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Original Article

QbD-Driven Hydrotropic UV Method for Simultaneous Quantitation of Poorly Soluble Drugs, Irbesartan and Hydrochlorothiazide in Bulk and Tablet Formulation

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ABSTRACT

Background: Developing a reliable and precise method for the simultaneous quantitation of poorly soluble drugs, Irbesartan (IRB) and Hydrochlorothiazide (HCTZ), in bulk and formulations poses significant challenges due to their poor aqueous solubility and low proportional ratio. A robust, sustainable, and AQbD-driven UV spectrophotometric approach is essential to overcome these limitations and ensure accurate quantification. **Materials and Methods:** A hydrotropic solubility enhancement technique was employed using sodium bicarbonate as the optimal hydrotrope. Systematic AQbD principles guided the selection and optimization of concentration (1M) and volume (5 mL) of hydrotrope to maximize solubility without compromising the UV spectroscopic signal. IRB and HCTZ exhibited absorption maxima at 231 nm and 272 nm, respectively. **Results:** The optimized method obeyed Beer's law in the concentration ranges of 5.0-30.0 mcg/mL for IRB and 0.75-2.50 mcg/mL for HCTZ. The optimum concentrations of IRB and HCTZ were 15 µg/mL and 1.25 µg/mL, with absorbance values of 0.539 and 0.418, respectively. Excellent linearity with regression coefficients of 0.9997 for IRB and 0.9991 for HCTZ, no interference from pharmaceutical excipients was observed. The method was validated according to ICH guidelines and successfully applied for routine analysis of IRB and HCTZ in bulk and formulations. **Conclusion:** This sustainable AQbD-driven approach simplifies the analysis of poorly soluble drugs. The method can be successfully used for the quality control of these drugs in fixed dose combination.

Keywords: Quality by design, Irbesartan, Hydrochlorothiazide, Hydrotropy, UV spectroscopy.

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INTRODUCTION

Irbesartan (IRB) and Hydrochlorothiazide (HCTZ) are commonly prescribed in combination to treat hypertension and edema.[1,2] IRB, chemically, 2-butyl-3-({4-[2-(2H-1,2,3,4-tetrazol-5-yl) phenyl] phenyl} methyl)-1,3-diazaspiro[4.4]non-1-en-4-one,[3] (Figure 1A) is an angiotensin-II receptor blocker that works by blocking the action of vasoconstrictor hormone, lowering blood pressure.[4] It is a poorly water-soluble compound, which can present challenges in its analysis and bioavailability. HCTZ, chemically, 6-chloro-1,1-dioxo-3,4-dihydro- 2H-1,2 ,4-benzothiadiazine-7-sulfonamide,[5] (Figure 1B) is a thiazide diuretic that inhibits reabsorption of sodium in the kidneys, leading to more urine output and lower blood pressure.[6] Like Irbesartan, Hydrochlorothiazide also exhibits limited solubility in water, further complicating the analytical quantitation of these drugs in bulk and pharmaceutical formulations.

Due to their low solubility in aqueous solutions, developing reliable and precise analytical methods for these drugs is challenging. Methods such as UV and visible spectrophotometry,[7-19] RP-HPLC,[20-45] UPLC,[46] HPTLC,[47-49] and LC-MS/MS[50] have been reported for the determination of IRB and HCTZ, alone and along with other drugs.[51-63] However, these methods often suffer from limitations such as lack of robustness, sensitivity, and reproducibility, making them less suitable for routine quality control. Traditional methods, often requiring high organic solvent content, can introduce issues with solubility, reproducibility, and environmental impact. To address these challenges, sustainable analytical techniques are essential. Hydrotropic solvents have emerged as effective alternatives to promote solubility of poorly soluble drugs in water. Hydrotropy offers several advantages: it increases solubility without significantly affecting the spectroscopic signal, reduces potential interference from the solvent, and is safer and more environmentally friendly

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compared to many organic solvents. Additionally, hydrotropic solutions tend to be more stable and less prone to precipitation, which enhances the reproducibility of analytical results.[64]

Despite significant advancements in Analytical Quality by Design (AQbD) approaches for UV spectroscopic method development, the integration of hydrotropy methodology remains largely unexplored. A comprehensive review of the literature reveals a lack of reported studies on AQbD-driven UV spectroscopic method development incorporating hydrotropic solubilization, highlighting a critical research gap. Addressing this gap, the present study aims to develop and optimize a novel AQbD-based UV spectroscopic method utilizing hydrotropy, ensuring enhanced analytical performance and reliability. The application of AQbD principles in optimizing hydrotrope concentration and selection further improves the robustness and precision of analytical methods. The combination of hydrotropy and AQbD-driven UV spectrophotometric analysis offers a sustainable and efficient method for quantification of poorly water-soluble drugs like Irbesartan and Hydrochlorothiazide, simplifying their analysis while promoting environmentally conscious practices.

MATERIALS AND METHODS

Drug Samples: Reference standards of IRB (98.5 to 101% w/w) and HCTZ (98 to 102% w/w) were generously provided as gift samples by Aurobindo Pharma Pvt. Ltd., Hyderabad. Tablet samples, specifically IRBOTAN-150H, were obtained from ZEELAB Pharmacy, Delhi.

Chemicals: All chemicals used in this study were of AR grade. Sodium bicarbonate was sourced from Finar Ltd., while distilled water was prepared in-house in the laboratory.

Instruments and Software: An electronic single-pan weighing balance (Shimadzu ATX224R) and a double-beam UV-visible spectrometer (Shimadzu UV-1800) were employed for the analysis. Spectra of standard, sample solutions were recorded using UV Probe Version 2.34 software, utilizing 1 cm quartz cells over a wavelength range of 200-350 nm. Experimental design and statistical analysis were executed using the licensed version of Design Expert Stat-Ease Version 13.

