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Research

Formulation Development and *In-Vitro* Characterization of Liquid and Solid Self Microemulsifying Drug Delivery System of Apremilast

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Abstract

Background: Most drugs are administered orally, but this route is limited for molecules with poor aqueous solubility, a key factor in achieving effective systemic drug concentrations for the desired pharmacological response. Many potential drugs face low solubility and dissolution rates, reducing absorption and low oral bioavailability.
Objective: This study focused on developing and evaluating liquid (L-SMEDDS) and solid (S-SMEDDS) self-microemulsifying drug delivery systems for the poorly water-soluble Apremilast. The L-SMEDDS formulation used oleic acid (oil), Tween 80 (surfactant), and Transcutol HP (co-surfactant). S-SMEDDS were prepared via adsorption onto Aerosil as a solid carrier. L-SMEDDS were assessed for self-emulsification time, droplet size, zeta potential, PDI, transmittance, and drug content. S-SMEDDS evaluations included micromeritic properties, drug content, in vitro release, and structural analysis via SEM, DSC, and XRD.
Result: The findings showed that solid SMEDDS significantly enhanced the dissolution rate of Apremilast, improving bioavailability by forming a microemulsion upon dilution in gastric fluids, which promotes better drug release.
Conclusion: Overall, the results indicate that solid SMEDDS can significantly improve the solubility and dissolution profile of poorly soluble drugs, offering potential to enhance oral bioavailability and therapeutic efficacy.

Keywords: Apremilast, Microemulsion, SMEDDS, Pseudo ternary Phase Diagram.

INTRODUCTION

Enhancing the oral bioavailability of poorly water-soluble drugs is a significant challenge in pharmaceutical development. Although oral drug delivery remains the most common route for chronic disease treatment due to its high patient compliance, about 50% of drug compounds face limitations due to poor solubility and high lipophilicity [1-3]. Nearly 40% of new drug candidates are poorly soluble in water, complicating the development of effective oral dosage forms. Various strategies have been employed to address these issues, including surfactants, cyclodextrins, micronization, liquisolid techniques, salt formation, pH adjustment, nano-sized delivery systems, solid dispersions, and permeation enhancers. However, each approach comes with its drawbacks. Micronization may cause chemical or thermal instability, leading to the degradation of drugs. Solid dispersions often require numerous carriers, resulting in large, difficult-to-swallow tablets or capsules, and the production methods, such as freeze-drying or spray-drying, can be expensive [4,5,6]. Cyclodextrin complexation is limited to drugs that are soluble in both aqueous and organic solvents.

Recent interest has shifted toward lipid-based formulations to improve bioavailability, particularly in the context of meals rich in fat. Lipid suspensions, solutions, and emulsions have shown promise, but self-microemulsifying drug delivery systems (SMEDDS) have gained significant attention [7-9]. These systems offer a solution to the challenges of traditional emulsions, such as stability and manufacturing issues. SMEDDS are isotropic mixtures of drugs, lipids, surfactants, and co-solvents that form fine emulsions upon mild agitation and dilution with aqueous media. The droplet size typically ranges from 100 to 300 nm, but SMEDDS can produce transparent micro-emulsions with droplet sizes of less than 50 nm [10-12].

The advantages of SMEDDS include their ability to increase membrane permeability due to the surfactants and enhance lymphatic absorption through the medium and long-chain oils used. These factors contribute to improved drug performance, offering faster absorption and better bioavailability [13-15]. Additionally, SMEDDS are physically stable, easy to manufacture, and can be encapsulated in soft gelatin capsules, where they form a micro-emulsion with a large surface area upon dispersion in the gastrointestinal tract. This emulsion enhances absorption through faster digestion by gastrointestinal enzymes and subsequent transfer to mixed micelles or absorption directly from the emulsion particle. Overall, SMEDDS represent a promising strategy for enhancing the oral bioavailability of lipophilic drugs [16-18].

MATERIALS AND METHODS

Materials

Apremilast was obtained as a gift sample from Mylan Laboratories in Telangana, India. Oleic acid (Cis-9-Octadecenoic acid, also known as (Z)-Octadec-9-enoic acid) was purchased from Universal Scientifics and Chemicals in Madurai. Tween 80 (Polysorbate 80, or sorbitan monooleate), serving as a surfactant, was also sourced from Universal Scientifics and Chemicals in Madurai. Transcutol HP (Diethylene glycol monoethyl ether), used as a co-surfactant, was acquired from Johns Chemicals in Madurai. Aerosil (Colloidal Silicon Dioxide) was received as a gift sample from Sai Mirra Innopharm in Chennai. All other chemicals and reagents used were of Analytical grade, obtained commercially, and used as received.

Method of preparation

Analytical method for the estimation of Apremilast

The analytical method used for determination of Apremilast is UV Spectrophotometric method. In the present study, Apremilast peak was observed at 230nm in UV Spectrophotometry.

Preparation of calibration standards

For the estimation of Apremilast, weighed accurately about 10 mg of Apremilast and dissolved it in few mL of methanol in a 10 mL volumetric flask and the volume was made up with methanol. The stock solution was subsequently diluted to get a series of dilutions 2, 4, 6, 8, and 10 µg/mL of solution using pH 6.8 sodium phosphate buffer and the absorbance was measured at 230 nm (UV- spectrophotometer, Shimadzu UV- 1700) against pH 6.8 sodium phosphate buffer as blank [19].

Solubility studies

The solubility of apremilast in various oils, surfactants, and co-surfactants was determined using the shake flask method. An excess amount of apremilast was added to 2 mL of each vehicle in separate glass vials. The mixtures were thoroughly mixed with a vortex mixer for 10 minutes. Following this, the mixtures were shaken in a water bath shaker for 48 hours to achieve equilibrium. Afterward, they were centrifuged at 3000 rpm for 15 minutes. The supernatants were filtered through a 0.45 µm membrane filter (Millipore filter). Methanol was used to dilute the filtered solutions, and the drug concentrations were analyzed using a UV-Visible spectrophotometer at a wavelength of 230 nm (λmax) [20, 21].

Drug excipient compatibility study using FT-IR

The compatibility of the drug with excipients was assessed using FTIR Spectroscopy (SHIMADZU FT/IR-410) with the diffuse reflectance method. Samples were prepared by mixing the drug with potassium bromide (KBr), triturating in a glass mortar, and placing it in the sample holder. IR spectra of the pure drug, oil phase, surfactant, co-surfactant, and formulation were analyzed in the 400-4000 cm-1 range. The spectra were compared for any shifts in functional peaks or the appearance/disappearance of new peaks. No changes in the drug's main peaks indicated no interaction with excipients, while changes suggested potential interactions [22, 23].

Construction of pseudo-ternary phase diagram

Phase behavior and composition relationships of the mixture were determined by constructing pseudo-ternary phase diagrams using the water titration method with oil, surfactant, and co-surfactant. The surfactant and co-surfactant weight ratios were varied (1:1, 2:2, 3:1). The oil and surfactant/co-surfactant mixture was prepared in different weight ratios (e.g., 1:9, 2:8, etc.). Water was added drop by drop under stirring at 37°C until a clear mixture was obtained, and component concentrations were recorded. These values were used to complete the phase diagrams, from which the appropriate ratios of oil, surfactants, co-surfactants, and water for SMEDDS preparation were selected. The microemulsion region was chosen based on the solution remaining clear even after dilution [24].

Formulation of Liquid SMEDDS of Apremilast

SMEDDS formulations were prepared based on the ternary phase diagram, selecting appropriate ratios of oil (Oleic acid), surfactant (Tween 80), and co-surfactant (Transcutol-HP). The surfactant and co-surfactant were mixed separately to form an S mix. The drug (Apremilast) was added in small amounts to the oil phase with continuous stirring until a clear solution formed. The Apremilast-containing oil phase was then added to the S mix and stirred until a homogeneous mixture was obtained. The final formulations were stored at room temperature [25-27].

Characterization of liquid SMEDDS [29-31]

Visual assessment

Apremilast liquid SMEDDS was diluted with 100 ml of purified water and gently stirred using a magnetic stirrer. The temperature should be maintained at 37°C.

Dispersibility test

The dispersibility test of SMEDDS was conducted to evaluate its ability to form an emulsion and the size of the resulting globules, categorizing them as SMEDDS. The test was performed using a USP paddle-type dissolution apparatus, where the formulation was added to 500 mL of water at 37 ± 0.5°C, and the paddle was rotated at 50 rpm. Upon titration with water, the SMEDDS formulation formed a mixture, allowing the in vitro performance of the formulation to be assessed based on the type of emulsion formed. It is represented by the following table 1

Table 1: Determination of Self Emulsification Time by its Dispersibility and Appearance

S.NO	Dispersibility and appearance	Grade	Time to self-emulsify (minutes)
1.	Rapidly forming (within 1 min) Nano or microemulsion having a clear or bluish appearance	A	Within 1
2.	Rapidly forming, slightly clear emulsion having a bluish white appearance	B	Within 1
3.	Fine milky emulsion that formed within 2 minutes	C	Within 2
4.	Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 mints).	D	Within 3
5.	Exhibit poor or minimal with large oil droplets presents on the surface.	E	Within 3

Determination of self-emulsification time

The emulsification time of SMEDDS was determined in the dissolution apparatus. One ml of each formulation was added dropwise to 500 ml of distilled water at 37±0.5ºC. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time was assessed visually.

