RESEARCH ARTICLE

Quality by Design Approach for Development and Validation of Analytical Method for Estimation of Furosemide in Bulk and Formulation

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Abstract

Background: A common loop diuretic used to manage edema, CHF, and hypertension is furosemide. The majority of described HPLC techniques for its estimation are linked to longer run times and higher solvent consumption, and they lack a systematic Quality by Design (QbD) approach.

Objectives: Using a QbD methodology, the current work sought to design and validate a reliable, quick, and economical HPLC technique for furosemide quantification in pharmaceutical formulations and bulk.

Materials and Methods: A central composite design was used to improve crucial procedure parameters like flow rate and mobile phase composition. Chromatographic separation was carried out using a column C18 with acetonitrile and 0.1% OPA (70:30 v/v) as the mobile phase at a flow rate 0.8 mL/min and detection at 277 nm. In compliance with ICH Q2(R1) standards, the developed method was verified for linearity, accuracy, precision, robustness, ruggedness, LOD, and LOQ.

Results: With a correlation coefficient (R2) of 0.9994, the method show outstanding linearity over the range of 5–30 ppm. Precision studies indicated %RSD values below 2%, while accuracy studies showed recovery between 98–102%. It was discovered that the approach was strong and resilient, with little change under various circumstances instruments. The results showed that the LOD and LOQ were 0.65 µg/mL and 1.97 µg/mL, respectively.

Summary: The new QbD-based RP-HPLC method is simple, precise, and appropriate for routine quantitative analysis of furosemide in bulk and medicinal dose forms.

Keywords: Central composite design, Furosemide, high performance Liquid chromatography, quality by design.
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Introduction

Analytical Chemistry

The area of science known as analytical chemistry employs cutting-edge technologies to determine composition through analytical methods. Both qualitative and quantitative outcomes are possible. In order to obtain accurate and high-quality analytical data, analytical tools are crucial. Therefore, equipment quality assurance should be a concern for everyone working in the analytical laboratory. Spectral, chromatographic, electrochemical, hyphenated, and other methods are examples of analytical techniques[1].

Analytical Method

A methodical process used to ascertain the identification, purity, concentration, or other properties of a drug or chemical compound in a sample is known as an analytical method. To get accurate and repeatable findings, a number of procedures are involved, such as sample preparation, measurement, and data interpretation. To guarantee the effectiveness, safety, and quality of pharmaceutical goods, analytical techniques are crucial[2].

Developing Analytical Methods

Analytical technique development is the process of selecting a precise test strategy to determine the composition of a formulation. It entails proving that an analytical method is appropriate for use in a laboratory to ascertain the concentration of subsequent samples. The ICH's guidelines and acceptance standards must be followed Q2(R1) when developing analytical methods, which should be utilized in GMP and GLP settings[3].

Analytical Method Validation

Verifying that the analytical method used for a particular test satisfies the necessary requirements is the goal of the analytical method validation procedure. Validations of pharmaceutical procedures may be based on FDA, ICH, USP, and other recommendations. The quality, consistency, and reliability of the method in relation to analytical findings

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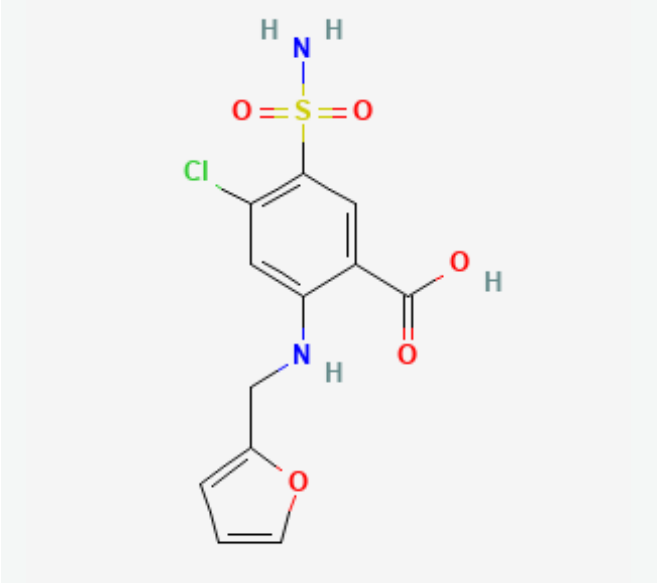

can be evaluated by looking at the validation results. Assay validation is important in the pharmaceutical business for two main reasons: first, it is an essential component of the quality-control system, and second, it is necessary for the regulation of actual manufacturing processes[4-8].

Analytical methods have been confirmed to meet Q2 (R1) ICH standards. The validation parameters include Specificity, Accuracy, Precision, Repetability, Reproducibility, Linearity, Range, Limit of Detection, Limit of Quantification, Robustness, Ruggedness, and System Suitability Test[9-10].

