Development and Optimization of Hydrophilic Matrix Based Molnupiravir Sustained Release Dosage Formulation using Full Factorial Design

Shawkat Islam[1], Nusrath Jahan Fariha[1], Shakil Ahmed[1], Omar Faruk[1] and Abu Shara Shamsur Rouf[2]

[1]Department of Pharmacy, Faculty of Sciences and Engineering, East West University
Dhaka-1212, Bangladesh
[2]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka
Dhaka-1000, Bangladesh

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ABSTRACT: Molnupiravir, an orally administered antiviral drug originally developed for influenza but not approved, inhibits the replication of SARS-CoV-2 and has been repurposed as an antiviral treatment for COVID-19. This research aimed to develop 400 mg sustained release tablets of molnupiravir for a dosage regimen of two tablets every 12 hours using design of experiment (DoE) approach. The study utilized 32 full factorial design, implemented through the use of Design Expert® software. The formulation was optimized using methocel® K15M and povidone K30 as independent variables, with drug release at 2, 8 and 12 h in pH 6.8 phosphate buffer as the dependent variables. An optimal formulation was identified through statistical analysis and empirical evaluation, requiring 6.84% methocel® K15M and 4.27% povidone K30. The sustained release tablets of molnupiravir exhibited release kinetics consistent with the Hixson-Crowell model. The results of this study allowed us to suggest a new tablet dosage form of molnupiravir, with the objective of enhancing both efficacy and adherence in the treatment of COVID-19.

Key words: Molnupiravir, sustained release, hydrophilic matrix, factorial design, DoE.

INTRODUCTION

The availability of a wide range of polymers offers formulation scientists valuable tools for developing sustained release dosage forms (SRDF) that are designed to release medication gradually over an extended period, maintaining a constant or nearly constant plasma drug concentration after administration with improved control over drug levels, enhanced patient adherence and more efficient drug utilization.[1-3]

The matrix system is frequently employed in the production of controlled release dosage forms due to its easier implementation of manufacturing processes.[4] Various polymers have been utilized for retarding drug release, with each polymer offering a distinct approach to the concept of matrix.[5] Hydrophilic matrices are a well-established extended release (ER) delivery platform in the design of sustained release formulations. Commercially available hydroxypropyl methylcellulose (HPMC) polymers, like methocel® K15M CR, are frequently used as rate-controlling polymers during the formulation process.[4-7]

Molnupiravir (MLP), a repurposed drug, was originally developed to treat influenza and has attracted considerable attention for its ability to impair SARS-CoV-2 replication, the causative agent of COVID-19.[8] MLP has been authorized to treat mild to moderate COVID-19 in adults.[9-10] The recommended dose for adult patients is 800 mg, administered as four 200 mg capsules taken orally every 12 h for 5 days.[8–11] Taking multiple capsules

Correspondence to: Abu Shara Shamsur Rouf and Omar Faruk
E-mail: rouf321@yahoo.com; omar.faruk@ewubd.edu

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twice daily can be challenging, leading to non-compliance, especially in patients with swallowing difficulties. High capsule intake may cause gastrointestinal discomfort and fluctuating drug levels, reducing treatment effectiveness and increasing the risk of side effects, particularly during peak concentrations.[12–14] At present, no sustained release formulations of MLP are available.

Experimental design is a systematic approach to investigate how controlled input factors affect responses in a process. By deliberately varying the input factors, DoE facilitates the identification of key factors, the optimization of factor settings to achieve desired responses, and the understanding of interactions between different factors. This methodical approach enables precise control over experimental conditions, leading to more reliable and actionable insights.[15–17]

Designing a formulation with optimal quality in a short timeframe and with minimal trials is crucial during the development of pharmaceutical dosage forms. A precisely controlled dissolution rate is key to optimizing sustained release formulations. To achieve this, computer aided techniques based on response surface methodology (RSM) and factorial design, are commonly employed. This approach requires fewer experimental runs and is more time efficient than conventional formulation methods. In recent years, there has been considerable research focused on the development of tablet formulations, particularly in the realm of oral sustained release drug delivery systems utilizing RSM.[18–19] The current study aimed to develop 400 mg sustained release MLP tablets as an alternative to the current multiple dose regimen utilizing polynomial equation-based Design Expert® software.

