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A Review on Analytical Techniques-Based Method Validation and Quality Standardization of Some Anti-Viral Active Pharmaceutical Ingredients Using Hplc

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ABSTRACT
This review aims to provide an overview of the quality standardization of specific antiviral active pharmaceutical ingredients (APIs) using high-performance liquid chromatography (HPLC). The demand for effective antiviral drugs has grown significantly due to the increasing prevalence of viral diseases worldwide. To ensure the safety, efficacy, and quality of these medications, it is crucial to establish rigorous quality control standards. High-performance liquid chromatography (HPLC) has emerged as a powerful analytical technique for the quality assessment of antiviral APIs. The review discusses the application of HPLC in the analysis of various antiviral drugs, focusing on their identification, quantification, and assessment of impurities. Additionally, it explores the utilization of HPLC in establishing the pharmacopoeial standards for these APIs. The review encompasses a wide range of antiviral drugs, including those used in the treatment of HIV, hepatitis, influenza, and other viral infections. It highlights the importance of method validation, specificity, accuracy, precision, and robustness in HPLC-based quality standardization. The discussion also touches upon the role of HPLC in detecting and quantifying potential impurities, degradation products, and related substances, which can impact the safety and efficacy of the final drug product. Furthermore, the review emphasizes the need for harmonized international standards in the quality control of antiviral APIs to ensure consistency and reliability across different manufacturers and regulatory authorities. It provides insights into the challenges and advancements in HPLC-based quality standardization, including the development of reference standards, analytical methods, and validation procedures specific to antiviral drugs. In conclusion, this review underscores the critical role of HPLC in establishing quality control standards for antiviral APIs. By highlighting the significance of rigorous quality assessment and standardization, it contributes to the overall safety and effectiveness of antiviral drugs in the global healthcare landscape.

Keywords: HPLC, Antiviral, Quality Standardization, Active Pharmaceutical Ingredients, Method Validation, Impurities, Pharmaceutical Analysis, Pharmacopoeial Standards

I. INTRODUCTION

Thesubstances include degradation products, synthetic impurities of drug substance, and manufacturing process impurities from the drug product.The presence of these unwanted chemicals even in small amounts may influence the efficacy and safety of the pharmaceutical products. Impuritydefined by the ICH -Any component of the medicinal product whichis not the chemical entity defined as the active substance or an excipient in the product.Various analytical methodologies were employed for the determination of related components in pharmaceuticals. There is a great need for development of new analytical methods for quality evaluation of new emerging drugs based on their regulatory requirement for the identification, qualification, and control of impurities in drug substance and their formulated products are being explicitly defined, through the International Conference on Harmonization (ICH)(Akkermans et al., 2020; Dudhrejiya et al., 2022; Reilly et al., 2020).

However, organic impurities can result either from the synthesis of the drug substance or from degradation of the drug substance under storage of the drug product. Organic impurities can be starting materials, by-products, intermediates, degradation products, reagents, ligands or

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catalysts.Identification of impurities is based on the chemical reactions involved in the synthesis; any materials used which could contribute impurities, and any possible degradation products.Impurity profiling includes the procedure aimed at the detection, structure elucidation/identification and the quantitative determination of these impurities. Efforts are mainly focused on the profiling of the organic impurities as the other possible groups, such as inorganic impurities and residual solvents, are easily identified and their toxicity is known. The presence of organic impurities in a drug substance is closely dependent on the process of manufacture. A different route of synthesis will tend to lead to a different IP(Shelekhova et al., 2022; Wu et al., 2022; Zhao et al., 2023).

In pharmaceutical research and development, IP is often decided by using high performance liquid chromatography (HPLC), mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectrometry. Direct coupling or multiple hyphenation of these techniques along with the use of modern software for spectral/ chromatographic searching is a valuable tool for the detection of impurities at trace levels. In case of volatile, but thermally stable compounds gas chromatography (GC) coupled with various detection systems still plays an important role. Investigation of the impurities in complex natural products by using matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) MS has been proposed. Capillary electrophoresis and solid phase microextraction/GC–MS have also been successfully used. Normally, more than one analytical system is applied for the confirmation of an IP(Almalawi et al., 2022; Pippalla et al., 2023; Shchukin et al., 2022; Swarnkar et al., 2021; Swarnkar and Maheshwari, 2021).

Isocratic and gradient reversed-phase HPLC with ultraviolet-visible (UV-Vis) detection remains the most suitable analytical procedure for routine impurity testing. Baseline separation of all the potential organic impurities and the active substance should be performed. Better specificity is established by using photodiode array detectors, when the method is under development. In certain applications ion pairing offers better peak separation and post-column derivatization lowers detection limits. GC and thin layer chromatography (TLC) are often applied in the industrial quality control (QC) laboratories for impurity testing. TLC determinations have a semi-quantitative nature, but allow the detection of impurities completely retained or those not retained at all by the stationary phase(Gaurav, 2022; Gautam et al., 2023; Salar et al., 2023)**.**

Inorganic impurities commonly arise from the manufacturing process and are usually known and identified. They include reagent, Ligands, catalysts, heavy metals, and inorganic salts.The common pharmacopoeial method for testing for these types of impurities is called residue on ignition.In this review, a comprehensive information is explored on the critical role of HPLC plays in the quality assessment and standardization of active pharmaceutical ingredients (APIs) with antiviral properties. With the increasing global demand for effective antiviral drugs, the need for stringent quality control and standardization is paramount. This manuscript offers a rational and evidence-based approach to addressing this pressing concern. HPLC is a powerful analytical technique known for its precision, sensitivity, and versatility in pharmaceutical analysis. The review delves into the rationale behind employing HPLC methods for assessing the quality of APIs with antiviral activity. It underscores the significance of ensuring the safety, efficacy, and consistency of antiviral medications, particularly in the context of emerging viral diseases and pandemics(Giordani et al., 2020; Pippalla et al., 2023; Stolarczyk et al., 2022; Swarnkar et al., 2021).

Furthermore, the manuscript discusses the challenges in standardizing antiviral APIs, considering their complex chemical compositions and the need for rigorous testing to identify and quantify impurities. It emphasizes how HPLC-based methods can address these challenges by providing a robust means of characterizing and quantifying active compounds, potential impurities, and degradation products. The rationality of this manuscript lies in its focus on bridging the gap between the increasing demand for antiviral APIs and the necessity for rigorous quality control. By highlighting the various HPLC methodologies available for quality assessment, this review equips researchers, pharmaceutical companies, and regulatory authorities with the knowledge needed to ensure that antiviral medications meet established quality standards. In essence, the manuscript serves as a valuable resource for promoting the rational development and standardization of antiviral pharmaceuticals, which is crucial in the global efforts to combat viral infections effectively.

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II. REVIEW FINDINGS

1.1. Pharmaceutical impurity assessment

Pharmaceutical impurity testing, identification and quantification are vital to address the purity, safety and control over the quality of drug substances or finished drug products.Pharmaceutical inorganic impurities can arise from several sources which include initial materials and their contaminants, reagents, catalysts, solvents, intermediates, excipients and their contaminants, leachable and degradation products. They can be organic impurities, process and drug-related, inorganic or elemental impurities.Significantly, these impurities are often present at very low levels in highly complex sample matrices, and consequently, sensitive and specific assay methods are required to determine the levels of the impurity to collect the data required to complete relevant risk assessments(Dobo et al., 2022; MM et al., 2016; Müller et al., 2006; Wichitnithad et al., 2023).

