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Research Article

EVALUATING THE BEST POLYETHYLENE GLYCOL AS SOLID DISPERSION CARRIER BY TAKING ETORICOXIB AS A MODEL DRUG

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ABSTRACT

Objective: The main objective of the current research is focused in discovering the best polyethylene glycol (PEG) as solid dispersion carrier using etoricoxib (ECB) as a model drug.

Methods: Varieties of PEG, namely PEG - 3350, PEG - 4000, PEG - 6000, PEG - 8000, and PEG - 20000, were evaluated as a carrier for making ECB solid dispersions. ECB:PEG was taken in the ratios of 1:1, 1:2, 1:4, and 1:6. The solid dispersions were prepared by microwave fusion method and compressed using 8 station tablet compression machine. The fabricated solid dispersion tablets were tested for physicochemical characteristics and drug release rates. The release of ECB from the prepared solid dispersions was further analyzed kinetically using the first order and Hixson-Crowell's plots.

Results: All the solid dispersion batches were shown satisfactory physicochemical characteristics. ECB solid dispersion batches with PEG - 6000 showed good solubility in distilled water (up to 2.29±0.01 µg/ml) and in 0.1 N HCl (up to 2.18±0.01 µg/ml) when compared with ECB alone (0.21±0.01 µg/ml and 0.32±0.01 µg/ml). The prepared solid dispersions with PEG 6000 are shown good ECB release.

Conclusion: Among PEG carriers, PEG - 6000 was found to be the best carrier for increasing the solubility and release rate of ECB form the solid dispersions compared to PEG - 3350, PEG - 4000, PEG - 8000, and PEG - 20000.

Keywords: Etoricoxib, Polyethylene glycol, Solid dispersions, Evaluation.

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INTRODUCTION

The industrial pharmacist makes so many trials with the aim to increase the solubility of poorly water-soluble drugs in an inexpensive way. Among the different techniques of increasing solubility, solid dispersion technique was attaining the fame [1].

Etoricoxib (ECB) is a nonsteroidal drug used in dealing with all the varieties of pain and arthritic inflammation. ECB is a poorly water-soluble drug with 92% protein binding and poor bioavailability [2,3].

The present exploration was to increase the solubility of ECB by making solid dispersions using polyethylene glycol (PEG) carriers [4-8], namely PEG - 3350, PEG - 4000, PEG - 6000, PEG - 8000, and PEG - 20000 and finding out the best polymer among them. The solid dispersions were prepared by microwave melting method.

MATERIALS AND METHODS

Materials

ECB was procured from Yarrow Chemicals. PEG - 3350, PEG - 4000, PEG - 6000, PEG - 8000, and PEG – 20000 were obtained from Amrutha Organics, Hyderabad. Microcrystalline cellulose, talc, and magnesium stearate were procured from Colorcon, India.

Methods

Compatibility studies

Stability studies

Physical remarks of drug and excipients were studied by taking ECB and excipients in 1:1 ratio and compatibility studied at stressed storage conditions, i.e., at a temperature of 40°C and RH of 75% in environment control chamber [9] (Classic Scientific India, Mumbai) was performed.

Hygroscopic studies

The hygroscopic study of ECB was done under 33, 53, and 75% RH for 4 days and the weight gain was studied [10]. These studies were performed in triplicates.

Solubility studies

ECB was tested for solubility in 0.1 N HCl, water, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and pH 7.4 phosphate buffer [11].

Fabrication of solid dispersions

Solid dispersions with different drug:polymer ratios, from 1:1, 1:2, 1:4, and 1:6 w/w, were prepared using a microwave-induced fusion method. ECB and PEG 3350 were weighed in the ratio 1:1 and mixed gently for 5 min using a mortar and pestle. A fixed amount (i.e., 2 g) of the mixture was subjected to microwave radiation for different durations (3, 4, 5, and 6 min) at a constant power of 590 W in a microwave reactor (CATA-2R, Catalyst Systems, Pune, India). Similarly, mixtures of other ratios (from 1:2, 1:4, and 1:6 w/w) were prepared. Only one beaker was placed at a time inside the microwave oven. Then, the beakers containing the samples were maintained at room temperature for the samples to solidify. The solid dispersions were collected and placed in a glass desiccator for 24 h, and then, the product was pulverized using a mortar and pestle. The pulverized powders were passed through an 80# sieve. Same procedure is adopted using PEG - 4000, PEG - 6000, PEG - 8000, and PEG - 20000 carriers. The various formulae of ECB with PEG are shown in Table 1.

