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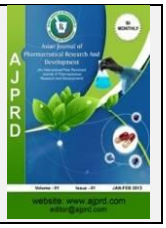

Open Access **Review Article**

A Review on AQBD-Based RP-HPLC Method Development for Simultaneous Quantification of Domperidone and Naproxen Sodium in Pharmaceutical Dosage Forms

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A B S T R A C T

Analytical Quality by Design (AQbD) has recently become an important methodology used for developing robust analytical techniques.The present review aims at the development of a robust RP-HPLC method for the simultaneous quantitation of Domperidone and Naproxen sodium in the pharmaceutical dosage form utilizing the AQbD principles.Risk assessment tools were employed to identify critical method parameters (CMPs) and critical quality attributes (CQAs), which were then optimized using design of experiment (DoE).A number of chromatographic parameters, such as composition of mobile phase, flow rate, pH, and column choice, have been optimized in order to obtain the optimal resolution and precision.As compared to trial and error techniques, AQbD methodology provides enhanced method robustness and reliability.The developed RP-HPLC method was validated according to the international council for harmonization guidelines, and the specificity, linearity, accuracy, precision, and robustness were established for the simultaneous analysis of two drugs.

Keywords: AQbD, RP-HPLC, Domperidone, Naproxen Sodium, DoE, Method Validation.

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INTRODUCTION:

Naproxen Sodium is a NSAID that is commonly used for its analgesic, anti-inflammatory, and antipyretic effects.It acts through inhibition of cyclooxygenase (COX-1 and COX-2) enzymes to inhibit prostaglandin formation causing pain, inflammation, and fever.

Domperidone is a dopamine D2 receptor antagonist that acts both as an antiemetic and prokinetic agent. It exerts antiemetic effects through blocking the dopamine receptors present at the CTZ level. Apart from acting as an antiemetic, it also stimulates motility of gastrointestinal tract by enhancing gastric emptying and gut movements.

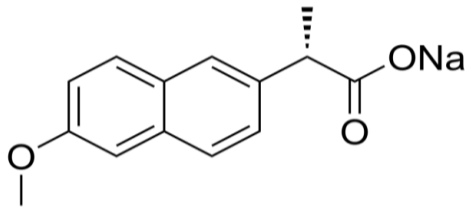


Figure: 1 Naproxen Sodium

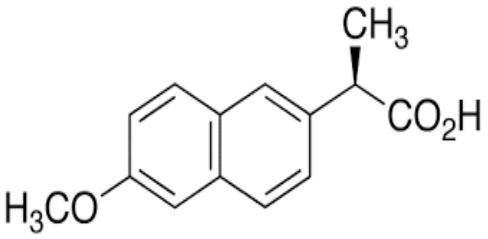


Figure: 2 Domperidone

Need for Fixed-Dose Combination:

- Single dosage form having two or more drugs
- Patient compliance and ease of use
- Gives synergistic effects
- Low side effects (For example, Domperidone reduces the incidence of gastric side effects due to Naproxen Sodium)
- Effective economically and eliminates medication error

Need for Simultaneous Analytical Method:

- Necessary for estimation of multiple drugs together
- Conserves time and cost savings than individual methods
- Saves effort in routine quality control
- Ensures accuracy and precision
- Needed in combination containing Naproxen Sodium and Domperidone

Limitations of Traditional Methods (OFAT):

- Studies one factor at a time, ignoring interactions between variables
- Time-consuming and inefficient for complex formulations
- Less robust and may not ensure consistent method performance
- Requires multiple experiments to optimize conditions
- Provides limited understanding of critical method parameters

Analytical Quality by Design (AQbD): Analytical Quality by Design (AQbD) is a systematic, science-based approach to analytical method development. It emphasizes understanding the method, controlling variability, and ensuring robustness. Key aspects include:

- Analytical Target Profile (ATP): Defines the purpose and performance requirements of the method
- Critical Method Attributes (CMAs) & Parameters (CMPs): Identify variables that affect method performance
- Risk Assessment & Design of Experiments (DoE): Optimizes method conditions efficiently
- Design Space: Defines safe operating ranges for robust and reproducible results

AQbD improves method reliability, reduces development time, and offers regulatory flexibility compared to traditional OFAT approaches..[1,2,3,4,5,6,7,8,9]

