Development and Validation of HPLC method for Estimation of Multidrug Formulations Using Quality by Design Approach: A Review

P. K. Tijare[1], N. I. Kochar[2], O. S. Bilone[3], A.V. Chandewar[4]
[1,2,3,4] *Department of Quality Assurance P.Wadhwani College of Pharmacy, Yavatmal, M.S. India*

Abstract—**Multidrug and fixed-dose combination formulations offer therapeutic and patient-convenience advantages but present significant analytical challenges due to differences in the physicochemical and chromatographic properties of multiple active pharmaceutical ingredients (APIs). Conventional one-factor-at-a-time HPLC development may require extensive experimentation and provides limited understanding of interactions among method variables. Analytical Quality by Design (AQbD) offers a systematic, science- and risk-based approach for developing robust and reliable chromatographic methods. This review discusses the application of AQbD to HPLC method development and validation for multidrug formulations, with emphasis on the Analytical Target Profile, critical analytical attributes, risk assessment, critical method parameters, Design of Experiments (DoE), response surface methodology, chromatographic optimization, Method Operable Design Region (MODR), control strategy, validation, and stability-indicating capability. Applications of factorial, screening, central composite, and Box–Behnken designs in simultaneous pharmaceutical analysis are critically considered. Integration of ICH Q14 and ICH Q2(R2) principles, together with green analytical chemistry, automation, chemometrics, and analytical lifecycle management, provides a contemporary framework for efficient and sustainable analytical procedure development. The review highlights the potential of AQbD to improve method understanding, robustness, reliability, and lifecycle performance for multidrug pharmaceutical formulations.**

Index Terms—**Analytical Quality by Design; AQbD; HPLC; multidrug formulation; Design of Experiments; Central Composite Design; Method Operable Design Region; method validation;**

I. INTRODUCTION

Pharmaceutical formulations containing two or more active pharmaceutical ingredients are widely used in contemporary drug therapy. Fixed-dose combination (FDC) products can provide therapeutic advantages, simplify dosing schedules and potentially improve patient convenience. From an analytical perspective, however, simultaneous determination of multiple APIs in a single formulation is considerably more complex than analysis of a single drug substance.[1-2] The constituent drugs may exhibit different physicochemical and chromatographic characteristics, including molecular size, polarity, ionization behaviour, aqueous solubility, lipophilicity, UV absorption and chemical stability. Consequently, development of a single analytical procedure capable of providing adequate separation and reliable quantification of all components represents a significant analytical challenge. A recent review of analytical development for FDC products emphasized the challenges associated with multiple analytes, complex sample preparation and the importance of chemometrics and Quality by Design approaches.[3-4]

High-performance liquid chromatography (HPLC), particularly reversed-phase HPLC (RP-HPLC), remains one of the most extensively used analytical techniques for pharmaceutical quality control. Its widespread application arises from its versatility, reproducibility, selectivity and ability to separate structurally diverse compounds. HPLC is routinely used for assay determination, impurity profiling, dissolution testing, stability studies and analysis of pharmaceutical formulations.[5-6]

Traditional chromatographic method development frequently involves sequential alteration of individual variables such as mobile-phase composition, pH, flow rate, column temperature and detection wavelength. Although such one-factor-at-a-time approaches may identify acceptable chromatographic conditions, they provide limited information regarding interactions among variables. Experimental design-based approaches address this limitation by evaluating several factors simultaneously and modelling their effects on analytical responses.[6]

Analytical Quality by Design represents a systematic extension of Quality by Design principles to analytical procedures. AQbD begins with a predefined analytical objective and uses scientific understanding, risk assessment and multivariate experimentation to establish a robust analytical procedure. Earlier literature established the application of QbD concepts to analytical methods and chromatographic separations, while subsequent reviews have demonstrated increasing use of DoE and AQbD in HPLC method development.[7-10]

