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Nanostructured Lipid Carrier Development and Optimization for Schizophrenia: A Psychological Study

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ABSTRACT

The experimental work and design on the creation and enhanced of a quetiapine fumarate nanostructured lipid transport system for oral drug delivery of used for disease treatment of Schizophrenia. Because quetiapine fumarate is a substrate for Para-glycoprotein inhibitors organize on the surface of the gut and endothelial cells of the BBB. An inhibitor of curcumin is used as drug aid substance entrance to these cells. It was also planned to increase the drug's bioavailability, as it belongs to biopharmaceutical categorization system class II and has a low oral bioavailability of 9%, with a low dose so that the drug's negative effects could be avoided. Hot homogenization method was used to design nanostructured lipid transport systems from cholesterol and oleic acid prepared from different types of lipids one is solid lipid and liquid lipid, respectively. Various types of Surfactant are used in the formulation of nano structured lipid transport system that is vitamin E, tocopherol and polyethylene glycol succinate, which has frequent properties. The primary aim was to enhanced lipid concentration through various experimental design. The respondent were simultaneously charcterized using Deringer's desirability function, which yielded a desirability value of D 0.893, indicating a high degree of global optimisation. To evaluate quetiapine fumarate and curcumin in formulations, a simultaneous approach using RP-HPLC was devised. The configuration of nanostructured lipid transport were characterised for several physiochemical properties, as well as the influence of cholesterol and oleic acid on particle size and transparency. Ex vivo permeability tests were performed to examine the effect of curcumin when coupled with quetiapine fumarate.

Keywords: Quetiapine fumarate, curcumin, nano structured lipid carrier, Deringer's desirability, *ex-vivo* permeability.

1. INTRODUCTION

According to Pharmacological classification Quetiapine fumarate is the second generation antipsychotic drug. Bipolar illness and schizophrenia are both widely treated with it. It was classified as a class II

biopharmaceutical classification system (BCS) drugs with a very low oral bioavailability [Clarie Davis (2007), Parvathi. et al (2014), Rang & Dale(2007)]. The dose of drug limit from 100 to 800 mg/day. The drug has molecular formula of $C_{46}H_{54}N_6O_8S_2$. It is a derivative of dibenzothiazepine. Quetiapine fumarate is also known by its chemical name, 2-[2-(4-benzo[b][1,4]benzothiazepin-6-yl)ethoxy]ethanol;(E)-but-2-enedioic acid. It is also working against serotonin receptors and having lower affinity towards dopaminergic receptors. The reason for poor bioavailability may be due to extensive hepatic metabolism and the drug is being para glycol protein(P-gp) substrate the entry of drug into blood brain barrier is highly affected. The drug also renders side effects like suicidal tendency, somnolence, dizziness, fatigue, irritability, weight gain, orthostatic hypotension, Steven -Johnson syndrome, dyspepsia, abdominal pain, back pain, diabetes mellitus. Though there are several routes to bypass liver like nasal, transdermal , buccal , sublingual, injectable the oral route is the most preferred as it is non- invasive and convenient route[Saller CF. et al,(1993), M.Ribolsi. et al,(2010),Michael Riedel. et al(2007), Sirijit Suttajit. et al,(2014), Arjun Narala.et al,(2013)].

Production of quetiapine fumarate into lipoidal nanoparticles along with curcumin could address the issues. Curcumin is lipophilic in nature. Molecular formula of curcumin is $C_{21}H_{20}O_6$. The chemical name of this substance is (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione[Kavirayani Indira Priyadarsini(2014)]. Colour of curcumin is yellowish–orange with crystalline in nature. It is generally called as Diferuloyl methane. It is extracted from the rhizomes of Curcuma longa Linn and is a member of the Zingiberaceae family. Antibacterial, anti-inflammatory, hypoglycemic, antioxidant, wound-healing, and antimicrobial properties are clearly demonstrated. Curcumin is wonder molecule along with his innumerable medicinal properties, its P-gp modulating ability as P- gp inhibitor it could facilitate the entry of drug in intestine and blood brain barrier (BBB) [Kulkarni SK. et al,(2010), Adhimoolam Karthikeyan. et al,(2020),Mishra. et al,(2008)]. Curcumin having potential to mitigate negative and cognitive symptoms has been proven. It is having ability to control positive symptoms [Joana Costa. et al.(2020),[15] Brietzke E. et al(2013)].

Pharma technology focused on nanoparticulate systems to achieve target and bioavailability. Among the available nanoparticulate drug delivery systems the lipoidal systems is advantageous over other. The lipoidal nano formulations were prepared various formulations like nano emulsions, liposomes, niosomes, Solid lipid nanoparticle and nano structured lipid transport. Among them NLC are considered as second and smarter generation of SLN. NLC are colloidal systems containing both solid lipid and liquid lipid with imperfect arrangement providing more space for drug loading with less leakage. According to a survey of the literature, oleic acid, vitamin E tocopherol polyethylene glycol succinate (TPGS), a surfactant, and P-gp, a modulator, are all described together with cholesterol as a solid lipid and a liquid lipid, respectively.

2. METHODOLOGY

Dr. Reddy's labs Ltd. in Hyderabad, India provided quetiapine fumarate as a gift sample. We collected curcumin from Natural Remedy, Bangalore, India, alongside potassium dihydrogen phosphate, sodium hydroxide, anhydrous acetonitrile, methanol, cholesterol, vitamin E, and tocopherol polyethylene glycol succinate from SD Fine Chemicals, Inc. Laboratory-grade chemicals were used for all experiments.

