Original Article

Tizanidine Nano emulsion: Formulation and in-vitro Characterization

Ahmed Y. Fadhel[1], Nawal A. Rajab[2]

[1]Department of Pharmaceutical, College of Pharmacy, University of Tikrit, Tikrit, Iraq

[2]Department of Pharmaceutical, College of Pharmacy, University of Baghdad, Baghdad, Iraq

Email: Ahmed82you@gmail.com

Abstract

An o/w nanoemulsion (NE) was used with an objective to select appropriate components including emulsifiers (surfactants and cosurfactants) and oils as well as the NE area of emulsifier ratio (Smix). Aqueous titration method was used to construct triangular co-ordinate emulsion diagrams. Tween 80 and cremephore EL as surfactant and ethanol as co-surfactant were used as emulsifiers with ratio 1:1 and 1:2 , oleic acid was used as oily phase. Twelve nanoemulsion formula was prepared by using aqueous titration method (low energy emulsification).

The NE was characterized for visual transparency, average droplet size, polydispersity index, zeta potential, % transmittance, drug content and in-vitro drug release.

The formula F11 were selected as optimum nanoemulsion according to results of characterization. (F11) nanoemulsion with Smix (1:2) : oil : deionized water (55: 5: 40) ratio is the optimized formula (best formula), because it is characterized by good droplet size range (16.9 nm), good PDI (0.552), good percent transmittance (99. 4%), percent of drug content was higher (98.5) and highest release of tizanidine from the formula.

Keywords: Nanoemulsion, Tween 80, Oleic acid, surfactant, Ethanol.

Introduction

Nanoemulsion is a dispersion of two immiscible liquids, such as oil and water, that is stabilized by an interfacial film of surfactant molecules and is thermodynamically stable, isotropic, and ally transparent. This type of dispersion is known as a nanoemulsion. The dispersed phase often consists of microscopic particles or droplets, with a size range that is anywhere from 5 nm to 200 nm, and it has an extremely low oil/water interfacial tension (1). Nanoemulsions can be formulated into a variety of dosage forms, including liquids, creams, sprays, gels, aerosol, and foams; they can also be delivered in a variety of ways, including topically, orally, intravenously, intranasally, pulmonaryly, and through the lungs. They have greater kinetic stability than coarse emulsions and a higher solubilization capacity than simple miceller dispersions (2).

Classification of nanoemulsions are most likely to be formed depending on the composition, there are three types of nanoemulsion: a. O/W Nanoemulsion: Wherein oil droplets are dispersed in the continuous aqueous phase. b. W/O Nanoemulsions: Wherein water droplets are dispersed in the continuous oil phase. c. Bi-continuous Nanoemulsions: Wherein microdomains of oil and water are interdispersed within the system (3).

Address for correspondence: Ahmed Y. Fadhel
College of Pharmacy, University of Tikrit, Tikrit, Iraq
Email: Ahmed82you@gmail.com

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Not just in the pharmaceutical industry, but also in the formulation of nutraceuticals, food items, and cosmetics, nanoemulsions have attracted a lot of attention. When it comes to medication administration. Nanoemulsions can be employed in a variety of different ways, including parenteral, oral, topical, ocular, pulmonary, mucosal, cosmetic, transdermal, controlled, and target delivery(4).

Tizanidine is a muscle relaxant that act on the central nervous system. It is a myotonolytic drug that acts as a central alpha-2 adrenoceptor agonist and is used to treat spasticity in patients who have suffered from cerebral or spinal injury. It is an antispastic drug with efficacy that is comparable to that of baclofen and a tolerance profile that is more favorable (5). It half life 2.1–4.2 hours and bioavailability is 34–40 due to first pass metabolism(6).

Material:

UV absorption maxima (λmax) determination

The stock solution of TZN (1 mg/mL) was made by dissolving 100 milligrams of TZN in 100 milliliters of ethanol. An ultraviolet absorption spectrum (λmax) of TZN was acquired over a wavelength range of 200 to 400 nm. The working solution was scanned with using of ethanol as a blank (7).

Construction of calibration curves

Calibration curves of TZN in ethanol were obtained by preparing serial dilutions of the drug through transferring (0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 mL) from the stock solution (1 mg/mL) to 10 mL volumetric flasks and diluted up to the sign (10mL). The absorbance of these diluted solutions were determined spectrophotometrically at the previously estimated λmax and plotted against concentration to get a calibration curve. The R^2 value and calibration curve equation were obtained.

