Formulation & Evaluation of Sustained Release

Mucoadhesive Buccal Patch of Pantoprazole

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Abstract

Pantoprazole mucoadhesive bilayer buccal patch was prepared using solvent casting method, 3^2 factorial design was used to study the effect of concentration changes in XG and PVA, which were selected as independent variables on the swelling index, mucoadhesive time, and invitro release responses. FB13 formulation showed satisfactory results of 226 ± 1.66, 280 ± 2.77, 88.59 ± 2.31 for swelling index, mucoadhesive time, and invitro release respectively. Release kinetics model was fitted in higuchi, with regression value of 0.998. Hence it has been selected as optimized formulation and evaluated for further parameters such as weight uniformity, thickness of patch, folding endurance, surface pH, drug content, mucoadhesive strength. Ex-vivo permeation study on FB13 was carried out in buccal.

Keywords

Pantoprazole, Xanthan gum, Polyvinyl alcohol and Optimization.

1. Introduction

Peptic ulcer is a disease characterized by the presence of ulcers in any portion of gastrointestinal tract (GIT) exposed to acid in sufficient concentration and duration. It occurs due to imbalance between aggressive factors like acid, pepsin, H-pylori and defensive factors such as gastric mucus, bicarbonate ions, and prostaglandins. Approximately 5,00,000 new cases and 4 million recurrences of peptic ulcer of Americans are reported each year, contributing to the approximately 10–15 % of the world population developing peptic ulcer disease in their lifetime. Most commonly these ulcerations occur in the stomach, and small intestine (duodenal ulcer). Pantoprazole is proton pump inhibitor (PPI) which suppress the gastric acid secretion by inhibition of H/K –ATPase enzymes activity, because of its local irritant effect on the stomach and its instability on acidic medium an alternative dosage form was needed (1). Among the various routes of drug delivery, the oral route is perhaps the most preferred one for patients and clinicians. Buccal drug delivery system involves administration of the drug to be absorbed through the buccal mucosa and directly introduced into the systemic circulation through the internal jugular vein avoiding acid decomposition and bypass drug from first pass metabolism leading to higher bioavailability. In this research, sustained release mucoadhesive buccal patch with an ethyl cellulose backing layer was formulated.
2. Materials and Methods

2.1. Materials

PNT was purchased from yarrow chem. (Mumbai), Xanthan gum (XG) was obtained from Thomas baker, Polyvinylalcohol (PVA), Propylene glycol (PG), Glycerol, and acetone were obtained from SD fine chem limited (SDFCL), ethanol, methanol, ethyl cellulose (EC) and Dimethyl sulfoxide (DMSO) were obtained from Finar. Hydroxypropyl methylcellulose (HPMCE-15) was obtained from Titan Biotech ltd.

2.2. Preparation of PNT buccal patch

2.2.1. Preparation of backing layer: The backing layer was prepared by dissolving (5%) of ethyl cellulose in a mixture of acetone: isopropyl alcohol (60:40) with glycerol (5%) as plasticizer. The plasticized backing membrane solution was added and allowed to dried on Petri dish.

2.2.2. Preparation of PNT buccal patch: PNT mucoadhesive patch was formulated using solvent casting method. The hydrophilic polymer PVA was allowed to soak for 30 minutes, ethanolic solution of PNT dissolved and xanthan gum was then added to drug polymeric solution and allowed to be stirred for 1 hour (2). HPMC E-15 was soaked in small quantity of water and kept in refrigerator to form a clear solution, 40% of PG from total weight of polymers was added to the polymeric solution as plasticizer and stirred with constant mechanical stirrer for 15-20mints. The polymeric solution was sonicated for 30minutes for complete removal of air bubbles. The resultant clear solution was then poured on ethyl cellulose pre-prepared backing layer in a glass Petri dish and dried in oven which kept at minimum temperature 50°C for 3hours to avoid the decomposition of PNT and excipients. The resultant patch was allowed to dry by air for the next 5hours.

2.3. Full factorial experimental design

A 32 factorial design was used to optimize the prepared PNT buccal patch. The design was used to study the effect of concentration changes of (PVA) and (XG) on predetermined evaluation parameters. The % concentrations of film forming agent PVA (x₁) and mucoadhesive polymer XG (x₂) were selected as independent variables. The two factors were evaluated, each at three levels -1, 0, 1 indicating higher, middle, and lower levels of each factor. The actual; units for factor (x₁) were 0.5%, 1%, 1.5% and for factor (x₂) were 1%, 1.5%, 2.0% respectively. The dependent or response variables were swelling ratio (y₁), mucoadhesive time (y₂), and cumulative release (y₃).

