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Formulation and Evaluation of Ranitidine Hydrochloride Floating Tablets by Using Co-Processed Excipients

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Keywords: Ranitidine HCl, Co-processed excipient, direct compression method, HPMC K100 LV, Xanthan gum, Floating tablet.

ABSTRACT

The Gastro retentive dosage form is designed to prolong the gastric residence time of the drug delivery system. The purpose of this study was to develop and characterize floating tablets of Ranitidine HCl using co-processed excipients method to extend its bioavailability for patient compliance. The co-processed excipients made from HPMC K100 LV and Xanthan Gum (XG) in different ratio 1:1, 1.25:0.75 and 0.75:1.25 was prepared by using distilled water. Co-processed excipients have the benefits of improving flow properties, improved compressibility, better dilution potential and improvement in binding properties. Floating tablets of Ranitidine HCl was prepared by using co-processed excipients as control release polymer in different concentration with sodium bicarbonate as gas generating agent by direct compression method and were evaluated for pre and post compression parameters. The floating lag time, floating time, swelling index and *in-vitro* release were tested in 0.1 N HCl which indicated that increase in polymer concentration decreases the drug release and extended released matrix tablet was prepared exhibiting good sustained drug release for a time period of 12 hours. From all developed formulation F2 with ratio 1:1 of HPMC K100 LV and Xanthan Gum gave complete drug release up to 12 hours and was selected as best formulation. The prepared formulation was shown good floating time, extended release and physical stability.

INTRODUCTION

Oral dosage forms are intended for systemic effects resulting from drug absorption through gastro intestinal tract. Therefore, different approaches have been proposed to retain the dosage form in the stomach. The control of placement of a Drug Delivery Systems (DDS) in a specific region of the gastro intestinal tract (GIT) offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem. These considerations have led to development of a unique oral controlled release dosage form with gastro retentive properties.

Drug absorption in the gastrointestinal tract is a highly variable procedure and it depends upon the factors such as gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form, and site of absorption of drugs. Drugs that are easily absorbed from the GIT and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. Also, the drugs which have a narrow absorption window (NAW) in the upper part of GIT are not suitable for oral sustained release drug delivery system due to the brief gastric emptying time as tablets have 2.7 ±1.5 hours stomach transit and 3.1 ±0.4 hrs intestinal transit time, thus the bioavailability of such drugs having absorption window in stomach is generally limited. Gastro retentive drug delivery (GRDDS) is one of those approaches to prolong gastric residence time, thereby targeting site specific drug release in the stomach for local or systemic effects. These dosage forms can remain in the gastric region for long periods than conventional dosage forms and hence significantly prolong the gastric retention time of the drugs. It will release the drug in stomach in a controlled manner so that the drug could be supplied continuously to absorption site in GIT i.e. stomach. Conventional drug delivery system maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day. Success of oral drug delivery system depends on its degree of absorption through GIT. Thus, the idea of enhancing drug absorption pioneered the idea of development of Gastroretentive drug delivery system (GRDDS). An absorption exists because of physiological, physicochemical or biochemical factor. Drug having site-specific absorption is difficult to design as oral GRDDs because only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. On the basis of the mechanism of mucoadhesion, floating, sedimentation or by the simultaneous administration of pharmacological agents, the

controlled gastric retention of solid dosage form may be achieved, which delays gastric emptying.

MATERIALS AND METHODS

Material: Ranitidine HCl was obtained as gift sample from Saraca Labs. Ltd., Hyderabad, India. HPMC K100 LV was provided as gift sample by Dow Chemicals, Mumbai. Sodium bicarbonate, Magnesium Stearate, Talc were purchased from Research Lab, Mumbai, India. All other chemicals used for this research study were of Analytical grade.

METHODS:

1. Preparation of co-processed excipients:

The Co-processed excipients were prepared from mixture of XG and HPMC K100 LV in different ratio of 1:1, 1.25:0.75 and 0.75:1.25. They were dispersed in required amount of distilled water. The prepared slurry was well stirred to ensure that all the powder was properly wetted by adding required amount of distilled water and stirred continuously until an even mixture was produced. The suspension was then transferred into a petri plates spread thinly and dried in the microwave at 320^{o}C for 10min. The dried film pill off and reduced the size of film by grinding in mortar and pestle. These prepared excipients sieved through mesh #120 to form fine powder.

The prepared Co-processed excipients of XG and HPMC K100 LV were stored in the desiccators until used.

Table 1: The Ratio of Material used in Co-Processed Excipient

Ratio of Material
Xanthan gum**:** HPMC K-100 LV
1:1
1.25:0.75
0.75:1.25

2. Formulation and compression of Ranitidine HCl floating tablets:

Sustained release floating tablets of Ranitidine HCl tablets were made using the Co-processed excipients method by direct compression technique. Ranitidine HCl, Sodium bicarbonate,

Magnesium stearate, talc and Co-processed excipients were sieved through mesh # 120 to achieve uniform particle size. All the sieved materials were mixed together geometrically for 15 min.

The blended mixture was compressed into tablet using single punch tableting machine (Rimek Mini Press IIMT [2381602]) at compression pressure of 3.50kN. Co-processed excipients prepared with different ratio of Xanthan gum and HPMC K-100 LV was used in various percentages to prepare the sustained release floating tablets.

Table 2 shows the formulations of different batches with varying percentage concentration of co-processed excipients with the Ranitidine HCl. All the tablets of formulations were stored in an air tight container till further use.

