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Evaluation, Formulation and Optimization Study of Myrrh (*Commiphora myrrha*) Resin as Rate Controlling Excipient in Sustained Release Matrix Tablets of Theophylline

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Authors' contributions

This work was carried out in collaboration between all authors. All authors designed the study and wrote the protocol. Author MN wrote the first draft of the manuscript, managed the analyses of the study and literature searches. Authors AB and NMJ supervised the entire work. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To investigate myrrh (*Commiphora myrrha*) resin as a rate controlling excipient in sustained release matrix tablets of theophylline, and to optimize formulation and process variables of the tablet preparation using central composite design.
Methodology: Wet granulation was employed for preparation of theophylline sustained release matrix tablets. Central composite design was used as an optimization tool having a total of 13 experimental runs with 5 central points. The myrrh resin amount (A) and compression force (B) were selected as independent variables. Cumulative % release of drug at 1 h, and 12 h and time to 50% drug release were taken as dependent variables.
Results: The moisture content and total ash values of myrrh resin were found to be 4.67±0.58% and 0.24±0.05%, respectively. The angle of repose for all formulated granules were less than 30°.

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The hardness of different formulations were found to be between 89.8±2.86 and 133.7±3.53 N while all tablets have passed the friability test (<1%). Analysis of dissolution data of the formulations indicated that the best fitting model was the first order kinetics whereas the mechanism of drug release pattern followed anomalous or non-fickian diffusion. An optimum region of 24.98%, 91.22% and 2.86 h was obtained for cumulative % release of drug at 1 h, 12 h, and time to 50% drug release, respectively when 17.5% myrrh resin amount and 13.9 KN compression force was used. For the optimized formulation, the experimental values were found to be in close agreement with the predicted values (relative errors ranged between -4.496 and 4.814%) confirming the predictability and validity of the model.

Conclusion: The results of this study showed that the myrrh resin from *Commiphora myrrha* can be used as a potential alternative rate controlling excipient for sustained release matrix tablet formulation.

Keywords: Myrrh resin; Commiphora myrrha; theophylline; sustained release; matrix tablet; optimization; central composite design.

1. INTRODUCTION

Oral dosage forms make up the lion's share of all medicinal products, and this is expected to grow in the years to come [1]. This route of drug administration has received the most attention as it is natural, uncomplicated, convenient, safer route, and due to its least sterility constraints and flexible design of dosage forms [2,3,4]. Conventional oral dosage forms often produce fluctuations of drug plasma level that either exceed safe therapeutic level or quickly fall below the minimum effective level [5,6]. Sustained release delivery systems are used to overcome these drawbacks and have gained great advancement in the world of medicine in the recent years [7,8].

The primary objectives of sustained drug delivery are to ensure safety and enhancement of efficacy of drugs with improved patient compliance. This delivery system is increasingly being used in the treatment of acute and chronic diseases as it provides blood levels that are devoid of the peak and valley effect for an extended period of time. Thus, sustained drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects [4,9,10,11]. Sustained release preparations provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time usually 8-12 h [4,12]. Among the different approaches for the design of oral sustained release dosage forms, the attention of pharmaceutical researchers has been attracted by the matrix tablets [5,13,14]. Matrix tablets still appear as one of the most efficient and interesting formulations from both the economic and the process development point of view. Drug-release retarding excipients are the key performers in matrix systems. These excipients provide the desired characteristics to the tablets and also influence the mechanism of drug release from the system [8,14,15,16].

The nontoxic behavior, easy availability, inexpensiveness, capability of chemical modifications, biodegradability and biocompatibility of natural excipients is making them more popular amongst formulation scientists for the development of oral sustained release dosage forms [17,18]. Myrrh is an oleo-gum resin, obtained from the stem of various species of *Commiphora*, family Burseraceae. The chief source is *Commiphora myrrha* (*C. myrrha*). Myrrh is composed of volatile oil (2-10%), ethanol soluble resin (25-40%) and water soluble gum (30-60%). Myrrh is phytotoxically safe raw material in industries like pharmaceuticals and food industries [19,20,21].

Theophylline is a methylxanthine alkaloid which is used as bronchodilator in the management of asthma and chronic obstructive pulmonary disease. It has narrow therapeutic range (10-20 µg/ml), while toxicity generally appears at concentrations above 20 µg/ml. Conventional dosage forms of theophylline should be administered 3 to 4 times a day to provide effective concentration and to avoid large fluctuations in blood concentration. Therefore, its narrow therapeutic index requires suitable formulation strategies aimed at achieving and maintaining average serum levels of the drug within the therapeutic range, without significant fluctuations. Sustained release oral formulations have emerged as the most useful preparations toward this aim [14,22,23].

Thus, the present study attempts to evaluate the local myrrh resin extracted from *C. myrrha* as rate controlling excipient in matrix tablets using theophylline as a model drug.

2. MATERIALS AND METHODS

2.1 Materials

Local myrrh (*C. myrrha*) was purchased from Natural Gum Processing and Marketing Enterprise of Ethiopia (NGPME). Anhydrous theophylline (Shandong Xinhua Pharmaceutical Co. Ltd, China) was kindly donated by Ethiopian Pharmaceutical Manufacturing Share Company (EPHARM). Lactose, Magnesium stearate (BDH Laboratory supplies, England), Ethyl alcohol (NALF, Ethiopia), Potassium phosphate monobasic (FARMITALIA CAROERBA, Italy), Hydrochloric acid, and Sodium hydroxide (BDH limited, Poole, England) were used as received.

2.2 Methods

2.2.1 Extraction of resin fraction of myrrh

The myrrh obtained was dried in oven (Kottermann® 2711, Germany) at 60ºC for 4 h, powdered in a grinder and passed through sieve with a mesh size of 224 µm. To extract the resin from oleo-gum-resin, myrrh powder was stirred with ethanol (90%) for 2 h. The ethanol slurry was filtered through Whatman No.1 filter paper. The filtrate was concentrated to a thick paste by evaporation of ethanol at 80ºC and hydrodistilled using distillation apparatus to isolate essential oil. Finally the paste was dried in oven at 40ºC and the yield was calculated [24,25,26].

2.2.2 Loss on drying (LOD)

One gram of the myrrh resin powder was transferred into Petri dishes and then dried in an oven (Kottermann® 2711, Germany) at 105ºC until a constant weight was obtained. The moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage [27].

