GMR
The Original

DEVELOPMENT, CHARACTERIZATION AND OPTIMIZATION OF DOLUTEGRAVIR SOLID DISPERSIONS USING PEG 6000 AND PVP K30: COMPARATIVE PROCESSING, FACTORIAL DESIGN AND TABLET DEVELOPMENT

Ms. Krupaben Pravinbhai Patel[1*], Dr.Sunil Thakral[2]

[1*]Research scholar, Madhav University, Abu road, Rajasthan. patelkrupaa105@gmail.com
[2]Supervisor, Madhav University, Abu road, Rajasthan, sunil.thakral@gmail.com

ABSTRACT
Background: Dolutegravir (DTG) is a potent HIV-1 integrase inhibitor with poor aqueous solubility, which can limit its dissolution and oral absorption.
Objective: To develop and optimize dolutegravir solid dispersions using hydrophilic carriers for enhancement of solubility and dissolution.
Methods: Solid dispersions were prepared using PEG 6000 by the melting method and PVP K30 by solvent evaporation at drug-to-carrier ratios of 1:1, 1:2, and 1:3. Corresponding physical mixtures were prepared for comparison. The formulations were evaluated for solubility, practical yield, drug content, and cumulative drug release (CDR). A 3^2 factorial design was applied using carrier and adsorbent concentrations as independent variables, with drug content and CDR as responses.
Results: Pure dolutegravir showed a solubility of 0.0028 ± 0.015 mg/ml. Among the preliminary formulations, DSD4 showed 8.19 ± 0.034 mg/mL solubility, whereas DSD10 prepared by solvent evaporation with PVP K30 showed the highest solubility of 10.90 ± 0.035 mg/mL, with 93.76 ± 1.53% drug content and 94.86 ± 1.18% CDR. The best physical mixture (DSD16) showed comparatively lower solubility (3.72 ± 0.020 mg/mL). The factorial models were significant for drug content ($p = 0.0343$) and CDR ($p = 0.0155$), with adsorbent concentration identified as the major influencing variable. Predicted and observed responses showed close agreement during model validation.
Conclusion: The developed solid-dispersion approach substantially improved dolutegravir solubility and dissolution compared with the pure drug and physical mixtures. The optimized formulation demonstrated satisfactory drug content and dissolution performance, confirming the potential of solid dispersion for improving the formulation characteristics of dolutegravir.

KEYWORDS: Dolutegravir; Solid dispersion; Solubility enhancement; Dissolution enhancement; PEG 6000; PVP K30; Hydrophilic carriers; Solvent evaporation; Melting method; Factorial design; Drug content

INTRODUCTION

Dolutegravir (DTG) is a second-generation HIV-1 integrase strand-transfer inhibitor with potent antiviral activity and a high genetic barrier to resistance. Its clinical importance has been demonstrated in major clinical studies, including the SINGLE trial (NCT01263015), FLAMINGO trial (NCT01449929), and VIKING-3 study (NCT01328041), supporting its use in both treatment-naïve and treatment-experienced HIV-1 patients [1-6].
Despite its therapeutic importance, the poor aqueous solubility of dolutegravir presents a formulation challenge and may limit its dissolution and oral drug absorption. In the present study, pure dolutegravir showed a solubility of 0.0028 ± 0.015 mg/mL, indicating the need for an effective solubility-enhancement approach [7-12].
Solid dispersion is a widely used pharmaceutical technique for improving the solubility and dissolution of poorly water-soluble drugs by incorporating the drug into a hydrophilic carrier [13-18]. Therefore, the present study aimed to develop and optimize dolutegravir solid dispersions using PEG 6000 by the melting method and PVP K30 by solvent evaporation, followed by evaluation of solubility, drug content, and dissolution performance. A 3^2 factorial design was employed to systematically optimize the formulation variables and obtain an improved dolutegravir solid-dispersion system [19-24].

2. MATERIALS AND METHODS

2.1 Materials

Dolutegravir was used as the model drug. Polyethylene glycol 6000 (PEG 6000) and polyvinylpyrrolidone K30 (PVP K30) were used as hydrophilic carriers for preparation of solid dispersions. Methanol was used as the solvent for the solvent-evaporation method, while phosphate buffer pH 6.8 was used as the dissolution medium. Starch paste, lactose, crospovidone, talc, and magnesium stearate were used for preparation of the optimized tablets.

Potassium bromide was used for FTIR analysis. The solid dispersions were prepared at drug-to-carrier ratios of 1:1, 1:2, and 1:3.

2.2 Preparation of Dolutegravir Solid Dispersions

Dolutegravir solid dispersions were prepared by the melting method and solvent-evaporation method using PEG 6000 and PVP K30 as carriers, respectively. Physical mixtures with the same drug-to-carrier compositions were prepared separately for comparison.

2.2.1 Melting Method

Dolutegravir and PEG 6000 were mixed at drug-to-carrier ratios of 1:1, 1:2, and 1:3 in a china dish and heated on a paraffin bath. The molten mixture was poured onto a tile and allowed to cool. The resulting solid mass was dried, pulverized, and passed through sieve No. 100.

2.2.2 Solvent Evaporation Method

Dolutegravir and PVP K30 were mixed at drug-to-carrier ratios of 1:1, 1:2, and 1:3 in methanol. The solvent was removed by evaporation under reduced pressure. The resulting mass was pulverized and passed through sieve No. 100.

2.2.3 Preparation of Physical Mixtures

For comparison, physical mixtures having the same compositions as the solid dispersions were prepared by triturating dolutegravir and the respective polymers in a porcelain mortar. The mixtures were passed through a 420 μm sieve and stored in amber-glass capped containers.

