

Investigative Study on Impact of Solid: Liquid Lipid Ratio and Stabilizer Amount on Some Characteristics of Nanostructure Lipid Carriers of Quetiapine Fumarate

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ABSTRACT

Aim: Nanostructured Lipid Carriers (NLCs) are the 2nd generation of Solid Lipid Nanoparticles (SLNs) designed to overcome limitations of SLNs. Their characteristics can be modulated by variations in formulation and process variables. The present study was aimed at investigating the influence of formulation variables, solid: liquid lipid ratio and stabilizer amount on some important characteristics of Quetiapine Fumarate Nanostructured Lipid Carriers (QF-NLC) like percent Entrapment Efficiency (%EE), Particle Size (PS), Polydispersity Index (PDI) and Zeta Potential (ZP). **Methods and Materials:** The study was carried out by varying the ratio of solid:liquid lipid and stabilizer amount sequentially in two sets of experiments and studying their impact on the selected characteristics of QF-NLC. Hot emulsification followed by ultrasonication was the method of preparation. Precirol ATO5, oleic acid and Phospholipon 90G (P90G) were selected as the solid lipid, liquid lipid and stabilizer respectively. **Results:** On varying the solid: liquid lipid ratios in the first set of experiments, %EE, PS and ZP ranged from 65.05-75.52%, 281.5-150.4nm and -16.4- -21.4mV respectively showing that decrease in the ratio was related to %EE and ZP inversely and to

PS and PDI directly. Increase in the amount of P90G in the second set of experiments showed %EE to be affected positively and PS and PDI negatively. ZP was less sensitive to changes in P90G. **Conclusion:** From the study it can be concluded that by varying the chosen formulation variables a QF-NLC formulation with desired characteristics can be formulated for the chosen objective.

Key words: Oleic acid, Phospholipon90G, PrecirolATO5, Quetiapine fumarate, Solid: liquid lipid.

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DOI: 10.5330/ijpi.2019.2.10

INTRODUCTION

Nanostructure Lipid Carriers (NLC) are the smarter, 2nd generation of Solid Lipid Nanoparticles (SLN) developed to overcome the limitations of SLN. The major drawbacks of SLN are limited drug loading capacity and drug expulsion during storage,^{1,2} due to the occurrence of polymorphic changes in the solid lipid used for making it. NLCs have a unique composition of the matrix comprising of a blend of spatially different lipids usually solid and liquid lipid resulting in formation of disordered lipid matrix with imperfections providing more space for accommodation of drug.³⁻⁷ Also, greater solubility of the drug in liquid lipid as compared to solid lipid gives higher entrapment efficiency.⁸⁻¹⁰ NLCs are also solid at room and body temperature but their melting point is lower than their corresponding SLNs¹⁰⁻¹² due to their disordered and imperfect crystalline structure.^{13,14}

In the present study an investigation of the impact of formulation variables like solid:liquid lipid ratio and stabilizer amount on some important NLC characteristics like percent Entrapment Efficiency (%EE), Particle Size (PS), Polydispersity Index (PDI) and Zeta Potential (ZP) was done. The objective of the study was to understand the influence of these formulation variables on important NLC characteristics which impact the physical stability (ZP, PDI) and pharmacokinetic parameters (%EE, PS, PDI) of the drug and delivery system and in turn assist the researchers in formulating more effective formulations for achieving the desired objective.

Quetiapine Fumarate (QF), a 2nd generation anti-psychotic,¹⁵ was chosen as the model drug because it has a very low oral bioavailability of 9% due to hepatic first pass metabolism by CYP3A4 enzyme in the liver. It is a BCS class II drug with a dose range of 100-800mg/day, used for treatment of psychotic problems like schizophrenia and bipolar disorders.¹⁶ Formulation of the drug in the form of Lipidic Colloidal Carrier (NLC) may help in intestinal lymphatic transport of the drug and thus aid in enhancement of oral bioavailability by bypassing the liver. The above hypothesis is supported by reports where researchers have shown that co-administration of drugs with lipids increases lymphatic uptake, giving it direct access to the systemic circulation, thus protecting it from hepatic first pass metabolism.¹⁷⁻¹⁹ As NLCs have been proven to be a better lipidic nanoparticulate system, they were chosen over SLN as the drug delivery system.¹¹

