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Research article

PREPARATION AND EVALUATION OF QUETIAPINE FUMARATE MICROEMULSIONS: A NOVEL DELIVERY SYSTEM

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ABSTRACT

Objective: In the present study, the main objective is to improve solubility and bioavailability of Quetiapine fumarate by formulation into micro emulsion.

Method: The Quetiapine fumarate micro emulsion was formulated by using mixture of Isopropyl myristate and oleic acid as oil phase, Tween-80 as surfactant, Isopropyl alcohol and Ethanol mixture as co-surfactant by phase titration method. The prepared formulations were evaluated for Limpidity (% transmittance), droplet size, Zeta potential, Electrical conductivity, Rheology, pH, percentage of drug (assay), emulsifying time, *in vitro* drug diffusion studies and *ex vivo* permeation studies.

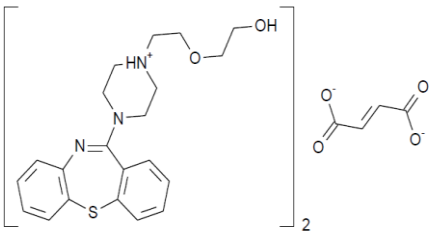
Results and conclusion: The Optimized micro emulsion (Micro emulsion 11) formulation containing Quetiapine fumarate (25mg), Surfactant mixture (50%w/w), Oil (12%w/w) and distilled water (38%w/w) has a droplet size of 26.70 nm with a zeta potential of -5.62 millivolts. The micro emulsion was characterized and compared with the pure drug suspension. Microemulsion showed 31.25 fold increased solubility than that of pure drug suspension. *In vitro* drug release and *ex vivo* permeation study results were comparable and correlative. The Microemulsion 11 formulation showed 1.4763 times more drug release than that of pure drug suspension. The formulation was found to be stable for three months.

Keywords: Microemulsion, Phase titration method, Quetiapine Fumarate, Emulsifying time.

INTRODUCTION

Drug solubility enhancement is one of the most challenging approaches in pharmaceutics. Nearly 40% of all new pharmacologically potent molecules show poor aqueous solubility, leading to their low effective concentration in biofluids and therefore poor bioavailability [1]. Micro emulsions are lipid based formulations [2] consisting of oil phase and an aqueous phase emulsified with surfactants. Micro emulsions generally have a droplet size in the range of 20-200nm [3].

Quetiapine Fumarate is chemically 2-[2-(4-{2-thia-9-azatricyclo[9.4.0.0{3,8}]pentadeca-1(11),3(8),4,6,9,12,14-heptaen-10-yl}piperazin-1-yl)ethoxy]ethan-1-ol is an atypical antipsychotic agent which acts as an antagonist at dopamine and serotonin receptors [4].



Quetiapine Fumarate is a BCS class II drug. It is reported to have very low oral bioavailability (9%) [5] reason being its limited absorption due to moderate solubility in water and extensive hepatic metabolism. The main purpose of this research work is to develop a novel delivery system i.e., micro emulsion (ME) as a formulation strategy to overcome its limitations posed by poor solubility.

Arjun Narela *et al.*, reported the solid lipid nanoparticles of Quetiapine Fumarate to improve its solubility [6]. The limitation of this technique is the difficulty in preparation and requires an additional step in order to attach or load the drug into the nanoparticles [7].

MATERIALS AND METHODS

Quetiapine fumarate (QF) was received as a gift sample from Richard Labs (Hyderabad, India), Isopropyl myristate was received from SL Scientifics, Anantapuramu, India, Tween 80 and oleic acid were received from Bros scientific lab, Hyderabad, India. All the solvents used in the study were of analytical grade.

Solubility analysis (Screening of Oils, Surfactants, Co-Surfactants)

The solubility of quetiapine fumarate in two different oils (Oleic acid, isopropyl myristate), surfactant (Tween-80, tween-20), and co-surfactants (isopropyl alcohol, ethanol) was determined. Excess amount of drug was added to the selected vehicle. The mixtures were shaken on an orbital shaker at 37°C for 24 hours and were centrifuged at 5000rpm for 15min and extracted with methanol. The solubility of drug in oils, surfactants and co-surfactants was determined at 254nm using UV-Vis spectrophotometer.

