# PROLONGED RELEASE OF DRUG FROM TRIACETYL-β-CyD COMPLEX FOR ORAL AND RECTAL ADMINISTRATION

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## ABSTRACT

Triacetyl-β-cyclodextrin (TA-β-CyD), a hydrophobic cyclodextrin derivative, that is insoluble in water, was used to form a complex with flufenamic acid (FA). FA-TA-β-CyD complex formation was demonstrated by differential scanning calorimetry and powder X-ray diffractometry. The release rate of FA from the FA-TA-β-CyD complexes in phosphate buffer pH 6.8 was significantly retarded compared to that of FA from the FA and glucose mixture. When the FA-TA-β-CyD complexes were administered directly into the intraduodenal lumen, the plasma concentration of FA remained at a plateau level (10-18 μg/ml) for 6-8 h. An increased mean residence time of FA following FA-TA-β-CyD complexes administration was observed. These results indicate that TA-β-CyD may serve as a hydrophobic carrier in prolonged-release preparations of FA.

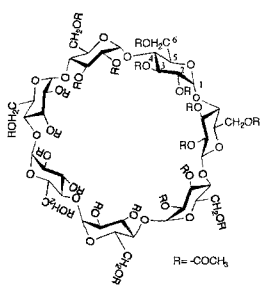
## 1. INTRODUCTION

Cyclodextrins (CyD), which can include many kinds of molecules within their cavities, are now being widely applied to pharmaceutical formulations to achieve improvements in low solubility, dissolution rate, stability, and the bioavailability of drugs.[1)] Hydrophobic CyD derivatives, such as ethylated and peracylated β-CyDs, have been employed in attempts as slow release carriers for water-soluble drugs to improve the release rate of the drugs.[2)] FA used as a model drug is poorly soluble in water and a short biological half-life in rats. The aim of this study was to evaluate the pharmaceutical applications of TA-β-CyD as a slow-release carrier for FA, compared to the use of glucose as a non-complex excipient.

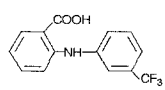
## 2. MATERIALS AND METHODS

**2.1 Materials** TA-β-CyD (molar substitution 3, purity > 99.9%) was donated by Ensuiko Sugar Refining Co. (Japan). FA was purchased from Wako Pure Chemicals Co. (Japan). Scheme I is shown the structure TA-β-CyD and FA.

**Scheme I Structure of TA-β-CyD and FA used in this study**




**Triacetyl-β-Cyclodextrin** Molecular Weight : 2018




**Flufenamic acid**

Molecular Weight : 281.24

**2.2 Preparation of Solid Complexes** Complexes of FA with TA-β-CyD at various molar ratios (1:1, 1:2, 1:3; FA-TA-β-CyD) were prepared by a kneading method using ethanol as a solvent.[3]

**2.3 Differential Scanning Calorimetry (DSC) and Powder X-Ray Diffraction** Complex formation was studied by DSC, using a Shimadzu DSC-50 (Shimadzu Corp.) with DSC crimp cell (sample size 2 mg, heating rate 5 °C/min). The powder X-ray diffraction pattern was determined with a MXP 3VA diffractometer (MAC Science Co.Ltd.).

**2.4 *In Vitro* Release Study** The release rate of drug from the FA-TA-β-CyD complexes in isotonic phosphate buffers pH 6.8 was measured by the dispersed amount method.

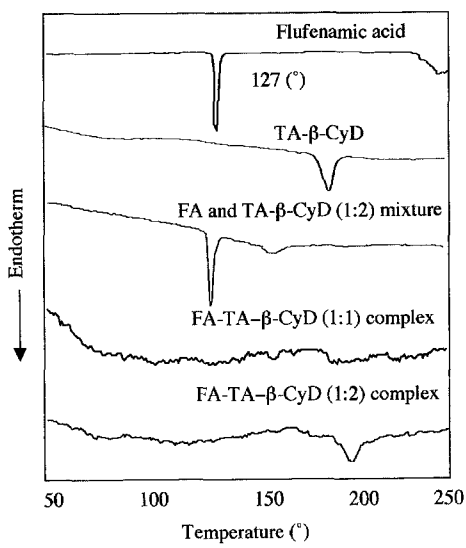
**2.5 Absorption Experiment** The absorption experiments were carried out with male Wistar rats (240-260g). The small intestine was exposed, and the duodenal segment was cut, and silicon tubing was inserted. The FA and TA-β-CyD mixture or the FA-TA-β-CyD complexes (equivalent to 2.81 mg FA) were administered directly into the intraduodenal lumen with a syringe through the silicone tubing and the remaining drug in the syringe was washed out twice with 0.5 ml isotonic saline. Rectal absorption of FA was carried out after insertion a suppository including the FA and TA-β-CyD mixture and the FA-TA-β-CyD complexes. At appropriate intervals for up to 10 h, blood samples were collected from the femoral artery.

