ORIGINAL ARTICLE

Ultrafine super self-nano emulsifying drug delivery system of dolutegravir for improved dissolution rate

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Abstract

Aim: This work aimed to generate and evaluate different formulations of L-Self-nano emulsifying Drug Delivery System (SNEDDS) using different oil and Smix ratios to augment the dissolution rate of DTG. **Methodology:** L-SNEDDS of DTG was formulated with cinnamon oil and Capmul MCM as oil, TWEEN 80 as a surfactant, and PEG 400 as co-surfactant after preliminary screening using various vehicles for successful SNEDDS formulation. To optimize the system phase diagram was created and a self-nanoemulsifying region was identified. Sixteen formulations with various oil, surfactant, and co-surfactant ratios were produced and characterized concerning globule size, Polydispersity index (PDI), dispersibility, optical clarity, robustness to dilution, phase contrast microscopy, cloud point measurement, viscosity, thermodynamic stability study, and *in vitro* dissolution study. **Results:** The particle size of the F16 formulation was resolved to be 132.9 nm, with a PDI of 0.362, among the 16 formulations. Cinnamon oil and Capmul MCM were each 12.5 % of the F16 formulation, which also included 50 % tween 80 and 25% PEG 400. F16 was chosen as the optimum formulation, and it's *in vitro* dissolution rate was compared to the marketed formulation and pure drug. In vitro dissolution studies of F16 (L-SNEDDS), Dolutegravir marketed tablet (DMT), and pure drug (DP) were compared, and it was found that the F16 formulation had the highest drug release of 96.68% at the end of 30 min, while the DMT and pure drug had 72.89% and 26.22%, respectively. **Conclusion:** The study revealed that the formulation of DTG as SNEDDS is a promising strategy to enhance the rate of dissolution.

Key words: Capmul MCM, Cinnamonoil, Dissolution, Dolutegravir, PEG400, Self-nanoemulsifying drug delivery system, Solubility, Tween 80

INTRODUCTION

Oral administration of poorly bioavailable drugs using a lipid-based drug delivery system is gaining popularity as a way to avoid drug transit through the hepatic portal vein and its subsequent hepatic breakdown. Lipid-based formulations, on the other hand, offer the potential to increase the oral bioavailability of low water-soluble drugs by delivering the drug in dissolved form in colloidal dispersions. Almost half of all newly discovered medicines have low solubility, and the majority of them have poor bioavailability when prepared as an oral dosage form. Because of the drug's weak water solubility, it has a low bioavailability with significant inter-and intra-subject variability, making it difficult for formulation scientists to manufacture it as an oral dosage form. BCS class II drugs formulated as Self-nano emulsifying Drug Delivery System (SNEDDS) have been shown to enhance drug solubility and therefore drug dissolution. The SNEDDS is an isotropic combination of natural or synthetic oil, surfactants, and co-surfactants with the unique capacity to produce fine oil-in-water (O/W) nano-emulsions in an aqueous medium under gentle agitation. A self-nano emulsifying drug delivery system is one of the lipid-based drug delivery methods currently being studied for its benefits, which creates a wide interfacial area for the drug to be partitioned between oil and GI fluid.[1,2] Dolutegravir (DTG) is an HIV1 anti-retroviral drug that inhibits HIV integrase and obstruct the strand transfer step of retroviral DNA integration in the host cell. It

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is developed to treat HIV-1 infection in adults and children aged 12 and above who weigh at least 40 kg. It works by inhibiting the enzyme integrase. This drug does not cure AIDS or completely eradicate the HIV virus, but it does assist to prevent further infection by decreasing the development of new viruses. DTG is used in combination with other antiretroviral drugs to slow the severity of HIV-1 infection.[3] The goal of the study was to create and evaluate various DTG loaded L-SNEDDS formulations with different Smix ratios of DTG to augment the dissolution rate.[4]

MATERIALS AND METHODS

Materials

DTG was provided as a gift sample from Macleods Pharmaceuticals Ltd., Baddi, Himachal Pradesh, India. Cinnamon oil was brought from Genuine chemical co. Ltd, Capmul MCM was obtained from Abitec Corporation. Tween80 (Polyoxyethylene 20 sorbitan mono-oleate) and PEG 400 (Polyethylene glycol) was purchased from Loba Chemie Ltd., Mumbai.

