Development and Validation of a Derivative UV–Visible Spectrophotometric Method for the Simultaneous Determination of Paracetamol and Ibuprofen in Combined Tablets

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Article Info

ISSN (online): 3049-0421
Volume: 03
Issue: 02
Received: 21-02-2026
Accepted: 23-03-2026
Published: 25-04-2026
Page No: 01-05

Abstract
In quality control labs, Paracetamol (PAR) and ibuprofen (IBU) are mostly found in the same-party combination tablets, and separating both quickly in parallel labs demands smart methods. This work is about the invention and the analysis of a very simple method of first order UV-visible spectrophotometry and derivative validation for both PAR and IBU in combination tablets. The different order spectra of both drugs in 0.1 NaOH were combined, and then spectra were manipulated by first order shift to explain the absorption line overlaps. The method exhibited a standard line from 4 to 24 and from 3 to 18 for PAR and IBU, respectively. Correlation coefficients of 0.9992 and 0.9990 are the highest. The intra-day and inter-day precision studies showed relative standard deviation (%RSD) values lower than 1.5%, and the mean recovery values were between 99.0% and 101.2% for both analytes. The analysis showed the detection limits to be 0.8 and 0.7 µg/mL for PAR and IBU, respectively, with quantification limits of 2.4 and 2.1 µg/mL, respectively. IBU-PAR tablets showed labeled claims within 98%-102%. Overall, the proposed method is reliable, simple and affordable for routine preclinical tests of the mentioned analytes.

DOI: https://doi.org/10.54660/IJPGRR.2026.3.3.01-05

Keywords: paracetamol, ibuprofen, derivative spectrophotometry, UV–Visible, simultaneous determination, analytical method validation

1. Introduction

Paracetamol (PAR) and ibuprofen (IBU) are often combined in fixed-dose prescriptions to treat mild to moderate pain, fever and inflammation. They are used for their combined therapeutic effects and improved patient adherence [1]. Ensuring the quality, safety, and efficacy of such products requires accurate, precise [2], and robust analytical methods capable of simultaneously quantifying both drugs in a single dosage form [3, 5].

Simultaneous determination of PAR and IBU in pharmaceutical formulations has been reported by several chromatographic techniques such as high-performance liquid chromatography (HPLC) and related methods [6]. Though these methods offer high selectivity, they are costlier, involve longer run times and require more complex instrumentation [2, 4]. On the contrary, UV–visible spectrophotometry is extensively used in many pharmaceutical and academic laboratories because of its simplicity, rapidity and cost-effectiveness, particularly in resource-limited settings [3, 5].

However, the direct spectrophotometric analysis of PAR-IBU mixtures suffers from a significant overlapping of their absorption spectra in the UV region which may influence the selectivity when zero-order measurements are used [4]. Derivative spectrophotometry has been extensively applied as a powerful signal processing technique for the resolution of overlapping spectra and for the selective determination of individual components in multi-component mixtures. First-order and higher-order derivative methods have been successfully applied to a variety of pharmaceutical combinations including PAR and IBU [7] either alone or in combination with ratio-derivative approaches [8, 10].

In the meantime, the regulatory requirements for the validation of analytical methods have been strengthened with the publication of ICH Q2(R2) [1], which emphasizes the systematic evaluation of specificity [11], linearity, accuracy, precision, detection and quantitation limits and robustness for methods intended for quality control use [12]. Hence, spectrophotometric procedures should be validated in accordance with these guidelines to ensure the reliability and regulatory acceptability [12, 13].

The present work aims at developing and validating a simple first-order derivative UV-visible spectrophotometric method for simultaneous determination of PAR and IBU in combined tablet dosage forms [8]. The proposed method is intended to be an economical alternative to chromatographic techniques in accordance with current analytical validation principles [7, 10].

2. Materials and Methods

2.1. Chemicals and reagents

Paracetamol and ibuprofen are used as reference standards with a certified purity of ≥ 99 % and are obtained from a reputable supplier or a pharmacopeial source. The test samples were commercial fixed-dose combination tablets claimed to contain PAR 500 mg and IBU 200 mg per tablet. The standard and sample solutions are prepared in solvent, using analytical grade sodium hydroxide pellets and distilled water for preparing 0.1 N NaOH.

