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RESEARCH ARTICLE

Box-Behnken Design-Based Response Surface Modelling for the Optimized Greener Spectrophotometric Methodology to Determine Betahistine in Pharmaceutical Formulations

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ABSTRACT

Betahistine is a novel drug used to treat vertigo. The research focuses on developing and optimizing a simple, environmentally sustainable spectrophotometric approach for the analysis of BH in tablet formulations. The present investigation is based on the reaction between BH and potassium iodide and potassium iodate, monitored by Ultraviolet-Visible spectrophotometry at 352 nm. The most influential variables were optimized using response surface methodology via Box–Behnken design, resulting in reduced chemical, energy, and analysis time, and ultimately the analysis cost. Environmental sustainability was assessed using Analytical Eco-Scale (92), Analytical Greenness (0.72), Blue Applicability Grade Index (72.5) and Environmental and Practical Performance Index (89.1) metrics, which confirmed outstanding greenness compared with other reported methods. The method was validated as per International Conference on Harmonization (ICH) guidelines. The linearity, LOD and LOQ values were 2.5–12.5, 1.25 and 3.45 μg/mL, respectively. The accuracy and precision were also excellent within the range. Moreover, the simplicity, reproducibility, and low-cost instrumental analysis of the drug enhance its wide applicability and provide a reliable solution for quality control in BH commercial formulations, chemical and pharmaceutical research laboratories, and academicians.

Keywords: Betahistine, UV-visible spectrophotometry, KI, KIO3, Box–Behnken design, Greenness method, AGREE, BAGI, AES, EPPI

1. Introduction

Betahistine (BH) is an antivertigo agent used to improve vertigo symptoms and is also a Class I drug in the Biopharmaceutics Classification System, which is highly soluble and highly permeable [1]. This may help with balance problems and is related to Meniere's disease [2]. BH is chemically known as N-methyl-2-(pyridin-2-yl) ethan-1-amine, which is a highly hygroscopic particle, very soluble in water and acidic in nature [1]. With advances in technology and innovative ideas in the pharmaceutical industry, it is possible to efficiently control toxic impurities and protect the human community during the development of new pharmaceutical drugs. Analytical methods could play a vital role in this regard, which are essential at every stage of drug development. Several analytical techniques, both traditional and instrumental, such as titrimetric, chromatography, spectroscopy, and electrophoresis, are used to ensure accurate determination [3]. Henceforth, the development of rigorous analytical approaches is crucial to ensure the efficacy and safety of active pharmaceutical ingredients and excipients, and to determine product quality in the pharmaceutical industry [4–6].

The literature survey showed the involvement of different analytical techniques for the quantification of BH in bulk, pharmaceutical formulation and

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biological fluids, among them are Ultraviolet (UV) spectrophotometry [7–9], UV–Visible spectrophotometry (UV-Vis) [10–12], conductometry [13], thin–layer chromatography (TLC) [14], high–performance liquid chromatography (HPLC) [14–19], fluorometry [20], Voltammetry [21] and LC–Mass spectrophotometry (LC–MS) [22, 23]. Among them, spectrophotometric analysis is more attractive, with a lower-cost setup that can also help to quantify BH in different matrices. UV analysis is usually performed using HCl as the solvent [7, 8] or methanol with phosphate buffer [9], which is contrary to environmentally friendly procedures. The developed UV-Vis procedure [10] used methyl orange and bromophenol blue with chloroform, whereas other reported methods [11] utilized 4–chloro–7–nitrobenzofurazan in the presence of disodium hydrogen phosphate, typically used for 30 minutes at 90 °C for each analysis. Donchenko et al. also enhanced the BH determination using 1,2 naphthoquinone–4–sulphonate [12]. All the reported spectrophotometric procedures are quite satisfactory in terms of linearity and quantification range. However, they are slightly deviated from the greener methodology. Therefore, it is necessary to adopt an accurate, greener analysis method. The proposed methodology utilized potassium iodide (KI) and potassium iodate (KIO_3) in distilled water only, without any other solvent, acid, or buffer. The procedures were also optimized using the response surface methodology (RSM)–Box–Behnken design (BBD). The RSM–BBD combination not only reduced the number of experimental trials but also decreased the amount of reagents, ultimately reducing the analysis cost [24–31].

The literature survey indicated that there is no procedure reported to determine BH's greenness assessment using any greener tools, which is very important for method development. The developed method's outcome as follows: (a) Proposed procedures' greener values were determined using the Analytical Eco-Scale (AES) [32], Analytical Greenness (AGREE) [33], Blue Applicability Grade Index (BAGI) [34] and Environmental and Practical Performance Index (EPPI) [35]; (b) Compared greenness assessment with the reported methods [9, 12, 15, 22]; (c) The developed method validated as per ICH guidelines; (d) Statical comparison performed using student's t–test and F–test; (e) Optimized the method using RSM-BBD. Overall, the current investigation is a simple, susceptible, robust, and eco-friendly spectrophotometric method. The broad applicability of this profitable approach might serve as an alternative method for research laboratories and academic settings. It could be employed in medical and quality-control research laboratories in emerging nations to quantify BH in bulk, tablet formulations and biological fluids.

