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Design and Optimization of Sustained Release Tablets of Axitinib—A DoE based approach

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Abstract: Axitinib is classified as BCS class II by the Biopharmaceutical Classification System (BCS). Axitinib is used to treat renal cancer patients. However, no sustained-release tablets have been documented using the Quality by Design (QbD) method. The aim of the research work was to design sustained release formulations of AXB, using response surface methodology through Box-Behnken statistical design (BBD) by wet granulation technique. The amounts of release retardant polymers investigated were HPMC K4M (X1), HPMC K15M (X2), and Polyvinyl pyrrolidone (PVP) (X3). *In vitro* cumulative percentage release in 0-24 (h), such as (R1), (R2), (R3), (R4), (R5), (R6), (R7), (R8), (R9), and (R10), are employed as dependent variables. The desirability 0.793 functions were found to be optimized in sustained-release formulations. Finally, the BBD proved valuable in improving the sustained release formulation and determining the impacts of formulation factors. The research finding is to develop the ideal formulation with great strength and long-term release.

Keywords: Axitinib; hydrophilic matrix tablets; Box-Behnken statistical design; dissolution; sustained release and stability

1. Introduction

Axitinib (AG-013736) (AXB) is a tyrosine kinase inhibitor that inhibits angiogenesis when taken orally (TKI). Angiogenesis, vascular permeability, and blood flow have all been inhibited by the compound *in vitro* [1,2]. AXB showed an anticancer effect in Phase III clinical studies against kidney neoplasms [3], including renal cell carcinoma (RCC) [4,5], pancreatic cancer [6], and thyroid cancer [7]. The first pharmacokinetic investigation utilized a rapid assay that combined liquid chromatography-tandem mass spectrometry (LC/MS/MS) with liquid-liquid extraction [8].

Ángeles et al. have demonstrated the oxidized lipids in the metabolic profiling of neuroendocrine tumors by utilizing RP-LC-ESI-QTOF-MS/MS [9]. Huynh et al. used LC-MS/MS to develop and validate a technique for simultaneously quantifying 14 tyrosine kinase inhibitors in human plasma [10]. Finally, Yu et al. have developed and validated the eight tyrosine kinase inhibitors by utilizing LC-MS/MS method simultaneously with pharmacokinetic studies [11]. The utilization of a new generation LC system and column with higher pressures and sub-2 m particles, which had not previously been employed for TKI medications using the QbD technique, may explain this approach's increased sensitivity compared to other approaches TKI drugs. The primary goal of anticancer drug development has been to develop molecules with improved efficacy and reduced toxicity commonly associated with anticancer treatment with dose management, as well as to improve the dissolution rate of poorly water-soluble drugs through the formulation of solid drug solutions in polymeric matrices. In this regard, experimental design trials, also known as the Design of Experiments (DoE), have been widely utilized to create (Quality by Design) QbD in both commercial and academic contexts, as well as a regular aspect of the robustness study of the pharmaceutical manufacturing process [12].

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Hydroxypropyl methylcellulose (HPMC) is extensively used in several application because of its unique properties and is extensively studied in different fields such as pharmaceuticals, biomaterials, agriculture, food, and water purification, etc [13]. The drug and HPMC ratio, particle size of HPMC and drug molecule, and compression force impacts the release of drug from the matrix [14]. The effect of mean particle size of HPMC and number of polymer particles on the release of aspirin from swelling hydrophilic matrix tablets was investigated [15]. HPMC pore formers have resulted in increased implant porosity and overall drug release, whereas methyl cellulose tends in lower porosity with slow, delayed release [16]. Authors reported that the water content of swollen matrices consisting of HPMC and theophylline could be measured using texture analysis [17]. Transport phenomena played a crucial role in water up-take, gel swells and erosion. Due to increased diffusivity, hydration occurs [18].

HPMC could be a potential enhancer of biopharmaceutical properties via ball-milled solid dispersion, and HPMC stabilizes the solid dispersions through a dilution mechanism have shown that in the *in-vivo* setting, matrix formulations with a lower HPMC concentration and higher lactose concentration are more likely to perform poorly. [19,20]. HPMC molecular weight, concentration, and effect of food could affect the in vivo erosion rate on HPMC matrix tablets [21]. Authors have developed the nateglinide controlled release tablet formulations and optimized by using mathematical response surface methodology [22]. Authors has suggested that drug release can be influenced by increased the methoxyl content of HPMC, whilst high content of hydroxypropoxyl can largely reduce the difference in drug release profiles [23].

