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International Journal of Pharmaceutics 274 (2004) 107–117
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Release behavior and photo-image of nifedipine tablet coated with high viscosity grade hydroxypropylmethylcellulose: effect of coating conditions

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Received 12 August 2003; received in revised form 15 December 2003; accepted 6 January 2004

Abstract

An orally applicable nifedipine-loaded core tablets was coated using high viscosity grade HPMC (100,000 cps) in ethanol/water cosolvent. The release of coated tablet was evaluated using USP paddle method in 900 ml of simulated gastric fluid (pH 1.2) for 2 h followed by intestinal fluid (pH 6.8) for 10 h. The surface morphologies using scanning electron microscope and photo-images using digital camera of coated tablet during the release test were also visualized, respectively. The viscosity of hydro-alcoholic HPMC solution largely decreased as the amount of ethanol increased. There was no significant difference in viscosity among plasticizers used. The distinct and continuous coated layer was observed using scanning electron microscope. However, the surface morphologies were highly dependent on HPMC concentration and ratio of coating solvents. The higher ratio of ethanol/water gave a longer lag time prior to drug release. Lag time also increased as a function of the coating levels based on weight gains due to increased thickness of coated layer. Lag time is inversely correlated with HPMC concentration in ethanol/water (5:1) cosolvent. As the HPMC concentration slightly decreased from 3.8 to 3.2% in hydroalcoholic coating solution, a large increase of lag time was observed. As the swelling (mixing) time of high viscosity grade HPMC in ethanol/water cosolvent increased from 1 to 5 h, the release rate was decreased due to enough plasticization of polymer. Based on photo-imaging analysis, the coated tablet was initially swelled and gelled without erosion and disintegration over 5 h. The disintegration of the coated tablet was occurred approximately 7 h after dissolution, resulting in pulsed release of drug. The high viscosity grade HPMC can be applicable for polymeric coating after careful selection of solvent systems. The release behavior and lag time could be controlled by coating conditions such as HPMC concentration, ethanol/water ratio as a coating solvent, coating level and swelling (mixing) time of coating solution. The current time-controlled release tablet coated with high viscosity grade HPMC with a designated lag time followed by a rapid release may provide an alternative to site specific or colonic delivery of drugs. In addition, the release behavior can be matched with body's circadian rhythm pattern in chronotherapy.

Keywords: High viscosity grade HPMC; Polymeric coating solution; Release; Lag time; Surface morphology; Photo-images

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doi:10.1016/j.ijpharm.2004.01.020

1. Introduction

Sustained-release formulations have been widely developed to improve the therapeutic performance of drugs, in particular, to increase pharmacological efficacy and reduce side effects (Pather et al., 1998; Sanchez-Lafuente et al., 2002; Kramar et al., 2003). Matrix-type or diffusion-controlled dosage forms by using polymeric excipients have been wide utilized to control the release rate of various drugs (Hogan, 1989). Most of all, polymeric coating techniques (Lee and Min, 1996; Lee et al.,1999a,b) have been widely applied in pharmaceutical industry for many reasons such as taste masking, protective barrier, stability improvement, and mostly controlled release of drugs for the preparation of various dosage forms (McGinity, 1989). In general, coating dispersions are applied on various drug-loaded cores such as nonpareil seed, pellet, bead, granule or tablet.

Hydroxypropylmethylcellulose (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 nontoxic property, ease of handling, small influence of processing parameters, and relatively simple manufacturing technology (Freely and Davis, 1988; Shah et al., 1996). High viscosity grades HPMC has been mainly applied to the formulation of sustained release matrix-type dosage forms such as tablet, pellet or granule (Ford et al., 1985). Although low viscosity grades of HPMC have widely utilized for polymeric film coating as an aqueous basis, high viscosity grades of HPMC as a coating polymer have not been deeply investigated (Dansereau et al., 1993; Heinamaki et al., 1997).

The high viscosity grade HPMC has some technical problems as an aqueous basis due to its large viscosity and swelling powers. An aqueous-based high viscosity grade HPMC solution is much viscous or gelled even at the low concentration so that spraying the coating solution could not be easily carried out. Only a very low concentration of HPMC could be used but still requires time-consuming coating processes. The need of organic solvents for the preparation of sprayable dispersion, mainly hydroalcoholic or organic-based ethanol/acetone cosolvent, was used for these reasons as a coating solvent (Maffion et al., 1993).

The purpose of this study was to investigate drug release behavior of coated tablets with high viscosity grades HPMC (100,000 cps). The influences of coating conditions such as HPMC concentration, ethanol/water ratio as a coating solvent, coating level and swelling (mixing) time of coating dispersion on release characteristics were then extensively investigated. The surface morphologies using scanning electron microscope and photo-images using digital camera of coated tablet during the release test were then visualized, respectively. Nifedipine, a calcium channel blocking drug widely used for the treatment of a variety of cardiovascular disorders such as essential hypertension and angina pectoris was chosen as a model drug (Sorkin et al., 1985).

