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Research Article

Dolutegravir Loaded Solid Self-Micro-Emulsifying Drug Delivery System for Enhanced Solubility and Dissolution

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ABSTRACT

Dolutegravir sodium (DG) is a recently approved antiretroviral drug belonging to BCS class II having poor aqueous solubility and only 16% oral bioavailability. Hence aim of the present work was to develop solid self micro-emulsifying drug delivery system (S-SMEDDS) of Dolutegravir for enhanced solubility and dissolution behaviour. Initially, solubility of DG was checked to select oil, surfactant, and co-surfactant. Pseudo ternary phase diagram was constructed to identify microemulsion region. Liquid SMEDDS of DG were prepared using Campul MCM, Tween 80 and Transcutol P as oil, surfactant, and co-surfactant, respectively. The effect of different oil, surfactant and co-surfactant concentrations on particle size, zeta potential and %transmittance was studied using Box–Behnken factorial design. The obtained liquid SMEDDS was evaluated for its thermodynamic stability, globule size, robustness to dilution, viscosity, dye solubilization test, cloud point, etc. Satisfactory formulations of liquid SMEDDS were converted to solid form by adsorption technique using Neusilin US2 as a solid carrier. Evaluation of S-SMEDDS showed that solubility of DG in S-SMEDDS increases from 0.270 to 33.52 mg/mL. *In-vitro* drug release of S-DG4 showed 99.86 ± 1.47% drug release within 120 minutes while plain DG showed 32.55 ± 1.52%. Hence study revealed that S-SMEDDS is a promising approach to enhance solubility, dissolution and hence bioavailability of poorly aqueous soluble drug like DG.

Introduction

Poor water solubility is a major challenge for the pharmaceutical industry for orally administered drugs. Poor water solubility and any drug's succeeding dissolution rate are among the most serious problems during formulation design and development.[1] Approximately 40 to 60% of new chemical entities synthesized by combinatorial selection programs with excellent pharmacological activities are poorly water-soluble, which is a major impediment in formulation development.[2] BCS Class II drugs have high permeability, low solubility. Solubility and permeability is a major physicochemical factors affecting drug absorption and therapeutic efficiency. Hence poor solubility is one of the major reasons for new drug not reaching the market effectively.[2]

Dolutegravir (DG) is an antiretroviral drug that belongs to class HIV integrase inhibitors Fig. 1 shows the chemical structure of dolutegravir. It is utilized for the cure of HIV-1 infection. Food and Drug Administration approved Dolutegravir on 13th August 2013. Dolutegravir inhibits the activity of integrase, which is an enzyme of HIV. HIV uses this enzyme to merge viral DNA into the DNA of the host cell. Thus, stopping integrase stops HIV replication and can reduce the amount of HIV in the body. This drug is always used in combination with other antiretrovirals. It can decrease viral load and also has a low risk of side effects. It was available in the name of Tivicay. The recommended standard dosage of Dolutegravir is 50 mg once daily.[3] DG is a poorly soluble drug as it belongs to the class II category according to the BCS classification, having high permeability and low solubility. DG has an

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oral bioavailability of only 16%. Therefore, increasing the solubility and dissolution rate of DG is necessary, which leads to improvement in oral bioavailability. DG is a class II category according to the BCS classification, which means low solubility and high permeability, so it has only 16% of oral bioavailability. Therefore, we have to improve its oral bioavailability by increasing its solubility.[4]

Different strategies are used, which maintain the dissolved form of the drug or alter the drug's solubility to improve oral bioavailability. For the oral delivery of Biopharmaceutical Classification System (BCS) class II drugs, lipid-based isotropic systems have recently received significant attention. SMEDDS receive more attention from scientists because they are more stable, self-dispersing in nature, easy to prepare, and easy to scale up. As a result, SMEDDS appears to be a potential method for increasing the bioavailability of water-insoluble drugs. "SMEDDS is defined as isotropic clear mixtures of drugs, lipids and surfactants, usually with one or more hydrophilic co-solvents or co-surfactants which upon mild agitation followed by dilution in aqueous media such as gastrointestinal (GI) fluids, which form fine oil-in-water (o/w) emulsions. Self-micro emulsifying drug delivery systems (SMEDDS) usually produce microemulsions of droplet size below 100 nm upon dilution".[5] The drug remains in solution form due to reduced free energy needs and increased surface area associated with fine globules, eliminating the need for dissolving and enhancing bioavailability.[5,6] SMEDDS have many advantages over other solubility enhancement techniques such as improved oral bioavailability by increasing solubility and efficient drug transport, improved patient compliance, reduced dosing frequency, ease of manufacture and scale-up. Compared to other lipid dosage forms, reduction in inter-subject and intra-subject variability, and food effects, ability to deliver active biomolecules including peptides that are sensitive towards enzymatic hydrolysis in GIT, etc.[7, 8] SMEDDS are normally prepared as liquids or encapsulated in soft gelatin capsules, which have some shortcomings, especially in manufacturing, leading to high production costs. Moreover, these dosage forms may be inconvenient to use and incompatibility problems with the soft gelatin shells are usual. Incorporating a liquid self-emulsifying formulation into a solid dosage form may combine the advantages of SMEDDS with those of a solid dosage form and overcome the disadvantages of the liquid formulations described above.

