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Formulation and Evaluation of Etoricoxcib Emulgel for Topical Delivery

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Abstract

Emulgel is the topical drug dosage form in which emulsions are gelled by mixing with gelling agents. Incorparation of emulsion into gel increase the stability of emulsion and provides the controlled release system . Emulgel is the promising drug delivery system for delivering of hydrophobic drugs. Emulgel has several favourable properties for dematological use such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non staining, long shelf life, and pleasant appearance. They have the dual drug releasing system ie., gel and emulsion. The aim of present study is to develop an emulgel formulation using Etoricoxcib an NSAID`S ,which effective in treatment of Osteoarthiritis, Rheumatoid Arthiritis , Acute Gouty Arthiritis, Ankylosing Spondylitis, etc.. geling agents like carbopol, HPMC with emulsifying agents span80 and tween80 and penetration enhancers like clove oil, olive oil, almond oil . Different formulations are developed and evaluated for the physical appearance, Ph, spreadability , phase separation, in-vitro drug release and skin irritation test.

Key words: Emulgel, Carbopol , clove oil , almond oil, span80, Etoricoxcib

INTRODUCTION

Topical drug delivery is an attractive route for local and systemic treatment. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment [1-3]. Topical drug delivery system has several advantages such as ability to deliver drug more selectively to a specific site, avoidance of gastro intestinal incompatibility and metabolic degradation associated with oral administration more over topical deliveries provide increased bio-availability by avoiding first pass metabolism by liver and consistent delivery for extended period[4-5]. 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. Therefore, to are referred as emulgels. Both oil-in-water and water-in-oil emulsions are extensively used as vehicles to deliver various hydrophilic as well as hydrophobic drugs to the skin in emulgel formulation. They also have a high ability to dissolve drug and to penetrate skin. Oil-in-water emulsions are mostly useful as water washable drug bases. The present research work aims at preparing emulgel containing Etoricoxib an analgesic agent. Etoricoxibis a Non-Steroidal Anti-inflammatory drug that exhibits anti-inflammatory, analgestic and antipyretic activities [6]. It is potent, highly selective which is described chemically as 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2, 3'-bipyridine. However its use has been associated with a number of gastrointestinal disorders. These potential side effects may be overcome by the topical administration of the drug [7]. In vitro, etoricoxib exhibits a greater selectivity for COX-2 over COX-1 compared with the COX-2 inhinitors rofecoxib, valdecoxib and celecoxib. Etoricoxib binds competitively to COX-2 with 1;1 stoichionetry in a reversible, noncovalent manner [8]. In healthy volunteers, oral etoricoxib is rapidly and completely absorbed. It reaches Cmax after approximately 1 hour and has up to 100% absolute bioavailability [9]. Etoricxib is indicates in the management of Osteoarthritis, Rheumatoid Arthritis, Ankylosing Spondylitis, Post operative pain, Chronic low-back ache and Gout.

MATERIALS AND METHOD:

Etoricoxib ,HPMC K4M, Carbopol 940 , carbopol 934, were produced from Horizon Chemical Ltd.

Span 80, twee80, propylene glycol methyl paraben, clove oil , almond oil, olive oil, were producrd from S.D. Fine Chem Ltd, Mumbai, India.

FORMULATION DEVELOPMENT

The gel in formulation were prepared by dispersing polymer in purified water with constant stirring at a moderate speed then the Ph are adjusted to 6 to 6.5 using Tri Ethanol Amine (TEA). The oi phase of the emulsion were prepared by dissolving span 80 in liquid paraffin and aqueous phase was prepared by dissolving Tween 80 in purified water. Methyl paraben was dissolvedin propylene glycol whereas drug (Etoricoxcib) was dissolved in ethanol and both solutions were mixed in aqueous phase. Clove oil, almond oil, olive oil, was added to oil phase which acts as penetration enhancers. Both oil phase and aqueous phase were separately heated to 40° to 50°C then oily phase were added to aqueous phase with constant stirring until cooled to room temperature. And mixing of gel and emulgel in ratio 1:1 to obtain emulgel .

Characterization of emulgel

1. Physical appearance:

The prepared emulgel formulations are inspected for their color, homogeneity, consistency and phase separation.(10)

2. pH:

The pH values of 1% aqueous solutions of the prepared emulgels were measured by a calibrated Ph meter.

