



Formulation Development And Characterization Of Gastroretentive Floating Tablets Of Ranitidine Hydrochloride

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Abstract: Gastroretentive dosage forms have potential for use as controlled-release drug delivery systems. Drugs with narrow absorption window and has highest solubility in gastric region are feasible for designing the floating drug delivery system. Ranitidine hydrochloride is histamine H₂-receptor foe. It is broadly recommended in component duodenal ulcers, gastric ulcers, Zollinger-Ellison issue, gastroesophageal reflux sickness, and erosive esophagitis. This study portrays preparation and appraisal of skimming matrix tablet of ranitidine in perspective of low thickness copolymer that holds estimations outline in stomach. Provide extended gastric living game plan time achieving drawn out pharmaceutical movement in gastrointestinal tract using chitosan and carbopol 940 as bolster release polymers. In overnight fasting condition the tablets emptied the stomach after 2 hrs of administration. This might be due to rapid gastric motility and insufficient resting volume of the stomach for the tablets to float in the stomach. But in fed condition, the same tablets showed a gastric residence time of more than 4.5 hrs. Hence the prepared tablet enhances the bioavailability making it as promising drug delivery system.

Keywords: Chitosan and Carbopol 940, Floating Drug Delivery System, Gastric, Ranitidine Hydrochloride, Stomach.

INTRODUCTION

Gastroretentive dosage forms have potential for use as controlled-release drug delivery systems. The use of floating dosage forms (FDFs) is one method to achieve prolonged gastric residence times (GRTs), providing opportunity for both local and systemic drug action, they can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability[1][2].

Floating dosage form is suitable drug delivery in the following contexts:

- Stomach is highly desirable for drug delivery.
- Locally active in stomach.
- Drug which possess narrow absorption window in stomach or in upper small intestine.
- Drugs which disturb colonic bacteria.
- Longer residence time in the stomach.
- Drugs with low solubility at high pH value.
- High variability in gastric emptying time.

Drugs with narrow absorption window and has highest solubility in gastric region are feasible for designing the floating drug delivery system. Floating force (F) of minimal level is required to keep the dosage form buoyant in gastric fluids. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. The success behind formulating a floating drug delivery system involves many techniques such as hydrodynamically balanced systems (HBS), low density system, high density system, super porous hydrogel and magnetic systems[3][4][5].

Since long time, individuals have been utilizing plants as hotspot for curing of different main problem, giving solid better wellbeing, moderating body bother for giving flavors or smell to sustenance. In India and China, wellbeing care framework concentrated on plants has been use for around 5000 years. In Europe, plants were being used as standard cures till around 50 years previous. India, China and Arabic nations straightforwardly have built up their own particular indigenous structures of meds. In any case, ayurvedic gameplan of pharmaceutical is considered as most unrivaled framework terms of essentialness of study expansion.

Approaches to gastric retention

Particular frameworks have been done to add to time hovering of oral estimations graph in stomach, including skimming structures, swelling and creating structure, changed shape structure, high thickness structures and other put off gastric handicapping contraptions. (Attracting frameworks, Super defenseless –biodegradable hydrogel structures).

Hydrodynamically adjusted structures (HBS) –incorporated light materials unite with contraption to float[6][7].

Flatboat structures unite alginate gels – these have carbonate range and, upon reaction with gastric ruinous, air stashes shape in gel, enabling floating.

Swelling kind of estimations structure are such that in wake of swelling, this thing swells to degree that keep out from stomach through pylorus. As, result, estimations structure held in stomach for more drawn-out time of time. These structures may be recommended as "Affiliation sort system"[8][9].

High-thickness unnoticeable segments breaker secured beds, and have thickness more unmistakable than that of stomach substance (1.004 gm/cm³). This is wrapping up by covering pharmaceutical with liberal unmoving

material, for event, barium sulfate, ZnO, titanium dioxide. This numbering of high-thickness pellet is in light of suspicion that liberal pellets may stay longer in stomach, since they are position in lower bit of antrum.

Another yielded gastric releasing considering interest circuit sham supporting of consumable polymers or unsaturated fat salts that charges motility arrangement, of stomach to joined with stage thusly diminishing gastric debilitating rate and permitting incredible prolongation of pharmaceutical release. In any case, some of this has specific needs, which could tie their uses depicted in table 1.

