

Development, Characterization, and *In vitro* Evaluation of Aceclofenac Emulgel

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Abstract

Aim: The present research work was aimed to develop a novel emulgel for aceclofenac to enhance the drug absorption by the topical application, which overcomes the demerits of oral dosage form and conventional gel system of aceclofenac. **Materials and Methods:** The emulgels were prepared with carbopol 934 as a gelling agent used in six different concentrations. Span 20 and Tween 20 were included as emulsifying agents in two different concentrations. Liquid paraffin was used as an oil phase, and methyl and propylparaben were included as preservatives. Ethanol was used to dissolve the drug for preparing the aqueous phase and Triethanolamine was added at the end of preparation, as quantity sufficient for pH adjustment. **Results:** All the formulated emulgels were screened for the parameters, namely, appearance, pH, rheology study, spreadability, swelling index, drug content, and *in vitro* drug release studies. The optimized formulation AG-4 showed 91.43% of drug release with sustained-release manner up to 6 h, and the particle size analysis reported good size range, and the emulgel was found to be nonirritant and nontoxic which was confirmed by HET CAM test. **Conclusion:** Aceclofenac can be successfully formulated as emulgel for better-sustained effect and can be a suitable alternative approach to the oral dosage forms for the management of arthritis.

Key words: Aceclofenac, carbopol 934, emulgel, viscosity

INTRODUCTION

Topical drug delivery system has been the most appropriate and convenient approach over the past two decades. Many conventional semisolid dosage forms such as creams, gels, and lotions found to have problems such as sticky in nature, lesser spreading coefficient, and stability issues.^[1]

To overcome such issues, a novel, stable topical drug delivery approach can be used to formulate successful drug delivery for hydrophobic drugs. In recent years, the concept of emulgel has gained significant interest in the topical drug delivery system.^[2]

An emulgel is a combination of emulsion and gel system, which is formulated by mixing emulsion either o/w or w/o with a gelling agent.^[3] Emulgel provides several benefits such as better loading capacity, stability, controlled release, improved patient compliance, avoids first pass metabolism, and gastric complications.^[4,5]

In the present investigation, a model anti-inflammatory drug aceclofenac was chosen

since its oral dosage form has demerits such as first pass metabolism, gastric ulcerogenic effects, and metabolic degradation.^[6]

Aceclofenac even though available in conventional gel form since it is a hydrophobic drug formulating it in emulgel makes it more fruitful way to deliver through the skin.^[7]

MATERIALS AND METHODS

Aceclofenac was procured from Remidex Pharma Private Ltd., Bengaluru. Carbopol 934, liquid paraffin, span 20, tween 20, methylparaben, propylparaben, ethanol, and Triethanolamine were purchased from HiMedia Laboratories, Mumbai.

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Methodology

Preparation of aceclofenac emulgel

The gel phase and emulsion phase were prepared separately. First, the gel phase was prepared by dispersing the different concentrations of carbopol 934 in distilled water and mixed by a mechanical stirrer. The emulsion phases were prepared by the addition of varying amounts of span 20 in varying quantities of liquid paraffin followed by mechanical stirring. The aqueous phase of emulgel was prepared by incorporating tween 20 in distilled water with continuous stirring, then methyl and propylparaben were added in propylene glycol, and aceclofenac (0.5 g) was dissolved in ethanol, and both the solutions were mixed with water phase of the emulsion. Both the water and oil phases were heated at 70–80°C for 20 min. Later, the oily phase was added to the aqueous phase by gentle stirring and allowed to cool. Finally, the prepared emulsion was mixed with gel base in a 1:1 ratio by manual stirring to get a clear emulgel of aceclofenac. The pH of all the prepared emulgels was adjusted by dropwise addition of Triethanolamine.^[8-10]

A quantity of 100 g of aceclofenac was prepared for all the six formulations and the formulation composition of aceclofenac emulgels is shown in Table 1.

