RESEARCH ARTICLE

Evaluation of effervescent floating matrix tablet formulations of salbutamol sulfate using full factorial design

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The purpose of this research was to formulate and optimize an effervescent floating tablet formulation of salbutamol sulfate using full factorial design. Salbutamol sulfate has an absorption window in the stomach and in the upper part of the small intestine. A 3^2 full factorial design (eight runs) was utilized to optimize the formulation wherein the content of hydroxylpropyl methyl cellulose (HPMC) (X_1) and sodium bicarbonate (X_2) were taken as independent variables and % drug release after 6 h (Y_1), $t_{50\%}$ (Y_2), and buoyancy lag time (BLT) (Y_3) were taken as the dependent variables. Salbutamol sufate, HPMC K4M and HPMC K100M CR, stearic acid, talc, dicalcium phosphate, polyvinyl pyrrolidone, and magnesium stearate were used for the current research work. Two viscosity grades of HPMC as matrix materials were used for formulating the tablets, which were prepared by wet granulation. The release data were evaluated by the model-dependent (curve fitting) method using the PCP Disso v2.08 software. Optimization studies were carried out using the Design Expert Software (Version 7.0.3). The *in vitro* drug release mechanism showed anomalous transport. An increase in the concentration and viscosity grade of the polymer resulted in a decrease in the release rate, but it was found that at a higher concentration of HPMC, the viscosity grade did not significantly affect the drug release. Concentration of both HPMC and sodium bicarbonate had a significant effect on the BLT. Optimized effervescent floating tablets of salbutamol sulfate were successfully prepared and a good correlation was observed between predicted and actual values of the dependent variables chosen for the study. Viscosity grade of HPMC did not significantly impact the floatability of the dosage form. Thus, we can conclude that a combination of HPMC, stearic acid, and sodium bicarbonate can be used to increase the gastric residence time of the dosage form up to 12 h.

Key words: *Buoyancy lag time, effervescent FDDS, full factorial design, HPMC, salbutamol sulfate*

INTRODUCTION

Salbutamol sulfate is a sympathomimetic agent selectively acting on the β_2-adrenergic receptor. It is used as a bronchodilator in the management of disorders such as reversible airways obstruction and chronic obstruction pulmonary diseases.[1] It shows site-specific absorption in the stomach and in the upper part of the small intestine.[2] The maximum plasma concentration occurs within 2.5 h and the plasma half-life ranges from 2.7 to 7.0 h. It is given orally at a dose of 2–4 mg, three to four times a day.[3] The oral bioavailability of salbutamol sulfate is ~40% because of extensive sulfonation in the gut and degradation in the colon.[4,5] Salbutamol sulfate thus has all the requisite characteristics for developing a gastroretentive dosage form.

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Various approaches that have been proposed to control the gastric residence of drug delivery systems in the upper part of the gastrointestinal tract include floating drug delivery systems (FDDS), high-density DDS, mucoadhesive systems, swelling and expanding DDS, modified shape systems, and other delayed gastric devices.[6-8] FDDS, also called hydrodynamically balanced system, is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug.[9] This technology is suitable for drugs with an absorption window in the stomach or in the upper part of the small intestine,[10] drugs acting locally in the stomach,[11] and for drugs that are poorly soluble or unstable in the intestinal fluid.[12] FDDS have a bulk density lower than the gastric fluid and thus remain buoyant in the stomach, without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly.[7] Based on the mechanism of buoyancy, two distinctly different technologies, i.e. noneffervescent and effervescent systems, have been utilized in the development of FDDS. The effervescent

system utilizes matrices prepared with swellable polymers and effervescent components, e.g. sodium bicarbonate and citric acid or stearic acid. The matrices are fabricated such that in the stomach carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. In noneffervescent FDDS, the drug is mixed with a gel-forming hydrocolloid, which swells on contact with the gastric fluid after oral administration and maintains relative integrity of shape and a bulk density of less than unity within an outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms.[7,13]

The purpose of this project was to prepare optimized effervescent FDDS tablet formulations of salbutamol sulfate using sodium bicarbonate and HPMC. A 3^2 full factorial design was employed to investigate the effect of two independent variables (factors), i.e. concentration of HPMC and sodium bicarbonate, on percentage of drug release after 6 h (rel_{6h}), time for 50% release of drug ($t_{50\%}$), and buoyancy lag time (BLT).

