

1/62

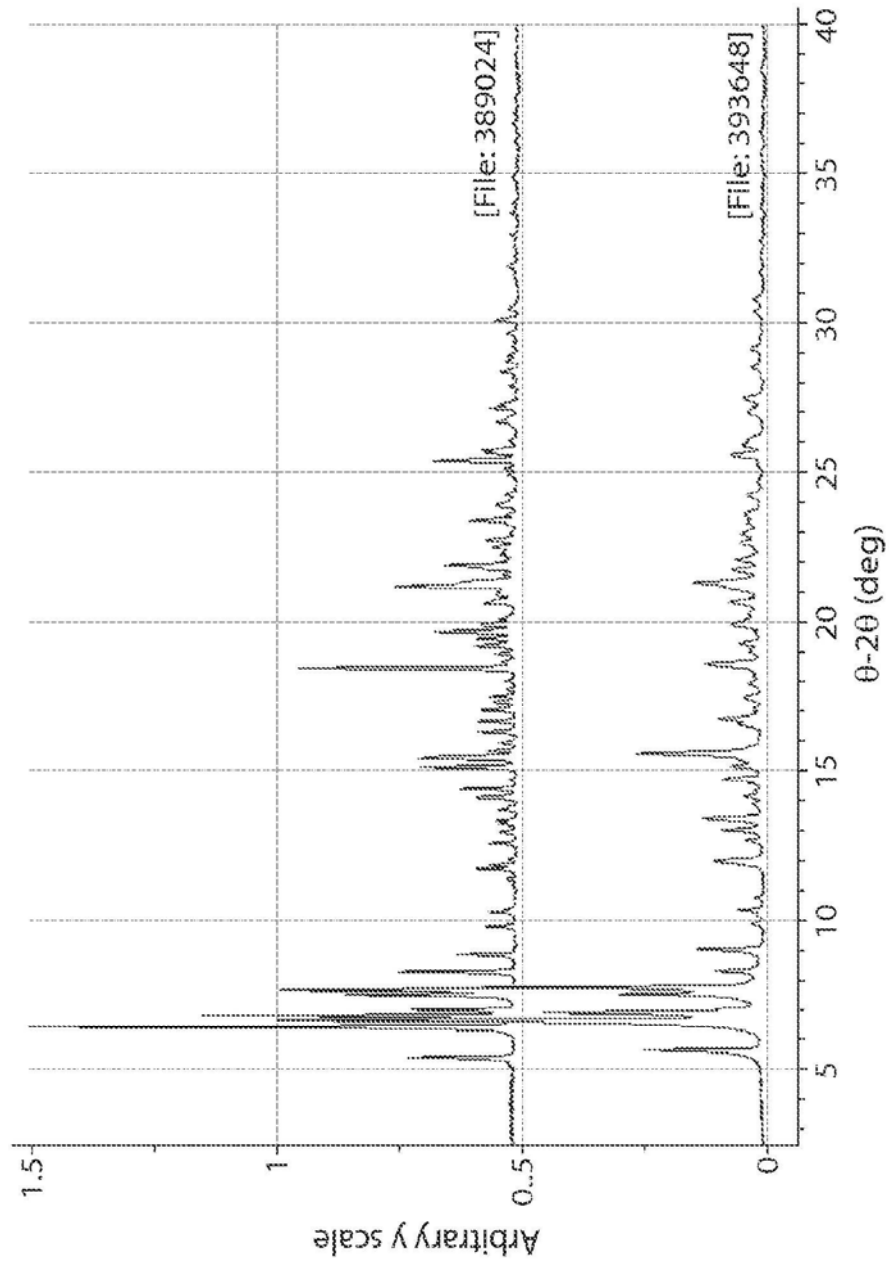


Fig. 1

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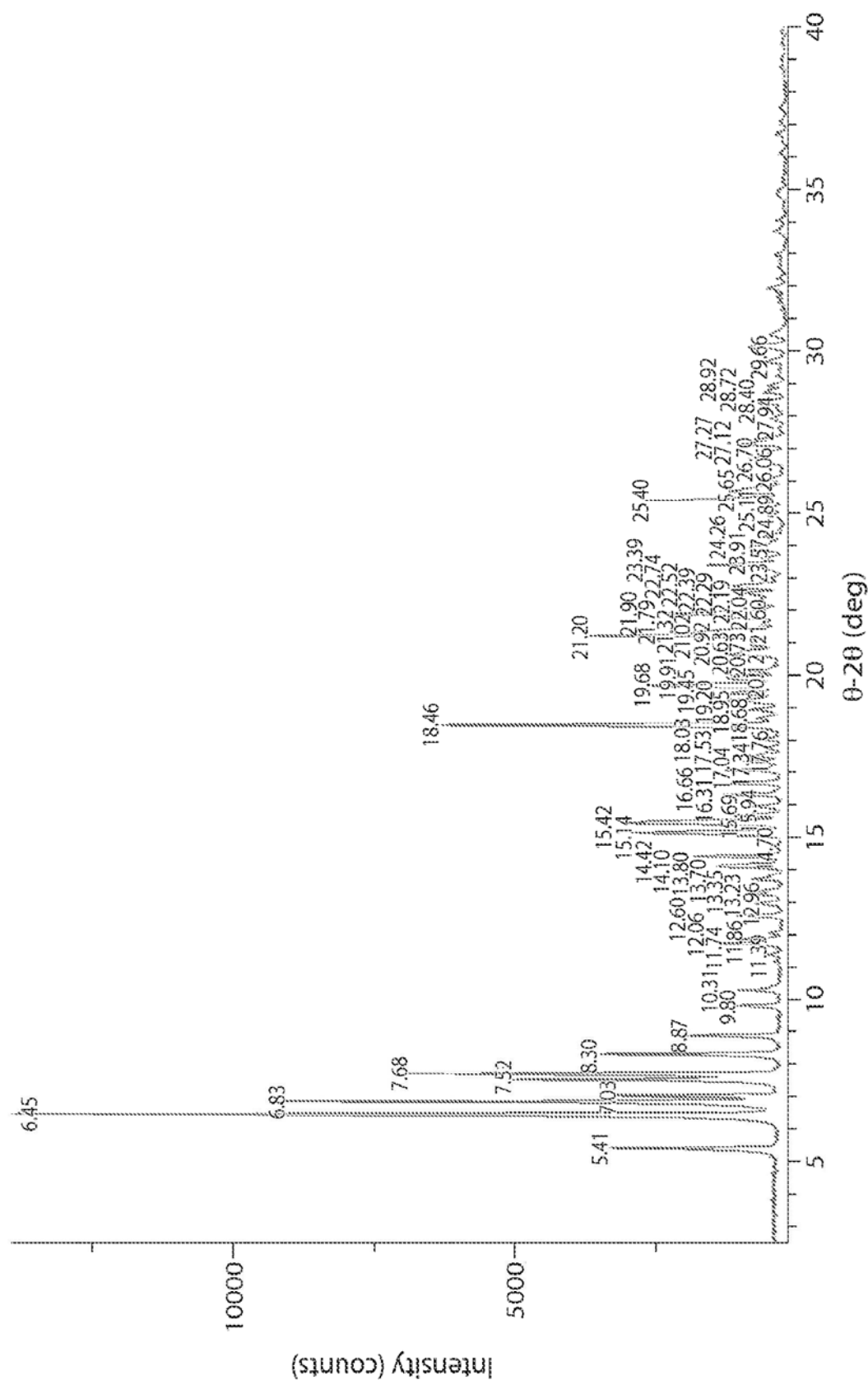


Fig. 2

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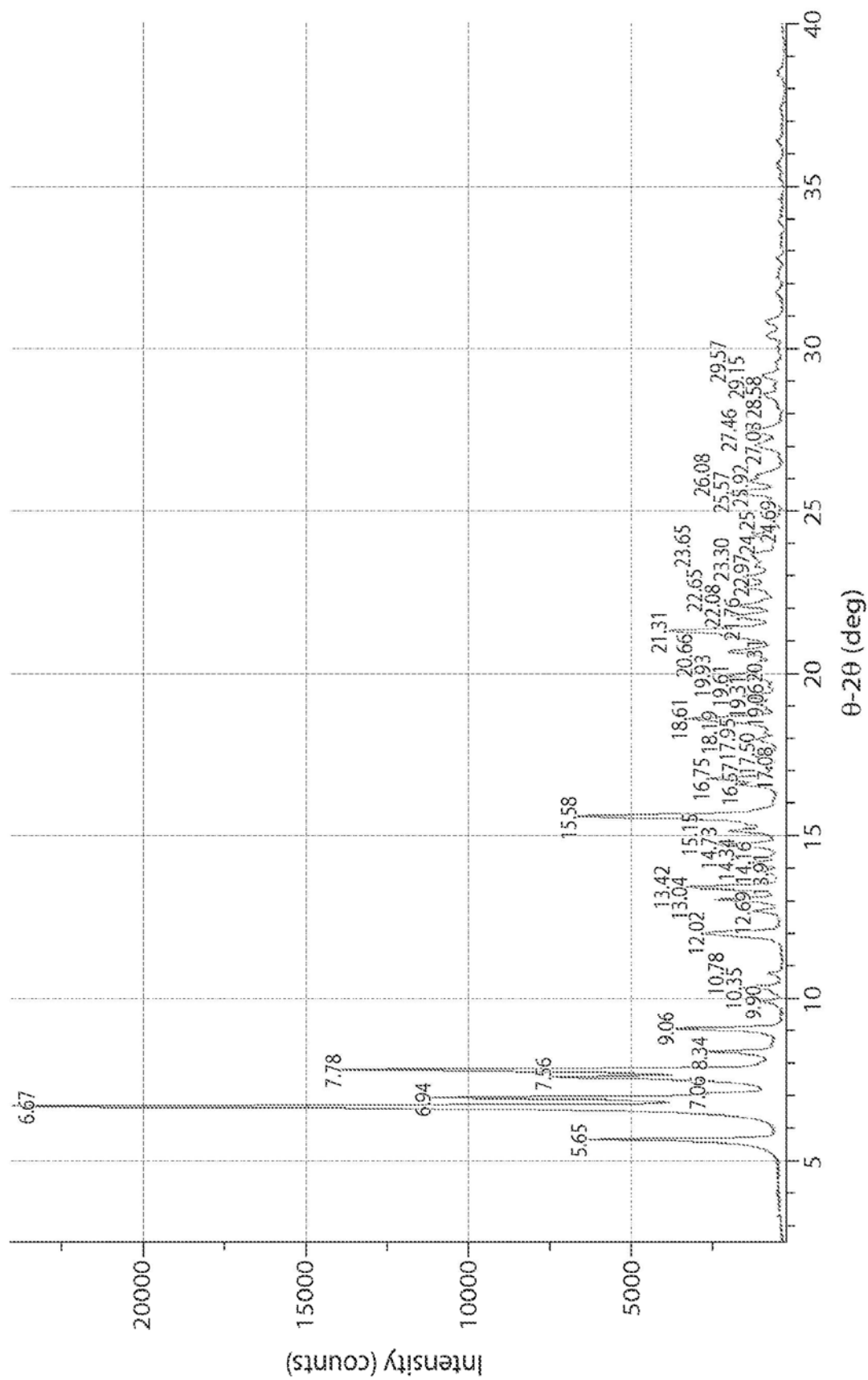


