug solubility and testing medium are major factors to modify the release profiles (1,8,9,18). The poorly water-soluble MT was released from the HPMC matrices by the diffusion of the gelatinous layer, followed by the erosion of the gel regardless of the testing pH.

Effects of Drug Loading

The gelling strength of the HPMC matrices for diffusion is important to control the release rate because the release rate is mainly governed by swelling and erosion. However, the release rates of drugs from HPMC matrices can be changed by modifying the ratio of polymer to drug and additives. The effect of drug loadings on the release profiles of an HPMC matrix tablet is shown in Fig. 3. As the drug loadings increased, the release rate slightly

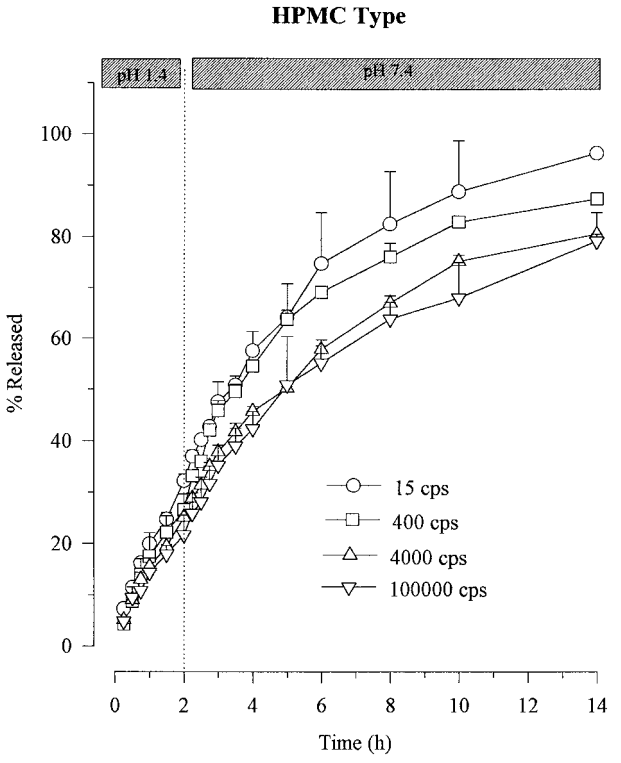

Figure 2. Effect of HPMC viscosity grades on the release profile of HPMC matrix tablets.

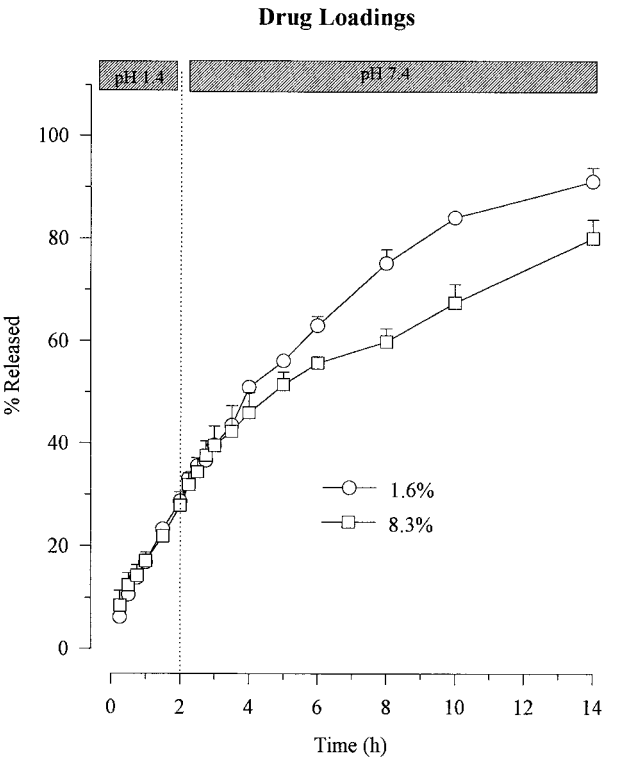

Figure 3. Effect of drug loadings on the release profile of a low viscosity grade of HPMC (100 cps) matrix tablet.