Quality by Design Approach

A QbD is defined as "a systemic approach to the method development that highlights product and process knowledge and process control, based on sound scientific knowledge and quality risk management, and begins with predefined objectives"[11].The understanding and use of ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality System standards served as the foundation for the QbD technique[12-14]. Analytical QbD is a science and risk-based paradigm for analytical method development that seeks to understand the preset objectives to control the critical method variables affecting the critical method attributes in order to achieve improved method performance, high robustness, ruggedness, and flexibility for continuous improvement. Analytical QbD, like process QbD, results in a well-known, robust, and suitable technique that reliably generates the intended output over the course of its life cycle[15-16]. Robustness and ruggedness for QbD and HPLC procedures should be evaluated early in the method's development stage to ensure the method's efficacy throughout the product's lifecycle[17]. Otherwise, redeveloping, revalidating, and retransferring analyses can be quite time-consuming. Otherwise, it could take a considerable amount of time and effort to design, revalidate, and retransfer analytical procedures if a non-rugged or non-robust system is altered. Finding failure modes and offering a reliable, functional design area or design space within crucial system compatibility requirements and continuous the management of life cycle have been the main goals of AqbD[18-21]. This study aims to develop and optimize a high-performance liquid chromatography (HPLC) method for the estimation of furosemide in pharmaceutical dosage forms by applying a Quality by Design (QbD) approach. Furosemide (FUR) is a one type of loop diuretic. 4-chloro-2-[(furan-2-ylmethyl)amino]-5-sulfamoylbenzoic acid is its chemical name. Several pharmacopoeias (USP-NF, 2008; BP, 2011; EDQM, 2014; IP, 2018) recognize it as official. Fursemide, Aisemide, Beronald, Desdimin, Lasilix, and other generic names are available for FUR[22]. Hepatic cirrhosis-related edema, persistent congestive heart failure, and hypertension are all treated with furosemide[23].

The Na+-K+_2Cl-symporter in the thick ascending limb is bound by loop diuretics, which disrupt its operation and prevent electrolyte transfer in this area of the nephron. Because the thick ascending limb has a huge capacity to reabsorb any Na+ that is not reabsorbed at the proximal tubular site, diuretics that only act on the proximal tubules have limited effectiveness. Similarly, because relatively little Na+ reaches these sites, diuretics that work mainly on site beyond the thick ascending limb likewise have limited efficacy. Conversely, loop diuretics—also referred to as high ceiling diuretics—act at the thick ascending limb and are quite effective. Loop diuretics also stop Ca2+ Mg+ reabsorption in the thick ascending limb by removing the transepithelial potential difference, which is the main catalyst for these cations' reabsorption. The proto-type loop diuretic is furosemide[24].

A literature showed that a number of techniques have been documented for the measurement of furosemide in pharmaceutical samples, biological samples, and bulk, either by itself or in conjunction with other medications. Furosemide has been estimated using UV spectrophotometric techniques alone[25], in combination with other medications[29-30], and utilizing the AUC approach[11,27], and charge transfer method[28]. HPTLC-densitometry techniques utilizing a model approach have been established for simultaneous determination using tablet formulation[32] and for the estimation of furosemide by RP-HPLC transfer of TLC screening[31] . A number of additional analytical techniques were documented, such

Table 1: Coded values for independent variables

Variables	*Low*	*Medium*	*Hign*
Mobile Phase ratio Acetonitrile : 0.1% OPA	60:40	50:50	70:30
Flow Rate (ml/min)	0.6	0.8	1.0

