CRYSTALLIZATION AND POLYMORPHIC TRANSITION BEHAVIOR OF CHLORAMPHENICOL PALMITATE IN 2-HYDROXYPROPYL-β-CYCLODEXTRIN MATRIX

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ABSTRACT

Chloramphenicol palmitate (CPP) was converted to an amorphous complex when spray-dried with 2-hydroxypropyl-β-cyclodextrin (HP-β-CyD), and no crystallization of CPP was observed for at least 2 months under the storage condition of 50 ℃ and 50% relative humidity. The dissolution rate of CPP/HP-β-CyD complex in aqueous HCO-60 solution was much faster than CPP polymorphs (complex > metastable forms (B and subB) > stable form (A)), which was reflected in the *in-vivo* absorption behavior of CPP following oral administration in dogs.

1. INTRODUCTION

It is important to control the crystallization and polymorphic transition of solid drugs, since crystal modifications affect various pharmaceutical properties, such as stability, solubility, dissolution rate and bioavailability of drugs. Since cyclodextrins (CyDs) can improve various pharmaceutical properties of drug molecules, they can serve as multi-functional drug carriers. From a practical point of view, amorphous CyDs such as 2-hydroxypropyl-CyDs are useful for the control of solid properties of poorly water-soluble drugs [1], because they convert crystalline drugs to amorphous complexes which are usually water-soluble. In this study, the crystallization and polymorphic transition behavior of chloramphenicol palmitate (CPP) in HP-β-CyD matrix was investigated.

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2. MATERIALS AND METHODS

Materials: CPP and HP-β-CyD (degree of substitution: 4.8) were donated by Sankyo Co. Ltd. (Tokyo, Japan) and Nihon Shokuhin Kako Co. (Tokyo, Japan), respectively. Chloramphenicol (CP) was purchased from Nakalai Tesqe (Tokyo, Japan).

Preparation of CPP polymorphs and CPP/HP-β-CyD complex:: CPP polymorphs (Forms A, B and C) were prepared according to the methods reported [2]. The complex of CPP with HP-β-CyD was prepared by the spray-drying method, *i.e.*, CPP and HP-β-CyD in a 1:2 molar ratio were dissolved in CH_2Cl_2-EtOH (1:1.2 %v/v) and subjected to spray-drying, using a Pulvis GA32 Yamato spray-dryer (Tokyo, Japan) under the following conditions: air flow rate, 0.45 $cm^3 min^{-1}$; air pressure, 1.0 $kgf\ cm^{-2}$; inlet and outlet temperatures, 85 and 55 ℃, respectively.

***In-vivo* absorption studies:** The sample (equivalent to 125 mg CPP) wrapped in a wafer was orally administered along with water (100 ml) to fasted beagle dogs (weight: 9-11 kg). Blood samples (1 ml) was collected from vengular vein using an injection syringe with heparin, and centrifuged (1000 g) for 10 min. CP in plasma was determined by high-performance liquid chromatography.

3. RESULTS AND DISCUSSION

The CPP/HP-β-CyD system showed a typical Ap-type [3] phase solubility diagram, whereas the parent β-CyD system showed a mixed Ap/Bs-type diagram with an ascending curvature at low β-CyD concentration (< about 9×10^{-3} M). The stoichiometry of the solid CPP/parent β-CyD complex was 1:2 (guest:host) molar ratio, and the stability constants of 1:1 and 1:2 complexes were 1900 M^{-1} and 4500 M^{-1} for the parent β-CyD complex and 1200 M^{-1} and 3400 M^{-1} for the HP-β-CyD complex, respectively. When CPP was spray-dried in the absence of additives, a metastable CPP (Form subB) was exclusively formed, which has exothermic and endothermic peaks at 64 ℃ and 88 ℃ due to the transition to the other metastable CPP (Form B) and the melting of Form B, respectively, in DSC curves. Form subB was easily converted to Form B with a half-life of 30 min at 50 ℃ and 50 % relative humidity (R.H.). On the other hand, CPP was converted to an amorphous complex when spray-dried with HP-β-CyD and no crystallization of CPP was observed for at least 2 months under the above storage condition, and only 7.2

% crystallization to Form B after 6 months. When the complex was stored for 2 weeks even at a severe condition of 80 ℃, 75 %R.H., it converted to a stable CPP (Form A) only in small amounts (0.7 %).

