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Preparation and Evaluation of Chronopharmaceutical Drug Delivery of Lansoprazole.

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Research Article

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ABSTRACT

The aim of the present investigation is to develop a pulsatile drug delivery system basedon an insoluble capsule body filled with Lansoprazole matrix tablet and sealed with HPMC K 100 plug. The Lansoprazole matrix tablets were prepared by wet granulation 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 (nocturnal time). 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 drugrelease 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.

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. The interest in pulsatile delivery has been developing in close connection with emerging chronotherapeutic views. In this respect, it is by now well established that the symptoms of many pathologies are subject to circadian variation patterns. Hence, the possibility of accomplishing effective drug levels in accordance with the specific temporal requirements of an illness state holds considerable appeal in that it could improve therapeutic outcome.

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.

Pulsatile delivery systems are generally classified into time controlled and site specific delivery systems. The release from the first group is primarily controlled by the system, while the release from the second group is primarily controlled by the biological environment in the gastro intestinal tract such as pH or enzymes.

Lansoprazole is an antiulcer drug belonging to the class of proton pump inhibitor. Lansoprazole is a benzimidazole sulfoxide derivative and produces long lasting inhibition of gastric acid secretion. Lansoprazole is effective in the treatment of duodenal or gastric ulcer, gastro esophageal reflux disease and in the treatment of zollinger-ellison syndrome.

In Peptic ulcer patients, pain, gastric distress and acute exacerbation of the disease are most likely in the late evening and early morning hours. Ulcer pain typically occurs after stomach emptying, following daytime meals

and in the very early morning, disrupting sleep. This is attributed to high gastric secretion and slows gastric motility and emptying at night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Once daily nocturnal administration of proton pump inhibitor medications not only reduce acid secretion more effectively but also promotes ulcer healing and reduce ulcer occurrence.

The rational of this study is to design and evaluate an oral site-specific, pulsatile drug delivery system containing Lansoprazole, 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 nocturnal acid secretion. In the present research work, we have attempted to develop a novel dosage form by using a chronopharmaceutical approach.

A pulsatile 'Tablet 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 gastric acid secretion,during the early morning hours, a time when the risk of peptic ulcer is the greatest [1,2].

In the present study, polymers such as Gum karaya, Xanthan gum, are selected for the preparation of matrix tablets of Lansoprazole by wet granulation method and isopropyl alcohol as granulating agent.

MATERIALS AND METHODS

Materials

Lansoprazole was obtained as a gift sample from Hetero labs (Hyderabad), Gum karaya, and Xanthan gum was gifted by Yarrow Chem. Products (Mumbai). All other excipients used were of analytical grade.

Method

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 [3].

Preparation of Lansoprazolegranules and tablets

Lansoprazole granules were prepared by using different drug: polymer ratioseach respectively as per formulae given in table 1.1. The tablets were formulated by employing wet granulation method using PVP K-30 as binder, isopropyl alcohol as granulating fluid, magnesium stearate as lubricant and talc as glidant. The required quantities of Lansoprazole, polymer, lactose, and PVP K-30 were weighed and mixed well. Then it was made into damp mass using a mixture of isopropyl alcohol as granulating fluid. The resulting damp masses were screened by passing them manually through a 12 no. mesh size and dried for 30 minutes at 35±0.5ºC in the oven and then screened through a 16 no. mesh and then dried to constant weight in the oven. The granules were then mixed with the required quantities of lubricants, glidant and then compressed into tablets using 5mm punches and dies on rotary tablet punching machine [4].

Flow properties of granules

Angle of repose

Ten grams of the granules was placed in a plugged glass funnel which had a distance of 10cm from the flat surface. The granules were then allowed to flow through the funnel orifice by removing the cotton plug from the funnel orifice. The height of the heap (*h*) formed as well as the radius of the heap (*r*) was noted. The angle of repose (θ) was calculated as

$$\text{Tan } \theta = h/r$$

Bulk and Tapped densities

Ten grams of the granules were carefully poured into a 50ml graduated cylinder. The volume occupied by the granules was read and the bulk density calculated in gm/ml. The cylinder containing the granules was tapped until constant volume was obtained using bulk density apparatus from a height of 2cm and the tapped density calculated in gm/ml.