Evaluation of emulgels

Drug-polymer compatibility by Fourier transforms infrared (FTIR) study

This study was carried out by FTIR spectroscopy to verify whether the drug and polymer are compatible with one another or not. It was evaluated by obtaining the IR spectral data of aceclofenac and physical mixture of aceclofenac with carbopol 934 using ATR-Bruker FTIR spectrophotometer. The interaction study was concluded from the interpretation of IR spectra.^[11]

Appearance

All the formulated aceclofenac emulgels were visually inspected for color, clarity, and homogeneity.^[12]

pH

The pH of all the formulated emulgels was measured by digital pH meter.^[13]

Rheological study

The viscosity of the emulgels was measured by Brookfield viscometer with “T” bar spindle at 5 rpm at a temperature of 25±2°C and the viscosity was recorded in cps.^[14]

Spreadability

An ideal topical gel should possess a sufficient spreading coefficient when applied or rubbed on the skin surface. This was evaluated by placing about 1 g of formulation on a glass slide. Another glass slide of the same length was placed above that, and a mass of 500 g was put on the glass slide so that the gel gets sandwiched between the two glass slides and spreads at a certain distance.^[15] The time taken for the gel to travel the distance from the place of its position was noted down. Spreadability was determined by the following formula.

$$S = \frac{M \times L}{T}$$

Where, S-Spreadability, g.cm/s
M-Weight put on the upper glass
L-Length of glass slide
T-Time for spreading gel in sec.

Swelling index

It was measured by placing 1 g of formulation in a porous aluminum foil and was placed in a 50 ml beaker containing 10 ml of 0.1 N sodium hydroxide. The samples were removed from beakers at different time intervals and put on the dry place for some time and reweighed.^[16]

The swelling index of emulgels was calculated using the following formula.

Table 1: Formulation design of aceclofenac emulgels

Ingredients	Formulation code					
	AG-1	AG-2	AG-3	AG-4	AG-5	AG-6
Aceclofenac	0.5 g					
Carbopol 934	0.5%	1%	1.5%	2%	2.5%	3%
Liquid Paraffin	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml
Span 20	0.2%	0.5%	0.2%	0.5%	0.2%	0.5%
Tween 20	0.2%	0.5%	0.2%	0.5%	0.2%	0.5%
Methylparaben	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
Propylparaben	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
Ethanol	5 ml					
Distilled water	q.s	q.s	q.s	q.s	q.s	q.s
Triethanolamine	q.s to adjust pH					

$$\text{Swelling index (SW) \%} = [(W_t - W_o)] / W_o \times 100$$

Where, (SW) % = Equilibrium percent swelling

W_t = Weight of swollen emulgel after time t,

W_o = Weight of emulgel before swelling at zero time, t.

Drug content

To determine the drug content of emulgel, 1 g of the formulation was diluted with 10 ml of phosphate buffer pH 7.4. The volumetric flask was shaken well followed by bath sonication for 2 min and the solution was filtered and scanned at 275 nm spectrophotometrically and the absorbance was noted. The amount of drug present in the emulgels was determined from the standard plot of aceclofenac.^[17]

In vitro drug release study

Release study of the emulgels was performed using modified Franz diffusion six cell apparatus which has donor and receptor compartment with a linear end for the solution withdrawal. A dialysis membrane, which was soaked overnight in phosphate buffer pH 7.4, was tied on the upper surface of the donor compartment. An amount of 12 ml of freshly prepared phosphate buffer pH 7.4 was put in receptor chamber. The dialysis membrane was sandwiched between the donor and receptor compartment. A magnetic bead was placed inside the receptor compartment by operating at 50 rpm and the apparatus assembly was maintained at $37 \pm 0.5^\circ\text{C}$. 500 mg of emulgel was placed on the dialysis membrane, which was mounted on the donor compartment. Aliquots of 1 ml were withdrawn at time intervals of every 30 min and diluted to 10 ml with phosphate buffer pH 7.4. The study was done for a time period of 6 h. All the solutions were scanned at 275 nm using UV Spectrophotometer. The amount of drug released was estimated, and the percentage cumulative drug release of the emulgels was calculated.^[18]

Particle size analysis

This study was done for optimized formulation of aceclofenac emulgel. The procedure involves dilution of 1 g of emulgel with distilled water which was observed under high resolution Biovis Particle Size Analyzer and the average size of the particles were measured in microns.^[19]

In vitro skin irritation study

For checking the skin irritation, an *in vitro* OECD recommended test was used known as Hen's Embryo Test-Chorioallantoic Membrane (HET-CAM test). In this method, hen eggs which are freshly laid were used and were embryonated to check the irritation on the developed chick embryo. Three groups were made, each containing three eggs.