The contemporary regulatory framework has further strengthened the importance of systematic analytical procedure development. ICH Q14 addresses analytical procedure development, while ICH Q2(R2) provides the current framework for analytical procedure validation. ICH Q2(R2) specifically recognizes that information generated during analytical procedure development can inform the design of the validation study. [11-13]

The objective of this review is therefore to critically examine the development and validation of HPLC methods for multidrug pharmaceutical formulations using AQbD principles, with emphasis on practical implementation, statistical optimization, robustness, validation, sustainability and analytical lifecycle management. [14]

II. ANALYTICAL CHALLENGES ASSOCIATED WITH MULTIDRUG FORMULATIONS

Simultaneous determination of multiple APIs presents several challenges that must be considered before chromatographic method development.

2.1 Differences in physicochemical properties

physicochemical and chemical properties, including molecular weight, pKa, polarity, lipophilicity, aqueous solubility, hydrogen-bonding characteristics, ionization behaviour, ultraviolet (UV) absorption maxima, and chemical stability. These inherent differences can significantly influence the chromatographic behaviour of individual active pharmaceutical ingredients (APIs), particularly their retention, selectivity, peak shape, resolution, and detector response. Consequently, the development of a single HPLC method capable of providing adequate separation and reliable quantitative determination of all components requires careful optimization of chromatographic conditions. Such complexity highlights the importance of a systematic, risk-based and multivariate approach, such as Analytical Quality by Design (AQbD), for identifying critical method parameters and establishing robust chromatographic conditions.

2.2 Different chromatographic retention behaviour

In RP-HPLC, compounds with different hydrophobicity may exhibit substantially different retention factors. A highly retained component may require a stronger organic phase, whereas a poorly retained component may elute close to the solvent front.

The resulting optimization problem is therefore multidimensional. Increasing organic solvent concentration may reduce analysis time for one component but decrease resolution between other components.

2.3 Different detector responses

Multidrug formulations may contain compounds having different molar absorptivities and absorption maxima. Selection of a common detection wavelength may therefore require consideration of sensitivity for all analytes rather than selection based on the maximum absorbance of a single component.

2.4 Formulation-related interference

Excipients, coating materials, preservatives, degradation products and other formulation components may interfere with analyte extraction or chromatographic detection.

Consequently, sample preparation is an important component of the overall analytical procedure and should not be considered independently from chromatographic development.

2.5 Stability-indicating requirements

For products containing multiple APIs, degradation pathways may differ among the components. A stability-indicating method should therefore demonstrate adequate separation of the APIs from their degradation products and formulation-related peaks.

III. CONCEPT OF ANALYTICAL QUALITY BY DESIGN

Analytical Quality by Design is a systematic approach in which analytical quality is intentionally incorporated into method development through predefined objectives, scientific understanding, risk assessment and experimental design.

The general AQbD workflow can be represented as:

Analytical Target Profile → Risk Assessment → Identification of Critical Method Parameters → Screening → Design of Experiments → Response Modelling → Optimization → MODR/Design Space → Control Strategy → Validation → Lifecycle Management

The literature describes AQbD as a systematic approach that moves analytical development away from reactive troubleshooting toward proactive identification and control of factors affecting method performance.

IV. ANALYTICAL TARGET PROFILE

The Analytical Target Profile is the starting point of AQbD-based analytical method development.

For a multidrug pharmaceutical formulation, a typical ATP may be defined as:

To develop a selective, accurate, precise, sensitive, robust and stability-indicating RP-HPLC analytical procedure capable of simultaneous identification and quantitative determination of all specified active pharmaceutical ingredients in the pharmaceutical formulation within a predefined analysis time and with acceptable chromatographic performance throughout the method lifecycle.

The ATP should define the intended purpose of the method rather than prescribing the chromatographic conditions.

