DEVELOPMENT OF MUCOADHESIVE BUCCAL PATCHES FOR CONTROLLED DELIVERY OF ANTI DIABETIC DRUG

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Abstract- The aim of the present investigation was to develop a controlled release drug delivery device of anti-diabetic drug i.e., Glipizide to maintain its bioavailability over an extended period of time and to circumvent the hepatic first pass effect. To achieve this object, Drugcoat and HPMC were used as a polymer for the preparation primary and secondary layer respectively, of controlled release bilayered mucoadhesive patches of drug. The prepared patches were evaluated for various in vitro and in vivo studies. From the study it was concluded that the developed bilayered mucoadhesive delivery system bears potential to deliver the drug in a controlled manner over an extended period of time.

Key words- HPMC, Glipizide, Buccal Patches.

I. INTRODUCTION

Non insulin dependent diabetes mellitus (NIDDM) represents a heterogeneous group comprising milder form of diabetes that occurs predominately in adults. The majority of diabetic patients have type 2 diabetes and Glipizide is one the most commonly prescribed drug for the treatment of type II diabetes [1, 2]. Glipizide is a second generation oral blood glucose lowering drug belongs to sulfonylureas class of antidiabetic category. It acts by stimulating the release of insulin from pancreas. Its short biological half life (3-4 hr) necessitates its administration in 2 or 3 doses of 2.5 to 10 mg daily. Moreover, about 90% of the drug is metabolized in liver forming several inactive metabolites [3,4] as well as oral therapy with Glipizide has also been associated with gastric disturbances like nausea, vomiting and sometimes severe and fatal hypoglycemia[1]. Therefore, there is always a need to develop a sustained controlled release formulation of Glipizide. Thus an attempt has been made to develop controlled release buccoadhesive patches bearing Glipizide for improving and enhancing bioavailability in controlled release fashion and circumvent the hepatic first pass effect by administering the drug through buccal mucosa. The present work deals with the formulation and characterization of Glipizide bearing mucosalhesive patches which were prepared by solvent casting method using drugcoat and HPMC as polymer.

II. MATERIALS AND METHODS

Material
Glipizide was received as a gift sample from USV, Mumbai. Mucoadhesive polymers HPMC and Drugcoat were obtained as gift samples from Pure Pharma, Indore and Vikram Thermo (India) Ltd., -

International Journal of Pharmacology and Pharmaceutical Technology, ISSN-2277-3436, Vol-2, Iss-1, 2018

Ahmedabad, respectively. All others chemical used in the study were of analytical grade.

Preparation of Buccoadhesive Patches
Bilayered buccoadhesive patches were prepared by solvent casting technique using aluminium foil cup with ethylcellulose as a backing layer, Drugcoat as a primary layer, and HPMC as a secondary layer polymers along with propylene glycol as a plasticizer. Ethyl cellulose (500 mg) was dissolved in 10 ml of acetone and then 0.2 ml of dibutylphthalate was added which serve as a film forming agent. This solution was poured over aluminium foil cups of diameter 9 cm and kept for drying. Primary layer solution was prepared by dissolving Drugcoat in 10 ml acetone, followed by addition of propylene glycol and 100 mg Glipizide with stirring. Then solution of primary polymer was poured over pre-dried backing layer. Petridish was kept aside for complete evaporation of acetone and for drying. Secondary layer was prepared by dissolving HPMC in 10 ml water followed by addition of propylene glycol and 100 mg Glipizide. After stirring, this solution was poured over pre-dried primary layer and kept aside for 24 hr for drying. Different patches were formed using different concentration of Drugcoat [5, 6] (Table 1).

Table 1, Different patches combinations.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Drug concentration (mg)</th>
<th>Polymer 1 (mg)</th>
<th>Polymer 2 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>100</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>P2</td>
<td>100</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>P3</td>
<td>100</td>
<td>600</td>
<td>400</td>
</tr>
<tr>
<td>P4</td>
<td>100</td>
<td>800</td>
<td>400</td>
</tr>
</tbody>
</table>
Polymer 1- Drugcoat; Polymer 2- HPMC

**Characterization of Buccoadhesive Patches**

Prepared formulations were characterized for the film weight, thickness, folding endurance, tensile strength, pH, percent swelling and drug content. The results are shown in Table 2 and Fig. 1

