Development of a Sustained-Release Oral Tablet of Tyrosine Kinase Inhibitor Imatinib Using Full Factorial Design

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ABSTRACT: Tyrosine kinase inhibitors (TKIs) have dramatically improved the outcomes for patients with leukemia. The conventional immediate-release tablets of imatinib exhibit fluctuating plasma levels. The aim of this study was to develop sustained-release tablets of imatinib to maintain a steadier plasma drug concentration. A 3^2 full-factorial design was used for the formulation optimization. The percentages of povidone K30 and methocel K15M were selected as independent variables and drug released after 24h in pH 6.8 phosphate buffer was chosen as a response. Statistical analysis of the response followed by empirical evaluation identified an optimum formulation that involved the use of 1.2% of povidone K30 and 3% of methocel K15M. The optimized formulation released 99.38% of the drug *in vitro* at pH 6.8 phosphate buffer after 24 hours, with an error of -0.353% to the predicted response and followed first-order release kinetics. The findings of this study enabled us to propose a new imatinib tablet dosage form for a more effective and patient-compliant leukemia therapy.

Key words: Factorial design, imatinib, hydrophilic matrix, sustained release, design of experiment (DoE)

INTRODUCTION

Sustained-release dosage forms (SRDFs) have numerous advantages, including prolonged drug release, reduced dosing frequency, improved patient compliance, minimized side effects and enhanced therapeutic efficacy.[1-7] The availability of a vast array of polymers aids formulation scientists to design SRDF, which are intended to release a medication at a predefined rate, thereby maintaining a steady concentration of drug in blood for a defined period while reducing adverse effects to a minimum.[8-10] The usage of hydrophilic matrix is a widely accepted approach in the development of sustained-release formulations. Commercially available hydroxypropyl methylcellulose (HPMC) variants, such as Methocel® K15M CR, are frequently employed as rate-controlling polymers in the formulation development.[11-13]

Imatinib, a game-changing drug, has dramatically improved the outcomes for patients with a type of blood cancer known as chronic myelogenous leukemia.[14] Immediate release imatinib tablets in conventional formulation generate rapid and significantly elevated peak drug concentrations in the bloodstream.[15] This approach may lead to the manifestation of adverse reactions and suboptimal therapeutic control.[16] Given in a sustained-release tablet dosage form, the risk of adverse effects could be reduced due to the slower release of drug from the tablet matrix, which might produce a more precise and controlled plasma drug level.[16,17]

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Quality by design is a strategy used to identify the link between elements that influence a process and the output of that process in a methodical and organized manner, leading to optimized output as responses and a better explanation of relationships among the input factors.[18] It maximizes the process knowledge with the minimum use of resources, identifies interactions of factors and establishes a design space, characterizes the relative significance of each factor, allows for the prediction of the process behavior within the design space, establishes a solid cause and effect relationship between critical process parameters (CPPs) and critical quality attributes (CQAs) and enables the optimization of CQAs through the appropriate selection of CPP settings.[19,20]

Design of experiments (DoE) are becoming more prominent in the field of developing sustained release dosage forms due to their ability to ensure the product's inherent quality.[21,22] The optimization of formulation within a limited timeframe and with minimal trial runs is a crucial concern in the development of pharmaceutical dosage forms. Compared to conventional trial and error technique, the software based DoE approach requires a fewer number of trial runs and is quicker to execute.[23] The utilization of statistical approaches also aids in the identification of critical formulation and process parameters that impact the product quality.[24] The aim of this study was to use the factorial design to establish an optimal formulation for a sustained-release 400 mg tablet of imatinib.

MATERIALS AND METHODS

Chemicals and reagents. Imatinib mesylate (potency = 99.8%) was a generous gift from Incepta Pharmaceuticals Limited, Bangladesh. Hydroxypropyl methylcellulose (Methocel® K15M CR, Colorcon, India), microcrystalline cellulose (Avicel PH 101, Mingtai Chemical Co. Ltd., China), dibasic calcium phosphate (Qualikems Fine Chem Pvt. Ltd., India), povidone K30 (Sisco Research Lab Pvt. Ltd., India), magnesium stearate (Loba Chemie Pvt. Ltd., India) and talc (Merck KGaA, Germany) were purchased from the local market. All the solvents and chemicals were of reagent grade.