Table 1. Formulation Design of Dolutegravir Solid Dispersions and Physical Mixtures

Preparation method	Formulation code	Carrier	Drug:Carrier ratio
Melting method	DSD1	PEG 6000	1:1
Melting method	DSD2	PEG 6000	1:2
Melting method	DSD3	PEG 6000	1:3
Melting method	DSD4	PVP K30	1:1
Melting method	DSD5	PVP K30	1:2
Melting method	DSD6	PVP K30	1:3
Solvent evaporation	DSD7	PEG 6000	1:1
Solvent evaporation	DSD8	PEG 6000	1:2
Solvent evaporation	DSD9	PEG 6000	1:3
Solvent evaporation	DSD10	PVP K30	1:1
Solvent evaporation	DSD11	PVP K30	1:2
Solvent evaporation	DSD12	PVP K30	1:3
Physical mixture	DSD13	PEG 6000	1:1
Physical mixture	DSD14	PEG 6000	1:2
Physical mixture	DSD15	PEG 6000	1:3
Physical mixture	DSD16	PVP K30	1:1
Physical mixture	DSD17	PVP K30	1:2
Physical mixture	DSD18	PVP K30	1:3

The formulation coding follows the preliminary trial-batch design reported in the thesis.

2.3 Evaluation of Dolutegravir Solid Dispersions

2.3.1 Practical Yield

The practical yield of the prepared solid dispersions was determined by collecting and weighing the obtained solid-dispersion mass.

2.3.2 Drug Content

An accurately weighed quantity of solid dispersion equivalent to 10 mg of dolutegravir was dissolved in 100 Ml of methanol. The solution was filtered and appropriately diluted, and the drug concentration was determined using a UV spectrophotometer at 260 nm against a blank.

2.3.3 Solubility Study

The solubility of pure dolutegravir and the prepared solid-dispersion and physical-mixture formulations was determined and expressed in mg/Ml.

2.3.4 In-vitro Dissolution Study

In-vitro dissolution studies were performed using a USP Type II dissolution apparatus. Samples equivalent to 10 mg of dolutegravir were introduced into 900 Ml of phosphate buffer Ph 6.8 maintained at 37°C and agitated at 50 rpm. Samples were withdrawn at predetermined intervals, filtered, and replaced with fresh dissolution medium. Dolutegravir concentration was determined spectrophotometrically at 260 nm after filtration through a 0.45 μm microfilter.

2.4 FTIR Studies

FTIR analysis was performed using a Shimadzu FTIR-8700 spectrophotometer employing the potassium bromide disc technique. Pure dolutegravir, physical mixtures, and selected solid dispersions were analyzed. The powdered

sample was thoroughly mixed with dry potassium bromide and compressed into a transparent disc for spectral analysis.

2.5 Stability Studies

The prepared solid dispersions were stored in sealed 40 cc HDPE containers with child-resistant covers in a stability chamber maintained at 40 ± 2°C and 75 ± 5% relative humidity. Samples were withdrawn after 1, 2, and 3 months and evaluated for in-vitro dissolution and drug content.

2.6 Factorial Design and Optimization

A 3^2 factorial design was employed to investigate the effects of carrier and adsorbent concentrations on the performance of dolutegravir solid dispersions. Carrier concentration (X1) and adsorbent concentration (X2) were selected as independent variables, while drug content (Y1) and cumulative drug release (Y2) were selected as dependent variables. The experimental design and statistical analysis were performed using Design-Expert software.

The coded levels were −1, 0, and +1. The actual levels selected for the independent variables were:

- X1 (Carrier): 45, 55, and 65 mg
- X2 (Adsorbent): 15, 35, and 55 mg

2.7 Experimental Design Batches

Table 2. Composition and Experimental Responses of 3^2 Factorial Design Batches

Batch	Carrier (X1), mg	Adsorbent (X2), mg	Drug Content (%)	CDR (%)
SD1	55	55	80.87 ± 1.38	78.87 ± 1.14
SD2	55	35	89.57 ± 1.21	86.44 ± 1.57
SD3	55	15	90.14 ± 1.05	91.59 ± 1.23
SD4	45	15	90.28 ± 1.17	94.52 ± 1.75
SD5	65	15	95.42 ± 1.69	91.29 ± 1.40
SD6	45	55	85.64 ± 1.32	84.08 ± 1.52
SD7	65	55	83.25 ± 1.44	80.61 ± 1.26
SD8	65	35	90.28 ± 1.53	89.69 ± 1.61
SD9	45	35	87.54 ± 1.48	89.38 ± 1.35

3. RESULTS

3.1 Preformulation Characterization of Dolutegravir

Dolutegravir was obtained as a solid, white, odourless powder. The melting point was found to be 190–192°C, indicating consistency with the reported standard characteristics of the drug. UV spectrophotometric examination showed a maximum absorption wavelength (λmax) at 260 nm, which was subsequently used for quantitative estimation of dolutegravir during drug-content and dissolution studies.

Table 3. Preformulation Characteristics of Dolutegravir

Parameter	Observation
Physical state	Solid
Appearance	Amorphous powder
Colour	White
Odour	Odourless
Melting point	190–192°C
λmax	260 nm

3.2 FTIR Characterization

The FTIR spectrum of dolutegravir was recorded in the range of 4000–400 cm^{-1} using the KBr pellet technique. The characteristic absorption bands corresponding to NH_2 stretching, C=O stretching, C–N stretching, C–O stretching, C–C stretching and C–F stretching were observed at 3167, 1648, 1272, 1083, 765 and 1321 cm^{-1}, respectively. The observed peaks corresponded with the characteristic functional groups of dolutegravir, supporting the identity of the drug.