Table 2: Formulation Table of Ranitidine HCl Floating Tablets

Ingredients	**Formulation (mg)**								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ranitidine HCl	150	150	150	150	150	150	150	150	150
Co-processed excipients	1:1			1.25:0.75			0.75:1.25		
	200	250	300	200	250	300	200	250	300
Sodium bicarbonate	40	40	40	40	40	40	40	40	40
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5

3. Characterization of drug and co-processed excipients[3,4,5]

Fourier Transform Infra Red (FTIR) Study:

For compatibility study of drug and co-processed excipient FT-IR spectrum of Ranitidine HCl, drug-co-processed excipient and drug-excipient were recorded as potassium bromide (KBr) powder at resolution of 4$cm^{-1}$for its authentication using FT-IR spectrophotometer (FT-IR 8400S, Shimadzu). The identified peaks were compared with the principle peaks of reported IR spectrum of drug and the sample was authenticated. FT-IR spectrum is shown in Figures 1 and 2.

Differential Scanning Calorimetry (DSC):

The DSC pattern was recorded on a METTLER TOLEDO (Star^{e} SW 920). Ranitidine HCl (2.9mg) was heated in crimped aluminum pan with a pierced lid at a scanning rate of 10^{0}C/min in an atmosphere of nitrogen flow (40mL/min) using the range of 40-200^{0}C. The DSC was calibrated for baseline using empty pans, and for temperature and enthalpy using indium. DSC thermogram of Ranitidine HCl is shown in Figure 3.

X-ray Powder Diffractometry (XRD):

XRPD pattern of pure Ranitidine hydrochloride was taken by X-ray diffractometer. Radiation generated from Copper source with wavelength of 20mA at 40 kV and the scanning rate employed was 1^{0}/min over the $5^{0}$to 50^{0} diffraction angle (2θ) range. The XRPD patterns of drug powder were recorded and is shown in Figure 4.

3. Evaluation of powder blend for formulation of floating tablets: [6,7,8]

The powder blends were evaluated for various evaluation parameters. The result of powder blends evaluation was given in Table 3.

1. Angle of repose
2. Bulk density
3. Tapped density
4. Hausner's ratio
5. Compressibility index

Angle of repose:

Angle of repose was determined by using fixed funnel method. The fixed funnel method was employed, a funnel that was sured with its tip at a given height (2cm), above the graph paper that was placed that was placed on a flat horizontal surface. Tablet blend was carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with r being the radius of the base of the conical pile Angle of repose was calculated using the following equation.

$$\Theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where, h =Height of pile

r=Radius of pile

Θ = Angle of repose

Bulk density:

Bulk density of granules was determined by pouring gently 10 g of sample through a glass funnel into 100ml graduated measuring cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

$$\text{Bulk density} = \frac{\text{Wt. of powder in gm}}{\text{Bulk volume}}$$

Tapped density:

Tapped density was determined by pouring gently 10 g of sample through a glass funnel into 100ml graduated measuring cylinder. Measuring cylinder was mechanically tapped 100 times and final tapped volume was recorded. Tapped density was calculated by formula following equation.

$$\text{Tapped density} = \frac{\text{Wt. of powder in gm}}{\text{Tapped volume}}$$

Compressibility index (Carr's Index) and Hausner's ratio:

Carr's index is the ability of powder to decrease in volume under pressure. The Hausner's ratio is used as an indication of the flow ability of powder materials. Both the Compressibility Index and the Hausner's ratio were determined by using ratio of bulk density and the tapped density of a powder. Compressibility index was calculated by following equation.

$$\text{Carr's index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \text{ X } 100$$

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

4. Evaluation of floating tablets

The tablets were evaluated for various parameters like hardness, disintegration time, wetting time, thickness, friability, drug content and weight variation and results are shown in Table 4.

Thickness and diameter:[3]

The thickness and diameter of tablet of the tablets were determined by using vernier caliper. Randomly 10 tablets were selected and used for determination of thickness and diameter of tablet that expressed in Mean ± SD and unit is mm.

Hardness test:[3]

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufacturers and with the different types of tablets. The hardness was tested using Pfizer hardness tester "Hardness factor", the average of the six determinations, was determined and reported. Hardness was expressed in Kg/ cm^2.

Friability test:[8]

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface during transportation or handling. Roche friabilator was employed for finding the friability of the tablets. Initial weight of 10 tablets is taken and theses are placed in the friabilator, which is rotated at 25rpm for 4 min for 100 rounds and drops the tablets by a distance of 15cm. The tablets were de-dusted and weighed again. The weight loss expressed as percentage and it should be preferably below 1.0%. The percentage of weight loss was calculated using the formula.

$$\text{Friability (\%)} = \frac{W_1 - W_2}{W_1} \times 100$$

Where,

W_1= weight of the tablet before test,

W_2= weight of the tablets after test

Uniformity of weight:[9]

The formulated tablets were tested for uniformity of weight. 20 tablets were collected and weighed individually. From the total weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is in permissible limits or not (±7.5%).The following formula was used to calculate weight variation.

$$\% \text{ Deviation} = \frac{\text{Individual weight - Average weight}}{\text{Average weight}} \text{ x } 100$$

Any variation in the weight of tablet (for any reason) leads to either under medication or over medication. So, every tablet in each batch should have a uniform weight. Deviation within the IP permissible limit of 5% is allowed as the tablet weighs over 500 mg. Corrections were made during the compression of tablets to get uniform weight.

Drug content:[10]

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to the average mass of one tablet was added in 100 ml 0.1N HCl followed by sonication for 2 hours. The drug content was estimated by recording absorbance at 224.70nm using a UV-Visible spectrophotometer.

Swelling index: [11]

The swelling index of the tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of tablet was determined at predefined time intervals and weighted till it come to constant weight and the swelling index was calculated by using following equation.

$$\text{Swelling index} = \frac{W_1 - W_0}{W_0} \text{ x } 100$$

Where,

W_1= the initial weight of the tablet

W_0= the weight of the tablets at time t.

