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NOVEL POLYMORPHS OF DOXOFYLLINE WITH NEW MORPHOLOGY

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ABSTRACT: Doxofylline [7-(1,3-Dioxolan-2-ylmethyl) - 1,3-dimethyl purine-2,6-dione] is a Xanthine derivative drug used in the treatment of Asthma. The molecular formula is C₁₁H₁₄N₄O₄. 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. It is also marketed as a combination drug with Terbutaline and Montelukast. Extensive literature survey revealed crystals with needle shape morphology. Novel crystal form (Form P) of Doxofylline with new rod shape morphology has been identified and fully characterized by a variety of analytical techniques such as Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimeter (DSC), Thermo Gravimetric Analysis (TGA) and Polarized Microscopy (PM). Since, rod shape crystals are preferable than needle shape crystals for filtrations in pharma manufacturing. The newly prepared novel crystal form (Form P) of Doxofylline with rod shape morphology is more suitable in Doxofylline manufacturing.

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 Asthma¹. The molecular formula is C₁₁H₁₄N₄O₄ (**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/5mL². It is also marketed as a combination drug with terbutaline and montelukast.

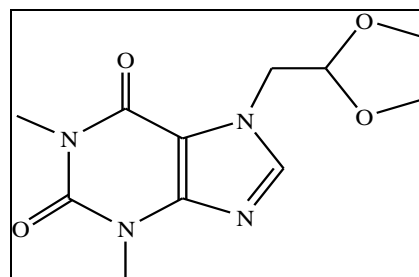


FIG. 1: STRUCTURE OF DOXOFYLLINE

In general, rod shape crystals are preferable than needle shape crystals for filtration. Extensive literature survey revealed that only needle shape crystal morphology is reported in Literature³. Various recrystallization techniques are used to alter the crystal habit^{4,5,6}. As part of our ongoing research program, the present paper reports the novel polymorph of Doxofylline with new morphology. A crystal modifications of Doxofylline was characterized by means of typical

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structure sensitive analytical techniques such as Polarized Microscopy, PXRD, DSC, TGA and Karl Fischer Titration.

Materials: Doxofylline (Designated as Form I) is obtained from SUVEN Life Sciences Limited, Hyderabad, India and the purity of this drug is > 99.8 %. The solvents used in the study are of analytical grade. All the solvents used were purchased from Sigma-Aldrich.

Preparation of Form P: Doxofylline (Form I, Compound reported in prior art, needle shape morphology), 200 mg, was taken in a round bottom flask containing 3 mL of methanol and 1 mL Toluene solvent. The mixture was slowly heated under constant stirring (100 rpm). The solids dissolved clear solution formed at 40 °C. The mass was cooled to 0 - 5 °C and maintained at the same temperature under stirring (200 rpm) for 1 hour. The crystalline solids obtained were then filtered and the mass was dried under reduced pressure to obtain crystalline product, Form P. The crystalline solids obtained were then filtered and the mass was dried under reduced pressure to obtain crystalline product (Form P), Yield: 70 mg.

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: 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 microcrystal size was measured individually, average was taken and their size range and mean diameter frequency was calculated.

Average Particle size is calculated by the formula,

$$\text{Average Particle size} = \sum nd/n$$

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

Thermo Gravimetric Analysis (TGA): Thermo gravimetry (TG) curves were obtained with a thermogravimeter (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/minute. 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 Titrimo, Metrohm Limited, Switzerland). The instrument was calibrated by using deionized water, before sample analysis.

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, monochromator 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.

RESULTS AND DISCUSSION: We prepared novel polymorph by using different Class II and Class III organic solvents. In principle, the first and foremost technique that is adopted after preparation of the new forms is to analyze the morphology. Based on our analysis, rod shape morphology is obtained from crystal recrystallized in mixture of methanol and toluene. We named this crystal form as Form P. No change in morphology is observed in other prepared forms. The difference in birefringence of Form I and Form II is the preliminary evidence for the existence of polymorphism.