Negative control: Here, the eggs were treated with 0.9% NaCl as a standard.

Test group: In this group, eggs were tested with the optimized formulation.

Positive control: In this, eggs were treated with 1% SDS (Sodium dodecyl sulfate) as an irritant for comparison with negative control and test.

Methods

The collected hen's eggs were placed on a metal tray which was kept in an incubator at temperature of $37 \pm 0.5^\circ\text{C}$ and relative humidity of $58 \pm 2\%$ required for the embryo development in the eggs. During incubation, the eggs were hand rotated 5 times in a day and this process was continued for 8 days. On 8th day, the incubated eggs were observed for the embryo growth and after confirmation the eggs were placed back to the incubator. On 9th day, the eggs were removed from the incubator and on the top surface; hole was drilled on the air sac of egg shell without harming the embryo. After making the hole, all the groped eggs were treated with respective solutions and observed for the signs of hemorrhage, coagulation, and lysis of blood vessels for a time period of 300 s (5 min).^[20,21]

The irritation effect was confirmed by getting the mean irritation score from the formula.

The irritation score (IS) formula is given below, followed by irritation score value with inference in Table 2.

$$\text{IS} = \frac{(301 - H)}{300} \times 5 + \frac{(301 - L)}{300} \times 7 + \frac{(301 - C)}{300} \times 9$$

Where, H-Hemorrhage.

L-Lysis of blood vessels.

C-Coagulation.

RESULTS AND DISCUSSION

FTIR spectroscopy

From the FTIR interpretation, it was observed that the peaks that are found both in the IR spectra of aceclofenac

Table 2: Irritation score value with inference for HET-CAM test

Irritation score	Inference
0–0.9	No irritation
1–4.9	Weak irritation
5–8.9	Moderate irritation
9–21	Severe irritation

and physical mixture of aceclofenac with carbopol 934 were found to be the same, and hence there was no interaction between the drug and polymer used. The FTIR spectral images of aceclofenac and physical mixture of drug and polymer are shown in Figures 1 and 2.

Appearance and pH

All the formulated aceclofenac emulgels were found to be white-colored translucent gels with good homogeneity. The pH of the emulgels was found to be in the range of 6.4–7.0 and was found to be satisfactory. The results of appearance and pH of the aceclofenac emulgels are discussed in Table 3.

Rheological study

The viscosity of the aceclofenac emulgels was found to be in the range of 438.6–622.4 cps. Results were reported in Table 3. From the study, it was observed that viscosity of the formulated emulgels was dependent on the concentration of carbopol 934. As the concentration of carbopol 934 was increased, the viscosity of emulgels was also increased.

Spreadability

The spreadability of all the emulgels was ranging from 11.54 to 42.24 g.cm/s. It was observed that formulations AG-4, AG-5, and AG-6 showed higher spreadability, which may be due to an increased concentration of carbopol 934. The spreadability test results are interpreted in Table 3, and spreadability test for aceclofenac emulgels is depicted in Figure 3.

Swelling index

Aceclofenac emulgels showed swelling index ranging from 15.92 to 30.08%, which was found to be satisfactory. The results of the swelling index are reported in Table 3.

Drug content

The drug content of all the formulated emulgels was in the range of 91.18–96.32%, and formulation AG-4 showed the highest drug content among the other five formulations. The results of the drug content are shown in Table 3.