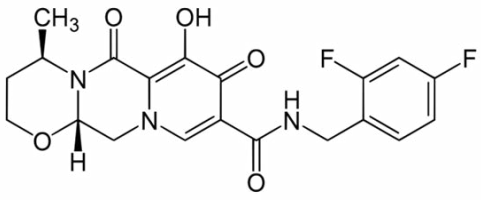

Fig. 1: Chemical structure of Dolutegravir

Bandhivadekar M. M., *et al.* (2011) prepared solid-SMEDDS by adsorbent technique to improve dissolution profile of Ramipril using Aerosil 200 as an adsorbent. The formulation showed a significant improvement in the dissolution profile of Ramipril. The studies suggested that solid-SMEDDS could be used as an effective oral dosage form to improve the dissolution profile of poorly aqueous soluble drugs.[9] Dong WY *et al.*, (2016) improved the dissolution and oral bioavailability of atorvastatin calcium by SMEDDS using Capmul(®) MCM (oil), Tween(®) 20 (surfactant), and tetraglycol (cosurfactant). Results suggested that S(M)-SEMDDS offers great potential for developing solid dosage forms with improved oral absorption of drugs with poor water solubility.[10] Dumpala R. L., *et al.*, (2021) enhanced the dissolution rate for the poorly water-soluble drug Nicardipine Hydrochloride by dissolving NH in surfactant, co-surfactant, and oil. Studies showed that *in-vitro* drug release shows the faster release of drug at 90.37% within 15 minutes. S-SMEDDS were obtained by using Neusilin as an adsorbent in optimized formulation.[11] Hence aim of the present study was to develop S-SMEDDS of DG for enhanced solubility and dissolution, which will help to enhance its oral bioavailability.

Materials and Methods

Materials

Dolutegravir (DG) was received from Cipla Ltd. in Mumbai as a gift sample. Transcutol P and Campul MCM were gifts from Abitec Corporation Limited (Columbus, Ohio) and Gattefosse India Pvt. Ltd., Mumbai, respectively. Tween 80 was bought from Mumbai's Loba Chemie Pvt. Ltd. A gift sample of neusilin was received from Mumbai's Gangwal Chemicals Pvt. Ltd. All other analytical grade additives are used.

Determination of the Saturation Solubility of DG in Oils, Surfactants and Co-surfactants

Solubility studies are conducted using the shake flask technique. In this process, small vials containing 2 mL of various oils, surfactants, and co-surfactants were taken individually, and excess drug was added to each vial. The vials were tightly closed and mechanically shaken continuously for 72 hours at 25°C. After that, undissolved DG was separated by centrifuging oils, surfactants, and co-surfactants at 10,000 rpm for 10 minutes. The sample was taken and diluted with methanol, and then the solubility of the sample was measured using UV spectroscopy (Shimadzu 1800) at 260 nm.[12]

Construction of Pseudo-Ternary Phase Diagram

Campul MCM, Tween 80, and Transcutol P were chosen as the oil, surfactant, and co-surfactant, respectively, based on solubility studies and screening of surfactants and co-surfactants. The microemulsion region was discovered by creating a pseudo ternary phase diagram with various

proportions of surfactants: co-surfactant i. e., S/Co (Km value of 1:1, 2:1, 3:1, 1:2 and 1:3), oil and water, to be necessary for the development of stable SMEDDS. In a pre-weighed test container, Smix and oil were combined in the following ratios: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. To determine the end point and after equilibrium, double distilled water was gradually added to the resulting mix up until the first indication of turbidity. If the system became clear, the water addition was then continued. The mixtures' ability to flow and to show clear phases was examined visually once complete equilibrium had been established. To create the pseudo-ternary phase diagram, CHEMIX School 10.0 was used.[13, 14]

Formulation of DG loaded Liquid SMEDDS using Box–Behnken design

From the constructed phase diagrams, the Km value that was necessary to produce a high microemulsion region was selected for further studies. The three points were selected from this microemulsion region and used to decide the composition of oil, surfactant and co-surfactant. To check the effect of concentration of campul MCM, Tween 80 and transcutol P on particle size, zeta potential and %transmittance Box–Behnken designs were used. Design Expert software version 13 was used for factorial design. 13 batches of Liquid SMEDDS (L-DG 1 to L-DG 13) of Dolutegravir (containing 50 mg of DG) were prepared by adopting the following procedure. After that, the components were thoroughly mixed at 37°C while gently stirring and vortexing. The mixture was then put into a glass vial, sealed, and kept at room temperature until it was needed.[15,16] Table 1 displays the composition of the liquid SMEDDS of DG.

Table 1: Composition of liquid SMEDDS of Dolutegravir

Batches	Run	Factor 1	Factor 2	Factor 3
		A: Capmul MCM conc.	B: Tween 80 conc.	C: Transcutol P conc.
		%	%	%
L-DG 1	1	20	33.75	10
L-DG 2	2	10	30	11.25
L-DG 3	3	15	33.75	11.25
L-DG 4	4	20	33.75	12.5
L-DG 5	5	15	30	10
L-DG 6	6	10	37.5	11.25
L-DG 7	7	15	37.5	10
L-DG 8	8	10	33.75	12.5
L-DG 9	9	15	30	12.5
L-DG 10	10	20	37.5	11.25
L-DG 11	11	10	33.75	10
L-DG 12	12	15	37.5	12.5
L-DG 13	13	20	30	11.25

*Each batch contains 50 mg of DG, Total weight of each batch is 1 g.

