Determination of Ibuprofen content in tablets using Raman spectroscopy

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Abstract

Background: Raman spectroscopy has emerged as a powerful analytical technique widely applied across various research fields due to its rapid, non-destructive nature. This study was conducted to explore the applicability of Raman spectroscopy in the quantitative analysis of pharmaceutical formulations and to contribute to the optimization of quality control processes during tablet manufacturing. **Materials and Methods:** Ibuprofen tablets with varying active ingredient contents were prepared to investigate their Raman spectral profiles. Chemometric approaches were applied to develop quantitative calibration models. The analytical method was validated in accordance with ICH and AOAC guidelines. **Results:** Spectral acquisition was performed over the range of 150 cm^{-1} to 2800 cm^{-1}, yielding distinct characteristic peaks. The optimal measurement conditions included intensity-based signal acquisition with an integration time of 27 seconds. The developed Raman method demonstrated high specificity, linearity, and accuracy within the concentration range of 32.4% to 48.6% w/w of Ibuprofen in tablets. Comparative analysis between the Raman and HPLC methods showed no statistically significant difference in quantification results. **Conclusion:** A reliable and validated Raman spectroscopic method was successfully developed for the quantification of Ibuprofen in 200 mg tablet formulations. The results obtained were consistent with those of the HPLC method described in the Vietnamese Pharmacopoeia, Edition V, confirming the potential of Raman spectroscopy as an alternative analytical tool for routine quality control.

Keywords*: Ibuprofen (IBU), Raman, High performance liquid chromatography (HPLC).*

1. BACKGROUND

Raman spectroscopy is currently one of the powerful tools widely used in many research fields with the advantages of a fast and non-destructive analysis process [1]. It offers significant benefits in pharmaceutical analysis, including the identification of raw materials, the quantification of active ingredients across diverse formulations [2]. Raman spectroscopy offers significant advantages for analyzing tablets, powders, and liquid formulations, as it reduces mechanical handling, thus preserving the physicochemical integrity of the samples. It is an effective technique for pharmaceutical analysis, enabling direct quality control measurements through blister packaging. This approach provides a fast and efficient method for drug quality assessment in the pharmaceutical industry, eliminating the need for unpacking or sample preparation, and streamlining the testing process [2, 3, 4]. Raman spectroscopy has been extensively investigated for its applicability in the quantitative analysis of active pharmaceutical ingredients (APIs) in solid dosage forms. Several studies have reported its successful use in determining compounds such as diclofenac sodium [5], thiamine hydrochloride [6], demonstrating high precision and reliability. As solid dosage forms-particularly tablets and capsules-remain the most common method of drug formulation and administration, Raman spectroscopy presents a promising, non-destructive analytical technique suitable for quality control and in-process monitoring within pharmaceutical manufacturing. It is well established that the bioavailability and stability of an active pharmaceutical ingredient (API) are significantly affected by its solid-state characteristics, making it essential to identify and characterize these dosage forms [7]. For this purpose, a range of chromatographic and spectroscopic techniques are utilized to ensure the quality and integrity of the final pharmaceutical products [8]. Ibuprofen (IBU), (2RS)-1[4-(2-methyl propyl) phenyl] propionic acid, is a nonsteroidal anti-inflammatory drug (NSAID) used to manage various conditions, including inflammatory diseases, rheumatoid disorders, mild to moderate pain, fever, dysmenorrhea, and osteoarthritis [9]. In the current Vietnamese Pharmacopoeia V [10], the quantification of IBU tablets is commonly conducted using high-performance liquid chromatography

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(HPLC). However, this method has drawbacks, including time-consumption and requirement of excessive chemical solvents, labor, and resources. Raman spectroscopy is a strong candidate in this context due to its rapid data acquisition, non-destructive nature, cost-effectiveness, minimal sample preparation, and broad applicability in aqueous media. These advantageous attributes make Raman spectroscopy an appealing technique for the analysis of solid-state pharmaceutical drugs [11]. Therefore, this study was conducted to evaluate the potential of Raman spectroscopy as a quantitative analytical technique in pharmaceutical applications, specifically through the development and validation of a method for the determination of Ibuprofen in tablet formulations. Furthermore, the performance of the Raman method was compared with that of the conventional HPLC method, with the goal of supporting improved quality control practices during the manufacturing process.