Figure 1 shows the dissolution profiles of the CPP/HP-β-CyD complex and CPP polymorphs (Forms subB, B and A) in 50 %v/v isopropanol/water and 0.01 %w/v HCO-60/water solutions. The initial dissolution rate of the complex in the isopropanol solution was rather slower than those of CPP polymorphs (rate: Form subB > Form B ~ complex > Form A), although the total CPP released from the complex was larger after 1 h. On the other hand, the complex dissolved rapidly in the aqueous HCO-60 solution, and the amount of dissolved CPP was much larger than those of the polymorphs (rate and amount: complex >> Form B > Form subB > Form A). The rapid dissolution of the complex in the aqueous HCO-60 solution may be due to its high wettability to water, compared with Form subB. Figure 2 shows the plasma level of CP *vs* time curves obtained after oral administration of the complex or CPP polymorphs to dogs. The plasma level of CP was enhanced by the administration of CPP/HP-β-CyD complex, and no ageing effect on the absorption of CPP was observed for the HP-β-CyD complex, even after 6 months at 50 ℃, 50 %.R.H.

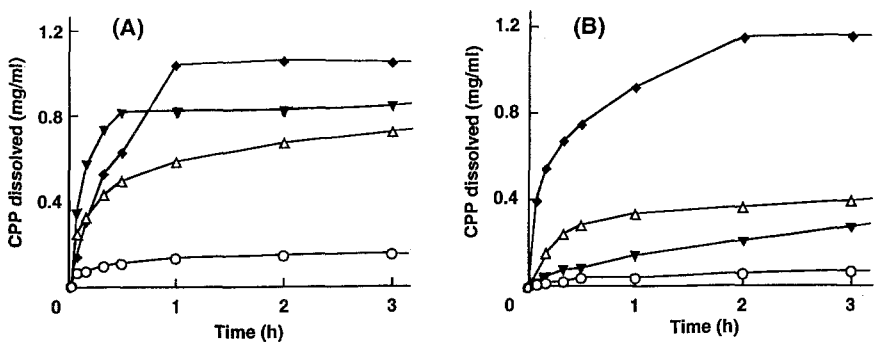

Fig. 1 Dissolution Profiles of CPP from Various Preparations (equivalent to 62.5 mg CPP) in 50 %v/v Isopropanol/Water Solution at 25 ℃ (A) and 0.01%w/v HCO-60/Water Solution at 37 ℃ (B), Measured by Dispersed Amount Method at 91 rpm
○ : Form A, △ : Form B, ▼ : Form subB, ◆ : HP-β-CyD complex.
Each point represents the mean of 2-4 experiments.

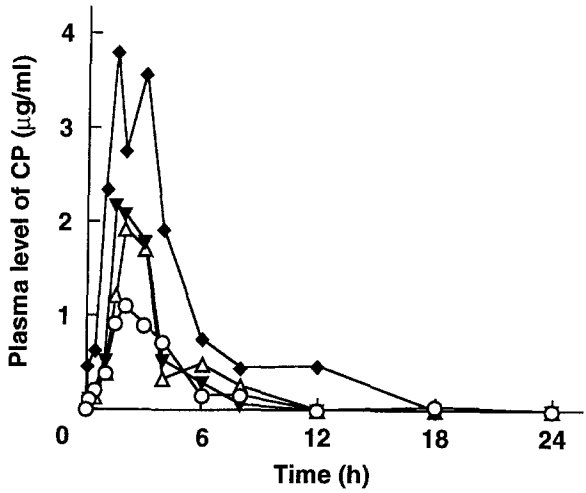

Fig. 2 Plasma Levels of CP after Oral Administration of CPP/HP-β-CyD Complex (equivalent to 125 mg/body CP) or CPP Polymorphs in Dogs
○ : Form A, △ : Form B, ▼ : Form subB, ◆ : complex.
Each point represents the mean of 3 dogs.

4. CONCLUSION

The present results suggest that HP-β-CyD is useful for the preparation and stabilization of amorphous CPP, and will provide a rational basis for the design of formulation and storage conditions in solid dosage forms of poorly water-soluble drugs.

REFERENCES

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