FORMULATION AND EVALUATION OF BUCCAL FILM OF AN ANTIHYPERTENSIVE DRUG

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Abstract
The aim of the study was to formulate and evaluate Losartan potassium buccal films, an angiotensin receptor blocker and is used to treat hypertension. Losartan potassium is having less bioavailability (33%), so the buccal films are expected to increase the bioavailability by avoiding hepatic metabolism. Ten formulations of buccal films were prepared by solvent casting method using HPMC K15 M as the main film-forming polymer in various proportions with various co-polymers such as Eudragit RL 100, Carbopol 940, Ethyl cellulose. Physicochemical characteristics, in vitro drug release, swelling index and residence time were evaluated. In vitro studies revealed that the release rate of Losartan potassium was higher for films containing HPMC K15 M and Eudragit RL100 in 3:1 ratio. The result of stability study indicated that no significant changes have occurred during the period of study.

Keywords: Losartan potassium, buccal films, HPMC K15 M, in vitro drug release, swelling index.

Introduction
Buccal drug delivery is an important route of drug administration and it is one of the novel drug delivery systems. The buccal mucosa is relatively permeable and provides affluent blood supply and permits a prolonged retention of a dosage form, especially with the use of mucoadhesive polymers without much interference in processes such as mastication unlike the sublingual route. Administration of the drug via the mucosal layer is a novel technique that delivers treatment more effective and safe, for both typical and systemic diseases [1].

Buccal drug delivery is also a safer mode of drug delivery and can be able to remove in case of toxicity and adverse effect. Buccal mucosa has an excellent accessibility, which leads to direct access to systemic circulation through the internal jugular vein bypasses the drugs from hepatic first pass metabolism. The administration of drugs through buccal route provides a direct entry of drug molecule into the systemic circulation via avoiding the first pass metabolism. Buccal film is defined as the dosage form which dissolves into the buccal mucosa or mouth and releases the medicament to provide local or systemic drug delivery and employs a water dissolving polymer (hydrocolloid bio adhesive polymer). These polymers allow the dosage form to adhere, hydrate and dissolve into the mouth. Thin film strips are typically designed for oral administration, with the user placing the strip on or under the tongue. As the strip dissolves, the drug can enter the blood stream enterically, or sublingually [2].

Material and Methods
Preformulation studies were conducted by evaluating physicochemical parameters. Tests for the identification of pure drugs and Compatibility studies of drug with excipients using FTIR spectroscopy were also carried out.

Development of Buccal Film of Losartan potassium
Preparation of Buccal Films of Losartan Potassium
The buccal films of Losartan potassium were prepared by solvent casting method with HPMC alone and in combination with different copolymers namely Eudragit RL 100, Carbopol 940 and Ethyl cellulose with propylene glycol as plasticizer. Small films of 2cm diameter containing 25mg of drug were prepared. First the film forming polymer was dissolved in solvent ethanol. To this required quantity of drug was added.

Finally, 1ml of propylene glycol was added as plasticizer and was mixed for about 30 min by using a magnetic stirrer. This solution was transferred into petridish slowly drop by drop in
order to get uniform spread of the solution and is kept for 24hrs at room temperature for drying. After drying these films were removed from the petridish and cut into definite shapes and are packed in butter paper and wrapped with aluminium foil and stored in desiccator until used for further study.

Table No.1: Formula Used For Development Of losartan Potassium Buccal Films

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>F 1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F 0</th>
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<tbody>
<tr>
<td>Losartan potassium(mg)</td>
<td>5</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<td>50</td>
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<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>HPMC K15(mg)</td>
<td>4</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>30</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Eudragit RL100(mg)</td>
<td>-</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Carbopol 940 (mg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ethyl cellulose (mg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
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<tr>
<td>Propylene glycol (ml)</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ethanol (ml)</td>
<td>2</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
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<td></td>
</tr>
<tr>
<td>Citric acid (mg)</td>
<td>5</td>
<td>5</td>
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<td>5</td>
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<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Peppermint oil(ml)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td></td>
</tr>
</tbody>
</table>

Characterization of the films
Formulated films were subjected to the preliminary evaluation tests.

Physicochemical characteristics
Physical appearance:
All the films were visually inspected for color, clarity, flexibility, and smoothness.

Film thickness
The thickness of film is measured by micrometer screw gauge. The thickness was evaluated at five different locations (four corners and one at center) and it essential to ascertain uniformity in the thickness of film since it is directly related to accuracy of dose distribution in the film.

Weight uniformity
For the mass uniformity, six films from each formulation were taken and weighed individually on electronic balance. The average weight was calculated.

Folding endurance
Folding endurance gives the brittleness of a film. It is measured by manually repeated folding of film at some place till it breaks. The number of times the film is folded without breaking is the folding endurance value.

