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Research Article

Formulation and Evaluation of Extended Release Gastroretentive Tablets of Metroprolol Succinate

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Abstract

This study aimed to produce a gastroretentive floating tablet of Metoprolol succinate and examine the effects of release retardant on *in vitro* drug release. Metoprolol succinate is a β1 selective antagonist used as an Anti-hypertensive, Antiarrhythmic, and Anti Angina. Metoprolol succinate has 48% oral bioavailability due to limited absorption from the lower gastrointestinal tract. The Metoprolol succinate floating tablets were designed to increase stomach retention, prolong drug release, and enhance drug bioavailability. To shorten the floating lag time, hydrophilic polymers like Hydroxypropyl methyl cellulose (HPMC K4M, K15M, and K100M), polyethylene oxide (PEO 303), and sodium bicarbonate as a gas-producing agent were incorporated into the formulation of the floating tablets. Different batches of Metoprolol succinate floating tablets were prepared by direct compression. All the formulations were evaluated for various quality control tests, such as weight variation, hardness, friability, swelling index, floating lag time, and total floating time. As a dissolution medium, 0.1 N HCl was used to conduct an *in vitro* release investigation on the tablets. The present study demonstrates the potential of the sustained-release floating tablets of Metoprolol succinate as an alternative to conventional formulations.

Keywords: Bioavailability, Floating tablet, antihypertensive drugs, extended release, Metoprolol succinate, Hydroxypropyl methyl cellulose.

INTRODUCTION

The oral bioavailability of numerous drugs are restricted by their unfavorable physicochemical properties or absorption in a well-defined region of the gastrointestinal tract (GIT) referred to as the "absorption window" [1]. Prolonged stomach retention increases bioavailability, decreases drug waste, and increases the solubility of less soluble drugs in an environment with a high pH [2]. Diverse methods, including floating systems, swelling and expanding systems, bioadhesive systems, modified shape systems, high-density systems, and other delayed gastric emptying devices, have been studied to increase the retention of oral dosage forms in the stomach [3].

Gastroretentive dosage forms are drug-delivery devices that remain in the stomach for an extended duration and permit both spatial and temporal control of drug release [4]. Essentially, gastroretentive systems swell after consumption and are held in the stomach for hours while continually releasing the integrated drug at a controlled rate to selected absorption sites in the upper gastrointestinal tract. In the case of drugs that are mostly absorbed in the upper GIT or unstable in the middle or distal intestinal areas, their application can be helpful. They can also be utilized in the treatment of the stomach locally [5]. Hydroxy propyl methyl cellulose (HPMC) is hydrophilic cellulose ether widely used as release retarding material. HPMC releases drugs by diffusion mechanism [6].

The study aimed to develop and analyze an extended-release Metoprolol succinate floating tablet that will reduce dose frequency, improve patient compliance, and reduce plasma concentration fluctuations. The primary goal of developing extended-release floating tablets was to achieve sustained release of Metoprolol succinate over an extended length of time to maintain a steady plasma drug concentration throughout the day [7]. Extended-release dosage forms are modified dosage forms that extend the duration of the drug's therapeutic effect [8]. Extended-release formulations give a continuous drug supply in the bloodstream to maintain the drug's impact throughout a set time period [9].

MATERIAL AND METHODS

Metoprolol succinate was obtained as a gift sample from Dr. Reddy's Labs, Hyderabad. PEO 303, HPMC, Microcrystalline cellulose, Sodium Bicarbonate, Citric acid, Magnesium Stearate, and Talc were acquired from S.D. Fine-Chem Ltd., India.

Calibration curve of Metoprolol succinate

100 mg of Metoprolol succinate was weighed and transferred into a 100 ml volumetric flask containing a small volume of 0.1N HCl for dissolution; the volume was then brought up to the mark using 0.1N HCl. From this stock solution, solutions with concentrations ranging from 0-50 µg/ml were diluted. At 224nm, the absorbance of the produced dilutions was measured. This calibration curve was utilized for dissolution tests and the assessment of drug content [10].

Drug - Excipients Compatibility Studies

Drug excipient interaction is one of the most important considerations in solid dosage form development and drug discovery programs. When the scientist embarks on drug excipient interaction testing, all these fundamental data should have been gathered and ready to be used as a template for the interaction evaluation. The drug excipients compatibility studies were performed at 40°c temperature and 75% RH in Stability Chamber for 45 days [11].

