Development of Mucoadhesive Buccal Films of Glipizide

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ABSTRACT: For improving bioavailability in controlled release fashion and to circumvent the hepatic first pass effect of glipizide mucoadhesive buccal films of glipizide were prepared by solvent casting technique. Buccal films were prepared using hydroxy propylmethylcellulose, sodium carboxymethylcellulose, carbopol-934P and Eudragit RL-100. Films were evaluated for their weight, thickness, surface pH, swelling index, in vitro residence time, folding endurance, in vitro release, ex vivo permeation studies and drug content uniformity. The films exhibited controlled release over more than 6 h. From the study it was concluded that the films containing 5 mg glipizide in 4.9 % w/v hydroxy propylmethylcellulose and 1.5 % w/v sodium carboxymethylcellulose exhibited satisfactory swelling, an optimum residence time and promising drug release thus proved to be potential candidate for the development of buccal films for therapeutic use.

KEY WORDS: Mucoadhesive, Buccal Film, Glipizide, In Vitro Studies, Ex Vivo Studies.

Introduction

Amongst the various routes of administration tried so far for novel drug delivery systems, localized delivery to tissues of the oral cavity has been investigated for a number of applications including the treatment of toothaches (Ishida et al., 1982) periodontal disease (Collins et al., 1989, Elkayam et al., 1988), bacterial and fungal infections (Samaranayake et al., 1989), aphthous and dental stomatitis (Nagai, 1985), and in facilitating tooth movement with prostaglandins (Nagai and Machida, 1985). Over the last two decades mucoadhesion has become of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within gastrointestinal tract) or systemic delivery, by retaining a formulation in intimate contact with the absorption site (e.g. the buccal cavity). Mucoadhesion maybe defined as a state in which two materials, one of which is mucus or a mucous membrane, is held together for extended period of time (Smart, 2005, Ahuja et al., 1997). Various studies have been conducted on buccal delivery of drugs using mucoadhesive polymers (Smart, 2005, Shojaei, 1998). Recently some scientists (Jasti et al., 2003, Salamat-Miller et al., 2005, Semalty, 2006) have reviewed the use of mucoadhesive polymers in buccal drug delivery and highlighted the use of novel mucoadhesive polymers. Attempts have been made to formulate various mucoadhesive devices including tablets (Ali et al., 1998), films (Kohda et al., 1997), patches (Nair and Chien, 1996, Perioli, L., et al., 2004), disks (Parodi et al., 1996, Ali et al., 2002), strips (Ilango et al., 1997), ointments (Bremecker et al., 1984), and gels (Shin et al., 2000). Buccal film may be preferred over adhesive tablet in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. Moreover, the buccal films are able to protect the wound surface, thus reducing pain and treating oral diseases more effectively (Nafee et al., 2003).

Glipizide is a second generation sulfonylurea compound used as an oral hypoglycemic or antidiabetic agent. Glipizide is one of the most potent of the sulfonylurea antidiabetic agents. It is 100 times more potent than tolbutamide in evoking pancreatic secretion of insulin. It differs from other oral hypoglycemic drugs in that tolerance to its action apparently does not occur. It also upregulates insulin receptors in the periphery, which seems to be the primary action. Its short biological half-life (3.4 ± 0.7 hours) necessitates its administration in 2 or 3 doses of 2.5 to 10 mg per day. Moreover, about 90% of the drug is metabolized in the liver forming several inactive metabolites (Foster and Plosker, 2000). Thus an attempt has been made to develop a buccal mucoadhesive dosage form of glipizide for improving and enhancing bioavailability in controlled release fashion. It may also be possible to circumvent the hepatic first pass effect by administering the drug through buccal mucosa.

