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Enhanced Dissolution and Bioavailability of Etoricoxib in Solid Dispersion Systems: An Investigation into the Role of Carrier Matrix on Stability, *In vitro* and *In vivo* Performance

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ABSTRACT

Etoricoxib (ECB) is a large, lipophilic molecule that is practically insoluble in water and exhibit an exceedingly slow dissolution rate making it a Class II compound in Bio pharmaceuticals Classification System. In the present article, the higher solubility advantage of ECB in solid dispersion is explored. More specifically, solid dispersion of ECB within different water soluble polymers such as polyethylene glycol 6000, polyvinyl pyrrolidone K40 and dextrin were prepared with different drug loadings by using solvent evaporation and fusion method, and the physicochemical properties, stability and *in vitro* and *in vivo* performance of the dispersions were evaluated. The pharmacokinetic studies were carried out by using Wistar rats. The solid dispersion prepared with dextrin exhibited improved aqueous solubility. The D60 (percentage drug release after 60 minutes) value for pure drug and optimized formulation (F10; Drug: Dextrin, 1:2) were found to 5.06 ± 3.0 and 16.43 ± 0.18 respectively. The C_{max} of pure drug and F10 were found to be 7.2 ± 1.32 $\mu\text{g/ml}$ and 15.5 ± 2.67 $\mu\text{g/ml}$ respectively. These results indicated the improved systemic exposure of ECB following dissolution from solid dispersions

INTRODUCTION

The enhancement of oral bioavailability of poorly water-soluble drug is one of the most challenging aspects in the pharmaceutical industry ^[1]. Different methods such as salt formation, complexation, particle size reduction and solid dispersion have commonly been employed to increase dissolution rate and there by enhance oral absorption of poorly soluble drug ^[2]. The term solid dispersion refers to a system in which a hydrophobic drug is homogeneously dispersed throughout the hydrophilic matrix. Within the dispersion, the drug compound may exist in an amorphous or crystalline form. The selection of the carrier has significant influence on the dissolution performance of the dispersed drug, since the dissolution rate of component from a surface is affected by the second component in a multiple mixture ^[3]. Therefore a water-soluble carrier results in a fast release of the drug from the matrix, and a poorly soluble or insoluble carrier leads to a slower release of the drug from the matrix. Hydrophilic carrier systems like polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and dextrin were widely used for their low cost and high aqueous solubility ^[2]. All the carriers are freely soluble in water and are available in various molecular weights, ranging from 10,000 to 700,000 for PVP and from 200, to in excess of 300,000 for PEG.

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be first-line drugs in the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA) which are most prevalent chronic illnesses resulting in diminished quality of life and carry

substantial economic cost^[4]. The clinical symptoms of OA and RA are pain, inflammation and prostanoids. The intermediate enzymes responsible for prostaglandin biosynthesis, cyclooxygenase (COX) 1 and 2, have been the target of arthritis therapy using nonsteroidal anti-inflammatory drugs. Clinical experience have shown that the improved GI safety COX-2 selective inhibitors such as valdecoxib, etoricoxib and parecoxib, represent a significant advance in the treatment of arthritis and other related inflammatory conditions^[5]. ECB (5-chloro-2-[6-methyl pyridin-3-yl]-3-[4-methylsulfonylphenyl] pyridine) is a novel, selective second-generation cyclooxygenase-2 inhibitor administered orally as an analgesic and anti-inflammatory drug^[6]. ECB does not inhibit prostaglandin synthesis in the gastric mucosa, even at doses above the clinical dose range of 60–120 mg^[7]. The chemical structure of ECB is shown in (Figure 1). It is an off-white crystalline powder, relatively insoluble in water, and freely soluble in alkaline aqueous solutions.

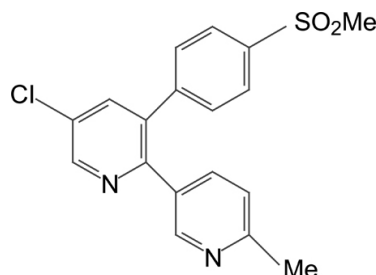


Figure 1. Chemical structure of ECB.

