Formulation Development and Optimization of Once Daily Quetipine Fumarate SR Tablets

Authors: Dinesh Kumar Das, **Anjan Kumar*** and Ch. Niranjan Patra

Roland Institute of Pharmaceutical Sciences, Biju Patnaik University of Technology, Odisha, India

*Corresponding Author
Dr. Anjan Kumar
Professor,
Roland Institute of Pharmaceutical Sciences, India,760010

ABSTRACT

Quetipine fumarate (QF) belongs to atypical antipsychotic class. The elimination half-life of QF is 6 h necessitates the development of sustain release formulation. In the current research, two polymers HPMC K100M and Polyox WSR N80 were used in combination as per the central composite design with an objective of sustained drug release for 24 h with low initial burst release. The SR matrix tablets of QF were prepared by wet granulation method. FT-IR and DSC study for the physical mixture of QF with HPMC K100M and Polyox WSR N80 in 1:1 ratio demonstrated compatibility. The selection of the optimum formulation highlights the precision of CCD in optimizing the formulation parameters to achieve the desired release profile. The integration of two polymers HPMCK100M and Polyox WSR N80 proved effective in modulating the drug release dynamics. Specifically, the polymers synergistically contributed to minimizing the initial burst release, thereby ensuring a steady and sustained release of QF over 24 h. 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*:* Formulation***,*** *In-Vitro* Dissolution, HPMCK100M, Polyox WSR N80, Sustain release, Matrix tablet

1. 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 film-coated 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 (API) 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). HPMCK100M based matrix tablets when exposed to gastrointestinal fluids, HPMC hydrates rapidly and forms a robust, viscous gel layer(9). This gel acts as a barrier, primarily controlling drug release through diffusion(10). It also contributes good compressibility and helps maintain mechanical strength. Polyox WSR N80 because of very high molecular weights tends to form a visco-elastic 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(11, 12). Hence in the current research, two polymers HPMC K100M and Polyox WSR

N80 were used in combination as per the central composite design with an objective of sustained drug release for 24 h with low initial burst release.

2. MATERIALS AND METHODS

2.1. Material

Quetipine fumarate (QF) was acquired as complimentary sample from Akshar Pharmaceuticals, Gujrat. HPMCK100M was received as gift sample from Colorcon, India. Polyox WSR N80 was procured from Chempoint, India.

2.2. Methods

2.2.1.Fourier Transform Infra Red (FT-IR) Study

FT-IR spectroscopic analysis was performed for pure drug QF and its physical mixtures with HPMCK100M and Polyox WSR N80 alone and also in combination in 1:1 ratio using IR Affinity, Shimadzu, Japan.

2.2.2. Differential Scanning Calorimetry (DSC) Study

Thermal analysis was performed for pure drug QF and its physical mixtures with HPMCK100M and Polyox WSR N80 alone and also in combination (1:1) ratio using DSC-60, Shimadzu, Japan. The DSC study was performed with a rate of rise in temperature of 10^0C per minute upto 250^0C under nitrogen atmosphere.

2.2.3. Preparation of Quetipine Fumarate SR Matrix Tablets

The sustain release (SR) matrix tablets of QF were prepared by wet granulation method. In the first step, drug and excipients were passed through sieve number 60. The drug, polymers (HPMCK100M and Polyox WSR N80) and other excipients as per Table 1 were dry mixed for 10 min in mortar and pestle. During dry mixing Avicel PH101 was also added as diluent. The wet binder solution (starch paste 10 % W/V) was added 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 (FBD) and dried under fluidized hot air stream at a temperature of 70^0C for 15 min. The dried granules were again passed through sieve number 20. 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 central composite design (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 selected CQAs for the above research were concentration of polymer HPMCK100M in the range of 20 to 60 mg per tablet and concentration of Polyox WSR N80 in the range of 30 to 50 mg per tablet. 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),

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 HPMCK100M (mg)	**20**	**40**	**60**
Concentration of Polyox WSR N80 (mg)	**30**	**40**	**50**

2.2.4. 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 (13) and moisture content (14) were determined as per standard procedure (15).

Table 2, Micromeritic Properties of Quetiapine Fumarate and its Granules

Run	Angle of Repose* (Ɵ) 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**

2.2.5. 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 (16).

