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Formulation and Evaluation of Hydrodynamically Balanced Tablets of Ranitidine Hydrochloride

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ABSTRACT

Purpose: The formulation and evaluation of hydrodynamically balanced tablets of ranitidine hydrochloride for gastric drug delivery was the specific aim of this research. Method: The hydrodynamically balanced tablets were prepared by direct compression technique with different ratios of polymers like hydroxyproylmethyl cellulose (HPMC K 4M), Ethyl cellulose, Xanthan gum and Guar gum. The prepared tablets were evaluated for their weight variation, hardness, drug content, friability, floating lag time, floating duration, in vitro dissolution and accelerated stability studies at 40°C± 2° C/75% RH ± 5% for eight weeks. **Conclusion:** The floating tablets of ranitidine hydrochloride (HCl) were evaluated for physicochemical characteristics like hardness, weight variation, friability, floating lag time and stability studies. The in vitro buoyancy studies, in vitro drug release studies and the results showed that the best formulation. F2 had sustained release up to 98% of ranitidine hydrochloride over a period of 24 h.

Key words: *Ranitidine hydrochloride, Gastric drug delivery, Polymer, Hydrodynamically balanced.*

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INTRODUCTION:

Ranitidine hydrochloride being a histamine H2-receptor blocker, is mostly used in the treatment of gastric ulcer, duodenal ulcer, Zollinger Ellison syndrome, erosive esophagitis and gastroesophageal reflux disease.[1] The normal oral dose of ranitidine hydrochloride is 150 mg two times in a day or 300 mg once a day. In the treatment of erosive esophagitis, ranitidine HCl is needed at a dose of 150 mg, four times a day. Hence, the conventional dosage forms that are clinically acceptable may not be successful. Conventionally a dose of 150 mg given can inhibit gastric acid secretion up to 5 h but not up to 10 h. An alternative dose of 300 mg leads to plasma fluctuations. Hence, to overcome these problems a sustained release dosage form of ranitidine HCl is advantageous. The short biological half-life of drug (~2.5-3 h) also favours formulation of a sustained release formulation.[2]

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The floating drug delivery systems are employed in the stomach and support the sustained delivery of the drugs that have the absorption window in a specific region of the gastrointestinal tract. These systems continuously release the drug before it reaches the absorption window, thus ensure the optimal bioavailability. It is also seen that, H2-receptor antagonist like ranitidine and famotidine used in combination with antacids support local delivery of these drugs to the receptor of parietal cell wall in treatment of gastric disorders. Local delivery of the drug also increases the bioavailability of stomach wall receptor site and increases the efficacy of the drug to reduce acid secretion.[3]

Alkaline pH may decrease the solubility of certain drugs and in such a case, gastric retention may increase solubility before they are emptied, resulting in improved gastrointestinal absorption of drugs with narrow absorption window as well as for controlling release of drugs having site specific absorption limitation. Gastric retention will offer benefit to the delivery of drugs with contracted absorption window in the small intestine region. In addition, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine. For example, in treatment of peptic ulcer disease improved bioavailability is expected for drugs that are absorbed readily upon release in the GI-

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tract. These drugs can be delivered ideally by slow release from the stomach.[4]

MATERIALS AND METHOD

The materials used included ranitidine hydrochloride (Bangalore fine chem., Peenya, Bangalore), HPMC K4M (Indian Fine Chemicals, Mumbai), ethyl cellulose (Loba Chemie, Mumbai), xanthan gum (Rolex chemical industry, Mumbai), guar gum (Loba Chemie, Mumbai), sodium bicarbonate (Thermo Fischer Scientific India, Mumbai), microcrystalline cellulose (Rolex laboratory reagent, Mumbai), Magnesium stearate (Loba Chemie, Mumbai), Talc (Loba Chemie, Mumbai) and citric acid (SD Fine Chem. ltd., Mumbai).

METHOD

Preparation of hydrodynamically balanced tablets:

Hydrodynamically balanced tablets of ranitidine hydrochloride were formulated employing direct compression technique. The drugs and polymers were accurately weighed and blended thoroughly using mortar and pestle manually in geometric proportion. Magnesium stearate and talc were added in the above blend. The powder blends were evaluated for the properties such as loose bulk density, tapped bulk density, compressibility index and angle of repose. The composition of different formulations of floating tablets is shown in table 1.