Preparation of Compression Coated Metoprolol Succinate Tablets

Preparation of Metoprolol succinate core tablets

Each core tablet (average weight 230 mg) was formulated with Metoprolol succinate, microcrystalline cellulose (MCC), talc, magnesium stearate, and polymer (Table 1). To guarantee complete mixing, the ingredients were weighed, combined, and passed through a mesh size of 60. On a 16-station tablet machine, 9 mm round, flat, and plain punches were used to immediately compress the properly mixed ingredients into tablets (Cadmach, Ahmedabad). Hardness was kept between 4.5 and 5.5 kg/cm^2, and friability was less than 1 [12].

Ingredients	Quantity(mg)
Metoprolol succinate	150
Microcrystalline cellulose	21
Talc	6
Magnesium stearate	3
HPMC K100M	50
Total Weight	230

Compression coating of core tablets

As indicated in Tables 2, 3, 4, and 5, the core tablets were compression coated with varying amounts of coating material. Half of the coating material was placed in the die cavity, and the core tablet was carefully placed in the center of the die cavity before the remaining coating material was added [13]. Compressing the coating material with 12 mm round, flat, and plain punches. On the compression-coated tablets, quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in the gastric medium were conducted [14].

Table 2: Composition of MF1-MF3 formulations of Metoprolol succinate containing HPMC K100M.

Ingredients	Quantity (mg) presenting the coat formulation		
	MF1	MF2	MF3
Metoprolol succinate	100	100	100
HPMC K100M	50	75	100
MCC	190	165	140
Sodium bicarbonate	65	65	65
Citric acid	5	5	5
Talc	7	7	7
Magnesium stearate	3	3	3
Total weight	420	420	420

Table 3: Composition of MF4-MF6 formulations of Metoprolol succinate containing HPMC K15M.

Ingredients	Quantity(mg) presenting the coat formulation		
	MF4	MF5	MF6
Metoprolol succinate	100	100	100
HPMC K15M	75	100	150
MCC	165	140	90
Sodium bicarbonate	65	65	65
Citric acid	5	5	5
Talc	7	7	7
Magnesium stearate	3	3	3
Total weight	420	420	420

Table 4: Composition of MF7-MF9 formulations of Metoprolol succinate containing PEO-303.

Ingredients	Quantity(mg) presenting the coat formulation		
	MF7	MF8	MF9
Metoprolol succinate	100	100	100
PEO-303	100	150	200
MCC	140	90	40
Sodium bicarbonate	65	65	65
Citric acid	5	5	5
Talc	7	7	7
Magnesium stearate	3	3	3
Total weight	420	420	420

Table 5: Composition of MF10-MF13 formulations of Metoprolol succinate containing HPMC K4M.

Ingredients	Quantity(mg) presenting the coat formulation			
	MF10	MF11	MF12	MF13
Metoprolol succinate	100	100	100	100
HPMC K4M	150	200	225	240
MCC	90	40	15	---
Sodium bicarbonate	65	65	65	65
Citric acid	5	5	5	5
Talc	7	7	7	7
Magnesium stearate	3	3	3	3
Total weight	420	420	420	420

Evaluation of Tablets

The formulated tablets were evaluated for pre-compression, post-compression, in vitro buoyancy and in vitro dissolution studies.

Pre Compression studies

Bulk Density (BD)

It is the ratio of mass to the bulk volume of the powder. It is useful in the determination of the compressibility index. Bulk density is a significant characteristic that impacts the pack size of the container. 2 g of drug blend with excipients from each formulation was placed into a 10 ml measuring cylinder, and the volume is indicated as bulk volume [15-16]. The BD was determined by the equation:

Bulk Density= mass of powder/ Bulk volume

Tapped density (TD)

After the determination of BD, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted [16]. The TD was calculated by the equation:

Tapped density= mass of powder / tapped volume

Angle of Repose

The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface [15-16]. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\mathbf{Tan\ \theta = h/r}$$

Where h and r are the height and radius of the powder cone, θ is the angle of repose.

Compressibility Index (Carr's Index)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is [15-16].

