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Development and Characterization of Solid SMEDDS for Enhanced Oral Delivery of Ticagrelor

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The purpose of this study was to develop and optimize a Self-Micro Emulsifying Drug Delivery System (SMEDDS) for the poorly water-soluble drug Ticagrelor, enhancing its solubility and bioavailability. The study aimed to systematically evaluate the formulation using a mixture L-optimal design to achieve maximum transparency and minimal self-emulsification time.

The solubility of Ticagrelor was significantly improved by utilizing a combination of Capmul-PG8, Tween-20, and PEG-400. The mixture L-optimal design helped identify the optimal formulation with oil, surfactant, and co-surfactant ratios, showing a percentage transparency of 99.6 ± 2.85% and a self-emulsification time of 15.4 ± 1.03 seconds. In vitro drug release studies indicated that liquid SMEDDS achieved a release of 99.2 ± 1.5% at 60 minutes, outperforming solid SMEDDS (94.3 ± 2.6%) and an aqueous drug solution (55.4 ± 2.4%). Stability testing demonstrated that the optimized formulation remained stable over 30 days under accelerated conditions.

The optimized SMEDDS formulation of Ticagrelor significantly enhanced the drug's solubility and release profile, suggesting its potential for improving bioavailability in poorly soluble drugs. These findings offer a promising strategy for the formulation of other hydrophobic drugs and could have significant clinical implications.

Keywords: Ticagrelor, SMEDDS, solubility, bioavailability, mixture L-optimal design.

1. Introduction

The oral administration of drugs remains the most convenient and widely accepted route for drug delivery; however, it presents significant challenges for drugs with poor water solubility. In recent years, self-microemulsifying drug delivery systems (SMEDDS) have garnered attention as an effective solution to enhance the oral bioavailability of lipophilic drugs. SMEDDS are isotropic mixtures comprising oils, surfactants, and co-solvents that, upon exposure to gastrointestinal (GI) fluids, spontaneously form fine oil-in-water (o/w) microemulsions through the digestive motility of the stomach and intestines. These systems do not require external energy for emulsification, making them ideal for thermolabile compounds.

The distinction between SMEDDS and self-emulsifying drug delivery systems (SEDDS) lies primarily in the size of the emulsified droplets and the oil content. SMEDDS typically produce microemulsions with droplet sizes ranging from 1 to 100 nm and have an oil content of less than 20%, whereas SEDDS tend to form emulsions with droplet sizes between 100 and 300 nm and an oil content between 40% and 80%. The smaller droplet size in SMEDDS offers a larger surface area for absorption and improved bioavailability, especially for drugs exhibiting dissolution-limited absorption [1–3].

The development of SMEDDS formulations necessitates the careful selection of oil-surfactant combinations that can solubilize the drug at therapeutic concentrations. These formulations are commonly filled into hard or soft gelatin capsules, offering stability and ease of manufacturing. SMEDDS formulations typically consist of oils, surfactants, co-surfactants, and sometimes antioxidants, with co-solvents added to enhance drug solubility and emulsification properties.

One of the most significant advantages of SMEDDS is their ability to enhance the oral bioavailability of poorly water-soluble drugs. The microemulsified droplets, typically ranging from 1 to 100 nm in size, provide a greater surface area for drug dissolution and absorption through the intestinal mucosa. For example, halofantrine formulated as SMEDDS demonstrated a 6- to 8-fold increase in bioavailability compared to conventional formulations.

Another critical advantage is the ease of manufacturing and scalability of SMEDDS. Unlike complex drug delivery systems such as nanoparticles or liposomes, SMEDDS require simple and cost-effective manufacturing equipment, such as basic mixers and liquid-filling machines. This simplicity in production facilitates large-scale industrial applications, making SMEDDS an attractive option for pharmaceutical development [4].

SMEDDS also reduce intra- and inter-subject variability, as well as food effects, on drug absorption. Many lipophilic drugs exhibit significant variability in absorption due to individual differences in gastrointestinal conditions or the presence of food. SMEDDS provide a consistent plasma profile, independent of food intake, ensuring improved

therapeutic efficacy and patient compliance [5].

Additionally, SMEDDS have the unique capability of delivering peptides and other macromolecules that are susceptible to enzymatic degradation in the GI tract. By protecting these molecules in a microemulsified form, SMEDDS can prevent enzymatic hydrolysis, facilitating the oral delivery of biologically active peptides and hormones [6].

The selection of excipients in SMEDDS formulations is a critical aspect that influences the system's performance and safety. The oils used in SMEDDS not only facilitate emulsification but also enhance the solubilization of lipophilic drugs. Medium-chain triglycerides (MCTs) are often favored due to their superior solubilizing capacity and rapid hydrolysis, promoting drug absorption through the intestinal lymphatic system. Modified vegetable oils and semisynthetic lipids are also commonly employed for their compatibility with surfactants and their ability to form stable emulsions [7].

Surfactants are essential for stabilizing the microemulsion. Non-ionic surfactants, particularly those with a high hydrophilic-lipophilic balance (HLB), such as polyoxyethylene sorbitan esters (e.g., Tween 80), are widely used due to their biocompatibility and ability to form stable emulsions. However, the concentration of surfactants must be carefully optimized, as high concentrations can cause gastrointestinal irritation. Co-surfactants, such as ethanol or propylene glycol, are often added to reduce interfacial tension and facilitate the formation of microemulsions [8–11].

Several factors influence the performance of SMEDDS, including the nature and dose of the drug, the polarity of the lipid phase, and the choice of surfactants and co-surfactants. The solubility of the drug in the oil phase plays a critical role in determining the system's ability to maintain the drug in a solubilized state. Furthermore, the polarity of the lipid phase, which is influenced by the chain length and degree of unsaturation of the fatty acids, affects the drug release profile. Proper formulation design is essential to prevent drug precipitation upon dilution in the gastrointestinal tract [12].

