

# Design and Development of Self-Micro Emulsifying Drug Delivery Systems of Rifaximin Using 3<sup>2</sup> Factorial Design

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## ABSTRACT

**Aim/Background:** This study aimed to enhance the oral bioavailability of Rifaximin by formulating a Self-Micro emulsifying Drug Delivery System, with the goal of improving its aqueous solubility and dissolution performance. **Materials and Methods:** A 3<sup>2</sup> full factorial design was applied, wherein the independent variables selected were olive oil and Tween 20, and the chosen responses were emulsification time and drug content. Rifaximin was used as a drug. Various excipients used in the formulation included oils (olive oil, coconut oil, cottonseed oil), surfactants (Tween 20, PEG 400, Span 20), co-surfactants (propylene glycol, Kolliphor RH 40), and solid carriers (microcrystalline cellulose and Aerosil 200). The prepared liquid SMEDDS were characterized by assessing their optical transparency, pH, emulsification time (34.33±1.52 to 57±1.0 sec), zeta potential(-22.7mV), globule size (98.7 to 483.3 nm), robustness to dilution, percent transmittance, viscosity, cloud point, and drug content. Solid SMEDDS were prepared using an adsorption technique. **Results:** The *in vitro* release profile showed that rifaximin from S-SMEDDS achieved 92.3624 ± 0.21% drug release, whereas the pure drug exhibited 62.8487 ± 0.24% release, indicating approximately 1.5-fold enhancement in drug release with the solid SMEDDS formulation compared to pure rifaximin. This enhanced release profile suggests improved solubility, which could potentially increase the bioavailability of Rifaximin, a drug known for its poor water solubility. **Conclusion:** The formulated SMEDDS significantly improved the dissolution behavior of rifaximin, which may potentially enhance its therapeutic performance. This study provides a foundation for future preclinical and clinical investigations of S-SMEDDS systems designed for poorly soluble drugs such as rifaximin.

**Keywords:** Adsorption Technique, Solubility Enhancement, Factorial Design, Rifaximin, S-SMEDDS, Emulsification Time.

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## INTRODUCTION

Although oral delivery is the most widely used route for administration of a drug, a significant proportion of newly developed drug candidates exhibit lipophilicity, leading to poor gastrointestinal absorption. Various formulations that enhance solubility are often employed to overcome the challenge of their limited solubility. However, these formulations can simultaneously reduce intestinal permeability despite improving solubility. Both solubility and permeability are crucial factors influencing oral drug absorption. However, the balance between these two properties can affect the effectiveness of solubility-enhancing formulations, potentially limiting their ability to improve overall drug absorption.<sup>1</sup>

SMEDDS are isotropic combinations of oils, surfactants, co-surfactants, and active pharmaceutical agents that, upon oral intake, rapidly generate nano-sized emulsions with droplet diameters typically less than 200 nanometers. In the gastrointestinal tract, this microemulsion helps dissolve the drug by trapping it within tiny lipid or surfactant-based particles in an aqueous environment. To improve the bioavailability of hydrophobic drugs, solidified SMEDDS can be formulated. They are formulated in solid and liquid dosage forms, often filled in either soft or hard gelatin capsules.

Drugs with poor water solubility often exhibit low bioavailability due to their inadequate aqueous solubility and moderate dissolution rates. To develop effective oral dosage forms, strategies to enhance solubility or dissolution are essential. SMEDDS are liquid-based formulations that improve the dissolution and increase the bioavailability of hydrophobic drugs by delivering them in a solubilized form within the GI tract.<sup>2</sup>

Rifaximin is a chemically modified derivative of rifampin, recognized for its potent antibacterial activity towards Gram-positive, Gram-negative, aerobic, and anaerobic bacteria.<sup>3</sup>



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It is synthesized by reacting rifamycin O, which is an oxidized form of rifamycin B, with 2-amino-4-methylpyridine.<sup>4</sup> It inhibits bacterial RNA synthesis through selective binding to the  $\beta$ -subunit of the DNA-dependent RNA polymerase. Additionally, it prevents bacterial adherence to epithelial cells and reduces the expression of pro-inflammatory cytokines.<sup>5</sup>

Rifaximin is a broad-spectrum oral antimicrobial that primarily acts in the gastrointestinal tract with minimal systemic side effects. It achieves high concentrations in the intestine and effectively targets various enteropathogens. Rifaximin is commonly used to treat conditions such as hepatic encephalopathy, irritable bowel syndrome, ulcerative colitis, *Clostridium difficile* infections, acute diarrhea, and travelers' diarrhea. As per the Biopharmaceutics Classification System (BCS), it is classified as Class IV. Rifaximin has poor water solubility and low oral bioavailability, measuring less than 0.4%.<sup>6</sup> However, it dissolves well in organic solvents like ethanol, dimethylformamide (around 30 mg/mL), and DMSO (10 mg/mL). Due to its low solubility, higher doses are needed to achieve a therapeutic effect. It is available in the market in 200 mg and 550 mg doses. Rifaximin, like other BCS Class IV drugs, also has low permeability. However, improving solubility has been shown to enhance the bioavailability of other Class IV drugs.<sup>7</sup> To address these challenges, lipid-based Self-Microemulsifying Drug Delivery Systems (SMEDDS) were employed as a strategic formulation approach, as they can maintain the drug in a solubilized state, generate fine droplets upon dilution, and enhance dispersion within the gastrointestinal environment. In addition, transformation of liquid SMEDDS into a solidified system offers practical benefits such as improved physicochemical stability, convenient handling, and the possibility of enhancing dissolution as well as absorption characteristics. Therefore, the design of a solid SMEDDS formulation provides a rational platform to overcome the inherent biopharmaceutical constraints associated with rifaximin.

Deepak and Sumit (2021) reported that Nanocarriers with a core-shell structure composed of chitosan and alginate, loaded with rifaximin, were formulated and evaluated for antibacterial applications.<sup>8</sup> Another study by Swapnil *et al.*, (2024) reported formulation, development, and evaluation of rifaximin-loaded SLNs to enhance rifaximin bioavailability and therapeutic efficacy.<sup>9</sup> Jatinder Kumar *et al.*, (2016) have developed a colon-targeted rifaximin nanosuspension to overcome the limitations of rifaximin, such as lack of solubility and permeability.<sup>10</sup>

When compared with earlier rifaximin delivery systems, the optimized S-SMEDDS exhibited a notable drug-release performance. Chitosan-alginate core-shell nanoparticles (Deepak and Sumit, 2021) reported a pH-responsive sustained release with nearly 80% drug release at pH 7.2, whereas rifaximin-loaded solid lipid nanoparticles (Swapnil *et al.*, 2024) achieved about 98.12%

cumulative release over 12 hr, reflecting an extended-release pattern. Likewise, colon-targeted nanosuspension/Eudragit nanoparticle formulations (Jatinder Kumar *et al.*, 2016) showed around  $85.506 \pm 2.13\%$  release, indicating controlled but relatively slower dissolution. In contrast, the present S-SMEDDS formulation released  $92.3624 \pm 0.21\%$  of rifaximin within 4 hr (240 min), demonstrating a comparatively faster and more efficient dissolution profile. These observations suggest that solidified SMEDDS may serve as a promising alternative to conventional nanocarrier approaches for enhancing rifaximin release.

Similar studies have been reported where the solubility and permeability of rifaximin were tried to improve using various approaches such as solid lipid nanoparticles, nanoparticles, and solid dispersions, but none have used the Solidified SMEDDS Approach.