2. Materials and Methods

2.1. Instruments and software

The UV-Vis spectrophotometer utilized throughout the experiments was a Jenway (Model 6300, Staffordshire, UK), which included a 10 mm glass cuvette for all spectral determination. Microsoft Excel 2013 (v. 15.0, Microsoft Corporation, USA) was used for data and statistical analyses. The RSM–BBD was used to optimize the experimental variables using Design-Expert software (Version 13.0.5.0, Free Trial, Stat-Ease Inc., USA). AGREE, BAGI, EPPI software's online version was used to evaluate the proposed method with the reported procedures.

2.2. Chemicals and reagents

The BH formulation brand name is Betagen, manufactured by Riyadh Pharma, Saudi Arabia, with batch no. 24DD35 was bought from the local pharmacy. KI and KIO_3 were purchased from Sigma-Aldrich, USA. All the chemicals and reagents used were of analytical grade.

2.3. Pharmaceutical and reagents solution preparation

Five BH tablets, each containing 24 mg, were ground into a fine powder using a mortar and pestle, then transferred to a 100 ml volumetric flask and made up to volume with distilled water. The mixture was shaken for 10–15 minutes and filtered with Whatman paper to remove insoluble material. An appropriate portion was further diluted with distilled water to obtain a 100 μg/mL and then further diluted as per the RSM-BB design. The KIO_3 (1×10^{-3} mol/L) and KI (2×10^{-2} mol/L) solutions were prepared as stock solutions in distilled water and further diluted according to the RSM-BB design.

2.4. Variables optimization studies

The absorbance of the product was highly dependent on the independent parameters, and three key variables were identified as affecting it in the analysis of BG in tablet formulations. The RSM–BBD optimized these variables at three levels (Table 1). This experimental plan is a convincing tool that helps to reduce the amount of reagents, decrease analysis

Table 1. Levels of the key variables for RSM-BBD matrix.

Key Variables	Unit	Symbol	Levels			Response
			Low	Medium	High	
Reaction time	Min	A	3	6	9	Absorbance
Potassium Iodate	M	B	2.5×10^{-6}	2.25×10^{-5}	4.75×10^{-5}	
Potassium Iodide	M	C	1.0×10^{-4}	5.5×10^{-4}	1.2×10^{-3}	

Table 2. The RSM-BBD design matrix and experimental data to quantify NAG in pharmaceutical tablets.

Runs	A: Reaction time	B: Potassium Iodate	C: Potassium Iodide	Absorbance
1	3	0.0000475	0.00065	0.104
2	3	0.0000025	0.00065	0.785
3	3	0.000025	0.0001	0.354
4	9	0.0000475	0.00065	0.328
5	6	0.000025	0.00065	0.785
6	6	0.0000475	0.0001	0.785
7	6	0.000025	0.00065	0.224
8	6	0.000025	0.00065	0.309
9	3	0.000025	0.0012	0.132
10	6	0.0000025	0.0001	0.294
11	6	0.0000025	0.0012	0.397
12	9	0.000025	0.0012	0.637
13	6	0.000025	0.00065	0.785
14	6	0.000025	0.00065	0.785
15	9	0.000025	0.0001	0.542
16	6	0.0000475	0.0012	0.471
17	9	0.0000025	0.00065	0.123

time, and costs. Design-Expert software enhanced the BBD matrix, which included 17 experimental runs, and the data were fitted into a second-degree polynomial equation to determine the response model coefficients.

2.5. Proposed method for BH determination

An aliquot of 1 mL of BH solution (100 μg/ml) was transferred to a series of 20 mL volumetric flasks. Different volumes of KI (2×10^{-2} mol/L) and KIO_3 (1×10^{-3} mol/L) as per the RSM–BBD design were added to each flask, made up to the calibration mark with distilled water, and then waited as per the design. The measurements were performed at 352 nm against a reagent blank comprising all components except BH. The BBD matrix was used to determine BH in pharmaceutical formulations and to optimize the variables (Table 2).

2.6. Validation

2.6.1. Specificity and selectivity

The ability of the method to determine accurately and specifically the analyte of interest in the presence of other components in a sample matrix (that may be expected to be present in the sample matrix) under the stated conditions of the test.

2.6.2. Linearity

The ability of the method to obtain test results proportional to the concentration of the analyte. The linearity was determined by dividing the response by the respective concentrations and plotting these 'relative responses' as a function of the concentration, on a log scale. The line obtained should be horizontal over the full linear range, with a positive deviation at low concentrations and a negative deviation at high concentrations.

2.6.3. Accuracy and precision

The accuracy of an analytical method is the extent to which test results generated by the method and the true value agree. The precision of a method is the closeness of agreement between independent test results obtained under stipulated conditions.

