

Design, Optimization and Evaluation of Etoricoxib Castor Oil Emulgel for acute gout therapy

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Abstract

Etoricoxib is a non-steroidal anti-inflammatory drug which showed anti-inflammatory, analgesic and antipyretic activities. Etoricoxib is indicated in the management of Osteoarthritis, Rheumatoid and Acute gout. The major drawback of topical dosage form is dissolution and diffusion of drug in the delivery of hydrophobic drugs, and permeation through stratum corneum is for hydrophilic drugs, thus, to be referred as emulgels. In emulgel formulations, oil-in-water and water-in-oil emulsions are commonly utilised as vehicles to deliver different hydrophilic and hydrophobic medications to the skin. They're also good in dissolving drugs and penetrating skin. Oil-in-water emulsions are mostly used as medication bases that may be washed away. The proposed research project intends to create an emulgel containing the analgesic drug Etoricoxib. The created emulgel containing etoricoxib medicines has a topical route that is more permeable, regulated, and localised. The analytical procedure of etoricoxib medicine was assessed using described UV spectrophotometric techniques in pH Phosphate buffer 6.8 and exhibited good linearity of data, as demonstrated by correlation coefficients greater than 0.998. For organoleptic characteristics, flow qualities, and partitioning, preformulation experiments were employed. All result of preformulation study was satisfactory and drug was examined visually for their feeling after application on skin, color intensity, pH determination, consistency and extrudability determination. The result concluded that ETEG4 was best formulation. This formulation ETEG4 was prepared emulgel Carbopol 940 (2g), PVP, castor oil base. The drug release profile and release kinetics are two important characteristics of the dosage forms, which play an important role for describing dissolution profile of dosage form. The dissolution data was obtained and ETEG4 showed supcase II transport mechanism.

Keywords: Etoricoxib, Castor Oil, Emulgel, Osteoarthritis, Rheumatoid, Acute gout

INTRODUCTION

Acute gout is characterised by the abrupt development of severe inflammation in a tiny joint (the most frequent being the metatarso-phalangeal joint of the great toe) as a result of the precipitation of urate crystals in the joint space. The affected joint becomes red, inflamed, and highly painful, necessitating rapid medical attention¹. The midtarsal joints, ankles, knees, fingers, wrists, and elbows are all typical locations. Urate crystals can be seen all throughout the body (e.g., in the vertebrae, skin, and soft tissues), resembling different illness conditions. Treatment for acute gout should begin as soon as symptoms appear in order to promote a speedy and full cure of symptoms. In the treatment of acute gout flares, oral corticosteroids, intravenous corticosteroids, NSAIDs, and etoricoxib are all equally effective. The first-line therapy is NSAIDs². The non-invasive, non-painful, non-irritating topical delivery of formulation is an alternative technique associated with several advantages such as delivery of drug to specific site of action with reduced systemic toxicity, avoidance of first pass metabolism and gastric irritation, increasing release rate of drug from formulation to improve percutaneous absorption, and for a moment topical application related to increase bioavailability. Skin penetration through the stratum corneum is also a major problem for researchers when it comes to transdermal delivery's systemic action³⁻⁵. Topical medication

administration allows for direct access to the skin as a target organ for diagnosis and therapy without having to worry about first-pass metabolism. Topical medication administration is a localised drug delivery strategy that can be used anywhere on the body via topical channels such as ocular, vaginal, rectal, and cutaneous⁶. Emulsion-gels have gained traction in the pharmaceutical industry as topical semisolid dosage formulations. Emulgels are emulsions that are gelled by combining with a gelling agent⁷. They can be oil-in-water or water-in-oil. Transparent gels have been widely used in cosmetics and medicinal preparations⁸. They belong to the principal group of semisolid preparations. Gels are semisolid systems comprising either suspensions of minute inorganic particles or large organic molecules interpenetrated by a liquid, according to the USP⁹. Small drug particles are captured and released in a controlled manner by a gel that forms a cross-linked network. Its mucoadhesive feature extends the time that drug is in touch with the skin¹⁰. Emulgel is being utilised to successfully include a hydrophobic therapeutic moiety and develop the unique properties of gels¹¹. Emulgel has the properties of both an emulsion and a gel, and it works using a dual control release method. Due to the inclusion of both aqueous and non-aqueous phases, Emulgel claims to be capable of delivering both hydrophilic and lipophilic drug moieties. It is suitable for application to the skin since it is non-greasy, as opposed to other topical

