RESEARCH ARTICLE

Solid Dispersion of Dolutegravir: Formulation Development, Characterization, and Pharmacokinetic Assessment

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ABSTRACT

A recently authorized antiviral drug called dolutegravir has solubility problems and could be a Biopharmaceutical Classification System (BCS) class II candidate. The current study aimed to improve dolutegravir's solubility and efficiency by employing the solid dispersion method. Different ratios of hydrophilic polymeric carriers, including polyethylene glycol (PEG) 6000, polyvinyl pyrrolidone (PVP) (30K), and hydroxypropyl methylcellulose (HPMC), were used. Dolutegravir (DTG) and soluplus were produced as a solid dispersion at 1:5 ratio using the solvent evaporation method. A variety of techniques were utilized to describe the solid state, including powder X-ray diffraction (XRD), differential scanning calorimetry (DSC), and fourier transform infrared spectroscopy (FTIR). Produced solid dispersion did not reveal any physicochemical interactions between the DTG and soluplus, but the X-ray diffractogram clearly showed that the drug's crystalline state had transformed to an amorphous state. DTG was released quickly from solid dispersion (92%) compared to pure drug (10.12%), physical mixture (22.06%), and commercially available DTG (62.90%). The formed solid dispersion's drug release kinetics was in line with the Higuchi Model. Finally, the rapid drug release from the solid dispersion formulation showed higher C_{max} (15.25 ± 0.40 µg/mL) compared to the physical mixture (5.11 ± 0.20 µg/mL) and pure drug (4.91 ± 0.73 µg/mL). DTG's enhanced bioavailability in experimental wistar rats (AUC: 147.99 ± 23.86 µg/h/mL) further supported this when compared to the AUC of animals administered with physical mixture (52.35 ± 4.32 µg/h/mL) and pure drug (43.32 ± 3.13 µg/h/mL). Thus, it could be inferred that by employing the solid dispersion delivery system and the hydrophilic carrier, soluplus, the bioavailability and dissolution profile of DTG could both be improved, which could be expected to improve the drug's effectiveness in treating Human immunodeficiency virus/Acquired immunodeficiency syndrome (HIV/AIDS).

Keywords: Acquired immunodeficiency syndrome, Dolutegravir, Human immunodeficiency virus, Solid dispersion, Solvent evaporation method, Soluplus.

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INTRODUCTION

Acquired immunodeficiency syndrome (AIDS), which is brought on by a specific infectious agent known as the human immunodeficiency virus (HIV), has gained notoriety in recent decades as one of the most significant health issues in the world. The causative retrovirus affects the human immune system by reducing the number of native cells, memory CD4+ T cells, macrophages, and dendritic cell activity as well as T-helper cells and native cells. [1] The World Health Organization (WHO) recently released guidelines that increased its support for the administration of anti-retroviral therapy for the care of people living with HIV. According to WHO estimates on HIV/AIDS at the end of 2021, there were 38.4 million people living with HIV worldwide, including 1.7 million children under the age of 15. Co-occurring, non-infectious diseases such as osteoporosis, type 2 diabetes, chronic renal disease, cardiovascular disease, and cancer are all very dangerous for HIV patients.[2] Drugs possess solubility issues have become the biggest challenge in the development of pharmaceuticals. Approximately 40% of the newly discovered chemical entities are insoluble.[1] Poor water solubility impedes drug's efficacy *in-vivo*, resulting in limited bioavailability, aberrant pharmacokinetic profiles, and inter-subject, inter-species variation, resulting in costly and time-consuming development.[3] The solubility of most antiviral medicines in aqueous solution is extremely poor. Thus, a variety of drug delivery techniques have been developed

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to increase the solubility of antiviral drugs, including solid dispersion, complex formation, micelles formation, liposomes, nanogels, nanoparticles, and nanocrystals.[4] Solid dispersions are increasingly being used to enhance the dissolution and solubility of drugs that have limited aqueous solubility. A polymeric solid dispersion is regarded as an effective technique to overcome low water solubility issues of an active pharmaceutical ingredient. Furthermore, these innovative technologies can control, target, or modulate drug delivery to improve the effect at the action site while reducing unintended and undesirable side effects.[5, 6]

Dolutegravir (DTG), a recently approved antiviral drug, has solubility concerns because it is a Biopharmaceutical Classification System (BCS) class II candidate. It is an integrase strand transfer inhibitor that prevents the viral DNA from being integrated into the DNA of the host cell, which is thought to be one of the key phases in the life cycle of HIV, and so inhibits the virus from replicating inside the host. DTG has a number of exceptional advantages, including a once-daily dose, a high genetic obstacle to drug resistance, and less drug interactions. DTG is available commercially in the form of DTG sodium salt. It has a bioavailability of only 16% and water solubility of less than 50 g/mL between pH 1 and 7. As a result, increasing DTG solubility and dissolution rate is required, which leads to improved oral bioavailability.[7] Since pure DTG and its salt have identical solubilities, the decision to include the salt form in the formulation was likely made more for its physical stability than for its better solubility. DTG is a model drug to formulate into solid dispersion because of its undesirable physicochemical features.[8] The purpose of the research was to produce DTG solid dispersions using a variety of polymers in order to improve solubility and dissolving rate. DTG is an antiviral drug that works by blocking the HIV integrase enzyme, which is required for viral replication.[9]