Table 1. Drawbacks Associated with Different Types Of GRDDS

Formulations	Drawback
Incorporation of passage delaying food excipient such as fatty acids	- Affect emptying mechanism of entire content.
Bio adhesive drug delivery systems	- Adhesive is non-specific - Efficiency is limited by possible interaction with food.
Biodegradable and non-biodegradable (swelling) formulation in which size and shape retain in dosage form.	- Present hazard of permanent retention and might lead to serious life-threatening effects if multiple dosing.

➤ **Approaches to Design Floating Dosage Forms**

• *Single-Unit Dosage Forms*

In Low-density approach at last, thing buoys on gastric liquid while discharging cure unobtrusive bit as fast as time allows more than drawn out time compass[10].

Liquid filled skimming chamber dividers in contact with liquid are settled so that undissolved methodology stays in that. The contraction is of swallowable size, keeps above water inside of stomach for drawn out time, and after complete discharge shell limits, goes off to digestive structure, and is wiped out[11]. Hydrodynamically adjusted structures (HBS) are relied on upon to drag out stay of estimations shape in gastro intestinal tract and help in overhauling support. Such structures are most fitting for arrangements having pervasive dissolvability in acidic environment other than for meds having particular site of support in upper bit of insignificant digestive system. To stay in stomach for drawn out time of time estimation's structure must have mass thickness of under 1. It ought to stay in stomach, keep up its focal dependability, and discharge calm reliably from estimations structure. The accomplishment of HBS case as unrivaled structure is best exemplified with chlordiazeopoxide hydrochloride.

HBS of chlordiazeopoxide hydrochloride⁴⁰ had equivalent blood level time profile starting three 10-mg business holders' Unmistakable sorts of tablets (bi-layered and structure) have been demonstrated to have floatable qualities. A touch of polymers utilized are hydroxypropyl cellulose, hydroxypropyl methylcellulose, cross-povidone, sodium carboxymethyl cellulose, and ethyl cellulose. Self-changing floatable uneven strategy pharmaceutical advancement system utilizes unequal 3-layer structure progress to control prescription release.

- *Specific Unit Dosage Forms*

The lighting up behind portraying out changing unit estimation's structure is to add to period endeavored methodology that has each one of upsides of lone unit structure other than is with no of early passed on hindrances of single-unit subtle parts. In trek for this try different particular unit floatable estimations structures have been manufactured. Microspheres have high stacking motivation driving constraint and unmistakable polymers have been used, for event, egg whites, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Round polymeric microsponges moreover proposed as "microballoons," have been prepared. Microspheres have trademark internal void structure and showcase phenomenal in vitro floatability[12]. In Carbon dioxide– generating gathered unit oral formulations few devices with parts that make, make, or are swelled through carbon dioxide made in contraptions after association together have been portrayed in late patent made work. These estimations structures are rejected from scope of pyloric sphincter if width of ~12 to 18 mm in their opened-up state is surpass.

- *Taxonomy of Floating DDS*

Floating pharmaceutical transport structure structures are managed ward upon use of two asking for variables: sputtering and non-frothing frameworks.

- *Foaming Floating Dosage Forms*

These are structure sorts of frameworks made with assistance out of swellable polymers, for case, methylcellulose and chitosan and unmistakable foaming mixes.

Ichikawa *et al.* added to another contrasting kind of drifting estimation structure made out of sputtering layers and swellable film layers secured on made discharge pills[13]. These sublayers were joined by swellable polymer layer containing polyvinyl acidic harming determination and disengaged shellac. CO₂ was made by goodness response between 2 foaming heads, going on swollen pills (like blow ups) with thickness under 1.0 g/ml. It was found that structure had surprising skimming most remarkable self-decision of pH and thickness and strategy (para-amino benzoic ruinous) discharged in saw over way (Figure 1).

