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Original Article

# Dolutegravir Solid Dispersions as Oro-Dispersible Tablets: To Ameliorate the Integrase Inhibition Effect

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## ABSTRACT

**Background:** Dolutegravir (DTG) is an integrase strand transfer inhibitor that prevents the integration of viral DNA into host cell DNA, which is one of the key phases in the life cycle of HIV, preventing the virus from multiplying inside the host. However, its therapeutic efficacy is constrained by its weak water solubility. **Objectives:** A simple conventional approach using Sulfobutylether-β-Cyclodextrin (SBE β-CD) and Soluplus® as carriers has been used to ameliorate the effect of DTG. Dispersible tablets have the great advantage of immediately converting a solid into a liquid after administration. Due to that reason, solid dispersions are converted into Oro dispersible tablets by using super disintegrant locust bean gum. **Materials and Methods:** Three methods were used to prepare solid dispersions: kneading, rota solvent evaporation, and lyophilization. The ratio of DTG to carrier varied between 1:1, 1:2, 1:3, and 1:4 w/w. Optimized DTG solid dispersions were then used in the direct compression method to create Oro-dispersible tablets with the addition of super disintegrants, i.e., locust bean gum and Croscarmellose Sodium. Prepared tablets were evaluated. **Results:** The drug release for pure DTG is only 14.6%. Lyophilization with SBE β-CD and Soluplus® led to the dissolution of DTG up to 86.17% and 98.11% after 2 hr. The application of Soluplus® significantly improved the solubility and dissolving rate of DTG. The Oro-dispersible tablets made with 12% locust bean gum were the best among the tested formulations. They disintegrated rapidly, taking only 11 sec, and showed the highest dissolution rate of 99.89%, better than the marketed INSTGRA™-50 mg tablets. Optimized rapid disintegration tablets of Dolutegravir can target integrase and potentially inhibit HIV.

**Keywords:** Ameliorative effect, Sulfobutylether-β-cyclodextrins, Lyophilization, Locust bean gum, and Soluplus®.

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## INTRODUCTION

Dolutegravir (DTG) is an integrase strand transfer inhibitor that prevents the integration of viral DNA into host cell DNA, which is thought to be one of the key phases in the HIV life cycle. It prevents the virus from multiplying inside the host.[1] DTG has multiple exceptional advantages, including a dosage frequency (a once-daily dose), a high genetic barrier to drug resistance, which helps to bind the drug itself covalently with the virus and produces inhibitory action even if the virus strands are changed, and fewer medication-drug interactions. Compared to other Antiretrovirals (ARVs), it is highly tolerated and metabolically compatible. It is a BCS class II medication with a high protein binding (98.9%),[2] less bioavailability (21%),[3] and restricted aqueous solubility of 0.1 mg/mL at 35°C.[4] Drug-metabolizing enzymes and efflux transporters also decrease the systemic bioavailability of DTG in the cell components and tissues, resulting in rapid clearance and constrained permeability. Due to the inherent difficulties in creating a suitable dosage form, solubility improvement of such components is crucial to drug delivery research. Numerous formulation strategies, such as surface modification, solid dispersion, nanoformulation, complexation, etc., were developed to address the problem. Solid dispersions are straightforward, convenient, and affordable.[5]

The current research aimed to develop a solid dispersion of Dolutegravir that would dissolve rapidly in the oral cavity and improve the rate of dissolution of the DTG. To develop solid dispersions, three generations of polymers are selected (mannitol-crystalline carrier, Polyethylene Glycol (PEG 4000), polyvinyl pyrrolidone (pvpK90), Hydroxypropyl Methylcellulose (HPMCE5LV), Sulfobutylether-β-cyclodextrin-Amorphous carrier, Gelucire 44/14, poloxamer 188, poloxamer 407and soluplus®-carrier+surfactant polymer).[6] Direct compression methods was used to formulate Oro-dispersible tablets by using optimized DTG solid dispersions with super disintegrants, i.e.,

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locust bean gum and Croscarmellose Sodium.[7] In addition, a comparison analysis was conducted between the invitro dissolution profile of the optimized tablet and the commercial product (INSTGRA™-50 mg).

## MATERIALS AND METHODS

Natco Pharma, Hyderabad, India, provided Dolutegravir with a complimentary sample. We received complimentary samples of Soluplus®, Poloxamer 188, and 407 from BASF, INDIA Ltd. Locust bean gum was obtained as a gift sample from Lucid Gums, Mumbai, India, SBE β-CD (CyDex Inc., USA). Hydroxy propyl methyl cellulose E5LV (HPMCE5LV), Polyvinyl Pyrrolidine K90 (PVPK90), Mannitol, and Polyethylene Glycol (PEG-4000). The remaining chemicals and solvents used in this research were purchased from Asian Scientific Instruments, Hyderabad, India.

### Experimental Methods

#### *Saturation solubility study*

The drug saturation solubility was assessed in distilled water and several buffers ranging in pH from 1.2 to 7.4. Glass vials (5 mL capacity) containing 3 mL of the various pH buffers and distilled water was used.[8] Each vial was filled with excess DTG and then stopper-sealed. Vials were placed in a shaking water bath. The constant temperature was maintained throughout the process at about 37±0.5ºC, while the shaking was done in 48 hr at a speed of 50 rpm. Then, the samples are filtered by using 0.45 mm filter papers. Then, the filtrate was analyzed using a UV-visible spectrophotometer (UV 1700, Shimadzu, Japan) at 260 nm.[9]

### Phase solubility study

Phase solubility studies with various carriers, including mannitol, PEG 4000, PVPK90, Poloxamer 188 and 407, Gelucire 44/14, Soluplus®, Sulfobutylether-β-cyclodextrins, and HPMC E5 LV, were used to determine the best carrier for Dolutegravir.[10]

Distilled water was used to make solutions of various concentrations, as presented in Table 2. An excess quantity of DTG was mixed with each polymeric aqueous solution in glass vials before being shaken for 72 hr at room temperature in a biological shaker (Orbital shaker SI 300, Jeio Tech, Korea). A 0.45 mm membrane filter was used to filter the contents after centrifuging them at 4000 rpm for 15 min. Spectrophotometric analysis (UV-visible spectrophotometer-UV 1700, Shimadzu, Japan) was used to determine the solubility at 260 nm.[11]

### Preparation of DTG Solid Dispersions (SD)

The method used to prepare solid dispersions must be economical and can enhance stability and prevent product degradation during the process. Kneading, solvent evaporation by rotary evaporator, and lyophilization were used to consider these factors. Details are summarized in Table 1.

