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Original Article

Formulation and evaluation of nanoparticles by emulsification method

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ABSTRACT

Quetiapine fumarate is a second-generation atypical antipsychotic used in schizophrenia, major depression, and bipolar disorder. As biological half life of drug is 6-7 hrs and that is why frequent dosing is require. To overcome with these problems, Nanoparticles of Quetiapine fumarate were formulated by using Ethyl Cellulose, HPMC K4M & Chitosan as a polymer by emulsification method. Among all the 12 formulations QF11 formulation is optimized, as it shows maximum drug release at the end of 12hrs which suits the controlled release drug delivery system criteria as per our studies, having acceptable particle size, SEM and Zeta potential value. From the drug release kinetics of QF11 formulation of Quetiapine fumarate Nanoparticles dispersion it was concluded that the QF11 formulation follows Zero order drug release with super case II transport mechanism.

Keywords: Quetiapine fumarate, Nanoparticles, particle size, SEM and Zeta potential

INTRODUCTION

Oral drug delivery is the most favoured manner of drug delivery for achieving mutually systemic and local therapeutic effects. But a variety of problems are also related with the conventional oral dosage forms, that it is frequently essential to take several times per day to retain the concentration of administered drug within the therapeutically effective range which results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. So to overcome such problems associated with conventional oral dosage form, the idea of controlled drug delivery systems was introduced. The real challenge in the development of a controlled drug delivery system is not just to control the drug release, also to extend the existence of the dosage form in the absorption site until all the drug is completely released in the preferred period of time. Nanoparticles formulation can overcome the above mentioned problems. Nanoparticles are colloidal particles ranging from 10 to 1000 nm, in which the active principles (drug or biologically active material) are dissolved, entrapped. And these are of different types include, nanospheres, nanocapsules, dendrimers, solid-lipid nanoparticle, polymeric micelles and liposomes. With the development in

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nanotechnology, it is now possible to produce drug nanoparticles that can be utilized in a variety of innovative ways. New drug delivery pathways can now be used to increase drug efficacy and reduce side effects.

Present work deals with the preparation and evaluation of Quetiapine-loaded nanoparticles by emulsification method.

MATERIALS AND METHODS

Solubility studies: Solubility of Quetiapine fumarate was carried out in different solvents – like Methanol, Ethanol, 0.1N HCL, 6.8pH buffer and 7.4 pH buffers. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 48 hr. at 25°C under constant vibration. Filtered samples (1ml) were determined spectrophotometrically at 250 nm.

Drug & excipient compatibility: There is always possibility of drug- excipient interaction in any formulation due to their intimate contact. The technique employed in this study is IR spectroscopy. IR spectroscopy is one of the most powerful analytical techniques, which offers possibility of chemical identification. The IR spectra were obtained by KBr pellet method. (Perkin-Elmer series 1615 FTIR Spectrometer).

Preparation of Quetiapine Fumarate Calibration Curve using 7.4 pH buffer: 10 mg drug was taken accurately in 10ml volumetric flask. It was dissolved in few ml of methanol and make up the volume upto the mark with 7.4 pH buffer to gives 1000 µg /ml. The standard stock solution was then serially diluted with 7.4 pH buffer to get 5 to 30 µg/ml of Quetiapine fumarate. The absorbance was measured against 7.4 pH buffer as blank at 250 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Method of Preparation of Nanoparticles: Quetiapine fumarate Nanoparticles were prepared by emulsification method. In this method Polymer was dissolved in organic solvent. Drug is dispersed in this solution. Then this mixuture emulsified in an aqueous phase containing surfactant (polyvinyl alcohol) make oil in water emulsion by using mechanical stirring, or sonication. After formation of emulsion the organic solvent evaporates by increased the temperature and reduced pressure with continuous stirring. And further processed to homogenisation of the resultant NPs dispersion.

Evaluation parameters of Nanoparticles Quetiapine fumarate

Entrapment efficacy: The freshly prepared Nanoparticles was centrifuged at 10,000 rpm for 20 min using ultracentrifuge. The amount of un incorporated drug was measured by taking the absorbance of the appropriately diluted 5 ml of supernatant solution at 250 nm using UV spectrophotometer against blank/control Nanoparticless. DEE was calculated by subtracting the amount of free drug in the supernatant from the initial amount of drug taken.

