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Emerging trend in gastroretentive floating tablets technology of ranitidine hydrochloride

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ABSTRACT

In the present investigation, an attempt is made to develop and characterize floating tablets of ranitidine hydrochloride to increase the safety of the drug and to extend its duration of action for patient compliance. Floating tablets of ranitidine hydrochloride were prepared using HPMC K4 M, Sodium CMC and Guar gum as control release polymers in different concentration with citric acid and sodium bicarbonate as a gas generating agent by direct compression method. The prepared formulations were evaluated for pre and post compression parameters such as angle of repose, bulk density etc. and weight variation, hardness, friability, drug content uniformity, floating lag time, total floating time, in-vitro drug release etc. Respectively. Out of fifteen formulations, formulation GTH1 was selected as promising formulation. The In-vitro drug release, floating lag time and floating time of GTH1 were found to be 97.36±4.6%, 10 mins and >12 hrs respectively. The different formulations of Ranitidine hydrochloride can be prepared by using HPMC K4M, Sodium CMC and Guar gum. The prepared formulations were shown good floating time, extended release and physical stability.

Keywords: Ranitidine hydrochloride, HPMC K4M, Sodium CMC, Guar gum and Carbopol.

INTRODUCTION

Ranitidine hydrochloride is a histamine H2-receptor antagonist that inhibits stomach production. Its chemical name is N'-[2-[[5-(Dimethylaminomethyl)-2-furyl] methylsulfanyl] ethyl]-N-methyl-2-nitro-ethene-1, 1-diamine[1]. It is commonly used in treatment of peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD). Ranitidine is also used alongside fexofenadine and other antihistamines for the treatment of skin conditions such as hives. Ranitidine HCl, the model drug for this study, 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 day [2]. 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 Ranitidine HCl is desirable [3]. The short biological half-life of the 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 an absorption window either in the colon or throughout the gastrointestinal tract. Ranitidine is absorbed in only the initial part of the small intestine and has 50% absolute bioavailability [4, 5]. Moreover, colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon [6]. These properties of Ranitidine HCl do not favor the traditional approach to sustained-release delivery. Hence, clinically

acceptable sustained-release dosage forms of Ranitidine HCl prepared with conventional technology may not be successful. 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 bioavailability. 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 drugs' ability to reduce acid secretion [7]. This principle may be applied for improving systemic as well as local delivery of Ranitidine HCl, which would efficiently reduce gastric acid secretion. An oral controlled release system has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. Gastro retentive dosage forms significantly extend the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance. Such retention systems are important for those drug that are degraded in the intestine like antacids or certain antibiotics, enzymes that act locally in the stomach [8,9].

In the present investigation floating tablets of ranitidine hydrochloride by direct compression technique using varying concentrations of different grades of polymers (HPMC K4, Sodium CMC, Guargum).

EXPERIMENTAL SECTION

The authors wish to thank: Samrudh Pharma Pvt Ltd, Tarapur, and Mumbai. India for sparing gift sample of Ranitidine hydrochloride for the research work. Thank you to SVET'S college of pharmacy Humanabad for providing chemicals like HPMC K4M, Sodium CMC, Guar Gum and other excipients.

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Preparation of Ranitidine Hydrochloride Floating Tablets:

The tablets of Ranitidine HCL were prepared by direct compression using HPMC K4M, Sodium CMC, and Guar Gum as drug release polymers, sodium bicarbonate and citric acid as gas generating agent, magnesium stearate and talc were used as lubricant and glidant respectively. The data of physical parameters for all the formulations is shown table no.1.

