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Original Article

SOLUBILITY AND THERMODYNAMIC MODELING OF QUETIAPINE FUMARATE IN SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS)

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ABSTRACT

Objective: The present study gives emphasis on the development of self-nanoemulsifying drug delivery system (SNEDDS) of poorly water-soluble drug using Apelblat model.

Methods: For the development of self-nanoemulsifying drug delivery system (SNEDDS) solubility in surfactant, co-surfactant and in oil phase are considered as an important key to avoid phase separation and precipitation after dilution. The solubility of quetiapine fumarate was determined by the isothermal mechanical shaking method for its individual components in the temperature range from 305.15 to 330.15K was measured. The experimental mole fraction solubility of quetiapine was good correlated with calculated data by using modified Apelblat model. Prepared SNEDDS were evaluated in centrifugation, freeze-thaw cycle study, self-nanoemulsification efficiency test. Physicochemical properties of prepared SNEDDS including particle size, zeta potential, viscosity and refractive index were carried out.

Results: The equilibrium saturated and mole fraction solubility of Quetiapine fumarate was found to be high in tween80 than SNEDDS, Labrafac lipophile WL 1349 and capryol 90. Quetiapine fumarate equilibrium saturated solubility, as well as mole fraction solubility, was found to be increased with increase in temperature in SNEDDS as well as in its individual components Prepared SNEDDS was found to be highly stable at centrifugation, heating and cooling cycles and freeze-thaw cycles and shows no sign of precipitation after dilution in water. All physicochemical parameters were observed within specification including droplet size observed as 26.37 nm, polydispersity index 0.0970, zeta potential-14.69 and the refractive index was observed as 1.458 which was nearer to the refractive index of water indicating the isotropic behavior of prepared SNEDDS.

Conclusion: The solubility study could be an effective approach for the development of thermodynamically stable SNEDDS formulation of poorly soluble drugs using Apelblat model.

Keywords: Quetiapine Fumarate, SNEDDS, Thermodynamic Modeling, Solubility Studies

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INTRODUCTION

Quetiapine fumarate is a psychotropic agent belonging to a chemical class of dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo [*b, f*] [1, 4] thiazepin-11-yl-1-piperazinyl) ethoxy]-ethanol fumarate (2:1) (salt). Quetiapine fumarate has an empirical formula C42H50N6O4S2• C4H4O4 and molecular weight of 883.09. The biological life and bioavailability of QF is 6 h and 9%, respectively (1-6). Quetiapine Fumarate is a BCS class II drug. Quetiapine fumarate is a weak acid with dissociation constant (pKa) 3.3 and 6.8 with moderate pH-dependent solubility, 94.3 mg/ml to 2.37 mg/ml at pH values from 1 to 9 reported. The main site for absorption for quetiapine fumarate is stomach as it exhibits very high solubility in gastric pH which falls drastically in intestinal pH. Thus, it would be more beneficial to retain quetiapine fumarate in the stomach (pH 1-3) for the prolonged duration to achieve maximum absorption and bioavailability [1-4].