2.2.3 Total ash determination

Total ash value of the myrrh resin powder was determined based on the method described in British Pharmacopoeia (28). Two grams of powder was weighed in a pre-weighed ashing dish followed by heating in a furnace (CARBOLITE, OAF 11/1, England) at 450ºC for 8 h. The sample was then removed and kept in a desiccator and weighed. Total ash values in the samples of interest were calculated using Equation 1.

$$\%\ \text{Total ash} = \frac{m_2 - m_1}{m} X\ 100 \quad (1)$$

where, m_1 is mass of the ashing dish, m_2 is mass of crucible with ash and m is mass of sample.

2.2.4 Preparation of granules

Granules were prepared by wet granulation method as per the formula given in Table 1. The required quantities of all ingredients except magnesium stearate were mixed thoroughly in a mortar and pestle by following geometric dilution technique. The granulating fluid (solvent blend of alcohol and purified water at 3:7 ratio) was added and mixed thoroughly to form a dough mass. The wet mass formed was passed through a 1.6 mm sieve to form granules and the resulting wet granules were dried in an oven (Kottermann® 2711, Germany) at 60ºC for 4 h. The dried granules were passed through 1 mm sieve to break the aggregates [29].

Table 1. Composition of granules for preparing theophylline matrix tablet

Ingredient	Amount (mg)
Theophylline	100
Myrrh resin	25.02-58.98*
Magnesium stearate	3
Lactose	q.s. to 300

q.s. indicates quantity sufficient
** Myrrh resin amount used in the formulations ranged between 25.02 mg (8.34%) and 58.98 mg (19.66%) as per central composite design*

2.2.5 Characterization of granules

2.2.5.1 Flow rate and angle of repose

Thirty grams of granule was placed in a funnel and allowed to flow through it from a fixed height of 10 cm. Time in seconds for the duration of flow was recorded. Flow rate was determined and the angle of repose was calculated as per the following equations:

$$\text{Flow rate} = {}^{m}/_{t} \quad (2)$$

where m is mass in gram and t is time in sec.

$$\text{Angle of repose } (\theta) = \tan^{-1}\left(\frac{h}{r}\right) \quad (3)$$

where h is height of the granule pile, and r is radius of circle formed by the granule.

2.2.5.2 Bulk density

From each sample, 30 g of granule was carefully poured into a 250 ml graduated glass measuring cylinder. The volumes of the sample granules were then noted. The bulk densities were determined using Equation 4.

$$\text{Bulk density } (\rho_B) = \frac{m}{V_B} \quad (4)$$

where *m* is mass of granule (in g) and V_B is the bulk volume of sample granule.

2.2.5.3 Tapped density

From each sample, 30 g of granules was carefully poured into a 250 ml graduated glass measuring cylinder and tapped 250 times using tapped densitometer (ERWEKA, SVM 20, Germany). The volumes of the sample granules were noted. Tapped density was calculated from the weight and tapped volume of the granule by using Equation 5.

$$\text{Tapped density } (\rho_T) = \frac{m}{V_T} \quad (5)$$

where *m* is mass of granule and V_T is tapped volume of the sample granule.

2.2.5.4 Density related properties

The Carr's index (compressibility) and the Hausner ratio were calculated from the bulk and tapped densities of the sample granules using Equations 6 and 7, respectively.

$$Carr's\ index\ (\%) = \left(\frac{\rho_T - \rho_B}{\rho_T}\right) X100 \quad (6)$$

$$Hausner\ Ratio = \left(\frac{\rho_T}{\rho_B}\right) \quad (7)$$

where ρ_B is bulk density and ρ_T is tapped density of sample granules.

2.2.6 Preparation of matrix tablets

A 1% w/w magnesium stearate, used as a lubricant, was passed through a sieve with a pore size of 224 µm and blended with the dry granules for 5 min in a Turbula mixer (Willy A. Bachofen AG, Turbula 2TF, Basel, Switzerland). The granules were compressed into tablets at the desired compression force by an instrumented Korsch single punch tablet machine (KORSCH XP1-K0010288, Berlin, Germany) which was fitted with 10 mm diameter flat-faced punches. The tablets were kept for 24 h at room temperature in glass containers before their properties were evaluated.

2.2.7 Evaluation of matrix tablet properties

2.2.7.1 Thickness

Ten tablets were taken and thickness was measured using sliding caliper scale (Nippon Sokutei, Japan).

2.2.7.2 Crushing strength

Ten tablets were taken from each batch and the crushing strengths of the tablets were determined using hardness tester (Schleuniger, 2E/205, Switzerland).

2.2.7.3 Friability

The friability of the tablets was determined by placing 20 pre-weighed tablets in a friability tester (ERWEKA, TAR 20, Germany) and rotating them for 4 min at 25 rpm. The loss of tablet weight was calculated as a percentage of the initial weight after dusting the tablets.

2.2.8 *In vitro* drug release

The *in vitro* drug release studies were performed using USP type II dissolution apparatus (ERWEKA, DT600, Germany) at 50 rpm. The dissolution was done in 0.1N HCl for the first 2 h and then changed to phosphate buffer pH 6.8 (900 ml) for the next 10 h. The temperature was maintained at 37±0.5ºC. Aliquot samples of 10 ml were withdrawn at pre-scheduled intervals (0.25, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h) and replaced with an equal volume of fresh dissolution medium which was kept at 37±0.5ºC to maintain sink condition. Each sample was diluted suitably and analyzed for the drug content at λ_{max} of 271 nm using a UV/Visible spectrophotometer (SOLAR Spectrofluorimeter, CM2203, Belarus).

Table 2. Experimental levels of the independent variables for optimizing theophylline sustained release formulation using myrrh resin

Variables	Levels				
	-α	-1	0	+1	+α
A, Myrrh resin amount (%)	8.34315	10	14	18	19.6569
B, Compression force (KN)	7.92893	10	15	20	22.0711

α=1.41421

2.2.9 Analysis of kinetics and mechanism of drug release

To evaluate the rate and mechanism of theophylline release from prepared matrix tablets, the dissolution data were fitted to zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models.

