



## A simple and reproducible crystallization method for the preparation of 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid (febuxostat) polymorphic form-B via acetic acid solvate

Chandra Kant Belwal<sup>1</sup> and Kaushik A. Joshi<sup>2</sup>

<sup>1</sup>Department of Chemistry, JJT University, Rajasthan, India

<sup>2</sup>M.V.M. Science & Home Science College, Rajkot, India

### ABSTRACT

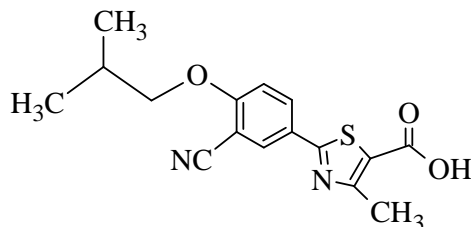
A simple and reproducible crystallization method was developed for the synthesis of xanthine oxidase inhibitor febuxostat polymorphic form- B via acetic acid solvate.

**Keywords:** Febuxostat, hyperuricemia, polymorphic forms, solvate, X-ray powder diffraction.

### INTRODUCTION

Febuxostat (formula-1) is a xanthine oxidase inhibitor used for treating gout caused by excessive levels of uric acid in the blood (hyperuricemia) [1, 2]. Uric acid is formed from the breakdown of certain chemicals (purines) in the body. Hyperuricemia occurs when the body produces more uric acid than it can eliminate. The uric acid forms crystals in joints and tissues, causing inflammation and pain. Elevated blood uric acid levels also can cause kidney disease and kidney stones. Febuxostat prevents the production of uric acid by blocking the activity of the enzyme (xanthine oxidase) that converts purines to uric acid.

Febuxostat is a non-purine selective inhibitor of xanthine oxidase [3]. It works by non-competitively blocking the channel leading to the active site on xanthine oxidase. Xanthine oxidase is needed to successively oxidize both hypoxanthine and xanthine to uric acid. Hence, febuxostat inhibits xanthine oxidase, therefore reducing production of uric acid.



Formula-1

Polymorphic forms of a drug substance can have different chemical and physical properties, including melting point, chemical reactivity, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure and

density. These properties can have a direct effect on the ability to process and/ or manufacture the drug substance and the drug product, as well as on drug product stability, dissolution and bioavailability

There are several methods reported to produce polymorph B of Febuxostat [4-6], but the challenge is to produce polymorph B with consistency. In view of these facts present method is developed to produce B polymorphic form of Febuxostat via acetic acid solvate in consistency.

### EXPERIMENTAL SECTION

All solvents used in the process were of LR grade.

Febuxostat was dissolved in acetic acid or a 1:1 mixture of organic solvent and acetic acid (table-1) under heating conditions, solution filtered through 0.2 micron filter paper and stirred at room temperature without applying any external cooling, solid filtered out which on drying at 40°C furnished an acetic acid solvate of 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid (febuxostat), X-Ray Powder Diffraction peaks at 6.88, 7.35, 11.12, 11.83, 14.76, 16.73, 17.67, 18.37, 22.20, 23.42, 26.05, 26.64, 29.47 and 29.77 (2 theta-Scale) and further drying of the same sample at 100°C leads the formation of polymorphic form- B of 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid (febuxostat), X-Ray Powder Diffraction peaks at 6.767, 8.09, 9.74, 11.54, 12.22, 13.59, 15.78, 16.25, 17.35, 19.41, 21.19, 21.56, 23.20, 24.79, 25.16, 25.71, 26.11, 26.69, 27.69 and 29.36 (2 theta-Scale) [4].

