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Enhancing Oral Delivery Of Carmustine Using Self-Microemulsifying Drug Delivery System

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Abstract

Objective

The goal of this study was to develop a self-microemulsifying drug delivery system to enhance the solubility of Carmustine, a chemotherapy drug that exhibit poor water solubility.

Significance

This study presents a self-microemulsifying drug delivery system based approach to enhance the solubility and dissolution of carmustine, addressing its poor oral bioavailability. The optimized formulation showed improved stability and nano-scale drug dispersion, offering a promising strategy for more effective oral chemotherapy delivery.

Methods

Solubility of Carmustine in different oils, surfactants and co-surfactants to identify the most effective combination. Ternary phase diagrams were then constructed to determine the optimal microemulsion region. The resulting formulations were assessed for drug content, stability and their ability to form emulsions. The best liquid self-microemulsifying drug delivery system formulation was later converted into a solid form using Neusilin UF2. Various physical characteristics such as particle size, zeta potential, drug release behavior and compatibility were evaluated using techniques like Scanning Electron Microscopy, Powder X-ray Diffraction, Fourier Transform Infrared Spectroscopy.

Results

The formulation F3 which consisted of olive oil, Tween 80 and PEG 400 was found to have a high drug content and excellent stability. It showed a significantly improved drug release rate compared to pure Carmustine with the drug evenly distributed in the nano-sized particles.

Conclusion

The optimized formulation enhanced drug release of Carmustine offering a potential solution for improving its oral bioavailability.

Key words: *Carmustine, BCNU, chemotherapy drug, solubility, SMEDDS, ternary phase diagram*

INTRODUCTION

Oral drug delivery remains the most preferred route for therapeutic administration due to its convenience, safety and patient compliance. However, the efficacy of this route is often limited by the poor aqueous solubility and low bioavailability of certain drugs, especially those classified under BCS Class II and IV [1]. To overcome these limitations, lipid-based formulations have gained considerable interest, with SMEDDS emerging as a promising strategy [2]. SMEDDS are isotropic mixtures of oils, surfactants and co-surfactants that spontaneously form fine oil-in-water microemulsions when exposed to gastrointestinal fluids under gentle agitation [3]. This spontaneous emulsification significantly enhances drug solubilization, gastrointestinal absorption and ultimately bioavailability of poorly water-soluble drugs [4, 5].SMEDDS offer several advantages including protection of drugs from degradation in the gastrointestinal tract, improvement in lymphatic transport and reduction in pre-systemic metabolism. They can maintain the drug in a dissolved state throughout its transit in the gastrointestinal tract, bypassing the dissolution step that limits the absorption of many lipophilic compounds [6]. Furthermore, the nano-sized droplets formed in SMEDDS provide a large surface area for drug release and absorption [7, 8]. Recent advancements in SMEDDS include solidified forms, solid SMEDDS, which improve

stability and offer better control over release kinetics [9,10]. The flexibility in formulation and potential to enhance oral bioavailability make SMEDDS an attractive delivery platform, particularly for oncology drugs with solubility and stability challenges [11].Carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea), BCNU, an alkylating nitrosourea compound, is a chemotherapeutic agent primarily used in the treatment of brain tumors, multiple myeloma, Hodgkin's disease and non-Hodgkin's lymphomas [12, 13]. Its mechanism of action involves alkylation of DNA and RNA, leading to cross-linking and inhibition of replication and transcription, which ultimately results in cytotoxicity [14]. Despite its clinical potential, Carmustine is characterized by poor aqueous solubility, rapid degradation in aqueous environments and dose-limiting systemic toxicity [15]. These issues contribute to erratic bioavailability and restrict its use in oral chemotherapy regimens [16].Given the limitations associated with the current parenteral formulations of Carmustine and the pressing need for an effective oral delivery alternative, the application of SMEDDS offers a novel solution. The lipophilic nature of Carmustine makes it a suitable candidate for lipid-based systems such as SMEDDS, which could potentially improve its solubility, protect it from hydrolytic degradation and enhance its oral bioavailability [17]. In addition, the encapsulation of Carmustine in SMEDDS may mitigate systemic toxicity by providing a controlled release profile and minimizing peak plasma concentrations [18].This study aims to develop and evaluate a SMEDDS formulation of Carmustine to address the challenges of solubility and stability and to explore its potential for oral administration. By leveraging the advantages of SMEDDS, this research seeks to provide a feasible platform for delivering Carmustine orally with improved therapeutic outcomes and patient compliance.

MATERIALS AND METHODS

Materials

Carmustine was generously provided by Emcure Pharmaceuticals Ltd (Mumbai, India). Olive oil, castor oil, sesame oil and soybean oil were purchased from India Mart. Tween 80 (Polyoxyethylene sorbitan monooleate), Tween 20 (Polyoxyethylene sorbitan monolaurate), Tween 60 (Polyoxyethylene sorbitan monostearate), Tween 40 (Polyoxyethylene sorbitan monopalmitate), Span 20 (Sorbitan monolaurate), Span 40 (Sorbitan monopalmitate) and Span 80 (Sorbitan monooleate) were purchased from Gangwal Chemicals Pvt. Ltd. (Mumbai, India). PEG 200, PEG 400, PEG 800, propylene glycol and Capryol 90 (Propylene glycol monocaprylate) were purchased from S.D. Fine Chemicals (Mumbai, India). All excipients and reagents used were of analytical grade and double-distilled water was freshly prepared as needed throughout the study.

Solubility study

The solubility of Carmustine was determined in various modified oils, surfactants and co-surfactants. Two milliliters of each oil, surfactant or co-surfactant were placed in screw-cap vials and an excess quantity of the drug was added. The mixture was vortexed to facilitate solubilization and agitated on a rotary shaker at 25°C for 48 hours to reach equilibrium. The samples were then centrifuged at 6000 rpm for 15 minutes and the supernatant was filtered using a 0.45 µm membrane filter. The filtered solution was appropriately diluted with methanol as a suitable solvent and the UV absorbance was measured at the specified wavelength of 227 nm.

Ternary phase diagram

The pseudo-ternary phase diagram was constructed using the aqueous titration method to determine the optimal oil-to-Smix ratio for microemulsion formation. The Smix ratios tested were 1:1, 1:2, 2:1 and 3:1, while the oil to Smix ratios ranged from 1:9 to 9:1 to evaluate the microemulsion boundaries. Each oil-Smix mixture was titrated with water and the optical appearance was monitored. The endpoint was determined by the transition from transparency to turbidity, marking the point at which water addition caused cloudiness. Samples that exhibited biphasic behavior with phase separation after turbidity were excluded from the phase diagram, while monophasic samples, which remained clear and transparent, were included. The emulsion area was defined by the monophasic liquid points and the process was repeated for all tested Smix ratios. The final phase diagrams were plotted using the Ternary Plot Generator. A larger emulsion area indicated a higher hydration capacity and was selected as the optimal composition for the microemulsion. Olive oil was used in conjunction with various Smix ratios, specifically testing Tween 80 and PEG 400 at different ratios.

