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Formulation and Evaluation of Self Emulsifying Drug Delivery System of Lopinavir

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ABSTRACT

Lopinavir (LOP) is a poorly water-soluble antiretroviral drug with limited oral bioavailability. The present study aimed to develop and evaluate liquid and solid self-emulsifying drug delivery systems (SEDDS) to enhance the solubility and dissolution behavior of lopinavir. Preformulation studies revealed a melting point of 104–106 °C and confirmed drug purity and compatibility by FTIR spectroscopy. Solubility screening identified Capmul MCM C8 EP as the most suitable oil, exhibiting a solubility of 75–100 mg/g, while Cremophor RH40 and Labrafil M 2125 CS showed superior emulsification efficiency with percentage transmittance values of 98.32% and 100.20%, respectively. Ternary phase diagram studies demonstrated a broad self-emulsifying region for the Capmul MCM C8–Cremophor RH40–Labrafil M 2125 system, maintaining fine emulsification up to 60% oil concentration. The optimized liquid SEDDS (L2) exhibited a mean globule size of 60.19 ± 3.27 nm in distilled water, 65.23 ± 3.15 nm in simulated gastric fluid, and 61.19 ± 3.15 nm in simulated intestinal fluid, with polydispersity indices below 0.45 and positive zeta potential values ranging from +13.12 to +14.23 mV. The formulation showed excellent robustness to dilution with transmittance values exceeding 98% and no drug precipitation for up to 12 h. In vitro dissolution studies demonstrated rapid drug release, with more than 85% lopinavir released within 20 min and complete drug release within 60 min in all dissolution media. The optimized L-SEDDS was successfully converted into tablet SEDDS (T-SEDDS), which complied with pharmacopeial quality parameters, including hardness (4.5 kg/cm^2), friability (0.54%), disintegration time (2 min 45 s), and drug content (99.52 ± 2.56%). The T-SEDDS exhibited complete drug release within 120 min, comparable to the liquid formulation. Stability studies conducted at 40 ± 2 °C/75 ± 5% RH for 3 months showed no significant changes in physical appearance, disintegration time, or drug content. These results demonstrate that SEDDS is an effective strategy for enhancing the oral delivery of lopinavir and offers a promising approach for improving the bioavailability of poorly water-soluble drugs..

Keywords: *Lopinavir; Self-emulsifying drug delivery system; Bioavailability enhancement; Lipid-based formulation; Tablet*

1. INTRODUCTION

Oral drug delivery remains the most preferred route of administration due to patient convenience and compliance [1]. However, poor aqueous solubility is a major challenge affecting the oral bioavailability of many therapeutic agents, particularly those classified under Biopharmaceutics Classification System (BCS) Class II. Lopinavir (LOP), a protease inhibitor widely used in the management of HIV infection, exhibits low aqueous solubility and variable oral absorption, leading to reduced therapeutic efficacy [2-3].

Self-emulsifying drug delivery systems (SEDDS) have emerged as an effective approach for enhancing the solubility, dissolution rate, and oral bioavailability of lipophilic drugs. SEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water emulsions upon mild agitation in gastrointestinal fluids. Conversion of liquid SEDDS into solid dosage forms further improves stability, handling, and patient acceptability [4-5].

The present research focuses on the systematic development of liquid and solid SEDDS of lopinavir using suitable lipid excipients, followed by comprehensive physicochemical characterization, in-vitro performance evaluation, and stability assessment.

2. MATERIALS AND METHODS

Materials

Lopinavir (LOP), used as the active pharmaceutical ingredient, was obtained as a gift sample from Cipla Laboratories, Mumbai, India. Capmul MCM C8 EP, employed as the lipid or oil phase in the formulation of self-emulsifying drug delivery systems, was procured from S.D. Fine Chemicals, Mumbai. Cremophor RH 40 was used as the primary surfactant, while Labrafil M 2125

CS served as the co-surfactant; both excipients were purchased from S.D. Fine Chemicals, Mumbai. Microcrystalline cellulose, used as a diluent in tablet formulation, was supplied by LOBA Ltd., India. Crospovidone was obtained from Qualigens, Mumbai, and was utilized as a superdisintegrant. Span 80 and Tween 80, procured from Qualigens, Mumbai, were used as lipophilic and hydrophilic surfactants, respectively.

Preformulation Studies

Melting Point Determination

The melting point of Lopinavir (LOP) was determined using the open capillary tube method, a standard and widely accepted technique for assessing the purity and identity of crystalline compounds. In this procedure, a small amount of finely powdered LOP was packed into a capillary tube, sealed at one end, and placed in a melting point apparatus. The temperature at which the sample began to melt and the point at which complete liquefaction occurred were recorded [6-9].

Fourier Transform Infrared (FTIR) Spectroscopy of Lopinavir (LOP)

Fourier Transform Infrared (FTIR) spectroscopy was employed to analyze the functional groups and confirm the chemical integrity of Lopinavir. A sample of pure LOP powder was thoroughly mixed with potassium bromide (KBr) in a 1:100 w/w ratio using a mortar and pestle to ensure uniform dispersion. The mixture was then compressed under pressure to form a transparent pellet, suitable for infrared transmission. The pellet was placed in the sample holder, and the IR spectrum was recorded using an IRAffinity-1 FTIR spectrometer (Shimadzu). The resulting spectrum was analyzed for characteristic absorption peaks corresponding to the functional groups present in LOP [10-12].

Determination of λ max and construction of calibration curve by UV-Visible spectroscopy

To determine the λ max and construct a calibration curve for LOP, a Shimadzu UV-Visible spectrophotometer (Model 1800) was utilized. A stock solution of LOP was prepared by accurately weighing 20 mg of LOP and dissolving it in 100 mL of methanol, resulting in a concentration of 200 µg/mL. Six serial dilutions of the stock solution were prepared, ranging from 20 µg/mL to 120 µg/mL, by appropriately diluting with methanol. The UV spectrum of the LOP standard solutions was recorded within the wavelength range of 200–400 nm using methanol as the blank. The λ max was determined by identifying the wavelength at which the maximum absorbance occurred for LOP [13].

A calibration curve of LOP in methanol was obtained by plotting absorbance at 259nm against drug concentrations and regression equations were computed. 259nm was selected as λ max for LOP in methanol. The absorbance of each standard solution was measured at the determined λ max. A calibration curve was constructed by plotting the absorbance values against the known concentrations of LOP. The linearity of the calibration curve was evaluated [14-15].

Solubility Study of Lopinavir in Various Vehicles

The equilibrium solubility of LOP was assessed in a range of lipid-based vehicles, including synthetic and semi-synthetic oils, as well as selected emulgents and co-solvents, to identify suitable excipients for formulation development. An excess quantity of LOP was added to each vehicle, and the mixtures were subjected to continuous stirring at 37±1°C for 72 hours to ensure solubility equilibrium [16].

Following equilibration, the samples were centrifuged at 2000 rpm for 10 minutes to separate undissolved drug. The resulting supernatant was then filtered through a 0.45 µm membrane filter to remove any residual particulates. A measured aliquot of the clear filtrate was appropriately diluted with methanol, and the absorbance was recorded at 259 nm using a double-beam UV/Vis spectrophotometer. The solubility of LOP in each vehicle was calculated based on standard calibration data [17].