Determination of tizanidine solubility in different oils and emulsifiers

The measurement of solubility was done by adding an excess amount of TZN powder to 5ml of each oil ,surfactant , and co-surfactant (oleic acid, peppermint oil, coconut oil, olive oil, sesame oil, castor oil, Tween 20, Tween 80, PEG 400, PEG 200, cremphore EL, and ethanol) as follow: The liquids were mixed by using a vortex mixer, then shaken using a water bath shaker at 25±1°C for 48 h to reach equilibrium.

After the necessary amount of ethanol was used to dilute the samples, they were then filtered using a membrane filter with a pore size of 0.45 microns. Spectrophotometric analysis using an ultraviolet spectrophotometer at the selected λmax (8).

Construction of pseudo-ternary phase diagrams

The spontaneous emulsification method, also known as the titration method, was used to construct the pseudoternary phase diagrams that contain oily phase, surfactant, and cosurfactant components, along with water (9). Following the blending of the tween 80 with a mixture of ethanl in fixed weight ratios (1:1, and 1:2), the cremephore EL was also blended with ethanol in fixed weight ratios (1:1, 1:2, and 1:3), and aliquots of each surfactant and cosurfactant mixture (Smix) were then mixed with oil at room temperature. For each phase diagram, the ratio of oil to Smix was altered as follows (in weight-to-weight terms): 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9. Under constant and vigorous stirring, water was added to each oil–Smix mixture in the form of droplets. After the equilibrium was reached, the samples were examined visually, and it was assessed whether or not they were clear NEs or emulsions. During the preparation phase, there is no heating that takes place. The CHEMIX School Ver. 3.50 software (MN, USA) was utilized in the preparation of the phase diagrams (10).

Preparation of tizanidine nanoemulsion:

In order to proceed with the evaluation, the (Oil:Smix) combination that incorporates the drug and has the smallest particle size was selected. As shown in table 1, TZN nanoemulsion was made by combining oleic acid as the oil phase with tween 80 and cremphore EL as surfactants and ethanol as a co-surfactant in varying ratios (surfactant: co-surfactant) (1:1, and 1:2) of surfactant to co-surfactant. The drugs was mixed in with each of these formulations at a concentration of 4 mg /1 ml. TZN nanoemulsions were made by dissolving the required amount of medication (4 mg) in an amount of oil that was specifically measured out. After that, the predetermined amount of Smix was added for the oil-loaded drug, and then the entire combination was mixed by using a vortex mixer for five minutes at a speed of 100 rpm. Then, the aqueous phase (deionized water) was titrated one drop at a time in order to obtain a nanoemulsion that was translucent and clear (o/w) (11).

Table 1: Formulation of Different TZN Loaded Nanoemulsion

NE-F	TZN %w/v	Oleic acid oil %v/v	Surfactant	Cosurfactant	Smix ratio	Smix %v/v	DDW %v/v
1	0.04	10	Cremophore EL	Ethanol	1:1	55	35
2	0.04	5	Cremophore EL	Ethanol	1:1	55	40

3	0.04	15	Cremophore EL	Ethanol	1:1	55	30
4	0.04	10	Cremophore EL	Ethanol	1:2	55	35
5	0.04	5	Cremophore EL	Ethanol	1:2	55	40
6	0.04	15	Cremophore EL	Ethanol	1:2	55	30
7	0.04	10	Tween 80	Ethanol	1:1	55	35
8	0.04	5	Tween 80	Ethanol	1:1	55	40
9	0.04	15	Tween 80	Ethanol	1:1	55	30
10	0.04	10	Tween 80	Ethanol	1:2	55	35
11	0.04	5	Tween 80	Ethanol	1:2	55	40
12	0.04	15	Tween 80	Ethanol	1:2	55	30

Tizanidine nanoemulsion characterization

Visual transparency

The optical transparency of the NE formula (F1-F24) was measured by placing the formula in clear and transparent glass vials, placing them in front of a good light source, and comparing the result to a black and white lighted background (12).

Thermodynamic stability studies

In order to avoid a metastable formulation, every one of the formulations that was prepared, put it through a variety of thermodynamic stability tests, including centrifugation, a heating-cooling cycle, and a freeze-thaw cycle (13).

Centrifugation test

After 30 minutes of centrifugation at 3,500 rpm, each of the generated nanoemulsion formulations were inspected for signs of phase separation, creaming, and cracking. In order to complete the heating-cooling cycle, stable formulations were used (14).

Heating-cooling cycle (H/C cycle)

The H/C cycle was used to investigate how the stability of nanoemulsions changed with changes in temperature. Six cycles at temperatures ranging from 4 to 45 oC, with storage at each temperature for no less than 48 hours. A cycle of freezing and thawing was performed on stable formulations that were not affected by the temperatures tested (15).