decreased. It was reported that the increase of HPMC content with the same drug content (relatively higher polymer ratio) resulted in a decreased release rate of drugs by leaving an HPMC matrix of low porosity and high tortuosity, which would presumably allow high gel strength and slow diffusion and erosion (5,6,8). On the other hand, increase of drug content with constant HPMC content decreased the percentage release rate of the poorly water-soluble indomethacin even though the weight release rate increased (6). Likewise, the presence of MT was considered to facilitate the maintenance of the HPMC gel structure, resulting in decreased percentage release rate.

Effects of Additives

The diffusion and erosion rate of swellable HPMC matrices can be widely changed by the incorporation of various additives during the manufacturing process (1–3,5,6,20). Disintegrants are often incorporated into tablet formulations to enhance the dissolution of the active ingredients. The disintegration phenomena occur by rapid uptake of water, followed by swelling and wicking behavior of the HPMC matrix tablet, depending on pH of the testing media (21,22). Four different types of disintegrants (Polyplasdone XL, Avicel, Primojel, and Ac-Di-Sol), widely used in oral pharmaceuticals in capsule and tablet formulations, were selected (21,23).

The effect of disintegrants on the release profiles of an HPMC matrix tablet is shown in Fig. 4. When Polyplasdone XL, Primojel, and Ac-Di-Sol were incorporated in an HPMC matrix tablet, the release rate was markedly increased compared to a tablet without disintegrant. However, Avicel resulted in a more retarded release rate. It was known that, in the case of Polyplasdone XL, Primojel, and Ac-Di-Sol as superdisintegrants, the particle swelling and disintegration forces are higher compared to those of Avicel (21). The high swelling behaviors of these superdisintegrants allow further penetration of the dissolution medium, resulting in rapid disruption and erosion of the HPMC matrices. It was assumed that Avicel could retard the swelling and hydration of the HPMC matrix tablet due to its low swelling and disintegrating forces, resulting in a decreased re-

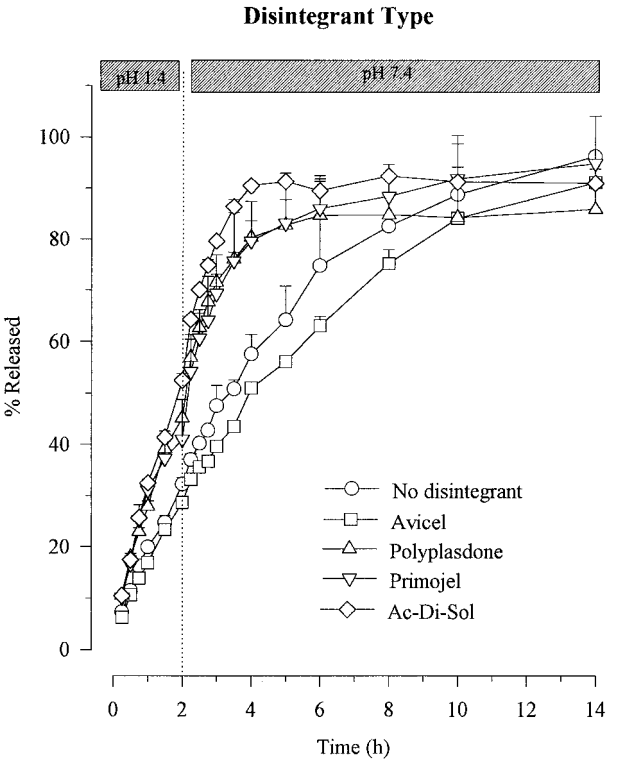

Figure 4. Effects of disintegrants on the release profile of a low viscosity grade of HPMC (100 cps) matrix tablet.

