

**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 upto 5 hour and the drug diffused is of **82.15%**. The kinetic models used were zero order, first order, Higuchi's and Peppas's model. The kinetic analysis of drug release data indicated that the Lisinopril follows Higuchi plot. The FTIR spectroscopy proved 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.<sup>[1]</sup> Whereas parenteral route is very painful for the administration of drug. Drugs with high molecular weight, poor skin penetration need other routes.<sup>[2]</sup> In recent days buccal drug delivery system acts as an alternate to the oral drug delivery system.<sup>[3-8]</sup> 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.<sup>[9-15]</sup> Buccal drug delivery offers safer method of drug usage as it can be terminated in case of emergency such as toxicity.<sup>[16-20]</sup> This drug delivery system is more preferable over other dosage forms such as tablets, gels, adhesive tablets, conventional matrix tablets as it was reported by several research groups. (Tej pratap singh et al),<sup>[21-28]</sup> 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).<sup>[22-26]</sup> As the angiotensin II (AT II) regulates the blood pressure and it is the main component of the rennin angiotensin aldosterone system (RAAS).<sup>[27-33]</sup> Lisinopril is used in the treatment of hypertension and symptomatic congestive heart failure and myocardial infarction.<sup>[34-38]</sup> The absorption of drug orally is 60% but it is of very extensive first pass metabolism and its bioavailability is about 25%. Its half-life is of 12.6 hours.<sup>[39-46]</sup> It is suitable for the administration via buccal drug delivery system which provides controlled release of drug without pre-systemic metabolism<sup>46-50</sup>. 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 a 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 Shimadzu Scientifics, Japan) was used for the estimation of standard calibration data of lisinopril. The absorbance was measured at 204nm.

## 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<sup>o</sup>c for time period of 24 hours. After complete drying the film was carefully removed from the mould and sized to 2×2cm and stored in dessicator for further evaluation by packing in a aluminium foil.

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

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	25	25	25	25	25	25	<b>25</b>	25	25	25
HPMC (mg)	0.4	0.5	0.6	0.7	0.8	0.9	<b>0.9</b>	0.9	0.9	0.9
PVP K30 (mg)	0.01	0.01	0.01	0.01	0.01	-	<b>0.01</b>	0.02	0.03	0.04
PG (% v/v)	1	1	1	1	1	1	<b>1</b>	1	1	1
Dis.water	q.s	q.s	q.s	q.s	q.s	q.s	<b>q.s</b>	q.s	q.s	q.s
Aspartame (mg)	0.02	0.02	0.02	0.02	0.02	0.02	<b>0.02</b>	0.02	0.02	0.02
Citric acid (mg)	0.02	0.02	0.02	0.02	0.02	0.02	<b>0.02</b>	0.02	0.02	0.02
Flavouring agent	q.s	q.s	q.s	q.s	q.s	q.s	<b>q.s</b>	q.s	q.s	q.s

### 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<sup>-1</sup>.

### 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.

#### 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<sup>0</sup>±0.2<sup>0</sup>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.

$$\text{Percent Swelling (\%S)} = (X_t - X_o / X_o) \times 100$$

Where X<sub>t</sub> = the weight of the swollen film after time t,  
X<sub>o</sub> = the initial film weight at zero time.

## 6. Moisture Content

The prepared films were weighed individually and kept in a desiccator 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 occasional 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 upto 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  $37^{\circ} \pm 0.5^{\circ} \text{C}$  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  $37^{\circ} \pm 0.5^{\circ} \text{C}$  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  $T_{50}$  and  $T_{90}$  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.

$$\text{Dissolution Efficiency (DE)} = \left( \frac{\int_0^t y \cdot dt}{y_{100} \cdot t} \right) 100$$

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  $DE_{30}$  would relate to the dissolution of the drug from a particular formulation after 30 minutes could only be compared with  $DE_{30}$  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,

$A_0$  is initial amount of drug in the dosage form,

$A_t$  is the amount of drug in the dosage form at time 't',

$k_0$  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.

$$\text{Log} C_t = \text{Log} C_0 - \frac{k_1 t}{2.303}$$

Where,

$C_t$  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.

$$\sqrt[3]{W_0} - \sqrt[3]{W_t} = k_s t$$

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).

$$A_t/A_\infty = Kt^n$$

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

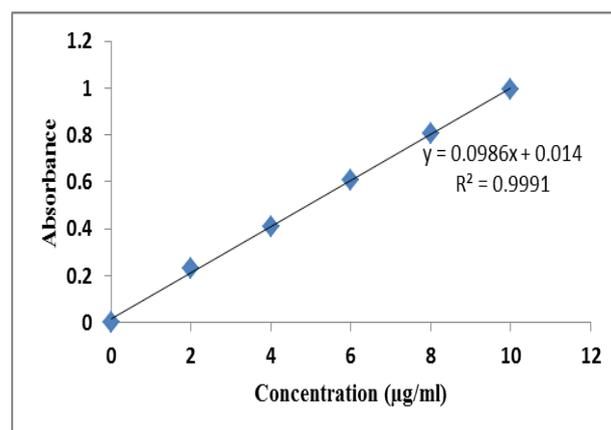
The prepared buccal films of lisinopril were characterizes for following studies.

