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FORMULATION AND EVALUATION OF FLOATING TABLETS OF RHCL USING NATURAL AND SYNTHETIC POLYMERS

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ABSTRACT

The present study involved development and characterization of newer floating tablets of Ranitidine hydrochloride by direct compression method using two different natural polymers like-Xanthan and Guar gum. Powders were evaluated for angle of repose, loose bulk density, tapped density, Carr's index and Hausner ratio whereas the prepared tablets were evaluated for weight variation, thickness and diameter, hardness, friability, drug content, floating lag time, total floating time, hydration behavior, and in vitro dissolution study. The drug release kinetic was fitted in three different mathematical models like- Zero order, Higuchi and Korsmeyer-Peppas model. The results indicate that the drug release mechanism was found fickian diffusion type in most of the formulations. The developed floating tablets of Ranitidine hydrochloride may be used in clinic for prolonged drug release for at least 12h, thereby improving the bioavailability and patient compliance.

Keywords: RHCL, GASTRORETENTIVE, FLOATING DRUG DELIVERY, SUSTAINED RELEASE

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1.0 INTRODUCTION

Despite tremendous advancements in drug delivery the oral route remains the preferred route of administration of therapeutic agents because of low cost of therapy and ease of administration lead to high levels of patient compliance. But the issue of poor bioavailability (BA) of orally administered drugs is still a challenging one, though extensive advancements in drug discovery process are made¹. Gastric emptying is a complex process and makes in vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 hours. The floating or hydrodynamically controlled drug delivery systems are useful in such application².

Ranitidine hydrochloride (RHCl) is a histamine H₂-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of ranitidine 4 times a day³. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 hours but not up to 10 hours. An alternative dose of 300 mg leads to plasma fluctuations; thus a sustained release

dosage form of RHCl is desirable⁴. The short biological half-life of drug (~2.5-3 hours) also favors development of a sustained release formulation. A traditional oral sustained release formulation releases most of the drug at the colon, thus the drug should have absorption window either in the colon or throughout the gastrointestinal tract. Ranitidine is absorbed only in the initial part of the small intestine and has 50% absolute bioavailability^{5,6}. Moreover, colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon⁷. These properties of RHCl do not favor the traditional approach to sustained release delivery. Hence, clinically acceptable sustained release dosage forms of RHCl prepared with conventional technology may not be successful⁸. The gastroretentive drug delivery systems 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 bioavailability⁹.

It is also reported that oral treatment of gastric disorders with an H₂-receptor antagonist like ranitidine or famotidine used in combination with antacids promotes local delivery of these drugs to the receptor of the parietal cell wall.

Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion⁹. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release¹⁰. In context of the above principles, a strong need was recognized for the development of a dosage form to deliver RHCl in the stomach and to increase the efficiency of the drug, providing sustained action. The present investigation applied a systematic approach to the development of gastroretentive RHCl dosage forms.

Floating drug delivery systems offer important advantages: as they are less prone to gastric emptying resulting in reduced intra and intersubject variability in plasma drug levels, effective for delivery of drugs with narrow absorption windows, reduced dosing and

increased patient compliance, reduced C_{max} and prolonged drug levels above the minimum effective concentration, and improved safety profile for drugs with side-effects associated with high C_{max}¹¹.

2.0 Material and methods:

Ranitidine HCL was received as a gift sample from Karnataka Antibiotics, Bangalore India. Hydroxy-propylmethylcellulose (HPMC) K4M, K100M and Guar gum, Xanthum gum were obtained as a gift sample from Karnataka Antibiotics Ltd. Bangalore and Shreeji chemicals, Mumbai. All other reagents used in this study were of analytical grade and obtained from standard sources.

2.1 Preparation of RHCL Floating Tablets

RHCl was dispersed in chloroformic solution of the required quantity of stearic acid. The dispersion was stirred and chloroform was evaporated to form an RHCl-stearic acid mixture. This mixture was then blended with other ingredients such as polymer, sodium bicarbonate and citric acid. The powder blend was then lubricated with magnesium stearate (1% wt/wt) and purified talc (1% wt/wt) and compressed on single punch tablet machine.