2.6.4. Limit of detection (LOD)

The LOD value is the experimental value which is higher than the uncertainty associated with it. As well, it also analyses the lowest concentration that can be detected but not essentially quantified in a sample. The LOD can be calculated with the help of standard deviation (S_O) and slope (b) of the calibration line, and using the following formula:

- $LOD = 3.3 \times S_O/b$

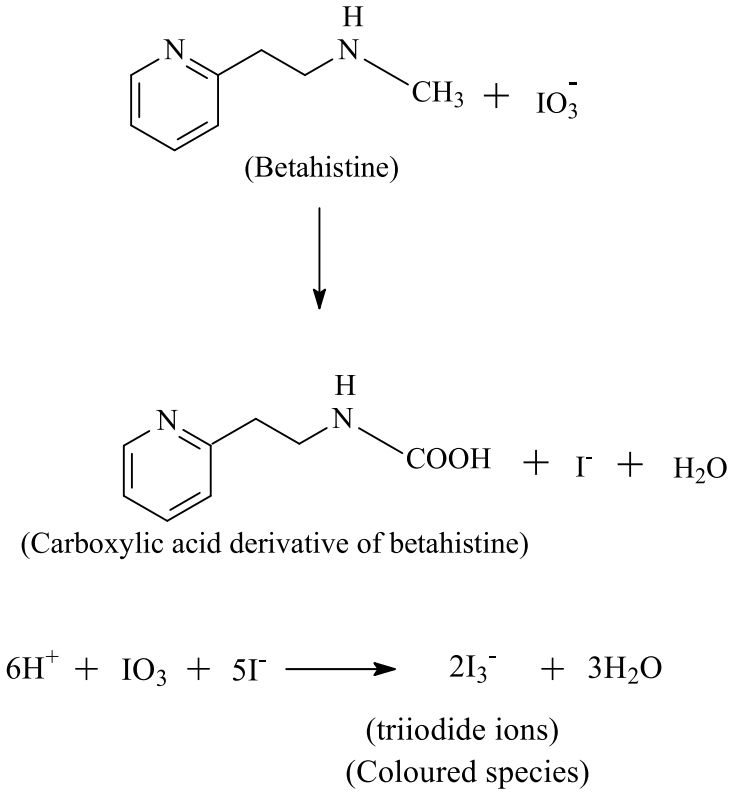


Fig. 1. Reaction mechanism of the proposed spectrophotometric method.

2.6.5. Limit of quantitation (LOQ)

The LOQ value is the analyte's lowest concentration that can be assessed quantitatively with realistic accuracy and precision values. LOD can be determined using the following formula:

- $LOQ = 10.0 \times S_O/b$

2.6.6. Ruggedness

The ruggedness parameter of the method can be determined by making small changes in the ecological conditions, which are made by the analytical process and observing the performance of the analytical process.

2.6.7. Robustness

The performance of the analytical process remains unaffected with the small deliberate differences in the procedures, which offers a hint of its consistency during usual practice.

3. Results and discussion

3.1. Proposed spectrophotometric mechanism

Literature reports that in the presence of organic/inorganic acids, the interaction of KI and KIO_3 solutions produces iodine, which, in an aqueous solution, reacts with an iodide ion to produce the triiodide ion, maximally absorbed at 290 and 360 nm. The BH's terminal methyl group ($-CH_3$) was converted to a carboxylic acid derivative due to oxidation. In the current investigation, the oxidation of BH with iodate formed the carboxylic acid derivative. Then the triiodide ion is generated by undergoing iodide is oxidized by iodate in the presence of acid form (Fig. 1), which maximally absorbs at 352 nm [36].

3.2. Method validation

3.2.1. Specificity

The specificity of the developed procedures was determined in pharmaceutical formulations. The tablets were crushed and produced a fine powder, which was dissolved in distilled water to prepare 10 μg/mL. The absorbance was measured and determine % recovery of the drug was found to be 99.85%, which indicated that the excipients such as mannitol, lactose monohydrate, microcrystalline cellulose, stearic acid, povidone, citric acid and povidone do not have any interference with the results.

3.2.2. Linearity

The linearity determination of BH established the method's appropriateness for its quantitation, in

Table 3. Determine the accuracy and precision of the proposed method using intraday and interday tests.

	Taken (μg/mL)	Found ± SD (μg/mL)	%Recovery	%RSD	SAE	CL
Intraday	4	3.947 ± 0.049	98.675	1.242	0.022	0.060
	8	7.918 ± 0.055	98.975	0.695	0.025	0.068
	12	11.985 ± 0.043	99.875	0.359	0.019	0.053
Interday	4	3.925 ± 0.053	98.125	1.350	0.024	0.066
	8	7.901 ± 0.051	98.763	0.646	0.023	0.063
	12	11.911 ± 0.075	99.258	0.630	0.034	0.093

[a]Mean of five analyses, RSD relative standard deviation for the five determinations, SAE standard analytical error, confidence limit at 95% confidence level and four degrees of freedom (t = 2.776).

which measured responses are directly proportional to the concentration. The obtained data were used to estimate the slope, intercept, and the correlation coefficient of the linear regression analysis within the linearity range. The linear dynamic range was found to be within the range of 2.5–12.5 μg/mL with a correlation coefficient of 0.99.

