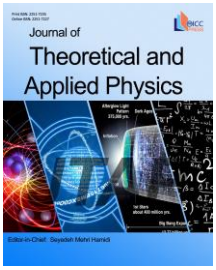

J. Theor. Appl. Phys 2026; 20(1): 33-44

Journal of Theoretical and Applied Physics
(JTAP)

https://doi.org/10.57647/jtap.2026.2001.04

Research Article

Safety Assay of Marketed Paracetamol Tablet by Using Raman Spectroscopy Technique

Mohadeseh Keshavarz Mohammadian, Somayeh Karimi,
Seyed Hassan Tavassoli*

Laser and Plasma Research Institute, Shahid Beheshti University, Evin, 1983969411, Tehran, Iran

***Corresponding author:** h-tavassoli@sbu.ac.ir

Article History:

Received:
14 September 2025

Revised:
19 October 2025

Accepted:
09 November 2025

Published Online:
06 December 2025

Published in Issue:
28 February 2026

©2026 the Author(s). Published by the OICC Press under the terms of the © CC BY 4.0, Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Abstract

Controlling and identifying the degraded products and impurities in the drug materials are the key issues in assuring the stability and quality of drugs throughout their shelf life, from both pharmaceutical and toxicological perspectives. Although, the drugs are packaged in a controlled environment at room temperature (25°C; 60% Relative Humidity (RH)), they may be exposed to elevated temperature and humidity during use, especially in regions with diverse climatic conditions. This study investigates the degradation of the Active Pharmaceutical Ingredient (API) of paracetamol tablet due to storage in inappropriate environmental conditions. The empirical method relies on the investigation of the respective Raman spectra of two groups of tablets; bare and packaged tablets. First, the accuracy of the analytical method used is evaluated, showing acceptable precision and accuracy within the range of the pharmacopeia guidelines with the Relative Standard Deviation (RSD)of less than ±5%. The tablet packaging effectively prevents moisture absorption; however, the API degradation process due to increased temperature is inevitable, and noticeable degradation in both tablet groups takes place after 30 minutes. The resulting data is validated using paracetamol tablets produced by different companies. Exposure to elevated temperatures leads to a noticeable degradation of paracetamol across different brands, all following similar trends. Also, the inappropriate environmental conditions result in the formation of the toxic compound P-aminophenol within the tablet. As the API degradation progresses, the corresponding characteristic Raman peak of P-aminophenol becomes more pronounced. Therefore, Raman spectroscopy technique can be operationalized as a standard method for online controlling of drug quality in both production lines and in the market.

Keywords: Raman spectroscopy; Stability testing; Paracetamol tablet; P-aminophenol, Storage condition; Tablet degradation

Cite this article: Mohadeseh. Keshavarz Mohammadian, Somayeh. Karimi & Seyed. Hassan. Tavassoli, (2026). Safety Assay of Marketed Paracetamol Tablet by Using Raman Spectroscopy Technique. *J. Theor. Appl. Phys.*, 20(1), 33-44. https://doi.org/10.57647/jtap.2026.2001.04

1. Introduction

Paracetamol (also known as acetaminophen or N-acetyl-p-aminophenol) is an analgesic and antipyretic drug and ranks as one of the most widely consumed non-prescription drugs worldwide . It has been used in various dosage forms; such as tablets, syrups, and suspensions, for different age groups, including children, women, pregnant women, and the elderly [4]. This drug is generally safe for human use at recommended doses. However, the use of fake or substandard drugs, as well as overdosing, can cause serious health risks to patient, including treatment failure, adverse reactions, and drug resistance [5-8]. In pharmacokinetic research, it is crucial to carefully examine various aspects of drug safety and stability from both pharmaceutical and toxicological perspectives [8-11]. The presence of the unwanted chemicals, even in small amounts, may influence the efficacy and safety of the pharmaceutical products. This also applies to paracetamol products. Poor quality may lead to the formation of P-aminophenol, a hydrolytic by-product with nephrotoxic and teratogenic effects [3]. According to the World Health Organization (WHO), more than a quarter number of drug products on sale for consumption have been reported as counterfeit or substandard products [12]. For this reason, understanding effective degradation mechanisms and controlling various drug parameters are essential to ensure stability and potency throughout manufacturing, storage, and patient use [13]. The objective of stability study is to determine the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic and microbial properties [14-16]. One of the main factors of the API degradation can be caused by inappropriate environmental conditions during transportation, storage and use, especially in tropical climates [6-8, 17]. Environmental factors, including increased temperature, high humidity level, oxidation, and exposure to light, cause to chemical and physical instability in the drugs [18-20]. Choosing appropriate drug packaging is crucial to maintain a product's effectiveness, safety, and performance throughout its shelf life [21-23]. Packaging should also protect against physical damage, material or ingredient loss, and the intrusion of harmful environmental factors like oxygen, water vapor, and light [23, 24]. Several pharmacopeias such as the International Conference on Harmonization (ICH), the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Japan Pharmacopoeia (JP), and etc. have developed globally recognized standard monographs to evaluate the stability and effectiveness of drugs at different climatic conditions (see Figure 1) [25-29]. Achieving an optimal formulation that involves carefully balancing the API content, drug dissolution profiles, and impurity levels are of great importance in guiding key processes such as mixing, drying, granulation, milling, and determining appropriate shelf life [30-32]. The requirement for ongoing quality and purity monitoring of medications and products has led to the development of various stability test techniques [3, 10]. Evaluating the parameters such as weight variation test, hardness, friability, disintegration, dissolution and assay test can be guaranteed the quality and efficacy of drugs [8, 22]. In this sense, analytical techniques such as electrochemical, spectroscopic, chromatographic, and electrophoresis methods have become increasingly prevalent [33-37]. Over recent decades, advances in chromatographic and spectroscopic methods have significantly led to changes in the guidelines in major pharmacopoeias [10, 38]. Updated monographs now incorporate more stringent and precise methodologies for testing drug materials, enhancing quality control and standardization across the industry [12]. Some of these methods though rapid, affordable, and precise, are nonselective and often have low accuracy. Also, they do not meet the criteria of standard monographs and the challenges such as a relatively large amount of sample, prevent from online using of these methods [10, 39-41]. As an instance, High-performance liquid chromatography (HPLC) lakes sufficient sensitivity and has the limited precision for assaying the drug content and detecting low levels of P-aminophenol in paracetamol tablets due to matrix interference [1-3]. Over the past few decades, there has been growing significant attention to ensuring the quality assurance and therapeutic efficacy of pharmaceuticals entering the market [3, 34, 42, 43]. Raman spectroscopy is a non-destructive and sensitive method that is used to for quality control, characterization of pharmaceutical formulations, monitoring of impurities, and identification of substandard drugs [44-46]. A major advantage of Raman-based analysis is its high accuracy and ability to reliably evaluate drug substances through a selective online control method at various stages, from production to consumption, even including from drug packaging [47-53]. Additionally, due to typically higher Raman scattering coefficients of APIs compared to common excipients, Raman spectroscopy can detect low levels of APIs and related substances [46, 53-55]. To the best of our knowledge, there are few studies on the quality evaluation of paracetamol tablets by using Raman spectroscopy [8, 56]. In Ref. [8], Raman imaging was used to study the stability of paracetamol tablets under different storage conditions. It has been demonstrated that p-aminophenol in paracetamol tablets can be detected at levels as low as 0.05%w/w, which is above the minimum levels established by pharmacopoeias.