### Kneading technique

The DTG and carrier were weighed and placed in a mortar at 1:1, 1:2, 1:3 and 1:4 (w/w). The mixture was mixed with methanol for 20 min until a damp mass was obtained. The resulting mass was crushed, dried at 40 degrees Celsius, and passed through a No. 100.[9]

### Solvent evaporation by rota evaporator

Drug and polymer were accurately weighed in proportions: In a mortar and pestle, 1:1, 1:2, 1:3, and 1:4(w/w) were thoroughly blended. After that, the mixture was properly dissolved in methanol to produce a solution. The resulting solution was then transferred into a Rotary Evaporator (RE100-Pro) and vacuum dried between 45-50ºC and 60 revolutions per minute. The dehydrated mass was scraped off, collected, and stored in a desiccator.[12]

### Lyophilization method

The drug (API): carrier ratios of 1:1, 1:2, 1:3, and 1:4(w/w) were used to prepare solid dispersions by using the lyophilization method. Dolutegravir dissolves in 1 mL of methanol. On the other hand, Sulfobutylether-β-cyclodextrin and Soluplus® dissolve separately in 20 mL of distilled water. Then, Drug and carrier solutions are homogenized by using a magnetic stirrer. When the mixture is uniform, it is dried using a freeze dryer (FD5508, Skadi, Europe), and the solid dispersions are then stored in a sealed container and placed in a desiccator until they are needed again.[13,14]

### Characterization of Solid Dispersions

#### *Drug excipients interaction study by FTIR (Fourier transform infrared spectrophotometry)*

To verify interactions between the API and selected carriers, the FTIR spectrum of the drugs was recorded using an Agilent Cary 630 FTIR (Shimadzu, Japan). The range of the instrument used was 400 to 4000 $cm^{-1}$. The pure drug's FTIR spectra, selected polymer FTIR spectra, and the drug and polymer-optimized formulations were examined separately. The sample was pressed to an appropriate size disc for measurement after being grounded with KBr.[15]

### Differential scanning calorimetry (DSC)

Thermal analysis of dolutegravir was performed using TA instruments, DSC2500, TRIOS Software version 5.5.0323. In DSC, the sample's heat change rate is measured concerning temperature when heated at a controlled rate under a given environment (N2).[16]

### X-ray Powder Diffraction (XRPD)

The powder diffraction analysis of Pure drug and optimized polymer was obtained using a high-resolution X-ray

diffractometer (Malvern panalytical empyrean 3). The scanning angle ranged from 0-40° of 2θ at 40 kV with Cu.[17]

## Scanning electron microscopy

A Scanning Electron Microscope (SEM) (FEI Quanta FEG 250, Netherlands) was used to study the surface morphology and shape of the prepared solid dispersions. With the help of double-sided adhesive tape and gold splatter coating, the samples were mounted on the aluminium studs.[12]

## Estimation of Drug content

Dolutegravir, 50 mg of an equivalent solid dispersion, is placed in 100 mL of a volumetric flask. One mL of methanol is added to solubilize dolutegravir, and then add pH 6.8 phosphate buffers to make up the final volume. Then, the samples were spectrophotometrically (UV-visible spectrophotometer, UV 1700, Shimadzu, Japan) analyzed to determine the drug content at 260 nm.[15]

## *In vitro* dissolution of solid dispersions

USP Type-II (model DS 8000, Lab India, Mumbai, India) paddle-type dissolution test apparatus performs *in vitro* dissolution studies. Dolutegravir, 50 mg of an equivalent solid dispersion, is placed in 900 mL of pH 6.8 phosphate buffer to continue the *in vitro* dissolution studies; during the process, periodically withdraw the aliquots and replace the same volume of buffer to maintain the sink conditions. The withdrawn aliquots were filtered using 0.45 mm filter paper and analyzed spectrophotometrically (UV-visible spectrophotometer-UV 1700, Shimadzu, Japan) at 260 nm.[10,11,18]

## Development of Oro-Dispersible Tablets (ODTS) With Solid Dispersions

The various formulations used in the study are presented in Table 3, and they were used to create Oro-dispersible tablets that contained 50 mg equivalent weight of Dolutegravir (DTG) solid dispersion. The powder mixer was compressed into tablets using a direct compression method with Minipress, an 8-station rotary punch with an 8 mm diameter tableting compression machine.[9] The compressed tablets underwent official and unofficial examinations and were packaged in airtight, light-resistant, and moisture-proof containers. The die and punch's surface were lubricated with magnesium stearate before compression.[7] Solid dispersion is one of the most important techniques for increasing a drug's solubility, dissolution, and bioavailability. Dispersible tablets can immediately convert a solid into a liquid after administration. Due to that reason, solid dispersions are converted into Oro dispersible tablets.[9]

**Table 1: The composition of Dolutegravir dispersions.**

| Code | Composition | Ratio | Method |
|---|---|---|---|
| F1-F4 | Drug+Soluplus® | 1:1,1:2,1:3 and 1:4 | Kneading method |
| F5-F8 | Drug+Soluplus® | 1:1,1:2,1:3 and 1:4 | Rota solvent evaporation method |
| F9-F12 | Drug+Soluplus® | 1:1,1:2,1:3 and 1:4 | Lyophilization method |
| F13-F16 | DTG+sulfobutylether β- CYCLODEXTRINS | 1:1,1:2,1:3 and 1:4 | Lyophilization method |
| F17-F20 | DTG+sulfobutylether β- CYCLODEXTRINS | 1:1,1:2,1:3 and 1:4 | Rota solvent evaporation method |
| F21-F24 | DTG+ sulfobutylether β- CYCLODEXTRINS | 1:1,1:2,1:3 and 1:4 | Kneading method |

**Table 2: Phase Solubility (mg/mL) of Dolutegravir with selected carriers at various concentrations.**

| Carrier concentration (% w/v) | 2 | 5 | 10 |
|---|---|---|---|
| Mannitol | 336.16±12 | 794.56±20 | 1359.92±21 |
| Polyvinyl pyrrolidine (PVPK90) | 290.32±15 | 641.76±19 | 1207.12±12 |
| Polyethylene Glycol (PEG 4000) | 488.96±10 | 855.68±08 | 1451.6±15 |
| Hydroxy Propyl Methylcellulose (HPMCE5LV) | 244.48±21 | 595.92±14 | 1100.16±19 |
| Soluplus® | 2689.4±21 | 3275.6±19 | 38640±15 |
| Gelucire 44/14 | 213.92±12 | 397.28±06 | 886.24±11 |
| Sulfobutylether-β-cyclodextrin | 2163.6±20 | 2759.20±15 | 33670±02 |
| Poloxamer 188 | 1451.6±12 | 2842.08±19 | 3972.8±21 |
| Poloxamer 407 | 1757.2±22 | 3132.4±15 | 4247.84±14 |

* For each value, the mean±standard deviation is shown ($n$=3).