3.2.3. Accuracy & precision

The proposed method's accuracy and precision were determined at lower, middle and higher concentrations, such as 4, 8 and 12 μg/mL. The tabulated data (Table 3) showed the % recovery results were 98.75–99.45 % that indicate the accuracy value, whereas the precision results were demonstrated by % relative standard deviation (%RSD) that were within the limit of ±2%.

3.2.4. LOD & LOQ

The LOD and LOQ results are excellent, which are 1.25 and 3.45 μg/mL, respectively, from the linearity experiment wherein a lower concentration of BH. The %RSD for 6 replicate injections of BH is found to be 0.24%.

3.2.5. Ruggedness & robustness

Ruggedness is executed by assessing the BH at 10 μg/mL in different locations. The % RSD was found to be 0.45%. The robustness of the method was tested by making deliberate changes in the conditions, such as reaction time. The outcome of the findings demonstrated that there was no variation in the % RSD found, and absorbance was also not affected.

3.3. RSM–BBD variables optimization and surface plots

The relationship between dependent and independent variables was established using the mathematical RSM–BBD model. The output responses, which were dependent variables with varying independent parameters, were used to control for the effects of the most significant independent factors, thereby optimizing the output responses and elucidating interactions among them. ANOVA that assessed the model *F*-value, lack of fit *F*-value, R^2, and PRESS value was applied in assessing the factor's impact, interactions and process optimization (Tables 4 and 5). These variables were statistically evaluated across 17 experimental runs using the BB Design. The percent contribution of the models is also represented (Fig. 1). Based on the results, a second-order polynomial equation was developed and validated. Equation 1 shows this polynomial, combining the evaluated experimental variables.

$$\text{Absorbance} = 0.561 + 0.0495\,A - 0.0494\,B - 0.0241\,C + 0.0575\,AB - 0.0425\,AC + 0.0918\,BC - 0.0976\,A^2 - 0.1099\,B^2 - 0.0744\,C^2 \quad (1)$$

The plots of predicted vs. actual represented the model's predictions as outcomes (Y-axis) versus experimental data (X-axis) to assess model fit. When y and x values are the same, the model is idealized as a straight line from the bottom-left to the top-right. The comparison of actual and predicted values (Fig. 3a) showed close agreement, with x and y values being nearly identical, supporting the model's validity and demonstrating that the experimental results are highly consistent. Whereas the residual vs. predicted plot shows predictions against model errors, providing a fundamental, indicative tool for verifying assumptions of linearity and constant variance. A linear plot indicates normally distributed error terms. In this study, the plot of externally studentized residuals (Fig. 3b) formed a straight line, confirming normality and independence of residuals. A normal probability plot assesses whether the response follows a normal distribution by comparing theoretical and actual percentiles (Fig. 3c). The graph of residuals vs. run, in which the data were collected, shows the model's errors against the run or order, tests for temporal and independence tendencies, and ideally exhibits random scatter around zero (Fig. 3d). The Box-Cox plot (Fig. 3e) facilitates finding the best power transformation (λ) to make the experimental data more usual, fitting ANOVA's theories, by

Table 4. ANOVA of the response surface quadratic model to evaluate BH in tablet formulations.

Source	Sum of squares	df	Mean square	F-value	p-value	PC%
Model	0.3588	9	0.0399	1.12×10^{6}	< 0.0001	
A-Reaction time	0.0196	1	0.0196	5.49×10^{5}	< 0.0001	5.83
B-Potassium Iodate	0.0195	1	0.0195	5.46×10^{5}	< 0.0001	5.80
C-Potassium Iodide	0.0047	1	0.0047	1.30×10^{5}	< 0.0001	1.40
AB	0.0132	1	0.0132	3.70×10^{5}	< 0.0001	3.92
AC	0.0072	1	0.0072	2.02×10^{5}	< 0.0001	2.14
BC	0.0337	1	0.0337	9.43×10^{5}	< 0.0001	10.01
A^2	0.1644	1	0.1644	4.60×10^{6}	< 0.0001	48.87
B^2	0.0508	1	0.0508	1.42×10^{6}	< 0.0001	15.10
C^2	0.0233	1	0.0233	6.52×10^{5}	< 0.0001	6.93
Residual	2.5×10^{-7}	7	3.57×10^{-8}			
Lack of Fit	2.5×10^{-7}	3	8.33×10^{-8}			
Pure Error	0.0000	4				
Cor Total	0.3588	16				

