

Quality Analysis and Quantum Classical Analysis of Acetaminophen

Naidu Dhanpal Jayram, T. Santosh, S. Jeyavijayan, M. S. Revathy, S. Sonia

Abstract: In recent year's Raman and IR spectroscopy has been widely used by pharmaceutical industry as a analytical tool for quality control. The present work Acetaminophen (common name paracetamol) is been characterized using Raman, FTIR, and UV-visible techniques. 5 different brands of tablets (name changed as A, B, C, D, and E) purchased from Medical shop for analysis and comparative studies. Spectrum recorded using Raman shows major peak in between 400-1600cm⁻¹ wavelength respectively; the Y-axis intensity for them varies along shift in x-axis but majorly all remains same except in Tablet C. FTIR spectroscopy doesn't show much variation in the reflectance spectra but slight variation in y-axis intensity is noted. UV-visible remains same for all the tablets. For comparison the optimized geometries, harmonic vibrational wave numbers and intensities of vibrational bands of Acetaminophen were determined using DFT-B3LYP with 6-311++G(d,p) level calculations. Weight variation and Tablet disintegration studies were also done to confirm weight in gms of individual tablet. The disintegration time shows breaking of tablets particles into smaller ones in particular time. The analysis of paracetamol quantity and its interdependence on the optical characterization such as Raman, FTIR, were interpreted through means of band width; functional group and bond length. UV-visible spectroscopy helps to determine the volumetric concentration dependence on functional group. The theoretical calculations were matched with experimental results.

Keywords : Acetaminophen; FTIR; FT-Raman; DFT, weight variation and Tablet disintegration

I. INTRODUCTION

Para-Acetaminophen commonly known as Paracetamol is an active form of Phenacetin[1-4]. This Para-Acetaminophen is used widely as an antipyretic and analgesic drug. Acetaminophen is 4 hydroxy acetanilide chemically consists of hydroxyl, carboxyl and nitrogen shown in Fig.1. Acetaminophen (Paracetamol) is generally available as a tablet for adults and syrup based fluid for children. It comes under non-steroidal and anti-inflammatory drug by many sources. Acetaminophen shows some anti-inflammatory

Revised Manuscript Received on December 15, 2019.

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effect in comparison with other painkiller drugs. Acetaminophen is available in different dosages as Paracetamol tablets, capsules, syrup based and also suspension solution [8-10]. It is low-cost antipyretic and analgesic drug available in world market. It is readily available in all local stores as a handy drug to reduce fever. There are numerous manufacturer of acetaminophen drug. The preparation of drug varies according to the methods and employs. Paracetamol is mainly used to reduce fever and body pain for all ages [5-7]. It is used with other combinations to counteract cold and other flu. Usage of this drug provides nearly no side effects. Overdose of the drug may cause serious damage to the liver [11-13]. The lowest dose of the Paracetamol for adult is 7.5g/kg in adults and 150mg in children. Paracetamol overdose causes Hepatotoxicity, which leads to serious liver complications. It is the common poisoning worldwide. More amount of Paracetamol toxicity leads to hepatic encephalopathy. Increased amount of dosage can cause stomach bleeding. (Vidhya and bhai 2006). Other than liver, calcified kidney is the second victim of Paracetamol toxicity. (Beasley et al., 2008) [14-16]. Prolong usage of this acetaminophen will thin the blood and the blood would lose the ability to clot. To avoid all the side effects caused by Paracetamol we have to analyze the quality of the available drugs in the market. There are many certified manufacturers of these drugs are found in India. In the present work, five popular brands of acetaminophen (named given as A, B, C, D, E) were recorded using Raman, FTIR, UV spectra respectively. The main purpose of the study is to find out the quality of the Paracetamol tablets by optical characterizations and quantity analysis through weight variation, dissolution test, and disintegration time.

II. EXPERIMENTAL

A. Materials and Methods

The comparison study with different brands of Paracetamol 500mg tablets showed notable results. Five different brands of Paracetamol tablets coded as A B C D E are tested using weight uniformity, disintegration time and dissolution test. The necessary data for a tablet sample are noted and the chemical composition mentioned in the Paracetamol tablet strip is noted. Only acetaminophen content in all of Paracetamol tablet brand strip is confirmed and noted. The expiry date is noted and taken into consideration prior to two years from the date of manufacture.

B. Weight Variation

Each tablet of different brand is weighed using a digital balance. The weight of the tablet varies from brand to brand even it is formally advertised as 500 mg of acetaminophen. The variation of weight in different tablet is very much important when dosage of the Paracetamol is concerned. This is one of the important test to test the amount of Paracetamol content is present in each tablet.

