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Preparation and Investigation of the Tenoxicam/β-Cyclodextrin Complex

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Abstract. A complex of tenoxicam with β-cyclodextrin was prepared by using co-grinding and freeze drying methods. The resulting products were studied by the solubility method, ultraviolet and infrared spectroscopy, differential scanning calorimetry and X-ray diffractometry. The dissolution behaviour of the products was also examined. The dissolution rate of the co-ground and freeze-dried products was faster than that of the pure drug and the physical mixture of drug and β-cyclodextrin. The enhanced dissolution rate of the products might be attributed to the amorphous state, the increased wettability of the drug and the inclusion complex formation.

Key words. Tenoxicam/β-cyclodextrin complexation, freeze-drying method, co-grinding method, characterization of inclusion complexes.

1. Introduction

Tenoxicam is a nonsteroidal antiinflammatory drug which is a thienothiazine derivative belonging to the oxicam class [1] (Figure 1). It is new drug having potential use in the treatment of rheumatoid arthritis, osteoarthritis, gout and anxylosing spondylitis [2]. However, tenoxicam is only slightly soluble in water and, as with all poorly soluble drugs, its dissolution may be the rate determining step in the absorption process. β-Cyclodextrin has been reported in a number of studies in the pharmaceutical field to interact with many drug molecules to form inclusion complexes [3]. These inclusion complexes have been extensively used to improve the solubility of poorly soluble drugs [4–6], the dissolution rate [7, 8] and also to improve the biopharmaceutical properties of some drugs belonging to the oxicam class [9]. Tenoxicam is a good candidate for inclusion complexation with β-cyclodextrin because of its poor solubility in water. The minimum requirement for inclusion complex formation is a size compatibility between host (β-cyclodextrin) and guest (drug) molecules [10]. Regarding the importance of the molecular size and structure of the guest molecule, tenoxicam with a molecular weight of 337.7 is suitable for complex formation with β-cyclodextrin.

The aim of the present work was to study the inclusion complexation of tenoxicam with β-cyclodextrin in order to improve the oral bioavailability by the enhancement of the dissolution rate. The methods used in the preparation of

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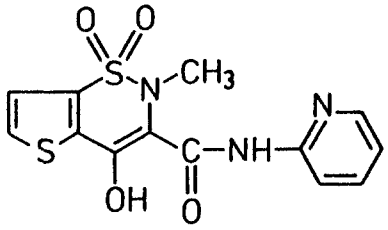

Fig. 1. Molecular structure of tenoxicam: 4-hydroxy-2-methyl-*N*-2-pyridinyl-2H-thieno(2, 3-*e*)-1,2-thiazine-3-carboxamide-1,1-dioxide.

tenoxicam/β-cyclodextrin complexes were co-grinding and freeze-drying. Characterization of the products was done by means of solubility studies, FTIR and UV spectroscopy, differential scanning calorimetry and X-ray diffractometry. Dissolution characteristics of the products were also investigated.

2. Experimental

2.1. MATERIALS

β-Cyclodextrin (Chinoin Pharmaceutical and Chemical Works, Hungary) and tenoxicam (Roche Müstahzarları Sanayi, A.Ş., Türkiye) were used as received. All other materials were of analytical reagent grade.

2.2. PRELIMINARY STUDIES

Solubility measurements were carried out according to the method of Higuchi and Connors [11]. An excess amount of tenoxicam was added to aqueous solutions of β-cyclodextrin at different concentrations and were shaken at room temperature for 48 h, at which time equilibrium was obtained. Aliquots were withdrawn, filtered and analyzed at 370 nm for their tenoxicam content, using a Shimadzu UV-160A spectrophotometer. No spectral shift was observed in the presence of β-cyclodextrin. The phase solubility diagram was then plotted (Figure 2). The solubility of tenoxicam increased with increasing concentrations of β-cyclodextrin showing an A_L type solubility curve [11].

The most reliable method for the preparation of solid inclusion compounds with cyclodextrins is to isolate them from the saturated aqueous solution. But this method is not applicable to the system with an A-type phase-solubility diagram, because of the formation of a soluble inclusion compound [12]. As an A_L type solubility was obtained in our preliminary studies, we were obliged to use another method, such as freeze-drying, which was suitable for our purpose. The co-grinding method was also used to justify our results. To obtain an amorphous compound with tenoxicam and β-cyclodextrin, co-grinding seemed to be superior to kneading since, due to the presence of water we might have recrystallization in the kneading method. In addition co-grinding is simpler.