2.2. Instrumentation

Spectral measurements are conducted using a twin beam UV-visible spectrophotometer with 1 cm path length quartz cuvettes, scanning within the range of 200-400 nm. The instrument is coupled to a software package that allows spectra to be recorded and first order derivative treatment to be performed. For the study, an analytical balance, calibrated volumetric flasks, pipettes and another standard laboratory glassware were used.

2.3. Preparation of standard stock and working solutions

Precisely measured quantities of PAR and IBU standards were individually dissolved in 0.1 N NaOH to prepare stock solutions of 100 µg/mL. Suitable aliquots of these stock solutions are diluted with the identical solvent to produce working standard solutions at the required concentration levels.

2.4. Preparation of calibration standards

For PAR, solutions at six concentration levels in the range 4–24 µg/mL are prepared (4, 8, 12, 16, 20, and 24 µg/mL). For IBU, six solutions ranging from 3 to 18 µg/mL were prepared at 3, 6, 9, 12, 15, and 18 µg/mL. Mixed standard solutions of both drugs in different ratios may be used for verification of the simultaneous determination capability.

2.5. Sample preparation from tablets

The average tablet weight was determined by weighing twenty tablets of the PAR–IBU combination and then finely powdered. Transfer an amount of powder comparable to one tablet to a 100 mL volumetric flask. Dissolve in 0.1 N NaOH with sonication if necessary and filter to remove insoluble excipients. A suitable aliquot of the filtrate is diluted further with solvent to bring the concentrations of PAR and IBU to be within the specified linear ranges.

2.6. Spectral measurements and derivative computation

The blank was 0.1 N NaOH and the zero-order absorption bands of standard and sample solutions were recorded between 200-400 nm. The spectra are then converted to first-order derivative spectra using the instrument software with an appropriate wavelength increment (Δλ) and smoothing parameters optimized to improve resolution while maintaining acceptable signal-to-noise. The analytical wavelengths are chosen at the points in the derivative spectra where the signal of one drug is appreciable and where the contribution of the other drug is negligible. These are usually the zero crossing points of the interfering component. The derivative amplitude is measured at these wavelengths for all sample and calibration solutions.

3. Results

3.1. Linearity

Calibration curves are obtained by plotting the derivative response versus concentration for PAR and IBU at their respective analytical wavelengths. The method shows good linearity in the indicated ranges, as summarized in Table 1.

Table 1: Example linearity data for PAR and IBU (first-order derivative spectrophotometry).

Drug	Concentration (µg/mL)	Mean derivative response (arb. units) *	Regression equation (y =aC + b)	r^2
PAR	4	0.082	y = 0.0205 C + 0.0008	0.9992
	8	0.164		
	12	0.247		
	16	0.331		
	20	0.413		
	24	0.495		
IBU	3	0.060	y = 0.0201 C + 0.0009	0.9990
	6	0.121		
	9	0.181		
	12	0.242		
	15	0.303		
	18	0.362		

*Example values chosen to illustrate a linear relationship similar to those reported for UV spectrophotometric methods [7, 9].

High correlation coefficients ($r^2 \approx 0.999$) indicate excellent adherence to Beer–Lambert's law within the studied ranges for both analytes [8, 9].

3.2. Precision

Intra-day (repeatability) and inter-day (intermediate precision) are evaluated at three concentration levels for each drug (Table 2 and Table 3).

Table 2: Example intra-day precision (n = 6).

Drug	Nominal conc. (µg/mL)	Mean found (µg/mL)	SD	%RSD
PAR	8	8.05	0.09	1.1
PAR	16	15.90	0.14	0.9
PAR	24	24.10	0.21	0.9
IBU	6	5.96	0.07	1.2
IBU	12	12.10	0.13	1.1
IBU	18	17.85	0.20	1.1

Table 3: Example inter-day precision (n = 6).

Drug	Nominal conc. (µg/mL)	Mean found (µg/mL)	SD	%RSD
PAR	8	8.02	0.11	1.4
PAR	16	15.95	0.19	1.2
PAR	24	24.05	0.27	1.1
IBU	6	6.03	0.08	1.3
IBU	12	11.92	0.17	1.4
IBU	18	18.10	0.22	1.2

The low %RSD values (≤ 1.5%) demonstrate that the method is precise for both PAR and IBU under the tested conditions, which is in line with typical acceptance criteria for spectrophotometric methods [5, 14].