Thermodynamic stability studies

The physical stability of a lipid formulation is very important for its performance as it can be adversely affected by the precipitation of the drug in an excipient matrix. Poor physical stability of formulation can lead to phase separation of excipients which affects bioavailability as well as therapeutic efficiency. Also, the incompatibilities between the formulation and shell of the capsule may cause brittleness, softness, and deleted disintegration or incomplete release of a drug. The following cycles were carried out for these studies.

Heating cooling cycle

The optimized SMEDDS formulations were diluted with 100 times distilled water. Six cycles between cooling temperature (4ºC) and heating temperature (45ºC) with exposure at each temperature for not less than 48 hours were carried. That formulation, which was stable, then was subjected to a centrifugation test.

Centrifugation

To estimate metastable systems, the optimized SMEDDS formulations were diluted with 100 times distilled water. Pass heating- cooling cycles are centrifuged at 3500 rpm for 30 minutes. Those formulations that do not show any phase separation are taken for the freeze-thaw stress test.

Freeze-thaw cycle

This test was performed for accelerated stability testing of the Nanoemulsion formulation. In this study, three freeze-thaw cycles of formulations were exposed between temperatures 21ºC-25ºC for each temperature cycle not more than 48 hours. For a better estimation of accelerated stability studies six such cycles should be run for each batch of formulation. The formulations which showed the maximum stability were selected for further study.

Cloud point measurement

Dilute the formulation 1 ml with 1000 ml of water in a beaker and place it on a water bath gradually increasing the temperature until the diluted formulation turned to cloudy or turbid. It gives the information about the stability of the microemulsion at body temperature.

Robustness to dilution

Robustness to dilution was studied by diluting SMEDDS to 50, 100, and 1000 times with water, phosphate buffer pH 6.8, and phosphate buffer pH 7.4. The diluted SMEDDS were stored for 12 hours and observed for any signs of phase separation or drug precipitation.

Refractive index and percent transmittance

The transparency of the formulation was confirmed through refractive index and percent transmittance measurements. The refractive index was determined using an Abbe refractometer, while percent transmittance was measured at 638 nm using a UV spectrophotometer with distilled water as the blank. To assess stability upon dilution, 1 mL of the formulation was diluted with 100 mL of distilled water, and transmittance was measured. Three replicate assays were performed for each sample.

Viscosity determination

The rheological properties of the microemulsion are evaluated by the Ostwald viscometer. These viscosity determinations confirm whether the system is w\o or o\w. If the system has low viscosity, then it is an o/w type of the system, and if high viscosities then it is a w\o type of the system.

Absolute drug content in L-SMEDDS

Liquid SMEDDS containing Apremilast, equivalent to 10 mg was diluted in a suitable quantity of methanol. The sample was mixed thoroughly to dissolve the drug in methanol by stirring. The solvent extract is filtered through a 0.45 µm membrane filter. Drug content was determined by measuring the absorbance in a UV spectrophotometer against the standard solvent solution of the drug.

Conversion of liquid SMEDDS into solid S-SMEDDS [26-29]

Solid SMEDDS were prepared by mixing liquid SMEDDS containing Apremilast with Aerosil in 1:1 proportion. Liquid SMEDDS was added dropwise over MCC and homogenized using a glass rod to ensure uniform distribution of formulation in a china dish.

Physiochemical characterization of SMEDDS [28, 29]

Micrometric properties

Prepared S-SMEDDS was evaluated for micrometric properties such as angle of repose, bulk density and tapped density, compressibility index, and Hauser's ratio.

a) Angle of Repose:

The angle of repose is the steepest angle between the surface of a powder pile and the horizontal plane. It is an indirect measure of powder flowability, reflecting inter-particle cohesion. A heap slides when its inclination overcomes frictional forces and stabilizes when gravitational forces balance them. The resulting angle between the pile's side and the horizontal is the angle of repose.

$$\textbf{Angle of Repose } (\theta) = \tan^{-1} (h / r)$$

Where, h = height of the heap, r = radius of the heap

Table 2: Angle of Repose

Angle of repose	Type of flow
<20	Excellent
20-30	Good
30-35	Moderate
35-40	Poor
>40	Very Poor

b) Bulk Density

Bulk density denotes the total density of the material. It includes the true volume of interparticle spaces and intraparticle pores. The packing of particles is mainly responsible for bulk. Bulk density is the ratio between a given mass of powder and its bulk volume. Apparent bulk density is determined by pouring the weighed granules into a graduated cylinder via funnel and measuring the volume. Bulk density is calculated by using the formula.

$$\textbf{Bulk Density} = \frac{\textbf{Weight of the powder}}{\textbf{Bulk volume of the powder}} = \frac{W}{V_0}$$

c) Tapped Density

A known quantity of sample is transferred to a graduated cylinder and placed on tapped density apparatus and operated for a fixed number of taps (100). It is the ratio of weight of sample to tapped volume.

$$\textbf{Tapped Density} = \frac{\textbf{Weight of the powder}}{\textbf{Tapped volume of the powder}} = \frac{W}{V_f}$$

d) Compressibility (or) Carr's index

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug is studied by using the following formula.

$$\textbf{Carr's index (\%)} = \frac{\textbf{Tapped Density} - \textbf{Bulk Density}}{\textbf{Tapped Density}} \times 100$$

Table 3: Carr's index

Compressibility Index (%)	Type of Flow
5-15%	Excellent
15-25%	Good
>25%	Extremely Poor

e) Hausner's ratio

Hausner's ratio is defined as the ratio of tapped density to bulk density of the powders. The Hausner's ratio is a number that is correlated to the flowability of a powder (or) granular material. It is calculated by using the formula:

$$\textbf{Hausner's ratio} = \frac{\textbf{Tapped Density}}{\textbf{Bulk Density}}$$

The values less than 1.25 indicate good flow (=20% Carr), whereas greater than 1.25 indicates poor flow (=33% Carr) Between 1.25 and 1.5, added glidant normally improves flow.

Drug content

The S-SMEDDS containing Apremilast, equivalent to 10 mg was diluted in a suitable quantity of methanol or ethanol and sonicated for 10-15 minutes. Then it was filtered through a 0.45µm membrane filter. Drug content was analyzed by measuring absorbance using a UV spectrophotometer.

***In-vitro* drug release of S-SMEDDS [28-32]**

The in vitro drug release of prepared S-SMEDDS was assessed in triplicate using a Dissolution Type II apparatus (Paddle type) at 37±0.5ºC. S-SMEDDS containing 10 mg equivalent of the drug was placed in 900 ml of dissolution medium (phosphate buffer pH 6.8 add 5g of sodium lauryl sulphate). The revolution speed of the paddle was maintained at 75 rpm. At predetermined time intervals, 5 ml of dissolution medium was collected, and filtered and the same volume of fresh dissolution medium was replenished to maintain the sink conditions. The samples were analyzed for the drug concentration using a UV spectrophotometer at 230 nm.

Kinetics of drug release [31-34]

To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained were fitted to various mathematical models such as zero order, first order, Higuchi matrix, Hixon-Crowell cube root law and Korsmeyer- Peppas equation. The regression co-efficient values were calculated. In this by comparing the regression coefficient values obtained, the best fit model was selected.

Evaluation of best formulation

Infrared (IR) spectroscopic studies:

Infrared (IR) spectrum analyses are carried out for the selected formulation of S-SMEDDS to find out the interactions between the drug and excipients by using an IR spectrophotometer. The pellets are prepared on KBr-press under hydraulic pressure method; the spectra are scanned over the wave number range of 4000 to 400 cm-1 at the ambient temperature [35].

Determination of Particle size and Zeta potential:

The mean particle size (z-average), and zeta potential of Apremilast SMEDDS formulations are determined by dynamic light scattering technique using a zeta size analyzer (Nano ZS 90, Malvern Instruments Ltd., UK). The dried powders are redispersed with water to obtain a proper scattering intensity before measurement [36].

Differential Scanning Calorimetry:

The physical state of Apremilast S-SMEDDS was characterized using a differential scanning calorimeter, thermo grams of Apremilast, and S-SMEDDS were measured in Perkin Elmer Pyris equipped with an intracooler 2P cooler accessory. Samples of 4mg are placed in standard aluminum pans and sealed with a lid. Heating scans by 100C/min is applied with a nitrogen purge of 20ml/min, over a temperature range of 350ºC to 3800ºC. An empty aluminum pan is used as a reference [37].

X-ray Powder Diffraction (XRPD) analysis:

The crystalline state of the samples, including the drug and dried powders are studied in an X-ray diffractometer (Bruker's X-ray Diffractometers). XRPD is carried out in symmetrical reflection mode using a Copper line as the source of radiation and the wavelength is set at 1.5405A˚. Standard runs using a 40 kV and 30 mA in this process. Samples are performed with a scanning rate of 0.1000◦/min and the scanning range of the 2 from the initial angle of 4˚ to the final angle of 90˚ [38].

