

Formulation and Evaluation of Aceclofenac Gel

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Abstracts: Aceclofenac is a Non-Steroidal Anti-Inflammatory Drug, used in the treatment of inflammation and degenerative disorder of the musculoskeletal system. It is widely prescribed for the treatment of osteoarthritis, rheumatoid arthritis, dysmenorrhoeal, 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 stomatitis and pancreatitis. The aim of this study was to formulate topical gel containing 1.5% Aceclofenac, 1% Benzyl Alcohol, 3% Linseed oil, 10% Methyl Salicylate, 0.01% Capsaicin, 5% Menthol and evaluate the same.

Key words: Aceclofenac Gel, Formulation and Development

1. Introduction

The Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) possess anti-inflammatory, analgesic and antipyretic activities. The Indian drug industry is always ready to cater to the needs of medical professionals by developing combinations of various kinds of drugs that are capturing substantial market share. Aceclofenac is a Diclofenac derivative of the Non-Steroidal Anti-Inflammatory Drug^{1,2,3}, which is chemically, (2-[2-[2-(2,6-dichlorophenyl)aminophenyl]acetyl]oxyacetic acid)^{4,5}. Aceclofenac exhibited potent Anti-Inflammatory Analgesic activity and is widely prescribe for the treatment of osteoarthritis, rheumatoid arthritis, acute lumbago, and dental pain condition⁶. Aceclofenac is well tolerated, with most adverse events being minor and reversible and affecting mainly the G.I system. Although the incident of gastrointestinal adverse events with Aceclofenac was similar to that comparator NSAID in individual clinical trial withdrawal rate due to these events were significantly lower Aceclofenac than with Ketoprofen and Temoxicam^{7,8}. Other adverse effects which are not common such as dizziness (1%), vertigo (0.3%) and tremor. In the present study is the development a formulation of Aceclofenac gel and to evaluate the same for drug content, pH and viscosity.

2. Material and method

2.1 Gel materials:

Aceclofenac and Propylene Glycol were obtained from Suyash chemicals, Mumbai and Monali petrochemicals Ltd, Chennai respectively. EDAT and Benzyl alcohol

were obtained from Adithya chemicals, Ahmedabad and Qualigens, Mumbai. PEG-400 and PVP K-30 were obtained from Laffans petrochemicals Gujarat and IFC Canada. Carbopol-934 and diethyl amine were obtained from Novion, USA and Balaj Amine Ltd, Maharashtra. All the chemicals used in the study were of pharmacopoeia quality (IP).

2.2 Methods of preparation of Aceclofenac Gel:

2.2.1 Water phase Details:

Transfer the purified water in to the stream-mixing vessel and heat it up to 70⁰C. Add EDTA in to the warmed purified water with continuous stirring. After completion of addition cool the mixture up to 50⁰C and mix the Carbopol-934 in to the above mixture under continuous stirring. After that homogenize the mixture for 20 minutes to get the uniform gel and free from lumps and bubbles. Cool the gel phase to 40⁰C by circulating chilled water.

2.2.2 Aceclofenac solution preparation details:

Warm the propylene glycol to 55-60⁰C and dispersed Aceclofenac in sufficient quantity of Propylene Glycol with constant mixing. Ensure that the mixture become free from lumps by visual checking bottom of the vessel should be clearly visible. If any stress of the drug found continue the mixing till it dissolved completely after that transfer the Aceclofenac solution in to the mixing vessel under continuous stirring.

2.2.3 Oil phase details:

Transfer the Capsaicin and Methyl Salicylate in to the jacket vessel and start mixing by stirring. Maintain the temperature of the mixture up to 50⁰C and add Linseed oil, Methanol in the above mixture under continuous

stirring for 15 minutes. After making clear solution filters through 100# and transfer it into main mixing vessel.

2.2.4 Addition of other ingredients:

Mix Polyethylene Glycol-400 with Cremophore and warm it about 45-50°C under continuous stirring in wax phase vessel. Transfer the above mixture into mixing vessel under continuous stirring and maintain the specific temperature of 40°C.

2.2.5 Addition of PVP K-90 details:

Heat purified water up to 50°C and soak PVP K-90 for 30 minutes in to the above warmed water. Make up the soaked PVP K-90 mixture in to the uniform solution by a continuous stirring and insure that no lumps in to the mixture. After cooling up to 40°C transfer the above mixture in to the mixing vessel in a thin stream under continuous stirring at high speed.

