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Original Articles

Design and development of quetiapine fumarate nanosuspension by media milling method

Diseño y desarrollo de nanosuspensión de fumarato de quetiapina mediante el método de fresado de medios

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Resumen

Introducción: Las propiedades críticas y complejas de las moléculas de ingredientes farmacéuticos activos de fumarato de quetiapina Clase II del Sistema de Clasificación Biofarmacéutica que complican la administración oral eficaz de estos ingredientes farmacéuticos activos incluyen una baja solubilidad acuosa y una biodisponibilidad reducida.

Objetivo: El objetivo de esta investigación es desarrollar una formulación de nanosuspensión de fumarato de quetiapina utilizando técnicas de molienda de medios para reducir eficazmente el tamaño de las partículas y mejorar la velocidad de disolución.

Método: Se prepararon nanosuspensiones de fumarato de quetiapina mediante el método de molienda en medios. El proceso de molienda se optimizó mediante el estudio de los efectos de los parámetros críticos del proceso sobre el tamaño de la nanosuspensión mediante un enfoque de diseño factorial. La nanosuspensión preparada se somete a diversas técnicas de caracterización, como tamaño de partícula, potencial Zeta, calorimetría diferencial de barrido, difracción de rayos X en polvo, microscopía electrónica de barrido y evaluación de la tasa de disolución in vitro.

Resultados: Los resultados obtenidos demuestran que el tamaño promedio de partícula de las nanosuspensiones preparadas es de 225 nm con un índice de polidispersidad de 0,530, mientras que el potencial Zeta promedio es de -38,2 mv. La estructura cristalina de la nanosuspensión de fumarato de quetiapina es evidente a partir de calorimetría diferencial de barrido y rayos X en polvo

Conclusión: La velocidad de disolución de la nanosuspensión es significativamente más rápida que la del fármaco fumarato de quetiapina puro, y la liberación acumulada del fármaco de la nanosuspensión es mayor que la del fármaco puro, lo que indica que el uso de la nanotecnología puede mejorar considerablemente la velocidad de disolución.

Palabras clave: Fumarato de quetiapine; Nano suspensión; Molienda de medios; Potencial Zeta; Tamaño de partícula.

Abstract

Introduction: The critical and complex properties of Biopharmaceutics Classification System Class II quetiapine fumarate active pharmaceutical ingredient molecules that complicate effective oral delivery of these active pharmaceutical ingredients include low aqueous solubility and reduced bioavailability.

Objective: The objective of this investigation is to develop a nanosuspension formulation of quetiapine fumarate using media milling techniques to effectively reduce particle size and enhance dissolution rate.

Method: Quetiapine fumarate Nano suspensions were prepared by the media milling method. The milling process was optimized by studying the effects of critical process parameters on the size of nanosuspension using a factorial design approach. The prepared nanosuspension is subjected to various characterization techniques such as Particle size, Zeta Potential, differential scanning calorimetry, X-ray powder diffraction, scanning electron microscopy, and in vitro dissolution rate assessment.

Results: The obtained results demonstrate that the average particle size of the prepared nanosuspensions is 225 nm with a Polydispersity index of 0.530, while the average Zeta potential is -38.2 mv. The crystalline structure of quetiapine fumarate nano-suspension is evident from differential scanning calorimetry and X-ray powder diffraction.

Conclusion: The dissolution rate of the nanosuspension is significantly faster than that of pure Quetiapine Fumarate, and the Cumulative drug release (%) of nanosuspension is higher than that of pure Quetiapine Fumarate , indicating that the use of nanotechnology can considerably enhance the dissolution rate.

Keywords: Quetiapine fumarate; Nano suspension; Media milling; Zeta potential; Particle size.

Highlights

Quetiapine Fumarate (QF) is a lipophilic drug with limited bioavailability (5–15 %) and low water solubility. It is extensively metabolised by the liver. The poor dissolution of relatively water insoluble drug cause problem in the formulation of the same dosage forms. The use of nanosuspensions is proposed as a strategy to improve the solubility of such drugs. The findings further indicate that a particle size of 235.36 nm, a % Cumulative Drug Release (CDR) of 94.59, and a zeta potential of -38.2, offering additional support for the ability to regulate particle size and enhance dissolution rate. The findings of this

research have important implications for improving the oral delivery of poorly water-soluble drugs, especially for medications used in the treatment of psychiatric conditions like schizophrenia.

Introduction

The critical and complex properties of BCS Class II drug molecules that complicate effective oral drug delivery include low aqueous solubility, less bioavailability, first pass metabolism, and the unsuitability of a drug in a gastrointestinal tract (GIT) environment.[1] Due to limited bioavailability, low water solubility of therapeutic molecules restricts medication delivery by oral or cutaneous modes of application.[2] It is discovered that more than 40 % of commercially available medications and many more drug candidates exhibit highly lipophilic characteristic.[3-4] When a drug's moiety is poorly soluble, it is difficult to achieve an effective blood plasma concentration during gastrointestinal (GI) transit due to its high lipophilicity and slow dissolving rate.[5]

A potential strategy that can be applied to medications that dissolve slowly is the approach of size reduction to increase the dissolving rate. This approach is universal since size reduction is feasible for every drug class.[6]

