

Preparation and in-vivo Evaluation of Ticagrelor Oral Liquid Self nano-emulsion

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Abstract

Ticagrelor is a new drug use to inhibit platelet aggregation induced by adenosine di phosphate (ADP) that's used to reduce atherothrombotic occurring in adults with acute coronary syndrome. Ticagrelor is class IV drug according to BCS drug classification, which is practically insoluble in water 10 µg/ml, with an absolute bioavailability of about 36 %, so this study intended to improve its water solubility and bioavailability.

Method: maximum solubility of drug in different oil and co surfactant was determined and a suitable surfactant was used according to HLB system, after that a 20 formula of Ticagrelor self-nano emulsion was prepared, and best formula was chosen according to different tests and subjected to an in-vivo evaluation.

Results: the obtained results showed that Oleic acid, Tween 20, and Propylene glycol combination are the best constituent to prepare Ticagrelor as self-nano emulsion formula, this combination gave a large nano region upon titration with water. The best formula F5 was 10% oil and 90% surfactant -co surfactant mixture (S mix) in ratio 4:1 (tween/ Propylene glycol), showed 25 nm particle size, 0.098 polydispersity index, 10 times improvement in drug release rate than pure drug powder, and about 10 time prolongation of drug clotting time in the in-vivo study.

Conclusion: the preparation of Ticagrelor as self-nano emulsion improve both the aqueous solubility of drug and the bioavailability.

Keywords: self nano-emulsion, Ticagrelor, HLB system, oleic acid.

INTRODUCTION

The oral route is the most preferred route of drug delivery for treatment of a number of diseases. Nearly 35 to 40% of newly launched drugs possess low aqueous solubility which leads to their poor dissolution and thereby low bioavailability (1), resulting in high intra & inter subject variability & lack of dose proportionality. For these drugs absorption rate from gastrointestinal tract is mainly governed by dissolution and improvement in solubility may lead to enhanced bioavailability (2).

There are number of techniques to overcome such problems arising out of low solubility and bioavailability, which may result into improved therapeutic efficacy of these drugs.

The techniques include complex formation with cyclodextrins, solid dispersion, liposomes formation, co precipitation, micronization, salt formation, use of micelles, co grinding and emulsification had been used for solubility improvement (3).

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Recently a new technique, in the last 10 years focusing on lipid as a carrier for drugs that have poor water solubility was increased. The effectiveness of new lipid excipient (that have acceptable safety profile for oral administration) in increasing the oral bioavailability of some drugs facilitated the production of lipid based formulations for drug delivery.

Lipid-based drug delivery(LBDD) systems considered very effective in improving solubility and bioavailability of drugs with poor water solubility, this advantage made these delivery system one of the most important drug delivery system in last decade. Several factors affect the absorption of drug from a lipid based system, including size of the lipid particle, emulsification degree, dispersion rate and occurrence of drug precipitation after dispersion in aqueous media in GIT (4). Drug can be formulated as lipid based formulations using many different formulation techniques, which can be prepared as an oil solution or suspensions of drug, incorporated in an internal oily phase of a self-nano or micro emulsifying drug delivery systems (SNEDDS/SMEDDS), or emulsion. The selection of convenient lipid vehicles, formulation technique and appropriate delivery system design will lead to the success of lipid based drug delivery systems (5).

Self-Emulsifying Drug Delivery Systems (SEDDS)

Are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively, one or more hydrophilic solvents & cosolvents/ co-surfactants use to improve the dissolution profile of drugs with low solubility (6).

The drug will be dissolved in the oily phase of an emulsion, so it will be administered in solution form and bypass the dissolution step of powder that decrease the absorption (7).

The most important uses of self nano-emulsifying drug delivery system SNEDDS is to improve the bioavailability of drugs with low water solubility, which are classified according to the Biopharmaceutics Classification System (BCS) as a class II drug (drugs having low water solubility and high permeability). In addition to that they can also be used to improve the bioavailability of class IV drug (drugs having low solubility and low permeability). The mechanism by which SNEDDS improve bioavailability of BCS class IV beside improving solubility they improve permeation through GIT membranes, by affecting physiological and metabolic factors, also the activity of protein transporters impeding in the cell membranes of the intestinal cells (8).

