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Monotropically More Stable Fenoprofen Calcium Dihydrate

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ABSTRACT

Fenoprofen calcium (FC) dihydrate is a non-steroidal anti-inflammatory drug. FC dihydrate is marketed with the name Nalfon. FC dihydrate is presently available only in tablet form with high oral dosages of 200 mg, 300 mg, 400 mg and 600 mg. A monotropically more stable, novel crystal form (Form II) of FC dihydrate with no change in aqueous solubility has been identified and fully characterized by a variety of analytical techniques such as Polarized Microscopy (PM), Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimeter (DSC), Thermo Gravimetric Analysis (TGA), Karl Fischer Titration (KFT) and Infrared Spectroscopy (FT-IR) techniques. Aqueous solubility is measured by using High Performance Liquid Chromatography (HPLC). Form II is obtained from less toxic and environment friendly class III organic solvent ethylacetate.

Keywords: Fenoprofen calcium dihydrate, Anti-inflammatory, XPRD, Aqueous solubility.

INTRODUCTION

Fenoprofen calcium (FC) dehydrate is chemically (RS)-2-(3-phenoxyphenyl) propionate dehydrate calcium salt is a non-steroidal anti-inflammatory drug used for symptomatic relief of rheumatoid arthritis, osteoarthritis and mild to moderate pain [1]. The molecular formula is $C_{30}H_{26}CaO_6.2H_2O$ (Figure 1).

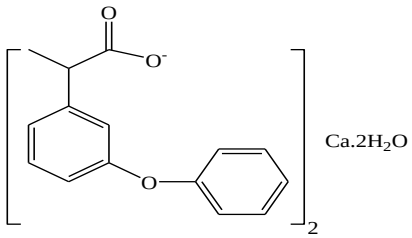

Figure 1: Structure of Fenoprofen Calcium

FC dihydrate is marketed with the name Nalfon. FC dihydrate is presently available only in tablet form with high oral dosages of 200 mg, 300 mg, 400 mg and 600 mg [2]. But limited research results are

reported in the literature on this drug. Therefore, there is a need to carry out further extensive research on this drug. The Georgetown study examined and recommended doses of 354 prescription drugs released from 1980 to 1999 [3-6]. Of those drugs, the instructions on label were corrected for 73 or 21 percent, after the drug came to the market. Recently in the field of pharmaceutical technology, great efforts are being directed towards the prefabrication of existing drug molecules in the way of solving problems related to poor water solubility, dissolution, bioavailability, dosing problems, stability and toxicity. Extensive literature survey revealed that no literature precedence is available pertaining to different crystal forms of FC dehydrate until now. Different crystal forms exhibit differences in shelf life, stability and melting point. By increasing melting point of the crystal structure (of drug substance), shelf life and stability of the drug substance can be increased. At present, pediatric formulations are not available in the market for FC dihydrate. Liquid formulations (solutions, suspension, syrups, etc) have been popular for pediatric, because of the ease of administering them to children of different ages and the ease of dosing more precisely according to body weight or body surface area. Unfortunately, liquid formulations tend to be less stable over time than solid ones. Therefore, more stable crystal form of FC dihydrate is preferable in research of pediatric formulations. As part of our ongoing research program, the present paper reports monotropically more stable novel crystal form (Form II) of FC dihydrate with no change in aqueous solubility. This novel crystal form (Form II) is suitable for carrying out further investigation. Crystal modifications of FC dihydrate was characterized by means of typical structure sensitive analytical techniques such as PM, PXRD, DSC, TGA, KFT and FT-IR.

MATERIALS AND METHODS

Materials: FC dihydrate (Designated by us as Form A) is obtained from SUVEN Life Sciences Limited, Hyderabad, India and the purity of this drug is > 99.4 %. The solvents used in the study are analytical grade. All the solvents used were purchased from Sigma-Aldrich.

Preparation of Form II of FC dihydrate: FC dihydrate (Form I), 2.0 g, was taken in a round bottom flask containing 5 mL of ethyl acetate. The mixture was slowly heated under constant stirring (400 rpm). The solids dissolved and a clear solution formed at reflux temperature. The mass was cooled to 0 - 5 ^{o}C and maintained for 1 hour under constant stirring (400 rpm) and kept in room temperature for another one hour under constant stirring (400 rpm). The crystalline solids obtained were then filtered and the mass was dried under reduced pressure to obtain crystalline product. Yield: 1.65 g.

