EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 4
972-977
Year: 2018

FORMULATION AND EVALUATION OF SOLID LIPID NANOPARTICLES OF QUETIAPINE FUMARATE BY HOT HOMOGENIZATION METHOD

Hari Anushree and P. Tripura Sundari*

Department of Pharmaceutics, Rbvrr Womens College of Pharmacy, Barkatpura, Hyderabad 500013.

***Corresponding Author: P. Tripura Sundari**
Department of Pharmaceutics, Rbvrr Womens College of Pharmacy, Barkatpura, Hyderabad 500013.

Article Received on 19/02/2018 **Article Revised on 11/03/2018** **Article Accepted on 31/03/2018**

ABSTRACT
The aim of the present study is to formulate and evaluate solid lipid nanoparticles of Quetiapine Fumarate. Quetiapine Fumarate is an antipsychotic drug used in the treatment of Schizophrenia. Quetiapine Fumarate has poor water solubility and oral bioavailability of 9% due to first pass metabolism. To overcome these problems an attempt was made to prepare Quetiapine Fumarate into Solid lipid nanoparticles which has ability to improve the solubility and enhance the oral bioavailability. In the present study Quetiapine Fumarate loaded SLNs was prepared by Hot Homogenization method. The Cutina® HR was used as the Lipid, Gelucire 50/13 as lipophilc surfactant and Kholliphor P 188 as Hydrophilic surfactant in the preparation. The five prepared formulations were evaluated for various parameters like entrapment efficiency, In Vitro drug release, particle size, Zeta potential and Stability studies. Among all the Preparations H2 formulation was best in terms of Entrapment efficiency of 88.6%, Drug release of 88.1%, Particle size of 99.6 nm with Zeta potential of -42 mV in Hot Homogenization. The present study conclusively demonstrated that the solubility of drug was improved by entrapment of drug into solid lipid carrier which led to prolongation of drug release.

KEYWORDS: Solid Lipid Nanoparticles, Quetiapine Fumarate, Cutina® HR.

INTRODUCTION
Oral administration of the drug is most convenient way and commonly used route for the delivery of the drugs because its advantages like ease of administration, high patient compliance, cost effectiveness etc.[1] The major challenge in designing the oral dosage form lies with their poor bioavailability. The oral bioavailability depends on several factors like aqueous solubility, dissolution rate, first pass metabolism, drug permeability, pre systemic metabolism etc. But most often cause of the low oral bioavailability is due to poor solubility and low permeability. Thus to overcome this problem of oral bioavailability the solubility of dug must be enhanced.

There are several techniques to enhance solubility there by bioavailability of the poorly soluble drugs. Novel techniques possess advantages over traditional techniques. Various novel techniques that are used to enhance the solubility are like solid lipid nanoparticles, Self emulsifying drug delivery systems, solid dispersions etc. Depending upon the problem associated with the drug the technique that is to be employed must be chosen. Here we chose solid lipid nanoparticles for the study of this drug Quetiapine fumarate.

Quetiapine Fumarate is an antipsychotic drug used in the treatment of schizophrenia. The Quetiapine fumarate belongs to the BCS class II drug which has poor solubility and high permeability. The oral bioavailability of quetiapine Fumarate is only 9% with plasma half life of 6 hours. The poor oral bioavailability is due to extensive first pass metabolism.[2] Possible methods to avoid first pass metabolism include transdermal, buccal, rectal and parenteral route of administration. But the oral route is considered as the natural, convenient and safest route of administration involving higher patient compliance with lesser complications.[3] The conventional preparations like solution, suspension or emulsion for drug delivery purpose has various boundaries like high dose and low availability, faster reach effect etc. The changes in blood plasma drug levels are also exhibited which do not provide sustained effect as well as reaching of drug to target site without any alteration in its physical and chemical properties.