Emulsification efficiency study

A. Selection of Surfactant(s)

To identify the most effective surfactant(s) for spontaneous emulsification of the oily phase Capmul MCM C8 EP (Cap MC8), selected from prior solubility studies—an emulsification screening study was conducted. A fixed amount of 300 mg of each surfactant was blended with Cap MC8 in a glass vial. The mixture was gently heated to 50–60°C, followed by vortexing on a cyclomixer for 3–4 minutes to achieve homogeneity. From this homogenized blend, 50 mg was accurately weighed and diluted to 50 mL with distilled water in a 100 mL volumetric flask. The emulsification efficiency was initially evaluated based on the number of flask inversions required to form a uniform emulsion. The formulation was then allowed to stand at room temperature for 2 hours, after which it was visually inspected for signs of turbidity and phase separation. To quantitatively assess emulsion clarity, the percentage transmittance (%T) of the resulting emulsions was measured at 638.2 nm using a UV-Visible spectrophotometer, with distilled water as the blank [18-20].

B. Selection of Co-Surfactant(s)

To enhance the emulsification performance of the selected surfactants—Cremophor EL (Cr-EL) and Cremophor RH40 (Cr-RH40)—a series of co-surfactants suitable for oral administration were screened. For each test, the surfactant:co-surfactant mixture was prepared in a 2:1 (w/w) ratio, and this blend was further mixed with Cap MC8 in a 1:1 (w/w) ratio. Specifically, 100 mg of co-surfactant and 200 mg of either Cr-EL or Cr-RH40 were added to 300 mg of Cap MC8 in a glass vial. The mixture was gently heated to 50–60°C and vortexed for 3–4 minutes to achieve a clear and isotropic dispersion [21-22].

From the resulting mixture, 50 mg was accurately weighed and diluted with 50 mL of distilled water in a 100 mL volumetric flask. The spontaneity of emulsion formation was assessed by recording the number of flask inversions required to obtain a fine emulsion or uniform emulsion. After standing for 2 hours at room temperature, the emulsions were evaluated for clarity by measuring % transmittance (%T) at 638.2 nm using a UV-Visible spectrophotometer, with distilled water as the blank.

Construction of Ternary Phase Diagram for Self-Emulsifying Systems

Ternary phase diagrams were constructed to identify the self-emulsifying regions within selected combinations of oil, surfactant, and co-surfactant using the flask inversion method, in accordance with the guidelines established by Pouton (2000). These diagrams aid in visualizing the proportions at which spontaneous emulsification occurs and help determine the optimal component ratios for a stable and efficient Self-Emulsifying Drug Delivery System (SEDDS) [23-25].

The concentration ranges for the formulation components were selected based on standard criteria for spontaneously emulsifying systems:

Oil phase: 25–70%

Surfactant: 30–75%

Co-surfactant: 0–30%

Two self-emulsifying systems were formulated based on prior solubility screening and emulsification performance:

Combination I: Capmul MCM C8 EP (Cap MC8) : Cremophor EL (Cr-EL) : Labrafil M 1944 CS (LM 1944)

Combination II: Capmul MCM C8 EP (Cap MC8) : Cremophor RH40 (Cr-RH40) : Labrafil M 2125 CS (LM 2125)

A total of thirty-five formulations for each combination were developed by systematically varying the proportions of oil, surfactant, and co-surfactant (Table 6.5 and 6.6). To assess the self-emulsification potential, 50 mg of each formulation was diluted with 50 mL of distilled water in a volumetric flask. Emulsification was facilitated through gentle flask inversion. The resulting emulsions were allowed to stand at room temperature for 2 hours, and their optical clarity was assessed by measuring percent transmittance (%T) at 638.2 nm using a UV-Visible spectrophotometer, with distilled water as the blank. Formulations that formed clear or slightly bluish emulsions in fewer than 10 flask inversions and exhibited transmittance above 95% were classified as efficient emulsion-forming systems. Formulations yielding milky or turbid emulsions with transmittance above 95% were categorized as coarse emulsions. Those requiring more than 20 flask inversions and still remaining turbid, with transmittance below 70%, were labeled as non-emulsifying systems. The data obtained from these evaluations were used to construct ternary phase diagrams, from which the emulsion-forming regions were identified [26-28].

Determination of Saturated Solubility of LOP in Selected Formulation Systems

To assess the solubilization efficiency of selected self-emulsifying systems, nine formulations from the Cap MC8: Cremophor RH-40: Labrafil M 2125 combination were chosen based on the ternary phase diagram—specifically those containing the highest proportion of the oily phase. These systems, upon aqueous dilution, formed spontaneous and fine emulsions, making them suitable candidates for further evaluation. The aim was to identify the most promising formulations capable of dissolving the maximum amount of LOP, thereby minimizing the number of formulations for in vitro testing. The selected systems contained Cap MC8 in the range of 45% to 55%, and a surfactant mixture of Cremophor RH-40 and Labrafil M 2125 in the remaining proportion. The saturated solubility of LOP in each of these systems was determined [29].

Compatibility Study of LOP with Selected Excipients by FTIR Spectroscopy

The compatibility of LOP with selected self-emulsifying excipients was assessed using FTIR spectroscopy to evaluate potential physical and chemical interactions. Mixtures of LOP with individual excipients Capmul MCM C8 (oil), Cremophor RH40 (surfactant), and Labrafil M 2125 (co-surfactant) were prepared in ratios guided by the solubility profile of LOP in each vehicle. These mixtures were stored at ambient conditions for 30 days and regularly inspected for any visual changes, including alterations in color or clarity, to preliminarily assess stability. The FTIR spectra of these mixtures were recorded and analyzed for any significant shifts or disappearance of characteristic functional group peaks compared to the spectrum of pure LOP [30].

Formulation of Liquid SEDDS of Lopinavir

Following the saturated solubility study of LOP, four formulation systems demonstrating the highest solubility of LOP were chosen for the development of L-SEDDS. These systems were optimized by adjusting the relative concentrations of the oil phase (Capmul MCM C8), surfactant (Cremophor RH40), and co-surfactant (Labrafil M 2125), while maintaining a fixed drug loading of 25 mg LOP per formulation unit [31]. The specific compositions of these SEDDS formulations are detailed in Table 5.3. The procedure is outlined below:

- **Step 1:** 25mg LOP was added to a vial containing the required quantity of Cap MC8. This mixture was gently heated in a water bath at 50–60°C to facilitate drug dispersion in the oil phase.
- **Step 2:** Pre-warmed surfactant (Cremophor RH40) and co-surfactant (Labrafil M 2125) were added to the oily mixture. The entire blend was homogenized for 10–15 minutes to form a clear system, indicating complete solubilization of LOP.
- **Step 3:** The resulting formulation was allowed to cool to room temperature and was kept undisturbed until in-vitro evaluations were carried out.
- **Step 4:** The optimized L-SEDDS formulation, weighing 380 mg (equivalent to 25 mg of LOP), was manually filled into hard gelatin capsules of size “2” and stored at room temperature until further use [32-34].

