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Effect of magnesium stearate or calcium stearate as additives on dissolution profiles of diltiazem hydrochloride from press-coated tablets with hydroxypropylmethylcellulose acetate succinate in the outer shell

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Abstract

Effect of magnesium stearate (MgSt) or calcium stearate (CaSt) on the dissolution profiles of diltiazem hydrochloride in the core of press-coated (PC) tablets with an outer shell composed of hydroxypropylmethylcellulose acetate succinate (HPMCAS) was evaluated by porosity and changes in IR spectra of tablets. In JP first fluid (pH 1.2), the lag time increased with decreasing porosity and was greatest by the addition of MgSt to HPMCAS. While, in JP second fluid (pH 6.8), it increased with decreasing porosity by the addition of CaSt, but hardly changed by the addition of MgSt. Thus, using tablets prepared with the same composition as the outer shell, the changes in IR spectra and uptake amount of the dissolution media after immersion in first fluid and second fluid were determined. The results suggested that some physicochemical interaction occur between MgSt and HPMCAS in tablets with HPMCAS and MgSt and the uptake increased markedly in each dissolution medium. These phenomena seem to cause a prolongation of lag time in first fluid but a shortening of it in second fluid in PC tablets with HPMCAS and MgSt. In contrast, CaSt and HPMCAS did not show such interactions and increased the hydrophobic properties of the outer shell. Consequently, the lag time was only slightly prolonged in first fluid, however, markedly prolonged in second fluid due to suppression of second fluid penetration into micro pores in the outer shell and HPMCAS gel formation on the surface in PC tablets with HPMCAS and CaSt.

Keywords: Press-coated tablets; Magnesium stearate; Calcium stearate; Hydroxypropylmethylcellulose acetate succinate; Dissolution; Porosity

1. Introduction

Recently, oral drug delivery systems for colon targeting have attracted a great deal of interest for the local treatment of a variety of bowel diseases

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(Hardy et al., 1987; Stolk et al., 1990) and for improving systemic absorption of drugs susceptible to enzymatic digestion in the upper gastrointestinal tract (Saffran et al., 1986). Various approaches have been reported to develop new methodologies for site-specific drug release (Stolk et al., 1990; Mooter et al., 1993; Gazzaniga et al., 1993).

Enteric coated formulations could be a simple and practical means for colon-specific drug delivery. However, such methods do not have sufficient site specificity because, with this type of formulation, most of the drug is released in the upper small intestine after gastric emptying even though drug release is effectively prevented in the stomach. Rate-controlled release systems such as sustained-release formulations are very promising. However, due to the potentially large variation of gastric emptying time of formulations in humans (Davis et al., 1986, 1988), in this approach the colon arrival time of formulations can not be accurately predicted, resulting in poor colonical availability.

Based on the physiological characteristics of the human gastrointestinal tract and the movement of formulations, (Davis et al., 1986, 1988; Khosla et al., 1990; Adkin et al., 1993), an appropriate integration of acid resistance and timed-release functions into a single unit formulation seems desirable to improve the site-specificity of drug release in the colon. That is, since the transit time of formulations in the small intestine is less variable, i.e. 3 ± 1 h, the timed-release function could work more effectively in the small intestine as compared with the stomach. The drug carrier will be delivered to the terminal ileum or colon through the small intestine due to a predetermined time after gastric emptying and drug release will begin. On the other hand, in the stomach, the drug release should be suppressed completely by acid resistance function in the formulations.

Previously, we developed press-coated tablets prepared with a powder mixture of hydroxypropylmethylcellulose acetate succinate (HPMCAS), magnesium stearate (MgSt) and calcium stearate (CaSt) in the outer shell for colon targeting formulations on the basis of the above concept (Fukui et al., 2001). In the process of this screening, we found that in MgSt, the lag time in second fluid was less than 2 h although drug release in first fluid was suppressed completely for 12 h. By contrast, in CaSt, the lag time was little suppressed in first fluid but could be prolonged as long as 9 h in second fluid. This was interesting since these two compounds are generally used as lubricants for tableting and seemed to have similar physicochemical properties (Butcher and Jones, 1972; Baichwal and Augsburger, 1988; Miller and York, 1988; Phadke and Sack, 1996).

Drug release from formulations using water insoluble polymer as a controlled-release membrane has been thought to involve a simple diffusion mechanism (Benita and Donbrow, 1982; Vidmar et al., 1982; Sakr et al., 1987; Ozturk et al., 1990). On the other hand, the drug release mechanisms for press-coated tablets using an enteric polymer as the main material in the outer shell seemed different in first fluid and in second fluid. Therefore, clarification of the dissolution behavior of drug could afford useful information for developing new colon targeting formulations or other drug delivery systems.

Thus, in the present study, press-coated tablets were prepared using a powder mixture of MgSt and HPMCAS or CaSt and HPMCAS in the outer shell under various conditions. Effects of MgSt or CaSt on the dissolution behavior (lag time and release rate) of diltiazem hydrochloride (DIL) as a model drug in first fluid and second fluid were investigated on the basis of porosity or the change of IR spectra of tablets.