2. MATERIALS AND METHODS

2.1. Materials and equipments

Sample preparation: IBU was manufactured by Shanghai Macklin Biochemical Technology Co., Ltd, with a purity of 98%. The excipients included corn starch, carboxymethylcellulose, sodium citrate, sodium laureth sulfate, magnesium stearate, aerosil, tapioca starch. IBU tablets are often commercially prepared at a content of 200 mg. To determine this IBU content by Raman method, the study prepared IBU tablets at various contents of 140 mg, 160 mg, 180 mg, 200 mg, 220 mg, 240 mg, 260 mg.

Equipments: Rotary Tablet Press NRTP-200, SHIMADZU LC-20A HPLC system (PDA detector (Japan), C18 stationary phase column (4.6 mm x 250 mm, 5 µm) from Thermo Electron Corporation (USA)). QT Raman system from B&W Tek (USA), 785 nm laser. Data analysis software includes B&W Tek Analyst and TQ Analyst.

2.2. Method

2.2.1. Preparation of test samples

To develop a quantitative procedure for Ibuprofen using Raman spectroscopy, tablet formulations at seven dosage strengths-140 mg, 160 mg, 180 mg, 200 mg, 220 mg, 240 mg, and 260 mg-were prepared. The granules were produced via the wet granulation method [12], with compositions consisting of IBU (53%), corn starch (40%), sodium carboxymethylcellulose (4%), sodium citrate (1%), sodium laureth sulfate (0.6%), magnesium stearate (0.5%), aerosil (0.5%), starch paste (0.4%), and purified water (*quantum satis*). For each target strength, the appropriate quantity of active granules was used, and differences in tablet weight among formulations were adjusted by incorporating placebo granules-identical in composition but devoid of IBU.

2.2.2. Analytical procedure

The conditions for spectral measurement were investigated using the QT Raman system from B&W Tek (USA), and a quantification model was selected using the TQ Analyst software.

The method was validated according to the guidelines of ICH [13] and AOAC [14], including specificity, linearity, range, accuracy, and precision.

A comparative analysis was conducted between the Raman spectroscopy-based quantification method and the high-performance liquid chromatography (HPLC) method as described in the Vietnamese Pharmacopoeia V [10], The chromatographic system comprised a C18 reversed-phase column (4.6 mm x 250 mm, 5 µm), with a mobile phase consisting of 0.01 M phosphoric acid and acetonitrile in a 60:40 (v/v) ratio. The flow rate was maintained at 1.5 mL/min, and detection was carried out at a wavelength of 224 nm using a UV detector. The injection volume was 20 µL.

Preparation of the standard solution: Approximately 100 mg of Ibuprofen reference standard was accurately weighed and transferred into a 50.0 mL volumetric flask. The standard was dissolved in the mobile phase and diluted to volume. The solution was mixed thoroughly to ensure complete dissolution.

Preparation of the sample solution: Twenty tablets were weighed after the film coating was removed to calculate the average tablet weight. The tablets were then powdered finely. An accurately weighed portion of the powder, equivalent to approximately 200 mg of Ibuprofen, was transferred into a 100.0 mL volumetric flask. Sixty milliliters of the mobile phase was added, and the mixture was shaken vigorously for 20 minutes to ensure complete extraction. Afterward, the volume was brought up to 100.0 mL with the mobile phase and mixed thoroughly. The resulting solution was filtered or centrifuged prior to injection into the HPLC system. The analytical results were then compared accordingly.

