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FORMULATION AND EVALUATION OF FLOATING TABLETS OF LOSARTAN POTASSIUM BY USING NATURAL POLYMERS

P.Meghana* and V. Saikishore

Department of Pharmaceutics, Bapatla College of Pharmacy, Bapatla - 522 101,

Abstract:

The aim of present research work is to formulate and evaluate controlled release floating tablet of Losartan Potassium in view to enhance bioavailability and therapeutic action.The tablets were formulated by employing direct compression method.The granules were evaluated for flow properties. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality. All the tablets were formulated using sodium bicarbonate as effervescent agent. All the prepared formulations floated immediately after placing into the beaker and the floating was maintained more than 14 hrs. It was observed that the carbon dioxide generated from sodium bicarbonate in presence of dissolution medium (0.1N HCL) was trapped in the polymer gel matrix formed by the hydration of polymer which decreases the density(<1) and makes the tablet buoyant. The correlation coefficient values (r) revealed that the dissolution profiles followed Zero order kinetics and the mechanism of drug release was governed by Peppas model. The n values are found to be more than 0.5 (n>0.5) indicted that the drug release was predominantly controlled by non fickian diffusion. Based on the release rate constant and % of drug release the formulations prepared with Dry mushroom powder shown prolonged retarding nature compared with the formulations prepared with Almond gum. Among all the formulations , F_3 formulation containing drug and Dry mushroom powder in 1:1.5 ratio was found to be optimized formulations.

Key words:*Losartan Potassium , Dry mushroom powder, Almond gum, Sodium bicarbonate*

Corresponding Author:

P.Meghana,

Department of Pharmaceutics,
Bapatla College of Pharmacy,
Bapatla - 522 101,
Guntur (D), A. P.,
Mobile number:8247632230
Email: meghanaparasaram@gmail.com

QR code

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INTRODUCTION:

Antihypertensive drugs have always been in the forefront of research because the cardiovascular disorders are on an increase globally. Now a day's millions of people are suffering from cardiac diseases and these drugs require chronic administration to get symptomatic relief[1].

Treatment for hypertension is a long term therapy where noncompliance is high; hence prolonged release dosage forms are required for quality health care. The hypertension condition requires the continuous availability of antihypertensive drug in the systemic circulation.Losartan Potassium is an Antihypertensive drug .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. The molecular weight of losartan potassium is 461.01. It is freely soluble in water .It has low bioavailability due to its first pass metabolism. Systemic bioavailability is about 33%. The half life of Losartan Potassium is approximately 3 hrs. It has absorption window in the gastric region[2].The objective of this study was to develop floating tablets of Losartan Potassium using natural polymer having desirable properties in order to achieve an extended retention in the upper gastrointestinal tract, which may result in enhanced absorption and there by improved bioavailability.

The gastroretentive drug delivery system can be retained in the stomach and assist in improving the oral sustained delivery of drugs.There is a need to investigate a number of indigenously available retardant material to make the concept of controlled release drug delivery more viable for the drug industry at more economical way[3].In the present study, natural polymers such as DrymushroompowderandAlmond gumwere selected for the preparation of floating tablets of Losartan Potassium . Sodium bicarbonate was used as gas generating agent. Tablets were prepared by wet granulation method using these polymers.

MATERIALS AND METHODS:

Losartan Potassium was obtained as a gratis sample from Hetero labs, Hyderabad.Almond gumand Dry mushroom powder were purchased from Yucca enterprises, Mumbai.PVP K 30 and Sodium bicarbonatewere purchased from Qualigens fine chemicals, Mumbai.All other ingredients were of analytical grade.

Preparation of Losartan Potassium floating tablets

Losartan Potassium was mixed with required quantities ofdrymushroom powder/ Almond gum, Sodium bicarbonate and Citricacid by geometric mixing . The tablets were formulated by employing dry granulation method using PVP K 30 as binder. Magnesium stearate and talc were used as lubricant and glidant respectively. The final blend was compressed into tablets using 7 mm punches and corresponding dies on rotary tablet compression machine [6].The composition of each formulation was given in Tables 1.

