International Journal of Drug Delivery 2 (2010) 154-158

http://www.arjournals.org/ijdd.html

Research article

ISSN: 0975-0215

An Emerging Trend in Tablet Technology:- Floating Tablets of Ranitidine HCl

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Abstract

The rationale of this research was to prepare a gastroretentive drug delivery system of Ranitidine HCL. Floating Drug delivery system used to target drug release in the stomach or to the upper part of the intestine. The oral delivery of Ranitidine is tested by preparing a non-disintegrating floating dosage form, which increase its absorption in the stomach by increasing the drug's gastric residence time. The polymer PVC and Sodium bicarbonate was used as the gas–generating agents. Sodium bicarbonate causes the tablets to floats for more then 24hr. The prepared tablets were evaluated on their physicochemical properties and drug release characters. *In-vitro* release studies indicate that the Ranitidine release form the floating dosage form was uniform followed zero order release. A combination of sodium bicarbonate (70mg) and citric acid (15mg) was found to achieve Optimum *in vitro* buoyancy. The tablets with methocel K100 were found to float for longer duration of time as compared to formulations containing methocel K15M. The drug release from the tablets was sufficiently sustained.

Keywords: Ranitidine; Floating tablets; Methocel

Introduction

Ranitidine ($C_{13}H_{22}N_4O_3S$) is a histamine H_2-receptor antagonist. It is extensively given in gastric ulcers, duodenal ulcers, and Zollinger-Ellison disease and gastro esophageal reflux disease [1]. The suggested 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 [2]. For the short term symptomatic relief of heartburn or non-ulcer dyspepsia a dose of 120 mg up to twice daily is suggested [3]. The short biological half-life of the drug (2.0-3.5 hrs) also favors growth of a sustained-release formulation [4]. A conventional oral sustained-release formulation releases most of the drug at the colon; thus, the drug should have an absorption window either in the colon or throughout the gastrointestinal tract. Ranitidine is absorbed in only the initial part of the small intestine and has 50% absolute bioavailability [5]. Colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon [6]. It has been reported that the oral action of gastric disorders with an H_2 receptor antagonist like ranitidine or famotidine used in grouping with antacids promotes local delivery of these drugs to the receptor of parietal cell wall. Local delivery also increases the stomach cell wall receptor site bioavailability and increases efficacy of drugs to reduce acid secretion [7]. Therefore this attitude could be useful for humanizing systemic as well as local delivery of Ranitidine, which would efficiently reduced gastric acid secretion [8].

doi:10.5138/ijdd.2010.0975.0215.02024

In the current research on floating tablets of ranitidine HCL were prepared by effervescent approach using two different grades of methocel these are as follow :-

- Methocel K100 and
- Methocel K15M.

The aim of the work was to evaluate the effect of gel-forming polymer methocil on floating property and release individuality of ranitidine tablets.

Materials and methods

Materials

Ranitidine was received as a gift sample from Mundipharma Pvt. Ltd. Delhi, India Methocel K100 (100 cPs apparent viscosity as a 2% solution) and methocel K15M (15,000 cPs apparent viscosity as a 2% solution) were received as gift samples from Colorcon Asia Pvt. Ltd., Goa, India. Magnesium stearate and hydrochloric acid were received as a gift sample from Torrent Research Centre (Ahemdabad India), Sodium bicarbonate, citric acid anhydrous, Lactose and purified talc were receive as a gift sample from Aristo Pharma Pvt. Ltd. Bhopal, India, Polyvinyl pyrrolidone K-30 (PVP K-30) was procured from S.D. Fine-Chem., Ahmedabad, India. All other ingredients were of the laboratory grade.

Methods

Preparation of floating tablets of ranitidine

The concentration of different ingredients of Ranitidine floating tablets which was used, shown in table 1. The ingredients were weighed accurately and mixed thoroughly. Granulation of ranitidine were prepared with a solution of PVP K-30 in adequate amount of isopropyl alcohol as a solvent .The granules were pass through 40 mesh size sieve and then dried in conservative hot air oven at about 40-50 °C, after few time drying of the granules was stopped. The loss on drying (LOD) value of dried granules was obtained between ranging from 1.5 to 3.5 %, by help of moisture balance at 100 ± 05°C for 10 min.Then dried granules were again sized through 40-60 mesh and lubricated with magnesium stearate (0.8% w/w) and purified talc (0.8%w/w) and then compressed on a single punch tablet machine (Cadmach single press Choukase Lab. Indore, India). The tablets were round and flat in shape with an average diameter of 11.5 ± 0.2 mm and a thickness of 3.1 ± 0.2 mm size.