The Analytical Target Profile (ATP) defines the intended purpose and required performance characteristics of an analytical method without prescribing specific chromatographic conditions. For the simultaneous analysis of multidrug pharmaceutical formulations, the ATP should specify the desired analytical performance, including selective and quantitative determination of all active pharmaceutical ingredients (APIs), adequate separation of APIs from relevant impurities and degradation products, suitable accuracy and precision, appropriate linearity across the intended concentration range, and adequate sensitivity where low-level determination is required. It should also establish acceptable chromatographic resolution between critical peak pairs, a suitable analysis time for routine quality-control applications, and consistent method performance under normal operational variations. Where the method is intended for stability studies, its stability-indicating capability should be clearly defined to ensure adequate separation of the APIs from their degradation products. In addition, consideration may be given to sustainability objectives, such as minimizing organic solvent consumption, waste generation, and overall environmental burden. Thus, the ATP serves as the foundation of AQbD-based analytical procedure development and subsequently guides the identification of critical analytical responses and critical method parameters required to achieve the intended analytical performance.

V. IDENTIFICATION OF CRITICAL ANALYTICAL ATTRIBUTES

Critical Analytical Attributes (CAAs) are measurable analytical responses that determine whether the analytical procedure fulfils its intended purpose.

For multidrug RP-HPLC methods, frequently investigated CAAs include:

5.1 Resolution

Resolution between critical peak pairs is one of the most important chromatographic responses.

Poor resolution may compromise specificity and quantitative accuracy.

5.2 Retention time

Retention time provides information regarding chromatographic efficiency and analysis duration.

5.3 Retention factor
Retention factor provides information about analyte retention and can assist in evaluating chromatographic separation.

5.4 Tailing factor
Peak symmetry affects integration accuracy and quantitative reliability.

5.5 Theoretical plates
Theoretical plate number provides an indication of chromatographic efficiency.

5.6 Peak area response
Peak area is directly related to quantitative determination and is therefore important for evaluating calibration performance.

5.7 Selectivity/specificity
The method should adequately distinguish each analyte from other APIs, excipients, impurities and degradation products.
A recent AQbD review similarly identifies chromatographic responses such as resolution, retention behaviour and efficiency as central responses for method optimization.

VI. RISK ASSESSMENT IN AQBD-BASED HPLC DEVELOPMENT

Risk assessment is an essential component of Analytical Quality by Design (AQbD) and is performed to systematically identify and prioritize analytical variables that may have a significant influence on method performance. In the development of HPLC methods for multidrug pharmaceutical formulations, potential sources of variability may include column chemistry and stationary-phase characteristics, mobile-phase composition, buffer concentration and pH, type and proportion of organic modifier, flow rate, column temperature, injection volume, sample concentration, detection wavelength, gradient profile, equilibration time, and sample preparation conditions. The influence of these variables may differ depending on the physicochemical properties of the analytes and the intended analytical purpose of the method. Risk assessment tools such as Ishikawa (fishbone) diagrams, Failure Mode and Effects Analysis (FMEA), risk-ranking matrices, and preliminary screening experiments can be used to identify and prioritize high-risk variables. The identified high-risk parameters are subsequently subjected to systematic experimental investigation, typically using Design of Experiments (DoE), to establish their individual and interactive effects on critical analytical attributes and to support development of a robust and reliable analytical procedure.

6.1 Ishikawa diagram
The Ishikawa or fishbone diagram can be used for systematic identification of possible sources of variability.
Typical categories include:
Instrument – Method – Material – Analyst – Environment – Measurement
6.2 Failure Mode and Effects Analysis
FMEA provides a structured approach for ranking risks according to severity, occurrence and detectability.
A risk priority number may be used as a prioritization tool:
RPN = Severity × Occurrence × Detectability
High-risk parameters can subsequently be evaluated experimentally using DoE.