In the present study, the solid lipid chosen was PrecirolATO5 (PreATO) (glyceryl palmitostearate), liquid lipid was oleic acid (OA) and stabilizer or lipophilic surfactant was Phospholipon90G (P90G) (soya lecithin). The study was carried out in 2 parts- in the 1st part, different ratios of solid: liquid lipid (PreATO: OA) were taken and different batches of QF-NLCs were formulated using these ratios by hot emulsification followed by ultrasonication by a probe sonicator. In this phase the amount of stabilizer, hydrophilic surfactant, volume of water as the dispersion medium, amount of drug were kept constant for all the

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formulations. Process variables like emulsification time and temperature, ultrasonication time and amplitude were constant for all the batches. The resulting formulation batches were checked for %EE, Ps, PDI, ZP. The batch with the highest %EE and most appropriate PS, PDI and ZP was selected and subjected to the 2nd part of study. In the 2nd part of study the amount of stabilizer used (P90G) was varied at 3 levels, keeping the solid:liquid lipid ratio constant. The resulting formulations were studied for the effect of change of amount of P90G on the selected characteristics (%EE, PS, PDI, ZP). This was done to clearly elucidate the impact of the two variables on the selected characteristics. The best batch of NLC was then subjected to solid state characterization by X-ray Diffraction (XRD). Formulation having the highest %EE, lowest particle size and PDI and highest ZP was considered as the best batch.

MATERIALS AND METHODS

Materials

Quetiapine fumarate (QF) was obtained as a gift sample from IPCA laboratories (Ratlam, India). Precirol ATO5, Compritol 888 ATO, Peceol and Labrafil M1944 CS were obtained from Gattefosse, Cedex, France, Dynasan114, Dynasan 116, Dynasan118 and Miglyol 812N from IOI Oleo GmbH, Witten, Germany as gift samples. Poloxamer 188 was kindly supplied by BASF (Mumbai, India). Phospholipon 90G was kindly supplied by Lipoid (Germany). Oleic acid was procured from Qualigens Fine Chem., Mumbai, India. Mannitol was purchased from Loba chemie. HPLC grade acetonitrile, triethylamine and methanol were obtained from Fisher Scientific, Mumbai. Water used in all experiments was ultrapure, obtained from Millipore Direct Q UV Ultrapure water system (Millipore, France). All other chemicals and reagents were of analytical grade.

Methods

Selection of solid and liquid lipid

Selection of solid lipid was based on semi-quantitative solubility studies performed on 5 lipids, Compritol888 ATO, Dynasan 114, Dynasan 116, Dynasan 118 and Precirol ATO5 at a temperature 5°C above their respective melting points.²⁰

Selection of liquid lipid was also done on the basis of solubility studies of the drug in 4 liquid lipids, oleic acid, Labrafil ILM 1944CS, Miglyol 812N and Peceol, by quantitative method. An excess amount of drug was added to stoppered vials, each having a fixed volume of liquid lipid. The vials were kept in an isothermal orbital shaker (Remi, CIS 24 Plus) for 24 h at 25±2°C for equilibration after which the contents of the vials were centrifuged to separate the supernatant which were analyzed by a validated spectrophotometric (using a Shimadzu 1800 series double beam spectrophotometer) method at 254nm for determining the drug concentration in mg/ml of lipid.²¹

Formulation of QF loaded NLC

QF-NLCs were prepared by hot emulsification (Remi Electrotechnik, Vasai, India, RQT 127/A/D) followed by ultrasonication (by a probe sonicator: PCI Analytics, PKS -750F). The selected solid and liquid lipid were mixed in different ratios (95:5, 90:10, 85:15, 80:20) in separate beakers. The total content of lipid was kept constant and only the ratio was varied. To this was added weighed quantity of drug (25mg) and P90g as the stabilizer (102mg). The quantity of drug was kept constant in all formulation batches in both the phases of study. Lipid mixture was heated on a water bath 5°C above the melting point of solid lipid. Poloxamer 188, as the hydrophilic surfactant, was dissolved in HPLC grade water to obtain the aqueous dispersion medium maintained at the same temperature as that of the lipid phase. This was then added to the lipid phase and mixed using a homogenizer (Remi Electrotechnik, Vasai, India, RQT

127/A/D) at 6000rpm for 3 min to obtain a hot coarse o/w emulsion. The emulsion formed was ultrasonicated using a probe sonicator (PCI Analytics, PKS -750F) at a temperature 5°C above the melting point of solid lipid. The resulting nanodispersion was cooled in an ice bath to obtain the NLCs.

