Full Length Research Paper

Formulation and evaluation of aceclofenac ophthalmic gel

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This study deals with ophthalmic gel of aceclofenac which is potent non-steroidal anti-inflammatory drugs (NSAIDs) and was formulated using polymers hydroxy propyl methyl cellulose (HPMC) (15) cps with methyl cellulose (40) cps and HPMC (15) cps with Carbopol (940). The gels (HP with MC) and (HP with CB), were sterilized and assessed for various parameters like clarity, pH, physical appearance, physical stability, viscosity and uniformity of drug content. The release rate from the aforementioned formulation within a period of 9 h were almost HP with MC batch H4 (84.66%) and for HP with CB batch C1 (80.46%); both ophthalmic gels obeyed zero order kinetics for drug release. The ocular irritation was carried out on male albino rabbits and found no redness, no inflammation and no increases tear. Both formulations in gel were found to be more stable at ambient, refrigerator and incubated temperature. The stability of the gels was evidenced by the degradation rate constant. Ophthalmic gel formulated by HP with MC and HP with CB gels proves to be viable alternative to conventional eye drops as it offers longer preconveal residence time and excellent ocular tolerance.

Key words: Carbopol 940 (CB), ophthalmic, gel, hydroxy propyl (HP), methyl cellulose (MC).

INTRODUCTION

Ophthalmic drug delivery is one of the most interesting and challenging factors facing the pharmaceutical scientist (Shivanand et al., 2008). Existing ocular drug delivery systems are fairly primitive and inefficient, due to low bioavailability of eye drops viscous liquid and semisolid preparations were tried as alternative therapeutic system. The bioavailability of these medicines can be increased by increasing the viscosity of the preparation up to gel like consistency using various polymer like Carbopol-940, sodium carboxy methyl cellulose (SCMC), hydroxy propyl methyl cellulose (HPMC), etc. The use of such polymeric vehicles proved to enhance the ocular bioavailability or the therapeutic efficacy of applied drugs, prolong the drug duration and reduce the patient non compliance problem (Naresh et al., 2008).

However, in the recent years, there has been explosion of interest in the polymer based delivery systems. By utilization of the principles of sustained release with semi synthetic polymers as embodied by ophthalmic gel offers an attractive approach to the problem of prolonging preconveal drug residence times (Quinones et al., 2008). The use of gel as a delivery system can increase the residence time of drugs in ocular cul-de-sac and consequently enhance bioavailability. Gel delivery systems have several advantages such as the ease of administration, none greasy, patient compliance, high residence time in eye and better drug release (Sankar et al., 2005). Aceclofenac is a novel, multiple action non-steroidal anti-inflammatory drug that is currently approved in many countries for the treatment of ophthalmic disease. Aceclofenac reduce pain and inflammation by inhibiting the enzyme cyclooxygenase II, which is involved in the production of prostaglandins, the pain and inflammatory mediator (Debnath et al., 2009).

According to views and research delivered by many

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authors in favor of sustained action of drug by semi synthetic polymers, HPMC (15) cps, methyl cellulose (40) cps and HPMC (15) cps, Carbopol (940) as gel delivery system. The objective of this study was to develop ophthalmic gels of aceclofenac using HPMC (15) cps, methyl cellulose (40) cps, HPMC (15) cps, and Carbopol (940) as mucoadhesives polymers, and evaluate it with the aim to provide sustained local action in the eye and improve patient compliance.

FORMULATION METHOD

Polymer hydration method

The polymer was taken in a 250 ml beaker and water was added. This was allowed to soak for about 1 h and to this, the required amount of drug and other additives was added. The stirring was continued to get a homogenous dispersion of the drug in the gel. The gel was buffered at a pH of 7.2 to 0.05 and was sterilized by ultraviolet (UV) radiation for 30 min, aseptically filled in sterile plastic container, and was labeled (Shivanand et al., 2008).

Experimental design (Taguchi method)

According to several engineering and pharmaceutical scientists, Taguchi method is a designer tool to predict the optimized formulations by considering the results from experimental formulations. The results obtained by Taguchi method mainly depends on many factors (variables) and levels.