MATERIALS AND METHODS

Chemicals and reagents. Molnupiravir (potency = 99.82%) was generously gifted by Incepta Pharmaceuticals Limited, Bangladesh. Microcrystalline cellulose (Avicel PH 101, Mingtai Chemical Co. Ltd., China), dibasic calcium phosphate (Qualikems Fine Chem Pvt. Ltd., India), hydroxypropyl methylcellulose (Methocel® K15M CR, Colorcon, 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. Fourier transform infrared spectroscopy (FTIR) was done to study the compatibility between API and excipients.

Preliminary screenings. Preliminary studies were done by preparing MLP formulations using methocel® K15M CR and povidone K30 at varying ratios (Table 1). The physicochemical properties and dissolution behaviors of these formulations were evaluated according to established protocols. Based on the dissolution rates observed, the upper and lower limits of these two excipients were identified for further investigation.

Preparation of tablets. The active ingredient, polymers, filler, glidant and lubricant were accurately weighed and passed through a no. 40 sieve. All ingredients, except for half of the talc and magnesium stearate, were blended in a laboratory mixer for 10 min. Isopropyl alcohol was added to form a dough, which was then passed through a no. 30 mesh sieve. The wet granules were dried for 50 min, after which the remaining talc and magnesium stearate were mixed in. The granules were then compressed using a rotary tablet press 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 12 h using USP type II (paddle type) dissolution apparatus. The cumulative percentage of drug releases at different time intervals were measured by UV spectrophotometer at 238 nm wavelength using the calibration curve of standard solution.

Experimental design and formulation optimization. Using Design Expert® software (V. 13 Stat-Ease Inc., Minneapolis, USA), 3^2 full factorial experiment was designed (Table 2). The percentages of methocel® K15M CR (Factor A) and povidone K30 (Factor B) were considered as covariates and the percentages of drug release at pH 6.8 phosphate

buffer after 2, 8 and 12 h were used as dependent variables. The experimental design incorporated low, medium and high levels for each covariate, resulting in nine suggested prototype formulations for further study (Table 3).

Table 1. Composition of MLP sustained release matrices during preliminary studies.

Name of the ingredients	Justification of use	Amount (%)	Amount (mg)
Molnupiravir	Active pharmaceutical ingredient	72.73	400
Povidone K30	Binder	1-6	5.5-33
Methocel® K15M CR	Rate controlling polymer	2-12	11-66
Avicel PH 101	Diluent	4.36-13.36	24-73.5
Dibasic calcium phosphate	Diluent	2.90-8.90	16-49
Purified talc	Glidant	1.2	6.6
Magnesium stearate	Lubricant	0.8	4.4

Table 2. Variables and responses for experimental design.

Variables	Levels used actual (coded)		
	Low (-1)	Mid (0)	High (+1)
A = Methocel® K15M CR	5	7.5	10
B = Povidone K30	1	2.5	5
Responses	Constraints		
Q_2 = Cumulative % drug release after 2 h	$0\% \leq Q_2 \leq 25\%$		
Q_8 = Cumulative % drug release after 8 h	$50\% \leq Q_8 \leq 75\%$		
Q_{12} = Cumulative % drug release after 12 h	$80\% \leq Q_{12} \leq 100\%$		

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

Batch	Molnupiravir	Povidone K30	Methocel® K15M CR	Avicel PH 101	Dibasic calcium phosphate	Talc	Mg stearate	Total
F1	400	5.5	27.5	70.67	35.33	6.6	4.4	550
F2	400	5.5	41.25	61.5	30.75	6.6	4.4	550
F3	400	5.5	55	52.33	26.17	6.6	4.4	550
F4	400	13.75	27.5	65.17	32.58	6.6	4.4	550
F5	400	13.75	41.25	56	28	6.6	4.4	550
F6	400	13.75	55	46.83	23.42	6.6	4.4	550
F7	400	27.5	27.5	56	28	6.6	4.4	550
F8	400	27.5	41.25	46.83	23.42	6.6	4.4	550
F9	400	27.5	55	37.67	18.83	6.6	4.4	550

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

RESULTS AND DISCUSSION

Drug excipient compatibility studies. The FTIR spectrum of MLP (Table 4) confirmed the presence of all the desired functional groups.[20] There were no notable changes in the spectra of the drug when compared to the mixtures (Figure 1) suggesting no interactions between the drug and excipients.

