

## Preparation and characterization of etoricoxib- $\beta$ -cyclodextrin complexes prepared by the kneading method

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The binary system of etoricoxib with  $\beta$ -cyclodextrin ( $\beta$ -CD) was prepared by the kneading method. Drug-cyclodextrin interactions in solution were investigated by the phase solubility analysis. Differential scanning calorimetry, infrared spectroscopy, powder X-ray diffractometry and microscopic study were used to characterize the solid state of all binary systems, whereas their dissolution properties were evaluated according to the USP XXIII paddle method. The results indicate partial interaction of the drug with  $\beta$ -CD in the physical mixture and complete interaction in the kneaded complex. The dissolution of etoricoxib was notably increased as compared to pure drug as well as its physical mixture. The complex showed more than 75% drug released in 30 min.

*Keywords:* etoricoxib, cyclodextrin, complexation, kneading method

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Etoricoxib (ET), 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine, a novel highly selective COX-2 inhibitor, is used for a variety of acute and chronic inflammatory diseases (1). However, its very low aqueous solubility and poor dissolution can cause formulation problems and limit its therapeutic application by delaying the rate of absorption and the onset of action (2). Solid dispersions of etoricoxib are reported with lipid carrier and polymers for improving dissolution (3, 4). Cyclodextrins are commonly used in drug formulations as solubility enhancers because of their ability to form water soluble inclusion complexes with poorly water soluble drugs (5, 6). Various anti-inflammatory drugs have been complexed with cyclodextrins, thus obtaining further advantages such as dose lowering, reduction of side effects (particularly gastric irritation) and taste masking (7, 8). The method of complexation may play a role in drug solubilization (9). Therefore, it seemed of interest to extend our investigations to a series of binary systems of etoricoxib with  $\beta$ -cyclodextrin.

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## EXPERIMENTAL

### *Materials*

Etoricoxib working standard was procured as a gift sample from Sun Pharmaceutical Industries Ltd., India.  $\beta$ -cyclodextrin ( $\beta$ -CD) was procured as a gift sample from Cadila Pharmaceuticals Ltd., India. Methanol and potassium dihydrogen orthophosphate were purchased from S. D. Fine Chem. Pvt. Ltd., India.

### *Phase solubility studies*

An excess of drug was added to 10 mL of water or  $\beta$ -CD aqueous solutions (3–20 mmol L<sup>-1</sup>) in 25-mL stoppered conical flasks and shaken at room temperature on a magnetic stirrer (10). At equilibrium after 2 days, aliquots were withdrawn, filtered (0.22  $\mu$ m pore size, Whatman UK) and spectrophotometrically assayed for drug content at 284.0 nm (Shimadzu UV-160A Spectrophotometer, Shimadzu, Japan). The apparent 1:1 stability constant of the etoricoxib-cyclodextrin complex was calculated from the phase-solubility diagram:

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

where  $K_c$  is the stability constant (L mol<sup>-1</sup>), slope is obtained from the linear relationship between the concentration of etoricoxib and  $\beta$ -CD and  $S_0$  is etoricoxib solubility (mmol<sup>-1</sup> L). Each experiment was carried out in triplicate (*RSD* < 3%).

### *Preparation of physical mixtures and the solid inclusion complex*

For physical mixtures, ET and  $\beta$ -cyclodextrin were weighed accurately at a 1:1 molar ratio, mixed thoroughly by trituration in a mortar and sieved through 0.25 mm sieve. All physical mixtures were stored in dessicator until further evaluation.

The inclusion complex of etoricoxib with  $\beta$ -CD was prepared at a 1:1 molar ratio by wetting the physical mixture in a mortar with a minimum volume of ethanol/water (1:1, by volume) mixture and kneading thoroughly with a pestle to obtain a paste, which was then dried under vacuum at room temperature, sieved through 0.25 mm sieve and stored in a dessicator until further evaluation.

### *Inclusion efficiency*

The kneaded complex and its physical mixtures (25 mg) were placed in 25-mL volumetric flasks. Methanol (10 mL) was added, mixed thoroughly and sonicated for 30 min. The volume was made up to the mark with methanol. The solution was suitably diluted with the same solvent and spectrophotometrically assayed for drug content at 284.0 nm. Etoricoxib content was calculated as above.