Drug Profile:

Table: 1[10,11,12,13]

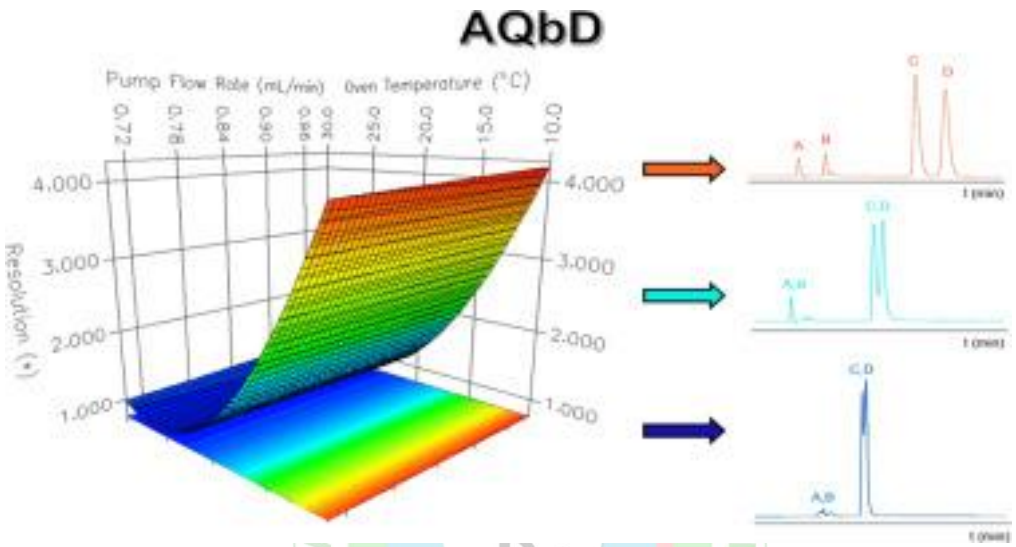
	Naproxen Sodium	Domperidone
Molecular Weight	252.24 g/mol	425.91g/mol
Class	Nonsteroidal anti-inflammatory drug	Dopamine -2(D_2) receptor antagonist
Solubility	Soluble in Water and Ethanol	Soluble / Freely Soluble in Water and Ethanol
Wavelength	272-273 nm	287.5 nm
Pka	4.15-4.2	7.9-8.0
Injection Volume	10-20 µL	20 µL
Column Temperature	25-30 °C	40 °C
Column	250×4.6 mm, 5µm	250×4.6 mm, 5µm
Polar / Non-Polar	More Polar	Less Polar
Flow Rate	1.0 ml/min	1.0 ml/min
Acidic,Basic	Acidic	Basic
Molecular Formula	$C_{14}H_{13}NaO_3$	$C_{22}H_{24}ClN_5O$

AQbD Framework for Method Development:

AQbD Approach to Method Development Analytical Quality by Design (AQbD) refers to a scientifically based approach to analytical method development, where a method is designed based on certain predefined objectives (ATP) and with controlled variations, hence, its robustness, accuracy, and regulatory compliance.

Major Attributes of AQbD:

1. Predefined Objectives: Establishing clear objectives for the method such as precision, accuracy, and resolution.
2. Risk Assessment: Evaluating critical factors that influence the method's performance (e.g., pH, flow rate, and mobile phase ratio).
3. DoE: Optimizing the method parameters through systematic design of experiments.
4. Design Space: Determining the parameter range for consistent method performance.
5. Continuous Monitoring: Method performance monitoring to assure reliability.



Figutre: 3 Analytical Quality By Design

Comparison between AQbD and Conventional Approach

The AQbD provides a scientific and structured analytical method development process that has various benefits compared to the traditional approach. The major differences are:

Table: 2 Comparisons between AQbD and Conventional Approach

Traditional Approach	AQbD Approach
Trial-and-error approach	Scientific approach
Low robustness	High robustness
Poor regulatory flexibility	Regulatory compliance
Undefined design space	Defined design space

As opposed to the traditional approach, AQbD utilizes risk assessment, DoE, and statistical modeling for developing robust and reliable methods.It also defines a design space to ensure consistent method performance, improves reproducibility, and facilitates regulatory approval and lifecycle management.