AQbD-based UV method development

AQbD facilitates the establishment of a robust method operable design region, MODR, where all method performance goals are met. The application of QbD principles, detailed in the ICH Q8,[65] Q9,[66] Q10,[67] Q11[68] and Q14[69] guidelines, to the analytical method development is known as the AQbD. It not only aids in developing reliable methods but also ensures method performance. This approach enhances data quality, strengthens interactions with regulatory authorities, elevates the efficacy of transfer of a validated method, that reduces queries during regulatory submissions.[70] AQbD starts with creation of comprehensive knowledge space and ends with its meticulous monitoring. The following systematic approach[71] (sequence of steps) was used for AQbD based UV method development.

Knowledge Space Creation

It serves as an essential basis for integrating quality into a method. The development of a QbD-driven hydrotropic UV method for the quantitation of selected drugs simultaneously in bulk and tablet formulations require a comprehensive knowledge space establishment. This includes a comprehensive understanding of physicochemical properties of IRB and HCTZ, identifying a suitable hydrotrope and optimizing its concentration to enhance solubility of the drugs without affecting spectrophotometric performance. Existing analytical methods,[7-63] such as UV-visible spectroscopy (AUC and derivative methods) and RP-HPLC for IRB and HCTZ, were critically reviewed to identify gaps in robustness, sensitivity, and sustainability. The chemical structures of the drugs were analyzed to predict their spectral behaviour and interactions with the hydrotrope.[71] Regulatory guidelines, ICH Q8(R2),[65] ICH Q14,[69] were followed to ensure compliance and to define the Analytical Target Profile (ATP), emphasizing method attributes like precision, accuracy, robustness, and environmental safety. This structured knowledge space laid the foundation for the systematic application of AQbD principles in method development and optimization, ensuring reliability and efficiency in the analysis of these poorly soluble drugs.

Establishment of ATP

In the next step of AQbD implementation, the goal (ATP) of the procedure development was defined. It indicated the method performance.[72] The ATP for the present method was designed to ensure its reliability, accuracy, and sustainability for the simultaneous quantitation of selected drugs. The intended purpose of method is to provide a robust and reproducible analytical procedure that supports routine quality control. A hydrotropic approach was selected, emphasizing simplicity, cost-effectiveness, and alignment with green analytical practices. The ATP links to CQAs, solubility enhancement, linearity, robustness, and matrix tolerance, ensuring accurate and reliable quantitation. Performance characteristics were defined to meet 98.0-102.0% accuracy, high precision (intra- and inter-day, %RSD≤2.0%), specificity (distinct quantification at 231 nm for IRB and 272 nm for HCTZ without interference), and a reportable range (IRB: 5.0-30.0 mcg/mL; HCTZ: 0.75-2.5 mcg/mL) with $r^2 \geq 0.995$ for both analytes. The ATP framework guarantees the development of a regulatory-compliant method, delivering precise and reproducible results.

Selection of Analytical Technique

Based on the intended purpose of developing a robust, cost-effective, and environmentally sustainable method, the UV-visible spectrophotometric technique was selected.

UV-visible spectrophotometry meets the ATP requirements by offering an easy and economical approach suitable for routine quality control. Using hydrotrope enhances the solubility of IRB and HCTZ without relying on organic solvents, making the method greener. It also ensures minimal solvent interference and provides accurate absorbance readings for IRB and HCTZ. Its accuracy, precision, and specificity align with the ATP goals, making it a practical and dependable choice for pharmaceutical analysis.

Risk Assessment (RA)

Risk assessment is vital for identifying critical variables and parameters that influence the ATP. The Ishikawa fishbone diagram (cause-and-effect diagram) (Figure 2), is an effective RA tool used in spectroscopic method development.[73] This diagram categorizes factors contributing to variability into branches resembling fishbones, such as equipment, materials, methods, personnel, and environment. By systematically identifying and visualizing potential sources of variation, it helps researchers address and mitigate these factors, enhancing the method's robustness and reliability.

Critical Method Parameters (CMPs), Critical Analytical Attributes (CAAs) Identification

Preliminary studies were conducted to identify the CMPs and CAAs.[74] These studies assessed the individual impact of parameters such as the selection of solvent, wavelength, concentration, and volume of the hydrotrope on the analytical response.

Selection of Solvent

The solubility of 10 mg of API (IRB and HCTZ) was tested in 10 mL of distilled water, 0.1N NaOH, 0.1 N HCl, and hydrotropic agents[75] viz, sodium acetate, sodium benzoate, urea, sodium citrate and sodium bicarbonate. Both drugs were practically insoluble in water, but their solubility improved significantly in sodium bicarbonate compared to the other agents. Thus, sodium bicarbonate was selected as the hydrotropic solvent for the estimation of the drugs.

Selection of wavelength

Standard solutions (10 mcg/mL) of IRB and HCTZ hydrotropic solution were scanned between 220-400 nm. The absorption maxima were identified at 231 nm for IRB and 272 nm for HCTZ, which were selected for analysis (Figure 4).

Selection of Concentration of Hydrotrope

To determine the optimal concentration of the hydrotrope for analysis, the drugs were tested with varying strengths of sodium bicarbonate, ranging from 0.1M to 1.5M. The results were provided in Table 1.

Selection of Volume of Hydrotrope

To select the appropriate hydrotrope volume, the drugs were analyzed with sodium bicarbonate volumes ranging from 1 mL to 10 mL. The results were summarized in Table 1.

