NOVEL POLYMORPHS OF DOXOFYLLINE WITH NEW MORPHOLOGY

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ABSTRACT: A Xanthine derivative medicine used to treat asthma, doxofylline is 7-(1,3-Dioxolan-2-ylmethyl) - 1,3-dimethyl purine-2,6-dione. C11H14N4O4 is the chemical formula. High oral doses of 400 mg, 800 mg, and 1200 mg of doxofylline are now available in tablet form.oral suspension containing 100 milligrams per milliliter, and syrup containing 100 milligrams per milliliter. Terbutaline and Montelukast are two more drugs that are sold together. Crystals having needle-shape morphology were found via an extensive literature study. Form P, a newly discovered crystal form of doxofylline with a rod-shaped morphology, has been thoroughly studied using a number of analytical tools, including Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimeter (DSC), Thermo Gravimetric Analysis (TGA), and Polarized Microscopy (PM). For filtering purposes in pharmaceutical production, rod-shaped crystals are better than needle-shaped crystals.
Production of Doxofylline is improved by the recently created new crystal form (Form P) of the drug, which has a rod-shaped morphology.

Keywords: Polymorphs, Polarized Microscopy, Asthma, PXRD, Aqueous solubility

INTRODUCTION: Doxofylline is chemically 7- (1, 3 - Dioxolan-2-ylmethyl)- 1, 3-dimethylpurine- 2, 6-dione is a Xanthine derivative drug used in the treatment of Asthma [1]. The molecular formula is $C_{11}H_{14}N_4O_4$ (**Fig. 1**). It is first disclosed in Farmaco edizione scientifica (1981), 36(3), 201-19. Doxofylline is presently available in tablet form with high oral dosages of 400 mg, 800 mg and 1200 mg, Syrup with oral dosage of 100 mg/5mL and Suspension with oral dosage of 100 mg/5mL [2]. It is also marketed as a combination drug with

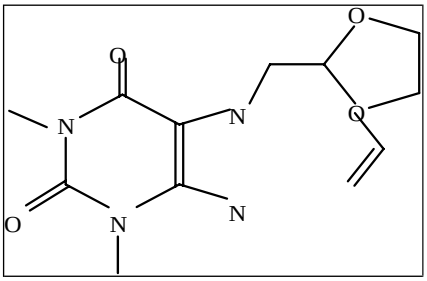

FIG. 1: STRUCTURE OF DOXOFYLLINE

In general, rod shape crystals are preferable than needle shape crystals for filtration. Extensive terbutaline and montelukast.
According to the literature review, only crystal morphologies with a needle form are described in Literature 3. Four, five, and six different recrystallization methods are used.

change the way crystals form. This study details the discovery of a new morphological variant of doxofylline as part of our continuing research effort. Doxofylline crystal alterations were identified using standard

tools for structurally sensitive analysis, including polarized microscopy, powder X-ray diffraction, gas

chromatography, and Karl Fischer titration.
Things needed: The medication doxofylline, which is sourced from SUVEN Life Sciences Limited in Hyderabad, India, has a purity level of above 99.8 percent. This investigation made use of analytical grade solvents. We bought all of the solvents from Sigma-Aldrich.
Getting Ready for Form P: Three milliliters of methanol and one milliliter of toluene solvent were added to a round-bottom flask containing 200 milligrams of doxofylline (Form I, Compound described in previous art, needle shape morphology). With continuous stirring (100 rpm), the mixture was heated gently. At 40 °C, a transparent solution was produced from the dissolved solids. A temperature of 0–5 °C was applied to the mixture, and it was stirred at 200 rpm for an hour to keep it at that temperature. After collecting the crystalline solids, Form P was created by filtering the material and drying it under decreased pressure. The resulting crystalline particles were filtered before being dried under reduced pressure to produce 70 mg of the crystalline product (Form P).
Research techniques:
Microphotographs were captured using a Nikon LV100 polarized microscope. The images were created using slightly crossed polarizers and transmitted light.
Finding the Size of Particles: A little amount of the formulation was placed on a slide and the particle size was determined using optical microscopy, a calibrated eye piece micrometer, and a stage micrometer. We measured the size of about 100 microcrystals one by one, averaged their results, and then determined the size range and mean diameter frequency.
The average size of a particle may be determined using the formula, average size = ɛnd/n.
Thermograms were taken using a differential scanning calorimeter (DSC) (Model Q100, TA instruments). The measurements were taken in a nitrogen-filled environment using an aluminum sample pan with samples ranging from around 2 to 10 mg, with a scanning speed of 2 °C/minute.