Table 3, 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**

2.2.6. In-Vitro Dissolution Study

In-Vitro dissolution test was performed for the optimized formulation for 24 h. In this study, the 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 temperature of 37 ± 0.5^0C. The dissolution samples diluted and analyzed spectrophotometrically at 239 nm (17). The drug dissolution data was put into zero order, first order, Higuchi and korsmeyer Pappa's equation for analyzing drug release kinetics and mechanism of drug release.

2.2.7. Stability Study

The stability study for the optimized tablet formulation was performed as per ICH guidelines (18) [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}.

3. RESULTS AND DISCUSSION

3.1. Fourier Transform Infra Red (FT-IR) Study

FT-IR study for pure drug QF confirms the presence of following functional groups by analyzing absorption bands (Figure 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 HPMCK100M 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.

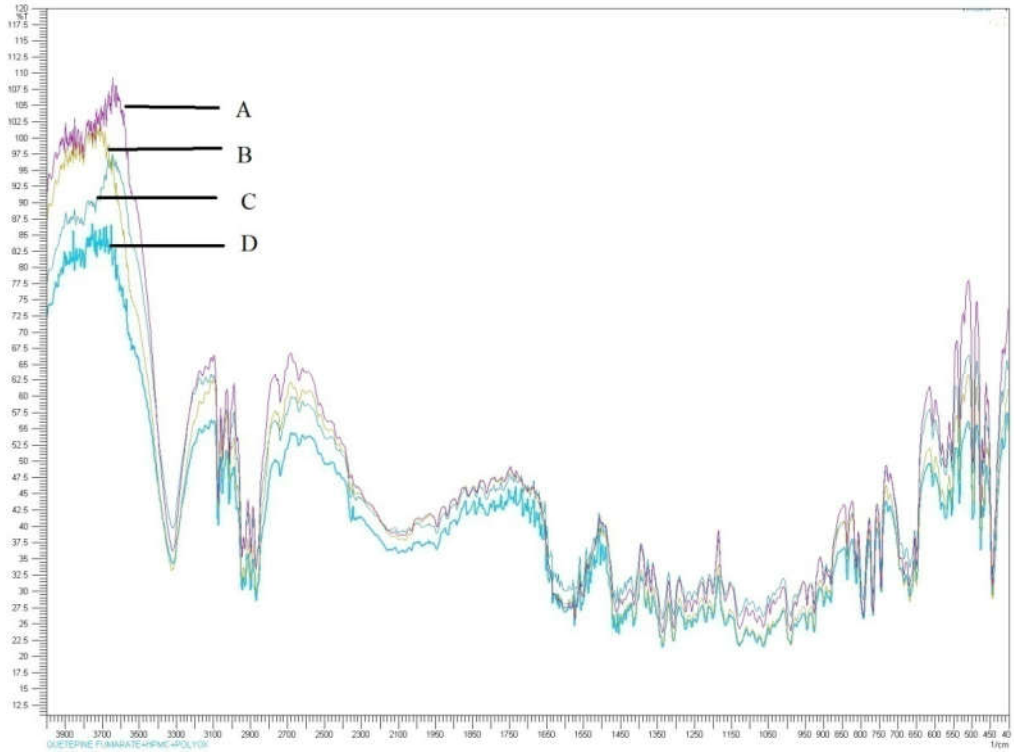

Figure 1: FT-IR spectra for QF (A), PM of QF with HPMCK100M (1:1) (B), QF with Polyox WSR N80 (1:1) (C) and QF with HPMCK100M (1:1) and Polyox WSR N80 (1:1:1) (D)

3.2. Differential Scanning Calorimetry (DSC) Study

The thermogram for QF exhibited a sharp melting peak at 180.7 ^{0}C with onset and endset temperature of 173.9 ^{0}C and 185.6^{0}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 Quetipine fumarate, HPMCK100 M and polyox WSR N80 (1:1:1) demonstrated peaks at 179.9^{0}C, 173.1^{0}C and 179.7^{0}C respectively. The peaks for all the three PMs were nearer to the peak of QF suggesting no incompatibility between

drug and polymers (Figure 2). All the PMs exhibited lower enthalpy in comparison to the enthalpy of QF (19).

