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Research Article

PREPARATION AND OPTIMIZATION OF ONCE DAILY QUETIPINE FUMARATE SUSTAIN RELEASE TABLETS

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ABSTRACT

Objective: Quetiapine fumarate (QF) belongs to the atypical antipsychotic class. The elimination half-life of QF is 6 h necessitates the development of sustain release (SR) formulation. In the current research, two polymers, HPMC K100M and Polyox WSR N80, were used in combination as per the central composite design (CCD) with an objective of sustained drug release for 24 h with low initial burst release.

Methods: The SR matrix tablets of QF were prepared by wet granulation method. Fourier transform infrared and differential scanning calorimetry study for the physical mixture of QF with HPMC K100M and Polyox WSR N80 in 1:1 ratio demonstrated compatibility between the drug and polymers. The selection of the optimum formulation highlights the precision of CCD in optimizing the formulation parameters to achieve the desired release profile.

Results: The integration of two polymers, HPMC K100M (58.2 mg/tablet) and Polyox WSR N80 (44.8 mg/tablet), proved effective in modulating the drug release dynamics. Specifically, the polymers synergistically contributed in attaining the desired responses *vis-à-vis* Q_1 9.73%, t_{50} 10.45 h, and Q_{18} 82.46%, thereby ensuring minimized initial burst release and sustained release of QF over 24 h.

Conclusion: The development of a once-daily formulation aligns with modern patient-centric approaches in pharmaceutical design, catering to convenience and improving quality of life for patients requiring long-term therapy.

Keywords: *In vitro* dissolution, HPMC K100M, Polyox WSR N80.

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INTRODUCTION

Quetiapine fumarate (QF) belongs to the atypical antipsychotic class [1]. It is primarily used in the treatment of several psychiatric conditions, including schizophrenia, bipolar disorder (both manic and depressive episodes), and as an adjunct for major depressive disorder [2]. Atypical antipsychotics like QF act on multiple neurotransmitter receptors, particularly dopamine and serotonin receptors, which underpin their therapeutic benefits and side effect profiles [3]. QF is predominantly metabolized in the liver by the cytochrome P450 enzyme CYP3A4. The recommended starting dose for adults is 25 mg taken orally twice daily [4]. The extended-release formulation of QF is most commonly marketed under the brand name Seroquel XR. In many markets, Seroquel XR is available as filmcoated tablets in several dosage strengths, with common strengths being 50 mg, 150 mg, and 300 mg. The oral bioavailability of QF is generally around 9% [5]. This means that although the drug is well absorbed from the gastrointestinal tract, a large portion of it is metabolized during its first passage through the liver, primarily via the CYP3A4 enzyme system, before reaching systemic circulation. The elimination half-life of QF is 6 h. The partition coefficient (logP) of QF is 2.8. Quetiapine, when formulated as QF, exhibits a pKa of approximately 7.0, which pertains to the ionizable tertiary amine group within the quetiapine structure [6]. Its short half-life necessitates the development of extended release formulation.

Matrix tablets offer excellent control over the drug release rate. By adjusting the composition of the matrix using different polymers, formulators can fine-tune how quickly the drug is released [7]. Matrix tablets tend to have better physical and chemical stability. The matrix can protect the active pharmaceutical ingredient from environmental factors like moisture and light. These tablets are versatile and can accommodate a wide range of drugs with different solubility profiles. Whether dealing with a water-soluble drug or a poorly soluble one, the matrix system can be adapted accordingly [8-10]. HPMC K100M-based matrix tablets, when exposed to gastrointestinal fluids, HPMC hydrates rapidly and forms a robust, viscous gel layer [11]. This gel acts as a barrier, primarily controlling drug release through diffusion [12]. It also contributes good compressibility and helps maintain mechanical strength. Polyox WSR N80, due to very high molecular weights, tends to form a viscoelastic sticky gel. Its slower erosion and dissolution properties help extend the drug release profile. Polyox can improve the pliability and overall stability of the matrix, which can be especially beneficial for drugs that require very prolonged release [13-15]. The combination of HPMC K100M and Polyox WSR N-80 offers a synergistic approach to sustained drug delivery. While Polyox provides rapid hydration and early gel formation, HPMC K100M ensures long-term matrix stability and controlled erosion [16]. This complementary behavior helps in minimizing initial burst release and maintaining a uniform drug release profile over an extended period. Furthermore, the blend allows fine-tuning of release kinetics by adjusting polymer ratios, enabling the formulation of dosage forms with desired release characteristics. Hence, in the current research, two polymers, HPMC K100M and Polyox WSR N80, were used in combination as per the central composite design (CCD) with an objective of sustained drug release for 24 h with minimized initial burst release.

MATERIALS AND METHODS

Material

Quetiapine fumarate (QF) was acquired as a complimentary sample from Akshar Pharmaceuticals, Gujarat. HPMC K100M was received as a gift sample from Colorcon, India. Polyox WSR N80 was procured from

ChemPoint, India. Avicel PH101, Talc, aerosil and starch were procured from Himedia, India.

