BioFlux ProEnvironmen Original Article
ProEnvironment 15/52 (2022) 469 - 474

The Characterization of pH Value of Sinus and Normal Paracetamol by Raman Spectroscopies

ANDRONIE Luisa[1], Aurelia COROIAN[2], Antonia ODAGIU[3], Andreea BEBU[4*], Adina Lia LONGODOR[1]

[1]Faculty of Forestry and Cadastre, University of Agricultural Sciences and Veterinary Medicine, Mănăştur Str. 3-5, 400272, Cluj-Napoca, Romania
[2]Faculty of Animal Science and Biotechnology, University of Agricultural Sciences and Veterinary Medicine, Mănăştur Str. 3-5, 400272, Cluj-Napoca, Romania
[3]Faculty of Agriculture, University of Agricultural Sciences and Veterinary Medicine, Mănăştur Str. 3-5, 400272, Cluj-Napoca, Romania
[4]University of Medicine and Pharmacy "Carol Davila", Traian-Vuisa 6, Bucharest, Romania
* Corresponding author e-mail: andreea.bebu@yahoo.com

Received 29 Octobre 2022; received and revised form 20 November 2022; ac cepted 30 November 2022; Available online 30 December 2022

Abstract

Paracetamols are non-steroidal anti-inflammatory drugs (NSAIDs) widely used in pain and inflammatory diseases. The present study aimed to analyse the paracetamol tablets (sinus and normal) using Raman spectroscopies for determination a differentiation and characterization the pH dependence (basic and acid). The active compound present in commercially tablets and their influence of pH value have been obtained and discussed.

Keywords: normal and sinus paracetamol, FR-IR (Fourier-trnsform Infrared Spectroscopy)

1. Introduction

Paracetamol is the most commonly used analgesic-antipyretic pharmaceutical, and the chemical structure of paracetamol is $C_8H_9NO_2$. Paracetamol appears as white solid-crystals, is soluble in organic solvents that methanol, ethanol, dimethylformamide, ethylene dichloride, acetone, ethyl acetate. While the precise mode of action is paracetamol in unclear, its effect is due to inhibition of prostaglandin synthesis. Paracetamol inhibits the enzyme (cyclo-oxygenase) [4] responsible for the biosynthesis of prostaglandins [12]. By reducing the synthesis of prostaglandins, paracetamol produces analgesia by elevating the pain threshold and reduces fever by 'resetting' the hypothalamic heat-regulating center of the brain. However, in contrast to aspirin, paracetamol is thought to act almost exclusively on the central nervous system, with little peripheral effect. This may explain why paracetamol, even in higher doses, has limited anti-inflammatory effect and is associated with fewer gastro-intestinal side effects. centrilobular hepatic necrosis with occasional observation of nephrotoxicity [8, 11] the mechanism of toxicity has been characterized [14, 15]. Additionally, H-NMR spectroscopy of urine has been used to investigate the biochemical sequelae of the toxic process in the overdose situation [20].

Allergic reactions to paracetamol have been reported, ranging from rashes [25] to bronchospasm [13, 23], and anaphylactic shock [7, 21]. The mechanism of paracetamol allergy is uncertain. There is occasional correlation with nonsteroidal anti-inflammatory drug hypersensitivity [19], suggesting that inhibition of cyclooxygenase may be responsible.The biological

activity and the pharmaceutical properties of drugs are strongly dependent on their structure.The use Raman spectroscopy in pharmaceutical industry is gaining much popularity as a quantitative tool due to its rapid and non-destructive nature, sample preparation, ease of use and less or no solvent consumption for monitoring quality as well as quantity of the raw materials and finished drug products. In literature studied shows a great number of papers dedicated to pharmaceutical drugs analysis using FT-IR and Raman spectroscopy [16, 18, 24].

Studies in IR and Raman [1 – 3] are already recorded in order to characterize and identify the three metastable forms of paracetamol, the transition between them, and the comparison between tablets and solutions. In the present work, because Raman spectroscopy is a powerful vibrational spectroscopic technique which has been applied in different biomedical applications, we propose the vibrational Raman characterization of two different commercial paracetamol tablets (normal and sinus), in order to distinguish the various action mode in terms of the pH value and to check the possibility to monitor both pharmaceutical species using spectroscopy.

