Formulation and Evaluation of Buoyant Type of Gastro Retentive Dosage Forms of Ranolazine Tablets

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Abstract

The objective of present study was to Design Buoyant type of Gastro retentive dosage forms of Ranolazine. The biggest problem in oral drug delivery is low and erratic drug bioavailability. The ability of various polymers to retain the drug when used in different concentrations was investigated. Hydroxypropyl methylcellulose (HPMC K4M), HPMC K100 M, Xanthan Gum and Guar Gum were evaluated for their gel forming abilities. In this work sodium bicarbonate is used as gas generating agent, Citric acid as to provide acidic medium at elevated pH levels of fed stomach and Stearic acid as a release rate retardant material. *In vitro* drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow both the Higuchi and the Korsmeyer and Peppas equation. The drug release mechanism was found fickian type in most of the formulations.

Key words : *Ranolazine , Grdds*

INTRODUCTION

In recent years, oral dosage forms for gastric retention have drawn more and more attention for their theoretical advantage in permitting control over the time and site of drug release [1]. The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper small intestine until all the drug is completely released in the desired period of time [2]. Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems (GRDDS) [3]. The controlled gastric retention of solid dosage forms may be achieved by Mucoadhesion [4], Floatation [5], Sedimentation [6], Expansion [7], Modified shape system [8] and Simultaneous administration of pharmacological agents. Gastro retentive drug delivery system (GRDDS) has bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [9]. Gastric restroretentive drug delivery system (GRDDS) offers a number of benefits for drugs with poor bioavailability because of narrow absorption window in the upper part of the gastrointestinal tract such as riboflavin (10), ranitidine (11), nitrofurantoin, furosemide (12), and theophylline (13). Floating dosage forms are retained at the site of absorption, and the longer retention enhances the bioavailability. Floating systems can be developed by two approaches first is the effervescent system which needs a gas generating agent that may alkalinize the microenvironment of the stomach and whose buoyancy would be dependent on the gas generating agent unlike the second which is a non-effervescent approach. Excipients which generate CO_2 in the stomach produce effective buoyancy for more than 24 h. Fukuda et al. (14) investigated floating hot-melt extruded tablets for gastroretentive controlled drug release system. Wei et al. (15) and Xiaoqiang et al. (16) reported that floating tablets containing HPMC and sodium bicarbonate generated CO2 gas in simulated gastric fluid and rendered the tablets buoyant. The aim of the present investigation was to design and evaluate buoyant type of Gastro retentive dosage forms of Ranolazine using hydrophilic polymers like HPMC K4M, HPMC K100 M, Xanthan and Guar Gum.

MATERIALS AND METHODS

Materials

Ranolazine was generously gifted by Aarthi Drugs Ltd, Mumbai. HPMC (K100LV, K4M) were purchased from Colorcon Asia Pvt Ltd. Guar and Xanthan Gum were Purchased from Kawarlal Industries. Sodium Bicarbonate, Stearic Acid, Citric Acid Anhydrous, Magnesium stearate were purchased from S.D. Fine-Chemicals Ltd, Ahmedabad, India. All the other chemicals and reagents used were of analytical grade only.

Preparation of metformin floating tablets

Floating tablets of Ranolazine were prepared by wet granulation technique using Different concentrations of HPMC K100 M, HPMC K4 M, Xanthan and Guar gum. All the ingredients were passed through sieve no 60# and were mixed uniformly. The compositions of different excipients in formulations are listed in (Table. I). Granulation was carried out with sufficient quantity of binder solution (PVP K 30 - 5% in isopropyl alcohol). Wet mass was passed through sieve no 12# and dried at 45-55oc for 2 hr. Dried granules were sized by sieve no. 8# and required quantities of magnesium stearate and talc, were passed through the sieve no # 40 and blended with dried granules. The lubricated granules were compressed in Cadmach-16 Station Tablet Punching Machine by using 19.2 x 8.11 mm oblong flat tooling.

