

## INVESTIGATION FOR QF PROCLAMATION BEHAVIOR OF IMPROVED FORMULATIONS OF NLC AND QF SUSPENSION

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### ABSTRACT:

The optimized formulations found with  $218.1 \pm 0.14$  nm of PS and  $93 \pm 0.16$  % of % EE. Results illustrated the superiority of developed QF loaded NLC formulation as a stable drug delivery system, providing better bioavailability with the possibility of better treatment for psychological disorders. The CCD consists of three factored design with five levels, plus and minus alpha (axial points), plus and minus 1 (factorial points) and the centre point. A mathematical relationship between variables was created by using Design Expert software Version 12. The statistical evaluations revealed that three independent variables were the important factors that affected the PS and % EE of QF loaded NLC. The best fitted mathematical model was linear and quadratic for PS and % EE respectively. The aim of present study is to investigate the potential of nanostructured lipid carriers (NLCs) in improving the oral bioavailability of quetiapine fumarate, a second-generation antipsychotic drug. Quetiapine Fumarate (QF) loaded NLC were prepared by hot homogenization followed by an ultrasonication method. Response surface methodology - central composite design (CCD) was used to systemically examine the influence of concentration of capmul MCM EP, concentration of poloxamer 188 and concentration of egg lecithin on particle size (PS) and % entrapment efficiency (% EE) and to optimize the NLC formulation.

**KEYWORDS:** Central composite design; Nanostructured lipid carriers; Poloxamer 188; Quetiapine Fumarate; Response surface methodology.

### INTRODUCTION:

Colloidal drug carriers have been used to address solubility issues of a drug. But these systems suffer from certain disadvantages like drug leakage, stability problems, high production cost and sometimes cytotoxicity. Similarly, lipid containing delivery systems such as lipid drug conjugate (LDC), solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) can be effectively used to solve customary drug delivery systems issues such as low bioavailability and low drug loading. Since last decades a tremendous rise has been observed in the psychological disorders, particularly bipolar disorder and Schizophrenia<sup>1</sup>. Quetiapine is one of the extensively prescribed drugs as monotherapy in treatment bipolar disorder and schizophrenia<sup>2, 3, 4, 5</sup> QF belongs to Biopharmaceutics Classification System class II<sup>6, 7</sup> drug

and exhibits 9% oral bioavailability. QF being weak acid get rapidly absorbs in the stomach but suffers from high first-pass effect. QF possesses half-life of 6 hours and requires frequent administration which in turn enhances chance of dose skipping<sup>8,9</sup>. Low oral bioavailability and high first pass effect lead to reduction in absorption which is a major obstacle in QF therapy. QF exhibits low solubility and low absorption at high pH. QF undergoes P-glycoprotein (P-gp) efflux leading to less concentration in the brain even after absorption.

However, LDC suffered with few demerits such as particle size growth, uncertain gelation tendency, sudden polymeric transitions and low drug loading<sup>10,11</sup>. In order to address LDC disadvantages, SLN system was developed<sup>8</sup>. SLN can be characterized as small lipid containing preparations which possess large surface area and have been considered as biocompatible and biodegradable systems<sup>12,13,14,15</sup>.

NLC (Lipid based systems) - The second-generation lipid carrier is usually composed of solid lipids and liquid lipids together in a system with surfactant<sup>16,17</sup>. This mixing causes depression in melting point of substrates and converts the mixture into solid form at body temperature. NLC shows a high drug loading with minimum drug expulsion<sup>18,19,20</sup> as compared to SLN. NLC bypass P-gp efflux due to other way for uptake (non receptor mediated endocytosis). In view of these facts, NLC system can be considered as effective alternate to overcome issues associated with QF therapy.

## **MATERIALS AND METHODS:**

### **Materials:**

QF was obtained as a gift sample from Aurobindo Pharma Limited, Hyderabad, India. For the production of NLC, Monegyl - T18 and Monegyl - D207 (Mohini organics Pvt. Ltd. Mumbai), Glycerylmonostearate, GMS (Micro Labs Limited, Bangalore), Capmul MCM EP (Intas pharmaceuticals Ltd., Ahmedabad), Poloxamer 188 (BASF India Limited, Navi Mumbai), Egg lecithin (Naproid life sciences Pvt. Ltd. Mumbai) were used. All the other reagents used were of analytical grade.

