PREPARATION, CHARACTERIZATION, AND EVALUATION OF ANTI-INFLAMMATORY ACTIVITY OF ETORICOXIB LOADED SOLUPLUS® NANOCOMPOSITES

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ABSTRACT

Objective: The objective of this study was to prepare and characterize etoricoxib (ECB) loaded Soluplus® nanocomposites to improve its physicochemical properties. The effect of polymer and surfactant concentration on particle size, *in vitro* percentage dissolution efficiency and the anti-inflammatory activity of nanocomposites were also investigated.

Methods: The nanocomposites were prepared by using a freeze-drying technique. The analytical evidence for the formulation of lyophilized nanocomposites in solid state were generated and confirmed by differential scanning calorimetry (DSC), fourier transformation infrared spectroscopy (FTIR), x-ray powder diffractometry (XPRD) and scanning electron microscopy (SEM). The *in vitro* drug release profile of nanocomposites was compared with pure ECB powder.

Results: The nanocomposites of ECB were contained in a nano range with particle size and zeta potential of 63.5 nm and 46.5 mv, respectively. The solubility and dissolution of the nanocomposites were significantly ($p<0.001$) improved as compared to ECB alone, evidenced by decreased log P values (1.90±0.002) of the nanocomposites. The characterization studies revealed the formation of amorphous nanocomposites of ECB with existence of physical interactions between drug and polymer. The anti-inflammatory activity of nanocomposites evaluated by carrageenan-induced rat paw edema model demonstrated non significant ($p>0.05$) increase in anti-inflammatory activity as compared to pure ECB.

Conclusion: From the results, it could be concluded that the formation of ECB nanocomposites with Soluplus® could be an effective and alternative approach to modify the physicochemical properties of ECB.

Keywords: Etoricoxib, Soluplus®, Nanocomposites, Physicochemical properties, Anti-inflammatory activity

INTRODUCTION

The formation of the nanocomposite of the drug is one of the most widely used techniques to enhance the solubility and dissolution rate of poorly soluble drugs [1, 2]**.** Nanocomposite is a multiphase solid material which contains one of the phases and has one, two or three dimensions of less than 100 (nm) [3]. Structures having nano-scale, repeat distances between the different phases that make up the material. Polymer nanocomposites have attracted interest in the last few decades, providing scope for improvement of physicochemical properties, of poorly water-soluble drugs.

Many molecules currently under development fall in BCS (Biopharmaceutical Classification System) class II category, i.e. low solubility and high permeability [4] and generally show dissolution rate-limited absorption. Etoricoxib (ECB) (5-chloro-2-[6-methyl pyridine–3–yl]-3-[4-methysulfonylphenyl] pyridine) (NSAID) is regarded as second generation coxib because of its higher selectivity for COX-2 inhibition than celecoxib and rofecoxib. It has poor solubility [5, 6]. However, very low aqueous solubility and poor dissolution of the coxibs can cause formulation problems and limit their therapeutic application by delaying the rate of absorption and onset of action [7]. Earlier Papers have reported that the improvement in the physicochemical properties of poorly water-soluble drugs could be achieved by the use of surfactants [8], inclusion complexation [9, 10], use of polymorph [11], and amorphous form of drug micronization [12], and solid dispersion [13, 14]. Improving oral bioavailability of the drugs given as solid dosage forms still remains a challenge for the formulation scientists due to solubility problems. Hence, improving their dissolution characteristics is of prime significance in order to establish its optimal therapeutic efficacy [15].

Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol grafted copolymer) is a novel amphiphilic polymeric solubilizer, with both hydrophilic and lipophilic properties. Due to its bi-functional nature, it is expected to act as an excellent matrix to dissolve the drug in an aqueous medium. This polymer is a novel polymer specially designed for fourth-generation solid solutions towards dissolution enhancement [16] and can increase the solubility and bioavailability of poorly soluble drugs. Soluplus® is an ideal for formulating novel drug substances [2, 15].

Insptite of powerful analgesic and anti-inflammatory potential [17, 18], ECB exhibits a delayed rate of absorption [17]. Therefore, efforts were made to improve the physicochemical properties of ECB using solid dispersion [19-21], drug amorphization [22-24], cyclodextrin complexation [25, 26] and spherical crystallization technique [27]. In this article, the formation of nanocomposites of ECB were attempted with Soluplus® to evaluate it for physicochemical properties as well as anti-inflammatory activity.