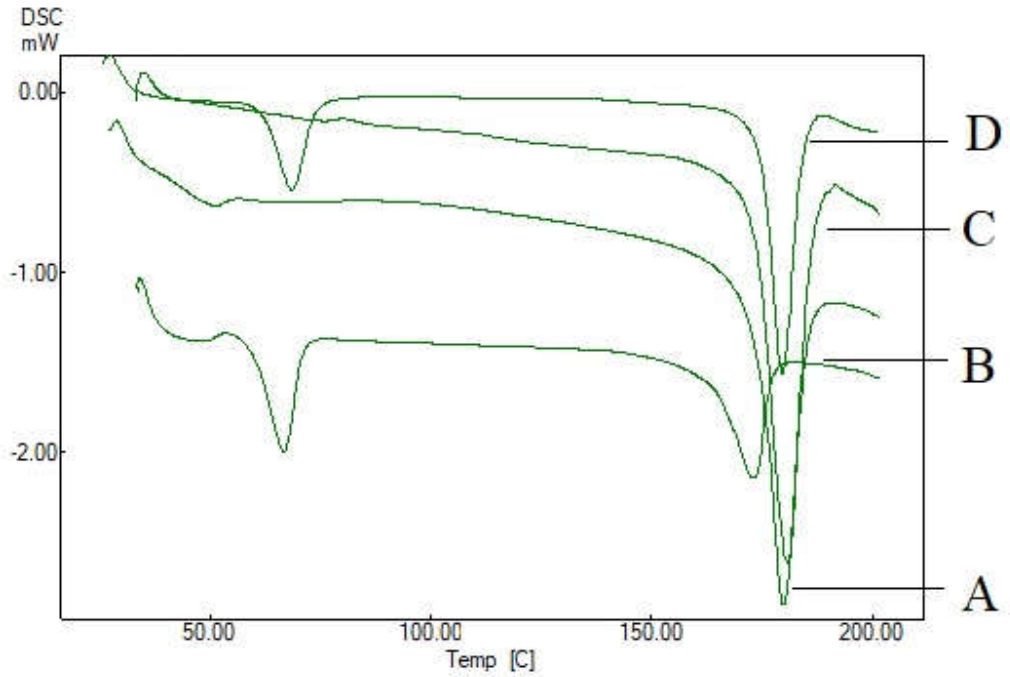

Figure 2: DSC Thermogram for QF (A), PM of QF with HPMCK100M (1:1) (B), QF with Polyox WSR N80 (1:1) (C) and QF with HPMCK100M and Polyox WSR N80 (1:1:1)

3.3. Preparation of QF SR Matrix Tablets

The QF SR matrix tablets were produced successfully with yield more than 97 % suggesting proper selection of processing parameters like 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 (20).

3.3.1. Characterization of Quetipine Fumarate SR Matrix Tablets

Response Surface Analysis

Figure 3 features a contour plot alongside a 3D representation of the Q_1 response i.e. 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 to 10 % in 1 h of dissolution study. The following runs i.e. 11 and 13 were able to control the release of QF in the percentage range of 8 to 10 %. The initial burst release was well controlled by increased concentration of HPMCK100 M and polyox WSR N80. A higher HPMCK100M and polyox WSR N80 content might favor diffusion-controlled release due to the formation of a more robust gel (8, 9, 21, 22).