Freeze-thaw cycle

All of the prepared nanoemulsion formulations went through three cycles of freezing and thawing at temperatures ranging from -21 to +25 oC, with storage at each temperature for not less than 48 hours. Stable formulations was taken for these tests (13).

Droplet size, poly dispersity index and zeta potential measurement

The measurement of the mean droplet size, the zeta potential (ʒ -potential; droplet surface charge), and the polydispersity index (PdI; size range of particles) using a dynamic light scattering technique (Zetasizer Nano ZS), in which the light scattering fluctuations were analyzed by particles brownian motion of NE formulations, were carried out (16). It provides precise measurements ranging from 0.3nm to 10 μm (17).

Diluting (0.1 mL) of each NE formula (F1-F24) with double distilled water (50 mL) under gentle agitation helped to reduce the viscosity of oleic acid and emulsifiers, and it also reduced the multiple scattering effect. 1 ml of diluted NE was injected into a folded capillary zeta cell, and the light scattering was monitored at a temperature of 22 oC (173o angle). The values for the average droplet size, ʒ -potential, and PdI were found to be registered (18).

Turbidity test (Transmittance percentage %T)

The prepared NEs were subjected to a turbidity test so that the translucence could be evaluated. This was accomplished by utilizing 2 mL of each NE formula (F1-F24) and measuring the absorbance at 650 nm (light wave length) with a UV-VIS spectrophotometer. The blank for this experiment was distilled water (19). The formula that was used to determine the transmittance percentage, denoted by the letter "percent T," is as follows: (20)

$$A = 2 - \log \%T \qquad Eq.\ 1$$

Where:

A: absorbance %T: transmittance percentage

Dye test

A water-soluble color called methyl orange was used for each nanoemulsion TZN formula. If the dye was able to mix evenly with the NE without resulting in any precipitation, this would suggest that the continuous phase is water, and that the NE structure is o/w (21).

Drug content

The drug content was calculated by using UV visible spectrophotometer. The formulation was diluted using ethanol as solvent, and the absorbance was measured at wave length against a solvent blank. The drug content was calculated as:

Drug content = Analyzed content/ Theoretical content x 100 …….Eq(2) (22)

In vitro release study

All of the prepared nanoemulsion formulations was subject to in-vitro drug release by using USP dissolving apparatus-II (paddle method). Phosphate buffer with a pH of 6.4 is recommended as the dissolution medium for TZN in the USP monograph. The temperature should be 37.5 oC, and the rotational speed should be 50 rpm, using dialysis bag technique 12000 daltons (23). Dialysis bags were let to soak overnight in phosphate buffer saline (PBS) with a pH of 6.4, which is equivalent to the pH of nasal fluid (24).

After placing nanoemulsion containing TZN corresponding to one dose (2 ml) in a dialysis bag and withdrawing 3 ml of dissolution medium at various time intervals (5, 10, 15, 30, 45, 60, 90, and 120 minutes), aliquots were taken out (25).

Results and Discussion

Drug characterization

UV Absorption Maxima (λmax) determination

Scanning the diluted solutions of tizanidine in phosphate buffer pH 6.4 using UV spectrophotometer at a range of 200-400 nm. shows λ max peaks at 319.5nm, 308.6 nm and 242.6nm, respectively, as seen in figures 1 and these results are in good agreement with results in the references(26).

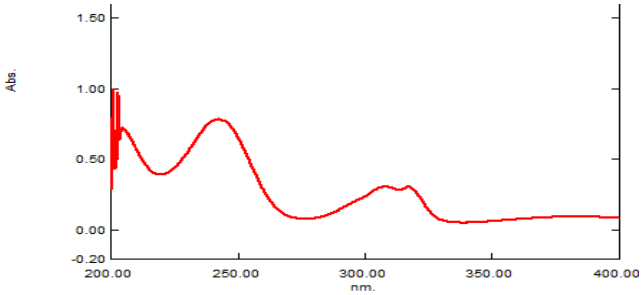

Figure 1: UV spectrum of Tizanidine in pH 6.4 phosphate buffer

Construction of calibration curves

The constructed calibration curves of TZN in phosphate buffer pH 6.4 with and in ethanol are seen in figures 2 and 3, respectively. By plotting the absorbance against concentration, a straight line was obtained with a large coefficient of determination, which indicates that the calibration curve obeys Beer's law within the range of concentration used.