The purpose of this study was to design and develop an SMEDDS of rifaximin to improve its aqueous solubility and hence bioavailability.

## MATERIALS AND METHODS

Rifaximin was received as a gift sample from Optrix Laboratories Private Limited, Telangana, India. Cottonseed oil, coconut oil, olive oil, Tween 20, PEG 400, Span 20, propylene glycol, microcrystalline cellulose, Aerosil 200, and Kolliphor RH 40 were procured from Research Lab Fine Chem Industries, Mumbai. All additional chemicals and reagents employed were of analytical grade.

### Compatibility study for Drug and polymer

FTIR and DSC studies were performed to analyze how polymers and processing techniques affect drug stability. The analysis of the drug alone and in mixtures with different polymers to understand any changes in its properties was carried out.<sup>11</sup>

### Infrared spectroscopy (FTIR)

Physicochemical compatibility between rifaximin and the selected polymers was evaluated using FTIR spectroscopy. Spectral analysis was performed on both the pure drug and a 1:1 physical mixture of the drug with polymers. The spectra were obtained using an FTIR-8300 spectrophotometer (Shimadzu, Kyoto, Japan) employing the potassium bromide (KBr) disc technique. The study was performed within the range 400 to 4000  $\text{cm}^{-1}$ , plotting wave number versus percent transmittance.<sup>12,13</sup>

### DSC analysis

Samples were enclosed in aluminum pans and analyzed by gradually heating from 25°C to 160°C at a uniform heating rate of 10°C per minute. After Warming, they were cooled to room temperature. All samples were maintained under nitrogen during cooling, and the cooling curves were recorded.<sup>14</sup>

## Saturation solubility study

To determine the solubility of rifaximin, an excess quantity of the drug was introduced into 5 mL of each selected oil, surfactant, and co-surfactant. They were subjected to agitation on an orbital shaker at 25°C for 48 hr to reach equilibrium. Following this, the samples were centrifuged at 3500 rpm for 15 min. The supernatant was then diluted with methanol and quantitatively assessed for rifaximin concentration at 454 nm using a validated UV-visible spectrophotometric method.<sup>15</sup>

## Pseudo-ternary phase diagram construction

The water titration technique was employed by mixing surfactant and co-surfactant in ratios of 1:1, 2:1, and 3:1, while keeping the concentration of the co-surfactant constant throughout the procedure. After vortexing for 5 min, oil was added to these mixtures in ratios from 1:9 to 9:1. Water was gradually added dropwise using a burette until turbidity or gel formation appeared. The titration endpoint was determined at the first sign of turbidity or gel formation. The collected data was then analyzed, and the micro-emulsification region was mapped using Ternary Plot software.<sup>16,17</sup>

## Development of Liquid SMEDDS Using 3<sup>2</sup> Factorial Design

In this study, a 3<sup>2</sup> full factorial design was employed, in which two independent variables were assessed at three different levels. Exploratory runs were conducted as shown in Table 1. The predictor variables considered were Olive oil (X1) and Tween 20 (X2), while the dependent variables included drug content and emulsification time.<sup>15,16,18</sup>

## Drug-loaded liquid SMEDDS formulations

Liquid SMEDDS formulations were prepared using various combinations of olive oil (as the oil phase), Tween 20 (surfactant), glycerin (co-surfactant), and 200 mg of rifaximin. Initially, rifaximin was dissolved in the olive oil, then combined with the Tween 20 and glycerin mixture in the beaker. The formulation was gently mixed using vortex agitation at 37°C until complete solubilization was achieved. The final mixture was stored at room temperature for later use. The detailed composition of the liquid SMEDDS is shown in Table 1.<sup>17</sup>

## Characterization of liquid SMEDDS

### Visual translucency

The prepared L-SMEDDS were typically clear, uniform, and single-phase systems, making optical transparency a crucial characteristic. The clarity of the formulated liquid SMEDDS (L1-L9) was evaluated by placing the samples in transparent containers and visually inspecting them under proper lighting conditions. Observations were made against both black and white

illuminated backgrounds while avoiding direct light reflection into the eyes.<sup>18</sup>

### pH

To determine the pH of the prepared liquid SMEDDS, 1 mL of liquid SMEDDS was added to a beaker containing 250 mL of water, and the resulting pH was determined using a digital pH meter.<sup>19</sup>

### Emulsification time

To determine the emulsification time, 1 mL of the prepared liquid SMEDDS was added to 500 mL of deionized water. The temperature was maintained at 37°C, at 50 rpm using a paddle apparatus. The emulsification time was noted based on the appearance of a transparent or slightly bluish microemulsion, indicating complete dispersion.<sup>19</sup>

### Zeta potential, Globule size, and Polydispersity Index (PDI) determination

An aliquot of 1 mL of the optimized liquid SMEDDS was carefully added to 250 mL of deionized water, resulting in an emulsion that was analyzed for globule size and zeta potential, and PDI using SZ 100 Horiba Zetasizer.<sup>19</sup>

### Measurement of Cloud Point

A microemulsion prepared by diluting liquid SMEDDS with distilled water in a 1:250 ratio was placed in a water bath with gradual heating. The temperature at which the formulation became turbid was recorded as the cloud point.<sup>19</sup>

### Robustness to dilution

Liquid SMEDDS were diluted 50, 100, and 1000 times using deionized water, pH 1.2, and pH 6.8, respectively. The formulations were then stored for 12 hr and visually noted for phase separation.<sup>20</sup>

### Percent transmittance

A 1 mL sample of the liquid SMEDDS was diluted 100 times using deionized water, and the % transmission was estimated using a Ultra Violet visible spectrophotometer at 454 nanometers with purified water serving as the blank for calibration.<sup>18</sup>

### Viscosity

The viscosity of the formulated liquid SMEDDS was determined by a cone-plate viscometer (CAP 2000+ viscometer, Brookfield) using spindle no.1 at 50 rpm at 25°C using a spatula. 1 drop of liquid SMEDDS was placed below the spindle at the center of the viscometer plate and the dial reading was noted.<sup>21</sup>

### Drug content

To determine drug content, 1 mL of the liquid SMEDDS was diluted with 10 mL of methanol. From this, a 1 mL aliquot

was taken and further diluted to 10 mL with methanol. The absorbance was measured at 454 nanometers ( $\lambda_{\text{max}}$ ) using a UV spectrophotometer.<sup>22</sup>

### Statistical Analysis Using Design Expert Software

In the past, formulation development was primarily done through the One- variable- at- a- Time method; among different mathematical models, the Design of Experiments is widely used. Design of Experiments makes controlled changes to input variables to get the maximum amount of information on the relationships between the selected variables and responses, with a minimum number of experimental runs. A factorial experiment is a study design that involves two or more factors, each having multiple levels. A full factorial design evaluates all possible factor combinations, allowing for the assessment of main effects and interactions between two factors.

A 3<sup>2</sup> full factorial design was employed in this work to evaluate the effects of two independent variables, Olive oil ( $X_1$ ) and Tween 20 ( $X_2$ ), on the emulsification time and *in vitro* Drug release as response variables. Statistical analysis was conducted using Design Expert 13 software.<sup>15,16</sup>

### Formulation of solid SMEDDS

Solid SMEDDS was formulated using the Adsorption technique.