Table 1: Composition of LOP SEDDS Formulations

Components (mg)	**L1**	**L2**	**L3**	**L4**
Lopinavir	25.0	25.0	25.0	25.0
Capmul MCM C8 EP	158.4	158.4	158.4	176.0
Cremophore RH 40	158.4	140.8	123.2	105.6
Labrafil M 2125 CS	38.2	55.8	73.4	73.4
Mass fill per capsule (mg)	380.0	380.0	380.0	380.0

Evaluation of Optimized Formulations of LOP SEDDS

Globule size, polydispersity index and zeta potential

A 50 mg sample of the developed L-SEDDS was diluted to a final volume of 50 mL with distilled water, SGF and SIF. The mean globule size, polydispersity index (P.I.), and zeta potential of the resulting emulsion were subsequently measured using a Malvern Zetasizer [35].

% Drug content

The L-SEDDS formulation containing 25 mg of LOP was accurately weighed and transferred to a 50 mL volumetric flask. Methanol was added to the flask, and the volume was adjusted to the mark. The mixture was sonicated in a bath sonicator for 15-20 minutes to extract and dissolve the LOP. The resulting solution was filtered through Whatman filter paper. The filtrate was then diluted with 0.05 M sodium acetate buffer (pH 4.5). The concentration of LOP was determined by measuring the absorbance at 259 nm, using the sodium acetate buffer as a blank. The LOP concentration was calculated using the calibration curve [36].

In vitro Dissolution Study

The in vitro dissolution of L-SEDDS of LOP (25 mg), filled in hard gelatin capsules, was conducted using USP apparatus I at 37 ± 0.5°C with a rotation speed of 100 rpm in 0.05 M sodium acetate buffer (pH 4.5). At predetermined time intervals (10, 20, 30, 60, 90 and 120 minutes), 5 mL aliquots were removed from the dissolution medium and replaced with fresh buffer to maintain sink conditions. The methanolic extract was then filtered through Whatman filter paper. The amount of LOP released in the dissolution medium was determined by measuring absorbance at 259 nm. The dissolution study was also carried out in other dissolution media, namely, 0.1 N HCl (simulating gastric fluid, SGF) and phosphate buffer pH 6.8 (simulating intestinal fluid, SIF), to assess the effect of pH on drug release [37].

Formulation of Powder SEDDS (P-SEDDS)

The optimized L-SEDDS (L2) formulation was successfully converted into a free-flowing powder through the adsorption of the liquid SEDDS onto Neusilin US2. To achieve this, the optimized formulation (L2) was gradually introduced drop by drop onto 2g of the adsorbent in a broad porcelain dish. After each drop of L-SEDDS was added, the mixture was thoroughly homogenized using a glass rod to ensure uniform distribution of the formulation across the adsorbent. The addition of L-SEDDS continued until the adsorbent exhibited satisfactory flowability. The process was halted when the appearance of lumps in the powder mixture signaled that the desired consistency had been reached. The resulting powder was then dried at ambient temperature and stored at room temperature until further evaluation [38].

Formulation of Tablet SEDDS (T-SEDDS) of LOP

Based on the reported of the disintegration studies, Crospovidone (2.5% w/w) was selected as the optimal disintegrating agent. The P-SEDDS formulation was thoroughly blended with crospovidone and MCC. Magnesium stearate (1% w/w) and talc (1% w/w) were subsequently added to the mixture to aid in lubrication. The final blend was then mixed thoroughly to ensure uniform distribution of all ingredients. The resultant powder mixture was compressed into tablets using a single punch tablet machine with a 12 mm punch [39-40].

Table 2: Composition of optimized lop Tablet-SEDDS (LOP T-SEDDS)

Ingredients	Quantity per Tablet (mg)	Property
LOP L-SEDDS	380.0	Self-emulsifying system
Neusilin US2	210.0	Adsorbing agent
Cross povidone	17.50	Super disintegrants
Magnesium Sterate	6.50	Glident
Talc	6.50	Lubricant
MCC	29.5	Directly compressible Diluents
Weight of Tablet	650	LOP T-SEDDS

Evaluation of LOP T-SEDDS [41-42]

Thickness

Average thickness of randomly selected six tablets was measured by using Vernier caliper and expressed in mm.

Hardness

The mean hardness of randomly selected six tablets was checked by using Monsanto hardness tester. It is expressed in kg/cm^2.

Weight variation

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average weight by more than 5% and none deviates by more than twice that percentage. IP official limit of percentage deviation for tablet weighing 650 mg is ± 5 %.

Friability test

Friability of the tablets was tested using Roche friabilator. Loss of less than 1% in weight is considered to be acceptable. The weight of randomly selected 10 tablets was noted initially (W1) and placed in the friabilator at 20rpm. The tablets were reweighed and noted as (W2).

Disintegration time

The in vitro disintegration test was carried out on six tablets using USP disintegration test apparatus with distilled water at 37±0.5ºC and the time taken for complete disintegration of the tablet was noted.

Drug content

Ten tablets were taken randomly and powdered, the tablet powder equivalent to 25mg of LOP was accurately weighed and transferred to 50mL volumetric flask and the volume was made up to 50mL with methanol. Bath sonicator was used for 10min to facilitate the extraction of LOP in methanol. The methonolic extract was filtered through Whatman filter paper; filtrate was further diluted with required quantity of SAB and the concentration of SRT was determined by measuring the value at 259nm using SAB as blank [43].

In vitro dissolution study

In-vitro dissolution of T-SEDDS of SRT and marketed tablet preparation of LOP (25mg) was studied using USP apparatus II at 37± 0.5°C with a rotating speed of 50rpm in three different dissolution media namely media 0.05 M Sodium acetate buffer pH 4.5, SGF and SIF to examine the effect of pH on drug release. During the study, 5mL of aliquots were removed at different time intervals i.e.10, 20, 30, 60, 90 and 120 min from the dissolution medium and replaced with fresh buffer to maintain the sink condition. The aliquots were filtered through Whatman filter paper. The amount of LOP released in the dissolution medium was determined by measuring at 259nm [42-43].

Stability Study of LOP T-Sedds Tablets

Stability of developed LOP T-SEDDS dosage form wAS assessed under storage conditions; 40±2°C/75±5% RH as per ICH guidelines. T-SEDDS were individually wrapped in aluminum foil and placed in air tight container. All formulations were stored at aforementioned storage condition in stability chamber for 3 months. Required number of samples wree removed on 0th, 30th, 60th, and 90th day of stability study [44].

RESULTS AND DISCUSSION

Preformulation studies

Melting point

At 104°C, a slight change in the consistency of the LOP powder within the capillary tube was observed, indicating the onset of physical transition. The melting process commenced at 104°C, with complete liquefaction observed at 106°C. These findings are in good agreement with the melting point values previously reported in the literature.