Flow properties

The fabricated solid dispersions were evaluated for micromeritic properties [12,13].

Preparation of tablets containing the solid dispersion

The prepared tablets with solid dispersions equivalent to 60 mg of ECB were prepared by direct compression method [14] after mixing with the

required amount of different ingredients as shown in Table 2 using 8 station tablet compression machine (Karnavati Engineering, Ahmedabad, India).

Evaluation of solid dispersions of ECB

The following parameters were tested for ECB solid dispersions [15-18].

Morphological characteristics

In this study, tablets were tested for size and shape.

Thickness

Tablets were evaluated for their thickness using Vernier Calipers (Qumos Enterprises, Mumbai, India). These trails were made in triplicates.

Table 1: Drug(ECB):carrier(PEG) ratios in various formulations

Drug: carrier	Ratio	Formulation name
ECB: PEG-3350	1:1	EPEG3-1
	1:2	EPEG3-2
	1:4	EPEG3-3
	1:6	EPEG3-4
ECB: PEG-4000	1:1	EPEG4-1
	1:2	EPEG4-2
	1:4	EPEG4-3
	1:6	EPEG4-4
ECB: PEG-6000	1:1	EPEG6-1
	1:2	EPEG6-2
	1:4	EPEG6-3
	1:6	EPEG6-4
ECB: PEG-8000	1:1	EPEG8-1
	1:2	EPEG8-2
	1:4	EPEG8-3
	1:6	EPEG8-4
ECB: PEG-20000	1:1	EPEG20-1
	1:2	EPEG20-2
	1:4	EPEG20-3
	1:6	EPEG20-4

ECB: Etoricoxib

Table 2: Formulation of a tablet containing solid dispersions

Ingredients	Quantity per tablet(mg)
Solid dispersions equivalent to 60 mg of ECB	125
Lactose	50
Starch	15
Microcrystalline cellulose	50
Magnesium stearate	5
Talc	5
The weight of the tablets	250

Hardness

The force of fracture was recorded using Monsanto tablet hardness tester (Vinsyst Technologies, Mumbai). These tests were performed in triplicates.

Uniformity in weight

A total of 20 tablets from each formulation were weighed individually using an electronic digital balance (Citizen, CY-104, Mumbai) and calculated the average weight and compared with the individual tablet weights. From this, percentage weight difference was calculated and then checked for IP specifications (limit ± 7.5% of average weight).

Friability

It is the occurrence in which tablet surfaces are injured when subjected to physical tremor or erosion. This test was performed using Roche Friabilator. 20 tablets were weighed before the test ($W_{initial}$) and moved into a friabilator. The equipment was run at a speed of 25 rpm for the

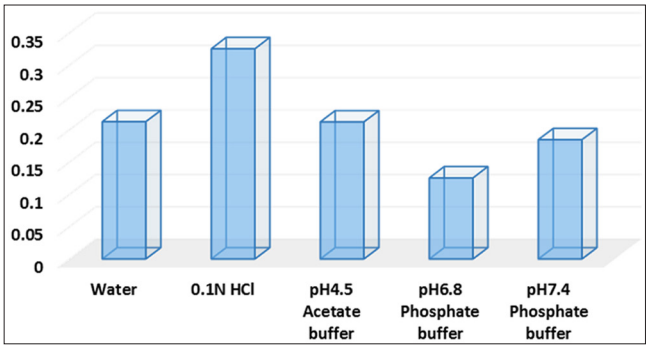

Fig. 1: Solubility of etoricoxib at various media

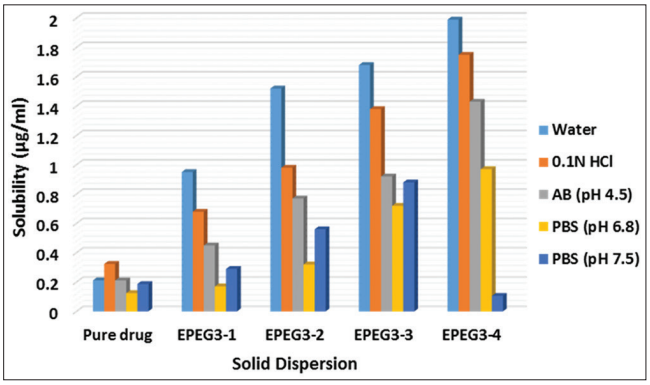

Fig. 2: Solubility of etoricoxib and solid dispersions with PEG - 3350 in various media