MATERIALS AND METHODS

Materials

Salbutamol sulfate was provided as a gift sample by Medioral Pvt. Ltd. (Satara, India). Hydroxylpropyl methyl cellulose (HPMC K4M and HPMC K100M CR) was provided as a gift sample by Colorcon Asia (Goa, India). Sodium bicarbonate was purchased from SD-Fine Ltd. (Mumbai, India) and stearic acid and talc from Cosmo Chem. (Pune, India). Dicalcium phosphate was gifted by Libra Drugs (Pune, India). Polyvinyl pyrrolidone and magnesium stearate were obtained as a gift sample from Signet Chemical Corporation (Mumbai, India). All chemicals used were of analytical grade.

Full factorial design

A 3^2 full factorial design was selected for this experiment. It consisted of eight full factorial design points. The independent variables selected for this study were concentration of HPMC (X_1) and sodium bicarbonate (X_2). The dependent variables included $\%rel_{6h}$ (Y_1), $t_{50\%}$ (Y_2), and BLT (Y_3).

Preparation of the salbutamol sulfate floating matrix tablet

The matrix tablet contained a mixture of drug, polymer, sodium bicarbonate, stearic acid, dicalcium phosphate, magnesium stearate, and talc. Two different polymer grades were selected, (i.e. HPMC K4M and HPMC K100M CR, of which formulations F1–F9 contained HPMC K4M and formulations F10–F18 contained HPMC K100M CR. The tablets were prepared by the wet granulation technique. All the ingredients in the requisite quantities [Table 1] were granulated using 8.5% w/v ethanolic polyvinyl pyrrolidone solution. The granules were dried in a tray dryer at 40°C for 24 h followed by lubrication and compression using an 8 mm single-station rotary compression machine (Rimek, Mumbai, India). Hardness of the tablets was kept to 6–7 kg.

Table 1: A 3^2 full factorial design and level of independent variables

Trial no.	Coded values*	
	X_1	X_2
1	–1	–1
2	–1	0
3	–1	1
4	0	–1
5	0	0
6	0	1
7	1	–1
8	1	0
9	1	1
Coded values	**Independent variables**	
	X_1	X_2
–1	20	21
0	40	42
1	60	63

X_1 is amount of HPMC in milligrams; X_2 is the amount of sodium bicarbonate in milligrams

Drug content and physical evaluation

The tablets were assayed for drug content using 0.1 N HCl as the solvent and the samples were analyzed spectrophotometrically (JASCO, V-530, Japan) at 276 nm. The tablets were also evaluated for hardness, friability, and weight variation.

BLT

The BLT of the tablets was studied at 37 ± 0.5°C in 100 ml 0.1 N HCl (pH 1.2) and acid phosphate buffer (pH 3.6, i.e. approximate pH of the stomach in fed conditions). The time required for the tablet to rise to the surface and float was determined as the BLT.

In vitro dissolution studies

The release rate of salbutamol sulfate from the floating matrix tablets was determined using the USP type II dissolution test apparatus (paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl at 37 ± 0.5°C and 75 rpm. Ten-milliliter aliquots were withdrawn at time intervals of 30 min for 12 h. The samples were replaced by their equivalent volume of dissolution medium. The samples were analyzed at 276 nm by a UV spectrophotometer (JASCO). Cumulative percentage drug release was calculated using the PCP Disso v2.08 software (Poona College of Pharmacy, Pune, India).