Construction of pseudo ternary phase diagrams

Different mixtures of surfactant to co-surfactants were prepared and the weight ratios were fixed to 1:1, 1:2, 2:1, 1:3 and 3:1. These mixtures (S/Co-S) were mixed with oil phase to give weight ratio of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9, water was added drop by drop i.e., water titration method at 25°C and stirred until homogeneous dispersion or solution was obtained [9]. After each addition the system was examined for appearance and flow property.

The end point of the titration was the point in which the solution becomes cloudy or turbid. The quantity of aqueous phase required to make the mixture turbid was noted. The pseudo ternary graphs are drawn by using CHEMIX software.

Drug excipient interaction studies

FT-IR Studies

Drug excipient interactions were determined by using FT-IR studies and DSC studies. FT-IR studies were performed for pure drug with/without excipients by using FT-IR Spectrophotometer (BRUKER ALPHA E) using OPUS software.

DSC Studies

DSC studies were performed using METTLER TOLEDO 822E by keeping the pure drug with/without excipients in hermetically sealed Al pans. Scanning rate was 10°C /min from 25°C to 250°C under nitrogen flow.

Preparation of micro emulsions containing quetiapine fumarate

ME formulations were prepared by the spontaneous emulsification method (phase titration method) [8] by varying the ratio of oil, Surfactant, co-surfactant, and water; keeping the quetiapine fumarate concentration of constant in each case. A quantity of 25mg drug was mixed in an accurate quantity of oil (Iso propyl myristate, 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 by drop until a stable and transparent ME was obtained. Various combinations were represented in Table 1.

Table 1: Various Microemulsion Formulations by using mixture of oleic acid (ME1 to ME8) and Isopropylmyristate (ME9 to ME14) as oil phase, tween-80 as surfactant and mixture of Isopropyl alcohol, Ethanol as co-surfactant.

Formulation code	Quetiapine Fumarate (mg)	Surfactant mixture (%w/w)	Oil (%w/w)	Water (%w/w)
ME1	25	38	6	56
ME2	25	34	8	58
ME3	25	32	8	60
ME4	25	40	6	54
ME5	25	52	6	42
ME6	25	46	4	50
ME7	25	46	6	48
ME8	25	44	6	50
ME9	25	60	15	25
ME10	25	58	14	28
ME11	25	50	12	38
ME12	25	54	5	41
ME13	25	54	4	42
ME14	25	54	3	43

EVALUATION OF MICROEMULSION

Identification of Type of Emulsion

Drop dilution test

The dilutions were made as 1 in 10,1 in 100,1 in1000 of microemulsion with water and it shows the miscibility with external phase and no separation was observed which indicates prepared microemulsion was o/w type [10].

Dye solubility test

To the water soluble dye (Amaranth), add the prepared o/w microemulsion. The dye readily tints the o/w emulsion. The dye solubilises and disperses uniformly throughout the microemulsion indicating the o/w type of emulsion.

Scanning Electron Microscopy

Scanning electron microscopy was carried out for drug formulation by using JEOL, JSM-6510LA-Analytical electron microscope [11].

Droplet Size Analysis

Droplet size measurement was a crucial factor which determines the rate and extent of drug release as well as stability of the microemulsion [12]. Droplet size measurement and zeta potential determination of optimized ME formulations was carried out by dynamic light scattering through Zetasizer HAS 3000 (Malvern Instruments Ltd., Malvern, UK).

Limpidity Test (% transmittance)

Transparency of microemulsion formulation was determined by measuring percentage transmittance through UV Spectrophotometer (UV-1800.SHIMADZU).Percentage transmittance of samples was measured at 650nm with purified water taken as blank and three replicates were performed for each sample [13].

Emulsifying Time

The time taken for the microemulsion to emulsify in the water and get miscible in it was considered as the emulsifying time of that microemulsion formulation. Take 1ml of microemulsion formulation and pour it into water and the time taken for emulsification was noted and kept for 24hours to categorize for its clarity and stability. Experiments were performed in three replicates for each sample. After 24 hours the resultant microemulsion was categorized for clear (transparent or transparent with bluish tinge), not clear (turbid), stable (no precipitation observed at the end of 24 hours) or unstable (showing precipitation within 24 hours) [14].

