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A Novel SMEDDS Approach To Enhance Solubility And Dissolution Of Poorly Water-Soluble Norethisterone

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Abstract: *The objective of this research was to formulate a self-microemulsifying drug delivery system (SMEDDS) to improve the dissolution profile of norethisterone. To identify appropriate excipients, solubility evaluations were carried out in different oils, surfactants, and co-surfactants. A ternary phase diagram was used to optimize the combination and concentration of components. The final formulation consisted of 5 mg norethisterone, 14.48% w/w Capmul PG8, 56.84% w/w Cremophor EL, and 28.68% w/w propylene glycol. It exhibited favorable characteristics, including a pH of 6.43 ± 0.05, drug content of 98.32 ± 0.95%, emulsification within 30 seconds, and a cloud point of 58.41 ± 0.45°C. In vitro dissolution studies confirmed a significantly improved drug release (99–100%) compared to pure norethisterone. The results indicate that SMEDDS can be an effective approach to improve the dissolution and potentially the bioavailability of drugs with low water solubility, such as norethisterone.*
Keywords: *Norethisterone, Drug dissolution, Lipid-based formulation, SMEDDS, Solubility enhancement.*

I. INTRODUCTION

Oral drug delivery is the most used and preferred route, largely because it is convenient, non-invasive, and generally well accepted by patients. However, a major challenge associated with this method is the limited water solubility of numerous active pharmaceutical ingredients, which can hinder their therapeutic effectiveness (1). Nearly 40% of marketed drugs and approximately 70% of investigational compounds are categorized as poorly water-soluble, which significantly impedes their absorption in the gastrointestinal (GI) tract, leading to erratic bioavailability and diminished therapeutic efficacy. Norethisterone, a synthetic progestin widely used in managing gynecological conditions such as menstrual irregularities, endometriosis, and as an oral contraceptive component, is classified under the Biopharmaceutics Classification System (BCS) (2) as a Class II drug. This classification indicates high membrane permeability but poor solubility in aqueous media. Due to its limited solubility, norethisterone experiences dissolution-rate-limited absorption when administered orally (3). This characteristic adversely impacts its bioavailability and necessitates innovative formulation strategies to enhance its solubility and subsequent systemic exposure. Over the years, various formulation techniques have been explored to enhance the solubility and bioavailability of drugs with poor water solubility (4). These approaches include micronization, use of co-solvents, formation of solid dispersions, inclusion complexes with cyclodextrins, development of nanocarrier systems, and lipid-based delivery systems. Among these, lipid-based formulations especially self-micro emulsifying drug delivery systems (SMEDDS)—have demonstrated significant promise in addressing solubility-related issues (5). SMEDDS are clear, stable mixtures composed of oils, surfactants, and co-surfactants, which can readily form fine oil-in-water emulsions when exposed to gastrointestinal fluids and gentle movements like intestinal peristalsis (6). The optimized formulation comprised 5 mg of norethisterone with 14.48% w/w Capmul PG8, 56.84% w/w Cremophor EL, and 28.68% w/w propylene glycol. This formulation was subjected to thorough evaluation to confirm its suitability for oral delivery. The pH of the final product was recorded as 6.43 ± 0.05, which aligns well with physiological conditions (7). The drug content was found to be 98.32 ± 0.95%, indicating uniform distribution of norethisterone within the formulation. Rapid self-emulsification occurred upon dilution in aqueous media, forming a clear microemulsion within 30 seconds (8). Additionally, the cloud point was measured at 58.41 ± 0.45°C, confirming thermal stability under expected storage and physiological conditions. In vitro dissolution studies were performed to compare the performance of the SMEDDS formulation with that of unformulated norethisterone (9). The SMEDDS achieved nearly complete drug release (99–100%), while the pure drug displayed limited dissolution under the same conditions. The improved dissolution rate observed with the SMEDDS is primarily attributed to the increased surface

area of the nanosized droplets and the maintenance of the drug in a solubilized state during the dissolution process (10). The results clearly demonstrate that the developed SMEDDS formulation significantly enhances the dissolution characteristics of norethisterone, suggesting the potential for improved oral bioavailability (11). This enhancement is particularly important for ensuring consistent therapeutic levels and improved patient outcomes, especially in long-term treatments where stable plasma concentrations are essential. Beyond its application to norethisterone, this study highlights the wider potential of SMEDDS technology in overcoming solubility barriers faced by other poorly water-soluble drugs. The simplicity of the formulation process and its scalability strengthen the case for its commercial feasibility (12). To further validate this approach, future investigations should include in vivo pharmacokinetic assessments, extended stability testing, and industrial-scale development to confirm clinical effectiveness and readiness for market deployment (13). In summary, the present work successfully demonstrates that a lipid-based SMEDDS formulation can significantly improve the solubility and dissolution rate of norethisterone (14). The careful selection of excipients, based on solubility studies and phase diagram evaluation, led to a formulation with favorable physicochemical properties and enhanced in vitro performance. This formulation strategy shows strong potential for improving the therapeutic outcomes of norethisterone and other lipophilic drugs (15).

2. EXPERIMENTATION

Preformulation studies

Organoleptic Parameters

The organoleptic properties of the norethisterone were investigated. The finding of the investigation assertion that the norethisterone drug was creamy white, odourless, non-hygroscopic, crystalline powder.

Melting Point

The capillary method was employed to determine the melting point of the norethisterone via melting point apparatus, The finding of the current study ascertained that the melting point of norethisterone in its bulk form was found to be 203.67°C±1.52-204.34°C±0.58, complies with the literature value of the melting point 203-204°C.

Absorption maxima of the norethisterone

The UV spectrum was employed to assess the norethisterone drug's absorption maximum. With the use of a UV spectrophotometer, a certain concentration of 10µg/ml was scanned in the 200– 400 range and recorded the UV spectrum. The UV spectrum of the test sample confirmed the 240nm absorption maxima of the norethisterone drug in methanol solvent the current finding complies with the literature value of the absorption maxima of the norethisterone.

Standard calibration curve

To construct the standard calibration curve, concentrations ranging from 2 to 18 µg/mL were chosen, as they complied with the principles of the Lambert-Beer law. A graph was plotted using concentration values on the x-axis and corresponding absorbance readings on the y-axis, resulting in a linear regression equation: Y = 0.0529x + 0.0016. The correlation coefficient (R^2) was determined to be 0.999, indicating excellent linearity, as depicted in the figure.

