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RESEARCH ARTICLE

Formulation and evaluation of sublingual tablets of losartan potassium by using natural and synthetic super disintegrants

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Abstract: The objective of the current study was to develop and optimize a sublingual tablet of Losartan Potassium, which is an effective drug in the treatment of hypertension. Owing to number of advantages associated with the quick onset of action and it can by passes the liver. Sublingual tablets offer effective and easier way for management of Hypertension. The basic approach used in development of sublingual tablet was the use of super disintegrates by direct compression method. Oral mucous drug delivery is one of the promising method of systemic drug delivery which offers several advantages. The literal meaning sublingual is "under the tongue." Hence the method includes the administration of drug via mouth so that it is absorbed via blood vessels (systemic) present under the tongue. The sublingual tablet is tablet that dissolves or disintegrates in the oral cavity without need of drinking water. Sublingual tablet traditionally has been used as an effective method to improve the dissolution properties and bioavailability of water-soluble drugs. In the Preformulation studies, Losartan Potassium was characterized by using UV, FTIR and DSC Studies.The UV spectroscopic method was established for quantitative estimation of the drug and the absorption maxima was 250 nm. The tablets were formulated by using the direct compression technique. The post compression studies i.e., Weight variation, Hardness, Friability, wetting time, Water absorption and Drug content determines the quality of the product.

Keywords: Oral cavity; Sublingual Tablets; Super Disintegrants; Losartan Potassium

1. Introduction

The formulation development process requires extensive research and experimentation to achieve optimal outcomes. Throughout this process, considerations must be given to various factors, including the selection of excipients, drug bioavailability, stability in the desired dosage form, cost-effectiveness, and manufacturing considerations. In contemporary formulation research, there is a departure from traditional methods, with a broader exploration of possibilities [1].

Oral administration, where a substance is taken through the mouth, is a common route for drug delivery. Many medications are administered orally to achieve a systemic effect, reaching different parts of the body through the bloodstream. The oral mucosal lining presents an advantageous route for both local and systemic drug administration and for treating specific diseases. Compared to enteral and parenteral routes, oral administration offers several benefits, such as a rich blood supply, rapid onset of action, improved bioavailability, avoidance of first-pass and food effects, increased patient compliance, and ease of self-medication [2].

The absorption of drugs through the oral mucosa (shown in Figure 1) is influenced by factors such as the permeability of the oral mucous membrane, the anatomy of underlying tissues, the physicochemical properties of drugs, and the formulation design [3, 4]. This research focuses on the latter two aspects, emphasizing the importance of understanding these elements. Such understanding not only facilitates the selection of suitable drug candidates for oral mucosal delivery but also optimizes the overall drug delivery process.

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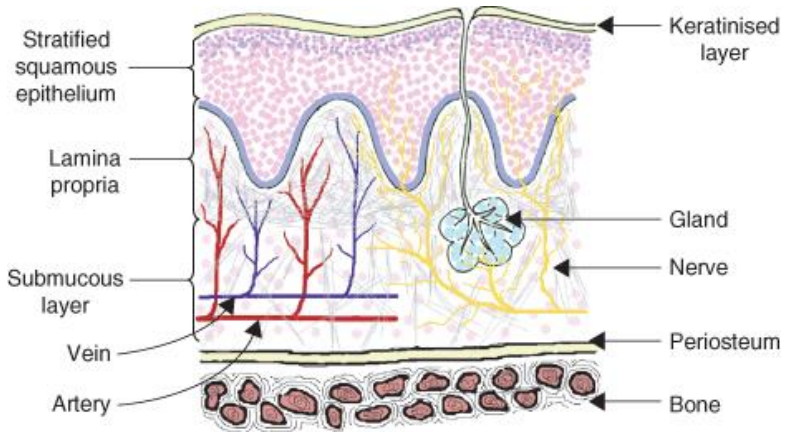

Figure 1 Anatomical structure of oral mucosa

2. Material and methods

2.1. Materials

Losartan Potassium (Aurobindo Pharma Limited), Mannitol, Microcrystalline cellulose, Cross carmellose sodium, Ispaghula husk, Magnesium Stearate, Talc, Sodium saccharin (Loba chemicals) were used.

