

## Development and optimization of metoprolol succinate gastroretentive drug delivery system

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Metoprolol succinate (MS) gastroretentive (GR) controlled release system was formulated to increase gastric residence time leading to improved drug bioavailability. Box-Behnken model was followed using novel combinations of sodium alginate (SA), sodium carboxymethylcellulose (NaCMC), magnesium aluminosilicate (MAS) as independent variables. Floating lag time (Flag),  $t_{25}$ ,  $t_{50}$ ,  $t_{75}$ , diffusion exponent as dependent variables revealed that the amount of SA, NaCMC and MAS have a significant effect ( $p < 0.05$ ) on  $t_{25}$ ,  $t_{50}$ ,  $t_{75}$  and Flag. MSGR tablets were prepared and evaluated for mass, thickness, hardness, friability, drug content and floating property. Tablets were studied for dissolution for 24 h and exhibited controlled release of MS with floating for 16 h. The release profile of the optimized batch MS01 fitted first-order kinetics ( $R^2 = 0.9868$ ,  $n = 0.543$ ), indicating non-Fickian diffusion or anomalous transport by diffusion and swelling.

**Keywords:** metoprolol succinate, gastroretention, Box-Behnken design, floating tablets, release kinetics, controlled release

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Gastric retention will provide advantages such as delivery of drugs with narrow absorption windows in the small intestinal region, namely proximal parts of the gastrointestinal tract (stomach and/or duodenum). Pharmaceutical dosage forms which remain in stomach for a prolonged period of time after oral administration and release the active ingredient in a controlled manner are important for the delivery of a wide variety of drugs (1-5).

Metoprolol succinate (MS) is a  $\beta_1$ -selective adrenergic blocking agent (6). Since the half-life of MS is ~3 to 4 h (7), multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance. It has also been reported that MS absorption mainly takes place in the duodenum and jejunum and is directly proportional to the dose available (8). A gastroretentive is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum seg-

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ments (9). MS is highly soluble throughout physiological pH. Drug solubility was 157 mg mL<sup>-1</sup> in water (pH = 5.5) and 183 mg mL<sup>-1</sup> in 0.1 mol L<sup>-1</sup> HCl solution (pH = 1.0). It is therefore a suitable candidate with high solubility for a monolithic system (10).

The present study involves the design and optimization of a novel gastroretentive, floating, swellable, controlled release tablet by combining three polymers with different concentrations: sodium alginate (SA) – rapidly hydrating, rate controlling polymer, sodium carboxymethylcellulose (NaCMC) – gel forming agent, and magnesium aluminosilicate (MAS) – swelling controlling agent. Furthermore, calcium sulphate dihydrate (CS) – cross linker, gel strength enhancer for SA, and sodium bicarbonate (SBC) as a gas generating agent were also used. The combined effect of these polymers on the floating behaviour and on *in vitro* release pattern of the MS has also been evaluated.

## EXPERIMENTAL

### *Materials*

Metoprolol succinate was received as a gift sample from Alembic Ltd., India. SA was purchased from Anshul Agencies and NaCMC from Auqualon, India. CS was purchased from JRS Pharma and SBC from S.D. Fine-Chem Ltd., India. MAS was purchased from Gangwal Chemicals, India. All the other chemicals used were of analytical grade.

### *Methods*

Calibration curves of MS were determined in 0.1 mol L<sup>-1</sup> HCl and in methanol at  $\lambda = 222$  nm ( $R = 0.9932$  and  $0.9982$ , respectively), using a UV-Visible spectrophotometer (Lambda 25, Perkin-Elmer, USA). The calibration curve in 0.1 mol L<sup>-1</sup> HCl was used for dissolution studies while drug content was determined using the calibration curve in methanol.

