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A review on uv spectroscopy and hplc methodologies for the development and validation of Dolutegravir

Prerana Jadhav,Shudham Jadhav, Vaishnavi Jadhav

ABSTRACT:

Dolutegravir, an integrase strand transfer inhibitor (INSTI), has become a pivotal antiretroviral therapy for managing HIV-1 infections since its FDA approval in 2013. Its mechanism of action involves inhibiting the integrase enzyme, disrupting the viral replication cycle. Dolutegravir boasts a high barrier to resistance, making it suitable for both treatment-naive and treatment-experienced patients. The drug's favorable safety profile and incorporation into fixed-dose combinations, such as Triumeq and Dovato, have enhanced patient adherence and treatment outcomes globally.

This paper discusses the importance of analytical method development and validation for dolutegravir, focusing on techniques like ultraviolet (UV) spectroscopy and high-performance liquid chromatography (HPLC). Method validation ensures the accuracy, precision, specificity, and compliance of analytical procedures, vital for maintaining drug quality and safety. Various studies utilizing UV spectroscopy and HPLC for quantifying dolutegravir alone and in combination with other antiretroviral agents are reviewed, highlighting their effectiveness in therapeutic monitoring.

The continued advancement of analytical methodologies will support optimized therapeutic use of dolutegravir, contributing to the global effort to combat the HIV epidemic.

KEYWORDS: Analytical method development, validation, Dolutegravir , Uv spectroscopy, HPLC

INTRODUCTION:

Dolutegravir is a powerful antiretroviral medication used to manage HIV-1 infections. It was approved by the FDA in 2013 and belongs to the class of integrase strand transfer inhibitors (INSTIs). These inhibitors work by blocking the action of the integrase enzyme, which is essential for the viral replication process in host cells. By preventing integrase from functioning, dolutegravir stops the HIV virus from integrating its genetic material into the DNA of human immune cells, thus disrupting the HIV replication cycle.

Compared to earlier antiretroviral drugs, dolutegravir has demonstrated a higher barrier to resistance, meaning that the virus requires fewer mutations to develop resistance to the medication. This makes it a preferred treatment, especially for patients who have developed resistance to other antiretroviral therapies. Clinical trials have shown that dolutegravir is effective in both treatment-naive and treatment-experienced patients.

Dolutegravir is generally well-tolerated, with few side effects. Common side effects include insomnia, headache, and gastrointestinal issues. However, there are concerns about potential neuropsychiatric effects, particularly in older patients. Recent studies have also investigated its association with weight gain, especially when combined with certain other antiretroviral drugs.

A significant development in the use of dolutegravir has been its inclusion in fixed-dose combination therapies, such as Triumeq (dolutegravir with abacavir and lamivudine) and Dovato (dolutegravir with lamivudine). These combinations simplify HIV treatment by reducing the number of pills taken daily, improving adherence to therapy, and maintaining high efficacy.

Globally, dolutegravir has been widely adopted as a cornerstone of HIV treatment in many low- and middle-income countries due to its effectiveness, affordability, and low pill burden. The World Health Organization (WHO) recommends dolutegravir as part of the first-line treatment for adults and adolescents with HIV. Its adoption has led to improvements in treatment outcomes and is contributing to broader efforts to control the global HIV epidemic. [1-7]

ANALYTICAL METHODS:

Analytical method development is a critical process in the pharmaceutical and chemical industries, aimed at creating reliable, precise, and reproducible methods for analyzing drugs and other chemical compounds. The goal is to ensure that methods are optimized to accurately quantify and qualify substances, detect impurities, and determine the stability and potency of compounds. A well-developed analytical method is vital for drug development, quality control, and regulatory compliance.

The development process involves several stages, including the selection of analytical techniques (e.g., chromatography, spectroscopy), method validation (assessing parameters like accuracy, precision, specificity, and sensitivity), and optimization to enhance performance. High-performance liquid chromatography (HPLC) and gas chromatography (GC) are common techniques used in the pharmaceutical industry for separating and quantifying drug components.