### *Dissolution studies*

Dissolution studies were performed in phosphate buffer (pH 7.4, 900 mL) at  $37 \pm 0.2$  °C, using USP XXIII apparatus (Electrolab, India) with a paddle rotating at 50 rpm (11). Solid products, each containing 60 mg of drug, were subjected to dissolution. At fixed time intervals, withdrawn samples were filtered (Whatman filter paper No. 41) and spectrophotometrically assayed for drug content at 284.0 nm. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time  $t$  (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time (12).

### *Differential scanning calorimetry (DSC)*

DSC analysis was performed using DSC (Model DT-60, Shimadzu). Samples (Shimadzu libror AEG 220 electronic balance, 5–7-mg) were heated in open aluminium pans at a rate of  $10$  °C  $\text{min}^{-1}$  in a 0–300 °C temperature range under a nitrogen steam. The instrument was calibrated using indium (melting point, 156.61 °C; enthalpy of fusion, 28.71 J  $\text{g}^{-1}$ ).

### *X-ray powder diffractometry (XRPD)*

X-ray powder diffraction patterns were recorded on an X-ray diffractometer (Model X'Pert, Philips, the Netherlands) using Ni-filtered, Cu K $\alpha$  radiation, voltage of 40 kV and 25 mA current. The scanning rate employed was  $1^\circ$   $\text{min}^{-1}$  over the 0–100° diffraction angle ( $2\theta$ ) range.

### *Fourier transform infrared (FTIR) spectroscopy*

FTIR spectra were recorded on samples prepared in KBr using FTIR-8400S with IR solution software (Shimadzu). Data were collected over a spectral region from 4000 to 650  $\text{cm}^{-1}$  with resolution 4  $\text{cm}^{-1}$  and 100 scans.

## RESULTS AND DISCUSSION

### *Preliminary studies*

The complexation of etoricoxib with  $\beta$ -CD was studied at molar ratios of 1:0.5, 1:1.0, 1:1.5, 1:2.0, 1:2.5, and 1:3.0. The complexes were prepared by the kneading method and were characterized by inclusion efficiency, dissolution, wettability and HPTLC studies. All complexes showed increased dissolution efficiency, reduced time required for 50% drug to be dissolved and improved wettability (less wetting time, 76–45 min, compared to pure drug) and almost constant inclusion efficiency. HPTLC of the complex suggested only one component in prepared systems (data not shown).

Higher dissolution (> 75% released in 30 min) was obtained using a 1:1 molar ratio of the drug to  $\beta$ -CD. Therefore further investigations were carried out for the 1:1 molar ratio.

### Phase solubility

Etoricoxib is a sparingly soluble drug. The solubility of etoricoxib in distilled water at pH 6.8 at room temperature was  $24.0 \mu\text{g mL}^{-1}$  and was notably affected by the presence of  $\beta$ -CD. Solubility of ET in  $4 \text{ mmol L}^{-1}$   $\beta$ -CD aqueous solution was  $0.025 \text{ mmol L}^{-1}$  while it was  $0.045 \text{ mmol L}^{-1}$  in  $20 \text{ mmol L}^{-1}$   $\beta$ -CD solution. The obtained phase solubility diagram was linear (Fig. 1) and could be classified as  $A_L$  type according to Higuchi and Connors (10). The slope of solubility diagram was less than one; it was therefore assumed that the solubility increase could be attributed to the formation of the 1:1 complex.

Stability constant value obtained for the etoricoxib-CD complex was  $170.13 \text{ L mol}^{-1}$ , which indicated that the etoricoxib- $\beta$ -cyclodextrin complex at a 1:1 ratio is adequately stable (10).

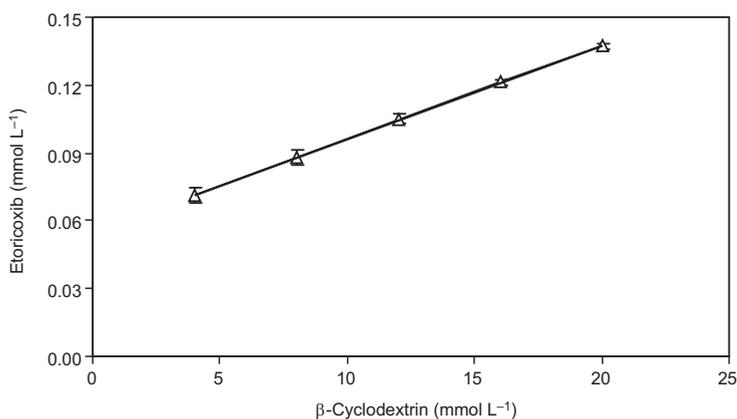


Fig. 1. Phase solubility diagram of etoricoxib in 3–15  $\text{mmol L}^{-1}$   $\beta$ -cyclodextrin aqueous solution (mean  $\pm$  SD,  $n = 3$ ). Linear equation is  $y = 0.0041x + 0.0547$  ( $R = 0.9988$ ).