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2.4. Evaluation parameters of optimized PNT buccal patch

2.4.1. Weight uniformity: Mass uniformity was tested in three different, individual, randomly selected 2cm² patch using electronic balance and the average has been calculated.

2.4.2. Thickness of patch: The thickness of the patch was determined by using standard Vernier calliper at three different positions and the average was calculated.

2.4.3. Folding endurance: Folding endurance of the patch was determined repeatedly by folding one patch at the same place till it broke or folded up to 300 times without breaking.

2.4.4. Drug content: PNT patch (without backing layer) was dissolved in phosphate buffer 6.8 pH and allowed to stirring for 24 hours. The resultant solution has been filtered, then required dilution has been diluted and measured at UV spectrophotometer at 288.4nm.

2.4.5. Surface pH: Buccal patch was allowed to swell for 2 hours on the surface of phosphate buffer 6.8. The surface pH was measured using glass electrode. The average pH was recorded.

2.4.6. Swelling studies: PNT buccal patch of 2cm² allowed to swell on the surface of Petri dish containing 5ml of phosphate buffer 6.8 and weight of the swollen patch recorded in the duration of 300 minutes.

\[(SI)\% = \frac{W_1 - W_0}{W_0} \times 100\]

\(W_1\): indicate the weight of swollen patch  
\(W_0\): indicate the weight of the patch at zero time

2.4.7. Mucoadhesion time: Ex-vivo mucoadhesion time has been performed on a locally disintegration apparatus. The fresh mucosal membrane has been extracted from freshly slaughtered sheep and the underlying fat was removed before get washed by phosphate buffer 6.8 pH at 37°C [3].

Buccal sheep mucosa was glued to the surface of glass slide. The patch was wetted on one side and pasted in surface of the sheep mucosa by gentle pressing for 30 seconds with the help of fingertip. the glass slide vertically mounted on the disintegration apparatus to allow ups and down movement and get immersed in 800ml of phosphate buffer 6.8 used as a medium. The time required for the patch to get detach from the assembly has been recorded.

2.4.8. Mucoadhesive strength: The force required to detach the attachment of mucoadhesive buccal patch from the mucosal surface was applied as a measure of the mucoadhesive strength. This study was carried out on a specially fabricated physical balance assembly. Buccal sheep

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mucosa was glued on a dry Petri dish surface by placing the mucosal surface outward and it was moistened with few drops of phosphate buffer 6.8 pH, the right-side pan of the balance was replaced by a glass disc glued with a buccal patch of 2cm² diameter (4). The balance was adjusted for equal oscillation by keeping sufficient weight on the left pan. A weight of 5g (W₁) was removed from the left pan, which lowered the pan and buccal patch bring in contact with pre-moistened mucosa for 5mins. then weights were increased gently on the left pan until the attachment breaks (W₂). The difference in weight (W₂-W₁) was taken as mucoadhesive strength. The mucoadhesive force was calculated as follow:

\[
\text{Mucoadhesive force (g)} = \text{Mucoadhesive strength (g)} \times \text{accelerated due to gravity (9.8 m/s}^2)\]

2.4.9. Invitro release study: The study carried out on dissolution apparatus type II rotating paddles. 2cm² drug loaded patch was fixed on a glass slide with the help of cyanoacrylate adhesive and the slide was kept on the bottom of the dissolution vessel filled with 200ml phosphate buffer 6.8 pH and maintained at 50rpm. Samples of 2ml were withdrawn at predetermined time intervals (5, 15, 30, 60, 120, 180, 240, 300 mins.) and replaced with an equal volume of the dissolution medium of phosphate buffer 6.8 pH. The samples were filtered through 0.45µm and diluted with phosphate buffer 6.8 pH, then measured spectrophotometrically.