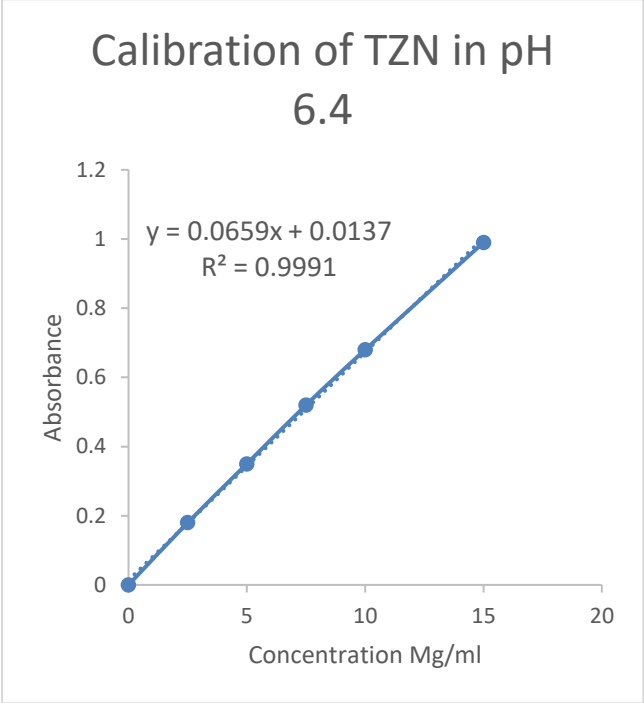

Figure 2: Calibration curve of Tizanidine in phosphate buffer pH 6.4

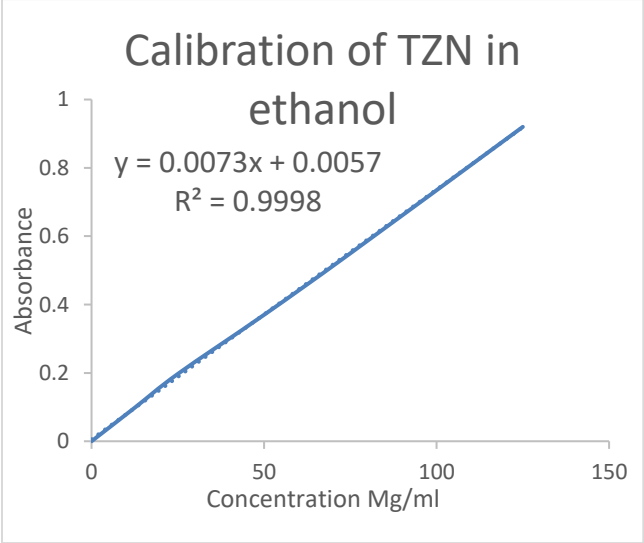

Figure 3: Calibration curve of Tizanidine in ethanol

Determination of TZN solubility in different oils and emulsifiers

The solubility of the drug in the oil phase is an important criteria for the selection of oils. This is particularly important in the case of nasal formulation development, as the ability of nanoemulsion to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in the oil phase.

The solubility of tizanidine was found to be highest in oleic acid (45.6mg/ml) and lowest solubility in coconut oil (2.6 mg/ml) as shown in figure 4 this due to oleic acid had a partition coefficient of 7.64, which could provide the highest

solubilizing capacity for tizanidine, whereas, coconut oil is the most polar among other lipids used in this study due to its high lauric acid composition. This limits its ability to dissolve tizanidine. Generally, oil molecules with a small molecular volume or high aromaticity produce a strong solvation effect, resulting in a higher penetration of the oil molecules into the surfactant chain layer, thus improving the rigidity and curvature of the interface. This would also affect the particle size, as various lipids are added (27) (28).

The tizanidine possesses higher solubility in cremophore EL than other surfactant this due to cremophore is a complex mixture of relatively hydrophobic 83% and hydrophilic molecules 17%, where it quite effective at solubilising very hydrophobic drugs (29). It was reported that alkyl chain structure of cremophore EL impact an effect on penetration of tizanidine onto the curved surfactant film and finally enhance the drug solubility (30).

The tizanidine possesses higher solubility in tween 80 in compare with tween 20 due to tween 20 had the higher HLB value of 16.7 and hence greater hydrophilicity while the tween 80 having lower HLB values 15 and hence greater lipophilicity (31).

The significantly higher solubility of the tizanidine in the cosurfactant is arranged in the order of PEG 400 > PEG 200 > ethanol which might be due the higher molecular weight and hydrophilicity of PEG 400 compared to the other (32).

