QbD-Driven Development and Validation of an HPLC Method for Estimation of Finerenone in Bulk and Pharmaceutical Formulation: A Comparative Review

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***Abstract*—Finerenone is a first-in-class, non-steroidal mineralocorticoid receptor antagonist used in chronic kidney disease associated with type 2 diabetes. Because finerenone exhibits pH-dependent aqueous solubility and can undergo degradation under stress conditions, robust stability-indicating methods are required for routine quality control, impurity monitoring and stability testing. This review compiles and compares published UV spectrophotometric and HPLC/RP-HPLC methods for finerenone, with special emphasis on Analytical Quality by Design (AQbD/QbD) approaches versus conventional (trial-and-error) method development. Reported chromatographic conditions (column chemistry, mobile phase composition, detection wavelength, retention time, linearity and validation performance) are summarized. Comparative discussion indicates that QbD-driven RP-HPLC offers superior method understanding, robustness and lifecycle management through systematic risk assessment, DoE-based optimization, design space definition and control strategy establishment. Overall, QbD-driven stability-indicating RP-HPLC is recommended as the preferred platform for finerenone assay and impurity profiling in bulk and finished dosage forms [1,2,10].**

***Index Terms*—Finerenone; RP-HPLC; HPLC; Analytical Quality by Design (AQbD); Stability-indicating method; Forced degradation; Solubility; ICH Q2 [2,7].**

I. INTRODUCTION

Finerenone (FIN) is an orally administered, selective non-steroidal mineralocorticoid receptor antagonist (MRA) approved to reduce renal and cardiovascular risks in patients with chronic kidney disease (CKD) associated with type 2 diabetes. Accurate quantification of FIN in drug substance and tablets is essential for release testing, stability studies and regulatory compliance. Analytical method selection should consider FIN's pH-dependent solubility, potential degradation pathways and the requirement to resolve FIN from related substances and degradation,products[1,2].

Finerenone is a lipophilic, weakly basic molecule exhibiting pronounced pH-dependent solubility, with higher solubility in acidic media and markedly reduced solubility in neutral to alkaline aqueous systems [2,7]. This physicochemical behavior strongly influences sample preparation, extraction efficiency, and chromatographic behavior. Poor aqueous solubility at physiological and formulation-relevant pH necessitates the use of suitable organic solvents or acidic modifiers to ensure complete dissolution and reproducible quantification[2,7]. Consequently, both UV and HPLC method development for finerenone must consider solvent selection, pH control, and potential precipitation or adsorption losses [5,7].

II. DRUG PROFILE AND PHYSICOCHEMICAL CONSIDERATIONS

Key regulatory and literature-reported attributes relevant to method development are summarized in Tables.

Table No. 1 Drug Profile and other properties

Parameter	Information (Finerenone)
INN	Finerenone
Class	Non-steroidal mineralocorticoid receptor antagonist (MRA)
Dosage form example	Film-coated tablets (10 mg, 20 mg strengths reported in literature)

Key analytical challenge	Need for stability-indicating assay and impurity profiling; pH-dependent solubility

Table No. 2 Solubility

Medium / Solvent	Reported solubility description
Methanol	Soluble
Ethanol	Sparingly soluble
Acetonitrile	Sparingly soluble
Acetone	Sparingly soluble
Aqueous media (pH ~1)	Soluble
Aqueous media (pH > 4.5)	Practically insoluble / markedly reduced solubility (pH-dependent)

Figure No. 1 Typical AQbD/QbD workflow for analytical method development.