Table1: Composition of the tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Ranitidine hydrochloride	150	150	150	150	150	150	150	150
HPMC K4M	50	20	-	-	-	-	50	20
Ethyl cellulose	20	50	50	20	-	-	-	-
Xanthan gum	-	-	20	50	50	20	-	-
Guar gum	-	-	-	-	20	50	20	50
Sodium bicarbonate	50	50	50	50	50	50	50	50
Citric acid	5	5	5	5	5	5	5	5
Microcrystalline cellulose	20	20	20	20	20	20	20	20
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5

**All the quantities of the ingredients are in mg.*

EVALUATION OF BLENDS BEFORE COMPRESSION

Angle of repose: Angle of repose was found by using funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was fixed in such a manner that the tip of the funnel just touched the tip of the heap of blend. The drug-excipient mixture was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height of cone and radius of cone base in that order. Angle of Repose less than 30 ° shows the free flowing of the material.[5]

Bulk density (BD): Apparent bulk density was determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight. Bulk density can be calculated by using following formula:

Bulk density = Weight of the powder / Volume of the packing.[5]

Tapped density (TD): It was determined by placing a graduated cylinder, holding a known weight of drug-excipients mixture. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 s intervals. The tapping was continued until no further change in volume was noted. Tapped density can be assessed by using following formula:

Tapped Density = Weight of the powder / volume of the tapped packing[5]

Compressibility index: The Compressibility indices of the blends were determined by using following formula:

$$\text{Compressibility index (\%)} = \left(\frac{\text{TD-BD}}{\text{TD}}\right) \times 100$$

EVALUATION OF THE TABLETS

Hardness: Tablet was placed between two anvils of Monsanto hardness tester; force was applied to the anvil and the crushing strength that just cause the tablet to break was recorded. Hardness is sometimes termed as tablet crushing strength.[6]

Friability: The friability of the tablets was determined by using Electrolab friabilator in the laboratory. Ten tablets are pre-weighed and subjected to the combined effects of abrasion and shock by employing a plastic compartment that rotates at 25 rpm, dropping the tablets from a height of six inches with each operation being conducted for 100 revolutions. The tablets were dedusted and reweighed. Friability is expressed as the loss of mass and it is calculated as a percentage of initial mass. The values for both hardness and friability can collectively indicate the mechanical strength of tablet.[5]

Weight Variation Test: Weight variation of tablets was calculated by weighing 20 tablets independently and estimating the average weight. Tablet meets the test if not more than two of the individual weights deviate from percentage limits. According to I.P. 2007 limits the tablets having weight of more than 250 mg, should not deviate more than 5%.[6]

Assay: 10 tablets were weighed and triturated. The tablet triturate equivalent to 150 mg of the drug was weighed accurately, dissolved in pH 1.2 buffers and diluted to 100 ml with the same. Further dilutions were prepared properly to obtain a concentration of 10 mcg/ml with simulated gastric fluid of pH 1.2. Absorbance was read at 315 nm against the blank.[6]

In vitro Floating Study: The in vitro floating behaviour of the tablets was calculated by inserting them in 900 ml of plastic containers filled with 900 ml of 0.1 N HCl. (pH 1.2, 37 ± 0. 5°C). The floating lag times (time period

between placing the tablet in the medium and tablet floating) and floating durations of the tablets were estimated by visual observation.[6]

In vitro Dissolution Studies: In vitro drug release studies of ranitidine hydrochloride were estimated using dissolution apparatus USP type II paddle method with a stirring speed of 50 rpm at 37 ± 0.5°C in 900 ml 0.1 N HCl for 24h. The samples were taken at pre-selected time intervals with replacement of identical quantity of dissolution media. The composed samples were diluted and the absorbance was measured spectrophotometrically at 315 nm. The percentage of ranitidine hydrochloride released at various time intervals were calculated from the standard graph and the kinetic release model was fitted on dissolution data.[6]

RESULT AND DISCUSSION:

Pre-compression Parameter: The powder mixtures were evaluated for the blend property like angle of repose, bulk density, tapped density and compressibility index.

The results of bulk density and tapped density were showed good flow properties of powder. The results were showed in the table 2.

Table 2: Evaluation of pre-compression parameters of formulations F1-F8.

Formulations	Bulk density	Tapped density	Angle of repose (°)	% Compressibility
F1	0.269	0.366	38.3	26.50
F2	0.435	0.538	28.47	19.14
F3	0.415	0.481	28.62	13.72
F4	0.397	0.481	27.84	17.46
F5	0.415	0.538	28.89	22.86
F6	0.435	0.538	30.83	19.14
F7	0.435	0.537	34.16	19.13
F8	0.457	0.538	27.84	15.05

Physicochemical Properties:

The prepared formulations were evaluated for the physical characteristics like thickness, hardness, friability, weight uniformity. The results obtained are shown in table 3. The deviation from the average weight was established to be inside the prescribed official limits. Hardness of tablets was found to be in the range of 4.5 to 6.5kg/cm^2 given in the table 3. The friability of all tablets was found to be in range of 0.52-0.94, which is smaller than 1% demonstrating fine mechanical strength.