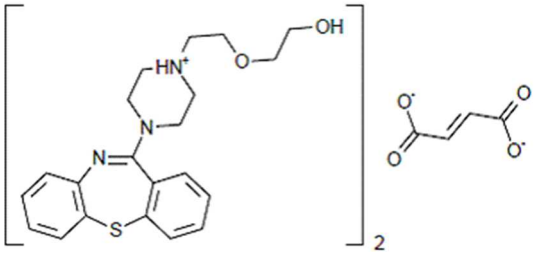

Fig. 1: Chemical structure of quetiapine fumarate

The self-nanoemulsifying drug delivery system (SNEDDS), which involves an isotropic Mixture of drug, surfactants and oil, is emerging as a means of augmenting the oral Bioavailability of hydrophobic drugs. This system produces (nano) emulsions after contact with aqueous medium with the gastrointestinal fluid [5, 6]. These emulsion droplets are advantageous for drug absorption due to their large interfacial surface area, resulting in improved and reproducible bioavailability of poorly water-soluble drugs. SNEDDS is known to enhance the solubility of poorly soluble drugs, determination of drug solubility in surfactant, co-surfactant and in its oil phase and in SNEDDS is very essential The present paper focuses on the application of Thermodynamic based mathematical models for prediction of solubility of quetiapine fumarate in SNEDDS [7]. Thus the mole fraction solubility of quetiapine fumarate in prepared SNEDDS and its surfactant, cosurfactant and in oil phase components was predicted using empirical model equations and modified Apelblat model at the temperature range of 305.15 to 330.15 K. This paper could illustrate the importance of mathematical modeling of solubility of poorly soluble drugs in SNEDDS in order to enhance solubility and oral bioavailability. The aim of this study was to provide a useful tool for mathematical modeling of poorly soluble drug in SNEDDS in order to enhance solubility, stability, dissolution and oral bioavailability.

MATERIALS AND METHODS

Materials

Quetiapine fumarate was received as gift samples from Wanbury Pharmaceuticals Ltd. (Mumbai, India). Caprylic/Capric Triglyceride, (Labrafac liphophile WL) Propylene glycol monocaprylate, (capryol 90)) was received as gift samples from Gattefosse (Mumbai, India). Tween 80 was purchased from Sigma Aldrich. All other chemicals and reagents were of highly purified grade and were used without further purification. All other chemicals used in the present study were of analytical reagent (AR grade). Their general properties are given in table 1.

Methods

Determination of quetiapine fumarate solubility in SMEDDS and its individual components

The saturated solubility of quetiapine fumarate in Labrafaclipophile, tween 80, capryol 90 and prepared SMEDDS were determined by using mechanical shaking method [8, 9] at atmospheric pressure and a temperature range from 305.15 K-330.15 K. An excess amount of quetiapine fumarate was added in SNEDDS and its individual components in stoppered glass vials in triplicates. Each solid-liquid mixture vortexes properly to perform experiments. Each sample was then kept in a mechanical shaker at 100 RPM for 24 h to reach equilibrium. Each experiment was repeated at a temperature range from 305.15 K-330.15K. After 24 h, all samples were taken out and allowed to settle drug (solute) particles for 2 h at the bottom of the glass vials. All the samples were subjected to centrifugation at 5000rpm for 15 min, supernatant from each sample was taken and diluted with methanol and subjected to analysis of quetiapine fumarate using UV-Visible spectrophotometer at 246.5 nm. From quetiapine fumarate content in each sample, equilibrium saturated solubility (mg/g) was determined. However, the experimental mole fraction solubility (x_e) of quetiapine fumarate was calculated using equation 1:

$$Xe = \frac{m1/M1}{m1/M1+m2/M2+m3/M3+ m4/M4}$$

Where m1 is the mass of quetiapine fumarate (solute) and m2, m3 and m4 are the mass of solvents (Labrafaclipophile, tween 80 and capryol 90, respectively). M1 represents the molecular mass of quetiapine fumarate and M2, M3 and M4 represent the molecular masses of Labrafaclipophile, tween 80 and capryol 90, respectively.

Table 1: General properties of quetapine fumarate, oil, surfactant and co-surfactant

Materials	Molecular formula	MW (g/Mol)	D (g/ml)	Chemical name
Quetapine fumarate	$C_{42}H_{50}N_6O_4S_2$• $C_4H_4O_4$	883.11	-	2-[2-(4-dibenzo [b,f] [1,4]thiazepin-11-yl-piperazinyl)ethoxy]–ethanol
Labrafac lipophile	C16H26O5	298.37	0.93-0.96	Caprylic/Capric Triglyceride
Tween 80	C64H124O26	1310	1.075	Polyoxyethylene (20) sorbitanmonooleate
Capryol 90	C11H22O3	202.29	0.93-0.95	Propylene glycol monocaprylate

Preparation of SNEDDS

Various SNEDDS formulations of Quetiapine Fumarate were prepared by spontaneous emulsification technique via the construction of pseudoternary phase diagrams as reported previously 6. Equilibrated saturated solubility of quetapine fumarate as shown in table 4 was carried out using mechanical shaking method and optimum composition of SNEDDS as shown in table 2 was formulated [6].