Table No.1- Formulation Table of Floating tablets of Ranitidine HCl

Formulation Codes	Ranitidine HCl(mg)	HPMC K4M	Sodium CMC	Guar Gum	Carbopol 934P	Citric acid	Sodium bicarbonate	Mg. stearate	Talc	PVP K-30	Lactose	Total wt.
GTH1	150	25	_	_	20	20	40	2	2	2	139	400
GTH2	150	50	_	_	20	20	40	2	2	2	114	400
GTH3	150	75	_	_	20	20	40	2	2	2	89	400
GTH4	150	100	_	_	20	20	40	2	2	2	64	400
GTH5	150	125	_	_	20	20	40	2	2	2	39	400
GTS1	150	_	25	_	20	20	40	2	2	2	139	400
GTS2	150	_	50	_	20	20	40	2	2	2	114	400
GTS3	150	_	75	_	20	20	40	2	2	2	89	400
GTS4	150	_	100	_	20	20	40	2	2	2	64	400
GTS5	150	_	125	_	20	20	40	2	2	2	39	400
GTG1	150	_	_	25	20	20	40	2	2	2	139	400
GTG2	150	_	_	50	20	20	40	2	2	2	114	400
GTG3	150	_	_	75	20	20	40	2	2	2	89	400
GTG4	150	_	_	100	20	20	40	2	2	2	64	400
GTG5	150	_	_	125	20	20	40	2	2	2	39	400

All quantities in mg per tablet; GTH: Formulations containing HPMC K4M; GTS: Formulations containing Sodium CMC; GTGFormulations containing Guar gum.

Drug Excipients Compatibility Study:
FTIR Spectroscopy:
FTIR spectrum of drug, physical mixture of drug and excipients and placebo was obtained using FT-IR spectrophotometer and the spectrum was recorded in the wavelength of 4000 to 400 cm-1 [10 11].

Evaluation of Powder Mixture:
Pre compression parameters
Angle of repose
Flow properties of the powder were evaluated by determining the angle of repose and the compressibility index. Static angle of repose was measured according to the fixed funnel and free standing cone method. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip at a given height (1 cm), h, above graph paper placed on a flat horizontal surface. The powder was carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. Thus, with 'r' being the radius of the base of the powder conical pile and angle of repose was calculated by using the equation[12].

$\tan \theta = h/r$

Where, θ is the angle of repose.

Bulk Density
Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A suitable amount of powder from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2.5cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula [13].

LBD = weight of the powder/ volume of the packing

TBD= weight of the powder/ tapped volume of the packing

Compressibility Index
Compressibility index of the powder was determined by Carr's index [12].

$\% \text{ Compressibility} = \{(\rho t - \rho b)/ \rho t\} \times 100$

Where, ρt= Tapped density.
ρb= Bulk density

Hausner Ratio= $\rho t/\rho b$

Evaluation of Floating Tablets:
Thickness
Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using micrometer screw gauge. Average thickness and standard deviation values were calculated [14].

Weight variation test
To study weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated [15, 16].

$\% \text{ Weight variation} = (WA - WI) \times 100/WA$

Hardness
Tablet hardness was measured by using Monsanto hardness tester. From each batch, six tablets were measured for the hardness and average of six values was noted along with standard deviations [17].

Friability test
From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

% Friability=W1-W2/W1 X100

Where, W1 = Initial weight of the 20 tablets
W2 = Final weight of the 20 tablets after testing.

Friability values below 0.8% are generally acceptable.

Content Uniformity
From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 100 ml of methanol was added and then the solution was subjected to sonication for about 2 hours. The solution was made up to the mark with methanol. The solution was filtered and suitable dilutions were prepared with methanol. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 310 nm by using UV-Visible spectrophotometer.

Buoyancy / Floating test
The *in-vitro* buoyancy was determined by floating lag time. Here, the tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT) [18].

Swelling Characteristics
To evaluate the water penetration characteristics, the pre-weighed tablets were immersed in 500ml beaker containing simulated gastric fluid [SGF] and maintained for 12hrs at 37±0.5°C. Swollen tablets were removed from the solution, immediately wiped with a paper towel to remove surface droplets, and weighed. The % swelling index [SW] was calculated according the following equation [19].

% Swelling index [Sw] = Wt-Wo/Wtx 100

Where, Wo = Initial weight of tablet.
Wt = Weight of the swollen tablet at time t.

