Research Article

Formulation and Evaluation of a Buoyant Ranitidine Hydrochloride System

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ABSTRACT

The present study was to develop a buoyant Hydrodynamically Balanced System (BHBS) for ranitidine hydrochloride (RH) as a single unit floating capsule. The formulated blends were prepared using physical mixing of drug and polymer(s) in varying concentrations. Drug compatibility with polymer was studied by FTIR, DSC and XRPD techniques. The bulk and tapped densities, Carr's compressibility index, Hausner's ratio and angle of repose were determined to study the micromeritic properties of physical mixtures of different blends. Prepared BHBS capsules were also evaluated for drug content, weight uniformity and in vitro drug release. The drug release pattern varied significantly with increase in polymer concentration and its type in the formulations. All the BHBS capsules of RH extended drug release compared to capsule contains only pure RH. The release data was best fit to first, zero order kinetics as well as diffusion model. All formulations depicted n value less than 0.5. This confirmed that the release is according to controlled diffusion.

Keywords: Buoyant Hydrodynamically Balanced System, Carr's index, Chitosan, HPMC, Ranitidine hydrochloride.

INTRODUCTION

Ranitidine hydrochloride is a histamine H2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome (ZES), gastroesophageal reflux disease (GERD) 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.[1-3] A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 h but not up to 10 h. An alternative dose of 300 mg leads to plasma fluctuations; thus a sustained release dosage form of ranitidine hydrochloride is desirable.[4] The drug has a short biological half-life of approximately 2–3 h, an absolute bioavailability of only 50%, and it is absorbed only in the initial part of the small intestine.[5-8] There are a number of approaches that can be used to prolong gastric retention time, such as floating drug delivery systems, also known as hydro dynamically balanced systems, swelling and expanding systems, polymeric bio adhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices.[9-11]

In the present study, an attempt was made to develop a gastro retentive floating capsules of ranitidine as single-unit floating capsules with the help of low density polymers, tried to study the different release modifier effect and $T_{90\%}$. We had tried to prolong the drug release and increase gastric residence time, to increase therapeutic efficacy of the drug compared to multiple conventional oral dosage forms.

MATERIALS AND METHODS

Materials

Ranitidine HCl (RH), Hydroxy propyl methyl cellulose (HPMC 4M), Chitosan, Polyethylene glycol (PEG6000), Stearic acid, Hard gelatin capsule shells (#00), Buffer solutions were purchased from Sigma Chemical Co., St. Louis. All water used was distilled and de-ionized. All other chemicals were of reagent grade and used as received.

Methods

Selection of Polymers

Accurately weighed 200 mg of different low density hydrophilic polymers were added in appropriate size of empty hard gelatin capsule shell (size# 00), which upon administration would attain a density less than that of gastric fluids and therefore would float. The polymer that shows maximum floating time was selected for further studies.

Floating capacity

Floating characteristics of the prepared formulations were determined by using USP 2 paddle apparatus at a paddle speed of 50 rpm in 900 ml of a 0.1 N HCl solution (pH=1.2) at 37±0.5°C for 12 h. The time between the introduction of capsule and its buoyancy on the simulated gastric fluid (floating lag time) and the time during which the dosage form remain buoyant (floating duration) were measured.

Formulation of HBS Capsules

RH was weighed and physically blended with polymer(s) using mortar and pestle until the whole blend has the same color (homogenous mixing) then, filled into hard gelatin capsule (size #00) manually. The qualitative amounts of drug and polymer are shown in table 1.

Table 1: Composition of BHBS capsule formulation

Formula	RH (mg)	HPMC (mg)	Chitosan	Stearic acid (mg)	PEG6000 (mg)
FD	300		-	-	-
F1	300	75	-	-	-
F2	300	150	-	-	-
F3	300	225			-
F4	300	300	-	-	-
F5	300	375	-	-	-
F6	300	450			-
F7	300	150	150	15	-
F8	300	150	150		15

Table 2: Micromeritic properties of different formulations of RH

Formula	BD (g/cm^3)	TD (g/cm^3)	HR	Carr's Index (%)	Angle of Repose
Drug	0.383	0.700	1.820	45.286	36.250^o
F1	0.230	0.350	1.500	34.290	42.310^o
F2	0.175	0.220	1.257	20.455	16.226^o
F3	0.259	0.280	1.080	7.500	18.450^o
F4	0.250	0.389	1.560	35.733	33.670^o
F5	0.226	0.250	1.11	9.600	14.110^o
F6	0.368	0.500	1.360	26.400	28.652^o
F7	0.350	0.438	1.251	20.090	26.832^o
F8	0.389	0.500	1.285	22.200	25.432^o