One of the concerns of the US FDA is nitrosamine related impurities such as NDMA which is the result of the manufacturing process. The limits of inorganic impurities are set up due to toxicity such as mercury, arsenic, hydrazine etc. Organic impurities arise at the time of synthesis, purification and storage of drug substance. Primarily, it is process-related or drug-related pharmaceutical impurities(Dey et al., 2019; Li et al., 2019). Organic volatile impurities are residual solvents that are produced during the synthesis of drug substances or in excipients used in the production of drug formulations.Inorganic impurities often derive from the manufacturing process such as reagents, ligands, catalysts, heavy or residual metals, inorganic salts, filter aids, or charcoals. Inorganic contaminants can be detected and quantified using pharmacopeial standards.The impurities in pharmaceuticals remain with the active pharmaceutical ingredients (APIs) or develop during the formulation. The presence of these unwanted chemicals even in trace amounts may influence the efficacy and safety of pharmaceutical products(Ashworth et al., 2023; Dobo et al., 2022; Schmidtsdorff and Schmidt, 2019).

The raw material in pharmaceutical manufacturing often has impurities which eventually contaminate the final products thereby affecting the efficacy and safety of the product.The impurities such as reagents in the manufacturing process like Anions, Chlorine, and Sulphur Monoxide are common impurities in many substances.The semi quantitative limit tests for chloride is based on the formation of silver chloride precipitation upon addition of silver nitrate reagent to the aqueous solution of the sample to be tested acidified with nitric acid. The turbidity of the resulting solution is compared visually by viewingagainst the black background with that of a standard solution containing a known quantity of chloride(Elgendy et al., 2023; Sawale and Dr.D.Umamaheshwari, 2020; Sharma et al., 2018; Shingote et al., 2022).Different types of impurities in the pharmaceuticals of active pharmaceutical ingredients has been depicted in the Figure 1.

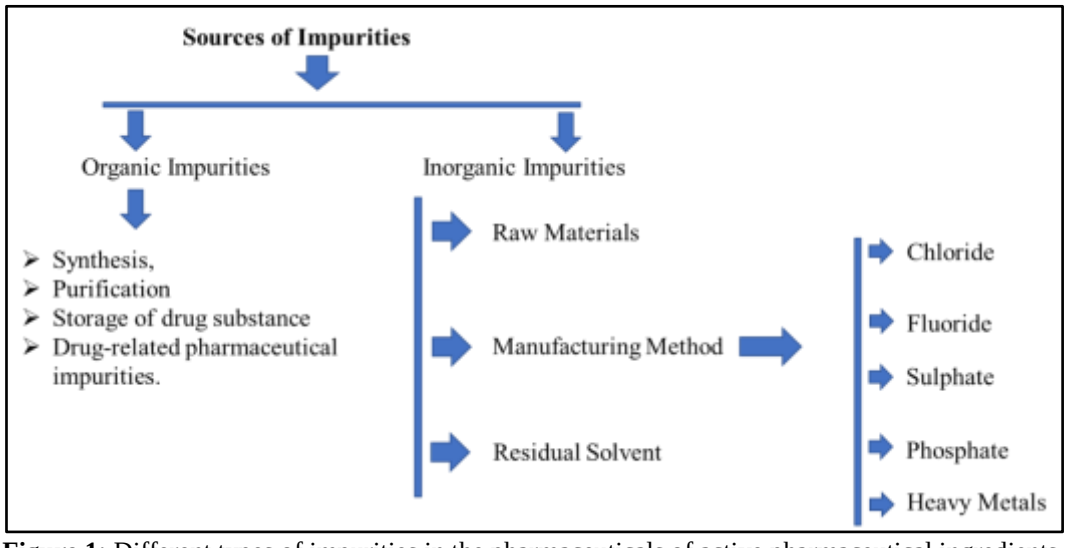

Figure 1: Different types of impurities in the pharmaceuticals of active pharmaceutical ingredients.

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1.2. Effects of Impurities

Toxic impurities may be injurious when present above a certain limit of the impurities such as lead, heavy metal, arsenic. Impurities present in traces may exert cumulative toxic effects after a certain period. It may lower the active strength of the substance and thus decreases its therapeutic effect. Moreover, impurities can cause change in physical and chemical properties of the substance. It can also bring technical glitches or disturbance in the formulation of the drug product. It can decrease the shelf life of the substance. Impurities may cause change in colour, taste and odour etc(Dongala et al., 2020; Paulino et al., 2022; Sauer et al., 2020; Thomas et al., 2022).

1.2.1. Residual Solvent, classification and risk assessment

Residual solvent are solvents that are used during the manufacturing process and may be detected after the product is in its final form.Some common solvents are benzene, chloroform, 1-4-dioxane, methylene chloride and trichloroethylene.The most common technique for measuring residual solvents is gas chromatography because of small size and volatile nature of solvent molecules.The term "tolerable daily intake" (TDI) is used by the International Program onChemical Safety (IPCS) to describe exposure limits of toxic chemicals and "acceptable daily intake" (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The new term "permitted daily exposure" (PDE) is defined in the present guideline as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADI's of the same substance(Council et al., 2019; Custers et al., 2014; Nischwitz et al., 2021).

1.3. Analytical method validation

Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability and consistency of analytical results; it is an integral part of any good analytical practice. Analytical methods need to be validated or revalidated as before their introduction into routine use, whenever the conditions change for which the method has been validated (e.g., an instrument with different characteristics or samples with a different matrix), whenever the method is changed and the change is outside the original scope of the method.

The USP has published specific guidelines for method validation for compound evaluation(Fan et al., 2006; Li et al., 2019; “Rapid and Simultaneous Analysis of Seven Oral Anti-Diabetic Drugs,” 2020).

1.3.1. Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. This is sometimes termed trueness. The accuracy of an analytical method should be established across its range. In the case of the assay of a drug in a formulated product, accuracy may be determined by application of the analytical method to synthetic mixtures of the drug product components to which known amount of analyte have been added within the range of the method. Minimum of test concentrations from 80% to 120% are normally used, for establishment of accuracy in assay of drug substance (or a finished product)(Fan et al., 2006; Ranetti et al., 2009).

1.3.2. 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.Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements(Dholakia et al., 2019; Fan et al., 2006).

1.3.3. Reproducibility and specificity

Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).Reproducibility can be assessed by means of an inter-laboratory trial. Reproducibility should be considered in case of the standardization of an analytical procedure, for instance, for inclusion of procedures in pharmacopoeias. Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically, these might include impurities, degradants, matrix, etc.to ensure

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the identity of an analytes based on purity tests to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e. related substances test, heavy metals, residual solvents content, etc. as well as assayfor the analyteto provide an exact result this allows an accurate statement on the content or potency of the analyte in a sample.ICH document state that when chromatographic procedure used, representative chromatograms should be used to demonstrate specificity and individual components should be appropriately detected. Peak purity tests may be useful to show that the analyte chromatographic peak is not attributable to more than one component (e.g., diode array, mass spectrometry)(Fan et al., 2006; Liu et al., 2015; Pippalla et al., 2023).

