Improvements of Dissolution Characteristics and Chemical Stability of 16,16-Dimethyl-*trans*-Δ^2-prostaglandin E_1 Methyl Ester by Cyclodextrin Complexation

KANETO UEKAMA *x, **FUMITOSHI HIRAYAMA** *, **YOSHITSUGU YAMADA** *, **KOJI INABA** ‡, and **KEN IKEDA** §

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Abstract □ Inclusion complexation of 16,16-dimethyl-*trans*-Δ^2-prostaglandin E_1 methyl ester (I), which is effective in early pregnancy termination, with cyclodextrins in water was ascertained by a solubility study. A solid complex of I-β-cyclodextrin in a 1:2 molar ratio was obtained, and its dissolution behavior and chemical stability were examined. The results indicated that the complex may have great utility as a rapidly dissolving form of I with prolonged storage time.

Keyphrases □ Prostaglandin E_1 derivatives—cyclodextrin complexation, dissolution, stability □ Cyclodextrin—complexation with prostaglandin E_1, dissolution, stability □ Complexation—prostaglandin E_1 with cyclodextrin, dissolution, stability

Some naturally occurring prostaglandins such as prostaglandins E_1, E_2, and $F_{2\alpha}$ (dinoprost) have clinical applications (1). 16,16-Dimethyl-*trans*-Δ^2-prostaglandin E_1 methyl ester[1] (I), a prostaglandin E_1 derivative, induced uterine contraction in rats with an efficacy 10 times that of prostaglandin $F_{2\alpha}$ (2, 3). This compound is more acceptable for early pregnancy termination than prostaglandin $F_{2\alpha}$ because it produces fewer side effects. However, the solubility and chemical instability of the prostaglandins, including I, in aqueous solution have limited dosage form development and resulted in a substantial challenge to the pharmaceutical scientist.

Cyclodextrins form inclusion complexes with various drug molecules (4–8). Since I is essentially a methyl ester of long chain unsaturated fatty acids, the relatively hydrophobic cyclodextrin cavity is expected to attract I as an adequate guest molecule (9–11). Thus, the present study dealt with inclusion complexation of I with α- and β-cyclodextrins in anticipation of improved solubilization and stabilization of I.

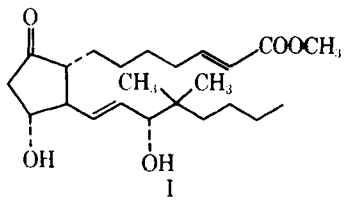
EXPERIMENTAL

Materials—Compound I[1], α-cyclodextrin[2], and β-cyclodextrin[2] were used as supplied. All other materials and solvents were analytical reagent grade. Deionized, double-distilled water was used.

Solubility and Dissolution Studies—Solubility measurement and analytical methods for I were essentially those reported previously (9).

Table I—Thermal Stabilities of I and Its β-Cyclodextrin Complex at 60°

Compound	Decomposition of I, % 1 Day	3 Days	8 Days	14 Days
I	2.2	8.8	30.2	54.0
Complex	0.1	0.5	2.5	4.0



I

The dissolution behaviors of I and its β-cyclodextrin complex in water were compared at the same I concentration according to the dispersed amount method (12). A 120-mg sample of a I-β-cyclodextrin complex as a 100–200-mesh powder was weighed and put in a dissolution cell. Because I is a viscous oil, an ether solution containing 18 mg of I was placed in the dissolution cell and evaporated to dryness. The dissolution medium (25 ml) was maintained at 25° and stirred at 93 rpm. At an appropriate interval, 0.5 ml of solution was sampled by a pipet with a cotton filter. The assay procedure for I was the same as that used in the solubility study (9).

Stability Studies—Stability tests for I and its β-cyclodextrin complex were conducted at 60° in a moisture-free environment. Intact I was quantitatively determined by high-performance liquid chromatography (HPLC). The liquid chromatograph[3] (20-cm column[4]) was operated at a flow rate of 0.5 ml/min, and the mobile phase consisted of acetonitrile–methanol–water (2:8:3). Under these conditions, the disappearance of the I peak was followed by a UV detector[5] at 215 nm.