The aim of this work was to investigate the physicochemical properties and anti-inflammatory activity of ECB by formulating it into its nanocomposites with soluplus® in the presence of tween 80. The aim was extended to study the effect of polymer and surfactant concentrations on the particle size and percentage dissolution efficiency of nanocomposites of ECB, prepared by freeze-drying technique. The lyophilized nanocomposites were characterized by differential scanning calorimetry (DSC), fourier transformation infrared spectroscopy (FTIR), x-ray powder diffractometry (XPRD), scanning electron microscopy (SEM), saturation solubility, partition coefficient determination (log P) and drug content uniformity. The dissolution performance of pure drug and nanocomposites were further examined in phosphate buffer (pH 7.4). The optimized batch

and pure drug were further evaluated for their anti-inflammatory activity by carrageenan-induced rat paw edema model.

MATERIALS AND METHODS

Materials

ECB was generously gifted by Ranbaxy, Mumbai, India. Soluplus® was obtained as a gift sample from BASF, Mumbai, India. Tween 80 and methanol were purchased from Loba Chemie Pvt., Ltd. Mumbai, India. Analytical grade reagents and glass distilled water were used throughout the experimental procedures. The substances were used directly without further purification.

Preparation of ECB loaded nanocomposites by freeze-drying method

The nanocomposites were produced by the freeze-drying method. Firstly, nanoemulsions of ECB in Soluplus®were prepared using probe ultrasonicator. The drug and polymer were dissolved in methanol in different polymer ratios to form the organic phase. 20 ml of distilled water with different ratios of Tween 80 surfactant formed the aqueous phase. The two mixtures were sonicated for 15 min. Using a syringe, the organic phase was slowly dropped into the aqueous phase. A continuous probe ultrasonication in an ice bath was used for effective homogenization of the two phases. The mixture was then magnetically stirred continuously for 24 h at room temperature (25°C±2) for removal of methanol, and then the mixtures were frozen for 25 h in a deep freezer (ELCOLD, Denmark) at -80°C. Then the frozen mixtures were lyophilized (DELVAC-mini Lyodel, India) at -80°C and gently ground to obtain free-flowing powders. The powders were then sieved though mesh of 100 μm sieve size and stored in desiccators until further analysis [15].

Determination of drug content

Drug content was determined by dissolving prepared nano composites equivalent to 5 mg of a drug in 10 ml of methanol and then the volume was adjusted up to 50 ml with distilled water. The solution was sonicated for 15 min and filtered through 0.2 μm membrane filter. The aliquots were suitably diluted and absorbance was measured at 234.5 nm by using UV-visible spectrophotometer (Shimadzu 1800, Japan).

Saturation solubility studies

Saturation solubility studies were performed as follows: Excess amount of pure ECB drug and nanocomposites were added to 10 ml of distilled water in solubility tubes and shaken on a mechanical shaker at room temperature 25±2 °C for 24 h. Once the equilibrium was achieved, appropriate aliquots were withdrawn and filtered through 0.2 μm membrane filter and the filtrate was analyzed UV spectrophotometrically (Shimadzu 1800, Japan) at 234.5 nm [28]. The results of solubility studies were statistically validated using ANOVA (Instat, GraphPad software, Inc. Version 3.05).

Particle size analysis

The nanocomposites were characterized for particle size using Horiba nanoparticle size analyzer (HORIBA SZ-100 for windows [Z-Types] Ver. 1.90, Kyoto, Japan). The particle size distribution was given by d (0.9), d (0.5), d (0.1) which were the particle size diameters determined at the 90th, 50th and 10th percentile of particle undersized, respectively [29, 30].

Zeta potential determination

The surface charge was determined by measuring the electrophoretic mobility of nanocomposites by using Horiba Nano particle size analyzer (HORIBA SZ-100 for windows [Z-Types] Ver. 1.90, Kyoto, Japan). The zeta potential was measured after dilution of the sample with distilled water at room temperature [29, 30].

