



Received on 03 September, 2014; received in revised form, 28 November, 2014; accepted, 27 January, 2015; published 01 May, 2015

FORMULATION AND OPTIMIZATION OF SUSTAINED RELEASE FLOATING MATRIX TABLETS OF SALBUTAMOL SULPHATE USING XANTHAN GUM AND HYDROXYPROPYL METHYLCELLULOSE POLYMER BLEND

Z. Yilma^{1,2}, A. Belete² and T. Gebre-Mariam^{*2}

Department of Pharmaceutics¹, School of Pharmacy, College of Health Sciences, Mekelle University, P.O.Box 1871, Mekelle, Ethiopia.

Department of Pharmaceutics and Social Pharmacy², School of Pharmacy, College of Health Sciences, Addis Ababa University, P.O. Box 1176, Addis Ababa, Ethiopia.

Keywords:

Floating tablet; Sustained release; Salbutamol sulphate; Optimization; Central composite design

Correspondence to Author: Tsige Gebre-Mariam

Professor of Pharmaceutics
Department of Pharmaceutics and
Social Pharmacy, School of
Pharmacy, College of Health
Sciences, Addis Ababa University,
P.O. Box 1176, Addis Ababa,
Ethiopia.

E-mail: tsigegmwm@gmail.com

ABSTRACT: Oral salbutamol sulphate has site-specific absorption in the stomach and upper part of the small intestine. Its bioavailability is about 40% due to several factors including narrow absorption window and extensive intestinal metabolism. The aim of this study was to formulate and optimize sustained release floating tablets of salbutamol sulphate in order to improve its bioavailability and reduce its dosing frequency. Accordingly, floating tablets were prepared by wet granulation technique and drug release analysis was performed by HPLC. The effects of polymer level, polymer type (XG or HPMC), polymer ratio (XG/HPMC; 1:1, 1:3, 3:1) and NaHCO₃ level on floating lag time, floating duration, cumulative release within 1 hr, and release rate were investigated. From preliminary studies, the polymer with 1:3 (XG:HPMC) ratio and NaHCO₃ were selected as significant factors and cumulative release at 1 hr and release rate were chosen as significant responses, respectively. Hence, the effect of these factors were further studied and optimized by central composite design. The most desirable representative optimal point was obtained at 24.79% of XG/HPMC and 5% of NaHCO₃ having release rate of 28.49 hr^{-1/2} and cumulative release at 1 hr of 24%. This formulation is expected to significantly improve bioavailability of salbutamol while remaining buoyant and sustained release

INTRODUCTION: Salbutamol sulphate is one of the widely used drugs in the treatment of respiratory disorders like bronchial asthma, chronic bronchitis and obstructive airway diseases¹. The relatively short acting injectable and aerosol dosage forms of salbutamol sulphate are recommended for instant relief in severe asthmatic attacks.

The recommended dose of aerosols in adults and children is 2 – 3 inhalations every 4 – 6 hr² and for conventional tablets, 2-6 mg (base) is administered three to four times a day³ which causes poor patient compliance, multiple administration associated side effects, and plasma drug level fluctuation.

Salbutamol sulphate has oral bioavailability of only ~40% due to extensive metabolism via intestinal sulphonation, first pass metabolism in the liver, narrow absorption window (site-specific absorption in stomach and upper part of small intestine⁴ and degradation in colon^{5, 6}). Hence, development of

QUICK RESPONSE CODE



DOI:

10.13040/IJPSR.0975-8232.6(5).1877-92

Article can be accessed online on:
www.ijpsr.com

DOI link: [http://dx.doi.org/10.13040/IJPSR.0975-8232.6\(5\).1877-92](http://dx.doi.org/10.13040/IJPSR.0975-8232.6(5).1877-92)

sustained release formulations which remain at the absorption site for an extended period of time would be beneficial to maximize the bioavailability and reduce frequency of administration of this drug. One feasible approach for achieving prolonged and predictable drug delivery profile in the GIT is to prepare Gastro Retentive Dosage Forms (GRDFs)⁷. Thus, the present work attempts to develop and optimize sustained release floating matrix tablets of salbutamol sulphate which release the drug in the stomach and upper part of small intestine.

MATERIALS AND METHODS:

Materials:

Salbutamol sulphate (Supriya Life Science Ltd., India), Xanthan gum, Povidone K-30, and Microcrystalline cellulose PH 101 (China Associate Co. Ltd, China) supplied by Addis Pharmaceutical Factory (APF); HPMC K 4000 cp (China Associate Co. Ltd., China) donated by Ethiopian Pharmaceutical Manufacturing Sh. Co.

(EPHARM). Sodium hexane-sulphonate (Merck, India) provided by East African Pharmaceuticals PLC; Sodium bicarbonate (UNI. CHEM., India), methanol (BDH Ltd., England), and hydrochloric acid (BDH Ltd., England) were all used as received.

METHODS:

Preparation of Granules:

Granulation was performed as per the method described by Shinde *et al.*⁸ with minor modifications. In this, all the ingredients (**Table 1**), except the magnesium stearate, talc and PVP K-30, were weighed and mixed by geometrical dilution. Wet mass was formed by adding isopropanol solution of PVP K-30 to the powder blend while mixing thoroughly. The wet mass was screened through a 1.6 mm mesh to form granules. The wet granules were dried for 12 hr at 40 °C and passed through a 1 mm mesh and then stored in air-tight containers.

TABLE 1: SALBUTAMOL SULPHATE TABLET FORMULATIONS INVESTIGATED IN THE PRELIMINARY STUDIES

Ingre.↓Formln →	FX1	FX2	FH1	FH2	FXH1	FXH2	FXH3	FXH4	FXH5	FXH6	FS1	FS2	FS3	FS4
Drug (%)	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2
Xanthan gum (%)	10	40	-	-	5	2.5	7.5	20	10	30	40	40	-	-
HPMC K4M (%)	-	-	10	40	5	7.5	2.5	20	30	10	-	-	40	40
NaHCO ₃ (%)	10	10	10	10	10	10	10	10	10	10	5	20	5	20
MCC (%)	69.8	39.8	69.8	39.8	69.8	69.8	69.8	39.8	39.8	39.8	44.8	29.8	44.8	29.8
Mg stearate (%)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc (%)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
PVP K-30 (%)	5	5	5	5	5	5	5	5	5	5	5	5	5	5

* FX: formulations that contain xanthan gum only

FH: formulations that contain HPMC only

FXH: formulations that contain both xanthan gum and HPMC

FS: formulations that contain different concentrations of NaHCO₃

Each tablet weighs 300 mg.

Characterization of granules:

Angle of repose:

Thirty grams of granule were made to flow through stem less funnel, with an internal diameter of 10 mm at the bottom and 100 mm at the top, on to a graph paper from a height of 10 cm. The height (h) as well as the diameter (d) of the pile was measured. Then the angle of repose (θ) was calculated from h and radius ($r = d/2$) using Equation 1. The experiment was done in triplicate.

$$\theta = \tan^{-1}(h/r) \quad \text{Eq. 1}$$

Density related properties:

Bulk and tapped density:

Thirty grams of granules were transferred into a 250 ml graduated cylinder and the volume of the granules was read after tapping the granules three times on a horizontal plane. Then, the mass (M) of the granule was divided by the volume obtained, the bulk volume (V_b), to obtain the bulk density (ρ_b), Equation 2.

$$\rho_b = M/V_b \quad \text{Eq. 2}$$

The granules were also tapped 250 times using Tap Densitometer (ERWEKA, SVM 20, Germany) and the mass (M) of the granules was divided by the volume obtained, the tapped volume (V_t), to obtain the tapped density (ρ_t), using Equation 3.

$$\rho_t = M/V_t \quad \text{Eq. 3}$$

The experiments were done in triplicate and mean and standard deviation were calculated.

Compressibility index and Hausner ratio:

The compressibility index (CI) and Hausner ratio were calculated from bulk and tapped densities, using Equations 4 and 5.

$$\text{Compressibility Index (CI)} = \frac{\rho_t - \rho_b}{\rho_t} \times 100 \quad \text{Eq. 4}$$

$$\text{Hausner ratio (H)} = \frac{\rho_t}{\rho_b} \quad \text{Eq. 5}$$

Preparation of floating tablets:

Talc and magnesium stearate were added onto previously prepared and dried granules and blended for 3 min in a Turbula mixer (Willy A. Bachofen AG, Turbula 2TF, Basel, Switzerland) at 49 rpm. The blend was compressed into tablets, adjusting the hardness to be between 60 N to 70 N, on eccentric tablet machine (EK0 Korsch, 8410-68, Berlin, Germany) which was fitted with 10 mm diameter flat-faced punches. The tablets were kept for 24 hrs at room temperature in glass containers before their properties were evaluated.

