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# Formulation development and characterization of aceclofenac gel containing linseed oil and ginger oleoresin

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**Abstract:** Aceclofenac is a Non-Steroidal Anti-Inflammatory Drug (NSAID), used in the treatment of inflammation and degenerative disorder of the musculoskeletal system. It is widely prescribed for the treatment of osteoarthritis, rheumatoid arthritis, dysmenorrheal, acute lumbago, musculoskeletal trauma and gonalgia (Knee pain). Aceclofenac is well tolerated, with most adverse events being minor and reversible and affecting mainly the G.I system. Most common events include dyspepsia, abdominal pain, nausea, ulcerative stomatis and pancreatitis. The aim of this study was to formulate topical gel containing aceclofenac, linseed oil and ginger oleoresin. Formulated gel was evaluated and compare with marketed Nusaid gel for pH, viscosity, spreadability, extrudability, drug content, *in vitro* drug diffusion and accelerated stability study.
**Key words:** Aceclofenac gel, linseed oil and ginger oleoresin, formulation and development.

## INTRODUCTION

The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid[1]. The inorganic particles form a three-dimensional "house of cards" structure. Gels consist of two-phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved in the continuous phase, randomly coiled in the flexible chains[2].

Gels are typically formed from a liquid phase that has been thickened with other components.

Aceclofenac is a Diclofenac derivative of the Non–Steroidal Anti-Inflammatory drug[3,4,5] (NSAID), which is chemically, (2-[2-[2-(2,6-dichlorophenyl) amino phenyl]acetyl] oxyacetic acid)[6,7].Aceclofenac is used in treatment of osteoarthritis, rheumatoid arthritis, acute lumbago, and dental pain condition[8, 9, 10]. However like other NSAIDs, oral administration of this drug is also associated with severe gastrointestinal side effects like- ulceration and gastro intestinal bleeding liver and kidney trouble. The solution of this problem lies in the fact that, topically applied NSAIDs are safer than and as efficacious as oral NSAIDs[11]. Furthermore, the transdermal route of administration has a high patient compliance, which derives from it

being non-invasive and the long interval between applications. Transdermal administration also provides a means to obtain constant systemic drug levels[12,13,14] .The aim of the present study is to develop and formulate a gel containing aceclofenac, ginger oleoresin and linseed oil and to evaluate and compare the same with marketed Nusaid gel.

## EXPERIMENTAL

### Materials

Aceclofenac was a kind gift from Medley Pharmaceutical Ltd., Daman, India. All other ingredients were of analytical grade and were supplied by S. D. Fine chemical Ltd. Mumbai. Nusaid gel of Molekule Pharmaceuticals Pvt. Ltd. was purchased from market.

### Methods of preparation of aceclofenac gel

**1) Gel with carbopol base**

Heat propylene glycol at $65^0$C and dissolve in it methyl paraben and propyl paraben, add water and carbopol, and keep it for 8 hours for adequate swelling of polymer. Add triethanolamine to neutralize the carbopol and adjust the pH 6.7 – 6.9. Take another vessel and heat propylene glycols at $65^0$C, add aceclofenac, cool at room temperature and add in carbopol base. Take IPA and dissolve menthol in it till the clear solution is obtained add it in above gel. Oil phase was prepared by dissolving tween 60,chremophore Rh 40, methyl salicylate, linseed oil and ginger oleoresin mix till the clear solution is obtained, oil phase is slowly added in the above aqueous carbopol gel while constantly stirring to get emulgel and adjust the pH 7.0 – 7.5. Gel was packed in aluminium collapsible tube. (Table: 01)

**2) Gel with hydroxy propyl methyl cellulose**

Aceclofenac was dissolved in propylene glycol. Menthol was dissolved in Isopropyl alcohol. The whole amount of HPMC was sprinkled on drug solution with slow stirring then methyl paraben and propyl paraben was added. The mixture of drug solution and polymer was kept aside for six hour to seven hour, for adequate swelling of polymer. The oil phase consisting of linseed oil, ginger oleoresin and methyl salicylate was added slowly in above aqueous gel with continuous stirring with overhead stirrer. The gel was packed in aluminium collapsible tube. (Table: 01)

