ORIGINAL ARTICLE

Multi-particulate Drug Delivery Systems of Methylphenidate Hydrochloride: Optimization of Formulation Using Statistical Experimental Design

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Abstract

Introduction: The objective of the present investigation was to develop a multiparticulate modified release system of methylphenidate hydrochloride (HCl) generating biphasic release profile from single core. **Materials and Methods:** Wurster (bottom spray fluid bed coating) process was employed to develop extended release (ER) pellets of methylphenidate HCl. Impact of various formulation variables was assessed using statistical interpretation such as analysis of variance. A 3^2 (two factor, three level) factorial design was employed to study the effect of independent variables (ER polymer [Eudragit RSPO/ Eudragit RLPO/Ethocel] concentration and plasticizer concentration), on dependent variables (drug release at 3rd and 8th h). Optimization was done by fitting experimental data to the software program (Design Expert). The design space for formulation variables (ER polymer concentration and plasticizer concentration) and its influence on drug release was developed. **Results and Discussion:** Fabricated pellets were characterized for various physicochemical parameters. *In vitro* release data observed from the optimized formulation was fitted into various kinetic equations. The optimized formulation showed desired drug release at both 3rd and 8th h as 60.33% ± 0.58% and 93.33% ± 0.58%, respectively. Capsules showed an initial burst release preceding a more gradual ER phase following first order kinetics and Fickian diffusion process. **Conclusion:** Methylphenidate HCl ER pellets were successfully developed by employing bottom spray fluid bed coating (Wurster) technique. The factorial experimental design facilitated the formulation and optimization of modified drug delivery system of methylphenidate HCl.

Key words: Factorial design, methylphenidate hydrochloride, modified drug delivery systems, pellets

INTRODUCTION

In the present era, multiparticulate dosage forms are gaining interest over single unit dosage forms, owing to their potential advantages include no risk of dose dumping, reduced risk of local irritation, less inter- and intra subject variability and increased bioavailability. Wurster (bottom spray fluid bed) process is one of the most promising techniques for fabrication of pellets, as it promotes uniform coating which leads to an efficient and predictable drug release.[1-3]

Quality by design is a holistic and proactive approach to support the pharmaceutical development in a more scientific, risk-based manner, by restricting the flexibility in the manufacturing process to ensure predetermined product specifications. It helps to assess the critical material attributes and critical process parameters that impacting the predefined critical quality attribute (CQAs). The design space concept is introduced as "the multidimensional combination and interaction of input variables (e.g., materials attributes) and process parameters that have been demonstrated to provide assurance of quality." Using this approach, it is essential to define

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the relationship between critical formulation/process parameters and CQAs.[4]

Response surface methodology (RSM) is one of the popular methods in the development and optimization of drug delivery systems. Based on the principles of design of experiments (DOEs), the methodology involves the use of various types of experimental designs, generation of polynomial mathematical relationships, and mapping of the response over the experimental domain to select the optimum formulation. Central composite design, three level factorial design, Box-Behnken design, and D-optimal design are the different types of RSM designs available for statistical optimization of the formulations. Factorial design is one type of RSM design enables, all factors to be varied simultaneously, allowing quantification of the effects caused by independent variables and interactions between them. Factorial design requires fewer experimental runs, less time and thus provides a cost-effective technique than the conventional processes of formulating and optimization of dosage forms. Hence, factorial design was selected as DOE.[5]

Methylphenidate hydrochloride (HCl) is an amphetamine-like central nervous system stimulant, commonly used to treat attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults. Its HCl salt is freely soluble in water, stable and well absorbed from the intestinal tract, with a short elimination half-life (i.e., 3-4 h). These favorable properties combined with a low dose and also need to decrease the dosing frequency, make methylphenidate as an ideal candidate for development of a new generation of modified release formulation, which offers the equivalent efficacy of repeated administration of immediate release product.[6]

The present investigation aimed to fabricate a methylphenidate HCl extended-release (ER) pellets. Preliminary trials were executed with various concentrations of seal coating polymer (3-10% w/w) and various types and concentration of enteric coating polymers (Eudragit L30 D 55 and hydroxypropyl methylcellulose HPMC AS 15-25% w/w). Optimization of the methylphenidate HCl ER pellets was done by employing factorial design as optimization technique, with constraints on release of drug after 3rd h (55-65%). The independent variables for this study were concentration of release retardant polymers (Eudragit RSPO, Eudragit RLPO, and ethyl cellulose) and plasticizer (triethyl citrate [TEC]). The dependent variables studied were drug release at 3rd h (55-65%) and 8th h (85-100%).

MATERIALS AND METHODS

Materials

Methylphenidate HCl was obtained from RA Chem Pharma Ltd., Hyderabad, as gift sample, sugar spheres (Arun Pharma), hypromellose (Dow Chemical's), povidone (BASF), talc (Luzenac), Eudragit RSPO (Evonik), Eudragit RLPO (Evonik), Ethocel 45 cps (Colorcon), Eudragit L 30 D55 (Evonik), HPMCAS (Shin Etsu), TEC (Merck), isopropyl alcohol (Avantor), purified water and empty hard gelatin capsule shells size 1 (ACG) were used as received.

Methods

Drug-excipient compatibility studies

Methylphenidate HCl and selected excipients were subjected for drug excipient compatibility study. The drug and individual excipients were intimately mixed in equal parts by weight and filled in glass vials stoppered with teflon plugs and sealed with aluminum seals. These samples were kept in incubators at 40°C/75% RH. Samples were analyzed for the solid state property of the drug in the blended mixtures using differential scanning colorimeter (DSC) at initial and 1 month (40°C/75% RH).