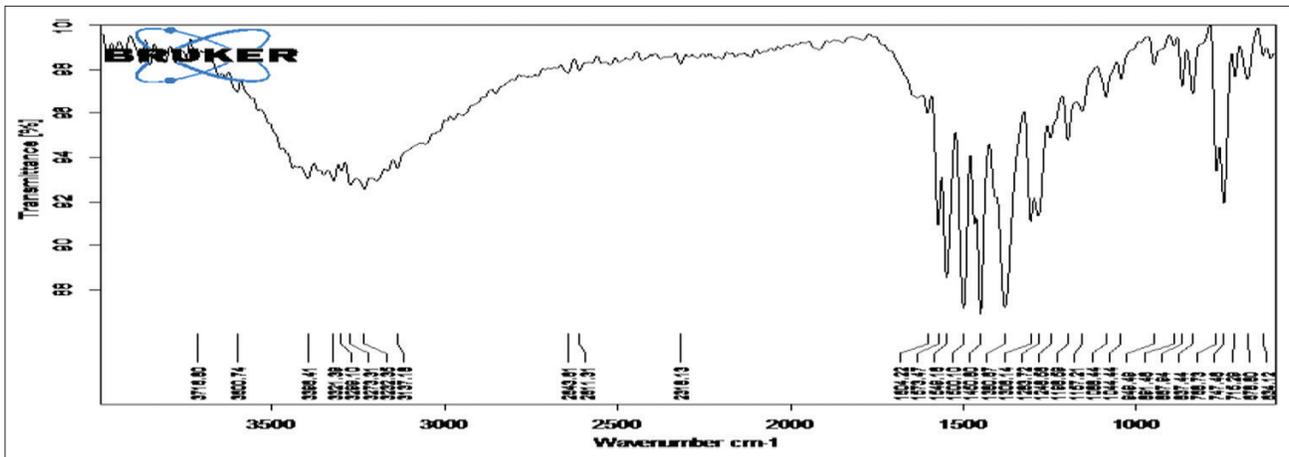


Figure 1: Infrared spectrum of pure aceclofenac drug

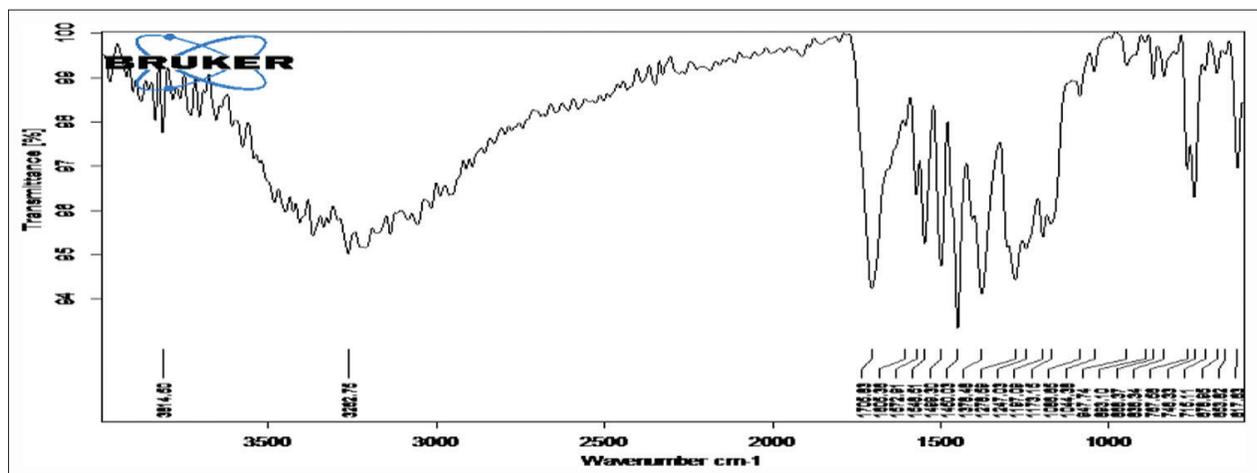


Figure 2: Infrared spectra of aceclofenac and carbopol 934 physical mixture

In vitro drug release study

From the drug release study, it was observed that formulations AG-1, AG-2, AG-3, and AG-4 showed the drug release from 72.54 to 91.43 up to 6 h. This might be due to the increase in the concentration of carbopol 934 from 0.5 to 2% along with increase in the amount of emulsifying agents added. The emulgels AG-5 and AG-6 showed drug release of 87.26 and 84.33 up to 6 h which may be due to the fact that increased concentration of carbopol 934 (2.5%) in

AG-5 and AG-6 (3%) was led to increasing the viscosity of these formulations which in turn makes the diffusion of drug through the dialysis membrane slower. Among all the six emulgels formulated, formulation AG-4 containing 2% of carbopol 934 and 8% of liquid paraffin showed highest drug release of 91.43% and was optimized as the best and was subjected for particle size analysis and *in vitro* skin irritation study. The drug release profile of aceclofenac emulgels is depicted in Figure 4.