Investigation methods

Polarized Microscopy (PM): Microphotographs were obtained by using Polarized Microscopy (Nikon LV100). Images were generated under transmitted light with partially crossed polarizers.

Particle Size Determination (PSD): Particle size determination was carried out using optical microscopy with a calibrated eye piece micrometer and stage micrometer by taking a small quantity of formulation on slide. About 100 microcrystals size was measured individually and average was taken.

Powder X-ray diffractometry (PXRD): The powder X-ray diffraction pattern was measured with an X-ray diffractometer (Model RINT Ultima, Rigaku Denki). The conditions of measurement were as follows: target Cu, monochrometer graphite, voltage 45 kV and current 40 mA, with a scanning speed of 1 °C/minute. Approximately 200 mg of sample were loaded into the sample holder.

Differential Scanning Calorimeter (DSC): DSC thermograms were obtained by a differential scanning calorimeter (Model Q100, TA instruments). The measurements were made using aluminum sample pan, using ~ 2-10 mg samples under nitrogen atmosphere, at a scanning speed of 2 °C min^{-1}.

Thermo Gravimetric Analysis (TGA): Thermogravimetry (TG) curves were obtained with a thermo gravimeter (Model Q500, TA instruments). The measurements were made using a 50 mg platinum pan

(sample weight about 10 mg) under nitrogen atmosphere at a scanning speed of 2 °C min^{-1}. Mass loss (%) was calculated based on the mass of the original sample.

Karl Fischer Titration (KFT): Water content (% *w*/*w*) of the samples (200 mg) was determined by Karl Fischer titrimetry (716 DMS Titrino, Metrohm Limited, Switzerland). The instrument was calibrated by using deionized water, before sample analysis.

Fourier transform Infrared Spectroscopy (FT-IR): FT-IR spectra were recorded on a Bomem MB-120 Infrared spectrometer. Spectra over a range of 500 to 5000 cm^{-1} with a resolution of 1 cm^{-1} (32 scans) were recorded using KBr pellets. For diffuse reflection analysis, samples weighing approximately 2 mg were mixed with 200 mg KBr by meas of an agate motor and pestle, and placed in sample cups for fast sampling.

Aqueous solubility measurement by High Performance Liquid Chromatography: Aqueous solubility is measured by Agilent HPLC system (1100 series) with YMC ODS-AM, 250 X 4.6 mm, 5 µm column having a UV visible detector. The mobile Phase was a mixture of Buffer (5mM Ammonium acetate in HPLC grade water, adjust the pH to 3.0 with formic acid) and acetonitrile (Gradient), and the flow rate was 1.0 mL min^{-1}. The detection wavelength is set at 232 nm. Sample volume of 10 µL was injected with an automatic injector.

Procedure: The aliquot was prepared by weighing accurately about 2 mg of sample and transferring it into a 2 mL eppendorf tube, 1 mL of HPLC grade water was added and vortexed for 2-5 min. The eppendorf tube was placed on a rugged rotator and kept under rotation at 30% speed by adjusting the knob. It was rotated for 48 hours and then removed from the rotator and centrifuged for 2 min at 3000 rpm and transferred the supernatant solution into a sample vial. The standard was prepared by weighing accurately about 2 mg of the sample. It was transferred to 10 mL volumetric flask, added 1 mL methanol and vortexed for dissolution. Finally it was made up to the mark with water (in parallel water was injected as a blank). Sample and standard were injected three times and recorded the areas of standard and sample.
Aqueous solubility calculation:

$$\text{Sample Concentration } (\mu g\ mL^{-1}) = \frac{\text{Area of sample}}{\text{Area of standard}} \times \text{Standard concentration } (\mu g\ mL^{-1})$$

Accelerated stability study: Form I and Form II was packed in polyethylene laminated aluminum foils of thickness 0.04 mm and stored for stability under ICH specified accelerated stability conditions of storage for zones III and IV at 40 °C / 75 % RH. The samples were characterized after 90 days by using PM, PXRD, DSC, TGA, KFT, FT-IR and HPLC.