In conclusion, SMEDDS represent a versatile and efficient platform for improving the bioavailability of poorly soluble drugs. By optimizing formulation components and processes, SMEDDS can overcome significant challenges in oral drug delivery, offering enhanced absorption, consistent therapeutic profiles, and ease of industrial scalability [13].

2. Methods & Materials

Ticagrelor, was obtained as a gift sample from Mehta Pharmaceutical Industries, Mumbai. Various oils, including Captex-355, Capryol-90, Capryol-PGMC, and Capmul-PG8, were procured as gift samples from Abitec Corporation Ltd., while other oils such as oleic acid, cinnamon oil, castor oil, and surfactants like Tween-20, Tween-80, Labrasol, and Span-80 were sourced from Chem Dyes Corporation, Vadodara, India. Co-surfactants, including PEG-400, propylene glycol, and Acrysol MC8, were also acquired from Chem Dyes Corporation. Adsorbents like Syloid 244 FP, Neusilin UFL 2, and Aerosil 300 pharma were obtained from Grace Division, Fuji Chemical Industry, and Evonik Industry, respectively. Solvents such as methanol, toluene, acetone, benzene, chloroform, acetonitrile, ethyl acetate, and diethyl ether were all supplied by Chem Dyes Corporation, Vadodara, India.

3. Research Methodology

Preformulation Study

Drug Identification

Fourier Transform Infrared Spectroscopy (FTIR): The FTIR spectrum of Ticagrelor was obtained to identify the drug. Potassium bromide (KBr) was mixed with the drug sample in a 1:1 ratio by weight. The mixture was compressed into a pellet using a KBr pellet press at 10,000 psi for 2 minutes. The FTIR spectrum was recorded in the range of 4000 to 400 cm^{-1} using a Shimadzu FTIR spectrophotometer, and the characteristic peaks were compared with the standard reference spectrum [14,15].

Melting Point Determination: The melting point of Ticagrelor was determined using the capillary method. About 5 mg of finely powdered drug was filled into a sealed capillary tube, and the tube was inserted into the digital melting point apparatus. The temperature was gradually increased, and the point at which the drug melted was recorded [16,17].

Solubility Study

The solubility of Ticagrelor was evaluated in various solvents including methanol, chloroform, acetone, toluene, and benzene. 1 mg of the drug was added to 1 mL of each solvent in glass vials, and the vials were vortexed for 5 minutes followed by sonication for 10 minutes. The solubility was visually assessed, and results were recorded based on clarity [18,19].

Analytical Method Development

Selection of λ max: Ticagrelor (10 mg) was accurately weighed and dissolved in methanol to prepare a stock solution of 100 µg/mL. From this, a 10 µg/mL solution was prepared and scanned between 200 to 400 nm using a Shimadzu UV-1900i UV-Visible spectrophotometer. The λ max was determined at the wavelength showing maximum absorption [20,21].

Calibration Curve in Methanol: A stock solution of 100 µg/mL was prepared by dissolving 10 mg of Ticagrelor in 100 mL of methanol. Standard solutions with concentrations of 2.5, 5, 7.5, 10, and 12.5 µg/mL were prepared by serial dilution. The absorbance was measured at the λ max, and a calibration curve was plotted by plotting absorbance versus concentration [22].

Calibration Curve in Phosphate Buffer (pH 7.4) and Methanol (1:9): A stock solution was prepared as described above using Phosphate Buffer (pH 7.4): Methanol as solvent in ratio 1:9. Aliquots of 0.2 to 2 mL (to obtain concentrations of 2 to 20 µg/mL) were withdrawn from the stock solution and diluted with same solvent mixture to 10 mL. Absorbance was measured at the λ max and used to plot the calibration curve [23].

Excipients Selection

The solubility of Ticagrelor was determined by adding the drug in 1 mg increments to 1 mL of various solvents (oils, surfactants, and co-surfactants) until no further dissolution occurred. The mixture was vortexed for 10 minutes and then sonicated to ensure thorough solubilization. The amount of drug dissolved in each solvent was calculated to assess

solubility, providing essential data for the formulation process [24].

Formulation development

preliminary trials for excipients selection: Eight trial batches were prepared using two oils, two surfactants, and two co-surfactants with higher solubilities based on solubility studies. Each batch contained 60 mg of Ticagrelor and 1 mL of oil-surfactant-co-surfactant mixture. The self-emulsification grade and % T (Percentage Transparency) were evaluated to select the optimal combination [25,26].

Ternary phase diagram construction: For constructing the ternary phase diagram, combinations of Capmul-PG8 (oil), Tween-20 (surfactant), and PEG-400 (co-surfactant) were used. Different formulations with varying concentrations (10% to 80%) of oil, surfactant, and co-surfactant were prepared, and the self-emulsification time was measured [27,28].

Optimization of Liquid SMEDDS using L-Optimal Design

The formulation was optimized using Design Expert Version 13 (File Version 13.0.1.0), with L-Optimal design employed for optimization. A quadratic model with randomized mixture design was used, with no blocks. The design involved point exchange with 16 runs. Independent variables included oil (X1), surfactant (X2), and co-surfactant (X3), while dependent responses were self-emulsification time and percentage transparency. The range for oil, surfactant, and co-surfactant was 10-30%, 40-80%, and 10-40%, respectively. Two checkpoint batches were formulated based on the optimized SMEDDS formulation. These batches were evaluated for transparency (% T) and self-emulsification time (SET). The optimization process was conducted using the software's numerical optimization tool [29].

Build Information of statistical design

Study Type: Mixture, Subtype: Randomized, Design Type: L-optimal, Point Exchange. Runs: 16, Design Model: Quadratic, Build Time: 46 milliseconds.

