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Effect of Solvents on Physical Properties and Release Characteristics of Monolithic Hydroxypropylmethylcellulose Matrix Granules and Tablets

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Effect of solvents on physical characteristics and release characteristics of monolithic acetaminophen (APAP) hydroxypropylmethylcellulose (HPMC) matrix granules and tablets were examined. Various types and amounts of solvents were employed for granulation and coating. APAP and other excipients were mixed and were then wet-granulated in a high-speed mixer. The dried granules were then directly compressed and film-coated with low viscosity grade HPMC. As the amount of water increased, the size of granules also increased, showing more spherical and regular shape. However, manufacturing problems such as capping and lamination in tableting occurred when water was used alone as a granulating solvent. The physical properties of HPMC matrix granules were not affected by the batch size. The initial release rate as well as the amount of APAP dissolved had a tendency to decrease as the water level increased. Addition of nonaqueous solvent like ethanol to water resulted in good physical properties of granules. When compared to water/ethanol as a coating solvent, the release rate of film-coated HPMC matrix tablets was more sensitive to the conditions of coating and drying in methylene chloride/ethanol. Most of all, monolithic HPMC matrix tablet when granulated in ethanol/water showed dual release with about 50% drug release immediately within few minutes followed by extended release. It was evident that the type and amount of solvents (mainly water and ethanol) were very important for wet granulation and film-coating of monolithic HPMC matrix tablet, because the plastic deforming and fragmenting properties of material were changed by the different strengths of the different solvents.

Key words: Solvents for granulation and coating, Monolithic, HPMC Matrix granules, Dual-release, Physical properties

INTRODUCTION

Hydroxypropylmethylcellulose (HPMC) has become very popular for the formulation of controlled release matrix tablets as a hydrophilic gel-forming substance (Ford *et al.*, 1985; Ebube *et al.*, 1997a). The HPMC matrix tablet is generally produced either *via* direct compression or granulation process. The release characteristics from the HPMC matrix tablet could also be varied by numerous parameters (Freely *et al.*, 1988; Shah *et al.*, 1996; Lee *et al.*, 1999a, 1999b; Cao *et al.*, 2004).

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In many cases, drug-HPMC mixtures do not have adequate flow characteristics for tableting or direct die filling (Liu *et al.*, 1993). In general, granulation process is commonly employed to produce HPMC based granules with a high degree of compressibility and good flow characteristics for controlled release HPMC matrix tablets (Liu *et al.*, 1993; Ebube *et al.*, 1997b). In pharmaceutical industry, technique based on fluidized bed granulation has been used as granulation and drying occur in a unit process (Watano *et al.*, 1997; Rambali *et al.*, 2003). However, compaction force and bulk density of the granules are needed for the controlled release. Contrarily, high-speed mixers with high-shear forces are widely used for wet granulation to produce controlled release matrix tablet (Shiraishi *et al.*, 1994; Farag Badawy *et al.*, 2000). Mixing, densification and agglomeration of wetted materials

are achieved through high shear forces to produce compact granules in a large scale with subsequent compression of the dried granules to form HPMC matrix tablet. The HPMC matrix tablet can also be coated either to improve surface roughness or to modify release profiles.

As during granulation numerous processing parameters may affect the quality and integrity of controlled release HPMC matrix tablet; the solvents used for wet granulation and coating process such as water, ethanol, isopropyl alcohol and methylene chloride should be carefully selected to assure reproducibility of HPMC based matrix granules or tablets. Most of all, water is widely utilized as a granulating solvent to prepare HPMC matrix tablet (Liu *et al.*, 1993; Ebube *et al.*, 1997b; McConville *et al.*, 2004). However, wet granulation or polymeric coating with water is not preferable because HPMC has a tendency to form gel and lumps in the presence of water (Liu *et al.*, 1993; Cao *et al.*, 2004). Nonaqueous solvents are also avoided due to their environmental and regulatory issues. Therefore, proper selection of a solvent or cosolvent for wet granulation and coating is very important to establish the quality and reliable release characteristics of HPMC based dosage forms. However, there are not much data available on the effect of type and amount of solvents (employed for granulation and coatings) on the physical properties and release characteristics of hydrophilic HPMC matrix granules or tablet.

The purpose of the present work was to investigate the effect of solvents on physical properties and release characteristics of monolithic HPMC matrix granules and tablets. The types and amounts of solvents employed for granulation and coating were varied at three different batch sizes of tablet (3000, 50000 or 100000T). Thereafter, physical properties of granules and tablet and dissolution profiles at different pH conditions were extensively investigated. The surface morphologies of granules were examined by a scanning electron microscope (SEM). In this study, APAP was used as a model drug. APAP is widely used as a non-prescription, non-narcotic analgesic and antipyretic drug (Walson *et al.*, 1989).