### Inclusion efficiency

The percentage of etoricoxib in the samples ranged from  $98.2 \pm 0.2$  to  $100.2 \pm 0.1$  ( $n = 3$ ), as reported in Table I. This indicated that etoricoxib was uniformly distributed in all the samples.

### Dissolution

The *in vitro* dissolution profiles of the drug, physical mixture and inclusion complex are shown in Fig. 2. The dissolution of complexes was higher compared to the drug alone. The dissolution profile of the kneaded complex (1:1 molar ratio) showed 80.0% drug released in 30 min while that of the 1:1 physical mixture and pure drug showed 50.8% and 40.7%, respectively. This enhancement can be attributed to the higher hydrophilic character of the systems due to the presence of the carrier, which can reduce the interfacial

Table I. Inclusion efficiency, dissolution efficiency,  $t_{50}$  and wetting time of the drug and its preparations<sup>a</sup>

Type	Inclusion efficiency (%)	Dissolution efficiency in 120 min (%)	$t_{50}$ (min)	Wetting time (min)
Drug	100.2 $\pm$ 0.1	47.3 $\pm$ 1.0	59.9 $\pm$ 2.4	149.0 $\pm$ 1.0
1:1 kneaded complex	98.2 $\pm$ 0.2	77.9 $\pm$ 0.3	3.7 $\pm$ 0.0	69.5 $\pm$ 1.0
1:1 physical mixture	99.5 $\pm$ 0.2	62.7 $\pm$ 0.7	7.2 $\pm$ 0.1	73.5 $\pm$ 1.0

<sup>a</sup> Mean  $\pm$  SD,  $n = 3$ .

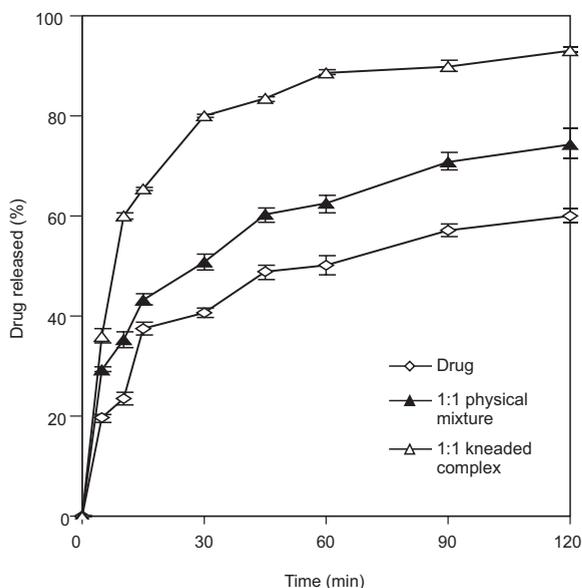


Fig. 2. Dissolution profile of etoricoxib and its preparations (mean  $\pm$  SD,  $n = 3$ ).

tension between the poorly water soluble drug and the dissolution medium (14). Moreover, in the case of  $\beta$ -CD, in the early stage of the dissolution process, the carrier dissolves more rapidly than the drug. Hence, it can act on the hydrodynamic layer surrounding the drug particles, resulting in an *in situ* inclusion process that improves the dissolution of the drug (14). In fact, the systems containing a larger amount of  $\beta$ -CD showed faster drug dissolution. It must be pointed out that the 1:1 kneaded complex showed improved drug dissolution compared to its physical mixture. As shown above, the kneaded complex showed 1.6 time higher dissolution in 30 min than the physical mixture.

$DE$  values and the time taken for 50% dissolution ( $t_{50}$ ) based on the dissolution data were calculated according to the Khan method (12) (Table I). Also, all the complexes of ET with  $\beta$ -CD exhibited higher  $DE_{120}$  values ( $DE$  for 120 min) than ET itself and its physical mixture, namely 77.9 *vs.* 62.7 and 47.3% respectively. Therefore, the 1:1 kneaded

complex and 1:1 physical mixture showed 1.7 and 1.3 times higher dissolutions efficiency compared to pure drug in 120 min. The  $DE_{120}$  values increased as the proportion of  $\beta$ -CD in complexes was increased.

