BIOLOGICALLY ESSENTIAL DRUG MATERIAL CRYSTALLIZATION AND CHARACTERIZATION

Bhavani K[1], Sankaranarayanan K[2] and Jerome Das S[3]

[1]Department of Physics, SRM University, Chennai, India.

[2]Department of Physics, Alagappa University, Karaikudi, India.

[3]Department of Physics, Loyola College, Chennai, India.

Corresponding Author: Bhavani.K, SRM University, Chennai. Mail:bhavani.k2006@yahoo.co.in

ABSTRACT:

An essential drug material of Paracetamol was crystallized in orthophosphoric acid using water as a solvent. Good quality of transparent crystals was crystallized within three weeks by slow evaporation method. The as grown drug crystals was characterized by Single X – Ray diffraction, FTIR, UV studies to know its cell parameters, functional groups present and the transparency. The dielectric and thermal analysis was also carried out to the grown bio material crystal.

Keywords: Paracetamol, orthophosphoric acid, crystals, characterize.

INTRODUCTION:

Crystallization is an indispensible process in pharmaceutical industry. More than 90% of drugs are delivered to the patients in crystalline form [1] due to its chemical stability, storage and easy handling [2]. Active Pharmaceutical Ingredient (API) of Paracetamol was crystallized, since it is official in Indian Pharmacopoeia (IP), United States Pharmacopoeia and British Pharmacopoeia (BP) [3]. Paracetamol also called Acetaminophen is a non opiate non – salicylate analgesic, antipyretic drug [4, 5] and reduces nephrotoxicity [6]. It is also an intermediate in the manufacturing process of azo – dyes and photographic chemicals [7].

MATERIALS AND METHODS:

Pharamceutical grade of Paracetamol was purchased from Sri Krishna laboratory, Hyderabad and orthophosphoric acid was purchased from Merck India Ltd, Mumbai. The final product crystal of our research work was harvested by slow solution evaporation method.

EXPERIMETNAL SECTION:

CRYTSAL GROWTH:

Paracetamol powder in one molar ratio was dissolved with double distilled water as a solvent. The solution was stirred well and heated at 45ºC for one hour. Now the desired amount of orthophasphoric acid was added to this solution and then the mixture was stirred another two hours. The solution was the filtered by using Whatman

grade I filter paper to the growth beaker. The growth vessel was covered with a perforated polythene cover kept in dust free atmosphere. By making pinholes on the cover, the solvent was allowed to evaporate. Nucleations were observed in the solution within next five days from the date of preparation. Without altering any experimental parameters, the nucleations were then allowed to grow another few days, in order to the desired size of the crystal. Finally the grown crystals were harvested from the glass vial before the solution gets dried. The obtained morphology of the grown crystals was shown in fig. (1). The final product drug crystal have the dimensions of $6\times5\times3mm^3$ and it was characterized by different analytical techniques to understand various physicochemical properties such as crystallinity, polymorphism, crystal habit, transparency and concentration, physical stability, dielectric property, decomposition and melting point since these are essential parameters for the drug design and formulation of the oral dosage [8].

RESULTS AND DISCUSSION:

CHARACETRIZATION OF DRUG CRYSTAL:

a. SINGLE X-RAY STUDIES:

Single crystal X-Ray diffraction analysis of 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 calculated cell parameters are a = 7.08Å, b = 9.38Å, c = 11.69 Å, β = 97.42°, V= $780Å^3$ and space group $P_{21/c}$. It was observed from the single XRD measurement that our product crystals belong to monoclinic system. In the pharmaceutical industry monoclinic system is thermodynamically stable at room temperature in all atmospheres and is one of the essential required physicochemical properties in this field [9].

b. FTIR SPECTRAL ANALYSIS:

Fourier Transform Infrared Spectroscopy accurately detects crystallinity ranging from 1 - 99% in pure material [10]. The recorded FTIR spectrum of Paracetamol is shown in fig.2. The table 1 gives the observed vibration wave number and their tentative assignments of Paracetamol crystal.

S.NO	PARACETAMOL	
	OBSERVED WAVE NUMBER cm^{-1}	**ASSIGNMENTS**
1.	3325	N-H hydroxyl
2.	3162	O-H hydroxyl
3.	2880	C-H hydroxyl
4.	2793	C=O & O – H carboxylic acid
5.	2714	C=O & O – H stretching

6.	1649	C=O amide
7.	1610	C-C aromatic function
8.	1563	C-N amide
9.	1505	C-C aromatic function
10.	1439	C-C aromatic function
11.	1371	CH3 rocking
12.	1327	O-H stretching
13.	1226	C-N amide
14.	1015	C-C-C aromatic function

Table 1. FTIR spectrum values assignments.