Fig. 3

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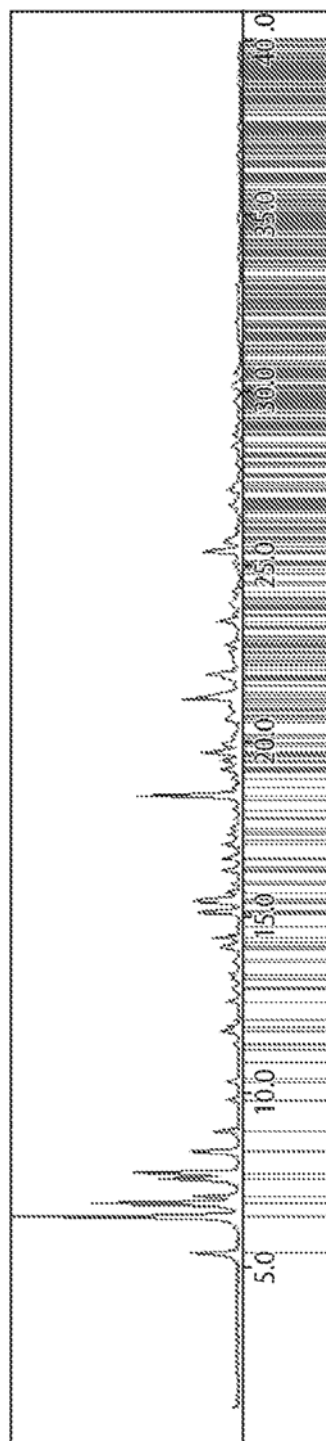


Fig. 4

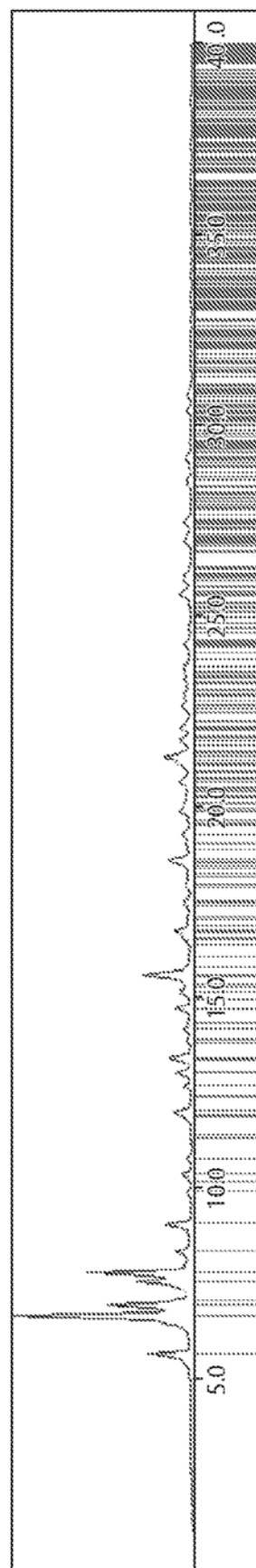


Fig. 5

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DSC

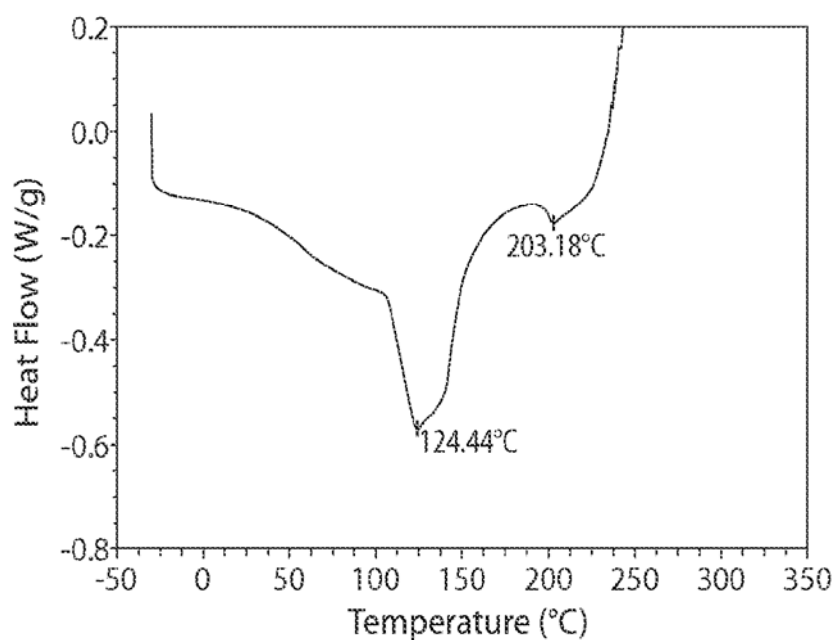


Fig. 6

TGA

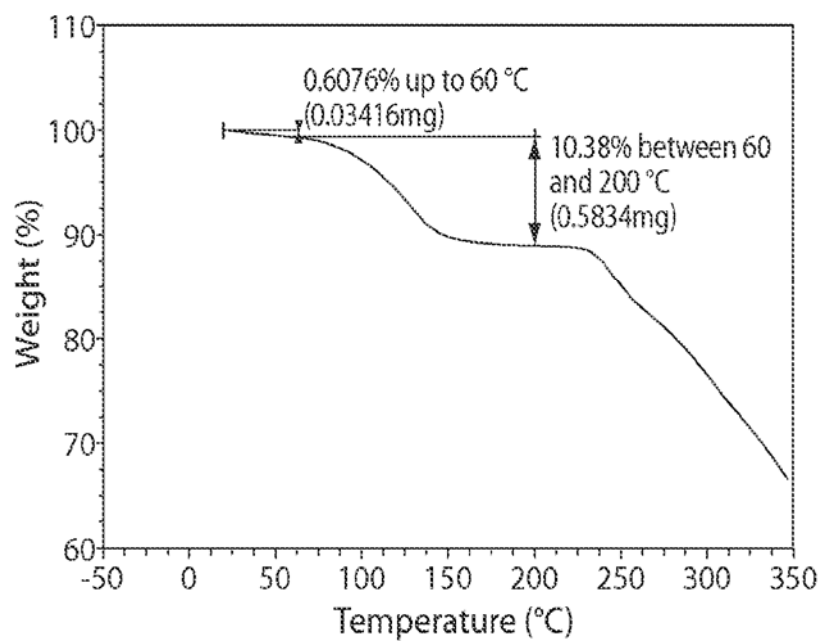


Fig. 7

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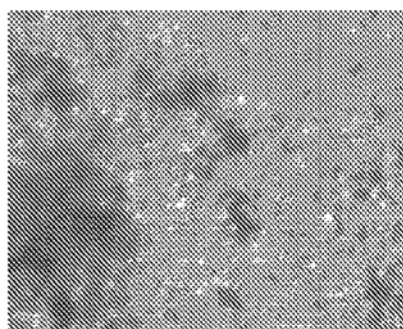