Methods

Drug excipient compatibility study

Fourier transform infrared (FT-IR) study

FT-IR spectroscopic analysis was performed for pure drug QF and its physical mixtures with HPMC K100M and Polyox WSR N80 alone and also in combination in 1:1 (W/W) ratio (10 mg of total sample) using IR Affinity, Shimadzu, Japan.

Differential scanning calorimetry (DSC) study

Thermal analysis was performed for pure drug QF and its physical mixtures with HPMC K100M and Polyox WSR N80 alone and also in combination (1:1 W/W) ratio using DSC-60, Shimadzu, Japan. The DSC study was performed for 10 mg of sample with a rate of rise in temperature of 10°C/min up to 250°C under a nitrogen atmosphere.

Preparation of QF sustain release (SR) matrix tablets

The SR matrix tablets of QF were prepared by wet granulation method. In the first step, the drug and excipients were passed through sieve number 60. The drug, polymers (HPMC K100M and Polyox WSR N80), and other excipients as per Table 1 were dry mixed for 10 min in a mortar and pestle. During dry mixing, Avicel PH101 was also added as diluent. The wet binder solution (starch paste 10% W/V) was added (15 mL) to the dry mix, and wet mixing was continued till the formation of damp mass. The wet damp mass was passed through sieve no 16 to obtain granules. The wet granules were transferred to fluidized bed dryer and dried under fluidized hot air stream at a temperature of 70°C for 15 min. The dried granules were again passed through sieve number 20. The amount of starch transmitted from the starch paste to the granules was approximately 15 mg/tablet. The lubricants talc and aerosil were mixed with dried and sieved granules for 5 min. The lubricated granules were compressed into circular, flat tablets of 8 mm diameter using Mini Press II, Karnavati, India. The batch size for each formulation was 100 tablets.

Optimization of QF SR matrix tablets was achieved through CCD utilizing Stat-Ease's Design Expert software (version 13.0) from Minneapolis, USA. Based on the recommended design, thirteen formulations were created and evaluated for important quality characteristics. Using the response surface approach, contour plots and three-dimensional plots were produced. To identify the relevant model factor, an ANOVA was employed. Critical quality attributes (CQAs) were optimized using upper and lower bounds. The coded factor levels for HPMC K100M per tablet were −1 (20 mg), 0 (40 mg), and +1 (60 mg). Similarly, the coded values for PolyoxWSR N80 per tablet were -1 (30 mg), 0 (40 mg), and +1 (50 mg). The design space was defined using an overlay plot. Three responses selected for optimization of research were *vis-à-vis* Q_1 (Cumulative percent drug release from SR matrix tablet in 1 h), t_{50} (time taken for release of 50% of QF) and Q_{18} (Cumulative percent drug release from SR matrix tablet at 18 h), The t_{50} value reflects the mid-point of the drug release profile, where the combined effects of polymer hydration, gel formation, diffusion, and matrix erosion are most active and balanced. At this stage, the release rate is highly responsive to variations in polymer type, polymer ratio, and matrix composition.

Micromeritic properties of granules

The pure drug QF powders and granules of all the formulations were subjected for evaluation of micromeritic properties. The following tests, such as angle of repose, Carr's index, Hausner's ratio, granular friability index (GFI) [17], and moisture content [18], were determined as per standard procedure [19,20].

Quality control tests for tablets

The following quality control tests, such as drug content, hardness, friability, thickness, and diameter of QF tablets, were determined as per standard procedure [21].

In vitro dissolution study

An in vitro dissolution test was performed for the optimized formulation for 24 h. In this study, 900 mL of 0.1 N HCl was used as dissolution medium for 1st 2 h, followed by phosphate buffer pH 6.8 for remaining 22 h. The dissolution was performed in paddle type apparatus with 100 rpm maintained at a temperature of 37±0.5°C. The sink conditions are maintained in the entire duration of dissolution as QF is having solubility of nearly 35.8 mg/mL and 2.2 mg/mL in 0.1 N HCl and phosphate buffer pH 6.8, respectively. The requirement of sink condition was maintained as concentration of QF in bulk (Cb) is <10% of saturation solubility (Cs). The dissolution samples diluted and analyzed spectrophotometrically at 239 nm [22]. The drug dissolution data were put into zero order, first order, Higuchi, and Korsmeyer-Peppas equation for analyzing drug release kinetics and mechanism of drug release.

Stability study

The stability study for the optimized tablet formulation kept in closed glass container was performed as per ICH guidelines [23,24] (Q1A[R2]) at 40°C±2°C/75% RH±5% RH for 6 months in a humidity-controlled oven (90L, Stability Chamber, Thermolab, India). Samples were collected at 0, 1, 3, and 6 months time intervals and analyzed for drug content, Q_1, t_{50}, and Q_{18}.