Temperature Gravimetric Analysis (TGA): A thermogravimeter (Model Q500, TA instruments) was used to produce thermo gravimetry (TG) curves. The results were obtained by scanning a 50 mg platinum pan in a nitrogen environment at a speed of 2 °C/minute, with a sample weight of around 10 mg. The mass loss percentage was determined using the mass of the first sample.
Known as Karl Fischer Titration, or KFT: Karl Fischer titrimetry (716 DMS Titrino, Metrohm Limited, Switzerland) was used to discover the water content (% w/w) of the 200 mg samples. Prior to conducting the sample analysis, the equipment was calibrated using deionized water.
Powder X-ray diffraction (PXRD): An X-ray diffractometer (Model RINT Ultima, Rigaku Denki) was used to measure the powder X-ray diffraction pattern. A scanning speed of 1 °C/minute was used in conjunction with the following measurement conditions: target Cu, monochrometer graphite, voltage 45 kV, current 40 mA. The sample container was filled with around 200 mg of material.
THESE OUTCOME AND COMMENTARY: Various organic solvents from Classes II and III were used to create the new polymorph. In theory, morphological analysis is the first and most important step following new form preparation. Our research indicates that crystals recrystallized in a methanol/toluene combination have a rod-shaped morphology. Form P is the name we gave to this crystal form. Other produced forms show no morphological change. Polymorphism may be inferred from the discrepancy between Form I and Form II's birefringence.

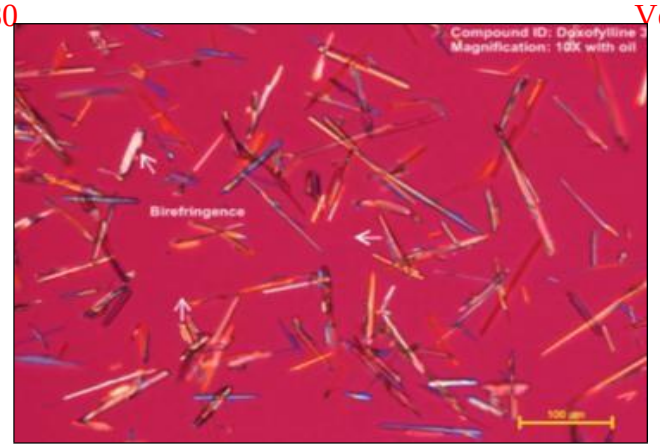

FIG. 2: MICROPHOTOGRAPH OF FORM A

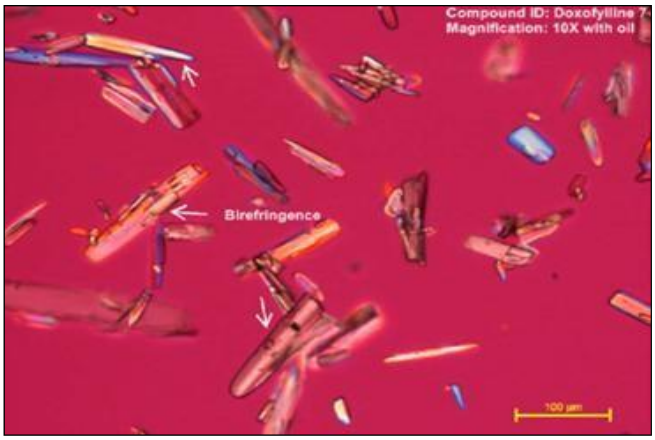

FIG. 3: MICROPHOTOGRAPH OF FORM P

Morphologies of Form I and Form P clearly indicate both Form I and Form P are crystalline in nature. Crystals of Form I are in needle shape with average particle size of 84.17 milli microns (**Fig. 2)** and crystals of Form P are in rod shape with average particle size of 72.97 milli microns (Fig**. 3**). Difference in morphology of Form P is further supported by the powder X-ray diffraction pattern. The sharp diffraction peaks of Form I and Form P indicates both forms are in crystalline nature (**Fig. 4** and **5**). Form I shows characteristic peaks at 10.21, 12.12, 14.39, 23.32, 24.43, 27.23, 28.60,
30.54, 32.28, 33.32, 34.38 and 36.12 ($2\theta \pm 0.2\ ^{o}2\theta$),
while Form P shows characteristic peaks at 8.20, 8.50, 10.92, 11.21, 14.44, 14.89, 15.49, 16.91, 17.18, 18.28, 18.49, 19.63, 22.57, 22.90, 23.21,
23.38, 24.08, 25.95, 29.79, 30.22, 30.51, 39.94,
40.09, 44.09 and 46.35 ($2\theta \pm 0.2\ ^{o}2\theta$)