The solubility of brick dust pharmaceuticals and lipophilic substances can be improved with the use of nanosuspension. They can be characterised as carrier-free, nano-sized, 100 % drug particles with a particle size of less than 1 nm, manufactured with the least amount of appropriate surfactants, polymers, or combinations of them.[7] Compared to other nanosuspension manufacturing procedures, wet media milling is a better option since it is easy to perform, inexpensive, highly reproducible, efficient, free of organic solvents, and simple to scale up.[8] Additionally, achieving these benefits is a priority while producing nanosuspensions.[9] On the other side, the key issue is the potential for contamination brought on by milling bead erosion. Additionally, controlling batch size may be complicated by the milling device's substantial weight caused by excessively loaded milling media, and additional issues may arise from prolonged milling times.[10] For wet media milling, the most important process variables are the temperature, milling time, milling speed, media volume, and milling size. Stabiliser type, viscosity, concentration, and medication concentration are typical formulation characteristics that impact final product quality.[11] Process optimization is becoming more vital because the development of pharmaceutical formulations frequently focuses on producing the best final medicine while using less energy and increasing production capacity.[12]

Quetiapine a 2-[2-(4-benzo[b] [1,4] benzothiazepine-6-yl piperazin-1-4) ethoxy] is an atypical antipsychotic drug that is believed to be more effective than several other atypical antipsychotic drugs and standard antipsychotics. After oral administration, Quetiapine Fumarate QF is a lipophilic drug with limited bioavailability (5–15 %) and low water solubility.[13] It is extensively metabolised by the liver. It is considered as suitable poorly soluble drug to improve the dissolution characteristics. The simple technique of kneading method has been found to be highly successful in enhancing the dissolution rate of poorly water-soluble drugs.[15] The poor dissolution of relatively water insoluble drug cause problem in the formulation of the same dosage forms.[16]

The objective of the research work was to design and evaluate a nanosuspension of the antipsychotic quetiapine fumarate using the media milling technique to enhance solubility, dissolution rate. Nanosuspension can overcome the challenges associated with solubility and dissolution rate. Quetiapine fumarate nanosuspensions were prepared by the media milling method. The objective of the article is to demonstrate the effectiveness of nanosuspension in improving the solubility, dissolution rate, and bioavailability of quetiapine fumarate.

Controlled-release formulations of quetiapine fumarate are designed to gradually release the drug over an extended period. This allows for less frequent dosing, which can improve patient compliance. However, these formulations have some drawbacks that dose cannot be adjusted by splitting or crushing the tablet, as this would disrupt the controlled-release mechanism. The rate and extent of drug absorption can vary depending on factors such as food intake and gastrointestinal transit time. Some patients may experience side effects such as dizziness, dry mouth, and weight gain.

The proposed immediate-release nanosuspension of quetiapine fumarate is prepared by a wet media milling method. This method reduces the drug particle size to the nanometer range, which can significantly increase the surface area and potentially enhance the dissolution rate. The nanosuspension form can significantly improve the solubility of quetiapine fumarate, which is a poorly water-soluble drug. As an immediate-release formulation, it could provide a faster onset of action compared to controlled-release formulations. The enhanced solubility and dissolution rate could potentially allow for a reduction in the dose required to achieve therapeutic effects.[17-18]

Materials and Methods

Materials

The sample of Quetiapine Fumarate [$(C_{21}H_{25}N_3O_2S)_2 \cdot C_4H_4O_4$] employed in this study was sourced from Astron Research Ltd., Ahmedabad. The non-ionic surfactants Poloxamer 407 and Brij 35 utilized in the experiments were purchased from Merck Pvt. Ltd. Mumbai. All additional chemicals, reagents, and solvents used were of analytical grade.

Methods

Drug -excipient Compatibility Studies

The Fourier-transform infrared (FT-IR) spectrum of the drug sample under investigation was subjected to comparative analysis with the FT-IR spectra of the QF API. The range of scanning was set between 500 and 4000 cm^{-1} for the purpose of the aforementioned analysis. The FT-IR spectra of quetiapine fumarate, excipients, and lyophilized samples were obtained using Shimadzu Fourier Transform Infra-Red spectrometer on the samples prepared in potassium bromide (KBr) disks. The spectra were scanned over a frequency range of 4000-500 cm^{-1}.[19]

Preparation of Nano suspension

Quetiapine fumarate was dispersed in an aqueous medium, followed by the addition of varying ratios of poloxamer 407 to the mixture. The resulting coarse pre-dispersion was subjected to comminution using zirconium oxide beads (milling media of size 0.4-0.7 mm) on a magnetic stirrer.[20] An initial evaluation of formulation parameters was conducted in the development of a nano-suspension formulation. Specifically, various stabilizers were utilized and their impact on particle size and zeta potential was assessed.[21] The process parameters of stirring time and poloxamer 407 concentration were systematically optimized using 3^2 factorial designs to achieve a minimum particle size.[22] The optimized formulation was subsequently subjected to lyophilization, with mannitol serving as the cryoprotectant in a final concentration (25mg/5ml).