Evaluation of granules and tablets. All formulations, except F7, showed excellent flowability of their granules (Table 5). All the tablets showed consistent size, weight and hardness (Table 6). All batches had a percentage friability below 1%, which suggests that the friability values were within the specified limits.

***In vitro* dissolution studies of F1-F9 formulations.** The dissolution profile for nine batches (Table 7) exhibited a range of variations. The initial 2 h release varied from 6.15 to 10.5%, while the drug released after 8 h ranged from 46.66 to 71.88% and the drug released after 12 h ranged from 76.42 to 96.03%. The dissolution data served as the basis for analysis, leading to the development of the optimal formulation.

Table 4. FTIR band positions of MLP.

Observed frequency (cm^{-1})	Standard frequency (cm^{-1})	Peak assignment
3500-3600	3300 – 3500	O-H
3368.48	3400 – 3650	N-H
1684.66	1685 – 1650.	C=O
1121.82	1050 -1150	C-O
1029.77	1030 – 1230	C-N
1448.65	1470 – 1430	$-CH_3$
1381.19	1380.9–1142.5	Pyrimidine ring

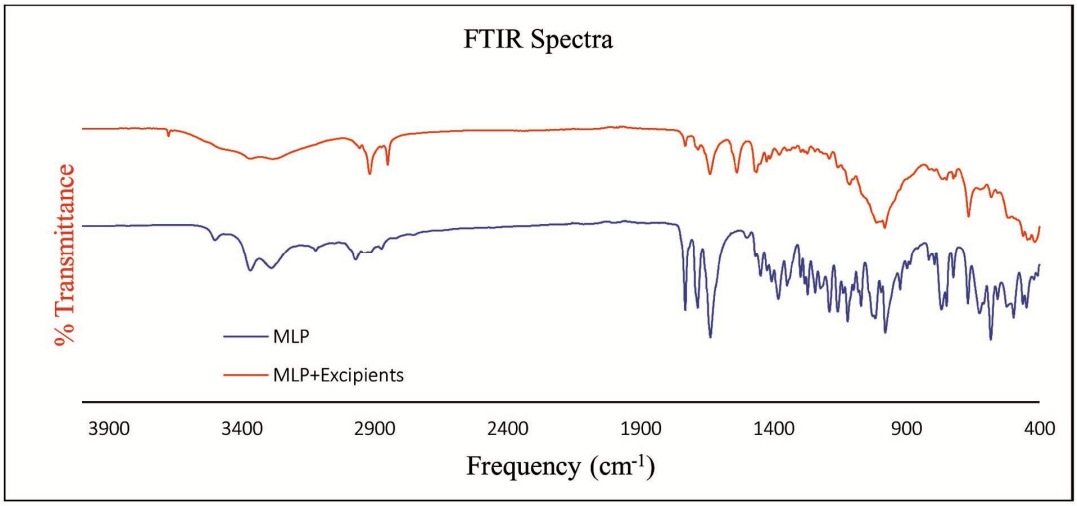

Figure 1. FTIR spectra of MLP and MLP/excipient combinations (1:1).

Table 5. Results of the evaluation of flow properties.

Batch	Hausner ratio	Carr's index (%)	Angle of repose (°)	Flow character
F1	1.04	4	17.10	Excellent
F2	1.03	3.06	15.48	Excellent
F3	1.09	8.77	23.30	Excellent
F4	1.06	5.66	24.78	Excellent
F5	1.04	3.70	21.04	Excellent
F6	1.06	5.36	27.61	Excellent
F7	1.11	10.17	30.31	Good
F8	1.05	4.93	23.30	Excellent
F9	1.06	5.59	28.98	Excellent

Table 6. Results of the evaluation of physical properties of tablets.