Methods

Solubility study

An excess quantity of DTG was dissolved in 1 ml of different oils, surfactants, and co-surfactants to assess its solubility. To promote proper solubilization of DTG with solvents, the obtained mixtures were vortexed using cyclomixer (CM 101 REMI Equipment, Mumbai, India) for 2 min then equilibrium at room temperature for 12 h. The equilibrated samples were centrifuged (Eppendorf centrifuge 5415 R, Germany) for 10 min at 5000 rpm. The supernate was dissolved in methanol and then suitably diluted with distilled water and the dissolved DTG in various vehicles were analyzed using UV spectroscopy method.[2,5]

Screening of surfactant and co-surfactant

An equal volume of surfactants (Tween 20, Tween 80, Span 20, and Span 80) and a chosen oil were thoroughly mixed to determine the emulsification efficiency. To homogenize the components mixtures were heated at 35–40°C. Then, 50 µl of this mixture was further diluted in 50 µl of distilled water, and the count of flask inversions needed to produce a uniform emulsion was monitored. Optical clarity was measured after 2 h at 638.2 nm with UV-Spectrophotometer. The efficacy of co-surfactants in improving the emulsification capacity of the screened surfactants was chosen. Co-surfactants like Propylene glycol, PEG 400, Transcutol, Labrasol were used. Co-surfactant, surfactant, and oil were mixed in the ratio of (1:2:3) and heated to enable proper mixing. Emulsification ability and clarity were measured by the same method as for surfactants.[5,6]

Construction of ternary phase diagram

Cinnamon oil and Capmul MCM were selected as oily phases, Tween 80 as a surfactant, and PEG 400 as co-surfactant. Using the water titration technique, a ternary phase diagram was built to recognise systems that may emulsify spontaneously upon dilution and produce transparent or translucent O/W nanoemulsion. Each formulation system (0.5 ml) was introduced drop wise to 250 ml beaker containing distilled water held on a magnetic stirrer with stirring at about 100 rpm and temperature maintained at 37 ± 0.5°C. Against a dark background, spontaneous emulsification was visually investigated. As a way to validate the clarity of the nanoemulsion, the optical clarity of each point in the phase diagram generated by systems with an average size of 200 nm or less, and a percent transmittance more than or equal to 90%, were evaluated in the nanoemulsion region and chosen for further assessment and production of DTG loaded L-SNEDDS. Chemix ternary plot software was used to create the ternary phase diagrams (Chemix School Ver. 9.00).[7]

Formulation of DTG loaded L-SNEDDS

After finding the self nanoemulsifying area, formulations with varying concentrations of oil (20–30%) and Smix (70–80%) were prepared. DTG loaded L-SNEDDS were developed by dissolving the desired amount of drug in oil and mixed using a vortex mixer. The required quantity of TWEEN 80 and PEG 400 were stirred continuously using a magnetic stirrer (2 MLH, REMI Instrument) in a glass beaker. Finally, the oil-containing drug was introduced into the Smix and stirring continued for around 45–60 min followed by 20 min sonication (Sonics-230 ± 10V). DTG loaded L-SNEDDS was stored (25°C) in an air-tight container. Table 1 presents the composition in the SNEDDS formulation.[8]

Characterization of DTG Loaded L-SNEDDS

Globule size, Polydispersity index (PDI), and Zeta potential

The Physical stability of nanoemulsion depends on its globule size; a smaller globule size in the formulation gives a non-flocculated system with better stability. Globule size indicates the rate and extent of drug release from the formulation. Distribution of size uniformly is figured by its PDI. Globule size, PDI, and Zeta potential was determined for the selected nanoemulsion formulation after dilution with distilled water 100 times using Malvern Zeta-Sizer (MALVERN Zeta-Sizer ZS90).[6]