2.2.6 Addition of Benzyl Alcohol and adjust the pH:

Add Benzyl Alcohol in to the mixing vessel under continuous stirring and adjust the pH of the Gel in the mixing vessel by adding sufficient quantity of Diethyl amine.

2.3 Evaluation of Aceclofenac gel

2.3.1 Preparation of standard solution:

Weigh accurately and transfer about 500mg of Methyl Salicylate working standard and 60mg of Aceclofenac working standard to 100ml volumetric flask. Add about 30ml of Methanol and make up the volume with Methanol. Pipette out 5ml of this solution in a 25ml volumetric flask and make up the volume with Methanol.

Preparation of sample solution:

Weigh accurately and transfer about 1.0g of sample to a 100ml volumetric flask, add about 30ml of Methanol, shake to dissolve and dilute up to the mark with Methanol.

Calculation:

Aceclofenac or Methyl Salicylate (%w/w) = (AT/AS)

(DS/DT) (P/100) 100, Where,

AT = Average area count for respective peak in the chromatogram of test preparation.

AS = Average area count for peak respective in the chromatogram of standard preparation.

DS = Dilution factor for the test standard preparation of respective.

DT = Dilution factor for test preparation of respective.

P = Percentage purity of respective working standard on as is basis.

2.3.2 Assay of Capsaicin:

Standard preparation:

Weigh accurately about 20mg Capsaicin working standard in 100ml clean and dry volumetric flask. Add about 60ml mobile phase sonicate to dissolve the drug completely and make up the volume with mobile phase. Transfer 5ml of this solution to 100ml volumetric flask and make up the volume with mobile phase. Again transfer 5ml of this solution 50ml clean and dry

volumetric flask and make up the volume with mobile phase.

Sample preparation:

Weigh accurately about 1.0gm of the sample (equivalent to 0.1mg) in clean and dry 100ml volumetric flask. Add about 60ml mobile phase. Shake vigorously sonicate for 10 min then heat on water bath at 40°C for 10 minutes, cool the flask then make up the volume with mobile phase, filter the solution.

Calculation:

$$\frac{\text{SPL area (Capsaicin E+ Capsaicin Z isomer)}}{\text{STD area (Capsaicin E+ Capsaicin Z isomer)}} \times \frac{\text{Weight of STD}}{\text{Weight OF SPL}} \times \text{Dilution factor of Standard} \times \text{potency of Standard}$$

= mg of Capsaicin

2.3.3 Assay of menthol:

Standard preparation:

Weigh accurately about 50mg menthol working standard and transfer to a 100ml volumetric flask. Add about 20ml of methanol and sonicate to dissolve. Make up the volume with methanol. Dilute 5ml of this solution to 50ml with 50% v/v methanol.

Sample preparation:

Weigh accurately sample equivalent to 50mg of menthol and transfer to a 100ml volumetric flask. Add 70ml of methanol and sonicate to dissolve. Make up the volume with methanol. Filter if necessary. Dilute 5ml of filter to 50ml with 50% v/v methanol.

Calculation:

$$\frac{\text{Sample Abs} \times \text{std. wt} \times 5 \times 100 \times 50}{\text{Std. Abs} \times 100 \times 50 \times \text{sample wt.} \times 5} \times 100$$

= Percentage w/w of menthol.

2.3.4 Assay for Benzyl Alcohol (by GC):

Preparation of standard solution:

Weigh accurately and transfer about 400mg of benzyl alcohol working standard to a 50ml volumetric flask. Add 5ml methanol, make up the volume with water. Pipette 5ml of this solution to a 50ml volumetric flask, and make up the volume with methanol.

Preparation of test solution:

Weigh accurately about 4.0g of sample and transfer to a 100ml volumetric flask. Add about 15ml of methanol and shake to disperse the sample uniformly. Add and make up the volume with methanol. Shake to dissolve.

Calculation:

$$\frac{\text{Sample abs}}{\text{Standard abs}} \times \frac{\text{Standard wt}}{50} \times \frac{5}{100} \times \frac{\text{Standard purity}}{100} \times 100$$

= Percentage of v/v benzyl alcohol.

