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Original Article

Preformulation Studies and Pseudo-Ternary Phase Diagram Development for Dolutegravir Sodium: A Foundational Step toward SMEDDS Design

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ABSTRACT

Background: Dolutegravir Sodium (DTG) is a poorly soluble antiretroviral drug that will find it difficult to achieve oral bioavailability. Preformulation and screening of excipients are mandatory as a stepping stone in formulation development. **Objectives:** To conduct comprehensive preformulation studies and build pseudo-ternary phase diagrams for DTG with a view to informing future development of a stable SMEDDS formulation. **Materials and Methods:** UV spectrophotometry was used to establish the maxima of absorption and to construct a standard calibration curve for DTG. Solubility studies were performed using various oils and surface-active agents. The efficiency of emulsification was used to screen the surfactants, while compatibility was established through the use of FTIR spectroscopy. Pseudo-ternary diagrams identified microemulsion regions with Capmul MCM C8 oil and Kolliphor EL/propylene glycol S_{mix}. **Results:** Enhanced solubility of DTG has been observed in Capmul MCM C8. Kolliphor EL and propylene glycol were chosen to be the surfactant and co-surfactant, respectively, for their emulsification capacity and high transmittance (>94%). FTIR established no meaningful incompatibilities between DTG and chosen excipients. Of S_{mix} ratios examined, 3:1 (Kolliphor EL:PG) showed the largest microemulsion area in pseudo-ternary phase diagrams. **Conclusion:** The study offers a clear preformulation platform for DTG, determining important excipients and a best-fit S_{mix} ratio for microemulsion development. Ternary phase diagrams were constructed to confirm the choice of ingredients for a possible SMEDDS. Subsequent research will construct on this basis to develop and assess a DTG-loaded SMEDDS for enhanced oral bioavailability.

Keywords: Dolutegravir sodium, Ternary Phase Diagram, SMEDDS, Lipid Based Systems.

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INTRODUCTION

Dolutegravir Sodium (DTG) is a 2nd generation integrase strand transfer inhibitor that plays a vital role in the treatment of HIV-1 infections. It has good antiviral potency, superior pharmacokinetic properties, and high resistance barrier. Its clinical applicability is somewhat compromised by its poor solubility, which renders the bioavailability and therapeutic benefits.[1-3]

Self-Microemulsifying Drug Delivery Systems (SMEDDS) have emerged as highly promising lipid-based systems to counter lipophilic drug solubility-limited absorption such as DTG.[4-6] These oil-surfactant-co-surfactant isotropic blends spontaneously generate fine oil-in-water emulsions when subjected to slight agitation in gastrointestinal fluids, thereby improving dissolution, absorption, and consequently bioavailability. Prior to the formulation of a SMEDDS, thorough preformulation studies are required. These encompass the determination of physicochemical characteristics like solubility, melting point, and compatibility with excipients.[7,8] In addition, the choice of excipients on the basis of efficiency in emulsification and solubilization capacity helps in the formulation of a stable and strong formulation.

Another key step in the design of SMEDDS is the development of pseudo-ternary phase diagrams.[9,10] These diagrams are used to determine the best ratios of oil, surfactant, and co-surfactant needed in formulating SMEDDS, and also help in determining

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boundaries of the microemulsion area. The current research is concerned with conducting systematic preformulation studies, excipient screening, and construction of pseudo-ternary phase diagrams for dolutegravir sodium. These initial studies are intended to lay a scientific foundation for future formulation development of SMEDDS.

MATERIALS AND METHODS

Materials

Dolutegravir sodium was gifted by Mylan Labs, India. Capmul MCM C8 was sourced from Yarrow Chemicals, Mumbai. Surfactants and co-surfactants were obtained from Sigma-Aldrich, India. Analytical grade solvents, including methanol and deionized water, were procured from Merck, India. All materials were used as received without further modification.

