



DEVELOPMENT AND IN VITRO EVALUATION OF BUCCOADHESIVE TABLETS OF LOSARTAN POTASSIUM

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ABSTRACT:

Buccoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. The unique environment of the oral (buccal) cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation. The Buccal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect). Oral controlled release (CR) systems continue to be most popular once amongst all the drug delivery systems. Mucoadhesive delivery systems offer several advantages over other oral CR systems by virtue of prolongation of residence time of drug in buccal mucosa, and targeting and localization of the dosage form at a specific site. Also, these mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting thereby in high drug flux through the absorptive tissue. Losartan potassium is an angiotensin II receptor (type AT1) antagonist. Administration of conventional tablets of Losartan potassium has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor site. Losartan Potassium is having less bioavailability (25-35%). In order to increase the bioavailability to avoid the hepatic metabolism, the buccal tablets of Losartan potassium were prepared.

KEY WORDS: Losartan Potassium, Buccal Tablets, Carbopol 934P, HPMC.

INTRODUCTION

The drugs that are administered orally, solid oral dosage form represent the preferred class of products. The reasons for this preference are as follows. Tablet is unit dosage form in which one usual dose of the drug has been accurately placed by compression. Liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain one dose of medication in 5 to 30 ml and the patient is then asked to measure his or her own medication using teaspoons, tablespoon or other measuring device. Such dosage measurements are typically in error by a factor ranging from 20 to 50% when the drug is self administered by the patient.

Buccoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. The unique environment of the oral (buccal) cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation. The Buccal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect).

Administration of a drug via the buccal mucosa (the lining of the cheek) to the systemic circulation is defined as buccal delivery. Despite, the buccal mucosa is significantly less permeable than the sublingual mucosa and usually not able to provide rapid drug absorption or good bioavailability; it is relatively more permeable than the skin and also offers other advantage over alternative delivery routes. The fact that the buccal mucosa is less permeable than sublingual floor makes it more desirable site for sustained drug delivery. Apart from avoiding enzymatic degradation and first pass metabolism, the non acidic conditions and lipophilic nature of the buccal tissue provide potential and promises for successful delivery of peptide and proteins.

Buccoadhesive also increases the intimacy and duration of contact between a drug-containing polymer and a buccal

mucosa. The combined effects of the direct drug prolonged residence time allow for an increased bioavailability of the drug with smaller dosage and less frequent administration. Drugs that are absorbed through the buccal mucosal lining of the tissues can enter directly into the blood stream and prevent from enzymatic degradation in the GIT and avoids the first pass metabolism in the liver.

BUCCOADHESIVE DRUG DELIVERY^{1,2}

The potential route of buccal mucosal route of drug administration was first recognized by Walton and others reported in detail on the kinetics of buccal mucosal absorption. Buccoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. The unique environment of the oral (buccal) cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation. The Buccal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect).

NEED FOR THE INVESTIGATION

Buccal drug delivery has been considered as an alternative to oral dosing for compounds subjected to degradation in the gastrointestinal tract or to hepatic first pass metabolism.

The preparation of pharmaceutical composition capable of ensuring a gradual and controlled release of active ingredients. Known systems like tablets where the active ingredient is released gradually by various mechanisms. So, the active ingredient i.e., Losartan Potassium is having less bioavailability (25-35%). In order to increase the bioavailability to avoid the hepatic metabolism, the buccal tablets of Losartan Potassium were prepared.

OBJECTIVE AND PLAN OF WORK

The aim of the present study was to design buccoadhesive bilayered tablets to release the drug unidirectionally in buccal cavity for extended period of time in order to avoid first-pass

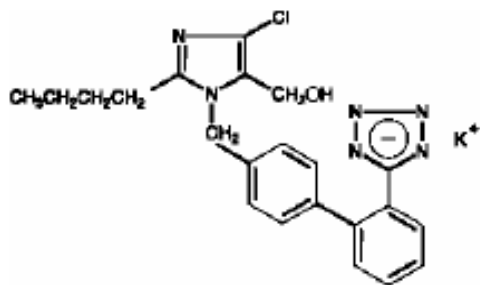
metabolism for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance.

An attempt has been made to develop buccoadhesive bilayered tablets comprising of drug containing bioadhesive layer and drug free backing layer to release the drug for extended period of time with reduction in dosing frequency. Tablets of Losartan potassium were prepared by direct compression method using bioadhesive polymers like Carbopol 934P, HPMC K4, HPMC E15LV and sodium carboxy methyl cellulose either alone or in combinations with backing layer of ethyl cellulose.