formulations such as ointments, creams, and lotions, which are thick and need excessive rubbing. It is put into gel to increase emulsion stability and penetration capabilities¹². Emulgels are used in dermatology because they are thixotropic, greaseless, readily spreadable, easily removable, emollient, nonstaining, water-soluble, have a longer shelf life, are bio-friendly, and have a clear and pleasing look¹³. Etoricoxib is a non-steroidal anti-inflammatory medication with anti-inflammatory, anti-analgesic, and antipyretic properties. Another therapy option for acute gout is etoricoxib. The US Food and Drug Administration (FDA) did not examine generic etoricoxib for this use until 2009, when branded etoricoxib was authorised. Nausea, vomiting, and diarrhoea are all common side effects. In individuals with hepatic or renal impairment, etoricoxib should be administered with care. The goal of this study is to create an emulgel containing Etoricoxib, an analgesic drug. However, it has been linked to a variety of gastrointestinal problems. The drug's possible negative effects may be mitigated by using it topically. When compared to the COX-2 inhibitors rofecoxib, valdecoxib, and celecoxib, etoricoxib has a higher selectivity for COX-2 over COX-1 in vitro. Etoricoxib binds to COX-2 in a reversible, noncovalent way with a 1:1 stoichiometry. Oral etoricoxib is fast and fully absorbed in healthy individuals. It has up to 100 percent absolute bioavailability and achieves C_{max} after around 1 hour. Etoricoxib is used to treat osteoarthritis and rheumatoid arthritis. The main disadvantage of topical dosage forms is drug disintegration and diffusion in the administration of hydrophobic medications, and drug penetration through the stratum corneum in the delivery of hydrophilic pharmaceuticals. As a result, they're referred to as In emulgel formulation, oil-in-water and water-in-oil emulsions are widely employed as vehicles to deliver different hydrophilic and hydrophobic medications to the skin. They're also good in dissolving drugs and penetrating skin. Oil-in-water emulsions are mostly used as medication bases that may be washed away. The goal of this study is to create an emulgel containing Etoricoxib, an analgesic drug.

MATERIAL AND METHODS

Table 1: A various composition of different emulgel formulations

Ingredient	ETEG1	ETEG 2	ETEG 3	ETEG 4
Etoricoxib (mg)	100	100	100	100
Carbopol 934 (g)	0.5	1	1.5	2
Castor oil (ml)	7.5	7.5	7.5	7.5
Tween 20 (ml)	0.5	0.5	0.5	0.5
Span 20 (ml)	1	1	1	1
Polyvinyl pyrrolidone (mg)	50	50	50	50
Ethanol (ml)	2.5	2.5	2.5	2.5
Water (ml)	q.s	q.s	q.s	q.s

Characterization of emulgel: The preparing systems was evaluated with various parameters such as Organoleptic Evaluation, physical Evaluation of gel, determination of pH, spread ability, tube Extrude ability, viscosity, in Vitro Diffusion Studies, skin irritation study, drug release kinetic data analysis: The release data was fitted to following mathematical models.

Visual inspection: The colour, appearance, and consistency of

Drug identifications: The drug samples (etoricoxib) will be studied for determination of absorption maxima (λ_{max}) in phosphate buffer pH 7.4. The analytical method was validated in terms of preparation of calibration curve etc. of 10 $\mu\text{g/ml}$, 20 $\mu\text{g/ml}$, 40 $\mu\text{g/ml}$, 65 $\mu\text{g/ml}$ and 80 $\mu\text{g/ml}$ respectively. The absorbance of each solution was measured separately at 257 nm in phosphate buffer pH 6.8 respectively for etoricoxib. The absorbance was measured and standard curve was plotted between absorbance vs. concentration.

Preformulation studies: Preformulation studies may carried out to standardize a spectrophotometric method of estimation for ETB and to investigate any possible drug polymer interaction. Melting point determination, Determination of distribution coefficient, Drug polymer interaction was studied by carrying out Fourier Transform Infrared (FTIR) spectral studies etc.

Preparation of emulgel: Emulgel made using the high-speed homogenization process with various medication combinations. By high-speed homogenization, the formulation was made with oil as a carrier, Edetate disodium, glycerin, and polysorbate 80 in filtered water. Various amounts of gelling agent and penetration enhancers were used to create the various formulations. In all of the formulations, the emulsion was prepared in the same way. The gel phase in the formulations was made by dispersing Carbopol 940 in distilled water with a mechanical shaker at a moderate speed, then adjusting the pH to 6–6.5. The emulsion's oil phase was made by dissolving span 20 in castor oil. Tween 20 was dissolved in distilled water to make the aqueous phase, and the needed weighed quantity of medication was dissolved in ethanol. Now that everything was ready, the aqueous phase and both solutions were mixed together. Both the oily and aqueous phases were heated to 70–80°C separately before the oily phase was introduced to the aqueous phase and stirred continuously until it reached room temperature. To make the emulgel, the resulting emulsion was combined with the gel basis in a 1:1 ratio with moderate stirring. Table 1 shows the chemical makeup of several formulations.

the created emulgel compositions were examined visually. The Feeling following application on skin, colour intensity, pH determination, consistency, and extrudability of the created emulgel compositions were all visually evaluated. Before the gels were poured into containers, they were visually inspected for uniformity. They were also examined for the appearance of aggregates and the existence of any.

