Research Article

Development and Validation of UV Spectrophotometric Method for the Determination of Ibuprofen by Using Quality by Design (QbD) Approach

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Received: 05-04-2024; **Revised:** 25-05-2024; **Accepted:** 03-06-2024; **Published on:** 15-06-2024.

ABSTRACT

Objective: To develop a simple, rapid, accurate, robust and inexpensive spectrophotometric method for the estimation of Ibuprofen by using quality by design (QbD)" approach.

Methods: A UV spectrophotometric method was developed on the Systronics AU-2701 UV-visible double beam spectrophotometer using ethanol and water as solvents. A wavelength of 228 nm was selected as absorbance maxima (max). The effect of input variables on spectrum characteristics was studied for the selection of critical parameters and the proposed method was validated for various parameters like system suitability, linearity, precision, accuracy, detection limits and quantification limits as per the International Conference on Harmonization guidelines ICH Q2(R1).

Results: The linearity of the method was found to be excellent over the concentration range of 5 to 25 µg/ml with a high correlation coefficient value of 0.9998. The detection and quantification limits were 0.59 µg/ml and 1.80 µg/ml respectively. The mean recovery was found to be 97.83% with a low percentage relative standard deviation (% RSD) value. The precision study also has shown a low % RSD value (<1). No interfering peaks were observed during specificity studies.

Conclusion: The obtained result indicated that the developed spectrophotometric method is simple, rapid and accurate for determining Ibuprofen.

Keywords: Quality by design, Ibuprofen, Analytical method validation, Spectrophotometric estimation, Ruggedness.

INTRODUCTION

A medication called ibuprofen belongs to the nonsteroidal anti-inflammatory drug (NSAID) class and is used to treat fever, pain and other conditions. The IUPAC designation for Ibuprofen is (RS)-2[4-(2-methylpropyl)phenyl]propanoic acid[1]. The molecular formula & molecular weight is $C_{13}H_{18}O_2$ & 206.29 g/mole respectively[2]. The melting point and boiling point of Ibuprofen are 75-78°C (167–172°F) & 157°C (315°F) respectively[3]. It is used to treat various illnesses, including mild-to-moderate discomfort, inflammation and fever[1]. It treats rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis and cramps during menstruation (dysmenorrhea)[4]. Beyond its benefits, ibuprofen has many drawbacks. It raises the danger of liver, renal and cardiac failure. It does not seem to raise the risk of a heart attack at low dosages, but it might do so at greater dosages. Ibuprofen has the analgesic and antipyretic properties[1,4].

Ibuprofen works through the mechanism of Cyclooxygenase (COX), which is necessary for prostaglandin synthesis via the arachidonic acid route and which changes arachidonic acid into prostaglandin H2 in the body. Inhibition of COX, which changes arachidonic acid into thromboxane A2, a crucial step in platelet aggregation that results in blood clot formation, is another way that anticoagulant effects are mediated. Because the maintenance of the gastric mucosa is disrupted, an overabundance of NSAIDs may result in the long-term inhibition of COX-1, a subtype of COX that may cause gastric toxicity. In short, it prevents cyclooxygenase I and II from being active, which reduces the production of prostaglandin and thromboxane precursors. This results in a reduction in prostaglandin synthesis by prostaglandin synthase, which is the primary physiological impact of the medication. In addition, thromboxane synthase produces less thromboxane A2 production when ibuprofen is taken, which prevents platelet aggregation[1].

The development of pharmaceutical processes uses concept quality by design (QbD) to assure predetermined product quality[5]. Guidelines from the International Conference on Harmonization (ICH) about pharmaceutical development (Q8) (R1), quality risk management (Q9) and pharmaceutical quality system (Q10) explain QbD ideas[6-8]. Based on sound science and quality risk management, QbD is defined as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control" in the ICH Q8 (R1) guideline[9]. QbD is a methodical approach to product development that involves comprehending how different input variables (such as materials and process parameters) affect the end output, which is the active component or medication product. Therefore, the QbD technique establishes suitable input parameter ranges that ensure the final product's quality[10]. The QbD methodology requires a thorough grasp of how the characteristics of the analytical technique and the operational environment

affect the analytical performance, much like analytical methods do. Analytical quality by design (AQbD) factors to consider may be the kind of analytical method selected, the chemicals utilized and the instrumental parameters[11].

