Research Article

FORMULATION AND EVALUATION OF BuccAL PATCHES OF CARVEDILOL PHOSPHATE
Sreekanth M.C 1*, Anusha Ajayakumar 2, K. Santhi 3
1Assistant Professor, Department of Pharmaceutics Nehru College of Pharmacy, Pampady, Thrissur, India
2Assistant Professor, Department of Pharmaceutical Analysis, Nehru College of Pharmacy, Pampady, Thrissur, India
3Professor, Department of Pharmaceutics, JSS College of Pharmacy, Mysoore, India
*Corresponding Author Email: sreekanthmc85@gmail.com

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ABSTRACT

Carvedilol is a non-selective adrenergic antagonist with no intrinsic sympathomimetic activity widely used to treat essential hypertension and angina pectoris. Although it is completely absorbed from the gastrointestinal tract, the systemic availability is approximately 25-35% because of high first-pass metabolism. The aim of the present study was to develop the mucoadhesive buccal patches of carvedilol phosphate and to evaluate in vitro performance of buccal patches of carvedilol by using Chitosan, PVP K 30, PVP K 90, HPMC, and propylene glycol as plasticizer. IR spectra of carvedilol along with polymers indicated no interaction between carvedilol and all the four selected polymers. After optimizing the formula from the three combinations of polymeric patches, three formulas were selected for drug loading, respectively from each combination they were loaded with 30mg (D1), 40mg (D2), 50mg (D3) and 60mg (D4) carvedilol phosphate. The in vitro studies shows that there was an increase in the extent of duration of drug release with increase in concentration of chitosan in the formula. Kinetic of release of drug from all the drug loaded batches were found to follow first order. The formulated buccal patches of carvedilol phosphate was found to be suitable buccal delivery system to avoid the first pass metabolism of carvedilol phosphate which will have other added benefits like longer duration of action and quicker onset of action as compared to tablets of carvedilol phosphate.

Keywords: Carvedilol phosphate, mucoadhesive buccal patch.

INTRODUCTION

The systemic delivery of drugs through novel methods of administration is one area in which significant changes and improvements have been made. Consequently, precise control of drug input into the body by a variety of routes is now possible. Controlled and sustained release formulations have been developed and are gaining in popularity and medical acceptance. Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enterable methods.

Transmucosal delivery of therapeutic agents is a popular method because mucous membranes are relatively permeable, allowing for the rapid uptake of a drug into the systemic circulation and avoiding the first pass metabolism. This efficient uptake offers several benefits over other methods of delivery and allows drugs to circumvent some of the body’s natural defence mechanisms.

Various mucoadhesive formulations were suggested for buccal delivery that includes buccal patches, adhesive tablets and adhesive gel. Buccal patches overcome some of the drawbacks of other dosage forms. They have unique characteristics including flexibility, relative rapid onset of drug delivery, sustained drug release and rapid decline in the serum drug concentration when the patch is removed. The patch is confined to the buccal area over which it is attached and therefore the absorption profile may have less inter and intra-individual variability.

Transmucosal routes of drug delivery offer distinct advantages over peroral administration for systemic drug delivery. These advantages includes possible bypass of the first pass effect, avoidance of presystemic elimination of gastro intestinal tract and depending on the particular drug. The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival). In general, the delivery of a drug requires some type of dosage form, present in the oral cavity, to release a drug, which then diffuses through the mucosa into the local blood circulation and is then taken further to the systemic blood circulation. Buccal drug delivery has several advantages over peroral delivery. Administration of compounds via the mucosa of the oral cavity avoids presystemic metabolism in the gastrointestinal tract (GIT) and hepatic first-pass elimination. In addition, the buccal mucosa is a well vascularized tissue and is easily accessible for both application and removal of a delivery device. It’s having facility to include permeation enhancer in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions etc.

Adhesion as a process, simply defined as the “fixing” of two surfaces to one another. There are many different terminological subsets of adhesion depending upon the environment in which the process occurs. When adhesion occurs in a biological setting it is often termed “bioadhesion”, furthermore if this adhesion occurs on mucosal membranes it is termed “mucoadhesion”. Bioadhesion can be defined as the binding of a natural or synthetic polymer to a biological substrate. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and is permeable to many pharmacologically active agents.
MATERIALS & METHODS

Pre-Formulation Study
Infra-Red Spectroscopy

Infra red spectroscopy can be used to investigate and predict any possible physicochemical interactions between different components in a formulation and therefore, it can be applied to the selection of suitable, chemically compatible excipients. The aim of the present study was to find out the possible interaction between the selected polymer chitosan and the drug carvedilol and also to identify the compatibility between the drug and the polymer.

