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Formulation and Evaluation of Sublingual Tablets of Lisinopril

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A B S T R A C T

Lisinopril is the drug of choice in hypertension. Bioavailability of the drug is 25% of orally. However, its extensive first pass metabolism results in poor bioavailability. The objective of present research work is to design and evaluate the controlled release of sublingual tablets of Lisinopril to increase the bioavailability by reducing the dosing frequency. In the present work tablets were prepared using Carbopol-934, Hydroxy propyl methyl cellulose K4M (HPMC), Poly vinyl pyrrolidine, Poly vinyl alcohol, Sodium carboxy methyl cellulose as mucoadhesive polymers, sodium saccharine was used to mask the taste of a tablet. Five formulations were developed with varying concentration of polymers. The tablets were evaluated for hardness, weight variation, thickness, percentage of drug content, Surface pH, *invitro* studies like swelling, mucoadhesive strength and drug release. Formulation L3 showed good mucoadhesive strength and maximum drug release of 98.7% in 1 hr. Formulation L3follows zero-order drug release. FTIR studies showed no evidence on interaction between drug and polymers. The results indicate that the sublingual tablets of Lisinopril may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Lisinopril.

Keywords: Lisinopril, sublingual tablets, buccal tablets.

A R T I C L E I N F O

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1. Introduction

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 pre-systemic metabolism in the gastrointestinal (GI) tract and hepatic first pass elimination.

Definition

Mucoadhesion is defined as the ability of material adheres to biological tissue for an extended period of time.The delivery of drugs via the mucous membranes lining the oral cavity (i.e., sublingual and buccal), with consideration of both systemic delivery and local therapy, is known as buccal drug delivery system. [1]

Advantages

a. The advantages of sublingual drug delivery over other delivery modalities are as follows:
b. Avoidance of 'first-pass' metabolism of drugs.
c. Ease of administration and termination of therapy in emergency.
d. Permits localization of the drug to the oral cavity for a prolonged period of time.
e. Can be administered to unconscious and trauma patients.
f. Prolongs the residence time of the dosage form at the site of absorption.
g. Due to an increased residence time it enhances absorption and hence the therapeutic efficacy of the drug.
h. Excellent accessibility.
i. Rapid absorption because of enormous blood supply and good blood flow rates increase in drug bioavailability due to first pass metabolism avoidance.
j. Drug is protected from degradation in the acidic environment in the GIT.
k. Improved patient compliance- ease of drug administration.
l. Faster onset of action is achieved due to mucosal surface.
m. Significant reduction in dose can be achieved, thereby reducing dose, dose dependent side effects, and eliminates peak-valley profile.
n. Drugs which are unstable in acidic environment of stomach or are destroyed by the enzymatic or alkaline environment of the intestine can be administered by this route.[2]

Limitations [3]

a. Drugs with large dose are difficult to be administered.
b. Eating and drinking may be restricted.
c. Possibility of the patient to swallow the tablet.
d. This route cannot administer the drugs, which are unstable at sublingual pH.
e. This route cannot administer drugs, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour.
f. Small surface area is available for absorption.

Lisinopril is an ACE inhibitor used in the treatment of hypertension. Lisinopril is slowly and incompletely absorbed following oral administration. Its oral bioavailability is about 25% only. The aim of the present study was to develop mucoadhesive sublingual tablets of Lisinopril to improve bioavailability and also to ensure satisfactory drug release.

2. Matirials and Methods

Preparation of sublingual tablets:

Lisinopril sublingual tablets were prepared by the direct compression method using different excipients. The excipients used were Carbopol-934, Hydroxy propyl methyl cellulose K4M (HPMC), Poly vinyl pyrrolidine, Poly vinyl alcohol, Sodium carboxy methyl cellulose, Mannitol (diluents), saccharine sodium (sweetening agent), crospovidone (super disintegrant). Different concentration of excipients was used to prepare different group of sublingual tablets.

