WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 21, 1099-1111. Review Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF FLOATING TABLET CONTAINING ANTI ULCERS AND ANTACID USING COMBINATION OF POLYMER

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Article Received on
20 Oct. 2023,
Revised on 10 Nov. 2023,
Accepted on 30 Nov. 2023
DOI: 10. 20959/wjpr202321-30458

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ABSTRACT

AIM: The aim of this research was to arrange a floating drug delivery system of Ranitidine hydrochloride (RHCL) so as to extend the gastric continuance and comparison of combination of polymer for excellent sustained effect. The tablets were prepared by direct compression. The drug: Polymer interactions make up my mind by IR spectroscopic method. The pre and post compression studies were performed by using IP standard formula and procedure. Drug release from the floating drug delivery system was studied using IPI. The release behavior of combination of polymer was compared per obtained data. The discharge data were subjected to different models zero order, first order Higuchi and Pappas so as to gauge their release kinetics and mechanisms. The hardness of all formulations was found to be within the range of 5.3±0.15 to 8.6±0.05 kg/cm². Among these all formulations (F1 to F8) prepared by direct compression, batch F6 was best formulation and showed very slow release i.e. 74.3% in 6 h. The drug release of the opposite formulation like F1, F2, F3, F4, F5, F7, F8 (94.2 %, 91.8 %, 88.51% 90.5 % 89.5 % 74.3% 86.12% 88.65% in 5.5h) was higher from the F1 formulation prepared by direct compression. The drug release was observed by fickian diffusion mechanism. the discharge kinetics of the formulation F1and F2, F3, F4, F5, F8 shows more release as compare to F6 and F7. Combination of polymer shows better sustained release properties. The formulation with Carbopol 934 and Tara gum HPMC different grade shows better sustained release effect. The developed floating tablets of RHCL could even be utilized in clinic for prolonged drug release for a minimum of 6hrs, thereby improving the bioavailability.

KEYWORDS: HCL, gastro retentive, floating drug delivery, sustained release.

INTRODUCTION

Despite tremendous advancements in drug delivery the oral route remains the popular route of administration of therapeutic agents thanks to low cost of therapy and straightforward administration cause high levels of patient compliance. But the problem of poor bioavailability (BA) of orally administered drugs remains a challenging one, though extensive advancements in drug discovery process are made 1. Gastric emptying could also be a posh process and makes in vivo performance of the drug delivery systems uncertain. so, on avoid this variability, efforts are made to increase the retention time of the drug-delivery systems for over 12 hours. The floating or hydro dynamically controlled drug delivery systems are useful in such application 2. Ranitidine hydrochloride (R HCl) could also be a histamine H2- receptor antagonist. it's widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastro gastroesophageal reflux disease, and erosive esophagi is. The recommended adult oral dosage of ranitidine is 150 mg twice daily.

APPROACHES FOR PROLONGING THE GASTRIC RETENTION TIME

1) High-density Systems. (HDS)
2) Floating Systems. (Fs)
3) Swelling and Expanding Systems.(Ss)
4) Mucoadhesive & Bioadhesive Systems.

FACTORS AFFECTING FLOATING TIME

Density, size and shape of dosage form, Fed and unfed stage, Nature of meal, Age and gender, Posture.

ADVANTAGES OF FDDS

- Enhanced bioavailability
- Sustained drug delivery/reduced frequency of dosing
- Targeted therapy for local ailments
- Within the upper GIT Reduced fluctuations of drug concentration
- Improved selectivity in receptor activation.

MECHANISM OF FLOATING SYSTEMS FDDS

Has density but gastric fluids then remain buoyant within the stomach without affecting the gastric emptying rate for a protracted period of your time.

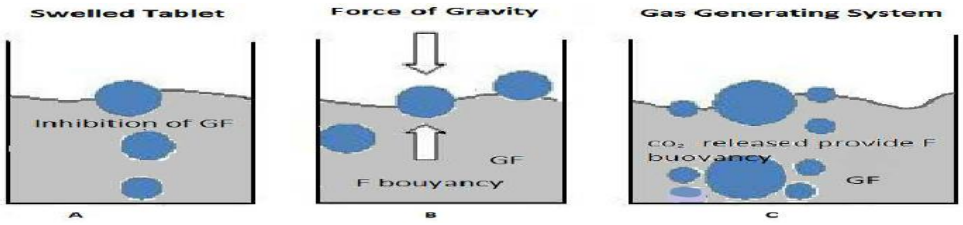
$$F = F_{buoyancy} - F_{gravity}$$

$$= (Df - Ds)$$

Where,

F= total vertical force, Df = fluid density, Ds = object density, v = volume and

g = acceleration due to gravity.