2. Materials and methods

2.1. Materials

Nifedipine was supplied from Pharm Tech Research Inc., (Seoul, South Korea). Microcrystalline cellulose (Avicel® pH 102) and cross-linked carboxymethylcellulose sodium (Ac-Di-Sol®) were kindly obtained from Seoul Pharma Co., Ltd. (Seoul, South Korea). Talc, a purified and hydrated magnesium silicate was purchased from Showa Chemical Co. (Tokyo, Japan) and magnesium stearate was purchased from Katayama Chemical Co. (Osaka, Japan). Hydroxypropylmethylcellulose (HPMC, 100,000 cps) was provided from courtesy of Richwood (Seoul, South Korea). Dibutyl sebacate (DBS), triethyl citrate (TEC) and polyethylene glycol 400 (PEG400) were purchased from Sigma (St. Louis, MO). Acetonitrile (HPLC grade) was purchased from Fisher Scientific (USA). All other chemicals were of reagent grade and used without further purification.

2.2. Preparation of compressed core tablet

Nifedipine, Avicel®, Ac-Di-Sol® and talc in a weight ratio of 4.4:87.6:4:2:2 were thoroughly blended together using a mortar and pestle. The Avice® and Ac-Di-So® were added as a disintegrator of core tablet. The resulting powder mixtures were then directly compressed into tablets using a rotary tablet machine (Korea Machine, Seoul, South Korea) equipped with the pillow-faced punch. The mean weight and hardness of core tablets (diameter:

8.6 mm) was 450 ± 18 mg and 75 ± 9.3 N, respectively. A theoretical drug content per core tablet was 20 mg.

2.3. Preparation of coating solution

The HPMC, plasticizer (20% w/w based on polymeric solid contents) and talc were added in 250 ml of water or ethanol/water cosolvents, and then continuously stirred for a given stirring time (1, 5 or 9 h). The dispersions were then kept at room temperature for at least for 12 h to ensure sufficient plasticization of the polymer. The DBS was invariably used as a plasticizer, otherwise mentioned. All coating dispersions were continuously stirred throughout the coating process. The detailed compositions for the preparation of polymeric coating solution are given in Table 1.

2.4. Tablet coatings

The core tablets were then coated using HPMC dispersions in ethanol/water mixtures by dipping method. The core tablet was completely dipped into the polymeric solution and then dried stepwise with a hair dryer. The dipping steps were repeated until the desired coating levels were obtained. The coating levels were designated as percentages of weight gains compared to uncoated core tablet.

2.5. Analysis of nifedipine

A reverse phase HPLC system was used for the analysis of nifedipine. The HPLC system consisted of the pump (Jasco PU-980), the UV-Vis spectrophotometric detector (Jasco UV-975), the auto sampler (Jasco AS-950-10), the degasser (Jasco DG-980-50) and the reverse phase column (Haisil C18, 5 μm, 150 mm × 4.6 mm). The mobile phase consisting of 40% acetonitrile in 0.01 M potassium dihydrogenphosphate solution (pH 6.1) was filtered using 0.45 μm nylon membrane filter (Gelman Sciences, USA) and degassed under vacuum. The flow rate of the mobile phase was 1.2 ml/min. Nifedipine concentration was determined at the wavelength of 238 nm. A 20 μl of the sample was injected into the HPLC system. The peak area ratios of nifedipine to the internal standard were used for the assay of nifedipine concentration.

To avoid light-induced decomposition of the samples, all works were performed in subdued light. The glasswares used throughout the procedures were also wrapped with foil. The HPLC chromatogram was also

Table 1
Compositions for the preparation of polymeric coating suspension

Codes	HPMC (g)	Plasticizer type[a]	Talc (g)	Ethanol/water (ml)	Coating level (%)[b]	Stirring time (h)
Pre-A	10 (3.8%)[c]	DBS	0.5	250 (0:1)[d]	–	1
Pre-B	10 (3.8%)	DBS	0.5	250 (1:1)	–	1
Pre-C	10 (3.8%)	DBS	0.5	250 (2:1)	–	1
Pre-D	10 (3.8%)	DBS	0.5	250 (3:1)	–	1
Pre-E	10 (3.8%)	DBS	0.5	250 (4:1)	–	1
F1-TEC	10 (3.8%)	TEC	0.5	250 (5:1)	–	1
F1-PEG	10 (3.8%)	PEG400	0.5	250 (5:1)	–	1
F1	10 (3.8%)	DBS	0.5	250 (5:1)	20	1
F2	10 (3.8%)	DBS	0.5	250 (6:1)	20	1
F3	10 (3.8%)	DBS	0.5	250 (7:1)	20	1
F4	10 (3.8%)	DBS	0.5	250 (5:1)	30	1
F5	10 (3.8%)	DBS	0.5	250 (5:1)	40	1
F6	10 (3.2%)	DBS	0.5	300 (5:1)	20	1
F7	10 (2.76%)	DBS	0.5	350 (5:1)	20	1
F8	10 (3.8%)	DBS	0.5	250 (5:1)	20	5
F9	10 (3.8%)	DBS	0.5	250 (5:1)	20	9

