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Synthesis, structural and characterization of biologically essential drug materials

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ABSTRACT

Single crystals of L – Phenylalanine mixed N-(4-hydroxyphenyl) acetamide were grown from ethanolic solution at room temperature by slow evaporation method. X-ray diffraction analysis reveals that the grown crystals belong to monoclinic system. The presence of functional groups in the grown crystal was identified using FTIR spectroscopy. Optical absorption investigation indicates very low absorption in the entire visible region when compared to other regions under study. The thermal analysis by TG-DTA shows good thermal stability of the grown crystal.

Keywords: Characterization, growth from Solutions, biological substances, organic compounds.

INTRODUCTION

Paracetamol (N-(4-hydroxyphenyl) acetamide) is an analgesic and antipyretic drug that is used worldwide in the manufacture of many millions of tablets and other dosage forms every year.

Three polymorphs of Paracetamol is used worldwide in the manufacture of many millions of tablets and other dosage forms every year. These three polymorphs were reported for paracetamol [1–3] but only two of them are stable enough for experimental structural investigations [4,5]. The polymorph I monoclinic) is the thermodynamically stable modification at room temperature [6]. It can be grown as single crystal from solution in using various solvents [7]. Several organic single crystals having diverse applications were grown and studied extensively [8 – 12]. Owing to the medicinal properties of hydroxyphenyl amino derivatives, the crystal growth of organic material L – Phenylalanine mixed N-(4-hydroxyphenyl) acetamide has been carried out by using slow evaporation technique. The grown crystals were subjected to various characterizations studies in order to understand their physical and chemical properties. The obtained results were discussed in detail.

MATERIALS AND METHODS

L – Phenylalanine was purchased from Merck India ltd, Mumbai and Paracetamol was obtained from Madras pharmaceuticals, Chennai. All other reagents used were purchased from Merck company.

Material Synthesis

A saturated solution consisting of N-(4-hydroxyphenyl) acetamide ($C_8H_9NO_2$) and L - Phenylalanine ($C_9H_{11}NO_2$) was prepared in the stoichiometric ratio of 1:2 using ethanol as a solvent and the resultant solution was stirred slowly for about three hours with mild heating (~35°C) so as to dissolve the undissolved particles. Then the solution was filtered carefully, transferred to a glass beaker (250ml) and kept undisturbed in a dust free environment to promote the growth of single crystals of the compound. Slow evaporation of the solvent facilitated with fine pin-holes at the cover of the beaker has resulted needle like crystals of size 13 × 1 × 0.8 mm^3 (Figure 1) after five days.

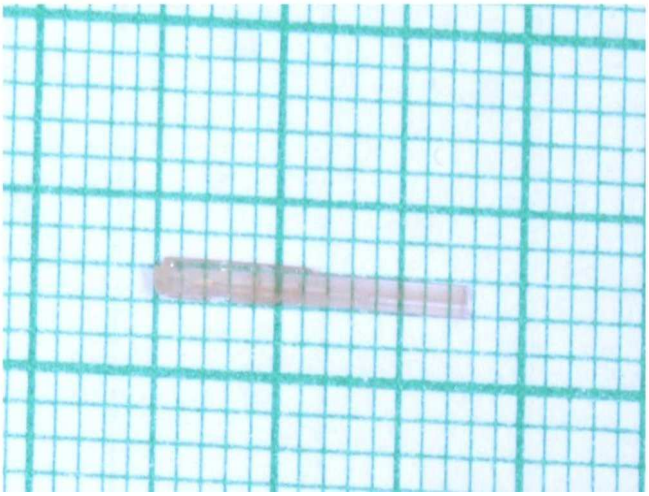

Fig.1 Photograph of as grown crystal

The grown crystal was observed to be thermally stable, non-hygroscopic and not decomposed when exposed to air at ambient temperature.