Batch	Length ± % RSD*	Width ± % RSD	Thickness ± %RSD	Average weight (mg) ± %RSD	Hardness (kg/cm^2)	Friability (%)
F1	17.25 ± 0.06	8.51 ± 0.09	6.12 ± 0.06	563.31 ± 0.08	11.2	0.27
F2	17.24 ± 0.04	8.52 ± 0.10	6.11 ± 0.05	575.76 ± 0.05	11.34	0.26
F3	17.16 ± 0.02	8.56 ± 0.04	6.06 ± 0.03	564.92 ± 0.04	11.30	0.19
F4	17.21 ± 0.05	8.53 ± 0.06	6.10 ± 0.04	570.67 ± 0.06	12.01	0.32
F5	17.25 ± 0.07	8.52 ± 0.08	6.11 ± 0.05	573.46 ± 0.05	11.07	0.33
F6	17.22 ± 0.04	8.53 ± 0.06	6.10 ± 0.04	566.82 ± 0.06	12.07	0.28
F7	17.17 ± 0.03	8.56 ± 0.05	6.07 ± 0.01	568.53 ± 0.03	11.05	0.29
F8	17.18 ± 0.05	8.55 ± 0.05	6.08 ± 0.02	567.72 ± 0.07	11.09	0.34
F9	17.19 ± 0.04	8.54 ± 0.06	6.09± 0.02	567.72 ± 0.07	11.04	0.22

*RSD-Relative standard deviation

Table 7. *In vitro* dissolution studies of F1-F9 formulations.

Time (hr)	Cumulative % of drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	10.5	9.48	8.74	7.9	7.62	7.31	7.12	6.81	6.15
8	71.88	63.76	56.34	55.3	54.13	53.47	52.51	47.23	46.66
12	96.03	91.53	90.23	89.13	86.34	83.11	81.66	78.13	76.42

Table 8. ANOVA summary and regression analysis for response variables.

ANOVA for the responses									
	R1			R2			R3		
Source	SS*	F	P	SS	F	P	SS	F	P
Model	13.30	20.79	0.0020	413.63	14.64	0.0049	334.36	189.21	<0.0001
A	1.84	5.75	0.0535	89.86	6.36	0.0452	48.51	54.90	0.0003
B	11.46	35.84	0.0010	323.77	22.91	0.0030	285.86	323.52	<0.0001
Residual	1.92			84.77			5.30		
Corrected total	15.22			498.40			339.66		
Fit statistics				Regression equation					
Source	R1	R2	R3	R1 = +11.55673 -0.221333A-0.683946B					
SD**	0.5655	3.76	0.9400	R2 = +77.60762-1.54800A-3.63524B					
Mean	7.96	55.70	85.84	R3 = +104.05027-1.13733A-3.41578B					
CV***	7.10	6.75	1.10						
AP****	11.7694	10.2669	35.654						

*SS-Sum of squares; **SD-Standard deviation; ***CV-Coefficient of variation; ****AP-Adequate precision.

Response analysis. The ANOVA results (Table 8) showed that the model strongly impacted all three response variables (R1, R2, R3). The model explained a significant amount of the variance, as seen in the F-values (20.79, 14.64 and 189.21) and the corresponding p-values (0.0020, 0.0049 and <0.0001). Factor B consistently demonstrates a robust and highly significant impact on all responses. The F-values (35.84 for R1, 22.91 for R2 and 323.52 for R3) are remarkably high, while the P-values are extremely low (all <0.01). These findings highlight the dominant role of Factor B in influencing the outcomes. Factor A, however, has a noteworthy impact on R2 (F = 6.36, P = 0.0452) and R3 (F =

54.90, P = 0.0003), but only a marginal effect on R1 (F = 5.75, P = 0.0535), indicating that its influence differs across the various responses. The residual variance is quite small, suggesting a strong fit of the model. This is reinforced by the high adequate precision values for all responses, which assure us that the model's predictions are dependable. Based on the regression equations, it is evident that both factors have a negative impact on the response values. The impact of the variables on the response is illustrated in figures 2, 3 and 4.

