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Research Article
Crystal Growth, Vibrational, Optical and Antimicrobial Activity Properties of N-(4-Hydroxyphenyl) Acetamide Nitrate Crystal

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Abstract

Background and Objective: The commonly used medicines of N-(4-hydroxyphenyl) acetamide can help to treat pain and reduce high temperature. It belongs to the classes of analgesic and antipyretic drugs. In this study, the effect of nitric acid on the N-(4-hydroxyphenyl) acetamide crystals obtained from the aqueous ethanol solutions using the slow evaporation method was examined. **Materials and Methods:** Raw materials of N-(4-hydroxyphenyl) acetamide, nitric acid, ethanol and distilled water were used for this crystallization. The 4-HPAN crystals had been grown with high transparency using the slow evaporation method. The pure crystalline nature was characterized using ultraviolet-visible-near infrared, FT-IR and FT-Raman spectra, powder X-ray diffraction and scanning electron microscopy. **Results:** Crystallization of 4-HPA in the presence of nitric acid may permit the alteration of crystal shape by solution growth technique. The molecular structure obtained using Chem3D software was connected through the O-H···O hydrogen bond. The FT-IR and FT-Raman spectra confirmed the presence of the functional groups in the synthesized material. Using ultraviolet-visible-near infrared spectral analysis, the optical quality of the grown crystal was studied and showed that the crystal has 100% transmittance with the lower cut-off wavelength of 305 nm. The plate-like morphology was confirmed by the scanning electron microscopy. The compound inhibits the growth of certainly tested microorganisms at high concentrations except for *Escherichia coli*. **Conclusion:** The synthesized N-(4-hydroxyphenyl) acetamide nitrate crystal has good crystallinity, functional group vibrations, high transparency in the visible region, plate like morphology with increasing oxygen and nitrogen composition and high inhibition against certain bacteria except *Escherichia coli*.

Key words: 3D molecular structure, infrared, Raman, optical study, antimicrobial, paracetamol

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The organic compound of N-(4-hydroxyphenyl) acetamide has analgesic and antipyretic activities which are also commonly known as paracetamol or acetaminophen[1]. The names of paracetamol and acetaminophen come from the words of chemicals used in the compound: Para-acetyl-amino-phenol and N-acetyl-para-aminophenol, respectively[2]. The structural simple compound of N-(4-hydroxyphenyl) acetamide ($C_8H_9NO_2$) has a six-carbon benzene ring with two small chemical groups attached and it is in a class of medications called analgesics (pain relievers) and antipyretics (fever reducers)[3]. This drug is available in a variety of forms in pharmaceutical products including syrup form, regular tablets, effervescent tablets, injections, suppositories and other forms to treat allergies, coughs, colds, flu and sleeplessness[4]. The N-(4-hydroxyphenyl) acetamide belongs to a nonsteroidal anti-inflammatory group of drug that exhibit anti-inflammatory activity in men but it did not show any anti-inflammatory activity in animals[5]. Also, it is used in combination medicines to treat muscle aches, menstrual periods, colds, sore throats, toothaches and backaches[6]. In nitric acid, the nitrogen atom is bonded to both a hydroxy group and two oxygen atoms[7] and is very soluble in water which also acts as a strong oxidizer[8]. It is used to prepare homeopathic medicines that are used to cure throat sore, tonsillitis, mouth ulcers, piles and skin issues[9]. Also, it is used for the production of various industrial products and various drugs. It electrophilically reacts with aromatic compounds such as benzene and also generates the nitro group in organic synthesis[10]. The present work was to investigate the effect of nitric acid addition on the growth of N-(4-hydroxyphenyl) acetamide crystal. Because of this, an attempt was made to grow the N-(4-hydroxyphenyl) acetamide nitrate (4-HPAN) crystal by solution growth method. This framework aimed to analyze the molecular structure, powder XRD, FT-IR, FT-Raman, UV-Visible-NIR spectroscopy, SEM with EDX and antimicrobial activity studies.

MATERIALS AND METHODS

Study area: At the Research Department of Physics, Devanga Arts College, Aruppukottai, Tamil Nadu, India, the 4-HPAN crystal was grown in October, 2022. For the harvested crystals, data were collected between December, 2022 and January, 2023.

Chemicals used: The N-(4-hydroxyphenyl) acetamide (98% Alfa Aesar), nitric acid, ethanol and distilled water were purchased from Modern Scientific Company, a laboratory equipment supplier in Madurai, Tamil Nadu.