The present work deals with the formulation and characterization of mucoadhesive buccal films of glipizide using mucoadhesive polymers like Hydroxypropylmethylcellulose, Carbopol-934P, Eudragit RL-100 and Sodium carboxymethylcellulose.
Table 1: Composition of Mucoadhesive Buccal Films of Formulations

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Glipizide (g)</td>
<td>0.30</td>
</tr>
<tr>
<td>HPMC-E15 (g)</td>
<td>1.30</td>
</tr>
<tr>
<td>Sodium CMC-H (g)</td>
<td>--</td>
</tr>
<tr>
<td>Eudragit RL100 (g)</td>
<td>--</td>
</tr>
<tr>
<td>Carbopol-934P (g)</td>
<td>--</td>
</tr>
<tr>
<td>Propylene Glycol (ml)</td>
<td>0.48</td>
</tr>
<tr>
<td>Ethanol (95%) ml</td>
<td>20</td>
</tr>
</tbody>
</table>

Abbreviations used: HPMC-Hydroxy propylmethylcellulose; Sodium CMC-Sodium carboxymethylcellulose.

Materials and Methods

Glipizide was obtained as a gift sample from USV Ltd (Daman, India). Hydroxy propyl methyl cellulose (HPMC-E15), Carbopol-934P (CP-934P), Eudragit RL-100 and sodium carboxymethylcellulose, 1500-400cps (SCMC) were procured from Central Drug House, Mumbai. Propylene glycol was procured from E. Merck (P) Ltd, Mumbai. All other reagents used were of analytical grade. The films were prepared by Solvent Casting Method.

Preparation of Mucoadhesive Buccal Films

Buccal films of glipizide were prepared by solvent casting technique employing aluminum foil cups (placed on glass surface) as substrate (Dev i and Paranjothy, 1998). Composition of a single circular cast film of various formulations is mentioned in Table 1. Buccal films were prepared by using HPMC-E15 alone and in combination with CP-934P, Eudragit RL-100 and Sodium CMC (High Viscosity Grade). Propylene glycol, a plasticizer is used in the concentration of 30 % w/w. Ethanol was used as a solvent.

The calculated amounts of polymers were dispersed in ethanol. 300 mg of glipizide was incorporated in the polymeric solutions after levigation with 30 % w/w propylene glycol which served the purpose of plasticizer as well as penetration enhancer. The medicated gels were left overnight at room temperature to obtain clear, bubble-free gels. The gels were caste into aluminum foil cups (9.0 cm diameter), placed on a glass surface and allowed to dry overnight at room temperature to form a flexible film. The dried films of 12 mm diameter were punched out from the cast films using a specially fabricated punch, packed in aluminum foil and stored in glass containers (maintained at room temperature and 58% relative humidity) until further use.

Characterization of Mucoadhesive Buccal Films

Film Weight and Thickness

For evaluation of film weight three films of every formulation were taken and weighed individually in digital balance (Fisher Brand PS-200). The average weights were calculated. Similarly, three films of each formulation were taken and the film thickness was measured using Micrometer Screw Gauge (Mitutoyo MMO-25DS) at three different places and the mean value was calculated.

Surface pH of Films

For determination of surface pH three films of each formulation were allowed to swell for 2 h on the surface of an agar plate. The surface pH was measured by using a pH paper placed on the surface of the swollen patch. A mean of three readings was recorded.

Percent Swelling

After determination of the original film weight and diameter, the samples were allowed to swell on the surface of agar plate kept in an incubator maintained at 37± 0.2°. Increase in the weight of the films (n=3) was determined at preset time intervals (1-5 h). The per cent swelling, % S, was calculated using the following equation:

\[
\text{Per cent Swelling} (\% S) = \left( \frac{X_t - X_o}{X_o} \right) \times 100,
\]

Where \(X_t\) is the weight of the swollen film after time t, \(X_o\) is the initial film weight at zero time (Semalty et al., 2005).

Folding Endurance

Three films of each formulation of size (2×2 cm) were cut by using sharp blade. Folding Endurance was determined by repeatedly folding a small strip of film at the same
place till it broke. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The mean value of three readings and standard deviation were shown in Table 2.