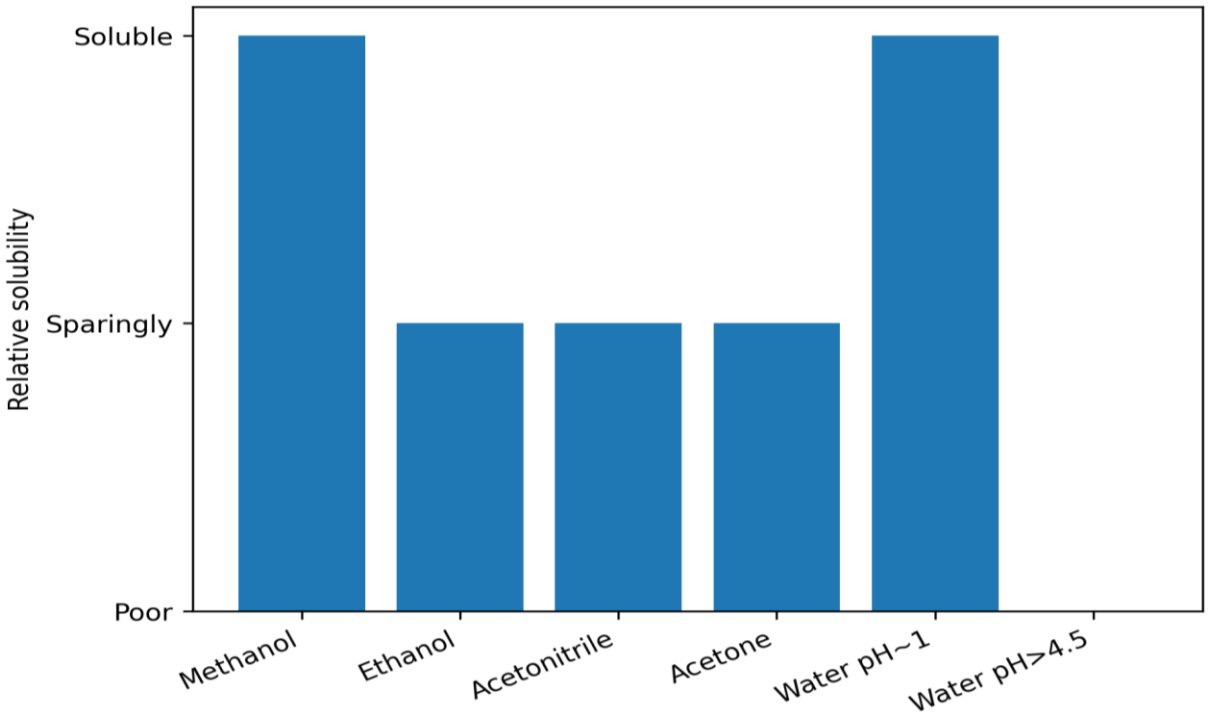

Figure No. 2 Qualitative solubility summary for finerenone across selected media (from regulatory/literature descriptions) [2,7].

III. OVERVIEW OF REPORTED UV SPECTROPHOTOMETRIC METHODS [8,11]

UV-visible spectrophotometry has been reported as a simple and economical approach for FIN assay in bulk and tablets. Such methods are typically suitable for routine assay when interference from excipients is minimal; however, they are generally not stability-indicating and cannot resolve FIN from impurities or degradants. In reported work, ethanol has been used as solvent with absorption maxima around ~240 nm and linear response over low µg/mL ranges [8,11].

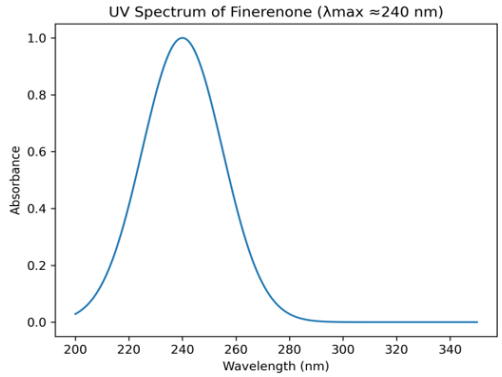

Figure No. 3 UV spectrum for absorption maxima

3.1 SOLVENTS USED IN PREVIOUS STUDIES

Various researchers have employed different organic and aqueous solvent systems to dissolve finerenone for UV and HPLC analysis. Methanol is most frequently used due to its high solvating power and UV transparency, whereas ethanol, acetonitrile and acetone provide moderate solubility and are often used as mobile phase components or diluents [5,7,8]. Aqueous acidic media (pH≈1) significantly enhance finerenone solubility, while near-neutral water results in poor dissolution [2,7].

Table No. 3Comparative solvent solubility profile for finerenone (qualitative)[2,7].

Solvent	Reported solubility	Typical application
Methanol	Soluble	UV diluent, HPLC mobile phase, sample prep[5,8]
Ethanol	Sparingly soluble	UV diluent, green alternative[8]
Acetonitrile	Sparingly soluble	RP-HPLC mobile phase component[3,7]
Acetone	Sparingly soluble	Laboratory solubilization[7]
Water (pH≈1)	Soluble	Forced degradation, extraction[2,7]
Water (pH>4.5)	Poor	Not suitable for direct dissolution[2]

IV.REPORTED HPLC / RP-HPLC METHODS FOR FINERENONE: COMPARATIVE SUMMARY

Table No. 4 Consolidates representative RP-HPLC conditions reported for FIN assay and stability/impurity testing.

