Development and In-vitro Evaluation of In-situ Nasal Gels of Zafirlukast

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ABSTRACT

Zafirlukast is a leukotriene receptor antagonist used for the maintenance treatment of Asthma. It rapidly gets absorbed from gastrointestinal tract because it is subjected to first pass metabolism. The objective of the present research work was to develop and evaluate mucoadhesive in-situ nasal gels of zafirlukast. This drug delivery system can overcome first pass metabolism, enhance nasal residence time due to its mucoadhesive strength and increased viscosity thereby subsequently improving the drugs bioavailability. The in-situ nasal gels of zafirlukast were formulated using different ratios of Guar gum and HPMC-K100M polymers and were subjected to various evaluation tests. From the in-vitro permeation results, it was found that formulation F6 containing guar gum and HPMC-K100M polymers in 0.3% w/v and 1.2% w/v concentrations respectively were found to be better as compared to remaining formulations. These results demonstrate the suitability of guar gum and HPMC-K100M polymers for the fabrication of sustained release mucoadhesive in-situ nasal gels of zafirlukast.

Keywords: Zafirlukast, Asthma; Mucoadhesive in-situ nasal gels; Guar gum; HPMC-K100M.
INTRODUCTION

Since ancient times, nasal drug delivery system has gained more interest among researchers and is known to be a better alternative for oral systemic drug delivery systems because, many drugs have shown better systemic bioavailability by self-medication through nasal route rather than oral administration. This is due to the rich vasculature and highly permeable structure of nasal mucosa coupled with the avoidance of hepatic first-pass elimination, gut wall metabolism, destruction of the drugs and gastro-intestinal side effects. Moreover, the nasal route is convenient because it is easy accessible [1,2].

However, the major limitations of formulations administered through nasal route are poor nasal mucosa contact and rapid clearance from the nasal cavity due to mucociliary clearance mechanism [3]. Whereas, the low bioavailability and failed therapeutic response exhibited by the conventional nasal preparations due to rapid mucociliary drug clearance can be overcome by using a gel system that can be instilled into the nose as drops which thereby undergoes a solution-gel transition in the cul de sac. Such type of dosage forms are called as in-situ nasal gels [4].

Initially, in-situ forming gels are liquids which upon instillation undergoes transition of phase to form visco-elastic gel. These gels also provide response to the environmental changes. In-situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange [5]. In the present research, an attempt has been made to develop in-situ nasal Zafirlukast gel for accuracy of dosing, easy administration, increased nasal residence time and thus improved nasal bioavailability.

MATERIALS AND METHODS

Zafirlukast pure drug, Guar gum and HPMC-K100M polymers, Mannitol were obtained from Yarrow chem. Ltd, Mumbai. Polaxamer, Benzalkonium chloride was obtained from S.D. Fine Chem. Ltd., Mumbai whereas; Poly Ethylene glycol was obtained from Sisco Research Lab, Mumbai. Remaining all other materials used was of analytical grade.

Pre-formulation studies

Procedure for analysis of Fourier Transform Infrared (FT-IR) spectras

The compatibility for pure drug zafirlukast, polymers and their respective physical mixtures utilized in the present formulations design of gels were checked by recording their spectra using FT-IR Spectrophotometer (Perkin Elmer, spectrum-100, Japan). The spectras were recorded by using 5% of the respective sample as the mixture with potassium bromide (KBr) which was made into a fine powder and was finally compressed as KBr pellets at compaction pressure of 4000 Psi for 2 min. The scanning range was 400-4000 cm⁻¹ and the resolution was 1 cm⁻¹.

Preparation of in-situ nasal gels of zafirlukast

The composition of various in-situ nasal gel formulations is shown in Table 1. For developing the formulation, initially pure drug zafirlukast was dissolved in methanol by constant stirring and to this solution PEG-400 and benzalkonium chloride; mannitol and pH 6.4 phosphate buffer saline were further added. Then polymeric solution of guar gum and HPMC-
K100M were prepared separately in 40 ml of distilled water and thoroughly mixed with the above zafirlukast solution mixture. The above solution mixture was then vigorously stirred on a magnetic stirrer and was then stored at 40°C, till clear gel formation takes place [4,6-8].

