

ORAL NANOEMULSION DELIVERY SYSTEMS OF QUETIAPINE FUMARATE FOR IMPROVED DISSOLUTION: DEVELOPMENT AND CHARACTERIZATION

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ABSTRACT

To evaluate the possibility of improved oral drug delivery for quetiapine fumarate, a BCS class II drug incorporated in nanoemulsions. Five drug loaded formulations were developed. Effects of components selection were studied by pseudoternary-phase diagrams of nanoemulsion system composed of corn oil as oil phase, Tween 80 and labrasol as surfactant, propylene carbonate as cosurfactants and deionized water. The highest nanoemulsion region was achieved at labrasol/propylene carbonate in the mass ratio of 2:1. Reproducible characteristics like dilution test, percent transmittance, emulsification efficiency, pH and viscosity of all quetiapine loaded nanoemulsions were investigated. In vitro dissolution study of optimized nanoemulsion formulation, with diameter <100 nm, showed more than twofold increase in drug release as compared with pure drug. According to the results of stability studies, nanosystems exhibited no stratification, creaming or cracking. In addition optimized formulation has shown 99.2% drug content with non-Fickian supercase-II transport diffusion mechanism of drug release from the systems. The results demonstrated the impending use of this system is a perfect technique for improving solubility and dissolution of quetiapine fumarate in antipsychotic therapy.

KEYWORDS: Components. Oral nanoemulsion, Solubility. Stability. Ternary diagram.

INTRODUCTION

In recent past, nanoemulsion has received increasing attention as an appropriate drug-carrier system for BCS Class II active compounds to increase their bioavailability and modify drug release characteristics. These thermodynamically stable isotropic systems cobble together for rapid action, efficacy, and stability of the drug, minimal dose and side effects.^[1]

(Boche 2016) Quetiapine fumarate (QPN), a synthetic dibenzothiazepine (2-[2-(4-dibenzo [b,f][1,4] thiazepine-11-yl-1-piperazinyl)ethoxy]-ethanol,(2E)-2-butenedioate) is used for schizophrenia, sudden episodes of mania and depressive disorder. Because of reported effects on mood, anxiety, and sleep, increase in quetiapine use had surpassed the other second-generation antipsychotics like risperidone, olanzapine, clozapine etc. However, limitations of QPN pose difficulty in its delivery through conventional route.^[2] These include, QPN a lipophilic drug with low water solubility and has very poor (5–15%) bioavailability. So a strategy can be designed which will help in increasing the solubility and bioavailability of QPN that can direct the higher drug concentration in brain avoiding the first-pass metabolism which in turn can reduce the dose of the drug.

Lymphatic delivery is an alternate choice to pass up the metabolism in oral drug delivery. Intestinal lymph vessels drain directly into a thoracic duct, further into the venous blood, thus bypassing the portal circulation.^[3] The main function of the lymphatic system is to facilitate absorption of long-chain fatty acids via chylomicron formation. Two different lipid-based approaches are known to enhance the lymphatic transport, which includes construction of a highly lipophilic prodrug and incorporation of drug in a lipid carrier.^[4] Nanoemulsion with low surface tension and large surface area facilitates oral absorption of drugs without the help of bile juices. The emulsified-oil droplets enzymatically degraded to di- and monoglycerides and free fatty acids, form micelles, and finally, solubilization and absorption of drugs occur.

In this study, we prepared quetiapine oral nanoemulsion using long chain triglycerides which can result in improved solubility and delivery to the brain through the oral lymphatic system by bypassing the first-pass metabolism and hence can enhance the bioavailability of drug.

The influence of the surfactant/co surfactant mass ratio (S_{mix}) on the nanoemulsion formation region was also performed for ascertaining the desired components effect on stability.

MATERIALS AND METHODS

Materials

Quetiapine fumarate was received as a gift sample from Alkem Laboratories (India). Double refined oils such as corn, castor, olive, peanut, soyabean, and sun flower oils were purchased from the local super market. Ethanol, glycerin, isopropyl myristate, PEG 400, propylene glycol, tween 20 and tween 80 were obtained from M/s. Merck Specialties Ltd., Mumbai, India. Labrafil. Labrafac and labrasol were purchased from Gattefosse Corporation (USA). Deionised double distilled water was used in the study.