**3) Gel with Sodium CMC base**

Aqueous gel base was prepared by dissolving of sodium CMC in water and with continuous stirring add propylene glycol. Dissolved drug was added. The SLS was charged slowly and with continuous stirring. Take IPA and dissolve menthol in it till the clear solution is obtained add it in above gel. Oil phase was prepared by dissolving, methyl salicylate, linseed oil and ginger oleoresin mix till the clear solution is obtained, oil phase is slowly added in the above aqueous gel while constantly stirring and lastly, methyl paraben was added to the gel. Gel was packed in aluminium collapsible tube. (Table: 01)

**Table 01: Preparation of hydrogels**

| Ingredients (% w/w) | Gels 100 gm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | A1a | A1b | A1c | A2a | A2b | A2c | A3a | A3b | A3c |
| Aceclofenac | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Linseed oil | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Ginger oleoresin | 0.5 | 1 | 1.5 | 0.5 | 1 | 1.5 | 0.5 | 1 | 1.5 |
| Methyl salicylate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Carbopol 974 P | 1 | 1.25 | 1.5 | - | - | - | - | - | - |
| HPMC | - | - | | 1 | 1.5 | 2 | - | - | - |
| Sodium CMC | - | - | - | - | - | - | 3 | 4 | 5 |
| Menthol | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Triethanolamine | 2 | 2 | 2 | - | - | - | - | - | - |
| Methyl paraben | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Propyl paraben | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | - | - | - |
| Chremophore Rh 40 | 4 | 4 | 4 | - | - | - | - | - | - |
| Sodium lauryl sulphate | - | - | - | - | - | - | 0.03 | 0.03 | 0.03 |
| Tween 60 | 1 | 1 | 1 | - | - | - | - | - | - |
| Isopropyl alcohol | 6.5 | 6.5 | 6.5 | 6.5 | 6.5 | 6.5 | 6.5 | 6.5 | 6.5 |
| Propylene glycol | 15 | 15 | 15 | 5 | 5 | 5 | 5 | 5 | 5 |
| Distilled Water Up to | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

## Evaluation of gel

The above formulated gel was evaluated for the following parameters:

**1) Appearance**

The prepared gels were inspected visually for clarity, colour and presence of any particle. The test is important regarding patient compliance. (Table: 02)

**2) pH**

pH of gel was determined using digital pH meter. About 2 gm pf gel was stirred in distilled water till a uniform suspension effected. The volume was made up to 40 ml and pH of the solution was measured. (Table: 02)

**3) Skin irritation**[13]

Ten healthy male and female volunteers were selected for skin irritation testing. 100 mg gel was applied on area of 2 cm2 for 6 hours, on the interior surface of upper arm and covered with cotton bandage. After 6 hr the sites were cleaned with acetone and readings are made according to the scale given by Draize. (Table: 02).

No irritation : 0
Slight irritation : 1
Irritation : 2

**4) Viscosity**

Viscosity of the gel was determined by using (LV) Brookfield viscometer (Dial type).

As the system is non-Newtonian spindle no. 4 is used. Viscosity is measured for the fixed time 2 min for 0.3 rpm. (Table: 02)

**Table 0 2 : Appearance, skin irritation, pH, viscosity tests**

| S. No | Formulation | Appearance | pH | Skin irritation | Viscosity(Cp) |
|---|---|---|---|---|---|
| 1 | A1a | Cream | 7.0 | 0 | 29600 |
| 2 | A1b | Cream | 7.0 | 0 | 30200 |
| 3 | A1c | Cream | 7.1 | 0 | 31000 |
| 4 | A2a | White | 7.0 | 0 | 30400 |
| 5 | A2b | White | 7.2 | 0 | 31400 |
| 6 | A2c | White | 7.1 | 0 | 32000 |
| 7 | A3a | White | 7.1 | 0 | 27000 |
| 8 | A3b | White | 7.3 | 0 | 28200 |
| 9 | A3c | White | 7.2 | 0 | 29200 |
| 10 | Nusaid gel | White | 7.15 | 0 | 30000 |

**5) Spreadability**[10, 13, 15, 16,20]

Spreadability of formulations was determined by an apparatus suggested by Multimer[45], which was fabricated itself in laboratory and used for slide fixed on wooded block and upper slide with one end tide to glass slide and other end tied with other end tied to weight pan. An excess of gel (2 – 5 gm) was placed in between two glass slides and then 1000 gm weight was placed on slides for 5 min to compress the sample to a uniform thickness. Weight (80 gm) was added to pan. The time (seconds) required to separate the two slides, was taken as a measure of spreadability.
(**Table: 03).**

It was calculated using formula,

$S = M. L / T$

Where, S = spreadability
M = weight tied to upper slide
L = length of glass slide
T = time taken

Shorter time interval, to cover distance of 6.5 cm, indicates better spreadability.

