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Formulation and evaluation of sublingual tablets of losartan potassium

Nikunj J. Aghera*, Suresh D. Shah, Kantilal R. Vadalia

Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot–360002, Gujarat, India

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ABSTRACT

Objective: Sublingual tablets of Losartan Potassium were prepared to improve its bioavailability, to avoid pre-systemic metabolism in the gastrointestinal tract and hepatic first pass elimination. **Methods:** The Sublingual tablets were prepared by direct compression procedure using different concentration of Starch 1500 and microcrystalline cellulose. Compatibility studies of drug and polymer were performed by FTIR spectroscopy and DSC. Preformulation property of API was evaluated. Postcompressional parameters such disintegration time, wetting time, water absorption ratio, *in vitro* drug release and *in vivo* bioavailability study of optimized formulation were determined. **Results:** FTIR spectroscopy and DSC study revealed that there was no possible interaction between drug and polymers. The precompression parameters were in acceptable range of pharmacopoeial specification. The disintegration time of optimized formulation (F3) was upto 48 sec. The *in vitro* release of Losartan Potassium was upto 15 min. The percentage relative bioavailability of Losartan Potassium from optimized sublingual tablets was found to be 144.7%. **Conclusions:** Sublingual tablets of Losartan Potassium were successfully prepared with improved bioavailability.

1. Introduction

Development of a formulation involves a great deal of study and experimental work to get optimum results. While doing so we have to keep in mind various factors are considered like choice of excipients, drug bioavailability, drug stability in required dosage form, cost effectiveness, manufacturing aspects *i.e.* scale-up and last but not the least we have to consider the patients compliance and convenience.

Now a day's formulation research is breaking barriers of conventional methods. Today, active ingredients can be delivered with a level of convenience, performance and bioavailability.

First pass metabolism can be overcome by sublingual drug delivery, and quick drug delivery into the systemic circulation can be obtained. Sublingual administration can offer an attractive alternative route of administration. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation bypassing

enzyme degradation in the gut and liver. These formulations are particularly beneficial to pediatric and geriatric patients. In addition sublingual mucosa and abundance of blood supply at the sublingual region allow excellent drug penetration to achieve high plasma drug concentration with rapid onset of an action [1, 2].

Hypertension is defined as a systolic blood pressure of 140 mmHg or greater and / or a diastolic blood pressure of 90 mmHg or greater. Losartan potassium is an angiotensin II receptor antagonist. It suppresses the effects of angiotensin II at its receptors, thereby blocking the rennin angiotensin system. The rennin angiotensin system plays a crucial role in the control of blood pressure, and in particular it is felt to play crucial role in hypertension. Losartan has been demonstrated to be superior to previous peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors because of its enhanced specificity, selectivity, and tolerability. Generally, losartan potassium is employed in the management of essential hypertension with lower incidence of side effects like cough. It is readily absorbed and undergoes rapid hepatic metabolism to an active metabolite, EXP-3174, via cytochrome P-450 system [3].

*Corresponding author: Nikunj J. Aghera Shree H.N.S.I.P.E.R., C/o B.M. Kyada Campus, Nr. LalPari Lake, B/H Marketing Yard, Amargardh – Bichari, Rajkot, 360002 (Gujarat) India.

Contact no: 9586973378

E-mail: nikunjaghera07@yahoo.com

2. Material and methods

2.1 Material

Losartan Potassium (Alembic Pharmaceutical Pvt. Ltd, Baroda), Pearlitol SD 200, Sucrose DC (Nir Life Healthcare Pvt. Ltd., Ahmedabad), Starch 1500 (Mepro Pharmaceutical Pvt. Ltd., Surendranagar), Sucralose (JK Sucralose, Mumbai) the above were the gift sample.

2.2 Methods

2.2.1 Formulation of Tablets

Composition of preliminary trials for Sublingual Tablet of Losartan Potassium by direct compression is shown in table 1. All the ingredients were passed through 80# mesh sieve. Required quantity of drug and excipient mixed thoroughly in a polythene bag. Finally the talc and aerosil was added and mixed thoroughly to get free flowing powder. The blend is compressed using rotary tablet compression machine with 6 mm tooling punch.