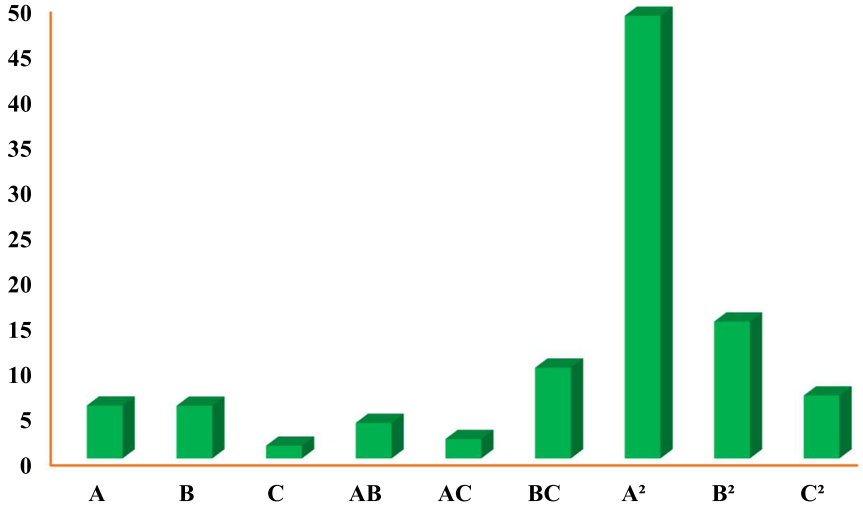


Fig. 2. Percent contribution of independent variables to establish the model.

Table 5. Sequential fitting model to determine BH in pharmaceutical formulations.

Sequential model sum of squares					
Source	Sum of Squares	df	Mean Square	F-value	p-value
Mean vs Total	2.47	1	2.47		
Linear vs Mean	0.0438	3	0.0146	0.6019	0.6252
2FI vs Linear	0.0541	3	0.0180	0.6913	0.5779
Quadratic vs 2FI	0.2610	3	0.0870	2.44×10^{6}	< 0.0001
Cubic vs Quadratic	2.5×10^{-7}	3	8.33×10^{-8}		
Residual	0.0000	4	0.0000		
Total	2.83	17	0.1665		
Model summary statistics					
Source	Std. Dev.	R^2	Adjusted R^2	Predicted R^2	Press
Linear	0.1557	0.1220	–0.0807	–0.4040	0.5038
2FI	0.1615	0.2728	–0.1636	–0.9324	0.6934
Quadratic	0.0002	1.0000	1.0000	1.0000	4.0×10^{-6}
Cubic	0.0000	1.0000	1.0000		

visualizing changed λ values and their subsequent regularity of the data. Perturbation plots (Fig. 3f) were used to estimate the effect of varying each factor from the process response's reference point while keeping other variables constant. These plots facilitate the identification of the most significant response factors. A steep response incline to a variable indicates high sensitivity, whereas a flat line suggests