**Table 1:** Composition of various in-situ nasal gel formulations.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zafirlukast (% w/v)</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>Guar gum (% w/v)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>HPMC-K100M (% w/v)</td>
<td>0.4</td>
<td>0.8</td>
<td>1.2</td>
<td>0.4</td>
<td>0.8</td>
<td>1.2</td>
<td>0.4</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>PEG 400 (% v/v)</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>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Mannitol (% w/v)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Benzalkonium chloride (% w/v)</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Methanol (ml)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Phosphate buffer saline pH 6.4 (ml)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Distilled water (ml)</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

**Evaluation tests for in-situ nasal gel formulations of zafirlukast**

**Formulation pH**

Each in-situ nasal gel formulation in 1 ml quantity, were transferred and diluted into a beaker containing 10 ml of distilled water. The resulting solution pH was determined in triplicate using calibrated digital pH meter (Systronics μ pH system 361, Gujarat, India.) [4,6-8].

**Gelling temperature and gelling time**

The term gelling temperature means the temperature at which the formulation meniscus will not move further upon slanting the test tubes at 90°. It was determined by keeping the test tube filled with sufficient quantity of prepared solutions in a water bath at 4°C. The water bath temperature was then slowly raised at a constant rate of 1°C for every 2 min whereas, gelling time was noted as the time for first detection of gelation. Because, these delivery systems exist in solution form initially, which after administration undergo gelation to form a gel.

The solution-gel transition temperature (Tsolgel) of the developed in-situ gel formulations was determined by filling 2 ml of the solution into a 10 ml test tube, with 1.0 cm diameter. Thereafter, test tubes were sealed with a parafilm, and were kept in a water bath at 37°C and after setting each temperature, equilibration was maintained for 10 min. Further, the test tubes were horizontally placed to examine the state of sample and gelation. Average of three obtained readings was recorded [4,6-8].
Viscosity measurement

Viscosity of the in-situ nasal gel formulations was determined using programmable Brookfield viscometer DV-II LV model (Brookfield Eng. Lab, Inc. USA). The developed formulations were then transferred into a beaker and the viscometer spindle was perpendicularly lowered into the formulation. The speed of spindle rotation was 100 rpm and the temperature was maintained at 37 ± 0.5°C. The viscosity measurements of all the formulations were performed in triplicate [4,6-8].

Gel strength

Strength of the gel was determined by transferring 50 g of the formulation sample in 100 ml of graduated cylinder and the gelation process was carried out by placing the in-situ nasal gel formulations in a thermostat maintained at 37°C. The gel strength was then determined by noting the time for a 35 g weight to sink 5 cm into the gel. Average of three obtained readings was recorded [4,6-8].

Spreadability

Spreadability of in-situ nasal gel formulations was determined using a rectangular glass slide of 10 × 4 cm. The sheep nasal mucosa from serosal side was tied with a thread onto the slide surface. The tied slide was then kept into a hot air oven (M/s Heat control instruments and services, Bengaluru, India) at 37°C and one drop of the gel was kept on the mucosal surface at 120° angle. Spreadability was then evaluated by measuring the distance moved by the gel drop (liquid) before its gelation. Average of three obtained readings was recorded [4,6-8].

Mucoadhesive strength

Mucoadhesive strength of in-situ nasal gel formulations was determined using nasal mucosa of the fresh sheep. For this purpose, the nasal mucous membrane was separated from the sheep by removing the loose tissues and underlying fat. The mucosal membrane was continuously washed thrice with distilled water and 6.4 pH phosphate buffer.

The experiment was designed using Modified balance method and was carried out by equilibrating the balance on both sides by placing one beaker on the left pan and a weight of 5 g on the opposite pan. The nasal mucosa of sheep was cut into 1 cm and glued over the glass support with cyanoacrylate, as such the smooth surface should face the upper side of the glass. The glued nasal mucosa of sheep was then wet with pH 6.4 phosphate buffer filled in the beaker on the right hand side of the balance by lowering the glass support. The above setup was placed below the right side of the pan. A thin film of the prepared in-situ gel (1 gm) was spread on the lower surface of the right pan. The right pan was then lowered by removing the beaker from the left pan. The pan was left aside for 2 min to ensure proper contact between the nasal mucosa and gel.

Following this setup, water was slowly added to the left pan using a burette until the nasal mucosa gets separates from the gel film. The mucoadhesive force was calculated by determining the weight required to separate the mucosa. The force was expressed in dynes per square centimeter (dyne/cm²) [4,6-8].
Drug content

For estimation of drug content, 1 ml of the prepared formulation was dispersed into 10 ml of distilled water with occasional stirring for 2 – 3 min. The resulting dispersion sample was then filtered through a 0.45 μm filter paper. The zafirlukast amount in the formulation was determined by using UV- visible spectrophotometer at 239 nm (Shimadzu UV-1800). The tests was carried out in triplicate and the mean values were recorded [4,6-8].

