Original Article

PREPARATION AND CHARACTERIZATION OF ETORICOXIB TERNARY COMPLEX FOR THE ENHANCEMENT OF SOLUBILITY

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Abstract

The objective of the present work is to formulate etoricoxib (EtR) cyclodextrin complexes by using ternary systems as citric acid, Tartaric acid and PVP K-30 in order to enhance solubility and evaluate the enhanced solubility by *in-vitro* dissolution. The inclusion complexes were prepared by spray drying method and the stability constants of the formed complexes were calculated from the phase solubility studies. The formulated complexes were evaluated for drug release by *in-vitro* dissolution. The prepared complexes were confirmed and characterized by FT-IR, DSC, XRD, SEM and *in-vitro* dissolution. The stability constant $K_{(1:1)}$ of EtR- βCD-PVP-K30 (1:1:2%) and EtR- HPβCD-PVP-K30 (1:1:2%) complex was found to be 57.56 mol^{-1} and 360.01mol^{-1}. Phase solubility studies of each type was found to be of A_N type. The release of Etoricoxib from complexes prepared with hydroxy propyl β-cyclodextrin (HPβCD) and citric acid (Cit) at the ratio of 1:1:2 M by lyophilization method shows a drug release 100.85 ± 4.34 %, significantly higher than other cyclodextrin ternary complexes.

Keywords: hydroxy propyl β-cyclodextrin, Etoricoxib, ternary system, inclusion complex, lyophilisation

1. Introduction

Musculoskeletal conditions are often progressive and associated with considerable pain and disability. These conditions place a huge burden on society in terms of lost productivity and the cost of treatment. Rheumatoid

arthritis (RA), osteoarthritis (OA), and spinal disorders (including chronic low back pain LBP) are among those musculoskeletal conditions with the greatest impact on society [1]. Approximately, 14% of all primary care visits are for musculoskeletal pain or dysfunction. Symptomatic OA affects approximately 10% of men and 18% of women over 60 years of age, while RA affects between 0.5 % and 1.5 % of adults worldwide (WHO 2022). Approximately, 2.0% of all disability-adjusted life years are lost due to musculoskeletal diseases, including 1.0% due to OA, and 0.3% due to RA [2].

Many studies have indicated that NSAIDs function as inhibitors of isoforms 1 and 2 of the cyclooxygenase enzyme (COX-1 and COX-2). COX-1, has constitutively expressed in tissues, stimulates prostaglandin synthesis. The gastric and renal side effects of NSAIDs may thus be explained by their indirect effect on prostaglandin (PG) E2, which has cytoprotective effects in the gastroenteric system, and on PGE2 and PGI2, which are involved in regulating renal blood flow [3]. As a result, efforts have been made to develop selective COX-2 inhibitors (coxibs), such as rofecoxib and celecoxib, and recently the number of COX-2-selective inhibitors has increased with the addition of the second generation coxibs valdecoxib, parecoxib, and etoricoxib [4].

Etoricoxib (EtR) is regarded as second generation coxibs because of its higher selectivity for cox-2 inhibition than celecoxib and rofecoxib. Etoricoxib, 5-chloro-6-methyl-3 [4-(methyl sulfonyl) phenyl]-2, 3–bypyridine, is a highly selective second generation Cyclooxygenage-2 (COX-2) inhibitor administered orally as an analgesic and nonsteroidal anti-inflammatory drug (NSAID) [5]. Coxibs were developed with the anticipation of reducing the serious gastrointestinal complications associated with NSAIDs use in high-risk patients. The development of newer coxibs and their use extend our knowledge in understanding the role of COX-1 and COX-2 [6]. EtR is a highly selective COX-II inhibitor used to treat pains of different etiologies. Etoricoxib has low aqueous solubility (201µg.mL) and high permeability and therefore classified as BCS class II drug. By formulating these drugs with cyclodextrins as inclusion complexes have shown to increase the bioavailability. Cyclodextrins when used as complexing agents, enhance the solubility of poor water-soluble lipophilic drugs.

The drug substance administered by any route must possess some aqueous solubility for systemic absorption [7]. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for therapeutic response. If a compound has a low aqueous solubility, it may be subject to dissolution rate limited absorption with the gastro-intestinal (GI) tract residence time.

