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PREPARATION AND EVALUATION OF CYCLODEXTRIN COMPLEXATION OF ETORICOXIB

Mettu Srikanth Reddy* and N. G. Raghavendra Rao

Department of Pharmaceutics, Jyothishmathi Institute of Pharmaceutical Science, Thimmapur, Karimnagar-505481, Andhra Pradesh, India

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Correspondence to Author:

Mettu Srikanth Reddy

Associate Professor, Jyothishmathi Institute of Pharmaceutical Sciences, Thimmapur, Karimnagar – 505481, Andhra Pradesh, India

E-mail: srikanthreddymp@gmail.com

ABSTRACT

Cyclodextrin complexes of etoricoxib (poorly water soluble COX-2 inhibitor) were prepared with the β-CD and HPβ-CD by different techniques (physical mixture, kneading and co-evaporation methods) at 1:1 and 1:2 molar ratios. Characterization of the complexes was done in solution by phase solubility analysis and in solid state using FTIR. The stoichiometry and stability constants of ECB-β-CD (1:1-200.4 M^{-1}) and ECB-HPβ-CD (1:1-166.94 M^{-1}) complexes were calculated by phase solubility method. Remarkable improvement in *in-vitro* drug release profiles in distilled water was observed with all complexes, especially with those prepared by kneading method than with physical and co-evaporation methods. HPβ-CD gave highest enhancement in the dissolution rate of ECB. Thus, it is concluded that stable and dissolution improved CD complexes can be prepared for etoricoxib with β-CD and HPβ-CD.

INTRODUCTION: Relatively most of the drugs in the pharmaceutical field, which are poorly soluble or practically insoluble in water, are facing the problem of low solubility and least dissolution profile in the formulation of oral dosage forms, that which affects the rate of absorption, onset of action and bioavailability. Therefore, there are several approaches where the solubility and dissolution rate of such drugs are improved by means of complexation using cyclodextrins [1, 2, 3].

Cyclodextrins are homologous cyclic oligosaccharides composed of 6-8 glucose pyranose units joined with (1-4) linkage with a hydrophilic outer surface and a hydrophobic central cavity [4]. Loftson and Brewster (1996) proved that the hydrophilic exterior renders the cyclodextrin water soluble and the hydrophobic interior provides a microenvironment for relatively non-polar drugs. In aqueous solutions, cyclodextrins can form inclusion complexes with lipophilic drugs by entrapping either the entire drug molecular or a part of it inside the hydrophobic cavity. Complexation with cyclodextrins has been reported to enhance the solubility, dissolution rate and bioavailability of poor water soluble drugs. They are known for their ability to molecularly encapsulate a wide variety of drugs into their hydrophobic cavity without the formation of any covalent bonds [5, 6, 7, 8]. They fit of the entire or at least part of the guest molecule in the cyclodextrin host cavity determines the stability and the selectivity of the complexation process. Therefore, the stability constant value of the cyclodextrin complexes is a useful index of the binding strength of the complex and is of great importance for the understanding and evaluation of the inclusion complex formation [9].

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Among the commercially available cyclodextrins, β-cyclodextrins is cyclic oligosaccharides containing 7∝-(1,4)-linked gluco pyranose units that delimit a relatively non polar cavity whereas hydroxy propyl β-cyclodextrin has gained wide acceptance in drug formulation by virtue of its ready water solubility, significant potential for solubilization and good safety profile [10]. Structure of β-cyclodextrin is shown in **figure 1**.

