

# Comprehensive Characterization and in Vitro Performance Evaluation of Acetazolamide-Loaded Self-Microemulsifying Drug Delivery System for Enhanced Dissolution

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## ABSTRACT:

Acetazolamide is a poorly soluble drug whose limited aqueous solubility can restrict its dissolution and oral drug delivery performance. The present study aimed to develop and comprehensively characterize acetazolamide-loaded self-microemulsifying drug delivery systems (SMEDDS) and compare the performance of liquid SMEDDS (L-SMEDDS) with its solidified form (S-SMEDDS). An optimized L-SMEDDS was developed using Capryol® 90 as oil, Cremophor® RH 40 as surfactant, and Transcutol® HP as co-surfactant. The formulation was optimized using a Box–Behnken experimental design considering globule size, polydispersity index (PDI), and transmittance as critical responses. The optimized L-SMEDDS exhibited a globule size of 78.4 nm, PDI of 0.221, transmittance of 96.8%, self-emulsification time of 20.3 s, and drug content of 98.6%. The optimized liquid formulation was converted into S-SMEDDS using Aerosil® 200 as a solid carrier by spray drying. The resulting S-SMEDDS showed satisfactory micromeritic properties and rapid reconstitution, producing globules of 80.6 nm with a PDI of 0.231. FTIR, DSC, and PXRD studies indicated compatibility between acetazolamide and the formulation components and reduced crystallinity of the drug following formulation. TEM analysis revealed predominantly spherical and uniformly distributed globules without prominent aggregation. In-vitro dissolution studies demonstrated markedly enhanced drug release from both SMEDDS formulations compared with pure acetazolamide. After 60 min, cumulative drug release was 96.8% for L-SMEDDS, 91.4% for S-SMEDDS, and 38.5% for pure acetazolamide. Release kinetic analysis showed the highest correlation with the Higuchi model, while the Korsmeyer–Peppas model indicated Fickian diffusion for L-SMEDDS. Both formulations maintained satisfactory physicochemical characteristics during 3 months of stability evaluation, although slightly greater changes were observed under accelerated conditions, particularly for S-SMEDDS. Overall, the findings demonstrate that SMEDDS, particularly the optimized liquid system, substantially enhanced the dissolution performance of acetazolamide and provided a promising formulation approach for improving its oral delivery characteristics.

**Keywords:** Acetazolamide; Self-microemulsifying drug delivery system; L-SMEDDS; S-SMEDDS; Solidification; Box–Behnken design; Dissolution enhancement; Spray drying; Lipid-based drug delivery; Stability.

## INTRODUCTION:

Oral drug delivery is widely preferred because of its convenience, patient acceptability, and ease of administration. However, the therapeutic performance of orally administered drugs can be limited by poor aqueous solubility and slow dissolution, particularly for drugs with unfavourable physicochemical properties. Improving drug solubilization and dissolution is therefore an important formulation strategy for enhancing the performance of poorly soluble drugs.<sup>1-2</sup>

Acetazolamide is a carbonic anhydrase inhibitor used in the management of several clinical conditions. Its limited aqueous solubility and crystalline nature can restrict dissolution in gastrointestinal fluids and may consequently affect its oral drug delivery performance. Various approaches, including particle-size reduction, solid dispersions, complexation, nanocarriers, and lipid-based delivery systems, have been explored to overcome such limitations.

Self-microemulsifying drug delivery systems (SMEDDS) are isotropic mixtures of oil, surfactant, and co-surfactant that spontaneously form fine emulsified droplets on contact with aqueous media. The formation of small droplets increases the interfacial area available for drug release and can maintain poorly soluble drugs in a solubilized state, thereby improving their dissolution behaviour. The performance of SMEDDS depends strongly on the selection and proportion of formulation components.<sup>3-5</sup>

Liquid SMEDDS (L-SMEDDS) can provide effective drug solubilization and rapid self-emulsification; however, their liquid nature may create practical limitations related to handling, packaging, and storage. Conversion of L-SMEDDS into solid SMEDDS (S-SMEDDS) using suitable solid carriers can improve handling characteristics

while retaining the self-emulsifying properties of the original formulation after reconstitution. Nevertheless, solidification may influence drug crystallinity, reconstitution behaviour, globule characteristics, and dissolution performance.<sup>6</sup>

Therefore, the present study was undertaken to comprehensively characterize and compare optimized acetazolamide-loaded L-SMEDDS and S-SMEDDS. The formulations were evaluated for physicochemical properties, reconstitution behaviour, morphology, solid-state characteristics, in-vitro drug dissolution, release kinetics, and stability. The study was intended to determine whether conversion of the optimized liquid formulation into a solid system could retain its desirable self-emulsifying and dissolution-enhancing characteristics.

## **MATERIALS AND METHODS:**

### **MATERIALS:**

Acetazolamide was obtained from A.G. Traders, Pune, Maharashtra, India. Capryol® 90, Labrafil® M 2125 CS, and Transcutol® HP were procured from Gattefossé, France, while oleic acid, Tween® 80, Kolliphor® EL, Cremophor® RH 40, polyethylene glycol 400, and propylene glycol were obtained from LobaChemiePvt. Ltd., Mumbai, India. Butylatedhydroxytoluene (BHT) was used as an antioxidant during formulation development. Acetazolamide-loaded L-SMEDDS comprised Capryol® 90, Cremophor® RH 40, and Transcutol® HP, whereas the optimized liquid system was further converted into S-SMEDDS using a suitable solid carrier. All chemicals and excipients were of pharmaceutical or analytical grade and were used as received.

### **Preformulation Studies**

Acetazolamide was evaluated for its organoleptic properties, melting point, equilibrium solubility, partition coefficient, and pKa as part of the preformulation assessment. The drug was visually examined for colour, odour, texture, and physical state. Its melting point was determined by the capillary tube method using a calibrated melting-point apparatus, with the onset and completion of melting recorded in triplicate. Equilibrium solubility was assessed by the shake-flask method in selected solvents and aqueous media, followed by filtration, appropriate dilution, and UV-visible spectrophotometric analysis. The partition coefficient was determined using the n-octanol/water shake-flask method, and the corresponding log P value was calculated from the concentration ratio between the two phases. The pKa was estimated by UV-visible spectrophotometry using drug solutions adjusted to different pH conditions, and the resulting absorbance profile was used to determine the ionization characteristics of acetazolamide. All determinations were performed in triplicate.<sup>7-10</sup>

## **Drug–Excipient Compatibility Studies**

### **Fourier Transform Infrared Spectroscopy**

FTIR spectroscopy was employed to evaluate the compatibility of acetazolamide with the selected SMEDDS components. Spectra of pure acetazolamide and its physical mixtures with Capryol® 90, Cremophor® RH 40, and Transcutol® HP were recorded over the appropriate infrared region. The characteristic absorption bands of the drug were compared to identify any notable changes indicative of possible drug–excipient interactions.<sup>11-12</sup>