Preparation of liquid SMEDDS

The Smix ratio and Oil/Smix ratio was selected from the ternary phase diagram. Smix (2:1) and Oil/Smix of 2:8 to 7:3 was taken to formulate six batches (Table 1). Carmustine (100 mg) was added in accurately weighed amount of oil into a screw-capped glass vial. The surfactant and co-surfactant were added to the oily mixture using pipette and stirred with vortex mixer. The formulations were further sonicated for 15 min and stored at room temperature until further use.

Table 1: Composition of Carmustine SMEDDS Formulations (% v/v) Showing Olive Oil, Tween 80 and PEG 400 Ratios

Formulation code	Composition(%v/v)		
	Olive oil	Tween 80	PEG 400
F1	20.00	53.33	26.67
F2	30.00	46.67	23.33
F3	40.00	40.00	20.00
F4	50.00	33.33	16.67
F5	60.00	26.67	13.33
F6	70.00	20.00	10.00

Characterization of liquid SMEDDS

Drug content

Carmustine from SMEDDS formulations were extracted in methanol using sonication technique. The solutions were filtered, using whatman filter paper of 0.45 µm pore size. The methanolic extracts were analyzed for the Carmustine content spectrophotometrically using UV-visible spectrophotometer at 227 nm using standard curve.

Emulsification time

One mL of SMEDDS formulation was added dropwise into 900 mL of distilled water and 0.1 N hydrochloric acid, with agitation set at 50 rpm using the USP Type II dissolution apparatus (paddle type). The temperature was maintained at 37 ± 0.5°C. The time required for the SMEDDS to fully self-emulsify and form a clear, stable emulsion was recorded, with continuous agitation ensuring uniform dispersion of the formulation [19].

Impact of dilution on stability and dispersion behavior of SMEDDS

The SMEDDS was subjected to various dilution ratios, namely 1:10, 1:50, 1:100 and 1:1000, using both distilled water and 0.1 N hydrochloric acid as diluents. The objective was to evaluate the impact of dilution volume on the dispersion behavior, drug precipitation and potential phase separation of the formulation. The resultant dispersions were monitored visually over a 24-hour period at a controlled temperature of 25°C for any observable changes, including phase separation or precipitation.

Transmittance

The percentage transmittance of the prepared SMEDDS formulations was measured using a UV-visible spectrophotometer. One mL aliquot of SMEDDS was diluted 100-fold with distilled water and analyzed at a wavelength of 227 nm. Distilled water was used as the blank for calibration. The percentage transmittance was recorded to evaluate the clarity and transparency of the emulsion [20].

Droplet size, polydispersity index and zeta potential

One mL of SMEDDS was dispersed in 100 mL of distilled water and the resulting formulation was subjected to droplet size, PDI and zeta potential analysis using a Zetasizer at 25°C. Droplet size distribution was determined via DLS technique. The PDI provided information regarding the homogeneity of the droplet size distribution, indicating the uniformity of the formulation. The zeta potential was measured to assess the surface charge of the emulsion droplets, which is indicative of the colloidal stability of the SMEDDS.

Drug loading capacity

To determine the drug loading capacity of the optimized SMEDDS, 2 mL of the formulation was placed in a small vial with an excess amount of the drug. The drug was solubilized using a vortex mixer, followed by agitation on a rotary shaker at 25°C for 48 hours. After equilibration, the formulation was

appropriately diluted with methanol (dilution factor = 2000). The UV absorbance of the solution was measured at a wavelength of 227 nm. This procedure was repeated three times to ensure reproducibility and accuracy.

Viscosity measurement

The viscosity of the optimized liquid SMEDDS was measured using an ViscoQC 300 viscometer (Anton Paar) at 50 rpm with spindle SC4-18. This measurement was performed to evaluate the flow properties and rheological behavior of the formulation.

Transmission electron microscopy

The TEM (JEM-1200EX, JEOL, Tokyo, Japan) was used in order to observe the morphology of L-SMEDDS contains Carmustine with a negative staining method. Briefly, a drop of diluted L-SMEDDS was spread on a copper grid and allowed to equilibrate. By creating high energy electron beams, the morphology of the formulation on the sample was examined.

Preparation of solid SMEDDS

The solid SMEDDS was prepared from liquid SMEDDS (optimized formulation F3) using Neusilin UF2 as a solid adsorbent carrier. A fixed quantity of liquid SMEDDS was gradually added dropwise to the adsorbent under vigorous mixing in a mortar, until a free-flowing powder was obtained. The resulting powder was then sieved through a 60# sieve to achieve a uniform particle size distribution. The prepared powder was stored in a desiccator under controlled conditions until further evaluation [21].

Characterization of solid SMEDDS

Powder flow properties

The angle of repose of the powder blend was determined using the funnel method. A precisely weighed amount of the powder blend was placed in a funnel, with the funnel height adjusted so that its tip just touched the apex of the powder pile. The powder was allowed to flow freely from the funnel onto a flat surface. The diameter of the resulting powder cone was measured and the angle of repose (θ) was calculated using the equation, $\theta = \tan^{-1} h/r$, where, h and r are the height and radius of powder cone. Carr's Index was calculated to assess the compressibility of the solid SMEDDS powder, which helps determine the maximum fill volume for capsules. Carr's index can be calculated using equation, Carr's Index (%) = [(Tapped density – Bulk density) x100]/Tapped density. Hausner's ratio was calculated using the equation, Hausner's ratio = Tapped density/Bulk density. These parameters provide insight into the flowability and compressibility characteristics of the solid SMEDDS powder.

FTIR spectroscopic analysis

To find any potential physicochemical interaction between the formulation components, FTIR was used. A Bruker FTIR spectrometer was used to analyze solid SMEDDS using attenuated total reflectance in the range of 500-3500 cm^{-1}.

Scanning electron microscopy

The microscopic characteristics (shape & morphology) of Carmustine loaded solid SMEDDS were examined by a SEM (FEI- Quanta 200F, Netherland). The samples were fixed on a brass sampling disc using double-sided adhesive tape. Then, they were rendered electrically conductive with the sputter coating of platinum (6 nm/min) using an EMI Teck Ion Sputter (K575K) under vacuum ($8x10^{-3}$ mbar) for 4 min at 15 mA.

Powder X-ray diffraction

The crystallinity of the samples was evaluated by PXRD, which was performed at room temperature using monochromatic Cu K_α radiation (λ=1.54178 Å) at 40 mA and 40 kV in the region of $5° \leq 2\theta \leq 80°$ with an angular increment of 0.02°/sec.