Applying QbD concepts to analytical methods has advantages identical to manufacturing processes and goods[12]. QbD ideas have been applied by several researchers to the process of developing analytical procedures. The development of a reliable and affordable analytical technique that can be applied at any point in the product's lifespan can be accomplished using the AQbD approach. Recently, several regulatory bodies have made it possible to switch analytical techniques without having to revalidate them if the AQbD approach was used when developing the method[13-18]. Establishing the method's analytical target profile (ATP) is the first step in the AQbD technique. As a measure of method performance, ATP establishes the goal of developing the analytical methods process. The ICH recommendations on validation of analytical processes, ICH Q2(R1), include several method performance parameters for an analytical technique. The ICH guidelines Q2 (R1) can therefore be taken into consideration when developing a QbD-based UV spectrometric technique[5].

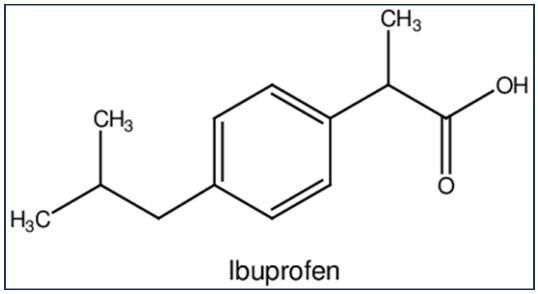

Figure 1: Structure of Ibuprofen

The objective of the current study was to use the analytical quality by design (AQbD) approach to create a UV spectrometric method that is straightforward, quick, reliable, versatile and affordable for estimating ibuprofen. The key parameters for the suggested technique were chosen by assessing the impact of method input variables on spectral shape, intensity of absorbance and absorbance maxima (λmax) to apply the QbD approach to the UV spectrophotometric analytical method. The suggested approach was then verified by ICH Q2(R1) requirements[10].

MATERIALS AND METHODS

Equipments and Chemicals

A UV spectrophotometer (Systronics AU-2701 UV-visible double-beam spectrophotometer) was used to perform the analysis. The supplier of ibuprofen was Yarrow chem products, Ghatkopar, Mumbai, India. The category of all other chemicals utilized as analytical reagents.

Preparation of stock and working solution

The solubility of Ibuprofen in several solvents was examined, including distilled water, 0.1N sodium hydroxide, 0.1N hydrochloric acid and ethanol. Ibuprofen was discovered to be most soluble in ethanol. Ethanol is used only to dissolve Ibuprofen and water is used for further dilutions. As a result, regular stock and working solutions are made with ethanol(10 ml) and water. To obtain 1000 µg/ml concentration, 100 mg of Ibuprofen was dissolved in 100 ml of ethanol and made up the volume with water to create the stock solution. Using dilution of stock solution, a standard working solution of 10 µg/ml was prepared and used for the UV spectrophotometer's first spectral scan.

Determination of wavelength of maximum absorption

A standard working solution (10µg/ml) of Ibuprofen was scanned from 200-400 nm in the UV spectrophotometer for selection of analytical wavelength. Ibuprofen showed maximum absorbance (λ_{max}) at 228 nm. Hence 228 nm was selected as an analytical wavelength.

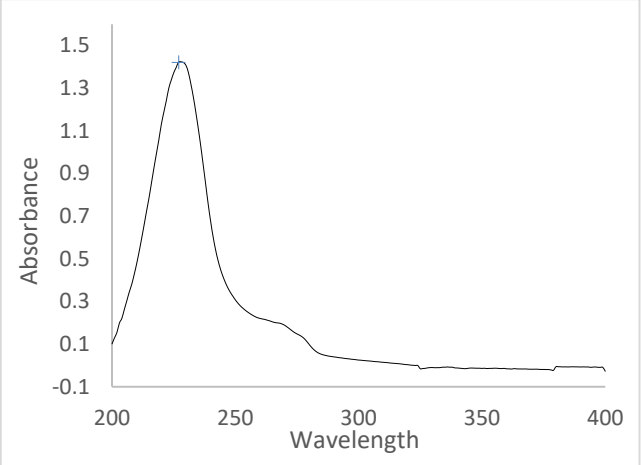

Figure 2: UV spectrum of Ibuprofen showing maximum absorbance (λ_{max}) at 228 nm

