ORIGINAL ARTICLE

Floating and bioadhesive delivery system of metoprolol succinate: Formulation, development and *in vitro* evaluation

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Aim of this study was to develop gastroretentive sustained release floating and bioadhesive drug delivery system (FBDDS) to prolong the gastric retention time of Metoprolol succinate. Tablets were prepared employing hydroxypropyl methylcellulose (HPMC K100M) as hydrophilic gel material, sodium bicarbonate as gas-generating agent and Sodium CMC (SCMC) as bioadhesive polymer. A 3^2 full factorial design and response surface methodology were used for designing of experiment, mapping change in responses and deriving optimum formulation. Selected independent variables were amounts HPMC K100M and SCMC polymer while floating lag time (FLT), bioadhesive strength, t_{50} (time taken to release 50% of drug) and t_{90} (time taken to release 90% of drug) were selected as dependent variables. Investigation of functionality of individual polymer to predict effect on dependent variable were statistically analyzed using the RSM. Tablets were also evaluated for physical properties, swelling and matrix erosion. Increase in concentration of HPMC and decrease in concentration of SCMC resulted in retardation of drug release. Furthermore, combination of HPMC K100M and sodium bicarbonate along with SCMC was found to affect buoyancy, bioadhesion strength and drug release. Optimized formulation showed values of dependent variables close to predicted values. Optimized formulation follows Higuchi kinetics with short buoyancy lag time, total buoyancy time of more than 24 hours and could maintain drug release for 24 hours. Content uniformity, hardness, friability, weight variation were all lying within limits. Hence, FBDDS was found to be very promising and alternative approach to increase gastric retention of dosage form and may improve bioavailability.

Key words: *Detachment force, factorial design, floating and bioadhesive system, floating lag time, metoprolol succinate*

INTRODUCTION

Oral sustained release systems is most popular drug delivery systems as it offer advantages over the conventional systems like reduction in fluctuation of steady state plasma levels which helps in effective treatment of disease condition, maximum utilization of drug enabling reduction in total amount of dose administered, reduction in health care cost through improved therapy. Moreover, it improves patient compliance and convenience due less frequency of dosing thereof, reduces treatment period.[1-4] However, rapid gastrointestinal transit of a sustained release dosage forms reduces its gastric residence time (short period of 6 hours only, normal intestinal transit time) thereof, lower the extent of absorption of drugs having narrow absorption window (upper gastrointestinal (GI) track), less solubility at basic pH (above 6) and get degraded or metabolized in intestine.[5-8] Hence, the formulation of a gastroretentive dosages form prolongs residence time of a drug at the absorption site and improves absorption.[9] Several approaches become known to extend gastric retention and to improve bioavailability of formulation viz high density, magnetic systems, unfoldable system, swellable, bioadhesive and floating systems amongst all floating and bioadhesive drug delivery systems are extensively used approaches

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as efficient tool to modulate release profile and GI residence time.[10-13] Dosage form reside inside the GI track affected by many physical parameters such as density and dimension of dosage form, the fasting or fed state of the patient[14-16] Floating drug delivery systems (FDDS), a low density system remain buoyant in the stomach and sustaining drug release over a desired period of time with predetermined rate at absorption site. The bioadhesive polymers in bioadhesive drug delivery systems (BDDS) get adhered to epithelial lining of the stomach and locally deliver drug at desired rate.[9,13,17] Furthermore, buoyancy of FDDS is limited to amount of gastric fluid present inside the stomach as gastric fluid content lowers (as in fasting state) buoyancy of dosage form get hinder and may pass down the GI track hence, buoyancy of dosage form may be restricted to only 3–4 hours (normal gastric emptying time). BDDS adhere to the mucosal lining inside the stomach, which otherwise get may displace due to gastric motility. The limitations of both FDDS and BDDS can be conquered using a combination of floating and bioadhesive system (FBDDS) which would improve contact time with gastric epithelial cells, therapeutics efficacy and bioavailability of a drug.[18-20] On the basis of principle involved in buoyancy, two different systems i.e., effervescent and non-effervescent have been utilized in the formulation of FDDS. Effervescent systems are matrix type of systems prepared using swellable polymers such as methyl cellulose, chitosan and various effervescent compounds such as sodium bicarbonate, tartaric acid, and citric acid. As effervescent systems came in acidic environment of GI track, carbon dioxide is liberated which gets entrapped in swollen hydrocolloids and provides buoyancy to the dosage form while, non-effervescent systems are formulated using polysaccharides, highly swellable hydrocolloids (e.g. cellulose-type), and matrix forming polymers such as polyacrylate, polymethacrylate, and polystyrene.[13]