Morphological studies of S-SMEDDS by using (SEM):

Morphological evaluation of the selected apremilast formulation is carried out in a scanning electron microscope (SEM). All samples are examined on a brass stub using carbon double-sided tape. Powder samples are glued and mounted on metal sample plates. The samples are gold coated (thickness ≈15–20 nm) with a sputter coater using an electrical potential of 2.0 kV at 25 mA for 10 min. An excitation voltage of 20 kV was used in the experiments [39, 40].

RESULTS AND DISCUSSIONS

Determination of λmax

The λmax of Apremilast was determined by scanning the solution with the concentration 10µg/ml of drug in Phosphate buffer pH 6.8 by UV- Spectrophotometer in the UV range of 200-400nm and thus the λmax of Apremilast was found to be 230 nm which were shown in figure 1.

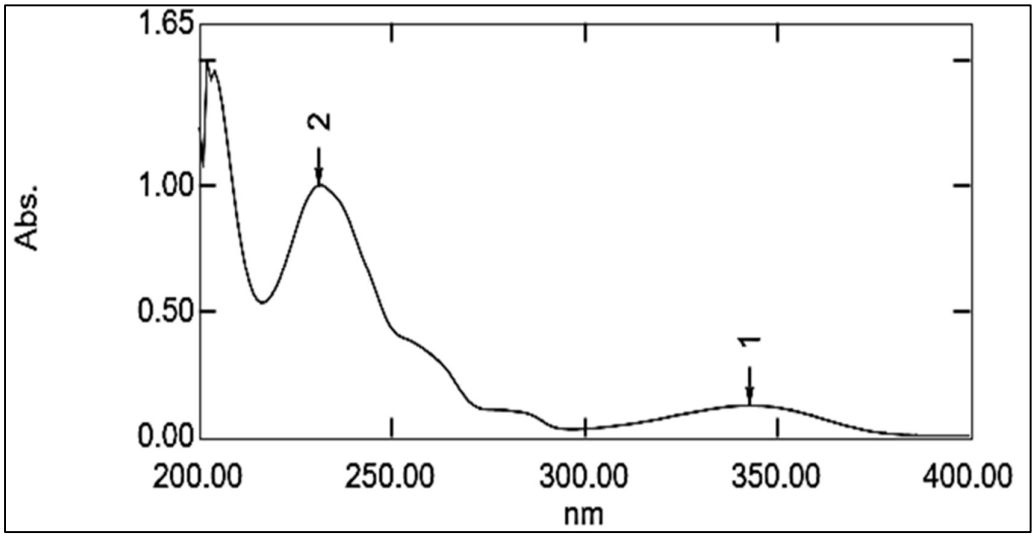


Fig 1: Determination of λmax of Apremilast

Standard Calibration Curve

The Calibration Curve of Apremilast was done in Phosphate buffer pH 6.8. The correlation coefficient was found to be 0.9993. Hence, Apremilast obeys Beer's law within the concentration range of 2-10 µg/ml. Calibration curve of Apremilast was drawn with Concentration on X axis and Absorbance on Y axis shown in figure 2.

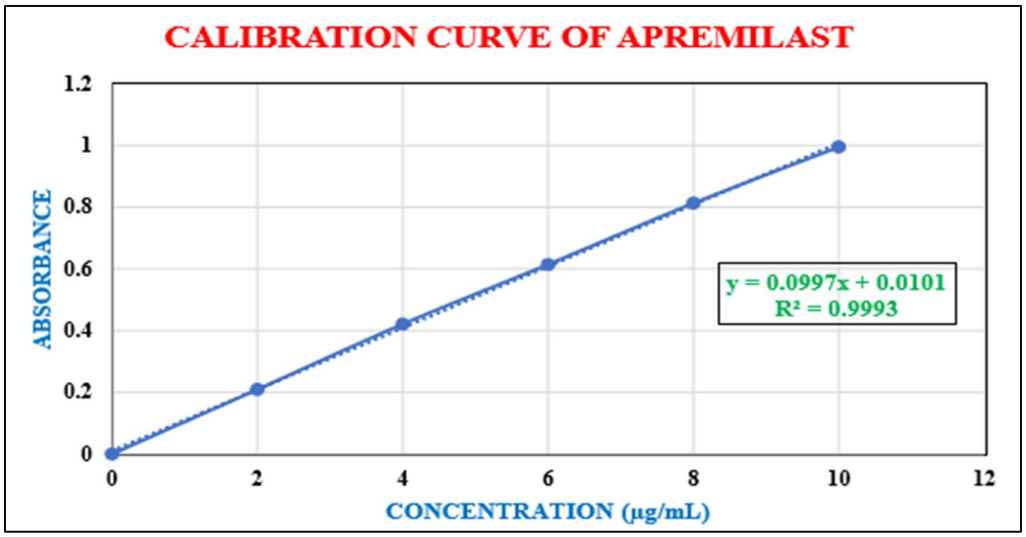


Fig. 2: Calibration curve of Apremilast

Solubility studies

From the results of solubility studies, apremilast drug was more soluble in oleic acid (oil), Tween 80 (surfactant), and Transcutol HP (Co-surfactant) shown in Figure 3. Hence oleic acid is selected as the oil phase, Tween 80 as surfactant, and Transcutol HP as co-surfactant for further studies due to their emulsification ability for optimum SMEDDS with improved drug loading capabilities.

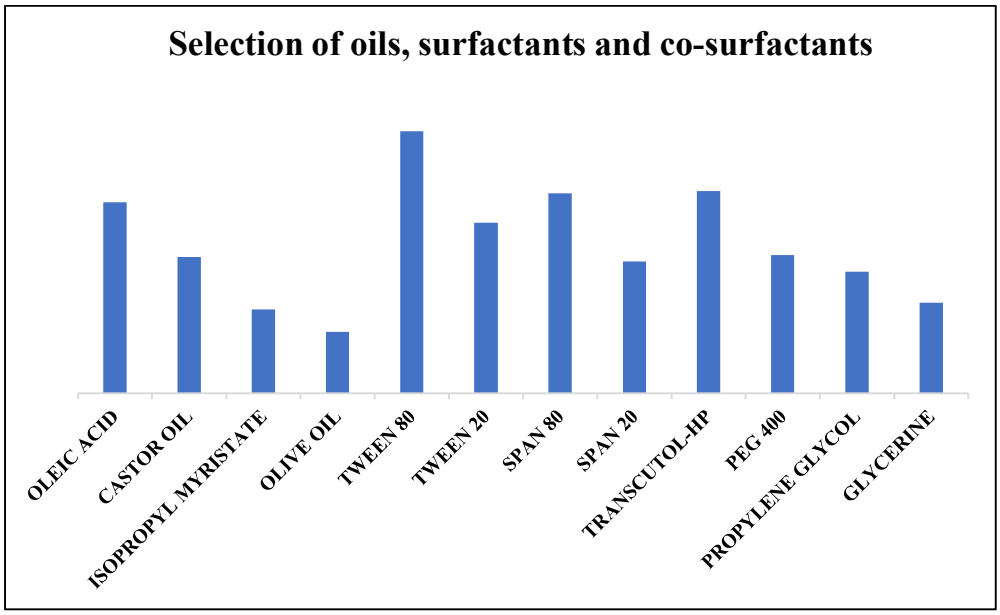


Fig 3: Solubility of Apremilast in various oils, surfactants, and cosurfactants

Drug excipients compatibility studies

The FTIR spectrum of Apremilast and its physical mixture were presented in Figures 4 and 5. The IR graphs indicate that the peaks characteristic of the pure drug is consistent, suggesting that there is no interaction between the drug and the excipients. It was observed that the functional peaks remained unchanged after the formation of the micro-emulsion using various excipients. This indicates that the pure drug has not undergone any functional alterations. Therefore, we conclude that there is no interaction between the drug and the excipients, implying that the drug remains stable and compatible with the other components throughout the process.