Effect of concentration and volume of hydrotrope on absorbance of two drugs depicted in Figure 3. Based on preliminary studies and the Ishikawa diagram, the concentration (M) and volume (mL) of the hydrotropic reagent were identified as CMPs. These parameters were further evaluated using a Design of Experiments (DoE) approach to study their impact on the absorbance intensities of IRB (Y_1) and HCTZ (Y_2). The identified CMPs and CAAs were listed in Table 2.

Method optimization by DoE

A Central Composite Design, CCD was utilized as DoE tool to optimize the method. CCD efficiently explores the factor space with minimal experimental runs,[76,77] enabling the modeling of nonlinear responses and optimization of the UV response. This approach allows for robustness assessment while reducing the overall experimental effort, making it a practical choice for method optimization.

Two independent variables were considered for method development: the concentration of the hydrotropic reagent (X_1) and the volume of the hydrotropic reagent (X_2). The absorbance of IRB (Y_1) and the absorbance of HCTZ (Y_2) were chosen as the responses in the experimental design. Five levels (-α, -1, 0, +1, +α) for each independent variable were outlined in Table 2.

CCD gave 13 experimental runs for selected CMPs and CAAs, with 4 factorial points, 4 axial points, and 5 center points, as outlined in Table 3. The results of the responses (Y_1 and Y_2) from these 13 runs were entered into Design Expert software (Version 13) a response surface quadratic model was then applied to analyze the effects of the CMPs on CAAs, aiming to achieve the best analytical method performance with optimized values.

Establishment of MODR

MODR, selected from the CCD generated quadratic prototype models presented below for response Y_1 and Y_2 using the Design Expert Software.

$$Yn=b0+b1\ X1+b2\ X2-b3\ X1\ X2-b4\ X12+b5\ X22$$

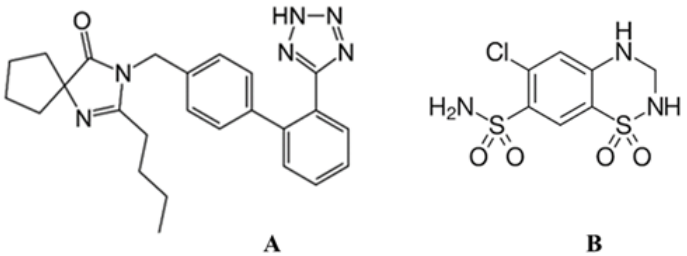

Figure 1: Structure of (A) Irbesartan (B) Hydrochlorothiazide.

In the above equation, Yn represents the method's response, while b_0 to b_5 are coefficients, and X_1 to X_2 are the CMPs. The sign of each coefficient reveals the nature of relationship between X_n and Y_n, with the coefficient value indicating its extent. To verify model reliability, the r^2 value was used to assess predictive accuracy. After confirmation, 2D-contour and 3D-surface were generated (Figure 4).

Method selection and verification

The targeted method responses (Y_1 and Y_2) were systematically simulated using Design Expert Software, and a candidate method was selected and experimentally validated. During the simulation, Y_1 was set to a target of 0.5 and Y_2 to 0.4. Numerical optimization was employed to achieve multiple goals, with all objectives given equal importance using 3 plus (+++) setting. The goals were combined into an overall desirability function (Figure 3), with a correlation deemed satisfactory if the correlation coefficient (R^2 value) between predicted and experimental responses exceeded 0.9. Contour and 3D surface plots were used to establish the MODR for the targeted responses and to define the variable ranges (X_1 and X_2) for the method. Details of the selected candidate method were provided in Table 4.

Control strategy

By implementing control measures to keep CMPs with in the defined limits, (X_1: 0.9M to 1.1 M and X_2: 4.9 mL to 5.1 mL) the method that align with the principles of quality control and desired criteria for accuracy, precision was selected. Other variables relating to machine, material, men and environment having low risk were controlled. The optimized spectrophotometric method conditions were outlined in Table 4.

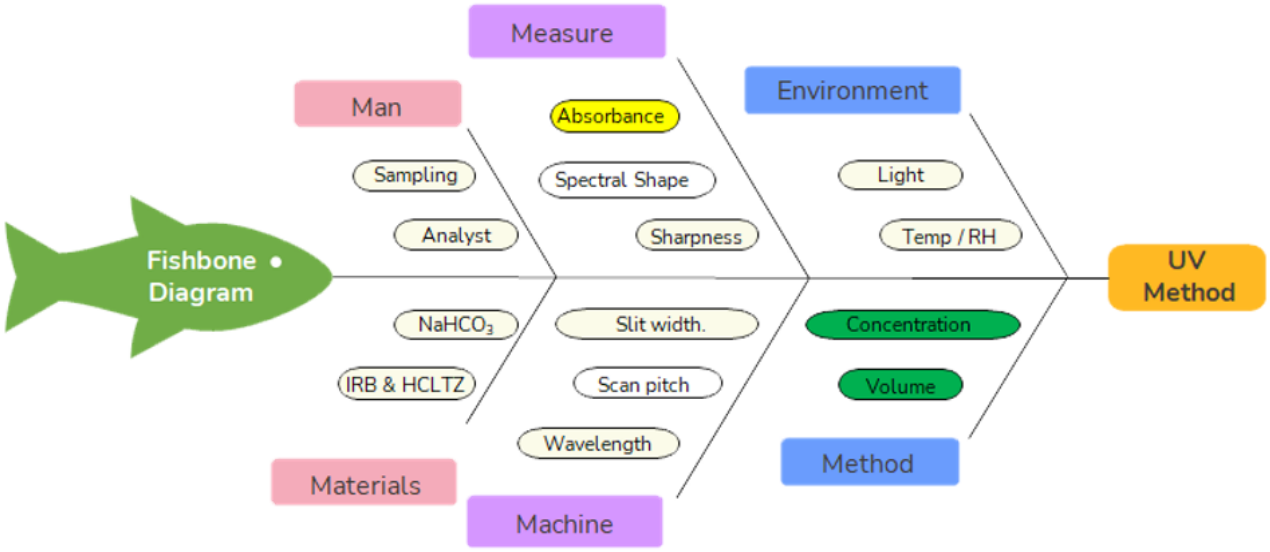

Figure 2: Ishikawa Fishbone diagram.

