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FORMULATION AND EVALUATION OF CELECOXIB EMULGEL FOR TOPICAL DRUG DELIVERY

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ABSTRACT

Osteoarthritis (OA) is the most common form of arthritis and is caused by degeneration of the joint cartilage and growth of new bone, cartilage and connective tissue. Celecoxib is a selected COX-2 inhibitor which is used as a nonsteroidal anti-inflammatory drug (NSAID) which has analgesic and antipyretic activity. It is one of the most potent nonsteroidal anti-inflammatory agents. Celecoxib belongs to BCS class II drug with its bioavailability being limited by the poor aqueous solubility. Emulgel is the promising drug delivery system for the delivery of hydrophobic drugs. Preparation of emulgel is done by incorporation method. percentage drug entrapment was found was 88.86±0.2, zeta potential -25.8mV. The emulgel showed 92.11±0.55 release after 24 hours in a controlled manner. The outcome of work recognized a unique, simple, and stable product having improved drug entrapment and increased bioavailability thus improved bioavailability at osteoarthritis disease with less adverse actions.

KEYWORDS: Osteoarthritis (OA), Celecoxib, Emulgel, NSAIDS, bioavailability.

INTRODUCTION

Topical drug delivery can be defined application of a drug formulation to the skin for treatment cutaneous disorder. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes.[1,2] Topical Drug Delivery is a system that can deliver drugs locally anywhere in the body via the eye, rectum, vagina, and skin as topical routes. The skin is one of the most accessible organs for topical administration in the human body and is the main route for topical drug delivery

systems. The basic components of topical drug delivery systems. Apply topical preparations to her skin to produce superficial, local, or systemic effects.[3]

In topical delivery, skin being a fundamental defence layer, considers the API's as external components and restricts their entry into the body. The outer most layer of epidermis called stratum corneum is the first and firm layer to overcome for drug penetration into the skin.[4] Various mechanisms have been explored to enhance the drug permeation. One such mechanism involves disruption of skin layer structure, which can be achieved using techniques such as chemical penetration enhancers, ultrasound, iontophoresis, sonophoresis, electroporation and microneedles.[5]

Local drug administration is a common treatment for both local and systemic diseases. In topical delivery systems, the drug is absorbed into the skin and reaches the site of action to produce a therapeutic effect. The rate of drug release from topical formulations is directly dependent on the physiological properties of the carrier.[6]

Emulgel are produced both as oil-in-water emulsions and as water-in-oil emulsions mixed with gels. Oil-in-water is used for lipophilic drugs and water-in-oil is used for hydrophobic drug delivery.[7] Emulgel is thixotropic, fat-free, easy to spread, easy to remove, has an emollient effect, does not leave behind any stains, is biologically compatible, aesthetically pleasing, transparent and cosmetically acceptable, and is suitable for use on the skin. It has many benefits, including being well absorbed. It has a long shelf life.[8] Emulsion and gel formulations each have unique properties. However, gels have some limitations in terms of hydrophobic drug delivery. This limitation is overcome by Emulgel. Gelling agents can be used to convert classical emulsions into emulgel.[9]

Osteoarthritis (OA) is a degenerative joint disease that affects millions of people worldwide. This is a complex disease, the pathogenesis of which changes in the tissue homeostasis of articular cartilage and subchondral bone determine the predominance of destructive processes. Interactions between cells and the extracellular matrix (ECM) play an important role in the pathophysiology of articular cartilage.[10,11]

In this research, the formulation celecoxib emulgel which has efficient treatment against osteoarthritis disorder, which is evaluated by particle size, zeta potential, release kinetics, in vitro study.

MATERIALS AND METHODS

Materials

Celecoxib (UniChem Laboratories Pvt. Ltd, Baddi India). All other chemicals propylene glycol (Fischer Scientific, Mumbai), Span 80 (molychem; Mumbai), Tween 80 (Thermo fisher Scientific India Pvt. Ltd), Oleic acid (Fisher Scientific, Mumbai), Carbopol 934 (Lubrizol Advanced Materials, India), Propyl paraben (BRM Chemicals), methyl paraben (BRM Chemicals).

