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Research Article

FORMULATION AND EVALUATION OF PANTOPRAZOLE FLOATING TABLET BY USING NATURAL GUM

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ABSTRACT

The objective of this research work was to formulate and evaluate the floating drug delivery system containing Pantoprazole tablets were prepared by direct compression technique. Formulations contained *Limonia acidissima,* Xanthan gum, and gas generating agent such as sodium bicarbonate and citric acid. Physical parameters like hardness, weight variation, thickness and friability were within pharmacopoeial limit. Percentage drug content in all floating tablet formulations was found to be 90% to 110%. A lesser floating lag time and a prolonged floating duration could be achieved by varying the amount of effervescent and using different polymer combinations. The *in vitro* drug release profiles obtained for tablets (F3) made with combinations of *Limonia gum* and xanthan gum showed lesser floating lag time(46 s) and a prolonged floating duration (18 hrs) which was a sustained release characteristic (94.30%) for 18h. Hydrophilic polymer like *Limonia gum* (10%) and Xanthan gum (10%) was found to be optimum. Xanthan gum was useful in the formation of matrix and Limonia gum was used as a drug release retardant. Among all the formulation, F4 showed drug release upto 94.30% at the end of 18 hours.

Keywords: *Limonia Acidissima,* Xanthan gum, Floating Tablet, Pantoprazole, swelling studies.

INTRODUCTION

Gastric floating drug delivery (GFDD) offers a number of benefits for drugs with poor bioavailability because of narrow absorption window in the upper part of the gastrointestinal tract. The gastric emptying time mainly depends upon on the design of the dosage form and physiological state of the subject, which last from a few minutes to 12hrs.[1, 2] The average gastric emptying time in human is 2-3hrs through major absorption zone (stomach and upper part of the intestine), which leads to incomplete drug release from the DDS leading to diminished efficacy of the administered dose.[3, 4] So drugs which have stability problem, GRDF plays an important role. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilities.

GRDF will also greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time.[5]

Pantoprazole is protein pump inhibitor (PPI) used for the treatment of acute duodenal ulcer, acute benign gastric ulcer, gastro-esophageal reflux disease (GERD) and prophylactic use in duodenal ulcer. It acts by competitive inhibition of H+/K+ ATPase enzyme of the gastric parietal cells resulting in reduced gastric acid secretion i.e. having local action in the stomach. The recommended oral dosage is generally 20 mg for acute duodenal ulcer, acute benign gastric ulcer and gastro esophageal reflux (GERD) and is prescribed for the duration of 8-12 weeks. The drug has a short biological half-life (1-2 h) and local action in stomach which makes it suitable candidate for FDDS.[6]

MATERIAL AND METHODS

Materials

Pantoprazole was obtained as a Kind gift sample by MNS Laboratories Ltd. *Limonia gum* was collected from the incised trunk of *Limonia acidissima* tree in Yawal region. Talc and Magnesium stearate from Loba Chem (Mumbai, India). All other chemicals and ingredients were used for study are of Analytical grade.

Characterization of Gum

Procurement of plant material

The gum of *Limonia acidissima* Linn was collected from local area in Yawal region of Jalgaon district Maharashtra.

Drying and size reduction

After collection and procurement, gum of *Limonia acidissima* Linn were subjected to drying in normal environmental conditions and then size reduction to coarse powder by pulverization. The powdered drug was stored in a tightly packed polythene bags.[7]

Extraction and Isolation *Limonia acidissima* of gum

The limonia gum was collected from *Limonia acidissima* trees (injured trunk site). It was dried, milled and passed through sieve no 80. Dried gum was stirred in distilled water for 6-8 h at room temperature. The supernatant was obtained by centrifugation. The residue was washed with water and the washings were added to separate supernatant. The procedure was repeated four more times. Finally the supernatant was made up to 500 ml and treated with twice the volume of acetone by

continuous stirring. The precipitated material was washed with acetone and dried at 50-60°C under vacuum. The dried gum was pulverized and stored in tightly closed container.

Physicochemical properties of *Limonia acidissima* gum

The physicochemical properties such as visual identification, solubility, pH, Ash value, and loss on drying, pre-compression parameters and microbial load of the *limonia* gum were determined according to official Procedures.