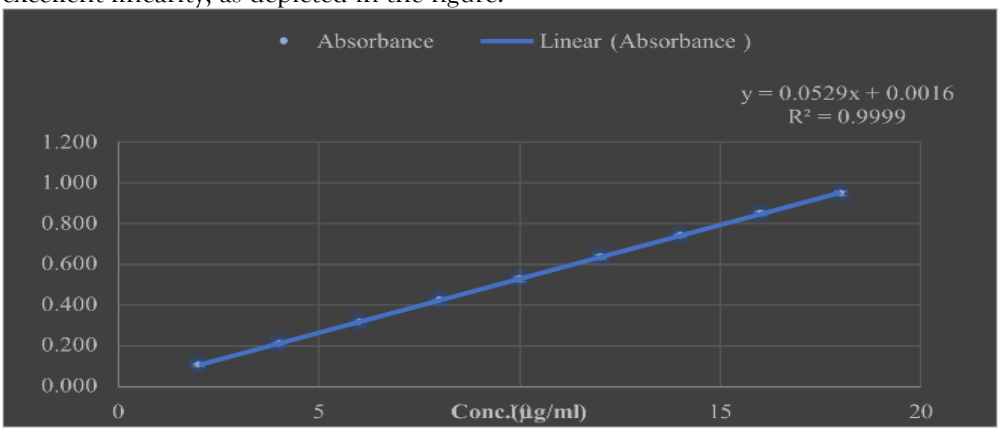

Figure 1: Standard calibration curve of norethisterone at 240nm

Partition coefficient of drug

Using the shake flask method, the partition coefficient of norethisterone was determined in a 1:1 mixture of water and n-octanol. The norethisterone drug moiety's partition coefficient was found to be 2.65±0.037 to the value of 2.72 given in the literature, indicating the norethisterone's lipophilic nature.

FTIR of Norethisterone drug and SMEDDS formulation

The FTIR spectrum of the pure drug norethisterone an final SMEDDS formulation is shown in figure 5.3-5.4. The FTIR spectrum of pure drug norethisterone demonstrated characteristics peaks of their functional group at wavenumber i.e. 3454.09cm^{-1} OH stretching, 2917.42 (2853.97) cm^{-1}: Aliphatic C-H stretching; 1694.59cm^{-1}: C=O stretching; 1563.95cm^{-1}: C=C stretching cm^{-1}; 1459.39cm^{-1}: C-H deformation; 1385.62cm^{-1}: CH3 deformation indicating the fingerprint zone of the norethisterone drug (Shroff and Moyer, 1975).

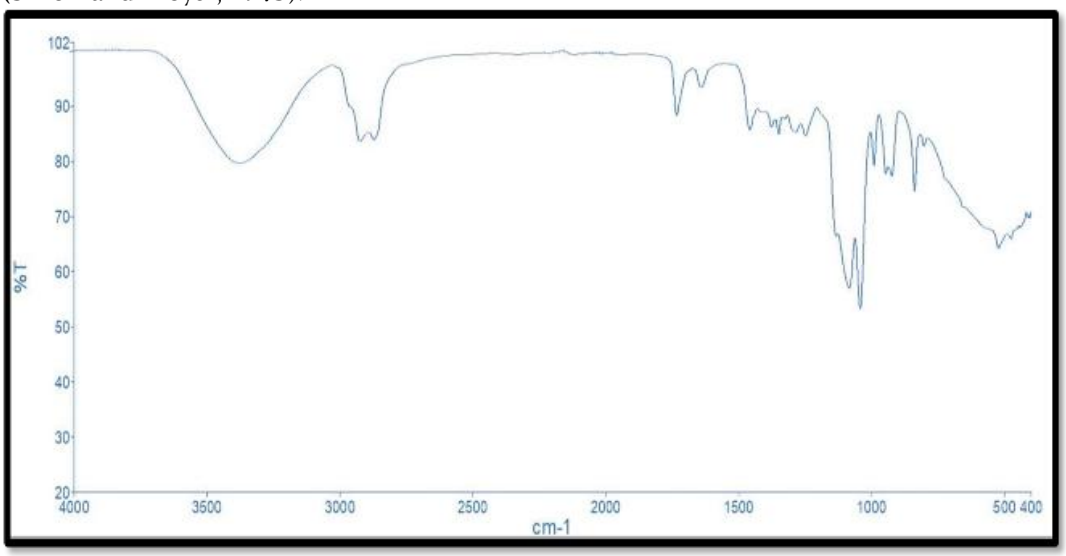

Figure 2: FTIR spectrum Optimized SMEDDS formulation NS5

Solubility in norethisterone in solvents

The solubility profile of norethisterone was evaluated in a range of aqueous, non-aqueous, and buffer-based solvents. Among the tested media, norethisterone exhibited the highest solubility in specific non-aqueous solvents, highlighting their potential suitability for use in formulation development aimed at enhancing drug solubility and bioavailability.

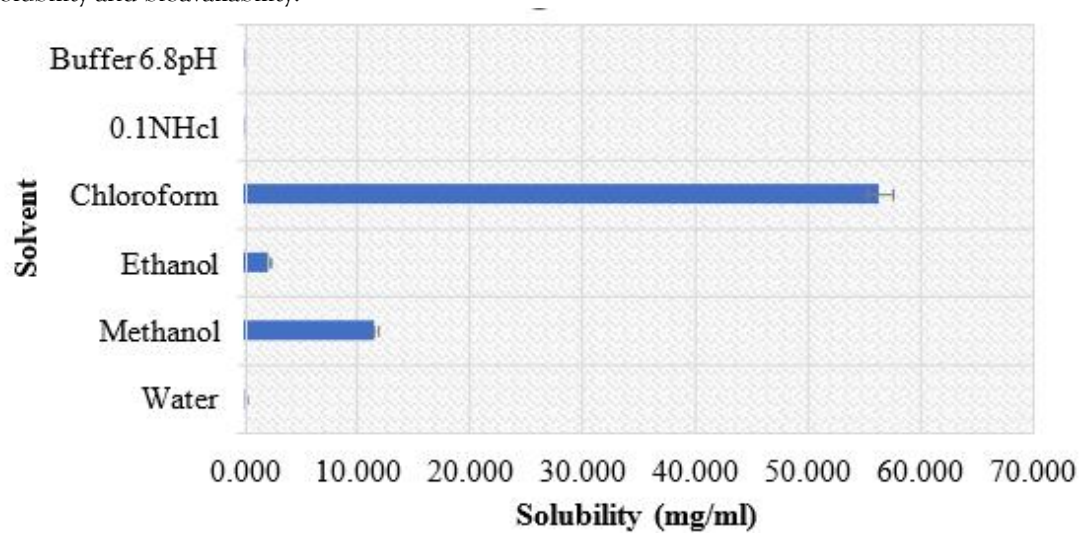

Figure 3: Solubility of norethisterone in various aqueous, non-aqueous and buffer solvents.

Solubility in norethisterone in oils

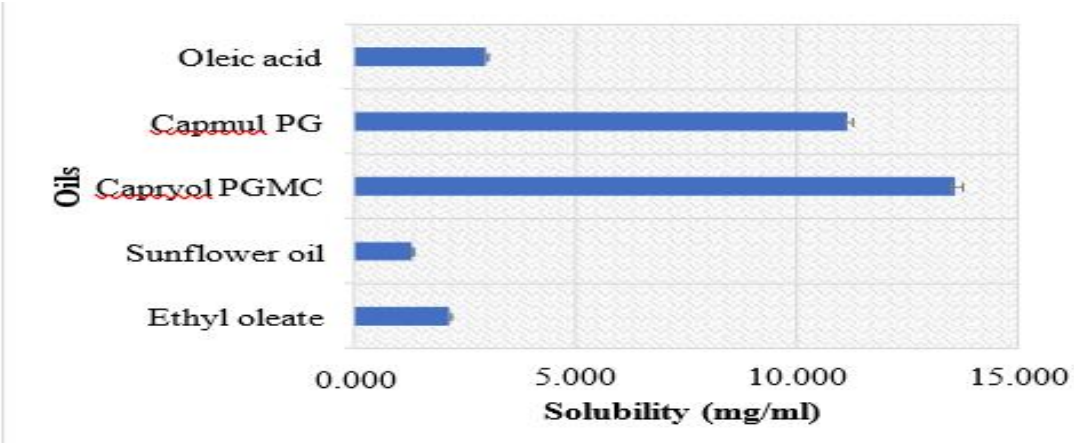

Figure 4: Solubility of norethisterone in oils

Figure shows the solubility of norethisterone in oils. According to the results of the current activity, Capryol PGMC had the highest solubility of 13.613±0.133mg/ml, followed by Capmul PG8 had a solubility of 11.181±0.079mg/ml. Oils are the foundation of SMEDDS because they may solubilize significant amounts the lipophilic drugs and make it easier for them to self- emulsify. In order to be emulsified, the medicine must be adequately solubilized in the oil.