**In vitro Residence Time**

The *in vitro* residence time was determined using USP disintegration apparatus. The disintegration medium was 800 ml of pH 6.6 phosphate buffer (PB) maintained at 37±2°. The segments of porcine buccal mucosa, each of 3 cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Three mucoadhesive films of each formulation were hydrated on one surface using pH 6.6 PB and the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The film was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the film from the mucosal surface was recorded (n=3) as given in Table 2.

**Drug Content Uniformity**

Three film units of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 6.6 phosphate buffer was added and continuously stirred for 24 h. The solutions were filtered, diluted suitably and analyzed at 274 nm in a UV spectrophotometer (Thermospectronic UV-1). The average of drug contents of three films was taken as final reading.

**In Vitro Release Study**

The USP XXIV six station dissolution apparatus type 1 (V Scientific Model No. DA-6DR) was used throughout the study. One Film of each formulation was fixed to the central shaft using a cyanoacrylate adhesive. The dissolution medium consisted of 100 ml pH 6.6 PB. The release study was performed at 37±0.5° with a rotation speed of 50 rpm. The release study was carried out for 6 h. After every hour, samples were withdrawn from each station, filtered, diluted suitably and then analyzed spectrophotometrically at 274 nm. The data presented were the mean of three determinations.

**Ex Vivo Permeation Studies**

In this study, porcine buccal mucosa was used as a barrier membrane. The buccal pouch of freshly sacrificed animal was procured from local slaughter house. The buccal mucosa was excised and trimmed evenly from the sides. It was then washed in isotonic phosphate buffer (pH 6.6) and used immediately (Junginger et al., 1999).

The *ex vivo* permeation studies of mucoadhesive buccal films of glipizide through an excised layer of porcine buccal mucosa were carried out using the modified Franz diffusion cell (Semalty et al., 2005). A 2.0 cm diameter film of each formulation under study was placed in intimate contact with the excised porcine buccal mucosa and the topside was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 100 ml of pH 7.4 phosphate buffer. The cell contents were stirred with a magnetic stirrer and temperature of 37±1° was maintained throughout the experiment. The samples were withdrawn at every hour, filtered, diluted suitably and then analyzed using UV- spectrophotometer at 276 nm (λ_max of glipizide at pH 7.4 PB).

**Results and Discussion**

Mucoadhesive buccal films of glipizide were prepared using mucoadhesive polymers HPMC-E15, CP-934P, Eudragit RL-100 and sodium CMC. Propylene glycol was used as the plasticizer as well as penetration enhancer. The drug delivery system was formulated as a matrix. The films were characterized for their physical characteristics, bioadhesive performance, release characteristics, surface pH, thickness, folding endurance, drug content uniformity and percent swelling (Table 2). The film thicknesses were observed to be in the range of 0.245 ± 0.028 mm to 0.282 ± 0.032 mm and weight was found to be in the range of 56 ±1.86 mg to 84 ± 0.74 mg.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Surface pH</th>
<th>Thickness (mm)</th>
<th>Swelling Index (2h)</th>
<th>In vitro Residence time (h)</th>
<th>Folding Endurance</th>
<th>Content Uniformity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>6.59 ± 0.015</td>
<td>0.282 ± 0.032</td>
<td>46.396 ± 0.332</td>
<td>2.25 ± 0.559</td>
<td>164.55 ± 4.527</td>
<td>4.64 ± 0.006</td>
</tr>
<tr>
<td>F2</td>
<td>6.50 ± 0.020</td>
<td>0.245 ± 0.028</td>
<td>46.84 ± 1.245</td>
<td>3.00 ± 0.721</td>
<td>234.33 ± 12.662</td>
<td>4.66 ± 0.045</td>
</tr>
<tr>
<td>F3</td>
<td>6.42 ± 0.032</td>
<td>0.258 ± 0.008</td>
<td>17.196 ± 1.155</td>
<td>1.75 ± 0.908</td>
<td>207.66 ± 11.372</td>
<td>4.82 ± 0.014</td>
</tr>
<tr>
<td>F4</td>
<td>6.15 ± 0.095</td>
<td>0.260 ± 0.023</td>
<td>32.04 ± 0.258</td>
<td>4.00 ± 0.087</td>
<td>290.00 ± 4.0</td>
<td>4.66 ± 0.062</td>
</tr>
</tbody>
</table>