### 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 a excitation voltage of 15Kv.

## RESULTS AND DISCUSSION

### A. Calibration curve of Lisinopril

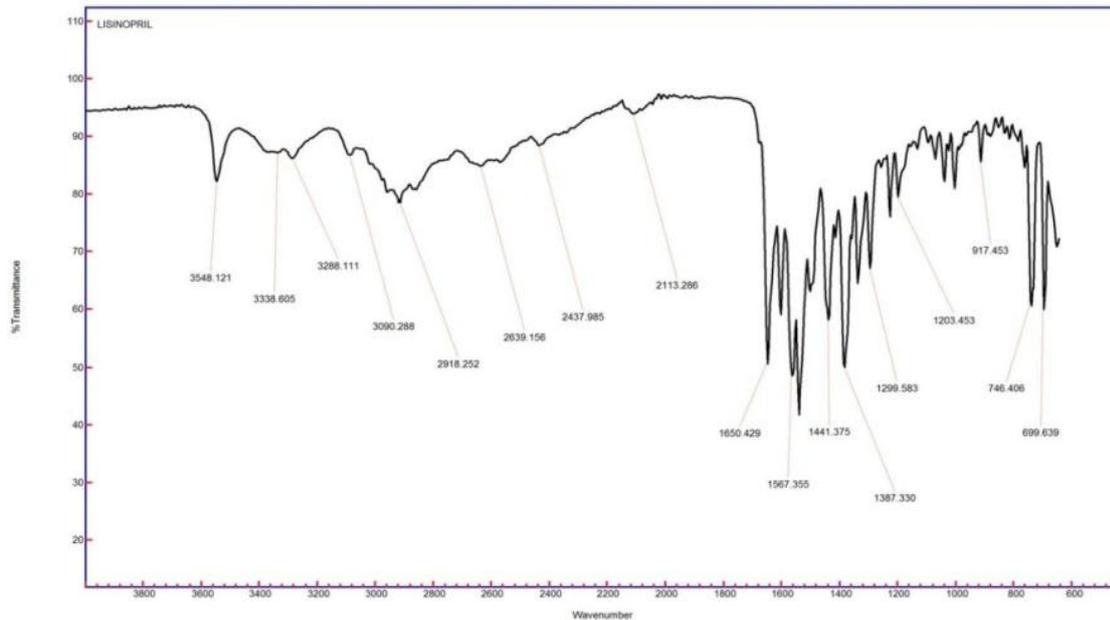
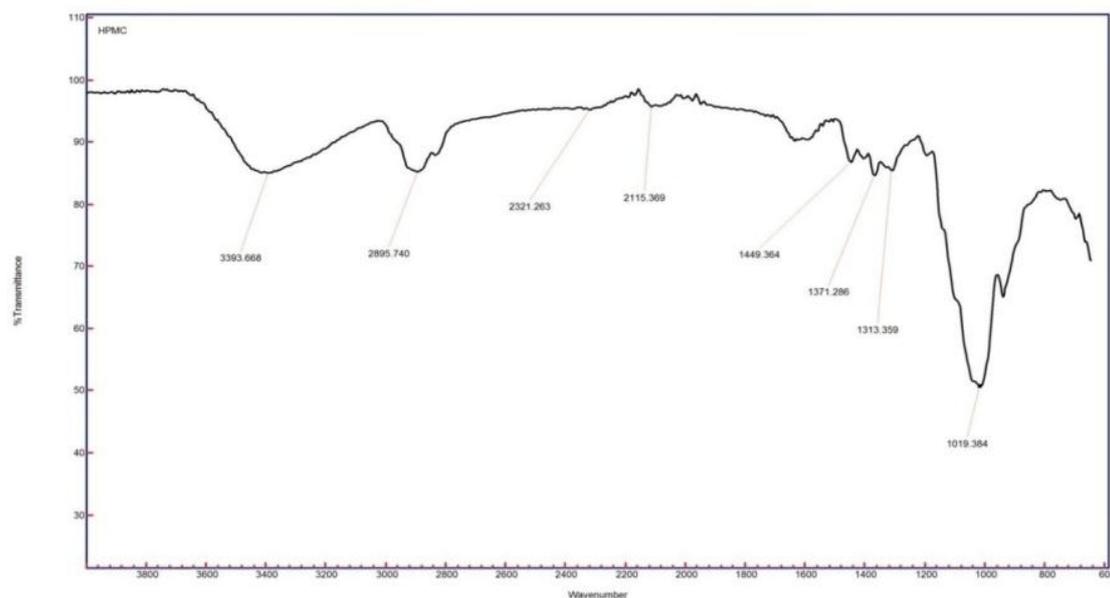