2.2.2 Compatibility Study

The pure drug Losartan Potassium and the solid admixture of drug and various excipients used in the preparation of sublingual tablet formulations were characterized by FT–IR spectroscopy and DSC to know the compatibility [4].

2.2.3 Evaluation of Tablets

All the tablets were evaluated for different parameters as, hardness, friability, weight variation, disintegration time, wetting time, water absorption ratio, drug content uniformity, dissolution study, stability study and in vivo study [5].

2.2.4 Hardness

Hardness was measured using the Monsanto hardness tester. Measured the pressure required to break diametrically placed matrix tablet, by a coiled spring.

2.2.5 Friability

20 tablets were weighed and placed in the roche friabilator test apparatus, the tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 evolutions the tablets were de-dusted and weighted again. The friability was determined as the percentage loss in weight of the tablets.

2.2.6 Weight Variation

It was performed as per the method given in the united state pharmacopoeia. Tablets were randomly checked to ensure that uniform weight tablets were being made. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.

2.2.7 Disintegration Time

The disintegration time for sublingual tablets was measured using the conventional test for tablets as described in the

pharmacopoeia. Tablets are placed in the disintegration tubes and time required for complete disintegration, that is without leaving any residues on the screen is recorded as disintegration time.

2.2.8 Wetting Time

A piece of tissue paper folded twice was placed in a small Petri dish (ID = 6.5 cm) containing 6 mL of simulated saliva pH, a tablet was put on the paper containing amaranth powder on the upper surface of the tablet, and the time required for formation of pink color was measured as wetting time. Three trials for each batch were performed and standard deviation was also determined.

2.2.9 Water Absorption Ratio

A piece of tissue paper folded twice was kept in a Petri dish (internal diameter 6.5cm) containing 6 mL of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighed.

2.2.10 Drug Content Uniformity

Twenty tablets were accurately weighed and finely powdered. A quantity equivalent to 25 mg of Losartan Potassium was transferred to a 100 mL volumetric flask. To it, 50 mL of Phosphate buffer 6.8 was added and shaken for 1 hour to dissolve drug. The solution was filtered and residue was washed with 25 mL of Phosphate buffer 6.8. The washing obtained was added to initial filtrate and volume was made upto 100 mL with Phosphate buffer 6.8. From above solution 1 mL of stock solution was diluted to 10 mL. The drug content was determined spectrophotometrically at 250 nm.

2.2.11 Dissolution Studies

Dissolution studies were carried out for all the formulation in USP paddle method (Apparatus 2) using Phosphate buffer 6.8, in the dissolution medium (300 mL) at 50 Rpm and 37 ± 0.5 °C. Samples were periodically withdrawn at suitable time intervals and volume replaced with equivalent amounts of plain dissolution medium. The samples were analyzed spectrophotometrically at 250 nm [6].

2.2.12 Stability Study

The storage conditions used for stability studies were accelerated condition (40 ± 2 °C / 75 ± 5 % RH) and Room temperature (30 ± 2 °C / 65 ± 5 % RH).

Stability study was carried out for the optimized formulations. Tablets of optimized formulation were striped packed and kept in humidity chamber for 30 days on above mention temperature [7, 8].

Test performed

- Dissolution profile.
- Assay
- Test for other physical parameters (Hardness and Friability).

2.2.13 In vivo Study

Testing of sublingual tablet, rabbit sublingual cavity serves same purpose as of human. Rabbit having non keratinized

sublingual mucosa as human to correlate in vivo bio-availability study of given formulation with conditions persisting in the human beings before performing the clinical trials in the human. For the assessment of the bioavailability of sublingual tablet Comparative review of several species demonstrate that non keratinized oral mucosa from rabbits, is acceptable model, yielding permeability values similar to those found for humans. Rabbit and dog are generally regarded as suitable animal models since the oral cavity of both are histologically similar to humans. The thickness of the rabbit mucosa (600 μm) is comparable to humans and offers adequate surface area for experimental work [9–11].

Rabbits were used as an animal model for in vivo study and permission for laboratory animal was approved by IAEC (IAEC/HNSIPER/RJK/13/2011).

HPLC analysis was performed on a reversed-phase column using phosphate buffer (pH 4.3), acetonitrile (750:250, v/v) as mobile phase with a flow rate of 1 mL/min. The limit of determination with UV detection was at 225 nm.