In-vitro permeation Studies

In-vitro release of zafirlukast from the gel formulation was evaluated using Franz diffusion cell apparatus, containing fresh nasal tissues having a permeation area of 0.785 cm² which were removed from the nasal cavity of sheep. The study was carried out by adding 20 ml of 6.4 pH phosphate buffer to the acceptor chamber and the temperature was maintained at 34°C. To ensure agitation and oxygenation, a mixture of 95% oxygen and 5% carbon dioxide was bubbled into the system. Formulation equivalent to 2.5 mg of zafirlukast was kept in the donor compartment. At predetermined intervals of time, 1 ml of samples were withdrawn from the acceptor compartment and the same equivalent amount was replaced with 6.4 pH phosphate buffer after each sampling time for a period of 12 hrs. The withdrawn samples were diluted suitably and spectrophotometrically measured at 239 nm. The tests were carried out in triplicate and the mean values were recorded [4,6-8].

Accelerated stability studies

Stability studies of the optimized in-situ gel formulation F6 was carried out as per ICH guidelines. The study was carried out by filling sufficient quantity of in-situ gel in nasal spray bottle and storing them in desiccator containing saturated solution of sodium chloride. The desiccator was then placed in a humidity chamber maintained at accelerated stability conditions (kept at 40 ± 2°C and 75 ± 5% RH) in a stability chamber. The samples were then withdrawn at intervals of 2, 4 and 6 months and investigated for the changes in pH, gelling time, viscosity, gelling strength, muco-adhesive strength, spreadability, drug content and in-vitro release profile of the stored formulations. All the tests were carried out in triplicate and the mean values were recorded [9,10]

RESULTS AND DISCUSSION

Preformulation studies

FT-IR studies

In order to identify drug polymer compatibility, the spectra of pure drug zafirlukast, polymers and their respective physical mixtures in gel formulations were recorded as shown in Figure 1. In the present research work, zafirlukast was used as the model drug and guar gum, HPMC K100M was used as polymers. Zafirlukast spectra have shown –NH, and –SO₂ stretchings due to the presence of characteristic peaks at 3358 cm⁻¹ and 1346 cm⁻¹ respectively. These are all the characteristic peaks of zafirlukast. The guar gum polymer spectra have shown –OH, –CH and -CO stretchings due to the characteristic peaks presence 3382 cm⁻¹, 2938 cm⁻¹ and 1241 cm⁻¹ respectively. Whereas, HPMC-K100M polymer spectra have shown –OH, -C-H and -C=O

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stretchings due to the characteristic peaks presence at 3474 cm\(^{-1}\), 2832 cm\(^{-1}\) and 1378 cm\(^{-1}\) respectively. Moreover, when the physical mixture spectras of zafirlukast was recorded with their respective polymers guar gum and HPMC-K100M as per the formulation table, and it was found that the respective higher spectra have also shown all the peaks corresponding to drug and polymers. As all the peaks were found to be intact, thus, it is an indication that the combination of the used drug and polymers can be suitable for designing an in-situ gel formulation needed for its desired therapeutic purpose.

![Figure 1: FT-IR spectras of a) Zafirlukast b) Guar gum c) HPMC-K100M d) Physical mixture of zafirlukast and guar gum e) Physical mixture of zafirlukast and HPMC-K100M](image)

**PH, Gelling temperature, gelling time, solution viscosity and gel strength**

In the present study, 9 in situ nasal gel formulations were prepared using varying concentrations of guar gum and HPMC-K100M as the base polymers. The HPMC-K100M polymer was used with an aim to prolong the residence time of gel in the nasal cavity because of its high viscosity nature following hydration in the nasal cavity and thus sustaining the release of zafirlukast. The pH, gelling temperature, gelling time, solution viscosity and gel strength of the prepared formulations are shown in Table 2. From the results, it was found that the pH of developed formulations ranged between 5.5 ± 0.009 to 5.9 ± 0.005 which indicated that it was in the acceptable range as the normal pH of nasal mucosa ranges between 4.5 to 6.5. The gelling temperature was found to range between 32.7 ± 0.68 to 34.3 ± 0.77°C and it too was in the acceptable range as the suitable gelling temperature required for thermo-reversible nasal gel ranges between 30°C to 36°C whereas, the gelling time and viscosity of the formulations was found to range between 8.3 ± 0.48 to 10.5 ± 0.66 sec and 186.84 ± 0.61 to 337.39 ± 0.98 cps respectively. From these results, it was found that as the concentration of polymers in the gel increases, the gelling time and viscosity was also found to be increased. It is due to the water absorbing capacity of hydrophilic polymers, which has increased the gelling time and viscosity. Moreover, the gel strength was found to range between 53.65 ± 0.47 to 62.39 ± 0.49 sec and from the result it was found that the strength was directly proportional to the concentration of hydrophilic polymer HPMC-K100M. Also, the combined use of polymers has significantly increased the viscosity as well as Mucohesive gel strength.
Table 2: pH, Gelling temperature, gelling time, solution viscosity and gel strength of the prepared in situ nasal gel formulations of Zafirlukast.