2. Materials and methods

2.1. Materials

Diltiazem hydrochloride (DIL) (Tanabe Seiyaku Co., Ltd. Osaka, Japan) was used as a high solubility drug. Cornstarch (CS) (Nihon Shokuhin Kako Co., Ltd. Tokyo, Japan), calcium citrate (CC) (Satsuma Kako Co., Ltd. Japan), polyvinylpyrrolidone (PVP) (BASF, Germany), carboxymethylcellulose-calcium (CMC-Ca) (Gotoku Chemical Co., Ltd. Tokyo, Japan) and magnesium stearate (Sakai Chemical Industry Co., Ltd. Osaka, Japan) were used for the preparation

of core tablets. Hydroxypropylmethylcellulose acetate succinate (HPMCAS) (AQOAT® AS-LF, Shin-etsu Chemical, Tokyo, Japan) was used as a dry coating material. Calcium stearate (CaSt) (Tokyo Chemical Industry Co., Ltd. Tokyo, Japan) and magnesium stearate (MgSt) (Katayama Chemical, Osaka, Japan) were used as additives in the dry coating material. All other chemicals were of reagent grade.

2.2. Preparation of core tablets

A wet granulation method was used to prepare the granules for the core tablets. A powder mixture of 300 g of DIL and 200 g of CS was kneaded with a binder including 30 g of PVP in 60 ml of ethanolic solution. The wetted mass was forced through a 1000 μm screen. The granules were dried and then sized by passing through a 710 μm screen. One hundred and twenty grams of CC, 40 g of CMC-Ca and 10 g of MgSt were mixed with the granules for 10 min.

For the preparation of core tablets, a compression force of 1060 kg/cm^2 and punch speed of 10 mm/min were applied, with a reciprocating press (Autograph IS-5000, Shimadzu Seisakusho Ltd., Kyoto, Japan). A flat-faced punch 6 mm in diameter was used and core tablets containing 30 mg of DIL per each tablet weighing 70 mg were obtained.

2.3. Press-coating with HPMCAS alone, HPMCAS/MgSt or HPMCAS/CaSt

HPMCAS alone, 80% HPMCAS and 20% MgSt, or 80% HPMCAS and 20% CaSt (weight ratio) were passed through a 500 μm screen and used for the outer shell. Press-coating of tablets was performed using a reciprocating press (Autograph IS-5000, Shimadzu Seisakusho) with a flat-faced punch 10 mm in diameter and punch speed of 10 mm/min. Some of the powder (120 mg) was filled into the die to make a powder bed on the center of which a core tablet was placed. The rest of the equivalent powder was filled in the die, and the total contents were compressed at a compression force of 380–1910 kg/cm^2.

The porosity in tablet or the outer shell of press-coated (PC) tablet with HPMCAS alone or the powder mixture was calculated using the following formula:

$$\varepsilon_{\text{tablet}} = 1 - \frac{R_{\text{AS}} \cdot \dfrac{W}{\rho_{\text{AS}}} + R_{\text{St}} \cdot \dfrac{W}{\rho_{\text{St}}}}{V_{\text{tablet}} - V_{\text{core}}},$$

where ε is the porosity of the outer shell composed of HPMCAS alone, 80% HPMCAS and 20% MgSt, or 80% HPMCAS and 20% CaSt, W is the total weight of the outer shell or tablet, R_{AS} and R_{St}, and ρ_{AS} and ρ_{St} are the mixing ratio and the true density of HPMCAS and, MgSt or CaSt, respectively, V_{tablet} is the total volume of the PC tablet or tablet, and V_{core} is the volume of the core tablet.

2.4. Preparation of tablets of which composition is the same as the outer shell

HPMCAS alone, the powder mixture of 80% HPMCAS and 20% MgSt, or the powder mixture of 80% HPMCAS and 20% CaSt were passed through a 500 μm screen. Then, tablets of 240 mg were prepared using a reciprocating press (Autograph IS-5000), with a flat-faced punch 10 mm in diameter and punch speed of 10 mm/min, under an adequate compression force.

2.5. In vitro dissolution tests

Dissolution study of the press-coated tablets was performed according to the paddle method described in the thirteenth edition of Pharmacopoeia of Japan (JPXIII) with 900 ml of dissolution fluid and 100 rpm of rotation speed at 37°C. JP first fluid (pH 1.2) and JP second fluid (pH 6.8) of disintegration test in JPXIII were used for the dissolution media. Aliquots of the dissolution medium were removed at specified time-intervals and assayed for the released amount of DIL by a spectrophotometer (UV-160, Shimadzu Co., Kyoto, Japan) at a wavelength of 265 nm.

The lag time of DIL dissolution performance was defined as the point of intersection of the time axis and the straight line of the dissolution pattern. The release rate of DIL was calculated from

the slope at the initial steady state, at which DIL release started, reported by Narisawa et al. (1994).

