ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 9, Issue 6, 2016

Online - 2455-3891
Print - 0974-2441

Research Article

FORMULATION AND EVALUATION OF GASTRORETENTIVE TABLETS OF ANTIULCER DRUG

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Received: 16 December 2016, Revised and Accepted: 28 July 2016

ABSTRACT

Objectives: Lansoprazole is proton pump inhibitor intended for oral administration used as antiulcer agent. The objective of the present investigation was formulation and evaluation of gastroretentive floating tablets of lansoprazole for prolongation of gastric residence time with a view to deliver the drug at the sustained and controlled manner in the gastrointestinal tract.

Methods: The tablets of lansoprazole were prepared by direct compression method using gas generating agent and different polymer combinations such as hydroxypropyl methylcellulose and psyllium husk. The prepared tablets of lansoprazole were evaluated for hardness, thickness, friability, weight variation, drug content uniformity, buoyancy lag time, total floating time, swelling index, *in-vitro* dissolution study, etc.

Results: The varying concentration of gas generating agent and polymers was found to affect on *in-vitro* drug release, floating lag time, and swelling index. *In vitro* drug release of floating gastroretentive tablet of lansoprazole shown that the formulation F_2 was found to be the best formulation as it releases 97.9% lansoprazole in a controlled manner for an extended period of time (up to 12 hrs).

Conclusion: Prepared floating tablets of lansoprazole may prove to be a potential candidate for safe and effective controlled drug delivery over an extended period of time for gastroretentive drug delivery system.

Keywords: Lansoprazole, Gastroretentive, Floating tablet, Total floating time.

 DOI: http://dx.doi.org/10.22159/ajpcr.2016.v9i6.10360

INTRODUCTION

The oral route is the most convenient route for administering different protein, drugs, and bioactive agents. The gastroretentive drug delivery systems (GTDDS) can assist in improving the oral bioavailability of various pharmaceutical drugs that have an absorption window in a particular region of gastrointestinal (GI) tract [1]. The design of new oral controlled drug delivery system should be aimed toward achieving maximum pharmacological action of the drugs on targeted site. However, the development process uses to encounter several physiological difficulties such as inability to restrain and localize the DDS with desirable regions of GI tract and large variation in the gastric emptying process [2].

This variability, in turn, may lead unpredictable bioavailability and times to achieve peak plasma levels since the majority of the drugs are absorbed in the upper part of small intestine. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa [3]. Thus, small intestinal transit time is an important criterion for drugs that are incompletely absorbed. Among the various approaches, the floating DDS offer the most convenient and effective; approach to achieve increased gastric residence time and sustained drug release compared to the other methods. Based on the mechanism of buoyancy, non-effervescent and effervescent technologies have been utilized in the development of floating DDS (FDDS). Non-effervescent systems commonly use gel-forming or highly swellable cellulose type hydrocolloids. Effervescent systems utilize swellable polymers and inclusion of gas generating agents, sodium bicarbonate, and citric or tartaric acid. Lansoprazole is a proton pump inhibitor intended for oral administration used in the treatment of ulcers, *Helicobacter pylori* infection, gastroesophageal reflux disease, etc. Floating GTDDS is suitable for lansoprazole drug because of most common ulcers form in the lining of stomach, and or just below the stomach. Floating gastroretentive tablets of lansoprazole were prepared with an objective to increases the bioavailability and site specific and local therapy for the ulcers [4].

METHODS

Materials

Hydroxypropyl methylcellulose (HPMC K4M, HPMC K100M) was procured from Meditab Specialities Pvt. Ltd., Satara. Psyllium husk was procured from Raptakos Brett and Co. Ltd., Mumbai. Lactose was procured from Okasa Pharma Pvt. Ltd., Satara. Sodium bicarbonate, PVP K-30, Magnesium stearate, Talc were purchased from Loba Chemie, Mumbai. Lansoprazole was received as a kind gift from Cipla Pvt. Ltd., Kurkumbh.

Formulation development

Preparation of matrix tablets

The matrix tablet contains a uniform mixture of drug, polymer and other excipients including the gas-generating agent. The tablets were prepared by direct compression method. Weighed quantities of ingredients given in Table 1. All ingredients were accurately weighed and except lansoprazole, all ingredients were passed through sieve (60#). First, lansoprazole and swelling polymers are mixed by trituration in mortar for 10 minutes to form uniform powder. Then, PVP K-30 and sodium bicarbonate were added to ensure the uniform mixing. Then, lactose, magnesium stearate, and talc were added and mix for 10 minutes. Powder blend was compressed into tablet using 8 station tablet punching machine with 9 mm punch.