VII. CRITICAL METHOD PARAMETERS

Critical Method Parameters (CMPs) are analytical procedure variables that can significantly influence Critical Analytical Attributes (CAAs) and, consequently, the overall performance of an HPLC method. In RP-HPLC, important CMPs may include organic solvent composition, mobile-phase pH, flow rate, column temperature, buffer concentration, gradient composition, injection volume, stationary phase, and detection wavelength. These parameters can affect analyte retention, selectivity, resolution, peak shape, chromatographic efficiency, sensitivity, and analysis time. However, not all identified variables need to be included in the final Design of Experiments (DoE). Risk assessment and preliminary studies should be used to identify the most influential parameters for systematic experimental investigation and optimization.

VIII. DESIGN OF EXPERIMENTS FOR HPLC METHOD DEVELOPMENT

Design of Experiments is one of the principal statistical tools used in AQbD.
Unlike one-factor-at-a-time experimentation, DoE allows multiple variables to be investigated simultaneously and permits interactions between variables to be identified.
A recent review of experimental designs in HPLC described applications including screening, mathematical modelling, optimization, chemometric approaches and validation.

8.1 Screening designs

Screening designs are used in AQbD to identify the most influential factors from a larger set of potential method parameters before detailed optimization. Common screening approaches include factorial, fractional factorial, Plackett–Burman, and Taguchi designs. These designs help determine which chromatographic variables significantly affect critical analytical attributes while reducing the number of experimental runs. For example, a Taguchi design has been applied to screen critical parameters in AQbD-based chromatographic analysis of multiple antihypertensive formulations before subsequent optimization using response-surface methodology.

8.2 Optimization designs

After screening, significant variables can be investigated using response-surface designs.
Common approaches include:

Central Composite Design

CCD is particularly useful where curvature and quadratic effects need to be estimated.
A general quadratic model can be represented as:

$$Y = \beta_0 + \Sigma\beta_i X_i + \Sigma\beta_{ii} X_i^2 + \Sigma\beta_{ij} X_i X_j$$

where:

- Y = analytical response;
- β_0 = intercept;
- β_i = linear coefficient;
- β_{ii} = quadratic coefficient;
- β_{ij} = interaction coefficient;
- X_i and X_j = coded independent variables.

Box–Behnken Design

Box–Behnken designs provide an efficient response-surface approach when three or more quantitative factors require optimization.

IX. MULTIPLE RESPONSE OPTIMIZATION

Multidrug chromatographic methods generally require simultaneous optimization of multiple analytical responses, including maximizing resolution and theoretical plate number while minimizing tailing factor and total analysis time and maintaining acceptable retention. Since these responses may have competing requirements, desirability-based optimization can be employed to identify a suitable combination of chromatographic conditions. Derringer's desirability function is commonly used to combine multiple responses into an overall desirability value and has been successfully applied in AQbD-based simultaneous determination of metformin hydrochloride, empagliflozin, and linagliptin.

X. METHOD OPERABLE DESIGN REGION

One of the major advantages of AQbD is that method development need not terminate at a single optimized chromatographic condition.
Instead, the experimental data can be used to establish a multidimensional region in which predefined analytical performance requirements are achieved.
This region is commonly described as the:

Method Operable Design Region (MODR)

The Method Operable Design Region (MODR) is a multidimensional region within which combinations of critical method parameters provide predefined acceptable analytical performance. For RP-HPLC methods, the MODR may include suitable ranges of organic-phase concentration, mobile-phase pH, flow rate, and column temperature. Operating the method within this established region can provide greater flexibility and help accommodate routine variations in chromatographic conditions while maintaining the required method performance and robustness.

XI. AQBD-BASED HPLC DEVELOPMENT FOR MULTIDRUG FORMULATIONS

Several published studies demonstrate the practical application of AQbD to simultaneous pharmaceutical analysis.

11.1 Antidiabetic combinations

An AQbD-oriented RP-HPLC method was reported for simultaneous determination of metformin hydrochloride, empagliflozin and linagliptin in a fixed-dose combination. A Central Composite Design was used to investigate organic-phase composition, mobile-phase pH and flow rate, while chromatographic responses included resolution, capacity factor and theoretical plate number.

