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FORMULATION AND EVALUATION OF QUETIAPINE FUMARATE LOADED MICROEMULSION

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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%). Hence In the present study, the main objective is to improve bioavailability of Quetiapine fumarate by formulation into microemulsion. The Quetiapine fumarate micro emulsion was formulated by phase titration method using mixture of oleic acid as oil phase, tween-80 as surfactant, isopropyl alcohol as co-surfactant. Optimized ratio of tween 80: isopropyl alcohol was selected after developing pseudoternary phase diagrams for different ratio and microemulsions were prepared. The optimized formulation was evaluated for drop dilution test, dye solubility test, emulsifying time, pH, viscosity, drug content, diffusion study, stability studies. FTIR analyses showed no significant interaction between pure Quetiapine fumarate with excipients. Emulsifying time of prepared microemulsion ranged from 27 to 38 seconds and drug content of prepared microemulsion ranged from 95.45 to 97.70 %. The % drug releases for formulations F1, F2, F3, F4 and F5 at the end of 7hr were found to be 93.454, 88.324, 79.625, 65.463, and 52.987 % respectively. The formulation containing oil and Smix in the ratio 9:1 (F1) was considered as an optimized formulation with lowest emulsifying time and highest drug release at the end of 7hr was found to be 27 second and 93.45 % respectively.

Keywords: Quetiapine fumarate, Oleic acid, Tween-80, Isopropyl alcohol

INTRODUCTION:

Nearly 40% of all new pharmacologically potent molecules show poor aqueous solubility, leading to their low effective concentration in bio-fluids and therefore poor bioavailability. Many studies have been focused on enhancing the solubility of poorly water-soluble drugs and improving bioavailability to administer them through oral route resulting in increasing their clinical efficacy. One of the most popular approaches is the incorporation of the active lipophilic component into inert lipid vehicles, such as oils, surfactant dispersions, emulsions, and liposomes. Microemulsion allows the incorporation of hydrophilic as well as lipophilic compound depending on their internal structure. These aggregates have been described as reservoir systems, which allow slow release of drugs, thus providing prolonged effects and avoiding high concentration in the blood **[1, 2, 3]**.

Microemulsions (MEs) are isotropic, thermodynamically stable, transparent (or translucent) systems of oil, water, and surfactant, frequently in combination with a co-surfactant with a droplet size usually in the range of 10-100 nm. These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity. A microemulsion as drug delivery tool show favorable properties like thermodynamic stability (long shelf-life), easy formation, optical isotropy, ability to be sterilized by filtration, high surface area (high solubilization capacity) and very small droplet size. The small droplets also provide better adherence to membranes and transport drug molecules in a controlled fashion **[4]**.

Quetiapine Fumarate is an atypical antipsychotic agent which acts as an antagonist at dopamine and serotonin receptors. It is reported to have very low oral bioavailability (9%) 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 formulation strategy to overcome its limitation supposed by poor solubility.

The research aim to develop Quetiapine Fumarate-loaded microemulsion to improve absorption by increase surface area there by increasing bioavailability.

Materials:

Quetiapine fumarate (QF) was received from Symed Labs Ltd (Hyderabad, India), oleic acid Tween 80 and Isopropyl Alcohol was received from Loba Chemie Pvt. Ltd, Mumbai India. All the chemical and reagent used in the study were of analytical grade.

Method:

UV spectroscopy

The stock solution (100µg/ml) was prepared by dissolving drug (10 mg) separately in 100ml of 0.1N HCl. The UV spectrum of Quetiapine Fumarate solution in 0.1N HCl was scanned at 400 nm to 200 nm and observed the λmax by using UV spectroscopy **[5]**.

Standard calibration curve

Standard calibration curve in 0.1 N HCl system

Accurately weighed 10 mg of Quetiapine Fumarate was dissolved in 100 mL of 0.1 N HCl to obtain working standard solution of 100 µg/mL. Aliquots of 0.2 to 1.0 mL from the stock solution representing 2 to 10 µg/mL conc. of drug were transferred to 10 mL volumetric flask and the volume was adjusted to mark with same blank solution. Absorbance of the above solutions was taken at λmax 237 nm by using UV spectrophotometer A graph of Absorbance vs. concentration was plotted **[6]**.