Taguchi method detects the optimized formulations by using the tool, that is, orthogonal array (OA). OA is the matrix of numbers arranged in columns and rows. The Taguchi method quantifies the present variations by signal to noise (S/N) ratio. These S/N ratios are used to measure the effect of factors (variables) on performing experimental formulations. According to closeness of the average response of optimized formulations, the S/N ratio determines the result from experimental formulations as type of characteristics: smaller is better, nominal is best and larger is better.

This design, 2^2 Taguchi orthogonal array, requires four experimental formulations with two parameters (concentration of polymer A (HPMC with methyl cellulose) and concentration of polymer B (HPMC with Carbopol 940), at two levels (high and low) of each. Interactions were neglected (Dobrzanski et al., 2007). There are two S/N ratios of common interest for optimization of static problems:

Smaller-the-better

\[ n = -10 \log_{10} \left( \text{mean of sum of squares of measured data} \right) \]

This is usually the chosen S/N ratio for all factors (variables) on performing formulations, like “concentration of polymers”, etc., for which the ideal value is zero. The generic form of S/N ratio then becomes,

\[ n = -10 \log_{10} \left( \text{mean of sum of squares of \{measured} - \text{ideal} \right) \]

Larger-the-better

\[ n = -10 \log_{10} \left( \text{mean of sum squares of reciprocal of measured data} \right) \]

This case has been converted to smaller-the-better by taking the reciprocals of measured data and then taking the S/N ratio as in the smaller-the-better case.

The results obtained by Taguchi method mainly depends on many factors (variables) and levels. Taguchi method detects the optimized formulations by using the tool, that is, OA. The best optimized batch for both ophthalmic gels was obtained by analyzing factors (variables) and levels for viscosity, drug content and cumulative drug release as calculated in Tables 1 to 13 and Figures 1 to 6.

Here, 22 taguchi designs is applied where 2 levels that is high and low with 2 factors that is concentration of polymers (A) HPMC with methyl cellulose and concentration of polymers (B) HPMC with carbopol 940 (Tables 1 and 2)

The method is applied on parameters (viscosity, drug content and percent cumulative drug release), each value is taken in triplicate. Observation is calculated as mean, standard deviation, log standard deviation and S/N ratio.

S/N ratio is calculated as by formula: \( 1/\text{value} \times M + 1/2nd \text{value} \times x. \) Third value MRC Km+ gives new value. Take log of new value and multiply with 10. Final S/N value is determined for individual parameters (Tables 2 to 9).

A1, A2 and B1, B2 graph for parameters (viscosity, drug content and percent cumulative drug release) is obtained by taking values of mean, log standard deviation and S/N ratio for both Gels. Where A1 is the average of = lower value + lower value/2, A2 is the average of = higher value + higher value/2, B1 is the average of = highest + second highest value/2, B2 is the average of = highest + lowest value/2. (Figures 1 to 6).

Table 1. Level of process parameters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Concentration of polymers</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Taguchi L_4 (2^2) orthogonal array for HPMC:methyl cellulose ophthalmic gel.

<table>
<thead>
<tr>
<th>No. of formulation</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPMC</td>
</tr>
<tr>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td>2</td>
<td>-1</td>
</tr>
<tr>
<td>3</td>
<td>+1</td>
</tr>
<tr>
<td>4</td>
<td>+1</td>
</tr>
</tbody>
</table>

Table 3. Taguchi L_4 (2^2) orthogonal array for HPMC:Carbopol 940 ophthalmic gel.

<table>
<thead>
<tr>
<th>No. of formulations</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPMC</td>
</tr>
<tr>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td>2</td>
<td>-1</td>
</tr>
<tr>
<td>3</td>
<td>+1</td>
</tr>
<tr>
<td>4</td>
<td>+1</td>
</tr>
</tbody>
</table>
Table 4. Experimental data (optimization of viscosity) for HPMC: MC Ophthalmic Gel.

