Journal of Inclusion Phenomena and Macrocyclic Chemistry **44:** 141–144, 2002.

Effect of 2-Hydroxypropyl-β-cyclodextrin on Release Rate of Metoprolol from Ternary Metoprolol/2-hydroxypropyl-β-cyclodextrin/Ethylcellulose Tablets

YOICHI IKEDA[1], SOHKO MOTOUNE[1], AYA MARUMOTO[2], YOH SONODA[2], FUMITOSHI HIRAYAMA[2], HIDETOSHI ARIMA[2] and KANETO UEKAMA[2]*

[1]*Healthcare Research Institute, Wakunaga Pharmaceutical Co. Ltd, 1624 Shimokotachi, Kodacho, Takatagun, Hiroshima 739-1195, Japan;* [2]*Faculty of Pharmaceutical Sciences, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan*

(Received: 7 May 2002; in final form: 1 October 2002)

Key words: ethylcellulose, gel, 2-hydroxypropyl-β-cyclodextrin, metoprolol, release control, tablet

Abstract

The effect of 2-hydroxypropyl-β-cyclodextrin (HP-β-CyD) on the release of a water-soluble β_1-selective adrenoreceptor antagonist, metoprolol (Met), from ternary Met/HP-β-CyD/ethylcellulose (EC) tablets was investigated. The release rate of Met from the ternary tablets was dependent on amounts of HP-β-CyD in the tablets, i.e., the rate decreased when small amounts of HP-β-CyD were added, while large amounts of HP-β-CyD accelerated the rate. The slowest rate was observed for the tablet consisted of a 30/10/60 weight ratio of Met/HP-β-CyD/EC. The analyses of the release rates by the Korsmeyer equation and their temperature dependence suggested that Met is released from the EC matrix containing HP-β-CyD according to the diffusion-controlled mechanism. The water penetration studies and the micro- and macroscopic observations suggested that the retarding effect of HP-β-CyD is attributable to a viscous gel formation in small pores on the surface of the tablets, where HP-β-CyD gels may work as a barrier for the water penetration into the tablets and the release of the drug from the tablets. The *in-vitro* release property of the ternary tablets was reflected in the *in-vivo* absorption profile in dogs. The results indicated that a combination of HP-β-CyD and EC is useful for the release control of water-soluble drugs such as Met.

Introduction

It is known that hydrophilic cyclodextrin (CyD) derivatives such as 2-hydroxypropyl-β-CyD (HP-β-CyD) and sulfobutylether of β-CyD can improve solubility and dissolution rate of poorly water-soluble drugs, while hydrophobic CyD derivatives such as ethylated and acylated CyDs can work as slow-releasing carriers for water-soluble drugs. Further, advanced controlled releases can be achieved by a pertinent combination of cyclodextrins (CyDs) and pharmaceutical polymers [1–3]. In previous studies, we found that a combination of short- and long-chain peracylated β-CyDs serves as a sustained release carrier for a water-soluble drug, diltiazem [4]. Further, a combination of hydrophilic and hydrophobic CyD derivatives such as 2-hydroxypropyl-β-CyD (HP-β-CyD) and per-O-butanoyl-β-CyD was useful for the release control of an ACE inhibitor, captopril, where the release rate was dependent on amounts of HP-β-CyD in the hydrophobic matrix [5]. In this study, we carried out the release control of a water-soluble β_1-selective adrenoreceptor antagonist, metoprolol (Met), by means of a combination of HP-β-CyD and a hydrophobic polymer, ethylcellulose (EC) and report here that HP-β-CyD can play an important role in the release of the drug from the EC matrix.

* Author for correspondence: E-mail: uekama@gpo.kumamoto-u.ac.jp

Experimental

Materials

Met tartrate and EC (49% ethoxy, 10 cp, mean particle size 6 μm, FP grade) were purchased from Sigma Co. (St. Louis, USA) and The Dow Chemical Co. (Midland, USA), respectively. HP-β-CyD (degree of substitution 4.5) was supplied by Nihon Shokuhin Kako Co. (Tokyo, Japan) and dried over P_2O_5 for 24 h in vacuum before use. Other chemicals and solvents were of analytical reagent grade, and deionized double-distilled water was used throughout the study.