MATERIALS AND METHODS

Materials

APAP and microcrystalline cellulose (Avicel® PH101) were donated by the Seoul Pharma Co., Ltd (Seoul, Korea). The HPMC (6 cps, 4000 cps) was supplied by courtesy of Richwood Trading Comany (Seoul, Korea). Starch 1500 (Prejel® P.A.-5) was purchased from Avebe (Veendam, Netherlands). Sodium lauryl sulphate (SLS) and sodium dihydrogen phosphate (NaH_2PO_4) were purchased from Sigma (St. Louis, MO, USA). Magnesium stearate and colloidal silicon dioxide (Aerosil® 200) were purchased from Katayama Chemical Co. (Osaka, Japan) and Degussa AG (Frankfurt, Germany), respectively. Propylene glycol (Chameleon Chemical Co., Osaka, Japan) and polyethylene glycol 6000 (Showa Chemical Co., Tokyo, Japan), titanium dioxide (Showa Chemical Co., Tokyo, Japan) and talc (Yakuri Chemical Co., Osaka, Japan) were obtained from the respective companies. Methylene chloride and ethanol were purchased from Duksan (Seoul, Korea). The commercial bi-layered Tylenol® ER tablet (Janssen Korea, Seoul, Korea) was purchased as the reference for comparison in the present study. All other chemicals were of reagent grade and used without any further purification.

Preparation of granules

The entire granulation process was carried out using a high-speed mixer at impeller speed of 100 rev/min for the production of three different batch sizes of 3000, 50000 or 100000 tablets. The chopper speed was kept constant at 2800 rpm. Formulation compositions of monolithic HPMC matrix tablet (745 mg) *via* granulation was 650 mg APAP, 32.85mg HPMC (4000 cps), 6.0 mg Aerosil®, 23.65 mg Avicel® PH101, 25 mg Prejel® (starch 1500), 1.0 mg SLS, 2.5 mg NaH_2PO_4 and 4.0 mg magnesium stearate, respectively. Except for lubricant, the powders (drug, HPMC polymer and additives) were thoroughly mixed in a high-speed mixer for 5 min by spraying granulating solvents at a constant rate. The resultant mixtures were further blended for 5 min and then wet screened using an oscillator equipped 18 mesh screens. The wet granules were then dried in a conventional oven at 60°C with the moisture content less than 2.3%. In order to exhibit good flow properties and compressibility, the resultant dried granules were further milled for 2 min and sieved using

Table I. Type and level of granulating solvents employed for the preparation of monolithic HPMC matrix tablets via wet granulation process

No.	Batch size of tablet	Solvent level (%)[a]		
		Water	Ethanol	Isopropyl alcohol
1	3,000	–	–	–
2	3,000	6	–	–
3	3,000	8	–	–
4	3,000	10	–	–
5	3,000	20	–	–
6	50,000	8	–	–
7	100,000	8	–	–
8	100,000	6	–	–
9	100,000	5	–	28
10	100,000	5	28	–

[a]Solvent level was the percentage of total batch weight

different mesh screens (25, 40, 60 or 100 mesh) to obtain a desired particle size suitable for direct compression of tablet. Table I shows the types and amounts of granulating solvents employed for the preparation of monolithic HPMC matrix tablets *via* wet granulation process at the different batch sizes.

Particle size distribution

Particle size distribution of the final dried granules was determined by sieve analysis using a Sifter (Model 35-VSS-300, Kukje Science, Seoul, Korea) equipped with a series of four standard stainless steel sieves (25, 40, 60, and 100 mesh). Approximately 20 g granule samples were sifted for 5 min in triplicate and then the collected particles on each screen were weighed.

Moisture content

Moisture content in the granules was determined by drying exactly the weighed quantity in a Scaltec® Moisture Analyzer (Scaltec Instruments GmbH, Goettingen, Germany) at 105°C for about 1 h until no further decrease in weight was observed. Moisture content was then calculated as the difference between initial and final weight of the granules.

Bulk and tap density

An appropriate amount of granule sample (3 g) was poured in a 10 mL tarred graduate cylinder. The cylinder was lightly tapped once to collect all the powders sticking to the wall of the cylinder to the bottom. The volume was then read directly from the cylinder and used to calculate the bulk density (ρ_{bulk}) according to the mathematical relationship; density (ρ) = mass/volume. For tap density (ρ_{tap}), the cylinder was tapped 500 times using an Erweka SVM12 tap density analyzer (Berlin, GmbH, Germany). The final volume of the sample was then read and used for the calculation of tap density. The percentage of compressibility (Carr's index) was then calculated using the equation as follow; Carr's index = $[(\rho_{tap} - \rho_{bulk})/\rho_{tap}] \times 100$, where ρ_{tap} and ρ_{bulk} are tap density and bulk density of the granules, respectively.

Angle of repose

The granules were poured into a fixed funnel with the help of a cone. The height (h) and radius (r) of the deposit were measured. The angle of repose (φ) was then calculated as follows.

$$\tan\varphi = h/r$$

Surface morphology

The surface morphology of HPMC matrix granules were visualized using SEM. The dried granules were coated with gold under argon atmosphere using a Jeol JFC-1100 sputter coater (Tokyo, Japan) for about 2 min to obtain about 200Å of the coating thickness. Micrographs were taken with a Cambridge Stereo Scan 200 (London, England) at an accelerating voltage of 15KV.