Characterization of tablets:

Tablets were characterized with respect to the following properties.

Drug content analysis:

Twenty tablets were weighed and finely powdered and equivalent to about 50 mg of salbutamol were transferred to a 2000-ml volumetric flask. Then 1200 ml of 1% acetic acid was added, shaken for 45 min by mechanical means, sonicated for the next 10 min, cooled to room temperature and was diluted with methanol to volume. It was then filtered with a 0.45 μm nylon filter. About 25 μl of this filtered solution was injected into the HPLC, the chromatogram was recorded, and the response for the major peak was measured. The quantity of $\text{C}_{13}\text{H}_{21}\text{NO}_3$ was calculated by comparing this peak

response with the major peak response similarly obtained on chromatographing the standard preparation previously diluted with a mixture of water and methanol (6:4) and filtered⁹. This was done in triplicate for each batch and mean and standard deviation were calculated

Tablet hardness:

The hardness of 10 tablets from each batch was determined using a hardness tester (CALIVA, THT2, England) and the average value was obtained.

Tablet thickness:

The thickness of 10 tablets from each batch was measured with a hardness tester (CALIVA, THT2, England) putting the tablet with its side (in an upright position).

Tablet friability:

The friability of the tablets was determined by placing 10 tablets in a friability tester (ERWEKA, TAR 20, Germany) and allowing them to rotate at 25 rpm for 4 min. The loss of tablet weight was calculated as a percentage of the initial weight after dedusting.

In vitro buoyancy studies:

The time the tablets took to emerge on the fluid surface (floating lag time) and the time the tablets constantly float on the fluid surface (floating duration) in a USP type II apparatus, filled with 500 ml of 0.1N HCl solution (pH = 1.2) at 37 ± 0.5 °C were recorded by using stopwatch. Both of the variables were determined in triplicate and mean and standard deviation were calculated.

Matrix integrity:

Matrix integrity was observed throughout the *in vitro* dissolution studies and whether or not the swollen mass of the tablets remain intact was checked⁸.

Calibration curve and system suitability tests:

Stock solution of salbutamol sulphate reference standard was prepared by transferring 12 mg of salbutamol sulphate reference standard to a 100 ml volumetric flask, adding 60 ml of 1% acetic acid, sonicating it for 5 min, and diluting with methanol to volume. From this stock solution, six different

volumes of the solution were transferred to 25 ml volumetric flasks and diluted with a mixture of water and methanol (6:4) to volume. The peak area readings of these solutions were measured at 276 nm using HPLC (LC-20AD, Shimadzu, Japan). The peak area versus concentration of solutions were plotted to obtain the calibration curve. The coefficients of determinations (R^2) were ≥ 0.997 . To determine the system suitability, five replicate injections of the standard preparation, required to demonstrate adequate system precision, were made before the injection of samples and the relative standard deviation was calculated ($\leq 2\%$)⁹.

In vitro drug release studies:

The release rate of salbutamol sulphate from floating tablets was determined using Dissolution Testing Apparatus II (paddle method). The dissolution test was performed in 500 ml of 0.1N HCl at 37 ± 0.5 °C and 50 rpm. Samples of 5 ml were withdrawn at predetermined time intervals (0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hr) and the samples were replaced with fresh dissolution medium which was kept at 37 ± 0.5 °C. The samples were diluted to 20 ml and filtered through 0.45 μ m nylon filter and were analyzed with HPLC (LC-20AD, Shimadzu, Japan) at 276.0 nm⁹.

About 100 μ l of a portion of the solution under test, previously passed through a 0.45 μ m nylon filter, was injected into the HPLC, the chromatogram was recorded, and the response for the major peak was measured. The quantity of salbutamol ($C_{13}H_{21}NO_3$) dissolved was calculated by comparing this peak response with the major peak response similarly obtained on chromatographing the standard preparation⁹.

HPLC conditions:

Assay of salbutamol sulphate using HPLC system was conducted as described in the United States Pharmacopoeia⁹. The following chromatographic conditions were employed:

Mobile phase: 1.13 g of sodium 1-hexanesulfonate was dissolved in 1200 ml of water, 12 ml of glacial acetic acid was added, and mixed. A filtered and degassed mixture of this solution and methanol (6:4) was prepared and used.

Standard preparation:

About 12 mg of reference salbutamol sulphate, accurately weighed was transferred to a 100 ml volumetric flask. Then 60 ml of 1% acetic acid was added, and sonicated for 5 min, and diluted with methanol to volume, and mixed. About 125 μ l to 1250 μ l of this solution was pipetted into a 25 ml volumetric flask, diluted with a mixture of water and methanol (6:4) to volume, and used.

Chromatographic system:

The liquid chromatography was equipped with a 276 nm detector and a 4.6 mm \times 15 cm column (MOS-1 Hypersil). The flow rate was about 1.5 ml per min. The standard preparation was chromatographed, and the peak responses were recorded following a standard procedure (USP 30 NF 25, 2007), i.e., the column efficiency determined from the analyte peak should not be less than 800 theoretical plates; the tailing factor for the analyte peak should not be more than 2.5; and the relative standard deviation for replicate injections should not be more than 2.0%.

Release profiles comparison:

Dissolution efficiency (*DE*) after 12 hr of release test was used to compare the results of dissolution tests of different formulations using Equation 6:

$$DE (\%) = \frac{\int_{t_1}^{t_2} y \cdot dt}{y_{100} (t_2 - t_1)} \times 100 \quad \text{Eq. 6}$$

where *y* is the percentage of dissolved product at any time *t*, *y*₁₀₀ denotes 100% dissolution, and the integral represents the area under dissolution curve between time points *t*₁ and *t*₂¹⁰.

Kinetics and mechanism of drug release:

In order to assess and describe the release kinetics and release mechanism of the drug from the tablets under study, the drug release data were fitted to the following release kinetic models: Zero order release model, First order release kinetic model, Higuchi square root model, Hixson-Crowell cube root model, and Korsmeyer–Peppas model¹¹ and the criteria for selecting the most appropriate model was chosen on the basis of goodness of fit test¹².

Experimental design:

On the basis of the preliminary studies, sodium bicarbonate (*X*₁) and one of the XG/HPMC ratios

(1:3, X₂) were identified as the two most important independent formulation variables which affect cumulative release in the first 1 hr and drug release rate in 12 hr period. Thus, central composite design

(CCD) was employed in order to optimize the factors with respect to the response variables. The selected formulation variables with their limits, units and notations are given in **Table 2**.

TABLE 2: INDEPENDENT VARIABLES AND THEIR LIMITS.

Variables	Limits				
	- α	-1	0	+1	+ α
NaHCO ₃ , X ₁ (%)	1.89	5	12.5	20	23.11
XG/HPMC, X ₂ (%)	3.79	10	25	40	46.21

$\alpha = 1.414$

CCD was chosen as it can detect any non-linearity in factor-response relationship¹³. According to the CCD matrix for two independent variables (n = 2), the total number of studies (N) was determined as: $N = (2^n + 2n + n_c) = 2^2 + (2 \times 2) + 5 = 13$. The 13 experimental runs of the CCD matrix were carried out and the observations were analyzed using Design-Expert 8.0.7.1 software to find the optimum area at which the desired responses are achieved, and to construct the response surface plots and contour plots for the fitted polynomial equations of the responses.

Drug-excipient interaction study:

Drug-excipient interaction was studied with Fourier transformed infrared (FT-IR) spectroscopy. FT-IR spectra for pure salbutamol sulphate and optimized salbutamol tablet formulation were acquired at room temperature using FT-IR spectrophotometer (FTIR-8400S, Shimadzu, Japan) in transmittance mode. The spectra were scanned between wave numbers 4000 - 400 cm⁻¹.

Statistical analysis:

The statistical analysis of all batches was performed with Microsoft Excel and plots of drug release profiles were constructed using Origin 8 Software (OriginLab Corporation, MA, and USA). One way analysis of variance (ANOVA) was applied for comparisons of all results. To demonstrate graphically the influence of each factor on responses and to indicate the optimum level of factors, the contour and response surface plots were generated using Design-Expert 8.0.7.1 software (Stat-ease, Corp. Australia). A *p* value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION:

Preliminary studies: Before applying the experimental design for optimization, preliminary

studies were conducted in order to compare the release characteristics of the polymers used and identify the most critical factors. Factors that could possibly have significant effects on the response variables, according to literature, were considered in the preliminary studies. These include polymer type, polymer concentration, polymers ratio and percentage of floating agent. The response variables considered in the preliminary studies include cumulative drug release at 1 hr, drug release rate, floating lag time, and floating duration.