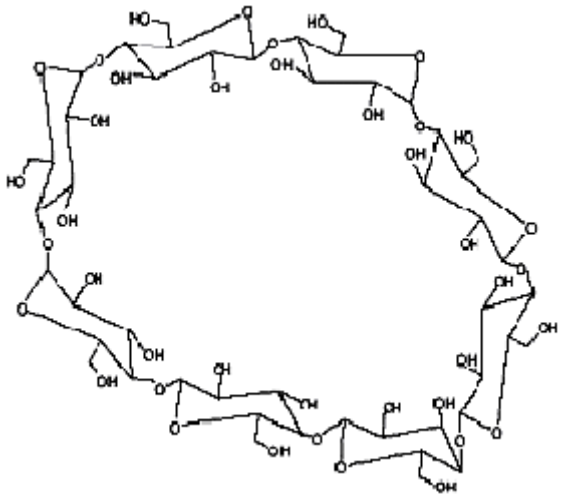

FIG. 1: STRUCTURE OF β-CYCLODEXTRIN

Etoricoxib is an novel selective second generation COX-2 inhibitor indicated for the relief of symptoms signs associated with osteoarthritis, rheumatoid arthritis, gouty arthritis, acute dental pain and primary dysmenorrhea [11, 12] and chemically known as (5-chloro-2-[6-methyl pyridine-3-yl]-3-[4-methyl sulfonyl phenyl] pyridine; chemical structure of etoricoxib is shown in **figure 2**, which is an off-white crystalline powder, relatively insoluble in water and freely soluble in alkaline aqueous solutions. Therefore for the improvement of solubility and dissolution rate of poorly soluble drugs is achieved by cyclodextrin complexation.

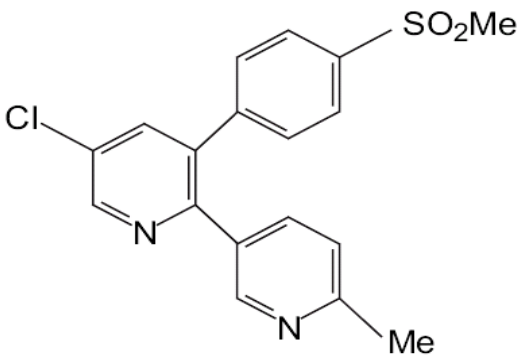

FIG. 2: STRUCTURE OF ETORICOXIB

MATERIALS AND METHODS: Etoricoxib was a gift sample from HETRO DRUGS (Hyderabad, India). Cyclodextrins (β-cyclodextrin and Hydroxy propyl β-cyclodextrin) was a gift sample from S.A pharma chem. (Mumbai, India), other chemicals like methanol, hydrochloride and sodium hydroxide are from (S.d fine chemicals Ltd (LR).

Phase solubility Studies: Phase solubility studies were performed according to the method reported by Higuchi and Connors [13]. The complexation of Etoricoxib was determined by the phase solubility studies.

As the solubility of Etoricoxib was increased linearly with an increase in the concentration of CD's giving A_L type solubility diagrams. An excess amount of ECB was added to the 10ml aqueous solutions of β–CD and HPβ-CD at various concentrations (0.001-0.015 M) taken in a series of 25 ml stoppered conical flasks and the contents were stirred for 2 days at 27°C on water bath shaker. After equilibration the suspensions were filtered using 0.45 μm membrane filters and the filtered samples were diluted suitably and assayed for the solubility of the etoricoxib at 235 nm, at against blank prepared in the same concentration of CD in water so as to cancel any absorbance that may be exhibited by the CD molecules by using UV/Vis spectrophotometer, Shimadzu Corp.(1700), Kyoto. Japan. The phase solubility studies were conducted in triplicate to show three consecutive estimations are the same. The apparent stability constant value was calculated from the straight portion of the phase solubility diagrams using the following equation:

$$K_{(1:1)} = \frac{\text{Slope}}{\text{So}(1-\text{Slope})}$$

Preparation of Solid Inclusion Complexes: The following inclusion complexes of ECB-CDs were prepared at (1:1) and (1:2) molar ratios.

Physical mixtures: The physical mixtures of ECB-CDs in (1:1) M were obtained by pulverizing the drug and CDs separately in glass mortar, sieved (mesh 85) and carefully mixed an accurately weighed quantity of drug and CDs in a clean dry china dish with a clean spatula for about 15 minutes and stored in dessicator over fused calcium chloride.