In vitro drug release studies

In vitro drug release studies of pure drug, liquid SMEDDS and solid SMEDDS were conducted using a USP type I (Basket) dissolution apparatus. Hard gelatin capsules of size "0" were filled with 50 mg of pure drug, 0.5 mL of liquid SMEDDS (containing 50 mg drug) and 500 mg of solid SMEDDS (containing 50 mg drug) and each was placed in 900 mL of 0.1N HCl at 37 ± 0.5°C, with a rotating speed of 50 rpm. At predetermined time intervals (5, 10, 15, 20, 30, 45 and 60 minutes), 5 mL samples were withdrawn and filtered through a 0.45 µm filter. An equal volume of fresh dissolution medium was replenished to

maintain a constant volume. The drug content of the samples was quantified using a UV-visible spectrophotometer at 227 nm. All measurements were performed in triplicate.

RESULTS

Solubility studies

The results of solubility of Carmustine in various oils, surfactants and co-surfactants screened were shown in Figure 1. The components in formulation of SMEDDS were selected to have maximum solubility of drug along with good miscibility with each other and to produce a stable formulation [22]. The results suggest that Carmustine is highly soluble in Olive oil (31.04±0.34 mg/ml), Tween 80 (782.31±10.42 mg/ml) and PEG 400 (87.10±0.47 mg/ml). Based on the solubility results the SMEDDS formulations were developed employing varying concentrations of Olive oil (20.00–70.00%), Tween 80 (20.00–53.33%) and PEG 400 (10.00–26.67%).

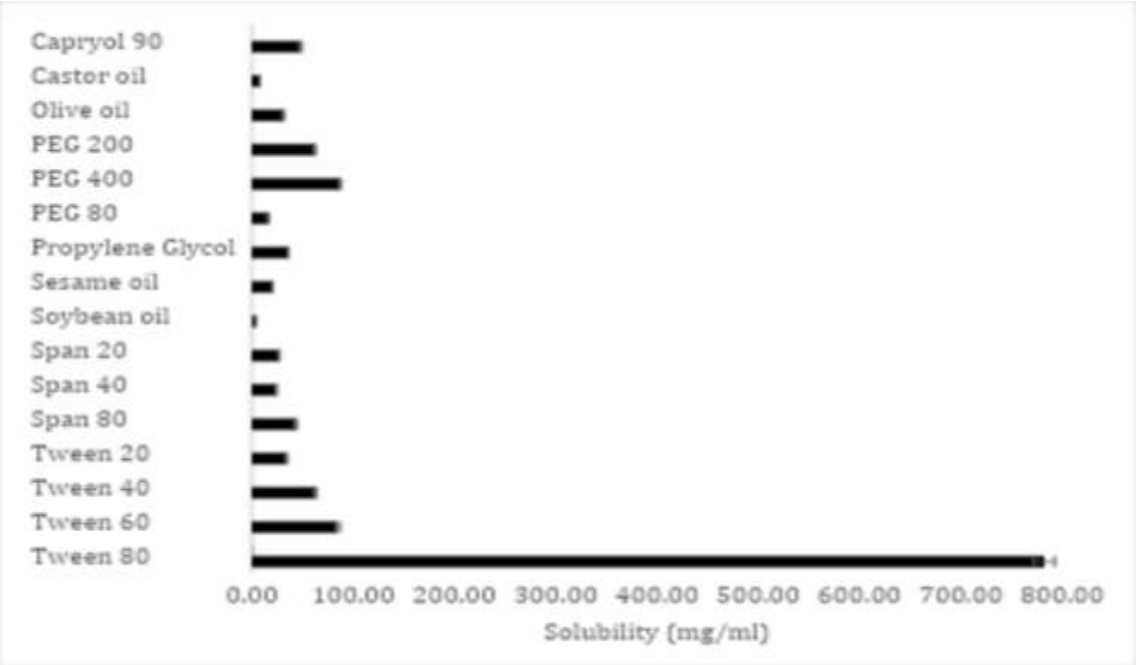

Figure 1: Solubility Studies of Carmustine in Various Solvents (Mean ± SD, n = 3)

Ternary phase diagram

The pseudo-ternary phase diagram, constructed using olive oil and varying Smix ratios (1:1, 1:2, 2:1, 3:1), revealed that the optimal formulation, characterized by the largest monophasic area, was achieved with a Smix ratio of Tween 80 to PEG 400 at 2:1 (Figure 2). This formulation exhibited the highest hydration capacity and produced a clear, stable, monophasic solution, confirming its suitability for microemulsion preparation (results shown in Table 2, Figure 3). The transparency and stability observed in this emulsion indicate a homogeneous system with minimal risk of phase separation. The success of the 2:1 Smix ratio can be attributed to the balanced interaction between Tween 80, with its high HLB value (HLB 15) and PEG 400, which enhances solubilization and reduces interfacial tension. This optimal combination allows for stable oil-in-water emulsion formation, with the oil phase well-dispersed in the aqueous phase. In contrast, other Smix ratios (1:1, 1:2, 3:1) resulted in smaller monophasic areas or instability, likely due to an imbalance in surfactant coverage or excessive interfacial tension. Overall, the phase diagram demonstrated that the 2:1 ratio produced the most stable and effective microemulsion, confirming its potential for optimal formulation in microemulsion systems.

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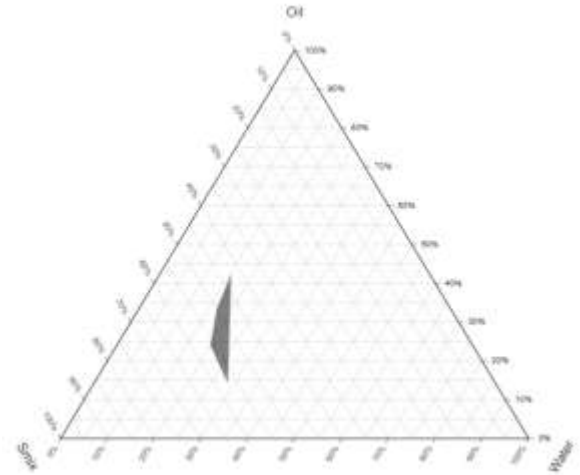
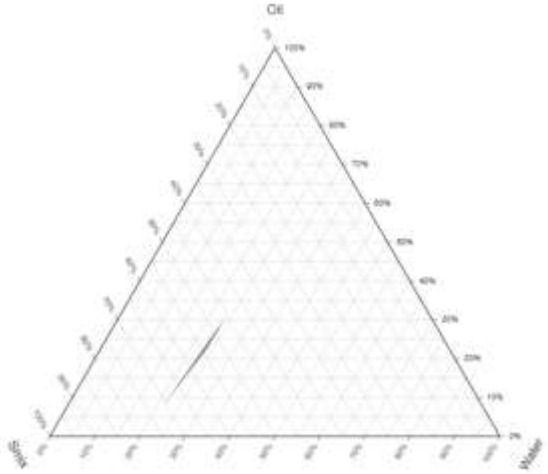
Table 2: Visual Observations of Phase Behavior in Ternary Phase Diagrams for Various Oil/Smix Ratios with Different Smix Compositions