RESULTS AND DISCUSSION

Crystallization of FC dihydrate (Form I) from ethyl acetate (class III solvent) at reflux (until clear solution) followed by cooling to 0-5 ^{o}C for 1 h resulted in the formation of Form II crystals. In principle, the first and foremost technique that is adopted after the preparation of the new form of crystal (Form II) is to analyze the morphology of Form II. Images of crystals representing, the morphologies of Form I and Form II are presented in figure 2 (scale of 100 milli microns) and figure 3 (scale of 50 milli microns). These figures indicate crystalline nature of both Form I and Form II. Crystals of Form I and II are in rod shape and the average size of particles of Form I is 8.08 milli microns and the average size of particles of Form II is 14.28 milli microns.

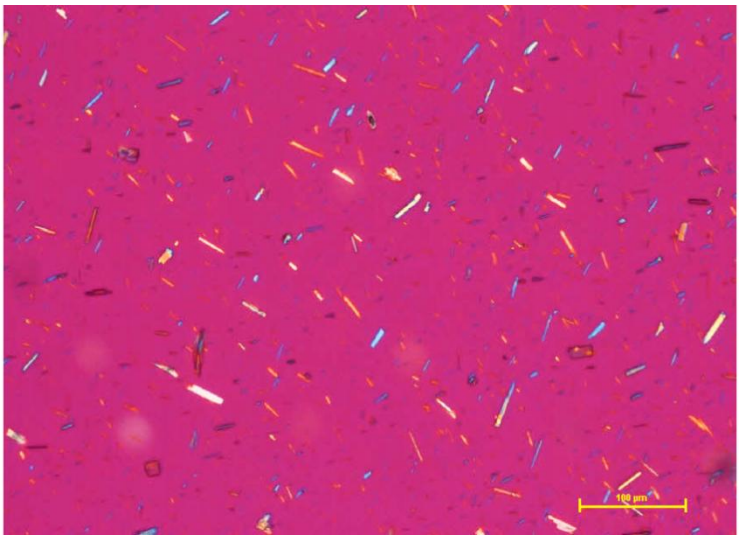

Figure 2: Microphotograph of Form I

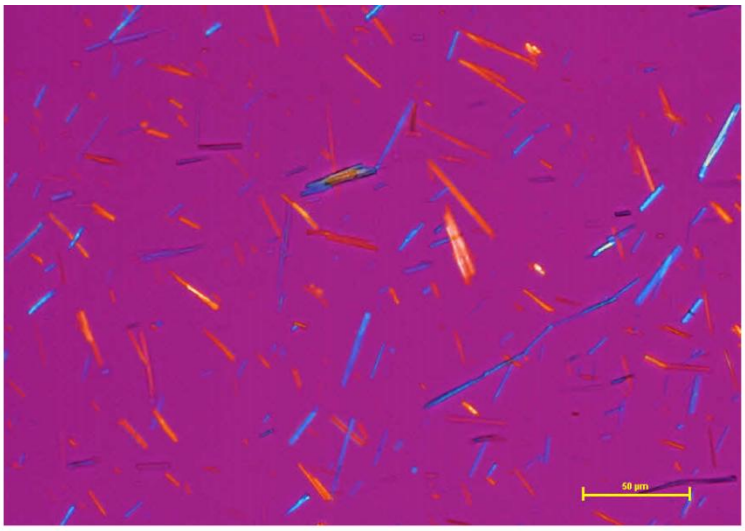

Figure 3: Microphotograph of Form II

The crystalline nature of Form II was further supported by the powder X-ray diffraction pattern (Figure 4 and Figure 5). The sharp diffraction peaks of Form I and Form II indicates both forms are in crystalline nature. Form I shows characteristic peaks at 5.84, 6.40, 6.59, 9.12, 12.29, 12.80, 13.15, 14.26, 14.58, 14.78, 15.25, 17.79, 18.08, 18.50, 19.25, 19.87, 20.27, 20.53, 20.75, 20.98, 21.89, 23.74, 23.87, 25.68, 26.47, 27.43, 29.33, 31.52 and 32.55 ($2\theta \pm 0.2^{o}$ 2θ). Form II shows characteristic peaks at 4.58, 4.95,6.39, 9.12, 12.24, 12.76, 13.10, 14.22, 14.56, 15.20, 17.11, 17.47, 18.15, 19.18, 19.85, 20.49, 21.02, 21.85, 22.26, 22.93, 23.75, 25.52, 25.78, 26.41, 27.38, 27.90, 28.58, 29.32, 30.08, 30.44, 31.45, 32.48, 33.12, 34.65, 35.26, 25.62 and 42.07 ($2\theta \pm 0.2^{o}$ 2θ). The observed patterns in the powder X-ray diffraction (PXRD) indicate that they have no difference in polymorphism.