Rheological Studies

The viscosity of the ME was evaluated by a Brookfield LVDV 11 + CP viscometer (Stoughton, MA) by using spindle number of CPE42 at shear stress of 21.9 and shear rate of range 9.60 to 93.8 for all formulations. Experiments were performed in triplicate for each sample [15].

Phase Analysis (conductivity studies)

The Conductivity of the ME was evaluated by an Electro conductivity meter (CM 180 conductivity meter. Elico, India) at ambient temperature [16]. Experiments were performed in triplicate for each sample.

pH Analysis

The pH of the microemulsions was evaluated by using pH meter (systronics, India). Experiments were performed in triplicate for each sample.

Assay of Drug loaded microemulsion

Microemulsion formulation was analyzed for drug content by U.V. spectrophotometer (Shimadzu, UV1800) at 254 nm by taking 1ml of emulsion and diluted with methanol appropriately. Experiment was performed triplicate for each sample [17].

***In vitro* Diffusion Studies**

In vitro drug diffusion studies were carried out by using modified dissolution apparatus. It is carried out by dialysis bag method to increase in the surface area available for transport from the donar to the receiver compartment and hence sink conditions are maintained [18]. The diffusion study was also conducted for pure drug suspension (25mg of Quetiapine Fumarate in 5ml of water). It is conducted by taking the 300ml of 0.1N Hydrochloric acid as a diffusion medium and the speed was maintained at 100rpm. The prepared microemulsion was taken in the dialysis bag with a pore size of 2.4nm by fastening both ends and the tied bag containing microemulsion was dropped in to the dissolution jar and the samples were taken at the regular intervals of time starting from 10 min to 210 min and analyzed spectrophotometrically at 254nm. Experiments were performed in triplicate for each sample.

***Ex vivo* Diffusion Studies**

The *Ex vivo* diffusion studies were performed in male albino rats weighing 150 to 250 gms. The rats were dissected and the stomach was separated and was stored in formalin solution until the study was performed. The method performed was everted sac method. The prepared optimized microemulsion was injected to the rat stomach and the diffusion study was conducted by taking 300ml 0.1N Hydrochloric acid at 100rpm speed by maintaining at a

temperature of 37.5°C. The samples were withdrawn at regular intervals of time and measured spectrophotometrically at 254nm. Experiments were performed triplicate of each sample.

Stability studies

The optimized ME was stored at three different temperature ranges for 3 months i.e., refrigerating condition (2°C– 8°C), room temperature and elevated temperature (40°C ± 2°C) and relative humidity (75±5% RH) and shelf life of the stored microemulsion system was evaluated by visual inspection (phase separation), Emulsifying time, Electrical conductivity, Rheological behavior, pH, Percentage transmittance, Assay and *In vitro* drug diffusion studies [20].

Centrifugation Studies

In order to estimate the metastable systems, the optimized microemulsion formulation was also centrifuged (Remi Laboratories, Mumbai, India) at different rpm like 5,000, 10,000 and 15,000 for 30 minutes at room temperature and observed for any change in homogeneity of microemulsion [20].

Stability studies

Stability studies were performed for the optimized formulation ME11 as per ICH guidelines for 3 months. The % transmittance, pH analysis, Emulsifying time, Electrical conductance, Rheological studies, Drug content were performed during and after study and the results were shown in the table 3. No significant difference was observed after stability studies indicating that the formulation was stable.

RESULTS AND DISCUSSION

Quetiapine Fumarate was identified by ATR and DSC techniques. The drug-excipient interactions studies were carried out using ATR and DSC. These results showed that the drug was compatible with all excipients used in the formulation.

Solubility analysis

The screenings of different solvents were done and the drug shows the better solubility in Isopropylmyristate (oil), Isopropyl alcohol (co-surfactant), Tween-80 (surfactant). The solubility of the drug in the microemulsion showed 31.25 folds increased solubility than that of pure drug suspension.

