Acta Pharm. **66** (2016) 35–51
DOI: 10.1515/acph-2016-0002

Original research paper

Design and statistical optimization of an effervescent floating drug delivery system of theophylline using response surface methodology

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The aim of this research was to formulate effervescent floating drug delivery systems of theophylline using different release retarding polymers such as ethyl cellulose, Eudragit® L100, xanthan gum and polyethylene oxide (PEO) N12K. Sodium bicarbonate was used as a gas generating agent. Direct compression was used to formulate floating tablets and the tablets were evaluated for their physicochemical and dissolution characteristics. PEO based formulations produced better drug release properties than other formulations. Hence, it was further optimized by central composite design. Further subjects of research were the effect of formulation variables on floating lag time and the percentage of drug released at the seventh hour (D_{7h}). The optimum quantities of PEO and sodium bicarbonate, which had the highest desirability close to 1.0, were chosen as the statistically optimized formulation. No interaction was found between theophylline and PEO by Fourier Transformation Infrared spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) studies.

Keywords: theophylline, gastroretentive, floating, central composite, PEO N12K

Accepted December 22, 2014
Online published January 18, 2016

An oral controlled-release drug delivery system allows less frequent dosing and increased patient compliance (1, 2). However, these drug delivery systems usually have a short gastric residence time, leading to poor bioavailability and incomplete drug absorption (3, 4).

Gastroretentive drug delivery systems (GRDDS) offer an alternative approach to avoid such difficulties and might provide a better therapeutic action than other drug delivery systems (5). Prolonged gastric retention enhances bioavailability, reduces drug waste and improves the solubility of drugs that are less soluble in a high pH environment. GRDDS limit fluctuations of plasma drug concentrations (6–8). This feature is vital for drugs such as theophylline, which have a narrow therapeutic window.

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In this study, theophylline is used as a model drug for the development of GRDDS. Theophylline is a bronchodilator used in moderate to severe reversible bronchospasms and in stable chronic obstructive pulmonary disease. It is a narrow therapeutic window drug (plasma concentration between 10–20 mg L^{-1}), which requires therapeutic drug monitoring (9, 10). Theophylline is mainly metabolized in the liver and has an elimination half-life of 6 hours (11). It has a good absorption window in the upper gastrointestinal tract, making it suitable for GRDDS. Effervescent floating tablets of theophylline have been developed in order to increase drug efficacy, to minimize fluctuation of drug plasma concentration and to reduce concentration-dependent adverse effects (12, 13).

In this study, an effervescent floating drug delivery system of theophylline was prepared using release retarding polymers such as ethyl cellulose, Eudragit® L100, xanthan gum and polyethylene oxide (PEO) N12K. Sodium bicarbonate was used as a gas generating agent. Ethyl cellulose and PEO N12K are hydrophobic and hydrophilic polymers, respectively (12, 13). Eudragit® is an anionic copolymer, whereas xanthan gum is a complex exopolysaccharide produced by *Xanthomonas campestris* (14, 15). The selected polymers have good swelling properties (5). When in contact with gastric fluid, polymers will form a viscous matrix and retard the release of the drug from the system (16). When in contact with gastric fluid, sodium bicarbonate will liberate carbon dioxide gas (16, 17). The gas entrapped within the matrix decreases the density of the tablet below 1 g cm^{-3}, providing buoyancy to the dosage form (16, 18). While the system is floating in the gastric medium, the drug will be released slowly at a controlled rate without affecting the gastric emptying rate (7, 19).

Based on previous studies, the floating lag time was significantly controlled by the quantity of sodium bicarbonate (20). The total polymer-to-polymer ratio and drug-to-polymer ratio significantly affected the drug release properties and total floating time (21).

The conventional optimization process allows only a single independent variable to be altered at a time, while other parameters remain constant under a specific set of conditions during formulation development (22). This results in the requirement for a large number of runs to achieve target responses (18). A statistical approach using response surface methodology (RSM) can be employed to optimize the formulation using a suitable experimental design such as central composite design (23). RSM reduces the cost of conducting analytical studies, limits random errors and predicts accurate quantities of the polymers to achieve the target formulation (23, 24).

The objective of the present study was to formulate an effervescent floating drug delivery system of theophylline using the gas generating agent sodium bicarbonate and release retarding polymers such as ethyl cellulose, Eudragit® L100, xanthan gum and PEO N12K. Other objectives included optimization of the formulation of theophylline by applying a statistical approach using a central composite design and examining the effect of formulation variables on the dependent variables.