2.2. Methods

2.2.1. Preparation of losartan potassium sublingual tablets

Sublingual tablets containing Losartan potassium, referred to as LP tablets, were prepared using the Direct Compression method. The formulation details are presented in Table 1. To create the tablets, all necessary ingredients, including the drug, were accurately weighed, excluding Magnesium stearate and talc. These weighed components were then combined in a mortar using a pestle. The resulting powder was sieved through a No. #80 sieve. Subsequently, Magnesium stearate and talc were introduced by additional mixing for 2-3 minutes within a polybag [5]. The compression of tablets was carried out using a Cadmach Machinery Co, Pvt Ltd machine equipped with a 10.0mm circular-shaped concave punch, achieving an average weight of 120mg for each tablet.

Table 1. Formulation table of Losartan potassium Sublingual Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan potassium	25	25	25	25	25	25	25	25	25
Mannitol	56	56	56	56	56	56	56	56	56
Microcrystalline cellulose	20.8	18.2	15.6	20.8	18.2	15.6	32	42	47
Cross carmellose sodium	4	6	8	-	-	-	-	-	-
Ispaghula husk	-	-	-	4	6	8	-	-	-
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1
Sodium saccharin	10	10	10	10	10	10	10	10	10
Total	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**

2.2.2. Compatibility study

Fourier Transform Infrared Spectroscopy (FTIR)

To ascertain the presence of the drug (LP) and assess the interaction between the active substance and the polymeric materials in question, Fourier Transform-Infrared (FT-IR) Spectroscopy was employed. Absorption spectrum data were collected using FT-IR for pure LP, all polymeric materials utilized in the formulation, and a combination of LP and polymeric materials. The FT-IR spectra were recorded for pure LP and LP combined with super disintegrants (in a 1:1 ratio physical mixture). The measurements were

conducted in the frequency range of 400-4000 cm^{-1} with a resolution of 2 cm^{-1}. The direct sampling method was employed with isopropyl alcohol as the solvent, utilizing an FT-IR Cary 630 spectrophotometer [6].

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was employed to assess the interaction between the drug and excipients. The DSC analysis was carried out using a TA model, with a heating rate of 10 ^{o}C per minute and a heating range spanning from 40 to 300^{o}C [7]

2.2.3. Evaluation of prepared tablets

Each tablet underwent assessment for various parameters, including hardness, friability, weight variation, disintegration time, wetting time, water absorption ratio, drug content uniformity, dissolution study, and stability study

Hardness test

Hardness was calculated with the hardness tester (Monsanto type) for three randomly picked tablets in each batch ($n = 3$) [8].

Friability

Friability was determined using a friability apparatus, which ran for a duration of 4 minutes at a speed of 25 rpm, testing ten tablets selected randomly ($n = 1$) from each batch [9]. This is quantified using the following formula

% Friability = ((initial wt-wt after test)/(initial wt)) X 100

Weight Variation

As per IP, the 20 tablets ($n= 20$) were selected randomly from each batch, weighed on an electronic balance. The mean and % deviation of weight, were calculated. The batch passes the weight variation test if NMT wt. of two tablets deviate from the mean tablet weight, of the batch [9].

Disintegration Time

The disintegration time of sublingual tablets was determined using the standard tablet test outlined in the Indian Pharmacopeia. The tablets were inserted into disintegration tubes, and the duration for complete disintegration, ensuring no residue remained on the screen, was noted as the disintegration time [10].

Wetting Time

A folded piece of tissue paper (12 cm X 10.75 cm) was positioned within a small petri dish (ID = 6.5 cm) filled with 6 ml of Sorenson's buffer at pH 6.8. Placing a tablet on the paper, the duration for full wetting was observed. This process was repeated three times for each batch, and the standard deviation was calculated. The time taken for water to diffuse from the moistened absorbent paper to the entire tablet was then recorded using a stopwatch [11]

Water Absorption Ratio

A folded piece of tissue paper is positioned within a small Petri dish containing 6 ml of water. A tablet is then placed on the tissue paper and allowed to fully absorb the water. The weight of the wetted tablet is subsequently measured. The water absorption ratio, denoted as R, is calculated using the provided equation [12].

$$R = (Wa-Wb)/Wa \times 100$$

Where,

Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption.