Fig. 8A

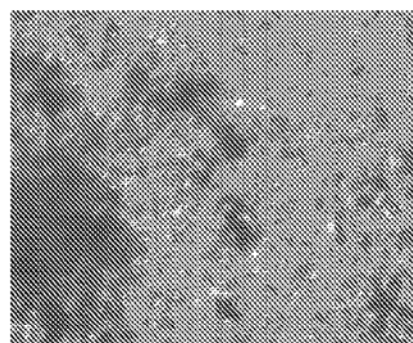


Fig. 8B

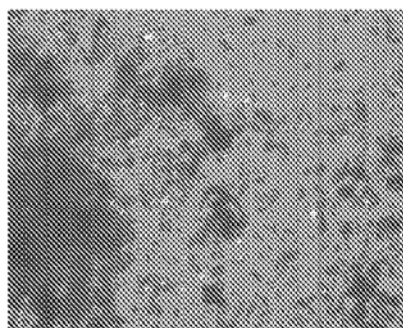


Fig. 8C

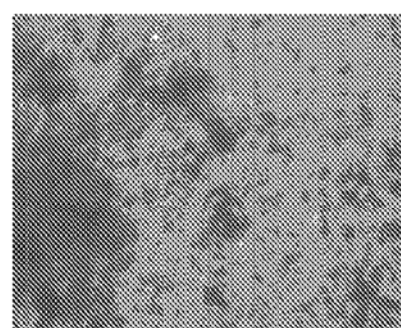


Fig. 8D

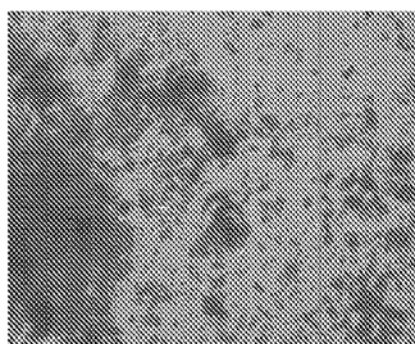


Fig. 8E

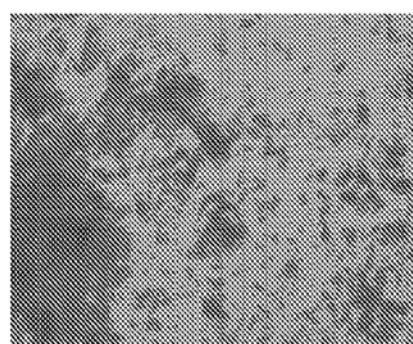


Fig. 8F

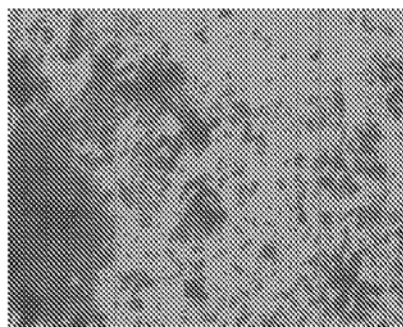


Fig. 8G



Fig. 8H

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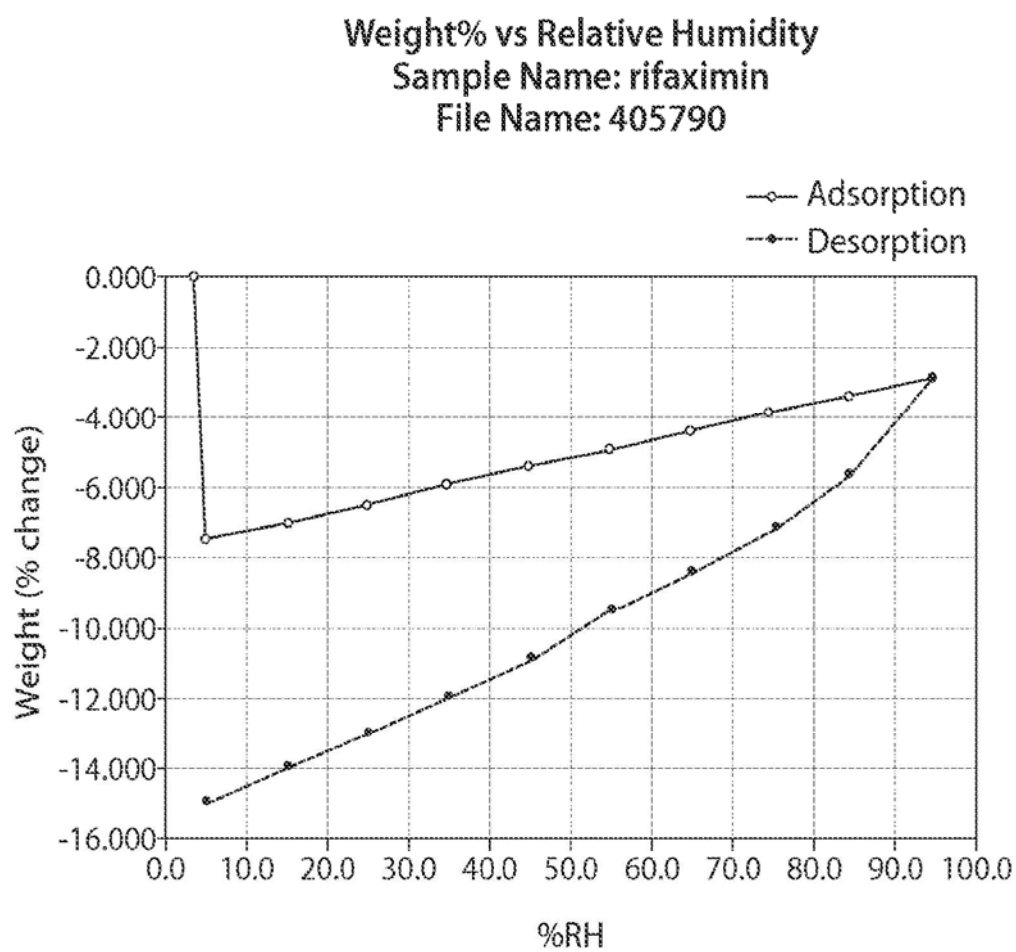


Fig. 9

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File Name 405790.Fsh
 Experiment Temp-RH
 Operator DSO
 Experiment ID 405790
 Sample Name rifaximin
 Sample Lot # 3973-44-03, LIMS #229836
 Notes Range 5% to 95%
 25°C at 10 % increments
 Drying OFF

 Max Equil Time 180 min
 Equil Crit 0.0100 wt % in 5.00min
 T-RH Steps 25, 5; 25, 15; 25, 25; 25, 35; 25, 45; 25, 55; 25, 65; 25, 75;
 25, 85; 25, 95; 25, 85; 25, 75; 25, 65; 25, 55; 25, 45; 25, 35;
 25, 25; 25, 15; 25, 5
 Data Logging Interval 2.00 min or 0.0100 wt %
 Expt Started 6/26/2010
 Run Started 6:21:03

Step	Time min	Elap Time min	Weight mg	Weight % chg	Samp Temp deg C	Samp RH %
n/a		0.1	10.063	0.000	24.82	3.40
175.8		175.9	9.311	-7.479	24.85	4.83
15.6		191.4	9.357	-7.017	24.85	15.11
16.7		208.1	9.410	-6.492	24.85	24.91
15.6		223.7	9.465	-5.947	24.84	34.86
16.1		239.8	9.518	-5.420	24.85	44.84
14.3		254.1	9.568	-4.919	24.85	54.94
14.8		268.9	9.620	-4.407	24.85	64.82
14.5		283.4	9.670	-3.905	24.86	74.51
14.6		298.0	9.720	-3.409	24.85	84.49
15.1		313.0	9.771	-2.903	24.85	94.81
183.7		496.8	9.498	-5.620	24.84	84.60
183.5		680.3	9.346	-7.134	24.85	75.45
149.9		830.1	9.218	-8.402	24.86	65.05
81.0		911.1	9.109	-9.486	24.86	55.15
121.4		1032.5	8.972	-10.848	24.86	45.15
75.7		1108.2	8.862	-11.939	24.86	35.04
68.4		1176.6	8.757	-12.987	24.86	25.02
52.7		1229.2	8.661	-13.932	24.85	15.12
46.8		1276.1	8.561	-14.934	24.85	5.05

Fig. 9
CONTINUED

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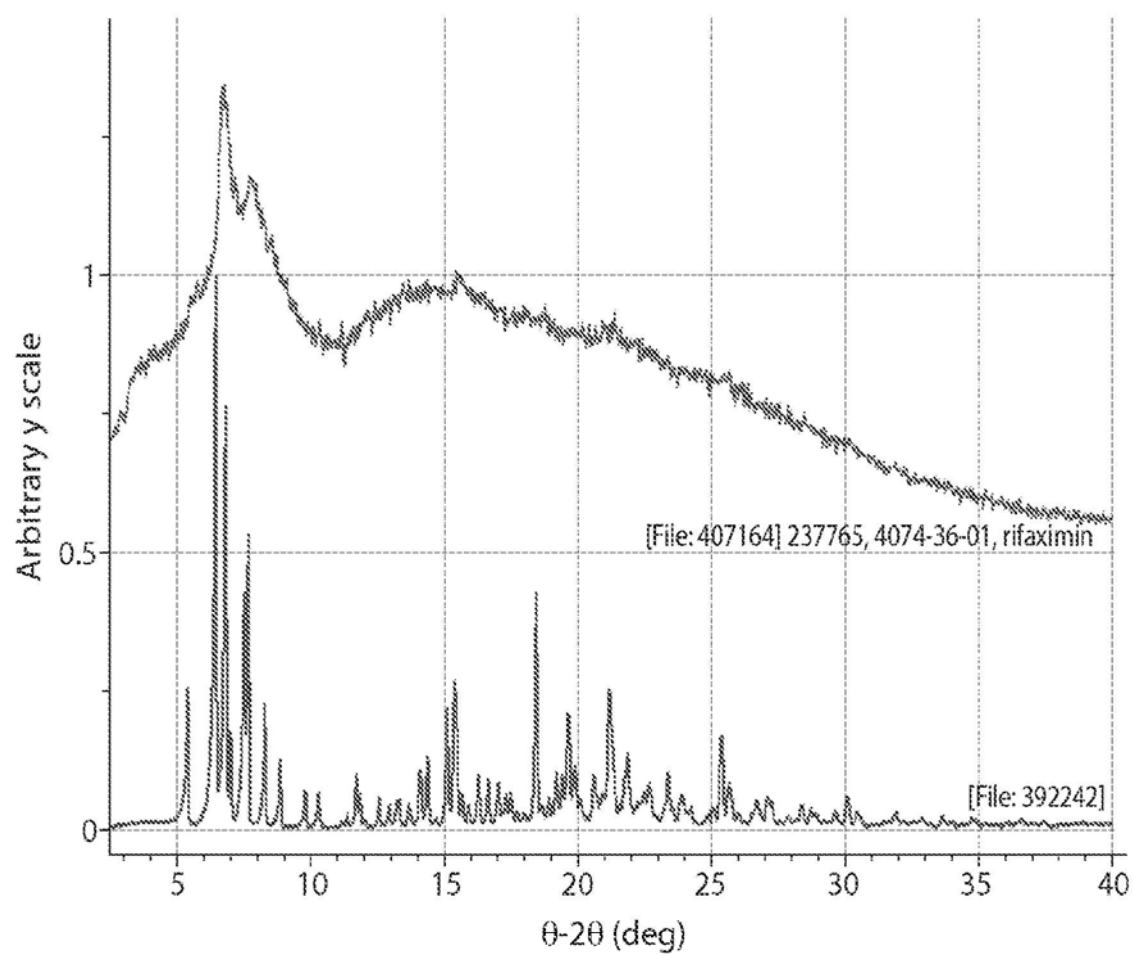


Fig. 10

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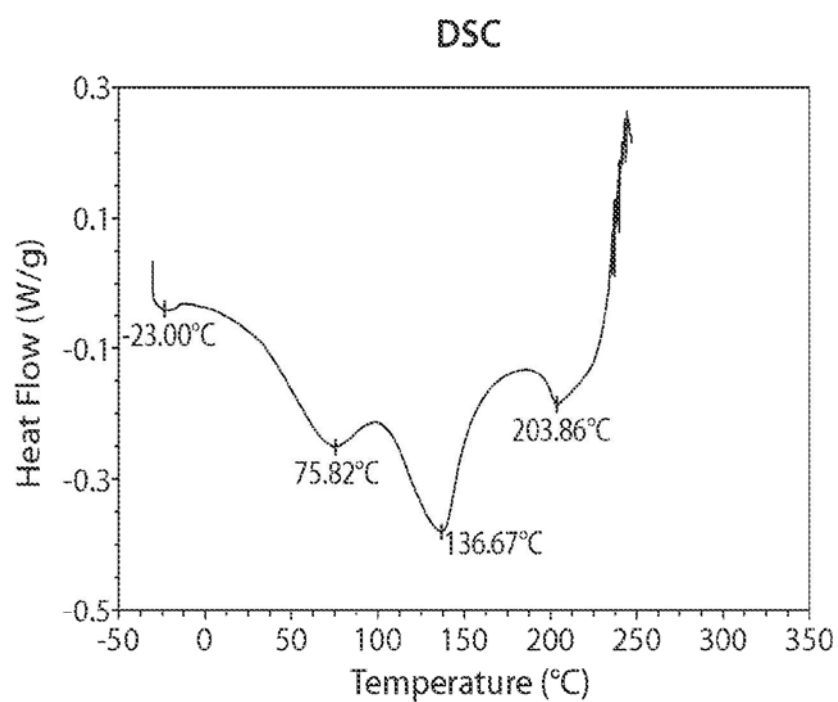


