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Development of sublingual tablets of losartan potassium with enhanced permeation through mucosa

Raja Sekhar Reddy Poonuru[1*], Ramya Sri Arepally[2], Rohini Cheruku[2], Pavan Juluri[2], Lasya Reddy Enugurthy[2], Sasya Asam[2], Shruthi Bonagiri[2].

[1]Principal and Head, St.Peter's Institute of Pharmaceutical Sciences, Hanamkonda, Pin-506001, Telangana, India.
[2]Students, St.Peter's Institute of Pharmaceutical Sciences, Hanamkonda, Pin-506001, Telangana, India.

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Corresponding author: Raja Sekhar Reddy Poonuru

Abstract

Losartan potassium is an orally active non-peptide angiotensin II receptor antagonist used in treatment of hypertension. Even though oral route is the most preferable and acceptable means of administration, it has become a drawback for those drugs having poor oral bioavailability. Hence sublingual route is one of the preferable routes to overcome such deviations and also ensures most rapid and complete absorption of the drug due to its high vasculature. The aim of the present work is to develop sublingual tablets of Losartan Potassium with enhanced permeation through mucosa since it is a highly water soluble and weakly basic drug with poor oral bioavailability. Two techniques have been used for the permeation enhancement: Lipid matrix systems and pH_{max} technique. Lipids like Compritol 888 ATO and Precirol ATO were used in lipid matrix systems and dibasic sodium phosphate was used as buffering agent in pH_{max} technique. The tablets were evaluated for various evaluation parameters. FTIR studies were also performed for drug excipient compatibility. The results showed both of the techniques were enough sufficient in improving the release of the drug.

Keywords: Sublingual, Losartan Potassium, Lipid Carrier, Buffering Agent, Lipid Matrix Systems.

Introduction

Oral mucosa delivery is an alternative method of systemic drug delivery [1-5]. Drug delivery classified as sub lingual, buccal and local. The drug delivery is differ for different regions through mucosal membrane based on various factors [6-9]. Sub lingual dosage form can be define as dosage form that is to be placed beneath tongue where it will dissolve and the drug will be absorbed directly through the sublingual mucosa. The dosage form not intended to be swallowed or chewed. The basic advantages of drug delivery across oral mucosa is that the drug escapes first-pass metabolism and protect from degradation due to pH and digestive enzymes, low dose can provide high efficacy which reduces side effects, Large contact surface area and high vascularisation [10-11]. Disadvantages also prevail like this site is not suitable for prolonged administration and administration cannot be done for uncooperative and unconscious patients [12].

Materials

Losartan Potassium was gifted by Dr Reddy Laboratories, Hyderabad, Compritol 888 ATOand Precirol ATO5 ATO gifted by Gattefosse, Mumbai, India, Mannogem was gifted by SPI Pharma, GMBH Germany, Pruv SSF gifted by JRS Pharma, Rosenberg, Germany, Dibasic sodium phosphate dihydrate was purchased from S.D.Fine Chem.Ltd, Mumbai, India.

Methods

Sublingual tablets were prepared by direct compression using Cadmach 18 stage rotary tablet punching machine after proper blending of various ingredients as shown in table 1.

Tab 1. Formulation by lipid matrix and pH controlled methods

	Lipid matrix tablets				pH tablets
Code	**F1**	**F2**	**F3**	**F4**	**F5**
Losartan Potassium	25	25	25	25	25
Compritol888ATO	12.5	-	15	15	-
Precirol ATO5	-	12.5	-	-	-
$Na_2HPO_4.2H_2O$	-	-	-	-	40
Mannogem	62	62	59.5	59.5	33
Pruv [SSF]	0.5	0.5	0.5	0.5	2
Total wt. [mg]	**100**	**100**	**100**	**100**	**100**

***In vitro* Disintegration studies**

Disintegration time for sublingual tablets was measured using USP tablet disintegration apparatus with 6.8 pH phosphate buffer as medium. The volume of medium was 900mL and temperature was 37±2°C. 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 [13].