Abbreviation: OPA= Orthophosphoric acid, ml/min = mili liter par minutes

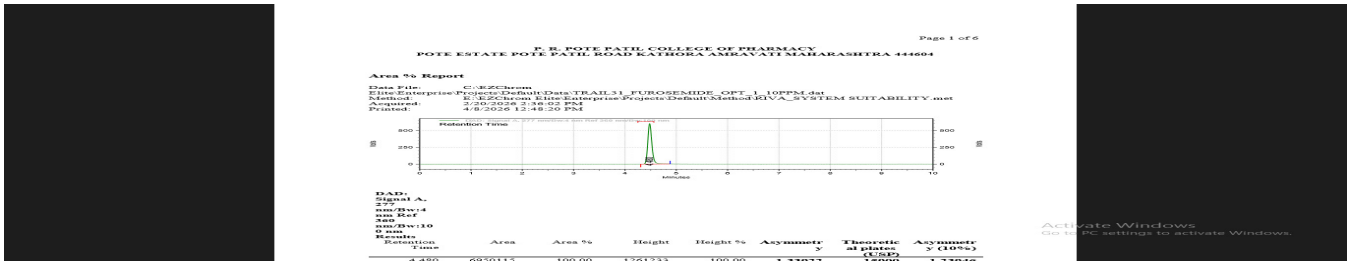

Figure 2: Trail -1

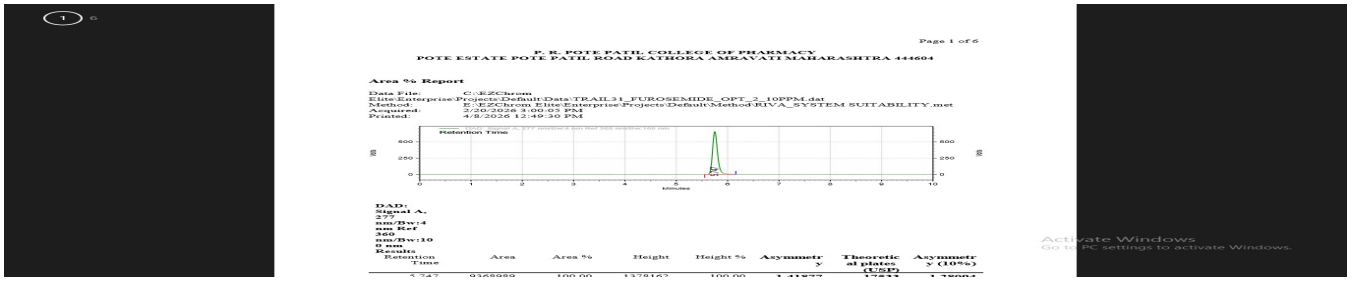

Figure 3: Trail -2

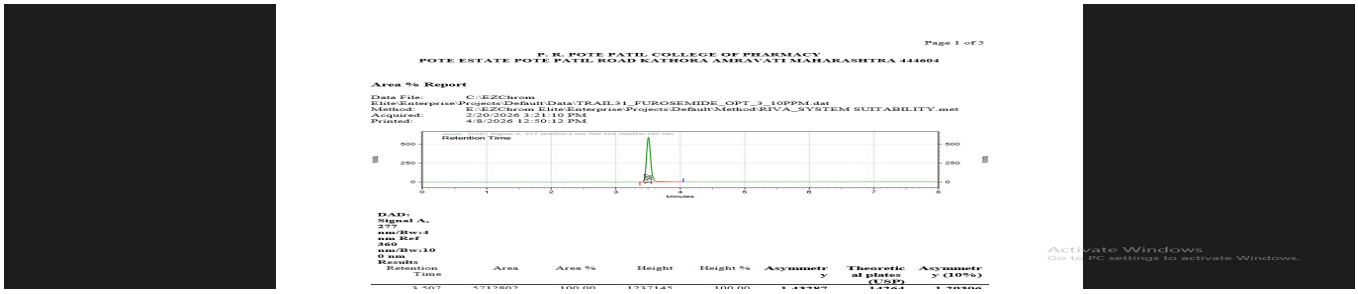

Figure 4: Trail -3

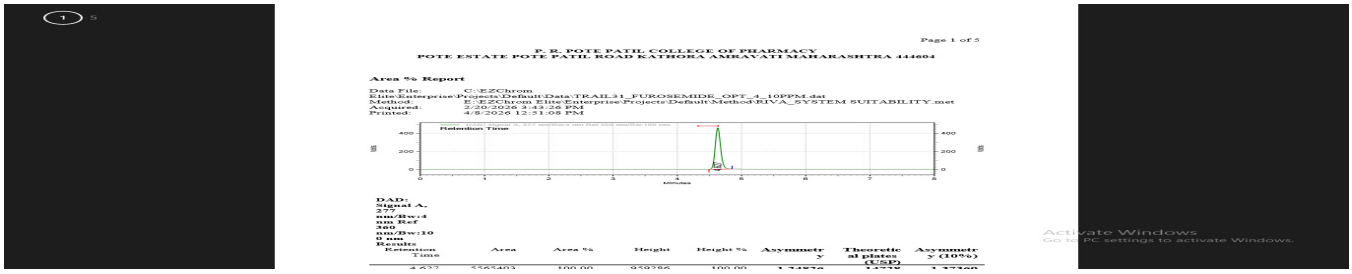

Figure 5: Trail -4

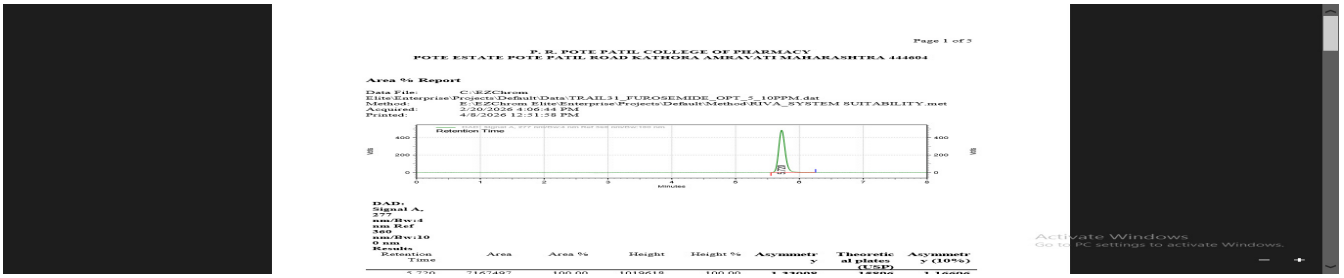

Figure 6: Trail -5

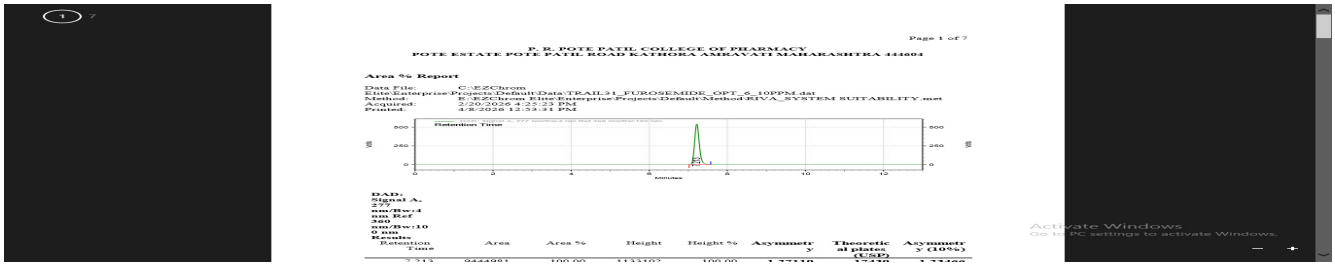

Figure 7: Trail -6

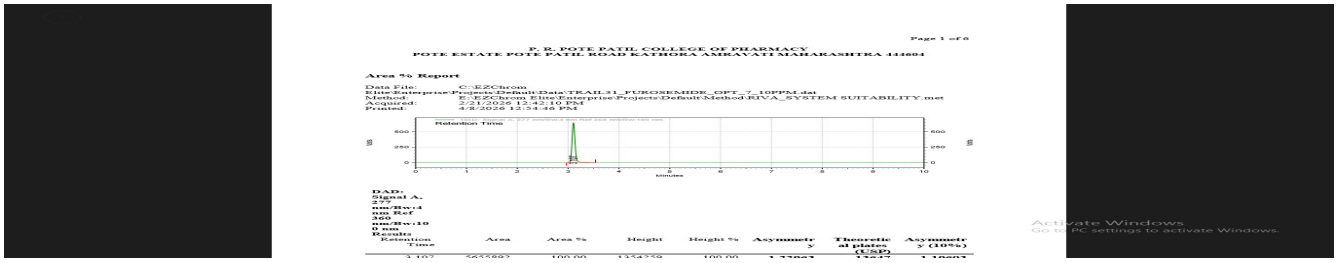

Figure 8: Trail -7

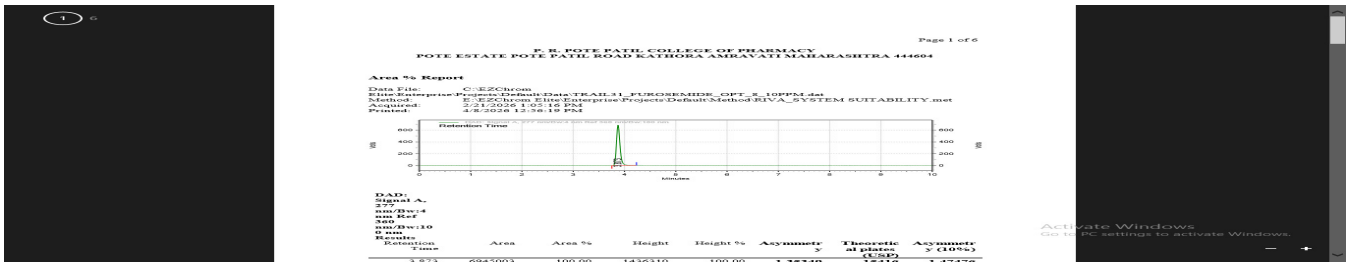

Figure 9: Trail -10

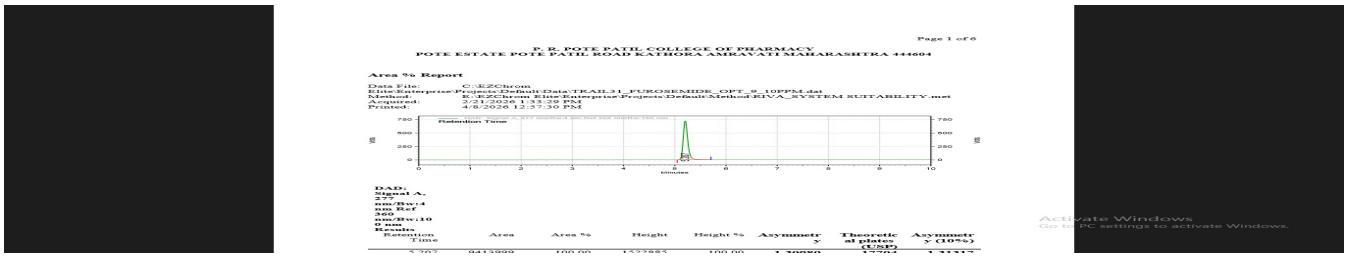

Figure 10: Trail -11

as the HPLC/MS assay of furosemide, spirolactone[33]. HPLC techniques have been published for the measurement of FUR utilizing pharmaceutical dose form alone[37-40], FTIR[34], ^{1}H NMR[35], and capillary electrophoresis[36]. The majority of published HPLC techniques for furosemide measurement lack a systematic Quality by Design (QbD) approach and are frequently linked to longer analytical run times, which raise solvent consumption and decrease method efficiency. In order to guarantee improved method performance and reproducibility, an effort was made in the current study to create a strong and dependable reverse-phase HPLC method based on QbD principles. To obtain a quick analysis