Estimation of Celecoxib by UV-visible spectrophotometer

The standard stock solution of Celecoxib (100µg/mL) was prepared in methanol. This solution was diluted with methanol, to obtain various dilutions (3-18µg/mL). Absorbance of these solutions was recorded at 252nm against methanol as blank using UV-visible spectrophotometer and standard curve was plotted against concentration. From the calibration curve intercept, slope, straight line equation and correlation coefficient were obtained.[12]

Solubility studies

The spontaneous interaction of two or more substances to form a homogenous molecular dispersion is called solubility. For quantitative solubility study, excess amount of drug was taken in thoroughly cleaned culture flasks containing 5 mL of different solvents (Methanol, Ethanol, Chloroform, pH 7.4 phosphate buffer saline, water) and test tubes were tightly closed. These test tubes were shaked on water bath shaker for 24 hrs. at room temperature. After 24 hrs., each sample was centrifuge for 15 minutes at 15,000 rpm and was suitably diluted and determined spectrophotometrically.[13]

Celecoxib emulgel formulation

Eight different formulations of the medication were made using the formulation code that was created.

Composition of celecoxib emulgel

Ingredients % (w/w)	Formulation Batches							
	F1	F2	F3	F4	F5	F6	F7	F8
Celecoxib	1	1	1	1	1	1	1	1
Carbopol 934	1	1	1	1	1	1	1	1
Tween 80	0.5	1	1.5	1	0.5	1	0.5	1
Span 80	0.5	0.5	1	1	1.5	1.5	2	2
Oleic Acid	5	7.5	5	7.5	5	7.5	5	7.5
Methyl Paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03

Propyl Paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Propylene Glycol	5	5	5	5	5	5	5	5
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Preparation of emulgel

Schematic representation of Emulgel synthesis is shown in figure 1

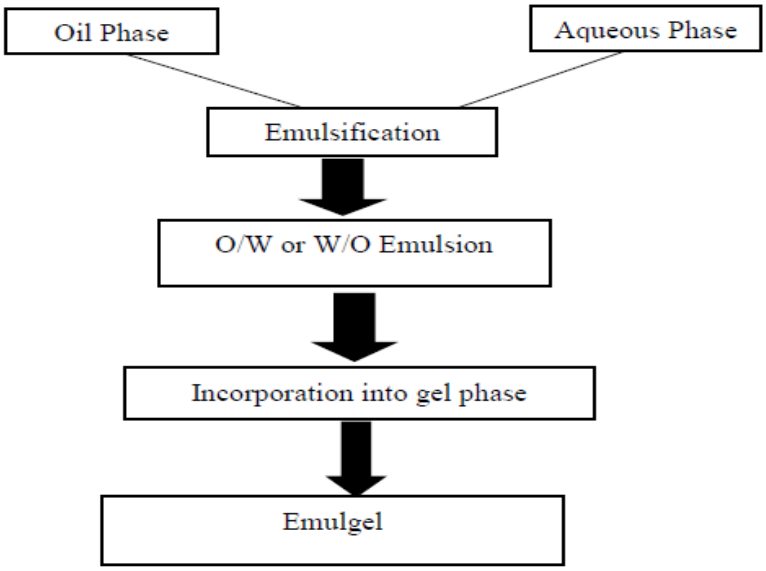

Figure 1: Schematic representation of emulgel synthesis.

Emulsion formation

The oily phase of emulsion was prepared by mixing Span 80 and Oleic acid. To this, methyl paraben, propyl paraben, dissolved in propylene glycol were added. Tween 80 was mixed in Hplc water to formulate aqueous phase. Both solutions were heated at 70-80 Cº separately. Oily phase added to aqueous phase with constant stirring to develop stabilized emulsion.

Method of preparation celecoxib emulgel

Gel Preparation: Using a mechanical shaker, mix different amounts of gelling agent into distilled water while continuously shaking at a medium speed to create the gel basis. After that, the water phase is continuously stirred with the addition of the oil phase until the mixture reaches room temperature. Emulgel preparation involves gently agitating a 1:1 ratio of emulsion to gel.[14]

Evaluation studies

a) FTIR studies

Fourier transform infrared Spectroscopies of different compounds were performed for identification of that particular compound. FT-IR Spectroscopy of pure drugs was done using

Celecoxib Powder. Various peaks in FT-IR Spectrum were interpreted for identification of different group in the structure of pure drugs. FT-IR Spectroscopy can also be used to investigate and predict any physicochemical interactions between different components.[15]

b) TEM Study

The size and shape of emulgel were examined by transmission electron microscope (TEM) with the image software. The drug loaded emulsion was spread on firmware-coated copper grids and absorbed after complete air drying.[16,17]

