Formulation and Evaluation of Diclofenac Potassium Emulgel using Essential Oils for the Pain Management in Arthritis

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ABSTRACT: This study aims to formulate & evaluate Diclofenac Potassium Emulgel using different essential oils for managing pain in arthritis. Emulgel is an effective drug delivery system for delivering of hydrophobic drugs. Diclofenac Potassium is a BCS class-II drug & a NSAID (Non-steroidal Anti-inflammatory drug) used for anti-pyretic, analgesic and anti-inflammatory activity. Topical delivery has many advantages over oral dosage forms hence have more patient compliance and effective treatment. Different essential oils like Turmeric oil, Clove oil and Peppermint oil were used as a penetration enhancer. Different formulations were prepared and evaluated on their physical appearance, phase separation, pH, viscosity, spreadability, globule size, zeta potential and *In-vitro* drug release test. Compatibility study was done by using Fourier-Transform Infrared (FTIR) Spectrometer. All the formulations were found to be acceptable on parameters such as physical properties like color, homogeneity and consistency, grittiness, spreadability, pH and viscosity. After 8hrs. of *In-vitro* diffusion study, FC2 batch containing 8% of Clove oil showed highest drug release i.e. 72.87% and appropriate viscosity. Therefore conclusion can be drawn out that the prepared emulgel formulation can be helpful and effective in relief from joints pain and arthritis.

Keywords: Carbopol 940; Diclofenac Potassium; Essential Oils; Hydrophobic drug; O/W type of emulsion.

INTRODUCTION

Today arthritis has become an increasing health problem worldwide especially to the geriatric people. Arthritis is a condition having inflammation or swelling in one or more joints. Various medications are used in the treatment of arthritis like NSAIDs, Disease-modifying anti-rheumatic drugs (DMARDs), steroids & other herbal treatments. Diclofenac potassium is a derivative of benzene acetic acid, potassium salt of diclofenac and a Non-steroidal anti-inflammatory drug (NSAID) having anti-inflammatory, analgesic & antipyretic activity. A non-selective, reversible competitive cyclooxygenase (COX) inhibitor, diclofenac potassium ultimately prevents arachidonic acid from being transformed into prostaglandin precursors. This suppresses the production of prostaglandins, which are responsible for pain, inflammation and fever[1]. Diclofenac Potassium is used to relieve the indications of arthritis (osteoarthritis or rheumatoid arthritis) like swelling, inflammation, joint pain and muscle stiffness. So, this study aims to formulate and evaluate Diclofenac Potassium emulgel using

various essential oils as penetration enhancers and also which are well known for treating arthritis. Medicines are administered to the human body in different ways, for example, orally, parenterally, rectally, sublingually. Though oral ways are the most common route of administration; they have drawbacks like poor solubility and bioavailability, poor patient compliance and first-pass metabolism. In such case, topical drug delivery system may be considered as a replacement to oral route. The topical system bypasses the first pass metabolism, avoids the risk of absorption such as gastric emptying time, various enzymes, pH changes, etc., and avoids problems associated with intravenous therapy[2], improves patient compliance and is easy to apply. Topical drug delivery systems are commonly used when other routes of drug delivery (oral, sublingual, rectal, parenteral, etc.) fail or for topical skin infections such as fungal infections[3] but, the lack of rapid delivery of hydrophobic drugs through the skin is the main drawback of the topical drug delivery system as a gel. There comes in, the emulgel, a promising topical delivery for water in-soluble or hydrophobic drugs. Emulgel is combination of emulsion and gelling agent. Emulsion can be water-in-oil (w/o) or oil-in-water (o/w) depending upon the intention to use. Due to both the water and oil phases, the emulsion gel acts as a dual regulator of drug release from the formulation. Emulgels are useful in dermatology because they are thixotropic, non-greasy, easily spreadable, easily washable, emollient, non-staining, longer shelf life, environmentally friendly, transparent, and have aesthetic appearance[4]. Various penetration enhancers, mineral oils and essential oils, emulsifiers, surfactants and gelling agents are used in its preparation. For the topical distribution of poorly water-soluble drugs, emulgel is a superior option. It has been found to be a better and more stable carrier for medications that are poorly water soluble or hydrophobic. This study will give a better alternative approach in topical delivery system and a hope in managing the pain in arthritis more effectively.