The following mechanisms are considered for improving drug permeability:

- 1- Prolonging gastric retention time: the oil in the SNEDDS will prolong gastric retention time and decrease the rate of gastric emptying (9).
- 2- Lymphatic transport: the oils in the SNEDDS will

improve the absorption of highly lipophilic drugs through the lymphatic system by promoting their interaction with chylomicrons in the enterocytes and by passing the metabolism in liver (10).

3- Alter the conformation of membrane-bound transporters and promote the inhibition of membrane-bound efflux transporters. Thus, the increase in drug permeability is a result of a reduced efflux.

4- First-pass metabolism: SNEDDS can alter the metabolizing effect of intestinal cytochrome P450 enzymes, which metabolizes drugs in the intestinal wall (11).

Ticagrelor is a nonthienopyridine antiplatelet drug that is the first oral P2Y₁₂ receptor antagonist with reversibly bind to receptor . it inhibit platelet aggregation induced by ADP that's used to reduce atherothrombotic occurring in adults with acute coronary syndrome (12).

Ticagrelor is class IV drug according to BCS drug classification, practically insoluble in water 10 µg/ml, the absolute bioavailability is about 36 %, so it is a good candidate for this study by formulating the drug as SNEDDS to improve both solubility and bioavailability (13).

Aim of study

This study aims to prepare Ticagrelor a class IV drug according to BCS drug classification as Self nano emulsion (SNE) to improve both the aqueous solubility and the bioavailability of the drug.

Materials and Method

Materials

the following material were purchased from

Ticagrelor (hyper chemical china), oleic acid, coconut, corn, sweet almond, avocado, sesame, olive, castor, grape seed, and eucalyptus oils, tween 20 (Solvochem UK) ,glycerin, propylene glycol,. (Gain land chemical community. UK)

Method

Determination of Ticagrelor Solubility in Oil and co Surfactant

The saturated solubility of TCG in different oils, and co-surfactant have to be determined to select the appropriate oil and co-surfactant for preparation of SNE, equilibrium solubility method is used.

Briefly, 5 mLs were taken from each of the following oils (coconut, corn, sweet almond, avocado, sesame, oleic, olive, castor, grape seed oil, and eucalyptus) and 5 ml of (glycerin, propylene glycol) as a co surfactant in a screw-capped test tube. Then, an excess quantity of ticagrelor was added to each tube and mixed with the aid of a vortex mixer and sonicates for 5 minutes. To establish an equilibrium, the formed suspension was incubated at 37 0 C for 72 hours in a

shaking water bath. then the insoluble drug was removed by centrifuging for 20 minutes at 3500 rotations per minute.

The supernatant was removed and filtered with a 0.45m millipore syringe filter after centrifugation and then, adequately diluted by ethyl acetate. Then, ticagrelor concentration in diluted samples was measured spectrophotometrically at λ max by applying a pre-constructed calibration curve (14, 15).

Selection of Surfactant

Surfactant selection was based on the HLB system. Hydrophilic - Lipophilic Balance (HLB) is the ratio of oil and water-soluble constituents of a non ionic surfactant , all surfactants have a hydrophilic head (water loving) that is composed of a water soluble group and a lipophilic tail (oil loving) which composed of a fatty acid or fatty alcohol (16). In the HLB System, any surfactant has an HLB value, and Each oil or wax intended to be used in emulsion formulation has a required HLB number, by using surfactants with HLB value that is required by the oil, trial and error effort will be reduced and optimum formula will be obtained . Surfactant combinations in the HLB range of 8 to 18 show suitable results for oil in water products. Water in oil emulsions usually requires surfactants in the HLB range of 4 to 6 (17).

The surfactant was chosen with an optimum HLB value to produce oil in water emulsion for oil that have higher solubility for ticagrelor (18).

Pseudo-Ternary Phase Diagrams Establishment

Taking into account the solubility , emulsification efficiency studies, and required HLB for oil, combinations of the oil phase, surfactant and co-surfactant were prepared. Oleic acid was chosen as oil, tween 20 as surfactant: propylene glycol as co surfactant.