(Mean values of triplicate readings (n=3) are followed by standard deviation)
Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymers, the surface pH of the buccal films was determined to optimize both drug permeation and mucoadhesion (Ch’ng et al., 1985; Park and Robinson, 1985). Attempts were made to keep the surface pH as close to buccal/salivary pH as possible. The surface pH of all the films was within the range of salivary pH. No significant difference was found in surface pH of different films.

Hydration is required for a mucoadhesive polymer to expand and create a proper “macromolecular mesh” of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network (Gu et al., 1998). However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bioadhesion occurs (Peppas and Buri, 1985). The effect of glipizide on the swelling behaviour and the residence time of various mucoadhesive polymers was also observed (Table 2). The addition of the water-insoluble drug increased the water uptake of the film. This is possibly due to micronized drug particles whisk exist between the polymer chains allowing each chain to hydrate freely, resulting in weak hydrogen bonding areas around the glipizide molecules. These areas may increase the strength of the swollen layer followed by an obvious increase in the amount of penetrated water (Panomsuk et al., 1996). Indomethacin, a practically water-insoluble drug, was found to increase the swelling behaviour of HPMC matrices (Panomsuk et al., 1996), while lower swelling indices were observed when the same drug was added to Gantrez-169 compressed matrix (El-Khodairy, 2001). The influence of drug on the swelling properties of polymer matrices is primarily dependent on the substituted groups of the polymer. The hydroxyl group in the molecules plays an important role in the matrix integrity of the swollen hydrophilic cellulose matrices. The amount and properties of the incorporated drug determine matrix integrity.

The comparative percentage swelling for various formulations was in order of F2 > F1 > F4 > F3. The percentage swelling of HPMC-E15 films was reduced by the addition of Carbopol 934P and Eudragit-RL100 and increased by the addition of SCMC. SCMC containing films showed higher percent swelling due to presence of more hydroxyl group in the SCMC molecules. The water-soluble hydrophilic additive dissolves rapidly resulting in high porosity. The void volume is thus expected to be occupied by the external solvent diffusing into the film and thereby accelerating the dissolution of the gel (Samuelov et al., 1979).

The incorporation of the drug induced significant reduction of the residence time of various formulations. The enhanced erosion rate was observed with the non-ionic polymers (HPMC with Eudragit RL100). As the particle swells, the matrix experiences intra-matrix swelling force which promotes disintegration and leaching of the drug leaving behind a highly porous matrix. Water influx weakens the network integrity of the polymer, thus influencing structural resistance of the swollen matrices, which in turn results in pronounced erosion of the lose gel layer (El-Khodairy, 2001). The water-soluble hydrophilic polymers like SCMC dissolve rapidly and introduce porosity. The void volume is thus expected to be occupied by the external solvent which diffuses into the film and thereby accelerate the dissolution of the gel (Samuelov et al., 1979). The in vitro residence time of the film was in order of F4 > F2 > F1 > F3. The folding endurance was measured manually, by folding the film repeatedly at a point till they broke. The breaking time was considered as the end point. Folding endurance was found to be highest for F4 (290 ± 4.0) and lowest for F1 (164.55 ± 4.527). It was found that folding endurance of HPMC films was increased by the addition of polymers in the order; Eudragit-RL100 > SCMC> Carbopol 934P. The folding endurance values of the films were found to be optimum and therefore the films exhibited good physical and mechanical properties.

Drug content in formulations was uniform with a range of 4.64 ± 0.006 mg (F1) to 4.82 ± 0.016 mg (F3). On this basis, it was found that the drug was dispersed uniformly throughout the film.

