

MIXTURE DESIGN-BASED OPTIMIZATION OF DOLUTEGRAVIR SMEDDS USING JMP® SOFTWARE: BRIDGING PREFORMULATION TO PRODUCT DEVELOPMENT

MOHAMMED MUKHTAR ALGHADEER¹, JAYADEV HIREMATH², NIMBAGAL RAGHAVENDRA NAVEEN³, NAGARAJA SREEHARSHA¹, PRAKASH GOUDANAVAR^{3*}, GIRISH MERA VANIGE⁴

¹Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University, Al-Hofuf, Al-Ahsa, Saudi Arabia.

^{2,3}Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B. G. Nagara-571448, Karnataka, India. ⁴Department of Biomedical Sciences, College of Medicine, King Faisal University, Al-Ahsa-31982, Saudi Arabia

*Corresponding author: Prakash Goudanavar; *Email: pgoudanavar01@gmail.com

Received: 19 Nov 2025, Revised and Accepted: 05 Mar 2026

ABSTRACT

Objective: To address this challenge, the current research undertaken optimize the formulation of Self-microemulsifying drug delivery systems (SMEDDS) by applying structured Quality by Design (QbD) methodology.

Methods: Initial formulation development was guided by preformulation studies and pseudo-ternary phase diagram construction, as detailed in Part 1. An Extreme vertices mixture design in JMP® software was employed for systematic optimization. Ten SMEDDS formulations were prepared and assessed for key quality attributes: drug content, emulsification time, droplet size, and transmittance.

Results: The Optimized formulation included Capmul mcm c8 (0.183), Kolliphor EL (0.603), and Propylene Glycol (0.214). It showed rapid emulsification (45.66 sec), high drug content (101.76%), fine droplet size (40.72 nm), and excellent clarity (99.22% transmittance). It also exhibited good thermodynamic stability, efficient self-emulsification (Grade A), and strong dilution tolerance. Liquid SMEDDS was made into a solid dosage form by adsorption onto Aerosil 200. The obtained S-SMEDDS exhibit acceptable flow properties, reflected by an angle of repose of 34.18°, Carr's index of 17.87%, and a Hausner's ratio of 1.21. It demonstrated high drug content uniformity (99.53%) and only a minimal increase in droplet size (46.2 nm), along with a zeta potential of -9.35 mV, confirming its physical stability.

Conclusion: Drug release studies showed enhanced drug release of (~100% within 60 min) from both liquid and S-SMEDDS indicating improved dissolution and potential bioavailability. The study supports S-SMEDDS as an effective delivery platform for poorly soluble drugs like DTG.

Keywords: Dolutegravir sodium, SMEDDS, JMP® software, Optimization

© 2026 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>) DOI: <https://dx.doi.org/10.22159/ijap.2026v18i3.57559> Journal homepage: <https://innovareacademics.in/journals/index.php/ijap>

INTRODUCTION

Dolutegravir sodium (DTG), plays a major role in combination antiretroviral regimens for managing Human Immunodeficiency Virus-1 infection. Even though DTG exhibits strong antiviral activity and a robust resistance profile, its clinical efficacy is constrained by low aqueous solubility, resulting in poor oral bioavailability [1-3]. To overcome this limitation, SMEDDS received considerable attention in enhancing the solubility and gastrointestinal uptake of Biopharmaceutics Classification System-class II drugs. SMEDDS are typically isotropic mixtures, have a mixture of surfactant, co-surfactant and oil, which spontaneously form an oil-in-water emulsion with the assistance of the agitation of the gastrointestinal tract, which supports enhancing the drug dissolution.

The preliminary phase of this investigation, described in Part 1 [4], involved systematic preformulation studies and the development of pseudo-ternary phase diagrams for DTG. This phase entailed an extensive evaluation of a range of oils, surfactants, and co-surfactants, selected based on their solubilizing capacity, physicochemical compatibility, and emulsification performance [5-7]. The resulting pseudo-ternary diagrams helped define the self-emulsifying region, providing a rational framework for subsequent formulation development. This foundational work facilitated the selection of excipient combinations capable of forming stable microemulsions with enhanced DTG solubilizing potential [8, 9]. Robustness to dilution was tested to simulate the formulation's stability upon exposure to various volumes of gastrointestinal fluids. Additionally, the self-emulsification efficiency or dispersibility test was conducted in determining the spontaneity and uniformity of emulsion formation [10-11]. Despite the advantages of liquid SMEDDS in enhancing bioavailability, their application may be limited by issues such as leakage, poor portability, and potential chemical instability. To address these concerns and improve

handling and storage, Optimized formulation will be converting into a solid SMEDDS (S-SMEDDS) using solid carriers through adsorption techniques. This transformation was carried out to retain the self-emulsifying properties of the liquid formulation while enhancing its physical stability and patient acceptability in a solid dosage form.

Following the findings from the initial phase, the present part of the research focuses on the design, refinement, and assessment of liquid and S-SMEDDS formulations incorporating DTG. A Quality by Design (QbD) strategy was implemented, incorporating Design of Experiments (DoE) methodologies to systematically evaluate the impact of formulation variables on critical quality attributes [12-14]. Optimization of the oil, surfactant and co-surfactant proportions was carried out using an Extreme vertices mixture design, implemented through JMP® software (version 17.2.0).

The use of Extreme Vertices mixture design is novel for DTG-SMEDDS because it enables optimization within a constrained formulation space defined by pseudo-ternary phase diagrams, ensuring that only feasible self-emulsifying compositions are evaluated. Unlike conventional factorial designs that may generate impractical formulations, this approach efficiently captures the true formulation domain with minimal experimental runs while maintaining strong predictive accuracy. A key formulation gap addressed in this study is the absence of statistically validated optimization strategies for DTG-SMEDDS that integrate formulation robustness with solidification feasibility. By combining constrained mixture modeling with Quality by Design and conversion into S-SMEDDS, this work bridges the gap between empirical formulation screening and scalable product-oriented development.

Extreme vertices mixture design. The resulting S-SMEDDS was evaluated for its flow properties to determine its suitability for further processing into tablets or capsules. Solid-state

characterization was also carried out to confirm the uniform distribution of DTG within the solid matrix. Furthermore, Drug content studies were performed to quantify the efficiency of drug incorporation and to ensure dosage uniformity. Collectively, this phase of research builds upon the foundation established in Part 1 and represents a comprehensive QbD-driven approach toward the development of an effective, stable, and scalable oral SMEDDS formulation for DTG.

MATERIALS AND METHODS

Chemicals and reagents

DTG used as the model drug in this investigation, was generously supplied by Mylan Laboratories, India. Prior preformulation studies and insights from pseudo-ternary phase diagram evaluations guided the selection of formulation excipients. Capmul 90, Kolliphor EL and Transcutol P were procured from Yarrow Chemicals, Mumbai. For the solidification of the liquid SMEDDS, solid carriers including Aerosil 200, Microcrystalline Cellulose (MCC), and Neusilin US2 were purchased from Vasa Scientific, Bangalore. All additional reagents and chemicals, acquired from Merck, India, were of analytical grade and used without any further modification, under appropriate storage conditions maintained throughout the study.

Capmul mcm c8 (glyceryl monocaprylate) and Capryol 90 (propylene glycol monocaprylate) are chemically different excipients with distinct properties such as Hydrophilic-Lipophilic Balance, viscosity, and solubilization capacity. In SMEDDS development, the selection of oil is crucial as it significantly influences drug dissolution, emulsification efficiency, droplet size,

and overall bioavailability. Any inconsistency in identifying the oil used can lead to variations in formulation performance and compromise the reproducibility of the study. Using Capryol 90 in place of Capmul mcm c8 could yield different results due to their differing physicochemical characteristics. This becomes particularly important when applying a QbD-based design, where accurate identification of components is essential for reliable statistical modelling and optimization. Therefore, consistent and accurate reporting of the excipients used is vital to ensure clarity, transparency, and reproducibility in formulation research.