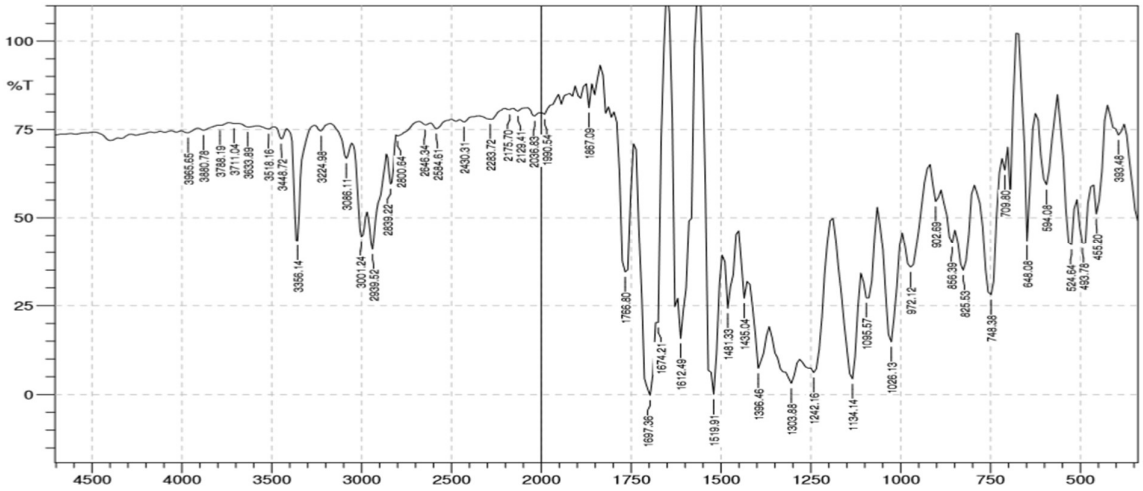


Fig 4: FTIR Spectrum of Apremilast

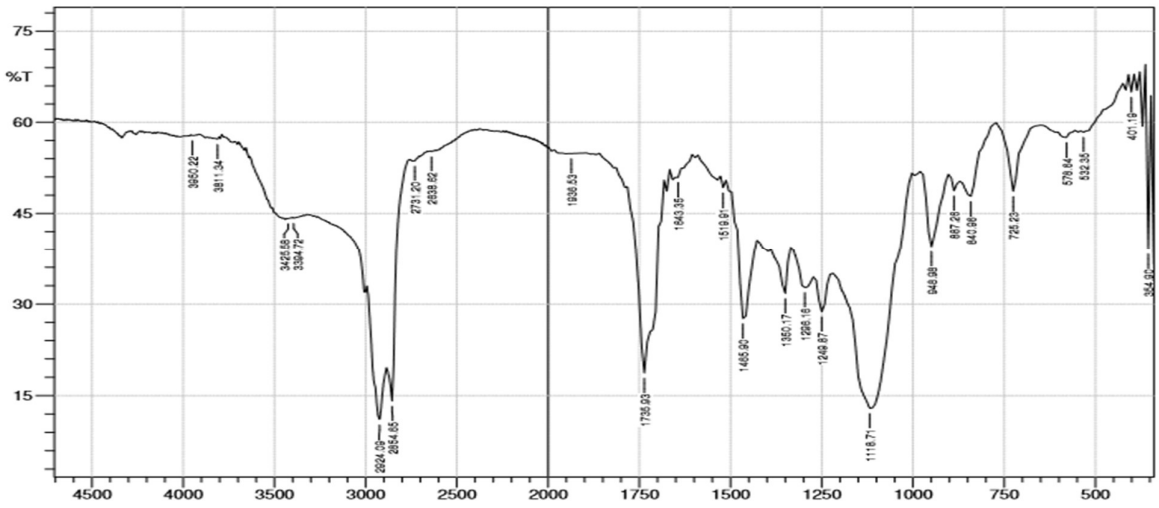


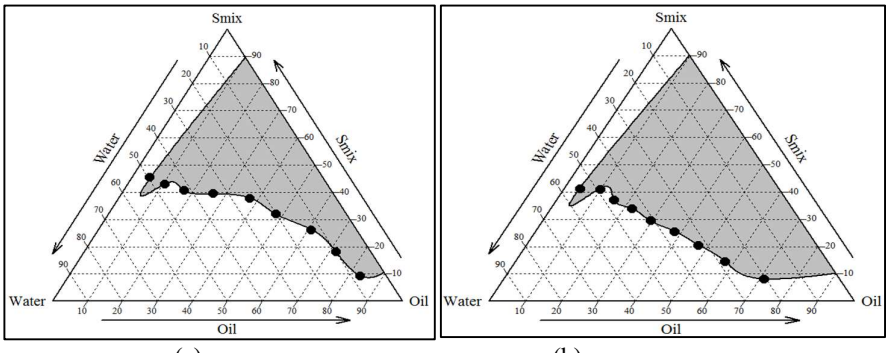
Fig 5: FTIR Spectrum of Apremilast with Physical Mixture

Construction of pseudo-ternary phase diagram

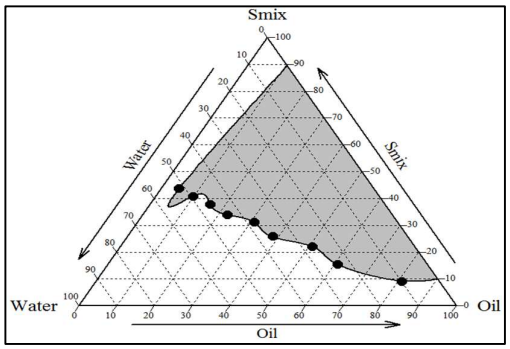
To determine the optimal concentrations of oil, surfactant, and co-surfactant, pseudo-ternary phase diagrams were constructed using CHEMIX software. SMEDDS form microemulsions when titrated with water under agitation, facilitated by surfactants that create a layer around oil globules. The polar head faces the aqueous phase, while the non-polar tail interacts with the oil, reducing surface tension. The surfactant-to-co-surfactant ratio (S/CoS) significantly influences microemulsion formation, as these components stabilize the interface and prevent coalescence. Phase diagrams were initially constructed at S/CoS ratios of 1:1, 2:1, and 3:1 to identify the optimal ratio. After fixing the surfactant concentration, the co-surfactant ratio was varied to evaluate the best formulations. The oil concentration was maximized at 90%, with S/CoS minimized to 10%.

Oil concentration was gradually decreased while increasing S/CoS levels. It was observed that higher oil concentrations formed poor emulsions, requiring minimal water for dilution. Conversely, increasing S/CoS concentration reduced the time needed to form microemulsions. The microemulsion region in various oil-to-Smix ratios is shown in Figure 6 (a,b,c). The darkest area indicates the highest emulsion stability, while regions around it shows moderate stability, and the lightest corners indicate no stability.

The most stable formulation was L-SMEDDS with Oleic acid, Tween 80, and Transcutol HP at a 2:1 Smix ratio. Oil concentration was a rate-limiting factor, as higher oil levels consistently resulted in poor emulsion formation. The microemulsion region is outlined by a black boundary; beyond this boundary, emulsions initially formed became turbid upon further dilution. Stable formulations producing fine emulsions were selected for further evaluation.



(a) (b)



(c)

Fig 6: Ternary phase diagram of Oleic acid, Tween 80, Transcutol HP (a) 1:1 (b) 2:1 (c) 3:1

Table 4: Formulation Of L-SMEDDS

FORMULATION	F1	F2	F3	F4	F5	F6	F7	F8	F9
DRUG (mg)	10	10	10	10	10	10	10	10	10
OLEIC OIL (%)	3.35	5	6.75	8.35	10	11.75	13.35	15	16.75
TWEEN 80 (%)	17.85	16.65	15.55	14.5	13.5	12.25	11.5	10	8.95
TRANSCUTOL HP (%)	8.85	8.35	7.75	7.5	6.5	6.15	5.5	5	4.5

Characterization of apremilast liquid smedds

Physical appearance

The Prepared Apremilast loaded L-SMEDDS were clear, transparent liquid, and had a homogenous appearance.

Self-emulsification time

All the formulations were rapidly emulsified within 2 minutes. Formulations F1, F2, F3, F5, F8 and F9 showed a rapid emulsification within 1 minute. These samples were further taken for the dispersibility test.

Dispersibility test for efficiency of self-emulsification

The self-emulsification efficiency study revealed that the formulation rapidly formed a clear, slightly bluish microemulsion within 1 minute. Grade A formulations (F1, F3, and F8) formed clear emulsions quickly, while Grade B formulations (F2, F6) produced bluish-white emulsions. Grade C formulations (F3, F4) resulted in bright white or greyish-white emulsions. Grades D and E formulations (F7, F9) showed poor emulsification, with large oil droplets visible on the surface.

Thermodynamic stability studies

The thermodynamic stability study evaluates the metastability of SEDDS through centrifugation (3,500 rpm), freeze-thaw cycles (-20°C to +25°C), and heating-cooling cycles (4°C to 45°C). No precipitation or phase separation was observed, indicating that formulations F1, F2, F3, F4, and F8 remained stable under all conditions.

Cloud point measurement

To assess stability, 1 mL of the formulation was diluted with 1000 mL of water and heated in a water bath until it turned cloudy, indicating stability at body temperature. Formulations F4, F7, and F9 exhibited phase separation due to drug precipitation at higher temperatures, deeming them unsuitable.

Robustness to dilution

From the results of the robustness to dilution study, it was observed that there was no sign of phase separation or drug precipitation. Hence, formulations F2, F5, F6, and F9 were rejected as they were also showing phase separation on dilution.

Droplet size analysis and zeta potential

The selected formulations (F2, F3, and F8) were evaluated for droplet size, zeta potential, and PDI. Globule sizes ranged from 140.7 nm to 181.2 nm, within the acceptable limit of 10–400 nm, with F3 showing the smallest size (140.7 nm). Droplet size was positively affected by oil concentration and negatively by Smix concentration. Zeta

potential values (-22.7 to -38.1 mV) indicated a stable, deflocculated system, while PDI values (0.295–0.384) confirmed uniform droplet size distribution.

