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Research Article

DESIGN AND DEVELOPMENT OF PULSINCAP FOR CHRONOPHARMACEUTICAL DRUG DELIVERY OF LOSARTAN POTASSIUM

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ABSTRACT:

The aim of the present investigation is to develop a pulsatile drug delivery system based on an insoluble capsule body filled with Losartan potassium microspheres and sealed with hydrogel plug. The microspheres were prepared by Emulsification internal gelation method. The plugs of varying thickness and hardness were prepared by direct compression which was then placed in the capsule opening. The drug delivery system was designed to deliver the drug at such a time when it was needed (early hours in morning). Dissolution studies of pulsatile capsule device in media with different pH (1.2, 7.4 and6.8) showed that drug release in colon could be modulated by optimizing the concentration of polymers in the plug and also the position of plug. The study showed that, lag time prior to drug release was highly affected by the plug position. The dissolution data revealed that the plug position and the composition of plug were very important to achieve a optimum formulation. Drug–polymer interaction studies indicated no interaction or complexation in between the drug and the polymer.

KEY-WORDS: *Emulsification internal gelation method, Hydrogel plug, Losartan potassium,pulsincap, Stability studies.*

INTRODUCTION:

A chronotherapeutic agent represents a pharmaceutical product that contains a dynamic element such as a delivery system to deliver the drug at the time when it is needed. A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid or controlled or sustained drug release. [1].

These systems are beneficial for drugs having high first pass effect; drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting to colon, to increase the stability of dosage form and cases where night time dosing is required. Cardiovascular diseases, several functions (e.g. BP,heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day whereas Platelet aggregation is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Careful analysis of trials illustrate that myocardial infarction (MI), stroke, ventricular ectopy, and sudden cardiac death occur between 6 am and noon. The peak blood pressure is between 6 am and noon, with activation of the sympathetic nervous system prior to awakening, blood pressure begins to increase with the heart rate. These changes in blood pressure corresponds the morning activation in catecholamines, renin, and angiotensin. Commonly used drugs are- Nitroglycerin, Calcium channel blocker, ACE inhibitors etc.

Losartan potassium is a Angiotensin II receptor blocker selectively and specifically

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antagonize the action of angiotensin II, a potent vasoconstrictor impacting BP regulation Angiotensin II receptor blocker are becoming increasingly popular for the treatment of hypertension because they are effective and well tolerated.Losartan potassium is the first orally active angiotensin II receptor antagonist, losartan is extensively metabolized in liver. It is widely prescribed in the treatment of hypertension. It undergoes extensive biotransformation and has an elimination halflife 1.5 – 2hr. It can used for the therapy of symptoms or disease that according to circadian rhythms and chronobiology become worse during night or in early morning. For these cases conventional drug delivery system are inappropriate for the delivery of drug, as they cannot be administrated just before the symptoms are worsened because at that time the patients are sleeping [2].

The rational of this study is to design and evaluate an oral site-specific, pulsatile drug delivery system containing Losartan potassium, which can be targeted to colon in a pH and time dependent manner, to modulate the drug level in synchrony with the circadian rhythm of blood pressure early in morning hours. In the present research work, we have attempted to develop a novel dosage form by using a chronopharmaceutical approach.

A pulsatile 'microspheres in Capsule' dosage form, taken at bed time with a programmed start of drug release early in morning hours, can prevent a sharp increase in the incidence of high BP ,during the early morning hours, a time when the risk of heart attack is the greatest[3].

MATERIALS AND METHODS:

Materials:

Losartan potassium was obtained as a gift sample from Aurobindo pharma Ltd (Hyderabad). $Baco_3$, Sodium alginate, guar gum and Xanthan gum was gifted by Himedia Lab's Pvt Ltd.

Methods:

Preparation of Cross-Linked Gelatin Capsules:

The '0' sized hard gelatin capsules; about 100 in number were taken. The bodies of the capsules were then placed on a wire mesh. 25ml of 15% v/v formaldehyde was taken into a desiccators and a pinch of potassium permanganate was added to it to generate formalin vapours. The reaction was carried out for 12 hours. After which the bodies were removed and dried at 50□C for 30 minutes to ensure completion of reaction between gelatin and formaldehyde vapour. The bodies were dried at room temperature to facilitate removal of residual formaldehyde [4].