<table>
<thead>
<tr>
<th>S/N</th>
<th>Observed viscosity</th>
<th>Mean</th>
<th>S.D</th>
<th>Log of S.D</th>
<th>S/N Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11000</td>
<td>11150</td>
<td>10875</td>
<td>11008.33</td>
<td>2.138</td>
</tr>
<tr>
<td>2</td>
<td>12000</td>
<td>12360</td>
<td>11840</td>
<td>12066.6</td>
<td>2.42</td>
</tr>
<tr>
<td>3</td>
<td>12000</td>
<td>11630</td>
<td>11540</td>
<td>11723.33</td>
<td>2.38</td>
</tr>
<tr>
<td>4</td>
<td>11650</td>
<td>11320</td>
<td>12000</td>
<td>11656.66</td>
<td>2.53</td>
</tr>
</tbody>
</table>

S.D: Standard deviation; MC: methyl cellulose.

Table 5. Experimental data (optimization of drug content) for HPMC: MC ophthalmic gel.

<table>
<thead>
<tr>
<th>S/N</th>
<th>Observed drug content</th>
<th>Mean</th>
<th>S.D</th>
<th>Log of S.D</th>
<th>S/N Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94.20</td>
<td>94.8</td>
<td>95.6</td>
<td>94.8</td>
<td>-0.153</td>
</tr>
<tr>
<td>2</td>
<td>95.3</td>
<td>94.1</td>
<td>95.9</td>
<td>95.1</td>
<td>-0.125</td>
</tr>
<tr>
<td>3</td>
<td>95.1</td>
<td>94.7</td>
<td>94.3</td>
<td>94.7</td>
<td>-0.3979</td>
</tr>
<tr>
<td>4</td>
<td>95.7</td>
<td>95.3</td>
<td>95.2</td>
<td>95.4</td>
<td>-0.577</td>
</tr>
</tbody>
</table>

S.D: Standard deviation; MC: methyl cellulose.

Table 6. Experimental data (optimization of cumulative drug release) for HPMC: MC ophthalmic gel.

<table>
<thead>
<tr>
<th>S/N</th>
<th>Observed cumulative drug release</th>
<th>Mean</th>
<th>S.D</th>
<th>Log of S.D</th>
<th>S/N Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74.40</td>
<td>74.72</td>
<td>75.05</td>
<td>74.72</td>
<td>-0.488</td>
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<tr>
<td>2</td>
<td>80.72</td>
<td>79.91</td>
<td>80.02</td>
<td>80.21</td>
<td>-0.357</td>
</tr>
<tr>
<td>3</td>
<td>76.94</td>
<td>75.91</td>
<td>76.04</td>
<td>76.29</td>
<td>-0.251</td>
</tr>
<tr>
<td>4</td>
<td>84.21</td>
<td>84.75</td>
<td>85.04</td>
<td>84.66</td>
<td>-0.375</td>
</tr>
</tbody>
</table>

S.D: Standard deviation; MC: methyl cellulose.

Table 7. Experimental data (optimization of viscosity) for HPMC: Carbopol 940 ophthalmic gel.

<table>
<thead>
<tr>
<th>S/N</th>
<th>Observed viscosity</th>
<th>Mean</th>
<th>S.D</th>
<th>Log of S.D</th>
<th>S/N Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8000</td>
<td>8260</td>
<td>7929</td>
<td>8063</td>
<td>2.24</td>
</tr>
<tr>
<td>2</td>
<td>7680</td>
<td>7150</td>
<td>8070</td>
<td>7633.3</td>
<td>2.66</td>
</tr>
<tr>
<td>3</td>
<td>7000</td>
<td>7650</td>
<td>7830</td>
<td>7493.3</td>
<td>2.64</td>
</tr>
<tr>
<td>4</td>
<td>8430</td>
<td>8850</td>
<td>8010</td>
<td>8430</td>
<td>2.62</td>
</tr>
</tbody>
</table>

S.D: Standard deviation; MC: methyl cellulose.

Table 8. Experimental data (optimization of drug content) for HPMC: Carbopol 940 ophthalmic gel.