Use of AQbD for simultaneous estimation of Domperidone (DOM) and Naproxen Sodium (NAP) guarantees robustness against minor fluctuations in CMPs, saves time, and reduces the frequency of method revalidation.

Here is Section 19: Applications in Pharmaceutical Industry in scientific review style with Vancouver citation references for publication review.

1. Analytical Target Profile (ATP):

Analytical Target Profile (ATP) states the purpose and desired performance features of the analytical method.It forms a basis for the development process by defining the requirements. For simultaneous determination of Domperidone and Naproxen Sodium by RP-HPLC, the ATP usually comprises:

- High accuracy (recovery between 98-102%)
- Satisfactory precision (%RSD ≤ 2%)
- Appropriate resolution (Rs ≥ 2)
- Short retention time
- Adequate peak symmetry and sensitivity.

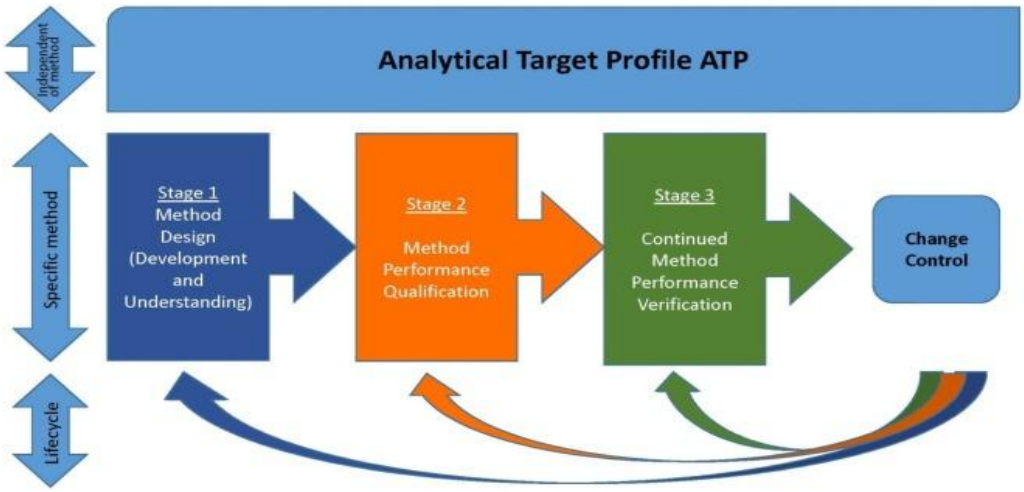


Figure: 4 Analytical Target Profile (ATP)

2. Critical Quality Attributes (CQAs):

Critical Quality Attributes (CQAs) are attributes of the analytical method whose control is required to meet the expected performance standards.In RP-HPLC method development, some important CQAs are:

- Resolution (Rs): Separation of two peaks; important for simultaneous estimation of drugs
- Tail Factor (T): Peak asymmetry; optimal tail factor is near unity
- Theoretical Plates (N): Efficiency of the chromatographic column; higher theoretical plates indicate better separation
- Retention Time (Rt): Elution time
- Peak Area: Quantitation of the analytes