Preparation of Liquid SMEDDS: The liquid SMEDDS formulation was prepared by mixing Ticagrelor (60 mg) with 1 mL each of the selected oil, surfactant, and co-surfactant. The mixture was vortexed at 500 rpm until clear, then sonicated for 30 minutes at room temperature to ensure complete emulsification.

Evaluation of Liquid SMEDDS

Self-emulsification grade: Self-emulsification grading was employed to assess the emulsification efficiency of formulations based on appearance, emulsification time, and clarity. Grade A represents rapid emulsification (<1 minute) with a clear or slightly bluish appearance, while grades B to E indicate progressively slower emulsification and decreased clarity, from bluish-white to coarse emulsions. This grading system provides a standardized evaluation of the formulation's ability to form stable microemulsions.

Self-Emulsification Time: The self-emulsification time was evaluated by adding 1 mL of the SMEDDS formulation dropwise to 200 mL of distilled water at 37°C under gentle stirring at 100 rpm. The time taken for complete emulsification was noted.

Percentage Transparency: The transparency of the SMEDDS formulations was measured by

diluting 1 mL of the formulation with 200 mL of distilled water. The transmittance was measured at 650 nm using a UV-Visible spectrophotometer [30].

Solid SMEDDS Preparation

Estimation of Optimum Liquid to Adsorbent Ratio: To determine the optimum liquid to adsorbent ratio, various incremental ratios of liquid SMEDDS to adsorbent were evaluated. Starting from a liquid to adsorbent ratio of 1:0.2, increments of 0.1 gm of adsorbent were added until the desired free-flowing consistency was achieved. Adsorbents tested included Aeroperl 300, Neusilin UFL 2, and Syloid 244 FP. For each ratio, key preformulation parameters such as Carr's index, Hausner's ratio, and the angle of repose were measured [31].

In Vitro Drug Release Study

The in vitro release of Ticagrelor from liquid and solid SMEDDS was evaluated using the dialysis bag method. A dialysis bag containing 1 mL of the SMEDDS formulation was placed in 200 mL of phosphate buffer (pH 7.4) maintained at 37°C and stirred at 60 rpm. Samples were collected at intervals of 5, 10, 20, 30, 40, and 60 minutes, and final aliquots were prepared by using methanol and maintaining 9:1, methanol: PBS saline ratio as solvent (9:1). Ticagrelor release was quantified using a UV-Visible spectrophotometer.

For comparison, an aqueous solution of Ticagrelor with the same drug concentration and volume (1 mL) was also subjected to the same conditions. The release profile of Ticagrelor from the aqueous solution was similarly assessed at the same time intervals to evaluate the efficiency of SMEDDS formulations in enhancing the release rate in comparison to the aqueous solution [32].

Stability Study

Accelerated stability studies were performed on the optimized liquid and solid SMEDDS at 40°C ± 2°C and 75% ± 5 RH for one month. Chemical and physical parameters were monitored throughout the study period [33].

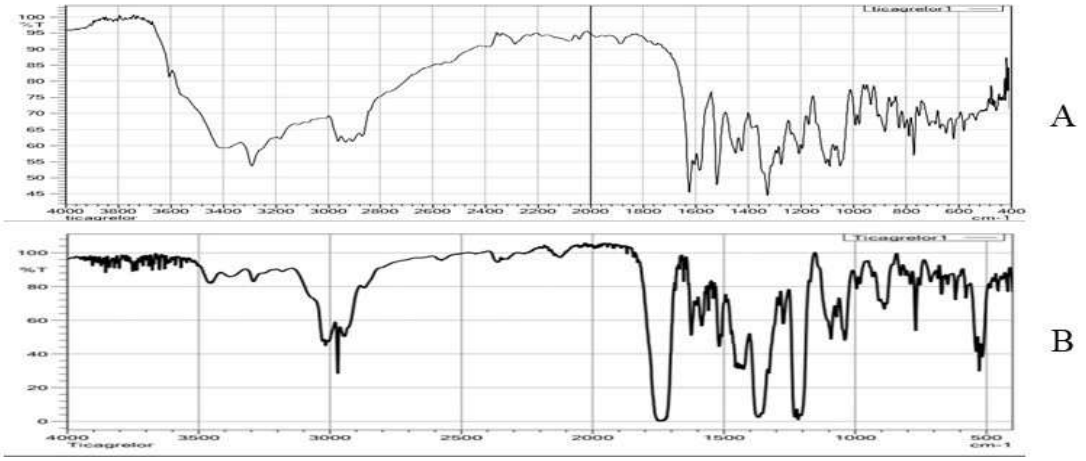
4. Results and discussion

Preformulation Study

Drug Identification

Fourier Transform Infrared Spectroscopy (FTIR):

Figure 1 FTIR Spectra of Reference (A) and Sample (B) Ticagrelor



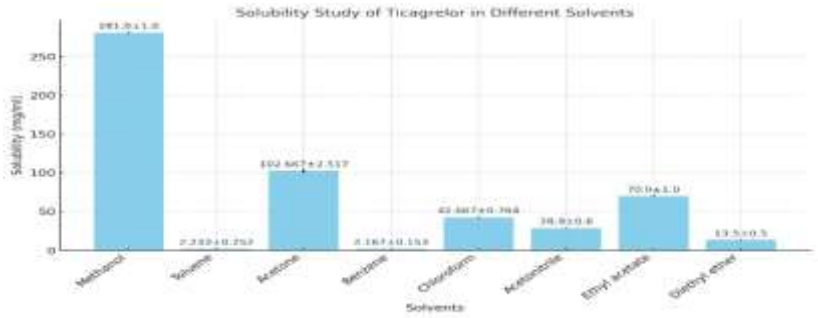
The FTIR spectrum of Ticagrelor was obtained to confirm the presence of characteristic functional groups and to assess the molecular integrity of the drug. The observed peaks were compared with standard reference values to verify the structure as shown in **Error! Reference source not found.**. The N-H stretching vibration, typically observed between 3400–3300 cm^{-1}, was detected at 3327.15 cm^{-1}, confirming the presence of the N-H functional group in the molecule. The C-N stretching vibration, expected between 1590–1640 cm^{-1}, was observed at 1623.76 cm^{-1}, aligning well with the standard range for this bond. Additionally, the -C-OH stretching vibration, typically around 1095 cm^{-1}, was detected at 1091.57 cm^{-1}, indicating the presence of the hydroxyl group. These results confirm that the key functional groups of Ticagrelor remain intact, validating the drug's molecular structure [34].