Kneading Method: Kneaded complexes of ECB-CDs at (1:1) and (1:2) molar ratios were prepared by mixing the weighed quantity of ECB and CDs in a glass mortar with small equivalent volume of solvent blend of (methanol and water) were added in drop wise to the mixture and mixed until a thick slurry is formed (for 45 min.) and dried at 45-50^{o}C. The dried mass was pulverized and sieved through mesh 85 and stored in a dessicator over fused calcium chloride until it was used.

Co evaporation Method: The aqueous solutions of cyclodextrins were added to the solution of ECB in a solvent blend of methanol and water (1:1). The resulting mixture was stirred for 1 hour on magnetic stirrer and evaporated at 50^{o}C until dry. The dried mass was pulverized and sieved through mesh 85 **a**nd stored in a dessicator over fused calcium chloride until it was used.

Detection of Inclusion Complexes In Solid State:

Infrared Spectrscopy: The IR spectra of etoricoxib and their complexes were obtained by KBr pellet method by Perkin Elmer FTIR spectrometer spectrum-1000 (Germany).

Dissolution Rate Studies: *In vitro* dissolution studies of pure drug, physical mixtures and prepared inclusion complexes at different molar ratios were carried out in 900 ml distilled water using USP-8 station dissolution test apparatus (model TDT-08L, M/s Electrolab) with a paddle stirrer. Samples equivalent to 60 mg of etoricoxib, at a speed of 50 rpm and a temperature of 37±1^{o}C were used in each test. Samples of dissolution media were with drawn at different time intervals filtered using a 0.45 μm nylon disc filter and assayed for etoricoxib by measuring absorbance at 235 nm. The dissolution experiment was conducted in triplicate.

RESULTS AND DISCUSSION:

Phase Solubility Studies: The complex formation between ECB and CDs are determined by the phase solubility studies. As from the results of phase solubility studies showed an increase in the solubility of etoricoxib with the increasing concentration of CDs in aqueous solutions. It shows that there was a linear increase in the solubility giving rise to A_L-type diagrams as shown in **figure 3.** This linear drug-CD correlation with a slope less than 1 suggests the formation of (1:1) M ECB-CDs inclusion complexes. As from the phase solubility diagram the stability constant of the etoricoxib in CD were calculated according to the following equation:

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

Where So is the intrinsic solubility of the drug.

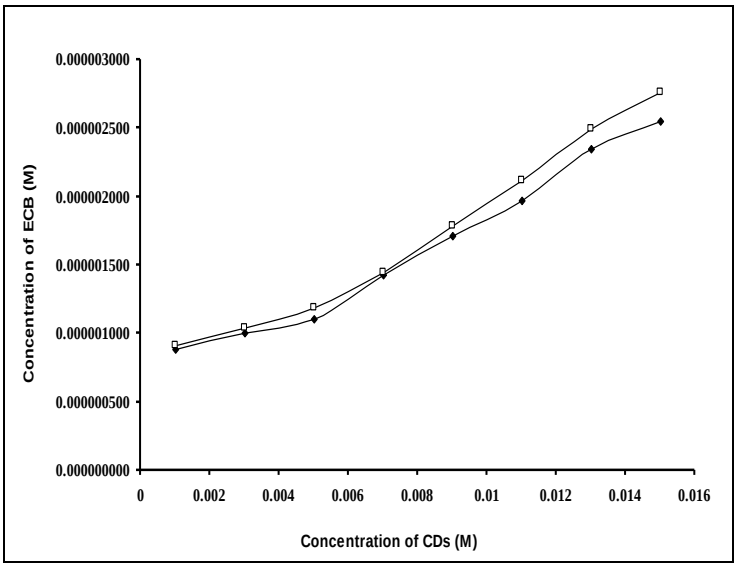

FIG. 3: PHASE SOLUBILITY PLOTS OF ECB IN β-CD AND HPβ-CD
Key: (◆) β-CD, (□) HPβ-CD

The calculated value of stability constant is 200.4 M^{-1} and 166.94 M^{-1} for β-CD and HPβ-CD respectively. The values of stability constants are well within the range of 100 to 1000 M^{-1} considered ideal [13].