The current effort focuses on the development of solid dispersions to promote supersaturation of the DTG solution, which will improve oral bioavailability. As a result, several formulation strategies have been implemented to enhance the drug's physiochemical characteristics and bioavailability. In order to develop solid dispersions, hydrophilic polymers such as polyethylene glycol (PEG) 6000, polyvinyl pyrrolidone (PVP) (30K), and hydroxypropyl methylcellulose (HPMC) 30K, soluplus, were selected. These polymers have high water solubility, low toxicity, a low melting point, a quick solidification rate, and physiological tolerance, and are inexpensive. These properties ensure that the polymers are the best suitable carriers for solid dispersion preparation.[10] As a result of altering the ratios of these carriers, amorphous solid dispersions were formed. DTG solid dispersions were characterized using powder X-ray diffraction (PXRD), scanning electron microscopy (SEM), fourier transform infrared spectroscopy (FTIR), and dissolution studies.[9] The present initiative focused on investigating the feasibility of using a hydrophilic carrier to improve the aqueous solubility of DTG.

MATERIALS AND METHODS

DTG was received from Emcure Pharmaceuticals Ltd., Ahmedabad, India, as a gift sample. The analytical quality chemicals and solvents used in the research were all provided by S.D. Fine-Chem Ltd in Mumbai, India. In-house generated double distilled water was used in the study.

Development of DTG Solid Dispersions by Solvent Evaporation Method

Solid dispersion is one of the most often used methods for the production of water-insoluble drugs readily soluble. It is considered a good, affordable, and useful technique to increase the solubility of drugs that are not water-soluble. Four carriers, HPMC, PEG 6000, PVP 30K, and soluplus in ratios of 1:1, 1:2.5, and 1:5 (Drug: Carrier), were used to produce DTG solid dispersions using solvent evaporation. Three formulations of each polymer were formulated as a result, for a total of 12 formulations. Methanol was added to the mixture after the drug and polymer had been weighed in the proper ratios. The solvent was entirely removed from the solution using a rotary evaporator that was set to 32 ± 1°C and reduced pressure. The solution was then poured into a round bottom flask. The solid dispersions that resulted were dried and pulverized. The prepared formulations were then placed in desiccators until they were used. The 12 formulations' composition is depicted in Table 1.[11]

Characterization of DTG Solid Dispersions

Saturation Solubility Study

This study set out to quantify the extent to which the prepared solid dispersions increased drug solubility. The prepared solid dispersions' excess powder was mixed with distilled water and poured in glass vials (10 mL). In a shaker water bath, the temperature of the produced solutions was held constant for 48 hours at 37 ± 0.5°C. The mixture was then diluted, filtered using a 0.45 m membrane filter, and then examined. [7,12]

FTIR

FTIR spectrophotometer was used to obtain infrared scans of pure DTG, HPMC, PEG 6000, and PVPK 30K, Soluplus, which examine the molecular interactions between the formulation's core elements. Briefly, separate samples were blended with FTIR-grade potassium bromide (KBr) in a mortar and pestle to produce a homogeneous mixture for FTIR analysis. The prepared samples were scanned with a resolution of 4 cm^{-1} and a wave number range of 4000 to 400 cm^{-1}.[13,14]

Differential Scanning Calorimetry (DSC)

DSC was used to analyze the physical mixture (drug and polymer) and the resulting solid dispersion for their thermal behavior. The samples were heated to temperatures between 25 and 400°C while maintaining a pace of 10°C per minute to produce thermograms of the samples. Individual samples (5 mg) were weighed accurately before being sealed in an aluminum pan with a lid and crimper.[15, 16]

Table 1: Composition of the prepared dolutegravir solid dispersion and their aqueous solubility.

S.No.	*Sample Code of Formulation*	*Drug-polymer ratio*	*Drug (mg)*	*Polymer (mg)*	*Aqueous Solubility ((µg/mL)**
Drug	Pure drug (Dolutegravir)	-	10	10	4.21 ± 0.05
PM-1	PM-D-HPMC	-	10	10	4.71 ± 0.10
PM-2	PM-D-PVP	-	10	10	4.89 ± 0.15
PM-3	PM-D-PEG	-	10	10	4.98 ± 0.12
PM-4	PM-D-S	-	10	10	4.91 ± 0.32
F1	SD-D-HPMC-1	1:1	100	100	12.54 ± 0.03
F2	SD-D-HPMC-2	1:2.5	100	250	17.30 ± 0.20
F3	SD-D-HPMC-3	1:5	100	500	15.20 ± 0.32
F4	SD-D-PVP-1	1:1	100	100	22.10 ± 0.12
F5	SD-D-PVP-2	1:2.5	100	250	23.10 ± 0.32
F6	SD-D-PVP-3	1:5	100	500	25.20 ± 0.25
F7	SD-D-PEG-1	1:1	100	100	31.78 ± 0.52
F8	SD-D-PEG-2	1:2.5	100	250	34.21 ± 0.32
F9	SD-D-PEG-3	1:5	100	500	32.13 ± 0.42
F10	SD-D-S-1	1:1	100	100	35.20 ± 0.32
F11	SD-D-S-2	1:2.5	100	250	41.10 ± 0.35
F12	SD-D-S-3	1:5	100	500	45.90 ± 0.35