2.2.3. Statistical analysis

The t-Test was used to compare the results obtained from Raman spectroscopy and HPLC. Before applying the t-Test, an F-test was conducted to compare the variances. If no significant difference in variances is found, the t-Test: Two-Sample

Assuming Equal Variances is used. If there is a significant difference in variances, the t-Test: Two-Sample Assuming Unequal Variances is applied [15]. The confidence level is 95% Or the significant differenceis less than or equal to 0.05.

3. RESULTS

3.1. Development of a quantitative method using Raman spectroscopy

3.1.1. Raman spectral acquisition

Through the survey process, the study selected the spectral range for measurement: from 150 cm^{-1} to 2800 cm^{-1} for spectral signals and characteristics. The type of spectral measurement chosen was Raman intensity. The sample scanning time, as optimized using B&W Analyst software, was determined to be 27 seconds. For constructing the quantitative model, each concentration level was scanned 10 times on two sides of each sample.

3.1.2. Analyst development of a quantitative model using TQ analyst software

The measurement results obtained from the QT Raman system by B&W Tek are exported, and the data are subsequently used to develop the quantitative model using TQ Analyst software.

Data preprocessing: Due to differences in pathlength, the absolute intensity of the spectral peaks may vary. Therefore, the Raman spectra of the samples will be normalized after measurement to ensure consistency between the spectra [15].

Assign spectral values: The spectra will be assigned to their corresponding concentrations (Table 1) to build the model using appropriate Chemometrics algorithms.

Table 1. *Active Pharmaceutical Ingredient Concentration in the Tablet Formulation*

	Tablet 140 mg	Tablet 160 mg	Tablet 180 mg	Tablet 200 mg	Tablet 220 mg	Tablet 240 mg	Tablet 260 mg
IBU granules 53% (mg)	18590.20	21246.00	23901.70	26557.50	29213.20	31869.00	34524.70
Placebo granules (mg)	15934.50	13278.70	10623.00	7967.20	5311.50	2655.70	0.00
Blended granules (mg)	34524.70	34524.70	34524.70	34524.70	34524.70	34524.70	34524.70
C% IBU (%)	28.40	32.40	36.50	40.50	44.60	48.60	52.70

Selection of Chemometrics Models: The Partial Least Squares (PLS) model and the Principal Component Regression (PCR) model are two commonly used methods for developing multivariate quantitative models, including the analysis of multivariate spectra to construct the quantitative model [15]. In these models, the spectra of the analyte will be computed directly or through some initial spectral preprocessing steps such as smoothing, derivatization, normalization, etc [15]. In PCR, data transformation into a new space is performed by using only information from the spectral features, such as the absorption data at specific wavelengths. In contrast, PLS regression can combine both feature information and observations, meaning it incorporates both the absorption at the wavelengths and the corresponding concentration measurements. Several studies have shown that PLS analysis can provide regression models with better results than the PCR method when applied to spectral data [16, 17]. Therefore, the Partial Least Squares (PLS) model is used to establish the quantitative method. The PLS algorithm is extensively employed as a calibration method in the quantitative analysis of complex mixtures [18]. The reliability of the calibration models was evaluated by determining the root mean square error of calibration (RMSEC) and prediction (RMSEP), the optimal number of factors used in model construction, as well as the correlation coefficients for both calibration and prediction phases [18, 19].