Selection of excipients. The excipients were chosen after critical review of literatures and performing drug-excipient compatibility studies. Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and x-ray diffraction analysis (XRD) were done to study the compatibility between the active pharmaceutical ingredient (API) and excipients.

Preliminary studies. Preliminary screenings were performed by preparing formulations of imatinib using methocel® K15M CR and povidone K30 at different ratios. The overall physicochemical properties and dissolution behaviors of the prepared formulations were investigated as per protocols.[25,26] Afterward, based on the dissolution rates, the upper and lower limit of these two excipients were selected for further investigation. Table 1 shows the overall ranges of excipients used to formulate imatinib SR tablet.

Preparation of tablets. The active ingredient, polymers, filler, glidant and lubricant were properly weighed and passed through a No. 40 sieve. The weighed active ingredient and excipients (except half of the talc and magnesium stearate) blended in a v blender (VB-50, GlobePharma Inc., USA) for about 10 minutes. Isopropyl alcohol was added to form a dough and the wet mass was then passed through a No. 30 mesh sieve. The wet granules were kept in a tray dryer (TD-24, Labtop Instruments Pvt. Ltd., India) for 50 minutes. The remaining talc and magnesium stearate were added to the dried granules and mixed properly. Then the appropriate amount of the granules was compressed using a rotary tablet press (Fette 2090i, Fette Compacting GmbH, Germany) at a compression force of 2 tons.

***In vitro* dissolution studies.** *In vitro* dissolution studies were conducted in pH 6.8 phosphate buffer for a period of 24 hours using a USP type II (paddle type) dissolution apparatus (DIS 8000, Electrolab, India).

DoE and formulation optimization. A 3^2 full factorial design was used with Design Expert®

software (version 13) considering two independent variables at three levels and one response. The independent variables selected were the % of povidone K30 and methocel K15M CR in the formulation (Table 2). The cumulative percentage of drug released after 24h at pH 6.8 phosphate buffer was considered as the response (R) of the study. Nine prototype formulations were suggested from the design (Table 3). The optimum formulation was selected after conducting statistical analysis (*e.g.*, fit summary analysis) of the responses.

***In vitro* drug release kinetics studies.** *In vitro* release kinetics for the optimized tablet batch were tested using zero-order, first-order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas plots.[26,27]

Table 1. Preliminary screening of imatinib sustained release tablet formulations.

Name of the ingredients	Justification of use	Amount (%)	Amount (mg)
Imatinib mesylate	Active pharmaceutical ingredient	72.42	478
Methocel® K15M CR	Release retardant polymer	1-6	6.6-39.6
Povidone K30	Binder	1-2	6.6-13.2
Avicel PH 101	Diluent	12.12	80
Purified talc	Glidant	1.52	10
Magnesium stearate	Lubricant	0.76	5
Dibasic calcium phosphate	Diluent	q.s. to 100	q.s. to 660

Table 2. Independent variables and their levels for experimental design.

Variables	Name	Unit	Type	Coded values			Actual values		
				Low	Mid	High	Low	Mid	High
A	Povidone K30	% (mg)	Numeric	-1	0	1	1.2 (7.92)	1.5 (9.9)	1.8 (11.88)
B	Methocel® K15M CR	% (mg)	Numeric	-1	0	1	3.0 (19.8)	4.0 (26.4)	5.0 (33)

Table 3. Formulations of nine different (F1 to F9) tablet batches (mg/tablet).