Matrix tablets using polymers such as hydroxypropyl methylcellulose (HPMC K15M, K4M), guar gum (GG) and sodium carboxymethyl cellulose (SCMC), alone or in combination were developed by Srivastava, A.K. *et al*, to prolong gastric residence time and increase drug bioavailability.[17] Natural gum and psyllium husk in combination with HPMC were evaluated for matrix forming property in development of FDDS by Dave *et al*, and Chavanpatil *et al*.[5,21] Chowdary K.P.R. designed and evaluated oral controlled release bioadhesive system using polymers like HPMC, Sodium CMC and Ethyl cellulose (EC).[22] FBDDS using different polymers such as HPMC K4M, Sodium CMC, polyacrylic acid (PAA) and polymethacrylic acid (PMA) and Sodium bicarbonate ($NaHCO_3$) as gas generating agent is developed and evaluated by Varshosaz *et al*.[23] Due to hydrophilic and gel forming property of hydroxypropyl methylcellulose and bioadhesive nature of sodium CMC are used as matrix forming polymer and bioadhesive agent respectively in development of FBDDS to achieve promising results.

Metoprolol succinate (MS), a β1-selective adrenergic blocking agent used to treat patients with hypertension or angina pectoris.[24] Due to short half-life (3-4 hours) and low oral bioavailability (40%) MS[25] requires to be administered in multiple doses to maintain a steady state plasma concentration for a good therapeutic response as selective β1 blockers at low concentrations have little impact on β2-mediated effects. However, as their plasma concentrations become greater, β1 blockers increasingly inhibit β2-mediated responses. Once-daily preparations simplifies the dosage regimen, reduces dosage frequency, facilitates compliance and decrease the risk of myocardial infarction and sudden cardiac arrest in the patients.[26-30]

Factorial design,[31] contour plots and response surface methodology are very useful tools to obtain various types of experimental designs, an appropriate mathematical model, and correlating the responses over desired experimental region with least number of trials for development and optimization of desired formulation. It is also a very efficient tool for studying the impact of each material, their interaction and the number of process variable affecting the formulation characteristics in limited number of trials. Optimization method is far more useful and economic than the traditional methods of formulating dosage forms as it needs less experimentation and time.[32-36]

The aim of present research work was to develop gastroretentive sustained release FBDDS and to study the effect of several formulation variables on the release rate floating and bioadhesive property of dosage form using MS as model drug. Further, A 3^2 full factorial design was used to develop appropriate mathematical model and to investigate the effect of two independent variables (factors) (i.e., the amounts of two swellable polymers) on release rate, floating and bioadhesive property. The *in vitro* release data was subjected to curve fitting analysis to obtain the release parameters t_{50} (time taken to release 50% of drug) and t_{90} (time taken to release 90% of drug).

EXPERIMENTAL

Materials

Metoprolol succinate was obtained as gift sample from Cipla Pharmaceuticals Ltd., (Goa, India), HPMC K100M were kindly supplied by Colorcon Ltd., (Goa, India). Sodium CMC was obtained from Lupin Pharmaceuticals (Pune, India). Ethyl cellulose was provided by Alembic Pharmaceuticals Ltd. (Vadodara, India). Other materials used were of AR grade and were purchased from S D Fine Chemicals (Mumbai, India).

Experimental design

Formulation and development

A full-factorial 3^2 design was applied for optimization. The design is very useful to obtain an appropriate mathematical model, and correlating the responses over

desired experimental region with less number of trials were performed with Design-Expert software (Trial, Version 7.1.2, Stat-Ease Inc. Minneapolis, MN) for development and optimization of desired formulation. The two factors were evaluated at 3 different levels and experimental batches were taken at all 9 possibilities. The amount HPMC K100M (X_1) and SCMC (X_2) were selected as independent variables while selected dependent variables are t_{50}, t_{90}, floating lag time (FLT) and detachment force. The proposed formulations are given in [Table 1].

Preparation of tablets

Sustained release gastroretentive tablets of MS were prepared by a direct compression. The tablets were prepared by blending (geometric type) required quantities of HPMC K100M, SCMC, EC, dicalcium phosphate (DCP) and sodium bicarbonate. All excipients were mixed using a mortar and pestle, and lubricated with magnesium stearate. The blended powders were compressed in to flat face tablets using 10 station rotary compression machine (Rimek, India) with 13 mm flat tooling and hardness was maintained in range of 7-9 kg/cm^2.

Evaluation of tablets

Assay and physical characteristics

Randomly selected three tablets of each formulation were assayed using 0.1N HCl (extracting solvent) and samples were analyzed spectrophotometrically (Shimadzu 2501PC, Japan) at 273.70 nm.[37] The assay was performed in triplicate and average values were reported. Tablets were also evaluated for hardness (n = 6) (Pfizer type hardness tester Cadmach, Ahmedabad, India), friability (n = 10) (Roche friabilator Remi Electronics, Mumbai, India), weight variation (n = 20) and thickness (n = 10) according to standard procedure of US Pharmacopeia.[37]

Determination of floating behavior of tablets

The floating lag time (FLT) and buoyancy duration were determined using a 500 ml beaker containing 0.1N HCl at 37 ± 0.5°C. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as FLT. Buoyancy duration is the time during which the tablet remains buoyant.[38]

