International journal of basic and applied research
www.pragatipublication.com
ISSN 2249-3352 (P) 2278-0505 (E)
Cosmos Impact Factor-5.86

Improved Solubility and Dissolution of Dolutegravir-Loaded Solid Self-Micro-Emulsifying Drug Delivery System

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A B S T R A C T

Dolutegravir sodium (DG) is a BCS class II antiretroviral medication that was just licensed. It has a 16% oral bioavailability and a low aqueous solubility. Therefore, the goal of this study was to create a solid self-micro-emulsifying drug delivery system (S-SMEDDS) for dolutegravir in order to improve its solubility and behavior during dissolution. DG's solubility was first examined in order to choose an oil, surfactant, and co-surfactant. To determine the microemulsion zone, a pseudoternary phase diagram was created. Using Campul MCM, Tween 80, and Transcutol P as the oil, surfactant, and co-surfactant, respectively, liquid SMEDDS of DG were created. Using a Box–Behnken factorial design, the effects of various quantities of oil, surfactant, and co-surfactant on particle size, zeta potential, and transmittance percentage were investigated. The resulting liquid SMEDDS was assessed for its viscosity, cloud point, resilience to dilution, globule size, thermodynamic stability, and dye solubilization test. Neusilin US2 was used as a solid carrier in the adsorption process to transform acceptable formulations of liquid SMEDDS into solid form. According to an analysis of S-SMEDDS, the solubility of DG rises from 0.270 to 33.52 mg/mL in S-SMEDDS. S-DG4 demonstrated an in-vitro drug release of 99.86 ± 1.47% within 120 minutes, while ordinary DG demonstrated 32.55 ± 1.52%. Therefore, the research found that S-SMEDDS is a viable strategy to improve the solubility, dissolution, and bioavailability of drugs that are poorly soluble in water, such as DG.

Introduction

One of the biggest problems facing the pharmaceutical business is poor water solubility when it comes to oral medications. Among the most important issues during formulation design and development are poor water solubility and the subsequent dissolving rate of any medicine.[1] Formulation development is severely hampered by the fact that 40–60% of newly created chemical entities with good pharmacological activity that are created using combinatorial selection methods are poorly water-soluble.[2] Drugs of the BCS Class II have poor solubility and high permeability. One of the main physicochemical parameters influencing medication absorption and therapeutic efficacy is solubility and permeability. Therefore, one of the main causes of new drugs not efficiently reaching the market is their low solubility.[2] Dolutegravir (DG) is a member of the HIV integrase inhibitor family of antiretrovirals. Dolutegravir's chemical structure is seen in Fig. 1. It's used to treat HIV-1 infection. On August 13, 2013, the Food and Drug Administration authorized dolutegravir. The HIV-related enzyme integrase is inhibited by dolutegravir. HIV integrates viral DNA into host cell DNA via this enzyme. Thus, inhibiting integrase may lower the body's HIV concentration by halting HIV replication. Antiretrovirals are usually used in conjunction with this medication.It has a minimal risk of negative effects and may lower the viral load. It was offered under the Tivicay brand. Dolutegravir is prescribed at a typical dose of 50 mg once day.[3] Because DG has low solubility and high permeability, it falls into the class II group of drugs under the BCS classification, making it poorly soluble. Oral bioavailability of DG is just 16%. Therefore, in order to enhance oral bioavailability, DG's solubility and dissolution rate must be increased. DG has just 16% oral bioavailability since it falls within the BCS classification's class II category, which denotes poor solubility and high permeability. Therefore, we must increase its solubility in order to enhance its oral bioavailability.[4]

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To increase oral bioavailability, many tactics are used, such as preserving the drug's dissolved state or changing its solubility. Lipid-based isotropic systems have drawn a lot of interest lately for the oral administration of Biopharmaceutical Classification System (BCS) class II medications. Scientists are paying increasing attention to SMEDDS because they are easier to produce, easier to scale up, easier to disperse in nature, and more stable. SMEDDS therefore seems to be a viable technique for raising the bioavailability of medications that are insoluble in water. "SMEDDS are isotropic, transparent mixes of medicines, lipids, and surfactants. Typically, these mixtures include one or more hydrophilic co-solvents or co-surfactants. These combinations, when diluted in aqueous media like GI fluids, create fine oil-in-water (o/w) emulsions after modest agitation. When self-micro emulsifying drug delivery systems (SMEDDS) are diluted, they often result in microemulsions with droplet sizes less than 100 nm.[5] The medicine does not dissolve, improving bioavailability, because of its heightened surface area and decreased free energy requirements linked to fine globules. Compared to previous solubility enhancement methods, SMEDDS provide a number of benefits, including increased patient compliance, easier manufacturing and scaling up, better oral bioavailability via increased solubility and effective drug transport, and a reduction in dosage frequency.