The water titration method was used for building up pseudo-ternary phase diagrams to identify nanoemulsion region for selection of best combination. Surfactant and co-surfactant that expressed as S mix was blended at different

weight ratios (4:0,4:1, 3:1, 2:1, 1:1, 1:2, and 1:3 w/w). For each of these ratios, oleic acid was added and mixed using vortex mixer to form a mixture with nine different oil: Smix ratios (ranged from 1:9 to 9:1 w/w). Then, yellow transparent and homogeneous mixtures of oil: Smix were titrated by slow addition of distilled water in a dropwise manner under continuous gentle magnetic stirring. After each addition of water, the mixture was visually checked for phase clarity and flowability. Titration was halted when the system became turbid and thick gel-like. To outline the phase boundaries in each diagram, the percent weight of oil, Smix, and water in a 100 % w/w combination were computed. TernaryPlot.com was used to plot phase diagrams. The shaded area was considered to be a visual clear area in triangle plot with one apex representing the oil, the second one representing water and the third representing S mix at a fixed weight ratio (19).

Preparation of Ticagrelor Liquid Self-nanoemulsion Formulas

Twenty formulas were prepared based on pseudo ternary phase diagram. So six different Smix (4:0,4:1, 3:1, 2:1 and 1:1 w/w) ratios were used. A quantity sufficient to fill 10 capsules was prepared, by dissolving 0.9 gm of Ticagrelor in 5 gm of oil and Smix , the oil concentration was ranged from 10 to 40% , and tween 20 and PG concentrations determined according to the Smix ratios used, as stated in table (1).

Oleic acid, tween 20 and propylene glycol were mixed in vortex mixer before adding drug for about 3 minutes to ensure homogeneity, then accurately weighted ticagrelor was added to the(oil, surfactant, and co surfactant) mixture, with continuous stirring in vortex mixer until solid dispersed in oil/Smix mixture, the mixture was transferred to the sonicator until all drug dissolved (20).

The prepared formulations were stored at room temperature for at least 48 hr and kept under visual observation of turbidity, components separation or precipitation that may happen before going further evaluation.

Table (1): Composition of Liquid Self nano-emulsion Formulations

Formula code (oil-smix ratio)	Smix ratio	Oleic acid(gram)	Tween 20 (gram)	PG (gram)	Ticagrelor (gram)
F1 (10-90)	4:0	0.05	0.45		0.09
F2 (20-80)	4:0	0.1	0.4		0.09
F3 (30-70)	4:0	0.15	0.35		0.09
F4 (40-60)	4:0	0.2	0.3		0.09
F5 (10-90)	4:1	0.05	0.36	0.09	0.09
F6 (20-80)	4:1	0.1	0.32	0.08	0.09
F7 (30-70)	4:1	0.15	0.28	0.07	0.09

F8 (40-60)	4:1	0.2	0.24	0.06	0.09
F9 (10-90)	3:1	0.05	0.34	0.11	0.09
F10 (20-80)	3:1	0.1	0.3	0.1	0.09
F11 (30-70)	3:1	0.15	0.263	0.087	0.09
F12 (40-60)	3:1	0.2	0.225	0.075	0.09
F13 (10-90)	2:1	0.05	0.3	0.15	0.09
F14 (20-80)	2:1	0.1	0.266	0.133	0.09
F15 (30-70)	2:1	0.15	0.233	0.116	0.09
F16 (40-60)	2:1	0.2	0.2	0.1	0.09
F17 (10-90)	1:1	0.05	0.225	0.225	0.09
F18 (20-80)	1:1	0.1	0.2	0.2	0.09
F19 (30-70)	1:1	0.15	0.175	0.175	0.09
F20 (40-60)	1:1	0.2	0.15	0.15	0.09

Note : quantity mentioned are to prepare 1 unit dosage form

Characterization of the Physical Properties the Prepared Ticagrelor Liquid SNE

In order to select the best SNE formula, sufficient and adequate characterization tests were performed on the prepared formulations.

Measurement of The Globules Size, Zeta Potential, and Polydispersity Index (PDI)

The effective globules size with the range of distribution size or Poly dispersity index (PDI) of nanoemulsion resulted from dilution were determined using dynamic light scattering technique. All measurements carried out at a laser scattering angle (90 0) and 660 nm at room temperature.

The liquid ticagrelor self nano emulsion formulation was freshly diluted to 100 fold (0.25mL of each formula in 25 mL) with filtrated distilled water and stirred thoroughly by magnetic stirrer to form a fine emulsion (21). After dilution, the resulting nanoemulsion was placed in a disposable cuvette in the sample compartment for droplet size and PDI measurement by analyzing light scattering fluctuation as a result of particles Brownian motion.

