Isolation and Identification of forced degradation products of Februxostat

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Abstract

The current study explains the acid degradation behaviour of febuxostat API, a non-purine xanthine oxidase inhibitor used to treat hyperuricemia. A degradation study was carried out as per ICH guidelines, while the study confirms that the febuxostat is largely stable in thermal, photolytic, oxidative, and basic hydrolytic conditions and labile in acid hydrolysis conditions. There were four different degradation products found during acid hydrolysis; of these, degradation products 2, 3, and 4 are new and have never been reported before, while degradation product 1 is well-known and has already been published. All these degradation products were identified using UPLC-MS analysis, purified by using preparative HPLC and characterized using HRMS and NMR techniques. The formed degradation products are by the hydrolysis of ester and cyano functional groups of the febuxostat molecule under acidic conditions. All degradation products structural characterization was carried out using nuclear magnetic resonance spectroscopy (NMR) and high-resolution mass spectrometry (HRMS).

1. INTRODUCTION

Febuxostat drug is a selective potent non-purine xanthine oxidase inhibitor used for the treatment of hyperuricemia and gout [1–2]. It is a potential alternative to allopurinol for patients with hyperuricemia and gout. It was given FDA approval in 2009 to treat hyperuricemia in gout patients. Monosodium urate crystal deposition in joints and tissues is the primary cause of gout. Gout and hyperuricemia are more likely to occur in people with chronic kidney disease (CKD). It works by blocking the production of urate in the body [3]. Recently genotoxic impurities are identified in the febuxostat drug substance by Balaji and co-workers [4]. ICH guidelines suggested that forced degradation is necessary to identify the degradation products which help in various areas of pharmaceutical development such as manufacturing, formulation, and storage conditions, and protect the drug from such conditions [5–9]. According to the literature, the febuxostat drug showed relatively lower degradation under thermal, photolytic, and oxidative conditions [10]. Forced Acid degradation tests of febuxostat were carried out according to the ICH guidelines. Recently Madhurima Saha and Co-workers report the identification of degradation products through MS/MS analysis [11]. Mahmoud Omar and Co-workers apply the spectrofluorimetric method and conduct a stability study of the drug under various stress conditions recommended by ICH guidelines [12]. But no one reported the structural characterization through NMR experiments. Few works of literature are available for the analysis of Febuxostat. Recently, several pseudo-degradation products are captured in a journal where acetonitrile and methanol are used as co-solvent and reacted with the drug during forced degradation [13–18]. Hence, the current study aimed to identify novel acid degradation products with advanced techniques (2D NMR, and HRMS). Here we performed forced degradation under acid conditions and methanol was used as diluent. Since the febuxostat API is soluble in methanol [12] and practically insoluble in acetonitrile and 1N HCl in a water mixture, methanol is used as a co-solvent. In this case, we found a known degradation product, namely DP-1 (11.03%; UPLC-MS m/z: 336.04), and three pseudo-degradation products named DP-2 (4.84%; UPLC-MS m/z: 331.14), DP-3 (3.35%; UPLC-MS m/z: 350.05) and DP-4 (1.28%; UPLC-MS m/z: 364.14) with a total degradation of

21.12% by UPLC-MS analysis. The known impurity is formed by the complete hydrolysis of cyano group under acidic conditions [19]. All degraded products were purified by preparative HPLC and confirmed their structure by 1DNMR, 2D NMR, and HRMS. These degradation products are identified as 2-(3-carboxy-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid (DP-1), 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylate (DP-2), 2-isobutoxy-5-(5-(methoxycarbonyl)-4-methylthiazol-2-yl) benzoic acid (DP-3) and methyl 2-(4-isobutoxy-3-(methoxycarbonyl)phenyl)-4-methylthiazole-5-carboxylate (DP-4) based on HRMS and 2D NMR analysis. [Table 1] provided the results of the degradation conditions, and Fig. 1 displays the chromatogram for the acid degradation condition. Figure 2 displays the structural confirmation of each DP. All the HRMS and NMR data for the degradation products were attached in the supplementary section. To the best of our knowledge, there are no reports of these three unique degradation products in the literature.

Table 1
Degradation percentage for Febuxostat under acid stress condition

Conditions	% of degradation product				
	DP-1 (Known)	DP-2	DP-3	DP-4	API
Febuxostat API	-	-	-	-	99.89
Acid hydrolysis (1N HCl reflux at 60°C for 2hr)	11.03	4.85	3.20	1.28	79.02

The degradation products DP-2 and DP-4 were characterized as methyl esters of a known degradation product, namely (2-(3-carboxy-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid (DP) of febuxostat API and DP-3 was characterized as a methyl ester of Febuxostat API. These degradation products are formed due to the presence of methanol in the stress solution.

2. MATERIALS AND METHODS

2.1 Chemicals & Reagents

The Febuxostat API was a free sample from famous pharma business in Hyderabad. Formic acid, trifluoroacetic acid, (LCMS grade), ammonium bicarbonate, HCl (AR grade), and acetonitrile (HPLC grade), were purchased from Merck India Ltd. in Mumbai, India. Dimethylsulfoxide-d6 (D, 99.9% + 0.03% v/v tetramethylsilane, NMR grade) procured from Cambridge Isotope Laboratories Inc. for this research. The water used is from a Millipore milliQ instrument manufactured in Amsterdam, the Netherlands.

2.2 Instrumentation and software

The UHPLC-MS equipment made by Waters Inc. and equipped with MassLynx 4.2 software are the analytical tools and supporting software used for the current work. The purifying equipment and supporting software used in this work are from the Waters autosampler 2707, detector-2489 with binary module 2545 and software used is Chrom scope-2.1. HRMS instrument used in this research was equipped with ESI ion source containing Thermo q-exactive orbitrap MS with an and a Dionex ultimate

3000 LC frontend and Xcalibur software. The NMR apparatus used in this experiment is a Bruker Avance Neo 400MHz with Topspin 4.09 software and an analytical balance from Sartorius-SQP-F.