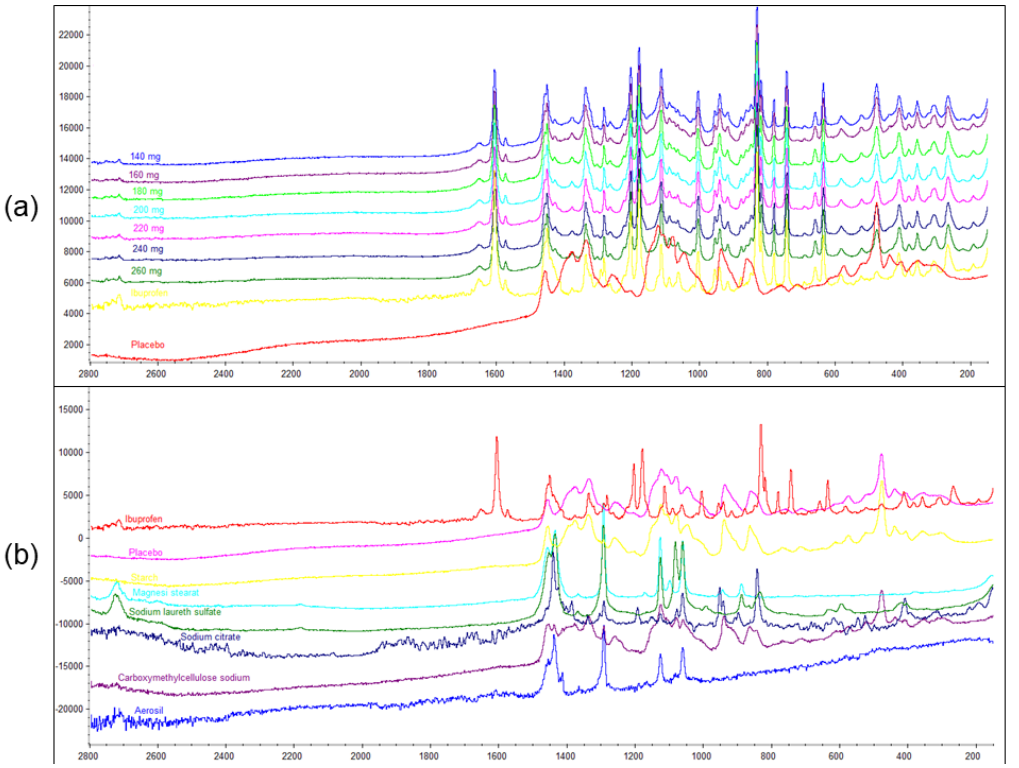

Figure 1. Raman spectrum of Ibuprofen tablets at different concentrations, Ibuprofen standard and excipients in the range of 150 cm^{-1} to 2800 cm^{-1} (a: IBU tablets spectrum at different concentrations, b: IBU standard and excipients spectrum)

Selection of the analyzed spectral range: based on the Raman spectrum of the Ibuprofen standard material (Figure 1), the analyzed spectral ranges are 170 - 445 cm^{-1}, 560 - 1300 cm^{-1} and 1530 - 1700 cm^{-1}.

Selection of the number of Factors: In multivariate analysis, the larger the number of factors, the more accurate the model becomes. However, increasing the number of factors can lead to overfitting, where the model becomes too closely aligned with the training data [15]. After performing the diagnostic using TQ Analyst software, the recommended number of factors selected was 3 in figure 2b.

3.1.3. The results of the developed quantitative model

After applying spectral preprocessing methods and data analysis using Chemometrics on the TQ Analyst software, the quantitative model for IBU by Raman, based on the C% value (percentage of Ibuprofen by weight relative to the total tablet weight, % w/w), is calculated as follows: Perform Raman spectrum scanning of the tablet, assign the measured spectra to the corresponding quantitative model to determine the C% value. The final C% value is the average of five scans.

3.2. Validation of the developed quantitative model

3.2.1. Specificity

During the analysis, it was observed that the Raman spectrum of the IBU standard material shows peaks in the spectral ranges of 170 - 445 cm^{-1}, 560 - 1300 cm^{-1} and 1530 - 1700 cm^{-1}. The spectrum of Ibuprofen combined with excipients also shows peaks in these spectral ranges. Furthermore, the spectrum of Ibuprofen at different concentrations (from 140 mg to 260 mg) combined with excipients in the tablet formulation also exhibits peaks in these ranges and is not affected by the spectrum of the excipients. Therefore, the model demonstrates high specificity for determining the Ibuprofen content in tablet formulations.

3.3.2. Linearity

The linearity of the method is evaluated through the R value (Corr. Coeff.) of the regression plot between the actual values and the calculated values (Figure 2a) from the model. With an R value of 0.99694, it indicates a strong linear correlation between the actual and calculated values.

