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Design and Development of Floating Tablets of Ranitidine hydrochloride by Using Natural Polymers

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Abstract:

The objective of this research is to design and develop controlled release floating tablets of Ranitidine hydrochloride to enhance bioavailability and therapeutic efficacy. The tablets were formulated using a direct compression method, incorporating either treated ghee residue or oyster mushroom powder as binders, and sodium bicarbonate as an effervescent agent. The powder blend was evaluated for flow properties, and the tablets were physically characterized for weight variation, hardness, and friability, confirming their physical integrity. All formulations exhibited immediate buoyancy upon placement in the beaker, maintaining floatation for over 14 hours. It was observed that the carbon dioxide generated by sodium bicarbonate in the presence of the dissolution medium (0.1N HCl) was trapped in the polymer gel matrix formed by polymer hydration, reducing the density (<1) and enabling tablet buoyancy. The correlation coefficient values (r) indicated that the dissolution profiles adhered to zero-order kinetics, and the drug release mechanism was governed by the Peppas model. The n values (n>0.5) indicated that drug release was predominantly controlled by non-Fickian diffusion. Formulations utilizing treated ghee residue demonstrated prolonged release compared to those with oyster mushroom powder. Among all formulations, the F3 formulation, comprising a drug to treated ghee residue ratio of 1:1.5, was identified as the optimal formulation to achieve the desired drug release profile.

Key words: Ranitidine hydrochloride, Oyster mushroom powder, Treated Ghee-residue , Sodium bicarbonate

Introduction:

Ranitidine hydrochloride, a histamine H2-receptor antagonist, is extensively prescribed for conditions such as active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. The standard adult oral dosage is 150 mg twice daily or 300 mg once daily. Due to its short biological half-life of 2.5±0.5 hours, there is a strong rationale for developing a sustained release formulation. Ranitidine hydrochloride is absorbed primarily in the initial part of the small intestine, with an absolute bioavailability of 50%, underscoring the need for sustained release dosage forms to improve therapeutic outcomes [1].

India, as a leading global producer of milk, generates a substantial amount of ghee residue, a byproduct rich in proteins, calcium, and phospholipids. Instead of being discarded as waste, this residue can be effectively utilized in various applications such as animal feed, biofuel production, and as ingredients in the food and pharmaceutical industries. The concept of byproduct utilization is gaining momentum globally due to the increasing volume of such waste.Researchers are focusing on developing valorization strategies to convert these byproducts into valuable resources [2].

Additionally, the white oyster mushroom (Pleurotus ostreatus) is recognized for its numerous health benefits. It contains protein, carbohydrates, fiber, vitamins, minerals, and amino acids, and exhibits antioxidant, anti-tumor, anti-hypercholesterolemic properties, while also enhancing immune status. Advanced valorization strategies are needed to harness these benefits, providing innovative solutions for the utilization of dairy byproducts and natural resources in pharmaceutical applications [3].In the present study, natural polymers such as Oyster mushroom powder gum and Treated Ghee-residue were selected for the preparation of floating tablets of Ranitidine hydrochloride.

Materials and methods:

Ranitidine hydrochloride was obtained as a gratis sample from Hetero labs, Hyderabad. Oyster mushroom powder gum and Treated Ghee-residue were purchased from local market . Citric acid and Sodium bicarbonate were purchased from Qualigens fine chemicals, Mumbai. All other ingredients were of analytical grade.

Treatment and Processing of Ghee- Residue:

Ghee residue possesses a soft and smooth texture initially but becomes progressively hardened over time, particularly within the first 15 days, and eventually turns hard and gritty by the end of a month. To mitigate these undesirable textural changes, the residue undergoes processing to maintain the soft and smooth texture necessary for edible applications. Initially, 2.5 kg of ghee-residue was collected through processing and lumps were obatined are broken and pulverized by passing them through a 40 mesh sieve. The residue is then washed with 50% alcohol and subsequently boiled in a 1% sodium bicarbonate solution. Further autoclaving of the residue with the addition of 2% vinegar effectively reduces the moisture content and enhances the texture of the product, making it suitable for various applications [4].