Fourier transform-infrared spectroscopy (FTIR)

FTIR spectra of drug, excipient and physical mixture of drug and excipient were studied to check for any interaction. Pure Quetiapine fumarate was mixed with KBr of IR grade in the ratio of 1:100 and compressed using motorized pellet press at 10-12 tones pressure. The pellets were then scanned over a wave range of 4000-400 cm^{-1} using FTIR spectrometer and spectra was obtained. The IR spectra of liquid samples such as oleic acid, isopropyl alcohol, tween 80 and physical mixture of drug and excipient was obtained by liquid membrane method which involves dripping several drops of the respective sample onto a KBr aperture plate and sandwiching it under another aperture plate, such that no gas bubbles are trapped. Finally, it was scanned over a wave range of 4000-400 cm^{-1} using FTIR spectrometer to obtain an IR spectra.

Preparation of Microemulsion

Microemulsion formulations were prepared by the phase titration method 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 (Oleic acid), and to that surfactant mixture (Tween 80 + Isopropyl alcohol) 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 microemulsion was obtained **[7]**.

Optimization of batch of oil to Smix

Phase studies were performed to define the restricted domain of oil and Smix which gives microemulsion. Optimization of

ration of oil: Smix was carried out by preparing following 5 batches with varying ratio of surfactant: co-surfactant from 1:1 and 2:1.

Optimization of prepared batches was carried out on the basis of evaluation parameters.

Table 1: Different batches for optimization

Sr. No	Ingredients	Formulations				
		F1	F2	F3	F4	F5
1	Quetiapine Fumarate (mg)	25	25	25	25	25
2	Oleic Acid (%)	9	8	7	6	5
3	Tween 80 (%)	1	2	3	4	5
4	Isopropyl Alcohol (%)	1	2	3	4	5
5	Distilled water (ml)	1.5	1.8	2.1	2.7	3.2

Evaluation of prepared microemulsion:

Identification of Type of Emulsion:

a) Drop dilution test

The dilutions were made as 1 ml microemulsion in 10 ml of distilled water, 1ml microemulsion in 100 ml of distilled water, 1 ml microemulsion in 1000 ml of distilled water **[8]**.

b) Dye solubility test

To the water soluble dye (Amaranth), add the prepared microemulsion and examine for uniformdistribution of dye within microemulsion.

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 **[9]**.

pH:

The pH of formulation was measured using a digital glass electrode pH-meter. The pH meter was firstcalibrated using solution of pH 7 **[10]**.

Viscosity

Viscosity of the formulated Microemulsions was determined by using Digital viscometer (Fungi lab).Viscosity was measured at 10 rpm for 30 seconds for microemulsion formulation **[11]**.

Drug content:

The drug content of each preparation is measured by diluting 1 ml of the formulation to 100 ml with an appropriate solvent and shaking intensely. 1 ml was remove from the solution and then diluted to 25 ml with the same solvent. The absorbance of the solution was determined spectrophotometrically at a specific wavelength. The drug content (%) was calculated by use of given equation: **[12]**

Drug content (%) = Drug concentration (sample solution) / Equivalent concentration (drug taken) * 100

Diffusion study:

Diffusion studies for each formulation were performed using Franz diffusion cells. An egg membrane was used as the diffusion membrane. The membrane was saturated in a 0.1N HCl solution for 24 Hrs before the experiment. The receptor chamber was filled with the 0.1N HCl solution and the membrane was placed over the cell. The microemulsion corresponding to 25 mg of drug was placed in the donor chamber. It was in contact with receptor compartment containing 0.1N HCl solution. The cell was agitated by a magnetic stirrer at 50 rpm and temperature was maintained at 32-34 °C using a circulating water bath. Aliquots were withdrawn at specific time intervals till 7 hrs and refilled with an equal amount of fresh 0.1N HCl solutions to maintain sink condition, filtered, and finally the absorbance of the drug was determined spectrophotometrically at 237 nm **[13]**.

Stability studies:

Stability study of formulated microemulsion was performed. Microemulsion are stored in clean, dryand airtight container. The sample were withdrawn at 15, 30, 45 days interval and evaluate for pH, drug content and phase separation **[7]**.

RESULTS AND DISCUSSION

UV spectroscopy:

The λ_{max} of Quetiapine Fumarate was found to be 237 nm.

Standard calibration curve

Standard calibration curve 0.1N HCl system

Graph of Absorbance vs Concentration was plotted and was found to be linear over the range of 2 to 10 µg/mL indicating its compliance with Beer's and Lambert's law. Results are shown in **Table 2 and Figure 1**.