2.6. Determination of fluid uptake

For determination of uptake amount in first fluid and second fluid, tablets prepared at compression forces of 380–1910 and only 1910 kg/cm^2, respectively, were used. They were taken out at intervals and the weight was measured after immerssion in 900 ml of first fluid or second fluid and subjected to 100 rpm of rotation speed at 37°C. The uptake amounts in first fluid and second fluid were calculated by subtraction of the initial weight of the tablet from the wet weight and subtraction of the dry weight from the wet weight, respectively.

2.7. IR spectroscopy

Various tablets prepared at a compression force of 1910 kg/cm^2 and each initial powder were placed in a dissolution vessel with 900 ml of first fluid and subjected to 100 rpm of rotation speed at 37°C for 3 h. The tablets were dried under vacuum at 40°C and were stored in a desiccator with a desiccating agent until measurement by IR. FT-IR spectra were measured by Horiba FT-IR (FT-300, Horiba Ltd, Kyoto, Japan) and the KBr disk method.

3. Results and Discussion

3.1. Dissolution behavior of DIL from press-coated tablets in first fluid

Three kinds of press-coated (PC) tablets with HPMCAS (H-PC tablets), 20% MgSt and 80% HPMCAS (MH-PC tablets) or 20% CaSt and 80% HPMCAS (CH-PC tablets) in the outer shell were prepared at various compression forces. The dissolution profiles of DIL from PC tablets were determined in first fluid (pH 1.2) and typical dissolution profiles are shown in Fig. 1.

The results showed that the times, at which DIL was first detected (lag times), were prolonged and the release rates of DIL after the lag times were decreased with increasing compression force in all the PC tablets. In MH-PC tablets, a prolonged lag time was clearly observed at low compression force. Most compositions used for outer shells were considered not to dissolve in first fluid since PC tablet shapes were retained. Therefore, the lag times and release rates could be considered to be caused by porosity formed in the outer shell. Also, since the variations of lag time and release rate in each PC tablet were much small in a constant compression force, lag time and release rate were evaluated using a porosity of each PC tablet prepared under different compression forces in the following study.

The relationships between porosity and lag time (A) and porosity and release rate (B) in first fluid are shown in Fig. 2. The lag times of H-PC and CH-PC tablets were less than 2 h in the porosity range of about 0.15–0.35. While, at around a porosity of 0.1, the lag times increased up to 8.5 and 18 h, respectively, and the dependency of lag time on porosity was remarkably different. In the case of MH-PC tablets, pattern of increase with decreasing porosity showed a similar tendency to that of other PC tablets, however, the lag time remarkably increased to 15–35 h compared to the other two tablets. This suggests that the dissolution behavior could be different from that the other two PC tablets.

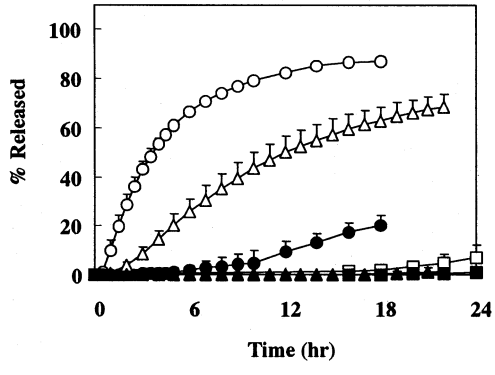

Fig. 1. Dissolution profiles of DIL from various press-coated tablets in first fluid. Compression force/outer shell composition: (○) 380 kg/cm^2/HPMCAS; (●) 1530 kg/cm^2/HPMCAS; (△) 380 kg/cm^2/HPMCAS and CaSt; (▲) 1530 kg/cm^2/HPMCAS and CaSt; (□) 380 kg/cm^2/HPMCAS and MgSt; (■) 1530 kg/cm^2/HPMCAS and MgSt. Each point represents the mean + S.D. ($n = 3$).

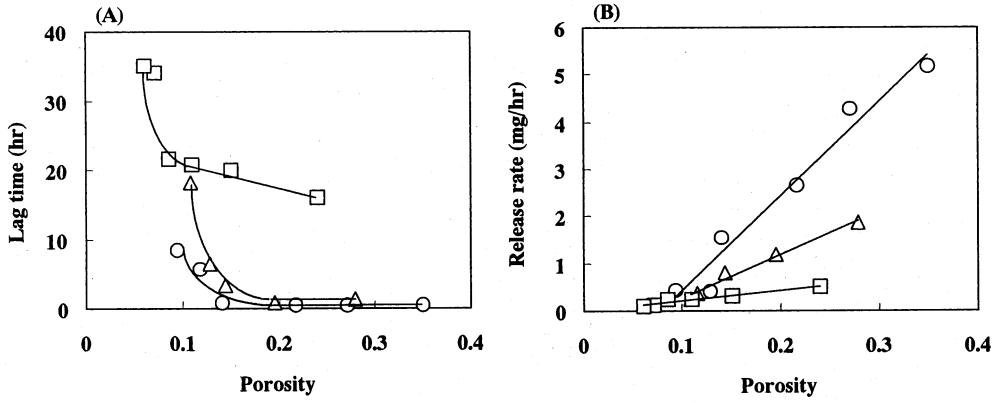

Fig. 2. Relationship between porosity and lag time (A) and porosity and release rate (B) in first fluid. Outer shell composition: (○) HPMCAS; (□) HPMCAS and CaSt; (△) HPMCAS and MgSt.