**Figure 1: Standard calibration curve of Lisinopril in salivary simulated fluid pH 6.8.**

From the above standard calibration curve of Lisinopril by using salivary simulated fluid pH 6.8 at  $\lambda$  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.**

S. no.	Functional group	Characteristic Peaks	Observed peaks	
			Lisinopril	Physical Mixture
1	O-H	3550-3200	548	3374
2	N-H	3000-2800	918	2952
3	C-N	1342-1266	299	1290
4	O-H	1390-1310	387	1388
5	C-O	1300-1000	299	1290

**Figure 2: FTIR Spectroscopy of Lisinopril.****Figure 3: FTIR Spectroscopy of HPMC.**

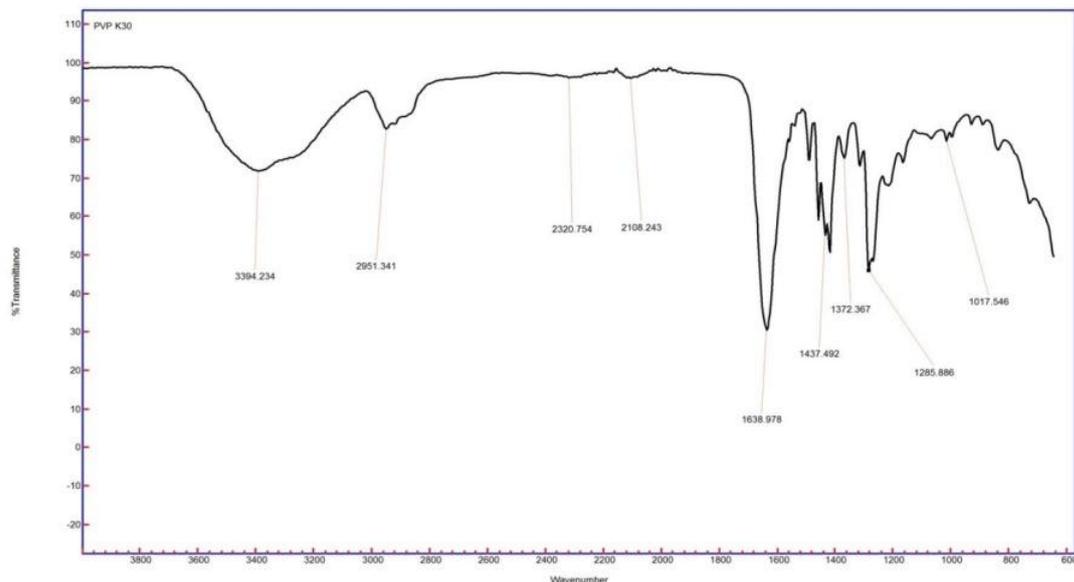


Figure 4: FTIR Spectroscopy of PVP K30.

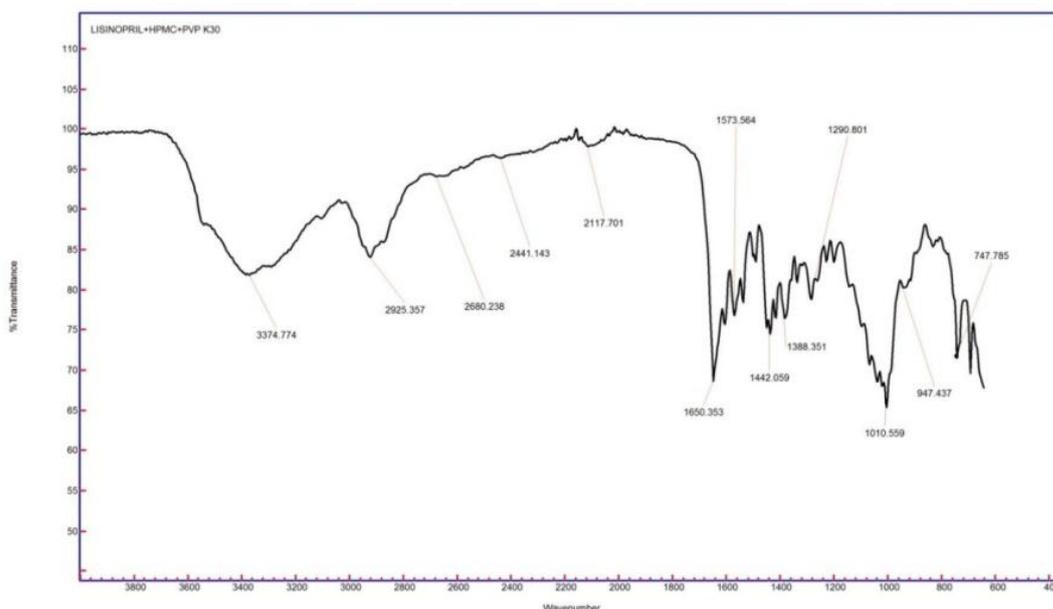


Figure 5: FTIR Spectroscopy of Mixture (Lisinopril+HPMC+PVP K30).