Structure No.01 Mechanism Of Floating Drug Delivery System Ranitidine

Ranitidine is employed to deal with ulcers of the belly and intestines and stop them from returning after they need healed. This medicinal drug is additionally wont to deal with positive belly and throat (esophagus) issues (which includes erosive esophagitis, esophageal reflux disease-GERD, and Zollinger-Ellison syndrome). It works with the aid of using decreasing the quantity of acid your belly makes. It relieves signs and symptoms like cough that does not get away, belly pain, heartburn, and problem swallowing. Ranitidine belongs to a category of medicine mentioned as H2 blockers. This drug has been withdrawn from the United States market thank you to issues with safety. A feasible cancer-inflicting impurity has been located in a few ranitidine products.

MOA: Patient/caregiver became told upon ranitidine and mechanism of movement of ranitidine as follows: 1.H2 receptors are located in parietal cells of belly. Histamine binds to those receptors in parietal cells of belly and stimulates secretion of gastric acid into the belly. This acid secreted facilitates with activation of a few enzymes inside the belly, which aids in digestion of food. Also, the particularly acidic environment inside the belly prevents increase of microorganisms and facilitates save you improvement of any infection. 2. Sometimes, because of extra acid with inside the belly, people can gift with signs and symptoms of

heartburn, dyspepsia, harm and erosion of the internal lining of belly and duodenum main to ulcer formation. Also, people can gift with signs and symptoms of reflux esophagitis, whilst the acid inside the belly thank you to diverse motives washes up into the esophagus and leads to signs and symptoms of GERD.

MATERIAL AND METHODS

Ranitidine HCL was received as a gift sample from Morden laboratories Indore. Hydroxy propyl methylcellulose (HPMC) K4M, Carbopol 934 and Tara gum, Tartaric acid, Sodium bi carbonate, mg stearate, Talc were obtained as a gift sample from Morden laboratories Ltd. Indore.

ANGLE OF REPOSE The angle of repose of powder blend decided by the funnel method. The accurately weight powder blend were taken within the funnel.

$\tan \Theta = h/r$

Where, h and r are the peak and radius of the powder cone.

BULK DENSITY AND TAPPED DENSITY Both loose bulk density (LBD) and tapped bulk density (TBD) decided of Two gm of powder blend from each formula, previously shaken to interrupt any agglomerates formed, was introduced in to 10 ml measuring cylinder. Then the initial volume was noted also the cylinder was allowed to comprise under its own weight on to a tough surface from the peak of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the next equations.

BD = M/Vo

TD = M/Vt

COMPRESSIBILITY INDEX The Compressibility Index of the powder blend make my mind by Carr's compressibility index. It is a straight forward test to judge the LBD and TBD of a powder and there for the rate at which it packed down. The formula for Carr's Index is as below:

Carr´s Index = (TD-BD)/TD×100

HAUSNER´S RATIO Hausner´s ratio is calculated using following formula

Hausner´s ratio = TD/BD

DRUG: POLYMER INTERACTION STUDY the pure drug and ready floating tablet were subjected to IR spectroscopic study using FT-IR spectrophotometer (IRAffinity-1, Shimadzu). The spectra were scanned over the frequency number range from 4000 – 400 cm-1. The pellet press techniques were used for sample testing's.

EVALUATION STUDIES

Table 01: Formulation Code.

Ingredients in mg	F1	F2	F3	F4	F5	F6	F7	F8
Ranitidine HCl	150	150	150	150	150	150	150	150
HPMC K4M	70	68	66	64	62	60	58	56
Carbopol 934	50	50	50	50	50	50	50	50
NaHCO3	45	45	45	45	45	45	45	45
Tartaric acid	30	30	30	30	30	30	30	30
Tara gum	70	72	74	76	78	80	82	84
Mg Stearate	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
Total weight	435	435	435	435	435	435	435	435

METHODS OF PREPARATION OF RHCL FLOATING TABLETS Eight preparations of effervescent floating tablets of Ranitidine HCl were formulated by using direct compression method using polymers namely Hydroxypropyl methyl cellulose K4M, Carbopol 934, Sodium bi Carbonate, Tartaric acid, Tara gum, Magnesium stearate, Talc Firstly all ingredients were weighed accurately on weighing balance and were then passed through sieve no. 40. The drug and excipients were mixed properly in a pestle and mortar in an attempt to get a uniform tablet blend. Finally, the compound was compressed into spherical tablet using Rotary tablet punch machine.