Characterizations of ECB-CD Complexation:

Infrared Spectrscopy: FTIR is one of the sensitive analytical methods used to study the complex formation. The spectra of complexes show some or other changes from the parent spectra i.e. pure drug and cyclodextrins. FTIR spectrum of etoricoxib, β-CD, HPβ-CD, physical mixture and inclusion complexes prepared by different methods like kneading and co-evaporation methods are shown in **figures 4 and 5**. FTIR spectra of etoricoxib (A) showed characteristic bands at 1598.4 cm^{-1} (for C=N stretching vibration), 1431.7cm^{-1}, 1298.4cm^{-1}, 1143.8cm^{-1} and 1084.9 cm^{-1}(for S=O stretching vibrations), and 839.4cm^{-1}, 771.5$cm^{-1}$and 635.5cm^{-1} (for C-Cl stretching vibration) respectively.

The IR spectrum of β-CD figure 4 B is characterized by intense bands at 3398.9 cm^{-1}, associated with the absorption of the hydrogen bonded OH-groups of β-CD. The vibration of CH and CH_2 groups appear in the 2962.1cm^{-1}region[14]. IR spectrum of HPβ-CD (Figure-5 B) is characterized by the prominent absorption bands at 3,401.7cm^{-1} (for O-H stretching vibrations) 2,926.5 cm^{-1} (for C-H stretching vibrations) and 1156.2cm-1 and 1076.9cm-1 (for CH, C-O stretching vibrations)[15].

IR spectrum of ECB-β–CD complexation: In IR spectrum of ECB–β-CD physical mixture, bands corresponding to S=O stretching appears to be slightly shifted (1432 cm^{-1}, 1297.7 cm^{-1}, 1153.8 cm^{-1} and 1081.3 cm^{-1}). This indicates that there was a small interaction between drug and β-CD in physical mixture. Where as in case of inclusion complexes prepared by the kneading method (figure 4 D and E) at different ratio's; (1:1) and (1:2) M using β-CD, the spectra of inclusion complexes showed a large change compared to that of the bands observed in physical mixture.

The spectrum of 1:1 M complex prepared by kneading method showed a shift in S=O stretching vibrations (1428.6cm^{-1}, 1307.3cm^{-1}, 1148.9cm^{-1} and 1078.7cm^{-1}). It indicates an intense interaction and formation of inclusion complexes between etoricoxib and β-CD prepared by kneading at (1:1) M ratio. While the IR spectrum of ECB-β-CD (1:2) M, prepared by kneading method showed peaks at 1461.4 cm^{-1}, 1306 cm^{-1}, 1148.1 cm^{-1} and 1083.3 $cm^{-1}$for S=O stretching. Small changes (i.e. shift in S=O stretching) with (1:2) M also indicates the formation of complexes.

In the IR spectrum of ECB-β-CD complex (1:1 M prepared by coevoparation method, figure 4 F appearance of a new band at 3367.4 cm^{-1}corresponds to hydrogen bonded –OH groups of β-CD, and a band appearing at 2923.4 cm^{-1} corresponds to the vibration of –CH and $–CH_2$ groups of β-CD, slight shift in the bands corresponding to S=O stretching of ECB (1428.6 cm^{-1}, 1307.3 cm^{-1}, 1148.9 cm^{-1} and 1078.7 cm^{-1}), indicate the formation of inclusion complexes between ECB and β-CD at 1:1 M.

In the IR spectrum of ECB-β-CD complex (1:2 M prepared by coevoparation method, figure 4 G, bands corresponding to S=O stretching appears to be shifted to 1427.8 cm^{-1}, 1307 cm^{-1} and 1066.4 cm^{-1} indicate the formation of inclusion complexes.

IR spectrum of ECB-HPβ-CD complexation: In the IR spectrum of HPβ-CD-ECB physical mixture (1:1) M (Figure-5 C) bands corresponding to –OH stretching of HPβ-CD appears at 3404.03cm^{-1}.