The main objective of the study was to investigate the possibility of improving the solubility and dissolution rate of ECB by formulating solid dispersion within polyethylene glycol 6000 (PEG 6000), polyvinyl pyrrolidone K40 and dextrin using solvent evaporation and fusion method. Differential scanning calorimetry (DSC) and Fourier Transform Infra-red (FTIR) have been used to characterize the prepared solid dispersions. Furthermore, the drug content of the solid dispersion and its solubility and dissolution performance were also examined and evaluated to develop an effective solid dispersion formulation of ECB. Finally, *in vivo* study of solid dispersions was carried out for quantitative estimation of drug in plasma. The pharmacokinetic profiles of solid dispersions were compared with free drug.

MATERIALS AND METHODS

Materials

ECB was obtained as a gift sample from Sun Pharmaceutical Industries Ltd., Mumbai, India. PVP K40, dextrin and PEG 6000 were purchased from Kemie Labs Mumbai, India. Methanol and acetonitrile (HPLC grade) were obtained from Qualigens fine chemicals, Mumbai, India. All other chemical and reagents used were of analytical grade.

Preparation of Solid Dispersion with PEG 6000

The solid dispersions of ECB with PEG 6000 were prepared by melting method^[8] at 1:0.5, 1:0.75 and 1:1 (ECB:PEG 6000) w/w ratio. Briefly, a required amount of PEG 6000 was melted in a glass container over a water bath maintained at about 50–60°C. A required amount of ECB is dissolved in small quantity of Dichloromethane and then added to the molten PEG 6000 and mixed thoroughly by a glass rod for 5 minutes. The molten mixture was then evaporated under vacuum until a hard mass was formed. The hardened mass was then powdered in a mortar, sieved through a #100 mesh screen and stored in a screw-cap vial in desiccator at room temperature.

Preparation of Solid Dispersion with PVP K40

The solid dispersions of ECB with PVP K40 were prepared by solvent method^[9] at 1:0.25, 1:0.5 and 1:0.75 (ECB:PVPK40) w/w ratio. The weighed quantity of the ECB and PVP K40 was dissolved in sufficient quantity of the Dichloromethane and sonicated for 5 minutes. Then the mixture was evaporated under vacuum until a hard mass was formed. The hardened mixture was then powdered in a mortar, sieved through a #100 screen and stored in a screw-cap vial in desiccator at room temperature.

Preparation of Solid Dispersion with Dextrin

The solid dispersions of ECB with Dextrin were prepared by solvent method^[10] at 1:0.5, 1:1, 1:1.5 and 1:2 (ECB:Dextrin) w/w ratio. The weighed quantity of the ECB was dissolved in sufficient quantity of the ethanol and the dextrin was dissolved in purified water. The alcoholic solution of the ECB was then poured into the aqueous solution of the carrier under continuous stirring. Then the mixture was evaporated under vacuum until a hard mass was formed. The hardened mixture was then powdered in a mortar, sieved through a 100 mesh screen and stored in a screw-cap vial in desiccator at room temperature.

FORMULATION AND DEVELOPMENT

Solid dispersions of the ECB were formulated by using PEG 6000, PVP K40 and Dextrin in various ratios as mentioned in (Table 1).

Table 1. Composition of various formulations.

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
ECB	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
PEG 6000	500	750	1000	-	-	-	-	-	-	-
PVP K40	-	-	-	250	500	750	-	-	-	-
Dextrin	-	-	-	-	-	-	500	1000	1500	2000
Solvents	A	A	A	A	A	A	B	B	B	B

All the weights in milligrams (mg); A – Dichloromethane; B – Ethanol : Water

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR was conducted using a Shimadzu 8300 spectrometer and the spectrum was recorded in the region of 4000-400 cm⁻¹. The procedure consisted of placing a sample, powder dispersed in KBr (200-400 mg) and compressed into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained. The ECB and excipients were scanned individually as well as combined form in order to find the drug- excipient interactions.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry was performed using DSC60 Shimadzu, Japan. Accurately weighed samples (About 2 mg of ECB or its equivalent) were placed in a sealed aluminum pans, before heating under nitrogen flow (2 ml/min) at a scanning rate of 10 °C/min from 25 °C to 250 °C. Indium oxide was placed in aluminum pan and used as a reference. The heat flow as a function of temperature is measured for the drug, polymers and solid dispersions. The glass transition temperature of the analytes was measured. Duplicate determinations were carried out for each sample.

