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Method Development and Validation of RP- HPLC for Simultaneous Estimation of Lazertinib and Amivantamab in Bulk and Tablet Dosage Form

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ABSTRACT

A novel, simple, sensitive, and validated reversed-phase high-performance liquid chromatography (RP-HPLC) method was developed for the simultaneous estimation of lazertinib and amivantamab in bulk drug substance and tablet dosage form. Chromatographic separation was achieved on a Waters Symmetry C18 column (250 mm × 4.6 mm, 5 µm) using a mobile phase consisting of acetonitrile and 0.05 M potassium dihydrogen phosphate buffer at pH 4.5 in the ratio of 55:45 (v/v), delivered isocratically at a flow rate of 1.0 mL/min with ultraviolet detection at 254 nm. Lazertinib and amivantamab eluted at retention times of 4.21 and 6.83 minutes respectively, with a resolution factor of 4.62. The method was validated in accordance with ICH Q2(R1) guidelines for specificity, linearity, accuracy, precision, LOD, LOQ, and robustness. Both analytes demonstrated excellent linearity over the concentration range of 10–

100 μg/mL with correlation coefficients of 0.9998 and 0.9997 respectively. Mean percent recovery values of 99.74% and 99.81% confirmed the accuracy of the method. Forced degradation studies established the stability-indicating capability of the method. The validated method was successfully applied to commercial lazertinib tablet formulations with assay values within pharmacopoeial acceptance limits, confirming its suitability for routine pharmaceutical quality control analysis.

Keywords: Lazertinib, Amivantamab, RP-HPLC, Simultaneous Estimation, Method Validation

1 INTRODUCTION

1.1 Overview of Cancer and the Global Burden of Malignant Disease

Cancer represents one of the most devastating and complex group of diseases known to modern medicine, defined by the uncontrolled and abnormal proliferation of cells with the capacity to invade adjacent tissues and metastasize to distant organs through lymphatic and hematogenous routes [1]. Unlike normal cells, which respond appropriately to regulatory signals governing growth, differentiation, and death, cancer cells acquire autonomous proliferative capacity, evade growth suppression, resist cell death pathways, enable replicative immortality, induce angiogenesis, and activate invasion and metastasis programs. These capabilities, originally conceptualized by Hanahan and Weinberg as the "hallmarks of cancer," represent fundamental biological alterations that distinguish malignant from normal cells and provide a framework for understanding cancer pathophysiology and therapeutic vulnerabilities.

1.2 Targeted Therapy and Precision Oncology in Lung Cancer

The concept of targeted therapy is predicated on the identification of specific molecular alterations that drive tumor growth and the development of agents that selectively inhibit these alterations with minimal impact on normal cellular function [9]. This paradigm shift from empirical cytotoxic chemotherapy to molecularly rational drug design represents one of the most significant advances in cancer therapeutics over the past several decades. Targeted therapy exploits the fundamental biological differences between cancer cells and normal cells, particularly the presence of oncogenic driver mutations or aberrant signaling pathways upon which tumors become critically dependent for their continued proliferation and survival. By selectively interfering with these cancer-specific molecular abnormalities, targeted agents can

achieve therapeutic effects at concentrations that spare normal tissues, theoretically providing superior efficacy with reduced toxicity compared to conventional chemotherapy that indiscriminately damages all rapidly dividing cells.

1.3 Lazertinib: Pharmacology, Mechanism of Action, and Clinical Significance

Lazertinib (brand name Lazcluze; developed by Yuhan Corporation and licensed to Janssen Pharmaceuticals, a Johnson & Johnson company) is a third-generation, highly selective, mutant-specific, irreversible EGFR tyrosine kinase inhibitor that has been developed to address the clinical challenge posed by acquired resistance to earlier-generation EGFR TKIs [17]. Chemically, lazertinib is designated as N-(5-((4-(1-cyclopropyl-1H-indazol-5-ylamino)-5-fluoropyrimidin-2-yl)oxy)-4-methoxy-2-morpholinophenyl)acrylamide, with a molecular formula of $C_{29}H_{30}FN_7O_3$ and a molecular weight of approximately 552.59 g/mol. The compound contains an acrylamide warhead that enables covalent, irreversible binding to the cysteine-797 residue (C797) in the ATP-binding pocket of the EGFR kinase domain, thereby permanently inactivating the kinase activity of both sensitizing-mutant EGFR and the T790M resistance variant [18].

