DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(1), 63-75 (1988)

IMPROVEMENT OF DISSOLUTION CHARACTERISTICS OF PIROMIDIC ACID BY DIMETHLY - β - CYCLODEXTRIN COMPLEXATION (★)

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ABSTRACT

Inclusion complex formation of piromidic acid (PA) with dimethyl -β- Cyclodextrin (DM-β-CyD) in aqueous solution and in solid state was confirmed by solubility method, power x-ray diffractometry. The apparent stability constant, Kc, of the complex was estimated as 244 M^{-1}. The stoichiometry of complex was given as the ratio 1:2 PA to DM-β-CyD.

(★) Presented partly in the 3rd International Pharmaceutical Technology Symposium, Ankara, Sempt. 1986.

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The inclusion complex was prepared two different methods, coprecipitation an neutralization.

The dissolution rate of PA/DM-β-CyD complexes were dissolved much more rapidly than intact PA.

INTRODUCTION

Priomidic acid (PA), 5,8 dihydro-8-ethly-5-oxo-2-pyrrolido pyrido [2,3-d] pyrimidine-6- carboxcyclic acid, is a pyrido pyrimidine derivative, a congener of nalidixic acid. PA is widely used as antibacterial activity pathogens (1,2).

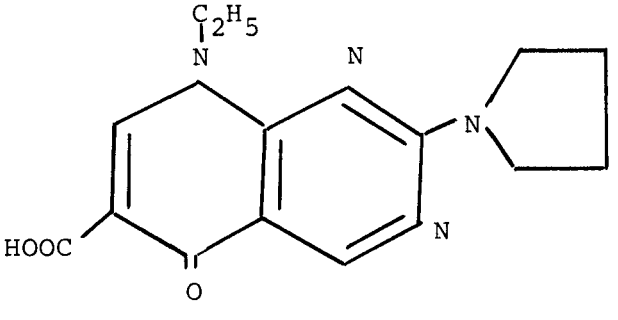

Chart 1. Chemical Structure of Piromidic Acid

Cyclodextrins (CyDs) or cycloamyloses are cyclic oligosaccharides containing 6(α-CyD), 7(β-CyD) or 8(γ-CyD) α-(1,4) linked glucose units. The important structural features of these compounds are their toroid or doughnut spape, their hydrophilic faces (3,4).

Recently, the chemically modified cyclodextrins have received considerable attention because their physicochemical properties and inclusion behaviors are different from those of the natural cyclodextrins. For example, the methylated β-cyclodextrins such as heptakis (2,6-di-*o*-methyl)-β-cyclodextrin (DM-β-CyD) and heptakis (2,3,6-tri-*o*-methyl)-β-cyclodextrin (TM-β-CyD), are exremely soluble in water (more than 30 $w/_v$ % at 25 ^oC), and they interact with a variety of drug molecules (5).

Cyclodextrins have been extensively employed to increase the solubility, dissolution rate, and absorption characteristics of poorly-soluble drugs (6,7, 8).

The present study deals with inclusion complexation of piromidic acid with dimethyl-β- cyclodextrin in anticipation of improving solubility and dissolution behaviour of the piromidic acid.

Inclusion complex formation of PA with DM-β-CyD in aqueous solution and in solid state was ascertained by solubility method, powder x-ray diffactometry, differential scanning calorimetry (DSC) and proton nuclear magnetic resonance (^1H-NMR) (9).

EXPERIMENTAL

Materials: "Piromidic acid" (Panacid) and cyclodextrins were supplied from Dainippon pharmaceutical Co, and

Nippon Shokuhin Kako Ltd., (Japan) respectively. All other materials and solvents were of analytical reagent grade.

Apparatus: The ultraviolet (UV) spectra, Hitachi 323, The powder x-ray diffactometer, Rigaku Dengi Geigerflex model D-2 (Japan).

METHODS

Solubility Studies: Solubility measurements were carried out according to Higuchi et.al., the method (10). Excess amounts of PA were added to solutions at pH 7.4 containing various concentrations of CyD polymers and shaken 37±0,5 ^{o}C. After equilibrium was attained (approximetely 4 days) an aliquot was filtered through a Toyo TM-2 membrane filter (0.45 μm). A portion of the sample was adequately diluted and analyzed using a spectrophotometer at 273 nm for concentration of piromidic acid.