The traditional models of optimization, where one factor is controlled at a time, since they do not take into account potential correlations between variables, which can lead to an inability to determine the optimal combination. An effective remedy for this issue could be statistical optimization, using a suitable experimental design. The recently developed QbD regulatory framework describes a highly practical approach to find the optimum product and process characteristics by applying the concept of experiments. DoE offers tremendous information from the least number of experimental runs through systematic variation of the conditions and simultaneous evaluation of the effects of multiple variables. DoE output variables have been recognized as an important strategy for the *in-vitro* dissolution profile of the drug development process. Several kinetic equations have been employed to interpret the drug release from immediate and sustained oral dosage formulations. DOE is used to optimize the variables of the process and formulation in order to achieve the most effective formulations.These studies are frequently used to develop and validate a robust manufacturing process. The following type of study is to better value the critical method parameters and impact of tiny changes in method conditions. Authors have reported the characterize and optimize loxoprofen immediate release (IR)/sustained release (SR) tablet utilizing a three-factor, three-level Box–Behnken design (BBD) combined with a desirability function [24]. Authors have demonstrated about the developed sustained release gastro floating tablets of metformin HCl using BBD method to find out the impact of formulation variables and process variable on response variables, including drug release rate were investigated [25]. Authors have reported the optimized chrono-modulated dual release bilayer tablets of fexofenadine and montelukast using BBD method [26]. Authors have developed the cinnarizine gastro-retentive floating tablets using hot melt extrusion coupled with 3D printing [27]. The goal of this study was to use a QbD technique to create once-daily sustained-release Axitinib tablets. The ideal formulation, a quadratic D-optimal experimental design, was utilized to examine the influence of matrix-forming polymer (HPMC) % and PVP (binder) cumulative ratio of medication released at different time intervals during 24 hours. The optimization approach would aid in the development of the design space and the establishment of formulation parameters for the development of sustained-release tablets with predictable properties.

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2. Material and Methods

2.1. Materials

Axitinib was kindly donated by MSN Laboratories, Hyderabad, India. HPMC K4M and HPMC K15M was gifted from Colorcon Pvt Limited; Mumbai, India; Avicel PH 101 (50 µm), Kollidon®30 polyvinylpyrrolidone K-30 (PVP), Magnesium Stearate were purchased from SRL India:, Isopropyl alcohol purchased from SD fine chem-Limited, India. All other chemicals and solvents were of analytical grade.

2.2. Compatibility Studies

2.2.1. Thermal Analysis

The melting point change of Axitinib was measured using a DSC instrument to evaluate its thermal behavior. Thermo gravimetric and Differential Scanning Calorimetry (TG-DSC, NETZSCH STA 449 F3 Jupiter ®Germany) from 30°C to 350°C with nitrogen purging gas at a ramping rate of 10 K/min.

2.2.2. FTIR Analysis

The physiochemical compatibilities of the drug and excipients were tested by Fourier transform infrared spectroscopy using Perkin Elmer Spectrum GX FTIR Spectrometer. SpectraGyrph 1.2 spectroscopy software was used to assess the spectral data. It used to detect the functional groups present in the Axitinib.

2.3. Experimental Design

In the current research, a 17 run, three-factor, three-level Box–Behnken design was employed for the optimization procedure using Design-Expert Software (Design-Expert® 11, Stat-Ease, Inc., Minneapolis, MN 55413, USA). The investigated factors independent variables were HPMC K4M content (X1), HPMC K15M content (X2), and PVP-30 content (X3). From adequate preliminary trials, the levels of these three factors were calculated. At three different stages, these independent variables are analyzed, such as low (-1), medium (0), and high (+1), as shown in Table 1. The cumulative percentages of drug released at 30 min,1,2,3,4,6,8,10,12, and 24 hours at (R1), (R2), (R3), (R4), (R5), (R6), (R7), (R8), (R9), and (R10), respectively were selected as dependent variables. Which are considered as prominent factors in the formulation ingredients on the drug release of sustained-release tablets.

Table 1. Experimental factor and levels of Box-Behnken design for axitinib.

Independent Variables		Levels	
		Low%	High%
HPMC K4M	X1	8	24
HPMC K15M	X2	8	24
PVP K 30	X3	2.5	4.5

2.4. Preparation of Axitinib Sustained Release Tablets

Using a glass mortar and pestle, 0.324 mg of Axitinib, HPMC K4M, and HPMC K15M were accurately weighed and blended for 20 minutes. The mixture was then granulated using a PVP (5% w/w) binder solution in isopropyl alcohol. The wet mass was sieved with a 16# sieve, and granules were dried in a tray drier at 50°C for 30 minutes. Finally, the dry granules were blended with MCC's requisite amounts and 1% magnesium stearate by weight. On a 10-station rotary tablet press (Rimek, Ahmedabad, India), amounts of the resulting granules equivalent to 100 mg of Axitinib were compressed using 5mm concave punches and a compression force of 9KN for all formulations.

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2.5. Preparation of Axitinib Immediate Release Tablets

The wet granulation method was employed to develop axitinib immediate release (IR) tablets. In a tumble mixer, 0.324 mg of Axitinib, lactose, and other excipients were blended for 5 min to form a wet mass. The powder blend was wetted with isopropyl alcohol containing PVP-K-30 as a granulating fluid. The moist bulk was then passed through BSS, which had a 1.7 mm opening aperture. The granules were collected and dried for 60 minutes at 60 C. Finally, the formulations 100mg of Axitinib were compressed using 5 mm concave punches (Rimek, Ahmedabad, India) at a compression force of 9 KN.

2.6. In Vitro Drug Release Profile

The release properties of Axitinib from the prepared formulations were determined using a Dissolution Tester (Lab India): DS 8000. According to the USP dissolution II paddle technique, 37 .5°C with a rotation speed of 50 rpm.In a 900 ml medium of 0.01NHCl, the release profile was evaluated at 50rpm and 37 ± 0.5°C. For time intervals 0 to 24 h, a 5 ml sample was taken and replaced with fresh dissolving media at specified time intervals. Millipore 0.45 m filters were used to filter the collected samples. After appropriate dilutions, the concentration of Axitinib in samples was quantified using a UV double beam spectrophotometer at 335nm (Shimadzu, Kyoto, Japan). The percentage of drugs released from the tablets was estimated and Plotted.