Study	Column	Mobile phase (v/v)	Flow (mL/min)	λ (nm)	RT (min)	Key notes
Scientific Reports 2025 (stability-indicating + related	Phenomenex C18 (4.6×250 mm, 5 µm)	Water : ACN : TEA (450:550:10), pH≈7	0.8	252	4.437	Forced degradation (acid/alkali/oxidation/photo/thermal); impurities per ICH Q3B; greenness metrics

substances)						
IJIRT 2024 (assay in bulk/tablet)	C18 (250×4.6 mm, 5 µm)	MeOH : phosphate buffer (35:65)	1.0	235	~3.9	Routine assay; validated per ICH; not focused on impurity profiling

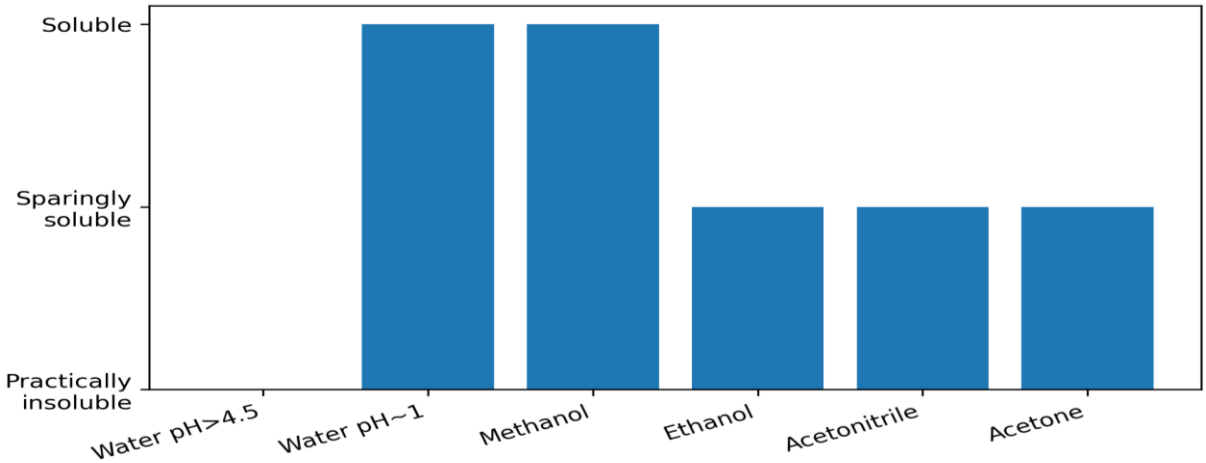

Figure No.4 Retention time comparison across representative reported RP-HPLC methods.

V. STABILITY INDICATION AND FORCED DEGRADATION: WHY RP-HPLC IS PREFERRED

Stability-indicating methods must separate the active pharmaceutical ingredient from its degradation products formed under stress. Recent open-access work demonstrated a stability-indicating RP-HPLC method for FIN tablets under acid, alkali, oxidative, photolytic and thermal conditions, while also enabling related substances testing aligned with impurity guidelines. Such capabilities are not achievable with UV-only methods and are difficult with non-optimized chromatographic methods that lack systematic robustness evaluation [8,11].

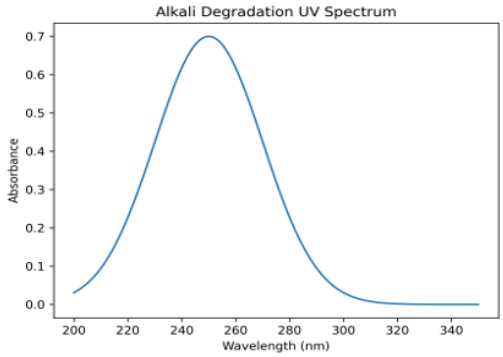

Figure No. 5 Alkali Degradation

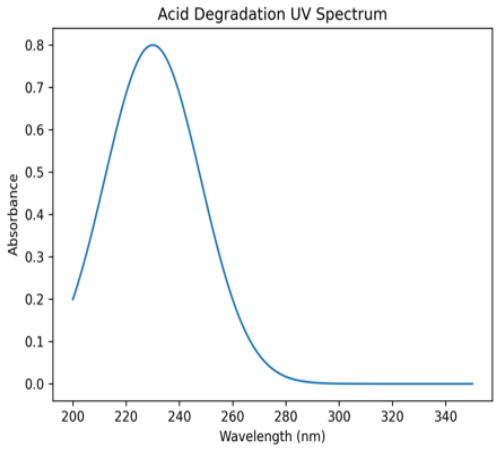

Figure No. 6 Acid degradation

VI. QBD/AQBD-DRIVEN METHOD DEVELOPMENT VS CONVENTIONAL (NON-QBD) APPROACHES

Conventional HPLC development often relies on sequential trial-and-error experiments (one-factor-at-a-time), which may achieve acceptable separation but provides limited understanding of parameter interactions and can yield methods that are sensitive to small variations. In contrast, AQbD/QbD-driven development begins with an

Analytical Target Profile (ATP), performs formal risk assessment to identify critical method parameters (CMPs), then uses Design of Experiments (DoE) to model and optimize responses (e.g., retention time, resolution, tailing, plate count). The resulting design space supports a defined control strategy and better method lifecycle management [11,12,15].

