Design and Evaluation of Sustained release Floating tablets for the treatment of Gastric Ulcers

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Abstract
The present study was carried out with an objective of preparation of ranitidine hydrochloride sustained release formulation for 24 hrs. Various formulations were prepared by wet granulation technique using the polymers, such as HPMC K100M and HPMC K15M. It was found that the best formulation for RT8 was having the floating lag time of 120 sec and showed 98.4% drug release at the end of 24 hours. This way the best formulation was achieved by using the combination of high and low viscous polymers HPMC K100M and HPMC K15M in the ratio of 1:1. *In-vitro* drug release studies of Ranitidine hydrochloride sustained release floating tablets showed that, the rate of drug release is diffusion controlled and follows zero order kinetics.
Key words: Ranitidine hydrochloride, Floating tablets, wet granulation technique.

Introduction

Oral drug delivery remains the most user-friendly form of drug delivery, having the highest degree of patient compliance, and still the preferred route of drug administration. As such, drugs for chronic conditions are often administered orally for ease of long-term use [1]. Drugs that are easily absorbed from the gastrointestinal tract and having short biological half-life are eliminated quickly from the blood circulation. An incomplete release of the drug and shorter residence time of the dosage form in the upper gastro intestinal tract, a prominent site for the absorption of the many drugs, will lead to lower bioavailability. There fore, prolonged gastric retention is important in achieving control over the gastro retention time because this helps to retain the controlled release system in the stomach for a longer and predicted time.

Drugs that require to be designed as gastro retentive systems are those acting locally in stomach, primarily absorbed from the stomach, poorly soluble in alkaline pH, absorbed rapidly from the gastrointestinal tract, and that degrades in the colon [2] . Small size tablets leave the stomach during the digestive phase while large size tablets are emptied during the house keeping waves [3]. Floating units remained buoyant on gastric fluids. These are less likely to be expelled from the stomach compared with the non floating units, which lie in the antrum region and are propelled by the peristaltic waves [4]. Various approaches have been worked out to improve the retention of an oral dosage form in stomach [5].

High density systems whose action is based on their dipping to the bottom of the stomach [6]. systems attaching to the mucus membrane are bioadhesive systems are retained in the stomach due to their ability to stick to and stay on the surface of the mucus membrane of the stomach [7]. Intra gastric floating systems are based on the phenomenon of drug floating in the gastric contents. There are three possible techniques to rendered drug floating. Gas contains floating systems: generation of co_2 via chemical reaction between sodium bicarbonate and hydrochloric acid of gastric juice. The gas kept in the stomach ensures its floatation. Thus prolongs the period of drug occurring in the stomach. Systems with low density core not subject to rapid chemical and physical changes, providing for the drug floatation. The core is coated with a gel or other polymeric shells from which drug are gradually released.

Hydrodynamically balanced systems; based on hydrodynamically gel forming polymers in gelatin shells, which dissolves in contact with the gastric juice to initiate the gel formation that provides for the gradual drug release. The floatation of such systems is provided by a hydrophilic or hydrophobic core of relatively low density. Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

Site-specific drug delivery: These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets [8].

Absorption enhancement**:** Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric-coated LASIX-long product (29.5%) [9].

Materials and Methods

Ranitidine hydrochloride was obtained as a gift sample from Dr.Reddy's LtD, Hyderabad. The polymers such as HPMC K100M and HPMC K15 M respectively from Dow chemicals, USA. Sodium bicarbonate was procured from Nitika chemicals, Mumbai. Talc and Magnesium stearate from Imifab,USA. Stearic acid and citric acid from Ferro industry, USA.

Formulation

The active product ingredient was sifted through #40 and other ingredients were sifted through #30 and transferred to a polybag and mixed well. Magnesium stearate and talc were passed through #30. These sifted lubricants were added to the above mixture and blended well using kalweka blender and the blend was characterized for the different physical parameters such as bulk density, Tapped density, Angle of repose, Hausners ratio and Carr,s index.

The prepared blend was compressed into tablets by using 16- Station rotary tablet press. 11.8mm punch and round die cavity embossed with R&D on one side was used. After the prepared blend was filled in the hopper, machine was switched on. The feed moved in to the rotary die cavity and the tablets were punched. Initially a single punch was used to adjust the tablet desired weight and hard ness. After the weight and hardness was set the number of punches was increased. During the process of punching total weight, diameter, thickness, and friability of the tablets were simultaneously measured.