Drug Content Uniformity

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in acetone, the drug content was determined measuring the absorbance at 250 nm after suitable dilution using Elico SL210 UV-Visible double beam spectrophotometer. The drug content was estimated from the standard curve of Losartan potassium.

Dissolution Studies

It was done on six tablets (n=6) with USP- Type II apparatus (Paddle) for a period of up to 25 min and the rpm was set at 50 rpm. The 900mL of pH 6.8 Phosphate buffer which is maintained at a temperature of 37 0C ± 0.5 0C. Sampling was done at the end of 5, 10, 15, 20, 25 min with a 5 ml pipette and filtered through 0.45 µ PTFE filter disc, dilutions were performed if necessary and analyzed spectrophotometrically at 250 nm to determine the amount of drug released. Sink conditions have to be maintained by replacing the 5 ml of dissolution medium after appropriate sampling [12]. The in vitro dissolution data was analyzed using the MS Excel 2007. The dissolution test parameters used are shown in Table 2

Table 2. *In vitro* dissolution parameters of Losartan potassium Sublingual Tablets

Parameter	**Particulars**
Apparatus	USP -Type II (paddle)
Dissolution medium	pH 6.8 PBS
Vol. of dissolution medium	900 mL
Speed	50 rpm
Temperature	37± 0.5 ºC
Vol. of medium withdrawn	5 mL
Time points	5, 10, 15, 20 & 25 min

3. Results and discussion

3.1. Standard Calibration Curve

The drug, LP, has maximum absorbance (λ_{max}) at 250 nm. This analytical method obeys Beer's law in the concentration range, 2-10 µg/mL defined by a straight line, y = 0.0513 x + 0.0179, with a regression (r^2) of 0.996 [4]. The results are shown in Figure 2.

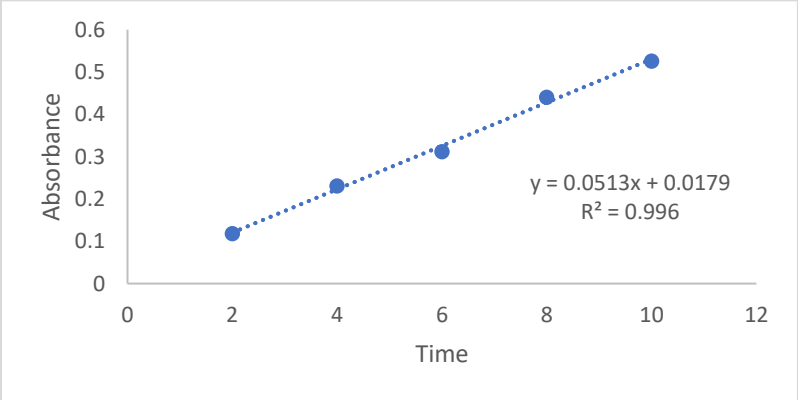

Figure 2. Standard curve for the estimation of LP in pH 6.8 PBS by UV Visible spectrophotometric method

3.2. Drug excipient incompatibility

3.2.1. FTIR studies

The FT-IR spectrum of pure LP is characterized by C = N stretching at 1417.98 cm^{-1} and N-H Stretching at 2949.07 cm^{-1}. The FTIR spectra of LP: Polymers (1:1 ratio physical mixtures) shows no significant shifts or reduction in intensity of the bands, hence they are compatible [5]. The results are shown in Figure 3.