Particle Size, Shape and Surface Morphology

The size of solid dispersion was determined by microscopic method using stage and eyepiece micrometers. The shape and surface morphology of the solid dispersion was studied by scanning electron microscopy (SEM) (JEOL, JSM 50A, Tokyo, Japan).

Determination of Drug Content

The weighed amount of solid dispersion (100 mg) was dissolved in 20 ml of methanol and filtered, and the filtrate was examined for the drug content against the reference solution consisting of methanol spectrophotometrically at 235 nm. The procedure was repeated in triplicate.

In vitro Drug Release Studies

Dissolution studies of ECB in powder form and solid dispersions were carried out as per U.S Pharmacopoeia (USP). The USP model digital tablet dissolution test apparatus 1 was used with the basket. Rotation speed of 50 rpm in distilled water as a dissolution media at 37 °C was used for drug release studies. The solid dispersions equivalent to 60 mg of ECB was weighed using a digital weighing balance and added into the dissolution medium. At the specified times (5, 10, 15, 30, 45 and 60 minutes), 10 ml samples were withdrawn. The samples were filtered through 0.22 µm membrane filter and then assayed for by measuring the absorbance at 235 nm using the UV-Visible spectrophotometer. Fresh medium (10 ml), which was pre-warmed at 37 °C, was replaced into the dissolution medium after each sampling to maintain its constant volume throughout the test. Dissolution studies were performed in triplicate (n=3), the calculated mean values of cumulative drug release were used while plotting the release curves.

Stability Studies

The optimized formulation (F10) of solid dispersion were packed using aluminum foil and subjected to stability studies at 40 ± 2 °C and 75 ± 5% relative humidity in a Thermo lab stability chamber. The stability studies were carried out for a period of 6 months. The initial drug content of optimized solid dispersion was determined. Samples were withdrawn at predetermined time intervals (15, 30, 60, 90 and 180 days) and evaluated for drug content. A plot of log percentage drug remaining versus days was drawn to analyze the stability of the formulation.

Pharmacokinetic Studies

The pharmacokinetic studies were carried out in male Wistar rats (200-250 g), obtained from Central Animal House, Manipal University, Manipal. They were housed in elevated wire cages, four animals per cage and given *ad libitum* of water. The study protocol was approved by the Institutional Ethical Committee, Kasturba Medical College, and Manipal. The overnight fasted animals were divided into 2 groups (n=6) and treated orally (50 mg/kg) as below.

Group I: Pure ECB in 0.5% CMC

Group II: Solid dispersion (F-10) equivalent quantity of ECB in 0.5% CMC

The blood samples were collected at predetermined intervals of 0.5, 1, 2, 4, 6,8,12 and 24 h post dose in to heparinized tubes from the orbital sinus. The plasma was separated immediately by using cold centrifugation (Remi Equipment's Ltd., Mumbai, India) at 10000 rpm for 5 min and the plasma was stored at -60°C until analysis.

Bioanalysis of Drug in Plasma

The analytical method based on HPLC was used to analyze the ECB in plasma [11]. The HPLC system (shimadzu class VP series having class VP 6.12 version software) consisted of two pumps (LC-10AT VP), a variable wavelength programmable UV/Vis detector (SPD-10A VP), a system controller (SCL-10A VP) and an RP C-18 column (Hypersil BDS C18; 250 cm × 4.6 mm; 5). Mobile phase was acetonitrile and phosphate buffer of pH 3.4 (40:60%v/v) and flow rate of 1 ml/min. The detection wave length was 235 nm.

