A SUPERSATURATED SELF-NANOEMULSIFYING SYSTEM FOR ENHANCED ORAL BIOAVAILABILITY OF TICAGRELOR: A NOVEL APPROACH TO OVERCOME SOLUBILITY BARRIERS

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ABSTRACT

The target of the current study is to achieve better drug stability and dissolution by developing self-nanoemulsifying super saturable drug delivery system or S-SNEDDS.

Goal: Ticagrelor (TCG) is put to use to forestall platelet aggregates in patients suffering from acute coronary syndrome; however, it's in vivo effectiveness is limited by its minimal accessibility and insoluble properties. For the purpose to enhance TCG's absorption by mouth and antiplatelet therapy efficacy, this study set out to create an optimal TCG-loaded supersaturated drug method of distribution that self-emulsifies (S-SNEDDS).

The materials and strategies: To recognize the best oils, surfactants, and cosurfactants, soluble and emulsification tests were carried out. The percentage that consists of any component used in the S-SNEDDS mixture was optimized using pseudo ternary schematic for phases in order to produce the best possible physical properties, such as high transmittance, minimal precipitation, tiny droplet size, and excellent concentration of TCG in S-SNEDDS.

Findings: When in contrast to TCG in Brilinta® (a commercial product), the modified TCG-loaded S-SNEDDS TCG-S-SNEDDS production, which constitutes 10.0% Capmul MCM (oil), 8% Tween 80 (surfactant), and 5% Propylene glycol (cosurfactant), greatly enhanced TCG dissolving in a variety of mediums. Compared to raw TCG solution, TCG-S-SNEDDS showed greater incorporation into cells and penetration in Caco-2 cells.

In conclusion: These findings imply that the created TCG-S-SNEDDS may be effectively applied as a means of achieving the increased digestibility and anti-platelets action of TCG.

Keywords: *effective optimization, its accessibility, aggregation of platelets, the antiplatelet success, ticagrelor, S-SNEDDS.*

1.INTRODUCTION

Owing to its painless application ,high patient acceptance and simplicity, oral medication is the most used technique for achieving pharmacological effects for effective illness treatment .Poor water solubility is a very difficult characteristic of many oral medications ,which can lead to both limited and highly variable drug absorption .Achieving the minimum threshold concentration required to produce therapeutic drug plasma levels is essentially made more difficult by limited absorption of the unprocessed medicines ,which eventually results in low bioavailability .Therefore ,the topic of how to address the increasing difficulty of creating appropriate formulations that significantly improve the solubility of weakly water-soluble active pharmaceutical ingredients (APIs) following intake by mouth emerges.

Gordan Amidon's 1995 implemented System of classification for biopharmaceutics (BCS) divides four classes of medications (class I-IV) according to the idea that a drug's oral bioavailability is primarily determined by its solubility and its permeability properties (Figure 1). Drugs classified as category II have a large permeability as well as poor solubility, while the fourth-class medications, on the other hand, are weakly soluble and inadequately permeable. Category II and IV medications are therefore ideal subjects for solubility improvement research.

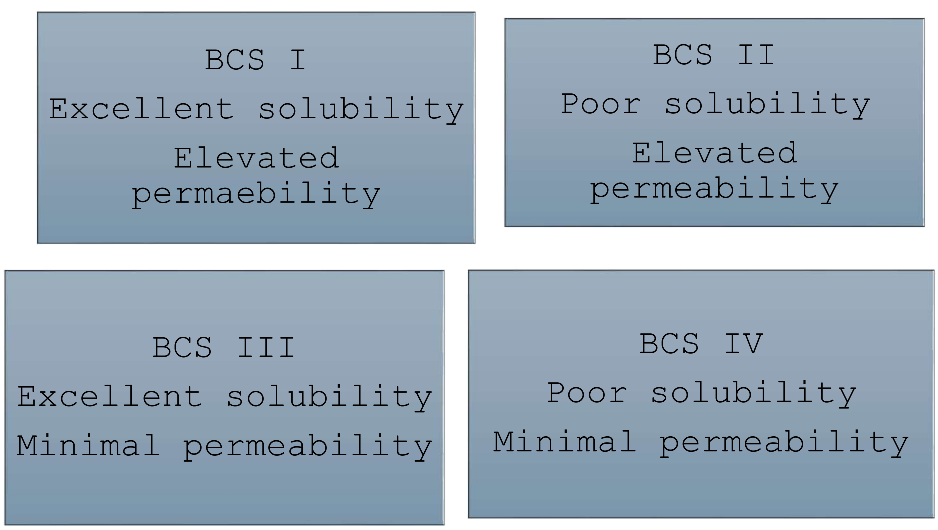

Figure 1: The System for classifying biopharmaceuticals (BCS) is depicted.

Among the main causes of myocardial infarction worldwide is acute coronary syndrome (ACS). It is a primary cause of hospitalizations and among the main reasons for mortality in our modern way of living. Platelets play a crucial part in atherothrombosis. Antiplatelet medications are very beneficial as treatments for thromboembolic disorders. Recent years have seen the development of strong inhibitors of platelet function, which have reduced the rates of restenosis and thrombosis following vascular stenting and angioplasty procedures. The gold standard antiplatelet medication for preventing myocardial infarction and other thromboembolic events has been aspirin.

