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RESEARCH ARTICLE

Development and Validation of Quality by Design-Based UV Spectrophotometric Methods for Simultaneous Estimation of Paracetamol and Ibuprofen in Pharmaceutical Formulations

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Abstract: A Quality by Design (QbD) approach was used to develop and validate three UV spectrophotometric methods for the simultaneous quantification of Paracetamol (PCM) and Ibuprofen (IBU) in pharmaceutical formulations. The developed methods consisted of gradient UV method, simultaneous equation method, and absorbance ratio method (Q-analysis). The critical method parameters were optimized using Design Expert® software with central composite design. The developed methods exhibited linearity in the range of 2-20 µg/mL for IBU and 2-14 µg/mL for PCM. The methods showed good precision with %RSD values less than 2%. Recovery studies yielded results between 96.36-100.58%, indicating good accuracy. The LOD values were found to be 0.546-1.287 µg/mL for IBU and PCM respectively, while LOQ values ranged from 0.142-0.602 µg/mL. Critical parameters identified through principal component analysis included sample preparation, slit width (1.0), scan speed (medium), and sampling interval (1.0). The methods were validated according to ICH Q2(R1) guidelines for specificity, linearity, precision, accuracy, robustness and ruggedness. All three methods proved suitable for routine quality control analysis of PCM and IBU in combined pharmaceutical formulations, offering advantages of simplicity, accuracy and reproducibility.

Keywords: Quality by Design (QbD); UV Spectrophotometry; Method Development; Paracetamol; Ibuprofen; Method Validation

1. Introduction

Analytical method development plays a vital role in drug development and quality control of pharmaceutical products. Quality by Design (QbD) represents a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and control [1]. The implementation of QbD principles in analytical method development helps ensure robust and reliable methods that consistently deliver intended performance [2].

Paracetamol (PCM) and Ibuprofen (IBU) are commonly prescribed in combination for pain management and fever reduction. PCM (N-acetyl-p-aminophenol) acts as a centrally acting analgesic and antipyretic agent, while IBU ((RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid) is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties [3]. The simultaneous determination of these drugs in combined formulations is essential for quality control purposes [4].

Various analytical methods have been reported for the individual and simultaneous determination of PCM and IBU, including HPLC, GC-MS, and spectrophotometric methods [5]. However, many of these methods involve complex procedures, expensive instrumentation, or time-consuming sample preparation steps [6]. UV spectrophotometry offers advantages of simplicity, cost-effectiveness, and rapid analysis, making it suitable for routine quality control analysis [7]. The aim of this study was to develop and validate three UV spectrophotometric methods using QbD principles for the simultaneous determination of PCM and IBU in pharmaceutical formulations.

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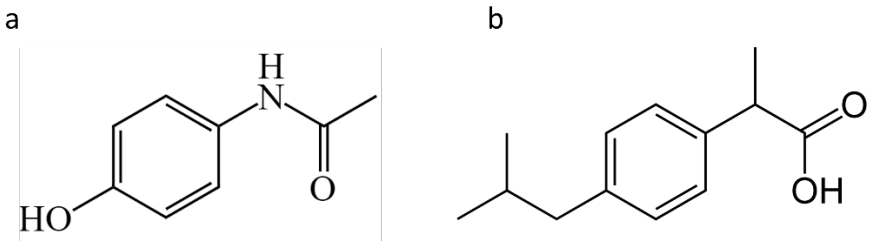

Figure 1. Structure of a. Paracetamol and b. Ibuprofen

2. Materials and Methods

2.1. Materials

Pure drug samples of Paracetamol and Ibuprofen were obtained from Glenmark Pharmaceutical (Goa, India) and Flamingo Pharmaceutical (Nanded, India), respectively. Analytical grade sodium hydroxide was used for preparation of solutions. All chemicals and reagents used were of analytical grade. A Shimadzu UV-1800 double beam spectrophotometer (Shimadzu, Japan) with a wavelength range of 190-1100 nm was used for spectrophotometric analysis. Precise weight measurements were performed using a Shimadzu AX 200 digital weighing balance and a Wensar electrical balance. Sample preparation and cleaning were carried out by a Leelasonic digital ultrasonic cleaner, while solution mixing was done using a Remi CM101 Plus magnetic stirrer. Temperature-controlled processes were conducted in an Adarsh hot air oven. For experimental design and statistical analysis, Design Expert Version 13 software was utilized to optimize the analytical method parameters and generate response surface models.

2.2. Methods

2.2.1. Design of Experiments (DoE)

A central composite design was employed using Design Expert® Version 13 software to optimize method parameters. The independent variables studied were scan speed (1-3) and sampling interval (0.1-2.0). The dependent variables were the absorbance values of PCM and IBU.