Therefore, there is a need for some novel carriers which could improve the above problems by reaching to its target site without making any adverse effects to body and can carry the drug easily and safely to its destination. Nanoparticles (NP) are a type of colloidal drug delivery system comprising particles with a size range from 10 to 1000 nm (diameter). The major advantages of nanoparticles are improved bioavailability by enhancing aqueous solubility, increasing resistance time in the body

(increasing half life for clearance/increasing specificity for its associated receptors and targeting drug to specific location in the body. This is why nanoparticle are increasingly used in variety of applications that includes drug carrier systems and to pass organ barriers such as the blood-brain barrier, cell membrane etc. They are based on biocompatible lipid that provide sustained effect by either diffusion or dissolution.[4,5] Moreover it can be said that nanoparticles are now a day's acting as very prolific device for drug delivery system.

Solid Lipid nanoparticles have ability to overcome the challenges associated with oral delivery of drugs that have low solubility, poor permeability, instability in the GIT and pre-systemic drug metabolism.[6] Thus to overcome the problems that are associated with drug quetiapine fumarate like low solubility and poor oral bioavailability, the quetiapine fumarate loaded solid lipid nanoparticles were prepared which are capable of improving above mentioned properties.

In the current study, the quetiapine fumarate loaded SLNs were prepared using cutina® HR as lipid and surfactants like Gelucire 50/13 and Kholliphor P 188 by hot homogenization followed by sonication. The prepared SLN were characterized and evaluated for various parameters like entrapment efficiency, invitro drug release, particle size and Zetapotential.

MATERIALS AND METHODS

2.1 Materials

Quetiapine Fumarate was obtained as a gift sample from Aurobindo Labs, Cutina® HR (BASF), Gelucire 50/13 (Gatteffose), Kholliphor P188 (polaxomer 188, BASF), dialysis membrane (HiMedia, Mumbai). All other reagents used were of analytical grade.

2.2 Preparation of Quetiapine Fumarate loaded solid lipid nanoparticles

Quetiapine Fumarate loaded SLNs were prepared by Hot homogenization method followed by sonication.

Hot Homogenization Method

Hot homogenization method is best suited method for the preparation of solid lipid nanoparticles as it can be performed at elevated temperatures to that of lipids melting point. The reduction in the particle size is due to cavitations and turbulences during homogenization.[7] In hot homogenization technique the drug was dispersed in the lipid and Gelucire 50/13(surfactant) by melting them above 5°C of their melting point. This is considered as oil phase. The aqueous phase was prepared by adding other surfactant kholliphor P 188 (polaxomer 188) in the distilled water and heated to the temperature of oil phase. The prepared oil phase was added to the aqueous phase drop by drop under continuous stirring of 3 hrs at 2700 rpm. The produced O/W emulsion is sonicated for half an hour and cooled to room temperature. At the room temperature the lipid recrystallizes and leads to formation of SLNs. The formulations prepared by Hot homogenization was coded by the Alphabet H. The various formulation is shown in table 1.

Table 1: Composition of quetiapine fumarate loaded SLN formulations by hot homogenization.

Formulation Code	Ratio (lipid : surfactant)
H1	10:1
H2	5:1
H3	2:1
H4	1:1
H5	1:2

In all SLN formulations the hydrophilic surfactant (kholliphor P188) was kept constant by taking 200 mg and drug concentration taken in all formulations was equivalent to dose i.e 300mg.

Evaluation of Solid Lipid Nanoparticles

Entrapment Efficiency

Entrapment efficiency is an important parameter for characterizing solid lipid nanoparticles. This parameter gives us an idea of the drug that was entrapped in SLNs by the carrier. In order to attain optimal entrapment efficiency, the varying concentrations of lipid to lipophilic surfactant ratio were used. The entrapment efficiency of prepared SLNs was determined by the centrifugation method. SLNs (containing equivalent to 300mg of drug) was centrifuged at 10000rpm for 40min in high speed research centrifuge to collect supernatant liquid. The collected liquid was filtered to measure amount of free drug concentration after suitable dilution with the fresh phosphate buffer of pH 6.6. The absorbance was measured at 290 nm in a UV spectrophotometer to calculate the entrapment efficiency using the formula:

$$E.E = \frac{\text{Amount of total drug - Amount of drug in aqueous phase}}{\text{Amount of total drug}} X100$$