Assay of formulation: [8]

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 97.5% or more than 102% w/w of the labeled drug content can be considered as the test was passed. The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100 ml of 0.1N Hydrochloric acid, followed by stirring. The solution was filtered through a 0.45µ membrane filter, the absorbance of resultant solution was measured spectrophotometrically at 224.70nm using 0.1 N Hydrochloric acid as blank.

***In-vitro* buoyancy study:** [12]

Tablets were placed in a 100ml beaker containing 0.1N HCl as the dissolution medium at 37°C. The time required for the tablet to rise to the surface and float was determined as floating lag time and total floating time. Total floating time for the formulations containing HPMC K100 LV with XG was maintained their matrix integrity for more than 12 hours. Results are shown in Table 6.

***In-vitro* release rate study of floating tablets:** [13]

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Details of Dissolution Test:

The release rate of Ranitidine HCl from the floating tablets was determined using USP Dissolution type II testing apparatus (paddle type). The dissolution test was performed using 900ml of 0.1N HCl at 37±0.5^{0}C and at 50rpm. 10ml withdraw hourly from the dissolution media for 12hrs and the sample was replaced with fresh dissolution medium. Each of the 10ml samples were filtered through Whatman filter paper. The absorbance was measured at 224.70 nm, the drug concentration in the sample was determined from the standard curve of the drug in stimulated gastric fluid. The data is given in Table 7.

8. Stability Study of Optimized Formulation: [14]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives.

Each tablet was individually weighed and wrapped in an aluminum foil and packed in black PVC bottled and put at 40 ^{0}C/75% RH ±5% in a heating humidity chamber for two months nth. After each month nth tablet sample was analyzed for appearance, hardness, thickness and drug release which is shown in Table 8.

RESULTS AND DISCUSSION

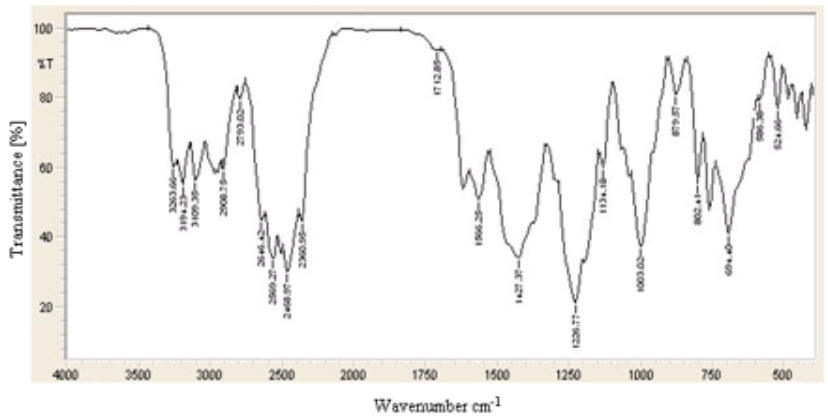
Characterization of drug and co-processed excipients

1. Fourier Transform Infra Red (FTIR) Study:

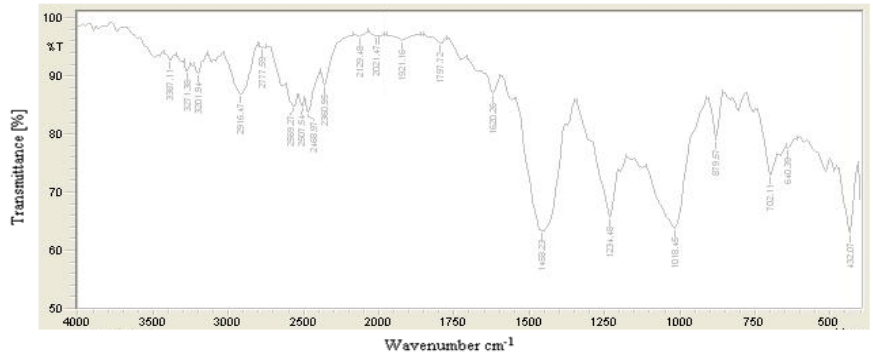
1. Compatibility Studies of Drug-Co-processed excipients:

The compatibility study of Ranitidine HCl and physical mixture of 1:1, 1.25:0.75 and 0.75:1.25 of different ratio of co-processed excipients was given below. The IR spectrum of pure Ranitidine HCl showed characteristic peak at 3263.66, 2908.75, 1566.25, 1427.37 and1226.77 that are assigned to O-H Carboxylic acid, C-H, NO_2, C=C, C-O-Cstretching respectively.The absence of Ranitidine hydrochloride peak i.e. NO_2 stretch at 1566.25cm^{-1}in IR spectrum of Ranitidine HCl + 1:1 co-processed excipients and Ranitidine HCl + 0.75:1.25 co-processed excipients, absence of C-O-C Stretch at 1226.77 cm^{-1} in IR spectrum of Ranitidine HCl + 1.25:0.75 co-processed excipients. These obtained results indicate that there was no positive evidence for the interaction between Ranitidine HCl and co-processed excipients. These results clearly indicated that the above polymer can be used without any interaction for preparation of floating tablets of Ranitidine HCl.