#### Adsorption technique

Solid SMEDDS was formulated by mixing liquid SMEDDS with solid carriers acting as adsorbents. Aerosil 200 and microcrystalline cellulose were placed in a porcelain dish, and liquid SMEDDS was added dropwise onto the adsorbents. Homogenization was then performed using a glass pestle to achieve a homogeneous distribution of the formulation. The mixture was then sieved through a sieve 80, followed by the addition of a small quantity of talc, and finally air-dried.<sup>17</sup>

#### Capsule filling

500 mg of Solid SMEDDS were encapsulated in size 0 capsules and stored in an airtight container for further evaluation.

### Evaluation of solid SMEDDS

#### Micromeritics properties

The Rifaximin-loaded Solid SMEDDS were assessed by angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's index.<sup>23</sup>

#### Reconstitution ability of Solid SMEDDS

To assess reconstitution of solid SMEDDS, 50 mg was dispersed in 50 mL of pH 1.2 buffer at 37°C and agitated using a magnetic stirrer. Emulsification and globule formation were observed. A clear emulsion indicated good reconstitution, while turbidity suggested drug precipitation and was marked as poor.<sup>17</sup>

#### Determination of Drug Content

For drug content analysis, 100 mg of rifaximin solid SMEDDS was dispersed in 10 mL of methanol, subjected to bath sonication for 30 min to ensure complete drug extraction. The solution was filtered, suitably diluted, and the rifaximin concentration was quantified using a calibration curve.<sup>24</sup>

#### Determination of Moisture Content

Moisture content in solid SMEDDS was evaluated by accurately weighing 1 g of the sample and drying it at 100°C for 4 hr. After cooling, the dried sample was reweighed. The percentage moisture content was calculated using the following formula:<sup>17</sup>

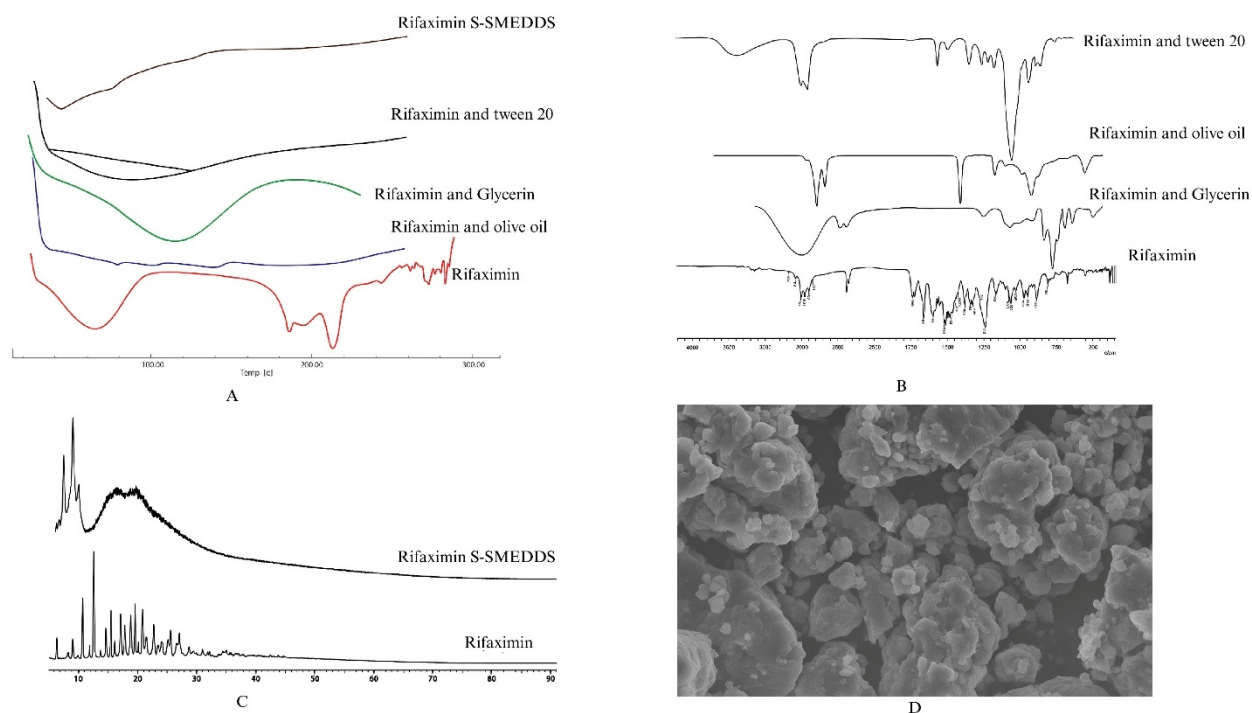
$$\% \text{ Moisture content} = \frac{(\text{Initial weight} - \text{Dried weight})}{\text{initial weight}} \times 100$$

#### Differential scanning calorimetry

Differential Scanning Calorimetric evaluation of solid SMEDDS was carried out using an SDT Q600 instrument (TA Instruments, USA). The sample was packed in an aluminum pan, and the temperature was gradually increased from 35°C - 350°C at a scale of 10°C/min. A nitrogen flux of 100 mL/min was maintained to ensure an inert environment.<sup>17</sup>

**Table 1: Experimental Design as Per 3<sup>2</sup> Full Factorial Design.**

Run	Batch	Coded Levels	Oil (mL)	Coded Levels	Surfactant (mL)
1	L1	-1	5	1	145
2	L2	0	30	-1	95
3	L3	1	55	0	120
4	L4	-1	5	0	120
5	L5	0	30	0	120
6	L6	0	30	1	145
7	L7	-1	5	-1	95
8	L8	1	55	-1	95
9	L9	1	55	1	145



**Figure 1:** Characterizations of formulations: (A) DSC curves; (B) IR spectra; (C) X-ray diffraction; (D) Scanning electron microscopy of Rifaximin S-SMEDDS at X500.

**Table 2: Saturation Solubility of Rifaximin Oil, Surfactant, and Cosurfactant.**

Sl. No.	Components	Concentration (mg/mL)
1.	Cotton seed Oil	1.18
2.	Coconut Oil	2.1
3.	Olive Oil	3.68
4.	Tween 20	3.38
5.	PEG 400	2.21
6.	Span 20	1.93
7.	Propylene Glycol	1.49
8.	Glycerin	2.18
9.	Kolliphor RH40	1.53

### X-ray diffraction study

XRD of rifaximin solid SMEDDS was performed by using an advanced diffractometer (Bruker AXS D8) equipped with Cu K $\alpha$  radiation (Ni filter), operating at 45 kV and 40 mA. The scanning was performed from 5° to 50° at a rate of 2°/min.<sup>20</sup>

### Scanning electron microscopy

The surface topography of the solid SMEDDS was evaluated using Scanning Electron Microscopy (SEM). A minimum quantity of the sample was carefully set up on an aluminum base using a double-sided adhesive carbon tape. The mounted sample was then coated with a thin film of gold under vacuum to improve conductivity. The coated sample was subsequently analyzed

under a scanning electron microscope at an accelerating potential of 15 kV. Pictures were captured at various magnifications to evaluate the surface characteristics and particle structure.<sup>20</sup>

### In vitro dissolution studies

*In vitro* dissolution studies were carried out by using a USP Type-II Dissolution Test Apparatus (paddle method) with 900 mL of pH 1.2 and 6.8 buffer as the dissolution media. The capsule was placed in the respective buffer, and 5 mL of the sample was collected at defined periods, replacing it with buffer to keep up sink conditions. An aliquot of 1 mL from the withdrawn sample was filtered and diluted to 10 mL using buffer solution. The absorbance was then determined at 435 nm (for pH 1.2) and 437 nm (for pH 6.8) by using a Ultra Violet visible spectrophotometer.<sup>25</sup>