[a] The amount of plasticizers used was invariably 30% of the polymer weight. DBS: dibutyl sebacate; TEC: triethyl citrate; PEG400: polyethylene glycol 400.
[b] Coating levels were designated as percentages of weight gains compared to uncoated core tablet.
[c] The parentheses indicate the percentage of polymer concentration in ethanol/water cosolvent.
[d] The parentheses indicate volume ratio of ethanol and water in cosolvent.

carefully inspected for any photosensitive stability of nifedipine during the whole experiments. However, we could not find any loss of drug contents or degradation peaks from the HPLC chromatogram, suggesting good stability during dissolution test and analytical procedure. Retention times of NFP and IS (testosterone) were 9.4 and 8.7 min, respectively.

2.6. Viscosity measurement of coating solution

The viscosity of HPMC coating solution as shown in Table 1 was measured with a rotational Brookfield viscometer (digital viscometer model DV-II+, Stoughton, MA, USA). The viscometer spindle was inserted into a previously equilibrated sample for several hours up to the level of the marked immersion groove. The viscometer speed was adjusted to 100 rpm with spindle #1, #2 or #4 at ambient temperature (25±1 °C). The viscosity of samples were then measured in triplicate after equilibration approximately every 30 s.

2.7. Surface morphology of coated tablet

The surface morphology and cross-sectional view of coated nifedipine tablet were visualized using scanning electron microscope (SEM) to evaluate the coating integrity. The dried tablet were coated with gold under argon atmosphere using a Jeol JFC-1100 sputter coater (Jeol, Japan) for about 2 min to obtain about 200 Å of the coating thickness. Micrographs were taken with a Cambridge Stereo Scan 200 (London, UK) at an accelerating voltage of 15 kV.

2.8. Release and photo-image of coated tablet

Release studies (Fine Scientific SDT600A, Seoul, South Korea) were performed using USP described in apparatus 2 (paddle method) at the rotation speed of 50 rpm. A sinker was used to prevent the flotation of the tablet. The release characteristics of coated tablet were evaluated using USP dissolution method II in 900 ml of simulated gastric fluid (pH 1.2, 0.1 M NaCl–HCl buffer) for 2 h followed by switching to intestinal fluid (pH 6.8, 0.2 M phosphate buffer) for 10 h at 37 ± 0.5 °C. The samples (1 ml) were collected at a given interval with replacement of equal volume of dissolution media. The solution was then filtered through a Millipore membrane filter. The amount of nifedipine dissolved was monitored by HPLC at a wavelength of 238 nm as mentioned previously. All the experiments were carried out in triplicate and the mean value was plotted as a function of time.

On the other hand, the photo-images of the coated tablet during release test were also observed as a function of time. The digital camera (Olympus, Tokyo, Japan) was used to take pictures of the coated tablet in dissolution fluids.

3. Results and discussion

3.1. Viscosity of high viscosity grade HPMC coating solution

Viscosity of HPMC-based coating solution is given in Table 2. The 3.8% w/w HPMC solution in

Table 2
Viscosity of HPMC-based coating solution

Codes	HPMC (%)	Ethanol/water ratio	Spindle number	rpm	Viscosity (cps)
Pre-A	3.8	0:1	–	–	ND (Gel)[a]
Pre-B	3.8	1:1	–	–	ND (Gel)[a]
Pre-C	3.8	2:1	–	–	ND (Gel)[a]
Pre-D	3.8	3:1	2	100	986.67 ± 0.06[b]
Pre-E	3.8	4:1	4	100	190.27 ± 0.23[b]
F1-TEC	3.8	5:1	1	100	28.60 ± 0.36
F1-PEG	3.8	5:1	1	100	29.40 ± 0.50
F1	3.8	5:1	1	100	33.77 ± 0.15
F6	3.2	5:1	1	100	26.67 ± 0.12
F7	2.76	5:1	1	100	23.10 ± 0.10

[a] Not determined due to its high viscosity by gelling.
[b] Not applicable for coating due to its high viscosity.

either pure water or hydro-alcoholic solution was transformed to viscous and gel-forming semisolid state when the ratio of ethanol and water was greater than 2:1. Although the Pre-D and Pre-E showed measurable viscosity, it seemed to be less suitable as a coating solution because of their higher viscosity and lower fluidity. As a result, HPMC coating solution with too much higher viscosity could limit further applications of coating process. Optimal ratio of ethanol and water as a cosolvent in HPMC-based coating solution was given at 5:1.