Granule and tablet characteristics of the preliminary formulations:

Physical evaluation:

All formulations exhibited excellent flow property except for formulations FH1, FH2, FS3 and FS4, which were prepared with HPMC alone and one of the formulations with combination of XG and HPMC (FXH5 with 1:3 ratio). Since HPMC, relative to xanthan gum, has poor flow property¹⁴, those formulations with only HPMC and higher proportion of HPMC (in the case of the combination formulations) showed fair to good flow property.

All the formulations showed values within the prescribed limits for tests of hardness, friability and drug content. Except FH1 and FXH2, all the formulations kept their matrix integrity for more than 12 hr.

Effect of polymer type and concentration:

In order to investigate the effect of the polymer type, formulations were prepared at 10% and 40% using the two polymers. The level of sodium bicarbonate was kept constant at 10%.

At 10% concentration, HPMC couldn't retain its physical integrity and released its whole content

within 1 hr, but XG retained its physical integrity for over 12 hr. When the polymer changed from HPMC to XG, the cumulative release in the first 1 hr was decreased from 100.35% to 25.90%. This is due to the fact that xanthan gum has a rapid hydration power than HPMC, which can prevent initial burst release of soluble drugs¹⁵. The floating lag time also changed from 1.2 ± 0.1 sec to 1.5 ± 0.1 sec. Moreover, only XG floated for more than 12 hr.

At 40% concentration, both HPMC and XG retained their physical integrity for a period of 12

hr and there was no significant change ($p > 0.05$) in cumulative release within the first 1 hr, but there was a significant change ($p < 0.05$) in release rate over 12 hr period when the polymer type changed from HPMC to XG. The floating lag time changed from 2.3 ± 0.42 sec to 4.8 ± 0.26 sec, but there was no change in floating duration, i.e., both formulations floated for more than 12 hr. **Fig. 1** shows the effect of polymer type on cumulative release within 12 hr period.

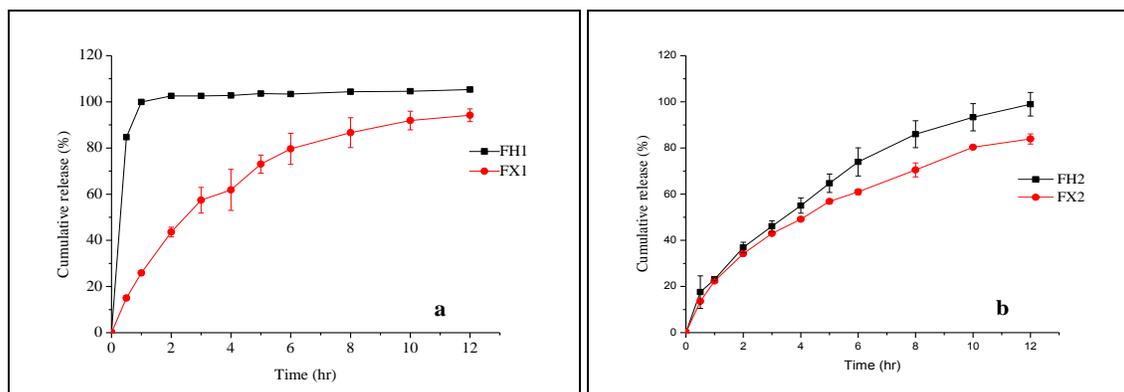


FIG. 1: EFFECT OF POLYMER TYPE (FH: HPMC AND FX: XG) AT 10% [a] AND 40% [b] ON CUMULATIVE RELEASE OF SALBUTAMOL SULPHATE.

In the case of XG, when the concentration increased from 10% to 40%, the cumulative release in the first 1 hr and the release rate decreased significantly ($p < 0.05$) (**Fig. 2**), and the floating lag time increased significantly ($p < 0.0001$). As the concentration increases the dosage form becomes more dense and needs time to swell and float. In the case of HPMC, the cumulative release in the first 1 hr decreased significantly ($p < 0.0001$) and the floating lag time changed significantly ($p < 0.05$) as the concentration increased from 10% to 40%. This observation was in agreement with those reported elsewhere¹⁶.

An increase in the polymer concentration causes increase in the viscosity of the gel and leads to formation of gel layer with a longer diffusion path causing a decrease in the diffusion of the drug and therefore a reduction in the drug release rate¹⁷. Within the range studied, the polymer concentration didn't show any significant difference in floating duration (> 12 hr) in the case of XG, but in the case of HPMC, it showed a great difference when the concentration increased from 10% (it disintegrated after few min) to 40% (> 12 hr).

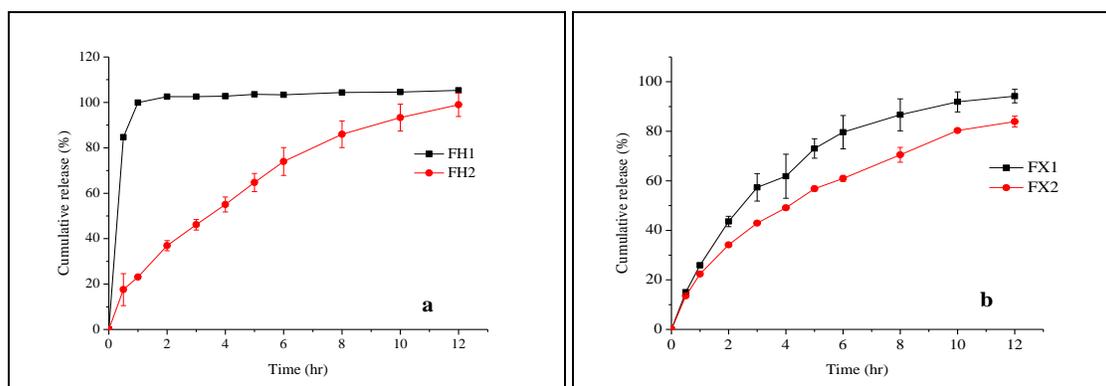


FIG. 2: EFFECT OF POLYMER CONCENTRATION: FH1 (10%) AND FH2 (40%) OF HPMC [a]; FX1 (10%) AND FX2 (40%) OF XG [b] ON CUMULATIVE RELEASE OF SALBUTAMOL SULPHATE.

Effect of polymers ratio:

Upon changing the XG/HPMC ratio from 1:1 to 1:3 (at 10% of the total polymer), the cumulative release increased significantly ($p < 0.05$) in the first 1 hr and the release rate changed significantly ($p < 0.05$) over the period of 12 hr. On the other hand, when the XG/HPMC proportion changed from 1:1 to 3:1, the cumulative release decreased ($p > 0.05$) in the first 1 hr and the release rate didn't show significant change over a period of 12 hr. This was because at lower concentration, HPMC showed burst release due to its low hydration power. However, xanthann gum, which has rapid hydration power to form a gel, can control the initial burst release of the water soluble drug¹⁵.

At 40% of the total polymer concentration, the cumulative release in 1 hr was increased ($p < 0.05$) when the XG/HPMC ratio changed from 1:1 to 1:3, but the change in release rate in 12 hr was not significant ($p > 0.05$). When the XG/HPMC ratio changed from 1:1 to 3:1, the cumulative release in the first 1 hr and the release rate in 12 hr didn't change at all ($p > 0.05$) because the total polymer was at higher concentration. As the percentage of polymer increases, it produces a greater entanglement of polymer chains, which results in

decreased porosity, and increased tortuosity retarding the release of drug from the gel¹⁸.

Effect of sodium bicarbonate:

In order to investigate the effect of sodium bicarbonate, formulations were prepared at 5%, 10%, and 20%. The levels of all other factors were kept constant at specified values (the total polymer was set at 40%).

As the concentration of NaHCO_3 increased from 5% to 20%, the cumulative release in the first 1 hr ($p < 0.0001$) and the release rate increased significantly ($p < 0.05$) in the case of tablets formulated with HPMC. For tablets formulated with XG, a regular pattern was not shown in the cumulative release in the first 1 hr, but it showed a significant increase in release rate ($p < 0.0001$) when the concentration of NaHCO_3 increased from 5% to 20% (**Fig. 3**). As the concentration of gas-forming agent increases, it would generate larger amounts of effervescence leading to an increase in the rate of pore formation, rapid hydration of the tablets' matrices and consequently a faster drug release rate¹⁹. The floating lag time decreased ($p < 0.05$), but the floating duration didn't show any change ($p > 0.05$) in both polymers, both of them floated for more than 12 hr.

