FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL FILMS OF LISINOPRIL

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ABSTRACT

The aim of the present study was to formulate the mucoadhesive buccal films and selection of most satisfactory formulation by in-vitro evaluation. Buccal delivery is considered to be an important alternative to the per-oral route for the systemic administration of drugs. The mucosa is relatively permeable, well supplied with both vascular and lymphatic drainage. Lisinopril is an anti-hypertensive drug with an oral bioavailability of 25% due to extensive first pass metabolism. Hence, this research work was designed to enhance the bioavailability of Lisinopril. Buccal films are prepared by using solvent casting method. In the present study Lisinopril buccal films were prepared by solvent casting method using different film forming polymers like HPMC, PVP K30 and PG as plasticizer. Buccal films of Lisinopril formulated from F1 to F10 are smooth, translucent with good flexibility were evaluated and characterized. Among all formulations of buccal films, F7 formulation exhibited good physical appearance, uniformity in weight, thickness, folding endurance, and surface pH. It showed better drug release of 80.62% in 60 min. The drug content is 98.73%. The drug diffusion can be extended up to 5 hour and the drug diffused is of 82.15%. The kinetic models used were zero order, first order, higuchi’s and peppa’s model. The kinetic analysis of drug release data indicated that the Lisinopril follows Higuchi plot. The FTIR spectroscopy propound that there was no chemical interaction between drug and excipients. The Scanning electron microscopy revealed that the F7 shows better surface morphology.

KEYWORDS: Buccal films, Lisinopril, HPMC, PVP K30, PG, Solvent casting technique.

INTRODUCTION

In comparison with other routes of drug delivery, oral route is mostly preferred for the administration of drug to the patient from many decades. 1 Whereas parenteral route is very painful for the administration of drug. Drugs with high molecular weight, poor skin penetration need other routes. 2 In recent days buccal drug delivery system acts as an alternate to the oral drug delivery system. 3,4 It can overcome problems such as high first pass metabolism and degradation of drug in GIT environment can be avoided by administering the drug through buccal route. Bioavailability of the drug can be increased. It shows rapid onset of action with minimal side effects. 5-15 Buccal drug delivery offers safer method of drug usage as it can be terminated in case of emergency such as toxicity. 16-20 This drug delivery system is more preferable over other dosage forms such as tablets, gels, adhesive tablets, conventional matrix tablets as it was repoted by several research groups. (Tej pratap singh et al), 21-28 It release the drug in a controlled manner in a unidirectional towards the mucosa.

Lisinopril is an potent competitive inhibitor which inhibits the angiotensin converting enzyme (ACE). The enzyme is responsible for the conversion of angiotensin I. Angiotensin (AT I) to angiotensin II (AT II). 22-26 As the angiotensin II (AT II) regulates the blood pressure and it is the main component of the rennin angiotensin aldosterone system (RAAS). 27-33 Lisinopril is used in the treatment of hypertension and symptomatic congestive heart failure and myocardial infarction. 34-38 The absorption of drug orally is 60% but it is of very extensive first pass metabolism and its bioavailability is about 25%. Its halflife is of 12.6 hours. 39-40 It is suitable for the administration via buccal drug delivery system which provides controlled release of drug without pre-systemic metabolism. 40-50 Thus lisinopril buccal films were prepared by solvent casting technique using polymers such as HPMC and PVP K30 as a film forming polymers, PG is used as a plasticizer, aspartame is used as sweetening agent, citric acid is used as an saliva stimulating agent and flavouring agent was also used. The prepared films should possess flexible, elastic, smooth and strong enough to withstand the activities in the mouth. The present study was designed on the basis of all these properties for buccal films.
MATERIALS AND METHODS

The materials used in this work are as follows:
- Lisinopril was obtained as a gift sample from TCI chemicals, Chennai, India. HPMC, PVP K30 and PG was purchased from Bross scientifics, Tirupati, India. Aspartame, citric acid, disodium hydrogen phosphate, potassium dihydrogen ortho phosphate and sodium chloride were purchased from S.D fine chemicals, Ltd., Mumbai, India. All the ingredients used were of analytical grade.

