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Celecoxib-Cyclodextrin Systems: Characterization and Evaluation of In Vitro and In Vivo Advantage

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ABSTRACT Solid dispersions of Celecoxib were prepared with hydroxypropyl β cyclodextrin by various methods such as physical mixture, cogrinding, kneading, and coevaporation. The dispersions were characterized by differential scanning calorimetry (DSC), X-ray diffraction patterns, infrared spectroscopy, and nuclear magnetic resonance studies. The DSC thermograms of the dispersions indicated potential of heat-induced interaction between Celecoxib and cyclodextrin that could influence in vitro drug dissolution. The dispersions exhibited faster rates of dissolution compared to that of Celecoxib. The kneaded dispersion with the fastest in vitro dissolution rate when compressed into tablets showed a better release profile compared to the tablets of pure Celecoxib. In vivo studies revealed that the kneaded dispersion provided for quicker response and was more effective in inhibiting rat paw edema as compared to Celecoxib alone, thus confirming the advantage of improved pharmacological activity of Celecoxib when administered as a solid dispersion with cyclodextrin.

KEYWORDS Celecoxib, Hydroxypropyl β cyclodextrin, Solid dispersion, In vitro dissolution studies, In vivo study

INTRODUCTION

Celecoxib (CXB), a nonsteroidal anti-inflammatory drug (NSAID), is the first selective cyclooxygenase-2 (cox-2) inhibitor used in the treatment of osteoarthritis and rheumatoid arthritis in adult patients. It is also indicated in treatment of acute pain, primary dysmenorrhea, and as an adjuvant in the treatment of familial adenomatous polyposis, a genetic disorder (Connor, 2003; Davies et al., 2000). When used in therapeutic concentration, CXB inhibits only cox-2 as it has a cox-2:cox-1 selectivity ratio of 375 and by sparing cox-1 exhibits lower incidences of gastrointestinal complications unlike traditional, nonselective NSAIDs (Jackson & Hawkey, 2000).

In spite of its high gastrointestinal (GI) permeability, CXB shows incomplete and poor oral bioavailability (www.emea.eu.int./humandocs/pdfs/EPAR/onsenal/370303en6.pdf, 2004). This could be attributed to low

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aqueous solubility of CXB, which leads to its inadequate dissolution in GI fluids and hence poor absorption, distribution, and target organ delivery. Improvement of aqueous solubility in such a case is a valuable goal to improve therapeutic efficacy. Approaches that have been reported earlier in the improvement of solubility of CXB include use of cosolvents like ethanol, glycerol, and polyethylene glycols (Seedher & Bhatia, 2003), and manipulations of the solid state of the drug, which involved preparation of solid dispersions by fusion techniques (Devi et al., 2003) where CXB was melted with various hydrophilic polymers such as polyvinyl pyrrolidone, polyvinyl pyrrolidne-vinyl acetate copolymer, polymethylvinylether-maleic anhydride copolymer, and polyethylene glycol 4000, and the molten mass was rapidly cooled to entrap the amorphous drug in the polymer matrix. The solvent evaporation technique provided fine particulate deposition of CXB from its solution on to the surface of super disintegrants such as sodium starch glycolate, croscarmellose sodium, and crospovidone, which presented a larger surface area for dissolution (Nagarsenker & Dixit, 2002).

The preparation of an inclusion complex of drug with cyclodextrins is another extensively used technique to improve its aqueous solubility and pharmacological activity (Bekerso et al., 1991). Enhancement in solubility of CXB using β cyclodextrin as a complexing agent has been reported (Rawat & Jain, 2004; Reddy et al., 2004). The present study was planned to improve the aqueous solubility and dissolution rate of CXB by preparing its solid dispersions with hydroxypropyl β cyclodextrin (HPBC), one of the highly water-soluble derivatives of β cyclodextrin (Yoshida et al., 1988) employing various methods such as physical mixing, cogrinding, kneading, and coevaporation. The study further aimed at evaluating the pharmacological activity of CXB powder and its solid dispersion by comparing the extent of inhibition of paw edema in rats.

MATERIALS

Celecoxib was obtained as a gift sample from Ethypharm Pvt. Ltd., (Mumbai, India); HPBC was obtained as a gift sample from Cerestar, Inc., (IA, USA); sodium starch glycollate (Primogel™, Avebe Inc., Ulceby, UK), maize starch (Avebe Inc., Ulceby, UK), croscarmellose sodium (Ac-Di-Sol™, FMC Corp., Princeton, NJ, USA), colloidal silicon dioxide (Cab-O-Sil, Cabot, Hanau, Germany), and magnesium stearate (Penwest Pharmaceuticals Co., NY, USA) were generously donated by Sun Pharmaceutical Industries Ltd (Mumbai, India). Directly compressible lactose (Pharmatose DCL 11) was obtained as a gift sample from DMV International, Veghel, Netherlands. All reagents used were of analytical grade. Male Wistar rats were procured from Bharat Serums and Vaccines Ltd., Mumbai, India.