Solubility in norethisterone in surfactant

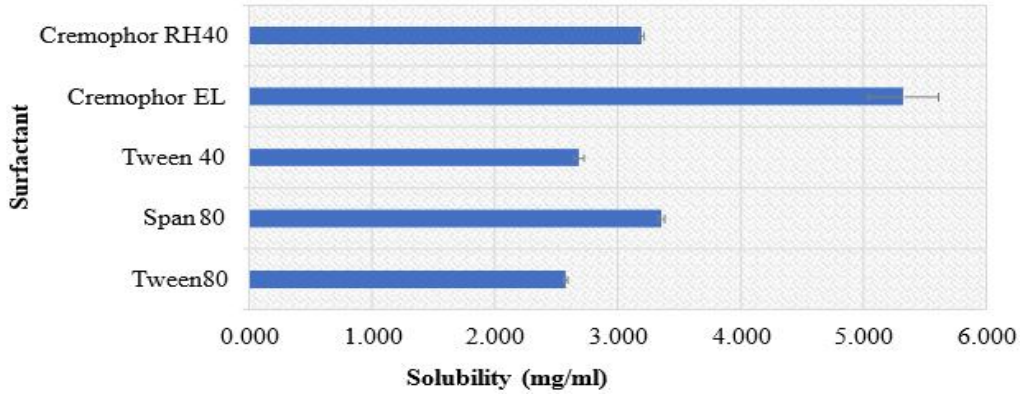

Figure 5: Solubility of norethisterone in surfactants

Figure shows the solubility of norethisterone in surfactant. The current activity's findings showed that the cremophor EL had a maximum solubility of 5.321±0.284mg/ml.

Solubility in norethisterone in co-surfactant

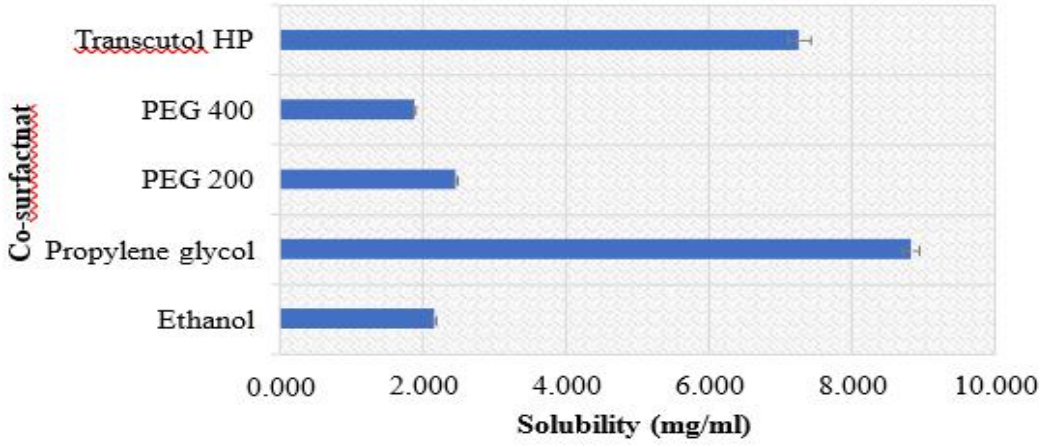

Figure 6: Solubility of norethisterone in cosurfactant

Screening of oil and surfactant through emulsification study

Percentage transmittance and visual appearance were used to screen the oil and surfactant for the development of the norethisterone-loaded SMEDDS formulation, as indicated in table.

Code	No. of Inversion	Appearance	% Transparency	% Transparency after 24 hr.
A1	20.5±2.112	Bluish transparent	85.965±0.431	Bluish transparent
A2	61±4.243	Turbid	16.425±1.124	Turbid
A3	50.5±3.536	Turbid	36.47±1.570	Turbid
A4	30±2.828	Slightly Turbid	69.65±0.665	Slightly Turbid
A5	23±1.414	Bluish Transparent	81.67±0.919	Bluish Transparent
A6	55±5.657	Turbid	42.255±1.039	Turbid
A7	39.5±2.121	Turbid	32.15±1.202	Turbid
A8	27±2.828	Slightly Turbid	57.405±1.010	Slightly Turbid
A9	39±4.243	Turbid	11.61±1.739	Turbid
A10	48.5±3.536	Turbid	9.49±0.750	Turbid
A11	58.5±4.950	Turbid	17.05±1.937	Turbid
A12	65±7.071	Turbid	25.455±1.266	Turbid

Table 1: Screening of oil and surfactants

In the current activity oil like the Capryol PGMC and Capmul PG8 was selected as each oil possesses adequate solubility of the norethisterone. The surfactant selected were cremophor EL, cremophor RH 40, Tween 80 and span 80 selected. On screening, the combination comprising the oil and surfactant was elected based on the percentage transmittance and no. of inversion. The findings of the study attributed the combination A1 and A5 comprising the Capryol PGMC and cremophor EL, and Capmul PG8 and Cremophor EL displayed a bluish transparent appearance post-dilution with water while demonstrating the maximum transmittance 85.965±0.431% and 81.67±0.919% respectively. Moreover, the combination of the oil and surfactant yielded the emulsion in a very less no. of the inversion 20.5±2.112 and 23±1.414 respectively. Thus, both combination A1 and A5 was selected for further screening of the cosurfactant.

Screening of co-surfactant with a combination of the oil and surfactant

Table shows the percentage transmittance and visual appearance that was employed in order to screen the cosurfactant with the oil and surfactant combination for the development of the norethisterone loaded SMEDDS formulation.