Methods

Determination of λ_{max}

10 mg of DTG was dissolved in 30 mL of methanol, diluted with water to make 100 mL of stock solution. From this, 1 mL was pipetted and diluted to 10 mL with water to create a 10 µg/mL solution, which was scanned in the 400-800 nm range on a UV-Visible spectrophotometer (Shimadzu-1601, Japan). λ_{max} at 257.5 nm was detected and had a distinct peak.[11,12]

Preparation of Standard Calibration curve of Dolutegravir sodium

Absorption maxima at 257.5 nm in a range of concentrations from 2-18 µg/mL, a calibration curve was prepared. Aliquots of 0.2 to 1.8 mL were pipetted and diluted with distilled water to 10 mL, and absorption was recorded at 257.5 nm.

Preformulation studies

Determination of melting point using Differential Scanning Calorimetry (DSC)

DSC thermograms of the pure drug were recorded (TA Instruments SDT-2960 instrument) using an indium standard for calibration. Hermetically sealed powder samples were heated from 35°C to 350°C at 10°C/min under nitrogen (100 mL/min).[13,14]

Determination of solubility

DTG solubility in oils, surfactants, and co-surfactants was determined by the equilibrium saturation method. Drug (excess) was added to 2 mL vehicle and vortexed 10 min. The tubes were shaken at room temperature for 48 hr to equilibrate. After centrifugation for 15 min at 5000 rpm, filtered samples through a Millipore filter of 0.45 µm to discard the supernatant. A UV spectrophotometer was employed to identify absorbance at 257.5 nm after diluting the filtrate with methanol.[15,16]

Screening of surfactant

Surfactant choice was decided on the basis of clarity (% transmittance) and efficiency of emulsification. The surfactants used for testing were Tween 20, Tween 80, Span 80, and Kolliphor EL. Each of these was blended with the chosen oil in 1:1 weight ratio and softly stirred at 50°C for 2 min to create a uniform mixture. This mixture was diluted with distilled water (1:100) and repeatedly inverted. The number of inversions of the flask needed to achieve a clear, stable emulsion that did not exhibit phase separation was noted. Following 2-hr standing, % transmittance at 650 nm was determined by a UV spectrophotometer (Shimadzu UV-1900). Surfactant yielding clear emulsion, minimal inversions, and high transmittance selected.[17]

Co-surfactants of screening

The chosen oil and surfactant were employed to screen various co-surfactants (PEG 400, Propylene Glycol, Span 20, and Ethanol). Emulsification efficiency was tried by combining 200 µL co-surfactant, 400 µL surfactant, and 600 µL oil. The emulsions were left at rest for 2 hr, and their percentage transmittance at 650 nm was measured with a UV spectrophotometer (UV-Shimadzu 1900). The surfactant which showed a clear emulsion with less inversion and maximum transmittance was selected for further investigations.[18]

Compatibility studies for the drug-excipients ATR-FTIR Analysis

ATR-FTIR spectra were obtained on a Bruker ATR Alpha at 25.0±0.5°C. Special sample preparation was not necessary. Samples were spotted on a zinc selenide crystal plate and fixed with the anvil and scanned from 4000-400 cm^{-1} to detect functional groups. The spectra were examined to find out any possible drug-excipient interactions.[19]

Pseudo-ternary phase diagram

Various groups of oil, surfactant, and co-surfactant were combined. Weight ratio combinations of 1:1, 1:2, 2:1, and 3:1 (w/w) were employed to blend the surfactant and co-surfactant (S_{mix}). S_{mix} and oil (Kolliphor EL: propylene glycol) were mixed in glass vials in different weight ratios (1:9 to 9:1) for each diagram. All mixtures were equilibrated after being slowly titrated with water and stirred for 2 min using a magnetic stirrer. Oil, S_{mix}, and water were plotted against the ternary phase diagram axes, which were utilized to graphically note and track changes from clear to turbid or vice versa. CHEMIX School 7 ternary plot computer software was utilized for drawing the diagrams.[20,21]

RESULTS

Analytical determination

A solution of dolutegravir sodium was prepared in accordance with the method described in the methodology section. UV

spectrophotometric analysis revealed the maximum absorbance at 257.5 nm in a solvent system comprising 30% methanol and 70% water and the corresponding UV spectrum is shown in Figure 1.