Another class of antiplatelet drug known as thienopyridenes (clopidogrel, prasugrel ,and ticlopidine) work by blocking the P2Y12 receptor on the surface of platelets to permanently prevent adenosine diphosphate-induced platelet aggregation .Even with close monitoring ,timely treatment of cardiac instability, thrombolytic activity, acute invasive procedures, and dual antiplatelet medication with aspirin and thienopyridines, one in three ACS patients die from repeat MI. Clopidogrel is the thienopyridine that is most frequently administered in ACS patients. It does, however, have certain restrictions. Patients who may need surgery or other intervention may be at higher risk of bleeding because it results in irreversible platelet suppression.

Additionally, because of pharmacogenomic variations, the conversion rate varies between individuals and necessitates hepatic conversion to an active metabolite, which postpones the start at work. At fairly high mean concentrations, clopidogrel prevents the aggregation of platelets caused by ADP. Therefore, a novel antiplatelet aggregation at moderately high mean values. Therefore, a novel antiplatelet agent free of these problems is required. Ticagrelor is anticipated to provide individuals with ACS with improved antiplatelet effects without these drawbacks. In order to elevate Ticagrelor's good stability and dissolution, the primary goal of this research is to bring about a self-nano emulsified system of super saturable drug delivery.

1.1. Over Supersaturated self-Nano-emulsifying system of drug delivery

The S-SNEDDS are finally homogeneous blend as oils, cosurfactants, as well as surfactants that, when gently shaken or stirred in aqueous settings, can generate nano emulsions (usually less than 100 nm). Their goal is to make drugs that aren't very soluble in water more bioavailable orally.

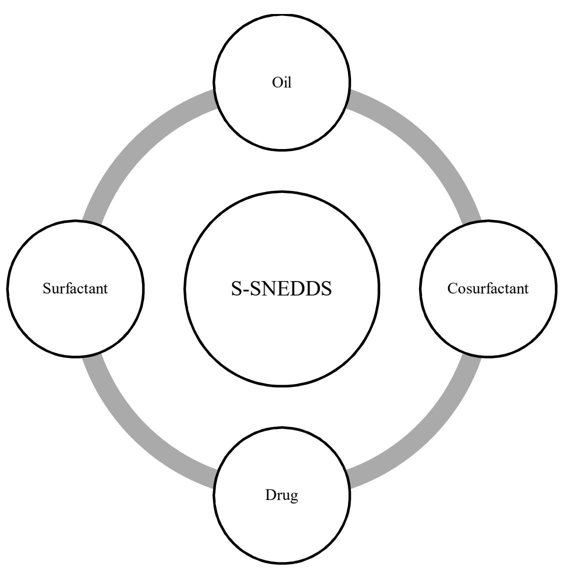

Figure 2: S-SNEDDS components are depicted

1.1.1. Ticagrelor-Loaded Supersaturated SNEDDS Benefits:

1. Better Solubility and Bioavailability: By encasing poorly soluble medications, such as ticagrelor, in a nano emulsion, S-SNEDDS can improve their solubility and bioavailability, facilitating improved absorption and therapeutic effectiveness.

2. Enhanced Antiplatelet Activity: The SNEDDS formulation can increase ticagrelor's antiplatelet activity, it is necessary for patients with acute coronary syndrome to stop accumulation of platelet0073, by increasing the drug's solubility and bioavailability.

3.Controlled Drug Release: By facilitating controlled drug release, SNEDDS may be able to reduce the requirement for frequent doses and produce a more lasting therapeutic impact.

1.1.2. Queries with Ticagrelor-Loaded SNEDDS with supersaturation:

1.Toxicity of Surfactants: SNEDDS formulations frequently include high quantities of surfactants, which at high dosages may irritate the stomach or be poisonous.

2.Complexity of Formulation: In order to produce the best Nano emulsion qualities, SNEDDS formulation can be complicated, involving careful selection of oils, surfactants, and cosolvents. SNEDDS

3.Stability Problems: SNEDDS formulations may experience stability problems, such as emulsion destabilization or drug precipitation, particularly during storage and transit.

1.1.3. Utilization of Ticagrelor-Loaded SNEDDS with supersaturation

1. Improved Oral Bioavailability: Ticagrelor's limited solubility in water restricts its absorption power. By keeping the gastrointestinal (GI) tract supersaturated, S-SNEDDS can greatly increase its rate of dissolution and bioavailability. This reduces dosage-related adverse effects and improves therapeutic efficacy at a lower dose.

2. Quick Start in Acute Coronary Syndrome (ACS): Patients with ACS need to have their platelets inhibited right away. S-SNEDDS is appropriate for emergency cardiovascular applications since it guarantees a quicker absorption and commencement of action than traditional formulations.

3. Better Drug Stability- The lipid-based nano emulsion keeps ticagrelor safe from oxidation and hydrolysis, which prolongs its shelf life and keeps it potent. Resolves problems with food's impact on drug absorption, guaranteeing steady pharmacokinetics.

4. Condensed Interpatient Divergence - P-glycoprotein (P-gp) and CYP3A4 enzymes affect ticagrelor metabolism; S-SNEDDS can get around these restrictions by encouraging lymphatic transport, which results in more consistent plasma drug concentrations.