### *Preparation of MSGR tablets*

MSGR tablets were prepared according to the composition of optimized batches (Table I). MSGR tablets (200 mg) were prepared by the direct compression method. Initially, all ingredients were sieved through 425- $\mu$ m sieve opening, weighed and mixed for 10 min in a planetary mixer (Kenwood PM 900, UK) at 10 rpm. The drug was mixed with SA, NaCMC, MAS, SBC and CS. Finally, the MAS was added as a lubricant and mixed for additional 2–3 min. Tablets were compressed on a tableting machine (Minipress by Clit, 10 stations, Chamunda Pharma Machinery Pvt. Ltd., India) fitted with a 10.4-mm circular shaped standard concave punch with tableting force of  $(3.5 \pm 0.5) \times 10^3$  kg.

### *Characterization of MSGR tablets*

The prepared MSGR tablets were tested for physical characteristics, *viz.*, mass variation, thickness (measured using a Vernier caliper, Mitutoyo Corporation, Japan), hardness (measured with a hardness tester, Erweka, Germany) and friability (determined using a Roche friabilator, Germany).

Table I. MSGR tablet composition

Formulation batch	CS (%)	SA (%)	NaCMC (%)	MAS (%)
MSO1	25.7	15.0	15.0	5.0
MSO2	35.7	10.0	10.0	5.0
MSO3	25.7	20.0	10.0	5.0
MSO4	25.7	10.0	20.0	5.0
MSO5	15.7	20.0	20.0	5.0
MSO6	35.7	10.0	15.0	–
MSO7	25.7	20.0	15.0	–
MSO8	25.7	10.0	15.0	10.0
MSO9	15.7	20.0	15.0	10.0
MS10	35.7	15.0	10.0	–
MS11	25.7	15.0	20.0	–
MS12	25.7	15.0	10.0	10.0
MS13	15.7	15.0	20.0	10.0
MS14	25.7	30.0	–	5.0
MS15	25.7	–	30.0	5.0
MS16	30.7	15.0	15.0	–

CS – calcium sulphate dihydrate, SA – sodium alginate, NaCMC – sodium carboxymethylcellulose, MAS – magnesium aluminium metasilicate.

All batches contain 33.3 % MS, 5.0 % SBC and 1 % magnesium stearate.

Total tablet mass is 600.0 mg.

### Drug content

Accurately weighed MSGR tablets (10 tablets) were crushed to form a fine powder. An accurately weighed quantity equivalent to 200 mg of MS was transferred to a 100-mL volumetric flask. To this, 50 mL methanol was added and sonicated for 15 min. Volume was made up to the mark with methanol. The solution was filtered through a 0.45- $\mu$ m filter and 1 mL of this solution was diluted to 50 mL with methanol. Absorbance was measured at 222 nm.

### In vitro dissolution studies

The release rate of MSGR tablets ( $n = 3$ ) was determined with a USP dissolution apparatus-II (paddle method) using 75 rpm speed and 900 mL of 0.1 mol L<sup>-1</sup> HCl as dissolution medium at  $37 \pm 0.5$  °C (11). A sample (10 mL of the solution) was withdrawn from the dissolution apparatus (Electrolab, India) at regular time intervals up to 24 h (1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 h) and replaced with the same volume of fresh dissolution medium. The samples were filtered through a 0.45- $\mu$ m membrane filter and diluted to a suitable concentration with 0.1 mol L<sup>-1</sup> HCl, and the absorbance of these solutions was measured at 222 nm. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

### *In vitro buoyancy studies*

The *in vitro* buoyancy studies were performed by measuring the floating lag times according to the method of Rosa *et al.* (12). The tablets were placed in a 100-mL beaker containing 0.1 mol L<sup>-1</sup> HCl. The time required for the tablet to rise to the surface and float was defined as the floating lag time (Flag).

### *Box-Behnken design*

Statistical analysis of the Box-Behnken design batches was performed by multiple linear regression analysis using SYSTAT 12. A Box-Behnken design was constructed to study the effect of the independent variables, *viz.*, the amount of SA ( $X_1$ ), the amount of NaCMC ( $X_2$ ) and the amount of MAS ( $X_3$ ) on dependent variables like  $t_{25}$ ,  $t_{50}$ ,  $t_{75}$ , Flag of MSGR tablets.