Thermodynamic Study

The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variation on SNEDDS formulations. Ticagrelor SNEDDS were diluted with aqueous medium and centrifuged at

15,000 rpm for 15 minutes and formulation were observed visually for phase separation.

After that, the stabled formulas were undergone heating and cooling cycle at two different temperatures (40 C and 450 C) which carried out for six cycles. At each temperature, formulas would stay at least 48 hr.

Then, Formulations were subjected to freeze thaw cycles (-20°C for 2 days followed by +25°C for 2 days). No change in the visual description of samples after freeze-thaw cycles. Formulations, which are thermodynamically stable, were selected for further characterization (22).

In Vitro Drug Release

The aqueous release of drug from the prepared ticagrelor self nano emulsion was measured using USP dissolution apparatus, Type II at 370 C, with 100 rpm was a rotating speed and 900 mL of 0.1N HCl containing 1% tween 80 as a dissolution medium (23). Dialysis bag method was used in this study, to ensure that only free drug particle passed to the dissolution medium without the interference of unreleased drug. The dialysis membranes (M.wt cut off 8,000-14,000 Dalton) were immersed in a 0.1N HCl solution for one day at room temperature. A 320 mg of each formula to be tested was diluted with 20 ml of distilled water, a 5 ml was drawn from each formula to be filled in 10 X 3.5 cm dialysis bag .Also a pure drug aqueous suspension was used in one of the bags, the dialysis bag was tightly ligated from both sides to prevent leakage, and then fixed on the rotation

paddles and immersed in the dissolution medium.

At fixed interval times, an aliquot (5 mL) sample was withdrawn from the beaker and 5 ml of fresh dissolution medium was replenished to ensure sink condition. The samples were analyzed for the drug release using UV-spectrophotometer at 254 nm (24).

In Vivo Drug Absorption

Best formula was selected for in vivo drug absorption test, 30 rats were divided into 2 groups, first group given only pure drug suspended in water, while the second group was given the chosen formula. The dose of drug was calculated according to the weight of rats which were about 0.2 kg, and the dose administered was 0.8 mg/kg. The weighted amount of formula, drug pure powder was diluted with 1 ml of water and given orally to the rats, the drug absorption was determined from pharmacological effect of the drug, by measuring the clotting time change before administering the drug and after, the clotting time for each animal was recorded before administering the drug, and after drug administration the clotting time was measured every 30 minute for 2.5 hour (25,26).

One or two drops of blood were drawn directly from the heart and clotting time was measured using slide method, the blood is placed on a glass slide, and glass rod or a stainless steel lancet in dipped continuously in blood drop and left vertically, until a thread of fibrin is seen attached to the lancet after lifting, the time at which this thread formed is set as clotting time (27).

Statistical Analysis

By employing the one-way analysis of variance (ANOVA) between the data of interest. The data expressed were analyzed at the level of 95 % confidence interval ($p < 0.05$) for determination of statistical differences. The result was significantly considered different when the probability value (p) was less than 0.05 using online good calculator on the web site <https://goodcalculators.com/one-way-anova-calculator/>

Results

Determination of Ticagrelor Solubility in Oil and co Surfactant

To prepare solid SNEDDS with minimum size, the oil with higher solubilization capacity to the drug should be used. The function of oil phase in SNEDDS is to solubilize the hydrophobic/lipophilic active moiety in order to improve both drug loading and bioavailability of the hydrophobic active moiety. Selection of oil plays a vital role in the formulation as it determines the amount of drug that can be solubilized in the system, although, overall drug solubility in SNEDDS is always higher than the solubility of drug in individual excipients that combine to form SNEDDS.

However, such higher solubility considerably depends on the solubility of drug in oil phase (28).

In this study, fixed oils with long chain triglycerides (LCT) used, coconut, corn, sweet almond, avocado, sesame, olive, castor, grape seed oil, and eucalyptus oil were used, also oleic acid a medium chain fatty acid.

The solubility in different oils (mg/ml) is shown in figure (1).