The release rates increased linearly with the increase of porosity and were smaller in the order of H-PC > CH-PC > MH-PC tablets, the inverse of lag time.

When insoluble films or outer shell layers are used for controlling release, the simple diffusion theory can be used to clarify the release mechanism by supposing the drug diffusion from the core to the outside through pores in the outer shell. In such a case, mass transfer is given by the following formula (1):

$$\frac{dM}{dt} = K = \frac{P \cdot (C_s - C_t) \cdot A}{h} \approx \frac{P \cdot C_s \cdot A}{h}, \quad (1)$$

where M is the amount of drug released, t is the dissolution time, K is the release rate, P is the permeability coefficient, C_s is the solubility of drug, C_t is the concentration of drug at time t, A is the surface area of tablet, and h is the outer shell thickness.

Further, the permeability coefficient is given by:

$$P = \frac{D \cdot \varepsilon}{\tau}, \quad (2)$$

where D is the intrinsic molecular diffusivity of drug, ε is the porosity of the outer shell, and τ is the tortuosity of the outer shell. Thus, porosity can be rewritten as:

$$\varepsilon = \frac{K \cdot \tau \cdot h}{D_{DIL} \cdot C \cdot A}. \quad (3)$$

In the case that the porosity of the outer shell is changed from ε_a to ε_b with increasing compression force, the relative value of tortuosity on the change from state a to b ($\tau_R = \tau_b/\tau_a$) is given by:

$$\tau_R = \frac{\tau_b}{\tau_a} = \frac{\varepsilon_b \cdot K_a \cdot h_a \cdot A_b}{\varepsilon_a \cdot K_b \cdot h_b \cdot A_a}, \quad (4)$$

where, τ_R can be calculated using the ε, K, h, and A values obtained experimentally in the state of a and b, respectively.

On the other hand, the total penetration rate of dissolution medium through the outer shell (k_{influx}) can be described using the lag time (t_{lag}) and outer shell thickness:

$$k_{influx} = \frac{h}{t_{lag}}, \quad (5)$$

where, h and t_{lag} were determined experimentally as described above, and k_{influx} can be determined in a given state 'b'. Fig. 3 shows the relationship between penetration rate (k_{influx}) and relative value of tortuosity (τ_R) which was determined regarding the state with the largest porosity as 'a'. Good linearity was maintained for all the PC tablets and this suggested that the prolongation of lag time was caused by the change in tortuosity.

As shown above, it was considered that there was a difference among the PC tablets in the dependency of the lag times and release rates on porosity. Thus, tablets, of which composition was the same as the outer shell, were prepared at

various compression forces and the uptake amounts into the tablets after immersion in first fluid are shown in Fig. 4.

In the case of tablets composed of HPMCAS alone (H tablets), and CaSt and HPMCAS (CH tablets), the uptake amount attained an equilibrium values within 1 h and decreased suddenly in the porosity range of 0.12-0.15 (A) and 0.10-0.14 (B), respectively. The porosity range agreed well with the point at which the lag times were suddenly prolonged (Fig. 2A).

In tablets composed of MgSt and HPMCAS (MH tablets), it did not attain an equilibrium values, and gradually increased even after 6 h (C). Also, the porosity did not have much of an effect compared to the other two tablets. In addition, the MH tablets apparently expanded, but the other two types did not. The results suggested that there could be some special physicochemical interaction between HPMCAS and MgSt in first fluid. Therefore, the IR spectra of these tablets before and after immersion in first fluid are shown in Fig. 5.

A single peak at around 1750 cm^{-1} in HPMCAS powder was observed and was assigned to the C=O group in succinoyl and acetyl groups based on HPMCAS technical information (Shin-Etsu Chemical Co, 1987). Two specific peaks were observed at around 1550 and 1580 cm^{-1} in MgSt powder. All the peaks of initial MH tablets were identical to those of HPMCAS and MgSt and it was suggested that these powders were not affected by compression. After immersion in first fluid, the two peaks that originated in MgSt disappeared in the outermost layer of MH tablets and new broad peaks appeared at around 1590 and 1640 cm^{-1}. However, such peaks could not be observed in the innermost layer and all the peaks agreed with those of the initial tablets.

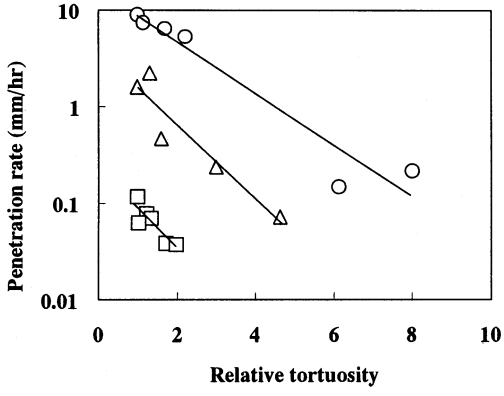

Fig. 3. Relationship between penetration rate and relative tortuosity in first fluid. Outer shell composition of press-coated tablet: (○) HPMCAS; (□) HPMCAS and CaSt; (△) HPMCAS and MgSt.