**Table – 1: Formation of acetic acid solvate with 1:1 mixture of different solvent and acetic acid and its conversion to polymorphic form-B by drying the solvate at 100°C**

S. N.	Solvent -A	Solvent-B	Polymorphic form obtained	
			drying at 40°C	drying at 100°C
1	Methyl isobutyl ketone	Acetic acid	Acetic acid solvate	Polymorph-B
2	Toluene	Acetic acid	Acetic acid solvate	Polymorph-B
3	n- Heptane	Acetic acid	Acetic acid solvate	Polymorph-B
4	Ethyl acetate	Acetic acid	Acetic acid solvate	Polymorph-B
5	Acetonitrile	Acetic acid	Acetic acid solvate	Polymorph-B
6	Ethanol	Acetic acid	Acetic acid solvate	Polymorph-B
7	Acetone	Acetic acid	Acetic acid solvate	Polymorph-B
8	Tetrahydrofuran	Acetic acid	Acetic acid solvate	Polymorph-B

#### Instrument Information

Melting point was determined using Mettler Toledo DSC 821e instrument. IR spectra recorded for KBr disc on a Perkin Elmer Spectrum RXI FT-IR system No. 55529. The X-ray powder diffraction pattern was performed on PANalytical Expert PRO with Xcelerator as detector