Melting Point Determination

DSC results showed an endothermic peak at 346°C, which is identical to the melting temperature. This sharp peak indicates a high degree of purity and crystalline integrity. The observed melting point aligns with standard data reported in DrugBank and other pharmacopeial references. The DSC thermogram is illustrated in Figure 3.

Solubility study

Capmul mcm c8 could solubilize 37.2mg DTG per mL which was highest among the oils screened. Intestinal mixed micelles (BS/PL/CH) are formed when lipids in the GIT cause an increased production of cholesterol, phospholipids, and bile salts, which further increases the GIT's capacity for solubilization (Table 1).

Screening of surfactant and cosurfactant

Emulsification efficiency and bioactivity are prioritized over drug solubility in selecting surfactants and co-surfactants. Nonionic surfactants are favored for SMEDDS due to their lower toxicity compared to ionic types. This study screened various nonionic surfactants for emulsification efficiency with the chosen oil phase. Well-formulated SMEDDS disperse within seconds under gentle stirring. High efficiency was defined by fewer than ten flask inversions and over 90% transmittance, with each inversion lasting about 1 sec (Tables 2, 3).

Compatibility study using FTIR

FTIR analysis was performed to assess the compatibility of dolutegravir sodium with selected excipients. Since there were no major shifts or disappearance of the main drug peaks in the formulation, thus concluded that there is no significant chemical interaction between the drug and the selected excipients (Figure 4).

Table 1: DTG solubility in oils.

Sl. No.	Oils	Solubility (mg/mL)
1	Capmul mcm c8	37.20
2	Cinnamon	28.52
3	Anise	5.84
4	Castor	2.41
5	Oleic acid	8.04
6	Coriander	17.56

Table 2: DTG solubility in surfactants.

Sl. No.	Surfactant	Solubility (mg/mL)
1	Tween 20	1.37
2	Tween 80	4.18
3	Span 80	3.73
4	Kolliphor EL	5.47

Table 3: Solubility of dolutegravir sodium in various co-surfactant.

Sl. No.	Co-surfactant	Solubility(mg/mL)
1	PEG 400	1.82
2	Propylene glycol	2.24
3	Span 20	1.12
4	Ethanol	0.52