Preparation of methylphenidate HCl ER pellets by Wurster process

Methylphenidate HCl ER pellets were prepared by employing bottom – spray fluid bed (Wuster) coating process (Glatt GPCG 1.1). The dosage form was designed to obtain the biphasic release profile from single population of pellets comprising immediate release and ER portions. Dose was distributed among the two portions equally, i.e., 50% as immediate release (IR) portion and second part as ER portion.

Drug loaded pellets were prepared by spraying the aqueous drug dispersion over nonpariel seeds (sugar spheres [20#-25# ASTM]) employing Wurster process (bottom spray fluid bed coating technology). The drug dispersion was coated onto sugar spheres using 1.0 mm of spray nozzle with a spray rate of 2-6 g/min, 0.8-1.0 kg/cm^2 of atomization air pressure, 45-60 cfm of air volume, and product temperature 38-42°C. The drug dispersion was sprayed until get desired weight gain. The drug loaded pellets were dried for 10 min at 38-42°C. Further, aqueous seal coating dispersion was coated onto the drug loaded pellets employing similar process parameters as drug loading process except 40-45°C as product temperature. Seal coated pellets were dried for 10 min at 40-45°C. Hydro-alcoholic (IPA:water - 80:20) ER coating dispersion was coated over the seal coated pellets using Wurster process at a spray rate of 4-8 g/min and 34-38°C as product temperature. The ER coated pellets were dried for 15 min at 34-38°C. Further, the aqueous enteric coating dispersion was coated onto the ER coated pellets at 28-32°C as product temperature and at a spray rate of 2-6 g/min. Enteric coated pellets were subjected for drying at 35°C for 15 min. Finally, drug dispersion of immediate release portion was coated over the enteric coated pellets using similar process parameters as that of earlier. Immeadiate release (IR) drug loaded pellets were dried for 10 min at a temperature of 38-42°C. Final pellets were sifted through #16-#20 ASTM mesh to separate the fines and agglomerates and collect the desired portion.

Experimental design

In preliminary trials, the formulation variables in each step of the manufacturing process were evaluated for their significance by analysis of variance (ANOVA). Finally, found that the type and concentrations of ER coating polymer, plasticizer concentration had a significant impact on drug release of prepared pellets.

The factorial design was used to evaluate the effect of independent variables (ER polymer and plasticizer concentration) on responses/dependent variables (drug release at 3rd h [Y_1] and 8th h [Y_2]) of methylphenidate HCl ER pellets. A two-factor, three-level design is used for exploring quadratic response surfaces and constructing second order polynomial models with Design Expert (Stat-Ease).

ANOVA is inevitably linked to experimental design, which was used to analyze the significance of the model and each selected response. It was also generate polynomial equations. The response (Y_1) in each trial was estimated by carrying out a multiple factorial regression analysis using the generalized quadratic model:

$$Y_1 = b_0 + b_1X_1 + b_2X_2 + b_1b_2X_1X_2$$

Where, Y_1 is the measured response associated with each factor level combination; b_0 is an intercept; b_1 and b_2 are regression coefficients computed from the observed experimental values of Y_1; and X_1 and X_2 are the coded levels of independent variables.

After fitting the response data in experimental design as in Table 1, the experimental results were analyzed by ANOVA. It demonstrated the various statistical parameters such as b coefficients, F values, P values of model terms and correlation coefficient (R^2) values. The suitability of model was authenticated by the predicted and adjusted R^2 values.[7]

Optimization of ER coating composition

The independent variables in ER coating were type and concentration of ER polymer, i.e., Eudragit RSPO, Eudragit RLPO, ethyl cellulose and concentration of plasticizer (TEC). Both variables were studied at three levels (−1, 0, +1). Percentage of drug release at 3rd h (Y_1) and percentage of drug release at 8th h (Y_2) were selected as responses. The impact of each selected ER polymer and plasticizer concentration on responses were studied and optimized individually.

Evaluation of methylphenidate HCl ER pellets

Micromeritic properties[8]

Bulk density (BD), tapped density (TD), and Hausner ratio (HR) of pellets were determined. BD and TD were determined by USP method I using a TD tester.
BD = Weight of the sample (g)/untapped volume (ml),
TD = Weight of the sample (g)/tapped volume (ml),
HR was calculated using following formulae:
HR = TD/BD

Where TD and BD are tapped and bulk densities.

Assay[9]

Methylphenidate HCl ER pellets equivalent to 20 mg of methylphenidate HCl were transferred into 100 mL volumetric flask, added diluent (methanol:acetonitrile: pH 4.0 sodium acetate buffer at a ratio of 4:3:3) and sonicated for 15 min to dissolve, made the volume up to the mark with diluent. Transferred 10 mL of this solution to 20 mL volumetric flask and made the volume up to the mark. The solution was filtered through 0.45 µ nylon membrane filter. The following chromatographic conditions were employed for analysis:

- Column: Kromosil 60, CN 250 mm × 4.6 mm, 5 µm or its equivalent
- Injection volume: 50 µL
- Flow rate: 1.5 mL/min
- Detector: Ultraviolet, 210 nm
- Runtime: 10 min.