Dispersibility study

The dispersibility studies were performed to find out the self-emulsification time and efficiency. The time needed by the formulation to form a homogeneous mixture on dilution is its self-emulsification time. Add 0.5 ml of the formulation drop-wise in a glass beaker containing 250 ml distilled water with agitation at100 rpm on magnetic stirrer and temperature

Table 1: Composition of DTG loaded L-SNEDDS

Formulation	Oil %	Surfactant %	Co-surfactant %	Smix		Oil/Smix
				Ratio	%	Ratio
F1	20	40	40	1:1	80	2:8
F2		26.66	53.33	1:2		
F3		20	60	1:3		
F4		53.33	26.66	2:1		
F5		60	20	3:1		
F6	25	37.5	37.5	1:1	75	2.5:7.5
F7		25	50	1:2		
F8		18.75	56.25	1:3		
F9		50	25	2:1		
F10		56.25	18.75	3:1		
F11	30	35	35	1:1	70	3:7
F12		23.33	46.66	1:2		
F13		17.5	52.5	1:3		
F14		46.66	23.33	2:1		
F15		52.5	17.5	3:1		
F16	25	50	25	2:1	75	2.5:7.5

F1-F15: Cinnamon oil, F16: Cinnamon oil+Capmul MCM. DTG: Dolutegravir, SNEDDS: Self-nano emulsifying drug delivery system

adjusted to 37°C ± 5°C. The time required for emulsification was recorded. The efficiency of the formulation to self-emulsify was visually analyzed using system of grades.[9]

Grade A- Nanoemulsion forms quickly (within 1 min), with a transparent or bluish appearance.
Grade B- Less clear, bluish nanoemulsion that was formed within 2 min.
Grade C- Forms a fine milky emulsion with a slightly oily appearance after 2 min.
Grade D- Dull, greyish white emulsion with a slightly oily appearance was formed after 2 min.
Grade E- poor emulsion forms (more than 3 min) with large oil globules on the surface.

Optical clarity

Reconstitute 50 µl of DTG- SNEDDS with distilled water 50 ml to form a nanoemulsion. The % transmittance was inspected using UV-Vis spectrophotometer at 650 nm.[10]

Robustness to dilution

This test was carried out by diluting the formulation 10, 100, and 1000 times with distilled water, 0.1 N HCl, and phosphate buffer pH 6.8. The diluted systems were observed for phase separation or signs of precipitation throughout 24 h.[5]

Phase-contrast microscopy

Phase-contrast microscopy (Leica S40, 230 ± 10V, 5W) was used to determine the morphology of DTG-L-SNEDDS by focussing the lens at 10× and 40×.[8]

Cloud point measurement

DTG-L-SNEDDS were diluted to 250 ml with distilled water and placed in a water bath with gradually increasing temperature. The temperature was noted visually when there was a sudden appearance of cloudiness.[11]

Viscosity

The viscosity of the formulation was measured at 25°C by Brookfield Viscometer using the S61 spindle at 50 rpm.[11]

Thermodynamic stability study

Centrifugation test

DTG-L-SNEDDS was diluted 100 folds with distilled water and were centrifuged for 30 min at 4000 rpm. It was observed visually for any instabilities.[11]

Heating-cooling cycle

It involves heat-cool cycles at alternating temperatures of 4°C and 45°C with storage at each temperature for 48 h.[12]

Freeze-thaw cycle

The formulations were subjected to accelerated cycles at (−21°C and +25°C) kept at specified temperatures for 48 h. The physical appearance was observed visually for any instabilities.[12]