2.2.1. Ultra-high performance liquid chromatography-mass spectrometry

Liquid chromatography separation was carried out on a single quadrupole detector (SQD2) coupled with Waters Acquity UPLC and Acquity photodiode array detector (PDA) frontend. For mass analysis, the SQD-2 mass spectrometer with an ESI source operating in dual polarity (positive and negative mode) was used. By utilizing scan mode between 100 and 1500 Da, MS optimization was carried out. The desolvation temperature, capillary voltage, and source temperatures were all set at 350°C, 140 ^{o}C, and 3.5 kV, respectively. The cone gas flow was set to 50 L/h, and the desolvation gas flow was 650 L/h. The massLynx 4.1 application manager was used to control the instrument for the liquid chromatography-mass spectrometer. Samples were ran through a 10.0 min chromatographic runtime at a temperature of 10 ^{o}C.

2.2.2. Method development (Optimization of chromatographic conditions)

To maximize the resolution, a variety of buffers employing a variety of columns were tested in search of an appropriate, repeatable, and reliable way. Trifluoroacetic acid, formic acid, ammonium bicarbonate buffers, and several columns, including Acquity C18, C8 and CSH C18, were initially used in the technique development experiments. During copious trials, YMC triart C18 50mmX2.1mm, 1.9µm with 0.05% formic acid in water (mobile phase-A) and 0.05% formic acid in acetonitrile (mobile phase-B), flow rate 0.6 mL/min; with binary gradient time (in min)/ Mobile Phase-B(%): 0/3, 0.4/3, 7/98, 9/98, 9.5/3,10/3 with column temperature 35°C showed encouraging and positive results and the other remaining trials got either poor resolution or peak shape. A photodiode array detector and a single quadrupole mass detector were used to observe the eluents. In this condition, all four peaks were effectively separated with good peak shape and resolution.

2.2.3. High-resolution mass spectrometry

An ESI source with a Thermo Q Exactive orbitrap MS was used to analyze the samples. The front end of the UPLC was the Dionex Ultimate 3000 with a PDA detector. The source dependent parameters were Capillary Temperature: 270°C; Spray Voltage: 3500 V, Aux gas heater Temperature: 440°C, Sheath gas flow rate: 53; Aux gas flow rate: 14; Sweep gas flow rate: 3 and S-Lens RF level: 50. To verify the mass correctness, reserpine (monoisotopic mass: 608.2734 Da) was utilized. Xcalibur software was used to gather large amounts of data. Chromatographic conditions were identical to UPLC-MS.

2.2.4. Semi Preparative high performance liquid chromatography

The Waters semi-preparative HPLC is outfitted with software chromscope-2.1, a 2545 pump module, a 2489 dual UV detector and an acquity QDA mass detector, as well as and 2707 sample manager and an auto fraction collector-III. Sunfire C18(250 x 25 mm), 5 µm in-house packed column, was used to isolate the DPs. The mobile phase included 0.1% v/v formic acid in aqueous (mobile phase A) and 0.1% v/v formic acid in ACN (mobile phase B). The flow rate was 20 mL/min. All separated fractions were lyophilized with a lyophilizer.

2.2.5. Nuclear magnetic resonance spectroscopy

A Bruker Avance Neo 400MHz NMR instrument was used to record the ^{1}H, ^{13}C, and 2D NMR spectra of Febuxostat and DPs in DMSO-d6 solvent. The reference signals for ^{1}H and ^{13}C were the tetramethyl silane (TMS) signal at zero ppm and the DMSO-d6 septet signal at 39.5 ppm, respectively.

2.3. Stress degradation procedure

The initial stress factors used were acid, base, oxidation, thermal, and photolytic conditions in accordance with ICH guidelines. Forced Acid degradation experiment of febuxostat was performed as per the ICH guidelines. An acid degradation study was carried out with 300mg of febuxostat in 1N HCl for 2hrs under reflux conditions at 60°C with a total degradation of 21.12% observed and the UPLC-MS chromatogram was shown in Fig-1 and the confirmed degradation products structures are shown in Fig-2. The resultant degradation reaction mass from the acid degradation stress study was neutralized with a diluted ammonia solution, lyophilized to produce a solid sample which was dissolved in water and acetonitrile (70:30) for purification.

2.4. Isolation of febuxostat degradation products

Acetonitrile and 0.1% aqueous formic acid were used as the mobile phase in the purification process, and the column used was the Sunfire C18 250mm x 19mm x 5µm. Following the infusion of successive raw sample solutions, the fractions were collected based on the mass parameter ion chromatograms. Following the degradation process, the degradation components were purified using semi-preparative HPLC to collect each fraction, which was then lyophilized to collect free solids.