The entrapment efficiency (EE %) could be achieved by the following equation:

%Entrapment efficiency= Drug content *100/Drug added in each formulation

Scanning electron microscopy: The morphological features of Quetiapine fumarate Nanoparticles are observed by scanning electron microscopy at different magnifications.

Particle size and shape: Average particle size and shape of the formulated Nanoparticless was determined by using Malvern Zetasizer ZS using water as dispersions medium. The sample was scanned 100 times for determination of particle size.

Zeta potential: There are three ways by which a solid particle (colloid) dispersed in a liquid media can acquire a surface charge. First, by the adsorption of ions present in the solution. Second, by the ionization of functional groups on the particle's surface. Third, due to the difference in dielectric constant between the particle and the medium. Attention should be paid to the formation of electric double layer at the solid-liquid interface. The zeta Potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and the electro-neutral region of the solution. The potential gradually decreases as the distance from the surface increases.

As the concentration of electrolyte increases in the medium, the zeta potential falls off rapidly due to the screening effect of the counter ions (Figure 2). The zeta potential cannot be measured directly; however, it can be calculated using theoretical models and from experimentally determined electrophoretic mobility data. The theory is based on electrophoresis and can be expressed as:

$$\mu = \zeta\varepsilon/\eta$$

Where (µ) is the electrophoretic mobility, (ε) is the electric permittivity of the liquid, (η)
Is the viscosity and (ζ) us the zeta potential.

***In vitro* drug release study:** In vitro Release studies Drug release from NPs in-vitro was carried out by dialysis method (Dialysis membrane-60 HI MEDIA, Mumbai). The donor chamber filled with 5ml of NPs dispersion, whereas reservoir chamber

containing the phosphate buffer pH 7.4. This total setup was placed on a rotary shaker rotating at 50 rpm at 37°C ± 0.5°C. In pre determined time intervals the content of receiver chamber was withdrawn and replaced with equal volume of fresh phosphate buffer, the amount of Quetiapine fumarate that diffused into the receiver chamber was quantified by UV- spectrophotometer at 250 nm. The results of in vitro release profiles obtained for the NDDS formulations were fitted into

Four models of data treatment as follows:
Different release kinetic equations (zero-order, first-order, Higuchi's equation and Korsmeyer-peppas equation) were applied to interpret the release rate of the drug from matrix systems for the optimized formulation. The best fit with higher correlation (r2) was calculated.

RESULTS AND DISCUSSION

Solubility studies: From the solubility studies in various solvents we can say that methanol shows highest solubility than other solvents.

Standard Calibration curve of Quetiapine fumarate: The linearity was found to be in the range of 5-30 µg/ml in pH 7.4 buffer. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

Drug and Excipients compatibility studies: From the compatibility studies it was concluded that the functional groups that were presented in the pure drug were present in the optimized formulation with very minute changes, from this we can concluded that the drug and excipients have no interactions.

Drug entrapment efficacy: The percentage of drug entrapment efficiency of formulation QF1-QF12 was found to be within the range of 95.05±0.05 to 101.45±0.01 %.

Invitro drug release study: Formulations QF1, QF2, QF3, QF4,containing the ethyl cellulose as polymer. QF1 shows 98.52±0.15 % drug release at the end of 4hrs. Whereas QF2 formulation shows 99.05±0.01 % drug release at the end of 6hrs. While the QF3 formulation shows 98.43±0.12 % drug release at the end of 8hrs. While the QF4 formulation shows 95.43±0.04 % drug release at the end of 10hrs. As the concentration of polymer increasing drug release time is increased. So further trails were performed using HPMC K4M with same proportions.

Formulations QF5, QF6, QF7, QF8 are containing the ethyl cellulose as polymer. QF5 shows 98.05±0.09 % drug release at the end of 6hrs. Whereas QF6 formulation shows 97.63±0.01 % drug release at the end of 8hrs. While the QF7 formulation shows 95.76±0.16 % drug release at the end of 10hrs. While the QF8 formulation shows 97.05±0.17 % drug release at the end of 10hrs. As the concentration of polymer increasing drug release time is increased. So further trails were performed using chitosan with same proportions.