In vitro dissolution study

The *in vitro* dissolution study was done using the USP dissolution apparatus I (LAB INDIA DS 8000). DTG loaded L-SNEDDS (equivalent to 10 mg) and pure drug (10 mg)

were filled in hard gelatin capsule size (0). DTG release from the prepared capsules was evaluated in phosphate buffer pH 6.8 containing SDS maintained at 37 ± 0.5°C, with baskets rotating at 50 rpm. The dissolution media has a volume of 900 ml. A 5 ml sample from the dissolution medium was withdrawn and replaced with an equivalent volume of buffer at 5, 10, 15, 20, 30, 45, and 60 min to maintain a constant volume of dissolution media throughout the study. The sample absorbance was then measured using a UV spectrophotometer at 257.80 nm.[8,13] Drug release kinetics was studied using 4 different kinetic models (zero-order, first-order, Higuchi, and Weibull equation). A measure of the model's appropriateness was determined by its R^2 value.[14] The statistical significance of observed variation in *in vitro* dissolution study for Dolutegravir marketed tablet (DMT), DP, and F16 (L-SNEDDS) was established using GraphPad Prism software (version 9.3.0 [463]) using one-way ANOVA. The differences were considered to be significant at ($P < 0.05$).

RESULTS AND DISCUSSION

Solubility Studies

Solubility studies were performed to find appropriate oily phase, surfactants, and co-surfactants for the formulation of DTG SNEDDS. Appropriate drug solubility in SNEDDS excipients is critical for effective formulation to avoid drug precipitate before in situ self-emulsification and in the gut where it is subjected to progressive dilution. Oil with a higher solubilization capability of the drug has a better drug loading potential. DTG has the highest solubility in cinnamon oil, Capmul MCM, and a combination of cinnamon oil and Capmul MCM (1:1) and were selected for further studies. The solubility of DTG in several excipients is shown in Figure 1.

Screening of Surfactant and Co-surfactant

Based on the drug solubility in excipients, HLB value and emulsifying ability surfactant and co-surfactant were selected. The % transmittance of the combination of surfactant and co-surfactant was used to assess the emulsifying capacity. Good emulsification is seen in surfactants with an HLB value >10. For oral administration, non-ionic surfactants are more preferred as they are less toxic and forms a stable emulsion. TWEEN 80 and PEG 400 had maximum solubility and emulsification efficiency with cinnamon oil and Capmul MCM and were selected for the formulation of DTG loaded L-SNEDDS. The % transmittance of the mixture is shown in Table 2.

Construction of Ternary Phase Diagram

A ternary phase diagram was established to find the self-Nano emulsifying region and to optimize the appropriate concentration of oil, surfactant, and co-surfactant for formulating DTG loaded L-SNEDDS. According to solubility study and preliminary screening cinnamon oil and Capmul MCM were used as oil phase, TWEEN 80 as a surfactant, and

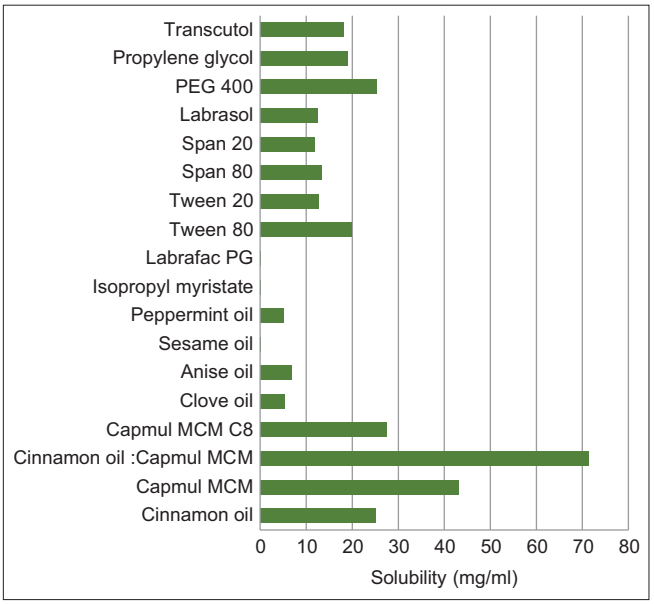

Figure 1: Dolutegravir solubility in various oils, surfactants and co-surfactants