Table 3: Kinetic analysis of the release data of different RH formulations

Formula	Model	R^2	Slope	Y-Intercept	n	$T_{90\%}$ (hrs)	Mechanism of Release
F1	Zero First Diffusion	0.934 0.342 0.976	5.977 -14.010 24.910	52.220 84.800 28.700	0.06	6.10	Diffusion
F2	Zero First Diffusion	0.759 0.990 0.991	3.395 -0.202 14.79	75.620 1.670 60.890	0.03	3.90	Diffusion
F3	Zero First Diffusion	0.712 0.947 0.952	9.420 -0.322 41.440	32.320 2.328 -9.399	0.09	4.80	Diffusion
F4	Zero First Diffusion	0.764 0.695 0.860	9.858 -0.371 42.670	27.130 2.527 15.030	0.06	5.50	Diffusion
F5	Zero First Diffusion	0.832 0.797 0.909	9.869 -0.267 42.070	23.020 2.396 -17.810	0.10	6.57	Diffusion
F6	Zero First Diffusion	0.932 0.918 0.980	10.330 -0.157 43.000	10.630 2.203 -33.000	0.10	8.18	Diffusion
F7	Zero First Diffusion	0.974 0.987 0.997	10.180 -0.106 42.05	1.713 2.126 -37.470	0.10	9.10	Diffusion
F8	Zero First Diffusion	0.889 0.891 0.956	9.603 -0.296 40.610	27.350 2.401 -11.69	0.10	5.30	Diffusion

Micromeritic properties [12]

Bulk density and tapped density

Both bulk density (BD) and tapped density (TD) were determined. A known quantity of powder from each formula was transferred into a 10 ml of measuring cylinder. The initial volume was observed and tapped volume was measured till standard tapping using tapping equipment (Campbell Electronics model PD-100 Prabhadevin. Mumbai-25, INDIA). BD and TD were calculated using the following formula:

BD = mass of the powder / volume of the untapped powder.

TD = mass of the powder / volume of the tapped powder.

Compressibility index (CI)

The compressibility index of the powder formulation was determined by Carr's compressibility index: Carr's index (%) = [(TD-BD) x 100]/TD]

Hausner's ratio (HR)

Hausner's was determined using BD and TD of the powder blend formulations:

H = TD/BD

Angle of Repose

The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of granules. Funnel used was a stainless steel funnel and the size of the orifice was 10 mm and the height from the beginning of funnel to end of orifice was 111 mm. The funnel was fixed in place, 4 cm above the bench surface. After the cone from 5 g of sample was built, height of the granules forming the cone (h) and the radius (r) of the base were measured. The angle of repose (θ) was calculated as follows:

$$\text{Tan } \theta = h/r; \text{ Angle of repose } (\theta) = \text{Tan}^{-1}\ \theta$$

A value of <30° indicates 'excellent' flow whereas >56° indicates 'very poor' flow. The intermediate scale indicates 'good' (θ between 31–35°), 'fair' (θ between 36–40°), 'passable which may hang up' (θ between 41–45°), and 'poor which must be agitated or vibrated' (θ between 46–55°).

Evaluation of BHBS capsules formulations

Weight Uniformity

10 capsules were weighed individually and the average weight was determined. Test was performed according to the official method.

Drug content

The HBS capsules contain was dissolved in ethanol and make up volume up to 100 ml with HCl pH 1.2 solutions (SGF) and filter. The absorbance was measured at 313 nm after suitable dilution by UV-Visible spectrophotometer (Shimadzu UV-1601, Japan).

Infrared analysis (FTIR)

The x-ray diffraction patterns of RH and F7 were performed in infrared spectrophotometer (Genesis II, Mattson, England). Radiation was provided by a copper target (Cu anode 2000W:1.5418 high intensity x-ray tube operated at 40 KV and 35MA). The monochromator was a curved single crystal (one PW1752/00). Divergence slit and receiving slit were 1 and 0.1 respectively. The scanning speed of goniometry (PW/050/81) USED WAS 0.02.20/5 and the instrument were combined with a Philips PM8210 printing recorder with both analogue.

X-ray Powder Diffraction Analysis (XRPD)

X-ray diffraction experiments were performed in a Scintag x-ray diffractometer (USA) using Cu K α radiation with a nickel filter, a voltage of 45 kV, and a current of 40 mA. Diffraction patterns for RH and F7 were obtained.