The bands corresponding to S=O stretching vibration of drug did not show any shift and appear at 1431.9cm^{-1}, 1297.6cm^{-1}, 144cm^{-1} and 1085.3cm^{-1}. It indicates that there was insignificant interaction between drug and HPβ-CD in the physical mixture form.

In case of inclusion complex prepared by kneading method at different ratios with HPβ-CD-ECB, figure 5 D appearance of bands of HPB-CD at 3395.8 cm^{-1} and 2925.9 cm^{-1} and there was a slight shift in the bands at 1432cm^{-1}, 1297.8cm^{-1}, 1144.8cm^{-1} and 1083.9cm^{-1}(of S=O stretching vibrations of drug).

The IR spectrum figure 5 (E) of ECB-HPβ-CD (1:2) M prepared by kneading method showed shifts of bands at 1443.3cm^{-1}, 1306.2cm^{-1}, 1144cm^{-1} corresponding to S=O stretching vibrations of drug, and disappearing of the bands observed at 1084.9cm^{-1} in pure ECB. Indicates the interaction between ECB and HPβ-CD and formation of inclusion complex.

The IR spectrum of ECB-HPβ-CD (F) complex prepared by (CV) method at (1:1) M showed bands corresponding to HPβ-CD at 3365.8cm^{-1} and 2963.5cm^{-1} and bands at 1428.2cm^{-1}, 1307.1cm^{-1}, 1146.8cm^{-1} and 1038cm^{-1} due to S=O stretching vibrations of ECB. In case of (1:2) M ECB-HPβ-CD prepared by (CV) method showed peaks at 1442.7cm^{-1}, 1307.4cm^{-1}, 1151.1cm^{-1} and 1070cm^{-1} (due to S=O stretching vibrations of ECB).

As from the above obtained peaks by the inclusion complexes shows slight shift. Indicating a small interaction between drug (ECB) and HPβ-CD during the (CV) method than that of the complexes prepared by the kneading method.

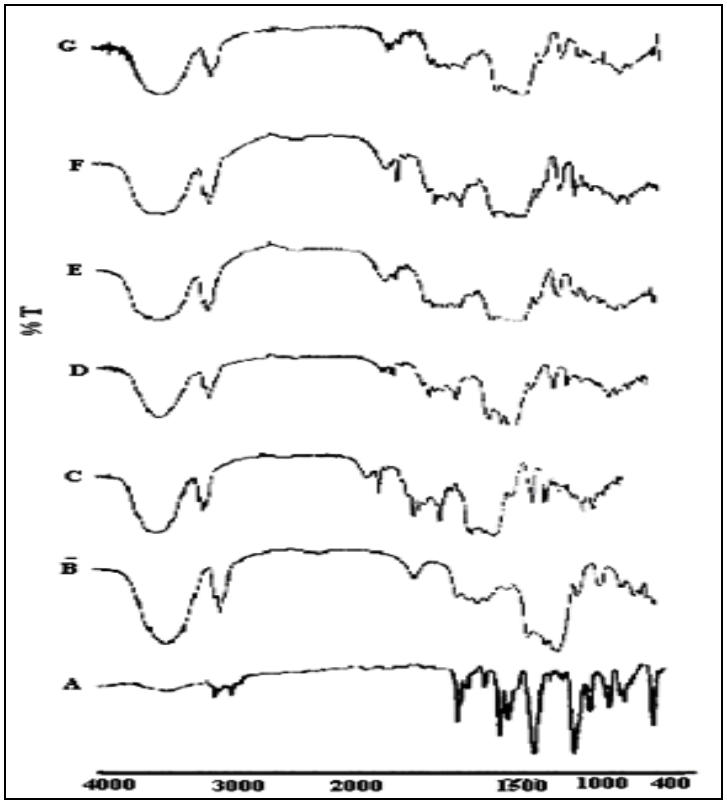

FIGURE 4: COMPARISION OF FTIR SPECTRA OF: (A) ECB, (B) β-CD, (C) EBPM, (D) EBK1, (E) EBK2, (F) EBC1, (G) EBC2 (Wave number (cm^{-1}))