DoE

To optimize the liquid SMEDDS formulation, the Extreme vertices mixture design was utilized through JMP® software (version 17.2.0). The experimental design was constructed after identifying suitable oil, surfactant, and co-surfactant components, selected based on outcomes from preceding formulation studies. DoE approach was selected due to its effectiveness in systematically studying SMEDDS formulations [15]. From the Classical category within the software, the Mixture Design was chosen for its practicality, particularly given the reduced number of experimental runs required-making it well-suited for the time constraints of this short-duration study. The dependent and independent variables, along with their levels selected for the mixture design, are presented in table 1. Upon defining the variables and responses, the algorithm has determined an optimal design with a randomized run order of 10 default runs providing a mixture design with a D-optimal criterion [table 2]. The Ten different formulation batches were prepared and checked for the Critical Quality attributes (CQAs).

Table 1: Variables in the mixture design

Variables	Coded limits		
	Low	High	
Independent variables*	Capmul mcm c8	0.1	0.25
	Kolliphor EL	0.56	0.67
	Propylene Glycol	0.18	0.22
Dependent variables	Emulsification time (sec)	Minimize	
	% Transmittance	Maximize	
	% Drug content	Maximize	
	Droplet size	Minimize	

*Component proportions sum to 1.0

Table 2: Liquid SMEDDS formulation table as per mixture design

Formulation*	Capmul mcm C8	Kolliphor EL	Propylene glycol
F1	0.11	0.67	0.22
F2	0.15	0.67	0.18
F3	0.22	0.56	0.22
F4	0.25	0.57	0.18
F5	0.25	0.56	0.19
F6	0.25	0.565	0.185
F7	0.235	0.56	0.205
F8	0.13	0.67	0.20
F9	0.20	0.62	0.180
F10	0.165	0.615	0.22

*Component proportions sum to 1.0

Formulation of SMEDDS

SMEDDS formulations were strategically prepared, varying the proportions of factors in accordance with the Mixture Design approach. The detailed composition of the ten experimental formulations (F1–F10) is presented in table 2. In each case, DTG (10 mg/ml) was incorporated into a mixture of Capmul mcm c8, Kolliphor EL, and Propylene Glycol. To enhance drug dissolution, the formulations were mildly heated to 40 °C using a thermostatic water bath [16]. Subsequently, vortex mixing was employed to achieve clear and uniform dispersions. All prepared systems were kept at room temperature until further characterization.

Drug content

To quantify the DTG content in SMEDDS formulations, 1 mL of each sample (corresponding to 10 mg of DTG) was diluted in methanol and gently agitated to ensure proper emulsification. A stock solution of concentration of 0.1 mg/ml was made by diluting the sample with methanol to a make a final volume of 100 ml. In succession, 1 ml of this stock was further diluted to 10 ml with methanol in a volumetric flask to obtain a solution for analysis containing 10 µg/ml of the drug [17]. Drug content was quantified at 258 nm using UV-Visible spectrophotometry with a validated calibration curve, analyzed in triplicate. As mandated by the principles of constrained mixture

experiments, the total proportion of oil, surfactant, and co-surfactant was fixed in the mixture design to add up to 1.0. This guarantees that, within a specified design space, all formulation trials maintain constant component ratios. Furthermore, rather than loading efficiency or theoretical incorporation, the response variable known as "% Drug content" represents the drug content as determined by assay (i. e., content uniformity). The phrase has been changed to "% Drug Content" and used consistently throughout the text to prevent misunderstandings and enhance readability.

The dilution process was precisely defined to improve drug content analysis's transparency and reproducibility. In particular, a 0.1 mg/ml stock solution was created by diluting 1 ml of the SMEDDS formulation, which contained 10 mg of DTG, with 100 ml of methanol. A final concentration of 10 µg/ml that was appropriate for UV spectrophotometric analysis was obtained by further diluting 1 ml to 10 ml. The absorbance readings were guaranteed to fall within the calibration curve's verified linear range thanks to this successive dilution. The accuracy and dependability of the analytical method were further confirmed by the dilution process, which was created to lessen matrix interference from excipients.

Emulsification time

Emulsification efficiency was assessed using a USP Type II dissolution apparatus by dispersing 1 ml of formulation in 500 ml of water at 37±0.5 °C under 50 rpm stirring. The time required to form a clear and homogeneous emulsion was recorded in seconds. All tests were conducted in triplicate to ensure experimental consistency.

Percentage transmittance

The optical transparency of the emulsions was determined by diluting each formulation 1:100 with double-distilled water. Solutions were analyzed at 630 nm by UV spectrophotometer to record % transmittance. Each measurement was repeated three times to ensure precision.

Droplet size

To determine droplet size and polydispersity index (PDI), sample was diluted and gently inverted to confirm uniform dispersion. The average droplet diameter and PDI were analysed using dynamic light scattering [Malvern Instruments, UK]. The dilution factor and medium used before analysis must be reported in order to guarantee the precision and repeatability of Dynamic Light Scattering (DLS) measurements. In order to minimize multiple scattering effects and guarantee optimal count rates during DLS assessment, the formulation was suitably diluted for droplet size and PDI measurement. Similarly, since the ionic strength and pH of the dispersing medium can greatly affect surface charge behavior, it is crucial to specify the dilution medium and factor used for zeta potential measurement. The formulation was diluted tenfold with filtered deionised water, mixed gently for effective dispersal, prior to DLS analysis. Average droplets' size and PDI was determined using Malvern Zetasizer (Malvern Instruments) at 25 °C (three replicate measurements). Zeta potential measurement was done in the aforementioned condition but instead diluted 10-fold in 1 mM KCl. By providing these specifics, methodological transparency is guaranteed, and results can be consistently replicated across labs.

Model fit

The response data obtained from all ten DTG liquid SMEDDS formulations were incorporated into the design to evaluate model suitability. Statistical analysis was performed by applying multiple regression models with the intercept constrained to zero [19, 20]. Significant models were identified for emulsification time (seconds), percent transmittance, Drug content efficiency, and droplet size. JMP® software was utilized for experimental design, data analysis, and the generation of three-dimensional surface and contour plots.

Optimization of formulation-numerical approach

Formulation optimization was facilitated using contour profiler plots, while simultaneous multi-response optimization through the mixture design was carried out using the desirability function approach [21]. The desirability score was derived from the

individual desirability values designated to each response parameter. This global desirability index ranges from 0 to 1, indicating the level of optimization achieved. Based on the optimized profiler output, the Optimized formulation was developed and assessed for key dependent variables.

Characterization of optimized liquid SMEDDS

Thermodynamic stability studies

The thermodynamic stability of the optimized SMEDDS was examined through a series of accelerated stress conditions to assess its physical robustness during storage and handling. Initially, the formulation was exposed to centrifugation at 10,000×g for 30 min (corresponding approximately to 12,000 rpm depending on rotor configuration) in order to identify any early indications of phase separation, creaming, or structural breakdown. Expressing centrifugation conditions in terms of relative centrifugal force (RCF) ensures improved reproducibility and consistency across different laboratory instruments. The formulation was subsequently subjected to heating-cooling cycles, consisting of three cycles between 4 °C and 45 °C, with each temperature maintained for 48 h, to evaluate thermal stress tolerance and formulation compatibility. This was followed by freeze-thaw cycling, performed for three cycles between -20 °C and 25 °C, with each cycle maintained for 24 h, to assess resistance against crystallization, surfactant destabilization, and phase instability under extreme temperature variations. Following each stress condition, samples were visually evaluated for changes in clarity, phase integrity, precipitation, creaming, or loss of uniformity. Formulations that remained physically unchanged throughout all testing conditions were considered to exhibit acceptable thermodynamic stability and were selected for further investigation [22].

Robustness to dilution

Each 1 ml SMEDDS formulation was serially diluted (1:10, 1:100, 1:1000) with distilled water, 0.1N HCl, and phosphate buffer (pH 7.8). Samples were stirred at 100 rpm at 37 °C using a magnetic stirrer for uniform mixing. After homogenization, they were stored at room temperature for 24 h and visually inspected for phase separation or instability.