Tablet No.1:- Composition of Tablet

INGREDIENTS	F1	F2	F3	F4
HPMC K4M	90			
HPMC K100M		90		
Xanthum gum			90	
Guar gum				90
Sodiumbicarbonate	50	50	50	50
Stearic acid	50	50	50	50
Citric acid	10	10	10	10
Mg. stearate (%)	1	1	1	1
Talc (%)	1	1	1	1
Floating lag time (Second)	37	29	90	120

Each formulation contains 336 mg of RHCL

3.0 DRUG POLYMER INTERACTION STUDY

Drug- excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between RHCL and the polymers used. Drug has given peaks due to furan ring, secondary diamine, alkene and two peaks due to nitro functional groups. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

3.1 EVALUATION OF POWDER BLENDS ^{12, 13, 14, 15}

3.1.1 ANGLE OF REPOSE

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend 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.

$$\tan \theta = \frac{h}{r}$$

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

3.1.2 BULK DENSITY

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following equations.

$$LBD = \frac{\text{Weight of powder blend}}{\text{untapped volume of the packing}}$$

$$TBD = \frac{\text{Weight of the powder blend}}{\text{Tapped Volume of the packing}}$$

3.1.3 COMPRESSIBILITY INDEX

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's index} = \frac{[TBD - LBD]}{TBD} \times 100$$

3.1.4 TOTAL POROSITY

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces, V)

$$POROSITY = \frac{V_{bulk} - V}{V_{bulk}} \times 100$$

3.2 CHARACTERIZATION OF FLOATING TABLETS:-

3.2.1 Weight variation:- The tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measured to help ensure that a tablet contains the proper amount of drug.

The weight variation test was determined by the USP XX – NF XV method. The test was carried out by weighing the 20 tablets individually using analytical balance than calculating the average weight, and comparing the individual tablet weights to the average. There was not more than two tablets are outside the percentage limit. The tablets was not differs by more than 2 times the percentage limit.

$$\text{Percentage of weight variation} = \frac{\text{Individual} - \text{Average weight}}{\text{Average weight}} \times 100$$

3.2.2 Hardness: - The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage

depends on its hardness. The instrument measures the force required to break the tablet when the force generated by anvils to the tablet. Tablet hardness is defined as the load required crushing or fracture a tablet placed on its edge. Sometime it is also termed as tablet crushing strength. The hardness test was performed using Pfizer hardness tester. The diametrical crushing strength test was performed on 10 tablets from each formulation. The tablet is placed between two anvils, force is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded.

3.2.3 Thickness: - The diameter and thickness of captopril tablets was performed on 10 tablets from each formulation. The thickness of individual tablets was measured using Vernier caliper. It is expressed in mm, which permits accurate measurements and provides information of the variation between tablets. Tablet thickness was controlled within a $\pm 5\%$ variation of a standard value.

3.2.4 Friability: - For each formulation, the friability of 20 tablets was determined using a Roche type friabilator. 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min. After removing of dusts, tablets were re-weighed and friability percentage was calculated using the following equation.

$$\text{percentage friability} = \frac{W - W_0}{W} \times 100$$

Where, W_0 = initially weight

W = weight after friability

3.2.5 PERCENTAGE DRUG CONTENT STUDY

Drug content was determined by dissolving sustained release granules equivalent to 100 mg of RHCL in 70 ml of distilled water. It was shaken for 15 min. and then diluted to 100 ml with distilled water. It was filtered through Whatman filter paper no. 41. One ml of this solution was transferred to 10 ml volumetric flask and final volume was made 10 ml. Absorbance of the resulting solution was measured at 315 nm. The drug content was determined by referring to the calibration curve.

$$\text{Drug content} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}}$$

3.2.6 Swelling index of RHCL floating tablets

The swelling index of tablets was determined in 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index(SI)} = \frac{W_t - W_0}{W_0} \times 100$$

Where,

W_t = Weight of tablet at time t.

W_0 = Initial weight of tablet

3.3 IN VITRO DISSOLUTION STUDIES

The release rate of RHCl from floating tablets was determined using United States Pharmacopeia (USP) I. Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl, at $37 \pm 0.5^\circ\text{C}$ and 75 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 315 nm using a Shimadzu UV-1800 UV/Vis double-beam spectrophotometer (Electro lab, TDT-08L). Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

3.4 STATISTICAL ANALYSIS

The Statistical analysis was performed using Graph Pad InStat3 software. All the parameters were run 3 times ($n=3$) except the pre-compression parameter. Experimental results were expressed as mean \pm SD., Student's t-test and one-way analysis of variance (ANOVA) were

applied to check significant differences in mean of post-compression parameter, % Cumulative Release, Zero order, First order, Higuchi kinetics, Peppas Equation between batch series 'F1' and batch 'F2'. Differences were considered to be statistically significant at $p < 0.05$.