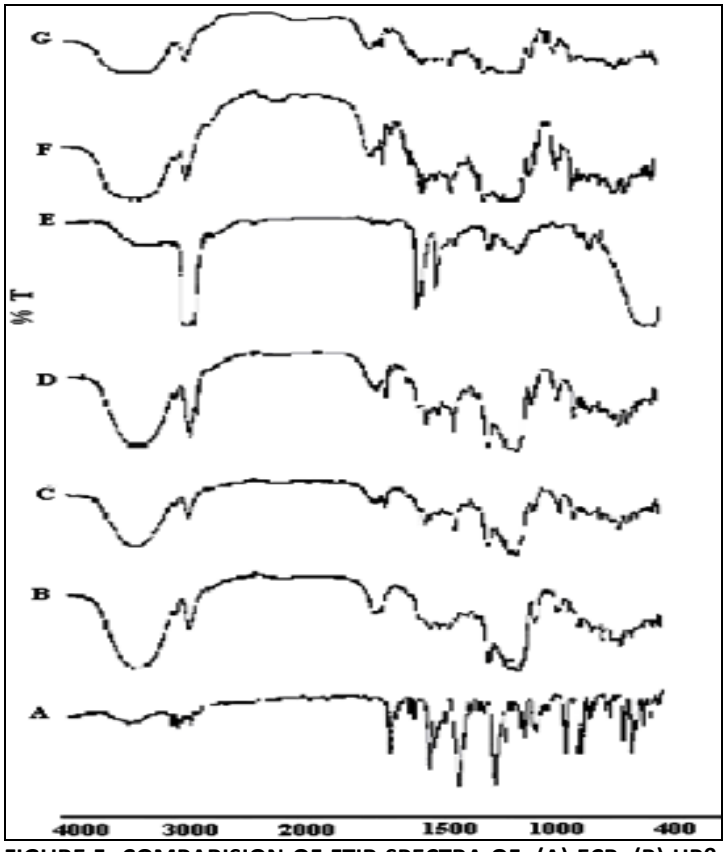

FIGURE 5: COMPARISION OF FTIR SPECTRA OF: (A) ECB, (B) HPβ-CD, (C) EHPM, (D) EHK1, (E) EHK2, (F) EHC1, (G) EHC2 (Wave number (cm^{-1}))

***In vitro* Dissolution Studies:**

Drug-β-CD complexation: It is assumed that the CD complexes show a higher release when compared to the pure drug. Rapid dissolution is the characteristic behavior of the inclusion complexes. The results in terms of $T_{50\%}$ and $T_{80\%}$ are presented in table 1. Figure 6 shows the dissolution behavior of drug, physical mixture and ECB-β-CD inclusion complexes prepared by kneading and coevoparation methods. The release profiles are known as the percentage ECB dissolved Vs time. The calculated $T_{50\%}$ and $T_{80\%}$ values of both physical mixture and cyclodextrin complexes decreased significantly ($P<0.05$) when compared with the pure ECB. $T_{50\%}$ and $T_{80\%}$ values decreased ($P<0.05$) when the ECB-β-CD ratio was increased from 1:1 to 1:2 M. Comparatively, $T_{50\%}$ and $T_{80\%}$ values of the EBC1, EBC2 formulations (prepared by coevoparation method) are more ($P<0.05$) than those of formulations EBK1 and EBK2. However, there is no variation ($P>0.05$) among the $T_{50\%}$ and $T_{80\%}$ values of EBC1 and EBC2 formulations.