***In-Vitro* Dissolution Study of Floating Tablets:**
In-vitro dissolution study was carried out in USP type-II dissolution apparatus (paddle method). Simulated gastric fluid 900ml of 0.1N HCl was used as dissolution medium. The temperature of dissolution media was maintained at 37±0.5°C.The paddle rotation speed was kept at 50 rpm. Aliquot of 5ml of sample was withdrawn at time intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11and 12hours. The volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after each sampling. The release studies were conducted in triplicates & the mean values were plotted versus time. Each sample was analyzed at 310 nm by using double beam UV -Visible Spectrophotometer against reagent blank [20].

RESULTS AND DISCUSSION

FTIR spectroscopic studies were conducted to determine possible drug-polymer interaction.IR spectrum of Ranitidine HCL, HPMC K4M, Sodium CMC, Guar gum and physical mixtures of ranitidine HCL with these polymers were obtained, which showed all the characteristic peaks of Ranitidine HCL and polymers present in the physical mixtures, which indicates that there is no interaction, which confirms the compatibility of drug with polymers.

The powder mixtures for all the formulation [GTI-GT15] were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner ratio, the results were shown in the table.no.2, which found to be in the range of 20.08˚±0.17 to 24.89˚±0.14, 0.3123±0.05 to 0.3456±0.06 g/cm^3, 0.3458±0.05 to 0.4323±0.03 g/cm^3, 13.48±0.03 to

19.78±0.10 % and 1.17±0.04 to 1.27±0.04 respectively. All these results indicated that, the powder mixture possess satisfactory flow and compressibility properties.

The hardness, thickness, % friability, weight variation and drug content of tablets was found to be in the range of 6.32±0.02 to 7.00±0.06 kg/cm^2, 3.96±0.07 to 4.19±0.07mm, 0.7 to 0.80% , 400.1±0.1 to 404.2±0.3 mg and 96.38±0.12 to 99.63±0.12respectively, which were within the acceptable limits, the results were given in the table.no.3.The floating lag time, floating time and swelling index of all the formulations were found to be in the range of 10 to 17 mins, 10 to 12 hrs and 71 to 90 % respectively (given in table no.4). The $t_{25\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$and *in vitro* drug release of all the formulations were in the range of 2.24 to 4.00 hrs, 4.48 to 7.48 hrs, 8.12 to 11.24 hrs, 10.48 to >12hrs and 6.35±2.10 to 97.36±4.60%respectively (given in table no. 5 and figure no. 2 and 3).

Among the fifteen formulations, formulation GTH1 was selected as promising formulation on the basis of *In Vitro* Buoyancy Study and *in vitro* drug release study. The floating lag time, floating time and swelling index of formulation GTH1 were found to be 10 min, >12 hrs. and 78% respectively given in table no.4. The $t_{25\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$and *in vitro* drug release of GTH1 formulation were found to be 2.24 hrs, 4.48 hrs, 8.24 hrs, 11.12 hrs and 97.36 % respectively.