Evaluation of DG-loaded Liquid SMEDDS

Thermodynamic Stability Studies

- *Heating Cooling Cycle*

There were six cycles between 4°C and 45°C in the refrigerator, with storage at each temperature lasting at least 48 hours. If SMEDDS shows stability at this temperature, then a centrifugation test was performed.[17,18]

- *Centrifugation Test*

SMEDDS that passed was centrifuged using a digital centrifuge (Remi motors Ltd.) for 30 minutes at 3500 rpm. SMEDDS was taken for the freeze-thaw stress test if it didn't show any phase separation.[17, 18]

- *Freeze-thaw Cycle*

For SMEDDS, three freeze-thaw cycles between -21°C and +25°C were performed, with storage at each temperature for at least 48 hours.[17,18]

- *Robustness to Dilution*

By diluting liquid SMEDDS by 50, 100, and 1000 times in water and buffer pH 1.2, robustness to dilution was investigated. The diluted SMEDDS were kept for 12 hours while any phase separation or drug precipitation indications were monitored.[18]

- *Assessment of Efficiency of Self-emulsification*

A USP-type-II dissolution test apparatus was used to evaluate the effectiveness of self-emulsification (Veego VDA-8DR). At 37°C, add 1-mL of liquid SMEDDS dropwise to 0.1 N, 200 mL of HCl. Then it was agitated at 50 rpm by a standard stainless steel dissolution paddle. The grading system evaluates SMEDDS visually based on the emulsification rate and final emulsion appearance.[19,20]

- *%Transmittance*

Add 1-mL of liquid SMEDDS to 100 mL of distilled water to dilute and observe for turbidity. %Transmittance was measured at 650 nm using a UV-vis spectrophotometer (Shimadzu-1800, Japan) against distilled water as a blank.[20,21]

- *Globule Size, PDI and Zeta Potential*

Malvern Zetasizer (Nano ZS90) was used to determine globule size, PDI, and zeta potential after diluting liquid SMEDDS ten times in distilled water by analyzing fluctuations in light scattering caused by the Brownian motion of the particles.[22,23]

- *Viscosity*

By employing spindle S18 at 20 rpm at room temperature with a Brookfield LVDV II + pro viscometer, the viscosity of the formulations (0.5 g) was assessed without its dilution.[24]

- *Dye solubilization Test*

Water soluble dye Eosin was sprayed onto the surface of the produced microemulsion and watched for spontaneous dispersion to confirm the oil-in-water nature of SMEDDS.[25]

- *Cloud Point Measurement*

Dilute the SMEDDS in a ratio of 1:250 with distilled water, then place it in a water bath and increase its temperature gradually. Measure the cloud point as a function of the temperature and visually observe the appearance of sudden cloudiness.[26]

Formulation of Solid Self Micro emulsifying Drug Delivery System (S-SMEDDS)

To develop S-SMEDDS, liquid SMEDDS containing Dolutegravir was combined 1:1 with Neusilin US2. SMEDDS was added dropwise over the adsorbent carrier and placed in a wide porcelain dish. To ensure that the formulation was uniformly distributed after each addition, the mixture was homogenized with a glass rod.[27, 28]

Solid State Characterization of DG loaded S-SMEDDS

FTIR Study

To examine any potential interactions between DG and Neusilin US2, FTIR experiments were conducted. Infrared spectra of pure drugs, physical mixtures of drugs and carriers were recorded in the 4000 to 400 cm^{-1} wavelength range. The compatibility of the ingredients in the formulations was determined through spectrum analysis.[29]

Powder X-ray Diffraction (PXRD)

The PXRD study was conducted using an X-ray diffractometer to confirm the physical condition of dolutegravir in its pure form and the changes in crystallinity in S-SMEDDS. Using an X-ray diffractometer (D8 Advanced, Bruker AXS), PXRD analysis of plain Dolutegravir, Neusilin US2, and selected S-SMEDDS was performed.[30]

Differential Scanning Calorimetry (DSC)

DSC was used to characterize the physical state of dolutegravir in S-SMEDDS. Using a differential scanning calorimeter (TA Instruments SDT-2960, USA), thermograms of DG, Neusilin US2, and S-SMEDDS were produced.[29]

Evaluation of S-SMEDDS

Micrometric Properties

Prepared batches of S-SMEDDS were evaluated for micrometric properties like angle of repose, bulk density, compressibility index, Hausner ratio, etc. [20, 31]

Drug Content

DG was extracted from S-SMEDDS to estimate the drug content. In an adequate amount of methanol, 10 mg of S-SMEDDS were dissolved. To extract the dolutegravir from the solution in methanol, it was sonicated for 10 to 15 minutes and then filtered. On a UV-visible spectrophotometer (Shimadzu-1800, Japan), the filtrate's absorbance was measured at 260 nm.[30]

Solubility Study of Dolutegravir and S-SMEDDS in Water

To check the enhancement of aqueous solubility of drug; saturation solubility study of dolutegravir and S-SMEDDS formulation of dolutegravir (S-DG 1 to S-DG 4) were determined in water at room temperature.[32]

In-vitro Dissolution Studies for DG-loaded S-SMEDDS

An *in-vitro* dissolution study of S-SMEDDS of dolutegravir and plain dolutegravir was conducted using USP-type-II dissolution test equipment. S-SMEDDS, which is the equivalent of 50 mg of dolutegravir, and plain dolutegravir were placed inside size '0' hard gelatin capsules. After that, add each capsule to a beaker with 900 mL of 0.01M pH 6.8 phosphate buffer at 37.50°C at a rotational speed of 50 rpm. At regular intervals of 5, 10, 15, 30, 60, and 120 minutes, 5 mL samples were taken and filtered through a 0.45 µm filter. An equivalent volume of the respective dissolution media was added to keep the volume constant. A UV spectrophotometer at 258 nm examined the sample's drug content.[33]

Results and Discussion

Determination of the Saturation Solubility of DG in Oils, Surfactants and Co-surfactants

The solubility study aimed to find oils and surfactants with a high solubilizing potential for DG. The solubility of DG in various oils, surfactant and co-surfactant are shown in Figs. 2-4. Results showed that, DG has higher solubility in Campul MCM, Tween 80 and Transcutol P.

