International Journal of Medical and Pharmaceutical Sciences
Open access peer-reviewed Journal
Volume 2, Issue 1, Page 125-142.
https://doi.org/10.5281/zenodo.18265885

Research Article

Solubility Enhancement, Formulation and Evaluation of Dolutegravir

Dr. Sachin Jain*, Dr. Nidhi Bais, Ravindra Gawahad

Oriental University, College of Pharmacy, Indore

The present study was aimed at solubility enhancement, formulation, and evaluation of dolutegravir, a poorly water-soluble antiretroviral drug, to improve its dissolution rate and oral bioavailability. Owing to its low aqueous solubility, dolutegravir exhibits dissolution-limited absorption, which necessitates the development of suitable formulation strategies. Solubility enhancement was carried out using appropriate techniques such as solid dispersion, use of surfactants, and/or hydrophilic carriers. The optimized drug–carrier system was further formulated into a suitable oral dosage form. Preformulation studies were performed to assess physicochemical properties, drug–excipient compatibility, and flow characteristics. The formulated products were evaluated for post-formulation parameters including drug content uniformity, disintegration time, in vitro dissolution, and stability. In vitro dissolution studies revealed a significant improvement in the dissolution rate of dolutegravir from the optimized formulation when compared with the pure drug. The formulation showed satisfactory physicochemical characteristics and complied with pharmacopeial requirements. The results of the study demonstrate that the adopted solubility enhancement approach was effective in improving the dissolution behavior of dolutegravir, thereby indicating its potential to enhance oral bioavailability and therapeutic efficacy.

Keywords: solubility enhancement, poorly water-soluble, Antiretroviral drug, dolutegravir.

INTRODUCTION

Solubility phenomena have great influence on pharmaceutical industry1. It is defined as dissolution of solute in solvent to give a homogeneous system2. The solubility of substance basically depends on the temperature, pressure and existence of other chemicals of the solution and also chemical and physical properties of solute3,4. Solubility take place under equilibrium, which means solubility, obtain from the simultaneous and diverging process of dissolution and phase joining5. Because of certain condition solubility may increases which give a supersaturated solution. IUPAC defined solubility; it is the analytical composition of a saturated solution expressed as a fraction of solute in a designated solvent. It may be asserted in units of molality, mole ratio and concentration6,7. It is applied to all areas of chemistry, organic, inorganic physical and biochemistry. In all areas it will depend on the important physical condition that is concentration, temperature and pressure and also enthalpy and entropy that are directly related to the solvents and solute. Solubility behavior of drugs in solvent is important because solvent blends are often used in preformulation and drug formulation. Also, it is important to obtained desired concentration of the drug in systemic circulation, to attain maximum utilityin newly developed drug and to increase the therapeutic effectiveness8,9. Solubility of drug substance can be changed by two ways, either through formulation approaches or through material engineering10. Active pharmaceutical ingredient with poor aqueous solubility is one of the major obstacles in formulation development of oral dosage form. Because of this reason solubility is on the utmost point of formulation scientist. The solubility of drug is essential factor in determining the rate and extent of absorption. More than 90% of drugs are taken orally. Drug absorption, bioavailability, pharmacokinetic

profile of orally taken drug, these factors is highly reliant on solubility of that compound in water11. About 90% of drugs approved since 1995 exhibit poor solubility. Nearly 40% of new chemical entities identified in combinatorial screening programs used by many pharmaceutical companies are practically insoluble in water and not well absorbed when taken orally, which affect dissolution rate and bioavailability, resulting in high intra and inter subject variability and lack of dose proportionality12. Only 8% of new drugs in the world possess high solubility and permeability13. Poor water solubility obstructs drug bioavailability and decreases its pharmaceutical development. Pharmaceutical development of drug with low water solubility requires creation of appropriate formulation with various techniques14. Lack of solubility is the most rate-limiting step in the process of oral drug absorption; therefore, there is need to increase the solubility of drug. The Noyes-Whitney equation gives relation between solubility and dissolution, an increase in dissolution gives a significant enhance in solubility15,16. For this reason, the drug entities are grouped into four classes which are mainly based on solubility and permeability and this categorization are called as Biopharmaceutical Classification System (BCS). G.L. Amidon invent this classification in 1995 and since then it has become a yardstick in the bioequivalence regulation of oral drug products17,18.

Biopharmaceutical classification system of drug

The Biopharmaceutical Classification System (BCS) is a scientific structure for categorizing drug moieties according on their aqueous solubility and intestinal permeability). The BCS plays vital role for formulation scientist, for advising strategy to increase the effectiveness of drug development by proper choice of dosage form and bioequivalence tests19,20. The BCS guidance depends on three major factors, solubility intestinal permeability and dissolution, which govern the rate and extent of drug absorption21,22. Solubility of the drug substance will not be principal parameter when the absorption of the drug substance is permeation rate limited and so that in vitro dissolution study can be used to express bioavailability or bioequivalence of the drug product through in vitro-in vivo correlation. BCS gives better understanding of the connection between drug release from the product and the absorption process. According to this, the rate limiting step has prime importance. If drug release or dissolution is rate limiting process, then the bioavailability will be influence only by the in vivo performance of dosage form. On the contrary, as long as the penetration through bio-membranes is a restricted course, bioavailability and bioequivalence are not so reliant upon the release of drug behavior of the dosage form23,24.