Drug content uniformity

Ten tablets were accurately weighed and finely powdered. A quantity equivalent to 40mg of Losartan potassium was transferred into a 100mL volumetric flask. To it, 50mL of 6.8 pH phosphate buffer was added, sonicated to dissolve drug and the volume was made up to the mark and the solution was filtered. From above filtered solution, 1mL of stock solution was diluted to 10mL to prepare 40µg/mL solution. The drug content was determined spectrophotometrically at 237nm [14, 15].

***In vitro* Dissolution studies**

Tablets were placed in the dissolution jars containing media. 5mL of samples were periodically withdrawn at time intervals of 5, 10, 15, 20, 30 and 45minutes, and the volume was replaced with equivalent amounts of plain dissolution medium. The samples were analyzed spectrophotometrically at 237 nm and the amount of drug release was calculated [16-18].

Fourier transforms infrared [FT-IR] spectroscopy

FTIR analysis was executed to assess any possible interactions that might have occurred between Losartan potassium and other excipients during the formulation. The infrared spectra of pure drug Losartan potassium, lipid [compritol 888 ATO] and optimized formulation were recorded between the range of 4000 and 400cm^{-1} on FTIR. The IR spectra for the test samples were obtained using KBr pellet method on FTIR spectrometer.

Results and Discussion

Micromeritic properties

Tab 2. Micromeritic properties of all formulations

Code	Bulk density [mg/mL]	Tapped density [mg/mL]	Carr's index	Hausner's ratio	Angle of Repose [^{0}]
F1	0.52	0.58	10.34±0.42	1.24±0.006	15
F2	0.57	0.65	13.15±0.44	1.19±0.006	16
F3	0.52	0.58	10.34±0.73	1.22±0.011	14
F4	0.58	0.66	13.44±0.39	1.25±0.006	15
F5	0.51	0.58	10.12±0.39	1.24±0.006	14

Data represents Mean ±SD [n=3]

All the formulations have shown good flow properties. The ingredients used in the formulations have inherently good flow ability which finally results in excellent flow of final blend of formulations. Angle of repose of all formulations showed less than 25, indicating the excellent flow property. Carr's index was found to be in the range of 5to 15 for all the formulations indicating excellent compressibility. Hausner's ratio also correlates with angle of repose and compressibility index showing fair flow property [1.19to 1.25].

Evaluation of tablets

Table3.Post Compression Parameters

Code	Wt. variation [mg]	Hardness [kg/cm²]	Thickness [mm]	Friability [%]	Disintegration time [sec]
F1	100±2.1	2.92±0.14	3.58±0.04	0.42	165
F2	99.6±2.4	3.04±0.07	3.173±0.03	0.44	170
F3	99.6±2.3	2.83±0.28	3.76±0.011	0.43	160
F4	99.3±2.1	3.08±0.14	3.526±0.01	0.52	150
F5	100±2.4	3.08±0.07	3.446±0.02	0.41	140

Data represents Mean ±SD [n=3], [n=20 for wt. variation]

Weight variation data indicates that the weights of individual tablet of all the formulations were within the acceptance limits i.e. less than 10% according to the USP limits for a tablet with an average weight between 130mg or less. Hardness of the tablet was fixed in between 2.5-3kg/cm² such that the effect of hardness should not interfere with the fast disintegration of the tablet. Friability test indicates the percentage weight loss of the tablet due to mechanical shock and abrasion. Due to the maintenance of low hardness the friability of the tablets was comparatively more, but within the limits [< 1%].Drug content uniformity of all formulations was within the limit range. This indicates that all formulations were in the acceptance limits.