FTIR spectrum of Lopinavir

The FTIR spectrum of lopinavir, a protease inhibitor, shows characteristic peaks corresponding to its different functional groups, including OH and N-H stretching vibrations, C-H stretching, C=O of amides, and C-N stretching. Specific peaks are typically observed at 3387.64cm^{-1} and 3284.37cm^{-1} for OH and N-H stretching, 2849.54 to 2955.15cm^{-1} for C-H aromatic and aliphatic, 1649.11 and 1556.42 cm^{-1} for C=O of primary and secondary amides, 1440.13 cm^{-1} for C-N stretching, and multiple peaks between 1289.44 and 1016.37 cm^{-1} for C-O stretching (Table 3 and Figure 1).

Table 3: FTIR Spectrum Interpretation of Pure Lopinavir

Observed Wavenumber (cm⁻¹)	Functional Group Assignment	Interpretation
3570	O–H stretching	Hydroxyl group in Lopinavir
3387.64	N–H stretching	Amide N–H vibration of Lopinavir
2955.15	C–H stretching	Methyl and methylene groups
1649.11	C=O stretching (amide I)	Confirming amide linkage
1563.19	N–H bending (amide II)	Confirms secondary amide structure
1440.13	C–H bending	Aliphatic hydrocarbon chains
1269.44	C–O stretching	Confirms oxygenated functional groups
1016.37	C–O–C stretching	Indicates presence of ether functionality

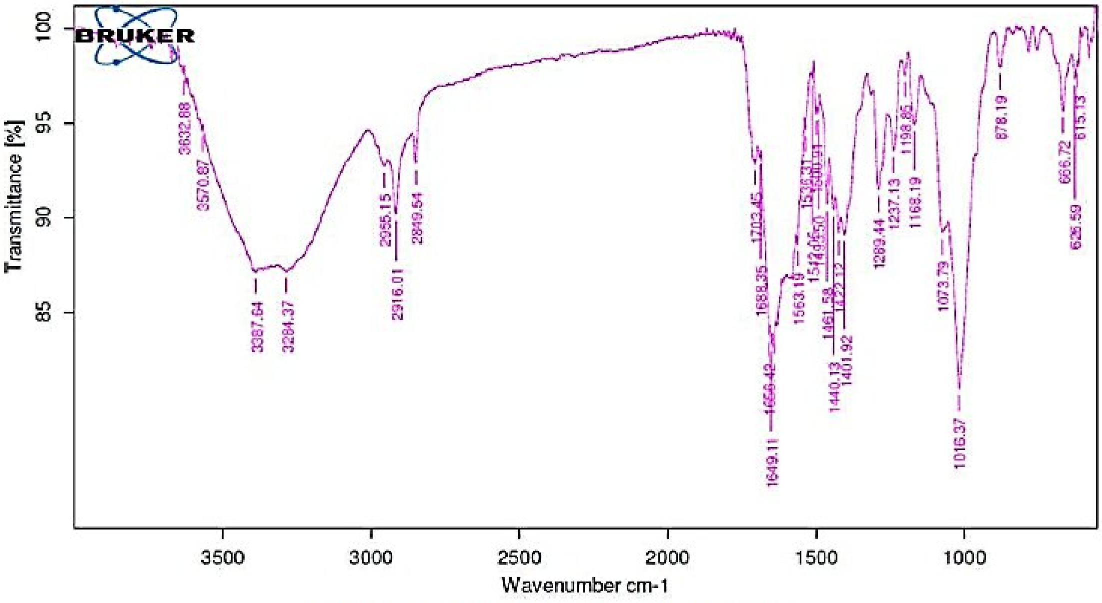

Figure 1. FTIR Spectrum of Pure Lopinavir Drug

UV-Visible Spectrum and Calibration Curve of LOP

Figure 2 presents the UV-Visible absorption spectrum of a 60 µg/mL standard solution of LOP in methanol. The spectrum exhibited multiple absorption peaks, with the maximum absorbance (λ_{max}) observed at 259 nm, indicating the wavelength of highest absorptivity. This observation is consistent with previous reports in the literature, which also identify 260 nm as the characteristic λ_max for LOP.

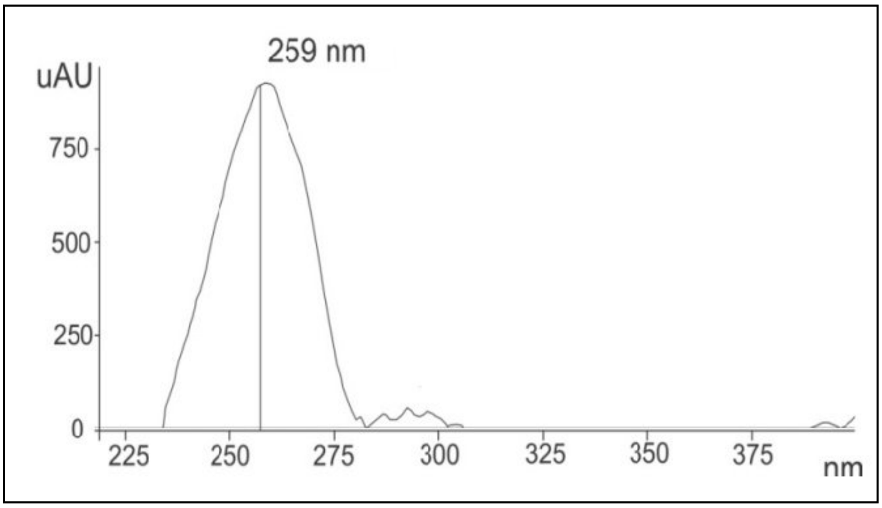

Figure 2: UV-VIS spectrum showing maximum wavelength for Lopinavir

The calibration curve of LOP in methanol, presented in Table 6.1 and Figure 6.3, demonstrated that Lopinavir follows Beer-Lambert's law over the concentration range of 20–120 µg/mL. The linear regression equation derived from the experimental data was $y = 0.0046x$, with a correlation coefficient (R^2) of 0.9999, indicating excellent linearity. This calibration curve was used for the quantitative estimation of LOP in subsequent analytical procedures.

Table 4: Calibration curve of LOP in methanol at 259nm

S. No.	Concentration (µg/ml)	Absorbance
1.	0	0.00
2.	20	0.0924
3.	40	0.1795
4.	60	0.2759
5.	80	0.3646
6.	100	0.4585
7.	120	0.5514