2.2.10 Experimental design

The most common and successful experimental design used in response surface methodology is the central composite design (CCD) which has equal predictability in all directions from the center and allowing investigation with the least number of experiments and selection of the optimal composition for achieving the presetting target [30,31,32]. CCD contains an imbedded (2^k) factorial design augmented with a group of star points (2k) and a "central" point. The star (axial) points allow estimation of curvature and establish new extremes for the low and high settings for all the factors. Hence, CCD are second-order designs that effectively combine the advantageous features of both factorial design and the star design [33,34,35].

A CCD with five coded values (Table 2) was employed in optimizing the oral sustained release dosage form of theophylline. The myrrh resin amount (A) and compression force (B) were selected as independent variables. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the experimental design. Percent of drug released at 1 h ($rel_{1\,h,}Y_1$), percent of drug released at 12 h ($rel_{12\,h,}Y_2$), and time to 50% drug release ($t_{50\%}$,Y_3) were taken as the response variables. According to this design, the total number of treatment combinations was 2^k+ 2k + n_o, where k is the number of independent variables and n_o is the number of repetitions of experiments at the centre point which was studied in quintuplicate [30,36]. For k=2, 2^2 + (2×2) + 5 = 13. A total of 13 experiments were carried out to find the optimum area, at which the desired responses are achieved.

2.2.11 Validation of the experimental design

To validate the chosen experimental design, the resultant experimental values of the responses were quantitatively compared with those of predicted values and the relative error (%) was calculated by the following equation [37]:

$$\%\ Relative\ error = \frac{(Predicted\ value - Experimental\ value)}{Predicted\ value} x\ 100 \qquad (8)$$

2.2.12 Statistical analysis

Origin 7 Software (OriginLab Corporation, MA, and USA) was used to statistically analyze the results and one way analysis of variance (ANOVA) was applied for comparison of all results. The contour and response surface plots were generated using Design-Expert 8.0.7.1 software (Stat-ease, Corp. Australia). At 95% confidence interval, p-values of < 0.05 were considered statistically significant. All the data measured and reported are averages of a minimum of triplicate measurements and the values are expressed as mean ± standard deviation.

3. RESULTS AND DISCUSSION

3.1 Physicochemical Properties of Myrrh Resin Powder

As indicated from Table 3, the color of myrrh resin was reddish brown. The percentage yield of resin from *C. myrrha* was found to be 31.17% (w/w).

It was also characterized for its moisture content and total ash to indicate to certain extent its stability and purity. The moisture content was calculated as percentage loss on drying and it was found to be 4.67±0.58%. The moisture content of myrrh resin was low suggesting its suitability in formulations containing moisture sensitive drugs.

The total ash content is designed to measure the total amount of residual material remaining after ignition which may include extraneous matters such as sand and soil. Thus, the ash values reflect the level of adulteration or handling of the excipient [15,38]. The total ash value for the myrrh resin was found to be 0.24±0.05% indicating low level of contamination.

Table 3. Physicochemical properties of myrrh resin (n = 3, mean ± SD)

Parameter	Result
Color	reddish-brown
Yield value (%)	31.17±0.40
Loss on drying (%)	4.67±0.58
Total ash (%)	0.24±0.05

3.2 Optimization

On the basis of the preliminary studies, the appropriate ranges of values were determined for the two independent variables (10 to 18% for the myrrh resin amount (MRA) and 10 to 20 KN for compression force (CF)). A CCD was used in which 2 factors were evaluated, each at 5 levels, and experimental trials were performed for all 13 possible combinations. The formulation layout for the CCD batches (F1-F13) is shown in Table 4.

3.3 Characterization of Granules

Granules prepared were evaluated for bulk density, tapped density, angle of repose, flow rate, Carr's index and Hausner ratio (Table 5). The angles of repose for all formulated granules were less than 30º indicating good flow properties. This was further supported by lower Carr's index (less than 15%) and Hausner ratio (less than 1.25) values.

3.4 Evaluation of Matrix Tablets

The formulated matrix tablets were evaluated for physical properties such as tablet hardness, friability and thickness (Table 6). The tablet thickness ranged from 2.79±0.01 to 3.02±0.02 mm. The hardness of different formulations were found to be between 89.8±2.86 to 133.7±3.53 N while all tablets passed the friability test (0.11% to 0.19%) which was less than 1%, showing enough resistance to the mechanical shock and abrasion.

3.5 *In vitro* Drug Release

The result of drug release profile from the different matrix tablet formulations was illustrated in Fig. 1. Sustained release up to 12 h was achieved in all formulations except F5 in which about 100% of the drug release was observed within 8 h. Complete release from F5 within short time was due to less MRA (8.34%).

For the majority of formulations, the rate of drug release was found to be higher during 2 h followed by a gradual release phase for about 10 h. The initial faster release might be due to surface erosion. The release rate then decreases because the external layers of the tablet become depleted and water must penetrate deeper layers of the tablet to reach the undissolved drug. This is probably responsible for a decrease drug release in the late stage. An inverse relationship was also observed between concentration of myrrh resin and release rate of theophylline from the matrix tablets under similar CF. It was observed that 90.22%, 94.98% and 99.96% of theophylline was released from F7, F9 and F5 containing 19.66, 14 and 8.34% of myrrh resin, respectively.

Table 4. The formulations for the central composite design batches of theophylline matrix tablets

Formulation	Point type	Factors MRA (%)	CF (KN)
F1	Factorial	18(+1)	20(+1)
F2	Factorial	18(+1)	10(-1)
F3	Factorial	10(-1)	10(-1)
F4	Factorial	10(-1)	20(+1)
F5	Axial	8.34(-α)	15(0)
F6	Axial	14(0)	22.07(+α)
F7	Axial	19.66(+α)	15(0)
F8	Axial	14(0)	7.93(-α)
F9	Central	14(0)	15(0)
F10	Central	14(0)	15(0)
F11	Central	14(0)	15(0)
F12	Central	14(0)	15(0)
F13	Central	14(0)	15(0)

Results of the dissolution parameters cumulative release at 1 h, 12 h and $t_{50\%}$ which were used as responses for the formulations are listed in Table 7. The release profile revealed that F3, F5 and F8 showed more than 30% drug release at 1st hour. It is reported in literature that more than 30% drug release in the first hour of dissolution indicates the chance for dose dumping [39]. This indicates formulations with lower levels of myrrh resin exhibited initial burst drug release. However, the rest of the formulations achieved sustained release with no burst or dose dumping effects. It was observed that among the different combinations of MRA and CF used in the

different formulations, F3 and F5 have shown highest drug release rate at the end of 12 h. In general, an optimal extended-release dosage form must have a minimal burst effect with most of the drug being released in a specific time period [40].