2. MATERIALS

- Medium-chain triglyceride oil, or Capmul MCM
- The surfactant Tween 80
- Propane-1,2-diol purified LR (Propylene glycol)
- The medication ticagrelor
- The precipitation inhibitor known as HPMC (hydroxypropyl methylcellulose)
- Water that has been distilled
- Optional ethanol

Tools

- ❖ Vortex mixer
- ❖ Ultrasonic mixer
- ❖ Mechanical stirrer
- ❖ Lyophilizer Freeze Dryer (Digital Pirani Gauge, Model: DPRG-1GH)
- ❖ FTIR spectrophotometer (Shimadzu IR Spirit)
- ❖ FTIR pellet maker (Athena Technology ISO 9001:2015, Model no: AT HP 15, Capacity 15 ton)
- ❖ Scanning Electron Microscope (JEOL, JSM-IT200 Purchased under RUSA)
- ❖ Zeta potential analyzer (Malvern Zetasizer)

3.METHODOLOGY

Preparation of a Supersaturated Ticagrelor Emulsion and Lyophilization

Begin Step 1: Weighing the Oily Phase

By carefully weighing 10 mL of Capmul MCM, which serves as the oily phase, into a boiler tube. Ensure the measurement is precise, as any deviation could impact the stability and consistency of the final emulsion. A medium-chain monoglyceride is Capmul MCM. that acts to be a lipid carrier, helping to enhance drug solubility and absorption.

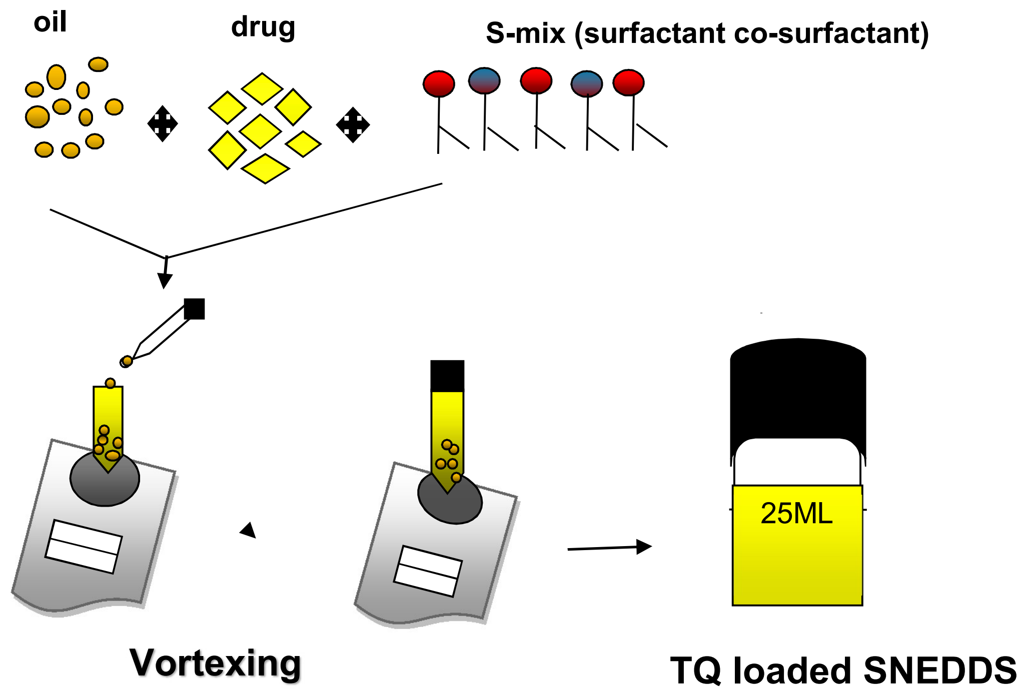

Figure 3: Diagrammatic illustration of the homogeneous blend with ticagrelor in the Cosurfactants, surfactants among others and the oil phase employed to construct S-SNEDDS that, when vortexed, produces a very fine emulsion.

Step 2: Incorporation of Ticagrelor into the Oily Phase

Once the oily phase is prepared, gradually introduce 500 mg of ticagrelor into the boiler tube over a period of 5 to 10 minutes. Use a vortex mixer to aid in the proper dispersion of ticagrelor within the oil. The vortex mixing should be continuous and vigorous, ensuring that the drug particles are evenly distributed throughout the oil and do not form clumps or sediment. This step is crucial as it enhances drug solubilization and prevents phase separation.

Figure 4: This figure illustrates a vortex mixture

Step 3: Preparation and Addition of the mixture of Co-Surfactant and surfactants (s-mix)

To improve the stability and solubility of the emulsion, a mixture of Co-Surfactant and surfactants (s-mix) is prepared. This is done by accurately measuring:
- 5 mL of propylene glycol (acting as the co-surfactant)
- 8 mL of Tween 80 (acting as the surfactant)

These two components are thoroughly mixed to create a homogeneous s-mix, which plays a crucial role in reducing interfacial tension and ensuring proper emulsification of the formulation.

Once the s-mix is prepared, it is slowly incorporated into the drug-containing oily phase. The addition should be done gradually while stirring to prevent sudden phase separation and to allow the surfactants to interact effectively with the drug-oil mixture. The slow addition ensures that the formulation remains homogenous and promotes proper self-emulsification.