MATERIALS AND METHODS

Materials

Diclofenac Potassium was obtained as a gift sample from Amoli Organics Pvt. Ltd., Gujarat, India. Pure Walnut oil and Pure Essential oils like Turmeric oil and Clove oil were purchased from Deve Herbes, New Delhi, India. Peppermint Oil, Carbopol 940 and Methyl Paraben were supplied by Analab Fine Chemicals, Mumbai, India. Other excipient such as Tween 20 was supplied by Molychem Lab, Mumbai. Span 20 and Propylene Glycol were supplied by Loba Chemie Pvt. Ltd., Mumbai. Propyl paraben, Tri-ethanolamine were supplied by Research-Lab Fine Chem. Industries, Mumbai, India.

Preparation of Emulgel

The aqueous phase of emulsion was made by dissolving Tween-20, methyl paraben & propyl paraben and the drug in water, propylene glycol and ethanol respectively and was mixed together and heated up to 70°C – 80°C. Similarly, the oil phase was also prepared by heating walnut oil, Span-20 and essential oils (according to the concentrations) at 70°C – 80°C. Then, at a stirring speed of 2000 rpm, the oil phase was poured drop by drop into the aqueous phase until the complete oil phase was mixed in it. After the both phases got mixed homogenously, the speed of the stirrer was lowered to 1000 rpm for 10 min and then at 500 rpm for next 5

minutes. The emulsion was cooled at room temperature and was incorporated into previously prepared Carbopol-940 gel base in the ratio of (1:1) with appropriate stirring[5].

Triethanolamine was put in quantity sufficient (q.s.) amount to adjust the pH of the emulgel. The prepared formulations batches of emulgel were then further evaluated on different parameters.

Formulation Table:

Table 1. Formulation table for emulgel preparations

Ingredients	FT1	FT2	FP1	FP2	FC1	FC2
Diclofenac Potassium (gm)	1	1	1	1	1	1
Carbopol 940 (gm)	1	1	1	1	1	1
Propylene Glycol (ml)	5	5	5	5	5	5
Walnut Oil (ml)	7.5	7.5	7.5	7.5	7.5	7.5
Tween 20 (ml)	1	1	1	1	1	1
Span 20 (ml)	1.5	1.5	1.5	1.5	1.5	1.5
Methyl Paraben (gm)	0.045	0.045	0.045	0.045	0.045	0.045
Propyl Paraben (gm)	0.015	0.015	0.015	0.015	0.015	0.015
Turmeric oil (ml)	4	8	-	-	-	-
Peppermint oil (ml)	-	-	4	8	-	-
Clove Oil (ml)	-	-	-	-	4	8
Ethanol (ml)	2.4	2.4	2.4	2.4	2.4	2.4
Distilled Water	upto 100ml	upto 100ml	upto 100ml	upto 100ml	upto 100ml	upto 100ml

Where, FT, FP and FC = Formulation containing Turmeric oil, Peppermint Oil and Clove oil respectively; q.s. = quantity sufficient

Evaluation Parameters

Physical evaluation

Appearance: Visual examination of the appearance of the prepared Diclofenac potassium emulgels such as colour, homogeneity and consistency, grittiness and phase separation has been carried out[6].

Phase separation: Used to measure physical stability. Emulgels were subjected to centrifuge in a suitable temperature at 6000 RPM for 10 min. to check for any creaming or phase separation[6].

Washability: The formulations were manually tested for ease and duration of application to the skin and rinsing off with water.

pH

The pH of topical dosage forms is very important as deviations from the normal pH can cause skin irritation. 1% aqueous solutions of the prepared emulgels were checked for their pH values using a calibrated digital pH meter[6].

Viscosity

The viscosity of Emulgel was measured by Viscometer (LABMAN) LMDV-60 at 30 RPM using spindle no. L4at room temperature. A suitable amount of each emulgel formulation was stored in a glass bottle in which the spindle groove was immersed and the rpm was set. Viscosity measurements were runned and the readings were measured after 1 minute and the viscosity of each formulation was calculated[7].