## RESULTS AND DISCUSSION

### *Physical characterization of the tablets*

Tablet mass of all the formulations was found to be  $600.0 \pm 20.0$  mg. Tablet thickness was found to be  $6.0 \pm 0.1$  mm. The hardness of the formulation was 70 to 90 N, indicating satisfactory mechanical strength. Percentage mass loss in the friability test was 0.2 to 0.5 % in all cases, which was an indication of good mechanical resistance of the tablet. Tablets of all the prepared batches containing MS were found to be within  $100.0 \pm 5.0$  % of the labelled content, indicating content uniformity of the prepared formulations.

### *In vitro dissolution studies*

Batch MS01 released 75 % of MS in 16 h with Flag of 48 s compared to batch MS13 which showed 75 % MS release in 16 h and the Flag of 540 s, and batch MS02 with a Flag of 45 s and  $t_{75}$  of 10.2 h. Based on this data, batch MS01 was considered the best formulation with desirable Flag, therefore this formulation was selected for factorial studies to optimize the formulation and to study the effects of variables on the formulation (Tables II and III). Prepared batches show variation in drug release due to different concentrations of polymers used during their preparation (Fig. 1).

### *In vitro buoyancy studies*

The results of *in vitro* buoyancy studies showed quick floating of the tablet within 2 min after placing the tablet in dissolution medium. Studies showed that no single polymer individually was sufficient to produce buoyancy and integrity of the tablet. Flag varied between 45 s to 15 min (Table II). Buoyancy mainly depended upon the quantity of MAS and SBC. SBC of 5 % was found optimal with optimum integrity and controlled release profile of the drug from the tablet. MAS produces swelling of the tablet while SBC has the ability to generate gas in the presence of hydrochloric acid, which gets entrapped in the tablet. This leads to reduction in the density of the tablet, thereby producing floating.

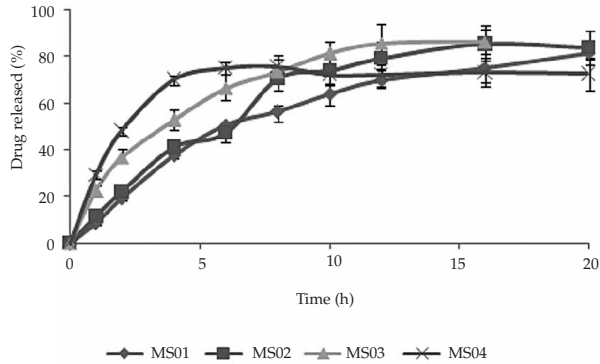


Fig. 1. MSGR tablets dissolution profile of batches MS01 to MS04. Mean  $\pm$  SD,  $n = 3$ .

In case of batches MS01 and MS02, the MAS quantity of 5.0 % produced Flag of 48 s and 45 s, respectively, while in batch MS13, the quantity of MAS of 10.0 % produced Flag of 540 s. The combination of polymer SA and NaCMC with CS showed integrity of the system and produced buoyancy in a minimum of time. These hydrophilic polymers hydrate and swell rapidly due to the imbibing of the gastrointestinal fluid by the tablet, density of the tablet is lowered due to swelling and gas formation which helps in system buoyancy.