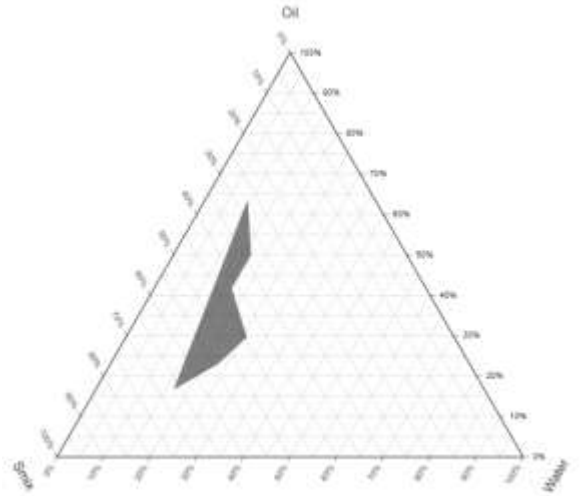
Oil/Smix	Smix 1:1		Smix 1:2		Smix 2:1		Smix 3:1	
	Water	Appearance	Water	Appearance	Water	Appearance	Water	Appearance
1:9	8	Turbid	2.7	Clear	4	Turbid	3	Clear
2:8	4	Clear	2.9	Clear	2	Clear	2.5	Clear
3:7	2.5	Clear	3.1	Clear	3	Clear	2.	Clear
4:6	2	Clear	3.1	Clear	3.5	Clear	1.5	Clear
5:5	1.8	Clear	3.1	Turbid	2	Clear	0.5	Clear
6:4	2.5	Turbid	2.2	Turbid	2	Clear	2	Turbid
7:3	1.7	Turbid	3.6	Turbid	1	Clear	1.5	Turbid
8:2	2	Turbid	3.6	Turbid	1.2	Turbid	2.3	Turbid
9:1	3	Turbid	6.1	Turbid	2.8	Turbid	1.5	Turbid



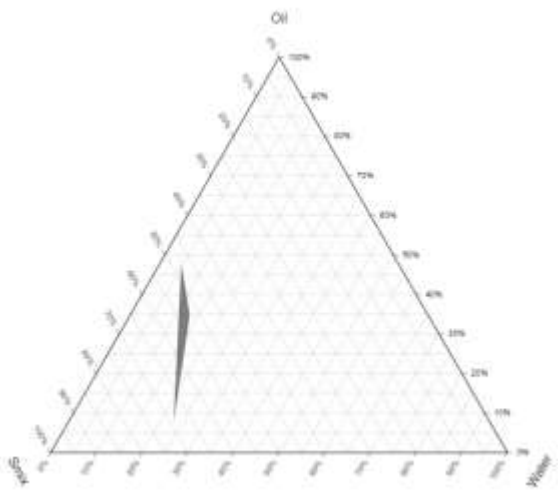
Smix 1:1



Smix 1:2



Smix 2:1



Smix 3:1

Figure 2: Ternary Phase Diagrams of SMEDDS Formulations Comprising Olive Oil, Tween 80/PEG 400 (at various ratios) and Water (dark area represents the region of stable emulsions

Smix 1:1

Smix 1:2

Smix 2:1

Smix 3:1

Figure 3: Visual Observations for Construction of Ternary Phase Diagrams Using Different Smix Ratios (1:1, 1:2, 2:1 and 3:1) with Water

Characterization of liquid SMEDDS

Drug content

The drug content across various SMEDDS formulations ranged from 11.87% to 92.08% (Table 3). Formulation F3, with 4 mL of oil and 6 mL of Smix, exhibited the highest drug content (92.08%), while formulations F5 and F6, with higher oil content and lower Smix, showed significantly lower drug content (11.87% and 14.86%, respectively). Based on these results, formulation F3 is suggested as the optimized formulation due to its high drug content and balanced oil-Smix ratio.

Table 3: Evaluation Parameters of Liquid SMEDDS Formulations Including Drug Content, Droplet Size, PDI, Zeta Potential, % Transmittance and Emulsification Time

Formulation	Oil (ml)	Smix (ml)	Drug Content (%)	Droplet size (nm)	PDI	zeta potential (mV)	% Transmittance	Emulsification Time (sec)	
								Distilled water	0.1N HCl
F1	2	8	31.49	593.47	0.311	-38.41	62.73 ± 2.8	21 ± 2	40 ± 3
F2	3	7	52.17	896.69	0.363	-39.23	64.34 ± 2.3	20 ± 2	42 ± 5
F3	4	6	92.08	842.51	0.245	-38.61	68.15 ± 1.4	17 ± 3	37 ± 2
F4	5	5	64.17	194.29	0.263	-37.89	45.38 ± 2.0	54 ± 5	79 ± 4
F5	6	4	11.87	305.21	0.213	-19.71	63.34 ± 2.4	90 ± 7	109 ± 3
F6	7	3	14.86	4294.87	0.134	-8.62	59.98 ± 3.1	98 ± 4	142 ± 8

Emulsification time

Emulsification times of the SMEDDS formulations varied significantly between distilled water and 0.1 N HCl (Table 3). Formulations F1, F2 and F3 showed quick emulsification, with times ranging from 17 to 21 seconds in distilled water and 37 to 42 seconds in 0.1 N HCl. In contrast, formulations F4, F5 and F6 exhibited longer emulsification times, particularly in 0.1 N HCl, reaching up to 142 seconds. Formulation F3, with the shortest emulsification times, is recommended as the optimal choice for rapid dispersion.

Impact of dilution on stability and dispersion behavior of SMEDDSThe impact of dilution on the stability and dispersion behavior of SMEDDS formulations was evaluated in both distilled water and 0.1 N HCl (Table 4). Formulations F1, F2 and F3 demonstrated stable microemulsion formation across all dilution ratios (1:10 to 1:1000) in distilled water and 0.1 N HCl, indicating good dispersion and stability. However, formulations F4, F5 and F6 showed instability at higher dilutions, with phase separation or drug precipitation occurring at certain ratios. Specifically, F4 exhibited instability at 1:1000 in both distilled water and 0.1 N HCl, while F5 and F6 were unstable at most dilution ratios, with phase separation observed from 1:50 onward. These results highlight the importance of the oil-to-Smix ratio in maintaining stability, with F3 being the most stable formulation across all dilutions.

