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FORMULATION AND EVALUATION OF SUSTAINED RELEASE FLOATING-MUCOADHESIVE TABLET OF RANITIDINE HCl

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Abstract

A new drug delivery system for H_2 receptor antagonist drug, Ranitidine hydrochloride, was developed utilizing both the concepts of adhesiveness and of flotation, in order to obtain a unique drug delivery system which could remain in the stomach for a much longer period of time. Floating-Mucoadesive tablets of Ranitidine hydrochloride were developed to prolong its release and improve bioavailability. Ranitidine has been the most widely used drug for the treatment of peptic ulcer. A floating drug delivery system (FDDS) was developed using gas-forming agents, like sodium bicarbonate, citric acid and hydrocolloids, like hydroxypropyl methylcellulose (HPMC) and carbopol 934P. Floating delivery system of Ranitidine hydrochloride was prepared using different grades of HPMC as drug release retarding polymer and sodium bicarbonate as source for carbon dioxide which helps tablets to float. Tablets were prepared by direct compression. The prepared tablets were evaluated their physicochemical properties and drug release, excipient compatibility, density, buoyancy test, mucoadhesion force, swelling study, drug content and *in-vitro* release profile.

INTRODUCTION:

Oral route of drug administration is oldest and safest mode of drug administration. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed. In oral controlled drug delivery the amount of drug release is constantly predetermined and these constant releases of drug provide a constant blood plasma level of drug for a therapeutic response. The oral controlled drug deliveries have much advantage to conventional delivery. It decrease the fluctuation of drug plasma conc., it reduce toxicity, provide a sustained effects, reduced the dosing frequency. Apart from other advantage it reduces total amount of drug used, improve patient compliance and reduced patient care time

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamics profiles with acceptable level of safety to the patient in recent years a wide variety of newer oral drug delivery systems like SR/CR dosage forms are designed and evaluated in order to overcome the limitations of conventional therapy. These products are able to maintain steady drug plasma levels for extended periods of time as a result the variations of the drug levels in the blood are prevented and minimized drug related side effects.

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT

and a better control of the fluctuations in plasma drug concentration.

Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion keeps the delivery system adhering to the mucus membrane. Transmucosal drug delivery systems show various merits over conventional drug delivery systems.

Mucoadhesive polymers facilitate the mucoadhesion by their specific properties. This article reviews desirable properties of mucoadhesive polymers and the latest advancement in the field.

Ranitidine hydrochloride is a histamine H2-receptor antagonist that inhibits stomach acid production. 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.

MATERIAL AND METHOD

Ranitidine was received gift sample of Ranbaxy of Devas. HPMC K-4, HPMC K-15, HPMCK-100 used as polymer. Cross povidone, Carmilose sodium, lactose, Magnesium stearate, talc. All ingredient and reagent were of analytical grade.

Method:

Preparation of Floating Tablet of Ranitidine

The ingredient were weighed accurately and mixed thoroughly powder passed through 44 mesh sieve. Implies direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. These materials possess cohesive and flow properties that make direct compression possible. Increasing attention is paid to this method because of incredible economy and efficiency offered by it.

Direct compression vehicles or carriers must have good flow and compressible characters these properties are imparted by predisposing these vehicles to slugging, spray drying or crystallization. Tablets were white and round. Hardness, friability and weight variation were evaluated.

Evaluation of powder

The flow properties of granules (before compression) were characterized in terms

of angle of repose9, tapped density, bulk density, Carr's index and Hausner ratio.

Physical evaluation of Ranitidine Tablet

Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odor, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, hardness (Monsanto tester) and friability using 10 tablets (Roche type friabilator)

Determination of Swelling Index

The swelling index of tablets was determined in 0.1NHCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 24 h. The swelling index (SI), expressed as a percentage, and was calculated from the following equation

SI = Weight of tablet at time (*t*) -Initial weight of tablet x 100/ Initial weight of tablet

***In Vitro* buoyancy studies**

In Vitro buoyancy studies were performed for all the twelve formulations as per the method. The randomly selected tablets from each formulation were kept in a 100ml beaker contain simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

Drug Content

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 313nm using 0.1 N hydrochloric acid as blank.

***In Vitro* dissolution studies**

The release rate of Ranitidine from floating tablets was determined using United States Pharmacopeia (USP). Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1Nhydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the

dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 313 nm using a UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.

Comparison with marketed product

The promising formulation was compared with marketed product of Ranitidine. The evaluation parameters tested and compared were drug content uniformity and in-vitro dissolution profile.

***In Vitro* drug release kinetic studies**

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order16, first order17,Higuchi square root18, Korsmeyer-Peppas model19.Thecriteria for selecting the most appropriate model was chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXCEL statistical function.