Table II. MSGR tablet-optimization batches in the Box-Behnken design

Batch code	Coded factor level <sup>#</sup>			$t_{25}$ (min) <sup>a</sup>	$t_{50}$ (min) <sup>a</sup>	$t_{75}$ (min) <sup>a</sup>	Flag (s) <sup>a</sup>
	$X_1$	$X_2$	$X_3$				
MS01	0	0	0	180 $\pm$ 0	360 $\pm$ 0	960 $\pm$ 0	48 $\pm$ 1
MS02	-1	-1	0	132 $\pm$ 0	390 $\pm$ 0	612 $\pm$ 0	45 $\pm$ 1
MS03	1	-1	0	72 $\pm$ 0	228 $\pm$ 0	492 $\pm$ 0	>1800 $\pm$ 10
MS04	-1	1	0	48 $\pm$ 0	132 $\pm$ 0	360 $\pm$ 0	100 $\pm$ 4
MS05	1	1	0	110 $\pm$ 0	228 $\pm$ 0	450 $\pm$ 0	420 $\pm$ 3
MS06	-1	0	-1	48 $\pm$ 0	132 $\pm$ 0	348 $\pm$ 0	900 $\pm$ 6
MS07	1	0	-1	42 $\pm$ 0	108 $\pm$ 0	348 $\pm$ 0	1320 $\pm$ 13
MS08	-1	0	1	120 $\pm$ 1	336 $\pm$ 0	690 $\pm$ 0	900 $\pm$ 5
MS09	1	0	1	132 $\pm$ 1	330 $\pm$ 0	690 $\pm$ 0	390 $\pm$ 6
MS10	0	-1	-1	30 $\pm$ 1	48 $\pm$ 0	132 $\pm$ 0	780 $\pm$ 7
MS11	0	1	-1	72 $\pm$ 0	144 $\pm$ 0	360 $\pm$ 0	485 $\pm$ 4
MS12	0	-1	1	126 $\pm$ 0	348 $\pm$ 0	660 $\pm$ 0	320 $\pm$ 8
MS13	0	1	1	120 $\pm$ 0	270 $\pm$ 0	960 $\pm$ 0	540 $\pm$ 5

<sup>a</sup> Mean  $\pm$  SD,  $n = 3$ .

Table III. Translation of coded levels into actual values

Coded level	Actual value (%)		
	$X_1$	$X_2$	$X_3$
-1	10	10	0
0	15	15	5
1	20	20	10

$X_1$ ,  $X_2$ ,  $X_3$  – conc. of SA, NaCMCS and MAS, respectively (%).

### Effect of the release modulating agent and swelling morphology

Effect of 5–10 % of MAS that increased the Flag and controlled the release profile was studied. This was due to its extremely fine, porous nature, which allows the medium to penetrate into the tablet through the small holes in its particles, leading to reduction in tablet density and producing swelling that increases the Flag. Medium uptake by the tablet was determined in 0.1 mol L<sup>-1</sup> HCl. MSGR tablet showed rapid hydration and gelling intact up to 12 h.

### Kinetics of drug release

Sigma Plot 10 was used for controlled release curve fitting to select the most appropriate model. The dissolution data for batch MS01 was fitted to the Bekker-Lonsdale, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models (13–15). The release profile of the optimized batch MS01 fitted best to the first-order ( $R^2 = 0.9868$  and  $n = 0.543$ ), indicating non-Fickian diffusion or anomalous transport, with release by diffusion and swelling (combination of diffusion and erosion-controlled release). Nevertheless, the Korsmeyer-Peppas model has also shown a good coefficient of determination (Table IV).

### Box-Behnken design

The dependent variables chosen were the times required for 25, 50 and 75 % the cumulative drug release and Flag; the results showed a wide variation (Table II). The data clearly indicate that the values of  $t_{25}$ ,  $t_{50}$ ,  $t_{75}$  and Flag are strongly dependent on the in-

Table IV. Kinetic modeling of drug release

Curve fitting with model/equation	$R^2$
First-order	0.9868
Hixson-Crowell	0.9588
Higuchi	0.9688
Baker-Lonsdale	0.9517
Korsmeyer-Peppas	0.9716
$n$	0.5430

dependent variables, *viz.* the amount of SA ( $X_1$ ), the amount of NaCMC ( $X_2$ ) and the amount of MAS ( $X_3$ ). The resultant equations of all responses are given below:

$$t_{25} = -460.0 + 35.6X_1 + 36.65X_2 + 31.75X_3 + 1.22X_1X_2 + 0.18X_1X_3 - 0.48X_2X_3 - 1.82X_1^2 - 1.76X_2^2 - 1.96X_3^2 \quad (R^2 = 0.994) \quad (1)$$

$$t_{50} = -284.25 + 12.9X_1 + 47.7X_2 + 79.8X_3 + 2.58X_1X_2 + 0.18X_1X_3 - 1.74X_2X_3 - 1.83X_1^2 - 2.79X_2^2 - 3.51X_3^2 \quad (R^2 = 0.989) \quad (2)$$

$$t_{75} = -3960.75 + 301.05X_1 + 293.25X_2 + 106.8X_3 + 0.90X_1X_2 + 0.0X_1X_3 + 0.72X_2X_3 - 10.41X_1^2 - 10.05X_2^2 - 7.23X_3^2 \quad (R^2 = 0.980) \quad (3)$$

$$\text{Flag} = 1942.94.75 - 265.01X_1 + 78.98X_2 - 210.40X_3 + 2.72X_2^2 - 9.30X_1X_3 + 5.15X_2X_3 + 9.25X_1^2 - 4.59X_2^2 + 23.92X_3^2 \quad (R^2 = 0.982) \quad (4)$$