Preparation of Losartan potassium microspheres by Emulsification internal gelation method:

Microspheres containing Losartan potassium were prepared employing sodium alginate alone and in combination with xanthan gum and guar gum,$Baco_3$as crosslinking agent. The homogeneous polymer(s) solution was prepared in distilled water stirred magnetically with gentle heat. The drug and cross-linking agent were added to the polymer solution and mixed thoroughly by stirring magnetically to form a viscous dispersion which was then extruded through a syringe with a needle of size no. 23 into light liquid paraffin containing 1.5% Tween 80w/v and 0.2%v/v glacial acetic acid being kept under magnetic stirring at 100 rpm. The microspheres were retained in the light liquid paraffin for 30 min to produce rigid discrete particles. They were collected by decantation and the product thus separated was washed with chloroform to remove the traces of paraffin oil [5]. The microspheres were dried at $40^{O}C$ under vacuum for 12 h.The compositions of the microspheres formulations are listed in Table 1.

Table:1 Composition of different microspheres formulations of Losartan potassium.

Formula	Drug + Sodium alginate			Drug + Sodium alginate + Guar gum			Drug + Sodium alginate+ Xanthan gum		
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
	1:4	1:6	1:8	1:4	1:6	1:8	1:4	1:6	1:8
Losartan potassium (mg)	500	500	500	500	500	500	500	500	500
Sodium alginate (mg)	2000	3000	4000	1000	1500	2000	1000	1500	2000
$Baco_3$ (mg)	500	500	500	500	500	500	500	500	500
Guar gum (mg)	-	-	-	1000	1500	2000	-	-	-
Xanthan gum (mg)	-	-	-	-	-	-	1000	1500	2000

Evaluation of microspheres:

a. Flow properties of microspheres[6-7]:

The prepared microspheres were evaluated for Angle of repose, Bulk density, Tapped Density, Carr's Index, Hausner's Ratio.

b. ***Size Distribution and Particle Size Analysis:***

The particle size of microspheres was determined by using optical microscopy method in which 100 particles were measured using light microscope.

c. ***Estimation of Losartan potassium content: (drug content) :***

The drug content in each formulation was determined by triturating 100mg microspheres and powder equivalent to average weight was added in 100ml of 6.8 pH phosphate buffer, followed by stirring. The solution was filtered, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 234 nm using 6.8 pH phosphate buffer as blank.

d. ***Entrapment Efficiency:***

Entrapment efficiency was calculated using the formula.

$$\text{Entrapment efficiency} = \frac{\text{Amount of drug entrapped in microspheres}}{\text{Total amount of drug}} \times 100$$

e. ***SEM Analysis:***

The samples for the SEM analysis were prepared by sprinkling the microspheres on one side of the double adhesive stub. The stub was then coated with fine gold dust. The microspheres were then observed with the scanning electron microscope.

f. ***%Yield of Microspheres :***

Microspheres recovered at the end of preparation were weighed and the yield was calculated as a percentage of the total amounts of polymer and drug added during the preparation of microspheres.

$$\%\text{Yield} = \frac{\text{Practical yield of microspheres}}{\text{Theoretical yield of microspheres}} * 100$$

Preparation and evaluation of Hydrogel Plug:

Four types of plugs were prepared by compressing polymer: lactose (1:1) ratio using 7 mm punches and dies on rotary tablet punching machine. The hydrogel plugs were evaluated for thickness, hardness, and lag time

parameters. The composition and evaluation values of different types of plugs were given in the table 5-6 respectively. Fig.1 represents the lag times of different hydrogel plugs.[8]

Designing of Pulsincap:

The Pulsincap was similar in appearance to a hard gelatin capsules, but the main body was water insoluble. Losartan potassium microspheres were placed into the formaldehyde treated bodies by hand filling. The capsules containing the microspheres were then plugged with optimized hydrogel plug. The joint of the capsule body and cap was sealed with a small amount of the 5% ethyl cellulose ethanolic solution. The sealed capsules were completely coated by dip coating method with 5% CAP in 8:2 (v/v) mixture of acetone: ethanol plasticized with dibutylphthalate (0.75%), to prevent variable gastric emptying. Coating was repeated until an 8–12% increase in weight is obtained. % weight gain of the capsules before and after coating was determined [9].