**Table 3: Composition of tablets containing Dolutegravir solid dispersions**

| Ingredients (mg) | L1 | L2 | L3 | L4 | C1 | C2 | C3 | C4 |
|---|---|---|---|---|---|---|---|---|
| Solid dispersion equivalent weight of Dolutegravir | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Locust bean gum | 6.25 | 12.5 | 18.75 | 25 | | | | |
| Croscarmellose Sodium | - | - | - | - | 6.25 | 12.5 | 18.75 | 25 |
| Avicel PH 101 | 138.75 | 132.5 | 126.25 | 120 | 138.75 | 132.5 | 126.25 | 120 |
| Talc | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Magnesium stearate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |

## Evaluation of Oro-Dispersible Tablets of Dolutegravir

### *Drug content*

The process involves weighing and grinding 20 tablets. Using a UV-visible spectrophotometer (UV 1700, Shimadzu, Japan), a sample of the powder containing 50 mg of the equivalent weight of solid dispersions of DTG was dissolved in 100 mL of pH 6.8 buffer, filtered, and then diluted as necessary.[7]

## Hardness

A testing tool (Monsanto hardness tester) determined the tablets' hardness. For mechanical stability, tablets with a hardness of 4-5 kg/cm$^2$ are considered sufficient.[19]

## Uniformity of weight (weight variation)

20 tablets were randomly selected from each batch and assayed gravimetrically on an individual tablet basis. The mean weight as well as standard deviation were calculated.[19]

$$\%\ deviation = \frac{\text{Individual weight} - \text{average weight}}{\text{averge weight}} \times 100$$

## Thickness and diameter

Vernier calipers were used to determine the thickness and diameter of the tablet.[20]

## Friability

Ten tablets were randomly selected, dusted, and weighed to evaluate the degree of friability of each batch. The tablets were placed in a Roche friabilater and subjected to tumbling action at 25 revolutions per minute for 4 min. Then, the tablet was again dusted and reweighed to determine the % weight loss.[18]

$$\%\ \text{friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

## *In vitro* disintegration time

A modified disintegration test device was utilized to calculate the tablet disintegration time. A tablet was placed in the center of a Petri dish filled with double-distilled water and gently shaken. The time it took for the pill to break down into tiny particles completely was noted.[21]

## Wetting Time

To test the water absorption ratio (R) of a tablet, a folded piece of tissue paper was placed on a culture plate with 6 milliliters of distilled water and a diameter of 6.5 cm. The tablet was then placed on the paper and the immersion time was recorded. Afterward, the weight of the wet tablet was measured, and the following formula was used to calculate the water absorption Ratio (R):[20]

$$R = \frac{Wa - Wb}{Wb} \times 100$$

$W_a$ and $W_b$ are the tablet's weight after and before the study.

## *In vitro* dissolution Studies of Dolutegravir tablets

The compressed tablets release studies are performed using a paddle type II dissolution test apparatus by placing 900 mL of phosphate buffer pH 6.8 with 100 rpm paddle speed at 37±0.5°C. periodically withdrawn the samples and replaced the same amount in the dissolution basket; the samples were filtered using pore size 0.45 µm Whatman filter paper and analyzed using UV 1700, Shimadzu, Japan spectrophotometer at 260 nm.[16]

## Comparison of dissolution profiles

The similarity factor f2 as defined by the FDA (Food and Drug Administration) and EMEA (European Agency for the Evaluation of Medicinal Products) is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test and reference products. When the two dissolution profiles are identical, f2=50*log (100)=100, and when the dissolution of one product (test or reference) is completed before the other begins, f2=50 * log {(1+1/n Σ (100) 2) -0.5 * 100}=-0.001, which can be rounded to 0:[7,29]

$$f2 = 50 * \log\left\{\left[1 + \left(1/n\right)\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]^{-0.5} * 100\right\}$$

Where *n*=number of dissolution time points,

$R_t$ and $T_t$ are the reference and test dissolution values at time t.

## Dissimilarity factor ($f_1$)

f1 measures the percent error between two curves over all time points. The percent error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles. It is generally accepted that values of f1 between 0- 15 do not indicate dissimilarity.[7,29]

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100$$

Where n is the sampling number, R and T are the % dissolved of reference and test products at each time point j.

## Stability testing

The formulated Oro dispersible tablets are evaluated for stability by exposing them to the environmental conditions (temperature and pressure) at 25°C±2°C/60±5% relative humidity and 40±2°C/75±5% relative humidity. The exposed tablets are evaluated for any changes in the properties of tablets (i.e. average weight, hardness, percentage friability, drug content, disintegration time, and release profiles of the drug) for 3 months and 6 months.[19]

# RESULTS

## Saturation solubility

Saturated solubility studies show that DTG has better solubility in phosphate buffer at pH 6.8 (0.792 mg/mL). A phosphate buffer with pH 6.8 was chosen as the dissolution medium for Dolutegravir.[20] The data for the saturated solubility test is shown in Figure 1.