Step 4: Sonication for Particle Dissolution

Following the incorporation of the s-mix into the drug-oil phase, the boiler tube containing the mixture is placed in an ultrasonicator for five minutes. The ultrasonic waves help break down any remaining drug particles and facilitate their complete dissolution in the formulation. Sonication enhances uniform dispersion and reduces the particle size, leading to a more stable emulsion with improved bioavailability.

Figure 5: This figure illustrates the ultrasonicator

Step 5: Preparation of the Aqueous Phase

For the aqueous phase, 1 gram of hydroxypropyl methylcellulose (HPMC) is dissolved in distilled water. HPMC acts as a stabilizer, increasing the viscosity of the aqueous phase and preventing phase separation.

Once the HPMC solution is prepared, it is kept under a mechanical stirrer in a plastic beaker (to prevent the risk of glass breakage during stirring).

Figure 6: This illustration shows how a mechanical stirrer constructs emulsion

Step 6: Emulsification Process

With the aqueous phase being stirred at a controlled speed of 3500 rpm, the drug-containing oily phase and s-mix mixture is gradually added while maintaining continuous stirring. This process should be done slowly and steadily to allow proper emulsification. The mechanical stirring continues for one hour and thirty minutes to assure the development of a white emulsion with a uniform droplet size distribution. The prolonged stirring facilitates the complete incorporation of all components, leading to a stable emulsion.

Step 7: Induction of Supersaturation and Lyophilization

To obtain a supersaturated solution, the prepared emulsion is rapidly cooled and allowed to rest for one day. The cooling process reduces molecular mobility, helping to maintain supersaturation without premature precipitation of the drug.

Finally, the supersaturated solution undergoes lyophilization (freeze-drying) for one week. During this process, water is removed through sublimation, resulting in a dry and stable product.

Lyophilization ensures that the final formulation remains stable for an extended period, improving its shelf life and handling properties.

Figure 7: This figure displays a Lyophilizer

Fabrication of Supersaturated self-nanoemulsifying drug delivery system loaded with Ticagrelor

S.NO	Required components	Role	F1	F2	F3
1.	Ticagrelor	Active pharmaceutical ingredient	0.09g	0.2g	**0.5g**
2.	Capmul MCM	Oil (Medium-chain mono-and diglycerides)	8g	5g	**10g**
3.	Tween 80	Surfactant	7g	3g	**8g**
4.	Propylene glycol	Cosurfactant	5g	2g	**5g**
5.	Hydroxy propyl methyl cellulose (HPMC)	Precipitation inhibitor	1g	0.1g	**0.45g**
6.	Distilled water	Base	10ml	10ml	**1**

Table 1: It presents the required components along with their corresponding formulations

4. ASSESSMENT OF TICAGRELOR LOADED SUPERSATURATED SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM

Using a variety of sophisticated analytical methods, the improved ticagrelor-loaded S-SNEDDS formulation was physiochemically characterized. In order to verify the chemical compatibility and lack of any notable structural alterations, Infrared Fourier transform spectroscopy (FTIR) was utilized in order to examine potential interactions while performing ticagrelor as well as additives. This crystalline drug's change into an unstructured or molecularly dispersed state within the nanoemulsion system was observed by scanning electron microscopy (SEM), which also shed light on the surface morphology. A droplet's size distribution was ascertained by particle analysis, which revealed the nanoscale characteristics necessary for enhanced solubility and bioavailability. Studies on zeta potential were also conducted to assess the consistency and surface charge of that nanoemulsion system.; the results indicated that the formulation had good physical stability. The efficacious design and utility of S-SNEDDS as an effective ticagrelor delivery system were validated by these thorough assessments.

1. Infrared Fourier transform spectroscopy (FTIR)

2. Electron- beam scanning Microscopy (SEM)

3.Zetapotential

4.1. FTIR Infrared Fourier transform spectroscopy

Shimadzu IR Spirit FTIR spectrophotometer, had been employed to capture the S-SNEDDS powder samples FTIR emission spectrum and that of pure ticagrelor. Using FTIR Pellet Maker (Athena Technology ISO 9001:2015, Model no: AT HP 15, Capacity 15 ton), sample (TCG-S-SNEDDS-0.004g) had been pressed with potassium bromide (KBR-0.036 g) at a rate of 1 ton/cm2 to create the disc. The range of the spectral scanning was 4000–400 cm−1.

Figure 8: The FTIR pellet maker used in this research is shown

Figure 9: the FTIR spectrophotometer used in this research is depicted

Effective methods like FTIR, it assesses the medication-excipient interactions in the creation by analyzing the drug's bands with the composition. The chemical interaction between the studied compounds may be the cause of any shifts such as non-appearance or spectra fall. Figure 10 and 11 depicts the FTIR spectra of Ticagrelor and S-SNEDDS respectively.