In vitro Drug Release

The in vitro drug release of quetiapine fumarate loaded SLNs was determined by dissolution apparatus using USP II with the help of dialysis bag dissolution technique. An accurately weighed amount of quetiapine fumarate SLNs containing the drug equivalent to 300mg was taken into the dialysis bag and sealed. This sealed dialysis bag was then suspended into the dissolution basket containing 900ml of phosphate buffer solution of pH 6.6 at the temperature of 37± 2°C, and stirred at a constant speed of 75rpm. Aliquotes were collected at the time intervals like 0.5,1,2,4,6,8,10,12 up to 24 hours and the same was replaced with the fresh buffer. The drug content was determined spectrophotometrically by measuring the absorbance at 290nm using the same buffer solution as the blank, to calculate the amount of drug released from the nanoparticles.

Particle Size Determination

The mean diameter of SLNs in the dispersion was determined by using instrument Nano Partica analyzer (HORIBA SZ-100) which works on the principle of

dynamic light scattering. Before the measurement, one drop of sample from each selected formulated SLN was taken and diluted to 10ml of dispersion medium (double distilled water).

Measurement of Zeta Potential

The zeta potential is a physical property, which is exhibited by all the particles in the preparation. The magnitude of the zeta potential gives an indication of the potential stability of the system. The zeta potential was determined by Nano Partica analyzer (HORIBA SZ-100).

Stability Studies

Stability studies were carried out for the formulations having high entrapment efficiency by storing the formulation at two different temperatures, in refrigerated condition and at room temperatures.

Fitting Data Into Kinetic Models

The obtained drug release data was fitted into various kinetic plots (zero order, first order, Higuchi and Peppas) in order to determine the order and mode of drug release from the formulated SLNs.

RESUTS AND DISCUSSION

Entrapment Efficiency

The entrapment efficiency of all the prepared SLN formulations by hot homogenization is shown in Table 2. The entrapment efficiency of the prepared SLNs by hot homogenization was found to be in the range of 56.6 to 88.6%.

The best entrapment efficiency was found in H2 formulation with 88.6% among all other formulation in hot homogenization method. Initially the entrapment was increased till H2 formulation and then decreased in further ratios. The high entrapment in H2 ratio was may be because of the optimum concentration of lipid used to that of surfactant ratio which is in accordance to the statement made by Volkhard Jenning *et al* that less order crystal lattices favour successful drug inclusion, as in glycerides.[8]

Table 2: Composition of quetiapine loaded SLNs containing different lipid to surfactant ratio and their entrapment efficiency by hot homogenization.

S.NO	FORMULATION CODE	RATIO	% ENTRAPMENT EFFICIENCY
1.	H1	10:1	83.5%
2.	H2	5:1	88.6%
3.	H3	2:1	76.3%
4.	H4	1:1	67.4%
5.	H5	1:2	56.6%

***In Vitro* Drug Release**

The *in vitro* drug release profile of quetiapine from various SLN formulation by hot homogenization. The *in vitro* release of quetiapine from SLN formulation by hot homogenization was found to be in the range of 52.8 to 88.1% at the end of 24 hours. All the prepared formulations by this method were compared with pure drug, which showed 38.3% at the end of 24 hours. Among them, the prepared formulation (H2) has showed best release at the end of 24 hours shown in the Figure:1.

The best formulation H2 was compared with pure drug and marketed SR tablet formulation shown in Figure: 2.