## Phase solubility study

Based on solubility studies, the solubility of DTG was tested in different carriers, and the results are presented in Table 2. Based on phase solubility studies, SBE β-CD and Soluplus® were selected as carriers for solid dispersion development because a greater increase in drug solubility was observed in their aqueous solutions. The solubility of Dolutegravir in distilled water is low, only 89±02 µg/mL. However, by adding Soluplus® to a 10% aqueous solution, the solubility of DTG was increased to

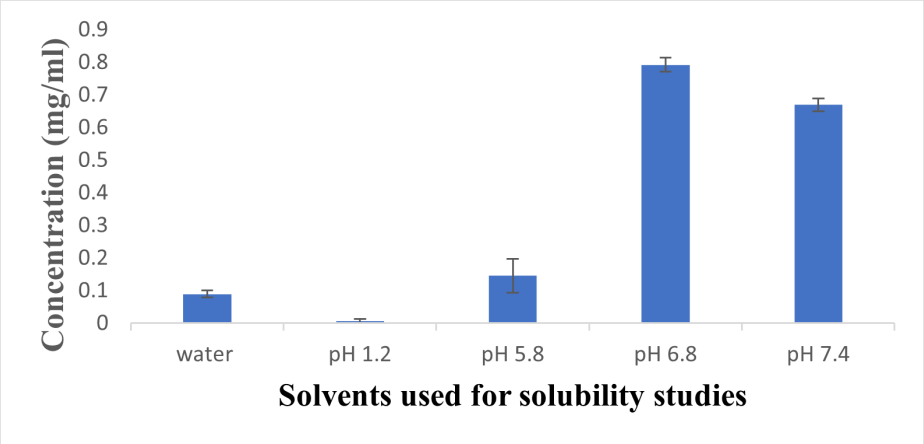


**Figure 1:** Saturation solubility of Dolutegravir. * For each value, the mean±standard deviation is shown (*n*=3).

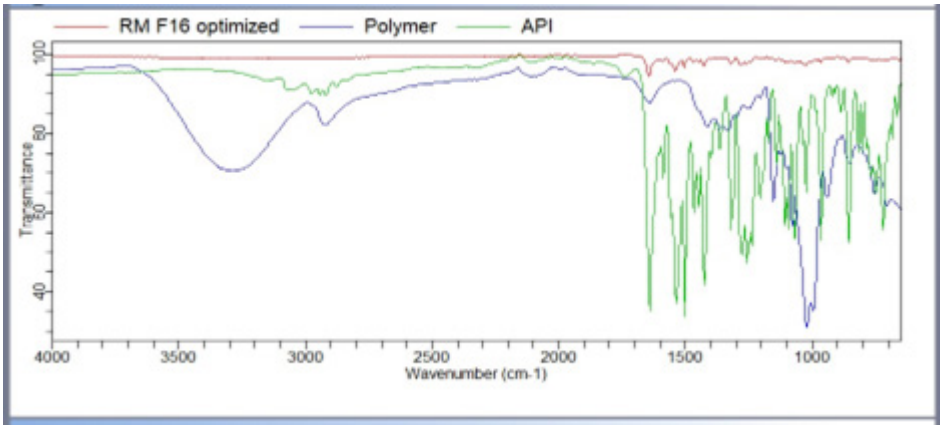


**Figure 2:** FTIR spectra of optimized formulation, polymer-sulfobutylether β-cyclodextrin and API-Dolutegravir.

38640±15 µg/mL. In comparison, when SBE β-CD was used, the solubility of DTG was increased to 33670±02 µg/mL, an increase of 434 and 378 times, respectively. Therefore, for further studies, Soluplus® and SBE β-CD were used.

## Characterization of solid dispersions of dolutegravir

### *Drug-excipient interaction studies*

### *Fourier-transform infrared (FTIR) analysis*

FT-IR studies determine drug carrier interactions. The FTIR spectra of optimized formulation, Polymer-Soluplus®, and API-Dolutegravir are depicted in Figure 2. The FT-IR spectra of pure DTG showed stretching vibrations at 3373 $cm^{-1}$(N-H), 1696 $cm^{-1}$ (C=O), and 1545 $cm^{-1}$ (C=C). The drug's purity is confirmed by the fact that these peaks align with the molecular structure of dolutegravir. The FTIR spectrum of Soluplus® showed N-H stretching at 3238 $cm^{-1}$, C=O stretching at 1604 $cm^{-1}$, and C=C vibration at 1556 $cm^{-1}$. FTIR spectra of the optimized formulations reveal several low-intensity DTG absorption bands and demonstrate weak drug-polymer interactions.[9,10] The formulation spectrum retains the peaks corresponding to the API's N-H stretching, C=O stretching, and C=C stretching vibrations. The stability of these peaks shows that the excipients do not cause any chemical reactions or changes to the drug's functional groups during the formulation process. This discovery is essential to guaranteeing Dolutegravir's chemical integrity in the improved formulation.

## Differential Scanning Calorimetry (DSC) study

Figure 3 shows the thermograms of the optimized formulation, Soluplus®, and dolutegravir API. In the thermogram of the pure drug, the endothermic melting peak is 242.16°C, indicating the crystalline nature of the DTG. The Soluplus has an exothermic peak at 141.8°C. On the other hand, the optimized formulation does not exhibit any drug-related endothermic peak. This indicates that the pure DTG in the optimized formulation has completely transformed to an amorphous state.[9,22] The observed shift in peak temperature and considerable drop in enthalpy in the F12 indicates a transition of Dolutegravir from its crystalline form to an amorphous state. Amorphization is often related to higher rates of solubility and dissolution, which can increase the drug's bioavailability.

## Powder X-ray Diffraction

Figure 4 shows the 2θ diffraction angles. The DTG diffraction pattern showed a crystalline nature as indicated by the internal peaks at 6.4,19.0,19.7,24.4 and 29.9 degrees; Soluplus® have peaks at 9.01°, 12.51°, 17.80°, 19.60°, 22.78°, 24.33°, 27.04°, and 35.88° optimized formulation. They are showing a significant decrease

**Table 4: Results of Pre-compression-properties**

| Sl. No. | Formulation | Bulk density (g/cm3) | Tapped density (g/cm3) | Angle of repose (○) | Carr's index (%) | Hausner's ratio |
|---|---|---|---|---|---|---|
| 1 | L1 | 0.5±0.002 | 0.617±003 | 21.61±004 | 10±002 | 1.11±002 |
| 2 | L2 | 0.5.783±0.001 | 0.732±005 | 23.96±003 | 9.34±003 | 1.126±003 |
| 3 | L3 | 0.523±0.004 | 0.89±002 | 23.05±002 | 11.2±008 | 1.168±005 |
| 4 | L4 | 0.535±003 | 0.610±006 | 23.45±008 | 11.74±001 | 1.13±007 |
| 5 | C1 | 0.635±006 | 0.669±005 | 22.05±005 | 14.50±004 | 1.126±003 |
| 6 | C2 | 0.566±001 | 0.75±004 | 21.08±008 | 13.06±006 | 1.103±005 |
| 7 | C3 | 0.525±002 | 0.709±005 | 23.05±006 | 12.81±004 | 1.145±002 |
| 8 | C4 | 0.552±007 | 0.65±001 | 21.41±001 | 17.36±005 | 1.150±003 |

* For each value, the mean±standard deviation is shown (*n*=3).