Data analysis

The release data were evaluated by the model-dependent (curve fitting) method using the PCP Disso v2.08 software. In the present study, the release profile followed the

Matrix–Peppas model. The Matrix–Peppas model indicates that the drug release mechanism deviates from Fick's laws and shows anomalous behavior. This is demonstrated by the following equation:

$$M_t/M_\infty = k.t^n \quad (1)$$

where M_t is the drug released at time t, M_∞ is the quantity of drug released at infinite time, k is the kinetic constant, and *n* is the release exponent. Design Expert Software (Version 7.0.3, Stat-Ease Inc., Minneapolis, MN, USA) was used to carry out the optimization studies. A statistical second-order model including interaction and polynomial terms was generated for all the response variables using multiple linear regression analysis (MLRA). The general form of the model is represented in equation (2) below:

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_1X_2 + \beta_4X_1^2 + \beta_5X_2^2 + \beta_6X_1X_2^2 + \beta_7X_1^2X_2 + \beta_8X_1^2X_2^2 \quad (2)$$

where β_0 is the arithmetic average of all the quantitative outcomes of nine runs and β_1–β_8 are the coefficients computed from the observed experimental values of Y. X_1 and X_2 are the coded levels of the independent variables. The terms X_1X_2 and X_i^2 (i = 1, 2) are the interaction and polynomial terms, respectively. The statistical validity of the polynomials was established on the basis of Yate's ANOVA provision in the Design Expert Software. A grid search was performed to locate the composition of the optimum formulations.[14,15] Besides this, three-dimensional response surface graphs were drawn in MS-Excel using the output files generated by the Design Expert Software.

RESULTS AND DISCUSSION

Effervescent floating tablets were formulated using 3^2 factorial designs. Here, three levels were selected to study the effect of variables from a lower concentration to a higher concentration of HPMC and sodium bicarbonate. Preliminary trials were carried out using different concentrations of HPMC and sodium bicarbonate to shortlist the levels required for the optimization studies. Stearic acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate, which significantly reduced the BLT of the tablets in 0.1 N HCl and acid phosphate buffer pH 3.6. Two grades of HPMC (K4M and K100M CR) were selected as a matrix-forming material because they had a pH-independent and reproducible drug release profile.

Drug content and physical evaluation

The assayed content of the drug in various formulations varied between 97.25 and 101.56%. The tablet weights varied between 148.9 and 150.8 mg and the hardness varied between 6.8 and 7.1 kg. Thus, the physical parameters of the compressed matrices were within control.

BLT studies

In the preliminary studies, salbutamol sulfate tablets were prepared using polymers such as HPMC K4M or HPMC K100M CR along with sodium bicarbonate added as a gas-generating agent, which induces CO_2 generation in the presence of 0.1 N HCl. The gas generated is trapped and protected within the gel, formed by hydration of the polymer, and thus decreasing the density of the tablet. As the density of the tablet falls below 1, the tablet becomes buoyant.[6]

All the factorial design batches showed good BLT in 0.1 N HCl, ranging from 30 to 263 s [Table 2]. As the content of sodium bicarbonate was increased from 21 to 63 mg, the BLT was found to decrease. The tablets remained buoyant throughout the duration of the dissolution studies, i.e. 12 h. As the content of the polymer in the matrix was increased from 20 to 60 mg, the BLT was found to decrease. In case of formulations F1 and F10, the BLT was much higher (263 and 202 s, respectively) due to the low level of sodium bicarbonate (21 mg) and polymer (20 mg). The viscosity of HPMC did not have a significant impact on the BLT [Table 2]. It was reasoned that at an HPMC concentration of 20% or more, the particles of HPMC are close enough to permit a faster establishment of the gel layer in a manner that minimizes the effect of the different viscosities of the polymer, although the rate of swelling of the particles with a high viscosity grade was slow compared with a low-viscosity HPMC [Table 2].