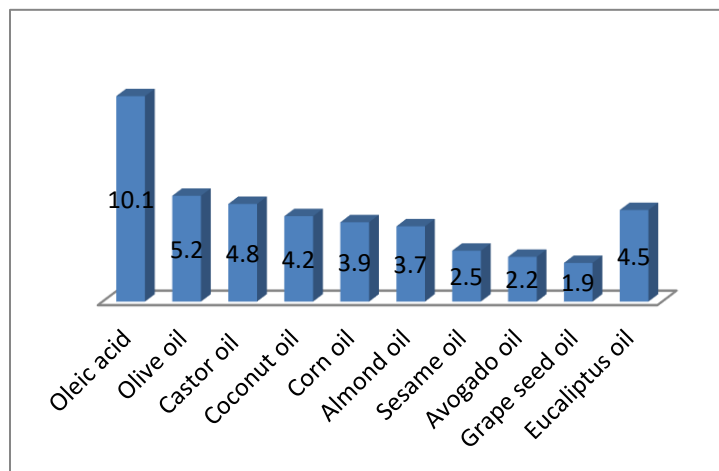


Figure (1): Saturation solubility of TCG in different oils

From the above figure, ticagrelor solubility in oleic acid (10.1 mg/ml) is the highest, while the second highest solubility was in olive oil (5.2 mg/ml), and the other oils are less soluble.

Statistically, It is found that there was a significant difference ($P < 0.05$) in solubility of ticagrelor in oleic acid and other oils, therefore, only oleic acid was used as oil in formulating the SNEDDS, also, solubility of ticagrelor in different co surfactant was examined (propylene glycol, PEG 200 and glycerin).

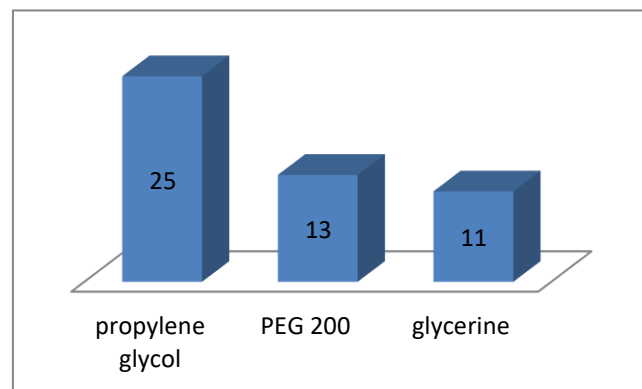


Figure (2): Saturation solubility of TCG in different co surfactants

From figure (2), solubility in propylene glycol is much higher than the solubility in PEG 200 and glycerin.

The production of an optimum SEDDS requires relatively high concentrations of surfactants, thus the concentration of surfactant can be reduced by incorporation of co surfactant. Role of the co-surfactant together with the

surfactant is to lower the interfacial tension to a very small even transient negative value (29).

Selection of Surfactant

Best surfactant for oleic acid to produce oil in water emulsion should have an HLB value about 17, tween 20 seems to be the best choice for producing emulsion with oleic acid, since tween 20 have HLB value 16.7, so tween 20 was chosen as the surfactant for the combination of TCG SNEDDS with oleic acid as oil, and propylene glycol as co surfactant (30).