A total of 4 formulations were prepared in the first set of experiments and 3 formulations in the second set of experiments.

Percent drug Entrapment Efficiency (%EE)

The prepared batches of NLC were checked for % drug EE by indirect method.²²⁻²⁵ The nanodispersion was centrifuged at 17,000 rpm for 40 min at 4°C in a cooling centrifuge (Remi cooling centrifuge, CPR 30 Plus, India) to separate the supernatant from nanoparticles. The supernatant was withdrawn, filtered through 0.22 µm membrane filter (Pconlab, Mumbai, India) to remove all the particles and analysed for the amount of untrapped drug by a validated HPLC method [IP 2014] (HPLC: Shimadzu, Kyoto, Japan. Model LC2010CHT). The %EE was calculated as follows-

$$\%EE = \frac{A_t - A_{ue}}{A_t} \times 100$$

where, A_t = weight of total drug taken, A_{ue} is the weight of untrapped drug present in supernatant.

Particle size, polydispersity index and zeta potential

The PS, PDI and ZP were determined by Dynamic Light Scattering (DLS) and electrophoretic light scattering techniques respectively by using a Zetasizer (Nano ZS, Malvern Instruments limited, U.K) at 25°C. For all determinations the samples were diluted appropriately with ultrapure water and sonicated to remove air bubbles.

Lyophilisation of NLC

The pellet of NLC obtained after centrifugation of nanodispersion was redispersed in HPLC grade water to get back the nanodispersion. D-mannitol was added to it as a cryoprotectant to prevent aggregation of particles during lyophilisation. The resulting mixture was frozen at -80°C in a deep freezer (Voltas, India) for 12 hr and then transferred to a lyophilizer (Virtis, India) for 24 h. The lyophilized product was stored in airtight screw-capped vials at -20°C till further use.

Solid state characterization

XRD study was done to determine the change in the form of drug and lipids after incorporation in NLC. XRD patterns were obtained on a powder X-ray diffractometer (Xpert Pro, PAN analytical, The Netherlands) by using Nickel-Beta filter, Copper Ka radiation, at a voltage of 45kV and a current of 40mA. The scanning range employed was from 5° to 50° at diffraction angle 2θ. XRD patterns were recorded for QF, physical mixture of drug and excipients and lyophilized QF-NLC.

RESULTS

Selection of solid and liquid lipid

Solid lipid was selected based on a semi-quantitative solubility study done previously using 5 lipids having different chain lengths, Dynasan 114 (trimyristate), Dynasan 116 (tripalmitate), Dynasan 118 (tristearate), PrecirolATO5 (glyceryl palmitostearate) and Compritol 888 ATO (glyceryl behenate). From this study Precirol ATO5 was found to have the highest solubilisation capacity for QF and was therefore selected as the solid lipid for the formulation.

Liquid lipid was also selected based on solubility studies conducted in 4 lipids, Oleic acid, Labrafil ILM 1944CS, Miglyol 812N and Peceol quantitatively. The solubility of QF was found to be maximum in oleic acid (46.88± 0.071 mg/ml). In Labrafil M 1944CS, Miglyol and Peceol the solubility was found to be 22044 ± 0.064 mg/ml, 0.2169 ± 0.021 mg/ml and 13.28 ± 0.123 mg/ml respectively. Thus, the solubilising capacity of

the liquid lipids can be given in the order -oleic acid > Labrafil > Peceol > Miglyol 812N. Thus, oleic acid was selected as the liquid lipid for formulation of NLCs.