Determination of partition coefficient (log *P*)

10 ml each of octanol and water were added in glass tubes and allowed to stand overnight for 24 h at room temperature. Excess amount (equivalent to 25 mg) of pure drug and/or its nanocomposites were added in glass tubes and shaken on an incubator shaker (REMI-CIS 24 plus Incubator Shaker, Mumbai, India) for 24 h at 25°C. Then the mixtures were added in the separating funnel and allowed to stand about 6 h for equilibration. Aqueous and organic phases were separated and concentration of drug in the aqueous phase was analyzed UV spectrophotometrically (Shimadzu 1800, Japan) at 234.5 nm [31]. The partition coefficient was calculated by following formula,

The partition coefficient (log P) = log ($C_{octanol}/C_{water}$) .... (1)

Where C is the concentration of the drug in octanol and/or water phase.

In vitro drug release

The dissolution studies of ECB and its nanocomposites were performed in triplicate in a dissolution test apparatus (ELECTROLAB dissolution apparatus, Mumbai, India) according to USP type II. Samples were placed in the dissolution vessel containing 900 ml of phosphate buffer (pH 7.4), maintained at 37±0.5 °C at 50 rpm according to US FDA guidelines. 60 mg of ECB or its equivalent amount of nanocomposites was added to 900 ml of phosphate buffer (pH 7.4). 5 ml of samples were withdrawn at appropriate time intervals. The volume of dissolution media was adjusted to 900 ml by replacing each 5 ml aliquot withdrawn with 5 ml of fresh phosphate buffer (pH 7.4) [21]. The solution was immediately filtered through membrane filter paper 0.2 μm, and adequately diluted if necessary and analyzed spectrophotometrically at 288 nm (Shimadzu 1800, Japan). The data obtained through dissolution studies were statistically analyzed by ANOVA (Instat, GraphPad software, Inc. Version 3.05).

DSC analysis

DSC analysis of pure ECB, Soluplus® and an optimized batch of nanocomposites were performed using DSC analyzer (TA Instruments, SDT Q600 USA). A sample (5 mg) was heated under a nitrogen atmosphere at a heating rate of 10 °C/min over the temperature range of 0-275 °C.

FTIR analysis

Attenuated Total Reflectance (ATR) is a sampling technique used in conjunction with infrared spectroscopy, which enables samples to be examined directly in the solid or liquid state without further preparation. Infrared spectra of all samples were obtained by using ATR (BRUKER–ECO–ATR–ALPHA, Germany). The samples were directly placed on sample pan and analyzed from 600 to 4000 cm⁻¹ spectral range with 24 scans.

XRPD studies

The XRPD patterns of pure ECB, Soluplus® and an optimized batch of nanocomposites were recorded by using X-ray diffractometer (BRUKAR–D₂ PHA–SER, Germany) with tube anode Cu, over the interval 10-90°/2θ. The operational data was as follows: Generator tension (voltage) 30 kV, Generator current 10 mA.

SEM analysis

The surface morphology of the drug and optimized batch of nanocomposites were evaluated by a scanning microscope (SEM-JOEL Instruments, JSM-6360, Japan) operated at an acceleration voltage of 20 kV and obtained micrographs were examined at ×200, ×500 magnifications.

Anti-inflammatory activity of ECB nanocomposites

All experiments were approved by the Institutional Animal Ethics Committee (the Approval No. RCP/IAEC/16-17/P09 dated 12.06.2017) and were carried out according to the guideline of the CPCSEA (committee for the purpose of control and supervision of experiments on animals) Healthy Wistar albino rats (procured from National institute of Biosciences, Bhor, Pune) of either sex weighing 275-250 g were used in the present study The animals were housed comfortably in a group of six in a single clean plastic cage with a metal frame lid on its top. They were housed under standard environmental conditions of temperature A 12:12 h light, dark cycle

was followed. All animals had free access to water and standard palletized laboratory animal diet feed.

Anti-inflammatory activity of nanocomposites was performed by using carrageenan-induced rat paw edema method. Male Wistar rats selected for the study were randomized based on their body weight and divided into six different groups consisting of 6 animals each. Rats were injected subcutaneously (S.C.) by injection of carrageenan (0.1 ml of 1 % solution in normal saline) into the plantar side of the left hind paw. The paw was marked with ink at the level of the lateral malleolus. The paw volume was measured up to the mark using digital plethysmometer before (-1 h) and at 1, 2, 3, 4, and 6 h after injection of carrageenan for all the animals. Paw edema volume was calculated by subtracting-1 h paw volume from the respective paw volumes at l, 2, 3, 4, and 6 h [32-36].