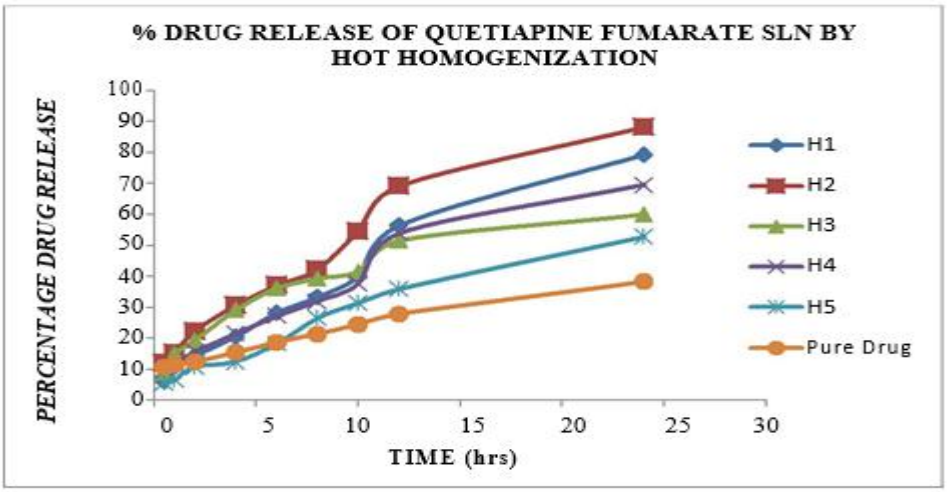

Fig. 1: Percentage drug release of Quetiapine Fumarate loaded SLNs with pure drug by Hot Homogenization Method.

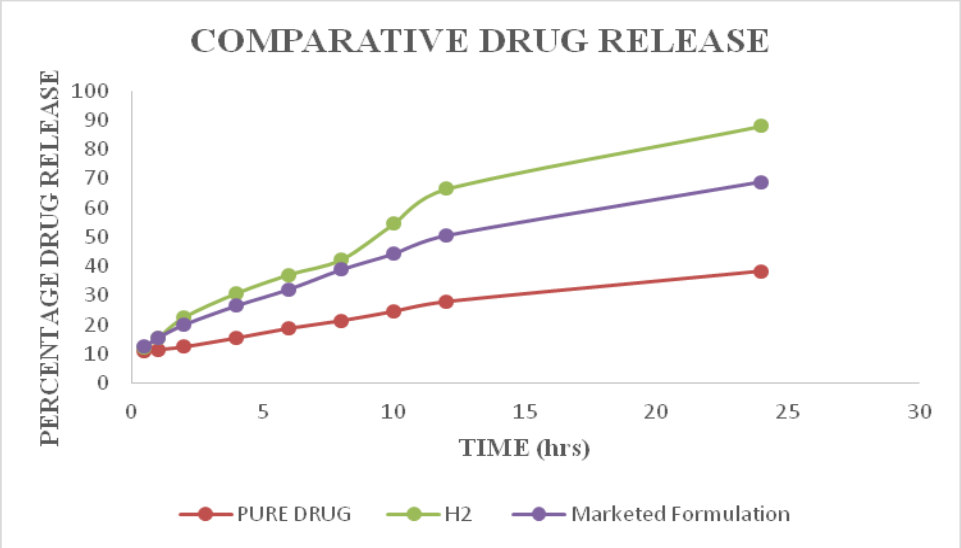

Fig. 2: Comparative drug release of pure drug, marketed formulation and prepared formulation (H2).

Influence of Lipid on *In Vitro* Drug Release

The entrapped drug has to show the release of drug to get therapeutic benefits of it. To know the release pattern of the drug *in.vitro* drug studies are carried out. The in vitro drug release from prepared formulations are in accordance with the entrapment efficiency. The drug release from all the prepared formulations was in the range of 52.8% to 88.1%. Among all ratios H2 in hot homogenization has shown better drug release profiles. The percentage drug release of H2 was 88.1% which may be due to less ordered crystals, due to lower drug expulsion from the imperfect lattice, contributing to prolonged release of the lipophilic drug.[9]

Influence of Suefactant on *In Vitro* Drug Release

The results obtained have revealed that surfactant concentration in formulations has influence on in vitro drug release. Formulation containing optimum concentration of surfactant only showed controlled drug release i.e. up to 24 hours which may be because of high affinity of drugs to lipids. Thus, the optimum ratio H2 showed 88.1% of drug release in hot homogenization method.