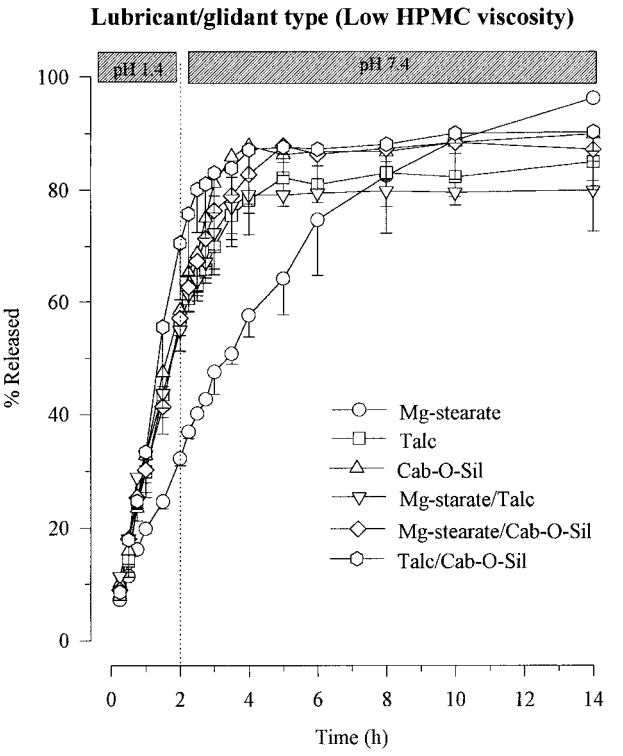

Figure 5. Effects of lubricants and glidants on the release profile of a low viscosity grade of HPMC (100 cps) matrix tablet.

lease rate (21,23). In addition, the tablet hardness was enhanced when Avicel was incorporated. Although the tablet hardness had little effect on swelling and erosion of the HPMC matrix tablet, the proper tablet hardness might be considered for further handling and coating process.

On the other hand, utilization of hydrophobic lubricants and glidants in direct compression of powdered mixtures for tableting is essential to reduce friction and improve fluidity without mechanical problems during the manufacturing process. The quantity, type, method of addition, blender type, and mixing time of lubricants with the powders and granules can significantly affect such physicochemical properties of the tablet as hardness, friability, and release rate (20,23). The widely used magnesium stearate, talc, and Cab-O-Sil were selected as hydrophobic lubricants and glidants (23).

The effects of lubricants and glidants on the release profiles of low (100 cps) and high (100,000 cps) viscosity grade HPMC matrix tablets are given in Fig. 5 and Fig. 6, respectively. There was no significant difference in the release profiles when a mixture of lubricants was incorporated into low viscosity grade HPMC matrix tablets. The drug completely released over 4 hr after the start of the dissolution. For a low viscosity grade of HPMC matrix containing magnesium stearate only as a lubricant, the release rate was significantly decreased. It is known that the highly hydrophobic materials may retard the hydration and swelling of the HPMC matrix tablet, resulting in decreased release rate of drugs (5,20).

On the other hand, the high viscosity grade HPMC matrix tablet resulted in a decreased release rate compared to the low viscosity grade HPMC, as mentioned previously (see Fig. 2). The HPMC matrix tablet with high viscosity (100,000 cps SR) containing Avicel, magnesium stearate, and Cab-O-Sil gave a zero-order release over 10 hr, while another type of HPMC (100,000 cps) showed a zero-order release over 4 hr, which then decreased. The decreasing effect of hydrophobic magnesium stearate on the release rate was not significant for high viscosity grade HPMC matrix tablets. However, the release rate of high viscosity grade HPMC matrix tablets significantly decreased when Avicel, with weak swelling and disintegrating forces, was added to magnesium stearate. It is assumed that the Avicel could also serve as an excellent binder and be able to improve the mechanical