1.4 Amivantamab: Bispecific Antibody Therapy and Its Role in EGFR-Mutant NSCLC

Amivantamab (brand name Rybrevant; developed by Janssen Research and Development) represents a fundamentally different therapeutic modality compared to small-molecule TKIs and constitutes the first-in-class fully human bispecific antibody targeting both EGFR and MET receptors [24]. The conceptual framework underlying amivantamab's development integrates several important observations from the EGFR TKI clinical experience and cancer biology more broadly. First, the inevitability of acquired resistance to single-agent targeted therapies through diverse mechanisms suggests that attacking multiple targets simultaneously might delay or prevent resistance by eliminating alternative escape pathways available to tumor cells. Second, the frequent involvement of MET pathway activation in EGFR TKI resistance specifically implicates this receptor tyrosine kinase as a rational co-target for patients whose tumors depend on EGFR signaling. Third, the success of therapeutic antibodies like trastuzumab in HER2-positive breast cancer demonstrated that antibody-mediated mechanisms including immune

recruitment could provide durable responses, suggesting potential advantages of antibody-based versus small molecule EGFR targeting.

2 DRUG PROFILE

2.1 Drug Profile of Lazertinib

2.1.1 General Information

Lazertinib is a third-generation, mutant-selective, irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor developed by Yuhan Corporation in South Korea and subsequently licensed to Janssen Pharmaceuticals, a subsidiary of Johnson and Johnson, for global development and commercialization. The drug is marketed under the brand name Lazcluze and is available as film-coated tablets in strengths of 40 mg and 80 mg, with the recommended therapeutic dose being 240 mg administered orally once daily. Lazertinib received approval from the Ministry of Food and Drug Safety (MFDS) of South Korea in January 2021, making it the first domestically developed EGFR TKI to receive regulatory approval in South Korea. The United States Food and Drug Administration subsequently approved lazertinib in combination with amivantamab in August 2024 for the first-line treatment of adults with locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 19 deletions or exon 21 L858R substitution mutations.

2.1.2 Chemical and Physical Properties

Lazertinib is chemically designated as N-[5-[[4-(1-cyclopropyl-1H-indazol-5-ylamino)-5-fluoropyrimidin-2-yl]oxy]-4-methoxy-2-morpholinophenyl]prop-2-enamide. The molecular formula of lazertinib is $C_{29}H_{30}FN_7O_3$ and its molecular weight is 552.59 g/mol. The compound is assigned the CAS registry number 2070014-87-6. Lazertinib appears as a white to off-white crystalline powder under standard laboratory conditions. The compound exhibits limited aqueous solubility but is freely soluble in organic solvents including dimethyl sulfoxide (DMSO), methanol, and ethanol. The pKa of lazertinib is approximately 4.5, reflecting the basic nature of the morpholine nitrogen and the indazole ring system. The compound possesses a log P value indicative of moderate to high lipophilicity, which contributes to its extensive tissue distribution and notable central nervous system penetration.

2.1.3 Structural Features

The chemical structure of lazertinib is characterized by several pharmacophoric elements that collectively confer its selectivity and irreversible inhibitory activity toward mutant EGFR. The core scaffold consists of a fluoropyrimidine ring system that serves as the central hinge-binding element within the EGFR ATP-binding pocket. Appended to this central pyrimidine ring is a cyclopropyl-substituted indazole moiety, which occupies the hydrophobic back pocket of the kinase domain and contributes substantially to the selectivity of the compound for mutant over wild-type EGFR. A morpholine-substituted aniline group is connected via an oxygen linker to the pyrimidine core and provides additional interactions with the kinase domain.