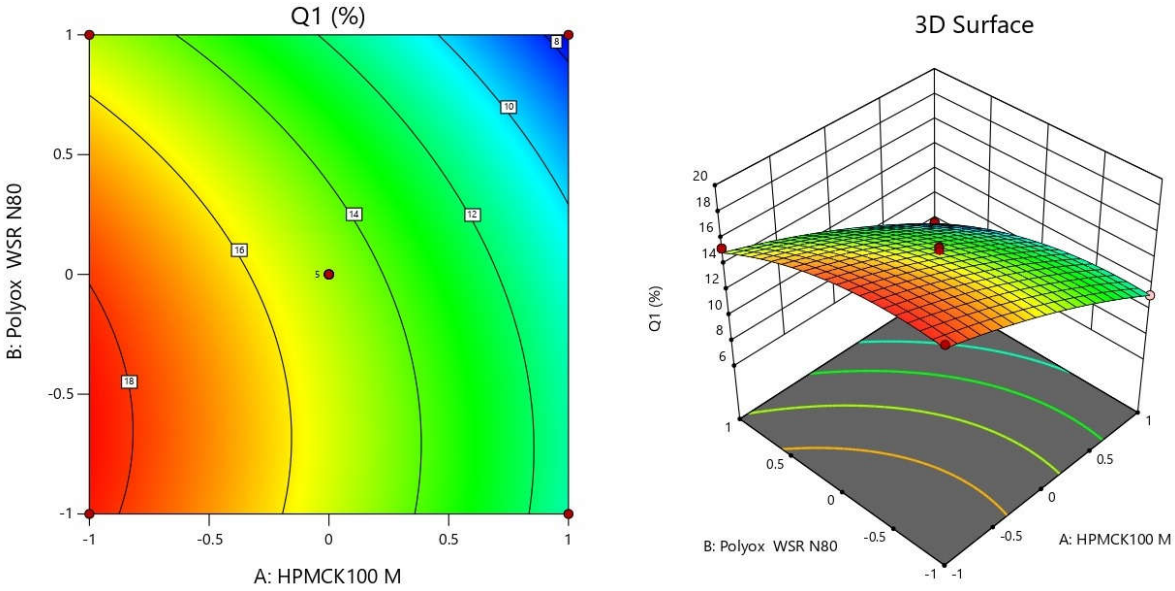

Figure 3: Contour plots and 3 D-Response surface plot showing the influence of significant factors on Cumulative % drug release at 1 h (Q_1)

Figure 4 features a contour plot alongside a 3D representation of the t_{50} response i.e. 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 drug was fixed in the range of 8 to 11 h. It was observed that increase in the concentration of both polymers resulted in 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 i.e. Run 3, 10 and 11.

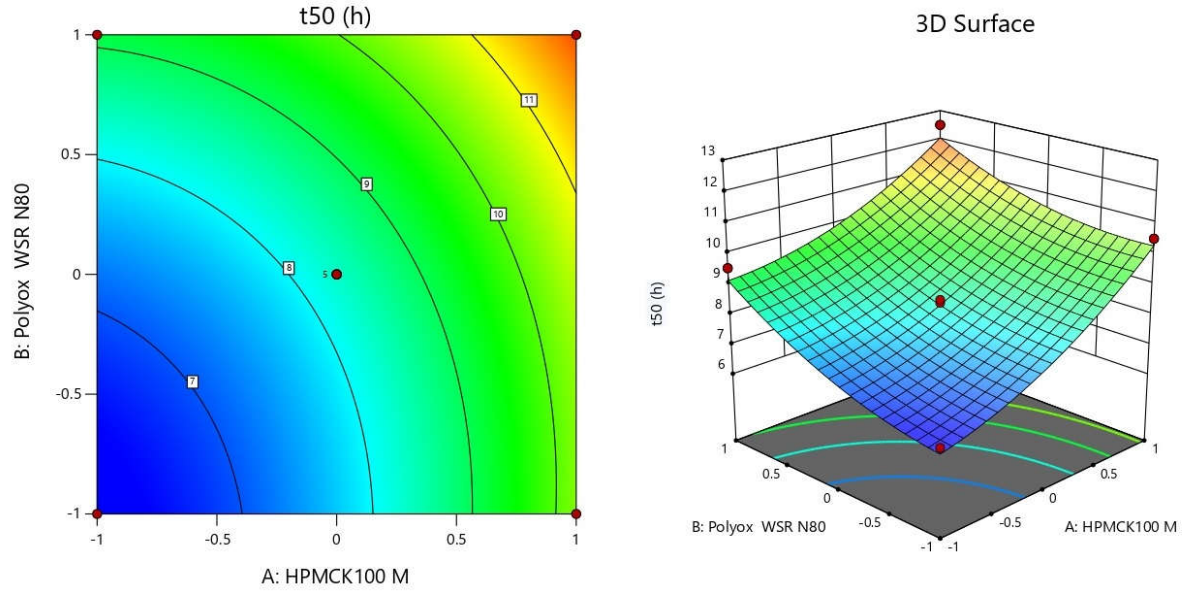

Figure 4: Contour plots and 3 D-Response surface plot showing the influence of significant factors on time taken for release of 50% drug (t_{50})

Figure 5 features a contour plot alongside a 3D representation of the Q_{18} response i.e. cumulative percent drug released in 18 h. The cumulative percent drug release ranges from 74.5 (run 13) to 100 (run 1, 2 and 8). The desirability was fixed in the range of 80 to 95 % of cumulative percent drug dissolution at 18th hour. The desirability of Q_{18} was attained by run 4, 5, 6, 7, 9, 10, 11 and 12.

