RESEARCH ARTICLE

INTERNATIONAL JOURNAL OF RECENT RESEARCH IN PHARMACY

IJRRP

FORMULATION AND DEVELOPMENT OF DRUG LOADED ACECLOFENAC EMULGEL FOR TOPICAL DRUG DELIVERY SYSTEM

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Received- 25/November/2020 **Revised-** 05/December/2020 **Accepted-** 12/December /2020 **Published-** 31/December/2020

ABSTRACT

For the delivery of hydrophobic medicines, emulgels has emerged as a promising drug delivery method. The purpose of the study was to prepare aceclofenac emulgel, an NSAID, with the use of Carbapol 934 as a gelling agent. The emulsion was prepared, and the gel base was incorporated. For rheological tests, spreading coefficient studies, power of bioadhesion, skin irritation studies, *in-vitro* release, *ex-vivo* release studies, anti-inflammatory activity and analgesic activity, the formulations were evaluated. Emulgel is one of the new NDDS technologies used for dual control release for topical use of emulsion gel. The consistency of the emulsion, when incorporeal into gel, is increased. The overall objective of the current research was the formulation and evaluation of aceclofenac emulgel. Which will improve the drug's skin penetration relative to the drug's existing commercialised preparations. In this analysis, five types of gelling agents were used to produce emulsifier formulations of aceclofenac: carbopol 934, hydroxyl propyl methyl cellulose, sodium carboxyl methyl cellulose, and sodium alginate. The release of the drug via a dialysis membrane from all gelling agents was assessed. Concerning colour, homogeneity, consistency, and pH value, all gels showed reasonable physical properties. The formulation of carbopol demonstrated superior drug release among all gel formulations than that of Na CMC, HPMC & Sodium alginate. Polymer can be used as emulsifiers and thickeners because the gelling ability of these compounds allows stable emulsions and creams to be produced by reducing surface and interfacial tension while increasing the aqueous phase's viscosity. Indeed, the presence in the water process of a gelling agent transforms a classical emulsion into an emulgel. On novel vesicular systems as well as on traditional systems, these emulgel have significant advantages in various aspects. The effect can be potentiated by different permeation enhancers, so emulgels can be used in current systems as improved topical drug delivery systems. The use of emulgels can be extended in analgesics and antifungal drugs.

KEYWORDS: Aceclofenac, Topical Drug Delivery System, Emulgel

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INTRODUCTION

The treatment of disease has been achieved in recent decades by administering drugs to the human body via various routes, including oral, sublingual, rectal, parental, etc.

Generally, the topical drug delivery system is used where these drug administration systems fail or in local skin infections such as fungal infections. This drug delivery route has gained popularity because it prevents oral administration-related first pass symptoms, gastrointestinal inflammation, and metabolic degradation. Just 25-45 per cent of the orally administered dose enters the blood circulation due to pre-systemic metabolism [1, 2, 3]. The gel formulations were suggested as topical application in order to bypass these drawbacks.

Topical distribution of drugs can be described as the application to the skin of a medication containing formulation to treat cutaneous formulation disorder directly. Dermatological products applied to the skin vary in formulation

and range from liquid to powder consistency but the most popular products are semisolid preparations includes ointments, creames, pastes, gels [4, 5]. Topical gel formulations provide medications with an appropriate delivery mechanism since they are less greasy and can be extracted quickly from the skin. The release of the drug from the formulation and permeation through the skin to enter the target tissue requires percutaneous absorption of drugs from the topical formulation [6]. The release of the drug from topical preparations depends on the physicochemical properties of the vehicle and the drug employed.

Topical Delivery Includes Two Basic Types of Products

External topical spread sprayed or otherwise applied on the skin tissues to cover the region affected. Internal topical that is applied orally, vaginally or on rectal tissue to the mucous membrane for local operation.

Aceclofenac is chemically [[[2- [(2, 6, Dichloro-phenyl) amino] phenyl] acetyl] oxy] acetic acid [7], is a new orally effective NSAID of the phenyl acetic acid group. It has excellent anti-inflammatory, analgesic, & anti-pyretic properties. Ongoing oral administration of aceclofenac results in ulcerative flatulence, indigestion (dyspepsia), vertigo, dizziness, dyspnoea, stomatitis, itching (pruritis) [8, 9]. When a drug protocol is topically introduced, the drug passively diffuses from its carrier or vehicle. A remarkable aspect of the pharmacology of aceclofenac is that it promotes the synthesis of glycosaminoglycans (GAGs), which in turn improves NSAID skin permeation [10]. When delivered in the form of a topical gel, aceclofenac can reduce local inflammation.

