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Development and characterization of sublingual tablet of Lisinopril

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ABSTRACT

Objective: Lisinopril is the drug of choice in hypertension. Bioavailability of the drug is 25% of orally administered dose. An attempt was made to provide safe medicine meeting pharmacokinetics requirement of plasma concentration by formulating a sublingual tablet of Lisinopril. The Objective of present study is to develop the sublingual tablet of Lisinopril and improve its bioavailability, in view to maximize therapeutic effect of the drug. **Method:** The directly compressed tablet of Lisinopril was formulated using Mannitol, Micro Crystalline Cellulose and Kyron T-314 as super disintegrant. Formulation (F1-F7) was evaluated for disintegration time and *in vitro* release study. Further the optimized sublingual formulation (F6) and marketed formulation was subjected to *in-vivo* comparative bioavailability study using white New Zealand rabbits. **Results:** It was observed that concentration of Micro Crystalline Cellulose, Kyron T-314 has significant effect on the disintegration time of Lisinopril sublingual tablet formulations. The super disintegrant concentration 5% w/w (Kyron T-314) was found optimum in all tablet formulations. AUC of optimized sublingual tablet and oral tablet are 925.35 μg×h/mL and 641.97 μg×h/mL with Cmax of 60.80 μg/mL and 41.21 μg/mL and Tmax of 4 h and 4 h respectively. The bioavailability of optimized sublingual tablet of Lisinopril was improved by 1.44 times as compared to conventional oral marketed tablet of Lisinopril. **Conclusions:** The present approach of formulating sublingual tablet of Lisinopril would definitely improve bioavailability leading to reduced conventional dose of this drug. The administration of sublingual tablet becoming easy and it will improve patient compliance to therapy for hypertension for pediatrics, geriatric and bed ridden patient.

1. Introduction

The role of drug delivery today is to select a therapeutically effective molecule with sub-optimal physicochemical and physiological properties and to develop an optimized product that will still be therapeutically effective but with added benefits. This is accomplished using the concepts of bioavailability enhancement and immediate release for predetermined period of time. The term drug delivery can be defined as techniques that are used to deliver the therapeutic agents inside the human body [1].

Sublingual drug delivery systems have been introduced to overcome the drawback of low bioavailability problems associated with conventional oral dosage forms. Therapeutically active molecules for the treatment and prevention of new and existing diseases are currently being developed. Although pharmacological activity is the primary requirement for a molecule to be used as a therapeutic agent, it is equally important that the molecule reaches its site of action, and hence drug delivery technologies have assumed importance. Nevertheless, many existing and new molecules provide challenges of poor pharmacokinetics leading to low bioavailability. Drug delivery systems such as sublingual dosage forms are used to overcome these challenges. Although the cost of these drug delivery technologies is considerably low and substantially less than the cost of developing a new molecule. Hence, a continued interest exists in developing novel drug delivery systems for the delivery of active agents [2]. In hypertension there is increase in blood pressure which may lead to sudden heart attack. Lisinopril is the drug of choice in hypertension. Oral

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administration of Lisinopril is associated with bioavailability problem.

Bioavailability of the drug is 25% of orally administered dose [7, 10, 12].Mucosa of a sublingual cavity is relatively permeable with rich blood supply, also sublingual drug delivery avoids pre systemic elimination of drug in GI Tract make this portal of drug administration quite attractive and feasible site for systemic delivery of drugs. So, the aim of present work was to develop and characterize sublingual tablet of Lisinopril with improved bioavailability.

2. Methods and materials

2.1 Materials

Lisinopril was received as gift sample from Linchon pharmaceuticals, Ahmadabad, India. β -cyclodextrin, Mannitol, Microcrystalline cellulose were received from Sun Pharmaceuticals, Baroda, India. Aerosil and KyronT-314 were received from Coral Pharma. Pvt. Ltd. Mumbai, India. All other reagents and chemical used of analytical grade.

2.2 Methods

2.2.1 Preparation of Sublingual Tablets

Tablets containing 10 mg of Lisinopril were prepared by direct compression method. The taste masking of drug was done by forming complex with beta-cyclodextrin. Initially, 1:4 ratio of Drug: beta cyclodextrin was taken. Slurry of beta-cyclodextrin was prepared by taking β -cyclodextrin: water (5 gm: 5 mL), stirred for 30 min and then kept overnight at room temperature to evaporate the water to get completely dried complex. After that all the ingredients were mixed in geometrical order. Lubricated with Aerosil by tumbling for 10 minutes and addition of talc was done. Thus blend obtained was directly compressed using 6 mm flat round punches in to tablets of 120 mg on 8-station rotary compression machine (Hardik Engineering Mini Press).

2.2.2 Pre-compressional Evaluation of Tablets

The powder blends of tablets from different formulation (F1 to F7) were subjected to pre-formulations studies (Infrared spectroscopic analysis, Differential thermal analysis, Bulk density, Angle of Repose and Percent compressibility *etc.*).

