Journal of Pharmaceutical Research Vol. 14, No. 4, October - December 2015 : 94-97

FORMULATION APPROACH TO IMPROVE THE GASTRIC RESIDENCE TIME OF BISOPROLOL FUMARATE BY GASTRO-RETENTIVE TABLETS

Ankit A, Mohammed Gulzar Ahmed*, Vinay C H and Sanjana A
Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, B. G. Nagar, Karnataka - 571 448. India.

Received on: 16.11.2015 Revised: 28.12.2015 Accepted: 30.12.2015

ABSTRACT

Purpose: Gastric retentive drug delivery devices can be used for controlled drug delivery systems containing drugs, which are degraded in the colon. The main objective of the present study is to design and formulate gastric retentive controlled release dosage form of bisoprolol fumarate in order to improve the gastric residence time, which in turn increases its bioavailability. **Approach:** Floating dosage form of bisoprolol fumarate was prepared by direct compression method using different concentration and grades of hydroxypropyl methylcellulose and sodium bicarbonate. Prepared powder mixtures and tablets were subjected to various pre-compression and post-compression evaluations respectively. **Findings:** Powder mixture showed good flow properties for uniform die filling. The SEM analysis showed minimum number of pores and erosion on the surface of the tablet. The optimized formulation F8 gave floating lag time less than 3 min with a floating time of 12 h, and an *in vitro* release profile very near to the desired release. The prepared dosage form reported to follow the zero order release and non-Fickian mechanism. Best formulations were subjected to accelerated stability studies. The assay results showed that the drug was stable for 3 months without any change in the drug content. **Conclusion**: Finally it can be concluded that the gastric retentive time of bisoprolol can be increased by formulating it in a floating dosage form.

Key words: *Bisoprolol fumarate; buoyancy time; drug release; SEM; Stability study.*

INTRODUCTION

Oral route of drug administration is one of the most convenient, easy and preferred means of drug delivery to the systemic circulation. This method is widely accepted due to its ease of administration and patient acceptance. An ideal drug delivery system is that which possesses two main properties i.e., *spatial placement* (drug targeting) and *temporal delivery* (release control).[1] Many researches has been attempted to fill these two requirements but unfortunately none of the developed methods are able to fulfil all the necessities that an ideal drug delivery system requires. This led to the development of systems such as sustained and controlled release drug delivery systems. These systems are primarily concerned with patient safety, compliance and convenient like frequent dosing and improved efficacy and safety of the drug.[2]

Drug delivery devices like sustained and controlled release formulations are having a number of advantages; they even suffer from a few drawbacks. These dosage forms pass through the small intestine, where most of the drug absorption takes place in less than 12 h. For the drugs, which are absorbed in stomach or get degraded in the colon, the sustained release and controlled release dosage form may not be suitable or the desired therapeutic effect may not be achieved.[3] So, several approaches have been tried out to form a suitable dosage form for above said conditions. The modulation of gastrointestinal transit time of the drug is a novel approach and can be achieved by formulating drug molecules into a gastric retentive drug delivery devices or systems.[4]

Gastric retentive dosage forms are primarily controlled release systems, which get retained in the stomach for longer duration, thus provide effective absorption of drug for the intended period of time.[5] These types of delivery devices can be useful for the spatial and temporal delivery of many drugs, like drugs that act locally in the stomach (antacids), drugs that are absorbed primarily in the stomach (albuterol), drugs that are poorly soluble in alkaline pH, drugs that have a narrow window for absorption (riboflavin, levodopa, P-amino benzoic acid), drugs that are absorbed rapidly from the GI tract (amoxicillin), drugs that degrade in colon (metoprolol, bisoprolol).

These types of retention systems are important for those drug molecules which are unstable in intestine or act locally in the stomach (certain enzymes and antacids). For drugs with poor solubility in intestine pH, gastric retention may increase solubility before they are emptied from the GI tract, resulting in the improved bioavailability.[6,7]

In this modern era, hypertension has become one of the major complications, which might be due to change in life style of the people and its timely treatment decreases morbidity and prolongs life expectancy. Beta blockers are the major class of antihypertensive drugs and used to treat hypertensive patients. Bisoprolol is one of the cardioselective beta blockers used in the management of hypertension. Bisoprolol is chemically 1-[4-[[2-(1-Methylethoxy) ethoxy]-methyl]-3-[(1-methylethyl) amino]-2-propanol.[8] The daily dose of bisoprolol is 5 to 10 mg. The maintenance of a constant plasma level of a cardiovascular drug is important for the