Batch	Imatinib mesylate	Povidone K30	Methocel® K15M CR	Avicel PH 101	Dibasic calcium phosphate	Talc	Magnesium stearate	Total
F1	478	11.88	33	80	42.12	10	5	660
F2	478	11.88	26.4	80	48.72	10	5	660
F3	478	7.92	19.8	80	59.28	10	5	660
F4	478	9.9	26.4	80	50.7	10	5	660
F5	478	9.9	33	80	44.1	10	5	660
F6	478	7.92	33	80	46.08	10	5	660
F7	478	9.9	19.8	80	57.3	10	5	660
F8	478	7.92	26.4	80	52.68	10	5	660
F9	478	11.88	19.8	80	55.32	10	5	660

RESULTS AND DISCUSSION

Drug-excipient compatibility studies. FTIR, DSC and XRD analyses indicated the compatibility of imatinib mesylate with all the excipients (Figure 1). The FTIR spectrum of active imatinib, imatinib with all the formulation excipients and powder of crushed imatinib SR tablet shows no significant chemical interaction between imatinib and the formulation

excipients (Figure 1a). The XRD diffractogram of active imatinib and imatinib with all the formulation excipients indicates the physical structural integrity of the drug molecule, suggesting no significant interaction between imatinib and formulation excipients (Figure 1b). Moreover, DSC thermograms indicated the retention of endothermic peak for imatinib in presence of formulation excipients, referring no significant interaction between the API and excipients (Figure 1c).

Evaluation of physical properties of granules and tablets. The granules of all formulations, except for F1, F2 and F5, exhibited excellent flow properties (Table 4). All the tablets were uniform in size, weight and hardness, with their respective variations being within the tolerance limits (Table 5). The percentage of friability for every batch was below 1% indicating that the friability values were within the prescribed limits and the tablets were physically stable against the shock and abrasion experienced during handling and transportation.

***In vitro* dissolution studies of formulated tablets.** The dissolution profile of nine tablet formulation batches showed a significant variation, with the drug released after 24 hours ranging from 80.81% to 98.83% (Table 6). Analysis of these responses (i.e., drug release after 24h) with respect to the chosen covariates (% of povidone K30 and methocel K15M CR) led to the development of optimum formulation.