RESULTS AND DISCUSSION

Crystal structure analysis

Single crystal X – ray diffraction analysis for the grown crystal has been carried out to identify the crystal structure and to get the lattice parameters using Bruker-kappa APEX2 diffractometer with MoKα (λ = 0.71073 Å) radiation. The crystal structure of the title compound was solved by direct method using the program SIR – 92 (WINGX) [11] Cell refinement was done using the programs APEX2 (Version 122) and SAINT-Plus (Version 6.0) [17]. The structure is refined by full matrix least-squares technique using SHELXL-97 (WINGX) computer program [18]. The water hydrogen molecules are refined with isotropic thermal parameters. Twenty five reflections ($9^o < \theta < 14^o$) collected by search routine on different zones of the crystal using graphite monochoromated MoKα radiation (λ = 0.71703 Å) are used for the measurement of lattice parameters. Single crystal X-ray data reveals that the grown crystal crystallizes into monoclinic system with space group $P2_1 / C$. The ORTEP diagram of the molecule with atom numbering scheme is shown in Fig 2. The structure is an infinite stacked system running along the b-axis direction as shown in Fig. 3.

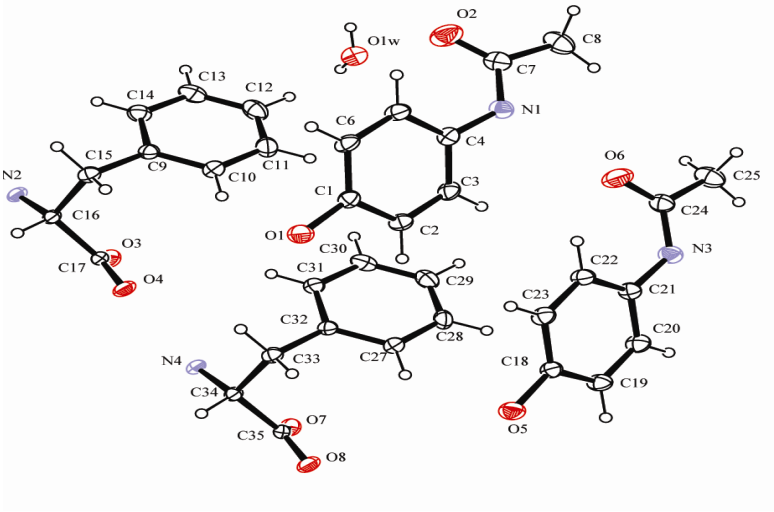

Fig. 2 The ORTEP diagram of the grown crystal

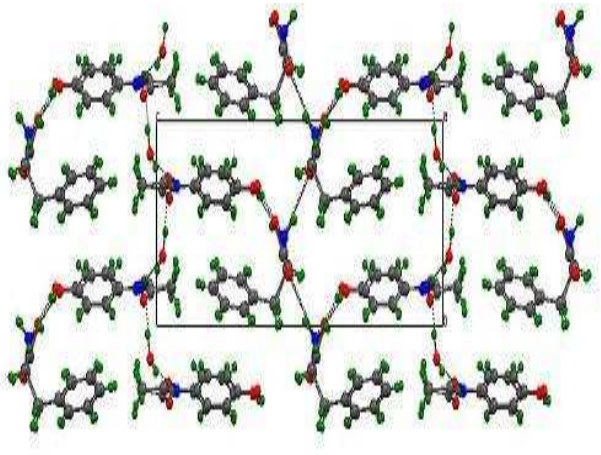

Fig. 3 Packing of the molecule for the grown crystal

Table 1: XRD Data Table

S.NO		Obtained Data
1.	Empirical Formula	$C_8H_9O_2$
2.	Formula weight	151.17
3.	Wavelength	0.7106 A°³
4.	Crystal system, space group	Monoclinic, $P2_1/c$
5.	Unit cell dimensions: a, b, c, α, β, γ	11.66,7.18,20.14,90.00°,100.9
6.	Volume	1656 A°³
7.	Atomic Number	4
8.	Density calculated	1.332 g/ m³
9.	Crystal size	13× 1 × 0.8 mm³
10.	Reflections collected/ unique	28111/8094
11.	Absorption correction	12802/1/185
12.	Final R indices [I42s(I)]	R1 =0.1516 for 7527
13.	R indices	R1 =0.2070 for all 12802
14.	Largest diff. peak and hole and σ	4.149, - 0.546, 0.177

The symmetric unit of the crystal shows one water molecules, one Paracetamol molecule, and two phenylalanine molecules. The data collection and refinement parameters are presented in Table 1. From the crystallographic data, the cell parameters for the grown crystals was found to be a = 11.66 Å, b = 7.18 Å, c = 20.14 Å, V = 1656 Å^3 and β = 100.94°, space group is $P_{21/C}$ and it belongs to monoclinic structure.