Floating lag time:

The tablets were placed in a 100ml beaker containing 0.1N hydrochloric acid. The time required for raising the surface and float was determined as floating lag time.

In-vitro dissolution studies:

The release rate of ranitidine hydrochloride from floating tablets (n=6) was determined using USP 24. Dissolution testing apparatus 2 (paddle method).the dissolution test was performed using 900ml of 0.1N hydrochloride at $37^0 \pm 0.5^0$ C and 75 rpm. A sample (10ml) of solution was with drawn from the dissolution apparatus hourly for 24 hrs, and the samples were replaced with

fresh dissolution medium. The samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions were measured at 314nm using a Schimadzu UV-1700 UV/VIS double beam spectrophotometer. Cumulative percentage drug release was calculated.

Results and discussion:

The first trial RT1 was carried out using the polymer HPMC K100M (high viscosity polymer) and other excipients to control the release of drug. The floating lag time and the total buoyancy time were found to be 5 minutes and 15 hours respectively. The drug release obtained was 5.317% in first two hours, which is not satisfactory. As per theoretical calculations 26% drug should be released in first two hours, 16.27% of the drug was found to be released in subsequent 7hours (Figure.1). Over retardation of the drug release was observed which is not desirable.

Next trial RT2 was planned by replacing the HPMC K100M (high viscosity polymer) with HPMC K15M (low viscosity polymer) to get desired drug release and buoyancy time. The floating lag time and total buoyancy time was found to be 3 minutes and 15 hours respectively. Total buoyancy time needed to be improved to 24 hours. The drug release in first two hours was found to be 36%, which is not satisfactory. 91.21% drug was released in subsequent 7 hours, which may be due to complete replacement of HPMC K100M (high viscosity polymer) with HPMC K15M (low viscosity polymer). Dark spots were observed on the tablets after 2 weeks of storage, which may be due to poor anti-oxidant property of tartaric acid.

The third trial RT3 was carried out by replacing the citric acid with tartaric acid to improve the stability of the tablets keeping other ingredients same as RT2. Floating lag time and total buoyancy time was found to be 140 seconds and 20hours respectively. The dosage form containing citric acid showed slightly more buoyancy time and less floating lag time than the formulation with tartaric acid (RT2). 77.86% drug was released in 8hours (Figure.2), which need to be further improved. Dark spots were not observed on the tablets, due to presence of citric acid, which is a good anti-oxidant.

The next trial RT4 was carried out by omiting the stearic acid and other ingredients were same asRT3. Floating lag time and total buoyancy time were found to be 3minute and 20hours respectively. 100.92% drug was released in 6 hours (Figure.3). The results show that stearic acid is necessary for sustained drug release because of its hydrophobic nature facilitates slow and sustained release of ranitidine hydrochloride, which is highly water-soluble. The fifth trial RT5was planned to know the effect of talc on flow property of granules keeping the other ingredients including magnesium stearate constant. Angle of repose was found to be 28.2˚ without talc. It shows that blend did not possess required flow property without talc.

The next trials RT6&RT7 were carried out to improve the drug release by increasing the quantities of HPMC K15M keeping the other ingredients constant as RT3. Floating lag time and total buoyancy time of two trials were found to be 150,150 seconds and 24&24hours respectively. 99.2% drug was released in 9 hours in RT6 &98.08% drug was released in 9hours RT7 trial (Figure.4 and Figure.5). Even though the quantities of HPMC K 15M were increased, the drug release was not satisfactory. There are no satisfactory results when a single grade of HPMC K15M was used. To get desired drug release a combination of two grades were planned in further trials.

