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Development and Validation of Stability Indicating Hplc Method for Quantification of Dolutegravir Sodium in Bulk as Well as Pharmaceutical Dosage Form

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KEYWORDS

Dolutegravir sodium,
HPLC,
Forced Degradation,
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ICH

ABSTRACT:

Objectives: The aim and objective of this research paper is the development and validation of a rapid, simple, sensitive, precise and specific stability-indicating high-performance liquid chromatographic (HPLC) method for the quantitative estimation of dolutegravir sodium in bulk drug and pharmaceutical dosage form.

Methods: The chromatographic separation was achieved on the Thermo Fischer Scientific C8 Synchronis (150x4.6mm, 5µm) using isocratic mode. Mobile phase composed of a mixture of Buffer: ACN in the ratio of 60:40 v/v at the flow rate of 1mL/min. The wavelength of detection is 258 nm. The retention time of DTG was 6.60.

Results: The proposed method shows a good linearity in the concentration range of 80–120% for DTG. Precision and recovery study results are in between 98 and 102%. In the entire robustness conditions, percentage relative standard deviation is <2.0 %. The peak for dolutegravir sodium was observed at 6.0±1.0 minutes. This method is validated for different analytical performance parameters like linearity, precision, accuracy, limit of detection, limit of quantification and robustness were determined according to the International Conference of Harmonization (ICH) Q2B guidelines. All the parameters of validation were found in the acceptance range of ICH guidelines. The developed method is stability indicating, precise and specific which can be applied for the routine quality control analysis of dolutegravir sodium.

1. INTRODUCTION

Dolutegravir sodium chemically known as sodium;(3S,7R)-13-[(2,4-difluorophenyl)methylcarbamoyl]-7-methyl-9,12-dioxo-4-oxa-1,8-diazatricyclo[8.4.0.03,8]tetradeca-10,13-dien-11-olate (Fig 1), is an integrase stand transfer inhibitor which is active against human immune-deficiency virus that binds to the integrase active site and block the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle and ultimately inhibits the viral activity.[1-4]

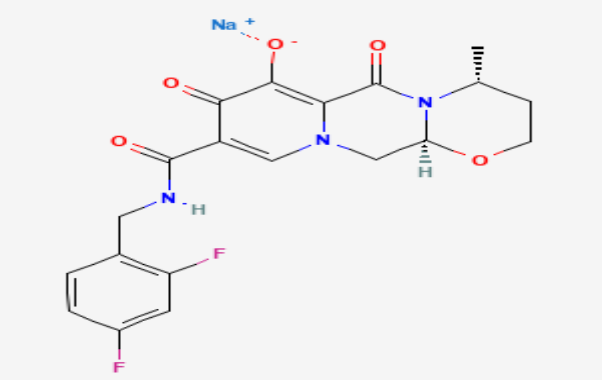

Fig 1: Structure of Dolutegravir Sodium

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The high mortality rate and increased transmission of human immunodeficiency virus (HIV) have made it a worldwide public health problem, which is mostly spreading out in the countries having middle and low financial resources[5-7]. There were approximate 39.9 million people living with HIV in 2023, and about 1.4 million of those were less than 15 years old. India has the third largest HIV epidemic in the world. In 2023, HIV prevalence among adults (aged 15-49) was an estimated 0.2%. This figure is small compared to most other middle-income countries but because of India's huge population (1.46 billion people) this equates to 2.5 million people living with HIV[8,9].

Integrase strand transfer inhibitors (INSTIs), the newest class of antiretrovirals, act by preventing HIV DNA from incorporating into the host T-lymphocyte genome, limiting virus propagation. Dolutegravir, the most recent INSTI, can be taken once daily[10]. The integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) is recommended as an alternative first-line HIV treatment to efavirenz (EFV) in the current World Health Organization (WHO) consolidated antiretroviral (ARV) guidelines[11], and is widely recommended in other international treatment guidelines[12-14]. The efficacy of DTG has been established in studies of the naive and pre-treated patients[15-18]. In particular, DTG has shown an improved safety profile compared to the non-nucleoside reverse transcriptase inhibitor (NNRTI) EFV as first-line treatment[19].Generic versions of DTG have already become available as a single tablet regimen.