Preparation of Solid Complexes: The solid complexes were prepared by two different methods, coprecipitation and neutralization method (Chart. 2) Amounts were calculated from the descending curvature of the phase solubility diagram (Fig. 2). These powder corresponded to 1:2 PA/DM-β-CyD complex.

The physical mixture of PA with DM-β-CyD in 1:2 molar ratio was perpared by simple blending a ceramic mortar.

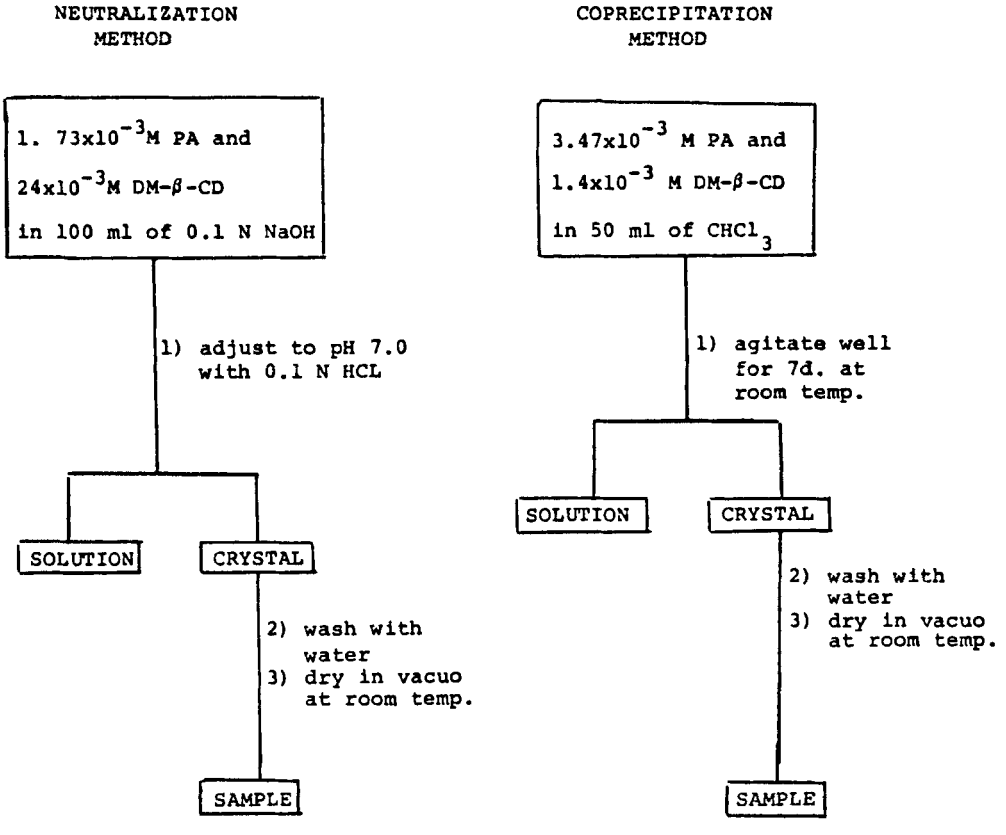

Chart 2. Methods for Mass Preparation of Inclusion Complex

Powder x-Ray Diffraction Study: The powder x-ray diffractometry was carried out using the diffractometer under the following conditions; x-ray, Ni filtered Cu-K_α radiation; voltage 32,5 kv; current 30 mA; time constant 25; scanning speed 1°/min.

Dissolution Studies: Dissolution rates of piromidic acid from the inclusion complex were measured by the method of Nogami et al.,(11). In brief, the sample powder (150 mesh) of drug or its equivalent amount of the complex

was put into 50 ml of buffer solutions pH 1.2 and pH 7.5 in a dissolution cell which was kept at 37±0.5 °C and the dissolution medium was filtered through a membrane filter (0.45 μm), dilüted and assayed spectrophotometricaly.

RESULTS AND DISCUSSION

Phase solubility diagrams obtained for PA with β-CyD and DM-β-CyD are shown in figure 1 and figure 2. The differences in the solubility curves are substantiated and obvious. The solubility of piromidic acid with increasing concentration β-CyD, showing Ap-type phase-solubility diagrams (10).

On the other hand the DM-β-CyD system showed a typical Bs-type solubility curve with precipitation of microcrystalline PA/DM-β-CyD complex (1:2 molar ratio) occuring at high DM-β-CyD concentrations.