Calculations:
Assay of methylphenidate HCl:

$$= \frac{A_T}{A_S} \times \frac{W_S}{100} \times \frac{10}{20} \times \frac{100}{W_T} \times \frac{20}{10} \times \frac{P}{100} \times A.W$$

$$= ---- \text{mg/capsule}$$

Table 1: Variables in factorial design

Factor	Levels used, actual (coded)		
	Low (−1)	Medium (0)	High (+)
ER polymer concentration (%w/w) (X_1)	2	3.5	5
Plasticizer concentration (%w/w) (X_2)	10	20	30
Dependent variables	**Constraints**		
Y_1=% drug release at 3rd h	$55 \leq Y_1 \leq 65$		
Y_2=% drug release at 8th h	$85 \leq Y_2 \leq 100$		

ER: Extended release

$$\% \text{ of label amount} = \frac{\text{Assay of methylphenidate}}{\text{Label claim}} \times 100$$

Where,
A_T = Peak area of methylphenidate HCl obtained from the sample solution,
A_S = Average peak area of methylphenidate HCl obtained from the standard solution,
W_S = Weight of methylphenidate HCl working standard taken in mg,
W_T = Weight of sample taken in mg,
P = Potency of methylphenidate HCl working standard used (on as is basis),
A = Average weight of the fill contents of capsules in mg.

In vitro drug release studies[10]

The methylphenidate HCl ER pellets equivalent to 40 mg methylphenidate HCl were accurately filled into size 1 hard gelatin capsules and evaluated for *in vitro* drug release studies, which were performed using USP Type I dissolution test apparatus. The volume of the dissolution medium was 500 ml with a stirring speed of 75 rpm, and the temperature was maintained at 37°C ± 0.5°C. These conditions were kept constant for all dissolution studies. The study was carried out in 0.01 N HCl for 2 h followed by pH 6.8 phosphate buffer at 1, 2, 3, 4, 6, and 8 h. 10 ml of sample was withdrawn periodically and replaced with equal volume of fresh dissolution medium. The collected samples were filtered through 0.45 µ nylon membrane filter and analyzed to assess the % drug dissolved by employing same chromatographic conditions as that of assay.

The % labeled amount of methylphenidate HCl dissolved at respective time intervals (Dn) was estimated from following formulae:

$$= \frac{A_T}{A_S} \times \frac{W_S}{100} \times \frac{5}{25} \times \frac{500}{\text{LC}} \times \frac{P}{100} \times 100 = -----\%$$

Where,
A_T = Peak area of methylphenidate HCl obtained from the sample solution,
A_S = Average peak area of methylphenidate HCl obtained from the standard solution,
W_S = Weight of methylphenidate HCl working standard taken in mg,
P = Potency of methylphenidate HCl working standard used (on as is basis),
LC = Label claim.

Calculate the correction factor (CFn) at each time point by using the following formula:

$$CFn = \frac{Dn}{500} \times 10$$

Drug release kinetics[11]

The drug release kinetics and mechanism from the formulations were studied by fitting the data obtained from the *in vitro* release study into several mathematical equations.

RESULTS AND DISCUSSION

Drug excipient compatibility studies

From the DSC thermograms, at the initial stage, the onset melting point of active pharmaceutical ingredient (API) and composite blend were observed at 220.34°C and 160.26°C, respectively, and peak melting point of API and composite blend were observed at 222.59°C and 164.64°C, respectively. From the endothermic peaks after 4 weeks storage at 40°C/75% RH, the onset melting point of API and composite blend were observed at 222.23°C and 183.16°C, respectively, and peak melting point of API and composite blend were observed at 224.38°C and 171.01°C, respectively [Figure 1]. Hence, it was concluded that there was no interaction between the drug substance and the chosen excipients. Hence, these excipients were considered for the use in the development of the formulation.

Preparation of methylphenidate HCl ER pellets

Methylphenidate HCl ER pellets were prepared by employing Wurster process. The impact of formulation variables at each stage such as seal coating (seal coating polymer concentration), ER coating (ER coating polymer type, concentration and plasticizer concentration), and enteric coating (enteric coating polymer type and concentration, plasticizer concentration) on release rate constant were evaluated in preliminary trials and results were interpreted by ANOVA. Process parameters were selected and established based on prior experience.

From the obtained results, 5% w/w HPMC E5 as seal coating polymer, 20% w/w Eudragit L 30 D 55 as enteric coating polymer with 20% w/w plasticizer concentration with respect to the polymer. ER coating polymer type (Eudragit RLPO, Eudragit RSPO and ethyl cellulose) and concentration (2%, 3.5% and 5% w/w), plasticizer concentration (10%, 20% and 30%w/w with respect to the polymer concentration) were identified as high-risk variables have a potential impact on drug release. Hence these factors were studied by a two-factor, three-level factorial experimental design, individually.