3. RESULTS AND DISCUSSION

3.1. Structural confirmation of degradation product-1

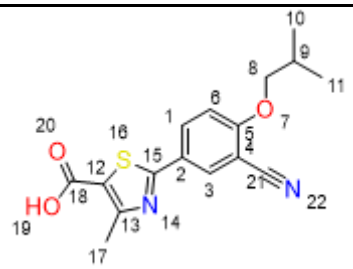
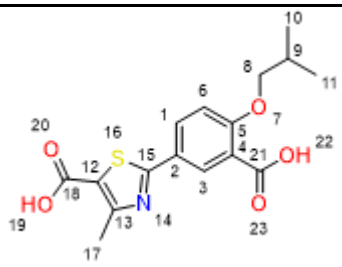
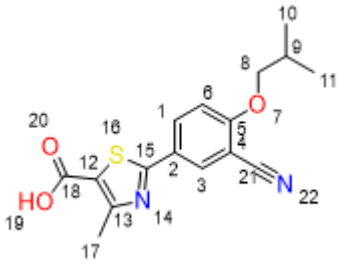
The known DP-1 was purified using febuxostat under stress-acid conditions and received first mass confirmation from UPLC-MS, The HRMS data predicted the chemical formula of $C_{16}H_{17}NO_5S$ for known DP and it is correlated with the MS spectra obtained from the UPLC-MS. According to the HRMS analysis, the mass is 336.0893 (positive mode) [Table 2]. Table 3 compares the chemical shift values and splitting pattern of ^{1}H-NMR and ^{13}C-NMR for known DP to the febuxostat API values. Two signals at 13.16 ppm in proton NMR indicate the presence of acid groups in the recognized DP structure. In the aromatic region, three protons were present at 7.22 ppm, 8.04 ppm, and 8.22 ppm and there is no splitting change from

the parent compound indicating the presence of the aromatic ring. In the aliphatic region methyl group protons are at 2.66 ppm, and isobutoxy group protons are at 0.99 ppm, 2.05 ppm and 3.89 ppm respectively. In ^{13}C NMR, the key change from the parent compound is missing nitrile carbon at 115.35 ppm and the presence of acid carbonyl carbon at 166.59 ppm, remaining carbons signals present at 110 ppm to 170 ppm, methyl, and isobutoxy carbons are shown at 15 ppm to 80 ppm, HSQC experiments conducted to distinguish the protonated carbons from quaternary carbons. Finally, in the HMBC experiment observed the key correlation is the H3 proton showing 3J connectivity to C21 carbon. All the NMR and HRMS data for the DP are attached in the supplementary section. All the above experimental data confirms that the nitrihydrolyzed as hydrolysed and converted to the acid group and the structure was 2-(3-carboxy-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid and is shown in Fig-3 & 4.

Table 2
HRMS data for febuxostat API and its acid degradation products

Product name	Formula	M + H calculated	M + H obtained	Mass error (ppm)
Febuxostat	$C_{16}H_{16}O_3N_2S$	317.0960	317.0948	-2.0520
DP-1 (Known)	$C_{16}H_{17}O_5NS$	336.0906	336.0893	-2.0452
DP-2	$C_{17}H_{18}N_2O_3S$	331.1116	331.1107	-1.2462
DP-3	$C_{17}H_{19}O_5NS$	350.1062	350.1060	0.9073
DP-4	$C_{18}H_{21}O_5NS$	364.1219	364.1207	-1.7619

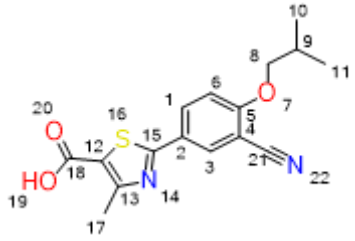
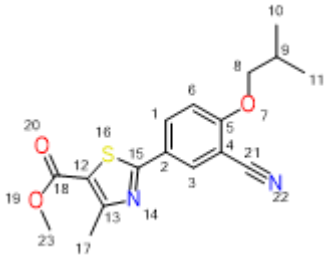
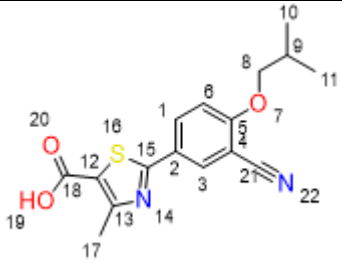
Table 3: Relative NMR assignments for DP-1 and DP-3

 Febuxostat API Exact Mass: 316.09				 DP-1 (Known) Exact Mass: 335.08			 DP-3 Exact Mass: 349.10		
Atom No	Type of Atom	^{1}H Chemical Shift (ppm) Coupling Const (J)	^{13}C Chemical Shift (ppm)	Type of Atom	^{1}H Chemical Shift (ppm) Coupling Const (J)	^{13}C Chemical Shift (ppm)	Type of Atom	^{1}H Chemical Shift (ppm) Coupling Const (J)	^{13}C Chemical Shift (ppm)
1	CH	8.19 (dd, 8.8Hz, 2.4Hz,1H)	133.01	CH	8.06 (dd, 8.8Hz, 2.4Hz,1H)	131.1	CH	8.06 (dd, 8.8Hz, 2.4Hz, 1H)	131.21
2	C	-	125.33	C	-	124.17	C	-	123.95
3	CH	8.27(d, 2.4Hz,1H)	131.5	CH	8.22 (d, 2.4Hz,1H)	128.68	CH	8.23 (d, 2.4Hz, 1H)	128.79
4	C	-	101.52	C	-	122.07	C	-	122.15
5	C	-	162.03	C	-	159.71	C	-	159.88
6	CH	7.35 (d, 8.4Hz,1H)	113.85	CH	7.22 (d, 8.4H,1H)	113.97	CH	7.23 (d,8.8Hz, 1H)	114.02
7	-	-	-	-	-	-			
8	CH_2	3.99(dd, 6.4Hz,2H)	75.09	CH_2	3.89(d, 6.4Hz,2H)	74.53	8	CH_2	3.89 (d,6.4Hz,2H)
9	CH	2.09(m, 6.8Hz,1H)	27.56	CH	2.05(m, 6.4Hz, 1H)	27.73	9	CH	2.03 (m, 6.4Hz, 1H)
10,11	CH_3	1.01(d, 6.4Hz,6H)	18.68	CH_3	0.99(d,6.8Hz,6H)	18.85	10,11	CH_3	0.99(d,6.8Hz,6H)
12	C	-	122.89	C	-	122.02	12	C	-
13	C	-	159.48	C	-	159.58	13	C	-
14	-	-	-						
15	C	-	166.16	C	-	167.46	C	-	168.13
17	CH_3	2.66 (s,3H)	17	CH_3	2.66 (s,3H)	17.03	CH_3	2.68 (s,3H)	17.16
18	CO	-	162.81	CO	-	162.88	CO	-	161.83
19	OH	-	13.4	OH	13.16(broad hump, 1H)	-	-	-	-
21	CN	-	115.35	CO	-	166.59	CO	-	166.6
22	-	-	-	OH	13.16(broad hump,1H)	-	OH	12.92 (broad hump,1H)	-
23	-	-	-	-	-	-			
24	-	-	-	-	-	-	CH_3	3.83(s, 3H)	52.32