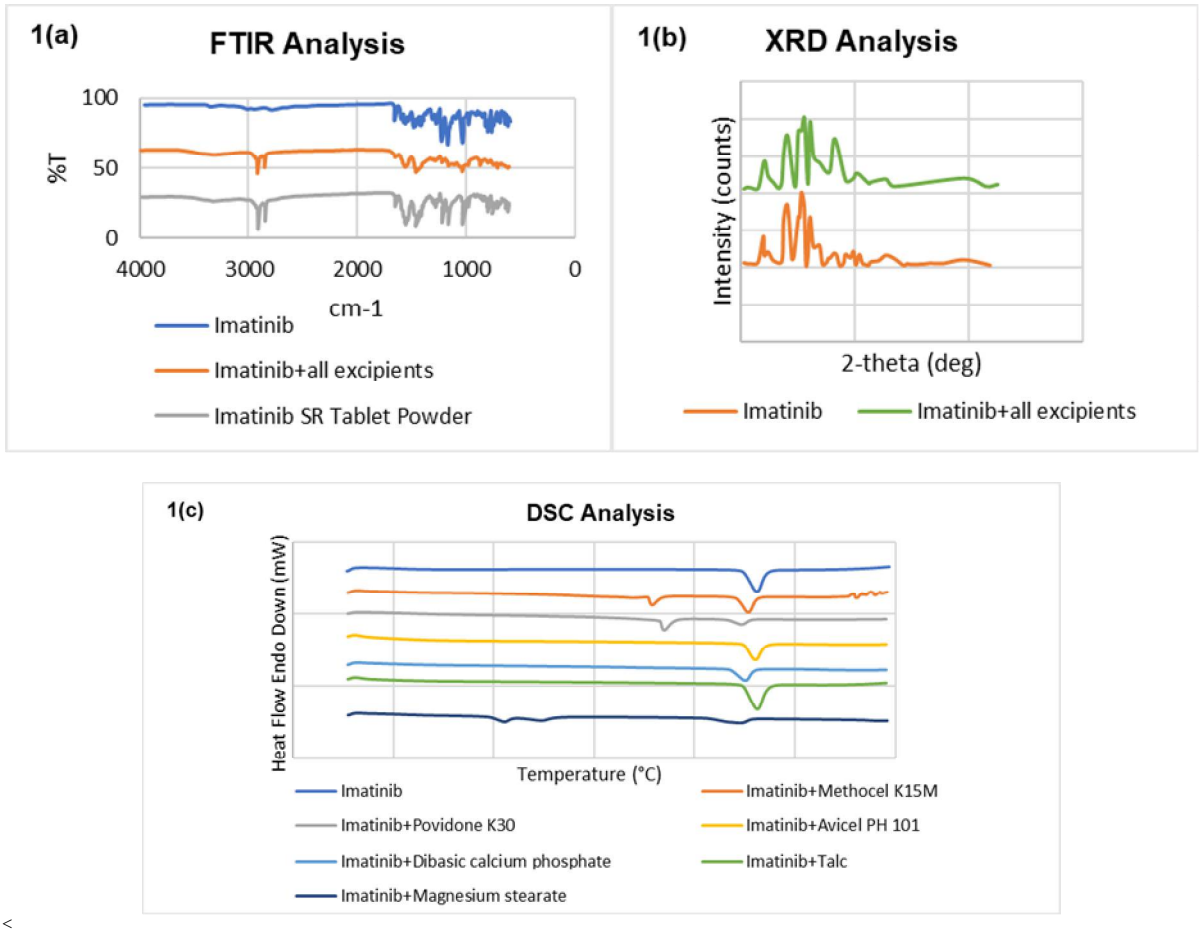

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Figure 1. Drug-excipient compatibility studies. (a) FTIR spectrums of pure imatinib, imatinib and all the formulation excipients and powder of crushed imatinib SR tablet; (b) XRD diffractograms of pure imatinib and imatinib and all the formulation excipients and (c) DSC thermograms of pure imatinib and imatinib with the excipients used in the formulation.

Analysis of response. Analysis of drug release profiles of nine different formulations of imatinib in relation to the percent composition of binder povidone K30 and release retardant polymer methocel K15M CR using Design Expert® software recommended a linear mathematical model (p<0.0001). The high F-value of 123.66 obtained from the model indicates that the model is significant and there is a less than 0.01% chance that an F-value this large could occur due to noise. The p-values (<0.05) further support that both factors A and B have a significant influence on the release profile of imatinib (Table 7). The predicted R^2 value of 0.9463 shows a reasonable agreement with the adjusted R^2 value of 0.9684, as the difference being less than 0.2. The determination of the signal-to-noise ratio using adequate precision yielded a ratio of 30.7023, indicating a satisfactory signal level, as a ratio greater than 4 being considered desirable to indicate that the tested model can precisely be used to navigate the space of design. The impact of the covariates on the response is illustrated in figure 2. The cumulative percentages of drug released after 24h decreases significantly with the increase of percent composition of both povidone K30 and methocel K15M CR, as indicated in contour and 3D response surface plots (Figures 2c and 2d).

Table 4. Flow properties of formulation blends of imatinib.

Formulations	Hausner ratio	Carr's index	Angle of repose (degrees)	Flow character
F1	1.14	12.28	33.28	Good
F2	1.13	11.37	31.36	Good
F3	1.04	3.82	27.11	Excellent
F4	1.09	8.23	29.18	Excellent
F5	1.13	11.46	31.85	Good
F6	1.10	9.15	29.63	Excellent
F7	1.05	4.80	27.76	Excellent
F8	1.06	5.90	28.49	Excellent
F9	1.08	7.46	28.92	Excellent

Table 5. Physical properties of imatinib tablets of different formulations.