METHODS:

Preformulation Studies:

Selection and Compatibility Studies of Solid Lipid (Cholesterol), Liquid Lipid (Oleic acid):

The small increments of amount of quetiapine fumarate and curcumin were added to molten cholesterol in vials with extended stirring till a clear melt was collected.[24] The maximum amount of active ingredient that could be dissolved is determined. The solubilization of quetiapine fumarate and curcumin was collected by

visual inspection of formation of transparent homogenous mixture solutions. According to visual inspection process active crystals is not present.[25]

In addition to selected liquid lipid oleic acid in a vial, increasing amount of quetiapine fumarate and curcumin were added and heated with stirring for 1 hour in isothermal shaker and then it was observed for transparent mixtures. The vial in which all the drug was dissolved completely containing minimum lipid was considered as endpoint. A miscibility study was conducted to determine the proportion of solid lipid (cholesterol) and liquid lipid (oleic acid).The mixtures are produced no smear and solid state. Based on the results the solid lipid chosen was cholesterol and the liquid lipid was oleic acid.[26-27] Among the ratios, 90:10 to 70:30 of cholesterol and oleic acid were chosen based on smearing and miscibility studies. Vitamin E TPGS was selected as surfactant and compatibility study of cholesterol, oleic acid and vitamin E TPGS also proved the miscibility.

Compatibility Studies:

FT-IR characterization:

FT-IR spectroscopy was done to study about drug and excipients interaction profile. The spectral region of FT-IR spectroscopy is 4000–400 cm^{-1}. An infrared absorption spectrophotometer (Shimadzu, Model 8033, Japan) was used to measure the interaction between the drug and its excipients.[28]

Differential Scanning Calorimetry

To check the properties of melting behaviour, the crystallinity, enthalpy and glass transition, and maintain the temperature of the drug, DSC investigation were performed. The physical states of cholesterol, quetiapine fumarate, curcumin and the physical mixture were performed. Nearly 8 mg of sample was sealed and placed on aluminium pan and heated to the temperature of 50ºC - 400ºC under nitrogen 40.0ml/min /N2, 60.0ml/min. A NETZSCH DSC 214 Polyma instrument was used to monitor the heat flow from 50 to 400˚C and the temperature alteration at 10˚C/min.

Preparation of Quetiapine Fumarate and Curcumin NLC

Hot homogenisation methods were used to develop NLC of Quetiapine Fumarate with curcumin. To the molten lipid mix, the quetiapine fumarate and curcumin (0.1% w/v) were added and heated to a temperature 90ºC on a water bath. In an isolated beaker, vitamin E TPGS (5% w/v) was taken enumerate to HPLC grade water and was maintained at 90ºC temperature. Similar to the lipid state, it can be compared to the beaker used to create the liquid lipid state. As per literature review the stirring speed was established as 12000 RPM (revolution per min.). By homogenizing both phases (Remi, Electronik, Vasai, India, RQT 127/A/D) for 10 minutes at 12000 RPM, the mixture of two phases has been homogenized. NLC formulations become hot, clear, and transparent after cooling. The developed clear and transparent NLC formulations have been under stability check-up. Different ratios of lipid and surfactant were also under processed. The formulation was optimized by design of experiment (CCD-RSM).[29,30]

Preparation of the formulation NLC by Design of experiments (DOE)

The main preliminary findings showed that the concentration of solid and liquid lipid states changed the particle size and transparency of the transport of nanostructured lipids. Using the central composite rotatable design-response surface methodology (CCD-RSM), a nanostructured lipid transport model was developed. The design of formulation were likely subjected accumulation by two factorial design at three levels (-1,0, +1)by CCD–RSM. As per design, it is a extensible design method produce high modify management over the entire design phase. It was picked by the two independent variables, X1 and X2. To examine their effectiveness on the response variables Y1 (particle size) and Y2 (transparent), solid lipid and liquid lipid were validated at three distinct levels (low, medium, and high). Two independent variables are taken and their states were chosen from abstract collected from various trial runs. The Design-Expert software (trial

version 13.0.0; Stat-Ease Inc. Minneapolis, USA) generated a matrix of design methodologies that was made up of results from thirteen lab runs. Based on the independent variables and their code, actual levels, and dependent variables, table 1 illustrates how constraints are created by using the independent variables. Based on a comparison of the lack of fit test and p-value for the second-order polynomial equation, the representative recommended by the software was selected.[31,32]

Table.1 CCD-RSM NLC preparation according to independent factors and appropriate levels

Independent Variable	**Units**	**Low**	**Medium**	**High**
Cholesterol	%	70	80	90
Oleic acid	%	10	20	30
Dependent Variable	-------	Constraints	--------	--------
Particle Size	nm	Minimize	----------	----------
Transparency	%	Maximize	---------	----------

Analytical method development process for quetiapine fumarate and curcumin by (RP-HPLC)

Curcumin and quetiapine fumarate concentrations in formulations for nanostructured lipid transport were determined using HPLC technique development. This type of method followed according to ICH guidelines and the chromatographic methods are developed. Separation and estimation of both drugs phenomenex kinetex XB-C18 100 working levels were done using chromatographic methods. The columns utilized were analytical columns (3.5 mm, 4.6 mm, 150 mm).It was done with the various solvents.[33]

Characterization of developed nanostructured lipid carriers Transparency

The transparency test was carried out using a UV-Visible Spectrophotometer (UV-1700, Shimadzu, Japan). Formulation of QC-NLC was evaluated in the range of 400-800nm. Distilled water was treated as blank. [34-35]

Cloud Point

The temperature at which a water-soluble surfactant solution becomes surfactant, this is referred to as Cloud point. It is critical to establish the storage capabilities of a surfactant used in developed formulations. The designed formulations were immersed in a hot water bath, with the temperature gradually increasing. According to literature review, production of cloudiness or decrease in transparency demonstrates as cloud point.[36]

Particle Size and Zeta Potential

The particle size and zeta potential of all QC-NLC formulations were determined using a combination of phase analysis, light scattering decay, laser Doppler micro-electrophoresis, and the zetasizer method (Nano ZS, Malvern Instruments, UK). This type of approach was discovered through triplication. The particle size and zeta potential of QC-NLC were calculated with the average size as the standard deviation. The polydispersity index (PDI) indicates the distribution of particle size.

