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FORMULATION AND EVALUATION OF FLOATING MATRIX TABLET OF LOCALLY ACTING H_2-ANTAGONIST

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ABSTRACT

In the present work, floating gastroretentive formulation of Ranitidine HCl was formulated to sustained release of Ranitidine HCl above its site of absorption. To modulate the release characteristics, HPMC (K4M) and natural swelling agent Psyllum husk are used for single-unit floating matrix tablets by a direct compression technique. The floating approach was achieved by the use of Sodium bicarbonate. The prepared floating tablets were evaluated for their floating behavior, swelling studies, *in-vitro* drug release studies and kinetic analysis of the release data. The optimize formulation shows floating lag time within 3 min. The effect of HPMC (K4M) and swelling agent Psyllum husk on drug release was observed. Ranitidine HCl shows drug release till 12 hrs due to gel forming property of HPMC (K4M) and swelling capacity of Psyllum husk. Form the results, it can be conclude that the prepared gastroretentive tablet of Ranitidine HCl shows desirable release profile, good floating and sustained effect in stomach. The Fourier Transform Infra Red Spectroscopy studies revealed that there is no molecular interaction which may have implications on drug release characteristics.

Key Words: Buoyancy, Floating matrix tablet, Gastroretentive, Ranitidine HCl.

1. INTRODUCTION

Ranitidine HCl is histamine H_2 receptor antagonist in treating gastric ulcer, duodenal ulcer, Zollinger Ellison syndrome, gastroesophegal reflux disease and erosive esophagitis.

Ranitidine HCl is having half-life of 2.5 to 3 hr and shows absorption in the initial part of small intestine with 50 % of absolute bioavailability. Moreover, colonic metabolism of Ranitidine HCl responsible for poor bioavailability through colon. Hence, clinically acceptable sustained release dosage form of Ranitidine HCl is not a successful. The recommended adult oral dosage of Ranitidine HCl is 150 mg twice day or 300 mg once day. The effective treatment of erosive esophagitis requires administration of 150 mg of Ranitidine HCl for four times a day [1]. 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 [2].

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 H_2 receptor antagonist like Ranitidine HCl 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 secretion[3]. This principle may be applied for improving systemic as well as local delivery of Ranitidine HCl, which would efficiently reduce gastric acid secretion.

Controlling the residence of a drug delivery system in a particular region of the gastrointestinal tract can utilize several approaches: Intragastric floating systems, high density systems, mucoadhesive systems, magnetic systems, unfoldable, extendable or expandable systems and super porous, biodegradable

hydrogel systems. Some of these devices are of practical use, whereas others are more or less in the development and theoretical stages. Whenever, extending the gastric residence time is considered, the physiology of the gastrointestinal tract must be well understood and all limitations should be taken into account. Factors such as pH, the nature and volume of gastric secretions, food, gastric mucosa and motility play an important role in drug release and absorption and also in dosage form placement[4].

Floating drug delivery systems, also known as hydrodynamically balanced systems (HBS). It has been suggested for the following instances that an active material should be formulated in the form of an HBS to enhance bioavailability: (a) having a dissolution and/or stability problem in the small intestine fluids (b) being locally effective in the stomach (c) being absorbed only in the stomach upper part of the intestine. Floating tablets, capsules, beads, microspheres and chambers have been reported in literatures[5].

In the present work, floating gastroretentive formulation of Ranitidine HCl was formulated to sustained release of Ranitidine HCl above its site of absorption by using gel forming polymer HPMC (K4M) and natural swelling agent Psyllum husk for single-unit floating matrix tablets by a direct compression technique.

2. MATERIAL AND METHODS

2.1 Materials

Ranitidine HCl was received as a gift sample from Cadila Pharmaceuticals Ltd, Ahmadabad, India. Hydroxypropyl methylcellulose (K4M) was obtained from Unichem Pharmaceutical Ltd. Magnesium stearate was obtained from S. P. Pharmaceuticals, Sodium bicarbonate, Psyllum husk, Microcrystalline cellulose was purchased from S.D. Fine-Chem. Ltd, Mumbai, India. All other ingredients were of laboratory grade.