This example demonstrates the suitability of multivariate optimization for formulations containing drugs with substantially different chromatographic characteristics.

11.2 Pregabalin–etoricoxib combination

An AQbD-based RP-HPLC method for simultaneous estimation of pregabalin and etoricoxib in a fixed-dose tablet was reported in the *Journal of AOAC International*. The study demonstrated application of experimental design for identifying influential chromatographic variables and subsequently validated the optimized procedure.

11.3 Antihypertensive formulations

AQbD and risk-management approaches have also been applied to simultaneous analysis of multiple combined antihypertensive formulations. A reported approach incorporated analytical risk assessment, Taguchi screening and Box–Behnken optimization before application to multiple pharmaceutical dosage forms.

11.4 Triple-combination cardiovascular formulations

Recent work has extended AQbD-based RP-HPLC development to triple cardiovascular combinations such as amlodipine, telmisartan and hydrochlorothiazide. The analytical target was explicitly linked to chromatographic resolution, peak symmetry, retention behaviour and environmental sustainability.

11.5 Five-drug combinations

The complexity of simultaneous pharmaceutical analysis has progressed beyond two- and three-drug combinations. A recent study described an AQbD-based HPLC method for simultaneous determination of aceclofenac, paracetamol, phenylephrine, cetirizine and caffeine, together with forced-degradation, dissolution and analytical greenness assessment.

These examples illustrate an important evolution from simple simultaneous estimation toward comprehensive, stability-indicating and sustainability-oriented analytical procedures.

XII. STABILITY-INDICATING HPLC METHODS

A multidrug analytical procedure intended for stability studies should demonstrate adequate stability-indicating capability by effectively distinguishing intact APIs from their degradation products. Forced degradation studies may include acidic, alkaline, oxidative, thermal, photolytic, and, where relevant, humidity stress conditions. The primary objective is to demonstrate that degradation products and other related components do not interfere with the quantification of the APIs. Recent AQbD-based HPLC studies increasingly incorporate forced degradation as an integral component of method development and evaluation, thereby strengthening the reliability of stability-indicating analytical procedures.

XIII. VALIDATION OF AQBD-BASED HPLC METHODS

AQbD development and analytical validation should be regarded as connected stages rather than completely independent activities.

ICH Q2(R2) provides the current framework for analytical procedure validation, while ICH Q14 addresses analytical procedure development. The current ICH Q2(R2) guideline explicitly recognizes the use of development knowledge and system suitability information in designing the validation strategy.

Validation of an AQbD-based HPLC method should demonstrate that the analytical procedure is fit for its intended purpose and provides reliable, consistent, and scientifically justified results. Specificity or selectivity should confirm accurate determination of

each API in the presence of other APIs, excipients, impurities, degradation products, and relevant matrix components. Linearity should establish an appropriate relationship between analyte concentration and detector response over the intended analytical range, supported by suitable statistical evaluation and assessment of residuals. Accuracy is commonly evaluated through recovery studies across the specified concentration range, while precision includes repeatability and intermediate precision and, where applicable, reproducibility. Detection and quantitation limits are particularly important for impurity and degradation-product determination. Robustness should demonstrate that method performance remains acceptable under anticipated variations in critical method parameters, while system suitability criteria should provide routine assurance of consistent chromatographic performance. Collectively, these validation characteristics establish the reliability and suitability of the analytical procedure for routine quality-control and stability-testing applications.

XIV. FUTURE PERSPECTIVES

Future development of multidrug HPLC methods is likely to move toward increasingly integrated analytical platforms.

A future AQbD framework may combine:

ATP + Risk Assessment + DoE + Chemometrics + MODR + Green Analytical Chemistry + Automation + ICH Q14 + ICH Q2(R2) + Lifecycle Management

The incorporation of sustainability directly into the ATP could provide a broader definition of analytical quality, in which performance, robustness, efficiency and environmental impact are considered simultaneously.