Characterization

Evaluation of granules

Flow properties of granules

The flow properties of granules (before compression) were characterized in terms of angle of repose, Carr's index, and Hausner's ratio. For determination of angle of repose (θ), the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of funnel. The tan-1 of (height of the pile/radius of its base) provided the angle of repose. Bulk density,

Table 1: Formulation of matrix tablets

Ingredients	Formulation code (quantities in mg)									
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Lansoprazole	30	30	30	30	30	30	30	30	30	30
HPMC K4M	100	100	-	-	75	75	25	25	50	50
HPMC K100M	-	-	100	100	25	25	75	75	50	50
Psyllium husk	30	30	30	30	30	30	30	30	30	30
Sodium bicarbonate	60	40	60	40	60	40	60	40	60	40
PVP K-30	20	20	20	20	20	20	20	20	20	20
Lactose	55	75	55	75	55	75	55	75	55	75
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2
Total weight	300	300	300	300	300	300	300	300	300	300

HPMC: Hydroxypropyl methylcellulose

tapped density, Carr's index, and Hausner's ratio were calculated using tap density apparatus [5-7].

Evaluation of tablets

Diameter and thickness

The diameter and thickness of tablet were measured by using a vernier caliper. It is expressed in mm. Three tablets were selected at random from each batch and the mean, standard deviation values were calculated [8].

Hardness test

Hardness or tablet crushing strength (the force required to break a tablet in a diametric compression) was measured using a Monsanto tester. The test was performed on three tablets from each formulation, and the average reading was noted. The mean ± standard deviation values of hardness were calculated [9].

Friability test

Friability test is performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. Friability of tablets was determined using a friabilator (B.R. Instruments). Ten preweighed tablets were placed in the friabilator, operated for 4 minutes at 25 rpm. After 100 revolutions, the tablets were taken out, dedusted and reweighed. The percentage friability of tablets was measured as per the following formula [10].

% friability = (Initial weight-final weight)/(initial weight) ×100

Weight variation test

It is desirable that every individual tablet in a batch should be uniform in weight, but a small variation in the weight of the individual tablet is liable to occur. Therefore, a little variation is allowed in the weight of tablet by the pharmacopoeia. The following percentage deviation in weight variation is allowed. To study weight variation, 20 tablets of each batch were weighed using an analytical electronic balance and mean weight was calculated. Not more than 2 tablets should deviate from the average weight of the tablets [11] (Table 1).

***In vitro* buoyancy or floating studies**

In vitro buoyancy was determined by the measurement of floating lag time (FLT) and total floating time (TFT). Tablet was placed in a 100 ml beaker containing 0.1 N. HCL. Time required for tablet to rise on the surface of medium and float was determined as "FLT." It is expressed in seconds or minutes. The duration of time by which tablet constantly emerges on the surface of medium was determined as the "TFT." It is expressed in hrs [12-14].

Swelling studies

The swelling properties were determined by placing the tablet in the dissolution test apparatus, in 900 ml of 0.1 N HCL at 0 37±0.5°C rotated at 50 rpm. The tablets were removed after 12 hrs from dissolution medium, blotted to remove excess water, and weighed. Swelling characteristics of tablets were expressed in terms of percentage water uptake (% WU). Water uptake or swelling index of tablets was calculated using the following formula [15,16].

Table 2: Relation between average tablet weight and % deviation allowed as per IP

Average tablet weight	deviation allowed %
80 mg or less	10
More than 80 mg but<250 mg	7.5
250 mg or more	5

% WU = Weight of swollen tablet-initial weight of tablet/initial weight of tablet ×100

***In vitro* dissolution studies**

In vitro dissolution study was performed in USP dissolution apparatus Type II, in 900 ml 0.1 N HCL (pH 1.2), maintained at 37±0.5°C at a speed of 50 rpm. At suitable time intervals, aliquots (5 ml) were withdrawn and immediately replaced with equal volume of fresh dissolution medium to maintain a constant volume for drug dissolution. The samples were filtered through a 0.45 µ membrane filter and diluted to a suitable concentration with 0.1 N HCL. The absorbance of these solutions was measured at 285 nm using a ultraviolet spectrophotometer (Dynamica Halo DB - 20). Cumulative percentage drug release was calculated using an equation obtained from a standard calibration curve [17-20].

Drug release kinetic study of optimized formulation

Drug release kinetics was obtained by applying the release data to various models such as zero order, first order, Higuchi matrix, Hixson Crowell, and Korsmeyer-Peppas model. Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The three parameters were used to study the release mechanism, i.e., release rate constant (k), correlation coefficient (R), and release exponent (n) and determine the best fit model for optimized formulation [21].

RESULT AND DISCUSSION

Flow properties of granules

Flowability of granules was found to be good as indicated by compressibility flowability correlation data. Granule characterization value was given in Table 3. All these values indicate that the prepared granules exhibited good flow properties.