### **Methods:**

#### **Optimization of ratios of solid lipid to liquid lipid:**

Solid lipid (Stearic acid, Monegyl- T18, Monegyl- D207, GMS) was screened by method given in literature survey<sup>21,22</sup>. Liquid lipid (oils) was selected depending on the solubility of the QF in liquid lipid<sup>23,24,25,26,27</sup>.

The mixture comprising of both solid and liquid lipids were prepared homogenous. To optimize the ratio of lipids, miscibility test between the selected lipids namely GMS and capmul MCM EP was performed. The selected solid lipids and oil were weighed in the different % ratios (60:40, 70:30, 63.636: 36.363) in glass vials. This blend was heated to a temperature 10°C above the M.P. of the solid lipid. Thereafter, the liquid blend vortexed and smeared on glass slide. Upon solidification, a dry filter paper was pressed on this lipid blend and observed for sign of oil drops, if any. The mixture that does not showed any oil drop on filter paper was considered as miscible and was selected for the development of QF loaded NLCs<sup>22</sup>.

#### **Preparation of QF loaded NLCs:**

QF loaded NLCs were fabricated by a slight modification of hot homogenization method followed by the ultrasonication method. Preliminary batches were prepared, examined and optimized for various process parameters such as water volume, sonication time, amplitude, PS, Zeta potential (ZP), Polydispersity index (PDI) of the NLC dispersion. This method resulted in consistent production of smaller size NLCs (<250 nm) with good PDI and good % EE. Egg lecithin was dissolved in 3ml mixture of methanol and chloroforms (1:1) and vaporized for 15 min to completely evaporate the solvents to achieve a film of egg lecithin. The GMS and capmul MCM EP were melted (10°C above the M.P. of the lipids used) and was added to above mixture. QF was added to attain a drug-lipid mixture. The hot surfactant solution (poloxamer 188) in water preheated to 10°C above the lipid's M.P. (70°C) was added to the clear lipid melt containing egg lecithin. Resulting mixture was exposed to high-shear homogenization at 2000 rpm for 10 min and heated to obtain a coarse emulsion. This coarse emulsion was then subjected to probe sonicator (PCi *analytics* PKS -750FL, Mumbai) for 15 minutes at 50°C by maintaining output amplitude at 50% and gap of 5 second to form NLC dispersion. Then hot NLCs obtained was cooled to room temperature to precipitate the lipid into the solid form to yield QF loaded NLCs . This technique is simple to prepared NLCs without any sophisticated instruments and can also be used for large scale production .

Preliminary batches of NLC and optimization of process variables:

Based on literature survey and trial batches, critical process variables were identified and subjected to optimization. QF suspension was formulated using 0.025gm of QF, 0.125gm of sodium carboxy methyl cellulose as a suspending agent and distilled water up to 25ml as vehicle for further studies. Selected process variable used were temperature (70°C), magnetic stirrer rpm (2000 rpm) for 10 min. The sonicator process used variable were amplitude at 50% and gap of 5 sec. for 15 min. (Table 1)

Table 1: Preparation of trial NLC batches

Sr. No.	Components (gm)	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
	Ratio of Solid lipid % to liquid lipid %	63.636:36.363	63.636:36.363	60:40	60:40	70:30
1	QF	0.025	0.025	0.025	0.025	0.025
2	Monegyl T 18	0.175	-	0.0875	-	-
3	GMS	-	0.175	0.0875	0.165	0.1923
4	Capmul MCM EP	0.1	0.1	0.1	0.110	0.0827
5	Poloxamer 188	0.375	0.375	0.375	0.375	0.375
6	Egg lecithin	0.250	0.250	0.250	0.250	0.250
7	Distilled water (ml)	25	25	25	25	25

Experimental design for QF loaded NLC:

Preliminary batches indicated that the variables viz. concentration of capmul MCM EP ( $X_1$ ), concentration of poloxamer 188 ( $X_2$ ), and concentration of egg lecithin ( $X_3$ ) were the important factors that affected the PS and % EE of NLC. Thus, response surface methodology- (CCD) was used to systemically examine the influence of these three independent variables on PS (nm) and % EE of the prepared NLCs. The CCD consisting of three factored design with five levels, plus and minus alpha (axial points), plus and minus 1 (factorial points) and the center point, hence 15 runs was used in this study. On the basis of the results obtained from preliminary batches, the optimize concentrations of different components was selected (Table 1). The details of the formulation design are listed in Table 2.