Preparation of ternary Met/HP-β-CyD/EC tablets

The ternary Met/HP-β-CyD/EC tablets were prepared by the following three methods: Method A, The Met/HP-β-CyD complexes with different molar ratios were prepared by the kneading method [6], i.e., kneading appropriate amounts of Met tartrate, HP-β-CyD and water for about 20 min, and the resulting complexes were dried under reduced pressure for 24 h. Then, the Met/HP-β-CyD complexes were physically mixed with EC in appropriate ratios and the mixture (200 mg) was directly compressed into a tablet of 10.0 mm diameter, under a pressure of 1000 kg/cm^2 for 1.0 min. Method B, Met was triturated simultaneously together with HP-β-CD and EC in small amounts of water, kneaded for

about 20 min, and dried under reduced pressure for 24 h. The resulting powder was compressed into a tablet under the same condition described above. Method C, The physical mixture was prepared by mixing simply the three components, and compressed into a tablet under the same conditions described above.

In-vitro *release studies*

The release rate of Met from tablets (containing the equivalent amount of 60 mg Met) was measured according the paddle method of the dissolution test in Japanese Pharmacopoeia (JP) XIII. The dissolution medium (JP XIII second fluid (pH 6.8), 500.0 mL) was stirred at 100 rpm at 37 °C. At appropriate intervals, an aliquot was automatically analyzed for Met at 275 nm by a Shimadzu UV-1600 spectrophotometer (Kyoto, Japan) equipped with a Toyama W-PAS-615 auto-sampler and a dissolution tester NTR-6000 (Osaka, Japan) controlled by a personal computer. Water-penetration rates into tablets were measured by means of the apparatus reported previously [7].

In-vivo *absorption studies*

The absorption studies were carried out using beagle dogs (9–11 kg) that were fasted for 24 h before drug administration. Tablets (200 mg) containing the ternary Met/HP-β-CyD/EC systems (equivalent to 60 mg Met, prepared by Method A) were administered orally with water (50 mL). Blood samples (3.0 mL) were withdrawn from the cephalic vein with a heparinized syringe and centrifuged at 1100 $\times$ g for 10 min. To 1.0 mL of the plasma sample was added 0.2 mL of 30% trichloroacetic acid, and the mixture was centrifuged at 1100 $\times$ g for 10 min. To 1.0 mL of the aqueous layer was added 0.5 mL of 1.0 M NaOH and 5.0 mL of dichloromethane, and the mixture was shaken for 5 min at room temperature. The organic phase (4.0 mL) was evaporated to dryness under reduced pressure and the residue was dissolved in 0.2 mL of the mobile phase of high-performance liquid chromatography (HPLC). The HPLC conditions were as follows: a LC-10ATVP pump equipped with a RF-10AXL fluorescence spectrophotometer and a CBM-10A communication bus module (Shimadzu, Kyoto, Japan), a Tosoh TSK-GEL ODS-80TS column (5.0 m, 4.6 $\times$ 150 mm, Tokyo, Japan), a mobile phase of 0.01 M sodium 1-hexanesulfonate in 0.1% acetic acid/acetonitrile (75:25 v/v), a flow rate of 1.0 mL/min, and an excitation of 230 nm and a detection of 300 nm.

Results and discussion

Figure 1 shows release profiles of Met from the ternary Met/HP-β-CyD/EC tablets prepared by the aforementioned methods (Methods A, B, and C). The dissolution of Met alone (diluent: lactose) or its HP-β-CyD complex (without EC) in JP XIII second fluid (pH 6.8) was very fast and completed within about 10 min, reflecting the high aqueous solubility of the drug (> 1 g/mL). The release rate of Met was significantly retarded by the addition of EC in the tablets prepared by the three methods (Figure 1A, B and C). In the tablets prepared by Method C (simple physical mixture of three components, Figure 1C), there was negligible effect of HP-β-CyD on the release rate of Met from the EC matrix. In the case of Method B (kneading product of three components, Figure 1B), the release rate was only slightly increased by the addition of HP-β-CyD in the EC matrix, but it was independent on the amount of HP-β-CyD in the matrix. In the case of Method A (mixture of the Met/HP-β-CyD complexes and EC, Figure 1A), the release rate changed significantly depending on the amount of HP-β-CyD in the matrix, i.e., the release slowed down as the amount of HP-β-CyD increased up to 10%w/w, but the further increase of HP-β-CyD content recovered the release rate. Therefore, the slowest release was observed for the tablet consisted of Met/HP-β-CyD/EC (30/10/60% w/w) prepared by Method A. No disintegration of the tablets was observed under the experimental conditions.