reduced variability both within and between subjects, less dietary impacts, and the capacity to transport active biomolecules such as peptides that are susceptible to enzymatic hydrolysis in the gastrointestinal tract, among other advantages over other lipid dosage forms.[7, 8] Typically, SMEDDS are made as liquids or placed within soft gelatin capsules; nevertheless, these capsules have several drawbacks, particularly during the manufacturing process, which drives up the cost of manufacture. Furthermore, there is a chance that these dose forms will be difficult to utilize, and soft gelatin shell incompatibilities are common. It may be possible to overcome the drawbacks of the liquid formulations mentioned above by combining the benefits of solid dosage forms and liquid self-emulsifying formulations into one.

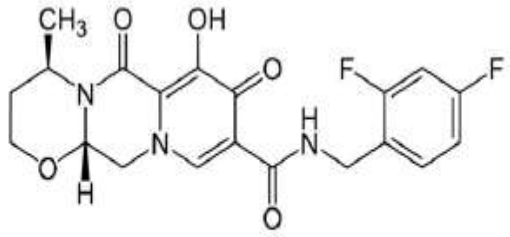

Fig. 1: Chemical structure of Dolutegravir

Materials and Methods

Materials

A gift sample of dolutegravir (DG) was obtained from Cipla Ltd. located in Mumbai. Abitec Corporation Limited (Columbus, Ohio) and Gattefosse India Pvt. Ltd. (Mumbai), respectively, gave Transcutol P and Campul MCM as presents. Loba Chemie Pvt. Ltd. of Mumbai was the source of Tween 80. Neusilin was given to me as a gift from Gangwal Chemicals Pvt. Ltd. in Mumbai. Every other ingredient of analytical grade is used.

Determining the Solubility of DG at Saturation in Oils, Surfactants, and Co-Surfactants The shaking flask method is used to perform solubility experiments. During this procedure, individual little vials holding 2 mL of different oils, surfactants, and co-surfactants were obtained, and extra medication was administered to each vial. At 25°C, the vials were mechanically shaken constantly for 72 hours while being firmly sealed. Centrifuging oils, surfactants, and co-surfactants at 10,000 rpm for 10 minutes was then used to separate the undissolved DG. The material was obtained, diluted with methanol, and its solubility was assessed at 260 nm using UV spectroscopy (Shimadzu 1800).[12]

Pseudo-Ternary Phase Diagram Construction

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Based on solubility tests and surfactant and co-surfactant screening, Campul MCM, Tween 80, and Transcutol P were selected as the oil, surfactant, and co-surfactant, respectively. The location of microemulsion was identified in Fig. 1: Dolutegravir's chemical structure was determined by constructing a pseudo-ternary phase diagram using different surfactant proportions, such as oil, water, and co-surfactant, or S/Co (Km value of1:1,2:1,3:1, and 1:2). This was shown to be essential for the construction of stable SMEDDS. Smix and oil were mixed in the following ratios in a test container that had been previously weighed: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. After equilibrium, double distilled water was progressively added to the resultant mixture until the first sign of turbidity was seen in order to ascertain the end point. The water addition was then resumed if the system cleared. After total equilibrium was attained, the mixes' flow and capacity to display distinct phases were visually assessed. Using CHEMIX School 10.0, the pseudo-ternary phase diagram was produced.[13, 14]

DG loaded Liquid SMEDDS formulation using the Box-Behnken design

The Km value required to create a high microemulsion area was determined from the phase diagrams that were created and will be the subject of future research. These three microemulsion sites were chosen, and their composition as an oil, surfactant, and co-surfactant was determined. Box–Behnken designs were used to examine the effects of concentrations of campul MCM, Tween 80, and transcutol P on particle size, zeta potential, and transmittance percentage. For factorial design, Design Expert software version 13 was used. The following protocol was used to generate 13 batches of Liquid SMEDDS (L-DG 1 to L-DG 13) of Dolutegravir, each containing 50 mg of DG. Subsequently, the ingredients were fully combined at 37°C and gently stirred and vortexed. Once the mixture was sealed and stored at room temperature until required, it was transferred into a glass vial.[15,16] The composition of the liquid SMEDDS of DG is shown in Table 1.