*Correspondence : email : mohammedgulzar1@gmail.com

desired therapeutic response. Since the half-life of the bisoprolol is about 3-4 h, multiple doses need to be taken in order to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance. Controlled release dosage forms of bisoprolol will help in the above said conditions. Since bisoprolol is reported to be degraded in the colon, where a gastric retentive drug gets absorbed and provides good therapeutic response.[9,10]

The present study was aimed to formulate gastro retentive drug delivery system of bisoprolol using various polymers, which would remain in the stomach for prolonged period of time with a view to maximize duration and bioavailability of the drug.

MATERIALS AND METHODS

Materials

Bisoprolol was procured from Yarrow Chem Products, India. HPMC 4,000 cps and HPMC 10,000 c.p.s were procured from Techno Scientific Products, Mumbai, India. All other reagents/chemicals used were of analytical grade.

Preparation of bisoprolol gastro-retentive tablets

Bisoprolol gastro-retentive controlled released tablets were prepared by direct compression method. All the ingredients were passed through sieves (80-mesh) separately and weighed as per the formula given in Table 1. Weighed ingredients were transferred into agitator mixture (Shakti multi attachment instrument) and mixed for about 15 m. After mixing thoroughly, the powder mixture was subjected to direct compression using (Lab press) punching machine. The powder was evaluated for various pre-compression parameters like bulk volume, tapped volume, bulk density, tapped density and angle of repose. After compression they were evaluated for weight variation, thickness, hardness, friability, duration of buoyancy, content uniformity, drug release, release kinetic and stability study.[11]

Table 1: *Formulation design of bisoprolol gastro-retentive tablets*

Ingredients	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Bisoprolol Fumarate	10	10	10	10	10	10	10	10
HPMC 4,000 cps	10	20	30	40	-	-	-	-
HPMC 10,000 cps	-	-	-	-	10	20	30	40
Sodium bicarbonate	10	10	10	10	10	10	10	10
Magnesium Stearate	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2
Lactose	qs	qs	qs	qs	qs	qs	qs	qs
Total Weight	120	120	120	120	120	120	120	120

*All quantities are in milligrams

Drug content estimation

The assay for drug content was carried out according to I.P. 1996. Twenty tablets from each batches were weighed and triturated using mortar and pestle. Powder mixture equivalent to 20 mg of bisoprolol fumarate was taken and transferred to 100 ml of volumetric flask and dissolved it in 100 ml buffer solution. Vigorous shaking was done to dissolve the powdered material in buffer solution. Samples were filtered using Whatmann filter paper. After proper dilution, the drug content was determined at 222nm using UV spectrophotometer (Shimadzu UV 1800).[11]

Buoyancy properties

In order to determine the duration of the buoyancy, 100 ml of simulated gastric fluid (pH 1.2) was taken into the beaker and tablet was placed into it. Buoyancy lag time and duration was measured by visual observation. Buoyancy lag time: The time taken by tablet to float on the surface of liquid medium was determined as floating lag time. Buoyancy time: Time duration in which tablet remained floating was determined as floating duration time.[12]

Scanning electron microscopy (SEM)

SEM analysis was conducted for optimized formulation only. Sample was coated with a thin gold layer by sputter coater unit (SPI, Sputter, USA). Then, the SEM photographs were taken by a scanning electron microscope (Scanning electron microscope EVO-18) operated at an accelerated voltage of 15kV.

Dissolution study

The *in vitro* drug release study was conducted using the USP-II (Paddle) dissolution apparatus (Lab India) at 50 rpm. The dissolution medium consisted of 900ml of simulated gastric fluid (without enzyme; pH 1.2). Due to inherent buoyancy of the system, sinkers were used, so that a perfect sink condition can be maintained at 37±0.5°C. An aliquot (5ml) was withdrawn at specific time interval. The samples withdrawn were analysed for the amount of drug release by UV- spectrophotometer at 222 nm.[10]

Release kinetic study

Further to analyse the mechanism of release and release rate kinetics of the dosage form, the data obtain25ºC/60% and 40ºC/75% RH ed from release studies were fitted into zero order, first order, Higuchi and Korsmeyer and Peppas release model. The data for regression analysis were obtained using MS-Excel 2010 statistical function.[12]