To gain insight into the release mechanism, the release profiles of Figure 1A were analyzed by the Korsmeyer equation (Equation (1)) [8]:

$$M_t = kC_a t^n, \tag{1}$$

where M_t and C_a are the amount of the drug released at time t and the total amount of drug in the tablet, respectively, and k and n are the release rate constant and the parameter characteristic of the release mechanism, respectively. The analysis of the release profiles (Figure 1A) by Equation (1) gave the following parameters: $k = 0.56h^{-n}$ and $n = 0.49$ (30/0/70%w/w Met/HP-β-CyD/EC), $k = 0.47h^{-n}$ and $n = 0.47$ (30/5/65%w/w), $k = 0.36h^{-n}$ and $n = 0.46$ (30/10/60%w/w), $k = 0.46h^{-n}$ and $n = 0.47$ (30/15/55%w/w), and $k = 0.53h^{-n}$ and $n = 0.48$ (30/20/50%w/w), respectively. The k value was the smallest at the composition of 30/10/60%w/w Met/HP-β-CyD/EC. The n value was approximately 0.5 in all compositions, indicating a diffusion-controlled release of the drug. The temperature dependence of the k value was studied for the (30/10/60%w/w) tablets at 27 °C, 32 °C, 37 °C and 42 °C and gave an activation energy of 9.4 kJ/mol which was in a range of the diffusion-controlled release [9]. These results suggested that the release of Met from the tablets prepared by Method A is controlled by the diffusion mechanism.

Figure 2 shows the water-uptake of the tablets, which were prepared by Method A, at 1 h after a contact with water. The water-uptake of the tablets decreased as the HP-β-CyD content increased to 10%w/w. This water-uptake behavior resembled the release behavior of Met from the ternary tablets, suggesting that HP-β-CyD inhibits the penetration of water into the tablets. During the water-penetration experiments, we found macroscopically that a viscous gel is formed on the surface of the tablets. Further, the microscopic observation by scanning electron microscopy (SEM) indicated that the ternary Met/HP-β-CyD/EC (30/10/60%w/w) tablet has a coarse surface with many void space, and this surface changes to a smooth surface with many tiny pores 1 h after the water-penetration experiment. These results

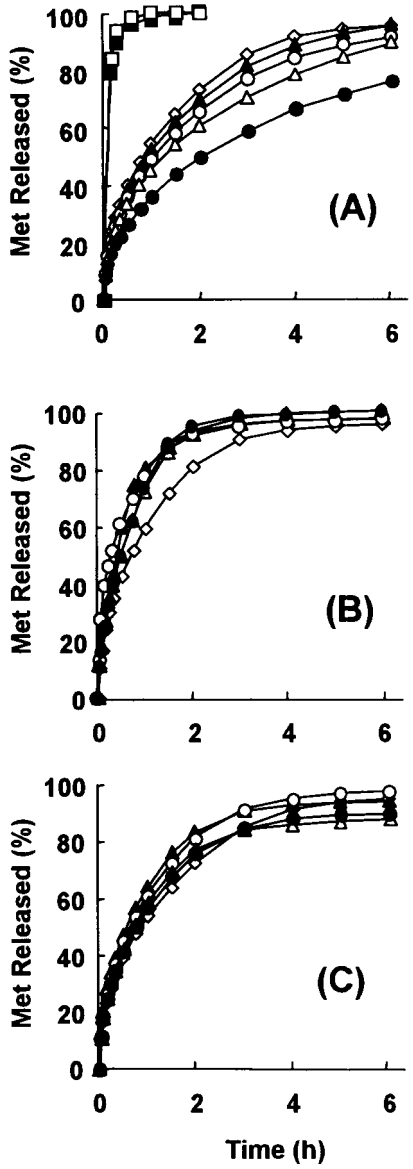

Figure 1. Release profiles of Met from Met/HP-β-CyD/EC tablets in JP XIII second fluid (pH 6.8) at 37 °C, measured by paddle method. (A) Tablets prepared by Method A. (B) Tablets prepared by Method B. (C) Tablets prepared by Method C. ◇: 30/0/70%w/w Met/HP-β-CyD/EC tablet, ○: 30/5/65%w/w tablet, ●: 30/10/60%w/w tablet, △: 30/15/55%w/w tablet, ▲: 30/20/50%w/w tablet, □: Met alone (diluent: lactose), ■: 30/70%w/w Met/HP-β-CyD complex alone (diluent: lactose).

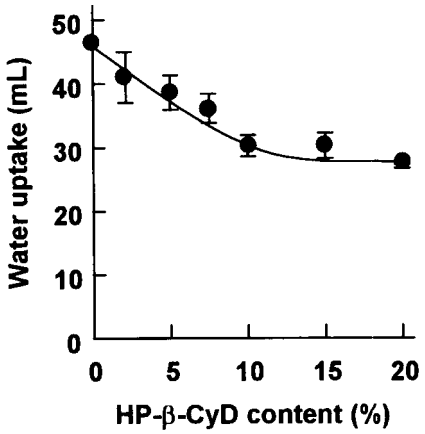

Figure 2. Amounts of water-uptake in Met/HP-β-CyD/EC tablets (diameter 4 mm, 50 mg) with different compositions, 1 h after a contact with water at 37 °C. The tablets were prepared by Method A.