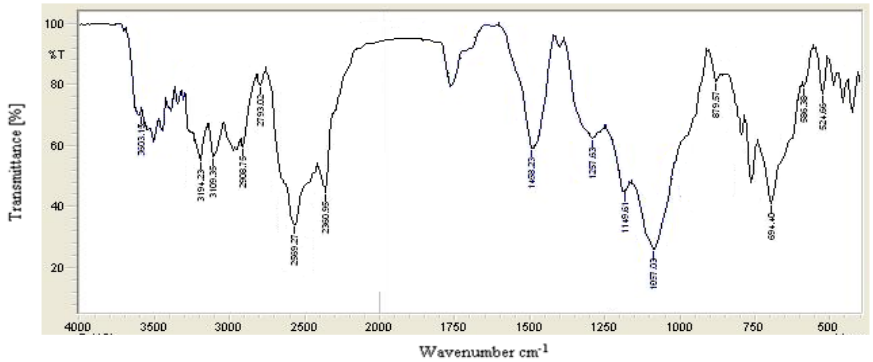
Ranitidine hydrochloride



A. IR Spectrum of Ranitidine HCl + 1:1 Co-processed Excipients



B. IR Spectrum of Ranitidine HCl + 1.25:0.75 Co-processed Excipients



C. IR Spectrum of Ranitidine HCl + 0.75:1.25 Co-processed Excipients

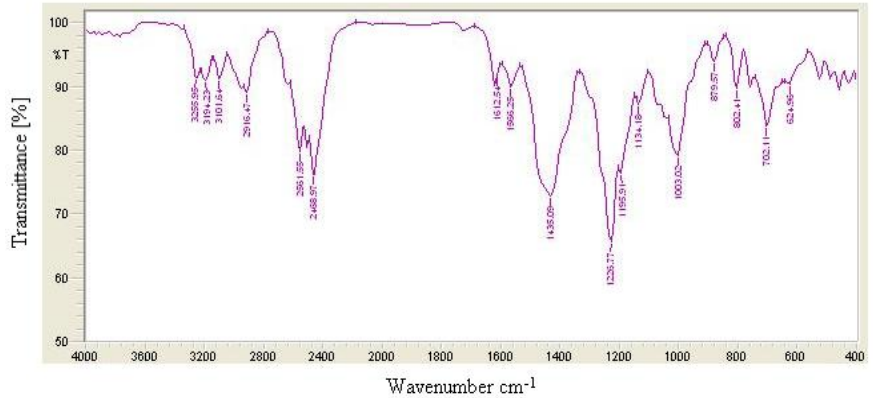


Figure 1: Infrared Spectrum of Ranitidine HCl. A- Infrared Spectrum of Ranitidine HCl + 1:1 Co-processed Excipients. B-Infrared Spectrum of Ranitidine HCl + 1.25:0.75 Co-processed Excipients. C-Infrared Spectrum of RanitidineHCl+0.75:1.25Co-processed Excipients

2. Compatibility Studies of Drug-Excipients:

The Drug excipient compatibility was studied by performing Fourier transform infrared spectroscopy (FTIR) spectrum for drug and trial formulation.

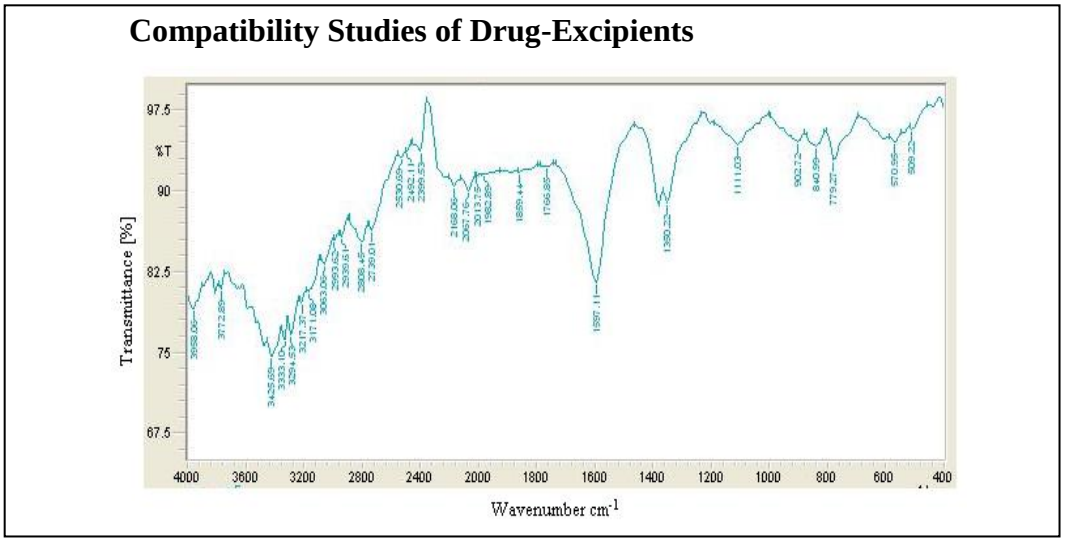


Figure 2: Infrared Spectrum of Compatibility Studies of Drug-Excipients.

3. Differential Scanning Calorimetry (DSC):

DSC thermogram of procured drug is shown in **Figure 3.**

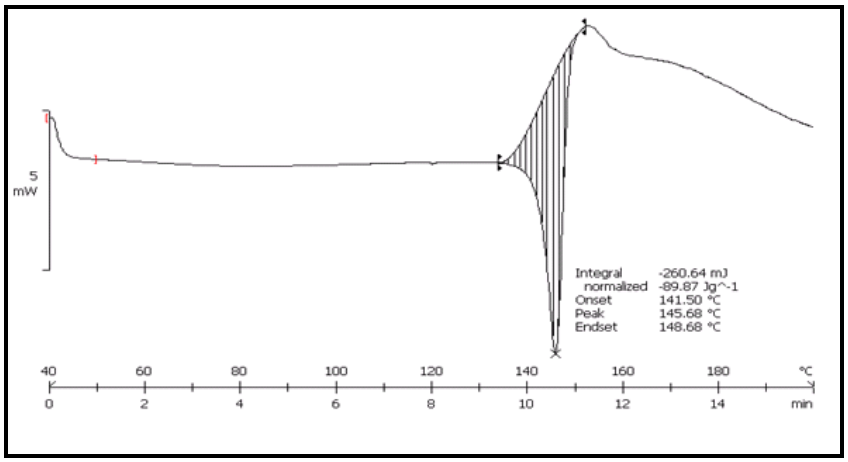


Figure 3: DSC of Ranitidine HCl

The DSC studies indicated sharp endoderm peak at 145.68^{o}C which is corresponding to melting point of pure Ranitidine HCl.

