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FORMULATION AND EVALUATION OF DICLOFENAC EMULGEL USING NATURAL PERMEATION ENHANCERS

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ABSTRACT
Background: This study aimed to formulate a stable diclofenac emulgel and determine the penetration rate using different natural penetration enhancers. **Methodology**: Carbopol (934) and Hydroxypropyl methyl cellulose (HPMC) were utilized as gelling agents due to their favorable viscosity characteristics, which render them widely used for regulating the flow properties of topically administered dosage forms. In the research, diclofenac served as the active ingredient, while Carbopol (934) & HPMC (0.5%) acted as gelling forms to form a proper gel base. Emulsion contains Tween-20 (0.05%), PEG (0.6%), liquid paraffin (0.75%), span-20 (0.1%), along with natural penetration enhancers (0.3%) initially prepared gel base & the emulsion with natural penetration enhancers combine conjointly to shape an appropriate diclofenac emulgel. **Results and discussion:** According to the study, the improved batch exhibits a 95.08% release in 48 hours and remains stable for about three. The optimized batch exhibits 46.6% suppression in the microbiological assay, whereas the marketed treatment only demonstrates 32.3% inhibition. However, the skin irritation test results have no erythema or edema. The rabbits' skin showed no signs of discomfort. According to stability experiments, the synthesized emulgel's antifungal activity, rheological analysis, in vitro drug release, and physical appearance did not alter after three months of storage. **Conclusion**: Overall, it was recommended that, in contrast to cream, the emulgel formulation come after the drug release for controlled, long-term drug delivery.

INTRODUCTION

Diclofenac Emulgel is a gelled emulsion that effectively delivers hydrophobic or poorly soluble medications. Its analgesic and anti-inflammatory properties make it acceptable for patients [1]. Emulgels are used to transport hydrophobic medicines to the skin. Two available emulgels are Diclofenac-containing Voveran emulgel and Aerodics emulgel, containing diclofenac combined with other analgesics [2]. Topical medication administration uses skin, vagina, rectal, and ocular channels to deliver drugs locally. The skin is the primary channel, and emulsion gels with oil microdroplets are used to treat skin conditions. Topical drug delivery offers direct delivery to the affected site for long-term effects [3]. Emulgel formulations have a slower pharmacological change than solution forms, but

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topical administration increases drug concentration. Diclofenac, an anti-inflammatory drug, is used locally to treat osteoarthritis and rheumatic pain, providing both analgesic and anti-inflammatory benefits [4-5]. Oil-in-water and water-in-oil emulsions are widely used in dermatology due to their therapeutic properties and ability to transfer medications to the skin. They are elegant, easy to remove, and can be controlled by the formulator. Water-in-oil emulsions are used for emollient and dry skin treatments, while oil-in-water emulsions are suitable for general cosmetic applications [5].

MATERIALS AND METHODS

Materials

Diclofenac was obtained from Yarrow Chemical in Mumbai, while Lobe Chemicals in Mumbai provided the liquid paraffin, Tween 20, Span 20, propylene glycol, and Carbopol 934. Double-distilled water was used for every experiment. Every substance was of pharmaceutical quality and utilized exactly.

Preparation of gelled emulsion containing diclofenac

A gelled emulsion was made Carbopol 934 was dissolved in purified water while being constantly stirred at a moderate pace to create the gel-in formulations, then HPMC of required quantity was added and heated on a hot plate at 40-60°C for 30 minutes, later cool it down in a refrigerator at 2-4°Cover night, then the pH are adjusted to 5.5 to 6.5 using sodium hydroxide (NaOH) to obtained a proper viscous gel base that acts as a matrix for drug delivery. Span20 was dissolved in liquid paraffin to create the emulsion's oil phase. Tween 20 was dissolved to create the watery phase, penetration enhancers (Rosemary oil, Eucalyptus oil, castor oil) which acts as penetration enhancers that increase absorption of drug into skin, propylene glycol in addition with pure drug (diclofenac) in purified water, then while stirring constantly, the oily phase was added to the aqueous phase. The required quantity of initially prepared gel base is mixed with the obtained emulsion, which results in a satisfactory diclofenac gelled emulsion. As indicated in Table 1 [6], the following formula is designed for the formulation of emulgel.