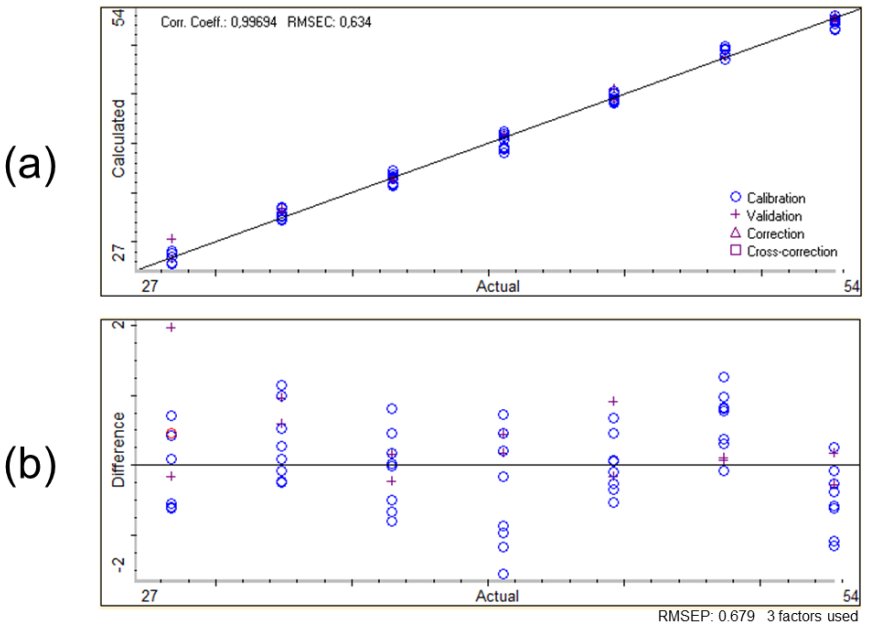

Figure 2. Quantitative model for Ibuprofen using Raman spectroscopy
(a: Regression plot of actual versus calculated values from the model, b: Deviation chart)

3.3.3. Accuracy

The accuracy of the model is evaluated by measuring the formulated tablets (with the content determined by the HPLC method) at concentration values of 160 mg, 200 mg, and 240 mg [13]. The recovery of Ibuprofen is determined based on the C% concentration values calculated from the Raman quantitative model. The requirement is that the recovery should be within 98.0% – 102.0%, with an RSD < 2% at the concentration levels specified by AOAC [14]. The results are presented in Table 2.

Table 2. Recovery of Ibuprofen content using Raman Spectroscopy

Sample	Tablet Weight (mg)	IBU Weight (mg)	Granules Concentration (%, w/w)	Raman-determined IBU Concentration (%, w/w)	Recovered IBU Weight (mg)	IBU Recovery (%)	Average ± RSD
160.1	497.10	161.21	32.43	32.65	162.30	100.68	100.21 ± 0.51
160.2	491.60	159.43	32.43	32.32	158.89	99.66	
160.3	500.20	162.21	32.43	32.52	162.67	100.28	
200.1	485.90	196.98	40.54	40.72	197.86	100.44	99.62 ± 1.05
200.2	506.50	205.34	40.54	39.91	202.14	98.45	
200.3	496.00	201.08	40.54	40.53	201.03	99.98	
240.1	490.50	238.63	48.65	48.57	238.24	99.84	98.81 ± 0.89
240.2	488.30	237.56	48.65	47.82	233.51	98.29	
240.3	489.70	238.24	48.65	47.83	234.22	98.31	

The results showed that the recovery of Ibuprofen was within the range of 98.0% - 102.0%, with an RSD < 2%, fulfilling the AOAC criteria.

3.3.4. Determination Range

From the results in Table 2, the method demonstrates accuracy and repeatability within the concentration range of 160 mg - 240 mg (or C% from 32.4% to 48.6%).