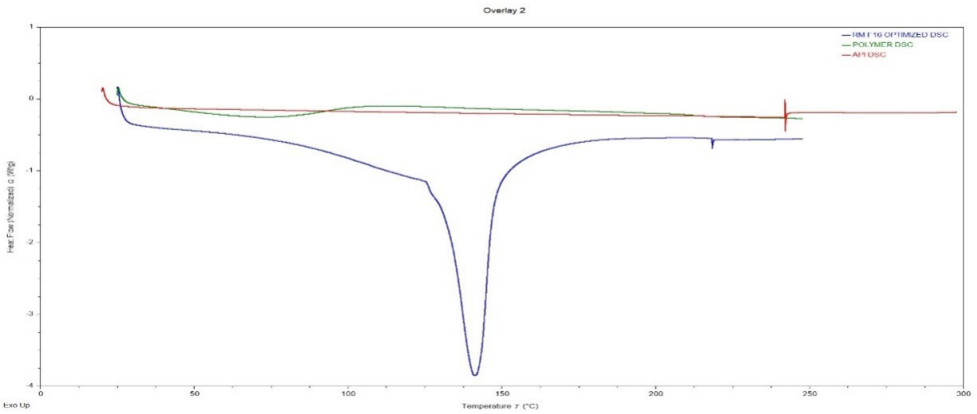


**Figure 3:** Thermograms of F12-optimized formulation, polymer-sulfobutylether β-cyclodextrin, API- Dolutegravir.

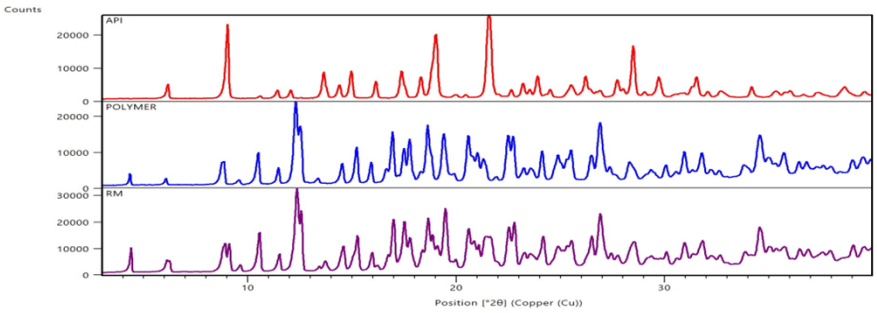


**Figure 4:** XRD patterns of a. API-Dolutegravir b. Polymer- sulfobutylether β-cyclodextrin and c. F12-optimized formulation.

**Table 5 Evaluation of post-compression parameter (*For each value, the mean±standard deviation is shown (*n*=3)**

| Post compression parameters | L1 | L2 | L3 | L4 | C1 | C2 | C3 | C4 |
|---|---|---|---|---|---|---|---|---|
| Diameter (mm) | 6.95±0.01 | 6.91±0.02 | 6.89±0.02 | 6.99±0.03 | 6.42±0.04 | 6.45±0.02 | 6.42±0.05 | 6.41±0.03 |
| Thickness (mm) | 3.74±0.02 | 3.71±0.05 | 3.72±0.04 | 3.73±0.03 | 3.81±0.06 | 3.79±0.07 | 3.80±0.02 | 3.80±0.05 |
| Friability (%) | 0.59±0.04 | 0.48±0.01 | 0.38±0.01 | 0.24±0.03 | 0.84±0.06 | 0.87±0.04 | 0.70±0.02 | 0.68±0.01 |
| Hardness (kg/cm2) | 3.32±0.15 | 3.59±0.10 | 4.25±0.20 | 4.98±0.10 | 3.56±0.72 | 3.87±0.49 | 3.56±0.77 | 3.49±0.56 |
| Wetting time (sec) | 19.18±1.3 | 16.09±1.5 | 15.10±0.1 | 12.8.23±0.1 | 78.31±2.1 | 53.16±4 | 42.11±1 | 39.23±3 |
| *In vitro* disintegration time (sec) | 19.13±1 | 17.30±2 | 15.51±2 | 12.8±1 | 59.20±5 | 53.32±4 | 42.21±6 | 28.5±5 |
| Drug content (%) | 99.45±0.15 | 98.99±0.25 | 99.28±0.70 | 99.89±0.30 | 97.75±1.03 | 96.59±0.56 | 98.22±0.87 | 97.27±0.92 |
| Weight variation | 200.21± | 201.46±1.9 | 200.67±1.1 | 200.55±2.2 | 201.48± | 201.04±2.0 | 200.48±1.4 | 200.45±0.9 |

**Table 6: Similarity factor ($f_2$) and Differential factor ($f_1$) Calculations.**

| Formulation | Similarity factor(f2) | Differential factor (f1) |
|---|---|---|
| L1 | 79.14 | 21 |
| L2 | 89.34 | 8 |
| L3 | 92.27 | 6 |
| L4 | 98.19 | 4 |

in the degree of crystallinity, as evident from the disappearance of sharp distinctive peaks keeping somehow the base characteristics of the initial one. In the optimized formulation, no characteristic peaks indicate that the compound was in the amorphous state in the final optimized formulation.[16,23]

## Morphologies of DTG-SD formulations

The shape and morphology of the surface of the prepared solid dispersions were examined using Scanning Electron Microscopy (SEM). They were crystals of DTG with a prismatic shape, and their dimensions varied between 8.793 µm to 13.41 µm. Optimized Solid dispersion had irregularly shaped spherical particles with rough surfaces (Figure 5). However, they found irregular spherical particles with a rough surface observed. The reason may be that the Soluplus® support completely coats the original DTG crystals and, therefore, has a rough surface. This coating prevents recrystallization of the DTG from solid dispersions.[12,24]