1.3.4. Determination of limit of detection and limit of quantitation

The limit of detection of 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. For instrumental and non-instrumental methods detection limit is generally determined by the analysis of samples of known concentration of analyte and by establishing the minimum level at which the analyte can be reliability detected.

The limit of detection (LOD) may be expressed as:

$$LOD = 3.3\ \sigma/s$$

Where, σ = the standard deviation of the response.

S = the slope of the calibration curve.

The slope S may be estimated from the calibration curve of the analyte.

The limit of quantitation 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 is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

For instrumental and non-instrumental methods quantitation limit is generally determined by the analysis of samples of known concentration of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision(Dongala et al., 2020; Pippalla et al., 2023; Ranetti et al., 2009; "Rapid and Simultaneous Analysis of Seven Oral Anti-Diabetic Drugs," 2020).

The limit of quantitation (LOQ) may be expressed as:

$$LOQ = 10\ \sigma/s$$

Where, σ = the standard deviation of the response.

S = the slope of the calibration curve.

1.3.5. Linearity and 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. The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.For the determination of linearity, a minimum of 5 concentrations is recommended. Linearity can be determined by a series of sample whose concentrations span 50-150% of the expected concentration range. Linearity is evaluated by graphically(Fan et al., 2006).

1.3.6. Ruggedness

Degree of reproducibility of test results obtained by the same samples under a different condition such as, different analysts, different laboratories condition, different instrument etc. normally expressed as the lack of influence on test results of operational &environmental variables of the analytical method. Ruggedness is a measure of reproducibility of test results under the variation in the condition normally expected from laboratory to laboratory and from analyst to analyst. By analysis of aliquots from homogenous lots in different laboratory, by different instrument and using operational and environmental condition that may differ but still with the specified parameters of the assay. Degree of reproducibility of test results is then determined as a function of the assay variables such as different operator in same laboratory, different equipment in same laboratory, different source of segment and solutionand different source of column(Abhay, 2011; "Rapid and Simultaneous Analysis of Seven Oral Anti-Diabetic Drugs," 2020).

1.3.7. 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.The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study. It should show the

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reliability of an analysis with respect to deliberate variations in method parameters such as stability of analytical solutions and extraction time. However, in the case of liquid chromatography, examples of typical variations areinfluence of variations of pH in a mobile phase, influence of variations in mobile phase composition, different columns (different lots and/or suppliers) and temperature and flow rate(Chhajed et al., 2023; "Rapid and Simultaneous Analysis of Seven Oral Anti-Diabetic Drugs," 2020).

III. HPLC BASED METHOD VALIDATION ANALYSIS

Analytical method validation is an essential component of pharmaceutical research and development, as it ensures the accuracy, reliability, and reproducibility of the data generated by high-performance liquid chromatography (HPLC) methods for the analysis of active pharmaceutical ingredients (APIs). Validating an HPLC method involves a comprehensive evaluation of its performance under specific conditions, and it is a critical step in the drug development process. The validation process begins with establishing the specificity of the method. This involves confirming that the HPLC method can accurately and selectively identify and quantify the API in the presence of potential impurities, degradation products, and other components of the sample matrix. The API's identity and purity are essential for determining its safety and efficacy in the final drug product(Bajpai et al., 2017; Li et al., 2019).

Precision and accuracy are fundamental parameters assessed during HPLC method validation. Precision refers to the method's ability to provide consistent and reproducible results when repeated multiple times. This is determined through intraday and interday precision studies, where the same sample is analyzed multiple times within the same day and on different days. Accurate results ensure that the reported values are close to the true concentration of the API.

Linearity and range assessment are vital for determining the method's dynamic range. Linearity verifies the relationship between the API's concentration and the detector response, ensuring that the method is applicable over a broad range of concentrations. The range defines the upper and lower limits of the method's applicability(Chhajed et al., 2023; Dholakia et al., 2019).

Sensitivity is evaluated by determining the limit of detection (LOD) and limit of quantification (LOQ). The LOD is the lowest concentration of the API that can be reliably detected but not necessarily quantified. The LOQ, on the other hand, is the lowest concentration at which the API can be both detected and quantified with acceptable precision and accuracy. Sensitivity studies help to establish the method's ability to detect low concentrations of the API(Abhay, 2011; Şenocak et al., 2022).

Robustness studies are conducted to assess the method's reliability under variations in operational and environmental conditions. These variations may include changes in mobile phase composition, flow rate, column temperature, and pH. Robustness studies demonstrate that the method is resilient and can provide consistent results despite minor fluctuations in the analytical conditions.Another critical aspect of method validation is evaluating the stability-indicating capacity of the HPLC method. This means that the method can detect and separate the API from its degradation products, which is crucial for monitoring the API's stability over time and under various storage conditions(Dholakia et al., 2019; Dongala et al., 2020).

Finally, the validated HPLC method's results are documented in a comprehensive report, which typically includes a description of the method, its validation parameters, and the acceptance criteria used for evaluation. The report provides evidence of the method's suitability for its intended purpose and serves as a crucial reference for regulatory submissions, ensuring the safety, quality, and efficacy of pharmaceutical products(Liu et al., 2015).

However, the validation of HPLC methods for the analysis of active pharmaceutical ingredients is a rigorous process that includes assessing specificity, precision, accuracy, linearity, range, sensitivity, robustness, and stability-indicating capabilities. These evaluations ensure that the HPLC method is reliable, accurate, and capable of providing precise and reproducible results, making it a critical tool in pharmaceutical research and development(Chhajed et al., 2023; T. S. and BABU, 2022)vv. The systematic representation of HPLC method for qualitative and quantitative analysis of sample has been depicted in Figure 2 while the current perspectives in analysis of some active pharmaceutical ingredients as anti-viral drugs has been described in the Table 1.

