Evaluation of Hydroxyethylcellulose as a Hydrophilic Swellable Material for Delayed-Release Tablets

Mitsuyuki MATSUO, Chizuko NAKAMURA, Kazuhiko ARIMORI, and Masahiro NAKANO*

Department of Pharmaceutical Services, Kumamoto University Hospital, 1-1-1 Honjo, Kumamoto 860, Japan.
Received September 5, 1994; accepted October 24, 1994

Delayed-release tablets of diltiazem hydrochloride (DIL) were prepared by using AL-15 type hydroxyethycellulose (HEC) as a matrix material. The tablet consisted of a core tablet containing 30 mg of DIL and an outer shell formed by compressing HEC. The lag time to start the rapid release of DIL was more prolonged in the tablets consisting of a smaller particle size (20—53 and 53—106 μm) of HEC than those of the larger particle size (106—250 and 250—355 μm). However, there was little difference in the release rate of DIL among the two kinds of tablets. The rate of water uptake was greater in the tablets prepared with the larger particle size than those with the smaller particle size. These results suggest that the rate of water uptake seems to be a rate limiting process in setting the lag time. Observation of the surface of the tablets by electron micrograph showed that with the larger the particle size the cavity grows larger and with the smaller the particle size the cavity grows smaller. The lag time was also prolonged with an increase in the amount of HEC. Consequently, the lag time can be controlled optionally by changing the particle size and/or the amount of HEC forming the outer shell. This delayed-release system using HEC will be useful for time-related symptoms which need time-controlled or site-specific delivery in the gastrointestinal tract.

Key words hydroxyethylcellulose; delayed-release tablets; diltiazem hydrochloride; viscosity grade; lag time; time-controlled delivery

Various approaches to controlled-release delivery systems have been investigated for oral application. Of these approaches, delayed-release preparations have been noted as orally applicable delivery systems which are useful for the time-controlled or site-specific delivery of a drug in the gastrointestinal tract.[1-6] For example, Ishino *et al.*[1] reported that a pulsatile release system, which consists of a less water-permeable outer shell and a swellable core tablet, is expected to rapidly release a drug after a certain period of time on the basis of the time-controlled disintegration mechanism. Ueda *et al.*[3] also reported that a time-controlled explosion system has a four-layered spherical structure, which consists of core, drug, swelling agent and water-insoluble polymer membrane and is characterized by rapid drug release with a programmed lag time.

In general, cellulose derivatives have been widely used for controlled-release formulations because of their safety and low cost. Water-soluble gel-forming cellulose polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose are popular as swellable matrices for sustained release tablets.[7-10] Hydroxyethylcellulose (HEC) is also a water-soluble gel-forming polymer in which is included a 30—50% substituted hydroxyethoxy group in cellulose. HEC has the characteristics of a wide range of viscosity and pH-independent release because of the non-ionic nature of the polymer, although the ionic nature of drugs may influence pH dependency.

In the present study, the application of HEC as a delayed-release dosage form, which rapidly releases a drug from a reservoir device after a predetermined lag time, was investigated. Diltiazem hydrochloride was chosen as a representative drug. It is a potent calcium-channel blocker and has been effective for preventing the time-related occurence of disease symptoms such as ischemic heart disease and hypertension.[11,12]

* To whom correspondence should be addressed.

Experimental

Materials Diltiazem hydrochloride (DIL) and verapamil hydrochloride were kindly supplied by Tanabe Seiyaku Co. (Osaka, Japan) and Eisai Co. (Tokyo, Japan), respectively. AL-15 type HEC (Fuji Chemical Co., Osaka, Japan) with viscosity values of 25 cps and an ash content of 11% was used for tablet formulation since the polymer has a medium viscosity relative to all HECs and is considered to give the required lag time without disintegration. The other materials used were of JP XII or reagent grade.

Preparation of Delayed-Release Tablets HEC polymers were used after being ground in a ball mill for 8 h. All the tabletting experiments were performed using a reciprocating press (potassium bromide press, Shimadzu Co., Kyoto, Japan) with a flat-faced punch and a die. A core tablet containing 30 mg of DIL with a diameter of 5 mm was compressed at the applied force of 200 kg/cm^2 and a compression time of 1 min. A half amount of HEC was filled into the die with a diameter of 13 mm to make the powder bed and then compressed at the applied force of 40 kg/cm^2 and a compression time of 5 s. The core tablet was placed on the center of the HEC disk. After being filled with the remaining half of the HEC, the die content was compressed at the applied force of 400 kg/cm^2 and a compression time of 2 min. The thickness of the disk was adjusted by changing the amount of HEC (particle size, 106—250 μm) under the same condition. A schematic representation of the preparation of the delayed-release tablet is illustrated in Fig. 1.

