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COMMUNICATION

Solubilization and Interaction of Sulindac with β-Cyclodextrin in the Solid State and in Aqueous Solution

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ABSTRACT

A sulindac–β–cyclodextrin complex was obtained by the coprecipitation method. Kneaded solids and physical mixtures were also prepared. The complex was shown by x-ray powder diffraction to be noncrystalline whereas pure drug and any of the other sulindac–β-CD system were crystalline. The endothermic peak of sulindac due to the fusion of drug disappeared in DSC thermograms for the coprecipitate product, which confirmed the interaction between sulindac and β-CD in the solid state. After a 1-year storage drug crystals could not be observed by x-ray diffractometry, which indicated that the complex formed was stable. The complex showed the fastest dissolution rate which might be attributed to the high-energy noncrystalline state and the inclusion complex formation in solution. UV spectra were modified and the apparent solubility of the drug increased with the addition of β-CD, which confirmed the interaction between sulindac and the ligand in solution. The apparent stability constant, $K_{1:1}$, for the complex at pH 2 and 25, 30, and 37°C was 340, 220, and 160 M^{-1}, respectively, which confirmed the influence of temperature on the complex stability. The value of $K_{1:1}$ at pH 6 and 25°C was 139 M^{-1}, which indicated that the complex is formed easier with the non-ionized sulindac. The enthalpy change, $\Delta H°$, showed that the binding process is exothermic.

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INTRODUCTION

Sulindac is a nonsteroidal anti-inflammatory agent, very slightly soluble in water, and when administered orally it can cause gastric irritation. β-cyclodextrin (CD) and its derivatives have been used in pharmaceutical formulations to enhance the solubility, dissolution rate, membrane permeability, stability, and bioavailability of slightly soluble drugs. By taking advantage of CD complexation many attempts have been made to reduce the side effects associated with drugs. It is well established that CD reduces the ulcerogenic potencies of several acidic anti-inflammatory agents. Several studies have reported the interactions of β-CD with other nonsteroidal anti-inflammatory agents such as: indomethacin (1–5), naproxen (6–17), ibuprofen (18–21), ketoprofen (14,17,18,20), ibufenac (18), aspirin (22,23), mefenamic acid (1,24), flufenamic acid (1), flurbiprofen (25), azapropazone (1), diclofenac (4), phenylbutazone (1), diflunisal (26,27), piroxicam (2,4,28), and tolmetin (17).

The purpose of the present study was to analyze the interaction of sulindac with β-CD in the solid state and in solution and to investigate the possibility of improving the solubility of the drug via complexation. The physicochemical properties of sulindac–β-CD systems in the solid state were reported by x-ray diffractometry and thermal analysis. The dissolution profiles were also characterized and the interaction in solution was studied by UV spectroscopy and solubility assays.

MATERIALS AND METHODS

Materials

Sulindac was kindly supplied by Merck Sharp and Dohme of Spain S.A. (Madrid, Spain) and β-CD (Kleptose) by Roquette of Spain S.A. (Larsa, Barcelona, Spain). NH_4OH (Merck, Darmstadt, Germany) was used in the complex preparation. The aqueous buffers of pH 2 and 6 have been respectively prepared with KCl and HCl or with KH_2PO_4 and Na_2HPO_4 (Merck). Double-distilled water was used throughout the study. The solvent and all reagents were of analytical grade.

Preparation of Sulindac–β-CD Systems

Solid complex of sulindac with β-CD was prepared by the coprecipitation method. Corresponding quantities of drug and CD (molar ratio 1:1) were dissolved separately in a solution of ammonium hydroxide (pH 12) at room temperature. They were then mixed and stirred continuously at 25°C. The solvent was evaporated in a rotary evaporator under vacuum at 40°C and the mixture was dried at 25°C in a desiccator over P_2O_5.

In the kneading method β-CD and water were mixed together in a mortar so as to obtain a homogeneous paste. Sulindac (molar ratio 1:1) was then added slowly while the mixture was ground. Grinding continued for 1 hr. During this process an appropriate quantity of water was added to the mixture in order to maintain a suitable consistency. The paste was dried under vacuum at room temperature over P_2O_5.

