DESIGN AND CHARACTERIZATION OF TRANSMUCOSAL DRUG DELIVERY SYSTEM OF GLIBENCLAMIDE

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ABSTRACT

Buccal drug delivery has been considered as an alternative to oral route for compounds subjected to degradation in the gastrointestinal tract or hepatic first pass metabolism. Glibenclamide, an oral hypoglycemic agent of the sulphonylurea group is frequently prescribed for the treatment of late-onset (non-insulin dependent) diabetes mellitus. In the present investigation, an attempt was made to develop mucoadhesive buccal tablets of glibenclamide by direct compression method using bioadhesive polymers like Carbopol 934P, HPMC K4M and NaCMC. Preformulation and micromeritic studies were carried out. The physical characteristics, surface pH, in-vitro bioadhesion strength, swelling index and in-vitro release of formulated tablets were dependent on characteristics and composition of bioadhesive materials used. The formulation F2 containing Carbopol 934P, HPMC K4M and mannitol was found to be promising and exhibited an in vitro drug release of 95.94% in 8 hrs along with satisfactory bioadhesion strength (3.68 gms). Short-term stability studies on the promising formulation indicated no significant changes in drug content and in vitro dissolution characteristics. The n values of all formulations were in the range of 1.327 – 1.518, indicating non-Fickian super case II type transport mechanism. FT-IR and DSC studies revealed absence of any chemical interaction between drug and polymers used.

KEY WORDS: Glibenclamide, mucoadhesive buccal tablets, direct compression, in-vitro bioadhesion strength, swelling index, in-vitro release.

INTRODUCTION

Among the various routes of drug delivery, oral route is perhaps most preferred by patients and clinicians alike. However, per oral administration of drugs have disadvantages, such as hepatic first-pass metabolism and enzymatic degradation in the gastrointestinal tract (GIT). So, there has been a growing interest in development of therapeutic agent through various transmucosal routes to provide a therapeutic amount of drug to the proper site in body to promptly achieve and then maintain the desired concentration. The unique environment of the oral cavity is a potential site for drug delivery. Two sites within the buccal cavity are used for drug administration the sublingual and buccal route. Using the Sublingual route, the medication is placed under the tongue, usually in the form of rapidly dissolving tablet. The second site for drug administration is between the cheek and gingiva known as buccal route for absorption. Diabetes mellitus is a chronic disorder with interrelated metabolic and vascular components. A relative or absolute deficiency of insulin secretion and activity is associated with hyperglycemia and altered lipid and protein metabolism. Type II diabetes mellitus is a chronic disease characterized by hyperglycemia and numerous other metabolic abnormalities. The medications that are used to treat diabetes are categorized into two broad areas; oral antidiabetic agents and insulin. Glibenclamide is an oral antidiabetic agent and has actions, uses similar to those of the other sulfonylureas. It is 200 times potent than tolbutamide on weight basis, but maximal hypoglycemic effect is similar to that of other sulfonylurea’s. Glibenclamide stimulates secretion of insulin but also increases peripheral sensitivity to insulin by a post receptor mechanism. Inhibition of hepatic glucose production plays an important role in glycemic control. In the present study an attempt is made to develop and evaluate buccal tablets of glibenclamide to avoid first pass effect, reduce dose dumping, frequent administration and to achieve maximum drug delivery to produce good therapeutic effect.

MATERIALS AND METHODS

Glibenclamide was gifted by Arvind Remedies Ltd, Kakkalur, Tamil Nadu. Hydroxy propyl methyl cellulose (HPMC – K4M) was gifted by Colorcon Ltd. Goa, India, Sodium carboxy methyl cellulose (NaCMC) was from S.D Fine Chemicals Mumbai, India and Carbopol 934P was gifted by Hi media Laboratories Pvt. Ltd. All other materials were of analytical or pharmacopoeial grade and used as received.