EXPERIMENTAL

Solubility Studies

A phase solubility study was carried out to investigate the effect of HPBC on the solubility of CXB, using the method reported by Higuchi and Connors (1965). Plain distilled water containing no HPBC and aqueous solutions of HPBC (avg. molecular weight—1371.6, degree of substitution—4.9) of different concentrations (5, 10, 15, 20, and 25 mM) were added to excess amounts of CXB and shaken at 30°C for 24 hours. After equilibrium, the solutions were filtered using Whatmann® No.1 filter papers and diluted suitably to determine the concentration of CXB spectrophotometrically at 250 nm. The graph of concentration of CXB was plotted against the concentration of HPBC. The stability constant for the complex was determined from the graph using following equation

$$Ks = \text{slope}/S_0(1 - \text{slope})$$

where slope is obtained from the graph and S_0 is the equilibrium solubility of CXB in water.

Preparation of Solid Dispersions

Solid dispersions of CXB and HPBC were prepared in the molar ratio of 1:1. The physical mixture (PM) was prepared by geometric mixing of CXB and HPBC without applying pressure. The coground dispersion (CD) was prepared by mixing and triturating CXB and HPBC for 15 to 20 minutes. The coevaporated dispersion (COEVAP 1) was prepared by using ethanol as solvent. The drug and HPBC were dissolved in ethanol, and ethanol was evaporated by controlled heating at 45–50°C with continuous stirring of

solution until nearly dry. In COEVAP 2, CXB was dissolved in ethanol and HPBC in water. Both the solutions were mixed and treated in similar fashion as for preparation of COEVAP 1. Kneaded dispersion (KD) was prepared by geometric mixing of powders, CXB and HPBC, and then kneading with 1:1 mixture of ethanol—water to obtain a mass with a pasty consistency, which was dried in a tray dryer at 45° to 50°C. The melt dispersion (MD) was prepared by heating KD to 170°C while stirring and allowing it to quench cool.

All the dispersions were prepared in triplicate and were sieved through BSS 85# sieve (Sieve diameter 180 μ) and stored over anhydrous calcium chloride in a dessicator.

Characterization of Solid Dispersions

Differential Scanning Calorimetry (DSC) Studies

Celecoxib, HPBC, and the solid dispersions, each weighing in the range of 3 to 5 mg, were scanned at a rate of 10°C/min on a Shimadzu DT-40 Thermal Analyzer between 30°C and 330°C under an inert atmosphere of nitrogen.

Infrared (IR) Spectroscopic Studies

The Infrared spectra of CXB, HPBC, and the dispersions were recorded on a Jasco FT/IR 5300 spectrophotometer by potassium bromide (KBr) pellet method.

X-Ray Diffraction (XRD) Studies

Powder X-ray diffraction patterns of CXB, HPBC, and their dispersions were recorded using a Phillips X-ray diffractometer (PW 1710) with a copper target, voltage 40 kV, current 30 mA at a scanning speed of 1° per minute.

Nuclear Magnetic Resonance (NMR) Studies

The ^{1}H NMR spectra of CXB, HPBC, kneaded dispersion, and melt dispersion in D_2O were recorded using the Bruker Ultra shield 500 MHz FT NMR at 298°K with relaxation time of 1 second.

Assay and Dissolution Studies of Solid Dispersions

The solid dispersions were evaluated for drug content and in vitro drug release profile. Dispersion equivalent to 10 mg CXB was weighed and dissolved by sonication in 100 mL of simulated intestinal fluid without enzyme (SIF) (pH 6.8), containing 0.5% polysorbate 80. The solution was suitably diluted and the absorbance was measured spectrophotometrically at 262 nm. The assay method was validated for linearity and intraday and inter-day variation and studied for possible interference of HPBC. Dissolution studies were performed in six replicates using USP Type 2 apparatus in 1000 mL of SIF (pH 6.8), containing 0.5% polysorbate 80 as the medium and maintained at 37°±0.5°C using the speed of 50± 2 rpm. CXB, 100 mg or equivalent quantity of dispersion was weighed accurately and dispersed in the dissolution medium. Aliquots were withdrawn at regular time intervals, filtered, suitably diluted, and read spectrophotometrically at 262 nm.

Formulation Studies

Tablets containing 100 mg of CXB were made by direct compression using Maize starch (26% w/w), directly compressible lactose (61% w/w), sodium starch glycollate (6% w/w), croscarmellose sodium (5% w/w), colloidal silicon dioxide (1% w/w), and magnesium stearate (0.2% w/w) as excipients. Tablets containing KD equivalent to 100 mg CXB were made similarly but excluding lactose. The blend was compressed on an eight-station single rotary machine (Cadmach, India) using capsule-shaped, standard concave punches to obtain tablets of 7 to 8 kg/cm^2 hardness and 5.1 to 5.2 mm thickness. For the assay, three tablets were powdered, and a blend equivalent to 10 mg of CXB was weighed and dissolved in 100 mL of SIF with 0.5% polysorbate 80 by sonication. The suspension was filtered, suitably diluted, and absorbance was read spectrophotometrically at 262 nm. The tablets were studied in six replicates for drug release profile using the same methodology as used for in vitro dissolution studies of the dispersions.