The values obtained for the coefficient of determination indicate a good fit. The data demonstrate that both  $X_1$  and  $X_2$  affect the drug release ( $t_{25}$ ,  $t_{50}$  and  $t_{75}$ ). It may also be concluded that the low level of  $X_1$  (amount of SA) and higher level of  $X_2$  (amount of NaCMC) favour preparation of gastroretentive-sustained release MS tablets. High values of the  $X_1X_2$  coefficient also suggest that the interaction between  $X_1$  and  $X_2$  had a significant ( $p < 0.05$ ) effect on  $t_{25}$ ,  $t_{50}$  and  $t_{75}$ . It can be concluded that the drug release pattern may be changed by appropriate selection of the  $X_1$ ,  $X_2$  and  $X_3$  levels. The results in Table II reveal that batches MS02, MS08, MS09 and MS12 were close to the required attributes of gastroretentive tablets in terms of  $t_{50}$ ,  $t_{75}$  and Flag, while batch MS01 was ideal because of its controlled release profile for 16 h (960 min) with the desirable Flag of 48 s. This was, therefore, considered the best formulation among all the prepared formulations.

The fitted equations relating to the response at  $t_{25}$ ,  $t_{50}$ ,  $t_{75}$  and Flag are shown in equations (5–8):

$$t_{25} = 520 - 64.2X_1 - 29.4X_2 + 6.38X_1X_2 + 1.48X_1^2 - 0.8X_2^2 - 0.008X_1X_2^2 - 0.164X_1^2X_2 \quad (R^2 = 0.874) \quad (5)$$

$$t_{50} = 2592.64 - 295.03X_1 - 155.83X_2 + 21.3X_1X_2 + 7.95X_1^2 - 0.206X_2^2 - 0.07X_1X_2^2 - 0.552X_1^2X_2 \quad (R^2 = 0.867) \quad (6)$$

$$t_{75} = 1481.78 - 385.45X_1 - 13.46X_2 + 37.62X_1X_2 + 13.75X_1^2 - 9.65X_2^2 + 0.18 X_1X_2^2 - 1.404X_1^2X_2 \quad (R^2 = 0.885) \quad (7)$$

$$\text{Flag} = -4344.0 - 1858.8X_1 + 2864.4X_2 - 100.03X_1X_2 + 163.02X_1^2 - 137.96X_2^2 + 10.48X_1X_2^2 - 8.65X_1^2X_2 \quad (R^2 = 0.891) \quad (8)$$

Values of the coefficients of determination indicate a good fit. As seen from the above equations, the individual factors, *i.e.*, the amount of SA ( $X_1$ ) and the amount of NaCMC ( $X_2$ ) had a negative effect on  $t_{25}$ ,  $t_{50}$ , and  $t_{75}$  but in combination ( $X_1X_2$ ) showed a significant ( $p < 0.05$ ) positive effect. In case of Flag,  $X_1$  showed a negative effect (decreasing floating lag time) whereas  $X_2$  had a positive effect (increasing floating lag time) while in combination they showed a negative effect (Fig. 2).