Preformulation studies

Melting Point Determination [4]

Melting point of the drug was determined by taking small amount of drug in a capillary tube closed at one end and placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed in triplicates and average value was noted [5].

Drug – Excepients Interaction Study [5]

The infrared (IR) spectra were recorded using an FTIR spectrophotometer (Perkin Elmer Spectrum GX) by the KBr pellet method in the wavelength region between 4000 and 400 cm^{-1}. The spectra obtained for Lisinopril and physical mixtures of Lisinopril with polymers were compared to check compatibility of drug with polymers [6].

Angle of repose [6]

The angle of repose a powder blend was determined by funnel method. The accurately weighed powder blend was taken into the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched to the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using formula [7].

$$\mathbf{Tan\ \theta = \frac{h}{R}}$$

Table1: Comparison between angle of repose and flow property

Angle of repose (θ)	Flow
< 25	Excellent
25- 30	Good
30- 40	Moderate
>40	Poor

Bulk density [6]

Both bulk density and tapped density were determined. a quantity of 2 gm of powder blend from each formula, previously shaken to break agglomerates formed, was introduced in to 10 ml measuring cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued

until no further change in volume was noted. Bulk density and tapped density were calculated by using following equation [8].

$$\text{Bulk density} = \frac{\text{Weight of the powder blend}}{\text{Untapped volume of the packing}}$$

$$\text{Tapped density} = \frac{\text{Weight of the powder blend}}{\text{Tapped volume of the packing}}$$

Hausner's ratio

It indicates the flow property, measured by the ratio of tapped density to the bulk density.

Table 2: Hausner's ratio

Hausner's ratio	Property
0 - 1.2	Free flowing
1.2- 1.6	Cohesive powder

Development of Sublingual Tablets of Lisinopril

Lisinopril, polymers like HPMC, **NaCMC**, PVP, PVA, Na Alginate, and lubricants like magnesium stearate, lactose, sodium saccharine were added by blending and sieve the drug and polymers mixture to get uniform and homogeneous mixture. Tablets were prepared by direct compression using 4mm diameter punch at 4-5kg/cm^2 pressure.

Table 3: Formulation of Sublingual Tablets of Lisinopril

	L1	L2	L3	L4	L5
Lisinopril	10mg	10mg	10mg	10mg	10mg
HPMC	50mg				
NaCMC		50mg			
PVP			50mg		
PVA				50mg	
Na Alginate					50mg
Lactose	5mg	5mg	5mg	5mg	5mg
Mg Stearate	3mg	3mg	3mg	3mg	3mg
Talc	2mg	2mg	2mg	2mg	2mg
Sodium saccharine	30mg	30mg	30mg	30mg	30mg

Evaluation of Formulated Sublingual Tablets of Lisinopril [7]

The evaluations of physicochemical parameters of Lisinopril sublingual tablets were done as per standard procedures .The following parameters were evaluation**.**

Hardness

The test was done as per the standard methods. The hardness of three randomly selected tablets from each formulation (F1 to F4) was determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying pressure until the tablet broke down into two parts completely and the reading on the scale was noted down in Kg/cm^2.

Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using vernier calipers (Pico India). The average values were calculated.

Uniformity of Weight

Weight variation test was done as per standard procedure. Ten tablets from each formulation (F1 to F4) were weighed using an electronic balance and the average weight was calculated..

Friability

The friability of tablets using 10 tablets as a sample was measured using a Roche Friabilator. Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were taken out, dedusted and reweighted. The percentage friability was calculated from the loss in weight as given in equation below. The weight loss should not more than 1%.

$$\textbf{\%Friability} = \frac{(\text{initial weight- final weight}) \times 100}{(\text{initial weight})}$$

Drug Content

Ten randomly selected tablets from each formulation (L1 to L5) were finely powdered and powder equivalent to 4 mg of Lisinopril was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of simulated saliva. The flasks were shaken to mix the contents thoroughly. The volume was made up to the mark with simulated saliva and filtered. One ml of the filtrate was suitably diluted and Lisinopril content was estimated at 218 nm using a double beam UV-visible spectrophotometer. This procedure was repeated thrice.