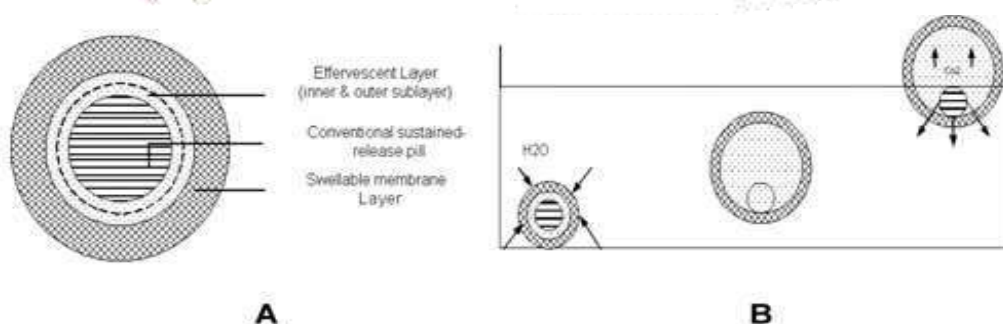


Figure 1. Multiple-Unit Oral Floating Drug Delivery System

➤ **Working Principle of Effervescent Floating Drug Delivery System**

Yang *et al.* added to swellable halter kilter three-layer tablet with skimming capacity to draw out stomach living methodology time of triple cure regimen (tetracycline, metronidazole, and clarithromycin) in Helicobacter pylori–associated peptic ulcers using HPMC and poly (ethylene oxide) (PEO) as rate-controlling polymeric film excipients[14]. The relationship of vehicle structure was in light of swellable unequal triple-

layer tablet approach. Tetracycline and metronidazole were solidified into inside of layer of triple-layer cross zone for controlled progress, while bismuth salt was joined in one of outside layers for minute release. The floatation was virtuoso by joining gas-creation layer including sodium bicarbonate: calcium carbonate (1:2 degrees) close to polymers. The in vitro results revealed that kept up transport of tetracycline and metronidazole more than 6 to 8 hours could be refined while tablet kept above water. (Figure 2)

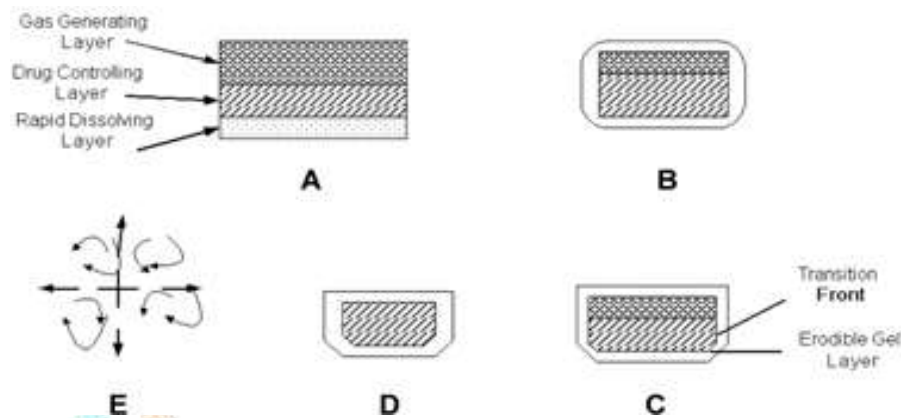


Figure 2. Schematic Presentation of Working of Triple-Layer System

AIM AND PLAN OF WORK

Ranitidine hydrochloride is histamine H₂-receptor foe. It is broadly recommended in component duodenal ulcers, gastric ulcers, Zollinger-Ellison issue, gastroesophageal reflux sickness, and erosive esophagitis. The proposed grown-up oral estimations of ranitidine is 150 mg twice reliably or 300 mg once orderly. The productive treatment of erosive esophagitis obliges relationship of 150 mg of ranitidine 4 times day. A traditional estimation of 150 mg can repress gastric dangerous transmission up to 5 hours however not up to 10 hours. A decision estimation of 300 mg prompts plasma changes; consequently, supported discharge measurement kind of ranitidine hydrochloride is desirable. The short common half-vicinity of arrangement (~2.5-3 hours) in addition sponsorships progress of managed discharge definition.

A standard oral reinforced discharge course of action discharges limitless piece of drug at colon. Ranitidine is absorbed just as a matter of first importance bit of minimal digestive tract and has half total bioavailability. Moreover, colonic osmosis game plan of ranitidine is to some degree responsible for poor bioavailability of ranitidine from colon. These properties of ranitidine hydrochloride don't support standard way to deal with oversee kept up discharge development. In this way, clinically adequate supervised discharge estimation sorts of ranitidine hydrochloride composed with routine advancement may not be beneficial.