EXPERIMENTAL

Materials

Ethyl cellulose and PEO N12K were obtained as gift samples from Colorcon Asia Pacific Ltd, Singapore. Eudragit® L 100 was obtained as a gift sample from Jebsen & Jessen

Table I. Working formulae of theophylline GRFT developed conventionally

Formulation	Theophylline (mg)	Polymers				Sodium bicarbonate (mg)	Diluents			Talc (mg)	Magnesium stearate (mg)	Total tablet mass (mg)
		Ethyl cellulose (mg)	Eudragit® L 100 (mg)	Xanthan gum (mg)	PEO N12K (mg)		Microcrystalline cellulose (mg)	Lactose (mg)	D-Mannitol (mg)			
B1	50	30	–	–	–	10	106	–	–	2	2	200
B2	50	30	–	–	–	30	–	86	–	2	2	200
B3	50	15	–	–	–	30	–	101	–	2	2	200
B4	50	50	–	–	–	40	–	–	56	2	2	200
B5	50	–	30	–	–	30	–	–	86	2	2	200
B6	50	–	50	–	–	40	–	–	56	2	2	200
B7	50	–	100	–	–	40	–	–	6	2	2	200
B8	50	–	150	–	–	40	–	–	6	2	2	200
B9	50	–	–	75	–	20	–	–	51	2	2	200
B10	50	–	–	–	50	20	–	–	76	2	2	200
B11	50	–	–	–	75	20	–	–	51	2	2	200
B12	50	–	–	–	90	20	–	–	36	2	2	200

Chemicals, Malaysia. Sodium bicarbonate was purchased from Ajax Finechem, Malaysia. Theophylline, xanthan gum, microcrystalline cellulose, lactose, D-mannitol min. 98 %, talc and magnesium stearate were purchased from Labchem Sdn Bhd, Malaysia.

Conventional formulation optimization

Twelve different formulations with varying quantities of different polymers were selected for the development of gastroretentive floating tablets (GRFT) of theophylline (Table I). The tablets were subjected to physicochemical tests and *in vitro* studies as described below.

Preparation of effervescent floating tablets of theophylline

All the ingredients were passed through a 500 μm sieve. Theophylline was homogenously mixed in geometrical ratio with the release retarding polymer, followed by sodium bicarbonate, diluent, talc and magnesium stearate. 1 % of talc and magnesium stearate were used in all the formulations.

The final blend was directly compressed into tablets with a 10-station rotary tablet punching machine (Rimek Mini Press-I) at a hardness of 3–4 kg cm^{-2}. Round flat punches of 8.0 mm die size were used. Fifty tablets were produced for each formulation.

Evaluation of floating tablets

All floating tablets were evaluated for physicochemical parameters as described below.

Mass variation test. – Twenty randomly chosen tablets were weighed individually. Each tablet mass was compared with the average mass to determine if it was within the acceptance limits. 200 mg ± 7.5 % is the percentage deviation allowed for a tablet weighing 200 mg (25).

$$\text{mass variation (\%)} = \frac{\text{average mass} - \text{mass of individual tablet}}{\text{average mass}} \times 100$$

Hardness test. – The hardness of ten randomly chosen tablets was measured using a Monsanto hardness tester (T-MMT-20, Tab machines, India). The fracture load (kg cm^{-2}) of ten tablets was determined individually to check tablet hardness, also represented as tensile strength. The mean values of fracture loads were used to calculate the hardness values.

Thickness test. – Twenty tablets were subjected to thickness testing using Mitutoyo vernier calipers (Model: 530-312, Japan). A thickness deviation within ± 5 % was allowed.

Friability test. – The friability test was performed using a Friabilator (Electrolab, Model: EF-2, India). Twenty pre-weighed tablets were placed in the rotating drum, which was subjected to 100 revolutions. The tablets were reweighed after rotations. The percentage mass loss should not be more than 1 % of total weight (26).

Content uniformity. – Ten randomly chosen tablets were powdered in a glass mortar and 50 mg of powder was transferred into a 100 mL volumetric flask. The powder was dissolved in 30 mL of methanol and made up to 100 mL with 0.1 mol L^{-1} HCl. The solution was filtered and 3 mL of filtrate was extracted and made up to 100 mL with 0.1 mol L^{-1} HCl. The concentration of theophylline was determined with a validated UV spectrophotometer (LAMBDA 25, Perkin Elmer) at 270 nm.

In vitro *buoyancy studies*

All the formulated tablets ($n = 6$) were subjected to *in vitro* buoyancy studies. The floating lag time was determined in a 1 L glass beaker containing 900 mL 0.1 mol L^{-1} HCl. The time required for the tablet to float was determined as the floating lag time. A floating lag time of less than 1 minute is desirable.

In vitro *dissolution studies*

In vitro release of theophylline ($n = 6$) was studied using an Electrolab TDT-08L dissolution tester (USP) employing a paddle stirrer. 900 mL of 0.1 mol L^{-1} HCl solution was

maintained at 37 ± 0.5 °C at a paddle speed of 100 rpm. 5-mL aliquots were withdrawn at specific time intervals using a syringe fitted with a 0.45 μm pre-filter and were immediately replaced with 5 mL of fresh dissolution medium. Each aliquot was filtered and diluted when necessary. The samples were analyzed using a UV spectrophotometer at 270 nm. The *in vitro* dissolution studies were triplicated for all batches (18).