Table 1: Preliminary trials for selection of stabilizer

Batch Code	Stabilizer (200 mg)	QF API (200 mg)	Particle size (nm)
A1	Polyvinylpyrrolidone (PVPK30)	Quetiapine Fumarate	387.5
A2	Hydroxypropyl methylcellulose (HPMC E5)	Quetiapine Fumarate	781.2
A3	Tween 80	Quetiapine Fumarate	514.2
A4	Poloxamer 407	Quetiapine Fumarate	235.3

Note: Polyvinylpyrrolidone (PVPK30) , Hydroxypropyl methylcellulose (HPMC E5)

Formulation of nano-suspension by using 3^2 factorial designs

3^2 Factorial designs were used for the development of quetiapine fumarate nanosuspension by media milling method using Design Expert Version 13 software. Poloxamer 407 concentration, and milling duration were chosen as the independent variables, and the response to the above factors was selected to be % CDR and particle size

Table 2: Independent Factors and levels

Independent variable	Levels		
	Low (-1)	Middle (0)	High (1)
Milling time (hr) (X1)	6	12	18
Amount of Poloxamer 407 (mg) (X2)	100	200	300

Statistical Analysis and validation of the design model

For investigating quadratic response surfaces and creating second-order polynomial models, factorial design is a suitable technique. This design consists of a set of duplicated centre points and the set of points located at the midpoint of the multidimensional cube, which define the region and turn it into a non-linear quadratic model that the design generates as a mathematical expression.[23]

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_{12} + \beta_{22} X_{22} + \beta_{12} X_1 X_2$$

Where; Y = a response,

β_0 = an intercept,

X_1 & X_2 = independent factors,

β_1 & β_2 = coefficients of independent factors.

Table 3: Composition of 3^2 factorial design batches of nano-suspension

Batches	QF API (mg)	Brij35 (mg)	Coded value		Actual value	
			Milling time (hr) (X1)	Amount of Poloxamer 407 (mg) (X2)	Milling time (hr) (X1)	Amount of Poloxamer 407 (mg) (X2)
M1	200	20	-1	-1	6	100
M2	200	20	-1	0	6	200
M3	200	20	-1	1	6	300
M4	200	20	0	-1	12	100
M5	200	20	0	0	12	200
M6	200	20	0	1	12	300
M7	200	20	1	-1	18	100
M8	200	20	1	0	18	200
M9	200	20	1	1	18	300

Differential Scanning Calorimetry Study

The differential scanning calorimetry (DSC) thermograms of the QF API, excipients, and selected nano-suspension samples were obtained using a DSC instrument (Mettler Instruments). The samples

were weighed and sealed in aluminium pans, and the DSC temperature and enthalpy scales were calibrated using the Indium standard. Nitrogen gas was purged through the system at a flow rate of 80 ml/min.[24] The samples were held at 50°C for 1 minute and then heated from 50°C to 300°C at a rate of 10°C/min. These procedures were carried out to perform the characterization of the nano-suspension. Using a Mettler Toledo Star SW 7.01, the DSC thermograms of bulk quetiapine fumarate powder and lyophilized nano-suspension were analysed.[25]

Particle size determination

The determination of the mean particle size and size distribution of the prepared nano-suspension was conducted through the utilization of Malvern zeta sizer nano-ZS. Specifically, the diluted nano-suspension was introduced into the sample cell made of quartz and inserted into the sample holder unit. The measurement was subsequently performed through the utilization of software. The Z-average size and polydispersity index were measured by dynamic light scattering using a Zetasizer nano ZS instrument. QF particle size was monitored during milling at predetermined time points (3, 6, 9, 15, 30 and 60 min) in order to assess the particle size reduction kinetics with the progression of milling process. Each sample was measured at least three times. Measurements were repeated after 7 days of storage of the nanosuspensions in a refrigerator (5±3°C), in order to assess product stability.[26]

Zeta potential

The zeta potential of the suspension was evaluated using a Malvern zeta sizer prior to, during, and post-milling. To determine the surface charge, zeta potential measurements were performed in distilled water with conductivity maintained at 50 ms/cm^2 by adding sodium chloride. Zeta potential was also evaluated in the first dispersion medium to estimate the properties of long-term stability. Using a Malvern Zetasizer 4 large bore capillary cell with a 20 V/cm field strength, the analysis was carried out. Using the Helmholtz-Smoluchowski equation, the electrophoretic mobility was changed into the zeta potential.[27]

Scanning Electron Microscopy (SEM)

The powder of Quetiapine Fumarate was affixed onto an Aluminium SEM stub with Carbon tape, and then imaged in the SEM under low vacuum conditions. Moreover, the surface properties of the nano-suspension of Quetiapine Fumarate before lyophilisation were also examined through scanning electron microscopy.[28]

Powder X-ray diffractometer analysis

The X-ray diffraction (XRD) analysis was performed on the bulk quetiapine fumarate powder and lyophilized nanosuspension. Polymorphic or morphological changes of nanosized particles can be checked by assessing the crystalline state and particle morphology. As nanosuspension formation experiences high attrition during bead milling, change in crystalline structure of formulation occurs which may be converted to either amorphous or other polymorphic forms.[29]