PLAN

1. Selections of Drug
2. Design of formulation and procurement of chemicals and solvents
3. Estimation of ranitidine hydrochloride
4. Preparation of floating matrix tablets
5. Evaluation of powder blend
6. Evaluation of tablets

RESULTS

➤ Estimation of Ranitidine Hydrochloride

An answer of ranitidine hydrochloride was designed in 0.1 N HCl and UV degree was taken using Shimadzu UV-1601 UV/Vis twofold bar spectrophotometer. The UV maxima of ranitidine hydrochloride was found to be 315 nm in 0.1 N HCl.

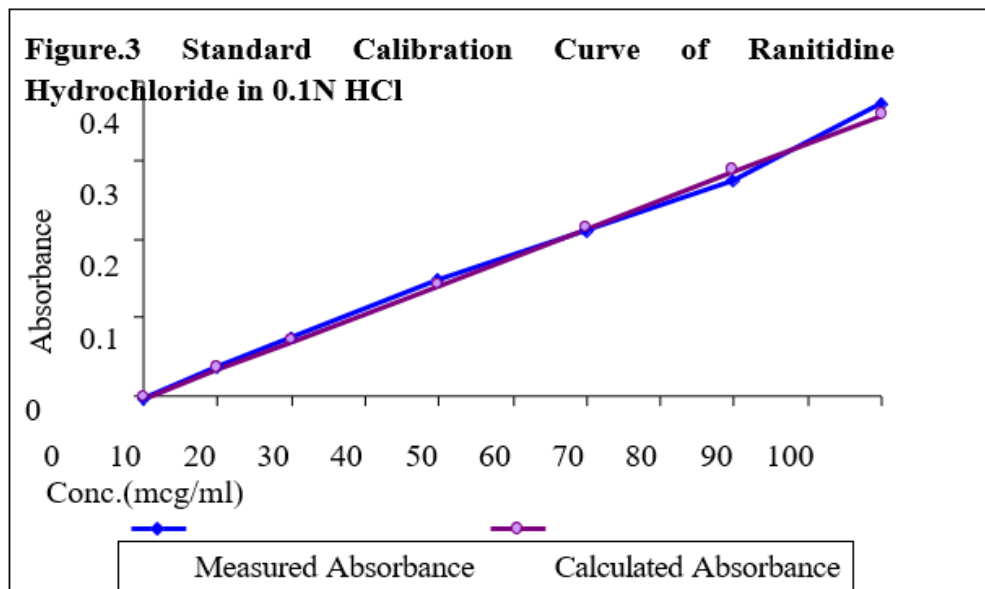
- *Preparation of Standard Calibration Curve of Ranitidine Hydrochloride*

Ranitidine Hydrochloride (10 mg) was disengaged in 0.1 N HCl and volume was made up to 100 ml in 100 ml volumetric holder. This course of action (100 mcg/ml) was further incapacitated with 0.1 N HCl to get graph of 10 to 100 mcg/ml. The possible eventual outcomes of standard turn status are indicated in table 2 and figure 3.

Concentration ($\mu\text{g/ml}$)	Absorbance			Average Absorbance	Calculated Absorbance
	1	2	3		
0	0	0	0	0	0.003
10	0.041	0.041	0.041	0.041	0.039
20	0.079	0.080	0.077	0.078	0.075
40	0.151	0.150	0.151	0.151	0.147
60	0.215	0.213	0.212	0.213	0.219
80	0.275	0.278	0.277	0.277	0.291
100	0.372	0.375	0.378	0.375	0.363

Correlation Co-efficient: 0.9962

Absorbance= 0.0036x conc. + 0.0025



➤ *Calculation of Theoretical Release Profile of Ranitidine Hydrochloride from Floating Matrix Tablets*

Estimation of instant Release Dose

$$IR = \frac{C_{SS} \times V_d}{F}$$

$$F = \frac{36 \times 1.4}{50}$$

$$50 = 100.8 \text{ mg}$$

Estimation of Maintenance Dose (MD)

$$MD = IR \left[\frac{1 + 0.693t}{t_{1/2}} \right]$$

$$= 100.8 \left(\frac{1 + 0.693 \times 8}{2} \right)$$

$$= 279.41 \text{ @ } 300 \text{ mg}$$

where, $t_{1/2}$ = half-life, C_{SS} = Concentration at steady state, IR = Immediate release, V_d = Volume of distribution, MD = Maintenance dose, F = Fraction bioavailable, t = time up to which sustain release is required

As per hypothetical profile medication discharge in first hour ought to be 100.8 mg (33.60 %). In remaining 7 hours medication discharge ought to be $(300 - 100.8 =) 199.2$ mg. Thus, following 1 hour 28.46 mg (9.48 %) medication ought to be discharge at consistent.