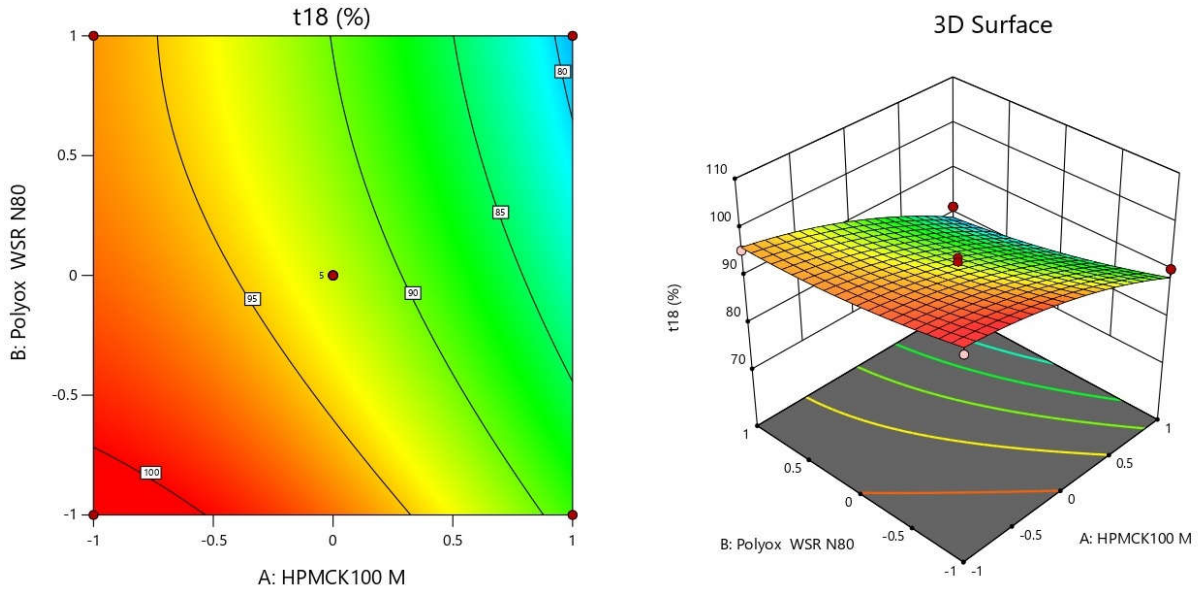

Figure 5: Contour plots and 3 D-Response surface plot showing the influence of significant factors on Cumulative % drug release at 18 h (Q_{18})

3.3.2. 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.

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

$$t_{50} = 8.32 + 1.72A + 1.15\,B - 0.2600\,AB + 0.6013\,A^2 + 0.5163\,B^2$$

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

Table 4 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 (HPMCK100M), B (Polyox WSR N80), their interaction (AB), along with their squared terms (A^2 and B^2), were statistically significant ($p < 0.001$). Similarly, for the t50 and Q18 response, A, B, AB, A^2, and B^2 emerged as significant contributors. Table 5 provides a summary of the CCD quadratic model employed during the optimization of the QF matrix tablets.

Table 4, 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-HPMCK100M	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 5, 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

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 6. Figure 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 HPMCK100M, 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 7 presents the composition of optimized formulation suggested by CCD.