Table 4. FTIR Interpretation of Dolutegravir

Type of vibration	Standard range (cm^{-1})	Observed (cm^{-1})
NH_2 stretching	3600–3200	3167
C=O stretching	1760–1690	1648
C–N stretching	1360–1180	1272
C–O stretching	1300–1050	1083
C–C stretching	800–600	765
C–F stretching	1400–1000	1321

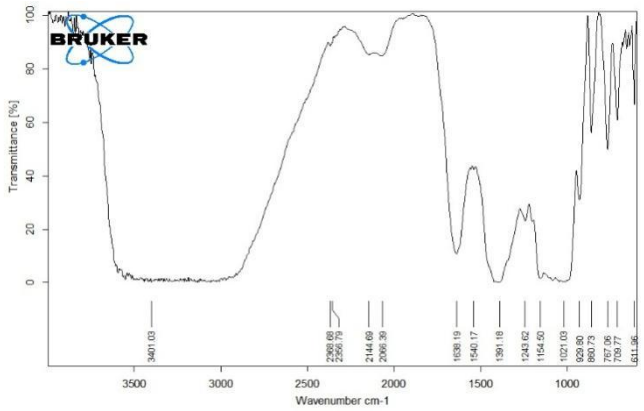

Figure 1. FTIR spectrum of dolutegravir showing characteristic absorption bands.

3.3 Preliminary Evaluation of Solid Dispersions Prepared by the Melting Method

Six preliminary formulations, DSD1–DSD6, were prepared by the melting method. DSD1–DSD3 contained PEG 6000 at drug-to-carrier ratios of 1:1, 1:2 and 1:3, whereas DSD4–DSD6 contained PVP K30 at the corresponding ratios. Among the PEG 6000 formulations, solubility ranged from 1.76 ± 0.015 to 4.22 ± 0.037 mg/mL. DSD1 exhibited the highest solubility among the PEG-containing batches at 4.22 ± 0.037 mg/mL.

The PVP K30-containing formulations showed comparatively higher performance. DSD4 exhibited the highest solubility of 8.19 ± 0.034 mg/mL, with a practical yield of 93.33 ± 1.62%, drug content of 93.55 ± 1.25%, and CDR of 95.62 ± 1.39%. DSD4 therefore demonstrated superior preliminary performance among the melting-method batches.

Table 5. Preliminary Characterization of DSD1–DSD6 Prepared by Melting Method

Formulation	Solubility (mg/mL)	Yield (%)	Drug content (%)	CDR (%)
DSD1	4.22 ± 0.037	90.11 ± 1.23	90.20 ± 1.87	90.82 ± 1.46
DSD2	2.64 ± 0.046	89.25 ± 1.45	88.12 ± 1.02	87.67 ± 1.18
DSD3	1.76 ± 0.015	90.62 ± 1.39	90.79 ± 1.10	87.98 ± 1.57
DSD4	8.19 ± 0.034	93.33 ± 1.62	93.55 ± 1.25	95.62 ± 1.39
DSD5	4.59 ± 0.028	91.67 ± 1.28	91.40 ± 1.38	89.33 ± 1.13
DSD6	3.52 ± 0.021	90.35 ± 1.15	91.37 ± 1.62	87.98 ± 1.20

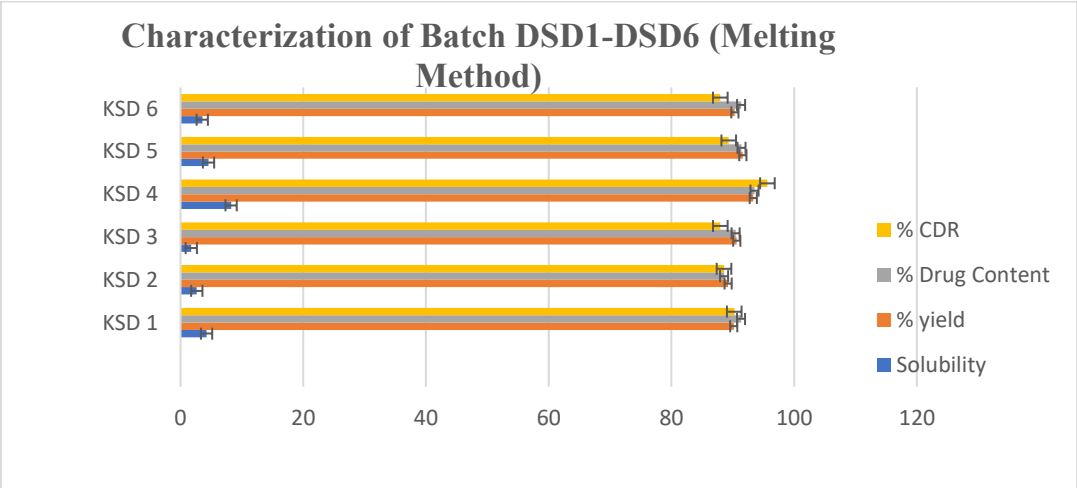

Figure 2. Preliminary characterization of DSD1–DSD6 prepared by the melting method.