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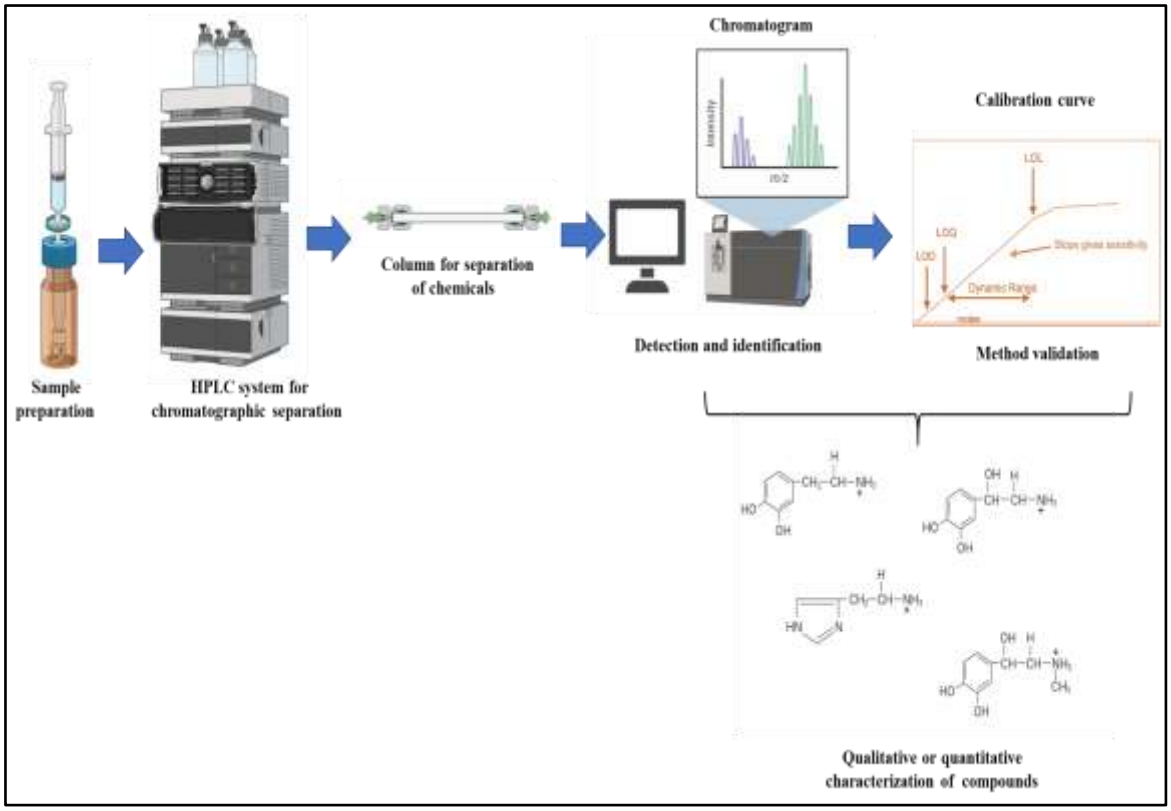

Figure 2: Systematic representation of HPLC method for qualitative and quantitative analysis of sample using HPLC method.

Table 1: Reported methods to validate active pharmaceutical ingredients as anti-viral components using HPLC method.

S. No	Drugs	Method	Description		Reference
1.	Atazanavir	RP-HPLC	**Mobile phase**	Ammonium Dihydrogen Phosphate Buffer, pH 2.5: Acetonitrile (55:45)	("A Validated RP-HPLC Method for the Simultaneous Estimation of Atazanavir and Ritonavir in Pharmaceutical Dosage Forms," 2016; Soundarya et al., 2022; Srinivasu et al., 2011)
			Column	ODS C_{18} (150 mm X 4.6 mm, 5 µ)	
			Flow Rate	1.5 ml/min	
			λmax	288 nm	
2.	Atazanavir	RP-HPLC	**Mobile phase**	Buffer, pH 3.0: Acetonitrile (80:20)	("A Validated RP-
			Column	ODS C_{18} (250 mm X 4.6 mm, 5µ)	

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			Flow Rate	1.0 ml/min	HPLC Method for the Simultaneous Estimation of Atazanavir and Ritonavir in Pharmaceutical Dosage Forms," 2016; Veerabhadram et al., 2017)
			λmax	212 nm	
3.	Atazanavir	Stability Indicating RP-HPLC	**Mobile phase**	Phosphate Buffer pH 4.5: Acetonitrile (700:300)	(Padmalatha et al., 2010; Veerabhadram et al., 2017)
			Column	X-Terra RP1-C_8 (150 mm X 4.6 mm, 5µm)	
			Flow Rate	1.0 ml/min	
			λmax	230 nm	
4.	Atazanavir Sulphate	RP-HPLC	**Mobile phase**	Ammonium Acetate Buffer pH 4.0: Acetonitrile (60:40)	(Dey et al., 2017)
			Column	Zodiac C_{18} (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	205 nm	
5.	Atazanavir Sulphate	Stability Indicating RP-HPLC	**Mobile phase**	Methanol: Water (pH 3.5) (900:100)	(Bhirud and Hiremath, 2013a)
			Column	Phenomenex C_{18} (250 mm X 4.6 mm, 5µm)	
			Flow Rate	0.5 ml/min	
			λmax	249 nm	
6.	Atazanavir Sulphate	Stability indicating RP-HPLC	**Mobile phase**	Methanol : Acetonitrile: Phosphate Buffer (45:35:20)	(Bandla et al., 2015)
			Column	Agilent C_{18} (250 mm X 25 mm, 5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	249 nm	
7.	Atazanavir Sulphate	Stability indicating RP-HPLC	**Mobile phase**	Phosphate Buffer, pH 3.0: Methanol (55:45)	(Bhirud and Hiremath, 2013a)
			Column	Hypersil BDS C_{18} (150 mm X 4.6 mm, 5 µ)	
			Flow Rate	1.0 ml/min	
			λmax	248 nm	

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<table>
<tr><td>8.</td><td>Atazanavir and Ritonavir</td><td>RP-HPLC and UV Spectro-photometry</td><td>Mobile phase</td><td>Potassium Phosphate Buffer, pH 2.5: Acetonitrile (40:60)</td><td>(Behera et al., 2012; Gade et al., 2015)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>X-tera C_{18}
(100 mm X 4.6 mm, 3.5 µ)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Flow Rate</td><td>1.2 ml/min</td><td></td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>236 nm</td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="2">UV Spectrophotometry
Wavelength:
247 nm was used for Atazanavir and 239 nm was used for Ritonavir</td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="2">Concentration Range:
6-30 µg/ml for Atazanavir and 2-10 µg/ml for Ritonavir</td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="2">Solvent: Methanol</td><td></td></tr>
<tr><td>9.</td><td>Atazanavir and Ritonavir</td><td>Stability indicating RP-HPLC</td><td>Mobile phase</td><td>Phosphate Buffer pH 3.4: Acetonitrile (50:50)</td><td>(Dey et al., 2017; Supare et al., 2021)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>Lichrosphere C_{18}
(250 mm X 4.6 mm, 5 µ)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Flow Rate</td><td>1.5 ml/min</td><td></td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>250 nm</td><td></td></tr>
<tr><td>10.</td><td>Atazanavir and Ritonavir</td><td>Related Impurities RP-HPLC</td><td>Mobile phase</td><td>Sol-A: Phosphate Buffer
Sol-B: Acetonitrile
<table>
<tr><th>Time (min)</th><th>Sol-A</th><th>Sol-B</th></tr>
<tr><td>0.01</td><td>75</td><td>25</td></tr>
<tr><td>5</td><td>60</td><td>40</td></tr>
<tr><td>8</td><td>60</td><td>40</td></tr>
<tr><td>10</td><td>55</td><td>45</td></tr>
<tr><td>13</td><td>55</td><td>45</td></tr>
<tr><td>15</td><td>40</td><td>60</td></tr>
<tr><td>15.5</td><td>75</td><td>25</td></tr>
<tr><td>18</td><td>75</td><td>25</td></tr>
</table></td><td>(Mantripragada et al., 2018)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>BEH C_{18}
(100 mm X 2.1 mm, 1.7 µ)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Flow Rate</td><td>0.4 ml/min</td><td></td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>240 nm</td><td></td></tr>
<tr><td>11.</td><td>Atazanavir and Ritonavir</td><td>RP-HPLC</td><td>Mobile phase</td><td>Phosphate Buffer pH 3.0: Acetonitrile (45:55)</td><td>(Gadhvi et al., 2013)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>Hypersil C_{18}
(250 mm X 4.6 mm, 5 µ)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Flow Rate</td><td>1.0 ml/min</td><td></td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>254 nm</td><td></td></tr>
</table>