Construction of Pseudo-ternary Phase Diagram

Campul MCM, Tween 80, and transcutol P were chosen as the oil, surfactant, and co-surfactant for the formulation of the microemulsion based on the results of the solubility studies. The phase diagram investigation of DG-loaded SMEDDS used 13 distinct possible combinations of surfactant mixture to oil at various Km values (Km value 1:1, 2:1, and 3:1). Each phase diagram revealed the o/w microemulsion's boundary layer. The shaded part of phase diagram shows a microemulsion region.[34] Pseudo-ternary phase diagrams at respective Km values are shown in Fig. 5. The microemulsion region increases along with a surfactant and co-surfactant concentration. The maximum self-micro emulsifying region was to be at a ratio of 3:1. Maximum self-micro emulsification was

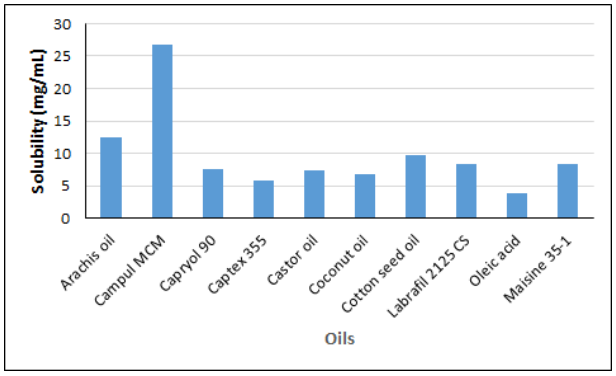

Fig. 2: Solubility of Dolutegravir in different oils

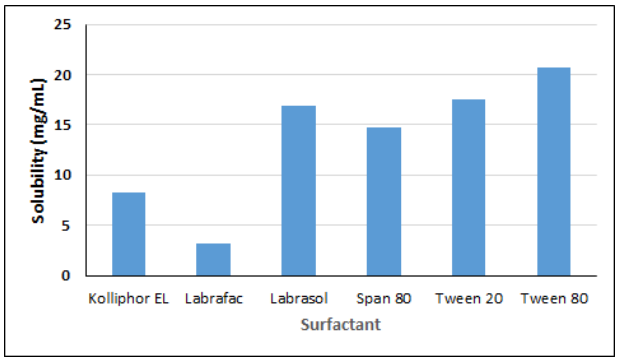

Fig. 3: Solubility of Dolutegravir in different surfactants

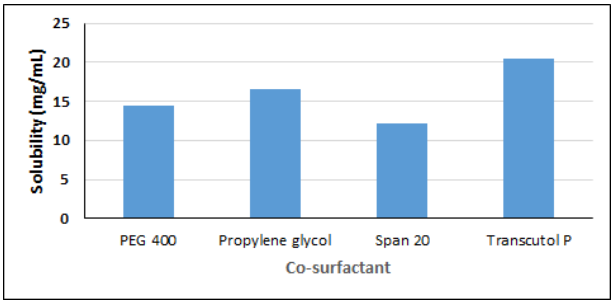

Fig. 4: Solubility of Dolutegravir in different co-surfactant

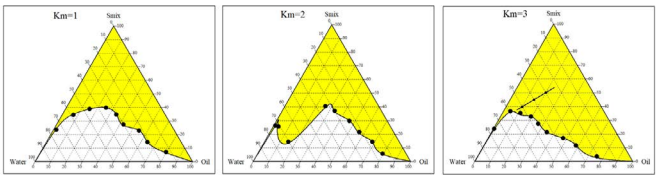

Fig. 5: Pseudo ternary phase diagram of Campul MCM, Tween 80, Transcutol P and water at Km=1, 2 and 3

intended to occur at a 3:1 ratio. As a result, the ideal ratio of surfactant to co-surfactant for the formulation of DG loaded SMEDDS was chosen to be 3:1. Study revealed that, as the concentration of surfactant and co-surfactant increases, the microemulsion region also increases.

Formulation of DG loaded Liquid SMEDDS

Total 13 batches of liquid SMEDDS containing DG were prepared successfully and were used for further evaluation.

Evaluation of DG-loaded Liquid SMEDDS

Thermodynamic stability studies, robustness to dilution and assessment of efficiency of self-emulsification

Results of thermodynamic stability studies, robustness to dilution and assessment of efficiency of self-emulsification are summarized in Table 2. The heating-cooling cycle test was observed to have been passed, and the formulation was then subjected to a centrifugation test. In the centrifugation test, SMEDDS did not exhibit any phase separation; hence, it was analyzed in the freeze-thaw stress test. SMEDDS exhibited good stability and was free of phase separation, creaming, and cracking. From the results of the robustness of the dilution study, it was observed that there was not any sign of phase separation or drug precipitation. It was determined from the robustness of dilution testing data that no evidence of phase separation or drug precipitation existed.