Analytical method development not only ensures product safety and efficacy but also supports cost-effective production by minimizing errors and ensuring consistency across batches. Regulatory guidelines, such as those from the International Council for Harmonization (ICH), set standards for method development, ensuring methods are scientifically sound and fit for their intended purpose. [8-10]

ANALYTICAL METHOD VALIDATION:

In accordance with ICH Q2 (R1), method validation is the process of providing documented evidence to ensure that a specific process consistently yields the desired results at predetermined specifications and quality standards. In simpler terms, it involves confirming that analytical procedures are appropriate for their intended use and can verify the identity, quality, purity, and potency of drug substances and products. Method validation is necessary when a new method is developed or when established methods are utilized in different laboratories by different analysts. The validation of various methods requires compliance with performance characteristics outlined in guidelines such as USP, ICH, FDA, and European standards. [11,12]

ANALYTICAL METHOD VALIDATION PARAMETERS:

- Accuracy
- Precision
- Repeatability
- Intermediate precision
- Reproducibility
- Specificity/Selectivity
- Limit of Detection (LOD)
- Limit of Quantitation (LOQ)

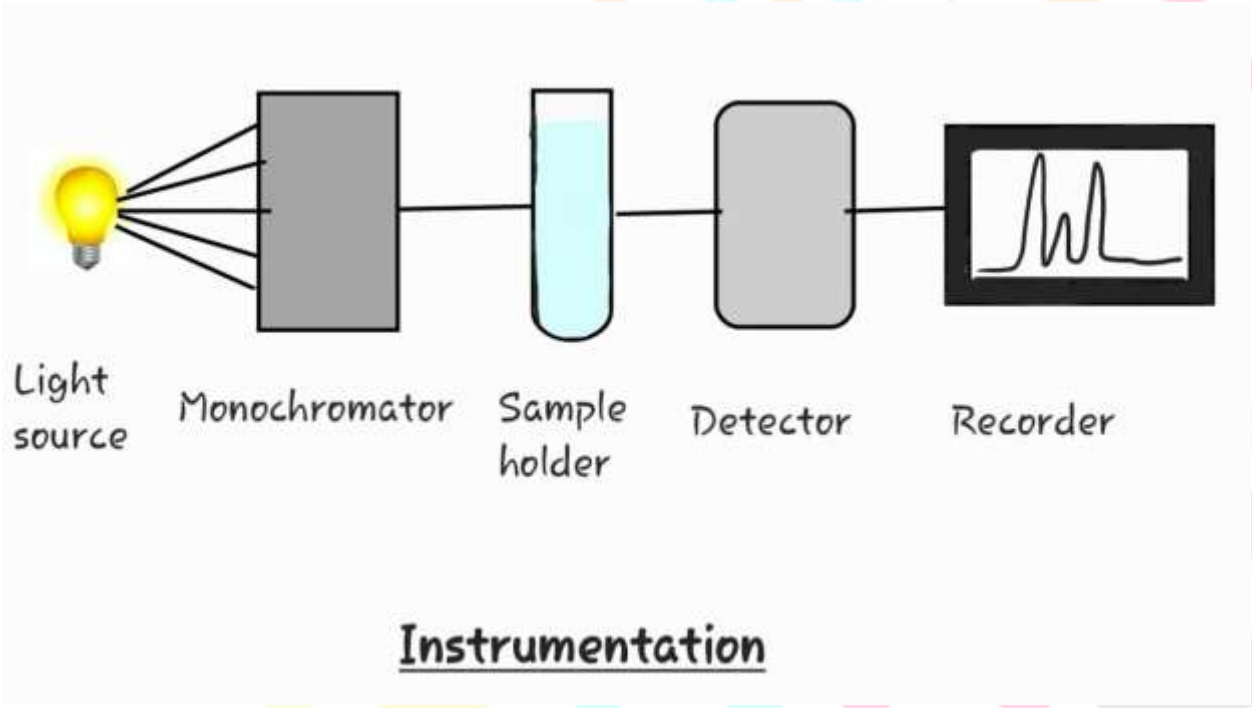
- Linearity
- Range
- Robustness
- Ruggedness
- System suitability testing. [13,14]