From the FTIR analysis it shows active ingredients and phosphoric acid were presented in the grown crystal [11].

c. UV – VIS SPECTRAL ANALYSIS:

The UV – Vis Spectrum was recorded using Varian Cary 5E UV – Vis Spectrometer in the range between 500 - 2500nm. The fig. 3 shows the UV- Vis absorption spectrum of the grown biomedicine crystal. From the obtained UV results illustrates clearly that the grown crystal was highly transparent between 800- 1500nm ranges. The maximum absorbance of Paracetamol was found to be 250 and 300nm, it shows low concentration of additives are presented in the crystals which can provide a means of controlling of water contents, crystal energy and order, dissolution rate and bioavailability. Such parameters are very useful in quality control testing of drugs and their products [12].

d. THERMAL ANALYSIS:

Thermo gravimetric and differential thermal (TG/DTA) analyses were carried out simultaneously for the grown drug crystals. A powder sample of API crystal 9.87 mg was used for the analysis in the nitrogen atmosphere at the heating rate of 20K/mint. The fig 4 shows the TG/DTA curves of the Paracetamol crystals. From the thermal analysis results reveals that no loss of weight observed around 100°C showing the absence of any absorbed water molecules in the sample but the crystals were starts to lose weight at 250°C and the weight loss ends at 350°C, due to the decomposition of the compound. In the DTA curve of Paracetamol crystal shows two significant exothermic peaks at 169.6°C and 335.4°C. The first peak was the melting point of Paracetamol and the second one may assign to solvent molecules evaporation. The preferred solid form of the compounds supports the previous literatures [13, 14].

e. DIELECTRIC STUDIES:

Good quality of Paracetamol crystals was selected for dielectric measurements using HIOKI 3532-50 LCR HITESTER. The selected sample was cut by a diamond saw and polished using paraffin oil. Fig 5 shows the variation of dielectric constant with frequency. The dielectric constant has high values in the lower frequency region and then it decreases with the applied frequency. The high value of dielectric constant at low frequencies may be due to the presence of all the four polarizations namely space charge, orientation, electronic and ionic polarization and its low value at higher frequencies may be due to the loss of significance of these polarizations gradually [15]. The dielectric loss of Paracetamol crystals was also studied as a function of frequency as shown in the fig. 6. These curves suggests that dielectric loss was strongly depends on the frequency of the applied field similar to that of dielectric constant.

CONCLUSIONS:

Medicinal cum biological importance of drug material crystals was successfully grown from aqueous solution at room temperature. Single X- Ray Diffraction results reveal that the grown drug crystal belongs to monoclinic system. The FTIR Spectrum confirms Paracetamol and other chemical compounds were present in the sample. From the UV Spectrum results that low concentration of additives were present in the crystal. The thermal analysis reveals that the biological crystal have the maximum chemical stability at 250°C was a very important factor for drug dosage, manufacturing and packaging. Dielectric studies indicate that the dielectric constant and loss depends the frequency of the applied field. This research attempt could be useful for drug discovery, delivery, development and synthesis process.

REFERENCES:

[1]. Michael F. Doherty, (2008), "From form to function: Crystallization of active pharmaceutical ingredients", AIchE. J, 5 (7), 1682-1688.

[2]. O.A. Lmarsson, M.J. Zaworotko, (2004), Chem. Commn., 17, 1889-1896.

[3]. British National Formulary (BNF 41), (2001), British medical association: London, 464.

[4]. Sweetman SCM, "The complete drug reference", 33rd edn., (2011), London pharmaceutical process, 417-421.

[5]. J.G. Hardman, L.E. Limbird, Goodman & Gilman's, (1987), "The pharmaceutical basis of therapeutics, 9th edn, McGraw – Hill companies.

[6]. M. Cazin, Y.C. Cazin, M. Lhermitte, D. Paluszerak, and A. Binochi, Acta Ther. 13, 224.

[7]. R.A. Granberg and A.C. Rasmuson, (1999) "Solubility of Paracetamol in pure solvents", J. Chem. Engg. Data, 44 (6), 1391 – 1395.

[8]. Chaturvedi A.K., Amita verma, (2012), "Solubility enhancement of poorly water soluble drugs by Solid dispersion", International Journal of Pharmaceutical Sciences and Research 3, (1); 26- 34.