2. Material and Method

Pharmaceutical tablets of paracetamol (Europharm) commercially available "sinus" and "normal" (500 mg active substance content), were used in our study and the solutions of paracetamol were prepared by dissolving 1 tablets in 10 ml distilled water resulting a concentratios of $3.3x10^{-1}$ M. The paracetamol normal tablet contains: 500 mg paracetamol active substance, 50 mg maize starch, 30 mg Avicel PH 102, 17.5 mg talc, 17.5 mg Sterotex®, and 30 mg sorbitol. The paracetamol sinus tablet contains: 500 mg paracetamol, 3 mg maleateclorfeniramin, 30 mg pseudo-ephedrine hydrochloride. The Raman spectra were recorded with a Dilor microspectrometer (Horiba-Jobin-Yvon, model LabRam) using the 514.5 nm excitation line from an argon ion laser (Spectra Physics, model 2016). The spectra were collected in the backscattering geometry using a microscope equipped with an Olympus LMPlanFL 50x objective with a spectral resolution of 5 cm^{-1}. The detection of Raman signal was carried out with a Peltier-cooled CCD camera. The laser power varied from 100 to 200 mW is indicated for each figure.

3. Results and Discussions

The Raman spectra of the two types of paracetamol solutions are presented in Fig. 1. The structure of paracetamol contains different functional groups including N-H, O-H, C=O and aromatic ring containing C=O. Paracetamol can crystallize in three different polymorphic forms known as form I, monoclinic (normal commercial form), II (identified by recrystallization from an ethanolic solution) is corresponds to an orthorhombic form and III was mentioned as a very unstable form [5, 22].

One can observe that the bands specific to sinus form of paracetamol is more intense in comparation whit bands characteristic paracetamol normal. The peaks are characteristic to the form I (monoclinic) of paracetamol, whereas the normal typed frequencies are representative for the form II (orthorhombic) of paracetamol [6, 10, 17].

Looking at both spectra (Fig. 1a, b) one can assume that in solution, both paracetamol types contain a mixture of those two forms, monoclinic and orthorhombic.

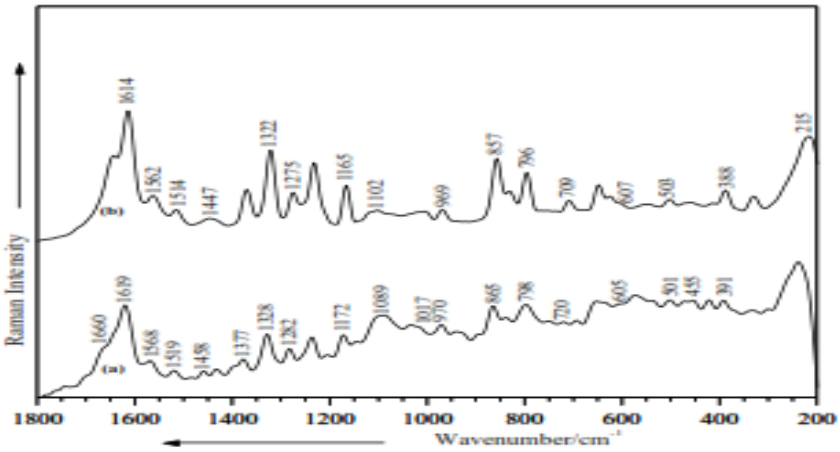

Figure 1. Raman spectra of normal (a) and sinus (b) paracetamol solution (3.3x10 M). Excitation: 514.5 nm (a, b), 200 mW (a, b).