Therefore, topical administration of aceclofenac can be effective for local inflammation or body pain, and also eliminates the side effects associated with oral therapy. A topical ointment containing aceclofenac has therefore been prepared [11]. It is known that gel formulations are superior to any other topical formulations since these systems have a better application of topical formulation. The aim of the current study was to develop aceclofenac gel formulations using four types of gelling agents: carbopol, hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (Na CMC) and sodium alginate. The effect of the propylene glycol penetration enhancer on release has been studied. The gels were evaluated for physical appearance, rheological behaviour, drug release. The drug release from all gelling agents through a standard cellophane membrane was evaluated using Keshary-Chien diffusion cell.

MATERIALS AND METHODS

Aceclofenac was a gift sample obtained from Akums Pharma, Haridwar, Uttarakhand, India. Carbopol 934, Sodium alginate Sodium CMC, HPMC 50, Light liquid paraffin, Tween 80, Propylene glycol, Ethanol, Methyl paraben was obtained from College Campus.

Standard graph of Aceclofenac in pH 7.4 Buffer

100 mg of accurately weighed aceclofenac was dissolved in 10 ml of 0.1N NaOH and up to 100 ml of volume was formed. This is regarded as the primary stock and, as shown in **Figure 1**, contains 1mg/ml of substance. 10ml of solution was diluted to 100ml with 0.1N sodium hydroxide from the primary stock. This is called secondary stock and contains a drug of 100µg/ml. 1 ml was diluted again from the secondary stock to 10 ml to get 10 µg/ml of medicine.

Table 1: Calibration Curve of Aceclofenac

S. No.	Concentration (µg/ml)	Absorbance
1	5	0.086
2	10	0.204
3	15	0.337
4	20	0.443
5	25	0.602
6	30	0.729
7	35	0.852

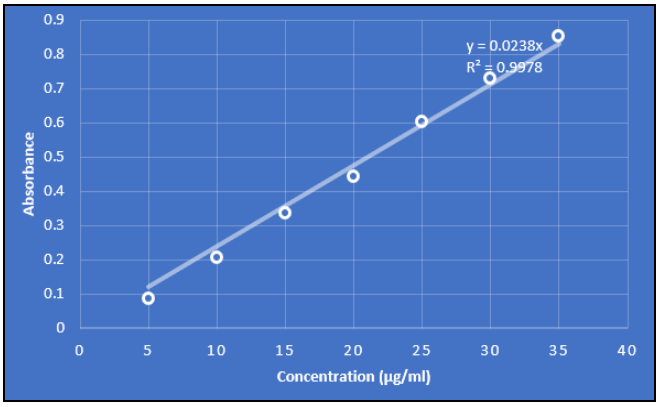

Figure 1: Calibration of Aceclofenac

The spectrometer was then scanned to obtain λ_{max} using 0.1N sodium hydroxide as a blank between 200-400 nm. Aceclofenac's maximal λ_{max} was detected at 273 nm by a UV-spectrophotometer. The graph was plotted based on the absorbance of

the dilutions by taking absorbance on the y-axis and x-axis concentration [4].

Formulation

Preparation of Emulsion Preparation of Aqueous Phase

The aqueous phase of the emulsion was prepared by dissolving tween 80 in purified water.

Preparation of Oil Phase

Methyl Paraben and Propyl Paraben were dissolved in propylene glycol and both solutions were combined with the aqueous process and dissolved in ethanol as a drug. Both the oily and aqueous phases were heated to 75 °C separately. In the aqueous phase, the oil phase was then added with continuous stirring until cooled to room temperature.

Preparation of Gel

The gel bases were prepared by separately dispersing different polymer concentrations in distilled water with continuous stirring using a mechanical shaker at a moderate level. Using triethanolamine, the pH of both formulations was changed to 6-6.5.

Preparation of Emulgel

The obtained emulsion was mixed with the gel with gentle stirring to obtain the emulgel.

Evaluation of Aceclofenac Emulgel

Physical Examination

For their colour, homogeneity, consistency, grittleness and phase separation, the prepared emulgel formulations were visually inspected.