Formulations	Length (mm) ±% RSD	Width (mm) ± %RSD	Thickness (mm) ± %RSD	Average weight (mg) ±%RSD	Hardness (kg/cm^2)	Friability (%)
F1	17.25±0.06	8.51±0.09	6.12±0.06	663.31±0.08	14.2	0.16
F2	17.24±0.04	8.52±0.10	6.11±0.05	675.76±0.05	13.8	0.19
F3	17.16±0.02	8.56±0.04	6.06±0.03	664.92±0.04	11.2	0.41
F4	17.21±0.05	8.53±0.06	6.10±0.04	670.67±0.06	12.9	0.24
F5	17.25±0.07	8.52±0.08	6.11±0.05	673.46±0.05	13.5	0.22
F6	17.22±0.04	8.53±0.06	6.10±0.04	667.72±0.07	13.1	0.25
F7	17.17±0.03	8.56±0.05	6.07±0.01	668.53±0.03	11.8	0.36
F8	17.18±0.05	8.55±0.05	6.08±0.02	666.82±0.06	12.3	0.32
F9	17.19±0.04	8.54±0.06	6.09±0.02	673.25±0.07	12.6	0.29

Optimization of formulation. The optimization criterion was to maximize the cumulative percentage of drug release after 24 hours in pH 6.8 phosphate buffer. Among the eight solutions generated by Design Expert® software, the formulation that yielded the highest desirability value was selected as

the optimized formulation, with the variable A suggested at 1.2% and variable B suggested at 3%. The empirical study using the variables A and B set at 1.21% and 3.03%, respectively, showed the drug release of 99.38% after 24 hours. Interestingly, this experimental response matched with the predicted response from the model, with an estimated error of -0.353% (Table 8).

Table 6. Dissolution profiles of formulated imatinib tablets.

Formulations	Cumulative % of drug release in pH 6.8 phosphate buffer after 24 hours
F1	80.81
F2	84.22
F3	98.83
F4	90.01
F5	84.56
F6	87.31
F7	96.72
F8	94.51
F9	92.88