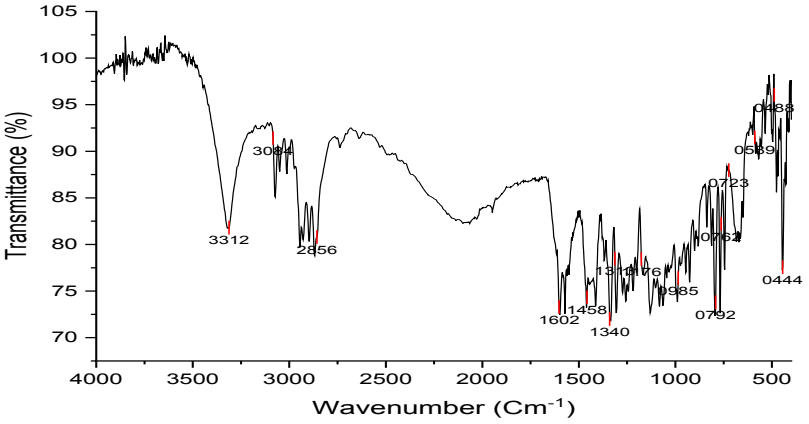
In Vitro Dissolution Study

The equipment used for the dissolution study was Electrolab india Pvt. Ltd. Dissolution studies were performed using the paddle method. The dissolution medium was 900 ml 0.1 N HCL and pH 6.8 phosphate buffer kept at 37 °C Nano-suspension containing 25 mg/5 ml of quetiapine fumarate was taken and put into the paddle apparatus.[30] The paddle was rotated at 50 rpm. The dissolution study was conducted for all the prepared Nano formulation and with the QF API. A sample of 10 ml was withdrawn at the specific time interval and analysed by UV-visible spectrophotometer at 250 nm.[30] Sampling intervals were 10, 20, 30, 45, 60, 75, 90, 120 min. 4 mL of samples were withdrawn and same number of fresh media was replaced. The dissolution profiles were evaluated by cumulative drug dissolved (%) to time.

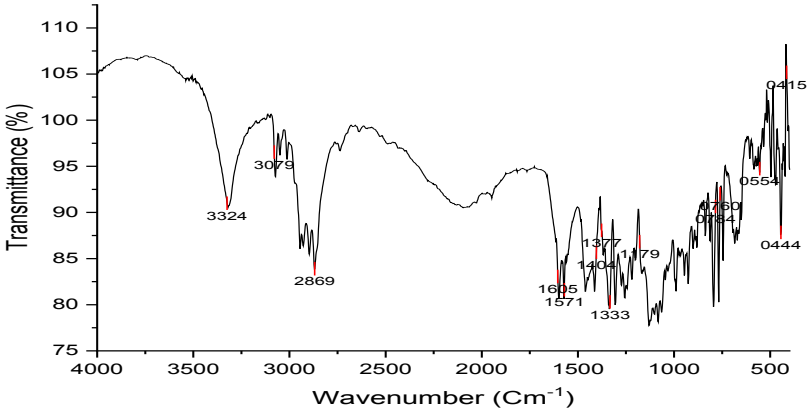
Results

QF API-excipient Compatibility Studies

The O-H stretching caused the QF peak's IR spectra to be observed at 3312 cm^{-1}, 3084 cm-1 for Ar-H stretching, 1602 cm^{-1} for C-N, 1458 cm^{-1} for N-H bending, 1340 cm^{-1} for C-H bending, 1070 cm^{-1} for C-C stretching, and 1030 cm^{-1} for the C-O-C group observed into the peak. The results show the QF API with poloxamer 407 and formulation had a distinctive peak of all the group present in the compound, it shows that a physical change in the QF API and poloxamer 407. To formulate Quetiapine fumarate Nano suspension, Poloxamer 407 can be utilised.



(A)



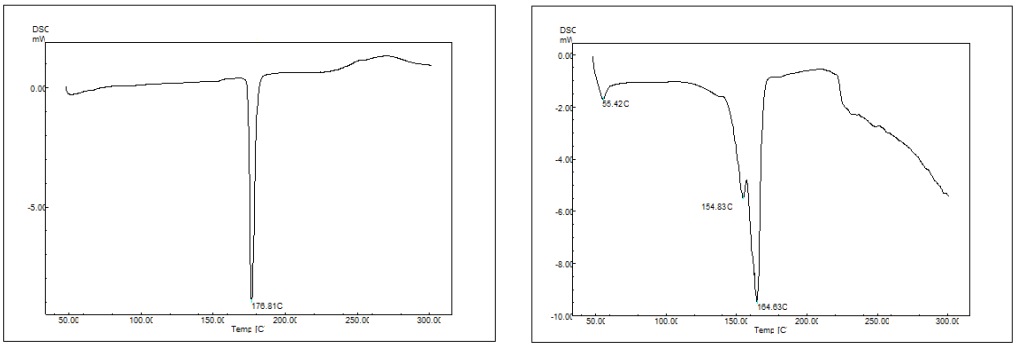
(B)

Figure 1: Fourier Transform Infrared Spectroscopy (FTIR) spectra of (A) Quetiapine fumarate; (B) Formulation M9

Differential Scanning Calorimetry Study

The thermal behaviour of the QF API and nanosuspension was investigated using DSC. The QF API shows a sharp endothermic peak, which is nearby to its melting point, which was observed at 176.81 °C shown in Figure 2(A). The Formulation of the QF shows a peak at the 164.63 °C shown in Figure 2(B). Physical mixture of QF API and polymer exhibits characteristic peaks of both QF API and polymer. This indicated the change in the crystalline nature of QF during the preparation of nanosuspension. The only difference observed was a slight shift in the fusion temperature. The shift also may be due to the

presence of stabilizers in the formulation when compared with the QF API. This suggests the crystalline state of the QF API with the nano-suspension formulation.