Formulation Code	No. of Inversion	Appearance	% Transparency	Appearance after 24 hr.
B1	29±1.414	Slightly Turbid	74.16±0.085	Slightly Turbid
B2	16.5±2.121	Transparent	96.95±0.368	Transparent
B3	34.5±3.536	Turbid	25.655±0.035	Turbid
B4	11.5±0.707	Transparent	98.115±1.124	Transparent
B5	22±2.828	Slightly Turbid	70.785±0.375	Slightly Turbid
B6	22.5±2.121	Turbid	15.385±1.167	Turbid

B7	31±1.414	Turbid	18.89±0.481	Turbid
B8	27.5±0.707	Slightly Turbid	65.07±1.485	Slightly Turbid
B9	23.5±3.536	Turbid	16.065±0.445	Turbid
B10	32±2.828	Turbid	21.57±2.051	Turbid
B11	31±2.459	Turbid	30.335±0.304	Turbid
B12	33.5±4.950	Turbid	34.84±0.396	Turbid

Table 2: Screening the cosurfactant with the combination of oil and surfactan

In the present study, co-surfactants such as propylene glycol, PEG 200, and Transcutol HP were incorporated with the selected oil-surfactant combinations labeled A1 and A5.On screening, the combination comprising the oil and surfactant was elected based on the percentage transmittance and no. of inversion. The findings of the study attributed the combination B2 and B4 comprising the Capryol PGMC, Cremophor EL, Transcutol HP; and Capmul PG8, Cremophor EL, Propylene glycol displayed transparent appearance post-dilution with water while demonstrating the maximum transmittance 96.95±0.368% and 98.115±1.124% respectively. Moreover, the combination of the oil and surfactant yielded the emulsion in a very less no. of the inversion 16.5±2.121 and 11.5±0.707 respectively. Thus, both combination B2 and B4 was selected for the ternary phase diagram.

Preparation of Pseudo ternary phase diagram

Based on the preliminary screening parameters like solubility, percentage transmittance and visual observation two combinations of the oil, surfactant and cosurfactant were elected for the determination of the microemulsion zone employing the pseudo ternary phase diagram.

Combination 1: B4: Capmul PG8, Cremophor EL, Propylene glycol

Combination 2: B2: Capryol PGMC, Cremophor EL, Transcutol HP

Pseudo ternary phase diagram comprising the combination 1

To determine the amount of the oil, surfactant and cosurfactant elected for the ternary phase diagram is shown in table below.

Code	Oil: Surfactant Ratios	Post dilutation visual observation
TCaCp1	0.5:9.5	Transparent
TCaCp2	1:09	Transparent
TCaCp3	1:08	Transparent
TCaCp4	1:07	Transparent
TCaCp5	1.5:8.5	Less Transparent
TCaCp6	2:08	Turbid
TCaCp7	3:07	Turbid
TCaCp8	4:06	Turbid
TCaCp9	5:05	Turbid

Table 3: Visual observation of the ratio employed in the preparation of the ternary phase diagram for combination1 while the Surfactant and cosurfactant ratio (1:1)

Code	Oil: Surfactant Ratios	Post dilution visual observation
TCaCp10	0.5:9.5	Transparent

TCaCp11	1:09	Transparent
TCaCp12	1:08	Transparent
TCaCp13	1:07	Less Transparent
TCaCp14	1.5:8.5	Less Transparent
TCaCp15	2:08	Turbid
TCaCp16	3:07	Turbid
TCaCp17	4:06	Turbid
TCaCp18	5:05	Turbid

Table 4: Visual observation of the ratio employed in the preparation of the ternary phase diagram for combination1 while the Surfactant and cosurfactant ratio (1:2)

Code	Oil: Surfactant Ratios	Post dilution visual observation
TCaCp19	0.5:9.5	Transparent
TCaCp20	1:09	Transparent
TCaCp21	1:08	Transparent
TCaCp22	1:07	Transparent
TCaCp23	1.5:8.5	Transparent
TCaCp24	2:08	Less Transparent
TCaCp25	3:07	Turbid
TCaCp26	4:06	Turbid
TCaCp27	5:05	Turbid

Table 5: Visual observation of the ratio employed in the preparation of the ternary phase diagram for combination1 while the Surfactant and cosurfactant ratio (2:1)

Pseudo ternary phase diagram comprising the combination 2

To determine the amount of the oil, surfactant and cosurfactant elected for the ternary phase diagram is shown in table.

Code	Oil: Surfactant Ratios	Post dilution visual observation
TCCT1	0.5:9.5	Transparent
TCCT2	1:09	Less Transparent
TCCT3	1:08	Less Transparent
TCCT4	1:07	Turbid
TCCT5	1.5:8.5	Turbid
TCCT6	2:08	Turbid

TCCT7	3:07	Turbid
TCCT8	4:06	Turbid
TCCT9	5:05	Turbid

Table 6: Visual observation of the ratio employed in the preparation of the ternary phase diagram for combination 2 while the Surfactant and cosurfactant ratio (1:1)

Code	Oil: Surfactant Ratios	Post dilution visual observation
TCCT10	0.5:9.5	Transparent
TCCT11	1:09	Less Transparent
TCCT12	1:08	Less Transparent
TCCT13	1:07	Turbid
TCCT14	1.5:8.5	Turbid
TCCT15	2:08	Turbid
TCCT16	3:07	Turbid
TCCT17	4:06	Turbid
TCCT18	5:05	Turbid

Table 7: Visual observation of the ratio employed in the preparation of the ternary phase diagram for combination 2 while the Surfactant and cosurfactant ratio (1:2)

Code	Oil: Surfactant Ratios	Post dilution visual observation
TCCT19	0.5:9.5	Transparent
TCCT20	1:09	Less Transparent
TCCT21	1:08	Less Transparent
TCCT22	1:07	Less Transparent
TCCT23	1.5:8.5	Turbid
TCCT24	2:08	Turbid
TCCT25	3:07	Turbid
TCCT26	4:06	Turbid
TCCT27	5:05	Turbid

Table 8: Visual observation of the ratio employed in the preparation of the ternary phase diagram for combination 2 while the Surfactant and cosurfactant ratio (2:1)

Ternary phase diagrams of the combinations 1 and 2 have been developed based on the findings of preliminary screenings in the following oil: Smix ratios: (0.5:9.5, 1:09, 1:08, 1:07, 2:8, 3:7, 4:6, and 5:5) and surfactant: cosurfactant ratios: 1:1, 1:1, and 2:1. Distilled water acts as the aqueous phase. The ternary phase diagram was prepared in order to assess the microemulsion transparent zone as indicated in Figs. 5.9-5.10. The colored areas in Figure depict the clear, and transparent, or microemulsion region, whereas

the non-colored areas represent the turbid formulations. The amount of the components selected from the microemulsion region for the development of the norethisterone-loaded SMEDDS formulation. The ternary phase diagram comprising the Capmul PG8, Cremophor EL and Propylene glycol displayed a wider region of the clear and transparent microemulsion region than the ternary phase diagram comprising the Capryol, PGMC, Cremophor.

Preparation of the norethisterone loaded SMEDDS formulation

With the help of the pseudo ternary phase diagram, the table 5.14 demonstrate the composition of the norethisterone loaded SMEDDS.