Assessment of self-emulsification efficiency (dispersibility test)

The emulsification capacity of SMEDDS formulations was tested using a USP Type II dissolution apparatus. A 1 ml sample was added to 500 ml of distilled water at 37±0.5 °C and stirred at 50 rpm. Emulsification time and clarity were visually assessed. Based on performance, formulations were graded: Grade A formed a clear or slightly bluish nanoemulsion within 1 min; Grade B produced a bluish-white dispersion with moderate clarity; Grade C yielded a uniform milky emulsion within 2 min; Grade D required over 2 min, resulting in a dull, greyish-white emulsion with slight oiliness; and Grade E showed poor emulsification with visible oil globules.

Determination zeta potential

Zeta potential of diluted SMEDDS was measured using a Zetasizer (Malvern, UK) to assess droplet surface charge, with samples analyzed in disposable cuvettes. This evaluation contributed to the overall physicochemical characterization of the formulations.

Conversion of optimal liquid DTG-SMEDDS into S-SMEDDS

Method of preparation of S-SMEDDS

Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS) were prepared by adsorption technique, with Aerosil® 200, Avicel® PH 102, and hydroxypropyl methylcellulose (HPMC) serving as solid carriers. Before formulation, the adsorption capacity of each of the carriers was studied experimentally so as to determine the maximum amount of liquid S-SMEDDS that may be loaded while maintaining the powder with acceptable flow. In brief, 1 g of each carrier was placed into a porcelain dish and continuously mixed using a spatula. Liquid SMEDDS was added drop by drop in small increments (0.1 ml per addition) while constantly stirring. After each addition, the powders were visually and physically assessed for flow and cohesiveness. The addition was continued until the powder

began to lose free-flowing characteristics and showed some initial level of agglomeration or stickiness, indicating the onset of saturation. The amount of liquid added at this point was recorded as adsorption capacity offered by the carrier (g liquid/g carrier). From the experimentally assessed adsorption capacity, S-SMEDDS formulation was prepared by slow addition of the required quantity of liquid SMEDDS to the chosen carrier under continuous manual mixing until a uniform wet mass was achieved. This was allowed to dry at ambient temperature to yield a free-flowing granular powder [23]. Dried S-SMEDDS were gently sieved to break soft agglomerates and stored in airtight containers for further characterization.

Flow properties of DTG S-SMEDDS

Flow properties of S-SMEDDS were evaluated per pharmacopeial guidelines. Angle of repose was measured using the fixed funnel method, calculated as $\theta = \tan^{-1}(h/r)$, where h is cone height and r is base radius. To evaluate powder density, bulk density (D_b) was measured by recording the powder mass (M) and its unsettled volume (V_b) in a graduated cylinder, applying the formula

$$D_b = M/V_b.$$

Tapped density (D_t) was estimated after repeated mechanical tapping until a constant volume (V_t) was achieved, using

$$D = M/V_t.$$

Powder compressibility was analyzed using Carr's Index (CI), calculated as

$$CI = \left[\frac{D_t - D_b}{D_t} \right] * 100,$$

while Hausner's ratio (D_t/D_b) was used to further assess flowability. The obtained values were interpreted in accordance with pharmacopeial classification systems to determine the flow behavior of the S-SMEDDS powders.

Evaluation of DTG S-SMEDDS

Percentage Drug Content Determination

The percentage drug content of DTG in the S-SMEDDS was determined using a UV spectrophotometric method. An accurately weighed amount of S-SMEDDS was dissolved in methanol and subjected to sonication for 10 min to ensure complete drug extraction. The filtrate's absorbance was measured at 257.5 nm using a UV-Vis spectrophotometer (Shimadzu UV-1700). Understanding the effectiveness and consistency of the adsorption process requires an explanation of the slight decrease in drug content from liquid SMEDDS (101.76%) to S-SMEDDS (99.53%). Minor drug loss may happen during the conversion of liquid to S-SMEDDS for a variety of reasons, including insufficient formulation transfer, drug surface adsorption on mixing equipment, or drug molecule retention on the solid carrier's exterior. The solidification process's dependability could be questioned if this loss is not measured or addressed. A useful way to assess how much drug is left in the final solid formulation in comparison to the theoretical amount is to compute the process yield or encapsulation efficiency. This shows that the transformation of liquid SMEDDS into S-SMEDDS gives a high process yield and encapsulation efficiency of 97.81%, indicating very good drug retention during solidification. The small drug loss observed could have been due to handling loss or surface adsorption. In general, the results confirm the robustness, reproducibility, and scalability of the adsorption-based formulation process. This aids in verifying that the dosage form satisfies quality standards and retains content uniformity. Incorporating such a computation not only enhances the formulation data but also promotes process scalability and reproducibility.

Particle size and zeta potential determination

The mean droplet size, PDI, and zeta potential of S-SMEDDS were evaluated in accordance with earlier sections. Prior to analysis, the formulation was dispersed in distilled water under gentle magnetic stirring, followed by incubation at 25 °C for 30 min to allow the undissolved particles to settle.

Differential scanning calorimetry (DSC)

DSC was used to analyze the thermal behavior of the pure drug, Aerosil 200, and S-SMEDDS (TA Instruments, SDT-2960, USA). The system was calibrated with indium for temperature and enthalpy. Powdered samples were sealed in aluminum pans and heated from 35 °C to 350 °C at 10 °C/min under a nitrogen purge (100 ml/min). The absence of a distinct melting peak for Dolutegravir in the DSC thermogram suggests a reduction in crystallinity, indicating that the drug may be present in an amorphous or molecularly dispersed form within the S-SMEDDS. However, the broad endothermic transition observed around 207 °C in the thermogram needs clarification, as it could originate from either an excipient or the amorphous form of the drug. Without assigning this peak, the interpretation of the drug's physical state remains inconclusive.

Comparative *in vitro* drug release study (liquid DTG SMEDDS, S-SMEDDS and pure drug)

In vitro drug release testing was conducted using a USP Type I (basket) dissolution apparatus (DS 8000, Lab Inida). The dissolution medium consisted of phosphate buffer at pH 6.8, maintained at a temperature of 37±0.5 °C, with the basket rotating at 50 rpm. Both liquid and S-SMEDDS formulations—each containing 10 mg of DTG—along with a reference sample of pure DTG (10 mg), were encapsulated in hard gelatin capsules. To avoid floating during the dissolution process, capsules were placed in cylindrical, inert mesh holders. At predetermined time points (5, 10, 15, 20, 30, 45, and 60 min), aliquots were collected, suitably diluted with the dissolution buffer, and analyzed for drug release using a UV-visible spectrophotometer at a wavelength of 257.5 nm. Dissolution studies were carried out using 500 mL of phosphate buffer at pH 6.8, maintained at 37±0.5 °C, to ensure adequate volume for sustaining sink conditions throughout the experiment. Following each withdrawal, the sampled volume was replaced with an equal amount of fresh medium to preserve the dissolution volume. Before UV spectrophotometric analysis, the collected samples were filtered using a 0.45 µm syringe filter to remove any residual formulation or undissolved drug particles, thereby enabling precise measurement of drug release.

RESULTS

Formulation of liquid SMEDDS by Extreme vertices mixture design

A 10-run D-optimal Extreme vertices mixture design was employed due to the constrained formulation space inherent to mixture experiments, where the proportions of oil, surfactant, and co-surfactant must sum to unity. Such designs are commonly used in preliminary formulation optimization studies, including SMEDDS development, to achieve experimental efficiency while maintaining reliable model predictability within a defined design space. Similar studies have successfully employed 8–12 experimental runs under comparable constraints.