The viscosity of hydro-alcoholic HPMC solution largely decreased as the amount of ethanol increased. Although the water-soluble plasticizers (TEC or PEG400) slightly reduced the viscosity compared to the water-insoluble platicizer (DBS), there was

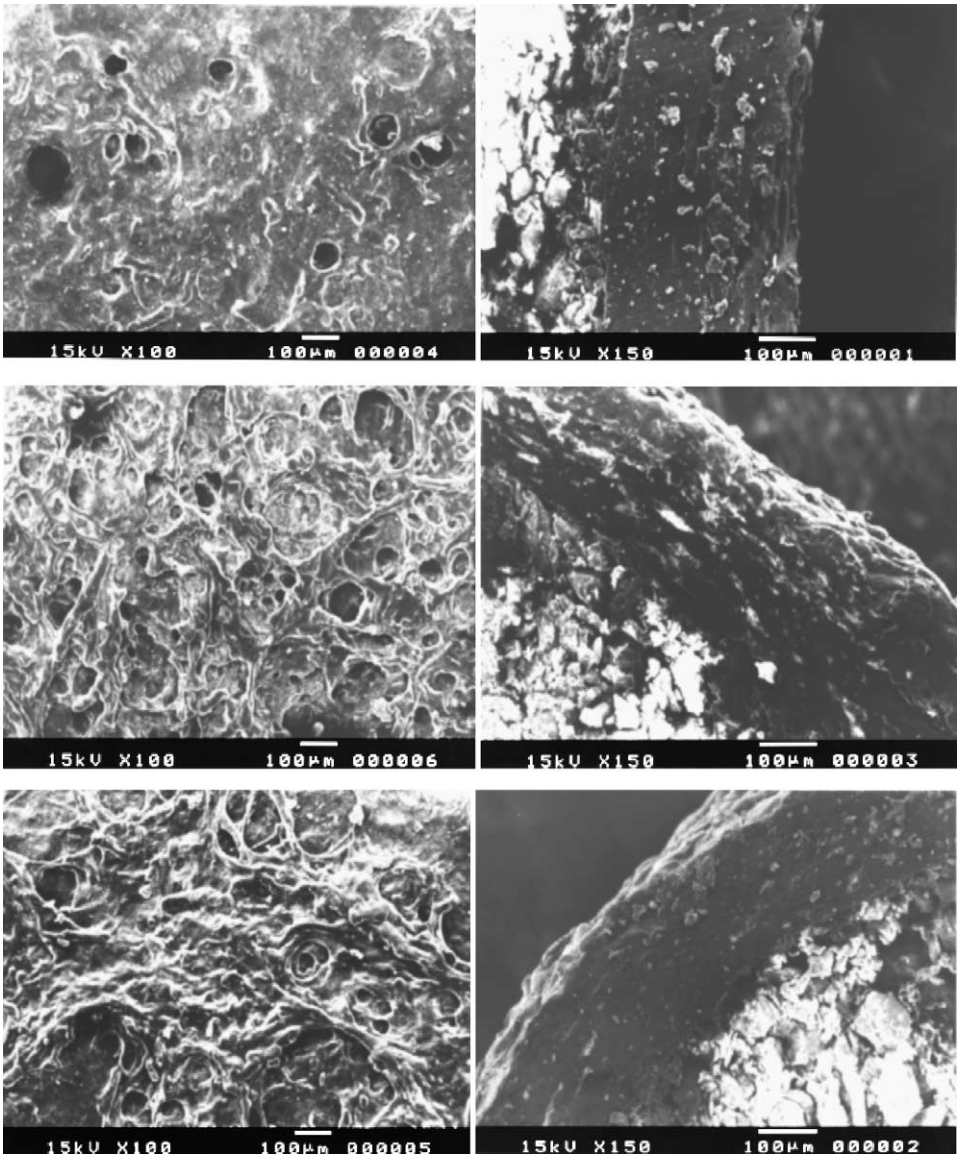

Fig. 1. Surface morphology (left) and cross-sectional view (right) of coated tablets with high viscosity grade HPMC. F1 (top); F2 (middle); F6 (bottom).

no significant difference in viscosity among plasticizers used. The applications and mechanism of water-soluble and water-insoluble plasticizers have been well reported (Johnson et al., 1991; Bodmeier and Paeratakul, 1997). Therefore, the DBS was invariably used for coating formulation. As the concentration of HPMC was decreased, the viscosity of coating solution was also gradually decreased (F1, F6, F7).