Table 3: ECB excipients(1:1) compatibility study physical observations

Binary mixture	Initial	Storage condition					
		Room temperature			40°C/75%RH		
		10 days	20 days	30 days	10 days	20 days	30 days
Etoricoxib	White to off-white powder	NCC	NCC	NCC	NCC	NCC	NCC
E+PEG-3350	White waxy powder	NCC	NCC	NCC	NCC	NCC	NCC
E+PEG-4000	White waxy powder	NCC	NCC	NCC	NCC	NCC	NCC
E+PEG-6000	White waxy powder	NCC	NCC	NCC	NCC	NCC	NCC
E+PEG-8000	White waxy powder	NCC	NCC	NCC	NCC	NCC	NCC
E+PEG-20000	White waxy powder	NCC	NCC	NCC	NCC	NCC	NCC
E+Lactose	Off-white powder	NCC	NCC	NCC	NCC	NCC	NCC
E+Starch	Off-white powder	NCC	NCC	NCC	NCC	NCC	NCC
E+MCC	Off-white powder	NCC	NCC	NCC	NCC	NCC	NCC
E+MS	Off-white powder	NCC	NCC	NCC	NCC	NCC	NCC
E+Talc	Off-white powder	NCC	NCC	NCC	NCC	NCC	NCC

E-Etoricoxib, PEG: Polyethylene glycol, MCC: Microcrystalline cellulose, MS: Magnesium stearate, ECB: Etoricoxib

period of 4 min and the final weight of tablets (W_{final}) was determined. The percentage friability was then measured by the following equation:

$$F = \frac{W\ initial - W\ final}{W\ initial} \times 100$$

Table 4: Hygroscopicity data(ECB)

Time interval	% weight change		
	33% RH	53% RH	75% RH
Day 1	0.00	0.0	0.0
Day 2	0.00	0.01±0.001	0.02±0.001
Day 4	0.00	0.01±0.001	0.01±0.001
Equilibrium RH			
Day 0	0.101±0.002		
Day 4	0.113±0.001	0.115±0.003	0.117±0.002
Inference	Non-hygroscopic		

All values mentioned as mean±SD, the number of trials(n=3), ECB: Etoricoxib

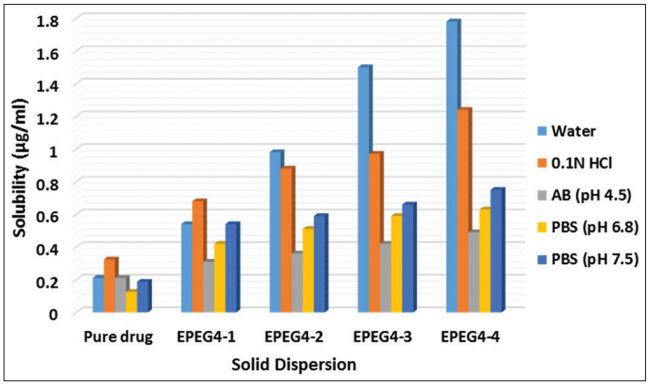

Fig. 3: Solubility of etoricoxib and solid dispersions with PEG - 4000 in various media

