

FORMULATION AND CHARACTERIZATION OF QUETIAPINE FUMARATE LOADED MUCOADHESIVE MICROEMULSION FOR INTRANASAL DELIVERY

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ABSTRACT

Schizophrenia is a highly disabling disease responsible for the loss of social contacts of the affected person. Quetiapine fumarate, a drug of choice, is available only as tablets and extended release tablets and suffers from the drawback of poor oral bioavailability (9%) and drug loss due to first pass metabolism. The attempt is made to formulate intranasal mucoadhesive microemulsion with the view to provide faster onset of action and improved bioavailability. The excipients used were Oleic acid (oil), Tween 80 (surfactant), PEG400 (co surfactant) and chitosan (Mucoadhesive agent). The optimized formulation was evaluated for transparency, mucoadhesive strength, globule size (61.9 nm), zeta potential (-22.7 mV), PDI (0.13), % drug content, SEM analysis. Hence it can be concluded that the formulation with enhanced solubility can have potential of improving bioavailability of Quetiapine fumarate can be a better alternative than the available formulation.

KEYWORDS: Quetiapine fumarate (QF); Microemulsion; pseudoternary phase diagram; solubility; Oil.**INTRODUCTION**

Schizophrenia is a chronic and severe mental disorder, characterized by disabling in emotions, language, thinking, perception, and behavior. Common experiences include hallucinations -hearing voices, delusions fixed false beliefs.^[1] Schizophrenia is a severe form of mental illness affecting more than 23 million people worldwide.^[2] Antipsychotic drugs are used for the treatment of both positive and negative symptoms of schizophrenia.^[3]

Quetiapine fumarate (QF), a second generation atypical antipsychotic drug with broad efficacy, and elicits a response in both positive and negative symptoms of schizophrenia and bipolar disorder, QF is poorly water soluble and solubility depends on pH at high pH conditions shows low solubility. Its plasma half-life is of 6 h and oral bioavailability is only 9%.^[4] However, the effectiveness of QF is limited by its high first-pass metabolism effect through oral route and poor entry through blood-brain barrier. Therefore, it required to make an alternative route for QF to improve its therapeutic effects.^[5]

In recent years, the intranasal drug delivery system is emerging and an attractive delivery option for targeting to brain as brain and nose compartment are connected to each other via olfactory/trigeminal route via peripheral circulation.^[6]

In recent years microemulsion based delivery systems in the area of nose to brain targeting have been studied extensively. Microemulsion is a thermodynamically stable, isotropically clear product that has a droplet size <0.15 μm . Microemulsions by virtue of their lipophilic nature and low globule size are widely explored as a delivery system to enhance uptake across nasal mucosa, and the addition of mucoadhesive agents such as polyelectrolyte polymer helps in the longer retention of the formulation in the nasal mucosa.^[7] Chitosan acts as a permeability enhancer and provides bioadhesion.^[8]

In the current proposal, we intend to make use chitosan as mucoadhesive agent to study its effect on enhancing mucoadhesion across nasal mucosa and help in achieving brain targeting when administered via intranasal route.

MATERIALS

Quetiapine fumarate was received from Hetero drugs Pvt limited (Hyderabad, India) as gift sample, Isopropyl myristate, Tween 80 and oleic acid was received from Sigma Aldrich. All the solvents used in the study were of analytical grade.

METHODS**Screening of oil**

The solubility of Quetiapine fumarate (QF) in various oils was determined by adding an excess amount of drug in 2 ml of the oils (coconut oil, lemon oil, castor oil, IPM, Oleic acid) separately in 5-mL-capacity vial, and

then mixed using a cyclomixer (CM 101, REMI, Mumbai, India). The vials were then kept for continuous stirring on water bath shaker (R100/TW, Luckham, England) at 25 °C for 48 h. After equilibrium, samples were removed from the water bath shaker and centrifuged (R2, REMI) at 10000 rpm for min.^[9] The supernatant was taken and filtered through a 0.45- μ m membrane filter. The concentration of Quetiapine fumarate was determined in oils using UV spectroscopy. The study was carried in triplicate.

Screening of Surfactants

Different types of surfactants were screened for microemulsion formulation, which included.

Acconon MC8-2, Cremophor RH 40 and Tween 80. In water, 2.5 ml of 15 wt. % surfactant solution was prepared, and 4 μ l of oil was added with vigorous vortexing. If a one-phase clear solution was obtained, the addition of the oil was repeated until the solution became turbid.