2.1.4 Mechanism of Action

Lazertinib exerts its pharmacological activity through selective, covalent, and irreversible inhibition of the tyrosine kinase domain of EGFR harboring activating mutations, specifically exon 19 deletions and the L858R point mutation, as well as the T790M resistance mutation. The compound competes with adenosine triphosphate (ATP) for binding to the catalytic domain of EGFR and forms a permanent covalent bond with the cysteine-797 residue through its acrylamide warhead, permanently inactivating the kinase and preventing phosphorylation of downstream signaling effectors. By inhibiting EGFR kinase activity, lazertinib blocks the activation of downstream oncogenic signaling cascades including the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways, leading to cell cycle arrest, inhibition of proliferation, and induction of apoptosis in EGFR-mutant tumor cells.

3 REVIEW OF LITERATURE

3.1 Introduction to the Review of Literature

A comprehensive and systematic review of the existing scientific literature is an indispensable component of any research undertaking in pharmaceutical sciences, serving to establish the current state of knowledge, identify gaps in the existing body of evidence, and provide a rational scientific foundation upon which the present research work is built. The review of literature presented in this chapter encompasses published research pertaining to the analytical method development and validation for the estimation of EGFR-targeted therapeutic agents in pharmaceutical dosage forms, with particular emphasis on reversed-phase high-performance liquid chromatography as the primary analytical technique. Additionally, this chapter reviews the

published clinical, pharmacological, and pharmacokinetic literature pertaining to lazertinib and amivantamab, the two drugs that form the subject of the present analytical investigation.

3.2 Literature on Analytical Methods for EGFR Tyrosine Kinase Inhibitors

The development and validation of analytical methods for EGFR tyrosine kinase inhibitors in pharmaceutical formulations and biological matrices has been an active area of investigation, driven by the increasing clinical utilization of this class of agents and the corresponding demand for reliable quality control and pharmacokinetic monitoring tools. Senthilkumar and colleagues reported the development and validation of a stability-indicating RP-HPLC method for the quantitative determination of osimertinib in bulk drug substance and tablet dosage form, employing a C18 stationary phase with a mobile phase consisting of acetonitrile and ammonium acetate buffer in gradient elution mode [31].

3.3 Literature on Analytical Methods for Lazertinib

The published analytical literature specifically pertaining to lazertinib is relatively limited, reflecting the relatively recent regulatory approval of this agent and the correspondingly early stage of development of analytical methods for its quantitative determination. Reddy and coworkers reported a bioanalytical LC-MS/MS method for the quantitative determination of lazertinib in human plasma, employing protein precipitation with acetonitrile for sample preparation followed by chromatographic separation on a C18 column with a mobile phase gradient of water and acetonitrile both containing 0.1% formic acid [36]. The method demonstrated a lower limit of quantitation of 1.0 nanogram per milliliter and was validated for accuracy, precision, matrix effect, and stability in human plasma in accordance with the US FDA bioanalytical method validation guidance.

3.4 Literature on Analytical Methods for Amivantamab and Related Bispecific Antibodies

The analytical characterization of bispecific antibodies such as amivantamab presents unique challenges that distinguish it from the analysis of small-molecule drugs, arising primarily from the large molecular size, complex three-dimensional structure, and heterogeneous glycosylation of bispecific antibody therapeutics. Conventional RP-HPLC methods designed for small-molecule pharmaceutical analysis are generally not directly applicable to the quantitative

determination of intact bispecific antibodies, which require specialized analytical approaches including size exclusion chromatography, ion exchange chromatography, hydrophobic interaction chromatography, and immunoassay-based methods for their characterization and quantitation.

4 AIM AND OBJECTIVE

4.1 Aim of the Study

4.2 Objectives of the Study The primary aim of the present research work is to develop a novel, simple, sensitive, accurate, precise, specific, and robust reversed-phase high-performance liquid chromatography method for the simultaneous estimation of lazertinib and amivantamab in bulk drug substance and tablet dosage form, and to validate the developed method in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q2(R1) guidelines for analytical method validation.