CHARACTERISATION OF GELLED EMULSION [7]

Physical Features

The manufactured diclofenac emulgel formulations were visually examined for colour, odour, homogeneity, and consistency to ensure they fulfilled the required quality criteria.

pH Test: 10mg of emulgel was dispersed in 10 mL of distilled water. pH was measured using a calibrated pH meter (calibrated using the standard buffer solutions 4,.0 7.0, and 10)

Spreadability: 0.5mg of emulgel was placed between two glass slides (20cm×20cm). A 500g weight was applied on the top of the slides for 5 minutes. Afterward, the diameter of the spread emulgel was measured using a scale or ruler.

Rheological Study: The sample was placed in the container and allowed to settle at 25°C for 30 minutes. Viscosity was measured using a Brookfield viscometer equipped with spindle 6. The spindle was positioned in the middle of the emulgel without touching the jar's bottom. Viscosity was noted after ten minutes of spinning the spindle at 12 rpm.

In vitro release study [8-9]**:** Drug diffusion across a membrane is studied using the Franz diffusion cell. An appropriate diffusion medium, such as phosphate buffer, is added to the receptor chamber, which is continuously stirred and kept at 37°C ± 0.5°C. To make sure there are no trapped air bubbles, an egg membrane is positioned between the donor and receptor chambers. The aspirin emulgel formulation is then put into the donor chamber. Samples are removed from the receptor chamber via a sampling port and replaced with new medium at predetermined intervals. The system is sealed to avoid evaporation. The samples are analyzed using UV-Vis spectrophotometry to determine the drug's diffusion rate.

Drug Content Determination: The drug concentration in the diclofenac emulgel was measured using UV spectrophotometer. A known quantity of the emulgel was dissolved in methanol through sonication, and the absorbance was recorded after dilution at 275nm to determine the diclofenac content.

Skin irritation test: Each site (two sites per rabbit) received a 0.5 g sample of the test material on a 1"x1" (2.54x2.54 cm) piece of skin covered with a double layer of gauze. After the emulgel was reapplied, the animals returned to their cages. The emulgel was removed after a day, and any last traces were cleaned off the test locations using tap water.

Consistency check: For three months, the manufactured diclofenac emulgel formulations were kept out of direct sunlight in a collapsible tube at 25±2°C, 40±2°C, and 4±2°C. After being

stored, the samples were examined for physical characteristics, pH, rheological behaviour, drug release, skin irritation test, and microbiological assay.

RESULTS AND DISCUSSION

Visual Detection: The manufactured diclofenac emulgel formulations (F3) have a homogenous appearance and are smooth, white, and viscous. The drug's physical appearance and melting point matched the specifications in the USP (2002), confirming the purity of the sample.

Solubility tests showed that diclofenac was slightly soluble in water but more soluble in methanol, ethanol, acetone, and ether. The maximum absorption wavelength (λ max) for diclofenac was 275 nm. As indicated in Table 2, the physical appearance of the optimised formulation was observed.

Table 1: Formula for the emulgel preparation.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Drug	1%	1%	1%	1%	1%	1%	1%	1%
Carbopol	1%	1%	1%	1%	1%	1%	1%	1%
HPMC	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
PEG	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Tween 20	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%
Liquid paraffin	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%
Rosemary oil	--	0.03%	--	0.03%	--	0.03%	--	0.03%
Eucalyptus oil	--	--	0.03%	0.03%	--	--	0.03%	0.03%
Castor oil	--	--	--	--	0.03%	0.03%	0.03%	0.03%
Span 20	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Water	QS	QS	QS	QS	QS	QS	QS	QS

Table 2: Physical appearance of optimized formulation (F1 to F8).

S N	Characteristics	Appearance
1	color	white
2	odor	Mild, typically characteristics
3	consistency	Semi solid
4	Texture	Smooth and non-gritty
5	Homogeneity	Free from clumps and aggregates

Spreadability: According to the spreadability values, the emulgel can be readily distributed with a minimal amount of shear force. Formulation F3 demonstrated a spreadability of 2.7 cm/sec, which was better compared to the marketed gel. F3 showed the highest spreadability. As indicated in Table 3, the spreadability of the optimised formulation was observed.

Rheological studies: The prepared emulgel was viscosity measured using a Brookfield DV-E viscometer. Formulation F3 exhibited the highest viscosity, while F6 showed the lowest. The increased viscosity in F3 may be attributed to the lower concentration of liquid paraffin and emulsifying agents in the formulation. As indicated in Table-3, the viscosity of the optimised formulation was observed.

pH: The pH values of all the prepared formulations ranged from 5.4 to 6.4, which is suitable for avoiding skin irritation, as the normal pH of adult skin is around 5.5. As indicated in table-3 the pH of optimised formulation was observed.