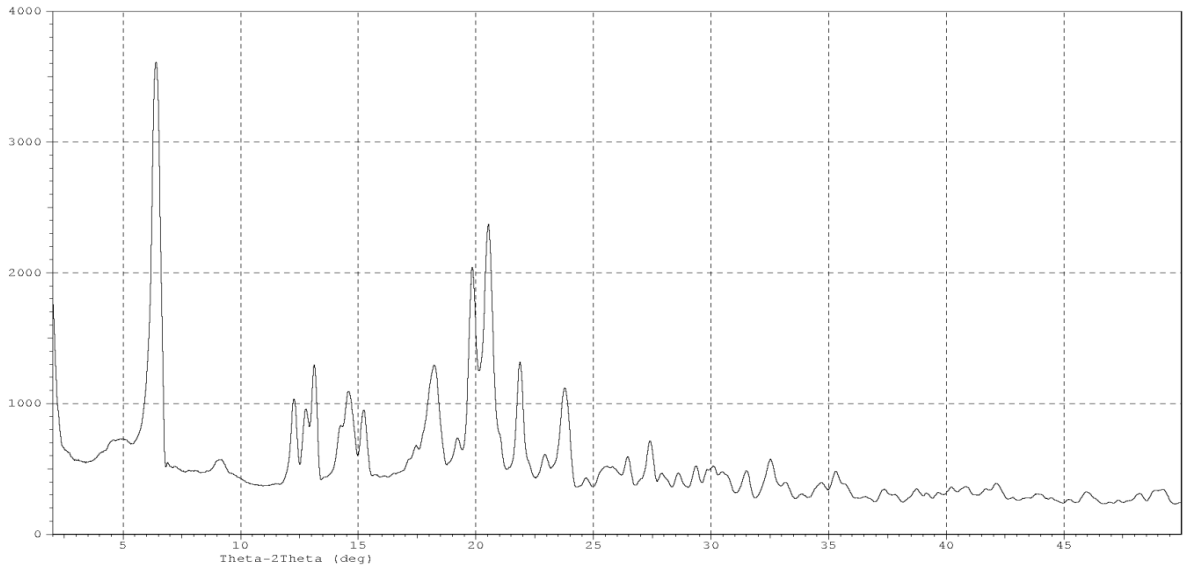

Figure 4: X-ray diffraction patterns of Form I

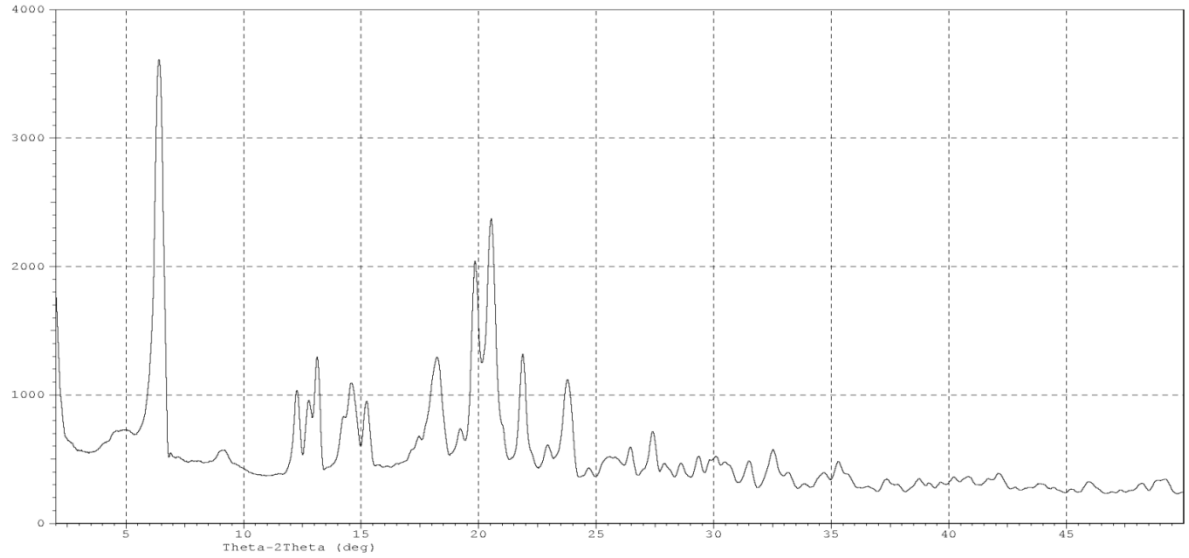

Figure 5: X-ray diffraction patterns of Form II

The crystalline nature and relative stability of Form I and Form II was determined by DSC thermogram (Figure 6 and Figure 7). Form I showed two single sharp endotherm peaks at 131.21 ^{o}C and 199.77 ^{o}C with a heat of fusions of 11.82 kJ mol^{-1} and 1.841 kJ mol^{-1} and Form II showed two single sharp endothermic peaks at 128.0 ^{o}C and 209.95 ^{o}C with a heat of fusions of 17.09 kJ mol^{-1} and 3.37 kJ mol^{-1}. These results suggest both Form I and Form II are crystalline nature. The DSC data provided insight into the relative stability of Form I and Form II. Based on the Heat of Fusion rule [7], the higher melting Form with higher enthalpy of fusion is monotropically more stable form. Thus, Form II is thermodynamically more stable than Form I at all temperatures up to melting points of either Forms. The thermodynamically most stable form is always preferred choice for pharmaceutical development. Therefore, Form II is suitable for doing further investigations on FC dihydrate.