In vitro dissolution studies

In vitro dissolution studies were performed on the 18 formulations to chart the dissolution profile in order to predict the *in vivo* profile. Formulations F2, F3, and F12 were found to disintegrate within 6 h. This can be attributed to

Table 2: Effect of pH on the buoyancy lag time

	Buoyancy lag time (s)	
	0.1 N HCl	Acid phosphate buffer*
F1	263	461
F2	88	277
F3	64	229
F4	180	672
F5	70	249
F6	49	215
F7	56	318
F8	57	224
F9	39	220
F10	205	210
F11	52	207
F12	48	163
F13	152	330
F14	59	322
F15	45	133
F16	71	285
F17	38	225
F18	30	214

*pH 3.6

the low level of polymer due to which the gel layer had comparatively poor strength and hence could not sustain the larger amount of gas generated due to the higher concentration of sodium bicarbonate. The concentration of sodium bicarbonate did not have a significant effect on the $\%rel_{6h}$. Formulations F4, F5, and F6 showed 79.53–83.28% release in 6 h and 100% release in 10 h whereas in formulations F13, F14, and F15, the drug release in 6 h was found to be in the range of 77.45–79.62% and 100% release in 11 h. As the content of HPMC (X_1) was increased, greater retardation of drug release was observed. Formulations F7–F9 showed 70.18–74.54% release in 6 h and 95.87–96.71% release in 12 h. Formulations F16–F18 showed 68.67–72.66% release within 6 h and 93.38–94.29% of release in 12 h [Figure 1]. It was found that at a higher concentration of the polymer, the viscosity grade of HPMC did not significantly affect the drug release [Figure 1].

Kinetics of drug release

In case of controlled or sustained release formulations, diffusion, swelling, and erosion are the three most important rate-controlling mechanisms. Formulations containing swelling polymers show swelling as well as diffusion mechanism because the kinetics of swelling include relaxation of polymer chains and imbibitions of water, causing the polymer to swell and changing it from a glassy to a rubbery state. The release exponent *n* is indicative of the mechanics of drug release from the formulation. A value of 0.5 is indicative of diffusion-controlled drug release and 1.0 indicates swelling-controlled drug release. A value of *n* between 0.5 and 1.0 indicates anomalous transport, i.e. both swelling- and diffusion-controlled release mechanism. Matrix tablets have *n*-values in the range of 0.45–0.89, signifying anomalous transport.[16,17] The value of *n* for all the formulations is presented in Table 3. These range from 0.710 to 0.890 while for the marketed formulation, the value was 0.785, indicating anomalous transport. The value of *n* was found to decrease as the concentration of the polymer increased [Table 3].

Response surface method optimization results

Mathematical modeling

Mathematical relationships generated using MLRA for the studied response variables are expressed in equations 3–8.

Equations for F1–F9

$$rel_{6h} = 83.26 - 11.59X_1 + 0.69X_1^2 + 1.78X_2 - 0.13X_2^2 + 0.45X_1X_2 - 0.049X_1^2X_2 - 0.044X_1X_2^2 + 0.17X_1^2X_2^2 \quad (3)$$

$$t_{50\%} = 2.96 + 0.40X_1 - 0.015X_1^2 - 0.14X_2 + 0.003056X_2^2 - 0.056X_1X_2 + 0.007083X_1^2X_2 + 0.00008333X_1X_2^2 - 0.007472X_1^2X_2^2. \quad (4)$$

$$BLT = 107.33 - 27.17X_1 + 3.83X_1^2 - 74.50X_2 + 17.83X_2^2 + 20.50X_1X_2 - 4.50X_1^2X_2 - 5.83X_1X_2^2 + 1.50X_1^2X_2^2 \quad (5)$$

Table 3: Release exponent (*n*) of the factorial design formulations

Formulations	Release exponent (*n*)
F1	0.798
F2	0.766
F3	0.741
F4	0.776
F5	0.736
F6	0.686
F7	0.755
F8	0.732
F9	0.710
F10	0.890
F11	0.857
F12	0.794
F13	0.869
F14	0.819
F15	0.777
F16	0.825
F17	0.781
F18	0.723

