

## Formulation and Evaluation of Aceclofenac Pain Relieving and Skin healing Nanoemulgel for Diabetic Persons

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### ABSTRACT:-

It is phenyl acetic acid derivative developed as anti-inflammatory agent. It has analgesic anti-inflammatory antipyretic and skin healing like actions like other NSAIDs. It is recommended in long term treatment of rheumatoid arthritis and Diabetes Mellitus, osteoarthritis and enclosing spondylitis. It is also useful acute miscue skeletal disorder post operative pain and dysmenorrhea. Aceclofenac pain relieving and skin healing combined gel was developed in different formulation methods. By employing different grades of polymers such as HPMC, Carbopol 934 etc. Aceclofenac preparations come in a variety of forms. However, the diabetic patient did not see any improvement with these gels. The formulation was assessed for a number of physical characteristics, including pH, spreadability, skin irritation, drug release excludability, and drug release processes. This gel has a maximum medication release of eight hours. The goal of this research is to develop a skin-healing and pain-relieving gel for diabetics using aceclofenac. This is a combined form of gel that provide rapid onset of action for both effect like analgesic and skin healing. And that is to get instant relieve for pain as comparison of plain aceclofenac and diclofenac tablet or gel. This formulation is much beneficial for the diabetic patent due to using vitamin C and turmeric to get cure fast of skin injury and buildup of skin growth or new epidermis layer of skin in the body. Gels are gaining popularity among semisolid dosage forms due to their superior percutaneous absorption and simplicity of application.

**Keywords:-** Combined Gel, Aceclofenac, Vitamin C, Turmeric, Analgesic, Skin healing etc.

### I. INTRODUCTION:-

Applying a medication-containing formulation directly to the skin to treat cutaneous conditions or the cutaneous symptoms of a general

disease with the goal of limiting the drug's pharmacological or other effects to the skin's surface is known as topical delivery. The topical delivery mechanism is dominated by semi-solid formulations in all of their variations. Regarding medication diffusion or release from the vehicle and administration through the skin, there have been issues with traditional topical dose forms such lotions, creams, ointments, and powders. Creams and lotions often provide poor bioavailability of the drug because they are rapidly cleared from the skin and poorly release the drug from the base. Non-hydrophilic ointments are oleaginous, greasy and are not convenient to patients, and also medicated powders for topical application have short residence time on the skin. (1)

Gels are semisolid systems in which a three-dimensional network of interacting particles or solvated macromolecules of dispersed phase limit the dispersion medium's movement. When applied to intact skin, the transdermal drug delivery system's discrete dose forms transfer the medication through the skin at a regulated rate to the systemic circulation. The oral route is currently the most popular method of medication delivery. The stratum corneum is the rate that offers the most resistance to penetration. The semisolid condition results from increased viscosity brought on by interlacing and subsequent internal friction. Additionally, a gel may be made up of twisted, matted strands that are frequently bound together by stronger Vander Waals forces to create both crystalline and amorphous areas throughout the system.

A new delivery method called nanoemulgel aims to improve the therapeutic profile of lipophilic medications. Poor solubility, erratic absorption, and limited oral bioavailability are only a few of the drawbacks of lipophilic formulations. Drug delivery for both instant and regulated release is made possible by the unique technique created

by incorporating nano-emulsion into gel, which also increases stability. The ability to accomplish targeted distribution, ease of application, lack of gastrointestinal degradation or first pass metabolism, and safety profile have all contributed to the increased interest on nano-emulgel.(8)

#### **Pain:-**

Pain is a distressing feeling often caused by intense or damaging stimuli. Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience that is linked to or similar to actual or potential tissue injury.(2)



Figure 1- Pain

#### **Skin Injury in Diabetic Patient:-**

Diabetes can cause changes in the small blood vessels. These changes can cause skin problems called diabetic dermopathy. Dermopathy often looks like light brown, scaly patches. These patches may be oval or circular. Diabetes can also cause wounds to heal more slowly, increasing the risk of infections and other severe complications.(10)



Figure 2- Skin injury in diabetes

## **II. DRUG PROFILE:-**

#### **Aceclofenac:-**

Diclofenac's nonsteroidal anti-inflammatory medication (NSAID) counterpart is aceclofenac. It is used to treat osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis by reducing pain and inflammation. It was authorized for use in medicine in 1992 after being patented in 1983. Aceclofenac has a molecular weight of 354.19 and is a crystalline powder. In water with high permeability, it is essentially insoluble. The primary metabolite produced by its metabolism in human hepatocytes and human microsomes is acetoxyacetic acid, which is subsequently conjugated.