Table 2: Percentage transmittance of different mixtures

Composition	Number of flask inversions	% transmittance
Cinnamon oil+Tween 20	9	93.48
Cinnamon oil+Tween 80	9	95.04
Capmul MCM+Tween 20	11	91.32
Capmul MCM+Tween 80	8	98.99
Cinnamon oil: Capmul MCM+Tween 20	7	97.85
Cinnamon oil: Capmul MCM+Tween 80	5	98.96
Cinnamon oil+Tween 20+PEG 400	14	96.37
Cinnamon oil+Tween 80+PEG 400	10	98.47
Cinnamon oil: Capmul MCM+Tween 80+PEG 400	5	99.48

PEG 400 as co-surfactant for constructing phase diagram. Compositions with 20–30% of an oil phase and 70–80% of Smix gives a clear self-nano emulsifying region which is illustrated in Figure 2. Above these concentration phases separation or turbidity was seen.

Globule Size, PDI, and Zeta Potential

The droplet size is an essential factor in the SNEDDS performance as it impacts the rate and amount of drug release as well as drug absorption. Furthermore, studies have shown that the smaller the particle size, the greater the interfacial surface area, which may contribute to faster absorption and improved bioavailability. The SNEDDS requirements are met by systems with a mean droplet size of <200 nm.

PDI is the measure of particle homogeneity that ranges from 0.0 to 1.0 and is used to represent the droplet size distribution. Particles are more homogenous when their PDI value is near zero.

The colloidal system's potential stability is determined by the magnitude of the zeta potential. When all of the particles have a large negative or positive zeta potential, they repel one another, resulting in dispersion stability. The results are shown in Table 3 and represented in Figure 3a and b.

Dispersibility Study

The formulations that spontaneously emulsified within 1 min were deemed excellent formulations. The formulations F1, F4, F5, F9, F10, and F16 showed an acceptable emulsification time. The self-emulsification time recorded for these formulations is short, indicating their capacity to emulsify easily and rapidly. Following administration, the SNEDDS should disperse entirely in GI fluids with no precipitation. The SNEDDS formulations that were clear and dispersed were considered Pass (A and B grade). All the formulations except F12, F13, and F15 passed the dispersibility test which is depicted in Table 3.