3.2. Structural confirmation of degradation product-2

Febuxostat on acid stress conditions, the isolated DP-2 was purified and taken preliminary confirmation from UPLC-MS, The molecular formula of $C_{17}H_{18}N_2O_3S$ for the DP-2 was predicted by HRMS analysis data and is correlated with the MS spectra obtained from the UPLC-MS. This compound has a molecular mass 14 units higher than the parent compound. The mass obtained in HRMS analysis is 331.1107 (positive mode) [Table 2]. In ^{1}H NMR a total 18 number of protons were shown, a major change from the API compound is the presence of methoxy protons at 3.84 ppm and the remaining protons are the same from API. In ^{13}C NMR a total 16 number of signals were showing, due to the symmetry of methyl carbons in the isobutyl group one carbon showed them at 18.67 ppm, ester methyl carbon at 52.39 ppm, nitrile carbon showed at 115.31 ppm, aromatic carbon signals were shown between 100 ppm to 170 ppm and aliphatic carbon were at 10ppm to 80 ppm [Table 4]. In the HSQC experiment ester methyl chemical shift was confirmed with 1J-^{1}H-^{13}C connectivity between H23 proton to C23 carbon. In the HMBC experiment, H23 protons showed 3J connectivity to C18 carbon and H3 proton showed 3J connectivity to Nitrile(C21) carbon [Figure 4]. All the NMR and HRMS data for the DP-1 are attached in the supplementary section. All the above information confirms that esterification happened for the carboxylic acid of the thiazole ring, the presence of nitrile group in the compound as methyl 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylate and is mentioned in Fig-3 & 4.

Table 4: Relative NMR assignments for DP-2 and DP-4

 Febuxostat Exact Mass: 316.09				 DP-2 Exact Mass: 330.10			 DP-4 Exact Mass: 363.11		
Atom No	Type of Atom	^{1}H Chemical Shift (ppm) Coupling Const (J)	^{13}C Chemical Shift (ppm)	Type of Atom	^{1}H Chemical Shift (ppm) Coupling Const (J)	^{13}C Chemical Shift (ppm)	Type of Atom	^{1}H Chemical Shift (ppm) Coupling Const (J)	^{13}C Chemical Shift (ppm)
1	CH	8.19 (dd, 8.8Hz, 2.4Hz, 1H)	133.01	CH	8.23 (dd, 9.2Hz, 2.4Hz,1H)	133.15	CH	8.10 (dd, 8.4Hz, 1H)	131.8
2	C	-	125.33	C	-	125.11	C	-	124.04
3	CH	8.27 (d, 2.4Hz, 1H)	131.5	CH	8.32 (d, 2.4Hz, 1H)	131.68	CH	8.27 (d, 2.0Hz, 1H)	128.86
4	C	-	101.52	C	-	101.58	C	-	120.61
5	C	-	162.03	C	-	162.2	C	-	160.01
6	CH	7.35 (d, 8.4Hz, 1H)	113.85	CH	7.28 (d, 8.8Hz,1H)	113.94	CH	7.26 (d, 9.2Hz,1H)	128.86
7				-	-	-			
8	CH_2	3.99 (dd, 6.4Hz, 2H)	75.09	CH_2	4.01 (d, 6.4Hz, 2H)	75.13	CH_2	3.90 (d, 6.0Hz, 2H)	74.64
9	CH	2.09 (m, 6.8Hz, 1H)	27.56	CH	2.07 (m, 6.8Hz, 1H)	27.54	CH	2.05 (m, 6.4Hz,1H)	27.74
10,11	CH_3	1.01 (d, 6.4Hz, 6H)	18.68	CH_3	1.01 (d, 6.4Hz, 6H)	18.67	CH_3	1.00 (d, 6.4Hz,6H)	18.81
12	C	-	122.89	C	-	120.99	C	-	120.34
13	C	-	159.48	C	-	160.32	C	-	160.43
14				-	-	-			
15	C	-	166.16	C	-	166.83	C	-	167.92
17	CH_3	2.66 (s, 3H)	17	CH_3	2.68 (s, 3H)	17.12	CH_3	2.68 (s, 3H)	17.14
18	CO	-	162.81	CO	-	161.74	CO	-	161.81
19	OH	-	13.4	OH	-	13.4	-	-	-
21	CN	-	115.35	CN	-	115.31	CO	-	165.33
22				-	-	-			
23				CH_3	3.84 (s, 3H)	52.39			
24	-	-	-	-	-	-	CH_3	3.83 (s, 3H)	52.34
25	-	-	-	-	-	-	CH_3	3.83 (s, 3H)	52.08