Table 4: Robustness to Dilution of Liquid SMEDDS Formulations in Distilled Water and 0.1N HCl

Formulation	Distilled water				0.1N HCl			
	1:10	1:50	1:100	1:1000	1:10	1:50	1:100	1:1000
F1	Y	Y	Y	Y	Y	Y	Y	X
F2	Y	Y	Y	Y	Y	Y	Y	X
F3	Y	Y	Y	Y	Y	Y	Y	Y
F4	Y	Y	Y	X	Y	Y	X	X
F5	Y	X	X	X	Y	X	X	X
F6	X	X	X	X	Y	X	X	X

Y = Clear micro emulsion formed; X = Unstable formulation which shows phase separation or drug precipitation

The % transmittance of various SMEDDS formulations was measured to assess the clarity and homogeneity of the microemulsion (Table 3). Formulation F3, containing 4 mL of oil and 6 mL of Smix, exhibited the highest transmittance at 68.15% ± 1.4, indicating the clearest and most stable microemulsion. Formulations F1, F2 and F5 also showed relatively high transmittance values, ranging from 62.73% ± 2.8 to 64.34% ± 2.3, suggesting good dispersion. In contrast, formulations F4 and F6, with higher oil content and lower Smix, demonstrated lower transmittance, with values of 45.38% ± 2.0 and 59.98% ± 3.1, respectively, indicating reduced clarity and potential instability. These results suggest that a balanced oil-to-Smix ratio, as seen in F3, enhances the formulation's transparency and stability.

Droplet size, polydispersity index and zeta potential

The droplet size, PDI and zeta potential of various SMEDDS formulations were assessed to evaluate their dispersion and stability characteristics (Table 3). Formulation F1, with 2 mL of oil and 8 mL of Smix, exhibited the largest droplet size of 593.47 nm and a moderate PDI of 0.311, indicating a relatively broad size distribution. As the oil content increased, droplet size generally increased, reaching 4294.87 nm in formulation F6, which contained 7 mL of oil and 3 mL of Smix, accompanied by a significantly low PDI of 0.134, suggesting a more uniform but larger droplet size. Formulations F3 and F4 displayed smaller droplet sizes (842.51 nm and 194.29 nm, respectively) and low PDIs (0.245 and 0.263), indicating better monodispersity. The zeta potential values were predominantly negative across all formulations, indicating good stability, with F1, F2 and F3 showing higher absolute values (ranging from -38.41 to -39.23 mV), suggesting strong electrostatic repulsion and enhanced colloidal stability. In contrast, formulations F5 and F6 had lower zeta potential values (-19.71 mV and -8.62 mV), which may indicate a reduced stability compared to the other formulations. These findings suggest that the oil-to-Smix ratio significantly influences droplet size, PDI and stability, with formulations F1, F2 and F3 demonstrating optimal characteristics for stable microemulsion formation.

Drug loading capacity

The drug loading capacity of the optimized SMEDDS formulation was 60.45 ± 0.04 mg/mL, with a very low relative standard deviation of 0.069%. This indicates that the drug loading process is highly precise, with minimal variation between replicate measurements, confirming the reproducibility and stability of the formulation.

Viscosity measurement

The viscosity and torque of the optimized liquid SMEDDS (F3) were measured, yielding a mean viscosity of 561.3 ± 37.7 cP and a mean torque of 87.7 ± 5.9%. These results suggest that the formulation exhibits

consistent rheological properties with manageable variability, demonstrating reliable performance across replicates.

Transmission electron microscopy

The morphology of the liquid SMEDDS was determined using TEM, which revealed spherical oil droplets with a good droplet size, as shown in the Figure 4. The TEM images showed relatively smaller droplets compared to those obtained by DLS. While DLS measures the hydrodynamic radius, TEM analysis provides the actual size of the oil droplets.

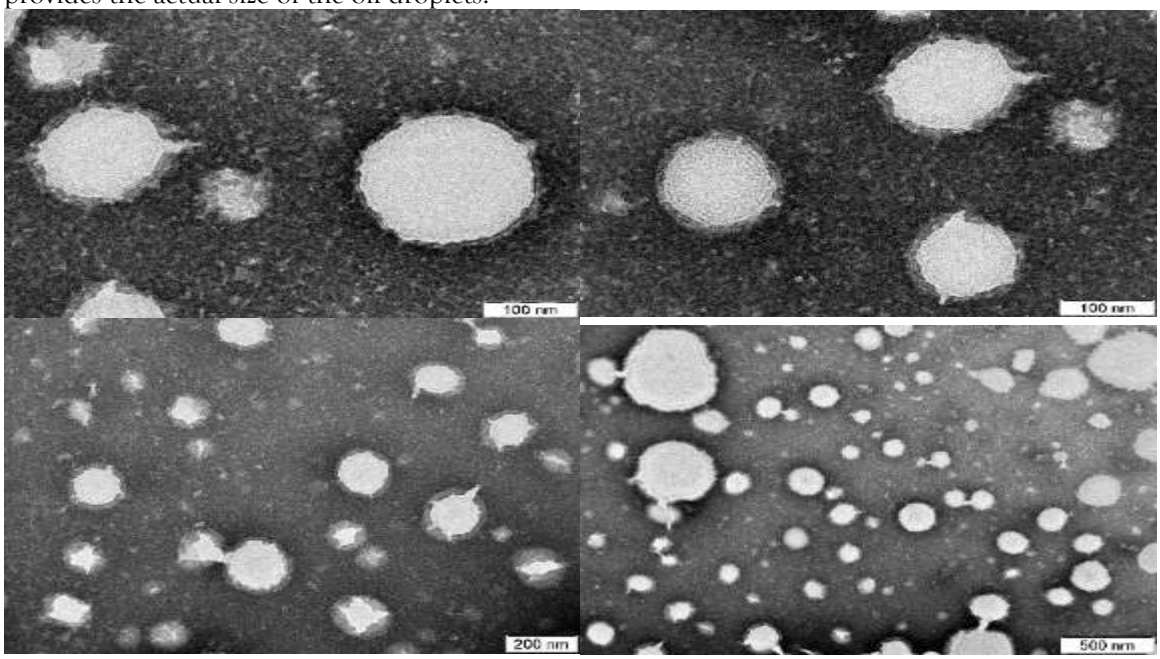


Figure 4: TEM Images of Liquid SMEDDS

FTIR spectroscopic analysis

The FTIR spectrum of solid SMEDDS is shown in Figure 5. The solid SMEDDS exhibited peaks at 1242 cm^{-1} and 1459 cm^{-1}, which correspond to COO- groups and a peak at 1090 cm^{-1}, which corresponds to the C=H double bond. Additional peaks appeared at 1352 cm^{-1}, 1296 cm^{-1}, 680 cm^{-1}, 1015 cm^{-1} and 2106 cm^{-1}, corresponding to aliphatic CH bending, N-O stretch, C-Cl stretch, N-N stretch and C-N stretch, respectively. There was no apparent shift in the bands or the emergence of new bands, confirming the absence of changes in the chemical bond formation between the drug and excipients.