Fig. 11

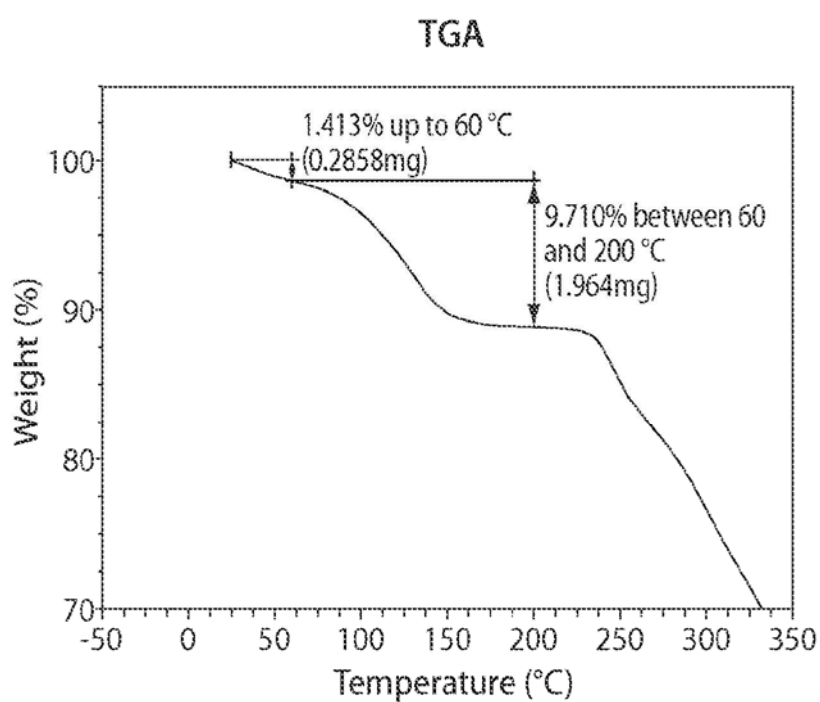


Fig. 12

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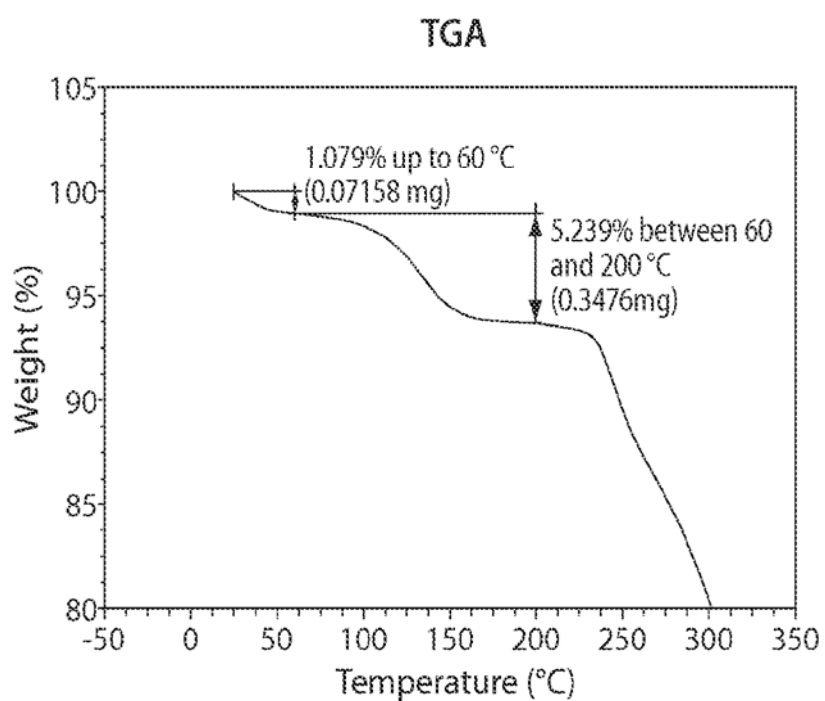


Fig. 13

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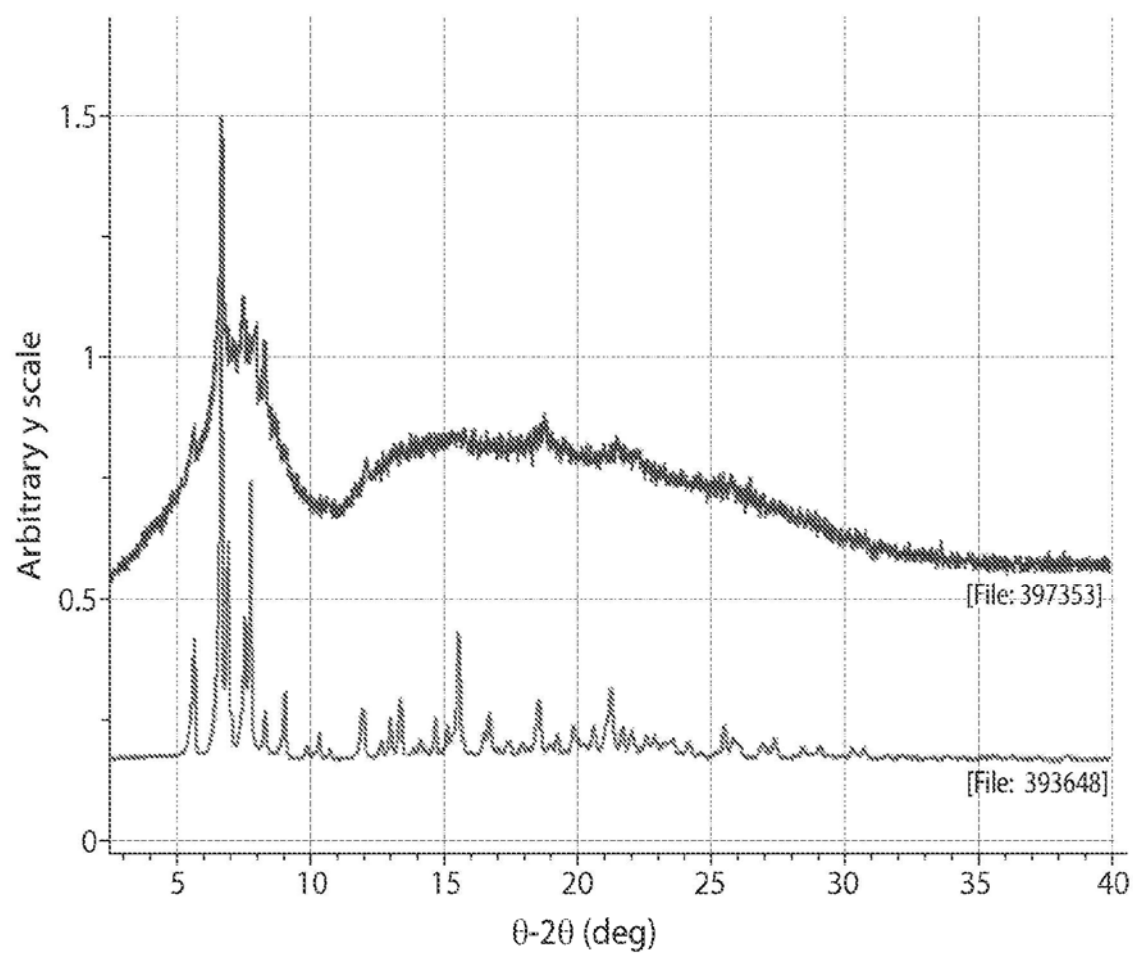


Fig. 14

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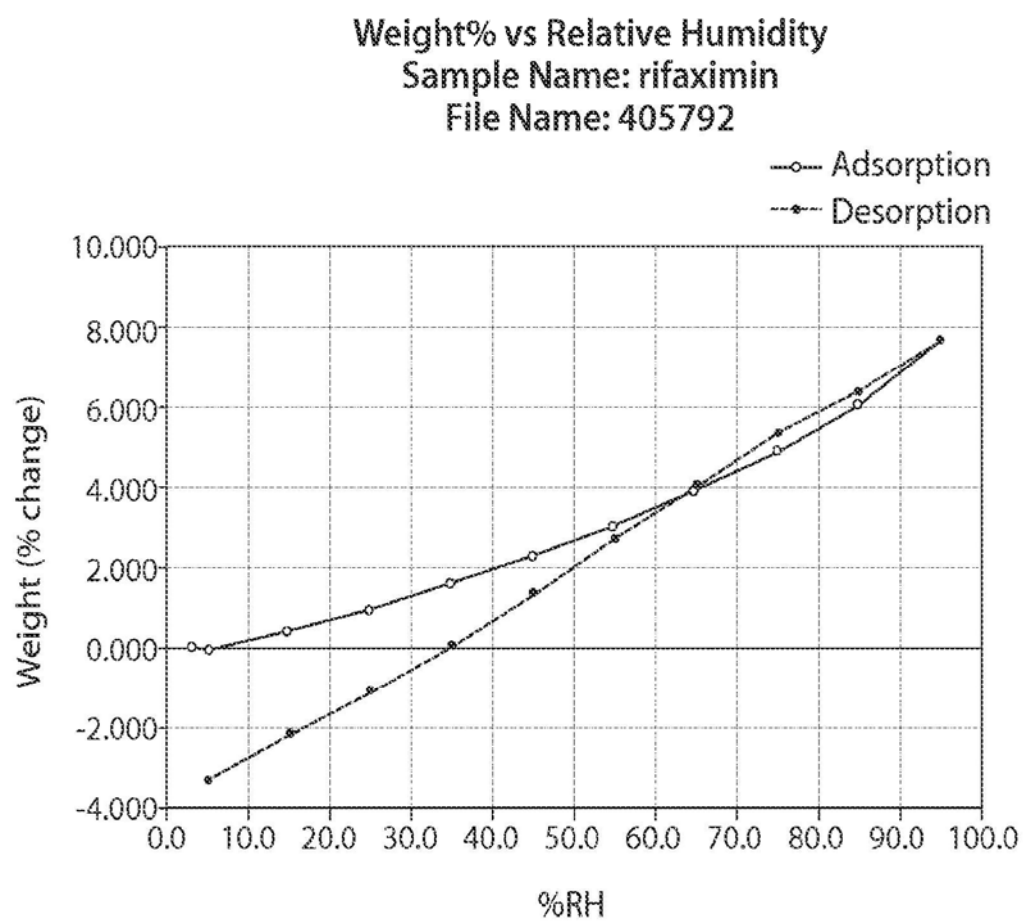


Fig. 15

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File Name 405792.Fsh
 Experiment Temp-RH
 Operator DSO
 Experiment ID 405792
 Sample Name rifaximin
 Sample Lot # 3973-62-01, LIMS #231571
 Notes Range 5% to 95%
 25°C at 10 % increments
 Drying OFF

 Max Equil Time 180 min
 Equil Crit 0.0100 wt % in 5.00min
 T-RH Steps 25, 5; 25, 15; 25, 25; 25, 35; 25, 45; 25, 55; 25, 65; 25, 75;
 25, 85; 25, 95; 25, 85; 25, 75; 25, 65; 25, 55; 25, 45; 25, 35;
 25, 25; 25, 15; 25, 5
 Data Logging Interval 2.00 min or 0.0100 wt %
 Expt Started 6/27/2010
 Run Started 8:28:38

