

FLOATING MULTIPLE UNIT MINITABLETS OF METOPROLOL SUCCINATE: FORMULATION, *IN VITRO* AND *IN VIVO* CHARACTERIZATION

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ABSTRACT

Objective: In this present research, formulation of floating multiple unit minitables of metoprolol succinate without using gas generating agent was attempted with an objective of increased residence time, sustained release, and improved oral bioavailability.

Methods: Solid dispersions were prepared with lipophilic carriers such as compritol AT0888, Gelucire 43/01, Gelucire 39/01, and precirol ATO 05 was formulated using fusion technique. Neusillin US2 was used as an adsorbent. The solid dispersions were compressed into minitables, weighing 20 mg, and then filled into '0' size capsule.

Results: Formulation F9, F10, F14, and F15 showed instantaneous floating lag time, i.e., 0 min, floating time more than 12 h, and sustained release up to 12 h. Pharmacokinetic study of the optimized formulation (F9) showed 2.46 times increase in area under the curve with increased residence time.

Conclusion: Hence gelucire 43/01 based floating multiple unit minitables of metoprolol succinate can be considered a promising approach.

Keywords: Gelucire 43/01, Bioavailability, Stability, Floating lag time

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INTRODUCTION

For a long time, oral controlled release (CR) formulations are popularly used for controlling the release of drugs. Short transit time of drug with absorption window in the stomach causes drug release in the non-absorbing distal segment of GIT, leading to poor bioavailability [1]. These features are responsible for the design of gastro retentive formulations [2, 3]. Dose-dumping is the main disadvantage of sustained-release single-unit dosage form due to the failure of formulations [4, 5]. Like other multiple unit systems, minitables can be considered a promising approach that releases the drug from the subunits (minitables) after the capsule's disintegration [6, 7].

The drug having a short biological half-life favors the development of a sustained release. In contrast, the drug with an absorption window in the upper GI tract favors developing a floating drug delivery system, respectively [8, 9]. Metoprolol Succinate, a β -selective adrenergic blocking agent, is used to treat patients with hypertension or angina pectoris [10]. Metoprolol succinate has a short half-life (3-4 h), and absorption window in the upper GI tract favors developing a sustained release and floating drug delivery system, respectively [11, 12]. It exhibits a high solubility at gastric pH 1.2. Hydrophobic polymer can be used in the preparation of sustained and floating formulations. Hydrophobicity of certain carriers such as Compritol ATO 888, Gelucire 43/0, Gelucire 39/01, and precirol ATO 05 is why their release retarding ability [13]. Their low melting point makes them suitable for the melt granulation method. Higher concentrations of lipophilic carriers promote better control of the drug release because of increased lipid matrix density and long diffusion path length [14, 15]. Hence in the present research work, it is planned to use hydrophobic carriers to formulate floating multiple unit minitables of metoprolol succinate to achieve floating with sustain release for 12 h.

MATERIALS AND METHODS

Metoprolol succinate was received as a gift sample from Mepro Pharmaceutical Ltd (Gujrat, India). Neusilin US2 was kindly provided as ex-gratis by Gangwal Chemicals Pvt Ltd (Mumbai, India). Compritol ATO 888, Gelucire 43/01, Gelucire 39/01, and precirol ATO 05 were provided as a gift sample from Gattefosse Pvt Ltd

(Mumbai, India). All other chemicals and solvents used were of analytical grade.

Preparation of floating minitables of metoprolol succinate

Fusion method was adopted for preparing the solid dispersion of metoprolol succinate with a lipophilic carrier such as compritol ATO 888, gelucire 43/01, gelucire 39/01, and precirol ATO 05. The lipophilic carrier was melted on a water bath with continuous stirring. To the molten lipid dispersion, metoprolol succinate was added and mixed for 10 min. The Neusillin US2 was added to the dispersion with continued mixing for 10 min to solidify the molten mass. Then the solid dispersion was sieved through mesh no. # 40. The resultant dispersion granules were compressed into 3 mm circular flat minitables and were filled into a gelatine capsule of size '0' [16].