3.4 Preliminary Evaluation of Solid Dispersions Prepared by Solvent Evaporation

DSD7–DSD12 were prepared by the solvent-evaporation method. DSD7–DSD9 contained PEG 6000, while DSD10–DSD12 contained PVP K30. The PEG 6000 formulations showed solubilities of 3.18 ± 0.016, 2.88 ± 0.038 and 1.15 ± 0.022 mg/mL, respectively.

A marked enhancement was observed with PVP K30. DSD10 exhibited the highest solubility among all preliminary solvent-evaporation batches at 10.90 ± 0.035 mg/mL, with 95.69 ± 1.20% yield, 93.76 ± 1.53% drug

content and 94.86 ± 1.18% CDR. DSD11 and DSD12 showed lower solubility but maintained CDR values of 94.58 ± 1.35% and 92.20 ± 1.41%, respectively.

Table 6. Preliminary Characterization of DSD7–DSD12 Prepared by Solvent-Evaporation Method

Formulation	Solubility (mg/mL)	Yield (%)	Drug content (%)	CDR (%)
DSD7	3.18 ± 0.016	88.16 ± 1.41	89.59 ± 1.25	88.43 ± 1.04
DSD8	2.88 ± 0.038	87.23 ± 1.06	86.69 ± 1.12	87.75 ± 1.27
DSD9	1.15 ± 0.022	85.66 ± 1.32	84.70 ± 1.47	85.21 ± 1.23
DSD10	10.90 ± 0.035	95.69 ± 1.20	93.76 ± 1.53	94.86 ± 1.18
DSD11	3.42 ± 0.026	90.70 ± 1.15	92.60 ± 1.64	94.58 ± 1.35
DSD12	2.36 ± 0.011	91.96 ± 1.29	90.59 ± 1.70	92.20 ± 1.41

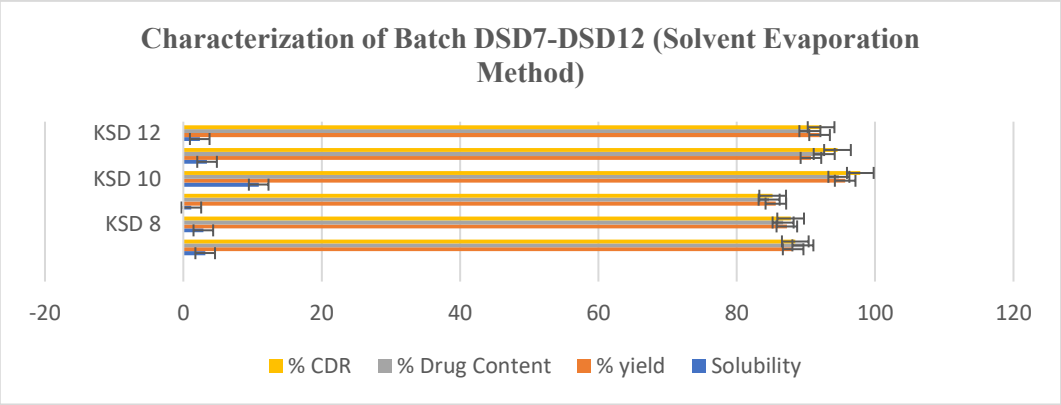

Figure 3. Preliminary characterization of DSD7–DSD12 prepared by the solvent-evaporation method.

3.5 Evaluation of Physical Mixtures

Physical mixtures DSD13–DSD18 were evaluated to establish the contribution of simple drug–polymer mixing without formation of a solid dispersion. The physical mixtures exhibited substantially lower solubility than the corresponding solid-dispersion systems. Solubility ranged from 1.18 ± 0.027 to 3.72 ± 0.020 mg/mL.

Among the physical mixtures, DSD16 showed the highest solubility (3.72 ± 0.020 mg/mL), with drug content of 89.52 ± 1.45% and CDR of 87.61 ± 1.34%. These results demonstrated that physical mixing produced considerably less improvement in solubility and dissolution than the optimized solid-dispersion systems.

Table 7. Characterization of Physical Mixtures DSD13–DSD18

Formulation	Solubility (mg/mL)	Yield (%)	Drug content (%)	CDR (%)
DSD13	1.18 ± 0.027	84.33 ± 1.24	86.73 ± 1.13	84.24 ± 1.20
DSD14	2.71 ± 0.012	83.65 ± 1.36	83.82 ± 1.07	85.55 ± 1.53
DSD15	2.68 ± 0.034	82.88 ± 1.53	81.47 ± 1.61	83.09 ± 1.10
DSD16	3.72 ± 0.020	87.84 ± 1.41	89.52 ± 1.45	87.61 ± 1.34
DSD17	2.73 ± 0.024	84.91 ± 1.27	84.44 ± 1.36	84.36 ± 1.47
DSD18	2.01 ± 0.039	80.20 ± 1.33	86.36 ± 1.19	82.03 ± 1.16