Implementation of the AQbD approach in the development of the analytical method

The Ishikawa technique utilized the AQbD diagram to investigate the relationship between variable input factors and spectrophotometric analytical method performance characteristics[19]. It was discovered that ethanol has the highest solubility of ibuprofen. For this reason, ethanol was chosen as the solvent in an ibuprofen analysis method using a UV Spectrophotometer. The absorbance spectrums for every other variable parameter displayed in the Ishikawa diagram were obtained by scanning the standard working solution (10 µg/ml) in the chosen solvent in the UV spectrophotometer from 200 to 400 nm.

The spectrum's shape, sharpness and absorbance intensity were measured and compared at various scan speeds (rapid, medium, slow, and very slow) and sample intervals (0.1, 0.2, 0.5, 1.0 and 2.0 nm)[11]. Spectrums were overlapping, as the figure 3 shows. Therefore, it can be concluded that variations in scan speed and sampling interval do not significantly alter the spectrum's spectral structure, sharpness, or absorbance intensity. The crucial parameters were chosen based on the above-mentioned

observation and the approach is further validated by the ICH recommendations Q2(R1) by employing the chosen variable parameters.

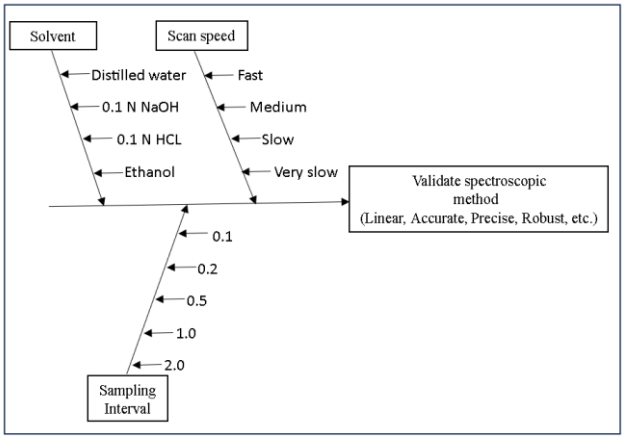

Figure 3: Ishikawa diagram showing the relationship between variable input parameters and the method performance characteristics of the spectrophotometric analytical methods

Table 1: Selected critical parameter for spectrophotometric analytical method of Ibuprofen

Parameter	Selected wavelength
Wavelength	228
Solvent	Ethanol
Scan speed	Fast
Sampling interval	0.2 nm

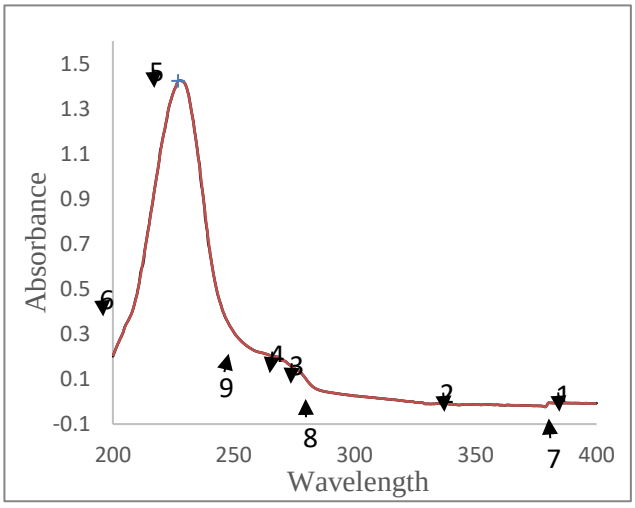

Figure 4: Overlay UV spectrum at varied scan speeds (fast, medium, slow and very slow) and varied sampling intervals (0.1,0.2,0.5,1.0 and 2.0 nm)