**Table – 2: X-ray diffraction data of acetic acid solvate of Febuxostat**

2θ value	Intensity	2θ value	Intensity
6.88	5.2	18.37	1.6
7.35	100	22.20	2.6
11.12	7.2	23.24	2.8
11.83	11.9	26.05	4.9
14.76	6.9	26.64	2.7
16.73	13.9	29.47	1.1
17.67	2.8	29.77	1.2

### RESULTS AND DISCUSSION

#### X-Ray diffraction analysis

X-Ray Powder Diffraction spectrum of Febuxostat solvate (Figure-1) and polymorphic form B (Figura-2) were recorded in Pan analytical 'X' pert PRO instrument. The X-ray diffraction data were indexed and the indexed data was compared with solvent and B polymorph data [4] and are presented in Table 2 and 3 respectively. The material of the grown pure crystal is thus confirmed to be solvate and B polymorphic form of Febuxostat.

Figure – 1: X-ray powder diffractogram of acetic acid solvate of Febuxostat

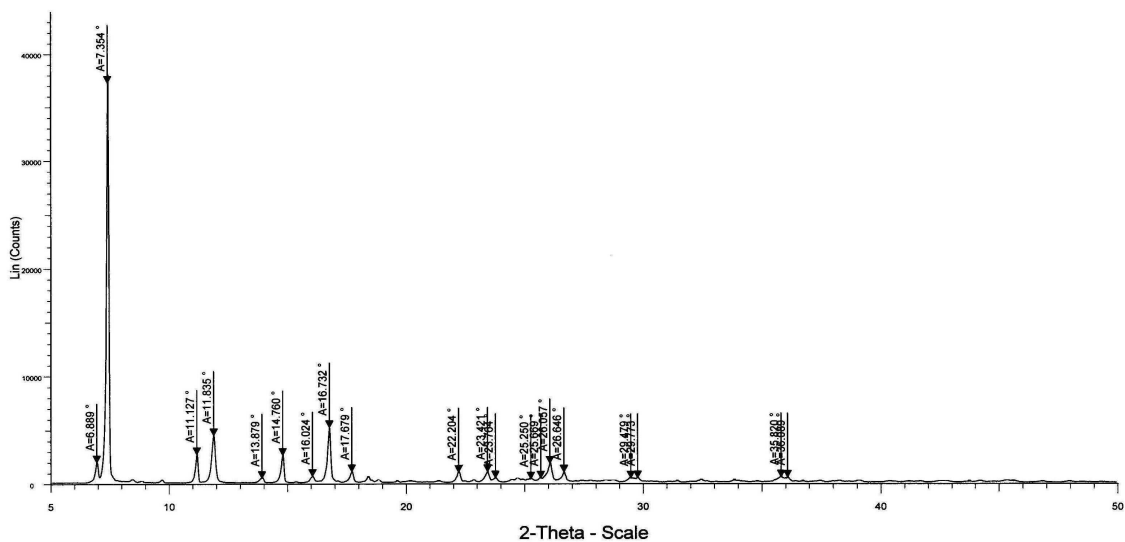
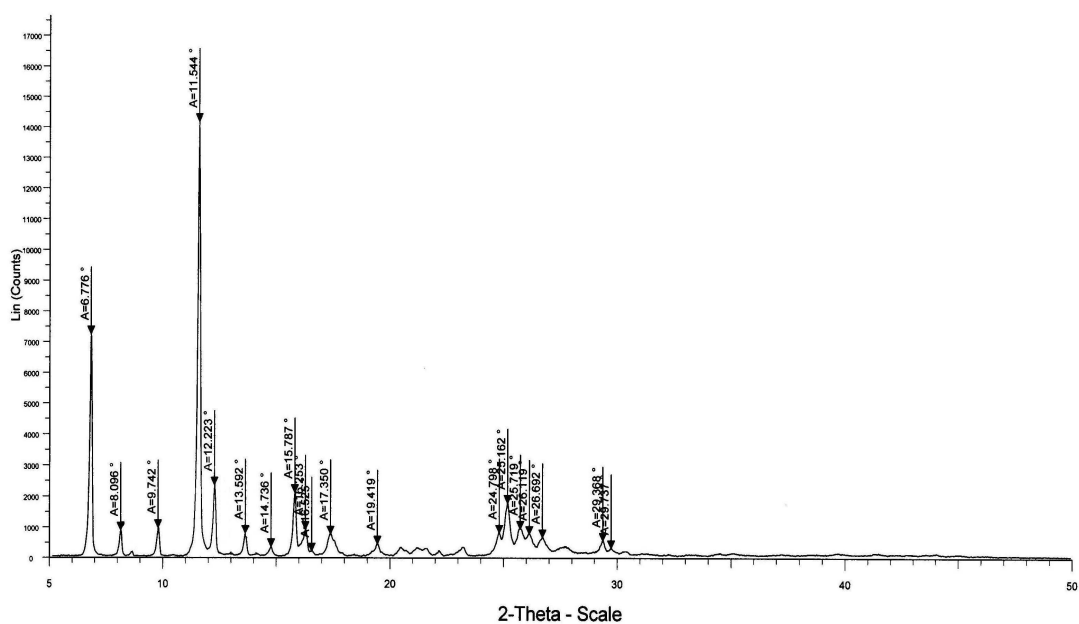