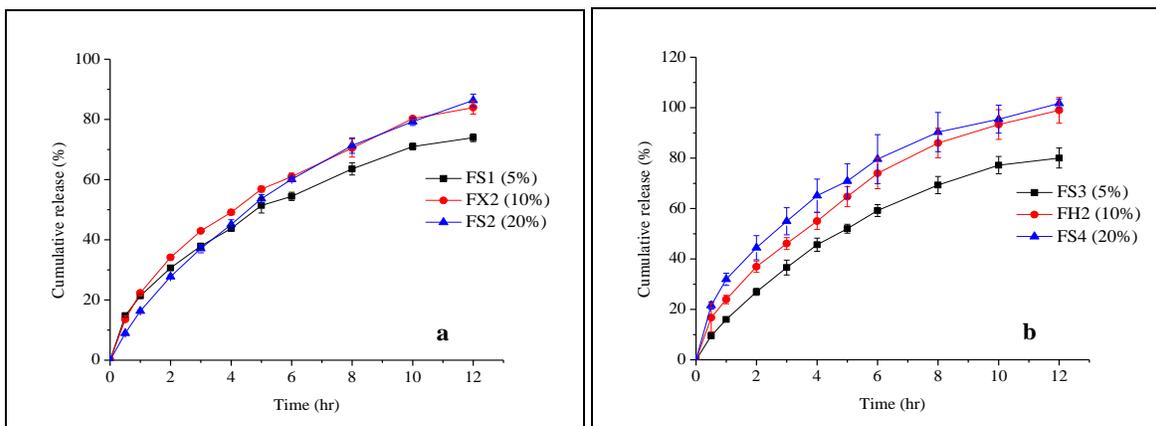


FIG. 3: EFFECT OF SODIUM BICARBONATE AT 5% (FS1, FS3), 10% (FX2, FH2), AND 20% (FS2, FS4) OF 40% XG [a] AND 40% HPMC [b], RESPECTIVELY, ON CUMULATIVE RELEASE OF SALBUTAMOL SULPHATE.

Selection of formulations:

As shown in **Fig. 4**, formulations with XG and those containing combinations of HPMC and XG, except FXH2 which released more than 60% within the first 1 hr, showed good release patterns. Among these formulations, the one with 1:3 polymer ratio (XG/HPMC) was selected for further optimization. This was so because it contains relatively high

amount of HPMC, which has low hydration power than XG, and hence can release sufficient amount of drug in the first 1hr as a bolus dose for rapid relief of asthma. In addition, this formulation also showed significant difference in cumulative release at 1hr and release rate, relative to the other formulations, when the polymer concentration increased from 10% to 40%.

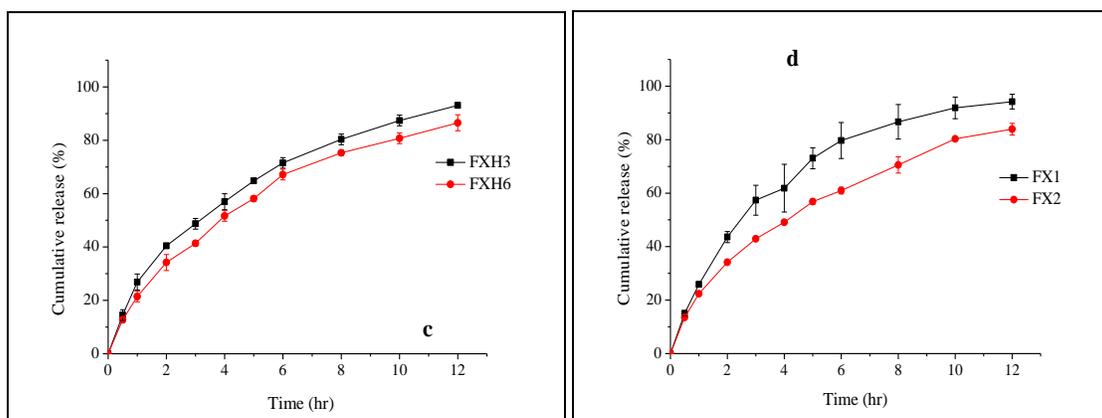


FIG. 4: EFFECT OF POLYMER CONCENTRATION ON CUMULATIVE RELEASE OF SALBUTAMOL SULPHATE: XG/HPMC (1:1) AT 10% (FXH1) AND 40% (FXH4) [a], XG/HPMC (1:3) AT 10% (FXH2) AND 40% (FXH5) [b], XG/HPMC (3:1) AT 10% (FXH3) AND 40% (FXH6) [c], XG AT 10% (FX1) AND 40% (FX2) [d].

Optimization:

As stated above, the formulation that contains 1:3 (XG/HPMC) ratio of the polymers was selected for further study and optimization by CCD. Hence, the percentage of XG/HPMC (1:3) and the percentage of NaHCO₃ were considered as the independent

variables and their effects on cumulative release in the first 1 hr and drug release rate were considered. On the basis of the preliminary studies, the range of the factors was expanded within 10% to 40% for the polymer (XG/HPMC; 1:3) and 5% to 20% for NaHCO₃. Accordingly, thirteen formulations were formulated (Table 3) using CCD.

TABLE 3: COMPOSITIONS OF THE THIRTEEN FORMULATIONS.

Formulation code	Point type	Factors	
		XG/HPMC (%)	NaHCO ₃ (%)
F1	factorial	10 (-1)	5 (-1)
F2	factorial	40 (+1)	5 (-1)
F3	factorial	10 (-1)	20 (+1)
F4	factorial	40 (+1)	20 (+1)
F5	axial	3.79 (-α)	12.5 (0)
F6	axial	46.21 (+α)	12.5 (0)
F7	axial	25 (0)	1.89 (-α)
F8	axial	25 (0)	23.11 (+α)
F9	center point	25 (0)	12.5 (0)
F10	center point	25 (0)	12.5 (0)
F11	center point	25 (0)	12.5 (0)
F12	center point	25 (0)	12.5 (0)
F13	center point	25 (0)	12.5 (0)

Granule characteristics:

The physical properties of the granules (bulk density, tapped density, compressibility index, Hausner ratio, and angle of repose) of all the 13 formulations were determined. The bulk density of the formulations ranged from 0.28 to 0.34 and the tapped density ranged from 0.29 to 0.38. The blend indicated excellent to good flow properties for all formulations with the angle of repose values ranging from 29.26° to 35.62° except for formulation F9 (36.50°). The values of compressibility index ranged between 5.46 and 9.43, while the Hausner’s ratios were between 1.06 and 1.10; indicating excellent flow properties.

Characteristics of tablets:

The tablets of the 13 different formulations were evaluated for hardness, thickness, friability, and drug content. The tablets mean thickness values ranged from 3.25 mm to 3.66 mm. The hardness of the tablets was between 61.33 to 73.33 N. The loss in friability was in the range of 0.22 to 0.41% and the percentage drug content of tablets was between 98.46% to 102.64%, which were within the limits of < 1% and 90% to 110%, respectively. Except for formulations F1, F3, and F5, which contain low percentage of the polymers, ≤ 10%, all other formulations kept their matrix integrity.

In vitro drug release:

The drug release profiles of the 13 different formulations are shown in **Fig. 5**. As shown in the figure, the percentage of polymer appears to influence the drug release pattern remarkably. Formulations F1 and F3 (10% polymer), and F5 (3.79% polymer) showed an initial burst release of 62.32%, 87.79% and 99.79%, respectively, in the first 1 hr. This is due to the lower percentage of the polymer concentration that can't keep the physical integrity of the tablets when CO₂ is released from the formulation upon contact with the acidic dissolution medium. Except for formulations F2 and F6, all other formulations having > 10% polymer showed similar trend with no significant difference in their release pattern over a period of 12 hr.

The lower release from F2 and F6 were due to their higher percentage of polymer concentration (40% and 46.21%, respectively) and lower percentage of sodium bicarbonate for F2.

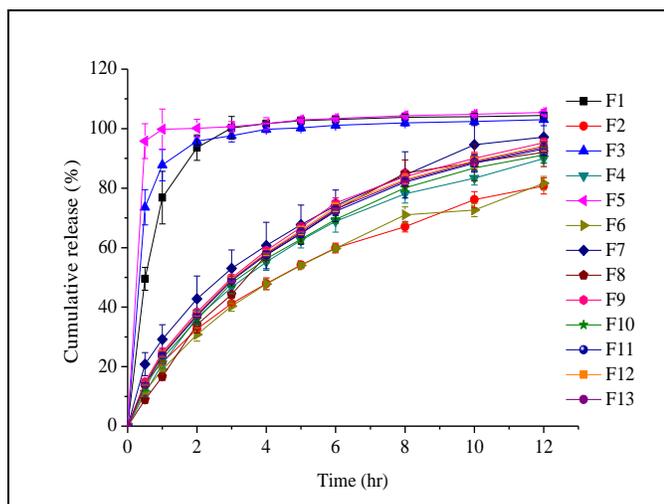


FIG. 5: EFFECT OF PERCENTAGE OF XG/HPMC AND NaHCO₃ ON THE IN VITRO DRUG RELEASE OF SALBUTAMOL SULPHATE.