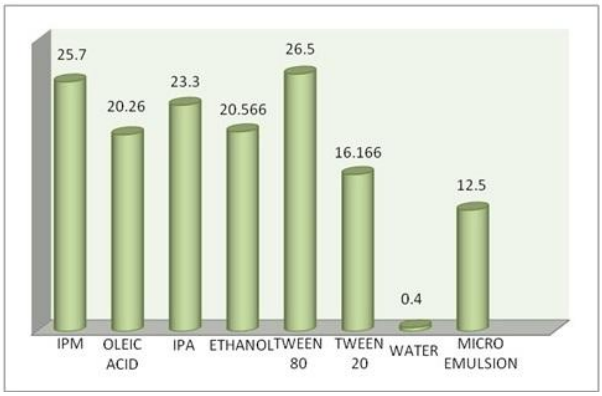


Fig. 1: Solubility (mg/ml) graph of drug in various vehicles

Pseudo ternary phase diagrams

The pseudo ternary phase diagrams were constructed by using CHEMIX software for the different ratios of surfactant mixtures with two different oils. The trails were conducted by selecting the points in the pseudo ternary graphs for optimizing the percentage of the surfactant mixture, oil and water in the formulation and the microemulsion formulations were prepared and the optimized formulations was given in the table 1 and the pseudo ternary plots of ME7 and ME11 were shown in Fig 2.

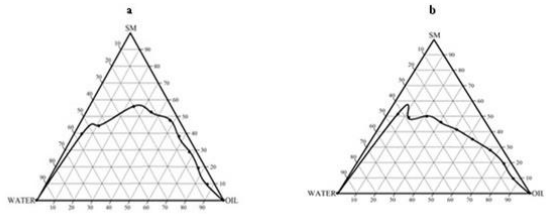


Fig.2: Pseudo ternary graph consisting of a) oleic acid as an oil,Tween-80 as an surfactant and ethanol as an co-surfactant, where surfactant to co-surfactant ratio was 1:2 b) Isopropyl myristate as an oil, Tween-80 as an surfactant and Isopropyl alcohol as an co-surfactant, where surfactant to co-surfactant ratio was 2:1

Scanning electron microscopy

Scanning electron microscopy was used to investigate the morphology of the micro emulsions. The microphotographs of microemulsion was shown in the fig.3 indicated that the oil globules in the emulsion have a smooth and homogenous texture and disperse.

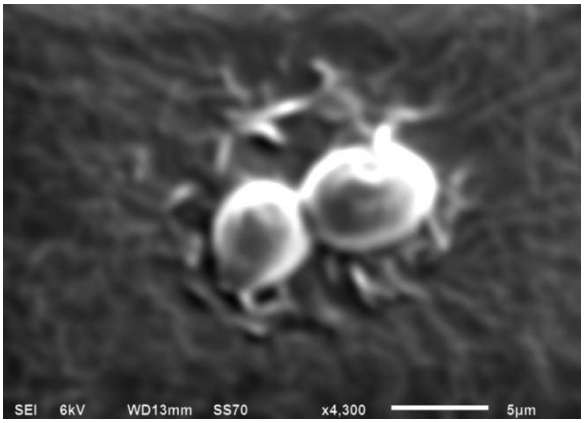


Fig. 3: Microphotograph of microemulsion

Droplet Size Analysis

The droplet size of the optimized formulation ME11 was found to be 26.7 d.nm and the zeta potential was found to be -5.62 mV by using the zetasizer and the graphs were shown in the fig.4.

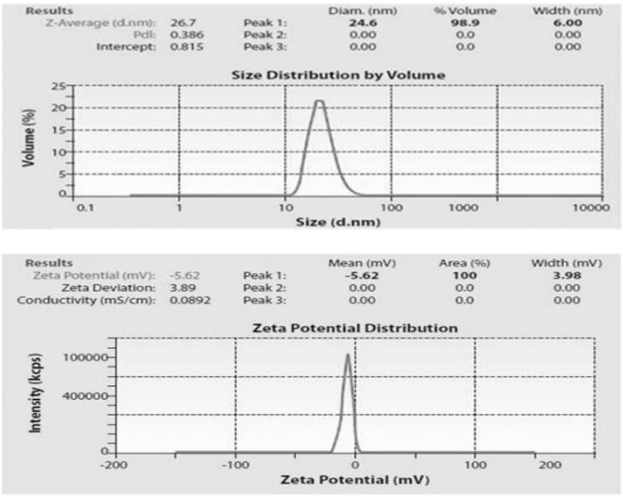


Fig. 4: Droplet size and Zeta potential analysis for best formulation (ME11)

As per dilution test when water is added to the emulsion, it readily gets dispersed in the emulsion that indicates that the formed emulsion was oil in water type.