To enhance the clarity and reliability of the statistical analysis, adjusted R^2 values have been explicitly included alongside R^2 to provide a more accurate assessment of model fit, especially when dealing with a limited number of experimental runs. In fig. 1, axis labels were revised to clearly denote the plotted relationship, such as "Actual vs. Predicted Droplet Size," improving interpretation of model performance. Table 3 was reformatted to correct header alignment issues, ensuring easier readability. Additionally, data values in Tables 5 and 6 were standardized using uniform decimal precision (e. g., reporting transmittance as 99.2%), promoting consistency in data presentation and facilitating comparison across experimental results. These adjustments contribute to a more precise and professional representation of the findings. These ten SMEDDS formulations were prepared according to the generated design and subsequently evaluated (table 3). The observed response values were then mapped into the design matrix, which enabled the prediction of results for untested intermediate compositions. This allowed the development of continuous response surface models, ultimately facilitating the identification of an Optimized formulation with desirable performance characteristics.

Table 3: Drug content, Transmittance, droplet size and Emulsification time of trial formulations

Formulation	Drug content (%)	Emulsification time (s)	Transmittance (%)	Droplet size (nm)
1	72.2±1.4	60.18±1.9	98.3±0.5	20.88±2.1
2	83.4±1.6	56.60±1.7	98.0±0.4	26.30±2.8
3	103.9±1.9	45.52±1.2	97.4±0.6	92.05±6.5
4	101.1±1.5	45.65±1.1	93.0±0.8	185.00±8.2
5	100.4±1.3	43.32±0.9	95.6±0.7	209.70±9.6
6	100.0±1.2	45.92±1.0	94.0±0.6	217.50±10.1
7	98.0±1.4	46.86±1.1	97.0±0.5	137.40±7.3
8	78.4±1.7	52.56±1.6	98.4±0.4	22.15±2.4
9	96.1±1.3	50.63±1.4	97.7±0.5	47.95±3.5
10	100.2±1.2	42.86±0.8	98.0±0.4	39.21±3.1

Results are expressed in mean±SD, n=3

Lack-of-fit analysis was performed for all four response models. The lack-of-fit was found to be non-significant ($p>0.05$) for percent drug content, emulsification time, percent transmittance, and droplet size, confirming the adequacy of the fitted models within the experimental domain.

Significant models were identified for all four responses: % drug content, emulsification time (seconds), % transmittance, and droplet size. Model adequacy was evaluated based on adjusted R^2 values where adjusted R^2 and predicted R^2 values are 0.8976, 0.7894 for transmittance and for droplet size is about 0.9845 and 0.8945 and corresponding p-values. Prediction plots for each response are illustrated in fig. 1. The regression models showed strong statistical relevance for % drug content ($R^2 = 0.97$, $p = 0.0029$), emulsification

time ($R^2 = 0.85$, $p = 0.04518$), % transmittance ($R^2 = 0.90$, $p = 0.0379$), and droplet size ($R^2 = 0.97$, $p = 0.0041$), confirming the predictive capability of the design.

While the p-value for emulsification time (0.04518) exceeds the conventional threshold for statistical significance (0.05), the model still exhibited a relatively strong R^2 value of 0.85, indicating a reasonable correlation between predicted and observed outcomes. Although the p-value obtained for emulsification time (0.04518) was marginal, the model demonstrated acceptable correlation ($R^2 = 0.85$) and practical relevance, as emulsification time is a critical quality attribute influencing SMEDDS performance [fig. 2]. Therefore, this response was retained for trend interpretation while being evaluated cautiously.

Table 4: Key model statistics

Response	Model p-value	Adjusted R^2	Predicted R^2	Adequate Precision	Lack-of-fit p-value
% Drug content	0.0029	0.96	0.89	>4	>0.05
Emulsification time	0.0452	0.85	0.78	>4	>0.05
% Transmittance	0.0379	0.90	0.79	>4	>0.05
Droplet size	0.0041	0.98	0.89	>4	>0.05

Given that emulsification time is a key quality attribute in SMEDDS formulation, directly influencing performance and patient acceptability, the model was considered useful for interpreting formulation trends. Despite its marginal statistical significance, it was included for its practical relevance, with the understanding that its predictive strength is limited and conclusions drawn from it are interpreted cautiously.

A global desirability function was employed for the simultaneous optimization of DTG-SMEDDS. Prediction profilers illustrating the desirability scores before and after optimization are shown in fig. 2. The design yielded an overall desirability value of 0.90, indicating a strong correlation between the selected formulation variables and the measured responses, confirming the model's reliability for identifying an optimal formulation [fig. 3].

Table 5: Optimized formula

Excipients	Quantity per ml
Capmul mcm c8	0.182907 \approx 0.183
Kolliphor EL	0.602777 \approx 0.603
Propylene glycol	0.214315 \approx 0.214

Table 6: Experimental values for CQA

CQAs	Experimental value*
% drug content	101.76±1.25
Emulsification time (sec)	45.66±3.0
% transmittance	99.22±2.87
Droplet size (nm)	40.72±2.48

*Data are presented as mean±standard deviation (n = 3).

Table 7: Comparison between experimental values and predicted value for Optimized formulation

Response variable	Predicted values	Experimental values	% error
% drug content	100.16	101.76	1.59
Emulsification time	43.201	45.66	5.69
% transmittance	98.654	99.2	-0.46
Droplet size	41.625	40.72	-2.17

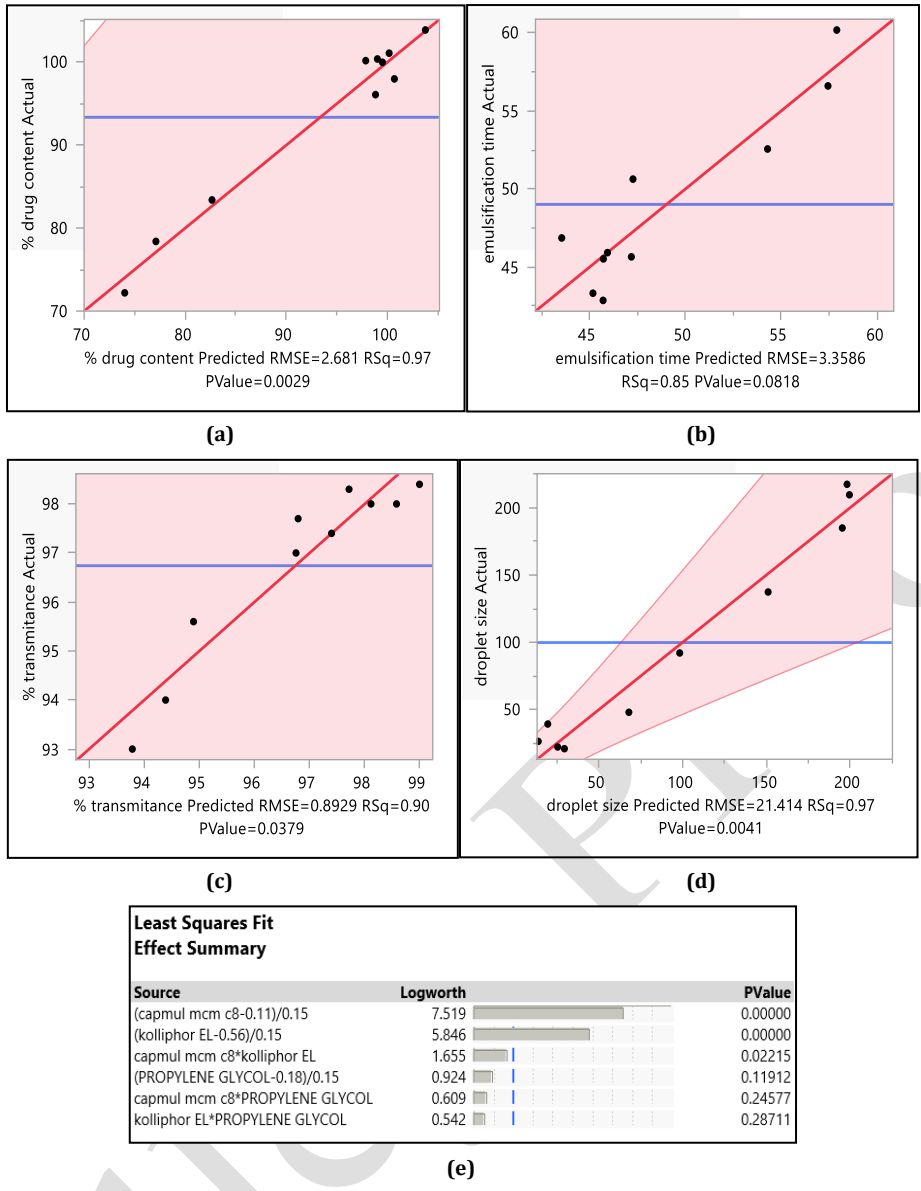


Fig. 1: Actual vs. Predicted plots for (a) Emulsification time, (b) % Transmittance, (c) % Drug content (d) Droplet size and (e) effect summary