Dissolution profiles of all the formulations were compared using dissolution efficiency and results of ANOVA from the dissolution efficiency values of the formulations revealed that there was significant difference ($p < 0.0001$) in the release profiles of the formulations. These differences in release profiles evidenced that changes in values of the investigated formulation variables had significant influence on the pattern of release and hence

optimization was required to achieve an optimum release over a fixed period of time.

Drug release kinetics:

All formulations were subjected to kinetic models except for three of the formulations (F1, F3, and F5), which released their whole content within the first 3 hr. All the other ten formulations exhibited best fit for Higuchi square root model with high linearity of $R^2 \geq 0.976$. Therefore, with the goal of sustaining the release of the drug from floating tablets for 12 hr period, Higuchi square root model was used to calculate the release rate. According to Higuchi model for more than 90% drug release in 12 h, the release rate should be between 26-30 hr^{-1/2}. Then, the optimization was done by targeting the drug release rate within this range.

The cumulative release in the first 1 hr was targeted to be between 24 and 30% in order to achieve sufficient bolus release and, at the same time, not to compromise the desired release rate. Similar range was set by Bomma *et al.*,²⁰ and Pasa *et al.*,²¹ in the formulations of sustained release matrix tablets.

The cumulative release in the first 1 hr and release rates obtained from the 13 formulations are shown in **Table 4**. These results were used as input in the Design-Expert 8.0.7.1 software for the optimization analysis.

TABLE 4: SUMMARY OF EXPERIMENTAL MEASUREMENTS OF CUMULATIVE RELEASE IN THE FIRST 1 HR AND RELEASE RATE FOR THE THIRTEEN FORMULATIONS.

Formulation code	Responses	
	Cumulative release in the 1 st hr (%)	Release rate (hr ^{-1/2})
F1	62.32	-
F2	21.42	24.51
F3	87.79	-
F4	22.94	28.77
F5	99.79	-
F6	20.08	25.68
F7	22.15	28.81
F8	35.07	32.32
F9	24.24	29.92
F10	22.68	29.24
F11	23.98	29.81
F12	24.77	30.15
F13	23.72	29.70

Response model selection: Suitable models for the responses were selected based on the fit summaries.

A model is selected if it is not aliased, Adjusted R-squared and Predicted R-squared are in a reasonable agreement (within 0.20 of each other), the model term's p-value is less than 0.05, and the lack of fit p-value is greater than 0.05.

Accordingly, linear contribution is suggested for release rate and the quadratic contribution is suggested for cumulative release at 1 hr (Table 5).

TABLE 5: FIT SUMMARY STATISTICS FOR RELEASE RATE AND CUMULATIVE RELEASE AT 1 Hr.

Response	Source	R-Squared	Adjusted R-Squared	Predicted R-Squared	p-value	Lack of fit p-value	Remark
Release rate	Linear	0.9448	0.9290	0.8445	<0.0001	0.0573	suggested
	2FI	0.9679	0.9519	0.8428	0.0827	0.0965	
	Quadratic	0.9900	0.9776	0.2762	0.0965	0.0034	aliased
	Cubic	0.9925	0.98813	-	-	-	
Cumulative release at 1hr	Linear	0.6209	0.5451	0.3199	0.0078	<0.0001	suggested
	2FI	0.6561	0.5334	0.2363	0.4089	<0.0001	
	Quadratic	0.9985	0.9974	0.9909	<0.0001	0.0615	aliased
	Cubic	0.9995	0.9989	0.9881	0.0519	0.1862	

It is also necessary to check the fitted models to ensure that it provides an adequate approximation to the real system. ANOVA Table (Table 6) has

been used to summarize the test for significance of regression model, test for significance for individual model coefficient and test for lack-of-fit.

TABLE 6: SUMMARY OF ANOVA RESULTS OF RESPONSE SURFACE LINEAR MODEL FOR DRUG RELEASE RATE AND RESPONSE SURFACE QUADRATIC MODEL FOR CUMULATIVE RELEASE AT 1 Hr.

Response	Source	Sum of squares	df	Mean Square	F-value	p-value	Remark
Release rate	Model	43.03	2	21.52	59.88	<0.0001	Significant
	NaHCO ₃ (X ₁)	14.18	1	14.18	39.46	0.004	Significant
	XG/HPMC(X ₂)	28.85	1	28.85	80.29	<0.0001	Significant
	Residual	2.52	7	0.36			
	Lack of fit	2.06	3	0.69	6.05	0.0573	Insignificant
	Pure error	0.45	4	0.11			
	Core total	45.55	9				
Cumulative release at 1hr	Model	8487.30	5	1697.46	928.01	<0.0001	Significant
	NaHCO ₃ (X ₁)	266.88	1	266.88	145.91	<0.0001	Significant
	XG/HPMC(X ₂)	5010.76	1	5010.76	2739.42	<0.0001	Significant
	(X ₁ X ₂)	247.91	1	247.91	135.53	<0.0001	Significant
	NaHCO ₃ ² (X ₁ ²)	221.90	1	221.90	121.32	<0.0001	Significant
	XG/HPMC ² (X ₂ ²)	2898.68	1	2898.68	1584.73	<0.0001	Significant
	Residual	12.80	7	1.83			
	Lack of fit	10.41	3	3.47	5.79	0.0615	Insignificant
	Pure error	2.40	4	0.60			
Core total	8500.10	12					

As shown in the table, models of both responses were significant. ANOVA results in the table also revealed that the main effects of both parameters, sodium bicarbonate percentage (p = 0.004) and percentage of XG/HPMC (p < 0.0001), were significant model terms for the linear model of release rate. For the quadratic model of cumulative release at 1 hr, the main effects of both parameters, the interaction effect (X₁X₂) (p < 0.0001), and the quadratic effects, X₁² (p < 0.0001) and X₂² (p < 0.0001) were significant model terms. The values of R² for the linear model of release rate and quadratic model of cumulative release at 1 hr were

0.9448 and 0.9985, respectively. These values indicate the degree of correlation between the experimental and the predicted values.

The adjusted R² and predicted R² values of release rate (0.9290 and 0.8445, respectively) and cumulative release at 1 hr (0.9974 and 0.9909, respectively) were in reasonable agreement. The values of adequate precision (signal to noise ratio) of 21.021 for release rate and 84.11 for cumulative release at 1 hr obtained were very high compared to the desirable value of greater than 4²², indicating that the model can be used to navigate the design space.

The normal probability plots of the residuals and the plots of the residuals versus the predicted response for cumulative release at 1 hr and release rate were observed (**Figures** not shown) which were considered as additional tests of model adequacy checking tools²³. Normal probability plot of residuals showed that points or point clusters are placed closely to the diagonal line implying that the errors are distributed normally for both responses. Plots of the residuals against predicted response

indicate that the points are randomly scattered, with no obvious pattern or structure.

Since both of the response models were significant, the adjusted and predicted R^2 of both response models were in good agreements, the adequate precision were over 4 and the residuals were well behaved; it is reasonable to conclude that the selected models were fairly accurate and could be used for further analysis. The final mathematical regression models in terms of coded factors (Eq. 7 and Eq. 8) were developed.

$$\text{Rel. rate } (Y_1) = 29.98 + 1.54X_1 - 3.19X_2 \quad \text{Eq. 7}$$

$$\text{Cum. rel.1hr } (Y_2) = 23.88 + 5.78X_1 - 25.03X_2 - 7.87X_1X_2 + 5.65X_1^2 + 20.41X_2^2 \quad \text{Eq. 8}$$

As evidenced from (Eq. 7 and 8), both responses are affected positively by the percentage of sodium bicarbonate (X_1) and negatively by the percentage of the polymer (X_2); however, the effect of the polymer was stronger than that of sodium bicarbonate on both of the responses. The second order interaction effect negatively affects the cumulative release at 1 hr. Quadratic effects (X_1^2 and X_2^2) were found to have positive relationship with cumulative release at 1 hr. These phenomena can be clearly seen in 2D contour and 3D response surface plots in **Fig** and **7**.

The series of parallel straight lines of the contour plot and the non-twisted response surface (**Fig. 6**) indicate that there was no interaction effect of the two parameters on the release rate. The plots show that the linear model components individually affect the release rate, with comparatively a more significant effect of XG/HPMC percentage. The same is indicated in the ANOVA results (**Table 6**), where XG/HPMC percentage showed more significant effect ($p < 0.0001$) than the percentage of sodium bicarbonate ($p = 0.004$) on the release rate.