C. Tablet Disintegration

Disintegration time is defined as the breakup of particles into smaller ones in particular period. The breakdown of the larger particles into smaller particle is noted. To test for the disintegration of the tablet we have to put the tablet in a beaker containing 0.1 N HCl acid at a temperature of 70 C the beaker is then placed in a magnetic stirrer at a constant frequency. The disintegration time for each of the acetaminophen were noted.

D. FTIR

FTIR is used to find infrared spectrum for solid, liquid or gas samples. Results for FTIR show the bonding between the molecules of the sample. It is the analysis of different compounds present in the material. FTIR gives peaks concerned to different bonding in the compound. The results are noted. Experimental data were recorded using

E. UV- absorption

UV – absorption for wavelength of region is observed. The absorption peak gives suitable results in the form of graph. The results are noted. UV-Visible analysis was carried out using UV- Visible spectrometer (Jasco V-640).

F. Raman

The shift in energy gives information about the vibrational, rotational and other low frequency transitions present in the molecules. Raman spectrometer (LABRAM-HR) with laser excitation lines of 514 and 632 nm respectively at room temperature with power of 15mW and acquisition of 6 seconds applied for the individual films.

III. RESULT AND DISCUSSION

A. Molecular geometry

The molecular structure of the Acetaminophen molecule was optimized using standard 6-311++G(d,p) basis set as shown in Fig.1. The global minimum energy of the optimized molecular structure of the molecule is calculated as -919.577287 and -919.709992 Hartrees respectively.

Vibrational spectral analysis

The Acetaminophen molecule contains 18 atoms and hence it has 48 (3N-6) normal modes of vibrations. The molecular geometry of the molecule possesses C₁ point group symmetry and all the normal modes of vibrations are present in both infrared (IR) and Raman spectra. The observed FT-IR and FT-Raman spectra of Acetaminophen molecule are presented in Fig. 2. The calculated, observed vibrational frequencies, infrared intensity, Raman activity and vibrational assignments listed in Table 2 [16-18]. In general, the calculated vibrational wavenumbers are usually higher than the corresponding experimental vibrational wavenumbers, which is due to the anharmonicity in the DFT calculations; basis set incompleteness and neglect of electron correlation. Therefore, in order to improve the calculated vibrational wavenumbers in agreement with the experimental ones, it is

necessary to scale down the calculated harmonic frequencies. A better agreement between the computed and experimental vibrational frequencies can be obtained by using scale factor [19] of 0.96 for B3LYP method.

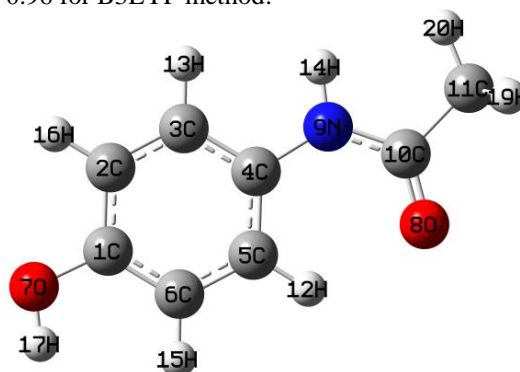


Fig.1. Molecular structure of Acetaminophen

A better agreement between the computed and experimental frequencies can be obtained by using scale factor [19] of 0.96 for B3LYP method. The resultant scaled frequencies are also listed

B. Mulliken charges analysis

The calculation of atomic charges describes a significant task in the application of quantum mechanical calculations to molecular systems [19]. Mulliken population analysis has been carried out for the comparison of different choice of the basis sets to describe the electron distribution in CHAP. The Mulliken charges calculated at different basis set calculations are listed in Table 4. The carbon atom C2 has the high negative charge, atoms C3 and C5 have positive charges since they are attached with OH, CO-CH₃ and Cl groups, respectively, which leads to redistribution of electron density. All the hydrogen atoms have a net positive charge because they are electron acceptors.