2.7. LC-MS/MS Analysis

Shimadzu LC-MS/MS 8030 system with electro spray ionization interface was used. We have utilized the LC-20AD pump, SPD-M20 PDA detector, CTO-20AC column oven, CBM-20 alite controller, SIL-20AC auto sampler and 20AC auto sampler. Lab Solutions software was used to develop the process. The chromatographic separation was performed using Zorbax C18 (50 mm x 4.6 mm i.d., 5 m) as a stationary phase in isocratic elution mode with 10 mM Ammonium formate (pH-4.5): acetonitrile in the ratio of 30:70 (v/v) with a flow rate of 0.87 ml/min and an injection of 30 µl whilst maintaining the column ambient temperature. The preliminary tests for designing the LC-MS/MS system for estimating Axitinib were carried out according to the literature reports.

3. Results and Discussion

3.1. Compatibility Studies

3.1.1. Thermal Analysis

Drug–excipient interaction study at an early stage of product development is an important exercise in the development of a stable dosage form. As shown in Figure 1a,b sharp endothermic peak was observed at 215 ◦C in DSC thermogram of Axitinib. However, the endothermic peak of Axitinib was well preserved at 215 ± 5◦C in the DSC thermogram of Axitinib-excipients mixtures. This result inferred that there was no interaction between drug and excipients. In isothermal stress testing, it was observed that there was no physical change (color and appearance) as well as drug content after storage of drug–excipient blends under stressed conditions which supported a previously reported result of DSC study on drug–excipient compatibility testing.

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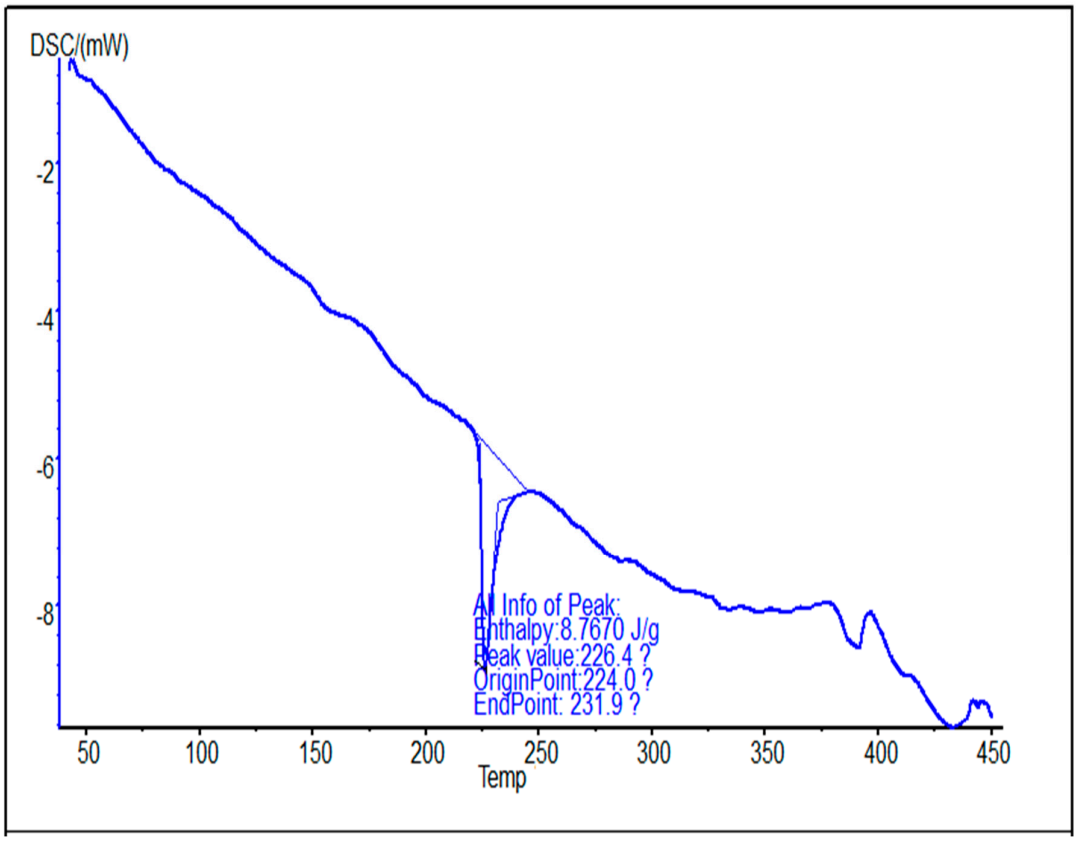
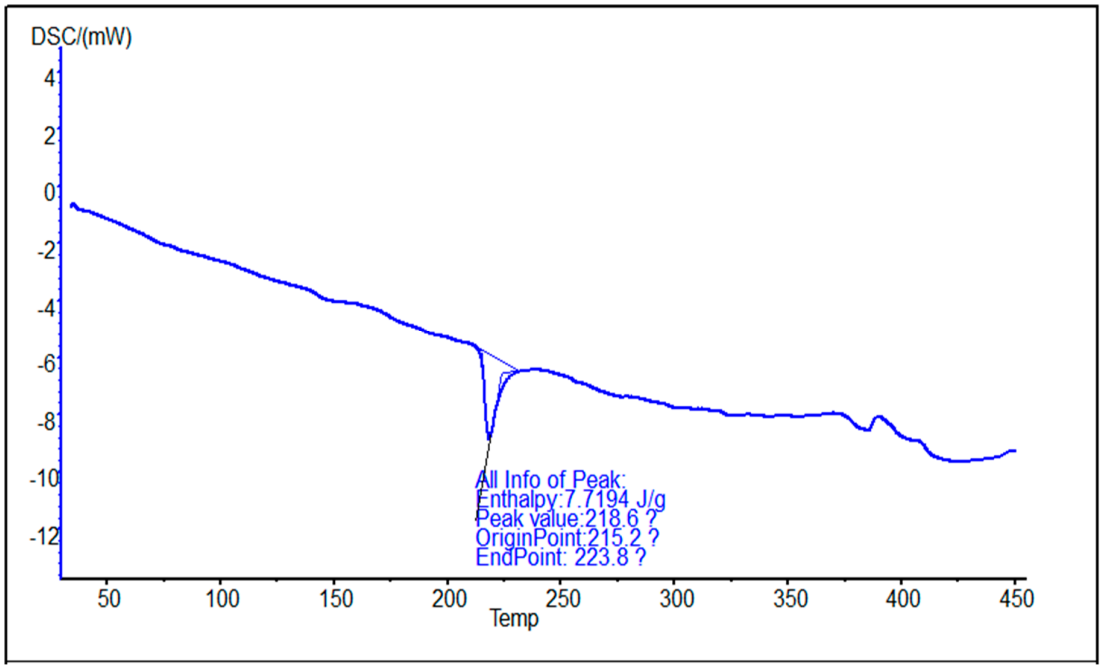