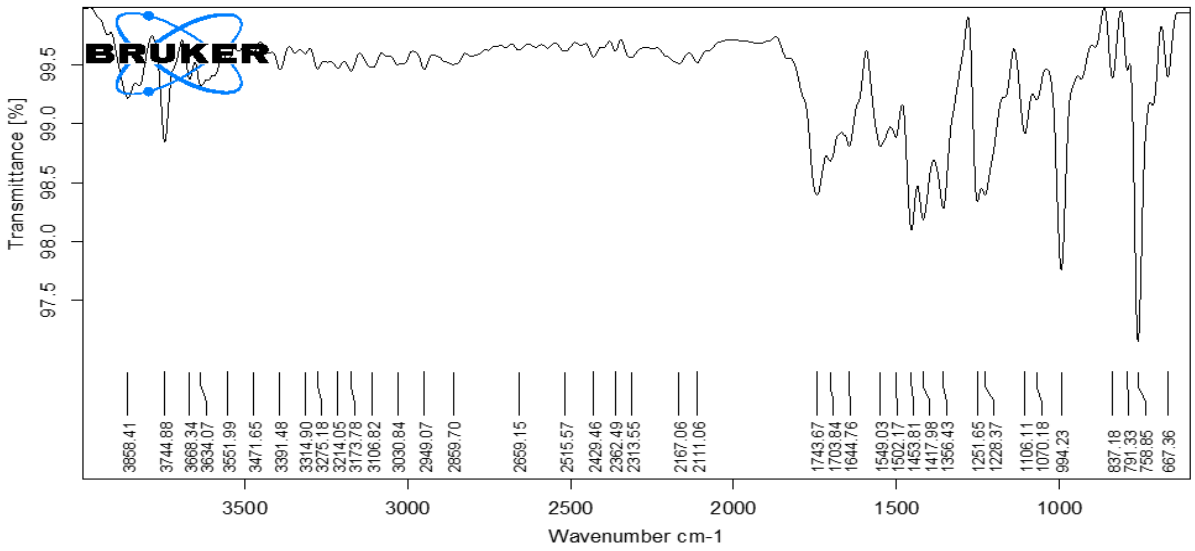

Figure 3. FTIR spectrum of Losartan potassium

3.2.2. DSC studies

The results of the DSC studies indicated the absence of drug-excipient interaction in the optimized formulation, F3. The sharp endotherm in the Figure 4, indicates the melting point of the drug, LP

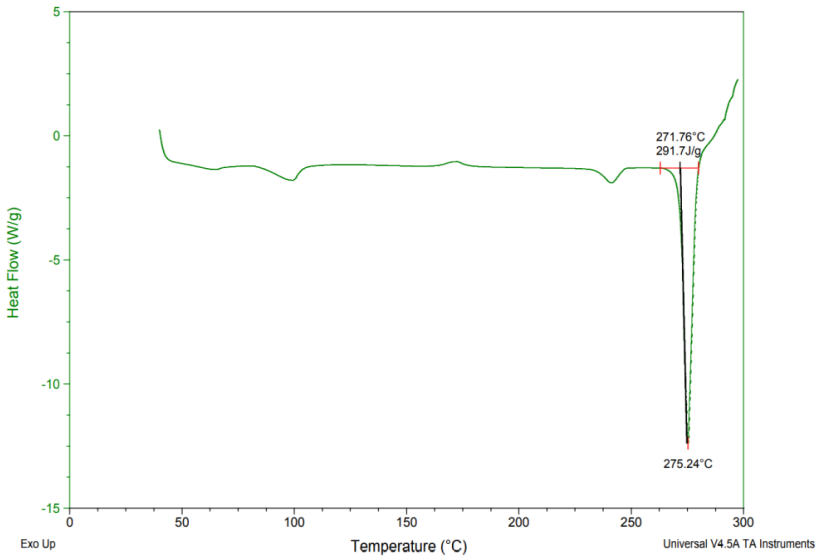

Figure 4. DSC Thermogram of Losartan Potassium Optimized Formulation(F3)

3.3. Results of precompression studies

The angle of repose is indicative of the powder's flowability. F1 and F6 exhibit lower angles of repose (30.96° and 27.23°, respectively), suggesting better flow properties. On the other hand, F2, F3, F4, F5, F7, F8, and F9 have relatively higher angles of

repose, indicating poorer flow characteristics. Bulk density and tapped density are crucial parameters affecting powder compaction. F2 shows the lowest bulk density (0.36 g/cm³), while F5 exhibits the highest bulk density (0.43 g/cm³). Tapped density values follow a similar trend. These variations suggest differences in particle packing and compaction behavior among the formulations.