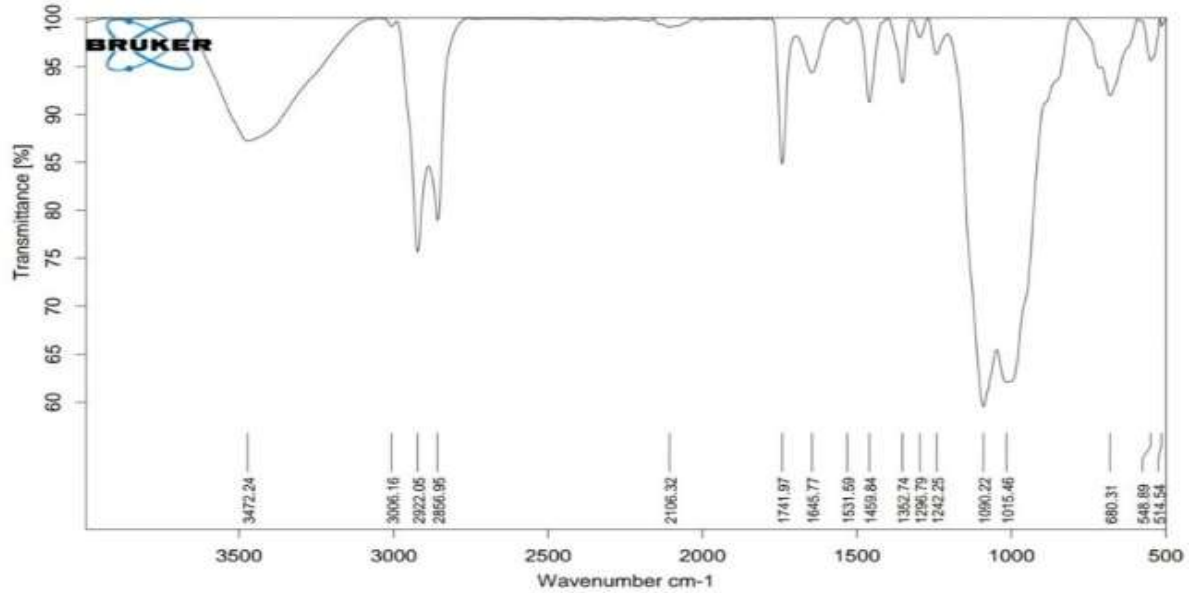


Figure 5: FTIR Spectrum of Solid SMEDDS

Characterization of solid SMEDDS

Powder flow properties

The flow properties of the solid SMEDDS powder were assessed using three key parameters: angle of repose, Hausner's ratio and Carr's index. The angle of repose was found to be 28.5° ± 1.57°, indicating excellent flow characteristics. The Hausner's ratio was 1.14 ± 0.02, which falls within the range that is considered to exhibit good flowability. Similarly, the Carr's index was 12.08% ± 1.5%, suggesting good compressibility. These results collectively indicate that the solid SMEDDS powder possesses favorable flow and compressibility properties, making it suitable for encapsulation and further processing.

Scanning electron microscopy

Scanning electron micrographs of the Solid SMEDDS is shown in Figure 6. This analysis revealed that amorphous nature of solid SMEDDS, smooth surface morphology, non-uniform solid particles and spherical shape.

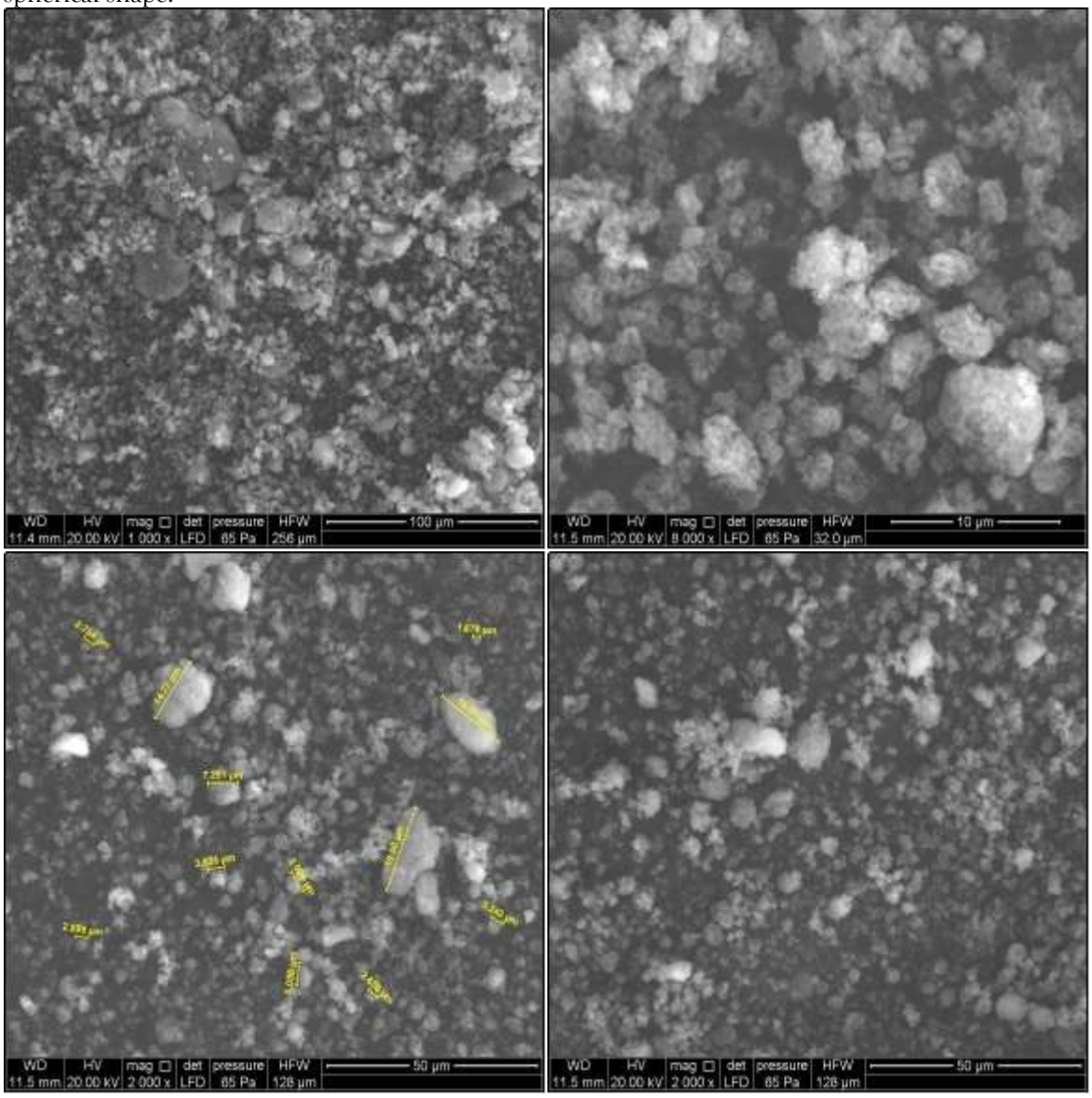


Figure 7: SEM Images of Solid SMEDDS

Powder X-ray diffraction

From the powder X-ray diffractometric profiles shown in Figure 7, the molecularly dissolved state of Carmustine in the solid SMEDDS was further verified. Carmustine has a typical crystalline nature, but these representative peaks were not seen in the PXRD pattern of solid SMEDDS, because the drug existed as an amorphous form in solid SMEDDS.