10.57647/jtap.2026.2001.04

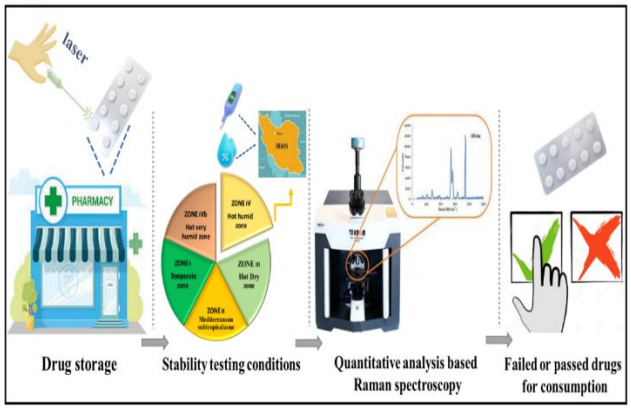

Figure 1. A Schematic representation of qualitative assessment of pharmaceutical materials using in situ Raman spectroscopy

Additionally, our previous works [46, 56] focused on evaluating the applicability and accuracy of Raman spectroscopy for the quantitative analysis of metformin hydrochloride and paracetamol tablets based on their spectra.

Our results indicate that Raman spectroscopy has a good adaption with pharmacopoeia monographs and can be applied as a routine method in the pharmaceutical industry. To the best of our knowledge, there are no quantitative Raman spectroscopy studies characterizing paracetamol API degradation or identifying P-aminophenol as a minor component in paracetamol tablets. The aim of the current study is to quantitatively investigate the degradation rate of API in marketed paracetamol tablets stored under inappropriate conditions, using Raman spectroscopy. In this regard, various experiments have been conducted to inspect the temporal changes of API under the elevated temperature and high levels of humidity, for the both groups of bare and packaged tablets.

Then, the trends of API degradation in the same environmental conditions are validated by using the products of different brands. The damaging effects of API degradation and the formation of p-aminophenol at elevated temperatures were evaluated using the Raman spectra of both tablet groups.

The importance of using appropriate packaging and maintaining optimal environmental conditions is investigated to ensure accurate API levels in paracetamol tablets available on the market.

Additionally, identifying impurities and degradation products can help prevent or at least control the risk of consuming substandard tablets. Finally, Raman spectroscopy offers a rapid and precise method for field testing the stability of packaged tablets throughout its shelf life.

2. Materials and methods

2.1. Materials

Paracetamol 500 mg tablets produced by the pharmaceutical companies Zagros Darou (S_0), Alborz Darou (S_1), Ariya Darou (S_2), Shafa (S_3), and Shahr Darou (S_4) were purchased from local pharmacies. The tablet batches used in the experiments were freshly manufactured and stored at room temperature under standard conditions following their purchase. In total, 198 tablets from sample S_0 and 30 tablets from S_1, S_2, S_3 and S_4 were used in the experiments. Additionally, five tablets of each sample were examined to determine the operational error in the experiments caused by various sources of error. Notably, half of the tablets were taken out of their packaging for testing (referred to as bare tablets), while the remaining tablets were analyzed in their original packaging.

2.2. Experimental methods

Simulated inappropriate storage conditions that mimic various climatic zones were used to conduct stability testing. For this aim, bare and packaged tablets from Zagros Darou (S0) were placed on clean petri dishes and stored in an oven at temperatures of 30± 2°C, 40± 2°C, 45± 2°C, 55± 2°C, and 65± 2°C. Furthermore, we stored some tablets (S0) in a controlled environment chamber at relative humidity of 85 ± 2% RH. Tablets from other companies were subjected to the same 65 ± 2 °C temperature test. In addition, empty packages were stored and tested independently at various time intervals. During the experiments, various intervals were sampled and Raman spectra were recorded. A Raman microscope was used to record Raman spectra with a 532 nm diode laser and a CCD detector with 1044 pixels (Teksan, Iran). The laser was focused onto the sample surface by a 4X objective lens, which produced a 100 µm laser spot. The spectrum was recorded in the spectral region from 4000 to 100 cm^{-1}, with an approximate spectral resolution of 15 cm^{-1}. The CCD exposure time was set to 2 s, with 10 scans collected per measurement. Spectra were randomly collected from three areas on the tablet surface to minimize error sources. Experimental data were plotted based on results from nine independent experiments using three tablets to estimate the reliable errors throughout the study. To this end, spectra were taken from three points of each tablet to determine the temporal evolution of API degradation during temperature changes and high level of humidity. Finally, errors were presented as mean standard deviations of nine values of quantitative parameter values obtained from the three tablets. To assess how well the tablets would tolerate inappropriate storage conditions, a weight test was done. Each brand´s tablets were carefully de-dusted and then weighed. They were reweighed after exposure to the specified testing conditions to determine the percentage of weight loss.

3. Results

The stability of drugs should be tested at each stage of manufacturing to consumption, to guarantee that the drug will produce the expected therapeutic response [3, 38, 57]. Herein, the capability and accuracy of Raman spectroscopy in evaluating 500 mg paracetamol tablets stored under inappropriate environmental conditions are investigated. According to the formulation design provided by the pharmaceutical companies, the paracetamol tablet contains 93.6% API, 4.9% Polyvinylpyrrolidone (PVP), 0.5% magnesium stearate and 1% croscarmellose sodium [58-61]. To investigate the quantitative analysis of the paracetamol API degradation, the Raman intensity variations of characteristics bands of API relative to PVP are analyzed within the tablets.

Figure 2 shows the Raman spectrum of a bare paracetamol tablet, with the Raman bands of the API and PVP clearly marked.

Due to interference of fluorescence effects of binding materials with vibrational spectra, baseline removal is often required before data analysis [62, 63]. An average baseline intensity of the spectrum was set and subtracted from the peak height during the quantitative calculations (the dashed line in Figure 2).

Since the signals exhibited in Raman spectra directly show the dosage of materials, the Raman intensity ratio of characteristic bands of API/PVP were used as a quantitative metric for analysis [46, 54, 56, 64-66]. Characteristic bands are selected as the Raman bands at 1611 cm^{-1}, corresponding to the vibrational mode of the O=C bond in the paracetamol API, and at 2933 cm^{-1}, corresponding to the vibrational mode of the C-H bond in PVP [23, 67-69]. The characteristic bands of API and PVP were selected based on their intensities and lack of overlap with other tablet ingredients, allowing accurate monitoring of API changes [46, 54, 64, 66]. It is noteworthy that PVP, commonly used as a binder in paracetamol tablet formulations, is a water-soluble polymer with high thermal and chemical stability, biocompatibility, and viscosity-regulating properties [70-73].

In previous work, our results indicate that the PVP molecules were not denatured during storage of tablets under heating or high humidity conditions, and there is no observable variations in the PVP characteristic band [56, 74, 75].

Consequently, changes in the value of API/PVP characteristic Raman peaks is due to the degradation of API in the tablet stored in the inappropriate conditions.

To validate the precision and repeatability of the utilized spectroscopic technique, first of all, the reliability of the data set extracted from the Raman spectra should be inspected [36].