Validation

To obtain the analytical target profile, the critical parameters that have been chosen must adhere to the method performance characteristics of the analytical method. In ICH guidelines Q2(R1), the ICH stated certain technique performance parameters for an analytical approach. Therefore, to apply the AQbD methodology, it is appropriate to verify a spectrophotometric analytical method by ICH guidelines Q2(R1) on the chosen crucial parameter. Therefore, the established method is further validated by using specific key parameters by the ICH recommendations Q2(R1)[9]. System suitability, linearity, precision, accuracy, specificity, the limit of detection (LOD) and the limit of quantification (LOQ) were the attributes that were examined.

System suitability

System suitability is done to demonstrate the suitability of the UV-Spectrophotometer system being used for the analysis. Six replicates of the standard solution (10µg/ml) of ibuprofen were prepared from a stock solution in the selected solvent (ethanol) and absorbance was determined at 228 nm of each replicate using a UV spectrophotometer. Percentage relative standard deviation (% RSD) was calculated for the absorbances[5].

Linearity

According to the ICH recommendations, the linearity of an analytical technique means that the test results are directly proportional to the analyte concentration (amount) in the sample. Six solutions ranging in concentration from 5 to 25µg/ml were prepared using ethanol for the linearity study using a standard ibuprofen stock solution. The absorbance of each solution was measured in triplicate at 228 nm. Plotting the absorbance versus concentration and % RSD produced the calibration curve, which was then created using regression analysis to determine the correlation coefficient[9].

Precision

The ICH guidelines state that the degree of precision of an analytical technique establishes the degree of agreement between results obtained from repeated measurements of the same homogenous sample. Tests for repeatability (intra-day precision) and intermediate precision (inter-day precision) were carried out to demonstrate the technique's precision. To demonstrate the repeatability (intra-day precision) of the test method, six replicates of the 10 µg/ml concentration (n=6) were analyzed on the same day. % RSD of the assay result of six replicates was calculated. Similarly, for intermediate precision (inter-day precision), six replicates of the 10 µg/ml concentrations were analyzed for assay on three consecutive days and % RSD was calculated[11-21].

Accuracy

An analytical method's accuracy demonstrates how closely the results match the actual conventional value. An ibuprofen recovery study was used to determine accuracy. To achieve a final concentration of 15µg/ml, 20µg/ml and 25µg/ml, a known amount of standard stock solution was added at different levels, namely 80%, 100% and 120%, to the known amount of standard solution (10µg/ml). The drug content of these solutions was then examined again. For the experiment, three duplicate sets of each level were made. Calculations were made to determine the sample's recovery and % RSD[9].

Limit of Detection (LOD) and Limit of Quantification (LOQ)

The lowest concentration of an analyte in the sample that can be accurately and precisely measured is known as the limit of quantification, whereas the limit of detection is the lowest amount of analyte in a sample that can be detected but may not necessarily be quantified as an exact value. According to ICH guidelines, the slope method and residual standard deviation of response were used to determine the limit of quantification and limit of detection concentrations for ibuprofen. For this, the calibration curve prepared for the linearity research was implemented[5].

Specificity

The ability to determine the analyte during the presence of possible components, like contaminants, degradants, excipients, etc., is termed specificity, according to ICH recommendations. The standard solution (10µg/ml), diluent and normal pharmaceutical excipients (oil and surfactant mixture) were studied to demonstrate the specificity spectra[9].

Ruggedness

The robustness of the suggested approach is determined for 20 µg/ml concentration of Ibuprofen by analyzing aliquots from a homogeneous slot by two analysts under identical operational and environmental conditions[20,22,23].

RESULTS AND DISCUSSION

System suitability

The absorbance of six replicates of the standard solution (10µg/ml) of ibuprofen is reported in Table 2. For system suitability % RSD of absorbance of replicate solutions should not be more than 2[24]. The results obtained meet the system suitability requirements; this indicates that the system was suitable for the analysis[25].