Preparation of tablets

The dried and size-distributed granules (25~60 mesh) as prepared previously were lubricated with magnesium stearate and then compressed using a rotary tablet machine (Korea Machine, Seoul, Korea) equipped with capsule-shape punches and a die to prepare the tablet. The compaction pressure was 150±20 N/mm^2.

Hardness test

The tablet hardness was measured in triplicate using an Erweka® hardness tester (Model SVM-12, Erweka GmbH, Heusenstamm, Germany).

Friability test

Tablet friability was determined using the friabilator (Model FAT-20, Labfine Inc., Seoul, Korea). About 20 randomly selected tablets were rotated at 40 rpm for 10 min and the percent weight loss was measured. The tablet capping and lamination phenomena were also checked by visually observing the horizontal striation of the tablet.

Film coating of tablets

Two types (Type A and Type B) of coating formulation were used in this study. Coating solution was prepared by continuously dispersing propylene glycol, polyethylene glycol and low viscosity grade of HPMC (6 cps) in either hydrophobic ethanol/methylene chloride (Type A) or hydrophilic 28% ethanol/5% water (Type B) using a mechanical stirrer for 1 h at room temperature until uniform dispersion was formed. Talc and TiO_2 were finally dispersed in the coating solution and mixed for 30 min. The final coating solution was then left overnight to subside air bubbles. The film coating was carried out using a Sejong® Hi-coater (Seoul, Korea) under the following processing condition: inlet temperature (79-81°C), outlet temperature (39-41°C), tablet bed temperature (33-35°C), inlet air flow (7.4-8.0 m^3/h), atomizing air pressure (1.5-2.0 bar), drum speed (3 rpm) and spraying rate (10 or 50 mL/min). The tablets were sampled at regular intervals and weighed to determine the weight gains of the film-coated tablets. When the required coating levels were achieved, spraying of the coating solution was stopped. The tablets were further dried in the coating drum using warm (40°C) or cool air (room temperature) to investigate the effect of drying condition on release of drug from coated tablet. The 745 mg weight of monolithic HPMC matrix tablet increased to 755, 760 or 780 mg per tablet after coating. There was approximately 1.3, 2.0 or 4.7% coat weight

gain in 5,000 batch size of tablet, respectively. The film-coated HPMC tablets were stored in plastic bags at room temperature until use.

Release study

The drug release from the tablets was investigated in triplicate according to the KP dissolution II paddle method at rotation speed of 50 rpm in 900 mL of the dissolution medium at 37 ± 0.5°C using a DST-600A dissolution tester (Labfine, Seoul, Korea). The dissolution test media were 0.1 N HCl solution (pH 1.2 ± 0.1, NaCl), phosphate buffer (pH 6.8 ± 0.1, (pH 4.0 ± 0.1) and distilled water, respectively. The 5 mL of dissolution samples were collected at a given interval with replacement of equal volume of fresh test medium kept at 37 ± 0.5°C to maintain the constant volume of the test fluid. The collected sample solution was filtered through 0.2 μm Millipore filter. The concentration of APAP in the dissolution sample was spectrophotometrically determined at the 254 nm wavelength in a Pharmacia LKB Ultrospec III spectrophotometer (London, England).

RESULTS AND DISCUSSION

Effect of granulating solvents

Surface morphologies of HPMC matrix granules

It has been known that either aqueous or nonaqueous solvents significantly influence the physical structure of hydrophilic HPMC granules and coated film (Liu *et al.*, 1993; Ebube *et al.*, 1997; McConville *et al.*, 2004). The surface morphologies of HPMC matrix granules in the presence of various granulating solvents were examined by SEM (Fig. 1). It was observed that as the amount of water increased, the granules gained more spherical and regular shape (Fig. 1A-D). The size of granules also increased due to agglomeration of hydrophilic HPMC granules by water. However, at levels of 20% water, granules could not be properly produced due to the formation of large mass of wetted granules. Contrarily, amount of water less than 5% could not agglomerate the granules due to shortage of binding solvent. It was also observed that HPMC matrix granules prepared by using water alone caused manufacturing problems of tableting such as capping and lamination. When nonaqueous solvents such as ethanol and isopropyl alcohol were used, the HPMC matrix granules were easily agglomerated and were regular in shape (Fig. 1E, F) and the formation of granules was very reproducible. Ethanol could be a better granulating solvent than isopropyl alcohol due to its high volatility (for drying) and as it imparts good physical properties to HPMC matrix granules as discussed hereafter.