<table>
<thead>
<tr>
<th>S/N</th>
<th>Observed drug content</th>
<th>Mean</th>
<th>S.D</th>
<th>Log of S.D</th>
<th>S/N Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94.3</td>
<td>94.1</td>
<td>93.9</td>
<td>94.1</td>
<td>-0.6980</td>
</tr>
<tr>
<td>2</td>
<td>93.0</td>
<td>93.4</td>
<td>92.6</td>
<td>93.0</td>
<td>-0.0245</td>
</tr>
<tr>
<td>3</td>
<td>93.6</td>
<td>93.1</td>
<td>92.8</td>
<td>93.1</td>
<td>-0.3935</td>
</tr>
<tr>
<td>4</td>
<td>92.1</td>
<td>93.1</td>
<td>92.8</td>
<td>92.6</td>
<td>-.2897</td>
</tr>
</tbody>
</table>

S.D: Standard deviation.
### Table 9. Experimental data (optimization of cumulative drug release) for HPMC: Carbopol 940 ophthalmic gel.

<table>
<thead>
<tr>
<th>S/N</th>
<th>Observed cumulative drug release</th>
<th>Mean</th>
<th>S.D</th>
<th>Log of S.D</th>
<th>S/N Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75.08</td>
<td>74.93</td>
<td>0.104</td>
<td>-0.993</td>
<td>-30</td>
</tr>
<tr>
<td>2</td>
<td>81.48</td>
<td>80.68</td>
<td>1.151</td>
<td>-0.061</td>
<td>-28.86</td>
</tr>
<tr>
<td>3</td>
<td>85.62</td>
<td>85.03</td>
<td>0.615</td>
<td>-0.211</td>
<td>-27.95</td>
</tr>
<tr>
<td>4</td>
<td>71.63</td>
<td>70.81</td>
<td>0.600</td>
<td>-0.221</td>
<td>-26.98</td>
</tr>
</tbody>
</table>

S.D: Standard deviation. MC: Methyl cellulose

### Table 10. Summary of analyses of factor effects for HPMC:MC ophthalmic gel.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean</th>
<th>Log(s)</th>
<th>S/N Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>+1</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>+1</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>Drug content</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>+1</td>
<td>+2</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>+1</td>
<td>+2</td>
<td>2</td>
</tr>
<tr>
<td>In vitro cumulative drug release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>+2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>+1</td>
<td>+2</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 11. Summary of analyses of factor effects for HPMC: Carbopol 940 ophthalmic gel.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean</th>
<th>Log(s)</th>
<th>S/N Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>+2</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>+2</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>Drug content</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>+2</td>
<td>+1</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>+2</td>
<td>+1</td>
<td>2</td>
</tr>
<tr>
<td>In vitro cumulative drug release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>+1</td>
<td>+1</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>+1</td>
<td>+2</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 12. Final optimized parameters values for HPMC:MC ophthalmic gel.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Optimized level</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+1 (High conc. of HPMC)</td>
</tr>
<tr>
<td>B</td>
<td>+1 (High conc. of MC)</td>
</tr>
</tbody>
</table>

### Table 13. Final optimized parameters values for HPMC:Carbopol 940 ophthalmic gel.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Optimized level</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-1 (Low conc. of HPMC)</td>
</tr>
<tr>
<td>B</td>
<td>+1 (High conc. of Carbopol 940)</td>
</tr>
</tbody>
</table>

### Figure 1. Cumulative drug release graphs HPMC and methyl cellulose gel. (A) Estimated factor effect; (B) Estimated factor effect on logs.

after seeing the graph of A1, A2 and B1, B2. A1 is considered as 1 and A2 is considered as 2. B1 is also considered as 1 and B2 is 2. The optimized batch was calculated by counting A and B for each parameter of both gels (Table 10 to 13).
Evaluation of aceclofenac ophthalmic gels

**Determination of pH**

Accurately 2.5 g of gel was weighed and dispersed in 25 ml of purified water. The purified water was used because it has aqueous solubility and it also match with the pH of lachrymal fluid. The pH of the gel was measured using glass electrode pH meter (Pandey et al., 2010).

**Determination of viscosity**

Viscosity of the gel was determined using a Brook field Viscometer, Spindle No 7 (Brookfield Engineering Labs., USA). All the formulated gels were sheared at 6 rpm for 5 min. The shear stress was recorded for each formulation (Vijayendra et al., 2005).