Evaluation Parameters

Flow properties of granules: The granules were evaluated for the following parameters [7].

a) Bulk density: 5 gm of blend was weighed and transferred to a measuring cylinder. Then bulk volume was noted. Bulk density was calculated by using the following formula

$$\text{Bulk density} = \frac{Massofthepowder}{Bulkvolume}$$

b) Tapped density: 5 gm of blend was weighed, transferred to a measuring cylinder and subjected to 100 tapings. Then volume was noted as tapped volume. Tapped density was measured by using the following formula

$$\text{Tapped density} = \frac{Massofthepowder}{Tappedvolume}$$

c)Carr's index

Carr's index was calculated by using the following formula

$$\text{Carr's index} = \frac{Tappeddensity - Bulkdensity}{Tappeddensity} \text{ X } 100$$

d) Hausner's ratio

Hausner's ratio was calculated by using the following formula

$$\text{Hausner's ratio} = \frac{Tappeddensity}{Bulkdensity}$$

e) Angle of repose

5 gm of blend was taken and poured into a hollow cylinder which was placed on a graph sheet. Then the cylinder was slowly lifted. Then height and diameter of the heap formed were noted down. The angle of repose (θ) was calculated by the formula

$$\text{Angle of repose, } \theta = \text{Tan}^{-1}\frac{h}{r}$$

Evaluation of Losartan Potassium floating tablets

a) Hardness: The hardness of the tablet was measured by Monsanto hardness 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 untilthe tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force [8]. The hardness was measured in terms of kg/cm^2.

b)Weight variation: Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated [8]. The percent weight variation was calculated by using the following formula.

$$\text{Percentage deviation of Weight Variation} = \frac{\left(\text{Individual tablet weight} - \text{Average weight of 20 tablets}\right)}{\text{Average weight of 20 tablets}} \times 100$$

c)Friability: The Roche friability test apparatus was used to determine the friability of the tablets. Twenty two pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula [8].

$$\text{Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X100$$

d) Swelling Index: Formulated tablets were weighed individually (W_0) and placed separately in Petri dish containing 50 ml of 0.1N Hydrochloric acid. The Petri dishes were placed in an incubator maintained at 37±0.5ºC. The tablets were removed from the petri dish, at predefined intervals of time and reweighed (Wt), and the % swelling index was calculated using the following formula [9]:

% W_U = (Wt-Wo/Wo) × 100

Where:

W_U – Water uptake
Wt – Weight of tablet at time t
Wo – Weight of tablet before immersion

e) In vitro buoyancy study : This test is characterized by floating lag time and total floating time. The test was performed using USP-Type II paddle apparatus using 900 ml of 0.1N Hydrochloric acidat paddle rotation of 100 rpm at 37 ± 0.5^0 C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time [10].

f) Drug content:20 tablets were weighed and powdered the powder weight equivalent to 40mg of Losartan Potassium was dissolved in 100ml of 0.1N Hydrochloric acid and filtered. 5ml of this was diluted to 50ml with water and drug content was estimated at 254nm by UV spectrophotometer [11].

g) In vitro dissolution test: The release of Losartan Potassium from the tablet was studied using USP-Type II paddle apparatus. Drug release profile was carried out in 900 ml of 0.1N Hydrochloric acidmaintained at 37 ± 0.5°C temperatures at 100 rpm. 5 ml of samples were withdrawn at regular time intervals. The samples was replaced by its equivalent volume of dissolution medium and was filtered through 0.45 µm Whatman filter paper and analyzed at 254 nm by UV spectrophotometer [12].

Drug Excipient Compatibility Studies: Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with Okra gum/ Almond gumused in tablet formulations [13].

Stability studies of optimized floating matrix tablets: The optimized floating matrix tablets were separated in to two groups. Each group of formulations were placed separately in stability chamber which is maintained at 25±5ºC/60% RH and 40±5ºC/75% RH respectively for three months and every month the formulations from each group were subjected to dissolution studies and % drug release was calculated[14].