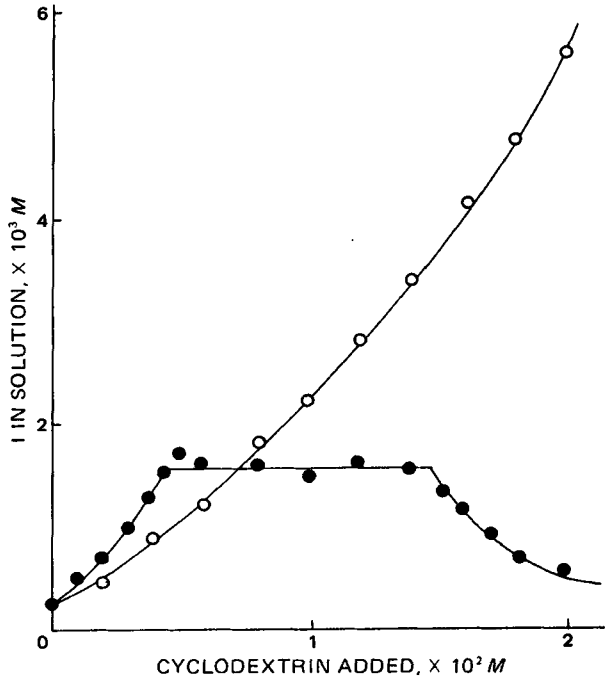


Figure 1—*Solubility of I as a function of cyclodextrin concentration in water at 25°. Key:* ○, *α-cyclodextrin; and* ●, *β-cyclodextrin.*

[1] 9-Oxo-11α,15α-dihydroxy-16,16-dimethyl-2-*trans*,13-*trans*-prostadienoic acid methyl ester (ONO-802). Supplied by Ono Pharmaceutical Co. Ltd., Osaka, Japan.

[2] Teijin Ltd., Tokyo, Japan.

[3] Model FLC-A700, Jasco, Tokyo, Japan.

[4] Packed with LiChrosorb RD-18, E. Merck, Darmstadt, West Germany.

[5] Model UVIDEC-1M, Jasco, Tokyo, Japan.

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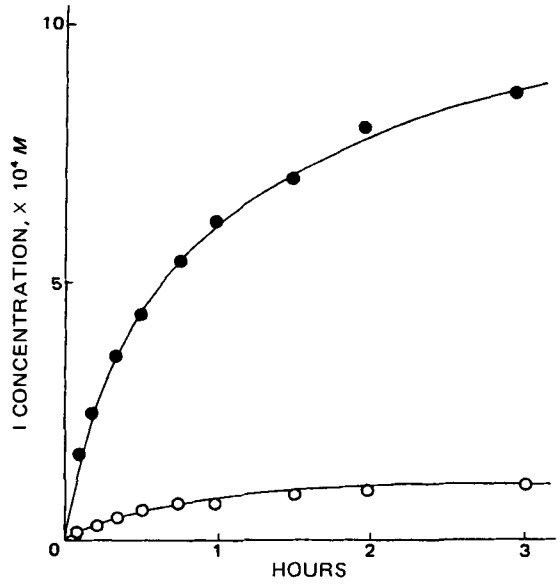

Figure 2—*Dissolution behavior of I* (○) *and its β-cyclodextrin complex* (●) *at the same I concentration in water at 25°.*

RESULTS AND DISCUSSION

The equilibrium phase solubility diagrams obtained for I with α- and β-cyclodextrins in water are shown in Fig. 1. In both of these systems, the solubility of I increased following cyclodextrin addition, and the solubility curves of α- and β-cyclodextrins can be generally classified as types A_p and B_s (13), respectively. According to Higuchi and Kristiansen (14), the stability constants for 1:1 (SL) and 1:2 (SL_2) complexes (S = I, and L = cyclodextrin) were calculated from ascending positive curvatures in Fig. 1. The stability constants for α- ($K_{1:1}$ = 820 M^{-1}, and $K_{1:2}$ = 260 M^{-1}) and β- ($K_{1:1}$ = 1600 M^{-1}, and $K_{1:2}$ = 370 M^{-1}) cyclodextrin complexes were obtained.

The β-cyclodextrin system deposited a crystalline complex of I–β-cyclodextrin (1:2) at high β-cyclodextrin concentrations. Stoichiometry based on the data in the plateau region (13) in Fig. 1 was in good agreement with that obtained by isolation and analysis of the crystalline complex. In sharp contrast, the α-cyclodextrin system did not give any solid complex, a smaller cavity size apparently allowing little penetration of the bulky guest molecule.

The dissolution behavior and chemical stability of the isolated β-cyclodextrin complex were examined. The dissolution rate of the complex in powder was extremely large compared with that of I in water (Fig. 2), indicating an improved bioavailability. As shown in Table I, the decomposition of I was significantly retarded by inclusion complex formation. Thus, the increased dissolution rate, together with improved chemical stability, suggested that the β-cyclodextrin–I complex may have great utility in the development of fast dissolving dosage forms with prolonged storage time.

Furthermore, thermal gravimetric analysis[6] showed that the volatility of I was extremely depressed by binding to β-cyclodextrin. The crystallinity of the complex should facilitate drug formulation, which is difficult with uncomplexed I because it occurs as a viscous oil.

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[6] Model DT-20B thermal analyzer, Shimadzu, Osaka, Japan.