In Vivo Studies

The protocol of studies in animals was approved by the Institutional Animals Ethics Committee. The

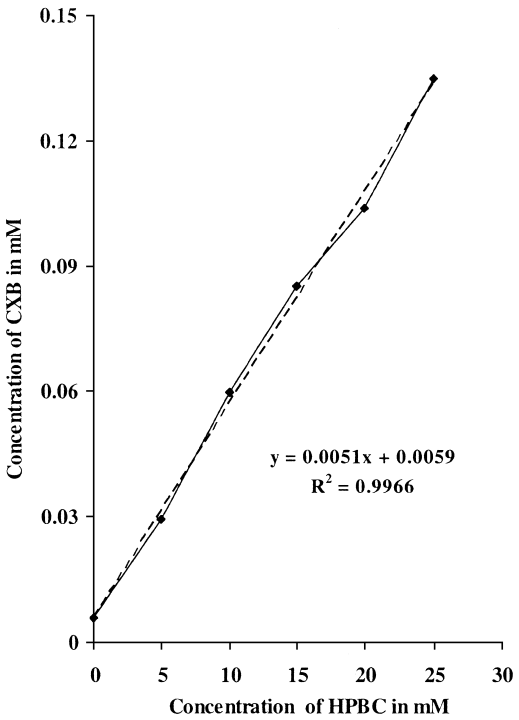

FIGURE 1 Solubility of CXB at Various Concentrations of HPBC.

carrageenan-induced rat paw edema model (Vogel & Vogel, 1997) was used to demonstrate and compare the anti-inflammatory effect of the drug when administered as a plain drug and as a KD.

Wistar rats (n=18) weighing in the range 150 to 170 g were used for the study. The overnight fasted animals were divided into three groups of six rats each, wherein one group was treated with CXB suspended in 0.5% carboxymethycellulose sodium (CMC) slurry; the second group was given an equivalent quantity of KD suspended in CMC slurry; and the third group, which received 2.5 mL of CMC slurry, was used as a control.

After 30 minutes of oral drug administration, rats of all three groups were challenged by a subcutaneous injection of 0.1 mL of a 1% solution of carrageenan in saline, into the plantar site of the left hind paw. The paw volumes were measured using Ugo basile 7140 Plethysmometer, just before and after 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours of carrageenan administration. The percent inhibition of edema at any time for each rat was calculated as

$$\% \text{ Inhibition} = 100 \times [1 - (\mathbf{A} - \mathbf{x}/\mathbf{B} - \mathbf{y})]$$

where **A** is paw volume after administration of carrageenan at time t, and **x** is paw volume before administration of carrageenan. **B** is the mean paw volume of control rats after administration of carrageenan at time t and **y** is mean paw volume of control rats before administration of carrageenan.

The anti-inflammatory activity of the drug and the dispersion was studied at the calculated dose of 11.66 mg/kg body weight of the rats (Dhavan, 1992). The results of the study were statistically evaluated using Nonpaired, two-tailed Student's t-test.

RESULTS AND DISCUSSION

Solubility Studies

The phase solubility diagram (Fig. 1) can be classified as Type AL according to Higuchi and Connors. As the slope of the line was less than unity, it was assumed that the increase in solubility observed was due to the formation of a 1:1 complex. Apparent stability constant $K_{1:1}$ was found to be 895 M^{-1}. It is reported that cyclodextrin-drug complexes with the values of stability constant in the range of 200 to 5000 M^{-1} show improved bioavailability Higuchi and Connors (1965). The stability constant of 895 M^{-1} is very well within the above-mentioned range, and therefore can be expected to improve bioavailability when CXB is used as its solid dispersion with HPBC.

Characterization of Solid Dispersions

DSC Studies

The thermogram of CXB showed a sharp melting endotherm in the temperature range of 159° to 170°C, while that of HPBC showed no thermal changes (Fig. 2A). A shallow endotherm was seen in the range of 157° to 163°C in all the dispersions, indicating partial amorphization of the drug due to drug HPBC interaction. Also, a characteristic endotherm was seen in the range of 250° to 290°C in all the dispersions. This endotherm was not observed in the thermogram of CXB as well as in that of CXB powder following trituration, evaporation from hydro-alcoholic solution, or kneading with the hydro-alcoholic mixture. This confirmed that the methods of preparation of dispersions like trituration and evaporation did not lead to the thermal event.