Also this crystal belongs to monoclinic form is the thermodynamically stable polymorph at room temperature and hence is the commercially used form of Paracetamol.

UV – Vis Spectral Studies

The UV – Vis Spectrum was recorded using Varian Cary 5E UV – Vis Spectrometer in the range between 200-400 nm and the resultant absorption spectrum is shown in fig.4.

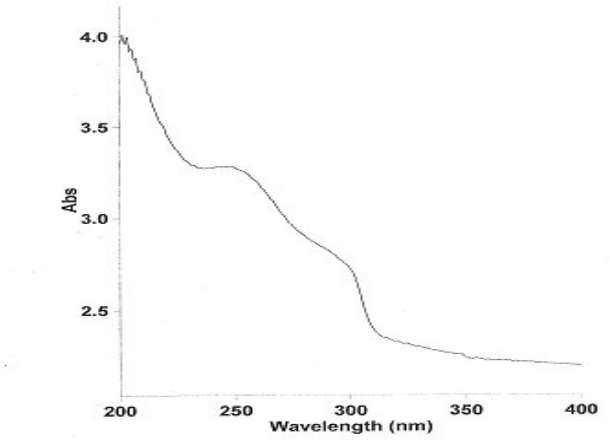

Fig. 4 Optical absorption spectrum of grown crystal

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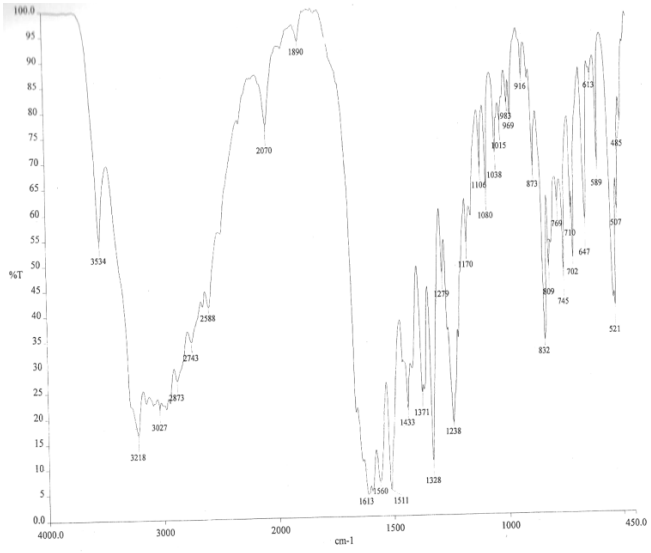

Fig. 5 FTIR spectrum of the grown crystal

Since the grown crystal possesses delocalized electron cloud for the charge transfer, the absorbance is

less between 320 – 400 nm. The UV region cut off wavelength is 230 nm, which enables it to be a good candidate for electro-optic and opto electronic applications.

FTIR analysis

The FTIR analysis of the grown crystals were carried out between 400 to 4000 cm^{-1} using IFS BRUKKER 66v spectrometer and the resultant spectrum is shown in fig.5

The bands at 1080 cm^{-1} and 702 cm^{-1} established the presence of benzene ring. The band at 3027 cm^{-1} corresponds to C - H stretching. The bands at 1613 cm^{-1} and 1433 cm^{-1} illustrates the presence of C = O anti symmetric and symmetric stretching respectively. A sharp peak at 1478 cm^{-1} is due to NH asymmetric stretching and the strong band at 2873 cm^{-1} shows the presence of CH_2 asymmetric stretching. The band around 1960 cm^{-1} suggested the presence of C = C stretching. The peaks at 1170 cm^{-1}, and 1080 cm^{-1} indicates the presence of C - C stretching. The band at 1040 cm^{-1} established the presence of C - N stretching. The bands at 873 cm^{-1} and 647 cm^{-1} established the presence of substituted ring 1, 4 distributions. The bands at 873 cm^{-1} and 745 cm^{-1} confirms the presence of NH_3 rocking and CH_2 rocking vibrations respectively. Paracetamol shows absorption bands for hydroxyl group around 3160 cm^{-1}, unsaturation (1613 cm^{-1}) and aromatic rings (1560, 1511 and 832 cm^{-1}). A sharp peak at 1238 cm^{-1} corresponds to C – O stretching while 1371, 1328 and 521 cm^{-1} attributed to CH_3 rocking, C – N and C = O stretching respectively. All these vibrational assignments confirmthe presenceof Paracetamol and L – Phenylalanine in the crystal lattice.