3. Spreadability :

The Spreadability of the emulgel formulations was determined 48hrs after preparation, by measuring the spreading diameter of 0.5g of emulgel which was palced

within a circle of 1cm diameter pre-marked on a galss plate over which a second galss palte (75gm) was placed. A weight of 425g was allowed to rest on the upper glass plate for5min where no more spreading was expected (11, 12). The increase in the dimeter due to spreading of the gel was noted. The speadability (g.cm.min-1)was calculated by using the formula: S=M×L/T

Where :

S is spreading ,

M is the weight of the upper plate and rested on it (g).

I is the diameter of the spreading emulgel (cm), and

t is the time taken (min) (13-15).

4. Extrudability study:

It is calculated bby the force required to extrude the emulgel from the tube. In this study emulgel extruded from lacquered aluminium collapsible tube on applications of weight in grams required to extrude at 0.5cm ribbon of emulgel in 10sec. for better extrudabitity, more quantity is extruded. For the measurement of extrudability, it is done in triplicate and the average values are calculated. The extradability is then calculated by using the following formula:Extrudability = weight applied to extrude emulgel from tube (in gm)/ Area(in cm2)

5. Drug content determination:

Take 1gm of emulgel. Mix it in suitable solvent. Filter it to obtain clear solution. Determine its absorption using UV spectrophotometer. Standard plot of drug is prepared in same solvent. Concentration and drug content can be determined by using the same standard plot by utilizing the values of absorbance.

6. Centrifugation :

This is the parameter could be measured to evaluate physical stability. Emulgel could be centrifuged at an ambident temperature and 6000RPM for 10 mi to evaluate the system for creaming or phase separation. System could be observed visually for appearance.(16)

7. In-vitro permeation study:

In-vitro release study is carried out using a modified Franz diffusion cell. 1g of the formulation was weighed and placed on the dialysis membrane having the surface area of 2.5cm2, which is placed between donor and receptor compartment of the diffusion cell. Phosphate buffer 7.4 was prepared and used as the diffusion media. The temperature of cell was maintained at 37 degree c. this whole setup was stirred using the Teflon coated magnetic stirrer at 50rpm. At specified time intervals 5ml of the sample solution was taken for analysis. Spectrophotometrically at 275nm. The cumulative % drug release was determined (17)

8. Skin irritation study:

The percentage is applied on the property shaven skin of wister rats and its adverse effects like change in color, change in skin morphology should be checked up to 72 hours. If no irritation is occurred test is passed. If the skin irritation symptom occurs in more than 2 rats the study should be repeated(18).

9. Stability studies:

The stability study (10) were conducted according to ICH guidelines by storing the TD systems at 40± 2°C/75% RH in the stability chamber for three months.

10. Fourier transforms infrared radiation (FTIR):

Fourier transforms infrared radiation (FTIR) spectra and a mixture of Etoricoxib and the selected excipients were performed in conditions 40°C±2/75%±5RH for one month storage.

11. Differential scanning calorimetry (DSC) study

The drug and all excipients were analyzed by using differential scanning calorimeter as maintaing a constant scanning speed. The DSC Thermograms were obtained at temperature range of 30-250°C & scanned rate of 10° C/min.

Table 1: Formulation of Etoricoxcib Emulgel

Ingridients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Carbopol 934	1%	-	-	-	1%	-	-	-	1%	-	-	-
Carbopol 940	-	1%	-	-	-	1%	-	-	-	1%	-	-
Carbopol 934+HPMC	-	-	2%	-	-	-	2%	-	-	-	2%	-
Carbopol 940+HPMC	-	-	-	2%	-	-	-	2%	-	-	-	2%
Span 80	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Liquid paraffin	7.5%	7.5%	7.5%	7.5%	7.5%	7.5%	7.5%	7.5%	7.5%	7.5%	7.5%	7.5%
Tween 80	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Propylene glycol	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Methyl paraben	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%
Ethanol	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Clove oil	8%	8%	8%	8%	-	-	-	-	-	-	-	-
Almond oil	-	-	-	-	8%	8%	8%	8%	-	-	-	-
Olive oil	-	-	-	-	-	-	-	-	8%	8%	8%	8%
water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

CHARACTERIZATION OF EMULGEL

1. Physical appearance:

The formulated emulgels were examined for their color, homogeneity, consistency and phase separation after 24 hr of preparation. They were white, homogenous, transparent to white to white opaque and from viscous gel preparations with a smooth homogeneous appearance and there was no significant phase separation observed in the formulations.