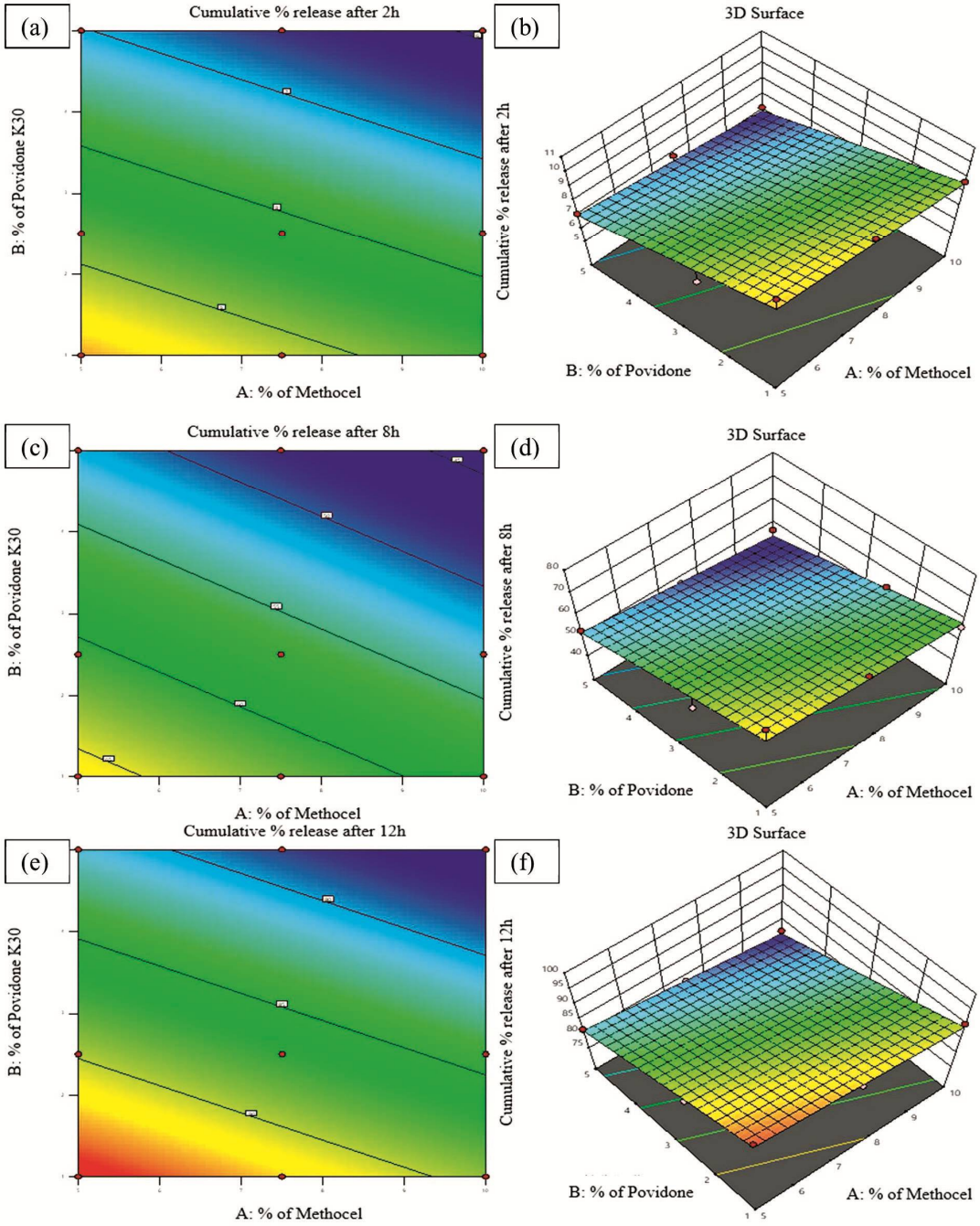

Figure 2. Two dimensional contour plot and three dimensional surface response plot for drug release after 2h (a, b), 8 h (c, d) and 12 h (e, f).