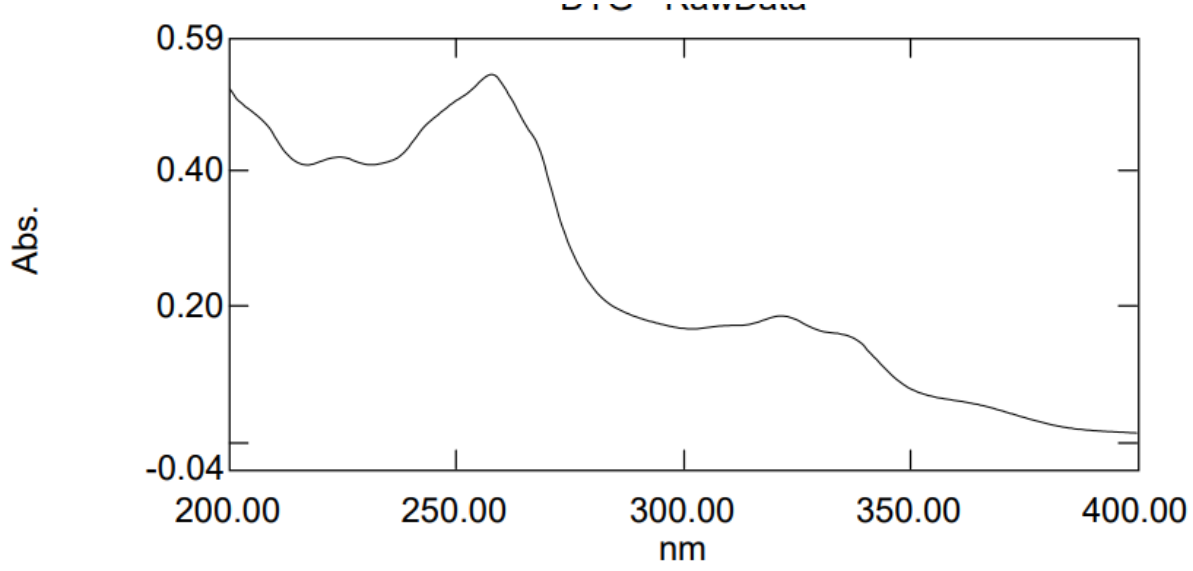

Figure 1: UV Spectroscopy of DTG.

Construction of pseudo-ternary phase diagram

Pseudo-ternary phase diagrams were constructed using Capmul MCM C8 as the oil phase and S_{mix} (a combination of Kolliphor EL and propylene glycol) in varying weight ratios of 1:1, 1:2, 2:1, and 3:1. The diagrams helped identify the microemulsion region by titrating the oil-S_{mix} mixtures with water (Table 6 and Figure 5).

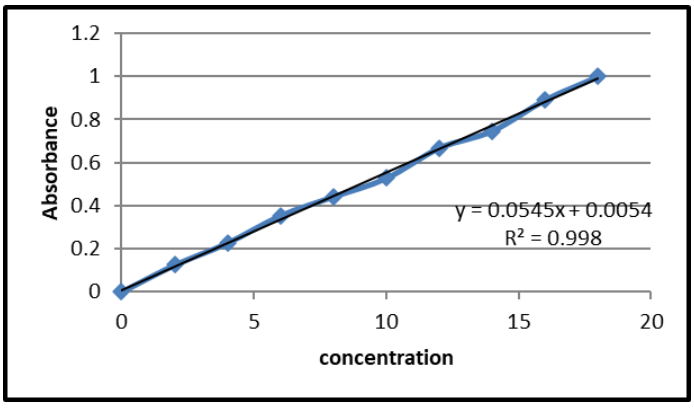

Figure 2: Standard calibration curve of DTG.

DISCUSSION

A standard calibration curve for dolutegravir sodium was prepared by measuring absorbance at concentrations from 2 to 18 µg/mL. With an R2 of 0.998, the curve demonstrated exceptional linearity and a robust relationship between absorbance and concentration. The line's slope was 0.0545, and its intercept was 0.0054. This confirms the suitability of the UV method for quantitative analysis of dolutegravir sodium. Absorbance data and the calibration plot are provided in Figure 2, respectively.

The important factor considered during the screening of excipients for SMEDDS was to overcome drug precipitation *in vivo* following the dilution in the gut lumen. Oils with high solubilization capacity were carefully selected to ensure complete drug solubilization in the formulation. SMEDDS components were chosen to maximize drug solubility and ensure good miscibility with the surfactant and co-surfactant for a stable formulation. Since oil creates a unique core inside the surfactant aggregate and has the property to enhance solubility, the drug's solubility in the oil is crucial since it enhances the microemulsion's