## *In vitro* dissolution of solid dispersions

The greatest homogeneity, close mixing, and amorphous content in the formulation ought to exhibit maximum dissolution. The dissolving profile of solid dispersions was better than pure DTG in all ratios. Pure DTG released only 14±0.64% at the end of a 2 hr study. The kneading method, solvent evaporation method, and lyophilization method were used at a ratio of 1:4, resulting in a % DTG release of 59.52±0.07%, 89.14±2.9, and 98.11±1.69%, respectively with soluplus®. % DTG release of 48.31±1.02%, 74.11±42%, and 86.17±0.7% respectively with sulfobutylether β-cyclodextrins details depicted in Figure 6. This improvement in the dissolution rates of the solid dispersions may be due to the drug wetting in dissolution media achieved by sulfobutylether β-cyclodextrin[14] and the surface activity of the Soluplus® carrier. The soluplus® surfactant property lowers the interfacial tension between the medium and the drug, which results in good dissolution.[12] The technique's efficiency in converting the drug to an amorphous form and producing a homogeneous product can lead to a difference in release produced by different preparation techniques.[25] Pressure applied manually at variable rates is the only principle used in kneading, which is inefficient for the drug's amorphization. With the help of the solvent evaporation

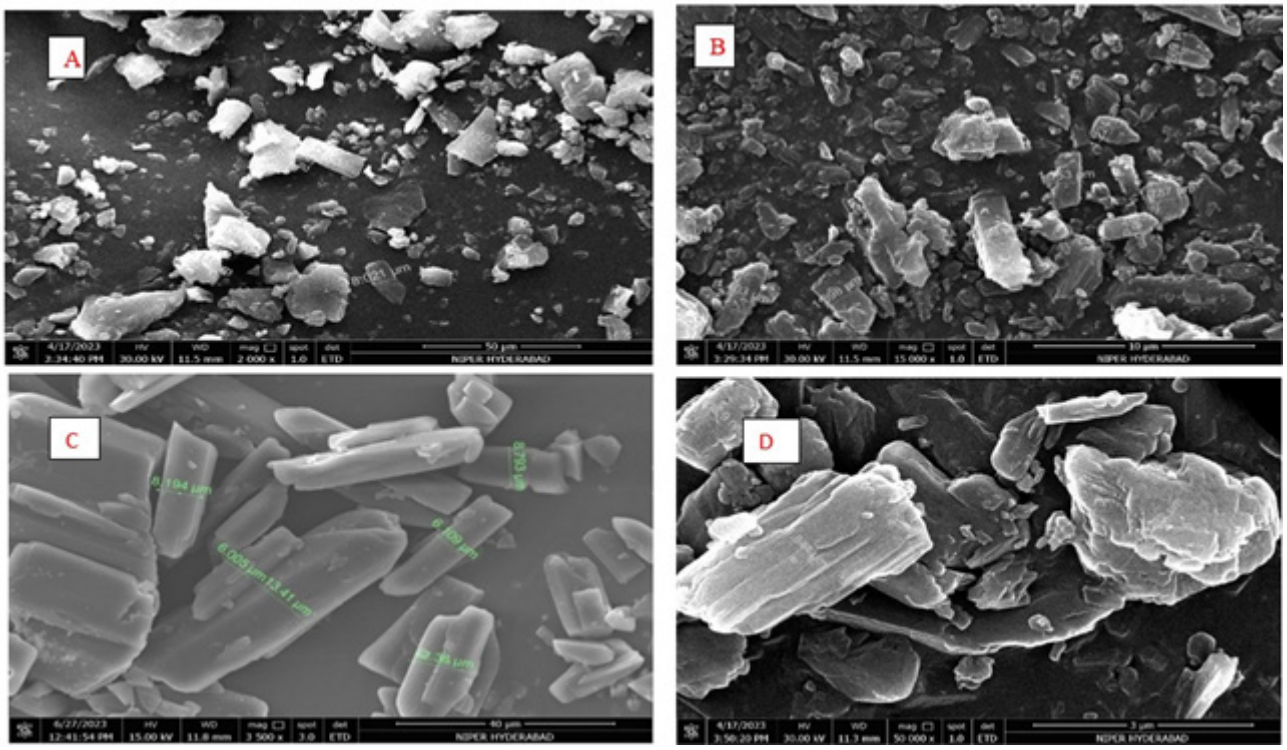


**Figure 5:** Photomicrographs of (A) DTG (35KX), (B) Sulfobutylether-β-cyclodextrins(15KX), (C) soluplus®(2KX) and (D) solid dispersion (50KX).

**Table 7: Results of stability studies.**

| Parameters | Initial | 40ºC/75% rh (3 m) | 40ºC/75% rh (6 m) |
|---|---|---|---|
| colour | Whitish to pale yellow. | Whitish to pale yellow. | Whitish to pale yellow. |
| drug content | 99.89% | 99.02% | 98.55% |
| Hardness | 6.0±0.10 | 5.9±0.25 | 5.85±0.10 |
| Friability | 0.24±0.01 | 0.25±0.02 | 0.27±0.05 |

* For each value, the mean±standard deviation is shown ($n$=3).

approach, the drug is covered by the polymer, and its crystallinity is reduced or increased, depending on the controlled evaporation, which produces uniformly distributed smaller particles.[26] The lyophilization technique produces more porous particles, softer, homogeneous chemical composition, and more stable than the other methods.[9,27,28]

## Formulation of Oro dispersible tablets

Based on the drug release of the solid dispersions, F12 is showing better drug release, So the same composition is used for preparing Oro dispersible tablets using various proportions of superdistegrants such as locust bean gum; Croscarmellose was taken at 3%, 6%, 9%, and 12% w/w of the tablet formulation and prepared by direct compression.[7,21] The formulation composition of Dolutegravir Oro dispersible tablets details is given in Table 3.

## Evaluation of Dolutegravir solid dispersion tablets

Pre and post-compression parameters of the produced tablets, including their diameter, thickness, friability, hardness, wetting time, *in vitro* disintegration time, and concentration of the drug present in the prepared tablets were assessed in detail and placed in Tables 4 and 5. The quantity of locust beans in various batches significantly affected the friability and hardness of the tablets. The results showed that the hardness and friability were 3.32±0.15 to 4.98±0.10 kg/cm$^2$ and 0.59±0.04 to 0.24±0.03% (L1-L4), respectively, and 3.56±0.72 to 3.49±0.56 kg/cm$^2$ and 0.87±0.04 to 0.68±0.01% (C1-C4). It was discovered that the ranges for wetting time and *in vitro* disintegration time (L1 to L4) were 19.18±1 to 12.83±1 sec and 19.13±1 to 12.8±1 sec, respectively. *In vitro* drug release of the Oro dispersible tablets L1-L4 was 81.91%, 84.46%, 88.23%, and 99.89%, as shown in Figure 7. The conclusions drawn from the f2 calculation and f1 factors showed a similarity of dissolution studies between L1 to L4 and DTG fast-dissolving marketed tablets (INSTGRA TM-50 mg). But out of all the formed batches, the f2 values of the L3 and L4 batches were the highest at 91.27 and 97.89, respectively.