FTIR spectroscopy study

Figure 2, 3, 4, 5 and 6 displays Fourier transform infrared spectrum of pure Quetiapine fumarate, oleic acid, tween 80, Isopropyl alcohol, and a physical concoction of Quetiapine fumarate and oleic acid, tween 80, Isopropyl alcohol respectively.

The FTIR spectrum of Quetiapine Fumarate highlights characteristic peaks. The peak at 3317.67 cm-1 could be assigned to Alcohol OH stretching vibrations. The peak at 1415.80 cm-1 could be assigned to C=C Aromatic vibrations of amide while that at 1219.05 cm-1 and 1130.32 cm-1 could be attributed C- O-C and C-OH stretching vibrations respectively.

The FTIR spectrum of Oleic acid highlights characteristic peaks. The peak at 3581.93 cm^{-1} could be assigned to Alcohol OH stretching vibrations. The peak at 2854.17 cm^{-1} could be assigned to C-H stretching vibrations while that at 1778.43 cm^{-1} and 1643.41 cm^{-1} could be attributed C=O and C=C stretching

vibrations respectively.

The FTIR spectrum of Tween 80 highlights characteristic peaks. The peak at 2858.60 cm^{-1} could be assigned to C-H stretching vibration while that at 1735.99 cm^{-1} could be attributed to C=O stretching vibrations of ketone. The peak at 1460.84 cm^{-1} could be assigned to CH_3 stretching vibrations while that at 1246.06 cm^{-1} and 1111.03 cm^{-1} could be attributed C-O-C and C-OH stretching vibrations respectively.

The FTIR spectrum of Isopropyl alcohol highlights characteristic peaks. The peak at 3510.56 cm^{-1} could be assigned to alcohol OH stretching vibrations. The peak at 2922.31 cm^{-1} could be assigned to C-H stretching vibrations while that at 1141.90 cm^{-1} could be attributed C-OH stretching vibrations respectively.

The spectral observations showed that all principle peaks which are observed in the spectrum of Quetiapine Fumarate alone are appeared in the spectra of physical mixture. This result indicates the compatibility between drug and excipient.

Evaluation of prepared microemulsion:

Identification of Type of Emulsion

a) Drop dilution test

The drop dilution test was performing for all formulation (F1 to F5) and it shows the miscibility with external phase and no separation was observed which indicates prepared microemulsion was o/w type. The results are show in **Table 3**.

a) Dye solubility test

The dye solubilizes and disperses uniformly throughout the microemulsion indicating the o/w type of emulsion.

Emulsifying Time

The emulsifying times were determined for all formulation and it was found to be in the range of 27 to38 sec. The results are show in **Table 4**.

pH:

pH values of all the formulations (F1-F5) were found to be between 3.5 to 5.5 as shown in **Table 5** which indicate suitability of the formulations for oral application of microemulsion.

Viscosity:

Viscosity of all the formulations (F1-F5) was found to be between 291 to 614 cP. It was observed that the viscosity is increases with increase in concentration of microemulsions. The result are summarized in **Table 6**.

Drug content:

The determined drug content values of all the formulations (F1-F5) ranged from 95.80 % to 97.70 % as shown in **Table 7**. It indicates that the drug is uniformly distributed in the microemulsion formulation.

Diffusion Study:

The in vitro release was carried out for all formulation using 0.1N HCl as medium.

The % drug release for formulations F1, F2, F3, F4 and F5 at the end of 7hrs were found to be 98.26 %, 89.29 %, 85.59 %, and 57.89 % respectively. The data of these studies are presented in **Table 8** and graphical representation of the % drug release shown in **Figure 7**.