Globule size and polydispersity index (PDI): The GS and

PDI of the emulsions were evaluated using the mean droplet size method, and the polydispersity index of the emulsions was assessed using the Dynamic Light Scattering (DLS) approach. The globule size and polydispersity index of the emulgel were measured.

Viscosity determination: A cone and plate viscometer with spindle 7 and Brook field viscometer was used to determine the viscosity of the prepared batches. The system was connected to a thermostatically controlled circulating water bath that was kept at a constant temperature of 25°C. Separately, a suitable amount of gel base was placed in a wide mouth jar, which should be adequate for dipping the spindle. The spindle was permitted to freely travel inside the emulgel, and the reading was taken while the spindle's RPM was set at 2.5 RPM. The formulas' viscosities were measured.

Spreadability: Spreadability was measured using an extensometer-like instrument that was developed in the lab and used for the research. This device is constructed out of a wooden block with a pulley attached to one end. The spreadability features of nanoemulsion gels were assessed using the 'slip' and 'drag' approach used in this spreadability technique. A ground glass slide is attached to the wooden block with a hook, while an upper glass slide with the same proportions as the fixed ground slide is attached to the ground slide with a hook. To generate a homogenous film, 2 g of emulgel was put between the glass slides and a weight of 1 kg was applied to the upper slide for 5 minutes. Excess of the formulation was scrapped off from the edges. The top plate was then subjected to a fixed weight of 100 g with the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7 cm was noted. A shorter interval indicates better spreadability. Spreading coefficient is determined by using the formula:

$$S + m * l / t$$

where, S = Spreadability, m = Weight tied to upper slide, l = Length of glass slides, t = Time taken to separate the slides completely from each other.

Drug content determination: One gram each of emulgel was taken and dissolved in methanol and sonicated for 1 h respectively. The resulting solutions were filtered with 0.45 µm filter to obtain clear solutions. The drug content was analyzed using a UV spectrophotometer method at 350 nm.

In-vitro permeation studies: Extracted hog ear skin was used to conduct in-vitro permeation tests on the produced gels. The pig ears were taken in phosphate buffered saline from a local slaughterhouse. The skin was sliced into little pieces after the hair was shaved off with a scapel, the subcutaneous/underlying tissue was scraped off, and the skin was cut into small pieces. The study eliminated skin with abnormalities or tears. Skin samples were kept at -20°C until they were needed. Permeation experiments of the formulations (emulgel) and M.C. were conducted using Franz diffusion cells (diffusion area of 3.8 cm²). Because of its physical closeness to human skin, pork ear skin was chosen as the tissue of choice for permeation testing. 75 mL of phosphate buffer (pH 6.8) was added to the receptor chamber and stirred constantly at 100 rpm with a magnetic stirrer. The stratum corneum was positioned towards the donor compartment and the pork skin was attached between the donor and receptor compartments of the cell and allowed to equilibrate for 30 minutes. The buffer medium was kept at a constant temperature of 37.50°C. On the surface of the pig skin, a 100mg formulation comprising emulgel was applied. At regular intervals of 0, 2, 4, 6, 8, and up to 24 hours, 1 ml of sample was taken from each cell and replaced with an equal volume of buffer medium. UV spectrophotometric tests at 350

nm were used to assess the quantity of etoricoxib in permeation samples. The proportion of medication retained on the skin was evaluated by washing the skin three to four times with methanol at the end of permeation trials. The solution was filtered through a 0.45 micron filter before being subjected to a UV spectrophotometric analysis to determine the drug concentration. The skin was sliced into small pieces and homogenised in methanol to determine the amount of medication retained in the skin. The resulting dispersion was sonicated for 10 minutes before being vortexed for another 15 minutes. The samples were centrifuged for 15 minutes at 6,000 rpm, then filtered through a 0.45 micron filter and tested for drug content.

RESULT AND DISCUSSION

UV spectrophotometric techniques were used to determine the analytical process of the medication etoricoxib. According to the available laboratory circumstances, the stated UV spectrophotometric procedures were slightly adjusted and optimised. In the dissolving medium, the medicines were estimated (pH Phosphate buffer 6.8). The calibration curves in the dissolving medium, phosphate buffer pH 6.8, were generated with known amounts of medication solutions. For phosphate buffer pH 6.8, the absorbance of each solution was measured independently at 234 nm. The absorbance was measured, and a standard curve between absorbance and concentration was drawn. The calibration curves provide good linearity of data, as shown by correlation coefficient values better than 0.998. (Table 1 and Figure 1).