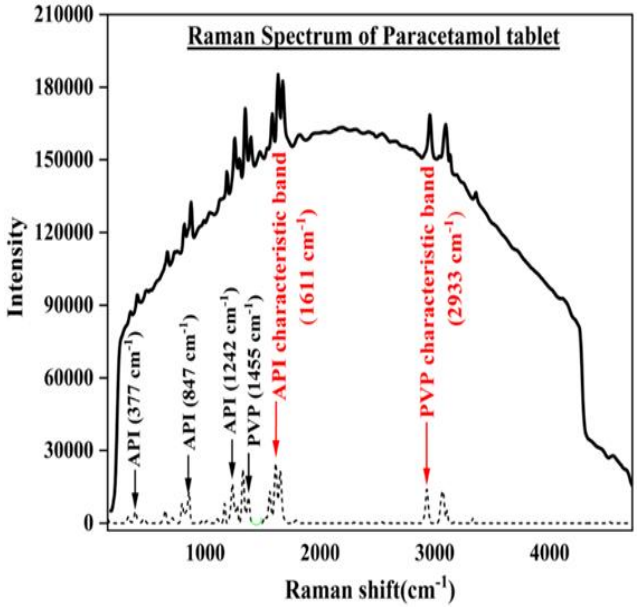

Figure 2. The Raman spectra of bare paracetamol tablet (solid line) and the baseline- subtracted Raman spectra (dashed line). The paracetamol API characteristic band (1611 cm^{-1}) and the PVP characteristic band (2933 cm^{-1}) were chosen for quantitative analysis

Table 1. The resulted values of variability from Raman intensity ratio of different samples

Sample name	Relative error of API/PVP Raman band ratio for bare tablets (%)	Relative error of API/PVP Raman band ratio for packaged tablets (%)
S_0	4.05	4.35
S_1	3.74	4.18
S_2	2.39	3.40
S_3	2.01	3.85
S_4	3.22	4.93

For this purpose, paracetamol tablets from different companies were purchased, and the Raman spectra of both bare and packaged tablets were recorded [76].

The complete characteristics of the samples, which are named as S_0–S_4 throughout the paper, are fully described in the previous section (see Experimental method). The main sources of error in the experiments including the systematic error due to device inaccuracy, the operational error due to user inaccuracy, and the errors referred to the sample inhomogeneity were considered. The significance of the resultant data was investigated in the repetitions of recorded spectrums within three randomly selected regions over all the surfaces of five tablets (S_0-S_4). Then, the indicator factor based on the Raman intensity ratio of characteristic bands of API/PVP and its %RSD were calculated for both bare and packaged tablet groups. The results are presented in Table 1. The data extracted from the packaged form of different brands of paracetamol tablets shows greater variations compared to the bare

samples. This goes back to the scattering of light via the tablet´s cover. The effect of cover in the Raman spectra of tablets will be discussed later. Based on the paracetamol tablet label claim, the API variation ranges from 90% to 110%, covering the 10% variation normally allowed [60, 61]. Our results imply that the accuracy of experiments for both groups of tablets are acceptable and significant with RSD of less than ±5%. Therefore, the Raman-based approach can be confidently utilized for the rapid assessment of low-quality products in accordance with standard guidelines [77, 78].

In the following, we investigate the feasibility of measuring API degradation in packaged sample using Raman spectroscopy. Figure 3 illustrates the effect of the tablet packaging on the quantitative analysis of degradation using Raman spectra. Figure 3a shows the temporal degradation of the API in several packaged tablets of sample S0 at 65°C. At each time interval, three tablets were removed from the oven, set at 65°C, and then, three regions of each tablet were analyzed at three different points. Therefore, each spectrum in Figure 3a represents the average of nine individual spectrums. Analysis of the spectra reveals that the characteristic peaks of API, PVP, and PVC bands show no significant shifts over time [46, 54, 56].

As shown in the inset of Figure 3a, the characteristic band of API decreases during storage at high temperatures, while the characteristic peak corresponding to PVP remains relatively constant [46, 54, 56]. It seems that the molecular interactions of the API change with increasing temperature, leading to its degradation, in contrast, the PVP molecular structure is less affected by temperature fluctuations [59-61, 70, 73, 79]. This result suggest that the significant stability of the peak associated with PVP supports its suitability as a metric parameter for quantitative analysis. Subsequently, the extent of degradation of the API at 65°C and various other temperatures will be discussed and examined further.

Figure 3b shows the Raman spectra of the tablet cover at various temperatures. Polyvinyl chloride (PVC) is a primarily amorphous film with excellent optical clarity, commonly used for packaging tablets and other pharmaceutical products because of its resistance to temperature increases [23, 80-83].

The Raman spectrum of this polymer can be broadly divided into three regions: the range from 100 to 700 cm^{-1}, which is attributed to symmetric and anti-symmetric stretching vibrations involving the C–Cl bond (643 cm^{-1} and 695 cm^{-1}); the range from 700 to 1500 cm^{-1}, which corresponds to C-C bending and rocking vibrations (1120 cm^{-1} and 1500 cm^{-1}); and the range from 2800 to 3000 cm^{-1}, which is associated with C-H stretching vibrations (2933 cm^{-1}) [82-84].

Since, the overlap of the characteristic peak of PVP with the PVC peak at 2933 cm^{-1} may influence the quantitative data analysis, the behavior of PVC Raman spectrum should be investigated.

Figure 3b confirms that the PVC molecules are not denatured during the heating process and the slight changes in the characteristic band of PVC may be due to the change in the initial layer thickness of the covers. In addition, the Raman intensity of the PVC is much lower than that of the PVP, which does not interfere with the quantitative evaluation of the tablet quality.

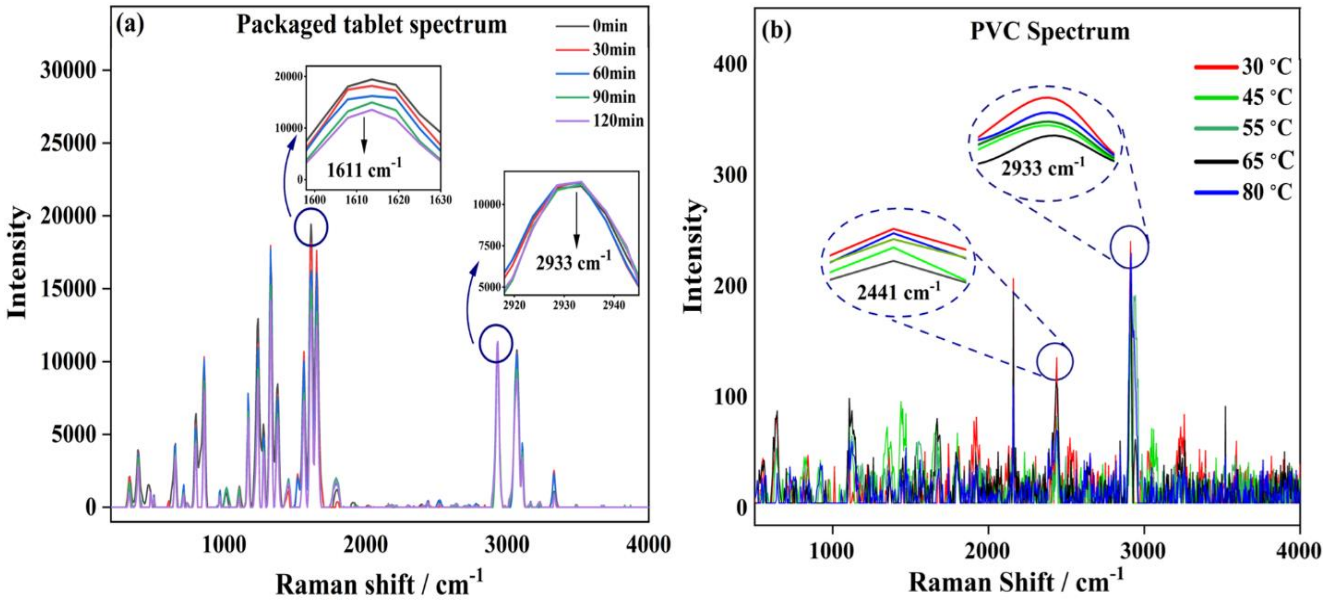

Figure 3. (a) The temporal variations in the Raman spectra of the packaged Paracetamol tablets (S_0) at 65°C; the variations in the characteristic band of API at 1611 cm^{-1} and the characteristic band of PVP at 2933 cm^{-1} were marked, (b) the Raman spectra of the tablet cover made of Polyvinyl chloride (PVC) at different temperatures