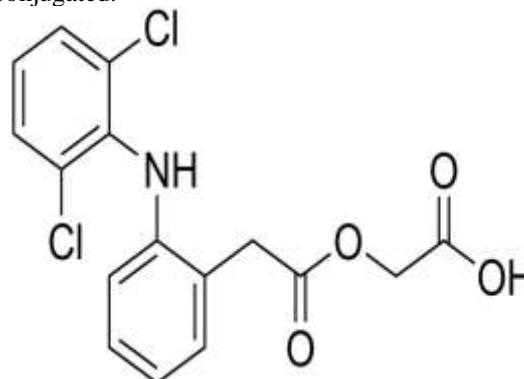


Figure 3- Structure of Aceclofenac

The Biopharmaceutical Classification System (BCS) divides pharmacological compounds into four groups based on their permeability and solubility. Aceclofenac acts by preventing cyclooxygenase from producing prostaglandins, which cause pain, swelling, inflammation, and fever.(1)

#### **Ascorbic acid:-**

Vitamin C also known as ascorbic acid and ascorbate is a water-soluble vitamin found in citrus and other fruits, berries and vegetables. It is also a generic prescription medication and some countries is sold as a non-prescription dietary supplement. As a therapy, it is used to prevent and treat scurvy, a disease caused by vitamin C deficiency.

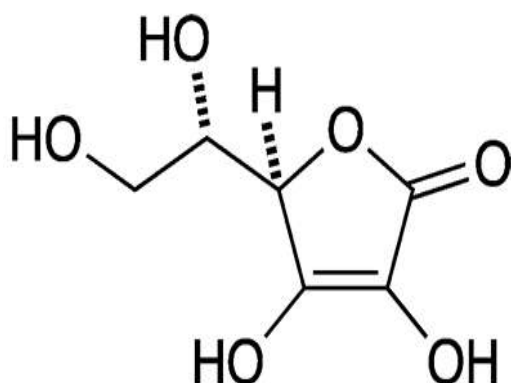


Figure 4- Structure of Ascorbic acid

Vitamin C is an essential nutrient involved in the repair of tissue, the formation of collagen, and the enzymatic production of certain neurotransmitters. It is crucial for the immune system's operation and necessary for the operation of numerous enzymes. It serves as an antioxidant as well. Vitamin C may be taken by mouth or by intramuscular, subcutaneous or intravenous injection.

### III. MATERIALS & METHODS:-

The API and other ingredients that should be used for the formulation is collected as per specification and well tested in laboratories.

Table 1: Ingredient table

S. No.	Name of Ingredients	Quantity	Functions
1.	Aceclofenac	1gm	Pain reliever
2.	Ascorbic acid	0.1gm	Skin healer
3.	Carbopol 934	1gm	Polymer
4.	HPMC K4M	1gm	Emulsifier
5.	Sodium CMC	0.5gm	Binder
6.	Triethanolamine	Q.S.	PH Stabilizer and Emulsifier
7.	Ethanol	5ml	Solvent
8.	Propylene glycol	5ml	Moisturizer
9.	Propyl Paraben	0.02gm	Preservative
10.	Distilled Water	Q.S.	Vehicle
11.	Menthol	1.5gm	Fragrance
12.	Liquid Paraffin	5ml	Surfactant
13.	Tween 80	10ml	Emulsifier

### IV. PREFORMULATION STUDIES:-

Characterization of Aceclofenac: The sample of aceclofenac was examined for its nature, color, and type of organoleptic properties as well as its taste. The melting point was ascertained using Thiesel's tube apparatus method. The drug excipient was very complex to do its formality and compatibility studies. The drug polymer and polymer-polymer interaction was examined using the FTIR spectrometer using a Shimadzu 8400-S. Two percent of the sample with respect to a potassium bromide disc was finally combined with dry KBr.