3.3.5. Intermediate Precision

Intermediate precision is determined by quantifying three independent IBU tablet samples of the same

contents: 160 mg, 200 mg, and 240 mg [13]. The results were analyzed in duplicate on two different days to assess the day-to-day precision. The requirement is that the RSD should be ≤ 3.0% at the concentration levels specified by AOAC [14]. The results are presented in Table 3.

Table 3. Intermediate Precision of the Method

Sample	Day 1		Day 2	
	Ibuprofen content (mg)	RSD (%)	Ibuprofen content (mg)	RSD (%)
160.1	32.65		32.74	
160.2	32.70	0.63%	33.57	1.40%
160.3	32.32		32.80	
200.1	40.72		40.39	
200.2	39.87	1.11%	40.07	0.80%
200.3	40.53		40.72	
240.1	48.57		48.76	
240.2	48.14	0.57%	48.04	0.86%
240.3	48.06		48.05	

The results demonstrate that both the intra-day and inter-day precision of the method have an RSD < 3.0%, meeting the AOAC requirements.

3.3.5. Comparison of ibuprofen quantification results using Raman spectroscopy and HPLC method

Quantification of 6 Ibuprofen tablet formulations was performed using Raman spectroscopy, and the same formulations were subsequently quantified using the HPLC method.

Tablets were weighed and then ground into a fine powder. An accurately weighed portion of the powder equivalent to one tablet was transferred to a suitable container, followed by the addition of 60.0 mL of the mobile phase. The mixture was shaken for 20 minutes to ensure complete extraction. After extraction, the volume was adjusted to 100.0 mL with additional mobile phase and mixed thoroughly. The resulting solution was filtered or centrifuged prior to HPLC analysis. The analytical results were then compared accordingly. The results obtained are presented in Table 4.

Table 4. Comparison of results obtained from HPLC and Raman spectroscopy methods

Sample	Ibuprofen Concentration in Tablets (mg)		F-Test Two-Sample for Variances	Use of Statistical Test	P(T<=t) two-tail	α
	Raman	HPLC				
200.1	200.97	201.04	P(F<=f) one-tail = 0.218	t-Test: Two-Sample Assuming Equal Variances	0.915	0.05
200.2	201.58	199.34				
200.3	203.56	204.94				
200.4	199.16	198.23				
200.5	200.20	201.81				
200.6	202.73	202.09				

The P-value (P(T<=t) two-tail) is greater than α (α = 0.05), indicating that the Ibuprofen quantification results in the tablet formulations obtained by Raman spectroscopy and HPLC methods do not show a statistically significant difference with 95% confidence.

A comparative analysis of the Ibuprofen content in 20 tablets was conducted using both Raman spectroscopy and the HPLC method specified in the Vietnamese Pharmacopoeia V. Initially, the 20 tablets were individually analyzed by Raman spectroscopy to determine their IBU content. The same tablets were then collectively weighed, finely pulverized, and an accurately weighed portion of the powder-corresponding to approximately 200 mg of Ibuprofen-was subjected to HPLC quantification. To statistically compare the results obtained by the two methods, a one-sample t-test was performed. The mean IBU

content determined by Raman spectroscopy was 200.66 ± 0.92 mg, while that obtained via HPLC was 201.78 mg. The calculated p-value ($p(T \leq t)$, two-tailed) was 0.858, which exceeds the significance threshold of $\alpha = 0.05$. This indicates that there is no statistically significant difference between the two methods, confirming the consistency and reliability of Raman spectroscopy for quantifying IBU in tablet formulations at a 95% confidence level.

4. DISCUSSION

IBU, first introduced in 1969 as a member of the propionic acid derivative class, is widely recognized as a safe, over-the-counter analgesic and antipyretic for both adults and children. According to the UK's spontaneous adverse drug reaction reporting systems, IBU is rated as the safest of the conventional NSAIDs. As one of the most commonly used medications globally, this study selects IBU as the focus material for further research. To develop a quantification model for Ibuprofen in 200 mg tablets, it is necessary to establish a linear range of IBU content from 140 mg to 260 mg, representing 70% to 130% of the target concentration, allowing for content determination and accuracy assessment according to ICH guidelines. For each tablet content, varying amounts of IBU granules are used, with differences in granule weight compensated by placebo granules (granules without Ibuprofen). The tablets are then compressed to an approximate weight of 490 mg each.