*All results are expressed as mean ± Std. Dev. (n = 3),
Abbreviation: Dolutegravir (D), Hydroxypropylmethylcellulose(HPMC), Polyvinylpyrrolidone (PVP), Polyethylene glycol (PEG),Soluplus (S), Solid dispersion (SD), Physical mixture (PM).

Powder X-ray diffraction (PXRD) Study

The PXRD spectra of solid dispersion, physical mixture, and DTG were recorded using a PXRD to record the X-ray diffraction patterns. PXRD spectra help explain how DTG changes from its crystalline form to its amorphous state when operated at a voltage of 30 kV and a current of 15 mA. The samples were analyzed using the 2 angle range of 1–50°, and the process parameters were set at a scan speed of 2° per minute.[16,17]

Estimation of Drug Content

Pandey *et al.*, UV-visible spectrophotometry-based method was used to estimate the amount of DTG present in the solid dispersion that had been created.[18] In a nutshell, a fairly accurate amount of solid DTG dispersion (10 mg of DTG) was dissolved in 100 mL of phosphate buffer (0.05 M, pH 6.8) while being stirred to produce an aqueous solution for the spectrum analysis of DTG. After that, a 0.45 µm membrane filter was used to filter the produced solution. Before being tested in a UV-visible spectrophotometer for absorbance at 260 nm, the filtered solution was properly diluted. A polymer blank solution was made and compared with the sample solution to avoid interference.[5,19,20] The content of DTG (%) in the solid dispersion was calculated according to eq. (1) described below:

$$\%\text{Yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \text{x } 100$$

Dissolution Studies

Using a paddle (USP type II)-based dissolution, the effectiveness of the pure drug DTG's *in-vitro* dissolution was evaluated to that of the physical mixture and solid dispersion. The dissolving investigations were then conducted utilizing the methodology outlined in the literature.[5] A dissolution flask containing 900 mL of dissolution media was used to disperse the testing materials, which included pure DTG (10 mg), a produced physical mixture (10 mg), and solid dispersion (equal to 10 mg). After sample dispersion, the media were heated to a constant 37 ± 0.5°C and swirled at a speed of 100 rpm for the duration of the experiment. The dissolution study was performed for 120 minutes. At selected time intervals (10 minutes), the samples were withdrawn, filtered (membrane filter, 0.45 µm), diluted and analyzed to measure the absorbance of the resulting solution on a UV-visible spectrophotometer at a maximum wavelength of 260 nm against the blank. The recorded absorbance values of each sample were used for the calculation of the percentage cumulative amount of release of DTG and solid dispersion. The kinetic release analysis of solid dispersion was also estimated by fitting the release data into different kinetic models such as zero order, first order and Higuchi models.[21] For 120 minutes, the dissolution investigation was conducted. The samples were taken out at predetermined intervals (10 minutes), filtered (membrane filter, 0.45 µm), diluted, and then tested for absorbance using a UV-visible spectrophotometer with a maximum wavelength of 260 nm in comparison to a blank. The percentage cumulative amount of DTG release and solid dispersion were calculated using the recorded absorbance values of each sample. The release data were fitted into various kinetic models, such as zero order, first order, and Higuchi models, to estimate the kinetic release analysis of solid dispersion.[21]

In-vivo studies

Oral bioavailability studies of solid dispersion of DTG were performed in albino wistar rats. The rats weighing 200 ± 20 gm were divided into two groups, with three rats in each group. Before starting the experiment, groups of rates have fasted overnight, but with free access to water. Halothane inhalation was used to induce a light anesthesia in the animals, and blood was taken from the retroorbital sinus in the amount of 5 mL. In accordance with a protocol that has been authorized. The institutional animal ethical committee of Columbia institute of pharmacy, Raipur, reviewed and sanctioned the protocol (CIP/IAEC/2018/127) dated November 11, 2018], blood samples were collected for the kinetic investigations at various periods. The serum was separated for analysis using HPLC after the blood was fractionated at 10,000 rpm for 10 minutes (model: Shimadzu i-series LC-2050C).[18] The maximum plasma concentration (C_{max}) and the time to achieve that concentration (T_{max}) were directly read from the plasma concentration-time profiles in order to derive non-compartmental pharmacokinetic parameters. It was determined that the area under the plasma concentration curve (AUC) was.[20]