MATERIAL & METHOD:

Table .1: List of drug, excipients and chemicals:

Sr.	Materials	Categories	Manufacturer/Supplier
1.	Dolutegravir	Antiviral	PharmaTech Solution
2.	Beta cyclodextrin	Solubility enhancer	Modern Sciences, Nashik B05096010
3.	Starch Sodium Glycolate	Superdisintegrant	Modern Sciences, Nashik S09951602
4.	Cross Carmellose Sodium	Superdisintegrant	Modern Sciences, Nashik 02153180712
5.	Microcrystalline	Binder	Modern Sciences, Nashik
6.	Magnesium Stearate	Lubricant	Modern Sciences, Nashik M01702211
7.	Talc	Glidant	Modern Sciences, Nashik 29540807
8.	Lactose	Diluent	Modern Sciences, Nashik L00602003

Table .2: List of Instruments/ Equipment:

Sr.no.	Name of Instruments	Make and Model
1.	Electronic balance	Shimadzu AUX220
2.	Tabletc ompression machine	Rimekminipress10STN, Karnavati
3.	FTIR Spectrophotometer	Shimadzu(8400S)
4.	Digital Melting point apparatus	Kumar Industries WMP-D
6.	Hardness tester	Mansanto Hardnesses
7.	Roche friabilato rtester	ElectronicsIndia902
8.	Dissolution apparatus	Electrolab /EDT-081x
10.	UV-Visible spectrophotometer	Shimadzu (UV2700)

EXPERIMENTAL WORK

Preformulation study

Organoleptic properties:

The sample of Dolutegravir was studied for organoleptic properties such as colour, odour, and appearance. The results are shown in Table

Melting point:

The melting point if the drug was determined by open capillary method using the melting point apparatus. The drug sample was filled into capillary tube which was previously sealed at the end. The tube was then placed in melting point apparatus. Temperature at which sample started melting and the temperature at which it completely melt was noted. The melting point is reported in Table Solubility: Solubility of Dolutegravir was determined in water, methanol, 0.1N HCI, pH6.8 Buffer and DMSO. The solubility was determined by addition of known quantity of drug to 2 ml of solvent each time until saturation. Solubility is determined on the basis of per ml dissolved sample. Results of solubility are shown in Table

Ultraviolet spectroscopy:

A) Calibration curve in Methanol:

Accurately weighed 10 mg of drug was transferred to calibrated 100 mL volumetric flask. It was dissolved in 20 mL methanol by sonication for 10 minutes. Final volume was made up to 100 mL with methanol to give the solution containing 100 µg/mL. From working standard solution, by pipetting out 5-25 µg/mL solution respectively into separate 10ml volumetric flask and diluting to volume with methanol to produce the concentration. The above solutions were scanned over the range of 400 nm to 200nm against blank (methanol). λ max was recorded and the absorbance of all solution was measured. The calibration curve was constructed by plotting concentration (5-25µg/mL v/s absorbance at λ max). Results shown in the Table

FTIR spectroscopy:

Infrared spectrophotometry is a useful analytical technique utilized to check the chemical interaction between the drug and other excipients used in the formulation. The sample (1 mg) was powdered and mixed with 10 mg of dry powdered potassium bromide. The powdered mixture was taken in a sample and the spectrum was recorded by scanning in the wavelength region of 4000-400 cm-1 using FTIR spectrophotometer Shimadzu(8400S). The IR spectra obtained is represented in Fig. No. and peaks values are mentioned in Table

Compatibility Studies:

To determine the compatibility of drug with excipients, drug-excipient compatibility study was carried out. Drug and excipient in 1:1% W/W were filled in the prewashed and dried amber colored glass vials and sealed with Aluminum cap. The sealed vials were kept at 40± 2°C for 1 day in oven. At the end of one day vials were removed from desiccator and were compared with control samples which were kept at room temperature. The control and test samples were examined. They were examined by FTIR method to study any interactions that may occur between drug and excipient. Peaks observed are shown in Figure.

Solubility Enhancement by Inclusion Complexation

Preparation of Inclusion Complexes:

For the preparation of binary inclusion complexes of Dolutegravir various technique like kneading method and various excipient. Polymer ratio was prepared out of which kneading method and β-Cyclodextrins were optimized as it gives better result than others.

Kneading Method:

Inclusion complex of Dolutegravir and Beta cyclodextrins were prepared by kneading method. In which distilled water was used to prepare drug: carrier complex in a mortar by grinding ingredients for half an hour. After grinding, the wet mass left to air dry at room temperature for 48 hours with intermit tent mixing and agitation. The complexes were made in different ratios with respect to drug and carriers.

Table 3: Formulation of Inclusion complex of dolutegravir and Beta cyclodextrin by Kneading method

Dolutegravir: Beta cyclodextrin	
Kneading Method	**Ratio**
KM-1	1:0.5
KM-2	1:1
KM-3	1:2

Characterization of each Approach:

Production Yield:

The Percentage yield of complexes of various combinations was calculated using the weight of final product after drying with respect to the initial total weight of the drug and carrier used for the preparation of complexes. Percent production yields were calculated as per the formula given below. Table

PY: Product yield
PY =WO/WT × 100
WO: Practical mass (complexes)
WT: Theoretical mass (carrier + drug)

Drug content:

About 10 mg drug equivalent of complexes (theoretical) were weighed accurately and transferred to 100 ml volumetric flask to which 20 ml methanol was added and sonicated for 15 min. Final volume was made up with methanol to give 100 ppm ck solution. From this stock solution (100 ml), 1 ml was withdrawn and further diluted up to 10 ml with method solution was used for the assay for dray content by UV spectrophotometer at Concentration of drug in stock solution was calculated by using calibration curve and form which percent drug content was calculated, Table

% Drug Content = WA/WT × 100

WA: actual drug content: WT: theoretical drug content.