### Kinetics of Drug Release

Predicting the release of an active agent over time is one of the crucial aspects of drug delivery, requiring the application of both simple and complex mathematical models. These models are essential for guiding the formulation design and verifying the *in vitro* drug release mechanism experimentally. To identify the specific drug release mechanism, the experimental data were compared with theoretical model solutions. Drug release kinetics from the formulated solid SMEDDS were evaluated by applying Zero-order, First-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas numerical models. The model exhibiting the

highest correlation coefficient ( $R^2$ ) was identified as the best fit for the release profile.<sup>26</sup>

### Stability of Rifaximin Solid SMEDDS

Rifaximin solid SMEDDS were subjected to stability testing by storing them for three months at Room Temperature (RT) and under accelerated conditions ( $40 \pm 2^\circ\text{C}$  and  $75 \pm 5\%$  relative humidity), conducted as per ICH guidelines, to determine the effects of temperature and humidity on the formulation. During the storage period, parameters such as reconstitution ability, drug content, and moisture content were analysed.<sup>27</sup>

## RESULTS

### Compatibility study for Drug and polymer

#### Infrared absorption spectral analysis

Figure 1 shows the FT-IR spectrum of pure rifaximin, exhibiting characteristic absorption peaks at  $3175.93\text{ cm}^{-1}$  (-OH stretching),  $1589.41\text{ cm}^{-1}$  (C=C stretching), and  $1723.47\text{ cm}^{-1}$  (C=O stretching), confirming the presence of functional groups in the drug. The spectrum of the drug with excipients in Figure 1 showed no notable physicochemical interactions.

#### Differential scanning calorimetry

As shown in Figure 1, the DSC thermogram of pure Rifaximin displayed a distinct peak at approximately  $205^\circ\text{C}$ , equivalent to its melting point.

#### Saturation solubility study

Among the lipids examined, olive oil, classified as a long-chain lipid, demonstrated the greatest solubility for Rifaximin, reaching  $3.68\text{ mg/mL}$ . Its superior solubilizing ability compared to medium-chain lipids is likely due to its composition, which primarily consists of glycerol esters with fatty acids, predominantly oleic acid (ranging from 55-83%). Tween 20 was the most effective surfactant, showing a solubility of  $3.38\text{ mg/mL}$ , which

can be attributed to its greater hydrophilic-lipophilic balance value of 16.7, enabling greater drug solubilization. Among the co-surfactants evaluated, glycerin exhibited the highest solubility for Rifaximin at  $2.18\text{ mg/mL}$ . The solubility values for each surfactant and co-surfactant are summarized in Table 2.

### Pseudo-ternary phase diagram construction

As illustrated in Figure 2, the red, orange, and blue zones in the phase diagrams denote the microemulsion regions, while the unshaded areas indicate turbid or conventional emulsion systems.

### Characterization of liquid SMEDDS

#### Visual translucency

All the prepared liquid SMEDDS formulations appeared visually clear and uniform, presenting as a single-phase system under light observation.

#### pH

The pH of all formulations ranged from 6.1 to 6.5, owing to the use of neutral excipients.

#### Emulsification time

The emulsification time of Rifaximin Liquid SMEDDS, ranging from  $28.67 \pm 1.52$  to  $62.33 \pm 1.15$  sec shown in Table 3, demonstrated its capability to rapidly self-microemulsify and disperse in GIT fluids.

#### Zeta potential, Globule size, and Polydispersity Index (PDI) determination

The zeta potential values for formulations L1 and L9 were measured at  $-12.3\text{ mV}$  and  $-22.7\text{ mV}$ , respectively, in diluted form, indicating excellent microemulsion stability. Globule size in all formulations ranged from  $98.7\text{ nm}$  to  $483.3\text{ nm}$ , with formulation L9 showing the smallest size at  $98.7\text{ nm}$ , PDI ranging from 0.245 to 0.407, indicating a uniform distribution of globule size throughout the formulations, as presented in Table 3.

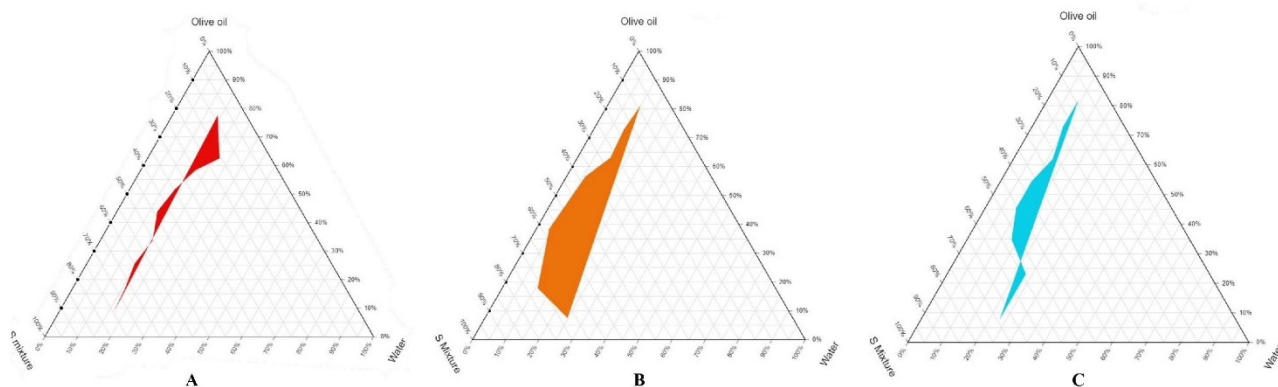
Table 3: Characterization of Liquid SMEDDS.

Formulation	Emulsification Time (sec)	Globule size (nm)	PDI	Drug Content %	Percent transmittance
L1	$62.33 \pm 1.15$	100	0.407	$96.4 \pm 0.001$	$90.12 \pm 0.19$
L2	$58 \pm 0.58$	418.5	0.369	$96.45 \pm 0.004$	$95.86 \pm 0.24$
L3	$55.67 \pm 0.58$	370.3	0.245	$97.3 \pm 0.0015$	$97.86 \pm 0.23$
L4	$47.776 \pm 0.58$	115.8	0.352	$97.56 \pm 0.002$	$98.86 \pm 0.23$
L5	$50 \pm 0.57$	148.1	0.297	$97.67 \pm 0.006$	$98.90 \pm 0.18$
L6	$42.33 \pm 1.0$	483.3	0.304	$98.3 \pm 0.002$	$99.86 \pm 0.20$
L7	$37.33 \pm 1.0$	413.8	0.361	$98.65 \pm 0.0052$	$99.90 \pm 0.17$
L8	$34.33 \pm 0.58$	199.9	0.243	$99.03 \pm 0.0053$	$99.95 \pm 0.20$
L9	$28.67 \pm 1.52$	98.7	0.334	$99.31 \pm 0.0012$	$99.98 \pm 0.21$

Values are mean  $\pm$  SD;  $n=3$ .