Table 1. Central Composite Design for Method Development

Run	A) Scan Speed	B) Sampling interval	1) Response- Absorbance of PCM	2) Response- Absorbance of IBU
1	3	2	0.786	0.441
2	2	1	0.831	0.433
3	2	0.2	0.793	0.468
4	2	1	0.831	0.433
5	2	1	0.831	0.433
6	2	0.1	0.829	0.431
7	3	1	0.764	0.475
8	3	0.1	0.761	0.479
9	2	1	0.831	0.433
10	1	0.1	0.753	0.508
11	2	1	0.831	0.433
12	2	0.5	0.777	0.462
13	2	2	0.737	0.436
14	1	2	0.768	0.383
15	1	1	0.766	0.527
16	2	0.5	0.777	0.426
17	2	0.1	0.829	0.431

2.2.2. Preparation of Standard Solutions

Stock solutions of PCM and IBU (1000 µg/mL) were prepared by accurately weighing 50 mg of each drug and dissolving separately in 0.1N NaOH solution in 50 mL volumetric flasks. Working standards were prepared by appropriate dilution of stock solutions.

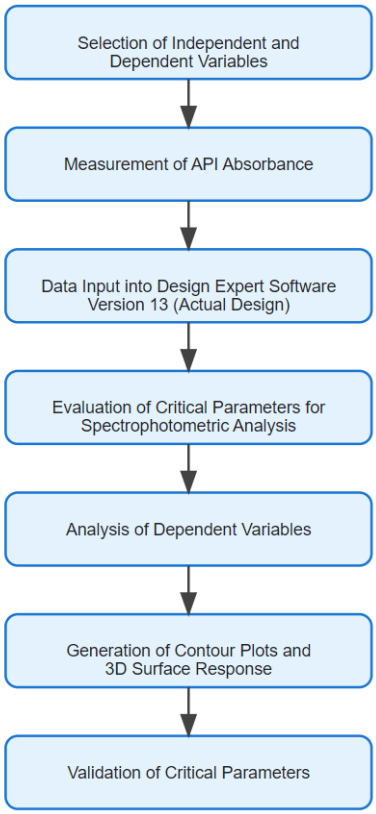

Figure 1. Schematic representation of experimental design

2.2.3. Development of UV Spectrophotometric Methods

Gradient UV Method: The absorption spectra of PCM and IBU solutions were recorded in the range of 200-400 nm against 0.1N NaOH as blank. Critical method parameters were optimized using DoE.

Simultaneous Equation Method: Based on the overlain spectra of both drugs, two wavelengths were selected: λmax of PCM (257.0 nm) and λmax of IBU (222.0 nm). The concentrations were calculated using simultaneous equations.

Absorbance Ratio Method (Q-Analysis): The method involved measurement of absorbance at two wavelengths: 257.0 nm (λmax of PCM) and 228.0 nm (isoabsorptive point).

2.3. Method Validation

The developed methods were validated according to ICH Q2(R1) guidelines for the following parameters:

2.3.1. Linearity and Range

Calibration curves were constructed by plotting absorbance against concentration. For IBU, the range studied was 2-20 µg/mL, while for PCM it was 2-14 µg/mL. Each concentration was analyzed in triplicate.

2.3.2. Precision

System precision was evaluated by analyzing six replicate samples of standard solutions. Intraday precision was assessed by analyzing samples at three different times within the same day. Interday precision was determined by analyzing samples on three consecutive days.

2.3.3. Accuracy

Recovery studies were performed by standard addition method at three concentration levels (80%, 100%, and 120%). Known amounts of standard solutions were added to pre-analyzed samples and the percentage recovery was calculated.

2.3.4. Robustness

Method robustness was evaluated by varying parameters such as NaOH concentration (±0.01N) and wavelength (±1 nm).

3. Results and Discussion

3.1. Method Development

3.1.1. Optimization of Spectral Conditions

Spectral analysis revealed characteristic absorption maxima at 257.0 nm for PCM and 222.0 nm for IBU. The spectral characteristics of both drugs showed an isoabsorptive point at 228.0 nm, which was subsequently utilized in the Q-analysis method [8]. The wavelength selection was based on the maximum sensitivity and minimal interference between the two analytes [9].