Fourier transform infrared spectroscopy (FT-IR)

FT-IR analysis of pure drug metoprolol succinate and its dispersion granules in 1:1 ratio with compritol ATO888, gelucire 43/01, gelucire 39/01, precirol ATO 05, and neusillin US2 were studied on IR Affinity-1 (Shimadzu, Japan) using potassium bromide discs. Samples were analyzed at a scanning speed of 2 mm/s with a resolution of 4 cm⁻¹ over the region 4000–400 cm⁻¹.

Differential scanning calorimeter (DSC)

The pure drug metoprolol succinate and its dispersion granules with carriers were examined for compatibility study employing DSC (Shimadzu Ltd., Japan). All the accurately weighed samples were placed in sealed aluminum pans before placing the pan on the sample holder at a scanning rate of 100C/min from room temperature up to 2200C. An empty aluminum pan was used as a reference. The DSC curve was plotted over a temperature range to predict the thermodynamic compatibility [17].

Drug content

Drug content of dispersion granules and mini tablets were determined by weighing an amount equivalent to 10 mg of metoprolol succinate in 0.1 N HCl, sonicated for 5 min, filtered, and analyzed UV spectrophotometrically at 273 nm.

Micromeritic properties of dispersion granules

The pure drug metoprolol succinate and dispersion granules of all the prepared formulations were characterized for various micromeritic properties. The bulk density, tap density, angle of repose, Carr's Index, and Hausner's ratio of all the formulations were determined as per standard procedure [18].

In vitro buoyancy studies

Measurement of floating lag time

The floating lag time was determined by conducting *In vitro* buoyancy studies for each of the formulation. The required number of floating minitables was placed in a dissolution jar containing 900 ml of 0.1N HCl. Floating lag time may be defined as the time required for each of the minitables to start floating on the surface of the dissolution media [19].

Measurement of floating time

Floating minitables were placed in USP dissolution apparatus-II containing 900 ml of 0.1N HCl to determine each formulation's floating time. Floating time is the total duration of floating when a dosage form is placed in a dissolution media [20].

Evaluation of post-compression parameters

The compressed minitables were subjected to various quality control tests such as weight variation, hardness, thickness, friability, and drug content as per the standard procedure [21-23].

In vitro dissolution studies

The *In vitro* dissolution studies of different floating minitables were conducted in a USP dissolution apparatus-II taking 0.1 N HCl as dissolution medium. 5 ml sample was withdrawn at regular time intervals up to 12 h (0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 h) and was analyzed using UV-spectrophotometer at 273 nm. The drug release study's kinetics were analyzed from the dissolution data by

using zero-order, first-order, Higuchi, and Korsmeyer-Peppas model [24, 25].

Accelerated stability study

Accelerated stability study of the prepared floating minitables (F9 and F14) of metoprolol succinate was conducted for a period of 3 mo as prescribed in ICH guidelines. The formulations were examined at the time points of 0, 1, 2, and 3 mo for the different parameters.

In vivo pharmacokinetic study

The dose of metoprolol succinate was calculated as 9.2 mg for each rabbit of weight approximately 2 kg. The optimized formulation and aqueous dispersion of metoprolol succinate were administered in dispersion to six male rabbits, each in two groups using Ryle's tube [26]. At different time points (0.5, 2, 4, 8, 12, and 24 h), a blood sample of 0.5 ml was withdrawn from the rabbit's marginal ear vein. Each blood sample was centrifuged for 10 min at 3000 rpm, and the supernatant layer, i.e., serum, was collected using a micropipette. All the samples were analyzed using the reverse-phase ultrafast liquid chromatographic (UFLC) method. The various pharmacokinetic parameters like elimination rate constant (K), half-life ($t_{1/2}$), peak plasma concentration (C_{max}), time to attain the peak plasma concentration (T_{max}), area under the curve (AUC), area under the first moment curve (AUMC) and mean residence time (MRT) were calculated. The animal experiment was approved by Institutional Animals Ethics Committee [926/PO/Re/5/06/CPCSEA, Approval No.97].