In-vitro release profile of pulsatile capsule containing Losartan potassium microspheres:

Dissolution studies were carried out by using USP XXIII dissolution test apparatus (paddle method). Capsule was tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 hours (since the average gastric emptying time is 2 hrs.), then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 hours (average small intestinal transit time is 3 hrs.), then the medium was removed and colonic fluid pH 6.8 buffer was added for subsequent hours[7]. Nine hundred milliliters of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5°C.A sample of microspheres equivalent to 50mg of losartan potassium was used in each test. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 234nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.

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 Xanthan gum, Guar gum and $BaCo_3$, used in microspheres formulations. In the present study 1:1 ratio was used for preparation of physical mixtures and analyzed for compatibility studies [11].

RESULTS:

Pulsincap dosage form was a capsule which consists of a water insoluble body and a water soluble cap. The drug formulation (microspheres) was sealed within the capsule body by means of a hydrogel plug.

The primary reaction of formaldehyde with gelatin (main constituent of capsule) probably is the formation of methylol amines. The tannin effect is due to a condensation reaction which transforms the methyl group into cross linking methylene bridges. The capsule bodies which were exposed to formaldehyde vapours for 12hrs were not dissolved in PH 7.4 phosphate buffer medium even after 48hrs (hardened capsule bodies were softened only after 24hrs). Thus for the present study, capsule bodies which were exposed to formaldehyde vapors to12hrs were chosen for the preparation of pulsincap. It was sealed with unhardened cap of the capsule. The formulations fitted with the various hydrogel plugs HP1,HP2, HP3, HP4 shown 0.2,6.18,16.37,18.84 of drug release respectively at the end of 5th hour . It was observed that 100 mg hydrogel plug (HPMC

K100 and lactose in 1:1 ratio) having 4.7kg/cm^2 hardness was satisfactory to retard the drug release in small intestinal fluid and to ejected out the plug in colonic fluid and releasing the microspheres into colonic fluid. The results were shown in the table 2 and figure 1.

Table:2 Evaluation characteristics of hydrogel plugs.

Hydrogel Plug Code	Thickness (mm)	Hardness (kg/cm^2)	Lag time (hours)
HP_1	3.16	4.7	5
HP_2	3.29	4.2	4.5
HP_3	3.24	3.8	4
HP_4	3.54	3.5	3

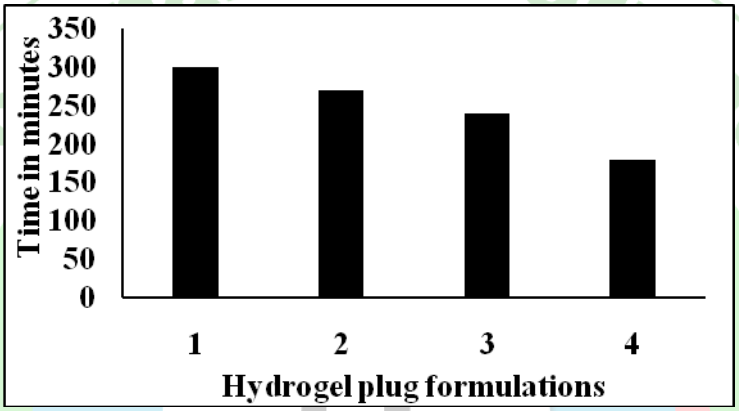

Figure:1 Lag time for hydrogel plugs:

HP_1: hydrogel plug prepared with 1:1 ratio of HPMC K 100 and Lactose.
HP_2: hydrogel plug prepared with 1:2 ratio of Carbapol and Lactose
HP_3: hydrogel plug prepared with 1:3 ratio ofNa CMC and Lactose.
HP_4: hydrogel plug prepared with 1:3 ratio ofMethyl cellulose and Lactose.