Physical properties of granules and tablets

To simplify many factors involved in production of HPMC matrix granules for tableting, granulation conditions such as high speed mixer (equipment), impeller speed, addition rate of granulation solvent and wet massing time were standardized, except for the changes in the granu-

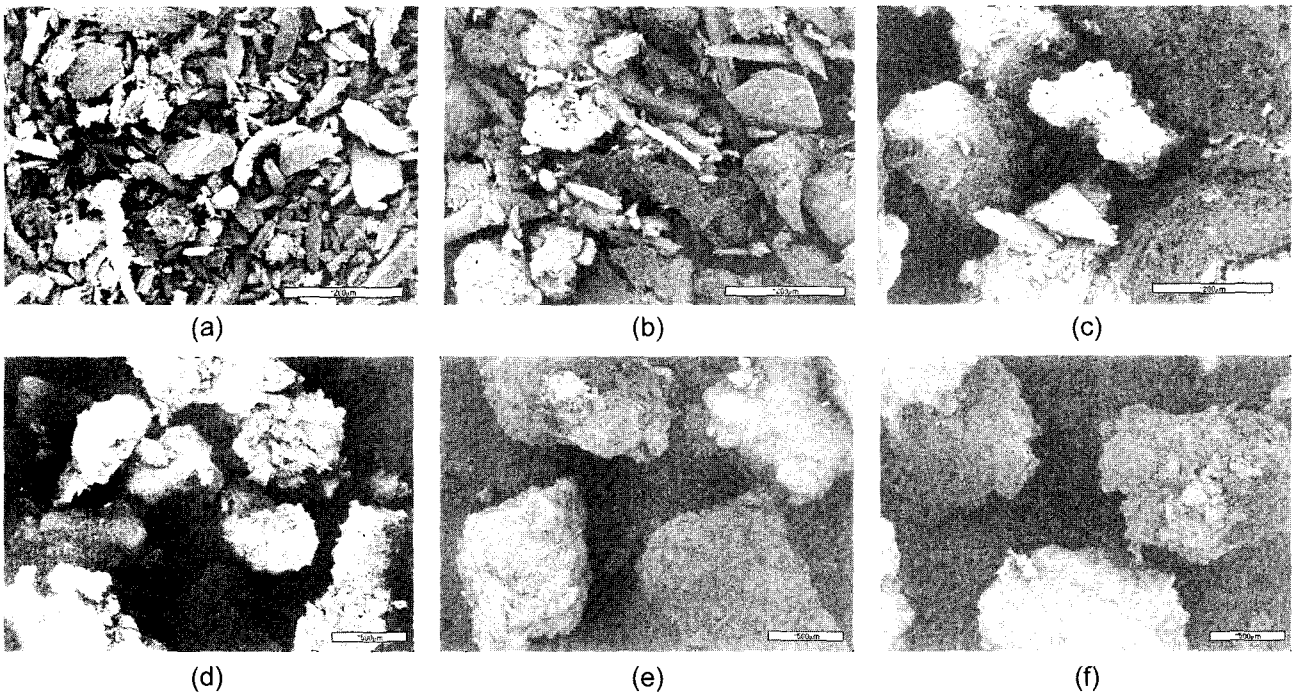


Fig. 1. The effect of various solvents on the surface morphologies of HPMC matrix granules as examined by SEM. (A) 6% water; (B) 8% water; (C) 10% water; (D) 20% water; (E) 28% ethanol and 5% water; (F) 28% isopropyl alcohol and 5% water.

Table II. Size distribution of HPMC matrix granules as a function of granulation solvent

Granulation solvent (% w/w)	Average percentage retained				
	<25 mesh	25-40 mesh	40-60 mesh	60-100 mesh	>100 mesh
6% water	1.57	15.77	16.45	26.49	39.72
8% water	4.91	31.36	15.65	15.27	32.82
10% water	8.08	40.40	25.61	12.46	13.45
28% alcohol + 5% water	36.6	22.30	16.04	13.45	11.92

Note) Granulation process was carried out to produce 100,000 tablet batch size.

lation solvents. The size distribution is important to check the size and quality of granules without agglomeration. Size distribution of HPMC matrix granules as a function of granulation solvent is compared in Table II. It was observed that size distribution was highly dependent on the type and level of solvents employed in the granulation process. In this study, the water levels added to the dry powder mixtures were generally controlled from 0 to 10% (in some cases, 20%). As the water levels increased, the size of granules also increased due to agglomeration of hydrophilic HPMC granules by water (Fig. 1), resulting in significant increase in the retention of HPMC matrix granules on lower sized mesh (25-40 mesh screen), as also reported by Phadke and Anderson (1990). Furthermore, when a mixture of water and ethanol was used as granulation solvent, much higher fraction of granules were retained on 25 mesh screen, i.e., larger granule size. The influence of the added solvent levels on size and growth of HPMC matrix granule can be explained by the wetting efficiency and degree of solvent saturation among granule particles during granulation process (Farag Badawy *et al.*, 2000). The higher degree of solvent saturation is associated with more free solvent on the surface of granule, giving increased fraction of larger size of granules due to enhanced compaction and granule coalescence (Kristensen, 1988).