**Table 4: Analysis of variance for Emulsification Time.**

Source	Sum of Squares	d.f. (degrees of freedom)	Mean Square	F value	p-Value	
Model	8.68	2	4.34	154.35	<0.0001	significant
A-Oil	7.80	1	7.80	277.35	<0.0001	
B-Surfactant	0.8817	1	0.8817	31.36	0.0014	
Residual	0.1687	6	0.0281			
Total(corrected) Correlation	8.85	8				
Coefficient(R <sup>2</sup> )	0.9809					
Adjusted R <sup>2</sup>	0.9746					
Predicted R <sup>2</sup>	0.9580					
Adequate precision	31.4715					
PRESS	0.3717					



**Figure 2:** Pseudo ternary phase diagrams of surfactant: co-surfactant ratios (A) 1:1; (B) 2:1; (C) 3:1.

### Measurement of Cloud Point

The Liquid SMEDDS formulations (L1-L9) exhibited cloud points above 85°C, indicating that the microemulsion will remain steady at body temperatures without any possibility of phase separation.

### Robustness to dilution

The L1 to L9 Liquid SMEDDS formulations demonstrated good physical stability when diluted 50, 100, and 1000-fold with distilled water, simulated gastric fluid (pH 1.2), and phosphate buffer (pH 6.8), and stored for 12 hr.

### Percent transmittance

The percent transmittance of all the prepared formulations was measured between 90.12 ± 0.19% and 99.98 ± 0.21%, indicating that the formulations appeared clear, transparent, and free from any precipitation, as presented in Table 3.

### Determination of Viscosity

The Formulation L9, containing 55 mL of oil and 145 mL of surfactant, was found to be highly viscous due to a greater

amount of surfactant. The viscosity of the formulation increases as the concentration of surfactant increases. The viscosity of the optimized L9 formulation was recorded at 357.6 cp.

### Drug Content

A UV-Spectrophotometer was used for the determination of drug content. The drug content of all formulations ranged from 96.4% to 99.31%, with formulations L8 and L9 exhibiting the highest drug content, as shown in Table 3. Which is within the limits as per IP2010 (90-110%)

### Optimization

Optimization involves selecting the best choice from a given group of possibilities. It refers to the process of making something as effective, functional, or ideal as possible. Numerical relationships were established between response variables and predictor variables using Design Expert version 13 to ascertain the optimal levels of factors that produce the best responses.

### ANOVA for Evaluating Emulsification Time

As presented in Table 4, the ANOVA results for emulsification time indicate that a linear model is the most appropriate fit. The model's statistical significance is supported by a high F-value of 577.69, suggesting there's only a 0.01% likelihood that such a result occurred due to random variation. Both factor A and factor B yielded P-values below 0.0500, confirming their significant influence on the model. The predicted R<sup>2</sup> (0.9891) is closely aligned with the adjusted R<sup>2</sup> (0.9931), with a minor difference of < 0.2, reflecting strong model consistency. The adequate precision value, which reflects the signal-to-noise ratio, was 59.968, well above the acceptable threshold of 4, indicating a robust signal and validating the model's reliability in guiding formulation design.

The final equation, expressed in terms of actual variables, is as follows:

$$\text{Emulsification Time (Y1)} = 49.52867 + 0.504467 * \text{Oil (X1)} - 0.153267 * \text{Surfactant (X2)}.$$

The equation is expressed as  $Y = b_0 + b_1X_1 + b_2X_2$ .

where:

Y represents the Responses,

b<sub>0</sub> denotes the average response obtained from the nine experimental runs, and

b<sub>1</sub> b<sub>2</sub> are the Calculated coefficients for the factors X<sub>1</sub> (oil) and X<sub>2</sub> (surfactant), respectively.

### ANOVA for Assessing Drug Content

Table 5 presents the ANOVA results for drug content, indicating that a linear model offers the best fit for the data. The model

exhibits a high F-value of 154.35, demonstrating strong statistical significance, with only a 0.01% chance that such a result could arise from random variation. The P-values, all below 0.0500, confirm the statistical relevance of the model terms, with factor A identified as a key influencing factor. The predicted R<sup>2</sup> value of 0.9580 closely aligns with the adjusted R<sup>2</sup> of 0.9746, with a minimal Variance of <0.2, signifying a strong correlation and good model fit. The adequate precision value, which evaluates the signal-to-noise ratio, was found to be 31.4715—well above the acceptable threshold of 4, indicating a strong signal and supporting the model's effectiveness in guiding formulation design.

The final equation is provided in terms of actual factors.

$$\text{Drug Content (Y2)} = 94.6422 + 0.045600 * \text{Oil(X1)} + 0.015333 * \text{Surfactant(X2)}$$

The equations follow the format  $Y = b + b_1X_1 + b_2X_2$

where:

Y is the Response,

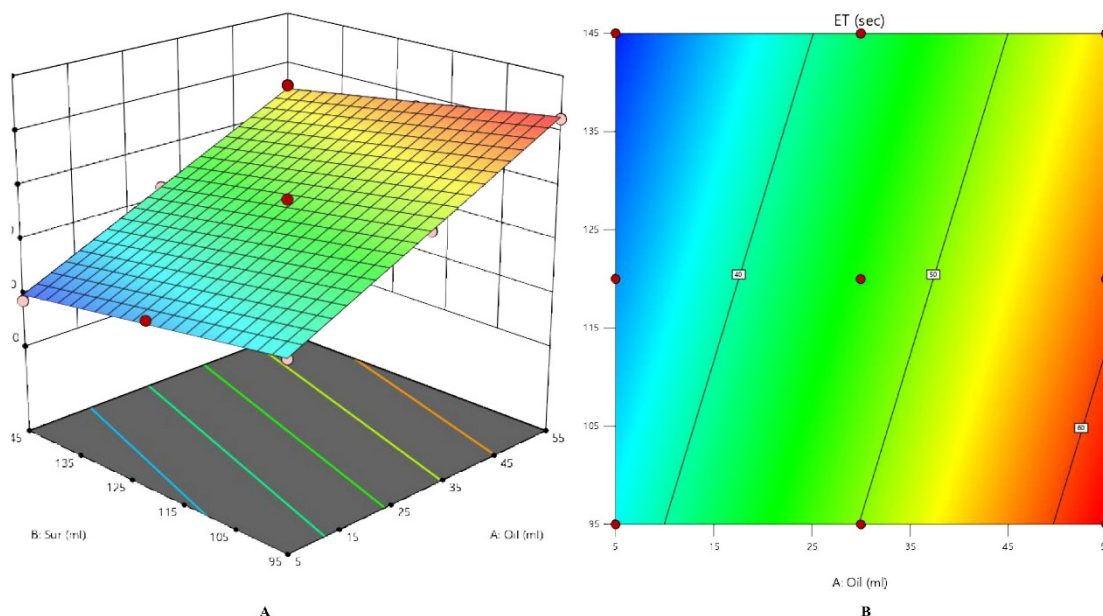
b<sub>0</sub> constitutes the average response obtained for all nine experimental trials.

b<sub>1</sub> and b<sub>2</sub> are the coefficients associated with factors X<sub>1</sub> and X<sub>2</sub>, indicating the average effect of changing each factor from its lower to higher value.

The interaction term (X<sub>1</sub>X<sub>2</sub>) shows the combined effect of simultaneously varying both factors on the response. Analysis of the polynomial equation revealed that both independent variables, X<sub>1</sub> and X<sub>2</sub>, have positive coefficients, suggesting a synergistic impact on the response Y<sub>2</sub>. In simple terms, increasing the amounts of oil and surfactant resulted in higher drug content.