Surface pH
Surface pH of the film can be determined by allowing three films of each formulation to swell for two hours on an agar plate surface. A pH paper was placed on the surface of the swollen film and a mean was calculated.

Drug content uniformity
Three films of each formulation were weighed individually and allowed the sample to swell by placing it on the surface of an agar plate kept in an incubator at 37°C. An increase in the weight of the film was noted at 1h intervals up to 5h. The percentage swelling, %S was calculated using the following equation

\[ \text{Percentage swelling} = \left( \frac{X}{X_0} \right) \times 100 \]

Where, \( X \) is the weight of the swollen film after time \( t \), \( X_0 \) is the initial film weight at zero time.

In-vitro release study
Dissolution studies were carried out in a USP dissolution apparatus using 900ml of dissolution medium at 37± 0.5°C, and a rotation speed of 50 rpm was used. An aliquot of sample was periodically withdrawn and replaced with fresh medium. The samples were filtered through whatman filter paper and analyzed spectrophotometrically.

Drug release kinetic studies
The drug release kinetic studies were done by various mathematical models. The model that gives high ‘r’ value is considered as the best fit of the release data. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r2) was determined.

Kinetic Data Analysis: Drug release models
Mathematical models:

Zero order release kinetics
Zero order release kinetics refers to the process of constant drug release from a delivery device. In its simplest form, zero order release can be represented as

\[ Q = Q_0 + Kt \]

Where \( Q \) is the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), \( Q_0 \) is the initial amount of drug in solution (it is usually zero), and \( K \) is the zero order release constant.

The plot made: % cumulative drug release vs. time (zero order kinetic model).

First order release kinetics
The release the drug is proportional to the amount of drug remaining in its interior, in such a way that the amounts of drug released by unit time diminish.

\[ \log C = \log C_0 - kt \]

Where, \( C_0 \) is the initial concentration of drug and \( K \) is first order constant.

The plot made: log cumulative % drug remaining vs. time (first order model).

Higuchi Model
Higuchi was the first to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion.


\[
Q_t = kH(t)^{0.5}
\]

Where, \(Q_t\) is the amount of drug released in time \(t\), and \(kH\) is the release rate constant for the Higuchi model. The linearity of the plots can be checked by carrying out linear regression analysis and determination of regression coefficient of the plot. The plot made: cumulative % drug release vs. square root of time (Higuchi model).

**Determination of Diffusion exponent**

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system, to find out the mechanism of drug release.

\[
\frac{M_t}{M_{\infty}} = k t^n
\]

Where \(\frac{M_t}{M_{\infty}}\), is fraction of drug released at time \(t\), \(k\) is the rate constant and \(n\) is the release exponent.

The plot made: log cumulative % drug release vs. log time

Values of the exponent \(n\) are found that would indicate a diffusion controlled drug release mechanism.

**Table No.2: Interpretation of Diffusional Release Mechanisms from Formulations**

<table>
<thead>
<tr>
<th>Release exponent ((n))</th>
<th>Drug transport mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
</tr>
<tr>
<td>0.5&lt;n&lt;0.89</td>
<td>Non – fickian transport</td>
</tr>
<tr>
<td>0.89</td>
<td>Case II transport</td>
</tr>
<tr>
<td>Higher than 0.89</td>
<td>Super case II transport</td>
</tr>
</tbody>
</table>

**Table No.3: Mathematical Models Used To Describe Drug Release Kinetics from Various Matrices**

<table>
<thead>
<tr>
<th>Kinetic model</th>
<th>Mathematical relation</th>
<th>Systems that follow the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero order</td>
<td>Release independent of drug concentration</td>
<td>Osmotic systems, transdermal systems</td>
</tr>
<tr>
<td>First order</td>
<td>Release proportional to the amount of drug remaining</td>
<td>Water soluble drugs in porous matrix</td>
</tr>
<tr>
<td>Higuchi</td>
<td>Release proportional to square root of time</td>
<td>Diffusion matrix formulations</td>
</tr>
</tbody>
</table>

**In-vitro residence time**

The in vitro residence time was determined using IP disintegration apparatus maintained at a temperature of 37±2°C using 900ml of the disintegration medium. The portion of porcine mucosa, each of 2 cm length, were glued to the surface of a glass slab, which is then vertically attached to the apparatus and allowed to move up and down. The films of each formulation were hydrated on one surface and upon contact with the mucosal membrane, the film was entirely dipped in the buffer solution. The time required for complete detachment of the film from the mucosal surface was recorded.