Oyster Mushroom (Pleurotus ostreatus) Powder: Oyster mushrooms, totaling 3 kg in weight, were cleaned and cut into pieces to yield 200 grams of powdered oyster mushrooms. These pieces were salted at a rate of 2% for one hour to mitigate the mushrooms' strong aroma. Subsequently, they were dried in an oven at 60°C for 48 hours, followed by pulverization in a blender and sieving through a 200 mesh sieve. Finally, the resulting powder was stored in jars for future use [5].

Preparation of Ranitidine hydrochloride floating tablets

Ranitidine hydrochloride was combined with specified amounts of Treated Ghee-residue or Oyster mushroom powder, Sodium bicarbonate, and Citric acid through geometric mixing. Tablets were prepared using the direct compression method. Magnesium stearate served as a lubricant and talc as a glidant. The resulting blend was compressed into tablets using 12 mm punches and corresponding dies on a rotary tablet compression machine [6]. Detailed formulation compositions are provided in Table 1.

Evaluation Parameters

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

a) Bulk density

15 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

15 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

15 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 Ranitidine hydrochloride floating tablets

a) Hardness: The hardness of the tablet was measured by Monsanto manual 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 until the 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.

$$\% \text{ Weight Variation} = \frac{\text{Average Weight - Individual Weight}}{\text{Average Weight}} X100$$

c) Friability: The Roche friability test apparatus was used to determine the friability of the tablets. Thirteen 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±0.5^{o}C. 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]:

$$\mathbf{\% \ W_U = (Wt\text{-}Wo/Wo) \times 100}$$

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 acid at 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 150mg of Ranitidine hydrochloride 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 315 nm by UV spectrophotometer [11].

g) In vitro dissolution test: The release of Ranitidine hydrochloride from the tablet was studied using USP-Type II paddle apparatus. Drug release profile was carried out in 900 ml of 0.1N Hydrochloric acid maintained 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 315 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 Treated Ghee-residue / Oyster mushroom powder gum used 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±5^{o}C/60% RH and 40±5^{o}C/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 of Ranitidine hydrochloride were developed by varying the concentrations of Treated Ghee-residue (F1-F3) and Oyster mushroom powder gum (F4-F6). The formulated granules underwent evaluation for several flow properties. Bulk densities across all formulations ranged from 0.517 to 0.528 g/cm³. The angle of repose for each formulation fell within the range of 25.042° to 27.631°. Carr's index values ranged from 15.57% to 14.85%, indicating good packing characteristics and free-flowing material (10-16% range). Hausner's ratios ranged from

1.176 to 1.185, suggesting satisfactory flow properties comparable to a ratio of 1.25, as shown in Table 2.

Floating matrix tablets were assessed for hardness and friability, with hardness values ranging from 4.6 to 4.9 kg and friability percentages consistently below 1%. Drug content analysis revealed uniformity ranging from 99.59% to 100.16% across formulations, meeting pharmacopoeial standards. All tablets passed weight variation tests within ±5% of target weight limits. These results affirm the tablets' adherence to quality standards for hardness, friability, and weight uniformity.

Sodium bicarbonate was used universally as an effervescent agent in all formulations. Tablets floated immediately upon immersion in a beaker and remained buoyant for over 14 hours. This buoyancy was attributed to carbon dioxide generated by sodium bicarbonate reacting with 0.1N HCl dissolution medium, trapped within a polymer gel matrix formed during hydration. This process reduced tablet density (<1), ensuring flotation. Detailed physical properties and in vitro buoyancy studies are summarized in Table 3.

In vitro dissolution studies conducted in 0.1N HCl over 12 hours demonstrated sustained floating and intact tablets throughout. Formulations (F1-F3) incorporating Treated Ghee-residue exhibited reduced drug release with increasing residue concentration. Formulation F3, with a drug and natural polymer ratio of 1:1.5, achieved maximal drug release at 12 hours. Dissolution profiles for F1-F3 are depicted in Figure 1. Similarly, formulations (F4-F6) containing Oyster mushroom powder showed decreased drug release with increasing powder concentration, with formulation F3 achieving maximum release at 11.5 hours. Dissolution profiles for F4-F6 are detailed in Table 6.11 and shown in Figure 2.