Formulation	Norethisterone (mg)	Capmul PG8 (%w/w)	Capryol PGMC (%w/w)	Cremophor EL (%w/w)	Propylene glycol (%w/w)	Transcutol HP (%w/w)
NS1	5	5.07	-	63.35	31.57	-
NS2	5	9.55	-	60.21	30.24	-
NS3	5	10.9	-	59.67	29.44	-
NS4	5	12.24	-	58.87	28.89	-
NS5	5	14.48	-	56.84	28.68	-
NS6	5	4.93	-	47.67	47.41	-
NS7	5	10	-	44.74	45.26	-
NS8	5	10.45	-	44.78	44.78	-
NS9	5	12.54	-	43.34	44.12	-
NS10	5	4.93	-	31.39	63.69	-
NS11	5	9.7	-	30.03	60.27	-
NS12	5	10.45	-	29.92	59.63	-
NS13	5	-	4.78	63.3	-	31.78
NS14	5	-	4.33	48.48	-	47.19
NS15	5	-	4.63	31.41	-	63.97

Preparation of the norethisterone loaded SMEDDS formulation involves the uniform homogenous mixture comprising the oil, surfactant and cosurfactant. Initially, the drug norethisterone was solubilized into the oil followed by the addition of the surfactant and cosurfactant as shown in figure

Figure 7: Norethisterone loaded SMEDDS formulation coded NS5

In vitro characterization of the norethisterone loaded SMEDDS

Visual Observations

Formulation	Physical appearance
NS1	Drug was not solubilized
NS2	Uniform, clear, transparent, light yellow colour
NS3	Uniform, clear, transparent, light yellow colour
NS4	Uniform, clear, transparent, light yellow colour
NS5	Uniform, clear, transparent, light yellow colour
NS6	Drug was not solubilized
NS7	Uniform, clear, transparent, slight yellow colour
NS8	Uniform, clear, transparent, slight yellow colour
NS9	Uniform, clear, transparent, slight yellow colour
NS10	Drug was not solubilized
NS11	Uniform, clear, transparent, slight yellow colour
NS12	Uniform, clear, transparent, slight yellow colour
NS13	Drug was not solubilized
NS14	Drug was not solubilized
NS15	Drug was not solubilized

As shown in Table 11, all formulations appeared slightly yellow in color and showed no visible drug particles. Most formulations were uniform, clear, and transparent. However, formulations NS1, NS6, N10, NS13, NS14, and NS15 failed to completely solubilize the norethisterone drug component. Consequently, these formulations were excluded from further evaluation.

pH

Formulation	pH
NS2	6.377±0.059
NS3	6.567±0.040
NS4	6.480±0.070
NS5	6.430±0.046
NS7	6.283±0.050
NS8	6.557±0.067
NS9	6.313±0.035
NS11	6.363±0.021
NS12	6.527±0.038

Table 12: pH of all prepared drug loaded SMEDDS

Table 5.16 indicated the value of the observed pH of all the prepared formulation. pH of the all investigated SMEDDS was observed to be in a range of the 6.283±0.050 to 6.567±0.040.

Percentage drug content

Formulation code	Percentage drug content
NS2	79.420±0.787
NS3	82.823±0.437
NS4	88.620±1.00
NS5	98.324±0.951
NS7	83.831±0.578
NS8	88.494±1.528
NS9	99.080±1.329
NS11	89.250±0.951
NS12	92.905±0.218

Table 13: Percentage drug content

Table 5.17 presents the percentage drug content of all the formulated SMEDDS preparations. All investigated formulations were found to have a drug concentration ranging from 79.420±0.787% to 99.080±1.329%. The maximum percentage drug content was found to be 98.324±0.951% and 99.080±1.329% for the NS5 and NS9 formulations, respectively.

Self-emulsification time

Formulation code	Emulsification time in (Seconds)
NS2	Within 30 sec
NS3	Within 30 sec
NS4	Within 30 sec
NS5	Within 30 sec
NS7	Within 30 sec
NS8	Within 30 sec
NS9	Within 30 sec
NS11	Within 30 sec
NS12	Within 30 sec

Table 14: Self emulsification time

The emulsification time is an effective way to assess a formulation's emulsification ability. Self-emulsification time of each formulation is shown in table 5.18. The self-emulsification process is believed to involve the rapid detachment of numerous tiny droplets from the surface of larger ones, rather than a slow and continuous reduction in droplet size. All investigated SMEDDS formulations produced microemulsions in less than 30 seconds, demonstrating the system's superior ability for self-emulsification (Goyal et al., 2012).

Cloud point

The cloud point temperature refers to the critical temperature above which non-ionic surfactant micelles in an aqueous solution begin to change structure, leading to swelling and distortion. At this stage, the curvature at the oil-water interface starts to shift. If the temperature continues to rise, the system may undergo a complete transformation—water becomes incorporated into the micelles, and the oil phase turns continuous. This phase inversion can lead to the precipitation of the drug from the microemulsion.

Formulation code	Cloud point (°C)
NS5	58.413±0.453
NS9	60.803±0.948

Table 15: Cloud point of the selected formulation NS5 and NS9

The cloud point temperatures for prepared microemulsion of the selected formulation NS5 and NS9 were observed to be 58.413±0.453°C and 60.803±0.948°C respectively. The observed cloud point is higher than the body's temperature ascertaining no alteration will be happened in the formed microemulsion inside the GIT tract (Dhaval et al., 2020).

In Vitro dissolution study

Time (min.)	Percentage dissolution of pure drug	Percentage dissolution of Formulation NS5	Percentage dissolution of Formulation NS9
1	13.066±1.801	44.938±0.856	30.987±0.786
3	23.955±2.569	64.786±0.900	54.692±1.195
5	35.524±1.021	83.728±0.708	66.147±0.589
7	48.681±1.040	95.070±0.681	74.541±1.040
10	62.064±0.900	99.267±0.520	83.728±1.874
15	70.004±0.856	100.401±0.393	96.885±0.786
20	71.251±0.589	100.287±0.196	99.720±0.708

Table 16: Comparison of In Vitro Dissolution Profiles Between SMEDDS Formulations and Pure Norethisterone

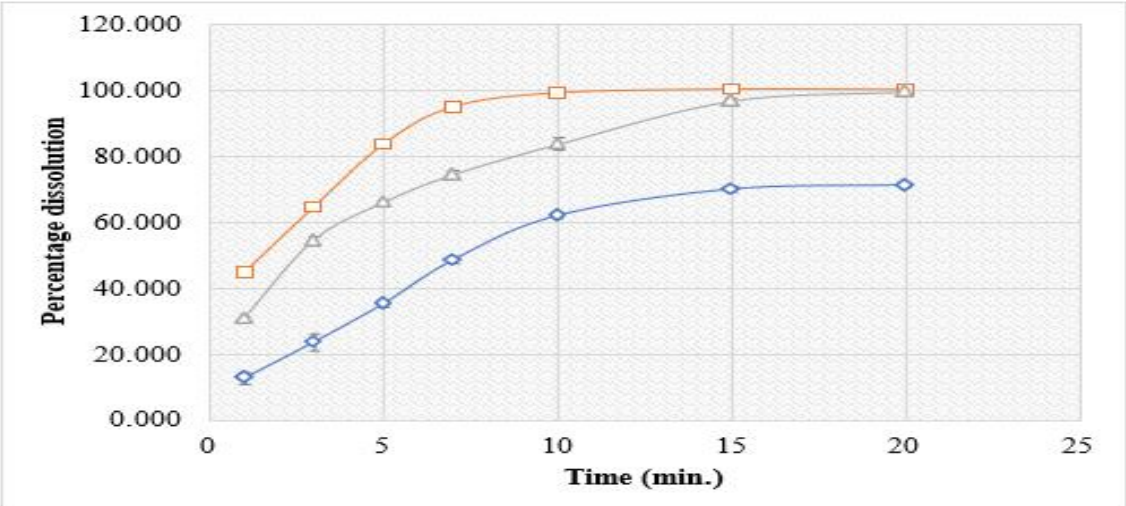

Figure 8: Comparison of In Vitro Dissolution Profiles of SMEDDS Formulations NS5 and NS9 with Pure Norethisterone