Artificial intelligence and machine-learning approaches may further assist prediction of chromatographic retention, selection of experimental conditions and optimization of complex multicomponent separations. However, such approaches should remain supported by scientifically interpretable models and appropriate experimental verification.

Future research in multidrug formulation analysis should focus on the development of robust methods for highly complex multicomponent formulations, particularly stability-indicating simultaneous assays and sensitive determination of impurities and degradation products. Greater emphasis should also be placed on automated sample preparation, green and sustainable HPLC practices, chemometric-assisted optimization, and efficient analytical method transfer. In addition, lifecycle-based performance monitoring and continuous improvement should be strengthened, with greater integration of analytical procedure development with pharmaceutical development and manufacturing data. These advances may further enhance the reliability, efficiency, sustainability, and practical applicability of AQbD-based analytical methods for multidrug pharmaceutical formulations.

XV. CRITICAL PERSPECTIVE

The principal contribution of AQbD to multidrug HPLC development is not merely the use of statistical software or an experimental design. Its broader significance lies in establishing a scientifically traceable relationship between the intended analytical performance, sources of variability, chromatographic parameters and analytical responses.

For multidrug formulations, this distinction is particularly important. A method that produces acceptable chromatograms under one set of experimental conditions may not necessarily be sufficiently robust for routine quality control. AQbD provides an opportunity to identify the variables that influence chromatographic performance, quantify their effects and define operating conditions within which predefined analytical requirements can be achieved.

Published examples involving binary, triple and higher-order combinations demonstrate the increasing applicability of AQbD to complex pharmaceutical products.

Nevertheless, AQbD should not be treated as a universal requirement to apply every possible statistical tool. The experimental strategy should be proportional to the intended purpose, complexity and risk of the analytical procedure. An appropriately justified risk assessment, suitable experimental design and scientifically supported control strategy are more important than simply increasing the number of experiments.

XVI. CONCLUSION

Analytical Quality by Design provides a structured and scientifically justified framework for the development of HPLC methods for multidrug pharmaceutical formulations. The approach begins with definition of an Analytical Target Profile and progresses through risk assessment, identification of critical method parameters, experimental design, multivariate optimization, establishment of a Method Operable Design Region and implementation of an analytical control strategy.

The increasing complexity of multidrug and fixed-dose combination formulations makes systematic analytical development particularly relevant because multiple APIs must frequently be separated and quantified within a single analytical procedure. Published studies demonstrate the application of AQbD to binary, triple and higher-order pharmaceutical combinations, including antidiabetic, antihypertensive, cardiovascular and analgesic formulations.

Integration of AQbD with ICH Q14 and ICH Q2(R2) provides a contemporary framework in which analytical procedure development, validation and lifecycle management can be scientifically connected. Future analytical development is expected to increasingly incorporate green analytical chemistry, chemometrics, automation and lifecycle monitoring.

Overall, AQbD-based HPLC development represents a transition from empirical chromatographic optimization toward a knowledge-driven analytical lifecycle in which analytical performance is deliberately designed, demonstrated, controlled and continuously monitored.

REFERENCES

[1] Settle F. A. “Handbook of Instrumental techniques for analytical chemistry”, Prentice Hall PTR, New Jersey, 1997, 1 st Edition, 17-19, 56-57.

[2] Skoog D.A., Holler F.J. and Crouch S.R. “Principle of Instrumental Analysis”, Thomson Publications, India, 2007, 6 th Edition, 1-3, 145-147, 180.

[3] Sahu PK, Ramisetti NR, Cecchi T, Swain S, Patro CS, Panda J. An overview of experimental designs in HPLC method development and validation. Journal of Pharmaceutical and Biomedical Analysis. 2018;147:590–611. doi:10.1016/j.jpba.2017.05.006.

[4] Rozet E, Ziemons E, Marini RD, Boulanger B, Hubert P. Quality by design compliant analytical method validation. [Relevant AQbD literature].