Figure – 2: X-ray powder diffractogram of B polymorphic form of Febuxostat



### Thermal Analysis

The TGA thermogram recorded for all the grown crystal, i.e. solvate and B form are presented in Figure 3 to 4. The thermogram 3 clearly shows the weight loss at around 100 to 110°C indicating that acetic acid molecule is present in crystal thus proving acetic acid solvate. On the other hand thermogram 4 shows decomposition only after 200° C confirming the polymorph-B which is free from solvent.

Figure – 3: TGA thermogram of acetic acid solvate of Febuxostat

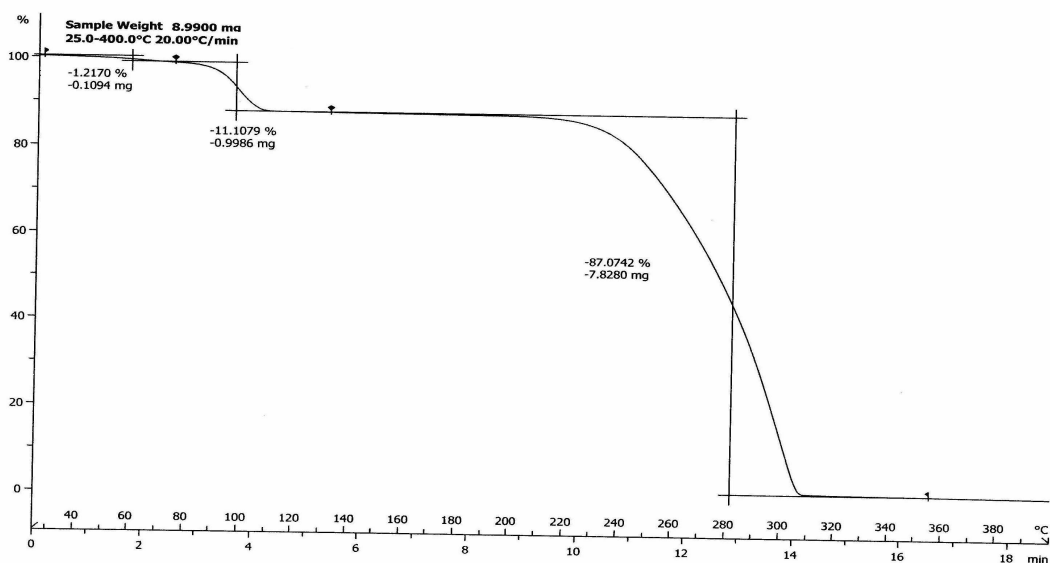
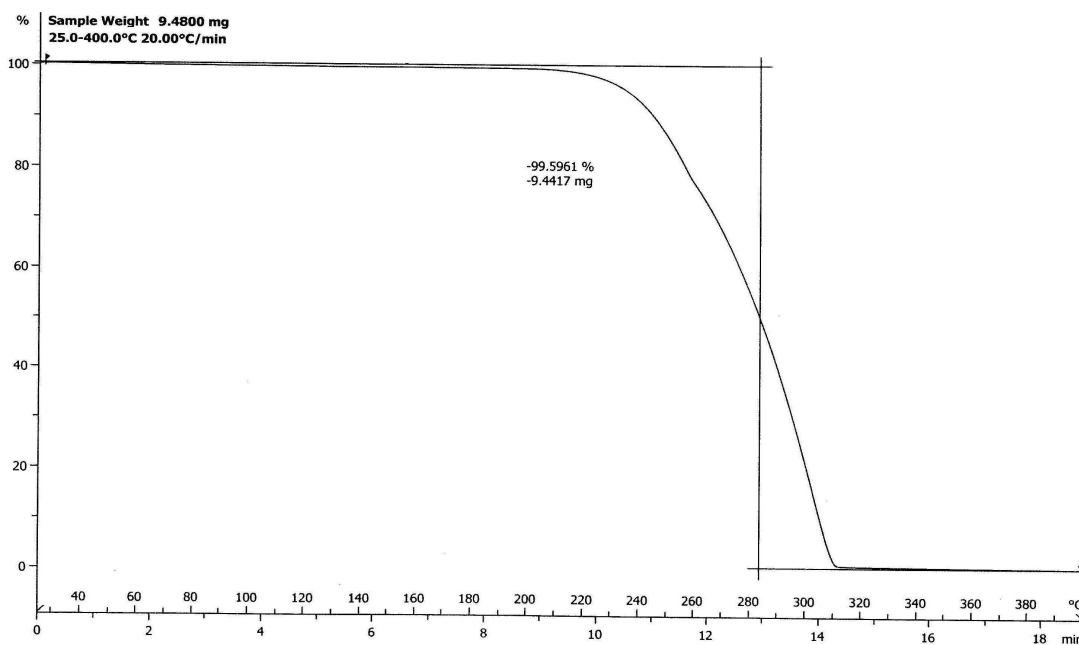


Figure – 4: TGA thermogram of B polymorphic form of Febuxostat

**IR Characterization of the test sample**

The IR spectra of sample clearly shows 3 characteristics peaks at 1713 cm<sup>-1</sup>, 1701 cm<sup>-1</sup> and 1680 cm<sup>-1</sup> Confirming the B polymorphic nature of Febuxostat [4,7].

Table – 3: X-ray diffraction data of B polymorphic form of Febuxostat

2θ value	Intensity	2θ value	Intensity
6.77	50.9	21.19	2.0
8.09	6.0	21.56	2.0
9.74	6.6	23.20	2.2
11.54	100	24.79	5.5
12.22	16.4	25.16	12.3
13.59	5.3	25.71	6.4
15.78	14.7	26.11	5.2
16.25	6.2	26.69	4.4
17.35	5.10	27.69	2.3
19.41	2.9	29.36	3.7

### CONCLUSION

Polymorphic form B of Febuxostat was prepared via acetic acid solvate route, both acetic acid solvate and polymorphic form-B was subjected to XRPD, TGA and IR analysis which confirmed the acetic acid solvate and polymorph-B of Febuxostat.

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