Table 1: Composition of SR matrix tablets of quetiapine fumarate as per central composite design

Run	Factor 1 HPMC K100 M	Factor 2 Polyox WSR N80	Response 1 (Q_1)	Response 2 (t_{50})	Response 3 (Q_{18})
1	0	−1.41421	14.69	7.56	100
2	−1	−1	18.56	6.5	100
3	−1	1	15.36	9.54	95.6
4	1	1	7.59	12.5	81.5
5	0	0	15.24	8.2	92.5
6	0	0	14.65	8.2	93.5
7	0	0	14.87	8.5	91.4
8	−1.41421	0	18.54	6.8	100
9	0	0	14.37	8.4	91.6
10	1	−1	11.24	10.5	90.5
11	0	1.41421	9.62	10.5	88.6
12	0	0	15.13	8.3	92.6
13	1.41421	0	8.61	11.6	74.5

Factors	Low (-1)	Medium (0)	High (+1)
Concentration of HPMC K100M (mg)	20	40	60
Concentration of Polyox WSR N80 (mg)	30	40	50

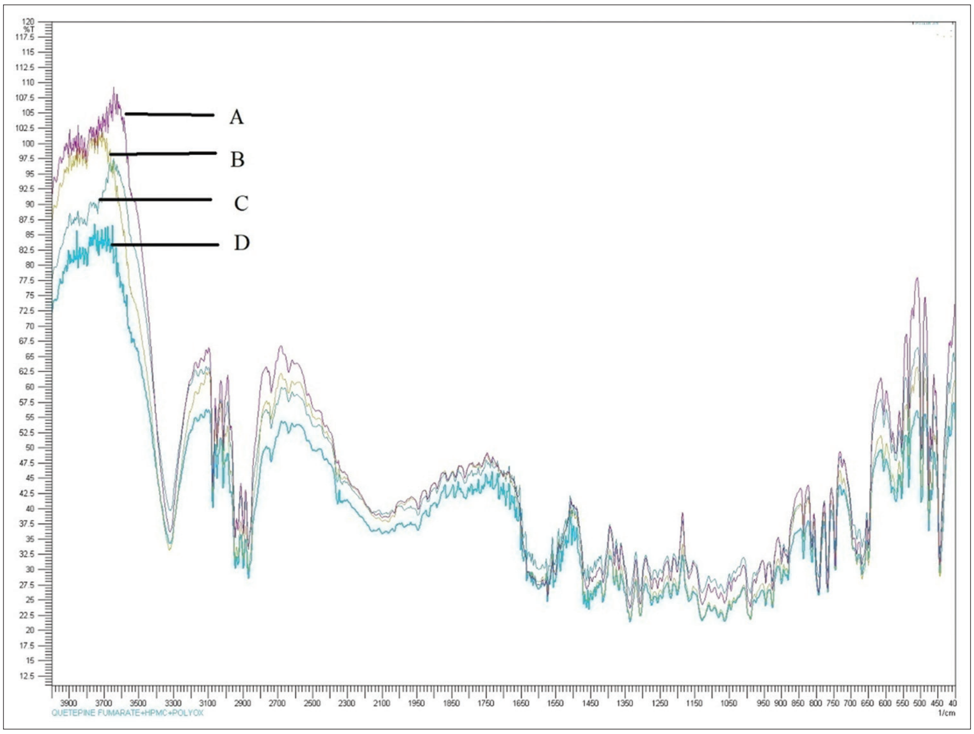

Fig. 1: Fourier transform infrared spectra for QF (A), PM of QF with HPMC K100M (1:1) (B), QF with Polyox WSR N80 (1:1) (C), and QF with HPMC K100M (1:1) and Polyox WSR N80 (1:1:1) (D)

RESULTS AND DISCUSSION

FT-IR study

FT-IR study for pure drug QF confirms the presence of the following functional groups by analyzing absorption bands (Fig. 1). The broad peak at 3050 cm^{-1} and 2849 cm^{-1} corresponds to aromatic C-H stretching and aliphatic C-H stretching, respectively. Peaks at 1698 cm^{-1}, 1435 cm^{-1}, 1280 cm^{-1}, and 1110 cm^{-1} are due to aromatic C=C stretching, C-H bending, C-N stretching, and C-O stretching, respectively. The PM of QF with HPMC K100M and polyox WSR N80 alone and also in combination exhibited absorption bands in the similar region, suggesting the compatibility between QF and polymers used in this study.

Differential scanning calorimetry (DSC) study

The thermogram for QF exhibited a sharp melting peak at 180.7°C with onset and endset temperature of 173.9°C and 185.6°C, respectively. This narrow melting temperature range with sharp peak clearly indicates that QF is a crystalline drug. The PMs of QF with HPMCK100 M (1:1), QF with polyox WSR N80 (1:1), and the PM of QF, HPMCK100 M, and polyox WSR N80 (1:1:1) demonstrated peaks at 179.9°C, 173.1°C, and 179.7°C, respectively. The peaks for all three PMs were nearer to the peak of QF, suggesting no incompatibility between the drug and polymers (Fig. 2). All the PMs exhibited lower enthalpy in comparison to the enthalpy of QF [25].