### **Differential Scanning Calorimetry**

The thermal behaviour and compatibility of acetazolamide with the selected excipients were investigated using DSC. Approximately 5 mg of each sample was sealed in an aluminium pan and heated from 40–300°C at 10°C/min under nitrogen purge. The thermograms were evaluated by comparing the characteristic thermal transition of acetazolamide with those of the drug–excipient mixtures.<sup>13-14</sup>

### **Screening of SMEDDS Components**

Acetazolamide solubility was evaluated in selected oils, surfactants, and co-surfactants by equilibrating excess drug in 2 mL of each vehicle at 25 ± 2°C for 48 h under shaking at 250 rpm. The samples were centrifuged at 3000 rpm for 15 min, filtered through a 0.45-µm membrane, diluted with methanol, and analysed spectrophotometrically at 287 nm. Based on drug solubilization and formulation suitability, the components were selected for further development.<sup>15-17</sup>

### **Construction of Pseudo-Ternary Phase Diagrams**

Pseudo-ternary phase diagrams were constructed using Smix ratios of 1:1, 1:2, and 2:1. Capryol® 90 and Smix were combined at ratios ranging from 1:9 to 9:1, followed by gradual addition of distilled water under gentle stirring. The systems were evaluated for clarity, homogeneity, and phase separation, with clear and isotropic

systems identified as the microemulsion region. The phase diagrams were generated using CHEMIX ternary plot software, and the Smix ratio showing the favourable microemulsion region was selected.<sup>18-19</sup>

#### **Risk Assessment for SMEDDS Formulation Development**

A systematic risk assessment was performed to identify formulation and process variables affecting the critical quality attributes (CQAs) of acetazolamide-loaded SMEDDS. The CQAs included globule size, PDI, zeta potential, self-emulsification time, drug content, and in-vitro drug release. Variables such as oil concentration, Smix concentration, drug loading, mixing conditions, and temperature were assessed using a risk estimation matrix and categorized as low, medium, or high risk. High-risk variables were subsequently selected for optimization using Design of Experiments (DoE).<sup>21-22</sup>

#### **Formulation and Development of L-SMEDDS Formulation**

Based on the optimization results, liquid SMEDDS was prepared using Capryol® 90 as the oil, Cremophor® RH 40 as the surfactant, and Transcutol® HP as the co-surfactant. The surfactant and co-surfactant were combined at the optimized Smix ratio of 2:1. Acetazolamide was dissolved in Capryol® 90 at 40–45°C under continuous stirring. The Smix was then added gradually with magnetic stirring and mixed for approximately 20 min until a clear, homogeneous, and isotropic system was obtained. The formulation was visually examined for phase separation and stored in airtight glass vials at room temperature for further characterization, including self-emulsification, droplet size, and in-vitro drug release studies.<sup>23-25</sup>

#### **Preparation of Solid SMEDDS (S-SMEDDS)**

S-SMEDDS was prepared by spray drying the optimized acetazolamide L-SMEDDS using Aerosil® 200 as the solid carrier. Briefly, Aerosil® 200 (1 g) was dispersed in 100 mL distilled water, followed by addition of 2 mL optimized L-SMEDDS and stirring for 30 min at room temperature. The resulting emulsion was heated at 50°C for 10 min and spray dried at an inlet temperature of approximately 160°C, outlet temperature of 45°C, feed rate of 5 mL/min, and aspiration rate of 85%. The resulting powder was collected and stored in a desiccator until further characterization.<sup>23-26</sup>

### **Characterization of SMEDDS<sup>24-34</sup>**

#### **Thermodynamic Stability Study**

The thermodynamic stability of the developed SMEDDS was evaluated by centrifugation, heating–cooling, and freeze–thaw cycles. Formulations were centrifuged at 3500 rpm for 30 min and visually examined for phase separation, creaming, cracking, or precipitation. Stable formulations were subjected to heating–cooling cycles at 4°C and 45°C and freeze–thaw cycles between –21°C and +25°C, maintaining each condition for 48 h for at least three cycles. Formulations showing no turbidity, phase separation, or precipitation were considered thermodynamically stable.

#### **Micromeritics and Reconstitution Properties**

The S-SMEDDS powder was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose. For reconstitution, S-SMEDDS was dispersed in 100-fold purified water and gently stirred for approximately 5 min at room temperature. The dispersion was examined for clarity, homogeneity, precipitation, phase separation, and aggregation. Reconstituted globule size, PDI, and zeta potential were subsequently determined using dynamic light scattering and zeta-potential analysis.

#### **Morphological Characterization**

The morphology of the reconstituted SMEDDS was examined by transmission electron microscopy (TEM). A suitably diluted formulation was placed on a carbon-coated copper grid, followed by staining and drying. TEM images were obtained at suitable magnification to evaluate droplet shape, size distribution, and aggregation.

#### **Determination of pH**

The pH of the SMEDDS dispersion was determined using a calibrated digital pH meter. The formulation was diluted with distilled water, and the pH was recorded after stabilization of the reading. The analysis was performed in triplicate.

#### **Determination of Viscosity**

The viscosity of the SMEDDS formulation was measured using a Brookfield rotational viscometer with a suitable spindle at a predetermined temperature and rotational speed. Measurements were performed in triplicate and expressed in cP or mPa·s.

#### **Determination of Refractive Index**

The refractive index of the SMEDDS was determined using a digital/Abbe refractometer at controlled temperature. The instrument was calibrated with distilled water before analysis. The formulation was placed on the prism, and the stabilized reading was recorded in triplicate.

### Powder X-ray Diffraction (PXRD)

The solid-state characteristics of pure acetazolamide and optimized S-SMEDDS were evaluated using powder X-ray diffraction. Diffraction patterns were recorded over the selected  $2\theta$  range and compared to assess changes in the characteristic crystalline peaks and determine alterations in drug crystallinity.

### In-vitro Drug Release Study

The in-vitro drug release of pure acetazolamide, L-SMEDDS, and S-SMEDDS was evaluated using a USP Type II dissolution apparatus. Phosphate buffer pH 6.8 (900 mL) was maintained at  $37 \pm 0.5^\circ\text{C}$  with a paddle speed of 50 rpm. Formulations equivalent to 20 mg acetazolamide were introduced into the dissolution medium. Samples (10 mL) were withdrawn at 10, 20, 30, 40, 50, and 60 min and replaced with an equal volume of fresh pre-warmed medium. After filtration through a  $0.45\text{-}\mu\text{m}$  membrane, the samples were suitably diluted and analysed spectrophotometrically at 287 nm. Cumulative percentage drug release was calculated and plotted against time.

### Drug Release Kinetic Model Determination

The in-vitro drug release data were fitted to zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models. The correlation coefficient ( $R^2$ ) was used to identify the best-fit model. The release exponent ( $n$ ) obtained from the Korsmeyer–Peppas model was used to assess the predominant drug-release mechanism.

### Stability Study

The optimized L-SMEDDS and S-SMEDDS were stored at  $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$  and  $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ . Samples were evaluated at predetermined intervals for globule size, PDI, and drug content, and the results were compared with initial values to assess formulation stability. The study was conducted with reference to ICH Q1A(R2) principles.