The other possibility was an interaction between CXB and HPBC promoted by the heating process

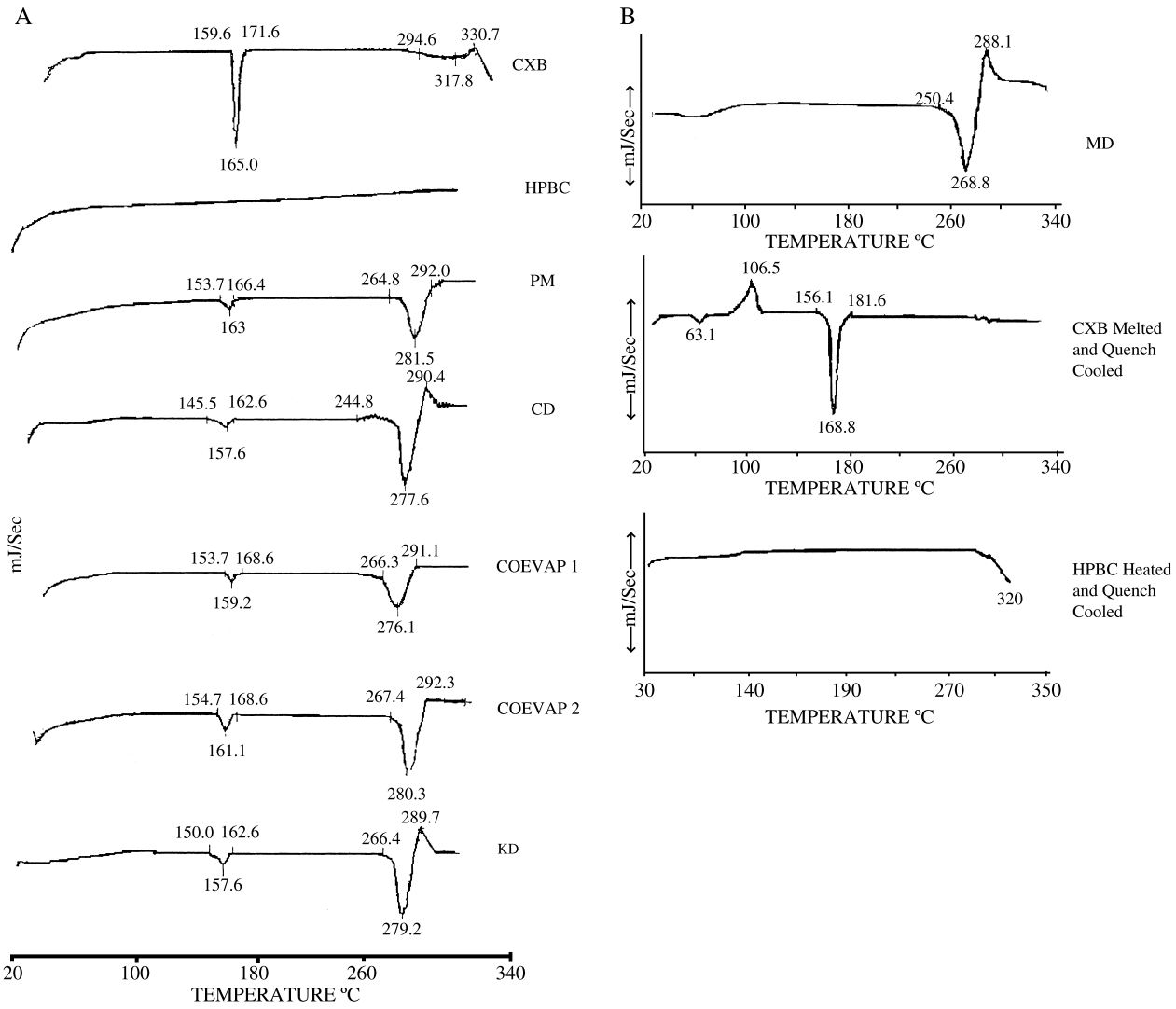

FIGURE 2 **(A) DSC Scans of CXB, HPBC, and Their Solid Dispersions. (B) DSC Scans of MD, CXB-Melted, and Quench-cooled: and HPBC, Heated and Quench-cooled.**

in the DSC operation. Melting of one of the components can facilitate interaction of drug and carrier (Ahsan & Viega, 2000). To investigate this possibility, MD was prepared by heating KD and allowing it to shock cool. The MD was subjected to DSC scan in which melting endotherm of the drug had disappeared completely but endotherm in the range of 250° to 280°C was observed (Fig. 2B). The CXB alone when melted and quench cooled was rendered in its amorphous form; the scan of which exhibited an endotherm at 63°C indicating glass transition, a recrystalization exotherm at 106°C followed by a melting endotherm at 168°C (Chawla et al., 2003). However, it did not show an endotherm in the range of 250° to 280°C as compared to the one seen in the DSC heating curve of the MD (Fig. 2B). Similarly, HPBC alone heated and quench cooled when subjected to DSC study did not exhibit any thermal event (Fig. 2B). This indicated heat-induced interaction of the drug with HPBC, which resulted in the formation of an association form exhibiting different thermal behavior compared to CXB and dispersions.