Method of preparation and evaluation of powder blend

Table No. 4 Formula for immediate release Tablet

Sr No.	Ingredients (mg)	F1	F2	F3	F4
1.	Dolutegravir: β-CD	185.31	185.31	185.31	185.31
2.	Starch Sodium Glycolate	8.19	5.69	-	-
3.	Cross carmellose Sodium	-	-	8.19	5.69
4.	Microcrystalline Cellulose	2.5	5	2.5	5
5.	Magnesium Stearate	2	2	2	2
6.	Talc	2	2	2	2
8.	Total	200	200	200	200

EVALUATION OF POWDER BLEND

Angle of repose - Angle of repose was determined using funnel method. The blend is poured through a funnel that can be lifted vertically to a maximum cone height (h) is obtained. The radius of the heap (r) is measured and angle of repose (θ) is calculated using following formula:

θ = Tan-1 (h / r)

Where, θ = Angle of repose

h = height of the pile r = radius of plane surface occupies by the powder

Table No. 5: Relationship between Angle of repose and Flowability

Angle of repose	Flowability
<20	Excellent
20-30	Good
30-40	Acceptable
>40	Very poor

The flow properties of powder blends were analyzed by determining angle of repose which was found to be between 26.26 to 28.59 indicating good flow property. Result of angle of repose are mentioned in Table

Bulk Density - The granular powder weighing 10 grams is placed in 100 ml measuring cylinder. The volume occupied by the powder was observed without disturbing the cylinder and bulk density was estimated by the following equation.

ρb = M / V

Where, ρb - is bulk density, M- is the weight of powder in gm. V- is the volume of powder in ml. The powder blend of formulation has the bulk density range between 0.520 to 0.580gm/ml. Result of bulk density is mentioned in Table

Tapped density- Weigh 10 gram of granular powder and placed in a 100 ml measuring cylinder. The cylinder was then subjected for the specified number of taps (100) until the powder bed has reached the lower limit. The last mass was read, and the tap density is computed by following equation.

Where,

ρt-is tapped density,

ρt = M / Vt

M-is the weight of the powder in gm. Vt- is the tapped volume in ml.

The powder blend of formulation has the tapped bulk density ranged between

0.592 to 0.680gm/ml. Result of tapped density are mentioned in Table

Compressibility index - the simplest method of measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index which is calculated as follows.

% Compressibility: tapped density-bulk density/ tapped density× 100

[% C.I. = ρt – ρb / ρt × 100]

Table No. 6: Relation between % Compressibility and Flowability

% Compressibility	Flowability
5-15	Excellent
12-16	Good
18-21	Fairly acceptable
23-35	Poor
33-38	Very poor
>40	Very very poor

The % compressibility index for all the formulation was found to be 10.34 to 17.18 indicates that powder have good flow compressibility. Result of % compressibility index are mentioned in Table

Hausner's ratio (H) - This is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's ratio= tapped density/ bulk density

[Hausner's ratio = ρt / ρb]

Where,

ρb = Bulk density ρt = Tapped density

Table No. 7: Relation between Hausner's Ratio and Flowability

Hausner's Ratio	Flowability
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very very poor

The Hausner's ratio of all the formulation was found in the range of 1.11 to 1.20 indicating that powder has good flow property. Result of Hausner's ratio is mentionedin Table

Compression of Powder blend into Tablet

After evaluation of powder blend the immediate release tablet were papered by direct compression method using 10 station rotary tablet compression machine equipped with flat faced 11.4mm punches. Before compression, surface of the die and punch were lubricated with aerosol. Four type of formulation containing variable amount of two main super disintegration were papered. All the preparation were stored in airtight containers at room temperature for further study.

EVALUATION OF IMMEDIATE RELREASE TABLET:

Characterization of prepared tablets:

Compressed tablets were characterized for their thickness, hardness, friability, weight variation and drug content parameters.

Thickness:

Three tablets were taken from each formulation and their thickness was determined by using Vernier caliper. The results are shown in Table

Hardness:

In this test crushing strength, which cause the breaking of tablet is measured for that tablet is placed

between two anvils and then applies the force. Tablets were taken from each formulation and their hardness was determined by using Monsanto hardness testers. The unit of hardness is Kg/cm2.The results are shown in Table

Friability:

Ten pre-weighed tablets from each formulation were placed at each time in the Roche friabilator (Rimek, India) which was then operated for 100 revolutions at 25rpm. The tablets were then dusted and reweighed. The friability was then calculated using following formula, the results are shown in Table

Fig No. 1 Friability

% friability = (initial weight – weight after 100 revolutions) / initial weight x 100

% friability of tablets which is less than 1% is considered acceptable.