3.3. Structural confirmation of degradation product-3

Febuxostat on acid stress conditions, the DP-3 was purified and taken preliminary confirmation from UPLC-MS, in which the molecule has positive ionization and shown $[M+H]^+$ - 350.1060 Table 2 & Fig-3. The molecular formula of $C_{17}H_{19}O_5NS$ for the DP-3 was predicted by HRMS analysis data and is

correlated with the MS spectra obtained from the UPLC-MS. This compound has a molecular mass 14 units higher than the known degradation product indicating the esterification of one of the COOH groups in the known degradation product which is confirmed by the signal at 3.83 ppm and one acid remains as such at the signal at 12.92 ppm [Table 3]. ^{13}C NMR shows a total 17 number of carbons, one carbon being excess than the parent compound, key observation in ^{13}C NMR is the absence of Nitrile carbon, and the presence of carboxylic acid carbon at 166.60 ppm. In the HSQC experiment, H24 protons attached carbon is shown at 52.32 ppm, this information confirms the presence of methyl ester in the compound, to know the esterification position HMBC experiment is mandatory [Figure 5]. In the HMBC experiment, H24 protons showed 3J connectivity to C18 carbon and H3 proton showed 3J connectivity to C21 carbon, this key correlation confirms the esterification and carboxylic acid of thiazole ring and nitrile group hydrolyzed as carboxylic acid on 1,2,5 tri-substituted ring hydrolyzed as 2-isobutoxy-5-(5-(methoxycarbonyl)-4-methylthiazol-2-yl) benzoic acid.

3.4. Structural confirmation of degradation product-4

Febuxostat on acid stress conditions, the DP-4 was purified and taken preliminary mass confirmation from UPLC-MS, in which the molecule has positive ionization and shown $[M + H]^+$ - 364.1206 [Table 2 & Fig-3]. The molecular formula of $C_{18}H_{21}NO_5S$ for the DP-4 was predicted by HRMS analysis data and is correlated with the MS spectra obtained from the UPLC-MS. This compound has molecular mass 28 units higher than the known degradation product indicating the esterification of both acid groups present in the known degradation product which is confirmed by the presence of signals at 3.83 ppm [Table 4]. The isobutyl group protons are found at 1.0 ppm, 2.05 ppm, and 3.90 ppm and the methyl signal showed at 2.68 ppm. In ^{13}C NMR ester carbonyl carbons showed at 161.81 ppm and 165.33 ppm and ester methyl carbons showed at 52.08 ppm and 52.34 ppm, missing nitrile carbon. HSQC experiment confirms the C19 and C24 carbons shifts with 1J- ^{1}H-^{13}C correlation. In the HMBC experiment H25 protons showed a 3J correlation to C18 carbon and H24, H3 protons showed 3J connectivity to C21 carbon [Figure 5]. Finally concluded the structure of DP-4 as, initially nitrile group was hydrolyzed into the acid group after that esterification happened on two carboxylic acids as methyl 2-(4-isobutoxy-3-(methoxycarbonyl)phenyl)-4-methylthiazole-5-carboxylate and is mentioned in [Figure 2].

4. CONCLUSION

Stress degradation of febuxostat API in acid condition indicates the formation of one known degradation product (DP-1) and three novel degradation products (DP-2, DP-3 and DP-4). Utilizing preparative HPLC, the degradation products' structures were successfully isolated and determined by UPLC-MS, HRMS, and NMR (1H, 13C, and 2D) spectroscopic methods. Hence, it can be suggested that methanol is not preferable as a co-solvent for stress degradation of febuxostat API.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Mr. Rajesh Kanagaddi carried out all the experimental analyses and purifications in this research paper. Mrs. Vaishnavi Chintala supported in conceptualisation and resources. Prof. Satya Sree Nannapaneni contributed to the theoretical analysis and participated in the design of the work and supervision. Dr. Naresh Kumar Katari helped in comparing theoretical and experimental test results and drafted the manuscript. Mr. Suresh Salakolusu was involved in the HRMS of degradation products, helped in manuscript design and finalization. Mr. Mahesh Ranga was supported for the NMR analysis of degradation products. Dr. JNSRC Murty has prepared the manuscript and participated in the interpretation of degradation products. Dr. Muralidharan Kaliyapermal helped in the literature collection and execution of the work..

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Conflicts of interest

The authors declare that they have no conflict of interests

Consent for publication

We authorize to the publication of the article without any conflict.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article [and its supplementary information files].