The above results indicate that dissolution rate of the drug from the physical mixture is more than pure ECB. The increase in the dissolution rate recorded for the physical mixture may be explained on the basis of solubility of the drug in aqueous β-CD solutions. Since the cyclodextrins dissolve more rapidly in the dissolution medium than the pure drug. It can be assumed that, β-CD molecules will operate locally on the hydrodynamic layer surrounding the particles of the drug. This action results in an insitu inclusion process, which produces a rapid increase of the amount of the dissolved drug[16] Comparision of dissolution parameters ($T_{50\%}$ and $T_{80\%}$), indicate that the release of the drug from the ECB-CDs prepared by coevoparation method are more and it may be due to better interaction of ECB with β-CD during the kneading process. Nm In case of ECB-β-CD complexes prepared by kneading method, the release increased ($P<0.05$) remarkably as the drug: β-CD ratio increased from 1:1 to 1:2 M. However, there was no similar increase ($P<0.05$) in the release of cyclodextrin complexes when the drug:CD ratio increased from 1:1 to 1:2 M prepared by coevoparation method. It indicates a better interaction of ECB with β-CD during the kneading process.

Drug-HPβ-CD complexation: The results in terms of $T_{50\%}$ and $T_{80\%}$ are presented in **table 1. Figure 6** shows the dissolution behavior of drug, physical mixture and ECB-HPβ-CD inclusion complexes prepared by kneading and coevoparation methods. The release profiles are given as the percentage ECB dissolved Vs time. The calculated $T_{50\%}$ and $T_{80\%}$ values of both physical mixture and cyclodextrin complexes decreased significantly ($P<0.05$) when compared with the pure ECB. $T_{50\%}$ and $T_{80\%}$ values decreased ($P<0.05$) when the ECB-HPβ-CD ratio was increased from 1:1 to 1:2 M. Comparatively, $T_{50\%}$ and $T_{80\%}$ values of the EHC1, EHC2 formulations (prepared by coevoparation method) are more ($P<0.05$) than the formulations EHK1 and EHK2. However, there is a variation ($P>0.05$) between the $T_{50\%}$ and $T_{80\%}$ values of EHC1 and EHC2 formulations, when the ECB-HPβ-CD ratio was increased from 1:1 to 1:2 M comparatively.