Preformulation studies used for the development of dosage forms of model drug substances. Etoricoxib was found to be light yellow, odorless, bitter taste in nature. Microscopic examination of drug was crystalline in nature. A bulk and tapped density of etoricoxib is to be 0.412 gm / cm³ to 0.426 gm / cm³, respectively. The particle size of unmilled etoricoxib powder was 113 µm. The milled drug powder exhibited showed excellent flow properties. The solubility of drug was very less soluble in all dissolution media and the result is shown in Table 2. The characteristic peaks of Drug and its blend with all excipients were summarized in Figure 2 - 3. The partition coefficient of etoricoxib was found to be (3.7) and **Hydrophobic or Lipophilic** in nature.

The prepared emulgel formulations were examined visually for their feeling after application on skin, color intensity, pH determination, consistency and extrudability determination. The emulgels were tested for homogeneity by visual inspection prior to the gels being filled into containers. The Formulation ETEG4 was best formulations among all the prepared formulations. The consistency of ETEG4 was excellent and the result is shown in Table 3. The globule size and polydispersity index (pdi) (Figure 4 - 7), viscosity, spreadability and drug content of prepared formulations also examined. All the result is shown in Table 4 and the result concluded that **ETEG4** was best formulation. This formulation ETEG4 was prepared emulgel Carbopol 940 (2g), PVP, castor oil base. The drug release profile and release kinetics are two important characteristics of the dosage forms, which play an important role for describing dissolution profile of dosage form. The dissolution data was obtained after in-vitro release performance, fitted to mathematical different models. The result of release data were shown in Figure 8 - 11. The release data were computed in graph and release kinetic values were optimized. The formulations ETEG1 to ETEG4 showed the values of n > 0.5, followed Fickian diffusion and supercase II transport mechanism. The value of **t50%** of ETEG4 is more than 17 h. it will shown better controlled release mechanism of prepared drug delivery system.

Table 1: Standard curve of etoricoxib in phosphate buffer pH 6.8 solution

S. No.	Concentration (ng/ ml)	Absorbance (234 nm)
1	0	0
2	5	0.322
3	10	0.652
4	15	0.969
5	20	1.234
6	25	1.598
r ²	0.998	
Slope	0.063	
Intercept	0.007	

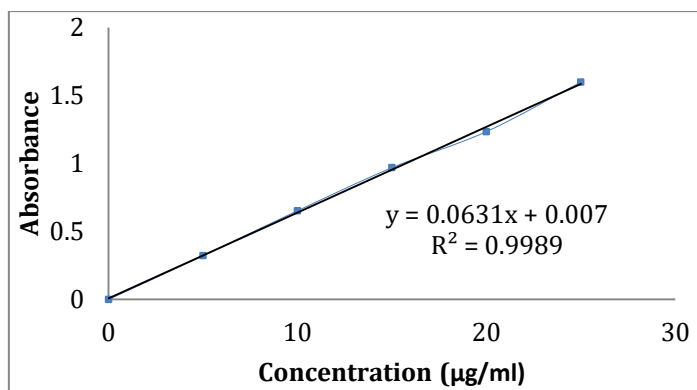


Figure 1: Standard curve of etoricoxib in phosphate buffer pH 6.8 solution

Table 2: The solubility of etoricoxib at different pH medium (n=3)

Media	Solubility (mg / ml)	Mean	% RSD	Standard error of Mean	Lower 95 % C I	P Value
Water	0.00093	0.00097	0.000021	0.00001	0.0117	< 0.0001
0.1 N HCl	0.00156	0.00165	0.000037	0.00004	0.0144	< 0.0001
Phosphate buffer pH 4.5	0.00091	0.0096	0.000025	0.00001	0.0101	> 0.01
Phosphate buffer pH 6.8	0.00101	0.00102	0.000188	0.00005	0.011	> 0.01
Phosphate buffer pH 7.4	0.00094	0.00093	0.000104	0.00077	0.0270	< 0.0001