Characterization of Drug and Excipients using Fourier transform infrared spectroscopy

FTIR spectra of pure Pantoprazole, *limonia* gum and physical mixture of drug and excipients were recorded on Shimadzu Corporation, (Tokyo, Japan) Model-1601 PC. The Fourier transform-infrared (FT-IR) spectrum of the sample was recorded in an IR spectrometer using potassium bromide (KBr) discs prepared from powdered samples. [8]

Formulation of Pantoprazole Tablet

On the basis of results obtained from prelimary formulation study. The floating tablets of pantoprazole using *Limonia acidissima* gum and xanthan gum combination were prepared by direct compression method. Drug, Polymer and other excipients (except talc and magnesium streate) were mixed thoroughly, passed thoroughly, passed through sieved number 40 and compressed using multi-punch tablet compression machine after adding talc and magnesium stearate. 8 different formulations were prepared in which amount of all the ingredients (except polymers) were kept constant including drug.

Table 1: Formulation of floating tablets of Pantoprazole

Formulation	F1	F2	F3	F4	F5	F6	F7
Drug	20	20	20	20	20	20	20
Limonia Acidissima	10	20	30	40	50	60	70
Xanthan Gum	70	60	50	40	30	20	10
Sodium Bicarbonate	50	50	50	50	50	50	50
Citric Acid	20	20	20	20	20	20	20
Talc	5	5	5	5	5	5	5
Mg Stearate	5	5	5	5	5	5	5
Lactose	20	20	20	20	20	20	20
Total	200	200	200	200	200	200	200

Evaluation of Pre-compression Parameters of Drug Polymeric Blend

Excipients, polymers and drug were characterized for their physical properties such as angle of repose, density, compressibility, Hausner's ratio.

Evaluation of Floating Tablets

Thickness
The crown thickness of individual tablets is measured with a Vernier Caliper. The crown thickness of individual tablets is also determined for the purpose of determining the density of tablet compacts.[9]

Hardness
Hardness of the tablet is determined using Monsanto hardness tester. The tablet to be tested is placed between the spindle and anvil and pressure is applied by turning the knurled knob just sufficiently to hold the tablet in position. The reading of pointer on scale is then adjusted to zero. The pressure is now increased as uniformly as possible until tablet breaks. The pointer now reads the pressure required to break the tablet.

Friability
Twenty tablets were accurately weighed and placed inside the chamber of friabilator. The apparatus was rotated for 100 revolutions. After rotations, the tablets were weighed and the loss in weight was determined. The loss in weight should not be more than 1%.

$$\% F = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Weight variation test
To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.[10]

Floating Behavior
The *in-vitro* buoyancy was determined by floating lag time and floating time. The tablets were placed in dissolution vessel containing 900 ml of 0.1N HCl. The time required for the tablet to rise to the surface and afloat was determined as floating lag time. The duration for which the tablet remains afloat on surface of solution is known as floating time [11]

Floating Lag Time
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Buoyancy Time
The time during which dosage forms remain buoyant was measured.[12]

Swelling Index
Swelling increases as the time passes because the polymer gradually absorbs water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolved and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form.[13]

Swelling Behavior of tablets

The swelling of the polymers can be measured by their ability to absorb water and swell. Water uptake studies of the formulation were performed using USP dissolution apparatus II. The medium used was 0.1 N HCl (900mL) rotated at 50 rpm, and maintained at 37 ± 0.5°C through- out the study. After a selected time interval, the formulation is withdrawn, blotted to remove excess water and weighed [14-15]. Swelling characteristics of the tablets expressed in terms of water uptake (WU) are calculated as follow-

$$WU\ \% = \frac{\text{Swollen weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Uniformity of drug content

From each batch 10 tablets were weighed. Tablets were triturated in mortar and quantity of powder equivalent to 10 mg of Pantoprazole was transferred to 100 ml volumetric flask. Sufficient quantity of 0.1N HCl was added with shaking and volume was made upto the mark. Further dilutions were made and the absorbance was recorded at 291 nm against 0.1N HCl as a blank. [16]