Step Time min	Elap Time min	Weight mg	Weight % chg	Samp Temp deg C	Samp RH %
n/a	0.1	11.041	0.000	24.86	3.08
15.2	15.3	11.033	-0.073	24.87	5.25
20.0	35.2	11.084	0.391	24.87	14.83
22.1	57.3	11.146	0.951	24.86	24.86
30.1	87.3	11.215	1.575	24.84	34.84
39.3	126.6	11.292	2.276	24.84	44.82
39.3	165.9	11.374	3.015	24.85	54.82
48.8	214.6	11.469	3.875	24.85	64.84
63.2	277.8	11.578	4.864	24.86	74.91
74.1	351.8	11.704	6.006	24.85	84.77
107.8	459.6	11.886	7.656	24.86	94.96
157.6	617.2	11.745	6.379	24.86	85.01
92.7	709.9	11.630	5.334	24.85	75.17
117.9	827.8	11.486	4.035	24.86	65.05
113.1	940.9	11.338	2.693	24.86	55.08
103.8	1044.7	11.189	1.342	24.85	45.00
97.5	1142.2	11.046	0.045	24.85	34.97
70.3	1212.4	10.922	-1.078	24.86	25.05
51.6	1264.1	10.801	-2.174	24.86	15.17
45.6	1309.6	10.675	-3.318	24.86	5.13

Fig. 15
CONTINUED

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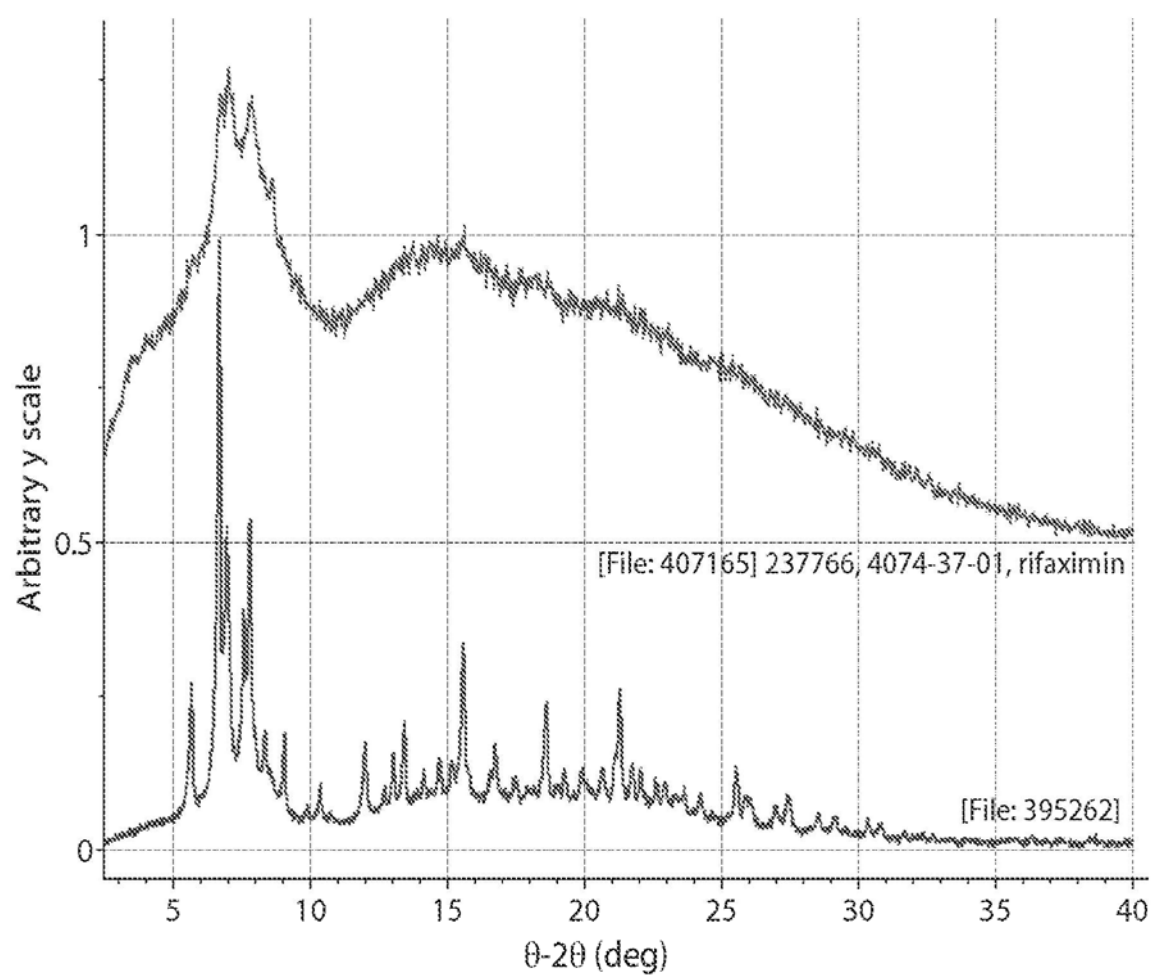


Fig. 16

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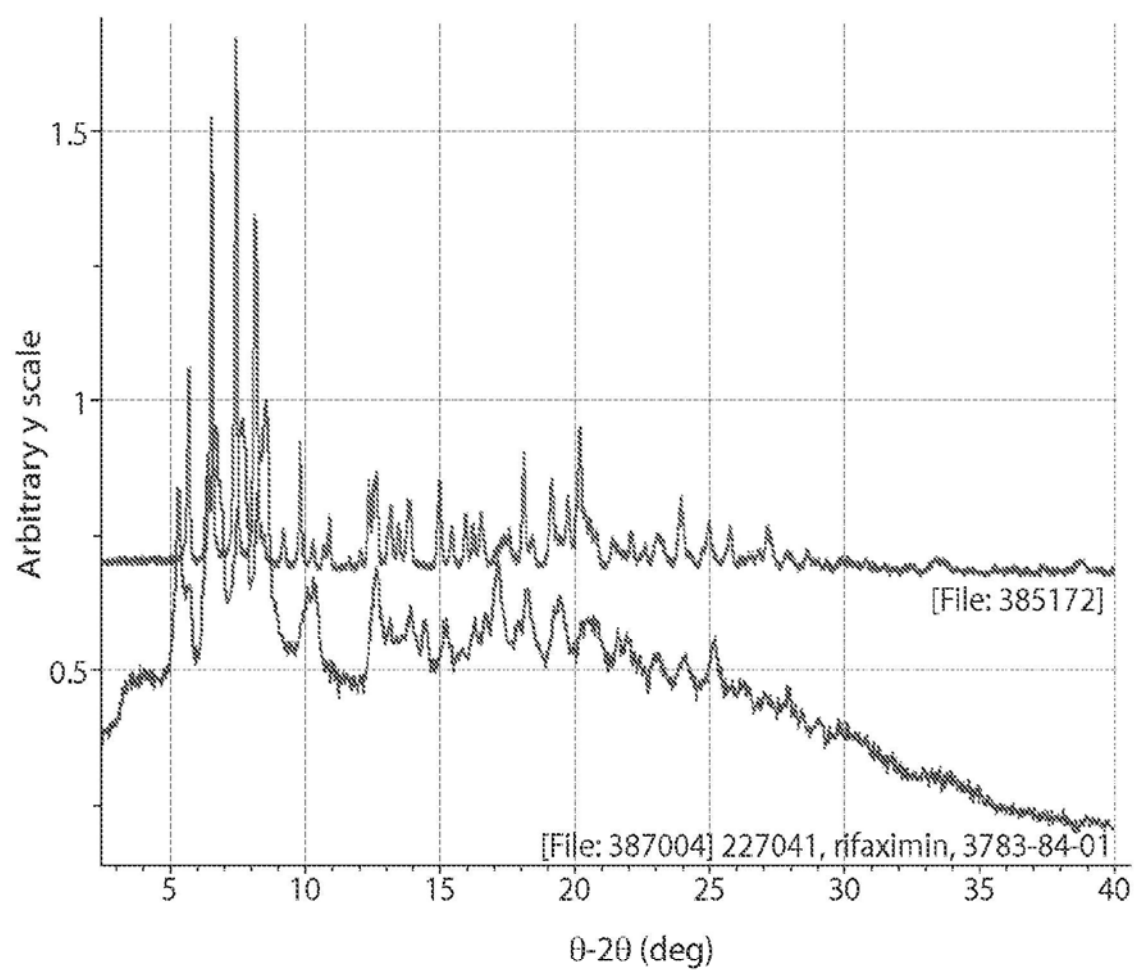


Fig. 17

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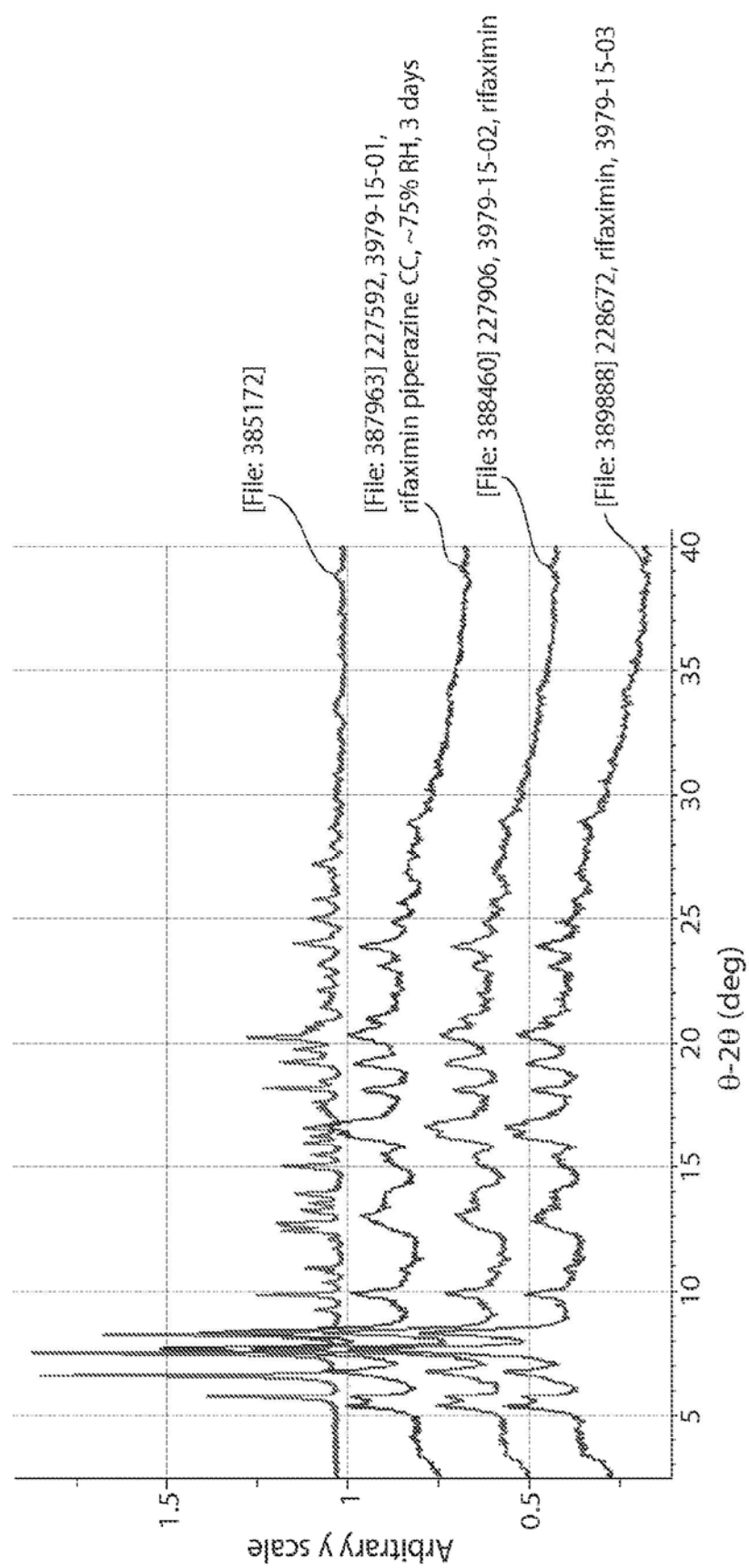