Physical properties of HPMC matrix granules and tablet as a function of granulating solvent are given in Table III. The type and amount of granulation solvent could affect the bulk and tap density of granules with significant changes in the compressibility of granules. The water level had no effect on tap density, but bulk density was decreased as the water level decreased, especially to 6% level. Compressibility of HPMC matrix granules increased as the water amount decreased. Addition of alcohol in water as a granulation solvent resulted in much lower compressibility when compared to water alone. Because the fraction of larger particle size of HPMC matrix granules increased when ethanol was added, good flow of granules with low proportion of fine granules could be obtained, as also demonstrated by Henz *et al.* (2000). Angle of repose of HPMC matrix granules was the lowest when lower water and higher alcohol level were used, suggesting better flow characteristics. An angle of repose and compressibility of HPMC matrix granules prepared with 5% water and 28% ethanol was 33° and 17%, respectively, indicating suitable flowability for tableting of the HPMC matrix granules. It has been found that less than 0.8% moisture levels of total weight have a tendency to cap the tablet while more than 2.3% moisture level exhibits lower tablet hardness and compressibility (Muti and Othman, 1989). Moisture content of HPMC matrix granules ranged from 0.8 to 2.3% throughout the whole experiment. The moisture content of granules gradually decreased as the water amount decreased, while moisture content of granules produced with 28% ethanol and 5% water was twice higher regardless of the drying rate when compared to water. Actually, there was no significant difference in moisture contents of HPMC matrix granules amongst the three water levels. Although increase in moisture content resulted in increase of tablet hardness, the moisture content of HPMC matrix granules within these ranges was suitable for tableting regardless of some manufacturing problems.

The types and amounts of granulating solvents employed to prepare HPMC matrix granules appeared to be of importance to establish good physical characteristics of monolithic matrix tablet. Hardness of tablet increased as the water levels increased during granulation process due

Table III. Physical properties of HPMC matrix granules and tablet as a function of granulating solvent

Granulation solvent	Batch size of tablet	Granules					Tablet	
		Bulk density (g/mL)	Tapped density (g/mL)	Compressibility (%)	Moisture contents (%)	Angle of repose	Hardness (kP)	Friability (%)
10% water	3000	0.46 ± 0.003	0.59 ± 0.006	23.05 ± 1.31	1.01 ± 0.005	42.03 ± 1.79	12.92± 2.54	Capping^{++}
8% water	100000	0.47 ± 0.004	0.63 ± 0.001	25.73 ± 0.67	0.97 ± 0.003	41.67 ± 2.66	10.57± 1.89	Capping^{+}
6% water	100000	0.42 ± 0.007[a]	0.61 ± 0.006	31.15 ± 0.39[a]	0.81 ± 0.009[a]	37.67 ± 2.07	7.35±1.28[a]	Capping^{+}
28% alcohol + 5% water	100000	0.47 ± 0.008	0.57 ± 0.008	17.01 ± 0.19[a]	2.01 ± 0.007[a]	33.64 ± 1.63	8.51±2.20[a]	0.72 ± 0.005

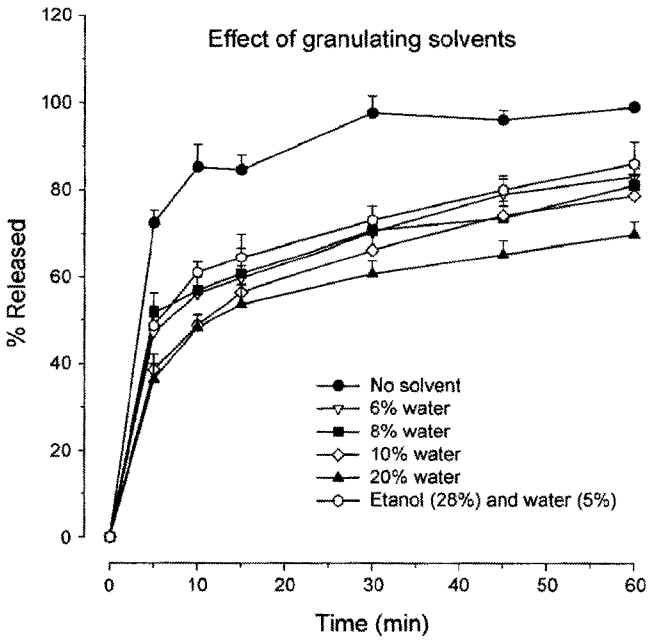
[a]$p < 0.05$ compared to 10% water.

$^{+}$ 2-3% (w/w) capping of total tablets; $^{++}$ over 5% (w/w) capping of total tablets.

to increased interaction between powder mixtures as demonstrated by Muti and Othman (1989) and Chowhan and Palagyi (1978). However, friability seemed to be independent of the hardness of tablets as well as moisture content. The capping and laminating phenomena occurred when water alone was used as a granulation solvent. Contrarily, monolithic HPMC matrix tablet prepared with a mixture of water and ethanol as granulation solvents had a low friability of 0.72% without exhibiting any manufacturing problems. It was also evident that the HPMC matrix granules produced with water alone as a granulation solvent in a large scale were unsatisfactory for tableting because of higher percentage of friability as well as manufacturing problems such as capping and lamination.