Differential scanning calorimetry (DSC)

Samples were placed in Al pan and heated at rate of 50°C/min with indium in the reference pan, in an atmosphere of nitrogen up to a temperature of 400°C.The DSC studies were performed for RH and F7.

In-vitro drug release studies

The dissolution of different formulations of BHBS compared to the plain drug, were determined using dissolution tester (VK 7000 Dissolution Testing Station, Vankel Industries, Inc., NJ) following the USP paddle method. All tests were conducted in 900 mL of 0.1N HCl (SGF) maintained at 37 ±0.5°C with a paddle rotation speed at 50 rpm. The amount of drug used was equivalent to 300 mg. After specified time intervals, samples of dissolution medium were withdrawn, filtered, and assayed for drug content spectrophotometrically at 313 nm after appropriate dilution with 0.1N HCl. The experiment was carried out in triplicate.

Effect of release modifiers

Stearic acid and polyethylene glycol 6000 (PEG 6000) were used at 5% concentration in the formulation to study their effect on the in vitro drug release study (Table 1).The release modifiers were added to the powder blend, physically blended in mortar and pestle for 15 min and filled into hard gelatin capsule (size #00) manually.

Kinetic analysis of release data[13,14]

To analyze the mechanism of drug release from the BHBS capsules the in vitro dissolution data were fitted to different model dependent kinetics and model independent approaches like zero order, first order, Higuchi release model and Korsmeyer-Peppas model.

RESULTS AND DISCUSSION

Floating capacity

The polymers selected were of inherent low specific gravity to formulate excellent BHBS to achieve the required prolonged release drug delivery system for the

highly soluble RH. The floating capacity of different BHBS was not less than 6 hours for F1- F6, whereas F7 and F8 depicted floating capacity 10 and 9 hours respectively.

Micromeritic properties

Table (2) illustrates the different micromeritic properties of different formulations.F2, F3, F5, F6, F7 and F8 depicted excellent flow properties (HR<1.5, CI <30, angle of repose<30^{O}).This an indication to the prominent effect of both polymers used (HPMC and Chitosan) on the poor flow properties of the drug which in turn improved the good mixing of drug with these concentrations of polymers used.

Evaluation of BHBS Capsules Formulations

Weight Uniformity

The average weight of capsules within each formulation was found to be uniform. This indicated uniform filling of powder blend during capsule filling. Not more than two of the individual weights deviated from the average weight by more than 7.5% and none deviated by more than twice that percentage, which provided good weight uniformity.[15,16]

Drug Content

In all the ten formulations, the values for drug content were found to be uniform among different batches of the floating drug delivery system (FDDS) and ranged between 95.8 and 103.5% of the theoretical value as per USP[17] .The value ensures good uniformity of the drug content in the capsules.

Infrared Spectra Analysis

Figure (1) illustrated the spectra of RH and F7, the spectra of both drug and F7 are superimposed. This confirmed the absence of both chemical interaction and physical change in RH.

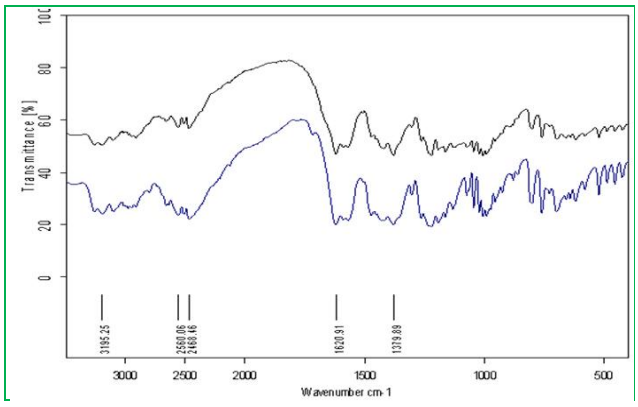

Figure 1: FTIR spectra of plain RH and F7

DSC Studies

DSC thermogram of pure RH in figure (2), showed sharp endothermic peak at 147.6ºC and in F7 the endothermic peak appeared at 149.8ºC. Little shifting of endothermic peak of the drug to left side indicates the stability of drug in presence of the two polymers (HPMC and Chitosan).This indicates that both viscosity of matrix and degree of cross-linking of the polymers eventually control the rate of drug release.