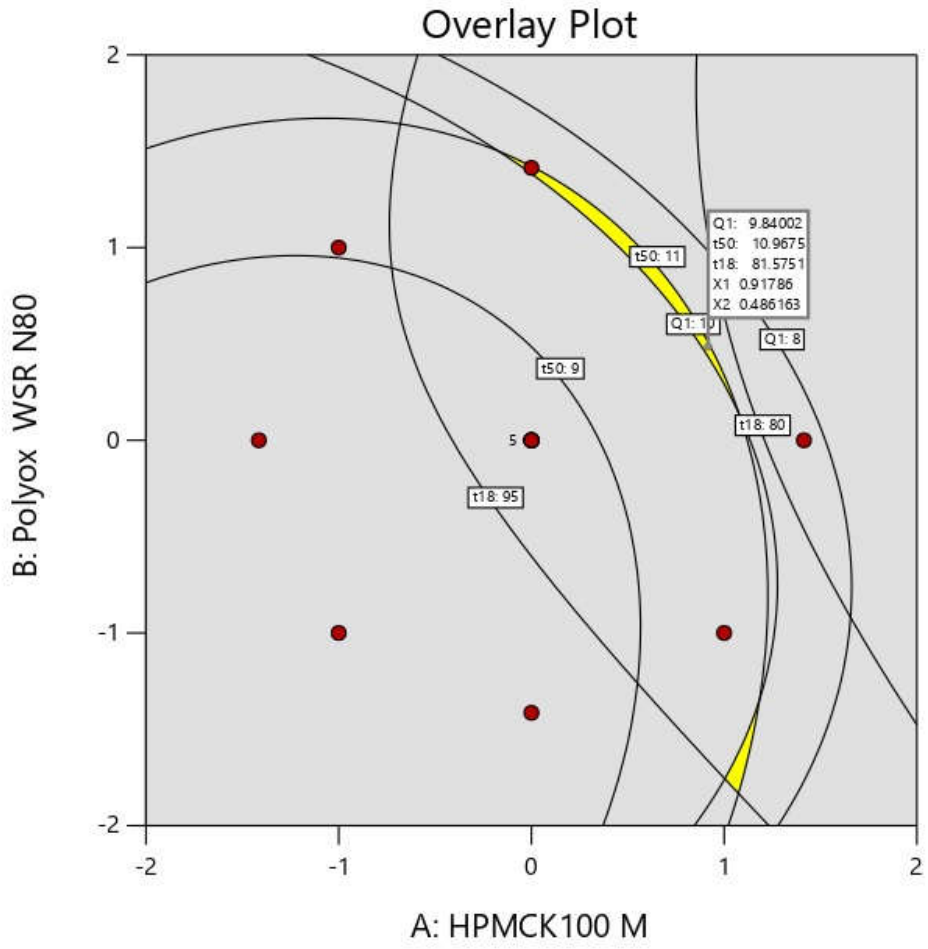

Figure 6: Overlay contour plots depicting the design space and delineate the optimized formulation of QF SR matrix tablets

Table 6: Constrains for the process of optimization

Name of Factor	**Lower Limit**	**Upper Limit**	**Optimized coded value**	**Optimized actual value**
A-HPMCK100M	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 7: 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 PH101	20	1.0
Starch paste (10% W/V)	21	1.05
Talc	4	0.2
Aerosil	2	0.1
Total	200	10.0

3.4. Micromeritic Properties of Granules

The evaluation of micromeritic properties of pure drug powder Quetipine fumarate suggest that it is poorly flowable drug and it needs to be granulated for improvement of flowability and compressibility (Table 2). All the 13 formulations showed micromeritic properties desirable for proceeding to the next process that is compression. The improvement in micromeritic properties suggest that the selection of binder, concentration of binder, sieve number and lubricating agent etc were appropriate achieving desirable flowability and compressibility (23, 24). Granular friability index (GFI) less than 1 % for all the 13 formulations also suggests selection of starch paste as right binder in right proportion (25).

3.4.1. Quality Control Tests for Tablets

All the 13 tablet formulations passed the quality control tests for tablets as the values were within the official specifications (Table 3). The drug content for all formulations were above 95 % suggests uniform mixing of drug with excipients. Weight variation or deviation was within the allowed specification i.e. ± 7.5 %. Hardness for all formulations was above 5 Kg/cm^2 and percent loss in weight in friability test was less than 1% suggesting optimum selection of binder. Hence the prepared passed the quality control tests.

3.4.2. *In-Vitro* Dissolution Study

In-vitro dissolution study for all the formulations was performed and it was found that Run 1, 2, 3 and 8 could not sustain the release of QF for more than 18 hours. The reason attributed can be because of lower proportion of either HPMCK 100M or polyox WSR N80. All other formulations exhibited QF release for 24 h in sustained manner. By considering the initial burst release and time for 50 % of release of 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 7. The dissolution profile of optimized run is presented in figure 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. HPMCK100M, 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 (26). The dissolution data for optimized run was put into different *In-Vitro* release kinetic equations (Table 8). Higher correlation coefficient for zero order equation suggests that QF release followed zero order kinetics. Higher correlation coefficient for Higuchi equation suggests that diffusion was primary release mechanism with slight erosion. Korsmeyer release exponent value suggests that the optimized formulation exhibited non-fickian diffusion controlled release mechanism (27, 28).