Assessment of Liquid SMEDDS Thermodynamic Stability Studies Loaded with DG

The Cycle of Heating and Cooling

The refrigerator had six cycles, ranging from 4°C to 45°C, and each cycle included at least 48 hours of storage at each temperature. In the event that SMEDDS remains stable at this temperature, a centrifugation test was conducted.[17, 18]

• The Centrifugation Test SMEDDS that passed was centrifuged for 30 minutes at 3500 rpm using a digital centrifuge (Remi Motors Ltd.).

If the freeze-thaw stress test revealed no phase separation, SMEDDS was obtained.[17, 18]

The Cycle of Freezing and Thawing

Three freeze-thaw cycles were carried out for SMEDDS, ranging from -21°C to +25°C. Each cycle included storage at each temperature for a minimum of 48 hours.[17, 18]

• Sturdiness in Diluting

Robustness to dilution was examined by diluting liquid SMEDDS 50, 100, and 1000 times in water and buffer pH 1.2. For a duration of 12 hours, the diluted SMEDDS were stored under observation for any signs of phase separation or drug precipitation.[18]

• Evaluation of Self-emulsification Efficiency

The Veego VDA-8DR USP-type-II dissolving test equipment was used to assess the efficacy of self-emulsification. Add 1 mL of liquid SMEDDS dropwise to 200 mL of 0.1 N HCl at 37°C. A typical stainless steel dissolving paddle was then used to stir it at 50 revolutions per minute. Based on the final emulsion look and emulsification rate, the grading system visually assesses SMEDDS.[19,20]

• %Transmission

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To check for turbidity, dilute 1 mL of liquid SMEDDS with 100 mL of distilled water. Using distilled water as a blank and a UV-vis spectrophotometer (Shimadzu-1800, Japan), transmittance was measured at 650 nm.[20,21]

• Zeta Potential, PDI, and Globule Size

After diluting liquid SMEDDS ten times in distilled water, the Malvern Zetasizer (Nano ZS90) was used to measure the zeta potential, PDI, and globule size by examining variations in light scattering brought on by the Brownian motion of the particles.[22, 23]

• Tackiness

The viscosity of the formulations (0.5 g) was measured without dilution using a Brookfield LVDV II + pro viscometer and spindle S18 at 20 rpm at room temperature.[24]

Table 1: Dolutegravir's liquid SMEDDS composition

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.

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• %Transmission

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Results and Discussion

Calculating the Saturation DG's Solubility in Surfactants, Co-Surfactants, and Oils

Finding oils and surfactants with a high solubilizing capacity for DG was the goal of the solubility investigation. Figures 2-4 illustrate how soluble DG is in different oils, surfactants, and co-surfactants. The results indicated that DG is more soluble in Tween 80, Transcutol P, and Campul MCM.

Pseudo-ternary Phase Diagram Construction

Based on the findings of the solubility investigations, Campul MCM, Tween 80, and transcutol P were selected as the oil, surfactant, and co-surfactant for the microemulsion formulation. Thirteen different surfactant mixture combinations were employed in the phase diagram analysis of DG-loaded SMEDDS to oil at different Km values (Km values of 1:1, 2:1, and 3:1). The boundary layer of the o/w microemulsion was visible in each phase diagram. The phase diagram's shaded area displays a microemulsion zone.[34]

Figure 5 displays pseudo-ternary phase diagrams at the corresponding Km values. The concentration of surfactants and co-surfactants rises in tandem with the microemulsion area.

A 3:1 ratio was to be the greatest self-micro emulsifying area. Maximum emulsification of self-micro was

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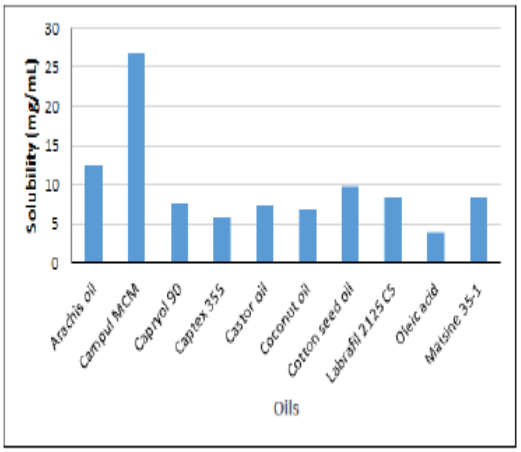