Computational details: The molecular structure of 4-HPAN crystal was obtained using the Chem3D desktop modeling program under gas-phase conditions in the version 16.0.

Methods: The grown crystal of 4-HPAN which was prepared by mixing the aqueous ethanol solution of N-(4-hydroxyphenyl) acetamide and nitric acid (3 drops) as shown in Fig. 1. The solution was stirred well for 1 hr at room temperature and filtered in the Petri dish. After 10 day's duration, crystals were obtained by the slow evaporation process. The schematic chemical structure of the 4-HPAN was shown in Fig. 2.

Experimental details: The XPERT-PRO X-ray diffractometer (Bruker India Scientific Pvt. Ltd., Bengaluru, Karnataka, India) with Cu Kα radiation (1.54060Å) was used to carrying out the process of the powder X-ray diffraction analysis at Alagappa University, Karaikudi. The SHIMADZU FT-IR spectrometer, Manufactured by Shimadzu, Tokyo, Japan was used to obtain the FT-IR spectrum in the wavenumber range 400-4000 cm^{-1} with a KBr disc at V.H.N.S.N. College, Virudhunagar. The BRUKER: RFS 27 Raman spectrometer (Bruker India Scientific Pvt. Ltd., Bengaluru, Karnataka, India) was used to prepare the FT-Raman spectrum in the wavenumber range 4000-400 cm^{-1} at SAIF, IIT Madras. The SHIMADZU-UV 1601, ()Manufactured by Shimadzu, Tokyo, Japan, a double beam spectrometer had

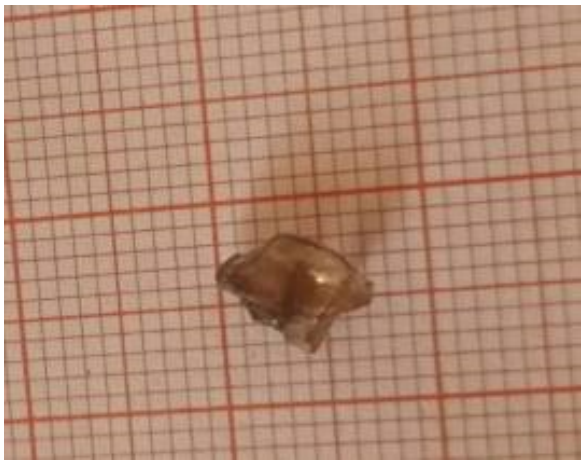

Fig. 1: Grown crystal of 4-HPAN

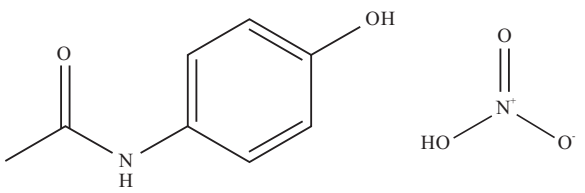

Fig. 2: Chemical structure for 4-HPAN crystal

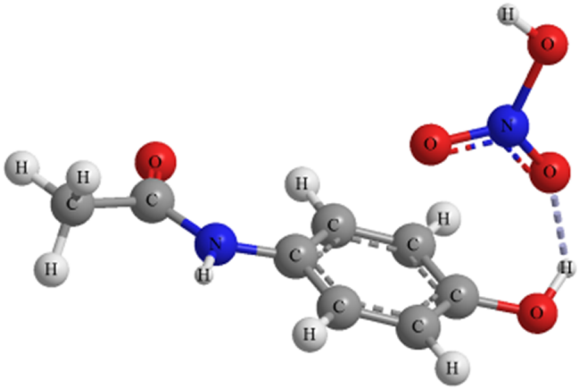

Fig. 3: Molecular model of 4-HPAN crystal

been used to record the optical absorption spectrum in the wavelength range 190-1100 nm at Virudhunagar Hindu Nadar's Senthikumara Nadar College, Virudhunagar. Using CARLZEISS EVO1 8 (Carl Zeiss India Pvt. Ltd., Bangalore, Karnataka) scanning electron microscope, the SEM with elemental analysis was performed at Kalasalingam University, International Research Centre, Krishnankoil, Tamil Nadu, India in Sri Kaliswari College, Sivakasi, Tamilnadu, India.