Melting Point Determination:

The melting point of Ticagrelor was determined using the capillary method as described in the methodology. The observed melting point ranged from 140-145°C, aligning closely with the reported standard range of 140-142°C. This consistency in melting point confirms the purity and thermal stability of the Ticagrelor sample used in this study [35,36].

Solubility Study

Figure 1 Solubility of Ticagrelor in Different Solvents with Standard Deviation (Mean ± SD, N=3).



The solubility study of Ticagrelor was performed in various solvents, including methanol, toluene, acetone, benzene, chloroform, acetonitrile, ethyl acetate, and diethyl ether as shown in Figure 1. Among these, Ticagrelor exhibited the highest solubility in methanol (281.00 ± 1.00 mg/ml), followed by acetone (102.67 ± 2.52 mg/ml) and ethyl acetate (70.00 ± 1.00 mg/ml). In contrast, the lowest solubility was observed in toluene and benzene. The results provide crucial insights for selecting appropriate solvents for formulating Ticagrelor-based delivery systems.

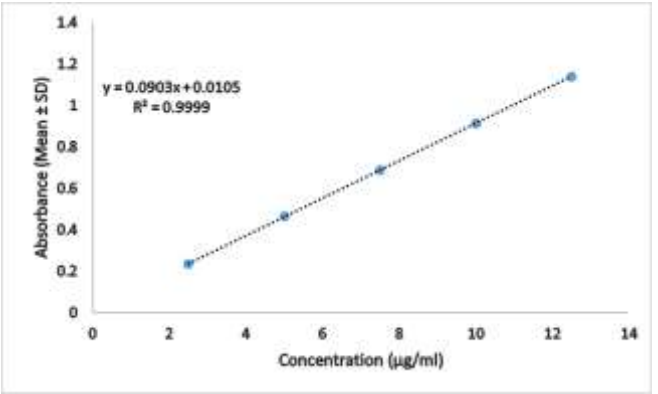
Analytical Method Development

Selection of λ max: The UV-visible spectrophotometric analysis of Ticagrelor in methanol showed an absorption maximum (λmax) at 255 nm. This wavelength is used as the reference for further quantitative analysis of Ticagrelor.

Calibration Curve in Methanol:

A calibration curve for Ticagrelor in methanol was established by measuring the absorbance of concentrations ranging from 2.5 to 12.5 µg/ml at 255 nm. The curve exhibited a linear relationship between concentration and absorbance with the linearity equation $y = 0.0903x + 0.0105$ and a strong correlation coefficient ($R^2 = 0.9999$), confirming the method's accuracy and precision. The data demonstrated a proportional increase in absorbance with concentration, validating the method's reliability for quantitative analysis of Ticagrelor as shown in **Error! Reference source not found.**

Figure 3 Calibration Curve of Ticagrelor in Methanol

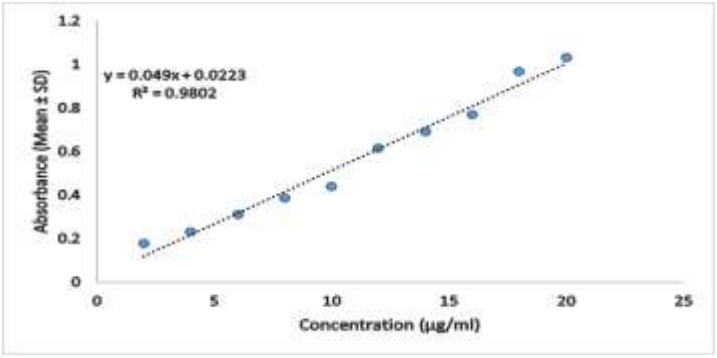


Calibration Curve in Phosphate Buffer Saline (PBS) (pH 7.4) and Methanol:

A calibration curve of Ticagrelor in Methanol: PBS (9:1) was generated by measuring the absorbance of varying concentrations (2–20 µg/ml) at 255 nm. The curve demonstrated a linear relationship between concentration and absorbance, yielding the linearity equation

Y = 0.049 x + 0.0223. The correlation coefficient (R^2) is 0.9802. This high correlation confirms the method's accuracy and precision, as the absorbance values showed a direct proportional increase with concentration, validating the reliability of the method for quantifying Ticagrelor in Methanol: PBS (9:1) as shown in Figure 2.