RESULTS AND DISCUSSION

Preparation and Optimization of Solid Dispersion

Solid dispersion technique can be used to integrate hydrophobic drugs with hydrophilic polymers to produce formulations that quickly release the drug that has been trapped inside them. The solvent evaporation method is the easiest and most feasible method for the formulation of solid dispersion in laboratories. We have used methanol as a common solvent. Various formulations of DTG containing solid dispersion were prepared using hydrophilic carriers i.e., HPMC, PEG 6000 and PVP 30K, Soluplus. In order to understand the effect of drug/carrier ratio on prepared solid dispersion, the solubility profiles of drug from solid dispersion were investigated as shown in Figure 1. All of the formulations showed a significantly higher dissolution rate than the pure drug. However, at the drug/carrier ratio of 1:5 (SD-D-S-3), formulation F_{12} exhibited a significantly higher solubility profile than other formulations. Thus, formulation F_{12} was chosen as the optimal formulation for further studies.[17,21]

Solubility Studies

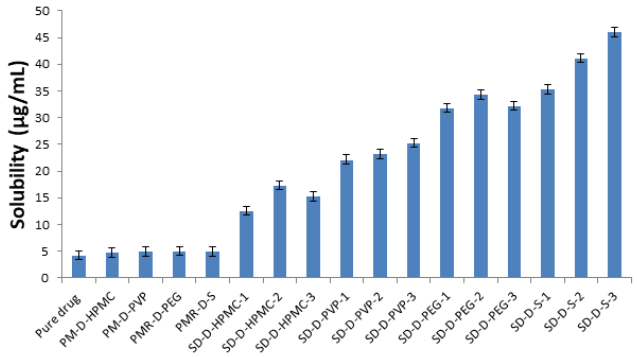
To determine solubility profiles of the physical mixture and solid dispersion of DTG ratio was used 1:1, 1:2.5, and 1:5, respectively. The low aqueous solubility of pure DTG, 4.21 ± 0.05 µg/mL, was most likely caused by both its low solubility and the high permeability profile of the BCS class II category. The physical mixture of DTG with different polymers displayed somewhat higher aqueous solubility compared to pure drug and their solubility range was between 4.21 ± 0.06 to 4.91 ± 0.32 µg/mL. The close association of the polymer with DTG, which resulted in the production of slightly modified DTG particles with higher water solubility and wettability characteristics, was thought to be the cause of the minor increase in aqueous solubility of all physical mixtures. Thereafter, The maximum solubility in Soluplus could be attributed to the surfactant's ability to self-agglomerate and produce micelles as a result. Improved hydrophilicity in liquid crystalline phases is a crucial component essential to solubilizing comparatively few drugs that are water-soluble to Soluplus. Among all formulations, the optimized (SD-D-S-3) formulation 12 (drug-carrier ratio 1:5) significantly enhanced the aqueous solubility of DTG to 45.10 ± 0.35 µg/mL. Comparing the obtained value to that of pure DTG and all physical mixtures with drug, it reveals a 10-fold increase in aqueous solubility. The solid dispersion's complexation of the carrier with the DTG particles was most likely the cause of the increased aqueous solubility. The drug's amorphous state inside this carrier may improve DTG's solubility in water.

FTIR

The interaction between the functional groups of various components of the formulation was confirmed by the FTIR analysis. The FTIR spectrum of pure DTG, prepared physical mixture of DTG polymer mixture, polymer and solid dispersion formulation are shown in Figure 2 (a-d), respectively. The units are represented as cm^{-1}. The FTIR spectrum of pure DTG is displayed in Figure 2a. In this figure, the absorption peaks observed at ~ 3273, 1696, 3165 and, 1645 cm^{-1} represent the secondary amide, carbonyl functional group, C=C stretching and O-H, respectively. The spectrum of soluplus exhibited the predominant absorption bands of inter molecularly hydrogen-bonded O-H stretching in the 3448.72 cm^{-1} range; asymmetric and symmetric C-H stretching at 2927 and 2857 cm^{-1}, respectively; ester carbonyl stretching at 1733 cm^{-1}; 1477 and C=O stretching for tertiary amide at 1628 cm^{-1}.[5] Figure 2b. The FTIR spectrum of soluplus polymer, exhibited absorption peaks at ~ 3165, 2451.4, 1361.1, 1230.7 and 3273. Figure 2c. The FTIR of the physical mixture of drug and polymer (1:2.5), exhibited absorption peaks at ~ 3274, 1695 and 2451.4, indicating that these peaks had additive characteristics of pure DTG and polymer. FTIR spectrum of formulation as shown in Figure 2d, exhibited absorption peaks at ~ 3165, 1361.1, 1584.8, 1739.1, 1528.2. The FTIR analysis supports the interaction between the functional groups of the formulation's various constituent parts. Additional peaks were visible in the solid dispersion formulation (SD-D-S-3-F_{12}). This additive peak shows that there are significant physicochemical interactions between the pure drug and carrier. As a result, the formulation's shifting of the absorption peaks points to a molecular interaction between the DTG and the carrier polymer, which may be the basis for the development of a solid dispersion of pure DTG with soluplus.[20]

DSC

The individual thermograms for the pure drug, soluplus, physical mixture, and solid dispersion were examined using DSC; they are displayed in Figure 3. The thermogram of pure DTG shows a single, sharp endothermic peak at a temperature of 333.5°C, which is the drug's melting point. Aside from that, the soluplus DSC thermogram displayed two broad endothermic peaks at 45.22 and 46.10°C. Furthermore, physical



Data represented are mean ± SD (n =3)

Figure 1: Screening of polymers to determine the aqueous solubility of Dolutegravir Sodium.

