WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 7, 1933-1942. Research Article ISSN 2277– 7105

QUENCHING METHOD - A NOVEL TECHNIQUE IN THE FORMULATION AND EVALUATION OF SOLID LIPID NANOPARTICLES TAKING QUETIAPIN FUMARATE AS A MODEL DRUG

P. Tripura Sundari* and Hari Anushree

Associate Professor, RBVRR Women's College of Pharmacy, Barkatpura.

Article Received on
19 Feb. 2018,

Revised on 11 March 2018,
Accepted on 01 April 2018,

DOI: 10.20959/wjpr20187-11787

***Corresponding Author**
P. Tripura Sundari
Associate Professor,
RBVRR Women's College
of Pharmacy, Barkatpura.

ABSTRACT

The aim of the present study is to formulate and evaluate solid lipid nanoparticles of Quetiapine Fumarate by quenching method. Quenching method is a novel technique in which the drug along with other substances are heated to elevated temperatures and then subjected to rapid cooling with the quenchants like ice cold water or polymeric solutions, which have high heat extracting potential which results in the formation of nanoparticles. 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 were prepared by a novel technique called Quenching. Ice cold distilled water was used as the quenchant. The Cutina® HR was used as the Lipid, Gelucire 50/13 as lipophilc surfactant and Kholliphor P 188 as Hydrophilic surfactant in the preparation. Among the five prepared formulations Q3 was best with the entrapment efficiency of 86.1%, Drug release of 90.2%, Particle size of 160 nm with Zeta potential of -35.9 nm. 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

The enhancement of solubility and oral bioavailability of poorly water soluble drugs remain one of the most challenging aspects of drug development. Now a days several novel techniques are been employed to improve these properties by overcoming the disadvantages of traditional ones.[1] A promising strategy to overcome these problems involves the development of suitable drug carrier system like solid lipid nanoparticles. 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. 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. Due to their unique size dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could be site targeting. Therefore, these novel carriers 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. Hence, solid lipid nanoparticle hold great promise for reaching the goal of controlled and site specific drug delivery.[2] 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 the plasma half life of 6 hours. The poor oral bioavailability is due to extensive first pass metabolism.[3] 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 and lesser complications.[4] 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. 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 by quenching method 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 Quenching method. The prepared SLN were characterized, and evaluated for various parameters like entrapment

efficiency, invitro drug release, particle size and Zeta potential.

MATERIALS AND METHODS

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 (Hi Media, Mumbai). All other reagents used were of analytical grade.

Preparation of Quetiapine Fumarate loaded solid lipid nanoparticles

Quetiapine Fumarate loaded SLNs were prepared by Quenching method followed by sonication.

Quenching Method

Quenching is a novel technique adopted in many fields now a days like Automobile industry, Pharmaceuticals etc. Quenching method makes use of cool substance like ice cold water or water soluble polymeric solutions as a vehicle. These act as quenchants in this method. Quenching method is a process in which the drug along with other substances are heated to elevated temperatures and then subjected to rapid cooling with the quenchants like ice cold water or polymeric solutions, which have high heat extracting potential which results in the formation of nanoparticles.[5,6] In quenching method the drug was dispersed in the lipid, Gelucire 50/13 and kholliphor P 188 (surfactants) by melting them above 5°C of their melting point. This is considered as oil phase. The aqueous phase was ice cold distilled water. The oil phase was kept under stirring and the aqueous phase ice cold water was added at once to the oil phase. The stirring was continued for 3 hours at 2700 rpm. The obtained emulsion was sonicated for 30 minutes and cooled to room temperature and stored in the refrigerator. The decrease in particle size shows tremendous increase in surface area. This method needs mild stirring to obtain a thermodynamically stable nanoparticles. The formulations prepared by Quenching technique was coded by the Alphabet Q. The various formulation is shown in table 1.

Table 1: Composition of quetiapine fumarate loaded SLN formulations by quenching method.

Formulation code	Ratio (lipid : surfactant)
Q1	10:1
Q2	5:1
Q3	2:1
Q4	1:1
Q5	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 pH 6.6. The absorbance was measured at 290nm 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 quenching method are in Table 2. The entrapment efficiency of the prepared SLNs by quenching method was found to be in the range of 45.5 to 86.1%. The best entrapment efficiency in quenching method was shown by Q3 formulation with 86.1% among all other prepared formulations. The ratio of lipid and surfactant concentration was optimum in Q3 and showed good entrapment of drug into the lipid matrices. The high entrapment in Q3 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.[7]

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

S.no	Formulation code	Ratio	% entrapment efficiency
1.	Q1	10:1	83.5%
2.	Q2	5:1	88.6%
3.	Q3	2:1	76.3%
4.	Q4	1:1	67.4%
5.	Q5	1:2	56.6%

IN VITRO DRUG RELEASE

The *in vitro* drug release profile of quetiapine from various SLN formulation by quenching method in Figure 1. The *in vitro* release of quetiapine from SLN formulation by quenching was found to be in the range of 58.1 to 90.2% at the end of 24 hours. All the prepared formulations were compared with pure drug, which showed 38.3% at the end of 24 hours. Among them, the prepared formulation (Q3) has showed best release at the end of 24 hours shown in the Figure: 1

The best formulation Q3 was compared with pure drug and marketed SR tablet formulation shown in figure 2.