2.4.10. Ex-vivo permeation studies: The study was carried out in Franz diffusion cell. Buccal mucosa obtained from freshly slaughtered sheep was fixed between the donor compartment and the receptor compartment so that soft surface will face the donor compartment (5). The drug loaded patch placed above mucosa membrane and the two compartments were clamped together. The donor compartment was wetted with 2ml of phosphate buffer 6.8 pH, receptor compartment was filled isotonic phosphate buffer 7.4 pH, the diffusion cell was thermo stated at 37°C and the receptor compartment was stirred at 50rpm. 2ml sample withdrawn at predetermined time intervals. The buffer was immediately replaced using blank buffer. After filtration through 0.45µm, an appropriate dilution of samples was analyzed for drug concentration by measuring the λ max at 288.4nm.
3. Stability Studies

The stability study was carried out on the optimized formulation for short term period. Optimized formulation was stored in air tight container in a room temperature for 3 months and the buccal patch was evaluated for any appreciable or deleterious changes in the physical characteristics, surface pH, drug content, and mucoadhesion time, at every 1 month interval.

4. Result and Discussion

Optimization of PNT buccal patch using central composite design. Central composite design is widely been used for fitting a second order model and to carry out minimum number of experiments to be performed (6). Design expert 7 software to investigate the combined influence of two independent formulation variables viz Polyvinylalcohol (x₁) and Xanthan gum (x₂) on swelling ratio (y₁), mucoadhesive time (y₂), and invitro release of the drug (y₃). Total 13 formulations were prepared by solvent casting method, and all other ingredients were maintained constant, the data obtained for the three responses in each trials were fitted to classical second-order polynomial model which expressed as 

$$Y = b_0 + b_1 x_1 + b_2 x_2 + b_3 x_1^2 + b_4 x_2^2 + b_5 x_1 x_2$$

where y is the measured response, b₀ is an intercept and b₁-b₅ are the regression coefficients, x₁, x₂ represents the main effect, x₁², x₂² the quadratic effect, and x₁x₂ is the interaction effect against the two factors. 3D surface plot showing the influence of each dependent variables were obtained.

5. Effect of formulation variables on swelling index

Swelling index is an important parameter to predict the drug release out of the polymers matrix and to predict mucoadhesion property of the patch. All formulated patches (Table 1) showed rapid swelling behaviour ranged between (186.07 ± 3.21 – 478.12 ± 2.76) due to presence of water soluble excipients like PVA, XG, and HPMC E-15 (7). Formulation BF5 containing highest concentration of XG (2.0%) and lowest concentration of PVA (0.5%) showed highest swelling index. On applying the expert design, the quadratic model was found to be significant with F-value of 12.05, P value < 0.0025, and R² value of 0.9332, which indicate that model is significant. The regression equation of the model is expressed as follow:

$$Y_1 = 15.21 - 2.12x_1 - 1.73x_2 + 1.0x_1^2 + 1.19x_2^2 + 0.58x_1x_2$$

6. Effect of formulation variables on mucoadhesion time

Mucoadhesion time is to predict the time required for the buccal patch to detach from the buccal mucosa after releasing the drug. Over thirteen formulations shown in (Table 1), mucoadhesion time ranged between (286 ± 2.34 – 268 ± 2.66), BF5 formulation containing 0.5% of PVA and 2.0% of XG showed best mucoadhesion time. On applying the expert design, the quadratic model was found to be significant with F-value of 11.74, P value < 0.0027, and R² value of 0.914, which indicate that model is significant. The regression equation of the model is expressed as follow:

$$Y_2 = 16.43 + 0.017x_1 + 0.33x_2 - 0.12x_1x_2 + 0.098x_1^2 - 0.041x_2^2$$
7. Effect of formulation variables on invitro cumulative release

Release retardation of PNT buccal patch was required to achieve gradual absorption into systemic circulation. PNT half-life is 1-1.5 hours, hence more frequent doses are required to achieve the therapeutic purpose due to rapid elimination. Cumulative release ranged between (87.451 ± 1.56 – 96.225 ± 2.31) as it shown in (Table 1), indicating that increasing XG concentration decrease the cumulative release due to entrapment of the drug into the polymeric matrix network. F8 showed highest cumulative release among other formulated formulation. On applying expert design, the quadratic model was found to be significant with F-value of 13.73, P-value >0.0017, and R² value of 0.907 which indicate the model significant. The regression equation of the model is expressed as follow:

\[ Y_3 = 9.32 + 0.066x_1 + 0.15x_2 + 0.032x_1x_2 + 0.19x_1^2 + 0.13x_2^2 \]