IR Spectroscopy

IR spectra of PM, CD, COEVAP 1, COEVAP 2, KD, and MD did not show any significant changes in the characteristic peaks when compared with the spectra of CXB and HPBC, thus indicating minimal interaction between CXB and HPBC during mixing, trituration, coevaporation, kneading, and melting.

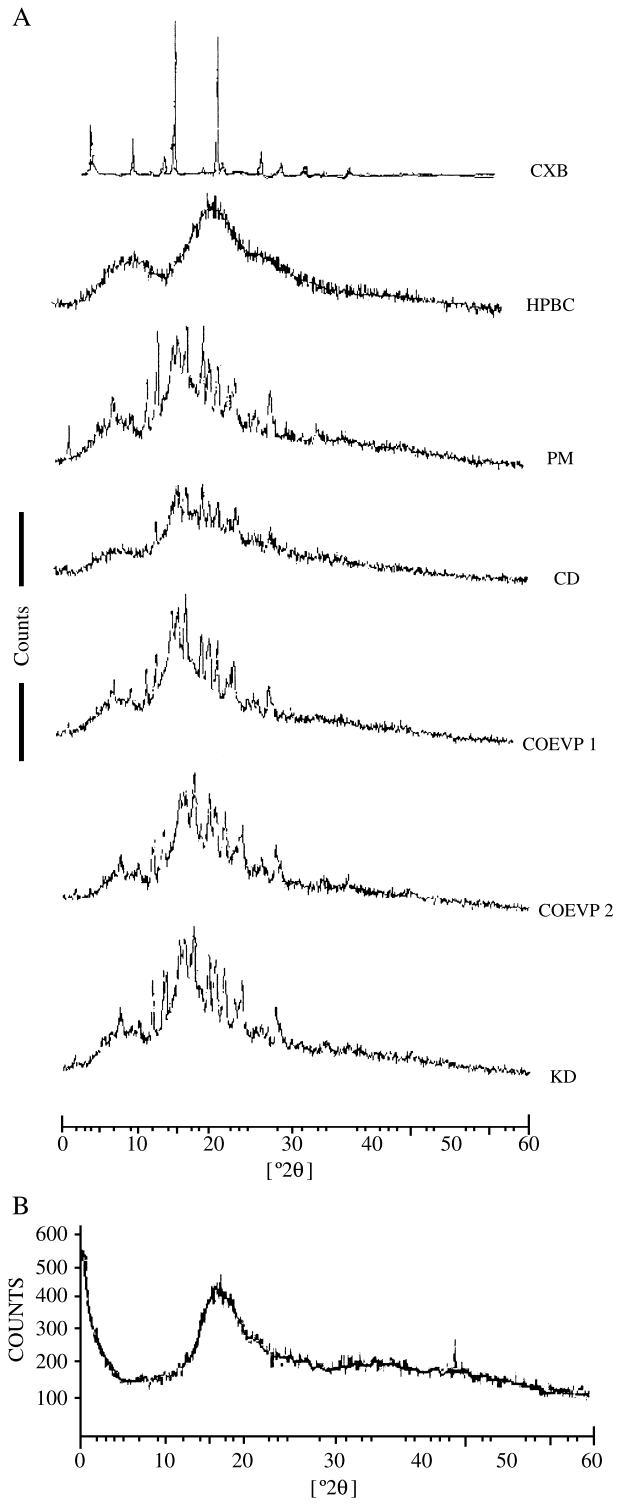

FIGURE 3 **(A) XRD Scans of CXB, HPBC, and Their Solid Dispersions. (B) XRD scan of MD.**

XRD Studies

The XRD scan of CXB showed intense peaks of crystallinity. Scans of PM, CD, COEVAP 1, and COEVAP 2 showed fewer peaks with lower intensity, indicating partial amorphization of the drug in its solid dispersions (Fig. 3A). The X-ray scan of KD showed greater amorphization of the drug.

The scan of MD was considerably different from that of CXB and solid dispersions in the region of 10–15° of 2θ (Fig. 3B). This suggested that the heating of drug with HPBC resulted in an association form, which exhibited different solid-state properties.

NMR Spectroscopy

The ^{1}H NMR spectra of CXB and its dispersions were studied to gain insight into the interaction of the drug with cyclodextrin. Spectrum of pure CXB in D_2O exhibited two triplets in the aromatic region (Fig. 4A). The triplet at 7.347 ppm signified protons at positions 13, 14, 16, and 17 (Fig. 4B). In the spectra of KD and MD, these protons were shielded slightly in the form of two doublets (Table 1). The triplet at 7.447 ppm in the spectrum of pure CXB is assigned to protons at positions 2, 3, 5, and 6. In the spectra of both KD and MD; these protons exhibited significant deshielding in the form of two doublets, which indicated possible inclusion of benzene sulfonamide ring (bearing these protons) in the cavity of HPBC. The spectrum of MD did not differ significantly from that of KD, thus providing no evidence for heat induced changes in mode of association of drug with HPBC.