Calculation of the stoichiometry of the complex based on the data in the plateu region in Figure 2 was in agreement with that obtained by isolation and analysis of the crystalline complex. In sharp contrast β-CyD systems did not yield any solid complex.

In cases, the magitude of apparent stability constant (Kc) values increased in order of DM-β-C-D > β-CyD. The Kc values of DM-β-CyD and β-CyD were found to be 244 M^{-1} and 77.5 M^{-1}, respectively.

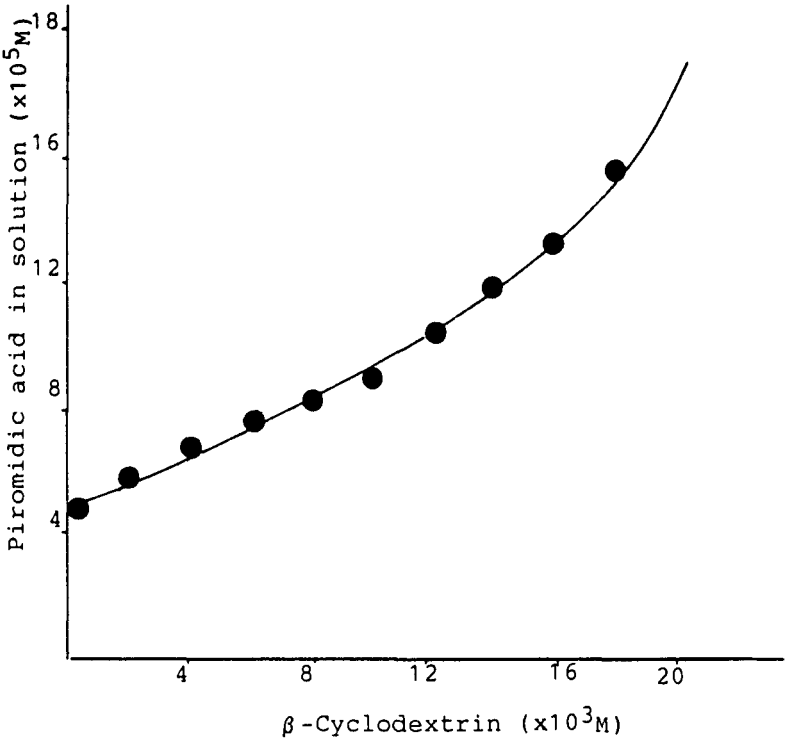

Fig.1. Phase Solubility Diagram of Piromidic acid-β-cyclodextrin System in Buffer Solution pH 7.4 at 37 °C

The ordinary method, e.g., the coprecipitation method based on phase solubility and the kneading method, are not appropriate to obtain PA/DM-β-CyD complex satisfactory efficiency and yield. However inclusion complex could be prepared easily the neutralizing procedure.

The principal advantages of neutralization method can be summarized as follows; a) the unnecessity of organic solvent, b) a good yield in a short operating time, and c) suitable for extension to manufacturing scale (12). Further, neutralization method is suitable

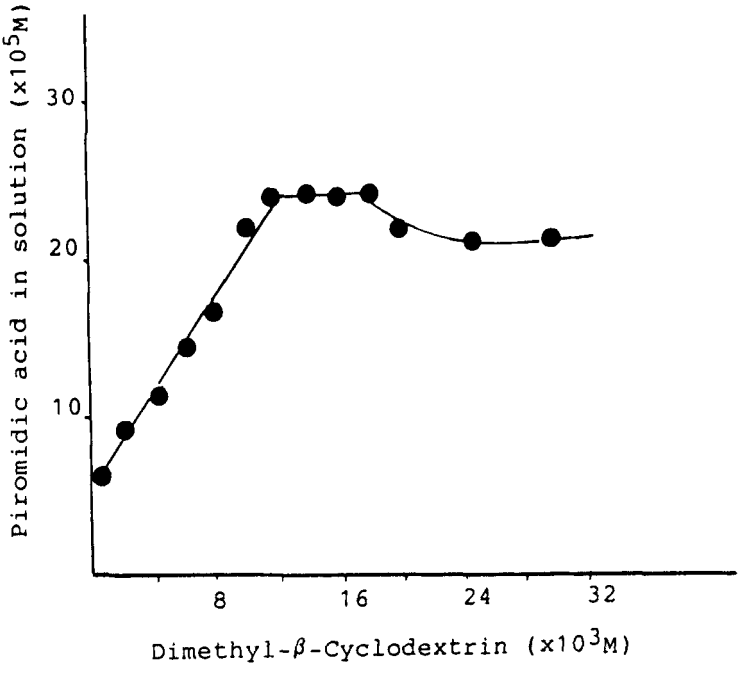

Fig.2. Phase Solubility Diagram of Piromidic acid-Dimethyl-β-cyclodextrin System in Buffer Solution pH 7.4 at 37 °C

for a preparation of complex with higher purity in short operating time.