Table 2: Independent variables, dependent variable and levels for design of NLCs

Variables	Levels				
1. Independent variables in gms	-1.68179	Low (-1)	Center	High (+1)	+1.68179
Concentration of capmul MCM EP ( $X_1$ )	0.0829552	0.1	0.125	0.150	0.167045
Concentration of poloxamer 188 ( $X_2$ )	0.140343	0.2	0.2875	0.375	0.434657
Concentration egg lecithin ( $X_3$ )	0.11591	0.150	0.2	0.250	0.28409
2. Dependent variable	Constraint				
Y1: PS (nm)	Minimize				
Y2: EE (%)	Maximize				

For all batches the quantity of QF (0.025gm), GMS (0.175gm), water up to (25 ml) was kept constant. The formulations were prepared in triplicate. Results of the study were validated through design expert software version 12 (State Ease, Inc., USA) for further analysis .

Optimization of QF loaded NLC formulation:

The solution that has ‘Desirability Factor’ close to 1 was selected as given by Design Expert software .

Freeze-Drying (FD) Study:

Several ratios of total lipids: cryoprotectant (Trehalose) at 1:2, 1:4, 1:6 and 1:8 were tried. The selected cryoprotectant was added after homogenization process. The blend was then subjected to freeze-drying (Labconco, 25 Plus) at  $-40\text{ }^{\circ}\text{C}$  for 24 hrs. The ratio that produced the smallest PS and PDI was selected.

Evaluation and characterization of QF loaded NLCs

Particle size and polydispersity index (PDI):

The FD samples of QF loaded NLCs were used after reconstitution with distilled water for analysis of PS and PDI. PS was calculated by using photon correlation spectrometer (Malvern Zeta sizer nano ZS 90) with a 4.0 mW internal laser. Dynamic light scattering was based on the particle diffusion associated with Brownian motion, which gives an idea about PS. PS was then estimated by the translational diffusion coefficient using the Stokes-Einstein equation by software. PDI was determined to confirm distribution of PS in the formulation.

Zeta potential:

The FD samples were used after dilution with distilled water to determine ZP of prepared formulation was evaluated by using the Malvern Zetasizer Nano ZS 90. The electrophoretic mobility of particles was transformed to the zeta potential. Zeta potential was determined using the 'Dip cell' with application of field strength 20 V/cm with 30 runs.

Entrapment efficiency and drug loading:

The drug loaded NLC was subjected to centrifuge at 45,000 rpm for 35 min. Then 1.0 ml of the supernatant was diluted with methanol. The samples were analyzed by using UV spectroscopy at 244 nm (UV 1650, Shimadzu, Japan) to calculate % EE<sup>42</sup>. For drug loading, QF from freeze dried powder was mixed with methanol. The QF quantity was analyzed by using UV spectroscopy at 244, against methanol as blank.

Drug excipients compatibility studies, (FTIR) study:

The FTIR spectrum of QF and final formulation were recorded by FTIR (FTIR-4800, Shimadzu, Japan). Briefly, solid sample (1 mg) along with 100 mg dried potassium bromide was compressed into a disc. For liquid sample, sample drops were dripped onto NaCl or KBr aperture plate and sandwiched it under other aperture plate by forming thin liquid membrane. Then, sample was scanned for absorbance in between 4000 ~ 400 cm<sup>-1</sup>. The obtained spectrum was then matched with standard group frequencies of QF. The obtained FTIR (4800, Shimadzu, Japan) spectrum was then compared with standard frequencies of QF.

Morphological study (SEM):

The surface morphology of FD sample (batch F3) was studied using SEM (TESCAN MIRA3, Czech Republic). The sample was dusted on double-sided tape onto aluminum stub, coated with gold by using cold sputter coater in SEM chamber of thickness 400 Å. The graphs were recorded with voltage of 15 kV electron beam.

Differential scanning calorimetry (DSC):

Thermal analysis data was recorded using a DSC (DSC 204 F1 Phoenix, NETZSCH). The freeze-dried sample (2 mg) was sealed in pin-holed standard 40 µl aluminumpan. The heating rate was 10°C/min from 30°C to 400°C and nitrogen purged rate of flow was 10 ml/min. The data was also recorded for QF (drug), GMS (solid lipid) and physical mixture.

