DESIGN AND IN VITRO EVALUATION OF MUCOADHESIVE MINITABLETS FOR NASAL DRUG DELIVERY OF SUMATRIPTAN

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ABSTRACT

The aim of the present investigation was to develop Sumatriptan Nasal Mucoadhesive Minitablets using different mucoadhesive polymers Chitosan, Carbopol 971P and Gum copal along with Methocel. Mucoadhesive minitablets of Sumatriptan were prepared by direct compression method. The minitablets were evaluated for thickness, hardness, swelling index, mucoadhesion and in vitro drug release. All postcompressional parameters were found to be within acceptable standard limits. It was observed that mucoadhesive minitablets contained polymer blend of Carbopol, Carbopol/Chitosan, Carbopol/Gum copal were successfully controlled the release of drug up to 7 days. The release data were fit into different kinetic models (zero order, first order and Korsemeyer- Peppas powers law equation) the mechanism of drug release was found to follow zero order release. N1 and N6 formulations were selected as optimum formulations based on evaluation studies.

Key words: Nasal drug delivery, Sumatriptan succinate, Minitablets.

INTRODUCTION

The nasal route of delivery has been used for delivery of drugs for treatment of local diseases such as nasal allergy, nasal congestion and nasal infections. Recent years have shown that the nasal route can be exploited for the systemic delivery of drugs such as low molecular weight polar drugs, peptides and proteins that are not easily administered via other routes than by injection, or where a rapid onset of action is required. From the pharmacokinetic standpoint, absorption is rapid, which provides a faster onset of action compared to oral and intramuscular administration. Hepatic first-pass metabolism is also avoided, allowing increased, reliable bioavailability 1,2.

Sumatriptan is an agonist for a vascular 5-hydroxytryptamine receptor subtype (probably a member of the 5-HT1D family). The vascular 5-HT1-receptor subtype that Sumatriptan activates is on human basilar artery and in the vasculature of human dura mater and mediates vasoconstriction. This action in humans correlates with the relief of migraine headache. Sumatriptan has previously been shown to have a low oral bioavailability in human volunteers (15%). The intranasal route may be a viable alternative for self administration where this limitation could be overcome. To overcome the rapid clearance and to facilitate the absorption, nasal mucoadhesive materials are used in nasal formulations 2.

In context of the above principles, a strong need was recognized for the development of nasal mucoadhesive dosage form to deliver Sumatriptan (model drug) to increase the efficiency of the drug, providing control release. The aim of the present study was to design and evaluate nasal mucoadhesive minitablets of Sumatriptan that would increase its residence time in the nasal cavity and at the same time increase the absorption of drug and hence its bioavailability.

MATERIALS AND METHODS

Materials

Sumatriptan Succinate was supplied by Natco Pharma Ltd, Hyderabad. Chitosan was provided by India sea foods, Cochin. Methocel K4M, Carbopol 971P and Talc were received as gift samples from FDC Limited, Mumbai. Gum copal received as gift sample from Genuine chemical co. Mumbai. All other reagents and chemicals used were of analytical reagent grade.

Methods

Preparation of Mucoadhesive Minitablets 4,5

The powder mixture Sumatriptan succinate (2% w/w), Carbopol 971P (90% 45 % w/w), Gum copal (90% 45 % w/w), Chitosan (90% 45 % w/w), Methocel K4M (5% w/w), and Talc (3% w/w), was obtained by homogeneously mixing the different compounds in a pestle and a mortar. The minitablets (diameter 3 mm, 10 mg) were prepared by compressing the powder mixture at a force of 1.0 kN using an eccentric compression machine (Korsch type EKO; Berlin, Germany). The production method was based on direct compression. Table 1 depicts the composition of all formulations.

Table 1: Composition of nasal mucoadhesive minitablets

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulations (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N1</td>
</tr>
<tr>
<td>Carbopol 971P</td>
<td>90</td>
</tr>
<tr>
<td>Gum copal</td>
<td>-</td>
</tr>
<tr>
<td>Chitosan</td>
<td>-</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>5</td>
</tr>
<tr>
<td>Talc</td>
<td>3</td>
</tr>
<tr>
<td>Sumatriptan Succinate</td>
<td>2</td>
</tr>
</tbody>
</table>

Evaluation of mucoadhesive minitablets

Content uniformity 6,7

Ten Minitablets were weighed and triturated to get fine powder. Each weight equivalent to 2% w/w of Sumatriptan Succinate was dissolved in 25 ml of phosphate buffer pH 6.2 and sonicated for 10 min. 1 ml of this solution was withdrawn and drug content was determined by using UV spectrophotometer at 265nm after suitable dilution. The experiments were performed in triplicate, and average values were reported.

Swelling study 8,9

Mucoadhesive Minitablets were weighed individually (Wp) and placed separately in petri dish containing 50 ml of phosphate buffer pH 6.2. The Petri dishes were placed in an incubator maintained at 37±0.5°C. The tablets containing hydrophilic polymers swell in the medium. At 4th h, the tablets were removed from the Petri dish, tablet weight was then reweighed (Wt) and the % swelling index was calculated using the following formula.

\[ \% \text{SI} = \left( \frac{W_t - W_p}{W_p} \right) \times 100 \]

Where, WU – Water uptake
Wp – Weight of tablet at time t
Wt – Weight of tablet before immersion
**Ex vivo mucoadhesion strength**