- Preformulation studies were mainly carried out to check the compatibility between the drug and polymers. Melting point was determined by capillary tube method. FTIR spectroscopy of the physical mixtures of polymers and the drug was studied. FTIR spectroscopy lisinopril was measured and it was compared with standard UV-spectrophotometer (UV-1800 Schimadzu Scientifics, Japan) was used for the estimation of standard calibration data of lisinopril. The absorbance was measured at 204nm.

Table 1: Composition of the buccal films of the Lisinopril buccal films.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>F1</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>F10</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC (mg)</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>PVP K30 (mg)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>-</td>
<td>0.01</td>
<td>0.02</td>
<td>0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>PG (%v/v)</td>
<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>1</td>
<td>1</td>
</tr>
<tr>
<td>Dis.water</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
</tr>
<tr>
<td>Aspartame (mg)</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Citric acid (mg)</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Flavouring agent</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
</tr>
</tbody>
</table>

FTIR Spectroscopy

Fourier transform infrared (FT–IR) spectral measurements were performed using Thermo-IR 200 FT–IR spectrophotometer. Potassium bromide pellet method was employed. The pure drug and the pure drug along with the polymer mixture used for the preparation of films was finely grounded with KBr to prepare pellets under a hydrolic pressure of 600psi and a background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of 4000-400 cm⁻¹.

Evaluation studies

1. Uniformity in weight
The film was taken and weighed using weighing balance. The average weight of the film and standard deviation was reported.

2. Thickness
Thickness of the film was measured using digital vernier calipers at different places of the film. The average thickness of the film and standard deviation was computed.

Preparation of Mucoadhesive Buccal Films

Buccal films containing drug were prepared by using different concentrations of polymers by solvent casting method. Require quantity of polymer was weighed and dissolved in sufficient amount of water until the complete clear solution was obtained with continuous stirring on magnetic stirrer for about 60 minutes. Plasticizer was added to the above solution during stirring until homogenous solution was obtained. The drug was added to the above polymer solution, likewise sweetening agent and saliva stimulating agent was also added. The resulting solution was kept aside without disturbing for complete removal of air bubbles. The final solution was cast into mould and kept aside undisturbed at temperature of 40-45°C for time period of 24 hours. After complete drying the film was carefully removed from the mould and sized to 2x2cm and stored in dessicator for further evaluation by packing in a aluminium foil.

3. Folding Endurance
Folding endurance was determined by folding the film manually at the same place till it broke. The number of times the film was folded at the same place without breaking gave the result of folding endurance. It was repeated for three films.

4. Surface pH Study
The prepared films were taken and placed in distilled water after dissolving, the pH was determined using pH meter for all the films.

5. Swelling Index
The films formulated were taken and weighed individually placed in 1-2ml of distilled water and kept in incubator maintained at 37±0.2°C and the samples were allowed to swell. An increase in the weight of the film was noted until 2 hours. The difference in the weight of the film after absorption of the water was calculated to get swelling index. The same procedure was repeated for three times and standard deviation was reported.

Percent Swelling (%S) = (X t - X o /X o) x 100
Where X t = the weight of the swollen film after time t,
X o = the initial film weight at zero time.
6. Moisture Content
The prepared films were weighed individually and kept in a dessicator containing anhydrous calcium chloride at room temperature for 24 hours. After 24 hours the films were removed and to be weighed. The percentage moisture content was calculated by using the following formula.

\[
\% \text{ moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100
\]

7. Drug Content Uniformity
The drug content was determined by dissolving the film in simulated salivary fluid of pH 6.8 until it dissolved under occassional shaking. The resulted solution was filtered and 1ml was withdrawn and transferred to 10ml volumetric flask and make up with simulated salivary fluid. Secondary dilution was done and the serial aliquots upt0 10µg/ml the resulted solution was observed under uv-spectrophotometer at 204nm. The same procedure was repeated for 3 times to determine average drug content uniformity and standard deviation was reported.

\[
\% \text{ Drug content} = \frac{\text{Observed value}}{\text{Actual value}} \times 100
\]

8. In-Vitro Drug Release Studies
The USP II dissolution test apparatus (paddle type) method was used to determine the in-vitro drug release studies of buccal films. The dissolution medium consists of 900ml of simulated salivary fluid of pH 6.8 and the temperature was maintained at 37±0.5°c at a rotation speed of 50rpm. The film was placed in beaker and the particular amount of sample was withdrawn at regular intervals of time. It was replaced with same amount of simulated salivary fluid of pH 6.8 to maintain sink condition. After proper dilution the sample was filtered and analysed spectroscopically at a wave length of 204nm.