3.6 Drug Release Kinetics

The *in vitro* drug release data from the matrix tablets of different formulations were evaluated for their drug release kinetics using various mathematical models: zero order, first order, Higuchi and Hixson-Crowell models. The results of the curve fitting into these mathematical models are given in Table 8. The drug release data of the tablet formulations did not fit satisfactorily to zero-order, Higuchi and Hixson-Crowell models but showed good fit to the first order kinetics (r^2 = 0.9546-0.9980) describing the drug release rate to be dependent on concentration of drug.

In order to investigate the mechanism of drug release, the dissolution data were also fitted to the well known exponential equation, Korsmeyer-Peppas model (Table 9).

As depicted in Table 9, the values of diffusion exponent (n) ranged from 0.6013 to 0.7861 indicating an anomalous diffusion (0.45<n<0.89) mechanism for cylindrical tablets [41]. Anomalous diffusion of drug release mechanism signifies a coupling of both diffusion and erosion mechanisms which indicate that the drug release is controlled by more than one process during the entire period of drug release [37].

Table 5. Flow properties of theophylline granules prepared with myrrh resin

Formula-tion	Angle of repose (^{o}) ± SD	Flow rate (g/sec) ± SD	Bulk density (g/ml) ± SD	Tapped density (g/ml) ± SD	Carr's index (CI) ± SD	Hausner ratio ± SD
F1	26.56±0.64	4.79±0.09	0.49±0.02	0.53±0.02	7.55±0. 25	1.08±0.01
F2	25.49±0.38	4.04±0.24	0.45±0.01	0.49±0.01	8.22±0. 19	1.09±0.00
F3	29.10±0.34	4.81±0.03	0.44±0.01	0.49±0.00	9.52±1. 18	1.10±0.01
F4	27.87±0.86	4.01±0.19	0.43±0.01	0.48±0.01	9.09±1. 16	1.10±0.01
F5	29.28±0.70	4.33±0.07	0.43±0.01	0.45±0.02	4.42±0. 15	1.05±0.01
F6	26.73±0.76	4.99±0.18	0.44±0.01	0.47±0.01	6.34±0. 16	1.07±0.00
F7	29.00±0.23	4.09±0.24	0.42±0.01	0.45±0.01	6.62±0. 09	1.07±0.00
F8	26.57±0.51	4.72±0.33	0.45±0.01	0.48±0.01	7.58±1. 15	1.08±0.01
F9	28.93±0.69	5.03±0.03	0.46±0.01	0.49±0.01	5.47±1. 14	1.06±0.02
F10	28.24±0.81	5.20±0.05	0.47±0.02	0.49±0.02	4.11±0 .13	1.04±0.00
F11	26.75±0.31	4.72±0.26	0.46±0.01	0.48±0.00	6.17±0 .14	1.07±0.01
F12	27.08±0.52	4.56±0.26	0.47±0.01	0.49±0.01	4.08±0 .06	1.04±0.00
F13	26.57±0.51	4.88±0.24	0.45±0.01	0.48±0.01	6.29±0 .15	1.07±0.00

Table 6. Characteristics of the formulations of theophylline matrix tablets

Formulation	Thickness (mm) ±SD	Hardness (N) ±SD	Friability (%) ±SD
F1	2.87±0.01	133.7±3.53	0.16±0.05
F2	3.00±0.01	92.5±2.17	0.17±0.06
F3	2.94±0.02	89.8±2.86	0.18±0.07
F4	2.79±0.01	126.6±3.53	0.11±0.02
F5	2.85±0.01	100.5±2.80	0.17±0.08
F6	2.82±0.01	120.2±3.33	0.15±0.03
F7	2.94±0.01	118.8±3.43	0.14±0.03
F8	3.02±0.02	90.0±2.31	0.19±0.06
F9	2.91±0.01	112.7±3.56	0.18±0.01
F10	2.93±0.01	110.6±2.67	0.14±0.02
F11	2.91±0.02	107.1±3.78	0.18±0.03
F12	2.90±0.02	105.4±3.66	0.14±0.04
F13	2.92±0.00	106.6±2.50	0.19±0.08

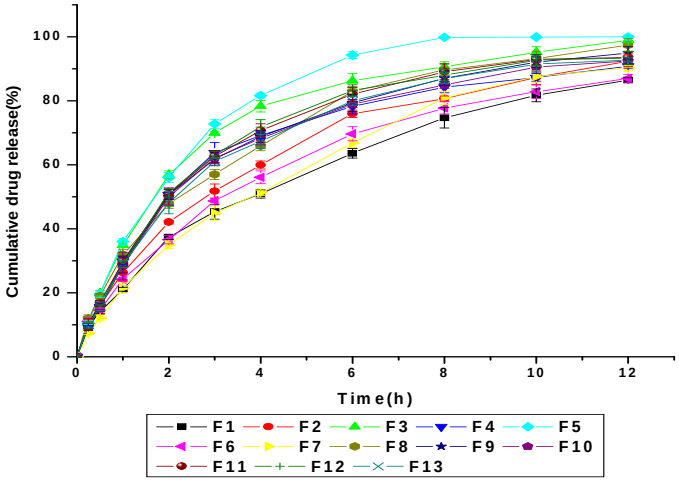


Fig. 1. *In vitro* release profiles of thirteen theophylline matrix tablet formulations prepared as per central composite design

Table 7. Responses of the thirteen theophylline matrix tablet formulations prepared as per central composite design

Formulation	Responses		
	Cumulative release (%)		$t_{50\%}$ (h) (Y_3)
	1 h (Y_1)	12 h (Y_2)	
F1	21.14	86.45	3.76
F2	26.32	92.48	2.92
F3	34.84	98.90	1.86
F4	29.85	90.86	2.40
F5	35.94	99.96	1.63
F6	24.20	87.03	3.43
F7	21.50	90.22	3.44
F8	31.93	97.47	2.30
F9	28.86	94.98	2.33
F10	28.43	92.46	2.39
F11	29.71	93.58	2.16
F12	28.95	93.34	2.15
F13	29.03	92.74	2.37

3.7 Selection of Mathematical Model

The relationship between the two independent variables (MRA and CF) and the three dependent variables (% drug release at 1 h, 12 h and $t_{50\%}$) were analyzed using response surface methodology. Polynomial models including linear, interaction and quadratic terms were generated for all the response variables using Design Expert software. The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the coefficient of variation (CV), the multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS) provided by the Design Expert software [42]. Responses rel_{1h} and rel_{12h} were found to follow linear model whereas the selected model for $t_{50\%}$ is quadratic model (Table 10).