Statistical analysis: The 3D molecular structure was obtained using Chem3D software version 16.0 chem office packages. From the literature survey, there is no report on the crystal structure of N-(4-hydroxyphenyl) acetamide nitrate. For the first time, the molecular structure was predicted and its vibrational, optical, morphology and antibacterial activity studies were reported. All the graphical spectral data was done using the origin pro 8.6 software. Without using any instrument, the diameter zone of inhibition was measured using a ruler by the naked eye in millimeters.

RESULTS AND DISCUSSION

Molecular structure: The structure of 4-HPAN molecule was drawn using Chem3D drawing program by running MM2 calculation. After minimizing the energy, the molecular structure was optimized for the total steric energy -24.6768 kcal mol^{-1}. The optimized molecular model of 4-HPAN crystal was displaced in Fig. 3. Here the N-(4-hydroxyphenyl) acetamide compound was interlinked with the nitric acid through O-H···O hydrogen bond. The molecular formula and molecular weight were calculated as $C_8H_{10}N_2O_5$ and 214.18 g mol^{-1}, respectively.

X-ray diffraction analysis: The experimentally recorded powder X-ray diffractograms of N-(4-hydroxyphenyl) acetamide without and with the addition of nitric acid was shown in Fig. 4. As can be seen from Fig. 4, the phase purity and crystallinity increased for the investigated sample when compared to that of pure N-(4-hydroxyphenyl) acetamide crystal. The powder XRD data of pure N-(4-hydroxyphenyl) acetamide and N-(4-hydroxyphenyl) acetamide nitrate crystals were reported in Table 1. The prominent peaks like 2θ = (26.4789°), (23.4317°) and (15.4492°) of N-(4-hydroxyphenyl) acetamide crystal shifted to (26.0019°), (23.8215°) and (14.9527°) when added a certain amount of nitric acid. Also, some additional peaks have appeared in N-(4-hydroxyphenyl) acetamide nitrate crystal. These results may indicated that a certain amount of nitric acid was entered into the lattice of N-(4-hydroxyphenyl) acetamide crystal. The particle size of both compounds was calculated as 55 nm using the Debye-Scherrer formula. There was no significant change in the crystalline size for 4-HPAN compounds when a convincing amount of nitric acid was added.

Vibrational spectra of 4-HPAN crystal: The molecular structure contains N-H (amide), O-H (phenol), C=O (amide), CH_3 (methyl), C-N, C-H (aromatic), C-C (aromatic), C=C (aromatic) C-N-C (amide) and nitric acid (-NO_2, O-NO_2, O-H and H-O-N) functional groups. The FT-IR and FT-Raman spectra of 4-HPAN was shown in Fig. 5a and b, respectively, values of wavenumbers and their assignments were collected in Table 2. The characteristic vibrations were assigned according to early reported works.

Vibrations of N-(4-hydroxyphenyl) acetamide: The stretching of O-H, N-H, C-H and CH_3 vibrations were seen in the high wavenumber region. Characteristic band with a peak at 3325 cm^{-1} in IR spectrum assigned to ν (O-H) vibration. The presence of an absorption band at 3256 cm^{-1} was an indication of the existence of the stretching mode of N-H. Shoulder peak at 3030 cm^{-1} in the IR spectrum and respective absorption band at 3065 cm^{-1} in the Raman spectrum assigned to stretching vibrations of the C-H group. The ν_{as} (-CH_3) mode was assigned at 2922 cm^{-1} (IR) and 2931 cm^{-1} (Raman) and ν_{s} (-CH_3) mode was attributed at 2876 cm^{-1} (IR).