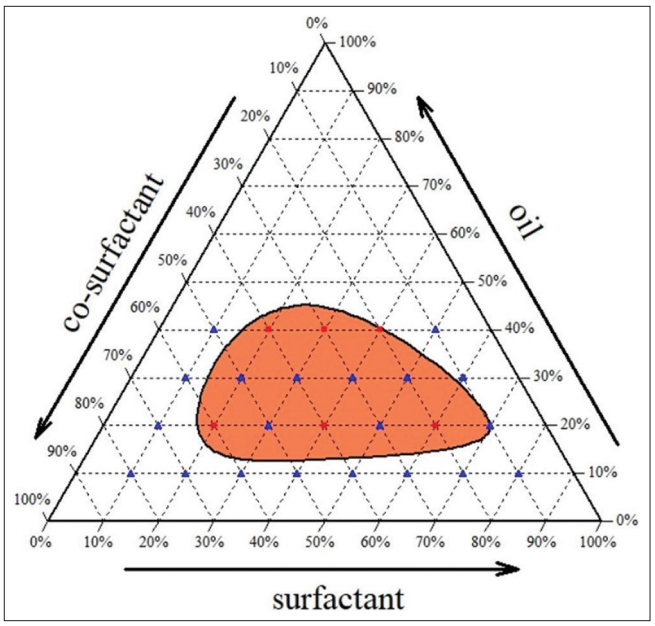

Figure 2: Ternary phase diagram

Table 3: Characterization of DTG loaded L-SNEDDS

Formulation	Average particle Size (nm)	PDI	Zeta potential (mV)	Self emulsification time (sec)	Dispersibility test	
					Grade	Inference
F1	281.5	0.497		47.32	A	Pass
F2	391.1	0.645		51.10	A	Pass
F3	275.2	0.429		54.29	A	Pass
F4	194.6	0.384		39.34	A	Pass
F5	219.0	0.360		45.38	A	Pass
F6	352.1	0.563		57.03	A	Pass
F7	396.3	0.705		89.87	B	Pass
F8	618.6	0.849		90.50	A	Pass
F9	180.4	0.484	−10.2	31.20	A	Pass
F10	277.6	0.475		48.28	A	Pass
F11	509.2	0.792		82.33	B	Pass
F12	782.7	0.789		135.02	C	Fail
F13	925.4	0.885		139.54	C	Fail
F14	451.1	0.480		91.24	B	Pass
F15	308.8	0.450		125.29	C	Fail
F16	132.9	0.362	−15.0	20.98	A	Pass

DTG: Dolutegravir, SNEDDS: Self-nano emulsifying drug delivery system, PDI: Polydispersity index

Optical clarity

A SNEDDS isotropic nature may be determined using the % transmittance. A % transmittance value near 100% indicated that all of the selected formulas were clear and transparent. The optical clarity of F16 was highest when compared to F9 and considered a good emulsion.

Robustness to Dilution

To utilize SNEDDS as a drug delivery vehicle, SNEDDS on dilution must not undergo phase separation and drug precipitation. Even after 24 h of dilution in distilled water, 0.1N HCl, phosphate buffer pH 6.8 of F9 and F16, the resultant nanoemulsion remained clear and transparent. Table 4 represents the data for robustness to dilution.

Phase-contrast Microscopy

The morphology of F16 L-SNEDDS was studied by PCM. Figure 4a and b shows the formation of spherical globules at 10× and 40×.

Cloud Point Measurement

When dealing with non-ionic surfactants, temperature-dependent phase behavior is one of the key difficulties connected with nanoemulsion. An ideal formulation should remain a one-phase clear system under its usage and storage temperature. Above the cloud point, temperature formulation clarity becomes cloudy. The cloud point of the F9 and F16 formulation was found to be 76°C and 79°C [Table 4] which indicates stability at physiological temperature.

Viscosity

For SNEDDS to describe the system physically and maintain its stability, the viscosity of SNEDDS is crucial for its aqueous phase dispersion. Higher viscosities slow the emulsification rate that might impact drug release. The viscosity of F9 and F16 was found 62.15 cps and 51.70 cps [Table 4] which implies a high degree of flow ability.

FT-IR Studies

The FT-IR studies were conducted on DTG pure drug, excipients, and formulation F16. The pure drug exhibited a sharp peak at 3044.74, 1645.33, 1627.97, and 1108.14 and F16 showed peaks at 3067.88, 1648.23, 1626.05, and 1106.21 which confirm that the molecule has not undergone any distinctive modifications, indicating that there were no incompatibilities found in the components utilized. Figure 5 illustrates (a) FT-IR data for DTG; (b) FT-IR data for F16 L-SNEDDS.