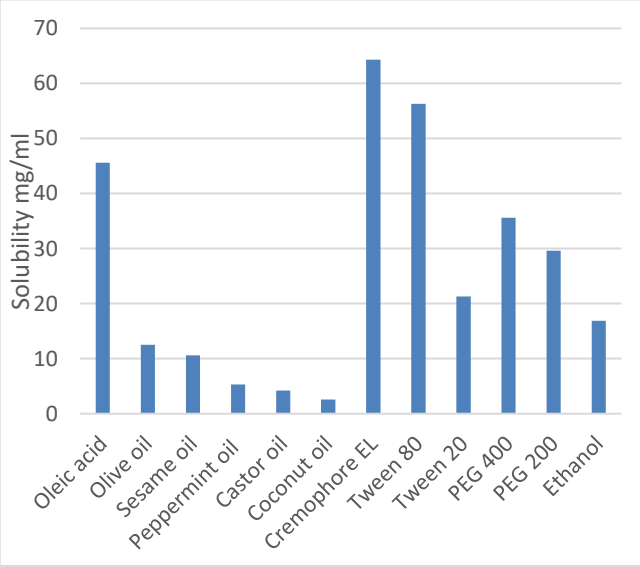

Figure 4: Solubility of tizanidine (mg/mL) in different oils, surfactants and co-surfactants

Construction of pseudo-ternary phase diagrams

The used oily phase is oleic acid based on solubility study and only one part of the oil was used since the increase in oil phase causes increase in Smix %v/v which may cause nasal irritation.

To study the relationship between the components of the nanoemulsion and their phase behaviour, phase diagrams were constructed using oleic acid as the oil phase, Cremephore EL and Tween 80 as surfactant mixture and ethanol as co-surfactant. In the present study, two surfactants Cremephore EL and Tween 80 were selected having HLB values 14 and 15 respectively. The darkened areas enclosed by lines roughly indicate the zone of nanoemulsion formation. The rest of the region on the phase diagrams represent the turbid and conventional emulsions(33) (34). The pseudo-ternary phase diagram plot for different S mix ratio (1:1, 1:2 and 2:1) were shown in the figures (5-9).

In order to reduce oil/water interfacial tension significantly and increase interfacial film fluidity, a combination of high HLB surfactants and low HLB co-surfactants. Co-surfactants are usually short or medium chain alcohols (C3–C8) that are added thus that the amount of surfactant used can be decreased (35).

the nanoemulsion region increased in the size as compared to the region in Smix (1:1) when surfactant concentration was increased as compared to cosurfactant, Smix ratio (2:1) the nanoemulsion area decreased as compared to smix ratio(1:2) (36).

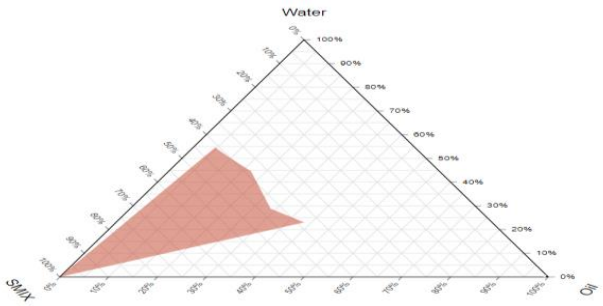

Figure 5: Pseudo ternary phase diagram plot for oliec oil, Smix ratios (tween 80: ethanol (2:1) and deionized water.

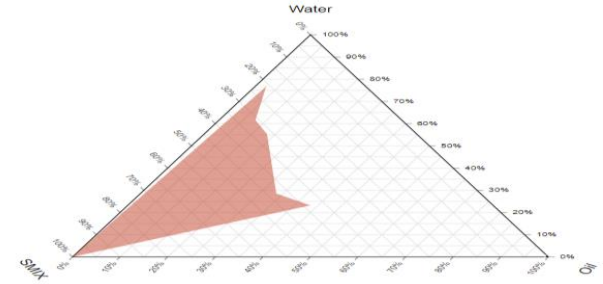

Figure 6: Pseudo ternary phase diagram plot for oliec oil, Smix ratios (tween 80 :ethanol) (1:1) and deionized water.

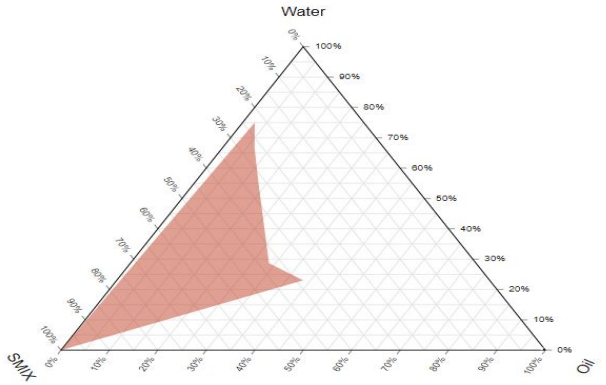

Figure 7: Pseudo ternary phase diagram plot for oliec oil, Smix ratios (tween 80 :ethanol) (1:2) and deionized water.