In the following, we study the stability of packaged and bare tablets under inappropriate storage or exposure to various climate zones [25, 64]. For this aim, a number of 168 packaged and bare paracetamol tablets (sample S_0) were placed on clean petri dishes and stored in an oven at temperatures of 30± 2°C, 40± 2°C, 45± 2°C, 55± 2°C, and 65± 2°C. Additionally, 30 tablets were exposed at the most commonly recognized temperature (30°C) and high humidity level (85% RH) in the controlled environmental chamber. Subsequently, the spectra of different tablet samples were recorded at various time intervals, and the quantitative parameter was calculated (see Figure 4). Figure 4a.

shows the Raman intensity ratio of characteristic bands of API/PVP at different time intervals as the temperature increases. Since, the values for the PVC and PVP characteristic bands show no meaningful changes over time, the decrease in the metric parameter suggests a reduction in the intensity of the API characteristic band. Based on our experiments, the API/PVP value at room temperature is 1.85 and 1.66 for bare and packaged tablets, respectively. Notably, the lower values of metric parameter for the packaged tablets are attributed to light scattering effects caused by the packaging. According to the USP monograph, a paracetamol tablet is considered expired if its API content falls below 90% (85).

As indicated by the decrease in the API/PVP Raman intensity ratio, samples stored at 30 and 40 °C maintained their API values throughout the oven storage period, while samples exposed to 45, 55, and 65 °C showed accelerated API degradation.

The API reached expiration in both the bare and packaged tablet groups after 7 hours at temperature 45°C, after 3 hours at 55°C and after 1 hour at 65°C.

Also, the accuracy of the data regarding API degradation remains acceptable for both groups of tablets at different temperatures.

Furthermore, similar to most chemical reactions, the degradation of both groups of tablets follows a logarithmic trend at different temperatures [56, 85, 86]. Consequently, the packaging of the tablets cannot protect the API from destruction against temperature increasing.

Figure 4b. shows the API stability testing under the commonly recognized temperature of 30°C and a high humidity level of 85% RH.

Similar to the thermal degradation of the API, the moisture absorption process in the bare tablets follows a logarithmic trend, with noticeable API degradation evident after just one hour.

In contrast, the packaging effectively prevents moisture absorption, ensuring that degradation does not occur. Therefore, the storing of tablets out of their package under the high humidity levels leads to very fast degradation process. To investigate the repeatability of the aforementioned trend in the thermal degradation of the paracetamol API, the stability tests were conducted on tablets manufactured by four different pharmaceutical companies [25, 64].

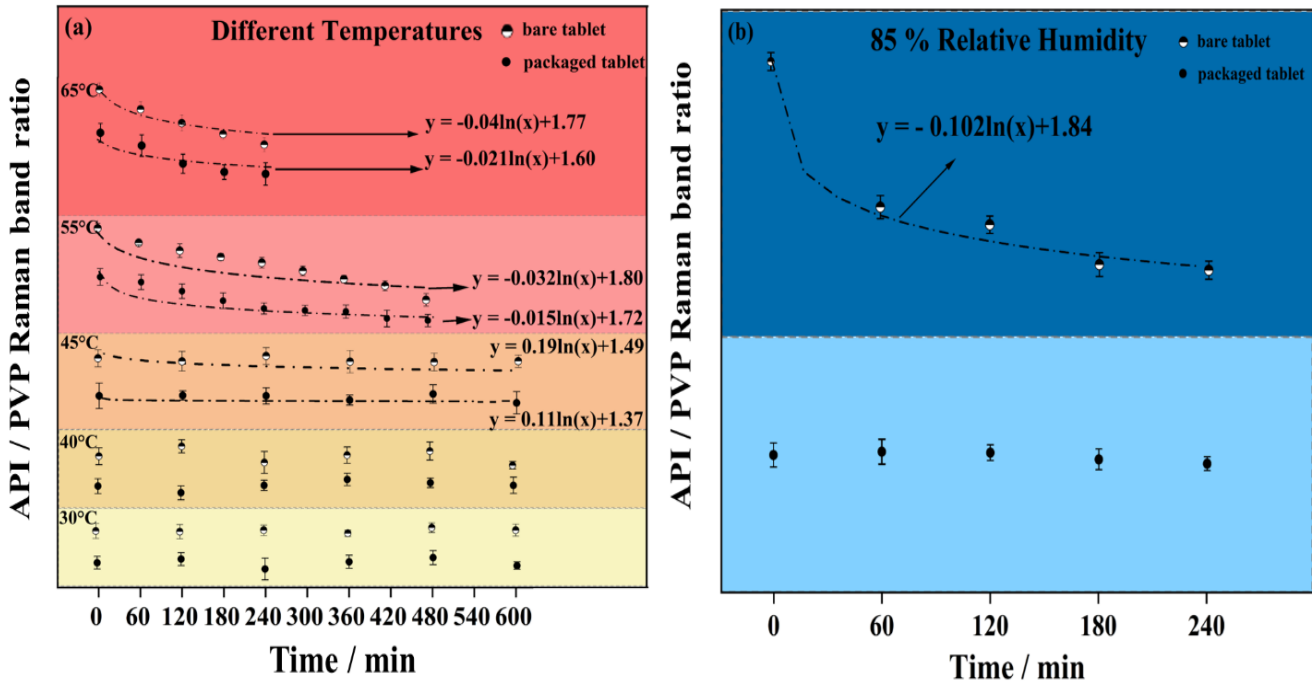

Figure 4. (a) Temporal dependency of API degradation at various temperatures, (b) Temporal dependency of API degradation at high level of humidity (85% R.H.)

10.57647/jtap.2026.2001.04

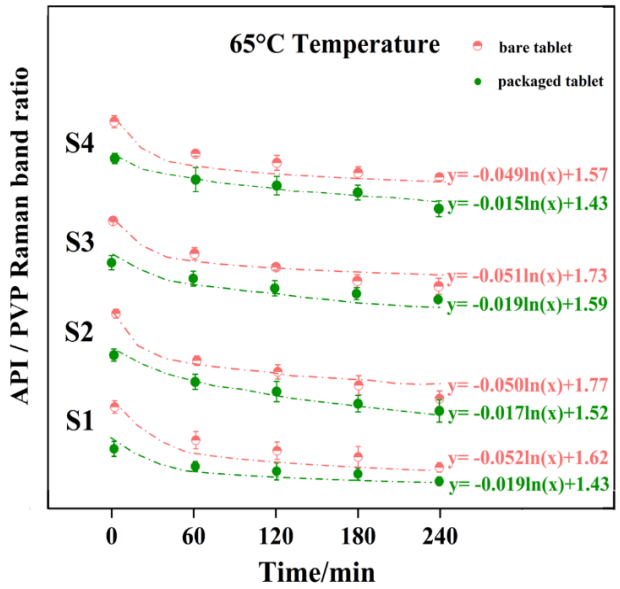

Figure 5. Temporal dependency of the API degradation at 65°C for samples S_1, S_2, S_3, and S_4

Figure 5. demonstrates the trends in the Raman intensity ratios of API/PVP for different samples. 30 tablets from each sample (S_1-S_4) were stored at temperature of 65 °C. At each time interval, three bare and three tablets with packaging were removed from the oven, and the spectra were recorded at three different points on each tablet30 tablets from each sample (S_1-S_4) were stored at temperature of 65 °C.