Refractive index and percent transmittance

The refractive index of the formulations ranged from 1.354 to 1.414, indicating that the prepared L-SMEDDS were clear and transparent. This value, higher than water's refractive index (1.333), is attributed to the refractive properties of oleic acid, Tween 80, and Transcutol-HP. The microemulsions showed transmittance above 90% (91.33%–97.47%), confirming their optical clarity and transparency.

pH determination and Viscosity

The pH of all formulations ranged from 5.29 to 5.76. Viscosity, measured at room temperature using a Brookfield viscometer, ranged from 182.16 cps to 244.32 cps.

Drug content of L-SMEDDS

The drug content of the prepared Apremilast L-SMEDDS ranged from 95.86% to 99.63%, with higher oil concentrations enhancing drug loading. Formulation F8 showed the highest drug content at 99.63 ± 0.34%.

Conversion of liquid SMEDDS into solid S-SMEDDS

Solid SMEDDS were prepared by mixing liquid SMEDDS containing Apremilast with Aerosil in a 1:1 ratio. The liquid SMEDDS was added dropwise to Aerosil and homogenized with a glass rod in a china dish for uniform distribution.

Characterization of S-SMEDDS

Micromeritic properties

Prepared S-SMEDDS was evaluated for micromeritic properties such as angle of repose, bulk density and tapped density, compressibility index and Hauser's ratio. Hence, all the formulation are within limit.

Drug content

The drug content of all S-SMEDDS formulations (F1–F9) ranged from 95.45% to 98.31%, indicating uniform drug distribution as shown in Fig. 7 and 8. Among the formulations, F8 showed the highest drug content at 98.31 ± 0.08%.

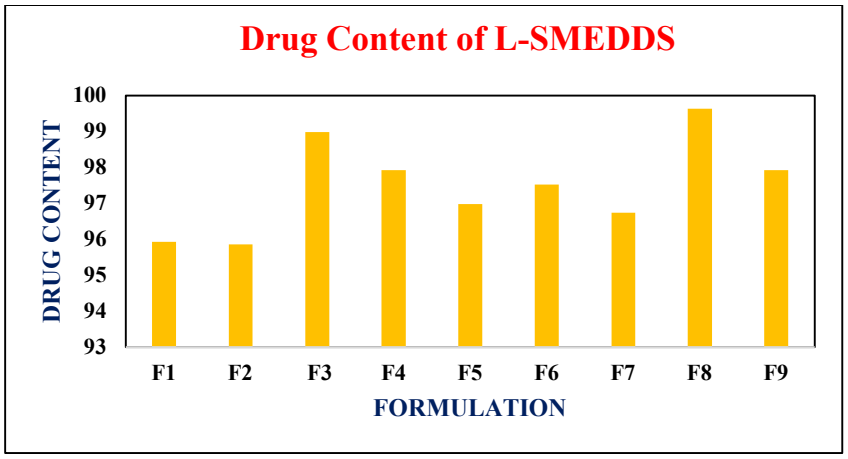


Fig 7: Graphical Representation of Drug Content of L-SMEDDS

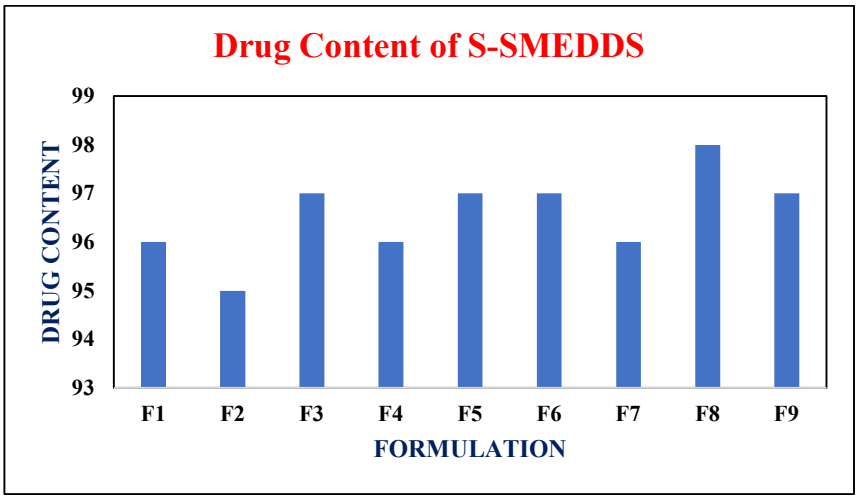


Fig 8: Graphical Representation of Drug Content of S-SMEDDS

***In-Vitro* drug release studies**

Dissolution studies were conducted in a phosphate buffer (pH 6.8) for two hours, comparing the in vitro drug release of all formulations with the pure drug and conventional tablet. The study involved filling hard gelatin capsules with equivalent amounts of powdered S-SMEDDS (10 mg of Apremilast per capsule). The cumulative drug release percentages of formulations F1–F9 are in the following order.

F3>F4>F2>F7>F5>F1>F6>F8>F9

Formulations F3, F4, and F2 exhibited better drug release compared to others. F3, prepared with oleic acid (6.75%), Tween 80 (15.55%), Transcutol HP (7.75%), and Aerosil (1:1), showed the highest release at 69.72 ± 0.3%, followed by F4 (oleic acid 8.35%, Tween 80 14.5%, Transcutol HP 7.5%, Aerosil 1:1) at 64.72 ± 0.3%, and F9 (oleic acid 5%, Tween 80 16.65%, Transcutol HP 8.35%, Aerosil 1:1) at 64.25 ± 0.2% after 120 minutes. F3 demonstrated the best release and optimal physicochemical characteristics, including globule size, PDI, zeta potential, viscosity, and drug content as shown in Fig.9-11.