Data analysis and model validation

Fitting of data to the model

Two factors with three levels factorial experimental design for triplicates require 27 experiments, the independent

Table 2: Observed responses in factorial design for methylphenidate HCl ER pellets

Independent variables		Dependent variables/responses					
ER polymer concentration (%w/w) (X_1)	Plasticizer (TEC) concentration (%w/w) (X_2)	% Drug release at 3rd h (Y_1)			% Drug release at 8th h (Y_2)		
		Eudragit RSPO	Eudragit RLPO	Ethocel	Eudragit RSPO	Eudragit RLPO	Ethocel
5	20	56±2.2	69±1.3	53±0.8	89±2.7	93±0.4	81±2.6
3.5	20	61±0.6	77±2.1	55±0.5	93±1.3	97±1.5	85±0.3
2	20	65±1.9	83±2.7	59±1.4	95±0.9	99±0.6	90±0.9
2	20	65±1.3	82±1.2	59±1.6	96±0.8	99±0.8	91±0.7
3.5	10	59±0.8	74±2.9	52±0.9	92±1.1	95±1.2	84±1.5
2	30	68±1.4	85±1.1	60±0.7	96±0.5	100±0.9	91±1.3
2	30	67±1.6	85±0.9	61±1.0	97±0.2	99±0.5	92±0.8
3.5	20	60±0.7	77±0.8	54±1.1	94±0.6	98±1.4	85±1.6
5	10	54±1.9	66±1.5	51±2.1	87±1.6	90±2.1	79±2.8
2	10	64±0.9	80±1.1	57±1.7	95±0.8	98±1.7	87±1.1
3.5	10	57±1.1	73±1.8	53±1.4	91±1.1	96±0.7	83±1.4
3.5	20	60±0.4	78±0.9	55±0.9	93±1.4	98±1.2	84±0.6
3.5	30	62±1.2	80±1.5	58±0.6	94±1.2	100±1.6	88±1.6
3.5	30	63±1.6	79±1.2	57±1.2	93±0.7	101±0.5	88±0.7
5	20	55±2.4	69±2.4	52±1.9	89±1.8	92±1.9	81±0.5
2	20	65±1.3	83±1.1	58±1.4	97±0.2	100±0.6	89±1.9
2	10	64±1.9	80±1.8	56±2.1	95±0.9	97±0.3	86±0.6
3.5	30	62±0.9	79±1.3	57±1.6	94±1.0	99±0.7	88±1.3
5	30	58±1.5	71±0.9	54±0.4	90±0.8	94±0.9	82±0.8
5	30	59±1.7	70±1.2	54±0.7	91±1.1	94±1.2	83±1.4
2	10	63±1.8	79±1.4	56±1.3	95±0.4	98±2.4	87±1.1
3.5	10	58±0.5	74±0.7	53±1.2	91±0.9	96±0.9	84±0.8
2	30	67±0.7	96±0.9	62±1.9	97±0.7	101±1.2	92±0.7
5	20	55±1.0	70±2.1	52±0.8	90±1.3	93±0.8	80±0.7
5	10	55±0.8	67±0.7	50±1.7	87±2.1	92±2.1	78±1.1
5	30	59±1.3	70±0.4	53±0.8	92±0.8	93±1.5	83±0.8
5	10	54±1.2	67±0.8	50±2.2	88±1.9	91±1.1	78±2.1

HCl: Hydrochloride, ER: Extended release, TEC: Triethyl citrate

variables and responses for all experimental runs are given in Table 2. Models of various responses were obtained using Design Expert (Stat-Ease). The values of R^2, adjusted R^2 and predicted R^2 were shown in Tables 3-5, for each response along with their ANOVA results. Values of probability $P < 0.05$ represent significant model terms. After elimination of nonsignificant ($P > 0.05$) coefficients in Tables 3-5, following correlations for response variables were obtained in terms of coded factors. The regression equations carry factors along with coefficients (positive/negative) which quantify response values. A positive sign of coefficient indicates synergistic effects, whereas negative sign represents an antagonistic effect.

All the responses observed for various formulations were fitted simultaneously to first order, second order and quadratic models using Design Expert. Responses Y_1 and Y_2 were found to follow quadratic and second order model, respectively, for the formulations prepared employing Eudragit RSPO as ER polymer. Responses Y_1 and Y_2 were found to follow quadratic model for formulations prepared employing Eudragit RLPO as ER polymer. Responses Y_1 and Y_2 were found to follow linear model for formulations prepared employing Ethocel as ER polymer.

From the obtained ANOVA results [Tables 3-5], in all the cases, main factors ER polymer (Eudragit RSPO/ Eudragit RLPO/ethyl cellulose) concentration and plasticizer (TEC) concentration caused variation on drug release. The model shows that the ER polymer concentration had a negative impact on drug release whereas plasticizer concentration had positive impact on drug release. The interaction terms

have a positive impact on Y_1 from formulations fabricated with Eudragit RSPO as ER polymer, and it shown negative impact on drug release from formulations prepared with Eudragit RLPO and Ethocel as ER polymer. In case of Y_2, interaction terms shown positive impact from formulations prepared with Eudragit RSPO and Eudragit RLPO as ER polymer, and negative impact from the formulations fabricated by Ethocel as ER polymer. Both responses (Y_1 and Y_2) were decreased with increasing the ER polymer concentration and increased with increasing the plasticizer concentration.