with a shorter run time and less solvent consumption, crucial process parameters were modified. Following validation in compliance with ICH requirements, the new approach showed acceptable levels of robustness, precision, accuracy, and specificity. As a result, the suggested approach is appropriate for the quantitative measurement of furosemide in pharmaceuticals and bulk drugs.

Materials and methods

The reference standards for furosemide was generously provided by Laxachem Organics Pvt. Ltd., situated in Amravati. Solvents utilized in this research included HPLC

Table 2: Parameters optimization by using central composite design

Trial No.	*Mobile Phase ACN : 0.1% OPA (V/V)*	*Flow Rate*	*Peak Asymmetry*	*Theoretical Plates*	*Retention Time*
1	60:40	0.6	1.25	17532	5.7
2	60:40	0.8	1.05	15907	4.5
3	60:40	1.0	1.45	14264	3.5
4	50:50	0.6	1.40	17438	7.2
5	50:50	0.8	1.20	15896	5.7
6	50:50	1.0	1.10	14728	4.6
7	70:30	0.6	1.50	17703	5.2
8	**70:30**	**0.8**	**1.15**	**15416**	**3.8**
9	70:30	1.0	1.10	13647	3.1

Abbreviation: ACN= Acetonitrile, OPA = Orthophosphoric acid,V/V = Volume per Volume

water, acetonitrile, methanol, and OPA, all bought from variety traders. A commercial tablet formulation Lasix 40 mg containing furosemide manufactured by Sanofi India was obtained from the local mediacal store for analysis.

