Diclofenac-β-Cyclodextrin Binary Systems: Physicochemical Characterization and In Vitro Dissolution and Diffusion Studies

Submitted: February 1, 2005; Accepted: July 15, 2005; Published: October 22, 2005

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ABSTRACT

The aim of this work was to study the influence of β-cyclodextrin (β-CD) on the biopharmaceutic properties of diclofenac (DCF). To this purpose the physicochemical characterization of diclofenac-β-cyclodextrin binary systems was performed both in solution and solid state. Solid phase characterization was performed using differential scanning calorimetry (DSC), powder x-ray diffractometry (XRD), and Fourier transform infrared spectroscopy (FTIR). Phase solubility analyses, and in vitro permeation experiments through a synthetic membrane were performed in solution. Moreover, DCF/β-CD interactions were studied in DMSO by ^{1}H nuclear magnetic resonance (NMR) spectroscopy. The effects of different preparation methods and drug-to-β-CD molar ratios were also evaluated. Phase solubility studies revealed 1:1 M complexation of DCF when the freeze-drying method was used for the preparation of the binary system. The true inclusion for the freeze-dried binary system was confirmed by ^{1}H NMR spectroscopy, DSC, powder XRD, and IR studies. The dissolution study revealed that the drug dissolution rate was improved by the presence of CDs and the highest and promptest release was obtained with the freeze-dried binary system. Diffusion experiments through a silicone membrane showed that DCF diffusion was higher from the saturated drug solution (control) than the freeze-dried inclusion complexes, prepared using different DCF-β-CD molar ratios. However, the presence of the inclusion complex was able to stabilize the system giving rise to a more regular diffusion profile.

KEYWORDS: diclofenac-β-cyclodextrin inclusion complex, dissolution, permeation.

INTRODUCTION

In recent years cyclodextrins (CDs) have been recognized as an important group of pharmaceutical excipients. They are cyclic oligosaccharides consisting of (α-1, 4)-linked α-D-glucopyranose units, with a relatively hydrophobic central cavity and a hydrophilic outer surface. The most abundant natural CDs are α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), and γ-cyclodextrin (γ-CD), containing 6, 7, and 8 glucopyranose units, respectively. The hydrophilic exterior surface of the CD molecules makes them water-soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized nonpolar molecules. CDs are capable of forming inclusion complexes with many drugs by including a whole drug molecule, or only some nonpolar part of it, inside their cavity. In an aqueous solution, the complexes are readily dissociated and free drug molecules are in relatively rapid dynamic equilibrium with drug molecules bound within the CD cavity.[1-4] These noncovalent complexes show new physicochemical characteristics when compared with the guest molecules. They include better stability, higher aqueous solubility, increased bioavailability, and less undesirable side effects.[1-4] Biological membranes are lipophilic and therefore passive diffusion is favored for relatively lipophilic molecules. However, the driving force for the passive diffusion is the high drug concentration and high drug activity in the aqueous fluid of the absorption site. Thus, bioavailability of drugs depends both on their water and lipid solubility. The formation of drug-CD inclusion complexes can increase the aqueous solubility of lipophilic drugs, hence increasing the driving force for the diffusion process across the biological membranes. Moreover, CD molecules can permeate a biological membrane with considerable difficulty[1,4] because of their large size and highly hydrophilic surface. Therefore, they also work as permeation enhancers because they increase drug availability at the absorption site. For this reason CDs have been studied as carriers for the delivery of different drugs through skin,[5] ophthalmic,[6] buccal,[7] and nasal mucosa.[8] However, it has also been reported that an excess amount of CDs can decrease drug absorption through the skin and eye cornea.[9]

In order to evaluate the influence of CDs on the delivery of drugs through biological membranes, a study of the physicochemical characterization, dissolution properties, and in vitro permeation behavior of diclofenac-β-CD (DCF-β-CD) binary systems was performed. Diclofenac, 2-[(2,6-dichlorophenyl)amino] phenylacetic acid (DCF, Figure 1)

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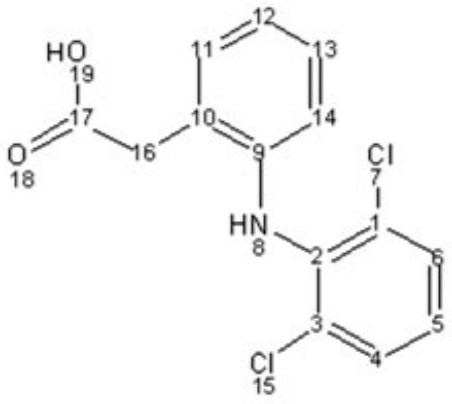

Figure 1. Chemical structure of diclofenac.

was chosen as a model drug because it is a potent nonsteroidal antiinflammatory drug, therapeutically used in inflammatory and painful conditions of rheumatic and nonrheumatic origin. It is an acid compound (pK_a 4.18 at 25°C) with a very low aqueous solubility (0.02 mM at 25°C) in the unionized form. For low water-soluble drugs, dissolution is the rate determining step in the absorption process. An improvement in the dissolution characteristics of these drugs results in higher plasma peaks, as a consequence of their increased absorption rate. In this work, it was investigated whether the low water-solubility problem could be overcome by the formation of DCF-β-CD binary systems.