Weight variation:

To study the weight variation, 20 tablets of each formulation were weighed using an electronic digital balance. The average weight of 20 tablets and standard deviation were calculated. The individual weight compared with average weight. If tablets pass the test if not more than two tablets are outside percentage limit and if no tablet differ by more than two times the percentage limit. The following % deviation in weight variations allowed according to USP. The results are shown in Table

Table No. 8: Percentage deviation Vs average weight according to USP

Sr. No.	Average wt. of Tablet	Maximum % Difference Allowed
1.	130 or less	10
2.	130-324	7.5
3.	More than 324	5

Disintegration time-

The in vitro disintegration studies were carried out using tablet disintegration test Apparatus. One tablet was placed in each of the six tubes of the basket assembly and disk was added us each tube. This assembly was then suspended in one liter booker containing water maintained at 37±2℃. The basket was then moved up and down through a distance of 5 to 6 cm at a frequency 28 to 32 cycles per minutes. The time required for complete disintegration of the tablet was recorded. The results are shown in Table

Fig No. 2 Disintegration time apparatus

Drug Content-

Five tablets were weighed and powdered using glass mortar and pestle. An accurately weighed 100 mg of powder was taken in to 50 ml volumetric flask, dissolved in Methanol and the solution was filtered through what man filter paper no. 41. The filtrate was collected and suitably diluted with phosphate buffer of pH 6.8. The drug content was determined at 260 nm by UV spectrophotometry. The results are shown in Table

In vitro dissolution test-

In vitro dissolution study of tablet was conducted using USP apparatus XXII paddle apparatus 900 ml of pH 6.8 buffer as dissolution media. The paddle speed was kept at 75 rpm throughout the study. Sample of 5 ml was removed at a time interval of 5, 10,15,20,25,30,35,40,45 min. and volume were replaced with the fresh medium. The samples were filtered and the concentration in each sample was determined by UV at 260nm with a spectrophotometer and reported as average of three determinations. Cumulative percent drug release was calculated using an equation obtained from standard curve. The results are shown in Table

Fig No. 3 Dissolution Test Apparatus

Drug release kinetics [84]:

To analyze the in-vitro release data various kinetic model were used to describe the release kinetics. The zero-order rate equation describes the system where the drug release rate is independent of its concentration. The First order equation describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on fickian diffusion equation.

a) Zero order kinetics:
   $Q=K0t$

b) First order Kinetics:

Log C = log C0 – Kt/ 2.303

c) Higuchi's model:
Q = kt1/2

d) Korsmeyer equation/ Peppa's model:
Mt / M0 = Ktn

Where, Q is Percentage drug released at time t and k was release rate constant, depending on the kinetic model used. Mt/Mo is the fraction of drug released into the dissolution medium and k was constant involving the structural and geometrical characteristics of the tablets. The term n was diffusion that characterizes drug released transport mechanism. The n value is used to characterize different release mechanism as given in the table below. The results are shown in Table

Table 9: Diffusion exponent and solute release mechanism

Sr. No	Diffusion exponent	Overall solute diffusion mechanism
1.	0.45	Fickian diffusion
2.	0.45 <n< 0.89	Non- Fickian diffusion
3.	0.89	Class II transport
4.	>0.89	Super case II transport

RESULT AND DISCUSSION

Preformulation study

Characterization of Dolutegravir

Organoleptic Properties of Dolutegravir

Dolutegravir was studied for organoleptic properties like color, odor and appearance.

Table No.10: Organoleptic Properties of Dolutegravir

Sr. No.	Properties	Observation
1	Appearance	Amorphous powder
2	Colour	White powder
3	Odour	Odorless
4	Taste	Bitter taste

Melting point:

The melting point of the drug matches with the values found in literature.

Table No. 11: Melting point of Dolutegravir

Drug	Practical	Theoretical range
Dolutegravir	192°C -193°C	190°C-193°C

Solubility:

Table No. 12: Solubility of Dolutegravir

Solvent	Observation
Methanol	Very Slightly Soluble
0.1 N HCl	Freely soluble
Distilled Water	Practically insoluble
DMSO	Soluble

Ultraviolet- Visible spectroscopy:

Determination of λ max Dolutegravir in 0.1N HCl:

UV spectrum of Dolutegravir solution in 0.1N HCl and exhibited wavelength of absorbance maximum at 260nm respectively. The spectrum of Dolutegravir is shown in Figure

Table No. 13: Maximum wavelength (λ max) of Dolutegravir in Methanol and 0.1 N HCL

Solvent	λmax(nm) Observed
Methanol	263
0.1N HCl	259

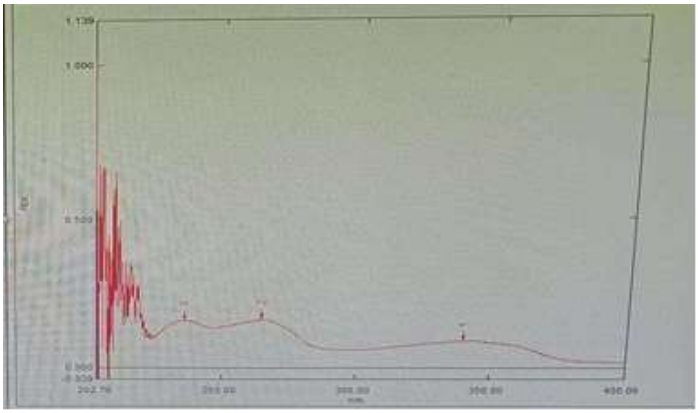


Figure No 4: UV-visible spectrum of Dolutegravir in Methanol

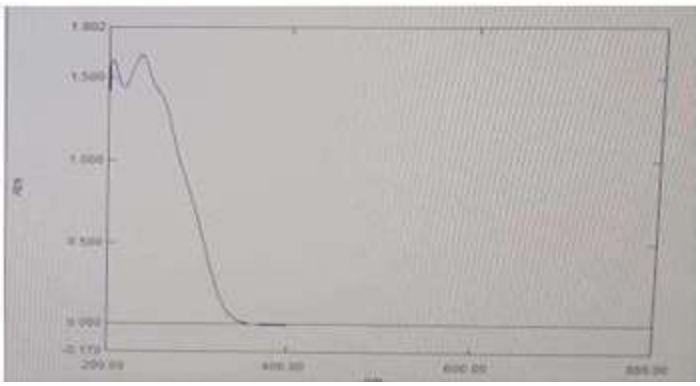


Figure No. 5: UV-visible spectrum of Dolutegravir in 0.1 N HCL

Calibration curve of Dolutegravir in Methanol:

Calibration curve of Dolutegravir was constructed in Methanol. A linear relationship was obtained in between 5-25 µg/ml and absorbance of Dolutegravir with R2value of 0.9881 at 260 nm is shown in Figure No. 8.3

Table No 14. Absorbance for calibration curve of Dolutegravir Methanol

Sr.no	Concentration (µg/ml)	Absorbance
1	5	0.14
2	10	0.275
3	15	0.391
4	20	0.551
5	25	0.671

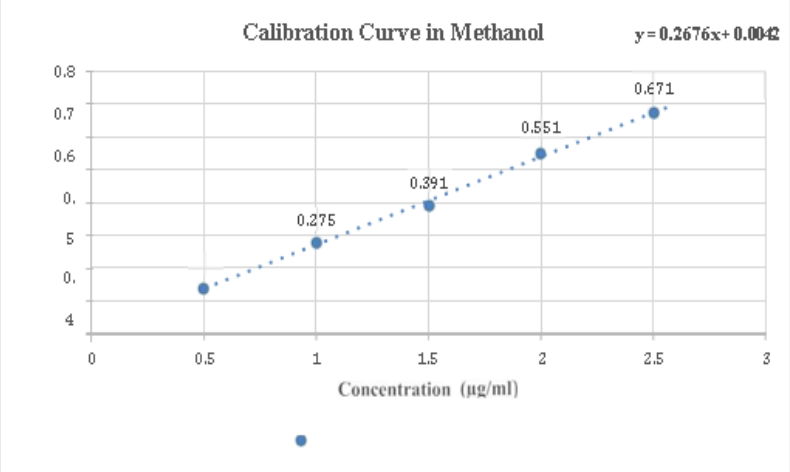


Figure No.6: Calibration curve of Dolutegravir in Methanol

Calibration curve of Dolutegravir in 0.1N HCl

Calibration curve of Dolutegravir was constructed in 0.1N HCl. A linear relationship was obtained in between concentration (5-25µg/ml) and absorbance of Dolutegravir in 0.1N HCl with R2 value 0.991 at 260 nm is shown in Figure No. 8.4. The data of absorbance areas shown in Table No. 8.6

Table no. 15 Absorbance for calibration curve of Dolutegravir in 0.1N HCl

Sr.no	Concentration (µg/ml)	Absorbance
1	5	0.3378
2	10	0.5415
3	15	0.7419
4	20	0.9527
5	25	1.1849

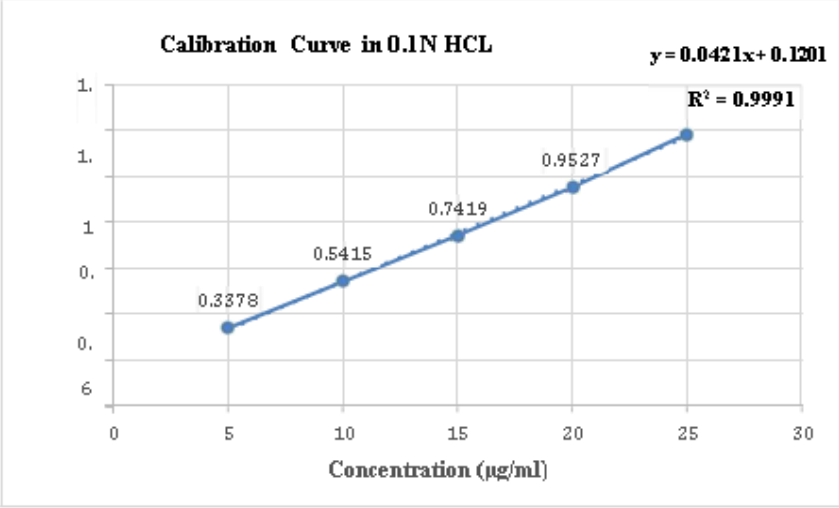


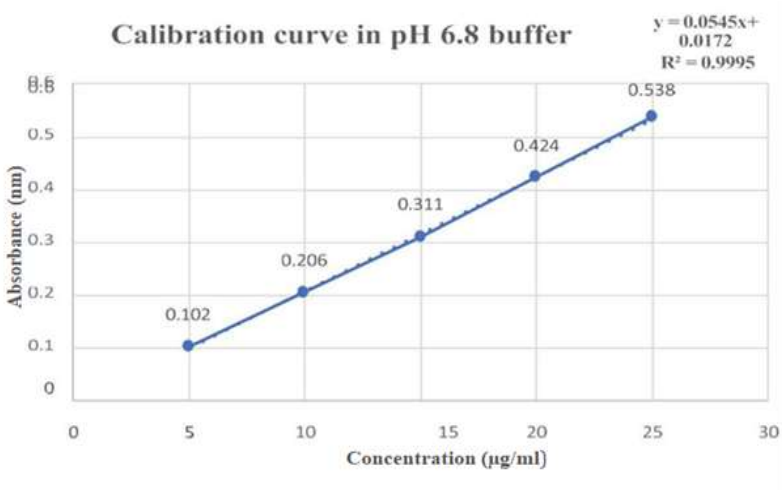
Figure No.7: Calibration curve of Dolutegravir in 0.1N HCL