RESULTS AND DISCUSSION:

Floating tablets ofLosartan Potassium were prepared by varying the concentration of Okra gum(F_1-F_3) and Almond gum(F_4-F_6) . The formulated granules were evaluated for various flow properties. The bulk density for all the formulations ranged from 0.525 to 0.532. The angle of repose for all the formulations was found to be in the range of 26^045^l-27^091^1. The Carr's index for all the formulations ranged from 15.33 – 15.94%. The value of bulk density indicates good packing characters. The value of angle of repose (25^0-30^0) for all the formulations indicates good flow property. The value of Carr's index (10-16%) indicates free flowing material. The values of Hausner's ratio were found to be between 1.182-1.189. The powder blend with Hauser's ratio of 1.25 has good flow properties. So the values indicate that the granules had acceptable flow properties. The flow properties were shown in table 2.

Floating matrix tablets were evaluated for hardness and friability. The hardness was found to be in

between 4.3 – 4.7 kg. The tablets satisfied friability requirement, as the % friability values were less than 1%.The drug content estimations showed values in the range of 99.87 to 100.11%, which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeia limits of ±5% of the weight. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

All the tablets were formulated using sodium bicarbonate as effervescent agent. All the prepared formulations floated immediately afterplacing into the beaker and the floating was maintained more than 14 hrs. It was observed that the carbon dioxide generated from sodium bicarbonate in presence of dissolution medium(0.1N HCL) was trapped in the polymer gel matrix formed by the hydration of polymer which decreases the density(<1) and makes the tablet buoyant. The results of various physical properties and*invitro* buoyancy studies were tabulated in table 3.

In vitro dissolution studies of all the formulations of floating matrix tablets were carried out in 0.1N HCl. The study was performed for 12 hrs and the cumulative drug release was calculated. All the formulations remained floating and intact throughout the dissolution studies. The formulations(F_1-F_3) containingDry mushroom powder showed decrease in drug release with increase in concentration of Okra gum. The drug release from formulation F_3containing drug and natural polymer in 1:1.5 ratio showed a maximum drug release at end of 12hours. The dissolution profile for the formulations F1- F3 was shown in figure 1.The formulations(F4-F6) containing Almond gumshowed decrease in drug release with increase in concentration of Almond gum. The drug release from formulation F_6containing drug and natural polymer in 1:1.5 ratio showed a maximum drug release at end of 10 hours. The dissolution profile for the formulations F4- F6 was shown in figure 2.

To ascertain the mechanism of drug release, the dissolution data was analyzed by zero order, first order, and Higuchi and Peppas equations. The correlation coefficient values (r) revealed that the dissolution profiles followed Zero order kinetics and the mechanism of drug release was governed by Peppas model. The n values are found to be more than 0.5 (n>0.5) indicted that the drug release was predominantly controlled by non fickian diffusion. The in-vitro drug release kinetic data was shown in Table 4.The swelling index studies showed a gradual increase with increase in concentration of natural polymer and were shown in Table 5.

The characteristics peaks confirmed the structure of Losartan Potassium . The same peaks were also reported in all drug loaded matrix tablet. There were no change or shifting of the characteristic peaks in matrix tablets suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in all formulations.Drug release from optimized formulations before and after storage under varying conditions were evaluated periodically at the regular interval of every month. The drug release profiles of all the formulations did not change significantly after storage at 25±2° C/60±5% RH and 40±2° C/75±5% RH for a period of 3 months. There is no significant difference in the drug content and release rate constants.The results indicated that the drug release from the optimized formulations were found to be quite stable.

CONCLUSION:

From the above results ,it is clearly evident that the invitro release of Losartan Potassium from the floating tablet was influenced by nature of natural polymer. Based on the release rate constant and % of drug release the formulations prepared withDry mushroom powder shown prolonged retarding nature compared with the formulations prepared with Almond gum. Among all the formulations , F_3 formulationcontaining drug and Dry mushroom powder in 1:1.5 ratiowas found to be optimized formulations.

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Table 1: Composition of Losartan Potassium floating tablets formulated with different natural polymers.