**Fig. 1** Percent swelling of different buccal patches

Table 2 Physical evaluation of different buccal patches.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Film weight (mg)</td>
<td>32.3±0.71</td>
<td>34.1±0.32</td>
<td>35.0±1.12</td>
<td>33.6±0.36</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>0.30±0.02</td>
<td>0.38±0.01</td>
<td>0.45±0.07</td>
<td>0.40±0.00</td>
</tr>
<tr>
<td>Folding Endurance</td>
<td>254±14</td>
<td>273±06</td>
<td>282±7</td>
<td>298±9</td>
</tr>
<tr>
<td>Tensile strength (g/cm²)</td>
<td>281±2.1</td>
<td>289±1.9</td>
<td>295±2.5</td>
<td>320±2.3</td>
</tr>
<tr>
<td>Surface pH</td>
<td>6.1±0.1</td>
<td>6.7±0.1</td>
<td>6.1±0.2</td>
<td>6.3±0.2</td>
</tr>
<tr>
<td>Drug content (mg/cm²)</td>
<td>6.24±0.7</td>
<td>6.19±0.3</td>
<td>6.21±0.2</td>
<td>6.31±0.6</td>
</tr>
</tbody>
</table>

Mean±SD (n=3).

**In Vitro Studies**

**Drug release**

The USP six station dissolution apparatus type-II was used for drug release study. The release study was carried out at 37 ± 0.5°C in PBS (pH 6.8) with a rotation speed of 50 rpm for 8 hr. The samples were withdrawn periodically and analyzed spectrophotometrically at \( \lambda_{	ext{max}} \) of 276 nm. Fig. 2 shows the results of in vitro drug release studies. Considering the desirable swelling index, drug content and other parameters as well as in vitro drug release the formulation P2 was selected for further studies.

**In vitro bioadhesion test**

The binding capability of the patches containing Glipizide to buccal mucosa was evaluated in triplicate by following the method reported by Kumar et al. 2010 [7] using goat intestinal mucosa. The total weight required for complete detachment of film was recorded and the bioadhesion force per unit area of the film was calculated as follows:

\[
F = \frac{(W \cdot g)}{A}
\]

Where \( F \) is the bioadhesive force (g cm\(^{-1}\)s\(^{-2}\)), \( W \) is the mass applied in gm, \( g \) is the acceleration due to gravity in cms\(^{-2}\) and \( A \) is the surface area of the film in cm\(^2\) (Table 3).

**In vitro buccal permeation studies**

**In vitro** buccal permeation study was conducted using modified diffusion cell [8] using of goat buccal mucosa. The samples were withdrawn at different time intervals, filtered, diluted suitably and drug concentration was measured spectrophotometrically at \( \lambda_{	ext{max}} \) 276 nm.

**Table 3** In vitro bioadhesion studies of selected buccal patch.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Bioadhesive strength (g/cm.s(^{-2}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2</td>
<td>70.22±1.76</td>
</tr>
</tbody>
</table>

Mean±SD (n=3).

**In vitro buccal permeation studies**

**In vitro** buccal permeation study was conducted using modified diffusion cell [8] using of goat buccal mucosa. The samples were withdrawn at different time intervals, filtered, diluted suitably and drug concentration was measured spectrophotometrically at \( \lambda_{	ext{max}} \) 276 nm.

**Figure 3**: In vitro drug permeation profile through goat buccal mucosa of P2 formulation.

**In Vivo Studies**

The study conducted was approved by Institutional Animal Ethical Committee of Dr. Hari Singh Gour Vishwavidyalaya, Sagar (MP) vide the letter no.
ANIMAL ETHICS COMMITTEE/10/09. The albino rabbits of either sex (1.5-2 Kg) were used for in vivo study. The animals were divided into 2 groups and each group having 3 animals (Group 1, plain Glipizide solution; and Group 2, Glipizide bearing buccal patch). All the animals were fasted overnight. Diabetes was induced in rabbits by i.v. injection of streptozotocin (65mg/kg) for 4 to 5 days.

First group of animals were given an oral suspension of Glipizide containing 800µg/Kg of Glipizide. Second group of animals were taken for buccal application of patches containing dose equivalent of 800µg/Kg. Following the treatment, blood samples via the marginal ear vein of rabbits at predefined time intervals were taken and analyzed for glucose content through Glucoimeter. Result shown in Fig. 4.

III. RESULT AND DISCUSSION

Buccoadhesive patches of Glipizide were prepared using mucoadhesive polymers HPMC and with different concentration of Drugcoat. The developed patches were characterized for their physical characteristics, bioadhesive performance, release characteristics, surface pH, thickness, folding endurance, drug content uniformity, percent swelling, ex vivo permeation and in vivo performance. Physicochemical characteristics of the patches were shown in Table 1. Based on the quantities of the polymer Drugcoat, ranging from 2 to 8% w/v, the film weight was found to increase with the marginal increase in thickness of the film. This may be due to increase in concentration of polymer. Whereas the surface pH of all the formulations was found to be near to salivary pH, this indicates that all the formulations are free from any type of mucosal irritation.