3.2. Surface morphology of coated tablet

The surface morphology and cross-section view of coated tablets with high viscosity grade HPMC (F1, F2 and F6) using SEM are visualized in Fig. 1. The distinct and continuous coated layer was observed. However, the surface morphologies were highly dependent on HPMC concentration and ratio of coating solvents at the same 20% coating level. The distinct coated layer without cracks or pores was visualized when lower HPMC concentration (F2) or higher ethanol/water ratio was used (F6). Some pores were also found on the surface of coating membrane when higher HPMC concentration and lower ethanol/water ratio was used (F1). The evaporation rate of hydroalcoholic coating cosolvent seemed to be much faster but the roughness of surface films increased when the amount of ethanol used was higher or when the HPMC concentration was lower.

It was evident that the more dense and compact film layer without pores could be formed when the lower HPMC concentration but higher ethanol/water ratio were used, resulting in increased lag time as discussed later. In case of F1 with higher HPMC concentration and lower ethanol/water ratio, some pores were observed even though the surface appeared smooth, suggesting fast drug release through these pores of coated tablet with an aid of swelling forces of superdisintegrants like Ac-Di-Sol® and Avicel® in core tablet. Depending on the thickness of the coated layer, the hydrophilic HPMC coated layer swells and slowly erodes through the hydration process, resulting in drug release after a predetermined lag time.

3.3. Release behaviors

The release of drug-loaded core tablet is shown in Fig. 2. The core tablet showed typical immediate release profile. Due to low solubility of model drug, the release rate reached over 20% for 3 h in gastric and intestinal fluid. The drug-loaded core tablet was then coated with high viscosity grade HPMC. However, the use of high viscosity HPMC in an aqueous-based

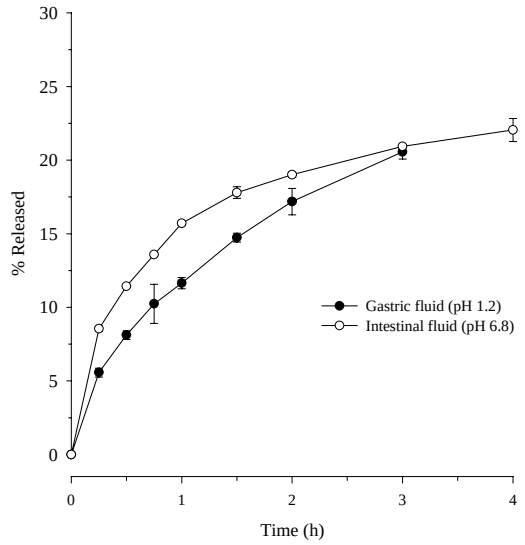

Fig. 2. Release of nifedipine-loaded core tablet in simulated gastric (pH 1.2) and intestinal fluids (pH 6.8).

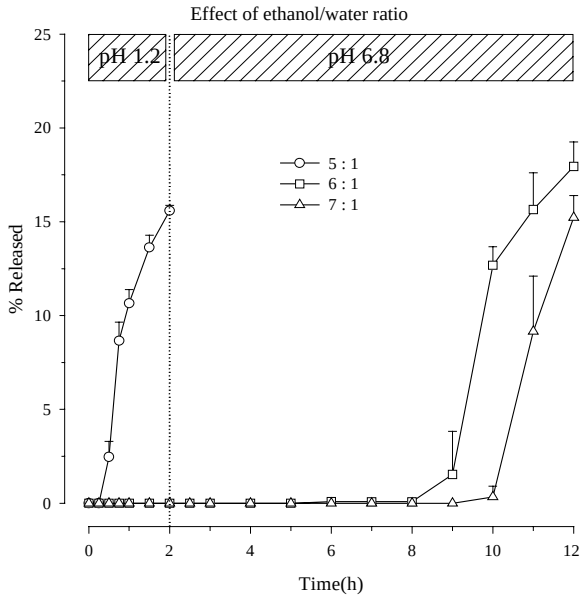

Fig. 3. Effect of ethanol/water ratio on release of nifedipine from tablets coated with high viscosity grade HPMC in simulated gastric fluid (pH 1.2) followed by intestinal (pH 6.8) fluids.

film-coating process would require very low polymer concentrations due to viscosity and fluidity. A water-miscible solvent like ethanol capable of limiting the water–polymer interaction could be used for the preparation of a coating dispersion to overcome these problems as mentioned previously (Maffion et al., 1993).

Effect of ethanol/water ratio on release of nifedipine from tablets coated with high viscosity grade HPMC in simulated gastric fluid (pH 1.2) followed by intestinal (pH 6.8) fluids is shown in Fig. 3. The distinct lag time of the HPMC-coated tablet was significantly dependent on ethanol/water ration as a coating solvent. The higher ratio of ethanol/water gave a longer lag time.