The aim of this work was to improve the pharmaceutical properties (ie, aqueous solubility, dissolution) of diclofenac. The binary products, prepared by the physical mixture or freeze-drying process, were characterized in solution by phase solubility studies, ^{1}H nuclear magnetic resonance (^{1}H NMR) spectroscopy and dissolution rate analysis, and in solid state by using differential scanning calorimetry (DSC), x-ray diffractometry (XRD), Fourier transform infrared (FTIR) spectroscopy. Moreover, the influence of different DCF-β-CD molar ratios on the diffusion of diclofenac across a lipophilic membrane was also studied. Permeation experiments were performed in vitro using vertical Franz diffusion cells and a saturated solution of the free drug as a reference. Silicone membrane, which offers a nonporous, hydrophobic, inert, and reproducible barrier, was chosen as a model membrane in order to evaluate factors such as drug activity on permeation. This study would be useful in evaluating the influence of CDs on the delivery of DCF across different biological membranes.

Materials and Methods

Materials

Diclofenac free acid was obtained from diclofenac sodium salt (Sigma Aldrich, Milano, Italy) by precipiting it with HCl. The obtained diclofenac free acid was filtered and dried at room temperature under a vacuum. β-cyclodextrin was kindly supplied by Roquette Co, Lestrem, France. Phosphate buffer solution (PBS) pH 7 was obtained from Carlo Erba Reagents (Rodano, Italy). High-performance liquid chromatography (HPLC)-grade methanol and propylene glycol were purchased from Sigma Aldrich.

Preparation of Solid Binary Systems

Diclofenac-β-cyclodextrin binary systems were prepared at 1:1, 1:2, and 1:3 molar ratio, as described in detail below.

Physical Mixtures

The required and accurately weighed amounts of DCF and β-CD were pulverized, sieved, and homogenously mixed in a ceramic mortar.

Freeze-drying Procedure

The required stoichiometric amounts of DCF and β-CDs were accurately weighed and dispersed in 2 mL of aqueous solutions until semisolid systems were obtained, which were then stored in a nitrogen atmosphere for 12 hours. Then, products were dissolved in 200 mL of distilled water and stirred under mechanical stirring for 40 minutes at 70°C-80°C. After filtration at the same temperature, the filtrate was frozen at −15°C/−20°C and then freeze dried for 24 hours at −70°C and 60 mmHg, using a Freeze-Dryer Criotecnica, (MMCOTA, Rome, Italy).

Characterization of Binary Systems

X-Ray Powder Diffractometry

X-ray diffraction (XRD) patterns were collected with a Seifert X3000 diffractometer operating at 35 mA and 50 KV using CuKα radiation and equipped with a graphite monochromator on the diffracted beam. XRD patterns were recorded in step scan mode in the range $3° \leq 2\theta \leq 50°$ with step size 0.05°, collecting at least 1000 counts for each step. The divergence and receiving slits were chosen in order to ensure a high resolution mode for the crystalline phases. On selected samples, Rietveld refinement was also performed using the Rietquan program.[10] The instrumental profile parameters were derived from the fitting of XRD data obtained from standard samples. Usual recommended fit procedure was adopted.[11]

Infrared Spectroscopy

Fourier transform infrared spectroscopy (FTIR) spectra of pure DCF and β-CD, as well as their binary products, were

obtained using a Perkin Elmer System 2000 FTIR spectrophotometer (Beaconsfield, UK) according to the potassium bromide disk method. Analyses were performed at room temperature.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) analysis was performed for DCF raw material, pure CD, DCF-β-CD binary systems (physical mixture and freeze-dried product) using a Perkin-Elmer DSC7 instrument, with pure argon flux and with a heating rate of 10 K/min in the temperature range of 303°C to 473°C. The analysis was repeated after cooling down to room temperature in order to estimate the DSC baseline. Each sample was accurately weighed (~1-3 mg) in an aluminum pan, crimped, and hermetically sealed. Temperature calibration was obtained using palmitic acid and indium.

Nuclear Magnetic Resonance Studies

^{1}H (300 MHz) nuclear magnetic resonance (NMR) spectra were recorded on a Varian VRX-300 spectrometer (Varian Inc, Palo Alto, CA) at 25°C, in d_6-DMSO solution using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed as ppm (δ).