RESULTS AND DISCUSSION

Otimization of batches

ECB and different ratios of polymer: surfactant batch was optimized based on its saturation solubility data.

Saturation solubility studies

The results of saturation solubility studies of all nanocomposites of ECB are shown in table 1. It was evident that solubility of all batches was enhanced significantly ($p<0.001$) as compared to pure drug alone. The aqueous solubility of the optimized batch (F6) was found to be 6.90 fold increase, as compared to pure ECB. Hydrophilicity of the polymer with a simultaneous reduction in particle size might have contributed for a substantial increase in solubility of formulations.

Table 1: Particle size and solubility data of various batches for optimization

Batch code	Drug to polymer ratio (mg: mg)	Amount of surfactant added (ml)	Particle size (nm)	Saturation solubility (µg/ml)*
ECB				42.44±0.20
F1	1:1	0.005	15.7	254.66±2.30**
F2	1:3	0.005	3.3	282.22±2.77**
F3	1:1	0.0095	149	197.77±2.03**
F4	1:3	0.0095	29.9	282.88±3.79**
F5	1:1	0.014	64.2	274.66±2.66**
F6	1:3	0.014	63.5	292.88±2.77**

ECB: etoricoxib; *mean±SD (n = 3): SD standard deviation; **significant differences compared to pure ECB ($p<0.001$).

Percent drug content

Percentage drug content of the freeze-dried optimized batch (F6) was found to be 99.1±0.45 (w/w).

Particle size analysis

The particle size analysis revealed that the nanocomposites of ECB were found to be in nano range (table 1). The particle of pure ECB was found to be in micron range 2.31 µm with a polydispersity index (PI) of 0.70. The particle size of the optimized batch F6 was measured to be 63.5 nm (fig. 1). However, nonuniform distribution of particles was noticed. Using the freeze-drying technique, the size of the pure drug was significantly reduced in nano size [29, 30].
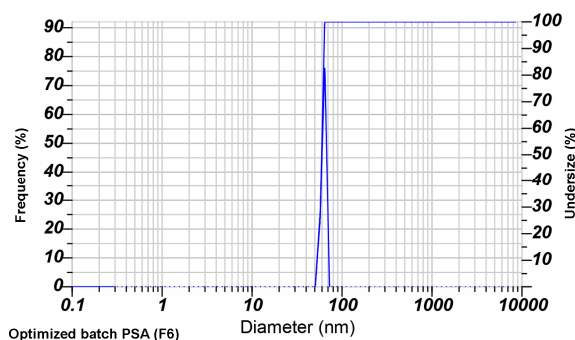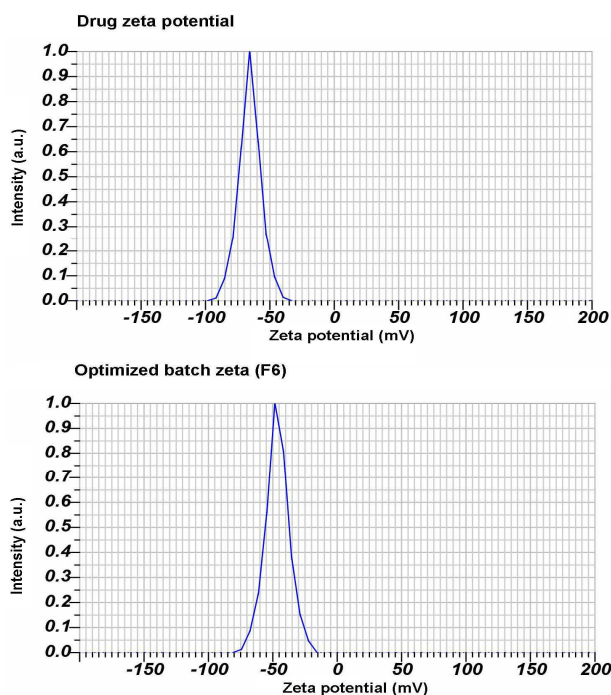

Fig. 1: The particle size distribution of optimized batch (F6); PSA: particle size analysis

Fig. 2: Zeta potential of drug (ECB), optimized batch (F6); ECB: etoricoxib

Zeta potential determination

Drug and optimized batch F6 were subjected to zeta potential analysis (fig. 2). The particles with zeta-potential values more positive and more negative than+30mV and-30mV, respectively, are generally considered stable. According to the data, the zeta potential was found to be-65.5 and-46.5 mV, respectively, indicating the formation of stable nanocomposites. The negative value of zeta potential indicates a negative charge on the droplets [29, 30].