2. Measurement of pH:

The pH of the emulgel formulations was in the range of 6.07 to 6.33, which lies in the normal pH range of the skin and would not produce any skin irritation.

3. Spreadability:

One of the essential criteria for an emulgel is that it should possess good spreadability. Spreadability is an important factor in therapy and it is shown as index of ease of application. The delivery of the correct dose of the drug depends highly on the spreadability of the Etorioxcib emulgel formulation following the spreadability test was found to range from 98g.cm/min to 128 g.cm/min for the formulations F1-F12. The values were given in table 2. The F8 has the better speradability.

4. Extrudability study:

The extradability is calculated by using the following formula:

Extrudability = weight applied to extrude emulgel from tube (in gm)/ Area(in cm2). The extrdability of the formulations was ranging from 185-199. The formulation F8 has shoen the greater extrudability of 199g/cm^2. The values were given in table 2.

5. Drug content determination:

The drug content of the formulations were determined by using standard plot and the values were given in table 2 and the values ranged from 91.22-98.25

6. Centrifugation:

The prepared emulgels were subjected to centrifugation test to determine the physical stability and there was no phase separation or creaming observed during this test which indicated that the formulations were stable.

7. Skin irritation study:

Skin irritation test as performed on the male wistar rats for all the developed formulations and there was no redness or swelling observed during the 24 hr test period.

8. Stability studies:

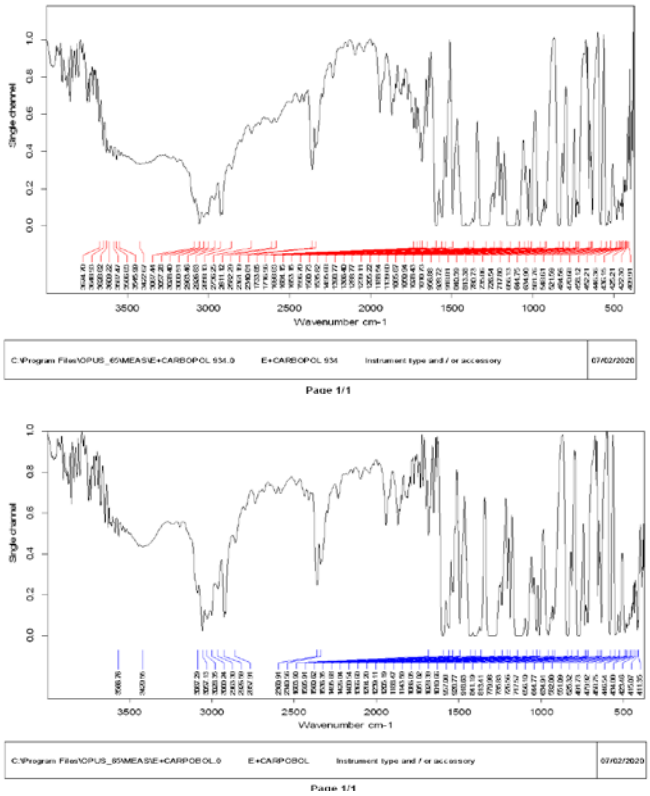
These formulations were stored at 40±2°C/75% RH in stability chamber for three months. After three months. Results did not show any significant variations ($p>0.05$). These results indicate that drug remain stable after stability studies.

9. Fourier transforms infrared radiation (FTIR):

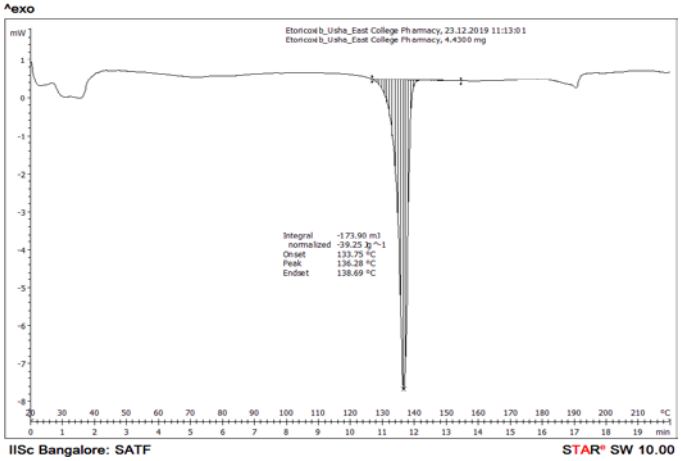
Fourier transforms infrared radiation (FTIR) spectra and a mixture of Etoricoxib and the selected excipients were performed in conditions 40°C±2/75%±5RH for one month storage. In comparison with pure drug the absorbance peak of the spectra of Etoricoxcib in combination with different polymers showed no shift and no disappearance of characteristics peaks suggesting there is no interaction between drug and polymer.