Assay and In Vitro Dissolution Studies

The method of analysis exhibited linearity in the range of 2 to 20 mcg/mL. Relative standard deviation was found to be less than 2% for intra and inter-day variation, and presence of HPBC did not interfere with the test. Drug content of all the solid dispersions of CXB when determined in duplicate was found to be 100%±2%, indicating chemical stability and content uniformity of CXB in its dispersion form. The KD, COEVAP 2, CD, PM, and COEVAP 1 showed improved rates of in vitro dissolution profile as compared to CXB in decreasing order (Fig. 5). Statistical evaluation of dissolution profiles using nonpaired, two-tailed Student's t-test revealed that at 95% confidence level ($p<0.05$), there was a significant difference between the amount of drug released from KD, CD, and COEVAP 2 and that of plain drug at 10, 20, 30, and 45 minutes intervals. The PM showed

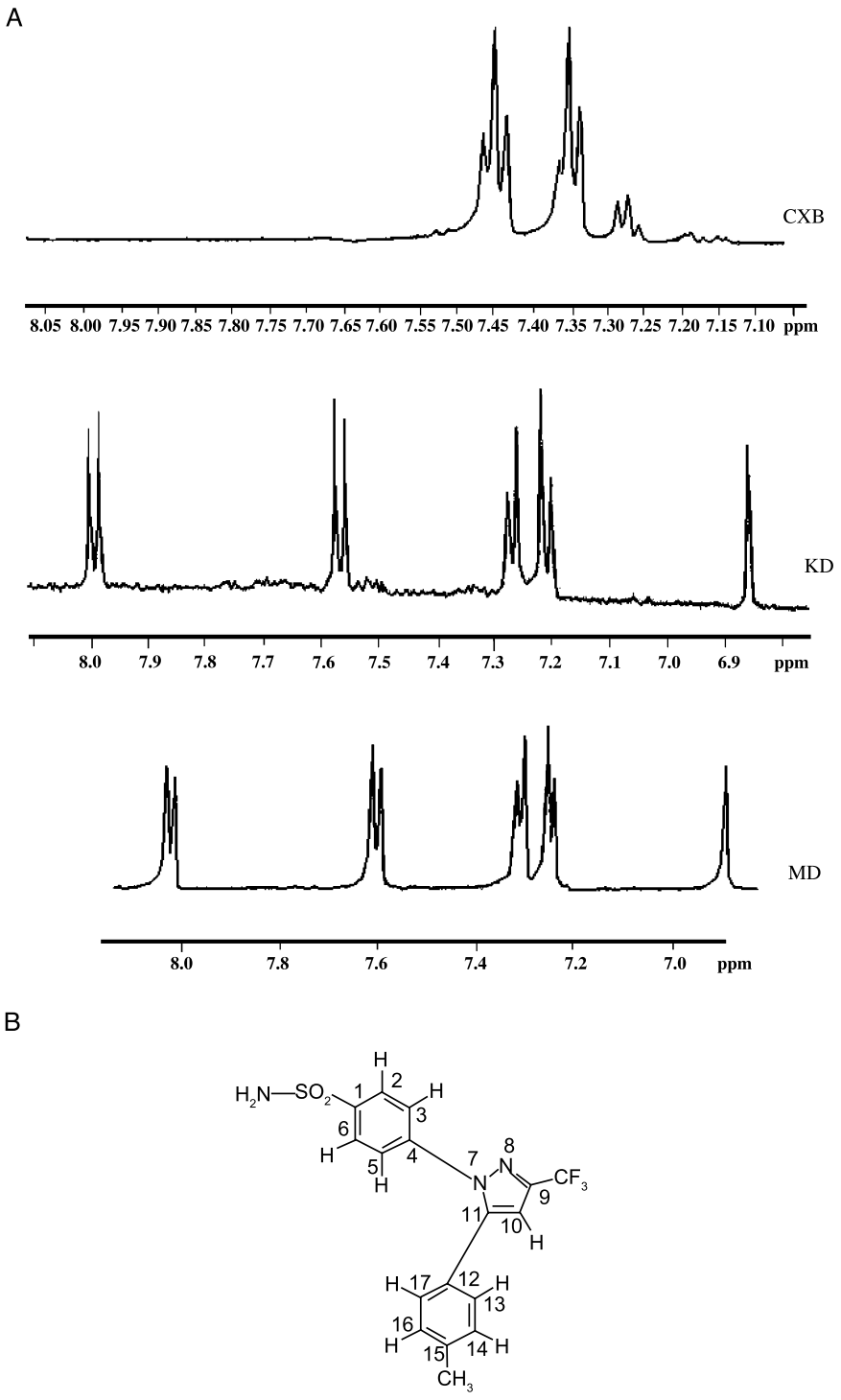

FIGURE 4 **(A) Proton NMR Spectra of CXB and its Solid Dispersions. (B) Structure of CXB.**

significantly higher release than drug at 45- and 60-minute intervals, which could be because of in situ interaction between CXB and HPBC in the dissolution medium leading to better dissolution of CXB. Complexation, partial amorphization of the drug, and its improved wettability in the presence of HPBC are factors that influenced the dissolution profile of drug in its solid dispersions. In the case of COEVAP 1, the absence of water as well as different rates of (crystallization of CXB and HPBC from their alcoholic solution could have resulted in poorer association between CXB and HPBC, which led to