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12.	Atazanavir and Ritonavir	RP-HPLC	**Mobile phase**	Methanol : Acetonitrile (70:30)	(Gade et al., 2015; Gadhvi et al., 2013)
			Column	Agilent C_{18} (250 mm 4.6 mm,5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	238 nm	
13.	Atazanavir and Ritonavir	RP-HPLC	**Mobile phase**	Phosphate Buffer: Acetonitrile (1:1)	(Bhavyasri et al., 2015)
			Column	Hypersil BDS C_{18} (150 mm X 4.6 mm, 5µ)	
			Flow Rate	1.0ml/min	
			λmax	248 nm	
14.	Cobicistat	RP-HPLC	**Mobile phase**	Methanol: Water (80:20)	(Ganji and Satyavati, 2015)
			Column	Phenomenex C_{18} (100 mm X 4.6 mm, 5µm)	
			Flow Rate	0.8 ml/min	
			λmax	249 nm	
15.	Cobicistat	RP-HPLC	**Mobile phase**	0.1% OPA Buffer: Acetonitrile (45:55),	(Madhavi and Rani, 2016)
			Column	Inertsil BDS C_{18} (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	210 nm	
16.	Cobicistat and Darunavir	RP-HPLC	**Mobile phase**	Sodium Acetate Buffer, pH 4.5: Methanol (60:40)	(Bichala et al., 2020)
			Column	ODS C_{18} (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.0ml/min	
			λmax	253 nm	
17.	Cobicistat and Darunavir	Stability Indicating RP-HPLC	**Mobile phase**	0.1% Perchloric Acid Buffer: Acetonitrile (38:62)	(M. V. S. S. Nalini et al., 2016; Rizwan et al., 2016; Sindu Priya et al., 2016)
			Column	BDS C_{18} (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	211 nm	
18.	Cobicistat and Darunavir	Stability Indicating UPLC	**Mobile phase**	Acetonitrile: 0.1% Ortho Phosphoric Acid Buffer, (70:30)	(Dadi and Sowjanya, 2023;
			Column	BEH C_{18} (100 mm X 2.1 mm, 1.7µm)	

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<table>
<tr><td></td><td></td><td></td><td>Flow Rate</td><td>0.27 ml/min</td><td rowspan="2">Madhavi and Rani, 2017)</td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>242 nm</td></tr>
<tr><td>19.</td><td>Cobicistat and Darunavir</td><td>RP-HPLC</td><td>Mobile phase</td><td>Acetonitrile: Phosphate Buffer, pH 4.6 (45:55)</td><td rowspan="4">(Bichala et al., 2020)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>X-terra C_{18}
(250 mm X 4.6 mm, 5 µm)</td></tr>
<tr><td></td><td></td><td></td><td>Flow Rate</td><td>1.0 ml/min</td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>255 nm</td></tr>
<tr><td>20.</td><td>Cobicistat and Darunavir</td><td>Stability Indicating RP-HPLC</td><td>Mobile phase</td><td>Acetonitrile : Water, pH 3.2
(70:30)</td><td rowspan="4">(Sankarshana and Musthafa, 2017)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>Kromosil C_{18}
(250 mm X 4.6 mm, 5 µm)</td></tr>
<tr><td></td><td></td><td></td><td>Flow Rate</td><td>1.0 ml/min</td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>289 nm</td></tr>
<tr><td>21.</td><td>Cobicistat and Darunavir</td><td>Stability Indicating RP-HPLC</td><td>Mobile phase</td><td>0.1 M NaH_2PO_4:Methanol (70:30)</td><td rowspan="4">(M. V. S. S. Nalini et al., 2016)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>Phenomenex C_{18}
(150 mm X 4.6 mm, 5 µm)</td></tr>
<tr><td></td><td></td><td></td><td>Flow Rate</td><td>1.0 ml/min</td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>260 nm</td></tr>
<tr><td>22.</td><td>Cobicistat and Elvitegravir</td><td>RP-HPLC</td><td>Mobile phase</td><td>Methanol: Phosphate Buffer, pH 3.3 (20:80)</td><td rowspan="4">(Kumar et al., 2019)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>ODS C_{18}
(250 mm X 4.6 mm, 5µ)</td></tr>
<tr><td></td><td></td><td></td><td>Flow Rate</td><td>1.0 ml/min</td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>254 nm</td></tr>
<tr><td>23.</td><td>Cobicistat, Emtricitabine Tenofovir Disoproxil Fumarate and Elvitegravir</td><td>RP-HPLC</td><td>Mobile phase</td><td>Sol-A: 0.1% TFA in water
Sol-B: Acetonitrile
<table>
<tr><th>Time (min)</th><th>Sol-A</th><th>Sol-B</th></tr>
<tr><td>0-2</td><td>90</td><td>10</td></tr>
<tr><td>2-3</td><td>10</td><td>90</td></tr>
<tr><td>3-8</td><td>10</td><td>90</td></tr>
<tr><td>8-8.10</td><td>90</td><td>10</td></tr>
<tr><td>8.10-10</td><td>90</td><td>10</td></tr>
</table></td><td rowspan="4">(Gummaluri et al., 2016; Jampala et al., 2014)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>Atlantis C_{18}
(100 mm X 4.6 mm, 5 µm)</td></tr>
<tr><td></td><td></td><td></td><td>Flow Rate</td><td>1.0 ml/min</td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>240 nm</td></tr>
</table>

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24.	Cobicistat, Emtricitabine Tenofovir Disoproxil Fumarate and Elvitegravir	Stability Indicating RP-UPLC	**Mobile phase**	Acetonitrile: 0.1% Ortho Phosphoric Acid Buffer, (700:300)	(Gummaluri et al., 2016; Jampala et al., 2014)
			Column	Endoversilo C18 (50 mm X 2.1 nm, 1.8 µm)	
			Flow Rate	0.3 ml/min	
			λmax	252 nm	
25.	Atazanavir and Cobicistat	RP-HPLC	**Mobile phase**	Buffer: Acetonitrile (65:35)	("METHOD DEVELOPMENT AND VALIDATION FOR THE SIMULTANEOUS ESTIMATION OF COBICISTAT AND ATAZANAVIR BY RP HPLC IN PHARMACEUTICAL FORMULATION," 2021; Venkata Padmini and Gowri Sankar, 2021)
			Column	C_{18} (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	240 nm	
26.	Atazanavir and Cobicistat	UPLC	**Mobile phase**	Acetonitrile: 0.1% Ortho Phosphoric Acid Buffer, (55:45)	(Veerabhadram et al., 2017)
			Column	HSS C_{18} (100 mm X 2.1 mm, 1.8 µm)	
			Flow Rate	0.2 ml/min	
			λmax	254 nm	
27.	Atazanavir and Cobicistat	Stability Indicating RP-HPLC	**Mobile phase**	0.01M sodium acetate buffer, pH 4.2: Methanol: Acetontrile (25:15:60)	(Veerabhadram et al., 2017)
			Column	Phenomenex C_{18} (250 mm X 4.6 mm, 5 µ)	
			Flow Rate	1.0 ml/min	
			λmax	235 nm	
28.	Atazanavir and Cobicistat	RP-HPLC	**Mobile phase**	Phosphate buffer, pH 7.0: Methanol (30:70)	(M. Nalini et al., 2016)
			Column	X-terra C_{18} (150 mm X 4.6 mm, 5 µm)	
			Flow Rate	0.8 ml/min	
			λmax	260 nm	