### Statistical Analysis

Experimental results were expressed as mean  $\pm$  standard deviation. Statistical analysis was performed using Student's t-test and one-way ANOVA. A  $p \leq 0.05$  was considered statistically significant, while  $p \leq 0.01$  was considered highly significant.

## RESULTS AND DISCUSSION:

### Pre-formulation Studies

#### Organoleptic Properties of Acetazolamide

Acetazolamide was obtained as a white to pale yellowish-white, odourless crystalline powder with a fine and uniform texture. No foreign matter or agglomeration was observed, confirming its satisfactory physical characteristics for further formulation studies.

#### Melting Point

Acetazolamide showed a narrow melting transition with a mean melting point of  $258.10 \pm 0.01^\circ\text{C}$ , indicating good reproducibility and confirming its crystalline nature.

#### Solubility Study

Acetazolamide exhibited variable solubility in the tested media. The highest solubility was observed in methanol ( $8.47 \pm 0.05 \text{ mg/mL}$ ), whereas distilled water showed considerably lower solubility ( $0.73 \pm 0.01 \text{ mg/mL}$ ). The limited aqueous solubility supported the investigation of SMEDDS for improving drug solubilization and dissolution.

#### Partition Coefficient

The n-octanol/water partition coefficient of acetazolamide was  $0.546 \pm 0.002$ , corresponding to a mean log P of  $-0.262 \pm 0.001$ . The relatively low log P indicated preferential distribution toward the aqueous phase and was considered during selection of lipidic formulation components.

#### Determination of pKa

The spectrophotometric study showed pH-dependent changes in absorbance, confirming the ionization behaviour of acetazolamide. The mean pKa was  $7.20 \pm 0.02$ , with a %RSD of 0.21%, indicating good repeatability.

**Table 1: Preformulation characteristics of acetazolamide**

| Parameter          | Result                                           |
|--------------------|--------------------------------------------------|
| Appearance         | White to pale yellowish-white crystalline powder |
| Melting point      | $258.10 \pm 0.01^\circ\text{C}$                  |
| Highest solubility | Methanol: $8.47 \pm 0.05 \text{ mg/mL}$          |
| Aqueous solubility | $0.73 \pm 0.01 \text{ mg/mL}$                    |

|                       |                    |
|-----------------------|--------------------|
| Partition coefficient | $0.546 \pm 0.002$  |
| Log P                 | $-0.262 \pm 0.001$ |
| pKa                   | $7.20 \pm 0.02$    |
| pKa %RSD              | 0.21%              |

Overall, the preformulation assessment demonstrated that acetazolamide was a crystalline drug with limited aqueous solubility and low lipophilicity. These characteristics provided a rationale for further development and evaluation of the L-SMEDDS and S-SMEDDS formulations.

#### FTIR Studies

The FTIR spectrum of pure acetazolamide showed characteristic bands at 3451.70, 1685.90, 1259.86, 1317.20, and 1507.25  $\text{cm}^{-1}$  corresponding to N-H, C=O, S=O, C-N, and aromatic C=C vibrations, respectively. These characteristic bands were retained in the acetazolamide-Capryol® 90-Cremophor® RH 40-Transcutol® HP mixture, with no major peak disappearance or shifting, indicating no prominent chemical incompatibility between the drug and selected excipients.

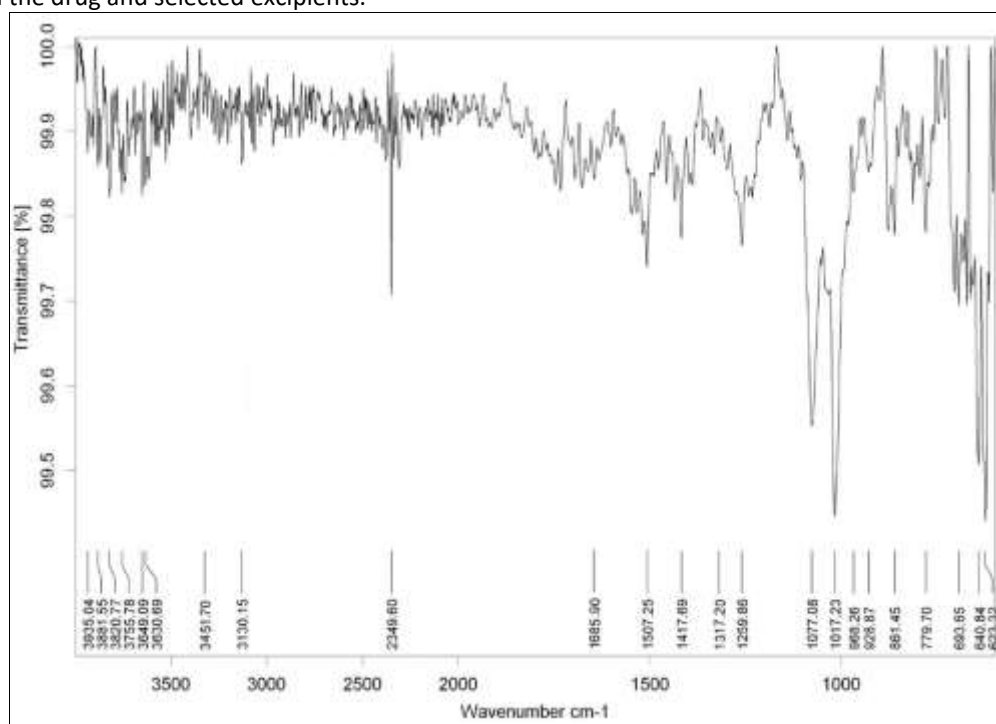


Figure 1: FTIR Spectra of Acetazolamide

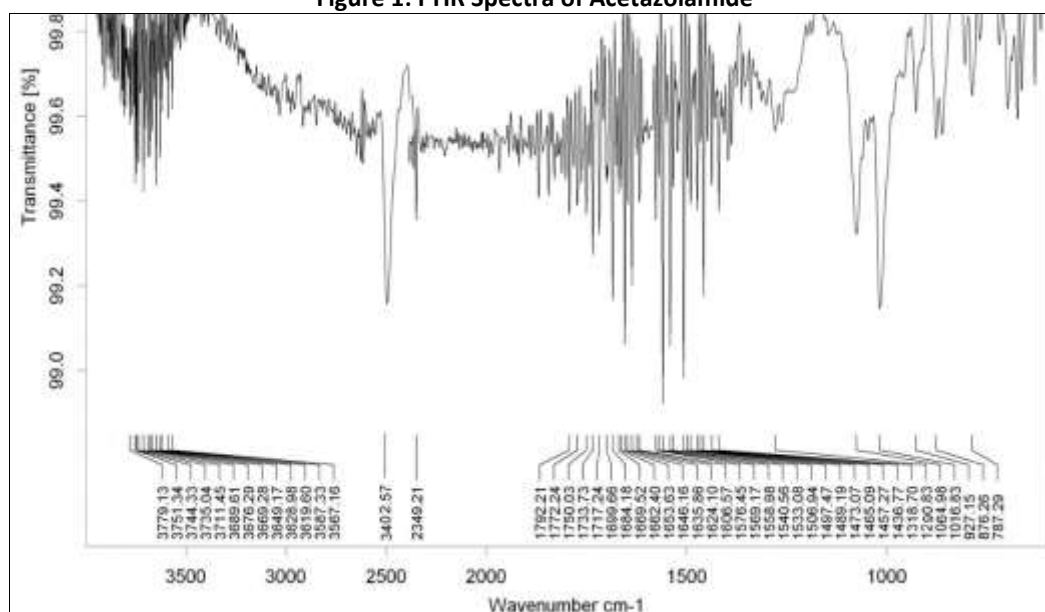


Figure 2: FT-IR Spectra of physical mixture of Acetazolamide, Capryol 90, Cremophor® RH 40 and Transcutol® HP