2.2.3 Post-compressional Evaluation of Tablets

The formulations (F1 to F7) were subjected to post-compressional evaluation such as friability (Roche Friabilator) [14, 16], Disintegration test (Indosati scientific lab.,Disintegration apparatus) [14], Hardness (Monsanto hardness tester), Weight variation (electronic digital balance, ML-300Satarions), Content uniformity [55] and Thickness (Verniear calipers, Himezer) *etc.*

2.2.3.1 Wetting Time

A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 mL of phosphate buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined. The wetted tablet was then weighed [14].

2.2.3.2 In-vitro Drug Release Profile

The in-vitro dissolution study was performed on modified USP dissolution test apparatus (Electro-lab Dissolution tester USP, TDT-06T) type II (paddle). 300 mL of the dissolution medium (simulated saliva pH 6.8) was taken in covered vessel and the temperature was maintained (37±0.5) ℃. The speed of the paddle was set at 100 rpm. Sampling was done at 5, 10, 15, 20, 20 and 30 min interval. For each sample 5 mL of the dissolution medium was withdrawn and the same amount of dissolution medium pre-warmed at 37℃ was replaced to the dissolution medium. The sample withdrawn was filtered with Whatmann filter paper and diluted with simulated saliva pH 6.8 prior to analyze in the UV spectrophotometer (Shimadzu-1800, Japan). The absorbance was measured at 211 nm and the cumulative Percentage release was calculated.

2.2.3.3 Kinetic Modeling of Dissolution Data

To study the mechanism of drug release from the mouth dissolving tablet, the *in vitro* drug release data were fitted to various kinetic models like zero-order, First order, Hixson Crowell and Weibull equation and coefficient of correlation (r) values were calculated for linear curves by regression analysis of the above plot. These models used to explain drug release mechanism along with gradual erosion of the tablet [54]

3.3 In-vivo bioavailability Study

3.3.1 Calculation for Drug Doses for Laboratory Animals

Calculation was carried out for appropriate drug doses given per animal's weight, the prescribed dosage of the drug(s) to be used, and recommended dose of drug given. Food and Drug Administration has suggested that the extrapolation of animal dose to human dose is correctly performed only through normalization to BSA, which often is represented in mg/m^2. The human dose equivalent can be more appropriately calculated by using the formula [3,11,31,55].

$$\text{HED (mg/kg)} = \frac{\text{Animal dose (mg/kg)} \times \text{Animal km}}{\text{Human km}}$$

$$\text{Animal dose} = \frac{\text{Human dose} \times \text{Animal weight}}{\text{Human weight}}$$

$$= 10 \times 3 \text{ kg}/60 \text{ kg}$$
$$= 0.5 \text{ mg/kg approx}$$

3.3.2 Sublingual Tablet Administration in Rabbit

In-vivo bioavailability study was carried out in New-Zealand white rabbits. Groups for studies were divided as test (No of animals = 3, Sublingual route) and standard (No of animals = 3, oral route). 0.5 mg/kg of Lisinopril dose was given to each. For sublingual tablet administration, the rabbit's mouth was opened, and a forceps was inserted between the jaws. The tongue was elevated by using flat forceps, and the tablet was placed underneath by using another pair of forceps. The mouth was gently but firmly held shut for 5 minutes to prevent chewing or swallowing the tablet. Water 0.3 to 0.5 mL was administered immediately after dosing to facilitate tablet disintegration. Additional 0.7 to 0.5 mL water was administered at the end of the 5-min immobilization time to remove any remaining drug from under the tongue [8, 35].

3.3.3 Blood Withdrawal From The Rabbit

The area of blood withdrawal was cleaned with alcohol. In order to better visualize veins, one of several methods of dilation was used [8]. The marginal ear vein was distended by flicking margin with the finger few times. The needle was inserted parallel to the vein and the tip directed into the lumen along the longitudinal axis. Marginal ear vein of the rabbit was used for collection of blood collection was fairly simple at this site. The area was shaved and cleaned with alcohol. The vein was occluded, the needle carefully inserted, and blood slowly withdrawn. A butterfly set used to avoid damage to the vessel if the animal moves. Gauze held with pressure over the veinpuncture site for a few minutes to prevent hematomas from forming.

3.3.4 Blood Sample Collection and Processing

New Zealand rabbits (2.0-3.0 kg) had free access normal standard chow diet and tap water. Animals were fasted for 24 h prior to the experiments and were given water freely. The protocol the experiments was approved by the institutional animal ethical committee as per guidance of the committee for the purpose of control and supervision of experiments on animals.(SU/DPS/IAEC/10018) In the present study, rabbits (n = 3 per each treatment) were given orally as well as sublingually tablet 0.5 mg/kg of Lisinopril. Blood samples were withdrawn from the marginal ear vein according to a predetermined time schedule at 0, 0.5, 1.0, 2.0, 4.0, 8.0 and 16 hours and collected in Lithium heparin containing tubes. Blood samples were centrifuged at 12000 rpm for 10 min (Remi, Cooling centrifuge). And the plasma was removed and processed for extraction [55].

