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Review Paper

Chemometric-Assisted Optimization of HPLC and HPTLC Methods In Pharmaceutical Quality Assurance

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ABSTRACT

Chromatographic analytical procedures are central to pharmaceutical quality control, development and stability assessment. High-performance liquid chromatography (HPLC) and high-performance thin-layer chromatography (HPTLC) are versatile platforms, but their performance is governed by multiple interacting experimental variables. Conventional one-factor-at-a-time development may therefore be inefficient for complex separations because it provides limited information about interactions between factors. Chemometric-assisted development, particularly when integrated with design of experiments (DoE), provides a structured framework for screening influential variables, modelling factor–response relationships and optimizing multiple analytical responses. This review discusses the role of chemometrics in HPLC and HPTLC method development, with emphasis on analytical target profile (ATP), risk assessment, critical method parameters, response selection, screening designs, response-surface methodology, regression modelling, analysis of variance, desirability-based multi-response optimization and confirmation experiments. Examples from published pharmaceutical analytical studies illustrate the practical application of DoE-supported optimization in both column and planar chromatography. The review also considers analytical procedure validation and the relationship of chemometric development with ICH Q14 and ICH Q2(R2). Advantages, limitations, practical challenges and future directions, including data-driven and machine-learning-assisted approaches, are discussed.

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INTRODUCTION

MATERIALS AND METHODS

This review was prepared by synthesizing the published analytical literature, scientific texts, pharmacopeial information and regulatory guidance cited in the manuscript. The review scope covers chemometric and design-of-experiments approaches applied to HPLC and HPTLC method development, optimization, confirmation and validation in pharmaceutical quality assurance. The literature examples retained in the manuscript include published applications of central composite design, Box–Behnken design and other experimental-design approaches to pharmaceutical chromatographic methods. Regulatory discussion is based on the ICH Q14 and ICH Q2(R2) documents and the pharmacopeial and regulatory references listed in the reference section. No new experimental data are presented in this review.

1. INTRODUCTION

Reliable analytical measurements are essential for pharmaceutical quality assurance because analytical procedures support identity testing, assay, purity and impurity determination, stability assessment and routine quality control. HPLC is among the most broadly applied separation techniques in pharmaceutical analysis, whereas HPTLC provides a planar chromatographic platform suited to rapid analysis, fingerprinting and quantitative densitometry. The performance of either technique depends on the appropriate selection and control of method variables.

Chromatographic development commonly involves selection of the stationary phase, mobile phase, detection conditions, elution mode, flow rate, temperature and other operating parameters. Because these variables can influence one another, sequential experimentation may fail to reveal

important interactions. For example, changes in organic -solvent proportion can alter retention and selectivity, while pH can change analyte ionization and consequently influence retention and separation.

Chemometric approaches provide a structured framework in which several factors can be studied simultaneously and their effects on predefined analytical responses can be quantified.

The objective of this review is to consolidate the role of chemometric and DoE -based approaches in HPLC and HPTLC method optimization, explain their relationship with analytical quality by design(AQbD), and discuss model evaluation, validation, applications, limitations and future directions relevant to pharmaceutical quality assurance.

2. FUNDAMENTALS OF HPLC AND HPTLC

2.1 High-Performance Liquid Chromatography

HPLC separates components according to their differential interactions with a stationary phase and a mobile phase under controlled flow. In reversed -phase HPLC, a non -polar stationary phase such as C18 is commonly combined with an aqueous -organic mobile phase. Analyte physicochemical properties and chromatographic conditions influence retention, selectivity, efficiency and peak shape.

2.2 High-Performance Thin-Layer Chromatography

HPTLC is a planar chromatographic technique performed on precoated plates containing a suitable stationary phase. Samples are applied as controlled spots or bands, the plate is developed with a selected mobile phase and separated components are detected using densitometry or other suitable optical systems. Important



observations include R_f , resolution, band shape and detector response. The ability to analyze multiple samples in parallel makes HPTLC useful for screening, identification, fingerprinting and quantitative analysis.