Locust bean gum was used as the super disintegrant in stability experiments for the manufactured batches, and the results showed no appreciable changes in the tablet hardness, friability, *In vitro*

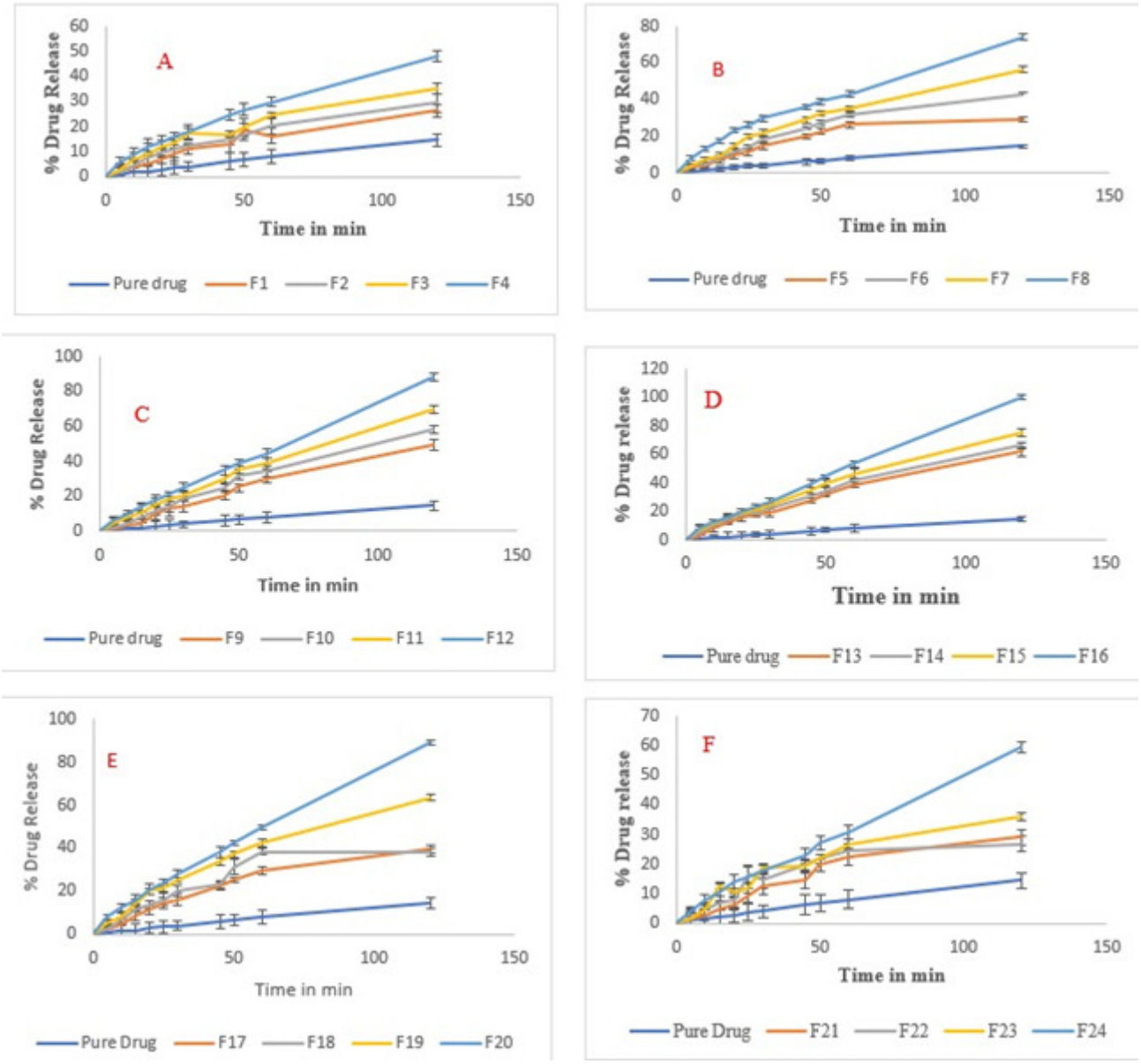


**Figure 6:** Drug release profiles of Solid dispersions A) Kneading method by using Soluplus®, B) Rota solvent evaporation method by using Soluplus®, C) lyophilization method by using Soluplus®, D) Lyophilization method by using Sulfobutylether-β-cyclodextrins, E) Rota solvent evaporation method by using Sulfobutylether-β-cyclodextrins, F) Kneading method by using Sulfobutylether-β-cyclodextrins.

drug release (Figure 8), and drug content (Table 7). The substance used in manufacturing the Oro dispersible tablet was discovered to be a factor in its super disintegrant activity. Using locust bean gum as a super disintegrant instead of cross carmellose sodium caused the tablets to dissolve significantly more quickly and consistently.