Table 5: Flow character specifications

Formulation	Flow properties				
	Angle of repose(^{0})	LBD	TBD	CI	HR
EPEG3-1	25.21±0.04	0.135±0.01	0.144±0.01	6.250±0.03	1.066±0.03
EPEG3-2	29.33±0.05	0.369±0.02	0.399±0.03	7.518±0.02	1.081±0.01
EPEG3-3	34.21±0.04	0.659±0.03	0.677±0.03	2.658±0.01	1.027±0.02
EPEG3-4	25.21±0.02	0.658±0.01	0.691±0.04	4.775±0.02	1.050±0.03
EPEG4-1	26.33±0.01	0.941±0.03	0.985±0.07	4.467±0.02	1.046±0.01
EPEG4-2	28.45±0.08	0.286±0.01	0.303±0.03	5.610±0.04	1.059±0.01
EPEG4-3	29.21±0.09	0.385±0.02	0.432±0.02	10.876±0.02	1.122±0.03
EPEG4-4	29.04±0.06	0.365±0.02	0.401±0.03	8.977±0.02	1.098±0.01
EPEG6-1	30.25±0.04	0.285±0.01	0.298±0.01	4.362±0.03	1.045±0.03
EPEG6-2	29.21±0.01	0.654±0.03	0.668±0.04	2.095±0.01	1.021±0.02
EPEG6-3	27.25±0.03	0.256±0.01	0.287±0.01	10.801±0.07	1.121±0.03
EPEG6-4	25.09±0.02	0.748±0.02	0.795±0.02	5.911±0.045	1.062±0.03
EPEG8-1	27.27±0.05	0.458±0.01	0.521±0.03	12.092±0.02	1.137±0.01
EPEG8-2	26.21±0.04	0.136±0.01	0.142±0.01	4.225±0.03	1.044±0.01
EPEG8-3	26.37±0.09	0.195±0.01	0.213±0.01	8.450±0.02	1.092±0.04
EPEG8-4	31.21±0.04	0.358±0.02	0.385±0.03	7.012±0.02	1.075±0.03
EPEG20-1	30.54±0.06	0.365±0.01	0.407±0.02	10.319±0.05	1.115±0.03
EPEG20-2	28.45±0.02	0.458±0.02	0.489±0.03	6.339±0.02	1.067±0.01
EPEG20-3	29.35±0.04	0.526±0.04	0.536±0.03	1.865±0.01	1.019±0.01
EPEG20-4	27.97±0.05	0.956±0.07	0.978±0.03	2.249±0.02	1.023±0.03

LBD: Loose bulk density, TBD: Tapped bulk density, CI: Carr's index, HR: Hausner's ratio, All values mentioned as mean±SD; the number of trials(n=3)

Table 6: Physical characteristics of prepared solid dispersions

Formulation	Physical parameters					
	Thickness (mm)	Hardness (cm^2)	Uniformity of weight(mg)	Friability (%)	Yield(%)	Assay(%)
EPEG3-1	4.5±0.02	4.5±0.01	253.1±0.03	0.51±0.05	97.5±0.06	98.6±2.33
EPEG3-2	4.5±0.08	5.2±0.05	254.3±0.01	0.41±0.02	98.3±0.05	99.4±0.01
EPEG3-3	4.6±0.05	7.3±0.01	250.2±0.02	0.33±0.01	99.6±0.06	98.9±0.06
EPEG3-4	4.51±0.01	5.3±0.04	251.2±0.01	0.36±0.01	99.8±0.06	97.6±5.24
EPEG4-1	4.53±0.02	4.5±0.02	255.1±0.03	0.51±0.08	92.1±0.06	96.3±0.95
EPEG4-2	4.50±0.03	5.2±0.02	250.9±0.01	0.17±0.01	95.3±0.06	99.2±2.38
EPEG4-3	4.51±0.01	6.3±0.07	252.3±0.01	0.52±0.05	94.6±0.06	100.9±6.35
EPEG4-4	4.53±0.07	5.3±0.01	253.8±0.02	0.25±0.02	96.8±0.06	97.6±0.09
EPEG6-1	4.50±0.02	4.5±0.03	250.5±0.01	0.44±0.05	97.2±0.06	98.3±0.09
EPEG6-2	4.51±0.05	5.2±0.02	250.1±0.03	0.85±0.08	97.5±0.06	99.0±0.01
EPEG6-3	4.53±0.09	6.7±0.01	254.2±0.01	0.53±0.02	96.3±0.06	102.1±0.01
EPEG6-4	4.50±0.08	8.3±0.01	252.2±0.02	0.25±0.02	96.9±0.06	99.2±0.08
EPEG8-1	4.51±0.01	4.5±0.03	250.3±0.01	0.15±0.01	97.8±0.06	96.5±0.95
EPEG8-2	4.53±0.02	5.2±0.09	252.6±0.02	0.62±0.05	98.4±0.06	97.5±0.01
EPEG8-3	4.50±0.05	7.3±0.01	251.2±0.02	0.56±0.04	98.6±0.06	99.2±2.38
EPEG8-4	4.51±0.06	5.3±0.02	250.5±0.01	0.25±0.08	97.3±0.06	98.2±0.15
EPEG20-1	4.52±0.02	4.5±0.02	250.3±0.01	0.54±0.01	98.2±0.06	100.1±0.08
EPEG20-2	4.50±0.08	5.9±0.07	251.2±0.01	0.62±0.02	97.6±0.06	97.3±0.15
EPEG20-3	4.51±0.05	6.3±0.01	250.1±0.05	0.53±0.08	94.1±0.06	98.5±0.09
EPEG20-4	4.51±0.01	5.3±0.01	252.1±0.01	0.63±0.04	97.3±0.06	97.9±0.81

