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COMMUNICATION

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Etodolac and Solid Dispersion with β-Cyclodextrin

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ABSTRACT

Etodolac/β-cyclodextrin (Eto/β-CD) dispersions were prepared with a view to study the influence of β-CD on the solubility and dissolution rate of this poorly soluble drug. Two systems were used: physical mixture of Eto/β-CD and kneading solid dispersion of Eto/β-CD. Physical characterization of the prepared systems was carried out by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), x-ray, and IR studies. The solubility and dissolution rate of Eto were increased with β-CD physical mixture as well as with Eto/β-CD kneading solid dispersion. However, enhancement was not statistically different among various cyclodextrin dispersions.

INTRODUCTION

Etodolac (Eto) ((±)-1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid) is a newly synthesized nonsteroidal anti-inflammatory drug (NSAID) with potent antiarthritic activity and weak ulcerogenic activity (1,2). Also, it is analgesic and an antipyretic agent. This drug has a very poor solubility in water that limits its use to solid dosage forms for oral administration. Cyclodextrins (CDs) are known to form an inclusion complex with many NSAIDs of appropriate molecular size and polarity in particular hydrophobic drug molecules. The resulting complex generally leads to an improvement in some of the properties of guest drugs, e.g., solubility, bioavailability and tolerability (3–5). Otherwise, the applicability of CD's inclusion complexes with high-dosage drugs (> 100 mg) in solid pharmaceutical formulations showed some practical limitation. The

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usually molar ratio CD–drug 1:1 results in relatively high weight of solid dosage forms (≥1g). From these observations the preparation of some dispersion forms with weight ratio drug–CD 1:1 looks more convenient.

The objectives of this study were to characterize some Eto/β-CD dispersions (physical mixture and kneading solid dispersion) regarding crystal structure and to investigate the influence of β-CD in dispersion Eto/β-CD on solubility and dissolution rate of Eto. For this purpose a comparative study of the dissolution rate of Eto was carried out on a physical mixture of Eto/β-CD versus kneading solid dispersion Eto/β-CD. To analyze the prepared products, selective physical determinations based on x-ray diffractometry, infrared (IR) spectroscopy, differential scanning calorimetry (DSC), and scanning electron microscopy (SEM) were used. Solubility diagrams and dissolution studies were also caried out.

MATERIALS AND METHODS

Materials

Etodolac (Eto) was donated by Srbolek (Beograd, Yugoslavia), β-Cyclodextrin (β-CD Kleptose®) was supplied by Roquette Freres (Lestrem, France). All other materials were of analytical reagent grade.

Methods

Preparation of Samples

Physical Mixture

The ground components Eto and β-CD in the same quantity (1:1 w/w) were mixed in a mortar and sieved through a 0.7-mm sieve.

Kneading Solid Dispersion

Kneading solid dispersion Eto and β-CD in the same quantity (1:1 w/w) were blended in a mortar and kneaded with an appropriate quantity of a water/ethanol mixture (1:1). The creamy product was dried at 70°C in order to maintain a suitable paste consistency. The paste was sieved (1.2 mm) and dried at room temperature until constant weight. The granules were sieved again and used for thermal analysis and dissolution tests.

Physicochemical Characterization

SEM

Samples of Eto, kneading solid dispersion Eto/β-CD, and physical mixture were examined by SEM, by using a Tesla BS 300 (CZ) scanning electron microscope with 20 kV accelerating voltage.

The surfaces of the sample for electron microscopy were previously made electrically conductive in a sputtering apparatus (Polaron Equipment Ltd., UK) by evaporation of gold.

DSC

Differential thermal analysis was performed using a thermal analyzer (Perkin-Elmer DSC-4) with a differential scanning calorimeter. All samples were heated at a scanning rate of 10°C min^{-1} under N_2 gas stream between 30° and 300°C.

Powder X-Ray Diffractometry

The physical state of Eto in various preparations was evaluated by x-ray diffraction. Powder x-ray diffractometry was carried out with a Philips x-ray diffractometer (PW 1820) using $CuK_{\alpha 1}$ radiation (1 = 15,418 × 10^{-10} m), a voltage of 40 × kV, and a current of 40 mA. The scanning rate was 6°/min over a 2θ range of 5–60°C chart speed 10 mm/min, and count range 1000 cps.