Fig. 2: Solubility of Dolutegravir in different oils

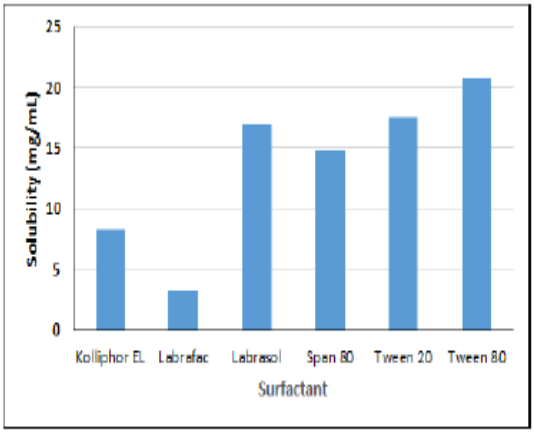

Fig. 3: Solubility of Dolutegravir in different surfactants

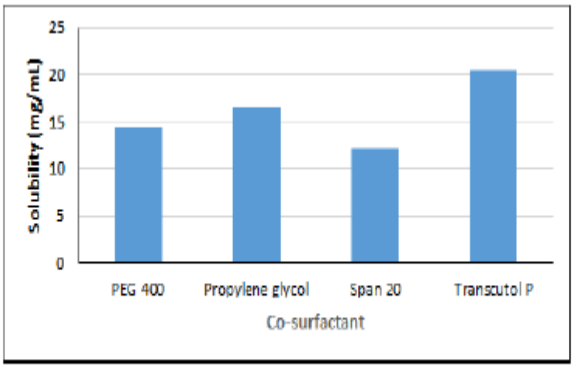

Fig. 4: Solubility of Dolutegravir in different co-surfactant

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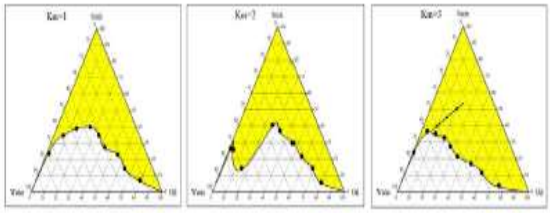

Pseudo ternary phase diagram of water at Km=1, 2, and 3, Tween 80, Transcutol P, and Campul MCM, meant to occur in a 3:1 ratio (Fig. 5). Consequently, it was determined that a 3:1 surfactant to co-surfactant ratio would be optimal for the formulation of DG-loaded SMEDDS. The microemulsion area grew along with the surfactant and co-surfactant concentrations, according to the study.

DG infused liquid SMEDDS formulation

Thirteen batches of liquid SMEDDS containing DG were successfully manufactured and used for further assessment.

Assessment of Liquid SMEDDS loaded with DG

Studies on thermodynamic stability, resilience to dilution, and evaluation of the effectiveness of self-emulsification

Table 2 summarizes the findings of the thermodynamic stability investigations, the resilience to dilution, and the evaluation of the self-emulsification efficiency. After it was determined that the formulation had passed the heating-cooling cycle test, it was centrifuged. SMEDDS was examined in the freeze-thaw stress test since it showed no phase separation in the centrifugation test. SMEDDS showed no phase separation, creaming, or cracking, and it was stable. There was no evidence of phase separation or drug precipitation, according to the robustness of the dilution study's data. The robustness of the dilution testing results led to the conclusion that there was no evidence of phase separation or drug precipitation.

Based on the evaluation of the effectiveness of the self-emulsification research, formulations L-DG 6, L-DG 7, L-DG 10, and L-DG 12 swiftly generated microemulsion grade A in less than a minute, which was transparent and somewhat blue in color. L-DG 1 to L-DG 4 and L-DG 8 and L-DG 11 quickly generated bluish-white, somewhat less transparent microemulsion grade B. Additionally, in less than two minutes, L-DG 5, L-DG 9, and L-DG 13 generated micro emulsion grade C, which had a brilliant white hue.

The dolutegravir liquid SMEDDS formulations were found to be resilient to dilution testing and to have passed early thermodynamic stability experiments. However, compared to other batches, L-DG 6, L-DG 7, L-DG 10, and L-DG 12 were shown to have higher self-emulsification test efficiency.

Results of viscosity, zeta potential, globule size, and transmittance are shown in Table 2.

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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

Measurement of cloud points and the dye solubilization test The kind of emulsion was verified using the dye solubilization test. Eosin, a pigment soluble in water, was rapidly added to the mixture, demonstrating that an o/w microemulsion had developed and that water was the continuous phase.

The cloud points of all liquid SMEDDS were found to be higher than 80 °C, suggesting that phase separation will not be an issue for mico emulsions when they are stable at physiological temperatures.