PRESS indicates how well the model fits the data, and for the chosen model it should be small relative to the other models under consideration [40]. As shown in Table 10 the selected models have smaller PRESS values of 8.44, 38.18 and 0.16 for $rel_{1h,}$ rel_{12h} and $t_{50\%}$ respectively, compared to other models.

For the model to fit to the experimental data better, the R^2 value should be close to 1. The smaller the value of R^2, the lesser will be the fit of

the model to the experimental data (43, 44). It can also be observed from Table 10 that R^2 is high (> 0.9) for all responses, which indicates a high degree of correlation between the experimental and predicted responses. In addition, the 'Predicted R^2' value is in good agreement with the 'Adjusted R^2' value, resulting in reliable models.

3.8 Model Adequacy Checking

The information about the model reliability was verified by using the analysis of variance (ANOVA). ANOVA is used to analyze the data to obtain the interaction between process of independent variables and responses [40]. The results of ANOVA (Table 11) indicated all models were significant ($p < 0.05$) for all response parameters investigated.

Lack of fit (LOF) is a special diagnostic test for adequacy of a model that compares the pure error and describes the variation of data around the fitted model. For a model to be successfully used for prediction, the LOF should be insignificant [44,45,46]. The p-values of LOF from Table 11 (0.1492, 0.1797 and 0.8463 for Y_1, Y_2 and Y_3, respectively) were greater than 0.05, which further strengthened the reliability of the models.

Table 8. Kinetic data from regression fitting of dissolution profiles of theophylline matrix tablets to several kinetic models

Formulation	Models							
	Zero order kinetics		First order kinetics		Higuchi equation		Hixson-Crowell model	
	K_o	r^2	K_1	r^2	K	r^2	K	r^2
F1	6.5013	0.9329	0.1599	0.9980	26.9519	0.9948	-0.1783	0.8242
F2	6.8192	0.8961	0.2033	0.9954	28.6759	0.9832	-0.1763	0.7824
F3	6.8439	0.7826	0.3294	0.9699	29.8188	0.9218	-0.1659	0.6631
F4	6.4715	0.7975	0.1917	0.9666	28.0689	0.9309	-0.1681	0.6779
F5	7.2734	0.7675	0.7268	0.9546	31.8343	0.9122	-0.1724	0.6599
F6	6.5029	0.9089	0.1659	0.9948	27.2049	0.9869	-0.1734	0.8085
F7	7.1853	0.9367	0.1971	0.9942	29.7115	0.9937	-0.1967	0.8217
F8	7.0677	0.8763	0.2851	0.9913	29.9215	0.9745	-0.1715	0.7652
F9	6.9489	0.8337	0.2414	0.9952	29.8255	0.9530	-0.1771	0.7069
F10	6.7430	0.8225	0.2131	0.9844	29.0377	0.9463	-0.1737	0.7001
F11	6.8829	0.8184	0.2373	0.9802	29.6828	0.9443	-0.1731	0.7017
F12	6.9044	0.8056	0.2334	0.9753	29.8776	0.9362	-0.1758	0.6896
F13	6.8609	0.8355	0.2229	0.9852	29.4332	0.9541	-0.1748	0.7167

Table 9. Kinetic data from regression fitting of dissolution profiles of theophylline matrix tablets as evaluated by the Korsmeyer-Peppas model

Formulation	Korsmeyer-Peppas model		
	K	r^2	n
F1	22.1233	0.9947	0.6169
F2	25.5288	0.9975	0.6491
F3	32.5724	0.9935	0.7618
F4	28.3119	0.9959	0.7822
F5	32.8965	0.9944	0.7704
F6	24.1819	0.9957	0.6013
F7	20.1818	0.9959	0.6996
F8	29.5148	0.9936	0.6193
F9	27.7511	0.9962	0.7861
F10	27.7351	0.9974	0.7779
F11	28.8749	0.9974	0.7519
F12	28.0938	0.9958	0.7832
F13	27.8119	0.9973	0.7491

Table 10. Fit summary statistics for responses ($rel_{1\ h}$, $rel_{12\ h}$ and $t_{50\%}$) of theophylline matrix tablets

Response	Source	R^2	Adjusted R^2	Predicted R^2	PRESS	Remark
Release at 1 h	Linear	0.9800	0.9759	0.9645	8.44	Suggested
	2FI	0.9800	0.9733	0.9420	13.78	
	Quadratic	0.9897	0.9823	0.9466	12.69	
	Cubic	0.9954	0.9889	0.9265	17.46	Aliased
Release at 12 h	Linear	0.9029	0.8835	0.8081	38.18	Suggested
	2FI	0.9080	0.8773	0.7494	49.84	
	Quadratic	0.9523	0.9183	0.7685	46.04	
	Cubic	0.9581	0.8994	-0.4732	293.06	Aliased
$t_{50\%}$	Linear	0.8428	0.8113	0.7391	1.30	
	2FI	0.8473	0.7964	0.6528	1.73	
	Quadratic	0.9870	0.9777	0.9677	0.16	Suggested
	Cubic	0.9887	0.9729	0.9517	0.24	Aliased

Table 11. Summary of ANOVA results for dependent variables from central composite design