Swelling index: Tablets were initially weighed, kept in 100 ml of 0.1N HCl acid solution and were drawn out of the solution determine time points, dried and their weights were taken.

$$\% SI = \frac{(W2-W1) \times 100}{W1}$$

Floating lag time: Three individual tablets from each formulation were put in an individual flask containing 400 ml of 0.1N HCl acid solutions. Then note time in minutes for each tablet to go from the bottom to the top of the flask is called as floating lag time was measured.

Floating Time: Three individual tablets from each formulation were put in an individual flask containing 400ml of 0.1N HCl acid solution. Then note the time for which tablets float on the surface of water.

Dissolution study: The 900 ml of the media is taken in the flask by using paddle type apparatus at 50rpm at 37°C various times interval the 5ml of sample was withdrawn and sink condition was maintained and all the samples were filtered and 1ml solution is pipette out and volume is made by appropriate solvent and was analyzed by U.V visible spectrophotometer at lambda max of 314nm.

Hardness: The Hardness of five tablets was measured and using Monsanto tester. The mean were computed and reported. It is expressed in Kg/Cm². The limit for Hardness of the tablet ranges from 5 To 8 Kg/Cm².

Weight variation: 20 Tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than 5% weight deviate from the average weight.

Friability Test: 10 Tablets were initially weighed and transferred into the Friabilator. The Friabilator was operated at 25 rpm for 4 min. After 4 min the tablets were weighed again. The Friabilator was then calculated using the formula, general acceptance limit is 0.5-1%

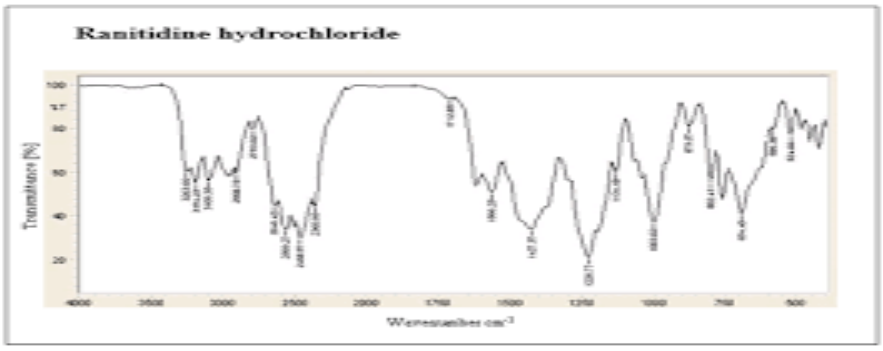
$$\text{Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

PERCENTAGE DRUG CONTENT STUDY 30 Tablets were weighed, and average weight was calculated. And 10 tablets crushed in mortar. The ability to 100 mg of Ranitidine was dissolved in 100 ml of 0.1 N HCl and shaken for 20 min. Solution was filtered and 5ml of the filtrate was diluted to100ml using 0.1N HCl acid. Absorbance of resultant solution was measured at 314 nm using 0.1 N HCl acids as a blank. The number of drug present in one tablet was calculated.

IN VITRO DISSOLUTION STUDIES the discharge rate of R HCl from floating tablets determined using Indian Pharmacopeia (IP). Dissolution Testing Apparatus I (paddle method). The dissolution test was performed using 900 ml of media, at 37 ±0.5°C and 50 rpm. A sample (10 ml) of the answer was withdrawn from the dissolution apparatus

hourly for six hours, and therefore the samples were replaced with fresh dissolution medium. The samples were filtered and diluted to an appropriate concentration Absorbance of those solutions was measured at 314 nm employing a Shimadzu UV-1600 UV/Vis double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a customary curve.