***In-vitro* dissolution studies**

In-vitro release of Pantoprazole from floating tablet was carried out using the USP dissolution test apparatus (Type-I). Dissolution media used was 900 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 50 rpm. At predetermined time intervals, 10 ml of sample was withdrawn and replaced with equal amount of 0.1 N HCI (pH 1.2). The collected samples were filtered and suitably diluted with 0.1 N HCI and analyzed spectrophotometrically at 291 nm to determine the amount of drug released in the dissolution medium.[17]

Accelerated Stability Testing

Stability testing of formulation batch was carried out to determine the stability of drug and carrier and also to determine the physical stability of formulation under accelerated storage condition at 45ºC/70%RH. The prepared tablets were placed in borosilicate screw capped glass containers. The samples were kept at condition of 45°C/70% RH and were analyzed at 7th, 14^{th,} 21st and 28th days for drug content, hardness and *in-vitro* dissolution study [18]

RESULT AND DISCUSSION

Physicochemical properties And Evaluation of *limonia acidissima gum*

The limonia gum is soluble in water and practically insoluble in alcohol, acetone and chloroform. The moisture content was low, suggesting its suitability in formulations containing moisture sensitive drugs. A 1% w/v solution of gum in water gave a pH of 6.9. The total ash and acid insoluble ash value of limonia gum was found to be 2.41% and 0.41%w/w respectively. The bulk density is 0.34 and tapped densities are 0.38. The compressibility index and angle of repose of limonia gum was 11.76% and 23.53° respectively, implying that the limonia gum has a good compressibility with moderate flow. The loss on drying, ash value and microbial count were well within official limits.

Characterization of Drug and Polymer

In order to determine possible interaction between the pantoprazole drug, limonia gum and other excipients used in the formulation, compatibility studies were conducted using FTIR spectroscopy. There was no significant shift in the positions of the wave numbers when compared to that of the pure drug values. Thus there was no interaction between the drug and other excipients of the formulation.

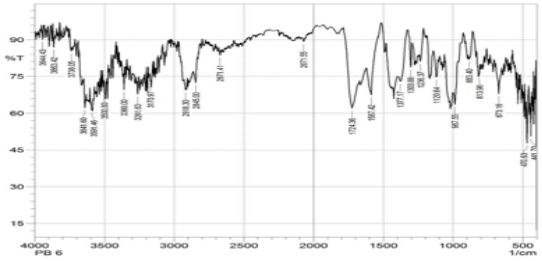

Figure 1: FT-IR spectrum of drug and polymer

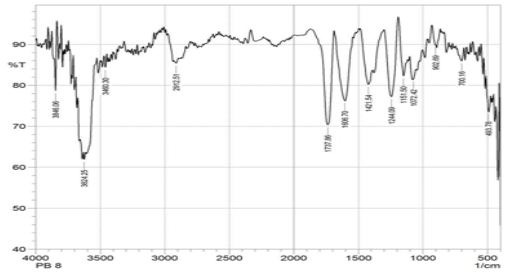

Figure 2: FT-IR spectrum of *Limonia acidissima*

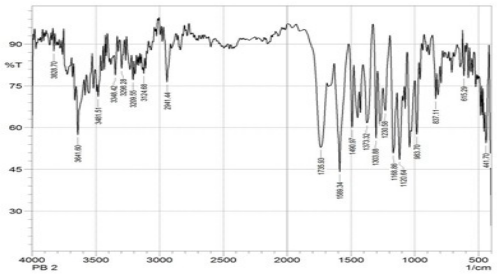

Figure 3: FT-IR spectrum of Pantoprazole + *Limonia acidissima* Gum

Pre-compression parameters

The bulk density obtained for all the formulations in the range of 0.655 to 0.726 (g/ml) and the tapped density in the range of 0.725 to 0.441(g/ml). The Angle of repose of the powder blend of all the formulations was found in range of 17.29° to 18.61° which is in the good or in the acceptable range means showing the good flowability necessary for proper flow of powder blend into the die cavity. The Carr's index of the powder blend of all the formulations was found in the range of 7.02 to 13.63% which is good or in the acceptable range means showing good or fair flowability for proper flow of powder blend. The Hausner's ratio was found to be in the range of 2.098 – 2.185. All these results indicated that, the powder mixture possess good flow of powder blend. The prepared powder mixtures were evaluated for the physical properties like bulk density, tapped density, Carr's index and angle of repose and Hausner's ratio. Results obtained are shown below:

Table 2: Physical parameters of powder blend contain *Limonia acidissima* gum

Formulations	Parameters				
	Bulk Density (g/ml) ±SD	Tapped Density (g/ml) ±SD	Angle of Repose (^{0}) ±SD	Carr's Index (%)±SD	Hausner's Ratio ±SD
F1	0.719±0.02	0.799±0.04	17.29±0.89	10.01±0.23	2.129±0.04
F2	0.706±0.01	0.814±0.02	18.61±0.18	13.26±0.46	2.178±0.006
F3	0.725±0.01	0.791±0.02	8.34±0.49	13.63±0.48	2.185±0.007
F4	0.726±0.03	0.91±0.03	18.10±0.51	20.39±0.49	2.103±0.006
F5	0.655±0.01	0.725±0.01	18.31±0.85	10.60±1.13	2.125±0.003
F6	0.701±0.03	0.761±0.04	16.44±0.56	7.88±0.58	2.098±0.007
F7	0.683±0.02	0.782±0.03	17.55±0.85	12.65±0.64	2.170±0.008

Evaluation of Floating Tablets

The prepared final formulation of floating tablets was evaluated for hardness, thickness, % friability and weight variation. The results obtained indicated that the physical parameters were within pharmacopoeial limit. As dissolution medium was imbibed into the matrix, the interaction of acidic fluid with sodium bicarbonate resulted in the formation and entrapment of carbon dioxide gas within the swollen gel thus, causing floatation as the matrix volume expanded and its density decreased. Therefore floating system was chosen to compromise the matrix integrity with the possible shortest lag time and floating duration more than 12 h. It was observed that all the tablets floated within 4-5 min after immersion into 900 ml 0.1 N HCl at 37 ± 0.5 °C in the dissolution vessels and the systems remain buoyant over the entire dissolution period in each case.

Tablets from each batch showed uniformity of content in the range 90% to 110% which is within pharmacopoeial specifications. All the formulations complies the test for uniformity of content as it found to be within the limit of 90-110%.

Table 3: Physical parameters of Pantoprazole Floating tablets

Batches	Parameters						
	Hardness (kg/cm^2)	Thickness (mm ±)	% Friability	Wt. Variation	F_{lag} (sec) (FLT)	Floating Time (h)	Uniformity of Content (%)
F1	4.4±0.20	2.148±0.05	0.454±0.305	198.9±2.286	46±1.52	>18	99.98
F2	5.6±0.50	2.218±0.02	0.7745±0.159	199.8±1.609	38±2.08	>18	99.38
F3	5.4±0.25	2.238±0.06	0.4172±0.102	198.75±2.29	52±3.05	>18	99.58
F4	5.2±0.50	2.144±0.03	0.4969±0.133	199.25±1.44	46±2.08	>18	99.78
F5	4.4±0.15	2.150±0.01	0.7304±0.189	199.9±1.943	34±3.51	>18	99.69
F6	4.6±0.60	2.362±0.05	0.6340±0.253	199±1.026	109±1.15	<12	99.48
F7	4.6±0.15	2.526±0.05	0.4044±0.165	199±1.712	135±1.23	<12	99.73

(n=3)

Swelling behavior

The matrices behavior can be ascribed to a natural hydration process. Hydrophilic matrices in contact with water swell and increase their volume and weight due to water diffusion through the matrix. The polymer is getting hydrated as it absorbs the dissolution medium. The increasing dissolution medium content dilutes the matrix until an extrication concentration is attained. At this point, the arrangements of polymer molecules become lose and polymer molecules tend to diffused into the bulk of the dissolution medium. Hence, due to polymer dissolution, the matrix volume decreases slowly. Simultaneously swelling, polymer dissolution and diffusion were observed in Polymeric matrices.