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<table>
<tr><td>29.</td><td>Emtricitabine</td><td>Related Degradation -HPLC</td><td>Mobile phase</td><td>Sol-A: ammonium formate buffer pH4.2
Sol-B: methanol
<table><tr><th>Time(min)</th><th>Sol-A</th><th>Sol-B</th></tr><tr><td>0</td><td>95</td><td>5</td></tr><tr><td>20</td><td>65</td><td>35</td></tr><tr><td>25</td><td>95</td><td>5</td></tr><tr><td>30</td><td>95</td><td>5</td></tr></table></td><td>(Panigrahy and Sunil Kumar Reddy, 2016), (Kokkirala and Suryakala, 2019; Sahoo et al., 2023)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>HiQSil C_{18}
(250 mm X 4.6 mm, 5µm)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>FR</td><td>1.0 ml/min</td><td></td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>280 nm</td><td></td></tr>
<tr><td>30.</td><td>Emtricitabine</td><td>RP-HPLC</td><td>Mobile phase</td><td>10mM potassium dihydrogen phosphate buffer pH 6.8: methanol-2% acetic acid (73:25:2)</td><td>(Ghode et al., 2022; Kapoor et al., 2020)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>Phenomenex C18
(250 mm X 4.6 mm, 5µ)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>FR</td><td>1.0 ml/min</td><td></td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>280 nm</td><td></td></tr>
<tr><td>31.</td><td>Emtricitabine and Ritonavir</td><td>RP-HPLC</td><td>Mobile phase</td><td>methanol and water (80:20)</td><td>(Rajeswari et al., 2022)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>Shim-packC_{18}
(250 mm X4.6 mm, 5µ)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>FR</td><td>1.0 ml/min</td><td></td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>251 nm</td><td></td></tr>
<tr><td>32.</td><td>Emtricitabine</td><td>RP-HPTLC</td><td>Mobile phase</td><td>acetone:water (70:30)</td><td>(Ghode et al., 2022)</td></tr>
<tr><td></td><td></td><td></td><td>TLC plate</td><td>Silica gel 60 F_{254}</td><td></td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>285 nm</td><td></td></tr>
<tr><td>33.</td><td>Emtricitabine</td><td>UV Spectometer</td><td colspan="2">Wavelength: 291 nm</td><td>(Shelke et al., 2022)</td></tr>
<tr><td></td><td></td><td></td><td colspan="2">Concentration: 1-10 µg/ml</td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="2">Solvent: methanol and 0.1N HCl (7:3)</td><td></td></tr>
<tr><td>34.</td><td>Emtricitabine</td><td>Stability-Indicating HPTLC</td><td>Mobile phase</td><td>Toluene : ethylacetate : methanol (2:8:1)</td><td>(Bhirud and Hiremath, 2013b; Rathore et al., 2012)</td></tr>
<tr><td></td><td></td><td></td><td>TLC plate</td><td>Silica gel 60 F_{254}</td><td></td></tr>
<tr><td></td><td></td><td></td><td>λmax</td><td>284 nm</td><td></td></tr>
<tr><td>35.</td><td>Tenofovir and lamivudine</td><td>RP-HPLC</td><td>Mobile phase</td><td>Acetonitrile and phosphate buffer PH 3.5 (80:20)</td><td>(Godela and Gummadi, 2021; Haribabu et al., 2021)</td></tr>
<tr><td></td><td></td><td></td><td>Column</td><td>HypersilTM BDS C_{18}
(250 mm X 4.6 mm, 5µm)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>FR</td><td>1.2 ml/min</td><td></td></tr>
</table>

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<table>
<tr><td></td><td></td><td></td><td>λmax</td><td>260 nm</td><td></td></tr>
<tr><td>36.</td><td>Tenofovir</td><td>Stability-Indicating RP-HPLC</td><td>Mobile phase</td><td>Sol-A:Ammonium acetate buffer (pH6.0):70%THF +30%ACN (990:10)
Sol-B: Ammonium acetate buffer(pH6.0):70%THF +30%ACN (500:500).</td><td rowspan="4">(Attaluri et al., 2021; Godela and Gummadi, 2021)</td></tr>
<tr><td></td><td></td><td>Column</td><td>Inertsil ODS C-18
(100 mm X 4.6 mm, 5µm)</td></tr>
<tr><td></td><td></td><td>FR</td><td>1.5 ml/min</td></tr>
<tr><td></td><td></td><td>λmax</td><td>260 nm</td></tr>
<tr><td>37.</td><td>Tenofovir</td><td>Stability-Indicating LC-MS</td><td>Mobile phase</td><td>Sol-A: 0.1% formic acid
Sol-B: acetonitrile</td><td rowspan="3">(Lamichhane et al., 2022; Saha et al., 2019)</td></tr>
<tr><td></td><td></td><td>Column</td><td>BEH C18
(50 mm X 1.0 mm, 1.7µm)</td></tr>
<tr><td></td><td></td><td>FR</td><td>0.6 ml/min</td></tr>
<tr><td>38.</td><td>Emtricitabine and Tenofovir,Efavirenz</td><td>HPLC</td><td>Mobile phase</td><td>Sol-A: methanol
Sol-B: ammonium acetate buffer at pH 4.5
<table>
<tr><th>Time(min)</th><th>Sol-A</th><th>Sol-B</th></tr>
<tr><td>0-10</td><td>10</td><td>90</td></tr>
<tr><td>10-22</td><td>65</td><td>35</td></tr>
<tr><td>22-25</td><td>10</td><td>90</td></tr>
</table></td><td rowspan="4">(A et al., 2016; Devrukhakar et al., 2013; Nadig et al., 2013; Raju and Begum, 2008; Ramaswamy and Arul Gnana Dhas, 2018)</td></tr>
<tr><td></td><td></td><td>Column</td><td>Zorbax SB CN C_{18}
(250 mm X 4.6 mm, 5µm)</td></tr>
<tr><td></td><td></td><td>FR</td><td>1.5 ml/min</td></tr>
<tr><td></td><td></td><td>λmax</td><td>260 nm</td></tr>
<tr><td>39.</td><td>Emtricitabine and Tenofovir</td><td>Stability Indicating RP-HPLC</td><td>Mobile phase</td><td>phosphate buffer pH 4.0 and methanol (70:30).</td><td rowspan="4">(Attaluri et al., 2021; Devrukhakar et al., 2013)</td></tr>
<tr><td></td><td></td><td>Column</td><td>Agilent TC-C18
(250 mm X 4.6 mm, 5µm)</td></tr>
<tr><td></td><td></td><td>FR</td><td>1.0ml/min</td></tr>
<tr><td></td><td></td><td>λmax</td><td>261 nm</td></tr>
<tr><td>40.</td><td>Emtricitabine and Tenofovir</td><td>RP-HPLC</td><td>Mobile phase</td><td>acetonitrile: phosphate buffer
(60:40)</td><td rowspan="4">(Ghode et al., 2022; Kokkirala and Suryakala, 2019)</td></tr>
<tr><td></td><td></td><td>Column</td><td>Phenomenex Luna C8
(250 mm X 4.6 mm, 5µm)</td></tr>
<tr><td></td><td></td><td>FR</td><td>1.0 ml/min</td></tr>
<tr><td></td><td></td><td>λmax</td><td>260 nm</td></tr>
<tr><td>41.</td><td>Emtricitabine and Tenofovir</td><td>HPLC</td><td>Mobile phase</td><td>Ortho-phosphoric acid BufferpH 2.5: Methanol. (30:70)</td><td rowspan="2">(Abdul Sattar and Achanta, 2018; Ramaswamy and Arul Gnana Dhas, 2018)</td></tr>
<tr><td></td><td></td><td>Column</td><td>Inspire C_{18}
(150 mm X 4.6 mm, 5µm)</td></tr>
</table>