***In Vitro* Drug Release** The dissolution test was carried out using the JP XII paddle method with 900 ml of a medium at 37 °C. The dissolution medium was a JP XII disintegration medium 2nd fluid (pH 6.8). The rotation speed was set at 100 rpm. The amount of DIL dissolved was determined by measuring the absorbance at 237 nm (dissolution apparatus, type NV-2F Toyama Sangyo Co. ; detector apparatus, Shimadzu Co., Kyoto, Japan). All the tests were performed in triplicate. The lag time of drug release was defined as the intersected point on the time axis when the part of the straight line of the release pattern is extended to the time axis. The release rate of a drug was calculated from the slope of the straight line of the release pattern to the time axis.

Water Uptake Study The water uptake by the delayed-release tablet was examined at room temperature using the apparatus described by Nogami *et al.*[13] Briefly, a tablet was placed in the center of a sample tube, and the amount of water decreasing with the elapse of time was measured.

© 1995 Pharmaceutical Society of Japan

NII-Electronic Library Service

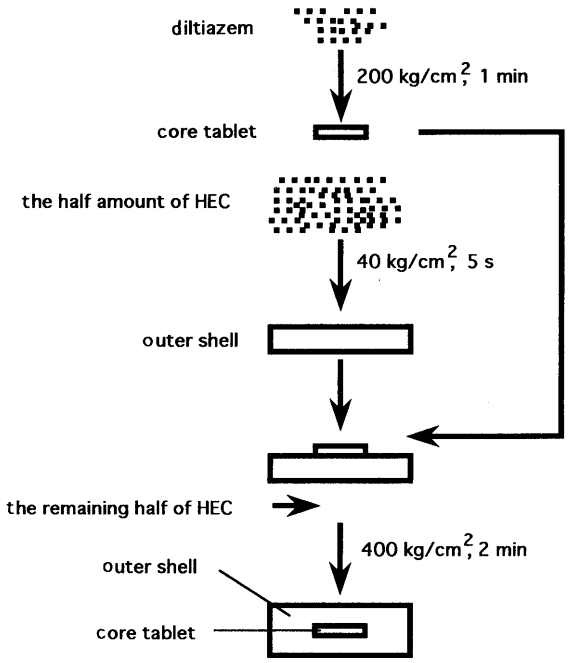

Fig. 1. Schematic Representation of HEC Delayed-Release Tablet

Scanning Electron Microscopy Electron micrographs of the surface of the delayed-release tablet were taken using a scanning electroscope (Hitachi S-510). The samples were coated with gold using a direct current sputter technique.

Results and Discussion

Effect of Particle Size of HEC on Release Patterns Figure 2 shows the effect of various particle sizes of HEC on the release patterns of DIL. The tablets prepared with four particle size distributions of HEC released the drug after a lag period of several hours. The lag time was more prolonged in the two tablets prepared with the smaller particle size of HEC (20—53 and 53—106 μm) than in those with the larger particle size (106—250 μm and 250—355 μm). The lag time was roughly classified into the two groups depending on the particle size of HEC bordering the neighborhood of 106 μm, even if there was little difference in the release rate of DIL among the tablets prepared with HEC of different particle sizes.

Effect of Particle Size on Water Uptake It is known that the penetration of fluid into tablets depends on the interfacial tension of the liquid–solid boundary, the contact angle, the pore-size distribution, the geometry of the pore surface, the viscosity of liquid, and the electrostatic charges involved.[14] Thus, to determine the amount of water uptake on the outer shell, the tablets were prepared with HEC of various particle sizes. Figure 3 shows the effect of particle size of HEC on water uptake. The rate of water uptake was larger in the tablets prepared with the large particle size (106—250 and 250—355 μm) than those with the smaller particle size (20—53 and 53—106 μm) during the first half hour. However, there was little difference in the water uptake between the particle sizes of 20—53 and 53—106 μm and between the particle sizes of 106—250 and 250—355 μm. This behavior of water uptake corresponded to the release profile of DIL from the tablets shown in Fig. 2. These results suggest