Drug Content

In an appropriate solvent, 1gm of emulgel was mixed and filtered for the purpose of obtaining a clear solution and absorbance determined by UV spectrophotometer. Standard plot of the drug was prepared in the similar solvent. The same standard plot using the absorbance values was used to determine concentration and drug content[8].

Spreadability

To measure the spreadability parallel plate method was used. This approach bases its measurement of spreadability on the "Slip" and "Drag" properties of emulgels. It is made up of a wooden slab that has a pulley on one end. The lower glass slide was fixed on this slab. 1gm of prepared emulgel was placed on this ground slide. The emulgel formulation was then placed between two glass slides with dimensions corresponding to a fixed bottom slide equipped with a hook. 100 g of weight was placed on top of both slides for five minutes in order to remove the air, so that a homogeneous film of gel can be formed between them. Excess emulgel was removed from the corners of the slides. After that, the top slide was pulled with a pull of 20 g using a string attached to the hook, and the time (in seconds) for the top slide to travel 6.5 cm was recorded.

The shorter the time interval better is the spreadability.

The formula, [S = M*L / T] is used to calculate the spreadability.

Where M = weight fastened to the upper slide, L = length of the glass slide (cm) and T = time required to separate the slides (sec.) [9]

***In-vitro* drug release studies**

The *In-vitro* drug releases of all formulations were conducted using Franz Diffusion cell (15ml) with cellophane membrane (previously soaked in PBS solution for overnight). It was fixed firmly to one end of the hollow glass tube of the dialysis cell. Specific amount of emulgel was spread on cellophane membrane surface. Freshly prepared PBS solution (pH 5.5) was poured into the receptor chamber to solubilize the drug. A magnetic stirrer was placed in the receiving chamber. The samples (1ml aliquots) were obtained at the appropriate time intervals and after adequate dilutions; absorbance was measured by UV visible spectrophotometer at 276 nm. As a function of time, the cumulative amount of drug released over the cellophane membrane is determined. The % release of drug using the standard calibration curve was calculated.

Briefs of dissolution testing:
Dissolution medium: Saline phosphate buffer pH 5.5
Velocity: 50rpm
Aliquots (ml) taken every time: 1ml
Temperature: 37 ± 2^0C
At wavelength: 276nm [10]

The size and distribution of Globules in emulgel and Polydispersity Index (PDI)

Globule size and its distribution were determined by Zeta Sizer (Malvern Panalytical Ltd). 1g of sample was dissolved and stirred to obtain a uniform dispersion. The sample was introduced into the photocell of Zeta Sizer and the mean globule size was determined. Also the average globule size was measured by a digital microscope at 40X magnification using Pixel Pro software. The polydispersity index (PDI) is a measure of the dispersion quality of particles and indicates whether the particles are monodispersed or polydispersed[11,12.]

Photomicrography

To examine the spherical structure, the emulgel was viewed under a digital microscope. A diluted emulgel was administered, placed on glass slide and examined with a magnification of 40x using a digital microscope[13].

Zeta Potential

Zeta potential is an important parameter to check the stability of an emulgel due to the size of the electrostatic or charge redistribution between particles. The Zeta potential is determined by using Zeta Sizer (Malvern Instrument, UK). Stabilized emulsions typically have zeta potentials in the range of -30 mV to +30 mV[14].