3.3.5 Extraction procedure for drug from blood plasma

0.15 mL of the spiked plasma in the eppendroff tube was taken.800 μl of methanol in the same eppendroff tube was added and vortexed the samples thoroughly for 2 min.

The samples were put in to centrifuge at 16000 rpm for 10 min. at 4 °C. (Remi, Centrifuge) The supernant was transferred in to another per labeled eppendroff tube. 20 μl of the sample was injected into HPLC system (Shimadzu, HPLC system) at the detection wavelength of 215 nm. [55].

3.3.6 Solution and Sample Preparation

3.3.6.a Mobile Phase Buffer Solution (phosphate buffer)

Phosphate solution: 4.1 g of monobasic potassium phosphate was dissolved in 900 mL of bi-distilled water in a 1000 mL volumetric flask. This solution was adjusted with phosphoric acid to pH = 2.0. The Phosphate solution was diluted with distilled water to volume and was mixed. Before using, the mobile phase was filtered through membrane filter with a pore size 0.20 μ.

Mobile Phase: 1.0 g of sodium 1-hexanesulfonate was dissolved in 800 mL of Phosphate solution. To the obtained solution was added 200 mL of acetonitrile. The mobile phase was mixed and filtered.

3.3.6.b Drug Stock Solution

Accurately weighed 10 mg of Lisinopril was transferred in to 10 mL volumetric flask and dissolved in 5 mL of water and diluted with water up to mark to give stock solution having a strength 1 mg/mL. Appropriate dilution of stock solution was made with distilled water to obtain working solutions from 0.3- 200 μg/mL of Lisinopril by serial dilution method.

3.3.6.c Chromatographic Condition

0.125% solution of sodium 1-hexanesulfonate in Phosphate solution (pH = 2): acetonitrile = 800 : 200 was used as a mobile phase at a flow rate of 1.5 mL/min. Column temperature was set at 40 °C

3.3.7 Preparation of Calibration Curve

From the drug stock solution of 200 μg/mL serial dilution made to prepare concentration range of 0.3- 200 μg/mL. 20 μl of each solution were injected in to HPLC system and analyzed. Calibration curve was obtained by plotting respective peak area ratio against concentration.

3.3.8 Pharmacokinetics and Statistical Analysis

Pharmacokinetics and statistical analysis for plasma concentration Vs Time profile of Lisinopril was performed on the data obtained from (Rabbit) [10, 11].

3.3.9 Pharmacokinetic Parameters

Pharmacokinetic parameters Tmax and Cmax were calculated using plasma concentration Vs time profile (Actual time of sample collection) data of Lisinopril in individual animal using statistical software. The area under the plasma concentration verses time curve from zero time to the last experiment point, (AUC0-24h) was calculated by trapezoidal method.

3.3.10 Trapezoidal Rule

The plasma concentration versus time plot was divided into geometric figures whose area can be determined individually using appropriate geometric formula for each figure. The area under the curve of plasma concentration time graph is obtained by adding the area of each segment represented by the geometric figure. This plot yields one triangle and remaining trapezoids. The following relationship was used to calculate area of each geometric Figure.

$AUC = \frac{1}{2}(t_2 - t_1) \times (c_1+c_2) + \ldots\ldots\ldots\ldots n$
Area of triangle = (0.5) (height) (base)
Area of trapezoid = (0.5) (height) (sum of two parallel sides)
AUC = Area of triangle + Area of trapezoid

$$\textit{Relative bioavailability} = \frac{\text{AUC sublingual}}{\text{AUC oral}} \times \frac{\text{Dose oral}}{\text{Dose sublingual}}$$

$$\textit{Relative bioavailability} = (925.35 / 641.97) \times 10/10$$
$$= 1.44142$$
$$= 144.142\%$$

3.3.11 Stability Study

The accelerated stability study was carried out at 40℃and 75% RH. The sublingual tablets were packed in suitable packaging and stored in stability chamber for maintaining 75% RH and temperature maintained at 40°C (Sun instrument. Pvt. Ltd., Stability chamber).The tablets were withdrawn after a period of 30 days and analyzed for physical characterization (Visual defects, Hardness, Friability, disintegrations, and dissolution *etc.*) and drug content.

4. Results

Various ingredients used in formulation are shown in Table 1. Directly compressible ingredients were use for formulation of sublingual tablets.

4.1 precompressional parameters

The results of precompressional parameters are cited in Table 2 which are in between their optimum range and passes the norm accordingly.