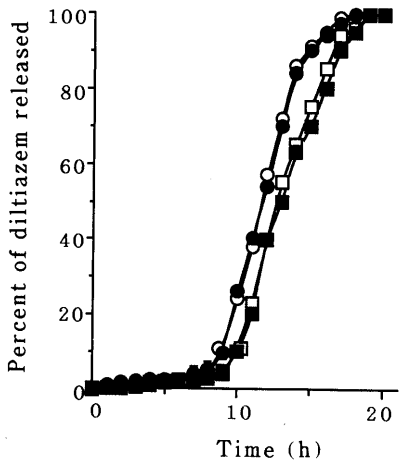

Fig. 2. Effect of Particle Size of HEC on Release Patterns of Diltiazem with JP Apparatus Paddle Method in JP XII 2nd Fluid (100 rpm, 37.0±0.5°C)

○, 250—355 μm; ●, 106—250 μm; □, 53—106 μm; ■, 20—53 μm.

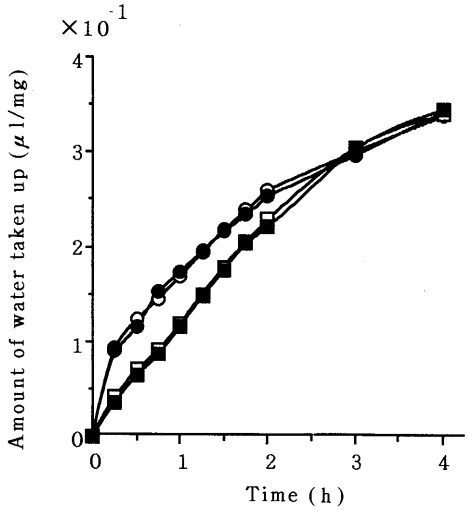

Fig. 3. Effect of Particle Size of HEC on Uptake of Water in JP XII 2nd Fluid at Room Temperature

○, 250—355 μm; ●, 106—250 μm; □, 53—106 μm; ■, 20—53 μm.

that the rate of water uptake seems to be a rate limiting process in setting the lag time. In general, the tablets prepared with a large particle size have a larger cavity between particles. Accordingly, the tablet with a larger cavity is considered to more easily absorb water compared with that with a smaller cavity, since water can penetrate a larger channel faster to hydrate the polymer. After gel-formation, there was little difference in the rate of uptake between particle diameters. This suggests that the particle size influences the initial gel formation. Consequently, it is considered that the delayed-release type tablet forms the hydrogel on the tablet surface by the absorption of water, and the gel formation thus slows the release process. The difference in the release profile of DIL from the delayed-release tablets is considered to be due to the difference in the rate of water uptake.

Scanning Electron Micrography The surface characteristics of the delayed-release preparations were examined by scanning electron micrography. Figure 4 shows