The mode of the physical mixture preparation was the simplest. The calculated and exactly weighed (1:1 molar ratio) amounts of sulindac and β-CD were pulverized in a ceramic mortar and carefully mixed.

Characterization of Sulindac–β-CD Systems

Powder x-ray diffractometry was carried out using a Siemens Kristalloflex 810 diffractometer system (Karlsruhe, Germany) with CuK_α radiation over the interval 2–30°/2θ. The operation data were as follows: voltage 40 kV, current 20 mA, filter Ni, time constant 4 sec and scanning speed 1°/min. The samples were lightly ground and packed into the aluminum sample container.

A Perkin-Elmer DSC 77 differential scanning calorimeter (Norwalk, CT) calibrated with 8 mg of indium and zinc was used in the thermal analysis at a heating rate of 10°C/min over the temperature range 60–200°C and employing nitrogen as purging gas. Pulverized samples (5 mg) were placed in aluminum sample pans. Measurements were made in triplicate.

Dissolution Studies

Dissolution rates of sulindac from these systems were compared with those of the pure drug in an aqueous phosphate buffer at pH 6. The dissolution tests were performed according to the USPXXIII-NFXVIII (1995) paddle method with a Dissolutest 07170025 dissolution apparatus (Prolabo, Paris, France) using a rotational speed of 100 rpm at 37 ± 0.1°C and with 900 ml of aqueous phosphate buffer solution at pH 6. Disks containing 35 mg of sulindac and sink conditions ($C << C_s$) have been used. The systems' samples were compressed by a hydraulic press for KBr tablets for infrared spectroscopy. Disks of 13 mm diameter and 0.074–0.149 mm particle size were prepared. The compression force was 44 kN/cm^2. At appropriate intervals 5-ml

samples were removed, replaced by fresh test fluids, and filtered through a 0.8-μm membrane filter (Millipore, Barcelona, Spain). The filtrate was suitably diluted and the samples were assayed spectrophotometrically at 285 nm using a Perkin-Elmer Lambda 2 spectrophotometer. The amount of sulindac dissolved was determined as a function of time. Dissolution runs for all samples were performed six times.

UV Spectroscopy

The change in absorbance of the drug (2.5×10^{-5} M) by the addition of various concentrations of β-CD (0.88×10^{-3}–7.93×10^{-3} M) was measured in the range 250–450 nm at pH 2 and 6. The UV spectra were recorded on a Perkin-Elmer Lambda 2 spectrophotometer. It should also be noted that a blank of β-CD was used during the runs so as to eliminate any absorbance that may arise due to the presence of cyclodextrin.

Phase Solubility Determinations

The phase solubility studies were carried out according to the method reported by Higuchi and Connors (29). Cyclodextrin solutions of different concentrations (0.88×10^{-3}–13.21×10^{-3}M) were prepared at pH 6 and 2 and an excess of sulindac (50 mg) was added to each. The samples were continuously stirred while they remained in a water bath (Selecta Unitronic 320 OR) thermostated at 25, 30, and 37 ± 0.5°C until equilibrium was achieved. The samples were then removed, filtered through a 0.8-mm nylon membrane (Millipore), adequately diluted, and analyzed spectrophotometrically at 305 nm (Perkin-Elmer Lambda 2 spectrophotometer) using second-derivative absorption which allowed the interference due to β-CD to be removed. The second derivative values were converted to the corresponding concentration by reference to a suitable calibration curve. The experiment was carried out in triplicate. The stability constants were calculated from the straight line of the solubility diagrams on the basis of a 1:1 stoichiometry according to the Higuchi and Connors equation (29):

$$K_{1:1} = \frac{\text{slope}}{\text{intercept } (1 - \text{slope})}$$

The enthalpy change associated with the complex formation, $\Delta H°$, has been determined from the Van't Hoff plot of ln $K_{1:1}$ against $1/T$.