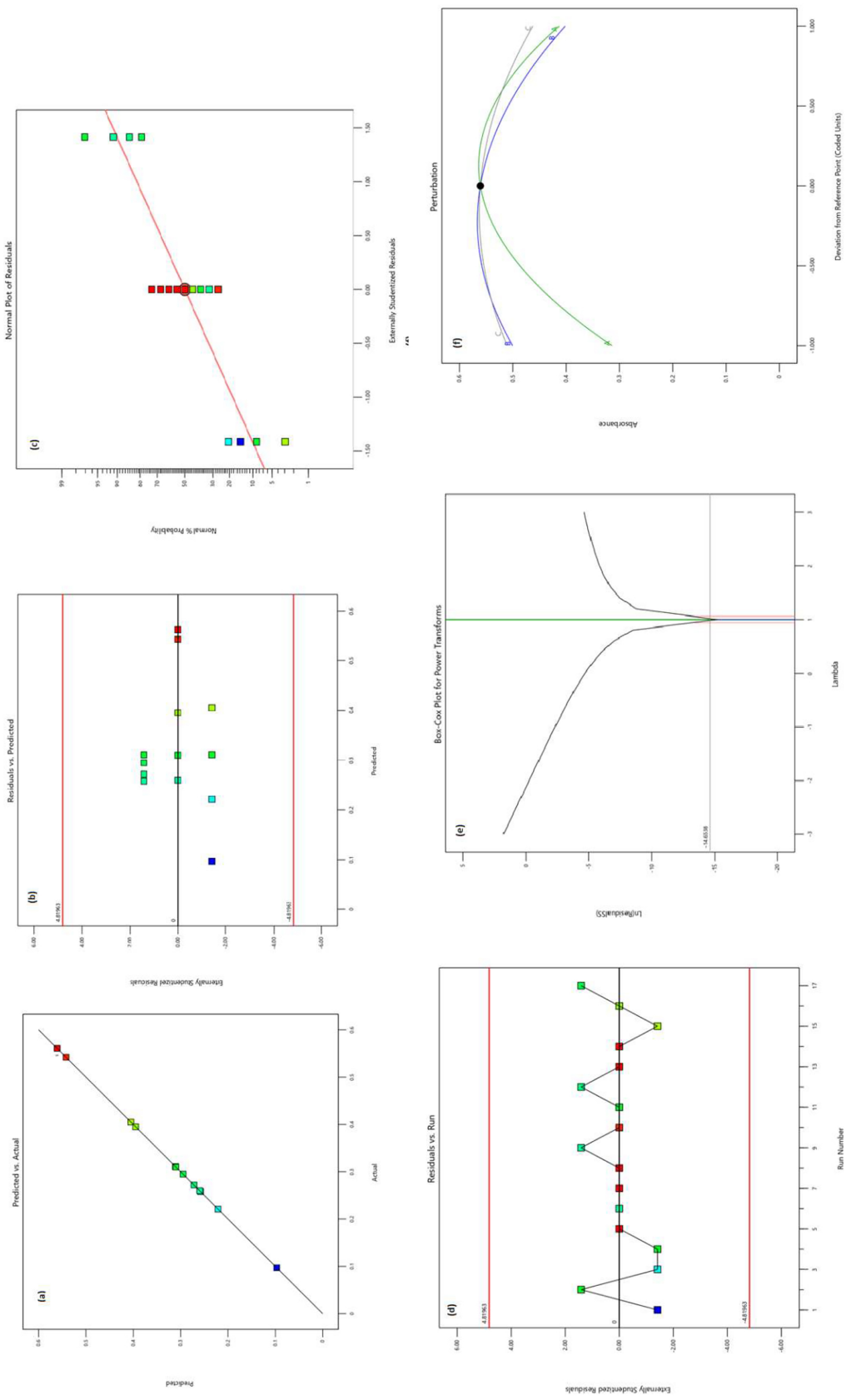


Fig. 3. ANOVA model (a) Predicted vs actual plot; (b) Residuals vs predicted graph; (c) Plots of residuals normal probability; (d) Plots of residuals vs run; (e) Box-Cox plot; (f) The perturbation plot.