Ex-vivo mucoadhesion measurement

Mecmesin ultra tester (detachment force) flag type

The detachment force (the force required to separate tablet from tissue surface) was measure using freshly obtained goat intestine. The goat intestine was cut in to pieces and was mounted with mucus surface towards upward side on wooden block [Figure 1] specially prepared for holding mucosal tissues for bioadhesion testing. The wooden block was placed with double sided adhesive tape to support the tissue on it. The thread was tied to firmly place the tissue on wooden block. The tablet was attached using cyanoacrylate glue and placed on the mucus membrane held on a wooden block. The entire set up was mounted on platform of test stand of *mecmesin ultra tester*. Before the measurement the mucus membrane was moistened with saline water at the predetermined force of 0.5 N for a contact time of 5 minutes.[39] The time and weight were kept constant for all batches. Contact time of tablet with mucosa is important as pre-swelling is necessary for bioadhesive polymer chain disentanglement and establishment of intimate contact between polymer and mucin chains. At the end of contact time, the upper support was withdrawn at a speed of 0.5 mm/sec to detach the membrane from the tablet. The detachment force (the force required to separate tablet from tissue surface) was reported as bioadhesive strength.[40,41]

Rotating cylinder method

Adhesion time was measured using USP type VI apparatus (Rotating cylinder), at 37 ± 0.5°C, at 50 rpm using 0.1N HCl

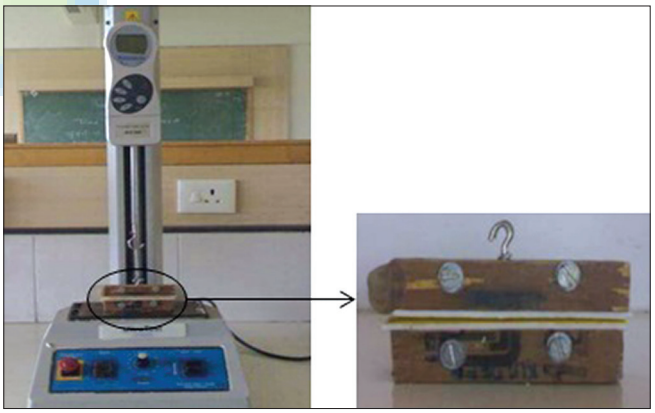

Figure 1: Mecmesin ultra tester and its wooden block

Table 1: 3^2 factorial design of MS formulation

Ingredients (mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprolol succinate	95	95	95	95	95	95	95	95	95
HPMC K100M	200	200	200	240	240	240	280	280	280
SCMC	50	75	100	50	75	100	50	75	100
EC	52	52	52	52	52	52	52	52	52
Sod. Bicarbonate	70	70	70	70	70	70	70	70	70
Mg-Stearate	3	3	3	3	3	3	3	3	3
DCP	130	105	80	90	65	40	50	25	---
Total	600	600	600	600	600	600	600	600	600

as a medium for 24 hours. Fresh goat gastric mucosa was procured from slotter house and attached to the cylinder using cyanoacrylate glue. The tablet was pressed gently on the mucosa for 1 minute and observed visually at an interval of 1 hour for 24 hours.[39]

Determination of swelling index and matrix erosion

The swelling index of pre weighed tablet was determined in USP type I dissolution apparatus (DISSO 2000 LABINDIA) at 50 rpm containing 500 ml of 0.1 N HCl maintained at 37 ± 0.5°C.[40-42] At selected time intervals, the tablets were removed, wiped gently with a tissue paper to remove surface water and weighed. Swelling characteristics of the tablet was expressed in terms of swelling index and calculated by using following formula.[11] The measurement was carried out in triplicate (n = 3).

$$\% \text{ swelling} = (W_2 - W_1) \times 100 / W_1 \quad (1)$$

Where W_1:- initial weight of tablet, W_2:- weight of disc after specified time interval.[43]

The swollen discs after 24 hours in swelling study were dried at 60°C in vacuum oven and subsequently dried desiccators for 2 days and reweighed (W3). Matrix erosion was calculated by using following formula:

$$\text{Matrix erosion} = (W1\text{-}W3) \times 100 / W1 \quad (2)$$

Where, W1- initial weight of disc, W3 = Weight of discs dried at 60°C for 24 hours in vacuum oven.