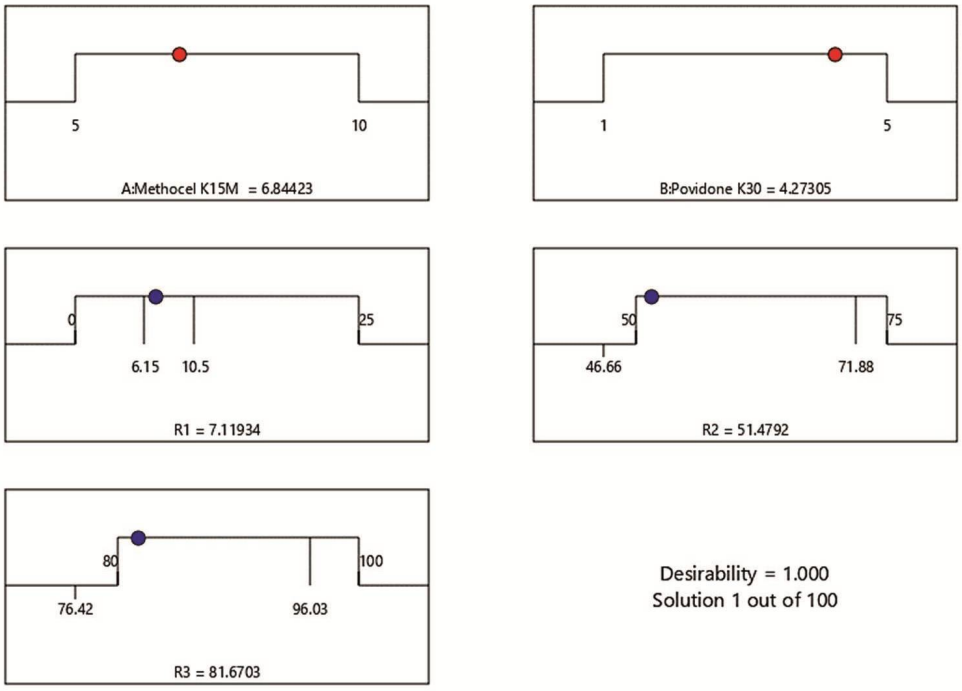

Figure 3. Levels of independent variables in theoretical optimized formulation with predicted response.

Table 9. Predicted and observed responses of the optimized formulation.

Responses	Predicted	Observed	Predicted error*	Remarks
Q_2	7.119	7.10	0.267%	Satisfactory
Q_8	51.479	51.33	0.289%	Satisfactory
Q_{12}	81.670	80.99	0.833%	Satisfactory

Predicted error* = (observed value-predicted value)/observed value × 100%; Tolerance = ±2%.

Formulation optimization. Figure 5 illustrated the results of an optimization analysis where the factors methocel® K15M and povidone K30 were adjusted to achieve optimal outcomes for three response variables (R1, R2 and R3). The optimal levels were found to be approximately 6.84% for methocel® K15M and 4.27% for povidone K30. These settings lead to predicted response values of 7.12 for R1, 51.48 for R2, and 81.67 for R3. The overall desirability score of 1.000 indicates that this combination of factor levels perfectly satisfies the desired criteria for all responses, making it the optimal solution out of 100 possible solutions. Table 9 presents the observed experimental values of the responses along with the percentage errors calculated from the predicted values.

***In vitro* drug release kinetics studies.** The optimized tablet batch exhibited the highest R^2 value of 0.9719 in the Hixson-Crowell model. Graphs for *in vitro* release kinetics studies are provided in figure 6.