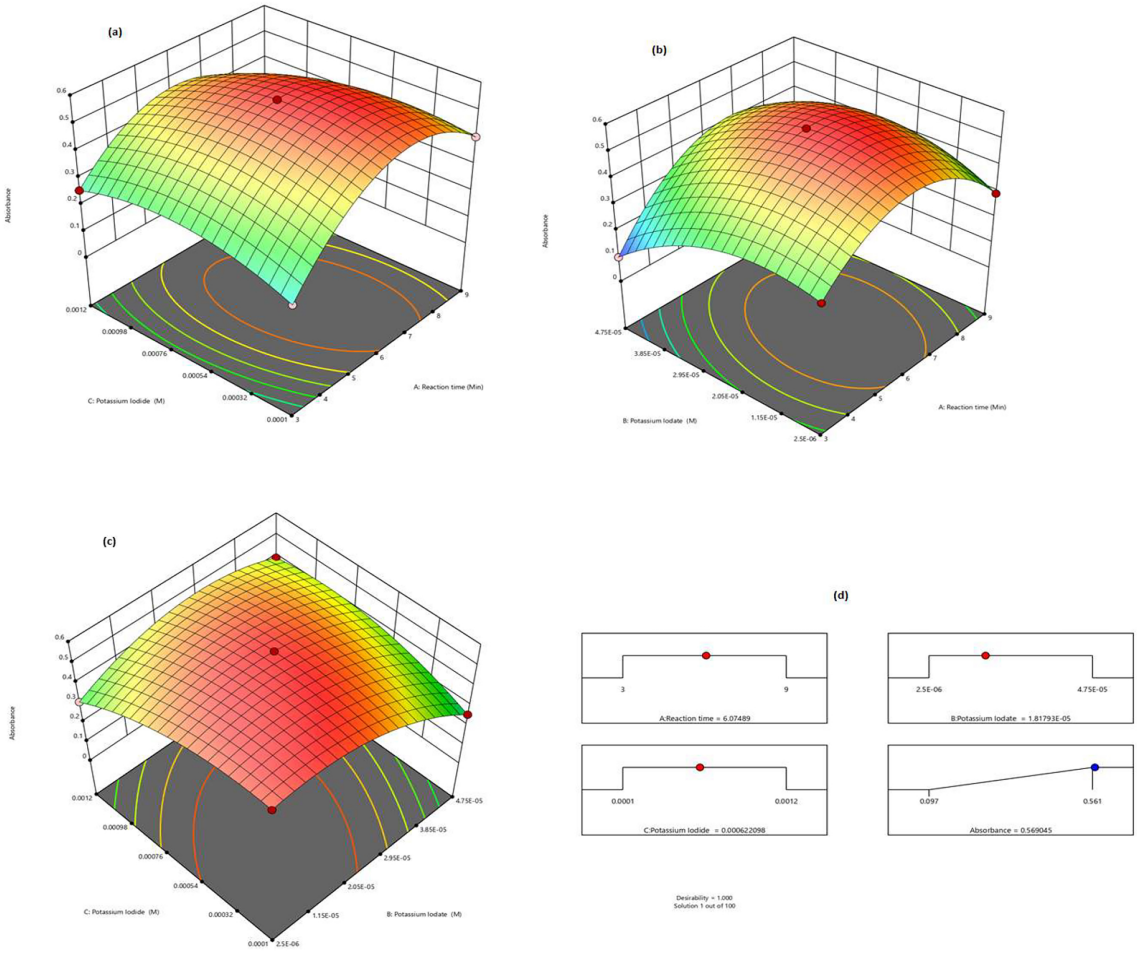


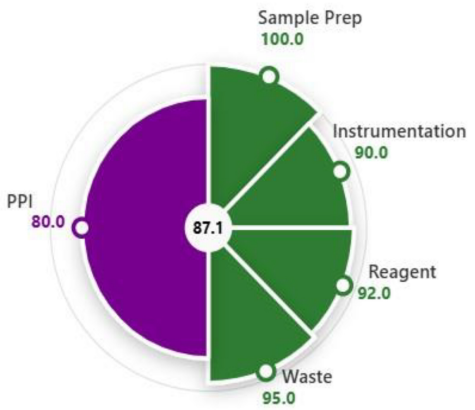
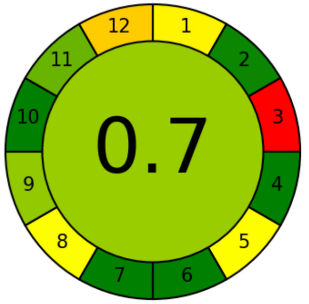
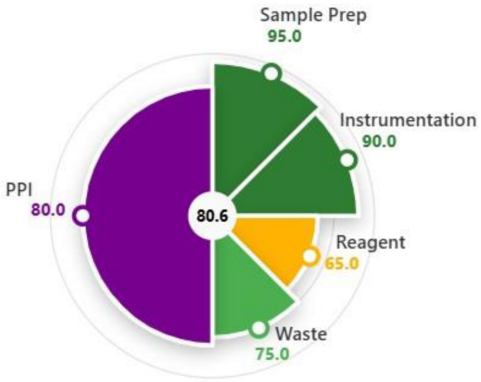
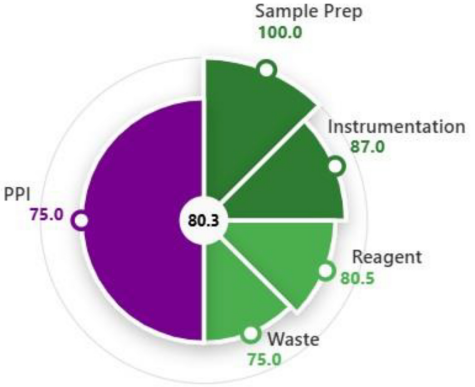
Fig. 4. 3D response surface plots developed from model (a) between (A) reaction time (min) and (C) potassium iodide; (A) reaction time (min) and (B) potassium iodate; (B) potassium iodate concentration and (C) potassium iodide concentration; (d) Optimized reaction conditions with a desirability value of 1 for the determination of BH in tablet formulation.

minimal influence. To fully interpret the responsive correlation between dependent and independent parameters, three-dimensional (3D) response surface plots were generated from the quadratic model. Interaction effects among all variables were significant, as indicated by p-values < 0.05. The 3D response surface plots (Fig. 4a, 4b, 4c) represent the interaction between two variables while keeping the other variable constant. The observed trend was that responses initially increased across all variables, peaked, and then declined. The controlled reaction condition achieved a maximum desirability function close to 1. The BH solution (100 μg/mL) was mixed with 6.2×10^{-4} M KI and 1.8×10^{-5} M KIO_3 solution in a volumetric flask. The colour intensity increased with a reaction time of 6.1 minutes, and absorbance was obtained (Fig. 4d). This was considered the optimized reaction condition for quantifying BH in tablet formulations.