The literature review revealed a liquid chromatography–tandem mass spectrometry method[20] and a sensitive HPLC–MS/MS method[21] for the estimation of dolutegravir in human blood plasma. A stability-indicating high performance thin liquid chromatography method[22] and ultra-high performance liquid chromatography method[23] were reported for the estimation of dolutegravir sodium with other drugs. One HPLC-ultraviolet method in combination with liquid-liquid extraction with isocratic elution was reported to analyze Dolutegravir plasma concentration[24]. Few studies of HPLC method are available yet for the quantitative determination of dolutegravir. Further, official monograph of dolutegravir sodium present in pharmacopoeia consists of gradient method. The aim of the present work was to develop simple, economic, precise, accurate, specific, stability-indicating HPLC method for the determination of dolutegravir in bulk form and/or in pharmaceutical dosage form. The developed method was validated as per International Conference on Harmonization (ICH) guidelines.

2. OBJECTIVES

- The objective of the present work is to develop a stability indicating analytical method for the quantification of active content of Dolutegravir in bulk and pharmaceutical dosage formulation, forced degradation studies according to ICH guidelines and quantification of degradants if present.
- The developed method may be applied in pharmaceutical industry to assure the good quality of drugs.
- The present work also can be extended for identification, isolation and characterization for potential degradation impurities which are found during stability testing, manufacturing process and stress study of formulation drug products by hyphenated techniques.
- Based on above objective and literature search we have selected dolutegravir tablet formulation for performing research in analytical method development and validation as follows:
  - Development and validation of a reverse phase-liquid chromatographic method for Dolutegravir in bulk and tablet dosage form.
  - Development and validation of a stability indicating RP-HPLC method for the estimation of dolutegravir in pharmaceutical formulations as per ICH guidelines.
  - Identification and characterization of a novel potential degradant if found.

3. MATERIALS AND METHODS

Instrumentation

Chromatographic separation was performed using the Agilent 1200 chromato-graphic system equipment with a reciprocating pump UV/Visible detector with a 20 µL fixed loop, and the data were analyzed by using Data Ace software. The analytical balance used for weighing

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the standard and sample was Mettler Toledo. An Ultrasonicator was used for sonication. The Thermo Scientific Forma 3960 Series environmental chamber was used for stress testing. The mixture was filtered through 0.45 µm membrane under vacuum.

Solvents & Chemicals

Dolutegravir sodium bulk drug was obtained from Cipla. The HPLC Water was obtained from a Milli-Q UF-Plus apparatus (Millipore) and was used to prepare all solutions for the method. Other chemicals and reagents used were of analytical grade.

Selection of Chromatographic conditions

Proper selection of the method depends up on the nature of the sample (ionic/ ionizable / neutral molecule), its molecular weight and solubility. The drug selected in the present study, was polar in nature. Thus reverse phase HPLC was selected for the initial separation because of its simplicity, suitability, ruggedness and its wider usage.

Selection of wavelength

Using photodiode spectrophotometer, the absorption spectra of the solution of dolutegravir were scanned in the UV region 200–400 nm spectra .The spectra of 10 ppm solution of dolutegravir in methanol were recorded on a UV spectrophotometer. The wavelength of the maximum absorbance was observed.

Preparation of Buffer and Mobile Phase

Mobile Phase A: Buffer Preparation

Transferred 500 mL HPLC grade/milli-Q water into a 1000 mL reagent bottle and 180 mg of EDTA disodium salt dihydrate was added to it and further diluted with 500mL of HPLC grade water. The solution was shaken until the particles get dissolved and sonicated to degas in an ultrasonic bath. Filter through 0.45µm membrane filter. It should be used within 3 days from the date of its preparation and appropriate proportion to prepare different volumes of solution and stored at room temperature.