Ingredients	**F_1 (mg)**	**F_2 (mg)**	**F_3 (mg)**	**F_4 (mg)**	**F_5 (mg)**	**F_6 (mg)**
Losartan	**50**	**50**	**50**	**50**	**50**	**50**
Drymushroom powder	**25**	**50**	**75**			
Almond gum				**25**	**50**	**75**
Micro crystaline cellulose	**85**	**60**	**40**	**85**	**60**	**40**
Sodium bicarbonate	**50**	**50**	**50**	**50**	**50**	**50**
Citricacid	**25**	**25**	**25**	**25**	**25**	**25**
Poly Vinyl pyrolidine	**10**	**10**	**10**	**10**	**10**	**10**
Magnesium stearate	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**
Talc	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**
Total weight	**250**	**250**	**250**	**250**	**250**	**250**

Table 2: Micromeritic properties of granules of Losartan Potassium floating tablets formulated with different concentrations of natural polymers.

Formulation code	**Angle of repose (°)**	**Bulk density (gm/cm^3)**	**Tapped density (gm/cm^3)**	**Carr's index (%)**	**Hausner's ratio**
F_1	27.14	0.52	0.62	13.88	1.16
F_2	29.37	0.49	0.58	14.82	1.14
F_3	26.32	0.57	0.68	15.93	1.18
F4	27.14	0.52	0.62	13.88	1.16
F5	28.38	0.58	0.69	12.10	1.13
F6	29.26	0.54	0.65	13.76	1.15

Table 3: Physical properties of Losartan Potassium floating tablets formulated with different concentrations of natural polymers.

Formulation	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating Lag time	Total floating time (hrs)
F_1	4.77	250±2.12	0.37	100.15	145	>14
F_2	4.28	250±1.78	0.37	99.78	137	>14
F_3	4.43	249±2.36	0.52	99.56	123	>14
F_4	4.3±0.012	200.13±0.15	0.66±0.007	99.87±0.16	2.28 min	>14
F_5	4.4±0.009	200.16±0.12	0.52±0.011	99.89±0.13	2.13min	>14
F_6	4.5±0.011	199.97±0.16	0.43±0.012	99.95±0.11	1.94 min	>14

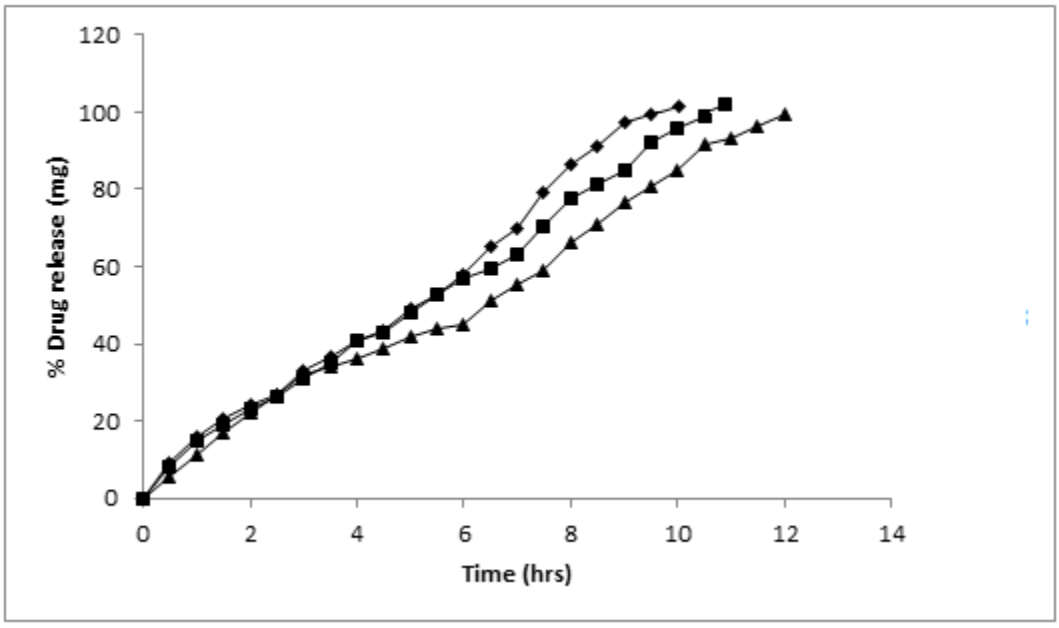
Table 4: *In vitro* drug release kinetic data ofLosartan Potassium floating tablets formulated with different concentrations of natural polymers