Complexation with cyclodextrin (CD) is known as an effective method for enhancing dissolution properties and bioavailability of poorly soluble drugs. The first is the use of chemically modified CDs, which present a higher solubility in water [8]. The second method consists in adding a water-soluble polymer like PVP or methylcellulose with the aim to increase the solubility of both the complex and the drug itself. The third method is the use of an acidic ternary compound. In the case of a basic drug, the acidic agent, for instance, citric acid, tartaric acid, promotes the solubilization of the guest molecule both by forming a salt and by increasing the stability constant of the complex [9].

In aqueous solutions cyclodextrins are able to form inclusion complexes with many drugs by taking up a drug molecule or more frequently some lipophilic moiety of the molecule, into the central cavity. No covalent bonds are formed or broken during the complex formation, and drug molecules in the complex is first order with respect to ligand and first or higher order with respect to substrate then A_L-type phase-solubility profiles are obtained [10]. If the complex is first order with respect to the substrate, but second or higher order with respect to the ligand then A_P-type phase-solubility profiles are obtained. A_N-type phase-solubility profiles can be difficult to interpret. The negative deviation from linearity may be associated with cyclodextrin induced changes in the dielectric constant of the aqueous complexation media, changes in complex solubility or self-association of cyclodextrin molecules. B-type phase-solubility profiles indicate formation of complexes with limited solubility in the aqueous complexation medium [11].

2. Experimental

2.1. Materials

Following ingredients were purchased: Etoricoxib (EtR) from Zydus Lifesciences Ltd., Ahmedabad, India. β-Cyclodextrin (βCD) and hydroxy propyl β-cyclodextrin (HP-βCD) obtained from Roquette pharma Pvt Ltd., Mumbai, India. PVP K-30, citric acid (Cit), tartaric acid from Loba Chemie Pvt Ltd., Mumbai, India. Analytical grade chemicals and regents were used in this study.

2.2. Phase solubility

Accurately weighed samples of ETR (12 mg) in quantities exceeding its aqueous solubility was shaken at room temperature with aqueous solutions of βCD/HP-βCD (phosphate buffer pH 6.8) in increasing concentrations (2–12 mM), subsequently; the same initial system was performed with the addition of 1% and 2% (w/w) of citric acid/ tartaric acid/PVP-K30 (EtR/βCD/citric acid, tartaric acid, PVP-K30) and for a period of 72h (3 days), until equilibrium was established [12]. The samples were filtered through a 0.45 µm membrane filter (Millex -HA filter units, Millipore) and suitably diluted with phosphate buffer pH 6.8 before analysis. The results were evaluated in terms of complex stability constant from the following equation (1).

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

The stability constant of EtR-β-cd complex was calculated using Higuchi-Connor's equation.

2.3. Preparation of complex by spray drying method

EtR was dissolved in methanol as such and along with cylodextrins and hydroxy acids (citric acid and tartaric acid) in 1:1:2 molar ratio and as 1:1:2 % for PVP-K30 proportions of drug:CD:carrier. The clear solutions were spray–dried using a spray dryer (Labultima, Model: LU 222 Advanced, Mumbai, India) under the following set of conditions: inlet temperature: 43-50 ^{o}C for solid inclusion complexes, outlet temperature: 35- 40 ^{o}C, cool temperature of 30 ^{o}C, feed pump speed: 1 mL/min, aspiration speed: 45, vacuum: -100– -150 mm of WC and atomization air pressure: 2 kg/cm^2 [12]. The resulting solid powder was placed in a vacuum drier for 24 hours to remove the residual solvent, if any and then stored in a desiccated environment until further study.

2.4. Evaluation of complex

2.4.1. Percentage yield

The efficiency of the process is determined by the yield obtained from the process. It is calculated as mentioned in the previous article [13].

2.4.2. Drug content estimation

60 mg of equivalent weight of the drug from the complexes was calculated, accurately weighed and transferred to 100ml volumetric flask. 5ml methanol was added to dissolve and final volume was made up to 60 ml with phosphate buffer pH 6.8. From this 1ml was taken in 100 ml volumetric flask and made up to the mark with same solvent [14]. The absorbance was measured at 284nm using phosphate buffer pH 6.8 as blank. The drug content was estimated using slope of calibration curve.