Determination of partition coefficient (log *P*)

The log *P* value of ECB and optimized batch (F6) were found to be 2.37±0.009 and 1.90±0.002 respectively ($p < 0.001$). The decreased log *P* value of optimized batch (F6) compared to ECB, clearly indicated an enhancement in hydrophilicity of optimized batch (F6).

In vitro drug release

The release rate profiles were expressed as the percentage of drug released (vs.) time (fig. 3). It was evident that nanocomposites have improved the dissolution rate of ECB

significantly. Table 2 shows % drug dissolved in 5 min (DP_5), 15 min (DP_{15}), 30 min (DP_{30}) and 45 min (DP_{45}) for ECB and its nanocomposites batches (F1 to F6). The dissolution efficiency values (DE_{45}) at 45 min have been reported and compared statistically. The dissolution efficiency (DE) is defined as the area under dissolution curve up to the time t expressed as a percentage of the area of rectangle described by 100%

dissolution in the same time [37]. The optimized batch (F6) of ECB showed faster dissolution than pure ECB alone. The % release of ECB was 66.75±0.60 from optimized batch (F6) within 15 min (DP_{15}). However, the release of ECB from pure ECB was only 7.45±0.06 within 15 min. Thus optimized batch (F6) of ECB with soluplus® had significantly improved the dissolution rate of the pure ECB (DE_{45}: 59.65±0.26, $p<0.001$).

Table 2: The dissolution data of pure ECB and its nanocomposites batches in phosphate buffer (pH 7.4) at 37±0.5 °C

Batch code	DP_5^*±SD	DP_{15}^*±SD	DP_{30}^*±SD	DP_{45}^*±SD	DE_{45}^*±SD
ECB	2.65±0.08	7.45±0.06	11.88±0.05	15.81±0.24	8.82±0.06
F1	31.80±0.30	45.80±0.52	59.55±0.15	62.85±1.22	48.49±0.32**
F2	26.55±0.75	43.85±1.27	58.40±0.60	68.50±0.60	48.34±0.35**
F3	28.55±0.82	35.85±0.39	46.56±0.40	48.80±0.52	38.18±0.14**
F4	37.50±0.25	57.05±0.52	67.20±0.79	68.85±0.98	55.61±0.33**
F5	37.66±0.96	50.85±0.65	62.70±0.60	66.75±0.60	52.97±0.19**
F6	37.10±0.45	66.20±0.52	68.60±0.67	71.00±0.62	59.28±0.43**

ECB: etoricoxib; *mean±SD standard deviation (n = 3); DP: % drug dissolved; % DE: % dissolution efficiency; indicates *p* value compared to pure ECB ($p<0.001$), i.e. **significant.
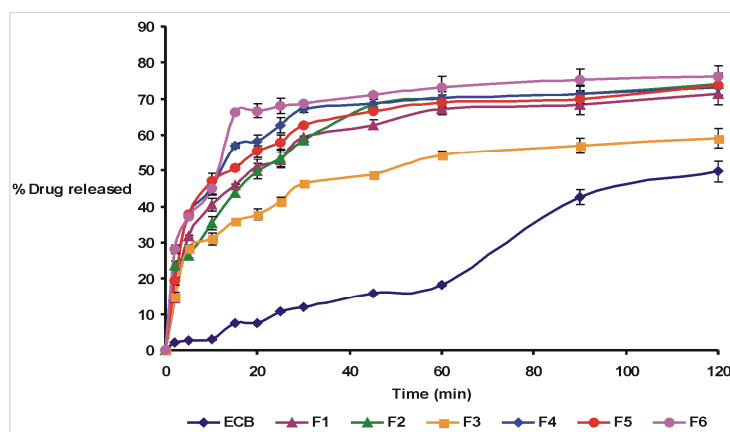