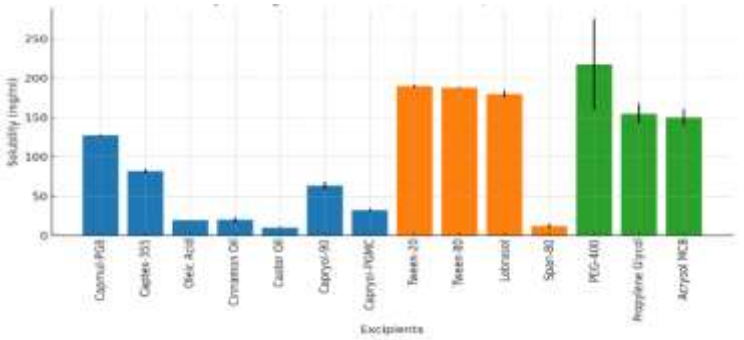
Figure 2 Calibration Curve of Ticagrelor in Methanol: PBS (9:1)



Excipients Selection

For the preliminary study as shown in Figure 3, Capmul-PG8 and Captex-355 were selected as oils due to their high solubility in Ticagrelor. Tween-20 and Tween-80 were chosen as surfactants for their strong emulsifying properties. PEG-400 and Propylene Glycol were selected as co-surfactants for their effective solubilization and emulsification efficiency. These excipients were chosen to optimize the SMEDDS formulation based on their solubility profiles.

Figure 3 Solubility Profiles of Oils, Surfactants, and Co-Surfactants for SEDDS Formulation



Formulation development

Preliminary Trials for Excipients Selection:

Table 1 Preliminary Trials for Excipients Selection

Formulation Code	Oil	Surfactant	Co-Surfactant	Emulsification Grade	Transparency (Mean ± SD) n=3
PT1	Capmul PG8	Tween-80	Propylene glycol	A	97.65 ± 0.53
PT2	Captex-355	Tween-20	PEG-400	A	96.50 ± 0.29
PT3	Capmul PG8	Tween-80	PEG-400	A	90.95 ± 0.34
PT4	Captex-355	Tween-80	Propylene glycol	B	89.72 ± 0.39
PT5	Capmul PG8	Tween-20	PEG-400	C	78.45 ± 0.24
PT6	Captex-355	Tween-20	Propylene glycol	B	80.12 ± 0.41
PT7	Capmul PG8	Tween-20	Propylene glycol	B	84.10 ± 5.32
PT8	Captex-355	Tween-80	PEG-400	C	71.32 ± 0.28

As shown in Table 1, based on the emulsification grade and percentage transparency (%T) data, the excipients were evaluated for their ability to form stable and transparent emulsions. Among the tested formulations, PT1 (Capmul PG8, Tween-80, and Propylene glycol) demonstrated the highest transparency (97.65 ± 0.53%) with an A-grade emulsification, indicating it as the most effective combination for oil, surfactant, and co-surfactant selection.

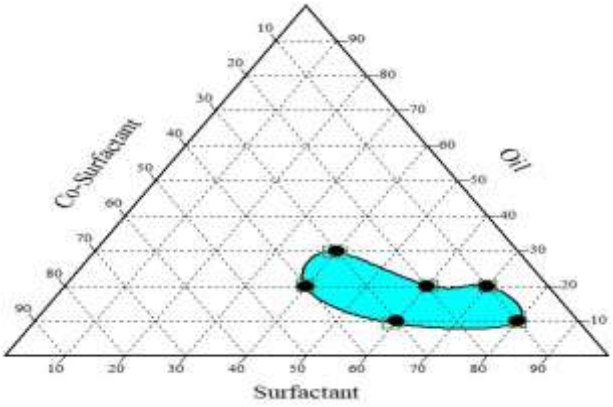
Ternary phase diagram construction:

The ternary phase diagram (Figure 4) was constructed to identify the self-emulsifying region by varying the proportions of oil, surfactant, and co-surfactant as shown in Table 2. Optimal formulations, characterized by grade A emulsification and transparency above 95%, were identified in the region where oil concentrations ranged from 10-30%, surfactants from 40-80%, and co-surfactants from 10-40%.

Table 2 Ternary Phase Compositions Based on Self-Emulsification Grade and % Transparency

Batch No.	Oil (%)	Surfactant (%)	Co-S (%)	Grade	%T (Mean ± SD) n=3
TP1	80	10	10	D	46.02 ± 0.51
TP2	60	10	30	D	59.90 ± 0.55
TP3	60	20	20	B	84.15 ± 0.80
TP4	60	30	10	B	82.85 ± 0.49
TP5	40	10	50	C	71.50 ± 0.36
TP6	40	20	40	D	63.97 ± 0.55
TP7	40	30	30	D	60.70 ± 0.56
TP8	40	40	20	C	73.65 ± 0.41
TP9	40	50	10	C	70.20 ± 0.16
TP10	30	30	40	B	81.60 ± 0.16
TP11	30	40	30	A	93.35 ± 0.25
TP12	20	10	70	D	63.40 ± 0.36
TP13	20	20	60	D	67.45 ± 0.45
TP14	20	40	40	A	97.45 ± 0.30
TP15	20	60	20	A	99.87 ± 0.11
TP16	20	70	10	A	97.35 ± 0.19
TP17	10	10	80	B	82.50 ± 0.39
TP18	10	20	70	B	86.75 ± 0.43
TP19	10	40	50	B	85.23 ± 0.27
TP20	10	60	30	A	95.20 ± 0.16
TP21	10	80	10	A	96.53 ± 0.29