From the results of assessment of the efficiency of self-emulsification study, it was found that, formulation L-DG 6, L-DG 7, L-DG 10 and L-DG 12, rapidly produced micro emulsion grade A within one minute that was clear with a slight blue color and formulation L-DG 1 to L-DG 4 and L-DG 8, L-DG 11 rapidly produced microemulsion grade B that was slightly less clear with a bluish-white color. Also, L-DG 5, L-DG 9 and L-DG 13 produced micro emulsion grade C within two minute which was bright white color. Results showed that all formulations of liquid SMEDDS of dolutegravir passed preliminary thermodynamic stability studies, and robustness to dilution test. But from the assessment of the efficiency of self-emulsification test L-DG 6, L-DG 7, L-DG 10 and L-DG 12 were found to be better as compared to other batches.

%Transmittance, Globule Size, Zeta Potential and Viscosity

Results of %transmittance globule size, zeta potential and viscosity are summarized in Table 3. %Transmittance of all formulations of DG-loaded liquid SMEDDS was found in between 72.38 to 97.62. This indicates that the prepared liquid SMEDDS is clear and not turbid. All formulations' zeta potential and globule size were found to range from 5.1 to 122.2 mV and 388.3 to 962.8 m, respectively. With an increase in oil concentration in the formulations, the size of the globules grew larger. However, there is hardly any difference in formulations in terms of globule size. All formulations' viscosities were found to be between 14.57 and 23.45 cP. Figs 6 and 7 showed globule size and zeta potential of batch L-DG 6, L-DG 7, L-DG 10 and L-DG 12, respectively. This revealed that globule size and viscosity decrease as the concentration of surfactant

Table 2: Thermodynamic stability studies, robust to dilution and dispersibility tests

Formulation	*Observations based on the thermodynamic stability studies, robust to dilution and dispersibility tests*					*Inference*
	H/C	*Cent.*	*Friz. Thaw*	*Robust*	*Dispers.*	
L-DG 1	√	√	√	√	Grade B	Passes
L-DG 2	√	√	√	√	Grade B	Passes
L-DG 3	√	√	√	√	Grade B	Passes
L-DG 4	√	√	√	√	Grade B	Passes
L-DG 5	√	√	√	√	Grade C	Passes
L-DG 6	√	√	√	√	Grade A	Passes
L-DG 7	√	√	√	√	Grade A	Passes
L-DG 8	√	√	√	√	Grade B	Passes
L-DG 9	√	√	√	√	Grade C	Passes
L-DG 10	√	√	√	√	Grade A	Passes
L-DG 11	√	√	√	√	Grade B	Passes
L-DG 12	√	√	√	√	Grade A	Passes
L-DG 13	√	√	√	√	Grade C	Passes

H/C: Heating cooling cycle, Cent.: Centrifugation, Friz. Thaw: Freeze thaw cycle, Robust.: Robustness to dilution Disperse, Dispers.: Efficiency of self-emulsification

Table 3: Results of %transmittance, globule size, zeta potential and viscosity

Formulation	*Globule size (µm)*	*Zeta potential (mV)*	*% Transmittance*	*Viscosity (cP)*
L-DG 1	658.2	42.5	82.39	18.49
L-DG 2	936.5	5.3	75.34	21.33
L-DG 3	660.1	44.5	86.65	19.28
L-DG 4	687.9	109.7	83.35	18.64
L-DG 5	930.6	5.4	72.38	21.67
L-DG 6	392.5	-99.4	94.28	14.57
L-DG 7	400.1	-122.2	90.71	17.38
L-DG 8	664.6	-6.7	88.82	19.26
L-DG 9	962.2	-14.5	73.43	23.45
L-DG 10	402.5	-13.6	92.42	15.27
L-DG 11	644.3	44.3	84.32	18.46
L-DG 12	388.3	-39.3	97.62	13.85
L-DG 13	962.8	5.1	74.28	22.93

and co-surfactant increases. This can be correlated with increase in %transmittance with an increase in the concentration of surfactant and a decrease.

Dye Solubilization Test and Cloud Point Measurement

The dye solubilization test was used to confirm the type of emulsion. The water-soluble pigment (eosin) was quickly incorporated into the system, proving that water was the continuous phase and an o/w microemulsion had formed. All liquid SMEDDS were found to have cloud points that

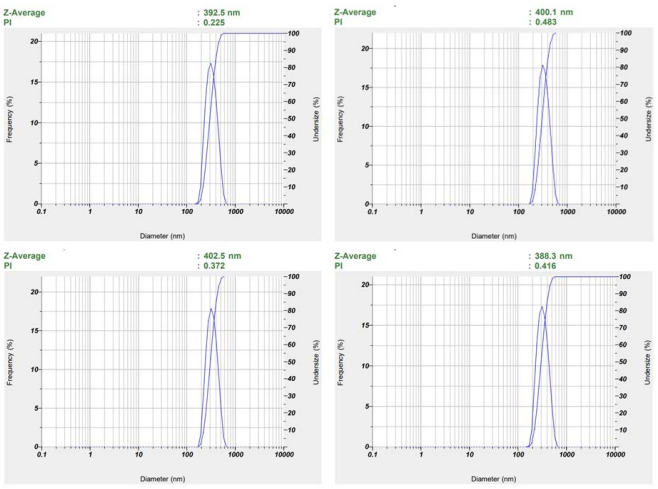

Fig. 6: Globule size of batch L-DG 6, L-DG 7, L-DG 10 and L-DG 12

were greater than 80°C, indicating that mico emulsions will be stable at physiological temperatures without phase separation concern.