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 ( $3548.121\text{cm}^{-1}$ ), N-H ( $3338.605\text{cm}^{-1}$ ), C-H ( $2918.252\text{cm}^{-1}$ ), C-O ( $1299.583\text{cm}^{-1}$ ), C=C ( $699.639\text{cm}^{-1}$ ). HPMC at N-H ( $3393.668\text{cm}^{-1}$ ), C-H ( $2321.263\text{cm}^{-1}$ ), C≡C ( $2115.369\text{cm}^{-1}$ ), C-N ( $1313.359\text{cm}^{-1}$ ), C-O ( $1019.384\text{cm}^{-1}$ ). PVP K30 at N-H ( $3394.234\text{cm}^{-1}$ ), C-H ( $2320.754\text{cm}^{-1}$ ), C=C ( $1638.978\text{cm}^{-1}$ ), O-H ( $1437.492\text{cm}^{-1}$ ), C-N ( $1285.886\text{cm}^{-1}$ ). Lisinopril, HPMC and PVP K30 at O-H ( $3374.774\text{cm}^{-1}$ ), C≡C ( $2117.701\text{cm}^{-1}$ ), C-H ( $1650.353\text{cm}^{-1}$ ), C=C ( $1573.564\text{cm}^{-1}$ ), O-H ( $1388.351\text{cm}^{-1}$ ), C-O ( $1290.801\text{cm}^{-1}$ ). 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.**

Formulation code	Film w.t (mg) n=3	Thickenss (mm) n=3	Folding endurance n=3
F1	68.05 ± 0.883	0.11 ± 0.012	262 ± 0.577
F2	79.18 ± 0.051	0.12 ± 0.005	265 ± 0.342
F3	83.43 ± 0.104	0.14 ± 0.005	222 ± 0.461
F4	89.21 ± 0.208	0.16 ± 0.023	285 ± 0.572
F5	99.35 ± 0.026	0.13 ± 0.005	290 ± 0.577
F6	93.08 ± 0.208	0.16 ± 0.005	320 ± 0.321
F7	95.25 ± 0.026	0.14 ± 0.027	328 ± 0.578
F8	96.28 ± 0.015	0.14 ± 0.017	325 ± 0.311
F9	86.23 ± 0.015	0.15 ± 0.005	327 ± 0.569
F10	88.36 ± 0.118	0.13 ± 0.005	322 ± 0.571

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

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

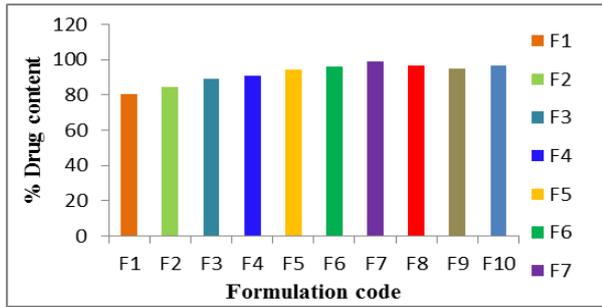


Figure 6: Graphical representation of Drug content uniformity of Lisinopril buccal Films.

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 60min. 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.

Time (min)	% Drug Release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
10	12.04 ±0.502	14.97 ±0.365	16.24 ±0.215	19.89 ±0.095	25.37 ±0.045	30.12 ±0.015	26.47 ±0.026	25.55 ±0.020	26.10 ±0.025	23.73 ±0.020
15	19.89 ±0.321	18.80 ±0.222	20.62 ±0.147	25.55 ±0.120	33.95 ±0.031	39.98 ±0.035	38.70 ±0.015	39.79 ±0.032	36.51 ±0.017	39.24 ±0.025
30	30.30 ±0.145	27.56 ±0.270	32.67 ±0.113	38.51 ±0.176	47.28 ±0.037	54.21 ±0.020	49.65 ±0.025	50.02 ±0.050	51.48 ±0.025	55.13 ±0.015
45	37.60 ±0.359	34.13 ±0.110	41.62 ±0.148	47.46 ±0.192	55.13 ±0.041	62.25 ±0.015	61.70 ±0.015	58.41 ±0.011	61.15 ±0.056	63.16 ±0.011
60	41.36 ±0.245	44.83 ±0.335	52.88 ±0.316	56.37 ±0.101	64.98 ±0.015	70.12 ±0.026	80.62 ±0.005	75.95 ±0.020	77.76 ±0.011	76.31 ±0.005