3. CHEMOMETRICS IN CHROMATOGRAPHIC METHOD DEVELOPMENT

Chemometrics is the application of mathematical, statistical and computational methods to obtain useful information from chemical measurements. In chromatographic development, chemometrics can support experimental planning, regression modelling, multivariate interpretation and optimization.

Rather than relying exclusively on trial -and-error experimentation, a planned design can generate information about main effects, interactions and, where appropriate, curvature within the experimental region.

3.1 Chemometric tool Role in analytical development

- 1. Design of Experiments:** Plans experiments to estimate factor effects efficiently.
- 2. Regression modelling:** Relates method factors to analytical responses.
- 3. ANOVA:** Assesses statistical significance and partitions variation.
- 4. Response Surface Methodology:** Models and visualizes response behaviour in the experimental region.
- 5. Desirability function:** Combines multiple response goals into an optimization criterion.
- 6. PCA / PLS:** Supports multivariate exploration or prediction when appropriate to the dataset.

3.2 Chemometric vs. Simple Calculation

Mean, standard deviation or %RSD calculations performed after experimentation are not, by themselves, chemometric optimization. A chemometric strategy uses structured multivariable information to build or interrogate a model and then verifies that the selected conditions provide the intended analytical performance.

TABLE 1. COMPARISON OF HPLC AND HPTLC IN CHEMOMETRIC METHOD DEVELOPMENT

Feature	HPLC	HPTLC
Format	Column	Planar plate
Primary migration measure	Retention time	R_f
Typical optimization variables	Mobile phase, pH, flow, temperature, gradient	Solvent composition, saturation, development distance, detection
Typical responses	Resolution, retention, plates, tailing, area	R_f , resolution, area/height, band shape
Major strength	High-resolution quantitative separation	Parallel analysis and fingerprinting



4. ANALYTICAL QUALITY BY DESIGN AND ANALYTICAL TARGET PROFILE

AQbD applies quality-by-design principles to analytical procedure development. The Analytical Target Profile (ATP) defines what the analytical procedure is intended to measure and the required performance characteristics. ICH Q14 provides a science - and risk -based framework for analytical procedure development and lifecycle management, while ICH Q2(R2) addresses validation of analytical procedures.

1. Define the analytical objective and ATP.
2. Identify product, analyte and method knowledge.
3. Perform risk assessment.
4. Identify potential critical method parameters.
5. Select critical analytical responses.
6. Apply DoE for screening and/or optimization.
7. Develop and evaluate the statistical model.
8. Define suitable operating conditions or an appropriate region.
9. Perform confirmation experiments.

10. Validate the finalized analytical procedure and establish an appropriate control strategy.

5. DESIGN OF EXPERIMENTS IN CHROMATOGRAPHIC DEVELOPMENT

DoE investigates multiple factors in a planned and statistically interpretable manner. The choice of design depends on the number and type of factors, development stage, experimental region and information required.

Design Main purpose Typical chromatographic application Two-level factorial Main effects and interactions Small number of factors Fractional factorial Efficient screening Several potential factors Plackett–Burman Factor screening Many factors with limited runs Central Composite Design Quadratic response modelling Optimization of selected quantitative factors Box–Behnken Design Quadratic optimization without extreme combinations Three or more quantitative factors Mixture design Optimization of component proportions Mobile-phase mixtures

TABLE 2. COMMON DOE DESIGNS AND THEIR ROLES

Design	Primary use	Typical application
Full factorial	Main effects and interactions	Small factor sets
Fractional factorial	Efficient screening	Several factors
Plackett–Burman	Factor screening	Many potential factors
Central Composite Design	Quadratic response modelling	Optimization of quantitative factors
Box–Behnken Design	Quadratic optimization	Three or more quantitative factors
Mixture design	Proportion optimization	Mobile-phase mixtures



6. SELECTION OF FACTORS AND RESPONSES

6.1 Critical Method Parameters

Factors should be selected using prior scientific knowledge, risk assessment, published evidence, preliminary experiments and practical operating limits. The investigated levels should cover a meaningful and scientifically justified region. Overly narrow ranges can conceal important behaviour, whereas unnecessarily broad ranges may generate unsuitable chromatographic conditions.