Instrumentation

Different instruments were employed during the method development process, such as HPLC by Agilent with 1100 Series and having EZChrom Elite chromatography software for data collection and analysis comprised the equipment used in this investigation. A Bruker FTIR Spectrometer running the OPUS software was used to perform Fourier Transform Infrared (FTIR) analysis. A Lab India 3092 UV Spectrophotometer with UV Win software was used to conduct UV-visible spectrophotometric measurements. The sample was prepared using an ultrasonicator by nucleus bioscience ats-2 and weighing balance by wesnar pgb 220. To guarantee the quality, accuracy, and dependability of the results, all instruments were calibrated before analysis.

Selection and Detection of Wavelength

For analytical purposes, the maximum absorbance (λmax) of furosemide was determined using wavelength selection. Acetonitrile : water (80:20) was used to generate a standard solution of 10 ppm, which was then scanned over the proper UV range. The drug's highest absorbance at 277 nm was chosen for additional examination. For quantitative estimation, this wavelength offered good sensitivity and repeatability. As a result, the analytical wavelength for all ensuing research was 277 nm.

Chromatographic Condition

Chromatographic conditions for the C18 column separation (250 mm × 4.6 mm, particle size of 5 µm). ACN and 0.1% OPA in a 70:30 (v/v) ratio made up the mobile phase. The injection volume was 10 µl, and the flow rate was 0.8 mL/min. A wavelength of 277 nm and a column temperature of 25°C were used for the study. The procedure took ten minutes to run in total.

Preparation of Mobile Phase

Mobile phase consisted of ACN 70 ml and 0.1% OPA 30 ml .To prepare 0.1% OPA take 0.3ml OPA and add 300ml HPLC grade water then stir it by using magnetic stirrer for 5 min then sonicate it for 15 min.

Standard Solution Preparation

To obtain 1000 ppm of concentration, 10 mg of the standard furosemide was carefully weighed, put into a 10 ml volumetric flask, and the volume was created using an 80:20 v/v mixture

Table 3: Linearity

Concentration (PPM)	*Area*
5	795518
10	1469393
15	2254061
20	2983548
25	3763247
30	4421202
R^2 =	0.9994

Abrivations: ppm = Parts per million, R2 = coefficient of determination

Table 4: Repeatability

Injection No.	*Peak Area*
1st injection	1974876
2nd injection	1962137
3rd injection	1934696
4th injection	1983425
5th injection	1940351
6th injection	1956780
Mean	1958711
Standard deviation	16932
%Residual standard deviation	0.86

Table 5: Accuracy

Level	*Volume of Standard Solution A (ml)*	*Volume of Test Solution B (ml)*	*Area*	*Mean Area*	*% Recovery*
80%	0.8	1.0	4042213		99.77%
80%	0.8	1.0	4021231	4044854	98.83%
80%	0.8	1.0	4101120		100.77%
100%	1.0	1.0	4571705		101.13%
100%	1.0	1.0	4490172	4541205	99.30%
100%	1.0	1.0	4561740		100.90%
120%	1.2	1.0	4972396		99.95%
120%	1.2	1.0	4980267	4981599	100.13%
120%	1.2	1.0	4992134		100.36%

Table 6: Intraday Precision

Concentration (PPM)	*1st Dilution*	*2nd Dilution*	*3rd Dilution*
10 PPM	1974876	1962139	1934696
10 PPM	1972981	1972001	1935369
10 PPM	1969897	1963102	1937690
	Mean= 1972584	Mean=1965147	Mean=1935918
	SD= 2494	SD= 5475	SD= 1612
	%RSD=0.13%	%RSD=0.28	%RSD=0.08

Abrivations: PPM = Parts per million, SD = Standard deviation,%RSD = percentage residual standard deviation

of ACN and water. The final concentration of the working standard solution is 10 ppm. From this, 0.1 ml was pipetted out and placed into another 10 ml volumetric flask. The volume was then adjusted using ACN: Water (80:20 v/v).

Sample Solution preparation from Marketed Formulation

20 tablets of Lasix 40 mg were weighed, powdered, and determined the average weight. The amount of tablet powder equal to 10 mg of Furosemide was then precisely transferred into a 10 ml volumetric flask in order to quantify the amount of Furosemide from the marketed formulation. After adding enough methanol and sonicating the mixture for 30 minutes, the mixture was diluted with the solvent and used Whatmann filter paper for filtration. To determine the final concentration, 0.1 ml of the filtrate was measured and diluted with ACN: Water (80:20 v/v).