Contour and three-dimensional (3D) response surface plot analysis

The design expert software (Stat-Ease) generated the contour and 3D surface plots are presented in Figures 2-4, which are very useful to study the interaction effects of the factors on

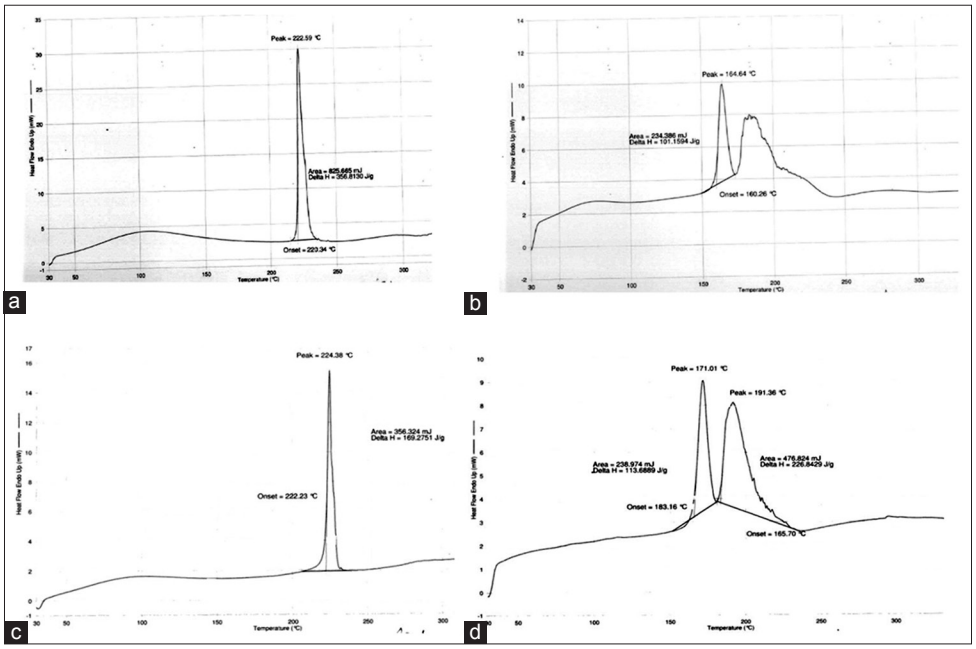

Figure 1: Differential scanning calorimetry thermograms: (a) Methylphenidate hydrochloride (HCl) active pharmaceutical ingredient (API)-initial; (b) methylphenidate HCl composite blend – Initial, (c) methylphenidate HCl API – 4 weeks at 40°C/75% RH, (d) methylphenidate HCl composite blend-4 weeks at 40°C/75% RH

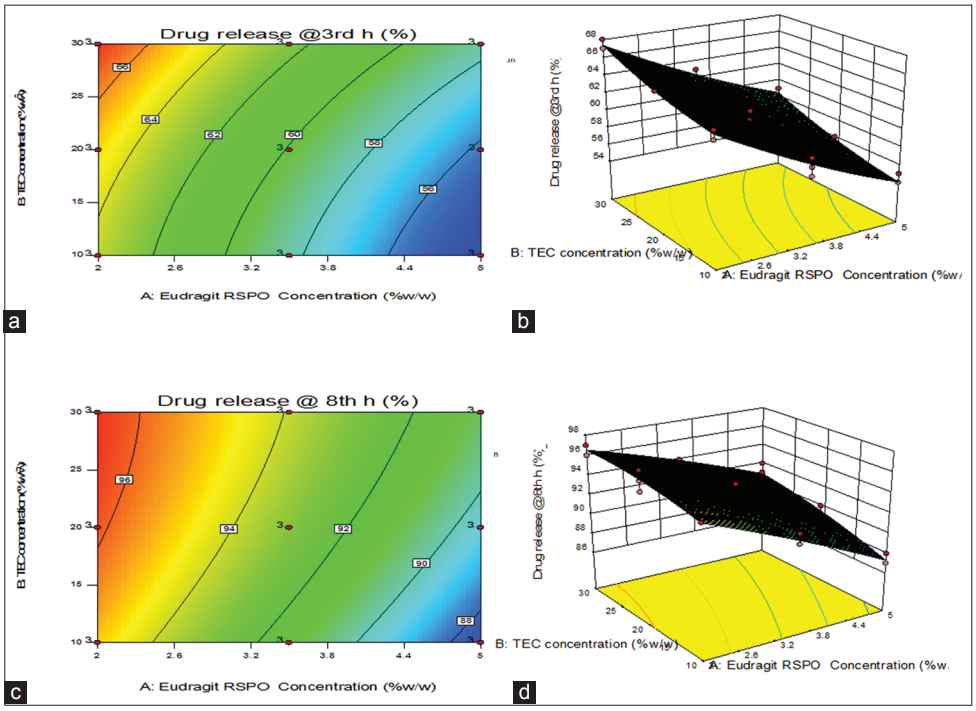

Figure 2: Contour plots (a and c) and response surface plots (b and d) showing the impact of factors (concentration of Eudragit RSPO and triethyl citrate) on % drug release at 3rd and 8th h

Table 3: ANOVA results for predicting % drug release at 3rd and 8th h employing Eudragit RSPO as ER polymer

Source	b-coefficient	Sum of squares	df	Mean square	*F* value	*P* value, *P*>*F*
*Y*1 (%)						
Model	72.03704	462.11	5	92.42	226.85	<0.0001
X_1	−4.85185	382.72	1	382.72	939.41	<0.0001
X_2	−0.033333	76.06	1	76.06	186.68	<0.0001
X_1X_2	0.011111	0.33	1	0.33	0.82	0.3760
X_1^2	0.22222	1.50	1	1.50	3.68	0.0687
X_2^2	5.00000	1.50	1	1.50	3.68	0.0687
Residual error		8.56	21	0.41		
Pure error		6.67	18	0.37		
Total		470.67	26			
R^2=0.9818; adjusted R^2=0.9775; predicted R^2=0.9703						
Y_2 (%)						
Model	100.18519	232.39	3	77.46	179.83	<0.0001
X_1	−2.88889	200.00	1	200.00	464.30	<0.0001
X_2	0.011111	29.39	1	29.39	68.23	<0.0001
X_1X_2	0.033333	3.00	1	3.00	6.96	0.0147
Residual error		9.91	23	0.43		
Pure error		8.00	18	0.44		
Total		242.30	26			
R^2=0.9591; adjusted R^2=0.9538; predicted R^2=0.9445						
Regression equation of the fitted model#: Y_1 (%)=72.03704−4.85185*X_1−0.033333*X_2; Y_2 (%)=100.18519−2.88889*X_1+0.011111*X_2+0.033333*X_1X_2						