6.2 HPLC Factors and Responses

1. Organic modifier proportion Elution strength, retention and selectivity Mobile-phase pH Ionization, retention and selectivity
2. Flow rate Retention, efficiency and analysis time
3. Column temperature Viscosity, retention, selectivity and peak shape
4. Gradient composition/slope Separation and total run time
5. Column chemistry Selectivity and peak shape
6. Common HPLC responses include retention time, resolution, theoretical plate count, tailing factor, peak area and precision indicators. Optimization should be based on predefined analytical objectives rather than on a single response in isolation.

6.3 HPTLC Factors and Responses

1. Organic-phase proportion R_f and resolution
2. Chamber saturation time R_f, development behaviour and reproducibility
3. Development distance Resolution and analysis time
4. Detection wavelength Peak response and sensitivity

5. Application conditions Band shape and precision

7. CHEMOMETRIC-ASSISTED HPLC OPTIMIZATION

HPLC optimization should begin with a scientifically reasonable chromatographic system. After preliminary selection of column and other conditions, selected high -risk variables can be investigated over a defined experimental region using an appropriate DoE.

7.1 Example Experimental Strategy

For illustration, organic-modifier proportion (X1), mobile -phase pH (X2) and flow rate (X3) may be selected after risk assessment. A Box–Behnken or Central Composite Design can be used to generate planned experimental runs. Resolution (Y1), retention time (Y2) and tailing factor (Y3) can then be measured. Regression models are fitted to describe the relationship between factors and responses, followed by model adequacy assessment and multi-response optimization.

7.2 Multi-Response Optimization

Chromatographic method development usually requires simultaneous control of several responses. Maximizing resolution alone, for example, may result in an unnecessarily long analysis. A desirability-based approach can combine goals such as maximizing resolution, minimizing analysis time and maintaining peak symmetry within an acceptable range. The predicted optimum should always be subjected to confirmation experiments.

7.3 Published HPLC Evidence

DoE-supported HPLC method development has been reported for pharmaceutical analysis. The supplied report highlights an RP-HPLC study of



torseamide and eplerenone in which Central Composite Design and response -surface methodology were used for multivariate optimization. Such studies illustrate how planned experimentation can replace extensive trial-and-error adjustment with a model-based development strategy.

8. CHEMOMETRIC-ASSISTED HPTLC OPTIMIZATION

HPTLC method development can similarly benefit from DoE because solvent composition, chamber saturation, development distance and detection conditions may jointly affect migration and separation.

The R_f value is particularly important because excessively low or high migration can reduce practical separation quality.

8.1 Published HPTLC Evidence

The supplied report identifies published DoE - supported HPTLC examples involving

efinaconazole, retapamulin, and a stability - indicating assay involving roxithromycin and ambroxol hydrochloride.

These examples demonstrate the use of response - surface designs, optimization of chromatographic variables and subsequent method validation.

8.2 HPTLC Optimization Workflow

1. Select a suitable stationary phase and establish an initial solvent system.
2. Identify high-risk chromatographic variables.
3. Select a screening or response-surface design.
4. Perform planned HPTLC experiments.
5. Measure R_f , resolution, response and other predefined attributes.
6. Fit the model and evaluate model adequacy.
7. Select the optimum region using predefined criteria.
8. Perform confirmation experiments.
9. Validate the finalized method.