Calibration curve of Dolutegravir in pH 6.8

Calibration curve of Dolutegravir was constructed in pH 6.8 buffer. A linear relationship was obtained in between concentration (5-25µg/ml) and absorbance of Dolutegravir in pH6.8 with R2 value 0.9995 at 260 nm is shown in Figure No. 8.5. The data of absorbances are as shown in Table No. 8.7

Table no. 16: Absorbance for calibration curve of Dolutegravir in pH 6.8

Sr.no	Concentration (µg/ml)	Absorbance
1	5	0.102
2	10	0.206
3	15	0.311
4	20	0.424
5	25	0.538



Fourier Transforms Infrared Spectroscopy (FTIR) study:

FTIR study of Dolutegravir was carried out to check out the purity of the drug. For this the powdered mixture of Dolutegravir and KBr was taken in a sampler and spectrum was recorded by scanning in wavelength region of 4000-400 cm-1 using FTIR spectrophotometer. FTIR spectrum of Dolutegravir is shown in the Figure

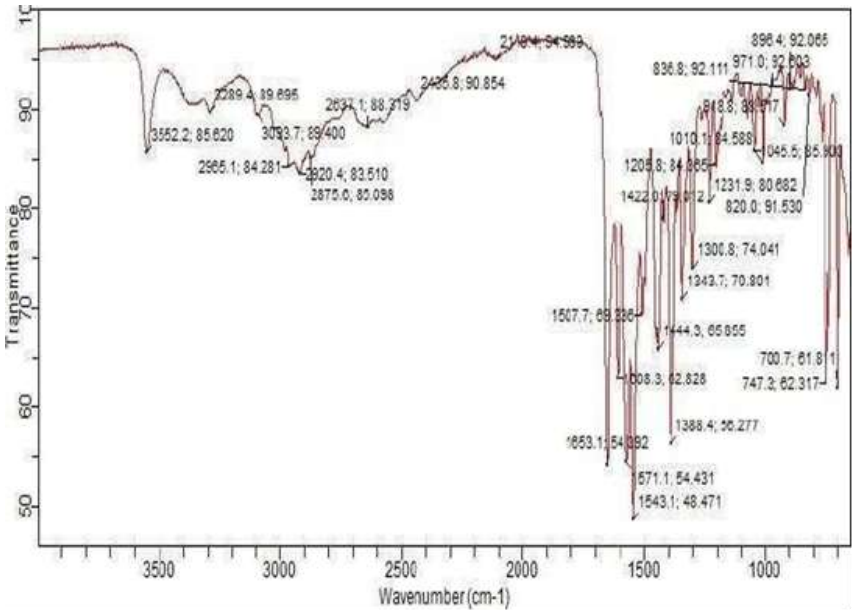


Figure No. 8: FTIR spectrum of Dolutegravir

The absorption bands shown by Dolutegravir are characteristics of the groups present in its molecular structure. The presence of absorption bands corresponding to the functional groups present in the structure of Dolutegravir confirms the identification and purity of Dolutegravir sample.

Table No. 17: Major peaks observed in FTIR spectrum Dolutegravir

Peak observed (cm-1)	Interpretation	Standard Value
2985.1	C-H stretching (alkane)	2840-2980
1010	C-F stretching	1000-1400
3289	C-NH stretching	3200-3600
1653	C=O stretching	1600-1700
3552	C-OH stretching	3450-3600
1301	C-N stretching	1266-1342
1205	C-O stretching	1050-1250

Drug-Excipients compatibility study: FTIR study: Drug excipient compatibility study showed no interaction between Dolutegravir and selected excipients as there were no significant shift of peaks in the IR spectrum. So, it was concluded that the selected excipients were compatible with the drug Dolutegravir.

8.3.1 Dolutegravir with - Cyclodextrin:

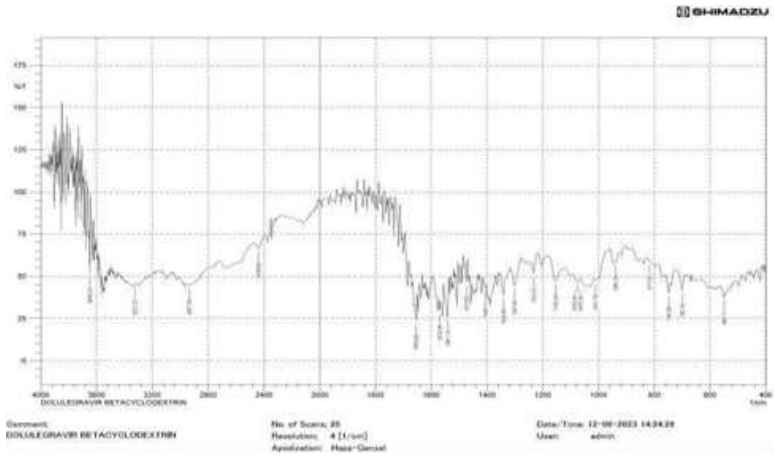


Figure No. 9: FTIR spectrum of Dolutegravir with beta-Cyclodextrin

Table No. 17: Major peaks observed in FTIR spectrum of Dolutegravir with Beta- Cyclodextrin

Peak observed (cm-1)	Interpretation	Standard Value
2937	C-H stretching alkane	2840-2900
3327	C-H stretching	3300-3400
1340	C-N bending	1266-1342
1670.36	C-F stretching	1000-1400