Methods

Screening of vehicles

Oils from natural and semi synthetic families were investigated for optimum solubility of quetiapine. The solubility of QPN was determined in different oils e.g. castor, corn, isopropyl myristate, labrafac, labrafil, olive, peanut oil, sunflower and soyabean oil. 2 mL of oils was taken in vials and excess amount of the drug was added. The vials were tightly stoppered and were continuously stirred for 72 hrs at $37 \pm 0.5^\circ\text{C}$, and centrifuged at 3000 rpm for 15 min. Then supernatant was filtered and after appropriate dilution with methanol, solubility was determined by U.V Spectrophotometer. Same method was adopted for solubility determination of drug in surfactant and cosurfactant. Solubility study was performed at three times and standard deviation was calculated.^[3]

Pseudoternary Phase Diagrams

The pseudo ternary phase diagram was developed by the water titration method. Predetermined ratio (1:1, 1:2, 1:3, 2:1 and 3:1) of surfactant and co-surfactant mixture (S_{mix}) was mixed with the oil at ambient temperature. For each phase diagram, the ratio of oil to the S_{mix} was varied as 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 (v/v). Water was added drop-wise to each oil- S_{mix} mixture under vigorous stirring. After equilibrium, the samples were visually checked for existence and clarity of NE. The area of the monophasic region was used as a tool for the selection of suitable surfactant and co-surfactant mixture.

Preparation of Nanoemulsion

Nanoemulsion (QPNE) was prepared by titration method using corn oil, labrasol, propylene carbonate as dispersed phase and purified water as continuous phase as shown in Table 1. Desired quantity of S_{mix} was blended into water by vortexing it for 15 min to form aqueous phase.^[5] Oil phase was developed by solubilizing 50mg of quetiapine into accurately weighed corn oil. The oil phase was then added drop-wise to the aqueous phase under probe sonication at 50 pulse 3 minutes, 40°C temperature.

Reproducible characteristics of Nanoemulsion

The prepared formulations were characterized for dilution test, emulsification time, percentage transmittance (%T), pH and viscosity for predicting the reproducible characteristics as shown in Table 2.

Dilution test and Emulsification time

A 1 ml of formulation was taken and diluted with 100ml of water, and the time taken for emulsification was noted and kept for 24 hrs to categorize for its clarity and stability. Emulsifying properties of prepared nanoemulsions were carried out by visual assessment. Experiments were performed in three replicates for each sample. After 24 hrs, emulsification efficiency of the resultant nanoemulsions was categorized by visual assessment.

Transmittance

The percentage transmittance of above diluted NE after 24 hrs was checked against distilled water using UV-Visible spectrophotometer (UV, 1700, Shimadzu, Japan) at 630 nm.

pH and Viscosity Determination

The pH of all QPNE formulations were measured by calibrated digital pH meter at $25^\circ\text{C} \pm 1^\circ\text{C}$. The pH was recorded in triplicate. Viscosity of the formulations was determined using Brookfield cone and plate Rheometer (Model LVDV III) using CPE spindle at the rotational speed of 5 rpm, shear rate of 10 at room temperature and the results were recorded.

In Vitro Release

In vitro release of quetiapine from nanoemulsion was studied using dialysis bag method in 0.1N HCl. Dialysis bags (molecular weight cut-off 12–14 kDa) were soaked in filtered diffusion medium for 24 h and kept under refrigeration until use. 10mL of nanoemulsion was placed in each dialysis bag, then sealed at both ends and tied to baffles of dissolution vessels. Study was carried out using dissolution apparatus at $37 \pm 0.5^\circ\text{C}$ with 50 rpm. Aliquots of 5 mL were withdrawn from dissolution medium at designed time intervals for 30 min by maintaining sink conditions. For comparison, *in vitro* release studies were carried out for QPN pure drug and QPN-loaded nanoemulsion.

Optimization of Nanoemulsion

The optimum formula for QPN loaded NEs was selected based on following parameters: clarity and transparency upon dilution and lower emulsification time, optimum viscosity and pH, higher transmittance percentage, low S_{mix} concentration and *in vitro* drug dissolution result. Further droplet size distribution, PDI, zeta potential was ascertained for nano-range droplets and stability.

Droplet size, polydispersibility index (PDI) and zeta potential

The droplet size, polydispersibility index (PDI) and zeta potential of QPNEs was determined using Malvern

zetalyzer (Horiba Scientific, HAS 3000, Singapore). Six replicates were measured, and values were measured as mean±standard deviation. The zeta potential of a droplet is the overall charge that the particle acquires in a particular medium. Knowledge of the zeta potential of nanoemulsions helps to assess the stability of the formulation during storage.