Stability studies

Whenever a new formulation is developed, it is mandatory to check the stability. Hence, to confirm the stability, the best formulation was subjected to stability studies at 25°C ±2°C/60% RH ± 5% and 40°C ± 2°C/75% RH ± 5% RH for the period of 3 months.[13]

RESULT AND DISCUSSION

Pre-compression

A flow property of the powder mixture was determined by angle of repose and Carr's compressibility index. Angle of repose was determined by funnel method and results obtained in the range of 23.96° to 16.93°. Bulk density and tapped density were determined by bulk density apparatus (Micro measures and instruments). The powder mixture showed bulk density and tapped density in the range of 0.286±0.101 to 0.439±0.107 and 0.338±0.091 to 0.5144±0.072 respectively. Compressibility index was found in the range of 11.69±0.034 to 20.14±0.099. Pre-compression

evaluation confirms powder mixture possesses good free flowing properties. The data were dissipated in Table 2.

Table 2: *Pre-compression evaluation results*

Batch	Bulk density G/CC	Tapped density G/CC	Compressibility index%	Angle of Repose (°)
F1	0.31±0.094	0.408±0.120	14.64±0.03	20.96±0.04
F2	0.286±0.101	0.341±0.034	12.14±0.094	17.64±0.067
F3	0.338±0.074	0.392±0.069	17.89±0.065	16.93±0.051
F4	0.294±0.089	0.338±0.091	16.72±0.074	18.14±0.079
F5	0.309±0.093	0.416±0.113	14.51±0.093	21.04±0.084
F6	0.414±0.112	0.495±0.108	11.69±0.034	20.19±0.099
F7	0.439±0.107	0.5144±0.07	219.47±0.10	717.59±0.021
F8	0.326±0.099	0.396±0.074	20.14±0.099	23.96±0.044

Post-compression

Results of post compression parameters were dissipated in **Table 3**.

Weight variation

The weight of tablets was found in the range of 119.5 mg to 121.4 mg. Hence all the tablet formulations were within standard limit i.e. ±5% deviation. Lowest deviation in weight variation was due to good flow properties of powder mixture.

Hardness

The hardness of prepared tablets was measured by Monsanto hardness tester. Hardness of bisoprolol gastro-retentive tablets ranged between 5.4±0.17 kg/cm^2 and 5.9±0.7 kg/cm^2, hence suitable for handling and packaging.

Friability

Roche friabilator was used to test the friability of prepared gastro-retentive tablets.

The value of friability was found in the range of 0.299% to 0.872%. Friability results showed tablet possess enough resistance to with stand the mechanical shock and abrasion during handling and transportation.

Drug content

The percentage drug content of formulation F1 to F8 was found in the range of 94.21-98.33%. This showed that mixing was proper and drug was uniformly distributed throughout the powder mixture.

Table 3: *Post-compression parameters*

Batch	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	119.5±0.04	5.5±0.07	0.872±0.14	94.21±0.069
F2	120.6±0.074	5.0±0.143	0.461±0.079	97.09±0.014
F3	119.4±0.084	5.4±0.074	0.341±0.096	95.08±0.056
F4	121.1±0.104	5.9±0.007	0.286±0.0074	98.07±0.074
F5	120.8±0.096	5.1±0.139	0.490±0.0014	96.48±0.089
F6	119.2±0.034	5.4±0.079	0.578±0.0019	94.57±0.015
F7	121.4±0.02	5.6±0.094	0.699±0.034	98.33±0.045
F8	119.1±0.067	5.1±0.047	0.299±0.14	95.94±0.036

Buoyancy properties:

Prepared tablets were tested for their buoyancy properties like buoyancy lag time and total buoyancy time. All the formulations were floated within 3 m, minimum floating time for these formulations might be due to presence of sodium bicarbonate, sodium bicarbonate in the acidic environment produces carbon dioxide. The evolved gas will get entrapped in the matrix leading to floating of the tablet. Total floating time was greater than 10 h except for formulations F1, F2, F5 and F6. It was observed that buoyancy time increased on increasing the concentration of release retardant polymer. Results of buoyancy test are shown in Table 4.