(a)



(b)

Figure 1. (a) Differential scanning calorimetry (DSC) spectra of axitinib. (b) Differential scanning calorimetry (DSC) spectra of axitinib and polymers.

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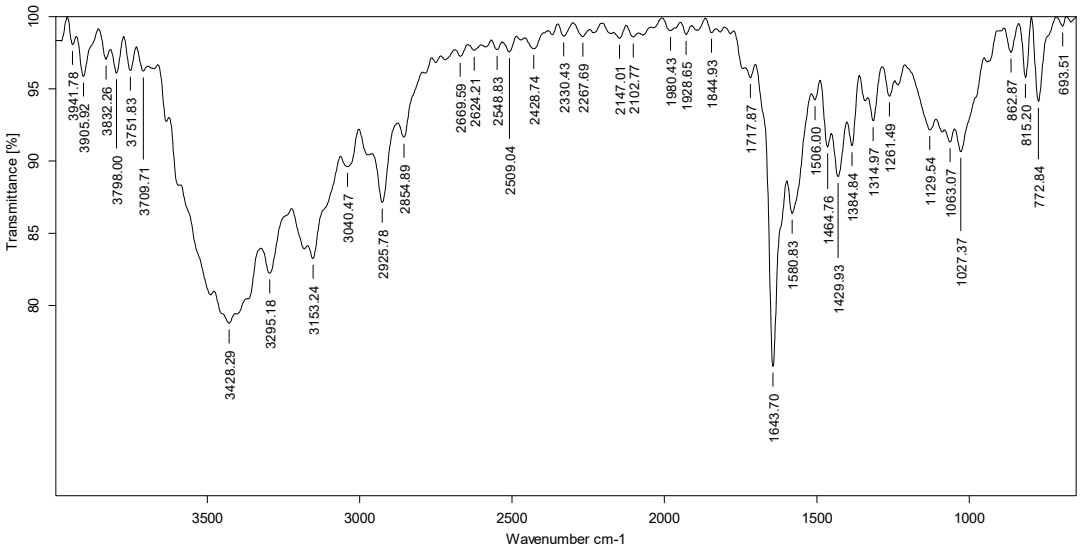
3.1.2. FTIR Analysis

The FTIR spectra of Axitinib, and Axitinib+excipient mixtures were obtained using Fourier transform infrared spectroscopy using Perkin Elmer Spectrum GX FTIR Spectrometer. Excipient polymer and drug peaks were not prominently observed in the pre-formulation as it might be available as a molecular dispersion within the polymer matrix. The results of the FTIR suggest the absence of any potential chemical incompatibility between the polymer and drug in the formulation Figure 2a,b.



(a)

Figure 2. (a) Infrared (IR) spectra of axitinib. (b) Infrared (IR) spectra of axitinib and polymers.

3.2. Evaluation of Physical Parameters of Granules and Tablets

From the angle of repose, compressibility index and Hausner ratio, the flow properties of granules can be measured. The angle of repose (almost) <30 C implies free flowing material and > 40 with weak flow properties. The <10 percent compressibility index shows excellent flow properties and >38 percent with weak flow properties. The Hausner ratio of 1.00-1.11 reveals free flow and weak flow characteristics of >1.60.