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Percentage compressibility (Carr's index) andHausner's ratio:

The percentage compressibility (CI) was calculated from the difference between the tapped (*Td*) and the bulk densities (*Bd*) divided by the tapped density and the ratio expressed as a percentage. The Hausner's ratio (HR) is the ratio between the tapped and bulk density.

$$CI = (Td - Bd)/ Td$$

$$HR = Td/Bd$$

The evaluation values of granules were showed in table 1.2.

Evaluation of tablets [4]

Tablet thickness

The thickness of ten tablets was determined using a vernier calliper and the mean of these readings was taken as the mean tablet thickness.

Tablet weight uniformity

Ten tablets were weighed individually on electric balance from which the mean was calculated and the percentage deviations determined.

Friability

The friability of the tablets was determined using the Roche friabilator. Five tablets were weighed and put into the friabilator and set to rotate at 25 rounds per minute for about four minutes. The tablets were then removed and weighed again. The friability (F) is given by the formula;

$$F = (1-W/Wo)\times 100$$

Hardness

The tablets to be tested are held between a fixed and a moving jaw of hardness test apparatus (Monsanto) and reading of the indicator is adjusted to zero. The screw knob was moved forward until the tablet breaks and the force required breaking the tablet was noted.

Drug content

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100 ml of 6.8 pH phosphate buffer, followed by stirring. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 285 nm using 6.8 pH phosphate buffer as blank.The evaluation values of tablets were showed in table 1.3.

Preparation and evaluation of Hydrogel Plug [5]

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 1.4 and table 1.5 respectively. Fig.1.1 represents the lag times of different hydrogel plugs.

Designing of Pulsincap [6]

The Pulsincap was similar in appearance to a hard gelatin capsules, but the main body was water insoluble. Lansoprazole tablets were placed into the formaldehyde treated bodies by hand filling. The capsules containing the tablets 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.

e-ISSN: 2320-1215
p-ISSN: 2322-0112

In-vitro dissolution profile of pulsatile capsule containing Lansoprazole matrix tablet [7]

Dissolution studies were carried out by using USP XXIII dissolution test apparatus. 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 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. 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. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 285 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.*In-vitro* dissolution profile of pulsatile capsule containing Lansoprazole matrix tablets prepared with xanthan gum and gum karaya were given in the table 1.6 and1.7 respectively.

Fig. 1.2 and 1.3 shows the percentage drug release profile of pulsatile capsule containing Lansoprazole matrix tablets prepared with xanthan gum and gum karaya.

Drug-Excipient Interaction Studies [8]

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, gum karaya, diluents and lubricants used in tablet formulations. In the present study 1:1 ratio was used for preparation of physical mixtures and analyzed for compatibility studies. Fig. 1.4, 1.5, and 1.6 were the FTIR graphs of Lansoprazole, physical mixture of Lansoprazole and xanthan gum, and physical mixture of Lansoprazole and Gum karaya respectively.

Stability Studies [9]

Stability studies as per ICH guidelines were carried out for optimized formulation. The stability studies were carried out at 25 ± 20 °C / 60 ± 5% RH and 40 ± 20 °C / 75 ± 5% RH for 3 months.

OBSERVATIONS AND RESULTS

Pulsincap dosage form was a capsule which consists of a water insoluble body and a water soluble cap. The drug formulation (matrix tablet) 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 pulsincaps. It was sealed with unhardened cap of the capsule.

Table 1.1: composition of Lansoprazole matrix tablets with different ratios of natural polymers.

Formula	Xanthan gum			Gum karaya		
	F_1	F_2	F_3	F_4	F_5	F_6
	1:1	1:2	1:3	1:1	1:2	1:3
Lansoprazole (mg)	30	30	30	30	30	30
Polymer (mg)	30	60	90	30	60	90
PVP K-30 (mg)	10	10	10	10	10	10
Lactose (mg)	75	45	15	75	45	15
Isopropyl alcohol (ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate (mg)	3	3	3	3	3	3
Talc (mg)	2	2	2	2	2	2
Total (mg)	150	150	150	150	150	150

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p-ISSN: 2322-0112

Table 1.2: Evaluation tests of granules.