Formulation optimization using experimental design

A central composite design was employed using the Design-Expert (7.1.6) software. The design contained two factors evaluated at two levels. The levels of two independent variables are shown below. Nine different formulations were generated by the software based on the conventionally optimized formulation (Table III). Tablets were prepared and characterized in the same manner as conventionally developed tablets. The formulation variables evaluated included:

Variables	Range and levels		
	–1	0	+1
PEO WSR N12K (mg) X_1	70	90	110
Sodium bicarbonate ratio X_2 (%, *m*/*m*)	5	10	15

X_1 = A = Amount of PEO N12K (mg)
X_2 = B = Percentage of sodium bicarbonate (%)

The response variables included:

Y_1 = Floating lag time (s)
Y_2 = D_{7h} (percentage of drug released at 7th h) (%)

Statistical analysis and optimization

Polynomial models including linear, interaction and quadratic terms were generated for all the response variables using the Design-Expert software. The best fitting model was selected by comparing the coefficient of variation (*CV*), adjusted coefficient of determination (adjusted R^2), the coefficient of determination (R^2) and the predicted residual sum of squares (PRESS) provided by the software. Regression coefficients test, *F* and *P* values were calculated by the software. Analysis of variance (ANOVA) showed the effect of factors on the responses.

Release kinetics

The dissolution profiles of all statistically formulated batches were fitted to the zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas. The order and mechanism of drug release from the matrix system were determined based on high regression (R^2) values (19).

The data were evaluated based on the following equations:

Zero order release kinetics: $Q_t = Q_0 + k_0 t$
First order release kinetics: $\log M = \log M_0 - k_1 t/2.303$
Higuchi model: $Q = k_H t^{1/2}$
Hixson-Crowell cube root model (erosion): $W_0^{1/3} - W_t^{1/3} = K_{HC} t$
Korsmeyer-Peppas model: $M_t/M_\infty = k_p t^n$

where, Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution, M_0 is the initial concentration of drug in the dosage form, M is the remaining amount of drug in the dosage form, W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t, M_t is the amount of drug released at time t, M_∞ is the amount released at time ∞ and n is the diffusion exponent. The n value is obtained as a slope by plotting the log percentage drug released against the log time for different batches (12). K_0, k_1, k_H, k_{HC} and k_p refer to the kinetic constants obtained from the linear curves of the zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas, respectively.

Validation of the experimental design

To validate the chosen experimental design, the experimental values of formulation responses were quantitatively compared with those of predicted values generated by the software. The percentage relative error was calculated by the following equation:

$$\text{Relative error (\%)} = \frac{\text{predicted value} - \text{observed value}}{\text{predicted value}} \times 100$$

In vitro buoyancy and dissolution studies of the statistically optimized formulation were performed for verification of the theoretical prediction (24).

Drug-excipient interaction studies

Differential scanning calorimetry (DSC). – DSC analysis of the drug, polymer and the statistically optimized formulation (F0) were done using a differential scanning calorimeter (Mettler Toledo DSC 823^e). 3–10 mg of the sample was heated under nitrogen atmospheres from 0 to 280 °C at a heating rate of 10 °C/min.

Fourier transformation infrared spectroscopy (FTIR). – The possibility of drug-polymer interaction was further investigated by FTIR using the potassium bromide pellet method. About 2–3 mg of the sample was ground with 200 mg of potassium bromide and compressed under high pressure to form a transparent disc. The disc was scanned by an IR spectrophotometer (Shimadzu, FTIR-8400S) in the region between 4000–650 cm^{-1}.

RESULTS AND DISCUSSION

The results of physicochemical characterization of twelve formulations developed by the conventional approach are shown in Table II. Variations of tablet thickness with the

Table II. Physicochemical properties and observed responses of the theophylline GRFT developed conventionally

Formulation	Mass (mg)	Hardness (kg cm^{-2})	Thickness (mm)	Friability (%)	Observed responses	
					Floating lag time (min)	Percentage drug released at 7th h, D_{7h} (%)
B1	198 ± 1.50	3–4	3.86	0.39	Does not float	68 ± 0.05
B2	205 ± 1.40	3–4	3.93	0.47	37	63 ± 1.73
B3	200 ± 1.44	3–4	3.90	0.41	40	64 ± 1.34
B4	201 ± 0.83	3–4	3.88	0.16	180	870.08
B5	202 ± 1.60	3–4	3.89	0.05	2	100 ± 0.98 (at 4th hour)
B6	204 ± 1.35	3–4	3.92	0.51	3	100 ± 1.22 (at 4th hour)
B7	199 ± 1.14	3–4	3.91	0.23	3	90 ± 1.01
B8	196 ± 1.21	3–4	3.84	0.27	20	100 ± 0.69 (at 6th hour)
B9	202 ± 1.10	3–4	3.89	0.48	2	84 ± 0.40
B10	200 ± 1.20	3–4	3.89	0.36	2	85 ± 2.48
B11	207 ± 0.97	3–4	3.95	0.30	0.05	83 ± 0.12
B12	203 ± 1.36	3–4	3.90	0.11	0.05	90 ± 1.31

Table III. Working formulae of the theophylline GRFT developed using experimental design

Ingredients (mg)	S1	S2	S3	S4	S5	S6	S7	S8	S9
Theophylline	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
PEO N12K	70.00	110.00	70.00	110.00	61.72	118.28	90.00	90.00	90.00
Sodium bicarbonate	10.00	10.00	30.00	30.00	20.00	20.00	5.86	34.14	20.00
D-Mannitol	66.00	26.00	46.00	6.00	64.28	7.72	50.14	21.86	36.00
Talc	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Magnesium stearate	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Total tablet mass	200	200	200	200	200	200	200	200	200

same tablet mass may be due to the differences in the condition of the punches and in the speed of tablet compression (27). The floating lag time of most of the formulations was more than 1 minute, except for B11 and B12 which took 3 seconds to float (Table II).