2.5. *In vitro* dissolution

EtR complexes equivalent to 60mg of ETR was used for the dissolution studies. Dissolution experiments were carried out in triplicate (n = 3). USP Type II paddle (Lab India Disso 2000) 37 ± 0.5^{o} C, RPM: 100; Dissolution medium: phosphate buffer 6.8 pH. Volume of medium: 900 mL; Sampling intervals: 5, 10, 20-, and 30 min. Sample volume: 5 ml withdrawn and replaced with 5 ml of 6.8 pH phosphate buffer. A sample of 5 mL withdrawn and filtered through 0.45 µm micron Whatman filter and 1mL of the filtrate was made up to 10ml with phosphate buffer 6.8 pH in 10 mL volumetric flask [15]. Suitable dilutions were further made when required. The absorbance of the sample was read at 284 nm against phosphate buffer as blank. The dissolution studies were also performed for pure drug [16].

2.6. Fourier Transform Infrared Spectroscopy (FTIR)

Fourier transform infrared spectroscopy (FTIR) was used to identify the drug-excipient interaction. Samples were analyzed by potassium bromide pellet method in an IR spectrophotometer (Shimadzu, FTIR 8700) in the region between 4000-500 cm^{-1}. Complex formation was evaluated by comparing the IR spectra of the solid complex with drug [17]. **Thermal analysis**

The thermal behaviour of inclusion complexes was studied using Differential Scanning Calorimetry in order to confirm the formation of solid complex [18]. When guest molecules are incorporated in the cyclodextrin cavity or in the crystal lattice, their melting, boiling and sublimation points are usually shifted to a different temperature or disappear within the temperature range. The samples were heated from 0 to 350 °C at a heating rate of 10 °C/min under a nitrogen flow, flowing at a rate of 40cc/min through the DSC cell.

2.7. Powder X-Ray diffraction study

X-Ray diffraction of inclusion complexes and the pure components was performed to identify the interaction of the drug with cyclodextrins using a PW 1720 X-ray generator and a PW 1710 diffractometer control (Philips Electronic Instrument). The scanning range (2θ) was from 5° to 90°, and the scan step and scan speed were 0.04° and 0.02°/s, respectively [19].

2.8. Stability study

The physicochemical stability of a complex in a stability compartment (Wadegati TM Labe Quip (P) Ltd., Model No. HTC-3003, Andheri (E), Mumbai, India) for 3 months at 45 ± 0.5 ºC and 60 ± 5% RH. FU-NE examined physical changes, drug content, and *in vitro* drug release at 1-month intervals [20].

2.10. Statistical analysis

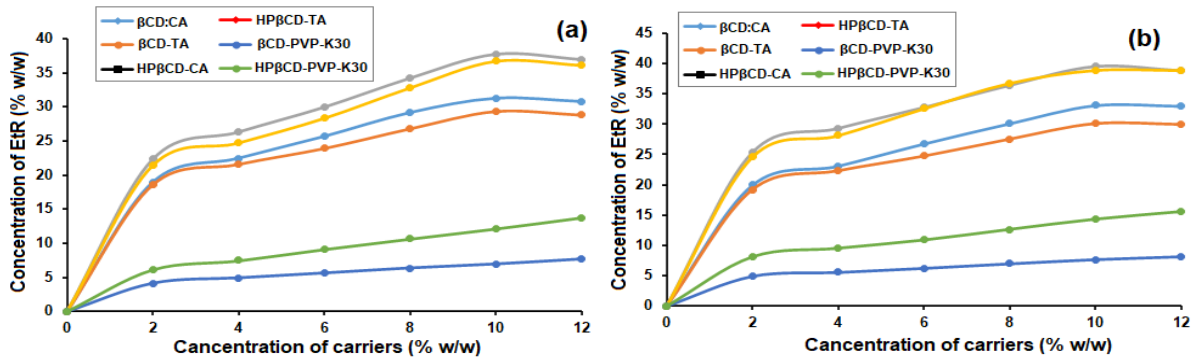
The tests were performed for a minimum of three times. The measurements were analyzed using the one-way method via ANOVA. Results analyzed and presented as mean ± SD (%). Statistically significant value of $p < 0.05$ were considered.