Measurement of pH

Using digital pH metres, the pH of the emulgel formulations was calculated. In 100 ml of distilled water, 1gm of emulgel was dissolved and held on one side for 2 hours. The pH of each formulation was determined in triplicates and the mean values were estimated.

Table 2: Physical Examination of Emulgel

S. No.	Formulation code	Colour	Phase separation	Homogeneity	Consistency
1	F1	White	None	Good	Better
2	F2	White	None	Good	Better
3	F3	White	None	Good	Better

The pH of the formulations was considered adequate in the 6.32 to 6.83 range to prevent the risk of skin irritation. The result is shown in Table 3. The optimised formulation (F2) pH was noted to be 6.83. As a function of time, there was no essential shift in pH values for all formulations.

Table 3: pH of Emulgel Formulations

S. No.	Formulation	pH
1	F1	6.32
2	F2	6.83
3	F3	6.56

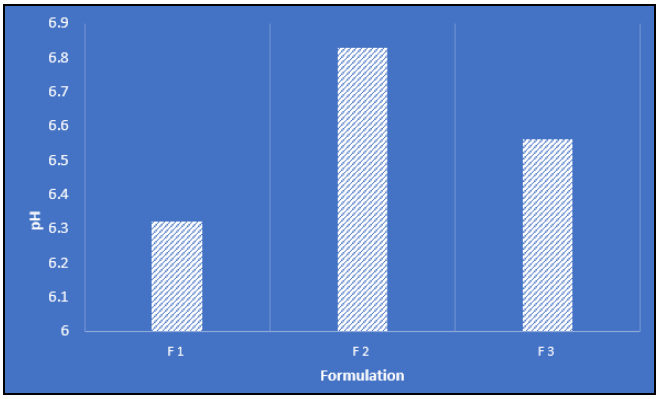

Figure 2: pH of Emulgel Formulation

Drug Content Determination

Weigh accurately 1gm of aceclofenac topical emulgel and it was dissolved in 100 ml of 0.1 N NaOH. The volumetric flask kept for 2 hours and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered. The absorbance was measured spectrometrically at 375 nm after appropriate dilution the drug content was determined using following formula.

Drug content= (concentration× dilution factor× volume taken) × conversion fact

The mean percent of drug content was contained in emulgel formulations (F-1 to F-3), respectively (87.32 percent, 89.08 percent, 86.87 percent). 89.08 percent higher drug content than other formulations were seen in F2 **Table 4**.

Extrudability

Clean, lacquered aluminium collapsible tubes with a 5 mm nasal tip opening were filled with the prepared emulgel formulations. Extrudability was then defined when a constant load of 1 kg was put over the pan by measuring the quantity of gel extruded through the tip.

Extrudability of prepared materials emulgel was calculated by using following formula.

Extrudability= Amount of gel extruaded from the tube / Total amount of gel filled in the tube × 100

Using a weight of 20 gms, the extrudability of formulations was calculated according to the method specified. Most of the gels displayed outstanding properties of extrudability. (+ fair, ++ average, +++ outstanding). The results of extrudability studies are summarised in **Table 5**.