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			FR	1.0ml/min	
			λmax	272 nm	
42.	Emtricitabine, Tenofovir and Bictegravir	Stability Indicating RP-HPLC	**Mobile phase**	0.2% Triethylaminebuffer and methanol (40:60).	(Attaluri et al., 2021; Deepthi and Sankar, 2019)
			Column	Octyldecylsilyl (ODS) C18 (250 mm X 4.6 mm, 5µm)	
			FR	1.2 ml/min	
			λmax	260 nm	
43.	Emtricitabine,Tenofovir and Rilpivirine	RP-HPLC	**Mobile phase**	phosphate buffer: acetonitrile (40:60)	("A NOVEL VALIDATED ANALYTICAL METHOD FOR SIMULTANEOUS ESTIMATION OF EMTRICITABINE, TENOFOVIR DISOPROXIL FUMARATE AND RILPIVIRINE – HYDROCHLORIDE BY RP-HPLC," 2022; Panigrahy and Sunil Kumar Reddy, 2015; Vijayai et al., 2019)
			Column	Zodiac C18 (250 mm X 4.6 mm, 5µm)	
			FR	1.0 ml/min	
			λmax	262 nm	
44.	Emtricitabine, Tenofovir and bictegravir	Stability-Indicating RP-HPLC	**Mobile phase**	0.1% ortho phosphoric acid Buffer:Acetonitrie (55:45)	(Attaluri et al., 2021; Singh and Divakar, 2019)
			Column	Zodiac C18 (150 mm X 4.6 mm, 5µm)	
			FR	1.0 ml/min	
			λmax	272 nm	
45.	Emtricitabine, Tenofovir and bictegravir	RP-HPLC	**Mobile phase**	0.01N KH2PO4 buffer pH 3.47 :Acetonitrie (58:42)	(Attaluri et al., 2021; Kokkirala and Suryakala, 2019)
			Column	BDS C_{18} (150 mm X 4.6 mm, 5µm)	
			FR	1.0 ml/min	
			λmax	272 nm	
46.	Emtricitabine,Tenofovir and bictegravir	LC-MS/MS	**Mobile phase**	Methanol : 0.1% formic acid (85:15)	(Haaland et al., 2023; Tanuja and Ganapaty, 2022)
			Column	Zorbax C_{18} (150 mm X 4.6 mm, 5µm)	
			FR	1.0 ml/min	
47.			**Wavelength:** 256,316,240 nm		(Mishra et al.,

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<table>
<tr><td></td><td>Emtricitabine,Tenofovir and Efavirenz</td><td>UV Spectometer</td><td colspan="2">Concentration: 10-50 µg/ml
Solvent: 0.1 N NaOH</td><td>2020; Ramaswamy and Arul Gnana Dhas, 2018)</td></tr>
<tr><td rowspan="4">48.</td><td rowspan="4">Ritonavir</td><td rowspan="4">RP-HPLC</td><td>Mobile phase</td><td>Phosphate Buffer, pH 4.0: Acetonitrile (50:50)</td><td rowspan="4">(Grace and Parthiban, 2022; Kapoor et al., 2020)</td></tr>
<tr><td>Column</td><td>Symmetry C_{18} (100 mm X 4.6 mm, 3.5 µm)</td></tr>
<tr><td>Flow Rate</td><td>1.0 ml/min</td></tr>
<tr><td>λmax</td><td>239 nm</td></tr>
<tr><td rowspan="4">49.</td><td rowspan="4">Ritonavir</td><td rowspan="4">RP-HPLC</td><td>Mobile phase</td><td>Methanol: Acetonitrile (20:80)</td><td rowspan="4">(Baje et al., 2019; Kumbhar et al., 2020; M and N, 2012)</td></tr>
<tr><td>Column</td><td>Symmetry C_{18} (250 mm X 4.6 mm, 5µm)</td></tr>
<tr><td>Flow Rate</td><td>1.0 ml/min</td></tr>
<tr><td>λmax</td><td>210 nm</td></tr>
<tr><td rowspan="4">50.</td><td rowspan="4">Ritonavir</td><td rowspan="4">Stability Indicating RP-UPLC</td><td rowspan="2">Mobile phase</td><td>Sol-A: Phosphate Buffer: Acetonitrile (80:20)
Sol-A: Milli-Q Water: Acetonitrile (20:80)
<table>
<tr><th>Time (min)</th><th>Sol-B</th></tr>
<tr><td>0.01</td><td>17</td></tr>
<tr><td>0.6</td><td>17</td></tr>
<tr><td>6</td><td>30</td></tr>
<tr><td>11</td><td>45</td></tr>
<tr><td>18</td><td>75</td></tr>
<tr><td>18.01</td><td>17</td></tr>
<tr><td>20</td><td>17</td></tr>
</table></td><td rowspan="4">(Koppala et al., 2015)</td></tr>
<tr><td>Column</td><td>BEH Shield RP18 (100 mm X 2.1 mm, 1.7µm)</td></tr>
<tr><td>Flow Rate</td><td>0.5 ml/min</td></tr>
<tr><td>λmax</td><td>240 nm</td></tr>
<tr><td rowspan="4">51.</td><td rowspan="4">Ritonavir</td><td rowspan="4">RP-HPLC</td><td>Mobile phase</td><td>Phosphate Buffer: Acetonitrile (50:50)</td><td rowspan="4">(Grace and Parthiban, 2022; Kapoor et al., 2020; Kumbhar et al., 2020)</td></tr>
<tr><td>Column</td><td>X-Terra RP C_{18} (100 mm X 4.6 mm, 3.5 µ)</td></tr>
<tr><td>Flow Rate</td><td>1.0 ml/min</td></tr>
<tr><td>λmax</td><td>239 nm</td></tr>
<tr><td>52.</td><td>Ritonavir and Valacyclovir</td><td>RP-HPLC</td><td>Mobile phase</td><td>Methanol: Acetonitrile: Water (35:41.5:23.5)</td><td>(Sathis Kumar et al., 2015)</td></tr>
</table>