Stability Study

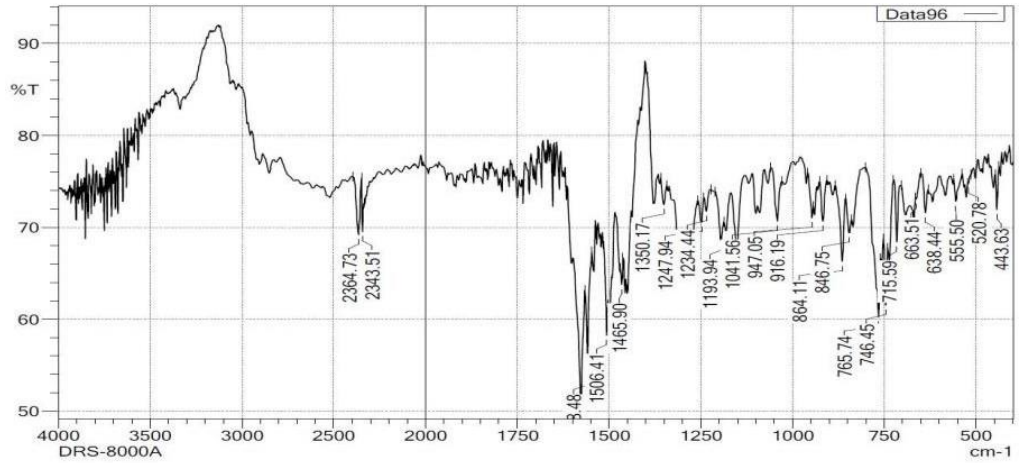
The stability of the optimized emulgel formula was tested; the formulations were packed in collapsible aluminium tubes and the studies were carried out for 3 months according to ICH guidelines, maintaining the temperature and humidity at 40 ± 2^0 C / 75 ± 5% RH, and samples were taken at regular intervals of 30, 60 and 90 days to evaluate their physical properties, pH, drug content, viscosity and drug release. Selection of appropriate storage conditions during the accelerated stability study is important to estimate the long-term stability of emulgel[15].

RESULTS & DISCUSSION

Pre-formulation studies

FTIR of pure drug

Infrared spectrum of Diclofenac Potassium was obtained using Fourier Transform Infrared spectrophotometer. The sample was scanned in the wavelength range 4000 to 400 cm^{-1} and compared with data found in the literature. Graphs 1 and 2 shows that there was no change in position or disappearance of any of the characteristic peaks of Diclofenac Potassium, indicating the compatibility of Diclofenac Potassium with the polymer carbopol 940.

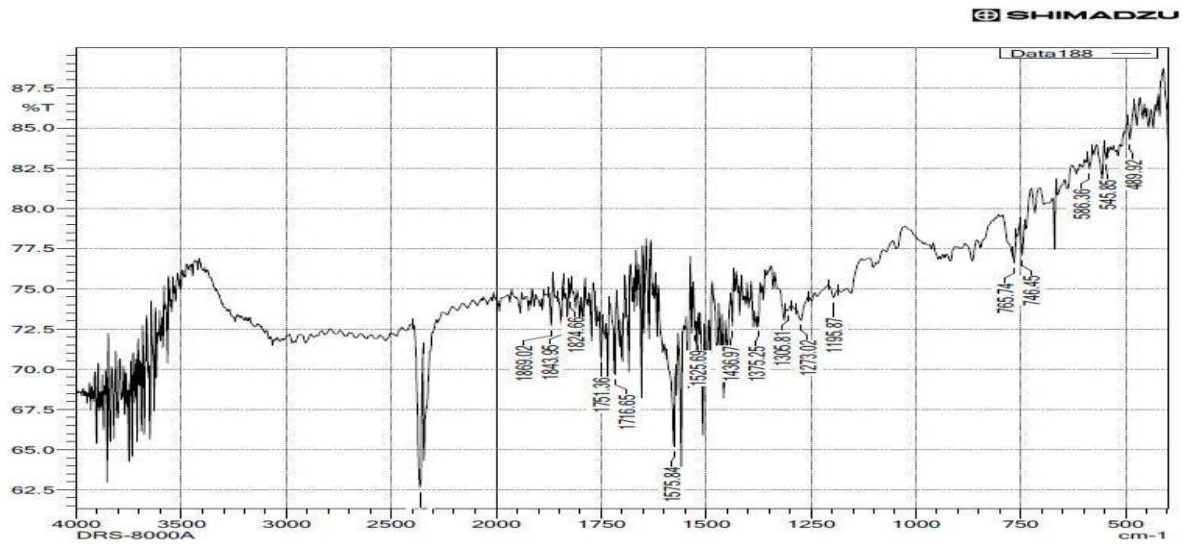


Graph 1. FTIR of Diclofenac Potassium

Table 2. Wavenumber with functional Group

Wave Number Range (cm^{-1})	Wave Number (cm^{-1})	Bonds
3500-3100	3250	(N-H) Stretching
1600-1475	1558.48	(C=C) stretching Aromatic
1350-1000	1248, 1350	(C-N) stretching
785-540	765.74	(C-Cl) Stretching
1720-1710	1716	(C=O) Ketonyl

