

DUAL ACTING ORAL FLOATING MATRIX TABLETS OF RANITIDINE HYDROCHLORIDE

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ABSTRACT: The main purpose of this work was to prepare floating matrix drug delivery system of Ranitidine. Floating matrix tablets of Ranitidine were developed to prolong gastric residence time and increase its bioavailability. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. Floating matrix tablets containing 100 mg Ranitidine were developed using different effervescent salts and polymer combinations. The tablets were prepared by direct compression technique, using polymers such as hydroxyl propyl methyl cellulose (HPMC K4M), Carbopol 934 in combination. Sodium bicarbonate, citric acid, calcium carbonate was incorporated as a gas-generating agent. The effects of sodium bicarbonate on drug release profile and floating properties were investigated. The formulation was optimized on the basis of acceptable tablet properties, floating lag time, total duration of floating and in vitro drug release. The formulated tablets with optimum hardness, uniform thickness, consistent weight uniformity and low friability. The results of dissolution studies, floating lag time indicated that formulations F4 exhibited good and controlled drug release. Applying the linear regression analysis and model fitting showed the selected formulation F4 showed diffusion coupled with erosion drug release mechanism, followed first order kinetics. Optimized floating matrix tablets F4 showed no change in physical appearance, drug content, or in dissolution pattern after storage at 25°C/ relative humidity 65% and 40°C / relative humidity 75% for a period of 3 months.

Key words: Ranitidine, floating tablets, direct granulation, in vitro release.

INTRODUCTION

Oral administration is the most convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received the more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes (Singh, B.N. and Kin, K.H., 2000, Timmerman, S.J. and Andre, J.M., 1994). For drugs with a narrow absorption window in the gastrointestinal tract or acting locally in the stomach, the challenging task is not only to prolong drug release but the retention of the dosage form in the upper gastrointestinal tract. This results in a higher bioavailability, reduced time intervals for drug administration and thus a better patient compliance (Moes AJ., 1993). Various approaches for gastro retentive dosage forms have been proposed including mucoadhesive systems, swellable and floating systems (Vyas, S.P. and Roop K.K., 2005). Floating drug delivery systems remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents (Timmerman, S.J. and Andre, J.M., 1994). Floating matrix systems containing HPMC as the matrix forming excipient begin to swell and form a gel layer with entrapped air around the tablet core after contact with gastric fluid, whereas this gel layer controls the drug release (Whitehead L., 1998). Another possibility for the induction of floatation lies in the incorporation of sodium bicarbonate, citric acid and calcium carbonate as gas forming agent dispersed in a HPMC hydrogel matrix as a method.

Ranitidine hydrochloride 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. 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 controlled release dosage form of RHC1 is desirable. The short biological half-life of drug (~2.5-3 hours) also favors development of a controlled release formulation.

MATERIALS AND METHODS

Materials

Ranitidine hydrochloride was obtained as a gift sample from Waksman Selman Pvt. Ltd, Anantapur, India. Sodium bicarbonate, citric acid, calcium carbonate was procured from S.D. Fine chemicals Mumbai. All the reagents used were of AR grade. The drug samples were characterized by means of UV spectrophotometric method along with determination of solubility and pH for their authentication.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Shimadzu Corporation, (Tokyo, Japan) Model-1601 PC. Samples were prepared in KBr disks by means of a hydrostatic press at 6-8 tons pressure. The scanning range was 500-4000 cm⁻¹.

Differential Scanning Calorimetry (DSC)

DSC analysis was performed using Shimadzu DSC-60, Shimadzu Limited Japan. A 1:1 ratio of drug and excipient was weighed into aluminum crucible and sample was analyzed by heating at a scanning rate of 20°C over a temperature range 20^o-300^o C under nitrogen environment.