Fig. 18

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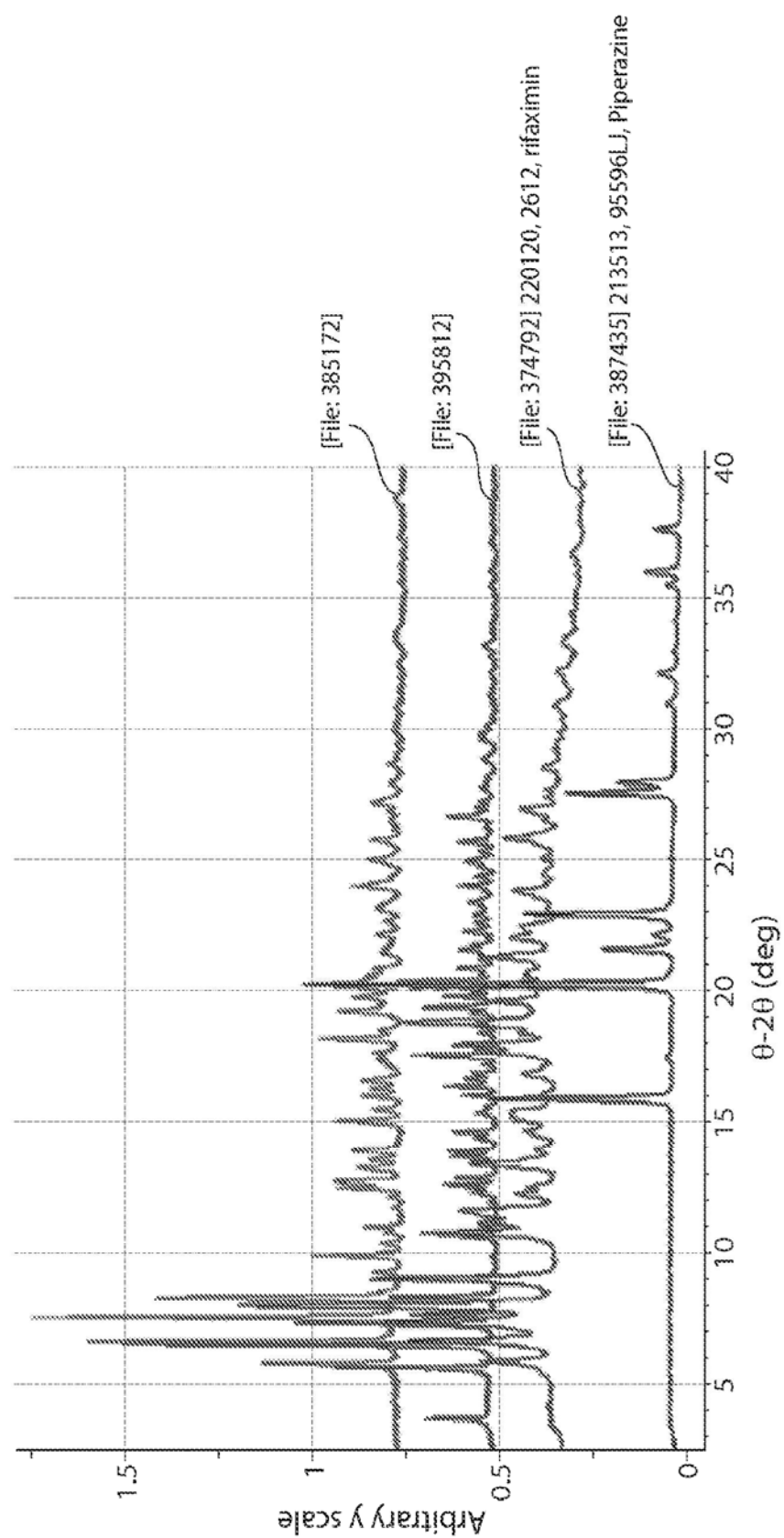