4. X-ray Powder Diffractometry (XRD):

The powder x-ray diffraction pattern of Ranitidine HClshown in **Figure 4.**

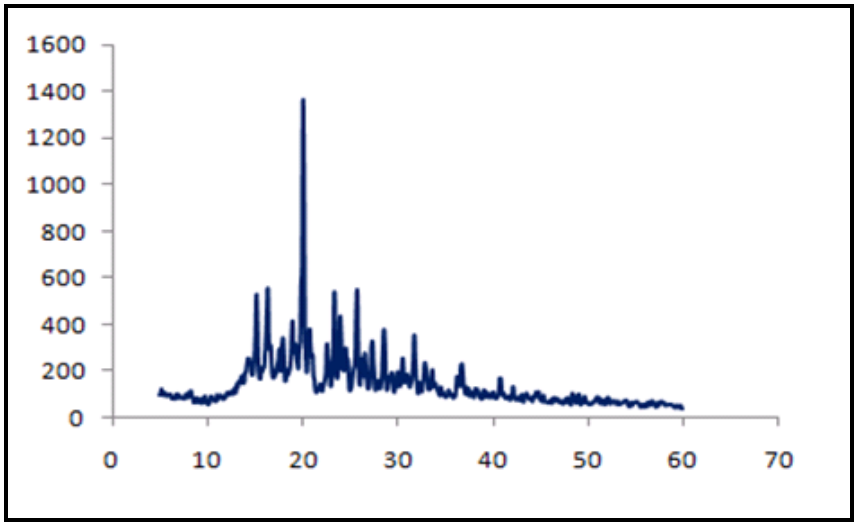


Figure 4: XRD of Ranitidine HCl

In powder x-ray diffraction pattern of Ranitidine HCl, peaks were observed which indicates the crystalline nature of the drug.

Evaluation of Powder Blend for Formulation of Floating Tablets:

The mixed blends were evaluated for various evaluation parameters. The result of blend evaluation was given below.

Table 3: Evaluation of Powder Blend for Formulation of Floating Tablets

Formulation	Parameter				
	Bulk density (g/cm^3)	**Tapped Density (g/cm^3)**	**Angle of Repose(Ɵ)**	**Compressibility Index (%)**	**Hausner's Ratio (H_R)**
F1	0.58 ±0.007	0.71 ±0.011	30.51 ±1.01	17.64 ±2.16	1.21 ±0.025
F2	0.58 ±0.010	0.69 ±0.0057	29.36 ±0.58	16.08 ±0.84	1.26±0.01
F3	0.58 ±0.0065	0.67 ±0.011	35.58 ±0.08	18.15 ±0.74	1.22 ±0.01
F4	0.56 ±0.007	0.69 ±0.0095	34.60 ±0.55	12.88 ±2.20	1.14 ±0.03
F5	0.58 ±0.0075	0.71 ±0.015	31.30 ±0.92	20.31 ±2.81	1.25 ±0.041
F6	0.56 ± 0.017	0.70 ±0.0052	30.09 ±0.21	17.95 ±1.64	1.21 ±0.026
F7	0.56 ±0.0065	0.64 ±0.012	30.74 ±0.83	14.83 ±0.70	1.17 ±0.011
F8	0.56 ±0.0080	0.70 ±0.0072	34.20 ±0.74	14.71 ±0.70	1.24 ±0.05
F9	0.56 ±0.014	0.66 ±0.0068	34.05 ±0.93	15.76 ±1.85	1.18 ±0.02

Value ±SD, n=3

From the results of pre-compression studies of the batch F1- F9, it is concluded that powder mixtures have good flow property and compressibility. The Bulk density of powder mixtures were found to be in the range of 0.56 and 0.58 g/cm^3. The values of Carr's index were in the range of 12.88to20.31%.and Hausner's ratio was in the range of 1.14 to 1.25 were suggesting fairly good flow properties.

The powder blend was compressed using direct compression technique. Tablets prepared by direct compression method have found to be good without any chipping, capping and sticking.

Evaluation of Floating Tablets:

The floating tablets were evaluated for hardness, thickness, friability, weight variation, *in-vitro* buoyancy study and *in-vitro* drug release study. The result of floating tablets evaluation shown **in Table 4.**

Table 4: Evaluation of Floating Tablets

Formulation	Parameter				
	Thickness and Diameter (mm)	**Hardness Test(kg/cm^2)**	**Friability Test (%w/w)**	**Drug Content (%)**	**Weight Uniformity Test(%)**
F1	4.14± 0.04	5.16±0.32	0.80 ±0.07	95.65±3.01	399.22 ±1.1
F2	4.25 ±0.07	4.32±0.11	0.75 ±0.12	97.54±2.4	448.35 ±1.2
F3	4.47±0.016	4.66± 0.05	0.89 ±0.20	99.64±0.7	498.28 ±1.8
F4	4.74 ±0.061	6.0±0.25	0.71 ±0.08	97.53±3.51	397.54 ±2.1
F5	4.16 ±0.08	5.20±0.12	0.85 ±0.09	94.90±0.25	448.99 ±1.4
F6	4.23 ±0.02	6.33±0.36	0.72 ±0.11	97.27±2.8	498.36 ±1.2
F7	4.19 ±0.05	5.10±0.17	0.80 ±0.05	99.48±0.42	399.41 ±1.0
F8	4.51 ±0.07	5.40±0.28	0.81 ±0.08	98.14±3.0	438.17 ±2
F9	4.16 ±0.041	5.0±0.11	0.7 ±0.07	97.89±3.5	497.7 ±2.1

Value ±SD, n=3

Various physical parameters like thickness, hardness, weight variation, friability, hardness, disintegration time were measured to evaluate tablets. It was found that the average thickness of the tablets also ranged between 4.14-4.51 mm; however, the variations have not alarming and remained within the acceptable range. Hardness of tablets of the different formulations varied widely ranging from 4.32– 6.33 kg/cm^2, The result of post-compression studies of the batch of F1-F9 is concluded that the all formulations were found to be within the acceptable limits.