Drug Release Profile

Tab 4. Percentage cumulative drug release profile of lipid matrix trial formulations

Time [min]	Percent cumulative drug release			
	F1	**F2**	**F3**	**F4**
0	0	0	0	0
5	21.9	11.9	11	17
10	57.4	34	34	45
15	94	65.1	71	88.8
20	104	106.2	117	122

Data represents Mean ±SD [n=3]

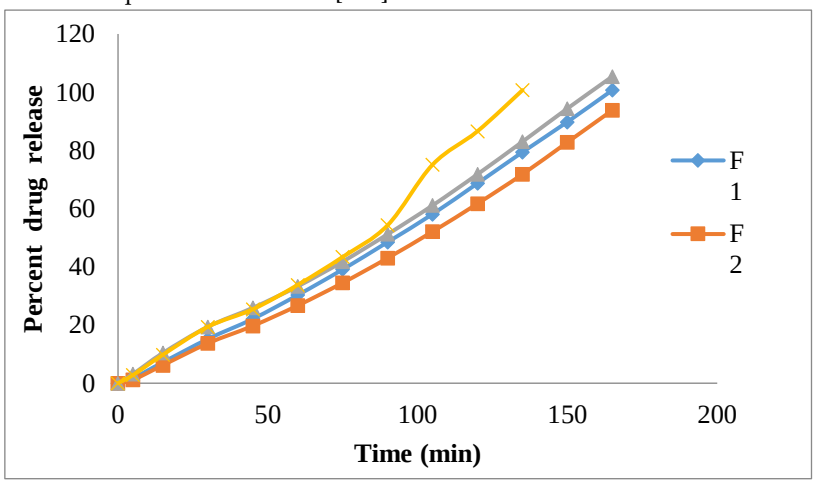

Fig.1. Drug release profile of formulation [F1-F4]

Tab 5. Percentage cumulative drug release profile of buffered tablet

Method.	pH tablets	
Time [min]	F5	Pure Drug
	% cumulative drug release	
0	0	0
5	17.7	75.9
10	46.62	117.6
15	81.01	-
30	91.59	-
45	115	-

The experimental formulation trails F1, F2, F3 and F4 were formulated with various selected lipid carriers such as compritol 888ATO in formulation [F1 and F3] and Precirol ATO in [F2 andF4] in various ratios. The percentage drug release of formulations F1 and F3 with Compritol 888 ATO as lipid carrier showed as 94% and 71% respectively for 15 minutes. Formulations F2 and F4 with Precirol showed the drug release percentage of 65.1% and 88.8% respectively.F5 formulation with buffering agent [dibasic sodium phosphate dihydrate] showed the drug release within 45 minutes. Losartan potassium is a water soluble drug hence it undergoes fast dissolution.

***In vitro* diffusion study**

Tab 6. *In vitro* drug release profile of formulation [F1-F4] through gelatin membrane

Time [min]	F1	F2	F3	F4
0	0	0	0	0
5	1.71	1.16	3.16	2.8
15	7.2	6.2	10.4	9.8
30	15.2	13.7	19.4	19.4
45	22.1	19.7	25.9	25.4
60	30.3	26.7	33.3	33.8
75	39.1	34.5	41.8	43.4
90	48.5	43.0	51.2	54.3
105	58.1	52.1	61.1	75.1
120	68.7	61.7	71.8	86.6
135	79.4	71.8	83.0	100.7
150	89.8	82.8	94.4	
165	100.7	93.8	105.4	