Formulation code	Angle of repose	Bulk density	Tapped density	Compressibility index	Haussners ratio
F_1	26.94±0.021	0.276±0.014	0.314±0.013	12.10±0.024	1.137±0.012
F_2	25.6±0.031	0.350±0.012	0.408±0.011	14.21±0.022	1.161±0.014
F_3	25.42±0.052	0.320±0.020	0.370±0.009	11.89±0.009	1.134±0.017
F_4	26.40.0±0.07	0.271±0.021	0.316±0.011	14.240±0.019	1.166±0.019
F_5	27.32±0.09	0.314±0.018	0.366±0.019	14.207±0.027	1.165±0.011
F_6	26.54±0.13	0.353±0.027	0.400±0.014	11.750±0.017	1.133±0.027

Table 1.3: Evaluation tests of tablets.

Parameters	Formulations					
	F_1	F_2	F_3	F_4	F_5	F_6
Tablet thickness (mm)	3.1±0.01	3.6±0.05	3.4±0.03	3.5±0.05	3.1±0.04	3.3±0.05
Hardness	4.7±0.021	4.5±0.025	4.8±0.032	4.7 ±0.02	4.4 ±0.04	4.8 ±0.02
Tablet weight uniformity (mg)	150±1	150±4	150±1	150±2	150±3	150±5
Friability	0.40±0.010	0.34±0.018	0.45±0.024	0.42±0.026	0.39±0.025	0.40±0.032
Drug content	100.1±0.13	99.78±0.15	99.56±0.11	101.52±0.23	99.87±0.41	100.23±0.46
Dissolution studies	99.24±0.06	99.68±0.04	99.31±0.09	99.38±0.08	98.94±0.11	98.85±0.10

Table 1.4: composition of hydrogel plugs.

Hydrogel plugs	Ingredients (1:1)	Quantity (mg)
HP1	HPMC K-100:Lactose	100
HP2	Carbapol:Lactose	100
HP3	Na CMC:Lactose	100
HP4	Methyl Cellulose:Lactose	100

Table1.5: Evaluation characteristics of hydrogel plugs.

Hydrogel Plug Code	Weight(mg)	Thickness(mm)	Hardness (kg/cm^2)	Lag time (hours)
HP1	100	3.16	4.5	5
HP2	100	3.29	4.2	4.5
HP3	100	3.24	3.8	4
HP4	100	3.54	3.5	3

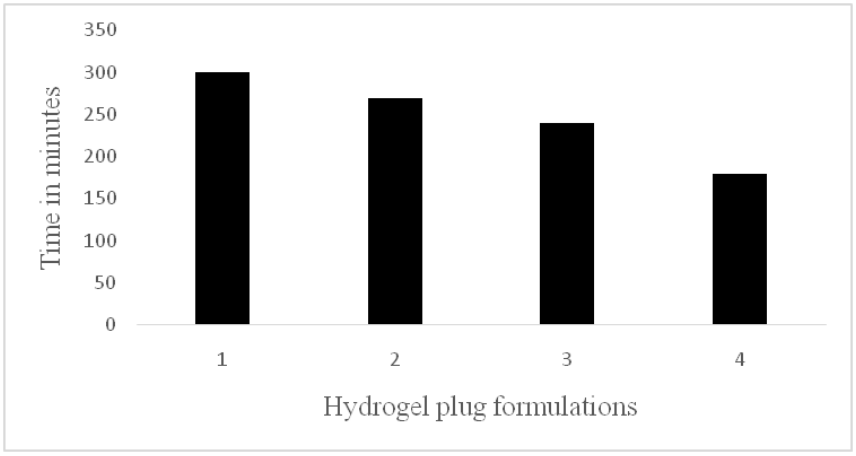

Figure 1.1: Plot of Lag times for hydrogel plugs.

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Table 1.6: *In vitro* Dissolution data of pulsatile devise consisting of Lansoprazole tablets prepared with xanthan gum in different ratios by wet granulation method.