Table 7: Interday Precision

Parameters (Days)	*Concentration (PPM)*	*Peak Area*	*SD*	*%RSD*
Day 1	10 PPM	1934694		
Day 2	10 PPM	1940351	26252	1.36%
Day 3	10 PPM	1983426		

Table 8: Robustness Results

Parameter	*Area*	*Mean Area*	*SD*	*%RSD*
Flowrate(0.72ml/min)	2435703			
	2445703	2439703	5033	0.21
	2437703			
Flowrate(0.88ml/min)	2109239			
	2089236	2099237	10001	0.48
	2099236			
Wavelength (276 nm)	2225000			
	2220000	2223300	2886	0.13
	2224900			
Wavelength (278 nm)	2089212			
	2079960	2086805	5916	0.28
	2091243			

Abrivation: ml/min = Mili liter per minute, nm = nanometer, SD = Standard deviation, %RSD = percentage residual standard deviation

Table 9: LOD and LOQ

Parameters	*Results (**µg/ml**)*
LOD	0.65
LOQ	1.97

Abrivation: LOD = limit of detection, LOQ = limit of quantification, µg/ml = micro gram per mili liter

Table 10 : Ruggedness

Parameter	*System 1 (Agilant 1100 series)*	*System 2 (Shimadzu LC)*	*% RSD*
Retention time	3.9	4.001	1.80
Area	1934694	1921249	0.49
Theoretical plates	15416	15200	1.0
Tailing	1.4	1.38	1.02

Abrivation: %RSD = percentage residual standard deviation

Factorial design

Following the definition of the QTPP and CQAs, two crucial elements—mobile phase and flow rate—were chosen and optimized using the central composite experimental design. Central composite design was used to investigate the different interaction effects and quadratic implications of the mobile phase composition and flow rate on the retention time, theoretical plates, and peak asymmetry. Using Design Expert® 13 software, a two-factor design with mobile phase composition and flow rate at three different levels produced the optimum response for second-order polynomials examining quadratic response surfaces[41].

Quadratic Equation

$Y=\beta 0+\beta 1\beta+\beta 2\beta+\beta 12\beta\beta+\beta 11\beta 2+\beta 22\beta 2$

Where:

Y = Response (Retention time / Tailing factor depending on response)

A = Mobile phase ratio

B = Flow rate

β_0 = Interceptβ_1,

β_2 = Linear coefficients

β_{12} = Interaction coefficientβ_{11},

β_{22} = Quadratic coefficients.

Evaluating the experimental results and setting final procedure parameters These method conditions were evaluated using the central composite design methodology. The initial step involved evaluating the circumstances for peak asymmetry, theoretical plates, and retention time. This led to different chromatographic conditions for furosemide[42].

Independent variables

Table 1 Coded values for independent variables

Optimization of parameters for analysis of furosemide using CCD

Table no. 2 Parameters optimization by using central composite design

Graphs of Trial Batches

Figure 2 Trail -1
Figure 3 Trail -2
Figure 4 Trail -3
Figure 5 Trial -4
Figure 6 Trail -5
Figure 7, Trail -6
Figure 8, Trail -7

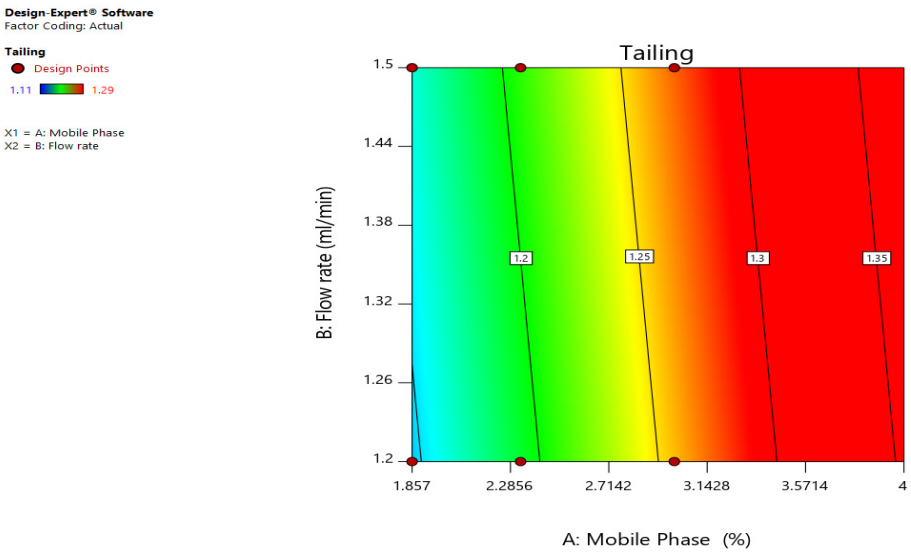

Figure 11: Surface map for the impact of factor combinations on furosemide's peak asymmetry using Central Composite Design

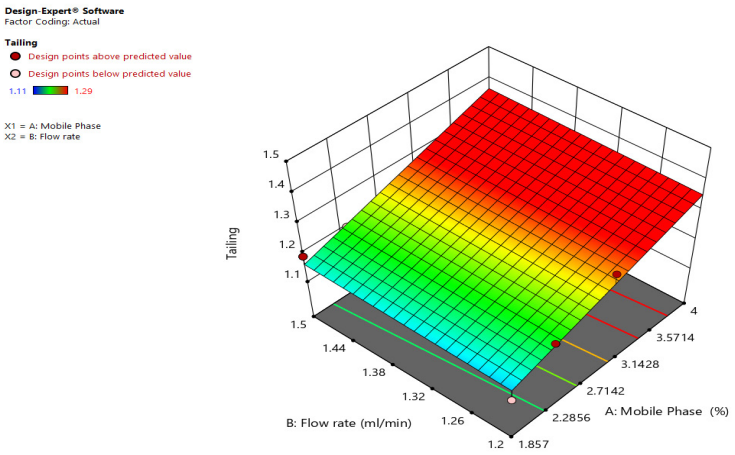

Figure 12: 3D Surface map showing the impact of factor combinations on furosemide's peak asymmetry using Central Composite Design