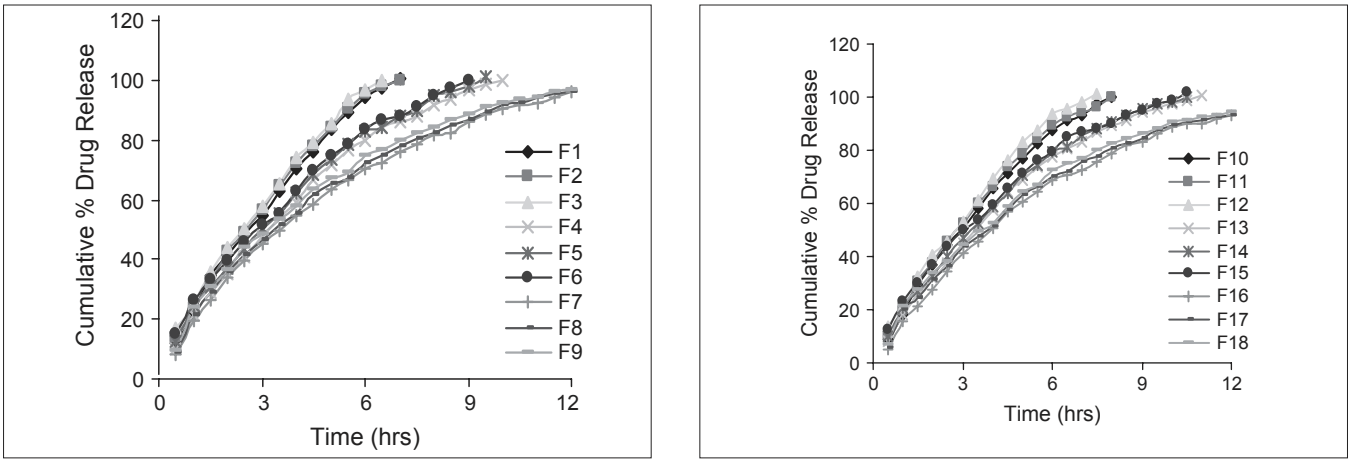

Figure 1: *In vitro* release profile of salbutamol sulphate from formulations F1 - F9 and F10 - F18 (n=3)

Equations for F10–F18

$$rel_{6h} = 79.83 - 9.85X_1 + 0.48X_1^2 + 2.11X_2 - 0.07X_2^2 + 0.62X_1X_2 - 0.51X_1^2X_2 - 0.076X_1X_2^2 + 0.21X_1^2X_2^2 \quad (6)$$

$$t_{50\%} = 3.29 + 0.46X_1 + 0.029X_1^2 - 0.15X_2 + 0.0098833X_2^2 - 0.057X_1X_2 + 0.012X_1^2X_2 - 0.024X_1X_2^2 - 0.00575X_1^2X_2^2 \quad (7)$$

$$BLT = 75.56 - 27.67X_1 - 1.56X_1^2 - 47.5X_2 + 12.94X_2^2 + 29X_1X_2 - 2X_1^2X_2 - 10.33X_1X_2^2 + 1.56X_1^2X_2^2 \quad (8)$$

All the polynomial equations were found to be statistically significant ($P < 0.01$), as determined using ANOVA. The polynomial equation comprises the coefficient for intercept, first-order effects, interaction terms, and higher-order effects. The sign and magnitude of the main effect signify the relative influence of each factor on the response. The value obtained for the main effects of each factor in equations (3) and (6) and (5) and (8) reveals that HPMC individually has a rather more pronounced effect on the values of %rel_{6h} and BLT, respectively. At a given set of factor levels, however, these higher-order polynomials yield results as the net effect of all the coefficient terms contained in the polynomial.

Response surface analysis

Figures 2–4 portray the three-dimensional response surface plots for the studied response properties viz. rel_{6h} (Y_1), $t_{50\%}$ (Y_2), and BLT (Y_3). The effect of X_1 (concentration of HPMC) and X_2 (concentration of sodium bicarbonate) on Y_1 is given in Figure 2. When X_1 is increased from the −1 level to the +1 level, Y_1 was found to decrease linearly from 94.35 to 74.54% in F1–F9 and 87.27 to 72.66 in F10–F18, which can be attributed to an increase in the strength and viscosity of the gel layer with an increase in the concentration of the polymer, which in turn delays the diffusion of water into the core of the tablet, leading to a uniform and a more sustained drug release, while X_2 did not significantly affect Y_1. A linear relationship was observed between X_1 and Y_2 whereas X_2 did not have a significant effect on Y_2 [Figure 3]. As the factors X_1 and X_2 increased from the −1 to the + 1 level, Y_3 decreased from 263 to 39 s for F1–F9 and 205 to 30 s for F10–F18 formulations [Figure 4]. Increase in X_1 and X_2 leads to the entrapment of a higher amount of gas in a denser gel layer resulting in faster attainment of buoyancy.

