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A Comprehensive Overview on 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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ABSTRACT:

Pharmaceutical industry deals with manufacturing, quality control and quality assurance of the bulk products as well as formulations. Analytical method development and validation are two major components of the pharmaceutical industry which are helpful in drug discovery, development and manufacturing process. Method development is a process designed based on various factors to evaluate the identity, quality, purity, and potency of the drug substances and drug products. However, Method validation is set of parameter which proves the authenticity and suitability of developed method. Validation parameters include specificity, accuracy, precision, linearity, limit of detection, limit of quantification, range, ruggedness and robustness. Forced degradation study also plays a vital role in drug development process. It provides information regarding degradation products present in any drug compound, degradation pathways, intrinsic stability of the drug molecule and validate stability indicating analytical methods. Today, due to increase in the production of drugs in the pharmaceutical industries, development of new analytical techniques has become necessary. Validation and Forced degradation study both are performed according to the regulatory guidelines such as International Council for Harmonisation (ICH). This article emphasizes on method development and validation and also provides an overview on stability indicating analytical method development and validation of dolutegravir sodium in pharmaceutical dosage form.

1. INTRODUCTION

Analytical chemistry

Analytical Chemistry is defined as “The science and the art of determining the composition of materials in terms of the elements or compounds contained.” This branch of chemistry, deals with both theoretical, practical and with the separation, identification, qualification, quantification and purification of a chemical components or medicine/pharmaceutical; the detection and estimation of impurities that may be present therein is also included. Methods of analysis are routinely developed, improved, validated, collaboratively studied and applied. In analytical chemistry it is of prime importance to gain information about the qualitative and quantitative composition of substances and chemical species that is to find out what substance is composed and exactly how much. Qualitative analysis gives an indication of the identity of the chemical species in the sample and Quantitative analysis determines the amount of one or more of these components. Each pharmaceutical organization believes on “Analytical chemistry” for development of accurate and precise analytical method and applies for analysis of drugs to get more highly accurate results. Pharmaceutical analysis deals not only with medicaments (drugs and their formulations) but also with their precursors i.e. with the raw material on which degree of purity and quality of medicament depends. The quality of the drug is determined after establishing its authenticity by testing its purity and the quality of pure substance in the drug and its formulations. Quality is important in every product or service but it is vital in medicine as it involves life. Unlike ordinary consumer goods there can be no “second quality” in drugs. Quality control is a concept, which strives to produce a perfect product by

Journal of Chemical Health Risks

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series of measures designed to prevent and eliminate errors at different stages of production[1-4]. Modern analytical techniques are playing key role in assessing chemical quality standards of medicine. Thus analytical techniques are required for fixing standards of medicines and its regular checking. Out of all analytical techniques, the technique which is widely used to check the quality of drug is known as "chromatography".

High pressure liquid chromatography

High pressure liquid chromatography (HPLC) was developed in the mid-1970's and quickly improved with the development of column packing materials and the additional convenience of online detectors. In the late 1970's, new methods including reverse phase liquid chromatography allowed for improved separation between very similar compounds. By the 1980's HPLC was commonly used for the separation of chemical compounds. HPLC is a form of liquid chromatography technique used to separate compounds that are dissolved in liquid phase/solution and analyte is forced to flow through a column under high pressure. The separation of the constituent components from the sample mixture is based on distributing/ partitioning between the mobile phase (a flowing liquid) and a stationary phase (sorbents packed inside a column).The different components in the mixture pass through the column at different rates due to differences in their partitioning behavior between the mobile liquid phase and the stationary phase. The four major separation modes of HPLC are normal phase, reversed phase, ion exchange chromatography, and size exclusion chromatography[5-6].