Using an agate mortar, the combination was ground into a fine powder before being crushed onto a KBr disc at 1000 psi in a hydraulic press. Using cosine apodization, each KBr disc was scanned 16 times at a speed of 2 mm/sec and a resolution of 4 cm<sup>-1</sup>. The distinctive summits were noted.(5)

### V. PROCEDURE:-

#### Step 1: Preparation of Nanoemulsion:

1. Dissolve aceclofenac in isopropyl myristate (oil phase).
2. Add Tween 80 and propylene glycol to oil phase.
3. Stir continuously with help of magnetic stirrer.
4. Add ethanol to improve solubility.
5. Slowly add distilled water drop wise with continuous stirring.
6. Subject mixture to high speed to homogenization.
7. Obtain clear/ translucent nanoemulsion.

#### Step 2: Preparation of Gel Base:

1. Disperse carbopol 934 in distilled water.
2. Allow to swell for 24 hours.
3. Add HPMC and Sodium CMC with continuous stirring.
4. Add propyl paraben and ascorbic acid.

5. Adjust pH using triethanolamine.
6. Add menthol and mix uniformly.

### Step 3: Preparation of Nanoemul gel:

1. Add nanoemulsion slowly into gel base (1:1)
2. Stir gently to avoid air entrapment.
3. Homogenize for uniform distribution.
4. Store in air tight container.



Figure 5: Prepared Formulation

## VI. EVALUATION TEST OF FORMULATION:-

- **Homogeneity:** The formulation were tested for homogeneity by visual appearance and by touch.
- **Appearance:** The appearance of the gel was very clear.
- **Acid Value:** 10 grams of the material should be dissolved in 50 milliliters of an equal proportion of alcohol and solvent ether. The flask was heated gradually until the material was fully dissolved by connecting it to a reflux condenser. After shaking for 30 seconds, add 1 milliliter of phenolphthalein and titrate with 0.1N NaOH until a light pink color appears. Acid Value =  $n \times 5.61 / w_n$  = number of milliliters of NaOH needed w = material weight
- **pH measurement:** A standard buffer solution was used to calibrate the pH meter. A digital pH meter was used to measure the pH of around 0.5g of gel that had been weighed and dissolved in 50ml of distilled water by dipping the electrode into it.
- **Irritancy test:** Mark an area (1 sq. cm) on the left hand dorsal surface. The gel was applied to the specified area and time was noted.
- **Irritancy, erythema, edema,** was checked if any for regular intervals upto 24hrs and reported.
- **Viscosity:** The formulation's viscosity was measured in triplicate using a Brookfield or Ostwald viscometer at 100 RPM and spindle number 7 at a temperature of 25°C. The average of the three readings was noted.
- **Accelerated stability testing:** Accelerated stability testing of prepared gel was conducted for 2 most stable formulations at room temp, studied for 7 days. The formulations were placed at 40°C + 1°C for 20 days. Both formulations were kept at room temp and elevated temp and observed on both, 5th, 10th, 15th and 20th day for any change in color, phase separation etc.
- **Subjective Properties:** Consistency, feel on application and irritation parameters are determined.
- **Spreadability:** Two glass slides of standard dimensions (20 × 5cm) were selected. The formulation was over one of the slide. The other slide placed on the top of the lotion such a that the formulation sandwiched between the two slides in an area occupied by a distance of 7.5 cm, alongside 100 gm weight was placed uniformly to form a thin layer. The weight was removed and the excess of lotion adhering to the slides was scrapped off. The two slides in a position were fixed to stand (45° angle) without slightest disturbance and in such a way that only the lower slide held firmly by the opposite fangs of the clamps allowing the upper slide to slip off freely by the force of weight tied to it. 60 gm of weight was tied to the upper slide carefully. The time taken for the upper slide to travel the distance of 5 cm and separate away from the lower slide under the direction of weight was noted. The experiment repeated for 3 times and the mean taken for three such dimensions was calculated. The results were recorded. The Spread ability is calculated by using formula:  $S = M \times L / T$  Where, S= Spread ability, L= Length of glass slide, M= Weight tied to the upper slide and T= Time.
- **Type of emulsion test:** Dye solubility and dilution test was conducted to determine the type of emulsion formed. A portion of lotion was applied on the forearms of 6 volunteers and left for 20 minutes. After 20 minutes any kind of irritation if occurred was noted.
- **Washability Test:** For ten minutes, a portion of the gel was placed to the hand's skin and left

to flow under the force of the tap water. The moment the gel was entirely withdrawn was recorded.