RESULTS AND DISCUSSION

Characterization of the Interaction in the Solid State

Figure 1 shows the x-ray diffraction patterns of suldinac alone, β-CD, physical mixture, kneaded solid,

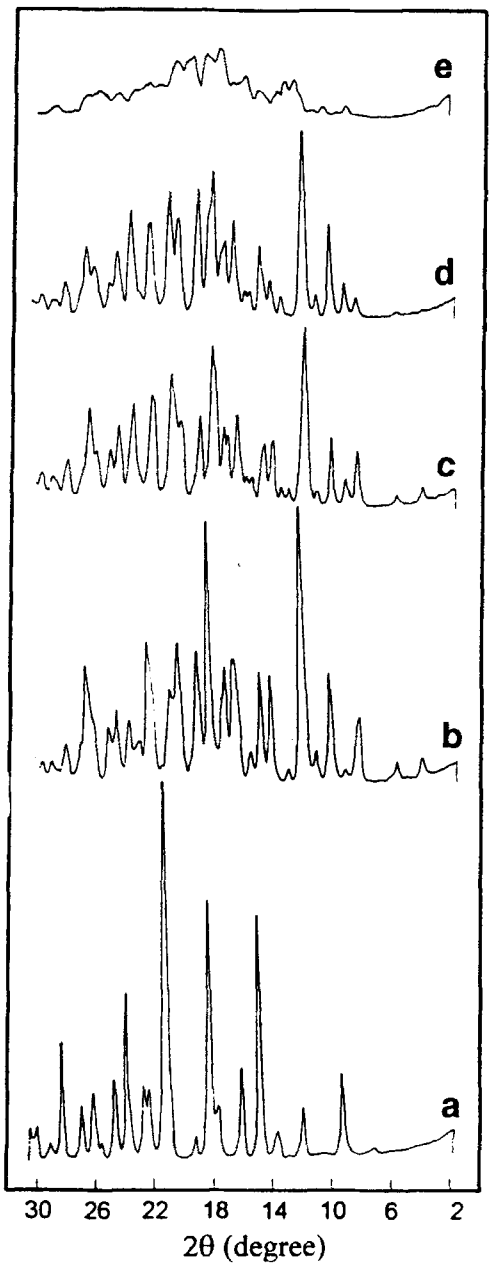

Figure 1. X-ray diffraction patterns of suldinac (a), β-CD (b), physical mixture (c), kneaded solid (d), and complex (e).

and complex prepared by coprecipitation. The diffraction patterns of physical mixture and kneaded solid are simply the superposition of each component with the different intensity peaks. Conversely, the diffraction patterns of sulindac–β-CD coprecipitate show only very few peaks with very low intensity, indicating that the complex formed is noncrystalline.

The DSC curves of sulindac, β-CD, and sulindac–β-CD systems are shown in Fig. 2. The interaction of sulindac with β-CD is accompanied by the complete disappearance of the endothermic peak of sulindac, which confirms that a complex has been formed. However, the fusion of sulindac at 187°C in the physical mixture and kneaded solid can be observed.

Dissolution of Sulindac–β-CD Systems

At 15 min nearly 83% of sulindac is dissolved from the coprecipitate complex compared with 66% from the physical mixture and 7% of sulindac alone. The increase in the dissolution of sulindac when physically mixed with β-CD is probably due to a local solubilization action, which improves the wettability and hence dissolution of the drug particles. The significant enhancement in the dissolution rate of the complex may be the result of a marked reduction in crystallinity.

Characterization of the Interaction in Solution

UV Spectral Studies

The spectra of sulindac at pH 6 and 2 showed a bathochromic shift at 285 nm as a result of complex formation, which may be explained by a partial shielding of the excitable electrons in the CD cavity. The intensity of the absorption maximum slightly decreased with increasing β-CD concentration. No isosbestic points have been found.