Release characteristics of tablets

Release profiles of monolithic matrix tablet by tableting HPMC matrix granules were examined. Effect of granulating solvents on release characteristics of monolithic HPMC matrix tablet in simulated intestinal fluid (pH 6.8) is shown in Fig. 2. The initial release rate as well as the amount of APAP released decreased as the water level increased. At 0% water level, dry powder mixtures were directly compressed into tablet. The directly compressed HPMC matrix tablet without using water (0%) showed the fastest release over 70% and a complete release of APAP (over 90%) was observed within 30 min while the HPMC matrix tablet prepared with higher water levels (20%) showed slower release rates. The faster release at the lower water level was probably due to decreased granule



. Effect of granulating solvents on release characteristics of hic HPMC matrix tablet in simulated intestinal fluid (pH 6.8).

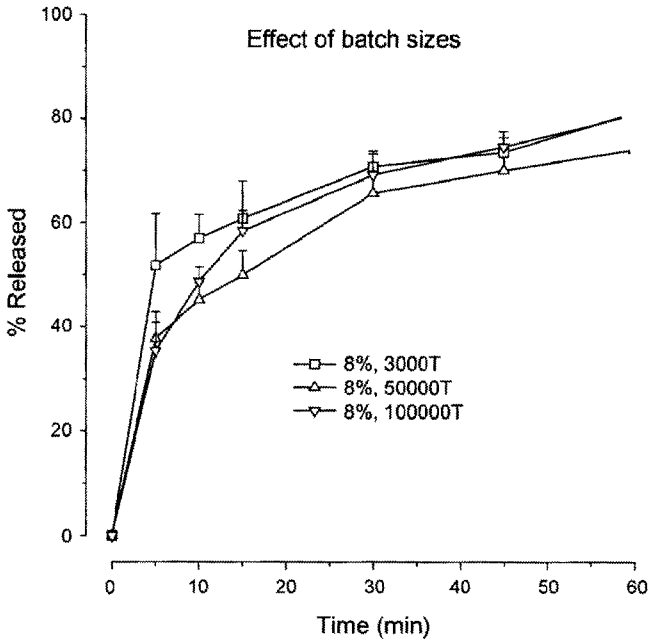


Fig. 3. Effect of batch sizes of granulation at 8% water level on release characteristics of monolithic HPMC matrix tablet in simulated intestinal fluid (pH 6.8).

compaction and coalescence by lower wetting and liquid saturation (Kristensen, 1988). The release rate was sustained possibly due to increased compaction and swelling of HPMC granules when the water levels increased. Contrarily, release profiles of monolithic HPMC matrix tablet were consistent when cosolvent (ethanol and water) was used for granulation. A mixture of ethanol and water would be better than water because of easiness of granule drying and reliable release rate.

In case of HPMC matrix tablet, the drug solubility and gel-forming properties of polymeric HPMC were very crucial for controlling initial release rate as well as amount of drug dissolved (Ford *et al.*, 1985; Lee *et al.*, 1999a, 1999b; Cao *et al.* 2004). Although the monolithic HPMC matrix tablet initially released drug over 40 to 70%, depending on the water levels, the capping and laminating phenomena occurred when water alone was used as a granulation solvent, as mentioned previously. Effect of batch sizes of granulation at 8% water levels on release characteristics of monolithic HPMC matrix tablet in simulated intestinal fluid (pH 6.8) is given in Fig. 3. The initial release rate within 10 min decreased as the batch sizes increased. The difference in release rate by varying batch sizes of granules might be due to the differences in the downward forces acting on the impeller of high-speed mixer and changes in the flow pattern of granules (Landin *et al.*, 1996).

Effect of coating solvents

The film coating of monolithic HPMC tablet with low

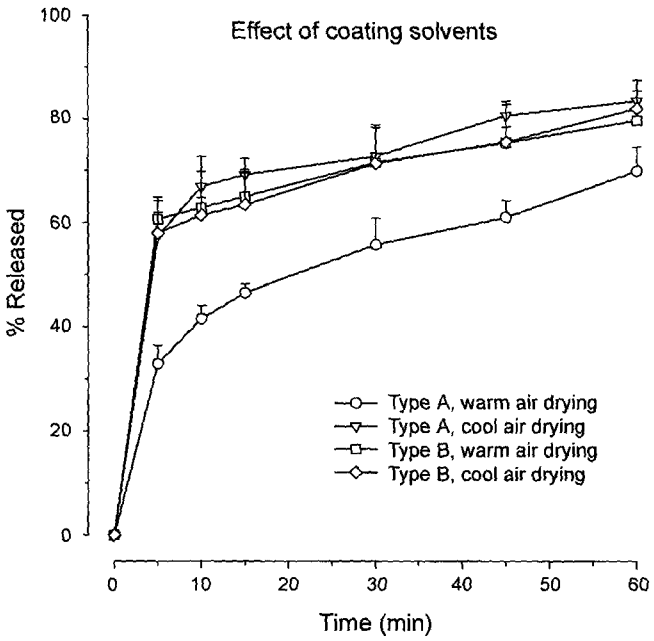


Fig. 4. Effect of coating solvents on release characteristics of monolithic HPMC matrix tablet in simulated intestinal fluid (pH 6.8). Coating levels: 1.3% per tablet, granulation solvents: 28% ethanol and 5% water (w/w).