Surface Morphology:

According to the literature review, TEM was used to determine the surface morphology of all QFC-NLC formulations. It is powered by a Philips EM-430 (USA) at an accelerating voltage of 200 kV. On a carbon-coated grid, samples were combined.A drop of 1.3% phosphotungstic acid was put to this grid. The grid was vacuumed dry and placed on a grid holder. Nanostructured was recognized by TEM. The atomic force microscopic study(AFM) was performed on the formulated optimized NLC (QFC-NLC) bring to the light the external morphology possessed by the NLC's. The formulation was diluted and using a drop that was dried as film on the slide the study was carried out using scanning probe microscope of the model.[37]

Optimization of drug loading and entrapment efficiency

A centrifuge was used to centrifuge optimized NLC formulations (QFC NLC) at 12000 rpm for 30 minutes with cooling temperature of 4°C (C-24, Remi). The supernatant liquid of 1ml was extracted and the amount of drug was calculated using the formula below. The free amount of quetiapine fumarate filtrates was collected and determined by RP- HPLC techniques after proper dilution.[38]

Following equation calculates EE:

$$\textbf{EE \%} = \frac{Total\ drug - Free\ drug}{Total\ drug} \times 100$$

$$\textbf{Drug loading}\% = \frac{Weight\ of\ drug}{Weight\ of\ lipid} \times 100$$

In-Vitro Drug Release

According to the literature analysis, the in-vitro drug release study of all developed formulations was estimated using a dialysis bag (5000 Da, Himedia, India). 1 mL of modified nanostructured lipid transport was placed in a dialysis bag. It has been securely sealed and is suspended in 50 mL of dialyzing media. The temperature was maintained at 34 ± 1°C using a thermostatically sealed chamber and rotated at 600 rpm using a magnetic stirrer.[39] For QFC-NLC formulations, several dialyzing mediums are utilized in the proportion (50:50) of Phosphate buffer pH 7.4 and methanol. [40-41] As per procedure, 2 mL of sample was obtained at predetermined intervals, and the receptor chamber was exchanged with the same volume of fresh dialyzing medium. The samples were analyzed in triplicate using the RP-HPLC technique. The results were expected to be the average cumulative proportion of drug released versus time.

Ex vivo permeation studies

In order to conduct the permeation study, a vertical Frankz diffusion cell with a 3.14 cm^2 diffusion area was used. The cell was filled with an optimum NLC solution and a fresh goat intestine was stitched into the shape of a circle. To counteract the effects of boundary layers, a pH 7.4 phosphate buffer solution was added to the receptor compartment and magnetically stirred. In order to keep the sink condition, samples were periodically withdrawn from the compartment. [42].

Stability studies

As per literature review Stability studies of all formulation were performed according to ICH guidelines. The designed formulation of NLC quetiapine fumarate was packed and sealed in class I glass vials with a screw lid and was kept for stability studies in long term (5° ± 3° C) as well as in accelerated stability conditions (at 25° ± 2° C / 60 % ± 5 % RH for six months).

3. RESULTS AND DISCUSSIONS

Compatibility studies

Fourier Transformation Infra-Red Spectroscopy (FTR-IR)

Drug and excipients interaction study were performed by using FTIR spectrophotometer. The results were no incompatibility of drug and excipients and characteristics peak of quetiapine fumarate and curcumin were determined [43- 49]. The results are display in figure 1.

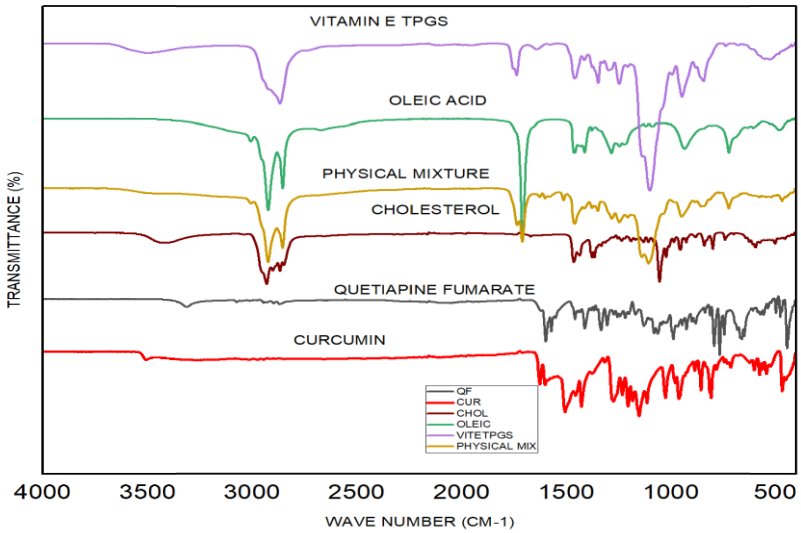


Fig.1 Drug-excipient compatibility studies were performed in FTIR spectrophotometer

Differential Scanning Calorimeter

The endothermic/ exothermic peak is characteristics of each compound. It is a crystallization and interaction between the excipients by the determination of variation of transition powerful tool to analyses the temperature and energy phase. The graphic record displayed a sharp exothermic peak at 173.64ºC for quetiapine fumarate. At the same time graphic record for curcumin the peak was observed at 183.03ºC that specify its characteristics. In case of cholesterol it was at 149.32ºC. These specified characteristic peaks were absent in the formulation indicating that drugs were perfectly blended in amorphous form and encapsulated within lipid matrix providing holistic picture of genuine encapsulation. The graphic record of individual components are display below in figure 2.