DRUG PROFILE

LOSARTAN POTASSIUM:

Losartan potassium^{3,4} is an angiotensin II receptor (type AT1) antagonist. Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted into a carboxylic acid metabolite. Losartan metabolites have been identified in human plasma and urine. In addition to the carboxylic acid metabolite, several metabolites are formed.



Structure:

Molecular Formula : C₂₂H₂₂ClKN₆O

Molecular Weight : 461.0

Chemical name :

2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

Limits:

Losartan potassium contains not less than 98.5 % and not more than equivalent of 101.0 % of calculated with reference to the anhydrous substance.

Properties:

Appearance: white to off-white free-flowing crystalline powder.

Solubility:

It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

Mechanism of action:

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both Losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT1 receptor and have much greater affinity (about 1000-fold) for the AT1 receptor than for the

AT2 receptor. In vitro binding studies indicate that Losartan is a reversible, competitive inhibitor of the AT1 receptor.

Pharmacokinetics:

Losartan is readily absorbed from the gastrointestinal tract following oral administration. It undergoes first pass metabolism to form a carboxylic acid metabolite E-3174 (EXP-3174). The terminal elimination half lives of Losartan and is about 1.5 to 2.5 hours. Losartan's bioavailability is about 32%. Following oral administration, 6 % of Losartan is excreted unchanged in the urine.

Dose:

Dosing must be individualized. The usual starting dose of Losartan potassium is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) and patients with a history of hepatic impairment. Losartan potassium can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

Storage:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep container tightly closed. Protect from light.

Adverse Reactions:

Adverse effects of Losartan have been reported to be usually mild and transient, and include dizziness and dose-related orthostatic hypotension. Hypotension may occur particularly patients with volume depletion (for example those who have high dose diuretics). Hyperkalaemia has been reported. It appears less likely than angiotensin-converting enzyme (ACE) inhibitors to cause cough.

Uses and Administration:

Losartan is an angiotensin II receptor antagonist with antihypertensive activity due mainly to selective blockade of AT1 receptors and the consequent reduced pressor effect of angiotensin II. It is given by mouth as the potassium salt in the management of hypertension. It has also been tried in heart failure.

In hypertension dose is 50 mg once daily. The maximum effect is achieved in about 3-6 weeks after initiating treatment. The dose may increase, if necessary, to 100 mg once daily. An initial dose of 25 mg once daily is suggested for the elderly over 75 years-of-age, and for patients with moderate to severe renal impairment (creatinine clearance less than 20 ml per minute), or intravascular fluid depletion. A reduced dose should also be considered for patients with hepatic impairment.

MATERIALS AND METHODS

Preparation of Buccoadhesive bilayered Tablets^{5,6}:

The buccoadhesive bilayered tablets were prepared using different polymers either alone or in combinations with varying ratios as summarized in [Table - 2]. Tablets were prepared by direct compression procedure involving two consecutive steps. The buccoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15 min. Magnesium stearate (MS) was added as a lubricant in the blended material and mixed. The blended powder was then lightly compressed on 8 mm punch using 16 station tablet compression machine (Cadmach). the upper punch was then removed and backing layer material ethyl cellulose was added over it and finally compressed at a constant compression force.

Construction of Calibration curve of Losartan Potassium

Accurately weighed 100 mg of Losartan potassium and transferred into 100 ml of volumetric flask and dissolved in small quantity of methanol and diluted with 6.8 phosphate buffer up to the mark to give stock solution 1 mg/ml. 1 ml

was taken from stock solution in another volumetric flask and diluted up to 100 ml to give a stock solution 10 µg/ml. Further dilutions were made from 2-40 µg/ml with 6.8 phosphate buffer and absorbance was measured at 235 nm.

EVALUATION OF TABLETS⁷:

The formulated tablets were evaluated for the following physicochemical parameters:

Weight Variation:

Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is within permissible limits or not. The results listed in the Table 3.

Hardness:

Hardness of the tablet was determined using the Monsanto harness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The results listed in the table 3.

Friability:

The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus, which was given 100 revolutions. After which the tablets were reweighed. The percentage friability was calculated. The results listed in the table 3.

Drug Content:

Five tablets of each formulation were weighed and powdered. The quantity of powder was equivalent to 100 mg. The equivalent weight Losartan potassium was transferred into 100 ml volumetric flask and by using methanol as the extracting solvent and samples were analyzed spectrophotometrically. The results listed in table 3.