Mobile Phase B: Solvent Mixture

Transferred 500 mL HPLC grade Acetonitrile into a 1000 mL reagent bottle. Pipette 1mL of HPLC grade Trifluroacetic acid into it and it is further diluted with 500 mL of HPLC grade Acetonitrile. Prior use, the solution was sonicated to degas in an ultrasonicator for 10 minutes and filtered through 0.45µm membrane filter. The solution should be used within 3 days from the date of its preparation and appropriate proportion to prepare different volumes of solution and stored at room temperature.

Mobile Phase Preparation

Prepare Mixture of Mobile Phase A and Mobile Phase B in the ratio of 60:40 v/v

Preparation of Diluent Solution (Methanol 60% v/v in water)

Transferred 600 mL of HPLC grade Methanol into a 1000 mL reagent bottle. Added 400 mL of HPLC grade water and mixed well. Sonicated and degassed in ultrasonic bath. Stored at room temperature and used within 3 days from the date of its preparation.

Experimental Method

Preparation of Standard Solution

Weigh accurately about 100 mg of Dolutegravir standard and transfer it into a 200mL volumetric flask. Add about 140 mL of diluent, sonicate to dissolve and dilute to volume with diluent and mix well. Further dilute 5mL to 50 mL with diluent.

Preparation of Test Solution

Take 20 tablets and weigh accurately top calculate the average weight. Accurately weigh and transfer 5 tablets into a 500 mL volumetric flask by using mechanical shaker until complete dispersion of tablets. Then add 350 mL of diluent and sonicate for 45 minutes with intermittent shaking at room temperature, dilute to the volume with diluent and mix well.

Preparation of Standard Stock Solution

Accurately weighed dolutegravir sodium standard equivalent to 100 mg dolutegravir was transferred into a 100-mL volumetric flask. It was dissolved in 70 mL of diluent by sonication for one minute and then further diluted to volume with the same diluent in order to obtain the standard stock solution of the concentration 1000 µg/mL of dolutegravir.

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Method Validation Studies

The HPLC method was validated as per the ICH guidelines [25-27].

System Suitability Parameters

Six replicate injections of system suitability solutions (working standard solution) were injected. The retention time, areas, theoretical plates, peak asymmetry, and resolution were calculated for standard solutions.

Precision

Precision of the method was verified by system and method precision (Repeatability).

- System precision was performed by six standard preparations of Dolutegravir injected at the nominal concentration level i.e., 100 ppm. The % RSD of the six determinations was calculated.
- Method precision/ Repeatability was determined by six separate solutions of Dolutegravir sample at a concentration of 0.05 mg/mL. %RSD for the content of Dolutegravir was calculated.

Accuracy

Dosage blends of Dolutegravir tablets was spiked with Dolutegravir API at different concentrations i.e., 80%, 100% and 130 % of target concentration level were prepared in triplicates and solutions were analyzed once separately. It has been prepared in such a way that the average weight of tablet is kept constant and the weight of API was varied. Test solution was injected and the assay was performed as per the test method.

Linearity

Linearity has been demonstrated in the range of 80-120% of target concentration of the assay. Five series of standard solutions in the above concentration range were injected in duplicate. Standard solution A calibration curve was determined for the drug independently by plotting the peak areas obtained against concentrations (in percentage). There exists a linear relationship in the two graphs for the two concentration ranges which are prepared. From the data obtained correlation coefficient, Y- intercept and slope were calculated to provide mathematical estimates of the degree of linearity.

Specificity

The specificity of the developed method was established by analyzing the sample solutions containing dolutegravir standard and prepared tablets in relation to interferences from formulation ingredients.

Ruggedness

Ruggedness also known as Intermediate precision was checked by repeating studies on two different days. Six separate solutions of Dolutegravir sample at a concentration of 0.05 mg/mL were analyzed. % RSD for the content of Dolutegravir was calculated.