Table 1. Composition of floating tablets of ranitidine (B = batch number).

Ingredients (in mg per tablet)	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10
Ranitidine	120	120	120	120	120	120	120	120	120	120
Methocel K100						75	65	60	55	50
Methocel K15M	75	65	60	55	50					
Sodium bicarbonate	70	70	70	70	70	70	70	70	70	70
Citric acid	20	15	15	10	10	20	15	15	10	10
PVP K-30	40	40	40	40	40	40	40	40	40	40
Lactose	80	80	80	80	80	80	80	80	80	80

Evaluation of granules

Flow properties of granules

The flow properties of granules were evaluated in terms of angle of repose, Carr index and Hausner ratio. For determination of angle of repose (θ) the granules were poured through the walls of a funnel, which was set at a place such that its lower tip was at a height of closely 2.0 cm above from ground surface. The granules were poured up to the time when upper tip of the pile surface touched the lower tip of the funnel. The $\tan^{-1}$ of (height of the pile / radius of its base) give the

angle of repose. Granules were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess granules were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Hausner ratio (HR) and Carr index (IC) were calculated according to the two equations which are follows:-

$$HR = \rho b / \rho t$$

$$IC = \rho t - \rho b / \rho t$$

Evaluation of floating tablets

The prepared floating tablets were evaluated for uniformity of weight using 20 tablets hardness test, by using Monsanto tester, friability using 10 tablets by Roche type friabilator at 100 rpm for 4min , and completed drug content, in vitro buoyancy and in vitro dissolution studies. The in-vitro buoyancy was determined by floating lag time, per the method accordingly Rosa *et al.* [9] the tablets were placed in a 100 ml capacity beaker which contains 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 [10].

The release rate of ranitidine from floating tablets was determined using United States Pharmacopoeia (USP) Dissolution Testing Apparatus 2 paddle method; (Choukase laboratory Indore India). The dissolution test was performed using 900 ml of 0.1N hydrochloric 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 about 322 nm using UV/Vis. double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve (Figure 1).

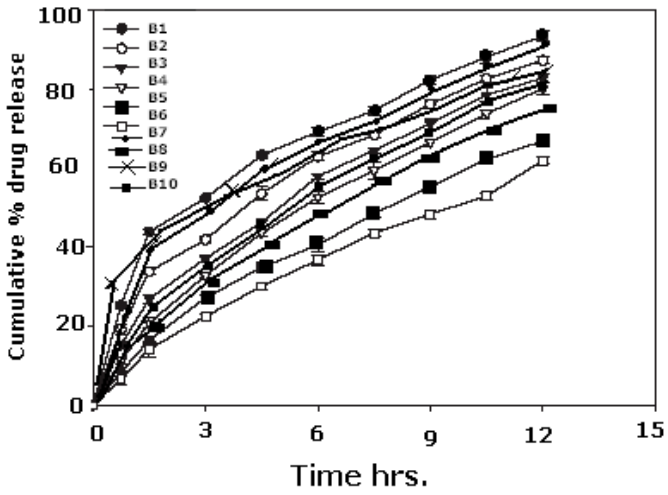

Figure 1. Dissolution profile of different batches of tablets.

Results and discussion

Granules

The granules prepared for compression of floating tablets were evaluated for their flow properties (Table 2). Angle of repose was in the range of 24.512 to 27.528 with granules containing methocel K100 and 29.653 to 24.840 with methocel K15M. Bulk density ranged between 0.561 to 0.582 gm/cm3 with granules containing methocel K100 and 0.593 to 0.624 gm/cm3 with methocel K15M. Tapped density ranged between 0.634 to 0.680 gm/cm3 with granules containing methocel K100 and 0.667 to 0.692 gm/cm3 with methocel K15M. Carr index was found to be ranged between 0.089 to 0.154 and Hausner ratio ranged from 1.098 to 1.182 for granules of different formulations. These values indicate that the prepared granules exhibited good flow properties.

Floating tablets

The floating tablets of Ranitidine HCL were prepared through effervescent technique by means of methocel (K100, K15M), sodium bicarbonate, citric acid and PVP K-30. The magnesium stearate was used as lubricant and talc was used as glidant. The results of the physicochemical characterization are given in table 3.