Surface pH of the buccoadhesive tablets⁸:

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The method adopted by Bottenberg et al was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute. The results listed in table 3.

In vitro swelling studies of buccoadhesive tablets⁹:

Buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37°C ± 1°C. At regular 1-hour time intervals until 6 hours, the tablet was removed from the Petri

dish, and excess surface water was removed carefully with filter paper. The swollen tablet was then reweighed (W2) and the swelling index (SI) was calculated using the formula. The results listed in table 4.

$$\% \text{ Swelling index} = [(W 2 - W 1) / W 1] \times 100$$

Bioadhesion time¹⁰:

The ex vivo mucoadhesion time was performed (n = 3) after application of the buccal tablet on freshly cut sheep buccal mucosa. The fresh sheep buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8, and was kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 hours. The time for the tablet to detach from the sheep buccal mucosa was recorded as the bioadhesion time. The results listed in figure no:3.

In-vitro dissolution studies of tablets¹¹:

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP XXVII paddle method and 900ml of pH 6.8 phosphate buffer as the dissolution medium. The medium was allowed to equilibrate to temp of 37°C + 0.5°C. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hrs in pH 6.8 phosphate buffer at 50 rpm. At definite time intervals of 5 ml of the aliquot of sample was with drawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 235 nm using uv-spectrophotometer.

Dissolution parameters:

Apparatus -- USP-II,

Dissolution Medium -- pH 6.8 phosphate buffer

RPM -- 50

Sampling intervals -- 0.5,1,2,3,4,5,6,7,8,10,11,12

Temperature -- 37°C + 0.5°C

Infrared spectra analysis:

Compatibility of the Drug with the excipients was determined by subjecting the physical mixture of the drug and the excipients of the main formulation to infrared absorption spectra analysis. Any changes in chemical composition of the drug after combining it with the excipients were investigated with I.R. spectral analysis. Infrared spectrum of Promethazine HCl was determined on Fourier transform infrared spectrophotometer using KBr pellet method. The base line correction was done using dried Potassium bromide. Then the spectrum of the dried mixture of drug and Potassium bromide was done.

RESULTS AND DISCUSSION

Table 1: Materials used for the formulation development

1	Losartan potassium	ART Pharmaceuticals, Mumbai	USP Grade
2	HPMC K4 M	SD Fine Chemicals Ltd., Mumbai	Pharmaceutical grade
3	HPMC E15 LV	SD Fine Chemicals Ltd., Mumbai	Pharmaceutical grade
4	Carbopol 934p	SD Fine Chemicals Ltd., Mumbai	Pharmaceutical grade
5	Magnesium stearate	Yarrow-Chem. Products, Dombivli	Pharmaceutical grade
6	Ethyl cellulose	SD Fine Chemicals Ltd., Mumbai	Pharmaceutical grade

Table 2: Composition of Losartan Potassium Tablets

Form. Code	Drug	Carbopol	HPMC K4m	HPMC E15LV	Sodium CMC	Mg Stearate	Ethyl cellulose
F1	25 mg	25 mg	75mg	-----	-----	5 mg	20 mg
F2	25 mg	33 mg	66 mg	-----	-----	5 mg	20 mg
F3	25 mg	50 mg	50 mg	-----	-----	5 mg	20 mg
F4	25 mg	25 mg	-----	75mg	-----	5 mg	20 mg
F5	25 mg	33 mg	-----	66 mg	-----	5 mg	20 mg
F6	25 mg	50 mg	-----	50 mg	-----	5 mg	20 mg
F7	25 mg	-----	-----	25 mg	75mg	5 mg	20 mg
F8	25 mg	-----	-----	33 mg	66 mg	5 mg	20 mg
F9	25 mg	-----	-----	50 mg	50 mg	5 mg	20 mg