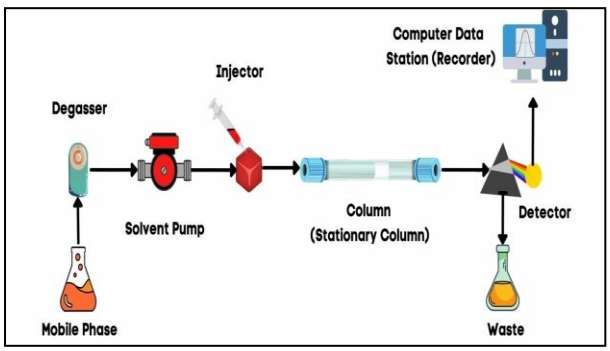

Figure 1: Schematic diagram of HPLC instrument

Dolutegravir sodium

Dolutegravir sodium is an organic monosodium salt of dolutegravir. Human immunodeficiency virus (HIV) infection is a current threat and can easily be termed as a curse upon the human race. Antiretroviral therapy (ART) has revolutionized HIV treatment in the past few decades. This therapy has lengthened the average life span of HIV-infected individuals to approach that of the general population while concurrently increasing the burden of comorbidities[7,8]. Accordingly, there is an increasing need for agents with few drug–drug interactions, reduced toxicity, high genetic barrier to resistance, low pill burden, and decreased cost. Dolutegravir is the most popular antidepressant drug.

Pharmacologically, Dolutegravir acts as a HIV-1 integrase inhibitor that blocks the strand transfer step of the integration of the viral genome into the host cell (INSTI). The effect of this drug has no homology in human host cells which gives it an excellent tolerability and minimal toxicity.

So in this background, considering the importance of analytical development in pharmaceutical sector and dolutegravir (DTG) as an alternative first-line HIV treatment to efavirenz (EFV), focus was given "to develop an Analytical Method for Antiretroviral (ARV) Drug Dolutegravir Sodium by HPLC". Focus was also given to perform degradation study of the tablet formulation according to ICH guidelines.

2. DETAILS OF PHYSICOCHEMICAL AND BASIC PHARMACOKINETIC ASPECTS OF DOLUTEGRAVIR

Dolutegravir (DTG) is the newest integrase strand transfer inhibitor to be approved for the treatment of HIV infection which exhibits a predictable pharmacokinetic profile and a well-defined exposure-response relationship. Dolutegravir is equivalent or superior to existing treatment regimens in both treatment-naïve and treatment-experienced patients including those with previous raltegravir or elvitegravir failure. The consistent efficacy coupled with excellent tolerability and infrequent drug–drug interactions make the co-formulation of dolutegravir with two nucleotide reverse-transcriptase inhibitors an attractive treatment option.

Journal of Chemical Health Risks

www.jchr.org

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Table 1: Physicochemical aspects of Dolutegravir

Parameters	Description
Molecular formula	$C_{20}H_{19}F_2N_3O_5$
Molecular weight	419.4 g/mol
Physical form	White to light yellow crystalline powder
Solubility	Soluble in Methanol, Acetonitrile, DMF
Melting Point	190-193ºC
Boiling Point	804.2^0C
Flash Point	440.20^0C
Log P	2.2
pKa	8.2
CAS No.	1051375-19-9
Therapeutic category/indications	Integrase Inhibitors; HIV infection treatment

Table 2: Details of basic pharmacokinetic aspects of Dolutegravir

Parameters	Description
Tmax	0.5 to 2 hours
Absorption	DTG is absorbed with no absorption lag time and a median t_{max} of 2 to 3 hours post dose. DTG absorption is increased with co-administration of food. Oral bioavailability is estimated to be at least 60-80%.
Cmax	3.67 mcg/mL
Clearance	1 L/hr
$T_{1/2}$	14 hours
Protein binding	98.9% bound to human plasma proteins
Metabolism	Dolutegravir is highly metabolized through three main pathways and it forms no long-lived metabolites. The first pathway is defined by the glucuronidation by UGT1A1, the second pathway by carbon oxidation by CYP3A4 and the third pathway is what appears to be a sequential oxidative defluorination and glutathione conjugation.
Route of Elimination	Excretion: 53% feces (unchanged); 31% urine (as ether glucuronide, benzylic carbon, or N-dealkylation product); <1% urine (unchanged)
Dose	50 mg

3. METHOD DEVELOPMENT PROCESS

Method development is the process of developing or designing an analytical method which is acceptable for use to measure the concentration of an active pharmaceutical ingredient (API) in a specific compounded dosage form which allows simplified procedures to be employed to verify that an analytical procedure, accurately and consistently will deliver a reliable measurement of an active ingredient in a compounded preparation. These methods used to ensure the identity, purity, potency, & performance of drug products. The factors to be considered in the method development which are[9].