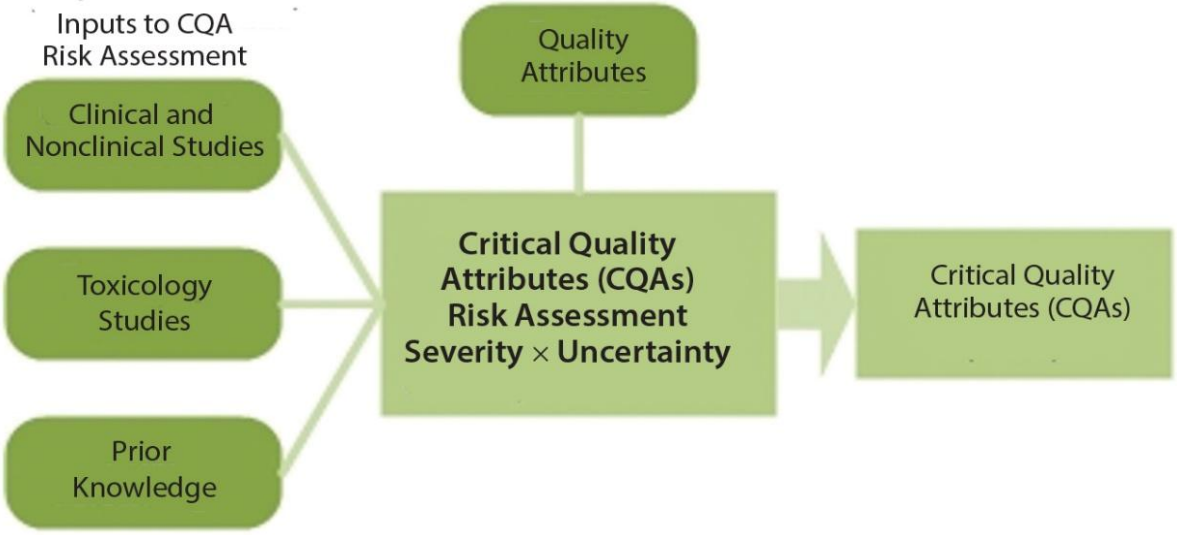


Figure: 5 Critical Quality Attributes (CQAs)

3. Risk Assessment:

It is a scientific and systematic process of identifying, analyzing, and assessing variables which could influence the Critical Quality Attributes (CQAs) of the analytical methodology.The role of risk assessment in AQbD lies in prioritization of variables, which must be tightly controlled to ensure reliable method performance.The main aim of risk assessment is the differentiation of high-risk, medium-risk, and low-risk variables in order to concentrate optimization efforts on certain aspects of the method.

Tools Used for Risk Assessment:

- Ishikawa (Fishbone) Diagram:
- It helps to identify the potential source of variation within each of the following categories:
- Method
- Materials
- Instruments
- Environment
- Analyst
- Failure Mode and Effects Analysis (FMEA):

It is a quantitative risk assessment technique, involving the evaluation of the risk level in accordance with:

- Severity (S)
- Occurrence (O)
- Detectabili(D)

These variables define the Risk Priority Number (RPN).

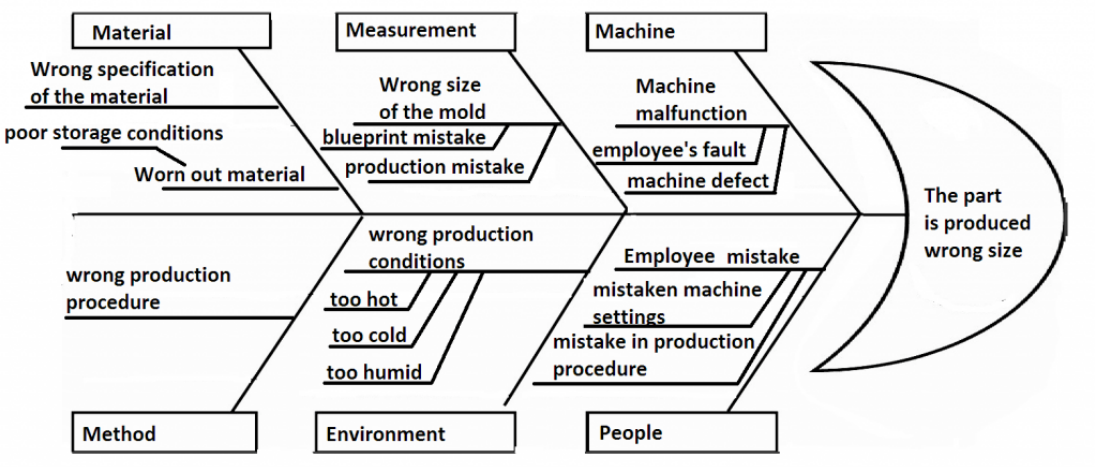


Figure: 6 Ishikawa (Fishbone) Diagram[14,15,16,17,18,19]

Critical Parameters Evaluated in AQbD-Based RP-HPLC:

Critical Parameters Considered in AQbD Approach for RP-HPLC Method: When developing a method for the simultaneous estimation of Domperidone and Naproxen Sodium, the following parameters are considered:

- pH of Mobile Phase: It impacts the ionization of compounds, thereby affecting their retention time, resolution, and peak formation.
- Flow Rate: This influences the analysis time, width of the peak, and system pressure.If the flow rate is incorrect, it can lower the resolution.
- Proportion of Organic and Aqueous Mobile Phase: It affects the efficiency and selectivity of the mobile phase.
- Column Type and Column Temperature: These factors affect the performance of columns.
- Detection Wavelength: This parameter should be selected based on the wavelength corresponding to the maximum absorption of compounds.[20,21,22,23,24]

High-Performance Liquid Chromatography (HPLC):

High-Performance Liquid Chromatography (HPLC) is a chromatography technique that uses high pressure and a liquid mobile phase to transport the sample mixture through a column packed with a stationary phase. Principle of High-Performance Liquid Chromatography (HPLC) High Performance Liquid Chromatography (HPLC) relies on the differential mobility of the compounds within the sample through a column at high pressure.

In HPLC, the sample mixture undergoes separation due to differences in their rate of movement within the column, based on their physicochemical characteristics.Factors involved in the separation mechanism of HPLC include the following:

1. Variance in Polarity:

In any sample mixture, the different compounds have varying polarities.

- Non-polar compounds have greater affinity for the non-polar stationary phase and consequently take longer to pass through the column.
- Polar compounds tend to elute faster since they prefer the polar mobile phase. Consequently, polarity becomes an essential determinant of elution sequence.

2. Compound-Stationary Phase Interactions:

Different compounds have different affinities for the stationary phase material (e.g., C18).

- A stronger affinity results in a slower movement, thus a prolonged retention time
- A weaker affinity causes a faster passage, hence a reduced retention time. These interactions may involve hydrophobic interactions, van der Waals interactions, and hydrogen bonding.

3. Solubility in the Mobile Phase:

The solubility of compounds in the mobile phase influences their mobility in the column.

- Compounds with high solubility move faster down the column than others
- Compounds that have low solubility in the mobile phase spend more time in the stationary phase

HPLC Instrumentation:

HPLC analysis uses highly advanced instrumentation systems for the accurate separation and detection of compounds. Components of HPLC include.

1. **Quaternary Pump**:
   - Conveys the mobile phase under constant high-pressure conditions.
   - Allows mixing of up to four solvents for gradient elution purposes.
   - Eliminates flow rate variations and improves separation efficiency.

2. Auto-sampler:

- Introduces the sample into the HPLC apparatus automatically.
- Increases sample precision and reproducibility of injections.
- Increases analysis efficiency and eliminates human errors.

3. Column Oven:

- Holds the HPLC column at a constant temperature during analysis • Serves to enhance resolution, reproducibility, and peaks shape
- Serves to control temperatures in case of temperature-sensitive analytes

4. UV/Visible Detector:

- Capable of detecting compounds based on UV/visible absorbance
- Displays the output in form of chromatogram showing retention times and peak areas
- Used for the analysis of analytes such as drugs such as Domperidone and Naproxen Sodium.

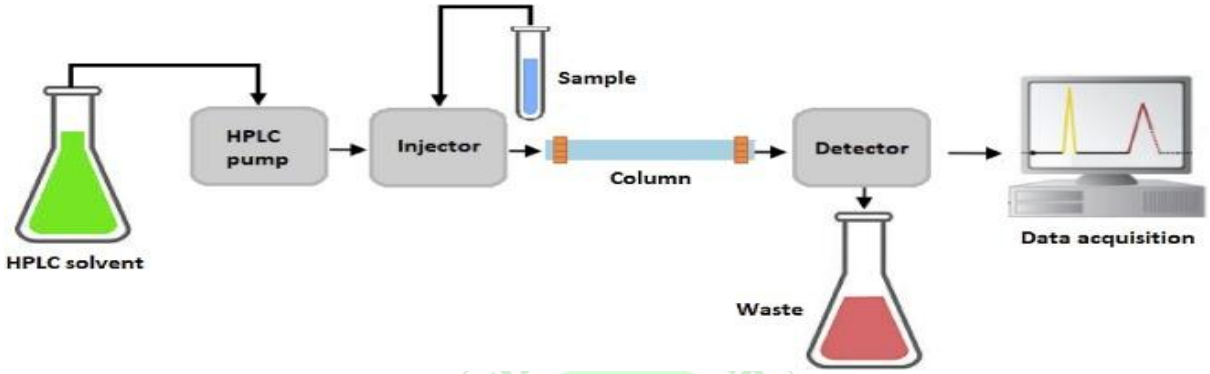


Figure: 7 High-Performance Liquid Chromatography (HPLC)

Chromatographic Conditions:

Chromatographic Conditions: Chromatographic conditions are important in the successful implementation of AQbD RP-HPLC Method for the simultaneous quantification of Domperidone and Naproxen Sodium.