RESULTS AND DISCUSSION

The composition of solid dispersion with different ratios (1:1, 1:2, 1:3, 1:4, and 1:5) of drug with the lipophilic carrier such as Compritol ATO 888, gelucire 43/01, gelucire 39/01, and precirol ATO 05 are given in (table 1). The ratio of lipophilic carrier to adsorbent Neusillin US2 to is maintained at 1:0.5. Each minitable weighing 20 mg is filled into a '0' size capsule. The composition of each formulation of floating minitables is illustrated in table 4.

Table 1: Composition of solid dispersion

Formulations	Metoprolol succinate	Compritol ATO 88	Gelucire 43/01	Gelucire 39/01	Precirol ATO 5	Neusillin US2
F1	1	1	-	-	-	0.5
F2	1	2	-	-	-	1
F3	1	3	-	-	-	1.5
F4	1	4	-	-	-	2
F5	1	5	-	-	-	2.5
F6	1	-	1	-	-	0.5
F7	1	-	2	-	-	1
F8	1	-	3	-	-	1.5
F9	1	-	4	-	-	2
F10	1	-	5	-	-	2.5
F11	1	-	-	1	-	0.5
F12	1	-	-	2	-	1
F13	1	-	-	3	-	1.5
F14	1	-	-	4	-	2
F15	1	-	-	5	-	2.5
F16	1	-	-	-	1	0.5
F17	1	-	-	-	2	1
F18	1	-	-	-	3	1.5
F19	1	-	-	-	4	2
F20	1	-	-	-	5	2.5

Drug-polymer interactions are an important parameter in selecting appropriate polymers. FT-IR spectroscopy study was employed to ascertain the compatibility between Metoprolol succinate and selected polymers. FT-IR study for the pure drug metoprolol succinate showed absorption bands at 3181 cm⁻¹ assigned to the NH group, absorption bands at 3040 cm⁻¹ assigned to OH group, and absorption bands at

2740 cm⁻¹ assigned to OCH₃ group. The dispersion granules of metoprolol succinate with different excipients such as Compritol ATO 888, gelucire 43/01, gelucire 39/01, precirol ATO 05 and neusillin US2 also showed absorption bands in a similar range; hence metoprolol succinate and carriers were compatible with each other [27]. The overlaying FT-IR spectrum was shown in fig. 1.

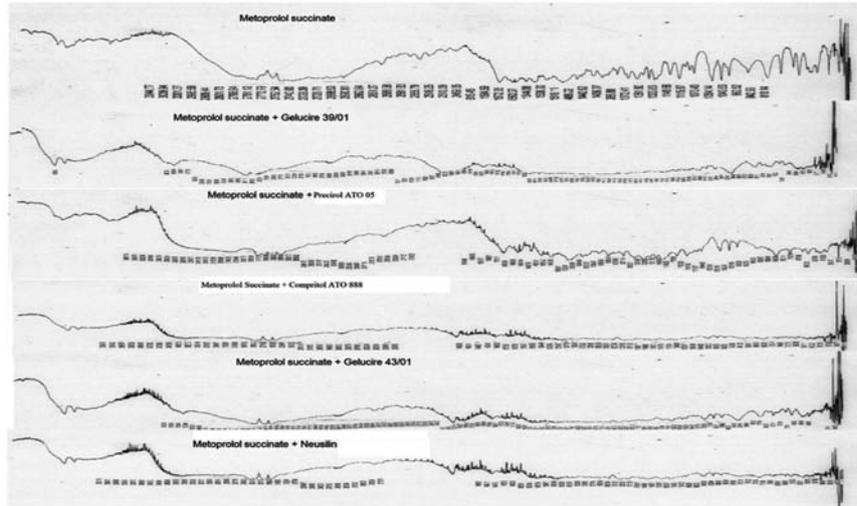


Fig. 1: FT-IR study for metoprolol succinate and its dispersion granules

DSC study revealed that the pure drug metoprolol succinate showed a sharp endothermic peak at 137.60C with a narrow melting range of onset temperature of 1340C and end set temperature 1420C. The peaks remained nearly the same in all formulations (fig. 2A and 2B).

This confirms that no significant overlapping or shifting of the peak in the thermogram. However additional peak for each carrier was observed [17]. These results of DSC ratifies that the carriers used in the present study are compatible with metoprolol succinate.