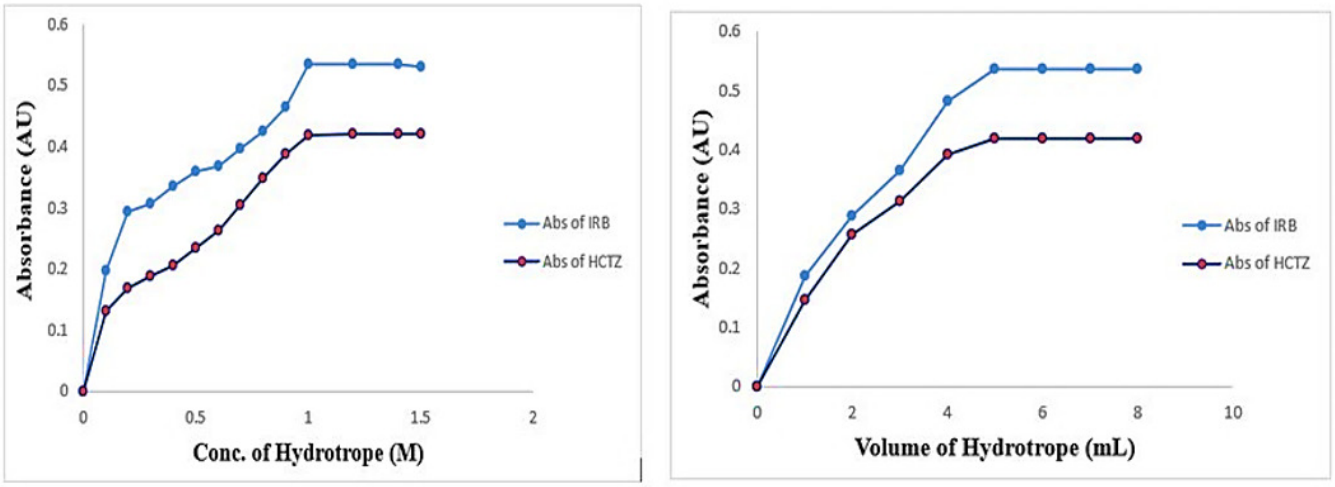

Figure 3: Effect of Concentration and volume of hydrotrope on absorbance of two drugs.

Table 1: Effect of concentration and volume of hydrotrope on absorbance of two drugs.

Conc. of Hydrotrope (M)	Abs of IRB	Abs of HCTZ	Volume of Hydrotrope (mL)	Abs of IRB	Abs of HCTZ
0.1	0.197	0.132	1	0.186	0.146
0.2	0.294	0.169	2	0.289	0.256
0.3	0.306	0.188	3	0.364	0.314
0.4	0.335	0.205	4	0.483	0.392
0.5	0.359	0.234	5	0.536	0.419
0.6	0.368	0.263	6	0.536	0.419
0.7	0.397	0.304	7	0.536	0.421
0.8	0.426	0.349	8	0.536	0.419
0.9	0.464	0.389	9	0.536	0.420
1	0.534	0.419	10	0.536	0.419
1.2	0.535	0.421			
1.4	0.534	0.420			
1.5	0.531	0.421			

Table 2: Selected factors with their levels and responses considered for DoE.

Variable	Variable Name	Units	-α	-1	0	+1	+α	Responses
X_1	Concentration of hydrotrope	M	0.29289	0.5	1	1.5	1.70711	Y_1: Abs of IRB
X_2	Volume of hydrotrope	mL	3.58579	4	5	6	6.41421	Y_2: Abs of HCTZ
Constraints: X_1: Not exceeding solubility limit; X_2: Maintained within stable volume range.								

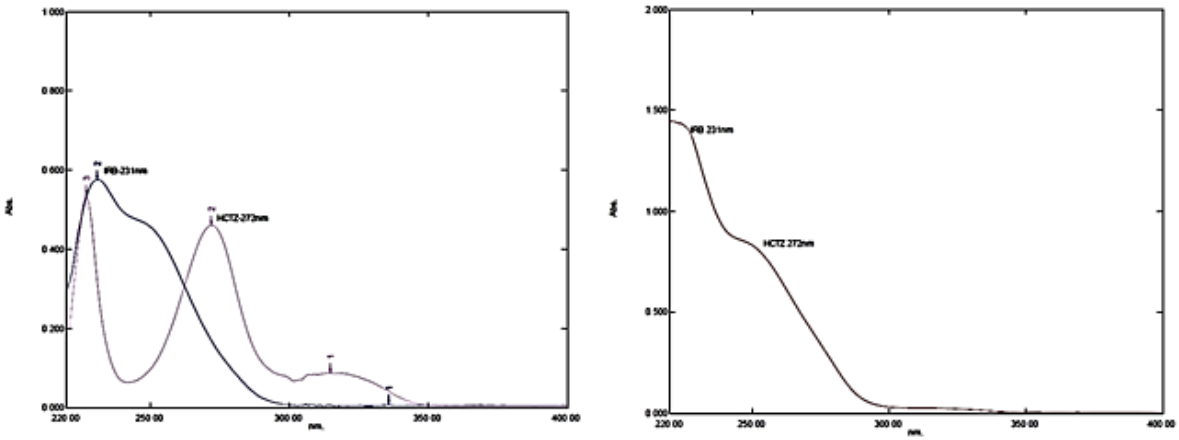

Figure 4: UV Spectra of (A) Standard drugs (B) Commercial sample.