4.2 Compatibility Studies

The drug-excipient compatibility studies were conducted in the preformulation phase by FTIR spectroscopy (Nicolet IS10, Thermo scientific, FTIR) and DTA (Stept-1600 Linseis, Germany, DSC/DTA/TGA) the results are presented in Figure 1, 2 and 3. The results indicate that they were no chemical incompatibility between drug-excipient.

4.3 Hardness

The average hardness of tablets was found to be 3.4 to 4 kg/cm^2. The average thickness of tablets (F1 to F7) determined and results are presented in Table 3.

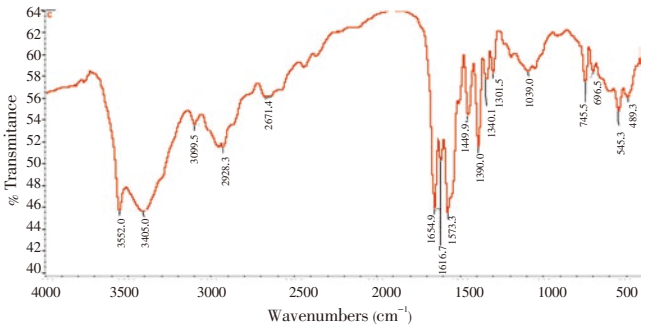


Figure 1: FTIR Spectrum of Lisinopril

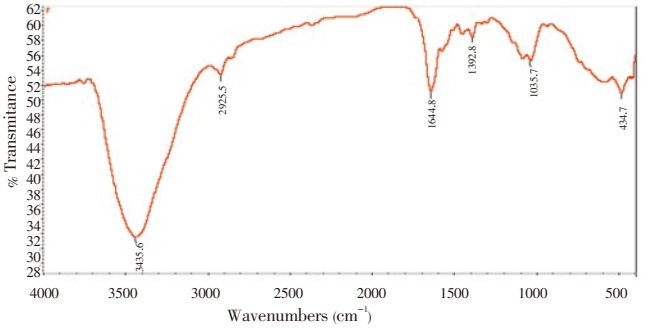


Figure 2: FTIR Spectrum of Lisinopril and Excipients (Formulation Mixture)

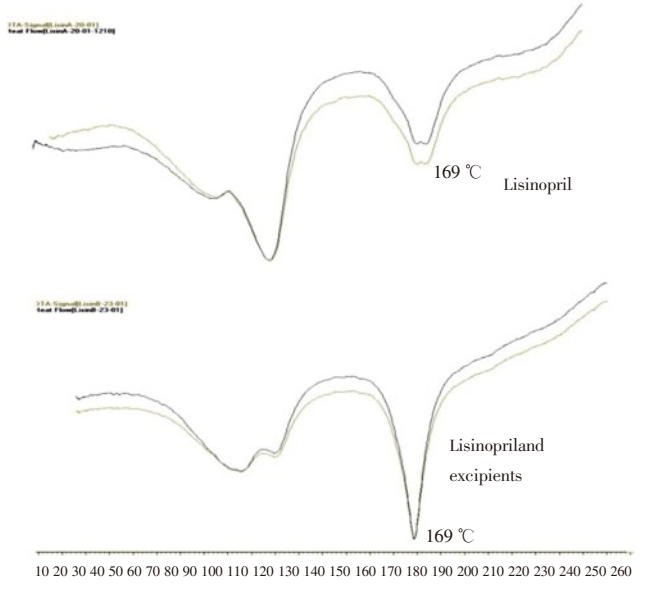


Figure 3: DTA Thermo Grams of a) Lisinopril and b) Physical Mixture of Lisinopril and Excipients

4.4 Thickness

The maximum and minimum average thickness of tablet

Table 1
Formulation of Lisinopril Sublingual Tablets

Ingredients	Formulation Code (Quantity in mg/Tablet)						
	F1	F2	F3	F4	F5	F6	F7
Lisinoipril	10	10	10	10	10	10	10
β – cyclo dextrin	40	40	40	40	40	40	40
Microcrystalline cellulose	18	15	12	–	–	–	15
Kyron T-314	–	–	–	1.2	3	6	6
Mannitol	45.5	48.5	51.5	62.3	60.5	57.5	42.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Aerosil	4	4	4	4	4	4	4
Total weight	120 mg/tablet						