Physicochemical properties of drug: For method development the study of physical properties like molecular weight range, nature of sample components, chemical structure of sample components, solubility, polarity, pKa and pH of the drug molecule is essential. Polarity is a physical property of a compound which helps the analyst, to decide the solvent and composition of the mobile phase.

Selection of chromatographic conditions: During initial method development, a set of initial conditions (detector, column, mobile phase) is selected to obtain the first "scouting" chromatograms of the sample. In most cases, these are based on reversed-phase separations on a C18 column with UV detection. A decision on developing either an isocratic or a gradient method should be made at this point. This step determines the optimum conditions to adequately retain all analytes; that is ensures analyte has a better capacity factor (excessive retention leads to long analysis time and broad peaks with poor delectability).

Selection of Column: An appropriately selected column can produce a good chromatographic separation which provides an accurate and reliable analysis. An improperly used column can often generate confusion, inadequate, and poor separations which can lead to results that are invalid or complex to interpret. There is large number of columns available for analysis, having stationary phase octadecylsilane, octylsilane, cyano,

Journal of Chemical Health Risks

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JCHR (2025) 15(3), 1577-1584 | ISSN:2251-6727

amino, phenyl base. Selection of the column is based upon nature of molecules like hydrophilic/ hydrophobic, acid/base, functional groups etc.

Selection of Chromatographic mode: Chromatographic modes are based on the analyte's molecular weight and polarity. The focus is on reversed phase chromatography (RPC), the most common mode for small organic molecules.

Selection of Mobile phase solvent strength: The solvent strength is a measure of its ability to pull analytes from the column. It is generally controlled by the concentration of the solvent with the highest strength. The aim is to find the correct concentration of the strong solvent. Choice of buffer is typically governed by the desired pH and solubility criteria of mobile phase. The typical pH range for reversed- phase on silica-based packing is pH 2 to 8. It is important that the buffer has a pKa close to the desired pH since buffer controls pH best at their pKa. Different type of buffer reagents are available for mobile phase preparation like sodium orthophosphate buffer, potassium ortho phosphate buffer monobasic or dibasic, citrate buffer and orthophosphoric etc. Different types of organic solvents are available like methanol, acetonitrile and tetrahydrofuran can be used for method development and it depends upon resolution and tailing of molecules on chromatographic condition.

Selection of detector: Selection of detector depends on the chemical nature of analytes, potential interference, limit of detection required, availability and/or cost of detector. UV-Visible detector is versatile, dual-wavelength absorbance detector for HPLC. This detector offers the high sensitivity required for routine UV-based applications to low-level impurity identification and quantitative analysis. Photodiode Array (PDA) Detector offers advanced optical detection for analytical HPLC, preparative HPLC, or LC/MS system solutions. Its integrated software and optics innovations deliver high chromatographic and spectral sensitivity. Refractive Index (RI) Detector offers high sensitivity, stability and reproducibility, which make this detector the ideal solution for analysis of components with limited or no UV absorption.

Selection of wavelength: Each molecule will be scan by UV region to identify the maximum wavelength absorbance. It will help in select the single wavelength for more molecules.

Selectivity optimization: The aim of this step is to achieve adequate selectivity (peak spacing). The mobile phase and stationary phase compositions need to be taken into account. Once the analyte types are identified, the relevant optimization parameters may be selected. Note that the optimization of mobile phase parameters is always considered first as this is much easier and convenient than stationary phase optimization. Initially gradient conditions or Isocratic condition should be optimized using a binary system based on organic solvent or aqueous buffer.

System parameter optimization: This is used to find the desired balance between resolution and analysis time after satisfactory selectivity has been achieved. The parameters involved include column dimensions, column-packing particle size and flow rate. These parameters may be changed without affecting capacity factors or selectivity.