Time (hrs.)	% of drug release		
	F_1	F_2	F_3
0.5	0	0	0
1	0	0	0
1.5	0	0	0
2	0	0	0
2.5	0	0	0
3	0	0	0
3.5	0	0	0
4	0	0	0
4.5	0	0	0
5	0	0	0
5.5	05.98±0.03	04.66±0.06	03.93±0.06
6	12.09±0.08	09.57±0.12	08.25±0.12
6.5	18.83±0.06	13.99±0.06	11.00±0.07
7	24.69±0.04	19.95±0.09	16.61±0.03
7.5	30.64±0.11	25.34±0.07	20.74±0.08
8	37.68±0.06	29.98±0.15	25.02±0.05
8.5	43.90±0.09	35.56±0.13	28.99±0.15
9	50.09±0.04	40.38±0.11	33.04±0.12
9.5	56.84±0.07	46.02±0.04	35.87±0.09
10	62.37±0.13	50.83±0.06	41.94±0.15
10.5	68.00±0.05	55.74±0.09	45.81±0.11
11	74.97±0.15	60.00±0.04	49.76±0.06
11.5	80.00±0.09	66.01±0.09	54.65±0.09
12	87.04±0.04	70.59±0.07	58.51±0.14
12.5	92.80±0.15	76.26±0.15	61.87±0.11
13	99.24±0.06	80.63±0.09	66.82±0.03
13.5		85.69±0.14	71.15±0.07
14		90.11±0.11	74.17±0.09
14.5		94.55±0.06	77.87±0.03
15		99.68±0.04	82.90±0.06
15.5			86.65±0.12
16			91.07±0.15
16.5			94.85±0.03
17			99.31±0.09

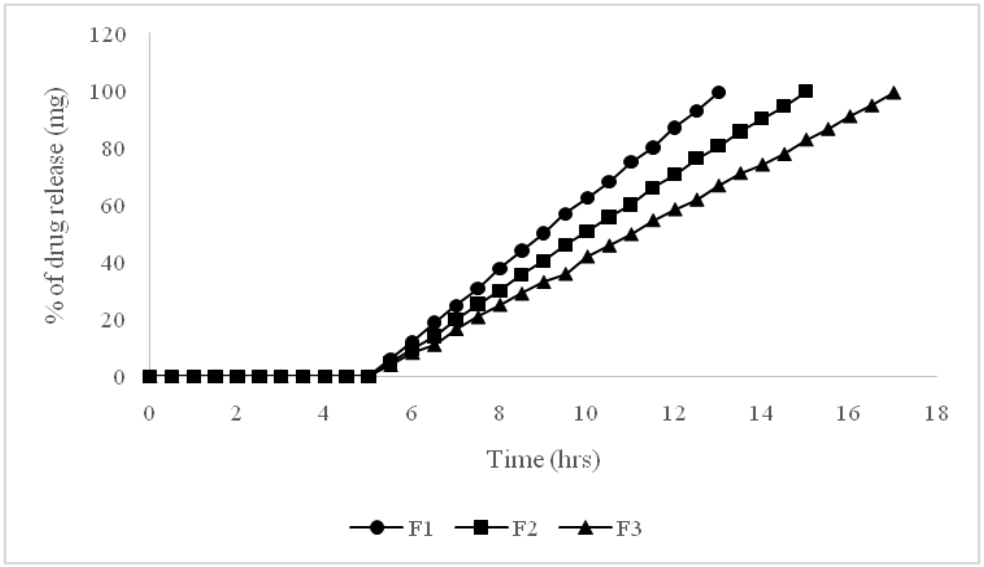

Figure 1.2: Comparative *In-vitro* drug release profile plot of Lansoprazole tablets prepared with xanthan gum in different ratios by wet granulation method.

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Table 1.7: In-vitro Dissolution data of pulsatile devise consisting of Lansoprazole tablets prepared with gum karaya in different ratios by wet granulation method.