### Differential Scanning Calorimetry (DSC) Study

Pure acetazolamide exhibited a sharp endothermic peak at approximately 268–270°C, confirming its characteristic crystalline thermal behaviour. The drug–excipient mixture showed a slightly shifted endothermic peak at 267.85°C compared with 269.58°C for acetazolamide. The retention of the characteristic thermal transition without any prominent new peak suggested the absence of major thermal incompatibility between acetazolamide and the selected excipients.

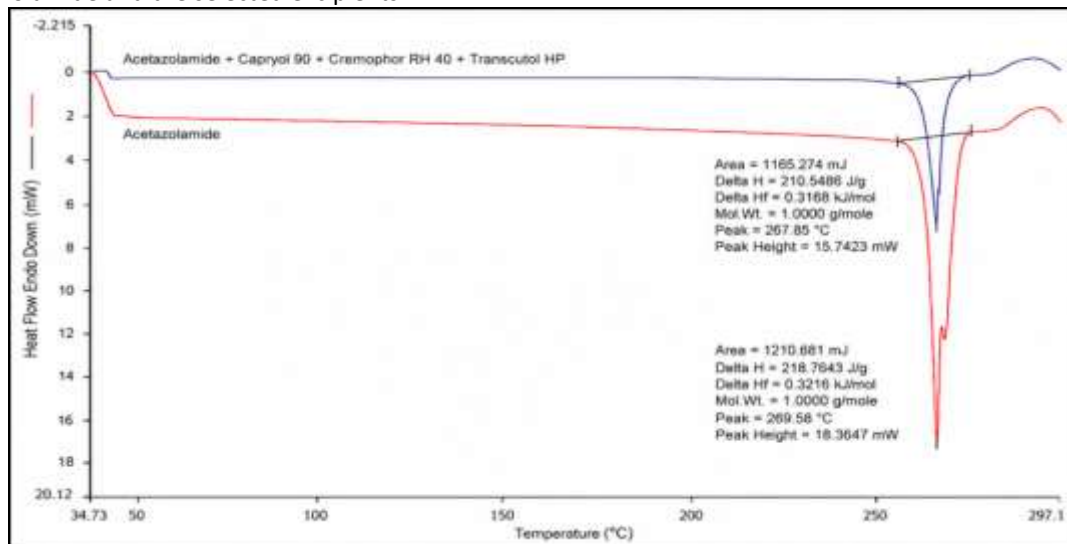


Figure 3: DSC Thermogram of Acetazolamide with excipients

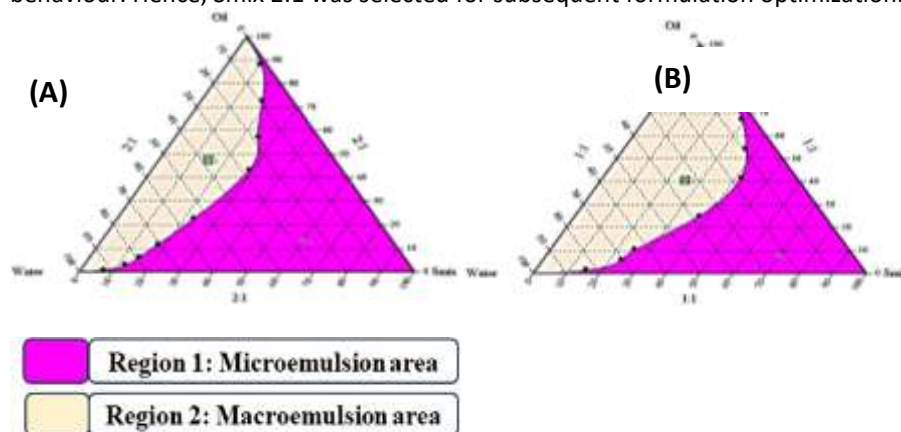
### SMEDDS Formulation Development of Acetazolamide

#### Screening of Components

Acetazolamide showed the highest solubilization in Capryol® 90 among the tested oils, Cremophor® RH 40 among the surfactants, and Transcutol® HP among the co-surfactants. Therefore, Capryol® 90, Cremophor® RH 40, and Transcutol® HP were selected as the oil, surfactant, and co-surfactant, respectively, for further SMEDDS development.

#### Construction of Pseudo-Ternary Phase Diagram

Pseudo-ternary phase diagrams were constructed using Smix ratios of 1:1, 1:2, and 2:1. The 2:1 ratio of Cremophor® RH 40® HP produced the largest microemulsion region, indicating favourable emulsification behaviour. Hence, Smix 2:1 was selected for subsequent formulation optimization.



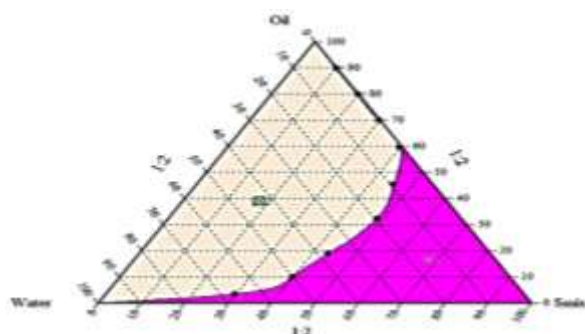


**Figure 4: Pseudo-ternary phase diagram of Capryol 90 (oil): Cremophor RH40: Transcutol HP (Smix) (A) 2:1, (B) 1:1, and (C) 1:2**

#### Optimization of Developed SMEDDS Formulation

A 13-run Box–Behnken design was used to optimize acetazolamide SMEDDS using oil concentration (A), Smix concentration (B), and drug loading (C). Globule size, PDI, and transmittance were selected as responses. The observed globule size, PDI, and transmittance ranged from 78.4–168.5 nm, 0.221–0.436, and 68.4–96.8%, respectively. Run 13 showed the optimum characteristics with 78.4 nm globule size, 0.221 PDI, and 96.8% transmittance.