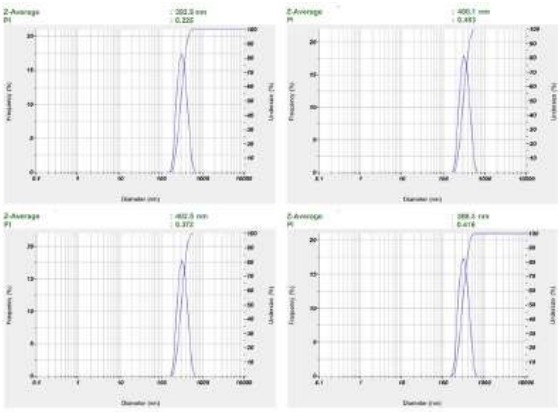

Fig. 6: Globule size of batch L-DG 6, L-DG 7, L-DG 10 and L-DG 12

Conclusion

S-smedds was created in the present effort to increase the solubility and dissolution of dg, which had a low water solubility. Based on the solubility tests of DG, campul MCM, tween 80, and transcutol p were selected as the oil, surfactant, and co-surfactant for the production of liquid smedds. Particle size, zeta potential, and percentage transmittance of liquid solids are all influenced by the concentration of oil, surfactant, and co-surfactant, as shown by the Box-Behnken factorial design. These qualities are used to choose the best batches to turn liquid into solid form. Solid smedds of DG were produced by adsorption using Neusilin US2 as a solid carrier. All batches of s-smedds were found to have improved solubility when compared to ordinary dg. Since the S-SMEDDS formulation s-DG 4 batch releases 99.86% of the DG in 120 minutes as opposed to 32.55% from ordinary DG, it was determined to be adequate.

According to the results, smedds is a potentially effective method for increasing the concurrent bioavailability, dissolution, and solubility of weakly water-soluble medications like dolutegravir.

References

1. Alshehri S, Imam SS, Hussain A, Altamimi MA, Alruwaili NK, Alotaibi F et al. Potential of solid dispersions to enhance solubility, bioavailability, and therapeutic efficacy of poorly water-soluble drugs: newer formulation techniques, current marketed scenario and patents. Drug Deliv. 2020;27(1):1625-43. Available from: doi: 10.1080/10717544.2020.1846638, PMID 33207947.

2. Sareen S, Mathew G, Joseph L. Improvement in solubility of poor water-soluble drugs by solid dispersion. Int J Pharm Investig. 2012;2(1):12-7. Available from: doi: 10.4103/2230-973X.96921, PMID 23071955.

3. Shiundu KA. Assessment of the clinical effectiveness of dolutegravirbased antiretroviral therapy among adults living with HIV at the Kenyatta National Hospital ([doctoral dissertation]. University ofNairobi).

4. Kandel CE, Walmsley SL. Dolutegravir–a review of the pharmacology, efficacy, and safety in the treatment of HIV. Drug Des Dev Ther. 2015;9:3547-55. Available from: doi: 10.2147/DDDT.S84850, PMID n 26185421.

5. Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother. 2004;58(3):173-82. Available from: doi: 10.1016/j. biopha.2004.02.001, PMID 15082340.

6. Parmar K, Patel J, Sheth N. Self nano-emulsifying drug delivery system for embelin: design, characterization and in-vitro studies. Asian J Pharm Sci. 2015;10(5):396-404. Available from: doi: 10.1016/j.ajps.2015.04.006.

7. Jaiswal P, Aggrewal G, Kaur A. Bioavailability enhancement of poorly soluble drugs by SMEDDS- A review. J Drug Deliv Ther. 2013;3(1):98-109.

8. Shukla JB, Koli AR, Ranch KM, Parikh RK. Self microemulsifying drug delivery system. Int J Pharm Pharm Sci. 2010;1(2):13-33.

9. Bandivadekar MM, Pancholi SS, Shelke N. Preparation and characterization of solid SMEDDS by adsorbent techniques to improve dissolution profile of poorly aqueous soluble drug ramipril. Int Res J Pharm. 2011;2(6):85-90.

10. Yeom DW, Son HY, Kim JH, Kim SR, Lee SG, Song SH et al. Development of a solidified self-microemulsif ying drug delivery system (S-SMEDDS) for atorvastatin calcium with improved dissolution and bioavailability. Int J Pharm. 2016 Jun 15;506(1-2):302-11. Available from: doi: 10.1016/j.ijpharm.2016.04.059, PMID 27125455.