Figure 3: Spreadability test for aceclofenac emulgels

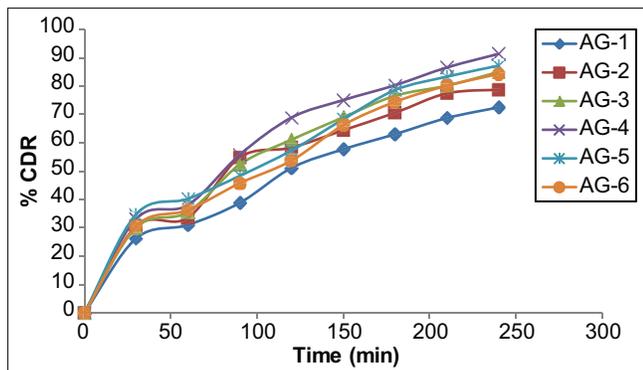


Figure 4: Drug release profile of aceclofenac emulgels

Particle size analysis

The mean particle size of emulgel AG-4 was in the range of 0.5–25 μ which was found to be good for drug penetration through the skin when applied topically. The data of particle size analysis are shown in Figure 5.

In vitro skin irritation

From the HET-CAM test, it was observed that chick embryo treated with 1% SDS caused lysis of blood vessels and hemorrhage with mean irritation score of 16.21 indicating severe irritation whereas there were no signs of irritation found with 0.9% NaCl and the optimized formulation, AG-4 showed mean irritation score of 0.04 with no signs of blood vessels lysis, hemorrhage, and coagulation after a time period of 5 min in HET-CAM test when compared with positive control and negative control, confirming that the optimized emulgel was nonirritant and nontoxic in nature. The images of the HET-CAM test are depicted in Figure 6.