Thermal Studies

The thermogravimetric analysis of the title crystal was carried out for the sample weight of 16.930 mg between room temperatures and 800ºC is shown in fig.6.

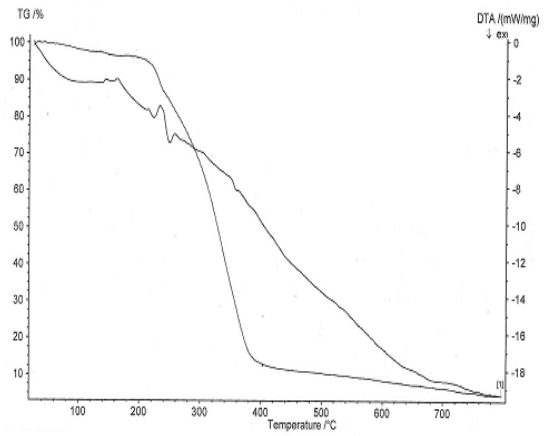

Fig.6 TG / DTA spectrum of the grown crystal

TGA shows that the sample is stable up to 144˚C after that it starts to decompose gaseous molecules like CO_2 and NH gradually by the loss of mass in the temperature range 230 –400˚C.The decomposition illustrates almost 100% of weight lost at 800˚C. DTA suggest that

weight loss occurs mainly in 6 steps. The first minor and major weight loss occurs at 144.1˚C and 162.9˚C which may be attributed to the loss of absorbed water and due to the melting point of the crystal. The second

minor and major weight loss occurs with 10˚C difference of 222.5˚C and 232.4˚C. The last two peaks were absorbed at 249.3˚C and 361.9˚C showing that after this point it is started to decompose. The DTA thermo gram also reveals that the sharp exothermic peak coinciding with that of TG, thereby confirming the thermal stability of the crystal. From, the thermal studies, the crystal can retain its texture upto 144˚C.

DSC studies

The grown crystals were subjected to DSC measurements using NETZSCH DSC 204. Samples of about 13.720 mg were employed and the heating and cooling rates were set at 10 K/min. The measurements were carried out under an atmosphere of dry N_2 gas with a flow rate of about 40 ml/min.

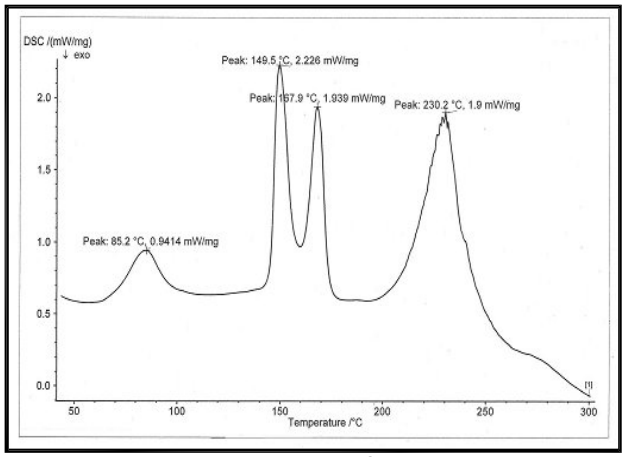

Fig. 7 DSC spectrum of the title crystal

The fig. 7 shows the DSC studies of the compound, which reveals a medium endothermic peak at 85.2˚C is assigned to the release of moisture from its surface. The next strong endothermic peak is at 149.5˚C is due to oxidation of molecules. The measurement made now may be more accurate due to usage of highly sensitive instrument which we used in our present investigations. Moreover, the DTA curve shown in Fig.8 confirms our result to be more correct.

CONCLUSION

Optically good quality single crystals of L – Phenylalanine mixed N-(4- hydroxyphenyl) acetamide were grown from alcoholic solution at room temperature by slow evaporation method. The structure of grown crystals was solved by using single crystal X – ray diffraction analysis. The presence of functional groups was confirmed quantitatively using FTIR analysis. Optical absorption studies reveal very low absorption and UV cut off is found to be at 230 nm. The crystal is thermally stable upto 144º C and was confirmed by DSC studies.

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