In vitro drug release

In vitro dissolution of all formulations was carried out in triplicate using rotating basket method (USP Type I apparatus) and 900 ml of preheated (at 37 ± 5°C) 0.1 N HCl as medium at 50 rpm. At fixed time intervals (every 2 hours up to 24 hours), 5 ml of each sample was taken and filtered through Whatman filter paper no. 31 and media was replaced with fresh 5 ml of dissolution media to maintain sink condition. The samples were analyzed by UV Spectrophotometer (Shimadzu 2501PC, Japan) at 273.70 nm and cumulative percent drug release was calculated using Microsoft excel 2007 software.[37]

Analysis of release data

Different mathematical models (zero-order, first-order, and Higuchi) were used to analyze the release data. The coefficient of determination (R^2) was used as criteria to choose the best model describing drug release. The release mechanism was determined by using the Korsmayer–Peppas mathematical model.

$$Mt/M\infty = kt^n \quad (3)$$

where, Mt is the drug released at time t, M∞ the drug released at infinite time, k the kinetic constant and n the release exponent[44] (the average sum of squares) differences of percent drug dissolved in test and reference products. Similarity Factor (f2) is a logarithmic reciprocal square root transformation of one plus the mean squared.

$$f_2 = 50 \log \{(1 + (1/n) \Sigma (Rj\text{-}Tj)^{2})^{-0.5} \times 100\} \quad (4)$$

j=1

According to FDA, the two dissolution profiles are similar if f_2 is between 50 and 100. In general f_2 values higher than 50 (50-100) indicate similarity of dissolution profiles.[44,45]

Data analysis and graph plotting was carried out by using Microsoft excel 2007 and GraphPad PRISM® version 5 (Trial) (Graph Pad Software Inc.) software.

Statistical analysis

All the data obtained was presented as mean ± SD. The ANOVA was applied to differentiate between two associated parameters using Graph Pad PRISM® version 5(Trial) (Graph Pad Software Inc.) software.

Stability study

The optimized formulation was wrapped in aluminium foil and subjected to 40 ± 0.5°C temperature for the period of one month. The formulation was analyzed for organoleptic characteristics, hardness, and drug content and *in vitro* drug release.[46] Similarity factor f_2 was calculated to determine the variation in drug release pattern after the storage period. The study was carried out in triplicate (n = 3).

RESULTS AND DISCUSSION

Evaluation of tablets

Thickness of tablets was found to be 4.7 ± 0.4 mm and tablet weights varied between 595 mg to 605 mg. Per cent weight loss in the friability test was found to be less than 0.5% in all formulations. Content uniformity was found 100 ± 2%. All results obtained were within acceptable limit. Hardness of tablets was retained in the range of 7 - 9 kg/cm^2.

Determination of floating behavior

An effervescent floating drug delivery was used to achieve *in vitro* buoyancy. Sodium bicarbonate, a gas-generating agent induced CO_2 generation in dissolution medium (0.1N HCl). Hydration of polymer forms a gel like structure which trapped the generated gas and thus lowering density (below 1) of the tablet thereby tablet becomes buoyant. A good correlation between *in vitro* and *in vivo* buoyancy of floating dosage forms was reported in literature.[47] All the tablets produced good gel strength, entrapping CO_2 gas and imparting stable and persistent buoyancy. All tablet batches (F1 to F9) exhibited satisfactory floatation ability and remained buoyant for more than 24 hours in dissolution medium (0.1 N HCl). Floating lag time (FLT), for all batches (F1 to F9) was found to be

5.05 ± 0.45 to 11 ± 1 min [Table 2]. These results indicate that the buoyancy lag-time was satisfactory. From results it can be concluded that floating lag time decrease from formulation F1 to F9 due to increase in quantity of both hydrophilic and swellable polymers such as HPMC K100M and SCMC. Hydration time of HPMC K100M and SCMC is inversely proportional to their concentration which speeds up water uptake and the gas generation processes which further decreases the floating lag time from formulation F1 to F9. In addition, the gas generating base ($NaHCO_3$) decreases the lag time by accelerating the hydration of the swelling polymer, thus allowing a higher floating duration because of constant generation and subsequent trapping of CO_2. Hence, tablets developed using effervescent technique prolongs the gastric residence time of formulation and may improve bioavailability. Two way ANOVA analysis suggested that both the polymers significantly ($P < 0.05$) influence on floating lag time.

Ex-vivo mucoadhesion measurement

Mecmesin ultra tester (Detachment force)

The results of the detachment force are given in [Table 2]. In all the formulations, as the concentration of both polymers increased, the detachment force was found to be increased and exhibited satisfactory adhesion duration ability and remained adhered for longer than 20 hours in dissolution medium (0.1N HCl). Bioadhesion involves the interaction between two surfaces (material and mucus membrane) which held together by interfacial forces. Hydrophilic polymers like HPMC and SCMC absorbed water from mucus membrane lining the epithelial cells when stick to mucosal surfaces and this assisted in adhesion to mucus membrane. Moreover, hydrophilic polymer formed hydrogen bonding with mucus which increased the bioadhesion strength. Hence, detachment force increased with increased polymer concentration. As polymer amount increased it provides more sites and polymer chains for interpenetration in mucin and bioadhesion, thereof bioadhesive strength got augmented. Hence, tablets developed using a bioadhesive polymers prolong the gastric residence time of formulation and may improve bioavailability. Application two way ANOVA suggested that both the polymers significantly ($P < 0.001$) modulate the bioadhesion strength.