- **In vitro permeation studies:** In vitro permeation studies of TRA gel across rabbit skin were carried out using two-chambered Franz-type diffusion cells (manufactured “in house”) having a receptor phase of ~5 ml, 2 and a diffusional area of ~0.788 cm<sup>2</sup>. Adult rabbit skin was used for permeation studies at 37 ± 0.5 C. Abdominal full thickness skin of male White New Zealand rabbit (3 - 4 kg weight) was carefully excised after sacrificing the rabbit. Subcutaneous fats and other extraneous tissues adhering to the dermis were completely removed and trimmed with forceps and scissor. The skin was cleaned with phosphate buffered saline (PBS) at pH 7.4 and stored in 500 ml normal saline in a refrigerator (18 – 20 C) The skin was used within one week of excision. Sheets of the skin were cut to appropriate sizes 2 (~ 1 cm in diameter) and soaked overnight in the receptor solution (PBS). The membrane was then placed between the two compartments of the diffusion cells with epidermis side facing the donor compartment while the dermal side was bathed with PBS at pH 7.4 (receptor fluid). The donor compartment was filled with PBS at pH 7.4 ± 0.1. This pH is close to that of human skin. The receptor fluid was stirred with a magnetic stirring bar at 500 rpm, keeping the temperature at 37 ± 0.5 C by means of a water jacket. Care was exercised to remove any bubbles between the underside of the skin and the solution in the receiver compartment. Vacuum grease was used to produce a leak-proof seal between the membrane and the two compartments of the diffusion cell, i.e., donor and receptor. Ultrasonic bath. To avoid evaporation from the compartments, the cell arm and donor compartment were covered with a para film. Constant mixing of the receptor phase was obtained with a magnetic stirrer placed in the receptor compartment. The diffusion cells were placed on a stirring-bed immersed in a water bath at 37 ± 0.05 C, to maintain the temperature of membrane surface. After 24 hours, both chambers were cleared of PBS and the receptor compartment was immediately refilled with pre-thermo stated PBS, while the skin remained intact. The donor compartment was charged with 1 ml of the lotion (test formulation). At time intervals of

5,15, 30, 60, 90, 120, 180, 240, 360 and 480 min, 0.2 ml sample was drawn, using a micropipette, from receptor solution followed by addition of same volume of pre-thermostated receptor solution to maintain sink conditions. The samples were analyzed spectrophotometrically at 271 nm using UV/Vis spectrophotometer to obtain the amount of TRA permeated through rabbit skin after diluting with 1.8 ml PBS. Since skin shows great sample to sample permeability variations, each of these analyses was conducted in pentuplicate (n = 5). To construct a calibration curve, 500 mg of TRA was dissolved in PBS (10 ml) in 100 ml volumetric flask and the final volume made up to 100 ml by adding PBS to prepare stock solution. From this solution, dilutions of 10, 20, 30, 40, 50, 60, 70, and 80 µg/ml were prepared. The resultant dilutions were analyzed spectrophotometrically for UV absorbance. Maximum UV absorbance of TRA was found at 271 nm. The linear equation of the constructed calibration curve was  $y = 0.022x - 2.0021$  and correlation coefficient (R) of 0.998. Steady-state flux was determined from the slope of the linear portion of the cumulative amount of permeation (Q) versus time (t) plot. The input rate of TRA permeating across rabbit skin was determined as in Eq Input rate =  $K_p \times C \times A$ .....Where,  $K_p$  is permeability coefficient, C is donor amount (µg), i.e., amount of drug in the donor compartment and A is the Franz cell area of 2 permeation (~0.788 cm<sup>2</sup>). Enhancement ratio (ER) was calculated by dividing the flux of the test formulation by the flux of control formulation.