4.0 Results and discussion

4.1 Evaluation of powder characteristic of floating tablets:- The powders prepared for compression of floating tablets were evaluated for their flow properties. The angle of repose of all formulations was found to be the range of 25.00 ± 0.59 to 28.57 ± 0.38 . The bulk density of all the formulation showed acceptable range. The bulk density of these powders was found to be in the range of 0.52 ± 0.15 to $0.67 \pm 0.11 \text{ gm/cm}^3$ for all formulations. The measured tapped density was in the range of 0.68 ± 0.52 to $0.79 \pm 0.004 \text{ gm/cm}^3$ for all formulations. Carr's index of powder was found the range of 15.18 ± 0.09 to $24.00 \pm 0.30 \%$ for all formulations. These values indicate that the prepared powder exhibited good flow properties.

Table 2: Pre-compression evaluation of RHCL floating tablets

Formulation code	Angle of Repose* ($^\circ$) \pm SD	Loose Density* (g/cm^3) \pm SD	Bulk Tapped Density* (g/cm^3) \pm SD	Bulk Carr's Index* (%) \pm SD
F1	27.00 ± 0.57	0.59 ± 0.02	0.77 ± 0.017	24.00 ± 0.30
F2	25.00 ± 0.59	0.61 ± 0.25	0.73 ± 0.006	16.44 ± 0.021
F3	28.57 ± 0.38	0.52 ± 0.15	0.68 ± 0.52	23.00 ± 0.20
F4	26.10 ± 0.12	0.67 ± 0.11	0.79 ± 0.004	15.18 ± 0.09

All the values are expressed as mean \pm SD= standard deviation ($n=3$).
Were preparations was significant ($p < 0.05$).

4.2 Floating Behavior of the Tablets

The floating tablets of RHCL with the synthetic polymer (HPMC) shows better floating lag time (37 F1 and 29 second F2) and it was floated up to 12 hrs, and formulation with natural polymers shows more floating lag time (90, 120second F3 and F4 respectively) but it was floated more than 12 hrs.

4.3 Dissolution Profile of the all formulation of the RHCL

The in vitro release of all batches of floating tablets showed the release with an initial effect. In the first hour % drug released were 12.16 ± 1.010 , 09.30 ± 0.100 , 09.33 ± 0.110 , 8.59 ± 0.480 , for FT1, FT2, FT3 and FT4 respectively. The % drug release of the all formulation was found to be 94.79 ± 1.020 , 88.73 ± 1.013 , 83.32 ± 1.110 and 76.02 ± 1.014 , for FT1, FT2, FT3 and FT4 respectively. The natural polymers showed more sustained effects as compared to synthetic polymers.

4.4 Drug Release Kinetics

The drug release data were explored for the type of release mechanism followed. The best fit with the highest determination r^2 coefficients was shown by both the zero order and Higuchi models. Zero order release describes the release rate independent of drug concentration. Higuchi square root kinetic model describes, release drug from the insoluble matrix as square root of time dependent process. It describes release of drug by

simple diffusion mechanism. The value of n with regression coefficient for all the formulations is shown in Table 3. The values of n were in the range of 0.4907 to 0.5312 (n is more than 0.5) indicating Nonfickian release governed by the drug diffusion. However as indicated by the values of r^2 both of the models (Higuchi and Peppas) were found to be efficient in describe the release 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 Peppas Equation between batch series 'F1' and batch 'F4' was indicating significant ($p < 0.05$).

4.5 Discussion

The precompression evaluation like bulk density, true density, compressibility, angle of repose were found as per standard range all the data indicating suitable formulation of the floating tablet. The post compression evaluation for the all formulation is complies with the standard 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 type of release mechanism followed. The best fit with the highest determination r^2 coefficients was shown by both the zero order and Higuchi models. Zero order release describes the release rate independent of drug concentration. Higuchi square root kinetic model describes, release drug

from the insoluble matrix as square root of time dependent process. It describes release of drug by simple diffusion mechanism. The values of n with regression coefficient for all the formulations were showed in the table 4. The values of n were in the range (n is more than 0.5) indicating Nonfickian release governed by the drug diffusion. However as indicated by the values of

R2 both of the models (Higuchi and Peppas) were found to be efficient in describe the release 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 Peppas Equation between batch series 'FT1' and batch 'FT4' was indicating significant ($p < 0.05$).