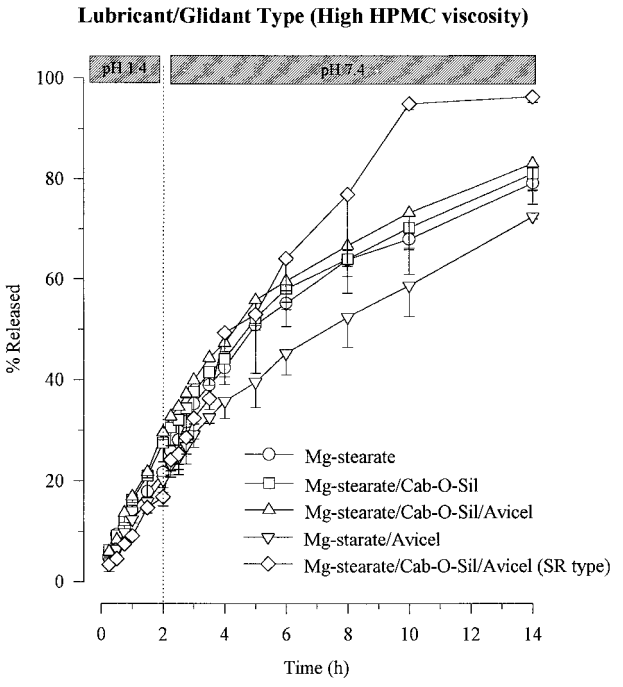

Figure 6. Effects of lubricants and glidants on the release profile of a high viscosity grade of HPMC (100,000 cps) matrix tablet. Another type of high viscosity grade HPMC (100,000 cps SR) matrix tablet was also used for comparison.

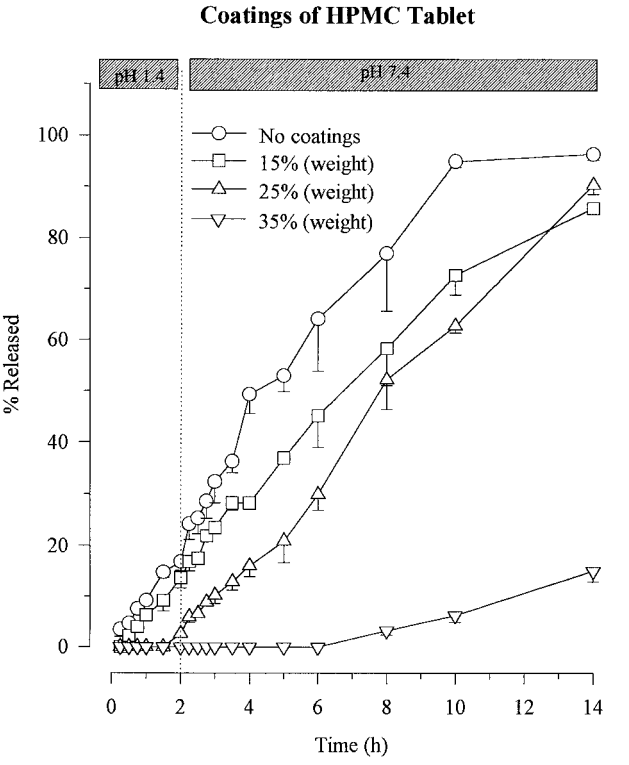

Figure 7. The release profile of HPMC (100,000 cps SR) matrix tablet as a function of coating level. The coating levels were expressed as percentages of weight gain compared to measurements for an uncoated tablet.

strength of some weak formulation substantially, resulting in a decreased release rate (see also Fig. 4). The decreasing effect of Avicel on the release rate was reduced when Cab-O-Sil was incorporated. Cab-O-Sil, as a glidant, gave it markedly increased flow characteristics due to its small particle size and large specific area, resulting in good tableting behavior. A combination of lubricant and glidant may be useful in the direct compression of the HPMC matrix formulation.

Based on physicochemical behaviors of HPMC matrix tablets, such as release rate, powder mixing, tablet hardness, and tableting process, studied previously, the matrix tablet with a high viscosity grade HPMC (100,000 cps SR), Avicel, magnesium stearate, and Cab-O-Sil (formulation 18) was selected as a sustained-release dosage form. Thereafter, the HPMC matrix tablet was further coated to control the release rate efficiently.