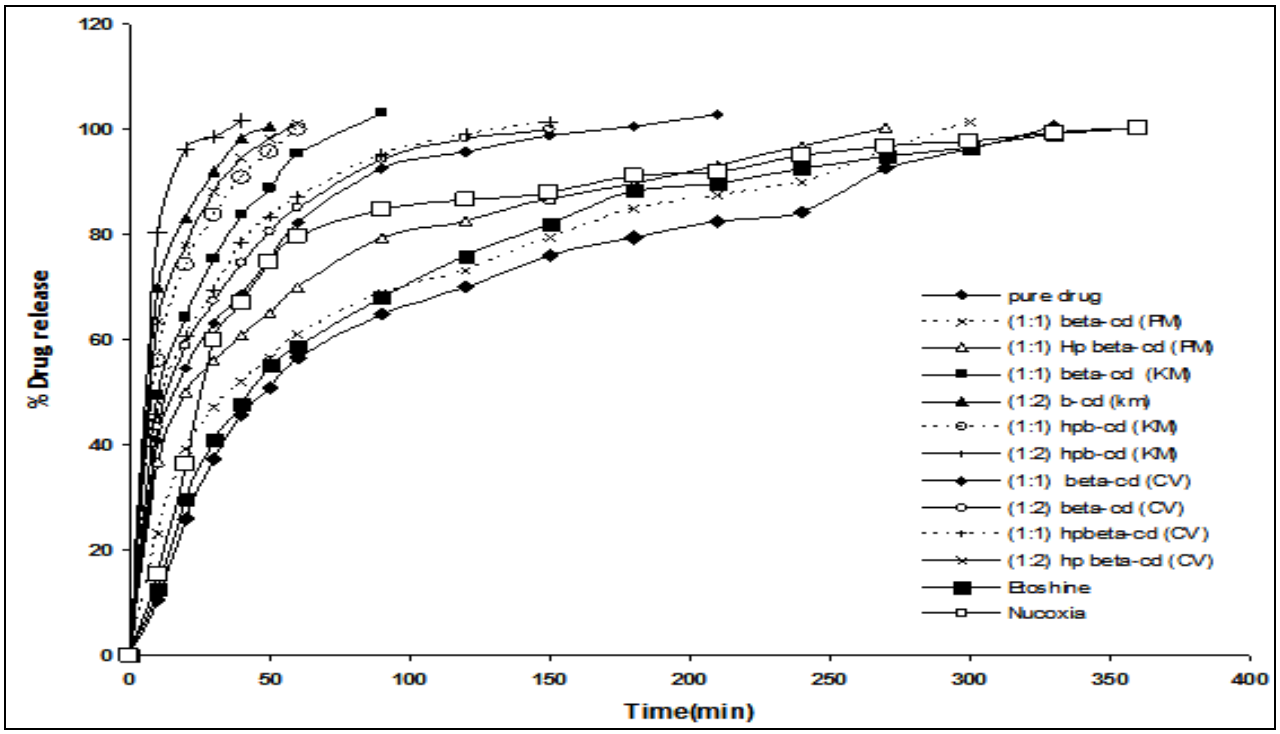

FIGURE 6: DISSOLUTION PROFILES OF ETORICOXIB AND ITS INCLUSION COMPLEXES WITH β-CD, HPβ-CD AND MARKETED PREPARATIONS

The above results indicate that dissolution rate of the drug from the physical mixture is more than pure ECB. The increase in the dissolution rate recorded for the physical mixture may be explained on the basis of solubility of the drug in aqueous HPβ-CD solutions. Since the cyclodextrins dissolve more rapidly in the dissolution medium than the pure drug, it can be assumed that, the HPβ-CD molecules will operate locally on the hydrodynamic layer surrounding the particles of the drug. This action results in an insitu inclusion process, which produces a rapid increase of the amount of the dissolved drug [16]. Comparision of dissolution parameters ($T_{50\%}$ and $T_{80\%}$), indicate that the release of the drug from the ECB-CDs prepared by coevoparation method, may be due to a better interaction between ECB and HPβ-CD during the kneading process. ECB-HPβ-CD complexes prepared by both (kneading and coevoparation) methods shows increase ($P<0.05$) in the release rate of ECB with the increase in drug:HPβ-CD ratios from 1:1 to 1:2 M. The release of ECB was always more ($P<0.05$) with the complexes prepared by kneading method.

Comparision of CD complex formulations with marketed products: The above results indicated that complexes produced by kneading method were superior and hence the release profiles of these formulations are compared (Figure 6) with the two marketed preparations (Etoshine-60mg and Nucoxia-60mg). Table 1 shows that $T_{50\%}$ and $T_{80\%}$ values of EBK2 and EHK2 formulations are smaller ($P<0.05$) than that of marketed preparations. This indicates that EBK2, EHK2 formulations can release the drug faster compared to the marketed preparations tested.

TABLE 1: $T_{50\%}$ AND $T_{80\%}$ VALUES OF ETORICOXIB IN β-CD AND HPβ-CD INCLUSION COMPLEXES AND MARKETED PRODUCTS

Formulations code	$T_{50\%}$ (min) ± SD, n=3	$T_{80\%}$ (min) ± SD, n=3
Pure drug	51.00 ± 1.00	182.67 ± 2.52
EBPM	36.33 ± 1.53	152.67 ±1.53
EBK1	11.00 ± 1.00	35.33 ± 1.53
EBK2	7.17 ± 1.04	14.67 ± 3.25
EBC1	15.83 ±0.02	54.00 ± 3.00
EBC2	15.67 ± 3.06	50.67 ± 3.51
EHPM	20.83 ± 0.76	97.33 ± 3.06
EHK1	9.00 ± 0.56	23.17 ± 1.26
EHK2	5.50 ± 0.10	9.40 ± 0.79
EHC1	12.00 ± 3.00	42.67 ± 1.53
EHC2	7.00 ± 0.50	21.83 ± 0.29
Etoshine	42.5 ± 0.6	138.5 ± 1.6
Nucoxia	25.0 ± 0.8	90.0 ± 0.4

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