<table>
<thead>
<tr>
<th>F.C</th>
<th>pH</th>
<th>Gelling temperature (°C)</th>
<th>Gelling time (sec)</th>
<th>Solution viscosity (cps)</th>
<th>Gel strength (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>5.7 ± 0.007</td>
<td>32.7 ± 0.68</td>
<td>8.3 ± 0.48</td>
<td>186.84 ± 0.61</td>
<td>53.65 ± 0.47</td>
</tr>
<tr>
<td>F2</td>
<td>5.5 ± 0.009</td>
<td>34.1 ± 0.81</td>
<td>8.6 ± 0.72</td>
<td>205.15 ± 0.93</td>
<td>54.20 ± 0.28</td>
</tr>
<tr>
<td>F3</td>
<td>5.8 ± 0.005</td>
<td>33.5 ± 0.59</td>
<td>9.1 ± 0.64</td>
<td>227.64 ± 0.77</td>
<td>57.55 ± 0.73</td>
</tr>
<tr>
<td>F4</td>
<td>5.5 ± 0.010</td>
<td>32.9 ± 0.64</td>
<td>9.3 ± 0.57</td>
<td>250.83 ± 1.06</td>
<td>55.87 ± 0.49</td>
</tr>
<tr>
<td>F5</td>
<td>5.7 ± 0.007</td>
<td>33.9 ± 0.72</td>
<td>9.6 ± 0.62</td>
<td>275.05 ± 0.94</td>
<td>58.44 ± 0.63</td>
</tr>
<tr>
<td>F6</td>
<td>5.9 ± 0.005</td>
<td>34.3 ± 0.77</td>
<td>9.9 ± 0.79</td>
<td>293.73 ± 0.89</td>
<td>60.92 ± 0.12</td>
</tr>
<tr>
<td>F7</td>
<td>5.6 ± 0.009</td>
<td>33.6 ± 0.62</td>
<td>10.2 ± 0.83</td>
<td>309.52 ± 0.71</td>
<td>57.19 ± 0.81</td>
</tr>
<tr>
<td>F8</td>
<td>5.8 ± 0.007</td>
<td>33.7 ± 0.57</td>
<td>10.3 ± 0.75</td>
<td>314.82 ± 1.15</td>
<td>60.86 ± 0.29</td>
</tr>
<tr>
<td>F9</td>
<td>5.7 ± 0.005</td>
<td>33.9 ± 0.65</td>
<td>10.5 ± 0.66</td>
<td>337.39 ± 0.98</td>
<td>62.39 ± 0.49</td>
</tr>
</tbody>
</table>

Note: F.C= Formulation code

Mucoadhesive strength, Spreadability and Drug content

The Mucoadhesive strength, Spreadability and drug content of the prepared in-situ nasal gel formulations of zafirlukast are shown in Table 3. The mucoadhesive strength of the formulations was found to range between 4053.92 ± 0.65 to 5536.54 ± 0.78 dyne/cm². From the results, it was found that as the concentrations of HPMC-K100M and guar gum polymers was increased; the mucoadhesive strength was also increased. It is due to the reason that mucin strands have interacted with polymeric chains to form weak chemical bonds because of stronger mucoadhesive force. The spreadability of the formulations was found to range between 6.8 ± 0.91 to 8.6 ± 0.62 cm. It was observed that the increased concentration of HPMC-K100M polymer in formulations was related to less spreadability. It is due to the reason that viscosity of HPMC-K100M polymer has increased because of its increased concentration whereas, the drug content was found to range between 98.28 ± 0.39 to 99.83 ± 0.72% which indicates within the acceptable range as it was found to be more than 95%.

