FORMULATION AND EVALUATION OF A NOVEL NON STEROIDAL ANTI INFLAMMATORY ZALTOPROFEN GEL

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ABSTRACT

Zaltoprofen drug is a novel NSAID sit has powerful inhibitory effects on acute & chronic inflammation with less adverse reaction on the gastrointestinal tract. The Zaltoprofen gel product was prepared in varied concentrations (5% and 10%) and evaluated using physiological measurements. The NSAIDs gel was formulated by using polymer such as Carbopol 934. The prepared gel formulations was evaluated by using the different parameter such as physical appearance, pH, viscosity, spread ability, Drug content and also skin irritation to observe toxicity or side effects of the formulation. The prepared gels formulations were evaluated for anti-inflammatory activity on albino mice. From the study it was concluded that gel formulation containing the concentration 10% have better spreadability and stability than concentration 5%. The gel formulation containing the zaltoprofen drug have clear appearance, Ph-7, good wash ability and good spreadability and No skin irritation. Finally it was concluded that the Zaltoprafen gel formulation was the best product as compare to marketed product.

KEYWORDS: Anti-inflammatory, zaltoprofen, Carbopol 934.

INTRODUCTION

Topical drug delivery systems are supported by many people. The numerous drugs have been effectively delivered by this route of administration for both local and systemic action.[1] Gels have better potential as a vehicle to administer drug topically in comparison to ointment, because the gel are non-sticky in nature.[1] Gel requires low energy during formulation.[1]
Drug delivery throughout the skin has been a promising concept for a long time because skin is easy to access, skin has a large surface area with vast disclosure to the circulatory and lymphatic networks and the route of administration is non-invasive.\(^1\)

Transdermal gel preparations are intended for superficial skin application or some mucosal surfaces for local action of medicament or for their soothing or protective action.

The inflammation is a self-protective reaction to injury with classical signs of warmth, reddening, pain, swelling and loss of function, which is of a acute inflammation or chronic inflammation type, this inflammation is also observed in cancer, bowel syndrome, hepatic and Alzheimer’s diseases.\(^{2,13}\) NSAIDs are generally used to treat inflammation. Many inflammatory processes are self-limiting and self-resolving.\(^3\)

Inflammation is a pathophysiological reaction of living tissues to injuries that leads to the local accumulation of blood cells and plasma fluid. The characteristics of inflammation are humorus like reddening, swelling, soreness and corresponding histological changes.

Topical application of anti-inflammatory drugs at the site of inflammation can overcome their systemic side effects and improve their activity.\(^4\) The use of non-steroidal anti-inflammatory drug is well recognized for regional inflammatory disorders such as muscle pain, osteoarthritis and rheumatoid arthritis.\(^5\)

Zaltoprofen is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, and analgesic activities also exhibits antipyretic and which is described chemically as 2-(10, 11 dihydro-10-oxodibenzo [b,f] thiepin -2-yl) Propionic acid. it is a more powerful inhibitory effects to bradykinin (BK) than other NSAIDs.

Zaltoprofen drug has been used clinically for therapy of post-operative pain and low back pain. Zaltoprofen having molecular weight of 298.4 and melting point in the range of 131-133 C can be considered ideal to permeate through the skin.\(^6\)

**MATERIALS AND METHODS**

**Chemicals**

Carbopol 934 (Merck Ltd), Propyl Paraben (Suprim Chemicals), Sodium carboxy methyl cellulose (Merck Ltd), Methyl Paraban (Suprim Chemicals), Triethanolamine (SD Fine
chemical Ltd Mumbai), Propylene glycol-400 (SD Fine Chemical Ltd). All chemicals and reagents and chemicals used for the work are analytical grade.

**Animal Used**
Healthy young adult albino mice (200-300gm) were maintained in identical laboratory conditions (20º- 30º C temperature and relative humidity of 55-60 % with alternate light and darkness 10-12 hours each) and fed with commercial pellet diet and water.