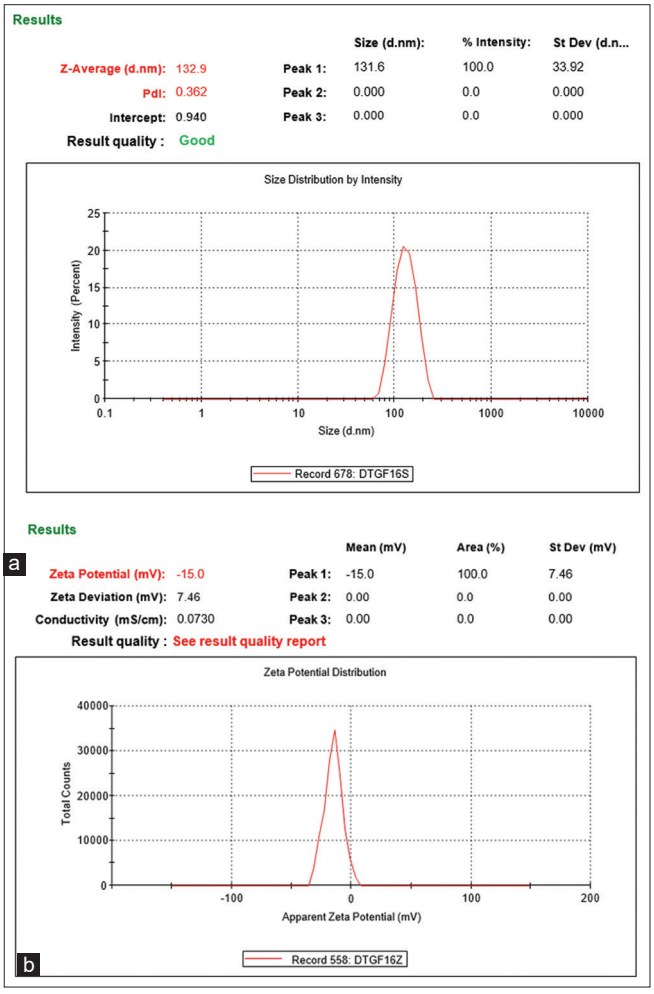

Figure 3: (a) Average size and Polydispersity index of F16 formulation, (b) Zeta potential of F16 formulation

Table 4: Optical clarity, dilution study, cloud point, viscosity and stability of optimized formulations

Formulation	Optical Clarity (%)	Robustness to Dilution			Cloud point (°C)	Viscosity (cps)	Thermodynamic stability studies
		Distilled water	0.1N HCl	Phosphate Buffer pH 6.8			
F9	97.18	✓	✓	✓	76°C	62.15	X
F16	98.79	✓	✓	✓	79°C	51.70	✓

✓: Pass, X: Fail

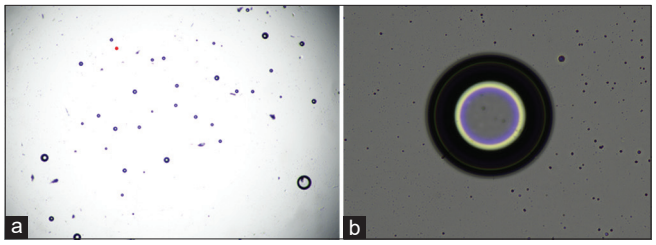

Figure 4: (a) Morphology of L-SNEDDS (10×); (b) Morphology of L-SNEDDS (40×). SNEDDS: Self-nano emulsifying drug delivery system