The following equations (9–12) show the effect of  $X_1$  and  $X_2$  on  $t_{25}$ ,  $t_{50}$ ,  $t_{75}$  and Flag:

$$t_{25} = 51.605 - 1.299X_1 - 3.715X_2 + 3.407X_1X_2 + 0.033X_1^2 - 1.415X_2^2 + 0.014 X_1X_2^2 - 0.113X_1^2X_2 \quad (R^2 = 0.942) \quad (9)$$

$$t_{50} = 154.843 - 5.639X_1 + 36.785X_2 + 2.066X_1X_2 + 0.106X_1^2 - 3.537X_2^2 + 0.071X_1X_2^2 - 0.086X_1^2X_2 \quad (R^2 = 0.950) \quad (10)$$

$$t_{75} = 287.407 - 1.763X_1 - 179.24X_2 + 34.446X_1X_2 + 0.062X_1^2 - 0.464X_2^2 - 0.178X_1X_2^2 - 1.089X_1^2X_2 \quad (R^2 = 0.853) \quad (11)$$

$$\text{Flag} = 154.912 + 79.046X_1 - 375.13X_2 - 12.53X_1X_2 - 1.420X_1^2 + 80.113 X_2^2 - 4.441X_1X_2^2 + 1.607X_1^2X_2 \quad (R^2 = 0.940) \quad (12)$$

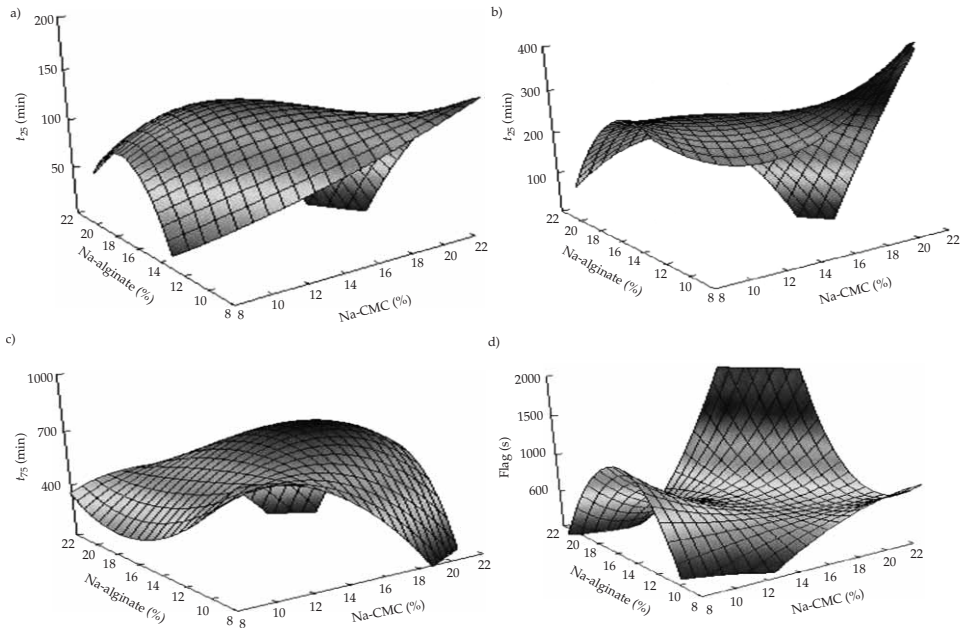


Fig. 2. Response surface plots of the concentration of SA ( $X_1$ ) and NaCMC ( $X_2$ ), vs. a)  $t_{25}$ , b)  $t_{50}$ , c)  $t_{75}$  and d) Flag.



Individual factors  $X_1$  and  $X_3$  showed a negative effect on  $t_{25}$ ,  $t_{50}$ ,  $t_{75}$  but their combination showed a significant ( $p < 0.05$ ) positive effect. Flag  $X_1$  showed a positive effect but  $X_3$  had a negative effect.

The following equations (13–16) show the effect of  $X_2$  and  $X_3$  on  $Y$  ( $t_{25}$ ,  $t_{50}$ ,  $t_{75}$  and Flag):

$$t_{25} = -185.00 + 28.20X_2 + 43.60X_3 - 1.04X_2X_3 - 0.80X_2^2 - 3.640X_3^2 + 0.164X_2X_3^2 - 0.036X_2^2X_3 \quad (R^2 = 0.974) \quad (13)$$

$$t_{50} = -462.214 + 69.771X_2 + 157.457X_3 - 7.260X_2X_3 - 2.006X_2^2 - 11.006X_3^2 + 0.552X_2X_3^2 + 0.00X_2^2X_3 \quad (R^2 = 0.974) \quad (14)$$