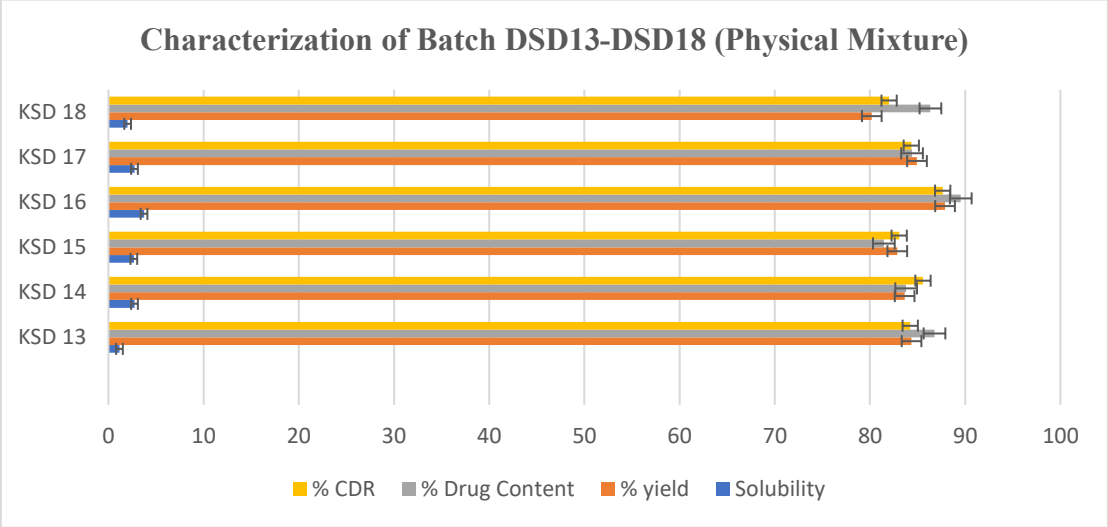

Figure 4. Characterization of DSD13–DSD18 physical mixtures.

3.6 Comparative Selection of Solid-Dispersion Systems

Comparison of the preliminary batches showed that the solvent-evaporation/PVP K30 system provided the highest solubility, whereas the melting/PVP K30 system also produced a substantial enhancement. DSD4 showed 8.19 ± 0.034 mg/mL solubility, while DSD10 showed 10.90 ± 0.035 mg/mL. In comparison, the best physical mixture, DSD16, showed only 3.72 ± 0.020 mg/mL.

Thus, incorporation of dolutegravir into a polymeric solid-dispersion system produced a substantially greater improvement in solubility and dissolution than physical mixing alone. DSD10 demonstrated the highest preliminary solubility and was therefore selected as the principal solid-dispersion system for subsequent optimization.

Table 8. Comparative Performance of Representative Formulations

Formulation	Preparation system	Solubility (mg/mL)	Drug content (%)	CDR (%)
Pure DTG	Drug	0.0028 ± 0.015	—	—
DSD4	Melting/PVP K30	8.19 ± 0.034	93.55 ± 1.25	95.62 ± 1.39
DSD10	Solvent evaporation/PVP K30	10.90 ± 0.035	93.76 ± 1.53	94.86 ± 1.18
DSD16	Physical mixture/PVP K30	3.72 ± 0.020	89.52 ± 1.45	87.61 ± 1.34

3.7 Design of Experiments and Factorial Optimization

A two-factor, three-level (3^2) factorial design was applied using response surface methodology. Carrier concentration (X1/A) and adsorbent concentration (X2/B) were investigated as independent variables, while drug content (Y1) and CDR (Y2) were selected as responses. The carrier was evaluated at 45, 55 and 65 mg, while the adsorbent was evaluated at 15, 35 and 55 mg.

Table 9. 3^2 Factorial Design and Experimental Responses

Batch	X1 Carrier (mg)	X2 Adsorbent (mg)	Drug content (%)	CDR (%)
SD1	55	55	80.87 ± 1.38	78.87 ± 1.14
SD2	55	35	89.57 ± 1.21	86.44 ± 1.57
SD3	55	15	90.14 ± 1.05	91.59 ± 1.23
SD4	45	15	90.28 ± 1.17	94.52 ± 1.75
SD5	65	15	95.42 ± 1.69	91.29 ± 1.40
SD6	45	55	85.64 ± 1.32	84.08 ± 1.52
SD7	65	55	83.25 ± 1.44	80.61 ± 1.26
SD8	65	35	90.28 ± 1.53	89.69 ± 1.61
SD9	45	35	87.54 ± 1.48	89.38 ± 1.35

The experimental data demonstrated that increasing adsorbent concentration from 15 to 55 mg generally reduced both drug content and CDR. The highest experimental drug content was observed for SD5 (95.42 ± 1.69%), whereas the highest CDR was observed for SD4 (94.52 ± 1.75%).

3.8 Response Surface Modeling

The quadratic model obtained for drug content was:

Drug content = $87.88 + 0.91A - 4.35B - 1.88AB + 1.87A^2 - 1.53B^2$

The model indicated a positive contribution of carrier concentration and a comparatively stronger negative contribution of adsorbent concentration to drug content.

For CDR, the quadratic model was:

%CDR = $86.75 - 1.06A - 5.64B - 0.060AB + 2.63A^2 - 1.68B^2$

The negative coefficient for B indicated the stronger adverse effect of increasing adsorbent concentration on CDR.

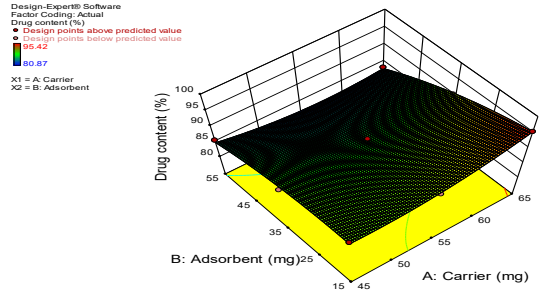

Figure 5. 3D response surface plot showing the effect of carrier and adsorbent concentrations on drug content.