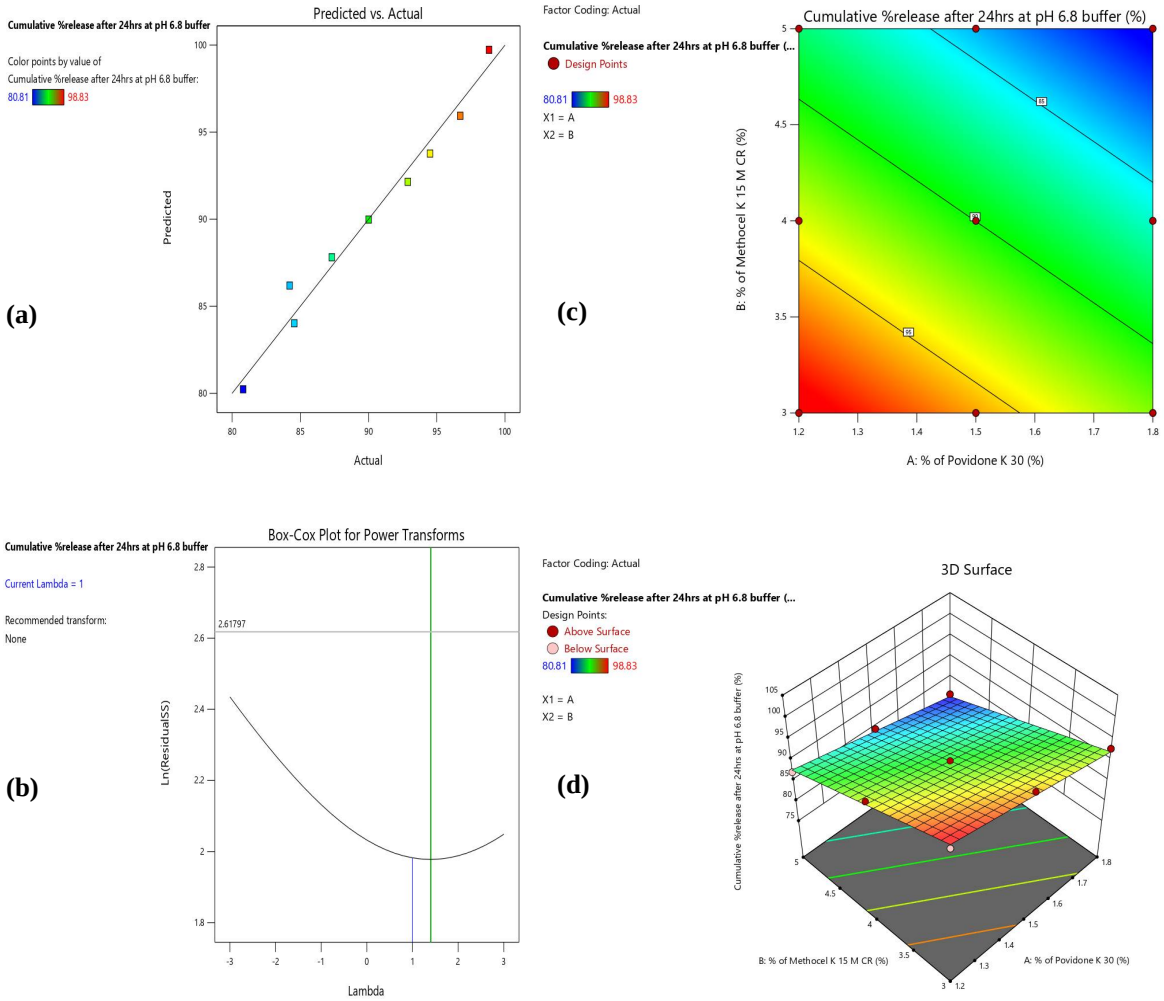

Figure 2. Impact of independent variables (% of povidone K30 and methocel K15M CR) on the response (cumulative % of drug release after 24 hours). (a) Predicted vs actual response plot, (b) Box-cox plot, (c) Contour plot and (d) 3D response surface plot.