Time (hrs.)	% of drug release		
	F_4	F_5	F_6
0.5	0	0	0
1	0	0	0
1.5	0	0	0
2	0	0	0
2.5	0	0	0
3	0	0	0
3.5	0	0	0
4	0	0	0
4.5	0	0	0
5	0	0	0
5.5	06.70±0.05	05.32±0.09	04.00±0.03
6	14.21±0.03	10.63±0.13	09.70±0.06
6.5	21.63±0.10	15.39±0.07	13.32±0.13
7	29.35±0.09	20.69±0.05	18.69±0.11
7.5	34.86±0.15	26.95±0.08	22.95±0.04
8	42.52±0.06	33.45±0.03	27.04±0.12
8.5	50.02±0.11	37.20±0.09	31.02±0.08
9	57.04±0.08	42.49±0.07	36.88±0.05
9.5	64.02±0.04	48.01±0.14	40.58±0.03
10	71.18±0.09	53.36±0.11	45.23±0.07
10.5	78.18±0.03	58.60±0.06	50.04±0.10
11	85.87±0.11	65.33±0.09	54.40±0.13
11.5	92.28±0.13	69.06±0.12	58.99±0.11
12	99.38±0.08	74.05±0.14	62.95±0.08
12.5		79.74±0.03	67.84±0.04
13		85.45±0.08	72.37±0.13
13.5		90.53±0.13	75.40±0.09
14		98.94±0.11	81.75±0.05
14.5			86.15±0.08
15			94.53±0.03
15.5			97.68±0.09
16			98.85±0.10

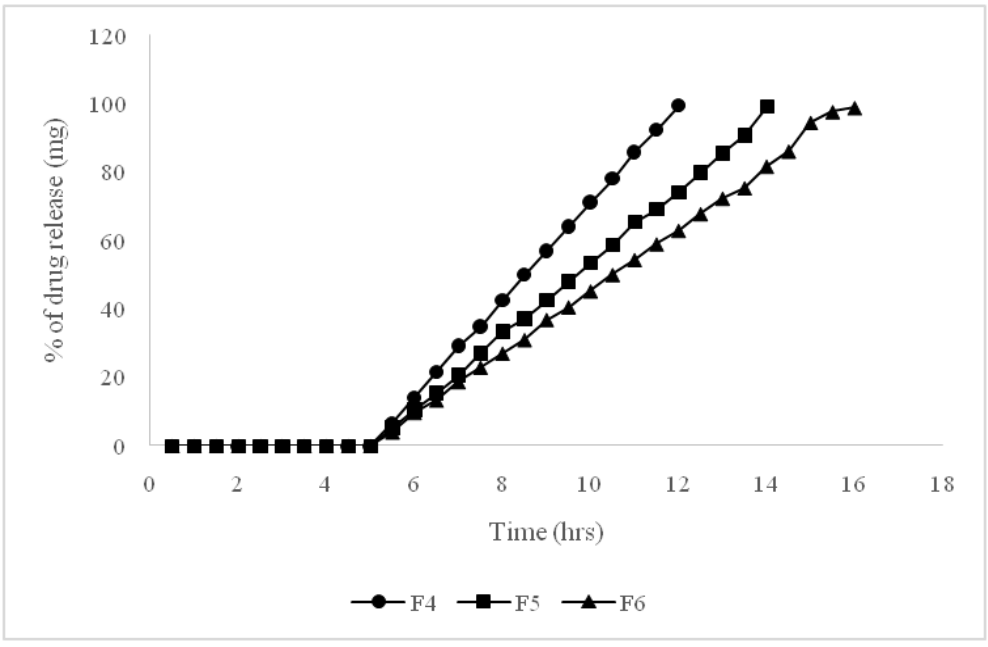

Figure 1.3: Comparative *In-vitro* drug release profile plot of Lansoprazole tablets prepared with gum karaya in different ratios by wet granulation method.