[5] Vogt FG, Kord AS. Development of quality-by-design analytical methods. Journal of Pharmaceutical Sciences. 2011;100(3):797–812. doi:10.1002/jps.22325.

[6] A brief review on application of design of experiment for the analysis of pharmaceuticals using HPLC. Annales Pharmaceutiques Françaises. 2024;82(2):203–228. doi:10.1016/j.pharma.2023.12.011.

[7] Deidda R, Orlandini S, Hubert P, Hubert C. Risk-based approach for method development in pharmaceutical quality control context: a critical review. Journal of Pharmaceutical and Biomedical Analysis. 2018.

[8] Orlandini S, Pasquini B, Del Bubba M, et al. Application of quality by design to the development of analytical separation methods. Analytical and Bioanalytical Chemistry. 2012. doi:10.1007/s00216-012-6302-2.

[9] Recent applications of analytical quality-by-design methodology for chromatographic analysis: A review. Chemometrics and Intelligent Laboratory Systems. 2024;254:105243. doi:10.1016/j.chemolab.2024.105243.

[10] Subrahmanyam CVS, et al. Quality-by-Design Approach for Chromatographic Analysis of Metformin, Empagliflozin and Linagliptin. Journal of Chromatographic Science. 2022;60(1):68–80. doi:10.1093/chromsci/bmab030.

[11] International Council for Harmonisation. ICH Q2(R2): Validation of Analytical Procedures. ICH; 2023, with subsequent correction.

[12] International Council for Harmonisation. ICH Q14: Analytical Procedure Development. ICH.

[13] Shah J, Kotadiya R, Patel R. Analytical Quality by Design-Based Robust RP-HPLC Method for Quantitative Estimation of Pregabalin and Etoricoxib in Fixed-Dose Combination Tablet Formulation. Journal of AOAC International. 2022;105(6):1536–1547. doi:10.1093/jaoacint/qsac082.

[14] Mapping Advantages and Challenges in Analytical Development for Fixed Dose Combination Products, a Review. 2024.
[15] Quality Risk Management-Based AQbD Approach to Development of VEER Chromatography Method for the Estimation of Multiple Combined Formulations of Anti-Hypertensive Drugs.
[16] Arunagiri T, Chanduluru HK, Kannaiah KP, Obaydo RH. Ecofriendly analytical quality by design-based HPLC method for a quintuple-drug combination: assay, forced degradation, dissolution profiling, and greenness assessment. Microchemical Journal. doi:10.1016/j.microc.2025.116016.
[17] Analytical quality by design (AQbD) approach for the simultaneous quantification of FDC in a cardiovascular drug by RP-HPLC method. Future Journal of Pharmaceutical Sciences. 2026.
[18] Kotadiya R. Enhancing Pharmaceutical Analysis with Analytical Quality by Design in UHPLC: A Review of Methodological Innovations (2014–2025). Critical Reviews in Analytical Chemistry. 2025. doi:10.1080/10408347.2025.2516607.
[19] Velhal SS, Chaudhari BP. Quality by design-based RP-HPLC methods for pharmaceutical analytical estimation: A review. Talanta. 2027;311:130236. doi:10.1016/j.talanta.2026.130236.
[20] International Council for Harmonisation. ICH Q2(R2): Validation of Analytical Procedures. ICH; 2023, with subsequent correction.
[21] International Council for Harmonisation. ICH Q14: Analytical Procedure Development. ICH.
[22] Drilling into "Quality by Design" Approach for Analytical Methods. Critical Reviews in Analytical Chemistry. 2023. doi:10.1080/10408347.2023.2253321.
[23] ‘Quality by Design’ approach for the analysis of impurities in pharmaceutical drug products and drug substances. TrAC Trends in Analytical Chemistry. 2018;101:24–33.
[24] Analytical Quality by Design-Based Robust RP-HPLC Method for Quantitative Estimation of Pregabalin and Etoricoxib in Fixed-Dose Combination Tablet Formulation. Journal of AOAC International. 2022;105:1536–1547.