Robustness:

To determine the robustness of the method, the experimental conditions, i.e. flow rate and temperature of the mobile phase, were deliberately altered. For changes in conditions, the sample was assayed in triplicate. The optimum mobile phase flow rate was 1.0 mL/min. This was changed by 0.1 units to 0.9 and 1.1 mL/min and the effects were studied. The effect of a change in temperature of the mobile phase was studied at 30ºC and 50ºC.

Forced Degradation Studies

Forced degradation of dolutegravir sodium sample solution was carried out with thermal degradation, thermal and humidity degradation, photolytic degradation, acid degradation, base degradation and oxidative degradation. The detailed forced degradation conditions are as given in Table 1. Chromatograms were recorded for all of the above solutions

Table 1: Forced Degradation Conditions

Stress condition	Description of the stress condition
Thermal Degradation	Exposed in hot air oven at 80°C for 24 hours
Thermal and Humidity Degradation	Exposed at 50°C / 90% RH for 24 hours in a humidity chamber
Photolytic Degradation	Exposed in the photostability chamber

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Acid Degradation	5 ml of 5M HCl acid solution and kept on water bath at 80°C for 5 hours
Base Degradation	5 ml of 5M NaOH solution and kept on water bath at 80°C for 5 hours
Oxidative Degradation	10 ml of 10% Hydrogen peroxide solution and kept on water bath at 40°C for 5 hours

4. RESULTS AND DISCUSSION

Chromatographic method for separation

The chemical nature of the sample provides valuable information for LC separation. The nature of the sample i.e. ionic, non-ionic or neutral, its molecular weight and solubility plays a major role in the selection of the method. Since the drug, dolutegravir is polar in nature, reverse phase chromatography was selected for separation.

Selection of Detection Wavelength

The spectra of dolutegravir showed the maximum absorbance at the wavelength 258 nm (Fig 2). So, the wavelength 258 nm was selected for the analysis.

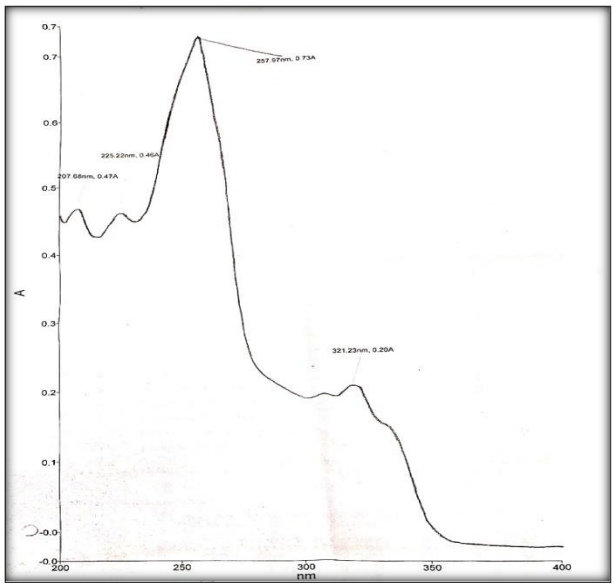

Fig 2: UV Spectrum of Dolutegravir

Chromatographic conditions

Optimized method for the estimation of Dolutegravir by RP-HPLC was finally achieved by using the following chromatographic conditions.

Table 2: Optimized Chromatographic Conditions for Dolutegravir

Mobile phase	Buffer : ACN (60:40 v/v)
Buffer	186 mg of EDTA was weighed into a 1000mL beaker, dissolved and diluted with1000mL with HPLC water.
Column	C8 Synchronis (4.6 x 150mm, 5µm)
Flow rate	1 mL/min
Wavelength	258 nm
Column Temperature	40ºC
Injection Volume	20µL
Autosampler	12ºC
Run time	15 minutes

Method Validation Results

System Suitability Parameters

System suitability was studied by injecting six replicates of the standard solution. The system suitability parameters are given in Table 3. The number of theoretical plates was found to be 12467, which indicates efficient performance of the column.

Table 3: System Suitability Parameters by the HPLC Method

Parameter	Result
Retention time (min)	6.60
Tailing factor	0.94
No. of theoretical plates	12467
Area	14376890

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Precision

The developed method was found to be precise as the % RSD values for system and method precision studies were less than 2%. The results are shown in Table 4 and 5.