Figure 1: Calibration curve of Losartan Potassium

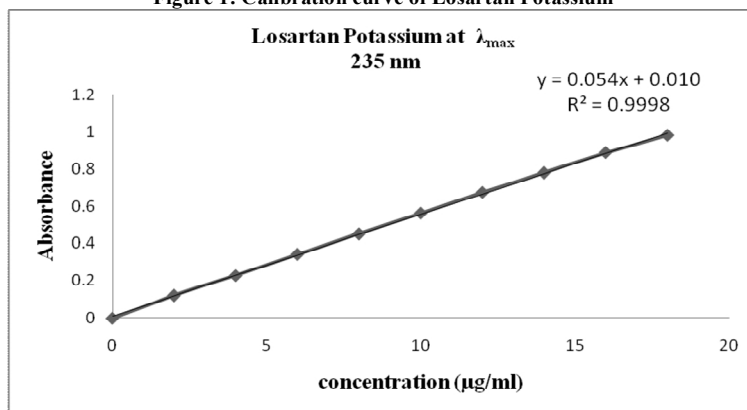


Table 3: Evaluation data of losartan potassium buccoadhesive tablets

Form. Code	Avg. Weight (Mean±S.D) (n=20)	Hardness (Kg/cm2) (n=3)	Friability (n=20)	% Drug content (n=3)	Surface pH
F1	150.6±0.74	7±0.72	0.42	99.80±0.46	6.34±0.003
F2	151.7±0.62	8±0.47	0.39	98.94±0.72	6.43±0.025
F3	150.1±0.47	9±0.62	0.46	99.89±0.58	6.21±0.015
F4	151.2±0.23	6±0.48	0.26	99.54±0.62	6.56±0.005
F5	149.9±0.32	6±0.68	0.54	99.49±0.47	6.41±0.020
F6	151.1±0.54	7±0.38	0.49	100.24±0.53	6.54±0.087
F7	150.4±0.39	8±0.72	0.48	99.9±0.62	6.63±0.032
F8	151.1±0.32	6±0.56	0.56	99.89±0.54	6.76±0.012
F9	149.8±0.43	4±0.72	0.68	100.4±0.48	6.23±0.017

Table 4: Swelling index of losartan potassium buccoadhesive tablets

Formulation Code	% Swelling index*				
	Time (hours)				
	0.5	1	2	4	6
F1	45.49±0.09	92.64±1.23	189.49±1.48	231.64±1.34	261.48±1.66
F2	38.42±0.95	74.84±0.52	147.43±1.66	168.27±1.41	198.49±1.21
F3	49.28±0.098	82.48±1.47	179.48±1.21	209.37±2.41	227.64±2.01
F4	41.42±0.99	84.14±1.48	167.49±1.66	182.43±1.41	218.68±1.98
F5	36.48±0.88	63.74±0.88	139.63±1.37	158.72±0.95	164.38±0.48
F6	50.24±1.16	83.48±1.21	185.67±0.78	218.37±1.23	248.47±1.14
F7	44.38±1.41	84.56±1.72	171.24±3.14	214.67±2.25	242.67±2.55
F8	52.63±0.88	88.96±2.11	182.46±3.32	236.11±3.45	274.40±3.14
F9	32.67±1.24	81.24±1.46	161.75±3.14	186.34±3.04	214.37±1.33

* Indicates mean±S.D. values

Figure 2: Swelling index profile of Losartan Potassium buccoadhesive tablets of F1 to F9

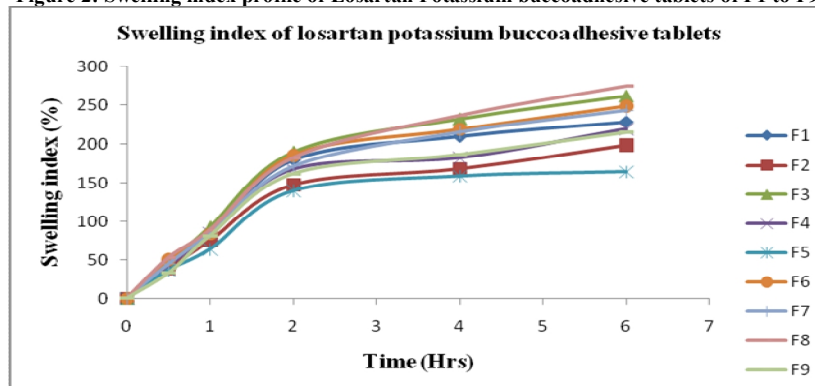


Figure 3: Bioadhesive profile of Losartan Potassium buccoadhesive tablets from F1 to F9