In H tablets, no changes were observed compared to initial HPMCAS. In MgSt, the two peaks observed initially declined greatly and shifted slightly to 1590 and 1540 cm^{-1}. A new peak, which appeared at around 1700 cm^{-1}, could correspond to the peak of stearic acid and indicated that MgSt changed to stearic acid in first fluid. Also, the peak of 1590 cm^{-1} agreed with the one sided peak of the outermost layer. However, steraic acid seemed to have released into first fluid since the new peak at around 1700 cm^{-1} could not be observed in the outermost layer of MH tablets immersed in first fluid.

As shown above, the peaks of 1590 and 1640 cm^{-1} observed in the outermost layer of MH-PC tablets immersed in first fluid could not be specified. However, some physicochemical interaction did occur between HPMCAS and magnesium ions, which was produced from MgSt, in limited closed spaces such as micropores. The new peaks might be associated with an interaction such as a polymer-metal complex between succinoyl or acetyl groups and magnesium ions. Therefore, it seemed that HPMCAS changed the original properties and showed expansion by the addition of MgSt.

The IR spectra of CH tablets before and after immersion in first fluid are shown in Fig. 6. The peaks in both the innermost and outermost layers after immersion in first fluid were corresponded to those of initial powders of HPMCAS and CaSt. It was suggested that the physicochemical interaction between HPMCAS and CaSt was far weaker than that between HPMCAS and MgSt.

Based on the above results, DIL release from each PC tablet in first fluid was considered to be as follows.

The micropores in the outer shell formed as small vacant spaces between particles upon com-

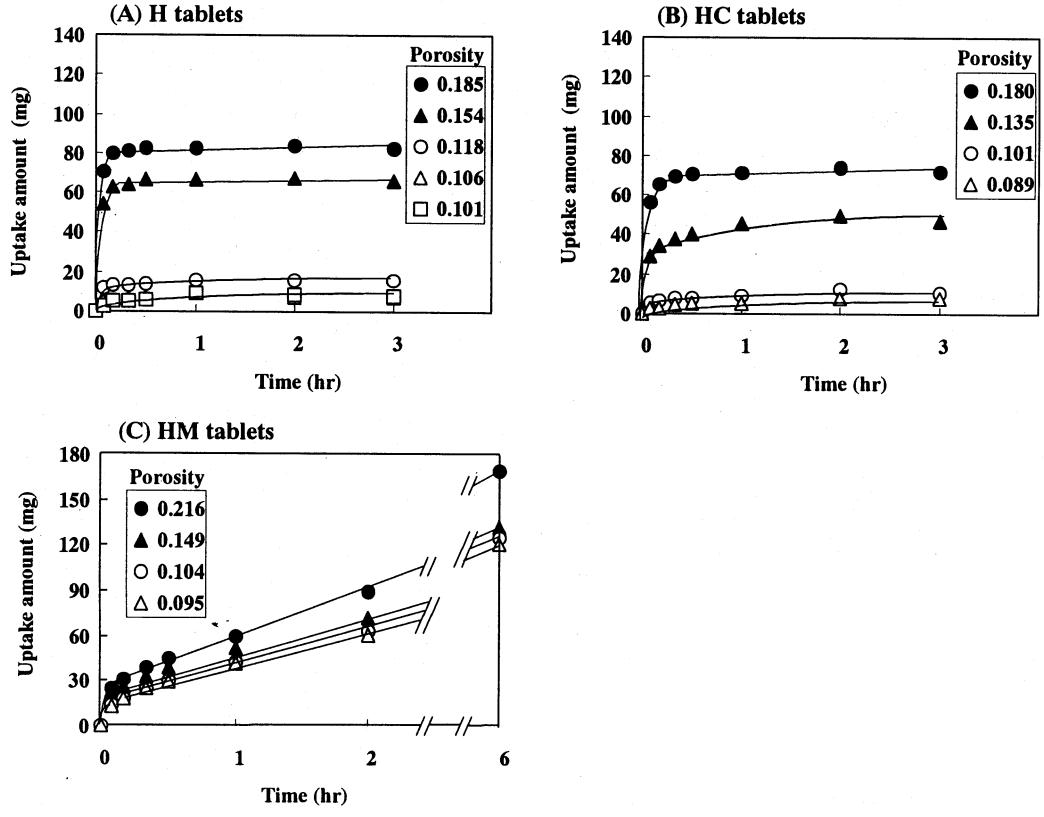

Fig. 4. Uptake amount of first fluid in tablets with various outer shell compositions.

pression. The combination of particles contacting each other could be classified in three types; HPMCAS-HPMCAS (H-H type), HPMCAS-hydrophobic additives (HA) (H-HA type) and HA-HA (HA-HA type). H-H type exists in only H-PC tablets, while, there are all three types in the other outer shells. The penetration rate of dissolution medium through the micropores is slower in the order of H-H > H-HA > HA-HA type since the uptake amount little increased in tablets prepared with hydrophobic additive alone (date not shown). The difference in the release rate and lag time between H-PC and CH-PC tablets at the same porosity (Fig. 2) was due to the wettability difference of the micropores. In MH-PC tablets, the physicochemical interaction between HPMCAS and MgSt occurs due to uptake of the medium and leads to the expansion of particles. Consequently, the area of micropores would decrease apparently since the extent of expansion was greater due to the interaction. Thus, the lag time of MH-PC tablets was more prolonged and the release rate after the lag time was more suppressed than those of other PC tablets.