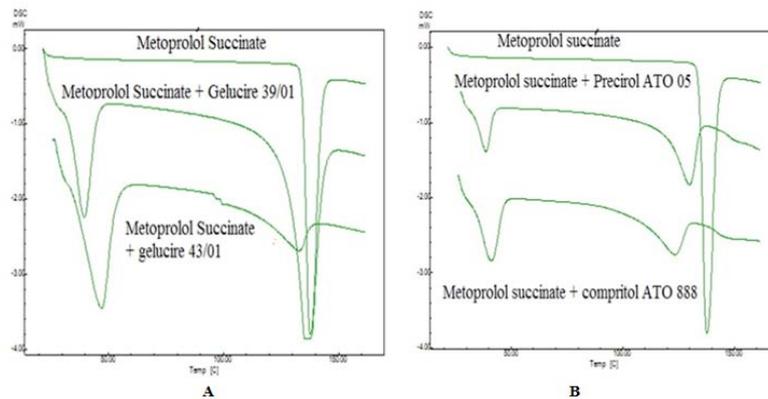


Fig. 2: DSC study for metoprolol succinate and its dispersion granules

Table 2: Micromeritic properties of solid dispersions

Formulations	*Angle of repose (°)	*Carr's index (C. I.)	*Hausner's ratio (H. R.)	*Drug content (%)
Metoprolol succinate	38±1.2	30±2.3	1.52±1.7	96.7±3.1
F1	34±1.5	28±2.2	1.32±0.2	99±3.9
F2	32±2.1	27±1.5	1.27±0.1	96.5±1.2
F3	35±2.2	28±2.1	1.28±0.2	96±2.3
F4	33±1.4	26±1.4	1.28±0.2	99±3.2
F5	32±2.2	29±2.1	1.29±0.3	98±1.4
F6	31±1.6	27±2.5	1.30±0.3	96±2.6
F7	32±3.2	26±1.4	1.31±0.2	97±3.1
F8	33±2.5	25±2.1	1.28±0.3	98±4.7
F9	35±3.6	26±2.4	1.30±0.3	99±2.3
F10	27±2.5	18±1.3	1.14±0.2	98±4.1
F11	24±2.1	19±2.1	1.31±0.4	97±3.3
F12	25±1.5	18±1.3	1.19±0.4	95±2.6
F13	22±2.4	18±2.4	1.17±0.3	97±3.7
F14	24±1.5	17±2.2	1.21±0.2	96±5.4
F15	23±2.1	19±1.5	1.25±0.2	98±6.2
F16	24±2.2	18±2.2	1.22±0.7	97±5.1
F17	22±3.0	17±1.3	1.18±0.4	96±3.2
F18	25±2.5	16±2.5	1.21±0.3	96±4.1
F19	28±2.1	20±1.3	1.22±0.2	98±5.2
F20	26±1.8	21±2.4	1.21±0.3	97±5.2

*mean±SD, n = 6

The drug content for all dispersion granules was more than 90 % indicating uniform mixing of drug with carriers (table 2). As the drug is dissolved in the molten mass of lipid, it exhibited better drug content than other granulation methods. The micromeritic parameters for all the formulation as well as the pure drug were studied, and the results are depicted in table 2. The pure drug's micromeritic properties revealed that the flowability and compressibility were very poor for processing into the tablet dosage form. All the dispersion granules showed that the value of angle of repose, C. I and H. R were within the specified limit. This may be due to the engulfment of the drug in the molecular structure of the lipid matrix. Due to high oil adsorption capacity, the high specific surface area of neusillin US2 helps improve compressibility and flowability of the prepared dispersion, which can be predicted from their micromeritic properties. Similar results were also reported about the oil adsorption capacity of neusillin US2 for gelucire based dispersion granules [16].