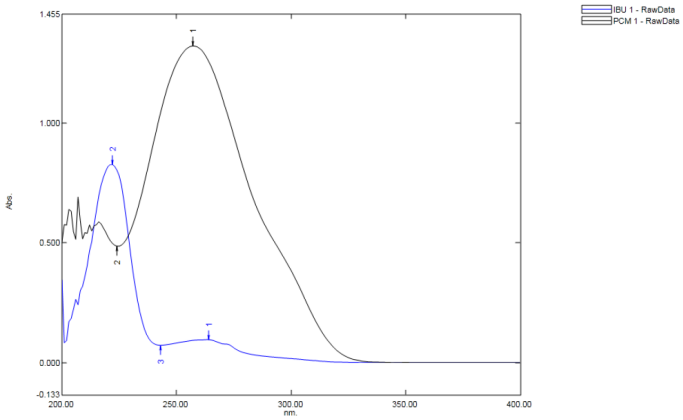

Figure 2. Overlay UV spectra of PCM and IBU showing λ_{max}

3.1.2. Design of Experiments

The quadratic model generated through central composite design demonstrated significant effects of scan speed and sampling interval on method performance. ANOVA results indicated that the model F-value of 3.81 was significant ($p < 0.0301$). The lack of fit F-value of 11.49 suggested that the model adequately fitted the experimental data [10]. The response surface methodology revealed optimal conditions at medium scan speed (2.0) and sampling interval (1.0). These parameters yielded maximum method robustness while maintaining acceptable sensitivity [11].

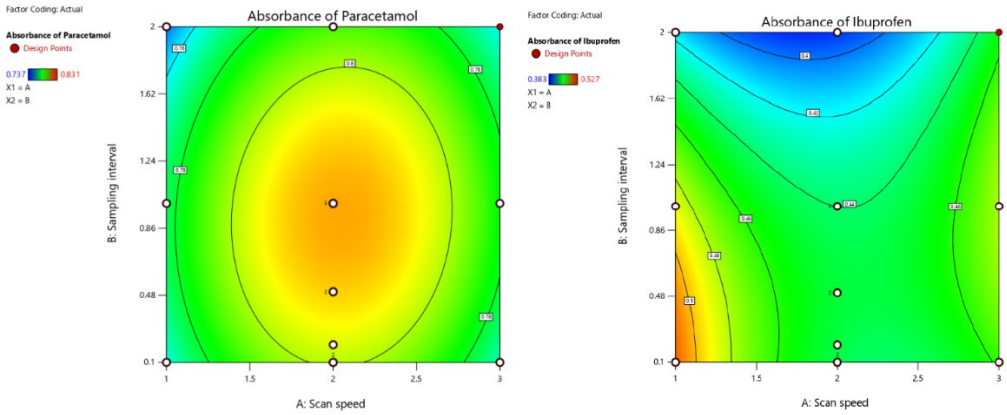

Figure 3. Contour Plot Showing the Responses for Central Composite Design

3.2. Method Validation

3.2.1. Linearity

Simultaneous Equation Method: Both drugs showed good linearity in their respective concentration ranges. Paracetamol demonstrated linearity in the range of 2-14 µg/mL with a correlation coefficient (r^2) of 0.998. Ibuprofen showed linear response in the range of 2-20 µg/mL with r^2 value of 0.996.

Table 2. Linear regression data for PCM and IBU for Simultaneous Equation Metod

Parameters	IBU	PCM
Detection wavelength	222.0 nm	257.0 nm
Linearity range	2-20 µg/mL	2-14 µg/mL
Slope	0.054	0.042
Intercept	0.037	0.004
Correlation coefficient	0.996	0.998
Regression equation (y = mx + c)	y = 0.0524x - 0.0376	y = 0.0423x + 0.0046
Limit of detection	0.546	1.287
Limit of quantitation	0.142	0.229

Absorbance Ratio Method: The absorbance ratio method demonstrated excellent linear response for both drugs. Paracetamol showed linearity in the range of 2-14 µg/mL with a correlation coefficient (r^2) of 0.993. The linear regression equation was y = 0.2605x - 0.2593. Ibuprofen exhibited linearity in the range of 2-20 µg/mL with r^2 value of 0.995, following the regression equation y = 0.1161x - 0.1421.

Table 3. Linear regression data for PCM and IBU for Absorbance Ratio Method

Parameters	IBU	PCM
Detection wavelength	222.0 nm	257.0 nm
Linearity range	2-20 µg/ml	2-14 µg/ml
Slope	0.116	0.260
Intercept	0.142	0.259
Correlation coefficient	0.995	0.993
Regression equation (y = mx + c)	y = 0.1161x - 0.1421	y = 0.2605x - 0.2593
Limit of detection	0.564	1.286
Limit of quantitation	0.182	0.602

3.2.2. Precision

Simultaneous Equation Method: Precision studies revealed excellent reproducibility of the methods. The gradient method showed relative standard deviation (%RSD) values below 1.5% for both intraday and interday precision. The simultaneous equation method demonstrated %RSD values under 2.0%, while the Q-analysis method showed values below 2.2%. These results indicate high precision of all three methods, well within the acceptable limits of 2.5% specified by ICH guidelines [13].