***c)* Entrapment efficiency[18]**

1. The percentage drug content of the celecoxib in each prepared batch of the emulgel gel was determined by solubilizing the accurately weighed gel equivalent to 50mg of drug in beaker containing 10ml of the methanol solvent.
2. The solution was vortexed for 1 min. followed by sonicated for 5min.
3. The sample was centrifuged at 5000rpm for 10min. the supernatant was transferred to the 10Ml volumetric flaks and suitable diluted with the methanol solvent.
4. The sample was scanned ranging 200-400nm using the UV spectrophotometer.
5. The UV spectrum of the sample was noted and absorbance of the ibuprofen was determined. The amount of the ibuprofen was determined using the standard calibration curve. The activity was performed in the triplicate manner.

$$\text{Drug Entrapment Efficiency} = \frac{\text{Initial Drug Content} - \text{Final Drug Content}}{\text{Initial Drug Content}} * 100$$

d) Visual appearance

Colour, phase separation, homogeneity, and consistency were visually assessed in prepared emulgel formulations.

e) pH evaluation

The pH of the gel was determined using calibrated pH meter. Determinations were carried out in triplicate and an average of these determinations was taken as the pH of the gel.[19]

f) Rheological research (Viscosity)

The viscosity of the formulated batches was determined using a Brookfield Viscometer with spindle no.7. The formulations whose viscosity was to be determined were added to a beaker and kept for 30 min to maintain them at the assay temperature (25±1°C) before the

measurement. Spindle was lowered perpendicular in to the center of emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 50 rpm for 10 minutes. The spindle was moved up and down giving viscosities at number of points along the path.[20]

g) Swelling index

1g of prepared emulgel formulations was taken on porous aluminum foil and then placed in the petri dish containing 10 mL 0.1N Hcl. The samples were taken from the Petri dish at a different time interval and left undisturbed in a dry place for some time so that the external liquid is removed and weighed. Swelling index is then calculated by using below formula,

Swelling Index (SW) % = [(Wt − Wo) / Wo] × 100 Where (SW) % = Equilibrium percent swelling, Wt = Weight of swollen emulgel after time t, Wo = Original weight of emulgel at zero time

h) Determination of drug content

By combining 1gm of the Emulgel with 100 mL of methanol, the drug concentration of each batch of Celecoxib Emulgel formulation was assessed independently. To obtain clear solutions, the resultant solutions were filtered through a filter. Further were centrifuged 10000 rpm for 30 min. Using methanol as a blank, the drug content of these samples was analyzed using UV-spectrophotometer scanning from 200- 400 nm.[21]

i) Zeta potential

Zeta potential for emulgel was estimated using Zeta sizer by using an electrophoretic light scattering method. The formulated sample was placed in zeta cells and results were analyzed. The average of three measurements with Standard Deviation (±SD) was reported.[22,23]

j) In vitro release study

The release of Celecoxib Emulgel through dialysis membrane was performed in Franz-type diffusion cells. The receptor medium was phosphate buffer (pH 7.4) which was constantly stirred at 100 rpm with a small magnetic bar. The receptor compartment was maintained at 37±0.20C by a circulating water jacket. 1 gram of Celecoxib Emulgel was placed in the donor compartment. Samples were withdrawn from the receptor compartment via the sampling part at 15, 30, 60, 120, 180, 240, 300, 360 and 480 minutes immediately replaced with an equal volume of fresh receptor solution. Triplicate experiments were conducted for each study and sink conditions were always maintained. All samples were analyzed for Celecoxib Emulgel content spectrophotometrically at 252 λmax of drug.[24,25]

k) ex-vivo drug release kinetics

- Zero Order Release
- First Order Release
- Higuchi Model
- Korsmeyer-Peppas Mode

RESULT

Determination of λmax and construction of calibration curve in methanol

The standard stock solution of Celecoxib (100µg/mL) was prepared in methanol. This solution was diluted with methanol, to obtain various dilutions (3-18µg/mL). and analysed spectrophotometrically at 252 nm. The results obtained are shown below in Table 4.4 and graphically shown in Figure 2. The standard curve of celecoxib as shown in graph indicated the regression equation Y = 0.0498x + 0.0035 and R^2 value is 0.9999p, which shows good linearity as shown in Tables 1, respectively.

Table 1: Calibration curve of Celecoxib in methanol (λ_{max} = 252 nm).