### DSC

DSC curves of the pure drug,  $\beta$ -CD, 1:1 molar physical mixture and 1:1 molar kneaded complex are shown in Fig. 3. DSC curve of the drug showed a sharp endothermic peak at 140.68 °C corresponding to the melting point of etoricoxib. DSC curve of  $\beta$ -CD showed a slightly sharp endothermic peak at 148.59 °C corresponding to the melting point of  $\beta$ -CD. DSC curve of the 1:1 molar ratio physical mixture of the drug and  $\beta$ -CD showed two broad endothermic peaks, one broad peak at 130.74 °C corresponding to etoricoxib and another broad peak at 139.18 °C corresponding to  $\beta$ -CD. DSC curve of the 1:1 molar ratio kneaded complex of the drug and  $\beta$ -CD showed two broad endothermic peaks, one broad peak at 133.20 °C corresponding to etoricoxib and another broad peak at 150.99 °C corresponding to  $\beta$ -CD. Peak temperatures in the physical mixture and kneaded complex were slightly shifted with respect to the drug alone.

The  $\Delta H$  values of the drug,  $\beta$ -CD, physical mixture and its complex were found to be  $-88.52$ ,  $-78.74$ ,  $-40.27$  and  $-22.45$  J g<sup>-1</sup>, respectively. The reduction of the kneaded complex  $\Delta H$  value compared to the pure drug and physical mixture could be attributed to the amorphous form of the drug in the complex.

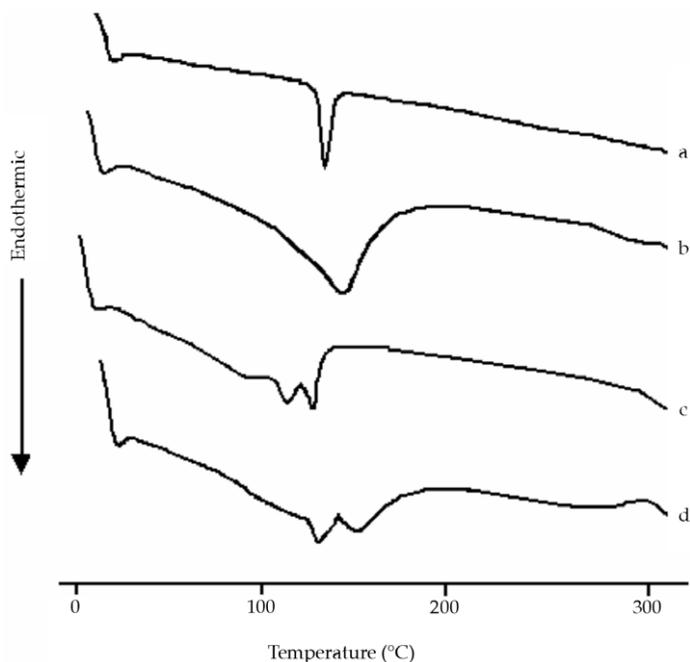


Fig. 3. DSC thermograms of: a) drug, b)  $\beta$ -CD, c) 1:1 physical mixture and d) 1:1 kneaded complex.