The *In vitro* buoyancy study was done, and the value of density, floating lag time, and floating time for all the prepared formulations are illustrated in table 3. As all floating minitables' density was much lower than the GI fluid density, it was expected that all minitables would float. However, peculiar results were observed in floating behavior. Minitables formulated with gelucire 43/01, and gelucire 39/01 showed an instantaneous floating behavior, i.e., floating lag time of 0 min and floating duration of more than 12 h. In contrast, floating minitables formulated with compritol ATO 888 and precinol ATO 05 did not exhibit floating despite the low density of minitables. However, Patel, 2015 reported good floating behavior for compritol based granules for ranitidine [15]. The *In vitro* buoyancy study reveals that hydrophobic lipid coat around drug particles' surface is the prime reason for floating behavior. It is also predicted that hydrophobicity and density alone may not be responsible for achieving desirable floating. The nature of the lipid matrix also played a significant role in achieving desired floating characteristics.

Table 3: Determination of density, floating characteristic of mini tablets

Formulations	*Density (g. cm ⁻³)	Floating lag time (min)	Floating duration (h)	% Floating
F1	0.24±0.01	No floating	No floating	No floating
F2	0.23±0.03	"	"	"
F3	0.27±0.03	"	"	"
F4	0.26±0.02	"	"	"
F5	0.23±0.04	"	"	"
F6	0.19±0.03	0	>24	100
F7	0.22±0.02	0	>24	100
F8	0.22±0.03	0	>24	100
F9	0.25±0.04	0	>24	100
F10	0.20±0.02	0	>24	100
F11	0.21±0.01	0	>24	100
F12	0.23±0.03	0	>24	100
F13	0.22±0.02	0	>24	100
F14	0.21±0.03	0	>24	100
F15	0.24±0.02	0	>24	100
F16	0.27±0.03	No floating	No floating	No floating
F17	0.23±0.03	"	"	"
F18	0.24±0.02	"	"	"
F19	0.22±0.01	"	"	"
F20	0.21±0.02	"	"	"

*mean±SD, n = 6

The result of the different formulations' quality control test showed that the various parameters such as drug content, hardness, friability, and disintegration test were within the acceptable specification. The *In vitro* dissolution study of the formulations was carried out, and the plot of cumulative percentage drug release

against time is illustrated in fig: 3A and 3B. The resultant plot suggests that the formulation F9, F10, F14, and F15 were found to achieve the desirability of sustaining the drug release for 12 h. Similar sustain release of drug was also reported for gelucire 43/01 based floating beads [14].

Table 4: Composition of floating mini tablets

Ingredients	Quantity drug and carriers (mg) in each solid dispersion formulation				Number of minitables for 100 mg dose
	Metoprolol succinate	Gelucire 43/01	Gelucire 39/01	Neusillin US2	
F6	8	8	-	4	13
F7	5	10	-	5	20
F8	3.65	11	-	5.5	33
F9	2.8	11.5	-	5.7	35
F10	2.3	11.8	-	5.9	44
F11	8	-	8	4	13
F12	5	-	10	5	20
F13	3.6	-	11	5.5	33
F14	2.8	-	11.5	5.7	35
F15	2.3	-	11.8	5.9	44

Table 5 depicts the results of different drug release kinetic coefficients for formulations. All formulations exhibited a higher correlation for Higuchi equation, and formulations F9, F10, F14, and F15 showed release exponent greater than 0.5 less than 1. F9 and F14 were found to achieve the desirability of sustaining the drug release for 12 h. Hence lipid carrier gelucire 43/01 and gelucire

39/01 are effectively control the drug release in a particular composition. Based on the dissolution study F9 and F14 can be predicted to satisfy all the floating multiple unit minitables. Formulation F10 and F15 also showed sustained release for 12 h; however, keeping in view the minimum amount of carrier, formulation F9 and F14 were selected.

Table 5: *In vitro* drug release kinetics

Formulations	Correlation coefficients (r^2)			Korsmeyer release exponent (n)
	Zero-order	First-order	Higuchi model	
F6	0.7593	0.9606	0.8190	0.2028
F7	0.8121	0.9732	0.9660	0.4211
F8	0.7237	0.9790	0.9986	0.5056
F9	0.9736	0.9902	0.9998	0.5299
F10	0.9665	0.9998	0.9914	0.5141
F11	0.6717	0.9873	0.9472	0.2157
F12	0.7928	0.9801	0.8375	0.2528
F13	0.8505	0.9948	0.8838	0.5284
F14	0.9418	0.9949	0.9927	0.5305
F15	0.9381	0.9956	0.9959	0.5249