Particle size

The prepared formulations were evaluated to know the size of the particle, whether they are in nano range by the particle size analyser. The best formulation was selected based on the entrapment efficiency and drug release parameters. The particle size of best formulation H2 was 99.6nm in hot homogenization method. The hot homogenization has showed lower particle size which may be because of higher temperatures. In general, higher temperatures results in lower particle size because of the decreased viscosity of inner phase.[10] The higher concentration of surfactant reduces the surface tension and facilitate the particle partition during homogenization as stated by the Siekmann *et al.* The decrease in particle size is connected with the tremendous increase in surface area. This may be the reason in accordance to the above statement for the decrease of particle size in hot homogenization. The Figure 3 illustrates the particle size of the best formulation in hot homogenization.

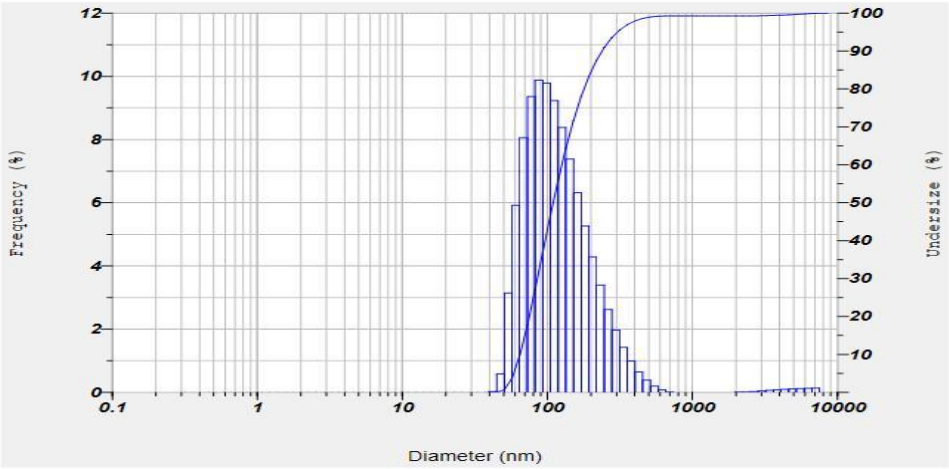

Fig. 3: Particle size report of H2 formulation of Quetiapine Fumarate loaded SLN by Hot Homogenization Method.

Zetapotential

The zeta potential states the stability of the prepared nanoparticles. The arbitrary value of zeta potential of nanoparticles is ±30. The higher zeta potential value of best formulation was -42mV in hot homogenization. The results obtained have revealed that the concentration of surfactant used was sufficient to cover the surface of nanoparticles efficiently avoid collection during the homogenization process. Thus adequate concentration of surfactant, induced surfaces to be well covered and aggregation of particles was reduced.

Stability Studies

The finalized formulation based on previous studies was kept for stability studies for 3 months at room temperature and refrigerated conditions. The stability studies of the best formulation by hot homogenization method in Table: 3.

Table 3: Stability study of best formulation H2 (% Entrapment Efficiency and % Drug release at refrigerated temperatures & room temperature) Hot Homogenization.

Time	Entrapment efficiency		Drug release	
Before Stability	**88.6 %**		**88.1 %**	
	Refrigerated Temperature	**Room Temperature**	**Refrigerated Temperature**	**Room Temperature**
After 15 days (%)	88.2 %	85.1 %	88.1 %	84.1 %
After 1 Month (%)	86.5 %	82.3 %	86.9 %	81.3 %
After 2 Months (%)	83.6 %	80.3 %	83.5 %	77.6 %
After 3 Months (%)	78.2 %	72.4 %	80.2 %	69.8 %

The stability studies revealed that there was aggregation of formed nanoparticles over the period and the aggregation was increased with temperature.

Fitting Data Into Kinetic Model

The drug release data was fitted in various kinetic plots (zero order, First order, Higuchi and Peppas) in order to determine the order and mode of drug release.