Table :2

Formulations	pH	Spredability (g.cm/min)	Extrudability	Drug content %
F1	6.28	121	185	96.05
F2	6.07	117	190	98.15
F3	6.33	98	192	95.88
F4	6.26	124	188	94.23
F5	6.14	94	194	93.11
F6	6.16	102	190	94.12
F7	6.29	122	192	92.47
F8	6.33	128	196	91.57
F9	6.08	126	199	98.25
F10	6.21	105	191	94.99
F11	6.13	111	189	93.78
F12	6.29	110	190	91.22



FTIR



DSC

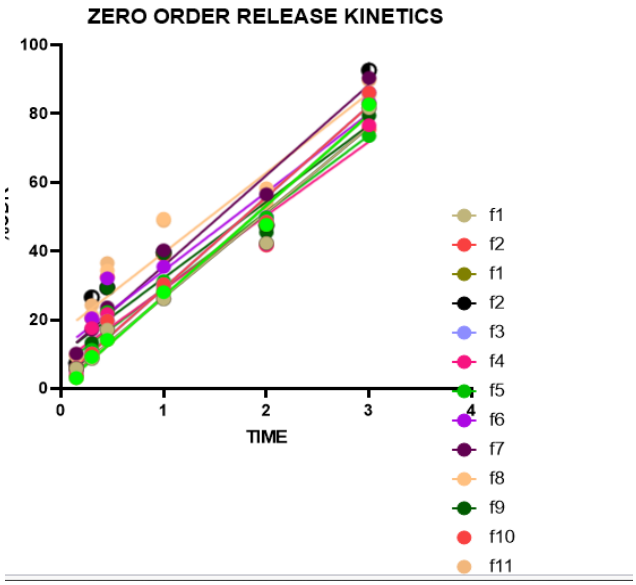
10. Differential scanning calorimetry (dsc) study

The drug and all excipients were analyzed by using differential scanning calorimeter as maintaing a constant scanning speed. The DSC Thermograms were obtained at temperature range of 30-250°C & scanned rate of 10° C/min.

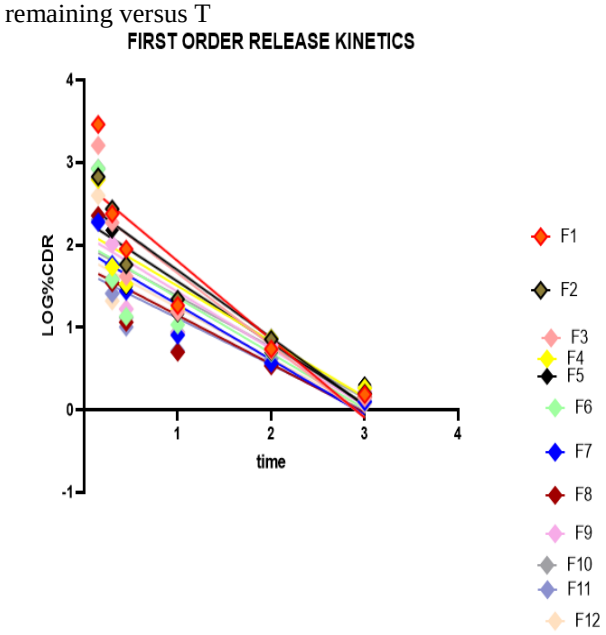
DSC curve of etoricoxib DSC curve of etoricoxib showed the endothermic peak at 136.12°c which is the melting point of the drug. The disappearance of the drug peak suggesting a molecular dispersion of etoricoxib into the loaded emulgel and that etoricoxib exist in amorphous state.