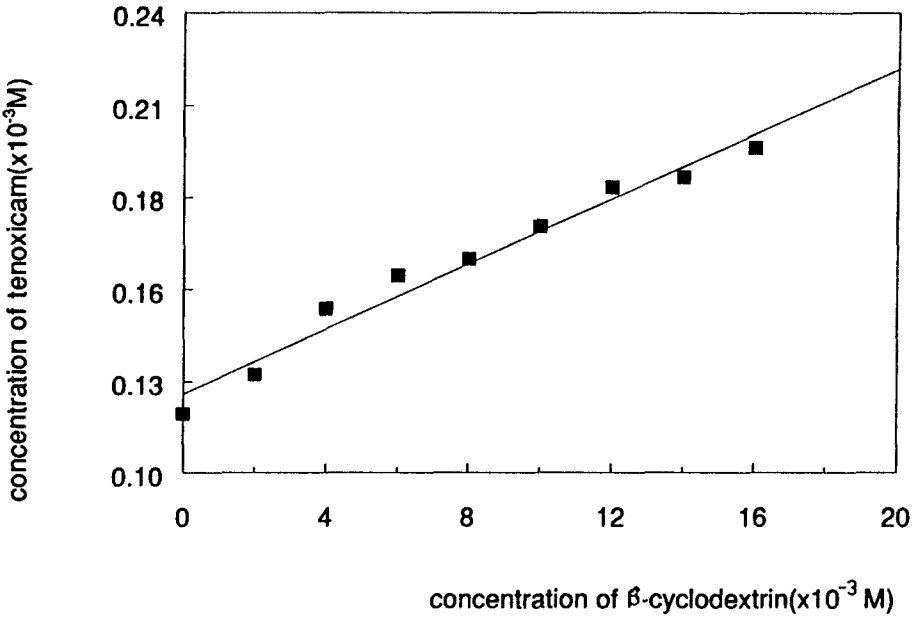

Fig. 2. Phase solubility diagram of the tenoxicam/β-cyclodextrin system in water at room temperature.

2.3. PREPARATION OF INCLUSION COMPOUNDS

2.3.1. *Physical Mixture*

A physical mixture of tenoxicam and β-cyclodextrin at a 1 : 1 molar ratio was prepared by simple mixing in a ceramic mortar.

2.3.2. *Co-grinding*

A ground mixture of tenoxicam and β-cyclodextrin at a 1 : 1 molar ratio was ground in a ceramic ball mill for thirty minutes.

2.3.3. *Freeze-drying*

Tenoxicam (0.337 g) was added to β-cyclodextrin aqueous solution (1.135 g/100 mL) at room temperature. A small amount of ammonium hydroxide was also added as a cosolvent. The resulting solution at a molar ratio of 1 : 1 was thereafter freeze-dried for 8 h using a Virtis Model Freezemobile 6 lyophilizer.

2.4. INVESTIGATION METHODS

2.4.1. *Differential Scanning Calorimetry*

The differential scanning calorimetry (DSC) thermograms were recorded by a Shimadzu DT-40 thermal analyzer with DSC detector at 10°C/min scanning rate under N_2 from 30°C to 270°C.

2.4.2. *X-ray Diffractometry*

Power X-ray patterns were obtained using a Philips PW4631/100 diffractometer, with Ni-filtered CuK_α radiation, voltage 40 kV, current 18 mA, at a scanning speed of 2°/min.

2.4.3. *Infrared Spectroscopy*

Studies of the infrared spectra were conducted with a Perkin Elmer 1710 Fourier Transform Infrared Spectrometer, using the KBr disc method.

2.4.4. *Dissolution Studies*

The USP paddle apparatus (Prolabo, France) was used at 100 rpm. The dissolution medium was 900 mL distilled water at 37°C. Samples were withdrawn at appropriate time intervals through the filter and assayed spectrophotometrically at 370 nm.

3. Results and Discussion

3.1. CHARACTERIZATION OF THE COMPOUNDS

DSC thermograms of the pure drug, β-cyclodextrin, the physical mixture and co-ground and freeze-dried products are shown in Figure 3. The endothermic peak (at 228°C) of tenoxicam due to the fusion of drug crystals disappeared in DSC thermograms of the freeze-dried products, whereas for the physical mixture, the endothermic peak remained. When drug molecules are included in the cyclodextrin cavity or in the crystal lattice, their melting, boiling and sublimation points are usually shifted to a higher temperature or disappear within the temperature range [10]. Here, the disppearance of the endothermic peak for the freeze-dried product is attributed to the amorphous state of the drug, or inclusion complex formation, or both [13]. On the other hand, co-grinding of tenoxicam with β-cyclodextrin showed a small peak in the DSC curve indicating that the formation of the amorphous complex was not complete and a crystalline portion of the drug is still found in addition to the amorphous complex [14].