Table 2
Pre compressional Parameters for Preliminary Batches With β-Cyclodextrin

Formulation	Angle of repose*	Bulk density*(gm/mL)	Tape density*(gm/mL)	Hausner's ratio*	Carr's index*(%)
F1	27.67±0.26	0.429±0.14	0.546±0.00	1.272±0.05	23.93±0.92
F2	24.19±0.52	0.547±0.03	0.624±0.04	1.140±0.04	12.33±0.84
F3	24.70±0.18	0.462±0.05	0.591±0.02	1.279±0.02	21.82±1.37
F4	24.70±0.48	0.519±0.04	0.683±0.07	1.315±0.07	13.46±1.42
F5	22.67±0.38	0.395±0.08	0.475±0.10	1.202±0.06	20.25±0.84
F6	21.12±0.38	0.409±0.77	0.531±0.04	1.298±0.10	22.97±1.79
F7	23.98±0.60	0.549±0.04	0.626±0.04	1.140±0.08	12.30±1.34

Note: The values are mean value of 3 observations (*N*=3) and values in parenthesis are standard deviation (±SD)

Table 3
Post-compressional parameters

Formulation	Hardness(kg/cm^2)	Diameter (mm)	Thickness (mm)	Uniformity of weight (mg)	Friability (%)	D.T. in sec
F1	3.4±0.68	6.16±0.05	3.4±0.023	122.5±1.49	0.667±0.19	141±0.05
F2	3.5±0.54	6.63±0.13	3.2±0.061	118.2±1.46	0.457±0.05	84±0.09
F3	4.1±0.26	6.13±0.20	3.4±0.091	119.6±2.41	0.372±0.02	106±0.11
F4	4.0±0.59	6.03±0.05	3.6±0.023	126.5±3.02	0.626±0.05	46±0.06
F5	3.9±0.89	6.18±0.01	3.4±0.033	119.4±1.26	0.539±1.0	33.5±0.06
F6	3.5±0.36	6..22±0.13	3.5±0.084	120.1±1.16	0.458±0.06	32.7±0.07
F7	4.5±0.77	6.14±0.06	3.4±0.064	121.4±1.64	0.869±0.03	42.5±0.13

Note: The values are mean value of observations (N) and values in parenthesis are standard deviation (±SD)

was found to 3.6 mm and 3.2 mm respectively as presented in Table 3.

4.5 Wetting time

In the formulation (F1-F7) wetting time was decreased with increase in the concentration of super disintigrants. In present study wetting time was decreased from (67 sec to 19 sec) presented in Table 4 and Figure 4.

Table 4
Wetting time and in-vitro Drug Content of Formulation

Formulation	Wetting time(sec)	Drug content (%)
F1	43±1.11	102.44±1.26
F2	51±1.42	101.07±1.14
F3	67±2.21	99.81±2.06
F4	39±0.84	97.89±1.69
F5	27±1.19	98.76±1.08
F6	19±0.79	100.21±1.17
F7	28±1.54	101.35±2.34

Note: The values are mean value of 3 observations (N=3) and values in parenthesis are standard deviation (±SD)

Table 5

In-vitro Drug Release Profile of Formulation F1-F7.

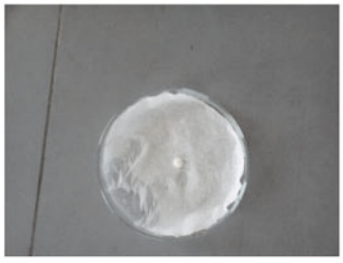
Time in h	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
5	38.15±2.89	38.9±2.48	38.23±3.48	39.66±1.27	39.65±1.27	41.01±2.78	38.01±3.99
10	68.77±6.07	61.68±1.11	58.69±5.03	55.09±1.97	61.11±1.97	59.64±1.09	59.15±3.58
15	86.92±2.19	85.81±1.92	87.60±2.47	86.45±3.09	86.09±3.09	92.64±4.39	86.78±3.77
20	95.84±0.62	95.65±1.16	96.60±1.21	95.65±1.39	94.82±1.36	98.55±0.80	95.87±0.61
25	99.39±0.26	98.02±1.27	98.87±0.56	97.45±0.70	97.64±0.70	99.87±0.32	98.43±1.70

Note: The values are mean value of 6 observations (*N*=6) and values in parenthesis are standard deviation (±SD)

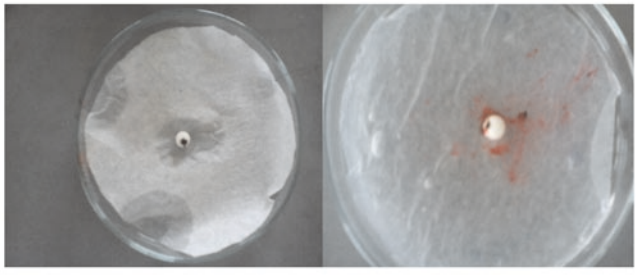
Table 6

Kinetic Modeling of Dissolution Data

Formulation	Zero order	First order	Higuchi	HixsonCrowell	Weibull	
	R^2	R^2	R^2	R^2	R^2	T_{di}(63.2%)
F1	0.827	0.942	0.972	0.944	0.989	8.28
F2	0.908	0.981	0.9858	0.991	0.984	8.12
F3	0.914	0.940	0.975	0.987	0.972	8.26
F4	0.912	0.964	0.972	0.975	0.953	7.96
F5	0.908	0.903	0.925	0.973	0.858	7.96
F6	0.895	0.923	0.968	0.913	0.954	7.70
F7	0.914	0.957	0.976	0.977	0.888	8.31



Before wetting



After wetting

Figure 4: Change in Appearance of tablet after wetting

4.6 Drug Content

The maximum percentage of drug content from the different formulations was found to be 102% and minimum percentage of drug content was found to be 97.89% which are presented in Table 4. Hence it is concluded that all the formulations are falling within the pharmacopoeial limits.