3.4. Comparative greener studies of the proposed method with the reported methods

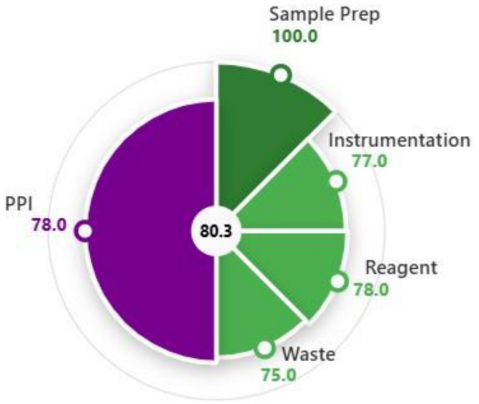
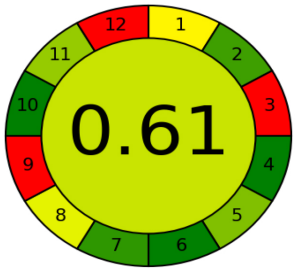
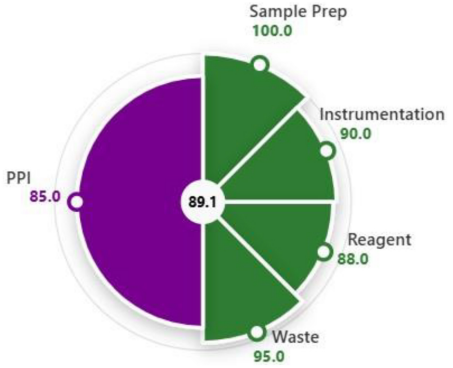
The AGREE, BAGI, AES and EPPI greener tools were applied to determine the eco-friendliness of the proposed procedure compared to the reported methods. The AGREE, BAGI, AES and EPPI values were considered UV [9], UV–Vis [12], HPLC [15] and LC–MS [22] with the proposed method. The AGREE results of the reported procedures ranged from 0.61 to 0.7, whereas the proposed method's assessed value was 0.72, indicating an excellent value for the greener assessment. Similar results were also found for BAGI, AES and EPPI between 72.5–82.5, 75–93, 80.3–87.1, in which the proposed procedure reported 72.5, 92 and 89.1, respectively, which are very close to those of the proposed method (Table 6). Therefore, the proposed method yielded higher greener-criteria values for determining BH in pharmaceutical formulations.

Table 6. Comparative Studies of Reported and Proposed Methods.

Conditions	EPPI	AES	AGREE	BAGI	Ref
Linearity: 2.52–38 μg/mL Solvent: Phosphate buffer pH 6.8 λ_{max}: 260 nm % Recovery: 95–105 % % RSD: 0.72% Sample: Tablet dosage form		93			[9]
Linearity: 24–40 μg/mL Solvent: 0.05 M NaOH λ_{max}: 485 nm % Recovery: 100.51–101.66 % % RSD: 0.42–1.58 % Sample: Tablet dosage form		87			[12]
Linearity: 2.5–15 g/mL Mobile Phase: Methanol: Monobasic Phosphate Buffer (20:80, v/v) Column: TC-C18 RP (250×4.6 mm, 5μ) % Recovery: 99.98% % RSD: 1.953 % Sample: Tablet		78			[15]

(Continued)

Table 6. Continued.

Conditions	EPPI	AES	AGREE	BAGI	Ref
Linearity: 10–501.6 pg/mL LOD: 0.5 pg/mL LOQ: 2.5 pg/mL Mobile Phase: 0.1% formic acid: Acetonitrile (20:80, v/v) Column: Zorbax Eclipse C_{18} (150×4.6 mm, 5μm) % Recovery: 97.40–100.47% % RSD: 1.953 % Sample: Human Plasma		75			[22]
Linearity: 2.5–12.5 μg/mL LOD: 1.25 μg/Ml LOQ: 3.45 μg/mL Solvent: Distilled water λ_{max}: 352 nm % Recovery: 95–105 % % RSD: 0.72% Sample: Tablet dosage form		92			Proposed Method

The statistical comparison was also carried out using Student's t–test and F–test, and were found to be 0.39, 0.25, 0.15 and 1.78, 1.61, 1.46, respectively, with the reference [9, 15, 22]. The validation data were also compared with the reference methods (Table 6), which demonstrated excellent correlation with the proposed method and the literature. These showed an excellent quantification procedure to determine BH not only in pharmaceutical formulations, but also can be used to quantify it in biological fluids as well.

4. Conclusions

The proposed method is an excellent alternative for routine analysis in chemical and pharmaceutical laboratories. It is an eco-friendly and stability-indicative method by visible spectrophotometry for the evaluation of BH in tablet formulations and is considered an excellent green analysis by the AES, AGREE, BAGI and EPPI criteria.

The proposed method is considered to be the first analytical technique that studied greenness assessment using different green metric tools to determine BH in tablet formulations. It is a simple, eco-friendly and reasonably economical method when compared with sophisticated chromatographic methods. No organic or toxic reagents were used to develop this method. Moreover, no laborious cleanup procedures are involved at any stage of analysis. RSM was observed to be an effective approach for optimizing significant variables, as it yields better results with desirable values and a high correlation between the actual and predicted values. Therefore, it can be a viable alternative method for BH determination in tablet formulations. Easy accessibility, eco-friendly reagents and instrumentation, and low cost enable frequent use in research laboratories, pharmaceutical industries, and hospitals in bulk, tablet and biological fluids.

Conflict of interest

The author declare no conflict of interest.

Author contributions

It's a single-author manuscript and is responsible for all work.

Data availability

No datasets were generated or analyzed during the current study.

Supplementary data

Supplementary data to this article can be found online at https://yjes.researchcommons.org/cgi/viewcontent.cgi?filename=0&article=1215&context=yjes&type=additional&preview_mode=1

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