Method validation

Performance characteristics, as per ICH Q2 (R2)[78] specificity, linearity, Limit of Detection (LOD), Limit of Quantitation (LOQ), accuracy, precision, and robustness were considered to validate the developed method.

Specificity

To evaluate the specificity of developed analytical method, blank and placebo solution was scanned between 220 to 400 nm. There should be no interference from blank at selected wavelength. Additionally, stress studies performed in acidic, alkaline, oxidation, thermal degradation conditions showed no effect on method performance.

Linearity and Range

To evaluate the linearity, from tablet sample solution, series of concentrations of 5.0, 10.0, 15.0, 20.0, 25.0 and 30.0 mcg/mL for IRB and 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25 and 2.5 mcg/mL for HCTZ were prepared and their absorbance were measured at 231 nm for IRB and 272 nm for HCTZ.

Table 3: CCD runs and their Responses.

Run	Space type	X_1	X_2	Y_1	Y_2
1	Factorial	0.5	4	0.297	0.312
2	Axial	1	6.4142	0.539	0.505
3	Axial	1	3.5857	0.515	0.405
4	Center	1	5	0.536	0.417
5	Factorial	1.5	4	0.542	0.509
6	Center	1	5	0.536	0.418
7	Factorial	1.5	6	0.540	0.463
8	Center	1	5	0.536	0.417
9	Axial	1.7071	5	0.541	0.418
10	Center	1	5	0.535	0.417
11	Factorial	0.5	6	0.298	0.316
12	Axial	0.2928	5	0.216	0.329
13	Center	1	5	0.532	0.416

Accuracy

It was assessed by recovery studies. The sample with known concentrations of standard solutions were analysed using the optimized method. The content of IRB and HCTZ was determined at three levels, 80%, 100%, and 120% of the working concentrations, in triplicate, resulting in 9 determinations to evaluate the method's accuracy.

Precision

Precision was assessed through six replicate analysis on the same day (n=6, intra-day) and on different days (n=6, inter-day).

LOD and LOQ

Slope and the standard deviation method were used to determine these parameters.

Robustness

It was assessed by deliberately changing the experimental condition of hydrotrope concentration by ±0.1 M from the optimized value. The absorbance of the solutions was measured under these modified conditions to evaluate the method's reliability and consistency against small, deliberate variations.

RESULTS

A simple, rapid, precise, and novel QbD-assisted UV spectrophotometric technique for the simultaneous quantitation of IRB and HCTZ in tablets developed and validated. Hydrotropy was employed as a solubility enhancement technique to address the solubility limitations of both drugs. Unlike previous methods that primarily used methanol or acetonitrile-based solvents, the present study employed a hydrotropic solvent system, improving environmental sustainability and safety. The method follows

Table 4: Optimized spectrophotometric method conditions.

Parameter	Optimized condition
Technique	UV Spectrophotometry
Hydrotrope	Sodium bicarbonate
Concentration, M	0.9-1.1
Volume, mL	4.9-5.1
Wavelength, nm	231 for IRB; 272 for HCTZ

systematic QbD principles, starting with the creation of a knowledge space. Understanding the physico-chemical properties of drugs such as their distinct log P values (IRB: ~4.3, HCTZ: ~1.6), molecular weights (IRB: ~428.5 g/mol, HCTZ: ~297.74 g/mol), guided the selection of UV spectrophotometry as the analytical technique. These properties directly influenced solvent selection, wavelength optimization, and sample preparation, ensuring method accuracy and precision. The ATP defined for this method focused on achieving an accuracy of 98-102% and precision with %RSD NMT 2%. Key method performance characteristics such as specificity, accuracy, precision, linearity, LOQ, LOD, and robustness were established as Analytical Method Performance Characteristics (AMPCs). Sodium bicarbonate was identified as the optimal hydrotropic solvent based on solubility studies. A concentration range of 0.1-1.5 M was tested, with the best results observed at 1M. Similarly, the volume of hydrotrope was screened between 1 and 10 mL, with 5 mL providing the highest sensitivity (Table 1 and Figure 3). Risk assessment was conducted using the Ishikawa fishbone diagram, identifying concentration (X_1) and volume (X_2) of hydrotrope as CMPs affecting the responses, absorbance of IRB (Y_1) and HCTZ (Y_2).

A CCD was employed to evaluate the interaction of these CMPs on method responses. Results from 13 experimental trials showed significant statistical correlations between CMPs and CAAs, as

Table 5: ANOVA table for quadratic model-Response 1 and Response 2.

Source	Response 1: Abs of IRB					Response 2: Abs of HCTZ					
	SS	d_f	MS	F	*p*	SS	d_f	MS	F	*p*	
Model	0.1644	5	0.0329	91.94	< 0.0001	0.0364	5	0.0073	4.83	0.0314	Significant
A-Molarity	0.1120	1	0.1120	313.28	< 0.0001	0.0276	1	0.0276	18.29	0.0037	
B-Volume	0.0001	1	0.0001	0.3794	0.5574	0.0012	1	0.0012	0.8189	0.3956	
AB	2.25×10^{-6}	1	2.25×10^{-6}	0.0063	0.9390	0.0006	1	0.0006	0.4142	0.5403	
A^2	0.0522	1	0.0522	146.00	< 0.0001	0.0045	1	0.0045	2.95	0.1293	
B^2	0.0011	1	0.0011	2.98	0.1280	0.0017	1	0.0017	1.10	0.3294	
Residual	0.0025	7	0.0004			0.0106	7	0.0015			
Lack of Fit	0.0025	3	0.0008	276.76	0.062	0.0106	3	0.0035	7039.61	0.059	Not Significant
Pure Error	0.0000	4	3.0×10^{-6}			2.0×10^{-6}	4	5.0×10^{-7}			
Cor Total	0.1669	12				0.0470	12				
Fit Statistics											
	Std. Dev.	Mean	%C.V.	R^2	Adjusted R^2	Predicted R^2	Adeq Precision				
Y_1	0.0189	0.4741	3.99	0.9985	0.9974	0.9893	28.27				
Y_2	0.0388	0.4109	9.45	0.9951	0.9914	0.9822	6.902				

presented in Table 5. The quadratic regression equations derived were given as follows.