In vitro drug release kinetics study

To study the kinetics and mechanism of QPN release from optimized NE formulation, data obtained from *in vitro* drug release study was plotted in various mathematical models such as zero order, first order, Higuchi's and Korsmeyer's models.

Stability Study

To evaluate the physical stability, QPN-loaded nanoemulsion of the optimum formulation was stored at 40°C and 75% RH for three months. Samples were withdrawn at designated time intervals of 1, 2, and 3 months and checked visually for change in appearance, sedimentation and drug content.

Drug Content estimation

Drug content was investigated quantitatively by diluting 0.1 mL of QPNE with methanol and then measuring the absorbance at λ_{max} 254 nm. The calculated drug amount was represented as percent of total amount of QPNE.

RESULTS AND DISCUSSION

Solubility study

The solubility of QPN in various oils, surfactants and co-surfactants was measured. Corn oil exhibited maximum solubility (0.852 mg/mL) and a closer solubility value was found with peanut oil (0.747 mg/mL). All the other oils reported very low solubility of QPN (Fig. 1) Therefore, corn oil was chosen as the oil phase. A long chain fatty acid like corn oil i.e rich in linoleic acid might enhance fluidity of the intercellular lipid barriers of BBB and helps in induction of highly permeable

pathways for QPN. Among all the surfactants, non ionic amphiphile, tween 80 and labrasol shown nearly similar solubility values (21.5 and 22.4 mg/mL). Thus, both the surfactants were used for further screening using ternary phase diagrams. The usual preference is to select formulations with the lowest surfactant concentration for oral administration hence, addition of cosurfactants was observed to enhance the emulsification region. Propylene carbonate was selected as cosurfactants in this study, as it solubilized QPN in larger amounts compared to others.

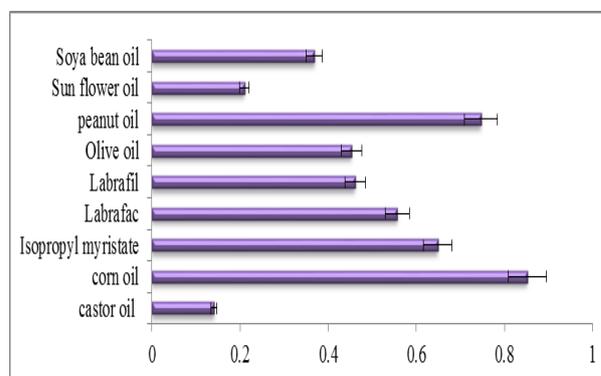


Fig. 1: Solubility studies of QPN in vehicles.

Pseudo Ternary Phase diagram

Ternary phase diagrams were constructed to define the extent and nature of nanoemulsion region. It was found that the existence of isotropic nano-region was higher with labrasol / propylene carbonate than with tween 80 / propylene carbonate combination. As from Fig. 2, the existence of nanoemulsion region was highest in 2:1 ratio of labrasol / propylene carbonate and it was observed that not a single nanoemulsion point was obtained with 1:1 and 1:3 ratios of labrasol / propylene carbonate (data not shown). In addition, increase of S_{mix} concentration resulted in increased nanoemulsion region. Hence labrasol and propylene carbonate of 2:1 ratio was selected as surfactant and cosurfactants in this study.