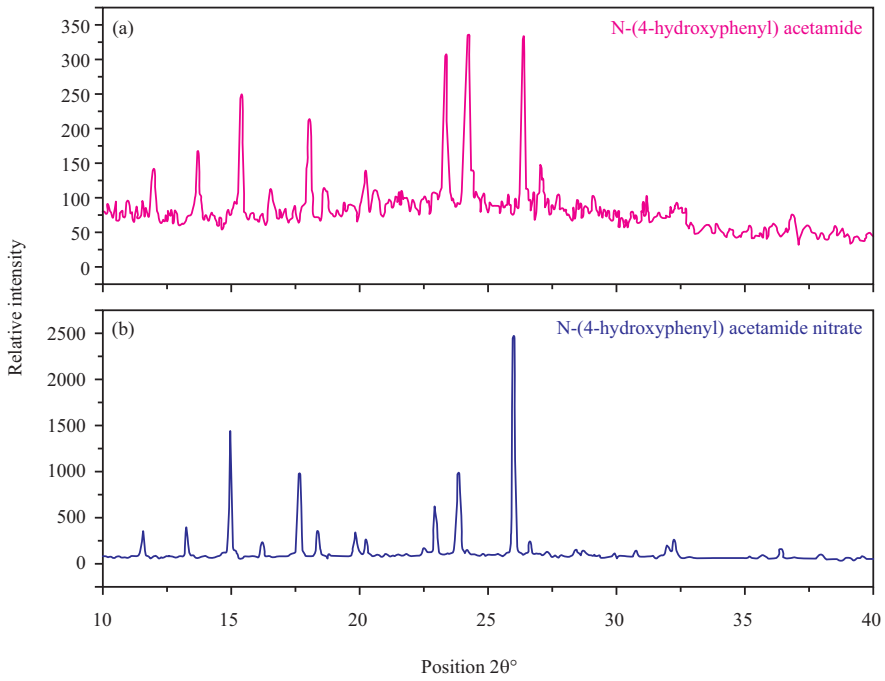

Fig. 4(a-b): Powder X-ray diffraction pattern for (a) N-(4-hydroxyphenyl) acetamide and (b) N-(4-hydroxyphenyl) acetamide nitrate crystals

Table 1: Powder XRD data of pure N-(4-hydroxyphenyl) acetamide and N-(4-hydroxyphenyl) acetamide nitrate crystals

N-(4-hydroxyphenyl) acetamide		N-(4-hydroxyphenyl) acetamide nitrate	
Position [2θ°]	d-spacing [Å]	Position [2θ°]	d-spacing [Å]
12.0241	7.36068	11.5406	7.66792
13.7664	6.43274	13.2393	6.68762
15.4492	5.73565	14.9527	5.92494
16.6462	5.32579	16.1818	5.47757
18.1070	4.89930	17.6243	5.03237
18.7276	4.73833	18.3408	4.83738
-	-	19.8268	4.47805
20.3169	4.37111	20.2227	4.39125
-	-	22.5330	3.94597
-	-	22.9333	3.87800
23.4317	3.79664	23.8215	3.73539
24.3134	3.66091	-	-
26.4789	3.36622	26.0019	3.42688
-	-	26.6275	3.34777
27.1284	3.28709	27.2907	3.26791
-	-	28.6011	3.12110
-	-	30.7545	2.90730
32.5044	2.75467	31.9655	2.79986
-	-	32.2580	2.77514
36.8819	2.43715	36.3834	2.46939

The stretching vibrations of C-C and C=C were attributed at 1612, 1584 and 1439 cm^{-1}, respectively. Corresponding peaks were identified in the Raman spectrum. The peak in the region 1325 cm^{-1} in both spectra was caused by ν (C-N) vibration. The ring breathing mode was clearly observed at 837 cm^{-1} in the FT-IR spectrum.

The N–H wagging mode was observed at 711, 685 cm^{-1} in the IR spectrum. The antisymmetric and symmetric bending vibrations of the -CH_3 group normally appear in the region of 1439 cm^{-1} (IR) and 1369 (IR), 1371 (Raman) cm^{-1}, respectively. The -CH_3 rocking mode was attributed at 1171 cm^{-1} and 1169 cm^{-1} in both spectra. The in-plane and out-of-plane