Swelling index:

The swelling properties of tablet containing drug were determined by placing the tablet in 0.1 N HCl, the tablets were removed periodically from the dissolution medium, blotted to removed excess water and weighted. Swelling index of floating tablets was given in Table 5 and the plot of swelling index Vs time as shown in Figure 5.

Table 5: Swelling Index of Floating Tablets of Ranitidine HCl

Time (hrs)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	17.83 ±1.7	21.05 ±2.0	19.87 ±1.2	21.6± 0.5	26.1 ±0.5	19.6± 1.7	20.49 ±1.1	18.26 ±1.5	16.85 ±1.2
2	23.74 ±1.2	28.67 ±1.5	33.16 ±0.8	32.00 ±0.5	33.5 ±1.2	26.66 ±0.6	23.54 ±0.7	20.58 ±0.8	18.68 ±0.7
3	37.13 ±1.0	39.81 ±0.7	41.88 ±1.5	48.51 ±1.6	49.3 ±0.2	34.50 ±0.2	31.27 ±1.3	26.41 ±2.4	17.62 ±2.1
4	45.85 ±0.7	44.17 ±0.8	47.00 ±0.2	59.12 ±1.7	58.6 ±1.5	42.83 ±1.1	39.89 ±0.8	29.52 ±0.1	20.46 ±0.7
5	56.18 ±1.1	59.78 ±2.0	53.06 ±1.2	66.1± 1.0	67.5 ±1.1	56.16 ±1.1	43.12 ±0.5	32.89 ±0.7	27.02 ±1.3
6	72.42 ±1.0	68.52 ±1.5	65.11 ±1.6	70.3± 0.5	72.0 ±0.5	63.41 ±0.8	56.85 ±2	41.12 ±0.5	32.86 ±1.8
7	68.70 ±0.7	72.03 ±1.0	69.61 ±0.2	78.00 ±0.3	78.8 ±0.6	77.16 ±0.5	61.21 ±1.6	48.00 ±1.1	36.61 ±2
8	79.54 ±1.2	77.69 ±1.0	75.02 ±1.3	85.2± 0.7	85.2 ±0.3	83.00 ±0.8	67.48 ±0.8	54.26 ±1.1	48.10 ±1.3
9	85.20 ±1.5	81.76 ±0.5	80.08 ±1.3	90.4 ±1	92.6 ±1.1	89.66 ±1.3	72.00 ±0.8	60.18 ±0.5	53.29 ±0.9
10	70.35 ±0.8	83.15 ±1.3	85.52 ±1.1	92.1 ±1.4	93.8 ±0.9	93.65 ±2.1	76.30 ±1.2	70.55 ±1.2	61.57 ±0.2
11	78.40 ±2	83.45 ±0.7	89.74 ±0.9	94.6 ±0.8	95.6 ±0.5	97.16 ±0.5	78.04 ±1.1	76.87 ±0.8	68.19 ±1.6
12	86.91 ±0.7	87.98 ±0.7	92.13 ±1.1	95.7 ±2.2	97.1 ±1.7	98.18 ±0.5	80.64 ±0.7	79.48 ±2.3	71.69 ±0.2

Value ±SD, n=3

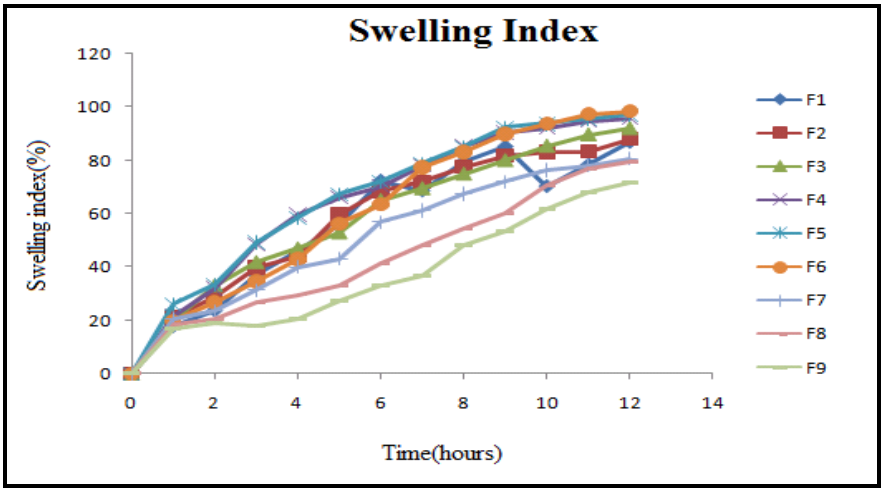


Figure 5: Swelling Index of Developed Formulations

Swelling index of all formulations was done and it measured in terms of percentage weight by the tablet. It was found that formulations F1-F9 having good swelling property for prolongation of drug release.