**Table 5: Analysis of Variance for Drug Content.**

Source	Sum of Squares	d. f. (degrees of freedom)	Mean Square	F value	p-Value	
Model	1042.41	2	521.21	577.69	<0.0001	significant
A-Oil	954.32	1	954.32	1057.74	<0.0001	
B-Surfactant	88.09	1	88.09	97.64	<0.0001	
Residual	5.41	6	0.9022			
Total(corrected)	1047.83					
Correlation						
Coefficient(R <sup>2</sup> )	0.9948					
Adjusted R <sup>2</sup>	0.9931					
Predicted R <sup>2</sup>	0.9891					
Adequate precision	59.9682					
PRESS	11.41					



**Figure 3:** Effect of X1 and X2 on the emulsification time (A) Response surface; (B) Contour plot.

**Table 6: Micromeritic Properties of Rifaximin S-SMEDDS.**

Formulation	Bulk Density (g/cm <sup>3</sup> )	Tapped Density (g/cm <sup>3</sup> )	Carr's index	Hausner ratio	Angle of repose (θ)
S-Aerosil 200	0.56	0.69	18.84	1.23	29.68
S-MCC	0.35	0.54	35.18	1.54	48.23

**Table 7: In vitro drug release profile of pure drug rifaximin and rifaximin S-SMEDDS in pH 1.2.**

Time (min)	% CDR of Pure Rifaximin	% CDR of Rifaximin S-SMEDDS
15	1.6727	5.3091
30	3.8638	9.7022
45	7.5216	15.5741
60	12.6541	20.0238
75	18.5422	26.6796
90	23.7354	35.5535
120	29.6840	45.2032

### Analysis Using Model Graphs

#### Influence of Independent Variables on Emulsification Efficiency

Figure 3 presents both 3D surfaces and contour plots demonstrating how variations in oil and surfactant concentrations influence emulsification time. The data clearly illustrate that both variables have a significant effect on the emulsification process.

#### Effect of Experimental Variables on Drug Content

Figure 4 displays contour plots and 3D surfaces that depict the effect of oil and surfactant levels on drug content. The findings

indicate that both components have a significant role in ascertaining the drug content of the formulation.

#### Optimized Formulation Selection

Out of the nine formulations, the optimized one was chosen based on the basis of low emulsification time and higher drug content. This optimized formulation (L9) consisted of 55 mL of oil and 145 mL of surfactant. It demonstrated an emulsification time of 28.67 sec and achieved a drug content of 99.31% in liquid SMEDDS.

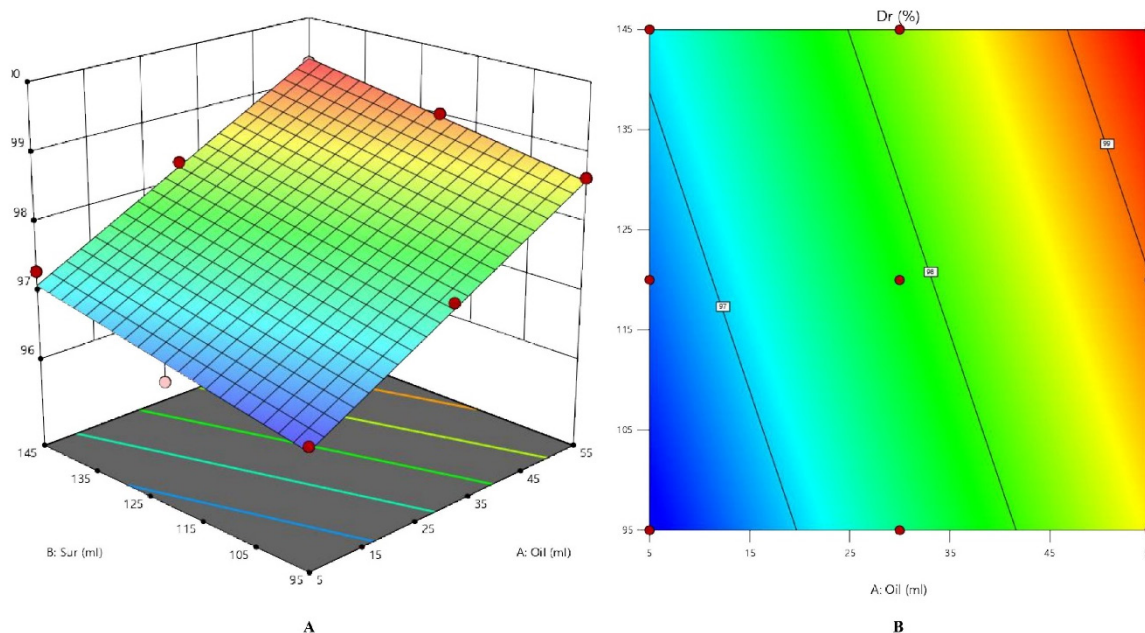
#### Adsorption technique

In this study, Aerosil 200 and microcrystalline cellulose were employed as solid carriers due to their water-insoluble nature. These materials were chosen for their superior capacity to retain lipid components, thereby reducing the quantity of carrier required for SMEDDS solidification. It was found that Aerosil 200 readily solidified rifaximin-loaded liquid SMEDDS as compared to microcrystalline cellulose. Hence, Aerosil 200 was used as an adsorbent for formulating Rifaximin Solidified SMEDDS.

#### Evaluation of solid SMEDDS

##### Micromeritics Properties

The solidified SMEDDS were assessed for various micromeritic parameters, including bulk density (0.56 g/mL), tapped density



**Figure 4:** Effect of X1 and X2 on the drug content (A) Response surface; (B) Contour plot.

**Table 8:** *In vitro* drug release profile of pure drug rifaximin and rifaximin S-SMEDDS in pH 6.8.

Time (min)	% CDR of Pure Rifaximin	% CDR of Rifaximin S-SMEDDS
15	1.3212	2.8311
30	6.2357	8.5090
45	10.8000	18.7480
60	15.0121	27.5338
75	23.0219	37.8777
90	28.8109	47.1459
120	36.1413	56.8418
150	43.5116	68.1000
180	52.4316	75.6443
210	58.1535	83.2285
240	62.8487	92.3624

(0.69 g/mL), Hausner ratio (1.23), Carr’s index (18.84), and angle of repose (29.68°). These values, summarized in Table 6.

### Reconstitution ability of Solid SMEDDS

Rifaximin Solid SMEDDS formulation was reconstituted within 2.5 min, indicating rapid microemulsion formation.

### Determination of Drug Content

The solid SMEDDS formulation of Rifaximin showed a drug content of 99.39%.

### Determination of Moisture Content

Moisture content was found to be 17.64

### Differential scanning calorimetry

The DSC thermogram of pure Rifaximin displayed a distinct endothermic peak at 205°C, suggesting its crystalline nature and purity. In contrast, the DSC curve of the solidified SMEDDS formulation showed a broad and diminished peak, as illustrated in Figure 1. The lack of a distinct endothermic peak in the solid SMEDDS suggests a transition of the drug from its crystalline state to an amorphous form.

### X-ray diffraction

The XRD pattern of pure Rifaximin shows sharp and intense peaks. However, the XRD pattern of solidified Rifaximin SMEDDS presented broad and less intense peaks, as shown in Figure 1.

### Scanning Electron Microscopy

The smooth surface of Rifaximin Solid SMEDDS indicated effective adsorption of the liquid SMEDDS onto Aerosil 200 with minimal aggregation, as shown in Figure 1.