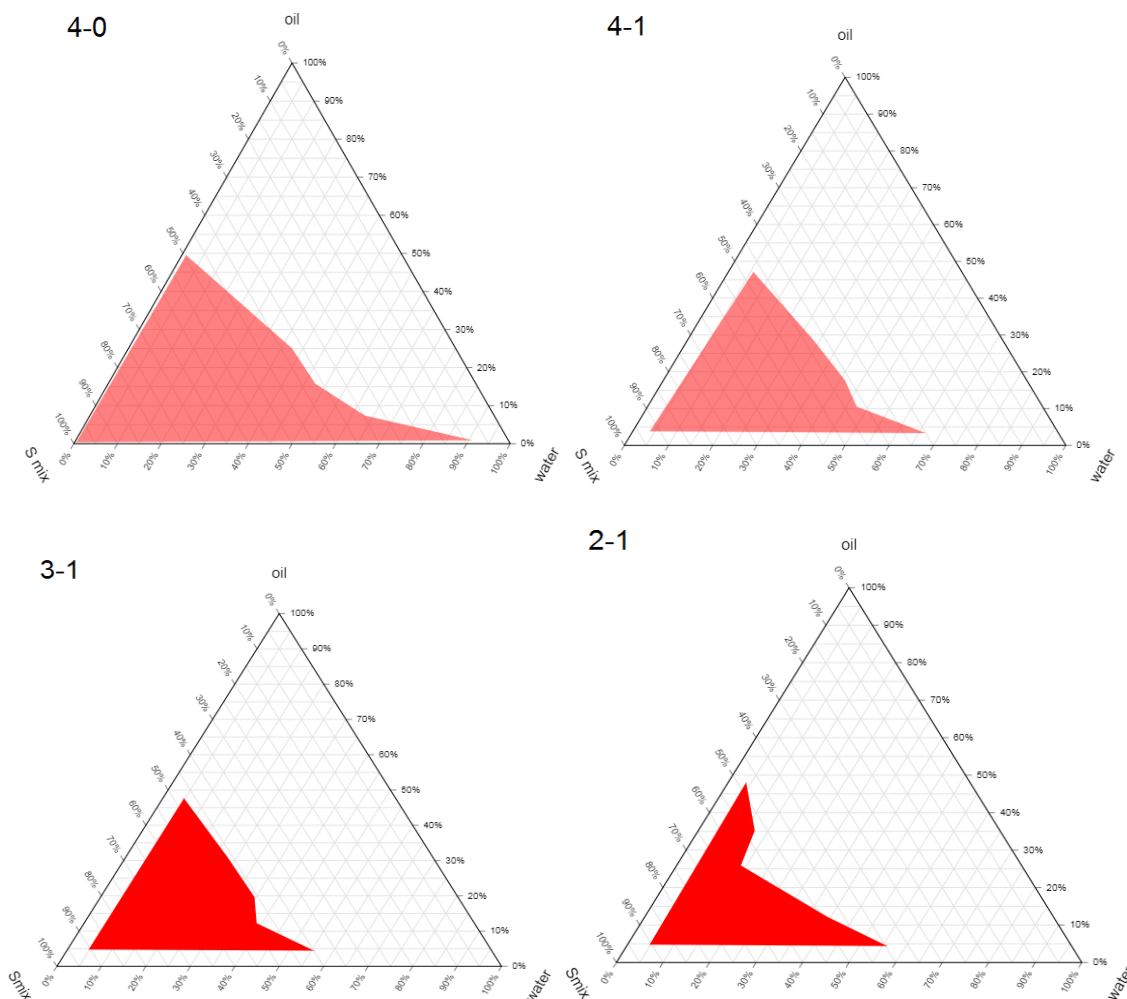
Pseudo-ternary Phase Diagrams Study

Ternary phase diagrams were constructed to identify the self-nanoemulsifying region and to select a suitable concentration of oil and surfactant for the development of SNEDDS. These phase diagram plays an important role in studying phase behavior of the prepared nanoemulsions. A simple ternary phase diagram comprises of oil, water, and Smix, each corner in the phase diagram represents 100% of that particular component. The surfactant is mixed with oil

phases at various ratios, and the mixture is titrated with aqueous phase (31).

In this study, oleic acid was used as the oil, while tween 20 act as a surfactant, and propylene glycol as a co surfactant. The Smix ratio between surfactant and co surfactant used were (1-2, 1-1, 2-1, 3-1, 4-1, and 4-0), the colored portion in the triangle represent the nano region, represented a transparent monophasic region. A wider nanoemulsion region indicates a better self-nanoemulsifying activity and perfect intermolecular interaction among the oil phase, Smix and water (32).

As seen from figure (3), increasing surfactant to co surfactant ratio form a larger nano region, similar results were reported by Grishma Patel et al (33), while at ratio(1-2) no nano-region observed, a white emulsion formed with the first drop of water titration, this may be due to an excessive amount of co-surfactant that may cause the system to become less stable for its intrinsic high-aqueous solubility and lead to an increasing droplet size as a result of the expanding interfacial film, as explained by the study of Jaydeep Patel et al (34).



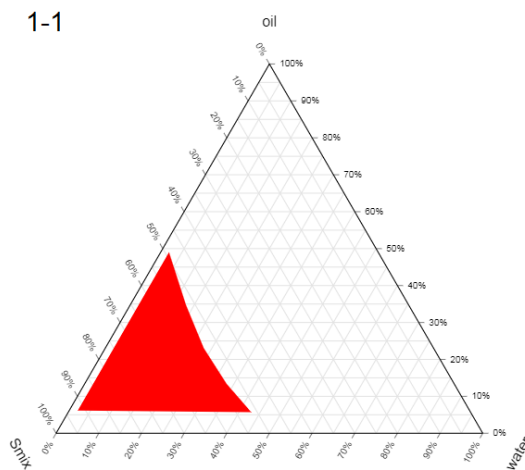


Figure (3): Pseudo-ternary phase diagrams plot (oleic acid, surfactant mix at different rates (Tween 20 and propylene glycol, and water) showing nanoemulsion (colored area)

Preparation of Ticagrelor Liquid Self-nanoemulsion Formulas

In this study, twenty formula was prepared, a quantity sufficient to make 10 unit dosage form was prepared for each formula, the weight for single unit dosage form is 0.590 gram.