At each time interval, three bare and three tablets with packaging were removed from the oven, and the spectra were recorded at three different points on each tablet. As can be seen in Figure 5, the logarithmic process takes place in the different brands of the paracetamol tablets.

The slope of API degradation in tablets prepared by different companies follows slightly different logarithmic trends, but the degradation time does not show a significant delay.

This can be attributed to the initial parameters of tablets, such as variations in tablet weight and differences in the diameter or shape of the tablet covers. The investigation of the degradation process was followed by additional studies, including a weight test and an analysis of the characteristic Raman band of p-aminophenol as a toxic component in the tablets.

In general, weight variations are a valid indication of corresponding changes in the drug content of individual tablets [22, 87, 88].

In addition to physical changes and volatilization of ingredients, the chemical degradation of API due to heating leads to weight loss of tablets (8).

According to the USP monograph, a maximum weight loss of samples shouldn't

be more than 1.00% for a tablet to be accepted [7, 8, 85, 87, 89].

To inspect the effect of temperature, increase on the weight of tablets, the tablet weight variation test was done.

The tablets of each brand were weighted before transferring them to the oven at 65 °C.

At each time interval, the tablets were removed from oven and weighted again.

The percentage of weight loss was calculated as the ratio of weight variation relative to the initial tablet weight.

This calculation was repeated for three tablets, and the average of the resulting data is presented in Table 2. As seen in Table 2, all samples from each brand experiences the weight loss at different times and the rate of weight loss increases over time. In addition, the weight loss at 1 hour is more than 1.00% for all brands (the accepted value is <1.00%) [89].

The weight loss values vary for tablets produced by different companies, and this difference is influenced by production conditions, including the pressure and press intensity during manufacturing.

Depending on the composition of the tablet and the type of materials used in its formulation, an increase in temperature leads to changes in the tablet properties [90-93].

Since, PVP and other ingredients in the tablet are resistant to temperature, the observed weight loss can be attributed to the degradation of API, which confirms the predicted API degradation based on the API/PVP ratio (see Figure 6).

The Raman spectra of the degraded tablets also contained other interesting information.

Figure 6 shows the temporal evolution of the P-aminophenol characteristic band for samples stored at 65 °C.

Table 2. the weight loss evaluation of samples

Loss weight	S_0 	S_1 	S_2 	S_3 	S_4 
Loss weight in 1 hour	2.40 ± 0.15	1.70 ± 0.23	2.06 ± 0.22	0.93 ± 0.15	2.16 ± 0.01
Loss weight in 2 hours	2.43 ± 0.85	2.63 ± 0.24	2.63 ± 0.32	0.96 ± 0.16	2.80 ± 0.04
Loss weight in 3 hours	2.50 ± 0.40	2.66 ± 0.15	2.83 ± 0.04	1.13 ± 0.16	2.96 ± 0.04
Loss weight in 4 hours	2.63 ± 0.11	3.36 ± 0.01	2.96 ± 0.28	2.86 ± 0.77	3.60 ± 0.19

10.57647/jtap.2026.2001.04

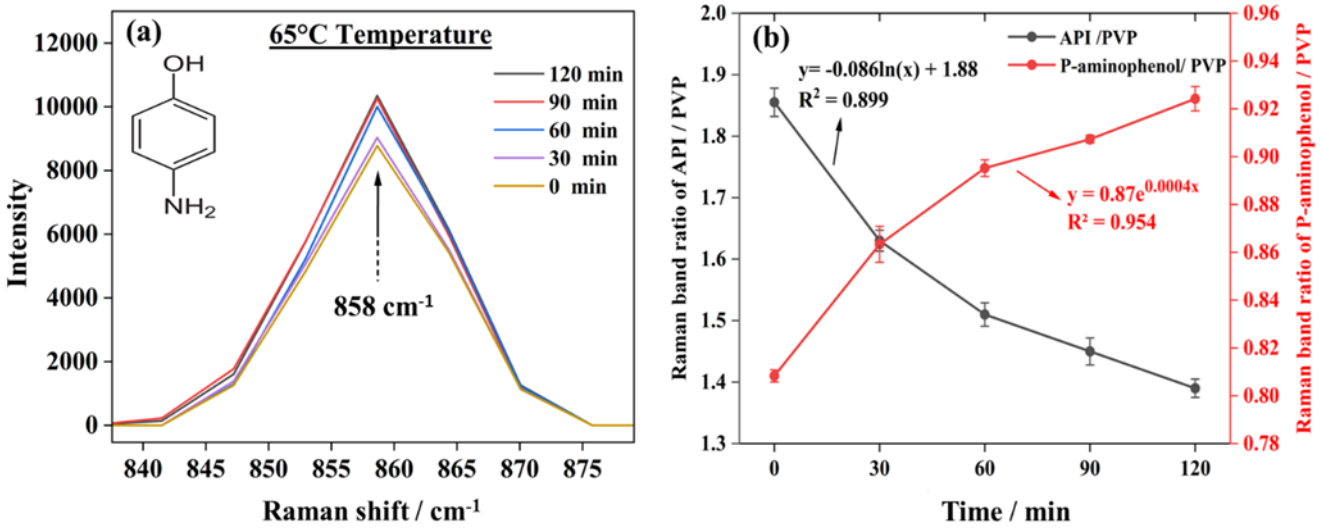

Figure 6. (a) The temporal evolution of the P-aminophenol characteristic band at 65°C (sample S_0), (b) Comparison of the trends in API degradation and P-aminophenol formation during tablet storage at 65°C

P-Aminophenol is known as an impurity in paracetamol tablet, which can be a synthetic intermediate or a product of hydrolytic decomposition of paracetamol [94-96]. Also, the decomposition of paracetamol under unfavorable environmental conditions leads to increase the amount of P-aminophenol [8, 96, 97].

This compound shows significant nephrotoxicity and teratogenic effects, and pharmaceutical guidelines have set a limit of 0.005 % w/w for its presence, determined by a manual colorimetric limit test [1, 8, 95].

The best peak of P-aminophenol at 858 cm^{-1}, which corresponds to the out-of-plane C-H bending vibrations mode, was selected as a characteristic band.

Despite of the overlap of this peak with the peak corresponding to the API (847 cm^{-1}), the intensity of this peak can be related to low dosage of P-aminophenol in the final paracetamol tablet (1).

As shown in Figure 6a, the spectrum of the paracetamol tablet before storage in the oven (at 0 min) also shows a peak at 858 cm^{-1}. Interestingly, the intensity of this peak increases when the sample is stored in the oven at 65 °C, while the other peaks corresponding to the API decrease. Therefore, the increase in the 858 cm^{-1} peak suggests the formation of P-aminophenol when temperature increases. Figure 6b shows the trends of the Raman intensity ratio of the characteristic bands of P-aminophenol/PVP and API/PVP, calculated as an average from nine spectra. According to the aforementioned discussion, the quantitative analysis of API based on Raman spectra yielded satisfactory results, enabling the detection of p-aminophenol formation in the presence of paracetamol.