3. Results and discussion

3.1. Phase Solubility Studies

Phase solubility studies recognized a valuable data on the effect of the various carrier on the solubility of EtR. The result revealing A_L (β-CD: PVP-K30 and HP-βCD: PVP-K30) type phase-solubility profile [21] (the solubility of the drug increased linearly as a function of carrier concentration). Also, A_N (β-CD: citric acid and HP-βCD: tartaric acid) type phase-solubility profile (negative deviation from linearity linearly as a function of carrier concentration) (Fig. 1a and b).

Figure 1. Phase solubilty diagram of various carrier at (a) 1:1 and (b) 1:2



While, increasing temperature and concentration of carrier, the solubility of EtR increased probably due to the changes in the interaction forces, such as Vander Waals and hydrophobic forces between EtR and carriers. The slope of the phase solubility diagram obtained (>1) in all carriers indicated the 1**:**1 complex stoichiometry [22,23]. The apparent $K_{1:1}$ calculated from the slope and intrinsic intercept values of solubility curves obtained by plotting concentration (% w/v) of dissolved EtR against concentration (% w/v) of the carrier (Table 1).

Table 1. Stability constant of various cyclodextrins and type of phase diagram

Carriers	**Hydroxy Acids**	**$K_{1:1}$**	**Phase Diagram**
β-CD	Citric acid	--	A_N Type
HPβCD	Tartaric acid	--	A_N Type
β-CD	PVP K-30	57.56	A_L Type
HPβCD	PVP K-30	360.21	A_L Type

The effect of cyclodextrin on aqueous solution of EtR was evaluated using phase solubility method. The phase diagrams for EtR in presence of two different cyclodextrin in phosphate buffer 6.8 pH. The solubility of EtR increased linearly as a function of βCD and HPβCD. The phase solubility profiles show that complexation with both cyclodextrins increases the etoricoxib solubility in a linear pattern, displaying A_L type phase diagrams in PVP K-30 and A_N type for hydroxy acids (citric acid, tartaric acid) according to the classification by Mohamed et al [24]. The complexation constants ($K_{1:1}$) of Etoricoxib: CD: PVP-K30 with each cyclodextrin are 57.61 mol^{-1} for βCD, 370.61 mol^{-1} for HPβCD using equation 1.

Complexation is generally due to the hydrophobic interaction between poorly water-soluble guest molecule, such as Etoricoxib and the polar cavity of cyclodextrin molecule [25]. The hydrophobicity, geometry and cavity size of the guest molecule and the derivative groups of the cyclodextrin are important for complex formation. In the present study, the enhancement of EtR solubility is highly dependent on the type of cyclodextrin used.

3.2. Percentage yield and drug content

Table 2 shows the percent yield and drug content of various complexes. β-CD, HP- βCD and PVP-K30 produced over 80% of the total output, with the highest absorption of β-CD measured between 200 and 400 nm, with a peak at 284 nm (data not showed). Due to limited size ranges, the drug content of produced β-CD, HP- βCD was determined to be 98.90 ± 5.31 to 96.42 ± 7.10%, respectively, which was within the reference (label amount) of 95.5 to 102% of EtR. CRL lipophilicity (log P = 2.79) can be attributed to these modest percent values, allowing it to be efficiently integrated into PVP/ β-CD/HP- βCD dual carriers in the prepared formulations [26].

Table 2. Various characterization parameters complexes (mean ± SD, n = 3).