Table No.2- Pre-compression Parameters of Ranitidine HCL Floating Tablets

Batch code	Bulk density* (g/cm^3)	Tapped density* (g/cm^3)	Carr's index* (I_C)	Hausner Ratio* (H_R)	Angle of repose* (θ)
GTH1	0.3123± 0.05	0.4098± 0.03	19.78± 0.10	1.24± 0.02	23.20 ± 0.12
GTH2	0.3172± 0.04	0.3458 ± 0.05	15.22 ± 0.11	1.17± 0.04	24.76 ± 0.14
GTH3	0.3201 ± 0.06	0.3550 ± 0.02	13.48± 0.03	1.18± 0.06	20.36 ± 0.18
GTH4	0.3388 ± 0.02	0.3866 ± 0.04	15.45± 0.06	1.18± 0.03	23.07 ± 0.13
GTH5	0.3409 ± 0.04	0.4166 ± 0.06	16.18 ± 0.09	1.22 ± 0.07	20.08 ± 0.17
GTS1	0.3234± 0.04	0.4267± 0.04	19.78± 0.11	1.19± 0.08	23.87± 0.09
GTS2	0.3153 ± 0.07	0.3745 ± 0.03	18.89± 0.11	1.23± 0.03	24.56± 0.13
GTS3	0.3234± 0.05	0.4207± 0.08	19.67± 0.11	1.21± 0.07	24.05 ± 0.10
GTS4	0.3464 ± 0.04	0.4143± 0.07	18.08± 0.11	1.19± 0.06	23.90± 0.12
GTS5	0.3144 ± 0.06	0.3699 ± 0.05	15.80± 0.11	1.19± 0.05	23.09± 0.15
GTG1	0.3135 ± 0.01	0.3746 ± 0.01	17.50± 0.07	1.21± 0.02	20.96 ± 0.12
GTG2	0.3144 ± 0.06	0.3699 ± 0.05	15.80± 0.11	1.19± 0.05	23.09± 0.15
GTG3	0.3558 ± 0.07	0.4098± 0.07	18.45± 0.05	1.22± 0.05	24.65± 0.08
GTG4	0.3234± 0.01	0.4196 ± 0.02	18.67± 0.09	1.27± 0.08	24.89± 0.14
GTG5	0.3456± 0.06	0.4323± 0.03	16.67± 0.10	1.27± 0.04	24.45± 0.16

**Average of three determination*

Table No.3- Post-compression Parameters of Ranitidine HCL Floating Tablets

Batch code	Weight Variation(mg)*	Thickness* (mm)	Diameter* (mm)	Hardness* (kg/cm^2)	Friability (%)	Drug content* (%)
GTH1	400.1±0.1	4.14± 0.04	12.09± 0.05	6.32± 0.02	0.72	99.27± 0.50
GTH2	401.2±0.3	3.97± 0.02	12.08± 0.02	6.32± 0.04	0.7	99.63 ± 0.12
GTH3	401.2±0.2	4.10± 0.07	12.05± 0.04	7.00± 0.06	0.71	99.71 ± 0.22
GTH4	403.2±0.1	4.19± 0.02	12.08± 0.07	6.51± 0.03	0.80	99.27± 0.50
GTH5	402.2±0.1	4.18± 0.04	12.03± 0.02	6.56± 0.02	0.72	99.47 ± 0.10
GTS1	402.2±0.1	4.14± 0.06	12.18± 0.04	6.9± 0.06	0.72	98.68 ± 0.20
GTS2	403.2±0.2	3.96± 0.03	12.03± 0.06	6.54± 0.05	0.71	99.38 ± 0.21
GTS3	404.2±0.3	3.98± 0.05	12.01± 0.03	6.12± 0.02	0.81	99.27± 0.50
GTS4	401.2±0.2	4.17± 0.04	12.04± 0.07	6.54± 0.06	0.80	99.27± 0.50
GTS5	403.2±0.2	4.10± 0.02	12.09± 0.09	6.84± 0.04	0.71	99.27± 0.50
GTG1	403.2±0.2	4.10± 0.02	12.09± 0.09	6.58± 0.04	0.71	99.27± 0.50
GTG2	401.2±0.1	4.10± 0.07	12.06± 0.05	6.58± 0.03	0.72	96.38 ± 0.12
GTG3	404.2±0.3	3.96± 0.07	12.09± 0.03	6.48± 0.03	0.72	99.27± 0.50
GTG4	402.2±0.2	3.98± 0.04	12.08± 0.05	6.52± 0.02	0.75	99.73 ± 0.13
GTG5	403.2±0.2	3.99± 0.05	12.02± 0.07	6.59± 0.07	0.81	99.28 ± 0.10

**Average of three determination*

Table No.4- Floating Ability of Various Ranitidine HCL Tablets Formulation

Batch Code	Floating Lag time (min)	Floating Time (hrs.)	Swelling index (%)	Integrity at 12 (hrs.)
GTH1	10	>12	56	Intact
GTH2	10	>12	71	Intact
GTH3	10	>12	75	Intact
GTH4	10	>12	76	Intact
GTH5	10	>12	78	Intact
GTS1	15	>12	85	Intact
GTS2	16	>12	85	Intact
GTS3	10	>12	84	Intact
GTS4	10	>12	89	Intact
GTS5	10	>12	90	Intact
GTG1	17	>10	82	Disperse
GTG2	16	>10	80	Disperse
GTG3	15	>10	80	Disperse
GTG4	10	>11	86	Disperse
GTG5	10	>12	89	Intact