Table. 3 Theoretical Release Profile of Ranitidine Hydrochloride	
Time (hr)	Theoretical Drug Release (%)
1	33.60
2	43.08
3	52.56
4	62.04
5	71.52
6	81.00
7	90.48
8	99.96

- *Preparation of Floating Matrix Tablets*

Unmistakable tablets approaches were dealt with by direct weight strategy. Every one of powders were passed however 80 cross zone sifters. Obligated measure of pharmaceutical, structure polymer and low-thickness copolymer were blended totally. Talc and magnesium stearate were at long last included as glident and oil wholeheartedly. The mix was full (12 mm width, level punches) utilizing multipunch tablet weight machine (Cadmach, Ahmedabad, India). Every tablet contained 336 mg of ranitidine hydrochloride (336 mg practically identical to 300 mg of ranitidine) and other pharmaceutical fixings as recorded in table in every range.

2 Evaluation of Powder Blend

- *Angle of Repose*

The edge of rest of powder mix was controlled by channel method. The without a doubt weight powder mix were taken in channel. The stature of have was balanced in such way tip of channel basically touched most astonishing reason for powder mix. The powder mix was permitted to hold fast to course uninhibitedly on to surface. The expansiveness of powder cone was measured and reason behind rest was enrolled utilizing running with trial light.

$$\tan q = h/r$$

Where, h and r are height and radius of powder cone.

- *Bulk Density*

Both free mass thickness (LBD) and tapped mass thickness (TBD) was resolved. A measure of 2 gm of powder blend from each experimental explanation, early shaken to break any agglomerates limited, was surely understood in with 10 ml measuring barrel. After that beginning volume was noted and barrel was allowed to fall under its own particular weight on to hard surface from stature of 2.5 cm at second breaks. Tapping was

continued until no further change in volume was noted. LBD and TBD were instructed using running with numerical articulations.

LBD= Weight of powder blend/Untapped Volume of packing

TBD=Weight of powder blend/Tapped Volume of packing

➤ *Compressibility Index*

The Compressibility Index of powder blend was facilitated by technique for Carr's compressibility list. It is sensible test to audit LBD and TBD of powder and rate at which it pushed down. The mathematical statement for Carr's Index is as underneath:

$$\text{Carr's Index (\%)} = [(TBD-LBD) \times 100] / TBD$$

➤ *Total Porosity*

Outright porosity was controlled by measuring volume included by picked weight of powder (V_{bulk}) and true-blue volume of powder mix (The space controlled by powder particular of spaces more unmistakable than intermolecular spaces, V)

$$\text{Porosity (\%)} = (V_{\text{bulk}} - V) / V_{\text{bulk}} \times 100$$

➤ *Drug Content*

An absolutely weight measure of ranitidine hydrochloride powder blend (100 mg) was removed with 0.1 N HCl and course of action was channel through 0.45 μ film. The absorbance was measured at 315 nm after suitable debilitating using Shimadzu UV-1601 UV/Vis twofold pole spectrophotometer.

Table 4 Micromeritic Properties of Powder Blend

Powder blend	Angle of Repose ($^{\circ}$)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility Index (%)	Total Porosity (%)	Drug Content (%)
A12	29.11	0.119	0.142	16.20	16.18	99.92– 100.01

EVALUATION OF TABLETS

➤ *Weight Variation Test*

To study weight mixed bag twenty tablets of definition were measured using Sartorius electronic counterbalance and test was performed by power framework.

➤ *Drug Content*

Five tablets were measured independently, and medication was extricated in 0.1 N HCl, medication substance was resolved as depicted previously.