9. In-Vitro Permeation Studies
The invitro permeation studies were carried out using open ended cylinder method. 500ml of simulated salivary fluid of pH 6.8 was used as diffusion medium. The egg membrane was tied to the cylinder and the film was placed on it. It should be dipped in the simulated salivary fluid of pH 6.8 and temperature was maintained at 37±0.5°c at 50rpm. 5ml of the sample withdrawn for every 1 hour until 5 hours and the same amount was replaced to maintain sink condition. The sample was filtered after proper dilution it was analysed under uv-spectrophotometer at 204nm.

10. Drug Release Kinetics
As a model-independent approach, comparison of the time taken for the given proportion of the active drug to be dissolved in the dissolution medium and figures such as T<sub>50</sub> and T<sub>90</sub> calculated by taking the time points of 50% and 90% of the drug dissolved and another parameter dissolution efficiency (DE) suggested by Khan were employed. DE is defined as the area under the dissolution curve up to the time ‘t’ expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

\[
\text{Dissolution Efficiency (DE)} = \left( \frac{\int_{0}^{t} y \cdot dt}{y_{100 \cdot t}} \right) \times 100
\]

The dissolution efficiency can have a range of values depending on the time interval chosen. In any case constant time intervals should be chosen for comparison. For example, the index DE<sub>30</sub> would relate to the dissolution of the drug from a particular formulation after 30 minutes could only be compared with DE<sub>30</sub> of other formulations. Summation of the drug dissolution data into a single figure DE enables ready comparison to be made between a large numbers of formulations.

As a model-dependent approach to describe the mechanisms and also the release kinetics, dissolution data were fitted to popular release models, which have been described as follows:

A. Zero order kinetics
Dissolution of drug from a dosage form that do not disaggregate and release the drug slowly that is where drug release rate is independent of its concentration can be represented as follows.

\[
A_0 - A_t = k_0 t
\]

Where,
A<sub>0</sub> is initial amount of drug in the dosage form,
A<sub>t</sub> is the amount of drug in the dosage form at time‘t’,
k<sub>0</sub> is the zero order release constant.

To study the release kinetics, in-vitro drug (25 mg) release studies were plotted as cumulative amount of drug release Vs time. This relation can be used to determine the drug dissolution of various types of modified release dosage forms e.g. some transdermal systems, matrix tablets with low soluble drugs, coated forms, and osmotic systems etc. The dosage forms following this profile, release the same amount of drug by unit time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

B. First order kinetics
The first order kinetics was first applied for drug dissolution studies by Gibaldi and Feldman in 1967 and later by Wagner in 1969. In this case the drug release rate is concentration dependent and this can be depicted in decimal logarithm as follows.

\[
\log C_t = \log C_0 - \frac{k_1 t}{2.303}
\]

Where,
C<sub>t</sub> is the amount of drug released in time‘t’,
$C_0$ is the initial amount of the drug in the solution, $K_1$ is the first order release constant.

To study the release kinetics, the data obtained are plotted as log cumulative percentage of drug remaining Vs time. Example for the dosage form follows this profile such as those containing water soluble drug in a porous matrices release the drug that is proportional to the amount of drug released by unit time diminish.

C. Hixon-Crowell cube-root model
To evaluate the drug release with changes in the surface area and the diameter of the particles, Hixon-Crowell in 1931 recognized that the particle regular area is proportional to the cubic root of its volume and designed an equation as follows.

$$\frac{3}{4}W_0^{\frac{1}{3}} - \frac{3}{4}W_t^{\frac{1}{3}} = k_s t$$

Where,
- $W_0$ is the initial amount of drug in the dosage form,
- $W_t$ is the remaining amount of drug in the dosage form at time ‘t’
- $K_s$ is a constant incorporating the surface volume relation

To study the release kinetics, cube root of drug percentage remaining in matrix data Vs time is plotted. This model applies to pharmaceutical dosage forms, where the dissolution occurs in planes that are parallel to the surface area of the drug. The geometrical shape of the dosage form diminishes proportionally all the time. This model is used by assuming that release rate is limited by the drug particles dissolution rate and not by the diffusion.