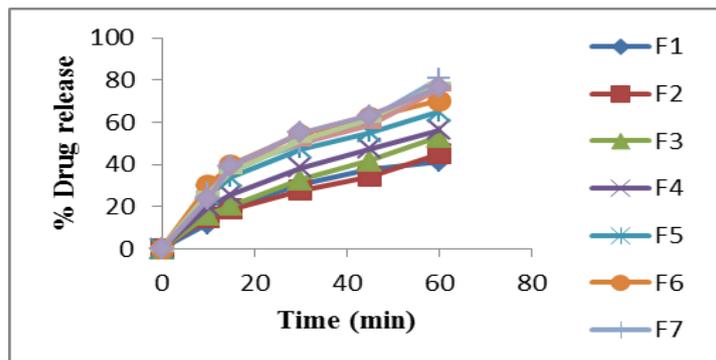


Figure 7: Graphical representation of *In-vitro* Drug release studies.

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

Time (min)	% Drug diffused									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
15	8.41 ±0.019	9.43 ±0.001	8.72 ±0.004	9.73 ±0.008	10.75 ±0.007	12.17 ±0.004	13.18 ±0.005	14.19 ±0.003	15.01 ±0.035	16.02 ±0.030
30	11.76 ±0.004	13.89 ±0.010	14.19 ±0.005	14.19 ±0.005	15.92 ±0.021	16.93 ±0.008	17.85 ±0.008	18.96 ±0.007	19.87 ±0.005	20.89 ±0.019
45	20.89 ±0.052	21.80 ±0.009	21.29 ±0.015	23.12 ±0.010	26.57 ±0.009	29.41 ±0.010	31.64 ±0.167	33.06 ±0.031	34.07 ±0.005	35.29 ±0.005

60	26.47 ±0.001	27.68 ±0.005	27.89 ±0.005	30.22 ±0.005	35.70 ±0.008	37.01 ±0.045	38.74 ±0.005	41.07 ±0.005	13.20 ±0.032	44.11 ±0.009
120	30.22 ±0.004	35.70 ±0.012	32.45 ±0.009	33.77 ±0.574	46.24 ±0.016	48.58 ±0.010	49.18 ±0.004	49.18 ±0.009	52.33 ±0.015	53.34 ±0.010
180	34.28 ±0.005	41.07 ±0.010	38.13 ±0.013	43.50 ±0.048	50.60 ±0.007	52.23 ±0.008	57.60 ±0.014	55.78 ±0.011	56.79 ±0.020	58.01 ±0.039
240	41.37 ±0.015	45.13 ±0.004	45.63 ±0.165	51.31 ±0.189	54.05 ±0.025	59.33 ±0.007	66.63 ±0.005	60.85 ±0.005	61.86 ±0.009	63.18 ±0.017
300	48.27 ±0.005	49.18 ±0.009	52.02 ±0.045	59.33 ±0.056	66.54 ±0.006	77.52 ±0.009	82.15 ±0.008	76.67 ±0.026	80.05 ±0.020	75.35 ±0.015

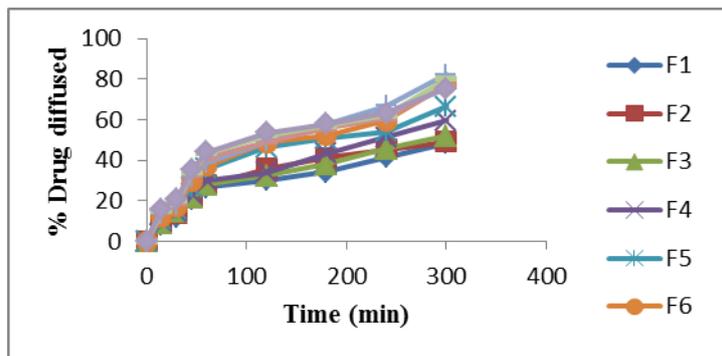


Figure 8: Graphical representation of In-vitro permeation studies of Lisinopril buccal films.

10. Drug release kinetics

Table 7: Kinetic profile for F7 formulation of Lisinopril.

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

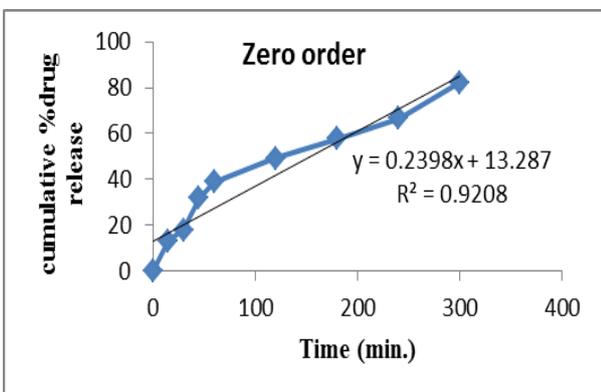


Figure 9: Zero order plot for Lisinopril buccal films of F7 Formulation.