NII-Electronic Library Service

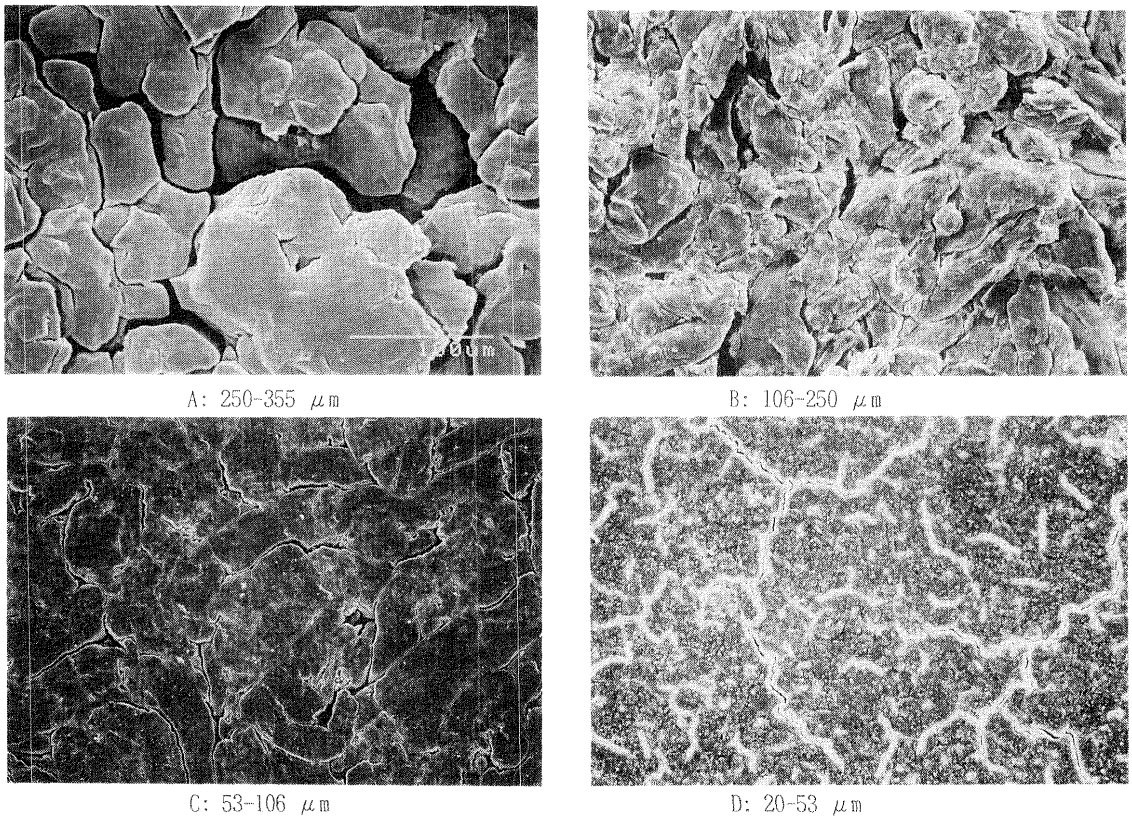

Fig. 4. Scanning Electron Micrographs of Surface of Tablets Prepared with HEC of Various Particle Sizes

electron micrographs of the surface of delayed-release tablets prepared with HEC of various particle sizes. It was observed that in the larger particle size the cavity grows larger and in the smaller particle size the cavity grows smaller.

Effect of Amount of HEC on Release Patterns The release profiles of DIL from the delayed-release tablets was examined by changing the amount of HEC, and they are shown in Fig. 5. The lag time was prolonged with an increase in either the amount of HEC or the thickness of the outer shell. However, there was little difference in the release rates of DIL after lag time (Table I). In general, the release rate from a gel-forming matrix tablet depends upon the diffusion of water into the tablet and the erosion of the matrix. In the present study, the tablets completely held their shape during the release since the AL-15 type HEC used in this study has a middle degree of viscosity (25 cps), enough to maintain the gel layer. Consequently, the release of DIL from this gel-forming reservoir tablet is considered to depend mainly on diffusion rather than erosion. This suggests that the lag time can be optionally controlled by changing the amount of HEC forming the outer shell.

The reason the lag time before release of the drug was observed may be explained in the following way. When the tablet was immersed in the aqueous solution, water began to penetrate the polymer layer. When the innermost part of the polymer layer was gelled, water began to dissolve the drug, and the drug in the solution started to permeate through the gel. The time period between the immersion of the tablet and the appearance of the drug

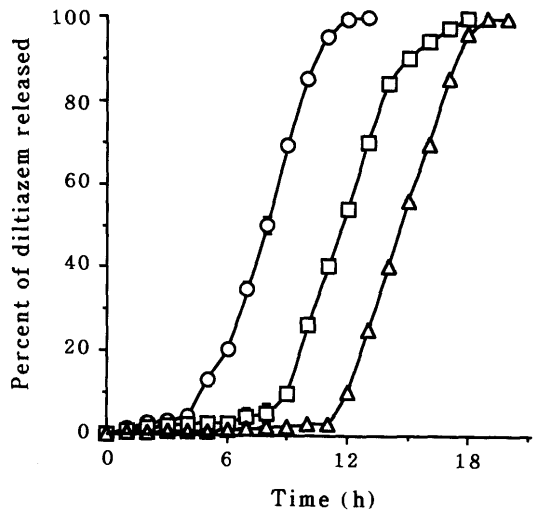

Fig. 5. Effect of Amounts of HEC on Release Patterns of Diltiazem from HEC Delayed-Release Tablets with JP Apparatus Paddle Method in JP XII 2nd Fluid (100 rpm, 37.0±0.5 °C)

○, 370 mg/tab; □, 570 mg/tab; △, 770 mg/tab.