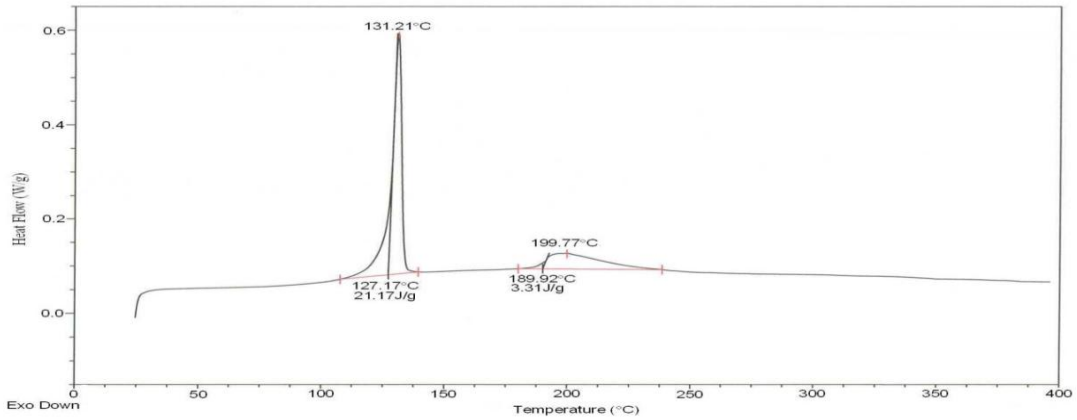

Figure 6: DSC thermogram of Form I

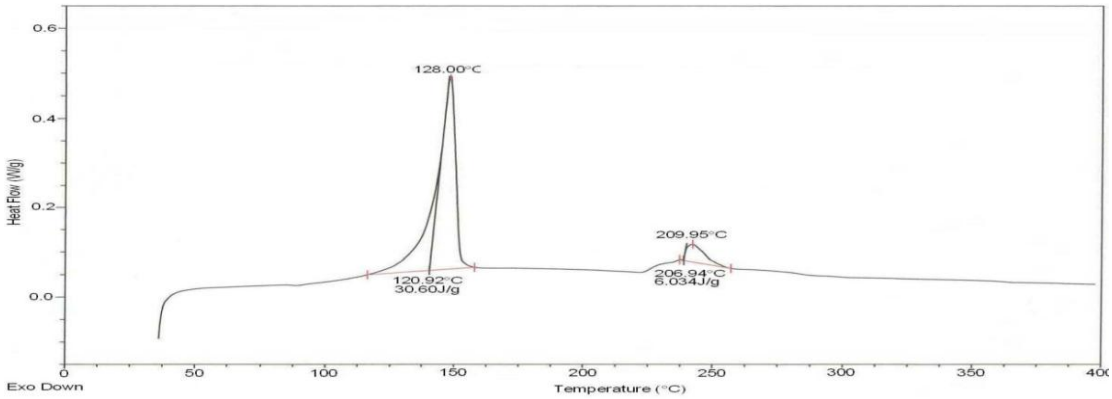

Figure 7: DSC thermogram of Form II

The TG curve of Form I and Form II (Figure 8 and Figure 9) showed weight loss of 6.74 % and 6.31 % in melting. These results suggest the Form I and Form II are dihydrate. Further evidence for the presence of dihydrate was supported by Karl Fischer Titration, which clearly indicate the presence of water content (6.78 % and 6.33 % in Karl Fischer Titration Analysis) in the crystal lattice of Form I and Form II. The data of KFT is in coherence with the results observed in TGA.