Values for angle of repose (θ), compressibility index (%), and Hausner ratio for all prepared granules were found to be in the range of 23.65–25.55 ◦C, 16.05-19.12%, and 1.19–1.25, respectively, Which indicates that the granules flow freely and can be used for compression of the tablet. Within the limit of ±5 percent (w/w) for all prepared tablets, the percentage of weight variation was observed, which is well accepted for uncoated tablets as per United State Pharmacopeia, National Formulary (USP,2004). Friability testing of all batches of the prepared tablet was passed (weight loss <1%, w/w), which assumed that tablets had adequate mechanical integrity and strength.

3.3. Effect of Model Independent and Dependent Factors of Dissolution Study

The amount of HPMC K4M (X1) and HPMC K15M (X2) in tablets were chosen as independent variables in a 32 full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

where, Y is the dependent variable, $b_0$is the arithmetic mean response of the 9 runs, and biis the estimated coefficient for the factor Xi. The main effects ($X_1$and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1,X2) showed how

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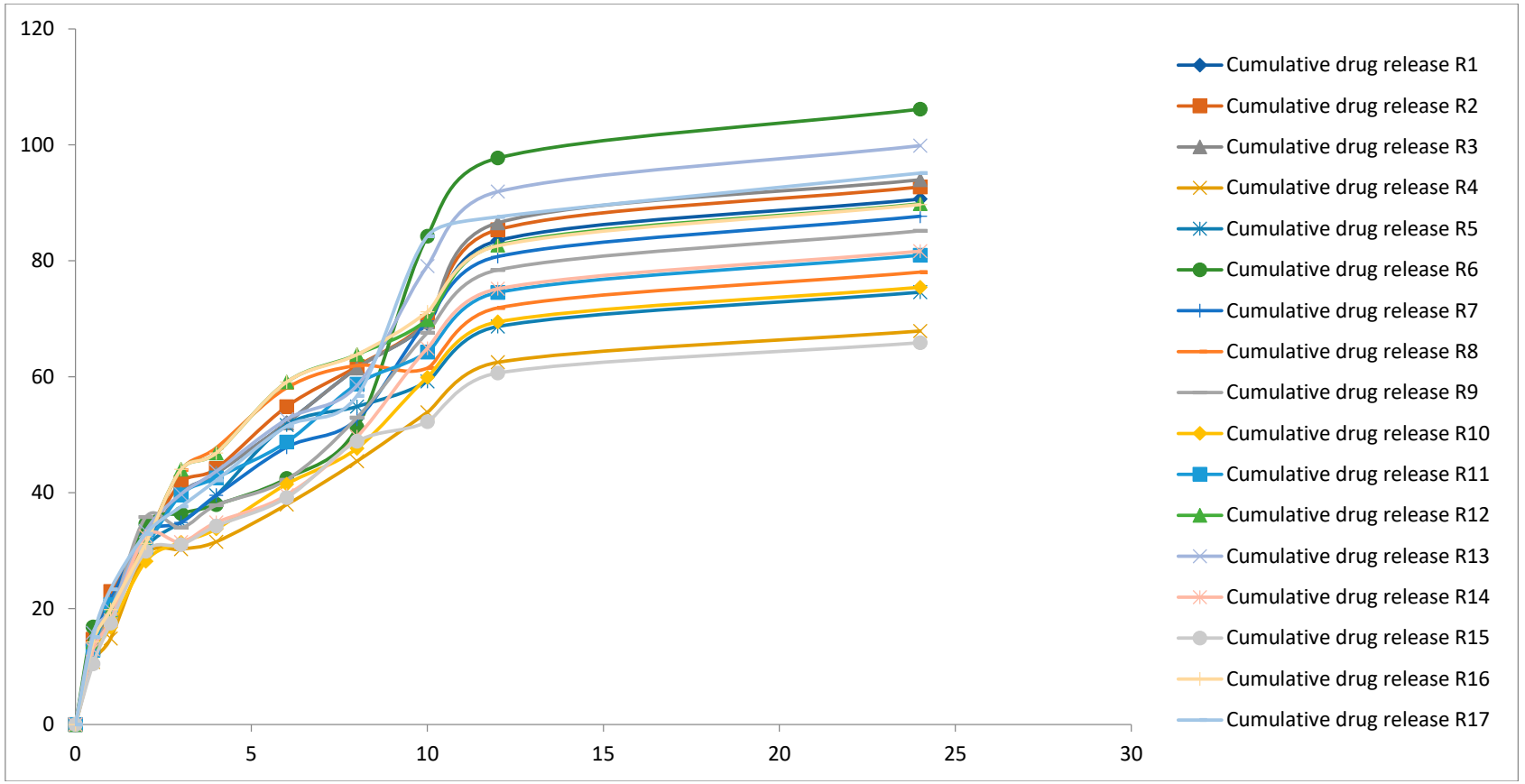
the response changes when two factors are simultaneously changed. The polynomial terms (X_{12}andX_{22}) are included to investigate nonlinearity.