The target drug release is about 85–90 % at the end of 8 hours (28). From the dissolution profiles shown in Fig. 1, ethyl cellulose-based formulations (B1-B3) showed that only 63–64 % of the drug was released at the end of 8 hours, which was not desirable. B1, B2 and B3 had poor matrix integrity. The tablets were completely disintegrated within 4–5 hours in the dissolution medium. In B4, where the quantity of sodium bicarbonate was larger than in previous batches (B1-B3), tablets took around 3 hours to float in the gastric medium and were retarded up to 8 hours. When *D*-mannitol was used as the diluent in B4, 90 % of the drug was released at the end of 8 hours. Hence, *D*-mannitol is considered as the most suitable diluent for formulating theophylline floating tablets.

The dissolution profiles of B1-B4 reveal clear differentiation of the effect of diluents on the drug release pattern. The effect of the solubility of the diluent on the drug release pattern was explored. The water-insoluble diluent, microcrystalline cellulose (MCC), significantly retarded drug release (B1), with 60–64 % of drug being released at the end of the eighth hour. On the other hand, lactose, a water-soluble diluent, showed rapid disintegration properties; dosage forms using lactose (B2-B3) could not control drug release for more than 4 hours. However, another water soluble diluent, mannitol, showed very good retardation properties compared to lactose and MCC. Hence, further compositions used mannitol as the diluent.

Ethyl cellulose had poor buoyancy properties. The floating lag time of B1-B4 was still more than 1 minute, although the percentage of sodium bicarbonate had been increased to 40 % and different diluents were used.

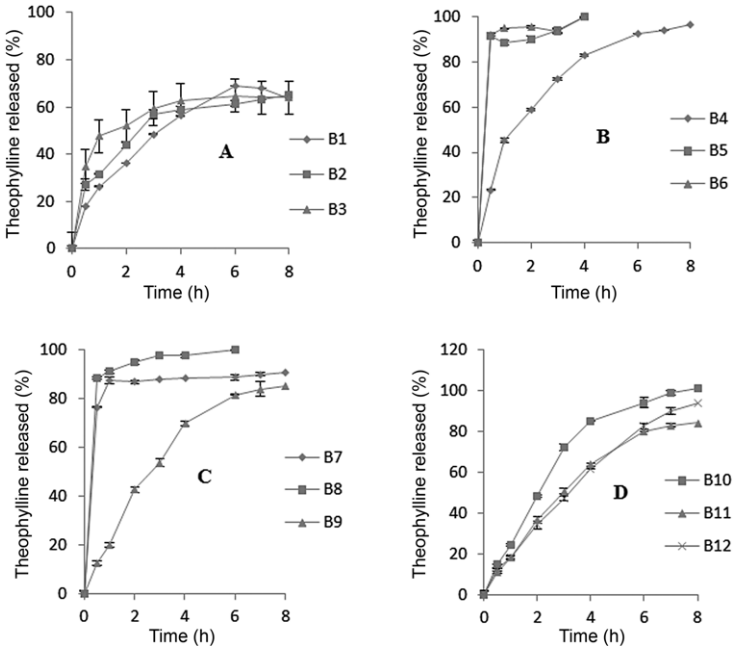

Fig. 1. Release profiles of theophylline from the conventionally optimized GRFT: a) B1–B3, b) B4–B6, c) B7–B9 and d) B10–B12.

On the other hand, Eudragit® L100 based formulations (B5-B8) showed a burst release pattern. Eudragit® L100 was not compatible with theophylline, as the tablets completely disintegrated within 3-4 minutes in the dissolution medium. Consistent with the previous literature, Eudragit® L100 is a good enteric coating polymer (14). However, this polymer is not useful for theophylline floating drug delivery systems. As the higher density of Eudragit® L100 may have prevented the formulation from floating on the gastric medium, the sodium bicarbonate concentration was increased to 10–30 % (*m*/*m*) to improve the buoyancy properties; however, this made the dosage form disintegrate rapidly. Therefore, a continuous floating system with prolonged release could not be achieved using Eudragit® L100 polymer (14).

PEO N12K and xanthan gum based formulations showed good drug release patterns and good matrix integrity. However, the xanthan gum-based formulation had poor buoyancy. Formulations based on PEO N12K were shown to be readily swellable in the gastric fluid, thus the tablets were buoyant in less than 1 minute (12). However, formulations containing less than 50 mg xanthan gum disintegrated rapidly in the dissolution medium (12).