Formulation of NLCs

Formulation of NLCs was carried out by a simple, reproducible method, hot emulsification followed by ultrasonication, successfully used and reported by several researchers,^{14,19,27,28} as this method requires no organic solvents. The variables related to homogenization and ultrasonication were fixed in preliminary studies. Table 1 and 2 show the composition of various NLC batches for the first and second set of experiments and the results of %EE, PS, PDI and ZP obtained therein respectively. From the first set of experiments, the NLC batch showing the most appropriate results for the selected characteristics was chosen as (N3: 85:15:: solid: liquid lipid) and subjected to second set of experiments in which the stabilizer amount (P90G) was used at 3 levels, to check its influence on %EE, PS, PDI and ZP. From Table 2 it can be established that N6 is the best batch with respect to %EE, PS, PDI and ZP as it has the highest %EE, low PS and an appropriate PDI and ZP.

Based on these results the influence of ratio of solid: liquid lipid and stabilizer amount on %EE, PS, PDI and ZP was interpreted, one variable at a time.

Study of effect of solid:liquid lipid ratio

%EE

The %EE for the first set of experiments ranges from 65.05% to 75.52% (from N1 to N4 batch) with change in solid: liquid lipid ratio from 95:5

to 80:20 in decrements of 5 for solid lipid and corresponding increment in liquid lipid. Stabilizer was taken at the level of 102 mg. From the results of %EE it can be seen that batch N3 having a solid: liquid lipid ratio of 85:15 shows the highest %EE (75.52%). Batch N4 (80:20::solid: liquid lipid) although having higher liquid lipid ratio as compared to N3, shows a lower %EE. Thus, based on %EE, batch N3 (85:15) was found to be the best.

Particle size and polydispersity index

Looking at the results of influence of solid: liquid lipid ratio with respect to PS and PDI (Table 1), it can be seen that PS changes from 281.5 nm to 150.4 nm and PDI changes from 0.200 to 0.163 with decrease in solid: liquid lipid ratio from N1 to N3 (95:5-85:15), demonstrating that with decrease in solid: liquid lipid ratio the PS as well as the PDI decrease. Several previous studies support these results.²⁹⁻³² But a further decrease in the solid:liquid lipid ratio to 80:20 demonstrates an increase in PS and PDI.

Zeta potential

The influence of varying solid:liquid lipid ratio on ZP shows an increasing trend towards negative side with decrease in the ratio, agreeing with research reports of several other groups.^{33,34} The ZP for QF-NLC batches N1 to N4 ranges from -16.4 to -21.4 mV.

Collective analysis of the results of the first set of experiments (%EE, PS, PDI, ZP) demonstrated batch N3 (solid: liquid lipid::85:15) to be the best batch for further studies. The %EE of N3 was found to be highest among all the batches studied. Its PS (150.4 nm) was appropriate for fulfilling the objective of intestinal lymphatic targeting as it has been reported that PS less than 500 nm (to be precise less than 200 nm), are readily taken up by the M-cells.³⁵ The PDI of N3 (0.163) was less than 0.3 making it a monodisperse system and ensuring its physical stability.³⁶ ZP of -19.8 mV, manifested sufficient surface charge³⁷ for physical stability along with steric stability (although N4 had higher ZP, but other characteristics were more suitable for N3). Thus, N3 was selected from the first set of experiments for further studies.

Study of the effect of stabilizer amount

The NLC batch selected (N3) from the first set of experiments was subjected to changes in the amount of stabilizer (P90G) at 2 different levels, a level lower and higher than the one used in the first set of experiments (97 mg and 107 mg respectively) to study its effect on various NLC characteristics like %EE, PS, PDI and ZP.