Figure 4 Ternary Phase Diagram Illustrating the Self-Emulsifying Region



Optimization of Liquid SMEDDS using mixture L-optimal design

Table 3 Results of Mixture L-optimal Design

RUN	X1 (% Oil)	X2 (% Surfactant)	X3 (% Co-S)	Y1 %T (Mean ± SD) n=3	Y2 SET (Sec.) (Mean ± SD) n=3
D1	19.1498	58.854	21.9963	98.2 ± 1.99	29.1 ± 2.02
D2	28.247	61.753	10	96.5 ± 1.46	47.2 ± 2.85
D3	30	42	28	95.1 ± 1.09	54.2 ± 3.26
D4	20	40	40	97.2 ± 1.67	40.3 ± 2.61
D5	19.1498	58.854	21.9963	98.33 ± 1.99	32.8 ± 2.03
D6	30	51.288	18.712	95.8 ± 1.21	59.9 ± 3.36
D7	20.0971	49.3955	30.5075	97.1 ± 1.77	36.6 ± 2.53
D8	12.4245	47.5755	40	98.6 ± 2.37	28.5 ± 1.69
D9	10	67.6974	22.3026	99.6 ± 2.85	15.4 ± 1.03
D10	11.0025	78.9975	10	99.0 ± 2.58	22.7 ± 1.4
D11	30	42	28	96.3 ± 1.3	56.1 ± 3.26
D12	19.1498	58.854	21.9963	98.3 ± 1.99	35.8 ± 2.03
D13	20	40	40	97.5 ± 1.67	45.2 ± 2.64
D14	18.5276	69.0222	12.4503	98.8 ± 2.46	25.6 ± 1.62
D15	28.247	61.753	10	97.1 ± 1.46	48.2 ± 2.85
D16	10	56.0246	33.9754	99.3 ± 2.68	18.2 ± 1.32

The results of the optimization study using the mixture L-optimal design for Liquid SMEDDS are presented in Table 3. Various combinations of oil (X1), surfactant (X2), and co-surfactant (X3) (Table 4) were evaluated for two key parameters: percentage transparency (%T) (Y1) and self-emulsification time (SET) (Table 5) in seconds (Y2). The results show varying %T and SET values, with %T ranging from 95.1% to 99.6% and SET ranging from 15.4 to 59.9 seconds, indicating the influence of the mixture components on the emulsification performance.

Table 4 Mixture Components Details

Name	Units	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
Oil	%	10	30	+0 ↔ 10	+0.5 ↔ 30	20.37	7.19
Surfactant	%	40	78.9975	+0 ↔ 40	+1 ↔ 80	55.25	11.42
Co-Surfactant	%	10	40	+0 ↔ 10	+0.75 ↔ 40	24.37	10.66

Table 5 Responses Details

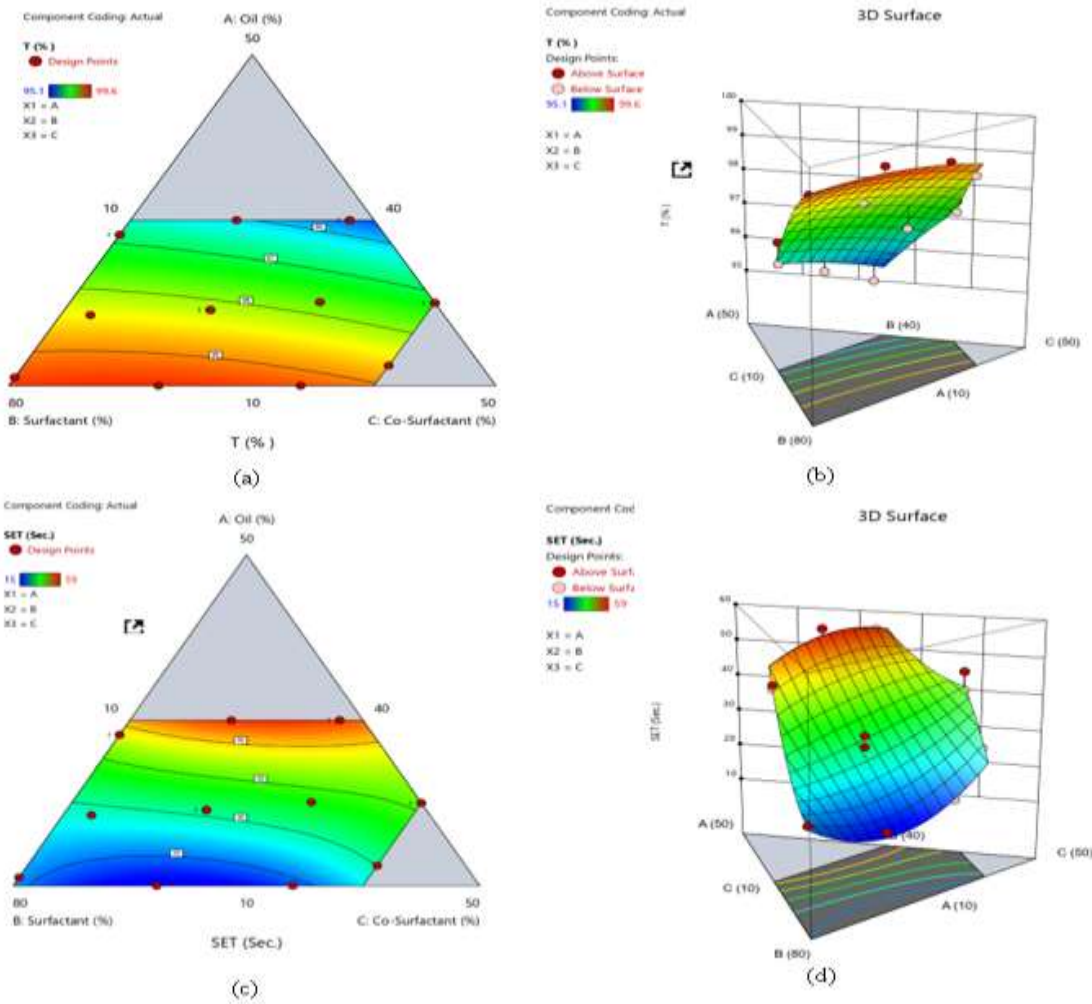
Name	Units	Observations	Minimum	Maximum	Mean

T	%	16.00	95.1	99.6	97.67
SET	Sec.	16.00	15	59	36.81

Table 6 Actual Equations for both Responses

% T	=	SET	=
+0.632930	Oil	+7.35041	Oil
+0.991595	Surfactant	+0.699257	Surfactant
+0.960689	Co-Surfactant	+4.01358	Co-Surfactant
+0.003920	Oil * Surfactant	-0.109507	Oil * Surfactant
+0.002443	Oil * Co-Surfactant	-0.250466	Oil * Co-Surfactant
+0.000884	Surfactant * Co-Surfactant	-0.084573	Surfactant * Co-Surfactant

Figure 5 (a) Contour Plot of Oil, Surfactant, and Co-Surfactant Effect on Transparency., (b) 3D Surface Plot for Transparency Response., (c) Contour Plot of Oil, Surfactant, and Co-Surfactant Effect on Self-Emulsification Time (SET)., (d) 3D Surface Plot for SET Response.