ULTRAVIOLET (UV) SPECTROSCOPY:

Ultraviolet (UV) spectroscopy, including ultraviolet-visible (UV-VIS) spectrophotometry, involves the measurement of light absorption in the UV and visible regions of the electromagnetic spectrum. This technique is widely utilized across various fields due to its affordability and straightforward implementation. A key requirement for samples is that they must be chromophores, meaning they absorb light in the UV-Vis range.

UV-VIS spectrophotometry is particularly useful for identifying and quantifying compounds within different samples. The core principle involves directing a beam of light through the sample and measuring the absorbance at specific wavelengths. The degree of light absorption is directly proportional to the concentration of the absorbing species in the sample.

This technique is complementary to fluorescence spectroscopy, and important parameters measured include absorbance (A), transmittance (%T), and reflectance (%R), along with their variations over time. [15-18]



Numerous techniques for figuring out Dolutegravir on its own and in combination with other medications have been reported.

Drugs	Method	Absorbance (AU)	Wavelength(nm)	solvents	detector	Concentration Rate (ug/mL)	Temperature (°C)	pH	Reference
Dolutegravir	UV spectroscopy	0.1-1.0	260nm	Water, Methanol	Uv visible	1-100	25	6.5	19

Dolutegravir +Lamivudine	Uv spectroscopy	0.1-1.0	260nm	Water, Acetonitrile	Uv visible	1-100	30	7.0	20
Dolutegravir +Abacarvir	Uv spectroscopy	0.1-1.0	265nm	Methanol, Phosphate buffer	Uv visible	1-100	25	6.0	21
Dolutegravir +Rilpivirine	Uv spectroscopy	0.1-1.0	270nm	Water, Ethanol	Uv visible	1-100	25	6.5	22
Dolutegravir + Tenofovir	Uv spectroscopy	0.1-1.0	260nm	Water, Acetonitrile	Uv visible	1-100	30	7.0	23
Dolutegravir (Stability Studies)	Uv spectroscopy	0.05-1.0	260nm	Water, DMSO	Uv visible	1-100	40	7.0	24

HPLC METHOD:

High-Performance Liquid Chromatography (HPLC) is a commonly utilized analytical technique across various industries, with particular significance in pharmaceuticals. Its primary function lies in the separation and quantification of key drugs, reaction impurities, synthesized intermediates, and degradants, thereby playing a critical role in drug development, manufacturing, and discovery processes. HPLC is integral to the accurate analysis of drug products and the assessment of their stability. This technique involves injecting the sample into a stationary phase and pumping a mobile phase through the column at high pressure. The separation principle is based on the solute's affinity for the stationary phase, leading to adsorption.