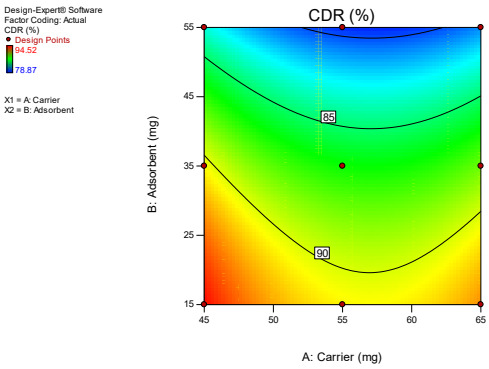

Figure 6. Contour plot showing the effect of carrier and adsorbent concentrations on drug content.

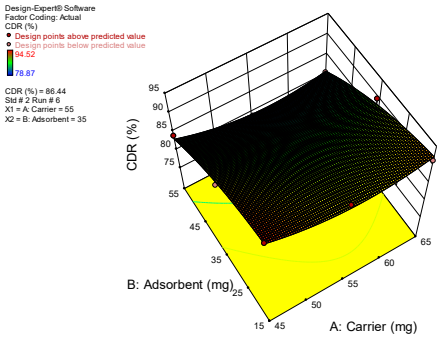

Figure 7. 3D response surface plot showing the effect of carrier and adsorbent concentrations on CDR.

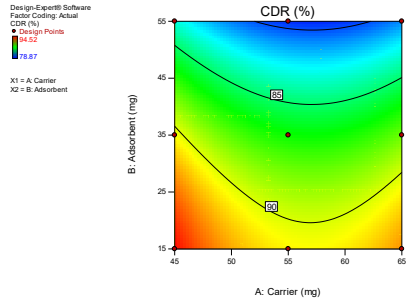

Figure 8. Counter plot showing the effect of carrier and adsorbent concentrations on CDR.

3.9 ANOVA of the Factorial Models

The response-surface quadratic model for drug content was statistically significant, with a model p-value of 0.0343. Among the investigated factors, adsorbent concentration (B) was significant (p = 0.0064), whereas the carrier concentration showed a comparatively smaller effect (p = 0.2462).

For CDR, the quadratic model was also significant (p = 0.0155). Adsorbent concentration was the principal significant factor (p = 0.0024), while carrier concentration showed a lower level of significance (p = 0.1681). The interaction term AB was not significant (p = 0.9389).

Table 10. ANOVA Summary for Response-Surface Models

Response	Model p-value	Significant factor	Factor p-value	Interpretation
Drug content	0.0343	B – Adsorbent	0.0064	Significant model; adsorbent was the major influencing factor
CDR	0.0155	B – Adsorbent	0.0024	Significant model; adsorbent was the major influencing factor

3.10 Model Validation and Optimization

The optimized formulation region was evaluated using checkpoint batches. For checkpoint C1, the selected carrier and adsorbent concentrations were 63.36 and 17.56 mg, respectively. The predicted drug content was 93.95%, compared with an observed value of 94.10%, while predicted CDR was 91.38% compared with an observed value of 92.65%.

For checkpoint C2, carrier and adsorbent concentrations of 65 and 15 mg, respectively, produced a predicted drug content of 95.36% versus an observed value of 96.50%, and predicted CDR of 92.33% versus an observed value of 93.68%. The close agreement between predicted and observed values confirmed the suitability of the developed models for formulation optimization.

Table 11. Predicted and Experimental Validation of Optimized Formulations

Checkpoint	Carrier X1 (mg)	Adsorbent X2 (mg)	Drug content predicted (%)	Drug content observed (%)	CDR predicted (%)	CDR observed (%)
C1	63.36	17.56	93.95	94.10	91.38	92.65
C2	65.00	15.00	95.36	96.50	92.33	93.68

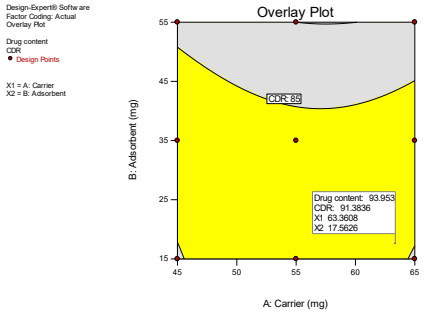

Figure 9. Predicted versus observed responses for model validation.

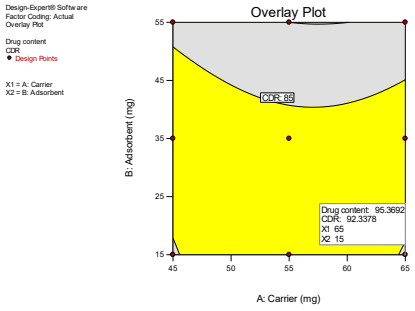

Figure 10. Overlay plot showing the optimized design space for drug content and CDR.

3.11 Development of Solid-Dispersion Tablets

Based on the optimized solid dispersion containing approximately 94% drug content, 100 mg of solid dispersion corresponded to 94 mg equivalent drug. Therefore, 53.19 mg of solid dispersion was calculated to provide an equivalent of 50 mg dolutegravir.

Two optimized tablet batches, CNF1 and CNF2, were prepared with a target tablet weight of 200 mg. Both formulations contained 53.19 mg solid dispersion equivalent to 50 mg drug. The quantities of starch paste and lactose differed between CNF1 and CNF2.