11. Kinetic analysis of in-vitro release rates of Etoricoxib emulgel

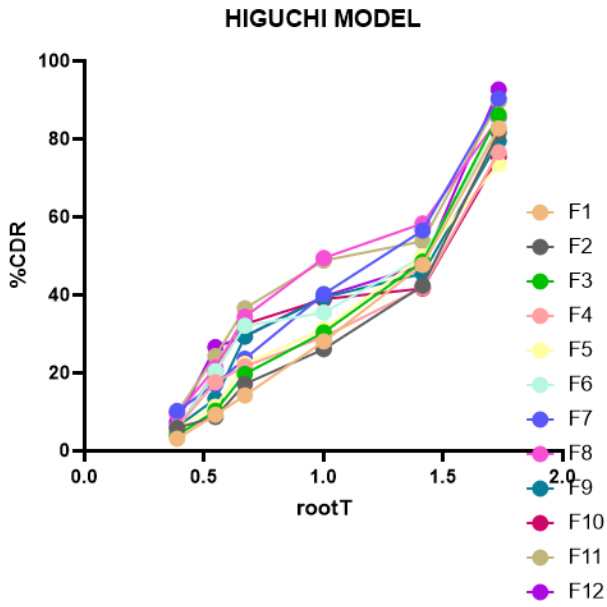
Zero order kinetics model- cumulative % drug release versus T



First order kinetic model-log cumulative percent drug remaining versus T



Higuchi`s model- cumulative percent drug released versus square root versus log T



Kosmeyer`s equation /peppa`s model- log cumulative percent drug released versus log T

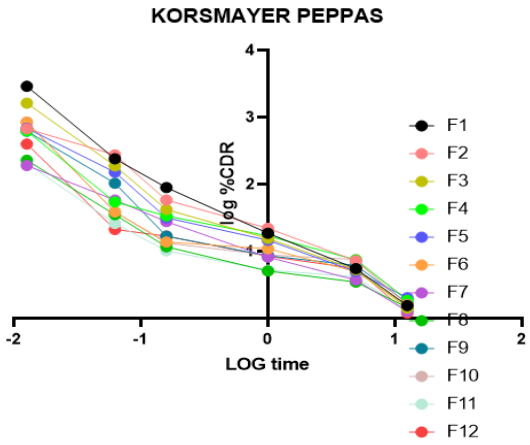


Table : 3: Regression co-efficient values of the kinetics

Formulations	Higuchi	Kosrmayers Peppas Plot
F1	0.883	0.982
F2	0.849	0.994
F3	0.891	0.980
F4	0.869	0.939
F5	0.942	0.983
F6	0.917	0.877
F7	0.912	0.996
F8	0.976	0.943
F9	0.919	0.940
F10	0.905	0.840
F11	0.935	0.914
F12	0.851	0.875

From the kinetic data, the regressions values of the higuchi formulations ranges from 0.849-0.976. The formulation f8 has shows drug release by higuchi (r^2=0.976) i.e., drug is by diffusion process.

The regression vales of korsmeyer-peppas plot 0.840-0.996. The formulation F7 has shown the best drug release. (r^2 =0.996). From the above kinetic data we can say that the formulation F7 has the better drug release.

CONCLUSION

Etoricoxib is a non steroidal anti inflammatory drug used in the treatments of arthritis, gout, rheumatoid arthritis, low back pain, and spondyosing. It is a selective cyclooxygenase inhibitor.

The following conclusion were drawn from the results

The formulation and evaluation of etoricoxib emulgel was carried out successfully

From the compatibility studied, it was conducted that drug and excipients were compatible with each other and thus suitable for the formulation.

The following conclusion was drawn from results obtained;

1. The FT-IT spectra reveled that was no interaction between polymer and the drug, hence they are compatible.
2. F1-F12, 12 formulations are formulated. All the formulations have passed evaluations with good values.
3. The formulation were found to be good stable and homogenous in nature, Ph of the formulations suggest that values were within the limits of the skin and there was no irritation, swelling and redness found in the test animal during the skin irritation study.
4. Emulgel F8 has shown better spreadability, better loading capacity, easy of application and good patient compliance.
5. In-vitro release of the test formulations was performed to determine drug release rate from emulgel. emulgel F12 formulation has shown the good release when compared with other formulations.
6. Considering the various dermatological topical preparations with various advantages and disadvantages , emulgel serve as the better alternative of the presence available marketed topical formulation for delivery of hydrophobic drugs

So from present study we conclude that the emulgel is suitable for tropical drug delivery.

Considering the various dermatological topical preparations with various advantages and disadvantages, emulgel serve as the better alternative of the presence available marketed topical formulation for delivery of hydrophobic drugs

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