TABLE I. Lag Time and Release Rate of Diltiazem from Tablets Prepared with Different Amounts of HEC

Amount of HEC (mg/tab)	Lag time (h)	Release rate (%/h)
370	3.79±0.19	20.2±1.33
570	7.59±0.39	19.3±0.59
770	11.0 ±0.69	21.9±0.19

Each value represents the mean±S.E.M. of three experiments.

NII-Electronic Library Service

in bulk solution may be defined as lag time.

Recent Progress After the present work was carried out, the following works became known to us. Conte *et al.*[15] reported in an Italian pharmaceutical journal that they employed both low and high viscosity hydroxypropylmethylcellulose to press-coat erodible barrier and gelling barrier tablets.

Another Italian group, Gazzaniga *et al.*,[16,17] employed high-viscosity hydroxypropylmethylcellulose to form an outer layer in a similar way to the present work to achieve time and/or site specificity.

Conclusion

We prepared the delayed-release tablets using AL-15 type HEC in the outer shell. DIL in the core was rapidly released from the tablets after a lag time of several hours. The lag time could be controlled mainly by changing the thickness of the outer shell. In addition, the advantage of this delayed-release system is that it is easy and inexpensive to fabricate. Consequently, HEC is considered to be an easily available excipient as the dry coating material for a reservoir type controlled-release tablet.

Acknowledgments The authors would like to thank Nobuo Kawamoto, Fuji Chemical, Osaka, for supplying us with samples of various grades of HEC. The present work was supported in part by the Japan Research Foundation for Clinical Pharmacology.

References

1) R. Ishino, H. Yoshino, Y. Hirakawa, K. Noda, *Chem. Pharm. Bull.*, **40**, 3036 (1992).
2) R. Ishino, H. Yoshino, Y. Hirakawa, K. Noda, *Chem. Pharm. Bull.*, **40**, 3094 (1992).
3) S. Ueda, T. Hata, S. Asakura, H. Yamaguchi, M. Kotani, Y. Ueda, *J. Drug Targeting*, **2**, 35 (1994).
4) S. Ueda, H. Yamaguchi, M. Kotani, S. Kimura, Y. Tokunaga, A. Kagayama, T. Hata, *Chem. Pharm. Bull.*, **42**, 359 (1992).
5) S. Ueda, R. Ibuki, S. Kimura, S. Murata, T. Takahashi, Y. Tokunaga, T. Hata, *Chem. Pharm. Bull.*, **42**, 364 (1992).
6) I. R. Wilding, S. S. Davis, M. Bakhshaee, H. N. E. Stevens, R. A. Sparrow, J. Brennan, *Pharm. Res.*, **9**, 654 (1992).
7) M. Nakano, N. Ohmori, A. Ogata, K. Sugimoto, Y. Tobino, R. Iwaoku, K. Juni, *J. Pharm. Sci.*, **72**, 378 (1983).
8) L. M. Prisant, B. Bottini, J. T. DiPiro, A. A. Car, *Am. J. Med.*, **93** (Suppl. 2A), 45S (1992).
9) H. Nakagami, M. Nada, *Drug Des. Deliv.*, **7**, 321 (1991).
10) H. Nakagami, M. Nada, *Drug Des. Discov.*, **8**, 103 (1991).
11) B. Lemmer, *J. Control. Release*, **16**, 63 (1991).
12) K. Traynor, D. W. Newton, W. J. M. Hrushesky, R. J. Reiter, *Am. Pharm.*, NS**32**, 261 (1992).
13) H. Nogami, T. Nagai, E. Fukuoka, T. Sonobe, *Chem. Pharm. Bull.*, **17**, 1450 (1969).
14) R. Shangraw, A. Mitrevej, M. Shah, *Pharm. Tech.*, **4**, 49 (1980).
15) U. Conte, L. Maggi, P. Giunchedi, A. La Manna, *Boll. Chim. Farm.*, **131**, 199 (1992).
16) A. Gazzaniga, P. Iamartino, G. Maffione, M. E. Sangalli, *Int. J. Pharmaceut.*, **108**, 77 (1994).
17) A. Gazzaniga, M. E. Sangalli, F. Giordano, *Eur. J. Pharm. Biopharm.*, **40**, 246 (1994).

NII-Electronic Library Service