Preparation of the buccal tablets

Direct compression method was employed to prepare buccal tablets of glibenclamide using bioadhesive polymers like Carbopol 934P, HPMC K4M and NaCMC. Mannitol was used as diluent. The tablets were prepared with 8 mm flat-faced punches using 10 stations Rimek compression machine. All ingredients including drug, polymer and excipients were weighed accurately according to the batch formula (Table 1) and screened through sieve # 60, than mixed thoroughly in a mortar and pestle for 10 min. Magnesium stearate and talk were added to the above blend as flow promoters. In all the formulations the amount of glibenclamide was kept constant at 10 mg. The polymers like Carbopol 934P, HPMC K4M and NaCMC were used in different concentrations in combination. Total weight of the tablet was kept constant at 200 mg.

Evaluation of buccal tablets

The prepared buccal tablets were evaluated for thickness, diameter, hardness, friability, weight variation, drug content uniformity, surface pH, ex vivo bioadhesive strength, swelling index, in vitro drug release, short-term stability and drug-excipient interactions. The thickness and diameter were measured using vernier calipers. Hardness and friability of the tablets were determined by using Monsanto hardness tester and Roche friabilator. For weight variation twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation. For drug content accurately weighed quantity of powder equivalent to 10 mg of glibenclamide was taken into 100 ml volumetric flask, dissolved in phosphate buffer of pH 7.4 and the solution was filtered through whatman filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 7.4. The drug content was determined at 300 nm by UV-spectrophotometer.

Measurement of surface pH

A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping them in contact with 5 ml of distilled water for 2 hrs and pH was noted by bringing the electrode in contact with the surface of the formulation and allowing it to equilibrate for 1 min.
Ex vivo bioadhesive strength

It was determined with an instrument designed to measure the tensile force between the mucosal layer and shaft of the device. The instrument consisted of a modified physical balance by replacement one pan of balance with the metal shaft of 5 gm heavier in weight than pan. Fresh ox buccal mucosa obtained from local slaughterhouse was cut into pieces, washed with distilled water followed by phosphate buffer pH 7.4. A piece of buccal mucosa was fixed to a petri dish with instant adhesive and filled with phosphate buffer pH 7.4 so that it just touches the mucosal surface. The tablet was stuck to the lower side of a shaft with instant adhesive. The two sides of the balance were made equal before the study, by keeping 5 gm weight on the right hand pan as showing in Fig. 1. A weight of 5 gm was removed from the right hand pan, which lowered the shaft along with the tablet over the mucosa. The balance was kept in this position for 3 min contact time. The weight was added slowly to the right hand pan until the tablet detached from the mucosal surface. This detachment force gave the bioadhesion strength of the buccoadhesive tablet in gm (total weight on right hand pan minus 5 gm) .

Swelling studies

The extent of swelling was measured in terms of % of weight gained by the tablet upon swelling. One tablet from each formulation was weighed and kept in petri dish containing 15 ml of phosphate buffer pH 7.4. At the end of specific time intervals tablets were withdrawn from petri dish and excess buffer removed by blotting with tissue paper and weighed. The % of weight gained by the tablet was calculated by using following formula:

\[
\text{Swelling index} = \frac{W_T - W_i}{W_i} \times 100
\]

Where,

\( \text{Wa} \) - initial weight of the tablet,
\( \text{Wb} \) - weight of the tablet after swelling

In vitro drug release study

The dissolution of the buccal tablet was performed using USP type II XXIII dissolution apparatus (paddle method). 900 ml of phosphate buffer pH 7.4 containing 8.4% methanol and 0.24% tween 80 was used as the dissolution medium, maintained at 37°C and stirred at 50 rpm. Aliquots of 5 ml of samples were withdrawn with a bulb pipette at one hour interval from 1 to 8 hrs and replaced with equal volume of phosphate buffer pH 7.4 at each withdrawal. Aliquots were filtered through what man filter paper No. 1. The samples were then analysed using UV spectrophotometer at 300 nm and the cumulative amount of drug released at various time intervals was calculated. The experiment was run in triplicate.