Table 2: Data for calibration curve of Quetiapine Fumarate in 0.1N HCl

Sr. No	Concentration (µg/mL)	Absorbance
1	2	0.799
2	4	1.031
3	6	1.257
4	8	1.475
5	10	1.663

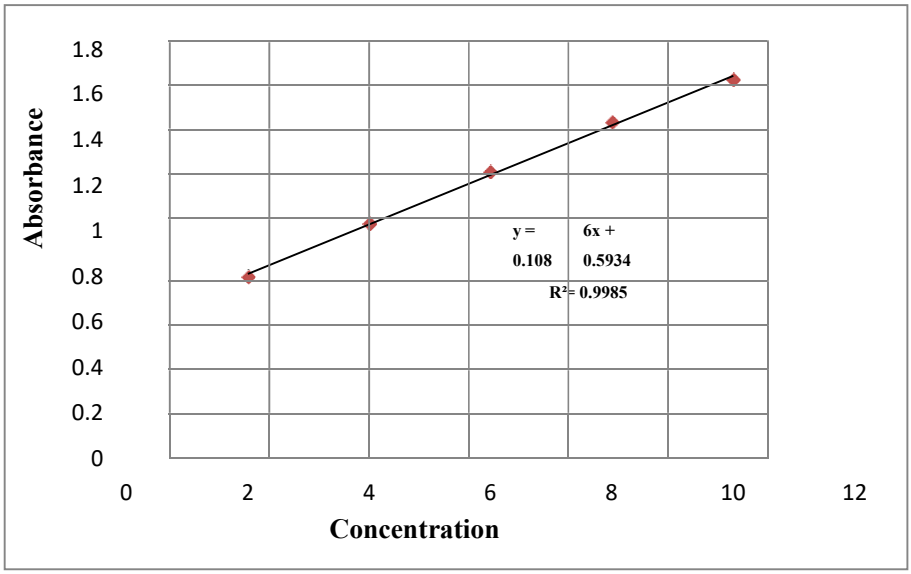

Figure 1: Calibration curve of Quetiapine Fumarate in 0.1N HCl

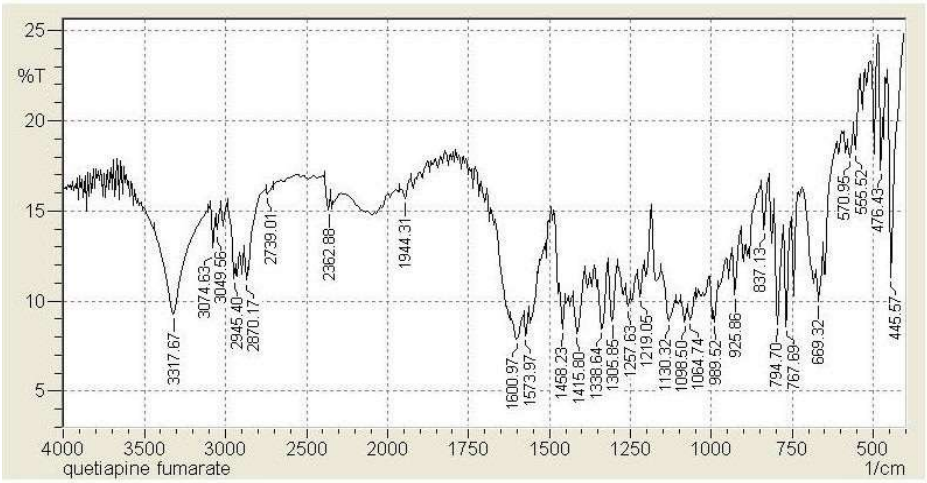

Figure 2: IR spectrum of Quetiapine Fumarate

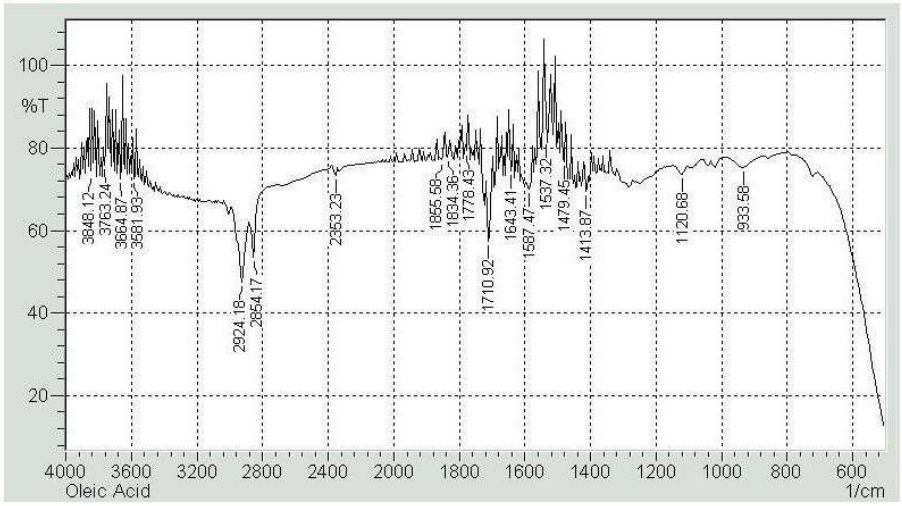

Figure 3: IR spectrum of Oleic acid