Infrared spectrum of Diclofenac Potassium and Carbopol 940 (1:1)



Graph 2. Compatibility study of Diclofenac Potassium and Carbopol 940

Solubility study

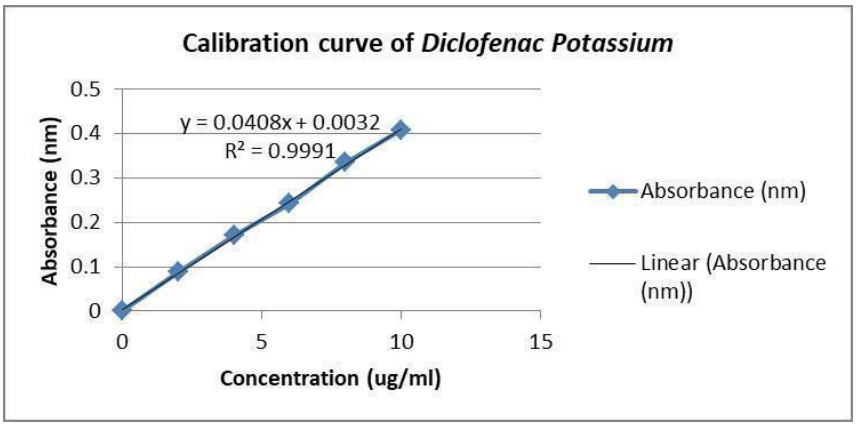
The solubility of Diclofenac Potassium was found to be very soluble in methanol. Besides this it has solubility in Ethanol, Tween 20, Span 20, Phosphate buffer 6.8 & 5.5 and slightly soluble in acetone.

Calibration curve of Diclofenac Potassium

Diclofenac potassium dilutions showed maximum absorption at λ 276 nm when scanned from 400 nm to 200 nm by UV spectrometer. The absorbance of the prepared solution was measured with a UV spectrophotometer at a wavelength of 276 nm. The drug followed Beers and Lamberts law between 0 to 10 µg/ml ranges.

Table 3. Absorbance values of Diclofenac Potassium in Phosphate buffer

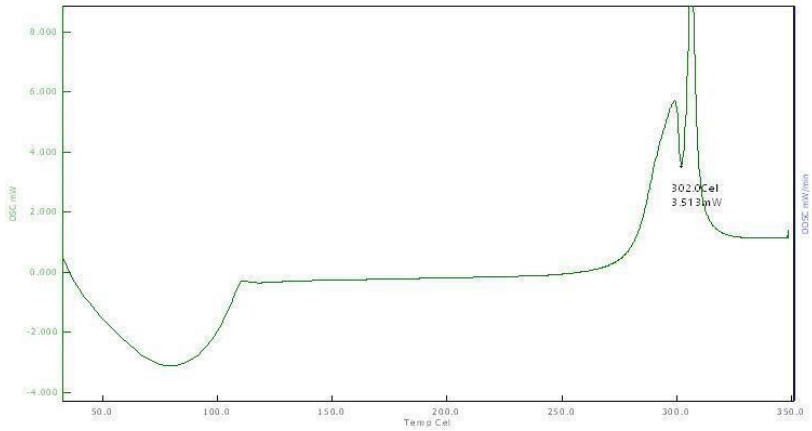
Concentration(µg/ml)	Absorbance (nm)
0	0
2	0.0875
4	0.1701
6	0.2419
8	0.3349
10	0.408



Graph 3. Calibration curve of Diclofenac Potassium

Differential Scanning Calorimetery (DSC)

Differential Scanning Calorimeter was employed to do the thermal analysis of pure drug. The sample (drug) was weighed directly on a perforated DSC aluminum pan and scanned in a dry nitrogen atmosphere at temperature range of 30-350^{0}C. A heating rate of 10°C/min was used and the obtained thermo-gram was observed for evaluation. Sample with wt. 1-2 mg was employed for testing[16]. Diclofenac Potassium showed sharp endothermic peak at 302^{0}C which indicates its crystalline nature.