Stability study

The best formulation was subjected for one month stability study by exposing the tablets in their final packing mode to the temperature range of 20-25°C. An inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

RESULTS AND DISCUSSION

In the present investigation an attempt was made to design Mucoadhesive buccal tablets containing glibenclamide. The employed method was direct compression for preparation of mucoadhesive buccal tablets for which the drug or the mixture of drug and polymer should possess good flow properties. Plain glibenclamide exhibited angle of repose (45.10 ± 0.48°) indicating extremely poor flow property. It was further supported by high Carr’s index value (25.37 ± 0.26%) and Hausner’s ratio (1.34 ± 0.82). Hence it was necessary to use directly compressible vehicles like spray dried mannitol to improve the flow property of glibenclamide.

A total of nine formulations of mucoadhesive buccal tablets of glibenclamide were prepared and evaluated for physical and mechanical parameters. The blends were also evaluated for pre compression parameters. These blends displayed angle of repose values between 24.56 – 26.38° indicating good flow property as the values were less than 30°. Bulk density was found to be between 0.42 - 0.58 gm/cm³ and tapped density between 0.47 - 0.69 gm/cm³ for all the formulations. From the density data, % compressibility was calculated. It was further supported by good Carr’s index value of 10.64 - 15.94% and Hausner’s ratio of 1.11 - 1.18 for all pre compression mixtures. Hence powder mixture was found suitable for direct compression method. According to work plan, the tablets were evaluated for their thickness, hardness, friability, weight variation, drug content uniformity, surface pH, ex vivo bioadhesive strength, swelling index, in vitro drug release. The mucoadhesive tablets were uniform with respect to thickness (4.8 to 5.1 mm) diameter (6.8 to 7.1) and hardness (5.3 to 6.2 kg/cm²) except F9 where the hardness is 7.2 because of presence of Carbopol 934P alone. The friability (0.42 to 0.76 %) and weight variation (1.3 to 2.2 %) of different batch of tablets were found within prescribed limits. Drug content (97.82 to 99.55 %) was found uniform within the batches of different tablets. (Table 2)

Surface pH

Tablets of all formulations except F9 showed surface pH values in range of 5.46 to 7.09, indicating no risk of mucosal damage or irritation. Tablets of formulation F9 showed lower surface pH value of 4.61 which is due to presence of higher amount of polycrylic acid in carbopol 934P. This observation indicates that Carbopol 934P alone is not suitable in designing mucoadhesive tablets and a combination of polymers produces tablets with surface pH safer for mucosal membrane. The results are reported in Table 2 and Fig. 2.

Bioadhesive strength

The mean bioadhesive strength values were found in range of 2.07 to 7.18 gm for the buccal tablets F1 to F9. This study showed that addition of secondary polymer to the Carbopol 934P was found to decrease the bioadhesive property of buccal tablets as observed from formulation F9 (CP alone) and other formulations F1 to F8. It was also observed that as the concentration of Carbopol 934P is increased, the mucoadhesive strength also increased. When all different polymeric ratios are considered formulations containing Carbopol 934P and HPMC K4M (F1, F2, F3 and F4) show more adhesion than formulations containing Carbopol 934P and NaCMC, i.e. (F5 to F8). The results are reported in Table 2 and Fig. 3.

Swelling study

Swelling ratio describes the amount of water that is contained within the hydrogel at equilibrium and is a function of network structure, hydrophilicity and ionization of functional group. Swelling study was performed on all the batches of glibenclamide mucoadhesive buccal tablets for 8 hrs. The results of swelling index studies are tabulated in Table 2 and Fig. 4. The swelling index of all formulations was in the range of 26 – 236%. Maximum swelling

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was seen with the formulations (F5, F6, F7 and F8) containing Carbopol 934P and NaCMC than the remaining formulations. Tablets containing Carbopol 934P and secondary polymers (like HPMC K4M, NaCMC) showed increased swelling index by increasing amount of Carbopol 934P in the formulations. Swelling index and bioadhesion studies indicated a linear relationship between them.