Optimization of DG Loaded SMEDDS by Box–Behnken Designs

Response 1: Particle Size

The influence of concentrations of Campul MCM, Tween 80, and Transcutol P on the globule size of liquid SMEDDS is shown by three-dimensional response surface plots and counter-plots. The full mathematical equation can be given as:

$$\text{Particle size} = 660.10 + 9.19A - 276.09B + 11.68C - 4.07AB + 2.35AC - 4.95BC + 3.46A^2 + 10.01B^2 + 0.1875C^2$$

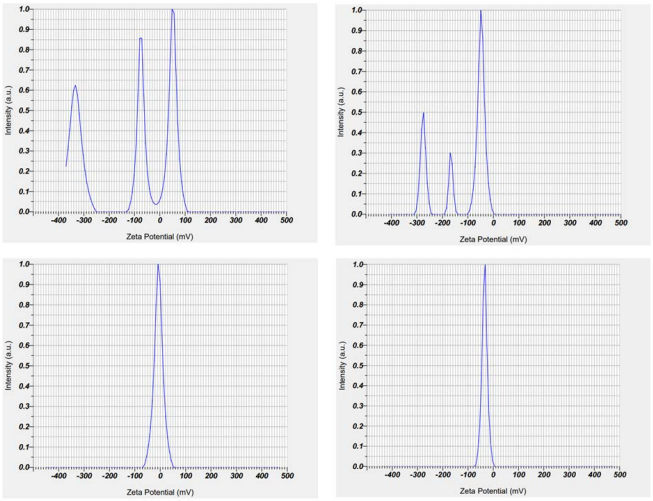

Fig. 7: Zeta potential of batch L-DG 6, L-DG 7, L-DG 10 and L-DG 12

It is possible to anticipate the response for specific levels of each factor using the equation expressed in terms of coded factors. By default, the factors' high levels are coded as +1 and their low levels as -1. The coded equation can be used to determine the factors' relative impact by comparing the factor coefficients. According to the study, globule size increases as oil concentration rises and decreases as surfactant and co-surfactant concentration rise. Fig 8 shows a counter and response surface plot illustrating the impact of variables on globule size.

Response 2: Zeta Potential

The colloidal stability is revealed by the zeta potential, which is obtained by measuring the droplets' electrophoretic mobility. Electrostatic forces that repel one another are present when the zeta potential is high (>40 mV), which minimizes the chances of particle aggregation.[35] The negative charge on SMEDDS in some liquid SMEDDS formulation was due to higher concentration of Capmul MCM, which contain esters and fatty acids. SMEDDS stability was proven by the formulations' negative zeta potential values. Fig. 9 shows a counter and response surface plot showing the effect of variables on the zeta potential.

The full mathematical equation can be given as:

Zeta potential = +44.50+25.03A-34.48B+9.90C+21.50AB+29.55AC+25.70BC+9.98A^2-80.12B^2 -7.02 C^2

Response 3: %Transmittance

Fig. 10 shows a counter and response surface plot showing the effect of variables on %Transmittance. The concentration of surfactant and co-surfactant shows a direct proportional relationship with %Transmittance. %Transmittance increases when surfactant and co-surfactant concentrations rise. Fig. 11 shows predicted

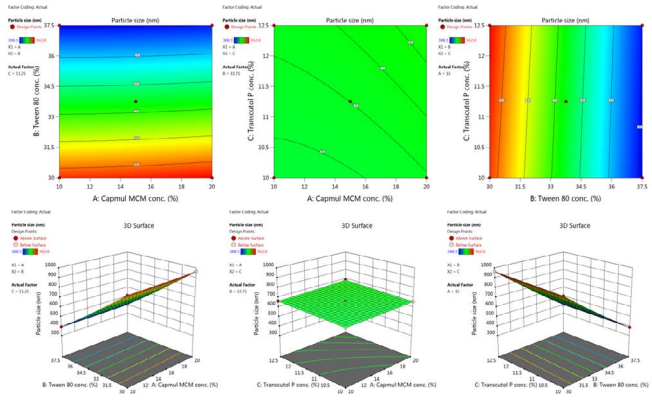

Fig. 8: Counter and response surface plot illustrating the impact of variables on globule size.