Checkpoint Batches

Table 7 Predicted and Observed Values for Transparency (% T) and Self-Emulsification Time (SET) of Two Checkpoint Batches

Batch	Oil (%)	Surfactant (%)	Co-Surfactant (%)	Predicted % T	Observed % T (Mean ± SD) n=3	Predicted SET (sec)	Observed SET (sec) (Mean ± SD) n=3
Batch 1	13.2	46.8	40	98.55	98.9 ± 0.23	31.5	29.3 ± 0.33
Batch 2	30	51.3	18.7	96.07	97.2 ± 0.78	57.06	54.1 ± 0.66

The results of the two checkpoint batches closely matched the predicted values as shown in Table 7. Batch 1 showed 98.9% ± 0.23 transparency (predicted: 98.55%) and 29.3 ± 0.33 seconds SET (predicted: 31.5 seconds). Batch 2 had 97.2% ± 0.78 transparency (predicted: 96.07%) and 54.1 ± 0.66 seconds SET (predicted: 57.06 seconds). Both batches

demonstrated minimal deviation, validating the formulation's accuracy and reliability.

For the optimization of Liquid SMEDDS using Design Expert software, numerical criteria were defined for independent factors: oil (X1) at 10-30% (minimized), surfactant (X2) at 40-80% (maximized), and co-surfactant (X3) at 10-40% (balanced). Dependent factors included percentage transparency (%T) (Y1), targeted for maximization between 98% and 100%, and self-emulsification time (SET) (Y2), aimed for minimization within 15-30 seconds. These criteria, with a desirability factor of 1.0, were applied to achieve an optimal formulation with high transparency and fast emulsification time.

Table 8 Formulation Details of the Optimized Batch

Formulation Code	Drug (mg)	Conc. of Oil (mL)	Conc. of Surfactant (mL)	Conc. of Co-S (mL)	Desirability
OB1	60	0.3	2.4	0.3	1.0

The final optimized formulation was developed using the selected statistical design model. The formulation contained 60 mg of Ticagrelor, with 0.3 mL of oil, 2.4 mL of surfactant, and 0.3 mL of co-surfactant, as shown in Table 8. The desirability factor for this formulation was 1.0, indicating that the formulation met all the targeted criteria, including optimal transparency and self-emulsification time. This high desirability score confirms the success of the optimization process, ensuring an effective and stable SMEDDS formulation.

Table 9 Results of Flow Properties Related Parameters for Various Ratios of Liquid: Adsorbent, Where CI Means Carr's Index, HR Means Hausner's Ratio, And AOR Means Angle of Repose. Average ± SD, N=3

Ratio mL:gm	Aeroperl 300 (Mean ± SD), n=3			Neusilin ULF 2 (Mean ± SD), n=3			Syloid 244 FP (Mean ± SD), n=3		
	CI	HR	AOR	CI	HR	AOR	CI	HR	AOR
1:0.2	Semi Solid Consistency								
1:0.3	Semi Solid Consistency								
1:0.4	34.54 ± 3.14	1.35 ± 0.03	33.45 ± 3.11	36.18 ± 2.54	1.26 ± 0.03	36.71 ± 2.16	23.51 ± 1.90	1.30 ± 0.05	47.70 ± 2.65
1:0.5	24.59 ± 3.01	1.24 ± 0.04	33.13 ± 3.70	24.53 ± 3.96	1.14 ± 0.01	45.63 ± 3.18	13.56 ± 0.51	1.14 ± 0.01	29.66 ± 2.28
1:0.6	24.46 ± 3.62	1.23 ± 0.02	37.26 ± 0.01	20.05 ± 1.39	1.17 ± 0.02	37.66 ± 2.31	17.48 ± 0.61	1.32 ± 0.02	38.19 ± 2.11
1:0.7	26.04 ± 3.06	1.21 ± 0.03	35.13 ± 0.03	22.12 ± 1.67	1.22 ± 0.05	38.22 ± 2.02	25.19 ± 2.75	1.33 ± 0.01	39.77 ± 2.67

Based on the results presented in Table 9, Syloid 244 FP was identified as the most suitable adsorbent among the three tested. At a liquid-to-adsorbent ratio of 1:0.5, the Syloid 244 FP formulation demonstrated superior flow properties, with a Hausner's ratio of 1.14 (Good), an angle of repose of 29.66° (Excellent), and a Carr's index of 13.56% (Good). These characteristics led to the selection of Syloid 244 FP as the optimal adsorbent for the Liquid SMEDDS formulation.

Table 10 In Vitro Release Profiles of Ticagrelor from Liquid SMEDDS, Solid SMEDDS, and Aqueous Solution in Phosphate Buffer (pH 7.4).