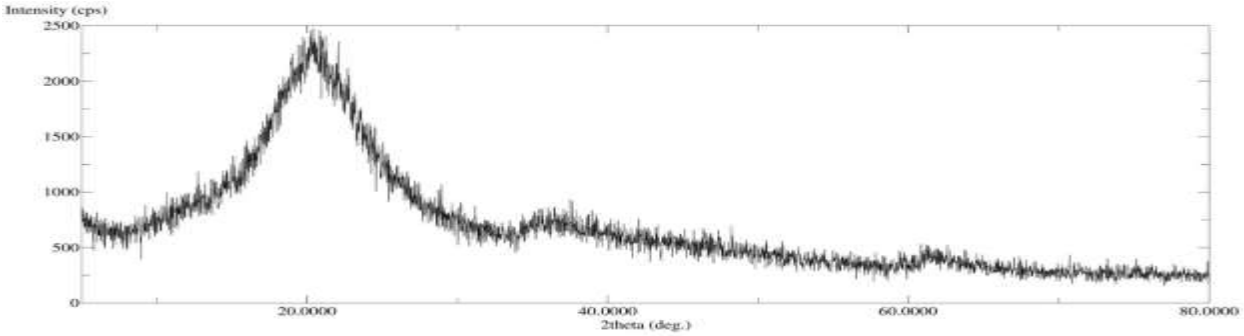


Figure 6: XRD of Solid SMEDDS

-vitro drug release studies

The in vitro drug release profiles of pure drug, liquid SMEDDS and solid SMEDDS are shown in Figure 8. The in vitro drug release profiles of pure drug, liquid SMEDDS and solid SMEDDS revealed enhanced drug release for the SMEDDS formulations at all-time points. At 5 minutes, liquid SMEDDS and solid SMEDDS released 24.52 ± 0.3% and 23.53 ± 0.2%, respectively, compared to 20.96 ± 1.7% for the pure drug. The release continued to increase with liquid SMEDDS reaching 73.17 ± 0.5% at 20 minutes and solid SMEDDS 71.58 ± 0.2% while pure drug release was only 30.28 ± 0.1%. At 60 minutes, liquid and solid SMEDDS released 4.74 ± 0.3% and 4.85 ± 0.3%, respectively, while pure drug release was significantly lower at 1.21 ± 0.2%. These results demonstrate that both SMEDDS formulations provide faster and more sustained drug release compared to the pure drug.

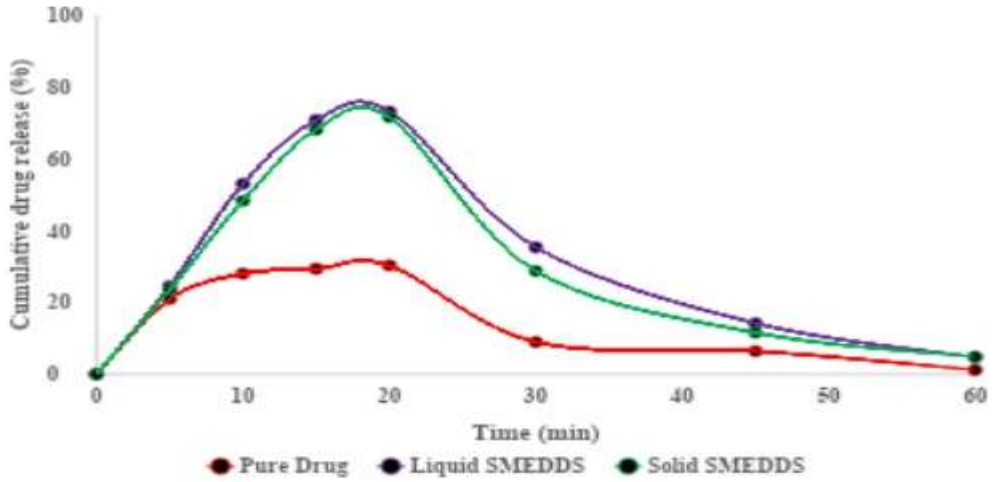


Figure 8: In Vitro Drug Release Profile of Liquid SMEDDS Formulations and Pure Carmustine

DISCUSSION

The solubility study identified Olive oil, Tween 80 and PEG 400 as optimal excipients for Carmustine, owing to their high solubilization capacity, excellent miscibility and ability to form a stable SMEDDS formulation [23]. Their compatibility minimized phase separation and supported efficient self-emulsification upon dilution [24]. The solubility data also guided the selection of appropriate concentration ranges, ensuring adequate drug loading and formulation stability. This rational selection strategy enhances oral bioavailability and underscores the importance of excipient screening in lipid-based drug delivery systems [25].The phase diagram analysis plays a critical role in identifying the optimal Smix