An optimum formulation of SNEDDS for solubility modeling was obtained by taking the required amount of Labrafil-Liphophile in a 5 g capacity vial. The required amount of Tween-80 and Capryol 90 was added to oil phase and vortexed for 5 min. Finally, required amount of distilled water (aqueous phase) was added to a mixture of oil phase and surfactant phase in dropwise manner till clear and transparent blank SNEDDS (without drug) obtained as shown in table 2.

Table 2: Composition of SNEDDS

S. No.	Formulation ingredients	Composition (%w/w)
1	Labrafac lipophile WL 1349	07.46
2	Tween 80	27.86
3	Capryol 90	14.92
4	Distilled water	49.75

RESULTS AND DISCUSSION

Thermodynamic study and evaluation test

Various SMEDDS formulations of quetiapine fumarate were developed and subjected to thermodynamic stability test to observe any phase separation, coalescence, creaming or conversion into the biphasic milky emulsion. Optimizes SNEDDS was selected for this study and was found to be highly stable at centrifugation, heating and cooling cycles and freeze-thaw cycles. Self-nano-emulsification efficiency test was carried out to evaluate signs of any precipitation or phase separation upon dilution with diluent. Distilled water was used as a diluent in this study. Prepared SNEDDS pass this test which indicated its suitability for SNEDDS.

Physicochemical characterization of prepared SNEDDS

The results of physicochemical characterization are listed in table 3. The mean particle size of prepared SNEDDS was observed as 26.37 nm with polydispersity index (PI) 0.0970. SNEDDS droplet size is a decisive point in the performance of self-emulsified formulations as it determines the rate and extent of drug release and absorption. Lowest value confirms its greatest absorption [6]. Polydispersability index below 0.3 indicates good uniformity in the globule size distribution after dilution with water. AS SNEDDS with increased globule size causes agglomeration of globules and suffers with the instability of the system [21]. The viscosity of SMEDDS was observed to be 0.890cp. Indicating short time of emulsification compared to those formulations with higher viscosity. Zeta potential of SNEDDS was found to be-14.69mv which indicated the stable formation of SMEDDS. The negative value of zeta potential may be due to the presence of free fatty acids. A Negative value to the zeta potential of the optimized formulations indicated that the formulations were negatively charged, and sufficient repulsion among emulsion droplets existed to form an un-coagulated system and therefore, gives an indication of a stable system The Refractive Index (RI) of SNEDDS was observed at 1.458 which was very nearer to RI of water (1.33). [6, 21] This indicated an isotropic behavior and o/w nature of prepared SNEDDS. Overall, all physicochemical parameters were found to suitable for SNEDDS.

Table 3: Characterization of SNEDDS

S. No.	Characterization parameters	Parameter value
1	Droplet size (nm)	26.37±0.208
2	PI	0.0970±0.0057
3	Zeta potential (mv)	-14.68±0.0057
4	Viscosity (cp)	0.890±0.01
5	RI	1.455±0.005

The values are expressed as mean±SD; n=3, polydispersibility index (PI), refractive index (RI),

Solubility data of quetiapine fumarate

The saturated equilibrium solubility of Quetiapine fumarate in Labrafac lipophile WL 1349, Tween 80, Capryol 90 and prepared SNEDDS at a temperature from 305 to 330 K are listed in table 4.

The saturated equilibrium solubility of Quetiapine fumarate was found to be increased exponentially with increase in temperature in all sample matrices investigated. The saturated equilibrium solubility was observed highest in Tween 80 followed by Capryol 90, Labrafac lipophile WL1349 and SNEDDS as shown in table 6.