10 mg of the sample and 30 mg of potassium bromide were taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet maker and was compressed at 10 Kg/cm² using a hydraulic press. The pellet was kept on the same sample holder and scanned from 4000 cm⁻¹ to 400 cm⁻¹ and 2000 cm⁻¹ to 400 cm⁻¹ in Perkin Elmer FT-IR spectrophotometer. Samples were prepared for the pure drug, pure polymer, physical mixture of drug and polymer. The spectra obtained through those samples were compared and interpreted for shifting of functional peaks, and appearance or disappearance of new peaks.

Preparation of Buccal patches

Buccal patches of carvedilol phosphate were prepared by using suitable amount of combinations of Chitosan, PVP K 30, PVP K 90, HPMC, and propylene glycol as plasticizer.

Optimization and study on effect of combination of polymers on film characteristics.

For studying the effect of different combinations of polymers on film characteristics and optimizing the formula for drug incorporations, we prepared three different combinations of polymers were used.

<table>
<thead>
<tr>
<th>Combinations</th>
<th>Formulations</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C1</td>
<td>Chitosan</td>
</tr>
<tr>
<td>BPF₀</td>
<td>1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>BPF₁</td>
<td>1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>BPF₂</td>
<td>1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>BPF₃</td>
<td>1%</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>C2</td>
<td>BPF₀</td>
</tr>
<tr>
<td></td>
<td>BPF₁</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>BPF₂</td>
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<td></td>
<td>BPF₃</td>
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</tr>
<tr>
<td></td>
<td>C3</td>
<td>BPF₀</td>
</tr>
<tr>
<td></td>
<td>BPF₁</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>BPF₂</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>BPF₃</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

PHYSICAL PROPERTIES

Physical Appearance and Surface Texture:
Physical appearance and surface texture evaluation includes visual inspection and evaluation of texture by feel or touch.

Weight variation
Ten patches of 1cm² were weighed individually and average of those of those patches measured.

Thickness
The thickness of the patch was measured using screw gauge with a least count of 0.01 mm at different spots of the patches. The thickness was measured at five different spots of the patch and average was taken.

Percent Swelling Index
Diameter method
The polymeric patches are cut in to small patches of 1.5 cm diameter. This patch was placed on the surface of the agar plate and the diameter at different time intervals where taken up to 5 hrs and the percentage swelling index was calculated using the formula,

\[
SD\% = \frac{D_t - D_o}{D_o \times 100}
\]

\[
SD\% = \% \text{ swelling by diameter method}
\]

\[
D_t = \text{diameter of swollen patch after time } t
\]

\[
D_o = \text{original patch diameter}
\]

Folding Endurance

The flexibility of patches can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2x2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gives the value of folding endurance.

Surface pH

Buccal patches were left to swell for 1 hour on the surface of the agar plate, the agar plate prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.6 under stirring and the solution was poured into the petridish, it was allowed to stand until it solidified to form a gel at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch.

MECHANICAL PROPERTIES

Tensile Strength:
The tensile strength of buccal patch refers to tension or force required to tear of the patch apart into two pieces. Tensile strength was determined using an instrument assembled in the laboratory.

Instrument
The instrument used to measure the tensile strength designed in our laboratory especially for this project work. The instrument is a modification of chemical balance, one pan of the balance was replaced with one metallic plate having a hook for attaching the
film. The equilibrium of the balance was adjusted by adding weight to the right pan of balance. The instrument was modified in such a way that the patch can be fixed up between two hooks of horizontal beams to hold the test film. A film of 2.5cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan.

**Method of Calculation:** The definition of tensile strength as per American Standard for Testing Material (ASTM) standard tests principles is, “the maximum load during the tensile strength test divided by the original minimum cross-sectional area of the specimen”. Thus, tensile strength,

\[ T = \frac{M \times g}{B \times t} \text{ Dynes/cm}^2 \]

Where, \( M = \text{mass in grams, } g = \text{acceleration due to gravity 980 cm/sec}^2, b = \text{breadth of the specimen in cm, } t = \text{thickness of sample in cm.} \)

**Percent Elongation at Break**

The percent elongation at break is defined as the elongation at the moment of rupture of the specimen divided by the initial gauge length of the specimen and multiplying by 100.

\[ \text{Percent elongation at break} = \frac{\text{LB} - \text{L0}}{\text{L0}} \times 100 \]

The instrument and procedure is similar to that used for tensile strength.

**Bioadhesive strength**

**Measurement of Bioadhesive Strength**

The tensile strength required to detach the polymeric patch from the mucosal surface was applied as measure of the bioadhesive performance.

**Instrument:** The apparatus was locally assembled and was a modification of the physical balance. The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by small stainless steel lamina vertically suspended. At the same side, a platform was maintained in the bottom in order to fix the model mucosal membrane.