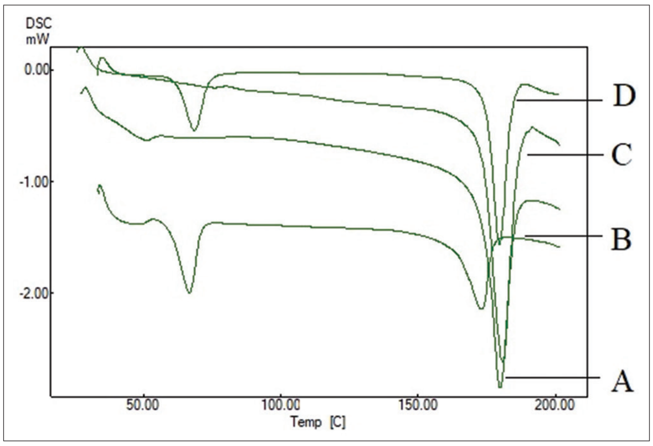

Fig. 2: Differential scanning calorimetry thermogram for QF (A), PM of QF with HPMC K100M (1:1) (B), QF with Polyox WSR N80 (1:1) (C), and QF with HPMC K100M and Polyox WSR N80 (1:1:1)

Preparation of QF SR matrix tablets

The QF SR matrix tablets were produced successfully with a yield more than 97%, suggesting proper selection of processing parameters such as dry mixing time, wet mixing time, amount of binder, less adhesion of wet mass to sieves, drying time, and temperature, and optimum mixing of lubricants [26].

Characterization of QF SR matrix tablets

Response surface analysis

Fig. 3 features a contour plot alongside a 3D representation of the Q_1 response, that is, cumulative percent drug release at 1 h. The value of Q_1 ranges from 7.59% (run 4) to 18.56% (run 02). The desirability of Q_1 was targeted in the range of 8–10% in 1 h of dissolution study. The following runs, that is, 11 (high levels [1.414] of polyox WSR N80) and 13 (with high levels [1.414] of HPMC K100M), were able to control the release of QF in the percentage range of 8–10%. The initial burst release was well controlled by increased concentration of HPMCK100 M and polyox WSR N80. A higher HPMC K100M and Polyox WSR N80 content might favor diffusion-controlled release due to the formation of a more robust gel [8,11,27,28].

Fig. 4 features a contour plot alongside a 3D representation of the t_{50} response, that is, time taken for dissolution of 50% QF. The value of t_{50} ranges from 6.5 (run 2) to 12.5 h (run 4). The desirability for dissolution of 50% of the drug was fixed in the range of 8 to 11 h. It was observed that an increase in the concentration of both polymers resulted in a delay in the time to reach the time for 50% of cumulative drug release. The desirability for t_{50} was attained only by 3 formulations, that is, Run 3

(-1 level of HPMC K100M and +1 level of polyox WSR N80), 10 (+1 level of HPMC K100M and -1 level of polyox WSR N80), and 11 (0 level of HPMC K100M and +1.414 level of polyox WSR N80).

Fig. 5 features a contour plot alongside a 3D representation of the Q_{18} response, that is, cumulative percent drug released in 18 h. The cumulative percent drug release ranges from 74.5 (run 13) to 100

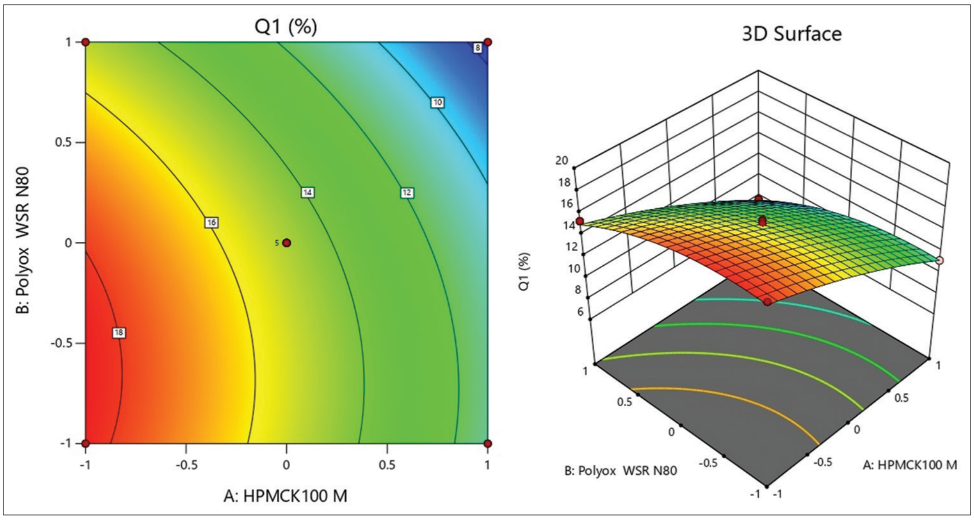

Fig. 3: Contour plots and 3D-response surface plot showing the influence of significant factors on cumulative % drug release at 1 h (Q_1)