X-ray diffraction (XRD):

The physical state of QF loaded NLCs was evaluated by XRD (Bruker AXS D8). The freeze dried NLC was smeared on low background sample holder and fixed onto stage in goniometer. Device was set with B-B

geometry. The voltage and current were set to 35 mA and 40 mV respectively and XRD was recorded. The data was also recorded for QF (drug), GMS (solid lipid) and physical mixture .

*In vitro* drug release:

The *in vitro* release of QF from optimized formulation F3 and prepared QF suspension was recorded using the dialysis bag diffusion method . The optimized NLC formulation equivalent to 5 mg of drug was transferred to a dialysis bag, sealed and suspended for 2 hrs in USP (type II) apparatus containing 900 ml 0.1 N HCl (pH 1.2), and then in phosphate buffer (pH 6.8) for 24 hrs with 50 rpm at 37°C ± 0.5°C. The 5 ml of the samples were taken out at intervals *viz.* 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 12 and 24 hrs filtered through 0.45 µm membrane filter and the same was replaced with fresh media to enables sink condition throughout release period. The QF release was analyzed after dilution at 207 nm using a UV–Visible spectrophotometer by taking the respective medium as a blank. Same procedure was repeated for QF suspension. All measurements were run in triplicates . Data was fitted to different kinetic models to obtain the release kinetics of NLCs . The highest r<sup>2</sup> value showed the actual mode of drug release .

Stability studies:

The stability study of FD batch F3 of NLCs was carried out in accordance with ICH guidelines. Formulation F3 were stored at 25°C±2°C /60% RH, ambient temperature and 40°C±2°C /75% RH) for 6 months. Effects of temperature and RH on PS and % EE were studied at the end of 0, 3 and 6 months respectively .

**RESULTS:**

Optimization of ratios of solid lipid to liquid lipid:

After solidification of selected solid lipid and liquid lipid in different % ratios (60:40, 70:30, 63.636:36.363), they were applied to dry piece of filter paper and the sample which did not show any oil droplets on the surface of filter paper was considered miscible was selected for use in the development of trial batches of QF loaded NLCs.

Results of preliminary batches and optimization of process variables of NLCs:

Preliminary optimization of stirring time, rpm and temperature was decided by literature survey and by conduction of the different experiments <sup>56</sup>. NLC Trial 2 batch demonstrated good result with PS as 240.6nm, ZP of -25.3 mv, PDI of 0.492 good result.

Experimental design with results for NLC formulation

The experimental results were showed in Table 3.

Table 3: Experimental design for formulation of QF loaded NLC

Batch	Independent variables			Dependent variables			
				Observed value		Predicted value	
	X <sub>1</sub>	X <sub>2</sub>	X <sub>3</sub>	Y <sub>1</sub>	Y <sub>2</sub>	Y <sub>1</sub>	Y <sub>2</sub>

F1	0.1	0.2	0.15	240.5±1.08	92.2±0.16	240.13	91.86
F2	0.15	0.2	0.15	242±0.81	83.5±1.22	241.94	83.84
F3	0.1	0.375	0.15	218.1±0.14	93±0.16	220.46	92.59
F4	0.15	0.375	0.15	220.8±0.16	84.2±0.29	222.26	84.16
F5	0.1	0.2	0.25	243.2±0.61	92.5±0.08	243.3	92.14
F6	0.15	0.2	0.25	245.1±0.08	83.5±0.4	245.1	83.51
F7	0.1	0.375	0.25	225±0.32	93.2±0.16	223.62	92.46
F8	0.15	0.375	0.25	225±0.81	83.5±0.08	225.43	83.43
F9	0.0829552	0.2875	0.2	231.3±0.08	95±0.81	231.26	95.91
F10	0.167045	0.2875	0.2	235±1.41	81.9±0.48	234.3	81.56
F11	0.125	0.140343	0.2	249.5±1.22	87±1.08	249.33	87.01
F12	0.125	0.434657	0.2	218.3±0.35	87±1.55	216.23	87.56
F13	0.125	0.2875	0.11591	232±0.73	88±0.81	230.12	88.08
F14	0.125	0.2875	0.28409	234.8±0.97	87.2±0.16	235.44	87.7
F15	0.125	0.2875	0.2	232.5±1.00	87.5±0.08	232.78	87.48

mean ± SD , n=3, X1: concentration of capmul MCM EP (gm); X2: concentration of poloxamer 188 (gm), X3: concentration of egg lecithin (gm), Y1: PS (nm), Y2:% EE (%)

Polynomial equation:

Polynomial equations for Y<sub>1</sub> and Y<sub>2</sub> were as follows:

$$Y_1 = +254.26800 + 36.09216$$

$$X_1 - 112.44751X_2 + 31.64568 X_3 \text{ -----(1)}$$

$$Y_2 = +115.34921 - 310.43642$$

$$X_1 + 17.39099X_2 - 3.41783X_3 - 45.71429$$

$$X_1X_2 - 120X_1X_3 - 22.85714X_2$$

$$X_3 + 708.09282X_1^2 - 9.15519 X_2^2 + 56.81505X_3^2 \text{ -----(2)}$$

Response 1 (Y<sub>1</sub>): Effect on PS

Results of all batches from ANOVA analysis, showed that independent factors were significantly affect the PS (p-value : <0.0001). The  $R^2$  value (0.9862) found near to 1 showed linearity. The linear model F value of 381.13 showed that the model was significant. PS of all 15 batches were in the range of  $218.1 \pm 0.14 \text{ nm}$  to  $249.5 \pm 1.22 \text{ nm}$  (Table 3). Equation (1) shows factors  $X_1$  (concentration of capmul MCM EP),  $X_3$  (concentration of egg lecithin) have positive effect on PS of NLCs and  $X_2$  (concentration of poloxamer 188) have a negative effect on PS of NLCs. This is also confirmed by equation of response  $Y_1$ .

The PS of NLCs increased with an increment in liquid lipid concentration, which was found similar to reports published by Hu et al., Tamjidi et al. and Dai et al. This may be due to disruption of lipid wall followed by aggregation and ultimately particle size growth with increase in liquid lipid content<sup>57</sup>. Elevation in interfacial tension results in swelling of NLC and higher liquid lipid concentration causes increase in PS.

Poloxamer in 1.5% concentration was sufficient to cover the surface of QF loaded NLC effectively during the formulation process due to reduction in interfacial tension between the water and oil phase which lead to separation of particle and surface area enlargement. But beyond the appropriate surfactant concentration, saturation occurs where the affinity between lipid and water phase gets decrease which would not permit the PS to decrease further<sup>60</sup>.

Response 2 ( $Y_2$ ): Effect on % entrapment efficiency:

Results from the ANOVA analysis indicates that all independent factors were greatly affect the % EE of NLCs (p-value: <0.0001). The  $R^2$  value (0.9899) was found near to 1 and showed linearity. The quadratic model with F value of 108.73 showed the model was significant. The % EE of all batches was in the range of  $81.9 \pm 0.48$  to  $95 \pm 0.81\%$  (Table 3).

The equation (2) showed linear and quadratic interactions for response  $Y_2$ . Factors  $X_1$  (concentration of capmul MCM EP) and  $X_3$  (concentration egg lecithin) had negative impact on % EE of NLCs and  $X_2$  (concentration of poloxamer 188) had a positive impact on % EE of NLCs.

The 3D plots showed the negative impact of  $X_1X_2$ ,  $X_1X_3$ ,  $X_2X_3$  interactions on % EE of NLCs. The negative impact of  $X_1X_2$  interaction (increase in concentration capmul MCM EP and concentration of poloxamer 188) or  $X_1X_3$  interaction (increase in concentration capmulMCM EP and concentration of egg lecithin) or  $X_2X_3$  interaction (increase in concentration of poloxamer 188 and concentration of egg lecithin) would decrease the % EE of NLCs.

The drug QF is lipid soluble which gets entrapped in the lipid matrix and showed good % EE. Its solubility decreases during cooling of lipid melt. Further, capmul MCM EP in the lipid mixture increases drug dissolution and also help in preventing separation and crystallization of QF from lipid blend on cooling, which is in good accordance with the findings of the earlier studies of Lohan et al and Muller et al<sup>28, 61</sup>.

The % EE of NLCs reduced greatly with an increment in liquid lipid concentration, which was found in agreement to earlier reports of Zhu et al., Ali et al., Soleimanian et al., Kudarha et al<sup>62, 63, 64, 65</sup>. This may be due to lipid precipitation during NLCs production. During cooling, re-crystallization of lipids results low drug entrapment. Thus, increase in the lipid concentration beyond certain limit leads to poor % EE.

Optimization of QF loaded NLC:



Optimization of QF loaded NLC was carried out to determine the appropriate concentration of independent variable. Results derived from design expert software 12, indicated that F3 has all characteristics to be considered as optimized batch (0.4% of capmul MCM EP, 1.5% poloxamer 188 and 0.6% egg lecithin).