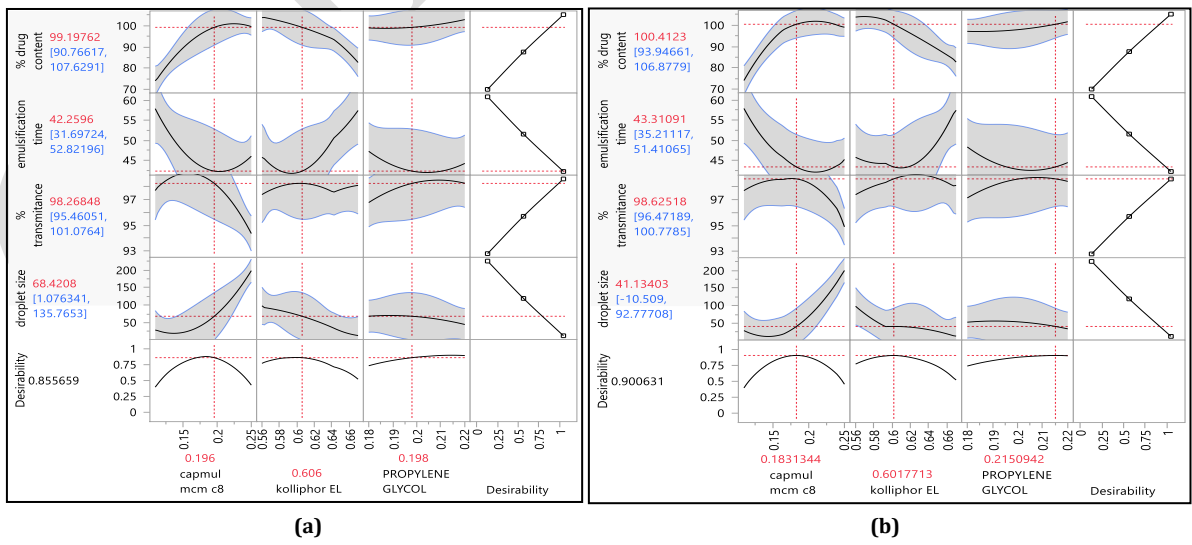


Fig. 2: Effect Summary plot showing the standardized influence of each component on the Critical Quality Attributes (a) before and (b) after optimization

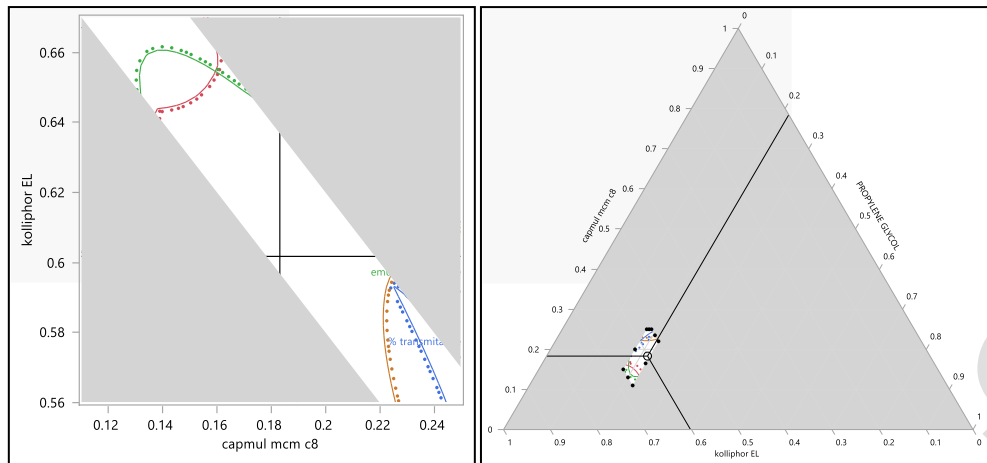


Fig. 3: Counter profile and mixture profiler

Characterization of optimized liquid smeddss

Self-emulsification efficiency and time

Based on the self-emulsification efficiency study, the Optimized formulation was observed to form a clear microemulsion within 45 sec, meeting the criteria for grade a emulsification.

Percentage transmittance

An inverse relationship was observed between oil concentration and % transmittance, where higher oil levels led to larger droplet sizes and increased turbidity. The Optimized formulation, however, exhibited high clarity with a transmittance value of 99.2%.

Percentage drug content

An increase in oil concentration led to enhanced Drug content, attributed to the higher solubility of DTG in the oil phase compared to the surfactant and co-surfactant. The Optimized formulation demonstrated a Drug content efficiency of 101.76%.

Droplet size and zeta potential

The droplet size of the resulting microemulsions varied across formulations, with the smallest size observed in formulation F1 (20.88 nm) and the largest in F6 (217.5 nm). These findings correlated well with the % transmittance results, where smaller droplet sizes were associated with higher clarity. An inverse relationship was noted—higher % transmittance corresponded to smaller droplet sizes. Interestingly, a direct relationship was also observed between droplet size and Drug content, as formulations with larger droplet sizes tended to show higher Drug content capacity.

For the optimized liquid SMEDDS, the average droplet size, zeta potential, and PDI were 40.1 nm, -11.5 mV, and 0.255, respectively. The low PDI value indicated a narrow size distribution, suggesting a uniform and monodisperse system.

Zeta potential is often considered a useful indicator of emulsion stability, with absolute values above ± 12 mV typically recommended to prevent coalescence of dispersed droplets by providing electrostatic repulsion. However, this threshold is based on empirical observations and may not universally predict the stability of SMEDDS formulations. In the current study, the zeta potential of -11.5 mV for the Optimized formulation is likely due to the presence of free fatty acids in the oil phase, imparting a negative surface charge. Although slightly below the conventional threshold, this value was adequate to maintain system stability, as reflected in the absence of phase separation [fig. 4]. The optimized liquid SMEDDS and S-SMEDDS exhibited zeta potential values of -11.5 mV and -9.35 mV, respectively. Although these values are lower than the conventionally accepted threshold for electrostatic stabilization (± 20 -30 mV), the formulation remained physically stable under the tested conditions. This stability can be attributed primarily to steric stabilization provided by the non-ionic surfactant Kolliphor EL, which forms a hydrated interfacial layer around the droplets and minimizes coalescence.

Thermodynamic stability studies

The Optimized formulation successfully passed the heating-cooling cycle and was subsequently evaluated through centrifugation, after which no phase separation was detected. Following this, the formulation underwent freeze-thaw stress testing. Throughout these cycles, the SMEDDS demonstrated excellent physical stability, with no evidence of phase separation, creaming, or cracking, confirming its durability under varying stress conditions.

Robustness to dilution

Based on the outcomes of the dilution robustness study conducted in 0.1 N HCl, distilled water, and phosphate buffer (pH 6.8), no evidence of phase separation or drug precipitation was observed during the storage period [table 9].

