RESEARCH ARTICLE

RP-HPLC Method Development for Impurity Profiling of Perindopril and Indapamide FDC Using Risk-Based AQbD Approach and Spectroscopic Characterization of Impurities

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ABSTRACT

Pharmaceutical impurities resulting from degradation, synthesis, or excipient interactions can severely impact drug safety and efficacy. Consequently, this project centers on developing a risk-based analytical quality-by-design (RB-AQbD) HPLC method for impurity profiling of the two common antihypertensives, Perindopril and Indapamide, present in combination (FDC) formulations. Method development was performed for the separation and quantification of the drugs along with their degradation products; subsequent isolation and characterization of the impurities were achieved using IR, LC-MS/MS, and NMR spectroscopy. The optimized HPLC method resolved Perindopril (tR: 3.5 min), Indapamide (tR: 7.3 min), and their corresponding major degradation products. Isolation of the impurities was done via preparative LC, and structure characterization was performed. Thus, this study contributes towards the quality control and regulatory compliance of Perindopril and Indapamide FDC formulations.

Keywords: Perindopril, Indapamide, Impurity Profiling, Risk-Based AQbD, HPLC, LC-MS/MS, NMR, IR Spectroscopy

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INTRODUCTION

Angiotensin-converting enzyme (ACE) blocker perindopril and thiazide-like diuretic indapamide are frequently used together to treat heart failure and hypertension.[1] Since the medications have distinct degradation pathways under various stress circumstances, which ultimately result in contaminants that may compromise the drug's safety and efficacy, drug stability is actually a critical factor for FDC formulations. From a regulatory standpoint, it is also necessary to assess these formulations utilizing stability-indicating techniques for the identification and measurement of degradation products under heat, humidity, light, and oxidation stress conditions[2].

A risk-based AQbD approach is applied in this study for methodelopment as validation HPLC method for impurity profiling purposes in Perindopril and Indapamide. After method optimization for separation of drugs and degradation products, isolation and structural characterization of impurities were done by IR, LC-MS/MS, and NMR spectroscopy[3]. The developed method ensures an all-inclusive data generation on the impurity's profile, thereby adding value to the quality assurance and compliance in the regulation of Perindopril and Indapamide FDC formulations.

HPLC Method Development Using RB-AQbD

RB-AQbD approach was used to identify the critical method parameters (CMPs) and method performance attributes (MPAs). Ishikawa diagram was used for analyzing factors affecting resolution, peak symmetry, and theoretical plates[4,5]. The above summarized optimized chromatographic condition is illustrated in Table 1.

The optimized HPLC method provided well-resolved peaks for Perindopril (3.5 min) and Indapamide (7.3 min), with their degradation products (Figure 1). The process was validating against parameters including linear nature, precision, accuracy, and robustness for the underlying purpose of routine quality control analysis[5].

Isolation of Impurities – Preparative LC

Preparative LC was used to isolate the major degradation products of Perindopril and Indapamide[6,7]. The isolated impurities were then characterized by spectroscopic methods spectroscopy[8,9]. The IR show characteristic absorption bands confirming the presence of functional

Table 1: Chromatographic Conditions

Parameter	Ideal Situation
Stationary Phase	C18
Mobile Phase	Acetonitrile: Phosphate Buffer 0.05 Molar (pH 3.5) (ration: 60:40)
Rate of Flow	1.0 Mili liter Per minutes
Wavelength employed	215 nm
Volume	20 Micro liter
Run Time	10 minutes

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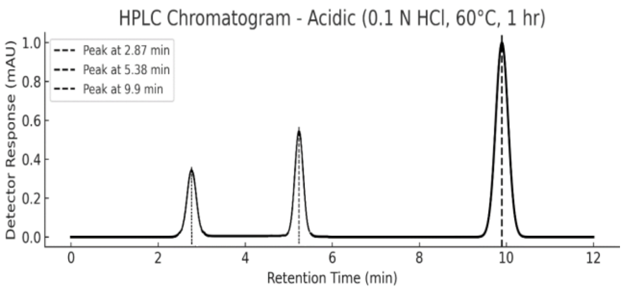

Figure 1a: Separation of impurities by HPLC method after acid forced degradation conditions

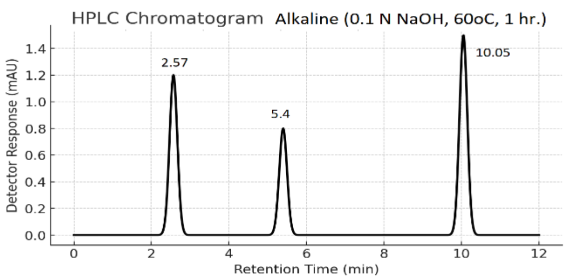

Figure 1b: Separation of impurities by HPLC method after basic forced degradation conditions