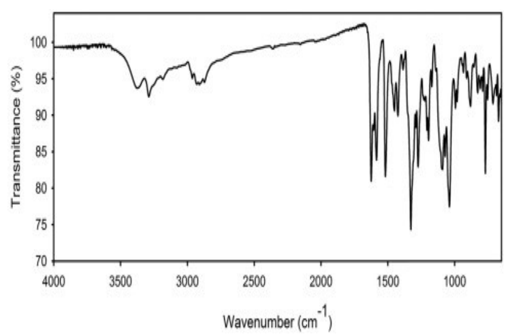

Figure 10: It illustrates the Fourier transform spectroscopy of Ticagrelor Drug

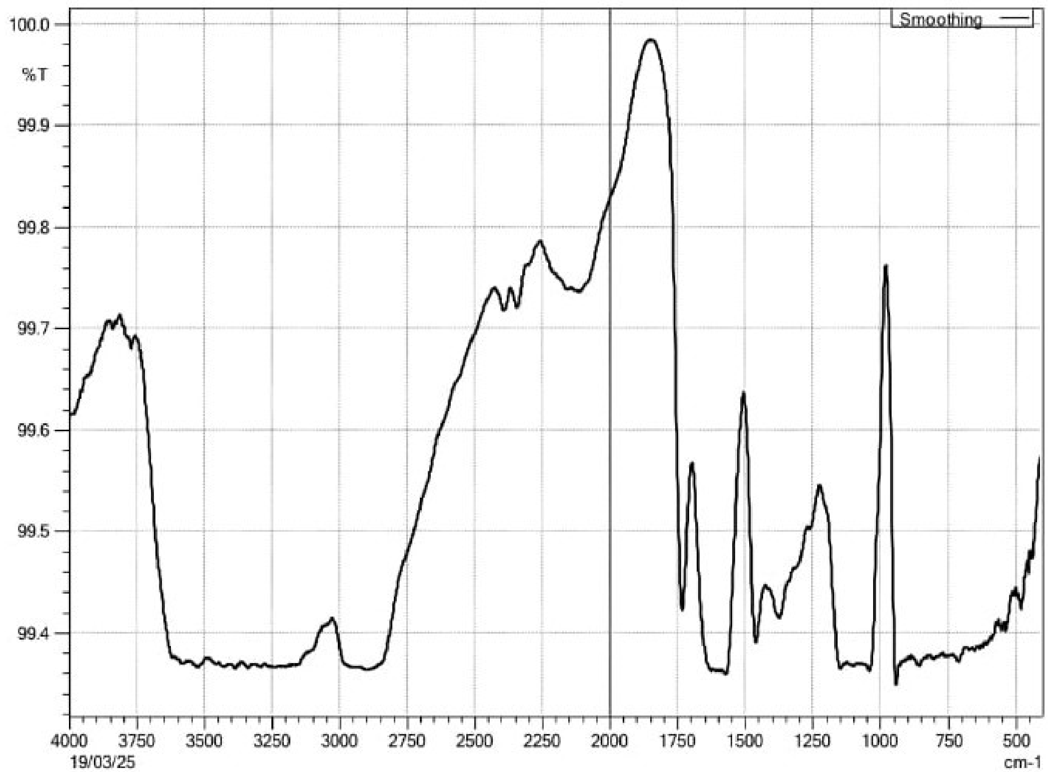

Figure 11: It illustrates the Fourier Transform spectroscopy of Ticagrelor loaded supersaturated self-nanoemulsifying drug delivery system.

The Ticagrelor-filled extremely saturated self-nanoemulsifying drug delivery system (S-SNEDDS) showed distinctive peaks in its FTIR spectrum that matched different functional groups found in the formulation's constituent parts. O-H stretching vibrations are represented by a broad and powerful peak seen at about 3400 cm^{-1}. These vibrations are caused by the presence of hydroxyl groups from Tween 80, propylene glycol, and potentially ticagrelor. Peaks at around 2920 cm^{-1} are a sign of C–H stretching vibrations from aliphatic –CH_2 and –CH_3 groups, which most likely come from surfactants and the lipid component Capmul MCM.

The carbonyl (C=O) stretching vibration, which is typical of the ester groups in Capmul MCM and potentially of the ester functionalities in the medication or excipients, is linked to a prominent absorption band at about 1740 cm^{-1}. The C=C stretching from the aromatic rings or amide-related vibrations, which are commonly seen in the Ticagrelor structure, can be connected to the peak about 1640 cm^{-1}. The existence of Tween 80 and propylene glycol is further confirmed by additional peaks in the 1100–1000 cm^{-1} range, which correspond to C–O stretching vibrations, which are typical in ether and alcohol groups. The presence of aromatic moieties in Ticagrelor is supported by weak to medium peaks in the 800–600 cm^{-1} region, which are ascribed to out-of-plane bending vibrations of aromatic C–H bonds.

Ultimately, there were no notable changes or disappearances of distinctive peaks in the Spectroscopic study, confirming the medication and additives' good inclusion in the finished product.

IR Absorption Band (cm^{-1})	**Peak Strength**	**Characteristic Moiety**	**Interpretation**
~3400	Strong/broad	-OH (hydroxyl)	O–H stretching (from Tween 80, PG, or Ticagrelor)
~2920	Medium	$-CH_2/-CH_3$(alkyl chains)	C–H asymmetric/symmetric stretching (lipid components)
~1740	Strong	C=O (ester, acid)	Carbonyl stretching (Capmul MCM, possible ester groups)
~1640	Medium	Aromatic=C or amide	C=C stretching or amide bending (Ticagrelor)
~1450-1370	Weak-medium	CH_3/CH_2 bending	C–H bending vibrations
$\sim 1100 - 1000$	Strong	C-O-C or C-O (ether/alcohol)	C–O stretching (Tween 80, PG)
~720-600	Weak-medium	Aromatic/alkene C-H bending	Out-of-plane bending (Ticagrelor aromatic regions)

Table 2: The FTIR spectra and interpretation for Ticagrelor-loaded S-SNEDDS are detailed.