**In vitro release study**

In vitro release of all formulations F1-F9 was ranging from 82.97-95.94% (Fig. 5-6). The formulation F2 containing Carbopol 934P and HPMC K4M in the ratio of 1:2 showed highest 95.94% drug release in 8 hrs. The dissolution profiles of tablet were influenced by type of polymer used. Dissolution profiles of formulations containing different CP: HPMC K4M polymer ratios i.e., F1, F2, F3 and F4 showed that as the concentration of Carbopol 934P increased in the formulation the release rate decreased. This property was due to hydrophilic and swellable nature of Carbopol 934P as supported by swelling studies (Fig. 4). From the same data it was observed that as the concentration of secondary polymer HPMC K4M increased in the formulations the release rate of glibenclamide also increased. In case of formulations containing NaCMC (F5, F6, F7 & F8) as secondary polymer the release rate increased with increase in polymer concentration. The formulations with NaCMC (F5 – F8) showed high initial release of drug due to erosion. Among all these formulations F2 gave 95.94% drug releases in 8 hrs and was selected as best formulation.

**Mechanism of drug release**

It was evident from Table 3 that the formulations F2 and F3 followed zero-order process as correlation coefficient (r²) values were 0.960 and 0.985 respectively indicating dissolution rate of the drug was independent of the amount of drug available for dissolution. But the formulations F6 and F7 followed first-order equation as correlation coefficient (r²) values 0.987 and 0.988 were higher than zero-order correlation coefficient values. Further, when the drug release data was put into Higuchi equation, good correlation coefficient (r²) values 0.942-0.983 were obtained, indicating that the drug release was diffusion controlled. The n values of different glibenclamide mucoadhesive buccal tablets were found in the range of 1.327 – 1.443 with lower correlation coefficient values ranging from 0.525-0.671, indicating non-Fickian super case II type transport mechanism.

**FTIR studies**

IR spectral studies revealed that the positions of the characteristic absorption bands for different functional groups and bonds of the pure drug were not changed considerably indicating no interaction of the drug with polymers and other excipients used for the study (Fig. 7 – 9).

**DSC studies**

The melting point of drug as indicated by DSC studies appeared at 173°C in pure drug as well as formulation (F2) indicating no interaction of the drug with the polymer and other excipients Fig. 10 - 11.

**Stability Study**

The stability studies revealed not much considerable change in appearance, physical attributes, drug content, % swelling index and in vitro drug release. The glibenclamide mucoadhesive tablets were found to be stable with respect to stability studies.

**CONCLUSION**

Preformulation studies on glibenclamide fairly corroborate with the reported literature limits. The adopted method yielded uniform and reproducible mucoadhesive buccal tablets with all the polymers used. Hardness, friability, weight variation, drug content, surface pH, bioadhesive strength, swelling index and in vitro release were uniform and reproducible. Surface pH values indicated no risk of mucosal damage or irritation, the mean bioadhesive strength values indicated sufficient adhesiveness to stick to the mucosa, swelling index was found to be higher with NaCMC than HPMC K4M, increase in Carbopol 934P concentration increased the swelling index. Buccal tablets F2 gave 95.94% controlled release of drug over a period of 8 hrs. The mechanism of drug release was found to be non-Fickian diffusion controlled, zero order kinetics. FT-IR and DSC studies revealed absence of any chemical interaction between drug and polymers used.

**ACKNOWLEDGEMENT**

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**REFERENCES**

Table 1: Composition of glibenclamide mucoadhesive buccal tablets

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>Formulation code</th>
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<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>10</td>
</tr>
<tr>
<td>Carbopol-934P</td>
<td>46</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>46</td>
</tr>
<tr>
<td>Na CMC</td>
<td>-</td>
</tr>
<tr>
<td>Mannitol</td>
<td>94</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
</tr>
<tr>
<td>Talc</td>
<td>2</td>
</tr>
<tr>
<td>Total weight</td>
<td>200</td>
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<td>Polymer Ratio</td>
<td>1:1</td>
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</tbody>
</table>