**2.6 Analytical Method** FA *in vitro* release was determined spectrophotometrically at 235 nm. FA in plasma was measured by HPLC according to the method of Dusci and Hacket.[4]

## 3. RESULTS AND DISCUSSION

**3.1 Interaction Behavior of TA-β-CyD in the Solid State** The interaction behavior in the solid state was investigated by DSC. The molar ratio of the complex between FA and TA-β-CyD obtained by DSC was found to be 1:1. Figure 1 shows a typical example of the DSC thermogram curves of the FA and TA-β-CyD mixture and the FA-TA-β-CyD complexes. The DSC thermogram of the FA and TA-β-CyD mixtures showed an endothermic melting peak around 127°C, corresponding to the melting peak of the free FA, and the mixture (1:2) was broadened. The FA-TA-β-CyD complex(1:1) showed no endothermic peaks, due to the melting of both components. Further, the diffraction peaks of FA also disappeared on complex formation (1:1).

Fig.1 Differential scanning calorimetry of FA, TA-β-CyD, FA and TA-β-CyD mixture and FA-TA-β-CyD complexes

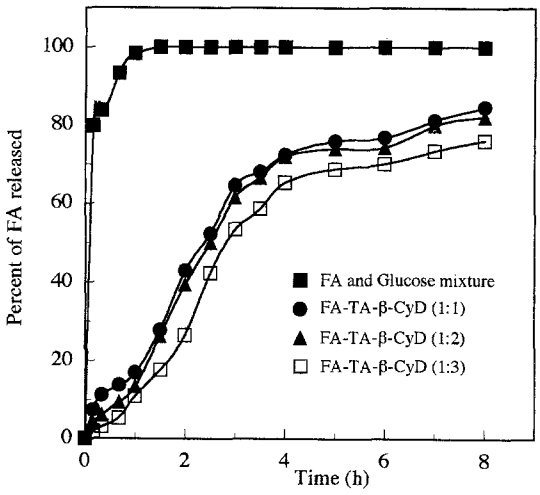



**3.2 Release Rate of FA from TA-β-CyD Complexes** The release rate of FA from the drug-glucose mixture was very fast, due to the high solubility in phosphate buffer pH 6.8, as shown in Fig.2. The FA-TA-β-CyD complexes released the drug very slowly and the release profiles of the drug from the complexes consisted of faster and very slow phase. The faster release in the initial stage depended on the free FA in the preparations, while the slower release was due to the release of FA from the complexes.

**3.3 Absorption Experiments** The

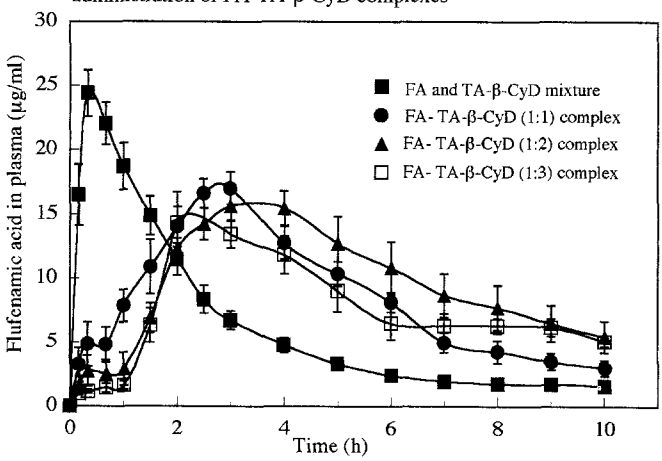
plasma concentration of FA versus time curves obtained after the intraduodenal administration of powder containing either the FA and TA-β-CyD mixture or the FA-TA-β-CyD complexes (equivalent to 2.81 mg of FA) to rats is shown in Fig. 3. When the equivalent doses of FA were administered the FA and TA-β-CyD mixture and the complexes, the intestinal absorption of FA in FA and TA-β-CyD mixture was very fast. On the other hand, the complexes did not show a sharp peak plasma concentration, but produced a prolonged plateau plasma level of FA for 6-8 h. Furthermore, the plasma levels of FA after administration of suppository including FA-TA-β-CyD complex (1:2) was similar behavior with that of FA intraduodenal administration of the complex.

Fig. 2 Dissolution profiles of FA and its TA-β-CyD complex in pH 7.4 isotonic phosphate buffer at 37℃




The pharmacokinetic parameters obtained from the data , where the area under the plasma concentration-time curves ($AUC_{0-10}$), the mean residence time (MRT) in the systemic circulation, and the variance of residence time (VRT). The $AUC_{0-10}$ values after administration of the complexes in the powder form were slightly lower than those of the FA solution and the glucose mixture following intraduodenal administration. However, there was no significant difference in absolute bioavailability between i.v. administration (100 %) and the drug TA-β-CyD mixture (90 %) or the complexes (1:1; 86 %, 1:2; 92 %, 1:3; 84 %). The MRT values after administration of the complex (1:2) were 2.2-fold and 2.0-fold those seen with the i.v. administration and with intraduodenal administration, respectively of the FA solution.