Graph 4. DSC thermogram of Diclofenac Potassium

Physical evaluation

Table 4. Color, Homogeneity, Grittiness and Phase separation of Emulgels

Batch	Color	Homogeneity & consistency	Grittiness	Washability	Phase Separation
FT1	Pale Yellow	Excellent	No	Excellent	No
FT2	Pale Yellow	Excellent	No	Excellent	No
FP1	White	Excellent	No	Excellent	No
FP2	White	Excellent	No	Excellent	No
FC1	White	Excellent	No	Excellent	No
FC2	White	Excellent	No	Excellent	No

pH

Table 5. pH of Emulgel

Batch	FT1	FT2	FP1	FP2	FC1	FC2
pH	6.1±0.25	5.7±0.15	5.5±0.2	5.3±0.15	5.9±0.2	5.7±0.15

(*test was performed in triplicate n=3, ±Standard Deviation [SD])

Viscosity

Table 6. Viscosity of Emulgel

Batch	FT1	FT2	FP1	FP2	FC1	FC2
Viscosity (mPa.s)	20269±4	19178±3.5	19417±5.77	18540±5.5	20028±6.5	18978±3

(*test was performed in triplicate n=3, ±SD)

Drug Content

Table 7. Drug content of Emulgel

Batch	FT1	FT2	FP1	FP2	FC1	FC2
% Drug Content	95.05±0.1	96.24±0.3	96.72±0.3	95.12±0.5	97.77±0.3	98.64±0.25

(*test was performed in triplicate n=3, ±SD)

Spreadability

Table 8. Spreadability of emulgel

Batch	FT1	FT2	FP1	FP2	FC1	FC2
Spreadability (gm.cm/sec)	23.63±0.56	25±0.96	28.26±1.23	32.8±0.81	26.53±0.84	29.5±1.06

(*test was performed in triplicate n=3, ±SD)

Extrudability

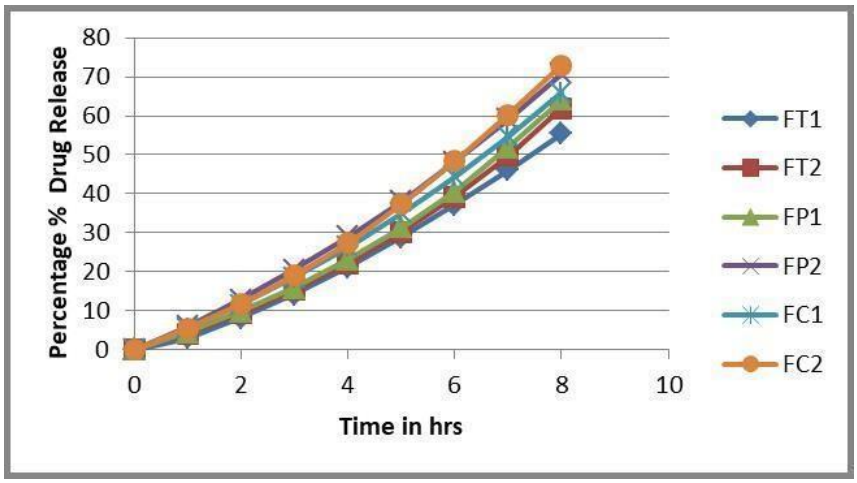
All formulations prepared were filled into collapsible aluminium tubes having standard caps and the ends were crimped shut to seal. The material was extruded from the tubes using enough pressure, and each formulation's extrudability was evaluated. All prepared formulations showed better extrudability.