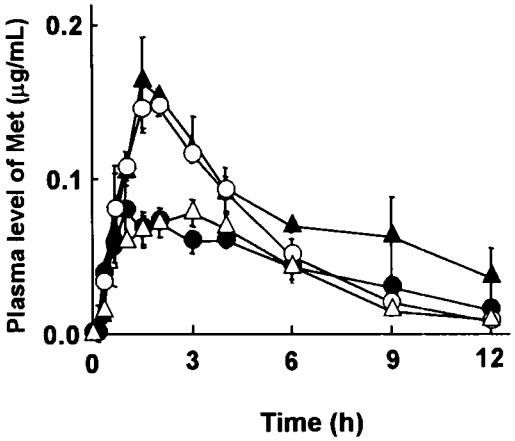

Figure 3. Plasma levels of Met after oral administration of Met/HP-β-CyD/EC tablets with different compositions or a commercial product (Lopressor SR®) in dogs. ○: 30/5/65%w/w tablet, ●: 30/10/60%w/w tablet, ▲: 30/20/50%w/w tablet, △: a commercial product (Lopressor SR®).

Figure 3 shows plasma levels of Met after oral administration of the ternary tablets in beagle dogs. The plasma levels of Met changed depending on the amount of HP-β-CyD, i.e., the Met levels of the (30/10/60%w/w) Met/HP-β-CyD/EC tablet were lower than those of the (30/5/65%w/w) and (30/20/50%w/w) tablets, and were similar to those of a commercial Met product (Lopressor SR®).

suggest that HP-β-CyD forms a gel layer in tiny pores on the surface, i.e., it forms a barrier for the water-penetration and the drug release. In the case of large HP-β-CyD contents, the Met/HP-β-CyD complexes may rapidly dissolved from the surface, leaving many large pores on the surface. Because the retarding effect of HP-β-CyD was observed only when it is formulated as the complexes (Method A) in the tablets, it may be necessary for the deceleration that Met is surrounded by HP-β-CyD gel in molecular level. The release profile of the (30/10/60%w/w) Met/HP-β-CyD/EC tablet was negligibly affected by changes in pH (1.2–6.8) of the release medium and in the rotation speed (50-200 rpm) of the paddle.

Conclusion

The release rate of Met changed depending on the amount of HP-β-CyD, when it is formulated as the complexes in the EC tables, i.e., the release rate decreased when appropriate amounts of HP-β-CyD are added in the hydrophobic EC matrix. This rate-decrease may be attributable to a gel formation of HP-β-CyD at higher concentrations. HP-β-CyD is widely used as a solubilizer and a fast-dissolving carrier for poorly-water soluble drugs. However, the present study showed that it may work as a retarding carrier for the release control of water-soluble drugs such as Met. Further

studies on the internal structure of the tablets prepared by Methods A, B and C and on a gel formation of HP-β-CyD at higher concentrations are under way, and will be reported elsewhere.

References

1. T. Loftsson and M.E. Brewster: *J. Pharm. Sci.* **85**, 1017 (1996).
2. T. Loftsson, N. Leeves, B. Bjornsdottir, L. Duffy, and M. Masson: *J. Pharm. Sci.* **88**, 1254 (1999).
3. Z. Wang, T. Horikawa, F. Hirayama, and K. Uekama: *J. Pharm. Pharmacol.* **45**, 942 (1993).
4. O.A. Soliman, K. Kimura, F. Hirayam, K. Uekama, H.M. El-Sabbagh, A.H. Abd El-Gawad, and F.M. Hashim: *Pharm. Sci.* **2**, 533 (1996).
5. Y. Ikeda, K. Kimura, F. Hirayama, H. Arima, and K. Uekama: *J. Control. Rel.* **66**, 271 (2000).
6. F. Hirayama and K. Uekama: in D. Duchene (ed.), *Methods of Investigating and Preparing Inclusion Compounds (Cyclodextrins and Their Industrial Uses)*, pp. 131–172, Editons de Sante (1987).
7. Y. Horiuchi, F. Hirayama, and K. Uekama: *J. Pharm. Sci.* **79**, 128 (1990).
8. R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, and N.A. Peppas: *Int. J. Pharm.* **15**, 25 (1983).
9. H. Nogami, T. Nagai, and A. Suzuki: *Chem. Pharm. Bull.* **14**, 329 (1966).