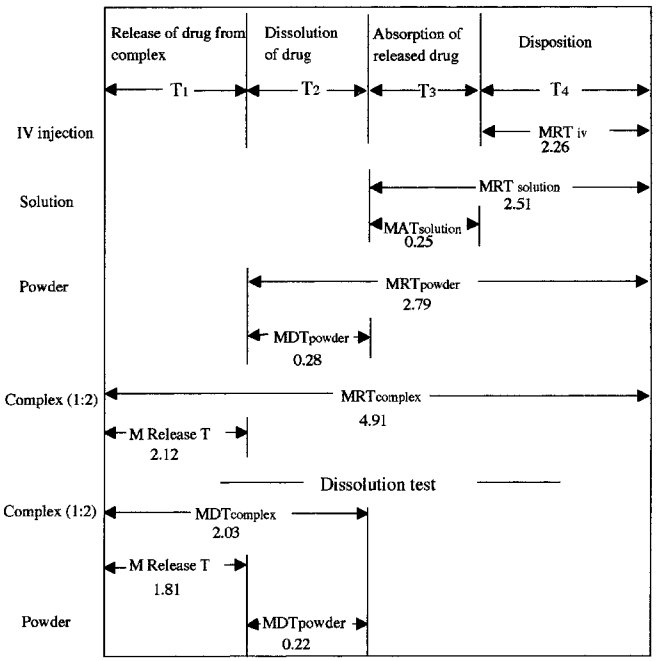
Fig. 3 Plasma concentration time curves of FA after intraduodenal administration of FA-TA-β-CyD complexes




Scheme II shows the MRT, the mean absorption time (MAT), the mean dissolution time (MDT), and the mean release time calculated by moment analysis.[5] The MRT of the FA-TA-β-CyD com-

plex ($MRT_{complex}$) was 4.91 h, and it consisted of $T_1+T_2+T_3+T_4$, where $T_1$ is the mean release time from the complex, $T_2$ is the mean time for the dissolution of drug, $T_3$ is the mean time for the absorption of the dissolved drug, and $T_4$ is the mean time for the elimination of drug from the body, shown as $MRT_{iv}$. The mean release time of the complex, 2.12 h *in vivo* experiments, was estimated by subtracting the values for the mean $MDT_{powder}$, $MAT_{solution}$, and $MRT_{iv}$ from the mean $MRT_{complex(1:2)}$ value. The mean release time of the complex in *in vitro* experiments was 1.81 h, similar to the value in the *in vivo* experiments. Thus, the increase in MRTcomplex value after the intraduodenal administration of the FA-TA-β-CyD complex (1:2) was due to the retarded release of the drug from the complex in the intestinal lumen, indicating that the release of FA from the complex was the rate-limiting step.

Scheme II Illustration of the meaning of the MRT, MAT, MDT and Mean Release Time




## 4. CONCLUSION

The present study show that an initial high plasma peak concentration does not occur after the administration of FA-TA-β-CyD complexes, suggesting that the side effects may also be reduced. The form of the FA-TA-β-CyD complex used here appears to be appropriate for practical clinical applications that would result in reduced side effects of the drug and prolonged action.

## REFERENCES

[1] Chow D.D. and Karara A.H., Characterzation, dissolution and bioavailability in rats of ibuprofen-β-cyclodextrin complex system, *Int.J.Pharm.*, **28**, 95-101 (1986).

[2] Uekama K., Horikawa T., Yamanaka M., Hirayama F., Peraclated β-cyclodextrins as novel sustained-release carrier for water-soluble drug, molsidomine, *J.Pharm.Pharmacol.* **46**, 714 -717 (1994).

[3] Tsuruoka M., Hashimoto T., Seo H., Ichimasa S., Ueno O., Fujinaga T., Otagiri M., Uekama K., Enhanced Bioavailability of phenytoin by β-cyclodextrin complexation,*Yakugaku Zasshi*, **101**, 360-367 (1981).

[4] Dusci L.J. and Hackett L.P., Determination of some antiinflammatory drugs in serum by high-performance liquid chromatography, *J.Chromatogr.*, **172**, 516-519 (1979).

[5] Tanigawara Y., Yamaoka K., Nakagawa T., Uno T., Momeny analysis for the separation of mean in vivo disintegration, dissolution, absorption, and disposition time of ampicillin products, *J.Pharm.Sci.*, **71**, 1129-1133 (1982)