Figure 4 shows the X-ray diffraction patterns of the pure drug, β-cyclodextrin, the physical mixture and products at 1 : 1 molar ratio prepared by freeze-drying and co-grinding methods. It is obvious that the pure drug, β-cyclodextrin and the physical mixture exhibit crystalline characteristics. The diffraction pattern of the physical mixture was simply the superposition of each component while that of the freeze-dried product was apparently different and showed an amorphous state, indicating that the crystals were converted to a disordered form. The diffraction pattern of the complex should be clearly distinct from that of the superposition of each component when a true complex exists [10]. On the other hand, although hollow patterns characterizing the formation of an amorphous state were not observed significantly compared to the freeze-dried product, the co-ground product showed a different diffraction pattern to that of the physical mixture. The presence of some diffraction peaks in the X-ray diffraction patterns of the co-

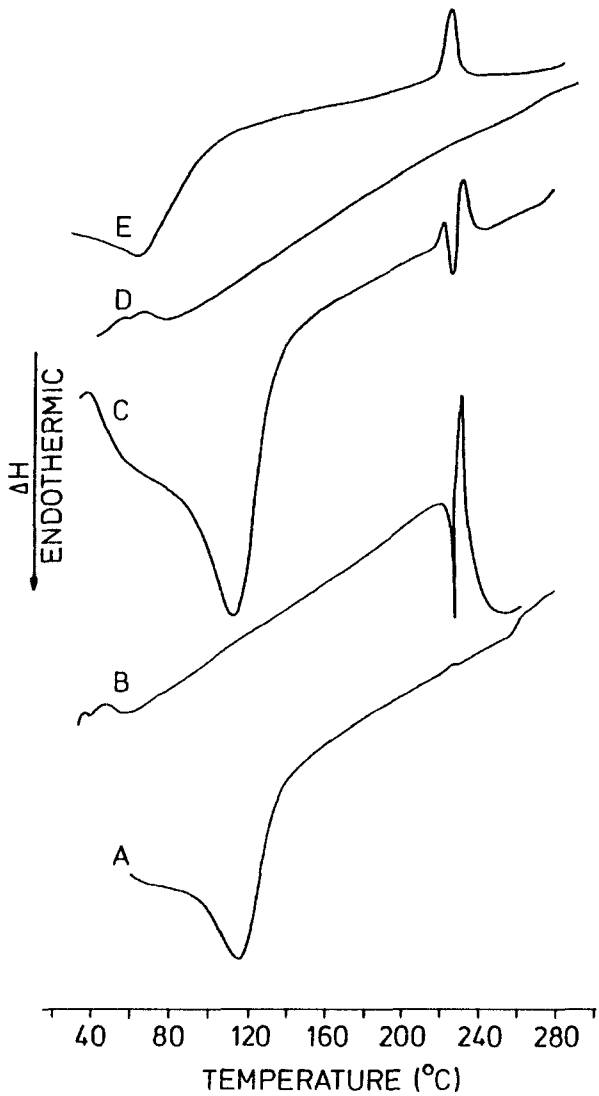

Fig. 3. DSC thermograms of β-cyclodextrin (A), tenoxicam (B), physical mixture (C), freeze-dried product (D), co-ground product (E).

ground product is attributed to the coexistence of the crystalline(non-included) components as well as the complex [15, 16].

Infrared analysis provides much valuable information about β-cyclodextrin complexes in powder or microcrystalline states. Figure 5 shows the infrared spectra of tenoxicam, a physical mixture of tenoxicam and β-cyclodextrin at a 1 : 1 molar ratio as well as those of the products obtained by co-grinding and freeze-drying. The infrared spectrum of tenoxicam showed two characteristic bands belonging to carbonyl at 1600 and 1640 cm^{-1}. These two bands, also observed for the 1 : 1 physical mixture, shifted to a higher wavenumber and broadened in the freeze-dried