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Figures

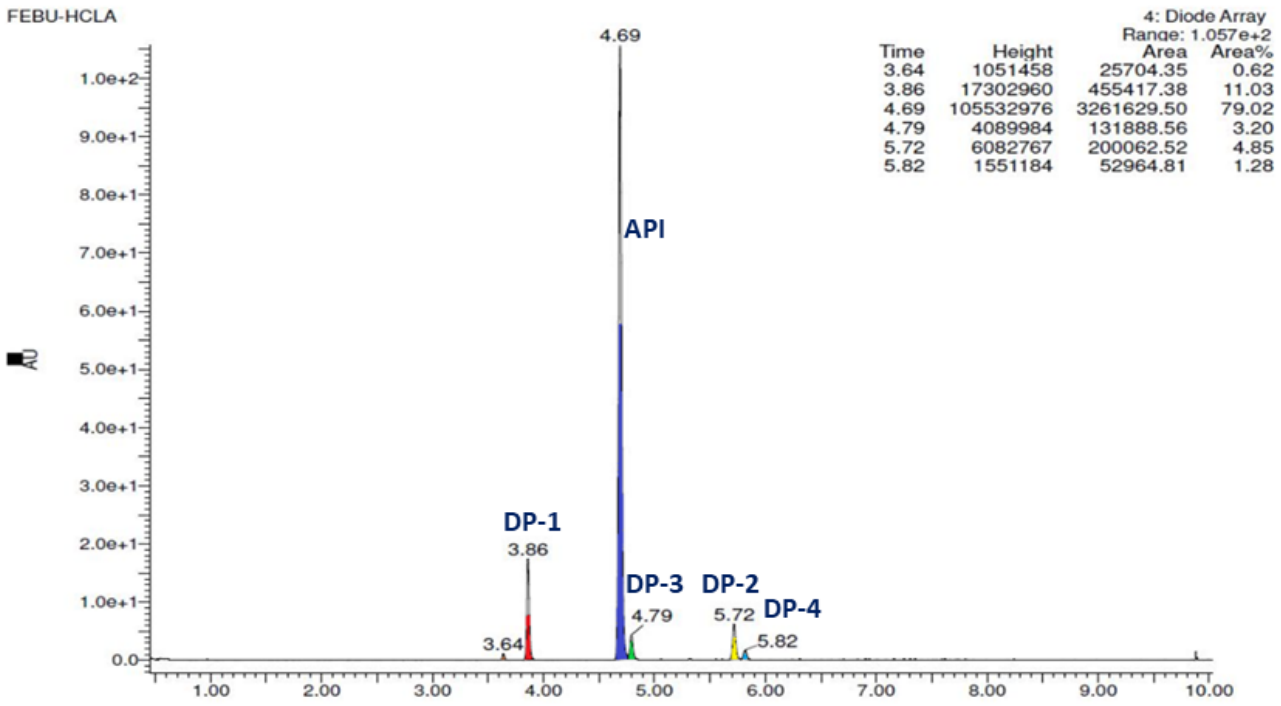

Figure 1

UPLC-MS Report for the acid degradation behaviour of Febuxostat API