TABLE 3. TYPICAL FACTORS AND RESPONSES

Technique	Factors	Responses
HPLC	Organic modifier, pH, flow, temperature, gradient	Resolution, retention time, tailing, efficiency, detector response
HPTLC	Solvent composition, saturation, development distance, application/detection	R_f , resolution, densitometric response, band shape

9. STATISTICAL MODELLING AND RESPONSE-SURFACE METHODOLOGY

For quantitative factors, a second-order polynomial is frequently used for response-surface modelling when justified by the selected design. The general form is:



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

Linear terms represent primary effects, interaction terms represent combined factor effects, and quadratic terms describe curvature. Model interpretation should consider statistical significance, model adequacy, residual behaviour, practical significance and experimental confirmation rather than relying on coefficient magnitude alone.

9.1 Model Evaluation

1. ANOVA of the fitted model.
2. Significance of relevant model terms.
3. Coefficient of determination together with suitable adjusted/predicted measures.
4. Lack-of-fit assessment where applicable.
5. Residual plots and identification of unusual observations.
6. Agreement between predicted and experimentally observed confirmation results.

9.2 Response-Surface Plots

Contour and three -dimensional response -surface plots can show how two factors jointly affect a response while another factor is held constant. Such plots are useful for visualizing regions that satisfy multiple criteria, but graphical interpretation should be supported by statistical evidence and confirmation experiments.

10. METHOD VERIFICATION AND ANALYTICAL VALIDATION

Optimization and validation are distinct activities. Optimization de termines suitable analytical conditions, whereas validation establishes that the finalized procedure performs adequately for its intended purpose. Depending on the analytical application, important characteristics include specificity/selectivity, accuracy, precision, linearity, range, detection limit, quantitation limit and robustness. System suitability is used to confirm system performance during analytical use.

TABLE 4. VALIDATION CHARACTERISTICS AND PURPOSE

Characteristic	Purpose
Specificity/selectivity	Demonstrate measurement of the intended analyte in the presence of relevant components
Accuracy	Assess closeness to an accepted/reference value
Precision	Assess agreement among repeated measurements
Response relationship/linearity	Demonstrate suitable relationship over the intended range
Range	Define interval over which required performance is demonstrated
LOD/LOQ	Characterize detection/quantitation



	capability when applicable
Robustness	Evaluate performance under deliberate small changes when appropriate
System suitability	Confirm system performance before/within analytical use

11. RELATIONSHIP WITH ICH Q14 AND ICH Q2(R2)

ICH Q14 provides a framework for science - and risk-based analytical procedure development and supports analytical procedure lifecycle thinking. ICH Q2(R2) provides the framework for demonstrating that an analytical procedure is fit for its intended purpose. Chemometric

optimization can connect these principles by translating the analytical objective into measurable responses, prioritizing factors through risk assessment, using DoE for structured experimentation, quantifying factor–response relationships through modelling, selecting an operating region, confirming predictions experimentally and then validating the final procedure.

TABLE 4. RELATIONSHIP TO CHEMOMETRIC OPTIMIZATION

Development element	Chemometric contribution
Analytical objective/ATP responses	Defines target performance and analytical
Risk assessment	Prioritizes factors for experimental study
DoE	Provides structured experimentation
Model development	Quantifies factor–response relationships
Optimization	Identifies suitable operating conditions or region
Confirmation	Tests model prediction experimentally
Validation	Validation
Demonstrates fitness for intended purpose	Demonstrates fitness for intended purpose
Lifecycle monitoring	Supports continued evaluation of analytical performance

12. APPLICATIONS IN PHARMACEUTICAL QUALITY ASSURANCE

1. Simultaneous estimation of multiple active pharmaceutical ingredients in combined
2. dosage forms.
3. Assay method development for single-component products.
4. Stability-indicating chromatographic method development.
5. Optimization of impurity and degradation-product separations.
6. Quality control of tablets, capsules, creams, solutions and other pharmaceutical formulations.
7. HPTLC fingerprinting and quantitative densitometry where appropriate.
8. Method robustness evaluation and analytical procedure transfer support. Development of efficient chromatographic procedures against predefined performance targets.