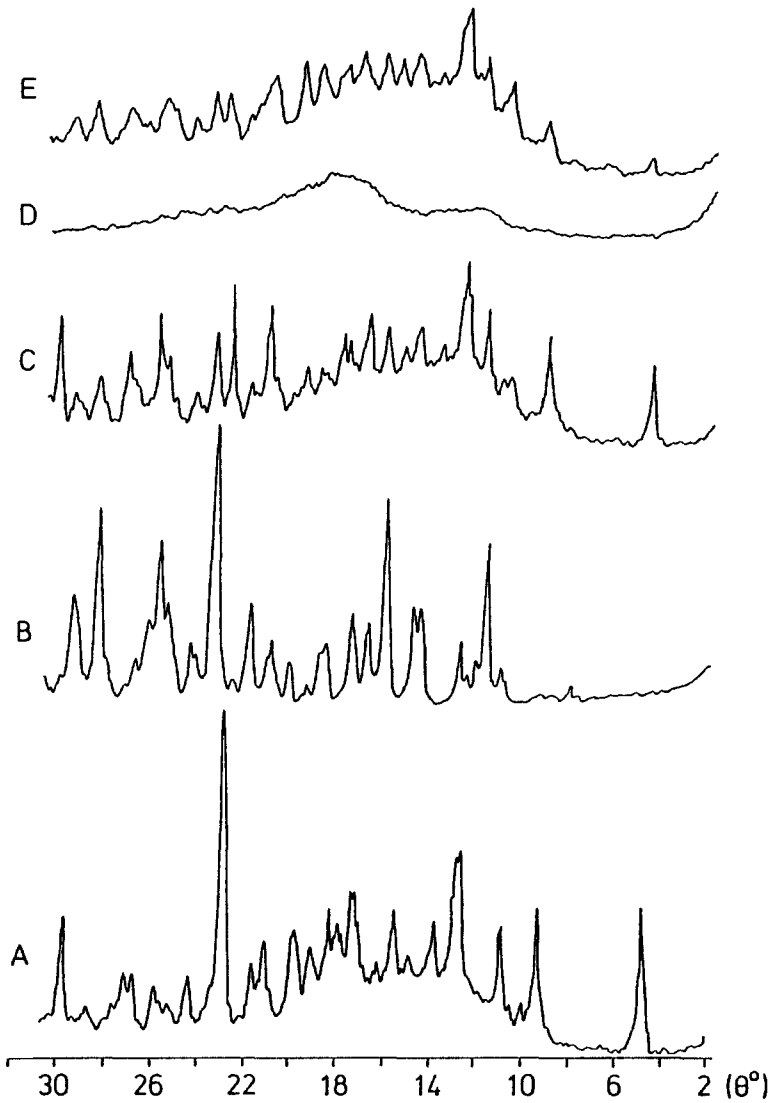

Fig. 4. X-Ray diffraction patterns of β-cyclodextrin (A), tenoxicam (B), physical mixture (C), freeze-dried product (D), co-ground product (E).

product, indicating the formation of an inclusion complex. This arises because the intermolecular hydrogen bonding of the guest (tenoxicam) is ruptured in the cyclodextrin cavity [10]. However, for the co-ground product, there was no remarkable change in the infrared bands. Only diminuation of the intensity was observed. This indicates that the inclusion of tenoxicam in β-cyclodextrin was not complete in the case of co-grinding [17].

Concerning the results of the different characterization methods used in this study such as differential scanning calorimetry, X-ray diffractometry and infrared