Time (minutes)	Liquid SMEDDS (% Release) (Mean ± SD),	Solid SMEDDS (% Release) (Mean ± SD),	Aqueous Solution (% Release) (Mean ± SD),

	n=3	n=3	n=3
5	25.3 ± 2.1	20.7 ± 1.9	12.5 ± 1.5
10	45.6 ± 2.3	38.4 ± 2.0	18.9 ± 1.7
20	69.5 ± 2.7	60.8 ± 2.3	28.6 ± 1.9
30	84.7 ± 2.1	76.2 ± 2.4	39.7 ± 2.1
40	92.4 ± 1.9	85.5 ± 2.5	45.9 ± 2.3
60	99.2 ± 1.5	94.3 ± 2.6	55.4 ± 2.4

The in vitro drug release profiles demonstrate a significant improvement in the dissolution of Ticagrelor when formulated as SMEDDS compared to an aqueous solution (As shown in Table 10 and in **Error! Reference source not found.**). Both liquid and solid SMEDDS exhibited faster and more complete drug release. At the 5-minute mark, liquid SMEDDS released 25.3% of the drug, while solid SMEDDS released 20.7%, both significantly higher than the aqueous solution's 12.5%. The liquid SMEDDS formulation achieved nearly complete release (99.2%) within 60 minutes, while solid SMEDDS released 94.3% over the same period. In contrast, the aqueous solution only released 55.4% of the drug. These results clearly indicate the superiority of SMEDDS formulations in enhancing the bioavailability of poorly water-soluble drugs like Ticagrelor.

Figure 8 Comparative in Vitro Drug Release of Ticagrelor from Different Formulations Over 60 Minutes.

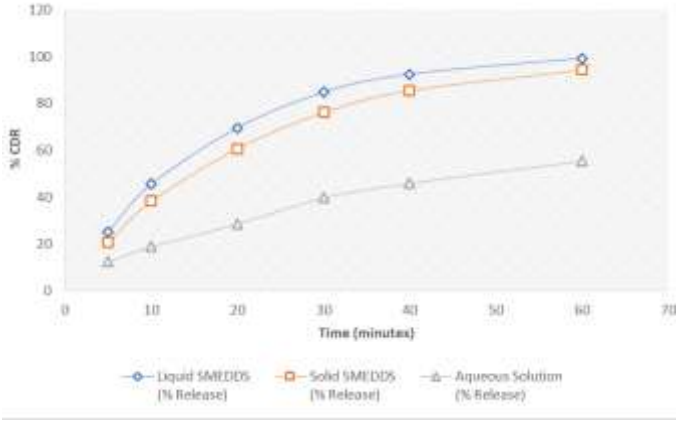


Table 11 Stability Study Results for Solid and Liquid SMEDDS Formulations

Day	Formulation	Appearance	% Transparency (Mean ± SD), n=3	Self-Emulsification Time (Sec) (Mean ± SD), n=3	Physical Stability
0	Solid SMEDDS	Clear	98.3 ± 0.2	32 ± 1.0	Stable
7		Clear	97.8 ± 0.3	34 ± 1.1	Stable
15		Clear	97.4 ± 0.4	36 ± 1.2	Stable
30		Clear	96.9 ± 0.5	38 ± 1.3	Stable
0	Liquid SMEDDS	Clear	99.1 ± 0.1	28 ± 0.9	Stable
7		Clear	98.9 ± 0.2	29 ± 1.0	Stable
15		Clear	98.6 ± 0.3	31 ± 1.1	Stable
30		Clear	98.3 ± 0.4	32 ± 1.2	Stable

The stability study for both solid and liquid SMEDDS formulations over 30 days showed clear physical appearance, maintaining transparency and stability. The % transparency for solid SMEDDS slightly decreased from 98.3% to 96.9%, with an increase in self-

emulsification time (SET) from 32 to 38 seconds. Similarly, liquid SMEDDS showed a minor decrease in % transparency from 99.1% to 98.3%, with SET increasing from 28 to 32 seconds. Both formulations exhibited stable emulsification properties and remained physically stable throughout the testing period.

5. Discussion

The study's findings demonstrate that both liquid and solid SMEDDS formulations exhibit favorable characteristics in terms of drug release and stability. In comparison with existing research, the rapid release of Ticagrelor from liquid SMEDDS, achieving over 99% release within 60 minutes, aligns with previous studies showcasing the enhanced bioavailability of SMEDDS formulations due to improved solubility and absorption of poorly water-soluble drugs. The solid SMEDDS formulation, while showing a slightly slower release profile compared to its liquid counterpart, still performed better than the aqueous solution, indicating the potential for solid-state formulations in providing controlled release with ease of handling.

The stability study results over 30 days confirmed that both formulations remained physically stable, with only minor reductions in transparency and slight increases in self-emulsification time, supporting the long-term viability of the formulations. These results are consistent with existing literature which emphasizes the critical role of formulation excipients in maintaining stability and ensuring sustained drug release.

6. Conclusion

The present study successfully developed and optimized both liquid and solid self-microemulsifying drug delivery systems (SMEDDS) for Ticagrelor, a poorly water-soluble drug, using a systematic formulation approach and mixture L-optimal design. Syloid 244 FP was selected as the most suitable adsorbent for solid SMEDDS due to its superior flow properties, as evidenced by a Carr’s Index of 13.73%, Hausner’s ratio of 1.15, and an angle of repose of 30.03°. The optimized liquid and solid SMEDDS formulations exhibited substantial improvement in Ticagrelor’s solubility and dissolution profile.

In vitro drug release studies revealed that the liquid SMEDDS formulation achieved 99.2% drug release within 60 minutes, whereas the solid SMEDDS demonstrated a slower but stable release of 94.3%, significantly outperforming the aqueous solution (55.4%). Furthermore, stability studies confirmed that both liquid and solid SMEDDS maintained their physical integrity, with consistent transparency and self-emulsification times over a 30-day period. These results underline the potential of SMEDDS as an effective delivery system for enhancing the bioavailability of Ticagrelor, warranting further investigation for in vivo efficacy and clinical applicability.

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Disclosure Statement

The authors declare that they have no competing interests

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