The quadratic models were significant, with Smix concentration showing the greatest influence on the responses, followed by oil concentration, whereas drug loading had a comparatively lower effect. The models showed high  $R^2$  values of 0.9913, 0.9963, and 0.9920 for globule size, PDI, and transmittance, respectively. Based on desirability optimization, the optimized formulation contained approximately 15% oil, 60–65% Smix, and 10 mg drug, producing approximately 78 nm globule size, 0.22 PDI, and >96% transmittance.

**Globule Size (nm) =**  $78.4 + 10.625A - 24.5375B + 3.8125C - 1.35AB + 0.20AC - 0.225BC + 36.4625A^2 + 14.2375B^2 + 30.5875C^2$  ..... (Eq. 1)

**PDI =**  $0.221 + 0.014875A - 0.0685B + 0.005625C + 0.0045AB + 0.00125AC + 0BC + 0.086625A^2 + 0.042875B^2 + 0.074125C^2$  ..... (Eq. 2)

**Transmittance (%) =**  $96.8 - 1.9875A + 8.75B - 0.8625C + 0.15AB + 0.025AC + 0.4BC - 11.6375A^2 - 5.0625B^2 - 9.6375C^2$  ..... (Eq. 3)

**Table 2: Optimization of Acetazolamide SMEDDS Formulation**

| Run | A (Oil) | B (Smix) | C (Drug) | Globule Size (nm) (R1) | PDI (R2) | Transmittance (%) (R3) |
|-----|---------|----------|----------|------------------------|----------|------------------------|
| 1   | -1      | -1       | 0        | 145.2                  | 0.412    | 72.3                   |
| 2   | +1      | -1       | 0        | 168.5                  | 0.436    | 68.4                   |
| 3   | -1      | +1       | 0        | 92.4                   | 0.256    | 91.5                   |
| 4   | +1      | +1       | 0        | 110.3                  | 0.298    | 88.2                   |
| 5   | -1      | 0        | -1       | 130.6                  | 0.365    | 78.6                   |
| 6   | +1      | 0        | -1       | 152.1                  | 0.389    | 74.2                   |
| 7   | -1      | 0        | +1       | 138.4                  | 0.372    | 76.8                   |
| 8   | +1      | 0        | +1       | 160.7                  | 0.401    | 72.5                   |
| 9   | 0       | -1       | -1       | 140.8                  | 0.395    | 75.6                   |
| 10  | 0       | +1       | -1       | 98.6                   | 0.268    | 90.3                   |
| 11  | 0       | -1       | +1       | 148.3                  | 0.408    | 73.1                   |
| 12  | 0       | +1       | +1       | 105.2                  | 0.281    | 89.4                   |
| 13  | 0       | 0        | 0        | 78.4                   | 0.221    | 96.8                   |

| Factors | Independent Variable | Level used, actual coded |            |           |
|---------|----------------------|--------------------------|------------|-----------|
|         |                      | Low (-1)                 | Medium (0) | High (+1) |
| A       | Oil (%)              | 10                       | 15         | 20        |
| B       | Smix (%)             | 50                       | 60         | 70        |
| C       | Drug Loading (mg)    | 5                        | 10         | 15        |

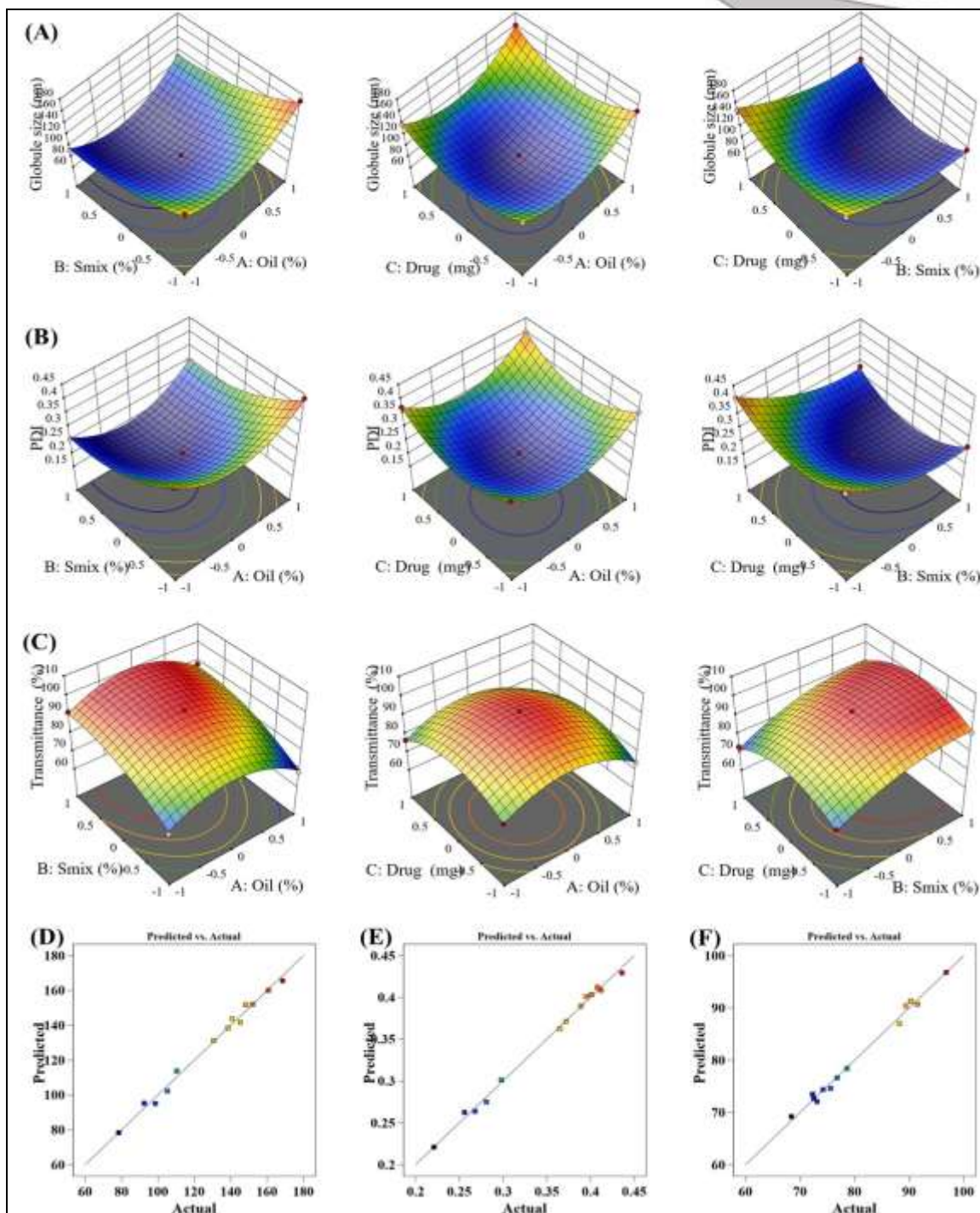


**Figure 5: Three-dimensional response surface plots for the effect of independent variables on (A) globule size, (B) PDI, and (C) % Transmittance. Linear correlation plots between the actual and predicted values for (D) globule size, (E) PDI, and (F) % Transmittance**

#### Final Optimized Formulation Composition

The optimized acetazolamide SMEDDS consisted of Capryol® 90, Cremophor® RH 40, and Transcutol® HP as the oil, surfactant, and co-surfactant, respectively. Acetazolamide (10 mg) was incorporated into Capryol® 90, followed by Cremophor® RH 40 and Transcutol® HP at a 2:1 Smix ratio. BHT (10 mg) was included as an antioxidant. The components were mixed thoroughly to obtain a homogeneous liquid SMEDDS preconcentrate. The optimized formulation exhibited approximately 78 nm globule size, 0.22 PDI, and >96% transmittance, indicating satisfactory formulation characteristics.