***In-vitro* Drug Release Study**

Table 9. *In-vitro* Dissolution study of all Batches

Batch	FT1	FT2	FP1	FP2	FC1	FC2
Time in (Hrs.)	8	8	8	8	8	8
% Drug released	55.38±0.78	61.92±0.65	63.96±0.68	70.72±0.81	66.90±0.72	72.87±0.77

(*test was performed in triplicate n=3, ±SD)

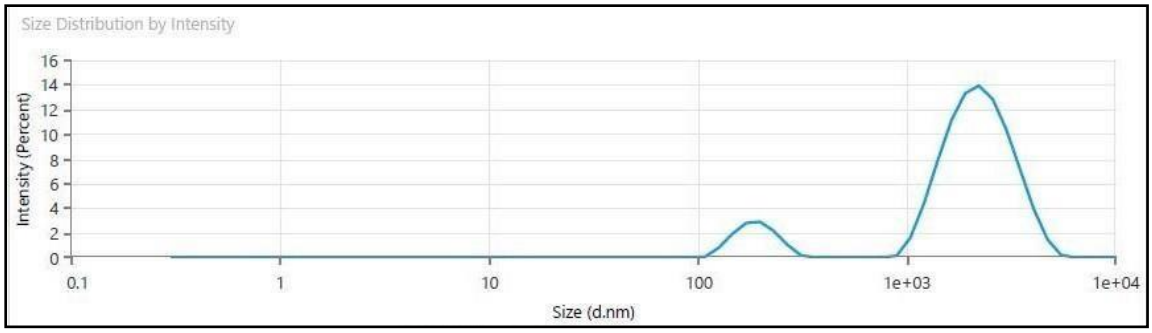


Graph 5. All formulations cumulative % drug release

The size and distribution of Globules in emulgel and Polydispersity Index(PDI)

Globule size of optimized batch came to be 1.176µm, also the average globule size of all emulgel batches measured under a digital microscope (LABOMED microscopy) with 40x magnification were 1µm–12µm. PDI was found to be

0.62, which is less than 0.7 indicating uniformity of the globule size distribution in emulgel. Hence the optimized batch was found to be stable.



Graph 6. Globule size of FC2 emulgel

Photomicrography

Perfect spherical globules of emulsion were observed from the photomicrograph. This study indicates a basic understanding about formation of emulsion and accomplishment of the method used.

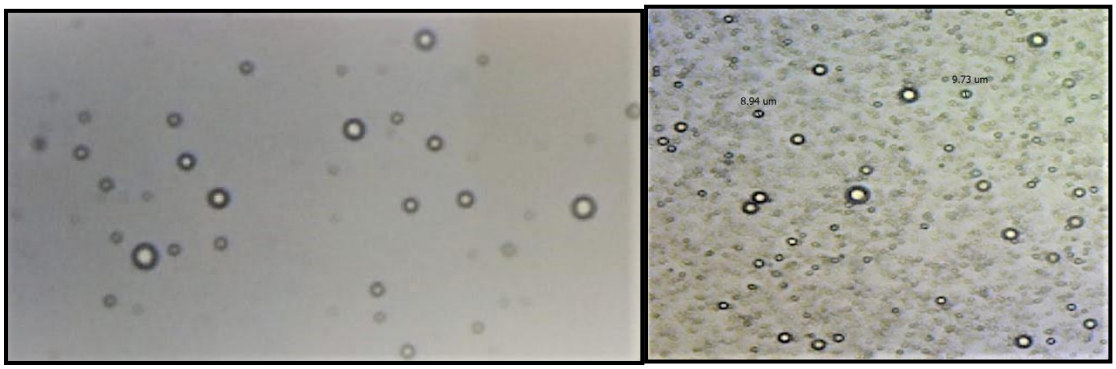
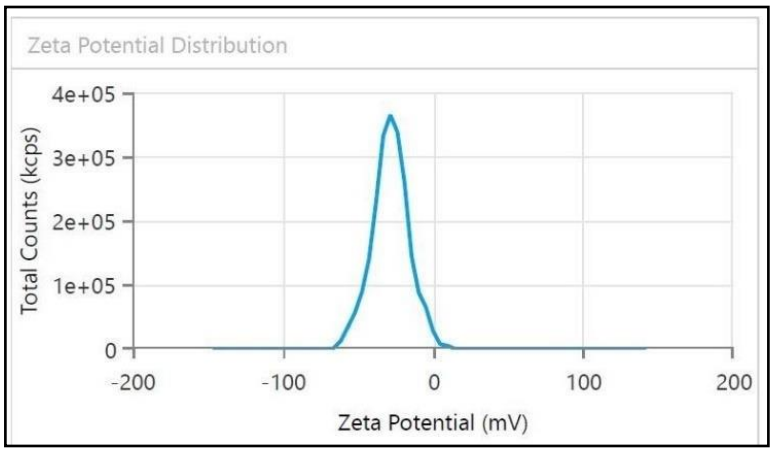