CI= (TD-BD) x 100/TD

Where, TD is the tapped density and BD is the bulk density.

Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index[15-16].

Post compression studies

Tablet weight variation

Twenty tablets were randomly selected and accurately weighed, in grams on an analytical balance[15-16]. Results are expressed as mean values ± SD.

Tablet thickness

A Vernier calipers was used to determine thickness of 10 randomly selected tablets [15-16]. Results are expressed as mean values ± SD.

Drug content uniformity

Ten tablets were individually weighed, crushed and quantity of powder equivalent to the mass of one tablet was extracted in 100 ml of 0.1N HCl. The solution was filtered through a cellulose acetate membrane (0.45 µm). The drug content was determined by UV spectroscopy at a wavelength 224 nm after a suitable dilution with 0.1N HCl [15-16].

Tablet Friability

According to the BP specifications 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus. The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, de-dusted and accurately weighed. The percent weight loss was calculated [15-16].

Tablet swelling ability

The swelling behavior of the tablets was determined in triplicate, according to the previously reported method [15]. Briefly, a tablet was weighed (W1) and placed in a glass beaker, containing 200ml of 0.1N HCl, maintained in a water bath at 37 ± 0.5°C. At regular intervals, the tablets were removed & the excess surface liquid was carefully removed by a filter paper. The swollen tablet was then reweighed (W2). The swelling index [SI] was calculated using the formula:

SI= (W2-W1) / W1

Tablet Floating behavior

The floating behavior of the tablets was visually determined, in triplicate, according to the floating lag time method. Briefly, a tablet was placed in a glass beaker, containing 200ml of 0.1N HCl, maintained in a water bath at 37±0.5°C. The floating lag time "the time between tablet introduction & its buoyancy" and total floating duration "the time during which tablet remains buoyant" were recorded [15-16].

Drug release studies

Drug release studies of the prepared extended release gastroretentive tablets were performed in triplicate, in a USP Dissolution Apparatus, type II (Paddle method) at 37±0.5°C. The paddles rotated at a speed of 100 rpm. The tablets were placed into 900 ml of 0.1N HCl solution (pH 1.2). Aliquots of 5ml were withdrawn from the dissolution apparatus at different time intervals & filtered through a cellulose acetate membrane (0.45µm). The drug content was determined spectrophotometrically at a wavelength of 224nm. At each time of withdrawal, 5ml of fresh medium was replaced into dissolution flask [15-16].

Release Kinetics

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from formulated tablets was described by using zero order kinetics or first order kinetics. The mechanism of drug release from tablets was studied by using Higuchi equation and the Peppa's Korsemeyer equation [15-16].

RESULTS AND DISCUSSION

Calibration curve of Metoprolol succinate

A spectrophotometric method for estimation of Metoprolol succinate, based on the measurement of absorbance at 224 nm in 0.1N HCl, gives a straight line with an equation: y = 0.018x - 0.012 and r^2 = 0.998 (Figure 1).

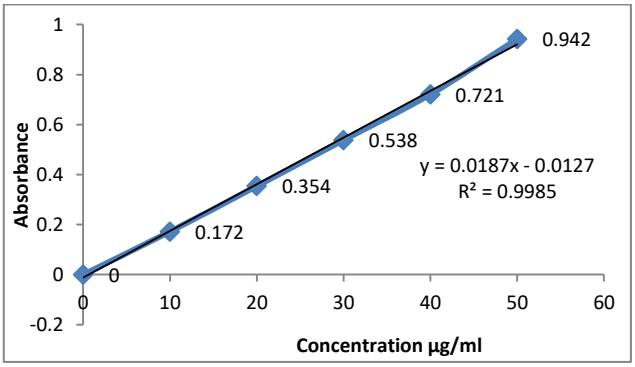

Figure 1: Calibration curve of Metoprolol succinate in 0.1 N HCl

Drug-Excipients Compatibility Study

This study was conducted to evaluate if the medicine underwent any physical changes when in contact with various formulation excipients. For drug and physical combinations, compatibility tests between drug and excipient were conducted. A drug excipients compatibility investigation revealed no change in the physical appearance or colour of the contents, indicating that there is no drug-excipient interaction.