Evaluation of granules (Indian Pharmacopoeia, 1996, Banker, G.S., 1987)

Prior to compression into tablets, the granules were evaluated for properties such as;

Angle of repose

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height (h), was obtained. Diameter of heap, (D), was measured. The angle of repose (Θ), was calculated by eq.1 and 2.

$$\tan \Theta = h / r \dots\dots\dots (1)$$

$$\Theta = \tan^{-1} (h / r) \dots\dots\dots (2)$$

Where, Θ is the angle of repose, h is the height in cm and r is the radius.

Bulk Density

Apparent bulk density was determined by pouring presieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by eq.3.

$$D_b = M / V_0 \dots\dots\dots (3)$$

Where, M is the mass of powder and V₀ is the Bulk volume of the powder

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug- excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by eq.4.

$$Dt = M / Vt \dots\dots\dots(4)$$

Where, M is the mass of powder and Vt is the tapped volume of the powder.

Powder flow properties

Carr's Index (I):

It is expressed in percentage and is expressed by eq.5.

$$I = Dt - Db / Dt \dots\dots\dots (5)$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Hausner ratio

It is expressed in percentage and is expressed by eq.6.

$$H = Dt / Db \dots\dots\dots (6)$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Compression of tablets

After evaluation of granules were then compressed into tablet using rotary tablet press (M/s Remek, Ahmedabad, India) under hardness of 3-4 kg/cm².

Evaluation of tablets (Ichikawa M., 1991, Yang L, Esharghi J., 1999)

Post compression parameters

The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, hardness (Monsanto tester), friability using 10 tablets (Roche type friabilator), drug content, *in-vitro* buoyancy and *in-vitro* dissolution studies. The results are expressed as mean \pm S.D. (n=5). The *in-vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time. 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 0.45 μ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 315nm using 0.1 N HCl as a blank. The release rate of ranitidine from floating tablets was determined using USP Dissolution Testing Apparatus 2 (paddle method; Systronics, Mumbai, India). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 \pm 0.5°C and 50 rpm. A sample (5 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 0.45 μ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 315 nm using a Shimadzu UV- 1700 UV/VIS double beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Stability studies

The promising formulation was tested for a period of 3 months at different temperature of 40°C with 75% RH, for their drug content (Remunan C., 1992)

RESULTS

The results of the physico-chemical characterization are shown in Table 3. The weight of the tablet varied between 496±8.94 to 501±4.85 mg. The variation in weight was within the range of ±7.5% complying with pharmacopoeial specifications. The hardness for different formulations was found to be between 5.62±0.15 to 7.81±0.59 kg/cm². The friability was ranged from 0.16±0.01 to 0.85±0.06. The drug content varied between 149.23±4.25 to 150.31±0.12mg (Table1 and 2). The drug release from floating tablets was found to be 85.51 to 98.29% for formulations F1 to F5. (Fig-1)

Fig 1: In-vitro drug release profile of formulated tablets

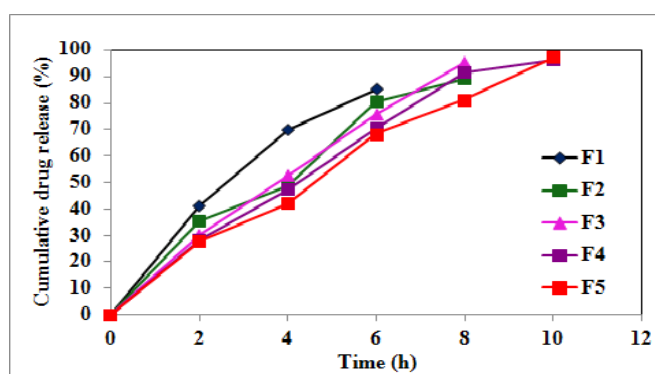


Table 1: Composition of various formulations

Ingredients (mg)	F1	F2	F3	F4	F5
Ranitidine hydrochloride	15	15	15	15	150
Hydroxy Propyl Methyl Cellulose (K4M)	10	20	30	40	50
Carbopol 934	10	20	30	40	50
Sodium bicarbonate	10	20	30	40	50
Citric acid	5	10	15	20	25
Calcium carbonate	10	10	10	10	10
Micro crystalline cellulose	29	26	22	19	155
Magnesium stearate	5	5	5	5	5
Talc	5	5	5	5	5