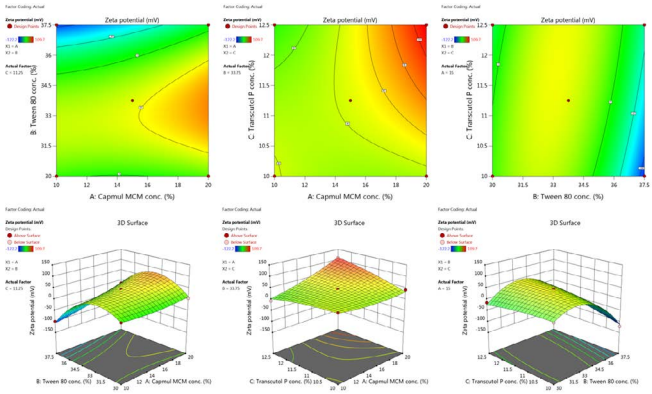

Fig. 9: Counter and response surface plot showing effect of variables on zeta potential

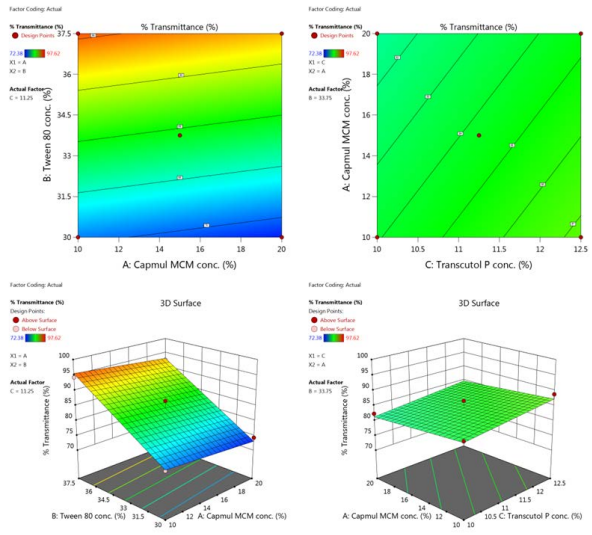

Fig. 10: Counter and response surface plot showing effect of variables on %Transmittance

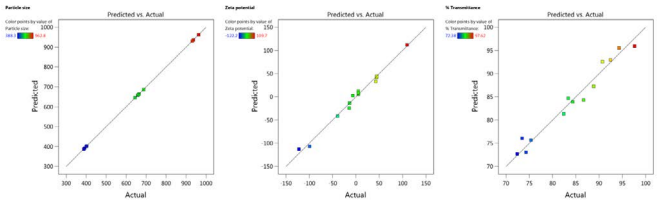

Fig. 11: Predicted vs actual plot of globule size, zeta potential and % transmittance

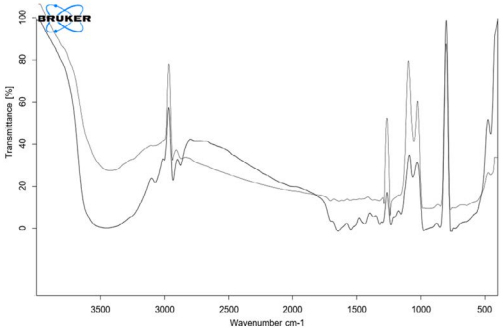

Fig. 12: FTIR Spectra of DG and DG loaded S- SMEDDS

vs. actual plot of globule size, zeta potential, and % transmittance. The full mathematical equation can be given as:

% Transmittance = +84.31-1.29 A +9.95 B +1.68 C

Formulation of Solid SMEDDS (S-SMEDDS) of Dolutegravir

Four satisfactory formulations of liquid SMEDDS of Dolutegravir such as L-DG 6, L-DG 7, L-DG 10 and L-DG 12 were successfully converted to S-SMEDDS (S-DG 1 to S-DG 4) by adsorption technique using Neusilin US2.

Solid State Characterization of DG loaded S-SMEDDS

FTIR Study

FTIR spectra of plain DG and DG loaded S- SMEDDS showed all characteristic peaks of dolutegravir. Hence, there was no interaction between dolutegravir and neusilin US2 and found to be compatible. Fig. 12 shows the FTIR spectra of DG and DG-loaded S-SMEDDS.

Powder X-ray Diffraction (PXRD)

The crystalline structure of DG was evident in the many peaks in its XRD spectrum, but it is observed in Fig 13 (C) that the peaks were absent from the diffractogram of the S-SMEDDS, indicating complete amorphization of DG in S-SMEDDS**.**

Differential Scanning Calorimetry (DSC)

DSC thermogram of DG, neusilin US2 and S-SMEDDS are shown in Fig. 14. Results showed that, sharp endothermic peak of plain DG at 367.26°C gets slightly shifted to 342.97°C in S-SMEDDS. It reveals that, there is no any interaction between neusilin US2 and DG.