Fig. 3: The dissolution profile of ECB and F1 to F6 batches at 37±0.5°C; ECB: etoricoxib

DSC analysis

DSC thermogram of ECB, polymer and optimized batch (F6) are shown in (fig. 4). ECB showed a distinct melting endotherm at 138 °C. The polymer Soluplus® showed a glass transition (T_g) endotherm at 62.58 °C. The nanocomposites of the optimized batch (F6) have shown the complete disappearance of pure ECB melting peck; indicating the decrease of the crystalline nature of the drug. Enhanced solubility and faster dissolution rates of the drug are known to result from the transformation of the stable crystalline state of the drug to some amorphous state in the formulations.

FTIR analysis

Fig. 5 illustrates the FTIR spectra of ECB, polymer and optimized batch (F6) studied by ATR-IR spectroscopy. IR spectrum of ECB is characterized by principal absorption peaks at 3052.89 cm^{-1} (C-H stretch aromatic benzene), 2882.17 cm^{-1} (C-H stretch aliphatic CH$_3$ *asym*), 1669.75 cm^{-1}, 1595.07 cm^{-1} and 1492.31 cm^{-1} (C= C aromatic), 1669.75 cm^{-1} (C=N), 1138.04 cm^{-1} (S=O sulphonyl), 1082.77 cm^{-1} (C-Cl), 837.98 cm^{-1} (*p*-substituted benzene) and 736.68 cm^{-1} (pyridine).

IR spectrum of Soluplus® exhibited characteristic IR bands at 3337.07 cm^{-1} and 3280.18 cm^{-1} (O-H stretching), 2916.80 cm^{-1} (aliphatic-CH stretching), 1732.15 cm^{-1} and 1634.93 cm^{-1} (C=O stretching).

In IR spectrum of the optimized batch (F6), the peak of ECB at 3052.89 cm^{-1} (C-H stretch aromatic benzene) was completely disappeared while other peaks were found to be diffused. The IR bands at 1082.77 cm^{-1} (C-Cl), 2882.17 cm^{-1} (C-H stretch aliphatic CH$_3$ *asym*) were shifted towards lower frequency 1084.39 cm^{-1} and

2890.81 cm^{-1}, respectively. The peaks of soluplus® at 3337.07 cm^{-1} (O-H stretching) were shifted to 3323.59 cm^{-1}. The intensity of the band at 1595.07 cm^{-1} (C= C aromatic) was also prominently decreased, indicating the existence of physical interactions.
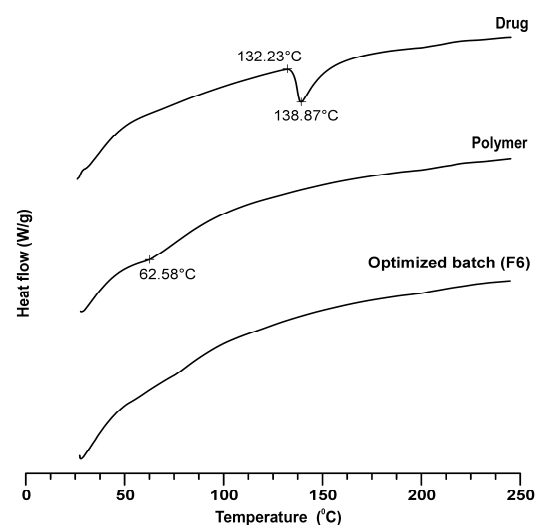