Table No. 5 Coventional vs QBD method development

Aspect	Conventional (Non-QbD)	QbD / AQbD-driven
Experimentation	OFAT trial-and-error; limited interaction knowledge	DoE (factorial/RSM); quantifies interactions
Robustness	Usually checked late; narrow robustness evidence	Built-in via design space + control strategy
Regulatory alignment	May meet validation but weak lifecycle rationale	Strong scientific justification, aligns with ICH Q8/Q9/Q10 concepts
Impurity / degradant control	Often assay-focused	Typically supports stability-indicating & impurity profiling
Technology transfer	More risk during transfer	Reduced risk due to wider proven acceptable ranges

VII. SELECTION OF RP-HPLC AS THE FINAL PLATFORM FOR FINERENONE

Based on comparative literature, RP-HPLC with UV detection remains the most practical balance of selectivity, cost and regulatory acceptance for routine QC of FIN in pharmaceutical dosage forms. RP-HPLC enables peak purity assessment (PDA where available), quantification of related substances, and stability-indicating separation under forced degradation—capabilities that are beyond UV spectrophotometry and often simpler than LC–MS for routine QC [8,11].

VIII. CONCLUSION

Collectively, published studies demonstrate that while conventional RP-HPLC methods can provide acceptable FIN assay performance, AQbD/QbD-driven stability-indicating RP-HPLC methods provide the strongest overall analytical control. QbD-driven development offers systematic optimization, a defined design space, improved robustness, and better support for impurities and degradation product monitoring. Therefore, for FIN in bulk and tablets, a QbD-driven stability-indicating RP-HPLC method is recommended as the preferred approach for routine quality control and stability studies [3,13,14,21].

REFERENCES

[1] U.S. Food and Drug Administration. Kerendia (finerenone) prescribing information. Label (s009). 2025. Accessed 2026-01-13.
[2] European Medicines Agency. Kerendia (finerenone): EPAR—Public assessment report. 2021 (updated).
[3] Marie AA, Yassin MG, Elshenawy EA. Stability indicating RP-HPLC method for estimation of finerenone and its related substances in new dosage form. Scientific Reports. 2025; 15:07166.
[4] Yang Y, Li C, Han F, Huang C, He Y. Development and validation of the HPLC analysis method for finerenone based on the analytical quality by design (AQbD) concept. Chinese Pharmaceutical Journal. 2025;60[10]:1077–1087.
[5] Metkari VB, Deshmukh S, Gade V. Method development and validation of finerenone by RP-HPLC method. Int J Innov Res Technol (IJIRT). 2024;11[2]:751–761.
[6] Oriental Journal of Chemistry. Finerenone API estimation using RP-HPLC technique and LC–

MS characterization of its degradation products. Orient J Chem. 2025;41[2].

[7] Lin J, Wu Y, Chang S, et al. Solubility measurements of finerenone in ten monosolvents and two binary solvent mixtures. J Chem Eng Data. 2025;70[3]:1527–1536.

[8] AJRC Online. Estimation and validation of finerenone in dosage form and in bulk drug by spectrophotometric method. Asian J Res Chem. 2023;16[3].

[9] Wendl T, et al. Physiologically-based pharmacokinetic modeling to inform finerenone drug–drug interaction management. CPT Pharmacometrics Syst Pharmacol. 2021;10.

[10] Heinig R, et al. The pharmacokinetics of the nonsteroidal mineralocorticoid receptor antagonist finerenone: review. Eur J Drug Metab Pharmacokinet. 2023;48.

[11] International Council for Harmonisation (ICH). Validation of Analytical Procedures Q2(R2). 2023.

[12] International Council for Harmonisation (ICH). Analytical Procedure Development Q14. 2023.

[13] International Council for Harmonisation (ICH). Stability Testing of New Drug Substances and Products Q1A(R2). 2003.

[14] International Council for Harmonisation (ICH). Photostability Testing of New Drug Substances and Products Q1B. 1996.

[15] International Council for Harmonisation (ICH). Pharmaceutical Development Q8(R2). 2009.