Table 4: Equilibrium saturated solubility of quetapine fumarate in labrafac lipophile wl 1349, tween 80, capryol 90 and SNEDDS

Sample	Temperature (K)	Solubility (mg/g)*
Labrafaclipophile WL 1349	305.15	40.012±0.01
	310.15	55.341±0.371
	315.15	65.444±0.387
	320.15	81.514±0.347
	325.15	90.243±0.120
	330.15	110.410±0.245
Tween 80	305.15	115.000
	310. 15	121.671±0.190
	315. 15	130.046±0.080
	320. 15	145.001±0.00
	325. 15	170.140±0.080
	330. 15	200.000
Capryol 90	305. 15	58.000
	310. 15	66.000
	315. 15	75.445±0.145
	320. 15	82.261±0.487
	32515	99.998±0.001
	330. 15	123.05±0.522
SNEDDS	305. 15	30.716±0.160
	310. 15	39.544±0.264
	315. 15	48.816±0.104
	320. 15	65.583±0.505
	325. 15	82.593±0.531
	330. 15	95.990±0.0577

The values are expressed as mean±SD; n=3, self-Nano emulsifying drug delivery system (SNEDDS).

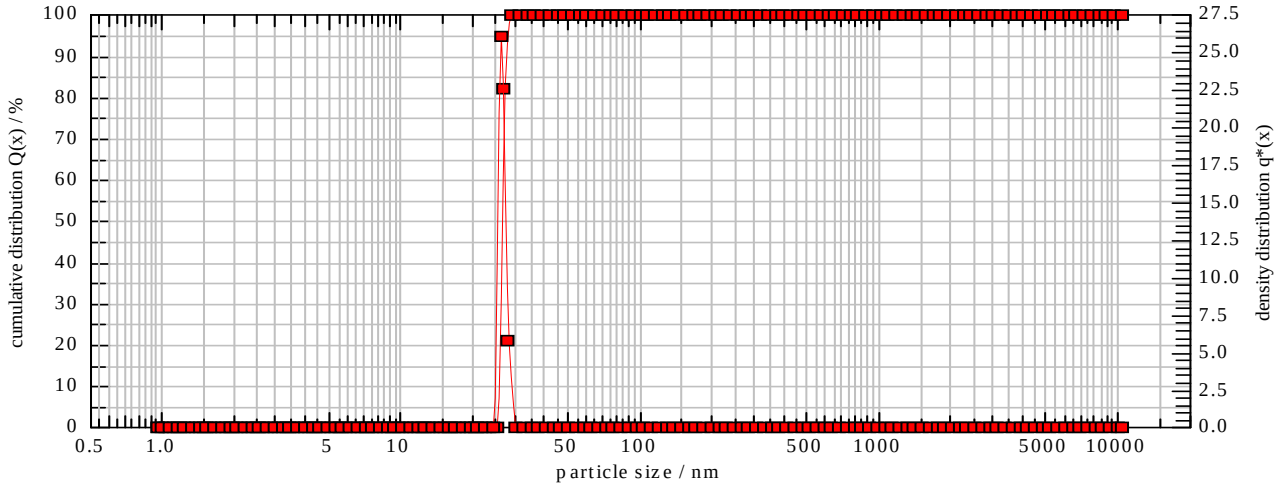

Fig. 2: Particle size of SNEDDS quetiapine fumarate

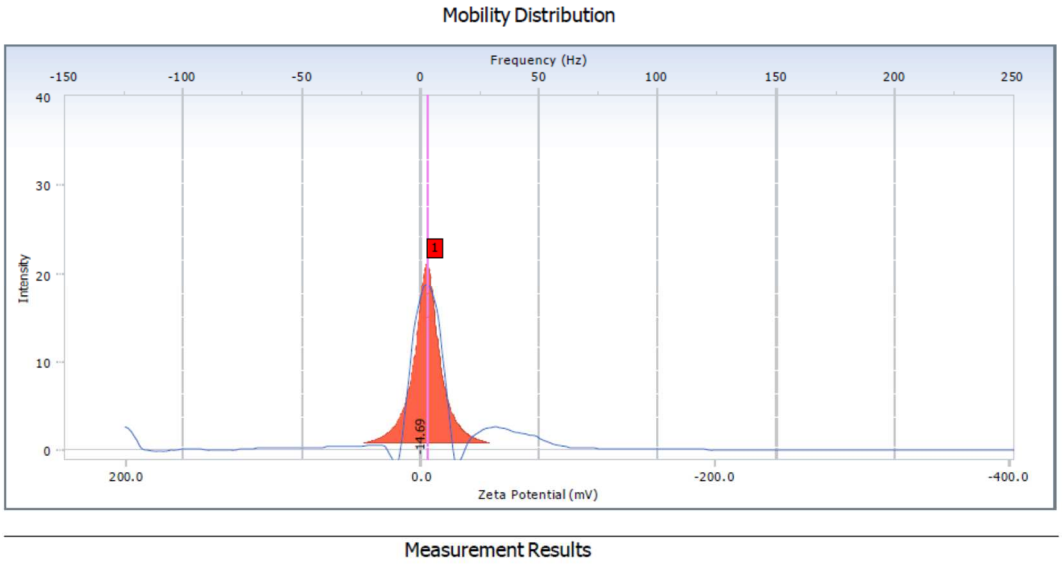

Fig. 3: Zeta Potential of SNEDDS

Table 5: The modified apelblat model adjustable parameters for quetiapine fumarate in labrafac lipophile WL1349, tween-80, capryol 90 and prepared SNEDDS

Sample	Apelblat model			
	A	B	C	R2
Labrafaclipophile WL1349	717.95	-37108	-104.991	0.9919
Tween 80	-742.17	33192	110.381	0.9987
Capryol 90	-691.95	29835	103.108	0.9940
SNEDDS	151.48	-11405	-21.121	0.9961

Table 6: Equilibrium saturated solubility (S), mole fraction solubilities experimental (Xe) and calculated solubilities (xc) for quetiapine fumarate in labrafac lipophile labrafac lipophileWL1349, tween-80, tween 80, capryol 90 and prepared SNEDDS

T/K	S (mg/g)*	(xc)	^{103}xc	(Xe)*	^{103}xe*	% AD
Labrafac lipophile						
WL 1349						