0 min Start to float10 min

10 min **5 hour** **12 hour**

Figure No.1- *In Vitro* Buoyancy Study

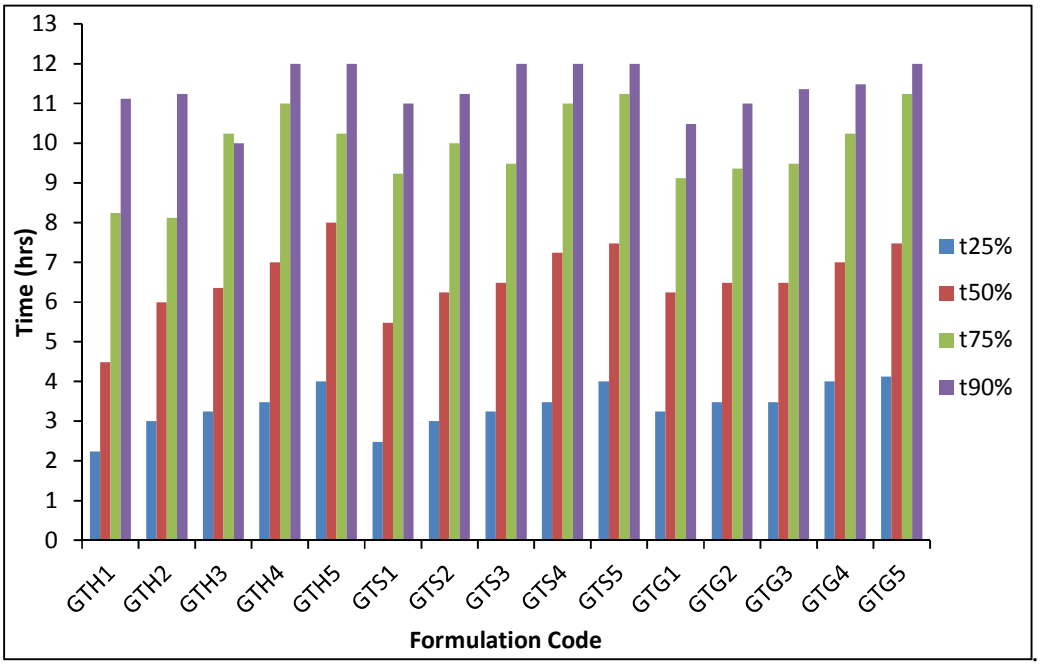

Figure No.2- Comparison of Dissolution Parameters ($t_{25\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$) Floating Tablet of Ranitidine Hcl