Freeze-Drying Study:

Various total lipid: trehalose ratio (1:1, 1:2, 1:4, 1:6) were tried. But 1:4 ratio was used in the formulations for further investigation as this ratio showed superior result with PS of 220nm, ZP of -29.5mv and PDI of 0.380 than other ratios.

Evaluation and characterization of QF loaded NLCs

Particle size and polydispersity index of QF loaded NLCs:

The particle size and PDI of optimized batch F3 was found  $218.1 \pm 0.14$ nm and 0.382 respectively. (Fig. 1)

Fig. 1: Particle size and polydispersity index of QF loaded NLCs

Zeta potential::

The ZP of F3 batch was found to be -29.5 mV, which imparts good stability of NLCs dispersion.

Percentage entrapment efficiency and drug loading:

All batches showed good % EE ranging from 81.9% to 95% (Table 3). The % EE for the batch F3 was found to be  $93.00 \pm 0.163$  %. The DL was found to be  $8.65 \pm 0.067$  %.

Fourier transforms infrared spectroscopy (FTIR) study:

As there is no change in the nature and position of the peak in the formulation, it can be concluded that the drug maintains its identification without any chemical interaction with excipients used.

Morphological study (SEM):

The micrograph of the optimized NLC (F3) demonstrated spherical droplets with average diameter of 50.47nm .

Differential Scanning Calorimetry (DSC):

The absence of peak in the endotherm of optimized formulation was due to Kelvin effect (nanoparticles melt at a temperature lower than the M.P. of solid lipid) <sup>68</sup>. This finding suggests the conversion of the crystalline QF to its amorphous state. Thus indicate no incompatibility .

X-ray diffraction (XRD):

The XRD spectra of QF showed intense peaks at  $2\theta$  scale, indicating the high crystalline structure of QF (i.e., two sharp peaks at  $2\theta = 22.617^\circ$  and  $25.2341^\circ$ ). The peaks of QF were absent in the XRD pattern of physical mixture and QF loaded NLC formulation, confirmed that the QF molecule was converted to an amorphous complex with the lipid matrix.

From stability results it can concluded that the formulation had satisfactory stability over 6 months period . (Table 4)

Table 4: Stability study of optimized formulation of NLC

Time (months)	0	3	6
Condition	25°C±2°C /60%±5 RH		
PS (nm)	218.1	220	220
% EE	93	93	93
Condition	Ambient temperature		
PS (nm)	218.1	218.1	218.1
% EE	93	93	93
Condition	40°C±2°C /75% ±5 RH		
PS (nm)	218.1	218.1	218.1
% EE	93	93	92

## DISCUSSION:

The particle size of NLCs increased with an increment in liquid lipid conc., same results as per earlier reports . This may be due to disruption of lipid wall then aggregation and ultimately particle size growth with increase in liquid lipid content . Interfacial tension increased and core of NLC swelled with greater liquid lipid concentration and thus observed increase in PS .

But beyond the appropriate surfactant conc., there exists saturation where the affinity between lipid and water phase gets explored entirely which would not permits the PS to decrease further .

The drug QF is lipid soluble, so it mostly entrapped in the lipid matrix and showed good % EE. The solubility decreases during cooling of lipid melt. Further, capmul MCM EP in the lipid mixture increases drug dissolution and also help in preventing separation and crystallization of QF from lipid blend on cooling .

## CONCLUSION

The % EE of NLCs reduced greatly with an increment in liquid lipid conc., which was same that found in earlier reports . This may be due to lipid precipitation during NLCs production. During cooling, re-crystallization of lipids results into a core with reduced drug content. So, increase in the lipid conc. beyond certain limit leads to poor % EE. These results were in good agreement with earlier reports .

QF loaded showed excellent stability specified by ZP, high % EE value, drug loading capacity with sustained action. Thus it can be concluded that NLC is a smarter drug delivery system with unique advantages such as higher drug loading; higher entrapment of drug, sustained drug release behavior and eventually enhanced drug absorption as compared with other lipid-based drug delivery system. The feasibility of large-scale production makes NLC as versatile delivery system. Thus, NLCs seems to be reasonable delivery systems for oral administration of QF and may be used as alternate strategy to achieve ameliorated release and prolonged action of QF. In future, QF loaded NLCs may be used in clinical subjects for achieving better outcomes.

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