viscosity grade (6 cps) of HPMC was carried out to improve the quality of tablet without any surface roughness. However, use of solvents for film-coating of monolithic HPMC tablet might change the release characteristics (Maffione *et al.*, 1993; Cao *et al.*, 2004). Effect of coating solvents on release characteristics of monolithic HPMC matrix tablet in simulated intestinal fluid (pH 6.8) is shown in Fig. 4. Effect of spraying rate and amount of coating solution is also given in Fig. 5. When type A film coating solution (organic methylene chloride/ethanol) was used, drug release was significantly affected by drying air temperature due to their high volatility and low boiling point when compared to water/ethanol solvent. The warm air-drying resulted in decreased release rate of monolithic HPMC matrix tablet. In addition, type A coating solution was also quite sensitive to coating levels and spraying rate. Spraying rate of coating dispersion as well as coating level changed the release rate of drug in about 10% ranges. Low coating levels and low spraying rate resulted in increased release rate. At the higher coating levels, the low spraying rate increased the release rate of coated tablet. The sensitivity of type A coating dispersion to drying and coating conditions such as spray rate and coating level might mainly result from the high volatility and low boiling point of methylene chloride as a coating solvent. Type A coating solution was not also suitable for film-coating due to environment hazardousness. Contrarily, the type B coating solution (ethanol/water) was less sensitive to drying air temperature and coating condition, resulting in reliable release rate of monolithic single layered HPMC matrix tablet. It would be also better to avoid use of harmful coating solvent like methylene chloride.

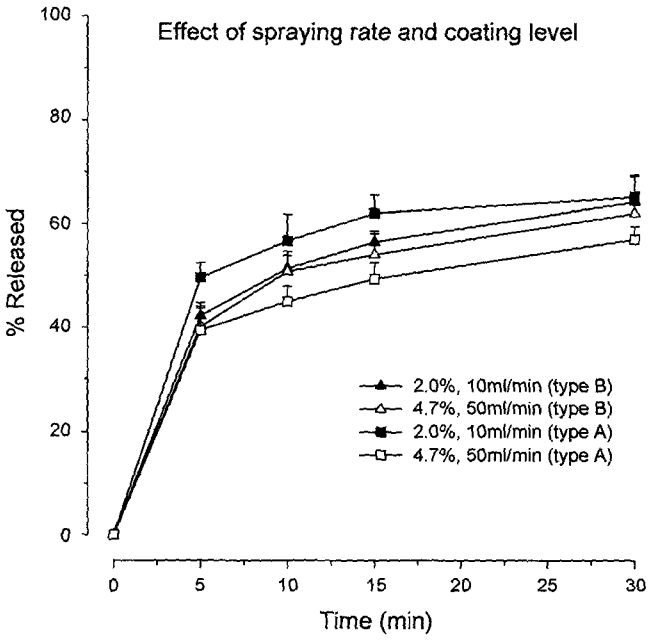


Fig. 5. *Effect of spraying rate and amount of coating solution (type A and B) on release characteristics of monolithic HPMC matrix tablet in simulated intestinal fluid (pH 6.8). Cool air-drying was employed at room temperature. Granulation solvents: 28% ethanol and 5% water (w/w).*

Comparative release profiles

After optimizing the effect of solvents for granulation and coatings, release profiles of monolithic HPMC matrix tablet (open symbol) and commercially available bi-layered Tylenol® ER (closed symbol) in four different dissolution media were investigated and compared (Fig. 6). Release profiles of monolithic HPMC matrix tablets were found to be in good agreement with commercial bi-layered Tylenol® ER. Interestingly, both dosage forms showed dual release with about 50% drug release immediately within few minutes followed by extended release.