D. Higuchi model
Higuchi in 1961 developed a model to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices. To study the dissolution from a planer system having a homogeneous matrix the relation obtained was follows.

$$f_t = A \sqrt{D(2C - C_s)C_s t}$$

Where,
- $f_t$ is the fraction of drug released in time ‘t’ per unit area,
- $A$, $C$ is the initial drug concentrations,
- $C_s$ is the drug solubility in the matrix media,
- $D$ is the diffusivity of drug molecules in the matrix substance.

In general, Higuchi model can be simplified as,

$$f_t = K_H \sqrt{t}$$

Where,
- $K_H$ is the Higuchi dissolution constant.

To study the release kinetics, data obtained were plotted as cumulative percentage drug release Vs square root of time. Drug dissolution from some modified release dosage forms like some transdermal systems and matrix tablets with water soluble drugs follows the above relationship.

E. Korsmeyer-Peppas model
In 1983, Korsmeyer developed a simple and semi-empiric model, when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time (t).

$$\frac{A_t}{A_\infty} = K t^n$$

Where,
- $n$ is the diffusion exponent for the drug release,
- $t$ is the release time,
- $K$ is the release rate constant
- $A_t/A_\infty$ is the fraction of drug release at time ‘t’ (Suvakanta dash, 2013, Chime Salome, 2003).

11. Characterization of buccal films
The prepared buccal films of lisinopril were characterized for following studies.

A. Scanning electron microscopy (SEM)
The surface morphology of the pure drug and the formulated films were assessed using a scanning electron microscope JSM – 6610. Samples were mounted on the round brass stubs (12mm diameter) using double – backed adhesive tape and then sputter coated for 8 minutes under argon atmosphere with gold before examination under the scanning electron microscope. Pictures were taken at an excitation voltage of 15Kv.

RESULTS AND DISCUSSION

A. Calibration curve of Lisinopril

![Image of calibration curve](image-url)

Figure 1: Standard calibration curve of Lisinopril in salivary simulated fluid pH 6.8.

From the above standard calibration curve of Lisinopril by using salivary simulated fluid pH 6.8 at λ max 204nm, the correlation coefficient (r) for the linear regression equation was found to be 0.9991, which indicates a positive correlation between the concentration of drug and the corresponding absorbance values.
B. FTIR Spectroscopy

Table 2: FT-IR interpretations of pure drug and excipients.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Functional group</th>
<th>Characteristic Peaks</th>
<th>Observed peaks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lisinopril</td>
</tr>
<tr>
<td>1</td>
<td>O-H</td>
<td>3550-3200</td>
<td>548</td>
</tr>
<tr>
<td>2</td>
<td>N-H</td>
<td>3000-2800</td>
<td>918</td>
</tr>
<tr>
<td>3</td>
<td>C-N</td>
<td>1342-1266</td>
<td>299</td>
</tr>
<tr>
<td>4</td>
<td>O-H</td>
<td>1390-1310</td>
<td>387</td>
</tr>
<tr>
<td>5</td>
<td>C-O</td>
<td>1300-1000</td>
<td>299</td>
</tr>
</tbody>
</table>

Figure 2: FTIR Spectroscopy of Lisinopril.