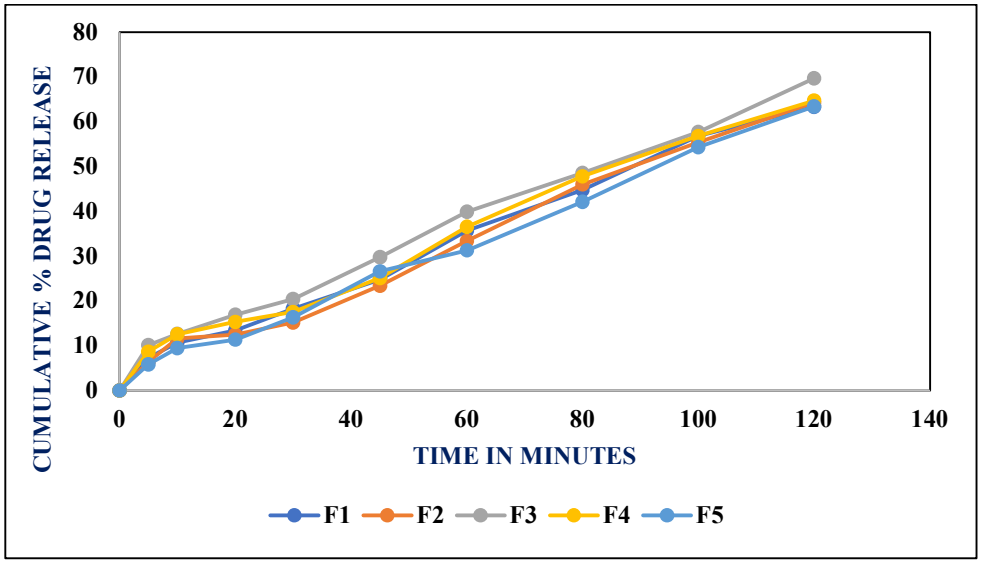


Fig 9: *In-Vitro* Drug Release studies of Formulations F1, F2, F3, F4 and F5

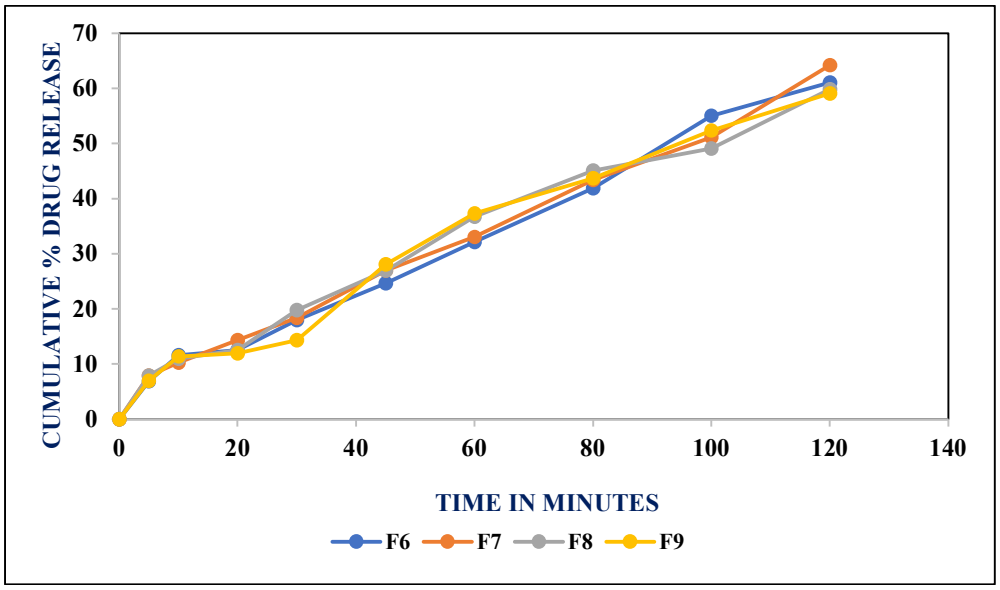


Fig 10: *In-Vitro* Drug Release studies of Formulations F6, F7, F8 and F9

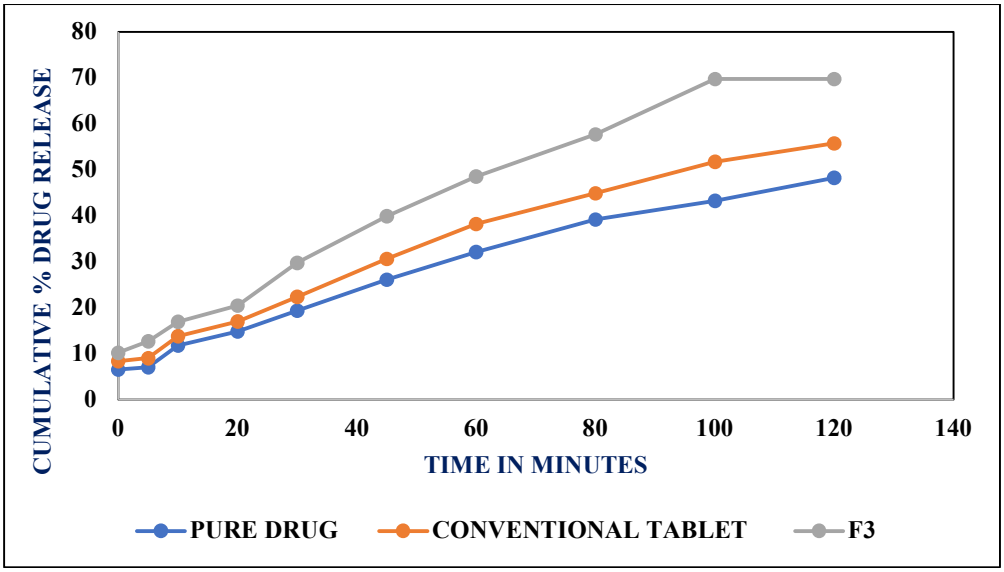


Fig 11: Comparison of *In Vitro* Drug Release of Pure Drug, Conventional Tablet and Best SMEDDS Formulation (F3)

In vitro release profile of the optimized formulation demonstrated a 69.72±0.3% release up to 120 minutes, while the conventional tablet showed a 51.72±0.2% release over the same period. This indicates that the drug from the optimized apremilast S-SMEDDS was released in a superior manner.

Effect of oil on release

The oil ratio in the system has an important role as many physiological parameters depend on it which eventually affects the dissolution of the drug hence concentration of oil phase increased drug release was decreased. F3 showed the best dissolution due to less amount of oil and balanced ratio of surfactant and co-surfactant.

Effect of co-surfactant on release

Transcutol HP was employed as a co-surfactant in the system which is widely known for increasing solubility along with a surfactant. When the concentration of co-surfactant was increased, the solubility of

apremilast also increased which leads more absorption of the drug in the GI, ultimately enhancing its bioavailability.

Effect of surfactant concentration on the release

In vitro release study in PBS 6.8 shows that the rate of drug release was faster in case of hydrophilic surfactant (tween 80). This is due to the hydrophilic nature of the surfactant. The broadness of the size distribution observed at higher surfactant concentrations could be due to the higher viscosity of the continuous phase, which disperses the stirring energy. Thus, the PDI value increased with increasing surfactant concentrations. Zeta potential increased with increasing concentrations of surfactant. The increase in concentration of surfactant resulted in a slight increase in encapsulation efficiency and loading capacity.

Drug release kinetics

To analyze the mechanism of drug release rate kinetics, *in vitro* release data can be plotted according to various kinetic models, such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas models as shown in Fig.12-16.