(A) (B)

Figure 2: Differential Scanning Calorimetry thermogram of (A) Quetiapine Fumarate; (B) Formulation M9

Particle size

After dilution with water, the particle size of all samples at various milling times was evaluated. In the media milling technique particle size was observed in nano size. QF particle size was monitored during milling at predetermined time points (3, 6, 9, 15, 30 and 60 min) in order to assess the particle size reduction kinetics with the progression of milling process. Each sample was measured at least three times. Measurements were repeated after 7 days of storage of the nanosuspensions in a refrigerator (5± 3 °C), in order to assess product stability.[26]

Table 4 : Particle Size and Polydispersity Index, Zeta Potential of Nano-suspension Formulations.

Sr no	Particle size (nm)	PDI	Zeta potential (mv)
M1	153.3	0.780	1.09
M2	281.0	0.866	1.36
M3	252.8	0.678	-0.80
M4	235.3	0.693	-3.67
M5	200.9	0.621	-1.11
M6	251.6	0.651	-1.89
M7	130.9	0.661	-5.30
M8	221.0	0.591	-6.81
M9	197.5	0.624	-38.20

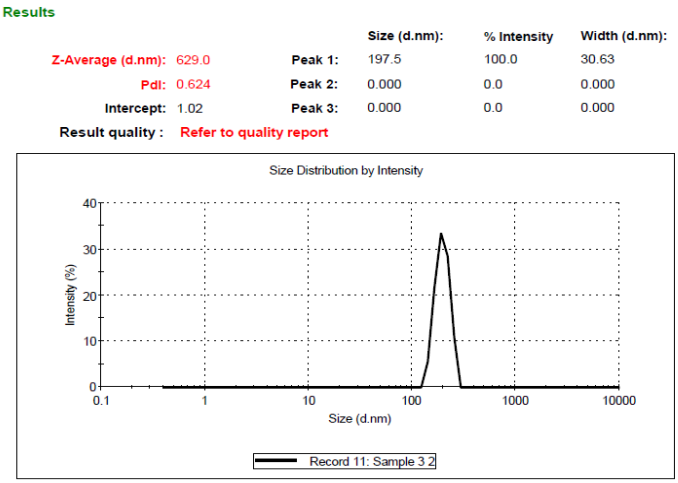


Figure 3: Particle size of formulation M9

Zeta Potential

Zeta Potential is a measurement of the electric charge on the particle's surface that shows if colloidal systems are physically stable. It is an indication for the long-term stability of particulate systems. For a physically stable suspension stabilized by electrostatic repulsion, a zeta potential of approximately ± 30 to ±40 mV is required as minimum. In a combined electrostatic and steric stabilization, as a rough guideline ±20 mV is sufficient. As the Zeta potential of all the batches were within the range, they have good physical stability but zeta potential of batch M9 is -38.20 which is highly negative indicating higher physical stability of formulation.[31] Batch M9's Zeta potential was found to be -38.2 mV. Poloxamer 407, a non-ionic surfactant, is used as a stabilizer that provides steric stabilization. However, medication nanocrystals, despite this stabilization, are often associated with poor Zeta Potential.[32]

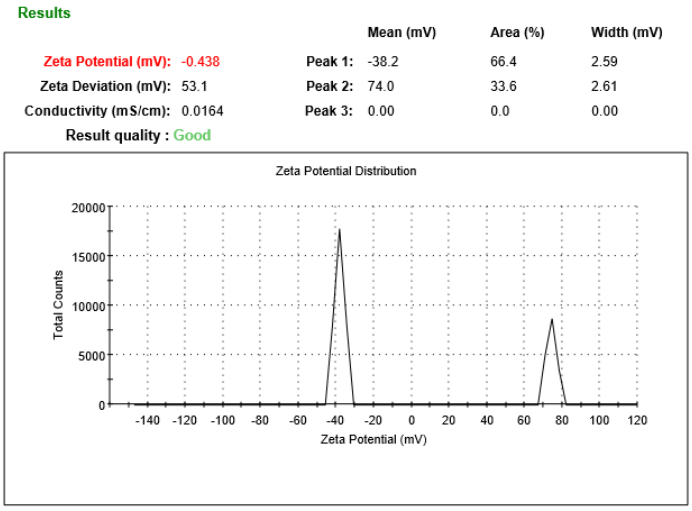


Figure 4: Zeta Potential of formulation M9

PDI (Polydispersity Index)

International standards organizations (ISOs) have established that PI values < 0.05 are more common to monodisperse samples, while values > 0.7 are common to a broad size (e.g., polydisperse) distribution of particles. M9 batch PDI has observed 0.439 which is less than 0.5.

Scanning Electron Microscopy (SEM)