Evaluation of tablets

Pre Compression studies

The values obtained for angle of repose for all formulations are tabulated in table 6. The values were found to be in the range of 23˚- 30˚. This indicates good flow property of the powder. The values obtained for compressibility index for all formulations are tabulated in table 6. Compressibility index value ranges between 9.75-20.45% indicating that the powder has the required flow property for compression. The values obtained for Hausner's ratio for all formulations are tabulated in table 6. Hausner's Ratio value ranges between 1.10-1.26% indicating that the powder has the required flow property for compression.

Table 6 : Pre Compression characteristics of Metoprolol Succinate powder blend of floating tablets. (Mean ± SD, n = 3)

Formulations	Angle ofrepose (˚) ±S.D	Bulk Density(g/cm³) ±S.D	TappedDensity (g/cm³) ±S.D	Carr's Index(%)±S.D	Hausner's Ratio ±S.D
MF1	23.00±0.72	0.71±0.01	0.82±0.02	13.14±0.42	1.15±0.01
MF2	25.24±0.71	0.64±0.01	0.75±0.05	16.92±0.67	1.17±0.04
MF3	26.05±0.73	0.52±0.04	0.66±0.03	20.45±0.56	1.26±0.10
MF4	27.97±0.81	0.72±0.06	0.84±0.04	14.28±0.67	1.16±0.02
MF5	28.25±0.11	0.74±0.02	0.82±0.02	9.75±0.59	1.10±0.11
MF6	30.00±0.17	0.65±0.05	0.76±0.03	14.47±0.37	1.16±0.09
MF7	29.56±0.32	0.53±0.05	0.63±0.04	15.87±0.28	1.18±0.11
MF8	24.33±0.12	0.56±0.06	0.66±0.05	15.15±0.14	1.17±0.01
MF9	27.43±0.16	0.58±0.04	0.69±0.02	15.94±0.43	1.18±0.03
MF10	28.49±0.72	0.65±0.05	0.75±0.03	13.33±0.37	1.15±0.09
MF11	29.24±0.71	0.68±0.05	0.78±0.04	12.82±0.28	1.14±0.11
MF12	28.50±0.73	0.72±0.06	0.81±0.05	11.11±0.14	1.12±0.01
MF13	28.02±0.62	0.70±0.04	0.82±0.02	14.63±0.43	1.17±0.03

Post Compression studies

Visual examination of tablets from each formulation batch showed circular shape with no cracks. The dimensions determined for formulated tablets were tabulated in table 7. Tablets mean thickness were almost uniform in all the formulations and were found to be in the range of 4.30 mm to 4.65 mm. The percentage weight variation for all formulations was shown in table 7. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets of each batch was shown in table 7, and were found to be in the range between 5.50 – 7.00 kg/cm². Tablet hardness was maintained constant in all the formulations. The values of Friability test were tabulated in table 7; the % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Table 7 : Results of physical parameters of Metoprolol Succinate floating matrixtablets (Mean ± SD, n = 3)

FormulationCode	Tablet weight (mg) Mean±SD	Hardness (kg/cm²) Mean ±SD	Thickness (mm) Mean ±SD	Friability(%) Mean±SD	Content uniformity (%) Mean±SD
MF1	651±1.5	6.59±0.388	4.40±0.21	0.59±0.15	100±0.60
MF2	650±2.87	7.00±0.055	4.55±0.07	0.45±0.19	98.55±0.83
MF3	648±3.15	6.00±0.035	4.55±0.06	0.29±0.10	102.55±0.20
MF4	650±1.12	6.50±0.135	4.65±0.05	0.27±0.25	100.67±0.67
MF5	647±1.28	6.750±0.025	4.45±0.03	0.49±0.18	101.80±0.75
MF6	653±3.55	7.00±0.050	4.30±0.02	0.53±0.15	102.56±0.77
MF7	652±4.50	5.50±0.157	4.58±0.01	0.18±0.19	100.65±0.15
MF8	650±1.66	6.35±0.267	4.33±0.05	0.26±0.10	99.95±0.15
MF9	653±1.12	7.00±0.165	4.50±0.02	0.28±0.25	101.50±0.56
MF10	649±3.55	6.96±0.050	4.40±0.02	0.48±0.18	102.56±o.77
MF11	647±4.50	5.50±0.157	4.58±0.01	0.52±0.23	100.65±0.15
MF12	652±1.66	6.32±0.267	4.43±0.05	0.49±0.15	99.95±0.15
MF13	650±1.12	6.82±0.165	4.40±0.02	0.51±0.35	101.50±0.56

The percentage of drug content was found to be between 98.55 to 102.56 %, which was within acceptable limits. Table no. 7, showed the result of drug content uniformity in each batch. Least Floating lag time was found to be 5sec and longest Floating lag time was found to be 32 sec. For all the formulations Total floating time was greater than 12 hrs (Table 8). Swelling index values were in the range of 51.72% to 126.87%.