4.7 Drug Release

The drug release pattern was studied for all formulations (F1 to F7) following standard procedure and the results are provided in Table 5. The drug release pattern of sublingual tablets varied according the amount of super disintegrant added. From in-vitro cumulative drug release profile of formulations it was concluded that by increasing the concentration of MCC in the formulations (F1 to F3), the drug release rate from the tablet was found to be increased and when the concentration of Kyron T-314 increased. This may be attributed to increased hydration followed by increased swelling index of super disintegrant with increase in concentration. The overall data on the in-vitro dissolution studies closely indicated that among the seven formulations, the formulation F6 was found to be the best with high

percentage of drug release.

4.8 Kinetic Studies

The release kinetics was for formulation (F1–F7) i.e. zero–order, first order and Higuchi, Hixcon Crowell and Weibull were conducted for all formulations and the data is shown in Table 6. The value of regression correlation co–efficient (R^2) was evaluated for all the formulations which value was close to 0.99. Hence it is conducted that all the formulations are following the zero–order drug release.

4.9 In–vivo Bioavailability Study

Results indicated that sublingual tablet produced plasma concentrations significantly higher than the oral tablet. AUC of optimized sublingual tablet and oral tablet are 925.35 μg×h/mL and 641.97 μg×h/mL with Cmax of 60.80 and 41.21 μg/mL and Tmax of 4 h and 4 h respectively as presented in Table 7. Area under curve for sublingual tablet was greater than the oral tablet as calculated in Table 8 which indicated improved bioavailability of sublingual dosage form compare to oral dosage form. Comparison of plasma concentration time profiles of Lisinopril oral tablet and optimized sublingual tablet is given in Figure 5.

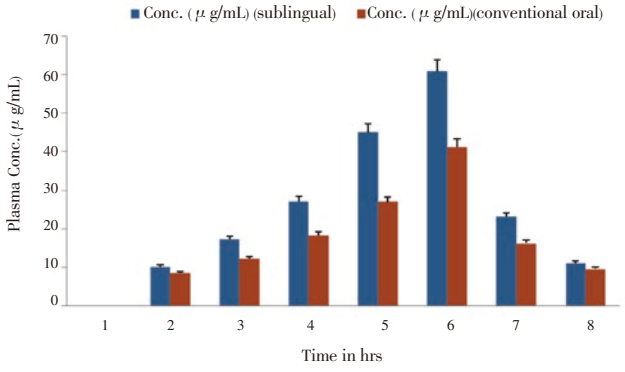


Figure 5: Comparison of Plasma Concentration Time Profiles of Lisinopril Oral Tablet and Optimized Sublingual Tablet.

Table 7

The Plasma Profiles of Lisinopril

Time in hrs.	Conc.(μ g/mL)(sublingual)	Conc.(μ g/mL) (oral)
0	0	0
0.5	10.12±0.165	8.57±0.077
1	17.29±0.051	12.27±0.161
2	27.12±2.084	18.30±0.066
4	44.95±0.652	27.01±0.359
8	60.80±0.325	41.21±0.166
16	23.13±0.296	16.28±3.924
24	11.18±0.347	9.64±0.255

Values are mean±S.E.M., n = 3, Statistical analysis: Student's 't' test (unpaired). ** P< 0.05 (significant)

Table 8

AUC for Plasma Concentration Time Profile of Lisinopril Oral Conventional Tablet and Sublingual Tablet

Parameter		Oral conventional tablet	Sublingual tablet
Segment	Geometric figure	Area (μ g×h/mL)	Area (μ g×h/mL)
A	Triangle	2.41	2.53
B	Trapezoid	5.21	6.85
C	Trapezoid	15.28	22.20
D	Trapezoid	45.31	72.07
E	Trapezoid	136.44	211.50
F	Trapezoid	229.96	335.72
G	Trapezoid	207.36	274.48
TOTAL		641.97	925.35

4.10 Stability Study

The results of accelerated stability study was checked for physical characterization (Visual defects, Hardness, Friability, disintegrations, and dissolution *etc.*) and drug content which indicated that there was not any big difference in the result of different parameters.

5. Discussion

5.1 Compatibility Studies

The results indicate that they were no chemical incompatibility between drug–excipient.