Therefore, the quantitative analysis using Raman spectroscopy data can be used from various aspects to conduct tablet stability tests throughout their shelf life.

5. Conclusion

In this study, we highlight the use of the Raman spectroscopy method to gain new insights into the hydrolysis/degradation behavior of commercial paracetamol tablets stored under inappropriate conditions. This method relies on analyzing the changes in the characteristic bands of the paracetamol API and PVP within their Raman spectra. Our results show that the API degradation follows a logarithmic trend, similar to results obtained from conventional methods in the pharmaceutical industry. Furthermore, the results demonstrate that Raman spectroscopy can accurately quantify the API degradation in accordance with the acceptable standards set by international guidelines. The effect of increasing temperature on API degradation is more pronounced for packaged tablets compared to changes in humidity. Also, the API degradation leads to the production of the toxic substance P-aminophenol. This emphasizes the importance of monitoring and controlling temperature conditions in the storage of pharmaceutical products.

Finally, as a cost-effective and reliable method, this approach offers a solution for drug quality assessment and stability testing.

Authors Contribution

All the authors have participated sufficiently in the intellectual content, conception and design of this work or the analysis and interpretation of the data (when applicable), as well as the writing of the manuscript.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Conflict of interests

The author states that there is no conflict of interest.

10.57647/jtap.2026.2001.04

References

[1] Bloomfield M. A sensitive and rapid assay for 4-aminophenol in paracetamol drug and tablet formulation, by flow injection analysis with spectrophotometric detection. Talanta. 2002;58(6):1301–10.

[2] Prescott LF. Paracetamol (acetaminophen) poisoning: The early years. Br J Clin Pharmacol. 2024;90(1):127–34.

[3] Mezaal EN, Sadiq KA, Jabbar MM, Al-Noor TH, Azooz EA, Al-Mulla EAJ. Green methods for determination of paracetamol in drug samples: A comparative study. Green Anal Chem. 2024;10:100123.

[4] Silva H. A Descriptive Overview of the Medical Uses Given to Mentha Aromatic Herbs throughout History. Biology (Basel). 2020;9(12):484.

[5] Sahle SB, Ayane AT, Wabe NT. Comparative Quality Evaluation of Paracetamol Tablet Marketed in Somali Region of Ethiopia. Int J Pharm Sci Res. 2012;3(2):545–50.

[6] Kockler J, Robertson S, Hope D, Haywood A, Glass BD. Stability of paracetamol tablets repackaged in dose administration aids for prn use: Implications for practice. Aust J Pharm. 2014;95(1130):56–8.

[7] Haider K, Akash MSH, Faheem A, Rehman K. Guidelines for Drug Stability and Stability Testing. In: Drug Stability and Chemical Kinetics. Singapore: Springer; 2020. p. 19–29.

[8] Blessy M, Patel RD, Prajapati PN, Agrawal YK. Development of forced degradation and stability indicating studies of drugs—A review. J Pharm Anal. 2014;4(3):159–65.

[9] Haywood A, Mangan M, Glass B. Stability Implications of Repackaging Paracetamol Tablets into Dose Administration Aids. J Pharm Pract Res. 2006;36(1):25–8.

[10] Cespi M, Bonacucina G, Casettari L, Ronchi S, Palmieri GF. Effect of temperature increase during the tableting of pharmaceutical materials. Int J Pharm. 2013;448(1):320–6.

[11] Haegens LL, Huiskes VJB, Bekker CL, van den Bemt BJF. Effect of a smart temperature logger on correctly storing biological disease-modifying antirheumatic drugs at home: a pre-post study. Eur J Hosp Pharm. 2025;32(6):557–63.

[12] Mehta S, Shah RP, Singh S. Strategy for identification and characterization of small quantities of drug degradation products using LC and LC-MS: Application to valsartan, a model drug. Drug Test Anal. 2010;2(2):82–90.

[13] Yilmaz H, Culha M. A Drug Stability Study Using Surface-Enhanced Raman Scattering on Silver Nanoparticles. Appl Sci. 2022;12(4):1807.

[14] Nasrin N, Asaduzzaman M, Mowla R, Rizwan F, Alam A. A comparative study of physical parameters of selected ketorolac tromethamine tablets available in the pharma market of Bangladesh. J Appl Pharm Sci. 2011;1(8):101–3.

[15] Sabee MMSM, Uyen NTT, Ahmad N, Hamid ZAA. Plastics Packaging for Pharmaceutical Products. In: Encyclopedia of Materials: Plastics and Polymers. Elsevier; 2022. p. 316–29.

[16] Das PS, Saha P, Krishan, Das R. Pharmaceutical Packaging Technology: A Brief Outline. Res J Pharm Dos Forms Technol. 2018;10(1):23.

[17] Tan JZY, Kwan YH. Stability of chronic medicines in dosage administration aids. How much have been done? Saudi Pharm J. 2016;24(1):21–8.

[18] Comanescu C, Racovita RC. An Overview of Degradation Strategies for Amitriptyline. Int J Mol Sci. 2024;25(7):3822.

[19] Z F, R R, S K. A Review on Stability Testing Guidelines of Pharmaceutical Products. Asian J Pharm Clin Res. 2020;13(10):3–9.

[20] Singh AP, Singh S, Malik R. A Post-marketing Surveillance, Single-Centric Study to Evaluate the Safety and Tolerability of VELNEZ as a Space-Occupying Dressing Pack After Ear Surgery. Cureus. 2024 Jan;16(1):e51732.

[21] Chidiac AS, Buckley NA, Noghrehchi F, Cairns R. Paracetamol (acetaminophen) overdose and hepatotoxicity: mechanism, treatment, prevention measures, and estimates of burden of disease. Expert Opin Drug Metab Toxicol. 2023;19(5):297–317.

[22] Kalidindi VR, Somalanka BM, Seethamraju SM, Nori LP. Pharmaceutical Impurities and Their Regulatory Aspects with a Special Focus on Genotoxic Impurities. Int J Pharm Res Allied Sci. 2024;13(2):1–15.

[23] Chen G, Warrack BM, Goodenough AK. Analysis of impurities and degradants in pharmaceuticals by high resolution tandem mass spectrometry and on-line H/D exchange LC/MS. Am Pharm Rev. 2010;13(3):20–7.

[24] Attia KAM, Nassar MWI, Sharaf El-Din MMK, Mohamad AAA, Kaddah MMY. A stability-indicating QTRAP LC-MS/MS method for identification and structural characterization of degradation products of indapamide. Anal Methods. 2016;8(8):1836–51.

[25] Jadhav SV, A.S. N, S.B. G. To Study the Regulatory Guidelines for API of Ibuprofen: A Review. Asian J Pharm Res Dev. 2024;12(1):98–106.

[26] Singh A, Afreen S, Singh DP, Kumar R. A Review on Pharmaceutical Impurities and Their Importance. World J Pharm Pharm Sci. 2017;6(10):1337–54.

[27] Pilaniya K, Chandrawanshi H, Pilaniya U, Manchandani P, Jain P, Singh N. Recent trends in the impurity profile of pharmaceuticals. J Adv Pharm Technol Res. 2010;1(3):302.