Diameter and thickness

Diameter and thickness of tablets of all batches were observed in between 9.05-9.09 mm and 4.36-4.49 mm, respectively. Results were given in Table 4.

Hardness test

The hardness of all the tablets was found to be in the range of 4.06 kg/cm^2-4.8 kg/cm^2. Results were given in Table 4.

Friability test

Friability was found to be <1% indicating good mechanical resistance. Results were given in Table 4.

Weight variation test

The average weight of the prepared tablets was found to be in the range of 297.8-299.4 mg. Results were given in Table 4.

***In vitro* buoyancy or floating studies**

The results of FLT and TFT are shown in Table 5. FLT of odd batches was found to be less as compared to even batches. A higher proportion of sodium bicarbonate shows the less FLT as well as lesser proportion of sodium bicarbonate shows the high FLT. FLT of all formulations was found to be in the range of 10-29.66 minutes. TFT of all the formulations were found to be >12 hrs. Photographs of *in vitro* buoyancy study of optimized formulation F_2 as shown in Fig. 1.

Swelling studies

Results of swelling index profile are shown in Table 6. Swelling index of all formulations is varied in between 138.46% and 220.73%. Swelling index of the formulation is depends on the type of polymers and amount of polymers used in that formulation.

Table 3: Characterization of granules

Formulation code	Angle of repose*(θ)	Bulk density*(gm/ml)	Tapped density*(gm/ml)	Carr's index*(%)	Hausner's ratio*
F_1	22.12±0.28	0.429±0.020	0.500±0.028	14.20±0.81	1.16±0.01
F_2	23.58±0.55	0.426±0.019	0.505±0.027	15.47±0.90	1.18±0.017
F_3	21.96±0.28	0.429±0.020	0.502±0.025	14.58±0.29	1.16±0.005
F_4	22.61±0.56	0.425±0.021	0.506±0.025	15.93±0.11	1.18±0.005
F_5	22.61±0.56	0.410±0.001	0.474±0.002	13.54±0.79	1.15±0.01
F_6	23.58±0.55	0.405±0.003	0.479±0.001	15.30±0.76	1.17±0.011
F_7	22.61±0.56	0.43±0.019	0.500±0.028	13.76±0.78	1.15±0.015
F_8	22.93±0.56	0.424±0.022	0.505±0.027	15.89±0.18	1.18±0.005
F_9	22.77±0.84	0.423±0.022	0.493±0.030	13.77±0.79	1.15±0.015
F_{10}	23.58±0.55	0.418±0.024	0.497±0.030	15.82±0.14	1.18±0.005

*All values are expressed in mean±standard deviation, n=3

Table 4: Evaluation of tablets

Formulation code	Diameter* (mm)	Thickness* (mm)	Hardness* (Kg/cm^2)	% friability (%)	Weight variation *(mg)
F_1	9.09±0.020	4.37±0.015	4.06±0.11	0.67	299.4±0.2
F_2	9.05±0.025	4.43±0.032	4.6±0.11	0.59	298.3±0.25
F_3	9.07±0.011	4.40±0.011	4.1±0.28	0.68	299.1±0.15
F_4	9.08±0.01	4.44±0.023	4.8±0.17	0.60	298.9±0.1
F_5	9.07±0.015	4.38±0.01	4.06±0.11	0.65	298.7±0.15
F_6	9.06±0.02	4.44±0.045	4.6±0.11	0.60	297.8±0.15
F_7	9.06±0.005	4.36±0.023	4.3±0.26	0.69	298±0.1
F_8	9.09±0.01	4.48±0.015	4.6±0.11	0.57	298.7±0.15
F_9	9.08±0.026	4.39±0.026	4.06±0.11	0.68	298.2±0.15
F_{10}	9.07±0.020	4.49±0.025	4.6±0.11	0.61	298.9±0.1

*All values are expressed in mean±standard deviation, n=3

Table 5: Buoyancy or floating lag time and total floating time

Formulation code	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
FLT (Seconds)*	10±1.73	13.66±1.52	15.33±0.57	29.66±1.15	10±1	14.33±0.57	22.33±0.57	26.33±0.57	12.33±0.57	24.66±1.15
TFT (hrs)	>12	>12	>12	>12	>12	>12	>12	>12	>12	>12

*All values are expressed in mean±standard deviation, n=3. FLT: Floating lag time