Formulations QF9, QF10, QF11, QF12 containing the chitosan as polymer. Among them QF11 formulation shows 97.76±0.86 % of drug release at the end of 12hrs. Among all the 12 formulations QF11 formulation is optimized, as it shows maximum drug release at the end of 12hrs which suits the controlled release drug delivery system criteria as per our studies.

CONCLUSION

Nanoparticulate carriers may provide a better therapeutic output by targeting drugs specifically to their site of action and by improving the pharmacokinetic profile of effective drugs low bioavailability and low half-life. In present investigation Nanoparticles were prepared by emulsification method. Total 12 nanoparticles formulations was formulated using Ethyl cellulose, HPMC K4M & Chitosan. Zeta potential value for the optimized formulation (QF11) was found to be within the acceptable limits. Average particle size of Nanoparticles of optimized formulations (QF11) was found to be 479nm. From the invitro studies we can say that formulation QF11 shows best drug release of 97.76±0.86 % within 12 hrs to release the drug. The drug release from the Nanoparticles was explained by the using mathematical model equations such as zero order, first order, and equation methods. Based on the regression values it was concluded that the optimized formulation QF11 follows Zero order drug release with super case II transport mechanism

Table 1: Formulation of Quetiapine Fumarte Nanoparticles (QF1-QF12)

Formulation code	Drug : polymer	Ratios	Concentration of PVA (%w/v)
QF1	Drug : Ethyl cellulose	1:1	2
QF2	Drug : Ethyl cellulose	1:2	2
QF3	Drug : Ethyl cellulose	1:3	2
QF4	Drug : Ethyl cellulose	1:4	2
QF5	Drug : HPMC K4M	1:1	2
QF6	Drug : HPMC K4M	1:2	2
QF7	Drug : HPMC K4M	1:3	2
QF8	Drug : HPMC K4M	1:4	2
QF9	Drug : Chitosan	1:1	2
QF10	Drug : Chitosan	1:2	2
QF11	Drug : Chitosan	1:3	2
QF12	Drug : Chitosan	1:4	2