Fig. 19

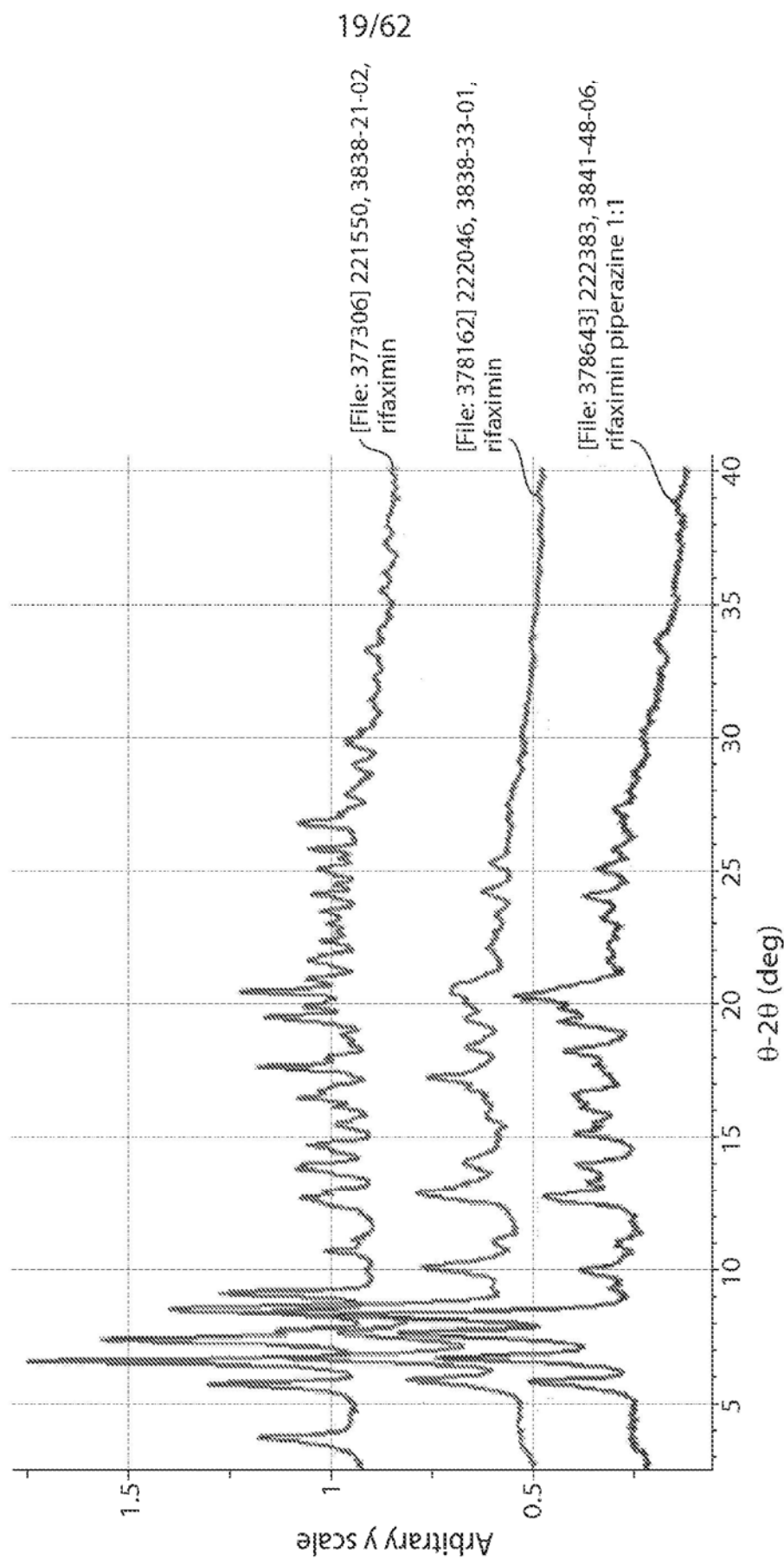


Fig. 20

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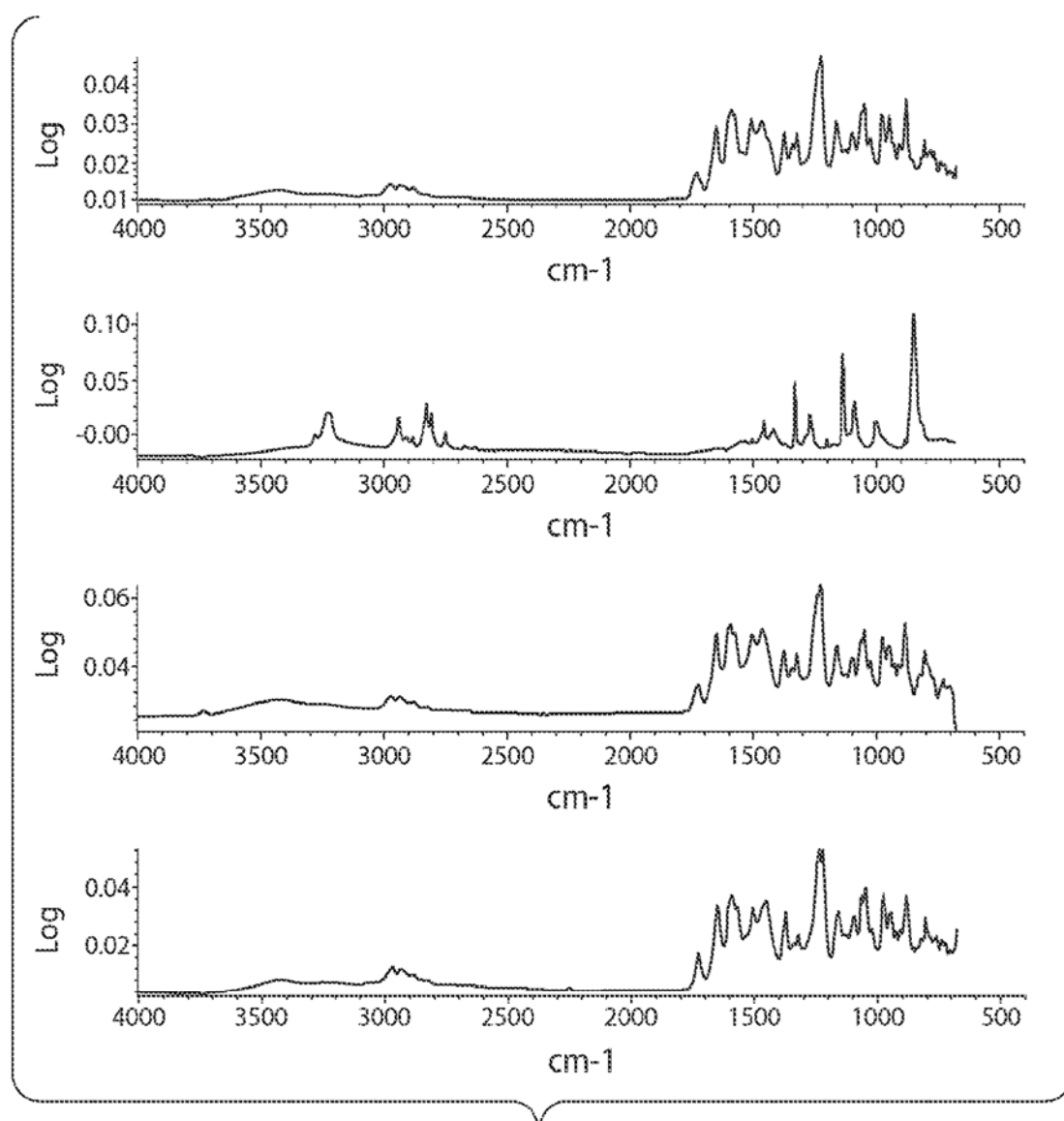


Fig. 21

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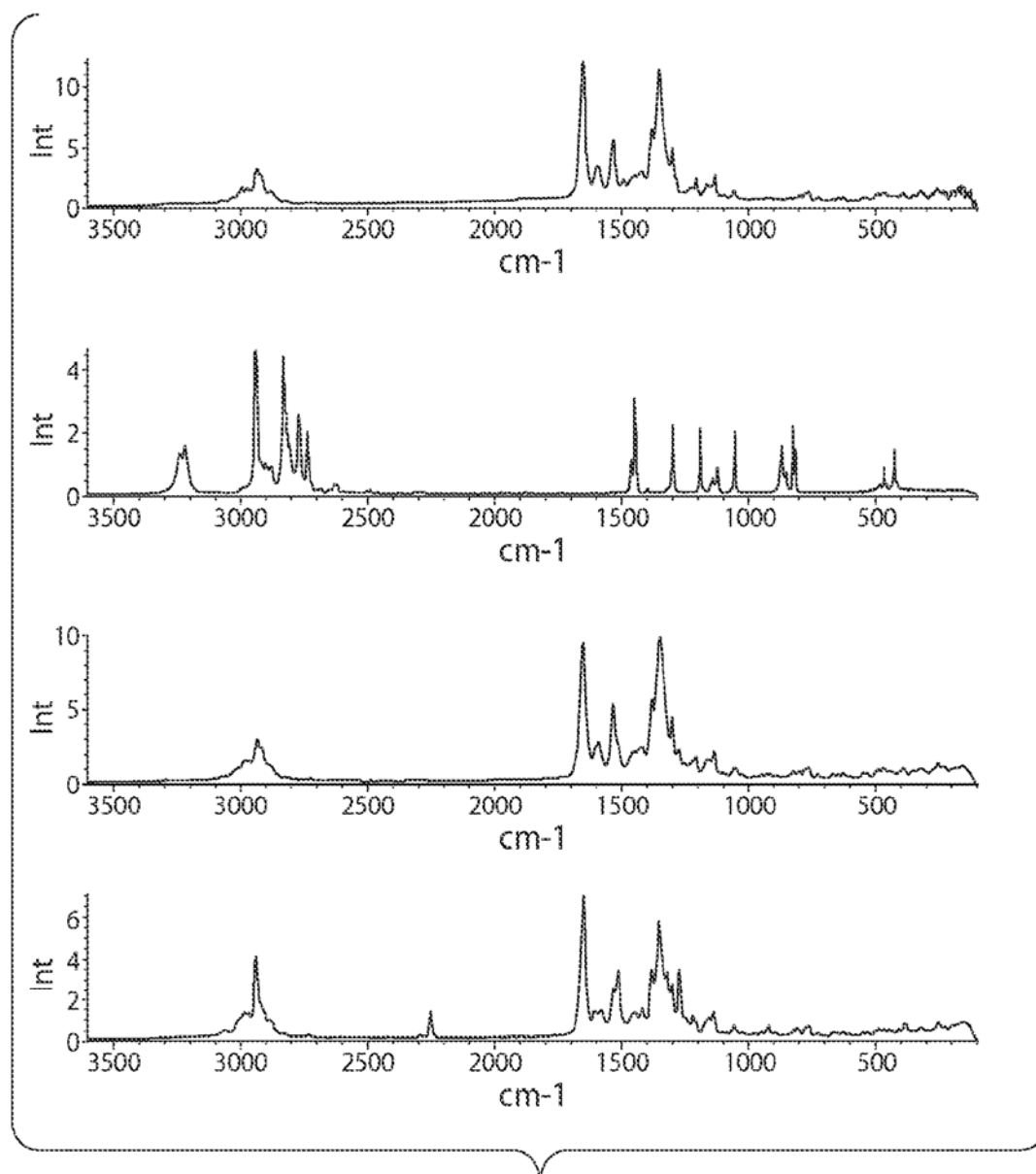


Fig. 22

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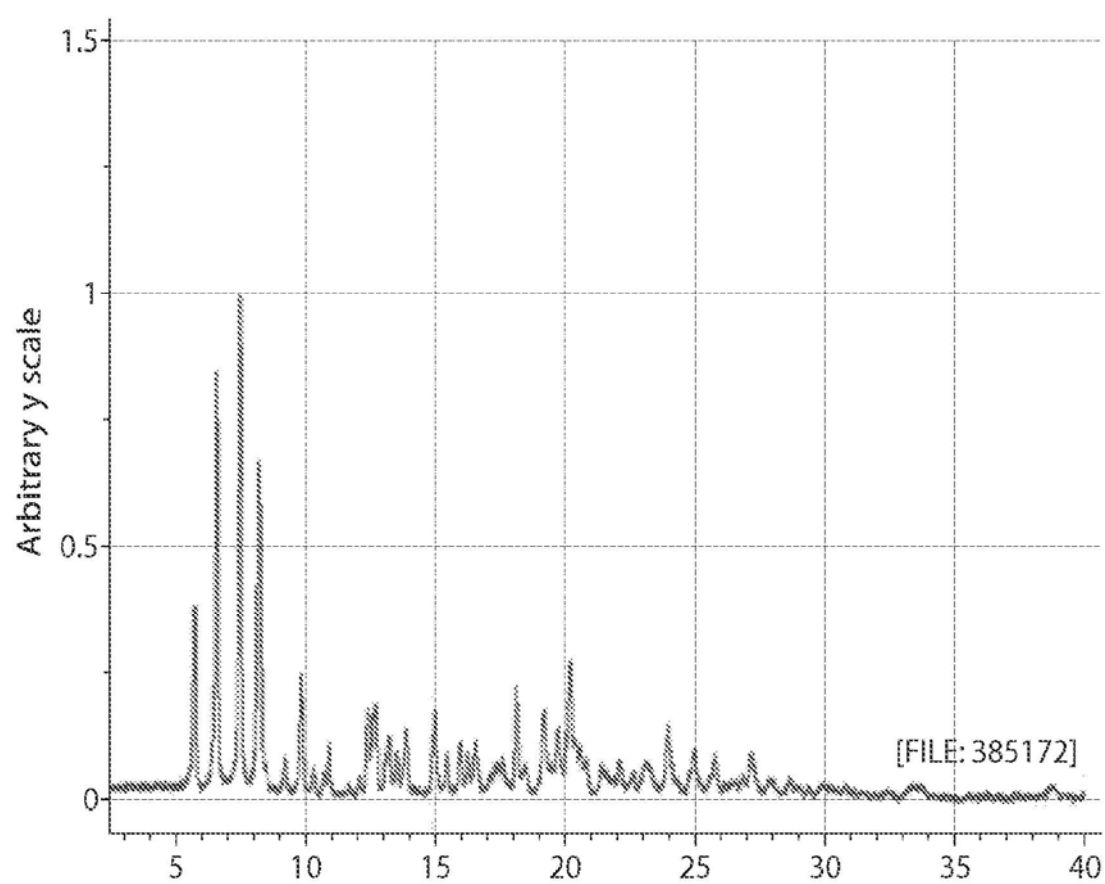


Fig. 23

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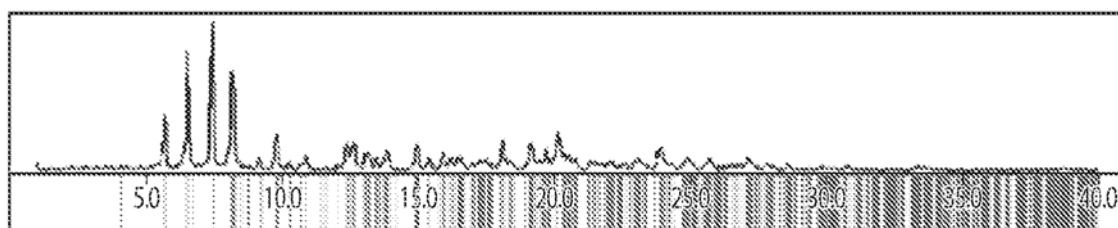