*P<0.05 considered as significant. #Only the terms with statistical significance are included. X_1: Eudragit RSPO concentration, X_2: TEC concentration, ANOVA: Analysis of variance, ER: Extended release, TEC: Triethyl citrate

responses. This type of the plot visualizes the effects of two factors on the response at a time. Figures 2 and 4 exhibit a curvilinear relationship with Y_1 and Y_2 whereas Figure 3 shown curvilinear relationship with Y_1 and nonlinear relationship with Y_2.

The data of % drug release at 3rd and 8th h for all batches executed with Eudragit RSPO as ER coating polymer ranges from 54-68% to 87-97%, respectively. The drug release from these formulations was well around the predetermined specifications. The data of % drug release at 3rd and 8th h for all batches executed with Eudragit RLPO as ER coating polymer ranges from 67-85% to 90-101%, respectively. At 5% w/w concentration also Eudragit RLPO fails to provide a controlled release. The data of % drug release at 3rd and 8th h for all batches executed with Ethocel as ER coating polymer ranges from 50-61% to 78-92%, respectively. The retarded drug release was observed with ethocel at 2% w/w concentration also.

Among the studied range, the concentration of 3.5% w/w Eudragit RSPO with 20% w/w TEC concentration has shown drug release at both 3rd and 8th h well within the predetermined specifications [Figure 5]. The drug release profile of optimized formulation is presented in Figure 6.

Evaluation of pellets

Micromeretic properties

The bulk and tapped density of batches range from 0.64-0.67 to 0.72-0.80 g/cc, respectively. The Hausner's ratio values (1.046-1.075) indicated good flow properties according to USP limits.

Assay

The assay of the all formulations was tested, and results were found in the range of 98.2-100.9%. Assay of the optimized formulation was observed to be 99.7%.

Drug release kinetics

The dissolution data of optimized formulation fitted into kinetic models, the obtained results concluded that the drug release followed the first order kinetics as R^2 values were higher for first order model (0.962) than zero order model

Table 4: ANOVA results for predicting % drug release at 3rd and 8th h employing Eudragit RLPO as ER polymer

Source	b-coefficient	Sum of squares	df	Mean square	*F* value	P value, *P*>*F*
Y_1 (%)						
Model	77.43210	979.37	5	195.87	541.76	<0.0001
X_1	−0.46914	854.22	1	854.22	2362.65	<0.0001
X_2	0.61111	112.50	1	112.50	311.16	<0.0001
X_1X_2	−0.033333	3.00	1	3.00	8.30	0.0090
X_1^2	−0.49383	7.41	1	7.41	20.49	0.0002
X_2^2	−6.11111	2.24	1	2.24	6.20	0.0213
Residual error		7.59	21	0.36		
Pure error		6.00	18	0.33		
Total		986.96	26			
R^2=0.9923; adjusted R^2=0.9905; Predicted R^2=0.9872						
Y_2 (%)						
Model	90.77160	262.68	5	52.54	79.70	<0.0001
X_1	4.09877	193.39	1	193.39	293.38	<0.0001
X_2	0.22500	43.56	1	43.56	66.08	<0.0001
X_1X_2	5.55556	0.083	1	0.083	0.13	0.7257
X_1^2	−0.91358	25.35	1	25.35	38.46	<0.0001
X_2^2	−2.2222	0.30	1	0.30	0.45	0.5099
Residual error		39.491	21	0.66		
Pure error		10.0000	18	0.56		
Total		276.519	26			
R^2=0.9499; adjusted R^2=0.9380; predicted R^2=0.9161						
Regression equation of the fitted model#: $Y_1(\%)=77.43210-0.46914*X_1+0.61111*X_2-0.033333*X_1X_2-0.49383*X_1^2-6.11111*X_2^2$; $Y_2(\%)=90.77160+4.09877*X_1+0.22500*X_2-0.91358*X_1^2$						

*P<0.05 considered as significant. #Only the terms with statistical significance are included. X_1: Eudragit RLPO concentration, X_2: TEC concentration, ANOVA: Analysis of variance, ER: Extended release, TEC: Triethyl citrate

Table 5: ANOVA results for predicting % drug release at 3rd and 8th h employing ethocel (ethyl cellulose) as ER polymer

Source	b-coefficient	Sum of squares	df	Mean square	*F* value	*P* value, *P*>*F*
Y_1 (%)						
Model	58.53704	252.50	2	126.25	340.17	<0.0001
X_1	−2.11111	180.50	1	180.50	486.34	<0.0001
X_2	0.20000	72.00	1	72.00	194.00	<0.0001
Residual error		8.91	24	0.37		
Pure error		6.00	18	0.33		
Total		261.41	26			
R^2=0.9659; adjusted R^2=0.9631; predicted R^2=0.9572						
Y_2 (%)						
Model	90.90741	435.61	2	217.81	577.25	<0.0001
X_1	−2.92593	346.72	1	346.72	918.92	<0.0001
X_2	0.22222	88.89	1	88.89	235.58	<0.0001
Residual error		9.06	24	0.38		

(Contd...)