The BBD produced a total of 17 confirmative runs that included the midpoint of each edge and the repeated center points to refine Axitinib sustained-release formulations. The 17 experiments were performed for optimizing the three independent variables (HPMC K4M, HPMC K15M and PVP K30 concentrations). The formulations developed were characterized by dependent properties, such as dissolution, and the values shown in Table 2. (Figure 3a,b) For the 17 formulations, the observed responses were evaluated using Statease Design-Expert software. A significant impact on the observed responses was shown by polynomial equations which identified the individual main effect, the interaction effect and the quadratic effect of the selected independent formulation variables. The optimum values of the variables were obtained by the Design-Expert software and based on the criterion of desirability Figure 4. Three dimensional reaction surface plots and the contour plots were conspired to interpret the influence of independent variables on the dependent responses Figure 5 Through two and three-dimensional graphs, they help decide the optimum range of experimental parameters and calculate the relationship between the input parameters and the interest response.



(a)

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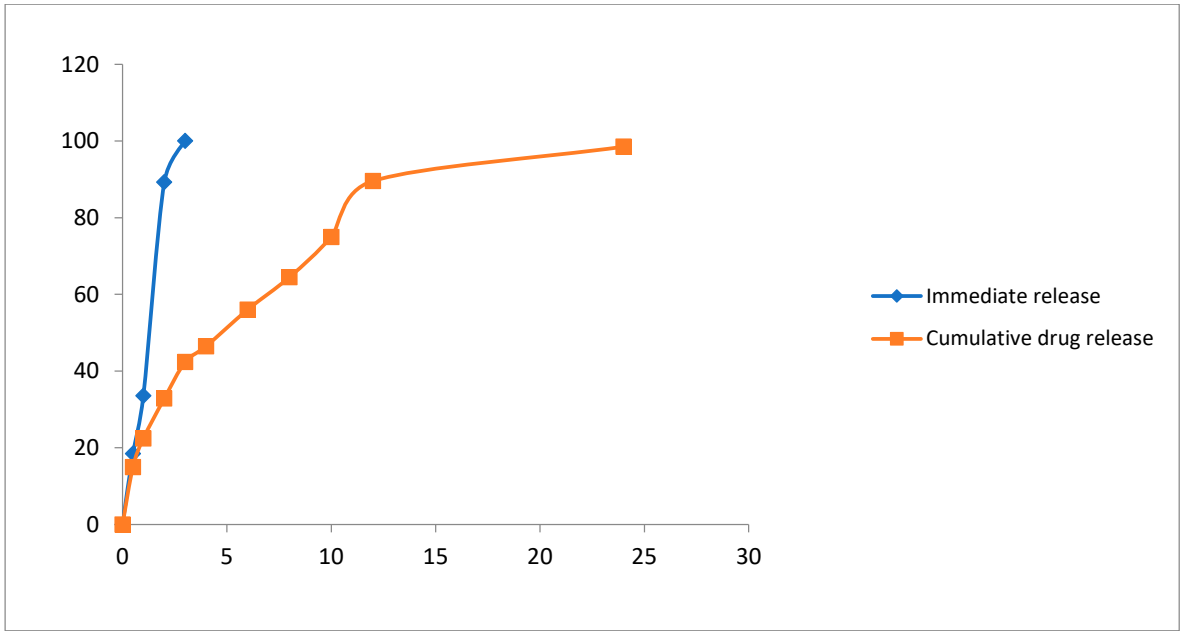

(b)

Figure 3. (a) Release profile of axitinib from HPMC (polymers) containing formulations. (b) Optimized mean dissolution profile for axitinib sustained and immediate release formulations.

Table 2. Summarization of Box-Behnken design with factors and levels with percentage Axitinib drug release.

		Factor 1	Factor 2	Factor 3	Drug Release									
Std	Run	A:HPMCK4M	B:HPMC K15 M	C:PVP	30 Minutes	1 hours	2 hours	3 hours	4 hours	6 hours	8 hours	10 hours	12 hours	24 hours
17	1	16	16	3.5	14.390	21.381	31.084	39.84	43.34	52.021	61.48	69.12	83.465	90.660
13	2	16	16	3.5	14.72	22.952	31.812	41.74	44.16	54.833	61.78	69.56	85.376	92.736
16	3	16	16	3.5	14.92	21.381	31.084	39.84	43.34	52.021	61.48	69.42	86.536	93.996
4	4	24	24	3.5	10.775	14.822	29.241	30.24	31.54	37.943	45.42	53.87	62.495	67.882
6	5	24	16	2.5	11.84	19.411	30.528	34.94	39.54	51.680	54.86	59.2	68.672	74.592
1	6	8	8	3.5	16.85	19.350	34.617	36.42	37.93	42.444	51.24	84.25	97.73	106.15
11	7	16	8	4.5	13.92	21.420	32.842	34.86	39.54	47.847	52.66	69.6	80.736	87.696