Wetting Time

The tablet was placed at the centre of two layers of absorbent paper fitted into a dish .After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish Containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

$$\textbf{R = Wa –Wb/Wa×100}$$

Where, Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption

Dissolution study of sublingual tablets of Lisinopril

100 ml of simulated saliva was prepared and taken in a 250 ml beaker and the Fast dissolving Lisinopril sublingual tablet is placed in it. Cellophane tape was used as backing membrane to the sublingual tablet to release the drug from single side of the tablet. The beaker was placed on magnetic stirrer. The program is set to the temperature at 37°C and the rpm at 50. The dissolution process is started and the samples of 2 mL were collected at regular interval of time period that is 1,2,3,4 and 5min, the dilutions were made. The dilutions absorbance has checked at the 220nm, by using simulated saliva as blank.

Release kinetics

Data obtained from invitro drug release studies was evaluated to check the goodness of fit to various kinetic equations or quantifying the phenomena controlling the release from the tablets. The kinetic models used were zero order, first order, higuchi and kosmeyer- peppas model. The

goodness of fit was evaluated using the correlation coefficient values (R^2).

Zero order: It describes the system in which the drug release rate is independent of its concentration.

$Q_t = Q_0 + K_0 t$

Q_t= the amount of drug dissolved in time t,

Q_0= initial amount of drug in the solution (0)

K_0= zero order release constant

If the zero order drug release kinetic is obeyed, then a plot of Q_t versus t will give a straight line with a slope K_0 and intercept at zero.

First order: It describes the drug release from the system in which the release rate is concentration dependent.

$\text{Log } Q_t = \log Q_0 + K_t / 2.303$

Q_t= the amount of drug dissolved in time t,

Q_0= initial amount of drug in the solution (0)

K= first order release constant

If the first order drug release kinetic is obeyed, then a plot of log (Q_t-Q_0) versus t will be straight line with a slope of K_t/ 2.303 and an intercept at t= 0 of log Q_0

Higuchi model:

It describes the fraction of drug release from a matrix is proportional to square root of time

$M_t / M_\infty = Kt^{1/2}$

M_t and M_∞ are cumulative amount of drug release at time t, and

K = higuchi diffusion constant reflection formulation characteristics.

If the higuchi model of drug release (i.e Fickian diffusion) is obeyed, then a plot of M_t / M_∞ versus $t^{1/2}$ will be straight line with slope of K.

Kosmeyer- peppas model (Power law)

The power law describes the drug release from the polymeric system in which release deviates from fickian diffusion as expressed in following equation

$M_t / M_\infty = Kt^n$

$\text{Log } (M_t / M_\infty) = \log K + n \log t$

Where

M_t and M_∞ are cumulative amount of drug release at time t, and infinite time

K = constant incorporating structural and geometrical characteristics of CR device.

n= diffusion release exponent indicative of the mechanism of drug release for drug dissolution.

To characterize the release mechanism

The dissolution data ($M_t / M_\infty < 0.6$) are evaluated.

3. Result and Discussion

Preformulation studies

Melting Point:

Melting point of lisinopril was determined by capillary tube method and it was found to be 146ºC (*n* = 3). This value is same as that of the literature citation.

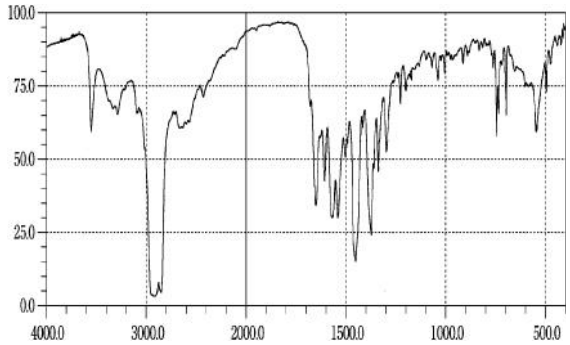

Figure 1: Drug – Excepients Compatibility Studies

The infrared spectroscopy studies were carried out for pure drug and along with polymers and there was no incompatibilty found

.