Infrared Spectroscopy

The IR spectra of samples were taken on an IR spectrophotometer (Perkin-Elmer 725) using the KBr disk technique.

Solubility Measurements

Phase solubility studies were carried out according to the Higuchi and Connors method (6). An excess amount of Eto (50 mg) was added to the aqueous solution of β-CD at various concentrations (from 3 mmol/1iter to 16 mmol/liter). The flasks were sealed and shaken at 25°C for 24 h. After equilibrium, the samples were filtered (0.45 μm filter) and properly diluted. The concentration of Eto dissolved was assayed spectrophotometrically (Perkin-Elmer, Lambda 17 UV/VIS spectrophotometer) at 278 nm.

Dissolution Studies

Dissolution rates from different Eto/β-CD mixtures were determined in 900 ml of phosphate buffer pH 7.2 (USP 23) at 37°C and at a rotation speed of 150 rpm. The USP 23 rotating basket apparatus (Erweka model DT6, Germany) was employed. An amount of each powdered sample equivalent to 200 mg Eto was put in

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a rigid gelatin capsule and was placed in the medium. The samples (3 ml) were withdrawn at various time intervals and filtered through a 0.22-μm filter. The volume in the vessel was replaced with pure pH 7.2 buffer after each sampling. The concentration of Eto dissolved in the medium was determined spectrophotometrically (Perkin-Elmer, Lambda 17 UV/VIS spectrophotometer) at 278 nm. The dissolution tests were carried out for 60 min.

RESULTS AND DISCUSSION

Solubility

The solubility of pure Eto in water is poor, but the literature gives no exactly data. In this study the solubility of Eto in water without β-CD was found to be about 0.0347 mM^{-1} (0.01 mg ml^{-1}). The influence of β-CD on Eto solubility was usually checked by phase solubility measurements (6) and the obtained results are presented in Fig. 1. The phase solubility profiles of Eto in β-CD aqueous solutions can be classified as being of the A_L type, as defined by Higuchi and Connors (6), showing linear increase with unchanged stoichiometry.

SEM

Fig. 2 presents the SEM photos of Eto, Eto/β-CD physical mixture, and Eto/β-CD kneading dispersion.

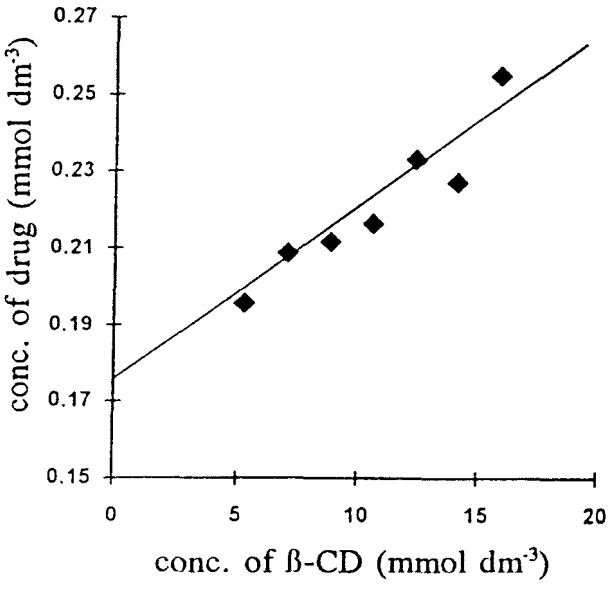

Figure 1. Phase solubility diagram of Eto/β-CD

The Eto crystal has a plato form [Figure 2(a)] and in a photo of Eto/β-CD physical mixture we can recognize the Eto-specific crystals and only part of the β-CD crystal [Figure 2(b)]. The morphology of particles of Eto/β-CD kneading dispersion are specific and original [Figure 2(c)]. The crystal has relatively cubic form with slippery layers and some recrystallized particles.