Source	Sum of squares	df	Mean square	F-value	p-value	Remark
Release at 1 h (Linear)						
Model	232.86	2	116.43	244.38	< 0.0001	Significant
MRA (A)	177.20	1	177.20	371.93	<0.0001	
CF (B)	55.66	1	55.66	116.83	<0.0001	
Lack of fit	3.91	6	0.65	3.06	0.1492	Insignificant
Release at 12 h (Linear)						
Model	179.60	2	89.80	46.48	< 0.0001	Significant
MRA (A)	75.67	1	75.67	39.17	<0.0001	
CF (B)	103.93	1	103.93	53.79	<0.0001	
Lack of fit	15.47	6	2.58	2.68	0.1797	Insignificant
Time required for 50% drug release (Quadratic)						
Model	4.93	5	0.99	106.43	< 0.0001	Significant
MRA (A)	3.10	1	3.10	334.67	<0.0001	
CF (B)	1.11	1	1.11	119.69	<0.0001	
AB	0.022	1	0.022	2.43	0.1630	
A^2	0.13	1	0.13	13.94	0.0073	
B^2	0.63	1	0.63	68.16	<0.0001	
Lack of fit	0.011	3	0.004	0.27	0.8463	Insignificant

Adequate Precision (signal to noise ratio) values higher than four for all the responses (44.29, 20.01 and 32.35 for Y_I, Y_2, and Y_3, respectively) confirmed that all proposed models can be used to navigate the design space. For all the models % CV were not greater than 10% (2.42, 1.49 and 3.78 for Y_I, Y_2, and Y_3, respectively) which indicate that models are reproducible [46,47].

In the response observation for rel_{1h} and rel_{12h} (Table 11), both linear terms (A and B) were found to be significant. For $t_{50\%}$, the linear terms (A and B) and quadratic terms (A^2 and B^2) were found to be significant while the interaction term (AB) was insignificant ($p > 0.05$).

It can be concluded from these analyses that the proposed models are adequate for the observed set of data and there is no reason to infer any violation of the independence or constant variance assumption [32,48]. Therefore in order to determine the levels of factors which yield optimum dissolution responses, mathematical relationships (after model simplification) were generated between the dependent and independent variables. The equations of the responses are given below:

$$Y_1 = 28.52 - 4.71 * A - 2.64 * B \quad (9)$$

$$Y_2 = 93.11 - 3.08 * A - 3.60 * B \quad (10)$$

$$Y_3 = 2.28 + 0.62 * A + 0.37 * B + 0.14 * A^2 + 0.30 * B^2 \quad (11)$$

These equations represent the quantitative effect of independent variables (A and B) upon the responses (Y_1, Y_2 and Y_3). A positive sign of

coefficient indicates a synergistic effect while a negative term indicates an antagonistic effect of the factor upon the response. Apart from the sign, the magnitude of the main effects signifies the relative influence of each factor on the response [40,49].

It is observed from equations [9,10] that all the coefficients are negative. It indicates that dependent variables (Y_1 and Y_2) are significantly affected by the antagonistic effect of linear terms of MRA (A) and CF (B). The values obtained from Equation 9 reveals that MRA has more pronounced effect on drug release at 1 h than CF.

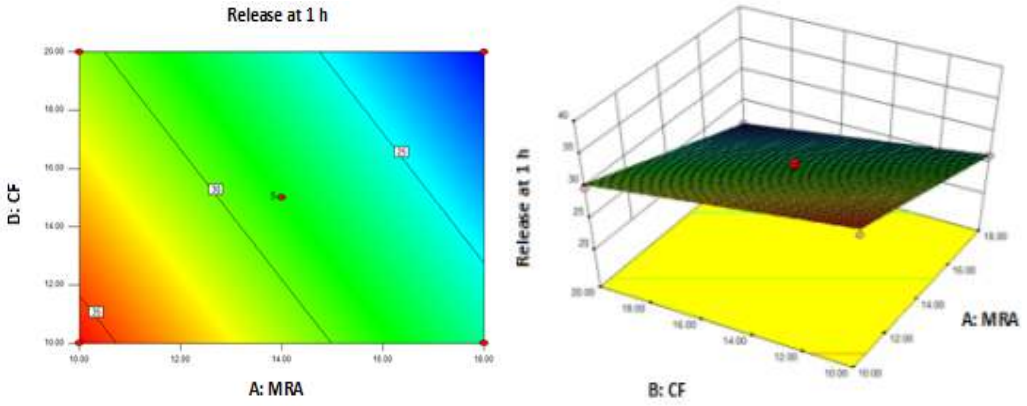
3.9 Contour Plots and Response Surface Analysis

These plots are very useful to study the interaction effects of the factors on the responses and show the effects of two factors on the response at a time [50]. Contour plots (Figs. 2a, 3a and 4a) and response surface plots (Figs. 2b, 3b and 4b) for the obtained responses (Y_1, Y_2 and Y_3) were drawn based on the model polynomial functions to assess the change of the response surface. The straight lines in Figs. 2a and 3a predicted linear relationship of factor A and factor B on the response Y_1 and Y_2. For responses Y_1 and Y_2, drug release decreases with increase in level of one variable while keeping other variable at a constant level. This showed that both the variables (MRA and CF) had negative effect on Y_1 and Y_2 as observed from Equations 9 and 10. However, the effect of MRA seems to be more pronounced as compared with that of CF in case of Y_1 as revealed by the response surface and the mathematical model.

However, factors A and B have non-linear relationship on the response Y_3 (Figs. 4a and 4b). Response surface plots show the relationship between these factors even more clearly. The contribution of the second order term from Equation 11 was interpreted as the presence of curvature and represents the nature of the response surface system (maximum, minimum or saddle system). Thus, the positive sign for quadratic terms (Equation 11) demonstrated the concave form of the curve, as observed in Fig. 4b. Analysis of Figs. 4b also shows that at constant level of MRA, $t_{50\%}$ decreased with increasing CF to a minimum after which it increased.