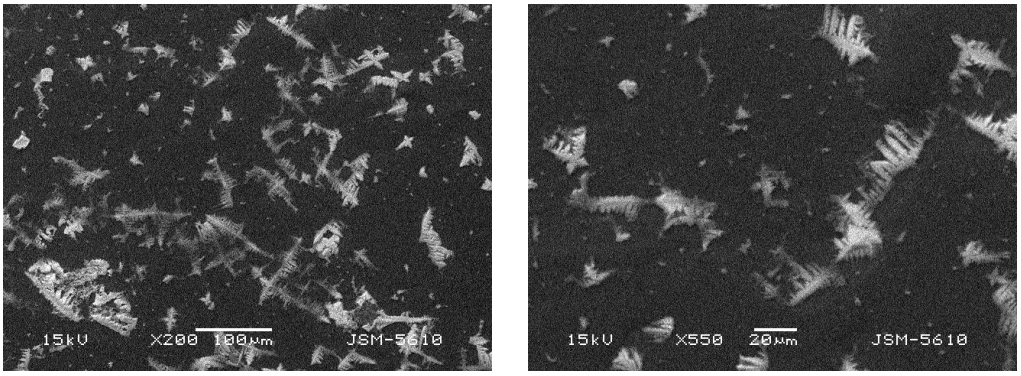
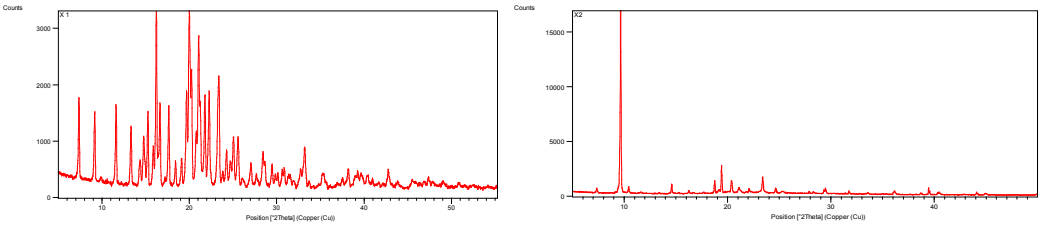


Figure 5: SEM Photographs of formulation M9

Here, many Nano-sized particles were seen in the image shown in Figure 5. The morphology of QF altered from crystalline irregularly shaped particles to spherical particles. When analysed by SEM, it confirmed the formation of nano particles of QF particle size less than 1000 nm (ranging from 128.4 nm to 781.2 nm).

X-ray diffraction

Quetiapine Fumarate powder showed Figure 6 a sharp peak or more peaks indicating the crystalline nature of these compound. Peaks disappeared in Nano-suspension formulation which indicates conversion of amorphous nature of QF powder from the crystalline nature.



(A) (B)

Figure 6: X-Ray diffraction (XRD) spectra of (A) Quetiapine Fumarate powder; (B) Formulation M9.

In Vitro Dissolution Study

In Vitro QF API release Study in 0.1N HCl

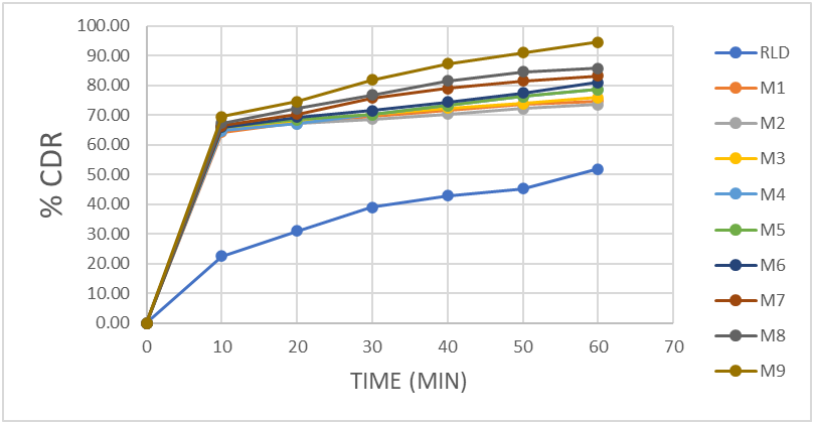


Figure 7: In vitro drug release study in 0.1 N HCl medium [**RLD: Reference Listed Drug*]

The formulation M9 had the drug release of 94.59 % within 60 min compared to the amount of the RLD 48.92 % within 60 min. The increase in dissolution rate may be caused by the increased accessible surface area to the dissolution liquid and the hydrophilic surfactant coating on the particle surfaces. Based on the data given, we can see that the % CDR for M1 is 72.33 and for M9 is 94.59. This indicates that the dissolution of M9 is higher than that of M1, suggesting a faster release of the QF API from formulation M9 compared to M1.

In vitro drug release study in Phosphate buffer solution 6.8

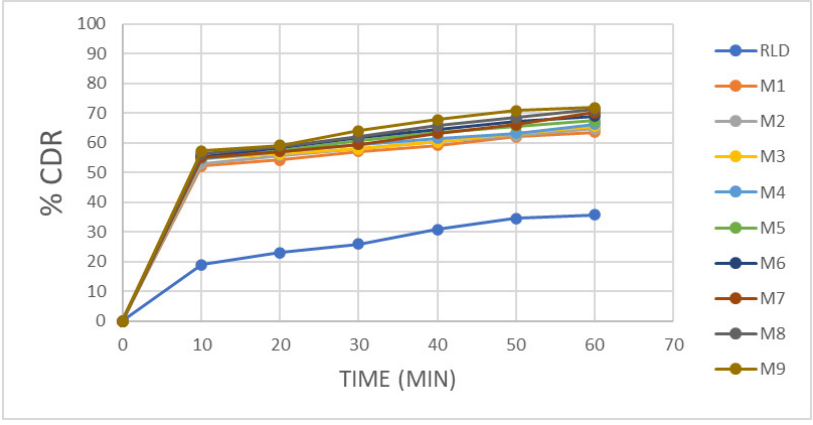


Figure 8: In vitro dissolution study in PBS 6.8*(*RLD: Reference Listed Drug)*

Dissolution studies were performed for the RLD & nano-suspension formulation. Formulation M9 had higher amount of QF API release of 71.87 % within 60 min compared to amount of drug release (32.47 %) from RLD within 60 min. The 60-minute time frame is often chosen for comparing QF API formu-

lations because it is a standard time point in dissolution studies. This time frame is significant as it approximates the gastric emptying time, providing an indication of how much of the QF API would be available for absorption in the small intestine after oral administration.[33]