Table2: Flow properties of granules

Formulation	Angle of repose (°)	Loose Bulk Density (g/cm ³)	Tapped Bulk Density (g/cm ³)	Hausner's ratio (H _R)	Carr's Index (I _c)
F1	27.52±0.16	0.560±0.01	0.630±0.02	1.129	0.116
F2	24.48±0.24	0.567±0.05	0.658±0.01	1.161	0.141
F3	27.19±0.11	0.575±0.05	0.671±0.05	1.130	0.118
F4	26.99±0.11	0.581±0.04	0.675±0.06	1.156	0.137
F5	24.59±0.05	0.574±0.03	0.679±0.04	1.181	0.155

Table 3: Physicochemical characterization of formulated floating tablets

Formulation	Weight of the tablet (mg)	Hardness (Kg/cm ²)	Friability (%)	Drug content (mg)	Floating lag time (sec)	Total floating time (hours)
F1	499±4.51	5.69±0.23	0.23±0.02	149.23±4.25	65.22±2.33	6.59±0.03
F2	496±8.94	6.84±0.62	0.16±0.01	150.20±6.85	61.51±2.15	7.15±0.04
F3	501±4.85	7.81±0.59	0.29±0.01	149.95±5.62	54.62±4.52	8.66±0.06
F4	498±3.61	5.62±0.15	0.85±0.06	149.94±2.16	51.20±2.25	9.11±0.07
F5	497±2.45	6.69±0.42	0.45±0.03	150.31±0.12	46.95±3.52	9.35±0.02

DISCUSSIONS

The floating tablets of Ranitidine hydrochloride were prepared by effervescent technique using Hydroxy Propyl Methyl Cellulose (K4M), carbopol 934, sodium bicarbonate, citric acid and Calcium carbonate. The magnesium stearate and talc were used as lubricant and glidant, respectively. The formulated floating tablets showed uniformity in weights. The variation in weight was within the range of $\pm 7.5\%$ complying with pharmacopoeial specifications. The hardness of formulated tablets was more than 5 kg/cm^2 indicates satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The formulated tablets showed uniformity in drug content. All the tablets were prepared by effervescent approach. The combination of sodium bicarbonate and citric acid provided desired floating ability but, additionally Calcium carbonate was included to increase the effervescent and it act as antacid. So, this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (Hydroxy Propyl Methyl Cellulose and Carbopol 934), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during *in-vitro* buoyancy studies. All the batches of tablets were found to exhibit short floating lag times due to presence of sodium bicarbonate and citric acid. Decrease in the citric acid level increased the floating lag time and tablets were found to float for longer duration. The pH of the stomach is elevated under fed condition (~ 3.5), therefore citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate; more over citric acid has an stabilizing effect on Ranitidine formulation. It is evident from the *in-vitro* dissolution data that increase in citric acid concentration increased the release rate but reduced the floating time, probably due to of excess carbon dioxide, disturbing the monolithic tablet. The prepared formulations sustained the drug release for a period of 8-10 hours. Comparing the two different grades of Hydroxy Propyl Methyl Cellulose (K4M), it was found that low-viscosity grade Hydroxy Propyl Methyl Cellulose K4M provided better-controlled release characteristics with excellent *in-vitro* buoyancy. It was observed that the release of Ranitidine from such formulations increased on decreasing the proportion of Hydroxy Propyl Methyl Cellulose in the formulation but duration of floating decreased.

CONCLUSION

The effervescent-based floating drug delivery was a promising approach to achieve *in-vitro* buoyancy. The addition of gel-forming polymer Hydroxy Propyl Methyl Cellulose (K 4M) and gas-generating agent sodium bicarbonate along with citric acid was essential to achieve *in-vitro* buoyancy. Incorporation of calcium carbonate results in increase in effervescent efficacy additionally it has antacid property. The drug release from the tablets was sufficiently controlled.

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