Table 8, In-vitro Release Kinetics for the Optimized formulation

Run	Correlation Coefficient			Korsmeyer Pappa's Plot	
	Zero order	First order	Higuchi Equation	Correlation	Slope
Run 7	0.9967	0.9442	0.965	0.998	0.75

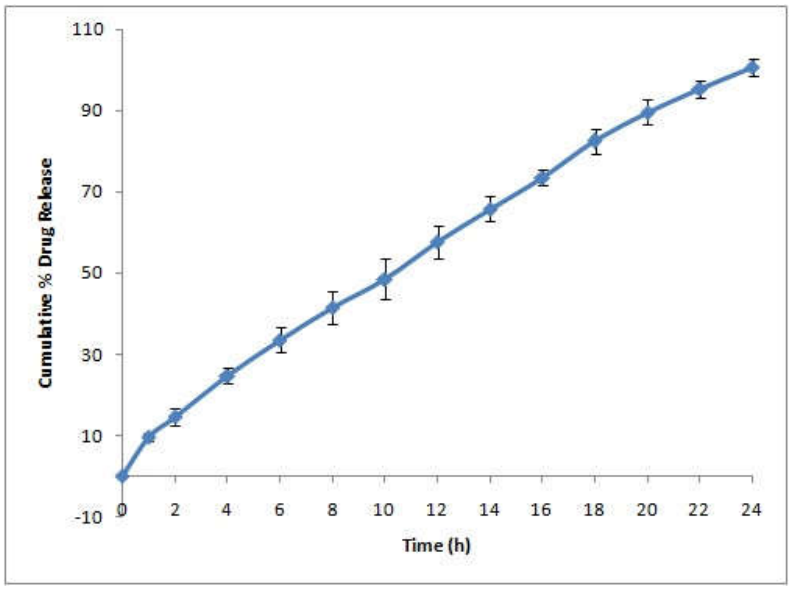

Figure 7: Dissolution profile for optimized run

Stability Study

The stability study for selected optimized run for 6 months indicates no significant change in drug content, Q_1, t_{50} and Q_{18} at $P < 0.05$ level. These data of stability study suggest that QF SR matrix tablets are stable (Table 9).

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

4. CONCLUSION

The need for a once-daily formulation of QF is underscored by its pharmacokinetic profile and therapeutic indications. The successful preparation and optimization of QF SR matrix tablets by wet granulation method and Central Composite Design (CCD) respectively marks a significant achievement in controlled drug delivery systems. The selection of optimized run highlights the precision of CCD in optimizing the formulation parameters to achieve the desired

release profile. The integration of two polymers HPMCK100M and Polyox WSR N80 proved effective in modulating the drug release dynamics. Specifically, the polymers synergistically contributed to minimizing the initial burst release, thereby ensuring a steady and sustained release of QF over 24 hours. The release mechanism of QF is by Non-fickian diffusion controlled release mechanism. Hence, 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.

FUNDING

This research received no external funding.

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

Conflict of Interest

The authors declare that they have no competing interests.

5. REFERENCES

1. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. Clinical pharmacokinetics. 2001;40:509-22.

2. Goren JL, Levin GM. Quetiapine, an atypical antipsychotic. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 1998;18(6):1183-94.

3. Oruch R, Pryme I, Fasmer O, Lund A. Quetiapine: An objective evaluation of pharmacology, clinical uses and intoxication. EC Pharmacol Toxicol. 2020;8(4):01-26.

4. Cutler AJ, Goldstein JM, Tumas JA. Dosing and switching strategies for quetiapine fumarate. Clinical therapeutics. 2002;24(2):209-22.

5. Agarwal S, HariKumar S, Negi P, Upadhyay N, Garg R. Quetiapine fumarate loaded nanostructured lipid carrier for enhancing oral bioavailability: design, development and pharmacokinetic assessment. Current Drug Delivery. 2021;18(2):184-98.

6. Kim D-W, Weon K-Y, Hong E-P, Chung EK, Lee K-T. Comparative physicochemical and pharmacokinetic properties of quetiapine and its active metabolite norquetiapine. Chemical and Pharmaceutical Bulletin. 2016;64(11):1546-54.

7. Teixeira MT, Sa-Barreto LL, Taveira SF, Gratieri T, Gelfuso GM, Marreto RN, et al. The influence of matrix technology on the subdivision of sustained release matrix tablets. Aaps Pharmscitech. 2020;21:1-9.