Ethyl cellulose has the highest drug retarding ability compared to PEO N12K and xanthan gum, whereas Eudragit® L100 has the least retarding ability. Drug retarding ability is affected by the molecular weight of the polymer (18). Higher molecular weight polymers retarded the drug more efficiently than polymers with lower molecular weight (12). Based on the present results, PEO N12K appeared to be the best polymer for formulating theophylline effervescent floating tablets. Therefore, B12 was further optimized by central composite design.

Table IV. Physicochemical properties and observed responses of the theophylline GRFT developed using experimental design

Formulation	Amount of PEO N12K (mg) A	Percentage of sodium bicarbonate (%) B	Mass (mg)	Hardness (kg cm^{-2})	Thickness (mm)	Friability (%)	Observed responses	
							Floating lag time (s) y_1	Percentage drug released at 7th h, D_{7h} (%) y_2
S1	70.00	5.00	201 ± 1.20	3.9 ± 0.01	3.91	0.31 ± 0.01	25	87.50 ± 0.67
S2	110.00	5.00	209 ± 1.47	3.8 ± 0.04	3.97	0.24 ± 0.02	45	74.50 ± 1.10
S3	70.00	15.00	199 ± 1.36	4.1 ± 0.02	3.86	0.26 ± 0.04	5	75.90 ± 2.12
S4	110.00	15.00	210 ± 1.13	4.2 ± 0.11	3.98	0.17 ± 0.06	7	69.10 ± 0.72
S5	61.72	10.00	202 ± 1.45	3.4 ± 0.06	3.92	0.43 ± 0.07	4	83.80 ± 0.70
S6	118.28	10.00	201 ± 1.42	3.8 ± 0.04	3.90	0.40 ± 0.08	17	81.10 ± 0.57
S7	90.00	2.93	198 ± 1.63	3.5 ± 0.05	3.87	0.12 ± 0.04	11	89.78 ± 0.77
S8	90.00	17.07	205 ± 1.34	4.0 ± 0.01	3.94	0.46 ± 0.05	3	82.24 ± 0.02
S9	90.00	10.00	196 ± 1.91	4.1 ± 0.03	3.85	0.38 ± 0.01	6	90.50 ± 1.17

All nine formulations satisfied the criteria of the physicochemical tests (Table IV). The floating lag time of S1-S9 was within 3 to 45 seconds. As the percentage of sodium bicarbonate increased, the floating lag time decreased. On the other hand, as the amount of PEO N12K increased, the floating lag time increased.

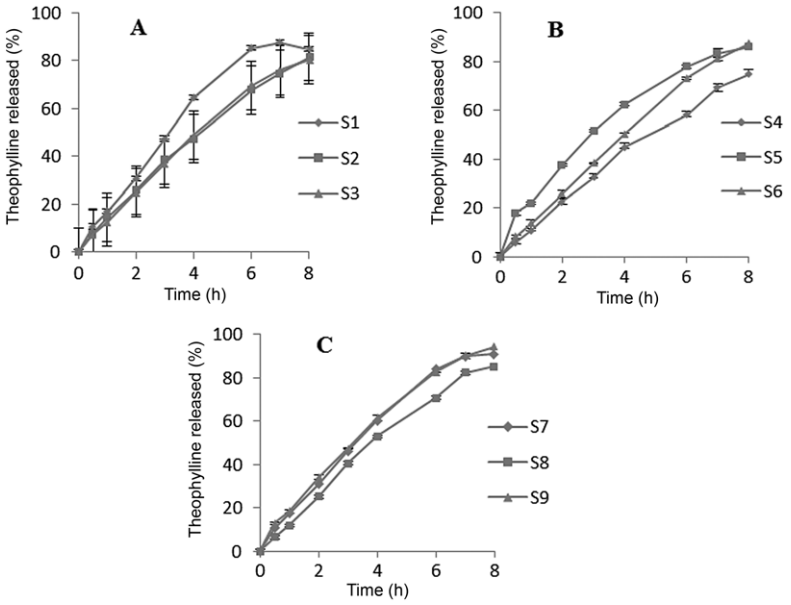

Fig. 2. Release profiles of theophylline from the statistically optimized theophylline GRFT: a) S1–S3, b) S4–S6 and c) S7–S9.

Table V. Correlation coefficient values and release kinetics of the statistically optimized theophylline GRFT

Formulation	Zero order		First order		Higuchi	Hixson-Crowell	Korsmeyer-Peppas	
	R^2	Slope (*n*)	R^2	Slope(n)	R^2	R^2	R^2	Slope (*n*)
S1	0.9463	11.425	0.9558	–0.1218	0.9562	0.9636	0.9918	0.8261
S2	0.9908	10.181	0.9871	–0.0893	0.9608	0.9978	0.9991	0.8606
S3	0.9880	10.361	0.9903	–0.0904	0.9544	0.9969	0.9964	0.9070
S4	0.9926	9.4671	0.9871	–0.0742	0.9500	0.9959	0.9970	0.9611
S5	0.9466	10.344	0.9975	–0.1075	0.9884	0.9927	0.9602	0.6047
S6	0.9935	11.153	0.9736	–0.1099	0.9493	0.9927	0.9963	0.8893
S7	0.9776	11.861	0.9743	–0.1392	0.9626	0.9906	0.9955	0.8406
S8	0.9870	11.139	0.9801	–0.1068	0.9510	0.9942	0.9972	1.0303
S9	0.9784	11.821	0.9706	–0.149	0.9713	0.9952	0.9858	0.7386
F0	0.9987	12.455	0.7764	–0.202	0.9217	0.9358	0.9961	0.9657