Sr. No.	Concentration (µg/mL)	Mean ±SD
1	0	0.00 ± 0.00
2	3	0.156 ± 0.002
3	6	0.304 ± 0.002
4	9	0.455 ± 0.003
5	12	0.595 ± 0.003
6	15	0.751 ± 0.002
7	18	0.899 ± 0.002

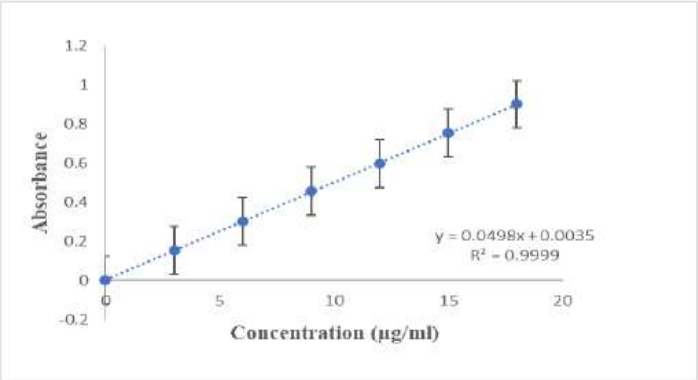

Figure 2: Calibration curve of celecoxib in methanol.

Solubility studies

Celecoxib's solubility in several solvents: Celecoxib's solubility in a range of oils, surfactants, and co-surfactants was ascertained. Celecoxib dissolves in different oils in the following

order: Oleic acid >Liquid paraffin > Triacetin > Soybean oil > Campul PG-8. Celecoxib is soluble in different surfactants and co-surfactants in the following order: Tween 80 > Span 20 Tween 20 > Span 80 >Propylene glycol > Glycerol >IPA.

Table 2: Celecoxib solubility in various oils.

Oils	Solubility(mg/g)
Oleic Acid	134.44±0.20
Liquid Paraffin	124.4±0.31
Triacetin	112.28±0.20
Soyabean Oil	74.67±0.31
Campul PG-8	29.02±0.40

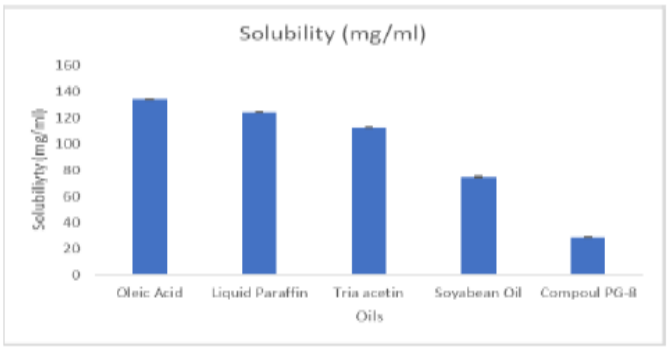

Figure 3: Solubility of celecoxib in various oils.

Table 3: Celecoxib solubility in various surfactants and co-surfactants.

Surfactants and Cosurfactants	Solubility(mg/g)
Tween 80	166.37±0.31
Span 20	105.59±0.2
Tween 20	58.27±0.31
Span 80	17.06±0.04
Propylene Glycol	116.57±0.31
Glycerol	62.62±0.4
IPA	52.31±0.2

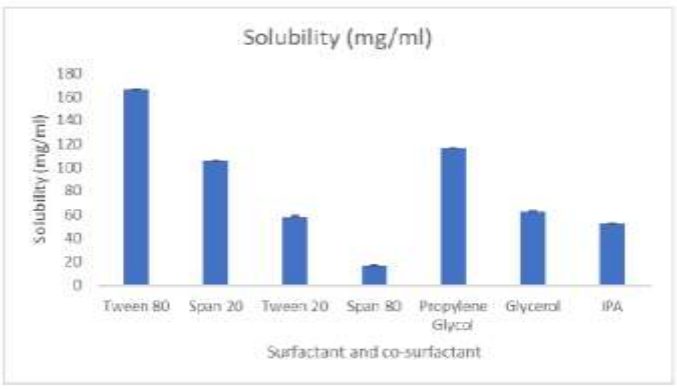

Figure 4: Celecoxib solubility in various surfactants and co-surfactants.

Evaluation studies

a) FTIR spectroscopy

The pure celecoxib has no obvious characteristic absorption peaks. The spectra of emulgel indicated intensive bands at ideal wavelengths shown in (figure 5).