- **Statistical analysis:** The receptor and donor compartments were filled with PBS at pH 7.4 ± 0.1. To remove air bubbles and preclude the development of air pockets in the receptor phase, PBS was degassed in gel. The results are expressed as mean ± standard deviation (SD, n = 5). Statistically significant differences between various permeation data were determined using F-test, Fisher's least significant difference (LSD), analysis of variance (ANOVA) and multiple range tests at 95% confidence level.
- **Preference Test:** The parameters of preference tests based on sensory evaluation were a scent, color, and sensation on the skin. The level of preference was assessed using a numerical

scale, i.e. 5 = like extremely, 4 = like, 3 = neutral, 2 = dislike, 1 = dislike extremely.

- **Test for thermal stability:** Thermal stability of the formulation gel was determined by the humidity chamber controlled at 60- 70% RH and  $37 \pm 1$ oC.
- **Patch test:** About 1-3gm of material to be tested was placed on a piece of fabric or funnel and applied to the sensitive part of the skin e.g. skin behind ears. The cosmetic to be tested was applied to an area of 1sq.m.of the skin. Control patches (of similar cosmetic of known brand) were also applied. The site of patch is inspected after 24 hrs. As there was no reaction the test was repeated three times. As no reaction was observed on third application, the person may be taken as not hypersensitive.

**Pathophysiology of Drug:-**

1. **COX Inhibition:** Aceclofenac primarily blocks cyclooxygenase (COX) enzymes, particularly COX-2, which are crucial for synthesizing inflammatory mediators like prostaglandins from arachidonic acid.
2. **Reduced Inflammatory Mediators:** By inhibiting COX, it reduces levels of prostaglandins (causing pain/swelling), Interleukin-1 $\beta$  (IL-1 $\beta$ ), and Tumor Necrosis Factor-alpha (TNF- $\alpha$ ).
3. **Chondroprotective Effects:** A metabolite, 4'-hydroxyaceclofenac, stimulates glycosaminoglycan (GAG) synthesis in

cartilage and inhibits cartilage-degrading enzymes (metalloproteinases), protecting joint tissues.

4. **Reduced Nitric Oxide & Adhesion:** It lowers nitric oxide production in chondrocytes and reduces neutrophil adhesion to blood vessel linings (endothelium) by decreasing L-selectin expression, further dampening inflammation.

**VII. RESULT AND DISCUSSION:-**

The objective of the present study was to formulate Aceclofenac pain relieving and skin healing nanoemul gel. This pain relieving and skin healing gel with different polymer ratios were prepared. In order to select the optimized formulation, various evaluation parameters were checked and subjected to in-vitro diffusion study and their release kinetic study were observed. The project was undertaken with the aim to design nanoemul gel formulation for topical delivery of aceclofenac pain relieving and skin healing nanoemul gel. Preliminary studies indicates that Carbopol 934, and HPMC, can be used as a gelling agents and ethanol as a solvent. Different formulation were screened at preliminary level o the basis of drug solubility, drug release, spreadability, excurtability, rheological behavior etc. The formulation have satisfactory spreadability, rheological behavior and their diffusion profile was comparable to marketed gel formulation.

Table 2 Evaluation Parameter and their result:-

S. no.	Parameter	Standard	Result
1.	Ph	4.84-7.41	5.92
2.	PKa	4.15	4.12
3.	Viscosity	3045.31	3023.81
4	Spreadability	23.05	23.03
5.	Physical Appearance	Clear	Clear
6.	Skin irritation	No irritation	No irritation
7.	Melting Point	275-277	276.4
8.	Solubility	Water	Soluble
9.	Washability	Easily washable	Yes

Table 3: Organoleptic test of gel

S. No.	Organoleptic features	Observations
1	Colour	Creamish Yellow
2	Odour	Aromatic & Pungent
3	Taste	Persistent or bitters
4	Texture	Smooth