Table 3: Evaluation of physicochemical properties of formulations F1-F8.

Formulation	Hardness (kg/cm2)*(±SD)	%Friability	%Weight Variation (mg)	Floating lag time (seconds)	Floating time (hours)
F1	5.2±0.18	0.013	302.45±1.30	11	22
F2	5.6±0.1	0.109	303.55±1.09	8	24
F3	5.9±0.14	0.71	302.75±1.25	14	9
F4	6.2±0.11	0.31	304.22±1.02	16	11
F5	4.9±0.21	0.54	304.43±1.19	1.11	9
F6	5.6±0.15	0.219	304.25±1.01	1.21	12
F7	4.9±0.22	0.039	304.21±1.11	1.01	21
F8	4.6±0.25	0.124	304.45±1.29	1.09	20

In vitro buoyancy study:

The in vitro buoyancy was assessed by floating lag time. The tablets were inserted in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was noted as floating lag time. The duration of time the dosage form steadily remained on the surface of 0.1N HCl was noted as the total floating time. The formulation (F2) showed better floating lag time (8 s) and it floated 24 h. The floating behavior of prepared batches is shown in table 3.

Drug-Excipient compatibility study:

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). Four samples were taken from the eight formulations. From F1 and F2, sample-A, from F3 and F4 sample-B, from F5 and F6 sample-C and from F7 and F8 sample-D was taken. The above samples were kept in 40°C ± 2°C/75% RH ± 5% for eight weeks.[7] The FTIR absorption spectra of ranitidine along with different polymers of different formulations did not show any significant interaction between ranitidine hydrochloride and polymers. Shown in figure 1-5.

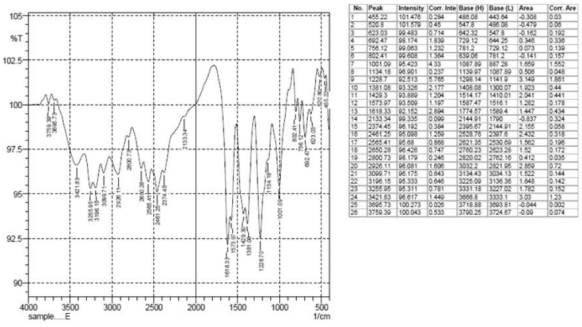

Figure 1: FTIR spectrum Ranitidine hydrochloride.

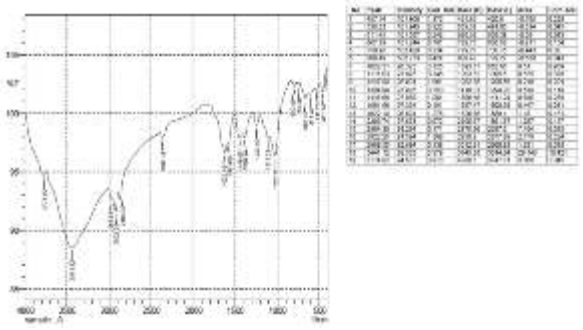

Figure 2: FTIR spectrum sample-A.

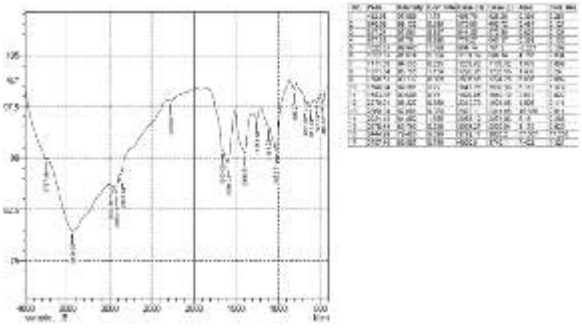

Figure 3: FTIR spectrum sample-B.

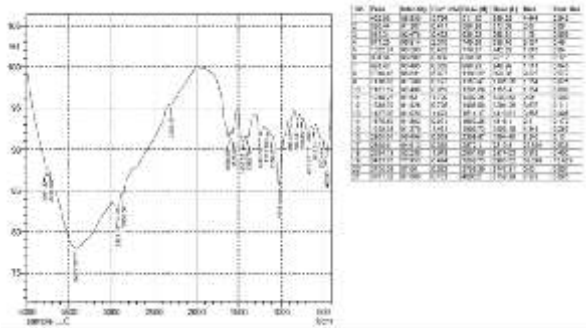

Figure 4: FTIR spectrum sample-C.