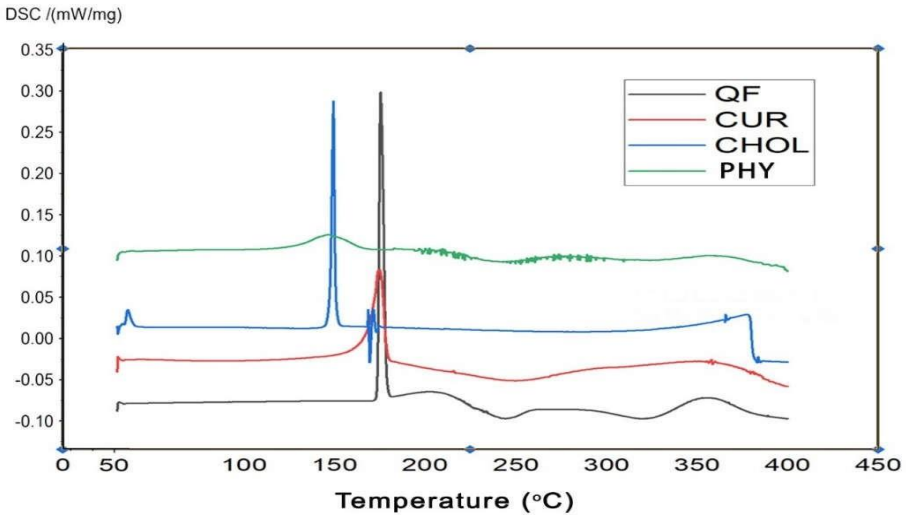


Fig 2. Differential scanning calorimeter of Quetiapine Fumarate, Curcumin, Cholesterol and Physical Mixture (Combined)

Fabrication of NLC and Experimental design:

The NLC's were formulated by hot homogenisation technique and as per CCRD-RSM design matrix and responses after conducting limited experiments are given in Table 2.

Table 2: Design matrix with proposed trials predicted and recognized responses

Formulation	Factor1	Factor2	Response1	Response2
CODE	A: Cholesterol(%)	B: Oleic acid(%)	Particle Size (Nm)	Transparency(%)
F1	70	10	119	80.12
F2	90	10	114.7	90.01
F3	70	30	124.5	84.24
F4	90	30	132.1	75.71
F5	65.85	20	94.14	85.96
F6	94.14	20	134	85.32
F7	80	5.85	113.13	87.54
F8	80	34.14	152	77.21
F9	80	20	94.14	85.96
F10	80	20	94.14	85.96
F11	80	20	94.14	85.96
F12	80	20	94.14	85.96
F13	80	20	94.14	85.96

According to experimental design , It was detected the various responses a model was fitted. The model name is quadratic model. This type of model is used for the study of comparative standards of Regression , Standard deviation and % cumulative value with the regression equation defined for the selected responses are given in Table 3. Only data of statistically important ($p<0.05$) coefficients are included in the equations. The conclusive amount indicates that the effect of the response and unfavourable value defines inverse relationship among the factor and the response.

Table 3: Statistical parameters for particle size and transparency obtained from ANOVA

Response	Regression model	Adjusted R^2	Model r value	% CV	Adequate Precision
Particle Size	+ 764.589 -15.4961A - 9.01737B + 0.02975AB + 0.0977937A2 + 0.190269B2	0.8211	0.0025	7.42	9.1947
Transparency	-24.6752 + 1.77769A + 4.23989 B -0.04605 AB -0.00531875 A2 -0.0216437 B2	0.9363	<0.0001	1.23	21.8829

Effect of solid lipid and liquid lipid on particle size:

As per the literature review study, the three-dimensional(3D)response surface plots for the most data of important variables on the evaluated parameters are display in figure3. The response surface design displayed that with increase in as cholesterol (solid lipid) concentration increases the particle size decreases up to certain level 80% and then particle size starts increasing slightly as it goes below 80%, similarly higher the liquid lipid oleic acid concentration particles size decreased till 20% and slight increase in particle size observed as oleic acid concentration decreased to 10%.The results are shown in figure3 (A,B).

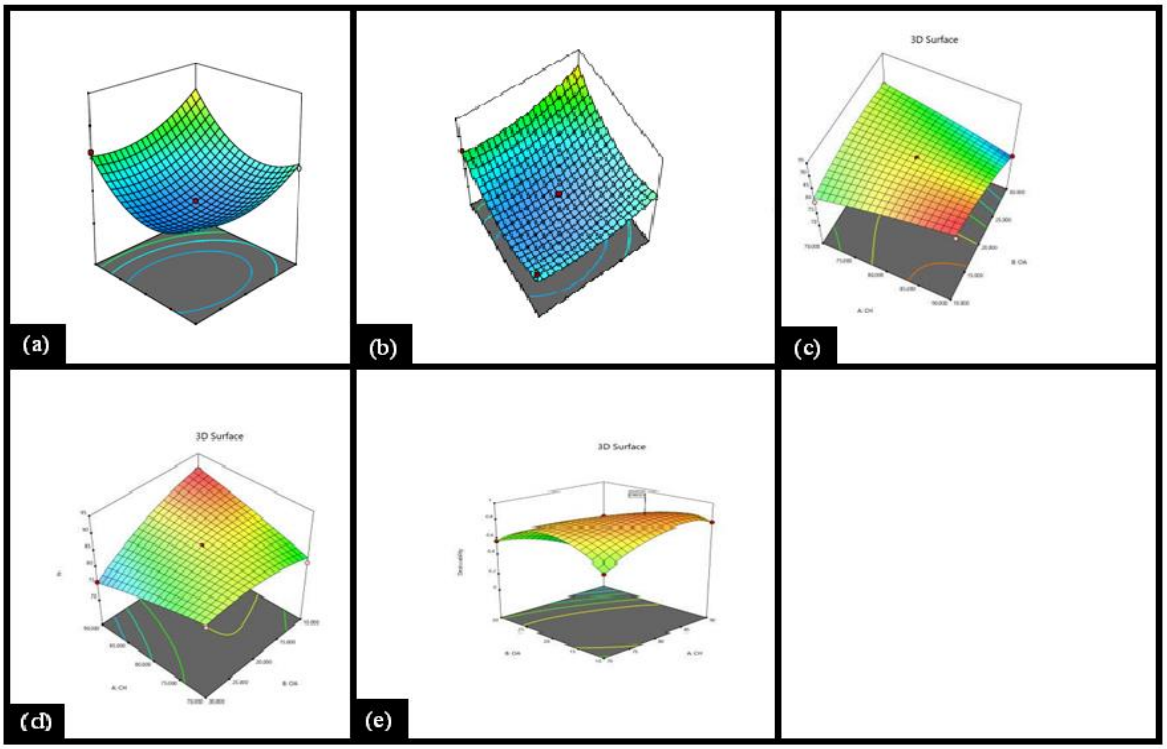


Fig 3. 3D Surface graph displaying effect of independent variables solid lipid and liquid lipid on particle size (A, B) and transparency (C, D, E)-Desirability function of the optimized formulation