From the stock solution (1 mg/ml), working standard solutions were prepared (0.2-40 µg/ml of ECB and 500 µg/ml of valdecoxib, an internal standard) in methanol (100%). The rat plasma (95 µl) was pipetted into micro-centrifuge tubes and spiked with 5 µl of the working standard solutions of the drug. To this, 25 µl of 500 µg/ml internal standard and 2 ml of dichloromethane and diethyl ether mixture (3:7%v/v) was added, and its vortexed for 4 min and centrifuged at 10000rpm for 10min in cold-centrifugation at 4°C. The clear supernatant was separated and evaporated in the nitrogen evaporator (Zymark nitrogen evaporator) at 50 °C. The residue was reconstituted with 150 µl of mobile phase and 20 µl was injected to the HPLC system. Standard curves were obtained by using drug/internal standard peak area ratio and theoretical concentration.

Statistical Analysis

Student's t-test was used to analyze the data (graph pad Instant Software-1.13 version) and p<0.05 was considered statistically significant. The pharmacokinetic parameters were calculated by using PK solutions 2 software.

RESULTS

FTIR and DSC Studies

The IR spectra of ECB, binary mixture of ECB and PEG in the ratio 1:1, binary mixture of ECB and PVP in the ratio 1:1 and binary mixture of ECB and dextrin in the ratio 1:2 are given in the (Figures 2A-2C). The spectrum of pure ECB presented characteristic signals at 2341.4, 1598.9, 1494.7, 1433.0, 1404.1, 1298.0, 1143.7, 1083.9, 839.0, 781.1 and 543.9 cm⁻¹.

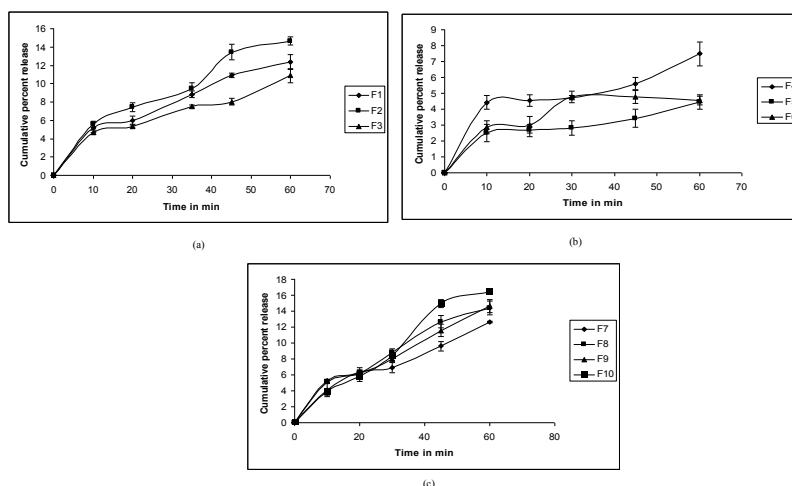


Figure 2. Dissolution profile of etoricoxib solid dispersion in (a) PEG 6000 (b) PVP K 30 (c) Dextrin.

DSC thermo grams for pure ECB, PEG 6000 and solid dispersions F1, F2 and F3 were presented in (Figure 2). ECB showed a melting endotherm at 137.96 °C with enthalpy of fusion at 37.15 J/g. The formulations F1, F2 and F3 showed the melting endotherm at 133.68 °C, 123.70 °C and 123.66 °C. The melting endotherm of formulations F4, F5 and F6 were 135.91, 139.22 and 139.34 °C. The formulation F7, F8, F9 and F10 showed that the melting endotherm peaks of ECB 137.00, 139.95, 137.26 and 138.53.

Particle Size, Shape and Surface Morphology

The particle size of solid dispersion prepared in the presence of PEG and PVP was in the range of 100-200 µm. Whereas the particle size of solid dispersion prepared in the presence of dextrin was in the range of 200-300 µm.

Drug content

The results of drug content determination of solid dispersions are shown in (Table 2). The drug content of solid dispersions was found to be more than 95.0%.

Table 2. Drug content and *in vitro* release results of ECB solid dispersions.