Screening of Cosurfactants

Tween 80 was combined with different types of solubilizers as cosurfactants, namely, Captex 200-P, and Polyethylene glycol 400. At a fixed Smix ratio of 3:1, the pseudoternary phase diagrams were constructed. Different combinations in different weight ratios of oil and Smix, 9:1 to 1:9, were taken so that maximum ratios were performed to delineate the boundaries of phases precisely formed in the phase diagrams.^[10,11] The pseudo ternary graphs are drawn by using CHEMIX software.

Preparation of micro emulsions containing quetiapine fumarate

QFME formulations were prepared by water titration method^[12] by different the ratio of oil, Surfactant, co-surfactant, and water; keeping the quetiapine fumarate concentration of constant. A quantity of 20mg drug was mixed in an accurate quantity of oil (Oleic acid), and to that surfactant mixture was added and mixed gently for 10 minutes room temperature. The mixture was titrated with distilled water drop wise until a stable and transparent ME was formed. MMEs were prepared by adding chitosan (low molecular weight) solution in 1% acetic acid to micro emulsion formulation. Different combinations were represented in Table 1.

Characterization of Formulation

Drug content

Drug content of QFME and QFMME was determined by taking formulation equivalent to 20 mg of Quetiapine and diluted using methanol. Samples were prepared in triplicate, and absorbance was measured at 254 nm using UV-Vis spectrophotometer.

Globule size, PDI and Zeta potential

Globule size, PDI and Zeta potential measurements were performed by photon correlation Spectroscopy using Zetasizer (Nano-ZS90, Malvern, Worcestershire, UK) by

taking 1 ml of formulation into polystyrene cuvettes for particle size and PDI and disposable folded capillary Cell for zeta potential at 25°C respectively.

Transmittance (% T)

Transparency of formulation was determined by measuring percentage transmittance through UV Spectrophotometer (UV 3000-LABINDIA). Percentage transmittance of samples was measured at 650nm with purified water taken as blank and three replicates were performed for each sample.^[13]

pH

The pH of Formulation was determined at room temperature using a calibrated digital pH meter by taking 10 ml of formulation individually in a beaker.

Viscosity

The viscosity of formulation was determined using Brookfield viscometer. Viscosity determinations were performed at 40 rpm at 25 \pm 0.3 °C.

Stability studies

The optimized QFME was stored at three different temperature ranges for 3 months i.e., room temperature, elevated temperature (40 \pm 2), refrigerating condition (2–8) and shelf life of the stored microemulsion system was evaluated by phase separation, Emulsifying time, Electrical conductivity, Rheological behavior, pH, Percentage transmittance, Assay and *In vitro* drug diffusion studies.^[12]

Statistical Analysis

Experimental data from more than triplicate are shown as means \pm standard deviations (SD).

RESULTS

Screening Criteria for Oil Selection

Hydrophilic drugs are preferably solubilized in w/o microemulsions, whereas o/w systems seem to be a better choice for lipophilic drugs. Drug loading in the formulation is a very critical design factor in the development of microemulsion systems for poorly soluble drugs, which is dependent on the drug solubility in various formulation components. The volume of the formulation should be minimized as much as possible to deliver the therapeutic dose of the drug in an encapsulated form. Solubility of the drug in the oil phase is an important criterion for the selection of oils. The ability of microemulsion to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in the oil phase. If the surfactant or cosurfactant is contributing to drug solubilization, there could be a risk of precipitation. Thus, an understanding of factors influencing drug loading capacity while maintaining the capability of the system to undergo monophasic dilution with water and minimizing the tendency for drug precipitation or crystallization in diluted systems is essential to the design of stable and appropriately low-

volume microemulsion systems for drug delivery applications.

The solubility of Quetiapine fumarate in different oils was determined (Table I). The solubility of Quetiapine fumarate was found to be highest in Oleic acid (18.2 ± 0.34 mg/ml) as compared to other oils.

Table I: Solubility of quetiapine fumarate in Different Oils at 25°C (mean \pm SD, n=3).

S. No	Solubility	Solubility (mg/ml)
1	Oleic acid	18.2 ± 0.34
2.	Castor oil	6.24 ± 0.12
3.	Lemon oil	2.03 ± 0.41
4.	Coconut oil	0.61 ± 0.38

Table II: Solubility of quetiapine fumarate in Different surfactants and cosurfactants at 25°C (mean \pm SD, n=3).