Table 8 : Floating lag time and Total floating time of all formulations of Metoprolol Succinate. (Mean ± SD, n = 3)

Formulations	Floating lag time (sec)	Total floating time (hrs)
MF1	16	12
MF2	25	12
MF3	32	12
MF4	10	12
MF5	16	12
MF6	20	12
MF7	07	12
MF8	10	12
MF9	15	12
MF10	05	12
MF11	08	12
MF12	10	12
MF13	16	12

In vitro dissolution studies

It indicates, the release was extended with the increase in HPMC percentage in tablets due to the increased percentage of swelling and the decreased percentage of erosion. The more the concentration of HPMC, thicker the gel layer offers more resistance to the drug diffusion and gel erosion, which results in the incomplete release. The combined matrix when exposed to an acidic environment, the HPMC hydrates to form a gel layer at the surface of the tablet, acting as a barrier to diffusion of the drug. Their proportion had significant effect on the release profiles. Formulation F4 (20% HPMCK 100M and 10% SA) released 100 % of MS in 12 h, with a FLT of 20 s, TFT and a better MI up to 12 h, when compared to other formulations with HPMC only. Hence, formulation F4 was considered the best formulation with desirable floating parameters and in vitro drug release profile (Figure 2, 3 and 4).

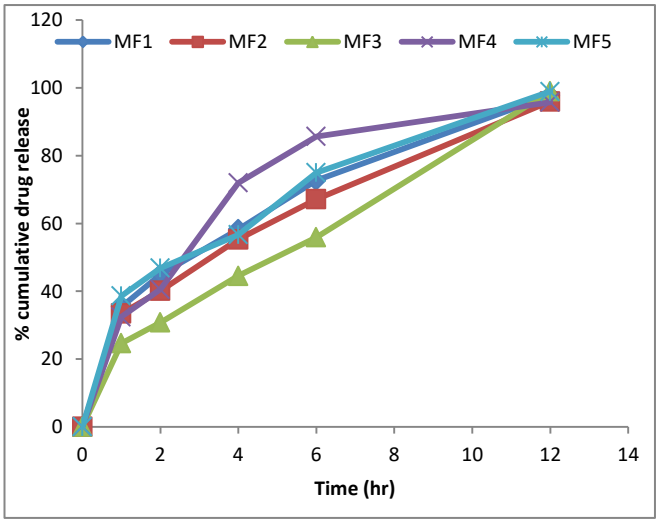

Figure 2: Release Profile of Metoprolol Succinate formulations MF1 to MF5.

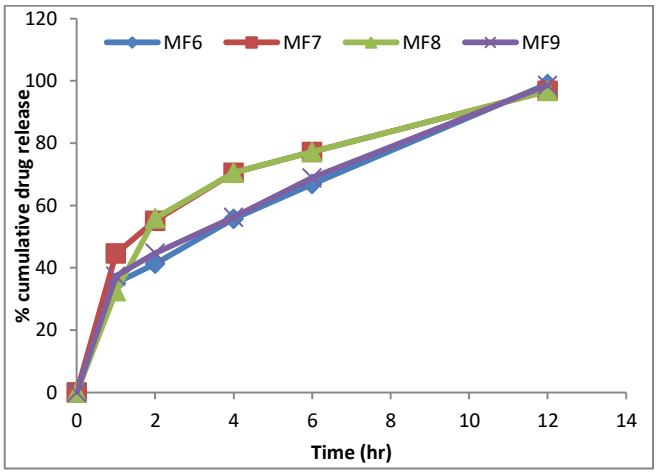

Figure 3: Release Profile of Metoprolol Succinate formulations MF6 to MF9.