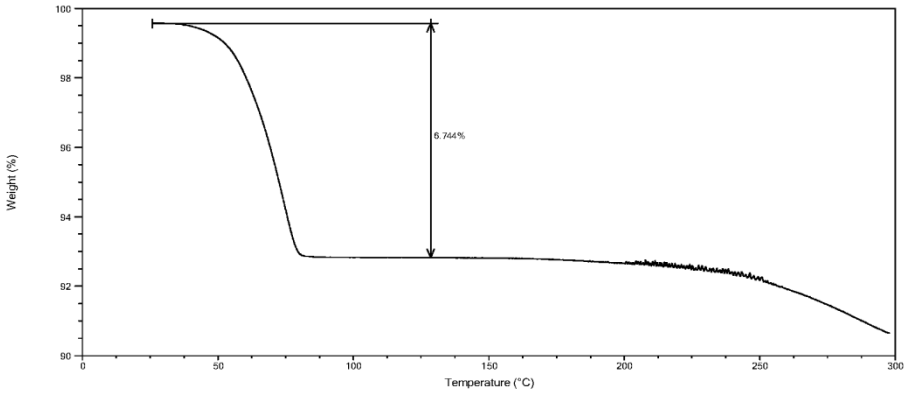

Figure 8: TG curve of Form I

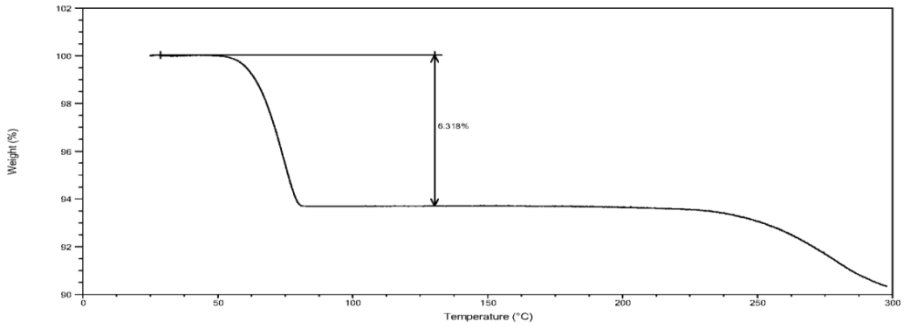

Figure 9: TG curve of Form II

The FT-IR spectra of Form I and Form II are shown in figure 10 and figure 11. No significant difference in wave lengths between Form I and Form II is seen in the finger print as well as in the functional group region. For instance, the IR stretching peaks of Form I are: 3601, 2428, 2139, 1868, 1796, 1442, 1309, 1264, 1248, 905, 811 cm^{-1} and the IR stretching peaks of Form II are: 3602, 1869, 1746, 1441, 1310, 1263, 1247, 904, 810 cm^{-1}.