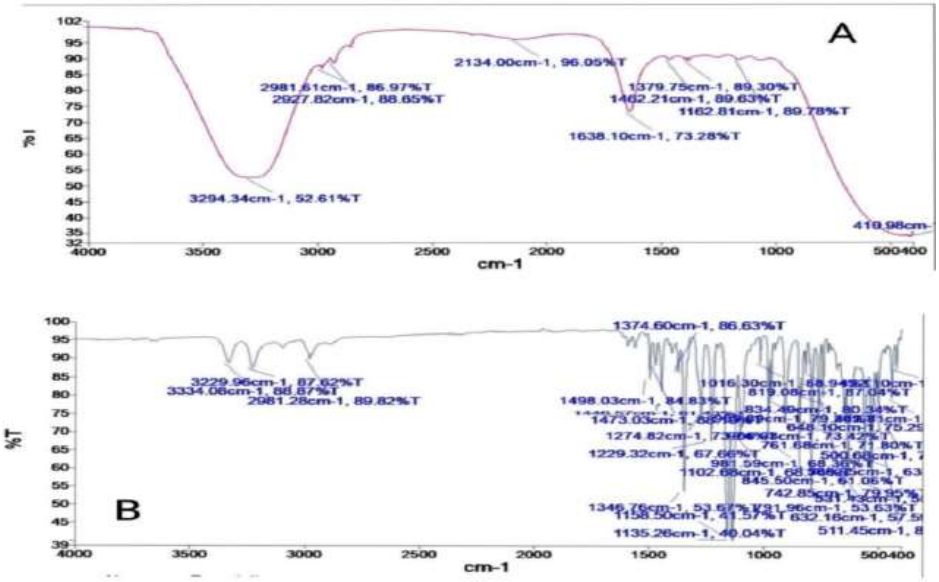

Figure 5: IR spectroscopy of (A) pure celecoxib & (B) celecoxib emulgel.

b) Transmission electron microscope study

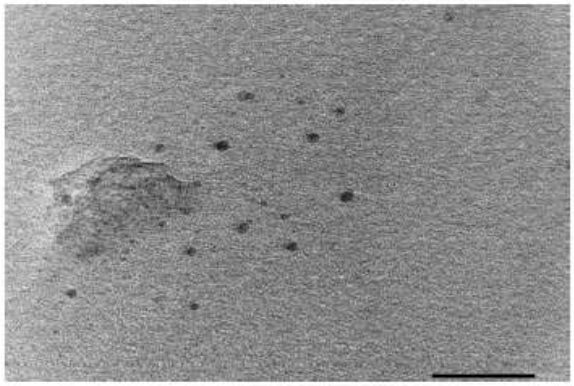

Figure 6: TEM Image.

Discussion: TEM was utilized to determine surface morphology of formulation. From above image evaluated that globules are spherical in shape and uniform.

c) Percentage drug entrapment

Percentage yield and drug entrapment of Emulsion were given a table no 4

Table 4: Percentage drug entrapment of different emulgel.

S. No.	Formulation Code	Percentage drug entrapment
1	F2	81.16±0.31
2	F4	86.85±0.2
3	F5	88.86±0.2
4	F6	82.63±0.2
5	F7	84.64±0.2
6	F8	76.54±0.31

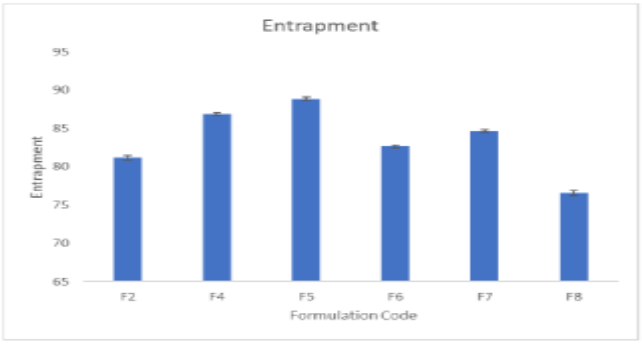

Figure 7: Percentage drug entrapment different Emulgel formulations.

Discussion: From figure no.7, it was found that increase the concentration of lipid percentage yield will increase and in case of percentage drug entrapment, entrapment of drug in polymer will increase on increasing concentration of polymer, but this increase and drug entrapment will follow a certain concentration of polymers after that no percentage entrapment will increase on increasing concentration of polymer. Maximum percentage yield and percentage drug entrapment was found of formulation F5 that was 88.86±0.2.

d) Organoleptic Characteristics and Globule size: Freshly prepared emulsions were investigated. Organoleptically for homogeneity, colour, and phase separation. All the emulsions were found to be homogenous, creamy white; no phase separation was observed. Globule size for F1 emulsion was up to 50 µ and F8 emulsion was up to 80 µ.