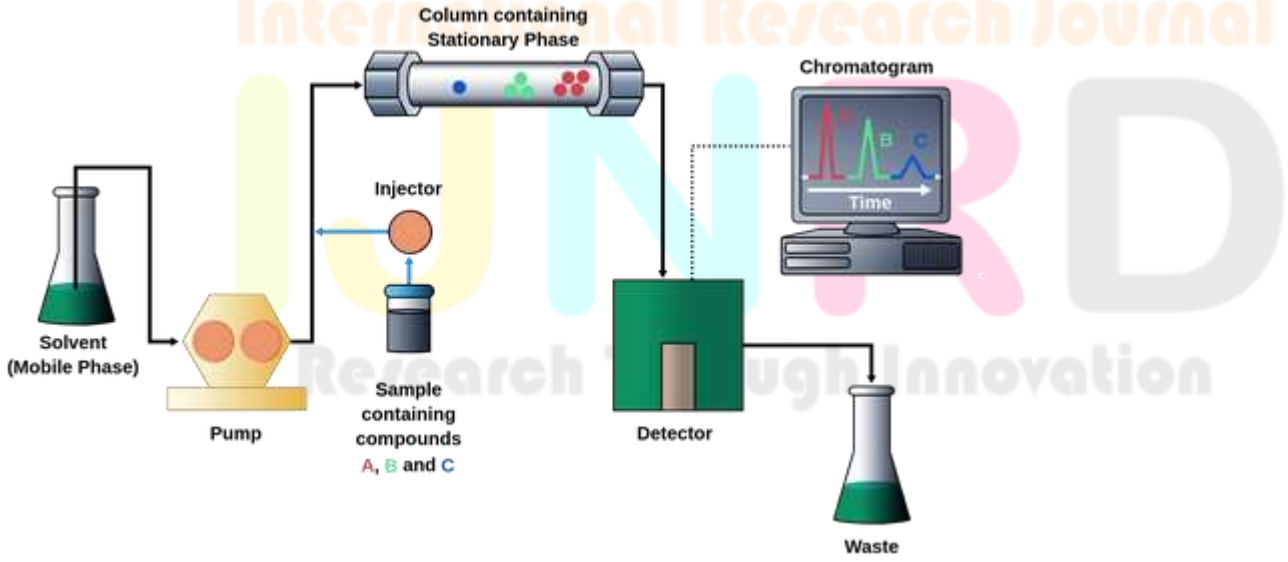


Fig:

REVERSED-PHASE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (RP-HPLC):

RP-HPLC is widely used in various fields for separating complex chemicals. It involves a polar solvent as the mobile phase and a nonpolar hydrophobic packing as the stationary phase. RP-HPLC uses stationary phases such as C8, C18 (ODS), phenyl, and Trimethyl Silane (TMS) columns, with the column temperature controlled by a column oven.[25-31]

Numerous techniques for figuring out Dolutegravir on its own and in combination with other medications have been reported.

DRUG	HPLC MAKE	METHOD	COLUMN	MOBILE PHASE	pH	WAVELENGTH	DETECTOR	FLOW RATE	COLUMN TEMPERATURE	REFERENCE
Dolutegravir	Jasco	RP-HPLC	Intersil ODS-3 C-18, (4.6 x 250 mm,5um)	Phosphate Buffer:Acetonitrile (40:60% v/v0	3.6	258nm	Uv detector	1ml/min	--	32
Dolutegravir	Waters 2695	RP-HPLC	Kromasil C-8 (150 X 4.6mm, 5um)	(A)0.1% fluoroacetic acid in water(B) Methanol water: Acetonitrile (50:50 % v/v)	--	240nm	PDA Detector	1.0 ml/min	35	33
Dolutegravir Sodium	Isocratic	RP-HPLC	Kromasil C18 (250 X 4.6 mm, 5um)	Acetonitrile: 0.1%OPA (70:30% v/v)	3.6	258nm	Uv detector	1 ml/min	40	34
Dolutegravir (API)	Waters 2695	RP-HPLC	Symmetry C18 (250 X 4.6 mm, 3.5 um)	Acetonitrile: Phosphate Buffer (30:70% v/v)	3.2	246nm	Uv detector	1ml/min	--	35
Dolutegravir + Rilpivirine	Waters e2695	RP-HPLC	Thermosil C18 (4.6 X 150 mm,5um)	Acetonitrile: Phosphate Buffer (45:55% v/v)	3.5	260nm	Uv – visible detector	0.8 ml/min	Ambient	36
Dolutegravir + lamivudine	Waters 2489	RP-HPLC	Sun fire C8 (150×4.6mm, 3.5 µm)	Acetonitrile: Potassium Dihydrogen orthophosphate (55:45%v/v)	3.5	260nm	Uv – visible detector	1.0 ml/min	25	37