Method optimization: The experimental conditions should be optimized to get desired separations and sensitivity after getting appropriate separations. Stability indicating assay experimental conditions will be achieved through planned/systemic examination on parameters including pH (if ionic), mobile phase components and ratio, gradient, flow rate, sample amounts, Injection volume and diluents solvent type.

Preparation of sample solutions for method development: During initial method development, preparations of the solutions in amber flasks should be performed until it is determined that the active component is stable at room temperature and does not degrade under normal laboratory conditions. The sample solution should be filtered; the use of a 0.22 or 0.45 μm pore-size filter is generally recommended for removal of particulates.

4. METHOD VALIDATION PROCESS

Once an analytical method is developed and optimized for its intended use, it must be validated as per ICH Harmonized Tripartite Guidelines. The extent of validation evolves with the drug development phase. Usually, a limited validation is carried out to support an Investigational New Drug (IND) application and a more extensive validation for New Drug Application (NDA)

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1577-1584 | ISSN:2251-6727

and Marketing Authorization Application (MAA). Typical parameters recommended by FDA, USP, and ICH are as follows[10].

System suitability testing: The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated.

Specificity: Specificity is the ability of the method to measure the desired analyte in the presence of other relevant components those are expected to be present in a sample. The relevant components might include impurities, degradants, matrix, etc.

Accuracy: The accuracy of an analytical procedure expresses the closeness of agreement between measured values to the true or accepted value. Accuracy indicates the deviation between the mean value found and the true value.

Linearity & Range: The linearity of an analytical procedure is its ability (within a given range) to obtain test results, which are directly proportional to the concentration (amount) of analyte in the sample. For the establishment of linearity, minimum of five concentrations are recommended by ICH guideline.

Precision: The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

Repeatability: Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.

Limit of Detection (LOD): The limit of detection (LOD) for an individual analytical procedure is the lowest amount of analyte in a sample, which can be detected but not necessarily quantitated as an exact value.

Limit of Quantification (LOQ): The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample, which can be quantitatively determined with suitable precision and accuracy. The limit of quantitation (LOQ) is a parameter of quantitative assays for low levels of compounds in sample matrices.

Robustness: The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

5. FORCED DEGRADATION STUDIES

Forced Degradation studies are also known as Stress Testing studies. This study is done for assessing the stability of the drug substance under conditions more severe than the normal conditions for storage and use. According to ICH guidelines, 'these studies illustrate the chemical stability of the molecule which further facilitates the development of stable formulation with suitable storage conditions.' ICH guidelines demonstrate certain degradation conditions like light, oxidation, dry heat, acidic, basic, hydrolysis etc[11].

There are numerous international guidelines that depict forced degradation studies. However, the ICH guidelines that are applicable to forced degradation studies are[11]:

ICH Q1A: Stability Testing of New Drug Substances and Products

ICH Q1B: Photo stability Testing of New Drug Substances and Products

ICH Q2B: Validation of Analytical Procedures: Methodology.

Importance of Forced Degradation studies[11-13]:

a. To determine the impurities present in AP
b. To determine degradation pathways in drug products
c. To demonstrate stability indicating nature of analytical methods
d. To identify and characterize degradants present in drug substances

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1577-1584 | ISSN:2251-6727

e. To determine intrinsic stability of a drug substance in the formulation.
f. To resolve stability related problems

6. LITERATURE REVIEW

As per the literature review, there are few analytical methods reported for the estimation of Dolutegravir in pharmaceutical dosage form by HPLC using PDA detector. Various literatures are available regarding the liquid chromatography–tandem mass spectrometry method[14], and a sensitive HPLC–MS/MS method for the estimation of Dolutegravir[15] either alone or in combination with other drugs in pharmaceutical dosage form. Some literature showed quantification of dolutegravir sodium in tablet dosage form using UV spectrophotometric method[16]. UHPLC method was also developed to analyze Dolutegravir in combination with other drugs. The validation and force degradation studies were performed as per ICH guidelines under the acidic, alkali oxidative and neutral conditions for different times[17]. For the first time, a HPLC-ultraviolet method was also developed in combination with liquid-liquid extraction with isocratic elution which was successfully applied to analyze Dolutegravir plasma concentration in 84 Chinese patients with HIV[18].