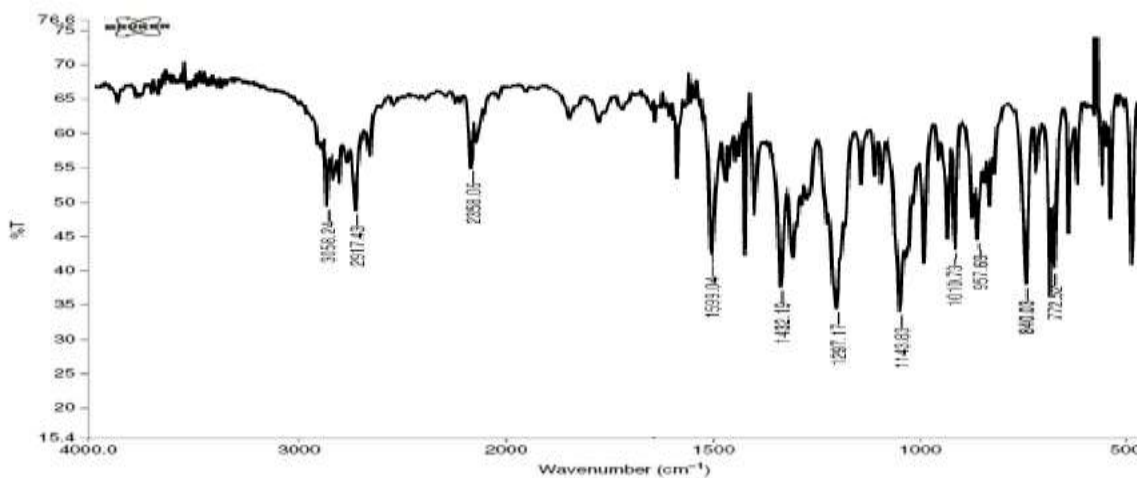


Figure 2: The I. R. Spectrum of sample of pure etoricoxib (S1)

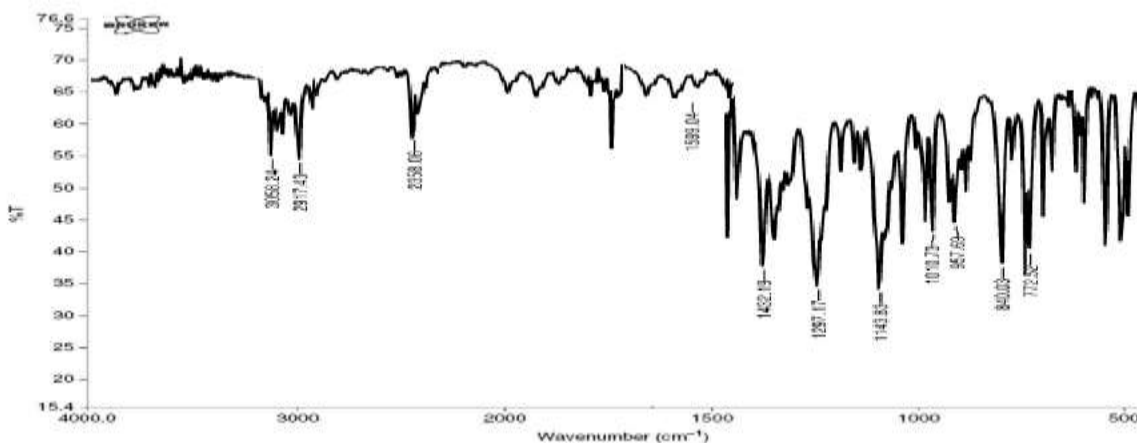


Figure 3: The I. R. Spectrum of sample of etoricoxib and all excipients (S2)

Table 3: Physical characterization of emulgel

Parameters	Formulations			
	ETEG1	ETEG2	ETEG3	ETEG4
Feel of application Skin	Smooth	Smooth	Smooth	Smooth
Consistency	Poor	Good	Good	Excellent uniform
Extrudibility	Good	Good	Excellent	Excellent
Globule (Particle) size nm	147.18	132.21	129.01	123.03
Polydispersity index (PDI)	0.248	0.241	0.236	0.225
Viscosity (cps)	1534	1423	1379	1335
pH	6.14	7.94	7.14	7.04
Spreadability (g.cm/sec)	8.9	11.01	11.67	13.01
Drug Content (%)	97.34	97.12	98.1	99.4