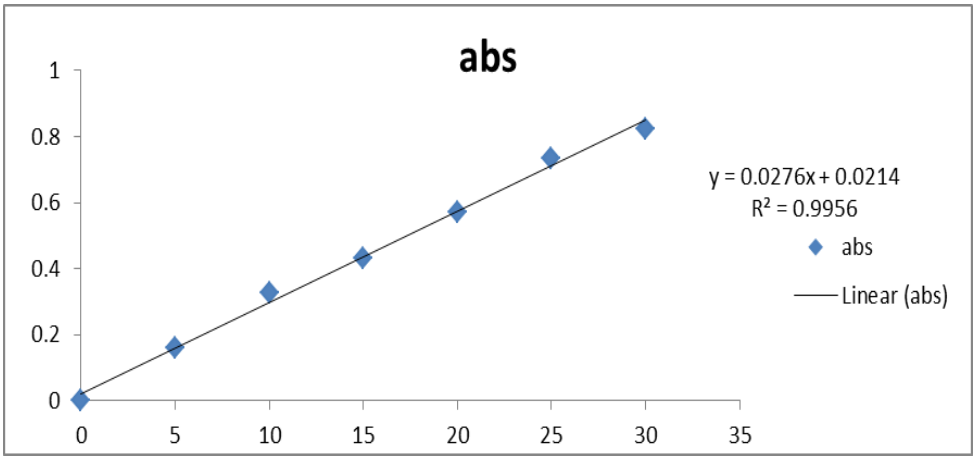
DRUG POLYMER INTERACTION STUDY Drug- Excipient interactions play an important role with relation to release of drug from the formulation amongst others. FTIR techniques are used here to review the physical and chemical interaction between drug and excipients used. Within the present study, it's been observed that there's no chemical interaction between RHCL and also the polymers used. Drug has given peaks thanks to furan ring, secondary di amine, alkenes and two peaks thanks to nitro functional groups. Form the figure it had been observed that there have been no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there have been no physical interactions thanks to some bond formation between drug and polymers.



Structure No.02 Ftir Spectra For Drug Compatibility Study.

Table 02: Calibration table of ranitidine HCL.

S.NO.	CONC. ug/ml	Abs.
1	0	0
2	5	0.161
3	10	0.325
4	15	0.432
5	20	0.572
6	25	0.733
7	30	0.824



Structure no. 03 calibration curve of ranitidine hcl.

Table 03: Pre-compression evaluation of rhcl floating tablet.

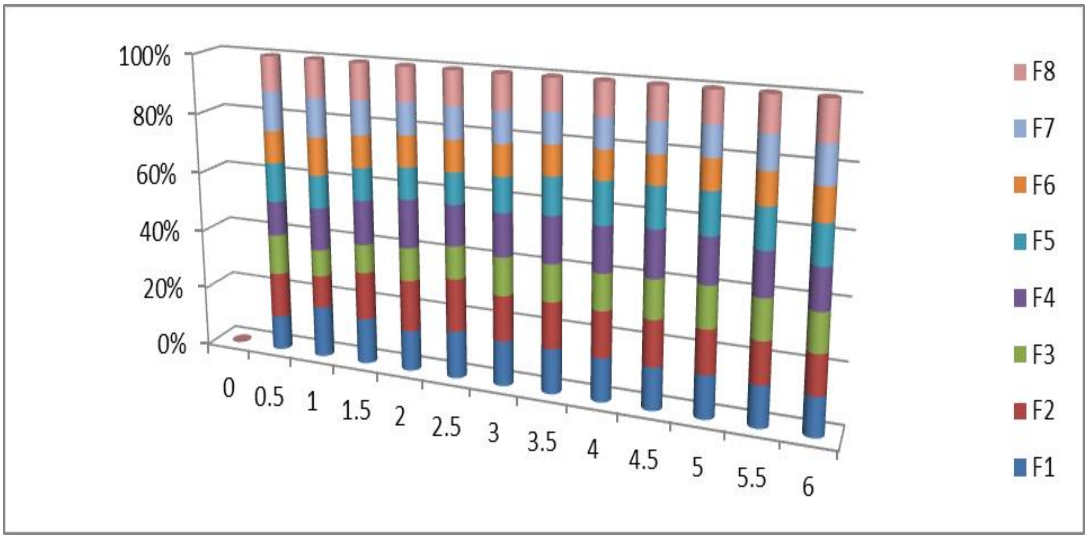
Formulation	Angle of repose ±S.E.M	Bulk density ±S.E.M	Tapped density ±S.E.M	Compressibility index	Hausner´s ratio ±S.E.M
F1	38.78±0.06	0.51±0.13	0.66±0.05	15.52	1.15±0.19
F2	30.35±0.05	0.43±0.01	0.45±0.08	14.54	1.14±0.18
F3	29.45±0.12	0.31±0.18	0.38±0.10	16.12	1.17±0.06
F4	27.35±0.02	0.40±0.05	0.42±0.18	20.15	1.16±0.12
F5	26.20±0.22	0.44±0.14	0.47±0.14	18.16	1.18±0.05
F6	24.30±0.21	0.18±0.05	0.20±0.15	12.21	1.12±0.10
F7	27.12±0.15	0.32±0.18	0.33±0.12	16.45	1.16±0.12
F8	26.41±0.16	0.25±0.20	0.26±0.10	17.12	1.17±0.19

Table 04: Post-Compression Evaluation Of Rhcl Floating Tablets.