## DISCUSSION

Different buffering systems were used to measure the solubility of DTG saturation; the findings are shown in Figure 1, where pH 6.8 buffers demonstrates superior solubility.[9] Phase solubility investigations are conducted to determine the carrier's aqueous solubility; Table 2 displays the results. The results indicate that SBE β-CD and soluplus® exhibit superior solubility enhancement compared to pure API; hence, these materials are chosen to develop solid dispersions.[10] Kneading, Rota solvent evaporation, and lyophilization were employed to make solid dispersions with varying ratios of chosen carriers.[12-14] The analysis is done on FTIR, DSC, and X-ray diffraction investigations to learn more about the interactions between the API and carrier. Figures 2 to 4 show the results. Figure 5 shows the optimized formulations, carriers, and pure API morphological characteristics. Twenty-four formulations are subjected to *in vitro* dissolving experiments; formulation F12 exhibits superior drug release compared to the other formulations. Figure 6 shows drug release profiles. F12 is utilized to prepare Oro dispersible tablets using different amounts of superdistegrants such as locust bean gum; Croscarmellose was

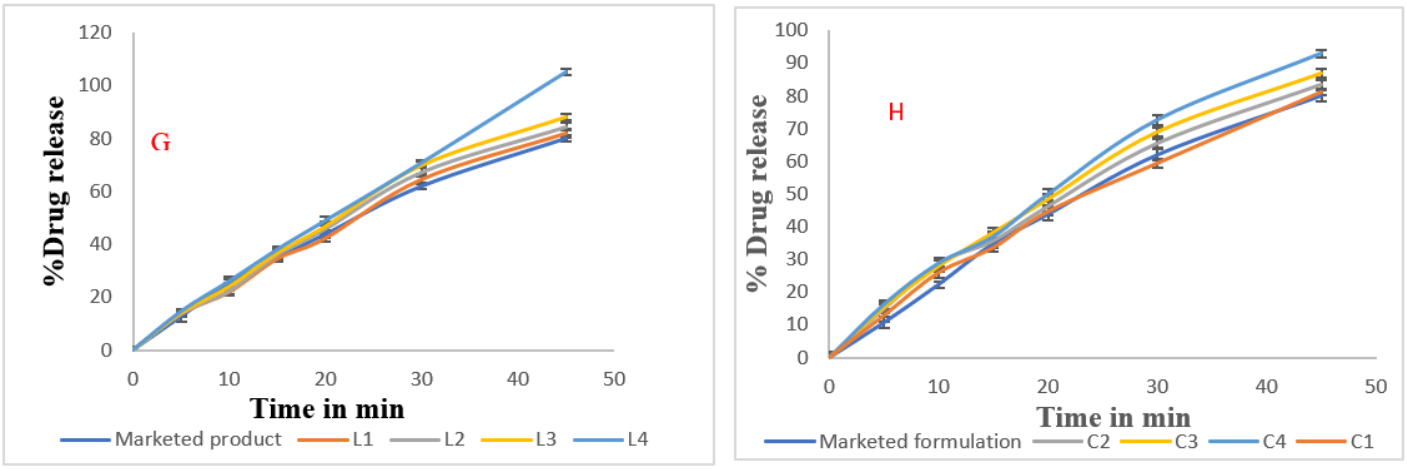


**Figure 7:** Dissolution profiles of (G)- locust bean gum, (H)-Croscarmellose based Oro dispersible tablets, comparison with marketed product.

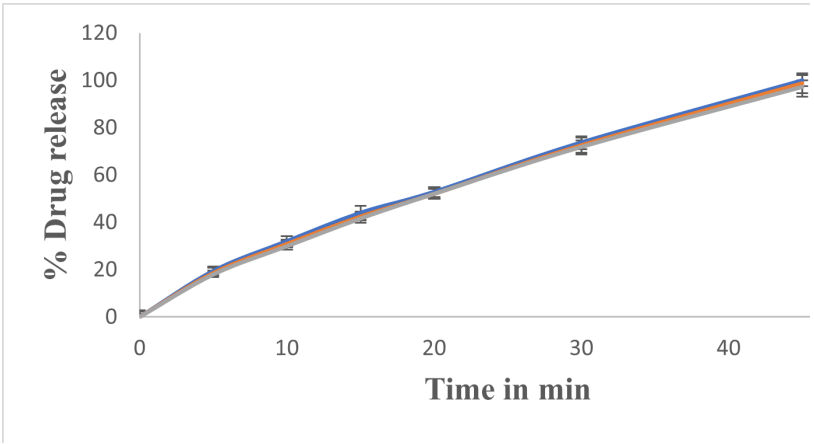


**Figure 8:** *In vitro* drug release studies comparison during the stability studies.

taken at 3%, 6%, 9%, and 12% w/w of the tablet formulation and prepared by direct compression method.[9] Precompression and post-compression properties of the developed fast-dissolving tablet are found and shown in Tables 4-5. For the developed tablets, comparisons are made between *in vitro* drug release studies and commercialized tablets (Instgra TM). In Figure 7, comparison profiles are presented. The percentage difference between optimized and marketed tablets is determined using the similarity factor (f2) and differential factor (f1) to compare release profiles.[7,29] The f2 calculation and f1 variables revealed identical dissolution studies of L1 to L4 and DTG fast-dissolving marketed tablets (INSTGRA ™-50mg). However, the L3 and L4 batches had the highest f2 values of all the produced collections, at 91.27 and 97.89; specifics are shown in Table 6. Stability studies are finally examined at zero, third, and six months.[19] The produced tablets did not exhibit any significant changes over time; the results are shown in Table 7 and Figure 8.

## CONCLUSION

In this study, Dolutegravir solid dispersions are formulated with sulfobutylether-β-cyclodextrins and Soluplus® by using the kneading method, Rota solvent evaporation, and lyophilization method. The formulated solid dispersions are ameliorating the dissolution (%) rate of Dolutegravir, based on the drug release Soluplus® solid dispersions are showing the best drug release. These solid dispersions are developed into Oro dispersible tablets using super disintegrants (locust bean gum and croscarmellose sodium). Locust bean gum shows a better disintegration time than compared to crosscarmellose sodium. The Oro dispersible tablets that had been made with Dolutegravir solid dispersions were steady and maintained their capacity for dissolution (%), disintegration time (sec), and drug content (%) for six months. To continue the further studies of the optimized Oro-dispersible tablets, comprehensively explore its bioavailability and therapeutic efficacy in HIV patients.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## ABBREVIATIONS

**DTG:** Dolutegravir; **SBE β-CD:** Sulfobutylether-β-cyclodextrin; **SD:** Solid dispersions; **FDA:** Food and Drug Administration; **EMEA:** European Agency for the Evaluation of Medicinal Products; **ODTs:** Oro dispersible tablets.

## SUMMARY

Dolutegravir (DTG) is an integrase strand transfer inhibitor that prevents the integration of viral DNA into host cell DNA, which is thought to be one of the key phases in the HIV life cycle. It prevents the virus from multiplying inside the host. In this research, we formulated solid dispersion-based fast-dissolving tablets to ameliorate the effect of DTG. The developed tablets showed better drug release profiles and similar profiles compared to the marketed formulation, and it could be a promising approach to ameliorate the integrase inhibition effect of DTG.

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