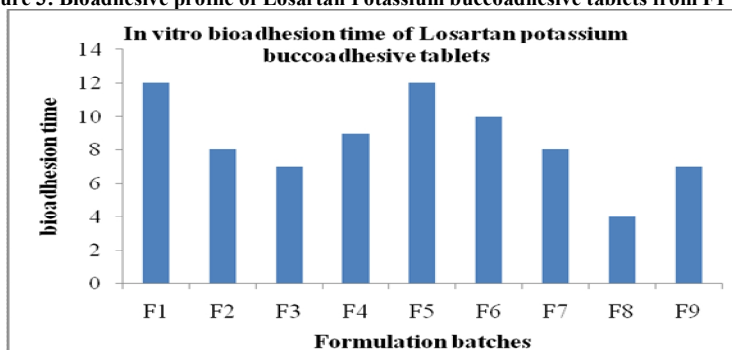
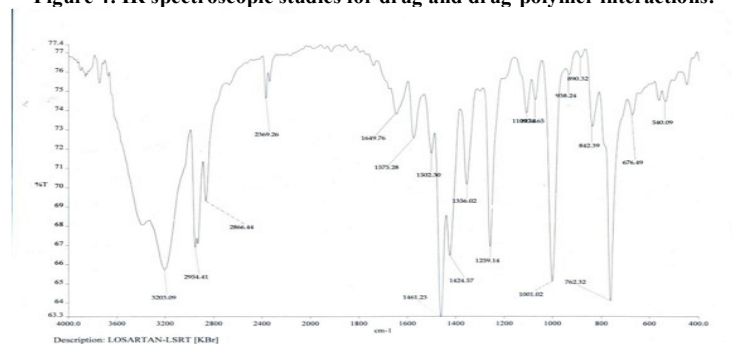


Table 5: Dissolution data of Losartan Potassium buccoadhesive tablets

Time(Hrs)	Cumulative % drug release Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	6.46±0.74	4.29±0.52	5.23±0.34	5.23±0.47	6.23±0.68	7.23±0.43	14.39±1.02	13.14±1.04	9.54±1.24
1	20.67±0.68	11.19±0.47	9.23±0.68	16.76±0.68	17.49±0.75	21.76±0.78	23.88±0.94	17.82±0.35	9.57±0.84
2	37.46±0.48	21.79±0.64	24.75±0.47	24.43±0.74	36.38±0.43	38.46±1.06	49.32±1.32	18.9±0.48	22.68±0.72
3	48.76±0.64	26.48±0.74	38.96±0.84	38.96±0.98	42.76±0.34	41.03±1.08	53.92±0.84	31.13±0.78	26.1±0.98
4	59.49±0.84	28.67±0.53	44.76±0.48	51.29±1.02	58.96±0.28	53.49±0.98	63.07±0.67	60.84±1.01	28.09±1.04
5	68.62±0.98	38.63±1.06	58.23±0.57	58.46±0.84	64.76±0.98	57.84±0.84	71.77±1.24	75.6±1.28	55.8±1.32
6	83.16±0.78	52.16±1.04	68.18±0.38	63.86±0.98	69.23±0.84	61.98±0.68	77.85±0.98	92.7±0.68	69.3±0.37
7	87.49±0.81	64.37±1.12	79.65±0.47	69.16±0.48	71.46±0.67	70.72±0.73	83.76±1.09	93.18±1.38	76.5±0.67
8	97.23±0.34	80.42±0.98	88.79±0.24	74.69±0.68	73.34±0.68	78.67±0.43	86.34±0.98	94.08±0.84	83.1±0.84
9	99.59±0.54	82.67±0.84	92.38±0.68	75.46±0.84	74.31±0.84	83.38±0.57	93.6±1.24	94.59±1.24	83.6±0.47
10	-----	85.46±0.67	94.49±0.74	82.46±0.76	76.69±0.76	85.64±0.48	93.67±1.42	95±0.84	84.6±1.24
11	-----	86.79±1.03	96.16±0.84	84.76±0.84	78.46±0.48	88.46±0.74	95.86±0.67	95.67±0.69	85.09±0.86
12	-----	88.97±0.68	97.79±0.48	86.16±0.67	80.23±0.78	91.23±0.66	97.7±0.82	96.24±0.84	85.79±0.78

Figure 4: IR spectroscopic studies for drug and drug-polymer interactions:



IR Spectral analysis for drug alone and in combination with other excipients was carried out. There is no change in peaks of mixture when compared to pure drug, it indicates the absence of interaction.

CONCLUSION

In conclusion, the aim of the present study was to develop buccoadhesive drug delivery system for Losartan Potassium with a prolonged effect and to avoid first pass metabolism. These buccoadhesive formulations of Losartan Potassium, in form of buccoadhesive tablets were developed to a satisfactory level in terms of drug release, bioadhesive time, physicochemical properties and surface pH.

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