Figure 3: FTIR Spectroscopy of HPMC.
FTIR spectra of lisinopril, HPMC and PVP K30 was performed. Interpretation of above mentioned compounds was done and the functional groups were identified at different wave numbers i.e., lisinopril at O-H (3548.121 cm⁻¹), N-H (3338.605 cm⁻¹), C-H (2918.252 cm⁻¹), C-O (1299.583 cm⁻¹), C=C (699.639 cm⁻¹). HPMC at N-H (3393.668 cm⁻¹), C-H (2321.263 cm⁻¹), C=C (2115.369 cm⁻¹), C-N (1313.359 cm⁻¹), C-O (1019.384 cm⁻¹). PVP K30 at N-H (3394.234 cm⁻¹), C-H (2320.754 cm⁻¹), C=C (1638.978 cm⁻¹), O-H (1437.492 cm⁻¹), C-N (1285.886 cm⁻¹). Lisinopril, HPMC and PVP K30 at O-H (3374.774 cm⁻¹), C=C (2117.701 cm⁻¹), C-H (1650.353 cm⁻¹), C=C (1573.564 cm⁻¹), O-H (1388.351 cm⁻¹), C-O (1290.801 cm⁻¹). FT-IR results showed without much shifting in the spectra of drug mixture suggested no chemical interaction between the drug and excipients.

Evaluation of Lisinopril buccal films

1. Film weight uniformity
The weight of the film varies from 68.05 mg to 99.35 mg and the results were shown in the table No.15. The results obtained shown that, the selection and the proportion of the carriers used for the preparation of the films have reduced the weight variation and improves the uniformity of drug distribution in casted films. The average film weight was found to be 87.84 mg.

2. Thickness
The thickness of the films was found to be in the range of 0.11 to 0.16 mm as shown in table.15. Obtained
results were shown that, as the concentration of the polymer increases the thickness of film also increases. It was observed that the films containing HPMC as film forming polymer, has the low thickness because of the less viscous nature of the HPMC. The average thickness of the films was found to be 0.13 mm.

3. Folding endurance
The folding endurance of the films was found to be in the range of 328 to 262 times as shown in table 16. F1 shows low folding endurance because it consists of low concentration of HPMC and PVP K30. It shows high folding endurance in F7 as it contains high concentration of HPMC. From the obtained results. The average folding endurance of the films was found to be 333 times.

4. Surface pH
The surface pH was found to be in the range of 6.56 to 6.95 as shown in the table 16. From the results it is clear that all films have the pH value closer to the neutral pH, which indicates films do not cause irritation to the buccal mucosa.

5. Swelling index
Swelling index of the films was found in the range of 10-15%. It was high in F9 as it contains increased concentration of PVP K30 as it increases swelling index also increases. It was found decreased where HPMC was in high concentration. The obtained results were tabulated in the table no.17

6. Moisture content
Moisture content was calculated for the developed films and it was in the range of 5.26-7.28. There is no major difference in moisture content between the films. The results obtained were tabulated in the table no.17.

7. Drug content
The percentage drug content of the films was found between 80.34-98.73%. It was observed that there was no major difference in the uniformity of drug content. It was performed for the 10 formulations and the results observed were tabulated in the table no.18 and the graphical representation of drug content uniformity was shown in figure no. 10.

Table 3: Film weight, thickness and Folding endurance of lisinopril buccal films.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Film w.t (mg) n=3</th>
<th>Thickness (mm) n=3</th>
<th>Folding endurance n=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>68.05 ± 0.883</td>
<td>0.11 ± 0.012</td>
<td>262 ± 0.577</td>
</tr>
<tr>
<td>F2</td>
<td>79.18 ± 0.051</td>
<td>0.12 ± 0.005</td>
<td>265 ± 0.342</td>
</tr>
<tr>
<td>F3</td>
<td>83.43 ± 0.104</td>
<td>0.14 ± 0.005</td>
<td>222 ± 0.461</td>
</tr>
<tr>
<td>F4</td>
<td>89.21 ± 0.208</td>
<td>0.16 ± 0.023</td>
<td>285 ± 0.572</td>
</tr>
<tr>
<td>F5</td>
<td>99.35 ± 0.026</td>
<td>0.13 ± 0.005</td>
<td>290 ± 0.577</td>
</tr>
<tr>
<td>F6</td>
<td>93.08 ± 0.208</td>
<td>0.16 ± 0.005</td>
<td>320 ± 0.321</td>
</tr>
<tr>
<td>F7</td>
<td>95.25 ± 0.026</td>
<td>0.14 ± 0.027</td>
<td>328 ± 0.578</td>
</tr>
<tr>
<td>F8</td>
<td>96.28 ± 0.015</td>
<td>0.14 ± 0.017</td>
<td>325 ± 0.311</td>
</tr>
<tr>
<td>F9</td>
<td>86.23 ± 0.015</td>
<td>0.15 ± 0.005</td>
<td>327 ± 0.569</td>
</tr>
<tr>
<td>F10</td>
<td>88.36 ± 0.118</td>
<td>0.13 ± 0.005</td>
<td>322 ± 0.371</td>
</tr>
</tbody>
</table>