- Stationary phase: C18 Columns (e.g., Shim-pack, Inertsil, Sunfire 250 x 4.6 mm, 5 µm).
- Mobile Phase: Phosphate buffer/methanol or acetonitrile (commonly used at pH 3.0 – 6.5)
- Detection Wavelength: Usually optimized at 272 nm – 273 nm.
- Flow rate: Commonly 1.0 mL/min

Method Validation (ICH Q2(R1/R2)):

Method validation is a critical stage in the analytical method development process to ensure that the developed method is fit for its intended purpose.In the development of AQbD RP-HPLC methods, method validation serves to confirm that simultaneous estimation of Domperidone and Naproxen Sodium is appropriate.

Validation is carried out following ICH Q2 (R1/R2) recommendations, where key parameters for evaluating an analytical method are outlined.

Specificity:

Specificity is the ability of an analytical procedure to quantify the analyte under specified conditions in the presence of the components present in the sample.

In the case of simultaneous estimation of Domperidone and Naproxen Sodium, specificity ensures accurate separation of drug peaks without interference by other formulation components.

Linearity:

- Shows how the method gives a response proportional to analyte concentration in a certain range.
- Usually evaluated by preparing different concentrations of both drugs and measuring their peak areas against the concentration.
- The correlation coefficient (R^2) should usually be ≥ 0.999.

Accuracy (Recovery):

- Measures how close the experimental value is to the actual value.
- Performed by adding known amounts of drugs into the sample and computing % recovery.
- Acceptable percentage: 98–102% for pharmaceutical formulations.

Precision:

The precision evaluates the repeatability and reproducibility of the analytical method:

- Repeatability (intraday): Single analyst; single day
- Intermediate precision (interday): Multiple days, instruments, or analysts.
- It is calculated in terms of % relative standard deviation (%RSD), which should be ≤ 2%.

Detection limit (LOD) and quantification limit (LOQ):

- LOD: Minimum concentration at which the analyte is detectable but not necessarily measurable
- LOQ: Minimum concentration that can be reliably measured.

- LOD and LOQ are calculated based on the signal-to-noise ratio (S/N = 3 for LOD, S/N = 10 for LOQ).

Robustness:

A measure of the method's resistance to minor intentional changes such as:

- Flow rate (±0.1 mL/min)
- Composition of mobile phase (±2%)
- Column temperature (±2°C)

System Suitability Test:

Tested prior to performing sample analysis to confirm proper function of the HPLC system

- Critical Parameters: o Resolution factor (Rs) > 2
- Tail factor (T) < 2
- Theoretical plates (N) > 2000
- %RSD for repeated injections < 2%[25-33]

Implementation of DoE on AQbD based RP-HPLC Method:

The Design of Experiment (DoE) is an important methodology in AQbD based RP-HPLC method development, which enables the determination of the Critical Method Parameters (CMP) affecting CQAs like resolution, tail factor, and theoretical plate number. Importance of DoE in the HPLC Method Development:

- For optimizing chromatographic conditions
- Saves time through reduction of trial-and-error
- Determines the relationship between various factors affecting the separation process • Guarantees a robust and reproducible method for estimating Domperidone and Naproxen Sodium

Common DoE Approaches:

1. Full Factorial Design - Tests all possible combinations of various factors at multiple levels.
2. Fractional Factorial Design - Tests only selected combinations to cut down the number of experiments.
3. Response Surface Methodology (RSM) - Maximizes/Minimizes factors and evaluates interactions; methods include:

- Box-Behnken Design
- Central Composite Design

Steps for Using DoE in AQbD-Based RP-HPLC:

1. Identification of Factors and Levels
   Mobile phase ratio, pH, flow rate, column temperature
2. Selection of Responses (CQAs)
   Resolution (Rs), tailing factor (T), theoretical plates (N), retention time
3. Experimental Design
   Application of statistical design (factorial design or RSM) for conducting experiments
4. Data Analysis
   Regression/ANOVA used to study effect of factors on responses.
5. Optimization
   Identifies optimized conditions for selected CQAs.
6. Design Space Identification
   Determines range within which method performance remains robust.