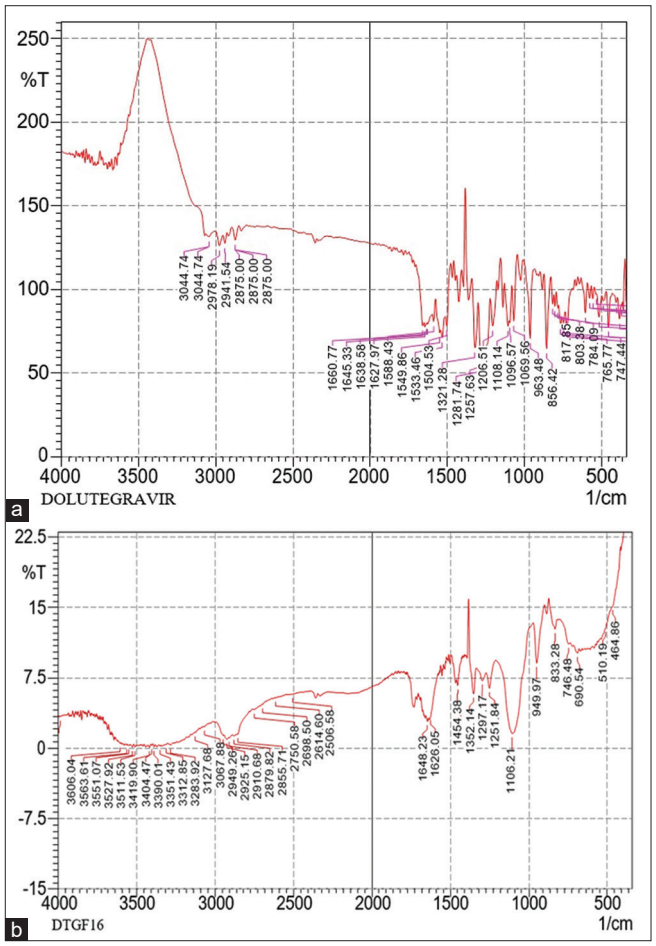

Figure 5: (a) FT-IR data for Dolutegravir; (b) FT-IR data for F16 L-SNEDDS. SNEDDS: Self-nano emulsifying drug delivery system

Thermodynamic Stability Study

After heat-cool cycles, centrifugation, and freeze-thaw cycles, formulation F9 showed signs of precipitation while formulation F16 exhibited no indications of precipitation, cloudiness, or separation mentioned in Table 4. Under these conditions, however, the overall stability of F16 was found to be satisfactory.

In Vitro Dissolution Study

The *in vitro* dissolution study of F16 (L-SNEDDS) DMT and Dolutegravir pure (DP) was compared and found that

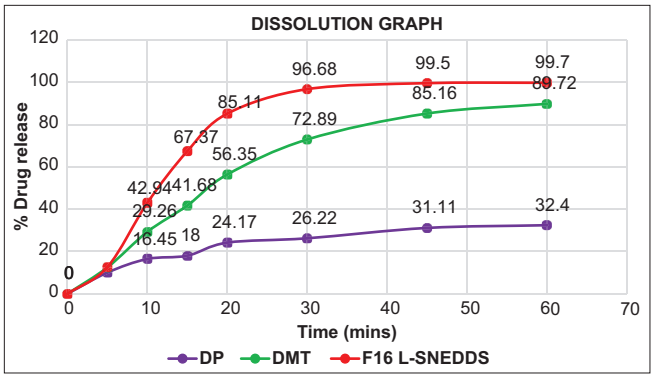

Figure 6: Comparative dissolution profile of DP, DMT, and F16 L-SNEDDS in 6.8 pH phosphate buffer with SDS. DP: Dolutegravir pure, DMT: Dolutegravir marketed tablet, SNEDDS: Self-nano emulsifying drug delivery system

maximum release 96.68% was observed with F16 formulation at the end of 30 min, and from the DMT and the pure drug was 72.89% and 26.22% respectively.[14] Data show DTG from the F16 formulation is released at a much higher rate than the marketed drug formulation which is represented in Figure 6. As a result, in vitro studies show that the F16 SNEDDS formulation increased DTG solubility.

The *in vitro* release data was then fitted to the zero-order and first-order kinetic equations, as well as Higuchi's square root of time equation and Weibull's equation. The model with the highest R^2 value was chosen as best suited drug release model. A 0.9998 R^2 value was found for the F16 SNEDDS kinetics data at pH 6.8. It was concluded that *in vitro* drug release at pH 6.8 from F16 SNEDDS best suited Weibull's model through mathematical analysis.

In vitro dissolution release for F16 (L-SNEDDS) was significantly higher than DP and DMT ($P < 0.0317$).

CONCLUSION

In the present study, DTG, a BCS Class II drug that was formulated in a self-nano emulsifying drug delivery system to increase its dissolution rate. Following optimization 16 formulations composed of cinnamon oil and Capmul MCM as oil, TWEEN 80 as a surfactant, and PEG 400 as co-surfactant. F16 was chosen as the best formulation which consisted of Cinnamon oil and Capmul MCM 12.5 % each, which also included 50% tween 80 and 25% PEG 400. F16 formulation showed a particle size of 132.9 nm, with a PDI of 0.362. It was observed that the F16 formulation had the maximum drug release of 96.68% at the end of 30 min, whereas the DMT and pure drug had 72.89% and 26.22%, respectively, in the in vitro dissolution testing.

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