TABLE- I: Mulliken charges analysis for acetaminophen

Atoms	Atomic charges (Mulliken)
C1	-0.320
C2	-0.256
C3	-0.362
C4	-0.354
C5	0.534
C6	0.009
O7	-0.246
H8	-0.346
C9	-0.080
O10	0.358
C11	-0.655
H12	0.246
H13	0.133
H14	0.255
H15	0.142
Cl16	0.194
H17	0.264
H18	0.183

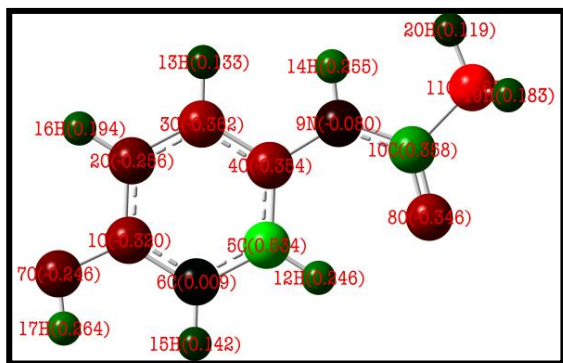


Fig. 2. The Mulliken atomic charge distribution of the paracetamol molecule.

C. HOMO-LUMO analysis

The frontier molecular orbitals (FMOs) such as highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) play an important role in the electric and optical properties, as well as in UV-vis spectra and chemical reactions[20]. The HOMO-LUMO orbital for acetaminophen is shown in Fig. 3. In this study, the HOMO is located over ring system, hydroxyl, carbonyl groups and LUMO: of π nature, (i.e. benzene ring) is delocalized over the whole C-C bond of the ring; consequently the HOMO \rightarrow LUMO transition takes place to the C-C bond of the benzene ring along with O-H and C=O group. The HOMO-LUMO energy gap is found to be 3.59 eV by B3LYP/6-311++G(d,p) method. This explains the ultimate charge transfer interaction within the molecule, which influences the biological activity of the molecule.

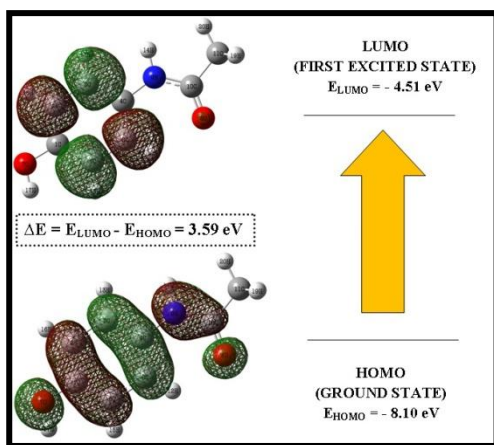


Fig.3. HOMO-LUMO for Acetaminophen

D. FTIR

The tablets of brand A and brand D show sharp peaks of 1014 and 1015 in the FTIR resultant graphs. Nearly all the FTIR result for the bands shows similar results other than brand A and brand D. The presence of strong C-N stretch is observed in the Paracetamol compound of brand A and brand D infers the results from other brands of Paracetamol. The presence of 1600 peak on all the compounds of A, B, C, D, E resembles C=O amide in stretch mode, NH bond and CH bond in differential manner [21]. Sharp peaks infer that the bonding is strong. The FTIR graph is shown in Fig. 4.

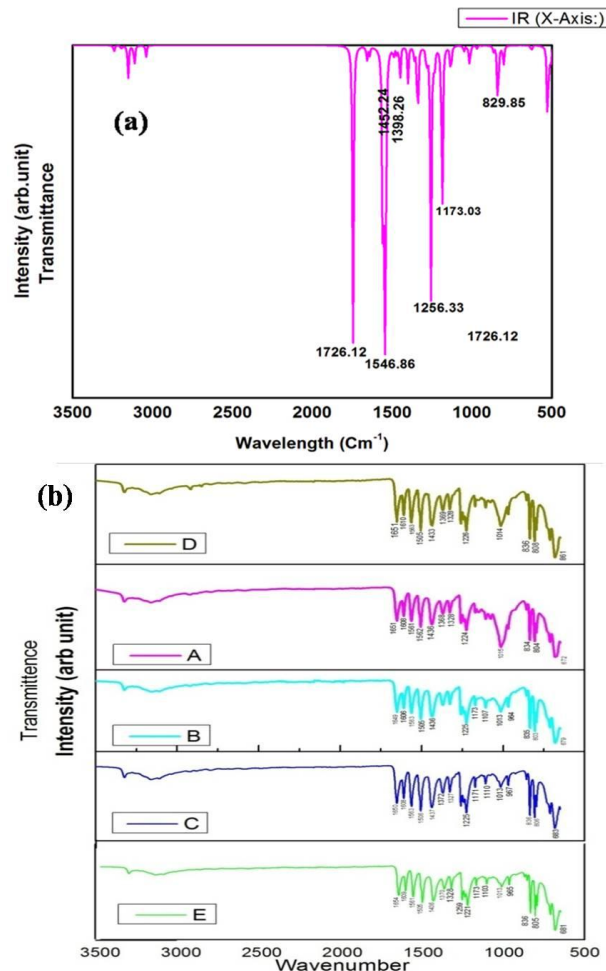


Fig.4. FTIR spectra Acetaminophen (a) spectra DFT-B3LYP (b) Experimental FTIR for 5 tablets