Fig. 4: DSC thermograms of drug (ECB), Soluplus®(polymer), optimized batch (F6); ECB: etoricoxib
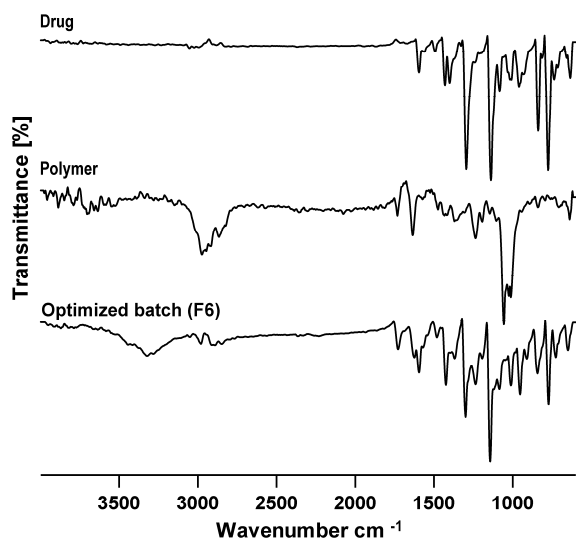
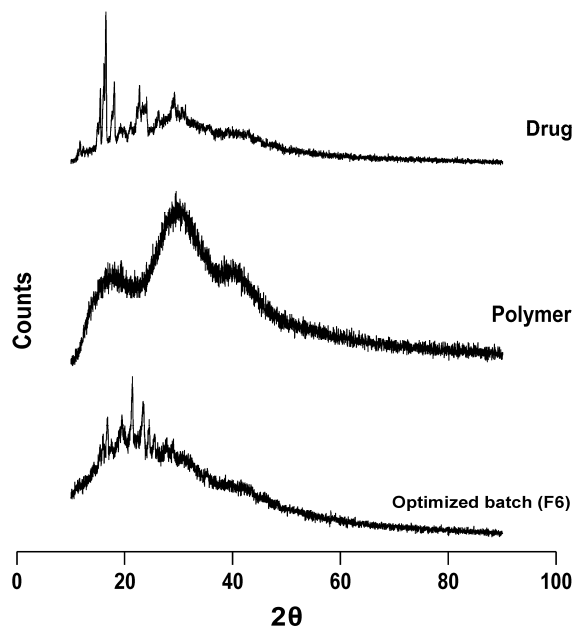**Fig. 5: FTIR spectra of drug (ECB), Soluplus®(polymer), optimized batch (F6); ECB: etoricoxib**

Fig. 6: XRPD patterns of of drug (ECB), soluplus®(Polymer), optimized batch (F6); ECB: etoricoxib

XRPD studies

The XRPD pattern of ECB displayed intense and sharp peaks, indicating its crystalline nature. ECB (fig. 6) showed 2θ values and peak intensities at 15.44 °(594), 16.45 °(1144), 16.31 °(635), 22.69 °(626), and 29.16 °(553). A typical halo-pattern was noted for Soluplus® (fig. 6), indicated its amorphous character. The peak height at 16.74 ° (2θ) was used for calculating the relative decrease in crystallinity (RDC) of ECB in optimized batch (F6) (fig. 6), as peaks of ECB with the highest intensity (16.45°) disappeared in these nanocomposites. However, other peaks of ECB were also disappeared. The disappearance of intense peaks of ECB in optimized batch (F6) suggested a loss of the crystallinity and possibility of the presence of some amorphous entities of ECB in these nanocomposites [38, 39].

SEM analysis

The surface morphology of the pure ECB powder, an optimized batch of nanocomposites (F6) is shown in (fig. 7). ECB was characterized by the presence of rod-shaped, uneven rough and broken particles. The surface morphology of freeze-dried nanocomposites (F6) batch showed irregular particles of some amorphous aggregates with narrow particle size distribution and the original morphologies of pure ECB decreased. The nanocomposites of ECB exerted amorphous form with a reduction in the particle size, thus remarkably affecting the drug solubility and dissolution rate [40].
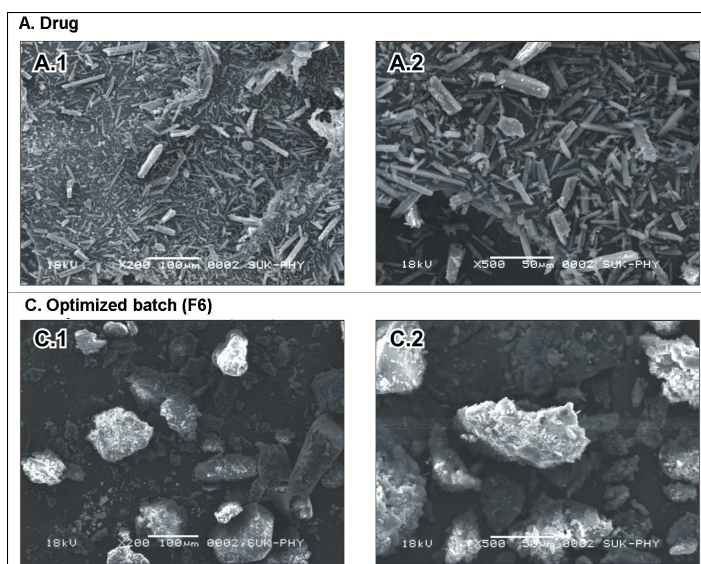