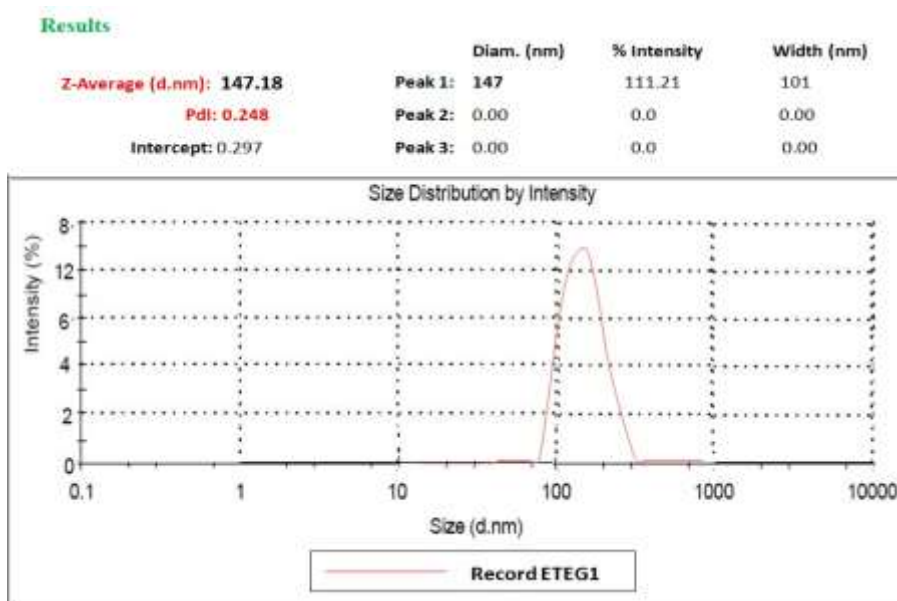


Fig. 4: Determination of Globule (Particle) size and Polydispersity index (PDI) of formulations (ETEG1)

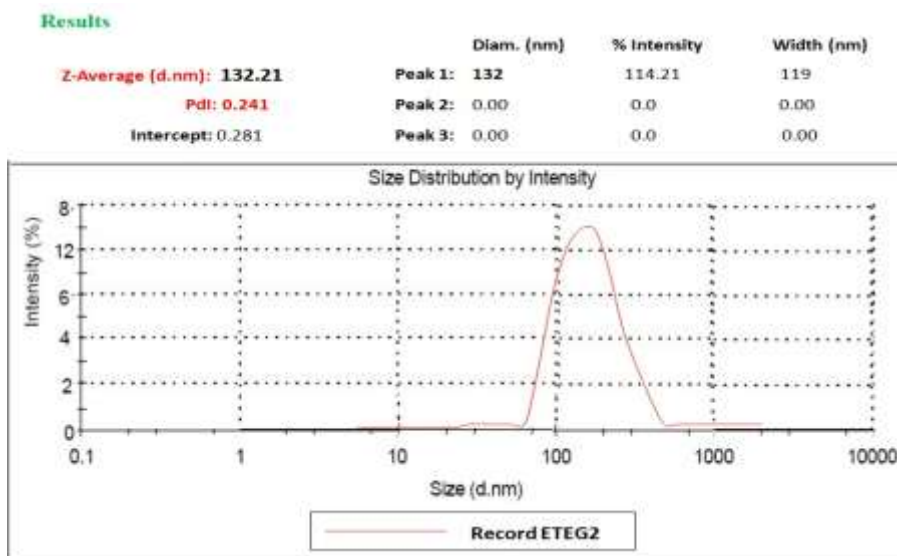


Fig. 5: Determination of Globule (Particle) size and Polydispersity index (PDI) of formulations (ETEG2)

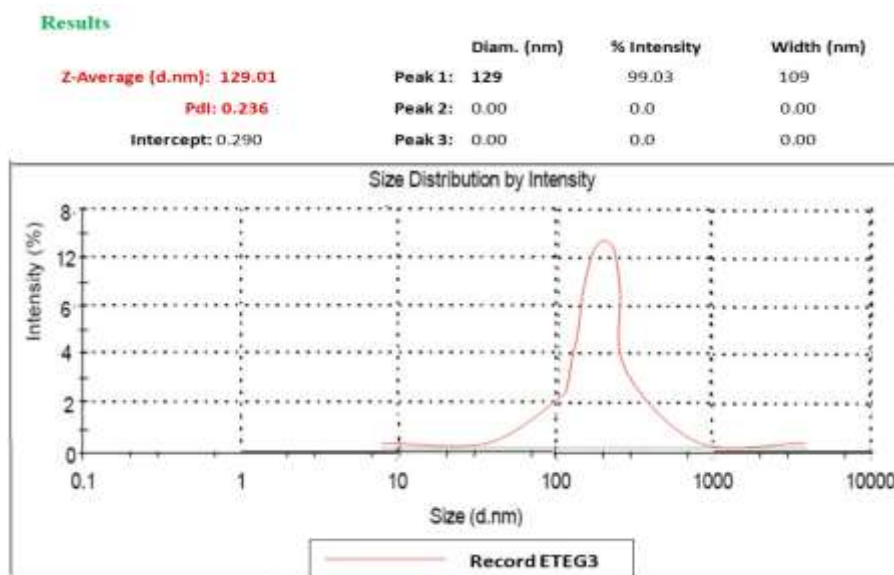


Figure 6: Determination of Globule (Particle) size and Polydispersity index (PDI) of formulations (ETEG3)