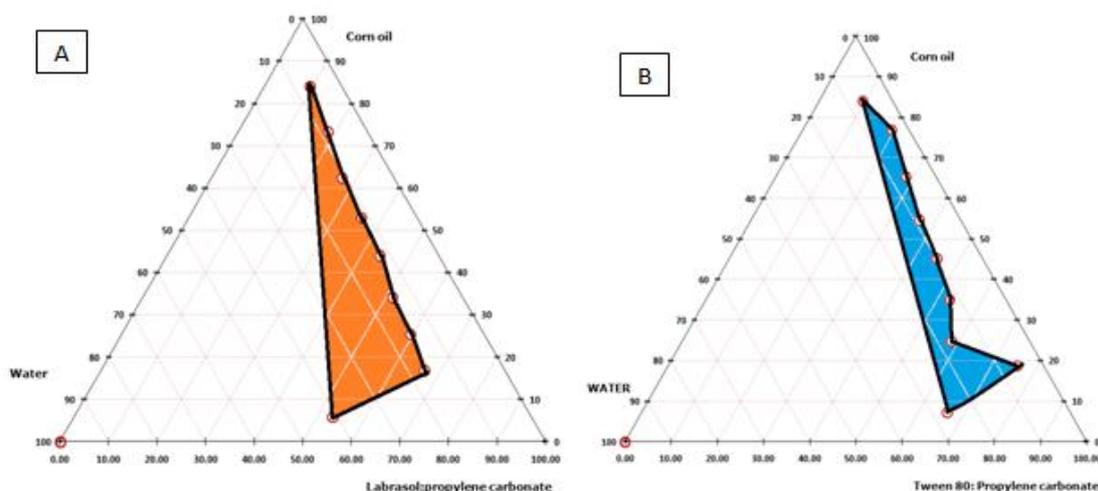


Fig. 2: Pseudoternary phase diagrams indicating o/w nanoemulsion region of (A) labrasol/propylene carbonate at 2:1, (B) tween 80/propylene carbonate at 2:1.

Preparation of QPN nanoemulsions

A total of five Quetiapine loaded nanoformulations were prepared with corn oil, labrasol as surfactant and

propylene carbonate, as cosurfactant as shown in Table 1.

Table 1: Composition of QPN nanoemulsions.

Formulation code	Drug (mg)	Oil (% w/w)	S _{mix} (2:1) (% w/w)	Water (% w/w)
QPNE1	50	7	30	63
QPNE2	50	7	35	58
QPNE3	50	7	45	48
QPNE4	50	7	50	43
QPNE5	50	7	55	38

Reproducible characteristics of Nanoemulsion

Dilution test and Emulsification time

All formulation showed very good emulsification efficiency and time for emulsification was found to be <2 minutes. Efficiency of emulsification majorly depends on concentration of oil and S_{mix}. As the concentration of S_{mix} increases, self-emulsification time decrease and if the oil content increases, then emulsification time increases simultaneously. All the preparations of QPNEs were found to be clear and transparent upon dilution except the QPNE4 formulation (Table 2).

% Transmittance

% Transmittance of all the formulations was measured by taking the absorbance of the diluted nanoemulsion. As per results of Table 2, QPNE3 formulation was found to have the highest percentage transmittance value of closer to 100% signified that formulation was clear and transparent. Besides clarity of the formulation, a percentage transmittance closer to 100% also indicates

that the globules were in the nanometer range. This in turn indicates that the drug in the formulation has a large surface area for release.^[3]

Viscosity and pH Determination

The viscosity of nanoemulsions is a function of the components/vehicles and their concentrations. Higher concentrations of oil led to increase in viscosity whereas lesser amount of surfactant and co surfactant increases the interfacial tension between water and oil resulting in rise of viscosity levels of w/o type of nanoemulsion and decrease in o/w type of emulsion. Nanoemulsions formulation results proved that as concentration of S_{mix} increased, viscosity of formulation were increased. Viscosity is also very important for stability as well as efficient release of drug from nanoemulsions. In general, formulation that possess lower viscosity, expected to exhibit faster release of active ingredients. As shown in Table 2, the pH values of all the formulations were found in the range of 6.2-6.9.^[6]

Table 2: Reproducible characteristics of QPN nanoemulsions

Formulation code	% T	Emulsifying time (secs)±SD	Dilution test	pH±SD	Viscosity (cps)±SD
QPNE1	91.2±0.22	77±1.25	Transparent	6.45±0.25	45±0.22
QPNE2	89.6±1.52	79±12.4	transparent	6.21±1.39	51±1.9
QPNE3	98.6±0.46	69±2.5	Transparent	6.95±0.11	36±0.37
QPNE4	84.9±0.14	98±1.9	slightly Transparent	6.01±0.47	69±2.78
QPNE5	90.6±0.94	83±2.4	Transparent	6.64±1.56	73±0.46