Amount of drug present: The amount of drug in the diclofenac gelled emulsion formulations ranged from 80.78±1.82% to 98.75±1.20%, with formulation F3 showing the highest drug content at 98.75±1.20%. Additionally, F3 also exhibited the highest drug release among the formulations. The drug content of the optimised formulation is shown in Table 3.

Skin irritation: No signs of skin irritation were observed after applying the diclofenac emulgel to the rabbit's skin for 24 hours. The primary irritation test revealed that the emulgel formulation caused no irritation. The below figure represents the skin condition of rabbit before and after 24hr of emulgel application. As shown in figure-1, the skin doesn’t exhibit any irritation.

Table 3: pH, spread ability, Drug content and viscosity studies of optimized formulations.

Formulation batch	pH	Spread ability(cm)	Drug content %	Viscosity (centipoise)
F1	7.76 ± 0.55	1.2 cm	91%	85000
F2	6.72 ± 0.47	3.0 cm	95%	93000
F3	5.45 ± 0. 73	2.7 cm	93%	95000
F4	5.09 ± 0. 38	2 cm	92%	89000
F5	7.07 ± 0.53	3.5 cm	88%	87000
F6	6.46 ± 0.64	3.1 cm	89%	80000
F7	5.64 ± 0.76	3.3 cm	87%	91000
F8	6.65 ± 0.67	3.8 cm	90%	90000

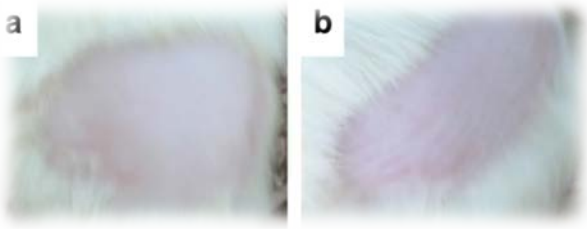


Figure 1: Skin irritation result of the optimised formulation.

Consistency check: By the International Conference on Harmonization's (ICH) guidelines, stability tests of the optimized formulation were conducted. Regarding pH, microbiological analysis, consistency, skin irritation test, and in vitro release research, it is evident that the emulgel formulation did not exhibit any significant changes. For three months, the formulation exhibits stability. Under all storage circumstances, no appreciable variations in the formulation's pH were noted for three months. The stability studies of the optimised formulation are shown in Table 4.

Diffusion kinetics: The several emulgel formulations of diclofenac and their in vitro release patterns are shown. All of the emulgel formulations exhibit improved drug release.

Table 4: Stability studies of optimised formulation (F1 to F8).

Sl. No.	Properties	Observation
1	Colour (initial)	white
2	Colour (after one month)	white
3	pH (initial)	6.2
4	pH (after one month)	6.2
5	% drug content	94%

Evaluation of diclofenac emulgel through 2^3 factorial design: A polynomial regression approach was employed to investigate the connection between the independent and response variables. This method uses a second-order model, which was expressed as an equation based on the 2n experimental design. The formula is:

$$Y = \beta 0 + \beta 1A + \beta 2B + \beta 3C + \beta 1\beta 2\ AB + \beta 1\ \beta 3\ AC + \beta 2\beta 3\ BC\ + \beta 1\beta 2\ \beta 3\ ABC$$

where the measured response is denoted by Y. The arithmetic mean answer is β0. The coefficients for factors A, B, C, AB, AC, BC, and ABC are β1, β2, β3, β1β2, β1β3, β2β3, and β1β2β3, respectively. These represent the percentages of Rosemary, Eucalyptus, and Castor oil and their interactions. The coefficients were determined using the following equation.

$$\beta = \frac{\Sigma\ XY}{2n}$$

Where, β: Coefficient, X: Penetration enhancers (A, B, C), Y: Response value (Percentage of drug release and viscosity range). n: Level.

It was discovered that the Penetration Time (PT) mathematical model was rather intricate. However, contour and 3D response graphs helped clarify the effects of the primary components and how they interacted with PT. According to the contour plot, which showed a linear connection, permeation enhancers like eucalyptus oil, compared to castor oil and rosemary oil, which can be held constant, may accelerate penetration. This was further demonstrated by the 3D response and surface plots, which showed that the emulgel's penetration time is influenced by the 0.3% permeation enhancer concentration.