Based on the dissolution profiles, only the S7 and S9 formulations showed more than 90 % drug release by the end of 8 hours. Other formulations required more than 8 hours to achieve 100 % drug release. Drug retardation was directly proportional to the quantity of PEO N12K because of the formation of strong compactness between the particles when the concentration of polymer was higher (Table IV). All statistical formulations floated in the dissolution medium for more than 8 hours and showed good matrix integrity (Fig. 2).

Most PEO N12K based formulations followed zero order kinetics associated with the erosion mechanism (Table V), which obeyed the rule of a controlled drug delivery system. S1, S3 and S5 formulations followed first order kinetics associated with the erosion mechanism. Release mechanisms changed from first order to zero order kinetics as the amount of PEO N12K exceeded 70 mg.

From the polynomial model fitting statistical analysis, floating lag time and D_{7h} were suggested to linear model. Calculated R^2 values for both the floating lag time and D_{7h} were close to zero, which was ideal for a good model. Results are shown in Table VI.

The application of response surface methodology yielded the following regression equations, which are an empirical relationship between the logarithmic values of the floating lag time and D_{7h}.Test variables in coded units:

$$\text{Floating lag time} = +13.67 + 5.05A - 8.66B$$
$$D_{7h} = +81.60 - 2.95A - 3.46B$$

Contour and response plots shown in Figs. 3 and 4 allowed more understanding of the relationship of two parameters at the time of formulation responses.

A numerical optimization technique using a desirability approach (bilateral) and a graphical optimization method using overlay plot (Fig. 5) were employed to generate optimized formulations with the desired characteristics. The optimized formulation was selected based on a minimal floating lag time, release of less than 20 % of the drug in the first hour, and a D_{7h} of 90 %. The recommended quantities of independent variables were calculated using the Design-Expert software based on the plots showing the highest desirability of 1.0. The optimum values of independent variables calculated by the software for the development of a GRFT of theophylline were 88.97 mg of PEO N12K and 10.46 % of sodium bicarbonate.

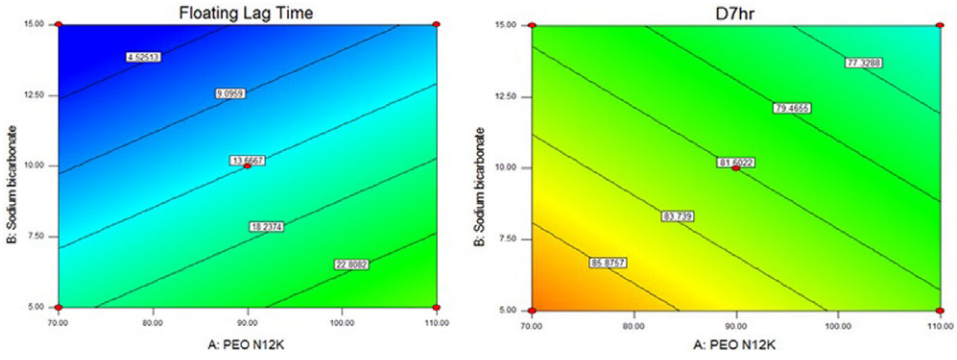

Fig. 3. Contour plots for the effect of: a) PEO N12K and b) sodium bicarbonate on floating lag time and D_{7h}.

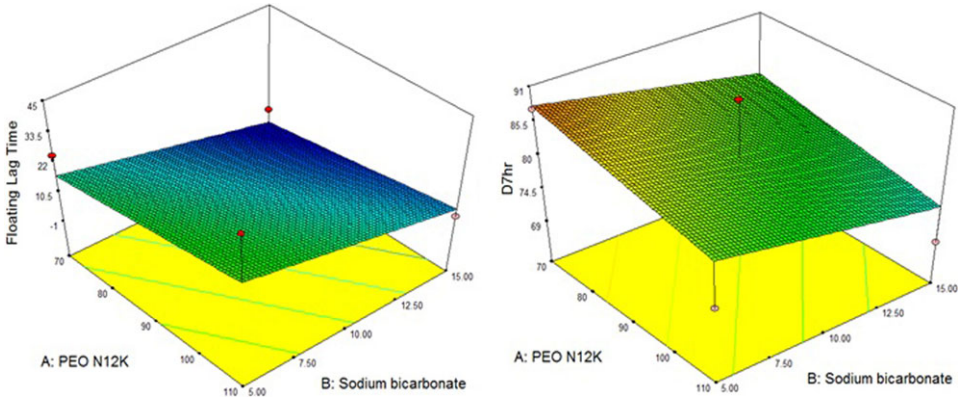

Fig. 4. Response surface plots for the effect of: a) PEO N12K and b) sodium bicarbonate on floating lag time and D_{7h}.