Advantages of Using DoE in AQbD-Based RP-HPLC:

- Reduction in experimental time and mistakes
- Scientific knowledge about factor interactions
- Improvement in robustness and reproducibility of methods
- Compliance to regulations because of demonstration of method control and flexibility

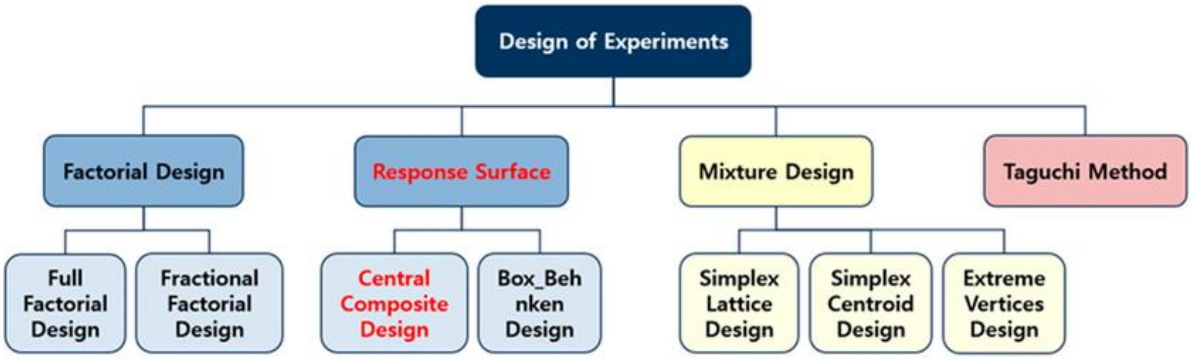


Figure 8: Design of Experiments (DoE)) [34,35,36,37,38]

Control Strategy:

Control Strategy is an important part of AQbD and is crucial for achieving an optimal analytical method through its entire lifecycle by assuring that it yields accurate and reliable results.A control strategy includes measuring, controlling, and monitoring the process of the analytical method to ensure that the CQAs are protected.

The main aspects of a control strategy in HPLC method development include the following: System suitability tests (SST): This is one of the most important parts of a control strategy, which includes such tests as the retention time, resolution, tailing factor, and theoretical plates.

Awell-defined operating range: This involves setting up the acceptable values for such CMPs as flow rate, mobile phase composition, pH, and column temperature to achieve

consistency and robustness.Calibration: Scheduling the calibration for instruments (HPLC pumps, detectors, balances) ensures accuracy in measurements.Trends: This is continuous monitoring and tracking of system suitability and chromatography performances to detect any changes.

The implementation of the control strategy in a structured manner, using the guidelines of AQbD, ensures the robustness of the process and also complies with the regulatory aspect of the lifecycle management approach to ensure the quality of results obtained during the simultaneous quantitation of DOM and NAP.[39,40,41,42,43,44,45]

CONCLUSION:

This current review brings into the limelight the importance of the Analytical Quality by Design (AQbD) technique in developing a reliable RP-HPLC technique for the estimation of both Domperidone and Naproxen Sodium in pharmaceutical preparations.

It is worth noting that the AQbD approach offers a scientific, methodical approach to analytical method development.The approach focuses on method understanding, risk management and variability control in all stages of analytical life cycle.Through ATP, CQA/CMP identification, and Design of Experiment (DoE), a highly optimized and efficient method of separation can be obtained.This method will have higher accuracy, precision, selectivity and ruggedness compared to the conventional trial-and-error methods.

In addition, the ICH guidelines based method validation will validate the efficiency and reliability of the developed method.Moreover, the implementation of forced degradation study ensures that the developed method has the ability to detect the presence of degradation products, whereas the use of control strategy ensures consistent performance over a period of time.

The application of AQbD improves not only the quality of the analytical method but also saves development time and cost.This review proves that AQbD based RP-HPLC techniques are highly suitable for estimating combination drugs.[46,47,48,49,50]

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