Table 3: Mucoadhesive strength, Spreadability and Drug content of the prepared in situ nasal gel formulations of Zafirlukast

<table>
<thead>
<tr>
<th>F.C</th>
<th>Mucoadhesive strength (dyne/cm²)</th>
<th>Spreadability (cm)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>4053.92 ± 0.65</td>
<td>8.6 ± 0.62</td>
<td>99.67 ± 0.68</td>
</tr>
<tr>
<td>F2</td>
<td>4874.05 ± 0.92</td>
<td>7.9 ± 0.27</td>
<td>98.95 ± 0.47</td>
</tr>
<tr>
<td>F3</td>
<td>5170.59 ± 0.29</td>
<td>7.3 ± 0.55</td>
<td>99.03 ± 0.81</td>
</tr>
<tr>
<td>F4</td>
<td>4217.42 ± 0.70</td>
<td>8.3 ± 0.39</td>
<td>99.15 ± 1.06</td>
</tr>
<tr>
<td>F5</td>
<td>5038.10 ± 0.63</td>
<td>7.8 ± 0.75</td>
<td>99.40 ± 0.65</td>
</tr>
<tr>
<td>F6</td>
<td>5492.68 ± 0.85</td>
<td>7.2 ± 0.83</td>
<td>98.28 ± 0.39</td>
</tr>
<tr>
<td>F7</td>
<td>4659.52 ± 0.59</td>
<td>8.2 ± 0.48</td>
<td>99.83 ± 0.72</td>
</tr>
<tr>
<td>F8</td>
<td>5329.81 ± 0.48</td>
<td>7.3 ± 0.72</td>
<td>99.52 ± 0.84</td>
</tr>
<tr>
<td>F9</td>
<td>5536.54 ± 0.78</td>
<td>6.8 ± 0.91</td>
<td>98.04 ± 0.75</td>
</tr>
</tbody>
</table>

Note: F.C=Formulation Code
In-vitro permeation studies

In the present research, the aim was to develop in-situ nasal gel formulations for increasing the nasal residence time, to sustain the release of Zafirlukast and thus to improve nasal bioavailability. For this purpose, various concentrations of mucoadhesive polymer guar gum and hydrophilic polymer HPMC K100M polymers were used with an aim to increase the viscosity and thus to delay the release of Zafirlukast.

From the results of in-vitro permeation studies as represented in Figure 2, it was found formulations F1, F2 and F3 released 99.03 ± 0.22, 98.73 ± 0.61 and 98.88 ± 0.77% of Zafirlukast at the end of 5, 7 and 10 hours respectively. Whereas, formulations F4, F5 and F6 released 98.44 ± 0.79, 99.60 ± 0.43 and 99.24 ± 0.57% of Zafirlukast at the end of 5, 8 and 12 hours respectively. Moreover, formulations F7, F8 and F9 released 98.89 ± 0.62, 99.03 ± 0.43 and 98.62 ± 0.90% of Zafirlukast at the end of 6, 8 and 12 hours respectively.

In all these formulations, F6 was considered as the best formulation as its release was superior while compared to the remaining formulations. It was also found that as the concentrations of guar gum and HPMC K100M polymers increases then the release rate of Zafirlukast from the formulation decreases. The delay in drug release may be due to increased viscosity of the formulation, which has increased with the increase in mucoadhesive guar gum and HPMC K100M polymers concentration.

Figure 2: In-vitro permeation profile of in-situ nasal gel formulations of zafirlukast (mean ± SD; n=3).

Accelerated stability studies

The results obtained at accelerated stability conditions revealed that there was very small variation (i.e., <1%) in pH, Gelling time, viscosity, gelling strength, mucoadhesive strength, spreadability, drug content and in-vitro release profile of the optimized in-situ nasal gel F6 formulation. The observed results have not shown any significant changes in all the parameters of the optimized formulation during the 6 month period of study. Thus, for the developed in-situ nasal gel F6 formulation, stability was found as per ICH guidelines.
CONCLUSION

A in-situ nasal gel formulation was successfully developed to sustain the release of zafirlukast in the nasal mucosa. The desired results were confirmed using in-vitro permeation studies. The optimized formulation was also stable according to ICH guidelines. Hence, the developed formulation can show prolong nasal residence time because of its higher viscosity thereby increasing the systemic bioavailability. This formulation can be also be more suitable for easy administration through nasal route as it is instilled as drops which thereafter undergoes a solution-gel transition in the cul de sac. Because of highly permeable structure and the rich vasculature of the nasal mucosa, the in-situ nasal gel formulation can be a better alternative to oral drug delivery systems.

REFERENCES