**6) Extrudability** [10, 17,18]

For a good gel formulation, it should extrude easily from the container. In this test, sample is extruded from the tube by usual procedure. A closed collapsible tube containing gel was passed firmly at crimpened end. When the cap was removed, gel extrudes until pressure was dissipates. The weight in grams required to extrude 0.5 cm ribbon of gel in 10 seconds was determined. The results for each formulation were recorded as extrusion pressure in grams. (**Table: 03)**

**Table 03: Spreadability and Extrudability, drug content of various formulations**

| Formulations | Time (sec) | Spreadability (g.cm/sec) | Extrudability (Wt. Required in gm) | Drug content (%) |
|---|---|---|---|---|
| A1a | 10 | 52 | 555 | 96.50 |
| A1b | 10 | 52 | 562 | 98.81 |
| A1c | 11 | 47.27 | 553 | 100.06 |
| A2a | 12 | 43.33 | 601 | 99.52 |
| A2b | 13 | 40 | 580 | 98.99 |
| A2c | 14 | 37.14 | 560 | 97.28 |
| A3a | 12 | 43.33 | 490 | 100.03 |
| A3b | 14 | 37.14 | 496 | 100.04 |
| A3c | 15 | 34.66 | 502 | 100.02 |
| Nusaid gel | 08 | 65 | 560 | 100.10 |

**7) Drug content** [19,20]

Take 1gm gel in a 100 ml of volumetric flask and dissolve with little amount of methanol and mixture was shaken till solution was affected. The volume was made up to 100 ml with methanol. The solution was filtered through Whatman filter paper (No. 41). Further dilute 5ml to 50 ml with methanol. The absorbance of the solution was measured at 275 nm against reagent blank. (**Table: 03)**

**8) *In vitro* drug diffusion study** [21]

All formulations were subjected to in vitro diffusion through cellulose membrane by using Keshary- Chein type cell. The receptor compartment was filled with saline phosphate buffer pH 7.4 and methanol (90:10) and kept at 32 $\pm$ $0.5^0$C and stirred with the help of magnetic stirrer. Methanol (10%) was added to maintained sink condition. About 200 – 300 mg of gel was placed on the cellulose membrane. One ml of sample was withdrawn from the receptor compartment at 1, 2, 3, 4, 5, 6, 7, 8 hour and replaced with same volume of medium. All samples were diluted up to 10 ml with medium and analysed for aceclofenac content spectrophotometrically at wavelength 275 nm. (Table: 04) .The drug diffusion profile of all formulation through cellulose membrane are shown in graph 01.

**9) Accelerated stability studies** [13]

All the selected formulations were subjected to a stability testing for three months as per ICH norms at a temperature of 40ºC ± 2ºC / 75% ± 5% R H. All selected formulations were analyzed for the change in appearance, pH and drug content by procedure stated earlier. (Table: 05)

**Table 04: Cumulative % Drug Release Profile of Aceclofenac Gels**

| Time (Hr) | Batches | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | A1a | A1b | A1c | A2a | A2b | A2c | A3a | A3b | A3c | Nusaid gel |
| 1 | 16.21 | 8.45 | 30.90 | 15.46 | 12.6 | 10.20 | 16.95 | 17.49 | 13.60 | 22.50 |
| 2 | 18.74 | 20.47 | 36.00 | 20.55 | 19.45 | 16.50 | 21.74 | 23.47 | 19.54 | 27.24 |
| 3 | 25.11 | 26.33 | 44.80 | 24.44 | 23.70 | 22.30 | 32.33 | 30.11 | 24.98 | 35.68 |
| 4 | 28.65 | 35.91 | 52.00 | 26.71 | 31.60 | 28.40 | 36.21 | 34.51 | 32.87 | 47.75 |
| 5 | 34.0 | 41.01 | 60.90 | 30.91 | 38.40 | 35.52 | 41.49 | 37.72 | 38.69 | 52.35 |
| 6 | 39.47 | 49.77 | 70.40 | 40.44 | 45.21 | 43.65 | 43.95 | 40.41 | 47.85 | 60.45 |
| 7 | 49.68 | 57.37 | 74.30 | 45.79 | 49.31 | 50.50 | 50.51 | 47.41 | 55.62 | 68.65 |
| 8 | 57.49 | 65.05 | 80.40 | 49.31 | 53.21 | 58.80 | 56.43 | 58.77 | 62.80 | 74.96 |