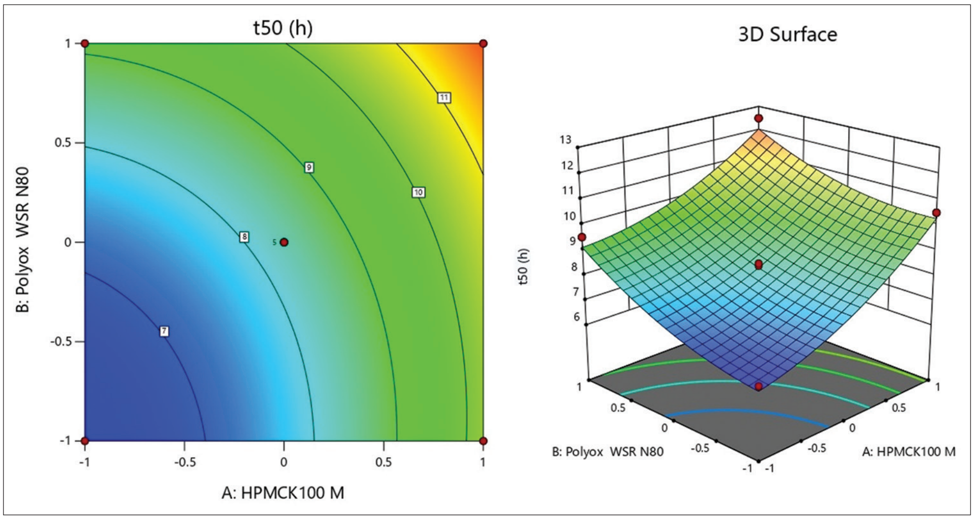

Fig. 4: Contour plots and 3D-response surface plot showing the influence of significant factors on time taken for release of 50% drug (t_{50})

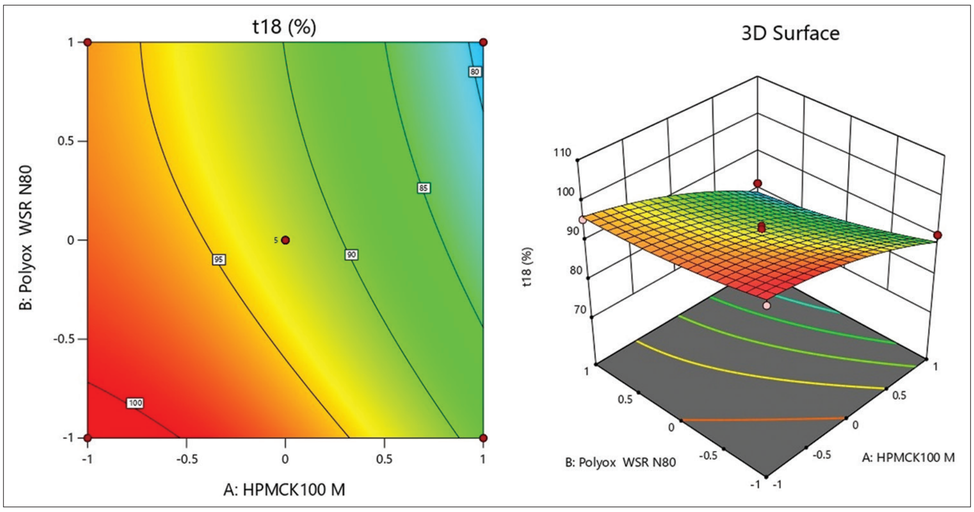

Fig. 5: Contour plots and 3D-response surface plot showing the influence of significant factors on cumulative % drug release at 18 h (Q_{18})

Table 2: Summary of ANOVA for different factors

Source	Q_1		t_{50}		Q_{18}	
	F value	p value	F value	p value	F value	p value
Model	233.02	<0.0001	53.63	<0.0001	33.28	<0.0001
A-HPMC K100M	864.46	<0.0001	165.22	<0.0001	121.01	<0.0001
B-Polyox WSR N80	200.20	<0.0001	73.95	<0.0001	29.63	0.0010
AB	0.4125	0.5412	1.89	0.2115	1.44	0.2694
A^2	17.64	0.0040	17.59	0.0041	9.61	0.0173
B^2	91.12	<0.0001	12.96	0.0087	3.06	0.1239

Table 3: Summary of design of experiment with various parameters fitting to quadratic model

Responses	Q_1	t_{50}	Q_{18}
R^2	0.9940	0.9746	0.9596
Adjusted R^2	0.9898	0.9564	0.9308
Predicted R^2	0.9769	0.8287	0.7379
Adequate Precision	47.7597	22.3290	18.4766
Standard deviation	0.3503	0.3782	1.92

(run 1, 2, and 8). The desirability was fixed in the range of 80–95% of cumulative percent drug dissolution at 18th h. The desired response for Q_{18} was obtained in runs 5, 6, 7, 9, and 11, where both polymers were present at medium levels. The desirability for Q_{18} was also attained by run 4 (+1 level of HPMC K100M and +1 level of polyox WSR N80), 10 (+1 level of HPMC K100M and -1 level of polyox WSR N80), and 11 (0 level of HPMC K100M and +1.414 level of polyox WSR N80).