In the present study, bovine cheek pouch was used as a model mucosal surface for bioadhesion testing. The bovine cheek pouch was procured from slaughter house, then excised and trimmed evenly from the sides. It was then washed in phosphate buffer (pH 6.2) and was preserved in the same or used immediately. Detachment force method was used to study the ex vivo mucoadhesion of tablets. The modified balance method was used to assess the tendency of mucoadhesive material to adhere to mucosal membrane. The left pan was replaced with a Teflon block B ring hung by a number of metallic rings. The 15mm diameter bovine cheek mucosa was attached to Teflon block A, and the tablet was attached to Teflon B using an adhesive. Block B was kept on block A kept in jacketed glass beaker filled with test medium (40ml of phosphate buffer pH 6.2 at 37°C). The right pan of the balance was replaced with a light weight beaker. By keeping suitable weight on the right hand side the pans were balanced so that Teflon block B attached with the tablet rest on the membrane attached to block A. After contact time of 4 min, weight was increased in the beaker on the right-hand pan by adding water until the tablet detached from the membrane. The excess weight in mg to the right hand side gave the mucoadhesive strength of the tablet.

**In vitro nasal diffusion study**

In vitro nasal diffusion study was done by using diffusion cell (Figure 1). A glass cylinder with both ends open, 10 cm height, 3.7 cm outer diameter and 3.1 cm inner diameter was used. Nasal mucosa of sheep was separated from sub layer bony tissue and stored in distilled water containing few drops of gentamycin sulphate injection. After the complete removal of blood from mucosal surface it was tied to one end of donor compartment.

One Minitablet was taken in one cell (donor compartment) and fixed on mucosal surface and the cell was immersed in a beaker containing 40 ml of phosphate buffer (receptor compartment) of pH 6.2 were used for study. The cell was immersed to a depth of 1cm below the surface of phosphate buffer in the receptor compartment, agitated by a magnetic stirrer and temperature maintained at 37±1°C throughout the study. Aliquots of 1ml were withdrawn periodically at intervals of 1 d for a period of 7 d and each time equal volume was replaced with fresh phosphate buffer previously heated to 37±1°C. The amount of drug release was estimated using UV spectrophotometer at 265 nm after suitable dilution.

Carbopol, Chitosan and Gum copal were selected as matrix forming and mucoadhesive polymers which help in mucoadhesion of minitablets and slow release of the drug. HPMC is included in all formulations for maintaining the viscous nature of all formulations after absorbing the medium. Tablets were found to be satisfactory when evaluated for thickness (1.9±0.122 mm); Hardness (5.02±0.136 kg/cm²); Friability less than 1% and Drug content (98.2% - 99.9%).

Swelling index describes the amount of water that is contained within the hydrogel at equilibrium and is a function of the network structure, hydrophilicity and ionization of functional groups. Results of swelling index are shown in Table 2. From the results it can be concluded that swelling increases with time because polymer gradually absorbs water due to its hydrophilicity. The outermost layer of the polymer hydrates, swells and a gel barrier is formed at the outer surface. In the present study, all formulations had same concentrations of polymer. The swelling index was highest for tablets of formulation N2 (166.15±2.12 %) and least N1 (90.0±1.25 %). This indicates that Gum copal stores more water content in matrix than Chitosan and Carbopol.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Drug content (% Mean±SD)</th>
<th>Swelling index (% Mean±SD)</th>
<th>Mucoadhesion Strength (g) Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>99.9±0.12</td>
<td>90.0±1.25</td>
<td>24±1.2</td>
</tr>
<tr>
<td>N2</td>
<td>98.75±0.14</td>
<td>166.15±2.12</td>
<td>15.1±1.4</td>
</tr>
<tr>
<td>N3</td>
<td>98.2±0.85</td>
<td>144.0±4.01</td>
<td>19.7±8.24</td>
</tr>
<tr>
<td>N4</td>
<td>98.5±1.2</td>
<td>134±1.9</td>
<td>21.5±1.9</td>
</tr>
<tr>
<td>N5</td>
<td>99.7±1.3</td>
<td>161±2.4</td>
<td>17.0±4.15</td>
</tr>
<tr>
<td>N6</td>
<td>99.05±1.6</td>
<td>109.18±1.4</td>
<td>22.85±2.78</td>
</tr>
</tbody>
</table>

The ex vivo mucoadhesion strength for all formulations were determined after 4 min from contact times (Table 2). Tablets containing higher proportion of Carbopol showed higher mucoadhesion than Chitosan and Gum copal. The strength of mucoadhesion of all formulations were found in the order of N1 > N6 > N4 > N3 > N5 > N2 (Figure 2).

**RESULTS AND DISCUSSION**

N1 and N6 formulations were selected as optimum formulations based on evaluation studies. These formulations are showing good mucoadhesion properties due to presence of Carbopol and Chitosan mucosal surface mucoadhesive polymers. Mucoadhesion studies reveal that formulations containing carbopol showed higher mucoadhesion property, due to which the formulation was retained for a longer duration on nasal mucosa.

**CONCLUSION**

In present study, it is concluded that Sumatriptan Succinate Nasal Mucoadhesive Mintablets can be successfully prepared using mucoadhesive polymers. The postcompressional parameters of Mucoadhesive Mintablets (hardness, thickness and drug content)
Figure 3: In vitro cumulative % drug release of nasal mucoadhesive minitablets

were within acceptable official IP limits. Results of mucoadhesion test indicated that carbopol polymer increases mucoadhesion properties of Minitablets. In vitro release results indicated that the drug release was more controlled in carbopol formulations.

The present study was a satisfactory preliminary attempt in development of Mucoadhesive intranasal Minitablets of Sumatriptan Succinate.

REFERENCES