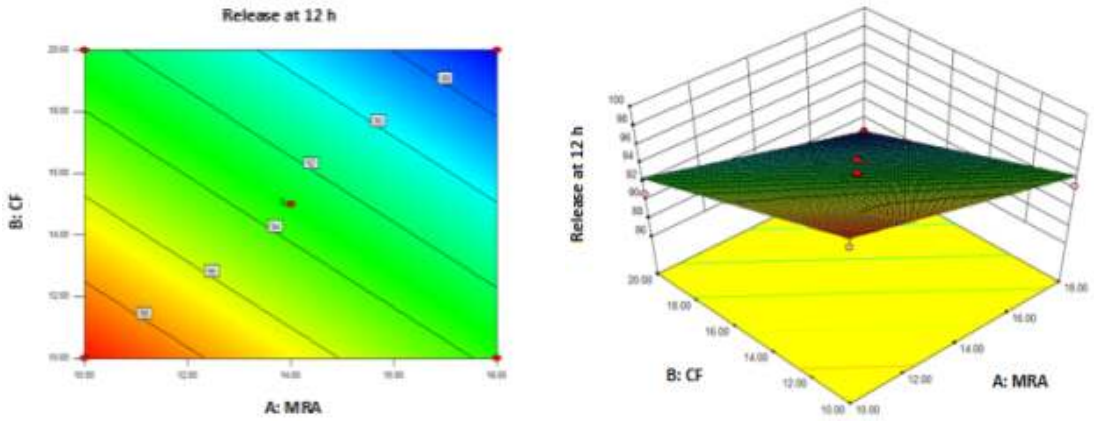
3.10 Optimization of $rel_{1\,h}$, $rel_{12\,h}$ and $t_{50\%}$

After generating the model polynomial equations to relate the dependent and independent variables, the process was optimized for all three responses. Optimum formulation was obtained based on the constraints set on the dependent variables (Table 12). These constraints are common for all the formulations. Hence the optimum values of the variables were obtained by graphical and numerical analyses using the Design-Expert 8.0.7.1 software. To optimize all the responses with different targets, a multi criteria decision approach like a numerical optimization technique by the desirability approach and graphical optimization technique by the overlay plot were used.



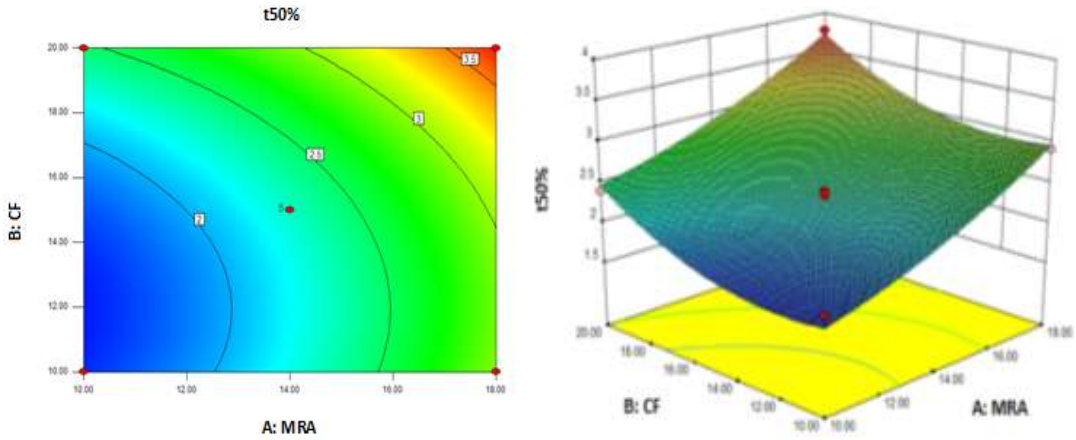
(a) (b)

Fig. 2. a) Contour plot and b) Response surface plot showing the effect of MRA (A) and CF (B) on $rel_{1\,h}$ (Y_1)



(a) (b)

Fig. 3. a) Contour plot and b) Response surface plot showing the effect of MRA (A) and CF (B) on $rel_{12\ h}$ (Y_2)



(a) (b)

Fig. 4. a) Contour plot and b) Response surface plot showing the effect of MRA (A) and CF (B) on $t_{50\%}$ (Y_3)

A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. Overall desirability function is a measure of how well the combined goals for all responses are satisfied. The best solution found by the Design-Expert solver for independent variables are 17.5% for MRA and 13.9KN for CF. The predicted optimum response values at these levels of parameters (at 17.5% MRA and 13.9KN CF) are 24.981%, 91.217% and 2.861 h, for Y_1, Y_2 and Y_3, respectively according to the set goals. In this study, the overall desirability of 1 was obtained as shown in Fig. 5.

The region of optimized formulations was also ratified using overlay plot. Based on the criteria indicated in Table 12, the overlay plot (Fig. 6) was drawn in which the yellow area represents the area satisfying the imposed criteria. The point identified by the flag was one of the solutions given by the software (same solution given by the numerical optimization technique). This flag predicts Y_1, Y_2 and Y_3 to be 24.981%, 91.217% and 2.861 h, respectively under the given condition for independent variables (17.5% for MRA and 13.9 KN for CF).

3.11 Evaluation of the Optimized Theophylline Matrix Tablet Formulation

The optimized formulation (MRA of 17.5% and CF of 13.9 KN) was evaluated for its granule and

tablet characteristics (Table 13). The angle of repose (25.61±0.37), Carr's index (7.03±0.91) and Hausner ratio (1.07±0.01) values showed the good flowability of the granules of the optimized formulation. Moreover the tablets showed hardness value of 99.30±1.65 and low friability (0.17±0.02) value which are acceptable.

In vitro dissolution study was carried out on the prepared optimized formulation using three different batches (Fig. 7). The result indicated that 24.11% and 92.45% of drug release was obtained at the end of 1 h and 12 h, respectively.

Table 12. Constraints for responses used during numerical and graphical optimization

Response	Goal	Lower limit	Upper limit	Importance
$rel_{1\ h}$	In range	24	28	5
$rel_{12\ h}$	In range	90	100	4
$t_{50\%}$	In range	2.75	4	3

The drug release of optimized formulation was best fitted to the first order kinetics model (R^2 = 0.9963). The value of the diffusion exponent (n) was found to be 0.7257 indicating that the mechanisms of drug release was diffusion coupled with erosion.