Carr's Index and Hausner's Ratio are used to assess powder flow properties and compressibility. Higher Carr's Index values (>20%) for F2, F3, F4, F5, F7, F8, and F9 indicate poor flowability and potential powder cohesion. F6 and F1, with lower Carr's Index values, exhibit better flow properties. Hausner's Ratio complements Carr's Index, with F2 having the lowest ratio (0.76) and F5 having the highest (1.29). Lower Hausner's Ratios suggest better flowability, while higher ratios indicate reduced flow properties and potential compaction challenges [6-8].

It is evident that formulations F1 and F6 demonstrate favorable powder characteristics, while F2, F3, F4, F5, F7, F8, and F9 may require further optimization to enhance flow and compaction properties. These findings provide valuable insights for formulators to tailor formulations based on specific manufacturing requirements. The results are shown in Table 3.

Table 3 Results of pre-compression studies

Formulation Code	Angle of repose* (°)	Bulk Density* (g/ cm³)	Tapped Density* (g/ cm³)	Carr's Index * (%)	Hausner's ratio*
F1	30.96±0.90	0.38 ±0.01	0.44±0.02	10.11±0.50	1.15±0.02
F2	28±0.20	0.36±0.05	0.42±0.03	21.11±0.54	0.76±0.012
F3	30±0.02	0.35±0.02	0.44±0.04	24±0.02	1.22±0.12
F4	33±0.02	0.40±0.01	0.048±0.01	23±0.02	1.21±0.012
F5	32±0.03	0.43±0.04	0.50±0.02	26±0.02	1.29±0.015
F6	27.23±0.2	0.39±0.02	0.45±0.02	10.11±0.3	0.81±0.013
F7	32±0.02	0.42±0.02	0.54±0.02	12±0.01	1.25±0.13
F8	30±0.01	0.45±0.02	0.53±0.02	20±0.02	1.14±0.12
F9	29±0.02	0.41±0.05	0.54±0.05	19.14±0.52	1.23±0.13

*Values of angle of repose, bulk density and tapped density are expressed as Mean ± SD, where n = 3 and the values of Hausner's Ratio and Carr's Index were calculated from the mean values of bulk density and tapped density

3.4. Results of post-compression studies

The results of post compression studies are shown in Table 4. The post-compression studies provide a comprehensive evaluation of various key parameters associated with the formulated tablets (F1-F9). These parameters, including hardness, friability, weight variation, water absorption ratio, drug content, wetting time, and disintegration time, offer insights into the physical and mechanical attributes of the tablets, as well as their performance characteristics. Tablet hardness is a crucial parameter influencing the mechanical strength of the tablets. The results indicate that formulations F2, F4, F5, F6, F8, and F9 exhibit higher hardness values, suggesting good tablet strength. F3, F7, and F1 also demonstrate acceptable hardness, indicating robust tablet structure.

Friability is a measure of the tablet's tendency to break or chip during handling and transportation. The low friability percentages across all formulations (ranging from 0.56% to 0.73%) suggest that the tablets possess sufficient mechanical integrity and are resistant to breakage under normal handling conditions.

Weight variation is an essential quality control parameter to ensure uniformity in tablet weight. The formulations show reasonable weight uniformity, with slight variations in the specified limits. This suggests consistency in the manufacturing process and accurate dosing of the drug in each tablet. Water absorption ratio provides insights into the tablet's ability to absorb water, which is crucial for disintegration and dissolution. The results indicate varying water absorption ratios among formulations, with F3 demonstrating

the highest ratio. This parameter could influence the tablet's behavior in different environmental conditions or in the presence of biological fluids. Drug content is a critical parameter reflecting the accuracy of drug dosage in the tablets. The formulations consistently exhibit high drug content percentages, indicating precise drug dosing during the manufacturing process. Wetting time is an important parameter influencing the disintegration and dissolution of the tablets. Lower wetting times, as observed in formulations F6, F7, and F8, suggest faster tablet disintegration when in contact with a liquid medium [9-11].

The disintegration time reflects the time taken for the tablet to break down into smaller particles. Formulations F6, F9, and F8 exhibit relatively shorter disintegration times, indicating efficient disintegration. This is crucial for drug release and subsequent absorption in the gastrointestinal tract. The post-compression studies collectively suggest that the formulations possess desirable mechanical strength, low friability, and consistent drug content. Variations in water absorption ratio, wetting time, and disintegration time among formulations may influence their performance characteristics and suitability for different applications.