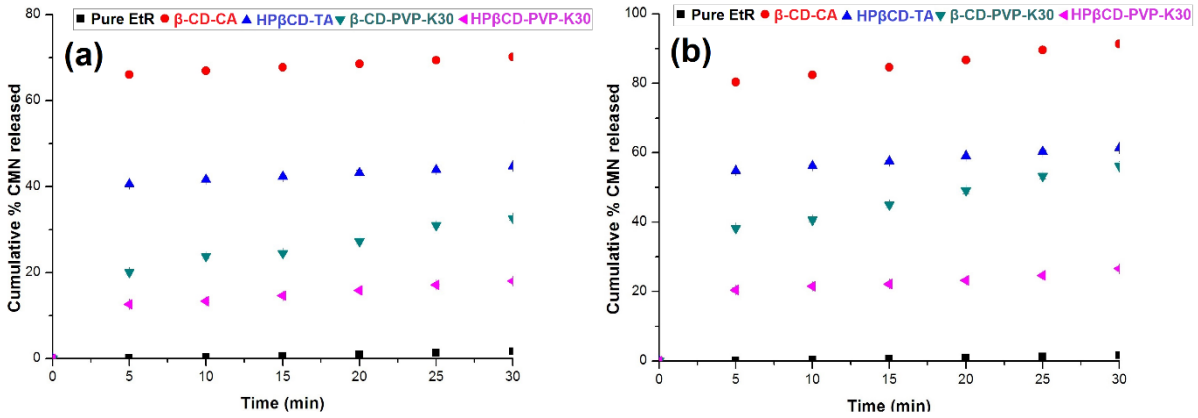
Carriers	**Hydroxy Acids**	**% Yield**	**Drug Content * (%)**
β-CD	Citric acid	97.6 ± 3.22	98.90 ± 5.31
HPβCD	Tartaric acid	96.7 ± 4.76	97.71 ± 6.21
β-CD	PVP K-30	95.8 ± 6.56	95.40 ± 7.31
HPβCD	PVP K-30	94.7 ± 4.90	96.42 ± 7.10

* Each value represents mean, n = 3 ± SD.

3.3. *In vitro* release

The *in vitro* release demonstrates after the burst release, the constant rate release profile observed with all complexes. These may occur due to the metastable supersaturation of EtR in the wet carrier matrix during dissolution. Aside from non-ionic attributes, viscosity suggested a perfect part in the dissolution of the drug by delaying the contact of the drug with the dissolution medium. At EtR complex with β-CD and HPβCD obtained were satisfactory in comparison to other carriers because the solubility due to a polar effect of inclusion and the formation of a hydrogen bond may improve solubilization [27]. The result showed the limited dissolution rate of PVP-K30 might be moderate amorphization of drug particles compared with pure drug powder.

Figure 2. In vitro dissolution release EtR from various complexes (a) Physical mixture (b) complex

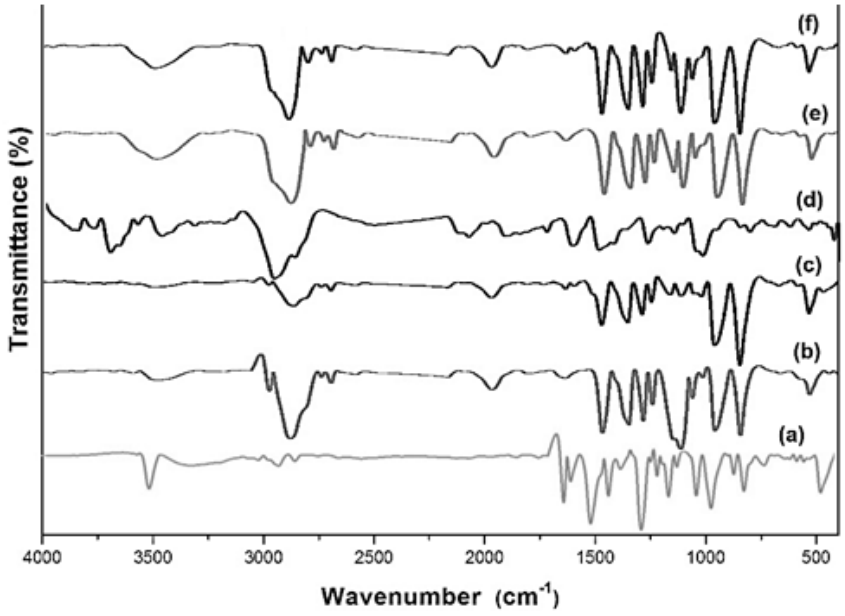


A marked enhancement in dissolution rates of EtR from EtR– HPβCD-CA (1:1:2M) complex prepared by freeze drying method. The higher dissolution rates were observed with inclusion complexes prepared by freeze drying method may be due to better interaction of EtR-cyclodextrin-CA.