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10	8	16	24	2.5	12.39	20.626	31.688	43.88	47.74	58.084	61.94	61.5	71.862	78.057
9	9	16	8	2.5	13.52	18.567	35.789	33.98	37.84	42.223	52.94	67.6	78.416	85.176
8	10	24	16	4.5	11.975	16.766	28.162	31.45	33.75	41.463	47.64	59.875	69.455	75.442
3	11	8	24	3.5	12.85	20.643	30.594	39.62	42.58	48.722	58.72	64.25	74.53	80.955
14	12	16	16	3.5	14.26	19.819	31.248	44.02	46.84	59.073	63.82	69.82	82.708	89.838
5	13	8	16	2.5	15.85	19.836	33.394	39.74	43.68	52.660	58.48	79.1	91.93	99.855
12	14	16	24	4.5	12.96	17.975	32.478	31.48	34.86	39.566	49.64	64.9	75.168	81.648
2	15	24	8	3.5	10.454	17.475	29.885	31.02	34.24	39.141	48.86	52.25	60.633	65.860
15	16	16	16	3.5	14.24	19.819	31.248	44.02	46.84	59.073	63.82	71.2	82.592	89.712
7	17	8	16	4.5	15.1	23.347	32.915	37.62	42.12	51.452	56.7	84.25	87.58	95.13

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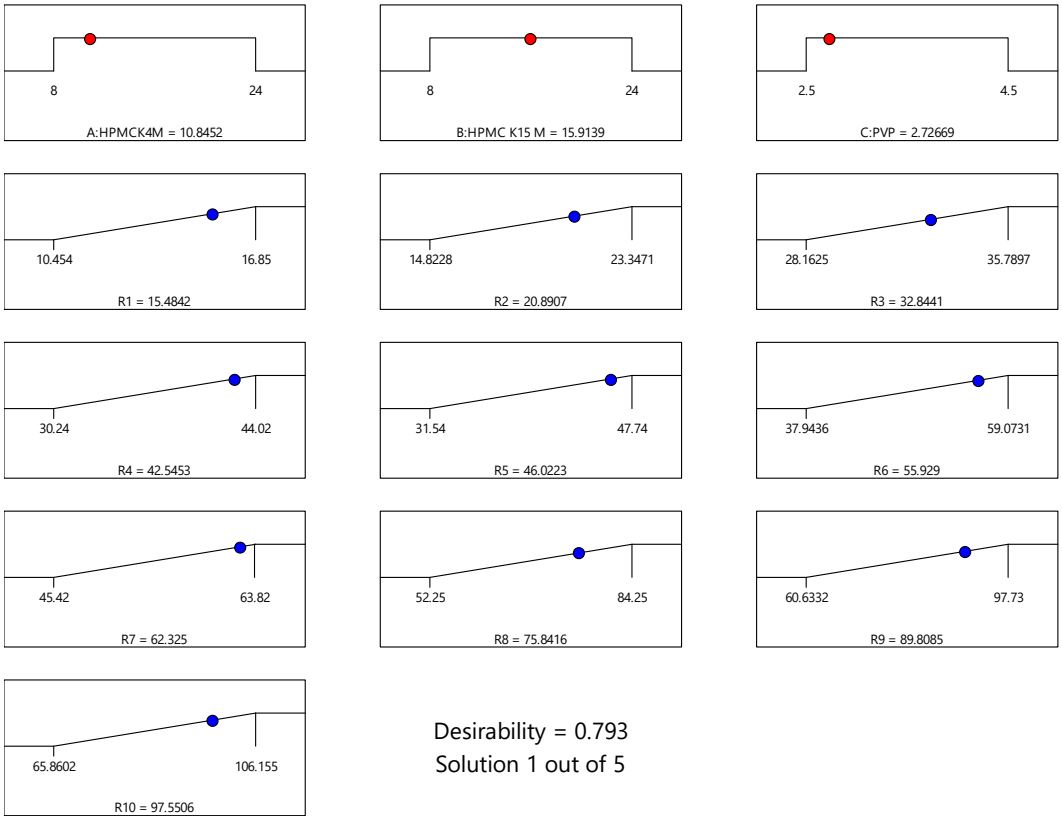

Figure 4. The optimum values of the variables were obtained by the Design-Expert software and based on the criterion of desirability for axitinib sustained release formulations.