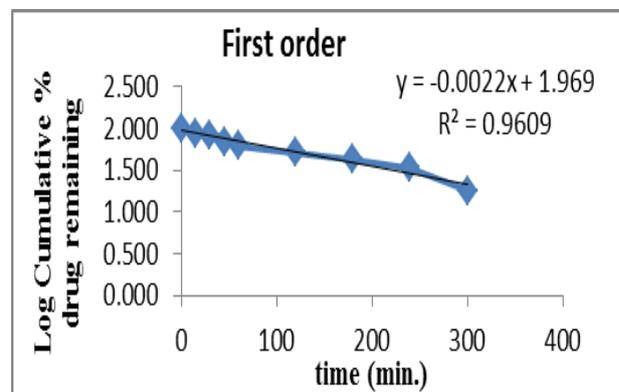


Figure 10: First order plot for Lisinopril buccal films of F7 Formulation.

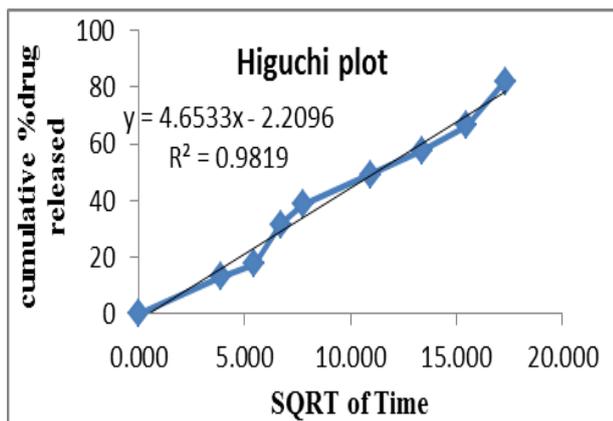


Figure 11: Higuchi plot for Lisinopril buccal films of F7 Formulation.

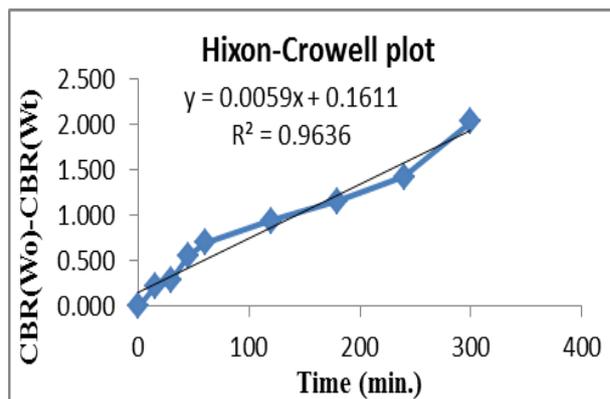


Figure 13: Hixson-crowell model for Lisinopril buccal films of F7 Formulation.

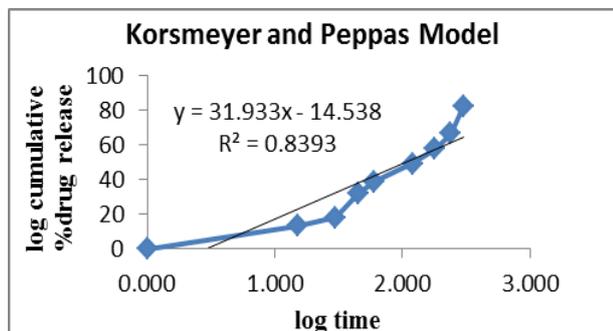


Figure 12: Korsmeyer and peppas model for Lisinopril buccal films of F7 Formulation.

Table 8: R<sup>2</sup> values of F7 formulation.

Fo Formulation	Zero order plot	First order plot	Higuchi plot	Peppas plot	Hixson-Crowell
F7	0.920	0.960	0.981	0.839	0.963

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<sup>2</sup> 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**