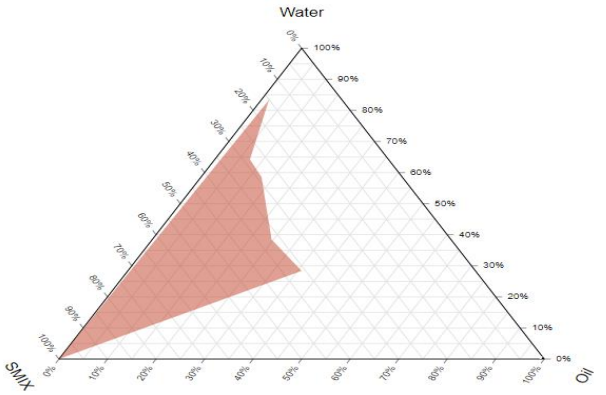

Figure 8: Pseudo ternary phase diagram plot for oliec oil, Smix ratios (Cremophore EL:ethanol) (1:1) and deionized water.

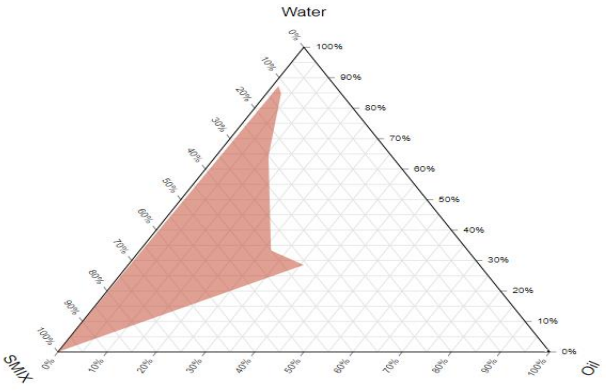

Figure 9: Pseudo ternary phase diagram plot for oliec oil, Smix ratios (Cremophore EL:ethanol) (1:2) and deionized water.

Preparation of the formulas

TZN loaded nanoemulsions was prepared by aqueous titration method. The quantity of TZN (4) mg that is required for preparation of (100) g formula was dissolved in the determined quantity of oleic oil, then Smix ratio was added to oil and TZN mixture and the whole mixture was mixed by using vortex mixer for 5 minutes , then deionized water titrated drop by drop up to 100 gm which is the final weight of the formula. clear, transparent (o/w) nanoemulsion was produced (37).

Tizanidine nanoemulsion characterization

Visual transparency

The all prepared NE formulas (F1-F12) were optically clear. The small droplet size causes weak light scatters (more transparent). Moreover, the small droplet size and narrow size distribution contribute to a high kinetic stability of NEs against aggregation and gravitational separation by Brownian motion, these results are in consistent with our previous tests (38).

Thermodynamic stability studies

All of the prepared nanoemulion formulations passed the thermodynamic stability test, which are centrifugation test, heating- cooling test and freeze-thawing test in order to obtain thermodynamic stable formulations of nanoemulsions that have no creaming, cracking and phase separation which may present in the macroemulsion (39). This suggested that the formulations were persisting against storage in extreme conditions.

Droplet size, poly dispersity index and zeta potential measurement

Table 7 shows average droplet size by intensity (diameter by intensity), PdI and zeta potential of the prepared NE formulas (F1-F12). The droplet size of the NEs is the net result of the controlling process parameters as the type of energy input and emulsification time besides dependency on concentration of dispersed phase and amount of Smix (40).

The increase of Smix ratio 1:1, and 1:2 decreases the droplet size up to certain size. The higher the surfactant ratios facilitated the interfacial film to condense and stabilize, whereas increasing the concentration of the cosurfuctant causes this film to expand (41). Small mean droplet size of most systems could be related to the penetration of co-surfactant molecules into the surfactant film. This would decrease the surface viscosity of the interfacial film, lowering the radius of curvature of the droplets and forming transparent systems. Thus, the relative proportion of surfactant to co-surfactant has varied effects on the droplet size (42)(43) .

It was observed that systems containing 15% oleic oil produced nanoemulsion with a larger particle size than systems containing 10% and 5% oleic oil, the larger the oil percentage, the larger mean droplet size, the mean droplet size increased significantly when more oil is incorporated owing to the expansion of oil droplets of the nanoemulsion (44).

Low value of poly dispersity index 0.08-0.7 is considered to be desirable for uniform distribution, high quality and homogeneity of nano-sized droplets within the preparation (45). The polydispersity index (PDI) of all formulae was in the range from (0.653-0.102) indicating uniform and narrow globule size distribution as seen in the table 2.

According to the zeta potential (ʒ – potential), all excipients

and the drug used in NEs preparation are non-ionic in nature but the presence of fatty acid (oleic acid oil) generally makes the surface charge of the droplet negative (46).