Table 4: *Buoyancy lag time and duration*

Formulations	Buoyancy lag time (s)	Duration of buoyancy (h)
F1	100.66	2.33 ± 0.035
F2	128.16	3.44 ± 0.027
F3	135.59	11.35 ± 0.039
F4	168.21	12.47 ± 0.039
F5	96.96	3.31 ± 0.076
F6	125.10	4.33 ± 0.248
F7	139.72	11.58 ± 0.443
F8	175.48	12.167 ± 0.303

Scanning electron microscopy:

Figure 1 presents SEM photograph of gastro-retentive tablets. The SEM images of prepared tablets showed minimum number of pores on the surface of the tablet. Erosion of the polymer was observed in the photograph which might be presence of gas generating agent i.e. sodium bicarbonate. The drug release occurred by both erosion and formation of pores on the surface of the gastro-retentive tablets.

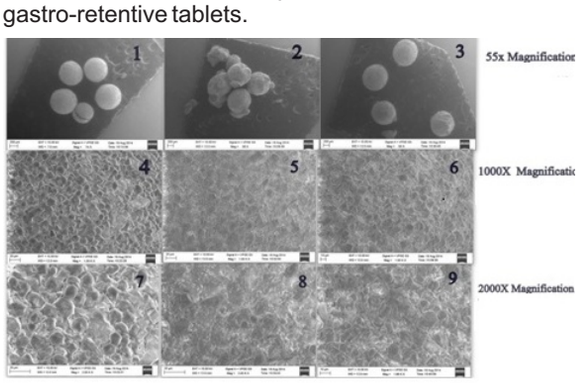

Fig. 1: *SEM image of bisoprolol gastro-retentive tablet containing HPMC 10,000 cps and sodium bicarbonate in 4:1 ratio (formulation F8)*

***In vitro* release study:**

USP type-II dissolution test apparatus was used for the determination of bisoprolol release from the prepared tablets and experiment was performed for 8 hr. The formulation containing HPMC 4000 cps showed early release compared to HPMC 10000 cps. Dissolution result also suggested that drug release was concentration dependent; when the concentration of polymer was increased the release rate was decrease. Formulation F1 (98.52%) and F5 98.12%) contains lowest concentration of release retardant showed almost all drug release within 5 hrs. Among all formulation, formulae F8 containing 4:1 ratio of HPMC 10000 cps and sodium bicarbonate showed highest percentage of drug release rate (98.77%) at the end of 8 h. The comparison of drug release of formulation F1-F8 is shown in fig. 2.

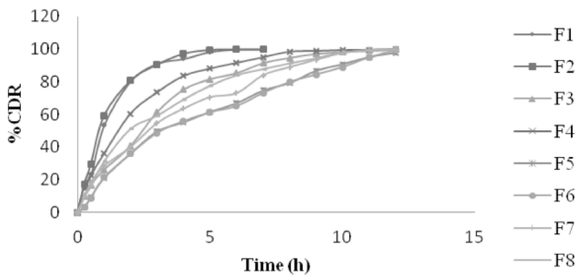

Fig. 2: *Dissolution study of bisoprolol in simulated gastric fluid*

Release kinetics studies:

In order to determine release kinetics, data of release profile were subjected to various kinetics models. The results showed prepared gastro retentive tablets follow the zero order release i.e. concentration non-dependent. The of release exponent 'n' values of Korsmeyer–Peppas model was found in between 0.536 to 0.789, indicating the drug release pattern was non-Fickian mechanism. The data of kinetics studies were dissipated in Table 5.

Table 5: *Release exponent values and rate constant values for different formulations*

Formulation code	Kinetics models					Best Fit Model	Drug release mechanism
	Zero order	First order	Higuchi	Korsmeyer-Peppas			
	R^2	R^2	R^2	R^2	n		
F1	0.987	0.898	0.844	0.648	0.684	Zero order	non- Fickian
F2	0.955	0.802	0.795	0.618	0.782	Zero order	non- Fickian
F3	0.983	0.959	0.762	0.593	0.743	Zero order	non- Fickian
F4	0.958	0.910	0.863	0.656	0.605	Zero order	non- Fickian
F5	0.979	0.885	0.739	0.637	0.536	Zero order	non- Fickian
F6	0.947	0.834	0.814	0.662	0.634	Zero order	non- Fickian
F7	0.985	0.939	0.780	0.685	0.789	Zero order	non- Fickian
F8	0.925	0.899	0.767	0.671	0.560	Zero order	non- Fickian

Stability studies:

Among eight formulations, the best formulation F8 was subjected to accelerated stability studies for the period of 3 month. The stored tablets did not show any drastic change in appearance, friability and drug content throughout its stability period. Hence formulation F8 was stable throughout the stability period. The results of stability studies were dissipated in Table 6.