To elucidate the mechanism of drug release, dissolution data were analyzed using zero order, first order, Higuchi, and Peppas equations. Correlation coefficient values (r) indicated that the dissolution profiles followed zero order kinetics, and the drug release mechanism was predominantly governed by the Peppas model. Values of n greater than 0.5 ($n > 0.5$) suggested that drug release was mainly controlled by non-Fickian diffusion. Detailed in-vitro drug release kinetics are presented in Table 4.

Swelling index studies demonstrated a gradual increase with higher concentrations of natural polymer, as outlined in Table 5. Characteristic peaks confirmed the structure of Ranitidine hydrochloride, which remained consistent across all drug-loaded matrix tablets. There were no observable changes or shifts in these peaks, indicating negligible drug-polymer interactions and the stable nature of the formulations.

The drug release profiles of optimized formulations were evaluated before and after storage under varying conditions over a period of 3 months at different temperatures and relative humidities (25±2°C/60±5% RH and 40±2°C/75±5% RH). No significant differences were observed in drug content or release rate constants, demonstrating the stability of the formulations under storage conditions.

Conclusion:

Overall, the in-vitro release of Ranitidine hydrochloride from the floating tablets was notably influenced by the properties of the natural polymer. Formulations containing Treated Ghee-residue exhibited a prolonged and retarding effect compared to those with Oyster mushroom powder gum. Among these formulations, F3, containing drug and Treated Ghee-residue in a 1:1.5 ratio, was identified as the optimized formulation based on release rate constants and percentage of drug release.

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Table 1: Composition of Ranitidine hydrochloride 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)
Ranitidine hydrochloride	150	150	150	150	150	150
Treated Ghee-residue	75	150	225	-	-	-
Oyster mushroom powder	-	-	-	75	150	225
Micro crystaline cellulose	190	105	40	190	105	40
Sodium bicarbonate	50	50	50	50	50	50
Citricacid	25	25	25	25	25	25
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total weight	500	500	500	500	500	500

Table 2: Micromeritic properties of granules of Ranitidine hydrochloride 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	26.73	0.521	0.617	15.59	1.185
F_2	25.91	0.524	0.618	15.24	1.181
F_3	25.42	0.528	0.620	14.87	1.176
F4	27.33	0.517	0.612	15.55	1.185
F5	26.95	0.520	0.614	15.50	1.184
F6	26.32	0.522	0.616	15.29	1.181

Table 3: Physical properties of Ranitidine hydrochloride floating tablets formulated with different concentrations of natural polymers.

Formulation	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating Lag	Total floating time
F_1	4.4±0.022	501.33±0.25	0.41±0.011	100.15±0.12	2.23 min	>15
F_2	4.8±0.026	500.61±0.23	0.33±0.017	99.76±0.13	2.14 min	>15
F_3	4.9±0.028	499.81±0.38	0.26±0.023	99.57±0.12	1.22 min	>15
F_4	4.4±0.018	500.22±0.12	0.46±0.016	99.53±0.13	2.37 min	>15
F_5	4.6±0.021	501.13±0.17	0.37±0.020	99.67±0.12	2.18min	>15
F_6	4.8±0.017	499.65±0.21	0.29±0.014	99.72±0.16	1.53 min	>15

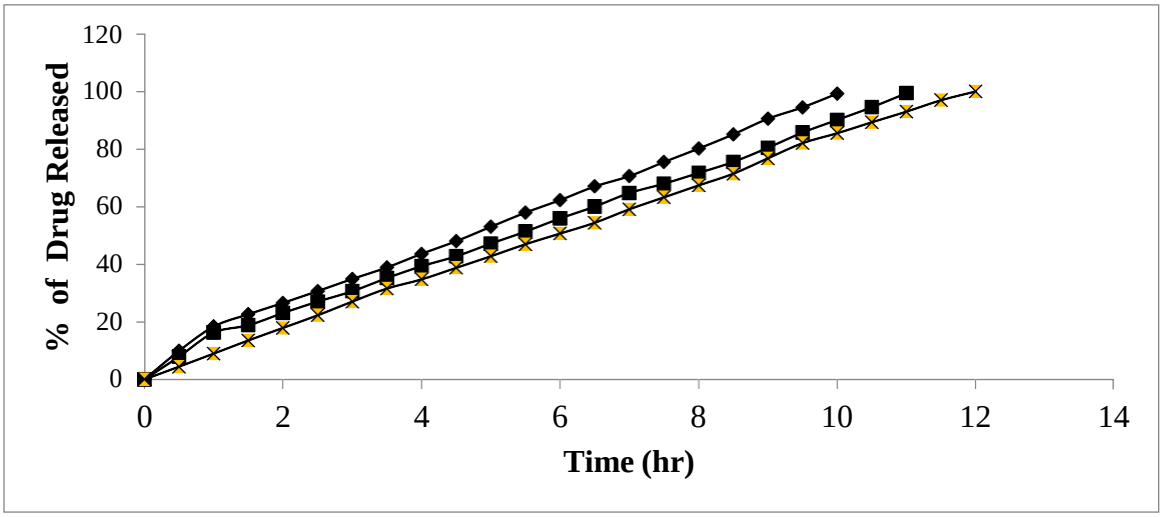
Table 4: *In vitro* drug release kinetic data of Ranitidine hydrochloride floating tablets formulated with different concentrations of natural polymers