All values mentioned as mean±SD; the number of trials(n=3)

Yield

The percentage recovery of formulated solid dispersion was resolute after complete removal of moisture. Thus, percentage recovery calculation involves the weight of dried solid dispersion to sum of the weight of drug and pharmaceuticals required for the formulation.

$$\% \text{ Yield} = \frac{\text{Actual weight of the solid dispersions}}{\text{Total weight of drug and excipients}} \times 100$$

Uniformity of drug content

Five tablets from each batch were taken and weighed and powdered in crushed in mortar and pestle. A weight equal to 60 mg of ECB was dissolved in 100 ml of 0.1 N HCl (pH 1.2). From this, 0.2 ml sample was withdrawn and diluted to 10 ml with 0.1 N HCl. The absorbance was determined [19] at 233 nm with double-beam UV-visible spectrophotometer (Lab India, Mumbai). Content uniformity was calculated from ECB standard graph.

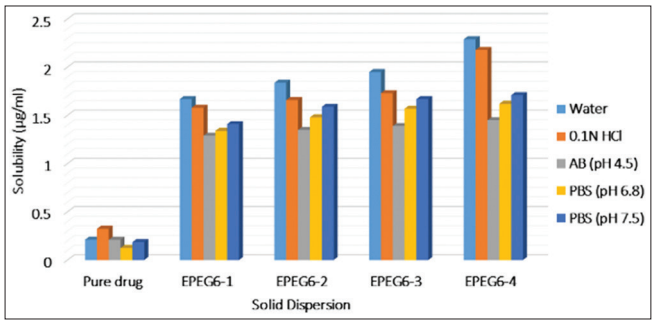

Fig. 4: Solubility of etoricoxib and solid dispersions with PEG - 6000 in various media

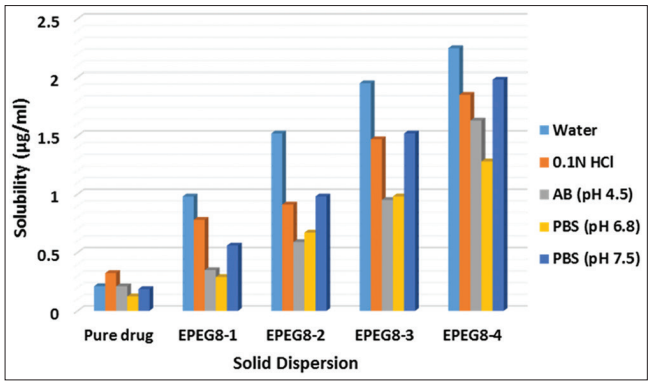

Fig. 5: Solubility of etoricoxib and solid dispersions with PEG - 8000 in various media

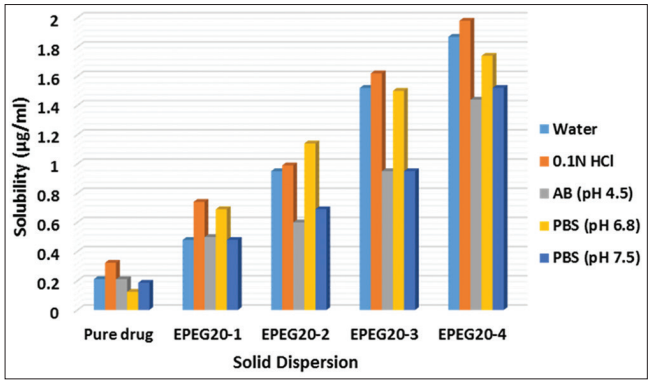

Fig. 6: Solubility of etoricoxib and solid dispersions with PEG - 20000 in various media

ECB calibration curve

The process of determining ECB by UV spectrophotometer at 233 nm was standardized and the drug was found to obey Beer–Lambert's law in 2–12 µg/ml concentration [20].