Table 4: Correlation coefficients of Quetiapine Fumarate loaded SLNs by hot homogenization method.

Formulation code	Zero order (r^2)	First order (r^2)	Higuchi plot (r^2)	Peppas plot (n)
H1	0.959	0.928	0.932	0.836
H2	0.727	0.989	0.974	0.801
H3	0.512	0.908	0.980	0.734
H4	0.833	0.971	0.958	0.747
H5	0.895	0.982	0.959	0.778

According to the data fit in kinetic plots, it was revealed that a good regression was obtained for first order kinetics and Higuchi equation, which indicated that all formulations released drug in sustained release, concentration dependent mode and drug release from lipid matrix was Higuchi diffusion. Release exponent, 'n' values of all SLNs formulations are greater than 0.5 indicating that release followed non fickian diffusion. (r^2 values were 0.989, n value was found to be 0.801 for H2 in hot homogenization method).

CONCLUSION

In the present research, the different formulations were prepared by using Cutina HR, Gelucire 50/13, Kholliphor P188 by employing hot homogenization method. The entrapment efficiency and drug release profile were depended up on the concentration of lipid and surfactant mixture employed. The results of in-vitro drug release studies demonstrated significantly controlled release of quetiapine fumarate from prepared SLNs. Among all the Preparations H2 formulation was best in terms of Entrapment efficiency of 88.6%, Drug release of 88.1%, Particle size of 99.6 nm with Zeta potential of -42 mV in Hot Homogenization. The drug release data revealed that a good regression was obtained for first order kinetics and Higuchi equation, which indicated that all formulations released drug in sustained release concentration dependent mode and drug release from lipid matrix was Higuchi diffusion. Release exponent, 'n' values of all SLNs formulations are greater than 0.5 indicating that release followed non fickian diffusion. (r^2 values were 0.989, n value was found to be 0.801 for H2 in hot homogenization method).

Hot homogenization was found to be the best method as particle size obtain was small, with high entrapment efficiency and higher zeta potential value which may be because of better association of surfactant with lipid particles. This method was found to be simple, cost effective, easy and suitable to produce SLNs of 50-220 nm. This method can be scaled up when compared with other preparations. Further it could be presumed that the obtained nanoparticles might increase oral bioavailability. Hence SLNs can be formulated Successfully by employing this Hot homogenization technique.

REFERENCES

1. S. R. K. Yellela, "Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs," Journal of Bioequivalence & Bioavailability, 2010; 2(2): 28-36.
2. S. C. Sweetman, Martindale, the Complete Drug Reference, Pharmaceutical Press, London, UK, 35th edition, 2007.
3. Arjun Narala and Kishan Veerabrahma, Preparation, Characterization and Evaluation of Quetiapine Fumarate Solid Lipid Nanoparticles to Improve the Oral Bioavailability, *Journal Of Pharmaceutics*, http://dx.doi.org/10.1155/2013/265741.
4. Cavalli R, Marengo E, Rodriguez L, Gasco MR., Effects of some experimental factors on the production process of solid lipid nanoparticles., *Eur J Pharm Biopharm.*, 1996; (43): 110–115.
5. Muller RH, Mader K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery – A review of the state of the art. Eur J Pharm Biopharm., 2000; 50: 161–77.
6. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: A modern formulation approach in drug delivery system. Indian J Pharm Sci., 2009; 71: 349–58.
7. P. Ekambaram, A. Abdul Hasan Santhali and K. Priyanka. Solid lipid nanoparticle: A review. Sci. Revs. Chem. Commun., 2012; 2(1): 80-102.
8. Liposphere in drug targets and delivery: Approches, Method and applications. Page no: 9.
9. Zur Muhlen A, Schwarz C, Mehnert W. Solid lipid nanoparticles (SLN) for controlled drug delivery – Drug release and mechanism. Eur J Pharm Biopharm., 1998; 45: 149–55.
10. Liposphere in drug targets and delivery: Approches, Method and applications. Page no: 5.