➤ *Hardness*

The hardness of five tablets was resolved utilizing Pfizer hardness analyzer and normal qualities were figured.

Density

The thickness of tables was dictated by utilizing vernier calipers. Five tablets were utilized, and normal qualities were computed.

Table 5 Evaluation Parameter of Tablets

Tablets Batch	Weight variation test (%)	Drug content (%)	Hardness (kg/cm ²)	Density (mm)
A12	Av. \pm 1.6	100 \pm 2	6.1 \pm 0.2	5.2 \pm 0.01

All values are expressed as mean \pm SE.

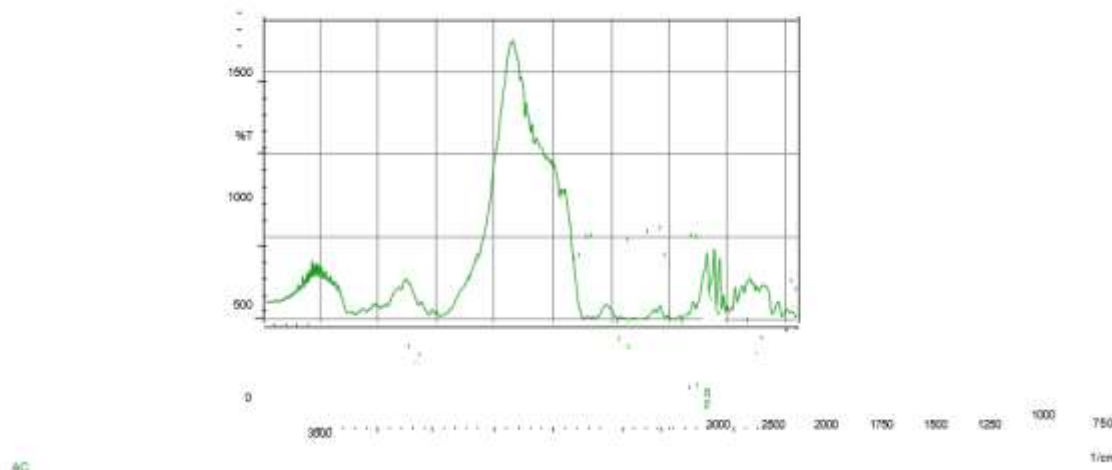
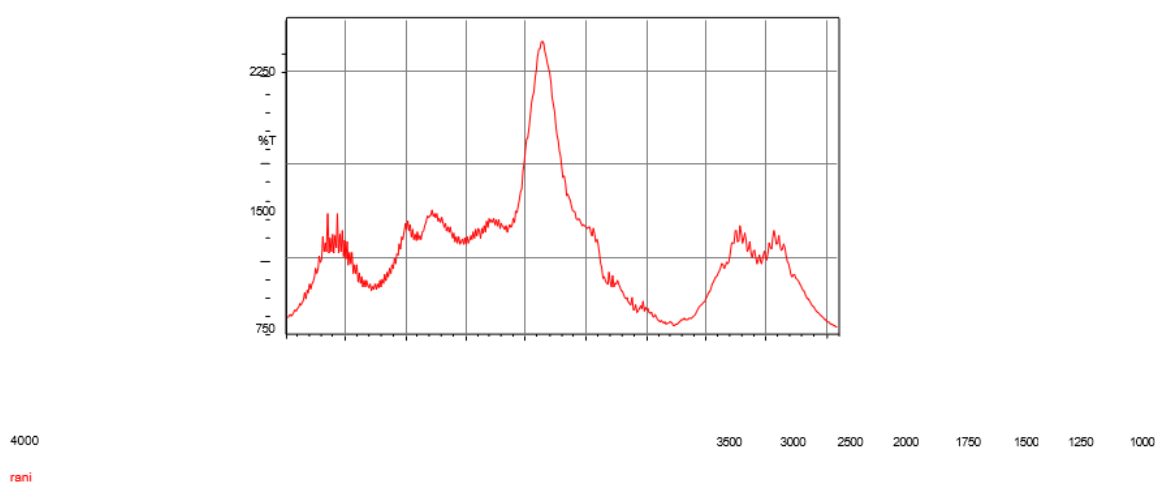
➤ *Results and Discussions*