Effects of Coatings

For coated HPMC matrix tablets with slightly permeable Eudragit RS polymers, the matrix swelling forces and mechanical properties of the film are very important for controlling the release behaviors (10). The release profile of HPMC (100,000 cps SR) matrix tablet as a function of coating level is given in Fig. 7. The amount of coatings, designated as percentages of weight gain, was 15%, 25%, and 35%, respectively, compared to uncoated tablets. The uncoated HPMC matrix tablet showed a near-zero-order release over 10 hr. As the coating level increased, the release rate gradually decreased. At the higher coatings levels, the lag time was also largely increased. The release rate of the HPMC matrix tablet was highly dependent on the pH-independent Eudragit RS coatings for modifying swelling and erosion rate.

Comparison of Coated Hydroxypropyl Methylcellulose Matrix Tablets with Commercial Products

The uncoated HPMC matrix tablet that showed a zero-order release was compared with two commercially available tablets. The release profiles of uncoated HPMC (100,000 cps SR) matrix tablet and two commercial prod-

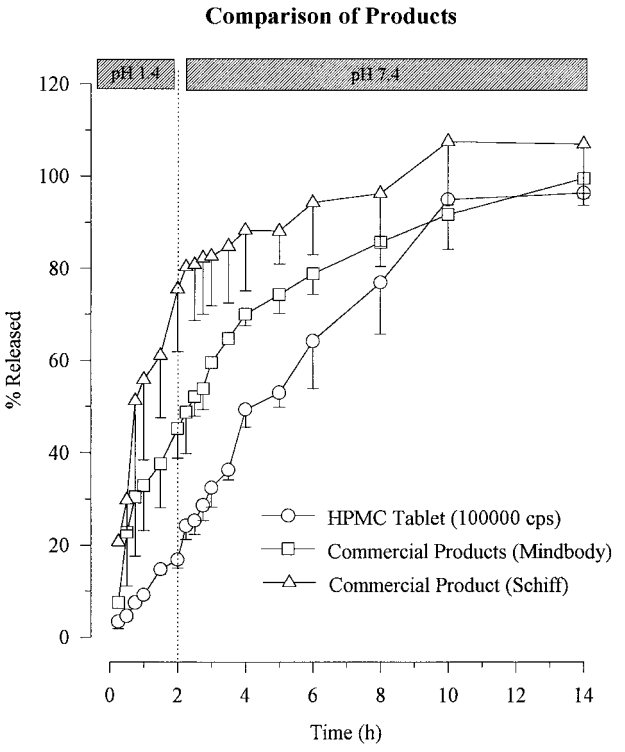

Figure 8. Comparison of the release profile of a coated HPMC (100,000 cps SR) matrix tablet and two commercial products containing MT.

ucts containing MT are given in Fig. 8. While the uncoated HPMC (100,000 cps SR) matrix tablet gave a zero-order release over 10 hr, the commercial product from Schiff Products (Salt Lake City, UT) showed immediate release with large deviation. The release profiles of the tablet from Mindbody (Kihei, HI), claimed by the manufacture to be a timed-release product, were further retarded when compared to Schiff. The current HPMC matrix tablet could provide an alternative to control the release rate of MT.

CONCLUSIONS

The release behaviors of MT-loaded hydrophilic HPMC matrix tablets prepared by direct compression were changed by HPMC type; drug loadings; incorporation of various disintegrants, lubricants, and glidants; and the aqueous polymeric coatings during the manufacturing process because the diffusion and erosion rates of HPMC matrices were modified. The current formulation approaches for HPMC matrix tablets for optimizing compressibility, flow properties, and release characteristics can be applied in the preparation of tablets containing other drugs via direct compression. The sustained-release HPMC matrix tablet with optimizing formulations may also provide an alternative for oral controlled delivery of MT and be helpful in the future in the treatment of circadian rhythmic disorders.

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