5.2 Hardness and Thickness

Hardness and thickness of the formulations were found to be suitable to formulate sublingual tablet.

5.3 Drug Content

The result of drug content study indicated that all the formulations were falling within the pharmacopoeial limits. (USP/NF – 90% to 110%)

5.4 Drug Release

The overall studies indicated that the Kyron T–314 and MCC in the ratio of 5% and 15% respectively showed satisfactory drug release properties. Among the 7 formulations, the formulation F6 using these Kyron T–314 in the above ratio with drug exhibited significant swelling properties with optimum release profile. Hence it can be concluded that the formulation F6 will be useful for sublingual administration for the treatment of anti–hypertensive.

5.5 Kinetic Studies

The value of regression correlation co-efficient (R^2) was evaluated for all the formulations which value was close to 0.99. Hence it is conducted that all the formulations are following the zero-order drug release.

5.6 In-vivo Bioavailability Study

Results indicated that sublingual tablet produced plasma concentrations significantly higher than the oral tablet. *In-vivo* studies in New Zealand white rabbits showed that bioavailability was improved by 1.44 times compared to conventional oral tablet of Lisinopril. (Listril, Sun Pharmaceuticals)

5.7 Stability Study

From the results of accelerated stability study it was concluded that there was not any big difference in the result of different parameters after one month storage which indicates that the product is safe.

6. Conflict of Interest Statement

We declare that we don't have conflict of interest.

7. Acknowledgement

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References

[1] Tripathi KD. Essentials of medical pharmacology. Jaypeebrother's medical publication (p) limited: New Delhi. 2003.p. 484-95.
[2] Subramanian CVS. Essential of physical pharmacy. Vallabh Prakashan. 2003. p. 308-46.
[3] Mader DR. Basic approach to veterinary care, clinical medicine and surgery. 1997. Philadelphia.p.160-68.
[4] Madan PL. Biopharmaceutics and pharmacokinetics. Jaypee Brothers. 2000. p. 18-24.
[5] Brahmankar DM. Jaiswal BS. Biopharmaceutics and Pharmacokinetics: A treatise. vallabh prakashan. 1997. p. 147-49.
[6] Tortora and grabowski. Principles of anatomy and physiology. vallabh prakashan. 2003.p. 741.
[7] Indian pharmacopoeia. Vol-1.Controller of publications. Ministry of health and family welfare. Government of India. 2007. p. 480.
[8] United States pharmacopoeia. USP 27/ NF22.USP convention vol. 2. Rockville. 2004, p. 2538.
[9] Shargel L. and Y. Applied Biopharmaceutics and Pharmacokinetics. Appletonand Lange.1999. p. 108-109 and 154-63.
[10]Gibaldi M. Biopharmaceutics and Clinical Pharmacokinetics. Lea and Febiger.1984. p. 43-56.
[11]Pandey S, and Goyani M,Formulation and evaluation of taste masked fast disintegrating tablets of Lisinopril.*IntJof PharmTech Res* 2010; **148**:1639-43.
[12]Suresh S, Pandit V, Preparation and evaluation of mouth dissolving tablets of Salbutamol sulphate. *Int J of pharm sci* 2007; **12**: 54-57.
[13]Neha N, J yoti S. Sublingual mucosa as a route for systemic drug delivery. *Int J Pharm Sci* 2010; **147**: 18-22.
[14]Verma P, Thakur AS, Deshmukh K, Routes of drug administration. *Int j pharms res* 2010; **75**: 54-59.
[15]Viswanathan S. Advances in Drug Delivery. *Pharmaceutical formulation quality* 2004; **25**: 20-28.
[16]Kuchekar BS, Atul CB, Mouth dissolving tablet: A novel drug delivery system. *Pharm times* 2003; **25**: 43-47.
[17]Takao M, Yoshinori M, Takeshi Y, Katsuhide T, Formulation design of novel fast disintegrating tablet. *Intl j of pharm* 2005; **45**: 83-90.
[18]Schiermeier S, Christian P, Fast dispersible ibuprofen tablets. *E j pharm sci* 2002; **35:** 295-05.
[19]Malpani A, Panda B, Bhojani R, Formulation of Lisinopril dihydrate tablet and study effect of granulation on response variables. *Int j pharml sci* 2009; **12**: 132-39.
[20]Hadidi N, Shafaghi B, Formulation and optimization of captopril sublingual tablet using D-optimal design, *Ira j pharm res* 2008; **14**: 259-67.
[21]Dali MM, Paul AM, Mathias NR, Smith RL, A Rabbit Model for Sublingual Drug Delivery: Comparison with human pharmacokinetic studies of Propranolol, Verapamil and Captopril. *J PharmSci* 2006; **24**: 37-44.
[22]Rasetti C, Grange V, Pharmacokinetic profiles of two tablet formulations of piroxicam. *Int J Pharm* 2005; **41**: 129-34.
[23]Francisco J, Jorge P, Bioavailability of two sublingual formulations of ketorolac tromethamine 30 mg: a randomized, open-label, single- dose, two-period crossover comparison in healthy mexican adult volunteers. *Clin theraputics* 2008; **11**: 1667-74.
[24]Mutasem Q, Estelle R, Keith J, Sublingual epinephrine tablets versus intramuscular injection of epinephrine: Dose equivalence for potential treatment of anaphylaxis. *J allergy and clin immuno* 2006; **34**:398-403.
[25]Dhaneshwar K, Lokesh R, Avinash T, Yogesh P, A review on oral mucosal drug delivery system. *Int j pharm sci res* 2010; **117**: 50-56.
[26]Gupta A, Mishra K, Gupta V, Recent Trends of fast dissolving tablet-an overview of formulation technology. *Int j pharml bio* 2010; **42**: 1-10.
[27]Nitin M, Adhikrao Y, Vaishali K, Novel Approaches in development of metronidazole orodispersible tablets. *Res j pharm tech* 2009; **44**: 283-86.
[28]Jha K, Geethalakshmi A, Bhatia V, Shukla T, Orally disintegrating tablets-technology for mankind. *J global pharm tech* 2011; **74**: 11-17.
[29]Apeji E, Oyi A, Musa H, Evaluation of the powder and compaction properties of microcrystalline starch (mcs) derived from cassava