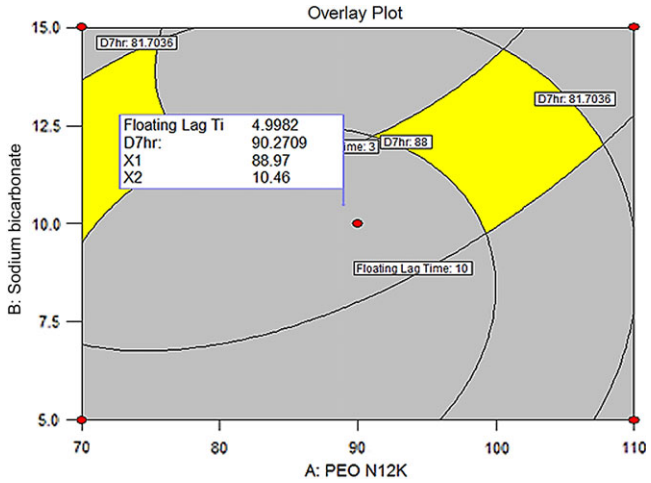

Fig. 5. Overlay plot for optimization of the theophylline GRFT.

F0 fulfilled all the physicochemical property tests (Table VII). *In vitro* buoyancy and dissolution studies of F0 were performed for verification of the theoretical prediction. *In vitro* studies of F0 showed an ideal result. The data from the assay indicated that the statistically optimized formulation had a drug content within the USP limits, between 97.34 and 98.76 %. Percentage relative errors for floating lag time and D_{7h} were 0 and 0.54 % respectively, which were within 5 %, hence showing close agreement with the model predictions; we confirmed the predictability and validity of F0.

Drug-excipient interactions were studied by DSC and FTIR. DSC thermograms of theophylline, PEO N12K and F0 are shown in Fig. 6. The DSC thermogram of theophylline showed a sharp endothermic peak at 273 °C that corresponded to its melting point. The

Table VI. Summary of ANOVA results for the response surface linear model

Parameters	Sum of squares	dF	Mean square	*F* value	*p* value Prob > *F*	Remark
Response 1: Floating lag time (s) (Linear model)						
Model	804.42	2	402.21	3.40	0.1030	–
A-PEO N12K	203.87	1	203.87	1.72	0.2372	
B-Sodium bicarbonate	600.55	1	600.55	5.08	0.0651	
Residual	709.58	6	118.26			
Cor total	1514.00	8				
Response 2: D_{7h} (%) (Linear model)						
Model	165.38	2	82.69	1.91	0.2285	–
A-PEO N12K	69.73	1	69.73	1.61	0.2518	
B-Sodium bicarbonate	95.66	1	95.66	2.21	0.1880	
Residual	260.20	6	43.37			
Cor total	425.58	8				

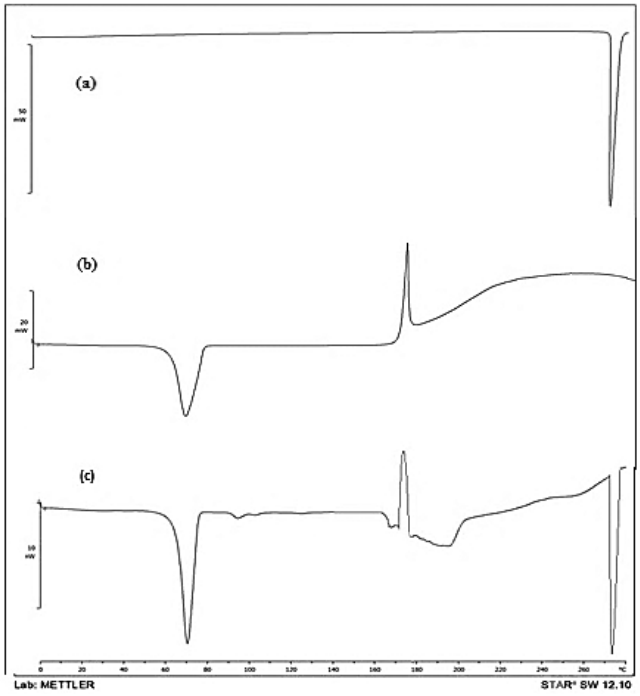

Fig. 6. DSC thermogram of: a) theophylline, b) PEO N12K and c) F0.