7. STEPS INVOLVED IN ANALYTICAL METHOD DEVELOPMENT, VALIDATION AND STABILITY STUDIES OF DOLUTEGRAVIR SODIUM

Analytical method development

The method developed comprises of following steps:

a. **Detection method & Selection of wavelength:** Solutions were prepared and scanned between 200 to 400nm using UV-Visible spectrophotometer.
b. **Selection of chromatographic condition:** 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.
c. **Initial separation condition**: Trials were made to decide the ultimate composition of the mobile phase. After reviewing many trials, considering good peak shape, retention time, tailing factor and theoretical plates obtained, the mobile phase composition was finalized.
d. **Effect of buffer:** On the basis of retention property, study results of the drug and reviewing the results buffer was decided.
e. **Effect of nature of stationary phase:** The following stationary phases Agilent zorbax SB C18 (4.6 x 150mm, 5µm), Phenomex-kinetex-XDB C18 (4.6 x 100mm, 5µm), Symmetry XterraC18 column, Symmetry C8 (4.6 x 100mm, 5µm) and Synchronis C8 (4.6 x 150mm, 5µm) were used and the chromatograms were recorded. Considering, the peak shape and resolution observed, column was finalized for further studies.
f. **Selection of flow rate:** Flow rate selection is done depending on the retention time, peak symmetry; hence many trials were made to decide the flow rate.
g. **Preparation of Solutions**: Mobile Phase, Diluent, Standard solution (in duplicate), Test solution (in duplicate) and standard stock solution.

Analytical method validation

The method developed was validated for the following parameters:

- System suitability
- Precision
- Accuracy
- Linearity
- Specificity
- Ruggedness
- Robustness

Table 3: Analytical Method Validation parameters with their acceptance criteria

Parameters	Acceptance Criteria
System suitability	• The tailing factor for Dolutegravir should be NMT 2.0. • The %RSD for the area of Dolutegravir obtained from the 6 replicates injections of standard should be NMT 2.0%.
Precision	• The %RSD for the content of Dolutegravir should be NMT

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JCHR (2025) 15(3), 1577-1584 | ISSN:2251-6727

	2.0%.
Accuracy	• The overall mean recovery should be within the range of 98.0% to 102.0%.
Linearity	• Correlation coefficient should not be less than 0.999 for analyte. • Y-bias should be within±2.0 % when calculated against 100 % level w.r.t working concentration of Dolutegravir.
Specificity	• Chromatogram of blank should not show any peak at the retention time of analyte peak.
Ruggedness	• The all individual assays of Dolutegravir should be within 98% to 102%. • Relative standard deviation of % assay results should not be more than 2.0% on two days.
Robustness	• The %RSD for the area of Dolutegravir obtained should be NMT 2.0%.

Forced Degradation Studies

The forced degradation of dolutegravir sodium sample solution was carried out in different degradation conditions as given below. Chromatograms were recorded for all of the solutions.

- Thermal Degradation
- Thermal and Humidity Degradation
- Photolytic Degradation
- Acid Degradation
- Base Degradation
- Oxidative Degradation

8. CONCLUSION

As per today scenario, Dolutegravir is the more potent antiretroviral medication for increasing number of HIV patients. It can be used in combination with other medication for treating HIV/AIDS. As per World Health Organization (WHO), DTG is enlisted as the most effective and safe medicine in the health system. Various researches have shown that combining of DTG with other drugs is very effective in controlling HIV and also minimizes the chances of the virus to become resistant to the therapy or treatment. Death rates and suffering has been declined due to the use of a potent ARV regimen in early stages of the diseases. In this review, we have summarized the development and validation of stability indicating HPLC method for the quantitative determination of Dolutegravir sodium. As HPLC offers high level of resolution, accuracy, efficiency and reproducibility, it is used in method development of dolutegravir sodium considering its cost effectiveness, easy and rapid performance.

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Journal of Chemical Health Risks

www.jchr.org

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