Formulation F9 and F14 were examined for 3 mo of stability study as prescribed in the method section. The parameters such as drug content, floating lag time, floating time, time taken for more than 95 percent drug release (T95%) of F9 and F14 at various intervals are illustrated in table 6. Analysis of variance ($p < 0.05$ levels) indicated no significant change of the

parameters during the stability study period for F9. However, formulation F14 showed a significant change in T95%, which may be attributed to softening of gelucire 39/01 at the stability study temperature of 40°C due to its low melting point. Hence floating minitab formulation F9 was selected for further pharmacokinetic study.

Table 6: Accelerated stability study for formulation F9 and F14

Time in months	Characterization of F9 formulation				Characterization of F14 formulation			
	*Drug content (%)	*Floating lag time (sec)	*Floating duration (h)	*T95 %	*Drug content (%)	*Floating lag time (h)	*Floating duration (h)	*T95% (h)
0	99±2.3	0	>12	12±0.2	96±5.4	0	>12	12±0.5
1	98±3.2	0	>12	12±0.3	97±3.2	0	>12	9±0.2
2	99±2.5	0	>12	12±0.5	96.5±2.5	0	>12	9.5±0.4
3	98±4.1	0	>12	12±0.4	96±4.1	0	>12	9.3±0.3
Significance	No sig	No sig	No sig	No sig	No sig	No sig	No sig	**

*mean±SD, n=6, No sig = No significant difference, **Significant

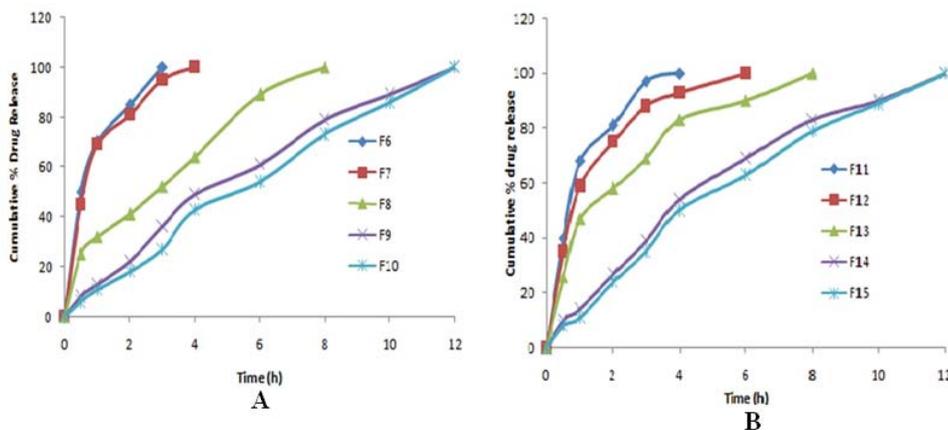
Fig. 3: *In vitro* drug release profile of gelucire 43/01 (3A) and 39/01 (3B) based floating minitab formulations

Fig. 4 illustrates the mean serum drug concentration of metoprolol succinate vs. time graph of the optimized formulation F9 and an aqueous suspension of the pure drug after conducting the pharmacokinetic study. UFLC method for estimating metoprolol succinate using mobile phase acetonitrile: potassium dihydrogen phosphate (90:10), C18 column, flow rate 1 ml/min estimates retention time of 3.7 min. Table 7 illustrates the calculated values of different pharmacokinetic parameters. The T_{max} for the pure drug was found to be 2 h, whereas T_{max} in the case of floating minitab formulation (F9) was 4 h, indicating sustain release of the drug. The AUC value of F9 was 167438.19 ng. h/ml. In contrast, it was 67821.98 ng. h/ml for pure drug, indicating that floating minitab

(F9) showed better bioavailability, which is 2.46 times than that of the aqueous suspension of pure drug metoprolol succinate. AUMC value for F9 was 2.6 times more than the pure drug. C_{max} for metoprolol succinate was found to be 32125.12 ng/ml, whereas, for the selected formulation (F9), it was found to be 40475.58 ng/ml. Nearly 1.2 times increase in C_{max} value for F9 indicated better absorption of the drug from the formulation. Higher mean residence time (MRT) for F9, i.e., 5.96 h in GI tract, indicates increased residence time of the dosage form leading to improved bioavailability. Hence it may be inferred that it is possible to prepare gastro-retentive minitab formulations using gelucire 43/01 as lipid matrix without using a gas generating agent.