S. No.	Solubility	Solubility (mg/ml)
1	Acconon MC 82	5.4 ± 0.67
2	Tween 80	15.69 ± 0.12
3	Cremophore RH 40	7.43 ± 0.69
4	PEG400	9.3 ± 0.76
5	Captex 200P	3.18 ± 0.53

Screening Criteria for Surfactants

The most critical problem related to the microemulsion based systems is the toxicity of the components. Large amounts of surfactants may cause nasociliary toxicity when administered intranasal. Therefore, the proper selection of surfactants becomes necessary. It is, therefore, important to determine the surfactant concentration properly and use the minimum concentration in the formulation. Hydrophilic surfactant and cosurfactant are considered to prefer the interface and to lower the necessary energy to form the microemulsions, consequently improving the stability. For example, the required HLB value to form o/w microemulsion is greater than 10. The right blend of low and high HLB surfactants leads to the formation of a stable microemulsion upon dilution with water. After selection of Oleic acid as the oil phase, the goal was to identify the surfactant that has the highest solubilization capacity for the oil. In the present study, three nonionic surfactants, namely, Acconon MC 82, Cremophor RH40, and Tween 80, were chosen for screening. Nonionic surfactants were selected since they are known to be less affected by changes in ionic strength and pH are generally regarded as biocompatible and safe, Ionic surfactants were excluded from the study due to toxicological concerns. The greater the microemulsion area is, the greater the microemulsification capacity of the surfactant. Tween 80 solubilized the maximum amount of Oleic acid.

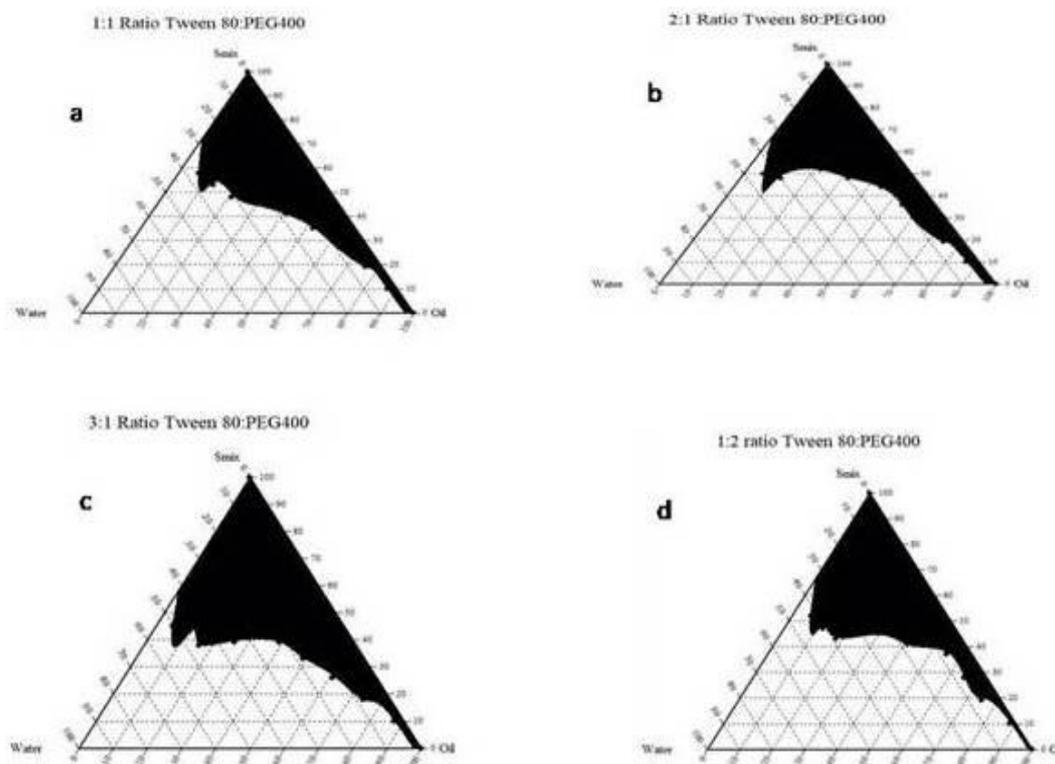


Fig. 1: Pseudo ternary phase diagram using oleic acid as oil, Tween 80 as surfactant, PEG400 as cosurfactant and water. Ratio of S mix (Tween 80: PEG400) a) 1:1, b) 2:1 c) 3:1 and d) 1:2.