(manihotesculentacrantz) starch by enzymatic hydrolysis. *J pharm health care* 2007; **44**: 314-319.

[30]Vijay S, Himanshu C, Role of taste and taste masking of bitter drugs in pharmaceutical industries an over view. *Int jpharm sci* 2010; **74**: 14-18.

[31]Noushin B, Naghmeh H, Seyed M, Bijan S, Development and optimization of a sublingual tablet formulation for physostigmine salicylate. *Acta pharma* 2009; **45**:301-12.

[32]Gohel MC, A review of co-processed directly compressible excipients. *J pharm Sci* 2005; **102**:76-93.

[33]Saptarshi D, Pintu D, Formulation of fast disintegrating tablets. *Intjdrug form &res* 2011; **23**: 45-51.

[34]Jose P, Maria E, Francisco J, Comparative Bioavailability of Ketorolac tromethamine after intramuscular and sublingual administration. Proc. *West pharmacological society* 2002; 6-7.

[35]Arora V, Gupta B, Advances in direct compression technology. Pharma times 2007; 74: 26-27.

[36]Dandagi PM, Gayakwad VM, Taste masked ofloxacin mouth disintegreting tablets. *Indian drugs* 2005; **17**: 52-54.

[37]Pfister W, Ghosh K, Intra oral drug delivery system-an overview, current status and future trends. *Indian drugs* 2005; **18**: 22-35.

[38]Ahmed A, Laila A, Marwan S, Spectrophotometric, spectrofluorymetric and lc determination Lisinopril. *J pharm bio ana* 2001; **15**: 913-22.

[39]Tzvetkova D, Obreshkova D, HPLC analysis of Lisinopril in tablets. *Acta pharma* 2005; **19**: 179-87.

[40]Evanovic D, Medenica M, Validation of an analytical procedure for simultaneous determination of hydrochlorothiazide, Lisinopril, and their impurities. *Acta chromatographica* 2007; **74**: 143-156.

[41]Chauhan E, A validated rp-hplc method for simultaneous estimation of amlodipine and Lisinopril in pharmaceutical dosage form. *Int j pharm sci res* 2011; **56**: 1712-15.

[42]Jamakhandi M, Javali C, Chougule S, Spectrophotometric determination of Lisinopril dosage form by condensation reaction. *Int j pharm sci* 2011; **48**: 185-87.

[43]Bhaskara A, Lakshmana R, Novel validated rp-hplc method for the simultaneous estimation of Lisinopril and amlodipine in bulk and tablet dosage form. *Intj pharm chem and biosci* 2011; **44**: 32-37.

[44]Olcay S, and Lale E, An hplc method for the determination of Lisinopril in human plasma and urine with fluorescence detection. *J of chromatography* 2004; **116**: 159- 65.

[45]Ishikawa T, Koizumi N, Mukai B, Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose and spherical sugar granules. *Chem pharm bull* 2001; **79**: 230-232.

[46]Somnache SN, M. Pharm thesis, Formulation and evaluation of sublingual tablets of an antiemetic drug. Rajiv Gandhi University of health sciences 2011.

[47]Suresh D. Shah.M. Pharm thesis, Formulation and evaluation of sublingual tablet of Sumatriptan succinate. Saurashtra University, 2010.

[48]Hypertension, Federal Bureau of Prisons - Clinical Practice Guidelines, May 2005.