The peaks characteristic for the monoclinic form is presented in spectra from paracetamol normal (a) at 1614, 1322, 1165 cm^{-1} and from paracetamol sinus (b) at 1619, 1328, 1172 cm^{-1}. The peaks at 857 cm^{-1} from paracetamol normal and the peak at 1282, 865 cm^{-1} from sinus paracetamol is characteristic for the orthorhombic form. The pH dependence Raman spectra of normal and sinus paracetamol aqueous solutions in the basic and acidic pH range are presented in Figs. 2, 3 and 4, 5, respectively. The paracetamol molecule can be treated as a slightly acidic compound because of the OH group presence in the para-position [27].In the Raman spectra of normal paracetamol solution at basic pH values (Fig. 2) a significant broadening of the 1619 cm^{-1} bands together with its two neighbouring shoulders, at 1696 and 1660 cm^{-1}, is observable. This band, in the basic pH range, is 12 cm^{-1} red shifted (1606 cm^{-1}) and may be assigned to the asymmetrical C=C aromatic and C-N stretching modes (Fig. 2, pH 13); the shoulders at 1696 and 1660 cm^{-1}, attributed to the CNH and C=O (amide I) stretching modes, are importantly red shifted at higher pH values (1689 and 1637 cm^{-1}, Fig. 2, pH 13).

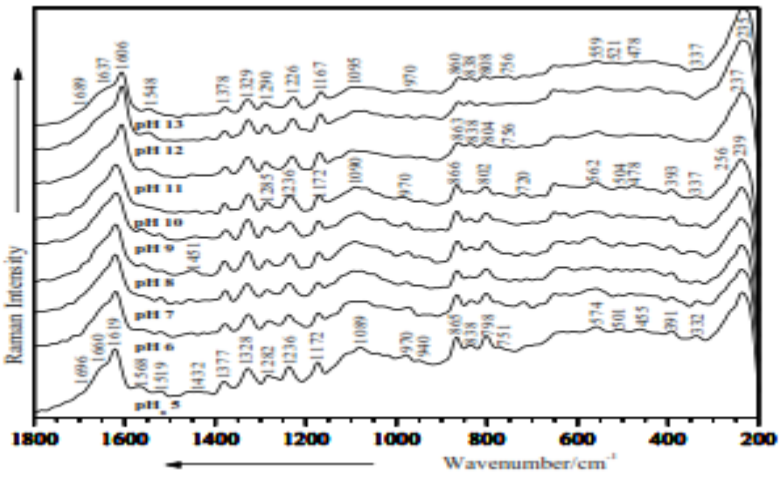

Figure 2. Raman spectra of 3.3x10 M normal paracetamol solution at different basic pH values. Excitation: 514.5 nm, 200 mW

The weak band at 1568 cm^{-1}, 20 cm^{-1} red shifted in the basic pH range, can be due to the in-plane N-H bending mode (amide II).

By analogy with the normal paracetamol, in the Raman spectra of the sinus paracetamol at basic pH values (Fig.3) a significant increasing in relative intensity and 14 cm^{-1} red shift of the band at 1614 cm^{-1}, which is attributed to the C=C aromatic and C-N stretching modes can be observed (Fig. 3, pH 13).

Moreover, the strong band at 1643 cm^{-1} that corresponds to the C=O (amide I) stretching mode, decreases in relative intensity, becomes a shoulder beginning with pH 10.5 and is 15 cm^{-1} red shifted; the weak medium band at 1562 cm^{-1} becomes broader, is 22 cm^{-1} red shifted, and can be due to the in-plane N-H bending mode (amide II) (Fig. 3, pH 13).

Furthermore, the weak signal at 1432 cm^{-1}, as a contribution of the asymmetrical CH_3 bending and phenyl stretching modes of the normal paracetamol, becomes broader and is 29 cm^{-1} blue shifted in the basic pH range.

The medium band at 1377 cm^{-1} is slightly decreased in relative intensity and is attributed to the symmetrical CH_3 bending mode. The signal correspondent to the C-N stretching mode (amide III) (1328 cm^{-1}) decreases in relative intensity, whereas the band correspondent to the C-O and C-N stretching modes (1282 cm^{-1}) increases in relative intensity in the basic pH range (Fig. 2, pH 13). With the pH increase, one can observe, first a broadening and then a red shifting (20 cm^{-1}) of the phenyl-N bending mode (1236 cm^{-1}), in comparison to the adjacent band at 1172 cm^{-1}, assigned to the phenyl-N and COH bending modes, which remain almost constant in relative intensity in the basic pH range (Fig. 2) and is slightly red shifted (5 cm^{-1}).