DSC

Thermograms of Eto, β-CD, their physical mixture, and kneading solid dispersion are shown in Fig. 3. Pure Eto exhibits endothermic peak at 147°C [Figure 3(a)] which represents melting point of the sample and is confirmed with literature data (7). The DSC curves of Eto/β-CD physical mixture [Figure 3(c)] show that a peak arises from Eto and slightly endothermic variates between 90 and 100°C in derivation from β-CD (water from β-CD). Figure 3(d) presents the DSC curve that was obtained from kneading solid dispersion of Eto/β-CD. Similar results were reported for diclofenac/β-CD physical mixture (5) and physical mixtures of norfloxacin/β-CD molecular ratios (1:1 or 1:2) (8).

IR Spectrophotometry

Fig. 4 demonstrates the IR spectra of pure Eto, β-CD, Eto/β-CD physical mixture, and their corresponding kneading solid dispersion. Physical mixtures of Eto/βCD and kneading solid dispersion of Eto/β-CD show spectra corresponding to a superposition of their parent products (Eto/β-CD).

X-ray Diffraction

X-ray powder diffraction patterns of Eto, β-CD, and their physical mixture and kneading solid dispersion are shown in Fig. 5. The pure Eto is of crystalline form as demonstrated by the sharp and intense diffraction peaks [Figure 5(a)]. X-ray powder diffraction patterns of Eto-β-CD physical mixture and kneading solid dispersion of Eto/β-CD showed several peaks corresponding to the crystalline form of Eto. Similar results were obtained for sulindac/β-CD physical mixture (9). The observed variations in some peaks in the x-ray diffraction patterns of Eto/β-CD kneading solid dispersion may result from the method of preparation of these dispersions. However, crystallinities of these systems were less than those of the physical mixture and original crystals of drug. These data agree with SEM data.

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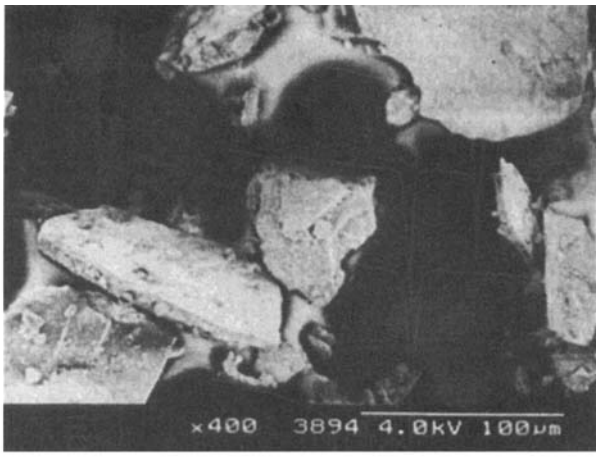
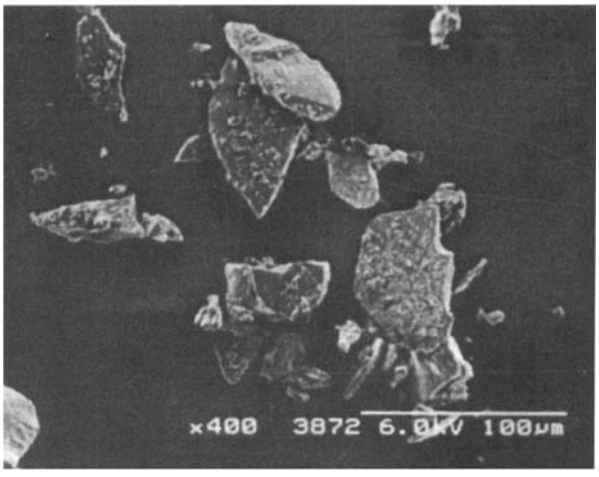
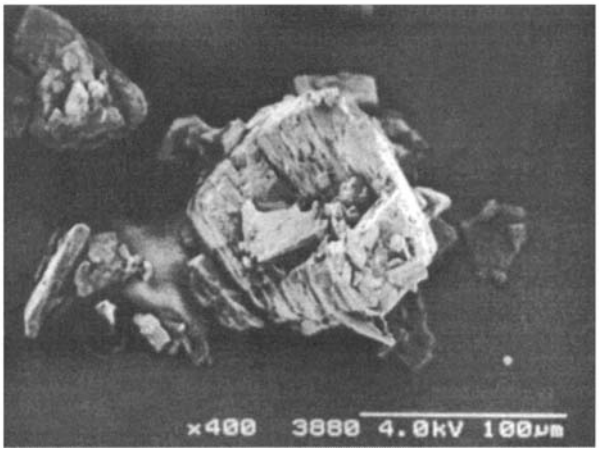


(a)



(b)



(c)

Figure 2. Scanning electron micrograph of (a) Eto crystals, (b) Eto/β-CD physical mixture, and (c) Eto/β-CD kneading dispersion.