When the low amount of ethanol was used in cosolvent system, relatively rapid drug release occurred, showing a less than 30 min lag time. However, the lag time were prolonged up to 8 and 10 h as the ethanol/water ratio increased due to rapid evaporation of hydroalcoholic coating cosolvent, resulting in continuous and compact film layer. The 10 h lag time could be obtained when 3.8% HPMC concentration in 250 ml ethanol/water cosolvent (7:1) was used for 20% coating levels. Even though the water content in cosolvent system varied from 12.5 to 16.7%, the lag time was drastically changed. It assumed that as the amount of water increased, the gelling and swelling forces of the HPMC-coated film for controlled release could be decreased, resulting in short lag time. Some pore or cracks through coated HPMC layer may be also a reason as mentioned previously. The increased viscosity of the coating solution should be noted.

The role of water or ethanol content in HPMC coating solution could play a role in controlling release rate of hydrophilic polymer like HPMC although these solvents were removed by drying process. For this reason, only low viscosity grade HPMC is commercially available for aqueous-based coating in pharmaceutical industry (Heinamaki et al., 1994, 1997; Johnson et al.,

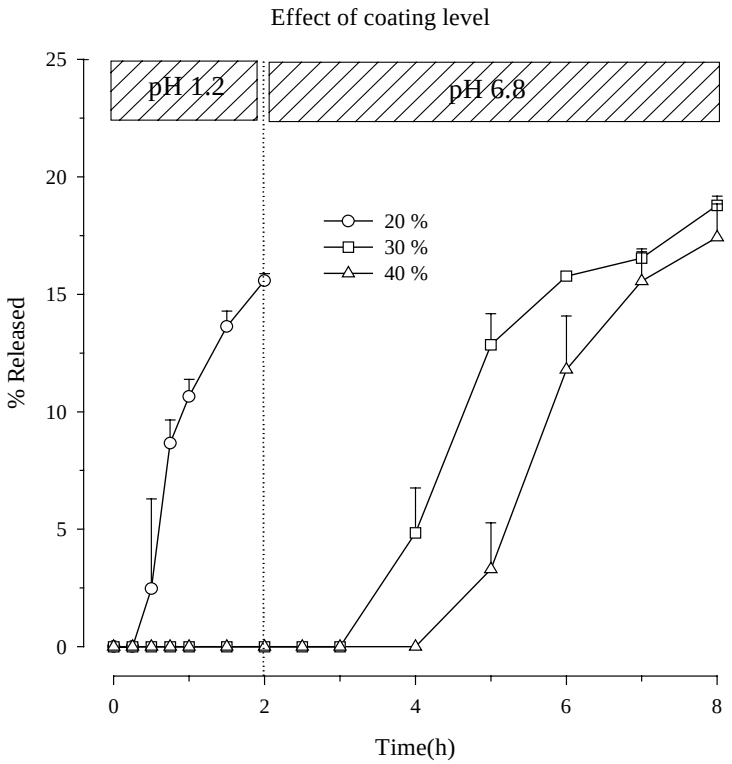

Fig. 4. Effect of coating level on release of nifedipine from tablets coated with high viscosity grade HPMC in simulated gastric fluid (pH 1.2) followed by intestinal (pH 6.8) fluids.

1991). However, the high viscosity grade HPMC can be also applicable for coating after careful selection of solvent systems with sprayable viscosity of coating solution.

Effect of coating level on release of nifedipine from tablets coated with high viscosity grade HPMC in simulated gastric fluid (pH 1.2) followed by intestinal (pH 6.8) fluids is given in Fig. 4. Unlike the uncoated core tablet, the time-controlled release profiles with a different lag time were obtained when coated with high viscosity grade HPMC. As expected, lag time increased as a function of the coating levels based on weight gains due to increased thickness of coated layer. Less than 20% coating levels had no significant retarding effect on HPMC-coated tablet. The 3 h lag time was obtained at 30% coating level when 3.8% HPMC concentration in 250 ml ethanol/water (5:1) was used. The lag time was then further increased at 40% coating level.

The coated tablet swelled and showed transparent gel layer when in contact with the dissolution medium. The swelled coated tablet was then disintegrated and ruptured after a designated lag time with an aid of high water uptake by superdisintegrants like Ac-Di-Sol® and Avicel®. The role of disintegration performance by superdisintegrants has been well recognized (1999a,b).