Accuracy

Satisfactory recoveries ranging from 98.5 to 99.1 % were obtained by the proposed method. The results obtained are given in Table 6.

Table 4: Results of System Precision

Sample ID	Area Counts	Theoretical Plates	Rt (min)	Tailing Factor
SYSTEM PRECISION – 1	3685682	12154	6.68	0.93
SYSTEM PRECISION – 2	3687077	12378	6.68	0.92
SYSTEM PRECISION – 3	3691781	12423	6.68	0.92
SYSTEM PRECISION – 4	3687886	12362	6.68	0.91
SYSTEM PRECISION – 5	3685407	12430	6.67	0.92
SYSTEM PRECISION – 6	3686305	12497	6.67	0.92
AVERAGE	3687124	12374	6.67	0.92
S.D.	2237.777	-	-	-
%RSD	0.06	-	-	-
LIMITS	NMT 2%	NLT 2000		NMT 2

SD indicates standard deviation.

RSD indicates relative standard deviation.

Table 5: Results of Method Precision/ Repeatability

Sample Injection	Assay %(w/w)
1	99.98
2	99.58
3	99.1
4	99.33
5	100.45
6	99.76
Mean	99.7
S.D.	0.48076
% RSD	0.5

SD indicates standard deviation.

RSD indicates relative standard deviation.

Table 6: Recovery results of Dolutegravir

Spiked Level	API Added (µg/mL)	API Recovered (µg/mL)	%Recovery
80%	39.88365	39.53894	99.1
100%	49.97986	49.39791	98.8
130%	65.18114	64.22667	98.5

* Mean of three determinations at all three spiked level.

Linearity

A linear relationship was observed by plotting the drug concentration against the peak areas. Dolutegravir showed a linear response in the concentration range of 80, 90, 100, 110 and 120 % by the HPLC method. The regression of the plot was computed by the least-squares regression method. Linearity results are presented in Table 7 and the linearity plot is shown in Fig 3.

Table 7: Linearity Results of Dolutegravir (80% to 120% w.r.t nominal concentration)

S. No.	% of Level	Concentration in (ug/mL)	Average Peak Area

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1	80	40.1076	2374509
2	90	45.1210	2657433
3	100	50.1345	2955145
4	110	53.4768	3158160
5	120	60.1614	3554266
Slope			**58811.63**
y-intercept			**10921.00**
Correlation Coefficient			**1.00**

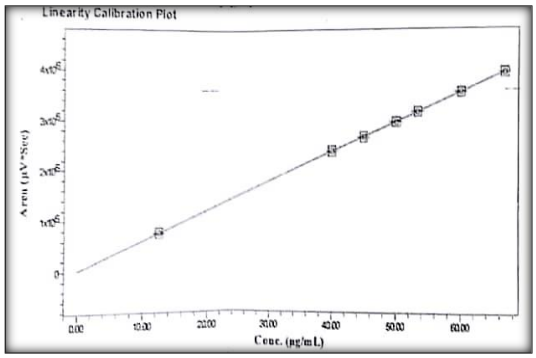

Fig 3: Linearity Graph For Dolutegravir

Specificity

It was found that there was no interference due to the excipient in the tablet formulation (Fig 4). A good correlation was also found between the retention time of the standard and sample of dolutegravir.

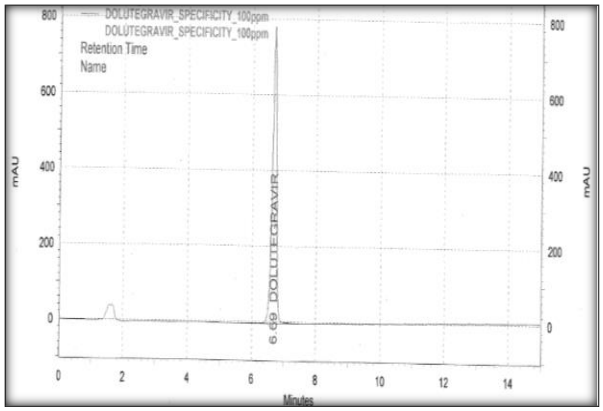

Fig 4: Representative Chromatogram of Sample for Specificity

Ruggedness (Intermediate precision)

The all individual assays of Dolutegravir and Relative standard deviation of % assay results were within the acceptance criteria on two days (Table 8).