2.2 Preparation Ranitidine HCl Floating Tablets

For obtaining the formulation with desired release pattern, it was desided to optimise the formulations without adding Sodium bicarbonate and the optimize formulation is final optimized for Sodium bicarbonate.

2.2.1 Preparation of Ranitidine HCl sustained release tablets

Different tablets formulations were prepared by the direct compression technique. All the powders were passed though an 80 mesh sieve (180 micrometer size). The required quantity of Ranitidine HCl, HPMC K4M and low-density powder were mixed thoroughly. Magnesium stearate was added as a lubricant. The blend was compressed (13 mm diameter, flat punches) using rotary tablet compression machine (Rimek mini press II). Each tablet contained 150mg Ranitidine HCl and other Pharmaceutical ingredients, as shown in table 1.

Table 1 Composition of Ranitidine HCl Sustained Release Tablet

Ingredients (mg/ tablet)	**Formulations**								
	F1	F2	F3	F4	F5	F6	**F7**	F8	F9
Ranitidine HCl Hydrochloride	150	150	150	150	150	150	**150**	150	150
Microcrystalline Cellulose	150	150	150	150	150	150	**150**	150	150
Psyllium Husk	-	-	-	150	300	450	**150**	300	150
HPMC K4M*	150	300	450	-	-	-	**150**	150	300
Magnesium Stearate(%)	1	1	1	1	1	1	**1**	1	1

*HPMC (K4M)- Hydroxy propylmethylcellulose

2.2.2 Optimization of Sodium bicarbonate for floating tablet

On the basis of drug release pattern of 9 formulations, F7 selected for the optimization of Sodium bicarbonate which is used in the proportion of 1:0.15, 1:0.25 and 1:0.05 respectively shown in table 2.

Table.2 Composition of Ranitidine HCl Floating Tablet

Ingredients	**Formulation F7 (1:1:1)**			
	F7a	F7b	F7c	
Drug: Sodium Bicarbonate	**1: 0.15**	1: 0.25		1: 0.50

2.3 Characterization of Powder of Optimize Floating Ranitidine HCl Tablet

The characteristic parameters of the powder were evaluated. The angle of repose was determined by the funnel method. The bulk density and tapped density were determined by the cylinder method and Carr's index was calculated [6].

2.4. Characterization of Floating Tablet

2.4.1. Drug Content and Physical Evaluation

The drug content of the tablets was determined and the samples were analyzed spectrophotometrically (Systronic 2201) at 313 nm for Ranitidine HCl. Tablets were also examined with regard to their weight variation (n = 20), friability (n = 20) and hardness (n = 6)[7] which is shown table 3.

Table 3 Characterization of Powder of Optimize Floating Tablet

Parameters	**Formulation f7a**
Angle of Repose	26.24 ± 0.05
Bulk Density(g/ml)	0.267 ± 0.24
Tapped Density (g/ml)	0.308 ± 0.13
Carr's Index	13.31 ± 0.15

2.4.2 Buoyancy lag-time studies

The *in-vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 1.2 pH solution. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time[8].

2.4.3 Swelling characteristics

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml 1.2 pH solution at 37 ± 0.5°C. The tablets were removed periodically from the dissolution medium and after removing free water, the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU %) [9].

2.4.4 In-vitro dissolution study

The i*n-vitro* dissolution studies (n=3) were carried out using USP dissolution test apparatus (type II). The release studies were performed at 50 rpm in 900 ml 1.2 pH solution at 37±.0.5 ^{0}C [10]. Aliquots 10 ml were withdrawn at 1 hr interval for 12 hr dissolution study and the volume of dissolution medium was maintained by adding the 10 ml of fresh dissolution medium.

The test sample was filtered (membrane filter, 0.45 μm) and the concentration of Ranitidine HCl was measured by UV-Visible Spectrophotometer at 313 nm. The release kinetics is given in table 5.

2.4.5 Drug excipients interaction study

The pure drug and its mixture with HPMC (K4M) scanned for IR. Drug-polymer interactions play a vital role in formulations. FTIR techniques have been used to study the physical and chemical interactions between drug and polymer used. It is shown in Fig 6.