The next trial RT8 (Table.1) was planned using a combination of HPMC K15M and

Table. 1 Formula for the blend of RT8

S.No.	Ingredients	Qty/unit(mg)	Qty/batch(g)
1	Ranitidine hydrochloride	336	75
2	HPMC (K 15M)	45	1.25
3	HPMC (K 100M)	45	11.25
4	Sodium bicarbonate	50	12.5
5	Stearic acid	50	12.5
6	Citric acid	10	2.5
7	Magnesium stearate	5(1%w/w)	1.25
8	Talc	5(1%w/w)	1.25
Total weight		546mg	127.5g

Table. 2 Preformulation parameters for RT8

S.No.	Parameter	Result
1	Bulk density	0.542 g/cc
2	Tap density	0.626 g/cc
3	Hausner's ratio	1.26
4	Compressibility index	13.4 %
5	Angle of Repose	16.02 ^{0}

Table.3 Physical parameters for the compressed tablets for RT8

(During compression)			
Parameter	**Result**		
	Minimum	Maximum	Average
Total weight (mg)	544	546	545.6
	5.18	5.21	5.20
Thickness (mm)	10.94	10.98	10.97
Diameter (mm)			
(After compression)			
Hardness(kp)	12-14kp		
Friability	1.02%		
Assay	99%		
Floating lag time(h)	120 seconds		
Total buoyancy time(h)	24h		

Table.4 *In-vitro* dissolution data for RT8

Time (hrs)	Absor-bance at 314nm	Concen-tration (µg/ml)	% Drug release
1	0.059	17.48	23.4 ±3.28
2	0.065	19.41	26.0 ±2.24
3	0.075	22.40	29.8 ± 3.25
4	0.083	24.64	33.01 ±0.27
5	0.092	27.34	36.61± 1.45
6	0.099	29.70	39.8± 2.54
7	0.105	31.65	42.92 ±2.62
8	0.115	34.40	46.08±3.75
9	0.125	37.63	50.40±2.43
10	0.136	41.05	54.98±2.34
11	0.145	43.39	58.12±2.74
12	0.149	44.97	61.27±2.54
14	0.164	49.25	65.97±1.25
16	0.177	53.29	71.38±3.25
18	0.196	59.26	79.37±2.32
20	0.215	63.72	85.34±3.25
22	0.229	69.20	92.7±2.32
23	0.243	73.22	98.2± 3.45
24	0.244	73.80	98.86±3.45