TABLE 1 Chemical Shifts of Protons of CXB and Its Solid Dispersions

Protons	Chemical shifts of CXB in ppm	Chemical shifts of KD in ppm	Chemical shifts of MD in ppm
2.6	7.447	8.04	8.06
3.5	7.447	7.574	7.634
13.17	7.347	7.207	7.273
14.16	7.347	7.268	7.336

its lower dissolution rate than other solid dispersions prepared at room temperature). In the case of MD, the entire dissolution profile was significantly lower than that of plain CXB. Melt quenching is reported to cause conversion of CXB from crystalline state to glass, which results in improved dissolution characteristics (Paradkar et al., 2003). However, such a phenomenon was not observed in the case of MD, which may be due to the presence of HPBC. The absence of water during preparation of MD could have affected the formation of an inclusion complex between CXB and HPBC, leading to a poor dissolution profile of melt dispersion compared to that of other solid dispersions. The cumulative drug release shown by MD at the end of 3 hours was about 30%, which was significantly lower than even CXB powder. In addition, the larger mean particle size of MD (110 μ), compared to that of CXB (60 μ), as well as greater crystalline interaction energy (Yalkowsky, 1981) in MD suggested by its higher melting point, could have contributed to the poor dissolution profile of MD.

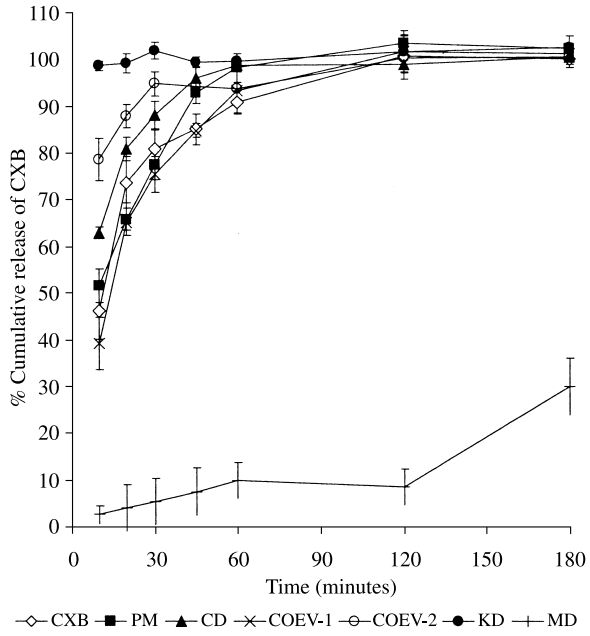

FIGURE 5 In Vitro Dissolution Profiles of CXB and its Solid Dispersions (Each Point is Mean ± s.d of Six Replicates).

Dispersion made by kneading (KD), which exhibited the best dissolution profile, was used for the formulation development and in vivo studies.

Formulation Studies

During in vitro dissolution studies, KD exhibited 100% drug release within 10 minutes, whereas tablets prepared by compressing KD provided drug release within 45 minutes with $T_{50\%}$ value of less than 20 minutes. Disintegration of tablets (disintegration time: 7 to 8 minutes) was the step that delayed the drug release slightly in comparison with dispersion. However, these tablets showed faster and reproducible release as compared to the tablets containing pure drug and no HPBC, which showed complete release in 3 hours with $T_{50\%}$ of 40 minutes (Fig. 6). This confirmed

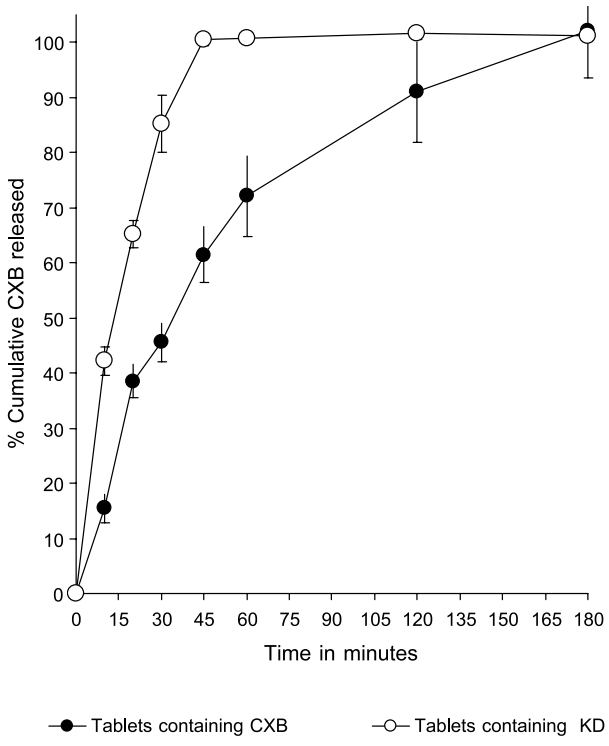

FIGURE 6 Comparative Drug Release Profiles of Conventional Tablets Containing CXB and Tablets Containing KD (Each Point is Mean ± s.d of Six Replicates).