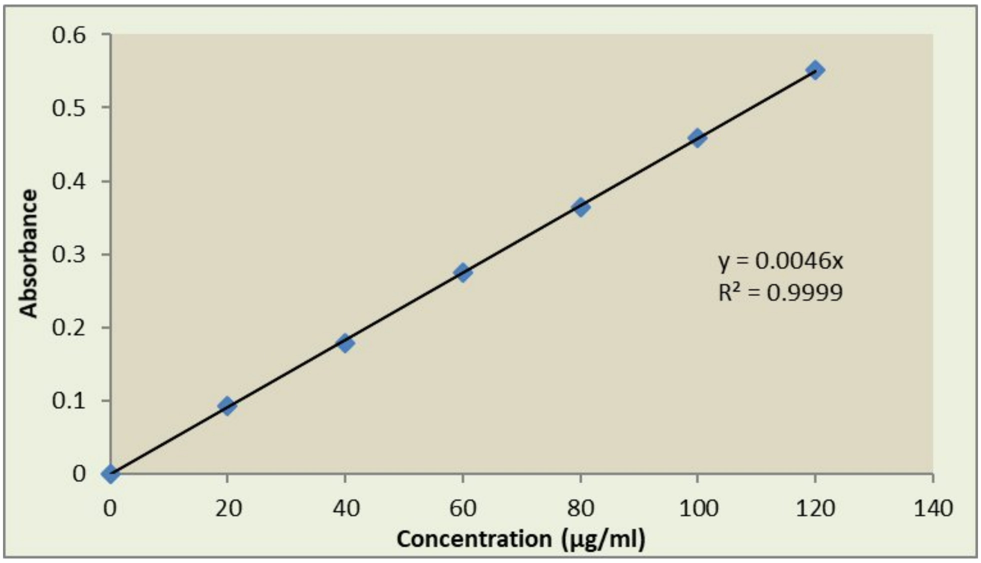

Figure 3: Calibration curve of LOP in methanol at 259nm

Solubility Profile of Lopinavir (LOP) in Oils

Based on findings from the literature review, solubility studies were focused on four oil phases that demonstrated a relatively high solubilizing capacity for Lopinavir (LOP), with solubility values exceeding 50 mg/g. These selected oily vehicles included Peceol, Capmul MCM EP, Capmul MCM C8 EP, and Isopropyl Myristate (IPM). Quantitative solubility estimations were carried out for each of these oils to determine their potential suitability as lipid phases for further formulation development (Table 5).

Table 5: Approximate solubility of LOP in various oily phases

OIL	25 mg	25 mg	25 mg	25 mg	Visual Observation	Approx. Solubility (mg/g)
Iso-Propyl Myristate	√	√	√	–	Soluble	50-75
Peceol	√	√	√	–	Soluble	50-75
Capmul MCM EP	√	√	√	–	Soluble	50- 75
Capmul MCM C8 EP	√	√	√	√	Soluble	75-100

Emulsification efficiency study

A. Selection of Surfactant(s)

The emulsification efficiencies of various surfactants were evaluated using Capmul MCM C8 (Cap MC8) as the selected oily phase. According to literature, a well-formulated Self-emulsifying Drug Delivery System (SEDDS) should disperse within seconds under mild agitation conditions. The percentage transmittance (%T) values for each surfactant–oil combination are summarized in Table 5. The results indicated that Cap MC8 exhibited varying emulsification behaviors depending on the surfactant used. Among the tested surfactants, Cremophor RH 40 (Cr-RH 40) demonstrated the highest emulsification efficiency, achieving a transmittance of 98.32% and forming a uniform fine emulsion with only 7 flask inversions (7FI). Cremophor EL (Cr-EL) ranked second, yielding 96.67%T and also requiring 7FI, matching the efficiency of Cr-RH 40 in terms of dispersion speed.

In contrast, Poloxamer 407 (PoL-407) and Poloxamer 188 (PoL-188) produced fine transparent or slightly bluish emulsions, with transmittance values of 96.30% and 92.74%, respectively. However, both required a significantly higher number of flask inversions (20FI) to achieve complete emulsification of Cap MC8. This reduced emulsification efficiency is likely attributed to the solid-state nature of the Poloxamers at room temperature, which hinders their ability to rapidly reduce interfacial tension during emulsification.

Table 6: Emulsification efficiency of surfactants for Capmul MCM C8 EP (Cap MC8)

Surfactant	No. of Flask Inversion	% Transmittance	Appearance
Cremophore EL	8	96.67	Slightly bluish
Cremophore RH 40	8	98.32	Transparent
Poloxamer L-407	20	96.30	Slightly bluish
Poloxamer L-188	20	92.74	Slightly bluish

B. Selection of Co-Surfactant(s)

Eleven co- surfactants were compared to increase the spontaneity of emulsification efficiency of selected surfactants Viz. Cr-RH40 and Cr-EL, to emulsify oily phase Cap MC8. The investigations clearly distinguished the ability of various co-surfactants, both hydrophilic and lipophilic, to improve the emulsification of selected surfactants. Table 7(a) and 7(b), reflects the ability of co-surfactants for their spontaneity to emulsify Cap MC8 along with surfactant.

The results of the solubility study revealed that LOP exhibited the highest solubility in Labrafil M 2125 CS (89.02 mg/g), followed closely by Labrafil M 1944 CS (87.29 mg/g). Given their high solubilization capacity, both Labrafil M 2125 and Labrafil M 1944 were selected as co-surfactants in the formulation development.

Table 7 (a): Spontaneity of emulsification by co-surfactants for surfactant for Cremophore RH40

Co-Surfactant	No. of flask inversion*	%Transmittance	Appearance
Ethanol	5	96.52	Slightly bluish
Iso-propyl Alcohol	5	93.65	Bluish white
PEG 400	5	96.12	Slightly bluish
Labrafil M 2125 Cs	2	100.20	Transparent
Labrafil M 1944 Cs	2	97.55	Bluish white

Table 7(b): Spontaneity of emulsification by co-surfactants for Cremophore EL

Co-Surfactant	No. of flask inversion*	%Transmittance	Appearance
Ethanol	4	97.84	Transparent
Iso-propyl Alcohol	4	94.58	Bluish white
PEG 400	3	95.35	Slightly bluish
Labrafil M 2125 Cs	2	97.54	Transparent
Labrafil M 1944 Cs	2	99.23	Transparent

Construction of Ternary Phase Diagrams

Based on emulsification ability of surfactants and their spontaneity enhancement by co-surfactants two distinguished systems were selected to plot ternary phase diagram to identify the possible mixture point producing emulsion. The phase diagrams of two different combination systems, Combination-I (CI); Cap MC8: Cr-EL: LM 1944 and Combination-II (CII); Cap MC8:

Cr-RH 40: LM 2125 are shown in Fig 4 and 6.5 respectively. The results clearly indicate that both combination systems demonstrated comparable efficiency in forming fine emulsions (transmittance >95%) up to an oily phase (Capmul MCM C8) concentration of 50% w/w. However, upon further increasing the oil content, divergent performance was observed between the two systems.

Combination-I, consisting of Cremophor EL (Cr-EL) and Labrafil M 1944, exhibited a decline in emulsification efficiency beyond 50% w/w Cap MC8. At higher oil concentrations, this system produced a coarse emulsion (%T <85%) and eventually formed a turbid dispersion (%T <50%), which could no longer be classified as a true emulsion and was therefore designated as 'No Emulsion'. In contrast, Combination-II, comprising Cremophor RH40 (Cr-RH40) and Labrafil M 2125, maintained its ability to form fine emulsions (%T >95%) even at elevated oil concentrations up to 60% w/w Cap MC8. This highlights the superior emulsification capacity and robustness of Combination-II under higher lipid load conditions.