**Table 3: Optimized Formulation Composition (For 10 mL)**

| Sr. No. | Ingredient                    | Function                               | Quantity |
|---------|-------------------------------|----------------------------------------|----------|
| 1       | Acetazolamide                 | Active pharmaceutical ingredient (API) | 10 mg    |
| 2       | Capryol 90                    | Oil phase (solubilizer)                | 1.5 mL   |
| 3       | Cremophor RH40                | Surfactant (emulsifying agent)         | 4.3 mL   |
| 4       | Transcutol HP                 | Co-surfactant (co-emulsifier)          | 2.2 mL   |
| 5       | ButylatedHydroxytoluene (BHT) | Antioxidant                            | 10 mg    |
| 6       | Purified Water*               | Diluent (for evaluation)               | q.s.     |

## Characterization of SMEDDS Formulation

### Thermodynamic Stability Study

The pure drug showed sedimentation and precipitation under stress conditions, whereas both L-SMEDDS and S-SMEDDS remained stable without phase separation or precipitation. L-SMEDDS remained clear and transparent, while S-SMEDDS showed slight opacity due to the solid carrier. Thus, both formulations demonstrated good thermodynamic stability.

**Table 4: Thermodynamic stability of developed formulations**

| Formulation | Centrifugation | Heating–Cooling | Freeze–Thaw      | Appearance         | Overall stability |
|-------------|----------------|-----------------|------------------|--------------------|-------------------|
| Pure drug   | Sedimentation  | Unstable        | Precipitation    | Turbid             | Unstable          |
| L-SMEDDS    | No separation  | Stable          | No precipitation | Clear, transparent | Stable            |
| S-SMEDDS    | No separation  | Stable          | No precipitation | Slightly opaque    | Stable            |

### Self-Emulsification

The developed SMEDDS formulations showed rapid self-emulsification, with emulsification times of approximately 24.1–48.3 s. The optimized F13 formulation exhibited a shorter self-emulsification time of  $20.3 \pm 0.7$  s, producing a clear and homogeneous dispersion. The rapid emulsification was attributed to the optimized oil–Smix composition.

### Cloud-Point Determination

The optimized SMEDDS showed a high cloud-point temperature of  $81.7 \pm 0.6^\circ\text{C}$ , indicating good thermal stability. The formulation remained clear at temperatures below the cloud point, suggesting satisfactory stability under normal storage and physiological conditions.

### Drug Content Determination

The drug content of the developed formulations ranged from 96.8–99.2%. The optimized F13 formulation showed  $98.6 \pm 0.7\%$  drug content, indicating satisfactory drug incorporation and formulation uniformity.

### Robustness to Dilution

The optimized acetazolamide SMEDDS showed good dilution robustness at 1:50, 1:100, and 1:250 in distilled water, 0.1 N HCl, and phosphate buffer pH 6.8. No precipitation or phase separation was observed, although slight opalescence occurred at 1:250 dilution.

**Table 5: Dilution robustness of optimized acetazolamide SMEDDS**

| Medium                  | 1:50          | 1:100         | 1:250                       |
|-------------------------|---------------|---------------|-----------------------------|
| Distilled water         | Stable, clear | Stable, clear | Stable, slightly opalescent |
| 0.1 N HCl               | Stable, clear | Stable, clear | Stable, slightly opalescent |
| Phosphate buffer pH 6.8 | Stable, clear | Stable, clear | Stable, slightly opalescent |

### Determination of Transmittance

The optimized SMEDDS showed  $96.8 \pm 0.5\%$  transmittance, confirming high optical clarity and efficient formation of fine droplets. This finding was consistent with the observed globule size of 78.4 nm and PDI of 0.221.

### Micromeritic and Reconstitution Properties

The S-SMEDDS exhibited satisfactory powder-flow properties, with a bulk density of  $0.421 \pm 0.008$  g/cm<sup>3</sup>, tapped density of  $0.487 \pm 0.006$  g/cm<sup>3</sup>, Carr's index of  $13.55 \pm 0.72\%$ , Hausner's ratio of  $1.16 \pm 0.01$ , and angle of repose of  $28.6 \pm 0.8^\circ$ . Upon 100-fold dilution with purified water, the powder rapidly reconstituted within 5 min without aggregation, precipitation, or phase separation. The reconstituted system showed a globule size of  $80.6 \pm 1.4$  nm, PDI of  $0.231 \pm 0.012$ , and zeta potential of  $-18.7 \pm 1.2$  mV, indicating retention of self-

emulsifying properties.

### Morphological Characterization

TEM analysis showed predominantly spherical, well-defined, and uniformly distributed droplets with no prominent aggregation. The observed droplet size ranged from 54.8–101.6 nm, with a mean size of  $78.4 \pm 5.8$  nm, consistent with the DLS measurement and confirming the formation of a nanosized, homogeneous dispersion.

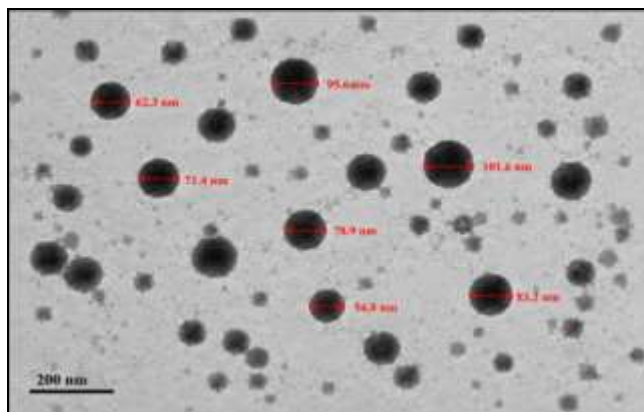


Figure 6: Transmission electron microscopic image of optimized acetazolamide-loaded SMEDDS

### Determination of pH

The pH of the SMEDDS formulations ranged from  $6.18 \pm 0.04$  to  $6.52 \pm 0.05$ . The optimized F13 formulation showed a pH of  $6.42 \pm 0.05$ , indicating good formulation consistency.

### Determination of Viscosity

The viscosity ranged from  $72.8 \pm 1.8$  to  $98.6 \pm 2.4$  cP. The optimized F13 formulation exhibited a viscosity of  $86.4 \pm 2.1$  cP, indicating suitable fluidity and consistency.