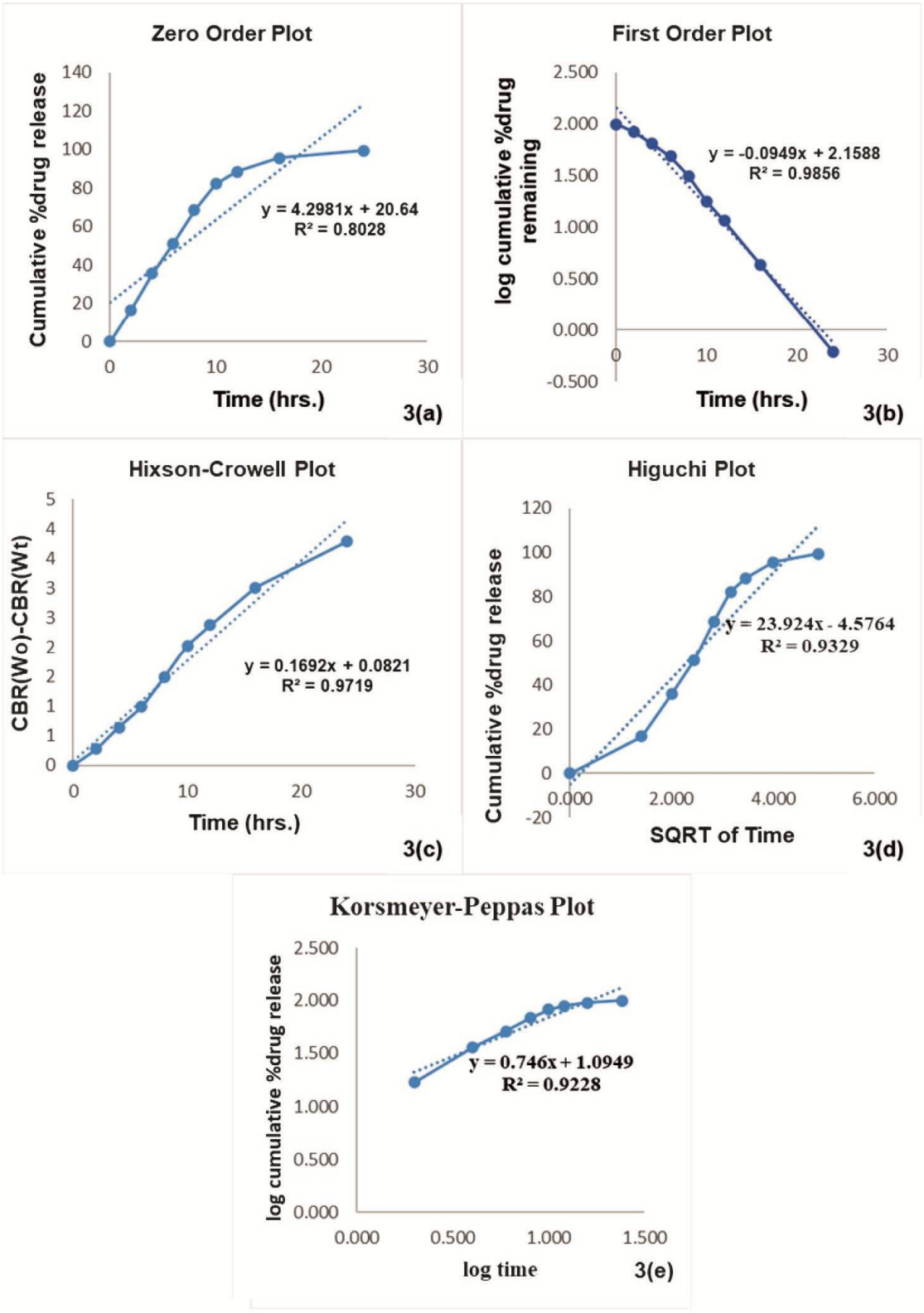

Figure 3. Release kinetics of the optimized tablet. (a) Zero order, (b) First order (c) Hixson-Crowell, (d) Higuchi and (e) Korsmeyer-Peppas plots.

Table 7. Model summary statistics, ANOVA and regression equation of responses.

Model summary statistics						
Source	R^2	Adjusted R^2	Predicted R^2		Remarks	
Linear	0.9763	0.9684	0.9463		Suggested	
2FI	0.9766	0.9625	0.9019			
Quadratic	0.9819	0.9517	0.7791			
Cubic	1.0000	1.0000	0.9996		Aliased	
ANOVA for linear model						
Source	Sum of squares	df	Mean square	F-value	p-value	Remarks
Model	299.20	2	149.60	123.66	< 0.0001	significant
A-% of Povidone K 30	86.18	1	86.18	71.24	0.0002	
B-% of Methocel K15M CR	213.01	1	213.01	176.08	< 0.0001	
Residual	7.26	6	1.21			
Cor Total	306.45	8				
Fit statistics for response						
Std. Dev.	1.10	Adjusted R^2		0.9684		
Mean	89.98	Predicted R^2		0.9463		
C.V. %	1.22	Adeq Precision		30.7023		
R^2	0.9763					
Final equation in terms of actual factors						
R = +132.76667-12.63333A-5.95833B						

Table 8. Optimized formulation and predicted error of the response.

Method	Povidone K30 (%)	Methocel K15M CR (%)	Response
Predicted values	1.2	3.0	99.731
Experimental values	1.21	3.03	99.38
Predicted error (%)			-0.353

Predicted error (%) = [(Experimental value-predicted value)/Experimental value] x100
Tolerance: ±2%

***In vitro* drug release kinetics studies.** The *in vitro* drug release profile of the optimized formulation tablet batch was assessed against zero-order, first-order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas kinetic models (Figure 3). The findings suggest that the optimized tablet formulation best fits with the first-order release kinetic (R^2= 0.9856).

CONCLUSION

A sustained release oral tablet formulation of imatinib using a combination of excipients was successfully developed by utilizing a 3^2 full factorial design. The formulation optimization based on the DoE approach gave an optimized tablet formulation with desirable drug release characteristics. The study assessed the *in vitro* drug release profiles which suggests that the drug release followed first order kinetics. Further investigations are needed to validate the *in vivo* performance of the developed sustained-release tablet formulation. Stability testing also needs to be performed to identify the long-term stability of the tablet formulation under various storage conditions.

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CONFLICT OF INTEREST

Not applicable.

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