Table 13. Granule and tablet characteristics of the optimized formulation of theophylline matrix tablets

Parameters	Experimental values (mean±SD)
Granule characteristics	
Angle of repose (º)	25.61±0.37
Flow rate (g/sec)	5.11±0.23
Bulk density (g/cm^3)	0.48±0.02
Tapped density (g/cm^3)	0.52±0.02
Carr's index	7.03±0.91
Hausner ratio	1.07±0.01
Tablet characteristics	
Thickness (mm)	2.92±0.02
Hardness (N)	99.30±1.65
Friability (%)	0.17±0.02

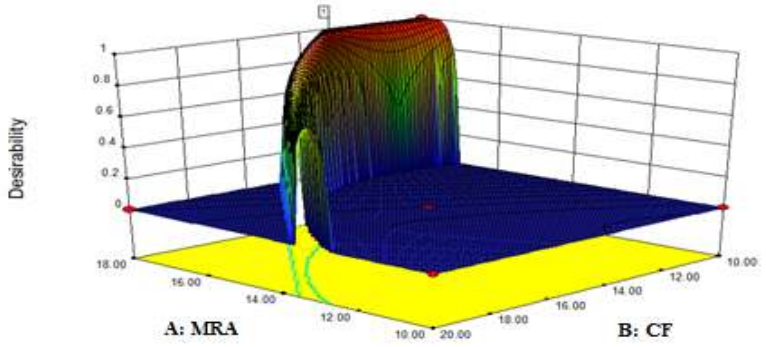


Fig. 5. 3D plot of the overall desirability function

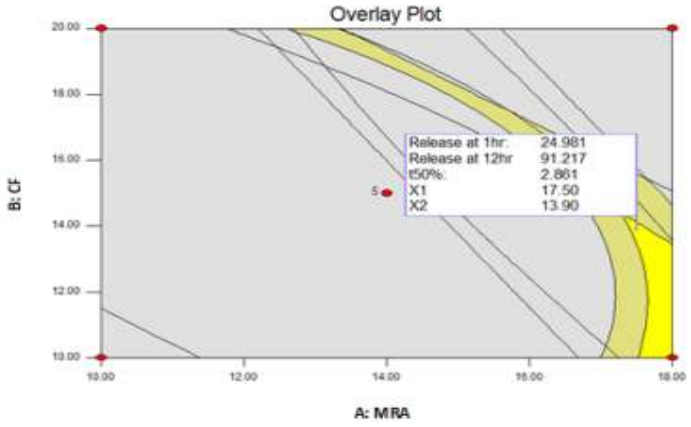


Fig. 6. Overlay plot of the three responses as functions of MRA and CF (X_1= MRA, X_2= CF).

3.12 Validation of the Optimized Formulation

Three checkpoint formulations (that are selected to be at factor levels different from those used in the CCD) were prepared and evaluated for dependent responses. Table 14 shows the composition of optimum checkpoint formulations with their experimental and predicted values of all the response variables, and the percentage error in prognosis.

The relative errors (RE) (%) between the predicted and experimental values for each response were calculated and the values found to be within 5% (ranged between -4.496 and 4.814%). Thus, the experimental values were found to be in close agreement with the predicted values confirming the predictability and validity of the model. This demonstrated that the optimization technique was successful in designing the theophylline sustained release matrix tablet formulation.

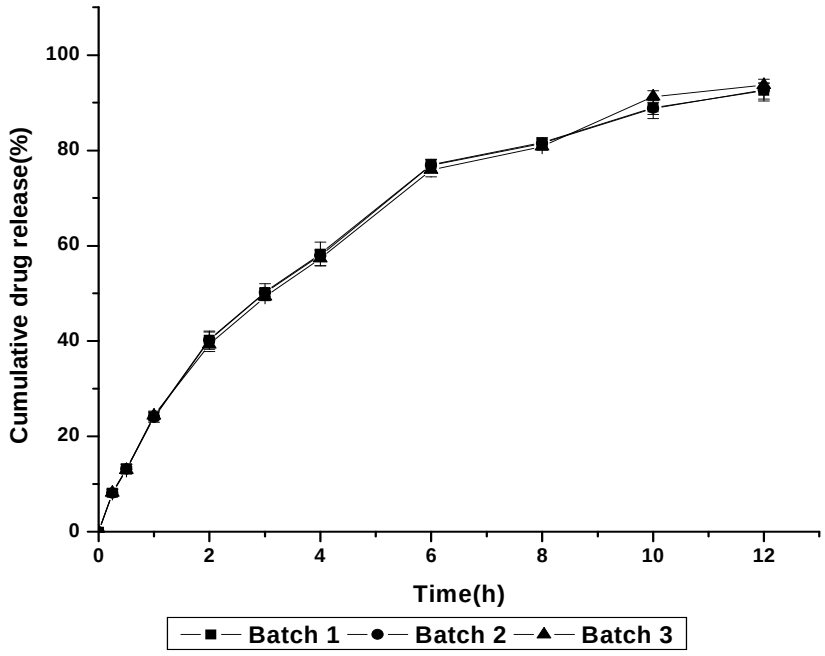


Fig. 7. *In vitro* release profile of the optimized theophylline matrix tablet formulation

Table 14. Checkpoint formulations comparing experimental and predicted values of the optimized formulations

No	Optimized formulation composition	Response variable	Experimental value	Predicted value	% RE
1	A=17.50%	Y_1	24.107	24.981	3.499
	B=13.90 KN	Y_2	92.446	91.217	-1.347
		Y_3	2.975	2.861	-3.998
2	A=17.58%	Y_1	23.983	24.941	3.841
	B=13.8 KN	Y_2	92.629	91.229	-1.535
		Y_3	2.989	2.874	-4.001
3	A=17.64%	Y_1	24.378	25.611	4.814
	B=12.39 KN	Y_2	93.698	92.197	-1.628
		Y_3	2.975	2.847	-4.496

4. CONCLUSION

Physicochemical, pre-compression and tablet properties of formulations prepared by wet granulation as per CCD were within the specifications.

The MRA and CF were found to be the determinant factors for formulation of theophylline sustained release matrix tablets. Accordingly, the CCD was successfully applied to optimize the combined effect of MRA and CF with respect to cumulative drug release at 1 h, 12 h and $t_{50\%}$.

The optimal conditions were obtained at 17.5% of MRA and 13.9 KN of CF. Under these conditions, the cumulative drug release at 1 h, 12 h and $t_{50\%}$ were 24.981%, 91.217%, and 2.861 h, respectively. The kinetic study showed the optimized formulation followed first order kinetics model with anomalous release mechanism. It was found that the mathematical models generated were statistically significant and valid for predicting values of response parameters at selected levels of formulation variables.

Therefore, the results of the present study suggest that optimum formulation with theophylline release over a period of 12 h in a sustained manner with absence of burst release can be prepared by using myrrh resin as rate controlling excipient. Thus, myrrh resin can be used as an alternative pharmaceutical excipient in the formulation and manufacture of sustained release matrix tablets.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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