Dolutegravir with All Excipients:

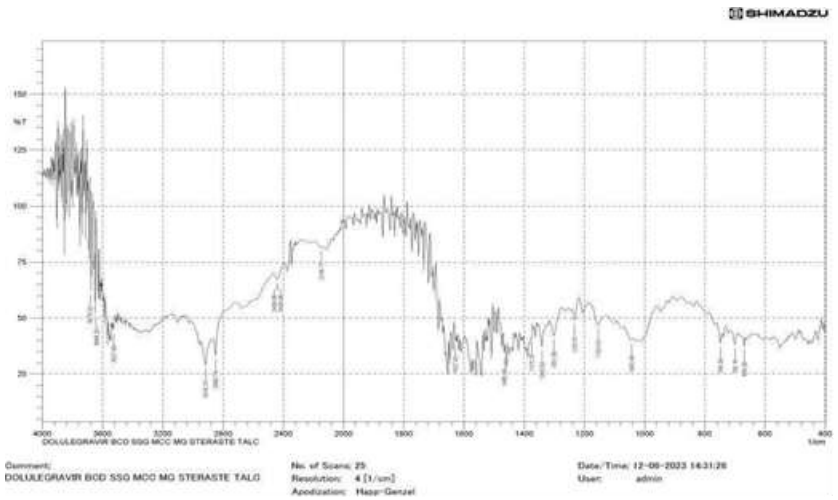


Figure No. 10: FTIR spectrum of Dolutegravir with All Excipient

Table No. 18: Major peaks observed in FTIR spectrum of Dolutegravir with All Excipient

Peak observed (cm-1)	Interpretation	Standard Value
3676	O-H stretching	3584-3700
2850	Stretching in alkane	2840-3000
1627	N-H bending amine	1580-1650
1465	C-H bending alkane	1465
1232	C-O stretching	1200-1275

Preparation of Inclusion Complex:

Table No.19 preparation of inclusion complex

Ratio	Percentage Yield	Drug Content
1:0.5	85.70	84.6
1:1	88.76	92.8
1:2	95.16	98.1

Evaluation of Pre-Compression Parameters:

The prepared powder blend was evaluated for properties like Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose. The developed formulations were subjected to evaluation of various pre-compression parameters before formulation into tablets, results are as depicted in Table All formulations exhibited good flow properties.

Table No. 20: Characteristics of powder blend

Formulation	Angle of repose (θ)	Bulk Density (gm/ml)	Tap Density (gm/ml)	% Compressibility Index	Hausner's Ratio
F1	28.59	0.58	0.66	11.76	1.13
F2	26.57	0.52	0.58	10.34	1.11
F3	27.26	0.53	0.58	17.18	1.20
F4	26.26	0.63	0.76	17.10	1.20

a) Angle of Repose:

The flow properties of powder blends were analyzed by determining angle of repose which was found to be between 26.26 to 28.59 indicating good flow property.

b) Bulk density:

The powder blend of formulation has the bulk density range between 0.520 to 0.580gm/ml.

c) Tapped density:

The powder blend of formulation have the tapped bulk density ranged between 0.592 to 0.680gm/ml.

d) % Compressibility index:

The % compressibility index for all the formulation was found to be 10.34 to 17.18 indicates that powder have good flow compressibility.

h) Hausner's ratio:

The Hausner's ratio of all the formulation was found in the range of 1.11 to 1.20 indicating that powder has good flow property.

Evaluation of Post-Compression Parameters:

Table No. 21: Results of post-compression parameters

Batch	Weigh Variation (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Disintegration Time	Drug Content (%)
F1	199.4±1.7	3.4±0.1	2.58±0.08	0.9	2min55 sec	74.4
F2	200.0±1.5	3.31±0.1	2.63±0.04	0.8	3 min 60 sec	89.1
F3	199.4±1,9	3.59±0.5	2.56±0.02	0.5	3 min 55 sec	77.3
F4	199.2±1.7	3.85±0.4	2.72±0.05	0.7	2 min 19 sec	86.7

Results are expressed as Mean ± Standard deviation (n=3)

a) Weight Variation

Weight variation of tablet formulation was found to be in 199.2 to 200 mg which is within acceptable limit as per IP (+5%)

b) Hardness

Hardness of tablet formulation was found to be ranging from 3.31 to 3.85 kg/cm2. Result obtained are within acceptable limit.

c) Thickness

Thickness of tablet formulation was found to be ranging from 2.56 mm to 2.72 mm. Variation of thickness in tablet formulation (F1 to F4) was found within the acceptable limits.

d) Friability

Friability of tablet formulation was found to be ranging from 0.5 to 0.9 %. Result obtained are within acceptable limit which is not more than 1 %.

e) Disintegration Time

Disintegration time of tablet formulation was found to be in 2 min 19 sec to 3 min 60 sec within acceptable limit as per IP (30 mints or as per monograph).

f) Drug Content

The Immediate release tablet showed drug content between 74.4- 89.1%. Thus, all tablets comply with USP standard.

In-Vitro Drug Release:

In vitro dissolution study of tablet was conducted using USP apparatus XXII paddle apparatus 900 ml of pH 6.8 buffer as dissolution media. The paddle speed was kept at 75 rpm throughout the study. Sample of 5 ml was removed at a time interval of 5,10,15,20,25,30,35,40,45 min. and volume were replaced with the fresh medium. The samples were

filtered and the concentration in each sample was determined by UV at 260nm with a spectrophotometer and reported as average of three determinations.