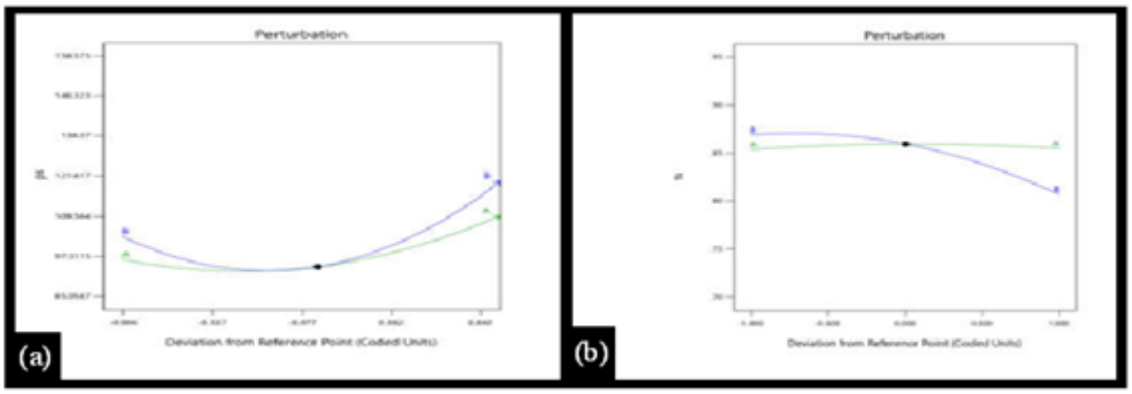


Fig 4. Perturbation Plot showing effect of lipids cholesterol (A) oleic acid (B) on particle size (a) and transparency (b)

Graphical representation of perturbation plotted out in figure 4. a and b determined as per procedure . This design plot displayed the effect on independent factor as per response, with all the others factor represented as

constant at a reference point. Factor A represents the cholesterol and Factor B represents oleic acid. The effect of factors on particle size can be understood either individually or in combined way.

Effect of solid lipid and liquid lipid on transparency:

The transparency of a nanoformulation can be determined by its particle ability to scatter the light. The optimum ability is connected directly with stability of the nano formulations indicating the homogeneity and size of the particles [50]. With increase in cholesterol concentration transparency increased. At the same time with decrease in oleic acid concentration transparency increased. This is clearly depicted in 3D surface plots shown in figure 3(C,D)

Optimization:

The characterization of the concentration ratio of the cholesterol and oleic acid was performed by using response surface methodology and determined the desirability function. According to statistical report, prime function is optimized various variables graphically. Based on the concept, quality of formula that has many unacceptable featured, one of them is outside of a particular limit.

Aim of the process adjusted variable to data that ensure the various compliance with criterion all of the involved responses and that provide some optimum value of particular joint response. This process can be achieved by converting various multiple responses converted into a single response, and then combined the individual responses into a composite function followed by its design [51].

The nominal data of variables solid lipid (cholesterol) and liquid lipid (Oleic acid) were 82.52% and 14.87%, respectively. The figure 5, ramp diagram showing exact relationship between optimized values and desired responses. The predicted responses were 95.981nm and 87.49% for mean particle size and transparency respectively. The measurements were done after the formulation of the designed formula as remarked responses were 96.02nm and 88%, respectively.

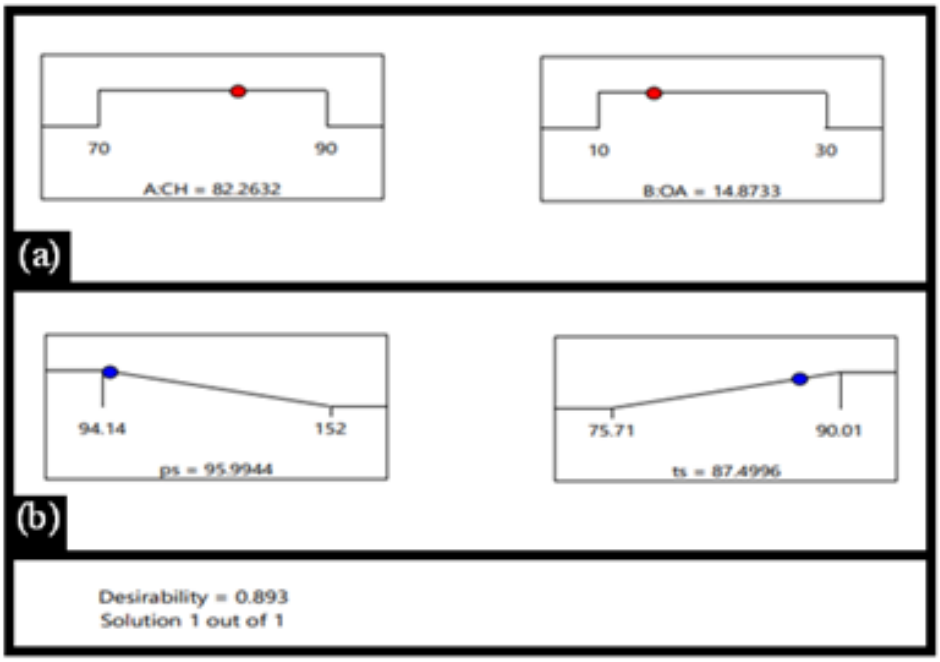


Fig 5. Ramp Diagram Showing the Optimized Ratio of Cholesterol and Oleic Acid Required to Produce NLC

According to study, particle size and transparency% displayed a better observed response, while the determined particle size was smaller than that real measured for the designed formula, the mean particle size and transparency of the designed formula is displayed in figure 5. All the responses were going to close expected values and it is gradually accepted deviation range. Based on study, the desirability function for the optimized process is equals to 0.04 for particle size and 1.70% for transparency, this value of response is very high enough to ensure acceptable values.