Final equation in terms of coded factors

$$Effect\ of\ viscosity\ in\ suitable\ time\ period = +90000.00 - 1000.00A + 1250.00B + 2750.00C - 250.00AB - 250.00AC + 1000.00BC + 500.00ABC$$

$$Effect\ of\ percentage\ of\ drug\ release\ in\ suitable\ time\ period = +86.13 + 10.13A + 7.37B + 8.88C - 9.13AB - 7.13AC - 10.37BC + 11.13ABC$$

It is evident from comparing the effects of castor oil (C) and eucalyptus oil (B) on viscosity and the percentage of medication release over an appropriate period that higher eucalyptus oil concentrations result in a higher penetration percentage. The

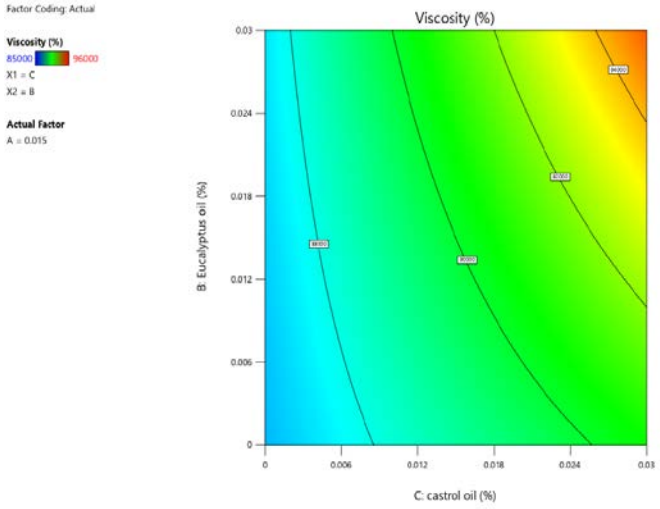
viscosity range and the drug release rate are also favourably impacted by other penetration enhancers, such as castor oil (C) and rosemary oil (A). The percentage of drug released within this range is linearly correlated with the amounts of castor oil (C) and eucalyptus oil (B) in Figure 2a. In particular, the viscosity range and drug release fall between 0% and 0.012% when the concentrations of eucalyptus oil (B) and castor oil (c) are between 0.03% and 0.012%. Furthermore, non-linear behavior is seen in viscosity and drug release between 0.03% and 0.024%. Consequently, more of the diclofenac emulgel enters within the appropriate time frame.

Optimum Formula

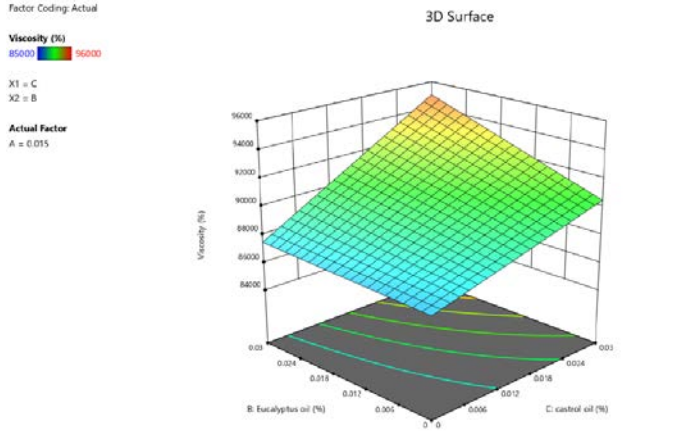
Larger doses of eucalyptus oil improve the penetration percentage when comparing the effects of eucalyptus oil (B) and rosemary oil (A) on viscosity and the percentage of medication release over an appropriate time period. The viscosity range and the percentage of drug release are also favourably impacted by the presence of other penetration enhancers, such as castor oil (C) and rosemary oil (A). The percentage of drug released within this range is linearly correlated with the amounts of castor oil (C) and eucalyptus oil (B) in Figure 2a. In particular, the viscosity range and drug release decrease between 0% and 0.012% when the concentrations of eucalyptus oil (B) and castor oil (C) are between 0.03% and 0.012%. Furthermore, between 0.03% and 0.024%, non-linear behaviour is seen in both viscosity and drug release. Consequently, a greater proportion of the diclofenac emulgel enters completely within the appropriate time frame. Formulation F3, which contained 0.3% eucalyptus oil, showed a good range of viscosity and a greater proportion of drug release within the desired time frame. This formulation is considered the best for diclofenac emulgel, offering results comparable to Formulation F8, which contains three penetration enhancers, including a novel natural one. However, because F3 employs a single, unique penetration enhancer, it was discovered to be more cost-effective.