Table 4: Surface pH, Swelling index, moisture content and drug content of lisinopril buccal films.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Surface pH n=3</th>
<th>Swelling index n=3</th>
<th>Moisture content n=3</th>
<th>Drug content n=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>6.73 ± 0.005</td>
<td>14 ± 1.527</td>
<td>7.82 ± 0.015</td>
<td>80.34 ± 0.555</td>
</tr>
<tr>
<td>F2</td>
<td>6.84 ± 0.010</td>
<td>13 ± 0.577</td>
<td>6.43 ± 0.004</td>
<td>84.52 ± 0.690</td>
</tr>
<tr>
<td>F3</td>
<td>6.56 ± 0.011</td>
<td>10 ± 0.785</td>
<td>7.62 ± 0.068</td>
<td>89.04 ± 0.571</td>
</tr>
<tr>
<td>F4</td>
<td>6.98 ± 0.005</td>
<td>13 ± 0.691</td>
<td>5.32 ± 0.449</td>
<td>91.13 ± 0.877</td>
</tr>
<tr>
<td>F5</td>
<td>6.54 ± 0.005</td>
<td>14 ± 0.771</td>
<td>7.21 ± 0.355</td>
<td>94.26 ± 0.446</td>
</tr>
<tr>
<td>F6</td>
<td>6.96 ± 0.015</td>
<td>13 ± 0.323</td>
<td>5.89 ± 0.047</td>
<td>96.34 ± 0.752</td>
</tr>
<tr>
<td>F7</td>
<td>6.78 ± 0.030</td>
<td>11 ± 0.809</td>
<td>5.26 ± 0.372</td>
<td>98.73 ± 0.421</td>
</tr>
<tr>
<td>F8</td>
<td>6.76 ± 0.015</td>
<td>11.2 ± 0.407</td>
<td>5.28 ± 0.161</td>
<td>96.69 ± 0.140</td>
</tr>
<tr>
<td>F9</td>
<td>6.83 ± 0.005</td>
<td>15 ± 0.597</td>
<td>6.05 ± 0.036</td>
<td>97.04 ± 0.285</td>
</tr>
<tr>
<td>F10</td>
<td>6.94 ± 0.015</td>
<td>13 ± 0.313</td>
<td>7.15 ± 0.060</td>
<td>96.39 ± 0.119</td>
</tr>
</tbody>
</table>
8. In-vitro Drug Release studies

In-vitro drug release study was carried out for 60 min with sampling at specific intervals. The release of the drug was based on the concentration of the polymers used in the formulation. The results obtained were tabulated in the table no.19 and represented graphically in figure no.11. Based on this, the formulation F7 with 0.9mg HPMC, 0.01mg PVP K30, 1% PG exhibited drug release of 80.62% in 60 min. an F7 was selected as optimized formulation.

9. In-vitro Permeation studies

In-vitro permeation studies was carried out using franz diffusion cell for 5 hour duration by withdrawing samples at specific time intervals. The permeation of the drug into the mucosa is dependent on the nature of polymers used in the formulation. The results obtained were shown in the table no.20 and was represented graphically in figure no.12. Based on the drug permeated, formulation F7 which consists of 0.9mg HPMC, 0.01 PVP K30, 1% PG exhibited drug release of 82.15% in 5 hours. F7 was selected as an optimized formulation.