$$t_{75} = -2176.07 + 323.65X_2 + 461.48X_3 - 39.96X_2X_3 - 10.029X_2^2 - 23.829X_3^2 + 1.404X_2X_3^2 + 0.888X_2^2X_3 \quad (R^2 = 0.724) \quad (15)$$

$$\text{Flag} = -584.786 + 238.529X_2 + 409.84X_3 - 51.35X_2X_3 - 8.934X_2^2 - 29.734X_3^2 + 2.50X_2X_3^2 + 1.050X_2^2X_3 \quad (R^2 = 0.724) \quad (16)$$

The above equations indicate that individual factors  $X_2$  and  $X_3$  show a significant ( $p < 0.05$ ) positive effect on  $t_{25}$ ,  $t_{50}$ ,  $t_{75}$  and Flag but their combination had a negative effect.

It followed from the systematic study, using the Box-Behnken design, that the amounts of SA, NaCMC and MAS had a significant effect ( $p < 0.05$ ) on  $t_{25}$ ,  $t_{50}$ ,  $t_{75}$  and Flag. Thus, by selecting a suitable concentration of the rapidly hydrating-rate-controlling polymer (SA), gel forming agent (NaCMC) and swelling-controlling agent (MAS), the desired dissolution profile can be achieved.

## CONCLUSIONS

The present study involved the design of a novel gastroretentive floating and swellable, controlled-release, tablet of MS. Its comprised the release-rate-controlling hydrophilic polymers, a release modulator and a gas generating agent. Upon administration, the MSGR tablet was hydrated and swelled rapidly due to imbibition of the gastrointestinal fluid; subsequent gas generation helped the system buoyancy and the desired release profile. Optimized batch formulation MS01 showed buoyancy with Flag time less than one min (48 s) and remained floating for 16 h. Minimum floating time and higher percentage of swelling of the MS01 formulation is required to increase its residence time in the stomach and eventually improve the extent of bioavailability. The present study confirmed the test of the suitability of gastroretentive platform technology developed for the MSGR tablet without changing any excipients and process parameters. The optimized batch MS01GR tablet, prepared using novel combinations of SA, NaCMC and MAS, can be successfully employed as a once-a-day oral controlled release drug delivery system.

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S A Ž E T A K

**Razvoj i optimizacija sustava za isporuku metoprolol sukcinata sa zadržavanjem u želucu**

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U radu je opisan razvoj sustava za isporuku metoprolol sukcinata (MS) s kontroliranim oslobađanjem i produljenim vremenom zadržavanja u želucu (GR), u svrhu poboljšanja bioraspoloživosti. Primijenjen je Box-Behnkenov model, a kao zavisne varijable izabrane su nove kombinacije natrijevog alginata (SA), natrijeve soli karboksimetilceluloze (NaCMC) i magnezijevog aluminometasilikata (MAS). Vrijeme plutanja (Flag),  $t_{25}$ ,  $t_{50}$ ,  $t_{75}$  i difuzijski eksponent kao zavisne varijable otkrili su da količina SA, NaCMC i MAS ima značajan učinak ( $p < 0,05$ ) na  $t_{25}$ ,  $t_{50}$ ,  $t_{75}$  i Flag. Pripravljenim tabletama određena je masa, debljina, tvrdoća, lomljivost, sadržaj ljekovite tvari i sposobnost plutanja. Oslobađanje MS praćeno je 24 h. Rezultati pokazuju da je oslobađanje kontrolirano, a vrijeme plutanja 16 h. Oslobađanje iz optimiranog pripravka MS01 slijedi kinetiku prvog reda ( $R^2 = 0,9868$ ,  $n = 0,543$ ), što ukazuje na difuziju koja ne slijedi Fickov zakon već anomalni transport difuzijom i bubrenjem.

*Ključne riječi:* metoprolol sukcinat, zadržavanje u želucu, Box-Behnkenovo dizajniranje, plutajuće tablete, kinetika oslobađanja, kontrolirano oslobađanje

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