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	0.9916	0.8294	0.9523	0.9964	15.32	0.7552	4.89	8.79
F_2	0.9952	0.8059	0.9441	0.9965	13.71	0.7977	5.49	9.89
F_3	0.9997	0.7314	0.9268	0.9999	12.71	0.9731	5.89	10.59
F4	0.9918	0.8359	0.9257	0.9969	16.13	0.7593	4.59	8.39
F5	0.9951	0.7893	0.9455	0.9969	14.41	0.8019	5.19	9.29
F6	0.9997	0.7802	0.9265	0.9999	13.07	0.9698	5.69	10.29

Table 5: Swelling index values of Ranitidine hydrochloride 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	54.35	78.94	149.25
F_2	57.46	91.47	157.24
F_3	60.13	98.57	171.40
F_4	52.70	76.65	145.01
F_5	55.25	89.90	154.02
F_6	58.54	96.11	168.52

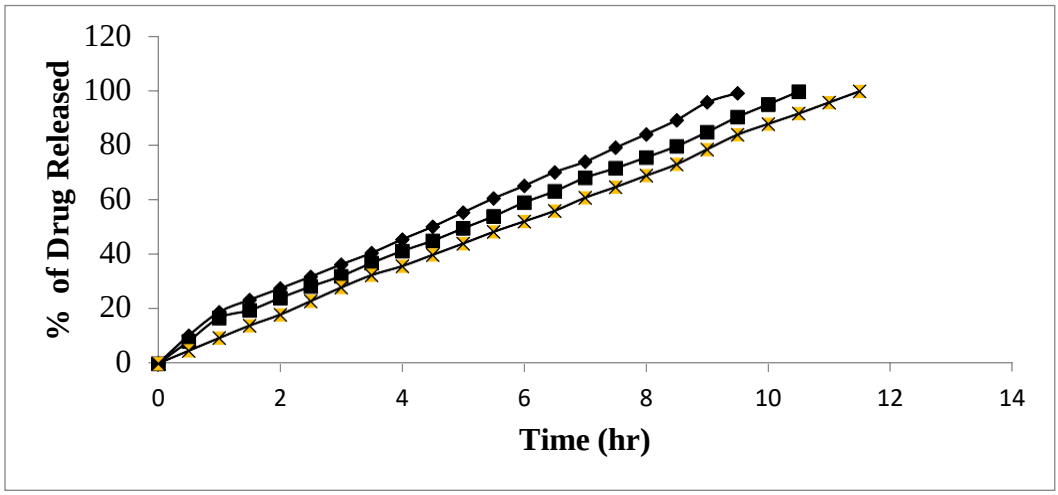
Figure 1: Comparative *in vitro* drug release profile of Ranitidine hydrochloride floating tablets formulated with different concentrations of Treated Ghee-residue



(-♦-)Floating tablets formulated with drug and Treated Ghee-residue in 1:0.5 ratio

(-■-)Floating tablets formulated with drug and Treated Ghee-residue in 1:1 ratio
(-×-)Floating tablets formulated with drug and Treated Ghee-residue in 1:1.5 ratio