Table 4: Drug Content Analysis of Emulgel Formulations

S. No.	Formulation	% Drug Content
1	TMF1	87.32
2	TMF2	89.08
3	TMF3	86.87

Table 5: Extrudability of Emulgel Formulations

S. No.	Formulation	Extrudability
1	F1	++
2	F2	+++
3	F3	++

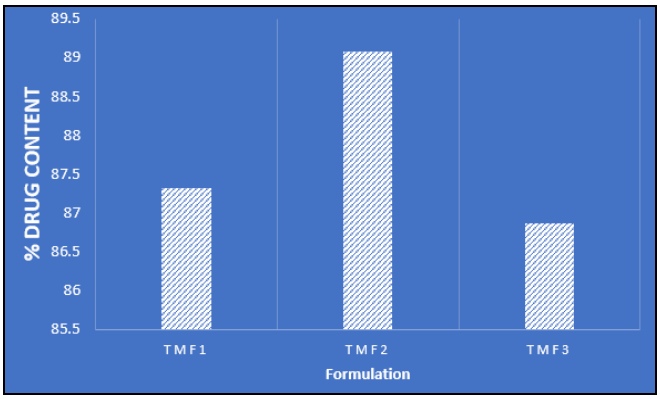

Figure 3: % Drug Content of Emulgel

Measurement of Viscosity

A Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 63 was used to create the viscosity of the formulated batches. The formulations were briefly applied to the beaker and allowed to settle at the assay temperature (25±1 °C) for 30 minutes before the measurement was taken. The spindle was lowered perpendicular to the emulgel centre to ensure that the spindle did not hit the bottom of the jar and rotated for 10 min at a speed of 50 rpm and the viscosity reading was noted. In the 1566.732 to 2182.674 cps range, the average formulation viscosity is. The viscosities of all gel formulations are shown in **Table 6** and were found to decrease by increasing the shear rate, i.e. the pseudo plastic behaviour was noted.

Table 6: Viscosity of Emulgel Formulations

S. No.	Formulation	Viscosity (CPS)
1	F1	1566.732
2	F2	1784.214
3	F3	2182.674

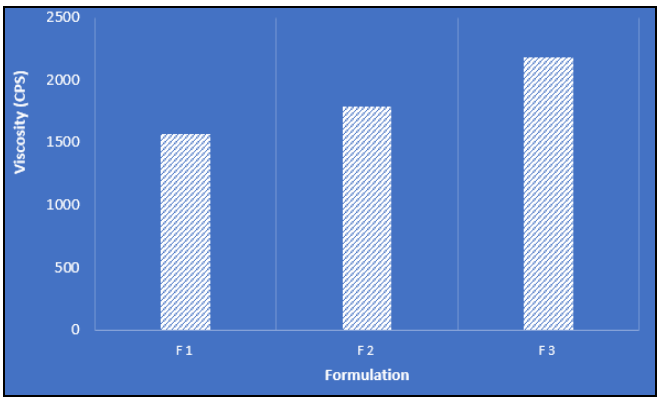

Figure 4: Viscosity of Emulgel

Spreadability

Spreadability is calculated by the apparatus proposed by Mutimer *et al.*, (1956), which is properly adjusted and used for analysis in the laboratory. It consists of a wooden block at one end, which is provided by a pulley. By this approach, spreadability is determined on the basis of 'Slip' and 'Drag' features of emulgels. On this block, a ground glass slide is fixed. On this ground slide, an excess of emulgel (about 2 gm) under analysis is positioned. Between this slide and another glass slide with the fixed ground slide dimension, the emulgel is then sandwiched and supplied with the hook.

A 1 kg weight is put for 5 minutes on the top of the two slides to expel air and to provide a uniform emulgel film between the slides. Excess is scratched off from the edges of the emulgel. The top plate is then subjected to an 80-gram tug. The time (in seconds) taken by the top slide to cover a distance of 7.5 cm should be noted with the aid of the string attached to the hook. Better spreadability implies a shorter interval. Using the formula, spreadability was determined by,

$$S = M.L/T$$

Where, S = Spreadability, M = Weight tied to upper slide, L = Length of glass slides, T = Time taken to separate the slides completely from each other.

Spreadability values ranging from 14.56-16.21 g.cm/s were found in the emulgel agent. The spreading coefficient of different formulations of emulgel is given in table 7 below.

Table 7: Spreadibility of Emulgels Formulations

S. No.	Formulation	Spreadability (g.cm/s)
1	F1	14.56
2	F2	16.21
3	F3	15.18

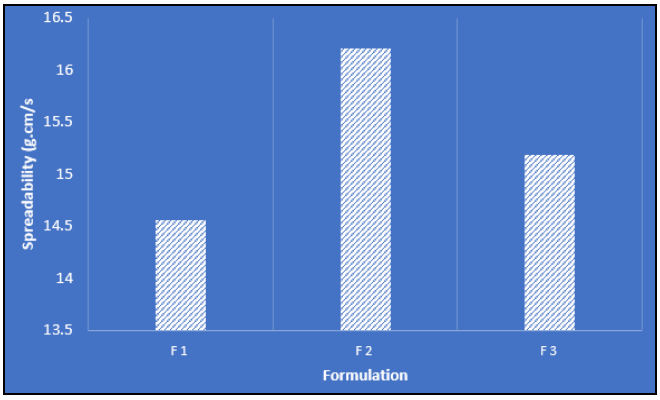

Figure 5: Spreadibility of Emulgel

In-vitro Drug Release Study

In-vitro drug release tests of emulgel were performed using the dialysis membrane in modified diffusion cells. The membrane was soaked in phosphate buffer solution (PBS) pH 7.4 for 9-12 hours and carefully clamped to one end of the dialysis cell's hollow glass tube. Emulgel (300 mg) was then distributed on the dialysis membrane evenly. As shown in **Figure 6**, 100 ml of pH 7.4 phosphate buffer solution used as a dissolution medium was applied to the receptor compartment.