**Method:** The fabricated balance was used for the bioadhesion studies. The bovine cheek pouch excised and washed was fixed to the platform. The mucosal surface was applied as measure of the bioadhesive strength.

**Evaluation of carvedilol phosphate polymeric patches.**

**Drug Content Determination**

The weight of the whole patch was determined and cut into 2cm². For determining the drug content, a single piece of patch was taken and crushed in a mortar using pestle. 0.1 N HCl was added and triturated to completely dissolve the drug it was then filtered and diluted if necessary. The absorbance of the solution was measured using UV spectrophotometer at 241nm and the drug loading was calculated. Percentage drug loading was calculated using formula.

\[ \% \text{ drug loading} = \frac{\text{Practical loading} \times 100}{\text{Theoretical drug loading}} \]

**In vitro release**

The in vitro release study was carried out using USP dissolution apparatus type 2 in 300ml phosphate buffer pH 6.6 at 50 rpm. A 2cm² patch was taken and attached to a glass slide in order to prevent floating of patch over the dissolution media. The in vitro release study was carried out for six hours. 5ml of samples were withdrawn at various times interval, replacing with fresh medium each interval, absorbance of the samples were measured at 241 nm, and the cumulative percentage release was calculated.

**Interpretation of data**

**Determination of order of release of drug from buccal patch by Graphical method**

To determine the order of release of drug from buccal patch by graphical method using the dissolution data, a graph was plotted with % drug release Vs time. Zero order release can be confirmed if a straight line or linearity is obtained. To find out the release rate constant, the slope of the curve was found out and multiplied with 2.303. Regression coefficient of the curve was determined to confirm the correlation between X and Y.

In the second stage, using the same dissolution data, a graph was plotted with log % remaining Vs time. If a straight line or linearity is observed, it can be confirmed that the drug release follows first order kinetics. The slope of the graph was found out and multiplied with 2.303 to obtain the first order rate constant \( k_t \). Regression co-efficient of the graph was found out to confirm the correlation between X and Y.

**Mechanism of drug release study**

In order to predict and correlate the release behaviour of drug from the hydrophilic matrix, it is necessary to fit the in vitro release data in to a suitable model. Hence the dissolution data were fitted according to the well known exponential equation, which is often used to describe the drug release behaviour from a polymeric system. The equation which is used to describe drug release mechanism is:
\[ \frac{M_t}{m_0} = kt^n \]

Where, \( \frac{M_t}{m_0} \) is the fraction release of the drug, \( t' \) is the release time, \( k' \) is the constant, which indicates the properties of the macromolecular polymeric system, and \( n' \) is the release exponent indicative of the mechanism of release. The \( n' \) value was used for the analysis of drug release mechanism from drug loaded buccal patches. The \( n' \) value was determined for all batches of drug loaded buccal patches by graphical method, which is explained below.

In the first stage, a graph plotted with log % time Vs log time. If a straight line is obtained, then the regression co-efficient was found out to confirm the linearity between X and Y. The slope (n) of the line was found out and if

\[ n \leq 0.5 \] : The release is by Fickian diffusion

\[ n > 0.5 \] and \( < 1 \) : The release mechanism is swelling

\[ n = 1 \] : Release is by case II transport release mechanism

### RESULTS

**Infra- red spectroscopy**

In order to investigate the possible interaction between drug and selected polymers, FT-IR spectroscopy studies were carried out. IR spectrum for pure drug and physical mixture of drug-polymers were obtained and analyzed for principle peaks.

![Figure 1: IR Spectrum of drug with polymers](image)