Table No. 22: Percent cumulative drug release from different formulations

Time (min.)	F1	F2	F3	F4
0	0	0	0	0
5	17.20	32.39	25.49	22.48
10	22.37	38.40	39.01	30.89
15	38.77	57.15	61.57	39.32
20	61.59	64.78	72.02	62.11
25	63.59	79.35	74.20	66.16
30	80.95	85.87	76.05	80.98
35	85.03	87.21	79.21	83.84
40	90.80	90.15	88.73	90.97
45	96.52	99.45	93.34	96.99

In-vitro drug release was found to be in between 93.34-99.45%. The percentage of drug release increase with increase in concentration of solubility enhancer and super disintegrant. F2 batch shows more drug release (99.45%) than other batches. Drug release kinetics of optimized batch formulation

Table No. 23: Drug release kinetics of optimized batch formulation

Batch Code	Zero order R2	First order R2	Higuchi R2	Korsmeyer- Peppas R2
F2 (opt.batch)	**0.913**	**0.9272**	**0.957**	**0.9748**

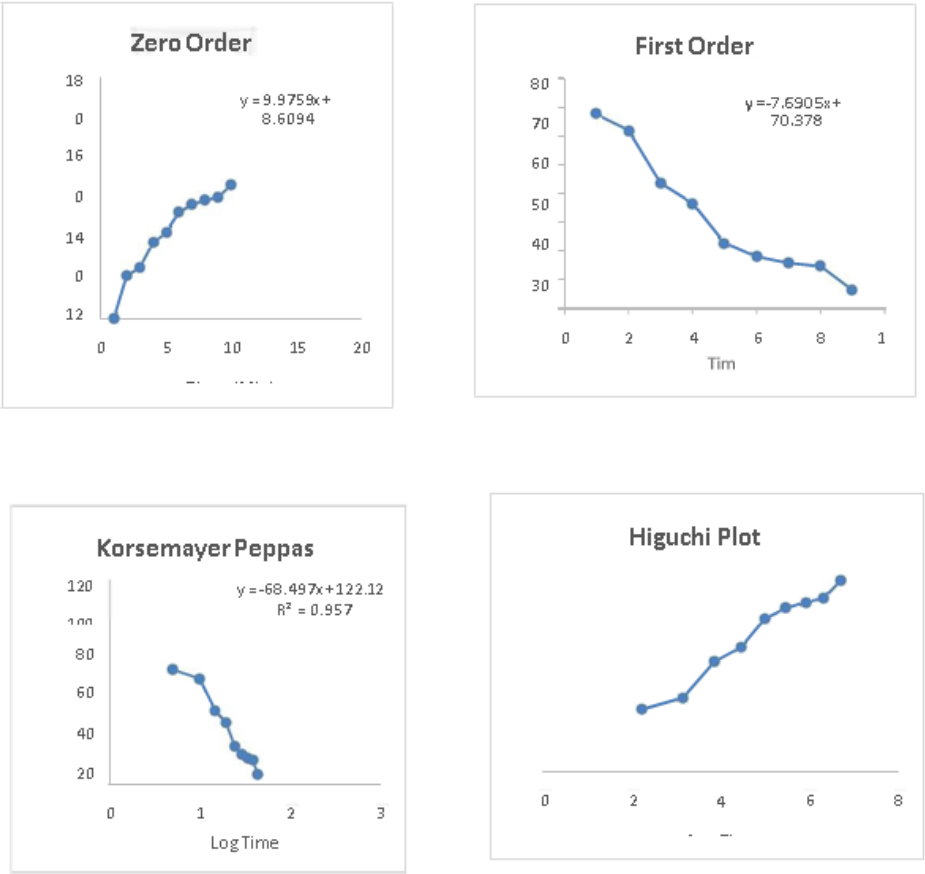


Fig No. 11: Drug released kinetic for optimized batch

CONCLUSION

The complex of dolutegravir was prepared using β-CD to improve solubility and bioavailability of drug inclusion complexation technique was preferred for enhancement of solubility. Different complexes were prepared by using kneading method. Solubility studies confirmed the improvement in drug solubilization and absorption form complex as compared to pure drug. β-CD shows more effect as complexing agent has found more advantage to increase solubility of drug by inclusion complexation. Apart from solubility method linearity was observed in concentration and solubility. Finally, it was concluded that the aims and objective of this work the enhancement of solubility of dolutegravir. Dolutegravir immediate release tablet was made by Direct Compression by using complexation technique. FTIR spectra shows there is no interaction between drug and excipients. Characterization of powder blend was carried out like angle of repose, bulk density, tapped density, carr's index, hausner's ratio. Then results shows that powder blend has good flow property. In this formulation super disintegrants (Sodium Starch Glycolate, Cross carmellose sodium) added to increase drug release.

REFERENCES

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 andvesicular 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. akshman 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
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. Tran TTD, Tran PHL. Insoluble polymers in solid dispersions for improving bioavailability of

poorly water-soluble drugs. Polymers (Basel). 2020;12.

14. 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 Pharm SciTech. AAPS Pharm SciTech; 2021; 22:1–12.
15. 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.
16. 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.

Cite: Dr. Sachin Jain*, Dr. Nidhi Bais, Ravindra Gawahad, Solubility Enhancement, Formulation and Evaluation of Dolutegravir, Int. J. Med. Pharm. Sci., 2026, 2 (1), 125-142. https://doi.org/10.5281/zenodo.18265885