Figure 2: Comparative *in vitro* drug release profile of Ranitidine hydrochloride floating tablets formulated with different concentrations of Oyster mushroom powder gum



(-♦-)Floating tablets formulated with drug and Oyster mushroom powder gum in 1:0.5 ratio

(-■-)Floating tablets formulated with drug and Oyster mushroom powder gum in 1:1 ratio

(-×-)Floating tablets formulated with drug and Oyster mushroom powder gum in 1:1.5 ratio

Figure 3 - FTIR spectrum of Ranitidine hydrochlorid

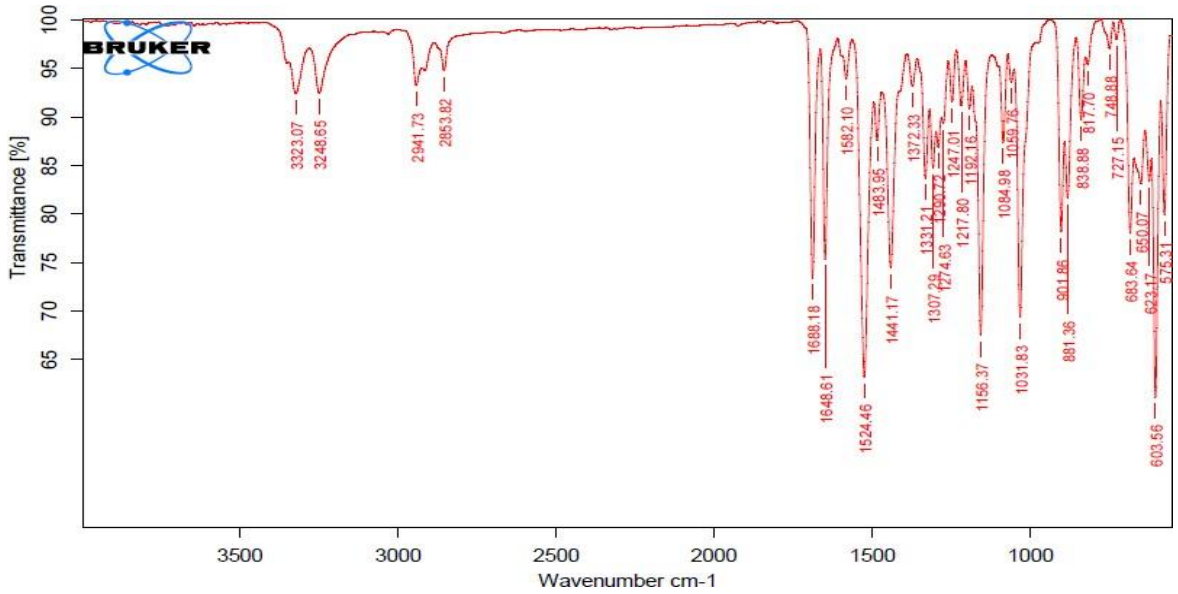


Figure 4- FTIR spectrum of Ranitidine hydrochloride floating tablet prepared with Treated Ghee-residue