Formulation	Correlation Coefficient Value				Release Rate Constant (mg/hr)k_0	Exponential Coefficient (n)	T_{50} (hr)	T_{90} (hr)
	Zero Order	First Order	Matrix	Peppas				
F_1	0.9912	0.9878	0.9581	0.9984	4.76	0.8756	5.25	9.45
F_2	0.9616	0.9547	0.9863	0.9971	4.45	0.7619	5.61	9.91
F_3	0.9032	0.9820	0.9988	0.9958	4.16	0.6752	6.0	10.81
F4	0.9916	0.8094	0.9581	0.9984	6.25	0.8756	4	7.2
F5	0.9943	0.7903	0.9632	0.9979	5.5	0.7938	4.54	8.1
F6	0.9957	0.7956	0.9780	0.9912	4.99	0.7455	5.01	9.01

Table 5: Swelling index values of Losartan Potassium floating tablets formulated with different concentrations of natural polymers

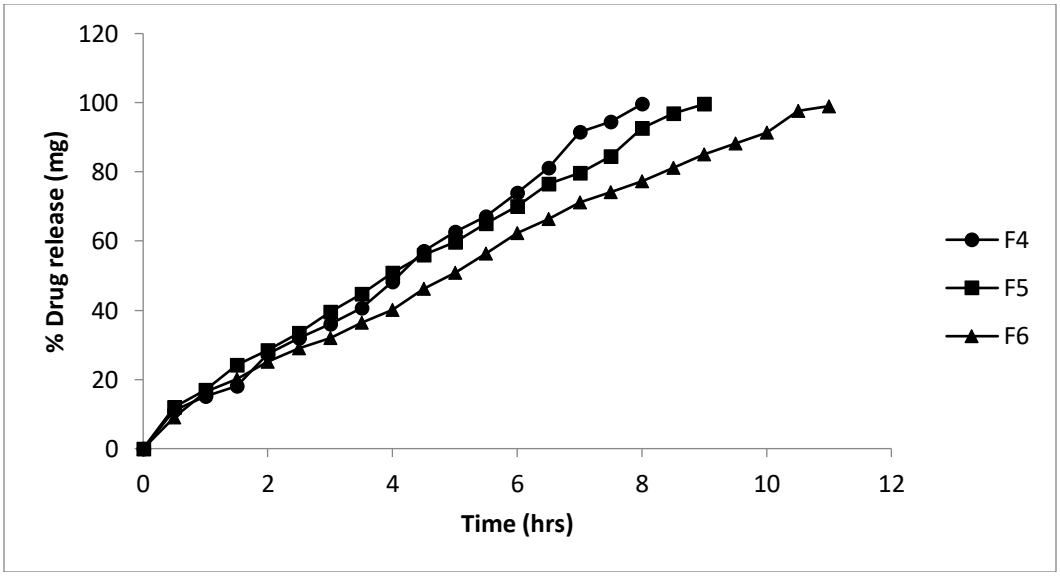
Formulation code	Swelling index		
	Time in hours		
	after 1 hour	after 2 hours	after 8hours
F_1	19.63	28.46	69.44
F_2	22.36	42.36	83.12
F_3	25.46	51.62	91.23
F_4	15.46	25.12	65.36
F_5	19.24	39.17	79.74
F_6	21.37	48.16	87.63

Figure 1: Comparative *in vitro* drug release profile of Losartan Potassium floating tablets formulated with different concentrations of Drymushroompowder



(-♦-)Floating tablets formulated with drug and Drymushroompowderin 1:0.5 ratio
(-■-)Floating tablets formulated with drug and Drymushroompowderin 1:1 ratio
(-▲-) Floating tablets formulated with drug and Drymushroompowderin 1:1.5 ratio

Figure 2: Comparative *in vitro* drug release profile of Losartan Potassium floating tablets formulated with different concentrations of Almond gum