To find out the flexibility and tensile strength of the patches, folding endurance test and tensile strength test were performed. The result of studies showed that upon increasing the concentration of polymer, the flexibility and tensile strength of the patches increases. This may be due to strong covalent bonding between polymer and drug. Drug content of different formulations was found to be in the almost uniform range which indicates that the drug was dispersed uniformly throughout the film (Table 2).

Appropriate swelling behavior of buccal films is the essential property for uniform and prolonged release of the drug with effective mucoadhesion. During the swelling studies, it was found that, in the first hr approximately 35% swelling occurred in all the four formulations. This may be due to the hydrophilic nature of the secondary layer polymer, which was HPMC. Further, negligible change in swelling and moisture sorption of the films from P1 to P4 were observed i.e., approximately 58% in 6 hr (Figure 1). This may be due to the hydrophobic nature of the Drugcoat polymer which avoided the penetration of water to the patches.

The drug release profiles of Glipizide from formulations P1 to P4 are shown in Figure 2. Results of drug release studies clearly indicate that the drug release was governed by polymer concentration. No lag time was observed as when the patch was directly exposed to the dissolution medium. In the first hr approximately 39-40% drug was released. This fast release of the drug was due to the erodible, hydrophilic layer of polymer. The hydrophilic polymer HPMC dissolves and creates pores as well as channels for the diffusion of drug from patches. Further slow release of the drug is due to the hydrophobic layer of Drugcoat. Maximum drug release was found to be with formulation P2, therefore it was selected for further studies.

The bioadhesive force and the mucoadhesive residence time studies indicated that the formulation P2 films showed the good mucoadhesive property, which is a desirable property for route of drug administration.

The results of in vitro permeation studies indicated that the rate of drug permeation was slow and it was found to be approximately 80% after 8 hr (Figure 3). The results of drug permeation studies revealed that Glipizide was released from the formulation and permeated through goat buccal membrane and hence could possibly permeate through the human buccal membrane, successfully.

The in vivo study was carried out in healthy, albino rabbits. In this study, the reduction in blood glucose level was determined after administration of Glipizide bearing buccal patches and compared with the reduction in blood glucose after oral administration of Glipizide suspension in an equivalent dose. It was observed that when the drug loaded buccal patch was administered; only 32% reduction in blood glucose was observed in first hr and it was maintained up to 8 hr and recovered after very long time. But when the drug was administered orally in suspension form, a
maximum reduction of 47% was observed at first hr and maintained up to only 4 hr and recovered within approximately 6 hr (Figure 4).

The sudden fall in blood glucose level after administration of Glipizide suspension may be due to the instantly availability of free Glipizide in blood circulation. This sudden fall in blood glucose level may leads to severe hypoglycemia, sometimes which may be fatal. But in case of buccal patches only approximately 32% reduction in blood glucose was found in first hr, which may be due to the fast release of drug from the secondary layer of the polymer HPMC. This layer is hydrophilic in nature, which absorbs water and starts swelling immediately. The absorption of water enhances the dissolution and release of the drug. In addition, polymer itself starts dissolving leading to the formation of pores, which further enhances the diffusion of the drug. The reduction in blood glucose was maintained up to 8 hr due to sustained release of Glipizide from the primary layer of the Drugcoat. Approximately 25% reduction in glucose levels is considered a significant hypoglycemic effect [8]. Therefore, the results suggested that when the drug loaded buccal patch was administered, the reduction in blood glucose levels were started from first hr and sustained over longer periods of time due to controlled release and prolonged absorption of Glipizide from the patches. Some researcher also reported controlled release of entrapped drug from buccal patches [10-12]. Thus it can be concluded that the developed bilayered buccoadhesive system have potential to deliver Glipizide in controlled fashion.

IV. CONCLUSION

The in vitro drug release and in vivo studies suggested that mucoadhesive buccal films bearing Glipizide were able to deliver the drug at a controlled rate for an extended period of time. The proposed system is expected to be a substitute of the tablets. Newly developed system would also likely to overcome all the drawbacks of the presently available therapy of Glipizide. Thus, developed system might be completely safe, effective and convenient drug delivery system for treatment of diabetes.

REFERENCES