Phase Solubility Studies

Phase solubility studies were performed, following the method previously described by Higuchi and Connors,[12] in solutions at pH 3.0, 5.5, and 7.0. Briefly, excess amounts of DFC (30 mg) were added to 10 mL of aqueous solutions containing different concentrations of β-CD (0-5 mM). Suspensions were vigorously stirred at 25°C ± 1°C for 7 days. When equilibrium was reached (7 days), samples were filtered through a polycarbonate membrane (0.45μm, Millipore, Billerica, MA) and suitably diluted. DCF concentrations were determined using HPLC, as described below. Data represent the mean values of 3 separate determinations. Phase solubility diagrams were plotted, and the apparent stability constants (Kc) were calculated according to the following formula:

$$Kc = \alpha / S_0 (1-\alpha), \qquad (1)$$

where S_0 represents the solubility of DFC and α represents the slope of the straight line.[12] Using the same procedure described above, a solubility study at pH = 5.5, in which an excess of the solid binary systems was added to aqueous solution, was also performed.

Quantitative determination of DFC was performed by an HPLC system consisting of a liquid chromatograph Alliance 2690 (Waters Corp, Milford, MA) equipped with a photodiode array detector and a computer integrating apparatus (Millennium 32, Waters). Analyses were performed at 227 nm with a Nova Pack C_{18} column (60 Å, 4 μm, Waters). The mobile phase was a mixture of 60% methanol and 40% PBS (vol/vol); delivered at a flow rate of 1.2 mL/min. Samples (20 μL) were injected using an auto sampler. The stock standard solution of diclofenac (1 mg/mL) was prepared by dissolving the drug in methanol and storing at 4°C. A standard calibration curve (peak area of DCF vs known drug concentration) was built up by using working, standard solutions (50-0.135 μg/mL) prepared by dilution of the stock standard solution with the mobile phase. Calibration graphs were plotted according to the linear regression analysis, which gave a correlation coefficient value (R^2) of 0.999. Sample preparation and analyses were performed at room temperature.

In Vitro Dissolution Studies

In vitro dissolution studies of pure drug and binary systems were performed using transparent gelatin capsules containing an amount of formulation equivalent to 25 mg of DCF. Tests were performed in 500 mL of unbuffered distilled water (pH 5.5), according to the *United States Pharmacopeia (USP)* rotating basket method (Erweka apparatus). The experiments were performed at 37°C ± 0.3°C at a rotation speed of 100 ± 2 rpm. At preselected times, 2 mL samples were withdrawn, filtered through polycarbonate membranes (0.45 μm, Millipore), and replaced with 2 mL of prethermostated fresh dissolution medium. Quantitative determination of DCF was performed by HPLC according to the method described above. Dissolution tests were performed in triplicate. Dissolution profiles were evaluated on the basis of dissolution efficiency (DE) and percentage of drug dissolved (DP) at 15 and 60 minutes.[13]

In Vitro Diffusion Studies

In vitro diffusion experiments of DCF from solid binary systems and DCF saturated solution in PBS across a silicone membrane were performed using vertical Franz-type diffusion cells, with an effective diffusional surface area of 0.636 cm^2. Receptor compartments were filled with 6 mL of isotonic phosphate buffer (pH 7), which was constantly stirred with a small magnetic bar and thermostated at 37°C throughout the experiments. A solution sample (1 mL) was applied to the silicone membrane, and the donor chamber was covered with parafilm. The receiving solution was withdrawn after elapsed times of 1, 2, 4, 6, and 8 hours, and the chamber was refilled with fresh prethermostated receptor fluid to ensure sink conditions.

At the end of the experiments, samples of the donor compartment were analyzed and checked for DCF content. Diffusion experiments were performed in triplicate.

Results and Discussion

Phase Solubility Studies

Results of the phase solubility studies are shown in Figures 2 and 3. In particular, Figure 2 presents the solubility profiles of DCF as a function of increasing concentrations of β-CD in aqueous solution at different pH values (ie, 3.0, 5.5, and 7.0). As can be seen, the solubility of the drug increased linearly with the increase of β-CD concentration (≤1 mM), giving rise to A_L-type solubility diagrams.[12] This linear DCF-β-CD correlation, with a slope of less than 1, suggests the formation of a 1:1 (mol/mol) DCF-β-CD inclusion complex, at the different studied pH values. The calculated stability constant values were 331, 214, and 159 M^{-1}, respectively, at pH 3.0, 5.5, and 7.0, indicating that DCF-β-CD complexes (1:1 molar ratio) are sufficiently stable. In fact, values of obtained stability constants are always within the range of 100 to 1000 M^{-1}, which is believed to indicate an ideal value.[14] Actually, smaller values of Kc indicate a too weak interaction between drug and CD, while larger values are symptomatic of an incomplete drug release from the inclusion complex. The Kc (1:1) and S_0 values, corresponding slopes and correlation coefficients of the phase solubility diagrams, are summarized in Table 1. Kc values increased as the pH decreased. These results are reasonable since inclusion complex formation is dependent on the hydrophobic interactions between the drug and the apolar cavity of the β-CD. In fact, at the different pH values, the Kc decreased according to the following order $Kc_{(pH\ 3)} > Kc_{(pH\ 5.5)} > Kc_{(pH\ 7)}$, and this is the consequence of the different hydrophobic character of the guest molecules. DCF is a carboxylic acid (pK_a = 4.18), which is almost completely dissociated at pH 5.5 (95.23%) and pH 7.0 (99.97%). Therefore, at pH 7.0 and 5.5 the DCF solubility is enhanced by the combined effect of ionization and inclusion complexation, which permits the preparation of stable solutions. The solubility diagram obtained at pH 3.0 shows the real contribution of CD on the increased solubility of DCF, because its carboxylic group is almost completely un-ionized at this pH value (5.93% ionized). Obviously, the drug solubility is lower than at pH 5.5 and 7.0, when DCF is also present in the ionized form, but the Kc is higher.