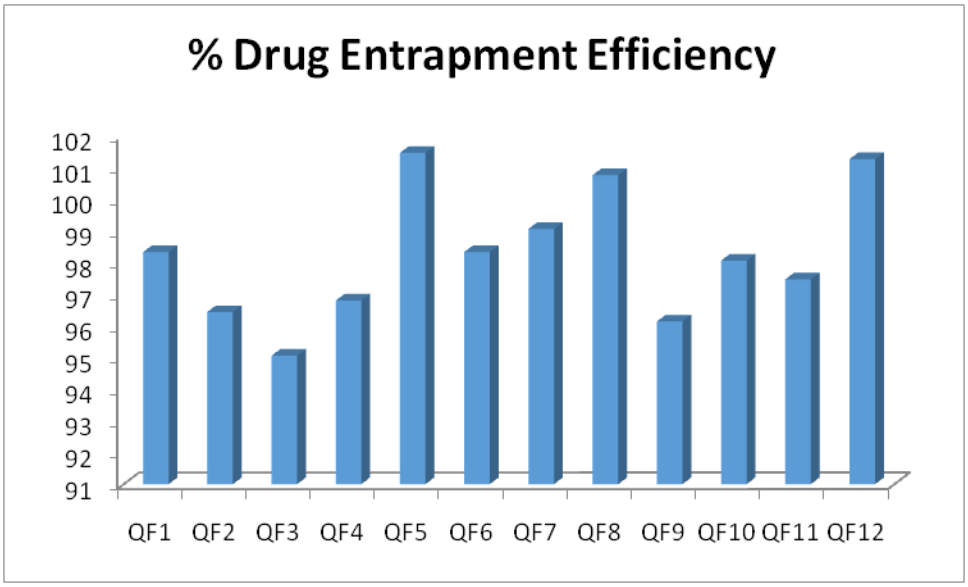

Figure 1: Percentage Drug entrapment efficiency of quetiapine nanoparticles

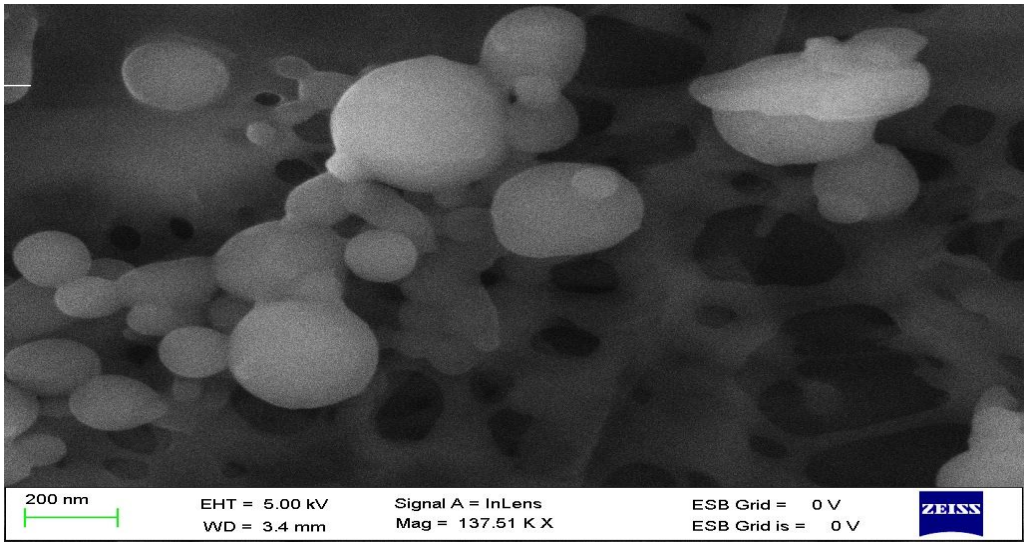

Figure 2: SEM Image of Optimized NP formulation.