In addition to figure 3, E is a 3D surface plot for desirability with factors of Cholesterol and oleic acid. These plots demonstrate that 82.25% of cholesterol and 14.86% of oleic acid plays a major role in the design to produce the quality and reproducible Quetiapine Fumarate loaded NLC formulation. The desirability factor of 0.893 achieved indicates the model is fitting good to produce the required NLC. It confirms that, when there is a change in parameter ranges, the responses also got changed accordingly. The global desirability value of D 0.893 indicates that the model is fitting good. There is good affinity between predicted and experimental values which defines that, the model is fitting good with a desirability value 0.893.

Qutiapine fumarate and curcumin can be measured simultaneously by RP-HPLC

Using the phenomenex kinetex XB-C18 100 equipment, it is highly helpful for separating the two drugs according to chromatographic procedures. With a flow rate of 1.0 mL/min, different analytical columns (3.5 m, 4.6 mm 150 mm) are utilized. The mobile phase is a mixture of methanol and water that is 70:30 by volume. A 200µL sample was properly injected, and a triplication chromatogram at 290 nm was recorded. Quetiapine fumarate was found to have a maximum absorption of 290 nm. At 421 nm, curcumin's maximum absorption was identified. When estimated at a significant single wave length, the evaluation of both drugs is possible. The highest absorption for the peak response of quetiapine fumarate and curcumin was at 290 nm, which is fixed for analysis. Curcumin and quetiapine fumarate had retention times of 2.10 and 4.60 minutes, respectively. The developed method's linearity, robustness, solution stability, inter- and intraday precision, and analyst variance were all validated in accordance with ICH criteria.

Characterization of formulated NLC:

The optimized formulation was labelled as QFC-NLC and it was evaluated for various characterization studies. The results are given in Table 4.

Table 4: Characterization of optimized QFC-NLC

Formulation Code	Parameter	Results
QFC-NLC	Particle size (nm)	96.02±3.12
	PDI	112
	Zeta potential	-20.68+0.5
	Cloud Point (°c)	77
	Transparency(%)	88

The particle size and zeta potential were determined for NLC formulations by Malvern Zeta sizer and particle analyser. The figure 6 (A,B)showing particle size and zeta potential of the optimized formulation.

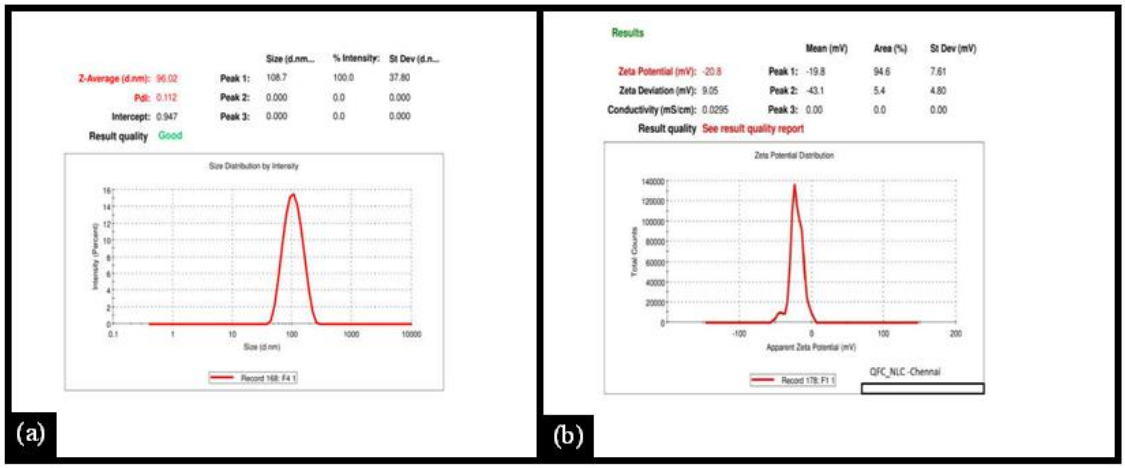


Fig 6. (A) -Particle size (B) -Zeta Potential of the optimized formulation QFC-NLC

Surface Morphology:

The images from TEM and AFM revealed spherical nature of prepared NLC. The image from AFM gave a three- dimensional view of QFC-NLC. The TEM image and AFM image were given in figure 7.

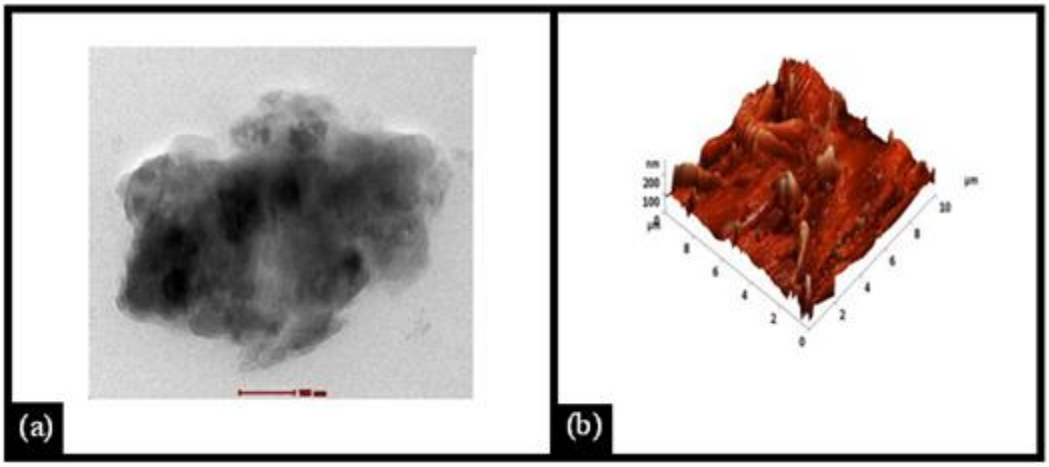


Fig.7 (A) and (B) Surface Morphology of the Optimized Formulation QFC-NLC by TEM and AFM imaging