During dissolution studies, it was observed that, the polymers used coat of the cellulose acetate phthalate was intact for 2 h in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 7.4, then the exposed polymer plug absorbed the surrounding fluid, swelled and released the drug through the swollen microspheres. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body; releasing the microspheres into simulated colonic fluid (pH 6.8 phosphate buffer). With all the formulations, there was absolutely no drug release in pH 1.2, thus indicating the efficiency of 5% CAP for enteric coating.

From the *In-vitro* release studies of device, it was observed that with all formulation, there was absolutely no drug release in simulated gastric fluid (acidic pH 1.2) for 2 hours and in simulated intestinal fluid (pH 7.4 phosphate buffer). Burst effect was found in colonic medium (pH 6.8 phosphate buffer). *In-vitro* releae profiles in colonic medium were found to have very good sustaining efficacy.This process produced uniform microspheres. These microspheres were characterized for size analysis, flow properties, % Drug Content,% Entrapment effiiency. All the formulations offered good flow property. The technique also showed good entrapment efficiency.The micrometric parameters like angle of repose, bulk density and tapped density of all microspheres confirms better flow and packaging properties. All the formulations showed good flow ability represents in terms of angle of repose, Carr's index, and Hausner's ratio.

The microspheres were found to be discrete, spherical and free flowing. The % yield was found to be in the range of 88%-93%. The mean particle size of the various formulations was found to be in the range of 625.34-718.68µm.The results are given in Table 3 and figure 2.

Table: 3 Evaluation Tests of Losartan potassium microspheres Formulated with Sodium alginate alone and as combinations with Guar gum and xanthan gum in Different Ratios.

Formulation	Angle of repose (θ)	Carr's Index (%)	Hausner's Ratio	Average Particle Size(µ)	% yield	%Encapsulation Efficiency	% Drug content
F_1	33.42	14.43	1.12	632.34	90	98	19.6
F_2	32.53	12.67	1.14	702.32	92	97.05	13.86
F_3	34.78	13.81	1.18	662.53	89	97.03	10.79
F_4	31.7	11.45	1.14	654.19	93	98.5	19.7
F_5	32.53	13.52	1.17	692.27	91	95.09	13.58
F_6	33.69	14.76	1.15	705.47	88	94.33	10.49
F_7	31.54	11.65	1.17	635.26	91	98.40	19.68
F_8	32.67	13.49	1.15	718.68	89	96.21	13.74
F_9	34.54	15.79	1.16	698.52	93	98.65	10.97

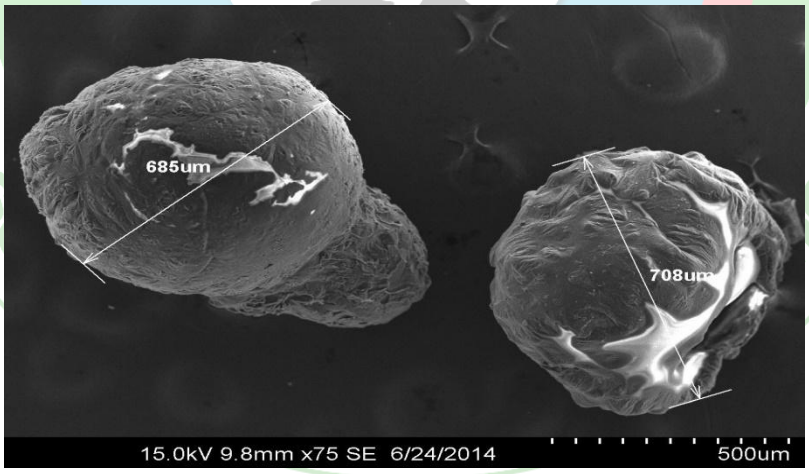

Figure:2 SEM Photograph showing particle size of microspheres:

Pulsincaps loaded with microspheres prepared with Losartan potassium and Sodium alginate in 1:4,1:6 and 1:8 ratios shown sustained drug release for a period of 7 hours (5^{th}hour to 12^{th} hour), 8 hours (5^{th} hour to 13^{th} hour) and 10.5 hours(5^{th} hour to 15.5^{th} hour) respectively. Pulsincaps loaded with microspheres prepared with Losartan potassium and Sodium alginate + Guar gum in 1:4,1:6 and 1:8 ratios shown sustained drug release for a period of 7.5 hours(5^{th} hour to 12.5^{th} hour), 8.5 hours (5^{th} hour to 13.5^{th} hour) and 11 hours(5^{th} hour to 16^{th} hour) respectively. Pulsincaps loaded with microspheres prepared with Losartan potassium and Sodium alginate + Xanthan

gum in 1:4,1:6 and 1:8 ratios shown sustained drug release for a period of 8.5 hours (5th hour to 13.5th hour), 10.5 hours (5th hour to 15.5th hour) and 12 hours(5th hour to 17th hour) respectively. Comparative *In-vitro* drug release profiles plot of Losartan potassium microspheres prepared with Sodium alginate, Sodium alginate + Guar gum, Sodium alginate + Xanthan gum in different ratios by Emulsification internal gelation method were shown in figure 3-5, shows that F9 formulation has more sustained action compared to other formulations.

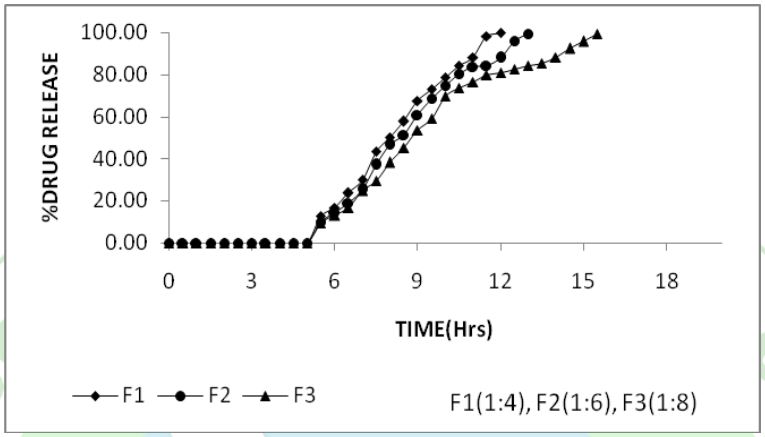

Figure:3In-vitro drug release profile plot of pulsatile device consisting of Losartan potassium microspheres prepared with Sodium alginate in different ratios

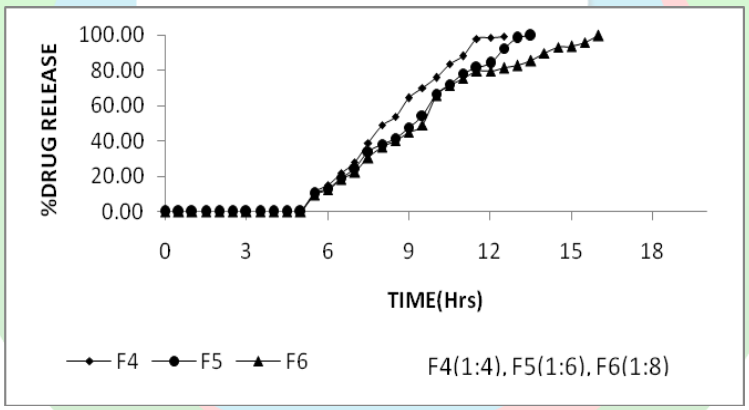

Figure: 4In-vitro drug release profile plot of pulsatile devise consisting of Losartan potassium microspheres prepared with Sodium alginate and guar gum in different ratios