The zeta potential (ʒ) of all the NE formulas (F1-F12) was found to be neutral (ʒ~ zero) due to strong H-bond (47).

The optimal droplet size was found in the range of 100–500 nm (48).Depending on the results of particle size measurement that explained in the table(2).

So selected the smaller particle size from the range (16.9-121.8nm),the formulas are(F1, F2 , F5 F7, F8, F10,F11).

Table 2: Mean Particle Size, PdI and ʒ-potential of Prepared NE Formulas

NE - F	Mean droplet size (nm)	Polydispersity index (PDI)	ʒ-potential (mV)
F1	102.3	0.456	-8.7
F2	85.5	0.620	0.354
F3	523.5	0.330	-6.6
F4	135.6	0.102	-0.540
F5	121.8	0.356	-5.62
F6	269.6	0.452	-6.8
F7	87.5	0.510	-6.7
F8	69.5	0.335	-7.7
F9	357.2	0.538	-5.8
F10	98.3	0.423	-3.06
F11	16.9	0.552	-4.25
F12	255.6	0.156	-7.4

Measurement of % Light Transmittance (%T)

The measurement of %T was made for the selected NE formulas at 650nm, keeping distilled water as blank. The results of %T of drug-loaded nanoemulsions were closer to 100 %. This indicates that all formulations of nanoemulsions appear as clear and transparent (49) as show in table 3.

Table 3: Measurement of % Light Transmittance (%T)

NE - F	% Transmittance
F1	98
F2	97.6
F5	96.7
F7	95
F8	98.5
F10	96.8
F11	99.4

Dye test

Methyl orange, 4-[4(dimethyl amino) phenyl azo] benzene sulfonic acid, is an azo dye miscible with water .After adding methyl orange dye, it was noted that the dye was miscible homogeneously with all Tizanidine NE formulations; with no aggregates or clumps formed (50).

Drug content

Drug content of all the prepared tizanidine nanoemulsion were more than 95% and there was no significant difference between the various formulations ($p > 0.05$), which meet BP (British pharmacopeia) requirement and were within an acceptable range (95%-110%) (51), indicating that, there was no precipitation of drug in any of prepared formulations, drug content percent of tizanidine nanoemulsion are illustrated in table 4.

Table 4: The Drug Content Percent of Tizanidine Nanoemulsion Formulation (mean ±SD) n=3.

NE - F	% Drug content
F1	98.7 ± 1.3
F2	96.4 ± 1.02
F5	98 ± 1.5
F7	99.4 ± 1.5
F8	99.2 ± 2.1
F10	98.3 ± 1.3
F11	98.5 ± 1.1

In vitro release study

The in-vitro release of TZN formulation (F2, F3 , F5 , F7, F8, F10, F11) show good drug release (72-100 %)within 120 minutes as illustrated in figure 10.

It was noticed as the concentration of oleic oil increase from 5% to 10% decrease in release rate due to small particle size obtain in low oil concentration and the small globule size with subsequent increase in surface area exposed to the release medium, the increased polarity of the formulations by the proper balance between the ratio of oil: Smix and high solubilization capacity of NE formulations were the contributing factors for high drug release as shown in figure 11 (52).

It was noticed as the concentration of ethanol increase (surfactant:cosurfactant 1:1, 1:2) the released increased and reach 100% faster as in figures 12, the reason behind this might be due to the effect of co-surfactant in the nanoemulsion systems reduce the interfacial tension and increase the fluidity of the interface. They also increase the mobility of the hydrocarbon tail and allow greater penetration of the oil in this region (53)(54).

It was noticed that tween 80 produce faster release in compare with cremephore, where within one hour F2 of cremophore produce 63% while F8 of tween 80 76% and also F5 of cremophore produce 69% while F11 of tween 80 produce 100% as in figure 9, the reason for this result may be due to

the difference in HLB value of the surfactants, where the HLB value for tween 80 and cremophor EL are 15 and 13, respective, emulsion droplet size decreased with a higher HLB. (55)(56).