**PREPARATION OF TOPICAL GEL**
Zaltoprofen try with various types of polymers such as Sodium CMC, Carbopol 934 using various formulae. The following some of the formulations with Carbopol 934 resulted in the best gel formulation, which was non-sticky, smooth and stable. Control sample also was formulated for testing of animal to check the activity of control formulation.

**Method for Preparation of Gel Containing zaltoprofen**
1 gm of Carbopol 934 was dispersed in 50 ml of distilled water with continuous stirring. 5 ml of double distilled water was taken and required quantity of methyl paraben and propyl paraben were dissolved by continues heating on water bath. Cool the solution, then to that added Propylene glycol 400. Further required quantity Zaltoprofen was mixed to the above mixture and volume made up to 100 ml by adding remaining double distilled water. Finally full mixed ingredients were mixed properly to the Carbopol 934 gel with continuous stirring and triethanolamine was added 3 to 4 drops to the formulation for adjustment of required skin pH (6.9-7) and to obtain the gel formulation at required consistency. The same method was followed for preparation of control sample without adding zaltoprofen.

**Formulation**
The method describes above and the formulae were tabulated in Table 1. Along with control sample gel were prepared with addition of 2.5g, 5g of zaltoprofen drug to prepared 5% and 10%Zaltoprofen gel respectively.

**Table 1: Different formulations prepared with this ingredients along with quantity**

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Ingredients</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Carbopol 934</td>
<td>1 gm</td>
</tr>
<tr>
<td></td>
<td>Methyl Paraben (0.5%)</td>
<td>0.2 ml</td>
</tr>
<tr>
<td></td>
<td>Propyl Paraben (0.2%)</td>
<td>0.1 ml</td>
</tr>
<tr>
<td></td>
<td>Propylene glycol 400 (5%)</td>
<td>5 ml</td>
</tr>
<tr>
<td></td>
<td>Triethanolamine (q.s)</td>
<td>1.2 ml</td>
</tr>
<tr>
<td></td>
<td>Distilled water</td>
<td>Up to 100 ml</td>
</tr>
</tbody>
</table>
EVALUATION OF TOPICAL GEL FORMULATION

Physical Evaluation
Physical parameters such as color and appearance were analyzed.

Washability
Gel formulations were applied on the skin surface and then ease and extent of washing with water were checked manually.

Measurement of pH
PH of the gel formulation was measured by using pH meter.

Spreadibility.\(^7\)
Spreadibility was measured by the apparatus which consists of a wooden block, which was provided by a pulley at one end\(^31\). By this method spreadibility was determined on the basis of slip and drag characteristics of gels. An excess of gel formulation (about 2 to 3 gm) under study was placed on this ground slide. The gel formulation was then sandwiched between this ground slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 kg weighted was located on the top of the two slides for 4 to 5 minutes to expel air and to provide a uniform film of the gel formulation between the slides. Excess of the gel formulation was scrapped off from the edges. The top plate was then subjected to pull of 80 gm. With the help of string attached to the hook and the time in seconds required by the top slide to cover a distance of 7.5 cm be noted. A small interval indicate better spreadibility. Spreadibility was calculated using the following formula.\(^7\)

\[
S = \frac{M \times L}{T}
\]

Where,
S = Spreadibility of the gel,
M = WeL = Length moved by the glass slide.
T = Time in sec. taken to separate the slide completely each other.

Stability Study.\(^7\)
The stability study was performed as per ICH guidelines 6. The gel formulation were filled in the collapsible tubes and stored at different temperatures and humidity conditions, viz. \(25^0\) C \(\pm 2^0\)C/ 60\% \(\pm 5\%\) RH, \(30^0\) C \(\pm 2^0\)C/ 65\% \(\pm 5\%\) RH, \(40^0\) C \(\pm 2^0\)C/ 75\% \(\pm 5\%\) RH for a period of 3 months and studied for appearance, pH, and spreadibility30 days.
Viscosity
Viscosity of gel formulation was determined by using Brookfield viscometer with spindle.