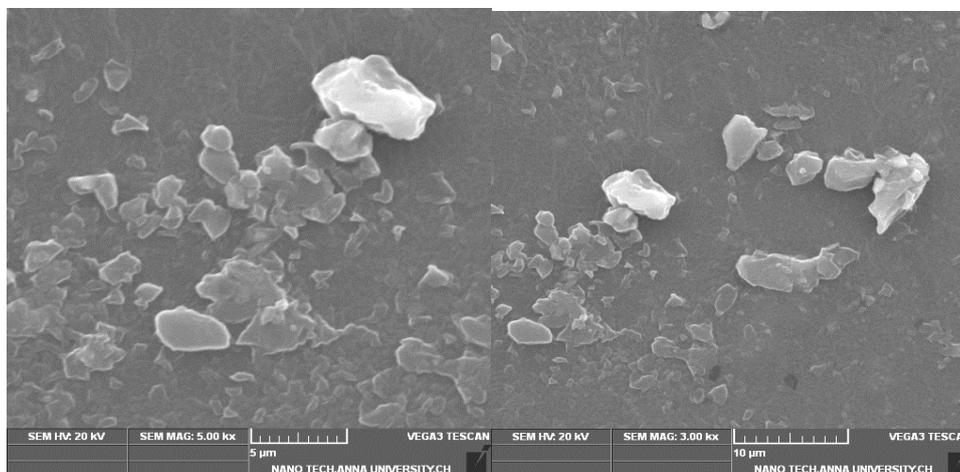


Figure 14: Scanning electron microscopy of (2x2) Lisinopril buccal film (F7).

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 of 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 an essential requirement for the hypertension patients.

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#### REFERENCES

1. Harshad GP, Janak JP, Tarun KP, Vishnu MP. Buccal patch: A technical note. *Int J Pharm Sci Review Res.*, 2010.
2. Bindu MB, Zulkar NK, Mohammed, Ravinder NA, David Banji. Mucoadhesive drug delivery system: An overview. *Journal of Advanced Pharmaceutical Technology & Research*, 2010.
3. Jinsong H, Paul WSH. Buccal Delivery Systems. *Drug Dev Ind Pharm*, 2003; 29: 821-32.
4. Mucoadhesive Buccal Films: An Innovative Drug Delivery System Sravanthi R.R, Rajalakshmi R, Krishna Moorthy S.B, Rupangada. V, Ramya Sudha. E., 2014.
5. Smart JD. The basics and underlying mechanisms of mucoadhesion, *Adv. Drug Deliv. Rev.*, 2005.
6. R.B. Gandhi, J.R. Robinson. Bioadhesion in drug delivery. *Ind. J. Pharm. Sci.*, 1988; 50(3): 145-152.
7. Shojaei Amir H., Buccal Mucosa As A Route For Systemic Drug Delivery: A Review, *J Pharm Pharmaceut Sci*, 1998; 1(1): 15-30.
8. Shinde Pramod, Salunkhe Vijay and Magdum Chandrakant. Buccal film an innovative dosage form designed to improve patient compliance, 2012.
9. Harris, D. and Robinson, J.R., Drug delivery via the mucous membranes of the oral cavity, *J. Pharm. Sci.*, 1992; 81: 1-10.
10. Wertz, P. W. and Squier, C. A., Cellular and molecular basis of barrier function in oral epithelium, *Crit. Rev. Ther. Drug Carr. Sys*, 1991; 8: 237-269.
11. Squier, C.A., Cox, P., and Wertz, P. W., Lipid content and water permeability of skin and oral mucosa, *The J. Invest. Dermat*, 1991; 96: 123-126.
12. Hooda, R., Tripathi, M., and Kapoor, K., A Review an oral mucosal drug delivery system. *The Pharma innovation*, 2012; 1(1): 14-21.
13. Siddiqui, M.D.N, Garg, G., and Sharma, P.K., A short Review on "A novel approach in oral fast dissolving drug delivery system and their patents". *Advances in biological research*, 2011; 5(6).
14. N.Salamat-Miller, M. Chittchang, T. Johnston, The use of mucoadhesive polymers in buccal drug delivery, *Advanced Drug Delivery Reviews*, 2005; 57.
15. Deepak Malpure Rajaram, Sharada Deore Laxman Buccal mucoadhesive films – A Review, 2017.
16. Squier CA, Wertz PW. Structure and function of the oral mucosa and implications for drug delivery. In: Rathbone M.J, ed. *Oral mucosal drug delivery*, Marcel Dekker, 1996;
17. Rathbone MJ, Tucker IG. Mechanisms, barriers and pathways of oral mucosal
18. Drug permeation. *Adv. Drug Del. Rev.*, 1993;
19. Deepak Malpure Rajaram, Sharada Deore Laxman Buccal mucoadhesive films – A Review, 2017.
20. Amir H Shojaei. Buccal Mucosa As A Route For Systemic Drug Delivery: A Review. *J Pharm Pharmaceut Sci.*, 1998; 1(1): 15-30,