Table 5: In-vitro Drug release studies of Lisinopril buccal films.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>F1</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>F10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>12.04 ±0.502</td>
<td>14.97 ±0.365</td>
<td>16.24 ±0.215</td>
<td>19.89 ±0.095</td>
<td>25.37 ±0.045</td>
<td>30.12 ±0.015</td>
<td>26.47 ±0.026</td>
<td>25.55 ±0.020</td>
<td>26.10 ±0.025</td>
<td>23.73 ±0.020</td>
</tr>
<tr>
<td>15</td>
<td>19.89 ±0.321</td>
<td>18.80 ±0.222</td>
<td>20.62 ±0.147</td>
<td>25.55 ±0.120</td>
<td>33.95 ±0.031</td>
<td>39.98 ±0.015</td>
<td>38.70 ±0.032</td>
<td>39.79 ±0.017</td>
<td>36.51 ±0.025</td>
<td>39.24 ±0.025</td>
</tr>
<tr>
<td>30</td>
<td>30.30 ±0.145</td>
<td>27.56 ±0.270</td>
<td>32.67 ±0.113</td>
<td>38.51 ±0.176</td>
<td>47.28 ±0.037</td>
<td>54.21 ±0.020</td>
<td>49.65 ±0.032</td>
<td>50.02 ±0.050</td>
<td>51.48 ±0.025</td>
<td>55.13 ±0.015</td>
</tr>
<tr>
<td>45</td>
<td>37.60 ±0.359</td>
<td>34.13 ±0.110</td>
<td>41.62 ±0.148</td>
<td>47.46 ±0.192</td>
<td>55.13 ±0.041</td>
<td>62.25 ±0.015</td>
<td>61.70 ±0.011</td>
<td>61.55 ±0.056</td>
<td>63.16 ±0.011</td>
<td>63.16 ±0.011</td>
</tr>
<tr>
<td>60</td>
<td>41.36 ±0.245</td>
<td>44.83 ±0.335</td>
<td>52.88 ±0.316</td>
<td>56.37 ±0.101</td>
<td>64.98 ±0.015</td>
<td>70.12 ±0.026</td>
<td>80.62 ±0.005</td>
<td>75.95 ±0.020</td>
<td>77.76 ±0.011</td>
<td>76.31 ±0.005</td>
</tr>
</tbody>
</table>

Table 6: In-vitro Permeation studies of Lisinopril buccal films.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>F1</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>F10</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>8.41 ±0.019</td>
<td>9.43 ±0.001</td>
<td>8.72 ±0.004</td>
<td>9.73 ±0.008</td>
<td>10.75 ±0.007</td>
<td>12.17 ±0.004</td>
<td>13.18 ±0.005</td>
<td>14.19 ±0.003</td>
<td>15.01 ±0.035</td>
<td>16.02 ±0.030</td>
</tr>
<tr>
<td>30</td>
<td>11.76 ±0.004</td>
<td>13.89 ±0.010</td>
<td>14.19 ±0.005</td>
<td>14.19 ±0.005</td>
<td>15.92 ±0.021</td>
<td>16.93 ±0.008</td>
<td>17.85 ±0.006</td>
<td>18.96 ±0.007</td>
<td>19.87 ±0.005</td>
<td>20.89 ±0.019</td>
</tr>
<tr>
<td>45</td>
<td>20.89 ±0.052</td>
<td>21.80 ±0.009</td>
<td>21.29 ±0.015</td>
<td>23.12 ±0.010</td>
<td>26.57 ±0.009</td>
<td>29.41 ±0.010</td>
<td>31.64 ±0.167</td>
<td>33.06 ±0.031</td>
<td>34.07 ±0.005</td>
<td>35.29 ±0.005</td>
</tr>
</tbody>
</table>
10. Drug release kinetics

Table 7: Kinetic profile for F7 formulation of Lisinopril.