%EE

As can be seen from the results of second set of experiments given in Table 2, on increasing the amount of P90G to 107 mg the %EE increased to 77.37% from 75.52% and on reducing the amount the %EE decreased to 66.33%. Thus, it can be interpreted that increase in P90G favours drug entrapment. Similar results have been reported by other researchers as well.³⁸

Particle size and PDI

The results from Table 2 show that with decrease in amount of stabilizer (P90G), PS and PDI both increase and vice-versa. On decreasing the amount of P90G the PS and PDI have increased to 177.4 nm and 0.175 respectively from 150.4 nm and 0.163 and on increasing its amount the PS and PDI have decreased to 133 nm and 0.130. These results are in agreement with the results of Patel *et al.* 2012.^{2,38}

Zeta potential

Table 2 shows the ZP to change very slightly on varying the amount of stabilizer. So, ZP for all the 3 batches of second set of experiments was found to vary very slightly between -18.1 and -19.9mV. The obtained ZP

Table 1: Composition of NLC batches and their results for first set of experiments.

Formulation code	Solid:liquid lipid ratio	Phospholipon 90G (mg)	%EE*	Particle Size (nm)	PDI	Zeta potential (mV)
N1	95:5	102	71.8 ± 0.758	281.5	0.200	-16.4
N2	90:10	102	72.5 ± 0.099	173.4	0.189	-18.2
N3	85:15	102	75.5 ± 0.597	150.4	0.163	-19.8
N4	80:20	102	65.0 ± 0.253	163.2	0.223	-21.4

*Mean ± SD (n=3), EE= Entrapment efficiency, PDI= Polydispersity index.

Table 2: Composition of NLC batches and their results for second set of experiments.

Formulation code	Solid:liquid lipid ratio	Phospholipon 90G (mg)	%EE*	Particle size (nm)	PDI	Zeta potential (mV)
N5	85:15	97	66.3 ± 1.389	177.4	0.175	-18.1
N3	85:15	102	75.5 ± 0.167	150.4	0.163	-19.8
N6	85:15	107	77.3 ± 0.151	133	0.130	-19.9

Mean ± SD (n=3), EE= Entrapment efficiency, PDI= Polydispersity index.

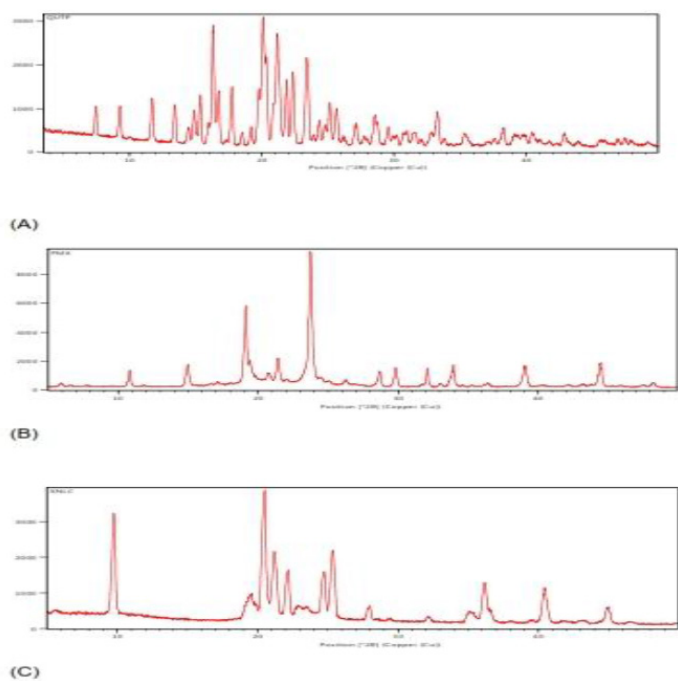


Figure 1: XRD of (A) QF (B) Physical mixture of drug and excipients (C) lyophilized NLC.

was sufficient to provide stability to nanoparticles as steric and electrostatic stabilization, both are into play.³⁷

Thus, the best batch of NLC from both the two sets of experiments was selected to be N6 on the basis of characteristics like %EE, PS, PDI and ZP. N6 batch showed the %EE of 77.37%, PS of 133 nm, PDI of 0.130 and a ZP of -19.9 mV. All its determined characteristics confirm its suitability for lymphatic intestinal targeting and ascertain its physical stability, thus fulfilling the aim of formulation of QF-NLC. N6 batch was lyophilized using mannitol as the cryoprotectant for improving its physical and chemical stability.