An in vitro dissolution study was conducted in 0.1N HCl to compare the dissolution behavior of the developed liquid SMEDDS formulation with that of the pure drug. The dissolution profiles of both the SMEDDS preconcentrate and pure norethisterone are illustrated in Figure 5.13. According to previous studies, norethisterone exhibits minimal solubility in 0.1N HCl. Literature also suggests that in a self-emulsifying drug delivery system, the formation of emulsions requires very little energy, allowing the oil and water phases to form an interface with ease. It is proposed that the interaction among oil, surfactant, co-surfactant, and water leads to swelling of the system, which reduces the size of the oil droplets and consequently enhances the dissolution rate of the drug. Figure 5.13 demonstrates that formulation NS5 displayed faster dissolution and possess a higher dissolution of 99-100% within the 10min while formulation NS9 achieved 100% dissolution up to 20min. Furthermore, the NS5 formulation achieves 99.267±0.520% dissolution compared to the 62.064±0.90% dissolution of the pure drug at 10min (Madagul et al., 2016).

Droplets size and PDI

S.No.	Formulation code	Droplets size (nm)	PDI
1	NS5	131.5	0.173

Table 17: Droplet size and PDI of the NS5 formulation

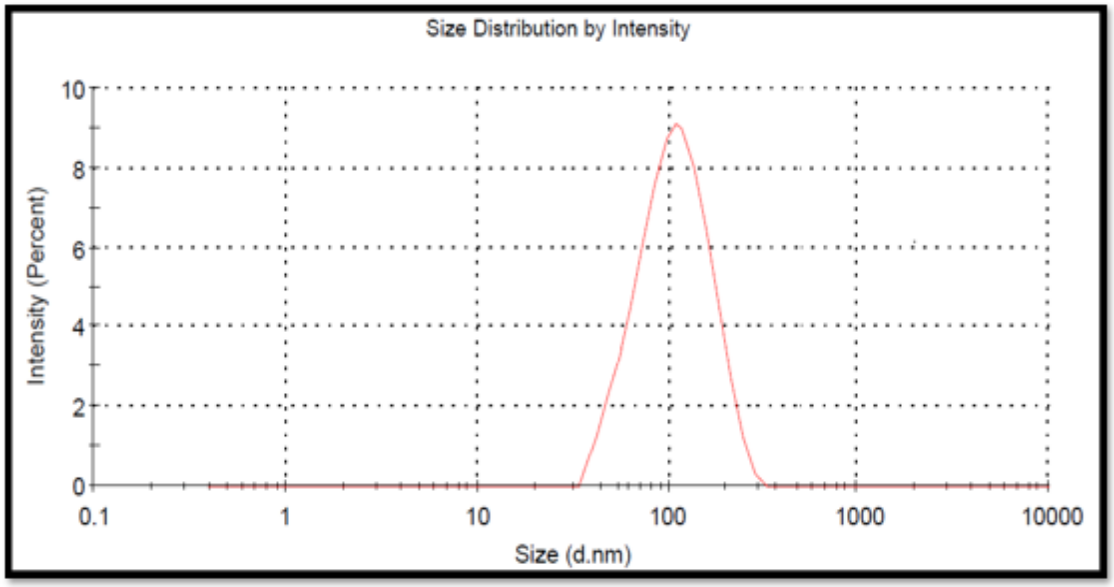

Figure 9: Droplets size distribution of the formulation NS5

The optimized SMEDDS formulation's rate of drug release is greatly influenced by the droplet size of the prepared microemulsion. Droplets size and PDI of the NS5 formulation was shown in table 5.14. For the drug to be released, a wide interfacial area is provided by the nano-ranged droplets. Figure 5.14 demonstrated the droplet size distribution of the prepared microemulsion post-dilution of the NS5 formulation with the water. The average droplet size was found to be approximately 131.5 nm, which falls within the accepted range for microemulsions (10–500 nm). The polydispersity index (PDI) was recorded at 0.173, suggesting a uniform and narrow droplet size distribution.

Zeta Potential

S.No.	Formulation code	Zeta Potential (mv)
1	NS5	-28.2

Table 18: Zeta Potential of the NS5 formulation

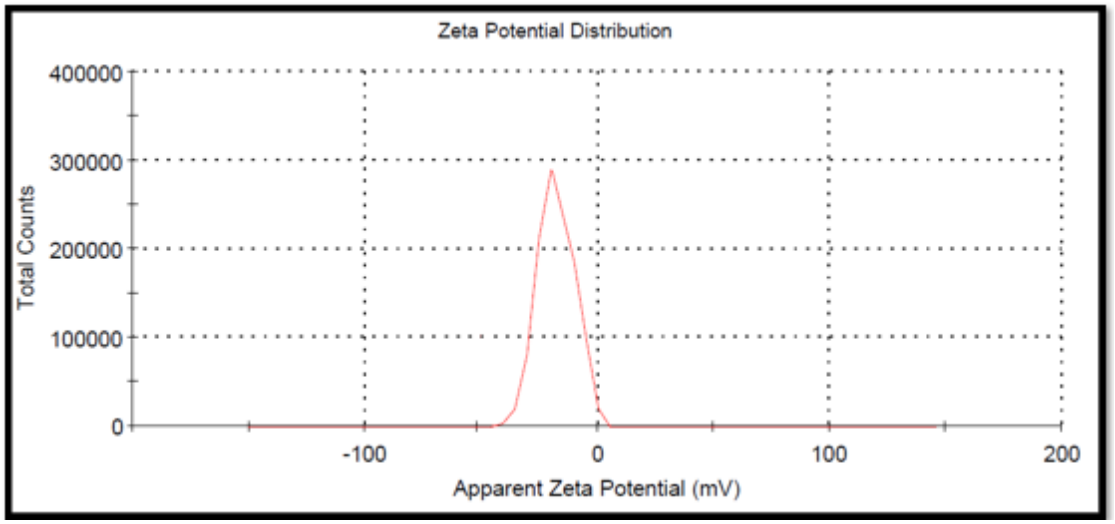

Figure 10: Zeta Potential of the NS5 formulation

The stability of an emulsion is significantly influenced by the surface charge of its droplets. Strong electrostatic repulsion between microemulsion droplets generally prevents their coalescence, resulting in a more stable three-phase system. The zeta potential value of the NS5 formulation, presented in Table 5.24, was measured at −28.2 mV, indicating excellent stability. This high negative surface charge creates sufficient repulsive forces to minimize droplet aggregation and phase separation. The negative charge is primarily attributed to the presence of free fatty acids in the oil phase, as reported by Vyas et al. (2005).