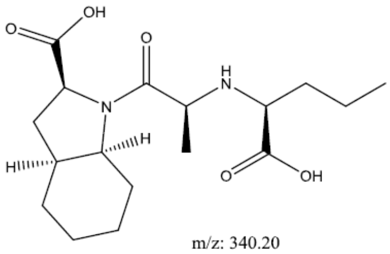

Figure 2a: Suggested basic degradation impurity of Perindopril

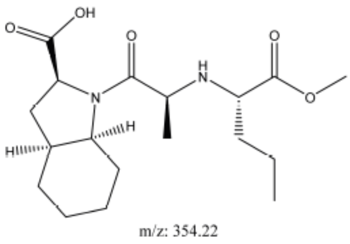

Figure 2b: Suggested acidic degradation impurity of Perindopril

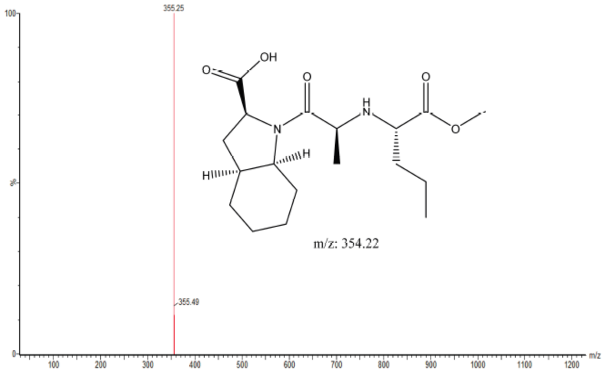

Figure 3a: MASS Spectra of basic degradation impurity of Perindopril

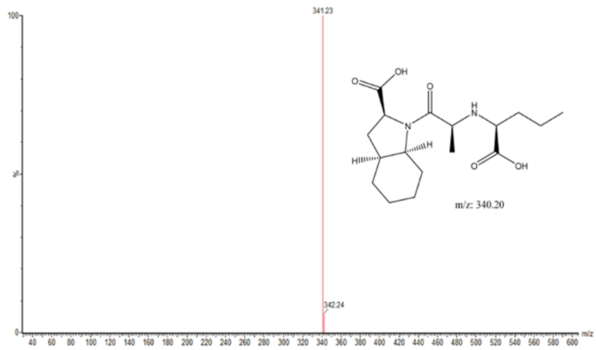

Figure 3b: MASS Spectra of acidic degradation impurity of Perindopril

Table 2: Characterization by Infrared (IR) Spectroscopy

Impurity	IR Absorption Bands (cm^{-1})	Functional Groups
Perindopril Impurity-I	3400 (N-H), 1725 (C=O), 1250 (C-OH)	Amine, Carbonyl, Hydroxyl
Perindopril Impurity-II	3200 (O-H), 1710 (C=O), 1100 (C-F)	Hydroxyl, Fluorinated Carbonyl
Indapamide Impurity-I	3360 (N-H), 1665 (C=O), 1225 (C-OH)	Amino, Hydroxyl, Carbonyl
Indapamide Impurity-II	3200 (O-H), 1715 (C=O), 1605 (C=C, aromatic)	Hydroxyl, Carbonyl, Aromatic

Table 3: Characterization by Mass Spectrometry (LC-MS/MS)

Impurity	Molecular Formula	Observed m/z (M-H)$^{-}$	Calculated m/z
Perindopril Impurity-I	$C_7H_7NO_4S$	200.10	201.20
Perindopril Impurity-II	$C_{11}H_{13}FO_2$	195.00	196.09
Indapamide Impurity-I	C_6H_7NO	109.07	110.08
Indapamide Impurity-II	$C_8H_8O_2$	135.08	136.09

groups: hydroxyl, carbonyl, and aromatic rings (Table 2). LC-MS/MS exploited molecular weights and fragmentation patterns (Table 3), while NMR spectroscopy confirmed the structural elucidation of the impurities (Table 4)[10](Figure 2, Figure 3).

CONCLUSION

In this study, an HPLC technique was created based on a RB-AQbD approach applied to the resolution of Perindopril, Indapamide, and their respective degradation products. The validation of the method included linearity, precision, accuracy, and robustness, further confirming its suitability for routine quality control analysis. The impure degradant were separated using traditional preparative LC, and their characterization by IR, LC-MS/MS, and NMR spectroscopy confirmed their structural elucidation. The present study provides considerable input for impurity profiling and quality control of Perindopril and

Table 4: Characterization by NMR Spectroscopy

Impurity	^1H NMR (δ ppm, Multiplicity)
Perindopril Impurity-I	7.55 (s, NH_2), 7.94–8.15 (m, Ar-H), 13.77 (s, OH)
Perindopril Impurity-II	1.246 (s, CH_3), 4.042 (s, CH_2), 6.979–7.359 (m, Ar-H)
Indapamide Impurity-I	6.82 (d, 2H, Ar-H), 7.92 (s, 1H, OH), 4.56 (s, 1H, NH_2)
Indapamide Impurity-II	2.12 (s, 3H, CH_3), 6.88–7.58 (m, 4H, Ar-H), 5.31 (s, 1H, OH)

Indapamide FDC formulations in support of regulatory compliance.

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