Table 12. Composition of Optimized Dolutegravir Solid-Dispersion Tablets

Ingredient	CNF1 (mg/tablet)	CNF2 (mg/tablet)
Solid dispersion equivalent to 50 mg drug	53.19	53.19
Starch paste	20.0	25.0
Lactose	91.3	86.3
Crospovidone	25.0	25.0
Talc	10.0	10.0
Magnesium stearate	0.5	0.5
Total	200	200

3.12 Precompression Evaluation

The optimized tablet formulations showed acceptable precompression characteristics. CNF1 and CNF2 exhibited solubilities of 2.01 ± 0.039 and 2.73 ± 0.024 mg/mL, respectively. The angle of repose was 36.87 ± 1.39° for CNF1 and 33.69 ± 2.47° for CNF2. Bulk densities were 1.03 ± 0.08 and 1.04 ± 0.12 g/mL, while tapped densities were 0.86 ± 0.17 and 0.91 ± 0.09 g/mL, respectively.

Table 13. Precompression Characteristics of Optimized Tablet Batches

Parameter	CNF1	CNF2
Solubility (mg/mL)	2.01 ± 0.039	2.73 ± 0.024
Angle of repose (°)	36.87 ± 1.39	33.69 ± 2.47
Bulk density (g/mL)	1.03 ± 0.08	1.04 ± 0.12
Tapped density (g/mL)	0.86 ± 0.17	0.91 ± 0.09
Carr's index (%)	19.8 ± 2.2	14.3 ± 1.9
Hausner ratio	0.8 ± 0.001	0.9 ± 0.002

3.13 Postcompression Evaluation

The compressed tablets showed disintegration times of 1.27 ± 0.23 min and 1.12 ± 0.39 min for CNF1 and CNF2, respectively. Friability was 0.21 ± 0.09% for CNF1 and 0.13 ± 0.04% for CNF2, while hardness was 4.5 ± 0.51 and 4.9 ± 0.34 kg/cm², respectively.

The drug content was 94.32 ± 1.24% for CNF1 and 95.17 ± 1.92% for CNF2. The corresponding CDR values were 92.34 ± 1.67% and 93.67 ± 1.72%, respectively.

Table 14. Postcompression Evaluation of Optimized Tablet Batches

Parameter	CNF1	CNF2
Disintegration time (min)	1.27 ± 0.23	1.12 ± 0.39
Friability (%)	0.21 ± 0.09	0.13 ± 0.04
Hardness (kg/cm²)	4.5 ± 0.51	4.9 ± 0.34
Wetting time (sec)	25 ± 4	22 ± 3
Weight variation (%)	0.8 ± 0.03	1.3 ± 0.07
Drug content (%)	94.32 ± 1.24	95.17 ± 1.92
CDR (%)	92.34 ± 1.67	93.67 ± 1.72

3.14 In-vitro Dissolution of Optimized Tablets

Both optimized formulations demonstrated progressive drug release over 60 min. CNF1 showed cumulative drug release of 11.57 ± 0.25% at 10 min, increasing to 62.76 ± 0.92% at 40 min, 81.18 ± 1.39% at 50 min, and 92.34 ± 1.67% at 60 min. CNF2 showed 10.24 ± 0.92% at 10 min, increasing to 63.08 ± 1.26% at 40 min, 84.47 ± 1.18% at 50 min, and 93.67 ± 1.72% at 60 min. Thus, CNF2 exhibited slightly higher final drug release than CNF1.

Table 15. In-vitro Dissolution Profile of Optimized Tablet Batches

Time (min)	CNF1 CDR (%)	CNF2 CDR (%)
0	0	0
10	11.57 ± 0.25	10.24 ± 0.92
20	25.32 ± 0.19	23.39 ± 0.39
30	40.51 ± 0.68	41.26 ± 0.74
40	62.76 ± 0.92	63.08 ± 1.26
50	81.18 ± 1.39	84.47 ± 1.18
60	92.34 ± 1.67	93.67 ± 1.72

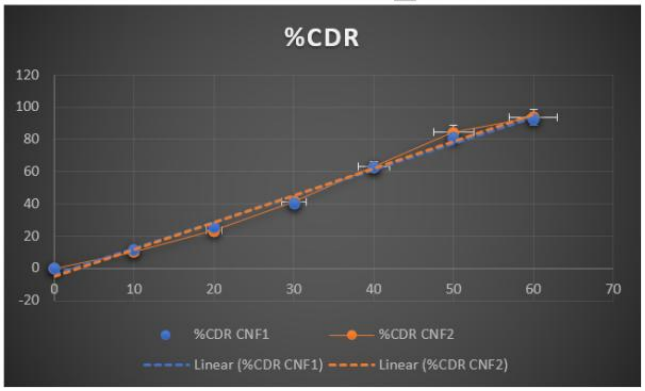

Figure 11. In-vitro dissolution profiles of optimized CNF1 and CNF2 tablets.

DISCUSSION

The present study demonstrated that solid-dispersion technology effectively improved the solubility and dissolution performance of dolutegravir. The pure drug exhibited very low aqueous solubility, whereas incorporation into hydrophilic carriers produced a marked improvement. Among the preliminary formulations, the PVP K30-based solvent-evaporation formulation DSD10 showed the highest solubility (10.90 ± 0.035 mg/mL) with satisfactory drug content (93.76 ± 1.53%) and CDR (94.86 ± 1.18%). The physical mixtures showed comparatively lower solubility, with DSD16 providing 3.72 ± 0.020 mg/mL, indicating the advantage of solid-dispersion preparation over simple physical mixing. The improved performance was attributed to the incorporation of dolutegravir into the hydrophilic carrier system.