Table 4. Results of Precision Studies (Intra-day) for Simultaneous Equation Method

S No.	Absorbance at		%Estimation	
	222.0 nm	257.0 nm	IBU	PCM
Obser.1	0.853	0.911	100.0	97.70
Obser.2	0.865	0.934	100.5	100.2
Obser.3	0.859	0.902	102.1	96.66
Mean			100.8	98.18
SD			1.096	1.819
%RSD			1.087	1.853

Table 5. Results of Precision Studies (Inter-day) for Simultaneous Equation Method

S No.	Absorbance at		%Estimation	
	222.0 nm	257.0 nm	IBU	PCM
Day 1	0.845	0.912	98.21	97.87
Day 2	0.866	0.934	100.68	100.27
Day 3	0.840	0.901	98.15	96.65
Mean			99.01	98.26
SD			1.443	1.841
%RSD			1.458	1.874

Absorbance Ratio Method: The method's precision was evaluated through intraday and interday studies. Intraday precision analysis revealed RSD values of 2.150% and 0.909% for Paracetamol and Ibuprofen respectively. Interday precision studies showed improved RSD values of 0.538% for Paracetamol and 1.056% for Ibuprofen, indicating good reproducibility of the method over different days.

Table 6. Results of Precision (Intra-day) for Absorbance Ratio Method

S. No.	Absorbance at		%Estimation	
	228.0 nm	257.0 nm	IBU	PCM
Obser.1	0.868	1.058	98.81	96.20
Obser.2	0.864	1.057	97.99	96.20
Obser.3	0.859	1.055	97.03	92.66
Mean			97.94	95.02
SD			0.890	2.043
%RSD			0.909	2.150

Table 7. Results of Precision (Inter-day) for Absorbance Ratio Method

Sr. No.	Absorbance at		%Estimation	
	228.0 nm	257.0 nm	IBU	PCM
Day 1	0.868	1.066	98.05	97.12
Day 2	0.857	1.061	96.00	96.87
Day 3	0.859	1.055	97.03	96.12
Mean			97.02	96.70
SD			1.024	0.520
%RSD			1.056	0.538

3.2.3. Accuracy

Simultaneous Equation Method: Recovery studies performed at three concentration levels demonstrated excellent accuracy for all methods. IBU showed recovery values ranging from 99.85% to 100.5%, while PCM exhibited recoveries between 97.00% and 100.6%. These results fall within the acceptable range of 95-105%, confirming the accuracy of the developed methods [14].

Table 8. Results of Accuracy Studies for Simultaneous Equation Method

Sr. No.	Amount Added (µg/ml)		% Recovery	
	IBU	PCM	IBU	PCM
1	12.8	10.8	99.85	100.6
2	16	13	100.5	98.53
3	19.2	15.6	100.2	97.00
Mean			100.1	98.71
SD			2.155	1.137
% RSD			2.037	2.479

Absorbance Ratio Method: Recovery studies were performed at three concentration levels. Paracetamol showed recovery in the range of 97.54-100.5%, while Ibuprofen demonstrated recovery between 97.32-99.98%. These values fall within the acceptable range for pharmaceutical analysis

Table 9. Results of Accuracy Studies for Absorption Ratio Method

Sr. No.	Amount Added (µg/ml)		% Recovery	
	IBU	PCM	IBU	PCM
1	12.8	10.8	97.40	100.5
2	16	13	99.98	96.36
3	19.2	15.6	97.32	97.54
Mean			98.23	98.13
SD			1.513	2.132
% RSD			**1.540**	**2.173**

3.2.4. Sensitivity

The methods demonstrated appropriate sensitivity for routine analysis. The limit of detection (LOD) values for IBU ranged from 0.546 to 0.564 µg/mL, while PCM showed LOD values between 1.286 and 1.287 µg/mL. The limit of quantitation (LOQ) values for IBU were found to be between 0.142 and 1.286 µg/mL, and for PCM between 0.229 and 0.602 µg/mL. These values indicate sufficient sensitivity for reliable quantification at low concentrations [15].

3.3. Comparison of Methods

The sensitivity of both methods was compared through their respective LOD and LOQ values. In the simultaneous equation method, Paracetamol showed LOD and LOQ values of 1.287 µg/mL and 0.229 µg/mL respectively, while Ibuprofen demonstrated values of 0.546 µg/mL and 0.142 µg/mL. The absorbance ratio method showed comparable sensitivity with LOD and LOQ values of 1.286 µg/mL and 0.602 µg/mL for Paracetamol, and 0.564 µg/mL and 1.286 µg/mL for Ibuprofen.