**Table 3: Physical evaluation results**

<table>
<thead>
<tr>
<th>Formulas</th>
<th>Appearance</th>
<th>Texture</th>
<th>Folding Endurance</th>
<th>Swelling-index</th>
<th>Average Weight(mg)</th>
<th>Thickness (mm)</th>
<th>Surface pH</th>
<th>Tensile strength (N/m²)</th>
<th>Bio adhesive strength (kg/m/s²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPF₄</td>
<td>Smooth</td>
<td>Flexible</td>
<td>341</td>
<td>86</td>
<td>9</td>
<td>0.03</td>
<td>7</td>
<td>9.6 X 10⁸</td>
<td>8.73</td>
</tr>
<tr>
<td>BPF₅</td>
<td>Smooth</td>
<td>Flexible</td>
<td>321</td>
<td>75</td>
<td>9</td>
<td>0.03</td>
<td>7</td>
<td>5.7 X 10⁸</td>
<td>8.73</td>
</tr>
<tr>
<td>BPF₆</td>
<td>Smooth</td>
<td>Flexible</td>
<td>306</td>
<td>78</td>
<td>9</td>
<td>0.03</td>
<td>7</td>
<td>6.0 X 10⁸</td>
<td>8.73</td>
</tr>
<tr>
<td>BPF₇</td>
<td>Smooth</td>
<td>Flexible</td>
<td>311</td>
<td>81</td>
<td>9</td>
<td>0.03</td>
<td>7</td>
<td>7.3 X 10⁸</td>
<td>8.73</td>
</tr>
<tr>
<td>BPF₈</td>
<td>Smooth</td>
<td>Flexible</td>
<td>310</td>
<td>78</td>
<td>7</td>
<td>0.04</td>
<td>7</td>
<td>4.9 X 10⁹</td>
<td>9.4</td>
</tr>
<tr>
<td>BPF₉</td>
<td>Smooth</td>
<td>Flexible</td>
<td>345</td>
<td>84</td>
<td>7</td>
<td>0.04</td>
<td>7</td>
<td>4.3 X 10⁹</td>
<td>9.4</td>
</tr>
<tr>
<td>BPF₁₀</td>
<td>Smooth</td>
<td>Flexible</td>
<td>330</td>
<td>80</td>
<td>7</td>
<td>0.04</td>
<td>7</td>
<td>4.1 X 10⁹</td>
<td>9.4</td>
</tr>
<tr>
<td>BPF₁₁</td>
<td>Smooth</td>
<td>Flexible</td>
<td>320</td>
<td>81</td>
<td>7</td>
<td>0.04</td>
<td>7</td>
<td>4.1 X 10⁹</td>
<td>9.4</td>
</tr>
</tbody>
</table>

From the physical evaluation results three formulas BPF₄, BPF₅, BPF₁₀ were selected for drug loading.

**Table 4: Drug content evaluation**

<table>
<thead>
<tr>
<th>Formulas</th>
<th>BPF₄ D₄</th>
<th>BPF₄ D₅</th>
<th>BPF₄ D₇</th>
<th>BPF₅ D₄</th>
<th>BPF₅ D₅</th>
<th>BPF₅ D₇</th>
<th>BPF₅ D₈</th>
<th>BPF₆ D₄</th>
<th>BPF₆ D₅</th>
<th>BPF₆ D₇</th>
<th>BPF₆ D₈</th>
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</thead>
<tbody>
<tr>
<td>Percentage drug loading</td>
<td>96.44</td>
<td>92.88</td>
<td>87.07</td>
<td>84.04</td>
<td>96.8</td>
<td>92.5</td>
<td>87.2</td>
<td>83.9</td>
<td>96.5</td>
<td>93.44</td>
<td>91.8</td>
</tr>
</tbody>
</table>

All the drug loaded batches showed a saturation capacity with that of the selected polymers at a concentration of 30mg/15ml of polymer.
In Vitro Dissolution Study

Batches shows best drug loading is selected for in vitro dissolution study.

Table 5: In vitro release study

<table>
<thead>
<tr>
<th>Time in min</th>
<th>Cumulative % released BPF,D1</th>
<th>Cumulative % released BPF,D2</th>
<th>Cumulative % released BPF,D3</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1.49</td>
<td>6.1</td>
<td>6.4</td>
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<tr>
<td>10</td>
<td>5.33</td>
<td>11.17</td>
<td>8.24</td>
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<td>60</td>
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<tr>
<td>120</td>
<td>63.62</td>
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<td>78.52</td>
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<tr>
<td>180</td>
<td>88.76</td>
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<td>91.86</td>
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<tr>
<td>240</td>
<td>92.84</td>
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</tbody>
</table>

Determination of order of release

![Figure 2: Order of release of formula BPF,D1](image)

![Figure 3: Order of release of formula BPF,D2](image)

![Figure 4: Order of release of formula BPF,D3](image)
To determine the order of release for each batch, percentage drug remaining to be released Vs time graph was plotted, and log percentage drug remaining Vs time graph also plotted. Regression values of two graphs were determined, linearity was observed in log percentage drug remaining Vs time. So the kinetic release study showed that the all the drug loaded buccal patches of carvedilol phosphate (BPF₄D₁, BPF₄D₂, BPF₄D₃) followed first order release.

**DISCUSSION**

The selected drug carvedilol phosphate shows saturation capacity to all the combination of polymer at a concentration of 30mg/15ml. The in vitro release studies shows that there was an increase in the extend of duration of drug release with increase in concentration of chitosan in the formula. Kinetic of release of drug from all the drug loaded batches were found to follow first order.

The formulated buccal patches of carvedilol phosphate was found to be suitable buccal delivery system to avoid the first pass metabolism of carvedilol phosphate which will have other added benefits like longer duration of action and quicker onset of action as compared to tablets of carvedilol phosphate.

**ACKNOWLEDGEMENT**

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**REFERENCES**


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