Table 5: ANOVA for factorial model of viscosity

Source	Sum of Squares	D-f	Mean Square	F-value	p-value
Model	9.200E+07	**7**	1.314E+07	1	P>0.05
A-Rosemary oil	8.000E+06	1	8.000E+06	7	P<0.05
B-Eucalyptus oil	1.250E+07	1	1.250E+07	7	P<0.05
C-castor oil	6.050E+07	1	6.050E+07	7	P<0.05
AB	5.000E+05	1	5.000E+05	7	P<0.05
AC	5.000E+05	1	5.000E+05	7	P<0.05
BC	8.000E+06	1	8.000E+06	7	P<0.05
ABC	2.000E+06	1	2.000E+06	7	P<0.05
Pure Error	0.0000	0			
Cor Total	9.200E+07	7			



a) Counter surface plot



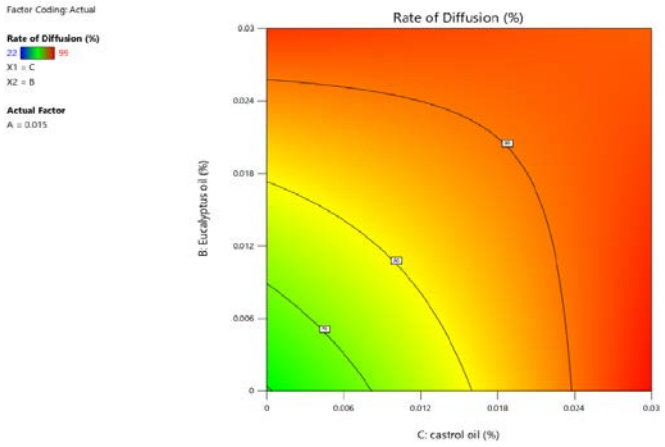
b) Response curve

Figure 2: (a) Counter plot, (b) Response surface plot of diclofenac emulgel.

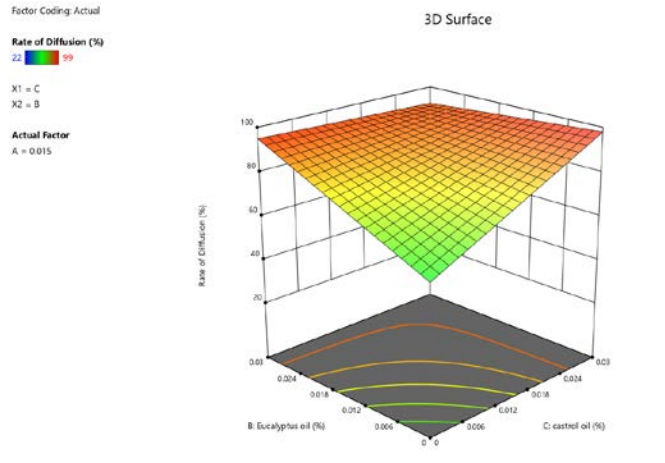
Table No: 6 ANOVA for factorial model of percentage of drug release:

Source	Sum of Squares	D-f	Mean Square	F value	P value
Model	4808.88	**7**	686.98	1	P>0.05
A-Rosemary oil	820.13	1	820.13	7	P<0.05
B-Eucalyptus oil	435.12	1	435.12	7	P<0.05
C-castor oil	630.13	1	630.30	7	P<0.05
AB	666.13	1	666.13	7	P<0.05
AC	406.13	1	406.13	7	P<0.05
BC	861.12	1	861.12	7	P<0.05
ABC	990.13	1	990.13	7	P<0.05
Pure Error	0.0000	0			
Cor Total	4808.88	7			

Factorial graphical representation of diclofenac emulgel in case of viscosity:



a) Counter surface plot



b) Response surface plot

Figure 3: (a) Counter plot (b) Response surface plot of diclofenac emulgel.

CONCLUSION

It was found that the formulation containing Eucalyptus oil was a clear, emollient oil that facilitated quick penetration. To develop diclofenac emulgel using a 2^3 factorial design, Eucalyptus oil was selected as the sole penetration enhancer. The optimized diclofenac emulgel formulation (F3), with 0.3% Eucalyptus oil, demonstrated an ideal viscosity range, maximum drug release, and better viscosity than other formulations, including commercially available ones. This optimum formula showed enhanced drug absorption, improved bioavailability, and rapid achievement of peak plasma concentrations. The study results confirmed that Eucalyptus oil enhanced penetration effectively, making it a promising penetration enhancer for emulgels containing poorly soluble drugs.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Chandra Sekhar Naik D was responsible for designing and planning the study and its objectives. Shaik Noor Mahammed reviewed the manuscript and edited the article. S. Vamsi, Mudigedu Samreen, and P. Hemalatha conducted the work, gathered data, and authored the manuscript.

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