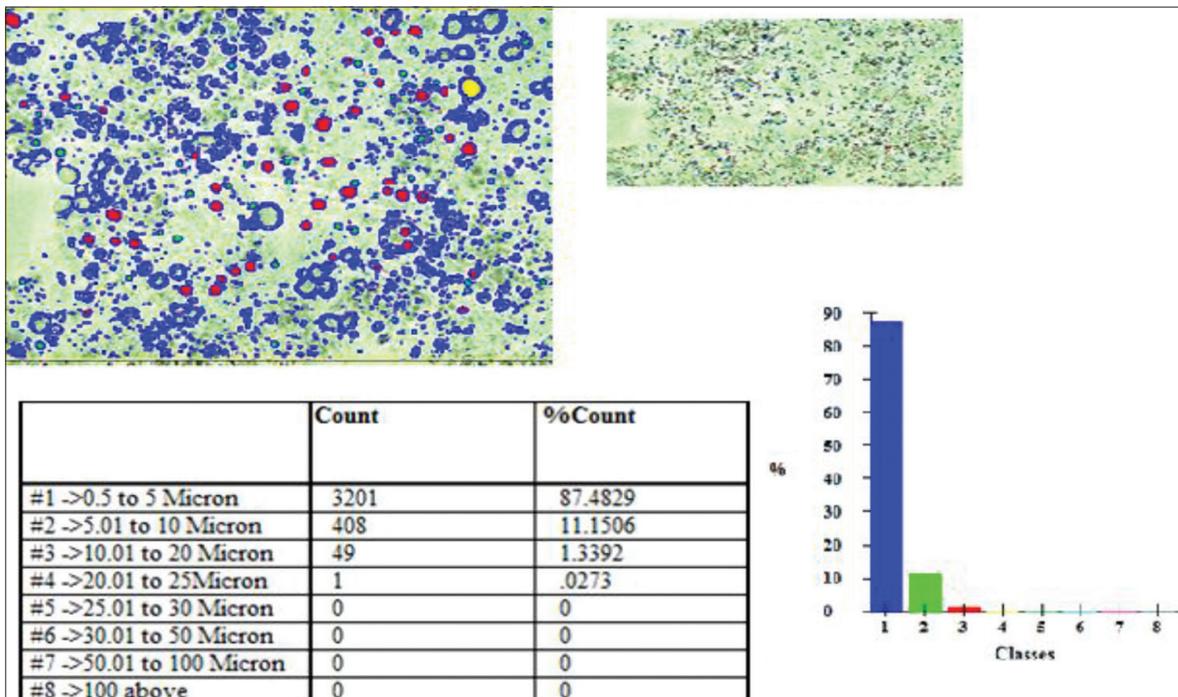
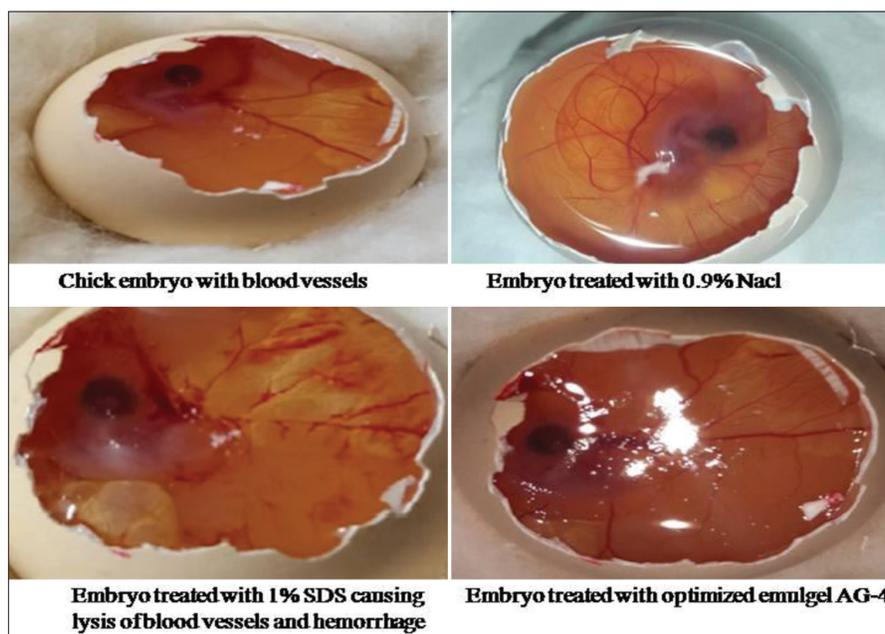


Figure 5: Particle size data for optimized emulgel formulation AG-4

Table 3: Results of appearance, pH, spreadability, swelling index, and drug content of aceclofenac emulgels

Parameter	Formulation code					
	AG-1	AG-2	AG-3	AG-4	AG-5	AG-6
Appearance	White translucent gel					
pH	7.0	6.7	6.4	6.5	6.5	6.7
Spreadability (g.cm/s)	21.25	14.16	11.54	40.43	42.24	36.8
Viscosity (Cps)	438.6	504.8	552.4	568.2	611.6	622.4
Swelling index (%)	28.44	23.58	27.77	30.08	15.92	20.53
Drug content (%)	91.18	93.80	94.37	96.32	95.22	92.46

**Figure 6:** HET-CAM test for *in vitro* skin irritation study

CONCLUSION

Aceclofenac emulgels were prepared using carbopol 934 as gelling agent with the aid of liquid paraffin as oily phase and span 20 and tween 20 as emulsifying agents. The prepared emulgels were evaluated for formulation parameters, and from the drug release study, the formulation AG-4 was optimized as best with higher drug release, and the formulation showed acceptable mean particle size with no signs of skin irritation that was confirmed by the HET-CAM test. Based on the results obtained with the current research, it can be concluded that emulgels will be better promising drug delivery approach for aceclofenac to enhance and achieve controlled drug release in comparison to its oral dosage forms and conventional gels.

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