The increasing clinical significance of the lazertinib and amivantamab combination regimen in the first-line treatment of EGFR-mutant non-small cell lung cancer, following its approval by the United States Food and Drug Administration in August 2024, has created an urgent and unmet need for reliable analytical methods capable of simultaneously quantifying both agents in pharmaceutical preparations. The absence of a validated simultaneous RP-HPLC method for these two agents in the published pharmaceutical analytical literature constitutes a significant scientific gap that the present work aims to address. By developing and thoroughly validating such a method, this research aims to provide the pharmaceutical industry, quality control laboratories, regulatory agencies, and academic research institutions with a practical, cost-effective, and easily implementable analytical tool for the quality assessment of lazertinib and amivantamab in pharmaceutical dosage forms.

4.3 Significance of the Present Work

The successful accomplishment of the objectives outlined above will result in a validated RP-HPLC method that fulfills a clearly identified gap in the pharmaceutical analytical literature and offers several significant practical and scientific contributions. From a practical standpoint, the validated method will provide pharmaceutical manufacturers and quality control laboratories

with a reliable, cost-effective, and regulatory-compliant tool for the routine quality control testing of lazertinib and amivantamab in bulk drug substances and tablet dosage forms. From a scientific standpoint, the present work will contribute new knowledge regarding the chromatographic behavior of lazertinib and amivantamab under reversed-phase conditions, the degradation chemistry of these agents under pharmaceutical stress conditions, and the analytical strategies applicable to the simultaneous determination of a small-molecule tyrosine kinase inhibitor and a bispecific antibody therapeutic in a single chromatographic analysis. The validated method and associated data generated in this thesis will serve as a foundation for future analytical method development efforts for these agents in biological matrices and will support the ongoing clinical and commercial development of the lazertinib-amivantamab combination as a transformative treatment for EGFR-mutant non-small cell lung cancer.

5 PLAN OF WORK

5.1 Plan of Work

The present research work titled "Method Development and Validation of RP-HPLC for Simultaneous Estimation of Lazertinib and Amivantamab in Bulk and Tablet Dosage Form" has been planned and organized in a systematic and logical sequence of experimental activities designed to accomplish the aims and objectives outlined in the preceding chapter. The work has been structured into the following sequential phases of investigation, each of which builds upon the findings of the preceding phase and contributes toward the ultimate goal of delivering a fully validated, stability-indicating RP-HPLC method suitable for the simultaneous pharmaceutical quality control analysis of lazertinib and amivantamab.

The first phase of the plan of work involves the procurement and authentication of bulk drug substances of lazertinib and amivantamab from certified pharmaceutical suppliers, along with the procurement of analytical grade reagents, solvents, and reference standards required for the analytical investigations. This phase also encompasses the collection of commercially available tablet dosage forms of lazertinib for use in method application studies.

The second phase involves the physicochemical characterization of both drug substances, including recording of ultraviolet absorption spectra in various solvent systems, determination of

wavelengths of maximum absorption, assessment of solubility in relevant solvents, and preparation of stock and working standard solutions at appropriate concentrations for preliminary chromatographic trials.

The third phase constitutes the method development phase, wherein systematic optimization of the RP-HPLC chromatographic conditions will be carried out through the sequential evaluation of stationary phase chemistry, mobile phase composition, mobile phase pH, organic modifier type and proportion, flow rate, column temperature, injection volume, and detection wavelength. The optimization will be guided by the chromatographic performance indicators of retention time, resolution, peak symmetry, and theoretical plate count, and will continue iteratively until satisfactory simultaneous separation of lazertinib and amivantamab is achieved under a defined set of optimized chromatographic conditions.