4.2. Electron- beam scanning Microscopy (SEM)

Electron- beam scanning Microscopy (SEM) (JEOL, JSM-IT200 Purchased under RUSA) aids in visualizing this morphology and particle size distribution of the nano emulsion droplets in the assessment of ticagrelor- filled supersaturated self- nano emulsified system of drug delivery (S-SNEDDS), verifying the stability and production of nano-sized particles.

Figure 12: The SEM instrument utilized for surface morphology evaluation is depicted

The Task of SEM:

Morphology: The spherical or nearly spherical form of the nanoemulsion droplets is confirmed by SEM images, which show their shape and structure. This is essential for effective medication solubilization and absorption.

Particle's size Distribution: To ensure that the nanoemulsion droplets fall within the intended nano-range (usually <100-200 nm) for improved absorption.

Stability: By tracking variations in droplet size or shape over time, SEM can be used to evaluate the SNEDDS formulation's long-term stability.

Ticagrelor's surface morphology and physical condition in the supersaturated self-nanoemulsifying drug delivery system (S-SNEDDS) were observed using SEM. The formulation appeared smooth, spherical, and amorphous in the figure (13,14,15,16,17), with no discernible drug crystals. This suggests that Ticagrelor was successfully dissolved and that a stable nano emulsion system was formed.

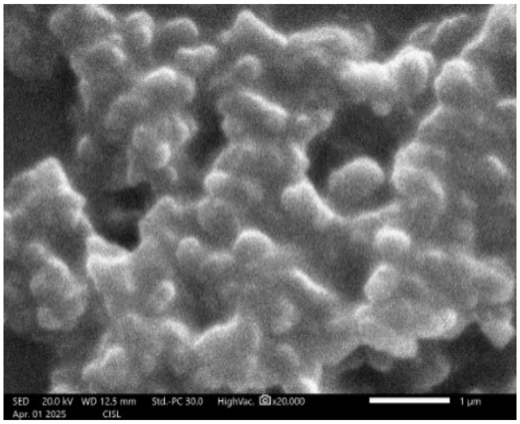

Figure [13]: SEM scan at 20,000× magnification (Scale bar: 1 μm)

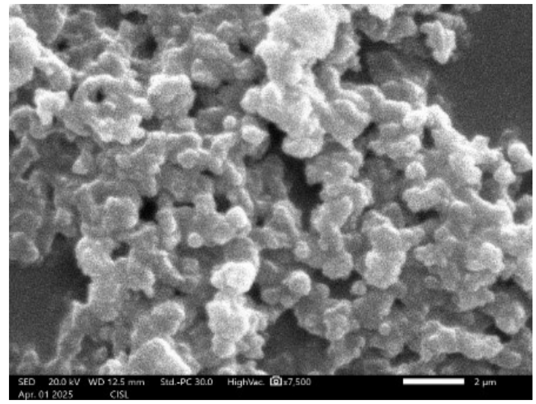

Figure [14]: SEM scan at 10,000× magnification (Scalebar: 1 μm)

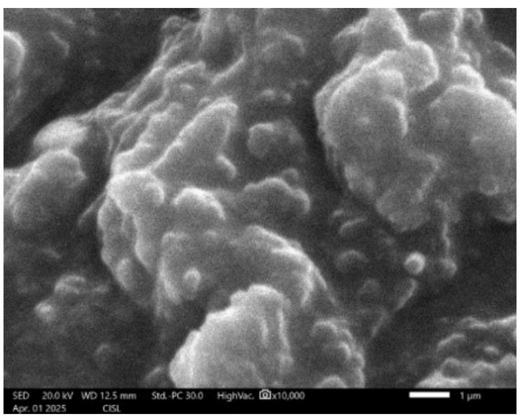

Figure [15]: SEM scan at 10,000× magnification (Scale bar: 1 μm)

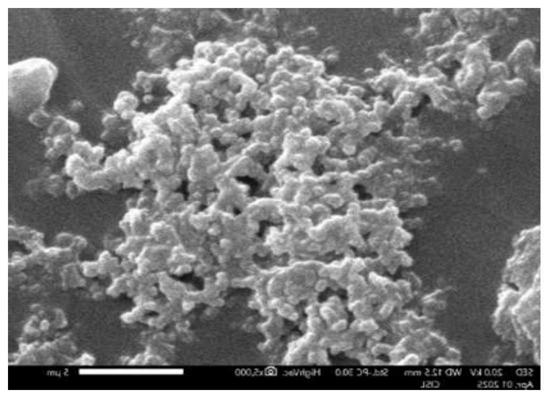

Figure [16]: SEM scan at 5000× magnification (Scale bar: 5 μm)

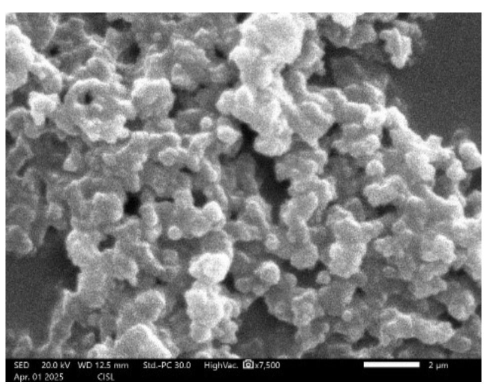

Figure [17]: SEM scan at 7500× magnification (Scale bar: 2 μm)

4.3. Zeta potential

A method for determining the surface charge of particles (such droplets, emulsions, or nanoparticles) in a system is called zeta potential evaluation. This value shows the probability of particle dispersion or aggregation, which sheds light on the formulation's stability.