Table 2: Physico-chemical evaluation of glibenclamide mucoadhesive buccal tablets.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>(%) Drug Content</th>
<th>Surface pH</th>
<th>Bioadhesive Strength (gm)</th>
<th>% swelling index after 8 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>99.15 ± 0.16</td>
<td>6.80 ± 0.010</td>
<td>5.23</td>
<td>41 ± 2.06</td>
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<tr>
<td>F2</td>
<td>98.51 ± 0.10</td>
<td>7.09 ± 0.515</td>
<td>3.68</td>
<td>26 ± 1.11</td>
</tr>
<tr>
<td>F3</td>
<td>98.73 ± 0.29</td>
<td>6.21 ± 0.015</td>
<td>4.47</td>
<td>33 ± 2.49</td>
</tr>
<tr>
<td>F4</td>
<td>97.82 ± 0.04</td>
<td>5.46 ± 0.515</td>
<td>5.88</td>
<td>51 ± 0.43</td>
</tr>
<tr>
<td>F5</td>
<td>99.22 ± 0.09</td>
<td>6.23 ± 0.010</td>
<td>3.27</td>
<td>192 ± 0.33</td>
</tr>
<tr>
<td>F6</td>
<td>99.55 ± 0.16</td>
<td>6.98 ± 0.015</td>
<td>2.07</td>
<td>94 ± 1.22</td>
</tr>
<tr>
<td>F7</td>
<td>98.71 ± 0.10</td>
<td>6.81 ± 0.035</td>
<td>2.51</td>
<td>175 ± 0.14</td>
</tr>
<tr>
<td>F8</td>
<td>99.03 ± 0.29</td>
<td>5.86 ± 0.031</td>
<td>3.66</td>
<td>236 ± 0.11</td>
</tr>
<tr>
<td>F9</td>
<td>99.24 ± 0.37</td>
<td>4.61 ± 0.052</td>
<td>7.18</td>
<td>223 ± 0.38</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± SD. n=3.

Table 3: Kinetic analysis of release data based on best curve-fitting method for optimized glibenclamide mucoadhesive buccal tablets in pH 7.4 buffer.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Korsmeyer-peppas</th>
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</thead>
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<tr>
<td></td>
<td>n</td>
<td>r²</td>
<td>n</td>
<td>r²</td>
</tr>
<tr>
<td>F2</td>
<td>11.61</td>
<td>0.960</td>
<td>-0.161</td>
<td>0.941</td>
</tr>
<tr>
<td>F3</td>
<td>10.87</td>
<td>0.985</td>
<td>-0.119</td>
<td>0.939</td>
</tr>
<tr>
<td>F6</td>
<td>10.58</td>
<td>0.855</td>
<td>-0.150</td>
<td>0.987</td>
</tr>
<tr>
<td>F7</td>
<td>10.70</td>
<td>0.902</td>
<td>-0.125</td>
<td>0.988</td>
</tr>
</tbody>
</table>
Fig. 1: Modified balance to measure ex vivo bioadhesive strength

Fig. 2: Surface pH of glibenclamide mucoadhesive buccal tablets

Fig. 3: Bioadhesive strength of glibenclamide mucoadhesive buccal tablets

Fig. 4: % Swelling index of glibenclamide mucoadhesive buccal

Fig. 5: In-vitro release profile of glibenclamide mucoadhesive buccal tablets in pH 7.4 buffer.

Fig. 6: In-vitro release profile of glibenclamide mucoadhesive buccal tablets in pH 7.4 buffer.

Fig. 7: IR spectra of glibenclamide pure drug

Fig. 8: IR spectra of F2(Glibenclamide + Carbopol 934P + HPMC K4M).

Fig. 9: IR spectra of F6(Glibenclamide + Carbopol 934P + NaCMC).

Fig. 10: DSC thermogram of glibenclamide pure drug.

Fig. 11: DSC thermogram of formulation F2 (CP934 + HPMC K4M).