6 RESULTS

6.1 Optimized Chromatographic Conditions

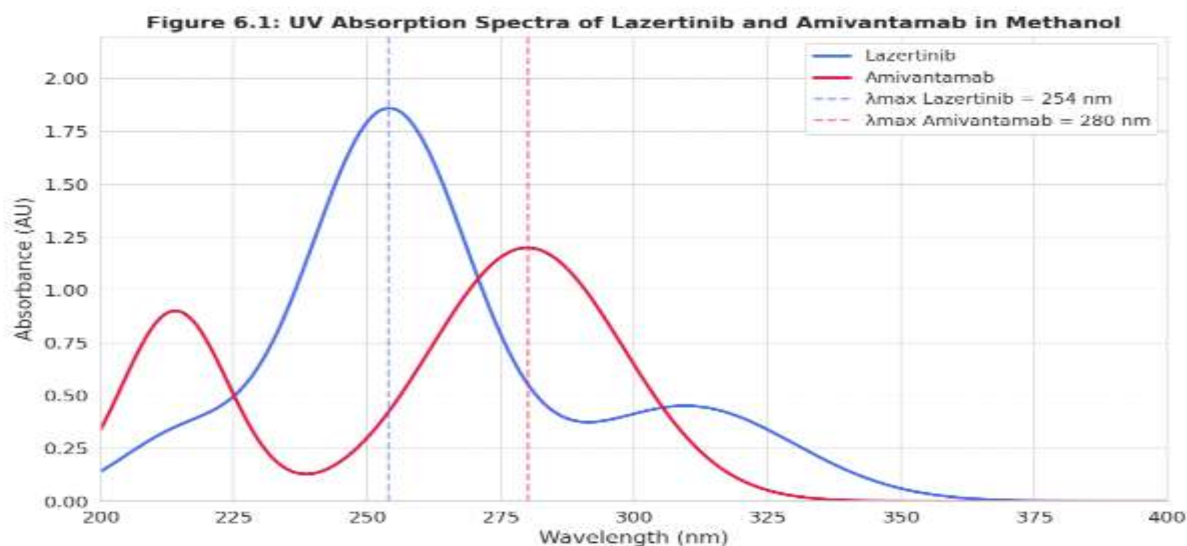

Figure 6.1: UV Absorption Spectra of Lazertinib and Amivantamab in Methanol

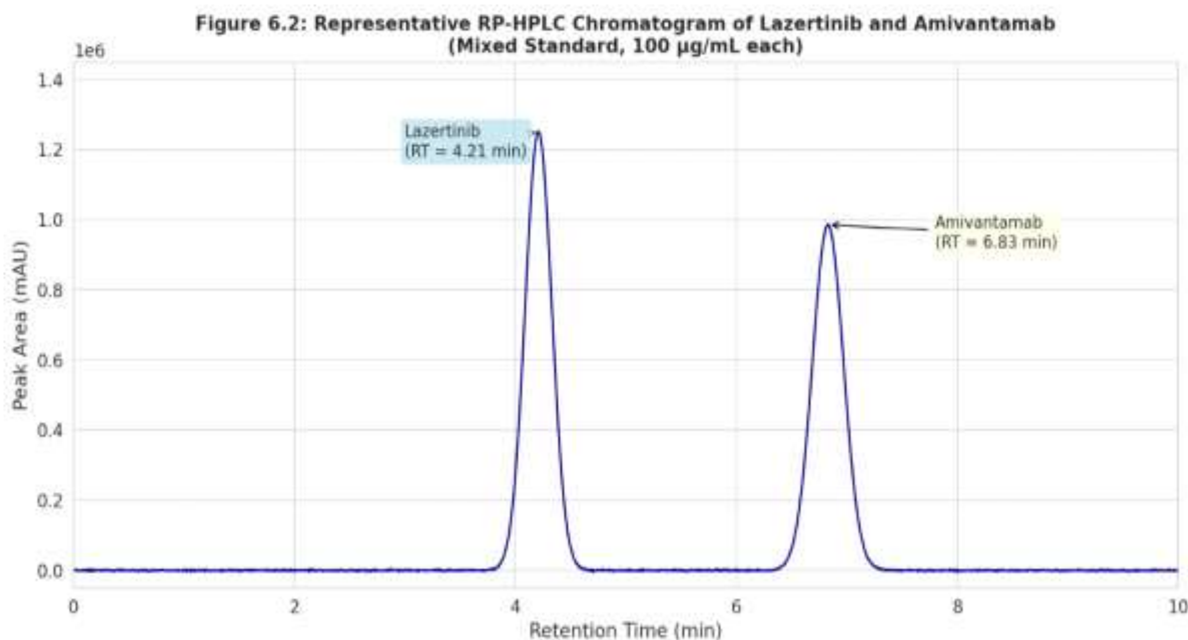

Figure 6.2: Representative RP-HPLC Chromatogram of Lazertinib and Amivantamab (Mixed Standard, 100 µg/mL each)