305.15	40.012±0.01	0.01355	13.55	0.01326±0.00	13.26±0.00	-2.27
310.15	55.341±0.371	0.01750	17.50	0.01825±0.001	18.25±0.001	4.19
315.15	65.444±0.387	0.02110	21.10	0.02151±0.101	21.51±0.101	-1.40
320.15	81.514±0.347	0.026300	26.30	0.02665±0.002	26.65±0.002	1.42
325.15	90.243±0.120	0.030747	30.74	0.02942±0.001	29.42±0.001	-4.62
330.15	110.410±0.245	0.034912	34.91	0.03576±0.020	35.76±0.020	2.44
Tween 80						
305.15	115.000	*0.14544*	*145.44*	*0.1450*±0.030	145.0±0.030	-0.43
310.15	121.671±0.190	0.15131	151.31	0.1525±0.0102	152.5±0.0102	1.065
315.15	130.046±0.080	0.16174	161.74	0.1611±0.101	161.1±0.101	-0.422
320.15	145.001±0.00	0.17731	177.31	0.1762±0.102	176.2±0.102	-0.848
325.15	170.140±0.080	0.19904	199.04	0.2006±0.00	200.6±0.00	0.8110
330.15	200.000	0.22845	228.45	0.2279±0.1012	227.9±0.1012	-0.189
Capryol 90						
305.15	58.000	0.01321	13.21	0.013042±0.004	13.04±0.004	1.36
310.15	66.000	0.01459	14.59	0.01482±0.102	14.82±0.102	-1.615
315.15	75.445±0.145	0.01648	16.48	0.016894±0.001	16.89±0.001	-2.54
320.15	82.261±0.487	0.01903	19.03	0.01845±0.203	18.45±0.203	-0.40
325.15	99.998±0.001	0.02243	22.43	0.02227±0.402	22.27±0.402	0.77
330.15	123.05±0.522	0.02694	26.94	0.02726±0.502	27.26±0.502	-1.20
SNEDDS						
305.15	30.716±0.160	0.0119	11.9	0.0120±0.502	12±0.502	0.840
310.15	39.544±0.264	0.0154	15.4	0.0155±0.101	15.5±0.101	0.645
315.15	48.816±0.104	0.0197	19.7	0.0189±0.204	18.9±0.204	-4.232
320.15	65.583±0.505	0.0249	24.9	0.0254±0.345	25.4±0.345	1.964
325.15	82.593±0.531	0.0311	31.1	0.0321±0.405	32.1±0.405	3.11
330.15	95.990±0.0577	0.0383	38.3	0.0375±0.407	37.5±0.407	-2.133

*The values are expressed as mean±SD; n=3, calculated (xc), experimental (xe), (%AD). The percentage of absolute relative deviation.