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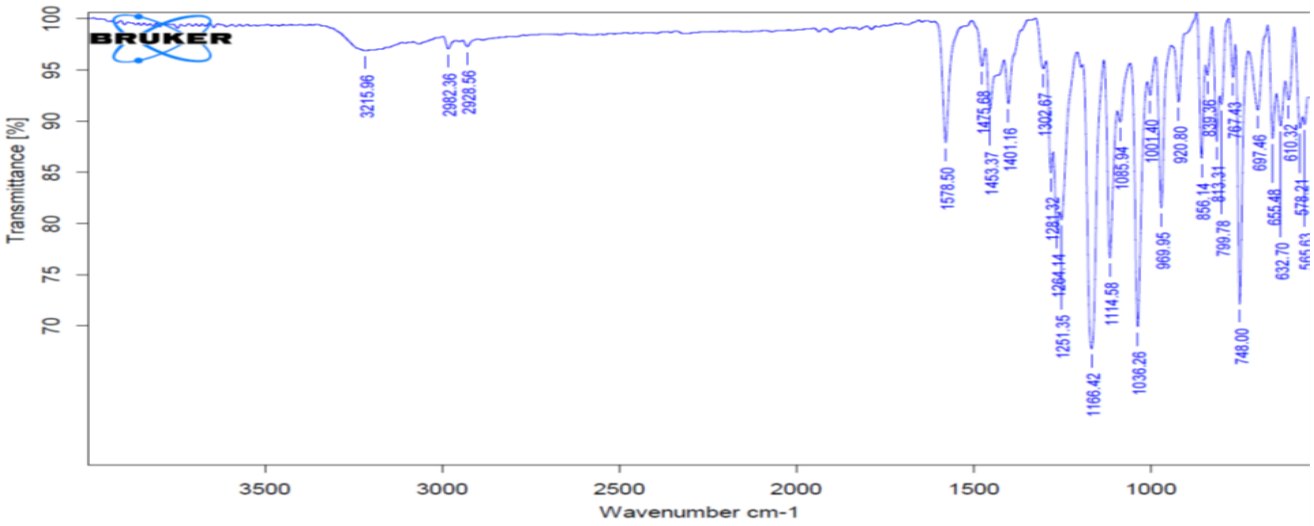

Figure 1.4: FTIR graph of Lansoprazole.

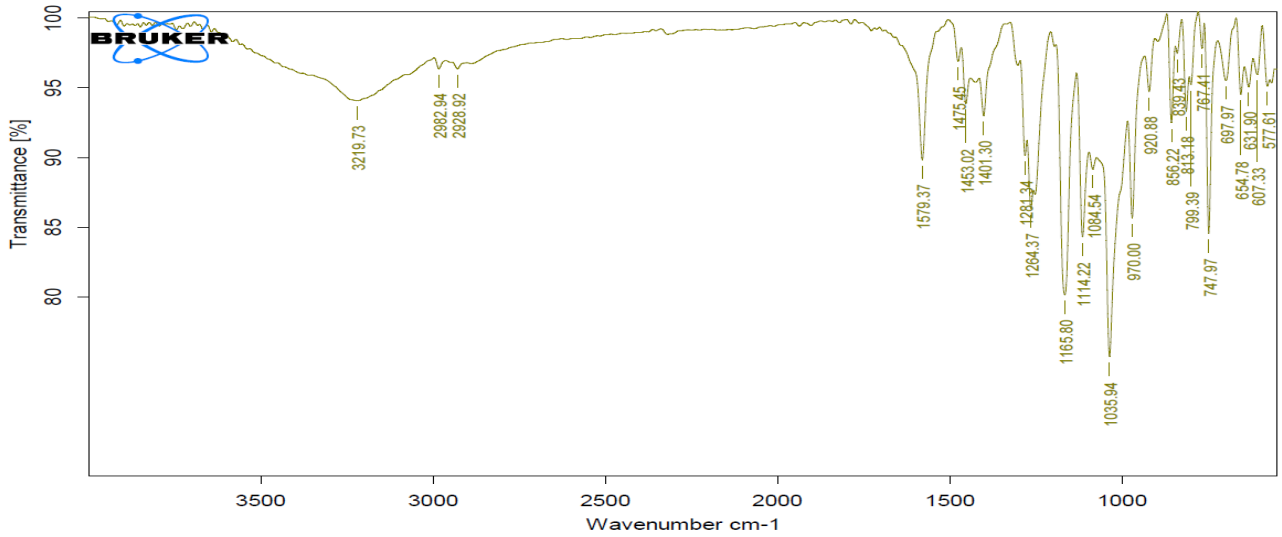

Figure 1.5: FTIR graph of formulation containing Lansoprazole and xanthan gum.