The 3^2 factorial design established the influence of carrier and adsorbent concentrations on drug content and CDR. The quadratic models were significant for both responses, with model p-values of 0.0343 for drug content and 0.0155 for CDR. Adsorbent concentration was the most influential factor for both responses. The close agreement between predicted and observed values in the validation batches confirmed the suitability of the developed models. The optimized solid dispersion was subsequently incorporated into tablets, which showed satisfactory precompression and postcompression characteristics. The optimized tablets exhibited drug content of 94.32 ± 1.24% (CNF1) and 95.17 ± 1.92% (CNF2), while CDR at 60 min reached 92.34 ± 1.67% and 93.67 ± 1.72%, respectively.

CONCLUSION

Dolutegravir solid dispersions were successfully developed using PEG 6000 and PVP K30 through melting and solvent-evaporation techniques, while corresponding physical mixtures were prepared by trituration for comparative evaluation. The developed solid-dispersion formulations demonstrated marked improvement in solubility and dissolution performance compared with the pure drug and physical mixtures. Among the preliminary formulations, DSD10, prepared using PVP K30 by the solvent-evaporation method, exhibited the highest solubility of 10.90 ± 0.035 mg/mL, along with satisfactory drug content and cumulative drug release.

The 3^2 factorial design effectively evaluated the influence of carrier and adsorbent concentrations on drug content and cumulative drug release (CDR), and the developed mathematical models were found to be significant for both responses. The optimized formulation showed close agreement between predicted and experimental responses, confirming the applicability of the factorial design for formulation optimization. Tshe optimized solid dispersion was subsequently incorporated into tablets, which exhibited satisfactory precompression and postcompression characteristics, acceptable drug content, and improved dissolution performance. The optimized tablets achieved drug content of 94.32 ± 1.24% and 95.17 ± 1.92%, with 60-min CDR of 92.34 ± 1.67% and 93.67 ± 1.72% for CNF1 and CNF2, respectively. Overall, the study demonstrates that solid-dispersion technology using hydrophilic carriers, combined with factorial optimization, can effectively improve the formulation performance of dolutegravir and support its development into an oral tablet dosage form.

REFERENCES

1. Cid AG, Simonazzi A, Palma SD, Bermúdez JM. Solid dispersion technology as a strategy to improve the bioavailability of poorly soluble drugs. Ther Deliv. 2019;10(6):363-382.
2. Vo CLN, Park C, Lee BJ. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. Eur J Pharm Biopharm. 2013;85(3 Pt B):799-813.
3. Huang Y, Dai WG. Fundamental aspects of solid dispersion technology for poorly soluble drugs. Acta Pharm Sin B. 2014;4(1):18-25.
4. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems: X-ray diffraction and aqueous solubility studies on griseofulvin-polyethylene glycol 6000 systems. J Pharm Sci. 1977;66(7):989-991.
5. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int J Pharm. 2002;231(2):131-144.
6. Ford JL. The current status of solid dispersions. Pharm Acta Helv. 1986;61(3):69-88.
7. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50(1):47-60.
8. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci. 1999;88(10):1058-1066.
9. Newmann A, Axon J. Solid dispersions: a review of preparation methods and pharmaceutical applications. Drug Dev Ind Pharm. 2012;38(1):1-12.
10. Baghel S, Cathcart H, O'Reilly NJ. Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, and formulation aspects. Int J Pharm. 2016;499(1-2):234-247.
11. Manogna K, Nagaveni P, Thyagaraju K. Enhancement of solubility of poorly soluble drugs by solid dispersion: an overview. Indian J Pharm Biol Res. 2017;5(4):17-23.
12. Dhande LB, Chandel S. A review on solubility enhancement by solid dispersion method. J Drug Deliv Ther. 2021;11(1):158-165.
13. Aggarwal AK, Singh S. Physicochemical characterization and dissolution study of solid dispersions of diacerein with polyethylene glycol 6000. Drug Dev Ind Pharm. 2011;37(10):1181-1191.

14. Margarit MV, Rodríguez IC, Cerezo A. Physical characteristics and dissolution kinetics of solid dispersions of ketoprofen and polyethylene glycol 6000. Int J Pharm. 1994;108(2):101-107.
15. Nokhodchi A, Bolourtchian N, Dinarvand R. Dissolution enhancement of poorly soluble drugs using solid dispersion systems. J Pharm Pharm Sci. 2007;10(2):239-249.
16. Sethia S, Squillante E. Solid dispersions: revival with greater possibilities and applications in oral drug delivery. Crit Rev Ther Drug Carrier Syst. 2003;20(2-3):215-267.
17. Singh UP, Bhat HR, Mazumder B. Physicochemical characterization and in vitro dissolution studies of solid dispersions of ketoprofen with PVP K30 and d-mannitol. Saudi Pharm J. 2013;21(1):77-84.
18. Ammar HO, Salama HA, Ghorab M, Mahmoud AA. Formulation and biological evaluation of glimepiride solid dispersions with different carriers. Drug Dev Ind Pharm. 2006;32(1):45-51.
19. Giradkar RP, Avari JG. Enhancement of dissolution rate of gliclazide using solid dispersions with polyethylene glycol 6000. AAPS PharmSciTech. 2008;9(1):87-92.
20. Mupparaju S, Suryadevara V, Doppalapudi S. Preparation and evaluation of dolutegravir solid dispersions. Int J Appl Pharm. 2021;13(1):193-198.
21. Alqahtani MS, 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. 2021;22:116. doi:10.1208/s12249-021-01995-y.
22. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet. 2013;381(9868):735-743.
23. Eron JJ, Clotet B, Durant J, et al. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING study. J Infect Dis. 2013;207(5):740-748.
24. Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm Res. 2008;25(4):781-791.