The electrical potential at a particle's sliding plane in a liquid is known as the zeta potential. Millivolts (mV) are used to measure it. Particles strongly oppose one another; hence a high absolute value (usually > +30 mV or < -30 mV) indicates good stability. Poor stability is indicated by a low absolute value (nearer 0), and particles may silt or agglomerate. For TCG-S-SNEDDS, the ζ potential was identified to be between -9.92 and -6.23 millivolts.

Dynamic light scattering (DLS) equipment typically uses methods such as electrophoretic light scattering.

The surface charge potential has been detected using a dynamic the scattering of light device called the Malvern Zetasizer Nano with the goal to assess the surface charge as well as colloidal stability of the produced Ticagrelor-loaded S-SNEDDS. Prior to measurement, samples were suitably diluted with deionized water to prevent multiple scattering effects. At 25°C, each measurement was made three times, and the average zeta potential value was noted.

Zeta Potential Report
v2.3

Malvern

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Sample Details

Sample Name:	N-7851A N seed zeta 2
SOP Name:	mansettings.nano
General Notes:	

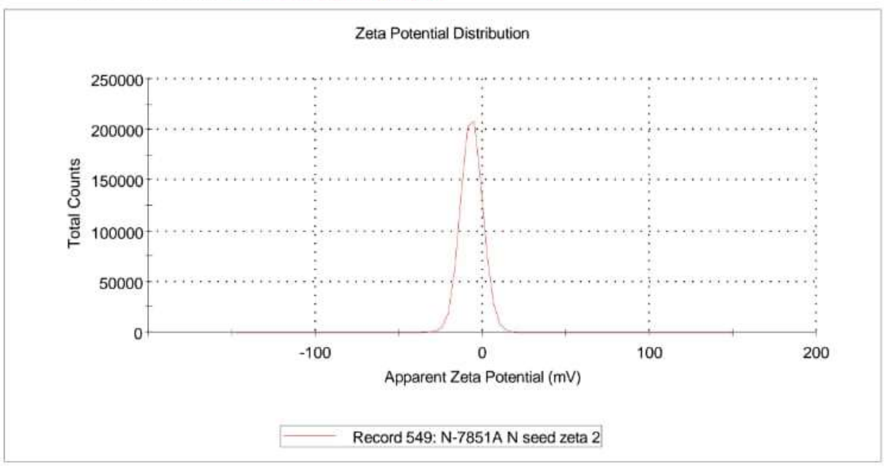
File Name:	Apr 2025.dts	**Dispersant Name:**	Water
Record Number:	549	**Dispersant RI:**	1.330
Date and Time:	Friday, April 25, 2025 1:45:30 PM	**Viscosity (cP):**	0.8872
		Dispersant Dielectric Constant:	78.5

System

Temperature (°C):	25.0	**Zeta Runs:**	22
Count Rate (kcps):	105.5	**Measurement Position (mm):**	4.50
Cell Description:	Surface zeta potential	**Attenuator:**	5

Results

			Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	-6.38	**Peak 1:**	-6.38	100.0	6.66
Zeta Deviation (mV):	6.41	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm):	0.141	**Peak 3:**	0.00	0.0	0.00
Result quality :	See result quality report				



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Zetasizer Ver. 7.13
Serial Number : MAL1054413

File name: Apr 2025.dts
Record Number: 549
25 Apr 2025 1:46:18 PM

Figure 18: The Zetapotential analysis S-SNEDDS is depicted

The improved formulation's zeta potential was -6.38 mV, which suggests rather poor electrostatic stability. The creation with surface charge potential values above +30 millivolts or below -30 millivolts are often regarded as electrostatically stable. The addition of a nonionic surfactant (Tween 80) is anticipated to offer significant steric stabilization, contributing to the physical stability of the nano emulsion droplets, even though the absolute value is lower than the traditional stability threshold. Because of the combination steric and electrostatic effects, the formulation is regarded as stable even with a low zeta potential. According to these findings, the created S-SNEDDS formulation is probably going to retain a respectable level of physical stability both during storage and while diluted in the gastrointestinal environment.

5. RESULTS AND DISSCUSSION

The research effectively created a supersaturated self-nanoemulsifying drug delivery system (S-SNEDDS) to improve the inhaled bioavailability and solubility of the poorly soluble antiplatelet medication ticagrelor (TCG). Capmul MCM was shown to be the best oil phase through systematic screening, while the best surfactant and cosurfactant were Tween 80 and propylene glycol, respectively. The strength of the pseudo-ternary phase diagram technique was confirmed by the optimized formulation, which included 10.0% Capmul MCM, 8% Tween 80, and 5% propylene glycol. It showed outstanding the emulsion efficiency, high transmittance, and little drug precipitation. When compared to pure TCG and market Brilinta®, testing showed that the TCG-S-SNEDDS greatly increased drug solubility across a range of media.