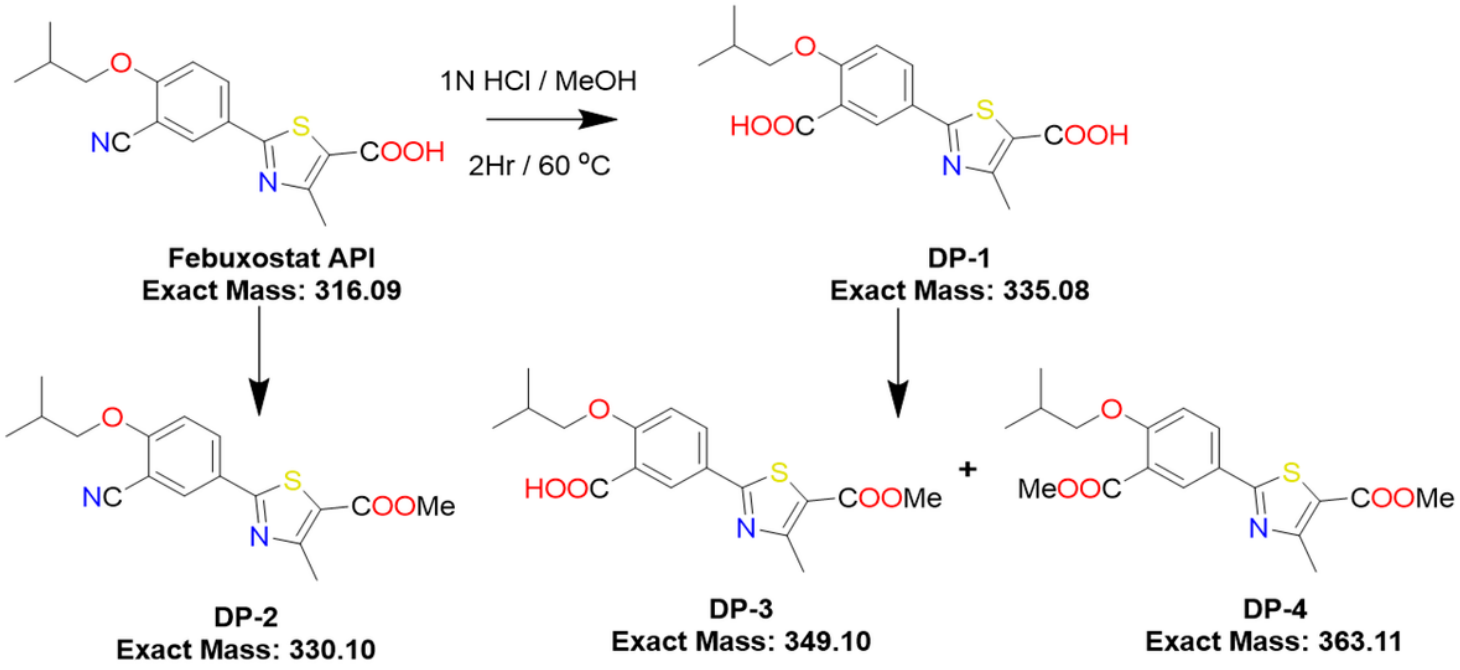

Figure 2

Acid degradation behaviour of febuxostat

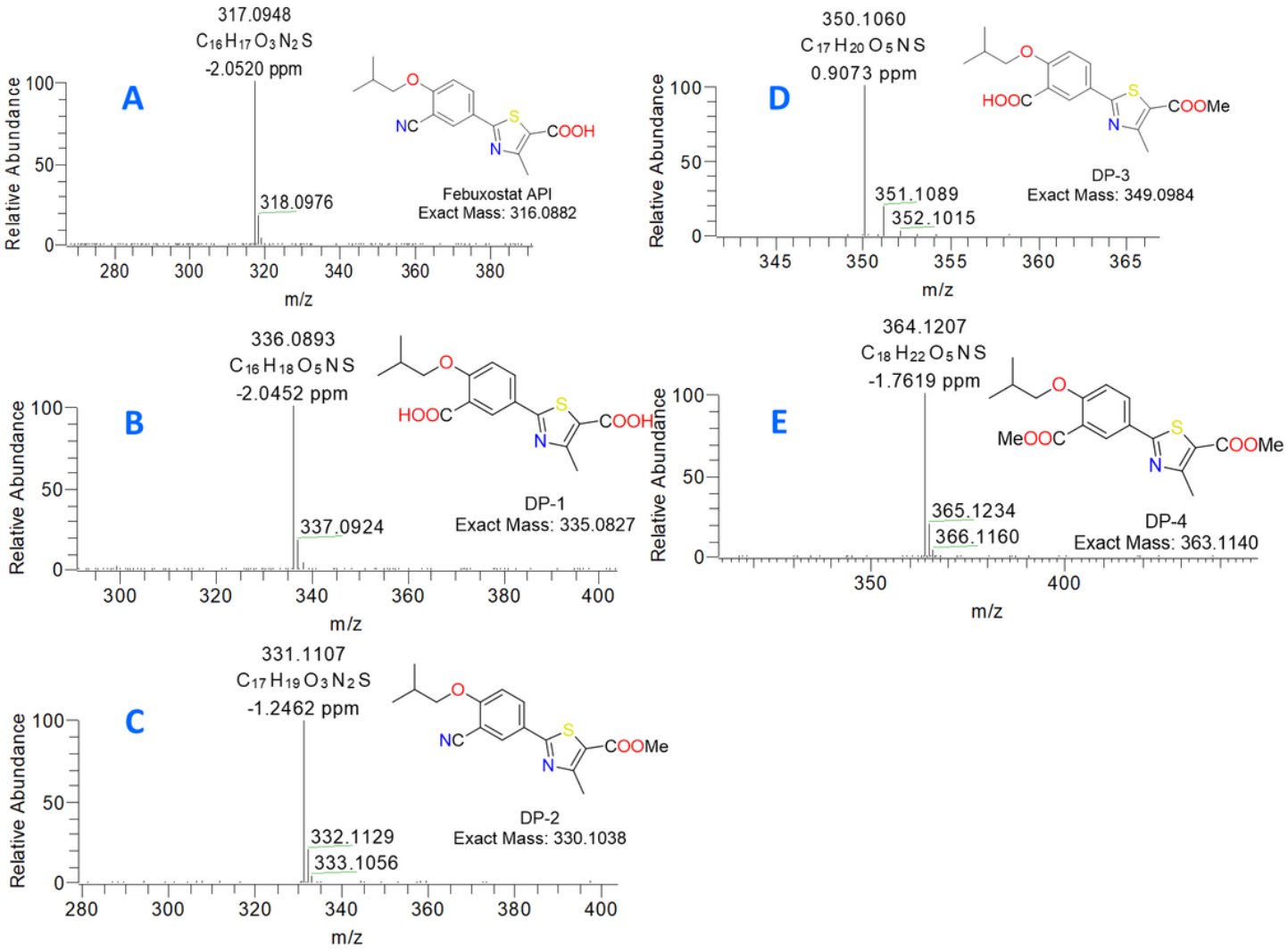

Figure 3

HRMS data for Febuxostat API(A), DP-1(B), DP-2(C), DP-3(D), DP-4(E)