E. Raman studies

The Raman spectrum of acetaminophen is dominated by peaks at 797, 858, 1236, 1324, 1560, 1611, and 1649 cm^{-1} , which are assigned to CNC ring stretching, ring breathing, C-C ring stretching, amide III, amide II, ring stretching, and amide I modes, respectively [22]

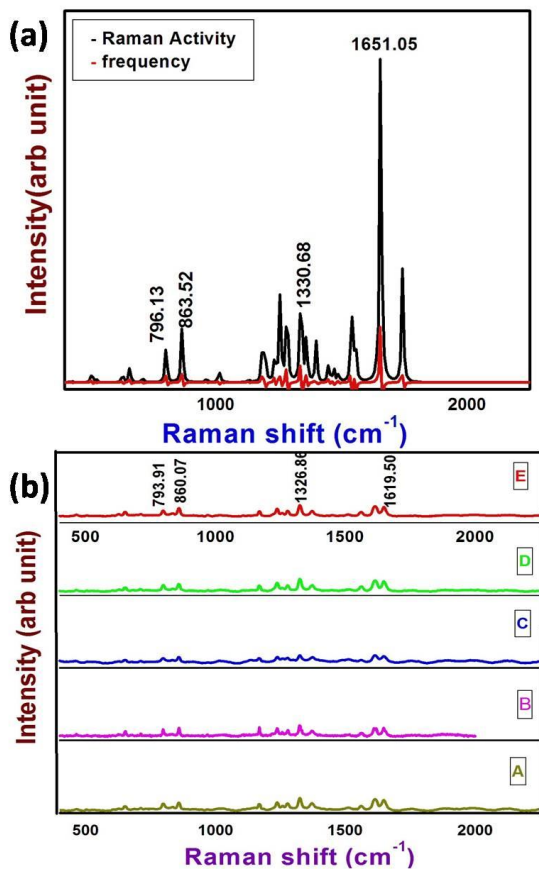


Fig. 5. Raman spectra for Acetaminophen (a) spectra DFT-B3LYP (b) Experimental Raman for 5 tablets

Table II. FTIR, Raman and vibrational frequencies (cm⁻¹) for Acetaminophen (a) Experimental (b) theoretical

No	Experimental frequencies		B3LYP 6-311++G(d,p)		
	FTIR	FT-Raman	IR intensity	Raman activity	Bonds
1			1726.12	1745.37	C=O Stretching
2	1651 1610	1619.50		1651	C-C Stretching
2	1563 1505	1558.21	1546.86	1543.	C-C Stretching
3	1433		1452.24	1444.58	C-C Stretching
4	1369 1328	1326.86 1374.33	1398.26	1372.25	C-C Stretching
5	1226		1256.33	1257.06	C-N Stretching
6		1162.05	1173.03	1179.94	C-H in plane bending
7	836 808 861	860.07	829.85	863.02	C-H out of plane bending
		793.91			

Through the table 3 we can able to find that all the vibrational frequencies are well matching experimentally and theoretically, which shows that the quality of tablets are well matched and good.

F. UV- absorption studies

The maximum absorption is observed at the wavelength of 243 nm for all the tablet samples taken. Tablet sample B and D shows maximum value of ~249 nm. With the calculation of the Beer lamberts Law $A \propto \epsilon c l$. Where, A is the absorbance and C is the concentration of the sample. Hence, concentration is directly proportional to the absorbance peak [23]. Thus maximum absorbance peak (i.e. 243nm) will be λ_{max} . The concentration of all samples remains nearly the same. Thus the concentrations of acetaminophen are same for all the brands of Paracetamol nearly. The UV-Absorbance graph is shown in Fig.5.