3.2. Releasing behavior of DIL from press-coated tablets in second fluid

The typical dissolution profiles in JP second fluid (pH 6.8) for the H-PC, CH-PC and MH-PC tablets are shown in Fig. 7.

All the PC tablets showed a lag time and released DIL rapidly after the lag time. Also, since the variation of lag time in each PC tablet was as small as the result of Fig. 1, lag time was evaluated using a porosity of each PC tablet prepared under different compression forces in the following study.

The effect of porosity on lag time in second fluid is shown in Fig. 8. The lag times were

approximately 1.5 h regardless of the porosity in H-PC and MH-PC tablets. In CH-PC tablets, it increased with decreasing porosity and was 3 to around 9 h at a porosity of less than 0.25. These results were quite different from the results in first fluid since HPMCAS could be dissolved at higher pH solution. These differences could be due to the difference in the dissolution rate of the outer shell. The ratio of uptake amount against each H, CH and MH tablet wet weight in second fluid is shown in Fig. 9.

The uptake ratio in CH tablets was approximately half of that in H tablets, however, both uptake ratios attained equilibrium at 30 min and did not markedly change until 3 h. While, in MH tablets, it attained a much higher equilibrium value at 1.5 h after rapid increase. The result

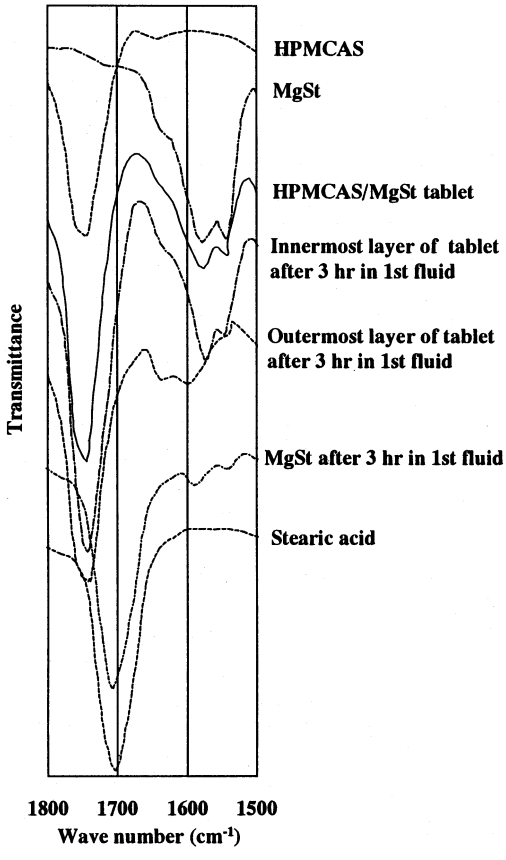

Fig. 5. IR spectra of tablets composed of HPMCAS and MgSt before and after immersion in first fluid.

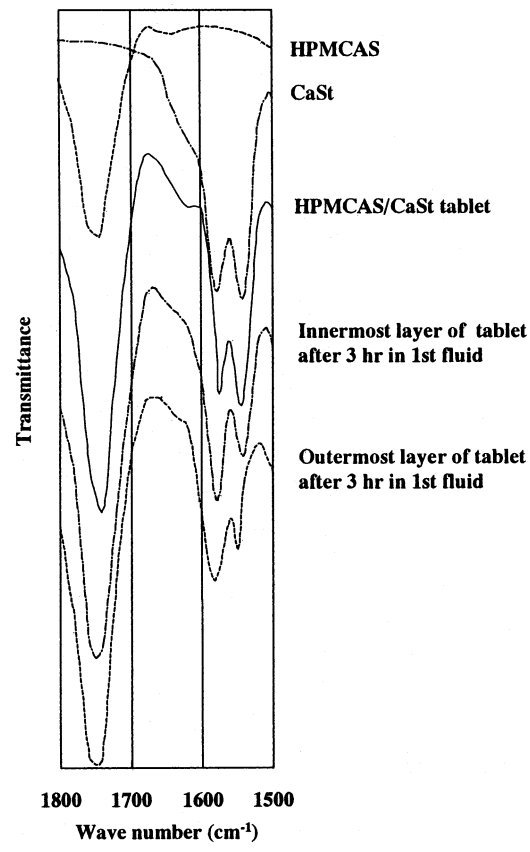

Fig. 6. IR spectra of tablets composed of HPMCAS and CaSt before and after immersion in first fluid.

indicated that MH tablets was more swellable than those of H and CH tablets.