In Raman spectroscopy, for qualitative analysis of sample components, the conventional method commonly used is backscattering Raman spectroscopy, which measures the surface layer of the sample. However, when this method is applied for quantitative analysis of solid dosage forms, it presents certain limitations. Backscattering Raman spectroscopy probes only the surface layer of the sample, and does not capture the overall composition of the bulk material. Since most solid dosage forms are heterogeneous mixtures, analyzing only the surface layer may not yield accurate or representative results. Consequently, for quantitative analysis of solid formulations using Raman spectroscopy, the transmission Raman method is employed. This technique collects signals transmitted through the entire thickness of the sample, providing spectra that are more representative of the bulk composition compared to conventional backscattering Raman measurements.

About chemometric method selection for quantitative analysis, Partial Least Squares (PLS) and Principal Component Regression (PCR) are two common multivariate regression methods used to develop quantitative models from spectral data. These models often include spectral preprocessing techniques such as smoothing, derivatization, and normalization. In PCR, data are transformed into a new space using only spectral features, such as absorbance at different wavelengths. Meanwhile, PLS combines both spectral data and reference concentrations during model construction. Some studies have shown that PLS can provide better performance than PCR for spectral data [17]. Therefore, the PLS model was selected for quantitative analysis in this study.

Compared to similar studies in the field, our work significantly advances the accuracy and applicability of Raman spectroscopy for the quantitative determination of Ibuprofen. Specifically, while Omar et al. (2020) [20] demonstrated the capability of quantifying Ibuprofen using Partial Least Squares (PLS) regression across a broad concentration range (7.1% - 92.3% w/w) with a Root Mean Square Error (RMSE) of 6.2% - a level considered acceptable for a rapid screening method-our investigation focused on a more stringent and pharmaceutically relevant concentration range typically found in commercial tablets (32.4% – 48.6% w/w). A key distinction of our methodology lies in the meticulous optimization of spectral acquisition parameters, including a broad spectral range of 150 - 2800 cm^{-1} and an integration time of 27 seconds, coupled with a thorough spectral preprocessing workflow. These optimizations enabled our PLS model to achieve superior quantitative accuracy and trueness. This is unequivocally demonstrated by the comprehensive validation results conducted in accordance with ICH and AOAC guidelines, which revealed no statistically significant difference when compared to the established HPLC method. This enhanced level of precision and accuracy, particularly within the target concentration range, strongly affirms that our developed Raman method is not merely suitable for rapid screening but possesses substantial potential for routine quality control applications, ensuring stringent adherence to pharmaceutical standards.

Using spectral characteristics and data processing algorithms in Chemometrics, this study successfully developed a quantification model for Ibuprofen in known formulated tablet samples. Building the model on known samples has the advantage of enabling future quantification by simply scanning the spectrum of the drug sample and applying it directly to the model to obtain immediate results. As

a result, this method allows for direct quantification with minimal to no sample preparation, leading to significant savings in time and costs, as well as increased productivity.

5. CONCLUSIONS

The study successfully established a direct quantification procedure for Ibuprofen in formulated 200 mg tablets using Raman spectroscopy. Raman spectral conditions were optimized with a 785 nm laser and a spectral range from 150 cm^{-1} to 2800 cm^{-1}, with a sample scan time of 27 seconds. The quantification procedure was validated, demonstrating high specificity and accuracy, with recoveries ranging from 98.76% to 99.92%. There was no statistically significant difference in Ibuprofen quantification results between the Raman spectroscopy method and the HPLC method at a 95% confidence level. Therefore, the Raman method, with its rapid sample measurement, provides reliable results and shows great potential in pharmaceutical production for quality assurance and productivity enhancement.

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