Table 4: Bulk density, tap density, angle of repose , hausner's ratio and angle of repose for L1 to L5

Formulation code	Bulk density g/cm^3	Tap density g/cm^3	Hauner's ratio	Angle of repose
L1	0.524	0.730	1.185	25.12±0.594
L2	0.792	0.721	1.070	24.99±0.613
L3	0.412	0.742	1.200	25.06±0.232
L4	0.698	0.747	1.060	25.23±0.690
L5	0.611	0.821	1.127	24.65±0.481

Bulk density was in the range between 0.412 to 0.792 g/cm^3, tap density was in the range between 0.721 to 0.821 g/cm^3, hausner's ratio were between 1.060 to 1.2.

Table 5: Hardness and Friability, Weight uniformity of L1 to L5

Formulation Code	Hardness (kg/cm^2)*	Friability*(%)	Weights (mg)
L1	2.5	0.25	100.2±1.003
L2	2.4	0.24	100±0.224
L3	2.5	0.24	100. 01±0.438
L4	4.1	0.25	100±0.294
L5	3.5	0.24	100. 9±0.708

Dropping the tablets through a distance of six inches with each revolution after that tablet was weighed and the percentage loss in tablets weight was determined in the range between 0.23- 0.25% according to procedure. The hardness of the tablet of each formulation was measured by Pfizer hardness tester the average range is in between 2.1-

7.4 kg/cm^2. The weight uniformity test has been carried out by using the digital weighing balance and all the formulations are showing the uniformity weight in the range from 24-26 mg.

Swelling studies:

Formulated tablets were weighed individually and placed separately in petridish containing 50ml of 0.1N HCl. The petridishes were placed in an incubator maintained at 37±0.5˚c. At regular 1hr time intervals until 4hrs the tablets were removed from the petridishes re-weighed (wt) and the % swelling index was in the range between 65- 105%. The optimized formulation L3 showed the maximum swelling index of 105%.

Table 6: Swelling studies for L1 to L5

Time (min)	Swelling(%)				
	L1	L2	L3	L4	L5
0	0	0	0	0	0
1	35	35	42	20	25
2	45	42	52	27	34
3	55	53	70	35	40
4	75	67	88	57	60
5	81	72	96	82	79

Drug content analysis:

The lisinopril tablets contain not less than 90% and not more than 110%. The optimized formlation L3 showed 98.167%.

Table 7: Percentage Drug Content of All the Formulations

Formulation Code	% Drug Content*
L1	92.57 ± 0.2078
L2	95.198 ± 0.2273
L3	98.167 ± 0.2044
L4	94.73 ± 0.1868
L5	91.770 ± 0.1889

***In- vitro* dissolution study:**

The *in vitro* dissolution studies are predictive. 100 mL of simulated saliva was prepared and taken in a 250 mL beaker and the Fast dissolving Lisinopril sublingual tablet is placed in it. Cellophane tape was used as backing membrane to the sublingual tablet to release the drug from single side of the film. The beaker was placed on magnetic stirrer. The program is set to the temperature at 37˚C and the rpm at 50. The dissolution process is started and the samples of 2 mL were collected at regular interval of time period that is 10, 15, 20, 25 and 30 min, the dilutions were made. The dilutions absorbance has checked at the 218nm, by using simulated saliva as blank and further calculations were done.