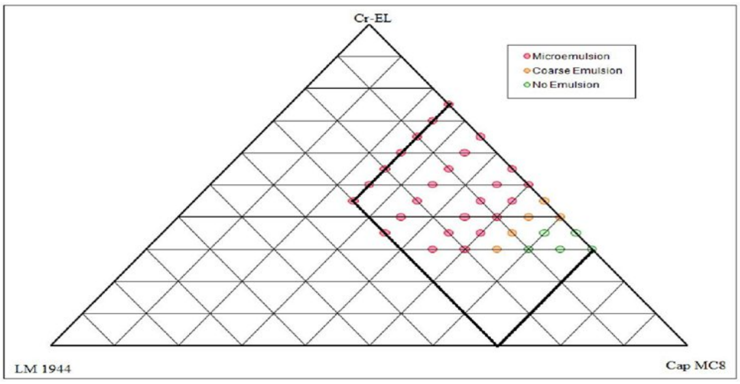

Figure 4: Ternary phase diagram of Cap MC8: Cr-EL: LM 1944 in distilled water

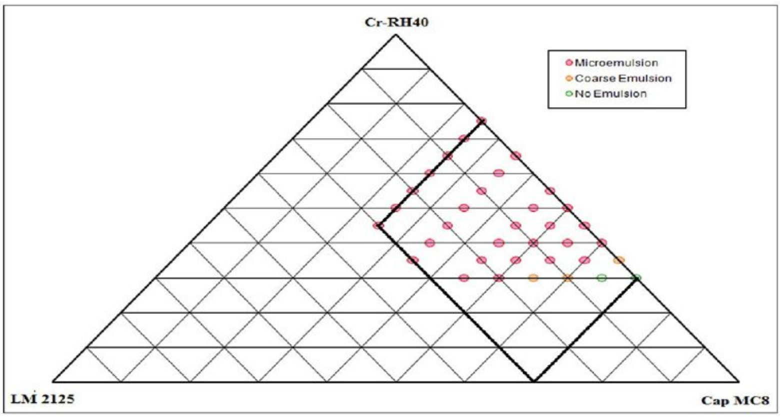

Figure 5: Ternary phase diagram of Cap MC8: Cr-RH40: LM 2125 in distilled water

Saturated Solubility of LOP in Selected Formulation Systems

For this study, various formulation systems under Combination-II were selected based on the analysis of ternary phase diagrams specific to this combination. The composition of each system, formulated with a total weight of 5 g, is detailed in Table 8 and Fig 6. These selected systems were evaluated for their ability to solubilize LOP. The solubility results indicated that all systems were capable of dissolving more than 73 mg/g of LOP. Notably, systems CII1, CII2, CII3, and CII6 exhibited enhanced solubilization capacity, each achieving LOP solubility values exceeding 77 mg/g. These formulations were therefore shortlisted for further investigation based on their superior drug-loading potential.

Table 8: Solubility profile of LOP in formulation systems selected from ternary phase diagrams

System No.	**Oil (Capmul MCM C8 EP)**		**Surfactant (Cremophore RH40)**		**Co-surfactant (Labrafil M 2125)**		**Solubility**
	(mg)	**(%)**	**(mg)**	**(%)**	**(mg)**	**(%)**	**(mg/g)***

CII_1	2250	45	2250	45	500	10	81.52 ± 2.15
CII_2	2250	45	2000	40	750	15	77.29 ± 1.24
CII_3	2250	45	1750	35	1000	20	78.10 ± 2.87
CII_4	2500	50	2000	40	500	10	73.00 ± 1.45
CII_5	2500	50	1750	35	750	15	74.36 ± 2. 21
CII_6	2500	50	1500	30	1000	20	79.92 ± 1.21
CII_7	2750	55	2250	45	0	0	72.32 ± 2.12
CII_8	2750	55	2000	40	250	5	72.30 ± 1.76
CII_9	2750	55	1750	35	500	10	73.92 ± 1.39

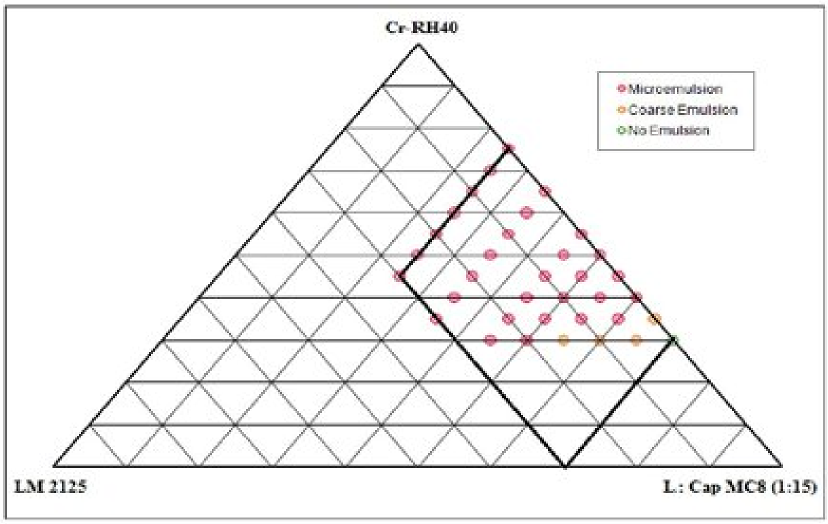

Figure 6: Ternary phase diagram of LOP loaded Cap MC8 (1:15): Cr-RH40: LM 2125 in sodium acetate buffer, pH 4.5

Drug excipients compatibility study

The compatibility of Lopinavir with selected excipients intended for the development of L-SEDDS was assessed using FTIR Spectroscopy. Visual inspection revealed no changes in color, texture, or appearance in any of the mixtures throughout the study duration, suggesting initial physical stability. Following storage, FTIR spectra were recorded for each mixture and compared against the spectrum of pure LOP. The comparative spectra, presented in Figure 6.6, show that the characteristic absorption peaks of LOP remained clearly identifiable in its physical mixtures with Capmul MCM C8 (oil) and with the surfactant–co-surfactant blend (Cremophor RH40 + Labrafil M 2125). No significant peak shifts or disappearance of functional group bands were observed (Table 9 and Figure 7).

Table 9: FTIR Interpretation of Lopinavir and Its Physical Mixtures

Characteristic Peak (cm⁻¹)	**Functional Group / Assignment**	**Interpretation**
3350–3450	N–H stretching (secondary amide)	Confirms presence of amide functional group in LOP
2950–2850	Aliphatic C–H stretching	Indicates alkyl chain vibrations
1650–1680	C=O stretching (amide I)	Characteristic carbonyl group of LOP
1540–1560	N–H bending (amide II)	Confirms peptide-like amide structure

1200–1100	C–O / C–N stretching	Confirms ester and amide linkages
3350–3450	N–H stretching	Retained LOP peak with slight broadening
2950–2850	C–H stretching	Presence of LOP and Cap alkyl groups
1650–1680	C=O stretching	No significant shift, indicating compatibility
3200–3600	O–H stretching	Broad band due to Cremophor RH40
2950–2850	C–H stretching	Enhanced due to surfactant alkyl chains
1650–1680	C=O stretching	LOP carbonyl peak retained with reduced intensity
1200–1100	C–O stretching	Characteristic of Cremophor RH40
3350–3450	N–H stretching	Slight broadening due to intermolecular interactions
2950–2850	C–H stretching	Contribution from LOP and LM2125
1650–1680	C=O stretching	Retained LOP peak indicating stability