Dolutegravie + Rilipivirine	Waters 2695	RP-HPLC	Agilent C18 (4.6 X 150mm, 5um)	KH2PO4 Buffer: Acetonitrile (45:55%v/v)	3.5	240nm	PDA Detector	1ml/min	30	38
Dolutegravir + Lamivudine	Waters 2695	RP-HPLC	Agilent C18 (4.6 X 150mm, 5um)	0.1%TEA: acetonitrile (60:40%v/v)	--	265nm	PDA Detector	1ml/min	26	39
Dolutegravir + Rilpivirine	Waters	RP-HPLC	Agilent C18 (4.6 X 150mm, 5um)	Buffer OPA: Acetonitrile (50:50%v/v)	--	257nm	Uv detector	1.0ml/min	30	40
Dolutegravir + Lamivudine	Waters 2695	RP-HPLC	Hypersil BDS C18 (250 X 4.6 mm)	Phosphate Buffer: Acetonitrile (60:40% v/v)	3	232nm	PDA detector	1.5ml/min	30	41
Dolutegravir, Abacavir and lamivudine	Waters	RP-HPLC	Agilent TC-C18 (4.6 X 250 mm, 5um)	Methanol: Water (70:30%v/v)	--	257nm	PDA Detector	1ml/min	--	42
Dolutegravir, Lamivudine and tenofovir	Waters 2695	RP-HPLC	Intersil ODS-3v C-18, (4.6 x 250 mm,5um)	(A) Buffer: Methanol (30:70%v/v), (B) OPA Buffer: Acetonitrile(70:30%v/v)	6.2	260nm	Uv detector	1ml/min	35	43
Dolutegravir, Emtricitabine and Tenofovir	Jasco	RP-HPLC	Qualisil 5 BDS C18 (250 X 4mm, 5um)	Acetonitrile: OPA 0.1% (43:57%v/v)	--	271nm	PDA Detector	1.2 ml/min	Ambient	44
Dolutegravir, Abacavir and	Alliance Waters 2695	RP-HPLC	Inertsil ODS (250 x 4.6 mm, 5um)	Composition Buffer: Acetonitrile: Methanol (50:20:30% v/v)	3	225nm	PDA Detector	1.0 ml/min	30	45

lamivudine										
Dolutegravir, Lamivudine and Tenofovir Alafenamide	Agilent	RP-HPLC	Agilent C18 (4.6 X250mm, 5um)	0.05 Phosphate Buffer: Acetonitrile (60:40%v/v)	6.2	260nm	PDA Detector	1ml/min	30	46
Dolutegravir, Abacavir and lamivudine	Isocratic Elusion	RP-HPLC	ODS 250 mm X 4.5 mm,5um)	Buffer: Acetonitrile (65:35%v/v)	3	257nm	PDA Detector	1 ml/min	30	47

CONCLUSION:

Dolutegravir has emerged as a cornerstone in HIV treatment due to its efficacy, low resistance potential, and favorable safety profile. Its integration into fixed-dose combinations simplifies treatment regimens, enhancing patient adherence and contributing to improved health outcomes globally, particularly in resource-limited settings.The development and validation of analytical methods, such as UV spectroscopy and HPLC, are crucial in ensuring the quality and consistency of dolutegravir formulations. Method validation parameters—such as accuracy, precision, and specificity—are essential for regulatory compliance and product safety. Both UV spectroscopy and HPLC techniques have demonstrated effectiveness in quantifying dolutegravir alone and in combination with other antiretroviral agents, ensuring reliable therapeutic monitoring.Overall, continued advancements in analytical methodologies will play a vital role in optimizing dolutegravir's therapeutic use and supporting ongoing efforts to combat the global HIV epidemic.

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