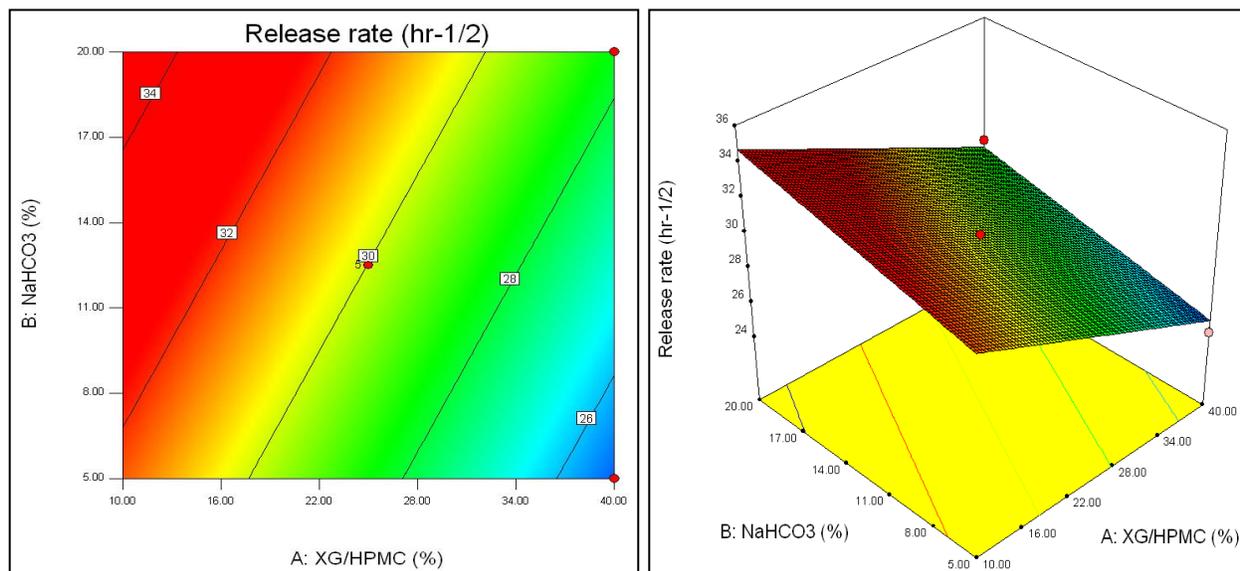


FIG. 6: CONTOUR (LEFT) AND RESPONSE SURFACE (RIGHT) PLOTS OF POLYMER PERCENTAGE (XG/HPMC) AND THE PERCENTAGE OF SODIUM BICARBONATE ON DRUG RELEASE RATE.

The combined effect of sodium bicarbonate percentage and XG/HPMC percentage on cumulative release at 1 hr is shown in **Fig. 7**. As the elliptical contours and twisted response surface

of **Fig. 7**, and the ANOVA results in **Table 6** ($p < 0.0001$) indicate, the interactive effect of the two variables is significant.

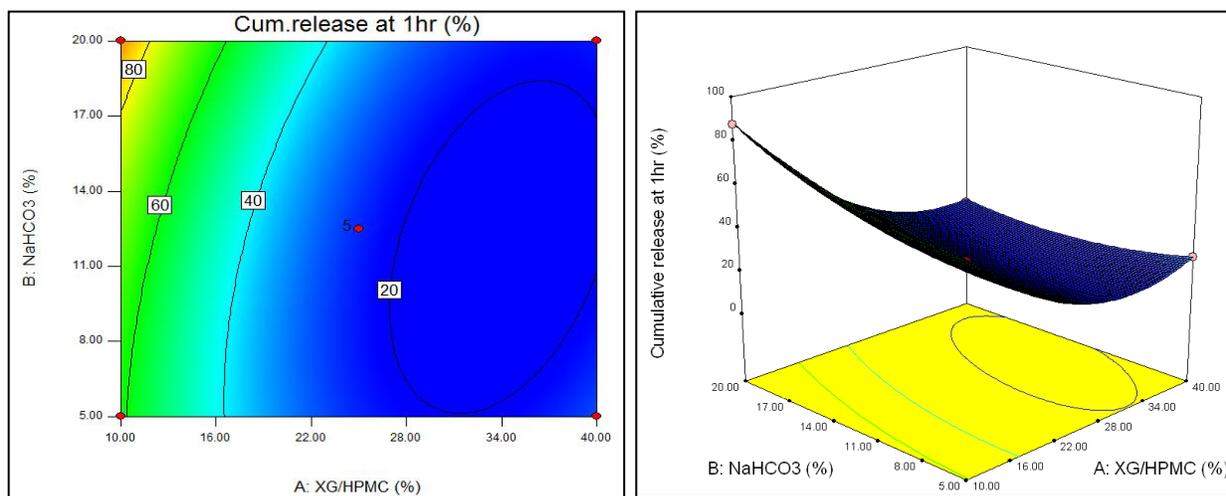


FIG. 7: CONTOUR (LEFT) AND RESPONSE SURFACE (RIGHT) PLOTS OF POLYMER PERCENTAGE (XG/HPMC) AND PERCENTAGE OF SODIUM BICARBONATE ON CUMULATIVE RELEASE AT 1 Hr.

Simultaneous optimization of cumulative release at 1 hr and release rate:

After generating the model polynomial equations to relate the dependent and independent variables, the formulation was optimized for the two responses simultaneously. The final optimal experimental parameters were obtained using both numerical and graphical optimization techniques by Design-

Expert 8.0.7.1 software, which allows compromise among various responses and searches for a combination of factor levels that jointly optimize a set of responses by satisfying the requirements for each response in the set. **Table 7** presents the criteria defined for factors and responses during optimization with both numerical and graphical techniques.

TABLE 7: CONSTRAINTS FOR FACTORS AND RESPONSES USED DURING NUMERICAL AND GRAPHICAL OPTIMIZATION.

Factor constraints				
Factor	Low	High		
NaHCO ₃ (%)	5	20		
XG/HPMC (%)	10	40		
Response constraints				
Response	Goal	Lower limit	Upper limit	Importance
Release rate (hr ^{-1/2})	Target = 28	26	30	5
Cumulative release at 1hr (%)	In range	24	30	4

Numeric optimization:

The desirability function approach is one of the most widely used methods for optimization of multiple responses²⁴. In the use of softwares like Design Expert, numerical optimization is used in order to find the specific point that maximizes the global desirability function. Accordingly, the predicted optimum values and the corresponding levels of parameters according to the set goals were obtained as presented in **Fig. 8**. A dot indicates the best solution found by the Design Expert solver.

Desirability function ranges from 0 to 1, with value closer to one indicating a higher satisfaction of response goal(s)²⁵. In this study, the values of individual desirability functions d_i of release rate

and cumulative release at 1 hr were obtained from the Design-Expert solver to be 0.7556 and 1, respectively, as calculated from the optimal point obtained ($Y_1 = 28.49 \text{ hr}^{-1/2}$, $Y_2 = 24\%$). The overall desirability function (D) was then obtained from the individual desirability functions to be 0.756 from the software solver calculated based on Equation 9.

$$D = [d_1^{p_1} d_2^{p_2} d_3^{p_3} \dots d_i^{p_i}]^{1/\sum p_i}$$

Where i is the number of responses, d_i the individual desirability functions and p_i is the relative importance of i^{th} response as compared to the others. Importance (p_i) varies from 1 to 5, from least two most important, respectively.

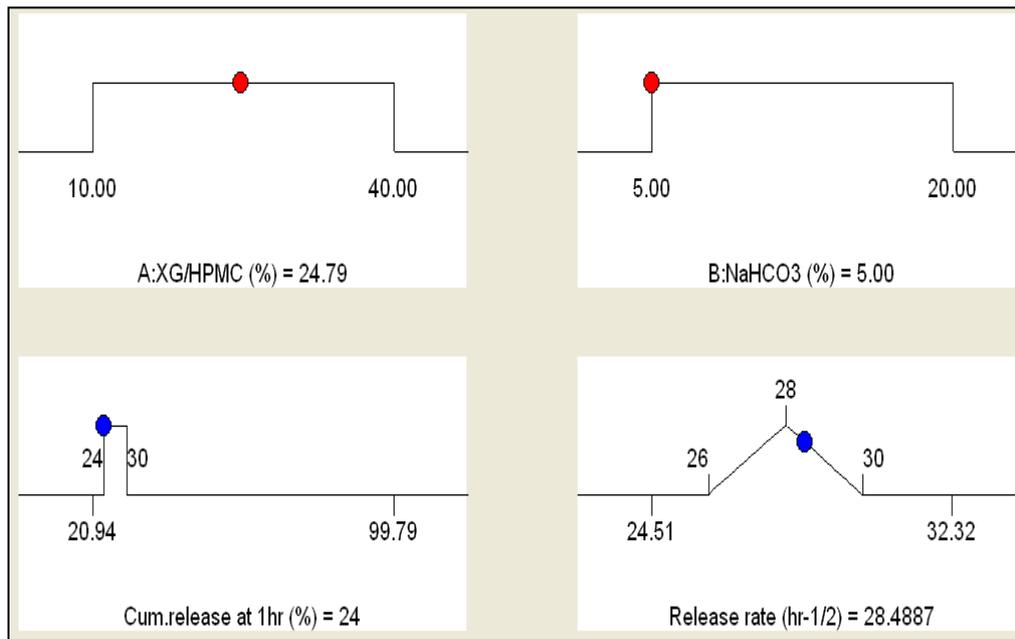


FIG.8: NUMERICAL OPTIMIZATION RESULTS OF PREDICTED OPTIMUM VALUES AND THE CORRESPONDING LEVELS OF PARAMETERS.