Table 6: *Results of stability studies for formulation F8 stored at 25°C ± 2°C/60% RH ± 5% and 40°C ± 2°C/75% RH ± 5% RH*

Storage period	Stored at 25ºC/60% RH			Stored at 40ºC/75% RH		
	Formulation F8			Formulation F8		
	% friability	% Drug content	% CDR	% friability	% Drug content	% CDR
Initial	0.229±0.1	95.99±0.3	98.77	0.229±0.1	95.99±0.3	98.77
After 1 month	0.230±0.3	95.98±0.1	98.68	0.232±0.1	95.84±0.2	98.06
After 2 month	0.233±0.2	95.62±0.2	98.34	0.239±0.3	95.41±0.3	97.75
After 3 month	0.235±0.1	95.34±0.3	97.50	0.241±0.2	94.91±0.3	97.14

CONCLUSION

The gastric retentive drug delivery devices can be used for controlled drug delivery systems containing drugs which are degraded in the colon. In present study, we conclude that HPMC 10000 cps grade is better than HPMC 4000 cps grades of HPMC in formulating swellable, floating and gastro-retentive release tablets. Formulation F8 containing 4:1 ratio of HPMC 10000 cps and sodium bicarbonate gave better controlled drug release, floating properties and stability in comparison to the other formulations. Hence the gastro-retentive floating tablet of bisoprolol is a novel approach to improve the gastric residence time, which in turn increases the bioavailability of the Bisoprolol fumarate.

REFERENCES

1. Chen RN, Hsiu-O H, Chiao Y. Development of swelling/floating gastro-retentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for Losartan and its clinical relevance in healthy volunteers with CYP2C9 polymorphism. Eur J Pharm Sci. 2010;39:82–9.
2. Zate SU, Kothawade PI, Mahale GH. Gastro-retentive bioadhesive drug delivery system: a review. Int J Pharm Res. 2010;2:1227-35.
3. Zaware SR, Gaikwad PD, Bankar VH, Pawar SP. A Review on floating drug delivery system. Int J Pharm Sci. 2010;2(3):834-47.
4. Praveen N, Sheefali M, Deepika S. Floating systems: a novel approach towards gastro-retentive drug delivery systems. Int J Pharm Pharma Sci. 2010;2(3):2-7.
5. Klusner EA, Lavy E, Barata M, Cserpes E, Friedman M, Hoffman A. Novel gastro retentive dosage form: evaluation of gastro retentivity and its effects on Levodopa absorption in humans. Pharm Res. 2003:20(9):1466-73.
6. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000;63:235-59.
7. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery System: a review. Int J Pharm Tech Res. 2009;1(3):623-33.
8. Budarari S, O'Neil MJ, Smit A, Heckelmann PE, editors. The merck index. 11th ed. USA: Merck & Co. Inc. 1989.
9. Polli JE, Rekha GS, Augsburger LL, Shah VP. Methods to compare dissolution profiles and a rationale for wide dissolution specifications for Metaprolol tartrate tablets. Int J Pharm. 1997; 86(6): 690-700.
10. Rathbone MJ, Hadgraft J, Roberts MS. Delivery technology drugs and pharmaceutical sciences. Marcel Dekker Inc, New York. 2003:203-16.
11. Dangat YT, Bari NA, Jagdale SC, Chabukswar AR, Kuchekar BS. Controlled release from Bisoprolol fumarate buccal patches. Der Pharmacia Sinca. 2012;3:317-20.
12. Jain SK, Jain NK, Agrawal GP. Gastroretentive floating drug delivery system: an overview. Drug Del Tech. 2005;5(7):1-9.
13. ICH Q1A (R2) Stability testing guidelines: Stability Testing of new drug substances and products. [online]. [Cited 2008 Nov 10]; Available from: URL:http://www.tga.health.gov.au/docs/pdf/euguide/inch/273699r2en.pdfean