From the above results, DIL release from each PC tablets in second fluid was presumed to be as follows.

After immersion, second fluid penetrated rapidly through the micropores in the outer shell. It was anticipated that the porosity affects the gel-forming rate, and consequently, lag time should increases with decreasing porosity. However, the results shown in Fig. 8 revealed that lag time hardly changed with the porosity in H-PC tablets. This seemed to suggest that the gel layer acts to prevent the dissolution medium from penetrating the outer shell since it was formed immediately on the tablet surface after immersion. Thus, the penetration is dependent on the gel layer and

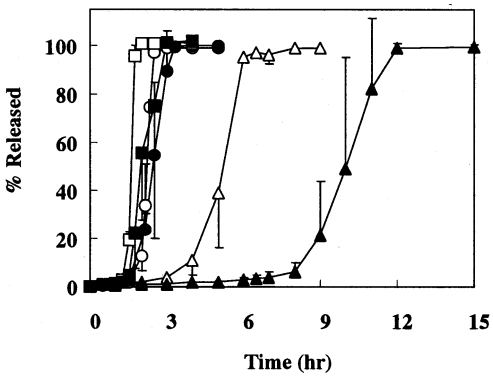

Fig. 7. Dissolution profiles of DIL from various press-coated tablets in second fluid. Compression force/outer shell composition: (○) 380 kg/cm^2 / HPMCAS; (●) 1530 kg/cm^2/HPMCAS; (△) 380 kg/cm^2/HPMCAS and CaSt; (▲) 1530 kg/cm^2/HPMCAS and CaSt; (□) 380 kg/cm^2/HPMCAS and MgSt; (■) 1530 kg/cm^2/HPMCAS and MgSt. Each point represents the mean ± S.D. ($n = 3$).

not on the micropores in the inner outer shell. The gel layer in contact with the dissolution medium would be more important than the micropores in the inner part of the outer shell.

By contrast, the decrease of porosity led to a prolongation of lag time in CH-PC tablets. This seems to be related to the hydrophobic property of CaSt. On CH-PC tablet surface after immersion, a gel layer was generated similar to that of H-PC tablets, but the uptake was the smallest among the three tablets. The surface area, which HPMCAS occupies on the tablet surface, could be

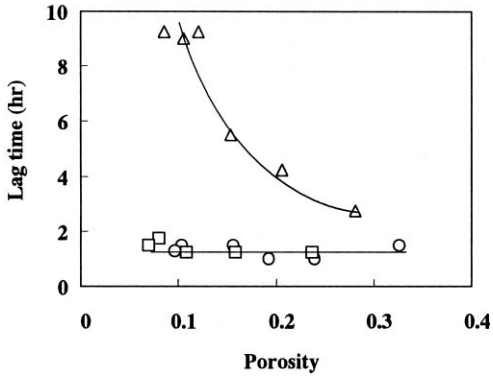

Fig. 8. Effect of porosity on lag time in second fluid. Outer shell composition: (○) HPMCAS; (□) HPMCAS and CaSt; (△) HPMCAS and MgSt.

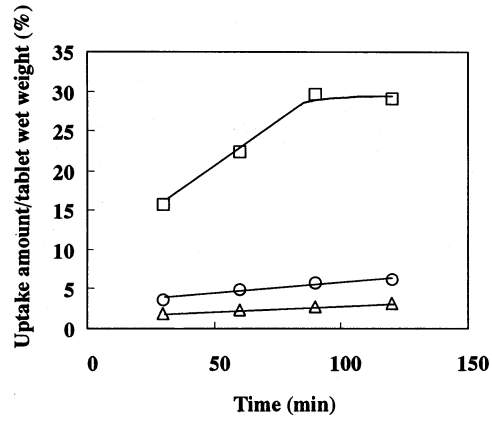

Fig. 9. Ratio of uptake amount of second fluid to tablet wet weight. Tablet composition: (○) HPMCAS; (□) HPMCAS and CaSt; (△) HPMCAS and MgSt.

reduced by addition of CaSt, however, increasing the compression force causes further spreading of CaSt on the surface. Therefore, the suppression of penetration by second fluid should be much larger due to the greater hydrophobic properties of CaSt.

As to MH-PC tablets, the lag times were less than 2 h regardless of porosity and the behavior was quite different from that of CH-PC tablets. Second fluid could penetrate the outer shell in a considerably brief time and the uptake was the greatest amount (Fig. 9). Although MgSt was added to afford hydrophobic properties to the outer shell, it apparently increased the hydrophilic properties. Some physicochemical interaction would be involved in this increase in medium uptake similar to that in first fluid. However, in second fluid, it was revealed that all the peaks originating from MgSt and HPMCAS remained by IR spectra were identical to those of initial powder (data not shown). Therefore, we examined dispersion properties of MgSt and CaSt in second fluid dissolved in 1% HPMCAS since this result was different from that in first fluid. MgSt was well dispersed in the HPMCAS solution, but CaSt was not. These results indicated that the wettability of MgSt could be improved by HPMCAS gel. Thus, even if MgSt spreads on the surface by compression, the dissolution rate of MH-PC tablets seemed to be faster due to faster swelling of the outer shell.