Table 5: Dissolution profile comparison of nanosuspension with RSD

Factor	M1	M2	M3	M4	M5	M6	M7	M8	M9
F1	52.92	53.69	54.18	54.69	55.65	56.33	55.81	57.12	58.04
F2	30.00	29.32	28.90	28.45	27.60	26.99	27.44	26.28	24.45

As shown in table 5, the dissolution profiles of the prepared nanosuspensions were not similar to that of RSD. The values of difference factors F1 are almost more than 50 [≤15 postulates similarity] while values of similarity factors F2 are less than 30 [≥50 postulates similarity] indicates that the dissolution profiles of nanosuspensions were very different compared to RSD. This was due to enhanced dissolution of the nanosuspension formulation. Further, values for F1 and F2 while comparing M1 and M9 were 10.89 and 60.98 respectively indicating that their dissolution profiles were similar. Thus, the dissolution profiles of nanosuspensions were different from that of RSD while comparable to each other.

Quetiapine fumarate is a weakly basic drug with a pKa value of 7.06. The solubility behavior of quetiapine fumarate, especially in its nanosuspension form, can vary in different media such as HCl and phosphate buffer. In an acidic environment like HCl (pH < 7), a weak base like quetiapine fumarate will primarily exist in its ionized form, which is more hydrophilic and could potentially lead to a faster dissolution rate in HCl compared to a phosphate buffer. On the other hand, in a phosphate buffer (pH > 7), quetiapine fumarate will primarily exist in its unionized form, which is more lipophilic and less likely to dissolve in aqueous media. This could potentially lead to a slower dissolution rate in phosphate buffer compared to HCl.

Optimizing nano-suspension formulation using design of experiments (DoE)

To analyse the effects of independent variables (X1 and X2), a 3^2 response surface methodology was utilized on the dependent variables (Y1 and Y2). The 2D counter plots was used for examining the impacts of independent variables. The three-dimensional (3D) response surface graph was helpful in determining the main and interaction effects of independent variables. Particle size (nm) and % CDR were chosen as independent variables for this investigation, whereas Milling Time (X1 hrs) and Amount of poloxamer 407 (X2 mg) were chosen as dependent variables. The particle size ranged from 130.9 to 281 nm, and the % CDR ranged from 72.33 to 94.59 % in all 09 experimental runs, as shown in Table 6.

Table 6: Experimental runs and the measured response of Nano-suspension

Batch	Actual value			
	X1	X2	Particle size (nm) (Y1)	(0.1 N HCl) %CDR (Y2)
M1	6	100	153.3	72.33
M2	6	200	281.0	75.89
M3	6	300	252.8	74.72
M4	12	100	235.3	79.81
M5	12	200	200.9	81.08
M6	12	300	251.6	78.73
M7	18	100	130.9	83.21
M8	18	200	221.0	85.86
M9	18	300	197.5	94.59

Particle size

Table 7: ANOVA data of particle size

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	15490.60	2	7745.30	12.52	0.0072	significant
X1-milling time	3475.23	1	3475.23	5.62	0.0555	
X2-amount of poloxamer 407	12015.38	1	12015.38	19.42	0.0045	
Residual	3712.40	6	618.73			
Cor Total	19203.00	8				

The model is suggested to be significant by the model's F-value of 15.81. Only 2.30 % of the time is it possible for noise to cause an F-value this large.

Model terms are considered significant when the p-value is less than 0.0500. X_1 and X_2 are important model terms in this instance. Model terms are not significant if the value is higher than 0.1000. Model reduction may enhance your model if it has a lot of unnecessary terms (except those needed to maintain hierarchy).

Y_1 (Particle size) $=248.63 + 52.75\ X_1 - 3.1X_2 - 7.33X_1X_2 - 65.15X_1^2 + 11.75X_2^2$

In the above equation X_1, and X_2 indicate the average result of changing one variable at a time from its low level to a high level. The negative values of these coefficients represent the factors that were inversely proportional to the particle size, while the positive value was directly proportional to the particle size. Here, increasing the poloxamer 407 concentration shows a reduction in the particle size while as the milling time is increased, the effect observed much more prominent with milling time than amount of poloxamer 407. The interaction terms X_1^2 have exhibited a negative relationship with the particle size of nanosuspension, whereas X_2^2 has a positive impact.

% CDR

Table 8: ANOVA data of %CDR

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	349.39	3	116.46	56.89	0.0003	significant
X1-milling time	276.35	1	276.35	134.99	< 0.0001	
X2-amount of poloxamer 407	17.24	1	17.24	8.42	0.0337	
X1 X2	55.80	1	55.80	27.26	0.0034	
Residual	10.24	5	2.05			
Cor Total	359.63	8				

Model significance is indicated by the model's F-value, which is 30.87. An F-value this large might be caused by noise only 0.12% of the time.

Model terms are significant when their P-values are lower than 0.0500. X_1, X_2 and X_1X_2 are important model terms in this instance. The variables in the model are not significant if the value is higher than 0.1000. Model reduction may enhance your model if it has a lot of unnecessary terms (except those needed to maintain hierarchy).