Dissolution rate/*in vitro* drug release

The dissolution specifications were as below [21].

Table 7: Concentration versus absorbance values for the estimation of ECB

Concentration(µg/ml)	Absorbance
2	0.125±0.0013
4	0.318±0.0011
6	0.473±0.0052
8	0.668±0.0013
10	0.851±0.0062

All values mentioned as mean±SD; number of trials(n=3), ECB: Etoricoxib

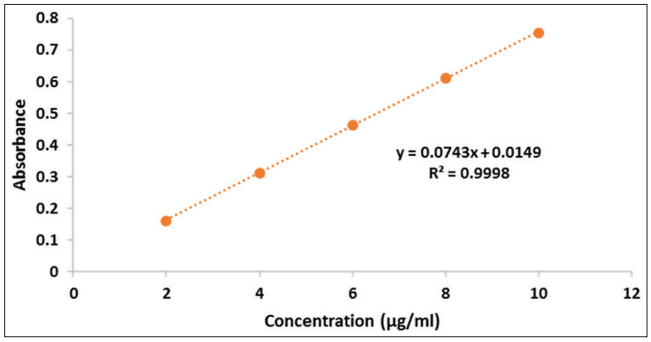

Fig. 7: Calibration curve for the estimation of etoricoxib

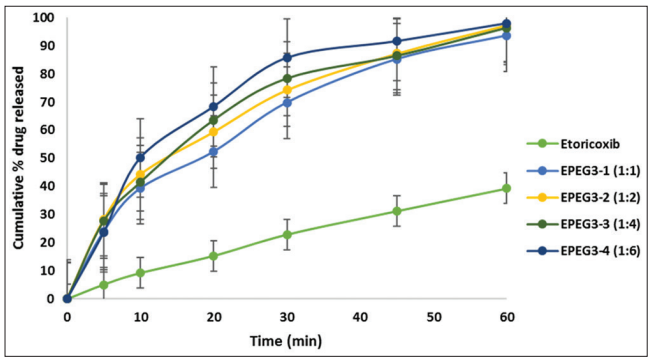

Fig. 8: *In vitro* drug dissolution plots of etoricoxib and PEG - 3350 solid dispersions

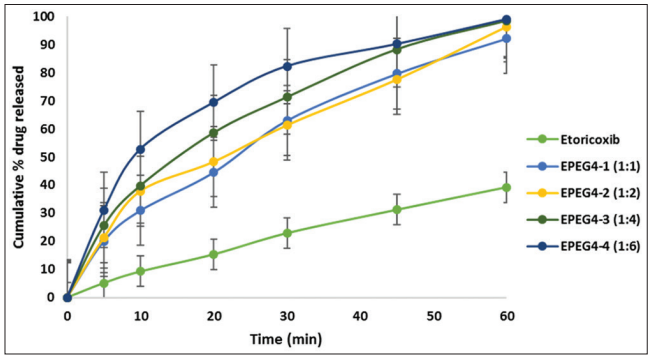

Fig. 9: *In vitro* drug dissolution plots of etoricoxib and PEG - 4000 solid dispersions

- Apparatus used: USP XXIII dissolution test apparatus (Lab India, Thane, India)
- Dissolution medium: 0.1 N HCl
- The volume of dissolution medium: 900 ml
- Temperature: 37±0.5°C
- The speed of basket paddle: 50 rpm
- Sampling intervals: 5 min
- Sample withdraws: 10 ml
- Absorbance measured: 233 nm.

Kinetic modeling of drug release

The mechanism of the drug release was analyzed and rate kinetics of the dosage form was obtained as [22,23]:

- Cumulative percentage drug released versus time (zero-order plots)
- Log cumulative percentage drug remaining versus time (first-order plots)
- Cube root of drug remaining versus time (Hixson–Crowell's plots).