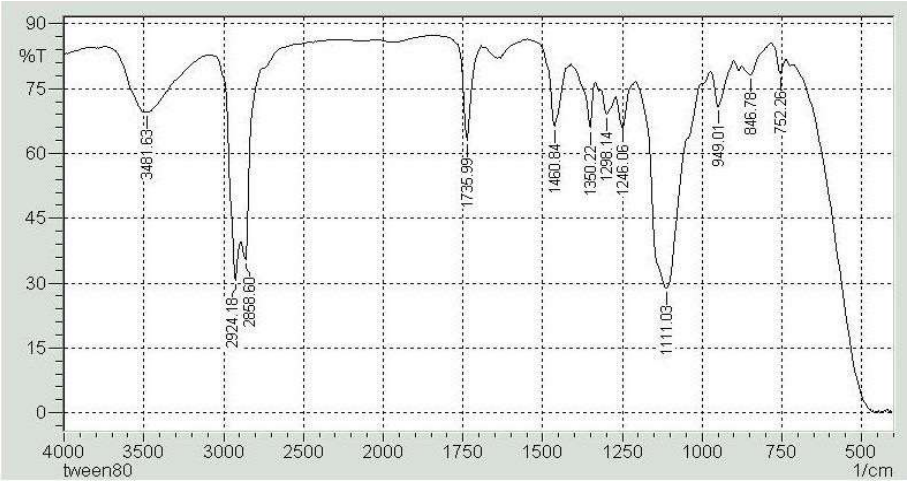

Figure 4: IR spectrum of Tween 80

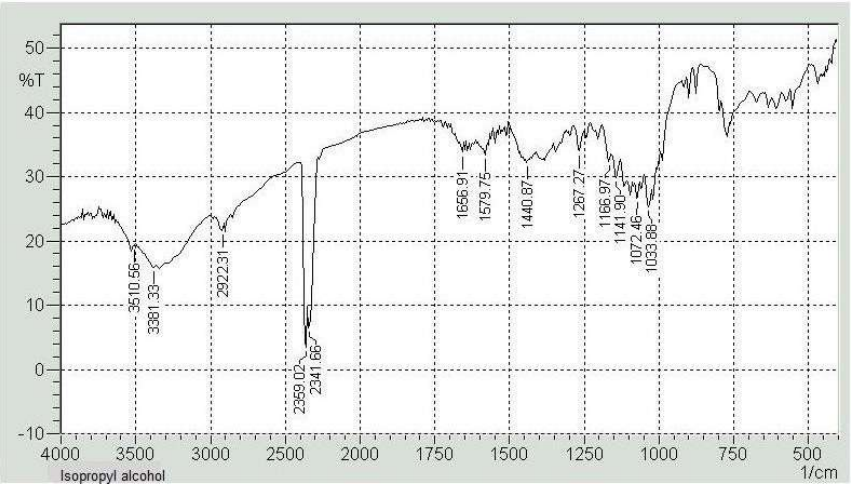

Figure 5: IR spectrum of Isopropyl Alcohol

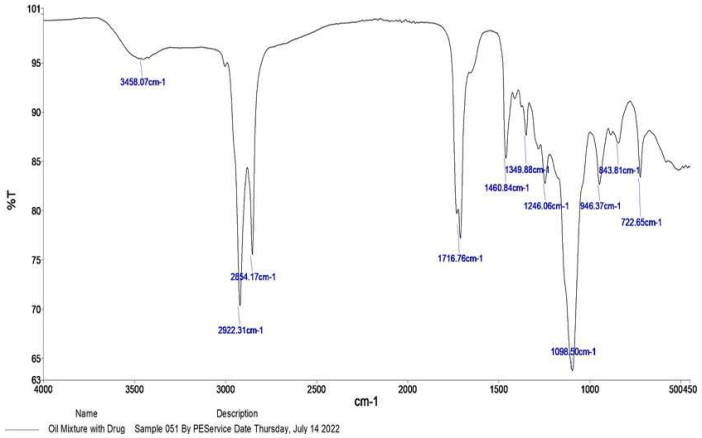

Figure 6: IR spectrum of physical mixture

Table 3: Phase separation and Type of microemulsion

Formulation code	Phase separation	Type of microemulsion
F1	No separation	o/w
F2	No separation	o/w
F3	No separation	o/w
F4	No separation	o/w
F5	No separation	o/w