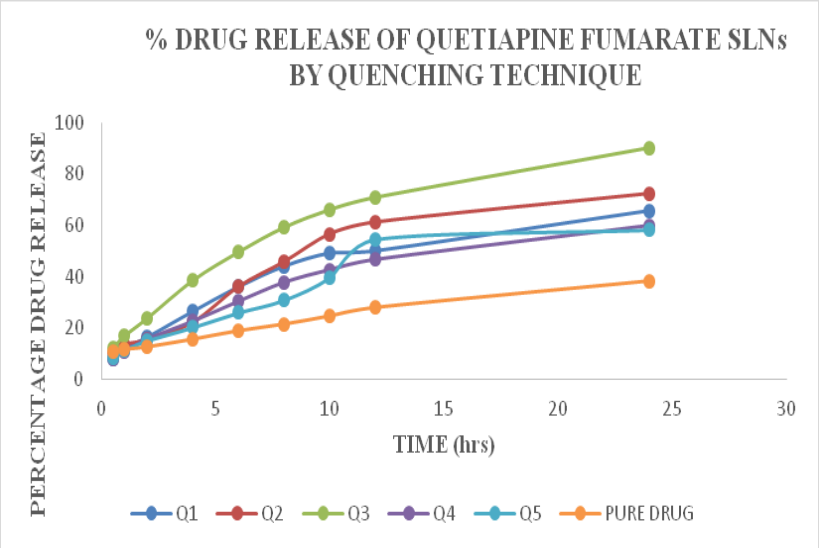

Fig 1: Percentage drug release of Quetiapine Fumarate loaded SLNs with pure drug by Quenching Method.

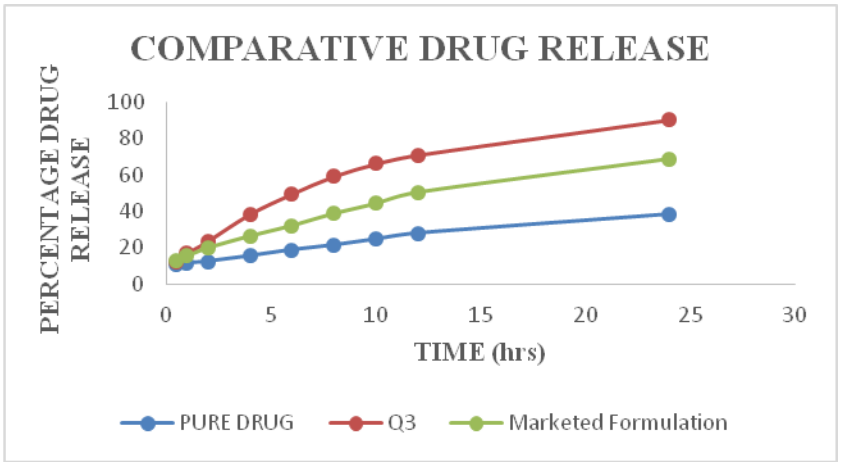

Fig 2: Comparative drug release of pure drug, marketed formulation and prepared formulation (Q3).

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. Q3 has shown better drug release profiles. The percentage drug release Q3 was 90.2% 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.[8]

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 slower drug release i.e. up to 24 hours which may be because of high affinity of drugs to lipids. Thus, the optimum ratio Q3 showed 90.2% of drug release.

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 best formulation Q3 showed particle size of 160nm in quenching method. 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. The Figure 3 illustrates the particle size of the best formulation in quenching method.