The prepared formulas showed a clear, homogenous amber color liquid, with no precipitation or phase separation during storage for 3 days at room temperature before further evaluation.

Measurement of the Globules Size, Zeta potential, and Polydispersity Index(PDI)

Globule size of nanoemulsion affects strongly the rate and extent of drug release from formulas, also the stability of emulsion is affected by globule size, zeta potential and polydispersity index.

PDI describe the ratio of standard deviation to particle size average, a low PDI means narrow droplet size distribution, indicating homogeneity, uniformity of size distribution, and stability upon storage for long time (35).

Table (2): List the Globule Size, PDI, and Zeta Potential for Twenty Formulas

Formula code	Globule size (nanometer)	PDI	Zeta potential
F1	15	0.09	- 48
F2	50	0.122	- 54
F3	89	0.113	-60
F4	146	0.134	-72
F5	25	0.098	-44
F6	155	0.145	-49
F7	276	0.132	-62

F8	403	0.162	-67
F9	90	0.233	-47
F10	249	0.198	-52
F11	485	0.298	-65
F12	598	0.144	-70
F13	195	0.233	-49
F14	487	0.187	-54
F15	605	0.234	-66
F16	743	0.266	-72
F17	300	0.265	-43
F18	692	0.398	-59
F19	892	0.364	-66
F20	1097	0.376	-73

From results in table (2) ,it's obvious that all formulas has a uniform globular size.

The particle size of formulas increase significantly (P < 0.05) by increasing the oil-surfactant ratio, this is may be due to a decreased availability of surfactant/co-surfactant for localization around the oil/water interface of a droplet in order to decrease interfacial tension and stabilize the system (36).

From the obtained results, formulas that formed emulsion with globular size greater than 200 nm was excluded from further evaluation.

Thermodynamic Study

Thermodynamic study is conducted to ensure the stability of the prepared formulations after emulsion formation against different environmental conditions.

The centrifugation test is conducted to assess the SNEDDS stability after an emulsion is formed, against the

gravity force. Centrifugation describes the gravity force that occurs on the droplets. The small size of droplets can minimize the gravity force and Brownian motion on the particles that prevent the occurrence of phase separation (37).

Freeze-thaw cycle test is conducted to examine the effect of heating, cooling against the stability of SNEDDS formula. Heating and freezing are potential to damage or break the droplets of an emulsion, leading to the formation of emulsion with different globular size or may lead to the precipitation of drug (38).

Results shown in table (14) shows the results of thermodynamic study on the 8 formulations that passed the previous tests. The formulations (F1-F4) failed to pass this test and show a precipitation of drug after centrifugation and also in freeze thaw cycles, this may be due to absence of co solvent in these formulation.

Table (3): Thermodynamic Study Result for Prepared Liquid TCG-SNE Formulations

Formula Code	Centrifugation test	Heating-cooling cycles test 45 and 4 °C	Freeze-thawing cycles test -20 and 25 °C	Indication
F1	x	--	---	failed
F2	x	--	--	failed
F3	x	--	--	failed
F4	x	--	--	failed
F5	pass	pass	pass	pass
F6	pass	pass	pass	pass
F9	pass	pass	pass	pass
F13	pass	pass	pass	pass

In Vitro Drug Release

Dialysis is a technique based on the diffusion of small solutes from a concentrated solution to a lower-concentration solution of this solute through a semi permeable membrane until equilibrium is reached, which is widely used in studies of in vitro drug release studies. Particularly, the procedure to determine the in vitro velocity of the drug release from the nano-size systems consists of placing them in the form of dispersion in a buffer inside a dialysis bag, and at certain intervals, aliquots of the receptor medium in which the dialysis bag is submerged are taken, which are replaced by the same volume of fresh receptor medium preheated to 37°C, temperature at which these studies are generally performed, in order to keep the volume of the receptor medium constant (38).