Evaluation of Floating tablets

The prepared floating tablets were evaluated for quality control tests like Floating lag time & Floating time, weight variation, hardness, friability and drug content uniformity.

(a) Floating lag time & Floating time

The time taken by the tablet to emerge on to the surface of the liquid (floating lag time) was determined by placing the tablets in a 100 ml beaker containing 0.1N HCl. The time up to which the tablets float constantly on the surface was determined as floating time[16].

(b) Thickness

The dimensions of the tablet like thickness, length were measured using vernier-calipers. Ten tablets were selected randomly for this test and the average value was reported.

(c) Hardness

Five tablets from each batch were selected at random and the hardness of each tablet was measured by Erweka tablet hardness tester. The mean values were given in Table 1.

(d) Friability

The friability test was carried out in Roche Friabilator. Twenty tablets from each batch were weighed (w_0) initially and put in a rotating drum. Then, they were subjected to 100 falls of 6 inches height. After the completion of rotations, the tablets were reweighed (W).The percentage loss in weight or friability was calculated.

(e) Estimation of drug content:

From each batch of prepared tablets, Ten tablets were collected randomly and powdered. A quantity of powder equivalent to 500 mg was transferred in to a 500 ml volumetric flask. 100 ml of 0.1N HCl was added and then the solution was subjected to sonication for about 30min. The solution was made up to 500ml with 0.1N HCl, filtered and suitable dilutions were prepared with 0.1N HCl. Same concentration of the standard solution was also prepared and the drug content was estimated by measure the absorbance of both standard and sample at 233nm by using UV-Visible spectrophotometer.

(f) In vitro Dissolution Studies

The *in vitro* drug release was carried out in triplicate at 37ºC ± 0.5 using USP XXII dissolution apparatus type II (paddle method) at a rotation speed of 100 rpm. Drug release from prepared tablet was studied in 900 ml of 0.1 N Hydrochloric acid for 0.5 – 10 hrs. Aliquots of sample (5ml) were withdrawn at regular intervals and analyzed at 233 nm using Double beam UV-visible spectrophotometer. Every time a fresh media (5ml) was replaced to maintain a constant volume. The solutions were then filtered by using 0.4 µ membrane filter and diluted to suitable concentrations and their absorbance were measured at 233 nm using Double beam UV-visible spectrophotometer.

Release kinetics:

The dissolution data are fitted to three popular release models such as zero order, first order, diffusion equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first order kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation.

Zero-order data is plotted as cumulative percentage drug released versus time.

$$Q = K_0 \, t$$

Where Q is the fraction of drug released at time 't',

K_0 = Zero order release rate constant.

First order is obtained by plotting log cumulative percentage drug released versus time.

$$\ln (1-Q) = - K_1 \, t$$

where Q = Fraction of drug released at time

K_1 = First order release rate constant

As per Higuchi's data is plotted as cumulative percentage drug released versus square root of the time.

$Q = K_2 \, t^{1/2}$

Where K_2 = release rate constant.

In vivo assessment of Gastro Retention:

The intragastric behaviors of floating tablets were performed on healthy human volunteers. These studies were done by incorporation of Barium Sulphate as a radiopaque material in the tablets and X – ray photography were taken at regular intervals, volunteers are allowed to take water [17,18].

RESULT AND DISCUSSION

The hardness of all formulations was found to be in the range of 2 – 9 kg/cm^2 with the friability values between 0.21 and 0.92. The drug content estimated in the prepared formulations was found to be ± 5% variation of the stated amount of Ranolazine (**Table 1**).

The % drug released from the formulation F1 containing 25 % of HPMC K4 M was 96.5% ± 0.9 within 8 hrs and from the formulations F2, F3, F4 (30%, 35%, 40% w/w of dose) were found to be 94.1% ± 1.5, 95.4% ± 1.8, 81.35% ± 0.8 respectively within 10 hrs. From the study conducted it was observed that as the polymer concentration increases, the drug release was decreased.