Table 2: Floating lag time and detachment force of formulations

Formulation	Floating lag time (FLT) (min)	Detachment force (mN)
	Mean ± SD (n = 3)	Mean ± SD (n = 3)
F1	11.00±1.00	265±10.81
F2	10.38±0.98	309±12.28
F3	9.16±1.04	343±9.53
F4	8.71±0.51	402±11.53
F5	7.71±0.56	445±13.28
F6	7.56±0.73	483±17.08
F7	6.03±0.56	557±7.54
F8	5.05±0.45	604±13.52
F9	5.26±0.92	646±10.53

Swelling index and matrix erosion

The swelling index of the formulation was calculated according to process described by Grabovac *et al*., 2005. The percentage water uptake of the formulations (F1–F9) at 24 hours ranged from 322.87 to 515.03%, shown in [Figure 2]. The water uptake capacity enhanced with increased concentration of both polymer as they are cellulose derivative and have a more tendency to attract water and so swelling index get increased. Drug release is markedly influenced by the diffusion path length as the diffusion length decreases the release rate increases and vice versa. The diffusion path length proportionally depends on hydration volume of the system as it expands swelling get increased. Increase in diffusion path length and tablet dimensions with increase in hydration volume is due to more flexibility, mobility and expansion of the polymer chains which leads to marked swelling. For a highly water soluble drug or BCS class one drug the rapid and higher swelling is important to sustain the release rate. Consequently, rapid and higher hydration results in faster carbon dioxide gas generation, thereof, reducing the floating lag-time (FLT). Hence, drug release was initially more and then sustained gradually. Increased concentration of SCMC in the formulations leads to higher percentage matrix erosion [Figure 3] as SCMC formed stable colloidal dispersion in water and thereby eroded to a greater extent. But on increasing concentration of HPMC matrix erosion get decreased as HPMC forms complex matrix network which maintained tablet integrity. Hence, tablets developed using swellable polymers prolong the gastric residence time of formulation and may improve bioavailability.

In vitro drug release

The results were shown in Figure 4. HPMC and SCMC are hydrophilic polymers. When tablets containing these polymers come in contact with water, hydrophilic polymers

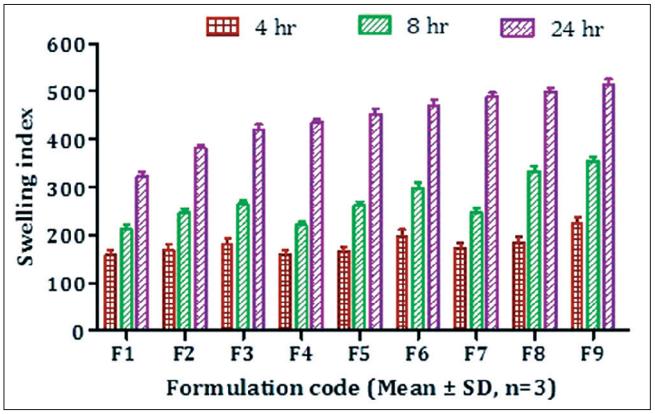

Figure 2: Swelling indices of different formulations

allow hydration of the tablet matrix, leading to swelling of the tablet as discussed before. Water decreases the glass transition temperature of the polymers to the experimental temperature. At this temperature glassy polymer is transformed into a rubbery state. Mobility of polymeric chains is enhanced in this state. This favors the transport of water into tablet and consequently transport of the dissolved drug from tablet core to the dissolution medium. Drug release from matrix tablet is determined by drug characteristics, delivery system and destination (site of drug release). Drug content of each tablet was 95 mg and 900 ml of dissolution medium was used for dissolution studies. Metoprolol was found to have 184.66 mg/ml solubility in 0.1 N HCl at 25°C. Maintaining sink condition is important during the dissolution experiment for consistent and accurate measurement of the dissolution rate. Sink conditions could be maintained throughout the dissolution study and drug solubility could not be a factor responsible for retardation of drug release from the formulations studied. Hence, retardation of drug release from the formulations could be attributed to the properties of polymers used in the formulations.

Drug release studies were made to determine whether the release of the drug is slow enough, i.e. which polymer percentage is enough to sustain the release of the drug for at least 24 hours. As Figure 4 shows, increasing the SCMC content of tablets increases the percentage of drug released. This is because of rapid swelling and erosion of SCMC in contact with water. Further, the increase in rate of drug release could be explained by the ability of the SCMC to absorb water, thereby promoting the dissolution, and hence, the release of the highly water soluble drug i.e. metoprolol succinate. Moreover, the hydrophilic polymers would leak out and hence, create more pores and channels for the drug to diffuse out of the system. Whereas, increasing the HPMC content of tablets decrease the percentage of drug released. These findings are in compliance with the ability of HPMC to form complex matrix network which leads to increase in the diffusion path so the amount of drug released decreases. Hence, tablets developed using combination of HPMC and SCMC polymers released drug at target site for prolong period of time.