Table 8: *In-Vitro* % Drug release of Lisinopril in Formulations L1-L5

Time (min)	L1 % CDR	L2 % CDR	L3 % CDR	L4 % CDR	L5 % CDR
0	0	0	0	0	0
1	21.617	18.95	40.29	21.25	14.55
2	40.666	27.22	53.2	39.04	21.39
3	56.81	40.97	68.32	55.96	37.96
4	82.91	54.09	86.13	70.6	44.26
5	91.78	81.77	99.19	88.24	78.33

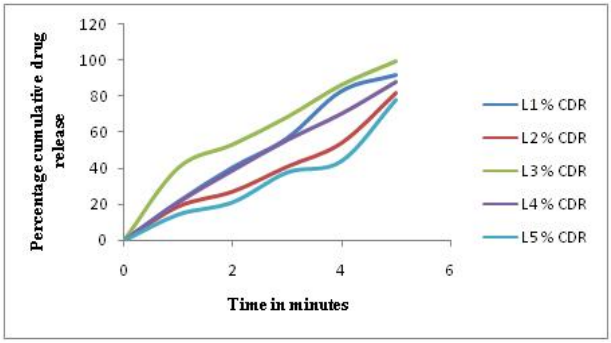

Figure 2: *In-Vitro* % Drug release of Lisinopril in Formulations L1-L5

The correlation coefficients of the formulation describes the formulation F5 following the anomolous non fickians zero order release kinetics.

Table 9: Correlation coefficients of different mathematical models for formulation F5

Formulation code	Zero- order		Higuchi model		Korsmeyer - peppas		First order	
	R^2	K_O	R^2	intercept	R^2	n	R^2	K_1
L3	**0.963**	**5.328**	**0.923**	**-12.796**	**0.9748**	**0.1660**	**0.927**	**2.074**

4. Conclusion

From the present study, the following conclusions can be drawn In the present study, an attempt was made to deliver lisinopril through buccal route in the form of fast dissolving sublingual tablets. Different formulations were prepared by using the Carbopol-934, Hydroxy propyl methyl cellulose K4M (HPMC), Poly vinyl pyrrolidine, Poly vinyl alcohol, Sodium carboxy methyl cellulose as mucoadhesive polymers by direct compression method. The preformulation parameters were studied like drug- polymer interaction and the melting point, etc. there was no interaction between the Lisinopril and the polymers was found by the preformulation studies. Sodium saccharine was used to mask the taste of a tablet to increase the patient compliance. Swelling studies were studied for 4 min and the results were found after 4^{th} minute in the range between 81-90% of swelling index.

The results indicate that the process employed to preparetablets in this study was capable of producing tablets with uniform drug content and minimal film variability.The formulation L3 shown the better result among all 5 formulations in drug dissolution study by sing simulated saliva as the dissolution medium. The maximum of drug release after 5 minutes was fond to be 99.197%. And following zero order release kinetics. The work is concluded that the fast dissolving sublingual tablets of Lisinopril were formulated successfully and the evaluation parameters have proved that Lisinopril was shown the maximum drug release in 5 min.

5. References

1. Surender Verma, Mahima Kaul, Aruna Rawat and Sapna Saini, An overview on buccal drug delivery system, *International journal of pharmacy & life sciences*, **2011**, 2(6).
2. Anay R. Patel, Dhagash A. Patel and Sharad V. Chaudhry, Mucoadhesive buccal drug delivery system, *International journal of pharmacy & life sciences*, **2011**, 2(6).
3. Pankil A. Gandhi, Dr. M.R.Patel, Dr. K.R. Patel, Dr. N. M. Patel, A review article on mucoadhesive buccal drug delivery system, *International Journal of Pharma Research and Development*, **2011**, 3(5): 159-173.
4. Harshad G. Parmar, Janak J. Jain, Tarun K. Patel, Vishnu M. Patel, B*uccal patch: A technical note*, 2010, 4(3).
5. David Harris, and Joseph R. Robinson, drug delivery via the mucus membranes of the oral cavity, *journal of pharmaceutical sciences*, **1992**, vol. 81.
6. Prasanth Vasantha Viswanadhan, Anand Padole, Buccal tablets of lisinopril by direct compression method for buccal drug delivery, *Intl. R. J. of Pharmaceuticals*, **2012**, Vol. 02(2): 30-38
7. Dipti S. Maheshwari, Pankaj H. Prajapati, C. N. Patel, Formulation and evaluation of sublingual dosage form of lercanidipine hcl, ijprbs, **2014**, 3(2): 990-1008.