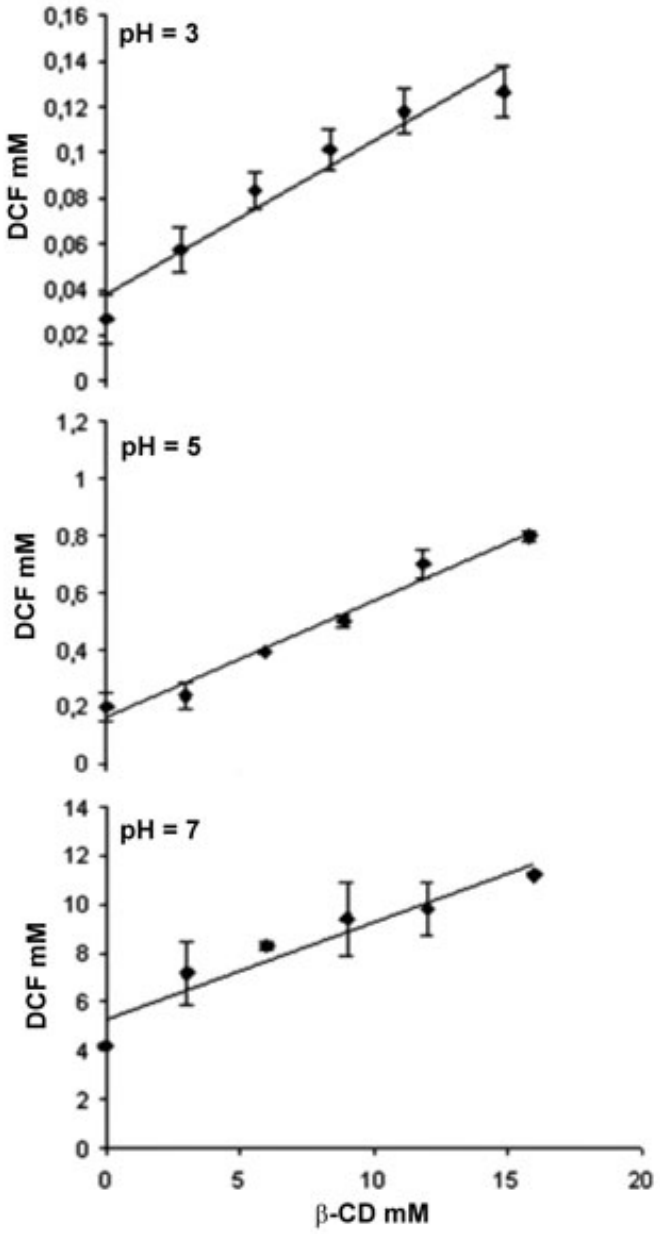

Figure 2. Combined effects of pH and β-CD concentration on the total solubility of diclofenac at 25°C (mean ± SD, n = 3, vertical bar): (A) pH 3.0, (B) pH 5.5, and (C) pH 7.0.

The solubility differences of DCF as a function of the method used for the preparation of the solid binary products, that is, physical mixture and freeze-dried products was also studied. Figure 3 shows that when the freeze-dried product DCF-β-CD (1:1 molar ratio) was used, the drug solubility increased by a factor of 3 compared with that of the physical mixture. Moreover, it was 6-fold higher than that of the pure DCF. On the other hand, the physical mixture also showed an improvement in the DCF solubility by

Table 1. Solubility of Pure Diclofenac (S_0), Slope (α), Stability constant (Kc), and Correlation Coefficient (R^2) as Obtained From the Diclofenac-β-Cyclodextrin Phase Solubility Diagrams

Medium	S_0 ± SD ($\times 10^{-3}$ M)	α	Kc (M^{-1})	R^2
pH 3.0	0.04 ± 0.01	0.0063	331	0.9461
pH 5.5	0.16 ± 0.05	0.0407	214	0.9763
pH 7.0	5.31 ± 0.12	0.3975	159	0.9125