Formulation Code	Hardness* (Kg/cm^2)	Friability * (%)	Weight variation*	Water absorption ratio*	Drug content* (%)	Wetting time * (Sec)	Disintegration time * (Sec)
F1	3.6± 0.25	0.71±0.02	11 8.20 ±1.0	36.12±1.26	94.32±1.10	40±0.03	48±1.56
F2	4.1± 0.38	0.64±0.04	12 1.04 ±1.4	39.18±2.01	96.56±1.24	47±0.05	29±1.96
F3	3.6± 0.15	0.66± 0.01	11 9.46 ±0.54	43.31±0.80	99.08±0.56	39±0.02	27±1.62
F4	4± 0.30	0.58±0.07	11 7.22 ±1.1	37.54±1.44	94.78±2.9	33±0.03	47±1.91
F5	4.1± 0.36	0.64±0.04	11 6.64 ±1.2	41.66±3.46	95.76±1.82	36±0.06	35±1.35
F6	4±0.45	0.73±0.04	11 7.04 ±1.08	40.12±2.78	98.11±0.98	30±0.04	24±1.67
F7	3.7±0.38	0.68±0.03	11 8.98 ±1.4	40.63±4.0	43.31±4.0	29±0.03	38±1.86
F8	3.9± 0.42	0.70±0.02	12 2.20 ±0.98	39.10±1.80	39.10±1.80	34±0.03	35±1.48
F9	4±0.36	0.56±0.06	12 1.85 ±1.1	42.22±2.76	42.22±2.76	39±0.03	39±1.54

*Values are expressed as Mean ± SD, where n = 3 and the test for friability was performed on 10 tablets from each batch

3.5. *In vitro* drug release studies

The results of *in vitro* drug release studies are shown in Table 5. At the initial time points (5 minutes), all formulations exhibit a relatively low cumulative percentage of drug released. Formulations F3, F6, and F2 demonstrate slightly higher release percentages compared to others, indicating potential differences in the early dissolution behavior. As the dissolution study progresses, distinct release profiles emerge for each formulation. Notably, F2 consistently releases the drug at a faster rate compared to the other formulations. F3, F6, F7, and F8 also show relatively rapid drug release, especially within the first 15 minutes. In contrast, F1, F4, F5, and F9 exhibit a slower and more gradual release. The differences in the cumulative percentage of drug released at each time point highlight variations in the formulations' release efficiency [12]. Formulations F2, F3, F6, F7, and F8 stand out for their comparatively higher drug release percentages across the studied time intervals. By the 25-minute mark, most formulations approach or achieve a plateau in drug release, indicating a substantial release of the drug from the tablets. F3, F6, and F2 maintain higher percentages of drug release, while F1, F4, F5, and F9 exhibit a slower approach to reaching the plateau.

The observed differences in dissolution profiles among formulations suggest that the choice of excipients and formulation parameters can significantly influence drug release kinetics. Formulation F3, with its faster release profile, might be suitable for drugs requiring rapid onset of action. Conversely, formulations with slower release profiles, such as F1, F4, F5, and F9, could be tailored for sustained release applications.

Table 5. In vitro dissolution data of losartan potassium sublingual tablets F1 to F9

Time (min)	Cumulative % Drug Released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	14.1	16.9	21.12	13.1	15.5	19.01	9.8	12	13.4
10	48.6	49.8	52	42.8	44.9	47.08	37.2	38.6	40
15	66.03	69.5	72.3	60.4	61.8	62.5	55.5	56.9	59
20	82.5	89.3	90.3	75.15	76.5	77.2	69.5	70.9	73.7
25	96.9	97.6	99	96.2	95.5	97.6	92.7	94.1	95.5

4. 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 the formulations 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 Mannitol, Microcrystalline cellulose, Cross carmellose sodium, Ispaghula husk etc. were ideal excipients and effective for formulating the sublingual tablets. The 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 and the uniformity of drug content.

Compliance with ethical standards

Acknowledgements

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Conflict of interest statement

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

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