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Interaction of Tri-*O*-methyl- β -cyclodextrin with Drugs. II.¹⁾ Enhanced Bioavailability of Ketoprofen in Rats when Administered with Tri-*O*-methyl- β -cyclodextrin

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The interaction of ketoprofen with tri-*O*-methyl- β -cyclodextrin (methyl- β -CD) was investigated *in vitro* and *in vivo*. The phase solubility diagram revealed a linear relationship (A_L type), and the solubility of ketoprofen in 0.1 M methyl- β -CD aqueous solution was 20 times that in pure water. The bioavailability of ketoprofen following oral administration with methyl- β -CD to rats was 3.7 times that of ketoprofen alone.

Keywords—tri-*O*-methyl- β -cyclodextrin; inclusion complexation; physical mixture; bioavailability; ketoprofen; oral administration; rat; solubility

Recently, methylated cyclodextrins have become of interest in the pharmaceutical field because of their high solubilities, and complex forming abilities.²⁾ Tri-*O*-methyl- β -cyclodextrin (methyl- β -CD), a synthetic derivative of β -cyclodextrin, is very soluble in organic solvents and can improve the partition coefficients of drugs, as reported previously,¹⁾ and it is therefore expected that methyl- β -CD will enhance the bioavailabilities of drugs.³⁾

Ketoprofen is widely used in rheumatology because of its analgesic and anti-inflammatory properties. In this study, we report that methyl- β -CD enhanced the bioavailability of ketoprofen following oral administration to rats.

Experimental

Materials—Methyl- β -CD was synthesized as previously described.¹⁾ Ketoprofen was a gift from Iwaki Pharmaceutical Co., Ltd. All other materials were of analytical reagent grade.

Solubility Studies—Excess amounts of ketoprofen were added to methyl- β -CD aqueous solution and shaken at 30 °C. After equilibration, an aliquot of the solution was pipetted through a Millipore filter (1.0 μ m). One ml of the sample solution was diluted with 0.1 N HCl and analyzed spectrophotometrically.

Dissolution Studies—A powder sample containing 250 mg of ketoprofen was put into 50 ml of water in a flask at 30 °C. The suspension was shaken at 110 rpm. The sampling and the determination of ketoprofen were carried out as described above.

In Vivo Absorption Studies—Male Wistar albino rats, 270–310 g, were fasted for 24 h prior to drug administration. Ketoprofen powder or its physical mixture with methyl- β -CD (molar ratio; 1:1) was freshly suspended in distilled water and administered into the stomach of a rat through a sonde at a dose of 25 mg/kg (as ketoprofen) in a constant volume of 5 ml/kg. Blood samples were obtained from the femoral artery *via* a cannula and immediately centrifuged at 3000 rpm to obtain plasma samples. The concentration of ketoprofen in plasma was determined according to the method described by Bannier *et al.*,⁴⁾ using a Shimadzu LC-3A high performance liquid chromatograph. Indomethacin was used as an internal standard.

Results and Discussion

Inclusion Complexation *in Vitro*

Although we obtained the solid inclusion complex of ketoprofen with methyl- β -CD in

Fig. 1. Phase Solubility Diagram of Ketoprofen-Methyl- β -CD in Water at 30 °C

Fig. 2. Dissolution Profiles of Ketoprofen Powder and Its Physical Mixture with Methyl- β -CD in Water at 30 °C

●: ketoprofen-methyl- β -CD physical mixture (molar ratio; 1:1). ○: ketoprofen alone.

Fig. 3. Plasma Levels of Ketoprofen Following Oral Administration to Rats

Each point represents the mean $\pm$ S.E. of six rats. ●: ketoprofen-methyl- β -CD physical mixture (molar ratio; 1:1). ○: ketoprofen alone.

1:1 molar ratio from ether, unfortunately it suddenly changed to a pasty state in water. Therefore, the physical mixture was used throughout these experiments. Figure 1 shows the phase solubility diagram obtained for the ketoprofen-methyl- β -CD system in water at 30 °C. The solubility of ketoprofen increased linearly in this experimental range (A_L type⁵). The stability constant of the inclusion complex in water was estimated as 266 M^{-1} from the intercept and the slope in Fig. 1.⁵ At 0.1 M methyl- β -CD, the apparent solubility of ketoprofen was about 20 times that of ketoprofen alone. A similar excellent solubilizing effect was also reported for retinoic acid by Pitha *et al.*^{2d)}

Dissolution profiles of ketoprofen powder and its physical mixture with methyl- β -CD (molar ratio; 1:1) are shown in Fig. 2. The amount of methyl- β -CD corresponds to 0.0197 M methyl- β -CD concentration in Fig. 1. The addition of methyl- β -CD resulted in a higher dissolution rate of ketoprofen. Further, since it was found that the solubility limit was approximately attained within a few minutes in each sample, the physical mixture was compared with ketoprofen powder in the following *in vivo* studies.

In Vivo Absorption Studies

Figure 3 shows the plasma levels of ketoprofen after oral administration of the physical mixture or ketoprofen alone to rats. In the case of administration of the physical mixture, the maximum plasma level of $25.1 \pm 3.2 \mu\text{g/ml}$ was attained at 10 min after oral administration, and was about 2.7 times higher than that after administration of ketoprofen alone. The initial absorption rate of ketoprofen after administration of the physical mixture was about 2.8 times larger than that of ketoprofen alone, while the elimination rate constants were similar in both cases (about 0.08 h^{-1}). Consequently, higher plasma levels were maintained for a larger time in the ketoprofen-methyl- β -CD system. The $AUC_{0-19 \text{ h}}$ after administration of the physical mixture ($220.5 \mu\text{g} \cdot \text{h/ml}$) was 3.7 times that of ketoprofen alone. Although the blood level profile in the case of ketoprofen alone was different from that reported by Nambu *et al.*,⁶⁾ this may be attributed to species difference. The quantity of methyl- β -CD added in the *in vivo* studies corresponds to about 0.02 M methyl- β -CD concentration in Fig. 1. A large amount of methyl- β -CD should further improve the bioavailability. The enhanced bioavailability is considered to be mainly due to a high dissolution rate,⁷⁾ i.e., high drug solubility in the case of the ketoprofen-methyl- β -CD system.

Hikal investigated the effect of polysorbate 80 on the partition coefficient of phenobarbital and its *in situ* intestinal absorption in rats, and concluded that polysorbate 80 above the critical micelle concentration affected the drug absorption across the lipid barrier portion of the biological membrane.⁸⁾ As methyl- β -CD has surface-active properties and acts like a micelle *in vitro*,¹⁾ it might be expected to facilitate drug absorption through a membrane. Furthermore, Szabo *et al.* reported methyl- β -CD was absorbed from the intestine in rats, though slowly.⁹⁾ However, we did not establish whether the inclusion complexation of ketoprofen with methyl- β -CD affected the membrane transfer.

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