Additionally, the modified Nano emulsion had smaller droplets, suggesting increased absorption capacity and better physical stability. The efficacy of TCG-S-SNEDDS to improve gastrointestinal absorption was further highlighted by cellular uptake tests, which showed that it increased cellular assimilation and permeability which are in Caco-2 cells.

The supersaturated self-nanoemulsifying drug delivery systems (S-SNEDDS) of ticagrelor were effectively produced utilizing the lyophilization procedure. The amounts of the active medicinal component (ticagrelor), oil (Capmul MCM), surfactant (Tween 80), co-surfactant (propylene glycol), precipitation inhibitor (HPMC), and distilled water varied between formulations F1, F2, and F3. In order to guarantee the stability, consistency, and effectiveness of the finished product, each stage of the formulation process was essential. The emulsions produced by all three compositions had different physical and optical characteristics. The most stable and aesthetically consistent white emulsion was created by Formulation F3, which included the highest concentrations of ticagrelor (0.5 g), oil (10 g Capmul MCM), and surfactants.

This showed a well-formed nanoemulsion system with fine droplet dispersion, which was explained by the efficient use of HPMC as a stabilizing agent and the ideal lipid to surfactant/co-surfactant ratio. However, following rest, F1 (which had the lowest drug concentration) had indications of mild creaming and phase separation, indicating inadequate stability and emulsification. Although it was less stable than F3, F2, which contained moderate amounts of components, displayed superior qualities to F1.

To get homogeneous dispersions, the emulsification process—which included mechanical stirring, sonication, and vortex mixing—was essential. While sonication further decreased particle size and improved solubility, vortex mixing allowed ticagrelor to disperse uniformly in the oily phase. A uniform droplet size was achieved in all formulations thanks to the progressive and regulated emulsification made possible by the mechanical stirring at 3500 rpm for 1.5 hours. It was clear how crucial it was to add the s-mix (propylene glycol and Tween 80) gradually because this reduced abrupt phase separation and encouraged consistent component interaction. The effectiveness of self-emulsification depended on the surfactants' ability to lower interfacial tension.

The methods were quickly cooled after emulsification in order to create a supersaturated condition. In order to preserve optimum medication solubility without crystallization, this procedure was crucial. F3 showed no signs of drug precipitation after a 24-hour rest period, indicating effective supersaturation. All formulations yielded dry, porous powders after the lyophilization process. F3, on the other hand, showed a more consistent and stable matrix, indicating improved structural integrity and entrapment. Its potential for oral or rehydrated use in clinical settings was highlighted by the ease with which the freeze-dried powder could be reconstituted.

In the drug's formulation, every element had a unique and important role: The amount of ticagrelor that Capmul MCM added had a direct effect on the emulsion's stability and clarity. Higher doses of Tween 80 and propylene glycol reduced interfacial tension and guaranteed effective emulsification. During the supersaturation and freeze-drying stages, HPMC effectively avoided drug precipitation, particularly at the higher concentration in F3. Using distilled water as the aqueous base promoted even mixing and acted as a droplet formation medium.

The formulation contained all of Ticagrelor's and the excipients' primary functional groups, according to the FTIR data. The medicine and other substances remained stable and did not react with one another because there were no significant changes in the peaks. The successful loading of ticagrelor into the S-SNEDDS is confirmed by this.

The optimized Ticagrelor-loaded S-SNEDDS showed a homogeneous and smooth surface morphology with no discernible drug crystals, according to Scanning Electron Microscopy (SEM) analysis. This suggests that the drug was successfully encapsulated in the nano emulsion system. Ticagrelor's amorphous dispersion within the formulation was validated by the lack of crystalline structures, which enhanced its solubility and dissolving properties.

Low electrostatic stability was indicated by the optimized Ticagrelor-loaded S-SNEDDS formulation's zeta potential, which was measured at -6.38 mV. Surfactants like Tween 80 provide steric stabilization despite the comparatively low zeta potential, indicating that the formulation will maintain its physical stability throughout time and during dilution in the gastrointestinal tract

6. CONCLUSION

The research addressed the limited bioavailability and poor solubility of ticagrelor by effectively developing and optimizing a supersaturated self-nanoemulsifying drug delivery system (S-SNEDDS). In comparison to both raw TCG and the commercial Brilinta®

formulation, the optimized TCG-S-SNEDDS showed improved cellular absorption, increased in vitro permeability, and superior solubility. According to these findings, the created S-SNEDDS may greatly enhance TCG's oral administration and antiplatelet effectiveness, making it a viable option for additional in vivo testing and clinical use in the treatment of acute coronary syndrome.

F3 is the best S-SNEDDS (Capmul MCM 10%, Tween 80 8%, Propylene glycol 5%) option for ticagrelor administration out of the three formulations since it showed the best physical properties, stability, and possible bioavailability. The findings imply that a stable, supersaturated, and lyophilized Nano emulsion system requires the right ratio of oil, surfactants, and precipitation inhibitor.

FTIR analysis confirmed the absence of chemical interactions, while SEM revealed smooth, amorphous particles without any crystalline structures. Additionally, zeta potential measurements demonstrated good stability. These findings indicate that the optimized S-SNEDDS formulation holds significant potential for enhancing the therapeutic efficacy of Ticagrelor.

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