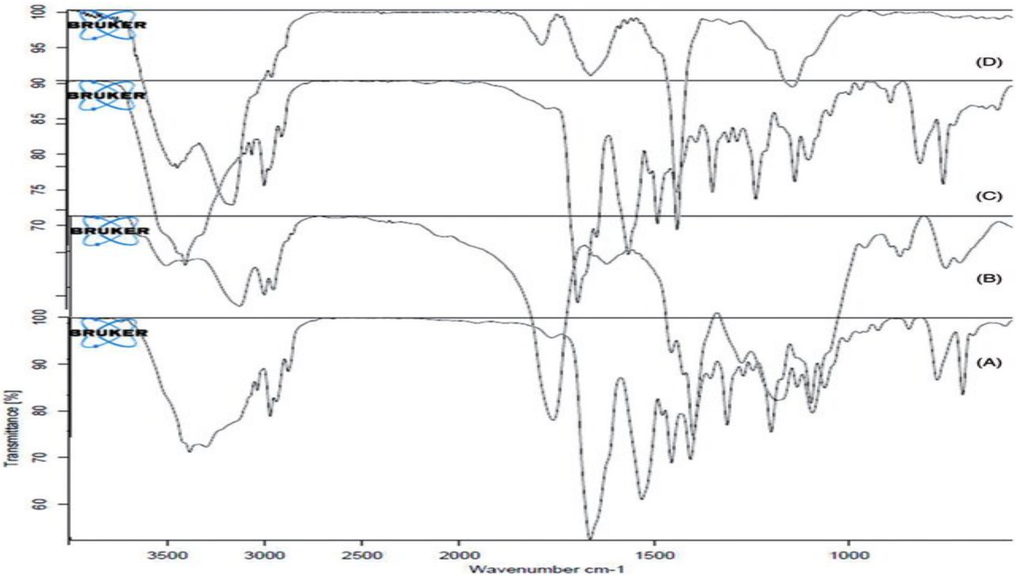

Figure 7. FTIR spectra of (A) Lopinavir, (B) LOP+Cap (C) LOP+Cr RH40 (D) LOP+LM2125

Evaluation of Formulated LOP L-SEDDS

Robustness to dilution study

The LOP-loaded liquid self-emulsifying drug delivery systems (L-SEDDS) were evaluated for robustness upon dilution in various aqueous media differing in pH. The impact of dilution on the stability and performance of the L-SEDDS formulations is summarized in Table 10. Formulation L2 demonstrated excellent robustness across all dilution conditions, exhibiting percent transmittance values exceeding 98%, indicative of clear and stable emulsions. Moreover, no drug precipitation was observed up to 12 hours post-dilution, confirming the formulation's stability and solubilization efficiency.

In contrast, formulations L1, L3, and L4 showed slightly lower transmittance values (~96%) and displayed a bluish or bluish-white appearance upon dilution, suggesting minor instability or larger droplet formation. Overall, the robustness to dilution study supports the selection of L2 as the optimized L-SEDDS formulation for LOP, based on its superior clarity, physical stability, and resistance to drug precipitation across a range of physiologically relevant pH conditions.

Table 10: Optimization of LOP L-SEDDS formulation by robustness to dilution study in distilled water

Formulation	Dilution	%Transmittance	Appearance	Drug

code				precipitation
L1	50	95.08	white	Stable
	100	96.12	white	Stable
	1000	96.25	Bluish white	Stable
L2	50	98.88	Clear	Stable
	100	99.56	Clear	Stable
	1000	100.12	Clear	Stable
L3	50	95.12	Bluish white	Stable
	100	95.63	Bluish white	Stable
	1000	95.62	Bluish white	Stable
L4	50	96.25	Slightly bluish	Stable
	100	95.18	Bluish white	Stable
	1000	95.21	Bluish white	Stable

Globule Size Analysis

The globule size of an emulsion is a critical parameter influencing the self-emulsification efficiency, drug release kinetics, and overall absorption profile. Smaller droplet sizes are known to enhance drug absorption and significantly improve oral bioavailability due to increased surface area and faster dissolution rates.

The optimized L-SEDDS of LOP demonstrated a mean globule size in the range of 60–65 nm (Table 11). Among the tested media, the globule size in SGF was marginally larger (65.23 ± 2.15 nm) compared to distilled water and SIF, although the difference was not statistically significant.

The PDI values for the LOP L-SEDDS (L2) ranged from 0.345 to 0.417 across all media, indicating a relatively narrow size distribution and good uniformity in droplet size. These results confirm the formation of a fine emulsion system with desirable characteristics for efficient drug delivery. It has been reported that emulsions with a positive surface charge (as indicated by zeta potential measurements) may exhibit enhanced mucoadhesive interactions.

Table 11: Globule size, Polydispersity Index and Zeta potential of L2 in various dilution media

Distilled water			**0.1N HCl (SGF)**			**Phosphate buffer pH 6.8 (SIF)**		
Globule Size (nm)	P.D.I.	Zeta potential (mV)	Globule Size (nm)	P.D.I.	Zeta potential (mV)	Globule Size (nm)	P.D.I.	Zeta potential (mV)
60.19 ± 3.27	0.345	+ 13.12	65.23 ± 3.15	0.417	+ 14.23	61.19 ± 3.15	0.412	+ 14.09

Drug Content

The drug content of the optimized L-SEDDS formulation (L2) was quantified using UV-visible spectroscopy and was found to be within the acceptable range, between 100.23% and 102.56% of the labeled claim. These results indicate that LOP is efficiently solubilized and homogeneously distributed within the self-emulsifying system.

In vitro dissolution profile of optimized LOP L-SEDDS (L2)

The results of in vitro dissolution profiles, of optimized LOP L-SEDDS (L2) filled in hard gelatin capsule, in various dissolution media are provided in respective Table 12 and Figure 8. L2 showed more than 85% LOP released in 20min irrespective of the dissolution media, indicating that the release of LOP from L2 was independent of the pH of the dissolution medium. L2 showed complete drug release at 45min. The rate and extent of LOP release from L2 was excellent suggested that L-SEDDS may improves the oral bioavailability of LOP.