Table 5: *(Continued)*

Source	b-coefficient	Sum of squares	df	Mean square	*F* value	*P* value, *P*>*F*
Pure error		5.33	18	0.30		
Total		444.67	26			

R^2=0.9796; adjusted R^2=0.9779; predicted R^2=0.9738

Regression equation of the fitted model#: Y_1 (%)=58.53704−2.11111*X_1+0.20000*X_2; Y_2(%)=90.90741−2.92593*X_1+0.22222*X_2

*P<0.05 considered as significant. #Only the terms with statistical significance are included. X_1: Ethocel (ethyl cellulose) concentration, X_2: TEC concentration, ANOVA: Analysis of variance, ER: Extended release, TEC: Triethyl citrate

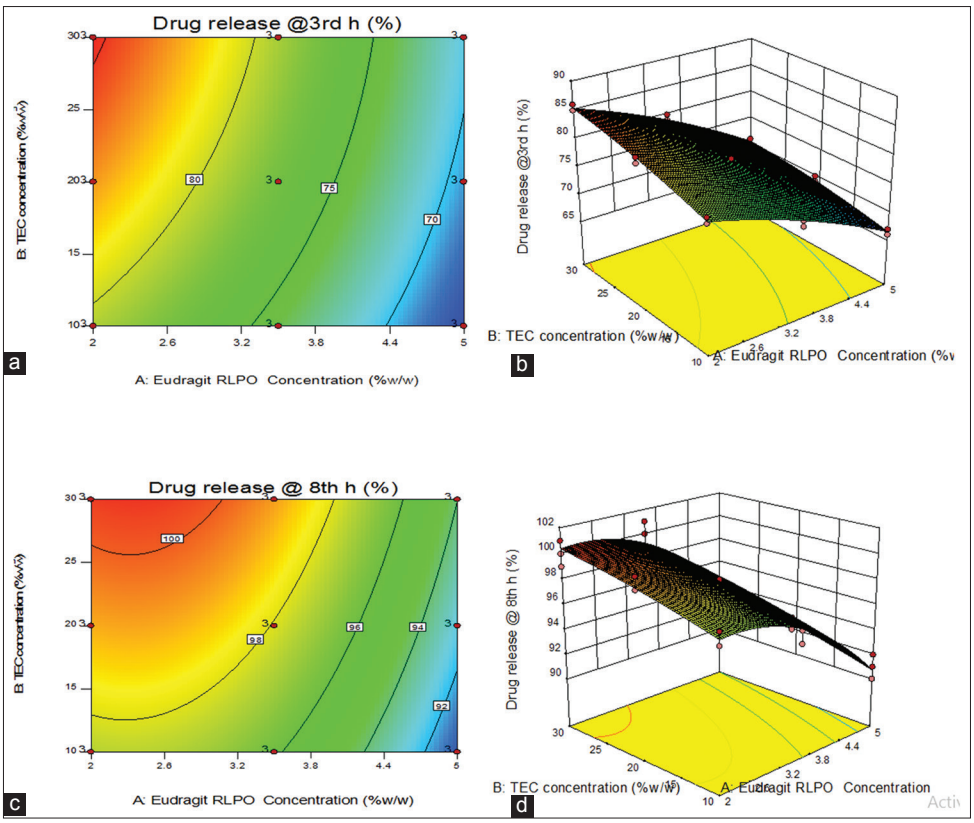

Figure 3: Contour plots (a and c) and response surface plots (b and d) showing the impact of factors (concentration of Eudragit RLPO and triethyl citrate) on % drug release at 3rd and 8th h

(0.768). The *n* value is <0.45 (0.261); hence, the mechanism of drug release was fickian diffusion.

CONCLUSION

Methylphenidate HCl ER pellets generating a biphasic release profile from single core were successfully fabricated by fluid bed coating technology. The effect of two independent variables (ER polymer concentration and plasticizer concentration) on two responses were studied and optimized systematically using RSM. This investigation revealed that independent variables had a significant impact on the measured responses. The quantitative effect of these factors at different levels on drug release could be predicted by polynomial equations. Linearity observed between the actual and predicted values of the response variables indicated that analytical ability of the selected design. The optimized batch showed 99.7% assay, and drug release was well within the predetermined specifications. Micromeritic properties of these pellets exhibited excellent flow properties, which are crucial to attain the uniformity