<table>
<thead>
<tr>
<th>Time in min</th>
<th>Cumulative % released (Q)</th>
<th>% Drug remaining</th>
<th>Square root of time</th>
<th>Log cumulative % drug remaining</th>
<th>Log time</th>
<th>Log cumulative % drug released</th>
<th>% Drug released</th>
<th>Cube root of % drug remaining (Wo-Wt)</th>
<th>(Wo-Wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0.000</td>
<td>2.000</td>
<td>0.000</td>
<td>100</td>
<td>0.000</td>
<td>4.642</td>
<td>0.000</td>
</tr>
<tr>
<td>15</td>
<td>13.18</td>
<td>86.82</td>
<td>3.873</td>
<td>1.939</td>
<td>1.176</td>
<td>1.120</td>
<td>13.18</td>
<td>4.428</td>
<td>0.214</td>
</tr>
<tr>
<td>30</td>
<td>17.85</td>
<td>82.15</td>
<td>5.477</td>
<td>1.915</td>
<td>1.477</td>
<td>1.252</td>
<td>4.670</td>
<td>4.347</td>
<td>0.295</td>
</tr>
<tr>
<td>45</td>
<td>31.64</td>
<td>68.36</td>
<td>6.708</td>
<td>1.835</td>
<td>1.653</td>
<td>1.500</td>
<td>13.79</td>
<td>4.089</td>
<td>0.553</td>
</tr>
<tr>
<td>60</td>
<td>38.74</td>
<td>61.26</td>
<td>7.746</td>
<td>1.787</td>
<td>1.778</td>
<td>1.588</td>
<td>7.10</td>
<td>3.942</td>
<td>0.700</td>
</tr>
<tr>
<td>120</td>
<td>49.18</td>
<td>50.82</td>
<td>10.954</td>
<td>1.706</td>
<td>2.079</td>
<td>1.692</td>
<td>10.44</td>
<td>3.704</td>
<td>0.938</td>
</tr>
<tr>
<td>180</td>
<td>57.60</td>
<td>42.40</td>
<td>13.416</td>
<td>1.627</td>
<td>2.255</td>
<td>1.760</td>
<td>8.42</td>
<td>3.487</td>
<td>1.155</td>
</tr>
<tr>
<td>240</td>
<td>66.63</td>
<td>33.37</td>
<td>15.492</td>
<td>1.523</td>
<td>2.380</td>
<td>1.824</td>
<td>9.03</td>
<td>3.219</td>
<td>1.423</td>
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<tr>
<td>300</td>
<td>82.15</td>
<td>17.85</td>
<td>17.321</td>
<td>1.252</td>
<td>2.477</td>
<td>1.915</td>
<td>15.52</td>
<td>2.613</td>
<td>2.029</td>
</tr>
</tbody>
</table>

Figure 8: Graphical representation of In-vitro permeation studies of Lisinopril buccal films.

Figure 9: Zero order plot for Lisinopril buccal films of F7 Formulation.

Figure 10: First order plot for Lisinopril buccal films of F7 Formulation.
The drug release profiles of the lisinopril buccal films were applied to various kinetic models such as zero order, first order, higuchi plot, korsmeyer-peppas and Hixson-crowell models were tabulated in table no.21 and were shown in the figure no.13, 14, 15, 16, 17. The $R^2$ values were shown on table no.22. The drug release kinetic results showed that the drug release pattern of the optimized formula F7 follows Higuchi plot.

G. Characterization studies

1. Scanning Electron Microscopy

![Figure 14: Scanning electron microscopy of (2×2) Lisinopril buccal film (F7).](image-url)
The SEM images of the lisinopril buccal films of F7 formulation made up of polymers like HPMC and PVP K30 were shown in the figure no. 18 respectively. From the above SEM images it is clearly evident that the films made up of drug and HPMC, PVP K30 combination has uniform distribution of the drug and the film appears clear. This is due to the less viscous nature of PVP K30 and HPMC and its freely soluble nature made them uniform distribution of drug.

H. Image of Buccal film

Figure 15: Image of Lisinopril buccal film of F7 formulation.

CONCLUSION

Lisinopril was successfully formulated as buccal films by using film forming agents in combination and plasticizer by solvent casting method. All the films are in smooth textured. Amongst all the prepared formulations from F1 to F10, the F7 formulation possessing HPMC and PVP K30 as film forming agents and PG as plasticizer considered as optimized formulation on the basis of % drug release, % drug diffused and surface morphology. The optimized formulation F7 of lisinopril releases 80.62% of its drug content in 60 min. 82.15 % of the lisinopril drug was diffused at the end of the 5 hour, the drug release kinetics follows higuchi model for both the moieties. The optimum formulation F7 has clear surface morphology. FTIR studies revealed that the absence chemical interactions between drug and polymer. The study is clearly evident that the lisinopril buccal films provide the fast onset of action by bypassing the first pass metabolism which is essential requirement for the hypertension patients.

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