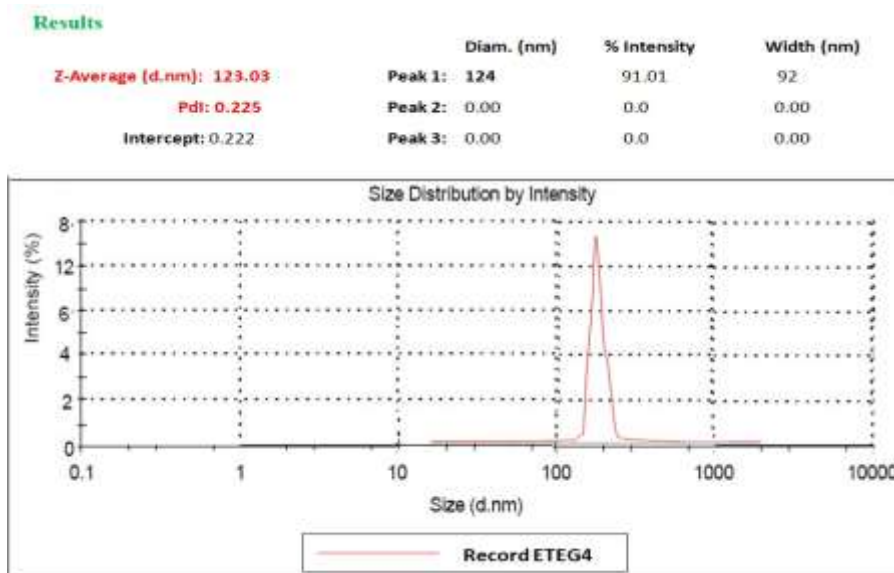


Figure 7: Determination of Globule (Particle) size and Polydispersity index (PDI) of formulations (ETEG4)

Table 4: Dissolution data of emulgel delivery system (ETEG1 to ETEG4)

Time	ETEG1	ETEG2	ETEG3	ETEG4
0	0	0	0	0
2	0.645	0.411	0.321	0.211
4	1.843	1.234	0.876	0.92
6	4.01	2.6	1.54	1.56
8	8.34	8.89	5.32	5.34
10	18.11	15.34	14.23	11.98
12	37.23	32.12	28.43	20.21
14	53.67	47.23	41.41	32.67
16	70.76	61.23	54.31	45.32
18	81.98	84.21	69.31	60.34
20	91.21	91.23	87.21	76.21
22	97.24	98.98	98.23	89.25
24	99.88	99.89	99.68	99.13

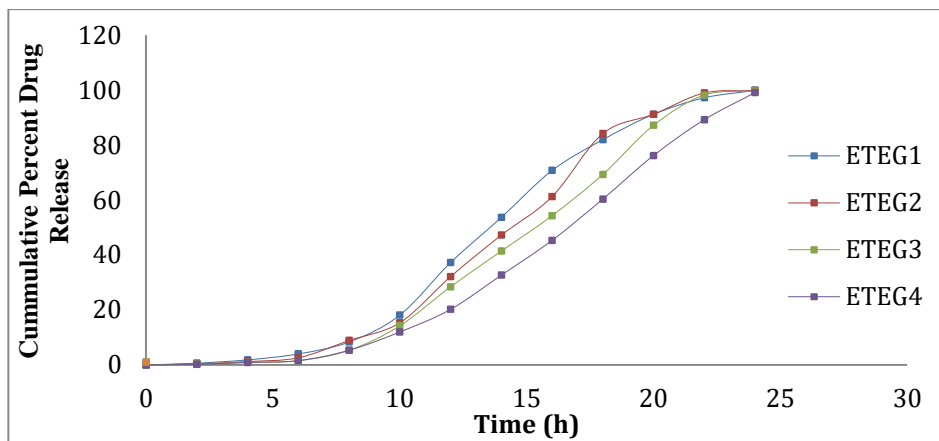


Figure 8: Zero-order plots for emulgel delivery system (ETEG1 to ETEG4)

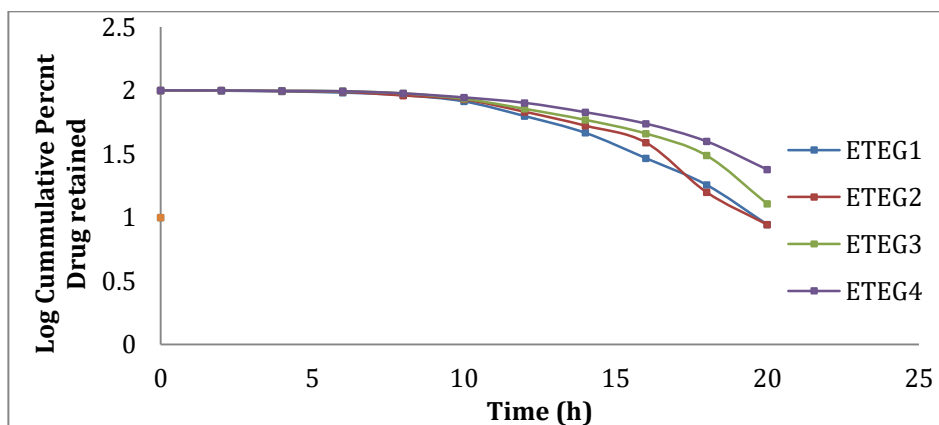


Figure 9: First-order plots for emulgel delivery system (ETEG1 to ETEG4)