[28] Fateixa S, Mulandeza O, Nogueira HIS, Trindade T. Raman imaging studies on the stability of Paracetamol tablets under different storage conditions. Vib Spectrosc. 2023;124:103488.

[29] Wei M, Yuan Y, Chen D, Pan L, Tong W, Lu W. A systematic review on electrochemical sensors for the detection of acetaminophen. Anal Methods. 2024;16(36):6134–55.

[30] Montaseri H, Forbes PBC. Analytical techniques for the determination of acetaminophen: A review. TrAC Trends Anal Chem. 2018;108:122–34.

[31] Chu Q, Jiang L, Tian X, Ye J. Rapid determination of acetaminophen and p-aminophenol in pharmaceutical formulations using miniaturized capillary electrophoresis with amperometric detection. Anal Chim Acta. 2008;606(2):246–51.

[32] Gorog S. Drug safety, drug quality, drug analysis. J Pharm Biomed Anal. 2008;48(2):247–53.

[33] Gumustas M, Kurbanoglu S, Uslu B, Ozkan SA. UPLC versus HPLC on Drug Analysis: Advantageous, Applications and Their Validation Parameters. Chromatographia. 2013;76(21–22):1365–427.

[34] Ghosh MK. HPLC Methods on Drug Analysis. Berlin, Heidelberg: Springer Berlin Heidelberg; 1992.

[35] Wang W, Zhang H, Yuan Y, Guo Y, He S. Research Progress of Raman Spectroscopy in Drug Analysis. AAPS PharmSciTech. 2018;19(7):2921–8.

[36] El Hosary R, El Wazzan VS, Hassan ES. Safety of Splitting Some Paracetamol Tablets in Egyptian Market for Children Administration: A Quality Control Overview. J Drug Res Egypt. 2016;37(1).

[37] Slikker W, de Souza Lima TA, Archella AD, de Silva JB, Barton C, Capes-Davis A, et al. Emerging technologies for food and drug safety. Regul Toxicol Pharmacol. 2018;98:115–28.

[38] Čapková T, Pekárek T, Hanulíková B, Matějka P. Application of reverse engineering in the field of pharmaceutical tablets using Raman mapping and chemometrics. J Pharm Biomed Anal. 2022;209:114496.

[39] Abebe K, Beressa TB, Yimer BT. In-vitro Evaluations of Quality Control Parameters of Paracetamol Tablets Marketed in Gondar City, Northwest Ethiopia. Drug Healthc Patient Saf. 2020;12:273–9.

[40] Carruthers H, Clark D, Clarke F, Faulds K, Graham D. Comparison of Raman and Near-Infrared Chemical Mapping for the Analysis of Pharmaceutical Tablets. Appl Spectrosc. 2021;75(2):178–88.

[41] Karimi S, Tavassoli SH. The feasibility of Raman spectroscopy for accurate assessment of essential criteria in pharmaceutical industry by investigation of Metformin hydrochloride tableting process. J Raman Spectrosc. 2024;55(6):688–94.

[42] Tondepu C, Toth R, Navin CV, Lawson LS, Rodriguez JD. Screening of unapproved drugs using portable Raman spectroscopy. Anal Chim Acta. 2017;973:75–81.

[43] Mansouri MA, et al. Quantitation of active pharmaceutical ingredient through the packaging using Raman handheld spectrophotometers: A comparison study. Talanta. 2020;207:120306.

[44] Nagy B, Farkas A, Borbás E, Vass P, Nagy ZK, Marosi G. Raman Spectroscopy for Process Analytical Technologies of Pharmaceutical Secondary Manufacturing. AAPS PharmSciTech. 2019;20(1):1.

[45] BiscevicTokic J, Tokic N, Ibrahimpasic E. Chromatography as Method for Analytical Confirmation of Paracetamol in Postmortem Material Together with Psychoactive Substances. Acta Inform Med. 2015;23(5):322–5.

[46] Ogemdi IK. A Review on the Properties and Uses of Paracetamol. Int J Pharm Chem. 2019;5(3):31.

[47] Almdaaf M, Al-Moghrabi M. Post-marketing quality assessment of paracetamol brands in the Libyan market. Med J Pharm Pharm Sci. 2023;3(4):73–9.

[48] Siddaling Kamble SK, Harish Kumar DR. Analytical Method Development and Validation Of Stability Indicating RP-HPLC Method For Assay and Related Substances of Paracetamol and Caffeine Effervescent Tablets: Review. Int J Multidiscip Res. 2024;6(2).

[49] Verma A, Singla S, Palia P. The Development of Forced Degradation and Stability Indicating Studies of Drugs- A Review. Asian J Pharm Res Dev. 2022;10(2):83–9.

[50] Gala U, Chauhan H. Principles and applications of Raman spectroscopy in pharmaceutical drug discovery and development. Expert Opin Drug Discov. 2015;10(2):187–206.

[51] Paudel A, Raijada D, Rantanen J. Raman spectroscopy in pharmaceutical product design. Adv Drug Deliv Rev. 2015;89:3–20.

[52] D'Souza AJM, Schowen RL, Topp EM. Polyvinylpyrrolidone–drug conjugate: synthesis and release mechanism. J Control Release. 2004;94(1):91–100.

[53] Neugebauer U, Rösch P, Popp J. Raman spectroscopy towards clinical application: drug monitoring and pathogen identification. Int J Antimicrob Agents. 2015;46:S35–9.

[54] Nie H, Liu Z, Marks BC, Taylor LS, Byrn SR, Marsac PJ. Analytical approaches to investigate salt disproportionation in tablet matrices by Raman spectroscopy and Raman mapping. J Pharm Biomed Anal. 2016;118:328–37.

[55] Qian F, et al. Is a distinctive single Tg a reliable indicator for the homogeneity of amorphous solid dispersion? Int J Pharm. 2010;395(1–2):232–5.

[56] Henson MJ, Zhang L. Drug Characterization in Low Dosage Pharmaceutical Tablets Using Raman Microscopic Mapping. Appl Spectrosc. 2006;60(11):1247–55.

[57] Mohammadian MK, Tavassoli SH, Karimi S. Rapid Assessment of Tablet Quality Based on Raman Spectroscopy Analysis: Investigating the Effect of Storage Conditions on the Degradation of Active Pharmaceutical Ingredient (API) of Acetaminophen Tablet. J Raman Spectrosc. 2025;56(3):278–85.

[58] Babaei R, Goli-Haghighi S, Savaloni H. Detection of overtone and combined peaks using Mn/Cu helical star-shaped (pine-tree-like) sculptured thin films in surface-enhanced Raman spectroscopy. J Theor Appl Phys. 2019;13(4):305–14.

[59] Meena AK, Desai D, Serajuddin ATM. Development and Optimization of a Wet Granulation Process at Elevated Temperature for a Poorly Compactible Drug Using Twin Screw Extruder for Continuous Manufacturing. J Pharm Sci. 2017;106(2):589–600.

[60] Luo Y, Hong Y, Shen L, Wu F, Lin X. Multifunctional Role of Polyvinylpyrrolidone in Pharmaceutical Formulations. AAPS PharmSciTech. 2021;22(1):34.

[61] Ben Osman Y, Liavitskaya T, Vyazovkin S. Polyvinylpyrrolidone affects thermal stability of drugs in solid dispersions. Int J Pharm. 2018;551(1–2):111–20.

[62] He S, et al. Baseline correction for Raman spectra using an improved asymmetric least squares method. Anal Methods. 2014;6(12):4402–7.