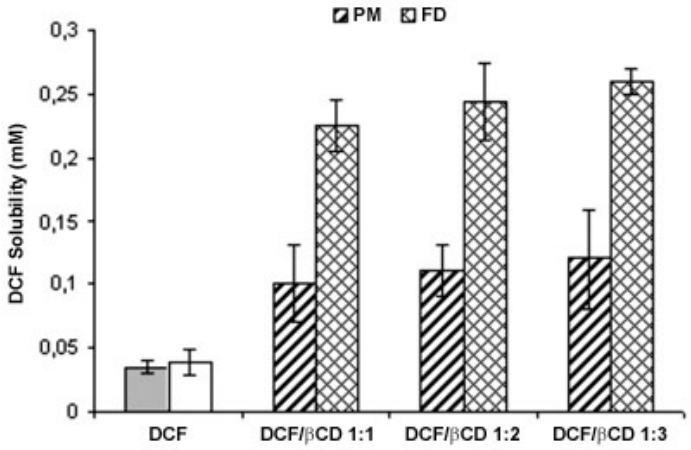

Figure 3. Solubility of diclofenac as a function of preparation method of the solid binary systems and DCF-β-CD molar ratios: Gray column, pure DCF; white column, lyophilized DCF.

a factor of 2 with respect to the pure DCF, while the lyophilized drug alone did not show any solubility enhancement. This result is also indicative that the freeze-drying process did not affect the solid state properties of DCF, as confirmed by the thermal behavior of the lyophilized drug.

Differences in DCF solubility indicate a different interaction between the drug and the β-CD in both methods of preparation. In particular, the higher solubility of the freeze-dried product and the statistical irrelevance of drug solubility improvement using different DCF-β-CD molar ratios indicate that the true inclusion complex was obtained only when the freeze-drying method was used. However, as reported above, the DCF solubility increased also when physical mixtures were prepared indicating that CDs are useful tools for promoting DCF solubility and, therefore, its bioavailability.

X-ray Powder Diffractometry

X-ray patterns of DCF, β-CD, and their binary systems (physical mixture and freeze-dried products) are shown in Figure 4.

Rietveld refinement of the diclofenac XRD pattern (not reported) indicates the presence of 98 wt% of HD2 phase (monocline, space group [SG] C2/c, a = 2.0226, b = 0.6971, c = 2.0061 nm, β 109.64°, Z = 8), while residual peaks are due to HD1 one (monocline SG P21/c, a = 0.8384, b = 1.0898, c = 1.4822, β 92.76°, Z = 4.[15]

The X-ray diffraction pattern of the physical mixture of DCF and β-CD is approximately the superposition of the patterns of the raw materials. On the other hand, the binary system prepared by the freeze-drying method has a completely different pattern, where XRD peaks of DCF are not visible. In particular, the two peaks at 23.5° and 28.5° are not present, thus confirming the existence of a new compound. This behavior can be related either to the formation of an inclusion compound or to the formation of amorphous structures.[16]

Infrared Spectroscopy

Comparison of FTIR spectra of pure DCF and β-CD, together with those of their DCF-β-CD binary systems showed a superimposition of DCF and β-CD signals in the physical mixture (Figure 5). However, the characteristic CO stretching band of DCF was slightly shifted to a higher frequency in the physical mixture. In fact, the CO band shifted from 1694 (pure DCF) to 1696 cm^{-1} in the physical mixture binary products. On the other hand, the CO stretching band of DCF disappeared in the spectrum of the freeze-dried product. These results support the conclusion that formation of the inclusion compound was obtained when the freeze-drying method was used, as previously reported by Barbato et al[17] who hypothesized that the interaction between DCF and β-CD in the freeze-dried system could involve the CO group.

Differential Scanning Calorimetry

Thermal analysis has been reported as a method to characterize CD complexes.[18] Figure 6 illustrates DSC profiles of DCF, β-CD, physical mixture, and freeze-dried products. Thermogram of pure DCF shows a characteristic endothermic peak at 182°C, which represents its melting point. The DSC curve of pure β-CD did not show any endothermic peaks in the melting point region of DCF. The loss of crystal water is observed at a lower temperature (~125°C) as an endothermic peak. The endothermic peak at

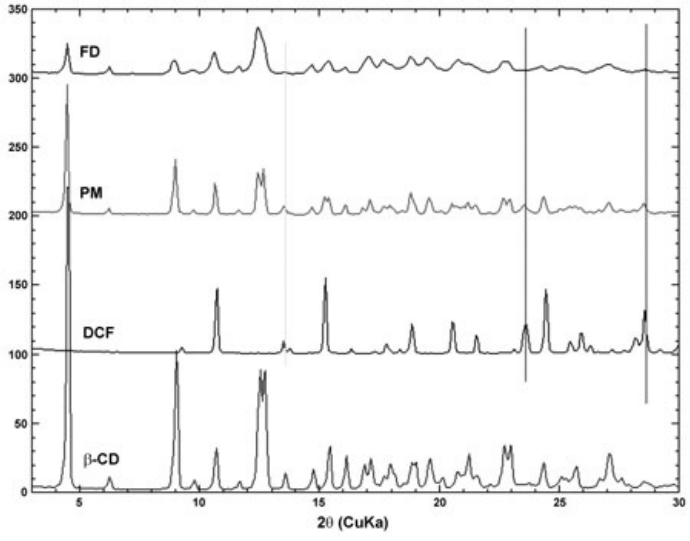

Figure 4. X-ray patterns of DCF, β-CD, and their binary systems: PM, physical mixture; FD, freeze-dried product.