Effect of HPMC concentration on release of nifedipine from tablets coated with high viscosity grade HPMC in simulated gastric fluid (pH 1.2) followed by intestinal (pH 6.8) fluids is given in Fig. 5. Lag time is inversely correlated with HPMC concentration in ethanol/water (5:1) cosolvent. As the HPMC concentration slightly decreased from 3.8 to 3.2% in hydroalcoholic coating solution, there was a large increase of lag time. The 7 or 8 h lag time was observed when 3.2 or 2.76% HPMC concentration was used for coating at 20% level, respectively. Coat-

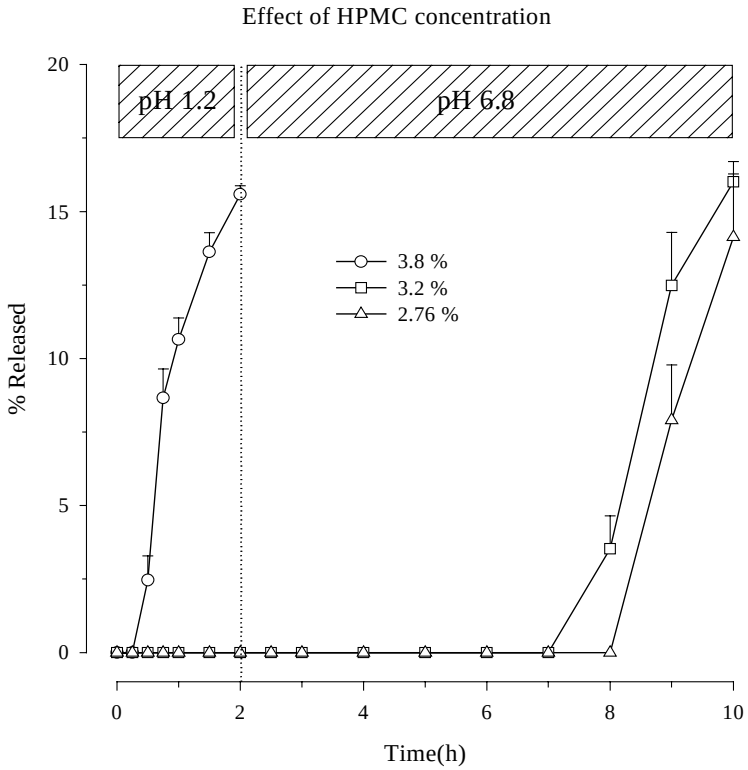

Fig. 5. Effect of HPMC concentration on release of nifedipine from tablets coated with high viscosity grade HPMC in simulated gastric fluid (pH 1.2) followed by intestinal (pH 6.8) fluids.

ing solution containing more than 4% (w/w) HPMC concentration in ethanol/water (5:1) cosolvent could not be processed in tablet coating because of marked tackiness and fragility of the polymeric film layer.

Effect of swelling (mixing) time of HPMC coating solution on release of nifedipine from tablets coated with high viscosity grade HPMC in simulated gastric fluid (pH 1.2) followed by intestinal (pH 6.8) fluids is given in Fig. 6. As the swelling (mixing) time of high viscosity grade HPMC in ethanol/water cosolvent increased from 1 to 5 h, the release rate was decreased due to enough plasticization of polymer. However, this effect was not significant after further increase of mixing time. At the lower ethanol contents as well as lower coating levels, the release rate as indicated by lag time was not efficiently controlled even though the swelling time increased.

3.4. Photo-images of coated tablet during release test

Based on the release characteristics, the visual images of the coated tablet with high viscosity grade HPMC were visualized as a function of time during release test in gastric fluid followed by intestinal fluid Photo-images of coated tablet (F6) during release test are shown in Fig. 7. Based on photo-imaging analysis, the coated tablet was initially swelled and gelled without erosion and disintegration at lease over 5 h after the release test. The disintegration of the coated tablet was occurred approximately 7 h after dissolution, resulting in pulsed release of drug. The photo-image was coincident with release profile as shown in Fig. 5. During the whole dissolution process, coated tablet for each formulation became slightly sticky to the dissolution vessel at the initial stage due to the hydration