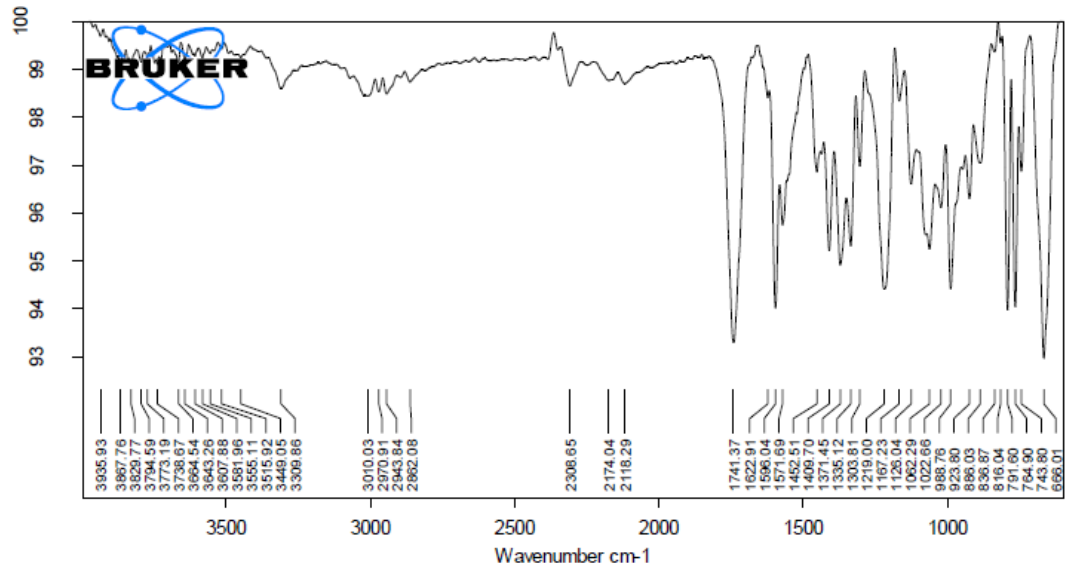

Figure 3: FTIR Spectrum of Quetiapine pure

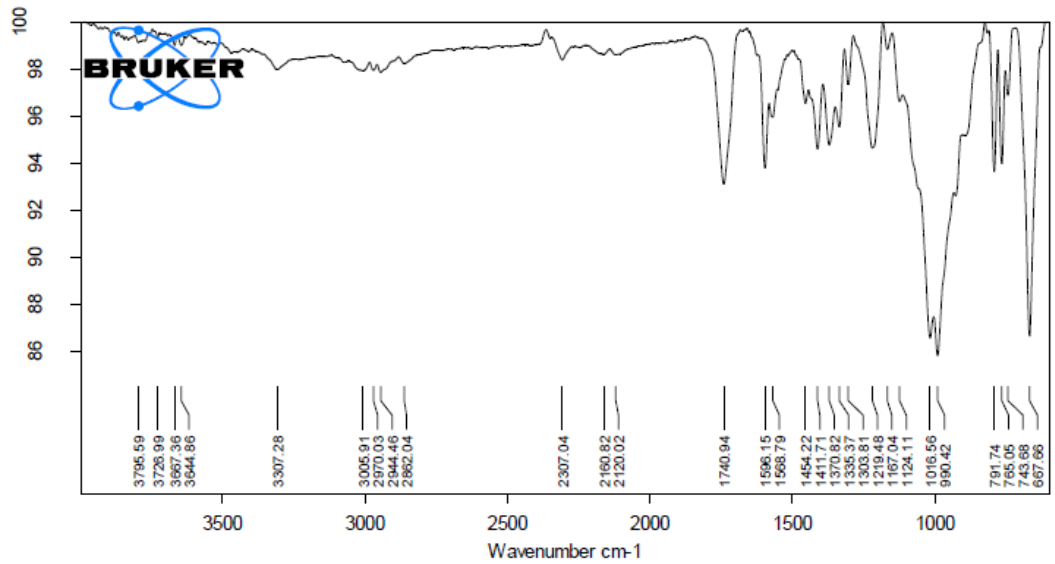

Figure 4: FTIR Spectrum of Quetiapine and Excipients

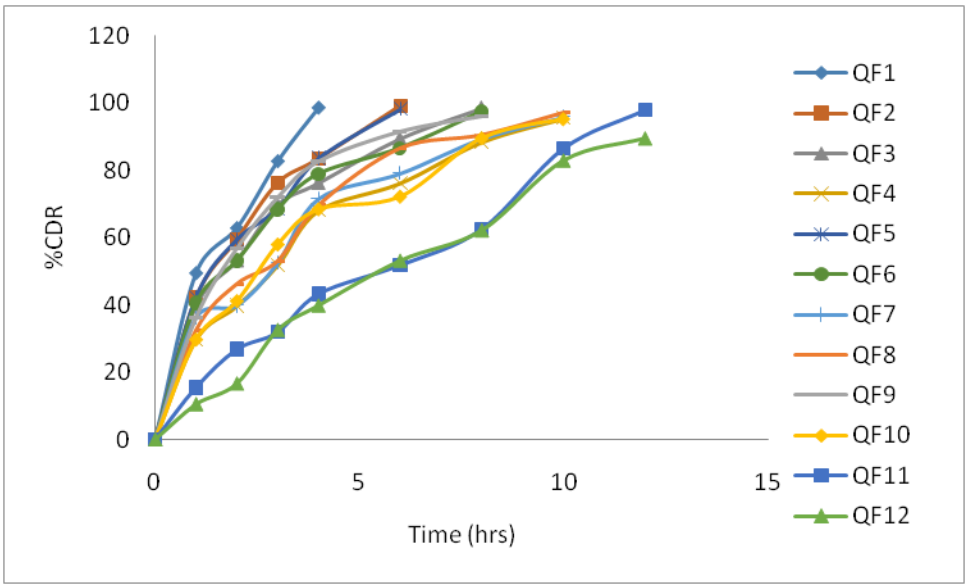

Figure 5: % CDR of Quetiapine Nanoparticles (QF1 – QF12)

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