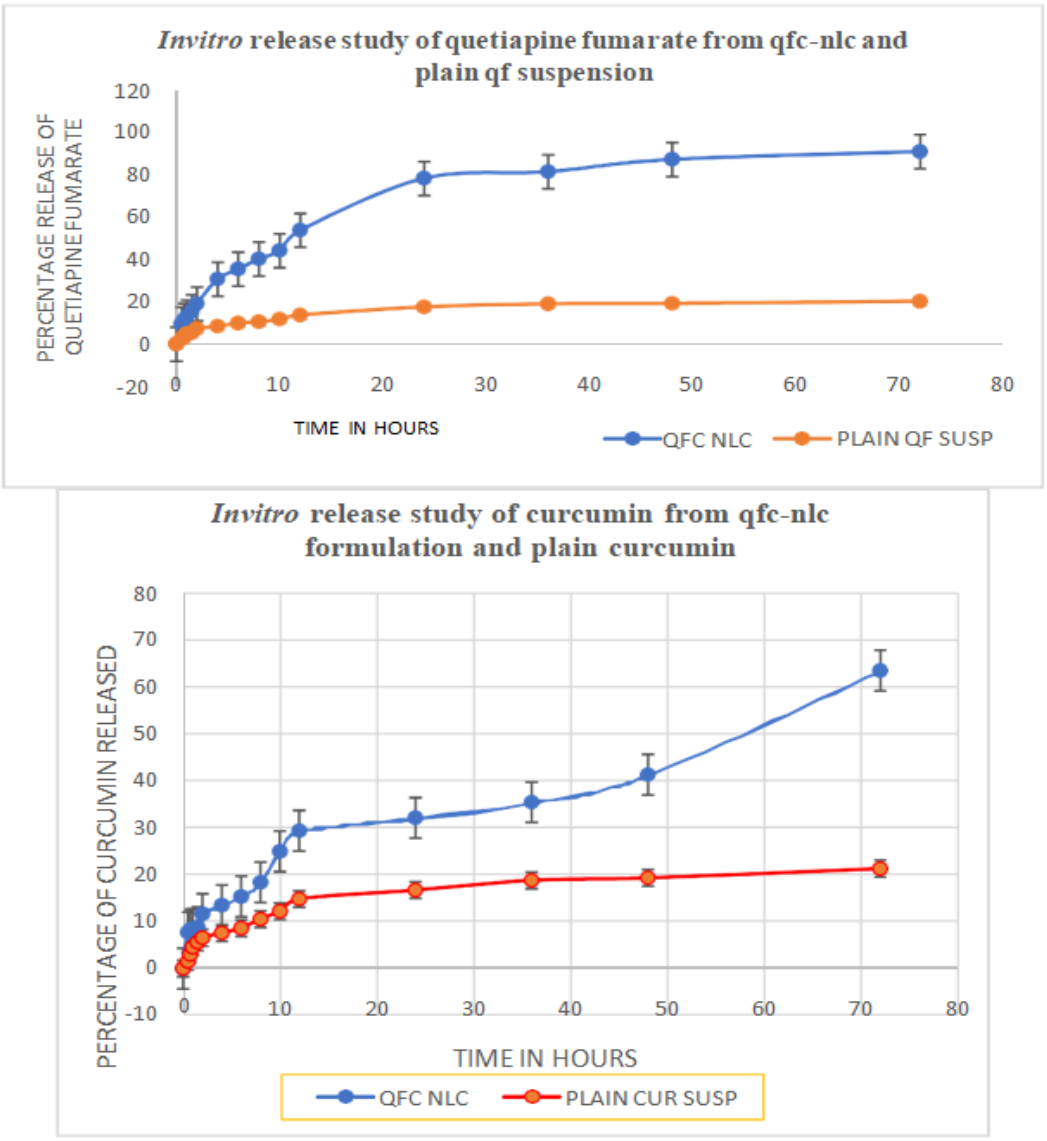
Drug Loading and Entrapment Efficiency

The drug loading and entrapment efficiency for the optimized QFC-NLC formulations were determined by centrifugation. The entrapment efficiency was about 88% for quetiapine fumarate and 82.5% of curcumin. The drug loading was found to be 15%.

In-vitro Release Studies

Dialysis method was performed to in-vitro drug release study from the designed QFC-NLC formulations. The percentage of quetiapine fumarate and curcumin was calculated from designed formulations QFC NLC determined. The release of drug from these optimized formulations was also compared with the release of pure quetiapine fumarate and curcumin from plain suspension. The studies showed that at the end of 72 hours, the release from quetiapine fumarate of optimized QFC-NLC formulation showed drug release of 90.73% of

quetiapine fumarate and 63.59% of curcumin. At the same time, the plain quetiapine fumarate suspension released 20.18% of quetiapine fumarate and the release of curcumin from plain curcumin suspension was 21.32%. This increase in release of quetiapine fumarate from the optimized formulation when compared to plain Quetiapine fumarate and curcumin suspension may be due to presence of components of NLC and the reduced particle size contributed. A biphasic pattern of initial burst release followed by sustained release was due to the adsorbed drug or free drug present on the surface of the NLC. The results of the invitro release studies are given in figure 8.



A. In-Vitro release study of Quetiapine from QFC-NLC and Plain of Suspension
B. In-Vitro release study of Curcumin of OFC-NLC Formulation and Plain Curcumin

Fig 8. A and B showing in-vitro release study of QFC-NLC and plain quetiapine fumarate suspension

Ex-vivo Permeability Studies

The intestinal permeability study of the optimized formulation (QFC - NLC) was done and compared with plain quetiapine fumarate suspension and quetiapine fumarate NLC using goat intestine in frankz diffusion cell with phosphate buffer pH7.4 and methanol. The results shown that percentage of quetiapine fumarate released from

QFC -NLC was more compared to plain quetiapine fumarate suspension and quetiapine fumarate NLC formulation. The presence of curcumin and oleic acid components in the optimized formulation may be the reason behind the increased drug release.