Table 3: Post-compression evaluation of RHCL floating tablets

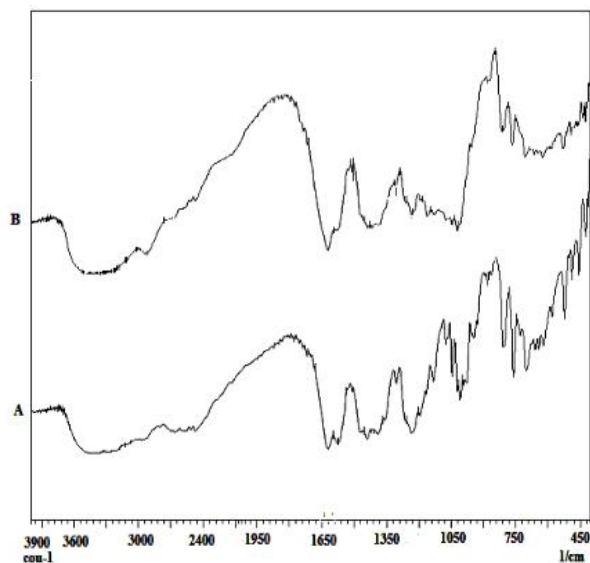
Formulation code	Thickness* (mm)±SD	Hardness* (kg/cm2) ±SD	Friability* (%)±SD	Tablet Weight* (mg) ±SD	Drug Content* (%)±SD
F1	4 ± 0.2	4.0±0.1	0.82±0.04	555.11±2.34	95.34
F2	4 ± 0.2	3.5±0.2	0.92±0.06	557.80±1.84	97.37
F3	4 ± 0.2	4.2±0.1	0.69±0.05	556.63±2.14	98.47
F4	4 ± 0.2	4.5±0.1	0.71±0.01	556.11±2.24	96.97

* All the values are expressed as mean ± SD= standard deviation (n=3).

Were preparations was significant ($p < 0.05$).

Table 4; *In Vitro* drug release Kinetics of floating tablets of RHCL

Formulation code	% Cumulative Release r^2	Zero order r^2	First order r^2	Higuchi kinetics r^2	Peppas Equation	
					n	r^2
F1	94.79	0.9819	0.8845	0.9033	0.5201	0.8980
F2	88.73	0.8845	0.8017	0.8297	0.4907	0.8278
F3	83.32	0.9848	0.8854	0.9035	0.5194	0.8351
F4	76.02	0.9918	0.8965	0.9061	0.5312	0.9123



Fig; 1 compatibility study (Where A- Pure drug
B- Physical mixer of drug and polymer)

CONCLUSION

This study discusses the preparation of gastroretentive tablets of RHCl. The effervescent-based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of gel-forming polymer HPMC K4M, natural polymer and gas-generating agent sodium bicarbonate was essential to achieve in vitro buoyancy. Addition of citric acid, to achieve buoyancy under the elevated pH of the stomach, caused an enhancement in drug release that was retarded by incorporation of stearic acid in the formulation. The release kinetics of the formulation F1 and F2 shows more release as compared to F3 and F4. natural polymer shows

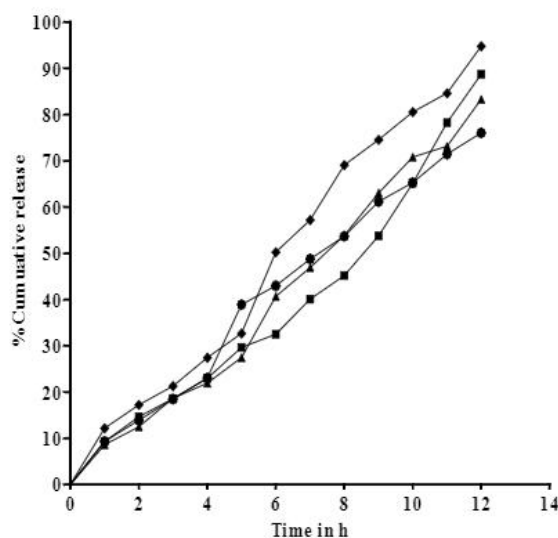


Fig 1; Effect of different polymer on in vitro release of formulation F1 (◆), F2 (■), F3 (▲) and F4 (✕) of RHCl Floating tablets

better sustained release properties than synthetic polymer.

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