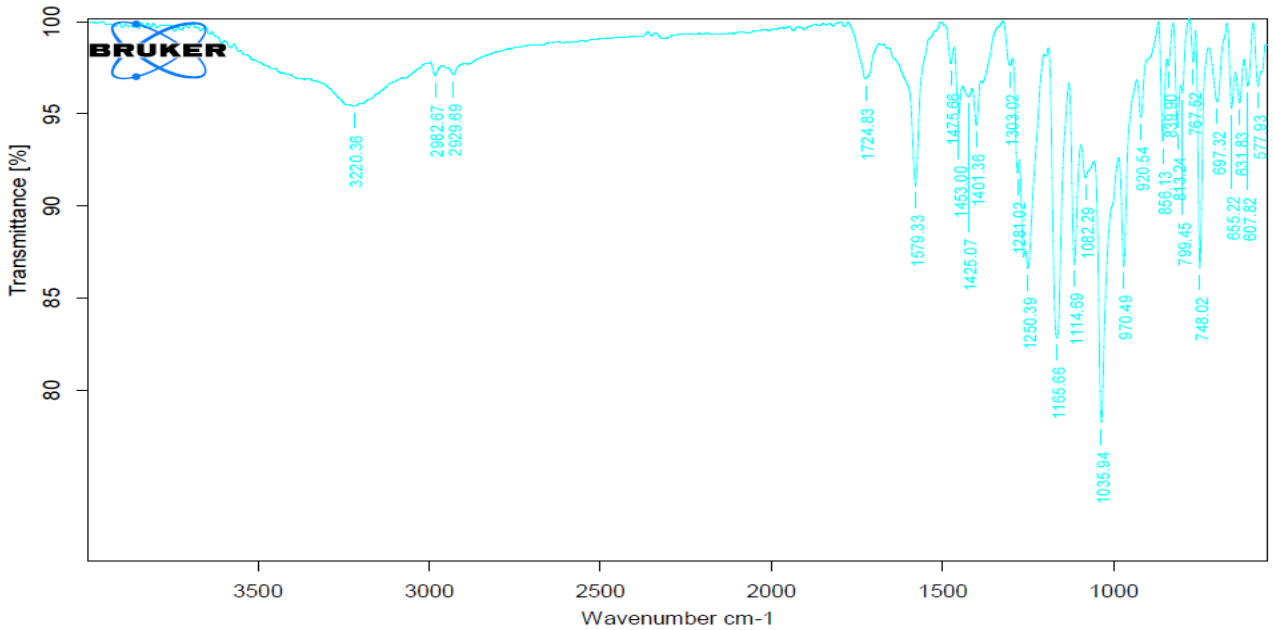

Figure 1.6: FTIR graph of formulation containing Lansoprazole and gum karaya.

The formulations fitted with the various hydrogel plugs HP1,HP2, HP3, HP4 shown 0.4% , 7.18 % , 15.65 % and 18.25 % 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 4.5kg/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 matrix tablet into colonic fluid.

During dissolution studies, it was observed that, the enteric 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 matrix. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body; releasing the matrix tablet 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* release profiles in colonic medium were found to have very good sustaining efficacy.

Pulsin caps loaded with matrix tablets prepared with Lansoprazole and xanthan gum in 1:1,1:2 and 1:3 ratios shown sustained drug rlelease for a period of 8 hours(5th hour to 13th hour), 10 hours (5th hour to 15th hour) and 12 hours(5th hour to 17th hour) respectively.

Comparative *In-vitro* drug release profiles plot of Lansoprazole tablets prepared with xanthan gum in different ratios by wet granulation method were shown in table 1.6 and in figure 1.2.

Pulsin caps loaded with matrix tablets prepared with Lansoprazole and Gum karaya in 1:1,1:2 and 1:3 ratios shown sustained drug release for a period of 7 hours(5th hour to 12th hour), 9 hours (5th hour to 14th hour) and 11 hours(5th hour to 16th hour) respectively.

Comparative *In-vitro* drug release profiles plot of Lansoprazole tablets prepared with gum karaya in different ratios by wet granulation method were shown in table 1.7 and in figure 1.3.

The FTIR study reveals that the same characteristic features of pure drug were also observed in the drug loaded matrix tablets. Thus there was no significant drug polymer interaction which indicates the stable nature of the drug in all formulations.

The pulsin capsules were packed in the screw capped bottles and stored at 25 ± 2ºC, 60 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% RH for 3 months. Drug release from pulsin capsules before and after storage under varying conditions was evaluated periodically at the regular interval of every month. The results indicated that the drug release from the pulsin capsules was not changed significantly when stored at varying conditions. Thus the drug release from pulsin capsules was found be quite stable.

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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