The initial burst release was due to the greater hydration at the tablet surface and effervescence of the tablet. But there after the drug release was sustained due to decreased effervescence.

In formulation F5 (Citric acid and Sodium bicarbonate in the ratio 1:9) the floating lag time was decreased up to 65 sec and the drug release was enhanced up to 98.21% ± 1.6 after 8 hours, when compared to other batches (F1, F2, F3, F4).

In formulation F6 (with Stearic acid) the drug release was about 84.7% ± 0.9 after 10 hours. The decreased drug release compared to other batches (F5 – 98.21% ± 1.6, F4 – 98.2% ± 1.6, F3 – 95.4% ± 1.87, F2 – 94.1% ± 1.5, F1 ± 96.5% ± 1.9) was due to the hydrophobic nature of the Stearic acid. Therefore Stearic acid acts as a release rate retardant. But at the same time the floating lag time was increased up to 160 sec.

Table: 1 Physical Properties of Floating Tablets of Various Formulations

FORMULATION	Evaluation parameters of Ranolazine floating tablets					
	Floating lag time (Sec)	Hardness (Kg/cm^2) (n=5)	Friability (%) (n=20)	Drug content (%) (n=3)	Thickness in mm (n=3)	Total Floating Time(hrs)
F1	180	8.1±0.22	0.38	95.26	5.49	>12
F2	280	7.5±0.19	0.34	98.94	5.75	>12
F3	310	6.9±0.24	0.42	97.32	5.81	>12
F4	360	7.2±0.40	0.38	96.54	5.92	>12
F5	65	8.9±0.16	0.24	98.77	5.52	<12
F6	160	7.5±0.24	0.62	95.56	5.80	>12
F7	45	8.5±0.34	0.64	96.21	5.21	<12 (2hrs)
F8	25	7.5±0.21	0.46	95.98	5.40	>12
F9	40	7.2±0.19	0.39	98.54	5.54	>12
F10	25	2.9±0.38	0.92	96.11	5.46	>12
F11	40	3.5±0.42	0.75	95.68	5.66	>12
F12	35	3.9±0.40	0.46	97.5	5.67	>12
F13	50	4.5±0.36	0.38	95.42	5.75	>12
F14	35	4.8±0.34	0.89	96.65	5.6	>12
F15	30	5.6±0.24	0.76	98.54	5.7	>12

Table: 2 Formulation Variables Used To Prepare Ranolazine Floating tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Ranolazine	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K4M	125	150	175	200	150	150	-	-	-	-	-	-	-	-	-
HPMCK100M	-	-	-	-	-	-	50	100	125	-	-	-	-	-	-
Xanthan Gum	-	-	-	-	-	-	-	-	-	100	125	150	175	-	-
Guar Gum	-	-	-	-	-	-	-	-	-	-	-	-	-	100	125
Sodium bi carbonate	125	125	125	125	90	90	75	100	100	100	100	100	100	100	100
Citric acid	-	-	-	-	10	10	-	-	-	-	-	-	-	-	-
Stearic acid	-	-	-	-	-	80	-	-	-	-	-	-	-	-	-
PVP K 30	30	30	30	30	30	30	25	25	25	30	30	30	30	60	60
Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium sterate	8	8	8	8	8	6	6	6	8	8	8	8	8	8	8
Talc	12	12	12	12	12	9	9	9	12	12	12	12	12	12	12

Formulations F7, F8, F9 were prepared with different rates of HPMC K100M. Formulation F7 showed less floating lag time of 45 sec but almost 97.4% ± 0.9 drug was released with in 2 hours. The reason might be polymer concentration was not sufficient enough to maintain the tablet integrity. Thus F7 batch failed to prolong the drug release up to 10 hr. Formulations F8 and F9 showed less floating lag time of 25, 40 sec and in vitro drug release of 98.4% ± 1.1, 96.2% ±1.2 in 10 hrs due to high amount of polymer.