Calculation for drug dose for laboratory animals [12]

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \left[\frac{\text{Animal weight (kg)}}{\text{Human weight (kg)}} \right] \dots (1)$$

$$\text{Animal dose} = \text{Human dose} \left[\frac{\text{Animal weight (kg)}}{\text{Human weight (kg)}} \right] \dots (2)$$

Procedure for tablet administering in rabbit

- For sublingual tablet administration, the rabbit's mouth was opened, and a wooden rod was inserted between the jaws.
- The tongue was elevated by using flat forcep, and the tablet was placed underneath by using another pair of forceps.
- The mouth was gently but firmly holds shut for 5 min. with the wooden rod.
- Wooden rod was placed to prevent chewing or swallowing the tablet.
- Water 0.3 to 0.5 mL was administered immediately after dosing to facilitate tablet disintegration.
- Additional 0.5 to 0.7 mL water was administered at the end of the 5 min. immobilization time to remove any remaining drug from under the tongue.
- A 0.5–1 mL blood samples were withdrawn before dosing and immediately after dosing at 30, 60, 120 and 240 min.
- Afterward Blood samples were refrigerate within 1 h of sampling and centrifuged at 4 °C.
- Losartan Potassium concentrations were measured by using HPLC.

Table 2

Hardness, Thickness, Diameter, Percentage Friability and Weight variation of Batch F1–F5

Batch	Hardness(kg/cm ²)	Thickness(mm)	Diameter(mm)	Percentage Friability	Weight variation (mg)
F1	3.8± 0.25	3.4± 0.04	6.04± 0.02	0.58± 0.03	129.76± 1.3
F2	3.9± 0.38	3.6± 0.02	6.07± 0.01	0.79± 0.04	131.61± 1.4
F3	4.1± 0.47	3.5± 0.03	6.03± 0.03	0.66± 0.03	130.29± 1.1
F4	3.9± 0.36	3.4± 0.01	6.06± 0.07	0.78± 0.07	132.17± 1.3
F5	4.1± 0.33	3.5± 0.02	6.03± 0.03	0.72± 0.01	132.46± 1.8

- AUC and percentage relative bioavailability was calculated. [10, 13]

% Relative bioavailability was calculated by following equation

$$\% \text{ Relative bioavailability} = \frac{\text{AUC Sublingual}}{\text{AUC Oral}} \times \frac{\text{Dose Oral}}{\text{Dose Sublingual}} \times 100\% \dots (3)$$

3. Results

The different batches of Losartan potassium sublingual tablets were prepared by direct compression method using various ingredients like Pearlitol SD 200, starch 1500, microcrystalline cellulose, sucrose DC, PVP, sucralose etc (Table 1).

Table 1

Formulation of Batch F1–F5 by Direct Compression Method

INGREDIENTS	Formulation code (Quantity in mg/Tablet)				
	F1	F2	F3	F4	F5
Losartan Potassium	25	25	25	25	25
Pearlitol SD 200	65	65	65	65	65
Starch1500	0	5	10	15	20
MCC	22	17	12	7	2
Sucrose DC	10	10	10	10	10
PVP	2	2	2	2	2
Sucralose	3	3	3	3	3
Aerosil	1	1	1	1	1
Talc	2	2	2	2	2
Total weight(mg)	130	130	130	130	130

The FT–IR and DSC study did not show any possibility of interaction between Losartan Potassium and excipients (Figure 1 and 2).

The Hardness of tablets was determined and was found to be in the range of 3.8 to 4.1 kg/cm². Percentage Friability was observed between 0.58 to 0.72 %, which was in the limit of range. Weight variation of all the formulations was observed which were within the acceptable limit as per United States Pharmacopoeia (Table 2).

The wetting time for all the formulations was found to be (18± 2.08) to (25± 3.12) seconds. The water absorption ratio for all formulations was found to be (37.65± 1.97) to (43.31 ± 3.62). The tablets were subjected for evaluation of *in vitro* disintegration time. *In vitro* disintegration time for formulations F1 to F5 was 48 to 58 seconds. The formulation

F3 showed rapid disintegrating time of 48 seconds this is due to rapid uptake of water from the medium and burst effect (Table 3).