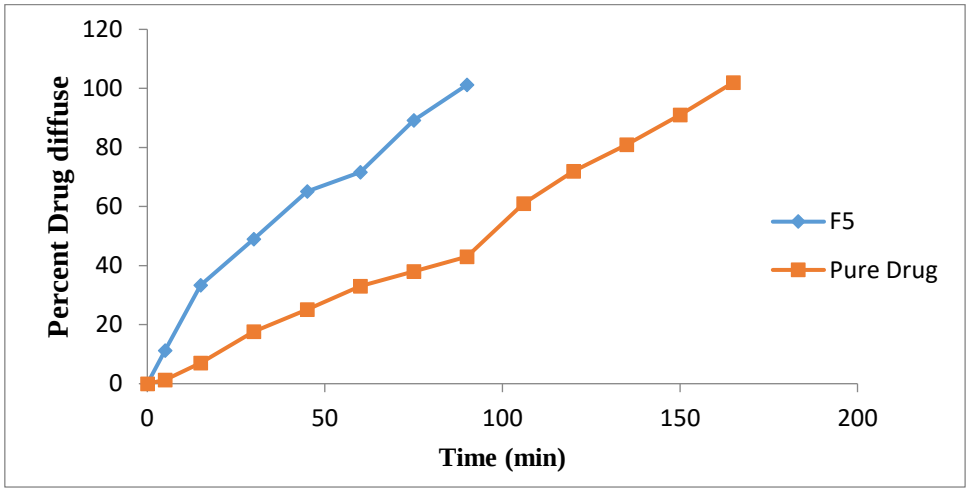

Fig.2.Diffusion study of buffered tablet [F5] and pure drug

In vitro diffusion study were carried out for formulations with selected lipid carriers through gelatin membrane. The diffusion for formulation F4 with Precirol ATO increased when compared to Compritol 888 ATO formulations. The optimized formulation F4 showed 100% of drug release at the end of 2hours 30 minuteswhereas F1, F2 and F3 showed 89%, 82%, and 94.4% respectively at the end of 2hours 30 minutes.The increased permeation might be due to the presence of lipid carrier.

***In vivo* diffusion study**

Tab 7.*In vivo* diffusion study of buffered tablet [F5]

Time [min]	F5 [Buffered tablet]	Pure Drug
0	0	0
5	11.2	1.26
15	33.4	7.0
30	49.0	17.6
45	65.1	25.1
60	71.6	33
75	89.2	38
90	101.2	43
106	-	61
120	-	72
135	-	81
150	-	91
165	-	102

The pure drug Losartan potassium showed 100% drug release for 2hours 45minutes, were formulation F5 containing buffering agent showed enhanced permeation when compared to pure drug. The drug release of F5 showed 100% for 1hour30minutes.When compared to lipid carrier formulations the formulation with buffering agent showed increased diffusion.

FTIR results

Tab 8.*In vivo* diffusion study of buffered tablet.

Functional group	IR range	Drug	Formulation [F4]	Buffered tablet	Buffering agent	Precirol ATO
C-H stretch	3000-2850cm^{-1}	2922.50 cm^{-1}	2913.93 cm^{-1}	2972.49 cm^{-1}	2923.15 cm^{-1}	2923.79 cm^{-1}
C-Cl	600-800cm^{-1}	722.2 cm^{-1}	721.98 cm^{-1}	722.15 cm^{-1}	721.99 cm^{-1}	720.20 cm^{-1}
CH_2bend	1350-1480cm^{-1}	1376.71 cm^{-1}	1376.93 cm^{-1}	1376.22 cm^{-1}	1376.29 cm^{-1}	1376.44 cm^{-1}

FTIR spectra of losartan potassium shows its characteristic peaks at 3000-2850cm^1 methyl and methylene C-H stretching. C-Cl peak at 600-800cm^1. CH_2 bend peak at 1350-1480cm^1 ranges. The characteristic peaks obtained in pure drug of desired functional group within IR range were also seen in formulation [F4] and buffered tablet but with slightly change in characteristic peak. This indicate that there is no chemical interaction between Losartan potassium pure drug and Lipid/excipients such as Compritol and buffering agent.

Conclusion

Sublingual tablets of Losartan Potassium with enhanced permeation were successfully developed

meeting the pre-determined objectives. Sublingual delivery of Losartan Potassium will promote the rapid release and immediate action of the drug in severe cases of hypertension. Both lipid matrix and pH technique offer enhanced permeation and rapid drug release. The lipid matrix tablets with Precirol ATO [F4] showed an improved permeation compared to the pure drug. The buffered tablet showed increased permeation compared to the formulation [F4] and pure drug.

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Conflicts of Interest

There are no conflicts of interest between the authors.

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