As per dye solubility test, amaranth is water soluble dye disperses uniformly throughout an emulsion and it get solubilises in the external phase that indicates that the formed emulsion is oil in water type.

Percentage transmittance of the microemulsion explains that the prepared micro emulsions were transparent and clear like homogenous single-phase liquid. There is no traces of undissolved drug was seen in all the formulations of micro emulsions.

The Emulsifying time for all the formulations was less than one minute. This represents the visual inspection of the resultant microemulsion after 24 hours was clear (transparent with bluish tinge) and was stable (no precipitation at the end of 24 hours).

By observing the rheological studies, as there is increase in the percentage of water in the microemulsion there is decreases in the viscosity.

By observing the conductivity studies, as there is increase in the percentage of water in the microemulsion there is increase in the conductivity.

The pH values of all the formulations were found in the range of 5.195 to 6.273.

The drug content of all the microemulsion formulations was found in the range of 98.266 – 99.466%.

Table 2: Results for % transmittance, viscosity, conductivity, emulsifying time, pH, Assay

Formulation code	%Transmittance* ±SD	Viscosity(cps)* ± SD	Conductivity* (μΩ)±SD	Emulsifying time*(sec) ±SD	pH* ±SD	Assay(% ±SD
ME1	99.23±0.05	71.83±0.57	238±0.00	10.63±0.041	6.27±0.11	98.26±0.21
ME2	99.43±0.11	48.42±0.81	241.6±0.57	10.57±0.011	6.20±0.11	99.46±0.32
ME3	99.33±0.15	26.93±0.61	259±0.00	9.66±0.034	6.18±0.11	99.46±0.21
ME4	99.46±0.15	216.63±4.30	229.3±0.57	18.18±0.011	6.026±0.0	98.933±0.2
ME5	99.56±0.05	232.23±3.18	213.6±0.57	20.28±0.005	6.19±0.01	98.93±0.46
ME6	99.43±0.11	72.56±0.40	236±0.00	9.296±0.005	6.03±0.04	99.46±0.23
ME7	99.43±0.11	43.86±0.64	231.66±0.5	12.27±0.017	6.25±0.04	99.33±0.23
ME8	99.3±0.13	29.20±0.51	235.66±0.5	15.59±0.005	6.15±0.04	99.33±0.46
ME9	99.53±0.05	93.93±0.611	158.33±0.5	9.84±0.023	5.34±0.01	98.66±0.46
ME10	99.46±0.05	62.66±0.32	162.33±0.5	11.62±0.005	5.30±0.00	98.93±0.61
ME11	99.43±0.11	35.06±2.40	177.33±1.1	19.43±0.011	5.31±0.02	99.46±0.23
ME12	99.43±0.20	49.2±0.51	188.66±0.5	10.67±0.005	5.19±0.01	99.33±0.23
ME13	99.3±0.173	23.46±0.57	198.33±0.5	15.62±0.005	5.34±0.02	98.93±0.23
ME14	99.3±0.12	15.66±0.11	208.66±0.5	18.56±0.005	5.32±0.04	98.53±0.61

***All values are expressed as mean ± standard deviation, (n=3)**

***In vitro* drug diffusion studies**

Among the formulations, ME7 and ME11 shows drug release of 99.033% and 99.255% at the end of 2 hour 15 minutes and 1 hour 50minutes respectively. The formulation ME11 shows good release when compared to ME7, it is due to the droplet size of the ME11 formulation was less when compared to ME7 formulation