Table 12: *In vitro* dissolution profile of optimized LOP L-SEDDS (L2)

Time (h)	**% Cumulative release**		
	0.1N HCl	**SAB pH 4.5**	**PBS pH 6.8**
0	0	0	0
10	40.71	43.52	38.11
20	70.23	73.19	68.15
30	87.37	89.23	86.12
60	96.89	97.19	97.12
90	100.02	101.17	101.12
120	100.07	101.23	101.04

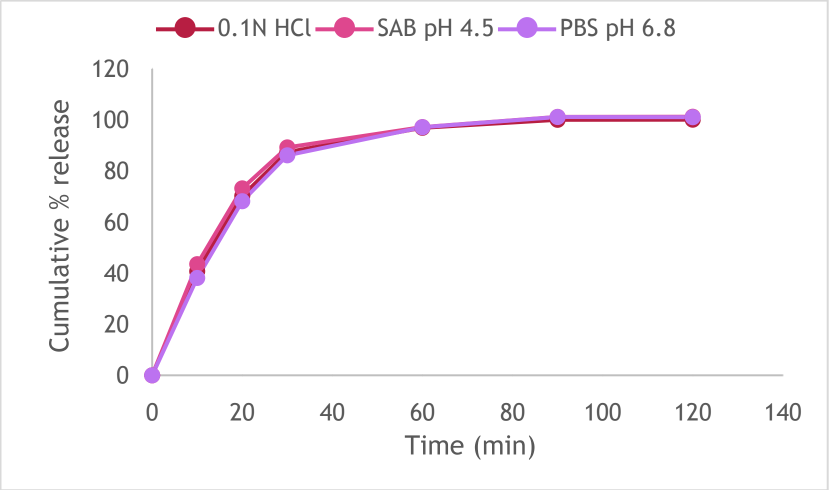

Figure 8: *In vitro* dissolution profile of LOP L-SEDDS (L2) in various dissolution media

Evaluation of LOP T-SEDDS

Physical Properties

The evaluation of physical parameters for the tablet formulation of SRT-loaded solid self-emulsifying drug delivery system (LOP T-SEDDS) is summarized in Table 6.10. The tablets exhibited consistent weight uniformity, with no individual tablet deviating by more than ±5% from the average weight and none exceeding ±10%, thereby complying with pharmacopeial requirements for weight variation.

The tablets demonstrated adequate mechanical strength, with an average hardness of 4.5 kg/cm², indicating their suitability for handling and transport. The average disintegration time for six tablets was 2 minutes and 45 seconds, confirming the effective functionality of crospovidone as a superdisintegrant, enabling rapid tablet disintegration and dispersion in the dissolution medium. Additionally, the T-SEDDS tablets successfully passed the friability test, with a friability value of less than 1%, further supporting their mechanical integrity and suitability for oral administration.

Table 6.11: Physical Evaluation parameters of T-SEDDS

Parameter	**Observation**	**Inference**
Drug content (%)	102.52 ± 2.56%	Within the acceptable limit
Weight variation	3.12%	Passes the test
Thickness	4.2 mm	Within the limit
Hardness	4.5 kg/cm²	Within the limit
Disintegration time	2 min 45 s	Passes the test
Friability	0.54%	Passes the test

Drug Content

The drug content of the LOP-loaded T-SEDDS was determined to be 99.52 ± 2.56%, indicating excellent content uniformity. This result confirms that LOP was uniformly distributed within the tablet matrix, demonstrating effective incorporation into the solid excipient blend.

In vitro Dissolution Profile of LOP T-SEDDS Tablet

The *in vitro* dissolution profile of the LOP tablet formulated from solid SEDDS (T-SEDDS) was compared with both the liquid SEDDS (L-SEDDS) as illustrated in Table 6.12 and Figure 6.8. The dissolution behavior of T-SEDDS closely mirrored that of the L-SEDDS, confirming that the self-emulsifying characteristics of the formulation were retained following compression into tablet form. Notably, complete drug release from the T-SEDDS was achieved within 120 minutes across all tested dissolution media, highlighting the formulation's robustness and efficiency in promoting rapid and complete drug release irrespective of the pH or composition of the medium. These findings underscore the suitability of T-SEDDS as an effective solid oral delivery system for LOP, offering comparable performance to its liquid counterpart with added advantages in stability and patient compliance.

Table 12: *In vitro* dissolution profile of optimized LOP T-SEDDS (L2)

Time (Min)	**% Cumulative release**		
	0.1N HCl	**SAB pH 4.5**	**PBS pH 6.8**
0	0	0	0
10	32.86	34.62	32.15
20	66.12	71.07	65.22
30	80.09	82.27	78.87
60	89.23	91.47	85.17
90	96.12	98.24	92.23
120	100.17	101.65	101.26

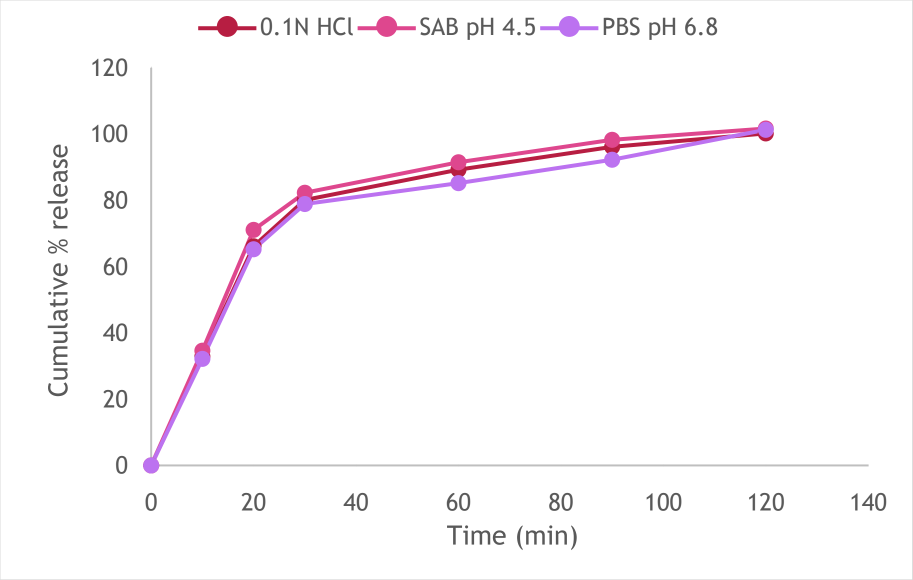

Figure 9: ***In-vitro*** **dissolution profile of LOP T-SEDDS in various dissolution media**

Stability Study of LOP T-SEDDS Tablets

Over a 90-day period, the optimized T-SEDDS tablets maintained its physical integrity, with no observable changes in color or surface, indicating good physical stability. A non-significant reduction in drug content was observed during the storage period. Importantly, the drug content across all tested samples remained within pharmaceutically acceptable limits, confirming the chemical stability and retention of formulation quality under the specified storage conditions (Table 13).

Table 13: Stability assessment of LOP T-SEDDS at 40°C ± 2°C / 75% ± 5 % RH for 3 months

Parameter assessed	**0th day**	**30th day**	**60th day**	**90th day**
Physical appearance	Smooth surface	Smooth surface	Smooth surface	Smooth surface
Drug content (%)	101.25	100.65	98.56	96.14
Disintegration Time	2min 45s	2min 45s	2min 45s	2min 30s

.

3. CONCLUSION

The study successfully demonstrated the feasibility and effectiveness of SEDDS technology in enhancing the solubility and dissolution of poorly water-soluble drugs. Both liquid and solid forms of SEDDS provided rapid drug release, uniform drug content, and excellent stability, making them promising candidates for improving oral bioavailability. The optimized formulations of LOP especially the solid SEDDS (T-SEDDS), offer advantages in terms of ease of administration, patient compliance, and commercial viability. These findings support the continued development of SEDDS-based delivery systems for a wide range of lipophilic drug molecules.

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