Formulation Code	Thickness (mm) ±S.E.M	Hardness (Kgcm-2) ±S.E.M	Friability (%) ±S.E.M	Average weight ± S.E.M	Content uniformity (%) ±S.E.M	Floating Lag time (min)	Floating Time (h)
F1	3.96 ± 0.15	5.3 ±0.15	0.71±0.09	439±0.63	81.46±0.03	1 min	3
F2	3.96 ± 0.06	4.8±0.13	0.60±0.10	425±0.26	79.56±0.02	3min	5
F3	3.98 ± 0.03	6.6±0.09	0.50±0.07	441±0.63	80.85±0.01	2 min 56 sec	4.5
F4	3.97 ±0.17	6.5±0.05	0.66±0.06	432±0.25	78.12±0.03	2 min	4
F5	3.92 ± 0.19	6.5±0.05	0.53±0.08	430±0.25	86.16±0.02	1.5 min	3
F6	3.91 ±0.19	6.2 ±0.19	0.5±0.10	434±0.23	88.63±0.01	4 min	6
F7	3.90 ±0.18	7.5 ± 0.06	0.45±0.09	440±0.25	76.56±0.02	2min 83 sec	5
F8	3.90 ±0.17	9.6±0.05	0.4±0.05	442±0.33	85.23±0.02	3 min	4

Table 05: In Vitro Drug Release Kinetic Of Floating Tablets Of Rhcl.

TIME (h)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	6.54	8.54	7.56	6.54	7.45	6.12	7.56	6.45
1	15.6	11.9	9.74	18.6	12	13.89	14.2	13.65
1.5	25.6	27.4	16.4	26.4	18.6	18.56	19.6	20.65
2	37.5	39.9	25.4	31.5	24.5	24.26	24.67	26.32
2.5	45	58.4	36.45	53	35.12	34.95	35.45	37.65
3	56.7	59.9	50.12	59.4	45.9	40.99	41.23	45.23
3.5	70.5	70.4	56.26	68.2	56.5	45.52	46.25	47.25
4	78.7	80	62.13	75.5	72.6	50.32	51.32	55.45
4.5	86.3	84.6	71.65	79.3	74.5	52.46	56.12	58.56
5	88.6	85	80.32	84	80.5	57.74	58.23	59.36
5.5	93.5	90.2	86.23	89.4	85.6	68.5	70.56	74.35
6	94.2	91.8	88.56	90.5	89.5	74.3	86.12	88.65



Structure no. 03 drug kinetic release order.

Table 06: swelling index for floating tablet.

TIME (hour)	F1	F2	F3	F4	F5	F6	F7	F8
1	21±0.55	18±0.32	28±0.33	21±0.21	25±0.66	36±0.12	29±0.12	30±0.66
2	65±0.52	75±0.65	70±0.55	69±0.32	70±0.32	164±0.13	45±0.65	65±0.32
3	80±0.54	120±0.25	80±0.65	130±0.23	120±0.45	212±0.12	120±0.25	90±0.45
4	90±0.56	135±0.25	112±0.33	165±0.34	135±0.12	235±0.15	126±0.23	120±0.12
5	135±0.25	145±0.32	130±0.66	177±0.54	156±0.21	255±0.22	135±0.32	135±0.21
6	166±0.24	165±0.12	145±0.55	185±0.34	170±0.33	265±0.32	145±0.12	165±0.33
7	190±0.35	180±0.12	160±0.66	195±0.12	185±0.33	280±0.22	165±0.22	180±0.32

Table 07: Release kinetics study of f6 formulation.