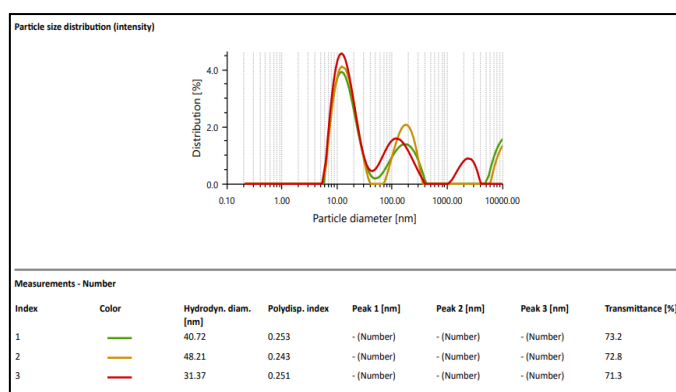
Table 8: Thermodynamic stability study

S. No.	Test	Observation
1	Heating-cooling cycle	No sign of instability
2	Centrifugation test	No phase separation (homogeneous dispersion)
3	Freeze-thaw stress testing	No sign of instability

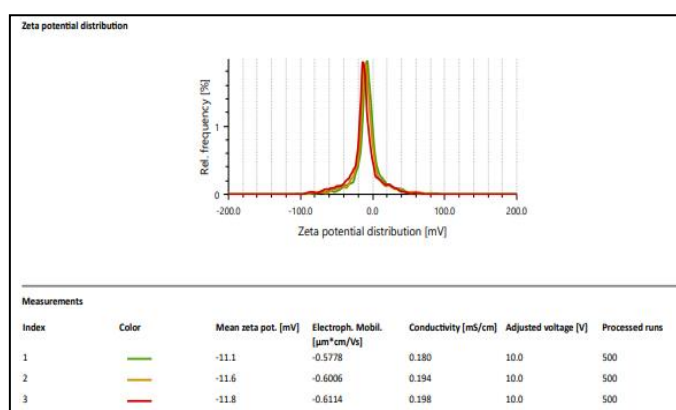
Table 9: Robustness to dilution

Dispersion medium	Volume of medium (ml)	Observation
Distilled water	10-1000	Stable and clear
0.1 N Hydrochloric acid		
Phosphate buffer pH 6.8		

Adsorption capacity was determined experimentally based on loss of powder flowability.



(a)



(b)

Fig. 4: (a) Droplet size distribution and PDI of the optimized liquid SMEDDS formulation (F-opt). (b) Zeta potential distribution of the optimized liquid SMEDDS formulation (F-opt) Optimized formulation

Table 10: Adsorption capacity of different solid carriers for the conversion of liquid SMEDDS to S-SMEDDS

Solid carrier	Weight of solid carrier (mg)	Volume of liquid adsorbed (ml)
Aerosil 200	500	1
Avicel pH 102	500	0.5
HPMC	500	0.3

Conversion of liquid to S-SMEDDS

The optimized liquid SMEDDS was converted to S-SMEDDS by using aerosil 200, Hydroxy propyl methyl cellulose and avicel pH 102 as the solid carrier by adsorption technique. This was prepared based on the adsorption capacity of the carrier [table 10].

Flow property evaluation

The angle of repose was determined using the funnel method and was measured at 34.18° , suggesting passable flow characteristics. The bulk density and tapped density of the S-SMEDDS were recorded as 0.57 g/cm^3 and 0.69 g/cm^3 , respectively—both falling within acceptable limits. These values were further used to calculate the compressibility of the powder blend.

Carr's Compressibility Index was employed to assess the flow properties, yielding a value of 17.87%, which is indicative of fair compressibility. Additionally, the Hausner's ratio, a commonly used measure of flowability, was calculated to be 1.21, also supporting the classification of the powder as having fair flow behavior.

Characterization of S-SMEDDS

One ml of formulation containing 10 mg of drug was loaded onto aerosil 200 and the % Drug content was found to be 99.53 %. As detailed in Section 6.7.6, the S-SMEDDS exhibited a particle size of 46.2 nm and a zeta potential of -9.35 mV .

DSC

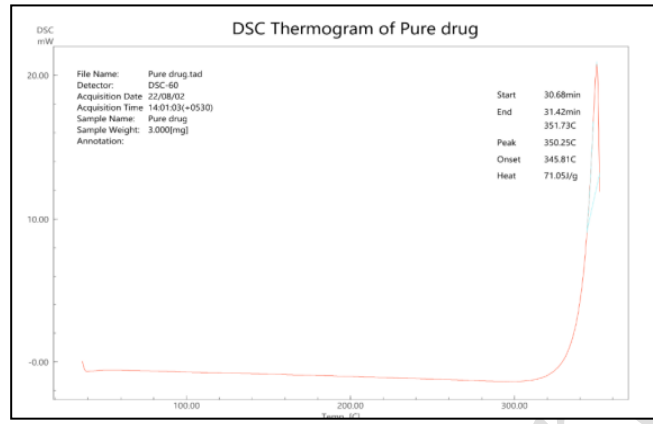
The DSC thermogram of pure DTG exhibited a sharp endothermic peak at 346°C , corresponding to its crystalline melting point. In contrast, the S-SMEDDS formulation showed complete disappearance of this characteristic melting peak, indicating conversion of DTG into an amorphous or molecularly dispersed state within the formulation. A broad endothermic transition observed around 207°C in the S-SMEDDS thermogram was assigned to excipient-related thermal events rather than residual drug crystallinity and attributed to excipient-related thermal events rather than residual drug crystallinity. This transition is attributed to dehydration of Aerosil 200 and melting transitions of the surfactant components, as confirmed by DSC analysis of physical mixtures of DTG with Aerosil 200 and other formulation excipients (fig. 5). These findings substantiate that the observed endotherm does not arise from crystalline DTG.

Comparative *in vitro* drug release study for liquid SMEDDS, S-SMEDDS and pure drug

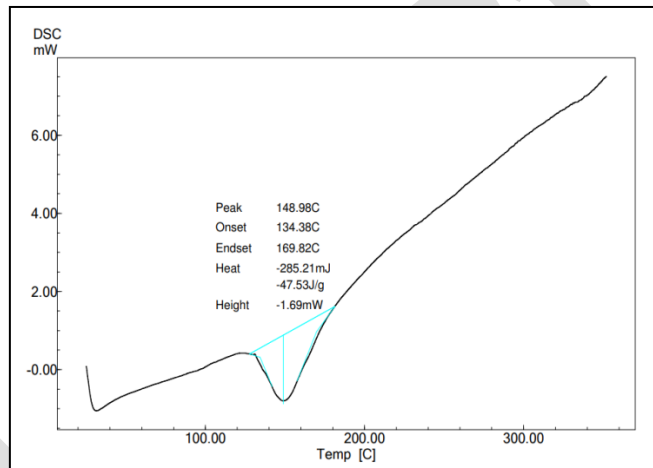
The comparative *in vitro* drug release study highlights the enhanced release behavior of DTG from both liquid SMEDDS and S-SMEDDS formulations in contrast to the pure drug. The L-SMEDDS showed a rapid and efficient drug release, reaching nearly 70% within the first 30 min and achieving complete release ($\sim 100\%$) by 60 min.

This superior performance can be attributed to the self-emulsifying nature of the formulation, which facilitates the formation of fine microemulsion droplets in the aqueous environment, leading to a greater surface area for drug dissolution. In comparison, the S-SMEDDS exhibited a slightly delayed release in the initial phase due to the presence of solid carriers that may temporarily retard emulsification. However, it still managed to achieve complete drug release by 60 min, confirming that the transformation from liquid to solid form does not significantly impair the self-emulsifying capability or the overall release efficiency.

To better interpret the release pattern, the slight delay observed in drug release from the S-SMEDDS compared to the liquid formulation should be explained based on formulation dynamics. This initial lag is likely due to the need for the drug to diffuse out from the solid carrier matrix into the dissolution medium before emulsification can proceed. In contrast to the liquid SMEDDS, where the drug is already solubilized, the solid form introduces an additional desorption step that may temporarily slow down release. Discussing this mechanism provides deeper insight into the release behavior and supports the design considerations behind the solidified system.