[9]. E. Marti, E. Kaiserberger, G.Kaiser (Eds.), (2000), Thermoanlytical Crystallization of Pharmaceuticals, Netzsch Annual , 12, 29.

[10]. Broman E, Khoo C, Taylor L.S, (2001) " A comparison of alternations Ploymer excipient and processing methods for moving solid dispersion of poorly water soluble drug", International Journal of Pharmacy ,1, 139- 151.

[11]. Ciurczak, E.W. and Drennen, J.K. III, (2001), Pharmaceutical and Medical applications of Near – In – frared Spectroscopy, Marcell Dekker, Inc., NewYork, 73 – 105.

[12]. Ghulam Murtaza et al., (2011) "Development of a UV – spectrophotometric method for the simultaneous determination of aspirin and Paracetamol in tablets". Scientific research and Essays, 6 (2) 417-421.

[13]. S.R.Byrn, R.R.Pfeiffer, J.G.Stowell, 1999, Solid State Chemistry of Drugs, SSCI, West Lafayette, Indiyana.

[14]. H. Brittain (Ed.), Polymorphism in Pharmaceutical solids, (1999), 95, Marcel Dekker, New York, 1999.

[15]. C.P.Smyth, (1956), Dielectric Behavior and structure; McGraw – Hill, New York, *Acta Cryst.* ,9, 838-839 .

Diagrams:

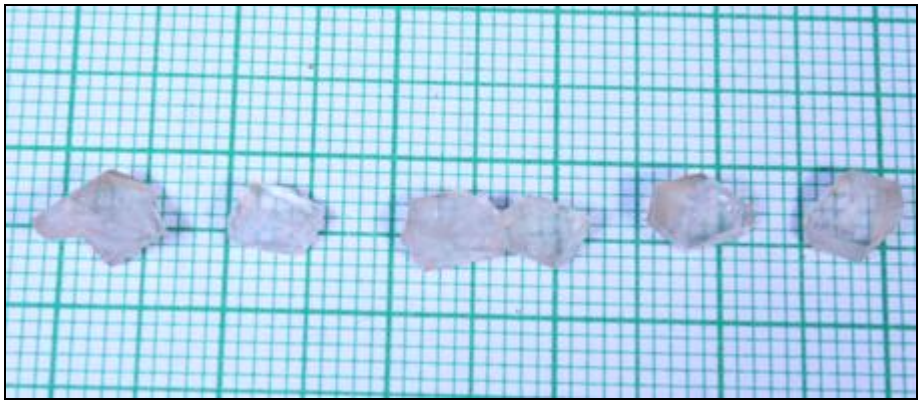

Fig. 1. Paracetamol crystals from orthophosphoric acid

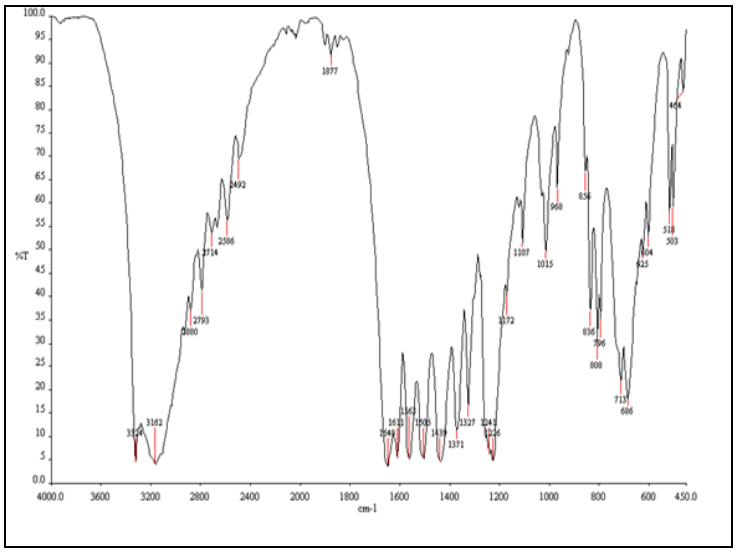

Fig. 2. FTIR spectrum of Paracetamol crystal

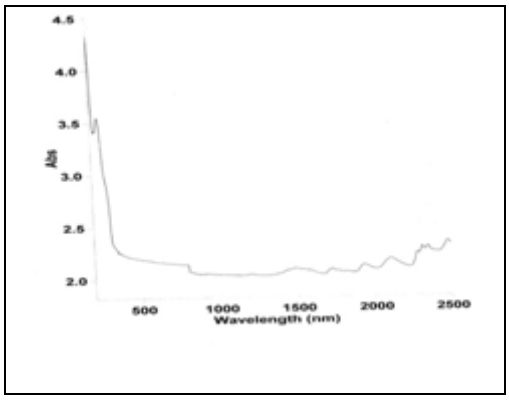

Fig. 3. UV – Vis spectrum of Paracetamol crystal

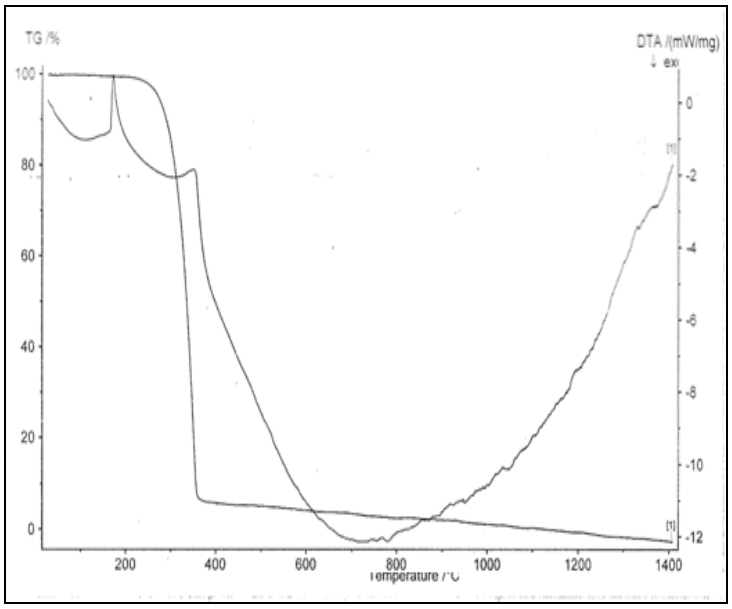

Fig. 4. TG/DTA analysis of Paracetamol crystal

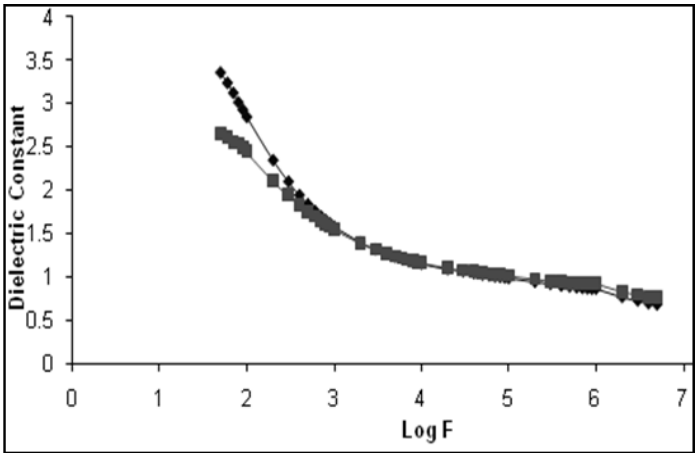

Fig.5. Dielectric constant of Paracetamol crystal

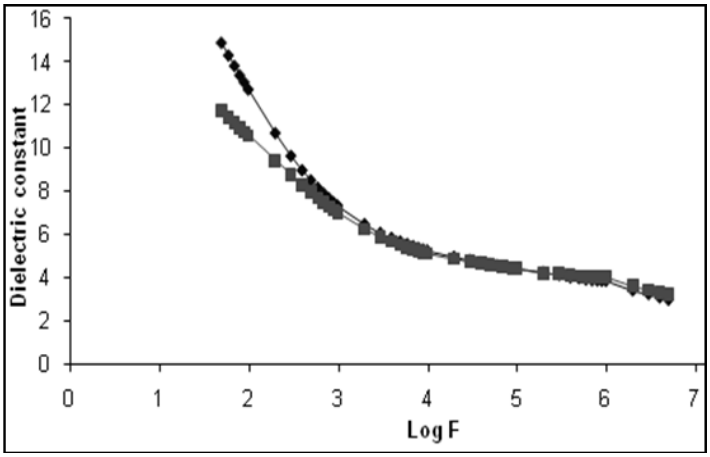

Fig.6. Dielectric loss of Paracetamol crystal