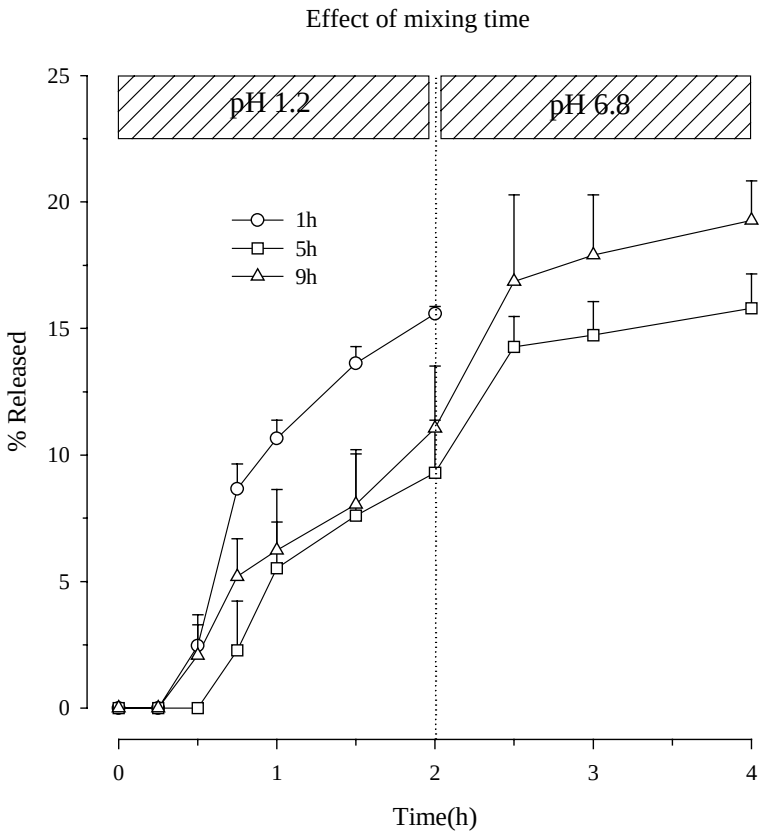

Fig. 6. Effect of swelling (mixing) time of HPMC coating solution on release of nifedipine from tablets coated with high viscosity grade HPMC in simulated gastric fluid (pH 1.2) followed by intestinal (pH 6.8) fluids.

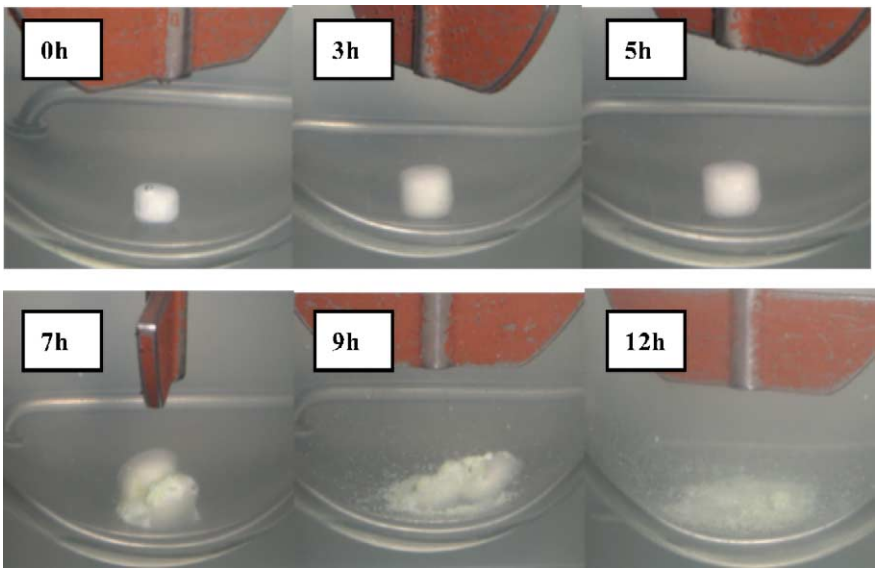

Fig. 7. Photo-images of coated tablet (F6) during release test.

property of polymer film. Even though the surface area of coated tablet was actually reduced, resulting in longer disintegration time than expected, the predetermined lagtime was not significantly changed for a long period of dissolution test. A sinker can be also used to overcome this matter.

4. Conclusions

The high viscosity grade HPMC can be applicable for polymeric coating after careful selection of solvent systems for sprayable viscosity of coating solution. Sustained or timed-controlled release behaviors of nifedipine-loaded tablet coated with high viscosity grade HPMC could be possible. The coated tablet swelled and showed transparent gel layer when in contact with the dissolution medium. The distinct timed-controlled release profiles with a different predetermined lag time were obtained. Lag time prior to the drug release could be controlled by coating conditions such as HPMC concentration, ethanol/water ratio as a cosolvent, coating level and swelling (mixing) time of the polymeric coating solution.

The current time-controlled release tablet coated with high viscosity grade HPMC with a designated lag time followed by a rapid release may provide an alternative to site specific delivery of drugs with optimal absorption windows or colonic delivery of drugs which are sensitive to low pH or enzyme action for the treatment of localized conditions such as ulcerative colitis, Crohn's disease and irritable bowel syndrome. Furthermore, by controlling a predetermined lagtime of drug from dosage form, the release behavior can be matched with body's circadian rhythm pattern in chronotherapy.

Acknowledgements

The work was partially supported by a grant of the Ministry of Science and Technology-NRL program (M1-0302-00-0080). This work was partially linked by a grant of the Health Fellowship Foundation (Bogun). The part of this research was also presented in the 2001 American Association of Pharmaceutical Scientists (AAPS) annual meeting held in Denver, CO, USA.

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