Table 2: Result of system suitability studies

Replicates of standard solution	Absorbance at 228 nm
1	0.556
2	0.552
3	0.560
4	0.552
5	0.561
6	0.557
Mean	0.5568
SD	0.003477
% RSD	0.624387

SD- Standard deviation, RSD- Relative standard deviation

Linearity

The calibration plot of absorbance versus concentration was linear over the range of 5 to 25 µg/ml as shown in Table 3 and Fig. 5. RSD was found to have a small value of 0.002. In contrast, the correlation coefficient (r^2) has a high value of 0.9998. Thus, test results were directly proportional to the analyte concentration (amount) in the sample[26,27].

Table 3: Result of linearity study of Ibuprofen

Concentration	Absorbance* mean±SD (n=3)
5	0.3154±0.002
10	0.5687±0.002
15	0.8069±0.003
20	1.0636±0.001
25	1.2975±0.002
R^2	0.9998
% RSD	0.002
Linear regression equation	y = 0.0492x+0.0727

*mean±SD, n=3, SD-standard deviation, RSD-relative standard deviation

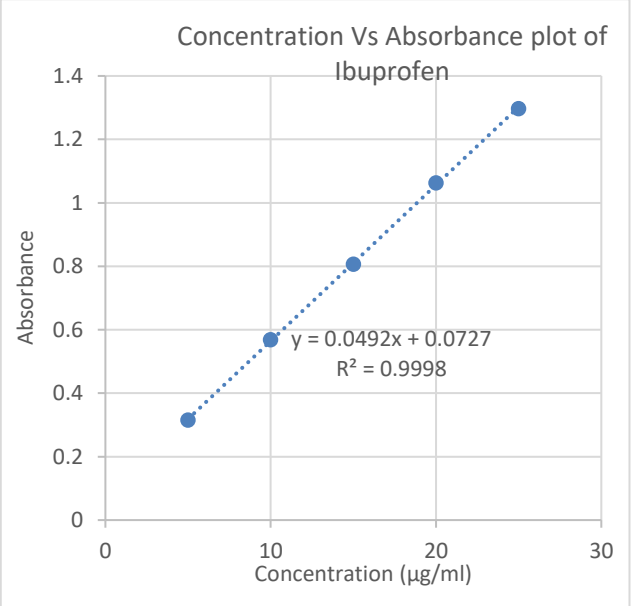

Figure 5. Calibration curve plot of Ibuprofen at 228 nm

Precision

The calculated RSD of intra-day and inter-day precision tests are reported in Table 4. For a precise analytical method, the % RSD of assay results of six replicates should not be more than 2. The RSD of the intra-day assay of six replicates was 0.86% and for inter-day assay, RSD were 0.68%, 0.54% and 0.84% respectively for three consecutive days. A low % RSD value indicates that the method was precise[28,29].

Accuracy

The purpose of this experiment was to prove the trueness of the assay results obtained by the proposed method. The results of recovery studies are reported in Table 5. The mean recovery was found to be 97.83% with a low RSD value of 1.28 (<2 %). These results demonstrate the accuracy of the method[5].

Table 4: Result of precision studies

Intra-day precision (Repeatability)			Inter-day precision (Intermediate precision)							
				Day 1		Day 2		Day 3		
Std. solution conc. (µg/ml)	Conc. found* (µg/ml) mean±SD (n=6)	%RSD	Std. sol. conc. (µg/ml)	Conc. found* (µg/ml) mean±SD (n=6)	%RSD	Conc. found* (µg/ml) mean±SD (n=6)	%RSD	Conc. found* (µg/ml) mean±SD (n=6)	%RSD
10	10.21±0.08	0.86	10	10.20±0.06	0.68	10.05±0.05	0.54	10.06±0.08	0.84

*mean±SD, n=6, SD-standard deviation, RSD-relative standard deviation

Table 5: Result of accuracy studies

Std. solution of known concentration (µg/ml)	Level of standard added (%)	Amount of drug added (µg/ml) (n=3)	Total amount of drug found (µg/ml)* mean±SD (n=3)	Amount recovered (µg/ml)	% recovery	Mean % recovery of 3 levels (50%, 100%, 150%)	% RSD
10	0	0	10.21±0.10	10.21	-	97.83	1.28
	50	5	15.16±0.07	4.95	99		
	100	10	19.86±0.14	9.65	96.5		
	150	15	24.91±0.11	14.7	98		