2.4.6. Accelerated Stability Study

The optimized formulation of matrix tablet was kept for short term stability study. The conditions for stability were 40^{0}C room temperature and relative humidity of 75 %. All tablets were suitably packed in group of 10 units in aluminum foil. The stability study conditions of 75 % RH were prepared using saturated solution of Sodium chloride in a desiccator. At the end of one month the sealed tablets were opened and evaluated.

3. RESULTS AND DISCUSSION

In the present work, preformulation studies on the samples of drug along with various excipients without Sodium bicarbonate were carried out prior to the actual formulation of floating tablets. After that number of formulations were prepared. Out of which best formulation were selected and considered for floating matrix tablet. These formulations were subjected to various evaluation parameters.

Floating of the gastroretentive layer can be achieved by using Sodium bicarbonate along with Psyllum husk, HPMC (K4M). Floating matrix tablet contain Psyllum husk which has swelling effect, it offers advantages of increased contact time with stomach mucosa and more effective absorption leads to increasing bioavailability of the drug.

The prepared powder for the Matrix tablet were characterized with respect to the angle of repose, bulk density, tap density and carr's index, which is shown in Table 3 for the optimized formulation. The Angle of repose was less than 27º for all the formulations indicating satisfactory flow behavior.

3.1 Physical evaluation

The weight variation, friability, hardness and drug content were found to be within acceptable limits, the result of physical parameter of optimized formulation is shown in Table 4. Thus, all the physical properties of tablets were satisfactory as per official standards [11].

Table 4 Evaluation of Floating matrix Tablet.

Parameters	Formulation F7a
Drug content (%)	99.17
Floating Lag-Time(min)	3
Swelling Index	229
Weight variation(mg)	623.5 ± 2.16
Friability	0.22
Hardness	6.87

3.2 Buoyancy lag-time studies

All tablet formulations exhibited satisfactory floatation ability and remained buoyant for more than 12 hrs in dissolution medium subjected to rotation. The buoyancy lag-time of tablets depends on the amount of Sodium bicarbonate involved in CO_2 formation. For a floating system, the ideal matrix or coating material should be highly permeable to dissolution media in order to initiate rapid generation of CO_2 and allow release of CO_2 to promote floating. Sustained layer contain HPMC (K4M), which leads to a reduced buoyancy lag-time, while Psyllum husk is swelling agent it get swell and help for floating. Formulation F7a showed buoyancy lag-times of 3 min (Table 4), the buoyancy lag-time was satisfactory when using 22.5 mg Sodium bicarbonate in the optimize formulation.

3.3 Swelling characteristics

Tablets composed of polymeric matrices form a gel layer around the core tablet when it comes in contact with aqueous medium. This gel layer governs the drug release. The kinetics of swelling is important because the gel barrier is formed by water penetration. Swelling is also vital to ensure floating. To obtain floating, the balance between swelling and water acceptance must be restored [12-13]. The swelling index of the best formulation after 8 hr was which may be because of the high viscosity and high water retention of HPMC (K4M) and Psyllum husk.

3.4 In- vitro dissolution studies

The Floating tablet shows controlled release of the drug with HPMC (K4M) and Psyllum husk as a hydrophilic matrix material (Table 1). Among the formulations F1, F2, F3, F7, F8, F9 exhibited a release of 108.66, 100.45, 69.13, 93.316, 80.89 and 108.057% respectively in 12 hrs while formulation F4, F5, F6 get dissolve within 1 hr, without HPMC(K4M), Psyllum husk act as disintegrating agent (Fig. 1). The concentration of HPMC (K4M) and Psyllum husk in the release layer was the key factor governing drug release. In the tablet, the drug release included the gelling agent forming gelatinous barrier which controls

the drug release without interference from gas bubbles generated in the floating formulation. From the dissolution profile three bathes (F3, F7 and F8) are suitable for floating matrix tablet but, the drug release of F3 and F8 showed very slow release of drug in 12hrs and the weight of the tablet is also one of the important factor for oral administration of the dosage form. While F7 shows 93% release within 12 hr. On the basis of dissolution profile and other parameters formulation F7 is selected for further optimization for Sodium bicarbonate. From the optimization profile of Sodium bicarbonate (Fig.2) and Table 2, we can be conclude that (F7a) formulation is more suitable for Gastroretentive floating formulation. The data obtained from *in-vitro* dissolution studies were fitted in different models viz. zero order, first order, matrix, peppas and Hix. Crowel. The zero order plots were found to be fairly linear (Fig.3) as indicated by their high regression values (r2 = 0.9938). Slope values (0.5<n<1.0) suggest that the release of Ranitidine HCl from floating tablets followed non-Fickian transport mechanism as shown in table 5.