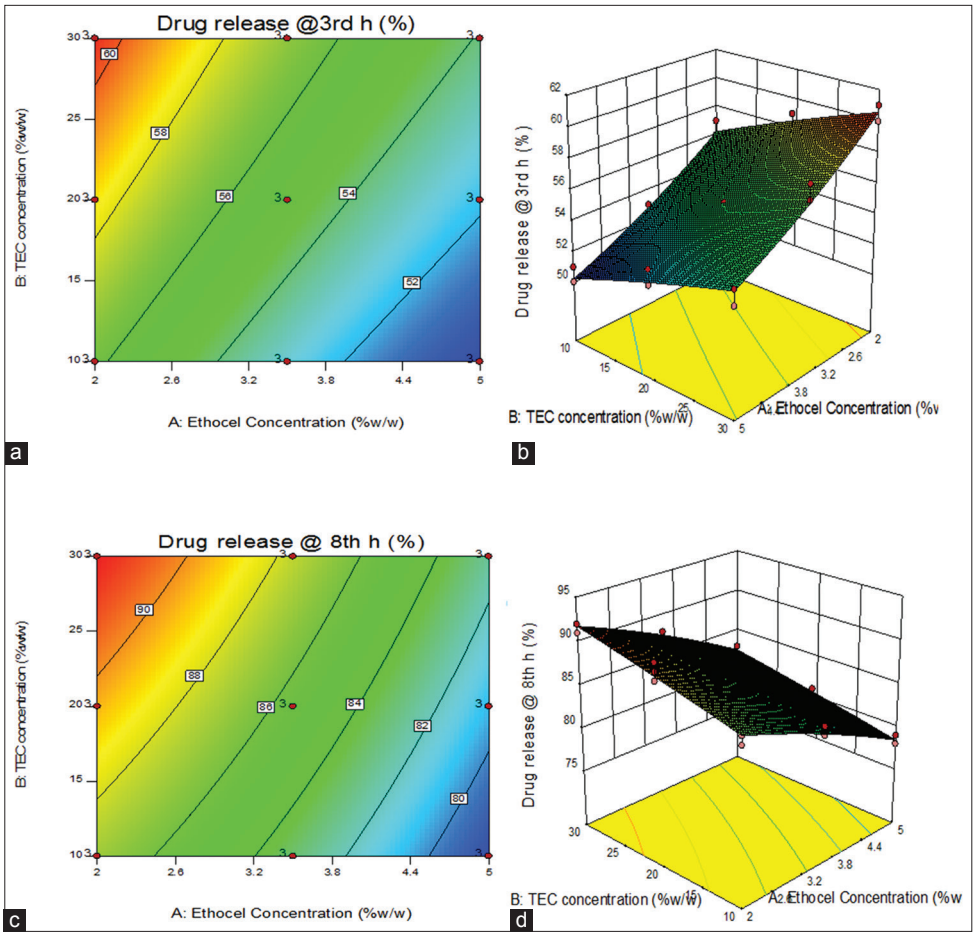

Figure 4: Contour plots (a and c) and response surface plots (b and d) showing the impact of factors (concentration of ethocel and triethyl citrate) on % drug release at 3rd and 8th h

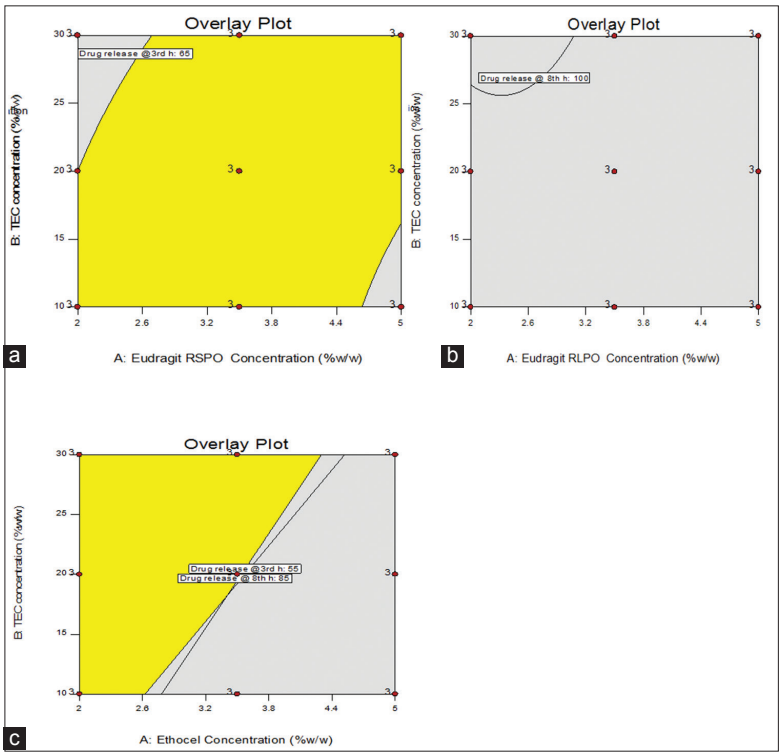

Figure 5: Overlay plots of: (a) Eudragit RSPO; (b) Eudragit RLPO and (c) ethocel

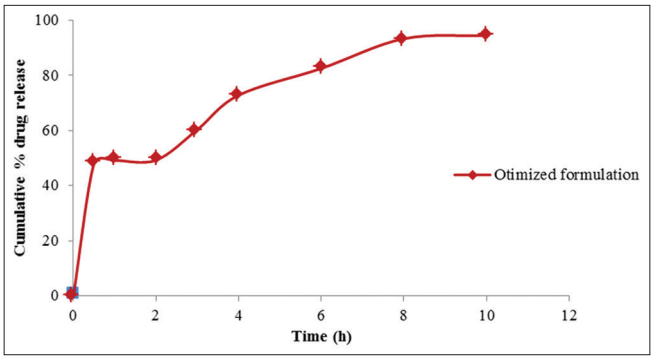

Figure 6: Dissolution profile of the optimized formulation

of dosage units in capsule filling. DSC studies evidenced that there was no interaction between drug and selected excipients. The optimized formulation can be used as an alternative to the marketed formulation. Hence, the applicability of RSM to optimize the formulation variables in the fabrication of methylphenidate HCl ER pellets is apt enough.

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