In comparison of formulations HPMC K4M and HPMC K100M, the formulations containing 20% and 25% of HPMC K100M showed lesser floating lag time (25sec & 45sec) better drug release than HPMCK4M. It indicates that higher viscosity of the polymer maintain good floating properties (ref: Chein, Y.W., *et al*)

Formulations F10, F11, F12, and F13 were prepared with different ratio of Xanthan Gum. All the formulations showed less floating lag time much below 60 sec and the duration of floating was increased up to 12 hrs. But at the same time they failed to maintain sufficient hardness and the friability was also increased.

Formulations F14, F15 prepared with different ratios of Guar Gum showed less floating lag time 35, 30sec respectively. In F14 about 96.2% ± 1.1 was released with 8hrs. In case of F15 the drug release was 94.2% ± 0.62. The polymer concentration 25% was sufficient to maintain the drug release up to 10 hrs.

On the comparison of both formulations prepared with Xanthan Gum and Guar Gum, formulations with less amount of Guar Gum showed much better drug release compared to high amount of Xanthan Gum. This may be

due to the high viscosity of Guar Gum (3000 – 3500 for 1% w/v aqueous solution) than Xanthan Gum (1200 – 1600cps for 1% aqueous solution).

Scanning Electron Microscopy of the optimized floating tablet taken at different time intervals (0, 2,4,10 hrs), initially the surface of Fresh tablet did not show any pores, at 2, 4, 10 hours confirmed pore formation with increased diameter **(fig 1,2 &3)**.

This confirmed formation of gelling structure indicating the possibility of swelling of floating tablets.So the formation of swollen matrix and pores confirmed that drug was released by diffusion mechanism and this may be responsible for the continuous drug release from matrix tablets.

Floating time

Floating characteristics like lag time, total floating time for all the formulations were studied and found satisfactory **(fig. 4)**

***In vivo* assessment of Gastro Retention:**

In-vivo studies were conducted on healthy human volunteers to find the gastric residence time of the tablet. The studies were based on X-ray radiography. Images were taken at different time points to find the location of the tablet, changes in the tablet locations indicates tablet did not adhere to the gastric mucosa and the gastric residence time was 240± 30 min (n=4) (**Fig. 5**).
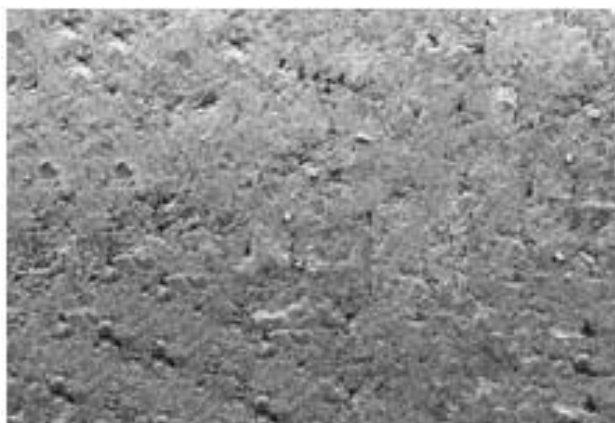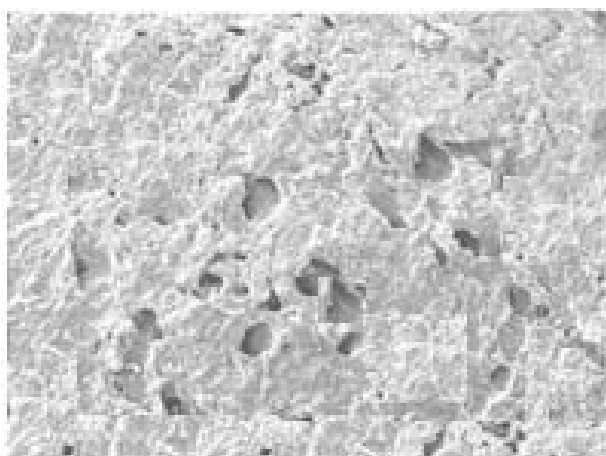