In vitro release studies of various formulations were performed using pH 6.6 phosphate buffer as dissolution medium and measuring drug concentration spectrophotometrically at 274 nm. Significant difference was observed in the release pattern of glipizide films containing Eudragit, Carbopol and SCMC. During dissolution, SCMC containing films swelled forming a gel layer on the exposed film surfaces. The loosely bound polymer molecules in these films were readily eroded, allowing the easy release of glipizide as compared to Eudragit RL-100 (Korsmeyer et al., 1983). After 6 h the release was found to be 89.50, 93.45, 69.89 and 78.65 % in formulation F1, F2, F3 and F4 respectively (Fig. 1).
SCMC and Carbopol polymers exhibited high swelling, the film weight of these polymers was noted to be increased to the extent of 25 to 60 % from the initial weight within 2 h (Table 2). Although the marked increase in surface area during swelling can promote drug release but the increase in diffusion path length of the drug may paradoxically delay the release. In addition, the thick gel layer formed on the swollen film surface is capable of preventing matrix disintegration and controlling additional water penetration (Rodriguez et al., 2000). SCMC films showed high dissolution rate as compared to Eudragit RL100 films. It was found that the drug release from the films followed the diffusion controlled mechanism in all the formulations. The plots of log cumulative percent drug retained versus time were found to be linear for the formulations. On the basis of plots it was concluded that the release of glipizide from the films have obeyed first order kinetics. The correlation coefficient values were found to be -0.997, -0.987, -0.898, -0.9922 for F1, F2, F3 and F4 respectively exhibiting good correlation. Negative values of the correlation coefficient indicate negative slope for the plot.

To confirm the mechanism of drug release Higuchi’s plots were drawn for all the formulations. Fig. 2 shows the graphical representation of cumulative percentage drug release versus square root of time. The Higuchi’s Plots were found to be linear with correlation coefficient values of 0.995, 1.037, 0.840 and 0.922 for F1, F2, F3 and F4, respectively. It was concluded that the release of drug from the films followed the diffusion controlled mechanism in all the formulations. The plots of log cumulative percent drug retained versus time were found to be linear for the formulations.

**Fig. 1** Cumulative percent drug release of formulations in pH 6.6 phosphate buffer.

**Fig. 2** Higuchi’s diffusion plot for different formulations.
It was also concluded that formulation F1 (containing HPMC alone) and F2 (containing HPMC with SCMC) showed good swelling, a convenient residence time as well as promising drug release pattern. On the basis of release pattern, swelling and residence time, F1 and F2 formulations were selected for ex vivo study. In ex vivo study, drug permeation through the porcine buccal mucosa was determined for formulation F1 and F2 (Fig. 3). The drug permeation was found to be 78.25% and 89.01% in F1 and F2 after 10 h. The ex vivo permeation studies were performed for the extended period (10 h) so as to observe the release pattern of the drug for the films which could be designed to have the greater residence in oral cavity by any means. The Higuchi Plots of F1 and F2 were found to be almost linear with correlation coefficient values of 0.9310 and 0.9748. This proves that the drug permeation followed the matrix diffusion process. The plots of log cumulative percent drug retained as a function of time were found to be linear for both the formulations. This linearity indicates that the permeation of glipizide from the films obeyed the first order kinetics. The correlation coefficient values were found to be -0.987 and -0.948 showing good correlation.

Conclusion

The present study indicates enormous potential of erodible mucoadhesive buccal films containing glipizide for systemic delivery with an added advantage of circumventing the hepatic first pass metabolism. The results of the study show that therapeutic levels of glipizide can be delivered buccally. It may be concluded that the films containing 5 mg glipizide in 4.9% w/v HPMC with 1.5% w/v SCMC (F2), show good swelling, a convenient residence time and promising controlled drug release, thus seems to be a potential candidate for the development of buccal film for effective therapeutic use. The further studies are required to enhance the residence time of the buccal films in the oral cavity, so that the potential therapeutic benefit can be received. In vivo studies need to be designed and executed to substantiate further in-vitro in-vivo correlation.

References