4. Conclusions

Effect of MgSt or CaSt as additives on dissolution profiles of DIL from PC tablets with HPMCAS in the outer shell was evaluated mainly by the porosity and change in IR spectra. MH-PC tablets led to the prolongation of lag time and delay of release rate in first fluid and shortening of lag time in second fluid. From the results of the effect of porosity on lag time, change in IR spectra and uptake of dissolution media after immersion in first fluid and second fluid, some physicochemical interaction indicated to occur between HPMCAS and MgSt. While, CaSt did not display such interaction and only acted to increase the hydrophobic properties of the outer shell. The hydrophobic property led to only a slight prolongation of lag time in first fluid but a marked change in second fluid due to suppression of penetration into micropores in the outer shell, interfering with the HPMCAS gel formation on the tablet surface.

References

Adkin, D.A., Davis, S.S., Sparow, R.A., Wilding, I.R., 1993. Colonic transit of different sized tablets in healthy subjects. J. Control. Release 23, 147–156.

Baichwal, A.R., Augsburger, L.L., 1988. Variations in the friction coefficients of tablet lubricants and relationship to their physicochemical properties. J. Pharm. Pharmacol. 40, 569–571.

Benita, S., Donbrow, M., 1982. Dissolution rate control of the release kinetics of water-soluble compounds from ethyl cellulose film-type microcapsules. Int. J. Pharm. 12, 251–264.

Butcher, A.E., Jones, T.M., 1972. Some physical characteristics of magnesium stearate. J. Pharm. Pharmacol. 24, 1P–9P.

Davis, S.S., Hardy, J.G., Fara, J., 1986. Transit of pharmaceutical dosage forms through the small intestine. Gut 27, 886–892.

Davis, S.S., Norring-Christensen, F., Kohsla, R., Feely, L.C., 1988. Gastric emptying of large single unit dosage forms. J. Pharm. Pharmacol. 40, 205–207.

Fukui, E., Miyamura, N., Kobayashi, M., 2001. An investigation of the suitability of press-coated tablets with hydroxypropymethyllcellulose acetate succinate (HPMCAS) and hydrophobic additives in the outer shell for colon targeting. J. Control. Release, 70(1-2) 97–107.

Gazzaniga, A., Iamartino, P., Maffione, G., Sangalli, M.E., 1993. Oral delayed-release system for colonic specific delivery. Int. J. Pharm. 108, 77–83.

Hardy, G., Healey, J.N.C., Reynolds, J.R., 1987. Evaluation of an enteric-coated delayed-release 5-aminosalycylic acid tablet in patients with inflammatory bowel disease. Aliment. Pharmacol. Therap. 1, 273–280.

Hydroxypropyl methylcellulose acetate succinate technical information, Shin-Etsu Chemical Co., Ltd., August, 1987.

Khosla, R., Davis, S.S., 1990. The effect of tablet size on the gastric emptying of non-disintegrating tablets. Int. J. Pharm. 62, R9–R11.

Miller, T.A., York, P., 1988. Pharmaceutical tablet lubrication. Int. J. Pharm. 41, 1–19.

Mooter, G.V., Samyn, C., Kinget, R., 1993. Azo polymers for colon-specific drug delivery. II: Influence of the type of azo polymer on the degradation by intestinal microflora. Int. J. Pharm. 97, 133–139.

Narisawa, S., Fukui, E., Yoshino, H., Hirakawa, Y., Noda, K., 1994. Porosity-controlled ethylcellulose film coating. V. Mechanism of drug release from beads coated with porous ethylcellulose film. Chem. Pharm. Bull. 42 (10), 2131–2134.

Ozturk, A.G., Ozturk, S.S., Palsson, B.O., Wheatley, B.O., Dressman, J.B., 1990. Mechanism of release from pellets coated with an ethylcellulose-based film. J. Control. Release 14, 203–213.

Phadke, D.S., Sack, M.J., 1996. Evaluation of batch-to-batch and manufacturer-to- manufacturer variability in the physical and lubricant properties of calcium stearate. Pharm. Tech. 20(3), 126–140.

Saffran, M., Kumar, G.S., Savariar, C., Burnham, J.C., Williams, F., Neckers, D.C., 1986. New approach to the oral administration of insulin and other peptide drugs. Science 233, 1081–1084.

Sakr, F.M., Zin, E.-D., Esmat, E., Hasheim, F.M., 1987. Release kinetics of some drugs from a suggested polymeric device. Acta Pharm. Technol. 33, 31–34.

Stolk, L.M.L., Rietbroek, E.H., Wiltink, E.H., Tukker, J.J., 1990. Dissolution profiles of mesalazine formulations in vitro. Pharm. Weekbl. Sci. 12 (5), 200–204.

Vidmar, V., Jalsenjak, I., Kondo, T., 1982. Volume of water-filled pores in the ethyl cellulose membrane and the permeability of microcapsules. J. Pharm. Pharmacol. 34, 411–414.