**Determination of mucoadhesives strength**

Mucoadhesive strength of 1% aqueous solution of optimized batch (H4 and C1) was studied with QTS-25 Texture Analyzer (Brookfield Engineering Labs., USA). Freshly excised goat by using goat conjunctival mucosa, was attached to the upper probe of the instrument, and drop of 1% gel solution was kept below that. The upper probe was then lowered at a speed of 10 mm/min to touch the surface of the solution. A force of 100 g was applied for 25 s, respectively, to ensure intimate contact between the membrane and the gel. The surface area of exposed mucous membrane was 1.13 cm² (Shyamoshree and Bandyopadhyay, 2010). The studies were
Figure 5. Drug Content HPMC and Carbopol 940 gel. (A) Estimated factor effect; (B) Estimated factor effect on logs.

Figure 6. Viscosity HPMC and Carbopol 940. (A) Estimated factor effect; (B) Estimated factor effect on logs.

also conducted for HPMC, methyl cellulose and Carbopol 940, and results were compared.

**Determination of drug content**

Drug content was determined by dissolving accurate weighed quantity of gel in phosphate buffer (7.2), because the drug is completely soluble on that pH. After suitable dilutions, the absorbance was recorded by UV Vis spectrophotometer at 273.6 nm. Drug content was determined using slope of the standard curve previously plotted (Pandey et al., 2010).

**Clarity testing (IP 2007)**

Clarity test was done against dark and white background board apparatus, for the presence of foreign particles.

**In-vitro release study**

In vitro release test was performed with Franz diffusion cell (KC cell) by using egg membrane for the study. The membrane was separated by dipping the egg in concentrated HCl solution; with properly rotating the egg, the membrane was obtained by dissolving the CaCO₃ coat of egg. The semi permeable egg membrane was tied on one end of open ended cylinder (diameter 1.6 cm²) which acts as donor compartment. One gram of the gel was placed outside the semi permeable egg membrane which acts as corneal epithelium. The entire surfaces of the membrane were in contact with the receptor compartment containing 25 ml of phosphate buffer pH 7.2. The receptor compartment was continuously stirred (50 rpm) using magnetic stirrer at 37°C. The study was carried out for 9 h. The sample was withdrawn at predetermined time intervals and the same volume was replaced with fresh buffer medium. The absorbance of the withdrawn sample was measured after suitable dilutions at 273.6 nm to estimate aceclofenac. The experiment was carried out in triplicate and average values were reported (Balasubramaniam et al., 2008).

**Drug release kinetics**

The drug release data was plotted using various kinetics, such as, zero order and first order. Higuchi's kinetics and Korsmeyer's equation were used to evaluate the drug release mechanism. The obtained data of present study for zero order equation were studied from in vitro drug release and were plotted as cumulative amount of drug release versus time (Jain, 2007).

\[ C = K_0t \] (Jain; 2001), (Lachman; 1991)

**Stability study**

Chemical and physical stabilities of optimized formulations were assessed under various storage conditions, namely room temperature (RT), 5±1 and 40±1°C and 75% RH as per ICH guideline (Jain, 2007).

**In-vivo studies**

**Ocular irritation test**

The potential ocular irritancy effects of the formulations were
evaluated by observing for any redness, inflammation or increase in tear production. Local irritation test was performed to provide estimation of human ocular response to the tested products (Griffith et al., 1980). Both formulations were tested on 2 albino male rabbits. The treatment was performed by single instillation (0.02 g) of gel under tests into the conjunctival sac of left eye every 24 h for 3 days. Plain gel base was instilled into the right eye. Both eyes of the rabbit under test were examined for any signs of irritation before treatment and up to 10 h after instillation (Shankar et al., 2005).

RESULTS AND DISCUSSION

The pH

The pH of the optimized formulations for batch H₄ was 7.2 and batch C₁ was 7.2. So this would not produce any irritation after administration (Optimization according to Taguchi design) (Tables 14 and 16).

Viscosity

The viscosity of various formulated aceclofenac ophthalmic gels by (HPMC, methyl cellulose) and (HPMC, Carbopol 940) is shown in Tables 14 and 16. Viscosities were determined for optimized batch H₄ as 11656.66 cps and batch C₁ as 8063 cps. All gels were found to have non-Newtonian type of flow. This was due to the concentration of polymer. When the concentration of polymers increased, the viscosity may also increase the interaction between polymers form gel (Tables 14 and 16).