Table 7: Pharmacokinetics parameters

Pharmacokinetic parameters	Metoprolol succinate	Minitablet (F9)
*C _{max} (ng/ml)	32125.12±234	40475.58±432
*T _{max} (h)	2±0.03	4±0.03
*AUC (ng. h/ml)	67821.98±478	167438.19±769
*AUMC (ng. h ² /ml)	192337.67±652	519309.97±983
*MRT (h)	2.8±0.04	5.96±0.02

*mean±SD, n =6

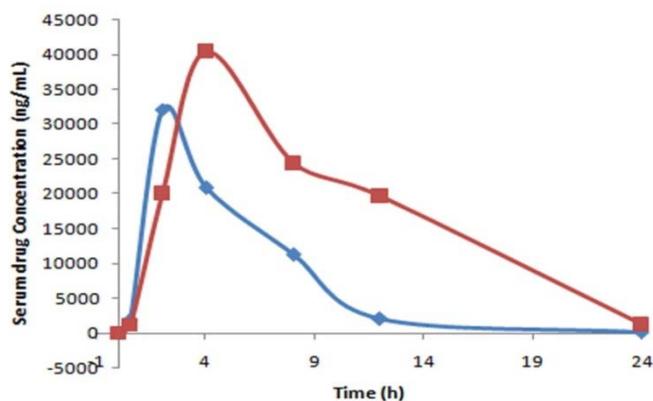


Fig. 4: Serum drug concentration-time profile of metoprolol succinate and floating minitab formulation (F9)

CONCLUSION

In this present research work, formulation and development of floating minitabts of metoprolol succinate were carried out with desired sustainability and gastric residence time. Solid dispersion with different ratios (1:1, 1:2, 1:3, 1:4, and 1:5) of drug with the lipophilic carrier such as compritol ATO 888, gelucire 43/01, gelucire 39/01, and precirol ATO 05 was formulated using fusion technique. The ratio of lipophilic carrier to adsorbent neussilin US2 is maintained at 1:0.5. Each minitabts weighing 20 mg is filled into a '0' size capsule. Floating minitabts prepared with compritol ATO 888 and Precirol ATO 05 did not exhibit floating, whereas gelucire 43/01 and 39/01 floating minitabts without gas generating agent exhibited desirable floating and sustain release characteristics. Stability study as per ICH guideline suggests that gelucire 39/01 based floating minitabts were not stable, but gelucire 43/01 based floating minitabts passed the stability test. The pharmacokinetics study of the selected formulation (F9) showed 2.46 times increase in AUC with increased residence time compared to an aqueous suspension of metoprolol succinate. From the above research work, it may be concluded that sustain release gastro-retentive minitabts can be prepared using gelucire 43/01 without using gas generating agents. Hence, gelucire43/01 based minitabts can be considered a promising approach for the formulation of sustain release with gastric retention.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

All authors declare no conflict of interest.