Figure 6: pH test of gel

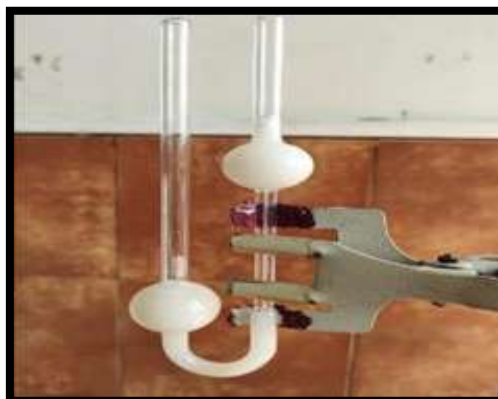


Figure 7: Viscosity test of gel



Figure 8: Spreadability test of gel



Figure 9: Consistency test of gel



Figure 10: Skin irritation test of gel

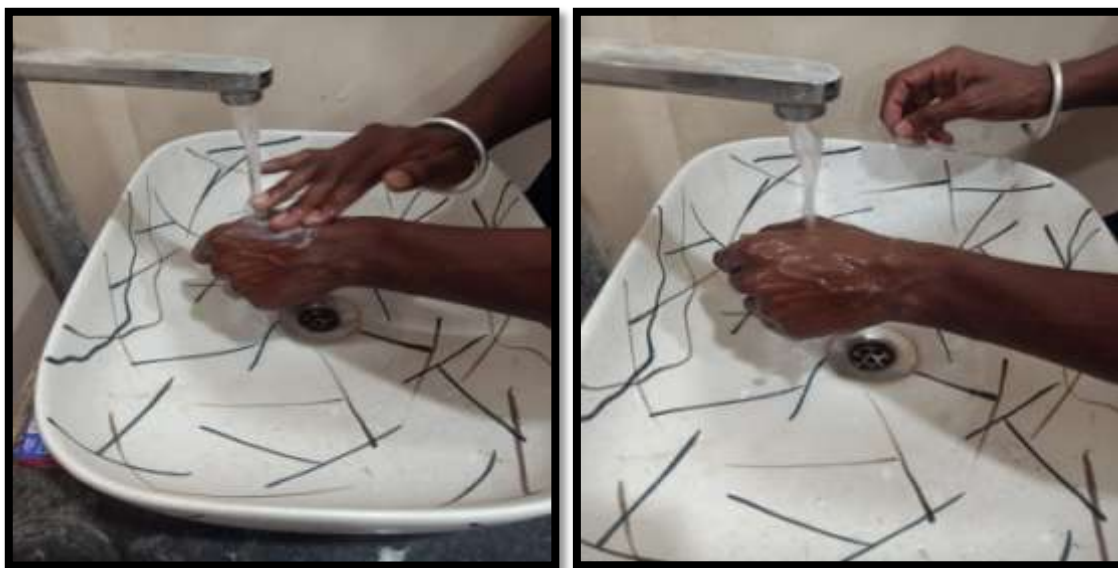


Figure 12: Washability test of gel

### VIII. CONCLUSIONS:-

It was observed that aceclofenac pain relieving and skin healing nanoemul gel in 1:2 ratio (produced better spreadability and consistency as compared to other formulations. The developed gel showed good homogeneity, suitable pH, no skin irritation and good stability. The maximum percentage of drug release was found to be 98.68% in 6 hours in formulation. The drug permeation from optimized formulation i.e. this was slow and steady and 0.89 gm of aceclofenac could permeated through rat abdominal skin membrane with a flux 0.071 gm hr<sup>-1</sup> cm<sup>-2</sup> and could possibly permeate through human abdominal membrane. The Carbopol 934P forms water washable gel because of its water solubility and has wider prospects to be used as a topical drug delivery system. Formulation batch (2% Diclofenac, Aceclofenac 10% PG, 0.15% Methylparaben, 0.05% PropylParaben, 1.5% Carbopol 940, 67.44% ethanol, 16.86% water) had shown higher amount of percent cumulative release as compared to marketed gel. Spreadability of formulation was good to cover the painful area. In formulation the ethanol in following concentration had shown the higher penetration enhancer activity which result in higher drug release, flux and permeability value. On the basis of organoleptic characteristic the improved patient acceptability was achieved through formulation. The improved patient convenience might thus be obtained by the administration of such a dosage form with minimal blood level fluctuations. The release penetration enhancer and other materials are cheap, readily available, safe, having wide regulatory acceptance

and easy to handle for economic point of view. It may beneficial to adopt such simple technology for the commercial production of Diclofenac Aceclofenac pain relieving gel(1). The future scope of this study is that formulation should be subjected for long-terms stability and in-vivo performance study.

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