2. *In-vitro* Buoyancy Studies:

All the formulations were prepared by effervescent approach. *In-vitro* Buoyancy and Total floating time were determined by using 100 ml beaker containing 0.1N HCl, the gas generated is trapped and protected within the gel formed by hydration of polymers thus decreasing density of the tablet. As the density of tablet falls <1, the tablet becomes buoyant.

Table 6: *In-vitro* Buoyancy Studies

Formulation	Floating lag time (s)	Floating time (hours)
F1	23±1.4	>12±0.48
F2	20±0.8	>12±0.31
F3	39±0.6	>12±0.44
F4	30±1.0	>12±0.52
F5	26±0.9	>12±0.55
F6	50±0.4	>12±0.33
F7	27±0.6	>12±0.45
F8	41±1.05	>12±0.65
F9	38±0.6	>12±0.37

Value ±SD, n=3

The result showed that the floating lag time was in the range of 20-50 s and total floating time up to 12 hours. Both floating lag time and total floating time increases with increase in concentration of polymers. Total floating time for the formulations containing HPMC K100M with XG were maintained their matrix integrity for more than 12 hours shown in **Table 6.**The floating lag time of F2 formulations were found to be 20-50 s and floating time more than 12 hours.

1. *In-vitro* Drug Release Studies:

The release rate of Ranitidine HCl from the floating tablets was determined using USP Dissolution type II testing apparatus (paddle type). The dissolution test was performed using 900ml of 0.1N HCl at 37±0.5°C and at 50rpm.

Table 7: *In-vitro* Release Rate Study of Floating Tablets

Time (hrs)	Formulations Cumulative % Drug Release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	16.17 ±0.9	13.60 ±2.5	10.39 ±1.4	10.75 ±1.3	13.68 ±0.8	8.78 ±0.4	14.92 ±0.7	16.17 ±0.9	11.78 ±0.6
2	27.83 ±1.2	23.49 ±1.2	15.33 ±1.1	22.87 ±1.6	31.76 ±1.1	16.19 ±0.4	32.06 ±0.5	25.64 ±0.5	17.69 ±0.8
3	38.60 ±0.6	33.70 ±0.4	20.89 ±1.5	35.05 ±1.0	35.77 ±0.6	23.30 ±0.3	39.88 ±0.6	37.19 ±0.5	24.32 ±0.6
4	46.86 ±1.1	43.29 ±0.7	27.73 ±0.9	44.00 ±0.7	39.52 ±1.4	30.23 ±1.8	44.64 ±1.0	45.35 ±1..7	30.88 ±0.9
5	52.05 ±0.5	48.88 ±1.1	33.30 ±1.6	45.36 ±2.2	49.03 ±0.6	39.63 ±0.1	51.41 ±0.4	49.65 ±0.8	36.49 ±2.7
6	53.86 ±1	54.97 ±1.8	34.32 ±0.8	52.28 ±0.4	57.53 ±1.6	41.46 ±2.0	56.21 ±1.8	57.58 ±1.6	40.03 ±0.6
7	56.85 ±1.4	64.20 ±0.6	41.56 ±0.8	55.77 ±0.4	61.15 ±0.9	47.39 ±0.7	60.18 ±2.2	63.98 ±0.4	42.80 ±1.3
8	62.21 ±2	73.59 ±0.2	50.64 ±0.5	61.42 ±1.1	67.00 ±0.5	50.17 ±0.7	63.89 ±0.7	68.47 ±0.4	51.67 ±0.5
9	66.56 ±1.7	83.22 ±1.5	53.19 ±1.2	67.14 ±0.5	70.04 ±2.1	56.16 ±0.3	68.57 ±0.5	70.26 ±2	55.38 ±11
10	69.81 ±2.6	89.70 ±1.3	54.90 ±2.8	70.23 ±2	71.31 ±0.7	61.41 ±0.7	70.33 ±0.3	72.40 ±0.3	60.60 ±0.7
11	75.68 ±0.9	93.21 ±0.5	67.03 ±0.9	73.36 ±0.5	75.76 ±0.7	64.44 ±2.3	73.48 ±2.4	75.89 ±0.9	63.32 ±1.9
12	83.42 ±2.2	98.11 ±1.4	70.95 ±1.7	76.43 ±0.5	79.20 ±1.6	71.15 ±1.0	77.42 ±2.1	80.73 ±1.1	67.74 ±0.4

Value ±SD, n=3

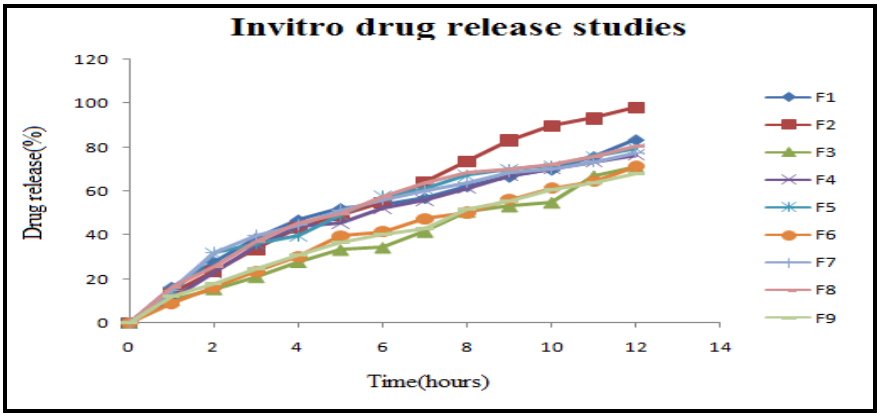


Figure 6: Graph of *In-vitro* Drug Release Studies.