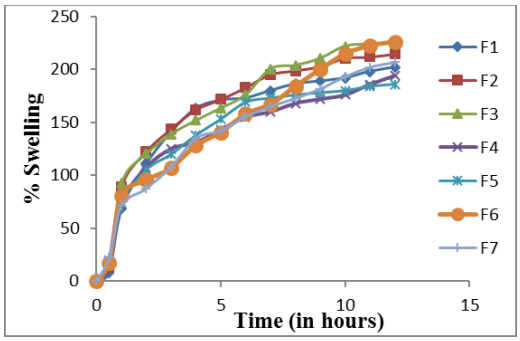

Figure 4: % Water uptake for F1-F7 Batches of Pantoprazole Floating tablets

In-vitro dissolution

Floating tablet showed sustained release of the drug in acidic condition (pH 1.2) and the drug release was found to be approximately linear. Approximately 4.95-10.65% of the drug was released initially. Furthermore, drug release from the floating tablet was controlled by the polymer. As the polymer content was increased and the drug loading was decreased, the release of drug was decreased significantly. In order to increase the release rate of drug, the ratio of polymer was decreased and plasticizer was increased. The combination polymer of final formulation F3, F4 &F5 showed best appropriate balance between buoyancy and drug release rate. Results of cumulative % release have been shown in tubular and graphical form. Among all the formulation, F3 shows 94.30% release at the end of 18 hrs. It was found cumulative percentage of drug release decreases with increase in limonia gum concentration.

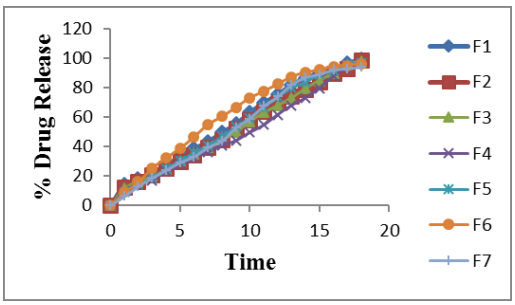

Figure 5: Dissolution profile of Pantoprazole floating tablets

KINETIC MODELING

In order to predict the drug release mechanism from formulations, kinetics treatment was applied to *in-vitro* drug release data as follows

Table 4: Kinetic model for the prepared batches

Formulations	Best Fit Model	R	k	n (Peppas)
F1	1st Order	0.9952	13.17	0.6966
F2	Higuchi matrix	0.9900	13.63	0.6576
F3	1st Order	0.9988	10.98	0.7723
F4	1st Order	0.9955	10.51	0.7305
F5	1st Order	0.9987	8.56	0.8422
F6	Higuchi matrix	0.9912	19.33	0.5081
F7	1st Order	0.9986	9.74	0.7965

Considering the correlation (r2) as obtained from the different kinetics equation, the drug release of the formulations was found to follow different models but the best fit model were selected. First order and Higuchi matrix model showed the highest r2 values compare to other models but, it follows first order for most of the formulations. The release components of "n" for the different formulations ranged from 0.5081-0.8422. Optimized formulation F4 shows the greater r2 value than the other, and was best fitted in first order kinetics and value is more than 0.5 which shows the first order release kinetics which met the requirements of sustained drug delivery system.

STABILITY STUDY

Accelerated stability studies (AST) was carried for optimized formulation F3 by exposing it to 40°C/75% RH for one month and analyzed the sample at the interval of 0, 15,30,45,60 days. The sample was analyzed for drug content, hardness and cumulative percentage drug release

Table 5: AST of F3 formulation

Parameters	Days				
	0	15	30	45	60
Hardness	5.2±0.50	5.2±0.15	5.2±0.13	5.2±0.13	5.2±0.10
Drug content	99.76±3.81	99.70±3.79	99.57±2.34	99.47±1.89	99.20±2.41
%Drug release	94.30±0.41	94.10±0.32	94.01±0.62	93.97±0.42	93.72±0.39

n=3

CONCLUSION

In present work, a floating gastro-retentive system for Pantoprazole was developed. Pantoprazole was selected for this investigation because less biological half-life, to improve bioavailability by retaining the drug in acidic environment as its solubility decreases with increasing pH and to reduce wastage. Step by step studies were carried out to develop and optimize oral floating tablet for Pantoprazole using hydrophilic polymers. The floating tablets were prepared by direct compression technique It may be concluded from the present study that slow and sustained release of pantoprazole over a period of 18 h was obtained (F1 to F7) by the using Limonia gum was successful in the formulation of floating tablet and at the same time it is effective in retarding the drug release. The cumulative percentage of drug release was decreased by increase in Limonia gum concentration.

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