Table 4: Emulsification time values of different formulation

Formulation code	Emulsifying Time (In sec)
F1	27
F2	30
F3	35
F4	33
F5	38

Table 5: pH of the formulations

Formulation code	pH
F1	4.6
F2	4.7
F3	4.7
F4	4.6
F5	4.7

Table 6: Viscosity of the formulations

Formulation code	Viscosity (cP)
F1	276
F2	385
F3	468
F4	582
F5	669

Table 7: Drug content of the formulations

Formulation code	Drug content (%)
F1	95.80
F2	95.45
F3	96.40
F4	96.76
F5	97.70

Table 8: % Drug Release of Formulation F1, F2, F3, F4 & F5

Time (In Hrs)	% Drug Release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	25.635	22.843	19.563	15.743	13.746
2	30.125	27.953	24.782	21.549	17.354
3	44.245	36.486	32.453	29.843	23.68
4	52.145	45.195	41.872	37.481	28.612
5	70.549	64.843	56.149	49.746	36.963
6	84.248	71.329	67.486	58.781	45.012
7	93.454	88.324	79.625	65.463	52.987

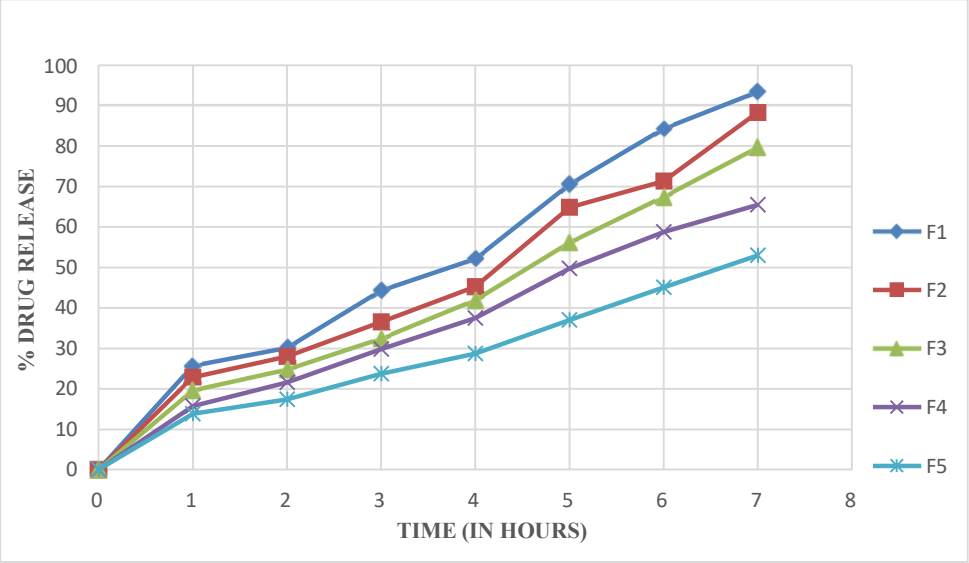

Figure 7: Graphical representation of the % drug release

CONCLUSION

Drug is partially soluble in water and from the study it is concluded that drug is soluble in various oils higher solubility containing excipients were chosen as MEDDS formula and trial batch were prepared.

Finally physically stable trial formulation was prepared using oleic acid as oil phases, Tween 80 as surfactant and Isopropyl alcohol as co-surfactant. Compatibility of drug with selected excipient was checked by using IR spectrometry from that it was concluded that there were no interaction between drug and excipient and remain stable. Then pseudo ternary diagram was constructed to identify micro-emulsifying zone and proper ratio of surfactant to co-surfactant mixture which gives idea about percentage concentration of oil phase and surfactant mixture in formulation to obtain micro emulsion after mixing with water. This range was then optimized by preparing different batches with different ratio of oil to surfactant mixture within the range. Prepared batches were then evaluated on the basis of evaluation parameter. Formulation having approximately 93% drug release at the end of 7Hrs was chosen as optimized formulation.

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Conflicts of interest

The authors have no conflicts of interest regarding this investigation.

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