Figure 3 shows the powder x-ray diffraction patters of the complexes prepared by two different methods in comparison with that of a physical mixture was found to be simple superposition pattern of the components, while that of the complex was apparently different, corresponding to a new solid phase. In addition, there was no difference in diffraction patterns among the complexes. These results indicate that PA interacted with DM-β-CyD to form an inclusion complex.

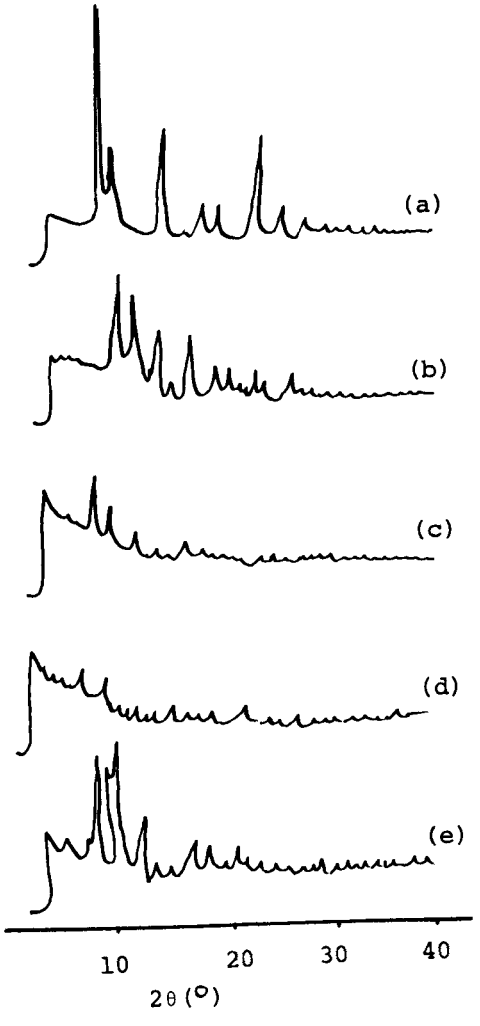

Fig.3. Powder X-Ray Diffraction Patterns of PA/DM-β-CyD System

(a), Intact PA; (b), Physical mixture of PA and DM-β-CyD; (c),Inclusion complex PA/DM-β-CyD (coprecipitation method); (d) Inclusion Complex PA/DM-β-CyD (neutralization method);(e), DM-β-CyD

Figure 4 and Figure 5 show the dissolution profiles of PA from DM-β-CyD complex and physical mixture and PA powders in pH 1.2 or pH 7.5 buffer solutions at 37±0.5 °C. It is evident that the rapidly than intact PA.