3.4. Fourier Transform Infrared Spectroscopy (FT-IR)

The FTIR spectra of pure EtR showed characteristic peaks at 1500.670 cm^{-1} (C=N stretching vibration), 1294.0cm^{-1} (S=O stretching vibration), 1587.47 cm^{-1}(C=C aromatic benzene) and 767.69 cm^{-1} (C-Cl stretching vibration), 2916.47 cm^{-1} (sp3 CH stretching), 3010.48 (sp^2 CH bending) and CN-1134 cm^{-1}. The FTIR spectra of citric acid showed (OH- acid) 3394.83 cm^{-1}, (sp3 CH stretching), 1734.64 cm^{-1} (C=O carbonyl), 1215.19 cm^{-1} (C-O). The FTIR spectra of PVP-K-30 showed 2956.97 cm^{-1} (sp3 CH), 1435.09 cm^{-1} (pyrole aromatic), 1660.77 cm^{-1} (ketone), 1282.71 cm^{-1} (CN stretching aromatic pyrrole). The FTIR spectra of MCC showed characteristic peaks at 3248.54 cm^{-1} for -OH stretch, 1028.1 cm^{-1} for C-O stretch, 2899.11 cm^{-1} for CH2 stretch and 111.48, 1165 and 1028 cm^{-1} for C1-O-C4. FTIR spectrum of EtR- HPβCD-CA/TA/PVP-K30 freeze dried complex shows characteristic broad peak at 3400.cm to 3415.63.cm^{-1}. This shift and broadening of peak indicate interaction between and HPβCD. Intermolecular hydrogen bonding was observed in Etoricoxib cyclodextrin complexes prepared by freeze drying, due to broad absorption at 3402.54 cm^{-1}.

Figure 3. FTIR spectrum of (a) EtR, (b) HPβCD, (c) βCD, (d) HPβCD-CA, (e) HPβCD-TA, and (f) HPβCD-PVP-K30

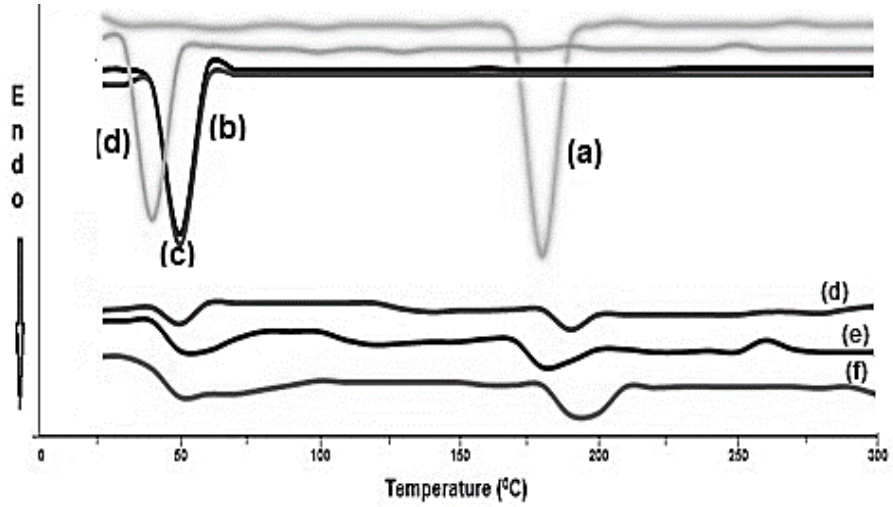


3.5. Differential Scanning Calorimetry (DSC)

The DSC curves of EtR, HPβCD and βCD, PVP-K30, its corresponding the complexes is shown in Fig. 4. Thermogram of EtR (134.8 ºC), HPβCD (62.8 ºC), and βCD (101.1 ºC) exhibited sharp endothermic peak, which complies with the reported data [28]. The physiochemical properties such as melting, boiling or sublimation point altered when the guest molecules interacted with the host molecules in all the complexes. A complex system of HPβCD and βCD, complete disappearance of the endothermic peak at corresponding to EtR could be due to release of water molecules or convert entirely amorphous form or dissolution of crystalline into molten carrier [29].

The small broad peak near 135 ºC observed in complex of PVP-K30 with reduced intensity may correspond to the melting of EtR shifted considerably to a higher temperature. It indicated a reduction in crystallinity of the drug.