(-♦-)Floating tablets formulated with drug and Almond gumin 1:0.5 ratio
(-■-)Floating tablets formulated with drug and Almond gumin 1:1 ratio
(-▲-) Floating tablets formulated with drug and Almond gumin 1:1.5 ratio

Figure 3 - FTIR spectrum of Losartan Potassium

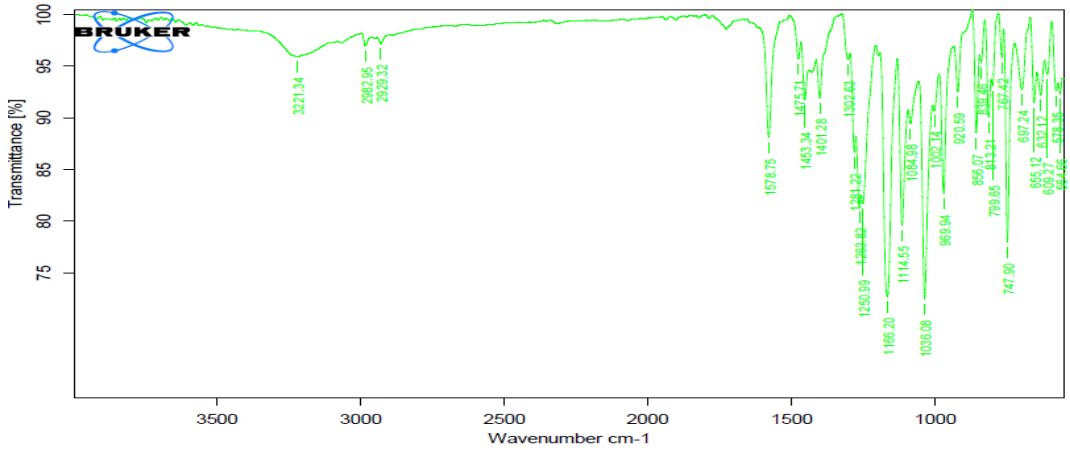


Figure 4- FTIR spectrum of Losartan Potassium floating tablet prepared with Drymushroom powder

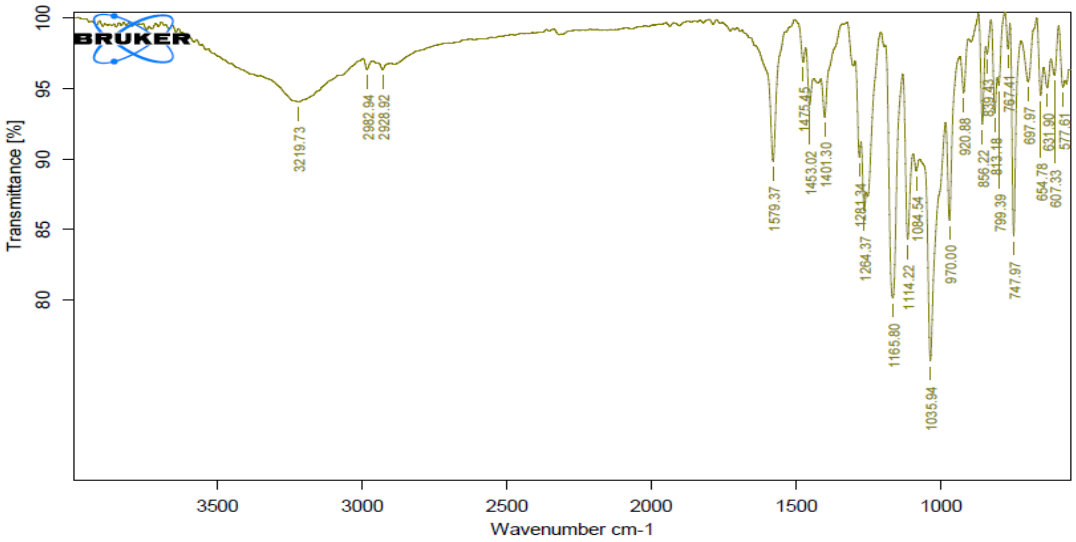


Figure 5 - FTIR spectrum of Losartan Potassium floating tablet prepared with Almond gum