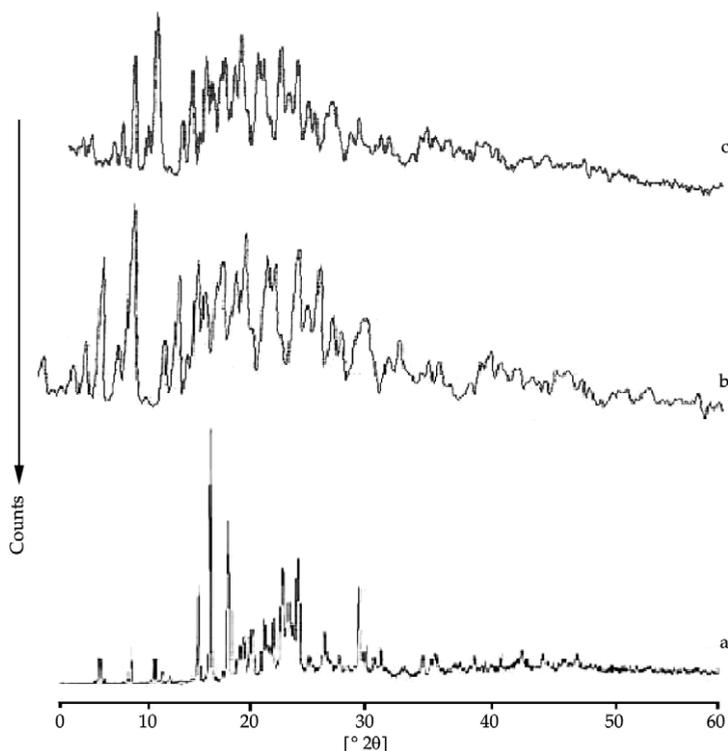


Fig. 4. XRD of: a) drug, b) 1:1 physical mixture and c) 1:1 kneaded complex.

### XRPD

The X-ray diffraction patterns of the drug, 1:1 physical mixture and 1:1 kneaded complex are presented in Fig. 4. Characteristic peaks appeared in the XRPD pattern of the drug alone, suggesting that the drug is present as a crystalline material. All the peaks of etoricoxib in the complex showed lower intensity compared to the pure drug and physical mixture. This result indicated that the drug in the complex is completely amorphous compared to the pure drug as well as physical mixture.

### FTIR

The FTIR spectra of pure etoricoxib showed characteristic peaks at  $1598.9\text{ cm}^{-1}$  (C=N stretching vibration),  $1433.0$ ,  $1300.0$ ,  $1130.2$  and  $1083.9\text{ cm}^{-1}$  (S=O stretching vibration) and  $839.0$ ,  $781.1$  and  $638.0\text{ cm}^{-1}$  (C–Cl stretching vibration). The spectrum of pure  $\beta$ -CD showed characteristic peaks at  $3290.3$  and  $3230.5\text{ cm}^{-1}$ . The spectrum of the physical mixture is exactly matched with the  $\beta$ -CD spectra and the crystalline drug spectrum. This indicated that no interaction occurred during simple physical mixing of the drug and  $\beta$ -CD. The complexes of etoricoxib with  $\beta$ -CD revealed a shift and slight broadening of

S=O stretching vibration ( $1080.1\text{ cm}^{-1}$ ) peak of etoricoxib and O–H stretching vibration peaks ( $3344.3$  and  $3290.3\text{ cm}^{-1}$ ) characteristic of the carrier. These observations might indicate the possibility of intermolecular hydrogen bonding via the S=O group of etoricoxib and OH group of  $\beta$ -CD.

### Wettability

The wetting time (13) for the drug, its physical mixture and its complex is presented in Table I. The wetting time of the drug was found to be 149.0 min while that of the complex (1:1 molar ratio) was found to be 69.5 min. These observations might indicate that the drug in systems was more hydrophilic and more easily wettable compared to pure drug in the dissolution medium. Increased wetting of the particles may be considered to be a major contributor to the enhanced etoricoxib dissolution from the complex system containing  $\beta$ -CD.

### CONCLUSIONS

The dissolution profile of the kneaded complex (1:1 molar ratio) showed more than 75% drug released in 30 min. Further study is required to prepare a prompt release oral formulation of etoricoxib by utilizing this complex.

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## S A Ž E T A K

### Priprava kompleksa etorikoksiba s $\beta$ -ciklodekstrinom metodom gnječenja i njihova karakterizacija

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Metodom gnječenja pripravljen je binarni sustav etorikoksiba s  $\beta$ -ciklodekstrinom ( $\beta$ -CD). Tijekom 30 minuta iz kompleksa se oslobodilo više od 75% ljekovite tvari, što je značajno više u odnosu na fizičku smjesu etorikoksiba i  $\beta$ -CD ili čistu ljekovitu tvar. Interakcije lijeka i ciklodekstrina u otopini ispitivane su analizom fazne topljivosti. Za karakterizaciju čvrstog stanja svih binarnih sustava korištena je diferencijalna pretražna kalorimetrija, infracrvena spektroskopija, difrakcija rentgenskih zraka na praškastom uzorku i mikroskopija. Oslobađanje je praćeno metodom lopatice prema USP XXIII. Rezultati ukazuju na djelomičnu interakciju ljekovite tvari s  $\beta$ -CD u fizičkoj smjesi te potpunu interakciju u kompleksu.

*Ključne riječi:* etorikoksib, ciklodekstrin, kompleksacija, metoda gnječenja

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