Stability studies

The promising formulation was tested for a period of 30 days at 30C with 75% RH, for their drug content and other parameters.[4]

RESULTS AND DISCUSSION

Formulation development & evaluation parameters have been performed in satisfactory data. Title of this study will be done for prolonged the bioavailability of the dosage form. It is a new drug delivery system to maximize effectiveness and compliance. Ranitidine HCL is use for gastric problems. The advantage of floating drug delivery system is to extend the release of drug, increases gastric retention time and enhances bioavailability by superior technology of floatation and adhesion to achieve gastric retention.

Swelling Index studies

Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release. Kinetics off swelling is important because the gel barrier is formed with water penetration.

Swelling is also a vital factor to ensure floating and drug dissolution. To obtain floating, the balance between swelling and water acceptance must be restored23-24. Tablets containing Carbopol934P (F9 and F10) showed less swelling index at the beginning but higher swelling index was observed at the end of 12 h. While HPMC K4M and HPMC K15M (F1to F8) swelled rapidly at the beginning in 0.1 N HCl and could not remain their matrix integrity up to 12 h. Tablets containing combination of Carbopol 934P, HPMC K4M and HPMC K15M (F12) showed constant increasing in swelling index up to 12 h. Combination of HPMC K4M and HPMC K15M resulted in a higher swelling index compared with HPMC K15M alone. The HPMC grade also affects the swelling and hydration with considerably higher swelling index for HPMC K4M than HPMC K15M. HPMC K15Mexhibited low swelling index, but there was no decrease in swelling rate. The reason for this appeared to be its high viscosity and high water retention property. Further, no significant effect of effervescent on swelling indices was observed. Swelling index values start decreasing when polymer erosion starts in the medium.

***In Vitro* dissolution studies.**

The performance of floating formulations has been reported to be greatly affected by physiological conditions such as food transport, gastrointestinal motility, and so on. A study 25 on floating mini tablets of atenolol has indicated lower bioavailability of drug. The reason for this lower bioavailability is attributed to small size of the dosage form, causing too short of a residence time and a premature exit from the stomach. The tablets in this investigation are much larger in size and are expected to be retained for longer duration in upper GIT. *In Vitro* dissolution studies of all the formulations of floating tablets of Ranitidine were carried out in 0.1NHCl. The study was performed for 24 h and cumulative drug release was calculated at every one hour time interval. *In Vitro* dissolution studies of all the formulations are shown in figure 2, 3 and 4. Three different polymers and their combinations (Table 1) were used to prepare floating tablets. It was observed that the type of polymer influences the drug release pattern. All the formulations contained equal amount of gas generating agent (sodium bi carbonate) a citric acid. A

significantly higher rate and extent of drug release was observed from the batches based on HPMC K4M.Varying the amount of HPMC K4M affect the drug release. Drug release from HPMC K15M was lesser owing to its high viscosity and also due to less permeability of water to HPMC K15M. Moreover the HPMC containing tablets F1-F8 could not bear their matrix shape until 24 h and the released the drug before24 h. After 1 h the drug dissolved from floating tablets composed of carbopol 934P, F9(16.0) and F10 (11.0) was less than tablets containing different grade of HPMC. This showed that HPMC hydrated more rapidly than carbopol 934P in the presence of 0.1 N HCl. Although combination of HPMC K15Mand HPMC K4M sustains the drug release for a longer time. As expected, the drug release rate was dependent on the viscosity grade and the concentration of the polymer used. Tablets containing HPMC and Carbopol combination (F12) showed constant drug release up to 24hr (98). This controlled release of drug from F12 could be attributed to the formation of a thick gel structure that delays drug release from the tablet matrix c.

CONCLUSION

This study discusses the preparation of floating tablets of Ranitidine. The effervescent-based floating drug delivery was a promising approach to achieve *In Vitro* buoyancy. The addition of gel-forming polymer HPMC K4 M, HPMC K15 M, carbopol 934P 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. The type of polymer affects the drug release rate and the mechanism. Polymer swelling is crucial in determining the drug release rate and is also important for flotation. A lesser FLT and a prolonged floating duration could be achieved by varying the amount of effervescent and using different polymer combinations. The *In Vitro* drug release profiles obtained for tablets (F12) made with combinations of HPMC K4M, HPMC K15 M FLT(30 s) and a prolonged floating duration (> 24hrs) which was a controlled release characteristic (98%) for 24h. Good stability was observed for 3 months during stability studies. Since the formulation showed sufficient release for prolonged period, the dose can be reduced and

possible incomplete absorption of the drug can be avoided.