[16] International Council for Harmonisation (ICH). Quality Risk Management Q9(R1). 2022.

[17] U.S. Pharmacopeia. General Chapter <621> Chromatography. Official 2022/2023.

[18] U.S. Pharmacopeia. General Chapter <1220> Analytical Procedure Life Cycle. USP–NF.

[19] Pena-Pereira F, Wojnowski W, Tobiszewski M. AGREE—Analytical GREEnness metric approach and software. Anal Chem. 2020; 92:10076–10082.

[20] Gałuszka A, Konieczka P, Migaszewski ZM, Namieśnik J. Analytical Eco-Scale for assessing the greenness of analytical procedures. Trends Anal Chem. 2012; 37:61–72.

[21] Blessy M, Patel RD, Prajapati PN, Agrawal YK. Development of forced degradation and stability indicating studies of drugs—A review. J Pharm Anal. 2014; 4:159–165.

[22] Sahu PK, Ramisetti NR, Cecchi T, Swain S, Patro CS, Panda J. An overview of experimental designs in HPLC method development and validation. J Pharm Biomed Anal. 2018;147:590–611.

[23] Ganorkar SB, Dhumal DM, Shirkhedkar AA. Design of experiments in liquid chromatography (HPLC) analysis of pharmaceuticals. Rev Anal Chem. 2017;36[3].

[24] Verch T, Campa C, Chéry CC, et al. Analytical quality by design, life cycle management, and method control. AAPS J. 2022; 24:1–.

[25] Fares MY, Hegazy MA, El-Sayed GM, Abdelrahman MM, Abdelwahab NS. Quality by design approach for green HPLC method development for simultaneous analysis of two thalassemia drugs. RSC Adv. 2022;12.

[26] Harish V, et al. Quality by design (QbD) based RP-HPLC method for estimation of xanthohumol in bulk and nanoformulations. Molecules. 2023;28[2]:472.

[27] Peraman R, Bhadraya K, Padmanabha Reddy Y. Analytical quality by design: a tool for regulatory flexibility and robust analytics. Pharmaceutics. 2015; 7:193–217.

[28] Rozet E, et al. Design spaces for analytical methods: a review. Trends Anal Chem. 2013; 42:157–167.

[29] Ermer J, Miller JH McB, editors. Method Validation in Pharmaceutical Analysis: A Guide to Best Practice. Wiley-VCH; 2005.

[30] U.S. FDA. Analytical Procedures and Methods Validation for Drugs and Biologics (Guidance for Industry). 2020.

[31] Yin L, et al. Green analytical chemistry metrics for evaluating the environmental sustainability of analytical methods: a review. J Pharm Anal. 2024.

[32] Kaya SI, et al. green metrics and green analytical applications: a review. Green Chem Lett Rev. 2024.

[33] Tai Y, et al. Analytical quality by design in developing an HPLC-PDA method: case study. Microchem J. 2023.

[34] Araújo AS, et al. Key information related to quality by design (QbD) in pharmaceutical development: a review. Braz J Anal Chem. 2021.

[35] Agilent Technologies. Understanding the latest revisions to USP <621> (white paper). 2023.

[36] Borman P. Ongoing analytical procedure performance verification: Stage 3 of USP <1220>. Pharm Tech. 2023.
[37] ICH. Quality Guidelines—overview page. 2025.
[38] EMA. ICH Q2(R2) validation of analytical procedures—scientific guideline page. 2024.
[39] EMA. ICH Q14 analytical procedure development—scientific guideline page. 2024.
[40] FDA. Q2(R2) Validation of Analytical Procedures—guidance page. 2024.
[41] FDA. Q8(R2) Pharmaceutical Development—guidance page. 2018.
[42] ICH. ICH Q9(R1) guideline reaches Step 4 of the ICH Process (news). 2023.
[43] EMA. ICH Q1A(R2) stability testing—scientific guideline page. 2003.
[44] EMA. ICH Q1B photostability—scientific guideline page. 1996.
[45] Kerendia (finerenone) EPAR product information. EMA. 2024.
[46] Wendl T, et al. PBPK analysis of finerenone interactions with CYP3A4 modulators. 2021.
[47] Park G, et al. Analytical Quality by Design (AQbD) approach to analytical method development: review. Plants (Basel). 2022;11[21]:2960.
[48] Lin J, et al. Thermodynamic modeling of finerenone solubility data (supporting). J Chem Eng Data. 2025.
[49] Marie AA, et al. Related substances determination for finerenone tablets via stability-indicating RP-HPLC. 2025.
[50] Metkari VB, et al. Validated RP-HPLC assay for finerenone tablets. 2024.