Robustness

Samples of dolutegravir were analyzed for different flow rate and change in temperature of the mobile phase. It was observed that there were no marked changes in chromatograms, which demonstrated that the developed method was robust in nature. The results are given in Table 9 and 10.

Table 11: Forced Degradation Studies Results

Mode of Degradation	Condition	%Assay	% Degradation	Peak Purity
Initial	No Treatment	101.8	NA	Pure
Thermal Degradation	80°C – 24hr	104.3	No degradation	Pure
Thermal and Humidity Degradation	50°C/90 % RH – 24hr	99	2.8	Pure
Photolytic Degradation	Control sample	103.2	NA	Pure
	Exposed sample	101.5	1.7	Pure
Acid Degradation	5 M HCl	90	11.8	Pure
Base Degradation	5M NaOH	102.1	No degradation	Pure
Oxidative Degradation	10% H_2O_2	100.5	1.3	Pure

SD indicates standard deviation.

RSD indicates relative standard deviation.

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Table 8: Ruggedness Results

Sample no.	Assay of Dolutegravir as % of labeled amount	
	Day-01	Day-02
1	99.83	100.16
2	99.72	99.78
3	99.12	99.91
4	99.75	99.59
5	99.74	99.57
6	99.91	99.32
Average	99.5	99.7
%RSD	0.4	0.3

RSD indicates relative standard deviation.

Table 9: Flow Rate Variations Robustness Results

Assay of Dolutegravir as % of labeled amount			
Low Flow rate (0.9 mL)		High Flow rate (1.1 mL)	
%RSD	% Assay	%RSD	% Assay
1.43	100.73 ± 1.44	1.24	100.09 ± 1.24

* Mean of three determinations.

RSD indicates relative standard deviation.

Table 10: Temperature Variations Robustness Results

Assay of Dolutegravir as % of labeled amount			
Low Temperature (30ºC)		High Temperature (50ºC)	
% RSD	% Assay	% RSD	% Assay
0.57	99.90 ± 0.57	1	99.63 ± 0.99

* Mean of three determinations.

RSD indicates relative standard deviation.

Forced Degradation Results of Dolutegravir

The main peak was found to be spectrally pure in all the degradation condition indicating that there is no co-elution with main peak. Thus, the method can be said to be stability-indicating. The numbers of the degradation peaks observed in different stress conditions are shown in Table 11.

5. CONCLUSION

A simple, reproducible and efficient reverse phase High performance liquid chromatography (RP-HPLC) method has been developed for estimation of Dolutegravir in bulk and in its tablet dosage form. Various mobile phase systems were prepared and used to provide an appropriate chromatographic separation, but the proposed mobile phase comprising of Buffer and Acetonitrile in the ratio 60:40 gave a better resolution and sensitivity. Chromatography separations were carried out on Thermo Fischer Scientific C8 Synchronis column (150 x 4.6mm; 5µm) at a flow rate of 1 mL/min and UV detection at 258 nm and the retention time for Dolutegravir is 6.61 minutes. The linear dynamic response was found to be in the concentration of 80-120 %. The slope, intercept and correlation coefficient was found to be 1.00 respectively. The percentage recovery of Dolutegravir was found to be 98.5 to 99.1 %. Forced Degradation studies result reveals that the purity of dolutegravir was unaffected by the presence of its degradation products. The percent assay of all the degraded samples varied between 90.0 and 104.3 %. Proposed methods were found to be simple, accurate, precise, rapid and economical and therefore could be used for routine analysis. sit. Arcu felis bibendum ut tristique et egestas quis.

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