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	Hydro-chloride		**Column**	Agilent TC- C_{18} (250 mm X 4.6 mm, 5µm)	
			Flow Rate	1.3 ml/min	
			λmax	222 nm	
53.	Ritonavir	RP-HPLC	**Mobile phase**	Acetonitrile: Ammonium Acetate Buffer (85:15)	(Anuradha et al., 2023; Baje et al., 2019; Jitta et al., 2022)
			Column	HiQSiL C_{18} (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	239 nm	
54.	Ritonavir (human plasma)	RP-HPLC	**Mobile phase**	Sodium Acetate, pH 4.8: Acetonitrile (55:45 v/v)	(Abhinandana.Patchala and Ramarao Nadendla, 2022; Mardia et al., 2014)
			Column	C_8 (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.5 ml/min	
			λmax	212 nm	
55.	Ritonavir and Atazanavir	RP-HPLC and UV Spectro-photometry	**Mobile phase**	Potassium Phosphate Buffer, pH 2.5: Acetonitrile (40:60)	(Abhinandana.Patchala and Ramarao Nadendla, 2022; Choi et al., 2007; Gade et al., 2015; Venkatesh et al., 2013)
			Column	X-tera C_{18} (100 mm X 4.6 mm, 3.5 µ)	
			Flow Rate	1.2 ml/min	
			λmax	236 nm	
			UV Spectrophotometry **Wavelength:** 247 nm was used for Atazanavir and 239 nm was used for Ritonavir		
			Concentration Range: 6-30 µg/ml for Atazanavir and 2-10 µg/ml for Ritonavir		
			Solvent: Methanol		
56.	Ritonavir and Atazanavir	Stability indicating RP-HPLC	**Mobile phase**	Acetonitrile: Methanol: Tetrahydrofuran: Buffer (175:100:100:625)	(Gade et al., 2015, 2014)
			Column	Hypersil BDS C_{18} (150 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.5 ml/min	
			λmax	250 nm	
57.	Ritonavir and	RP-HPLC	**Mobile phase**	Phosphate Buffer, pH 3.0: Acetonitrile (45:55)	(Abhinandana.Patchala and Ramarao Nadendla, 2022;
			Column	Hypersil C_{18} (250 mm X 4.6 mm, 5 µ)	

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	Atazanavir		**Flow Rate**	1.0 ml/min	Chinnaiah et al., 2015; Venkateswara Rao et al., 2016)
			λmax	254 nm	
58.	Lopinavir	RP-HPLC	**Mobile phase**	Methanol: Water (65:35)	(Deepthi et al., 2019; Grace and Parthiban, 2022; Indira et al., 2022; M and N, 2012; "METHOD DEVELOPMENT AND VALIDATION FOR THE SIMULTANEOUS ESTIMATION OF RITONAVIR, LOPINAVIR AND EFAVIRENZ BY RP- HPLC," 2022; Namratha and Vijayalakshmi, 2018; Rathnasamy et al., 2018; Varma et al., 2012)
			Column	Kromosil C_{18} (150 mm X 4.5 mm, 5µm)	
			Flow Rate	0.8 ml/min	
			λmax	265 nm	
59.	Lopinavir	RP-HPLC	**Mobile phase**	Acetonitrile: Methanol: Phosphate buffer, pH 3 (50:30:20)	
			Column	Symmetry C_{18} (150 mm X 4.6 mm, 5 µ)	
			Flow Rate	1.0 ml/min	
			λmax	210 nm	
60.	Lopinavir	RP-HPLC	**Mobile phase**	Methanol: Water (65:35)	
			Column	Kromosil C_{18} (150 mm X 4.5 mm, 5µm)	
			Flow Rate	0.8 ml/min	
			λmax	265 nm	
61.	Lopinavir	RP-HPLC	**Mobile phase**	Acetonitrile: phosphate buffer, pH 7.8 (85:15)	
			Column	Phenomenex C_{18} (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	215 nm	
62.	Lopinavir	RP-HPLC	**Mobile phase**	Acetonitrile: Water (70:30)	(Anuradha et al., 2023; M and N, 2012)
			Column	Phenomenex C_{18} (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	198 nm	
63.	Ritonavir and Lopinavir	RP-HPLC	**Mobile phase**	Buffer: Acetonitrile (60:40)	(Anuradha et al., 2023; Ayeen et al., 2019; Grace and Parthiban, 2022)
			Column	ODS C_8 (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	250 nm	
64.	Ritonavir	RP-HPLC	**Mobile phase**	acetonitrile: 0.05M	

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	and Lopinavir			phosphoric acid (55:45)	
			Column	Agilent TC C_{18} (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.2 ml/min	
			λmax	240nm	
65.	Ritonavir and Lopinavir	RP-HPLC	**Mobile phase**	Phosphate Buffer: Methanol (70:30)	
			Column	Intersil C_{18}	
			Flow Rate	0.8 ml/min	
			λmax	260nm	
66.	Ritonavir and Lopinavir	RP-HPLC	**Mobile phase**	Orthophosphoric acid: Methanol(40:60)	(Anuradha et al., 2023; Ayeen et al., 2019; Prasanthi and Sankar, 2022; Rane et al., 2015)
			Column	Hypersil C_{18} (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	273nm	
67.	Ritonavir and Lopinavir	RP-HPLC	**Mobile phase**	Phosphate Buffer (pH 3.5): Acetonitrile (50:50)	
			Column	$ODSC_{18}$ (250 mm X 4.6 mm, 5 µm)	
			Flow Rate	1.0 ml/min	
			λmax	273nm	
68.	Ritonavir and Lopinavir	RP-UPLC	**Mobile phase**	0.1% H_3PO_4 in acetonitrile: methanol (85:15)	
			Column	Acquity UPLC $BEHC_{18}$ (50 mm X 2.1 mm, 1.7 µm)	
			Flow Rate	0.4 ml/min	
			λmax	215nm	

IV. CONCLUSION

In conclusion, the review on "HPLC Based Quality Standardization of Some Anti-viral Active Pharmaceutical Ingredients" provides a comprehensive overview of the critical role that HPLC methods play in ensuring the quality, safety, and efficacy of antiviral drugs. The rationality behind this review is evident in its focus on addressing the pressing need for rigorous quality control measures in the development and standardization of antiviral pharmaceuticals. The review underscores the significance of HPLC in overcoming the challenges associated with the complex chemical compositions and the potential impurities of antiviral APIs. It offers a rational approach to tackling the demand for reliable antiviral medications, particularly in the context of emerging viral diseases and pandemics. The methods discussed in the review provide a robust means of characterizing and quantifying active compounds and related impurities, ensuring the consistency of these essential medications. This review is a valuable resource for researchers, pharmaceutical companies, and regulatory authorities, equipping them with the knowledge and insights necessary to meet established quality standards for antiviral pharmaceuticals. As the world faces ongoing challenges from viral infections, this review serves as a rational guide for the development and standardization of antiviral drugs, furthering our collective efforts to combat viral diseases effectively and safeguard public health.

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Conflict of interest
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