### *In vitro* Drug Release

The *in vitro* release profile showed that rifaximin from S-SMEDDS achieved 92.3624 ± 0.21% drug release, whereas the pure drug exhibited 62.8487 ± 0.24% release, indicating approximately 1.5-fold enhancement in drug release with the solid SMEDDS formulation compared to pure rifaximin. The corresponding results are summarized in Tables 7 and 8 and visually depicted in Figure 5. This enhancement is attributed to spontaneous emulsification, reduced globule size, micellar solubilization, and a larger interfacial area, all contributing to more efficient drug release from the SMEDDS matrix.

## Kinetics of Drug Release

The findings of *in vitro* drug release highlight the release pattern, with correlation coefficients for different kinetic models shown in Table 9. For Rifaximin Solid SMEDDS, Korsmeyer-Peppas was the best-fit model at pH 1.2, while Higuchi was the best-fit model at pH 6.8, indicating that the release mechanism is complex and may involve multiple processes. An 'n' value of 0.7384 indicates that the *in vitro* drug release mechanism follows non-Fickian diffusion. According to the Higuchi model, the drug diffuses predominantly in a single direction. For the pure Rifaximin formulation, the Korsmeyer-Peppas and First-order models provided the best correlation, with an 'n' value of 0.7801, also reflecting non-Fickian release behaviour.

## Stability studies

After 3 months of storage, there was no notable decline in Rifaximin content, confirming the continued chemical stability of the formulation.

## DISCUSSION

The physical mixture retained all characteristic peaks of the drug's functional groups without any noteworthy shifts in wavenumber ( $\text{cm}^{-1}$ ), although slight peak broadening was observed, suggesting no major interaction between the components.

When Rifaximin was combined with olive oil, Tween 20, and glycerin, the resulting mixtures did not exhibit any significant shift in the thermal peak, indicating that the drug remains stable and is compatible with the selected excipients.

Solubility testing was performed using various oils (such as olive, coconut, and cottonseed oils), surfactants (Tween 20, PEG 400, and Span 20), and co-surfactants (including propylene glycol, Kolliphor RH 40, and glycerin). Based on the findings, olive oil as the oil phase, Tween 20 as the surfactant, and glycerin as the co-surfactant were selected for the preparation of the SMEDDS.<sup>28</sup>

The most extensive microemulsion area was observed when the surfactant-to-cosurfactant ratio was maintained at 2:1. This finding aligns with the results reported by Harini *et al.* (2016). Therefore, this specific ratio was chosen from the pseudo-ternary phase diagram for developing the liquid SMEDDS formulation.<sup>17</sup>

No visible drug crystals or solid particles were present, suggesting excellent optical clarity and complete solubilization of the drug. These observations are in line with the results reported by Jadhav *et al.* (2010).<sup>29</sup>

The pH of all formulations ranged between 6.1 and 6.5, which made them suitable for oral administration. These results were close to the report by Harini *et al.*, 2016.<sup>17</sup>

Emulsification time means the capability to rapidly self-microemulsify and disperse in the GIT fluids. This behaviour is likely due to the influence of Tween 20, which effectively alters interfacial properties, including interfacial tension. These findings were similar to the report by Patel and Sawant *et al.*, 2019.<sup>30</sup>

The findings of Zeta potential, Globule size, and Polydispersity Index (PDI) of our formulated L-SMEDDS suggested that strong electrostatic repulsion between droplets effectively prevents coalescence, thereby avoiding phase separation. The globule size and Polydispersity Index (PDI) of the resulting microemulsion played a vital role in maintaining the drug in a solubilised form. Smaller globules contributed to a greater surface area, thereby enhancing the drug's absorption efficiency.<sup>31</sup> The Polydispersity Index (PDI) indicated the uniformity of particle size distribution, which is a crucial parameter used to assess the stability of colloidal systems.

The cloud point refers to the critical temperature at which micelles in a nonionic surfactant-based aqueous system begin to expand and lose their structural integrity. At this stage, the interfacial curvature between the oil and water phases begins to shift. With further temperature elevation, a phase inversion may occur, resulting in the oil becoming the continuous medium and

**Table 9: Regression coefficient (R<sup>2</sup>) value of different kinetic models of Pure Drug Rifaximin and its Solidified SMEDDS.**

Formulation code	Zero order model (R <sup>2</sup> )	First order model (R <sup>2</sup> )	Higuchi model (R <sup>2</sup> )	Hixon Crowell model (R <sup>2</sup> )	Korsmeyer Peppas model		Best fit model
					(R <sup>2</sup> )	n	
Pure Drug Rifaximin (pH1.2)	0.9851	0.9841	0.9553	0.9848	0.9918	0.7801	Korsmeyer Peppas
Rifaximin S-SMEDDS (pH1.2)	0.9921	0.9808	0.9572	0.9858	0.9941	0.7384	Korsmeyer Peppas
Pure Drug Rifaximin (pH6.8)	0.9852	0.9976	0.9904	0.997	0.9641	0.7347	First order model
Rifaximin S-SMEDDS (pH6.8)	0.9688	0.9629	0.994	0.9926	0.9577	0.7675	Higuchi model

water being incorporated within the micelles. Such a transition can destabilize the system and may lead to drug precipitation from the microemulsion.<sup>32</sup>

No evidence of phase separation or drug precipitation was observed throughout this period, which aligns with findings previously reported by J. Patel *et al.* (2011).<sup>33,34</sup>

The percentage of transmission for all prepared microemulsions was more than 90%, which was clearly evident. (Rajashree *et al.*, 2022).<sup>24</sup>

In order to make sure that the prepared SMEDDS are physically stable, the viscosity is evaluated. Dispersion of SMEDDS in an aqueous medium is a crucial step, since the smaller emulsification time of high viscosity formulations can affect drug release and bioavailability.<sup>29</sup>

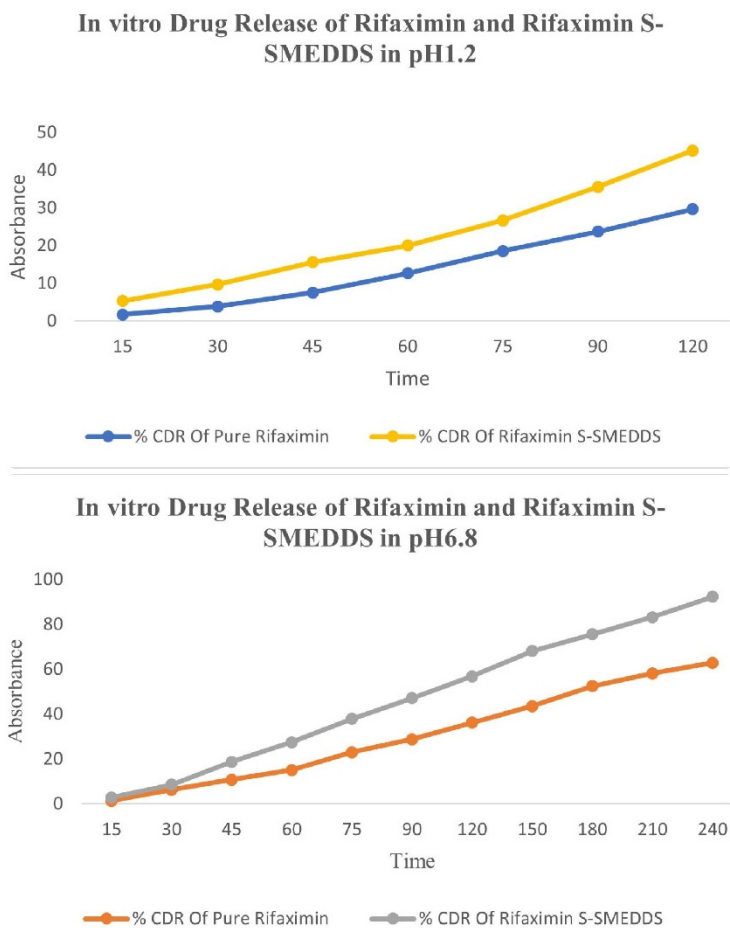
Dependent variables are influenced by modifications in the independent variables. In contrast, predictor variables are those deliberately adjusted or regulated by the researcher to observe their effect on the outcomes. In this study, olive oil (X1) and Tween 20 (X2) were chosen as the predictor variables, whereas

emulsification time and *in vitro* drug release of the liquid SMEDDS were treated as the response variables.