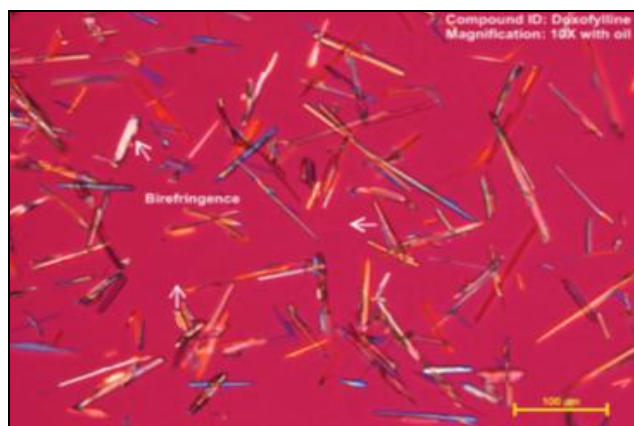


FIG. 2: MICROPHOTOGRAPH OF FORM A

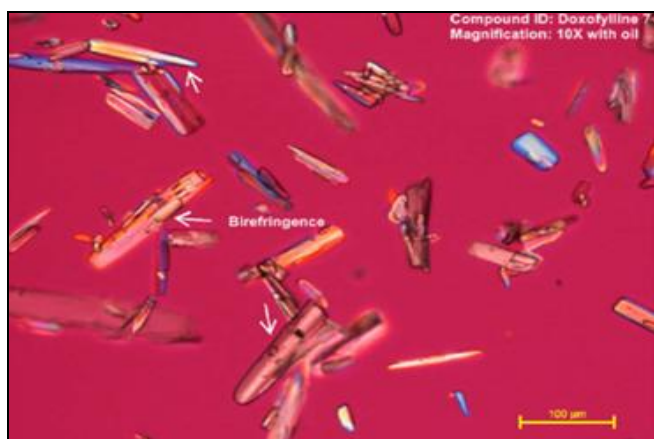


FIG. 3: MICROPHOTOGRAPH OF FORM P

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 ($2\theta \pm 0.2^\circ 2\theta$), 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 ($2\theta \pm 0.2^\circ 2\theta$)

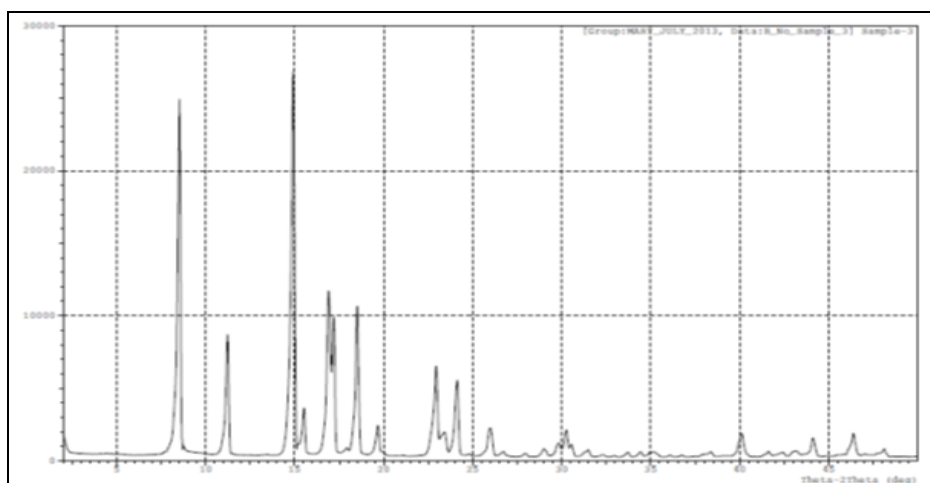


FIG. 4: X-RAY DIFFRACTION PATTERNS OF FORM I

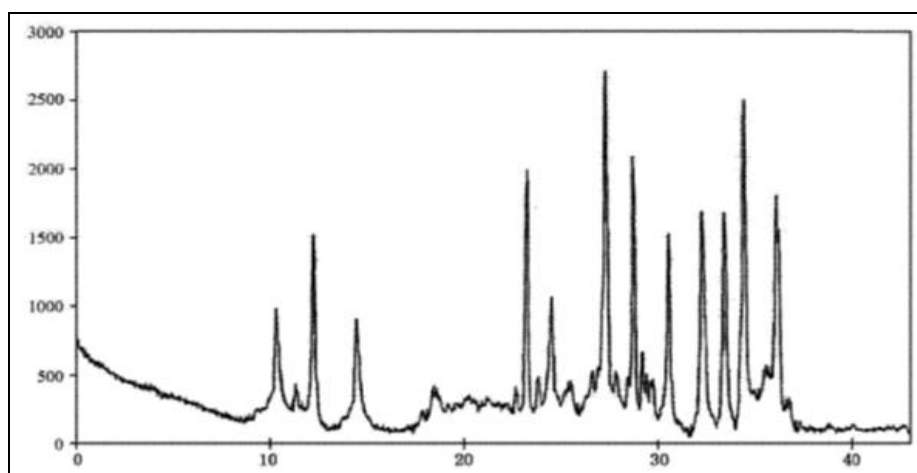


FIG. 5: X-RAY DIFFRACTION PATTERNS OF FORM P

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 °C with a heat of fusion of 92.96 kJ/mol and

Form P showed single sharp endotherm peak at 144.39 °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.