Validation of optimized formulations

The formulations were optimized for the responses Y_1–Y_3 using the grid search method and the optimized formula was arrived at by maximizing %release at 6 h, $t_{50\%}$, and minimizing the BLT to obtain the desired levels of X_1–X_2. The results from the optimization clarified that the content of HPMC affected the release after 6 h and $t_{50\%}$ and content of both HPMC and sodium bicarbonate affected BLT. The results also illustrate that the viscosity grade of HPMC significantly affected release profile, except at a higher concentration, as well as the BLT. Six checkpoint formulations were evaluated to validate the design and the results of the physical evaluation and the tablet assays were found to be within limits. Table 4 lists the composition of the checkpoints, the predicted and experimental values of all the response variables, and the percentage error in prognosis. Figure 5 shows the linear

Table 4: Comparison of experimental results with predicted responses of the effervescent floating tablet formulations

Formulation	Composition			Response variables	Predicted value	Experimental value	Percentage error
	X_1 (mg)	X_2 (mg)	HPMC grade				
G1	49	48.3	K4M	rel_{6h} (%)	77.17	76.97	−0.26
				$t_{50\%}$ (h)	3.22	3.23	0.31
				BLT (s)	132.85	128	−3.789
G2	51	43.05	K4M	rel_{6h} (%)	75.53	75.45	−0.106
				$t_{50\%}$ (h)	3.3	3.31	0.302
				BLT (s)	150.47	155	2.923
G3	52	50.4	K4M	rel_{6h} (%)	75.73	75.51	−0.291
				$t_{50\%}$ (h)	3.26	3.25	−0.308
				BLT (s)	120.31	127	5.268
G4	44	43.05	K100M CR	rel_{6h} (%)	76.03	76.12	0.118
				$t_{50\%}$ (h)	3.52	3.51	−0.285
				BLT (s)	119.52	123	2.829
G5	50	29.4	K100M CR	rel_{6h} (%)	73.9	73.82	−0.108
				$t_{50\%}$ (h)	3.63	3.6	−0.833
				BLT (s)	84.37	91	7.286
G6	53	24.15	K100M CR	rel_{6h} (%)	72.08	72.29	0.29
				$t_{50\%}$ (h)	6.75	6.78	0.442
				BLT (s)	86.96	81	−7.358

Mean (± SEM) of percentage error 0.3572 ± 3.116.

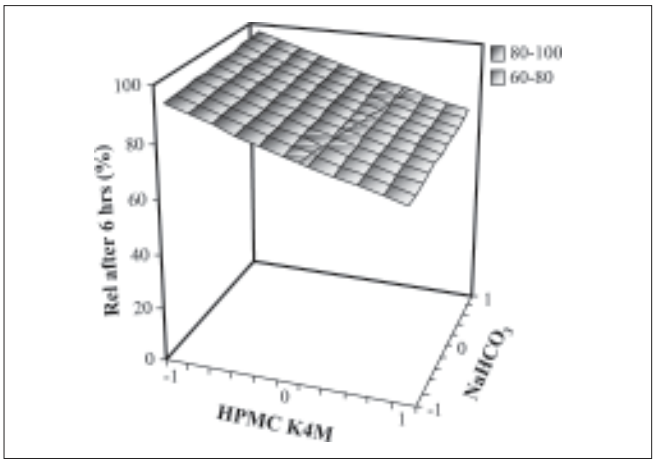

Figure 2: Response surface plot showing the influence of HPMC K4M and sodium bicarbonate on rel_{6h}