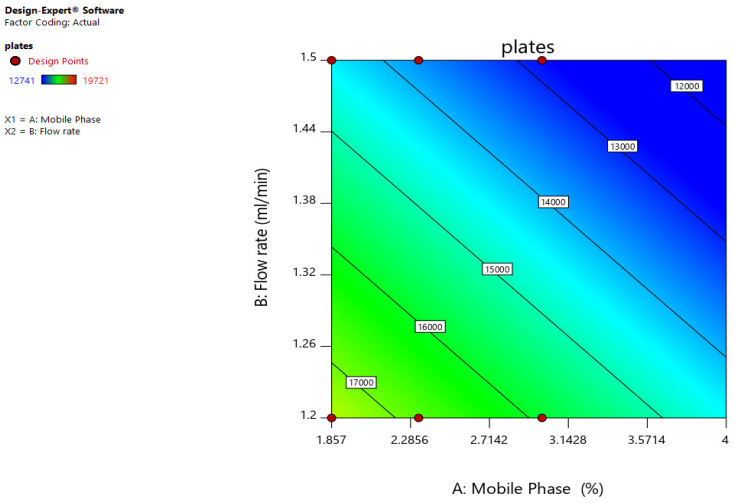

Figure 13: Surface map utilizing Central Composit Design to show the impact of a mix of factors on theoretical furosemide plates

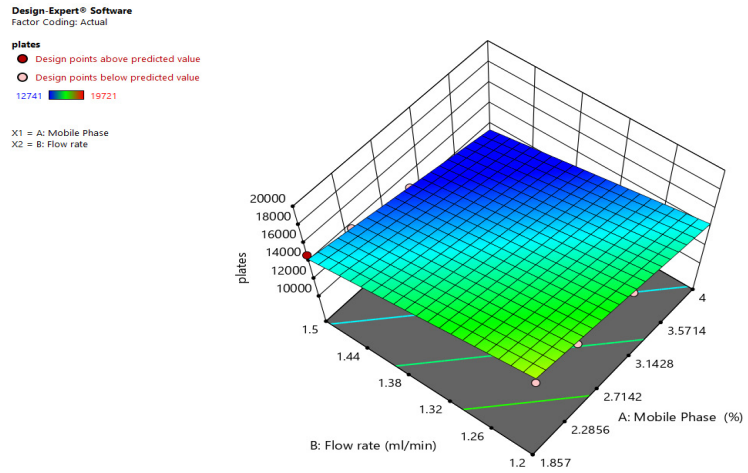

Figure 14, 3D Surface map utilizing Central Composit Design to show the impact of a mix of factors on theoretical furosemide plate

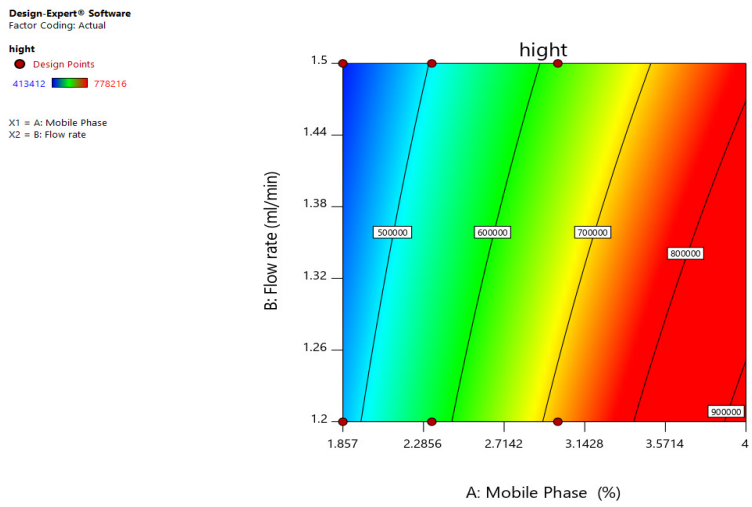

Figure 15, Surface map utilizing Central Composit Design to show the impact of a mix of factors on Retention time

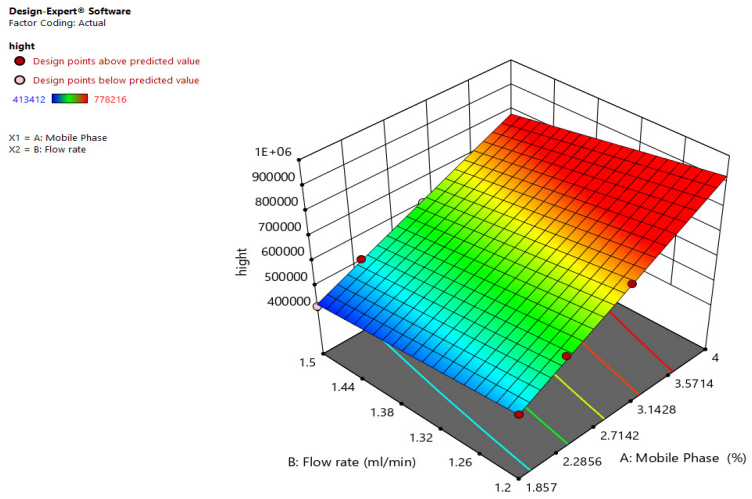

Figure 16: 3D Surface map utilizing Central Composit Design to show the impact of a mix of factors on Retention time.

