SHORT NOTE

FORMULATION AND IN-VITRO EVALUATION OF ZOLMITRIPTAN IN SITU GEL FOR NASAL ADMINISTRATION

ABSTRACT

The aim of present investigation was formulation and in-vitro evaluation of in situ gel for the nasal delivery of zolmitriptan. The in situ gel was prepared by temperature induced gelation technique using Pluronic with mucoadhesive polymer hydroxy propyl methyl cellulose K₄M in different ratios. The in situ gels so prepared were characterized and from the evaluation studies, batch PH₂ was optimized and further subjected for stability studies at 30±2°C and 60±5% RH for 90 days. These formulations retained good stability at accelerated conditions and also did not show any remarkable damage to nasal mucosa in histopathological study. Owing to these properties it can be used as an effective delivery system for the nasal route.

Keywords: Zolmitriptan, In situ gel, HPMC K₄M, mucoadhesion, temperature induced gelation technique.

EXPERIMENTAL

Materials

Zolmitriptan was from Zydus Cadila, Ahmedabad, India. Pluronic F-127 from Sigma Chemicals (Germany), HPMC K₄M from Dow Chemical Company (US), benzalkonium chloride from Optho Remedies Ltd. (New Delhi, India). All other reagents used were of analytical grade.

Methods

Formulation (Cold Method)

Pluronic F127 (PF127) and zolmitriptan were solubilized in ultra-pure water containing 1% propylene glycol. Small amount of citric acid was also used to solubilize zolmitriptan. 18% (w/V) concentration of PF127 was used, because 18% (w/V) was found to be the lowest concentration of PF127, that exhibited thermoreversible property below 34°C (temperature of the nasal cavity). The liquid was left at 4°C until a clear solution was obtained. Bioadhesive polymer HPMC K4M was slowly added to the solution with continuous agitation (Table I). Appropriate quantities of sodium chloride and benzalkonium chloride were also added; simultaneously pH of formulations was adjusted from pH 4.5-5.5 using 0.1N HCl. Formulations were filled in vials, sealed and stored in a refrigerator (4–8°C) until use.

INTRODUCTION

Nasal delivery has been focused as an important route because of its several advantages. In situ gelling systems are the aqueous polymeric solutions that are transformed into gels due to changes in environmental conditions, like temperature and pH. Zolmitriptan is a second-generation triptan prescribed for patients with migraine attacks. It has a selective action on serotonin receptors (5-HT1B/1D). The nasal dose is claimed to be absorbed rapidly, with detectable plasma zolmitriptan concentrations within 2 min after administration. Patients with migraine generally suffer from nausea and vomiting, therefore oral treatment can be inconvenient or could fail. The absolute bioavailability of zolmitriptan is up to 40% for both oral and nasal dosage forms. The faster clearance of the drug from the nasal cavity causes the low bioavailability for the nasal formulation. The aim of the present study was to overcome the problem of poor bioavailability and therapeutic response exhibited by the conventional nasal solution. This drawback can be overcome by the use of in situ gelling systems, which gives increased residence time of drug and aids drug absorption giving rapid onset of action.
Table I: Composition of zolmitriptan in situ gelling systems containing Pluronic F-127 and HPMC K4M

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Formulations composition (% w/V)</th>
<th>PH0</th>
<th>PH1</th>
<th>PH2</th>
<th>PH3</th>
<th>PH4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zolmitriptan</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>Pluronic F-127</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>HPMC K4M</td>
<td>-</td>
<td>0.5</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Sodium Chloride</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Benzalkonium Chloride</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Ultrapure water</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

*q.s., quantity sufficient, Where: PH0 - Pluronic without HPMC K4M, PH1, PH2, PH3, PH4 - Pluronic with HPMC K4M

Table II: Evaluation parameters of the in situ gel (# indicates that values are Mean ± Standard Deviation, n= 3)

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Formulation code</th>
<th>*Degree of gelation</th>
<th>#Viscosity Study (cP)</th>
<th>#Gel strength (Sec.)</th>
<th>#Mucoadhesion force (dyne/cm²)</th>
<th>#Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PH0</td>
<td>+ +</td>
<td>82.70± 2.61</td>
<td>1021.26±28.85</td>
<td>94.63 ± 1.00</td>
<td>4103.56± 2.34</td>
</tr>
<tr>
<td>2</td>
<td>PH1</td>
<td>+ + +</td>
<td>99.20± 4.55</td>
<td>1435.26±109.89</td>
<td>68.79 ± 2.08</td>
<td>4793.5± 4.33</td>
</tr>
<tr>
<td>3</td>
<td>PH2</td>
<td>+ + +</td>
<td>110.71± 3.17</td>
<td>3577.12±108.53</td>
<td>41.28 ± 1.82</td>
<td>5274.21± 5.43</td>
</tr>
<tr>
<td>4</td>
<td>PH3</td>
<td>+ + + +</td>
<td>141.85± 6.47</td>
<td>4308.07±193.22</td>
<td>32.45 ± 1.00</td>
<td>5942.52± 8.53</td>
</tr>
<tr>
<td>5</td>
<td>PH4</td>
<td>+ + + +</td>
<td>204.52± 4.96</td>
<td>6289.32±132.44</td>
<td>21.36± 2.50</td>
<td>6589.24± 5.03</td>
</tr>
</tbody>
</table>

*Grades of gelation, (-) No gelation,(+) weak gelation; dissolves rapidly,(+ +) Immediate gelation remains for few hrs (less stiff gel),(+ + +) Immediate gelation remains for extended period (stiff gel), (+ + + +) very stiff gel.