The weight of the tablet varied between 480.9 mg to 486.6 mg for different formulations with low standard deviation values, indicating uniformity of weight. The variation in weight was within the range of ±4.5

complying with pharmacopoeia specifications. The hardness for different formulations was found to be between 4.2. to 5.2 kg/cm2 indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content varied between 119.20 – 119.79 mg in different tablets indicating content uniformity in the prepared batches.

Table 2. Flow properties of granules.

Code	Angle of repose (θ)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Hausner ratio (HR)	Carr index (IC)
B1	27.528±0.2350	0.561±0.032	0.634±0.043	1.130	0.115
B 2	24.512±0.2900	0.567± 0.045	0.660 ±0.057	1.164	0.141
B 3	27.210±0.3520	0.574± 0.058	0.652±0.083	1.135	0.119
B 4	27.050±0.2520	0.582± 0.026	0.674±0.048	1.158	0.136
B 5	24.625±0.3740	0.575± 0.048	0.680±0.061	1.182	0.154
B 6	28.561±0.3800	0.624± 0.043	0.691±0.053	1.107	0.096
B 7	24.840±0.972	0.624± 0.043	0.667±0.063	1.098	0.089
B 8	29.653±0.784	0.605±0.086	0.682± 0.049	1.127	0.113
B 9	28.462±0.8500	0.611±0.048	0.679 ± 0.057	1.111	0.100
B 10	27.389±0.6740	0.593±0.053	0.692 ± 0.075	1.167	0.130

All the tablets were prepared by effervescent technique. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid).

Table 3. Various tests data of ranitidine tablets.

Code	Uniformity of weight (mg)	Friability (%)	Hardness (kg/cm2)	Drug content (mg)	Floating lag time (s)	Total floating time (h)
B1	484.2 ±0.19	0.59±0.02	4.2±0.21	39.85±0.15	33.25±1.96	10.26
B2	483.3 ±0.25	0.59±.08	3.9±0.22	39.60±0.25	54.21±1.56	9.25
B3	484.2 ±0.29	0.61±0.02	5.1±0.19	39.55±0.12	69.36±1.99	10.22
B4	480.9 ±0.47	0.59±0.09	4.6±0.23	39.48±0.13	33.88±1.55	12.8
B5	488.2 ±0.21	0.60±0.01	4.5±0.19	39.46±0.15	69.99±2.33	15.24
B6	482.9 ±0.81	0.53±0.71	4.3±0.17	39.52±0.12	68.5±2.8	12.06
B7	486.6 ±0.21	0.54±0.61	4.8±0.25	39.18±0.21	52.8±1.8	9.02
B8	484.2 ±0.36	0.56±0.32	4.7±0.24	39.49±0.20	65.25±2.95	10.08
B9	483.9 ±0.13	0.59±0.41	5.2±0.14	39.52±0.19	46.65±1.48	9.22
B10	488.2 ±0.11	0.61±0.01	4.6±0.19	39.46±0.15	69.79±2.37	16.24

The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore 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 (methocel), 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 shorter 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 tablets with low-viscosity grade methocel K100 exhibited short floating lag time and floated for longer duration as compared with formulations containing high viscosity.Grade methocel K15M. This indicated that the molecular weight distribution or viscosity of the gel-forming. Polymer methocel influenced the in vitro buoyancy.The pH of the stomach (1-3) is elevated under fed condition (~3.8), therefore citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate; more over citric acid has an stabilizing effect ranitidine formulation. The effect of two different grades of methocel in the tablet with varying proportion of citric acid and sodium bicarbonate was studied on the release characteristics.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. Formulations containing sodium bicarbonate and citric acid in ratio of 3:1 with varying amount of methocel were studied for their effect on release profile of ranitidine. It was observed that the release of ranitidine from such formulations increased on decreasing the proportion of methocel in the formulation but duration of floating decreased. The data obtained from in vitro dissolution studies and plot a graph time vs. % drug release.

Conclusion

The effervescent-based floating drug delivery system was a promising approach to achieve in vitro buoyancy. The addition of gel-forming polymer methocel with different grade and gas-generating agent such as sodium bicarbonate along with citric acid was essential to achieve *in vitro* buoyancy. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Acknowledgments

The authors thank to Mundipharma Pvt Ltd Delhi, India for a gift sample of Ranitidine, Colorcon Asia Pvt. Ltd., Goa, for gift sample of Polymers, and also thanks for Torrent Research Centre Aristo Pharma and Fine-Chem. Ltd for provide other chemical as gift samples.

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