Table 5: Physical appearance data.

Emulsion	Homogeneity	Colour	Phase separation	Globule size
F1	Heterogenous	White	Separated	Up to 50µ
F2	Homogenous	Less Turbid	None	Up to 80µ
F3	Heterogenous	Turbid	Separated	Up to 80µ
F4	Homogenous	Less Turbid	None	Up to 80µ
F5	Homogenous	White	None	Up to 80µ
F6	Homogenous	Turbid	None	Up to 80µ
F7	Homogenous	Less Turbid	None	Up to 80µ
F8	Homogenous	Turbid	None	Up to 80µ

Discussion: From the above result it was determine that F1, F3 shown phase separation. These two formulations did not proceed further evaluation. F2, F4, F5, F6, F7, F8 was evaluated further.

e) pH of Emulgel of Celecoxib

The pH of Emulgel of Celecoxib was shown in table 6.

Table 6: pH data of Emulgel of Celecoxib.

Sr. no.	Formulation Code	pH
1	F2	6.5±0.3
2	F4	6.8±0.1
3	F5	7.4±0.2
4	F6	7.1±0.1
5	F7	7.0±0.1
6	F8	6.6±0.3

Value is expressed as mean ± SD; n=3

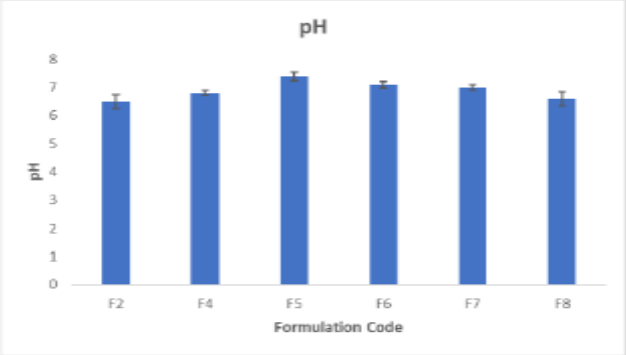

Figure 7: pH of Emulgel of Celecoxib

Discussion: From the Table 6 & fig. 7, it was found that pH of all formulation was found to be in a range 6.5±0.3 to 7.4±0.2.

f) Viscosity of emulgel of celecoxib

The viscosity of Emulgel of Celecoxib is shown in table 7.

Table no. 7: Viscosity of emulgel of celecoxib.

Sr. No.	Formulation code	Viscosity(cPs)
1	F2	1218±4
2	F4	1877±5
3	F5	4586±3.6
4	F6	3245±3.5
5	F7	3926±1.5
6	F8	3580±11.6

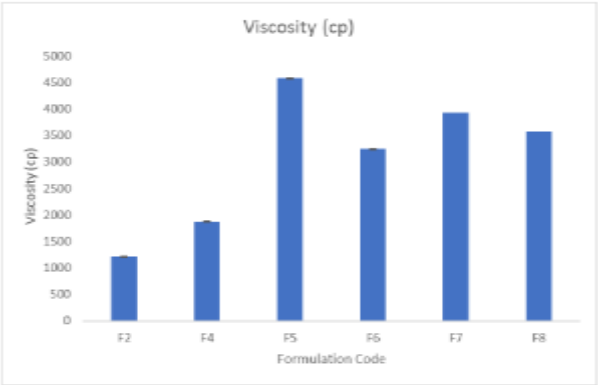

Figure 8: Viscosity of emulgel of celecoxib.

Discussion: The Viscosity of the gel at different formulation was found to be in the range from 1218±4 to 4586±3.6

g) Swelling index of emulgel of celecoxib

The Swelling index of Emulgel of celecoxib is shown in table 8.

Table 8: Swelling index of emulgel of celecoxib.