Solid state characterization

XRD

X-ray diffraction patterns of QF, physical mixture of drug and excipients and lyophilized NLC (N6) have been given in Figure 1. Diffractogram of QF (Figure 1a) shows sharp peaks at 2θ angles of 16.31°, 20.04°, 20.33°, 21.13°, 21.86°, 23.48° indicating its crystalline nature. XRD of the physical mixture of drug and excipients shows most of the characteristics peaks of the drug except a few which may be missing due to the formation of a homogenous mixture during sample preparation for XRD. Diffractogram of lyophilized formulation N6 shows a halo with very few broadened and shifted peaks.

Thus, XRD analysis shows most of the drug to be entrapped inside the NLC in amorphous state and the lipid to be having greatly reduced crystallinity after formulation.

DISCUSSION

Selection of solid and liquid lipid was done on the basis of solubility study. From the solubility study Precirol ATO5 and oleic acid were found to have the highest solubilisation capacity for QF from the selected solid and liquid lipids. The high solubility of QF in oleic acid can be attributed to the weakly basic nature of QF.³⁹ N6 was found to be the best batch from the two sets of experiments with respect to %EE, PS, PDI and ZP as it has the highest %EE, low PS and an appropriate PDI and ZP.

On determining the effect of variation of solid:liquid lipid ratio on %EE in the 1st set of experiments N3 demonstrated highest %EE. High %EE of N3 can be attributed to the higher ratio of liquid lipid as compared to N1 and N2. A high ratio of liquid lipid creates more crystal defects and disturbances giving more space in the solid lipid matrix thus allowing for incorporation of more drug in the matrix.^{40,29} Also, results have shown that QF has high solubility in liquid lipid, therefore increasing its proportion in lipid matrix would also result in solubilisation (and hence entrapment) of more drug.^{11,33,41-45} The high solubility of QF in OA can be explained on the basis of hydrogen bonding interactions between the groups of drug molecule (-OH and -COOH group) and -COOH group of OA^{46,47} as has also been reported by Cao *et al.* for some drugs.⁴⁸ Peceol (predominantly glyceryl monooleate) and Miglyol (triglyceride of C8 and C10 fatty acids) being mono, di or triglycerides have no free -COOH groups available for hydrogen bonding and the hydroxyl or ester groups present in them have smaller hydrogen bonding tendencies in comparison to carboxylic group because of their lower polarities resulting in lower solubilities in these lipidic solvents. Labrafil M 1944 CS (mono and diester of OA with PEG-6) is also deficient in carboxylic acid groups for hydrogen bonding resulting in low solubility of drug in it.³⁸ Batch N4 (80:20::solid: liquid lipid) although having higher liquid lipid ratio as compared to N3, shows a lower %EE maybe because of an excess of liquid lipid in the matrix which may have expelled out on solidification taking with it solubilised drug and thus resulting in a decrease in %EE.^{30,31,49} It has also been reported that at low concentration of liquid lipid, the oil molecules are dispersed uniformly in the lipid matrix but at higher concentrations, oil forms tiny nano-compartments, surrounded by solid lipid matrix^{11,30,50} creating lesser crystal defects resulting in accommodation of lesser drug.

Study of changes in solid: liquid lipid ratio on PS and PDI manifested decrease in PS and PDI with decrease in solid: liquid lipid ratio. This behaviour can be attributed to reduction in viscosity of core and NLC dispersion on increase in liquid lipid content, enhancing fluidity and decreasing surface tension resulting in a decrease in particle size with a smaller particle size distribution indicating a greater homogeneity in formulation. Small values of PDI indicate adequate amount of surfactant and stabilizer for maintaining the particle size and preventing their aggregation. But a further decrease in the solid:liquid lipid ratio to 80:20 demonstrates an increase in PS and PDI probably due to an increase in amount of liquid lipid which increases the fluidity of the internal lipids and that of the surfactant layer causing its disruption. This results in aggregation of the particles and their growth in size.^{29,51} A PDI value between 0-0.5 is considered acceptable⁴⁷ as it indicates a narrow size distribution which relates to a monodisperse system favouring physical stability of nanoparticles.⁴³