8. Sarangi DK, Patro CS, Patra CN, Sahoo NK, Das NR, Kaur K, et al. In vivo assessment, formulation, characterization and enhancing pharmacotherapy of encapsulated mini tablets for immediate release Sildenafil citrate and sustained release Bosentan. Results in Chemistry. 2024;9:101652.

9. Patra C, Kumar A, Pandit H, Singh S, Devi M. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride. Acta Pharmaceutica. 2007;57(4):479.

10. Patra CN, Padhy S, Sen T, Bhattacharya S, Swain S, Sruti J, et al. Formulation development and evaluation of SR matrix tablets of stavudine. Ind J Pharm Edu Res. 2013;47:214-20.

11. Vanza JD, Patel RB, Dave RR, Patel MR. Polyethylene oxide and its controlled release properties in hydrophilic matrix tablets for oral administration. Pharmaceutical development and technology. 2020;25(10):1169-87.

12. Martin LM, Rajabi-Siahboomi AR. Applications of polyethylene oxide (POLYOX) in hydrophilic matrices. Hydrophilic Matrix Tablets for Oral Controlled Release: Springer; 2014. p. 123-41.

13. Garg N, Pandey P, Kaushik D, Dureja H. Development of novel multifunction directly compressible co-processed excipient by melt granulation technique. International journal of pharmaceutical investigation. 2015;5(4):266.

14. Rantanen J, Antikainen O, Mannermaa J-P, Yliruusi J. Use of the near-infrared reflectance method for measurement of moisture content during granulation. Pharmaceutical development and technology. 2000;5(2):209-17.

15. Sinko PJ. Martin's physical pharmacy and pharmaceutical sciences: Lippincott Williams & Wilkins; 2023.

16. Aulton ME, Taylor K. Aulton's pharmaceutics: the design and manufacture of medicines: Elsevier Health Sciences; 2013.

17. Chhajed S, Agrawal S, Bastikar V, Gosavi R, Kunte S, Wagh R. Estimation of quetiapine in bulk drug and tablet dosage form. International Journal of Chemical Sciences. 2009;7(2):951-60.

18. Bhavyasri K, Vishnumurthy KM, Rambabu D, Sumakanth M. ICH guidelines–"Q" series (quality guidelines)-A review. GSC Biol Pharm Sci. 2019;6(3):89-106.

19. Ghanbari E, Picken SJ, van Esch JH. Analysis of differential scanning calorimetry (DSC): determining the transition temperatures, and enthalpy and heat capacity changes in

multicomponent systems by analytical model fitting. Journal of Thermal Analysis and Calorimetry. 2023;148(22):12393-409.

20. Tahara K, Yamamoto K, Nishihata T. Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910. Journal of controlled release. 1995;35(1):59-66.

21. Sujja-Areevath J, Munday D, Cox P, Khan K. Relationship between swelling, erosion and drug release in hydrophillic natural gum mini-matrix formulations. European journal of pharmaceutical sciences. 1998;6(3):207-17.

22. Sung K, Nixon PR, Skoug JW, Ju TR, Gao P, Topp E, et al. Effect of formulation variables on drug and polymer release from HPMC-based matrix tablets. International journal of pharmaceutics. 1996;142(1):53-60.

23. Patra CN, Swain S, Mahanty S, Panigrahi KC. Design and characterization of aceclofenac and paracetamol spherical crystals and their tableting properties. Powder Technology. 2015;274:446-54.

24. Jammula S, Patra CN, Swain S, Panigrahi KC, Nayak S, Dinda SC, et al. Design and characterization of cefuroxime axetil biphasic floating minitablets. Drug Delivery. 2015;22(1):125-35.

25. Prakash SS, Patra CN, Santanu C, Kumar PH, Patro VJ, Devi MV. Studies on flowability, compressibility and in-vitro release of Terminalia chebula fruit powder tablets. Iranian journal of pharmaceutical research: IJPR. 2011;10(3):393.

26. Talevi A, Ruiz ME. Korsmeyer-Peppas, Peppas-Sahlin, and Brazel-Peppas: Models of drug release. The ADME Encyclopedia: A Comprehensive Guide on Biopharmacy and Pharmacokinetics: Springer; 2022. p. 613-21.

27. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. International journal of pharmaceutics. 1983;15(1):25-35.

28. Lee PI. Kinetics of drug release from hydrogel matrices. Journal of Controlled Release. 1985;2:277-88.