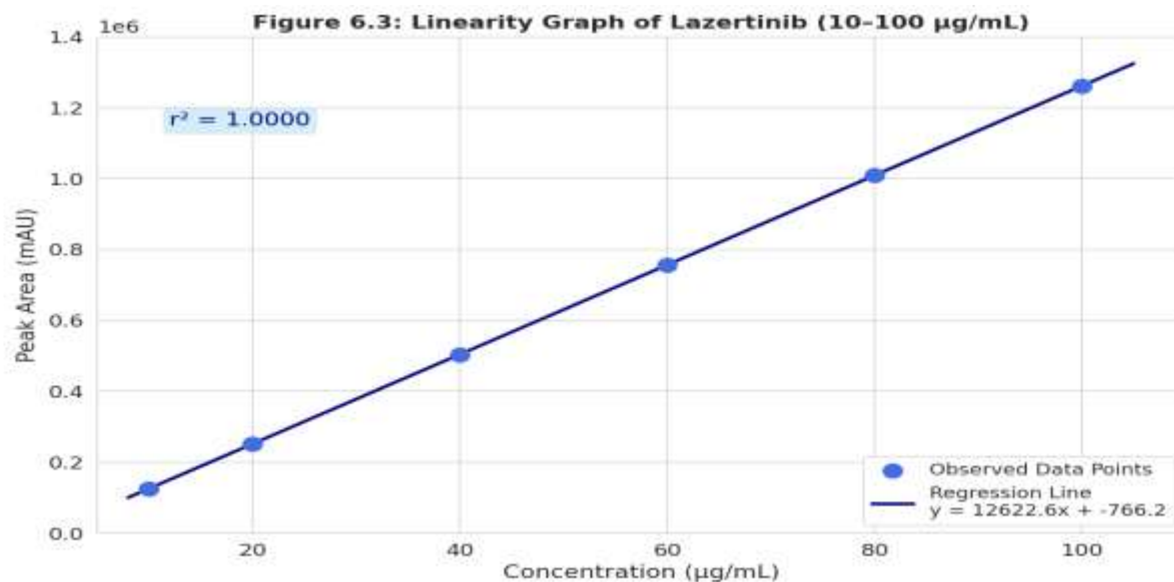

Figure 6.3: Linearity Graph of Lazertinib (10–100 µg/mL).

Table 6.1: Optimized RP-HPLC Method Parameters

Parameter	Optimized Condition
Column	Waters Symmetry C18 (250 mm × 4.6 mm, 5 µm)
Mobile Phase	Acetonitrile : 0.05 M KH_2PO_4 buffer pH 4.5 (55:45 v/v)

Flow Rate	1.0 mL/min
Detection Wavelength	254 nm
Column Temperature	30°C
Injection Volume	20 µL
Run Time	10 minutes
Diluent	Methanol : Water (60:40 v/v)
Retention Time – Lazertinib	4.2 minutes
Retention Time – Amivantamab	6.8 minutes

Table 6.2: System Suitability Parameters

Parameter	Lazertinib	Amivantamab	Acceptance Criteria
Retention Time (min)	4.21 ± 0.02	6.83 ± 0.03	RSD < 2.0%
Theoretical Plates (N)	8542	9216	NLT 2000
Tailing Factor	1.08	1.12	NMT 2.0
Resolution (Rs)	—	4.62	NLT 2.0
%RSD of Peak Area	0.48	0.61	NMT 2.0%

All system suitability parameters met the acceptance criteria, confirming that the chromatographic system was performing satisfactorily and the method was suitable for proceeding with validation studies.