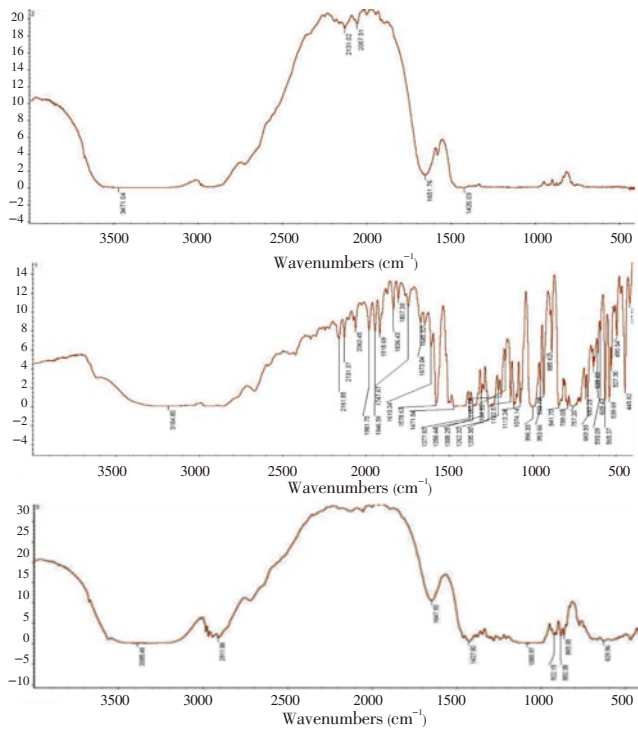


Figure 1: FTIR spectrum of Losartan potassium, Excipients and Physical Mixture of Drug+Excipients

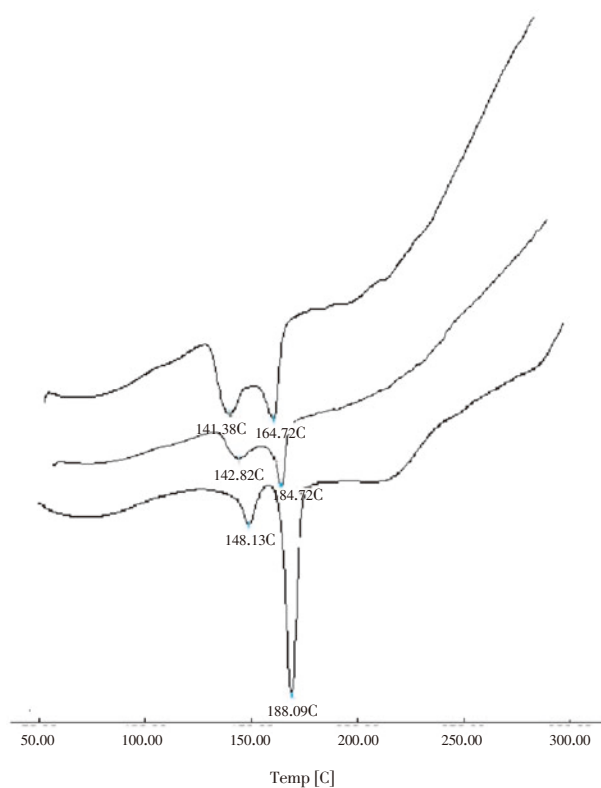


Figure 2: DSC Study of Losartan potassium, Excipients and Physical Mixture of Drug+Excipients

Table 3

Disintegration Time, Drug Content Uniformity, Wetting Time and Water Absorption ratio of Batch F1–F5

Batch	Disintegration Time (sec)	Drug Content Uniformity	Wetting Time (sec)	Water Absorption Ratio
F1	57± 3.10	98.76± 1.20	25± 3.12	38.16± 2.12
F2	54± 2.24	99.83± 2.21	21± 2.78	37.65± 1.97
F3	48± 2.22	99.32± 1.30	18± 2.08	41.63± 2.34
F4	55± 2.01	98.51± 0.98	22± 1.93	43.31± 3.62
F5	58± 1.58	99.01± 1.37	25± 2.26	40.12± 1.28

Percentage drug content of all the formulations was found to be 98.51 to 99.83 of Losartan Potassium which was within the acceptable limit.

It was observed that batch F3 showed faster drug release than all other batch (figure 3). Batch F3 showed 99.13 % cumulative drug release in 15 minute. t50 % of batch F3 was found to be 3 min. Batch F3 was formulated with 10 mg starch 1500 and 12 mg MCC. Batch F3 was considered as an optimized formulation because of rapid disintegration time and dissolution profile.