TEM electron microscopy

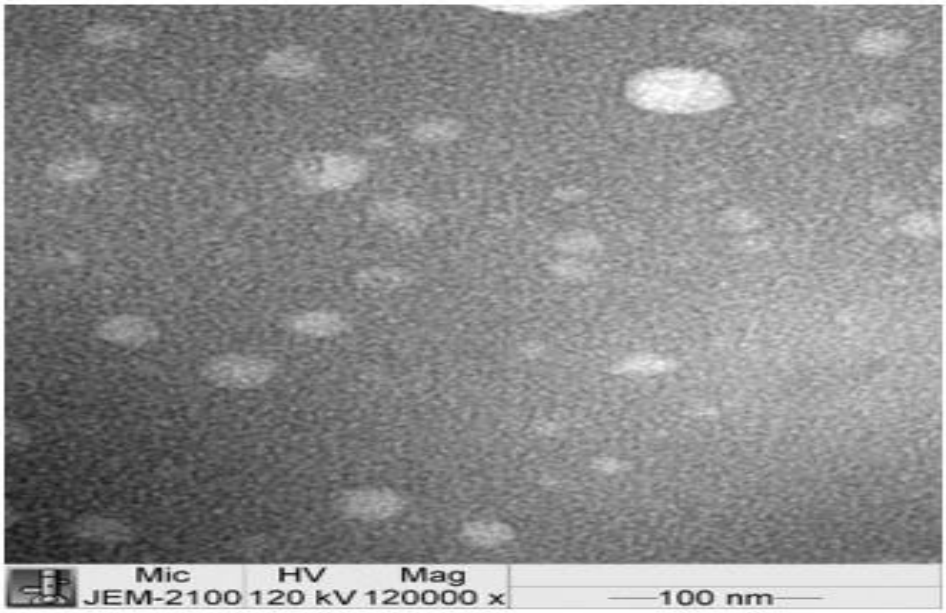

Figure 11: TEM image of the formulation NS5

To examine the morphology of the oil droplets, formulation NS5 was diluted with distilled water to form a microemulsion. Transmission electron microscopy (TEM) images revealed that the resulting droplets were spherical and exhibited smooth surfaces, as depicted in the corresponding figure.

In vitro drug release kinetic study

The dissolution profile of the SMEDDS formulation NS5 was subjected to various kinetic models like zero order, first order, Higuchi order and Hixson-Crowell order model.

Zero order

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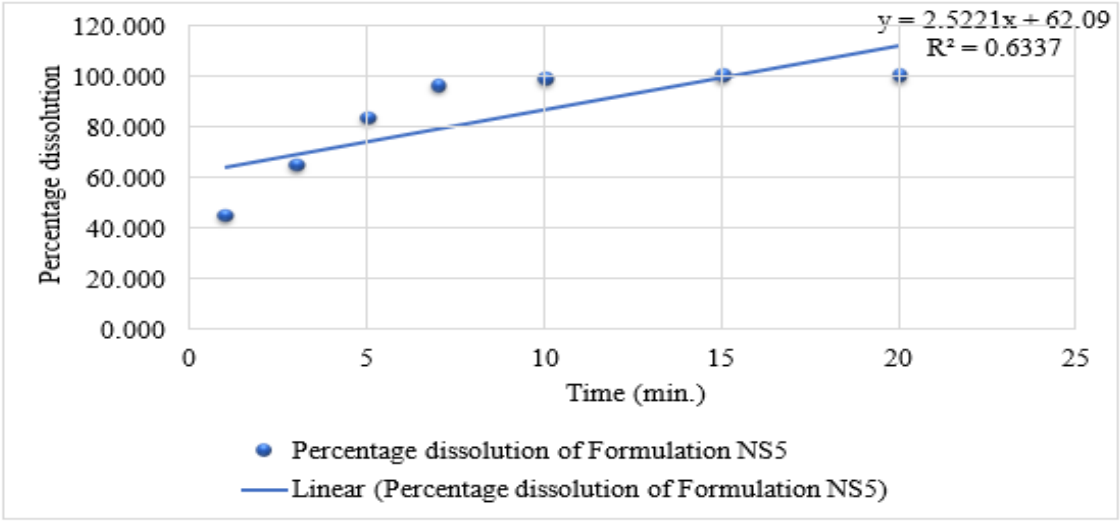