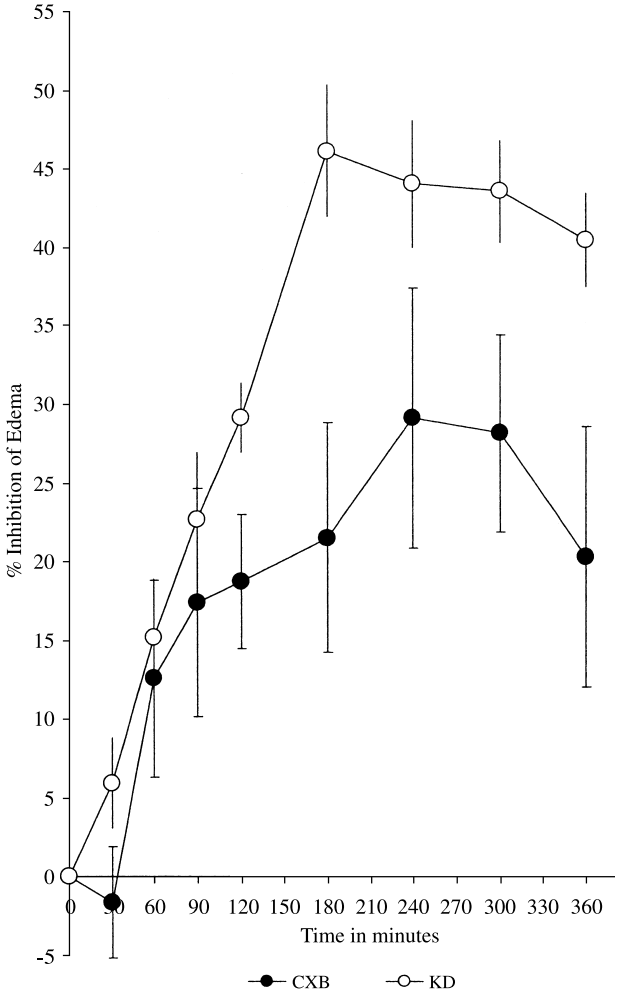

FIGURE 7 **In Vivo Studies of CXB and its Solid Dispersion (Each Point is Mean ± s.d of Six Observations).**

the advantage of improved aqueous solubility of CXB in its solid dispersion form, which can be formulated as tablets with better dissolution characteristics.

In Vivo Studies

The anti-inflammatory activity of CXB was evaluated on the basis of its ability to inhibit the edema produced in hind paw of rats after challenging with the carrageenan. Increase in paw volumes after challenge with carrageenan in untreated, drug-treated, and dispersion-treated groups was compared to assess possible improvement in activity of drug when associated with HPBC. The paw edema values were treated suitably to obtain % inhibition of edema at each time point, and the results wire statistically evaluated by applying nonpaired, two-tailed Student's t-test. The drug in the form of KD showed maximum inhibition of edema at 180 minutes, whereas the drug alone provided maximum activity at 240 minutes (Fig. 7). The value of inhibition of edema provided by drug in the form of KD was higher at all the time points of evaluation and significantly higher at all time points after 120 minutes at 95% confidence level ($p<0.05$) compared to the plain drug. Thus, CXB in the form of KD was faster and more effective in inhibiting rat paw edema as compared to CXB alone. This confirmed the advantage of enhanced anti-inflammatory activity due to improved bioavailability of CXB when administered as KD with HPBC over pure drug.

CONCLUSIONS

The CXB-HPBC association in the form of solid dispersions prepared at room temperature exhibited improved aqueous solubility leading to superior in vitro dissolution profile. This was attributed to amorphization of CXB as revealed by DSC, XRD, and NMR studies. However, complete inclusion was not clearly demonstrated. The CXB-HPBC association at higher temperature in the form of melt dispersion did not provide an advantage in the in vitro dissolution profile compared to that of CXB. The tablets prepared by compressing KD released drug at a slower rate compared to the quick drug dissolution exhibited by powder dispersion. The release profile of the tablets containing KD was better and reproducible as compared to that of the tablets in which HPBC was not used. In vivo studies confirmed the advantage of enhanced anti-inflammatory activity due to improved dissolution rate, which must have resulted in better availability of CXB when administered as its solid dispersion over drug alone.

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