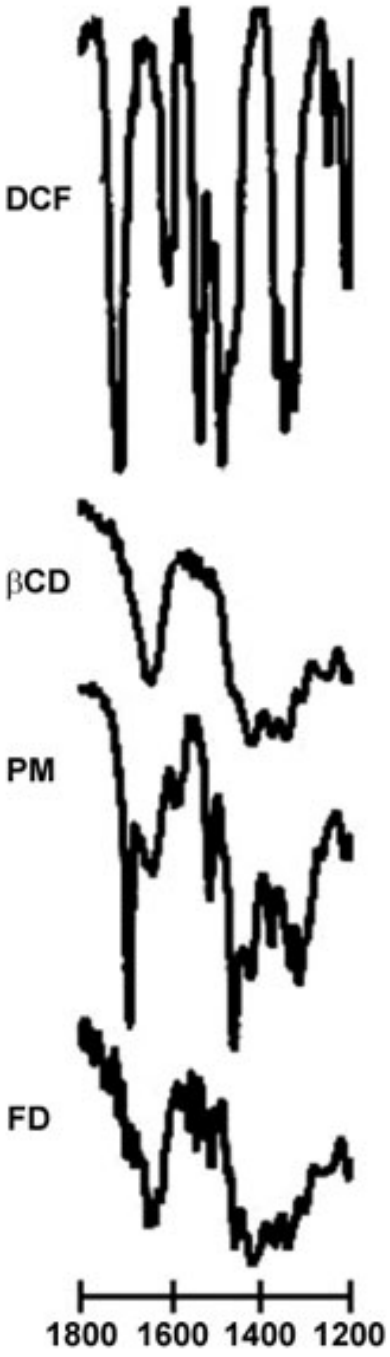

Figure 5. FTIR spectra of DCF, β-CD, and their binary systems: PM, physical mixture; FD, freeze-dried product.

182°C, which is characteristic of DCF, is present in the thermograms of the physical mixture but not in those of the inclusion complexes prepared by the freeze-drying method. These results confirm the real inclusion of DCF into β-CD in the products prepared by the freeze-drying process. In fact, when guest molecules are embedded in the β-CD cavities, their melting point disappears or shifts to lower temperature.[19] Similar behavior was reported in the roll mixing systems of ibuprofen with β-CD, which was attributed to the molecular interaction between drug and β-CD.[20]

Nuclear Magnetic Resonance Studies

NMR spectroscopy is one of the most useful tools for the structural analysis of inclusion complexes. This is because of selective line broadening and/or chemical shifts displacements of ^{1}H NMR signals when a molecule is included in the CD cavity. The ^{1}H NMR spectrum of free DCF (Figure 1) showed the following chemical shifts: δ = 7.53 ppm (H-4,6); δ = 7.20 (H-5); δ = 7.07 (H-13); δ = 6.87 (H-12); δ = 6.29 (H-14), and δ = 3.71 ppm (H-16). In the presence of β-CD, all the aromatic protons were slightly shifted. In particular, all DCF protons were downfield shifted of ~0.09 ppm. These results are in agreement with findings of several authors. In fact, it is known that the inclusion of a guest molecule in a CD ring shifts the ^{1}H NMR signals of the included guest downfield and those of affected CD protons upfield,[21] as a consequence of hydrophobic interaction between host and guest molecules.[22] The fact that all aromatic protons of DCF are shifted suggests that both aromatic rings (Figure 1) may be involved in the complex formation, as already reported by different authors.[17,23] However, it must be pointed out that other investigators found different chemical shift behavior, which led them to suggest that only the aromatic ring holding the