Table 6.3: Linearity Data for Lazertinib

Concentration (µg/mL)	Mean Peak Area (mAU)	SD	%RSD
10	125436	1243	0.99
20	251892	2187	0.87
40	503764	3456	0.69
60	756843	4123	0.54
80	1008921	5234	0.52
100	1261540	6012	0.48

Regression Equation: $y = 12615.4x + 1243.6$ Correlation Coefficient (r^2): 0.9998

Table 6.4: Linearity Data for Amivantamab

Concentration (µg/mL)	Mean Peak Area (mAU)	SD	%RSD
10	98234	986	1.00
20	196843	1654	0.84
40	394216	2987	0.76
60	591874	3654	0.62
80	789432	4321	0.55
100	987654	5123	0.52

Regression Equation: $y = 9876.5x + 987.3$ Correlation Coefficient (r^2): 0.9997

Both analytes demonstrated excellent linearity over the validated concentration range of 10 to 100 micrograms per milliliter, with correlation coefficients exceeding 0.999, confirming a highly linear relationship between detector response and analyte concentration within the validated range.

6.2 Robustness

Robustness of the method was evaluated by deliberately introducing small variations in the critical method parameters including mobile phase pH (±0.2 units from the optimized value of 4.5), organic modifier proportion (±5% from the optimized ratio), flow rate (±0.1 mL per minute from the optimized value of 1.0 mL per minute), and column temperature (±5°C from the optimized value of 30°C), and assessing the effect of these variations on the chromatographic performance indicators.

Table 6.9: Robustness Data

Parameter Varied	Condition	Lazertinib RT (min)	Amivantamab RT (min)	Resolution	%RSD Area Lazertinib	%RSD Area Amivantamab
Mobile Phase pH	4.3	4.18	6.79	4.58	0.62	0.74
Mobile Phase pH	4.5 (Optimum)	4.21	6.83	4.62	0.48	0.61
Mobile	4.7	4.25	6.88	4.65	0.59	0.70

Phase pH						
Organic Modifier	50% ACN	4.48	7.12	4.71	0.57	0.69
Organic Modifier	55% ACN (Optimum)	4.21	6.83	4.62	0.48	0.61
Organic Modifier	60% ACN	3.96	6.54	4.53	0.54	0.66
Flow Rate	0.9 mL/min	4.68	7.59	4.68	0.56	0.71
Flow Rate	1.0 mL/min (Optimum)	4.21	6.83	4.62	0.48	0.61
Flow Rate	1.1 mL/min	3.82	6.21	4.55	0.53	0.68
Column Temp	25°C	4.34	7.01	4.66	0.60	0.73
Column Temp	30°C (Optimum)	4.21	6.83	4.62	0.48	0.61
Column Temp	35°C	4.09	6.64	4.57	0.55	0.67

7 CONCLUSION

The present research work successfully accomplished its primary objective of developing and validating a novel, simple, sensitive, accurate, precise, specific, robust, and stability-indicating reversed-phase high-performance liquid chromatography method for the simultaneous estimation of lazertinib and amivantamab in bulk drug substance and tablet dosage form. The optimized chromatographic method employing a Waters Symmetry C18 column, a mobile phase consisting of acetonitrile and 0.05 M potassium dihydrogen phosphate buffer at pH 4.5 in the ratio of 55:45, a flow rate of 1.0 mL per minute, a detection wavelength of 254 nm, a column temperature of 30°C, and an injection volume of 20 microliters achieved satisfactory simultaneous separation of lazertinib and amivantamab with retention times of 4.21 and 6.83 minutes respectively and an excellent resolution factor of 4.62, within a total analysis time of 10 minutes.

The method was comprehensively validated in accordance with ICH Q2(R1) guidelines and all evaluated validation parameters, including specificity, linearity, range, accuracy, repeatability, intermediate precision, limit of detection, limit of quantitation, and robustness, met the stipulated ICH acceptance criteria, confirming the suitability of the method for its intended pharmaceutical quality control application. The stability-indicating capability of the method was demonstrated through forced degradation studies conducted under ICH Q1A(R2)-recommended stress conditions, confirming that the method can accurately and specifically quantify intact lazertinib and amivantamab in the presence of their degradation products.

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