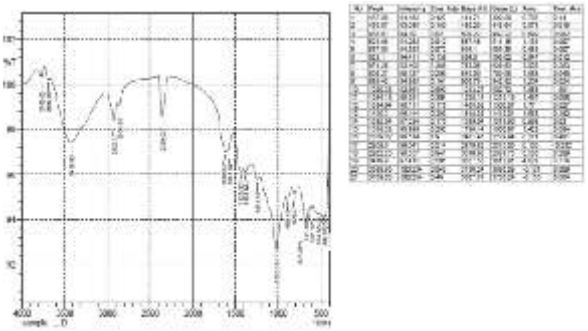

Figure 5: FTIR spectrum sample-D.

STABILITY STUDY

The stability study was carried out using the best batch. The selected batch was kept at condition of 40±2°C/75 ±5% RH and was analyzed at 60 days.[8] F2 showed no significant changes as to the physical properties, drug content and drug release. It was concluded that tablets are stable after stability studies. The FTIR spectrum of the optimised batch, as shown in figure 6 was also taken and it also showed no significant effect or interaction.

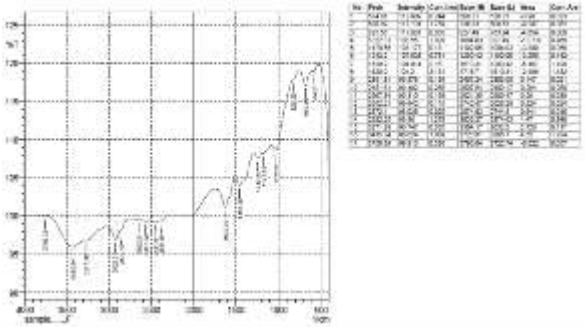

Figure 6: FTIR spectrum of selected formulation F2.

In vitro drug release study:

The data of in vitro release of ranitidine hydrochloride from different formulation combination are shown in table 4 and figure 7. In formulation F1, F2, F7 and F8 showed 91, 98, 94 and 93% drug release at the end of 24 h respectively.

The formulation F4, F5 and F6 were found to be 94, 92 and 90% upto 12 h respectively. The formulation F3 showed 91% drug release at the end of 10 h. The formulation F1, F2, F7 and F8 have sustained the release of the drug. But based on floating lag time (8 s) and floating time (24 h), F2 was selected as the best formulation because it achieved sustained release of 98% of ranitidine hydrochloride for a period of 24 h.

Table 4: % Drug release of formulation F1-F8.

Time	F1	F2	F3	F4	F5	F6	F7	F8
0 min	0	0	0	0	0	0	0	0
15 min	8.78	10.26	14.17	11.32	10.66	10.13	4.13	7.42
30 min	19.25	18.43	38.58	28.59	25.80	32.98	14.18	23.42
1 h	28.78	30.26	48.45	48.31	31.45	44.89	22.63	30.11
2 h	32.34	38.43	57.24	57.65	37.15	52.32	33.18	36.56
4 h	46.90	40.09	66.38	66.17	53.52	59.50	45.85	40.50
6 h	57.59	49.17	73.78	70.58	68.96	68.79	49.58	54.35
10 h	66.34	58.72	91.65	85.50	86.87	79.06	68.52	58.15
12 h	78.43	76.62	-	94.12	92.87	90.28	79.47	65.20
24 h	91.21	98.33	-	-	-	-	94.52	92.46

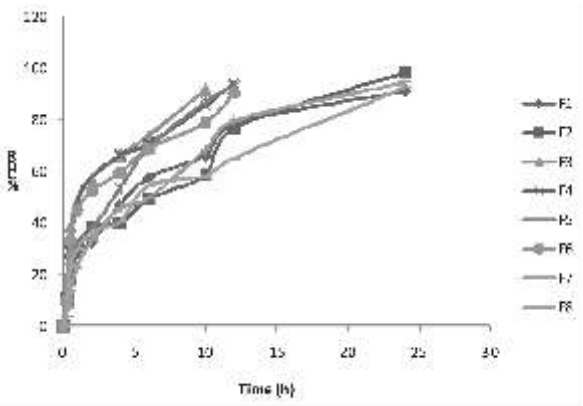

Figure 7: % Drug release of ranitidine hydrochloride.

CONCLUSION

The present study was aimed at developing an oral hydrodynamically balanced system for ranitidine HCl using combination of polymers like HPMC K 4M, ethyl cellulose, xanthan gum and guar gum. The floating tablets were prepared by using direct compression technique. The floating tablets of ranitidine HCl were evaluated for physicochemical characteristics like hardness, weight variation, friability, floating lag time and stability studies. The in vitro buoyancy studies, in vitro drug release studies and the results were found that the formulation F2 showed slow and sustained release of ranitidine hydrochloride up to 98% over a period of 24 h.

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