Formulations	Amount of ECB in 100 mg of solid dispersion (mg)	Drug release (%) in 60 min
Pure drug	-	5.06 ± 0.30
F1	64.04	12.35 ± 0.82

F2	68.64	14.66 ± 0.46
F3	44.43	10.87 ± 0.76
F4	93.46	7.50 ± 0.75
F5	67.43	4.46 ± 0.46
F6	56.53	4.55 ± 0.28
F7	70.70	12.68 ± 0.09
F8	71.30	14.38 ± 0.85
F9	31.11	14.64 ± 0.39
F10	31.71	16.43 ± 0.18

In Vitro Drug Release Studies

The *in vitro* drug release studies of ECB solid dispersions were carried out in distilled water (dissolution medium) using USP type I dissolution apparatus. The different ratios of drug and PEG 6000 (1:0.5, 1:0.75 and 1:1) have been tried and the results of *in vitro* drug release studies of ECB solid dispersions with PEG 6000 are shown in (Table 2 and Figure 2). The results of *in vitro* drug release studies of ECB solid dispersions with PVP are shown in (Table 2 and Figure 2). In another set of experiments, we prepared the solid dispersions of ECB with dextrin in different ratios (1:0.5, 1:1, 1:1.5 and 1:2; drug and dextrin, respectively). The results of *in vitro* drug release studies are also shown in (Table 2 and Figure 2).

Stability Studies

The drug content of ECB during the stability studies is given in the (Table 3). The log percentage drug remaining of ECB was plotted against the time as shown in (Figure 3).

Table 3. Stability studies of ECB solid dispersions at 40 ± 2°C and 75 ± 5% RH.

Time in days	Log percent drug remaining	
	F10	
0	2	
15	1.9972	
30	1.9936	
45	1.9895	
60	1.9858	
90	1.9748	
180	1.9722	

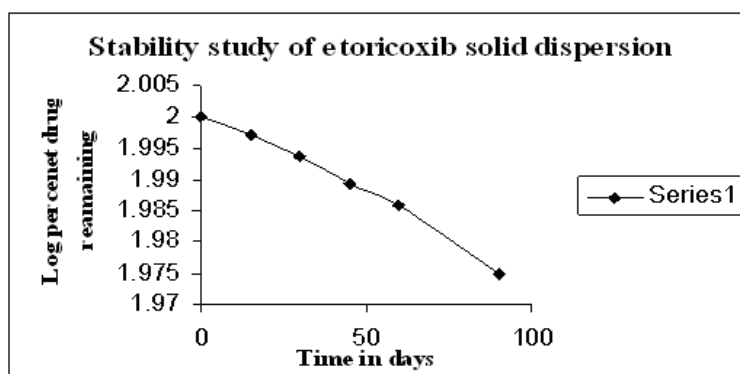


Figure 3. Stability study of ECB solid dispersions at 40 ± 2°C and 75 ± 5% RH.

In Vivo Studies

The pharmacokinetics study profile (plasma concentration versus time) of pure drug and optimized solid dispersion formulation were carried out using Wistar rats is shown in (Figure 4). The pharmacokinetic parameters were calculated from the plasma concentration-time curves and are presented in (Table 4).

DISCUSSION

Formulation Development

ECB is a potent anti-inflammatory agent, belongs to BCS class II drugs for poorly soluble, highly permeable. Together with permeability, the solubility and dissolution behavior of ECB are key determinants of its oral bioavailability. Hence the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. Solid dispersion is a promising technique to considerably enhance the aqueous solubility of poorly soluble drugs. Hence the present study has been undertaken to increase the aqueous solubility of ECB by solid dispersion methods and prepared by Solvent method and Melting solvent method were employed. Among these, solvent method is the easiest and economic method. This method was used to prepare solid dispersions

of ECB with PVP K40 and Dextrin; whereas with PEG 6000, prepared by melting solvent method, since PEG 6000 was not easily soluble in the common solvent i.e., dichloromethane. The ratios of drug and carrier were selected based on the previous reports.