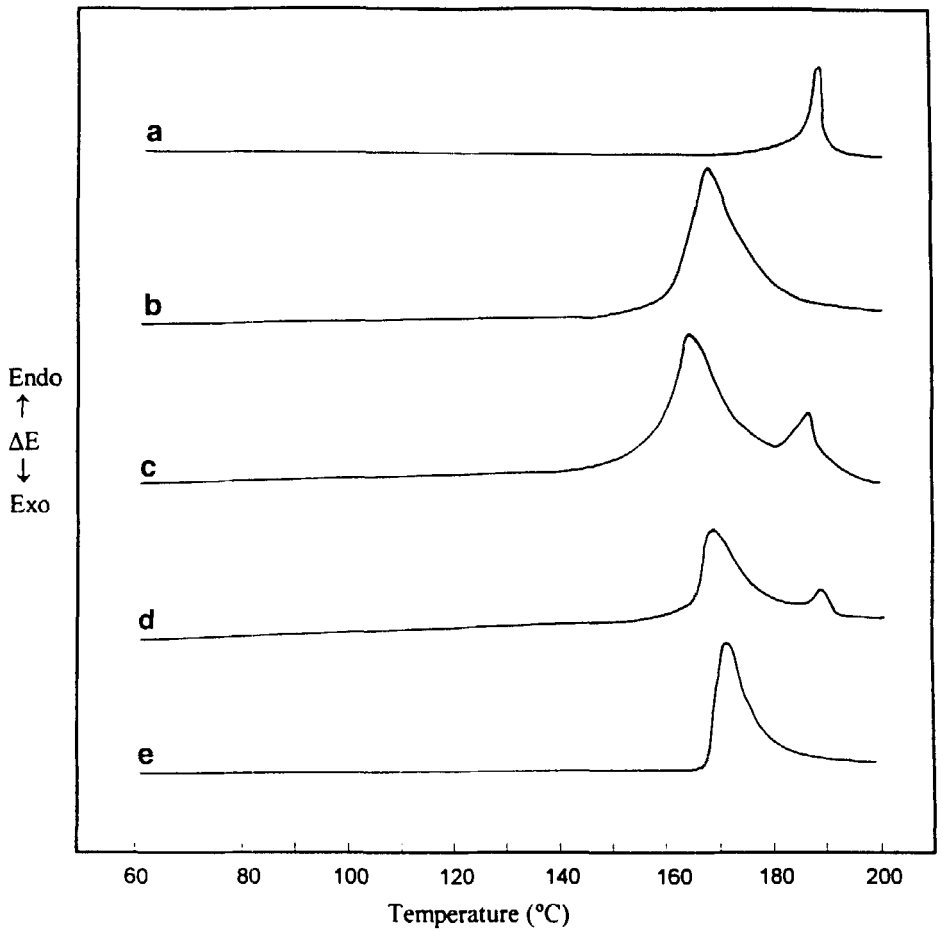

Figure 2. Differential scanning calorimetry curves of sulindac (a), β-CD (b), physical mixture (c), kneaded solid (d), and complex (e).

Solubility Studies

The solubility of sulindac was found to increase with the addition of β-CD due to the formation of an inclusion compound. At pH 6 and 25°C the increase was 2.5 times the solubility of sulindac alone (Fig. 3) and at pH 2 it was 6, 4, and 3 times at 25, 30, and 37°C, respectively (Fig. 4). These results confirmed the influence of pH and temperature on the interaction between the drug and the ligand.

The straight line obtained for sulindac β-CD systems can be classified as diagram type A_L ($r > 0.99$), indicating the formation of a soluble complex of constant composition between the substrate and the ligand (29). It was assumed that the formation of a complex with stoichiometry 1:1 because the ascending line of the diagram had a slope less than 1. The apparent stability constants, $K_{1:1}$, of sulindac complexes calculated from the slope and the intercept of the phase solubility diagrams are shown in Table 1. The value of $K_{1:1}$ for sulindac with β-CD at 25°C was greater than at 30 and 37°C. It can also be observed that $K_{1:1}$ decreased when the pH increased, indicating that the unionized drug interacts more strongly with β-CD compared to the ionized sulindac.