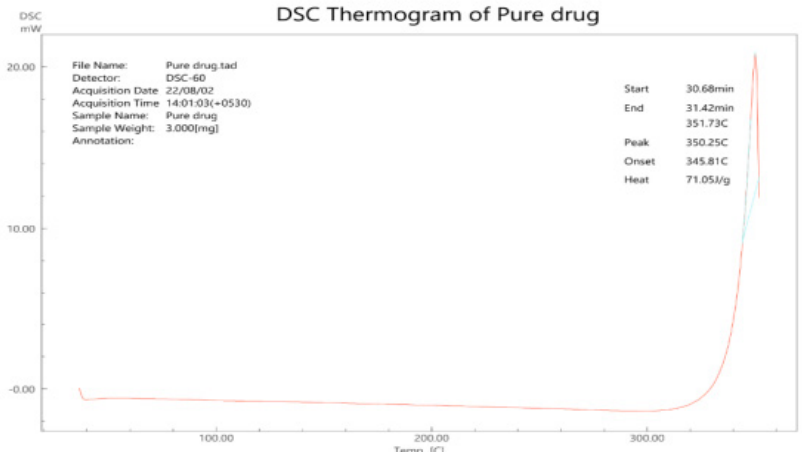

Figure 3: DSC thermogram of DTG.

Table 4: Co-Surfactants screening.

Sl. No.	Ingredient	No. of flask inversions	% transmittance	Phase separation
1	PEG 400	2	97.3	No
2	Propylene glycol	2	97.2	No

Table 5: Surfactants screening.

Sl. No.	Surfactant	No. of flask inversions	% transmittance	Phase separation
1	Tween 80	2	93.9	No
2	Kolliphor EL	2	94.7	No
3	Tween 20	2	96.9	No
4	Span 80	3	55.6	Yes