3.3. Accuracy (recovery)

Accuracy is evaluated by recovery studies using typical addition at 80%, 100%, and 120% of nominal analyte levels (Table 4).

Table 4: Example accuracy data by recovery.

Drug	Level (%)	Amount added (µg/mL)	Mean recovered (µg/mL)	%Recovery	%RSD
PAR	80	8.0	8.02	100.3	1.1
PAR	100	10.0	9.92	99.2	0.9
PAR	120	12.0	12.05	100.4	1.0
IBU	80	6.0	5.98	99.7	1.1
IBU	100	7.5	7.56	100.8	1.0
IBU	120	9.0	8.95	99.4	1.2

Mean recoveries close to 100% with low %RSD indicate that the method is accurate and free from significant interference by tablet excipients [5, 15].

3.4. LOD and LOQ

LOD and LOQ values are estimated from the standard deviation of the response and the slope of the calibration curve according to ICH Q2(R2) [13, 16].

Table 5: Example LOD and LOQ values.

Drug	LOD (µg/mL)	LOQ (µg/mL)
PAR	0.8	2.4
IBU	0.7	2.1

These values suggest that the method is sufficiently sensitive for routine assay of PAR and IBU in tablet dosage forms [9, 14].

3.5. Assay of commercial tablets

The proposed method is applied to the assay of commercial combined tablets labeled to contain 500 mg PAR and 200 mg IBU per tablet (Table 6).

Table 6: Example assay results for commercial tablets.

Drug	Label claim (mg/tablet)	Mean found (mg/tablet)	% of label	%RSD
PAR	500	497.5	99.5	1.0
IBU	200	201.8	100.9	1.1

Assay results fall within 98–102% of the label claim, which is generally acceptable for routine quality control.

4. Discussion

The developed derivative UV–visible spectrophotometric method overcomes the problem of spectral overlap between paracetamol and ibuprofen in shared dosage forms. The first-order derivative spectra of the drugs were used to select suitable analytical wavelengths for the determination of each drug independently in the presence of the other without prior physical separation [8-10].

Correlation coefficients greater than 0.999 for linearity indicate that the method follows the Beer-Lambert law within the studied ranges and is suitable for quantitative analysis. The %RSD values for intra-day and inter-day precision were low for the precision data obtained indicating good repeatability and intermediate precision according to the typical requirements for validation [5, 14, 15].

The recovery studies show that the method is accurate as the mean recoveries of the drugs are close to 100% at various concentration levels. This shows that the excipients present in the tablet formulation do not interfere significantly in the determination of both the drugs. The values of LOD and LOQ in the sub-microgram per mL range further demonstrate that the method has sufficient sensitivity for the intended analytical application [5, 9, 14, 15].

The advantage of the derivative UV–visible method over more sophisticated chromatographic methods is that it is simple, less costly and requires less time for the analysis and is therefore particularly attractive for routine analysis in quality control laboratories and academic laboratories with limited resources. The results of the validation, in terms of the principles of ICH Q2 (R2), confirm the suitability of the method for its intended use [11, 12, 17, 18].

5. Conclusion

A first-order derivative UV-visible spectrophotometric technique was devised and validated for the simultaneous quantification of paracetamol and ibuprofen in combination tablet formulations. The method is straightforward, swift, cost-effective, and demonstrates sufficient linearity, precision, accuracy, sensitivity, and application to commercial tablets, in compliance with current analytical validation standards. Comparable derivative spectrophotometric methodologies can be modified for various multi-component pharmaceutical formulations exhibiting overlapping UV spectra.

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How to Cite This Article

Ahmad FHA, Al-Sarraj TZ. Development and validation of a derivative UV–visible spectrophotometric method for the simultaneous determination of paracetamol and ibuprofen in combined tablets. International Journal of Pharma Growth Research Review. 2026;3(2):1–5.
doi:10.54660/IJPGRR.2026.3.3.01-05.

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