The negative zeta in the formulated NLC batches could be due to the presence of carboxylic acid groups in oleic acid and free fatty acid in solid lipid.⁵² Therefore, with respect to the 1st set of experiments, the batches having a higher ratio of oleic acid have shown more negative ZP. Some of the negative charge could also be due to P90G, which is an amphoteric surfactant.^{30,53} It has been reported that a minimum of -30mV of ZP is required for stability of lipid nanoparticles^{54,55} but -20mV is also sufficient for nanodispersions stabilized by a combination of electrostatic and steric surfactants (P90G and Poloxamer 188 respectively) as steric stabilization improves stability even with lower surface charge.³⁷ Thus, steric and electrostatic surfactants together can provide adequate stability to the NLCs.²⁴ Additionally, lyophilisation of the formulation also provides enhanced chemical and physical stability by minimizing collisions between nanoparticles.⁵⁶

Considering the 2nd set of experiments which study the effect of variations in stabilizer amount on %EE, PS, PDI and ZP, the increase in %EE

with increased P90G may be because P90G is a phospholipid and works as a lipophilic surfactant and can increase the solubility of drug in the lipid phase.⁵⁷ Another reason for increased %EE could be reduced drug loss to the external phase as an excess of P90G forms a barrier on the surface of nanoparticles.^{24,58}

The reason for increase in PS and PDI on decreasing P90G could be that increased amounts of stabilizer produce more stable nanoparticles minimizing their aggregation, thus giving a smaller PS and narrower particle size distribution.⁵⁹ The PS obtained is appropriate for intestinal lymphatic absorption as it is less than 200 nm.³⁵ The PDI value manifests monodispersity in the system indicating its physical stability.⁵⁰

A factor influencing the ZP is solid: liquid lipid ratio as the free fatty acids in the solid lipid and carboxylic acid group in the oleic acid could be the contributors of negative surface charge. Since both these factors have been kept constant in this set of experiments, change in ZP is minimal. Another factor contributing to ZP, amount of stabilizer (P90G), has been varied to a small extent because of which the slight change in ZP can be seen showing that ZP is less sensitive to changes in P90G

Presence of halo in the diffractogram of lyophilized N6 formulation depicts the amorphous state of the drug and the lipid. Occurrence of some peaks maybe due to the presence of mannitol and of a small amount of poorly entrapped drug at the periphery of the nanoparticles.

CONCLUSION

In the present investigative study, the influence of solid:liquid lipid ratio and stabilizer amount on certain characteristics (%EE, PS, PDI and ZP) of QF-NLC formulated by hot emulsification-ultrasonication was successfully evaluated. The results demonstrated that solid:liquid lipid ratio had an impact on %EE, PS, PDI and ZP. From the results it could be established that with decrease in solid: liquid lipid ratio, %EE increased, PS decreased, PDI decreased and ZP increased. Increased amount of stabilizer (P90G) influenced the %EE positively but PS and PDI negatively. ZP showed less sensitivity to the changes in amount of P90G. XRD studies confirmed the encapsulation of QF in amorphous form and a drastic reduction in crystallinity of the lipid after formulation. The study confirmed that by variations in the chosen formulation variables a QF-NLC formulation with desirable characteristics can be prepared and used for fulfilling the desired objective.

ACKNOWLEDGEMENT

The authors are grateful to IKGPTU, Kapurthala for the support in carrying out the research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

%EE: Percent entrapment efficiency; **NLC:** Nanostructured lipid carriers; **OA:** Oleic acid; **PDI:** Polydispersity index; **PreATO:** PrecirolATO5; **PS:** particle size; **P90G:** Phospholipon 90G; **QF:** Quetiapine fumarate; **QF-NLC:** Quetiapine fumarate nanostructured lipid carriers; **SLN:** Solid lipid nanoparticle; **XRD:** X-ray diffraction; **ZP:** Zeta potential.

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Cite this article: Agarwal S, Garg R, Kumar SLH. Investigative Study on Impact of Solid: Liquid Lipid Ratio and Stabilizer Amount on Some Characteristics of Nanostructure Lipid Carriers of Quetiapine Fumarate. *Int. J. Pharm. Investigation*. 2019;9(2):47-52.