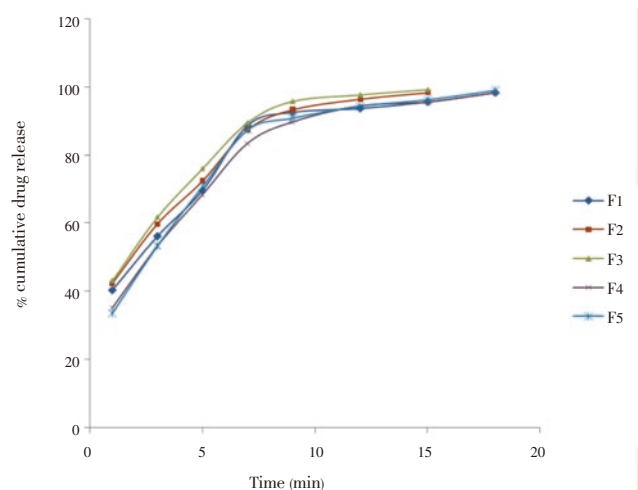


Figure 3: Drug Release Profile of Batch F1–F5
Stability study was performed on batch F3. Various evaluated parameter is shown in table 4 and figure 4.

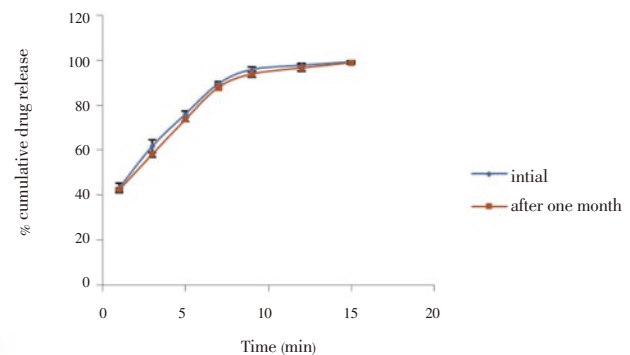


Figure 4: Comparison of Drug Release Profile of Batch F3 for Stability Study

Table 4

Comparison of Various Parameters for Stability Study

Evaluation Parameter	Initial	After One month
Hardness	4.10± 0.47	4.30± 0.36
Percentage Friability	0.66± 0.03	0.64± 0.06
Disintegration Time (sec)	48.00± 2.22	51.00± 1.47
Drug Content	99.32± 1.30	98.00± 1.12

In vivo study was also performed by taking optimized formulation F3 and result was compared with oral Losartan Potassium tablet. Rabbit was used as animal model for *in vivo* studies. The blood samples were withdrawn at different time intervals were analyzed for the drug content by HPLC. AUC for plasma concentration time profile of sublingual and oral Losartan Potassium are shown in figure 5–8. C_{max} and T_{max} for sublingual Losartan Potassium was found to be 51.25 μg/mL and 2 h respectively. The percentage relative bioavailability was calculated by equation 3 and was found to be 144.7%. Results of *in vivo* study showed that sublingual Losartan Potassium have improved bioavailability.

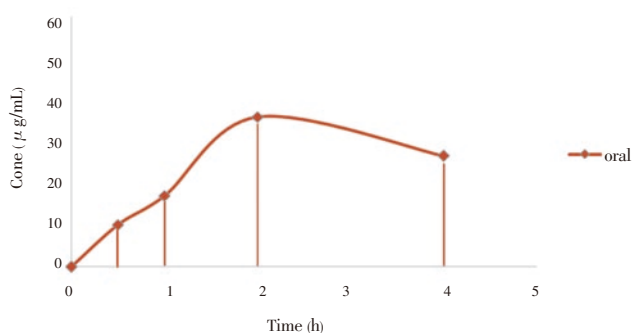


Figure 5: AUC for Plasma Concentration Time Profile of Oral Losartan Potassium Tablet