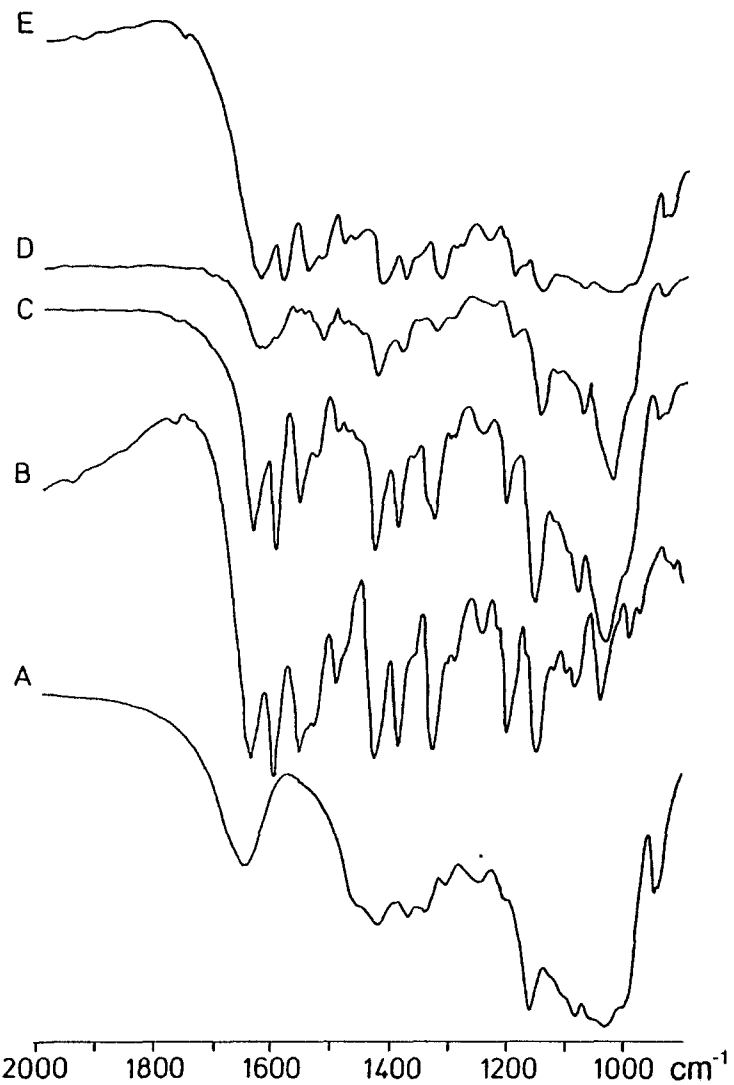

Fig. 5. IR spectra of β-cyclodextrin (A), tenoxicam (B), physical mixture (C), freeze-dried product (D), co-ground product (E).

spectroscopy, it can be concluded that the co-grinding method did not lead to a real inclusion complex whereas the freeze-drying technique led to a true possible inclusion of tenoxicam in the β-cyclodextrin.

3.2. DISSOLUTION STUDIES

The dissolution rate of the products prepared by co-grinding and freeze-drying methods was much faster than that of the physical mixture and the pure drug (Figure 6). With the freeze-dried product the amount of tenoxicam dissolved in 30

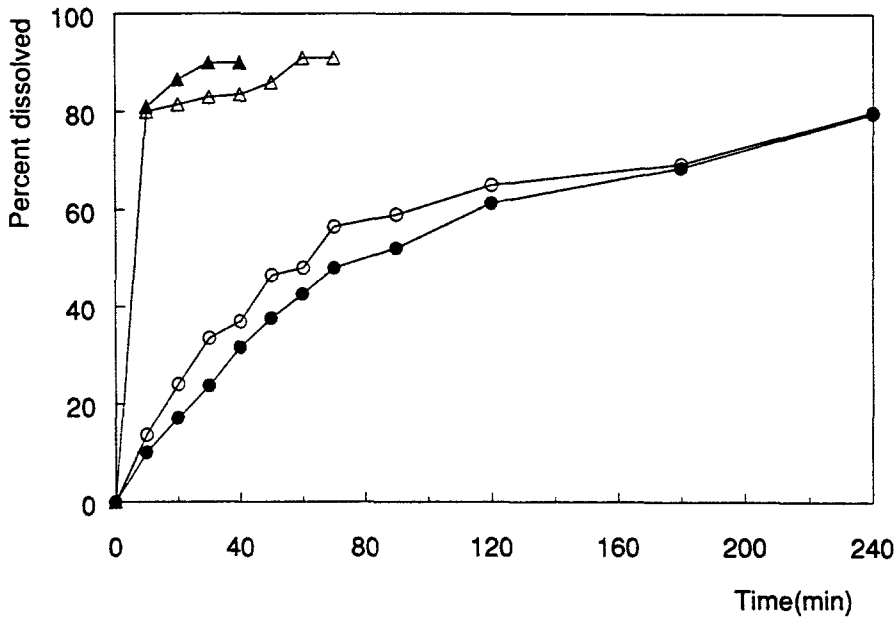

Fig. 6. Dissolution profiles of tenoxicam (●), physical mixture (○), freeze-dried product (▲) and co-ground product (△).

minutes was 90%, while for the co-ground product, the physical mixture and the pure drug the dissolved amount was 83, 33.5 and 23.7%, respectively. This can be attributed to the surfactant-like properties of β-cyclodextrin which can reduce the interfacial tension between water-insoluble drugs and the dissolution medium, leading to a higher dissolution rate [18]. The increase in dissolution rate with the physical mixture can be explained by hydrophilization of tenoxicam by β-cyclodextrin. With the co-grinding method, partially amorphous inclusion product was obtained resulting in weaker bonds, and therefore in the dissolution medium these bonds were easily broken thus the dissolution rate was increased. The enhanced dissolution rate of the freeze-dried product might be because of the decrease in crystallinity and formation of an inclusion compound [13].

Depending on the purpose co-grinding would be better, but according to our results it cannot be accurately said that an inclusion complex was obtained. On the other hand by freeze-drying, it was possible to obtain a drug in an amorphous state and with the greatest possibility of obtaining an inclusion complex, which is very soluble to give a higher bioavailability.

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