### Determination of Refractive Index

The refractive index ranged from  $1.4478 \pm 0.0011$  to  $1.4564 \pm 0.0013$ . F13 showed a refractive index of  $1.4528 \pm 0.0012$ , consistent with its clear and homogeneous appearance.

Table 6: pH, viscosity, and refractive index of acetazolamide-loaded SMEDDS

| Formulation                | Oil (%)   | Smix (%)  | Drug (mg) | pH                                | Viscosity (cP)                   | Refractive index                      |
|----------------------------|-----------|-----------|-----------|-----------------------------------|----------------------------------|---------------------------------------|
| F1                         | 10        | 50        | 10        | $6.24 \pm 0.04$                   | $78.6 \pm 1.9$                   | $1.4486 \pm 0.0011$                   |
| F2                         | 20        | 50        | 10        | $6.18 \pm 0.04$                   | $98.6 \pm 2.4$                   | $1.4564 \pm 0.0013$                   |
| F3                         | 10        | 70        | 10        | $6.36 \pm 0.05$                   | $74.2 \pm 1.7$                   | $1.4502 \pm 0.0012$                   |
| F4                         | 20        | 70        | 10        | $6.29 \pm 0.04$                   | $91.5 \pm 2.2$                   | $1.4548 \pm 0.0012$                   |
| F5                         | 10        | 60        | 5         | $6.48 \pm 0.05$                   | $76.4 \pm 1.8$                   | $1.4494 \pm 0.0011$                   |
| F6                         | 20        | 60        | 5         | $6.32 \pm 0.04$                   | $94.2 \pm 2.3$                   | $1.4552 \pm 0.0013$                   |
| F7                         | 10        | 60        | 15        | $6.45 \pm 0.05$                   | $79.8 \pm 1.9$                   | $1.4498 \pm 0.0011$                   |
| F8                         | 20        | 60        | 15        | $6.27 \pm 0.04$                   | $96.1 \pm 2.4$                   | $1.4558 \pm 0.0013$                   |
| F9                         | 15        | 50        | 5         | $6.31 \pm 0.04$                   | $84.7 \pm 2.0$                   | $1.4518 \pm 0.0012$                   |
| F10                        | 15        | 70        | 5         | $6.52 \pm 0.05$                   | $80.5 \pm 1.9$                   | $1.4532 \pm 0.0012$                   |
| F11                        | 15        | 50        | 15        | $6.22 \pm 0.04$                   | $87.9 \pm 2.1$                   | $1.4524 \pm 0.0012$                   |
| F12                        | 15        | 70        | 15        | $6.39 \pm 0.05$                   | $83.1 \pm 2.0$                   | $1.4538 \pm 0.0012$                   |
| <b>F13<br/>(Optimized)</b> | <b>15</b> | <b>60</b> | <b>10</b> | <b><math>6.42 \pm 0.05</math></b> | <b><math>86.4 \pm 2.1</math></b> | <b><math>1.4528 \pm 0.0012</math></b> |

### Powder X-ray Diffraction (PXRD)

Pure acetazolamide showed sharp characteristic diffraction peaks at approximately  $8.4^\circ$ ,  $11.2^\circ$ ,  $14.6^\circ$ ,  $17.3^\circ$ ,  $20.1^\circ$ ,  $22.8^\circ$ ,  $25.6^\circ$ ,  $28.4^\circ$ ,  $31.2^\circ$ ,  $34.7^\circ$ ,  $37.9^\circ$ , and  $42.1^\circ$  ( $2\theta$ ), confirming its crystalline nature. In contrast, S-SMEDDS showed markedly reduced peak intensity with a broad halo around  $20.3^\circ$  ( $2\theta$ ). This reduction indicated decreased crystallinity and greater molecular dispersion of acetazolamide within the S-SMEDDS matrix, which may contribute to improved dissolution.

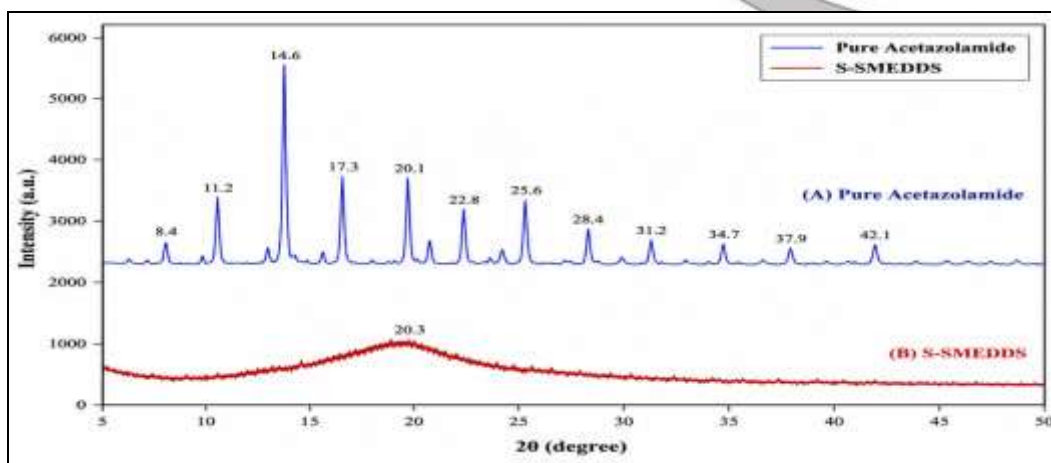


**Figure 7: Powder X-ray diffraction patterns of (A) pure acetazolamide showing characteristic crystalline diffraction peaks and (B) optimized S-SMEDDS showing markedly reduced crystallinity and a broad diffuse halo**

#### Determination of In-vitro Drug Release from Developed SMEDDS Formulation

The pure drug showed slow dissolution, with drug release increasing from 12.5% at 10 min to 38.5% at 60 min. In comparison, L-SMEDDS showed markedly higher release, increasing from 48.3% to 96.8%, while S-SMEDDS showed 41.2% to 91.4% over the same period. Thus, the release followed the order L-SMEDDS > S-SMEDDS > pure drug.

The enhanced release from both SMEDDS formulations may be attributed to improved drug solubilization and formation of fine droplets upon aqueous dilution. The slightly lower release from S-SMEDDS compared with L-SMEDDS may be associated with the solid carrier and reconstitution step. The release profiles of both SMEDDS formulations showed the best fit to the Higuchi model, indicating predominantly diffusion-controlled release.