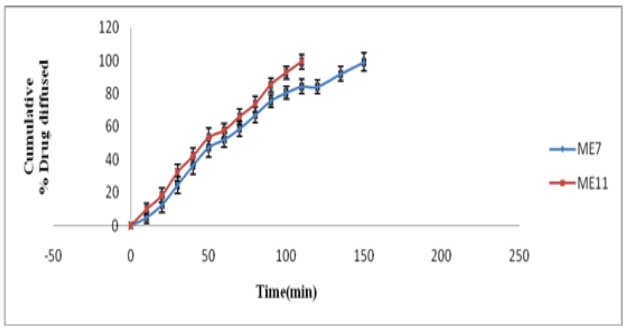


Fig. 5: Comparison of cumulative% drug diffused plots of(-▲-) ME7 and (-■-) ME11

The *ex vivo* drug diffusion studies were conducted to the optimized formulation ME11. The drug release of ME11 formulation from the everted sac of the rat (94.564%) was similar to that of *In vitro* drug release of ME11 formulation (99.155%). The ME11 formulation showed 1.4763 times enhanved drug release when compared to that of pure drug suspension.

Table 3: *in vitro* drug diffusion studies for drug suspension, ME11 and *ex vivo*

Drug diffusion studies for ME11

Time(min)	Cumulative % drug diffused*±SD		
	Pure drug suspension	ME11	*Ex vivo* for ME11
0	0	0	0
10	4.345±2.78	9.844±2.45	14.987±2.7
20	10.786±2.34	18.33±2.67	20.1664±234
30	19.234±2.76	30.265±3.78	36.543±2.98
40	24.897±2.78	37.999±4.01	42.987±2.76
50	29.765±3.09	46.222±3.87	54.098±2.93
60	34.987±2.78	54.633±2.98	62.98±2.49
70	42.123±2.65	64.999±2.67	71.098±2,34
80	53.765±2.43	73.666±3.45	78.987±3.76
90	58.234±2.87	85.233±2.78	82.765±3.78
100	62.987±2.76	92.566±2.45	89.998±3.24
110	67.162±2.87	99.155±2.65	94.564±2.98
120	74.098±2.38		

***All values are expressed an mean ± Standard deviation, (n=3)**

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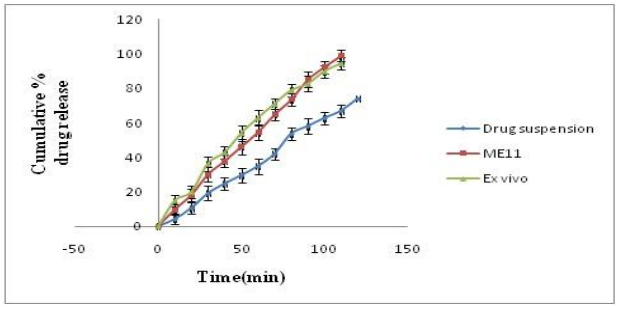

Fig. 6: Comparison of cumulative drug diffused plots of(-▲-) pure drug suspension, (-■-)*in vitro* and (-▲-)*ex vivo* of ME11.

Stability studies

Stability studies were performed for the optimized formulation ME11 as per ICH guidelines for 3 months. The % transmittance, pH analysis, Emulsifying time, Electrical conductance, Rheological studies, Drug content were performed during and after study . Dissolution testing was performed during and after study. After testing there was no significant difference in the results indicating that the formulation was stable.

Table 4: Stability study results for optimized formulation ME11

	Optimized formulation ME11				
Evaluation	**0 days**	**15 days**	**30 days**	**60 days**	**90 days**
Appearance	Clear and Transparent	Clear and Transparent	Clear and Transparent	Clear and Transparent	Clear and Transparent
Phase separation	No	No	No	No	No
Percentage Transmittance*±SD	99.43±0.115	99.32±0.112	99.23±0.203	99.432±0.118	99.345±0.231
Emulsifying time(sec)* ±SD	19.43±0.011	19.34±0.023	19.87±0.023	19.678±0.034	19.998±0.012
Rheological behavior(cps)* ±SD	35.06±2.40	35.67±2.341	35.46±2.324	36.45±2.123	39.89±2.098
Phase analysis (μΩ)* ±SD	177.33±1.15	177.89±2.123	178.23±1.98	177.45±1.231	178.90±2.123
pH analysis*±SD	5.31±0	5.34±0.023	5.31±0.034	5.45±0.054	5.34±0.023
Drug content(%)*±SD	99.46±0.230	99.34±0.123	99.456±0.23	99.675±0.453	99.123±0.186

***All values are expressed as mean ± standard deviation, (n=3)**

Stability studies were performed for the optimized formulation ME11 as per ICH guidelines for 3 months. Dissolution testing was performed during and after study. Results of dissolution were shown in table 5 and figure 7. No significant difference was observed after stability studies indicating that the formulation was stable.