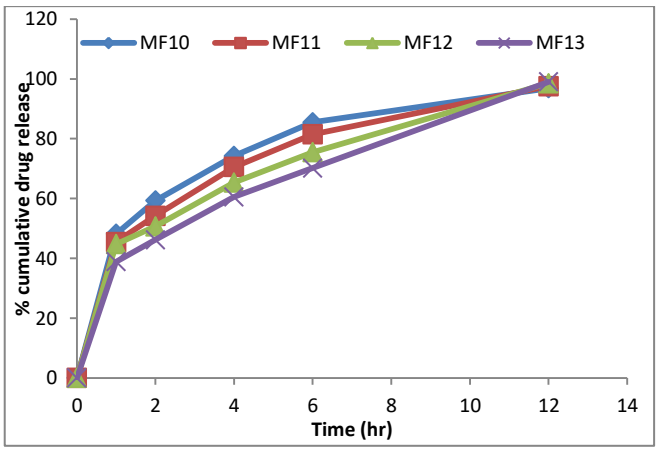

Figure 4: Release Profile of Metoprolol Succinate formulations MF10 to MF13.

Release Kinetics

The drug release kinetics of optimized formulation F9 fitted best to the Zero-order (R^2 =0.9124). The (R^2 =0.9901) value in case of Higuchi release was found to be higher than Zero order and First order, suggesting that the drug release process is predominantly by diffusion (Table 10).

Table 10: Drug release kinetics of Metoprolol Succinate floating matrix tablets

Formulations	Zero order (mg/min)		First order (min^{-1} or $hour^{-1}$)		Peppas		Higuchi	Similarity factor
	R^2	K	R^2	K1	R^2	n	R^2	(f2)
MF1	0.9006	7.2077	0.9277	0.341	0.9833	0.4493	0.9901	**61.513**
MF2	0.9247	6.9580	0.9185	0.262	0.9818	0.4569	0.9922	**67.618**
MF3	0.9723	7.0692	0.6885	0.252	0.9748	0.5676	0.9732	44.673
MF4	0.8036	6.8915	0.9836	0.283	0.9448	0.4612	0.9563	48.169
MF5	0.8951	7.2637	0.9025	0.412	0.9616	0.4308	0.9830	**58.515**
MF6	0.9255	6.8791	0.8200	0.294	0.9749	0.4376	0.9912	**70.650**
MF7	0.7937	6.5742	0.9424	0.375	0.9866	0.3451	0.9606	41.177
MF8	0.8110	6.8047	0.9646	0.313	0.9544	0.4245	0.9631	49.323
MF9	0.9124	6.8758	0.8563	0.310	0.9722	0.4167	0.9901	**77.665**
MF10	0.7270	6.1692	0.9288	0.317	0.9738	0.3035	0.9267	42.797
MF11	0.7872	6.5362	0.9441	0.349	0.9794	0.3411	0.9561	46.927
MF12	0.8479	6.7708	0.9272	0.374	0.9712	0.3624	0.9767	**55.694**
MF13	0.8951	6.7793	0.8212	0.341	0.9787	0.3985	0.9890	**77.632**

Accelerated stability studies

Results of accelerated stability studies of optimized formulation F9 indicate it is stable at 40^0C/75% RH up to 3 Months. As there were no significant differences in hardness, drug content, floating characteristics (FLT, TFT & Matrix integrity) and % drug release at 12^{th} hr.

CONCLUSIONS

This study involved the development of an unique gastroretentive, swellable, controlled-release Metoprolol Succinate tablet. It consists of hydrophilic polymers that regulate the release rate, a release modulator, and a gas-generating agent. Upon ingestion, the Metoprolol Succinate floating tablet was rapidly hydrated and inflated due to absorption of gastrointestinal fluid; subsequent gas formation contributed to the system's buoyancy and desirable release profile. In the above view of findings the formulation F9 (PEO 303) is better suited for GRFT of Metoprolol Succinate than other formulations with HPMC K100M, K15M and K4M. It was concluded that the optimization of hydrophilic polymer, had significant effect on extending the release profiles of Metoprolol Succinate. A matrix design of this kind can serve as an alternative strategy to targeted drug delivery by GRFT.

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Conflicts of Interest: Author reported no conflicts of interest.

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