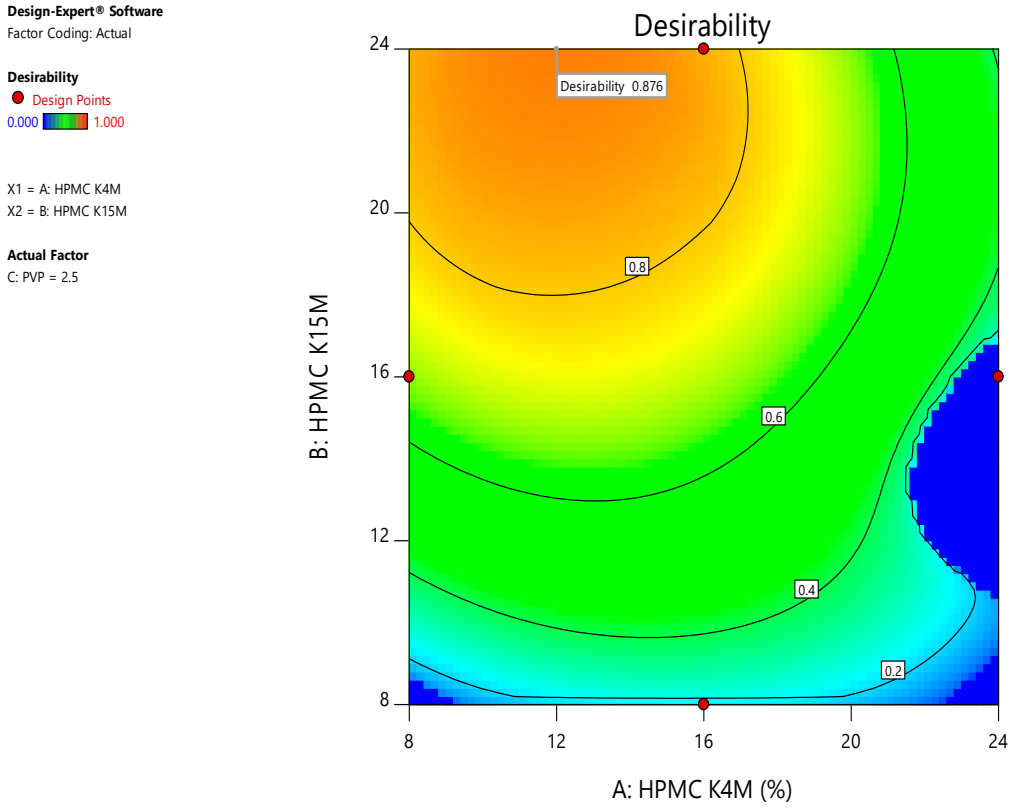

Figure 5. Contour plot for drug release of different time intervals for axitinib sustained release.

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3.4. LC-MS/MS Analysis

Five tablets were weighed and thoroughly powdered, and a weight of powder equal to 10 mg Axitinib was transferred to 10 ml volumetric flask. The contents were dissolved with acetonitrile and filtered. The filtered solutions were diluted to get a Conc.10µg/ml of Axitinib. The linearity range for axitinib was found to be 10,20,30,40, and 50 ng/ml with correlation coefficient (r^2) 0.99. The present method was capable of quantifying the lower concentration of Axitinib accurately. %nominal values for all the standards were within the limits of 98.37–98.68 which was between 80 and 120%, as per the US-FDA guidelines. Initially, acetonitrile, methanol, and buffer species containing ammonium acetate and ammonium formate (each at 20 and 50 mM strength) with differing pH (between 3.0 and 5.0) and variable flow rate (between 0 and 100 mL/min) were used to measure different combinations of mobile phase 0.5 and 2.0 mL/min). Because of the quick chromatographic separation (i.e., lower Rt) seen in Figure 6, preliminary studies proposed using acetonitrile and formate buffer (pH 3.0) as an appropriate mobile phase mixture.

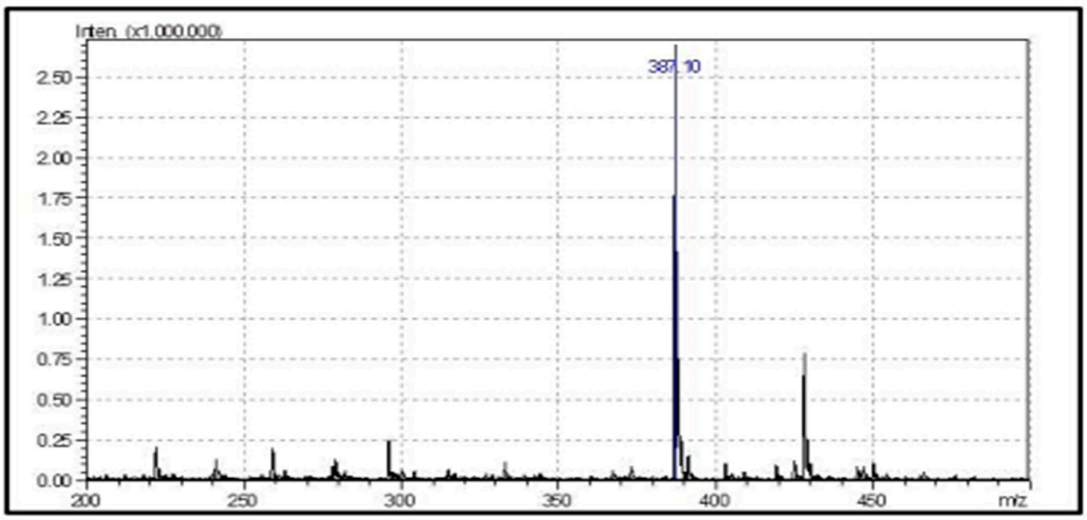

Figure 6. LC-MS-MS of chromatogram of Axitinib.

4. Conclusions

The current study focused on the formulation of sustained release tablets of Axitinib by using HPMC as a matrix forming water soluble polymer. The sustained release formulations were successfully formulated using the wet granulation method. This study has proven that the DoE approach allows quick finding of a formulation having a desired dissolution profile and helps to in experimental design to analyze the influence of formulation factors on the in vitro dissolution behavior. BBD was used to study and optimize effect of formulation variable on dissolutions on different time intervals. The combination of both the HPMC K4M and K15M at different concentrations in the tablets of various formulations (SR-1 to SR-17) was attempted through a response surface approach involving 32 randomize full factorial design to optimize the concentration of HPMC K4M and HPMC K15M. Optimization was performed based on desirability value. The optimized batch sustained release formulations attained the desirable 98.52% drug release with first order kinetics.

Conflict of interest: The authors declare no conflict of interest, financial or otherwise.

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