ANOVA of experimental design

For each response, Q1, t_{50}, and $Q_{18,}$ a regression equation based on coded factors was derived. This model enables the prediction of the relative influence of each factor. Below are the quadratic equations obtained from the regression analysis for each CQA.

$$Q1 = 14.84 - 3.64A - 1.75B - 0.1125AB - 0.5509\,A^2 - 1.26\,B^2$$

$$t_{50} = 8.32 - 1.724 + 1.15\,B - 0.2600\,AB + 0.6013\,A^2 + 0.5163\,B^2$$

$$Q_{18} = 92.32 - 7.46\,A - 3.69\,B - 1.15\,AB - 2.25\,A^2 + 1.27\,B^2$$

Table 2 summarizes the ANOVA results, highlighting the significance of various factors in our quadratic model. Analysis of the design matrix reveals that the model's F-value and p-value substantiate its significance for Q_1, t_{50}, and Q_{18}. For the Q1 response, the analysis revealed that the factors A (HPMC K100M), B (Polyox WSR N80), along with their squared terms (A^2 and B^2), were statistically significant ($p<0.001$); however, the interaction of AB was not significant. Similarly, for the t50 and Q18 response, A, B, AB, A^2, and B^2 emerged as significant contributors. Table 3 provides a summary of the CCD quadratic model employed during the optimization of the QF matrix tablets.

Optimization and construction of overlay plot

For optimization, target specifications were set for responses Q_1, t_{50}, and Q_{18}. The constraints in the process of optimization are presented in Table 4. Fig. 6 shows the overlay plot within the design space and illustrates the final optimized QF SR matrix tablet. The optimal single-dose SR tablet, developed using CCD, comprises 50 mg of QF, 58.2 mg of HPMC K100M, 44.8 mg of Polyox WSR N80, and additional excipients including starch paste (10% W/V), 20 mg of Avicel PH102, 4 mg of talc, and 2 mg of aerosil. Table 5 presents the composition of optimized formulation suggested by CCD.

Micromeritic properties of granules

The evaluation of micromeritic properties of pure drug powder QF suggests that it is poorly flowable drug and it needs to be

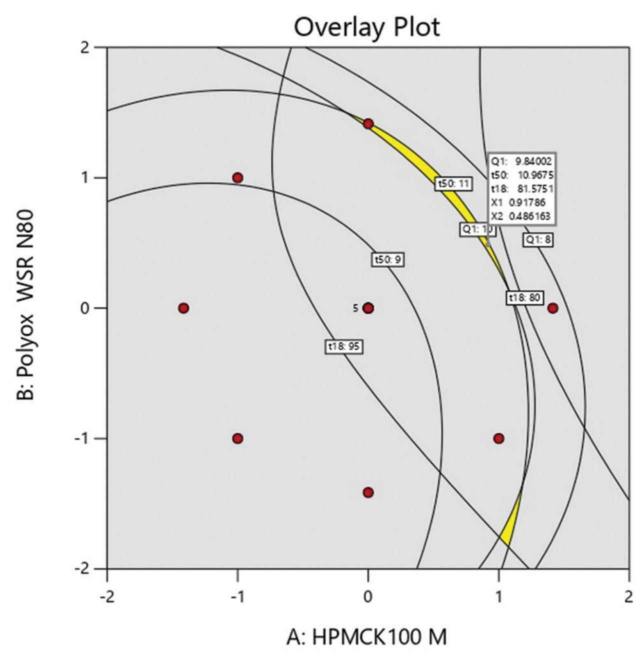

Fig. 6: Overlay contour plots depicting the design space and delineate the optimized formulation of Quetiapine fumarate sustain release matrix tablets

granulated for improvement of flowability and compressibility (Table 6). All the 13 formulations showed micromeritic properties desirable for proceeding to the next process that is compression. The improvement in micromeritic properties suggests that the selection of binder, concentration of binder, sieve number, and lubricating agent, etc., were appropriate, achieving desirable flowability and compressibility [29,30]. GFI <1% for all 13 formulations also suggests the selection of starch paste as the right binder in the right proportion [31].

Quality control tests for tablets

All13 tablet formulations passed the quality control tests for tablets as the values were within the official specifications (Table 7). The drug content for all formulations was above 95 % suggests uniform mixing of drug with excipients. Weight variation or deviation was within the allowed specification, that is, ±7.5%. Hardness for all formulations was above 5 Kg/cm2, and the percent loss in weight in friability test was <1%, suggesting optimum selection of binder. Hence, the prepared passed the quality control tests.

