Formulation and Development of Ketorolac Tromethamine ophthalmic Solution

Deepak Kumar Sarangi*

*Roland Institute of Pharmaceutical Sciences, Brahmapur, Odisha, India

ABSTRACT

An acetic acid derivative ketorolac tromethamine has found its applicability in both gram positive and gram negative bacterial ocular infection and used commonly associated with multiple doses. Ophthalmic medication stored in multiple dose containers is required by the U.S. Food and Drug Administration to contain a preservative so that patients are provided with microbe free medication. Benzalkonium chloride in concentrations from 0.1% to 0.0001% induced dose-dependent growth arrest and conjunctival epithelial cell death, either delayed or immediately after administration. In such case, a preservative Benzalkonium chloride must be used within reasonable bound. Benzalkonium chloride can provide more help than harm. Hence the present study focusing on to formulate a formulation for ketorolac tromethamine (0.5%) ophthalmic solution using different concentration of Benzalkonium chloride as preservative.

KEYWORDS:
Ketorolac tromethamine, Ophthalmic, benzalkonium chloride

1.INTRODUCTION

Ketorolac is used for short-term management of moderate to severe pain[^10]. It is usually not prescribed for longer than five days. Ketorolac is effective when administered with paracetamol to control pain in neonates because it does not depress respiration as do opioids. Ketorolac is also an adjuvant to opioid medications and improves pain relief. It is also used to treat dysmenorrhea. Ketorolac is used to treat idiopathic pericarditis, where it reduces inflammation.

Ketorolac is used for short-term pain control not lasting longer than five days, and can be administered orally, by intramuscular injection, intravenously, and by nasal spray. Ketorolac is initially administered by intramuscular injection or intravenously[^15]. Oral therapy is only used as a continuation from the intramuscular or intravenous starting point. Ketorolac is used during eye surgery to maintain mydriasis, or the 'relaxing' of the iris muscles that will allow surgeons to perform cataract surgery.

Ketorolac is contraindicated in those with hypersensitivity, allergies to the medication, cross-sensitivity to other NSAIDs, prior to surgery, history of peptic ulcer disease, gastrointestinal bleeding, alcohol intolerance, renal impairment, cerebrovascular bleeding, nasal polyps, angioedema, and asthma. Recommendations exist for cautious use of ketorolac in those who have experienced cardiovascular disease, myocardial infarction, stroke, heart failure, coagulation disorders, renal impairment, and hepatic impairment.[^2][^3]

Ketorolac is effective in treating ocular itching. The ketorolac ophthalmic formulation is associated with a decreased development of macular edema after cataract surgery and is more effective alone rather than as an opioid/ketorolac combination treatment.[^18][^19] Ketorolac has also been used to manage pain from corneal abrasions.

2.MATERIAL AND METHODS

Ketorolac tromethamine was received as generous gift from MSN Laboratories Ltd, Medak, A.P India. Benzalkonium chloride USP, Sodium chloride USP, Disodium EDTA USP, Sodium hydroxide USP, Hydrochloric acid USP, were received from Merck Chemicals Mumbai. All other chemicals used were of analytical reagent grade, available commercially and used as such without further processing.

*Correspondence to:
Deepak Kumar Sarangi
Roland Institute of Pharmaceutical Sciences,
Brahmapur, Odisha, India
Email: sarangi.dipu@gmail.com
Methods: The excipients Benzalkonium chloride is used as preservative, sodium chloride as isotonic modifier and remaining are as diluents.

3.RESULT & DISCUSSION

<table>
<thead>
<tr>
<th>Name of the Ingredients</th>
<th>T1 (mg/ml)</th>
<th>T2 (m/ ml)</th>
<th>T3 (m/ ml)</th>
<th>T4 (m/ ml)</th>
<th>T5 (m/ ml)</th>
<th>T6 (m/ ml)</th>
<th>T7 (m/ ml)</th>
<th>T8 (m/ ml)</th>
<th>T9 (m/ ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac tromethamine</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>0.00</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Disodium EDTA</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>7.9</td>
<td>7.9</td>
<td>7.9</td>
<td>7.9</td>
<td>7.9</td>
<td>7.9</td>
<td>6.0</td>
<td>6.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Octoxynol-40</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
<td>adj pH</td>
</tr>
<tr>
<td>Water for injection</td>
<td>Qs</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
</tr>
</tbody>
</table>

Table : 1 Formulation of Ketorolac Tromethamine Ophthalmic Solution

PROCEDURE FOR PRESERVATIVE EFICACY TEST:
Take required number of product containers to collect 15ml of product and transfer the product into the six sterile test tubes. Label all the containers with Name of Sample, B. No., Name of the organism and Date. Incubation. vortex the selected tube of the respective culture and add 0.15ml of the selected culture suspension of organisms to the tubes containing 15ml of sample each vortex the contents.