Data treatment

The R^2 values of various models are given in [Table 3]. In all the formulations the R^2 values were higher for Zero order model than for first order model indicating that the drug release from the formulation followed zero order kinetics. The R^2 value ($R^2 > 0.9712$) obtained for Higuchi equation, indicated that the drug release mechanism was diffusion controlled. The values of 'n' in Peppas model also indicated

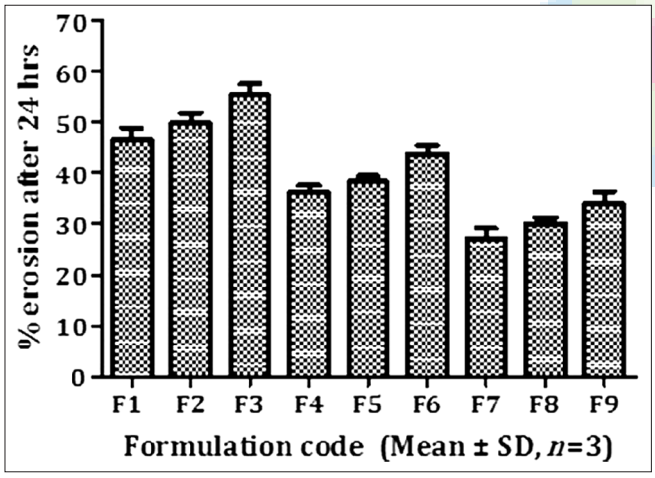

Figure 3: Per cent erosion of different formulations

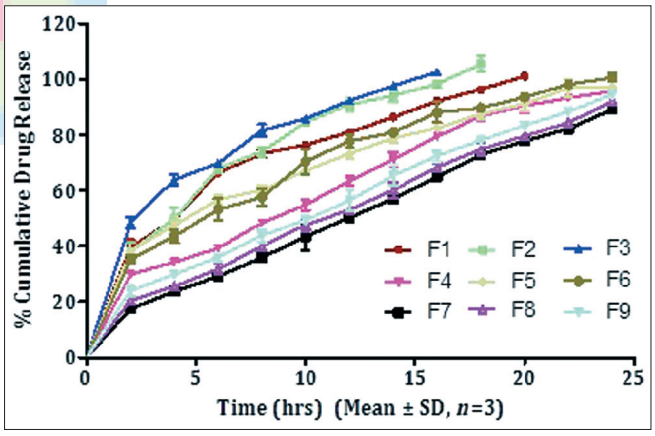

Figure 4: Dissolution profiles of formulations

Table 3: Drug release kinetics of formulations

Formulation	Zero order		First order		Higuchi		Korsemayer-Peppas	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	N
F1	0.9445	3.1961	0.9417	–0.068	0.9846	19.72	0.9867	0.4086
F2	0.9431	4.033	0.9488	–0.102	0.9853	23.84	0.9881	0.4713
F3	0.9649	3.687	0.9179	–0.101	0.9712	20.63	0.9954	0.3579
F4	0.9795	3.3621	0.9422	–0.059	0.9963	21.84	0.9573	0.5412
F5	0.9799	2.699	0.8982	–0.064	0.9893	17.77	0.9925	0.3934
F6	0.9595	3.0122	0.8909	–0.079	0.9893	19.97	0.9876	0.4527
F7	0.9987	3.3695	0.9249	–0.039	0.9741	21.07	0.9837	0.6926
F8	0.9991	3.451	0.8761	–0.048	0.9736	22.24	0.9756	0.6580
F9	0.9915	3.55	0.9449	–0.045	0.9849	22.35	0.9839	0.6701

and supported that diffusion and erosion were key factor controlling drug released.

Optimization data analysis

Response surface methodology (RSM) is very useful tool in the development and optimization of formulation. Design Expert software (trial version) was used in the current optimization study to generate various polynomial models (including interaction) and quadratic terms for all dependent parameters using multiple linear regression analysis (MLRA) approach. The generalized MLRA equation is given below:

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_1X_2 + \beta_4X_1^2 + \beta_5X_2^2 \quad (5)$$

where, β0 is the intercept representing the arithmetic average of all quantitative outcomes of 9 runs; β_1 to β_5 are the coefficients of observed experimental values of Y; and X_1 and X_2 are the coded levels of independent variable(s). The terms X_1X_2 represents the interaction. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative). The analysis of variance (ANOVA) was performed to identify the insignificant factors and reduce the equation in order to get better lack of fit.[34,48,49]

Model assessment for the dependent variables

Model for t_{50}

After putting the data in Design Expert software and application of fit summary the linear model had been suggested by the software so as per this model the equation was as follows. The response surface plot given in [Figure 5].

Model equation in coded terms:

$$t_{50} = +6.31 + 4.37A - 1.04B \quad (6)$$

The result of multiple linear regression analysis (linear model) revealed that, on increasing the concentration of HPMC t_{50} increased and reverse for SCMC as the signs were positive and negative respectively.

Model for t_{90}

After putting the data in Design Expert software and application of fit summary the linear model had been suggested by the software so as per this model the equation was as follows. The response surface plot given in [Figure 6].