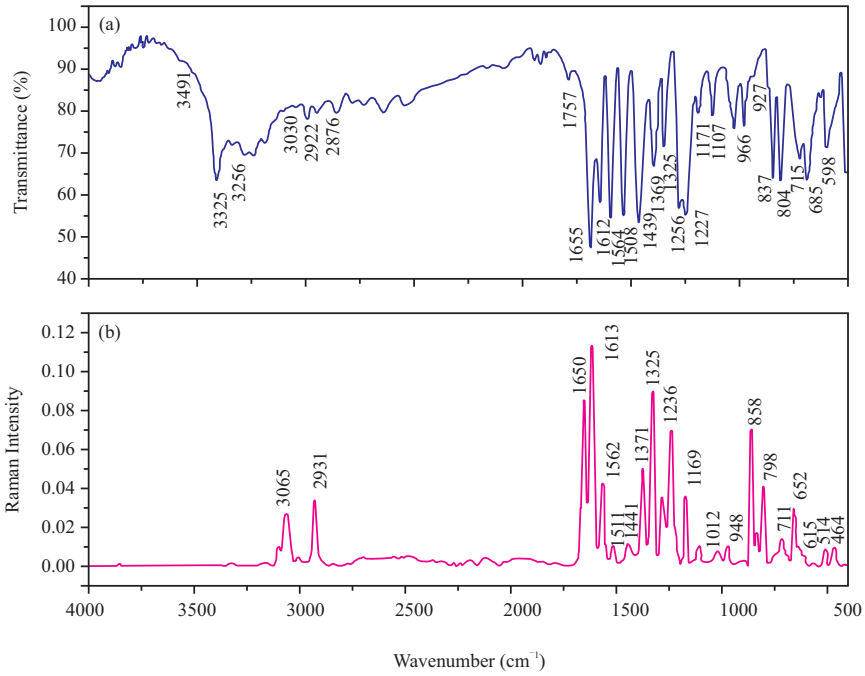

Fig. 5(a-b): (a) FT-IR spectrum and (b) FT-Raman spectrum of 4-HPAN crystal

bending vibrations of O-H was assigned at 1439 cm^{-1} and 966 cm^{-1}. The remaining molecular vibrations were summarized in Table 2.

Vibrations of nitric acid: The antisymmetric and symmetric stretching of NO_2 was observed as a weak band at 1757 cm^{-1} and as a medium band at 1325 cm^{-1} in the IR spectrum. The weakly emerging bands at 3491 cm^{-1} in the IR spectrum were assigned to O-H stretching mode of nitric acid. The O-NO_2 stretch was attributed at 625 and 615 cm^{-1} in the IR and Raman spectra. The band due to NO_2 in-plane bending was observed at 928 cm^{-1} (IR) and 858 cm^{-1} (Raman). The medium intensity peak at 598 cm^{-1} in the IR spectrum was assigned for O-NO_2 bending mode. The vibrational peak at 804 cm^{-1} (IR) and 798 cm^{-1} (Raman) shows the NO_2 out-of-plane bending mode of nitric acid. The O-H torsion vibration produces characteristic band at 461 cm^{-1} in IR spectrum. All the main modes of 4-HPAN crystal were furnished according to the previously reported related literature compounds[11-20].

These vibration assignments demonstrated the existence of N-(4-hydroxyphenyl) acetamide with nitric acid. Further, the spectral investigations strongly suggest that there is no major shift corresponding to the internal modes of N-(4-hydroxyphenyl) acetamide crystal. This study recommends that N-(4-hydroxyphenyl) acetamide does not react with the nitric acid and there is no formation of complex compound.

Tauc plot analysis: Figure 6 and 7 illustrated the UV-Vis-NIR optical absorbance spectrum measured in the wavelength from 200 to 800 nm and the Tauc plot of 4-HPAN crystal, respectively. As can be seen in Fig. 6, the main absorption band of 4-HPAN crystal in ethanol was in the region 200-290 nm with the maximum at around 281, 260, 239 and 213 nm. The lower cut-off wavelength was found at 305 nm and the grown crystal had large transmittance in the entire visible region.

The Tauc plot was drawn between $(\alpha h\nu)^2$ Vs photon energy ($h\nu$). Apply the extrapolation technique, the optical band gap was estimated from Fig. 7. The evaluated optical band gap value of 4-HPAN crystal was 4.2 eV. A described work by Patel *et al.*[21], the optical band gap of 4-HPA was determined as 5eV and this analysis showed that the optical band gap of N-(4-hydroxyphenyl) acetamide (4-HPA) decreased with the addition of nitric acid.

SEM with EDX analysis: The surface morphology of 4-HPAN crystal has been shown with 500x and 2.5kx magnifications in Fig. 8a and b, respectively. The structural morphology consists of the plate-like shape. The EDX analysis was accomplished for the 4-HPAN crystal. The EDX analysis was presented in Fig. 9. The chart showed the characteristic peaks of C, O and N. The results of EDX analysis of the 4-HPAN sample were presented in Table 3 as seen in Fig. 9. These values were compared with previous studies of pure 4-HPA compound[22]. According to this