The micromeritic properties of powder blend of best assembling deciding were checked, wherein purpose behind rest was found to be around 29.110, which shows sublime spilling property of blend. The free mass thickness and tapped mass thickness were found to be 0.119 g/ml and 0.142 g/ml independently which is surprising. The compressibility record and total porosity was seen to be 16.20 % and 16.18 %. The arrangement substance was in level of 99.92 – 100.01 %, which passes official need. The remedy substance in every one of packs of ranitidine hydrochloride skimming tablets was in level of 98 to 102 % (i.e., mixed sack of \pm 2%). This ensured consistency of pharmaceutical substance in tablets. Weight mixed sack data of prepared tablets displayed no isolating disperse quality in immeasurability of individual tablet from regular worth. Hardness of prepared tablets was seen within level of 6.1 \pm 0.2 kg/cm². Thickness of significant number of tablets was found in level of 5.2.

Drug Excipient Interaction Study

The unadulterated game plan, ranitidine hydrochloride and mix of it with polymer chitosan – carbopol 940 and PSDVB copolymer powder was mixed uninhibitedly with IR grade KBr and taking gander at pellets were built by applying 10 tons of weight in water-controlled press. The pellets were looked over wave number level of 400 to 4000 cm⁻¹ in FTIR 8400S model instrument.

Drug-excipient joint attempts expect significant part concerning touching base of medicine from definition amongst others. FTIR methodologies have been used here to consider physical and created correspondence in middle of cure and excipients used. In present study, it has been watched that there is no composed relationship between ranitidine hydrochloride and polymers used. Game plan has given peaks by uprightness of furan ring, discretionary diamine, alkene and two tops as eventual outcome of nitro utilitarian gatherings. Structure figure it was watched that there was no adjustment in these boss tops in IR spectra of mix of pharmaceutical and polymers, which show there were no physical facilitated endeavours as postponed result of some security blueprint in middle of medicine and polymers.

Figure 4 Infrared Spectra of Ranitidine Hydrochloride**Figure 5 Infrared Spectra of Chitosan**

Summary & Conclusion

The reason for study was to make and physio-misleadingly delineated Gastroretentive matrix tablet of ranitidine hydrochloride in context of low thickness copolymer. Ranitidine hydrochloride has short regular half-life (2.1 ± 0.2 hours) and 50 % overpowering bioavailability. Advancement of oversight release criticalness of ranitidine hydrochloride can be helpful, that can give drag out gastric upkeep and accumulate ampleness of estimation structure. A standard oral kept up release arrangement releases lion's offer of pharmaceutical at colon, in this way arrangement should have maintenance window either in colon or all through gastrointestinal tract. Ranitidine is devoured just in starting bit of insignificant digestive tract and has half totally bioavailability.

Different sorts of framework encompassing polymers were centred around: chitosan, carbopol 940, HPMC K4 m, HPMC K15 M, HPMC K100 M, sodium alginate, psyllum, sesbania gum, guar gum, gum acacia for study. The tablets isolated upon contact with release medium, and relative essentialness of pharmaceutical dispersal, polymer swelling and tablet deteriorating for coming about release structures changed in wide sense with sort of cross area past.

Gastro retentive (low thickness) tablets of ranitidine hydrochloride were readied utilizing Poly (Styrene Di vinyl Benzene) copolymer which offered delicacy to purposes of interest and furthermore decreased

skimming slack times to heavenly increment. The use of PSDVB copolymer in system tablets as thickness lessening powers has given substitute look. Amidst study with copolymer particular properties of material were seen; like essentially permeable round structure, unfathomable compressibility, amazing stream property with medication and assorted copolymers, no indispensable impact on prescription discharge and similarity with arrangement and unmistakable polymers as seen through IR spectra.

It is compacted and mulled over that chitosan-carbopol 940 and HPMC K100 M can be sufficiently utilized as bit of game plan of ranitidine hydrochloride kept up discharge Gastroretentive skimming prescription transport framework utilizing low thickness copolymer.

In overnight fasting condition the tablets emptied the stomach after 2 hrs of administration. This might be due to rapid gastric motility and insufficient resting volume of the stomach for the tablets to float in the stomach. But in fed condition, the same tablets showed a gastric residence time of more than 4.5 hrs. Hence the prepared tablet enhances the bioavailability making it as promising drug delivery system.

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