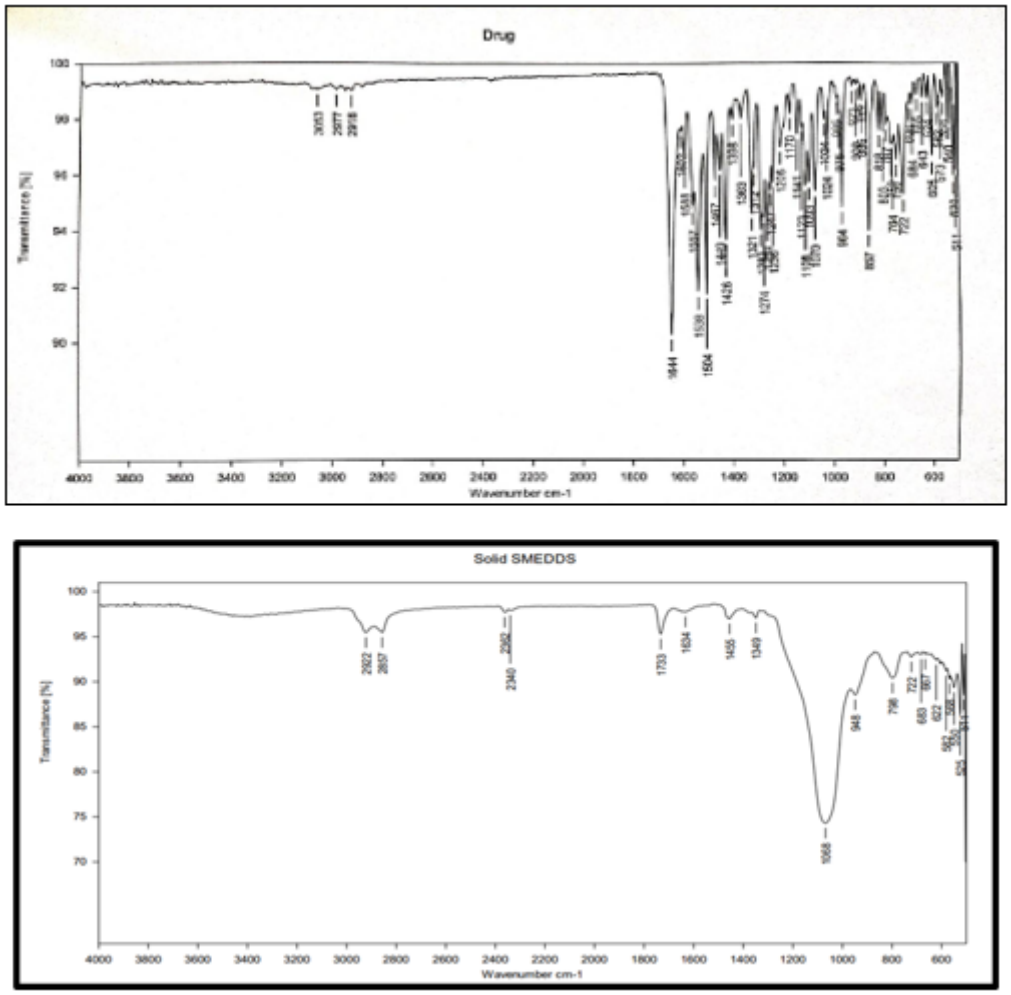

Figure 4: a) FTIR spectrum of DTG and b) Physical mixture of DTG and all selected.

ability to load drugs. Among the various oils capmul mcm c8 was selected for formulation development.

The emulsification study clearly demonstrated the varying abilities of surfactants to emulsify the selected oil (Capmul MCM C8). Results showed that Kolliphor EL emulsified Capmul MCM C8 more effectively than the other surfactants tested. The % transmittance value of various microemulsions and their ease of formation monitored by number of VFl are demonstrated in Table 4. kolliphor EL renders good micro emulsification ability with oil in shortest time and also has inhibitory effects on Pgp and metabolic enzymes[1] therefore it was selected for further investigation.

Several reports support using co-surfactants in SMEDDS to enhance drug loading, reduce self-microemulsification time, and improve thermodynamic stability. In this study, various co-surfactants were evaluated for solubilizing capacity, emulsification ease, and percentage transmittance. The solubility study results are presented in Table 5. Propylene glycol and PEG 400 exhibited good emulsification efficiency and percent transmittance (97.3 and 97.2% respectively) with capmul mcm c8 and kolliphor EL (oii:S:Co-S, 3:2:1) with only two flask inversions. Propylene glycol provided the highest solubilizing capacity for DTG compared to PEG 400 hence propylene glycol was selected as cosurfactant. The selected Kolliphor EL (HLB:12-14) and PG (HLB:3-5) with high and low HLB values, respectively, will help in the formation of a stable spontaneous emulsion with fine globule size.

Dolutegravir sodium spectrum had peaks at 3053 (aromatic C-H), 1644 (C=O), 1602 (C=C), 1312-1363 (C-N), confirming the drug's functional groups. In the spectrum of the solid SMEDDS mixture (dolutegravir sodium with Capmul MCM C8, Kolliphor EL, and propylene glycol), peaks were seen at 2922 and 2857 cm^{-1} (aliphatic C-H stretching), 1733 and 1735 cm^{-1} (ketone and carboxylic C=O stretching), 1349 cm^{-1} (C-N stretching), and at 1096 and 1043 cm^{-1} (C-F stretching) (Figures 4a and b). These peaks correspond to both the drug and the excipients. Therefore, the components are compatible and suitable for further development.

As shown in the corresponding diagrams and results presented in Table 6 and Figure 5, the S_{mix} ratio of 3:1 exhibited the largest

Table 6: Titration reading for different S_{mix} ratios.

Oil mL	S_{mix} (1:1) mL	Water mL
0.1	0.9	10
0.2	0.8	5.5
0.3	0.7	1.8
0.4	0.6	0.5
0.5	0.5	0.2
0.6	0.4	0.1
0.7	0.3	0.1
0.8	0.2	0.1
0.9	0.1	0.1
Oil mL	S_{mix} (1:2) mL	Water mL
0.1	0.9	10
0.2	0.8	1.6
0.3	0.7	0.6
0.4	0.6	0.4
0.5	0.5	0.2
0.6	0.4	0.1
0.7	0.3	0.1
0.8	0.2	0.1
0.9	0.1	0.1
Oil mL	S_{mix} (3:1) mL	Water ml
0.1	0.9	10
0.2	0.8	10
0.3	0.7	5
0.4	0.6	4.1
0.5	0.5	0.2
0.6	0.4	0.1
0.7	0.3	0.1
0.8	0.2	0.1
0.9	0.1	0.1
Oil mL	S_{mix} (2:1) mL	Water mL
0.1	0.9	10
0.2	0.8	7
0.3	0.7	2.5
0.4	0.6	2.3
0.5	0.5	0.2
0.6	0.4	0.1
0.7	0.3	0.1
0.8	0.2	0.1
0.9	0.1	0.1