Table 5 Release Kinetic of Floating Matrix Tablet

Release Kinetic	R value	K value
Zero order	0.9938, n=1.0563, k=7.7121	8.4946
1st order	0.9169	-0.1922
Matrix	0.9528	24.2793
Peppas	0.9991	11.5505
Hix.crow.	0.9723	-0.0462

3.4.1 Effect of HPMC(K4M) on drug release

Tablets prepared with HPMC (K4M) (formulation F1, F2, F3) contain increasing proportion of copolymer that is 1:1, 1:2, 1:3 retained their integrity throughout the study and released the drug in a controlled manner. As the concentration of HPMC (K4M) increases in the formulation, the release rate was found to decrease. HPMC (K4M) forms a strong viscous gel in contact with aqueous media, which

may be useful for the controlled delivery of highly water-soluble drugs. An increase in the concentration of HPMC did not significantly prolong the drug release. Faster release of the drug from the hydrophilic matrix was probably due to faster dissolution of the highly water soluble drug from the core and its diffusion out of the matrix forming the pores for entry of solvent molecules[14]. On the basis of the results which are shown in Fig.4, HPMC (K4M) was consider for further studies and preparation of a floating drug delivery system.

3.4.2 Effect of swelling agent on drug release

The results obtained from the *in-vitro* dissolution study of matrix formulations containing Psyllum husk revealed that there was a significant change in drug dissolution profile as shown in Fig.5. A marked increase in the release rate was observed, if only swelling agent is added instead of polymer (F4, F5, F6), as shown in Fig.1, all the formulation get dissolved within a hour. While the combination of polymer along with swelling agent shows marked sustained effect, as both in combination, forms gel matrix around the drug and help for retardation of release. From Fig 5, it can be conclude that polymer and Psyllum husk in proportion 1:1(F7 and F8) shows most prominent result as compared to1:2 (F9) proportion. As well as Psyllum husk also help for floating of tablet, as formulation F9 get floats without addition of Sodium bicarbonate.

3.4.3 Effect of floating agent on drug release

The results obtained from the study of optimization of Sodium bicarbonate Fig.2, it can be conclude that as the concentration of floating agent increases the floating lag time decrease but altimetly increase the release rate.

3.5 Drug excipients interaction study

In the present study, it was found that there is no chemical interaction between Ranitidine HCl and HPMC (K4M) used. From the Fig. 6, it was observed that there were no changes in the functional groups of drug and polymers, which shows that there were no physical interactions between drug and polymers.