This dialysis bag method was employed to determine the free soluble drug molecule that is not entrapped in oil globule or in micelle, the ticagrelor formulation that pass this test, indicates the improvement of solubility of the drug in aqueous media, but not the permeation which class 4 drug like ticagrelor suffer from, which will further be studied in vivo drug absorption (39).

Figure (4) illustrates the release of drug from the best 4 formulas during 120 minutes. the fastest and highest release profile was obtained from formula F5 (96 %). While the other formulas shows a less percentage of drug release F6(60), F9 (80), and F 13 (72). while pure powder of ticagrelor show only 10 % of drug release.

From data obtained after releasing the 4 formulas, there was a significant difference between the release of drug from F5 and other formulas (p < 0.05).

The results obtained from this study, show that the globular size has a great effect on the release of drug from dialysis bag. Therefore the formula with smallest globular size shows the highest release.

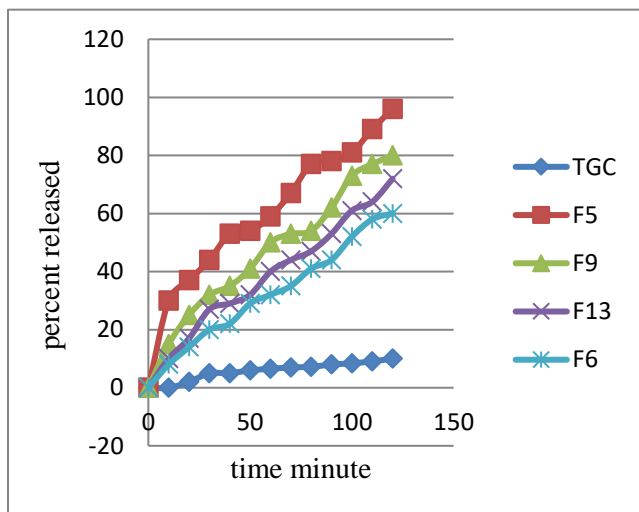


Figure (4): Release of ticagrelor self emulselfying formulations in 0.1N HCl containing 1% tween 80

Selection of Optimum Liquid Ticagrelor-loaded SNE Formula

According to the results obtained from these studies, F5 which consists of (10 % oleic acid, 72% tween 20, 18% propylene glycol) was chosen as the best formula, this formula passed all thermodynamic tests successfully, with the smallest globular size and acceptable PDI and zeta potential and showed the highest release of drug.

In Vivo Drug Release

These dose–exposure–response relationships and thus the dose of a drug required to achieve a certain effect are determined by the drug’s pharmacokinetics and pharmaodynamic properties. Pharmacokinetics describes the time course of the concentration of a drug in a body fluid, preferably plasma or blood that results from the

administration of a certain dosage regimen.

Pharmacodynamics describes the intensity of a drug effect in relation to its concentration in a body fluid, usually at the site of drug action.

The change in clotting time of blood gives an idea about the pharmacological response to the drug since ticagrelor act as an anti- platelet drug (40). Difference in

prolongation time and onset of action between tested samples give an indication that there is a difference in the rate and extent of drug absorption.

The results of this experiment are illustrated in table (4). The mean results of group member was taken with standard deviation was considered .

Table (4): Clotting Time Change in Rats After Administration of Drug Suspension and F5

	Zero time	30 min	1 hour	1.5 hour	2 hour	2.5 hour
Drug suspension	20 se	23 sec	25 sec	25 sec	26 sec	25 sec
F 5	20 sec	320 sec	400 sec	460 sec	500 sec	490 sec

From the above results, the T max for ticagrelor is 2 hr , which is the same T max mentioned in drug references (41), there is a significant difference in clotting time between drug suspension and F5 ($p < 0.05$), indicating that F5 improved drug absorption.

Conclusion

The results from this study showed that ticagrelor was easily prepared as SNE formula by choosing a suitable oil and surfactant mixture by applying simple mixing technique. The best formula contained 10% oil , 90 % surfactant mixture in 4:1 ratio (tween 20/ propylene glycol) showed an improvement in aqueous release rate of drug in comparison with pure powder of drug about 10 time faster, and longer inhibition in platelet action and fibrin clot formation than pure powder of drug. Formula can be filled in a soft gelatin capsule or solidify and fill in a hard gelatin capsule or compressed as tablets.

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