Prepared formulations were evaluated for various parameters like drug content, viscosity study, gelation studies and mucoadhesive strength using the method described by Murthy et al., 2006. Gel strength determination was performed using ‘Gel strength apparatus’ modified at laboratory as mentioned by Yong et. al., 2001.

**In-Vitro Diffusion Studies**

It was carried out on Franz diffusion cell using the method reported by Murthy et al., 2006. After a pre-incubation time of 20 min, formulation equivalent to 2.5 mg of zolmitriptan was placed in the donor chamber. Gelation was induced using temperature.
Fig. 2: Photomicrograph of sheep nasal mucosa used in mucosal toxicity study of in situ gel formulations (PH2) (A: PBS treated mucosa & B: PH2 treated mucosa)

At predetermined time points, 1.0 mL samples were withdrawn from the receptor compartment, replacing the sampled volume with PBS pH 6.6 after each sampling, for a period of 270 min. The samples withdrawn were filtered and used for analysis. The amount of drug permeated was determined using UV spectrophotometer (UV-1700, Shimadzu, Japan) at 222.0 nm. The results obtained from this in-vitro study were subjected to release order kinetic study.

Ex-Vivo Permeation Studies

It was performed using a modified method described by Murthy et al, 2006. Sampling and analysis was done in similar manner as done in the in-vitro diffusion study.

Permeability coefficient (P) was calculated by following formula

\[ P = \frac{dq}{dt} \times \frac{C_0}{A} \]  
Eq. 4

Where, dq/dt is flux or permeability rate (mg/hr), C_0 is Initial concentration in donor compartment, A is effective surface area of nasal mucosa.

Histopathological Evaluation of Mucosa

It was done using the method described by Mahajan et. al., 2010. Sections were examined to detect any damage to the tissue during ex-vivo permeation study of formulation PH2.

Stability Study

Optimized formulation was selected for stability studies at 30±2°C temperature and relative humidity of 60±5 %. Formulation PH2 was evaluated at an intervals of one month for the occurrence of turbidity, gelation, drug content, gel strength and in-vitro drug release.

RESULTS AND DISCUSSION

As shown in Table II, the drug content of the formulations was ranging from 98.34 % to 99.54 %. In PH0 to PH4 series of formulations, there was slight difference in viscosities of solutions but the large difference was observed in gel state of same formulation series. As the viscosity of formulations in gel state was found to be proportionate with the increasing polymer concentration.

As per the visual inspection, the preformed gels were graded (Table II). From the results of gelation study the optimum concentration of HPMC K4M was found to be 0.5 % to 2.0% (w/V) in combination with Pluronic F127. Ideally, the gelation temperatures of an in situ gel should be in the range of 25°C to 34°C. As the temperature of the nasal cavity is 34°C, this study aimed at preparing the liquid formulations of PF127 that may gel below 34°C.

The gel strength value in the range 25-50 sec is considered to be sufficient. Thus from the results it can be concluded that the formulation PH2 and PH3 had optimum gel strength (Table II).

In case of Pluronic gels, the mucoadhesion force increases proportionally with increase in HPMC K4M concentration. It was observed that 1.0 % (w/V) concentration of HPMC K4M with 18 % (w/V) concentration of Pluronic showed the significant mucoadhesion (Table II).

In-Vitro Diffusion Studies

As shown in Fig. 1, it was observed that formulation batch PH2 had better drug release. The initial rates of drug release were very rapid due to incomplete
gel formation, but as the time progresses the release rate decreases due to complete gel formation. From the above results, it was concluded that, batch PH2 was the optimized formulation and therefore it was subjected to further study. The results of release order kinetic study indicates the anomalous (non-Fickian) release kinetic, i.e. release of zolmitriptan followed erosion-diffusion mechanism.

Ex-Vivo Permeation Studies

Formulation PH2 was further subjected to ex-vivo permeation studies. The percent drug permeated after 270 min was found to be 93.57 %. The permeability coefficient (P) was also calculated and found to be 0.2830 cm/hr for PH2. Slight increase in permeability of drug from Pluronic formulation can be correlated with the surfactant nature of Pluronic F127.

Histopathological Study

As shown in Fig. 2, the section of mucosa treated with formulation PH2 showed no degeneration of nasal epithelium along with no erosion. There was increased vascularity in basal membrane and superficial part of submucosa as compared with PBS-treated mucosa. This might be the result of mucoadhesive and permeability enhancing property of HPMC K4M in the formulation.

Stability Study

The optimized formulation batch PH2, which was subjected to stability study showed good stability with no remarkable change in drug content, gelation property, gel strength and in-vitro drug release profile.

CONCLUSION

The objective of formulating a thermo sensitive in situ gel of zolmitriptan was successfully accomplished in this study. The most important advantage of the in situ gel is that it is fluid-like prior to contact with the nasal mucosa; this feature is satisfactory for convenience of administration for patients, maintaining accuracy of drug dosing, and avoidance of the bitter taste of the drug. And after instillation into nasal mucosa it shows conversion into gel form which is an essential feature for the formulation to be retained in nasal mucosa for extended period. Moreover the gel formed shows sustained release of drug.

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