Mucoadhesives strength

The mucoadhesives strength of optimized formulations provides intimate contact of gel to the ocular cul-de-sac and improves sustained action of drug. The mucoadhesives strength was determined by texture analyzer using goat conjunctival mucosa. The applied force by probe was 100 g and residence time was 25 s. As per observations obtained from Table 3, batch H₄ (HPMC, methyl cellulose gel) and batch C₁ (HPMC, Carbopol 940 gel) show H₄ (14.49) and C₁ (13.83) according to Taguchi design (Tables 14 and 16).

Drug content

The drug content values of all batches from both ophthalmic gels were found to be in range between 95 and 99% (Tables 14 and 16).

Clarity testing

All formulations were found to be off white and clear. Due to the presence of foreign particles formulation leads to ocular irritation. So, the preparations are free from foreign particle so that it improves ocular tolerance.

In-vitro release study

The results of the in vitro release study from different gels by the KC cell (25 mm), are as shown in Figure 1. In vitro release for both gel formulations showed a linear relationship between cumulative percentage release versus time. In H₄ batch of HPMC, MC showed 84.66% drug release. In C₁ batch of HPMC, Carbopol 940 showed 80.46% drug release, through KC cell within a period of 9 h. Drug release obeys zero order kinetics (Figure 2). The in vitro release order of different ophthalmic gel formulations was expressed in the decreasing order after 9 h. The difference in release rate could be due to viscosity and solubility of aceclofenac in HPMC with MC and HPMC with Carbopol 940. As given in (Tables 15 and 17 and Figures 7 and 8).

Drug release kinetics

The release profiles of optimized formulation were best described by a model that represents systems where drug diffusion occurs through a polymeric structure or network,

\[
\frac{M_t}{M_\infty} = k^n (r^2=0.942) \text{ and } (0.902)
\]

where \(M_t/M_\infty\) is the fractional release of the drug, \(t\) is the release time, \(k\) is a constant, and \(n\) is the release constant, indicative of the mechanism of drug release.

From Table 8, it was clear that optimized formulations and zero order release kinetics H₄ have \(r^2=0.942\) and C₁ have \(r^2=0.902\) (Tables 20 and 21).

Stability studies

Stability studies of optimized formulations were carried out on the basis of ICH guidelines and the observed values of K (Stability constant), \(t_{0.5}\) (half life), and \(T_{10%}\) (shelf-life) of optimized formulation after different storage conditions are shown in Tables 18 and 19.

### Table 14. Physico-chemical parameters of the optimized formulations. HPMC:Methyl cellulose aceclofenac ophthalmic gel.

<table>
<thead>
<tr>
<th>Optimized batch: H₄</th>
<th>pH</th>
<th>Viscosity</th>
<th>Drug content</th>
<th>Mucoadhesive strength</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.2</td>
<td>11656.66</td>
<td>95.4</td>
<td>14.49</td>
</tr>
<tr>
<td></td>
<td>7.2</td>
<td>11656.66</td>
<td>95.4</td>
<td>14.49</td>
</tr>
</tbody>
</table>


Table 15. *In vitro* drug release of optimized batch H4.

<table>
<thead>
<tr>
<th>Optimized Batch code H4</th>
<th>Time (h)</th>
<th>0</th>
<th>0.08</th>
<th>0.25</th>
<th>0.50</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>16.81±0.571</td>
<td>20.40±0.260</td>
<td>26.91±0.779</td>
<td>32.54±0.282</td>
<td>36.47±0.25</td>
<td>49.82±0.170</td>
<td>61.96±0.100</td>
<td>79.41±0.176</td>
<td>84.66±0.439</td>
</tr>
</tbody>
</table>

Table 16. HPMC:Carbopol 940 aceclofenac ophthalmic gel: physico-chemical parameters of the optimized formulations.