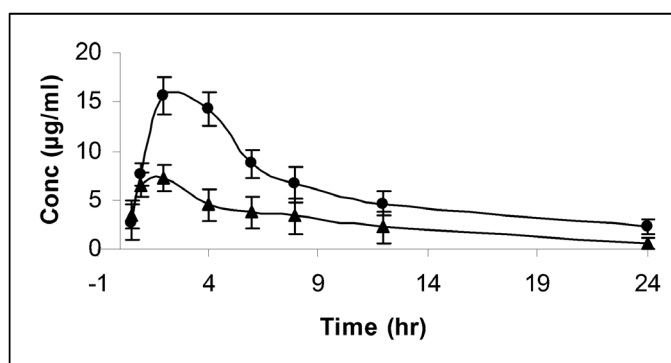


Figure 4. Plasma drug concentration-time curve for etoricoxib in rats. Pure drug (—▲—) Optimized formulation (F10) (•)

Table 4. Pharmacokinetic parameters from plasma concentration vs time curves.

Parameters	Pure ECB	Formulation (F10)
C_{max} (µg/ml)	7.2 ± 1.32	15.5 ± 2.67
T_{max} (h)	1.5 ± 0.5	2.0 ± 0.5
AUC(0- 24hrs) (µg/hr/ml)	90.35 ± 8.25	160.05 ± 14.62

All values are expressed as Mean ± SD, n=6; C_{max} = Peak plasma concentration; T_{max} = Time of peak plasma concentration, AUC= Area under the curve; Significant compared to pure drug (P < 0.001).

FTIR and DSC Studies

FTIR and DSC studies have performed in order to study the drug excipient interactions. The interactions between the drug and the carrier often lead to identifiable changes in the infrared profile of solid dispersions [12]. The IR spectra of solid dispersions were compared with the standard spectrum of ECB. The interaction which could occur might be reflected in N-H or C=N or S=O vibrations, depending on the extent of interaction. The spectra of SDs were equivalent to the addition spectrum of PEG 6000 and ECB. These results indicated that there was absence of well-defined interactions between ECB and PEG 6000. Although it could be expected as the reported methods that hydrogen bonding between the hydrogen atom of NH_2 of ECB and one of the ion pairs of oxygen atom in PEG 6000 may take place and it could not be demonstrated [13].

The increase in the concentration of polyethylene glycol resulted in the decrease in the melting point of ECB. It may be speculated that ECB was started dissolving in PEG and hence sharp DSC peaks could be observed. The decrease in the DSC peaks of ECB in the formulations envisaged that the drug was solubilized in the liquid phase. Similar results have been reported previously [14]. However, the results can be confirmed by X-ray diffraction method. There was no significant change in the melting point of ECB in presence of PVP. The results indicated that there was no polymorphism exists for ECB and the interaction of PVP with drug did not vary the transition. The results also envisaged that there was no dissolution of ECB as like with PEG. There was less variation of melting point of ECB when it was compared with the formulations. The melting point was not altered for ECB and the transitions were unaffected. The increase in the concentration of dextrin also resulted in the unalteration of ECB [15]. The results suggested that there was no interaction of ECB with dextrin. The DSC thermogram of pure ECB and the binary mixture of ECB with dextrin, PVP and PEG were given in the (Figure 5) respectively.

Particle Size, Shape and Surface Morphology

It was found that the presence of polymer in the solid dispersion influenced the particle size of the resultant agglomerates. The size of the particles increased with an increase in deposition of polymer on the surface of drug. The SEM results are shown in (Figure 6). The surface morphology studies revealed that the solid dispersion was closely compacted into small spherical form.

Drug content

The drug content of solid dispersions was found to be more than 95.0%. These results indicated that solvent and melting solvent methods are suitable to prepare ECB solid dispersions. The very little loss of drug in the formulation may be due to process involved in these methods.

In Vitro Drug Release Studies

The results showed that the cumulative amount of drug released at the end of 1 h was increased with an increase in PEG 6000 ratio up to 1:0.75 (drug and PEG 6000), but further increase in the PEG 6000 content to 1:1 (F3) reduced the cumulative amount of drug released at the end of dissolution study period. This could be due to the formation of a viscous hydrophilic layer around the drug particles. Among the different ratios, drug and PEG in the ratio of 1:0.75 was found to be better with respect to *in vitro* release studies.