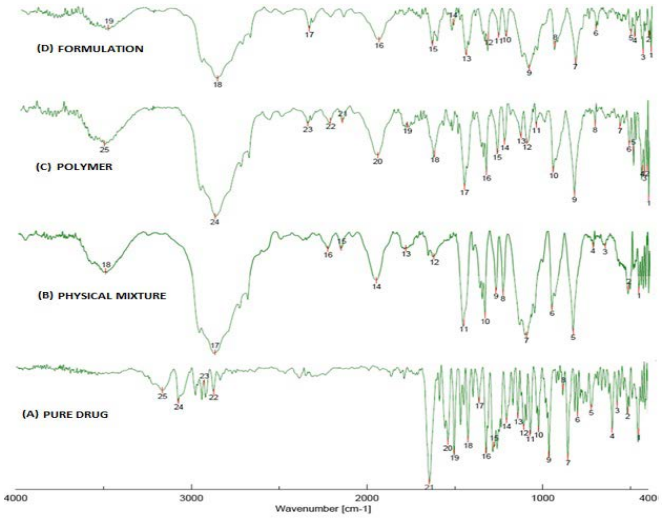


Figure 2: FTIR spectra of (a) Pure drug dolutegravir, (b) Polymer soluplus (c) The physical mixture of dolutegravir and soluplus, and (d) prepared solid dispersion (SD-D-S-3)formulation (F_{12})

mixture and solid dispersion were characterized by peak intensity reduction while compared with pure drug spectra pattern. This suggests that a lower concentration of DTG than in the formulation (SD-R-S-3-F_{12}) is present in the physical mixture and that there may be physicochemical interactions between them. It also suggests that as the thermal temperature was raised to a favorable level, the pure DTG and carrier polymer melted together and formed a partial mixture, which is why the peaks had lower intensities than those for the pure DTG and formulation (SD-R-S-3-F_{12}).

The conclusion drawn from the comparison discussed above is that pure DTG and polymeric carriers interact strongly, resulting in the formation of an amorphous solid DTG dispersion.[19]

Powder X-ray Diffraction (PXRD) study

Figure 4 displays the results of a PXRD investigation of a pure physical mixture and a solid dispersion on a 2θ scale. Thermograms of pure DTG have demonstrated its peculiar crystalline nature with melting endotherms at 3.35°C, 5.78°C, and 9.89°C on a 2θ scale. At 20.12°C and 22.13°C, the spectra

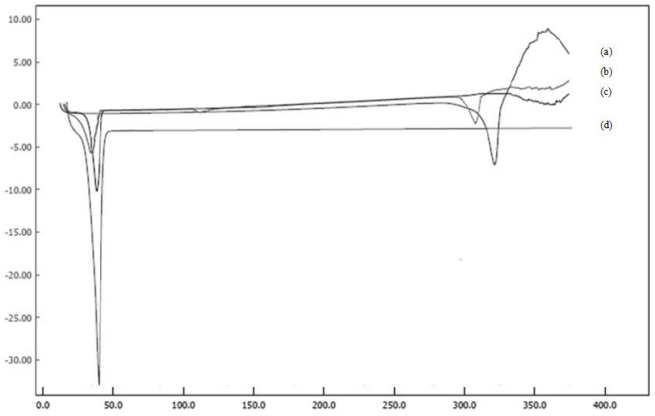


Figure 3: DSC thermograms of (a) pure ranolazine, (b) the physical mixture of ranolazine and soluplus, and (c) prepared solid dispersion (SD-D-S-3) formulation(F_{12}), (d) Polymer (soluplus)

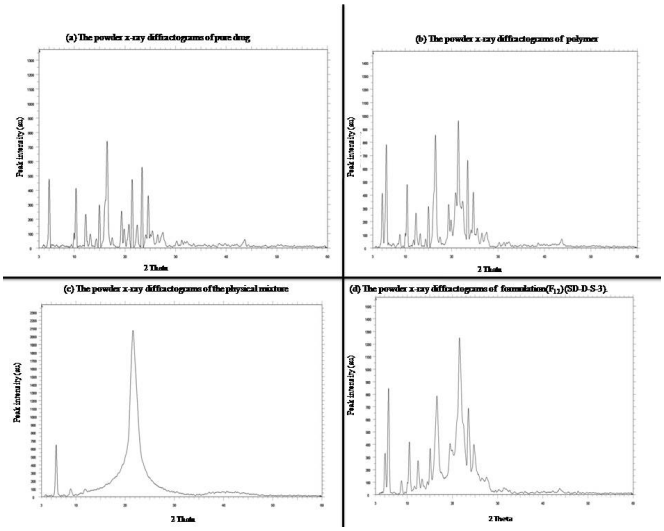


Figure 4: The powder x-ray diffractograms of (a) pure drug dolutegravir, (b) Polymer (soluplus) (c) the physical mixture of dolutegravir with soluplus, and (d) prepared solid dispersion (SD-D-S-3)formulation(F_{12}).