The robustness of both methods was evaluated by deliberately varying the concentration of NaOH (0.09-0.11N). Both methods maintained their performance with RSD values below 2.5%, indicating good robustness. The absorbance ratio method showed slightly better tolerance to these variations compared to the simultaneous equation method.

Using the Design of Experiments, optimal conditions were established with a scan speed of 2, sampling interval of 1.0, and slit width of 1. Under these conditions, both methods proved suitable for routine analysis of Paracetamol and Ibuprofen in pharmaceutical formulations. The absorbance ratio method showed marginally better precision, while the simultaneous equation method showed superior sensitivity for Paracetamol quantification

4. Conclusion

The implementation of Quality by Design principles in the development of UV spectrophotometric methods for simultaneous determination of Paracetamol and Ibuprofen proved successful. The three developed methods - gradient UV, simultaneous equation, and absorbance ratio method - demonstrated excellent analytical performance characteristics. The optimization through Design of Experiments yielded robust analytical conditions with medium scan speed and sampling interval of 1.0. All methods showed good linearity in the concentration ranges of 2-20 µg/mL for Ibuprofen and 2-14 µg/mL for Paracetamol, with correlation coefficients greater than 0.990. The methods demonstrated high precision with RSD values below 2.2% and excellent accuracy with recovery values between 96.36-100.58%. The sensitivity parameters indicated reliable quantification at low concentrations. The developed methods are simple, cost-effective, and suitable for routine quality control analysis of Paracetamol and Ibuprofen in combined pharmaceutical formulations. The QbD approach ensured method robustness and reliability throughout the analytical range, making these methods valuable tools for pharmaceutical analysis.

References

[1] Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding pharmaceutical quality by design. The AAPS Journal. 2014;16(4):771-783.

[2] Maggio RM, Vignaduzzo SE, Kaufman TS. Practical and regulatory considerations for stability-indicating methods in pharmaceutical analysis. TrAC Trends in Analytical Chemistry. 2013;49:57-70.

[3] Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. Inflammopharmacology. 2013;21(3):201-232.

[4] Rainsford KD. Ibuprofen: from invention to an OTC therapeutic mainstay. International Journal of Clinical Practice. 2013;67:9-20.

[5] Jain DK, Patel N, Kushwaha A, Raghuwanshi N, Jain N. Development and validation of spectrophotometric method for simultaneous estimation of paracetamol and ibuprofen in bulk and tablet dosage form. Chemistry Research Journal. 2017;2(4):42-49.

[6] Dousa M, Hosmanova R. Rapid determination of ibuprofen in pharmaceutical formulations by HPLC using experimental design approach. Journal of Pharmaceutical and Biomedical Analysis. 2019;170:25-33.

[7] Kumar R, Singh P, Singh H. Development of UV spectrophotometric method for estimation of paracetamol in bulk and tablet formulation. International Journal of Pharmaceutical Sciences and Research. 2017;8(4):1881-1885.

[8] Sangoi MS, Wrasse-Sangoi M, Oliveira PR, Rolim CM, Steppe M. Simultaneous determination of drugs by spectrophotometry: A review. Journal of the Brazilian Chemical Society. 2017;28(7):1133-1147.

[9] Moreno AH, Salgado HR. Development and validation of a new spectrophotometric method for determination of ibuprofen. Physical Chemistry. 2012;2(1):6-11.

[10] Bezerra MA, Santelli RE, Oliveira EP, Villar LS, Escaleira LA. Response surface methodology (RSM) as a tool for optimization in analytical chemistry. Talanta. 2008;76(5):965-977.

[11] McPherson B, Williams R, Jahan S. Quality by design in the analytical laboratory: A practical implementation. Journal of Pharmaceutical Sciences. 2018;107(8):1872-1884.

[12] Rozet E, Ziemons E, Marini RD, Boulanger B, Hubert P. Quality by design compliant analytical method validation. Analytical Chemistry. 2012;84(1):106-112.

[13] ICH Harmonized Tripartite Guideline. Validation of analytical procedures: Text and methodology Q2(R1). International Conference on Harmonization. 2005.

[14] Ermer J, Miller JH. Method Validation in Pharmaceutical Analysis: A Guide to Best Practice. 2nd ed. Wiley-VCH; 2015.

[15] Swartz ME, Krull IS. Analytical Method Development and Validation. CRC Press; 2018.