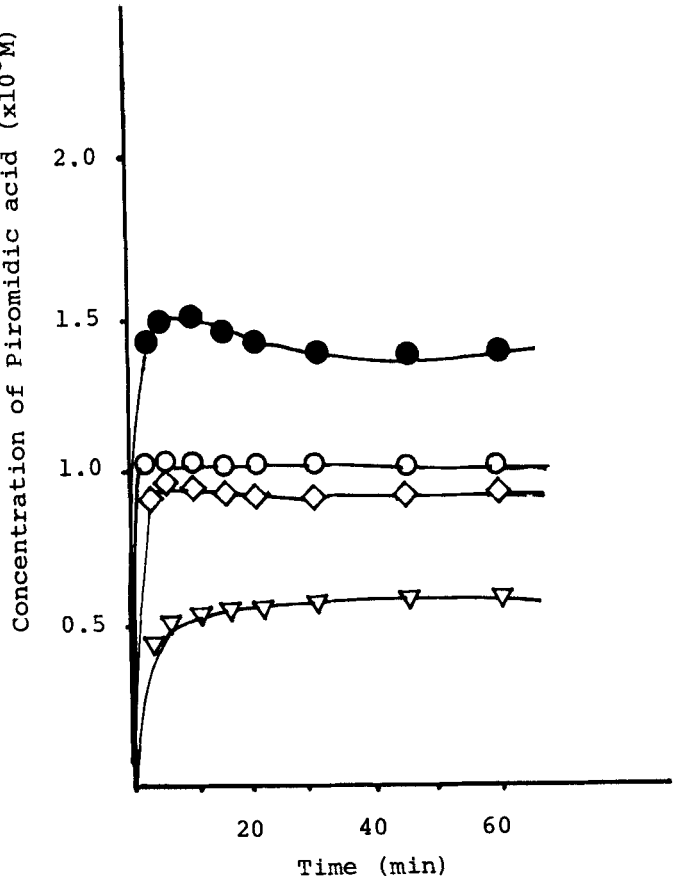

Fig.4. Dissolution Profiles of Piromidic acid and its DM-β-CyD complexes in pH 1.2 Buffer solution at 37 °C

▽, Intact PA, ◇, Physical mixture of PA and DM-β-CyD; ○, PA/DM-β-CyD inclusion complex (coprecipitation method); ●, PA/DM-β-CyD inclusion complex (neutralization med-hod).

The PA/DM-β-CyD complex prepared by neutralization method was dissolved larger than that of coprecipitation method. Also the dissolution profiles of PA in pH 7.5 larger than that the pH 1.2. This result dependent

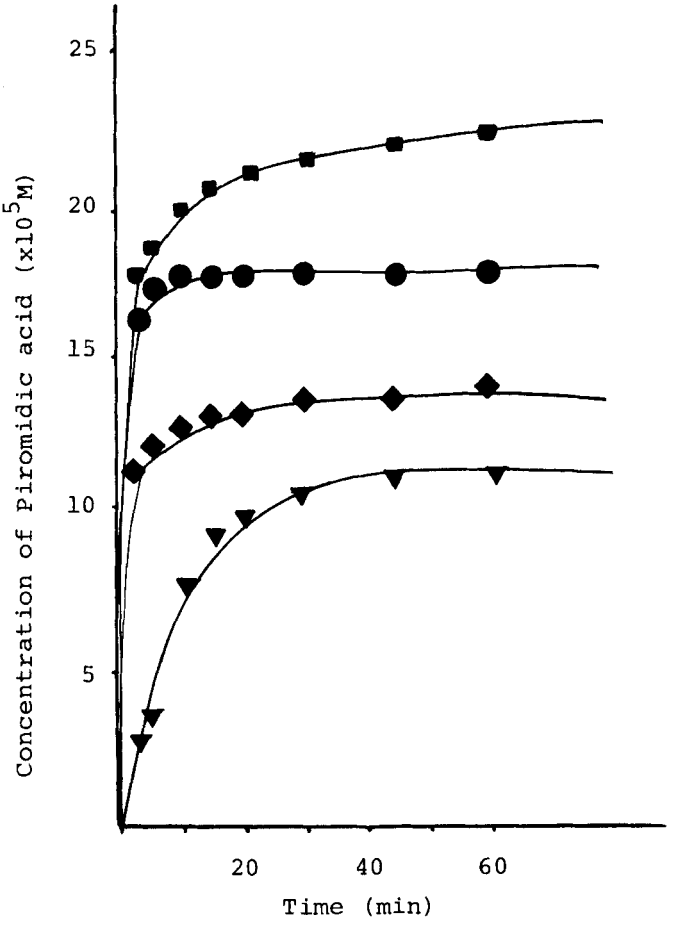

Fig.5. Dissolution Profiles of Piromidic acid and its DM-β-CyD complexes in pH 7.5 Buffer Solution at 37 °C

▼, Intact PA; ◆, Physical mixture of PA and DM-β-CyD; ●, PA/DM-β-CyD inclusion complex (coprecipitation method); ■, PA/DM-β-CyD inclusion complex (neutralization method)

on solubility properties of drug and due to the greater solubility of DM-β-CyD available for complexation.

The enhanced dissolution rate may be due to the increase in solubility and the decrease in crystallinity

of the drug by the inclusion complexation as expected from Figure 2 and Figure 3 respectively.

Thus, the remarkable increase in dissolution characteristics suggested that the complexed form of PA, particulary for DM-β-CyD, might improve bioavailability.

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