Despite its efficacy in the treatment of COVID-19, sustained release (SR) tablet formulations of molnupiravir are not yet available in either national or international markets, probably due to shifting of the research priorities as the pandemic subsided. The urgency of the COVID-19 pandemic necessitated the focus on immediate-release (IR) formulations, which although effective, are associated with limitations such as fluctuating plasma concentrations, increased risk of adverse effects during peak levels and reduced patient adherence due to the high dosing frequency of four 200 mg capsules every 12 hours. In

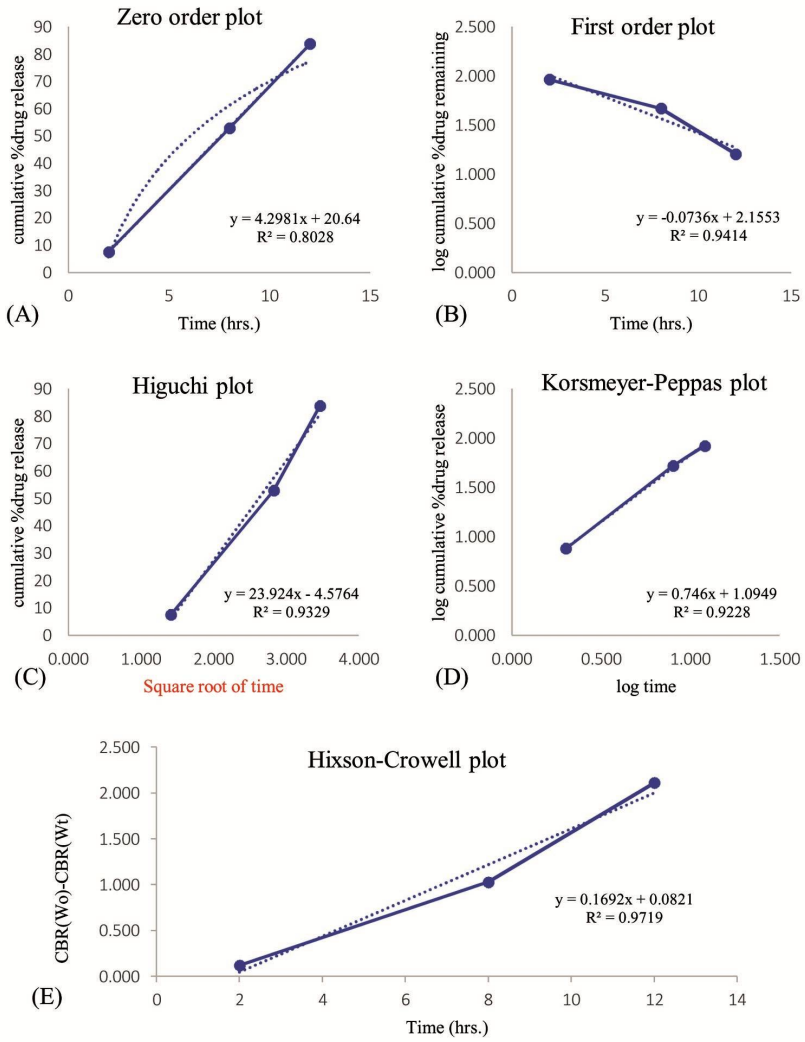

Figure 4. Release kinetics of the optimized batch in (A) Zero order, (B) First order, (C) Higuchi, (D) Korsmeyer-Peppas and (E) Hixson-Crowell plot.

this study, these challenges were addressed through the development of an SR tablet using a hydrophilic matrix system. Methocel® K15M served as a rate-controlling polymer and formed a gel matrix to modulate drug release. Employing a 3^2 full factorial design, the formulation was systematically optimized for drug release at 2, 8 and 12 hours. It demonstrated a release profile consistent with the Hixson-Crowell model, which ensured uniform and predictable drug release. The optimized formulation developed in this study offered a dosage regimen of two 400 mg tablets every 12 hours, thereby reducing the dosing frequency, ensuring stable therapeutic levels and enhancing patient compliance.

CONCLUSION

A novel sustained release formulation of molnupiravir was successfully developed using a combination of excipients. The formulation was optimized by utilizing 3^2 full factorial design in Design Expert® software, which allowed for systematic evaluation of various factors and their interactions. The formulation optimization process based on the DoE approach led to the development of

an optimized formulation that exhibits optimal drug release characteristics. The research findings also highlighted the significance of meticulously selecting suitable excipients and optimizing their levels in order to attain the intended drug release characteristics.

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CONFLICT OF INTEREST

Not applicable.

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