Model equation in coded terms:

$$t_{90} = +18.31 + 4.61A - 1.13B \quad (7)$$

The result of multiple linear regression analysis (linear model) reveals that, on increasing the concentration of HPMC t_{90} increased and reverse for SCMC as the signs were positive and negative respectively.

Model for floating lag time (FLT)

After putting the data in Design Expert software and application of fit summary the linear model had been suggested by the software so as per this model the equation was as follows. The response surface plot given in [Figure 7].

Model equation in coded terms

$$FLT = +7.87 - 2.37A - 0.63B \quad (8)$$

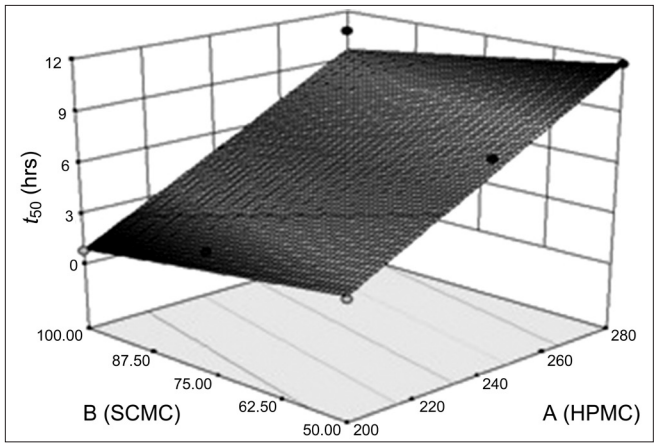

Figure 5: Response surface plot of t_{50}

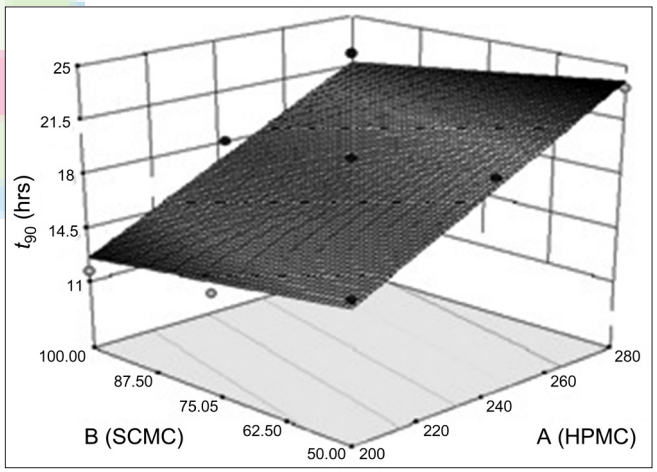

Figure 6: Response surface plot of t_{90}

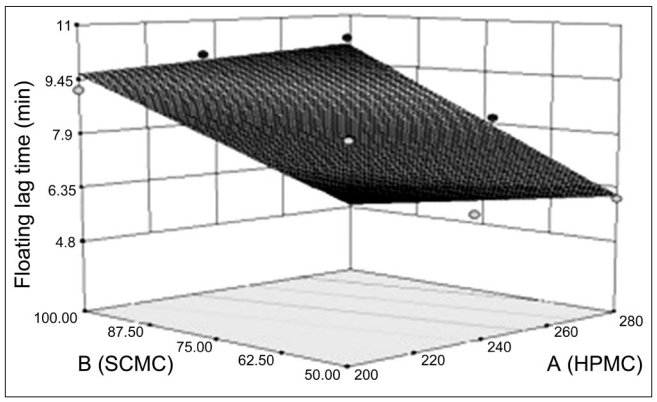

Figure 7: Response surface plot of floating lag time

The result of multiple linear regression analysis (linear model) reveals that, on increasing concentration of HPMC and SCMC, FLT was decreased.

Model for adhesion strength

After putting the data in Design Expert software and application of fit summary the linear model had been suggested by the software so as per this model the equation was as follows. The response surface plot given in [Figure 8].

Model equation in coded terms

$$\text{Adhesion strength} = +443.33 + 148.33A + 41.33B + 2.75AB + 10.67A^2 \quad (9)$$

The result of multiple linear regression analysis (linear model) reveals that both HPMC and SCMC increased the adhesion strength of tablets.