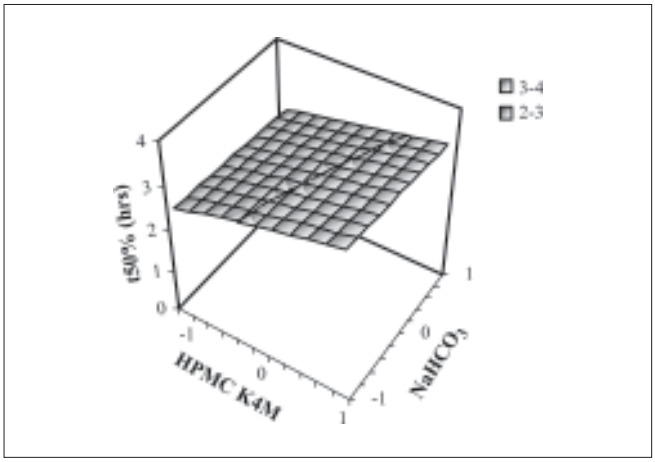

Figure 3: Response surface plot showing the influence of HPMC K4M and sodium bicarbonate on $t_{50\%}$

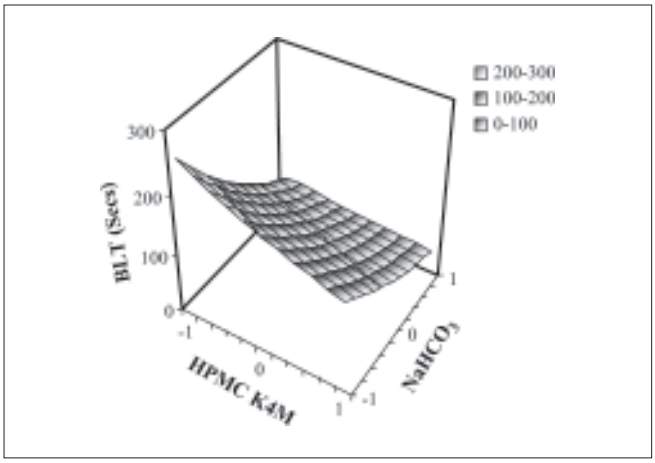

Figure 4: Response surface plot showing the influence of HPMC K4M and sodium bicarbonate on BLT

correlation plots between the observed and the predicted values of rel_{6h}, $t_{50\%}$, and BLT. The linear correlation plots drawn between the predicted and the observed responses