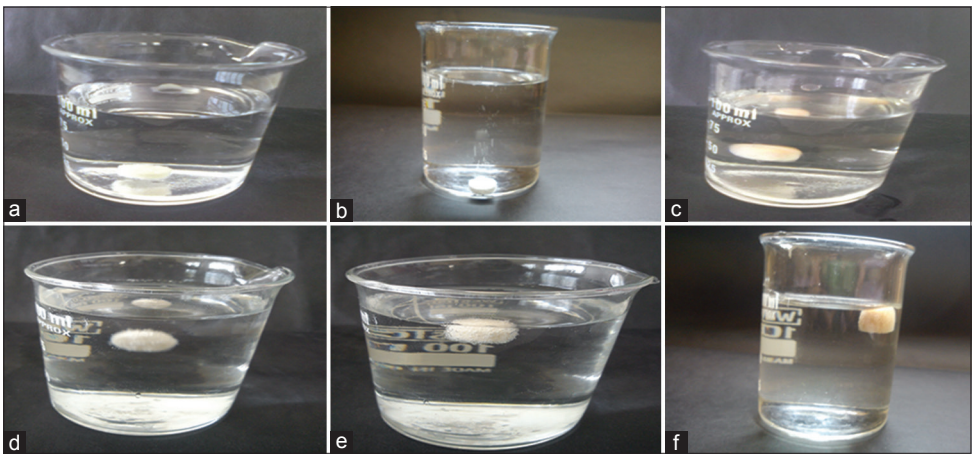

Fig. 1: Photographs of *in vitro* buoyancy study of optimized formulation F_2. (a) At initial time, (b) after 3 seconds, (c) after 6 seconds, (d) after 10 seconds, (e) after 13 seconds, (f) after 12 hrs

Table 6: Swelling index

Formulation code	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Swelling index (after 12 hrs) (%)	146.4	181.27	147.98	212.37	138.46	185.90	145.30	220.73	150.33	195.30

Table 7: *In vitro* drug release of F_1-F_{10} formulation

Time (after12 hrs)	% cumulative drug release									
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
	91.36	97.9	90.9	94.23	80.03	84.46	79.9	83.26	87.16	90.93

Table 8: Release kinetics of optimized formulation (F_2)

Model	Zero order	First order	Higuchi matrix	Hixson crowell	Korsmeyer-peppas	Best fit model
k	8.6694	−0.2220	24.7498	−0.0495	11.1448	Korsmeyer-peppas model
R	0.9955	0.8512	0.9505	0.9539	0.9994	
n	-	-	-	-	0.8864	

All formulations containing the psyllium husk as natural polymers in same proportions and HPMC K4M, HPMC K100M used in the different formulations in different proportions. Depend on these proportions swelling profile of formulation is changed. Formulation containing psyllium husk and higher proportion of HPMC K100M shows the higher swelling index as compared to formulations containing psyllium husk and HPMC K4M, HPMC K100M shows good swelling property than HPMC K4M.

***In vitro* dissolution studies**

The data obtained from *in vitro* release for formulations are tabulated in Table 7. As compared to other batches, batches containing a higher proportion of HPMC K4M with less proportion of sodium bicarbonate show maximum release. The comparison of drug release profile of all formulations, formulations F_2 which contains psyllium husk and more amount of HPMC K4M with less amount of sodium bicarbonate showed maximum drug release. The maximum *in vitro* drug release shown by F2 formulation.

Drug release kinetic study of optimized formulation

The three parameters were used to study the release mechanism, i.e., k, R, and n. Release rate constant, correlation coefficient, and release exponent of batch F_2 for these models are reported in Table 8.

The n value of the Korsmeyer-peppas model for F_2 formulations was found to be 0.8864 indicating non-fickian diffusion principle. The model that best fits the release data were selected based on the correlation coefficient 'R' value in various models. The model that gave the high 'R' value was considered as the best fit of the release data. From the result, best fit model for optimized F_2 formulation is Korsmeyer-peppas model.

CONCLUSION

Sodium bicarbonate mainly affects on FLT, FLT was decreased by increasing the concentration of sodium bicarbonate as well as FLT was increased by decreasing the concentration of sodium bicarbonate. The formulation containing less concentration of sodium bicarbonate they show the better drug release. Higher concentration of HPMC K100M as compared to HPMC K4M, and psyllium husk they shown the high swelling index. HPMC K100M shows the higher swelling properly than HPMC K4M. Natural polymer psyllium husk also helpful for swelling, they increase the residence time in the stomach, which eventually improves the extent of bioavailability. *In vitro* drug release of floating gastroretentive tablet of lansoprazole shown that the formulation F_2 was found to be the best formulation as it release 97.9% lansoprazole in a controlled manner with constant fashion over extended period of time (up to 12 hrs).

Hence, finally, it was concluded that the prepared floating gastroretentive tablet of lansoprazole may prove to be potential candidate for safe and effective controlled drug delivery over an extended period of time for GDDS.

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