12.1 Why It Matters to Quality Assurance

A well-developed analytical procedure reduces the risk that analytical variability will obscure true product quality. Chemometric development can make relationships between method parameters and analytical performance more explicit, supporting rational control of critical variables and risk-based pharmaceutical quality systems.

13. ADVANTAGES, LIMITATIONS AND PRACTICAL CHALLENGES

13.1 Advantages

1. Systematic rather than purely trial-and-error development.
2. Simultaneous investigation of multiple variables.

3. Ability to estimate interactions within the experimental region.
4. Efficient use of experiments when designs are appropriately selected.
5. Quantitative prediction of responses within a suitable model region.
6. Facilitation of multi-response optimization.
7. Support for risk-based and lifecycle-oriented analytical development.

13.2 Limitations

1. Requires appropriate statistical understanding.
2. Incorrect factor selection can produce misleading optimization.
3. Models are dependent on experimental region and underlying assumptions.
4. Chromatographic peak integration and response measurement remain potential sources of error.
5. Optimization software cannot replace chromatographic expertise.
6. Predicted optimum conditions require experimental confirmation.
7. Validation remains necessary for the intended analytical application.

13.3 Practical Challenges

The major practical challenge is translating chemical and chromatographic knowledge into suitable factors and measurable responses. A statistically sophisticated design cannot compensate for inappropriate stationary-phase selection, poor sample preparation, unsuitable detection conditions or unrealistic operating ranges. Chemometrics should therefore complement, rather than replace, chromatographic expertise.



FUTURE PERSPECTIVES

Analytical development is increasingly moving from traditional one-factor-at-a-time experimentation toward structured DoE, AQbD and data -driven optimization. Future developments may integrate automated experimentation, richer chromatographic datasets, multivariate modelling and machine -learning approaches. For HPTLC, DoE -supported optimization is likely to remain useful because several solvent and development variables can jointly affect migration and separation. The priority should not simply be increasing model complexity; it should be obtaining better analytical knowledge, improving robustness, reducing unnecessary experimentation and maintaining scientific interpretability.

CONCLUSION

Chemometric-assisted optimization provides a rational framework for HPLC and HPTLC method development by combining analytical knowledge, risk assessment, DoE, statistical modelling and multi-response optimization. HPLC development may investigate mobile-phase composition, pH, flow rate, temperature, gradient conditions and column chemistry, whereas HPTLC development may investigate solvent composition, chamber saturation, development distance, application and detection conditions. Published pharmaceutical examples demonstrate that DoE -supported optimization is a practical approach. Nevertheless, the predicted optimum should be experimentally confirmed and the finalized procedure appropriately validated. Integration with ICH Q14 and ICH Q2(R2) strengthens the connection between analytical method development, risk -based decision-making and analytical lifecycle management. The most effective implementation is therefore not simply the use of statistical software, but a scientifically justified sequence

linking the analytical objective, critical factors, responses, model adequacy, confirmation and validation.

16. RESULTS AND DISCUSSION

The reviewed literature demonstrates that chemometric and DoE-based approaches can be integrated into pharmaceutical chromatographic development to study multiple method variables, quantify interactions and support multi-response optimization. The principal findings are summarized in the following tables and workflow.

17. AUTHOR DECLARATION

The author declares that this manuscript is a review article prepared through substantial restructuring, expansion and critical synthesis of an M.Pharm academic report and relevant scientific literature. The manuscript has not been previously published as a journal article and is not being considered simultaneously by another journal. The author has reviewed and approved the final manuscript. Any journal-specific requirements concerning prior academic-report or thesis-derived content will be disclosed to the target journal. The author declares no conflict of interest related to this manuscript.

18. CONFLICT OF INTEREST

The author declares that there is no conflict of interest associated with this review article.

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