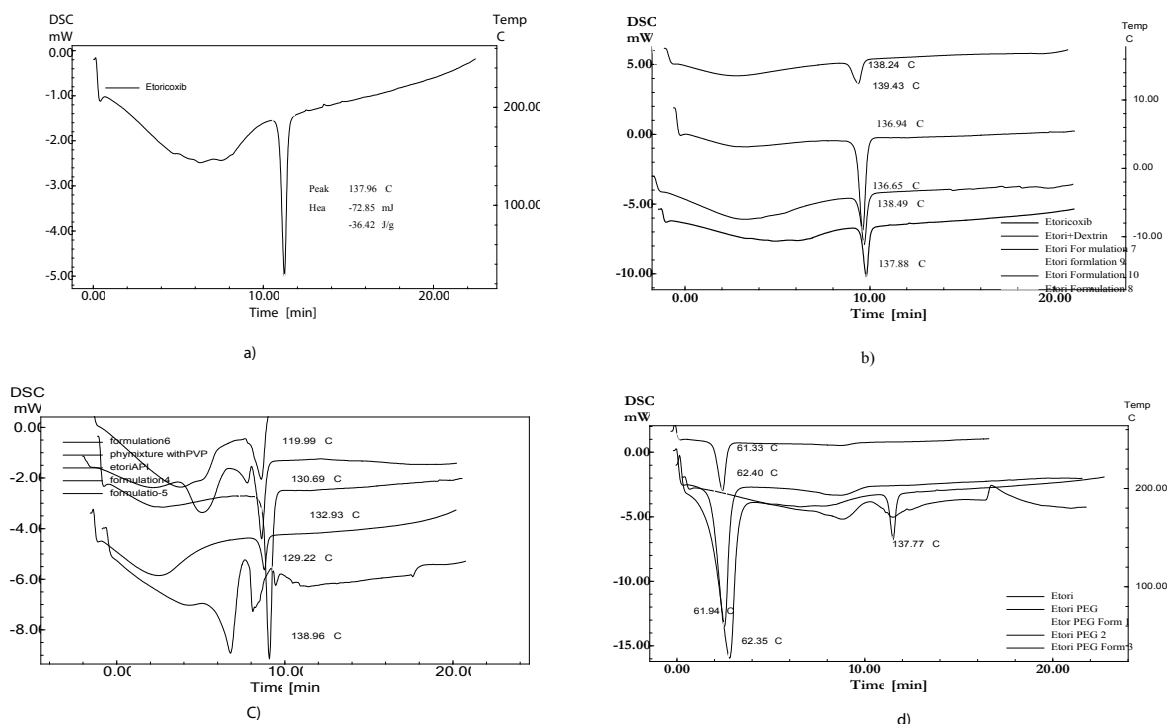


Figure 5. DSC of ECB.a. Pure ECB, b. ECB + Dextrin, c. ECB + PVPK40, d. ECB + PEG 6000.