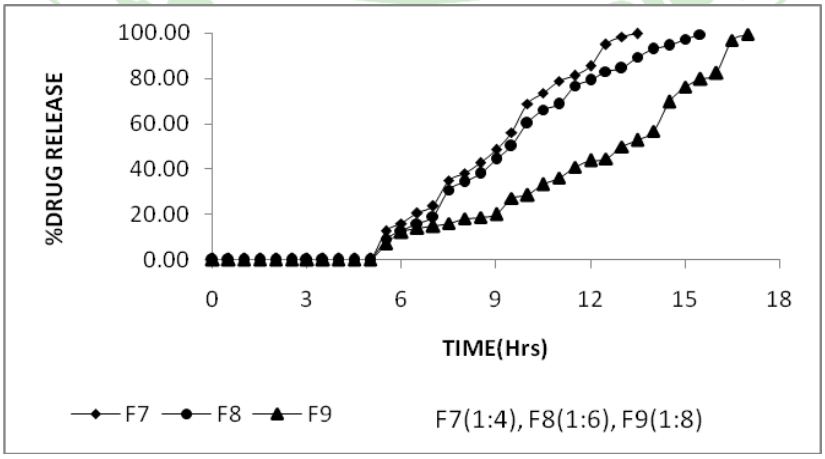

Figure: 5In-vitro drug release profile plot of pulsatile device consisting of Losartan potassium microspheres prepared with Sodium alginate and xanthan gum in different ratios

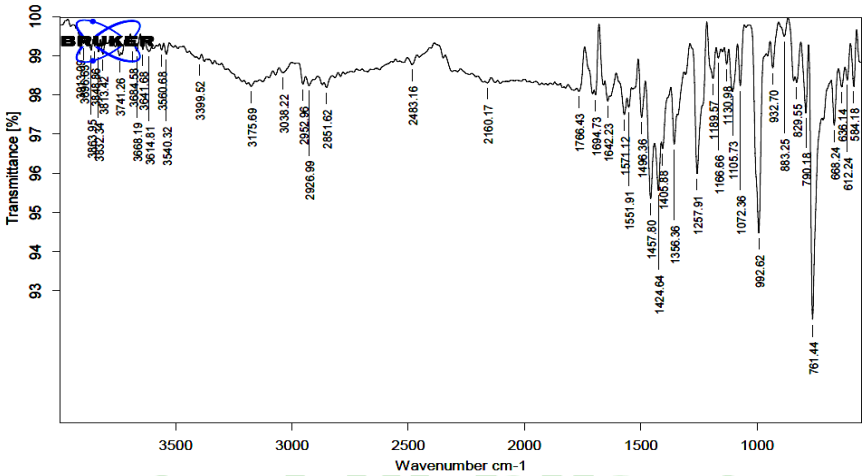

Figure:6 FTIR graph of formulation containing Losartan potassium:

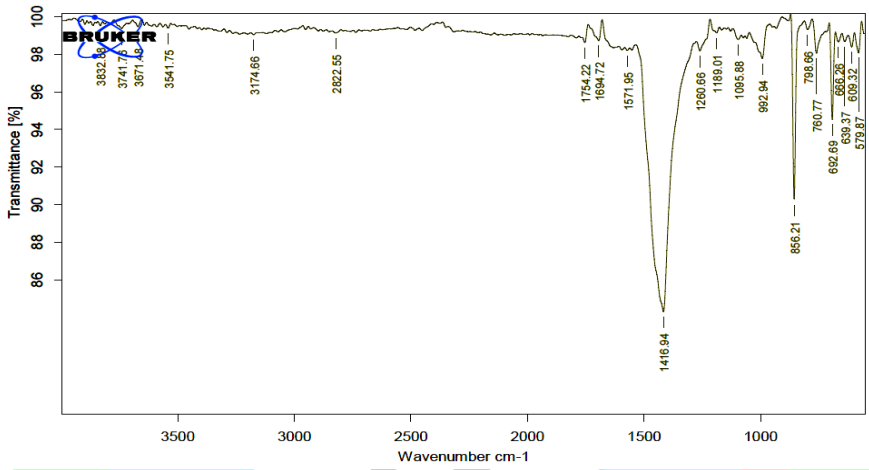

Figure:7 FTIR graph of formulation containing Drug + Sodium alginate + Baco$_3$:

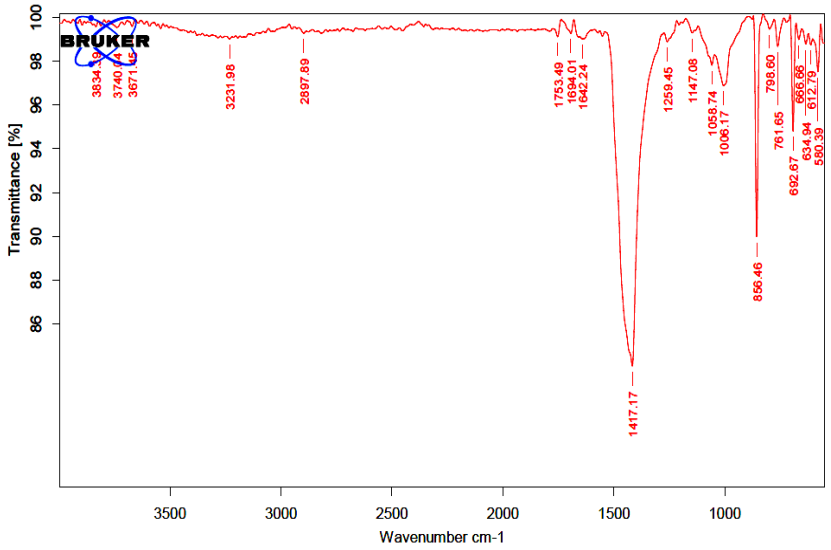

Figure:8 FTIR graph of formulation containing Drug + guar gum + Baco$_3$:

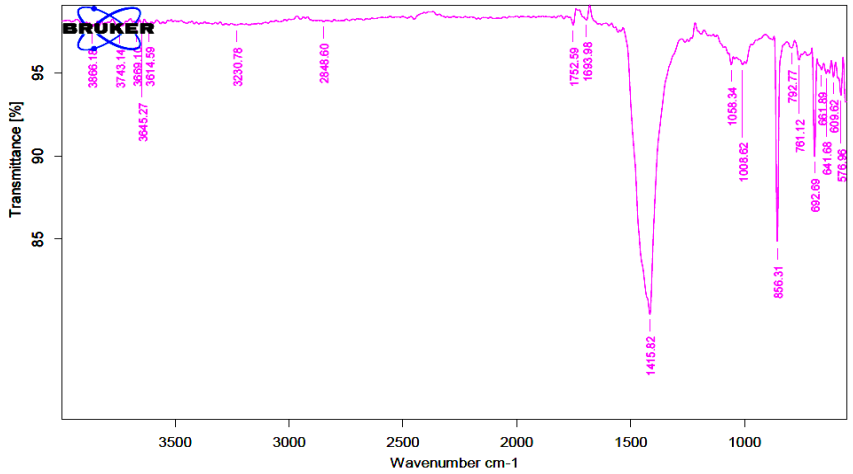

Figure:9 FTIR graph of formulation containing Drug + xanthan gum + Baco$_3$:

Compatibility studies of Losartan potassium (FTIR):

Drug- excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. The characteristic absorption peaks of Losartan potassium appeared at 3038.22,3399.52,1130.98,1642.23,1356.36,1571.12 and 2926.99 denoting stretching vibration of C-H-,N-H-,O-H-,C=N,C-N,N=N and aromatic ring, respectively. Form the figures (6-9) it was observed that same peaks were also reported in all drug loaded microspheres. There was no change or shifting of characteristic peaks in drug loaded microspheres suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in all formulations.

CONCLUSION:

It is possible to release a drug over a predetermined period of time with specific release rates by controlling the polymers used to prepare plugs. The obtained results showed the capability of the system in delaying drug release for a programmable period of time and the possibility of exploiting such delay to attain colon targeting.

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