Fig. 7: SEM of drug (ECB) A1, A2; optimized batch (F6) C1, C2; ECB: etoricoxib

Anti-inflammatory activity of ECB nanocomposites

From the histogram (fig. 8) and table 3, at 0 h drug showed negative % inhibition due to poor absorption. However, at 0 h, F6 batch showed % inhibition indicating faster absorption of nanocomposites due to particle size reduction of drug and enhancement of solubility. There was no significant difference between drug and F6 at all hrs. Hence, the result concluded that the nanocomposites showed the same activity [34-36].
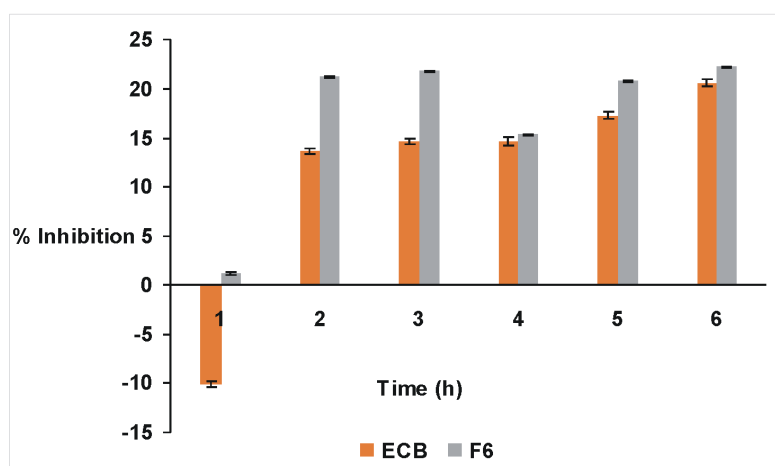
Fig. 8: Histogram of % inhibition of ECB; F6 (optimized batch nanocomposites); ECB: etoricoxib

Table 3: The anti-inflammatory activity by carrageenin-induced hind paw edema in rat

Hours/System		Control	ECB	F6**
0	Increase in paw volume* ml	1.87±0.007	2.06±0.28	1.85±0.16
	% inhibition*	-	-10.16	1.06
1	Increase in paw volume* ml	2.50±0.14	2.16±0.26	1.97±0.05
	% inhibition*	-	13.6	21.2
2	Increase in paw volume* ml	2.66±0.02	2.27±0.32	2.08±0.07
	% inhibition*	-	14.66	21.80
3	Increase in paw volume* ml	2.80±0.042	2.45±0.37	2.36±0.08
	% inhibition*	-	14.64	15.35
4	Increase in paw volume* ml	2.98±0.04	2.45±0.37	2.36±0.08
	% inhibition*	-	17.28	20.80
6	Increase in paw volume*ml	3.01±0.02	2.39±0.39	2.34±0.07
	% inhibition*	-	20.59	22.25

*mean±SD (n=6); SD standard deviation, **non-significant difference compared to pure ECB ($p > 0.05$); ECB: etoricoxib, F6: optimized batch F6

CONCLUSION

The present investigation demonstated successful formation of the nanocomposites of ECB using amphiphilic polymer soluplus®by freeze-drying technique. Freeze drying technique has shown a significant reduction of particle size and improved the solubility and dissolution rate of the drug. The characterization of freeze-dried nanocomposites revealed that the drug was converted into an amorphous form. The application of freeze-drying technique gave a statistically systematic approach for the formulation of nanocomposites with desired particle size and percentage drug release within 45 min. The formulation F6 batch was selected as an optimized batch with desired properties and produced non significant anti-inflammatory activity in rats. Thus, it could be concluded that the use of freeze-drying technology, amphiphilic carrier, and tween 80 to prepare polymeric nanocomposites could improve physicochemical properties of ECB.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

The authors declare no conflict of interests

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