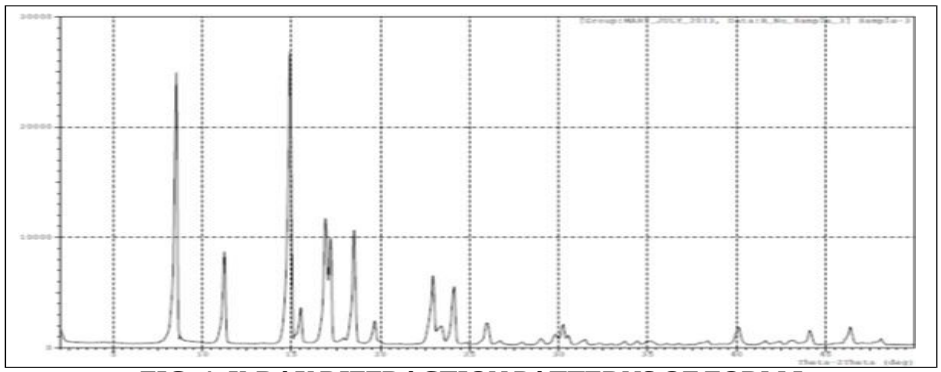

FIG. 4: X-RAY DIFFRACTION PATTERNS OF FORM I

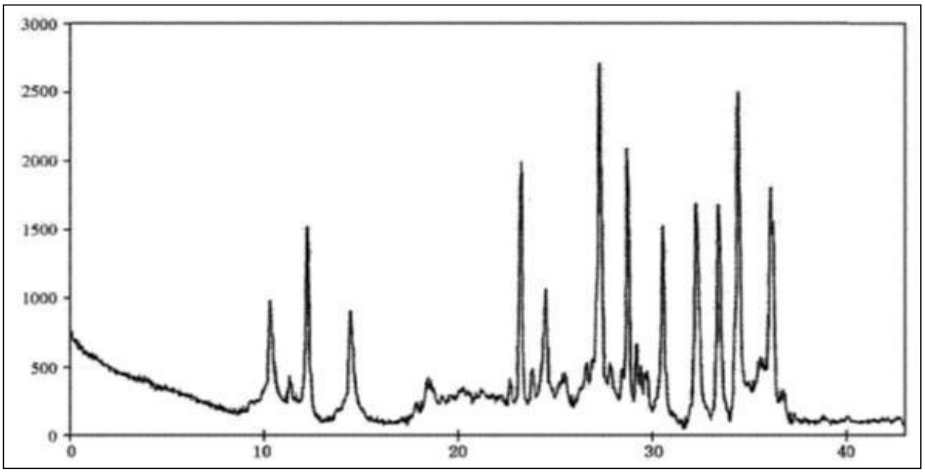

FIG. 5: X-RAY DIFFRACTION PATTERNS OF FORM P

The Observed pattern in the powder X-ray diffraction (PXRD) indicates that they possess different crystal structure and therefore two polymorphic forms of Doxofylline. The crystalline nature and relative stability of Form I and Form P were determined by DSC thermogram (**Fig. 6** and **7**). Form I showed single sharp endotherm peaks at
143.78 ^{o}C with a heat of fusion of 92.96 kJ/mol and

Form P showed single sharp endotherm peak at
144.39 ^{o}C with a heat of fusion of 92.96 kJ/mol. These results suggest both, Form I and Form P are crystalline nature. The DSC data provided insight into the relative stability of Form I and Form P. The presence of single endothermic peak of DSC thermogram indicates absence of solvate or hydrate in Form I and Form P.