In contrast to the normal paracetamol, in the Raman spectra of the sinus paracetamol (Fig. 3), the weak peak at 1447 cm^{-1}, with the same assignment as for the normal paracetamol, seems to increase in relative intensity at pH 8 and after that, beginning with pH 9 becomes broader and disappear at higher pH values.

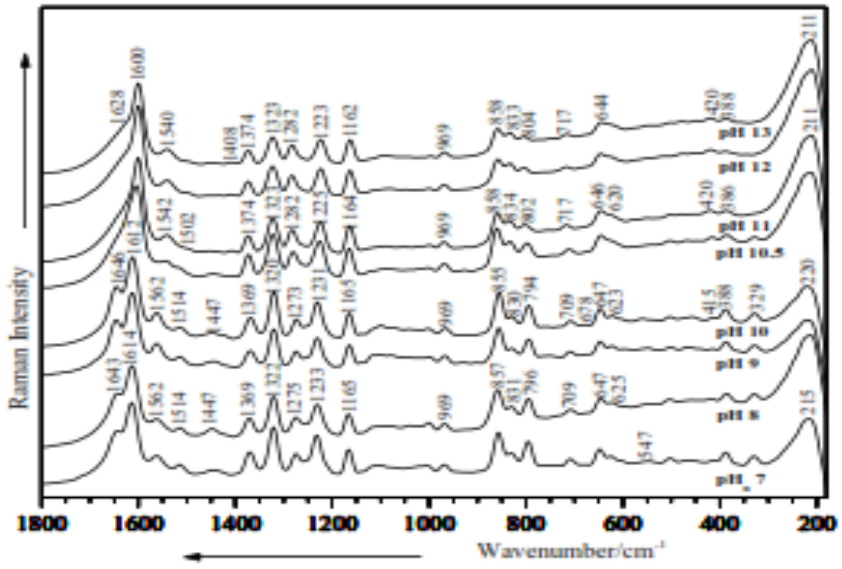

Figure 3. Raman spectra of 3.3x10M normal paracetamol solution at different basic pH values. Excitation: 514.5 nm, 200 mW

The next two bands (1369 and 1323 cm^{-1}) in the Raman spectra of the sinus paracetamol, which were attributed as for the normal paracetamol, decrease in relative intensities and are slightly blue shifted.

The following peak at 1275 cm^{-1} is 5 cm^{-1} blue shifted and increases in relative intensity, whereas the signal at 1233 cm^{-1} becomes broader, is slightly decreased in relative intensity and 10 cm^{-1} red shifted (Fig. 3, pH 13).

The bands at 865, 838 and 798 cm^{-1} from the Raman spectra of normal paracetamol (Fig. 2, pH 5 to 10) are slightly decreased in relative intensity, become weaker with the pH increasing, and are slightly shifted; they are attributed to the out-of-plane C-C skeletal deformation, to the out-of-plane C-H bending mode and to the phenyl-N bending mode, respectively. Similar bands from the Raman spectra of the sinus paracetamol observed at 857, 831 and 796 cm^{-1} (Fig. 3), decrease in relative intensity, are changed in shape and are slightly blue shifted. The weak band at 574 cm^{-1}, which corresponds to the out-of-plane phenyl-N deformation mode of the normal paracetamol, is slightly decreased in relative intensity and 15 cm^{-1} red shifted in the basic pH range (Fig 2, pH 13), whereas in the case of sinus paracetamol, the analogous band at 547 cm^{-1} decreases in relative intensity and then disappears (Fig. 3, pH 9-13). In general, all bands due to the C-N, N-H, phenyl-N, COH and C=O vibrational modes of paracetamol, become weaker and are red shifted.

These facts come to suggest the deprotonation of paracetamol in the basic pH range. Comparing Figs. 2 and 4, the Raman spectra of the normal paracetamol solutions remain mainly unchanged in the pH range from 5 to 3. Small differences can be observed in the 1700-1000 cm^{-1} spectral region at pH 2, whereas at pH 1 the disappearance of the shoulder at 1696 cm^{-1} and an overall blue shift were observed. Additionally, in the 1000-700 cm^{-1} wavenumber region, the band at 838 cm^{-1} increases in relative intensity (Fig. 4, pH 2) and can be due to the out-of-plane C-H bending mode.