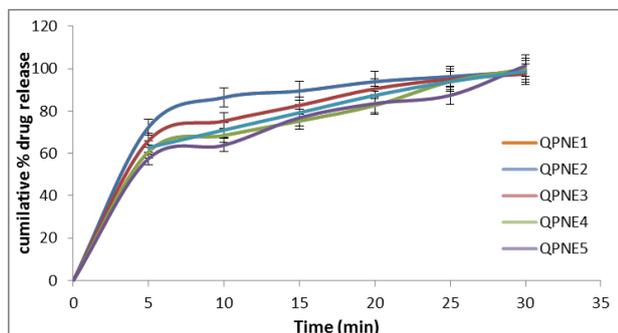
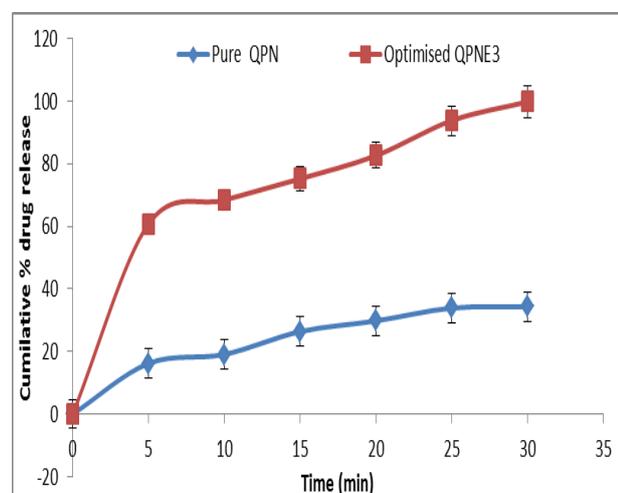
In Vitro Release

Results of cumulative QPN released percentage from all the five NE formulations are shown in Table 3. All prepared NEs showed highest drug release in less than 30 min. This could be attributed to the fact that the quantitative release of QPN from NE formulations is droplet size dependent. It proposed that larger interfacial area exists in NE with small droplets and promotes rapid drug release.^[7] Also drug release was faster at S_{mix} concentration lower than 45% and this is may be due to, high concentrations of S_{mix} may lead to impounding of the drug into the surfactant micelles or emulsified corn oil droplets and delay the release of the drug via the dialysis bag.^[8,11] On the basis of in vitro drug release study, QPNE3 formulation was found to be better than the other nano-formulations due to the high thermodynamic activity of drug and hence was selected

as the optimized formulation (Fig. 3). The results clearly affirm that the percentage of QPN dissolved from NE-3 reached 99.8% within 30 min, while about 34.3% of plain QPN was dissolved after 30 min (Fig. 4).

Table 3: *In-vitro* dissolution profile of QPN nanoemulsions.

Time (min)	QPNE1	QPNE2	QPNE3	QPNE4	QPNE5	Pure QPN
5	72.3±0.12	66.1±0.42	60.8±0.44	57.5±0.63	62.8±0.88	16.2±0.88
10	86.3±0.47	75.2±0.04	68.4±0.78	63.8±0.86	71.02±0.42	19.0±0.75
15	89.4±1.12	82.6±0.21	75.2±0.11	76.7±0.71	79.1±0.06	26.4±0.56
20	93.8±0.01	90.4±0.84	82.6±0.77	83.5±0.23	87.3±0.85	29.8±0.81
25	96.2±0.82	95±0.45	93.8±0.41	87.3±0.58	93.8±0.13	33.9±0.66
30	98.7±0.72	97.4±0.17	99.8±0.89	101.3±0.41	98.7±0.84	34.3±0.43

Fig. 3: *In Vitro* Release profile of QPNE formulations.Fig. 4: *In Vitro* Release profile of pure QPN and optimized QPNE formulation.

Selection of optimum nanoemulsion

Based on clarity and transparency, nanoemulsions with optimum pH (6.95 ± 0.11), lower viscosity (36 ± 0.37 mPa.s), high transmittance % (98.6 ± 0.46 %), lower emulsifying time (69 ± 2.5 min), lower S_{mix} concentrations (45% w/w) and highest release ($99.8 \pm 0.89\%$) compared to other NE formulations, QPNE3 formulation was selected as an optimum preparation which consisted of 7.012 % w/w of corn oil, 30.25% w/w of labrasol, 15.09% w/w of propylene carbonate and 48.36% w/w of deionized water. Further the QPNE3 formulation was characterized for droplet size, polydispersibility index (PDI) and zeta potential and stability.