Screening of Cosurfactants

Cosurfactants are added to obtain microemulsion systems at low surfactant concentration. The presence of the cosurfactant/secondary surfactant and its type can thus affect the phase behavior of the microemulsion.

Based on the Pseudoternary phase diagram, PEG400 was found to be an efficient cosurfactant for its maximum microemulsion area 3:1 ratio shown in fig 1, and hence, it was selected as the cosurfactant for the microemulsion formulation development.

Table III: Composition of microemulsions containing quetiapine fumarate.

Formulation	Drug (mg)	Oil (%)	Smix (%)	Water (%)
QF 1	25	5	30	65
QF 2	25	5	40	55
QF 3	25	5	50	45
QF 4	25	5	60	35
QF 5	25	10	30	65
QF 6	25	10	40	55
QF 7	25	10	50	45
QF 8	25	10	60	35
QF 9	25	15	30	65
QF 10	25	15	40	55
QF 11	25	15	50	45
QF 12	25	15	60	35

Characterization of formulation

The microemulsions were selected so that all the formulations contain increasing concentrations of oil and Smix (Table III). Table IV depicts the characteristics of these formulations. The droplet size increased with increase in the concentration of the oil in the formulations (Table IV). However, the droplet size of all

the formulations was in the nano range. The low poly dispersibility values observed for all the formulations indicated uniformity of droplet size within each formulation. chitosan used as a mucoadhesive agent to increase adhesion of formulation to nasal mucosa. Optimized formulation shown in Table V.

Table IV: Characterization of Formulations. Data shown as mean \pm SD (n=3).

Formulation	Globule Size	Zeta size	PDI	pH	Viscosity
	(nm)	(mV)			
QF 1	109.8	-22.4	0.14	6.56	179
QF 2	52.6	-29.5	0.16	6.51	181
QF 3	86.2	-23.4	0.14	6.62	178
QF 4	61.9	-22.7	0.13	6.54	164
QF 5	54.8	-27.4	0.19	6.58	191
QF 6	92.7	-26.2	0.17	6.78	190
QF 7	62.5	-25.1	0.18	6.85	184
QF 8	89.5	-28.7	0.12	6.73	205
QF 9	134.4	-24.8	0.13	6.81	276
QF 10	102.3	-27.8	0.14	6.75	248
QF 11	93.2	-23.6	0.15	6.57	262
QF 12	85.5	-24.5	0.16	6.79	227

Table V: Optimized formulation.

Formulation	Drug (mg)	Oil (%)	Smix (%)	Water (%)	Chitosan	Globule Size (nm)	Zeta size (mV)	PDI	pH	Viscosity (mPa-s)
QF MME	25	5	60	35	0.1%	61.9	-22.7	0.13	6.54	164

The droplets in the microemulsion appear dark, and the surroundings are bright; a "positive" image was seen using SEM (Fig. 2). Some droplet sizes were measured using SEM, as it is capable of point-to-point resolution. Viscosity tends to increase with the oil content.

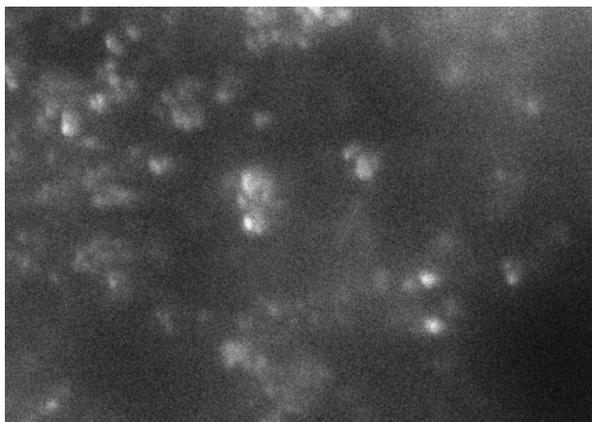


Fig 2: SEM Image of optimized formulation.

As the oil content was increased from 5%wt/wt to 20%wt/wt, an increase in the viscosity of the formulations was observed (Table IV). The viscosity of formulation QF4 was significantly lower than that of the other formulations, which might be due to its lower oil content. Overall, very low viscosity of the formulations was observed.

SUMMARY AND CONCLUSION

Proper selection of components is critical to an efficient microemulsion formulation. Optimized mucoadhesive microemulsion showed lesser globule size, PDI, zeta potential. Hence it can be concluded that the formulation with enhanced solubility can have potential of improving bioavailability of Quetiapine fumarate formulation and increase in mucoadhesion property.

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