***In vitro* dissolution study**

In vitro dissolution study for all the formulations was performed, and it was found that Runs 1, 2, 3, and 8 could not sustain the release of QF for more than 18 h. The reason attributed can be because of a lower proportion of either HPMCK 100M or polyox WSR N80. All other formulations exhibited QF release for 24 h in a sustained manner. By considering the initial burst release and time for 50% of release of

Table 4: Constrains for the process of optimization

Name of factor	Lower limit	Upper limit	Optimized coded value	Optimized actual value
A-HPMC K100M	20	60	0.918	58.2
B-Polyox WSR N80	30	50	0.486	44.8
Responses (CQA)	**Desirable lower limit**	**Desirable upper limit**	**Predicted responses**	**Experimental responses**
Q_1	8	10	9.81854	9.73
t_{50}	9	11	10.9982	10.45
Q_{18}	80	95	81.3047	82.46

Table 5: Composition of optimized SR tablet of quetiapine fumarate

Name of the ingredient	Quantity per tablet (mg)	Quantity per 50 tablets (g)
Quetiapine Fumarate	50	2.5
HPMC K100M	58.2	2.91
Polyox WSR N80	44.8	2.24
Avicel PH 101	20	1.0
Starch paste (10% W/V)	21	1.05
Talc	4	0.2
Aerosil	2	0.1
Total	200	10.0

QF, the composition for optimized formulation was suggested by the design, which did not include any of the suggested 13 formulations. The composition of optimized run is given in Table 5. The dissolution profile of optimized run is presented in Fig. 7. The release mechanism of QF from optimized run can be attributed to the release of QF by the complex interplay of diffusion and polymer matrix erosion. HPMC K100M, a high-viscosity hydrophilic polymer, forms a gel-like barrier upon contact with aqueous media. This gel structure acts as a rate-controlling layer, slowing drug diffusion and mitigating the initial burst effect. Meanwhile, Polyox WSR N80 complements this mechanism by enhancing matrix integrity and providing controlled erosion properties. Together, these polymers create a robust drug delivery matrix that harmonizes sustained release with protection against burst release [32]. The dissolution data for optimized run were put into different *in vitro* release kinetic equations (Table 8). A higher correlation coefficient for zero order equation suggests that QF release followed zero-order kinetics. A higher correlation coefficient for Higuchi equation suggests that diffusion was the primary release mechanism with slight erosion. A Korsmeyer–Peppas release exponent (n) value of 0.75 indicates that the optimized formulation followed a non-Fickian (anomalous) transport mechanism characterized by the combined contribution of drug diffusion and polymer relaxation/erosion processes [33,34].

Stability study

The stability study for the selected optimized run for 6 months indicates no significant change in drug content, Q1, t50, and Q18. These data of the stability study suggest that QF SR matrix tablets are stable (Table 9) as per student t test at p<0.05 level.

Table 6: Micromeritic properties of Quetiapine Fumarate and its Granules

Run	Angle of repose* (ϴ) in degree	Carr's index* (%)	Hausner's ratio*	Granular friability index (%)	Moisture content* (%)
Quetiapine fumarate	37.23±2.81	25.32±0.87	1.75±0.01	**	11±0.8
1	24.17±1.12	16.68±0.97	1.24±0.02	0.82±0.03	3.45±0.4
2	24.56±1.31	17.45±1.37	1.22±0.01	0.73±0.02	4.74±0.2
3	22.58±0.87	18.14±0.22	1.23±0.02	0.35±0.03	5.24±0.7
4	23.91±1.68	17.61±0.58	1.25±0.04	0.25±0.05	5.61±0.6
5	25.52±1.64	18.34±0.39	1.24±0.07	0.74±0.04	4.12±0.3
6	22.87±0.94	18.97±0.68	1.21±0.04	0.89±0.05	3.85±0.3
7	23.84±1.24	19.57±0.73	1.24±0.03	0.75±0.07	4.25±0.2
8	24.63±1.19	17.95±1.12	1.23±0.06	0.15±0.02	3.15±0.3
9	21.87±2.87	18.51±0.78	1.22±0.04	0.37±0.08	4.55±0.4
10	23.91±1.76	16.64±0.12	1.24±0.04	0.52±0.03	3.27±0.7
11	24.65±1.47	17.34±0.84	1.21±0.04	0.37±0.03	2.54±0.6
12	22.87±1.54	19.53±0.45	1.24±0.06	0.24±0.04	4.91±0.5
13	23.12±2.84	16.37±0.62	1.23±0.03	0.54±0.03	4.68±0.3