**Graph01: Cumulative % drug release profile of aceclofenac gels**

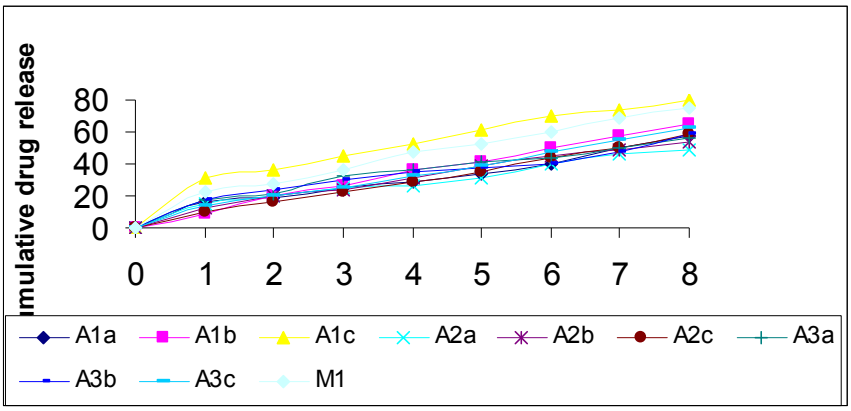


**Table05: Accelerated stability study data**

| S No. | Batches | Month | Appearance | pH | Drug content (%) |
|---|---|---|---|---|---|
| 1 | A1c | Initial | Cream | 7.1 | 100.06 |
| | | 1 | Cream | 7.1 | 100.01 |
| | | 2 | Cream | 7.0 | 99.35 |
| | | 3 | Cream | 7.0 | 98.60 |
| 2 | A2a | Initial | White | 7.0 | 99.52 |
| | | 1 | White | 7.0 | 99.00 |
| | | 2 | White | 7.0 | 98.65 |
| | | 3 | White | 6.9 | 98.01 |
| 3 | A3b | Initial | White | 7.3 | 100.04 |
| | | 1 | White | 7.3 | 99.56 |
| | | 2 | White | 7.2 | 98.88 |
| | | 3 | White | 7.2 | 98.40 |
| 4 | Nusaid gel | Initial | White | 7.1 | 100.10 |
| | | 1 | White | 7.1 | 99.78 |
| | | 2 | White | 7.0s | 99.09 |
| | | 3 | White | 7.0 | 98.88 |

## RESULT AND DISCUSSION

All the aceclofenac hydrogels formulations were good feel and showed no clogging and lumps which indicate good texture of system. pH of hydrogels was around the neutral pH and in the range of 7.0-7.5.All the formulations showed no significant skin irritation on intact skin. Thus, indicating skin acceptability of these formulations for topical application.

Viscosity is an important parameter for characterizing the gels as it affects the spreadibility, extrudability and release of the drug. Viscosity of formulations were ranges between 27000-31400 cps.

Easy spreadability is one of the important characteristics of any topical preparation as far as patient compliance is concerned. Gel is considered to be good if it takes minimum time to spread on the surface. Among the various gels studied A1c aceclofenac gel has better spreadability. The values of spreadability indicate that the gel is easily spreadable by small amount of shear.

Extrusion of gel from the tube is important during application and for the patient compliance. The values of extrudability of different formulations were ranges in between 490-601.

Drug content uniformity of all formulations were observed and A1c batch shows the 100.06% drug content. Maximum drug diffusion was observed from A1c aceclofenac gel as compare to marketed Nusaid gel. Finally selected formulations were subjected to a stability testing for three months and drug content of batch A1c was found to be 98.60%.

Depending up on different evaluation parameters made on all formulations, batch A1c declared as an optimized batch.

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