Dissolution rate of Floating tablet for batches FT-III to FT-VI

Figure 1 Zero Order release rate of Floating tablet for batches FT-III to FT-VI

First order release rate of Floating tablet for batches FT-III to FT-VI

Figure 2 First Order release rate of Floating tablet for batches FT-III to FT-VI

Higuchi Plot of Floating tablet for batches FT-III to FT-VI

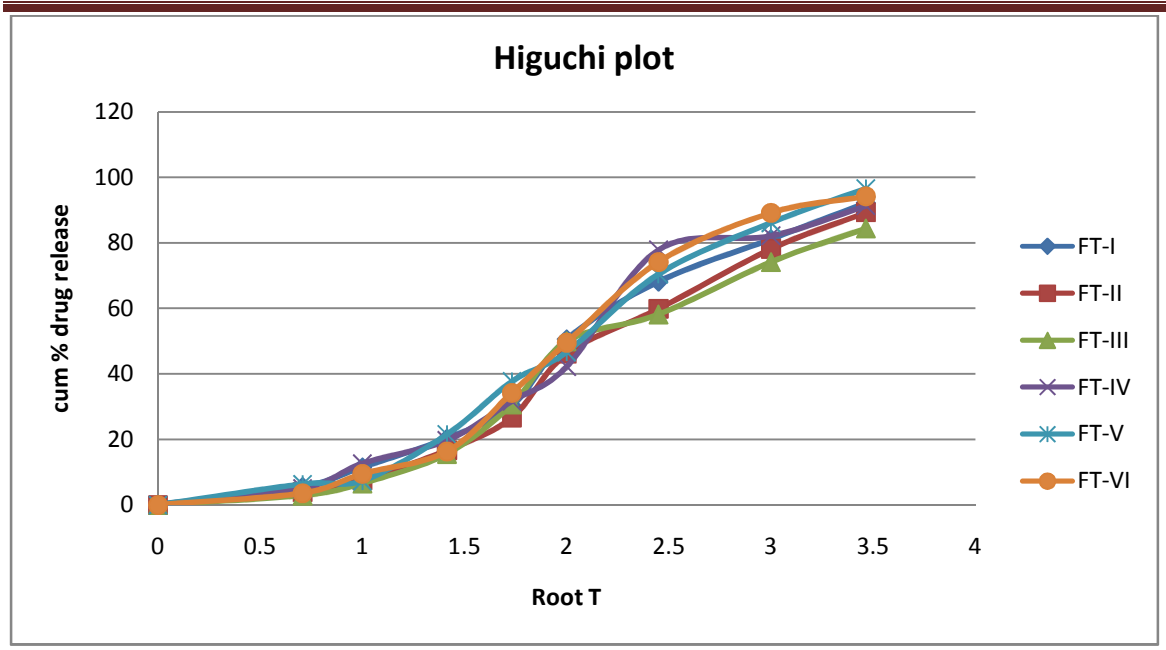

Figure 3 Higuchi Plot of Floating tablet for batches FT-III to FT-VI

Hixon Crowell plot of Floating tablet for batches FT-III to FT-VI

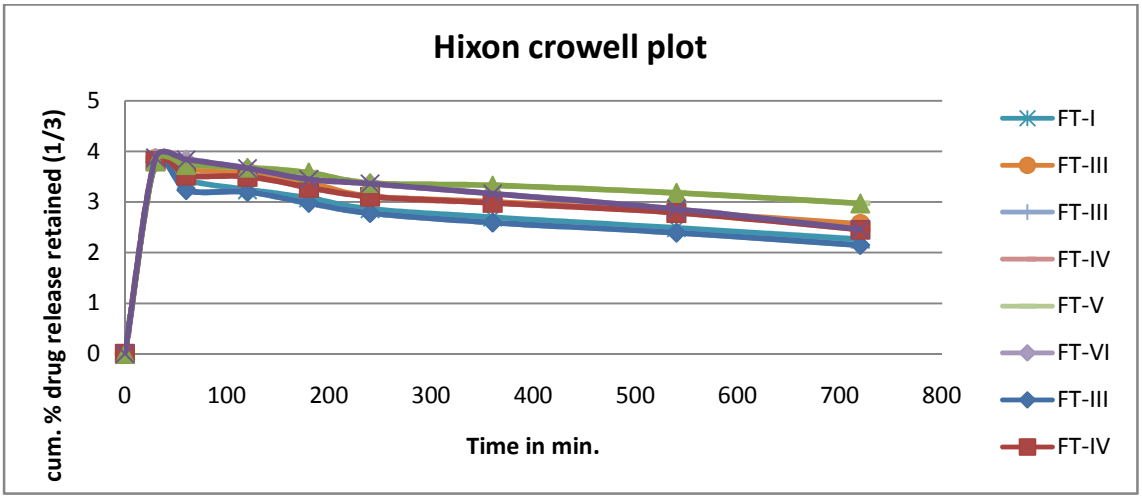

Figure 4 Hixon Crowell plot of Floating tablet for batches FT-III to FT-VI

Table 1

Composition of floating-mucoadhesive tablet of ranitidine HCl.