Table 5: *In vitro* % drug diffusion for optimized formulation (ME11) during and After stability studies

	Cumulative %drugdiffused*±SD				
Time(min)	**0 days**	**15 days**	**30 days**	**60 days**	**90 days**
0	0	0	0	0	0
10	9.844±2.45	9.876±2.98	9.876±2.67	9.889±2.65	9.987±2.34
20	18.33±2.67	19.56±3.45	18.90±2.45	19.87±2.67	19.98±2.54
30	30.265±3.78	31.786±3.09	30.765±3.23	30.435±2.76	30.456±2.87
40	37.999±4.01	37.897±3.12	38.234±3.09	37.234±2.89	37.887±3.45
50	46.222±3.87	46.876±4.02	46.234±3.76	45.987±3.09	45.567±3.09
60	54.633±2.98	55.876±2.67	55.453±4.01	54.345±3.01	56.876±3.13
70	64.999±2.67	64.765±2.45	64.098±2.76	64.765±2.78	64.324±4.09
80	73.666±3.45	74.987±2.54	73.654±2.96	73.876±2.56	74.765±2.34
90	85.233±2.78	85.543±2.76	85.098±2.45	85.123±2.98	86.765±2.65
100	92.566±2.45	92.677±2.54	95.345±2.76	95.098±2.76	95.987±2.45
110	99.155±2.65	99.045±2.98	99.234±2.45	99.156±2.56	99.178±2.34

***All values are expressed as mean ± standard deviation, (n=3)**

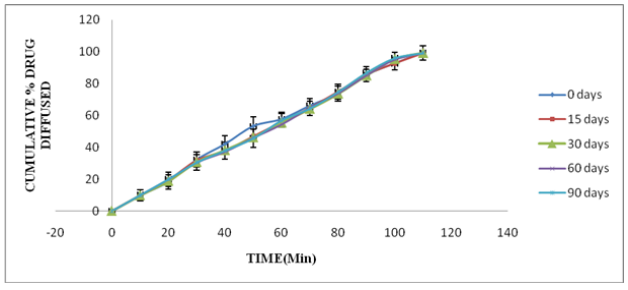

Fig. 7: *In vitro* drug diffusion of ME11 during and after stability studies

The resultant values were fitted in the different kinetic models like zero order, first order, Hixson Crowell, Higuchi and Korsemeyer Peppas plots. For all formulations, the r^2 values of Zero order were greater than the r^2 values of first order so, the drug release follows zero order kinetics. The r^2 values of Higuchi plots were greater than the r^2 values of Hixson Crowell, represents that the drug release follows diffusion mechanism. The n-value of all formulations are >0.5 and <1 represents that the drug release follows non-fickian diffusion.

Among all formulations ME11 formulation showed fast drug release with good droplet characteristics. The r^2 (0.988) of Zero order was greater than the r^2 (0.760) of first order so, the drug release follows zero order release. The r^2 (0.950) of Higuchi plot was greater than the r^2 (0.905) of Hixson Crowell, represents that the drug release follows diffusion mechanism. The n-value of ME11 formulation was 0.962 which represents that the drug release follows non-fickian diffusion.

CONCLUSION

It is concluded that the Quetiapine Fumarate microemulsion prepared by phase titration method was best suitable method to prepare microemulsion for this drug. The developed microemulsion containing 50% of surfactant mixture (tween-80: Isopropyl alcohol), 12% of oil (Isopropyl myristate) and 38% of water was found to be

transparent fluid with a particle size of 26.7nm. The drug release showed higher drug release when compared to the drug suspension. The *Ex vivo* drug release from ME11 formulation was also similar to that of *In vitro* drug release.

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