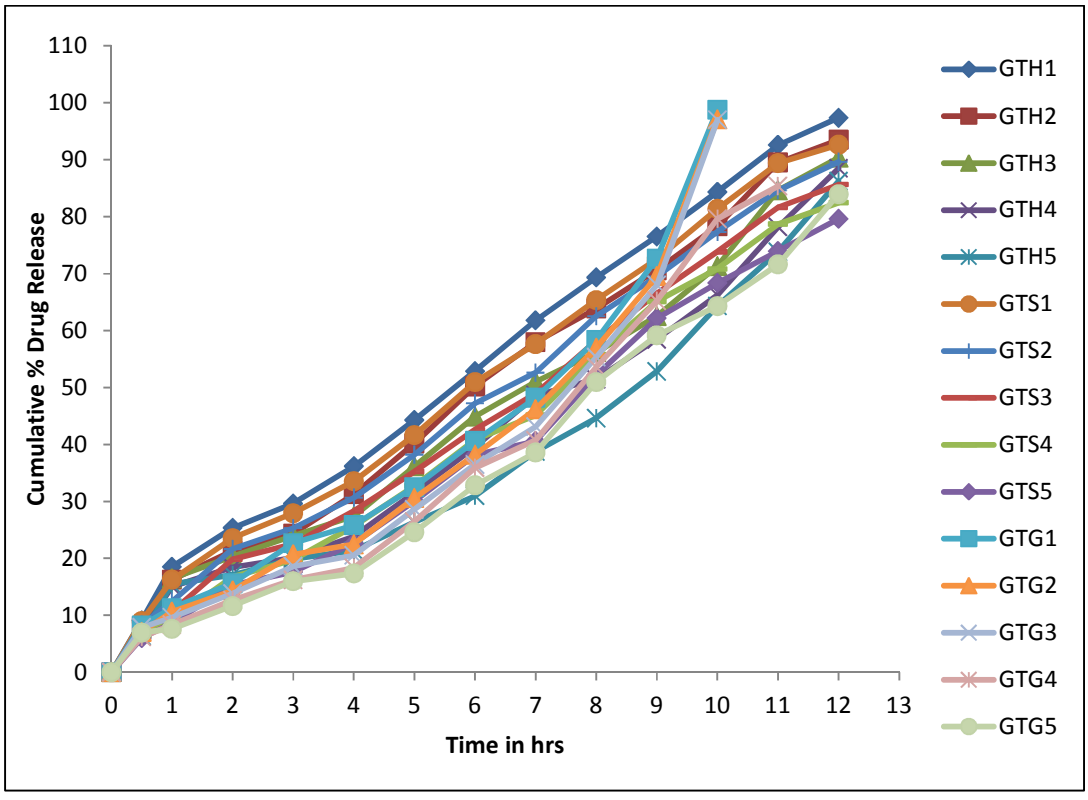

Figure No.3- Cumulative percent drug release vs time plots (zero order) of all formulations

Table No.5-Dissolution Parameters for the Formulations

SI. No.	Formulation Code	$t_{25\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)	Cumulative % drug release in 12 (h)
1	**GTH1**	2.24	4.48	8.24	11.12	97.36
2	**GTH2**	3.00	6.00	8.12	11.24	93.52
3	**GTH3**	3.24	6.36	10.24	>12	90.36
4	**GTH4**	3.48	7.00	11.00	>12	88.47
5	**GTH5**	4.00	8.00	10.24	>12	86.25
6	**GTS1**	2.48	5.48	9.24	11	92.36
7	**GTS2**	3.00	6.24	10.00	11.24	89.62
8	**GTS3**	3.24	6.48	9.48	>12	85.63
9	**GTS4**	3.48	7.24	11.00	>12	82.46
10	**GTS5**	4.00	7.48	11.24	>12	79.62
11	**GTG1**	3.24	6.24	9.12	10.48	---
12	**GTG2**	3.48	6.48	9.36	11.00	---
13	**GTG3**	3.48	6.48	9.48	11.36	---
14	**GTG4**	4.00	7.00	10.24	11.48	---
15	**GTG5**	4.12	7.48	11.24	>12	83.96

CONCLUSION

In the present study, it was concluded that the floating tablets of ranitidine HCl can be prepared using HPMC K4M, Sod. CMC and Guar gum by direct compression method.

The GTG1 to GTG3 have released only 61 to 64% drug in 12 hr. whereas, formulations GTH1 to GTH5 have released 67 to 95% during the same period of time. This increasing drug release from these formulations can be attributed to the lower viscosity grade HPMC K4M (2,600-5,600 cps 2% in water). Among these Fifteen formulations, GTH1 formulation has shown promising dissolution parameters and shorter lag time (not >10 min).

Dissolution parameters i.e., $t_{50\%}$, $t_{75\%}$ values were selected as dependent variables. Formulation codes of the fifteen formulations along with dissolution parameter values (t_{50}%, t_{75}%) and cumulative percent drug released in 12 hrs. gastric floating drug delivery system for improved bioavailability. Due to system remains in acidic pH which improves solubility of ranitidine HCL.

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