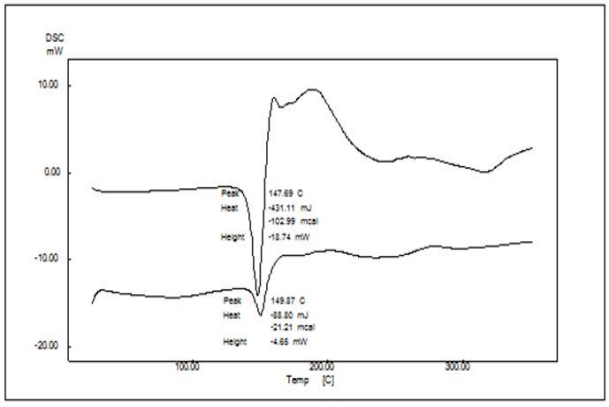

Figure 2: Thermograms of RH and F7

XRPD Studies

XRPD pattern of RH and formulation F7 showed in figure 3. It reveals that the intensity of the peaks for the pure drug was sharp, but when it was incorporated into the polymer matrix, the intensities of the peaks decreases due to decrease in crystalline properties of RH.

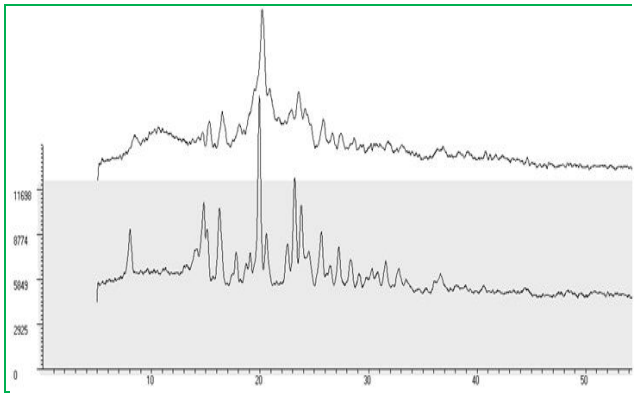

Figure 3: XRPD of RH and F7

***In-vitro* Drug Release Study**

Figure 4 depicted the release pattern of RH from different formulations. F7 depicted the ideal drug release pattern during the appointed time; the released amount of RH after 9 hours was about 86.9%.This is due to presence of a blend of HPMC, Chitosan which controlled the drug release throughout the polymeric matrix by virtue of a high degree of cross-linking and increased viscosity. The presence of Chitosan as a drug carrier retard RH release to a great extent because Chitosan is a cationic polymer insoluble in acid medium but swells forming stiff matrix retarding RH release. Also presence of stearic acid increases the toughness of the matrix. F2, F3 and F4 depicted their maximum drug release after 7 hours (100%).This is due to the lower polymer concentration. Incorporation of PEG600 in F8 accelerates drug release compared to F7. This is due to its channeling effect.

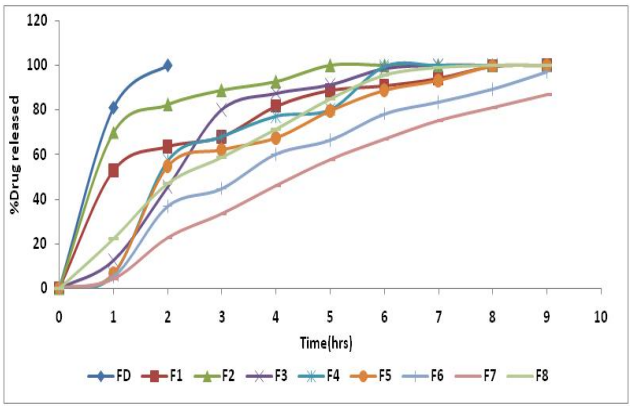

Figure 4: Release pattern of different formulations of RH in 0.1N HCl at 37°C

Kinetic Analysis of Release Data

The drug release from polymer matrix was eventually due to diffusion mechanism. This was further confirmed by Korsmeyer-Peppas plots that showed fair linearity with slope values less than 0.5, indicating that drug release mechanism from the matrix was according to controlled diffusion. This finding was in accordance with other reported works.[18,19]

CONCLUSION

It was concluded that, on the basis of in vitro drug release patterns and $T_{90\%}$ that the formulations F7 showed an ideal drug release profile and suitable $T_{90\%}$ (9.1 h) to control the drug release up to 12 h as compared to capsules contains only pure RH. The increased polymer concentration in the formulations decreased the rate of RH released. The incorporation of hydrophobic and hydrophilic release modifiers in the formulations greatly affected the pattern of RH release from the polymer matrix.

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