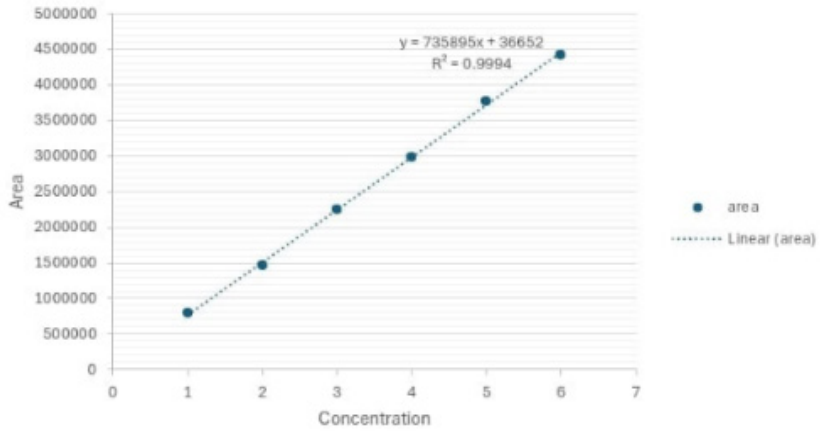

Figure 17: Calibration curve

Figure 9, Trail -8
Figure 10, Trail -9

Contour Plot And 3d Surface Showing Effect Of Cpp On Tailing Factor

Figure 11, Surface map for the impact of factor combinations on furosemide's peak asymmetry using Central Composite Design.

Figure 12, 3D Surface map showing the impact of factor combinations on furosemide's peak asymmetry using Central Composite Design.

Contour Plot And 3d Surface Showing Effect Of Cpp On Theoretical Plates

Figure 13, Surface map utilizing Central Composit Design to show the impact of a mix of factors on theoretical furosemide plates

Figure 14, 3D Surface map utilizing Central Composit Design to show th0e impact of a mix of factors on theoretical furosemide plates

Contour Plot And 3d Surface Showing Effect Of Cpp On Retention Time

Figure 15, Surface map utilizing Central Composit Design to show the impact of a mix of factors on Retention time.
Figure 16, 3D Surface map utilizing Central Composit Design to show the impact of a mix of factors on Retention time.

Method Validation

Analytical techniques have been validated in accordance with Q2 (R1) ICH criteria. Linearity, Specificity, Accuracy, Precision, Repetability, Reproducibility, Limit of Detection, Limit of Quantification, Robustness, Ruggedness are the validation parameters[9-10].

Linearity

An analytical method's linear connection is assessed by determining whether the calibration curve, which shows response vs concentration, corresponds to a straight line. In this investigation, a primary stock solution containing 1000 µg/mL of furosemide was create a calibration curve[11].The method linearity was assessed in the current investigation over a concentration range of 5–30 ppm. By precisely take 10 mg of the medication and dissolving it in 10 mL of ACN:Water (80:20) to achieve a concentration of 1000 ppm, a standard stock solution of the drug was created. Next, pipette out 0.1 ml and dilute it using the same solvent to get 100 parts per million. To create working standard solutions of 5 ppm-30 ppm, appropriate aliquots of this stock solution were further diluted with ACN:Water (80:20). Under ideal chromatographic circumstances, each concentration level was examined, and the results were noted. Plotting concentration against absorbance produced a calibration curve that demonstrated a linear relationship within the chosen range, verifying the method's linearity.

Accuracy

The correctness of the method was tested through recovery studies conducted at 80%, 100%, and 120% of the test concentration, with each level tested three times[11]. for preparing 80%,100% and 120% use 100 PPM standard solution and 100 PPM sample solution.

Precision

Interday Precision

For Interday precision, a standard solution with concentrations of furosemide 10PPM was utilized. These solutions were subjected to Interday precision analysis in three different days.

Intraday precision

Intraday precision analysis was performed by using 10ppm solution of furosemide in multiple times on the same day itself. % RSD was then estimated from these tests to determine precision.

Repeatability

Repeatability was assessed by introducing a standard solution into the system of furosemide (10ppm) six times. The chromatogram obtained were analysed, and peak areas were recorded to evaluate repeatability.

LOD and LOQ

LOD and LOQ for the drugs were established using data collected from linearity. Afterwards, calculated using a specified Equation.
LOD=3.3*SD/Slope
LOQ=10*SD/Slope

Robustness

As described in the Chromatographic circumstances section, the robustness research was carried out under chromatographic circumstances to evaluate the impact of small deviations. This study looked at variables that were identified as major causes of operating procedure variability. In particular, changes were made to the wavelength by ± 2 nm and the carrier solvent's flow rate by ± 10%. The mobile-phase components' composition did not alter during these studies. The impact of these changes on the system's fitness for standard preparation was then assessed[11]

Results And Discussion

Linearity

Table no.3 Linearity
Figure 17, calibration curve

Assay of marketed formulation

For the Assay we use Lasix 40 mg tablet as marketed formulation and assay was found to be 97.33%

Repeatability

Table No. 4 Repeatability

Accu2racy

Table No. 5 Accuracy

Precision

Intraday Precision

Table no. 6 Intraday Precision

Interday Precision

Table no.7 Interday Precision

Robustness

Table no. 8 Robustness Results

LOD and LOQ

Table no. 9 LOD and LOQ

Ruggedness

Table no. 10 Ruggedness

Conclusion

The study demonstrates how the Quality by Design approach was effectively used to create a solid and trustworthy RPHPLC method for furosemide quantification. Overall, the method is easy, simple, economical, and suitable for routine quality control analysis; it showed excellent linearity, accuracy, and precision with %RSD values within acceptable limits; it was found to be robust and reproducible across different conditions and instruments.

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