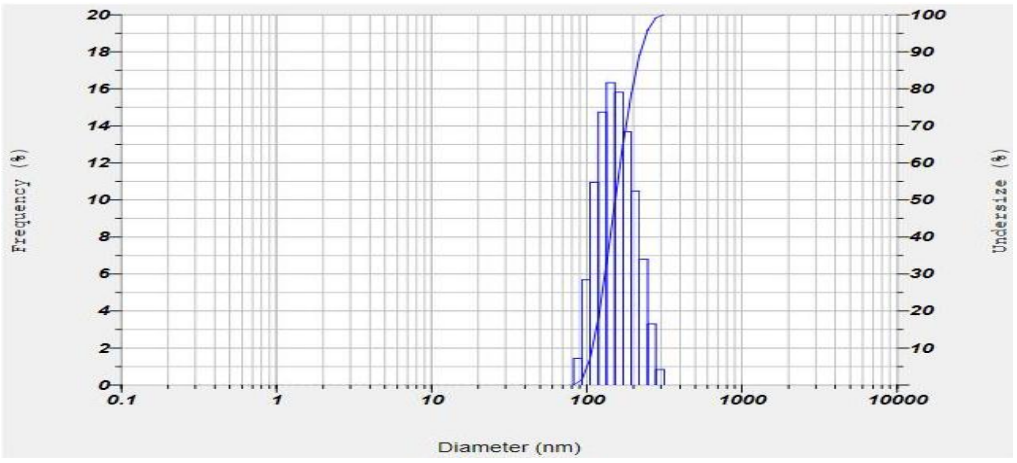

Fig: 3 Particle size report of Q3 formulation of Quetiapine Fumarate loaded SLN by Quenching Technique.

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 -35.9mV in quenching method. 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 quenching method in Table: 3.

Table: 3 Stability study of best formulation Q3 (% Entrapment Efficiency and % Drug release at refrigerated temperatures & room temperature) by Quenching Method.

Time	Entrapment efficiency		Drug release	
Before Stability	86.1 %		90.2 %	
	Refrigerated Temperature	Room Temperature	Refrigerated Temperature	Room Temperature
After 15 days (%)	86.0 %	85.6 %	90.1 %	89.3 %
After 1 Month (%)	83.9 %	80.8 %	88.9 %	85.4 %
After 2 Months (%)	81.2 %	78.4 %	84.5 %	81.7 %
After 3 Months (%)	79.2 %	75.2 %	80.6 %	77.8 %

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 Quenching technique.

Formulation Code	Zero Order (R^2)	First Order (R^2)	Higuchi Plot (R^2)	Peppas Plot (n)
Q1	0.557	0.873	0.961	0.796
Q2	0.461	0.867	0.949	0.790
Q3	0.801	0.965	0.961	0.910
Q4	0.695	0.948	0.989	0.772
Q5	0.712	0.887	0.941	0.754

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 value was 0.965, n value was 0.910 of Q3 in quenching method).

CONCLUSION

In the present research, the different formulations were prepared by using Cutina HR, Gelucire 50/13, Kholliphor P188 by employing Quenching technique. 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 formulations Q3 was found to be the best formulation in terms of entrapment efficiency of 86.1%, Drug release of 90.2%, Particle size of 160 nm with zeta potential of -35.9 nm. All formulations showed the release pattern following first order kinetics with non fickian diffusion type of mechanism (r^2 value was 0.965, n value was 0.910 of Q3 in quenching method). It was observed that, this preparation method was found to be cost effective and can be scaled up when compared with other preparation methods. This method overcomes the problem associated with heat. So thermolabile drugs can also be formulated in to SLNs by this technique. Further it could be presumed that the obtained nanoparticles might increase oral bioavailability. Hence SLNs can be formulated successfully by employing Quenching method.

REFERENCES

1. Sandhiya Jatwani, Avtar chand Rana, Gurpreet singh and Geeta Aggarwal, "An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach" International journal of Pharmaceutical Sciences and research, 2012; 3(4): 942-956.
2. S. Mukherjee, S. Ray and R. S Thakur, "Solid lipid nanoparticles: A Modern Formulation Approach in Drug Delivery System" Indian journal of Pharm Sci., 2009; 71(4): 349-358.
3. S. C. Sweetman, Martindale, the Complete Drug Reference, Pharmaceutical Press, London, UK, 35th edition, 2007.
4. Arjun Narala and Kishan Veerabrahma, Preparation, Characterization and Evaluation of

Quetiapine Fumarate Solid Lipid Nanoparticles to Improve the Oral Bioavailability, *Journal of Pharmaceutics*, 2013. http://dx.doi.org/10.1155/2013/265741.

5. Mohammad M. Mojahedian, Saeid Daneshmouz, Soliman Mohammadi Samani, Arman Zargaran, "A novel method to produce solid lipid nanoparticles using n-butanol as an additional co- surfactant according to the o/w microemulsion quenching technique, Chemistry and physics of lipids, 2013; 174: 32-38.
6. https://en.wikipedia.org/wiki/Quenching, accessed on 9th March 17, 2018 at 2.30 pm
7. Liposphere in drug targets and delivery: Approches, Method and applications, 9.
8. 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.