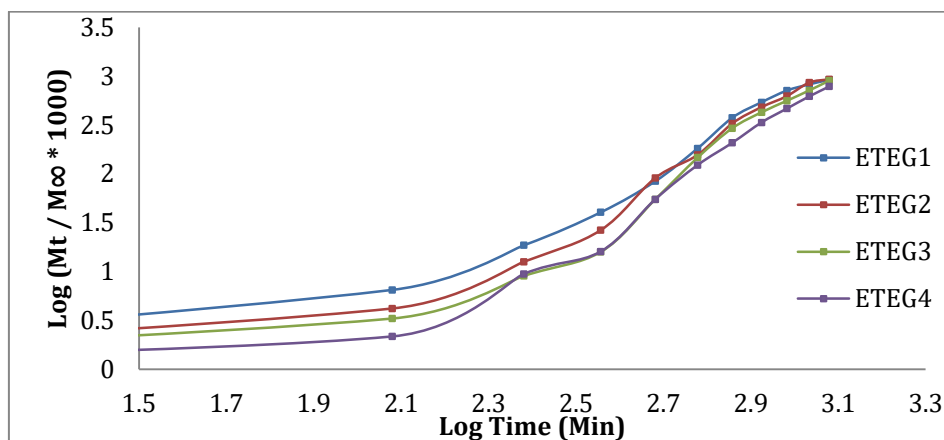


Figure 10: Korsmeyer's-Peppas plot for emulgel delivery system (ETEG1 to ETEG4)

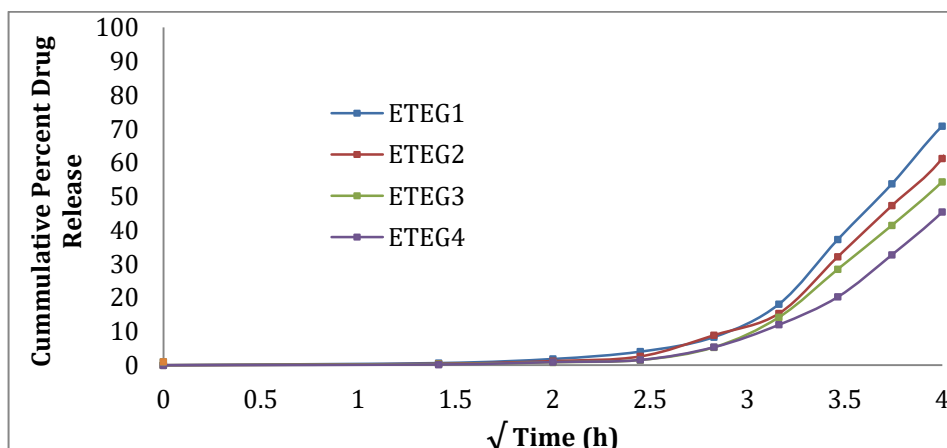


Figure 11: Higuchi kinetic plot for emulgel delivery system (ETEG1 to ETEG4)

SUMMARY AND CONCLUSION

Oral route is the majority ideal route close to patient execution; though, oral administration is additional prone to hepatic first pass metabolism required higher dose of drug. Topical drug administration is a localized drug delivery system everywhere in the body during ophthalmic, vaginal, rectal and skin as topical routes. Skin is one of the most readily available organs on human body for topical management and is the major route of topical drug delivery system. Emulsion as a dispersed system, which consists of small droplets and well distributed in to immiscible vehicle. Emulgel ensures tolerable localization and dispersion of the drug by passable percutaneous absorption within the skin to enhance its local efficacy and/or through the skin to the circulation to polish its systemic effect. The present investigation was to develop emulgel of etoricoxib drug with better-permeable, controlled and localized delivery via topical route. The estimation procedures for drugs were found to be sensitive, precise and reproducible. The prepared emulgel formulations were examine visually for their feeling after application on skin, color intensity, pH determination, consistency and extrudability determination. The result concluded that **ETEG4** was best formulation. This formulation ETEG4 was prepared emulgel Carbopol 940 (2g), PVP, castor oil base. The drug release profile and release kinetics are two important characteristics of the dosage forms, which play an important role for describing dissolution profile of dosage form. The dissolution data was obtained after in-vitro release performance, fitted to mathematical different models. The formulations ETEG1 to ETEG4 showed the values of $n > 0.5$, followed Fickinan diffusion and supercase II transport mechanism. The value of $t_{50\%}$ of ETEG4 is more than 15 h. it will shown better controlled release mechanism of prepared drug delivery system.

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