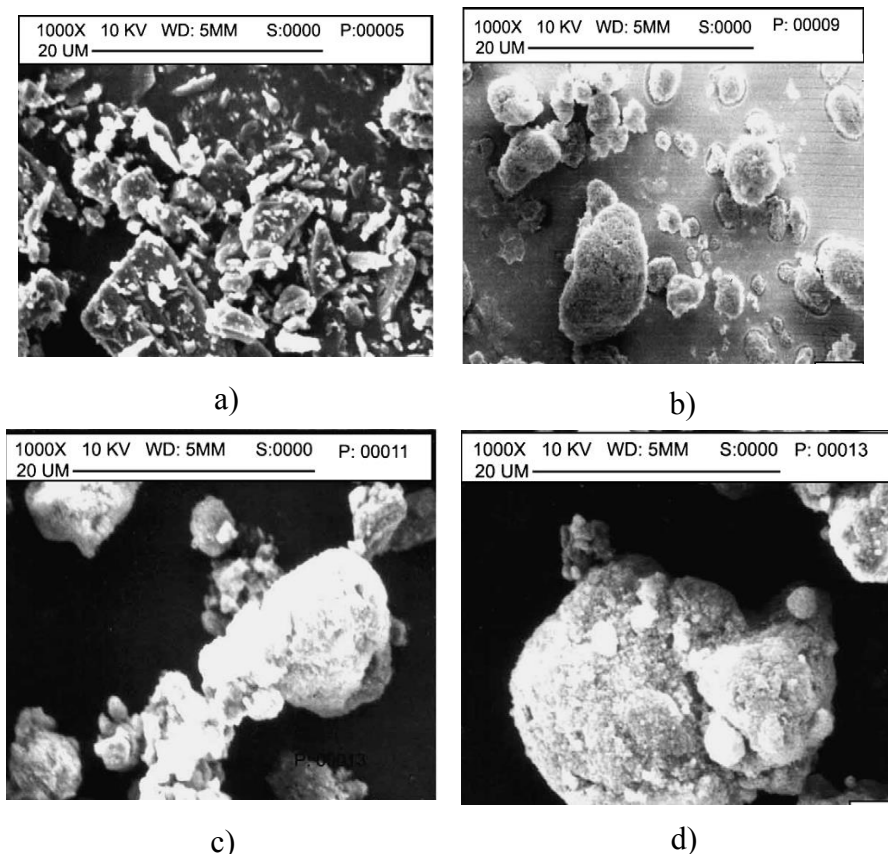


Figure 6. Scanning electron microscopy of solid dispersion containing (a) Pure ECB (b) PEG 6000+ ECB (c) PVP K40 + ECB (d) Dextrin + ECB.

Furthermore, we have also used PVP K40 as a carrier to prepare ECB solid dispersions (drug and PVP in the ratios of 1:0.25, 1:0.5 and 1:0.75). The results showed that the cumulative amount of drug released at the end of 1 h was decreased with an increase in PVP K40 content. Among these dispersions, drug and PVP K40 in the ratio of 1:0.25 showed a maximum release; but less than that of PEG dispersions. The other two ratios (F5 and F6) exhibited cumulative amount of drug release lesser than that of the pure drug. This could be due to the formation of a viscous hydrophilic layer around the drug particles at the higher ratios of PVP K40.

The results of *in vitro* drug release studies from dextrin based formulations are shown in (Table 2 and Figure 4). The results

showed that the cumulative amount of drug released at the end of 1 h was increased proportionately with an increase in dextrin content. Among these, the solid dispersion with the ratio of 1:2 (drug and dextrin, respectively) exhibited a maximum release when compared to other 3 ratios. Among the selected ratios of dextrin, the drug release was not decreased with higher contents, which was observed with PVP K40 and PEG 6000 earlier.

Between the carriers used in the present study, dextrin (F10; drug and dextrin in the ratio of 1:2) provided a maximum drug release when compared to all other dispersions (16). With this dispersion (F10), the cumulative percentage of drug release at the end of 1 h was 16.43% which is almost 3 times more than that of the pure drug (5.06% at the end of 1 h). Hence in the present study, optimized ratio of drug and dextrin was found to be 1:2 (F10) based on *in vitro* drug release studies. The F10 formulation was further taken to stability and *in vivo* studies.

Stability Studies

The drug content during the stability studies and the log percentage drug remaining of ECB plotted against time are summarized in (Table 3 and Figure 5), respectively. Upon storage, the F10 solid dispersion did not show considerable change in the drug content for a period of six months at accelerated conditions when compared to initial value, which indicates good stability of solid dispersion.

In Vivo Studies

The two fold increase in C_{max} and 1.7 fold high AUC was observed in solid dispersion of ECB (F10) when compared to the free drug. The mean values were found to statistically significant ($P < 0.001$) at 99% confidence intervals levels. The higher value of AUC along with higher C_{max} values observed with F10 solid dispersion clearly indicated improved absorption of drug, which could be due to improved solubility and dissolution rate of ECB.

CONCLUSION

The present study showed that the dissolution rate of ECB was enhanced to a greater extent by solid dispersion technique using solvent evaporation and fusion methods. Both the methods are industrially feasible and thus can be adopted on a commercial scale to enhance the dissolution profile of ECB. Dextrin showed the most prominent results as compared to PEG 6000 or PVP K30 based solid dispersions indicating the usage of this carrier for solubility improvement of ECB. Furthermore, the solid dispersion technique has clearly increased the AUC level when compared to pure drug. In addition, the drug within solid dispersions was found to be stable for 180 days under accelerated conditions.

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