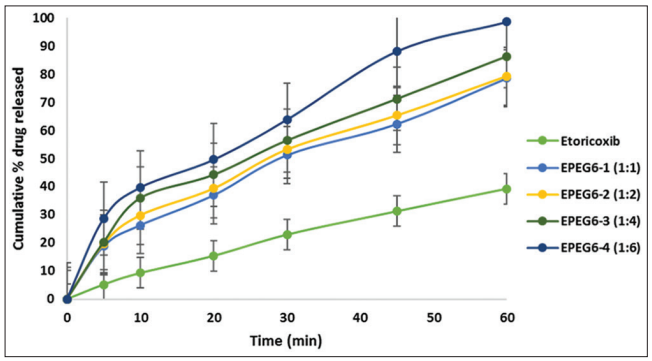

Fig. 10: *In vitro* drug dissolution plots of etoricoxib and PEG - 6000 solid dispersions

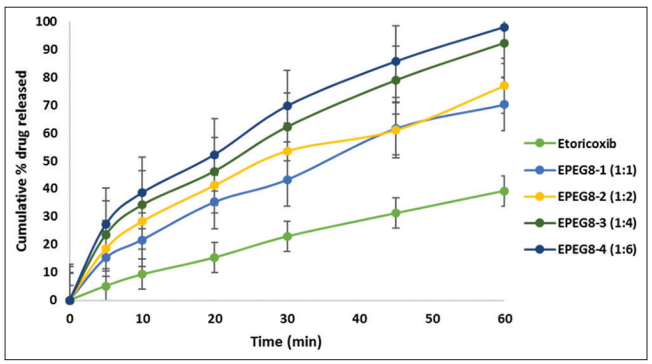

Fig. 11: *In vitro* drug dissolution plots of etoricoxib and PEG - 8000 solid dispersions

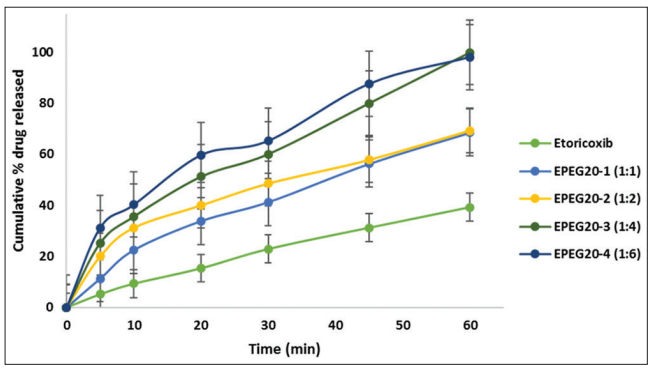

Fig. 12: *In vitro* drug dissolution plots of etoricoxib and PEG - 20000 solid dispersions

Accelerated stability studies of ECB solid dispersions

The evaluated ECB solid dispersions were then subjected to stability studies for a period of 3 months under stressed storage conditions [24].

RESULTS

The compatibility study revealed that ECB was found to compatible with the excipients used and they are tabulated in Table 3.

Physical observations of excipients compatibility study at stressed storage conditions

The hygroscopic study of ECB at room temperature (25±2°C) and humidity conditions is shown in Table 4.

The solubility of ECB pure drug in various solvents is shown in Fig. 1.

The fabricated ECB solid dispersions were characterized for flow properties and the values are shown in Table 5.

Evaluation of ECB solid dispersions (in tablet dosage form)

The fabricated ECB solid dispersions tablets were observed for physicochemical characteristics and they are tabulated in Table 6.

Solubility studies of ECB solid dispersions

The solubility of ECB and prepared ECB solid dispersions are shown in Figs. 2-6.

Calibration curve of ECB

The calibration curve of ECB is shown in Table 7 and Fig. 7.

Dissolution data of ECB from PEG solid dispersions

The dissolution of prepared tablets was found good in formulations containing ECB:PEG ratios 1:4. These are shown in Figs. 8–12.

Kinetic modeling of drug release

The drug release mechanism from prepared tablets formulations was determined by kinetic treatment of *in vitro* drug dissolution data. The