<table>
<thead>
<tr>
<th>Optimized batch: C1</th>
<th>pH</th>
<th>Viscosity</th>
<th>Drug content</th>
<th>Mucoadhesive strength</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.2</td>
<td>8063 cps</td>
<td>94.1</td>
<td>13.83</td>
</tr>
</tbody>
</table>

Table 17. *In vitro* drug release of optimized batch C1.

<table>
<thead>
<tr>
<th>Optimized Batch code H4</th>
<th>Time (h)</th>
<th>0</th>
<th>0.08</th>
<th>0.25</th>
<th>0.50</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>17.04±0.280</td>
<td>21.32±0.195</td>
<td>25.89±0.096</td>
<td>29.91±0.508</td>
<td>34.75±0.091</td>
<td>43.86±0.136</td>
<td>52.62±0.220</td>
<td>67.91±0.136</td>
<td>80.46±1.15</td>
</tr>
</tbody>
</table>

Table 18. Shelf-life of optimized formulation batch F4.

<table>
<thead>
<tr>
<th>S/N</th>
<th>Parameter</th>
<th>5 ± 1°C</th>
<th>Room temperature</th>
<th>40 ± 1°C, 75% (RH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K (day⁻¹)</td>
<td>3.65 × 10⁻⁴</td>
<td>2.5 × 10⁻⁵</td>
<td>5.3 × 10⁻⁶</td>
</tr>
<tr>
<td>2</td>
<td>t½ (days)</td>
<td>1874.53</td>
<td>2736.84</td>
<td>1290.92</td>
</tr>
<tr>
<td>3</td>
<td>T₁₀% (days)</td>
<td>284.93</td>
<td>416</td>
<td>196.22</td>
</tr>
</tbody>
</table>

Table 19. Shelf-life of optimized formulation batch C1.

<table>
<thead>
<tr>
<th>S/N</th>
<th>Parameter</th>
<th>5 ± 1°C</th>
<th>Room temperature</th>
<th>40 ± 1°C, 75% (RH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K (day⁻¹)</td>
<td>3.5 × 10⁻⁴</td>
<td>3.3 × 10⁻⁴</td>
<td>6.6 × 10⁻⁷</td>
</tr>
<tr>
<td>2</td>
<td>t½ (days)</td>
<td>1943.75</td>
<td>2073.35</td>
<td>1036.6</td>
</tr>
<tr>
<td>3</td>
<td>T₁₀% (days)</td>
<td>295.45</td>
<td>3315.15</td>
<td>157.57</td>
</tr>
</tbody>
</table>
Figure 7. Normal rabbit eye after 24 h of gel administration

Figure 8. HPMC:Carbopol and HPMC:Methyl cellulose gel in-vitro drug release studies of various formulations.
Table 20. Diffusion kinetics parameters of optimized formulation H4.

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Higuchi equation</th>
<th>Korsmeyer’s Peppas equation</th>
<th>First order equation</th>
<th>Zero order</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>R²</td>
<td>N</td>
<td>R²</td>
</tr>
<tr>
<td>H4</td>
<td>24.24</td>
<td>0.97</td>
<td>0.404</td>
<td>0.250</td>
</tr>
</tbody>
</table>

N- Release exponent, R- Correlation coefficient.

Table 21. Diffusion kinetics parameters of optimized formulation C1.

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Higuchi equation</th>
<th>Korsmeyer’s Peppas equation</th>
<th>First order equation</th>
<th>Zero order</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>R²</td>
<td>N</td>
<td>R²</td>
</tr>
<tr>
<td>C1</td>
<td>17.57</td>
<td>0.934</td>
<td>0.321</td>
<td>0.207</td>
</tr>
</tbody>
</table>

N- Release exponent, R- Correlation coefficient

In-vivo studies

Ocular irritation test

None of the optimized formulation showed any sign of redness, inflammation and increase in tear production, after comparison with placebo formulations.

Conclusion

According to graphs and tables delivered by ophthalmic gels. It is concluded that both aceclofenac ophthalmic gel prepared with HPMC:methyl cellulose and HPMC:Carbopol 940, are viable alternative of conventional eye drops, because it proves to increased contact time, frequency of administration and excellent ocular tolerance; so, in all ways it improves patient compliance.

REFERENCES