*mean±SD, n=3, SD-standard deviation, RSD-relative standard deviation

Limit of detection (LOD) and limit of quantification (LOQ)

By using the calibration curve, the standard deviation of the response (σ) and slope of the calibration curve (S) were determined. Calculation was carried out using equations (3.3 × σ)/S for LOD & (10 × σ)/S for LOQ. The LOD was found to be 0.59 µg/ml and the LOQ was found to be 1.80 µg/ml. Results are reported in Table 6. These results indicated the high sensitivity of the proposed UV method[30].

Table 6: Limit of detection (LOD) and limit of quantification (LOQ) determination

Parameter	Observed value
Slope of regression (S)	0.0478
Residual standard deviation (σ)	0.008587
Standard error of intercept	0.003840
LOD concentration (µg/ml)	0.59
LOQ concentration (µg/ml)	1.80

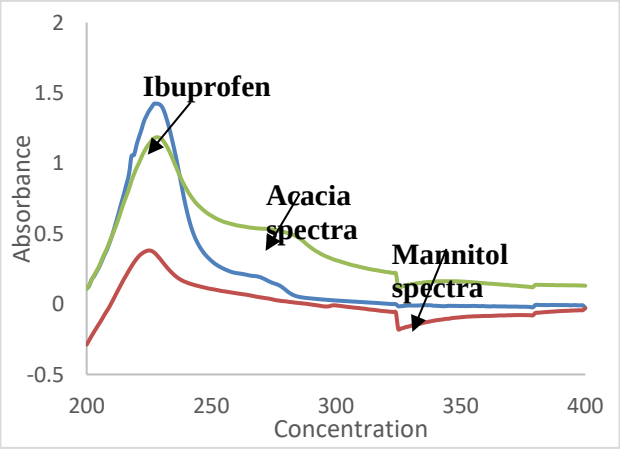

Figure 6: Specificity studies by comparing the spectra of Ibuprofen, possible pharmaceutical excipient and diluent (solvent)

Specificity

For a specific analytical method, there should be no interfering peak of diluent and possible excipient with the analyte[31]. Fig. 6 shows that no interfering peaks were observed during the analysis. Hence method was specific.

Ruggedness

The peak area of the identical concentration solutions was tested six times. The final results fall within the acceptable range. Table 7 presents the results of the study. The results of the study showed that the %RSD was under 2%[20].

Table 7: Result of ruggedness study

Component	Amount taken (µg/ml) (n=3)	Amount found (%)	
		Analyst 1 ± SD	Analyst 2 ± SD
Ibuprofen	20	99.13±0.61	99.30±1.27

Table 8: Summary of Ibuprofen results

Parameter	Result
Regression Equation (y = mx+c)	y = 0.0492x + 0.0727
Measured Wavelength	228 nm
Linearity range	5-25 (µg/ml)
Slope	0.0492
Intercept	0.0727
Correlation coefficient (R^2)	0.9998
Limit of Detection (LOD) (µg/ml)	0.59
Limit of Quantitation (LOQ) (µg/ml)	1.80
Accuracy (Mean % Recovery)	97.83
Accuracy (%RSD)	1.28

CONCLUSION

A simple, rapid, sensitive, accurate, precise and inexpensive spectrophotometric method was developed for the estimation of ibuprofen in bulk by using the analytical quality by design (AQbD) approach. Based on an investigation of the effect of method input variables on absorbance pattern, the critical parameters have been selected for the proposed method and it was further validated as per the ICH guidelines. The developed method does not involve complexity and thus has an economic advantage over common chromatographic methods. Therefore, the developed spectrophotometric method can be used flexibly and efficiently for the determination of ibuprofen either in bulk or in the dosage formulations. With these advantages, the proposed methodology can be adopted in routine quality control testing of ibuprofen in its pharmaceutical dosage forms. The developed chromatographic method can be effectively applied for routine analysis in drug research.

Authors contributions

All the authors have contributed equally.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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