**In-vitro buccal permeation study**

Porcine buccal mucosa obtained from a local slaughter house has been used within 2h of slaughter. The film was attached with the mucosa and the compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer (pH 6.8) and the receptor compartment of 20 ml capacity was filled with phosphate buffer (pH 7.4). One ml of the sample was withdrawn at 1-hour interval for a period of 6 hours and analyzed. The experiments were performed in triplicate.

**Stability studies**

Films were stored at different temperatures like 27±2°C, 5-8±2°C, 40±2°C for a period of 30 days, and the drug content was estimated at anintervals of 10 days. [30]

**Results and Discussion**

**Preformation Studies**

**Table no.4 organoleptic properties**

<table>
<thead>
<tr>
<th>Character</th>
<th>Property of the drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>White to off-white</td>
</tr>
<tr>
<td>Odor</td>
<td>Odorless</td>
</tr>
<tr>
<td>Taste</td>
<td>Tasteless</td>
</tr>
<tr>
<td>Texture</td>
<td>Crystalline powder</td>
</tr>
</tbody>
</table>

**Solubility study**

Solubility studies shown that Losartan potassium was freely soluble in water and methanol, soluble in isopropyl alcohol, slightly soluble in acetonitrile and methyl ethyl ketone, insoluble in chloroform.

**Identification of pure drug**

**Melting point determination**

It was found to be 183-185°C in accordance with the reference standard of 184°C.

**FTIR spectra of the drug**

The Fourier transform infrared spectroscopy studies were carried out for pure drug (Losartan potassium). Drug exhibited characteristic peaks at 1259, 1460, 2669, 2856, and 2925 cm⁻¹. It was found in accordance with the reference standard (IP 2007).

**Fig.no.1: FTIR Spectrum of Losartan Potassium**

The \(\lambda_{max}\) of the drug was found to be 218 nm. The wavelength of the maximum absorption was noted and UV spectrum was recorded.
Compatibility studies of drug with excipients using FTIR spectroscopy.

The Fourier transform infrared spectroscopy studies were carried out for Losartan potassium-polymer physical mixtures. There were no changes in the major peaks of Losartan potassium in the presence of various polymers. This revealed that the drug and the polymers are compatible with each other.

Development of Buccal films of Losartan Potassium

Preparation of buccal films of Losartan Potassium

Ten formulations of buccal films were prepared using different polymers in different proportions as per table no.1. Formulation F4 showed extensive tackiness and hence was excluded from further studies. This may be possibly due to the low concentration of HPMC K15M-Eudragit RL100 polymer mixture. All other films obtained were of good quality.

Evaluation

Physicochemical characteristics

Physical Appearance

All polymer combinations used for fabrication of buccal films showed good film forming properties and reproducibility. The fabricated films were thin, flexible, elastic and smooth.

Film thickness

The thickness of each film was determined; it was an average of 0.20±0.26 mm and indicated that there was no much difference in thickness within the formulations.

Weight uniformity

The weight of films ranges from 0.15 mg to 0.19 mg.

Folding endurance

The films has values >200 and indicated that all formulations have ideal film characteristics.

Surface pH

All the formulation were found to have pH between 6 to 7 and reveals that it may not cause any irritation to buccal mucosa since value is almost equal to the buccal pH.

Drug content uniformity

The average percentage drug content in various films ranged from 81.2% to 90.8% and observed that there was no significant difference in the drug content between the samples taken from the same formulation.

Swelling index

The average swelling index was found to be 92%. Results showed that all formulations showed good swelling properties, and found that when the concentration of polymer increases, the swelling of films also increases.

In vitro drug release

The release of Losartan Potassium from the buccal films varied according to the type and concentration of polymer.

Drug release kinetic studies

The results obtained from in vitro release studies were plotted in different kinetic models. Regression coefficient (R²) values of different kinetic models are shown in figure 6, 7 and 8. The criteria for selecting the most appropriate model was on the basis of goodness of best fit.

Log % CR

Time (min)

Fig.no.4: Zero order plot for F2

Fig.no.5: First order plot for F2
The release kinetics data indicates that F2 follows zero order kinetics as the correlation value is higher in case of zero order equation.

**In vitro buccal permeation study**
Formulation F2 has showed maximum release (93%) compared to all other formulations.

**Stability studies**
The selected formulations were subjected to stability testing. Changes in the appearance, surface pH, folding endurance, and drug content of the stored films were investigated for a period of 1 month and there was no deviation from the original value.

**Conclusion**
The results of the study confirm the benefits of using Losartan potassium in the form of buccal films prepared by using HPMC K15 M as the main film-forming polymer and Carbopol 940, Eudragit RL 100, Ethyl cellulose as the copolymers in optimized concentration for giving immediate relief for hypertensive patients.

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**Conflict of interest**
No Conflict of interest

**Ethical approval and Inform Consent**
Not Required
References