Drug content.\(^8\)
A specific quantity (100mg) of developed gel formulation and marketed gel formulation were taken and dissolved in 100ml of phosphate buffer of pH 6.8. The volumetric flask containing gel solution was shaken for 2 hours on mechanical shaker in order to get complete solubility of drug. This gel solution was filtered and estimated spectrophotometrically at 256.0 nm using phosphate buffer (pH 6.8) as blank.

Permeability studies: (diffusion cell)
Phosphate buffer of pH 6.8 was used for in vitro release as a receptor medium. The pre-treated skin of albino mice or was used in diffusion cell. The gel formulation was applied on the skin or cellophane membrane and then fixed in between donor and receptor compartment of diffusion cell. The receptor compartment contained phosphate buffer of pH 6.8. The temperature of diffusion medium was thermostatically controlled at 37º ± 1º by surrounding water in jacket and the medium was stirred by magnetic stirrer. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated at 256 nm against their respective blank.

Skin irritation test
0.5 gms of the gel was used as the test substance was applied to an area of approximately 6 cm\(^2\) of skin and covered with a gauze patch. The patch was loosely held in contact with the skin by means of a semi-occlusive dressing for the duration of 1 hour and gauze was removed. At the end of the exposure period, i.e., 1 hour, residual test substance was removed, without altering the existing response or integrity of the epidermis. Observations have recorded after removal of the patch. Control animals were prepared in the same manner and 0.5 gms of the gel base i.e., gel formulated using all ingredients except the herbal mixture was applied to the control animals and observations were made as similar to the test animals\(^8\). The gel was applied to the skin once a day for 7 days and observed for any sensitivity and the reaction if any was graded as\(^9\):
A – No reaction, B – Slight patchy erythema, C – Slight but confluent or moderate but patchy erythema, D – Moderate erythema, E – Severe erythema with or without oedema.
RESULTS

Appearance
The Zaltoprofen gel was Whitish in colour and translucent in appearance in table no.2,3,4,5.

PH and Spreadability
pH and Spreadability data of the all two gel formulation were given in table 2.3,4,5. For Spreadability lesser the time taken for the top plate to cover a fixed distance, indicates that there is less friction between surface and gel, hence it can be said that, gel is easily spreadable on skin.

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

Skin Irritation Test
The skin irritation test of the Zaltoprofen gel (F1, F2) formulations dose not showed a skin irritation. (Table.6.)

Table 2: Physical evaluation of all formulations (Initial month).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Colour</th>
<th>Appearance</th>
<th>Spreadibility</th>
<th>Ph</th>
<th>Washability</th>
<th>Skin Irritation Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>White</td>
<td>Clear and transparent</td>
<td>16.12</td>
<td>7</td>
<td>Good</td>
<td>Nil</td>
</tr>
<tr>
<td>F- I (5%)</td>
<td>White</td>
<td>Clear and transparent</td>
<td>18.21</td>
<td>7.1</td>
<td>Good</td>
<td>Nil</td>
</tr>
<tr>
<td>F – II (10%)</td>
<td>White</td>
<td>Clear and transparent</td>
<td>20.56</td>
<td>7</td>
<td>Good</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Table 3: 25 C ± 2 C/ 60% ± 5% RH at 2 months.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Colour</th>
<th>Appearance</th>
<th>Spreadibility</th>
<th>Ph</th>
<th>Washability</th>
<th>Skin Irritation Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>White</td>
<td>Clear and transparent</td>
<td>16.12</td>
<td>7</td>
<td>Good</td>
<td>Nil</td>
</tr>
<tr>
<td>F- I (5%)</td>
<td>White</td>
<td>Clear and transparent</td>
<td>20.01</td>
<td>7</td>
<td>Good</td>
<td>Nil</td>
</tr>
<tr>
<td>F – II (10%)</td>
<td>White</td>
<td>Clear and transparent</td>
<td>20.03</td>
<td>7.1</td>
<td>Good</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Table 4: 300 C ± 20C/ 65% ± 5% RH at 3rd months.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Colour</th>
<th>Appearance</th>
<th>Spreadibility</th>
<th>Ph</th>
<th>Washability</th>
<th>Skin Irritation Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>White</td>
<td>Clear and transparent</td>
<td>16.12</td>
<td>7</td>
<td>Good</td>
<td>nil</td>
</tr>
<tr>
<td>F- I (5%)</td>
<td>White</td>
<td>Clear and transparent</td>
<td>20.01</td>
<td>7.1</td>
<td>Good</td>
<td>nil</td>
</tr>
<tr>
<td>F – II (10%)</td>
<td>White</td>
<td>Clear and transparent</td>
<td>20.01</td>
<td>7.1</td>
<td>Good</td>
<td>NILL</td>
</tr>
</tbody>
</table>
Table 5: 400 C ± 20C/ 75% ± 5% RH at 3rd months