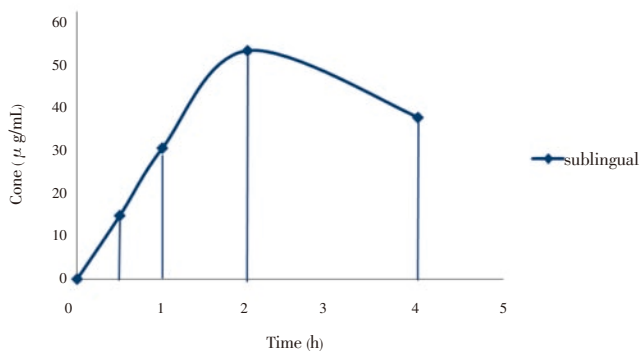


Figure 6: AUC for Plasma Concentration Time Profile of Sublingual Losartan Potassium Tablet

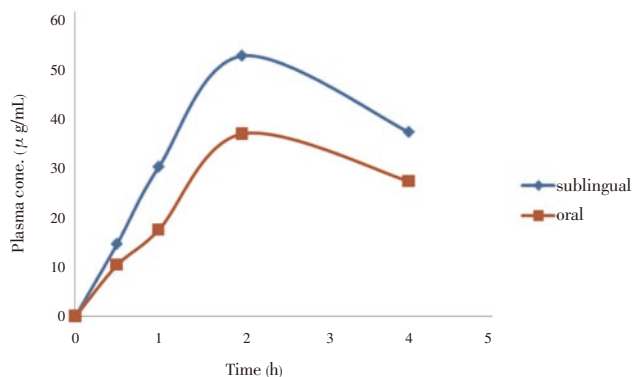


Figure 7: Plasma Concentration Time Profile of Oral and Sublingual Losartan Potassium Tablets

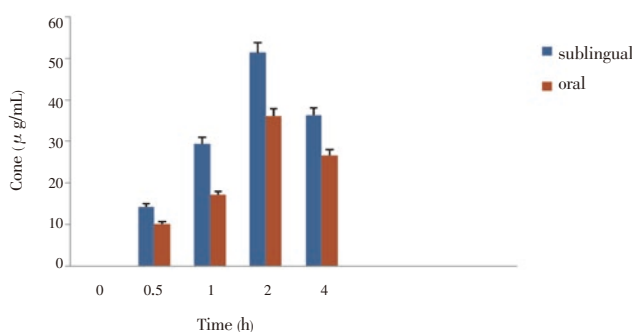


Figure 8: Comparison for Plasma Concentration Time Profile of Sublingual and Oral Losartan Potassium Tablets

4. Discussion

The different batches of Losartan potassium sublingual tablets were prepared by direct compression method using various ingredients like Pearlitol SD 200, starch 1500, microcrystalline cellulose, sucrose DC, PVP, sucralose etc. Total number of five formulations with different concentration of starch 1500 and MCC were prepared and evaluated. Result are shown in Table 2, 3 and 4

The FT–IR and DSC study revealed that there was no any possibility of interaction between Losartan Potassium and excipients. Pearlitol SD 200 act as a diluents and it also act as a sweetener. There was direct correlation between wetting time and disintegration time. Starch 1500 and microcrystalline cellulose act as a disintegrating agent. Batch F3 was considered as a optimized formulation. Disintegration of batch F3 was less than all other batch. Hardness and Friability of batch F3 were also good. Stability study and *in vivo* study were performed on Batch F3. Stability study indicated that there was no any change after one month. *In vivo* study was performed on rabbits. *In vivo* study revealed that sublingual tablets have improved

bioavailability

5. Conclusion

The concept of sublingual tablets containing Losartan Potassium offers a suitable and practical approach in serving the desired objective of management of Hypertension. The excipients used in the formulation were inexpensive and are easily available. Most of the excipients used in formulation are water-soluble and hence have a better patient acceptability. The present work of formulating a sublingual tablet containing Losartan potassium was successful in terms of reducing manufacturing difficulties, cost and providing a better patient compliance with effective medication.

It has been observed from the above study that excipients like Pearlitol SD 200, Microcrystalline cellulose, Starch 1500, Sucrose DC etc. were ideal excipients and effective for formulating sublingual tablets. Sublingual tablets provide several advantages especially when administered to children and elderly patients. Rapid absorption into the systemic circulation within short time period may be achieved. The batch F3 was considered to be the best among all other batches since it exhibited a good dissolution profile, disintegration time, uniformity of drug content and further good stability and In vivo absorption profile.

Conflict of interest statement

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

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