Droplet size, polydispersibility index (PDI) and zeta potential

The droplet size of optimized formulation was found to be in nano-range (100 nm), this was attributed to the moderate concentration of S_{mix} in the optimized

formulation QPNE3. The PDI value reported was < 0.21 . This low PDI indicated uniform distribution of droplets size within each formulation. The zeta potential of optimized nanoemulsion was -33.56 ± 1.04 . Higher zeta potentials suggested colloidal nanodispersions that are more likely to be stable as the charged droplets exhibit stronger repulsion, thus overcoming the natural tendency to aggregate.^[9]

In vitro drug release kinetics study

The kinetics of the best formulation dissolution data was well fitted to zero-order, firstorder, Higuchi and 60% of release data were fitted to Korsmeyer-Peppas equation. The best fit of QPN loaded NE formulation with the highest (R^2) value was found to be shown by zero order release model. The exponential (n) values for all of these formulations were above (1), indicating non-Fickian supercase-II transport diffusion mechanism. This could be illustrated as leakage of QPN molecules from the NE followed a linear release as long as the corn-oily barrier is intact.^[10]

Stability Study

The QPNE3 formulation does not change in its appearance after 3 month stability period i.e., there was no stratification, precipitation, creaming or cracking. This may be due to that the NE formation and stability are not affected by ionic strength or pH changes due to the presence of surfactants. The drug content of optimized stable formulation after 3 months was $99.23 \pm 0.27\%$.

CONCLUSION

The facts accrued from this research, far suggest that nanoemulsions lead in producing a groundbreaking enhancement of QPN solubility and dissolution in terms of rate and extent to a great value than the available conventional formulations. It was accomplished that the designing of nanosystems entrapped in carriers like oils, surfactants and cosurfactants require indispensable selection. The developed optimum NE formula (QPNE3) was a mixture of 7.012% w/w of corn oil, 30.25% w/w of labrasol, 15.09% w/w of propylene carbonate and 48.36% w/w of deionized water. Thus we conclude that optimized QPN loaded NEs using long chain triglycerides like corn oil resulted in improved solubility and delivery to the brain through the oral lymphatic system bypassing the first-pass metabolism. Thus the systems would be more effective against psychosis activity.

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REFERENCES

1. Azeem A, Rizwan M, Ahmad FJ. Nanoemulsion Components Screening and Selection: a Technical Note. *AAPS PharmSciTech*, 2009; 10(1): 69-76.
2. Arjun Narala and Kishan Veerabrahma. Preparation, Characterization and Evaluation of Quetiapine Fumarate Solid Lipid Nanoparticles to Improve the Oral Bioavailability. *J. Pharmaceutics*, 2013.
3. Khan AA, Mudassir J, Mohtar N, Darwis Y. Advanced drug delivery to the lymphatic system: lipid-based nanoformulations. *International Journal of Nanomedicine*, 2013; 8: 2733-2744.
4. Suresh G, Manjunath K, Venkateswarlu V, Satyanarayana V. Preparation, characterization, and in vitro and in vivo evaluation of lovastatin solid lipid nanoparticles. *AAPS Pharm Sci Tech.*, 2007; 8(1): E162-E170.
5. Souto EB, Nayak AP, Murthy RS. Lipid nanoemulsions for anti-cancer drug therapy. *Die Pharmazie-An Int J Pharm Sci.*, 2011; 66(7): 473-478.
6. Pouton, C.W. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. *Eur. J. Pharm. Sci.*, 2000; 11: S93-S98.
7. Sharma B, Sharma A, Arora S, Gupta S, Bishnoi M. Formulation, optimization and evaluation of atorvastatin calcium loaded microemulsion. *J Pharm Drug Deliv Res.*, 2012; 1(3): 1-7.
8. Sainsbury F, Zeng B, Middelberg AP. Towards designer nanoemulsions for precision delivery of therapeutics. *Curr Opin Chem Eng*, 2014; 4: 11-17.
9. Samira Khani, Fariborz Keyhanfar & Amir Amani. Design and evaluation of oral nanoemulsion drug delivery system of mebudipine, *Drug Delivery*, 2015; 23(6): 2035- 2043.
10. Shen Q, Wang Y, Zhang Y. Improvement of colchicine oral bioavailability by incorporating eugenol in the nanoemulsion as an oil excipient and enhancer. *Int J Nanomedicine*, 2011; 6: 1237-43.
11. Zhang Y, Lam YM. Study of mixed micelles and interaction parameters for polymeric nonionic and normal surfactants. *J Nanosci Nanotechnol*, 2006; 6(12): 3877-3881.