TIME (min)	Log Time	Square root of time	Cumulative % drug released	Log Cumulative % drug released	Cumulative % drug remained	Log Cumulative % drug remained
0	0	0	0	0	0	0
30	0.30	1	6.12	0.79	93.88	1.96
60	0.48	1.41	13.89	1.14	86.11	1.92
90	0.60	1.73	18.56	1.29	81.44	1.89
120	0.70	2	24.26	1.38	75.74	1.83
150	0.78	2.23	34.95	1.54	65.05	1.80
180	0.85	2.45	40.99	1.62	59.01	1.75
210	0.90	2.64	45.52	1.66	54.48	1.73
240	0.95	2.82	50.32	1.70	50.96	1.68
270	1	3	52.46	1.72	47.54	1.66
300	1.04	3.16	57.74	1.75	42.26	1.64
330	1.08	3.31	68.5	1.82	31.5	1.51
360	1.28	3.46	4.3	1.86	25.7	1.42

DISCUSSION

The pre compression evaluation like bulk density, true density, compressibility, angle of repose were found as per standard range all the info indicating suitable formulation of the floating tablet. The post compression evaluation for the all formulation is complies with the quality monograph. The post compression parameters like hardness, friability, thickness, drug content. The obtained data was best fitted for the floating tablet. The drug release data were explored for the kind of release mechanism followed. The most effective fit with the very best determination r2 coefficients was shown by both the zero order and Higuchi models. Zero order release describes the discharge rate independent of drug concentration. Higuchi root kinetic model describes, release drug from the insoluble matrix as root of your time dependent process. It describes release of drug by simple diffusion mechanism. The values of n with parametric statistic for all the formulations were showed within the table 4. The values of n were within the range (n is quite 0.5) indicating Non fickian release governed by the drug diffusion. However as indicated by the values of R2 both of the models (Higuchi and Pappas) were found to be efficient in describe the discharge of RHCL from the floating tablets. All the parameters were run 3 times (n=3). The difference in mean of Zero order, First order, Higuchi kinetics and Pappas Equation between batch series‘F6.

CONCLUSION

The sample of ranitidine HCl was identified for Color, odor and taste which were observed color colorless to yellow odorless. The solubility of Ranitidine HCl was observed free soluble

in water and soluble in methanol, sparingly soluble in ether and slightly soluble in Chloroform. The temperature of Ranitidine HCl was observed to be 134°C. The parameters such tapped density, Bulk density, Carr´s index, Hausner´s ratio and angle of repose were determine and therefore the results were reported. The majority density and tapped density were tabulated and was found to be 0.51 to 0.57 and 0.56 to 0.66 respectively. Carr´s index and Hausner´s ratio was to found to be in between 11.11 to 23.94% and 1.12 to 1.27. The angle of repose for various formulations was but 30, which indicates good flow properties of the powder. The worth was found to be in between 26. 0 to 29.7. Of these results indicate that the powder possessed satisfactory flow properties. The results were found to be within limits and satisfactory. The thickness of the tablet was found to be within the range of three.91 ± 0.19 mm to 3.96 ± 0.06. Consistently with the load variation test in IP the share deviation of the tablets weighing within the range of over 250 mg is ± 5%. The load of all tablet formulation was as per the official requirements. Good uniformity in drug content was found among different formulations and drug content was over 85 %. The hardness of the tablets was found to be within the range of 5 to eight kg/cm². The friability for all the formulations was below 1% indicating that the friability was within the proportion of limit. Tablet containing higher amount of Tara gum and hydroxy acid generally showed longer total floating time. It ranged from 5.5 to 6 h. F6 had total floating time 6 h thanks to the synergistic effect of Tara gum and hydroxy acid, higher amount of polymer that made dosage form excellently buoyant because of maximum swelling. Dissolution was disbursed in IP apparatus I paddle type six buckets dissolution apparatus. Formulated (F1,F2, F3,F4,F5,F6,F7,F8) tablets were fixed with sinkers and put within the buckets of the dissolution apparatus full of 900 ml of water maintained at a temperature of 37 ± 0.5ºC and paddle rotation speed at 50 rpm. Samples were withdrawn at time points 30, 60, 90, 120, 150, 180, 210, 240, 270 300, 330, 360. Min and analyzed in UV-spectrophotometer (Shimadzu UV-1600) at lambda max of 314 nm. The values of absorbance obtained were accustomed calculate the number of drug release. Further kinetics study was finished optimized formulation F6 using zero order, first order. This shows R^2 value 0.995. On the idea of present study, it had been calculated that floating tablets of Ranitidine HCl can increase the bioavailability still as gastric continuance and thus better patient compliance could also be achieve.

ACKNOWLEDGMENTS

The authors are thankful to modern laboratories Indore for providing gift sample of Ranitidine HCl. The authors are also thankful to Astt. Professor Miss. Nikita Sohaney, Head

of institute Dr. Sapna Malviya Technical campus Modern institute of pharmaceutical science Indore for providing laboratory facilities.

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