One can perceive that the out-of-plane phenyl-N deformation mode (574 cm^{-1}) is represented by two weak peaks at pH 3 (572 and 549 cm^{-1}) (Fig. 4) and at pH 0 remains a unique band, which is 17 cm^{-1} red shifted (557 cm^{-1}). In the low wavenumber region, the band at 332 cm^{-1} changes in shape, relative intensity, is 7 cm^{-1} red shifted (325 cm^{-1} at pH 3, Fig. 4), and may be due to the out-of-plane phenyl-N deformation mode. Thus, the fully protonated normal paracetamol molecule predominates at low pH values [9, 27, 26]. Finally, taking into account the major changes in the band shape attributed to phenyl-N Raman bands at acidic pH values, a protonation of the NH group is very likely.

Comparing Figs. 3 and 5, the Raman spectra of the sinus paracetamol remains unchanged in the pH range from 7 to 0, which demonstrates that at neutral pH 7, the sinus paracetamol exists in the zwitterionic form.

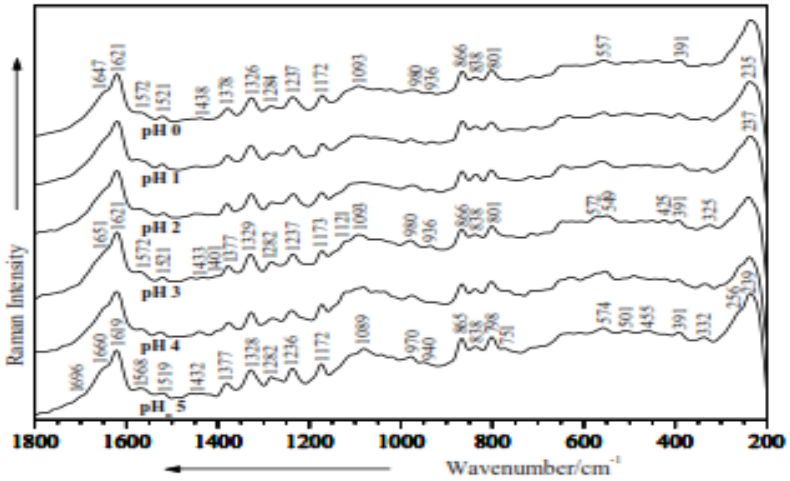

Figure 4. Raman spectra of 3.3x10 M normal paracetamol solution at different acidic pH values. Excitation: 514.5 nm, 200 mW

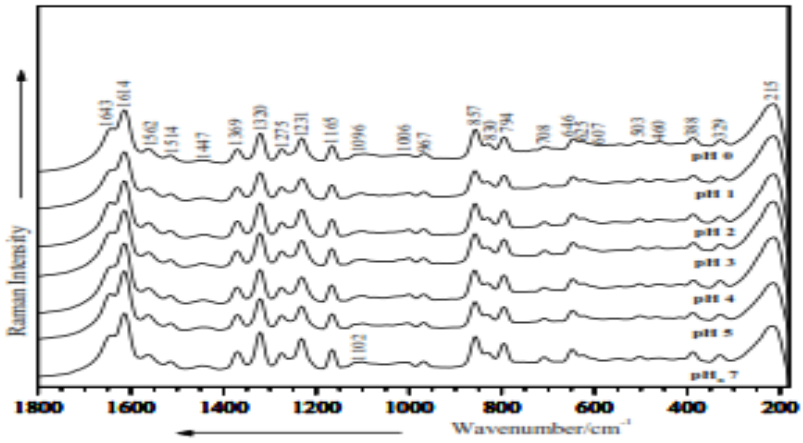

Figure 5. Raman spectra of 3.3x10M sinus paracetamol solution at different acidic pH values. Excitation: 514.5 nm, 200 mW

4. Conclusions

The Raman spectra of both paracetamol tablets were recorded, and the marker bands of the characteristic functional groups were identified. Analyzing both types of the paracetamol solutions, a change in the molecular identity, (paracetamol → protonated form), ongoing from basic to acidic pH values could be evidenced by analysing the Raman spectra.

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