Sr. No.	Formulation code	At 10min	At 20min	At 30min
1	F2	45±0.1	72±0.1	94±0.12
2	F4	49±0.1	76±0.1	96±0.54
3	F5	61±0.1	92±0.1	115±0.45
4	F6	56±0.1	83±0.1	105±0.24
5	F7	59±0.1	86±0.1	111±0.1
6	F8	52±0.1	79±0.1	99±0.1

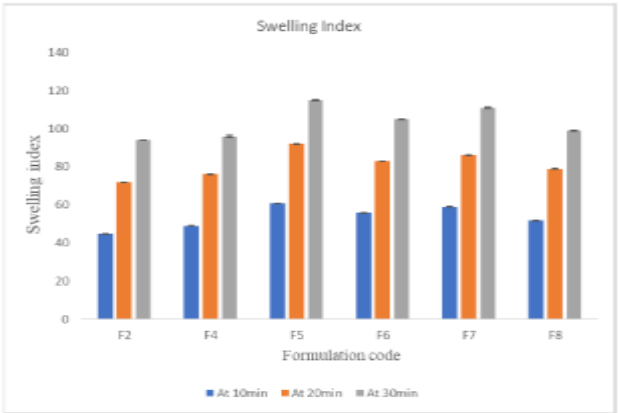

Figure 9: Swelling index of emulgel of celecoxib.

h) Drug content of emulgel of celecoxib

The percentage drug content of Emulgel of Celecoxib was shown in table 9.

Table 9: % Drug content of emulgel of celecoxib.

Sr. No.	Formulation code	% Drug content
1	F2	93.273±0.201
2	F4	96.888±0.875
3	F5	98.896±0.702
4	F6	94.478±0.201
5	F7	92.938±0.760
6	F8	91.198±0.307

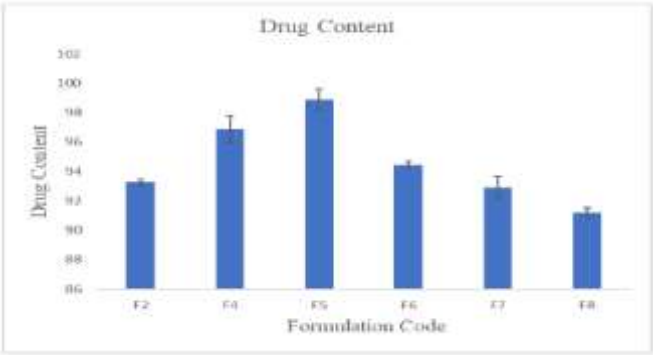

Figure 10: Drug content of emulgel of celecoxib.

Discussion: The drug content of formulations was found to be 91.198±0.307 and 98.896±0.702 %, respectively. The percentage drug content of all formulations was found to be satisfactory. Hence, the method adopted for formulations was found to be suitable.

i) Zeta potential analysis

Zeta potential of the formulation was determined be Antor Paar Zeta sizer instrument. Zeta potential of formulation was as shown in figure: 11. The zeta potential study depicts good stability of the F5formulation which lies desired mV range.

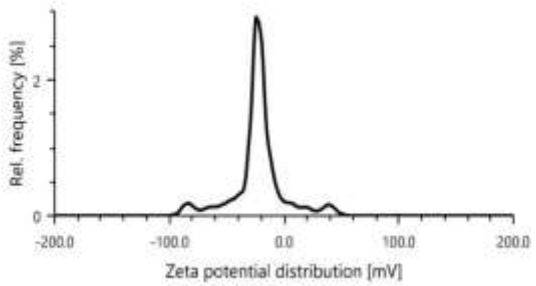

Figure 11: Zeta Potential of F5 Formulation.

Zeta Potential indicate the degree of electrostatic repulsion between a similar charge particle in a dispersion. High zeta potential value (positive or negative) suggest that particle will repel

each other preventing aggression and thus maintaining stability. It indicates -25.8 good stability.

j) In vitro release study

The in-vitro drug release of pure drug & Formulation F5 in phosphate buffer (pH 7.4) Results of the dissolution efficiencies upto 24hrs are shown in Fig 12

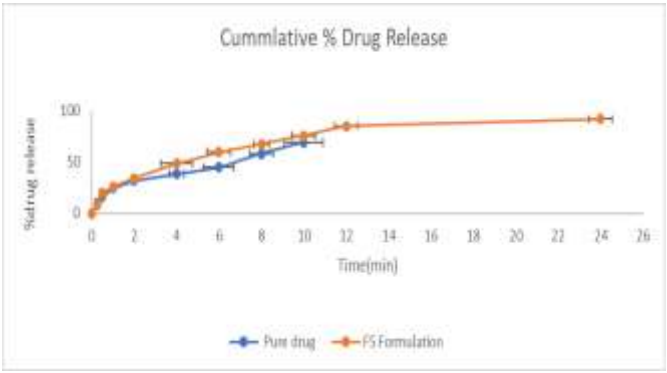

Figure 12: *In vitro* release study.

k) In-vitro drug release kinetic

1. Zero order

Figure 13: Zero order graph of formulation F5.