[63] Ramos PM, Ruisánchez I. Noise and background removal in Raman spectra of ancient pigments using wavelet transform. J Raman Spectrosc. 2005;36(9):848–56.

[64] Mojica ERE, Zapata J, Vedad J, Desamero RZB, Dai Z. Analysis of Over-the-Counter Drugs Using Raman Spectroscopy. In: ACS Symposium Series. 2018. p. 69–91.

[65] Omar J, Boix A, Ulberth F. Raman spectroscopy for quality control and detection of substandard painkillers. Vib Spectrosc. 2020;111:103147.

[66] Stasiłowicz A, Mizera M, Tykarska E, Lewandowska K, Miklaszewski A, Cielecka-Piontek J. The Possibility of Using X-Ray Powder Diffraction, Infrared and Raman Spectroscopy in the Study of the Identification of Structural Polymorphs of Acetaminophen. Acta Pol Pharm. 2019;76(6):997–1004.

[67] Szostak R, Mazurek S. Quantitative determination of acetylsalicylic acid and acetaminophen in tablets by FT-Raman spectroscopy. Analyst. 2002;127(1):144–8.

[68] Pestaner J, Mullick F, Centeno J. Characterization of Acetaminophen: Molecular Microanalysis with Raman Microprobe Spectroscopy. J Forensic Sci. 1996;41(6):1060–3.

[69] Mukta NJ, et al. Effect of Temperature and Additives on the Interaction of Ciprofloxacin Hydrochloride Drug with Polyvinylpyrrolidone and Bovine Serum Albumin: Spectroscopic and Molecular Docking Study. J Oleo Sci. 2021;70(3):397–407.

[70] Been S, et al. Improvement of Medication Adherence and Controlled Drug Release by Optimized Acetaminophen Formulation. Macromol Res. 2021;29(5):342–50.

[71] Peniche C, Zaldivar D, Pazos M, Paz S, Bulay A, San Roman J. Study of the thermal degradation of poly (N-vinyl-2-pyrrolidone) by thermogravimetry-FTIR. J Appl Polym Sci. 1993;50(3):485–93.

[72] Taghizadeh M, Abdollahi R. Ultrasonic Degradation of Polyvinyl Pyrrolidone (PVP): Effect of Power of Ultrasound, Temperature and Concentration. Am Chem Sci J. 2015;9(3):1–11.

[73] Li C, Tian Y, Liu C, Dou Z, Diao J. Effects of Heat Treatment on the Structural and Functional Properties of Phaseolus vulgaris L. Protein. Foods. 2023;12(15):2869.

[74] Bu F, Nayak G, Bruggeman P, Annor G, Ismail BP. Impact of plasma reactive species on the structure and functionality of pea protein isolate. Food Chem. 2022;371:131135.

[75] Bouzari HH, Matin LF, Malekfar R, Shafiekhani A. Experimental and theoretical investigation of spontaneous and surface-enhanced Raman scattering (SERS) spectroscopy of pure and boron-doped carbon nanotubes. J Theor Appl Phys. 2018;12(2):101–11.

[76] Sharma S, Khurana G, Gupta R. A Review on Pharmaceutical Validation and Its Implications. Indian J Pharm Biol Res. 2013;1(3):100–4.

[77] Roy S, et al. A systemic approach on understanding the role of moisture in pharmaceutical product degradation and its prevention: challenges and perspectives. Biomed Res. 2018;29(17):3336–43.

[78] Mohammad MH, Saeed AA. The influence of gamma rays on the physical properties of polyvinyl chloride. J Theor Appl Phys. 2024;18(Special Issue).

[79] Akovali G. Plastic materials: polyvinyl chloride (PVC). In: Toxicity of Building Materials. Elsevier; 2012. p. 23–53.

[80] Vyacheslav Lyashenko AMB, Sotnik S. Features of Packaging from Polymers in Pharmaceutics. Saudi J Med Pharm Sci. 2018;4(2).

[81] Pannico M, Musto P. Migration of plasticizers from flexible PVC: Monitoring the concentration profiles by confocal Raman microspectroscopy. Polymer (Guildf). 2024;294:126731.

[82] Prokhorov KA, et al. Raman Spectroscopy Evaluation of Polyvinylchloride Structure. J Phys Conf Ser. 2016;691(1):012001.

[83] Ludwig V, et al. Analysis by Raman and infrared spectroscopy combined with theoretical studies on the identification of plasticizer in PVC films. Vib Spectrosc. 2018;98:134–8.

[84] Rawat T, Pandey IP. Forced degradation studies for drug substances and drug products- scientific and regulatory considerations. J Pharm Sci Res. 2015;7(5):238–41.

[85] Ashenef A, Teklu L, Adugna E. Quality Evaluation of Paracetamol Tablets obtained from the Common Shops (Kiosks) in Addis Ababa, Ethiopia. Int J Pharm Sci Res. 2014;5(9):3502.

[86] Abdulla AA, Oshi MA. A simple approach to enhance dissolution of commercial paracetamol tablets for fast relief of pain. Br J Pain. 2024;7:01–8.

[87] Vandy A, et al. Physicochemical quality assessment of various brands of paracetamol tablets sold in Freetown Municipality. Heliyon. 2024;10(3):e25502.

[88] G. PS, et al. Sublimation of Drugs from the Site of Application of Topical Products. Mol Pharm. 2023;20(6):2814–21.

[89] Singh S, Bhutani H, Mariappan T, Kaur H, Bajaj M, Pakhale S. Behavior of uptake of moisture by drugs and excipients under accelerated conditions of temperature and humidity in the absence and the presence of light. 1. Pure anti-tuberculosis drugs and their combinations. Int J Pharm. 2002;245(1–2):37–44.

[90] Shalaev E, Ohtake S, Moussa EM, Searles J, Nail S, Roberts CJ. Accelerated Storage for Shelf-Life Prediction of Lyophiles: Temperature Dependence of Degradation of Amorphous Small Molecular Weight Drugs and Proteins. J Pharm Sci. 2023;112(6):1509–22.

[91] Kestur US, Lee H, Santiago D, Rinaldi C, Won YY, Taylor LS. Effects of the Molecular Weight and Concentration of Polymer Additives, and Temperature on the Melt Crystallization Kinetics of a Small Drug Molecule. Cryst Growth Des. 2010;10(8):3585–95.

[92] Yesilada A, Erdogan H, Ertan M. Second Derivative Spectrophotometric Determination of p-Aminophenol in the Presence of Paracetamol. Anal Lett. 1991;24(1):129–38.

[93] Korany MA, Bedair M, Mahgoub H, Elsayed MA. Second Derivative Spectrophotometric Determination of Acetaminophen and Phenacetin in Presence of Their Degradation Products. J AOAC Int. 1986;69(4):608–11.

[94] Kalatzis E. Reactions of Acetaminophen in Pharmaceutical Dosage Forms: Its Proposed Acetylation by Acetylsalicylic Acid. J Pharm Sci. 1970;59(2):193–6.

[95] Mohamed F. Selective spectrophotometric determination of p-aminophenol and acetaminophen. Talanta. 1997;44(1):61–8.

[96] Fogg AG, Sausins PJ, Smithson JR. The determination of paracetamol and aspirin in mixtures by nonaqueous potentiometric titrimetry or by ultraviolet spectrophotometry. Anal Chim Acta. 1970;49(2):342–5.

[97] Shende C, Smith W, Brouillette C, Farquharson S. Drug Stability Analysis by Raman Spectroscopy. Pharmaceutics. 2014;6(4):651–62.