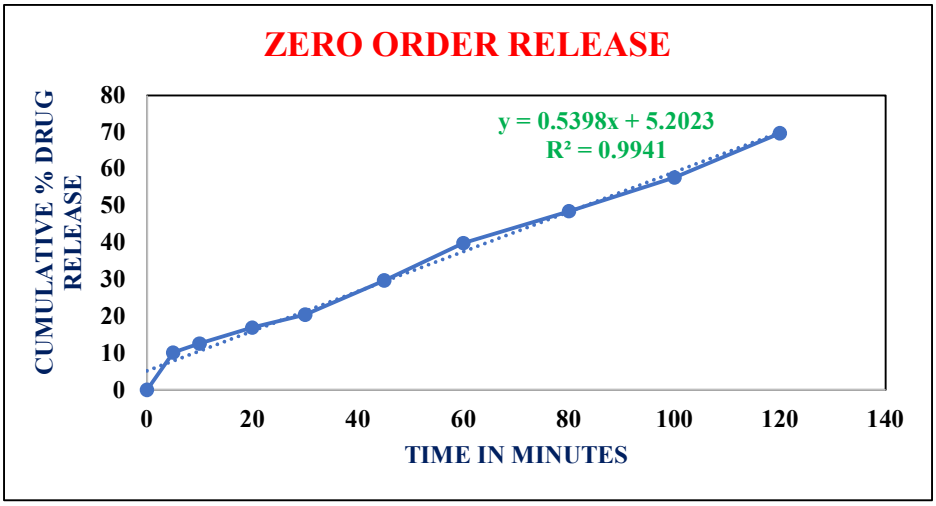


Fig 12: Zero Order Release Kinetics

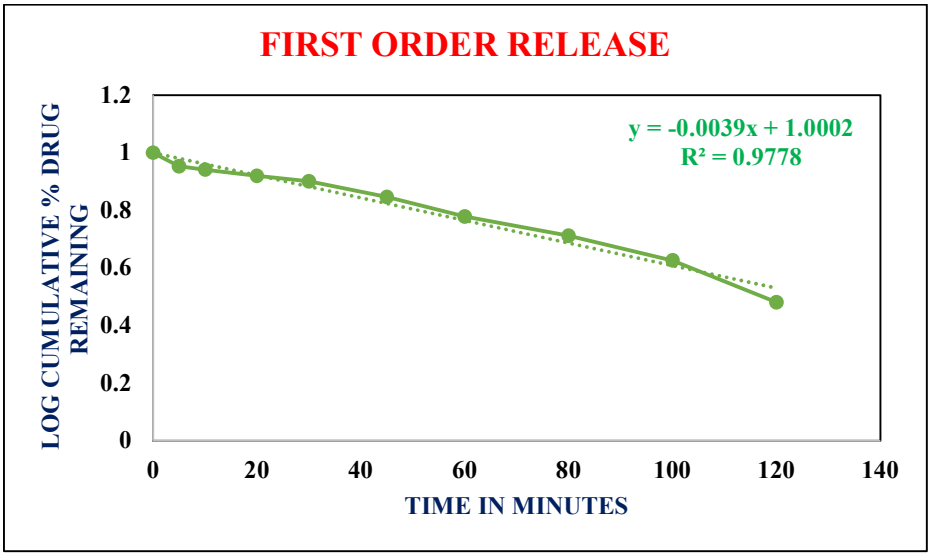


Fig 13: First Order Release Kinetics

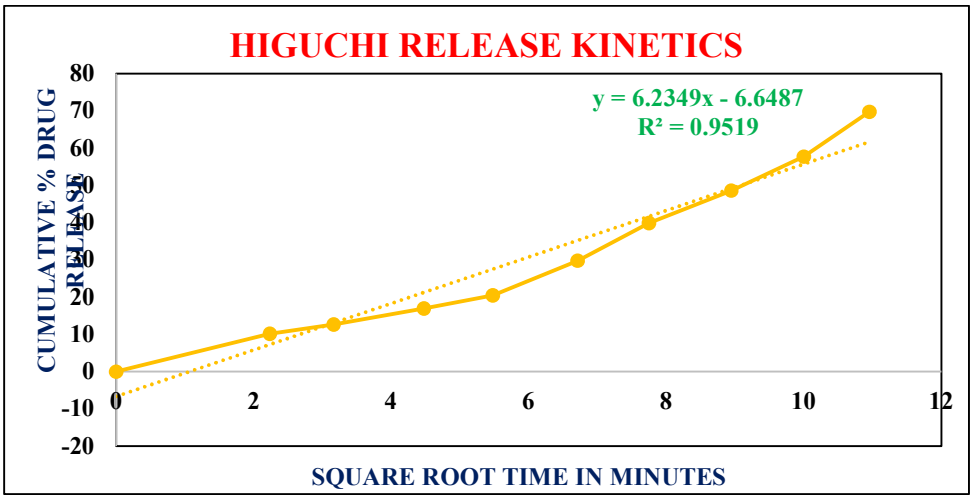


Fig 14: Higuchi Release Kinetics

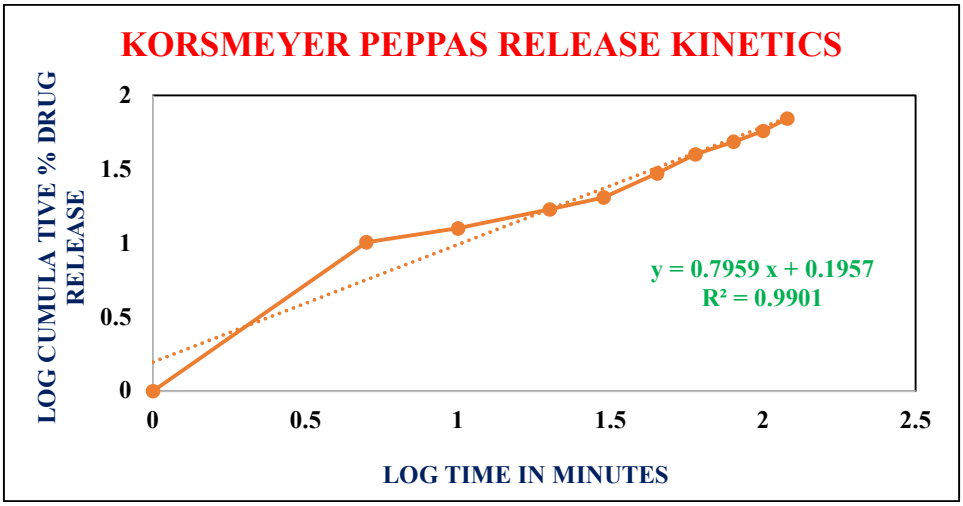


Fig 15: Korsmeyer Peppas Release Kinetics

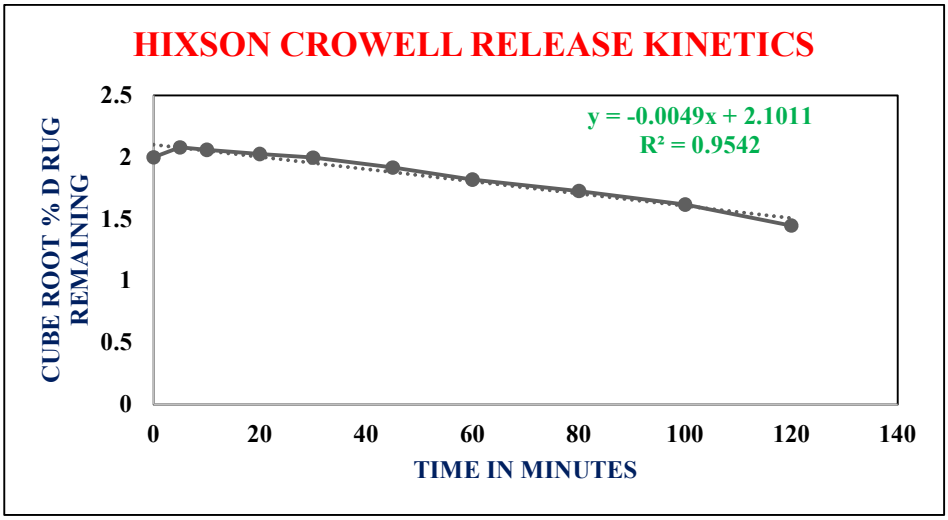


Fig 16: Hixson Crowell Release Kinetics

Based on the findings, it was determined that the Korsmeyer-Peppas model exhibited the highest correlation coefficient, R^2 (0.9901), making it the best fit for the optimized apremilast-loaded self-microemulsifying drug delivery system (S-SMEDDS). The calculated value of "n," which was found to be 0.7959 (within the range of 0.45 to 0.89), indicates that the drug release from the polymeric matrix follows a non-Fickian or anomalous transport mechanism. This release mechanism involves not only diffusion but also other processes such as matrix swelling, erosion, and relaxation.

Evaluation of best formulation

Fourier Transform Infra-Red Spectroscopic (FT-IR)

The Chemical compatibility study of the best formulation (F3) was carried out using FTIR Spectrometer.

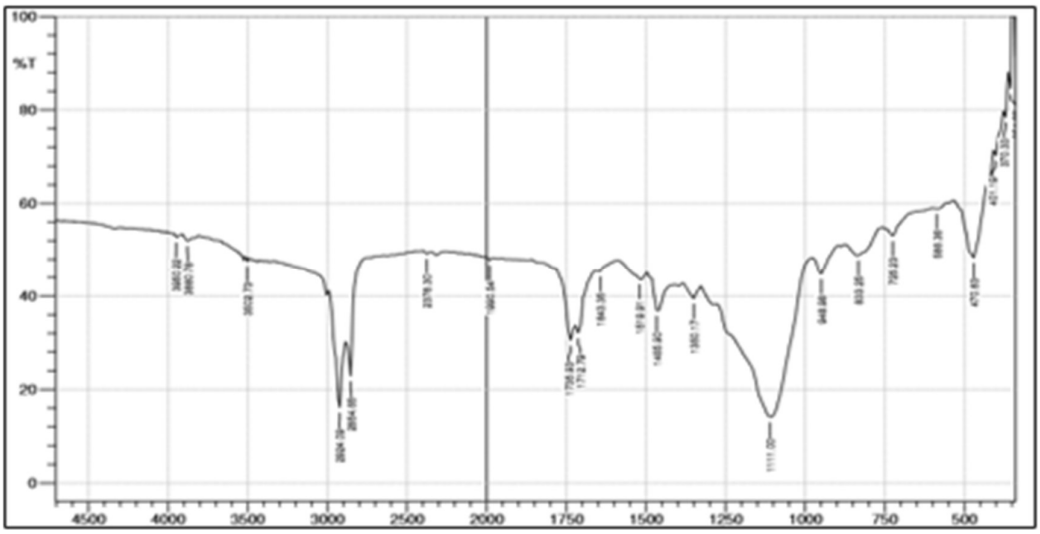


Fig 17: FT-IR Spectrum of Best Formulation

Based on this analysis, the optimal formulation is one in which there are no changes in the main peaks of the drug in the IR spectra. This indicates that there are no physical interactions between the excipients and the drug.

Zeta Potential, Globule Size, PDI, and Particle Size

Formulation (F3) with optimum ratio of surfactant (tween 80) and co-surfactant (Transcutol HP) was considered to be best among all the formulations. Furthermore, it has been reported that the smaller particle size of the emulsion globules may lead to more rapid absorption and improve the bioavailability.

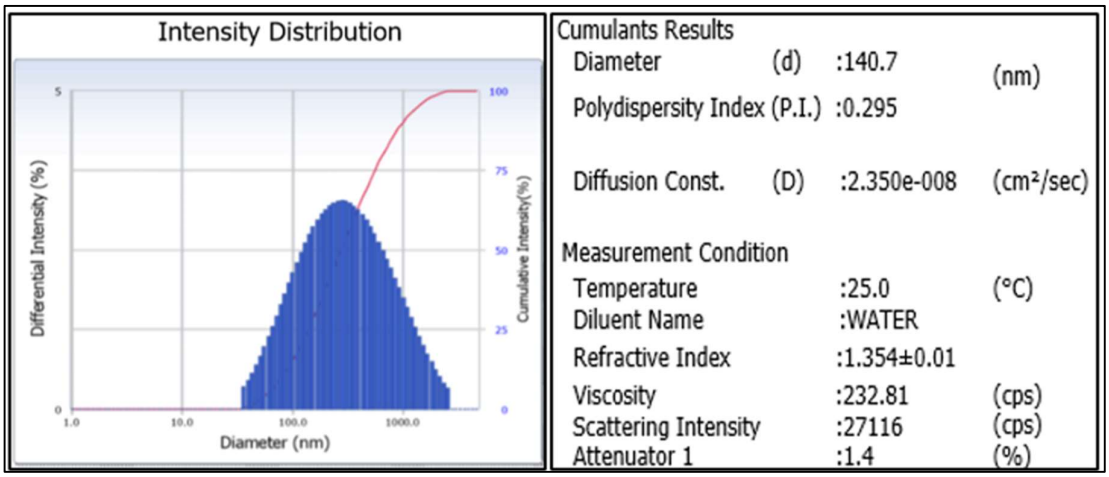


Fig 18: Mean globule size and size intensity distribution graph of best formulation F3

A dividing line between stable and unstable aqueous dispersions is generally taken at either ±30 mV. Particles with zeta potentials more negative than -30 mV are normally considered stable. Formulations F3 may be considered stable as it was having more negative zeta potential value than -30 mV.