$$Y1=0.535+0.1183X1+0.0041X2-0.00075X1X2-0.0866X1^2-0.0124X2^2$$

$$Y2=0.417+0.0587X1+0.0124X2-0.0125X1X2-0.0253X1^2+0.0154X2^2$$

Response surface plots (Figure 5) illustrated the impact of CMPs on responses, confirming the significant effects of X_1 and X_2. The model F-value of 91.94 ($p<0.05$) indicated strong statistical significance. Optimization was achieved using numerical method (Figure 7), targeting absorbances of Y_1=0.5 and Y_2=0.4 by adjusting X_1 (0.5-1.5 M) and X_2 (4.0-6.0 mL). Multidimensional optimization within the MODR highlighted 1 M sodium bicarbonate with 5 mL volume as an optimal condition was shown in Figure 6. The final method (Figure 7) was verified and aligned with ATP criteria, demonstrating excellent linearity, precision, and robustness for two drugs in their marketed samples. Control strategies implemented through Design Expert 13.0 ensured consistencies and reliability under defined conditions. Specificity was confirmed as the blank showed no interference at the selected wavelengths, 231 nm for IRB and 272 nm for HCTZ. Linearity was established with a correlation coefficient >0.995 for the two drugs in marketed samples demonstrating the method's accuracy over the tested concentration ranges, as shown in Figure 8. The method obeyed Beer's law, ensuring consistent quantification of IRB and HCTZ in tablets. Accuracy was evaluated by recovery studies at 80%, 100%, and 120% levels, with recoveries between 98.5-101% for IRB and 98.7-102% for HCTZ, meeting the

Table 6: IRB and HCTZ Data of optical Characteristics and validation parameters.

Parameters	IRB	HCTZ
λ_{max}, nm	231	272
Molar absorptivity, L mol^{-1} cm^{-1}	0.1531×10^5	0.0993×10^6
Sandell's sensitivity, mcg/cm^2	0.03344	0.002982
Beers law limit, mcg/mL	5.0-30.0	0.75-2.5
Correlation coefficient	0.9996	0.9991
Regression equation	y=0.0299x+0.0899	y=0.3353x+0.0053
Specificity	No interference	No interference
Accuracy, (% recovery, Mean±SD)		
At 80% level	99.16±0.12	100.08±0.05
At 100% level	100.04±0.08	99.13±0.19
At 120% level	101.02±0.17	99.02±0.64
Precision, % RSD		
Repeatability	0.4542	0.4892
Intermediate precision	0.6354	0.6419
LOD, mcg/mL	0.1531	0.0184
LOQ, mcg/mL	0.4639	0.05598
Robustness, % RSD	0.4716	0.4684

acceptance criteria. The slight improvement in the recovery values in the current method demonstrate its reliability in accurate drug estimation, likely due to optimized hydrotropic solubilization.

Precision, assessed as repeatability and intermediate precision, showed %RSD values below 2% for both intra-day and inter-day variations, confirming the method's reliability. The LOD and LOQ, calculated based on the slope and standard deviation method ensures sensitivity for detecting and quantifying these drugs. The LOD and LOQ values in the developed method were 0.1531 µg/mL and 0.4639 µg/mL for IRB and 0.0184 µg/mL and 0.05598 µg/mL for HCTZ, respectively. The significantly lower LOD and LOQ values compared to previously reported methods highlight the method's enhanced sensitivity, making it a more reliable approach for detecting trace amounts of IRB and HCTZ in pharmaceutical formulations. Robustness was tested by varying the hydrotrope concentration (±0.1M), and the %RSD values remained below 2%, indicating the method's resilience to small variations. optical characteristics and validation parameters were depicted in Table 6 shows method reliability.

DISCUSSION

The developed UV spectrophotometric method for the simultaneous quantitation of IRB and HCTZ aligns with the principles of QbD, ensuring robustness and reproducibility. By addressing solubility challenges through hydrotropy, the method overcomes limitations commonly associated with poorly soluble drugs. The selection of sodium bicarbonate as the hydrotropic agent was supported by systematic solubility studies, with optimal conditions determined through a structured risk assessment and DoE. The application of CCD enabled the identification and optimization of CMPs, ensuring precise control over method performance. The significant interaction between concentration and volume of hydrotrope on the absorbance responses depicts the importance of risk during method development. The derived quadratic models and response surface plots provided information about the influence of critical parameters that facilitates the method optimization within the MODR. The method's validation, as per ICH Q2 guidelines, demonstrated its specificity, linearity, accuracy, precision and Robustness. The established analytical parameters, including LOD, LOQ, and optical characteristics, further enhance the applicability of method in pharmaceutical analysis.