Figure 4. DSC thermogram (a) EtR, (b) HPβCD, (c) βCD, (d) HPβCD-CA, (e) HPβCD-TA, and (f) HPβCD-PVP-K30

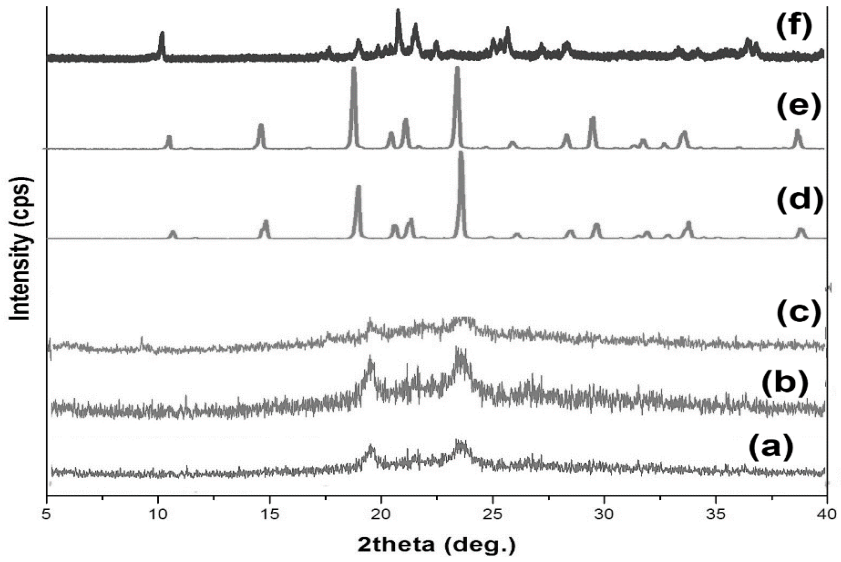


3.6. PXRD

The XRD patterns of EtR, HPβCD and βCD are illustrated in Fig. 5. EtR exhibited sharp peaks (presence of a crystalline form of the drug) at 2θ of 4.34º, 10.34º, 16.12º, 17.12º, 18.97º, 19.14º and 23.23º and many tiny peaks at 24.22º, 21.43º, 26.26º, 27.68º and 28.1º [56]. The carrier typical peaks such as HPβCD (2θ of 20.16º and 23.67º) and βCD (2θ of 20.24º and 22.56º) indicate crystalline domain of amorphous polymeric material. Many diffraction peaks with high intensity observed at PVP-K30 (strong and intense peak at 2θ of 17.12º, 21º and 23.11º) shown crystallinity pattern [30]. In contrary, βCD-CA and βCD-TA was showed amorphous characteristics due to lack of complete stereo uniformity and presence of the large lateral group in the carrier.

In both HPβCD-CA and HPβCD-TA, we observed that amorphous nature was prominent in both complexes due to the reduced intensity and various characteristic peaks of the drug in the complex. These result confirmed that high concentration of the drug was dissolved in the solid state carrier matrix in an amorphous structure signifying the conversion of the crystalline form of EtR to amorphous form in the complex [31]. Amorphous nature of carrier had been established at the complex entirely in their respective diffractogram. These were found to be superimposable with the X-ray diffractogram of pure carriers. The X-ray pattern of formulations prepared with different methods showed 1 sharp peak at a high intensity range of 500 to 1000 cps. The complexed formulation of EtR showed the sharp peaks with decrease intensity range of 400 – 500 cps. The x – ray scan showed the partial amorphous characteristics. The decreased intensity of peak suggests the partial conversion of crystalline to amorphous form which can assume to responsible for solubility enhancement of the drug.

Figure 5. PXRD pattern of (a) EtR, (b) HPβCD, (c) βCD, (d) HPβCD-CA, (e) HPβCD-TA, and (f) HPβCD-PVP-K30



4. Conclusion

In the present investigation inclusion complexes of Etoricoxib were prepared with HPβCD and βCD. These systems are useful in enhancing aqueous solubility and hence oral bioavailability BCS class II drugs. Complexes prepared with HPβCD and citric acid by freeze drying method has shown good release of drug. Physical mixture of drug, cyclodextrin and inclusion complexes was characterized by FTIR, XRD, DSC and SEM analysis for any physical and chemical alteration of the drug characteristics. From the results it was concluded that there was no interference of the functional groups as the principal peaks of the Etoricoxib were found to be unaltered in the spectra of the inclusion complexes.

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