(a)



(b)

Fig. 5: DSC thermograms of (a) pure DTG and (b) the optimized DTG-loaded S-SMEDDS

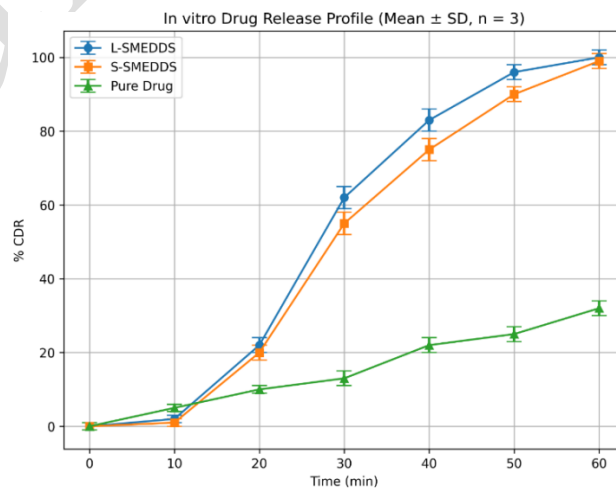


Fig. 6. Comparative *in vitro* drug release, results are expressed in mean±Sd (error bars), n=3

DISCUSSION

Systematic optimization of the SMEDDS formulation with minimum laboratory trials was aided by the design of experiments (DoE). A mixture design was applied to check the effects of varying proportions of oil, surfactant, and co-surfactant on critical quality attributes which include percent drug content, emulsification time, percent transmittance, and droplet size. The formulation limits defined from the pseudo-ternary phase diagram ensure that all compositions stay within the self-emulsifying region. The D-optimal design with ten experimental runs generated in JMP® software was adequate for modeling the formulation space, as shown by the absence of significant lack-of-fit and the close correlation between adjusted and predicted R^2 values for all responses (Tables 5-7), suggesting a high predictive ability with minimal bias. The regression was conducted with the zero-intercept model, in line with the mixture systems principles that hold that the sum of proportions of all components equals unity. Among the comparative evaluations, the zero-intercept model was regarded as the best because it recorded lower Akaike Information Criterion value and an increased adjusted R^2 . Optimization via desirability functions aimed at attaining high drug content and transmittance, rapid emulsification, and small droplet size. The optimized formulation scored high on overall desirability, confirming the successful simultaneous achievement of multiple performance criteria. Experimental validation of the optimized formulation showed closer agreement between predicted and observed values, with percentage error for all responses within 10%, thus supporting the robustness of the optimization strategy (Tables 5-7). The optimized SMEDDS displayed high clarity, rapid self-emulsification, uniform droplet size, and excellent drug loading efficiency, indicating suitability for oral delivery applications (fig. 3). Physical stability is paramount in ensuring that SMEDDS will indeed be able to perform, as any drug precipitation and consequent phase separation may compromise therapeutic reliability [24, 25]. This optimized formulation is, in fact, stable, as verified during testing for centrifugation, heating-cooling cycles, and freeze-thaw stress conditions, confirming the thermodynamic stability and suitability for storage and handling of this formulation (table 8). *In vitro* drug release studies in pH 6.8 phosphate buffer demonstrated a comparative rise in dissolution behavior for both liquid and solid SMEDDS as compared to the pure drug (fig. 6). Liquid SMEDDS released about 70% of the drug in 30 min and 100% within 60 min, the fast release of drug being attributed to the spontaneous nanoemulsification and the increase in interfacial surface area. Solid SMEDDS exhibited an almost similar release profile with minor lag in the beginning, which can be associated with drug diffusion from the adsorbed matrix before emulsification. In contrast to the pure drug, which demonstrated poor dissolution (<35% release at 60 min), it is indicative of the low aqueous solubility and poor wettability of the drug [26]. Maintaining sink conditions is crucial for the determination of reliable dissolution kinetics, and the solubility of 10 mg of DTG in 500 ml of pH 6.8 buffer showed that the dissolution was not impeded by saturation effect, therefore validating the release data [27]. In conclusion, the results presented in this study indicated that the dissolution performance of the optimized SMEDDS formulation was greatly enhanced, with excellent stability of the formulation and reproducibly [28]. Solid systems, on top of that, would contribute practically to better handling, storage stability, and acceptability by the patient, underlining their potential for large-scale oral delivery of scarcely water-soluble drugs [29].

CONCLUSION

The study successfully demonstrates the formulation and optimization of DTG SMEDDS using a QbD-guided, statistically driven approach. By employing JMP®-based Extreme vertices mixture design, a robust and efficient liquid SMEDDS was developed with optimal droplet size, drug content, and self-emulsification characteristics. The Optimized formulation showed excellent stability under various stress conditions and maintained its performance in both aqueous and acidic environments. Conversion into S-SMEDDS using Aerosil 200 yielded a free-flowing, stable formulation with acceptable powder properties and preserved drug release characteristics. Comparative *in vitro* studies confirmed a

remarkable improvement in dissolution for both liquid and S-SMEDDS compared to the pure drug, indicating a promising strategy for enhancing the bioavailability of poorly water-soluble antiretrovirals. Overall, this two-part investigation—from preformulation to final product—lays a strong foundation for future scale-up, *in vivo* evaluation, and clinical translation of DTG-SMEDDS formulations.

FUNDING

This work was supported by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia [Grant No. KFU260647].

AUTHORS CONTRIBUTIONS

Jayadev Hiremath: Conceptualization, Methodology, Data Curation, Investigation, Writing – Original Draft. Nimbagal Raghavendra Naveen: Methodology, Validation, Writing – Review and Editing. Nagaraja Sreeharsha: Writing – Review and Editing. Santosh Fattapur: Critical Data Analysis, Visualization. Prakash Goudanavar: Supervision, Project Administration, Resources.

CONFLICT OF INTERESTS

Declared none

REFERENCES

- Goyal U, Gupta A, Rana AC, Aggarwal G. Self microemulsifying drug delivery system: a method for enhancement of bioavailability. *Int J Pharm Sci Res.* 2012;3(1):66-79. doi: [10.13040/IJPSR.0975-8232.3\(1\).66-79](https://doi.org/10.13040/IJPSR.0975-8232.3(1).66-79).
- Chavda H, Patel C, Anand I. Biopharmaceutics classification system. *Syst Rev Pharm.* 2010;1(1):62-9. doi: [10.4103/0975-8453.59514](https://doi.org/10.4103/0975-8453.59514).
- Thomas N, Holm R, Rades T, Mullertz A. Characterising lipid lipolysis and its implication in lipid-based formulation development. *AAPS J.* 2012;14(4):860-71. doi: [10.1208/s12248-012-9398-6](https://doi.org/10.1208/s12248-012-9398-6), PMID [22956477](https://pubmed.ncbi.nlm.nih.gov/22956477/).
- Hiremath J, Raghavendra Naveen NR, Goudanavar P, Meravanige G, Almuqbil RM, Aldhubiab BE. Preformulation studies and pseudo-ternary phase diagram development for dolutegravir sodium: a foundational step toward SMEDDS design. *Indian J Pharm Educ Res.* 2025;59(3s):s874-80. doi: [10.5530/ijper.20252845](https://doi.org/10.5530/ijper.20252845).
- Nigade PM, Patil SL, Tiwari SS. Self emulsifying drug delivery system (SEDDS): a review. *Int J Pharm Biol Sci.* 2012;2(2):42-52.
- Kumar S, Gupta SK, Sharma PK. Self-emulsifying drug delivery systems for oral delivery of lipid-based formulations: a review. *Afr J Basic Appl Sci.* 2012;4(1):7-11. doi: [10.5829/idosi.ajbas.2012.4.1.61217](https://doi.org/10.5829/idosi.ajbas.2012.4.1.61217).
- Singh B, Bandopadhyay S, Kapil R, Singh R, Katare OP. Self-emulsifying drug delivery systems (SEDDS): formulation development characterization and applications. *Crit Rev Ther Drug Carrier Syst.* 2009;26(5):427-521. doi: [10.1615/CritRevTherDrugCarrierSyst.v26i5.10](https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v26i5.10), PMID [20136631](https://pubmed.ncbi.nlm.nih.gov/20136631/).
- Barakoti H, Choudhury A, Dey BK. An outlook for a novel approach: self-microemulsifying drug delivery system (SMEDDS). *Res J Pharm Technol.* 2019;12(4):2055-64. doi: [10.5958/0974-360X.2019.00340.8](https://doi.org/10.5958/0974-360X.2019.00340.8).
- Asha BR, Goudanavar P, Koteswara Rao GS, Gandla K, Raghavendra Naveen N, Majeed S. QbD driven targeted pulmonary delivery of dexamethasone-loaded chitosan microspheres: biodistribution and pharmacokinetic study. *Saudi Pharm J.* 2023;31(9):101711. doi: [10.1016/j.jsps.2023.101711](https://doi.org/10.1016/j.jsps.2023.101711), PMID [37564747](https://pubmed.ncbi.nlm.nih.gov/37564747/).
- Dokania S, Joshi AK. Self-microemulsifying drug delivery system (SMEDDS) challenges and road ahead. *Drug Deliv.* 2015;22(6):675-90. doi: [10.3109/10717544.2014.896058](https://doi.org/10.3109/10717544.2014.896058), PMID [24670091](https://pubmed.ncbi.nlm.nih.gov/24670091/).
- Narayana Reddy KA, Kunchithapatham J, Dang R, Ramnarayanan C. Design and development of darunavir-loaded self-microemulsifying drug delivery system using extreme vertices mixture design in a quality by design framework. *Indian J Pharm Educ Res.* 2020;54(2):337-48. doi: [10.5530/ijper.54.2.39](https://doi.org/10.5530/ijper.54.2.39).
- Patel PV, Patel HK, Panchal SS, Mehta TA. Self micro-emulsifying drug delivery system of tacrolimus: formulation *in vitro* evaluation and stability studies. *Int J Pharm Investig.* 2013;3(2):95-104. doi: [10.4103/2230-973X.114899](https://doi.org/10.4103/2230-973X.114899), PMID [24015381](https://pubmed.ncbi.nlm.nih.gov/24015381/).