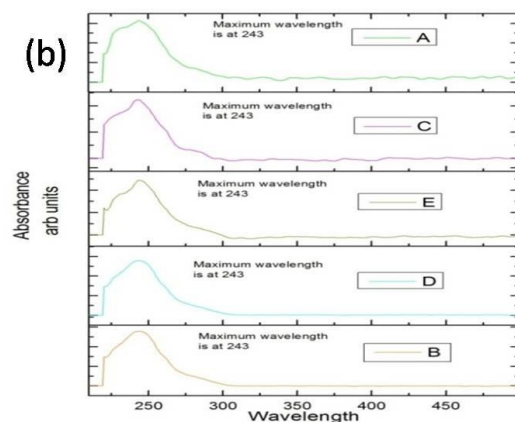
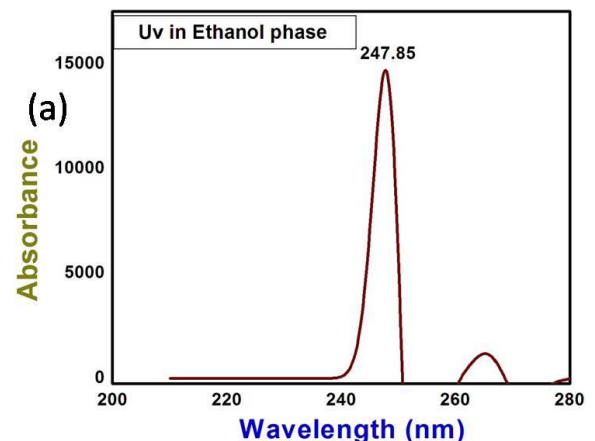


Fig. 6. UV-vis spectra for Acetaminophen (a) spectra DFT-B3LYP (b) Experimental UV-Vis for 5 tablets

IV. QUANTITATIVE ANALYSIS

A. Weight Variation

Each tablet of different band is weighed using a digital balance. The weight of the tablet varies from brand to brand even it is formally advertised as 500 mg of acetaminophen. The results are tabulated below in Table- II. The weight variation is also graphically represented in Fig. 2.

Table- II: Different wt in gms for tablets

Tablet	Weight in gms
A	0.5870
B	0.5878
C	0.6282
D	0.5850
E	0.6172

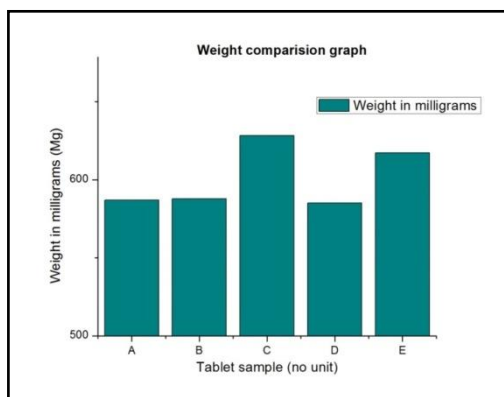


Fig. 7. The weight variation

B. Tablet Disintegration

Tablets of Acetaminophen disintegrated in the self-made solution of 0.1 Normal Hydrochloric acid in variable time ranging from seconds to minutes. Higher the Disintegration time greater is the tablet dissolves. Table- III shows variable results. Thus immediate action and side effects are more in tablets which have higher disintegration time. The tablet sample A has lowest disintegration time. Specific binding agents provide easy disintegration in the gastric fluid[22-23]. The results were graphically represented in fig. 3.

Table- III: Disintegration time versus Tablet name

Tablet sample	Disintegration time (seconds)
A	38
B	140
C	50
D	628
E	85

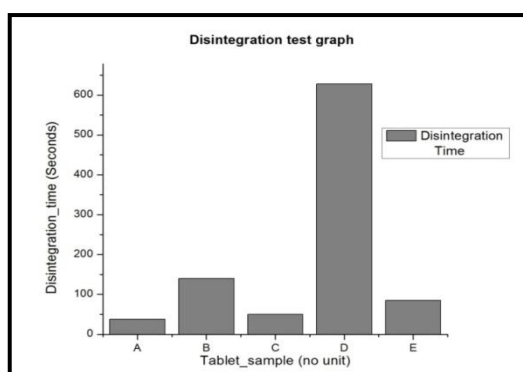


Fig. 8. Disintegration time for Tablet (name)

V. CONCLUSION

Corresponding FTIR, Raman and UV spectra for different tablets were recorded experimentally and compared with theoretical values. The optimized geometries, harmonic vibrational wavenumbers and intensities of vibrational bands of Acetamenophen were determined using DFT-B3LYP with 6-31+G(d,p) and 6-311++G(d,p) level calculations. The normal modes of Acetamenophen were studied by FTIR and FT-Raman spectroscopies on the basis of C_1 point group symmetry. These results will be of assistance in the quest of the experimental and theoretical evidence for acetaminophen in reaction intermediates, pharmaceuticals industries. The overall conclusions shows that the quality of the Paracetamol tablets by optical characterizations well matches experimentally and theoretically whereas the quantity analysis through weight variation, dissolution test, and disintegration time shows variation in weight and dissociation time.

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