Y_2 (% CDR) $= 80.83 + 6.58\ X_1 + 2.48X_2 + 2.55X_1X_2$

In the above equation X_1, and X_2 indicate the average result of changing one variable at a time from its low level to a high level. The negative values of these coefficients represent the factors that were inversely proportional to the particle size, while the positive value was directly proportional to the particle size.

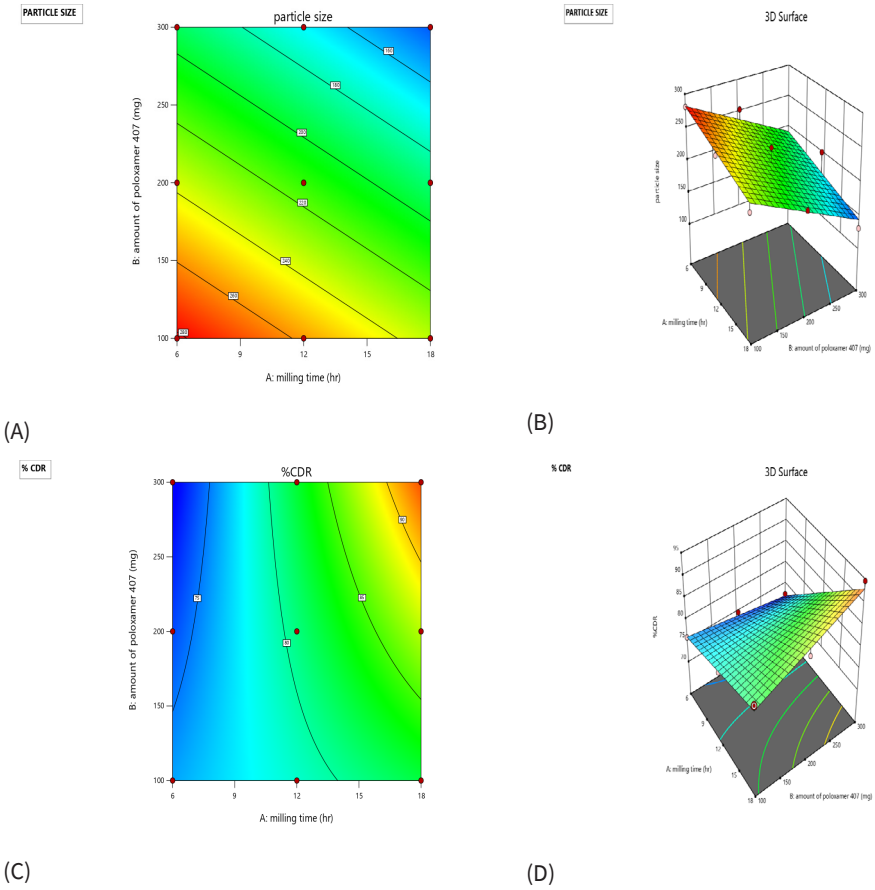


Figure 9: Contour plot and 3D Surface plot of milling time & Poloxamer 407 concentration effect on % CDR of Quetiapine fumarate nano-suspension [For particle size (A, B) % CDR (C, D)].

Discussion

The wet media milling technique is increasingly utilized for scaled-up manufacturing to improve the bioavailability of poorly soluble substances, while ensuring the absence of organic residues. According to research it shows that Stabilizer type, milling time, and milling speed had a significant effect on particle size of the nanosuspensions. Nanosuspensions effectively improved the dissolution rate and bioavailability of the water-insoluble drug by reducing the compound particle size to the nanoscale and employing a proper formulation. In this research it is confirmed the formation prepared by considering milling time and stabilizer type of nanoparticles of QF particle size less than 1000 nm (ranging from 128.4 nm to 781.2 nm). On addition of poloxamer as stabilizer it shows effect on the particle size reduction. During the in vitro dissolution study, it was observed that the QF API alone exhibited limited absorption or release on its own, but when formulated into a nanosuspension, it demonstrated improved drug release. Nanosuspensions can significantly improve the bioavailability of poorly soluble drugs, leading to increased therapeutic effectiveness. The nanoscale particle size in the suspension promotes faster dissolution, ensuring quicker onset of action and improved QF API performance. The scalability of nanosuspension technology allows for efficient and reproducible large-scale manufacturing, facilitating the transition from laboratory development to industrial production.

Conclusion

The research successfully developed a Quetiapine Fumarate nanosuspension by the media milling method, which is expected to improve the solubility and dissolution rate of the drug. Further studies are needed to confirm the impact on bioavailability. This acknowledges the work done while also indicating the need for further research. The nanosuspension exhibited smaller particle size and enhanced drug release compared to the RLD. The formulation was optimized using DoE, indicating that milling time and Poloxamer 407 concentration were critical factors in controlling particle size and drug release. The optimal outcome was found to be achieved at a 1:3 ratio. The characterization procedures that include DSC, SEM, XRD, FT-IR, solubility, and dissolution studies validate the formation of the Nano-suspension. The findings further indicate that Formulation M9 demonstrates a particle size of 190.08 nm, a % CDR of 94.59, and a zeta potential of -38.2, offering additional support for the ability to regulate particle size and enhance dissolution rate. The findings of this research have important implications for improving the oral delivery of poorly water-soluble drugs, especially for medications used in the treatment of psychiatric conditions like schizophrenia.

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