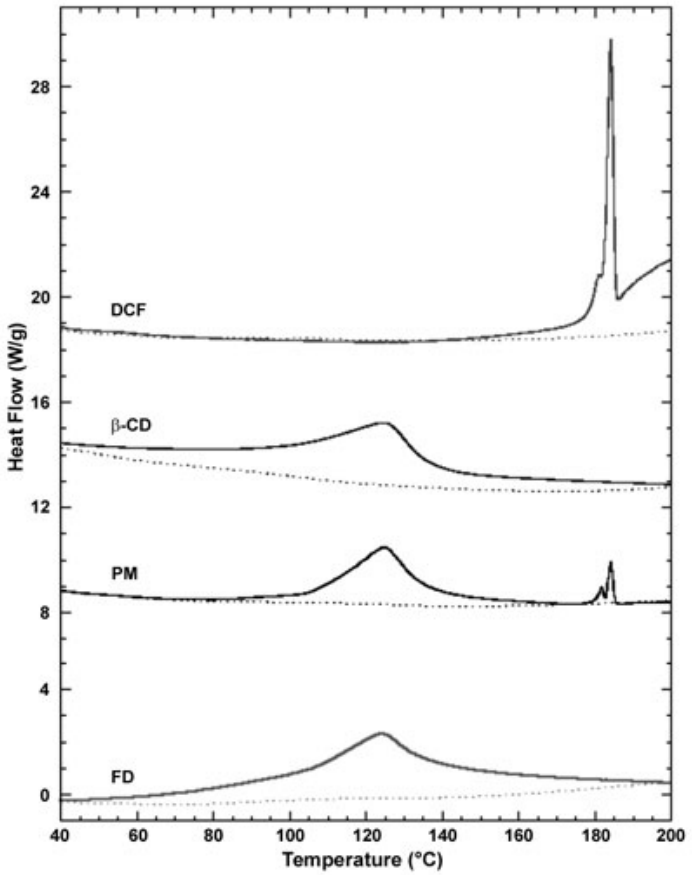

Figure 6. DCS thermograms of DCF, β-CD, and their binary systems: PM, physical mixture; FD, freeze-dried product. Thicker lines correspond to first run, thinner ones to second run.

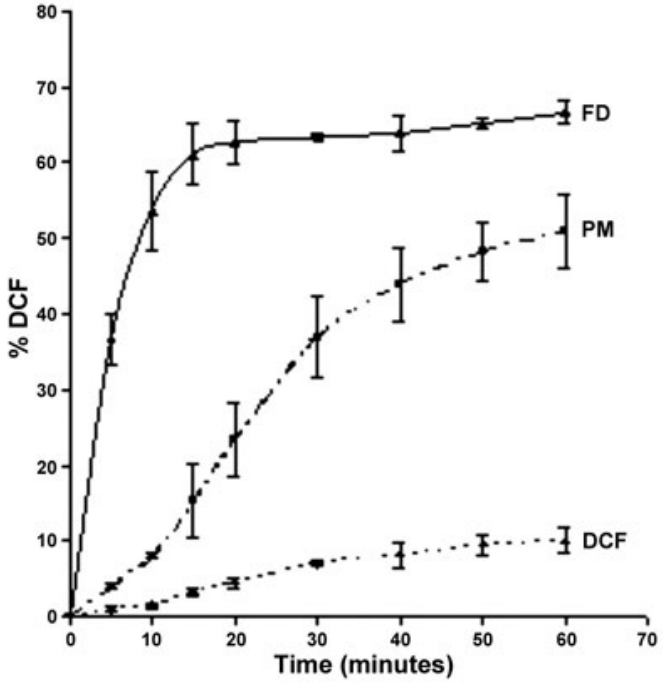

Figure 7. Dissolution profiles of diclofenac and DCF-β-CD binary systems in water (pH 5.5) at 37°C: PM, physical mixture; FD, freeze-dried product.

carboxylic group was involved in the complex formation.[24] The ^{1}H NMR spectra obtained during this study did not show separate signals for free and complexed DCF as a consequence of the fast exchange between the free and included forms.

In Vitro Dissolution Studies

Figure 7 shows dissolution profiles of the 2 DCF-β-CD binary systems (physical mixture and freeze-dried) in comparison with that of the pure drug. In Table 2, dissolution efficiency and dissolution percentage at 15 and 60 minutes are reported together with the time needed to dissolve 50% of drug (t_{50}). As can be seen, all dissolution parameters demonstrated that binary products had better dissolution properties than DCF alone. In particular, both dissolution efficiency and dissolution percentage values increased from the pure drug to the physical mixture to the freeze-dried product, while the time needed to dissolve 50% of drug decreased. After 15 minutes, the percentage of dissolved drug was ~3% for the pure drug, more than 15% for physical mixture and above 61% for freeze-dried product. Therefore, in the first 15 minutes of the dissolution study there was a 5-fold improvement in DCF dissolution when the drug was simply mixed with CDs and a 20-fold increase when the freeze-dried inclusion complex was tested. Dissolution curves show that freeze-dried product was always more effective than the corresponding physical mixture in enhancing DCF dissolution. The fastest dissolution rate was always obtained using DCF-β-CD 1:1 molar ratio. In fact, no significant difference in drug dissolution behavior could be found by increasing the CD amount in the binary systems (data not shown).

The faster dissolution rate obtained with the freeze-dried product is caused by the decrease in DCF crystallinity as a consequence of the specific DCF-β-CD interactions produced by the preparation method. This was demonstrated by the physicochemical characterization of the freeze-dried product. The better dissolution properties of the physical mixture can be attributed both to improvement in drug wettability and to in situ formation of soluble complexes in the dissolution medium.[25]

Diffusion Studies

In order to analyze the influence of different DCF-β-CD molar ratios on the diffusion of DCF across a lipophilic membrane, an in vitro study of drug permeation through a silicone membrane was performed. The experiments were performed in vertical Franz diffusion cells using a DCF saturated solution as a reference. Silicone membranes are useful tools for diffusion experiments because they are lipophilic as the biological membranes, but they are not able to interact with CDs. Therefore, they can be used to optimize CD formulations and to evaluate the true drug thermodynamic activity in the presence of the complexing agent.