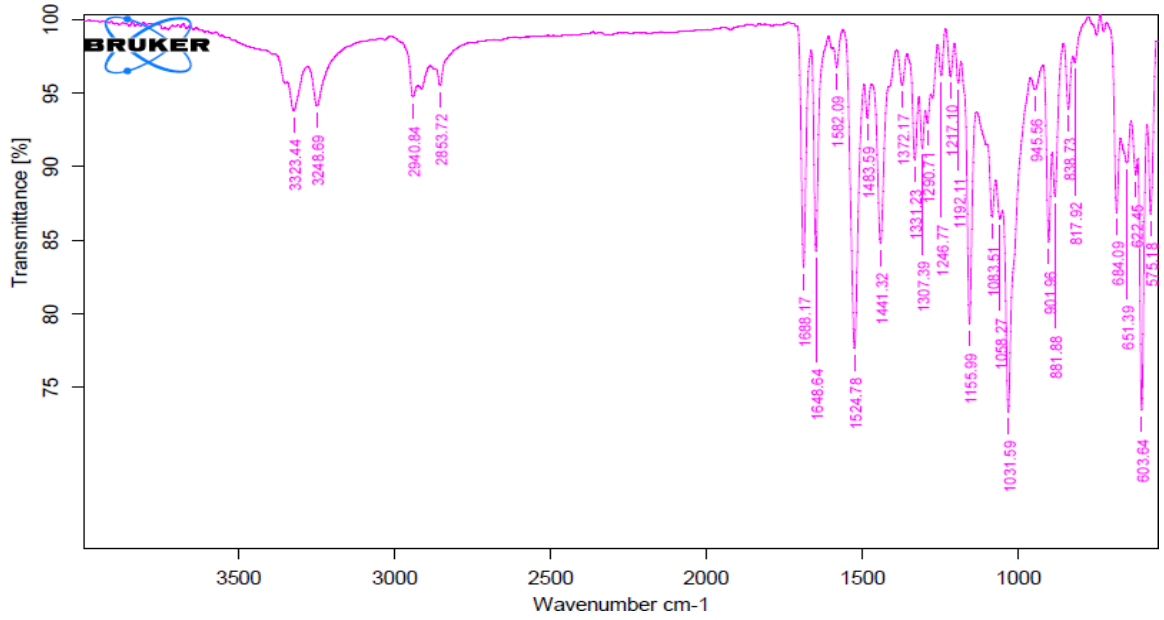


Figure 5 - FTIR spectrum of Ranitidine hydrochloride floating tablet prepared with Oyster mushroom powder gum

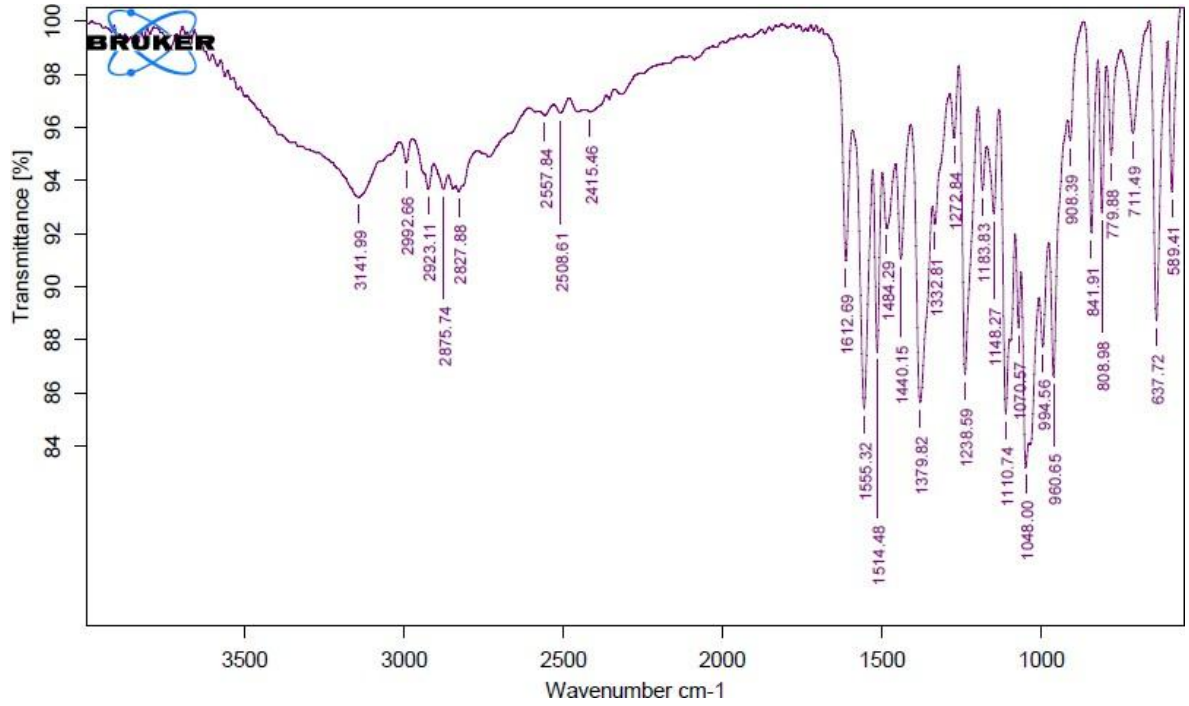


Figure 6: Photographs of floating tablets