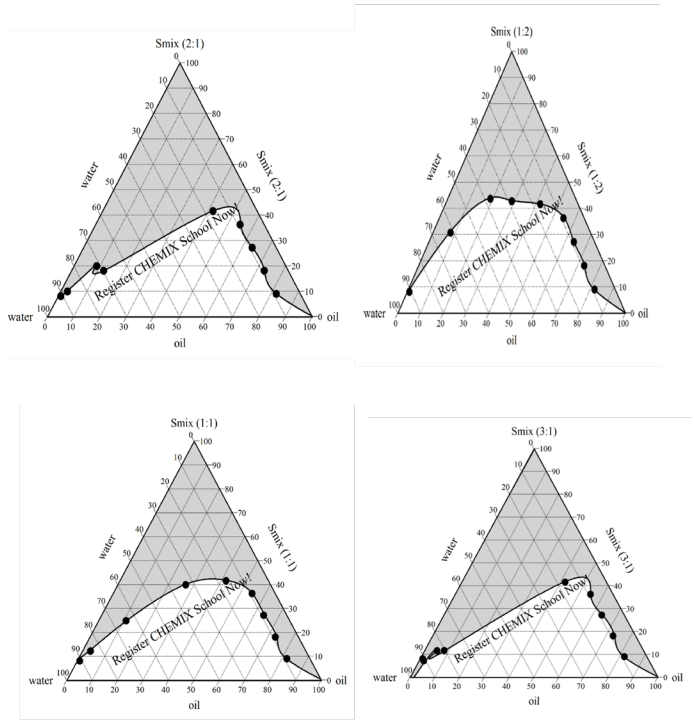

Figure 5: Pseudo-Ternary Phase Diagram for various S_{mix}.

microemulsion region compared to other ratios. This indicates better self-emulsification and dispersion potential, making it the optimal ratio for further formulation development. Additionally, this study helped determine the lower and upper concentration limits of oil required for stable microemulsion formation, which will guide future formulation trials.

CONCLUSION

The present study focused on preformulation evaluation and phase behavior analysis of dolutegravir sodium with the aim of facilitating future lipid-based formulation strategies. Capmul MCM C8 emerged as the most suitable oil based on its high solubilizing capacity, Kolliphor EL and propylene glycol were selected as surfactant/co-surfactant for efficient emulsification. FTIR showed no drug-excipient interactions. The pseudo-ternary phase diagram indicated that a 3:1 S_{mix} ratio provided the widest microemulsion region, making it optimal for formulation development. These results support further exploration of a dolutegravir sodium SMEDDS in the next research phase.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ABBREVIATIONS

DTG: Dolutegravir Sodium; **SMEDDS:** Self-Microemulsifying Drug Delivery System; **DSC:** Differential Scanning Calorimetry.

SUMMARY

This study focused on the preformulation of Dolutegravir Sodium (DTG), a poorly soluble antiretroviral drug, to support the development of a self-Microemulsifying Drug Delivery System (SMEDDS). Solubility and emulsification studies identified Capmul MCM C8 as the optimal oil and Kolliphor EL with propylene glycol (3:1 ratio) as the most effective surfactant/co-surfactant blend. FTIR analysis confirmed excipient compatibility, and pseudo-ternary phase diagrams highlighted the largest microemulsion region at the selected S_{mix} ratio. These findings provide a foundational framework for future formulation of a DTG-loaded SMEDDS to improve oral bioavailability.

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