**Table 7: Cumulative percentage drug release of acetazolamide formulations**

| Time (min) | Pure Drug              |                | L-SMEDDS               |                | S-SMEDDS               |                |
|------------|------------------------|----------------|------------------------|----------------|------------------------|----------------|
|            | Conc. Released (µg/mL) | % Drug Release | Conc. Released (µg/mL) | % Drug Release | Conc. Released (µg/mL) | % Drug Release |
| 10         | 2.5                    | 12.5           | 9.6                    | 48.3           | 8.2                    | 41.2           |
| 20         | 3.7                    | 18.7           | 13.5                   | 67.9           | 12.3                   | 61.8           |
| 30         | 4.9                    | 24.3           | 16.4                   | 82.5           | 15.4                   | 77.6           |
| 40         | 6.2                    | 31.2           | 18.3                   | 91.6           | 17.3                   | 86.5           |
| 50         | 7.1                    | 35.4           | 19.2                   | 94.2           | 18.1                   | 89.7           |
| 60         | 7.8                    | 38.5           | 19.8                   | 96.8           | 18.6                   | 91.4           |

Overall, both L-SMEDDS and S-SMEDDS substantially improved acetazolamide dissolution compared with the pure drug, with L-SMEDDS showing the highest release. The results demonstrate improved in-vitro dissolution performance of the developed SMEDDS formulations.

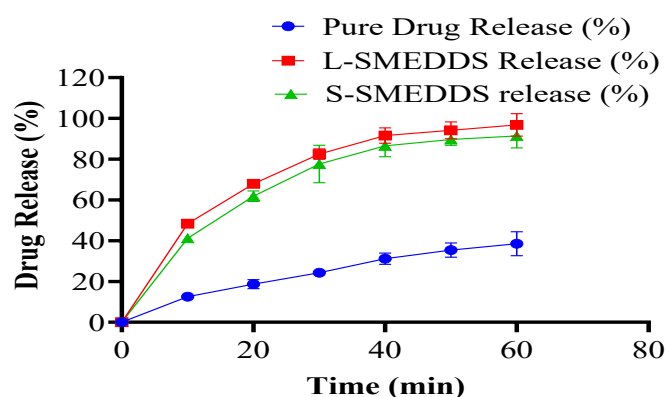


**Figure 8: Drug release across dialysis membrane for 60 min**

### Drug Release Kinetic Study

The release data of pure acetazolamide, L-SMEDDS, and S-SMEDDS were fitted to zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models. The Higuchi model showed the highest  $R^2$  values for pure drug (0.9829), L-SMEDDS (0.9981), and S-SMEDDS (0.9979), indicating predominantly diffusion-controlled release. The Korsmeyer–Peppas values were 0.648, 0.467, and 0.545 for pure drug, L-SMEDDS, and S-SMEDDS, respectively. L-SMEDDS showed Fickian diffusion ( $n < 0.5$ ), whereas pure drug and S-SMEDDS showed anomalous release ( $0.5 < n < 1$ ).

**Table 8: Drug release kinetic model analysis**

| Kinetic model    | Pure drug ( $R^2$ ) | L-SMEDDS ( $R^2$ ) | S-SMEDDS ( $R^2$ ) |
|------------------|---------------------|--------------------|--------------------|
| Zero-order       | 0.9718              | 0.8942             | 0.9226             |
| First-order      | 0.8123              | 0.9014             | 0.9164             |
| Higuchi          | 0.9829              | 0.9981             | 0.9979             |
| Hixson–Crowell   | 0.9818              | 0.9883             | 0.9906             |
| Korsmeyer–Peppas | 0.9761              | 0.9895             | 0.9704             |
| n value          | 0.648               | 0.467              | 0.545              |

Overall, the Higuchi model provided the best fit for all formulations, demonstrating predominantly diffusion-controlled drug release, with L-SMEDDS showing the highest model fit.

### Stability Study

The optimized L-SMEDDS and S-SMEDDS formulations were evaluated for stability under long-term storage conditions of  $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$  and accelerated conditions of  $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$  for 3 months. The formulations were periodically assessed for globule size, PDI, and drug content and compared with their initial values.

Under long-term conditions, L-SMEDDS showed a slight increase in globule size from 78.4 to 80.6 nm and PDI from 0.221 to 0.231, while drug content decreased from 98.6 to 97.8% after 3 months. Similarly, S-SMEDDS exhibited an increase in globule size from 80.6 to 83.0 nm and PDI from 0.231 to 0.243, with drug content decreasing from 98.4 to 97.6%. Under accelerated conditions, the changes were slightly greater. After 3 months, L-SMEDDS showed a globule size of 83.1 nm, PDI of 0.241, and drug content of 97.2%, whereas S-SMEDDS showed corresponding values of 86.8 nm, 0.259, and 96.9%, respectively.

Overall, both formulations maintained their nanosized characteristics with only minor changes in globule size, PDI, and drug content during the study period. The changes were more pronounced under accelerated conditions, particularly for S-SMEDDS. Based on the measured parameters, both formulations demonstrated satisfactory short-term stability, with L-SMEDDS showing comparatively smaller changes during storage.

**Table 9: Comparative stability data of optimized L-SMEDDS and S-SMEDDS**

| Formulation | Storage condition                              | Initial size (nm) | 3-month size (nm) | Initial PDI | 3-month PDI | Initial drug content (%) | 3-month drug content (%) |
|-------------|------------------------------------------------|-------------------|-------------------|-------------|-------------|--------------------------|--------------------------|
| L-SMEDDS    | $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$ | 78.4              | 80.6              | 0.221       | 0.231       | 98.6                     | 97.8                     |
| L-SMEDDS    | $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ | 78.4              | 83.1              | 0.221       | 0.241       | 98.6                     | 97.2                     |
| S-SMEDDS    | $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$ | 80.6              | 83.0              | 0.231       | 0.243       | 98.4                     | 97.6                     |
| S-SMEDDS    | $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ | 80.6              | 86.8              | 0.231       | 0.259       | 98.4                     | 96.9                     |

## CONCLUSION:

The present study successfully developed and comprehensively characterized acetazolamide-loaded L-SMEDDS and S-SMEDDS. The optimized L-SMEDDS, comprising Capryol® 90, Cremophor® RH 40, and Transcutol® HP, exhibited a small globule size, low PDI, rapid self-emulsification, high transmittance, and satisfactory drug content. Conversion of the optimized liquid formulation into S-SMEDDS using Aerosil® 200 produced a free-flowing powder with acceptable micromeritic properties and rapid reconstitution while retaining nanosized globules.

Solid-state characterization indicated reduced crystallinity of acetazolamide in the S-SMEDDS, supporting improved molecular dispersion of the drug within the formulation. Both L-SMEDDS and S-SMEDDS substantially enhanced the in-vitro dissolution of acetazolamide compared with the pure drug, with L-SMEDDS showing the highest dissolution performance. The dissolution profiles were predominantly diffusion controlled, with L-SMEDDS exhibiting Fickian release behaviour according to the Korsmeyer–Peppas model. Stability evaluation further demonstrated that both formulations maintained satisfactory physicochemical characteristics over 3 months, although slightly greater changes were observed under accelerated conditions. Overall, the findings establish that acetazolamide-loaded SMEDDS can effectively enhance dissolution performance and provide a suitable lipid-based formulation platform for further development. The optimized L-SMEDDS showed comparatively better performance than S-SMEDDS under the investigated conditions. However, the present study was limited to in-vitro performance and further in-vivo pharmacokinetic and bioavailability studies are required to establish whether the observed dissolution enhancement translates into improved systemic exposure.

#### CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest.

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