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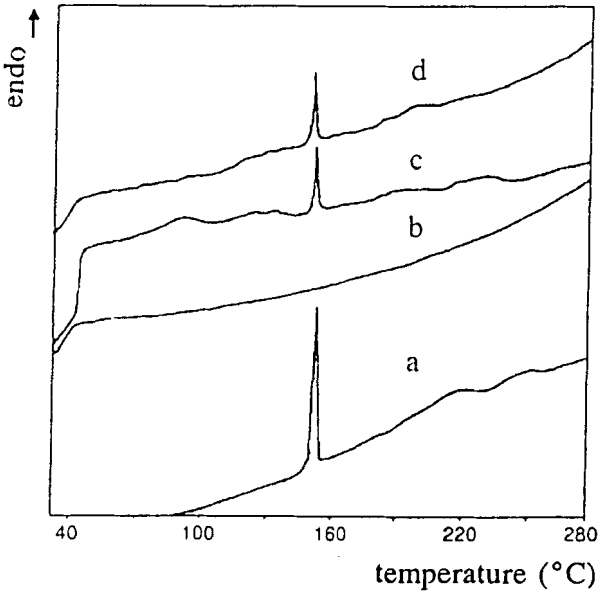

Figure 3. DSC curves of (a) Eto, (b) β-CD, (c) Eto/β-CD physical mixture and (d) Eto/β-CD kneading dispersion.

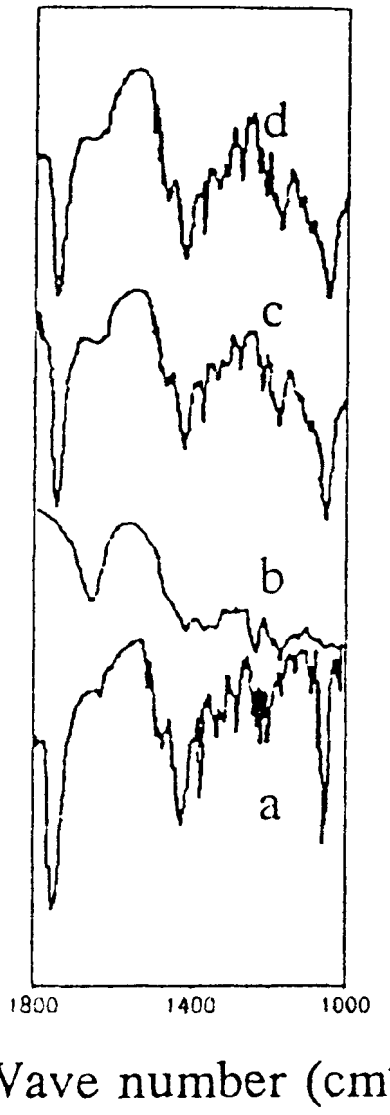

Figure 4. IR spectra of samples (for symbols see Fig. 3).

Dissolution Tests

The dissolution profiles plotted from experimental values of pure Eto and its physical mixture and kneading solid dispersion with β-CD are shown in Fig. 6. From this figure it is clearly obvious that the physical mixture of Eto/β-CD, as well as the prepared kneading solid dispersion of Eto/β-CD, show an increase in dissolution rate as compared to pure drug. During a 10-min time period, 47.6% and 60.5% were dissolved from Eto/β-CD kneading solid dispersion and the physical mixture Eto/β-CD, respectively. At this time, dissolution of Eto was only 24.2% from pure drug. Thus, Eto dispersions with β-CD (drug/β-CD weight ratio 1:1) led to a twofold increase in initial dissolution rate. The main dissolution promoting factor is probably the hydrophilic environment surrounding the drug due to the presence of CD, resulting in a better wettability of drug (10). However, enhancement was not significantly different from the mean dissolution rate of Eto/β-CD physical mixture and that of Eto/β-CD kneading solid dispersion.