Note: The volume of culture suspension used should be in between 0.5% and 1% of the volume of the product in the container.

9.5 Record the calculation details of quantity of culture suspension required for each organism in format for Sample preparation. Carry out the Initial count of the cultures which is added to the Sample as given in 6.1.2 to 6.1.6; 8.0 & 9.0 to a dilution up to 10⁻⁷ and using 9ml of Sterile Dey-Engley Neutralizing broth as Diluent and document the colony count details in the Report for Initial count. At the end of 6 hours (From the culture addition to the product), carryout the serial dilution of the sample test tube as per illustration below. Select the container which is inoculated with Escherichia coli, mix the solution by using vortex mixer and transfer 1ml to 9ml of sterile neutralizer (Dey-Engley Neutralizing broth). Label the tube with organism name and dilution (10⁻¹). Vortex the tube (10⁻¹) and transfer 1ml each of dilution to a set of sterile petridish labeled as 10⁻¹ with the name of Sample, B. No. Time interval and Date. and to a tube containing 9ml of sterile neutralizer, Label the tube with organism name and 10⁻². Follow step number 13.2 for serial dilution up to tube labeled as 10⁻⁶. Pour about 20ml of pre-sterilized media of Soyabean casein digest agar to each petriplate and gently rotate the plates in clockwise and anticlockwise direction on the LAF bench for uniform mixing of culture and media. Allow the plates to solidify. After solidification of plates, incubate all the plates at 30 to 35°C for 3 days. Repeat the step 13.1 to 13.5 with, Pseudomonas aeruginosa, Staphylococcus aureus & Environment Isolate Repeat with A. niger & C. albicans except using Sabouraud dextrose agar and incubating at 20°C to 25°C for 5 to 7 Days. Record the colony counts in the format for Report for 6 Hrs. The inoculated sample contains has to be stored at 20 to 25°C up to 28 days for further testing as per schedule time point. Repeat the procedure for 24 hours, 7th day, 14th day and 28th days & Record in the respective Time point reports. Calculate the log reduction after each time point of test as per formula in Report. Acceptance Criteria For Parenteral and ophthalmic preparations.

Collect of water for injection in a cleaned glass container and parching it with nitrogen gas for 30 min. Take some of water for injection of in cleaned stainless steel vessels to it add and dissolve EDTA disodium, octoxynol40, sodium chloride under continuous stirring to get a clear solution. Weigh accurate batch quantity of Ketorolac tromethamine add and dissolve it into the bulk solution of under constant stirring to dissolve it completely. Measure accurate quantity of benzalkonium chloride and add and dissolve it into the bulk solution of step no3 to dissolve it completely. Check the pH of the resultant bulk solution and if necessary, adjust the pH to 7.4 using 1N Sodium Hydroxide solution for 1N Hydrochloric acid solution. Make up the volume of the bulk solution to 1 lit using water for injection. Remove the resultant solution (approx) as a before filtration sample and submit it for analysis. Filter the remaining bulk solution through 0.22 μ PVDF membrane filter submit the after filtration sample for analysis. Fill the filtered bulk solution into 5ml 3 piece and 5ml BFS containers with fill volume of 3ml.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Log reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 Hours</td>
</tr>
<tr>
<td>Bacteria</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Fungi</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>B</td>
</tr>
</tbody>
</table>

* NR: No recover
** NI: No increase

Table 2: Microorganism Log reduction
The A criteria express the recommended efficacy to be achieved. In justified case where the A criteria cannot be attained, for example for reasons of an increased risk of

### Table no 3: Stability Protocol

**Stability Design:**
The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of drug substance and from stability studies on the drug substances. The likely changes on storage and the rationale attributes to be tested in formal stability studies should be stated.

**CONFLICTS OF INTEREST**
The authors do not have any conflict of interest.

**REFERENCE**