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Colour</th>
<th>Appearance</th>
<th>Spreadibility</th>
<th>Ph.</th>
<th>Washability</th>
<th>Skin irritation test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>White</td>
<td>Clear and transparent</td>
<td>16.12</td>
<td>7</td>
<td>Good</td>
<td>nil</td>
</tr>
<tr>
<td>F-I (5%)</td>
<td>White</td>
<td>Clear and transparent</td>
<td>20.01</td>
<td>7.1</td>
<td>Good</td>
<td>nil</td>
</tr>
<tr>
<td>F – II (10%)</td>
<td>White</td>
<td>Clear and transparent</td>
<td>20.02</td>
<td>7.2</td>
<td>Good</td>
<td>nil</td>
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</table>

Table 6: Skin irritation study results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>F-I (5%)</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>F – II (10%)</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

DISCUSSION

NSAIDs have been broadly used in the treatment of rheumatoid arthritis.[9] Topical application of gel formulation on the skin offer great advantage in a faster release of drug directly to site of action, independent of water solubility of the drug as compared to ointments and creams s.[10] The diffusion studies were performed using cellophane membrane.[11] Zaltoprofen is a novel non-steroidal anti-inflammatory drug it has powerful inhibitory effects on acute & chronic inflammation with less adverse reaction on the gastrointestinal tract than other NSAIDs. Topical formulations are very important classes of drug delivery systems, and their use are more widespread. Moreover, the experimental model exhibits a high degree of reproducibility. The results of anti-inflammatory activity after topical administration of Zaltoprofen gel reported in Table 2,3,4,6. The results showed that the NSAIDS effect of the formulation containing 5% of the Zaltoprofen gel and another gel formulation extract was equivalent to the effect of Standard gel formulation. From the overall results, we can conclude that topical gel formulation 5% and 10% and another formulation possesses both antinociceptive effect and anti-inflammatory which can be useful for the treatment of local inflammation. The data presented in this study demonstrate that the reported Zaltoprofen possess significant topical NSAIDS properties. Carbopol gels are prepared by the dissolving of polymer in distilled water, in which it swells up to 1000 times the original volume and neutralises the system. Carbopol 934P is a highly cross-linked polymer.

There are numerous procedures reported to prepare a gel among those the procedures which gives a best result that was selected.

The developed formulations could be better alternative in treating inflammatory conditions compared to marketed formulations of synthetic drugs.
CONCLUSION
Zaltoprofen is a novel non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory activities. From the above results it can be concluded that the Zaltoprofen gel formulation F1 and F2 was suitable for topical application and it shows comparable results with that of marketed product. It is inferred from results that the gel formulation good in appearance, homogenate and easily spreadable.\(^{[12]}\)

ACKNOWLEDGEMENT
The authors are thankful to Principal Dr. P. D. Patil, college of Pharmacy, Pune and Dr. S. P. Mahaparale, for providing necessary facilities to carry out this research work.

REFERENCES
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