ratio for developing stable microemulsion systems within SMEDDS formulations [26]. Among the various ratios investigated, the 2:1 Smix ratio (Tween 80 to PEG 400) emerged as the most effective, exhibiting the largest monophasic region in the pseudo-ternary phase diagrams. This extensive monophasic zone is indicative of enhanced microemulsion stability, reflecting minimal risk of phase separation and a greater capacity to incorporate the oil and aqueous phases without compromising system integrity [27, 28]. The superior performance of the 2:1 ratio can be attributed to the synergistic action between Tween 80 and PEG 400 [29]. Tween 80, a non-ionic surfactant with a high HLB, effectively reduces the interfacial tension between the oil and aqueous phases, while PEG 400, a hydrophilic co-surfactant, further fluidizes the interfacial film and improves the flexibility of the surfactant layer [30]. This balance ensures rapid and spontaneous emulsification, which is essential for SMEDDS performance upon dilution in the gastrointestinal tract.In contrast, other ratios such as 1:1, 1:2 and 3:1 either failed to provide sufficient interfacial stabilization or led to excessive rigidity or fluidity, thus reducing the size of the monophasic region and compromising emulsion stability. The optimized 2:1 Smix ratio ensures efficient emulsification, droplet size reduction and long-term physical stability of the formulation. This finding underscores the importance of precise surfactant/co-surfactant balancing in the design of robust SMEDDS capable of improving the solubility and bioavailability of poorly water-soluble drugs like Carmustine. The optimization of the oil-to-Smix ratio plays a pivotal role in developing an effective SMEDDS. Drug loading studies clearly demonstrated the influence of this ratio on the formulation's capacity to solubilize Carmustine. Among the tested formulations, F3, which maintained a balanced oil-to-Smix ratio, exhibited the highest drug content, highlighting its superior solubilization potential. This balance ensures that an adequate quantity of surfactants is available to emulsify the oil phase, facilitating the efficient incorporation of the lipophilic drug [31]. In contrast, formulations such as F5 and F6, which contained excessive oil relative to Smix, showed markedly lower drug loading. This can be attributed to the reduced emulsification capacity in these formulations, where the surfactant concentration was insufficient to stabilize the larger oil volumes, leading to phase separation and drug precipitation [32].The performance of formulation F3 also extended to its emulsification behavior. It demonstrated rapid self-emulsification, a critical characteristic of SMEDDS, which supports immediate drug release upon contact with gastrointestinal fluids. Faster emulsification times correlate with enhanced surface area for drug absorption, which is essential for improving bioavailability [33]. Furthermore, formulation F3 remained stable under high dilution conditions, maintaining a clear and homogenous microemulsion without signs of precipitation or phase separation. This is particularly important for oral delivery systems, which encounter significant dilution upon administration.In contrast, other formulations such as F4, F5 and F6 were unstable under similar dilution conditions, often resulting in turbid dispersions, phase separation, or drug crystallization. These issues underscore the destabilizing effect of an imbalanced oil-to-Smix ratio and reinforce the importance of achieving a precise formulation balance to ensure system stability [34].Clarity, as assessed by percentage transmittance, further validated the superiority of formulation F3. Its high transmittance values reflected the formation of a uniform and optically clear microemulsion, indicating good miscibility and dispersion. Lower transmittance values observed in formulations F4 and F6, particularly those with higher oil content, suggested the presence of larger droplets or emulsion instability, leading to reduced clarity and potential issues with reproducibility and patient acceptability [14, 35].Droplet size analysis and PDI measurements provided additional insights into the physical stability of the formulations [36, 37]. Formulation F3 exhibited a small mean droplet size with a narrow PDI, indicating a uniform and stable microemulsion. While F5 and F6 showed relatively low PDIs, their larger droplet sizes pointed to incomplete emulsification and reduced kinetic stability. These characteristics are suboptimal for oral SMEDDS, as they may compromise absorption efficiency and lead to batch variability.Finally, the viscosity and torque measurements of F3 indicated favorable flow properties, which are advantageous for both manufacturing scalability and oral administration. Consistency in viscosity values also implies robust formulation characteristics that are less likely to vary under industrial processing conditions [38].Collectively, these findings emphasize that a balanced oil-to-Smix ratio, as exemplified by formulation F3, is essential for achieving high drug loading, rapid emulsification, excellent physical stability and reproducibility. These attributes position F3 as a promising candidate for further development and potential clinical translation in the delivery of poorly

water-soluble drugs such as Carmustine [39].The characterization of the solid SMEDDS formulation provided critical insights into its structural and physicochemical properties, validating its potential as an effective oral delivery system for Carmustine. TEM confirmed the nanoscale droplet size observed in DLS analysis, revealing uniformly spherical oil droplets. This morphological consistency supports the formulation's stability and efficient emulsification behavior, which are key for enhancing drug dissolution and absorption [40, 41].Further structural evaluation through FTIR confirmed the chemical integrity of Carmustine within the formulation. The absence of significant peak shifts or new bond formations indicated that there were no strong chemical interactions between Carmustine and the excipients, thus affirming the compatibility and stability of the formulation components. This preservation of chemical structure is essential for maintaining the therapeutic efficacy of the drug throughout the formulation process [42].SEM analysis of the solid SMEDDS revealed an amorphous surface morphology with irregular particle size distribution and smooth textures. These features are indicative of effective drug dispersion throughout the lipid matrix [43]. The amorphous nature, further validated by PXRD, is particularly advantageous, as the absence of crystalline peaks suggests that Carmustine was successfully transformed into an amorphous form. This transition is known to significantly enhance solubility and dissolution rates, both of which are critical for improving oral bioavailability [44].Together, these findings demonstrate that the solid SMEDDS formulation not only maintains structural and chemical stability but also improves the physicochemical properties of Carmustine. The uniform dispersion, amorphous conversion and favorable morphology highlight the formulation's robustness and make it a promising candidate for further pharmaceutical development aimed at enhancing the oral bioavailability of poorly soluble anticancer drugs.The in vitro drug release studies revealed that both liquid and solid SMEDDS formulations exhibited markedly enhanced release profiles in comparison to the pure Carmustine. The formulations demonstrated a biphasic release pattern, characterized by an initial rapid release phase followed by a sustained release over time. The rapid initial release can be attributed to the spontaneous formation of fine oil-in-water microemulsions upon contact with aqueous media, which significantly increases the surface area for drug diffusion. This immediate release is particularly advantageous for achieving prompt therapeutic plasma concentrations. The subsequent sustained release phase is likely due to the gradual diffusion of the drug from within the oil droplets, ensuring prolonged systemic exposure and potentially reducing dosing frequency [45].These improved release characteristics highlight the ability of SMEDDS to enhance the apparent solubility and dissolution rate of poorly water-soluble drugs like Carmustine. Moreover, the comparable performance of both liquid and solid SMEDDS underscores the successful conversion of the formulation into a solid dosage form without compromising its functional attributes. Overall, these findings emphasize the potential of optimized SMEDDS formulations as a viable strategy for improving the bioavailability and therapeutic efficacy of lipophilic anticancer agents.

CONCLUSION

This study successfully developed and characterized a SMEDDS for Carmustine to address its inherent challenges of poor aqueous solubility and instability. Through a systematic solubility screening and ternary phase diagram construction olive oil, Tween 80 and PEG 400 were identified as optimal excipients with a Smix ratio of 2:1 yielding the largest monophasic region and best microemulsification potential. Among the six formulations, F3 demonstrated superior performance in terms of drug content, rapid emulsification time and minimal precipitation upon dilution. The optimized SMEDDS exhibited nano-sized droplets with favorable zeta potential and high transmittance confirming its stability and clarity. Solid SMEDDS was successfully prepared using Neusilin UF2 as an adsorbent exhibiting excellent flow properties, amorphous drug distribution as confirmed by PXRD and SEM and compatibility between drug and excipients confirmed via FTIR. In vitro drug release studies demonstrated significantly enhanced release of Carmustine from both liquid and solid SMEDDS compared to pure drug indicating improved solubility and potential for enhanced oral bioavailability. The developed SMEDDS platform offers a promising strategy for oral delivery of Carmustine.

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