The stability constants reflect a favorable positioning of the sulindac molecule inside the cavity of the β-CD. The hydrophobic nature of the drug and steric factors between sulindac and β-CD were responsible for these interactions. The enthalpy change, ΔH°, calculated from the Van't Hoff plots was -46 kJ/mol, indicating that the binding process of sulindac with β-CD is exothermic and hydrogen bonds and dipole-dipole interactions between host and guest participated in the complex formation.

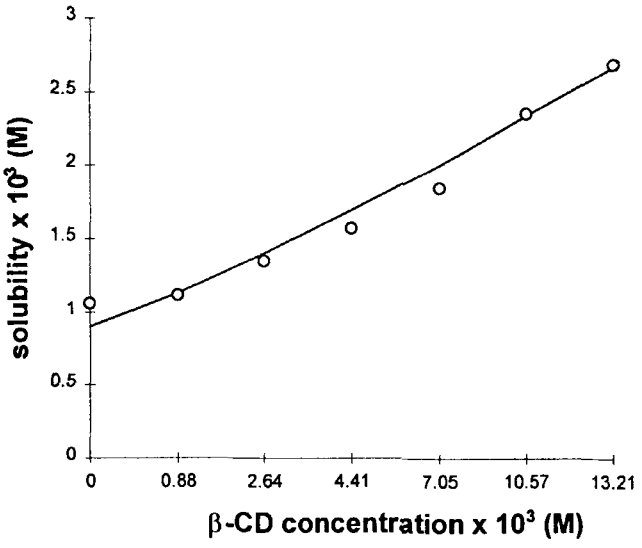

Figure 3. Phase solubility diagram for sulindac-β-CD system at pH 6 and 25°C.

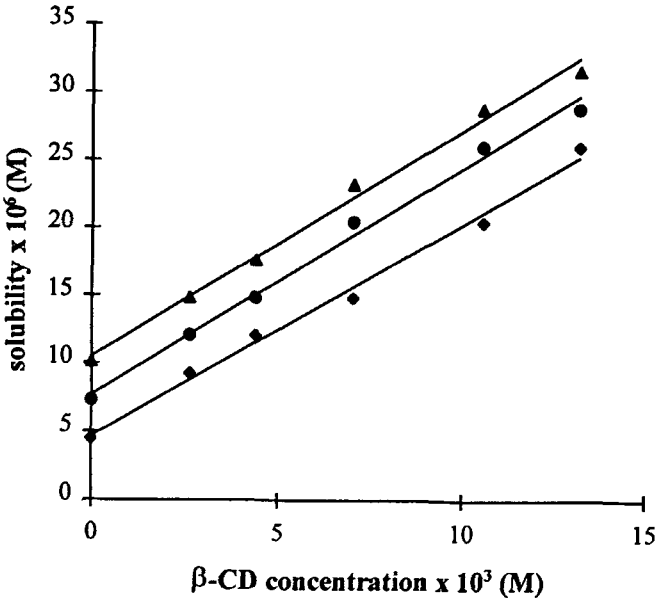

Figure 4. Effect of temperature on the phase solubility diagram for sulindac-β-CD system at pH 2 and 25 (◆), 30 (●), and 37°C (▲).

CONCLUSIONS

Sulindac was found to form a stable complex with β-CD in solid state which was noncrystalline. No changes were observed after 1 year storage. Moreover, an interaction in solution between the drug and β-CD was confirmed. The binding process was shown to be exothermic and it could be also demonstrated that the complex was better formed with the non-ionized drug.

Table 1

Apparent Stability Constants of Sulindac-β-CD Complex

	T (°C)	$K_{1:1}$ (M^{-1})[a]
pH 2	25	340
	30	220
	37	160
pH 6	25	139

[a]Values are the mean of three measurements.

These results led to an increase in the aqueous solubility of sulindac by forming an inclusion complex with the ligand. This is of great interest in the pharmaceutical formulations of rapid dissolving forms of sulindac with prolonged storage time.

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