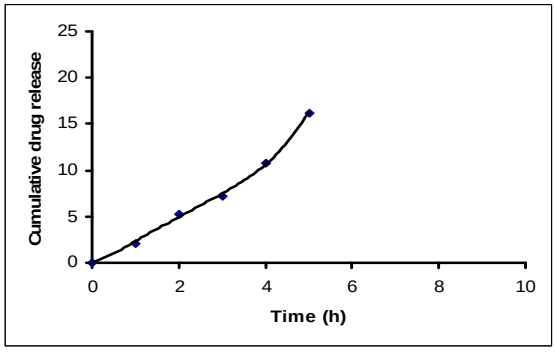

Figure. 1. *In-vitro* dissolution profile for RT1

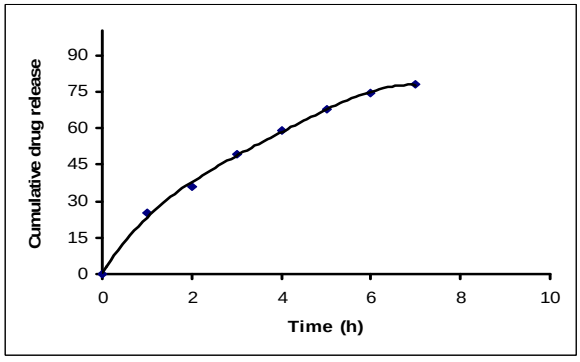

Figure.2 *In-vitro* dissolution profile for RT3

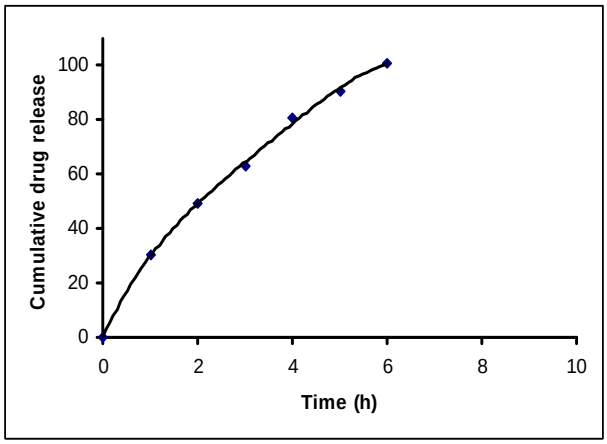

Figure.3 In-*vitro* dissolution profile for RT4

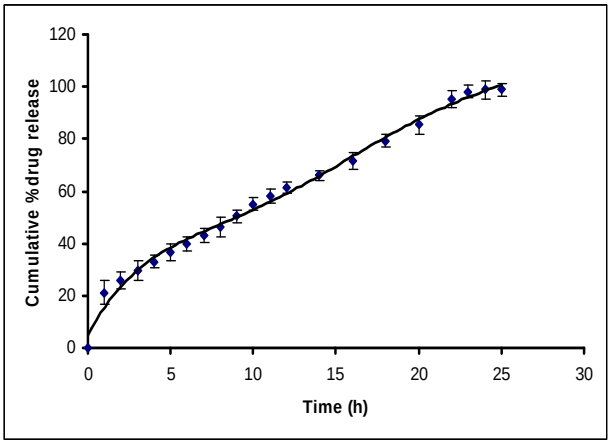

Figure.6 In-*vitro* dissolution profile for RT8

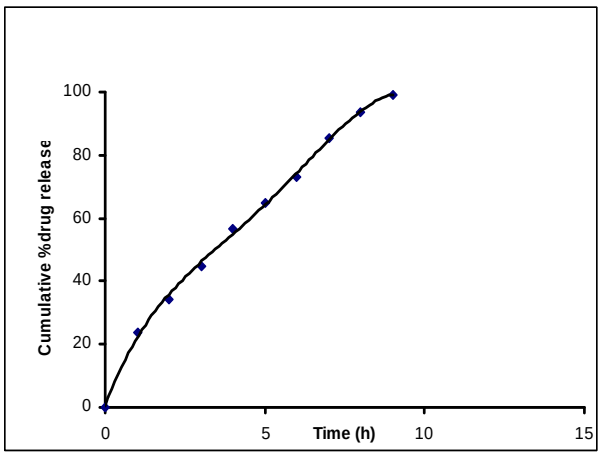

Figure.4. *In-vitro* dissolution profile for RT6

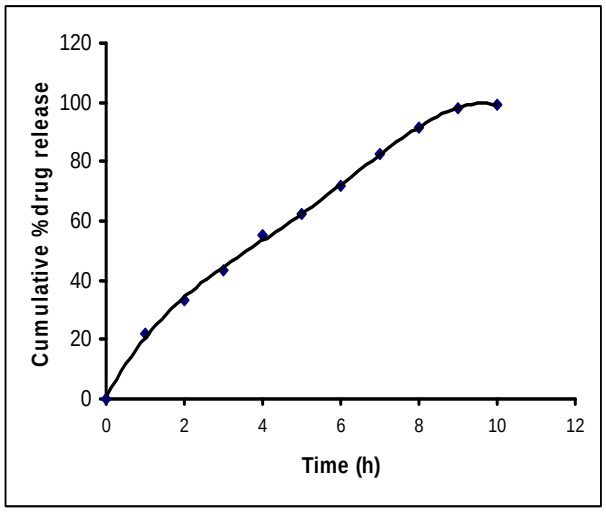

Figure.5 *In-vitro* dissolution profile for RT7

HPMC K100M in the ratio of 1:1. Preformulation studies of the granules (Table.2) and physical parameters of the compressed tablets (Table.3) were found to be satisfactory. The floating lag time and total buoyancy time was found to be 120 seconds and 24 hours respectively. 26% of the drug release in first two hours was found to be satisfactory (Table.4 and Figure.6). 98.4% drug was released in subsequent 24hours. According to all the results obtained by various trials, trial RT8 was found to be satisfactory.

The formulation was optimized by varying the ratio of polymers i.e. HPMC K15M & HPMC K100M in ratios of 1:2 and 2:1 respectively for the trials RT9 AND RT10 but drug release was not satisfactory in both the trials. The final data obtained from RT 8 was fit into mathematical models and the r^2 value obtained from these models showed that the drug release is diffusion controlled and follows zero order kinetics.

Conclusion

Thus, it may concluded that sustained release ranitidine hydrochloride GRFDDS would be a novel approach to encounter the problems associated with the normal conventional tablet form 150mg that inhibits acid secretion for 5 hours only, but with the new sustained release ranitidine

hydrochloride GRFDDS there was continuous release of drug for an extended period of time and therefore, prolonged inhibition of acid secretion could be made possible. Another major advantage is patient compliance because this enables once in a day administration of drug.

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