Table 2: Wavenumber assignments for 4-HPAN crystal in FT-IR and FT-Raman spectra

FT-IR ($\bar{\upsilon}$ cm^{-1})	FT-Raman ($\bar{\upsilon}$ cm^{-1})	Assignment
3491 (s)	-	ν $(O-H)_{acid}$
3325 (m)	-	ν $(O-H)_{phenol}$
3256 (m)	-	ν $(N-H)_{amide}$
-	3065 (w)	ν (C-H)
3030 (w)	-	ν (C-H)
3007 (w)	-	ν (C-H)
2992 (w)	2931 (m)	ν_{as} $(-CH_3)$
2876 (w)	-	ν_s $(-CH_3)$
1757 (w)	-	ν_{as} $(-NO_2)_{acid}$
1665 (s)	1650 (s)	ν $(C=O)_{amide}$
1612 (m)	1613 (s)	ν (C-C)
1564 (s)	1562 (m)	ν (C-C)
1508 (s)	1511 (m)	ν (C-N-C)
1439 (s)	1441 (m)	ν (C=C), $\delta_{as}(CH_3)$, β(O-H)
1369 (m)	1371 (m)	δ_s (CH_3)
1325 (m)	1325 (m)	ν (C-N), $\nu_s(-NO_2)_{acid}$
1256 (m)	1279 (m)	δ $(H-O-N)_{acid}$
1227 (m)	1236 (m)	β (C-H)
1171(w)	1169 (m)	β (C-H), τ $(-CH_3)$
1015 (w)	-	β (C-H)
966 (w)	-	β (C-H), γ(O-H)
928 (sh)	-	β $(-NO_2)_{acid}$
-	858 (m)	β $(-NO_2)_{acid}$
837 (m)	-	Ring breathing mode
804 (m)	798 (m)	γ (C-H), $\gamma(-NO_2)_{acid}$
716 (m)	711 (w)	ω (N-H), γ(C-H)
685 (m)	652 (m)	ω (N-H)
625 (w)	615 (w)	ν $(O-NO_2)_{acid}$
598 (w)	-	δ $(O-NO_2)_{acid}$
515 (m)	514 (w)	Ring deformation
503 (m)	-	Ring deformation
461 (w)	464 (w)	t$(O-H)_{acid}$

s: Strong, m: Medium, w: Weak, sh: Shoulder, ν: Stretching, ν_s: Symmetric stretching, υ_{as}: Anti symmetric stretching, δ: Bending, δ_s: Symmetric bending, δ_{as}: Antisymmetric bending, β: In-plane bending, γ: Out-of-plane bending, t: Twisting, ω: Wagging and τ: Rocking

Table 3: Atomic percentage of elements for 4-HPA and 4-HPAN crystals

4-HPA[22]		4-HPAN	
Element	Atomic (%)	Element	Atomic (%)
C	63.6	C	64.0
O	21.2	O	25.5
N	9.3	N	10.5

Table 4: Effect of the 4-HPAN on the growth inhibition of different microorganisms tested

	Diameter inhibition (in mm) with different concentrations (µg mL^{-1})		
Microorganisms	15	25	75
Escherichia coli	-	-	-
Vibrio	-	10 mm	14 mm
Klebsiella	-	-	18 mm
Bacillus	16 mm	17 mm	19 mm

comparison, the atomic percentage of carbon did not change but the atomic percentage of oxygen and nitrogen was increased due to the addition of nitric acid. This result confirms that nitric acid was entered into the crystal lattice of the 4-HPA compound.

Antimicrobial activity: The antibacterial activity study was performed by agar well diffusion method in Mueller Hinton Agar (MHA) plates with DMSO as a positive control[23]. The bacterial strains selected to perform microbiological tests were: *Escherichia coli*, *Vibrio*, *Klebsiella* and *Bacillus*. The results of the antimicrobial activity have been presented in Table 4 for 15 µL, 25 µL and 75 µL, concentrations. The antimicrobial activity zone of inhibition against different microorganisms tested was shown in Fig. 10. The compound had shown high antibacterial activities with diameter