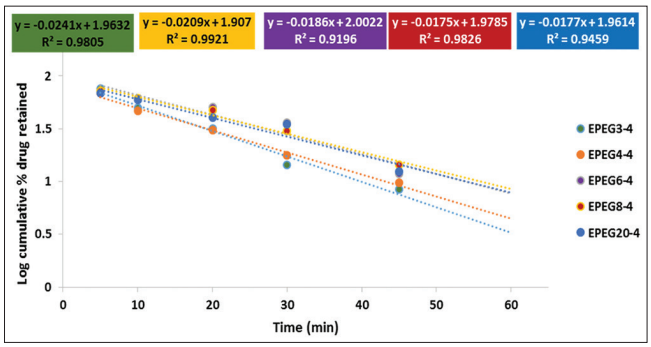

Fig. 13: First-order plots for EPEG tablets

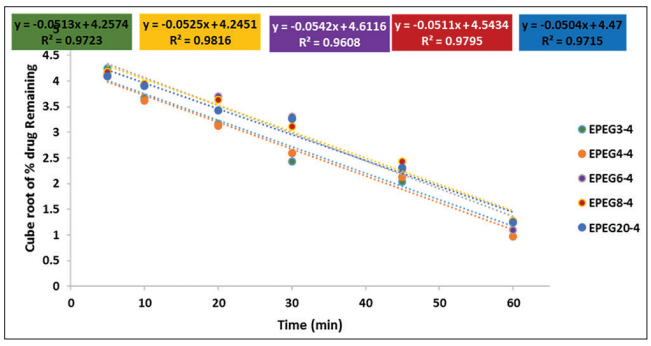

Fig. 14: Hixson–Crowell's plots for EPEG-4 tablets

correlation (r2) values from the different kinetics equations were shown in Figs. 13 and 14.

DISCUSSION

The compatibility study revealed that ECB was found to compatible with the excipients used. The hygroscopicity study of the drug used ECB indicates that drug is non-hygroscopic, as the percentage weight increase in the samples at the study was <0.2%.

ECB pure drug showed good solubility in 0.1 N HCl (0.325±0.0011 µg/ml) and water (0.212±0.0021 µg/ml). The solubility of ECB was found to be 0.212±0.0023, 0.125±0.0051, and 0.185±0.0065 µg/ml in pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and pH 7.4 phosphate buffer, respectively. The solubility data indicate that ECB has very poor solubility. The fabricated ECB solid dispersions were found to have excellent flow properties.

The fabricated ECB solid dispersion tablets were observed to have a uniform in size, shape, off-white in color, and odorless with smooth surface. The prepared tablets were found to have a uniform thickness (4.5 mm) and weight. The loss on friability was <1% and the hardness was more than 4 kg/cm^2 indicating that the prepared tablets having good mechanical strength. The percentage yield of solid dispersions was found to good (>90%) and the drug content was also found to be uniform.

The solubility of prepared tablets was found good in distilled water and 0.1 N HCl. All the ECB solid dispersion batches with PEG - 3350 showed good solubility in distilled water (up to 1.99±0.01 µg/ml) and 0.1 N HCl (up to 1.75±0.02 µg/ml). All the ECB solid dispersion batches with PEG - 4000 showed good solubility in distilled water (up to 1.78±0.01 µg/ml) and 0.1 N HCl (up to 1.24±0.01 µg/ml).

All the ECB solid dispersion batches with PEG - 6000 showed good solubility in distilled water (up to 1.21±0.01 µg/ml) and 0.1 N HCl (up to 0.81±0.01 µg/ml).

All the ECB solid dispersion batches with PEG - 80000 showed good solubility in distilled water (up to 2.25±0.09 µg/ml), in PBS (pH 7.5) (up to 1.98±0.05 µg/ml), and in 0.1 N HCl (up to 1.85±0.03 µg/ml).

All the solid dispersion batches of PEG - 20000 showed good solubility in 0.1 N HCl (up to 1.98±0.07 µg/ml) and distilled water (up to 1.87±0.01 µg/ml). The dissolution of prepared tablets was found good in all the formulations containing ECB.

The drug release mechanism from prepared tablets formulations was determined by kinetic treatment of *in vitro* drug dissolution data. The correlation (r^2) values from the different kinetics equation revealed that the drug release from the prepared solid dispersions was found to follow different models, but the best fit model was selected. First order and Hixson Crowell's plots. The optimized formulation (EPEG6-4) when subjected to accelerate stability studies, it retained its drug content, hardness, and cumulative percentage drug release.

CONCLUSION

This investigation was performed to the best PEG carrier for preparing solid dispersions by taking ECB as a model drug. The formulation EPEG6-4 in the ratios 1:6 was found to have good solubility and drug dissolution characteristics. Moreover, among the PEG - 3350, PEG - 4000, PEG - 6000, PEG - 8000, and PEG - 20000, polyethylene glycol was found to be the best PEG among the tested one as solid dispersion carrier.

AUTHORS' CONTRIBUTIONS

All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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