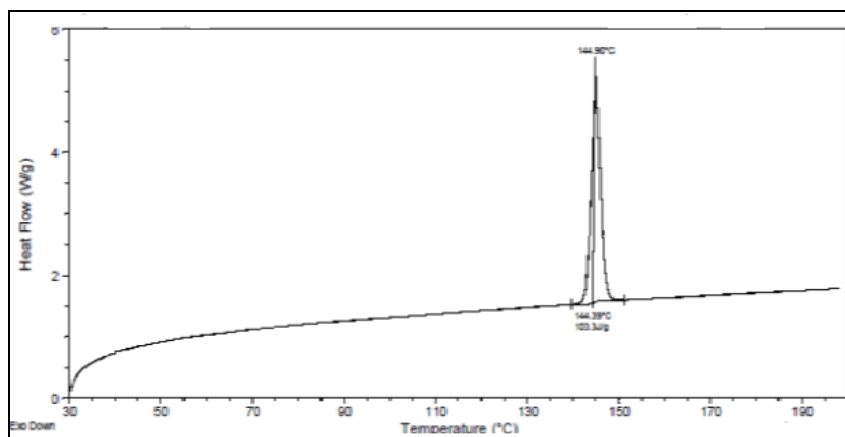


FIG. 6: DSC THERMOGRAM OF FORM I

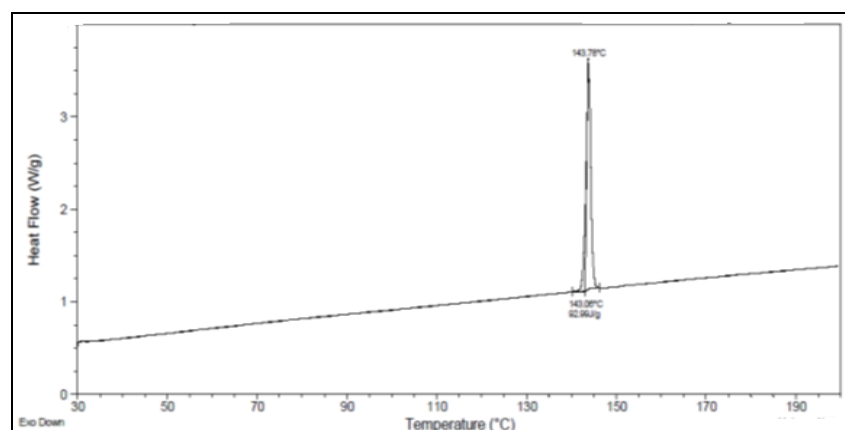


FIG. 7: DSC THERMOGRAM OF FORM P

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

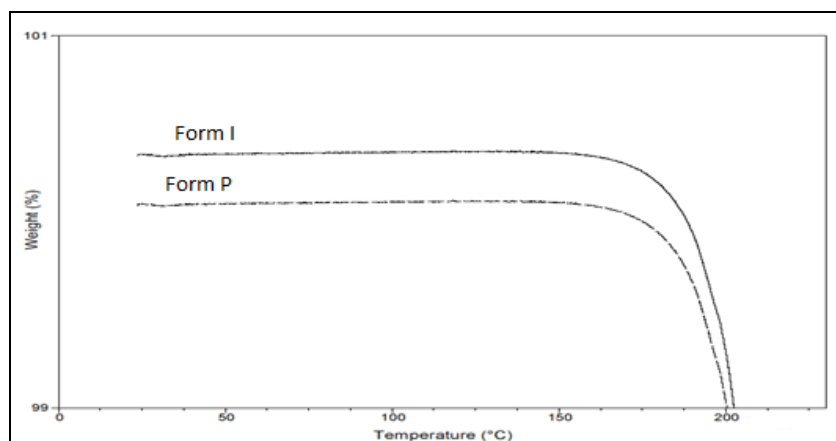


FIG. 8: TG CURVE OF FORM A AND FORM I

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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CONFLICT OF INTEREST: No conflict of interest.

REFERENCES:

1. <https://pubchem.ncbi.nlm.nih.gov/compound/doxofylline#section=Top>.
2. <http://www.druginfosys.com/drug.aspx?drugcode=2193&type=1>.
3. Liu Shaocheng, Gao Changrong, Yang Xizeng, Ning Guotao; Synthesis of doxofylline; CN 1041728C.
4. Abdul Khaliq and El-Zhry El-Yafi: Technical crystallization for application in pharmaceutical material engineering. *Asian Journal of Pharmaceutical Sciences*; 2015; 10(4):283-291.
5. Arindam Chatterjee; Madan Mohan Gupta and Birendra Srivastava: Spherical crystallization: A technique use to reform solubility and flow property of active pharmaceutical ingredients. *International Journal of Pharmaceutical Investigation*; 2017;7(1):4-9.
6. S.K. Putta and P. Srikumar: Spherical crystallization and its process optimization. *Journal of Chemical and Pharmaceutical Research*; 2016; 8(7):611-623.
7. <http://www.unilab.com.ph/assets/product-info/doxofix.pdf>.
8. <https://www.ncbi.nlm.nih.gov/labs/articles/28414142/>.
9. <https://www.drugbank.ca/drugs/DB09273>.
10. Panduranga Rao Nagawaram and Vashishta Kanchanpally: Comparative study of theophylline and doxofylline in the treatment of stable chronic obstructive pulmonary disease; *International Journal of Basic & Clinical Pharmacology*; 2016; 5(2): 251-256.
11. Sami Manzoor Margay, Samina Farhat, Sharanjit Kaur and Hilal Ahmad Teli: To Study the Efficacy and Safety of Doxophylline and Theophylline in Bronchial Asthma; *Journal of Clinical and Diagnostic Research*; 2015; 9(4): FC05-FC08

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