13. Safhi AY, Naveen NR, Rolla KJ, Bhavani PD, Kurakula M, Hosny KM. Enhancement of antifungal activity and transdermal delivery of 5-flucytosine via tailored spanlastic nanovesicles: statistical optimization *in vitro* characterization and *in vivo* biodistribution study. *Front Pharmacol.* 2023;14:1321517. doi: [10.3389/fphar.2023.1321517](https://doi.org/10.3389/fphar.2023.1321517), PMID 38125883.
14. Sreeharsha N, Gajula LR, S SK, Bhavani PD, Goudanavar P, AR. Enhancing flowability of lamivudine through quasi-emulsion solvent-diffusion (QESD) crystallization: a comprehensive study on surfactant impact particle morphology by QbD concepts and tablet compression challenges. *Eur J Pharm Sci.* 2024;200:106835. doi: [10.1016/j.ejps.2024.106835](https://doi.org/10.1016/j.ejps.2024.106835), PMID 38908413.
15. Chudasama AS, Patel VV, Nivsarkar M, Vasu KK, Shishoo CJ. *In vivo* evaluation of a self-emulsifying drug delivery system for oral delivery of nevirapine. *Indian J Pharm Sci.* 2014;76(3):218-24. PMID 25035533.
16. Bhagwat DA, Souza JI. Formulation and evaluation of solid self-microemulsifying drug delivery system using aerosil 200 as solid carrier. *Int Curr Pharm J.* 2012;1(12):414-9. doi: [10.3329/icpj.v1i12.12451](https://doi.org/10.3329/icpj.v1i12.12451).
17. Rajdeo P, Amey S, Akash N, Ravi R. Liquisolid technique: a novel approach to enhance solubility of poorly soluble drugs. *Int J Sci Res.* 2018;7(4):426-9.
18. Thoke SB, Sharma YP, Rawat SS, Nangude SL. Formulation development and evaluation of an effervescent tablet of alendronate sodium with vitamin D3. *J Drug Deliv Ther.* 2013;3(5):65-74. doi: [10.22270/jddt.v3i5.623](https://doi.org/10.22270/jddt.v3i5.623).
19. Madan JR, Patil K, Awasthi R, Dua K. Formulation and evaluation of solid self-microemulsifying drug delivery system for azilsartan medoxomil. *Int J Polym Mater Polym Biomater.* 2021;70(2):100-16. doi: [10.1080/00914037.2019.1695206](https://doi.org/10.1080/00914037.2019.1695206).
20. Nguyen TT, Duong VA, Maeng HJ. Pharmaceutical formulations with P-glycoprotein inhibitory effect as promising approaches for enhancing oral drug absorption and bioavailability. *Pharmaceutics.* 2021;13(7):1103. doi: [10.3390/pharmaceutics13071103](https://doi.org/10.3390/pharmaceutics13071103), PMID 34371794.
21. Elsheikh MA, Elnaggar YS, Gohar EY, Abdallah OY. Nanoemulsion liquid pre-concentrates for raloxifene hydrochloride: optimization and *in vivo* appraisal. *Int J Nanomedicine.* 2012;7:3787-802. doi: [10.2147/IJN.S33186](https://doi.org/10.2147/IJN.S33186), PMID 22888234.
22. Date AA, Nagarsenker MS. Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. *Int J Pharm.* 2007;329(1-2):166-72. doi: [10.1016/j.ijpharm.2006.08.038](https://doi.org/10.1016/j.ijpharm.2006.08.038), PMID 17010543.
23. Balakumar K, Raghavan CV, Selvan NT, Prasad RH, Abdu S. Self-nanoemulsifying drug delivery system (SNEDDS) of rosuvastatin calcium: design formulation, bioavailability and pharmacokinetic evaluation. *Colloids Surf B Biointerfaces.* 2013;112:337-43. doi: [10.1016/j.colsurfb.2013.08.025](https://doi.org/10.1016/j.colsurfb.2013.08.025), PMID 24012665.
24. Wu L, Qiao Y, Wang L, Guo J, Wang G, He W. A self-microemulsifying drug delivery system (SMEDDS) for a novel medicative compound against depression: a preparation and bioavailability study in rats. *AAPS PharmSciTech.* 2015;16(5):1051-8. doi: [10.1208/s12249-014-0280-y](https://doi.org/10.1208/s12249-014-0280-y), PMID 25652729.
25. Vithani K, Hawley A, Jannin V, Pouton C, Boyd BJ. Solubilisation behaviour of poorly water-soluble drugs during digestion of solid SMEDDS. *Eur J Pharm Biopharm.* 2018;130:236-46. doi: [10.1016/j.ejpb.2018.07.006](https://doi.org/10.1016/j.ejpb.2018.07.006), PMID 29981444.
26. Yarlagaadda DL, Nayak AM, Brahmam B, Bhat K. Exploring the solubility and bioavailability of sodium salt and its free acid solid dispersions of dolutegravir. *Adv Pharmacol Pharm Sci.* 2023;2023:7198674. doi: [10.1155/2023/7198674](https://doi.org/10.1155/2023/7198674), PMID 37383518.
27. Nair AB, Chaudhary S, Jacob S, Patel D, Shinu P, Shah H. Intranasal administration of dolutegravir-loaded nanoemulsion-based in situ gel for enhanced bioavailability and direct brain targeting. *Gels.* 2023;9(2):130. doi: [10.3390/gels9020130](https://doi.org/10.3390/gels9020130), PMID 36826300.
28. Patel H, Patel P, Patel M, Mehta D, Misan C. Development and characterization of a liquid and solid self-microemulsifying drug delivery system of tacrolimus. *Asian J Pharm.* 2012;6(3):204-11. doi: [10.4103/0973-8398.104837](https://doi.org/10.4103/0973-8398.104837).
29. Singh A, Singh V, Rawat G, Juyal D. Self-emulsifying systems: a review. *Asian J Pharm.* 2015;9(1):13-8. doi: [10.4103/0973-8398.150031](https://doi.org/10.4103/0973-8398.150031).