21. Nishan N. Bobade , Sandeep C. Atram, Vikrant P. Wankhade, Dr. S.D. Pande, Dr. K.K. Tapar. A Review on buccal drug delivery system, 2013.
22. Shinkar DM, Dhake AS, Setty CM. Drug delivery from the oral cavity: a fo-cus on mucoadhesive Buccal drug delivery systems. PDA J Pharm Sci Technol, 2012.
23. Radha Madhavi B1, Varanasi SN Murthy, Prameela Rani A and Dileep Kumar Gattu. Buccal Film Drug Delivery System-An Innovative and Emerging Technology.
24. Surender V, Mahima K, Aruna R, Sapna S. An Overview on Buccal Drug Deliv-ery System. IJPSR, 2011; 2(6): 1303-21.
25. Aleksovski A, Dreu R, Gašperlin M, Planinšek O. Mini-tablets: a contem porary system for oral drug delivery in targeted patient groups. Expert Opinion Drug Deliv, 2015.
26. Javier O. Morales, Jason T. McConville Manufacture and characterization of mucoadhesive buccal films, 2010.
27. Danckwerts MP Intra oral drug delivery: A comparative review. Am J Drug Deliv, 2003; 1: 149-224.
28. Akbari J, Nokhodchi A, Farid D, Adrangui M, Siahi-Shadbad MR, et al. Development and evaluation of buccoadhesive, 2004.
29. Propranolol hydrochloride table formulations: Effect of fillers. Farmaco, 59: 155-161.
30. Pfister WR, Ghosh TK Drug delivery to the oral cavitymolecules to market. Marcel Dekker, New York, USA, 2005.
31. Suhel khan, Nayyar Parvez, Pramod Kumar Sharma, Md Aftab Alam, Musarrat Husain Warsi Novel Approaches – mucoadhesive buccal drug delivery system, 2010.
32. Bhura N, Sanghvi K, Patel U, Parmar B, Patel D A review on fast dissolving film. IJPRBS, 2012; 1: 66-89.
33. RathaAdhikari SN, Nayak BS, Nayak AK, Mohanty B Formulation and evaluation of buccal patches for delivery of atenolol. AAPS Pharm Sci Tech., 2010; 11: 1038-1044.
34. Donnelly R, McCarron P, Tunney M, Woolfson A Potential of photodynamic therapy in treatment of fungal infections of the mouth. Design and characterisation of a mucoadhesive patch containing toluidine blue O. JPhotochem Photobiol B., 2007; 86: 59-69.
35. Khanna R, Agarwal SP, Ahuja A Preparation and evaluation of mucoadhesivebuccal films of clotrimazole for oral Candida infections. Indian J Pharm Sci., 1997; 59: 299-305.
36. Repka M, Prodduturi S, Stodghill S Production and characterization of hot melt extruded films containing clotrimazole. Drug Dev Ind Pharm, 2003; 29: 757-765.
37. Kulkarni N, Kumar LD, Sorg A Fast dissolving orally consumable films containing an antitussive and a mucosa coating agent. U.S. Patent 2003/206942, 2003.
38. Ali S, Quadir A High molecular weight povidone polymer-based films for fast dissolving drug delivery applications. Drug Del Technol, 2007; 7: 36-43.
39. Cilurzo F, Cupone IE, Minghetti P, Selmin F, Montanari L Fast dissolving films made of maltodextrins. Eur J Pharm Biopharm, 2008; 70: 895-900.
40. Nishimura M, Matsuura K, Tsukioka T, Yamashita H, Inagaki N, et al. In vitro and in vivo characteristics of prochlorperazine oral disintegrating film. Int J Pharm, 2009; 368: 98-102.
41. Consuelo ID, Falson F, Guy RH, Jacques Y Ex vivo evaluation of bioadhesive films for buccal delivery of fentanyl. J Control Release, 2007; 122: 135-140.
42. Agresti C, Tu Z, Ng C, Yang Y, Liang JF Specific interactions between diphenhydramine and  $\alpha$ - helical poly [glutamic acid] –A new ion-pairing complex for tastmasking and pH-controlled diphenhydramine release. Eur J Pharm Biopharm, 2008; 70: 226-233.
43. Suzuki H, Onishi H, Takahashi Y, Iwata M, Machida Y Development of oral acetaminophen chewable tablets with inhibited bitter taste. Int J Pharm, 2003; 251: 123-132.
44. Xu J, Bovet LL, Zhao K Taste masking microspheres for orally disintegrating tablets. Int J Pharm, 2008; 359: 63-69.
45. Morales JO, Mc Conville JT Manufacture and characterization of mucoadhesivebuccal films. Eur J Pharm Biopharm, 2011; 77: 187-199.
46. Dixit RP, Puthli SP Oral strip technology: Overview and future potential. J Control Release, 2009; 139: 94-107.
47. Anders R, Merkle H Evaluation of laminated muco-adhesive patches for buccal drug delivery. Int J Pharmaceut, 1989; 49: 231-240.
48. Chinna Reddy P, Chaitanya K.S.C., Madhusudan Rao Y A review on bioadhesive buccal drug delivery systems:current status of formulation and evaluation methods, 2011
49. Mona semalty A.Semalty, G.Kumar Formulation and evaluation of mucoadhesive buccal films of glipizide.. 2008
50. Ankita Saxena, Gulab Tewari, Shubhini Awasthi Saraf Formulation and Evaluation of mucoadhesive buccal patches of acyclovir utilizing inclusion phenomena, 2011.