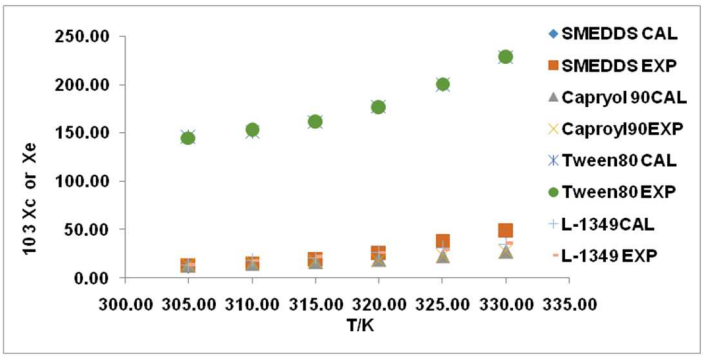

Fig. 4: Experimental and calculated mole fraction solubilities of quetiapine fumarate in tween 80, capryol 90, labrafacliphophile WL 1349 and self-nanoemulsifying drug delivery system (SNEDDS) at temperatures ranging from 300 to 335 K

Thermodynamic modeling of solubility of quetiapine fumarate

Numerous models including NRTL, UNIQUAC, UNIFAC, COSMOPACE, GEQUAC have been used to correlate experimental mole fraction solubility with theoretical mole fraction solubility [10-20]. As the modified Apelblat model is more accurate and reliable model it was selected for correlation of experimental and calculated data. According to the modified Apelblat model, the temperature-dependent mole fraction solubilities of quetiapine fumarate at different temperatures can be calculated by the following equation:

In Xe= A+B/T+CIn (T)

Where

Xe is the experimental mole fraction solubility of quetiapine fumarate

T is the absolute temperature (k)

A, B and C are adjustable parameters.

The percentage of absolute relative deviation (%AD) of Quetiapine fumarate was determined by using following equation (2)

%AD =Xe-Xc/Xe x 100

Xe and Xc indicates experimental and calculated mole fraction solubilites of quetiapine fumarate respectively. Experimental mole fraction solubilities (Xe) and Apelblat model correlation of Quetiapine fumarate in Capryol 90 and in Labrafil Liphofile WL 1349, Tween-80, and SNEDDS. are shown in fig. 4. The correlation coefficient value for quetiapine fumarate (R2) was obtained as 0.9920,0.9987,0.9940,0.9961 for Labrafaclipophile WL 1349, Tween 80, Capryol 90 and for SNEDDS as shown in table 6.

Thus solubility data were interrelated by experimental values and calculated values from the modified Apelblat equation and shows appropriate to each other.

CONCLUSION

In this thermodynamic modelling approach, the equilibrium saturated solubility, as well as the mole fraction solubility of quetiapine fumarate in prepared SNEDDS and its individual components in the temperature range from 305.15to 330.15K, were measured. The solubility of quetiapine fumarate in surfactants tween 80 was found to be significantly higher than capryol 90, SNEDDS and labrafac liphophile WL1349. The solubility data of each experimental sample matrix were well correlated by the modified Apelblat model. The values of correlation coefficients (R2) in the range of 0.9960–0.9990 showed that the modified Apelblat model provided a good fitting of experimental solubility data of quetiapine fumarate. These preliminary studies on solubility could be a useful tool for the development of an efficient and thermodynamically stable SNEDDS formulation of various poorly soluble drugs to enhance their stability, solubility, dissolution and oral bioavailability.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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