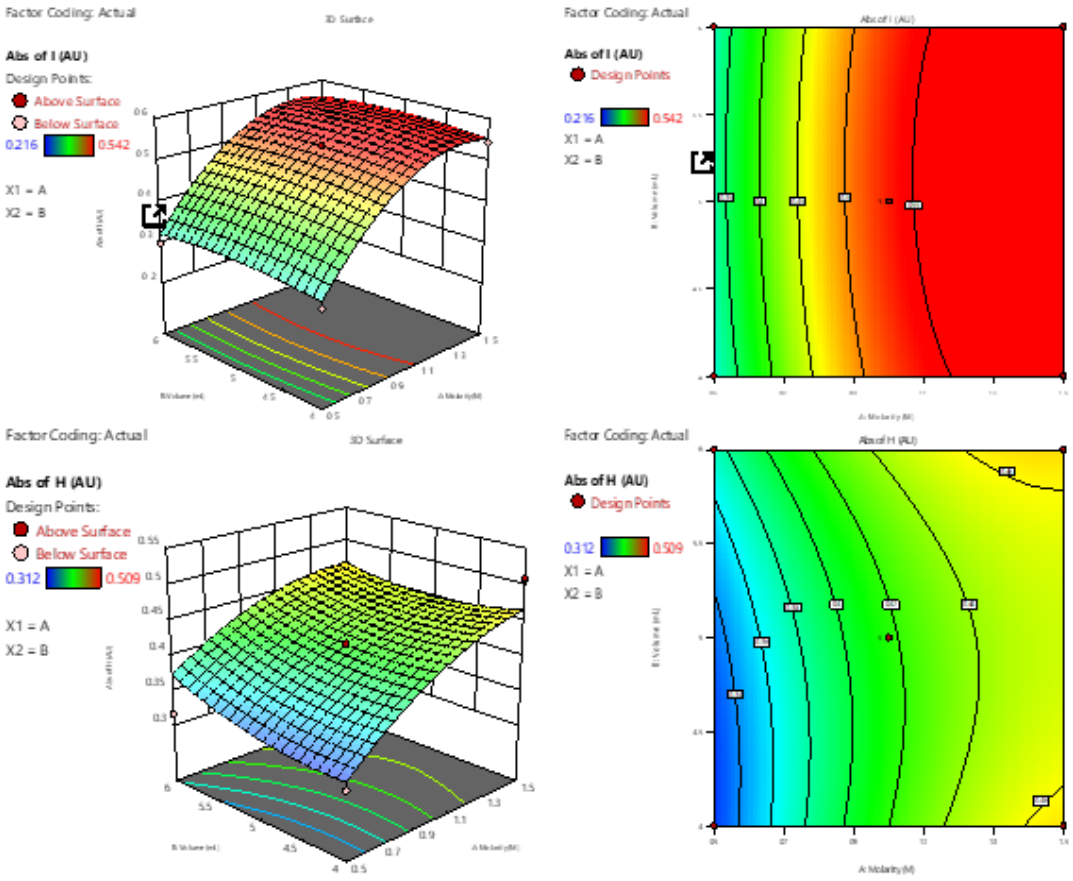

Figure 5: 3D and 2D plots for the selected responses Y_1 & Y_2.

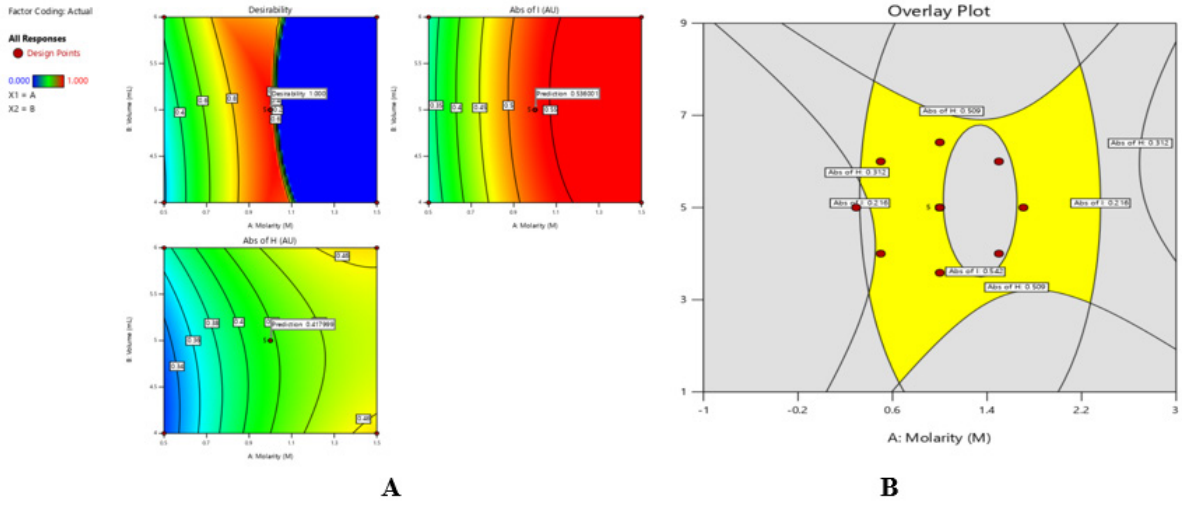

Figure 6: (A) 2D plots and (B) Overlay plot of optimized method.