Furthermore, CD dispersions increase significantly the dissolution rate of Eto as compared to pure drug. The improvement of dissolution rate was not found to be dependent on the dispersion preparation method. Finally, it can be concluded that the β-CD is a convenient partner of Eto for enhancing its dissolution properties.

These results might have some practical implications. Interaction of other NSAIDs with β-CD is known to result in more rapid absorption of drug, hence the shorter time of contact between the active agent and mucosa may reduce the potential for gastric lesions (11). The solid dispersions of Eto/β-CD might be used for preparing formulations of the drug with less harm to the stomach and improved bioavailability than the standard Eto formulation.

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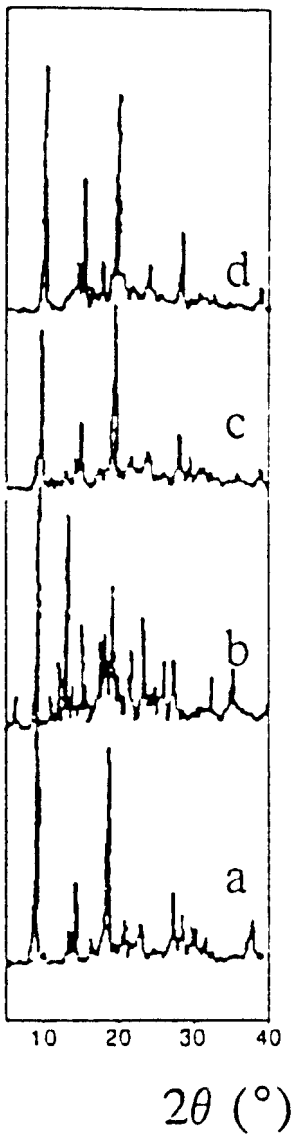

Figure 5. X-ray diffraction patterns of samples (for symbols see fig. 3).

CONCLUSION

Our results demonstrated that solubility of pure Eto in water is 0.01 mg/ml. The phase solubility profiles of Eto in β-CD aqueous solution could be classified as being of the A_L type, showing linear increase with unchanged stoichiometry. The solubility and dissolution rate of Eto were increased with CD physical mixture as well as with Eto/β-CD kneading solid dispersion. Within a 10-min time period, 47.6% and 60.5% were dissolved from Eto/β-CD kneading solid dispersion and the physical mixture Eto/β-CD, respectively. At this time, dissolution of Eto was only 24.2% from pure drug. Thus, Eto dispersion with β-CD led to a twofold increase in initial dissolution rate. The improvement of dissolution rate was not found to be dependent on the dispersion preparation method. It can be concluded that the β-CD is a convenient partner of Eto for enhancing its dissolution properties.

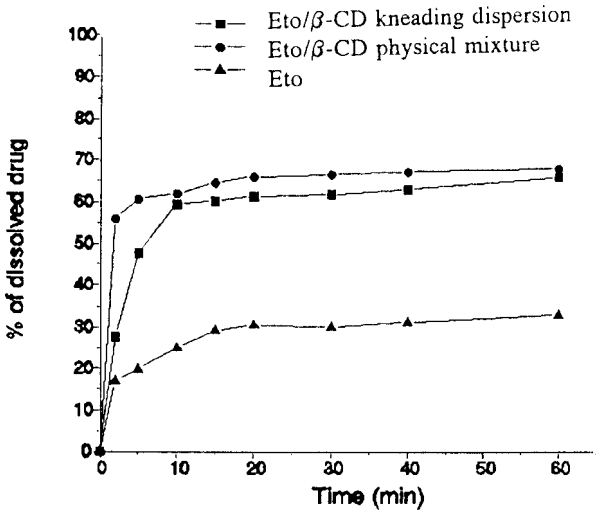

Figure 6. Dissolution profiles of Eto, Eto/β-CD physical mixture, and Eto/β-CD kneading dispersion.

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