Table 8: *In-vitro* Drug Release

S. No.	Time (min)	F1	F2	F3
1	0	0.00	0.00	0.00
2	5	8.10	5.20	7.18
3	10	10.40	12.56	11.31
4	15	22.93	26.54	28.92
5	20	28.00	31.81	34.68
6	30	34.77	34.30	47.65
7	60	50.97	48.61	53.23
8.	120	68.74	59.69	65.56
9.	240	75.77	73.32	78.19

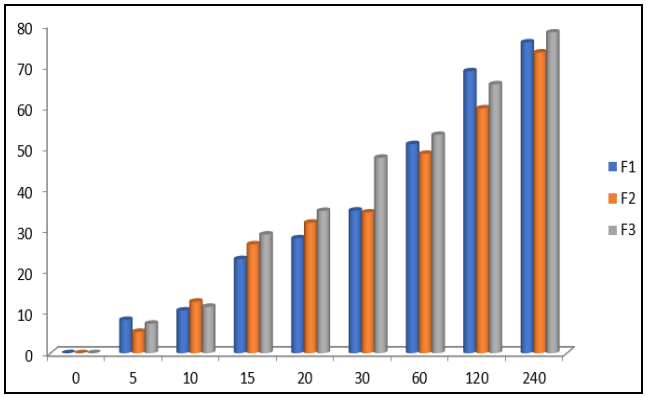

Figure 6: *In-vitro* Drug Release Profile

This entire assembly was kept on a magnetic stirrer and continuously stirred the solution on the receptor side using a magnetic bead and held the cell temperature at 37±0.5 °C. At appropriate time intervals, the sample (10ml) was removed and replaced with equivalent quantities of new dissolution media. Samples and the cumulative percentage of drug release were analysed spectrometrically at 273 nm [6].

RESULTS AND DISCUSSION

As a model drug, emulgel was prepared by taking aceclofenac. The gels tended to be transparent when all of the formulations were physically tested, indicating that the substance was fully solubilized rather than dispersed/ suspended in the gel matrix. Impact of 934P carbomer conc. It's been studied. Subject to viscosity measurement, a total of three formulations were prepared. Conc 1.5 percent was found to be ideal for its fast spreadability, as well as washability. With a 2% conc. too much viscosity has been detected, so that it can not be easily distributed. Conc. at 1 percent it is very poor in viscosity, so it is not applicable.

The *in- vitro* drug release analysis for the F2 batch was found to be optimal. After a four-hour release analysis, drug release was found at 88 percent. Different kinetic study models were applied to the in vitro release results. The minimum value of some of the square of residue was considered to be the first order kinetic model (SSR). As a water-soluble base, polyethylene glycol 400 was used to make the emulgel readily washable. Tween-80 is used as a surfactant to emulsify the emulsion of drug entrapment. Various models have been studied for SSR. Aceclofenac emulgel formulation follow first order kinetics model.

CONCLUSION

An attempt was made in this study to prepare and describe the emulsifier of aceclofenac. It was concluded from the results that aceclofenac emulgel formulations prepared with various gelling agents exhibited reasonable physical and drug release properties. Formulation F2 showed further release, so the optimised formulation was chosen for this formulation. Since emulgel emerged as a modern and innovative technique for the delivery of topical drugs. So, for hydrophobic drugs, it can be very effective.

ACKNOWLEDGEMENT

Authors are thankful to Dr. Pushpendra Kannojia (Principal), BIU College of Pharmacy, Bareilly International University, Bareilly for his valuable suggestion in writing this paper.

CONFLICT OF INTEREST

None

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How to cite this article:

Suman, Tiwari SP, Bijauliya RK and Singh PK. "Formulation and development of drug loaded aceclofenac emulgel for topical drug delivery system". International Journal of Recent Research in Pharmacy (IJRRP), 2020; 1(1A), pp. 223-228.