The percentage quetiapine fumarate permeated from optimized QFC NLC formulation was 80.24% at the end of 6 hours whereas the quetiapine fumarate released from NLC formulation without curcumin was 70.31%. When compared to Plain quetiapine fumarate suspension, the release from both NLC formulations was higher, this may be due to lipoidal components such as oleic acid, vitamin E TPGS, curcumin enhances the permeation of quetiapine fumarate. The curcumin and vitamin E TPGS act as P-gp inhibitors thus paving way more for permeation of quetiapine fumarate through the intestine. The results are shown in figure 9.

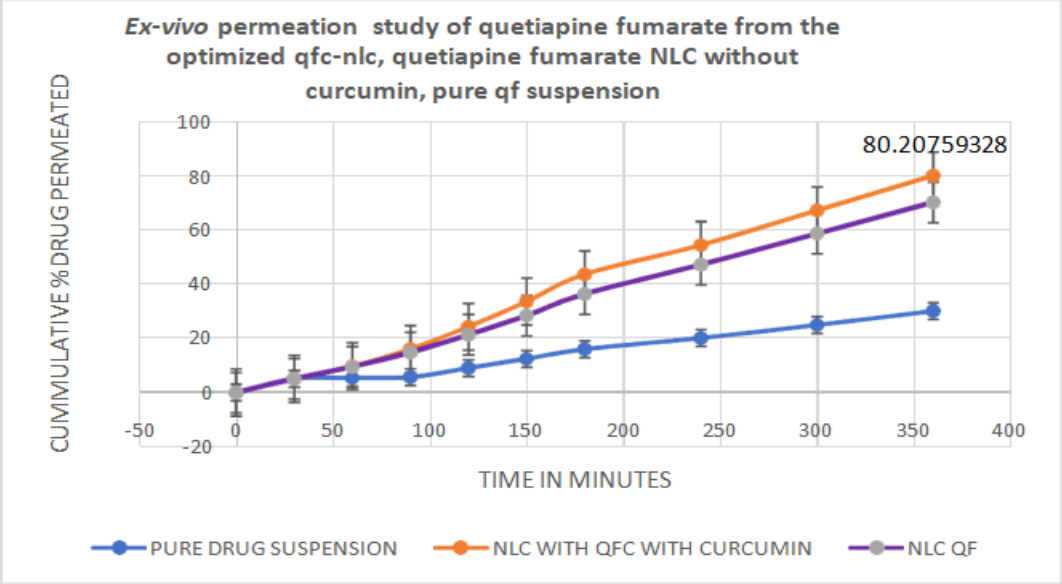


Fig 9. Ex-Vivo permeation study of quetiapine fumarate from the optimized QFC-NLC, quetiapine fumarate NLC without curcumin pure quetiapine fumarate suspension

Stability studies

The stability studies of QFC-NLC formulation define that there were no frequent changes in the physicochemical properties of the formulation at long term stability condition of 5° ± 3° C till 12 months period 25° ± 2° C / 60 % ± 5 % RH till 6 months as well as stable at stability condition of the stability study results of QFC-NLC are presented in table 5 and 6 respectively.

Table 5: Stability study results of QFC-NLC at accelerated stability condition (25° ± 2°C/60% ± 5% RH)

Parameters	Accelerated Stability studies				
	0 month	1 month	2 months	3 months	6 months
Particle Size (nm)	96.02 ± 0.11	96.0±0.43	95.8±0.38	95.4±0.54	95.1±0.41
Zeta potential (mV)	-20.8±0.41	-20.9±0.21	-21.0±0.60	-21.2±0.44	-21.5±0.57
PDI	112	112	111	110.5	110
Entrapment efficiency	88±0.32	87±0.31	87.5±0.51	86.8±0.18	86±0.64
Cummulative in-vitro drug release at 24 hours (%)	90.73±0.62	89.2±0.27	89±0.34	88.5±0.22	88.1±0.39

n = 3; Mean ± S.D

Table 6 : Stability study results of QFC-NLC at long term stability condition (5ºC ± 3ºC)

Parameters	Long term Stability studies				
	0 month	3 months	6 months	9 months	12 months
Particle Size (nm)	96.02 ± 0.11	96.0±0.42	95.9±0.12	95.6±0.61	95.1±0.34
Zeta potential (mV)	-20.8±0.42	-21.9±0.64	-21.5±0.56	-21.8±0.41	-21.0±0.30
PDI	112	112	111	110.4	110
Entrapment efficiency	88±0.32	87.5±0.48	87±0.33	86.2±0.26	86±0.28
Cummulative in-vitro drug release at 24 hours (%)	90.73±0.62	89.8±0.36	89.2±0.45	89±0.16	88.05±0.46

CONCLUSION

We prepared the NLC from quetiapine fumarate and curcumin by homogenizing them with cholesterol as a solid lipid and oleic acid as a liquid lipid using the hot homogenization technique. The NLC was formulated using the CCRD-RSM by fitting a quadratic model. According to the study performed to the response value under designed conditions of cholesterol 82.52% and oleic acid 14.87%. These results of designed formulation defined that the NLC obtained in this study could potentially be produced as a carrier for quetiapine fumarate. Another study according ex-vivo parameter disclose the presence of P-gp inhibitor like curcumin and vitamin E TPGS increased drug permeation of quetiapine fumarate. Adding to this NLC formulation containing optimized lipoidal combination of cholesterol and oleic acid in right amount administering orally could effectively achieve the desired therapeutic effect and patient compliance with reduced dose. In nut shell, successful treatment in chronic therapy of schizophrenia and bipolar disorders could be accomplished with less dose and minimal side effect by this formulation.

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