Figure 12: Zero order kinetic graph

First order

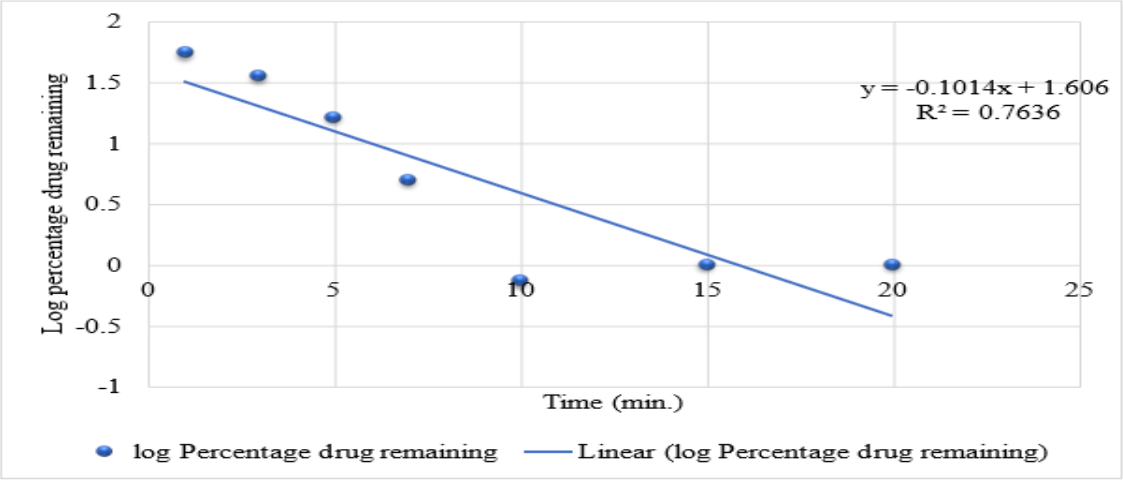

Figure 13: First order kinetic graph

Higuchi Model

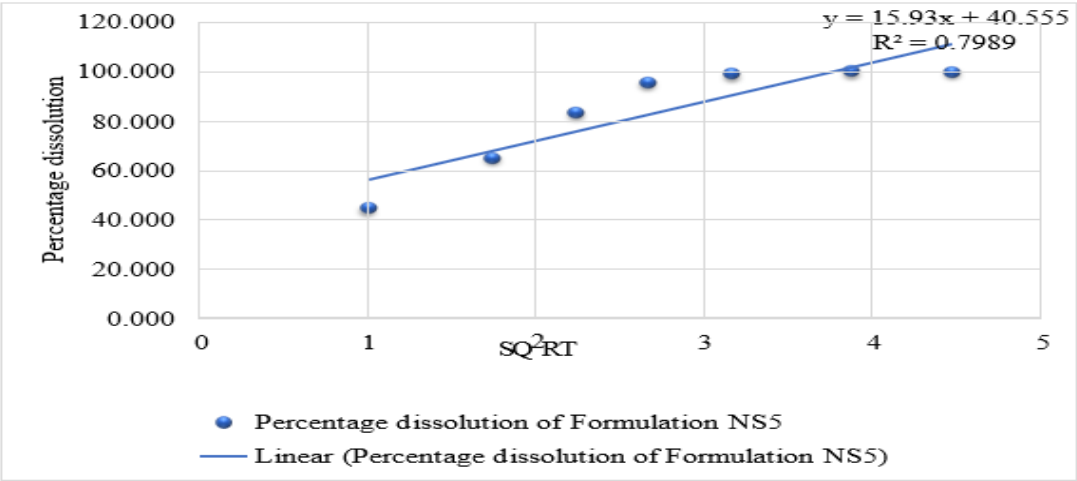

Figure 14: Higuchi kinetic order graph

Hixson-Crowell's order model

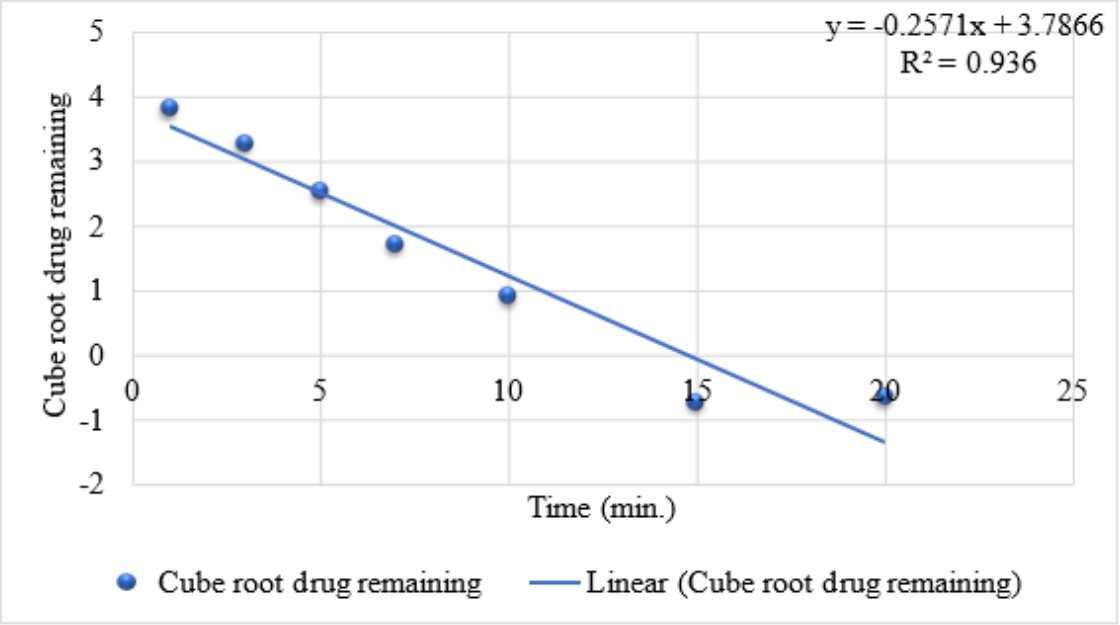

Figure 15: Hixson-Crowell's kinetic graph

Hixson-Crowell's order model

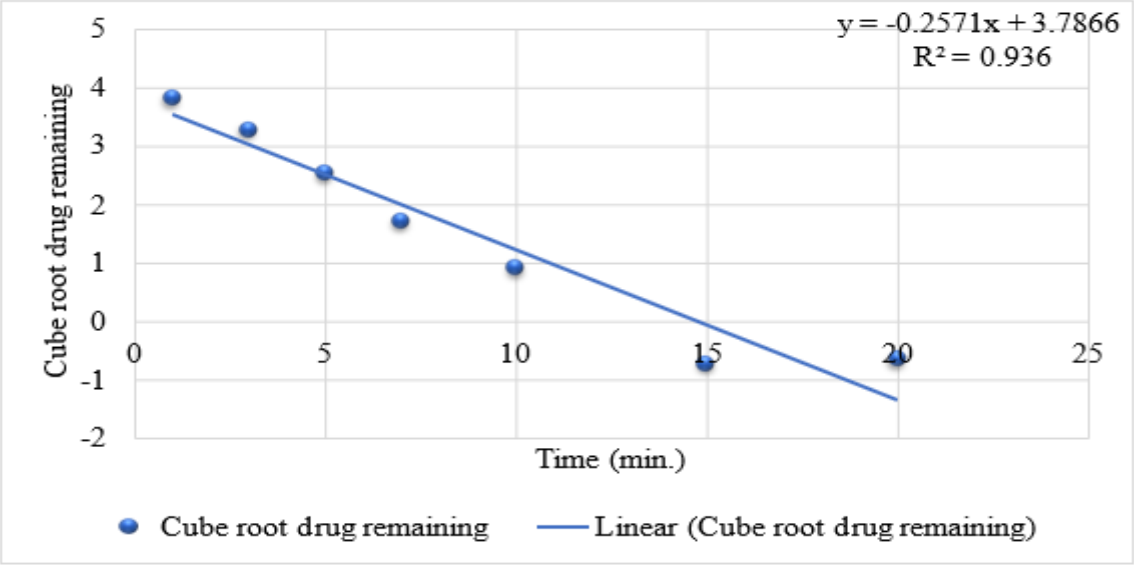

Figure 16: Hixson-Crowell's kinetic graph

In vitro, drug release kinetic study demonstrated that among all release kinetic models, the dissolution followed by the Hixson-Crowell's kinetic model as it possesses the value of regression coefficient 0.936 higher than the value of regression coefficient of the other kinetic model.

3. CONCLUSION

The current study successfully formulated and evaluated a Self-Microemulsifying Drug Delivery System (SMEDDS) aimed at improving the solubility and dissolution rate of norethisterone, a drug known for its poor water solubility. After conducting detailed solubility screenings, Capmul PG8, Cremophor EL, and propylene glycol were selected as the optimal oil, surfactant, and co-surfactant, respectively. Pseudo-ternary phase diagrams confirmed that these components could form a stable and transparent microemulsion system. Among the tested formulations, NS5 showed the most promising results,

including a small droplet size (~131.5 nm), low polydispersity index (PDI 0.173), and rapid self-emulsification time (under 30 seconds). The formulation also displayed a high drug content (98.32 ± 0.95%) and excellent in vitro drug release (~99.27% within 10 minutes), significantly outperforming the pure drug. The findings confirm that the SMEDDS strategy is a promising and efficient method for enhancing the solubility and dissolution rate of lipophilic drugs like norethisterone. This method could lead to better oral bioavailability and therapeutic consistency.

4. SOME OF THE ADVANAGES FROM THE ABOVE RESULTS

a) Enhanced Solubility: The developed SMEDDS formulation significantly improved the solubility of norethisterone, making it more appropriate for oral delivery.

b) Rapid Drug Release: The selected formulation released the drug quickly and completely, which could help achieve faster therapeutic effects.

c) Uniform Drug Content: Consistent drug loading was observed across all formulations, reflecting good formulation precision and dosing reliability.

d) Strong Self-Emulsifying Ability: Upon dilution, the formulation rapidly formed a stable emulsion, confirming its effective self-emulsifying properties.

e) Small Droplet Size for Improved Absorption: The nanosized droplets provided a larger surface area, aiding in better absorption and increased drug bioavailability.

f) Stability at Body Temperature: A high cloud point ensured that the formulation remained physically stable under physiological conditions, minimizing the risk of separation.

g) Scalable Manufacturing Process: The method used for formulation was simple and can be adapted for large-scale production, making it suitable for industrial application.

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