Figure 1. Photomicrograph of Emugel

Zeta potential

The optimized batch of emulgel formulation showed a zeta potential of **-28.1 mV**. This negative value of zeta potential indicates that electrostatic repulsion between particles prevents their agglomeration and thus stabilizing particle dispersion.



Graph 7. Zeta potential of (FC2) Emulgel

Stability Study

All the prepared emulgels showed to be stable during the storage of three months and no significant changes was observed in their physical characteristics, pH, viscosity, drug content and drug release.

Table 10. Stability study of Optimized Batch (FC2) for 3 months

Time	Appearance	Homogeneity	pH	% Drug Content	Viscosity (mPa.s)	% Drug Released
30 days	White	Excellent	5.7	98.61±0.135	18978±3	72.18±0.93
60 days	White	Excellent	5.7	98.53±0.155	18979±2	71.37±0.75
90 days	White	Excellent	5.8	98.46±0.120	18981±2	70.56±0.81

(*test was performed in triplicate n=3, ±SD)

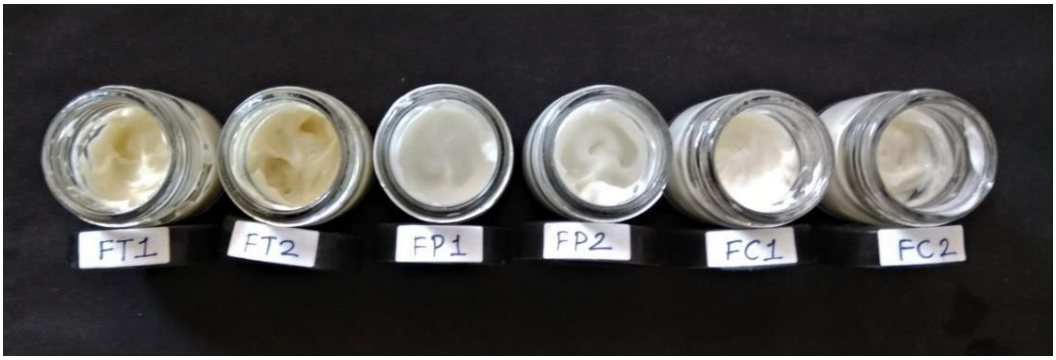


Figure 2. Formulation batches of emulgel

CONCLUSION

The study of formulating & evaluating Diclofenac Potassium emulgel was performed successfully. Diclofenac Potassium is a Non-steroidal anti-inflammatory drug used in the ankle sprain, osteoarthritis and spondylosis. The Diclofenac potassium emulgels were prepared using different essential oils as a penetration enhancer and also to give a synergistic effect in pain relief from arthritis.

The compatibility study showed that the drug and excipients are compatible with each other and therefore suitable for the dosage form. The FT-IR spectra have shown no interaction of polymer with the drug, which makes them compatible.

From the results we saw that the 6 formulations prepared, passed the evaluations with acceptable values. All the formulations showed good stability and homogeneity, while the pH values showed that they met the skin's requirements.

Emulgel (FC2) has shown better spreadability, drug content, viscosity and *In-vitro* drug release i.e. 72.87% in 8hrs of diffusion study. The PDI value showed that the globules are in uniformed state.

Though the study is not supported by the *in-vivo* study, the API and other supporting essential oils are well known for their activity in treating arthritic conditions.

Emulgel may be preferable to the already available topical formulations for the delivery of hydrophobic medications when taking into account the various dermatological topical formulations and their benefits and drawbacks.

Thus, based on this study, we conclude that the emulgel formulated is appropriate for topical delivery of drug and gives a new hope for easing pain in arthritis.

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Conflict of Interest: None

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