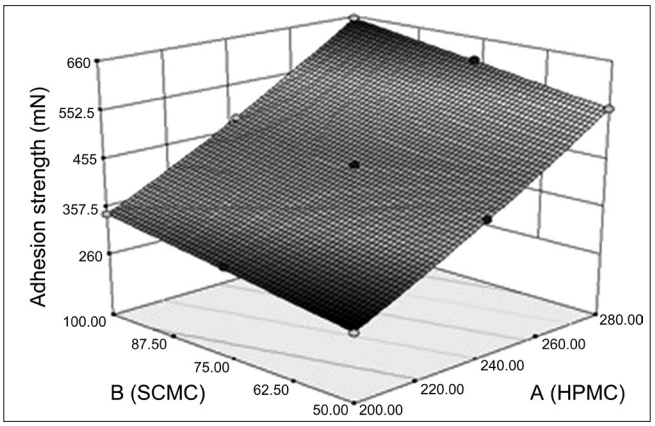

Figure 8: Response surface plot of adhesion strength

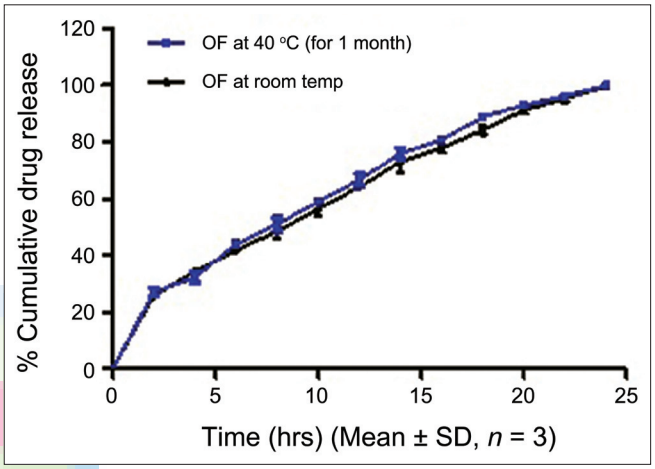

Figure 9: Floating lag time of optimized formulation

Optimization result

The optimization was performed on the basis of response surface modeling by using the numerical and graphical optimization method. Desirability was a key function that ranges from zero (outside the limits) to one (at the goal). The numerical optimization finds a point that maximizes the desirability function. The characteristics of a goal may be altered by adjusting the weight or importance. For several responses and factors, all goals get combined into one desirability function. The goal of optimization was to find a good set of conditions that will meet all the goals.

The composition of the optimized formulation suggested by the software was given in [Table 4]. Tablets were compressed with hardness 8 kg/cm^2 and evaluated for all the tablet parameters mentioned above. The predicted and experimental results of the optimized formulation were given in [Table 5]. The comparison between predicted and experimental values was carried out to estimate the resemblance. In physical evaluation of tablets, thickness was found to be 4.7 ± 0.6 mm. Tablet weight and content uniformity were found to be 598 mg and 99.92 2% respectively. All results obtained were within acceptable limits. The floating lag time of the optimized formulation was shown in [Figure 9].

Figure 10: Dissolution profiles of OF at room temperature and at 40°C

Stability study

In physical evaluation of tablet, hardness was found to be 8 kg/cm^2. Thickness, weight, and content uniformity of tablets were found to be 4.5 ± 0.6 mm, 597 mg and 98.92 ± 3% respectively. Results of dissolution profile for

Table 4: Composition of optimized formulation

Optimized formulation	Metoprolol succinate	HPMCK100M	SCMC	EC	Sod. bicarbonate	Mg- stearate	DCP	Total
Quantity (mg)	95	254.76	75.27	52	70	03	52.5	600

Table 5: Predicted and experimental values obtained for optimized formulation

Responses	Predicted values	Experimental values Mean ± SD (*n* = 3)
t_{50} (h)	7.91	8.60±0.56
t_{90} (h)	19.99	20.31±0.96
Floating lag time (min)	6.99	6.25±0.67
Adhesion strength (mN)	500	492±10.21

short term stability testing of optimized formulation (OF) were as depicted in the [Figure 10]. Short-term accelerated stability data obtained for optimized formulation revealed that drug content, thickness, hardness, *in-vitro* dissolution were within the acceptable limit and similarity factor f_2 was found to be 77.50. Thus the formulation was found to be stable.

CONCLUSION

Floating and bioadhesive drug delivery system of metoprolol succinate was successfully developed. The combination of gel-forming polymer, HPMC K100M and gas-generating agent, sodium bicarbonate along with SCMC was crucial to accomplish the objective for the buoyancy, bioadhesion strength and drug release. Furthermore, it can be concluded that the drug release was affected by both the polymers. Increase in concentration of HPMC and decrease in concentration of SCMC resulted in retardation of drug release. The tablets prepared using HPMC K100M and SCMC demonstrated high swelling index which also prolong gastric residence time. The tablet with high swelling index was able to maintain its physical integrity which will also assist in sustaining the drug release. High degree of predictability of 3^2 full factorial design confirm that RSM is an efficient tool for mapping the change of responses and identifying the optimized area. The optimized formulation demonstrated release parameter like t_{50} and t_{90} which were close to the predicted responses. The optimized formulation follows Higuchi kinetics with short buoyancy lag time, total buoyancy time of more than 24 hours and could maintain drug release for 24 hours. The content uniformity, hardness, friability, weight variation were all lying within the limits. Based on floating lag time, floating duration, bioadhesive strength and swelling index of the formulation it can be concluded that the development and formulation of FBDDS may prolong residence time of dosage form inside the gastrointestinal tract. Hence, a combination of floating and bioadhesive system was found to be a very promising and alternative approach to increase gastric retention of dosage form and may improve the bioavailability.

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