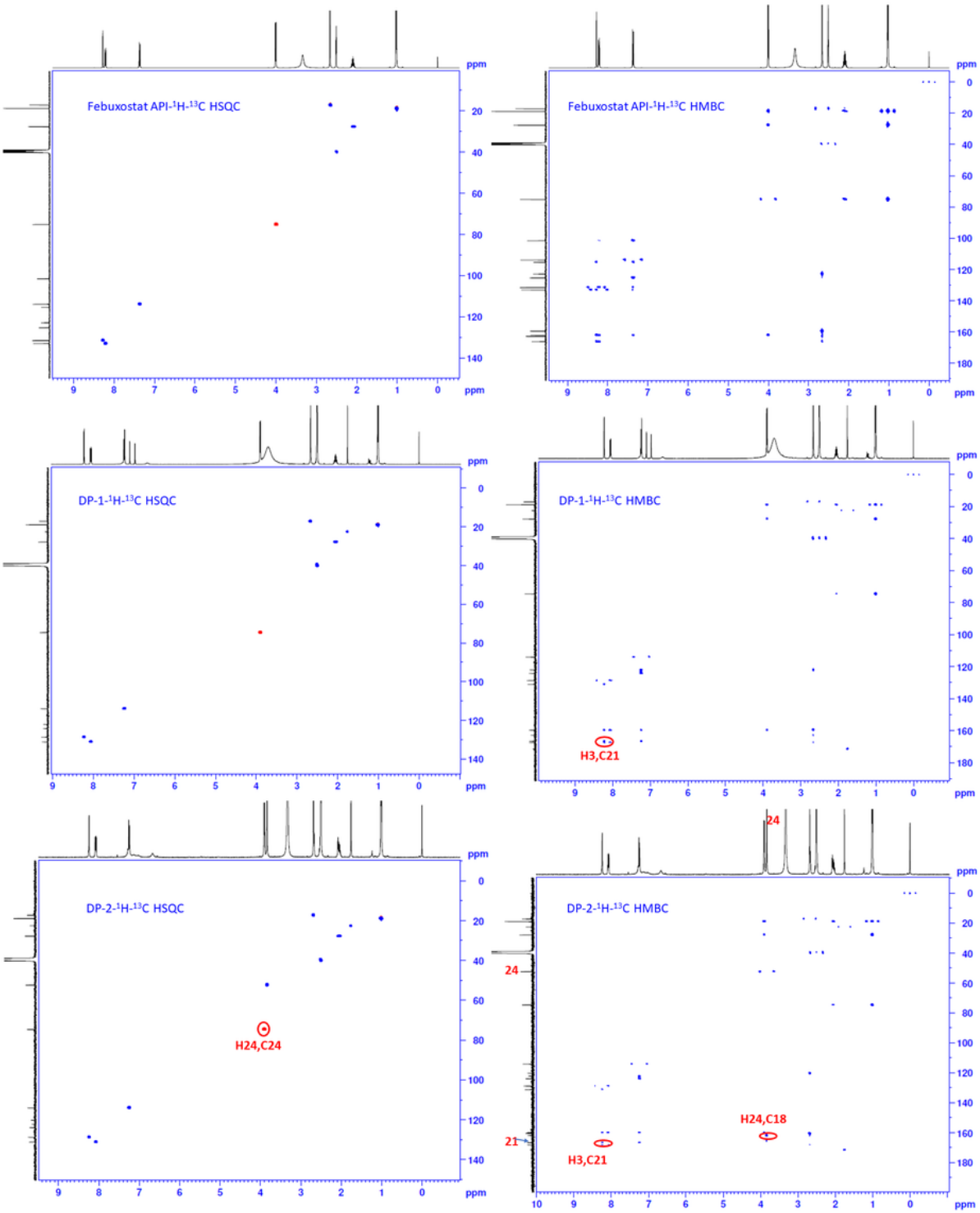

Figure 4

HMBC and HSQC NMR reports for Febuxostat API, DP-1 and DP-2

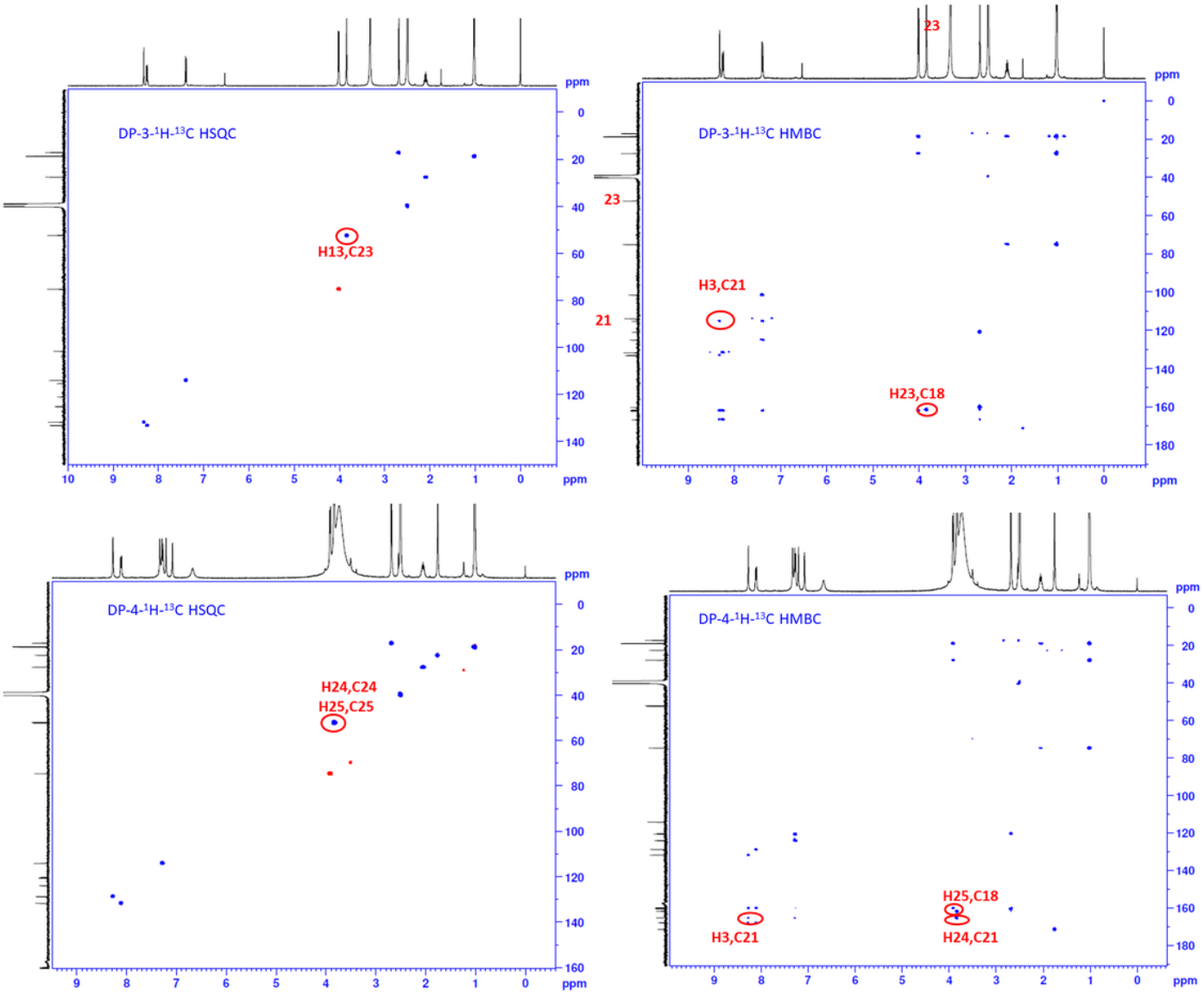

Figure 5

HMBC and HSQC NMR reports for Febuxostat API, DP-3 and DP-4

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS11HNMR13CNMRandHRMSreportsforFebuxostatAPI.docx
- FigureS21HNMR13CNMRandHRMSreportsforFebuxostatDP1.docx
- FigureS31HNMR13CNMRandHRMSreportsforFebuxostatDP2.docx

- FigureS41HNMR13CNMRandHRMSreportsforFebuxostatDP3.docx
- FigureS51HNMR13CNMRandHRMSreportsforFebuxostatDP4.docx