Table (1): Experimental plan and observed responses values of PNT buccal patch

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Responses Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>X1 (PVA)</strong></td>
<td><strong>X2 (XG)</strong></td>
</tr>
<tr>
<td>BF1</td>
<td>0</td>
</tr>
<tr>
<td>BF2</td>
<td>1</td>
</tr>
<tr>
<td>BF3</td>
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<td>BF12</td>
<td>0</td>
</tr>
<tr>
<td>BF 13</td>
<td>0</td>
</tr>
</tbody>
</table>

8. Optimization of formulations

Data collected from the central composite design was analyzed to select the best optimized formulation to perform further parameters. In swelling index, if swelling index is high, this may lead to patient uncomforted, while low swelling index can fail to retard the drug release, so a desirable limit of (200-250%) has been set. In mucoadhesion time, if mucoadhesion is too high, the buccal patch might be attached for longer time causing local irritation to buccal mucosa, while low mucoadhesion time will not permit the buccal patch to produce its therapeutic effect, so a limit of (20-25g) has been set (8). From the collected data as it shown in (Table 1) that FB13 formulation showed satisfactory results with acceptable swelling index of 226.52 ± 1.66, mucoadhesion time of 280 ± 2.77, and cumulative invitro release of 90.70%. Hence FB13
formulation was selected as the optimized formulation and evaluated for further parameters as it shown in (Table 3,4).

9. Mathematical modelling of release kinetics

The data obtained from the invitro release studies of FB13 optimized formulation was analyzed by Excel sheet to understand the mechanism of drug release and release rate kinetics. The invitro drug release data was estimated to various mathematical models such as zero order, first order, Higuchi matrix, Korsemeyer Peppas, Hixon crowll. Regression analysis were 0.835, -0.0264, 0.998, 0.639, and 12.01 respectively as it shown in (Table 2). The data were shown to fit higuchi model which indicate that initial drug concentration in the matrix is much higher than drug solubility (Figure 1,2).

Figure (1): Response surface plot showing the influence of PVA & XG on SI%, MT and %CR

Table (2): Regression values for different kinetics model of optimized formulation (FB13)

<table>
<thead>
<tr>
<th>Code</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi model</th>
<th>Korsemeyer pepas</th>
<th>Hixon crowll</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R2</td>
<td>K</td>
<td>R2</td>
<td>K</td>
<td>R2</td>
</tr>
<tr>
<td>FB13</td>
<td>0.835</td>
<td>0.336</td>
<td>-0.264</td>
<td>0.008</td>
<td>0.998</td>
</tr>
</tbody>
</table>

10. Evaluation parameters of optimized formulation

Table (3): Evaluation of optimized Pantoprazole buccal patch (FB13)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight uniformity</th>
<th>Thickness</th>
<th>Folding endurance</th>
<th>Drug content</th>
<th>Surface pH</th>
<th>Mucoadhesive strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>FB13</td>
<td>0.163 ± 0.003</td>
<td>0.18 ± 0.003</td>
<td>350 ± 4.44</td>
<td>9.80 ± 1.73</td>
<td>6.92 ± 0.03</td>
<td>25.4 ± 1.7</td>
</tr>
</tbody>
</table>
11. **Ex-vivo permeation study**

**Figure (2):** Comparison of Ex-vivo permeation of pure drug with FB13 formulation

12. **Stability study**

**Table (4):** Stability study on physical appearance, surface pH, drug content and mucoadhesion time after 3 months duration

<table>
<thead>
<tr>
<th>Evaluation parameter</th>
<th>1st month</th>
<th>2nd month</th>
<th>3rd month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color &amp; appearance</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Surface pH</td>
<td>6.9</td>
<td>6.84</td>
<td>6.79</td>
</tr>
<tr>
<td>Drug content</td>
<td>18.80 ± 0.34</td>
<td>17.55 ± 0.51</td>
<td>17.55 ± 0.32</td>
</tr>
<tr>
<td>Mucoadhesion Time</td>
<td>280 ± 1.45</td>
<td>278 ± 4.21</td>
<td>277 ± 3.5</td>
</tr>
</tbody>
</table>

13. **Conclusion**

Buccal patch with ethyl cellulose backing membrane was prepared to sustain the pantoprazole release, avoid the first pass metabolism, thus maintain the therapeutic blood concentration for a prolonged period of time, and reduce the dose frequencies and concentration can be achieved. The invitro release and permeation study profiles showed a promising results with specified mucoadhesion period indicating that Pantoprazole buccal patch would be a potential drug delivery system.

14. **References**