In case of APAP, dual release profiles would be more desirable for the patients to obtain rapid onset and long duration of antipyretic and analgesic effect in clinical therapies due to its short half-life. The bi-layered Tylenol® ER tablet containing 650 mg APAP prepared using a specialized double compression tablet machine is commercially available in Janssen. Various controlled dosage forms with immediate and/or extended release at the same time have been also investigated for this purposes (Ebube *et al.*, 1997a; Shah and Ho, 2000; Anaebonam *et al.*, 2001). However, a monolithic HPMC matrix tablet with

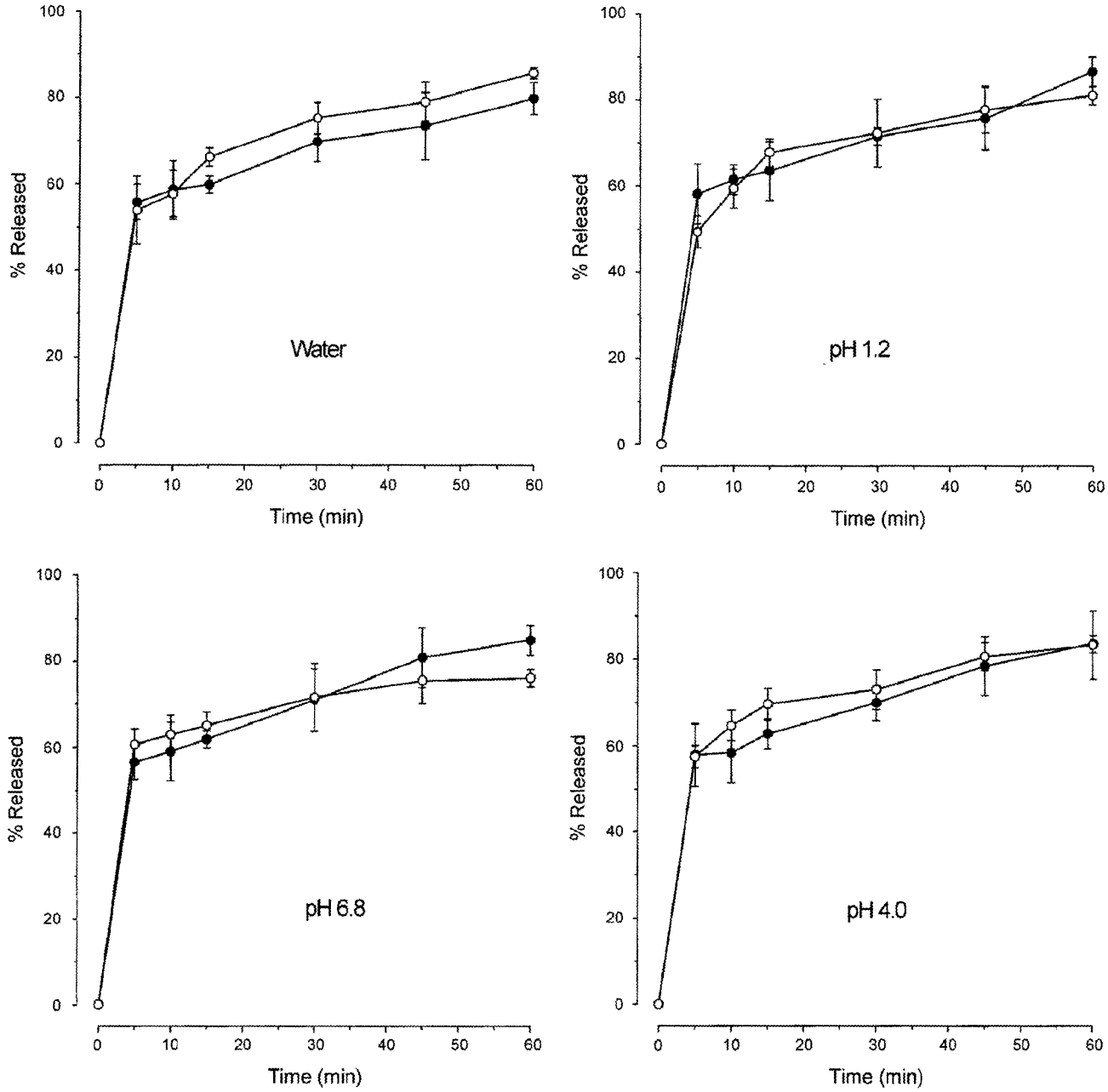


Fig. 6. Release profiles of monolithic HPMC matrix tablet after film coating (open symbol) and commercially available bi-layered Tylenol® ER (closed symbol) in four different dissolution media. Batch size: 100,000 tablets.

dual release (currently approved as Timerol® ER in Korea) established *via* wet granulation of HPMC-based powder mixtures would be more desirable to provide an alternative to marketed bi-layered Tyrenol® ER tablet.

CONCLUSION

Type and level of solvents for wet granulation and polymeric film-coating were crucial to establish HPMC matrix granules and tablets because the plastic deforming and fragmenting properties of hydrophilic HPMC and excipients used were altered by the different strengths of the various solvents. A mixture of ethanol and water (28%/5% based on total batch weight) as a granulating or coating solvent would be more desirable rather than water only or harmful coating solvent like methylene chloride. The current monolithic HPMC matrix tablet via wet granulation process was easily produced using a conventional tablet machine and provided better flexibility for dual release profiles as compared with commercial bi-layered Tylenol® ER tablet.

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