2. First order

Figure 14: First order graph of formulation F5.

3. Higuchi model

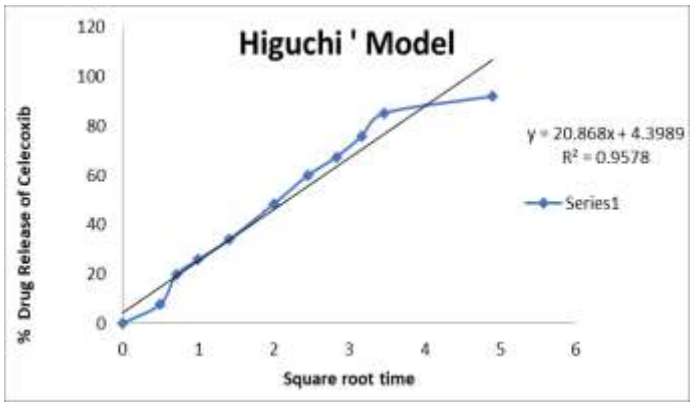

Figure 15: Higuchi order graph of formulation F5.

4. Korsmeyer Peppas model

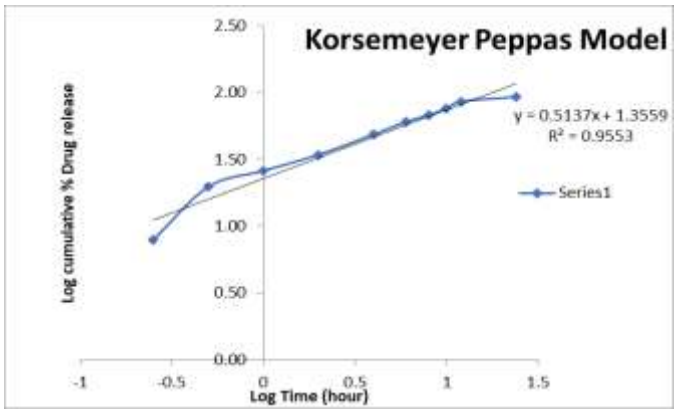

Figure 16: Korsmeyer Peppas order graph of formulation F5.

Formulation Code	Zero order		First order		Higuchi		K. Peppas	
	K_0	R^2	K_0	R^2	K_0	R^2	K_0	R^2
F5	3.8355	0.7695	-0.0464	0.9515	20.868	0.9578	0.5137	0.9553

CONCLUSION

Celecoxib belongs to BCS Class II drug which has low solubility and high permeability. This study aimed to increase solubility. Preformulation study of Celecoxib was carried out by all the parameters for Ultraviolet absorption maxima reported as 252λ max, partition coefficient reported as 3.42±0.006, solubility study freely soluble in methanol. The drug excipient interaction analysis revealed that there is no chemical interaction between the drug and the polymer. The emulsion was prepared and it was incorporated into gel base to form emulgel. Formulations weas prepared using gelling agents in same concentration. They have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, long shelf-life bio-friendly, transparent and pleasing appearance.

Using Oleic acid as the oil phase, span 80 as the surfactant, PEG as the co-surfactant, and water as the aqueous phase, Celecoxib emulsion was effectively created. The F5 formulation was evaluated for pH determination reported as 7.4±0.2, Rheological studies reported as 4586±3.6, Spreadability studies reported as 7.7±0.3, Swelling index reported as At 10min 61±0.1, At 20min 92±0.1, At 30min 115±0.45, Zeta potential -25.8 and In-vitro Drug release study of 92.11±0.55%, was deemed to be optimal based on the acquired results. The formulation F5 was found to be explained by Higuchi's model, Korsemeyer Peppas release model, zero-order drug release and first order drug release based on the results of the kinetic experiments.

Emulgel is a new method that has shown to be the most effective, easy, and better delivery technique available. Compared to traditional topical delivery systems, it provides superior drug release and gel-like qualities due to its non-greasy nature and lack of oily bases. Emulgel is efficient at delivering drugs to their intended location and has a high drug loading capacity. Polymer selection for emulgel formulation and oil, surfactant, and co-surfactant screening was carried out based on the solubility values for emulsion formulation. F5 is regarded as the optimal formulation based on evaluation parameters since it shows improved drug solubility of the hydrophobic celecoxib which ultimately lead to enhance bioavailability of drug. Emulgel proved be a efficient drug delivery system for BCS class II drugs.

Conflict of interest

The authors have no conflicts of interest regarding this investigation**.**

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