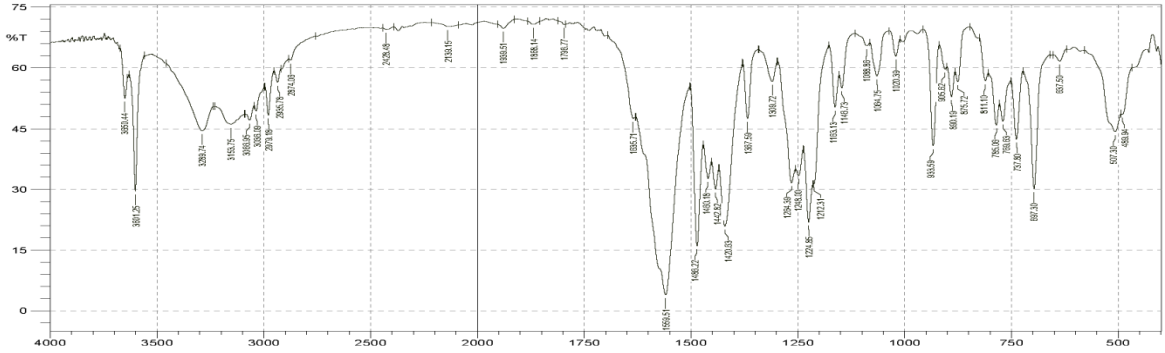

Figure 10: IR spectra of Form I

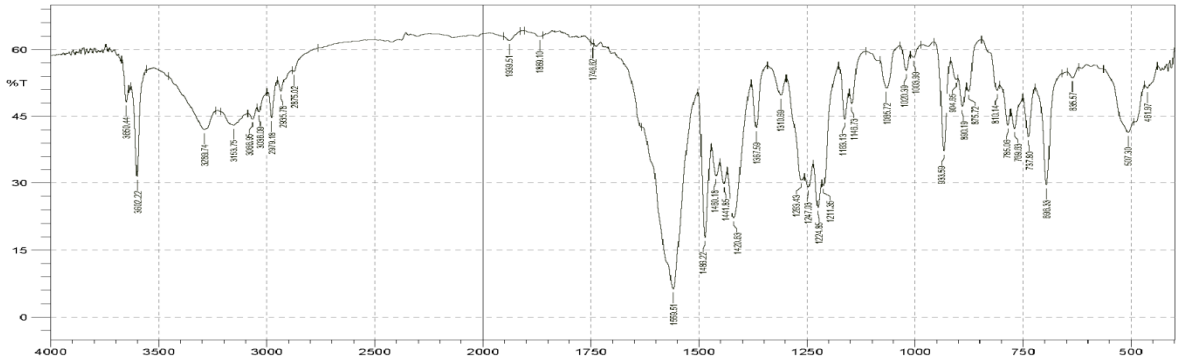

Figure 11: IR spectra of Form II

Determination of aqueous solubility of Form I and Form II was measured by HPLC. The aqueous solubility of Form I is 0.0039 µg mL^{-1} and Form II is 0.0041 µg mL^{-1}. These results clearly indicate no change in aqueous solubility of Form II when compared to the aqueous solubility of Form I. Form I and Form II were subjected for accelerated stability study and were found to be stable under ICH specified [8]

accelerated stability conditions of storage for zones III and IV at 40 °C / 75 % RH. No change is observed in aqueous solubility, morphology, desolvation, melting behaviors and powder X-ray diffraction pattern. The differences in particle size, water content and solubility of Form I and Form II resulted differences in melting point of DSC for Form I and Form II.

APPLICATIONS

Fenoprofen calcium (FC) dihydrate is a non-steroidal anti-inflammatory drug. This prepared Form II is from less toxic and environment friendly class III organic solvent ethylacetate. So it can be used.

CONCLUSIONS

The newly prepared novel crystal form (Form II) of Fenoprofen calcium dihydrate is monotropically more stable form with no change in aqueous solubility. Therefore, Form II can be used for carrying out further research of Fenoprofen calcium dihydrate.

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