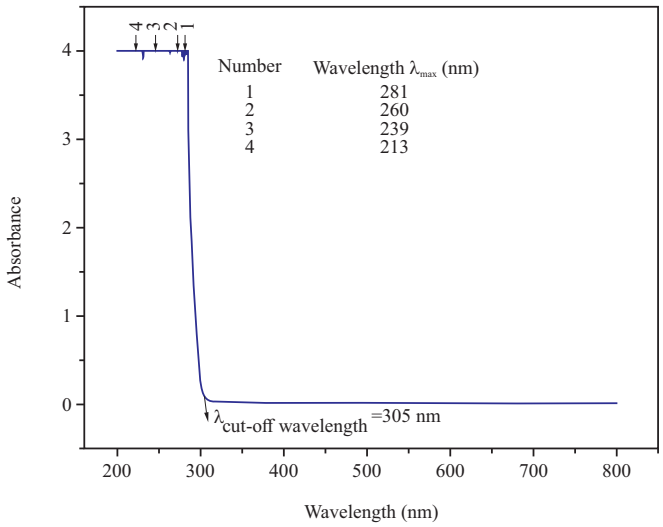

Fig. 6: Absorbance spectrum for 4-HPAN crystal

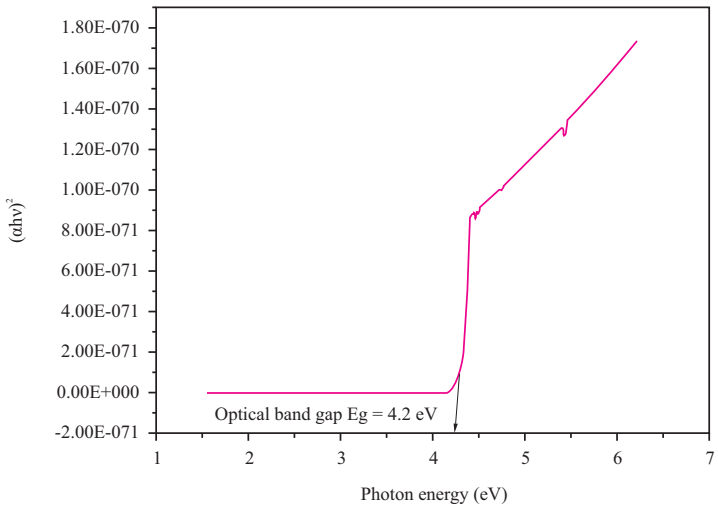

Fig. 7: Tauc plot for 4-HPAN crystal

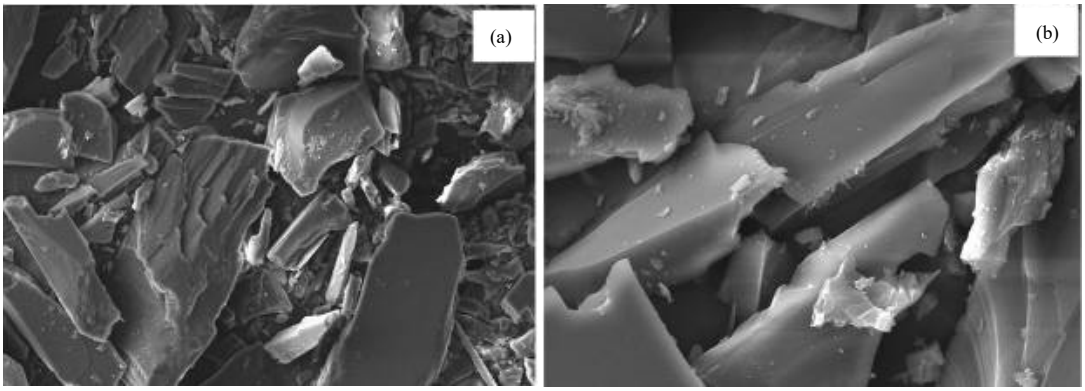

Fig. 8: SEM images of 4-HPAN crystal with (a) 500x and (b) 2.5 kx

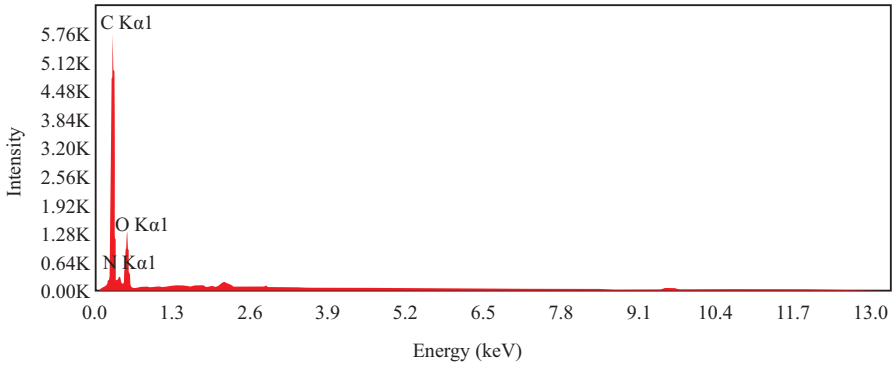

Fig. 9: EDX chart for 4-HPAN crystal

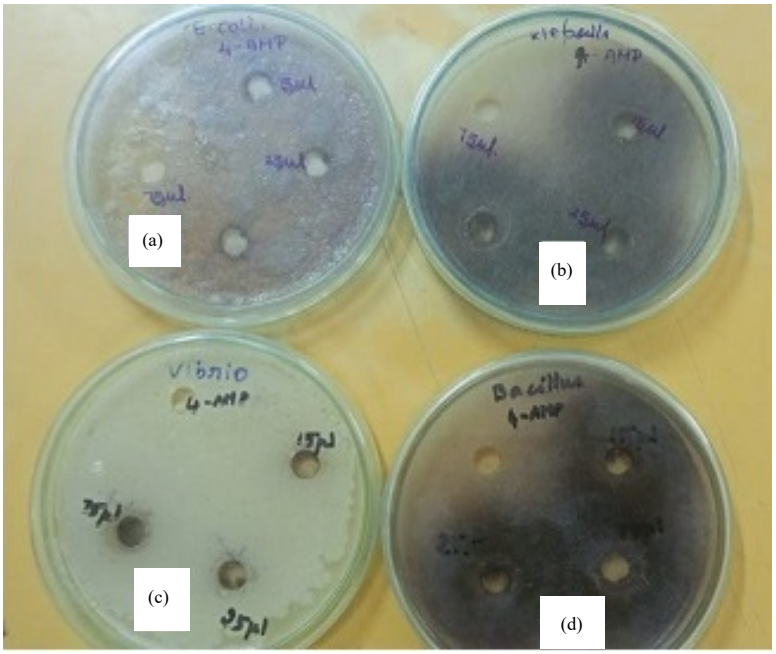

Fig. 10(a-d): Photographic view showing inhibition region of 4-HPAN crystal against, (a) *Escherichia coli* (b) *Vibrio* (c) *Klebsiella* and (d) *Bacillus* microorganisms at 15 µg mL^{-1}, 25 µg mL^{-1} and 75 µg L^{-1} concentrations

inhibition of 18 mm against *Klebsiella* and 19 mm for *Bacillus* at 75 µL, concentration. Against the *Vibrio*, the antimicrobial activity had only shown with diameter inhibition at 25 µL and 75 µL. Moreover, 4-HPAN compound described here has no antimicrobial activity against *Escherichia coli* at all concentrations used.

Effect of nitric acid in the N-(4-hydroxyphenyl) acetamide nitrate crystal did not change the crystallite size and there is no shift in vibrational frequency of major modes. But it slightly shifted the optical band gap and morphology. The antibacterial activity enhanced with the addition of nitric acid against certain bacterial strains.

CONCLUSION