INGREDIENTS	SR-I	SR-II	SR-III	SR-IV	SR-V	SR-VI
	mg	mg	Mg	mg	mg	Mg
Ranitidine HCl	50	50	50	50	50	50
HPMC K4M					65	30
HPMC K5M	80	70				
HPMC K15M				60		30
HPMC K100M			50			
Carbopol 934P	20	40	30	30	25	30
Sodium bicarbonate	40	40	30	30	30	30
Citric acid	20	20	24	24	24	24
Aerosil			3	3	3	3
Magnesium stearate	3	3	3	3	3	3
Lactose	85	75	108	98	98	98
Talc	2	2	2	2	2	2

(Weight– 300mg)

Table 2

Various Evaluating Parameter of Batch-I to Batch-VI batches of Ranitidine Floating-mucoadhesive

Batch	Angle of Repose (θ°)	Bulk Density (g/cm^3)	Tapped Density	Compressibility Index	Hausner Ratio
SR-I	28	0.385	0.569	31.17	1.37
SR-II	28	0.384	0.502	23.21	1.27
SR-III	32	0.366	0.506	25.32	1.12
SR-IV	30	0.356	0.515	28.32	1.25
SR-V	32	0.365	0.509	25.30	1.29
SR-VI	28	0.384	0.505	30.17	1.15

Table 3

Evaluation Parameter of floating-muucoadhesive tablets

Batch Code	Hardness (kg/cm^2) N=5	Thickness (mm) N=10	Friability (%)	Weight variation N=10	%Drug content Ranitidine Hydrochloride
FT-I	3.5 ± 0.12	4.0 ± 0.17	0.218	5.8± 1.05	91± 1.2
FT-II	4 ± 0.56	4.0 ± 0.15	0.225	5.1± 1.18	96 ± 1.1
FT-III	4 ± 0.31	4.0 ± 0.21	0.221	5.3± 1.21	94 ± 1.4
FT-IV	3 ± 0.17	4.0 ± 0.19	0.233	6.2± 1.07	95±0.96
FT-V	3.9 ± 0.24	4.0 ± 0.14	0.199	4.6± 1.14	95 ± 0.8
FT-VI	3.5 ± 0.35	4.0± 0.15	0.282	5.1± 0.98	97 ± 1.1

Table 4

***In Vitro* buoyancy studies**

Batch	Floating lag time (min)	Floating time (hr)									
		1	2	3	4	5	6	8	10	12	24
FT-I	0.49±1.5	+	+	+	+	+	+	+	+	-	-
FT-II	2.45±0.3	+	+	+	+	+	+	+	+	-	-
FT-III	3.31±0.4	+	+	+	+	+	+	+	+	+	+
FT-IV	1.34±1.0	+	+	+	+	+	+	+	+	+	+
FT-V	1.56±0.1	+	+	+	+	+	+	+	+	+	+
FT-VI	2.49±0.3	+	+	+	+	+	+	+	+	+	+

Table 5

Percent swelling index of batches FT-I to FT-VI

Batch	Time in hrs					
	1	2	3	4	5	6
FT-I	51.52	82.32	111.45	126.46	138.21	145.08
FT-II	53.76	85.67	117.86	132.48	144.42	152.22
FT-III	55.70	89.90	121.24	136.71	149.91	158.79
FT-IV	56.09	95.12	124.39	143.90	158.70	167.81
FT-V	56.41	92.30	115.36	141.02	152.21	166.42
FT-VI	60.01	85.10	102.5	120.10	136.48	154.21

Table 6

***In Vitro* drug release studies of Ranitidine Floating Tablet**

Time	Formulation code					
in min.	FT-I	FT-II	FT-III	FT-IV	FT-V	FT-VI
30	6.17	19.73	10.71	9.375	4.68	2.16
60	8.75	25	15.40	19.41	2.88	1.08
120	6.84	18.32	21.42	23.10	3.24	5.4
180	8.16	19.17	23.43	18.41	9.72	8.28
240	8.88	18.89	20.75	19.08	24.48	11.88
360	8.39	20.58	28.99	27.4	20.88	16.2

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