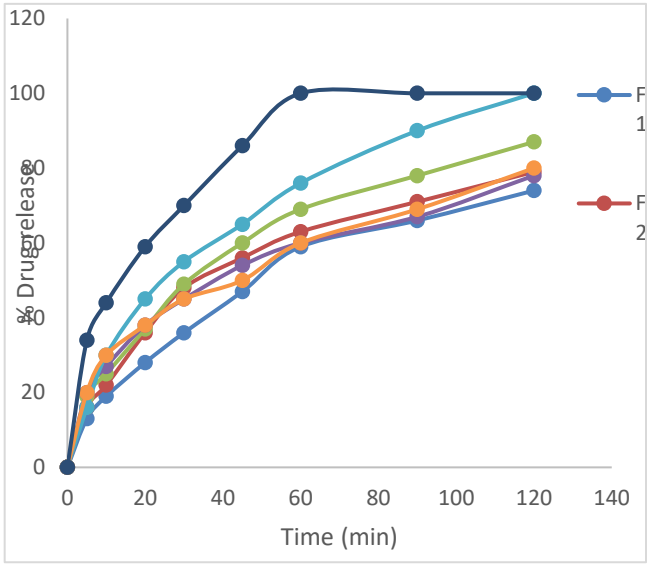

Figure 10: In-vitro release of TZN formulation (F1, F2 , F5 , F7, F8,F10, F11)

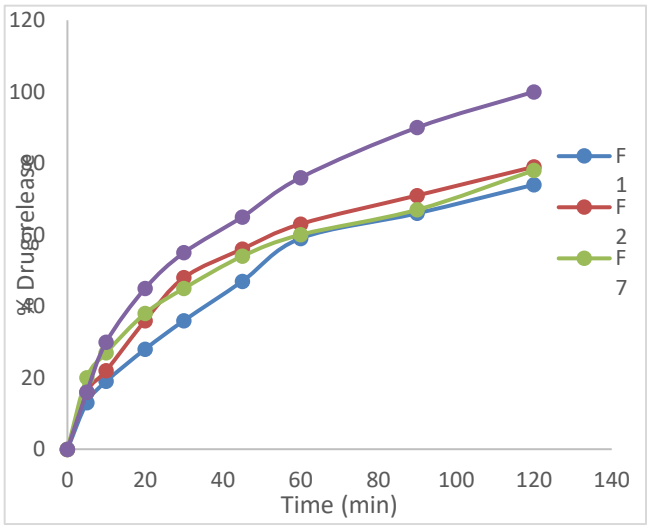

Figure 11: Effect of oil ratio in release profile of TZN (F1, F2, F7 and F8)

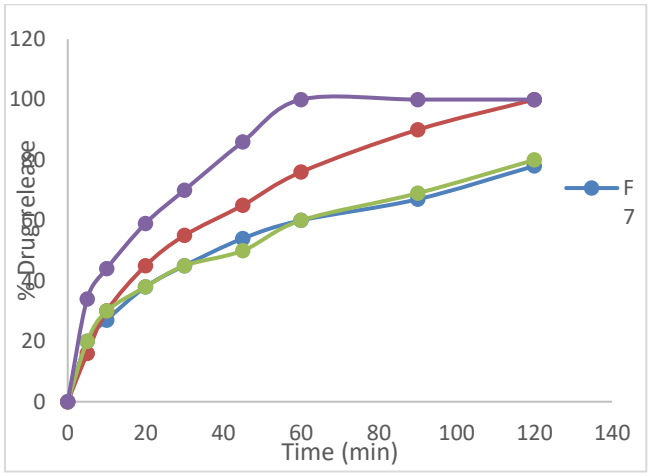

Figure 12: Effect of surfactant: co-surfactant ratio (1:1, and 1:2) in release profile of TZN (F7, F8, F10 and F11)

Selection of optimum tizanidine-nanoemulsion

After analysis of the characterization data of prepared tizanidine nanoemulsions which are droplet size, polydispersity index (PDI), light percent transmittance (%T), drug content and in vitro release of a drug. There was an indication that the (F11) nanoemulsion with Smix (1:2) : oil : deionized water (55: 5: 40) ratio is the optimized formula (best formula), because it is characterized by good droplet size range (16.9 nm), good PDI (0.552), good percent transmittance (99. 4), percent of drug content was higher (98.5) and highest release of tizanidine from the formula.

Conclusion:

Nanoemulsion, used as a good delivery system used to enhance the solubility of tizanidine which is slightly water-soluble drugs class II according to biopharmaceutics classification system (BCS) and also undergo extensive the first-pass metabolism so introducing this drug into nanoemulsion to ehance its solubility and also minimize the first-pass effect by absorption through lymphatic system.

The study results indicated the possibility of application of nanoemulsion (NE) technology with low energy emulsification in the formulation of the tizanidine nanoemulsion.

In this study: The optimum NE formula (F 11) rational blends of oil (i.e. oleic acid oil), Smix (i.e. Tween 80: ethanol in ratio 1:2) was developed successfully according to pseudo-ternary phase diagram studies. Characterization and in vitro evaluation for all the prepared formulas had been applied and showed the (F11) nanoemulsion highest and faster release of tizanidine from the other formulas.

The present study may act a good method to enhancing the drug solubility for poorly water-soluble drugs as nanoemulsion drug delivery system.

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