REFERENCES

- Hoffman A. Pharmacodynamic aspects of sustained-release preparations. *Adv Drug Delivery Rev* 1998;33:185-99.
- Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. *Expert Opin Drug Delivery* 2006;3:217-33.
- Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. *Drug Delivery* 2011;18:97-110.
- Abdul S, Chandewar AV, Jaiswal SB. A flexible technology for modified-release drugs: multiple-unit pellet system (MUPS). *J Controlled Release* 2010;147:2-16.
- Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics (*in vitro*) and floating behavior (*in vivo*). *J Controlled Release* 1991;16:279-89.
- Lingam M, Ashok T, Venkateswaralu V, Rao MY. Design and evaluation of a novel matrix type multiple units as biphasic gastroretentive drug delivery systems. *AAPS PharmSciTech* 2008;9:1253-61.
- Panda M, Rao MEB, Patra CN, Panda J, Panigrahi KC, Patro G. Formulation and development of floating multiple-unit minitabts of nimodipine without using a gas-generating agent: *in vitro* and *in vivo* characterization. *Future J Pharm Sci* 2020;6:1-9.
- Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J Controlled Release* 2000;63:235-59.
- Lopes CM, Bettencourt C, Rossi A, Buttini F, Barata P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. *Int J Pharma* 2016;510:144-58.
- Sharma F, Jain H, Kanzariya V, Upadhyay U. Formulation and evaluation of controlled release osmotic tablet of metoprolol succinate. *Asian J Pharm Clin Res* 2014;7:38-43.
- Rao GK, Mandapalli PK, Manthri R, Reddy VP. Development and *in vivo* evaluation of gastroretentive delivery systems for cefuroxime axetil. *Saudi Pharm J* 2013;21:53-9.
- Kendall MJ, Maxwell SRJ, Sandberg A, Westergren G. Controlled release metoprolol. *Clin Pharmacokinet* 1991;21:319-30.
- Panigrahi KC, Patra CN, Jena GK, Ghose D, Jena J, Panda SK. Gelucire: a versatile polymer for modified release drug delivery system. *Future J Pharm Sci* 2018;4:102-8.
- Jain SK, Gupta A. Development of gelucire 43/01 beads of metformin hydrochloride for floating delivery. *AAPS PharmSciTech* 2009;10:1128-36.
- Patel DM, Patel NM, Patel VF, Bhatt DA. Floating granules of ranitidine hydrochloride-gelucire 43/01: formulation optimization using factorial design. *AAPS PharmSciTech* 2007;8:E25-31.

16. Jammula S, Patra CN, Swain S, Panigrahi KC, Nayak S, Dinda SC. Design and characterization of cefuroxime axetil biphasic floating minitables. *Drug Delivery* 2015;22:125-35.
17. Zheng X, Yang R, Tang X, Zheng L. Part I: characterization of solid dispersions of nimodipine prepared by hot-melt extrusion. *Drug Dev Ind Pharm* 2007;33:791-802.
18. Fonner DE, Banker GS, Swarbrick J. Micromeritics of granular pharmaceutical solids I: physical properties of particles prepared by five different granulation methods. *J Pharm Sci* 1966;55:181-6.
19. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. *AAPS PharmSciTech* 2005;6:E372-90.
20. Shakya R, Thapa P, Saha RN. *In vitro* and *in vivo* evaluation of gastroretentive floating drug delivery system of ofloxacin. *Asian J Pharm Sci* 2013;8:191-8.
21. Aulton ME, Taylor K. *Aulton's pharmaceuticals: the design and manufacture of medicines*. Elsevier Health Science, London; 2013.
22. Fatema K, Shahi S. Development and evaluation of floating tablet of metoprolol succinate for increased bioavailability via *in vivo* study. *Asian J Pharm Clin Res* 2018;11:79-84.
23. Dighe PP, Tank HM. Design and statistical optimization of a bilayered tablet of metoprolol succinate sustained-release and atorvastatin calcium immediate release: once a day formulation in the management of hypertension. *Asian J Pharm Clin Res* 2018;11:293-302.
24. Boldhane S, Kuchekar B. Development and optimization of metoprolol succinate gastroretentive drug delivery system. *Acta Pharm* 2010;60:415-25.
25. Thakkar VT, Shah PA, Soni TG, Parmar MY, Gohel MC, Gandhi TR. Goodness-of-fit model-dependent approach for release kinetics of levofloxacin hemihydrates floating tablet. *Dissolution Technol* 2009;16:35-9.
26. Panigrahi KC, Jena J, Jena GK, Patra CN, Rao MEB. QBD-based systematic development of bosentan SNEDDS: formulation, characterization and pharmacokinetic assessment. *J Drug Delivery Sci Technol* 2018;47:31-42.
27. Chandana CH Y, Kumar G, Vishnu YV, Madhuri MM. Metoprolol succinate sustained-release matrix tablets-formulation development and *in vitro* evaluation. *Int J Pharm Pharm Sci* 2014;6:481-6.