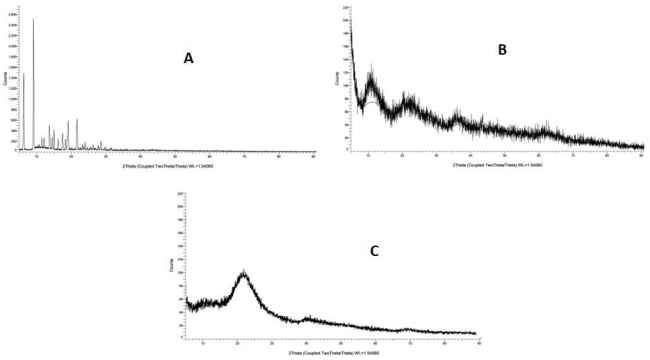

Fig. 13: XRD Spectra of A) DG, B) Neusilin US 2 and C) S-SMEDDS

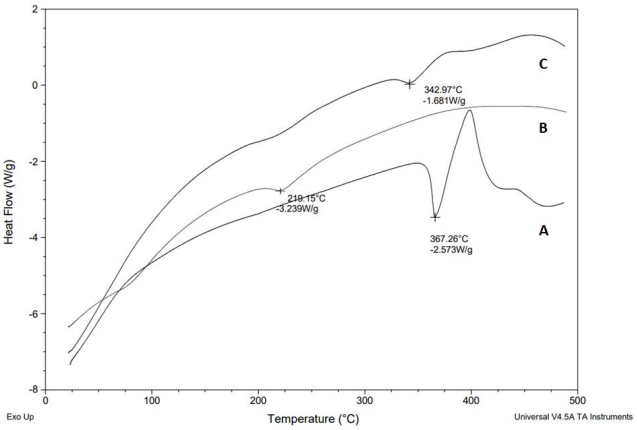

Fig. 14: DSC thermogram of A) DG, B) Neusilin US 2 and C) S-SMEDDS

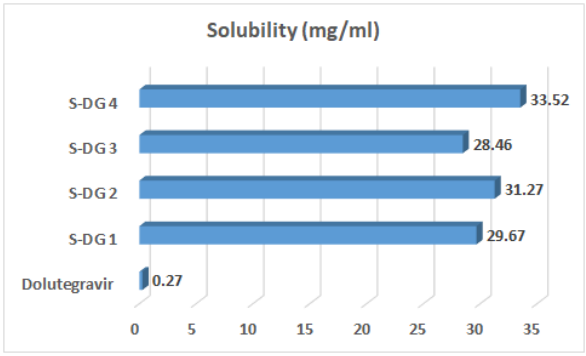

Fig. 15: Solubility of DG and DG loaded S-SMEDDS in Water

Evaluation of S-SMEDDS of Dolutegravir

Micrometric Properties and Drug Content

Table 4 provides an overview of the results for the angle of repose, bulk and tapped density, compressibility index, Hausner ratio, and drug content. All formulations of S-SMEDDS were found to be good flow properties with excellent drug content.

Saturation Solubility

Solubility of batches S-DG 1 to 4 of S-SMEDDS of DG in water is displayed in Fig. 15. The outcomes demonstrated that

Table 4: Micrometric properties and drug content of DG-loaded S-SMEDDS

Formulation	*Angle of repose*	*Bulk density (g/mL)*	*Tapped density (g/mL)*	*Compressibility index (%)*	*Hausner's ratio*	*Drug content (%)*
S-DG 1	23.71 ± 1.28	0.625 ± 0.05	0.781 ± 0.03	20.00 ± 0.15	1.25 ± 0.04	97.44 ± 2.16
S-DG 2	21.92 ± 1.43	0.676 ± 0.03	0.865 ± 0.05	21.88 ± 0.18	1.28 ± 0.02	98.69 ± 1.85
S-DG 3	20.67 ± 1.67	0.659 ± 0.04	0.811 ± 0.02	18.70 ± 0.17	1.23 ± 0.03	98.47 ± 1.22
S-DG 4	18.63 ± 1.21	0.613 ± 0.02	0.723 ± 0.03	15.25 ± 0.12	1.18 ± 0.01	99.84 ± 1.13

All value represents Mean ± SD (n=3)

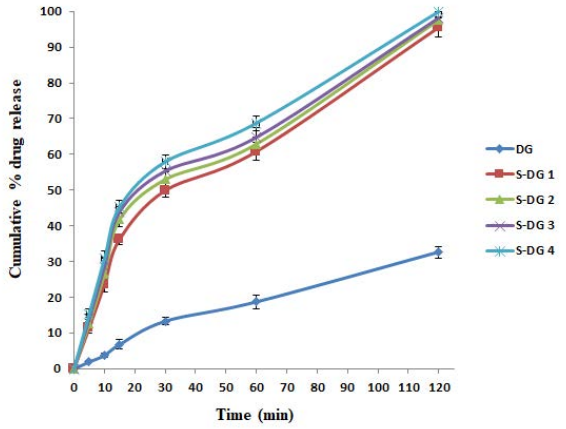

Fig. 16: Cumulative % drug release of DG from S-SMEDDS and Plain DG

water solubility of DG has significantly increased after the formulation of S-SMEDDS.

In-vitro Dissolution Studies of DG Loaded S-SMEDDS

Fig. 16 displays DG's cumulative %drug release from S-SMEDDS and plain DG. Results showed that S-SMEDDS of batch S-DG 4 released 99.86% of DG in 120 minutes compared to 32.55% from plain DG. Hence, the amount of DG released from S-SMEDDS batches was significantly increased compared to plain DG.

Conclusion

In the current work, s-smedds was developed to improve the solubility and dissolution of dg, which was poorly water-soluble. Campul MCM, tween 80, and transcutol p were chosen as the oil, surfactant, and co-surfactant for the manufacture of liquid smedds based on the solubility studies of DG. The Box-Behnken factorial design demonstrated that the concentration of oil, surfactant, and co-surfactant affects particle size, zeta potential, and % transmittance of liquid smedds and that these properties were determinants for selecting optimized batches to convert liquid into solid form. Neusilin US2 was used as a solid carrier in an adsorption method to produce solid smedds of DG. The solubility of all batches of s-smedds was found to be enhanced as compared to plain dg. The S-SMEDDS formulation s-DG 4 batch was found to be satisfactory because it releases 99.86% Of DG in 120 minutes versus 32.55% From plain DG. The findings suggest that smedds is a promising strategy for improving the solubility, dissolution, and concurrent bioavailability of medicines like dolutegravir that are poorly water-soluble.

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Conflict of Interest

Mahesh Biradar and Parul Mehta declare that they have no conflict of interest.

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