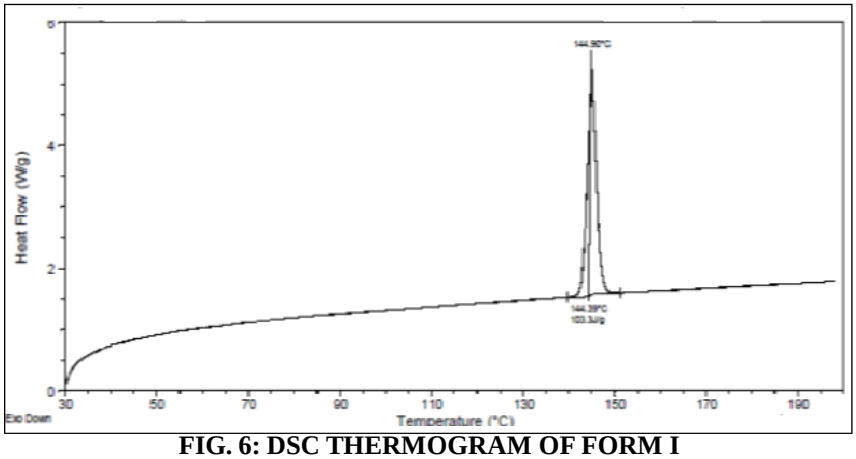

FIG. 6: DSC THERMOGRAM OF FORM I

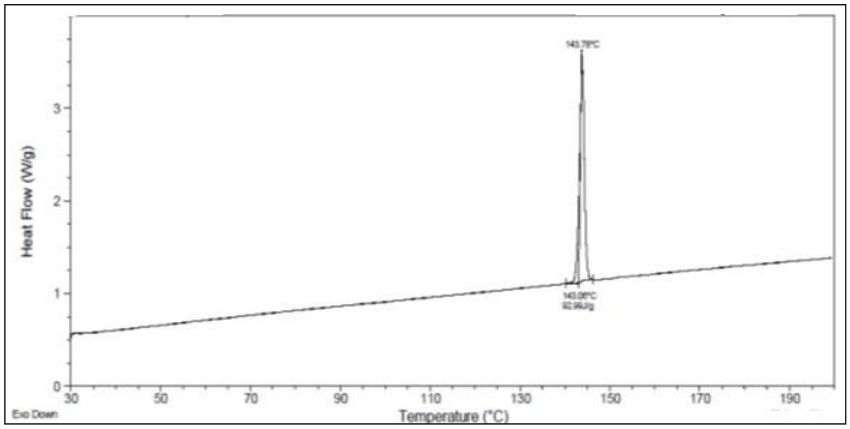

FIG. 7: DSC THERMOGRAM OF FORM P

The TG curve of Form I and Form P (**Fig. 8)** showed no weight loss in melting. These results suggest both Form I and Form P are neither solvated nor hydrated

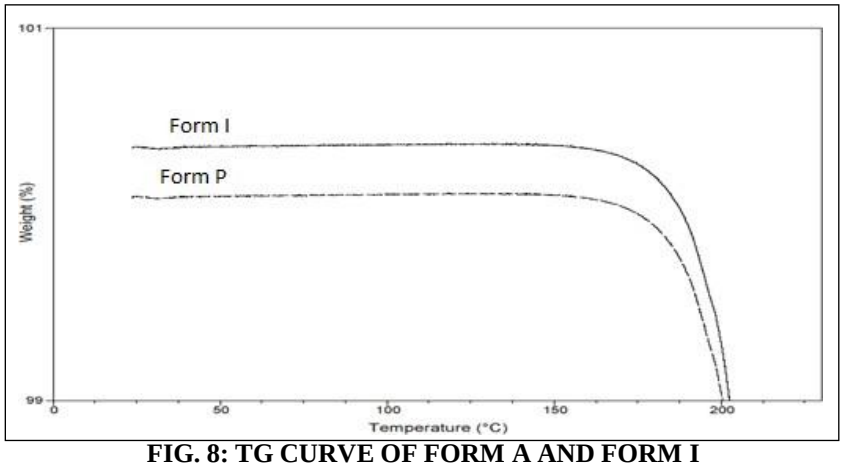

FIG. 8: TG CURVE OF FORM A AND FORM I

Further evidence for the absence of solvates and hydrates was supported Karl Fischer Titration, which clearly demonstrated that no water content is found in Form I and Form P, furthermore these data is in concurrence with the results observed in TGA and DSC.

CONCLUSION: Since, rod shape crystals are more preferable than needle shape crystals for filtrations in pharma manufacturing. The newly prepared novel polymorph (Form P) of Doxofylline with rod shape morphology is more suitable for filtrations.

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