The experimental data were evaluated using Stat-Ease Design Expert version 13, and statistical interpretation was performed through Analysis of Variance (ANOVA), as described by Patil *et al.* (2004).<sup>35</sup>

The interaction term (X1X2) demonstrates how the response is affected when both factors are changed at the same time. It was observed that independent variable X1 has a positive coefficient, suggesting a synergistic effect on the outcome Y1, whereas variable X2 has a negative coefficient, indicating an antagonistic effect on Y1. Specifically, the emulsification time increased with a higher concentration of oil but decreased as the surfactant concentration increased (Patil *et al.*, 2004).<sup>35</sup>

The interaction term (X<sub>1</sub>X<sub>2</sub>) shows the combined effect of simultaneously varying both factors on the response. Analysis of the polynomial equation revealed that both independent variables, X<sub>1</sub> and X<sub>2</sub>, have positive coefficients, suggesting a synergistic impact on the response Y<sub>2</sub>. In simple terms, increasing the amounts of oil and surfactant resulted in higher drug content.



**Figure 5:** *In vitro* drug release of Rifaximin and its solidified SMEDDS (A) pH1.2; (B) pH6.8.

The data clearly illustrates that both variables have a significant effect on the emulsification process.

The findings indicate that both components have a significant role in ascertaining the drug content of the formulation.

Previous research by Yeom *et al.* (2015) highlighted the effectiveness of SMEDDS in significantly enhancing the dissolution rate and oral bioavailability of Atorvastatin.<sup>36</sup> Building upon this concept, the current investigation focused on formulating a Solid Self-Microemulsifying Drug Delivery System (S-SMEDDS) by incorporating liquid SMEDDS into suitable solid carriers. This approach aims to harness the advantages of converting liquid formulations into solid forms to facilitate the development of more stable and convenient solid oral dosage forms.<sup>23</sup>

Solid carriers used in S-SMEDDS formulations are generally classified as either water-soluble or water-insoluble. When water-soluble carriers are used, the SMEDDS components can be effectively released or desorbed upon reaching the gastrointestinal tract, as these carriers fully dissolve in aqueous environments. However, a key limitation of water-soluble carriers is their relatively poor capacity to absorb lipid-based materials compared to their water-insoluble counterparts.

The high specific surface area of the solid carrier showed rapid disintegration and contributed to improving dissolution (Nekkanti *et al.*, 2010; Planinšek *et al.*, 2011).<sup>37,38</sup> However, the hydrophobic nature of these carriers can result in incomplete release of SMEDDS components, as interactions between the drug and the solid matrix may hinder desorption (Nazzal *et al.*, 2002; Van Speybroeck *et al.*, 2012).<sup>39,40</sup>

Aerosil 200 and Microcrystalline Cellulose were evaluated to determine their suitability as adsorbents. The formulation exhibits acceptable flow characteristics. Similar findings were reported by Rajashree *et al.*, (2022).<sup>24</sup>

The absence of phase separation or phase inversion after 2 hr confirmed the stability of the resulting microemulsion (Vadlamudi *et al.*, 2016).<sup>17</sup>

The XRD pattern of pure Rifaximin confirmed its Crystalline nature, whereas the XRD pattern of solidified Rifaximin SMEDDS indicates a transition of the drug to an amorphous form (Vadlamudi *et al.*, 2016).<sup>17</sup>

SEM analysis confirmed the Microscale Morphology in the prepared solid SMEDDS.<sup>41</sup> The SMEDDS formulation demonstrated significantly enhanced drug release across both media, indicating its capability to provide pH-independent release throughout the gastrointestinal tract. This improvement is likely due to the rapid formation of an Oil-in-Water (o/w) microemulsion with a fine droplet size, which supports the maintenance of Rifaximin in a dissolved state under varying

pH conditions.<sup>41</sup> Furthermore, the fast emulsification process facilitates more efficient drug dispersion into the aqueous environment, thereby increasing dissolution rate (Yan *et al.*, 2011).<sup>42,43</sup>

The release kinetics were best described by the model that exhibited the highest correlation coefficient, indicating the most suitable fit for the drug release profile. According to the Higuchi model, the drug diffuses predominantly in a single direction. According to the First-order kinetic model, the drug release rate is directly dependent on the concentration of the drug remaining in the dosage form (Costa and Sousa, 2001).<sup>44</sup>

The SMEDDS formulation was evaluated for reconstitution ability, drug content, and moisture content. Stability study results indicated that Solid SMEDDS maintained their stability, as no significant changes were observed in physical characteristics or *in vitro* drug performance. (Rajashree *et al.*, 2022).

## CONCLUSION

A 3<sup>2</sup> full factorial design was employed in this investigation to evaluate the influence of formulation variables. The experimental design included two independent variables, each evaluated at three distinct levels, resulting in a total of nine formulation combinations. The independent variables considered were Olive oil (X<sub>1</sub>) and Tween 20 (X<sub>2</sub>), while the dependent variables measured were drug content and emulsification time. Compatibility studies confirmed the stability of the excipients with the drug, and the selection of optimal components and formulations was guided by extensive characterization, including phase diagram analysis and globule size evaluation. The solid SMEDDS prepared using Aerosil 200 for its superior adsorption properties showed enhanced drug release, with a 1.5-fold enhancement in dissolution observed compared to the pure drug. Kinetic studies indicated that release patterns were best described by Korsmeyer-Peppas and Higuchi models at different pH levels. Stability studies confirmed the formulation's robustness under various conditions. Overall, Solid SMEDDS of Rifaximin offer a promising approach to enhance drug solubility, warranting further *in vivo* studies for clinical evaluation.

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## ABBREVIATIONS

**SMEDDS:** Self-Microemulsifying Drug Delivery System; **GI:** Gastrointestinal; **DSC:** Differential Scanning Calorimetry; **ANOVA:** Analysis of Variance; **PDI:** Polydispersity Index; **XRD:**

X-ray Diffraction; S-SMEDDS: Solid Self-Microemulsifying Drug Delivery System.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## SUMMARY

This research focused on improving the oral bioavailability of Rifaximin, a poorly water-soluble antibiotic, by developing a Self-Microemulsifying Drug Delivery System (SMEDDS). Using a 3<sup>2</sup> factorial design, the study optimized formulations with olive oil and Tween 20 as key components. The prepared liquid SMEDDS were extensively characterized, and solid SMEDDS were developed using an adsorption technique with carriers like microcrystalline cellulose and Aerosil 200. *In vitro* drug release studies showed that the solid SMEDDS significantly enhanced Rifaximin release by about 1.5 times compared to the pure drug, indicating better solubility and potential for improved bioavailability.

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