All the Chromatographic conditions are given in the table no: 1

Table 1: Chromatographic condition

	Assay for Aceclofenac and Methyl Salicylate	Assay for capsaicin	Assay for Benzyl Alcohol
Column	Micro bondapak C18, 10 μ m	300x4.0 mm, 5 μ , phenyl	BP -20 Wax – 15 mts. x0.53 mm x 1.0 μ m.
Wavelength	280 nm	280 nm	280 nm
Flow rate	1.5 ml/min	1.0 ml/min	5.0 ml/ min
Injection volume	20 μ l	100 μ l	1.0 μ l
Run time	15 min	11.5 & 14.0min (Capsaicin E & Z)	20 minutes
Assay result % w/v	101.15 and 97.8	99.0	97.5

3 Results and discussion

The basic goal of therapy is to achieve a best formulation of Aceclofenac Gel and as well as to improve the all-physical parameter. The design of proper dosage regimens is an important element in accomplishing this goal. During the trial, the excipients concentrations are gradually increasing as a result several problems are coming. At the stage of trial: 4 only the spreadability problem is coming, so only the Cremophor amount is increased which are responsible for spreadability. As a result trial: 5 become the best trial batch. During this trial, in the first 4-batch trial, several problems are coming and this are given in the (table no: 2), so that the trial batches are rejected. On the farther case 5th trial batch is best. As a result farther evaluation is to be carried out on this batch only. In the case of 5th batch, all the evaluation parameters are complies with standerd

Table no: 2: Problem Associated with these trials

Trial: 1	Trial: 2	Trial: 3	Trial: 4	Trial: 5
1. Dehydration Problem 2. Fine particles are observed 3. Aceclofenac is not dissolve properly 4. Viscosity Problem	1. More Creaming 2. Phase Separation 3. Viscosity Problem 4. Aceclofenac is not dissolve properly	1. Consistency is not good 2. Viscosity Problem 3. Spreadability is poor	1. Spreadability is poor	Nil

5. References

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specification. Assay results and Compatibility Studies are given in the table no: 1 and table no: 3.

4. Conclusion

A Gel provides a successful approach in delivering combination products hence for the present study a Gel system has designed to deliver the drug Aceclofenac and also improve physical appearance of the gel. The most significant part is the high performance polymer Carbopol-934 was used as the gelling agent; also Cremophor as base maker, as well as for improving spreadability and PVP K-90 is used as a thickening agent. Five trials of Gels were prepared on industrial scale as the work is out in industrial environment. Among the five trials, Trial no-5 was chosen as the best and will be subjected to further studies.

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Table no: 3 : Compatibility Study

Sl no	Ingredients (Drug + Excipients)	25°C, RH 60+/-5		40°C, 70+/-5 RH		Ingredients (Excipient + Excipient)	25°C, RH 60+/-5		40°C, 70+/-5 RH	
		14 days	28 days	14 days	28 days		14 days	28 days	14 days	28 days
1	Propylene glycol+PEG-400	Compatible	Compatible	Compatible	Compatible	Propylene glycol+PEG-400	Compatible	Compatible	Compatible	Compatible
2	Benzyl Alcohol +Diethyl amine	Compatible	Compatible	Compatible	Compatible	Benzyl Alcohol +Diethyl amine	Compatible	Compatible	Compatible	Compatible
3	PVP K-90 + Cremophore	Compatible	Compatible	Compatible	Compatible	PVP K-90 + Cremophore	Compatible	Compatible	Compatible	Compatible
4	Aceclofenac+ EDTA + Carbopol-934 +Propylene Glycol	Compatible	Compatible	Compatible	Compatible	EDTA + Carbopol + Propylene Glycol	Compatible	Compatible	Compatible	Compatible
5	Aceclofenac+propylene Glycol+EDTA+Carbopol-934 + Cremophore + PEG -400 + PVP K-90 + Benzyl alcohol + Diethyl Amine + Purified Water	Compatible	Compatible	Compatible	Compatible	Propylene Glycol + EDTA +Carbopol-934+ Cremophore + PEG-400 + PVP K-90 + Benzyl alcohol + Diethyl Amine + Purified Water	Compatible	Compatible	Compatible	Compatible
6	Aceclofenac + Capsaicin + Methyl Salicylate + Linseed Oil + Menthol + propylene Glycol + EDTA +Carbopol-934 + Cremophore + PEG -400 + PVP K-90 + Benzyl alcohol + Diethyl Amine + Purified Water	Compatible	Compatible	Compatible	Compatible	Propylene Glycol + EDTA +Carbopol-934 + Cremophore + PEG -400 + PVP K-90 + Benzyl alcohol + Diethyl Amine + Purified Water + Capsaicin + Methyl Salicylate + Linseed Oil + Menthol	Compatible	Compatible	Compatible	Compatible