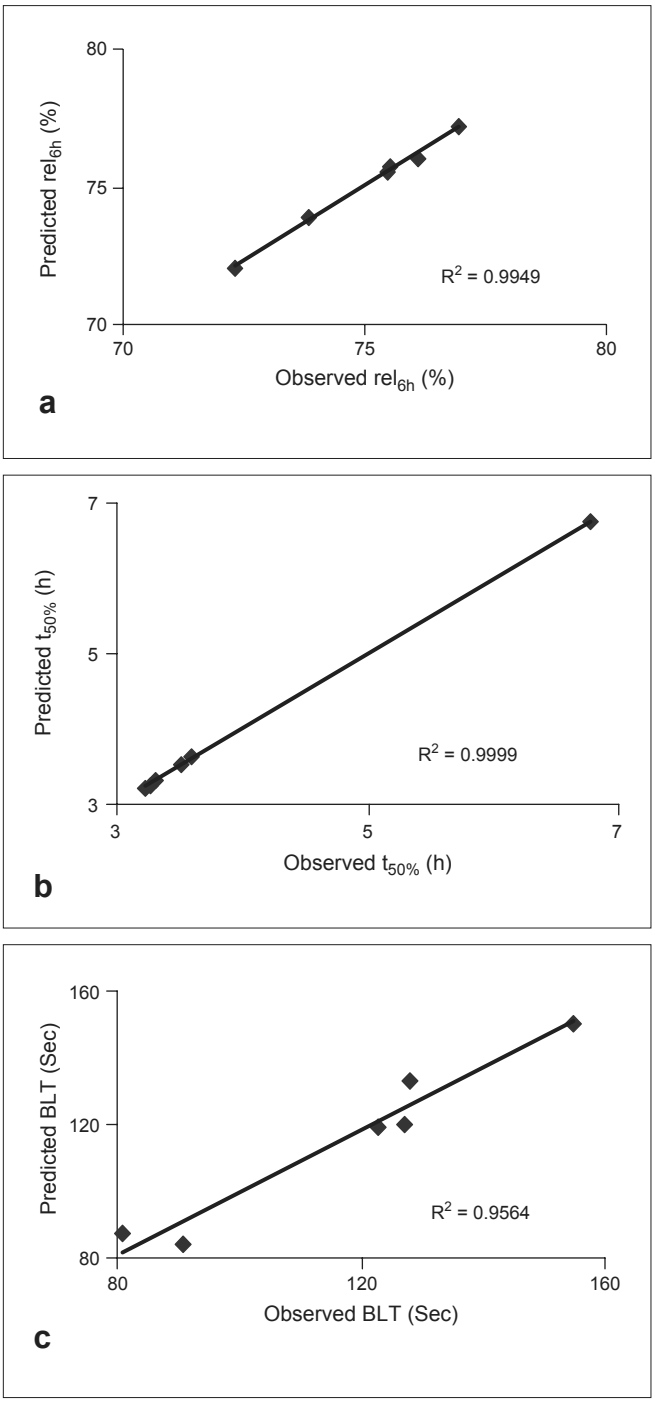

Figure 5: Linear plots between observed and predicted values of (a) rel_{6h} (b) $t_{50\%}$ and (c) BLT

demonstrated higher values of r^2 (ranging between 0.9564 and 0.9999), indicating excellent fitting of the model ($P < 0.001$). Comparing the observed responses with that of the anticipated responses revealed that the prediction error varied between 7.358 and 7.286%. Thus, the low magnitudes of error as well as the significant values of r^2 in the current study indicate a high prognostic ability of effervescent floating matrix tablet formulations of salbutamol sulfate using response surface method optimization validations.

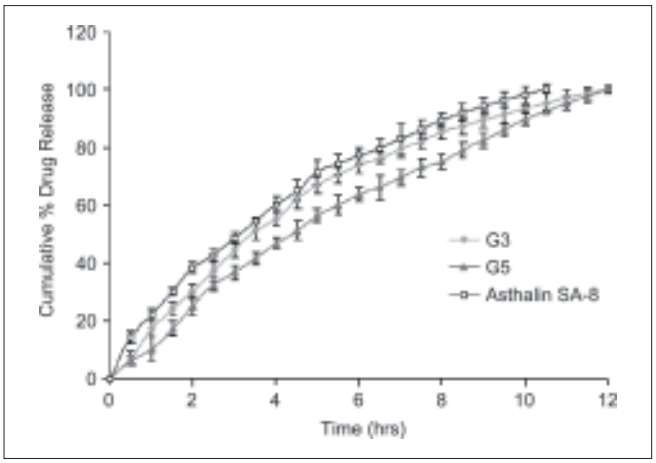

Figure 6: Comparison of release profile of optimized formulations (G3 and G5) and marketed SR tablet (Asthalin SA-8, Cipla)

Figure 6 shows the comparison of dissolution parameters of the marketed brands ASTHALIN SA-8 (Cipla) with two of the selected optimized formulation, G3 and G5. Here, two optimized formulations contained different grades of HPMC. The drug release of G3, G5, and ASTHALIN SA-8 at 8 h was 85.28, 75.1, and 89.52%, respectively, indicating a good sustaining property of the optimized formulations [Table 4].

CONCLUSION

The effervescent floating tablets of salbutamol sulfate were prepared using HPMC and a gas-generating agent (sodium bicarbonate and stearic acid). Stearic acid provides an acidic environment to sodium bicarbonate, which reduces the BLT in the fed condition. All formulations had a desired floating time regardless of the viscosity grade of HPMC. The mechanism of drug release was found to be of the anomalous type, which validates the reported behavior for the matrix tablets.

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