The 4-HPAN crystal was grown by the slow evaporation method at room temperature successfully. The molecular structure was optimized with steric energy -24.6768 kcal moL^{-1} by Chem3D professional software. The powder XRD study confirmed that a certain amount of nitric acid was doped into the 4-HPAN crystals without changing their particle size. The spectral investigations by FT-IR and FT-Raman spectroscopy strongly suggested that the N-(4-hydroxyphenyl) acetamide with nitric acid was present in the 4-HPAN crystal. The maximum absorption peaks and the lower

cut-off wavelength were identified from the UV-Vis-NIR spectrum. The optical band gap was determined as 4.2 eV and this study revealed that the addition of nitric acid decreased the band gap of 4-HPA crystal (5 eV). The morphology with the elemental analysis confirmed that the composition of carbon elements was not changed other than oxygen and nitrogen compounds when added a certain amount of HNO_3. Moreover, the antimicrobial activity study presented in this paper has revealed that *Klebsiella* and *Bacillus* had more sensitive than *E. coli* to 4-HPAN solutions compared to the control at high concentrations.

SIGNIFICANCE STATEMENT

This study realizes the synthesis of a new drug-acid hybrid that can play a widespread role in medicinal chemistry. This study will help the researcher discover a new pharmaceutical important drug compound. The use of more than one drug is taken together or within a short period, either intentionally or unintentionally to improve the physical performance of the human body.

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