Graphical optimization:

With the aim to definitively pointing out the optimal conditions of the release rate and cumulative release at 1 hr, a graphical optimization was conducted using the Design-Expert 8.0.7.1 software. The methodology essentially consists of overlaying the curves of the two models obtained from the CCD according to the specific criteria imposed in **Table 7**. **Fig. 9** shows the overlay plot

in which the yellow area represents the area satisfying the imposed criteria.

The point identified by the flag was chosen in the graph as representative of the optimized area corresponding to percentage of sodium bicarbonate to be 5.0% and percentage of the polymer (XG/HPMC) to be 24.79%. Under these conditions the model predicts release rate of 28.49 hr^{-1/2} and cumulative release of 24.003% in the first 1 hr.

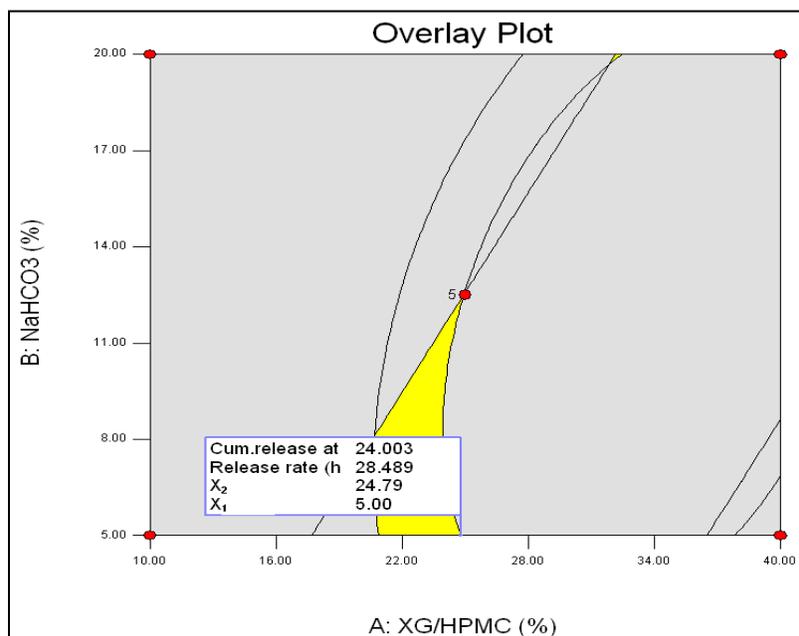


FIG. 9: OVERLAYING PLOTS OF CUMULATIVE RELEASE AT 1 Hr AND RELEASE RATE AS FUNCTIONS OF PERCENTAGE OF SODIUM BICARBONATE AND PERCENTAGE OF XG/HPMC.

Validation test:

To experimentally confirm the validity of obtained optimal point, confirmatory studies were carried out in triplicate at the optimal combinations of the factors ($X_1 = 5\%$, $X_2 = 24.79$). **Table 8** provides the predicted values, experimental results and the percentage error values obtained at optimal levels

of the factors. As seen in the table, the values of percentage errors had fallen within about 5% and thus confirming that the experimental values of the optimized formulations agreed well with the predicted values²⁶.

TABLE 8: RESPONSE VALUES OF PREDICTED, EXPERIMENTAL AND PERCENTAGE ERROR OBTAINED AT OPTIMAL LEVELS OF THE FACTORS.

Response	Predicted value	Experimental value	% Error
Release rate (Y1, hr-1/2)	28.49	29.08	2.03
Cumulative release at 1 hr (Y2, %)	24.00	25.45	5.69

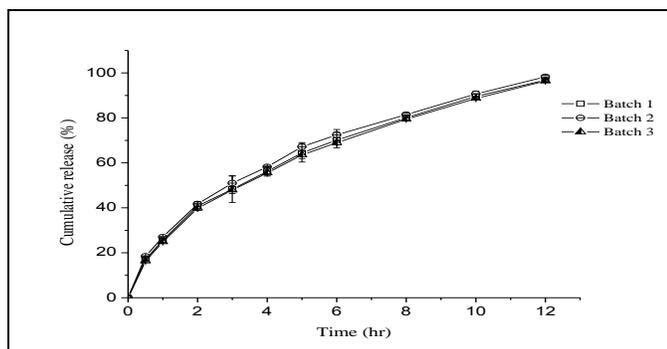
Evaluation of the optimized floating salbutamol sulphate tablets: The optimized formulation was evaluated for its granule and tablet properties. The

results are presented in **Table 9**. Excellent granule flow property and good tablet quality are obtained.

TABLE 9: GRANULE AND TABLET PROPERTIES OF THE OPTIMIZED SALBUTAMOL SULPHATE FORMULATION

Parameters	Experimental values
Granule properties	
Bulk density (g/cm ³)	0.32 ± 0.01
Tapped density (g/cm ³)	0.35 ± 0.00
Angle of repose (°)	28.45 ± 1.13
Carr's Index (%)	8.41 ± 0.03
Hausner ratio	1.09 ± 0.03
Flow rate (g/sec)	2.02 ± 0.12
Tablet properties	
Hardness (N)	65.33 ± 1.53
Thickness (mm)	3.65 ± 0.05
Friability (%)	0.35
Assay (%)	98.96 ± 0.00
Matrix integrity	Intact
Floating lag time (sec)	2.21 ± 0.1
Floating duration (hr)	> 12

The release profiles of the optimized formulation were evaluated using three different batches as presented in **Fig. 10**. ANOVA of the release profiles based on DE values of the three batches, 65.06 ± 0.8 , 65.71 ± 1.14 and $64.73 \pm 0.66\%$, revealed that there was no statistically significant difference ($p = 0.1871$) in the release profiles of the formulations.

**FIG.10: RELEASE PROFILES OF THREE BATCHES OF THE OPTIMIZED SUSTAINED RELEASE FLOATING MATRIX TABLETS OF SALBUTAMOL SULPHATE.**

The release profile curves presented in the figure also support the ANOVA results of DE that the release patterns are similar among the batches, leading to the conclusion that the optimal formulation obtained yields reproducible results. The results also confirmed that formulation of sustained release floating matrix tablet of salbutamol sulphate that releases the drug for 12 hr in a sustained manner *in vitro* was achieved.

The drug release mechanism from the optimized formulation was evaluated using the Korsmeyer-Peppas model at 60% release and the results showed that n value ranges from 0.562 to 0.588 indicating drug release from the optimized formulation follows non-Fickian diffusion release mechanism.

Drug-excipient interaction study: Drug-excipients interaction was studied using Fourier

transformed infrared (FT-IR) spectroscopy. Fig. 11 depicts the IR spectra of the overlap of pure salbutamol sulphate and the optimized formulation. As shown in the figure, the characteristic peaks of salbutamol sulphate were observed: C-O stretching vibrations of primary alcohol at 1112 cm^{-1} , C-O vibrations of phenol at 1205 cm^{-1} , C-H bending

vibrations of tertiary carbon at 1338 cm^{-1} and C-H stretching vibrations at 2952 cm^{-1} ²⁷. These characteristic peaks also appear in the spectrum of the optimized formulation at the same wave numbers indicating that there was no interaction between the drug and formulation excipients.