Fig. 3 SEM of swelled tablet after 4 hrs dissolution

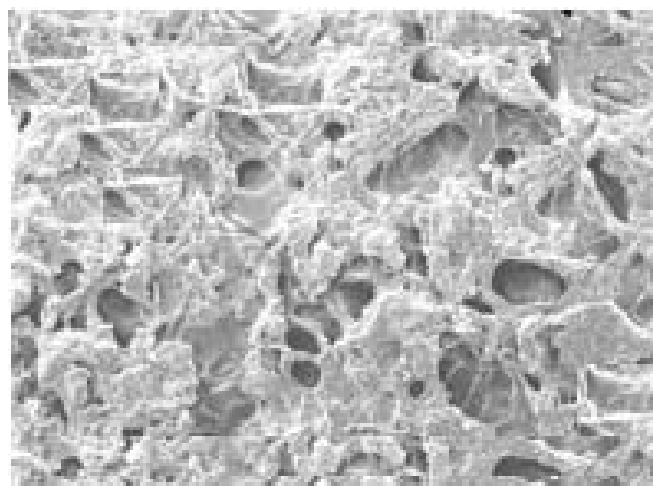**Fig. 1 SEM photo of fresh tablet surface**

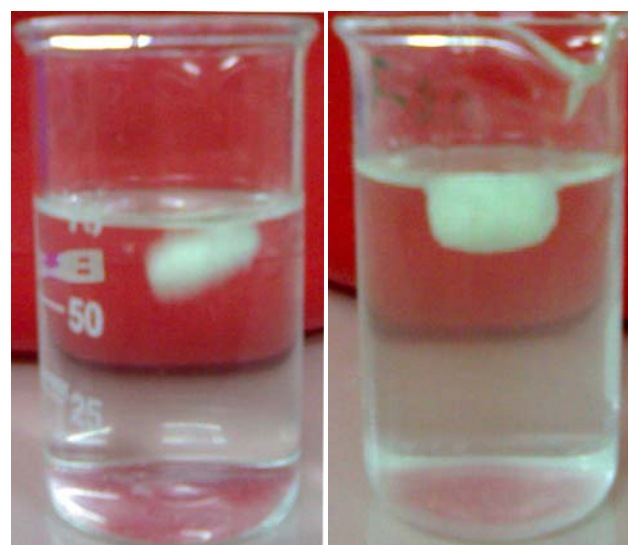**Fig. 2 SEM photo of swelled tablet after 2 hrs dissolution**
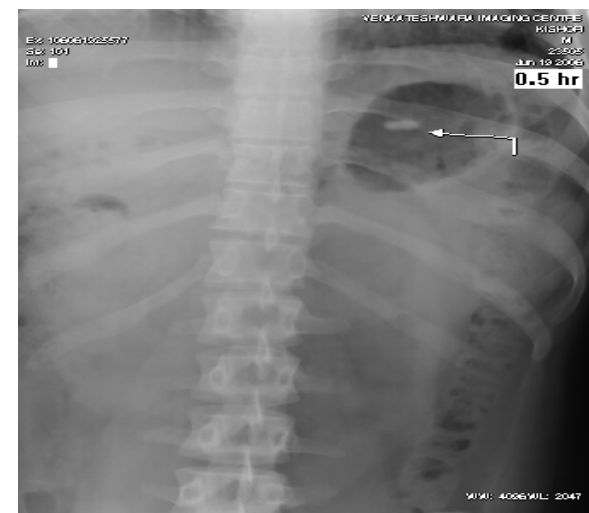

Fig. 4. Floating properties

Fig. 5. Radiographic pictures of tablets at different time periods

CONCLUSIONS

The GFDDS of Ranolazine prepared from all the 4 polymers were found to be of good quality, fulfilling all the official and other requirements. The effect of different formulation parameters such as concentration of effervescent agent and swellable polymer on floating properties and drug release kinetics were studied and formulations were optimized.

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