of Soluplus showed two strong peaks. Due to the interaction between the drug carrier and formulation, these peaks were lowered in the improved formulation along with an increase in amorphous nature. The transition from a crystalline to an amorphous state was confirmed by XRD analysis. This transformation serves to improve bioavailability by boosting solubility and dissolution rate. [21]

Amorphous and less crystalline materials contain more free energy than their corresponding crystalline forms. Therefore, altering the crystalline nature through nanosizing may be the perfect tool for improving drug molecules' solubility and dissolution rates, ultimately enhancing their bioavailability. The DSC results revealed that a sharp peak for DTG sodium was observed at 9.89, and 10.12°C. A sharp endothermic peak for Soluplus was observed at 20.12°C. The high melting point of DTG (335.7°C) indicates that the crystal lattice energy is high. Poor aqueous solubility results from several reasons, one of which is the high melting point. Therefore, any method that modifies the crystal structure and/or lowers crystal lattice

Table 2: Kinetic model analysis of *in-vitro* release data of solid dispersion formulation.

Formulation Code	*Zero Order Model*		*Frist Order Model*		*Hixon crowell Model*		*Higuchi Model*		*Korsemeyerpeppas Model*		
	R^2	$K(mg^{-1})$	R^2	$K(mg^{-1})$	R^2	$K(mg^{-1})$	R^2	$K(mg^{-1})$	R^2	*n*	$K(mg^{-1})$
F_2	0.989	2.111	0.993	-0.014	0.983	-0.039	0.967	13.121	0.986	0.771	0.734
F_6	0.980	2.049	0.989	-0.012	0.979	-0.040	0.960	12.687	0.991	0.540	0.873
F_8	0.984	2.558	0.991	-0.017	0.989	-0.053	0.956	15.779	0.984	0.378	0.891
F_{12}	0.985	2.133	0.998	-0.013	0.983	-0.041	0.985	13.207	0.982	0.490	0.966

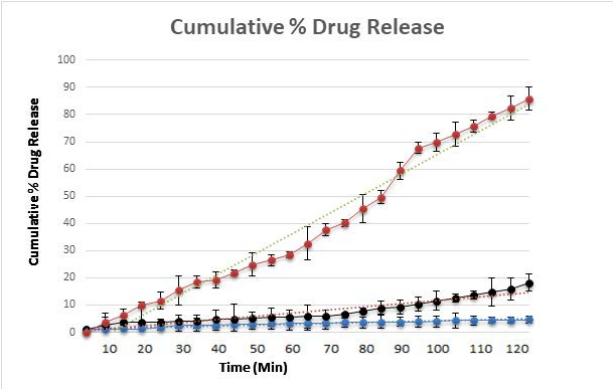


Figure 5 :*In vitro* dissolution profiles of pure dolutegravir, physical mixture and the prepared solid dispersion (SD-D-S-3) formulation(F_{12}).

Table 3: Pharmacokinetic study of ranolazine in pure drug and optimized solid dispersion formulation.

S.no.	*Parameters*	*Pure drug*	*Optimized solid dispersion formulation (SD-D-S-3-F_{12})*
1	Cmax (µg/mL)	4.91 ± 0.73	15.25 ± 0.40
2	Tmax (h)	3.00 ± 2.00	4.00 ± 0.00
3	AUC (h.µg/mL)	81.01 ± 22.53	147.99 ± 23.86
4	Kel (h-1)	0.036 ± 0.002	0.028 ± 0.004
5	t1/2 (h)	19.37 ± 1.16	25.16 ± 3.26

energy would increase the drug's solubility in water drugs can lose their crystalline nature when they are solid-state dispersed into water-soluble carrier molecules, which take their position in the crystal lattice. This results in either a partial or whole loss of crystallinity as well as a significant increase in solubility. Soluplus, a water-soluble polymer, has been shown to inhibit drug crystallization and limit its growth, producing amorphous solid dispersions with greater drug solubility and dissolution rates.

Estimation of Drug Content

The ratio 1:5 of the formulation (SD-R-S-3 F_{12}) showed the highest percentage of drug content at 97.40 0.19% w/w, while the ratios 1:2.5, 1:5, and 1:5 of the other formulations F_2, F_6, and F_8 showed lower percentages of DTG content at 93.40:0.29, 94.30:0.39, and 95.20:0.79%, respectively. The SD-R-S-3 F_{12} was among all the formulations thoroughly considered out to be optimized for further analysis.

Dissolution Studies

A slight modification to an earlier method described by Pandey *et al*., was used to evaluate the *in-vitro* dissolution of DTG from the prepared solid dispersion. The experiment was conducted with 900 mL of phosphate buffer (pH 6.8) as the dissolution media at 37 ± 0.5°C and 50 rpm for two hours. In the *in-vitro* dissolving tests on pure drug, physical mixture, solid dispersion (solid dispersion equal to 50 mg DTG), and commercial product ((Xapavir tablet containing 50 mg of DTG) was employed. In Figure 5, the dissolving profiles of DTG, physical mixture, and solid dispersion.