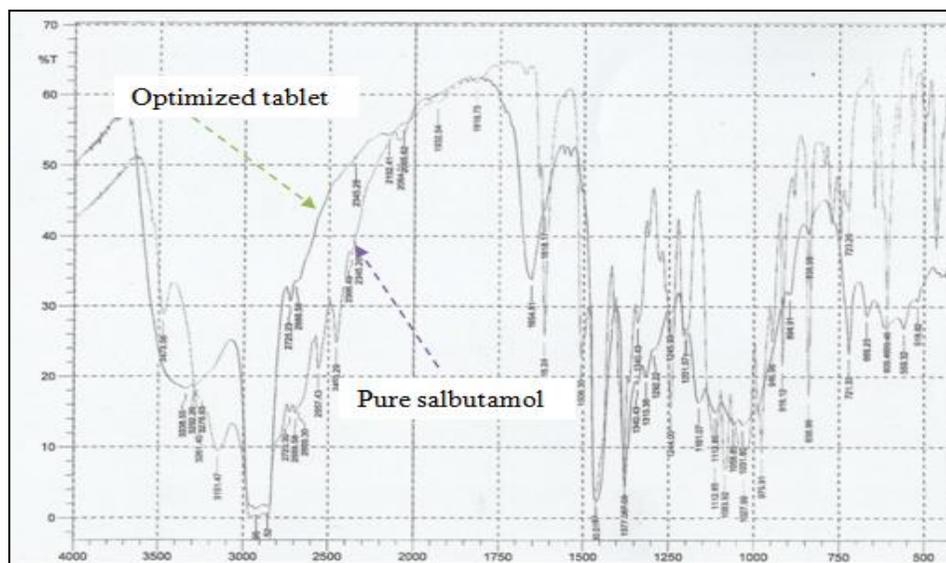


FIG.11: OVERLAP OF FTIR SPECTRA OF PURE SALBUTAMOL AND THE OPTIMIZED TABLET.

CONCLUSION: Preliminary studies on floating sustained release salbutamol sulphate matrix tablets revealed that formulation variables like polymer type, polymer ratio, polymer concentration, and NaHCO_3 concentration have significant effect on release rate, cumulative release at 1 hr, and floating lag time, but not on floating duration. Among formulations developed in the preliminary study, XG/HPMC polymer blend at 1:3 ratio showed relatively good release pattern and was optimized using CCD approach. The optimized formulation containing 24.79% of XG/HPMC (1:3) and 5% of NaHCO_3 was experimentally evaluated and showed good agreement with the predicted response values. In conclusion, this study has come up with an optimum formulation for the preparation of floating matrix tablet of salbutamol sulphate that could remain buoyant in the gastric content and release the drug over a period of 12 hr in a sustained manner. From *in vitro* perspective, this optimized formulation may improve the overall bioactivity of oral salbutamol sulphate and patient compliance.

ACKNOWLEDGEMENTS: The authors would like to thank Addis Pharmaceutical Factory PLC. (APF) and Food, Medicine and Healthcare

Administration and Control Authority of Ethiopia (EFMHACA) for providing access to their facilities and School of Graduate Studies, Addis Ababa University (AAU) for financing the study. ZY is also grateful to Mekele University for sponsoring his study at AAU.

REFERENCES:

1. Pathan A., Channawar M., Bakde B., Chandewar A. Development and *in-vitro* evaluation of salbutamol sulphate mucoadhesive buccal patches. *Int. J. Pharm. Pharmaceut. Sci.* 2011; 3:39 - 44.
2. Fishwick D., Bradshaw L., Macdonald C. Cumulative single-dose design to assess the bronchodilator effects of beta-2-agonists in individuals with asthma. *Am. J. Resp. Crit. Med.* 2001; 163:474 - 477.
3. AHFS. American Hospital Formulary Service: *Drug Information 2008*®. USA: American Society of Health-System Pharmacists Inc; 2008, p. 1340 - 1352.
4. Swarbrick J. Encyclopedia of pharmaceutical technology, 3rd ed, Vol 1, USA: Pharmaceu Tech, Inc; 2007, p. 1253.
5. Mamidala R., Ramana V., Sandeep G., Lingam M., Gannu R., Yamsani M. Factors influencing the design and performance of oral sustained/controlled release dosage forms. *Int. J. Pharm. Sci. Nanotechnol.* 2009; 2:583 - 594.
6. Ravikumar K., Vinaya O., Santhikrishna U. Development of floating matrix tablets of salbutamol sulphate and study of drug release kinetics. *Int. J. Res. Pharm. Biomed. Sci.* 2012; 3:1346 - 1354.
7. Kavitha K. and Mehaboob Y. Microballoon as a drug delivery system: an emerging trend. *Int. J. Res. Pharm. Biomed. Sci.* 2011; 2:44 - 51.

8. Shinde S., Magdum S., Waikar S., Mishra M., Chandak K. Development and evaluation of floating tablets of salbutamol sulphate. *Int. J. Pharm. Res. Dev.* 2010; 2:1 - 7.
9. USP 30/ NF 25. United States Pharmacopoeial Convention, Inc. Rockville, Maryland; 2007.
10. Sadray S., Honary S., Ebrahimi P., Jafari P., Sezaee R. Dissolution profile comparison: Model dependent and model independent approaches. *Int. J. Pharm. and Bio Sci.* 2010; 2:1 - 10.
11. Shoaib M., Tazeen J., Merchant H., Yousuf R. Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. *Pak. J. Pharm. Sci.* 2006; 19:119 - 124.
12. Akelesh T., Sapkal SB., Sivakumar R., Jothi R., Venkatnarayanan R. Formulation development of gastro retentive floating tablet of acyclovir using natural gums. *Der Pharmacia Lettre* 2011; 3:254 - 261.
13. Singh K., Gupta S., Singh A., Sinha S. Experimental design and response surface modeling for optimization of Rhodamine B removal from water by magnetic nanocomposite. *Chem. Eng. J.* 2010; 165:151 - 160.
14. Talukdar M., Michoel A., Rombaut P., Kinget R. Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrices for controlled-release drug delivery I. Compaction and *in vitro* drug release behaviour. *Int. J. Pharm.* 1996; 129:233 - 241.
15. Tiwari S. Rajabi-Siahboomi A. Applications of complementary polymers in HPMC hydrophilic extended release matrices. *Drug Deliver. Technol.* 2009; 9:19 - 27.
16. Hu L., Li L., Yang X., Liu W., Yang J., Jia Y., Shang C., Xu H. Floating matrix dosage form for dextromethorphan hydrobromide based on gas forming technique: *In vitro* and *in vivo* evaluation in healthy volunteers. *Eur. J. Pharm. Sci.* 2011; 42:99 - 105.
17. Rajukar M., Vaka T., Hygreevachary K., Venkateswarlu E., Rakesh K. Design fabrication and characterization of controlled released tablets of Trimetazidine di hydrochloride. *Der. Pharmacia Sinica.* 2011; 2:59 - 66.
18. Maderuelo C., Zarzuelo A., Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. *J. Control. Rel.* 2011; 154:2 - 19.
19. Tadros M. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and *in vitro-in vivo* evaluation in healthy human volunteers. *Eur. J. Pharm. Biopharm.* 2010; 74:332 - 339.
20. Bomma R., Naidu R., Yamsani M., Veerabrahma K. Development and evaluation of gastroretentive norfloxacin floating tablets. *Acta Pharm.* 2009; 59:211 - 221.
21. Pasa G., Mishra US. Tripathy NK. Sahoo SK., Mahapatra AK. Formulation development and evaluation of didanosine sustained release matrix tablets using HPMC K15. *Int. J. Pharm.* 2012; 2:97 - 100.
22. Aziz H., Kamaruddin A., Abu-Bakar M. Process optimization studies on solvent extraction with naphthalene-2-boronic acid ion-pairing with trioctylmethyl ammonium chloride in sugar purification using design of studies. *Separ. Purif. Technol.* 2008; 60:190 - 197.
23. Kusic H., Jovic M., Kos N., Koprivanac N., Marin V. The comparison of photooxidation processes for the minimization of organic load of colored waste water applying the response surface methodology. *J. Hazard. Mater.* 2010; 183:189 - 202.
24. Takayama K., Fujikawa M., Obata Y., Morishita M. Neural network based optimization of drug formulations. *Adv. Drug Deliver.* 2003; 55:1217 - 1231.
25. Yang K., El-Haik B. Design for Six Sigma: a Roadmap for Product Development. 2nd ed. New York: McGraw-Hill Co. Inc; 2008, p. 611 - 642.
26. Mohajeri L., Aziz H., Isa M., Zahed M. A statistical experiment design approach for optimizing biodegradation of weathered crude oil in coastal sediments. *Bioresource Technol.* 2010; 101:893 - 900.
27. Prasanthi N., Krishna C., Gupta M., Manikiran S., Rao N. Design and development of sublingual fast dissolving films for an antiasthmatic drug. *Der. Pharmacia Lettre.* 2011; 3:382 - 395.

How to cite this article:

Yilma Z, Belete A and Gebre-Mariam T: Formulation and Optimization of Sustained Release Floating Matrix Tablets of Salbutamol Sulphate Using Xanthan Gum and Hydroxypropyl Methylcellulose Polymer Blend. *Int J Pharm Sci Res* 2015; 6(5): 1877-92. doi: 10.13040/IJPSR.0975-8232.6(5).1877-92.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **ANDROID OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)