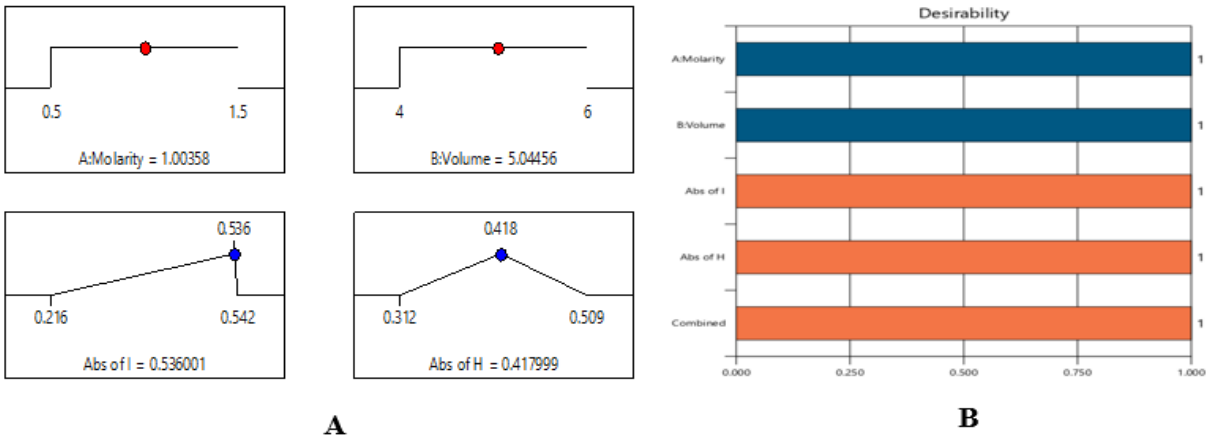

Figure 7: (A) Ramp plots (B) Bar graph for desirability analysis.

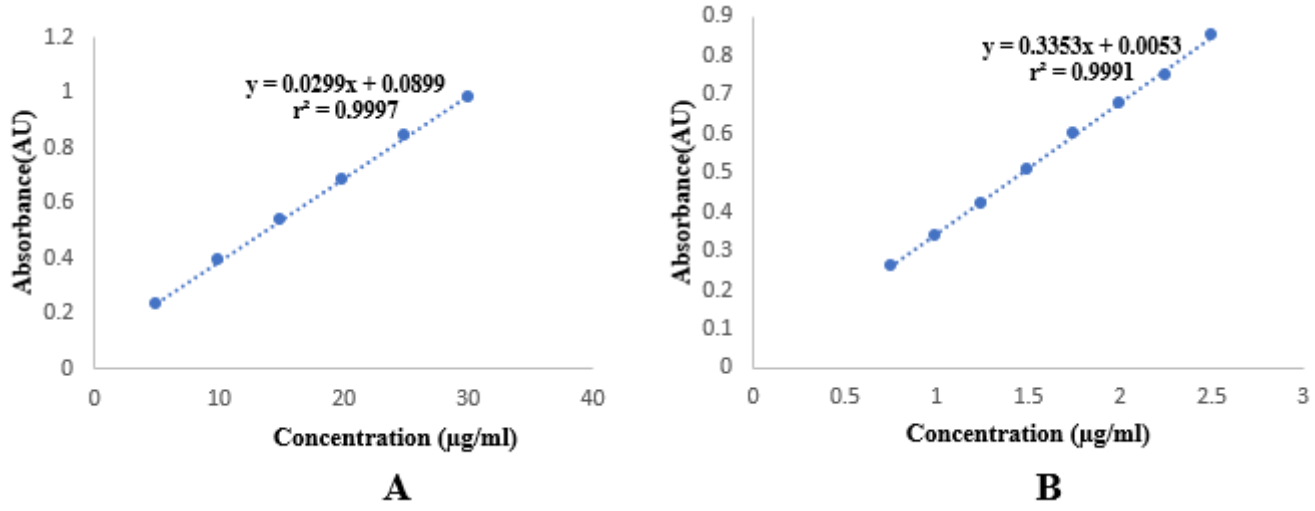

Figure 8: Linearity curves of (A) IRB and (B) HCTZ.

CONCLUSION

The developed method rooted in QbD principles and utilizing 1M Sodium bicarbonate as a hydrotropic agent, offers a cutting-edge approach for quantifying IRB and HCTZ in both bulk and tablet forms. This innovative method not only addresses the challenge of estimating poorly water-soluble drugs but also reduces the dependence on organic solvents. By employing a non-toxic, non-volatile hydrotropic agent, the method emerges as a cost-effective and eco-friendly solution for drug analysis. Validation conducted according to ICH Q2 (R1) guidelines demonstrates exceptional reproducibility and accuracy, supported by robust statistical parameters and recovery test data.

Furthermore, analysis of authentic samples confirms the absence of interference from common additives or auxiliary substances. With the integration of QbD principles, this method not only ensures analytical reliability but also underscores a commitment to continuous improvement and optimization in pharmaceutical quality control practices.

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ABBREVIATIONS

ANOVA: Analysis of variance; **AQbD:** Analytical quality by design; **AMPCs:** Analytical Method Performance Characteristics; **ATP:** Analytical target profile; **CAAs:** Critical analytical attributes; **CMPs:** Critical method parameters; **DoE:** Design of experiments; **HPTLC:** High Performance Thin Liquid Chromatography; **HCTZ:** Hydrochlorothiazide; **ICH:** International Conference on Harmonisation; **IRB:** Irbesartan; **LC-MS:** Liquid Chromatography-Mass Spectrometry; **M:** Molarity; **MODR:** Method operable design region; **MS:** Mean square; **nm:** Nano meters; **LOD:** Detection limit; **LOQ:** Quantitation limit; **QbD:** Quality by design; **RA:** Risk assessment; **r^2:** Correlation coefficient; **RP-HPLC:** Reverse phase High Performance Liquid Chromatography; **SS:** sum of square, **UPLC:** Ultra-Performance Liquid Chromatography; **UV:** Ultra violet; **%RSD:** Relative standard deviation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

No animals/humans were involved in this work.

SUMMARY

A QbD-driven UV spectrophotometric method was developed for the simultaneous quantitation of IRB and HCTZ in bulk and tablet formulations, utilizing 1M sodium bicarbonate as a hydrotropic agent to enhance solubility. The method, optimized through DoE and validated as per ICH Q2 guidelines, which demonstrated robustness, accuracy, and eco-friendliness by reducing the use of organic solvents. This approach ensures reliable quantification of poorly soluble drugs, emphasizing cost-effectiveness and sustainability in pharmaceutical analysis.

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