Pure DTG dissolved at 10.63 ± 4.125% after 120 minutes. When compared to pure DTG, the PM-D-S demonstrated a slight increase in DTG dissolution rate and extent (18.27 ± 3.146 after 120 min). Additionally, tiny particle size solid dispersion increases cell membrane adhesiveness, enhancing the bioavailability of drugs with weak water solubility. For BCS class II drugs, the rate-limiting phase is dissolution. To increase DTG bioavailability, the low water solubility of BCS-II drugs must be addressed. DTG, which is only weakly water-soluble, showed greater dissolving rates, indicating enhanced bioavailability. DTG, which is only weakly water-soluble, showed enhanced bioavailability through a faster rate of dissolution. The optimised solid dispersion formulation demonstrated the highest dissolving efficiency, with 85.14 ± 1.242% of DTG released in distilled water compared to pure DTG and a physical mixing. The solvent evaporation process may be associated with the increased solid dispersion dissolving rate. For instance, solvent evaporation transforms crystalline drugs into partially amorphized powders, increasing the rate at which pharmaceuticals with low solubility dissolve. First-order, zero-order, Higuchi, and Korsmeyer-Peppas kinetic models were used to analyse the results of solid dispersion formulations. Given that the first-order model has a higher correlation coefficient value ($R^2 = 0.998$) than the zero-order and first-order models ($R^2 = 0.985$ and 0.998, respectively), it is the best-fit kinetic model for solid dispersion formulations. Diffusion was found to be the primary process underlying the release exponent (n) for the optimum solid dispersion formulations, which is 0.49 (Table 2).

In-vivo-studies

The pharmacokinetic profile of the DTG formulation was then evaluated in rats in comparison to that of the pure drug. Table 3 provides an overview of the pharmacokinetic parameters Cmax (highest concentration attained), T_{max} (time to reach peak

concentration), AUC (area under the plasma concentration-time curve) and $t^{1/2}$. When compared to the pure drug, the solid dispersion formulation showed significantly higher plasma concentration. The solid dispersion group's C_{max} (15.25 ± 0.40 µg/mL) and AUC (147.99 ± 213.86 µg/mL) values were higher than those of the pure drug group, respectively. The improved rate of drug dissolution and subsequent absorption in rats may be the cause of the increased oral bioavailability of DTG in the solid dispersion formulation.

CONCLUSION

The study demonstrated the feasibility of using solid dispersion (SD-R-S-3-F_{12}) as a polymeric delivery strategy to enhance DTG's solubility in water. The solvent evaporation method was used to produce an amorphous solid dispersion (SD-R-S-2-F_{12}) of DTG with increasing amounts of soluplus polymer. The assessment of physicochemical characteristics (such as DSC, FTIR, and PXRD) and functional characterization studies (solubility analysis, *in-vitro* and pharmacokinetics) were employed to confirm the solid dispersion. When compared to pure DTG and a physical mixture, the water solubility, rate, and extent of DTG's dissolution were all significantly improved by the optimized solid dispersion (SD-R-S-2-F_{12}) formulation. It was discovered that the drug was released more rapidly in phosphate buffer within the first hour, which was further supported by the increased bioavailability of the drug in experimental rats. DTG's improved dissolving can be due to a number of variables, including its increased surface area, transformation into an amorphous form, enhanced dispersibility, improved wettability, and reduced particle aggregation and agglomeration. The acquired significant results further demonstrated the good viability of using soluplus as a polymeric carrier to enhance the overall biopharmaceutical characteristics of DTG and other comparable drugs with low water solubility. As a result, solid dispersion is a novel and optimistic strategy for enhancing the physiochemical and functional qualities of BCS class II drugs. In conclusion, solid DTG dispersion utilizing Soluplus would provide a potential platform for enhancing the drug's solubility in order to improve bioavailability and therapeutic efficacy against HIV/AIDS.

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AUTHOR'S CONTRIBUTION

Monika Bhairam performed the analysis, reported the results and prepared the first draft. The corresponding author Ravindra Kumar Pandey revised the calculations and prepared the final manuscript. Shiv Shankar Shukla and Beena Gidwani guided and proofread. All authors have read and approved the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCE

1. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: Review of recent advances and business prospects. Acta Pharm Sin B. 2015;5:442–53.
2. Govender RD, Hashim MJ, Khan MA, Mustafa H, Khan G. Global Epidemiology of HIV/AIDS: A Resurgence in North America and Europe. J Epidemiol Glob Health. 2021;11:296–301.
3. Krstić M, Manić L, Martić N, Vasiljević D, Mračević SĐ, Vukmirović S, *et al*.. Binary polymeric amorphous carvedilol solid dispersions: In vitro and in vivo characterization. Eur J Pharm Sci. 2020;150.
4. Himawan A, Djide NJN, Mardikasari SA, Utami RN, Arjuna A, Donnelly RF, *et al*.. A novel in vitro approach to investigate the effect of food intake on release profile of valsartan in solid dispersion-floating gel in-situ delivery system. Eur J Pharm Sci [Internet]. Elsevier B.V.; 2022;168:106057. Available from: https://doi.org/10.1016/j.ejps.2021.106057
5. Pandey R, Bhairam M, Shukla SS, Gidwani B. Colloidal and vesicular delivery system for herbal bioactive constituents. DARU, J Pharm Sci. DARU Journal of Pharmaceutical Sciences; 2021;29:415–38.
6. Mandal DSC. Good Laboratory Practices: Present Status and Future Expectations. Indian Pharm Assoc. 2021;
7. Lakshman D, Chegireddy M, Hanegave GK, Sree KN, Kumar N, Lewis SA, *et al*.. Investigation of drug-polymer miscibility, biorelevant dissolution, and bioavailability improvement of Dolutegravir-polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer solid dispersions. Eur J Pharm Sci [Internet]. Elsevier B.V.; 2020;142:105137. Available from: https://doi.org/10.1016/j.ejps.2019.105137
8. Noorbasha K, Nurbhasha S. A new validated stability-indicating RP-HPLC method for simultaneous quantification of dolutegravir and lamivudine in bulk and pharmaceutical dosage form. Futur J Pharm Sci. Future Journal of Pharmaceutical Sciences; 2020;6.
9. Mutalik SP, Mullick P, Pandey A, Kulkarni SS, Mutalik S. Box–Behnken design aided optimization and validation of developed reverse phase HPLC analytical method for simultaneous quantification of dolutegravir sodium and lamivudine co-loaded in nano-liposomes. J Sep Sci. 2021;44:2917–31.
10. Tekade AR, Yadav JN. A review on solid dispersion and carriers used therein for solubility enhancement of poorly water soluble drugs. Adv Pharm Bull [Internet]. 2020;10:359–69. Available from: https://doi.org/10.34172/apb.2020.044
11. Kim NA, Oh HK, Lee JC, Choi YH, Jeong SH. Comparison of solubility enhancement by solid dispersion and micronized butein and its correlation with in vivo study. J Pharm Investig [Internet]. Springer Singapore; 2021;51:53–60. Available from: https://doi.org/10.1007/s40005-020-00486-9
12. Telange DR, Ukey SA, Hemke AT, Umekar MJ, Pethe AM, Kharkar PS. LIPOID SPC-3-Based Coprecipitates for the Enhancement of Aqueous Solubility and Permeability of Ranolazine. J Pharm Innov. Journal of Pharmaceutical Innovation; 2021;16:643–58.
13. Priya Dharshini K, Ramya Devi D, Banudevi S, Vedha VH. In-vivo pharmacokinetic studies of Dolutegravir loaded spray

dried Chitosan nanoparticles as milk admixture for paediatrics infected with HIV. Sci Rep [Internet]. Nature Publishing Group UK; 2022;12:1–12. Available from: https://doi.org/10.1038/s41598-022-18009-x

14. Tran TTD, Tran PHL. Insoluble polymers in solid dispersions for improving bioavailability of poorly water-soluble drugs. Polymers (Basel). 2020;12.
15. Chaudhary S, Nair AB, Shah J, Gorain B, Jacob S, Shah H, *et al.*. Enhanced Solubility and Bioavailability of Dolutegravir by Solid Dispersion Method: In Vitro and In Vivo Evaluation—a Potential Approach for HIV Therapy. AAPS PharmSciTech. AAPS PharmSciTech; 2021;22:1–12.
16. Bhairam M, Pandey RK, Shukla SS, Gidwani B. Enhanced solubility and bioavailability of ranolazine by solid dispersion method in vitro and in vivo evaluation. Int J Health Sci (Qassim). 2022;6:3729–48.
17. Srinivas M, Singh A. Formulation and Optimization of Dolutegravir Fast Dissolving Tablets Using Various Solubility Enhancement Methods. Int J Life Sci Pharma Res. 2021;11:51–9.
18. Wang X, Penchala SDi, Amara A, Else L, McClure M, Boffito M. A validated method for quantification of dolutegravir using ultra performance liquid chromatography coupled with uv detection. Ther Drug Monit. 2016;38:327–31.
19. Sriveni T, Naveen V, Rupa VS, Renuka A, Porika S, Akiful Haque M, *et al.*. Development and validation of dolutegravir in bulk and formulation: An anti-retroviral drug using uv-spectroscopy. Int J Pharm Qual Assur. 2021;12:57–60.
20. Serag A, Hasan MA, Tolba EH, Abdelzaher AM, Elmaaty AA. Analysis of the ternary anti-retroviral therapy dolutegravir, lamivudine and abacavir using UV spectrophotometry and chemometric tools. Spectrochim Acta - Part A Mol Biomol Spectrosc [Internet]. Elsevier B.V.; 2022;264:120334. Available from: https://doi.org/10.1016/j.saa.2021.120334
21. Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga Y, Ohike A, *et al.*. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine. J Control Release. 2005;108:386–95.