Figure 8 shows diffusion profiles obtained from a DCF saturated solution and freeze-dried binary systems, with different DCF-β-CD molar ratios. As can be seen, drug diffusion profiles obtained from the different freeze-dried binary systems were very similar. Moreover, DCF diffusion rate was higher from the control saturated solution. These results confirm that β-CDs do not interact significantly with the silicone membrane.[26] Moreover, although drug diffusion was very similar for all the freeze-dried products, DCF diffusion rate slightly decreased as the CD amount increased. This behavior is the consequence of different

Table 2. Dissolution Efficiency and Dissolution Percentage Values at 15 and 60 Minutes and Time to Dissolve 50% Drug for Diclofenac and Diclofenac-β-Cyclodextrin Systems*

	DE_{15}	DP_{15}	DE_{60}	DP_{60}	$t_{50\%}$
DCF	1.21	3.22	17.88	44.44	> 60
PM	6.60	15.36	30.97	50.96	60
FD	40.31	61.09	57.49	66.68	< 10

*DE indicates dissolution efficiency; DP, dissolution percentage; $t_{50\%}$, time to dissolve 50% of drug; DCF, diclofenac; PM, physical mixture; and FD, freeze-dried. DE was calculated from the area under the dissolution curve at 15 and 60 minutes and is expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time.

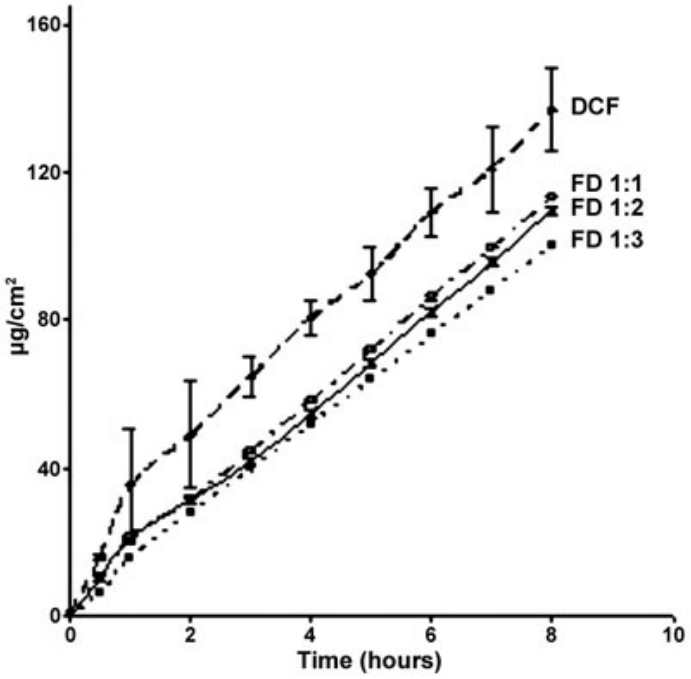

Figure 8. Cumulative amount (%) of diclofenac diffused through a silicone membrane from a saturated drug solution and freeze-dried (FD) binary systems with different DCF-β-CD molar ratios.

drug thermodynamic activity in the studied systems. In fact, for saturated solutions, the thermodynamic activity is constant despite the amount of dissolved drug. In addition, only free molecules can diffuse through the rate-limiting membrane. Therefore, the drug activity is only related to its free molecules in solution. In the presence of β-CD, DCF solubility increases because of the formation of the inclusion complexes, but the actual thermodynamic activity is lower than that of the drug alone. Similar results were recently reported by different authors.[26,27]

As shown in Figure 8, the diffusion profile obtained from the saturated solution is very irregular (R^2 = 0.9589) with high standard deviations. This is a consequence of the higher instability of this system when compared with the DCF-β-CD binary products, which gave a very regular DCF diffusion profile (always $R^2 > 0.995$) with standard deviation less than 4%. Therefore, data obtained from the diffusion study suggest that β-CD is able to both stabilize the system and regularize the diffusion profile, despite any improvement in drug diffusion.

CONCLUSION

Results obtained during this study showed that β-CD is able to improve DCF dissolution properties. The best results were obtained from freeze-dried product, in which a true inclusion of DCF with β-CD was confirmed by studies both in the solid and liquid phase. Despite their different solubility, drug diffusion through a model silicone membrane was higher for the saturated drug solution than the freeze-dried inclusion complexes that were able to stabilize the system leading to a more regular diffusion profile.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support of MIUR (Ministero Istruzione, Università e Ricerca, Rome, PRIN 2003).

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