Table VII. Tableting and buoyancy characteristics of optimized formulation F0

Statistically optimized formulation	Tableting characteristics					Buoyancy characteristics	
	Mass (mg)	Hardness (kg cm^{-2})	Thickness (mm)	Friability (%)	Assay (%)	Floating lag time (s)	Percentage drug released at 7th h, D_{7h} (%)
F0	200 ± 0.12	3–4	4.6	0.42	98.045 ± 0.79	5	89.78 ± 0.87

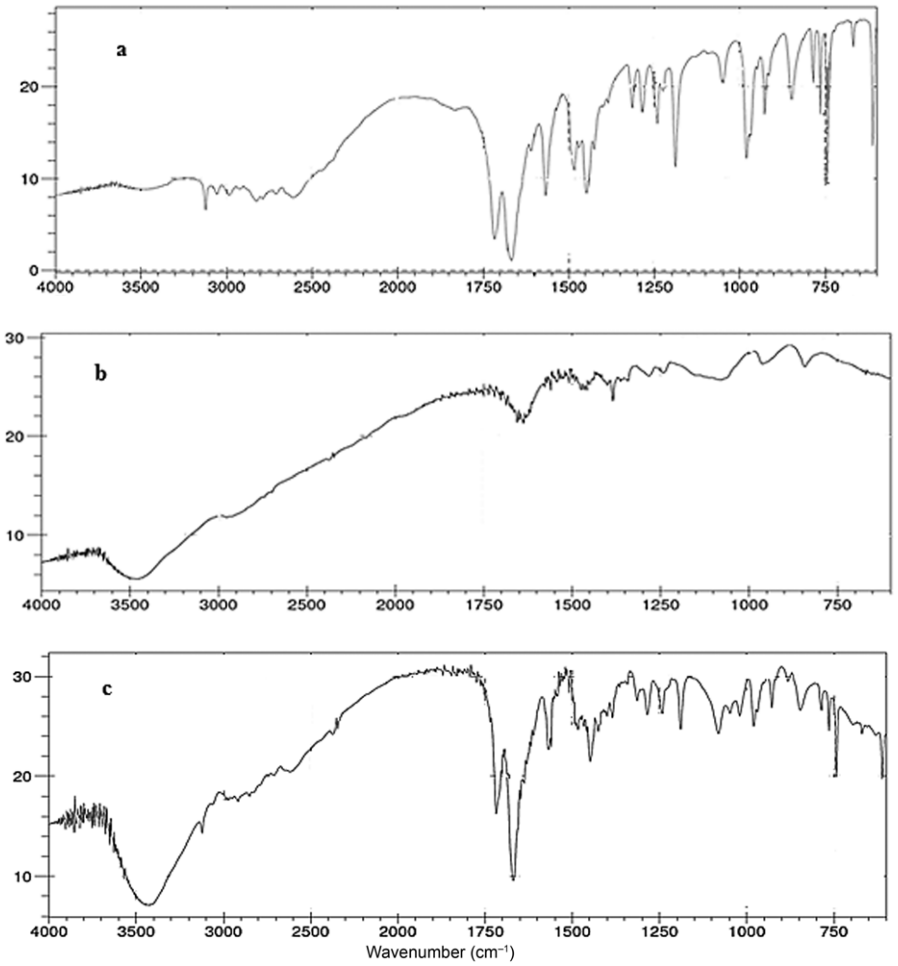

Fig. 7. FTIR spectra of: a) theophylline, b) PEO N12K and c) F0.

DSC thermogram of PEO N12K showed an endothermic peak at 70.92 and an exothermic peak at 172 °C.

Based on the F0 thermogram, the peaks observed at 272.1, 70 and 170.9 °C corresponded to the peaks of the drug and the polymer. Slight decreases in the melting points were due to the crystallinity of the drug. The absence of any major changes in the F0 DSC thermogram indicated that there was no chemical reaction between the drug and the polymer.

The FTIR spectra of theophylline, PEO N12K and F0 are shown in Fig. 7. Theophylline showed characteristic peaks of C=O stretching at 1716.7–1668.48, N-H stretching at 3387.11–3261.74, C=N stretching at 1568.69, C=C stretching at 1820.86 and C-N stretching at 1313.57–1284.63 cm^{-1}. The FTIR spectrum of PEO N12K showed characteristic peaks of alcoholic OH stretching broadly at 3464.27–3437.26 and C-O stretching at 1301.99–1003.02 cm^{-1}.

The FTIR spectrum of F0 showed all the characteristics peaks of theophylline and PEO N12K with minor shifts, which were not significant. This proved the absence of drug-polymer interactions.

CONCLUSIONS

The present study successfully indicated the capability of using the release retarding polymer PEO N12K to formulate effervescent tablets of theophylline that can float continuously in the gastric medium and release drug in a controlled manner for 8 hours. The study has also proved that optimization using a statistical approach can reduce the number of experiments required to determine accurately the quantities of polymer and sodium bicarbonate to produce the desired tablet characteristics, avoiding unnecessary wastage of excipients and thereby reducing the cost of the final product. DSC and FTIR studies showed no chemical interaction between theophylline and the polymer.

Acknowledgements. – The authors are grateful to the International Medical University (IMU) for providing research facilities and for financial support to carry out this research (Project ID-BP 1-01/11(07)2014). The authors thank Prof. Brian L. Furman, University of Strathclyde, Glasgow, United Kingdom, for improving the manuscript in terms of English and grammar correction.

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