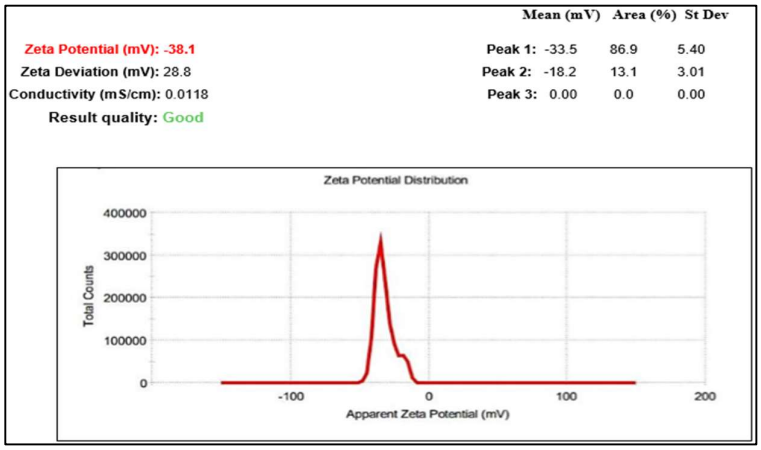


Fig 19: Zeta potential determination of best formulation F3

Differential Scanning Colorimetry

The DSC thermogram of pure Apremilast showed a sharp endothermic peak, indicating high crystallinity. The physical mixture of S-SMEDDS (apremilast and aerosil) showed negligible changes in the peak, suggesting no interaction or modification of the drug by the excipients. This indicates inhibition of crystallization due to solubilization with lipid surfactants and physical mixing with the solid carrier was showed in Fig.20 and 21.

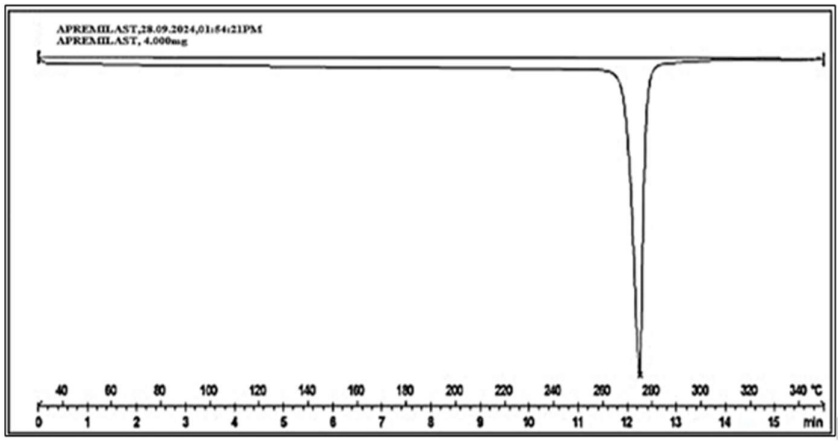


Fig 20: DSC Thermogram of Pure Apremilast

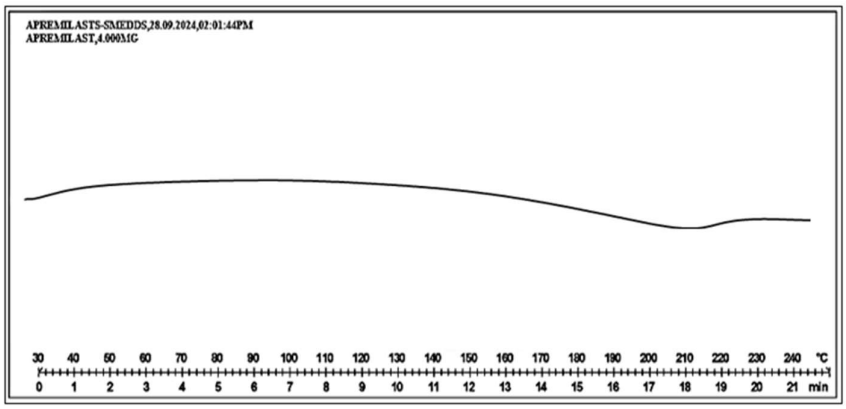


Fig 21: DSC Thermogram of Apremilast S-SMEDDS

X-ray Powder Diffraction

XRPD data were collected for the apremilast S-SMEDDS formulations to investigate any changes in physical form following the development process. The diminished peak suggests that the drug has been converted into an amorphous form. This notable reduction in peak intensities may contribute to increased dissolution rates of the S-SMEDDS preparation as shown in Fig.22.

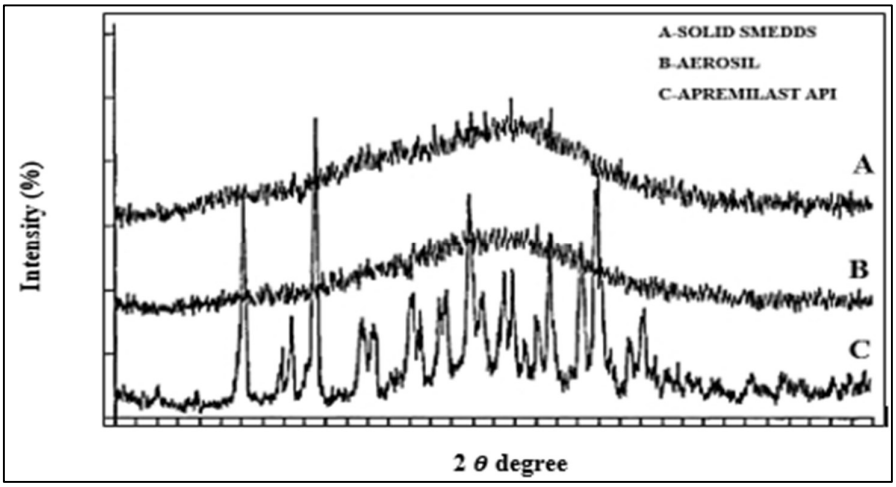
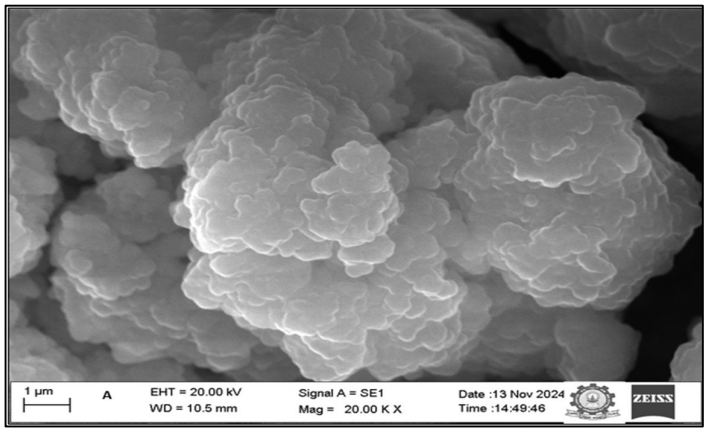


Fig 22: XRPD Pattern of Pure Drug, Aerosil & S-SMEDDS

Scanning Electron Microscopy (SEM)



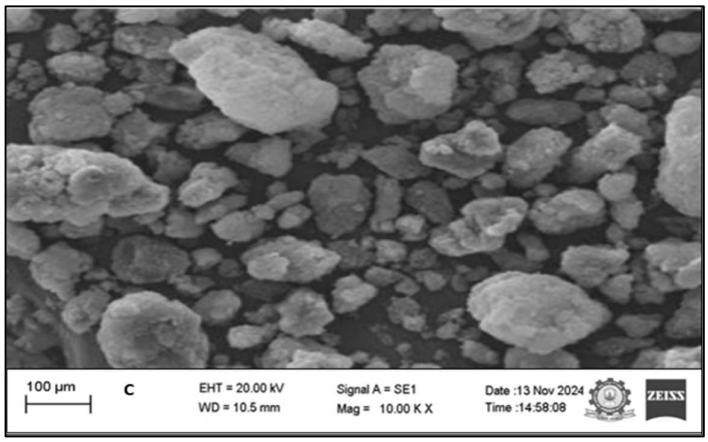


Fig 23: SEM image of Apremilast Loaded S-SMEDDS in Various Magnification

The Apremilast-loaded S-SMEDDS were analyzed using a Scanning Electron Microscope (SEM) (Zeiss, Model EVO 18) to characterize their surface morphology. The SEM photographs revealed that the particles of Apremilast S-SMEDDS were uniformly spherical was showed in Fig.23.

SUMMARY AND CONCLUSION

This study aimed to improve the solubility of apremilast, a poorly soluble anti-psoriatic drug (BCS class IV), using solid self-emulsifying drug delivery systems (S-SMEDDS). Solubility studies identified oleic acid (44.98±0.1 mg/mL), Tween 80 (61.71±0.4 mg/mL), and Transcutol HP (47.65±0.3 mg/mL) as the optimal oil, surfactant, and co-surfactant. Pseudo-ternary phase diagrams identified the micro-emulsion region, and formulation F3 (2:1) exhibited the best dissolution profile with 69.72 ± 0.3% drug release in 120 minutes. The optimized SMEDDS was characterized by droplet size analysis, zeta potential, and SEM, confirming spherical globules. Solid SMEDDS were prepared by adsorbing them onto aerosil carriers. Compared to the marketed drug, F3 showed improved dissolution. XRD, FTIR, and DSC studies revealed no drug-excipient interactions, and XRD showed reduced crystallinity in the formulation. In conclusion, the study successfully enhanced the solubility of apremilast using S-SMEDDS.

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Conflicts of interest

There are no conflicts of interest regarding the publication of this article to disclose.

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