Fig 1: Dissolution Profile of Ranitidine HCl

Fig 2: Optimization of sustained release layer for Sodium bicarbonate

Fig 3: Dissolution Profile of Ranitidine Hcl in Floating Matrix Tablet

Fig.4: Effect of HPMC(K4M) on Drug Release

Fig.5: Effect of Floating Agent on Drug Release

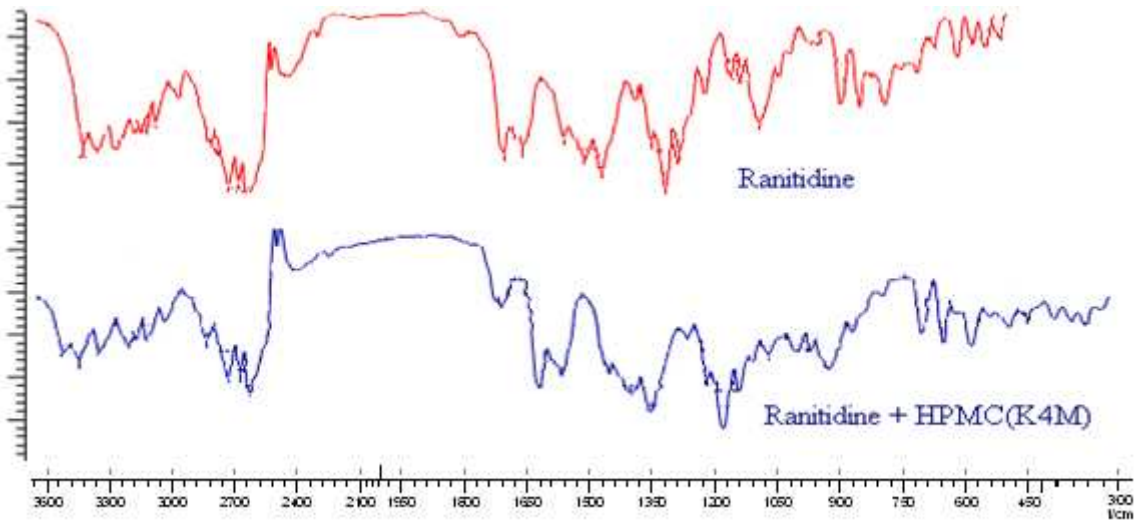

Fig. 6 FTIR Spectra for Ranitidine HCl along It's Physical Mixture

3.6 In-vitro Dissolution Test After Stability Study

After stability study, *in-vitro* release dissolution test of matrix tablet was carried out which is shown in Fig.7. From the results of dissolution test of floating matrix tablet, it was concluded that there is no significant change in dissolution release pattern of tablet after stability study.

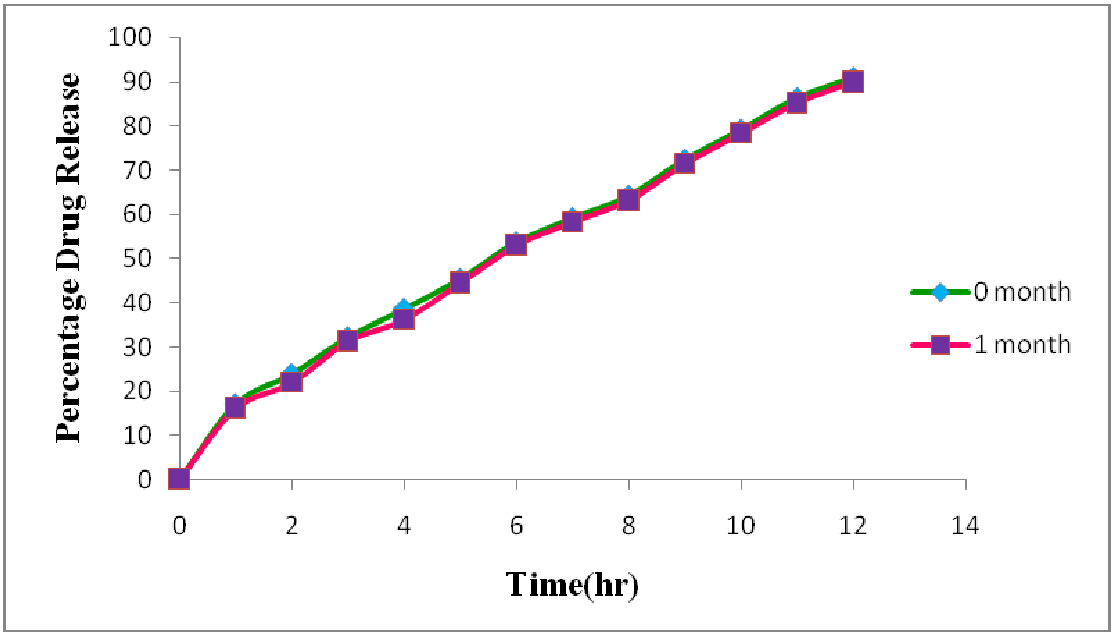

Fig.7 Results of Dissolution Profile of Ranitidine HCl after Stability Study

CONCLUSION

In this study, we successfully developed Floating Drug Delivery System which exhibits a floating and sustained release effect for prolonged residence in the stomach. The optimized tablet formulation showed a satisfactory dissolution profile, floating characteristics. The tablets remained floating in the stomach for more than 12 hrs. There is a further scope to conduct the *in-vivo* studies by using various experimental animal models and correlate the *in vitro-in vivo* correlation.

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