Mean±SD. n=6. **Could not be determined for powders

Table 7: Quality control tests for SR tablets of quetiapine fumarate

Run	Hardness* (Kg/cm^2)	Thickness* (mm)	Friability* (%)	Drug content** (%)	Weight variation*** (mg)
1	5.9±0.5	2.45±0.3	0.7±0.01	96.23±4.15	200±4.51
2	5.7±0.4	2.37±0.1	0.6±0.02	96.54±3.27	200±6.91
3	5.8±0.6	2.41±0.1	0.3±0.03	96. 28±3.16	200±10.25
4	5.4±0.2	2.52±0.2	0.4±0.02	96.51±4.12	200±12.37
5	5.9±0.3	2.44±0.3	0.2±0.04	97.48±4.76	200±5.46
6	5.7±0.7	2.65±0.4	0.8±0.02	97.27±4.51	200±6.79
7	5.1±0.1	2. 14±0.2	0.3±0.04	96.15±3.17	200±4.14
8	5.0±0.8	2.63±0.3	0.4±0.07	97.15±3.19	200±5.19
9	5.3±0.7	2.52±0.2	0.5±0.06	98.18±1.23	200±6.97
10	5.5±0.6	2.73±0.3	0.6±0.03	95.12±3.17	200±7.14
11	5.8±0.5	2.36±0.2	0.7±0.05	97.34±4.14	200±5.57
12	5.9±0.7	2.44±0.2	0.9±0.06	98.18±3.19	200±6.19
13	5.6±0.2	2.38±0.3	0.6±0.03	98.23±4.67	200±8.29

Mean±SD, *n=6, **n=10, ***n=20

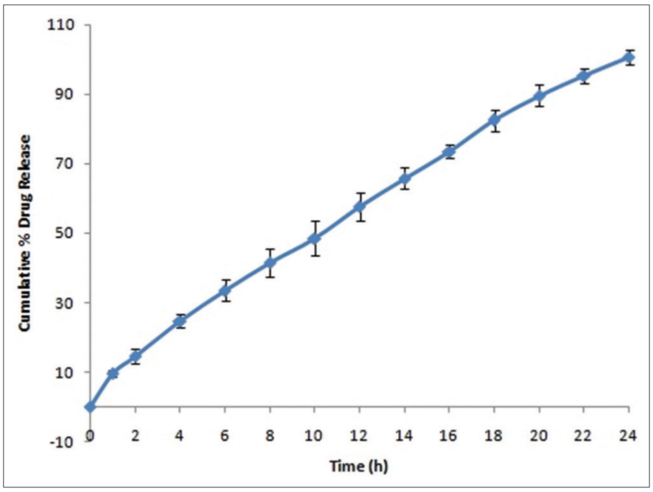

Fig. 7: Dissolution profile for optimized run

Table 8: *In vitro* release kinetics for the optimized formulation

Run	Correlation coefficient			Korsmeyer-Peppas plot	
	Zero order	First order	Higuchi equation	Correlation	Slope
Run 7	0.9967	0.9442	0.965	0.998	0.75

Table 9: Stability study for optimized formulation

Months	Drug content (%)	Q_1 (%)	t_{50}(h)	Q_{18} (%)
0	98.85±2.74	9.73±0.64	10.45±0.37	82.46±4.91
1	98.43±3.62	9.19±0.42	10.54±0.29	82.84±3.24
3	98.95±2.54	9.86±0.33	10.62±0.37	83.17±3.54
6	98.79±3.87	9.81±0.37	10.14±0.25	81.35±2.67
p<0.05	NS	NS	NS	NS

Mean±SD, n=6, NS=Not significant

CONCLUSION

Overall, the study demonstrates the successful design of a once-daily sustained-release QF formulation that meets therapeutic objectives while enhancing patient convenience and adherence. The outcomes highlight the effectiveness of polymer synergy and statistical optimization tools in controlled drug delivery and reinforce the formulation's The present study successfully addresses the need for a once-daily sustained-release formulation of quetiapine fumarate (QF). The systematic development of QF sustained-release matrix tablets using the wet granulation technique, coupled with formulation optimization through CCD, represents a significant advancement in controlled oral drug delivery. Optimization studies identified an ideal polymer combination consisting of HPMC K100M (0.918 level; 58.2 mg/tablet) and Polyox WSR N80 (0.486 level; 44.8 mg/tablet), demonstrating the robustness and precision of CCD in defining critical formulation variables to achieve the desired 24-h release profile with minimized burst release. The rational integration of these two hydrophilic polymers proved highly effective in modulating drug release behavior, with Polyox WSR N80 facilitating rapid matrix hydration and early-phase control, while HPMC K100M ensured long-term matrix integrity and sustained drug release. Importantly, the optimized formulation successfully minimized the initial burst effect and maintained a controlled and uniform release of QF throughout the 24-h period. Release kinetic analysis further revealed that drug release followed a non-Fickian (anomalous) diffusion mechanism, indicating a combined influence of diffusion and polymer matrix relaxation/erosion processes potential to improve the quality of life of patients requiring long-term antipsychotic therapy.

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CONTRIBUTIONS BY EACH AUTHOR

Dinesh Das: Performed the practical experimental work. Anjan Kumar: Guided the candidate while executing the work. Ch. Niranjan Patra: Assisted in writing the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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