The results obtained in the *in-vitro* drug release for all formulations F1 to F9 are tabulated in Table 11. The cumulative percent release of formulations F1 to F9 in 0.1 N HCl is shown in Figure 7. *In-vitro* drug release was done to determine the percentage drug release from floating tablets. From *in-vitro* results, it was observed that as the concentration of polymer increased, initial release rate of Ranitidine HCl from the formulations decreased. The F2 formulation showed complete drug release up to 12 hours.

Stability Study of Optimized Formulation:

The stability study of optimized formulation was studied. Optimized formulations of floating tablet were stored at 40 ^{0}C/75% RH ±5% up to 60 days and results are shown in **Table 8.**

Table 8: Stability Study of Optimized floating Tablet of Ranitidine HCl

Time Period	**Parameter**	**Stability Condition (40 ^{0}C/75% RH)**
Initial	Appearance	Yellowish white
	Hardness (kg/cm^2)	4.32
	Buoyancy lag time (s)	20±0.8
	Drug Release (%)	98.11
	Total floating time (hours)	>12
After 1 month	Appearance	Yellowish white
	Hardness (kg/cm^2)	4.32
	Buoyancy lag time (s)	21
	Drug Release (%)	97.72
	Total floating time (hours)	>12
After 2 month	Appearance	Yellowish white
	Hardness (kg/cm^2)	4.41
	Buoyancy lag time (s)	21
	Drug Release (%)	97.42
	Total floating time(hours)	>12

Table 9: Dug Release Profile of Optimized Formulation F2 at 40 ^{0}C/75% RH

Time (hours)	Cumulative % drug release		
	F2 Formulation		
	Initial	After 1 month nth	After 2 month nth
0	**00**	**00**	**00**
1	13.60±2.5	13.46±1.2	13.27±1.5
2	23.49±1.2	23.18±0.7	22.95±2.4
3	33.70±0.4	33.58±1.9	32.78±2.1
4	43.29±0.7	42.80±0.4	40.73±1.7
5	48.88±1.1	48.60±1.2	48.02±1.0
6	54.97±1.8	53.89±1.5	53.47±0.7
7	64.20±0.6	63.55±2.0	62.11±0.7
8	73.59±0.2	71.83±0.8	71.66±1.6
9	83.22±1.5	82.75±0.8	81.99±1.01
10	89.70±1.3	89.14±2.1	88.52±0.7
11	93.21±0.5	91.87±1.1	91.06±2.0
12	98.11±1.4	97.72±1.8	97.42±1.6

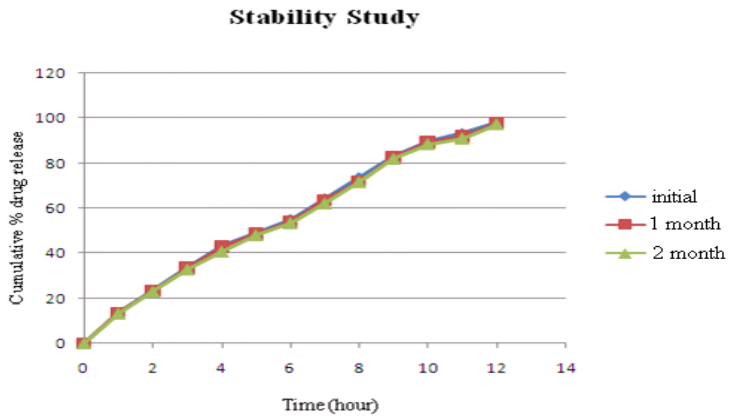


Figure 7: Stability Study of Optimized Formulation.

The results of stability study of optimized formulation shown in Table 8, Table 9 and Figure7 done at 40 ^{0}C/75% RH ±5% for 2 months. There was no significant change in appearance, hardness, buoyancy, lag time, drug release, total floating time of optimized formulation. Thus the formulation F2 was found to be a stable at the end of stability studies.

CONCLUSION:

Ranitidine HCl is an anti-ulcer and BCS class III drug. It is absorption window limited drug and has short half life of 2.5-3 hours. In the present study, it was planned to prepare sustained release floating tablets of Ranitidine HCl by using co-processed excipients.

The procured sample of drug was authenticated by pre-formulation study like melting point, IR spectra, DSC study, XRD study were done. Results of pre-formulation studies show that Ranitidine HCl was pure and complies with standard.

The co-processed excipients were prepared by using combination of HPMC K-100 LV and Xanthan gum in different ratio. The powder blend of co-processed excipients in different ratio was evaluated for various physicochemical parameters like bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio. From this study, it was found that powder blend has good flow properties and compaction property.

The compatibility study between drug and different ratio of co-processed excipients 1:1, 1.25:0.75 and 0.75:1.25 was studied by FTIR. There was no any interaction observed between drug and co-processed excipients, so co-processed excipient were found to be suitable for sustained release floating drug delivery system.

The formulation containing co-processed excipients as swelling agent, sodium bicarbonate as gas generating agent, magnesium stearate and talc as lubricant and glidant which was compressed in to tablet by direct compression method.

Formulations were evaluated for various evaluation parameters like hardness, thickness, weight variation, friability, drug content, floating lag time, floating time, swelling index and *in-vitro* drug release. From the results of evaluation parameters, it was observed that formulation F2 showed best results for floating lag time 23 s, floating time up to 12 hours and consistent drug release 98.11 % as compared to other formulations. So formulation F2 was finalized as an optimized formulation and were used for further study.

The stability study of formulation F2 was performed at 40^0C/75% RH for 2 month. The optimized formulation was found to be stable after accelerated stability study.

The floating tablets of Ranitidine HCl using co-processed excipients was able to release drug completely up to 12 hours which has ability to improved bioavailability of drug.

On the basis of above finding, it was concluded that sustained release floating drug delivery system was successfully achieved.

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