Fig. 24

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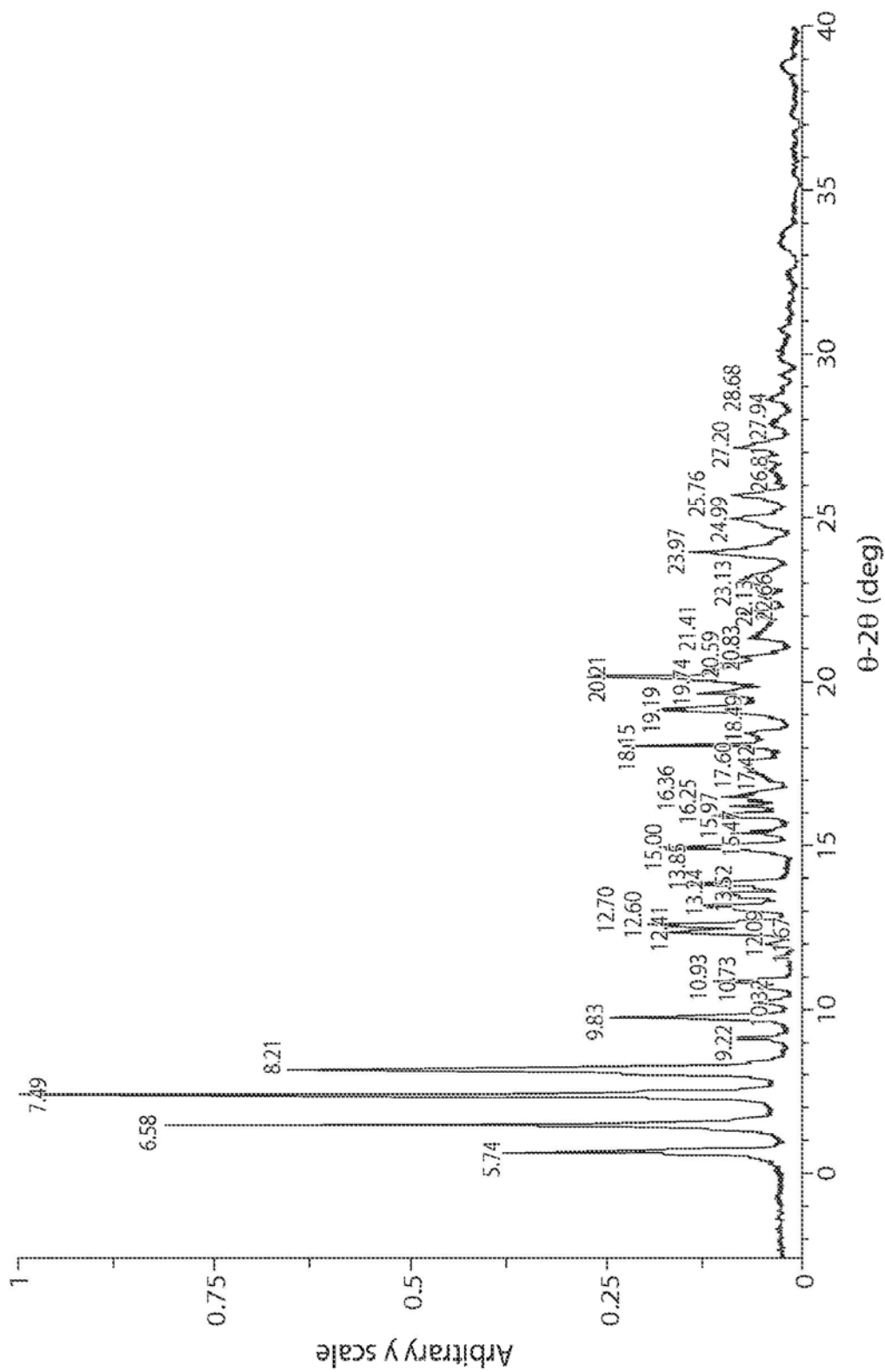


Fig. 25

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2θ	d space (Å)	Intensity (%)
5.74 ± 0.10	15.410 ± 0.273	38
6.58 ± 0.10	13.435 ± 0.207	83
7.49 ± 0.10	11.804 ± 0.160	100
8.21 ± 0.10	10.772 ± 0.133	66
9.22 ± 0.10	9.593 ± 0.105	8
9.83 ± 0.10	8.999 ± 0.092	25
10.32 ± 0.10	8.570 ± 0.084	6
10.73 ± 0.10	8.244 ± 0.077	6
10.93 ± 0.10	8.093 ± 0.074	11
11.67 ± 0.10	7.585 ± 0.065	4
12.09 ± 0.10	7.323 ± 0.061	5
12.41 ± 0.10	7.132 ± 0.058	17
12.60 ± 0.10	7.024 ± 0.056	18
12.70 ± 0.10	6.968 ± 0.055	19
13.24 ± 0.10	6.688 ± 0.051	12
13.52 ± 0.10	6.548 ± 0.049	10
13.88 ± 0.10	6.380 ± 0.046	14
15.00 ± 0.10	5.906 ± 0.039	17
15.47 ± 0.10	5.728 ± 0.037	9
15.97 ± 0.10	5.549 ± 0.035	11
16.25 ± 0.10	5.456 ± 0.034	10
16.56 ± 0.10	5.355 ± 0.032	12
17.42 ± 0.10	5.090 ± 0.029	6
17.60 ± 0.10	5.039 ± 0.029	9
18.15 ± 0.10	4.887 ± 0.027	22
18.49 ± 0.10	4.800 ± 0.026	7
19.19 ± 0.10	4.626 ± 0.024	17
19.74 ± 0.10	4.498 ± 0.023	15
20.21 ± 0.10	4.395 ± 0.022	25
20.59 ± 0.10	4.313 ± 0.021	11
20.83 ± 0.10	4.264 ± 0.020	9
21.41 ± 0.10	4.150 ± 0.019	7
22.13 ± 0.10	4.017 ± 0.018	7
22.66 ± 0.10	3.925 ± 0.017	5
23.13 ± 0.10	3.845 ± 0.016	8
23.97 ± 0.10	3.713 ± 0.015	15
24.99 ± 0.10	3.564 ± 0.014	10
25.76 ± 0.10	3.458 ± 0.013	9
26.85 ± 0.10	3.321 ± 0.012	5
27.20 ± 0.10	3.279 ± 0.012	9
27.94 ± 0.10	3.193 ± 0.011	4
28.68 ± 0.10	3.113 ± 0.011	5

Fig. 26

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2θ	d space ($\text{\AA}$)	Intensity (%)
5.74 ± 0.10	15.410 ± 0.273	38
6.58 ± 0.10	13.435 ± 0.207	83
7.49 ± 0.10	11.804 ± 0.160	100
8.21 ± 0.10	10.772 ± 0.133	66
9.83 ± 0.10	8.999 ± 0.092	25

Fig. 27

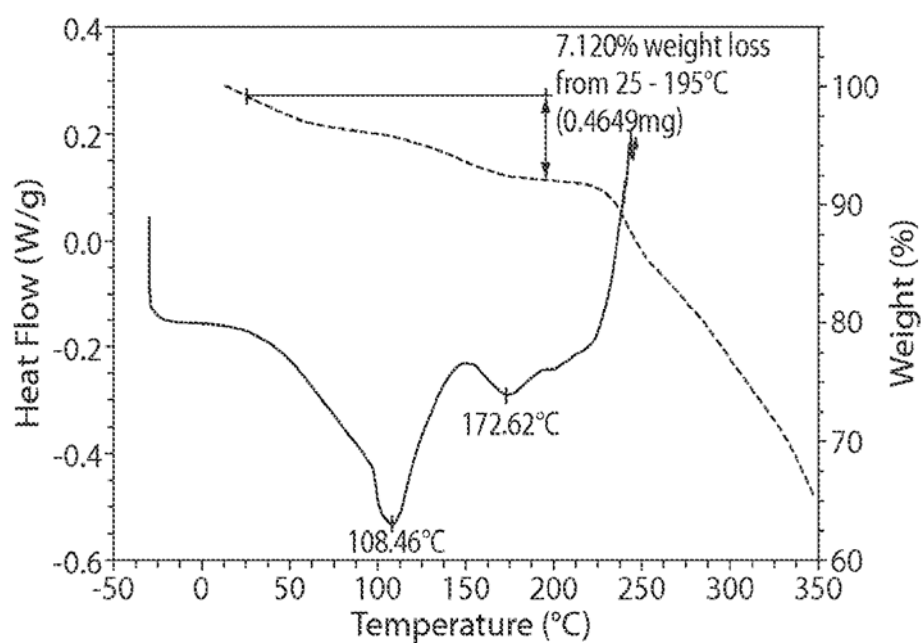


Fig. 28

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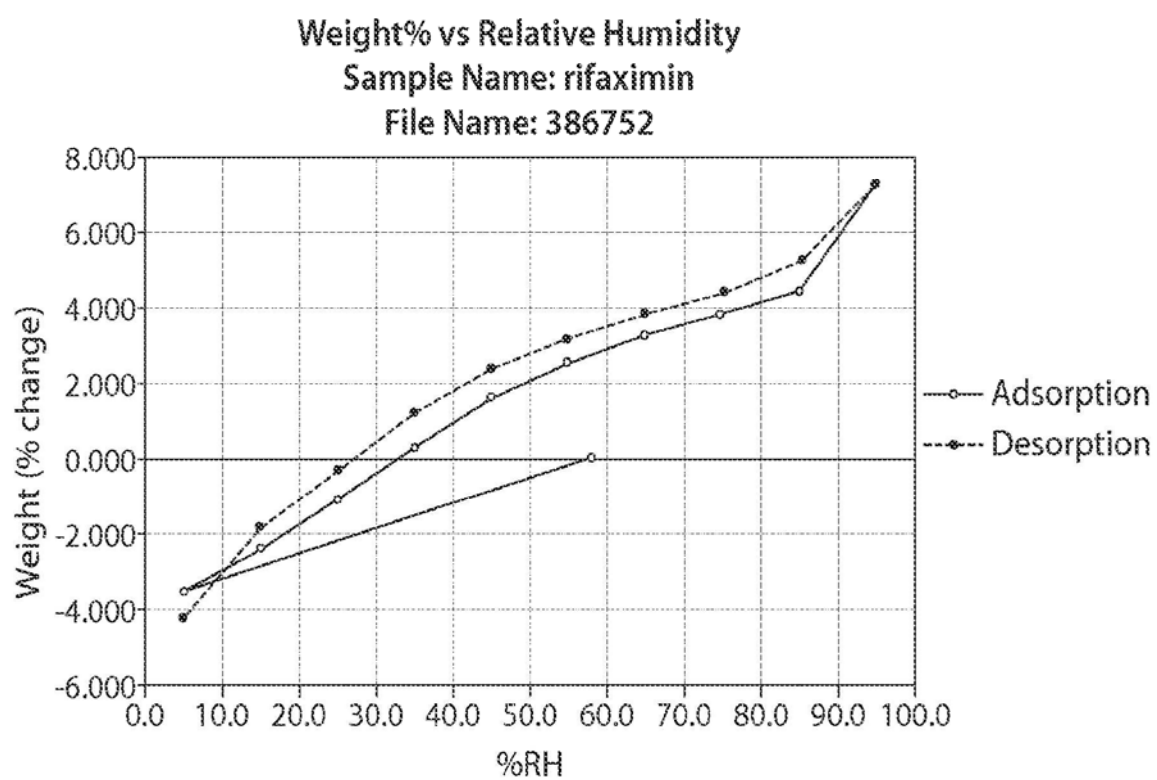


Fig. 29

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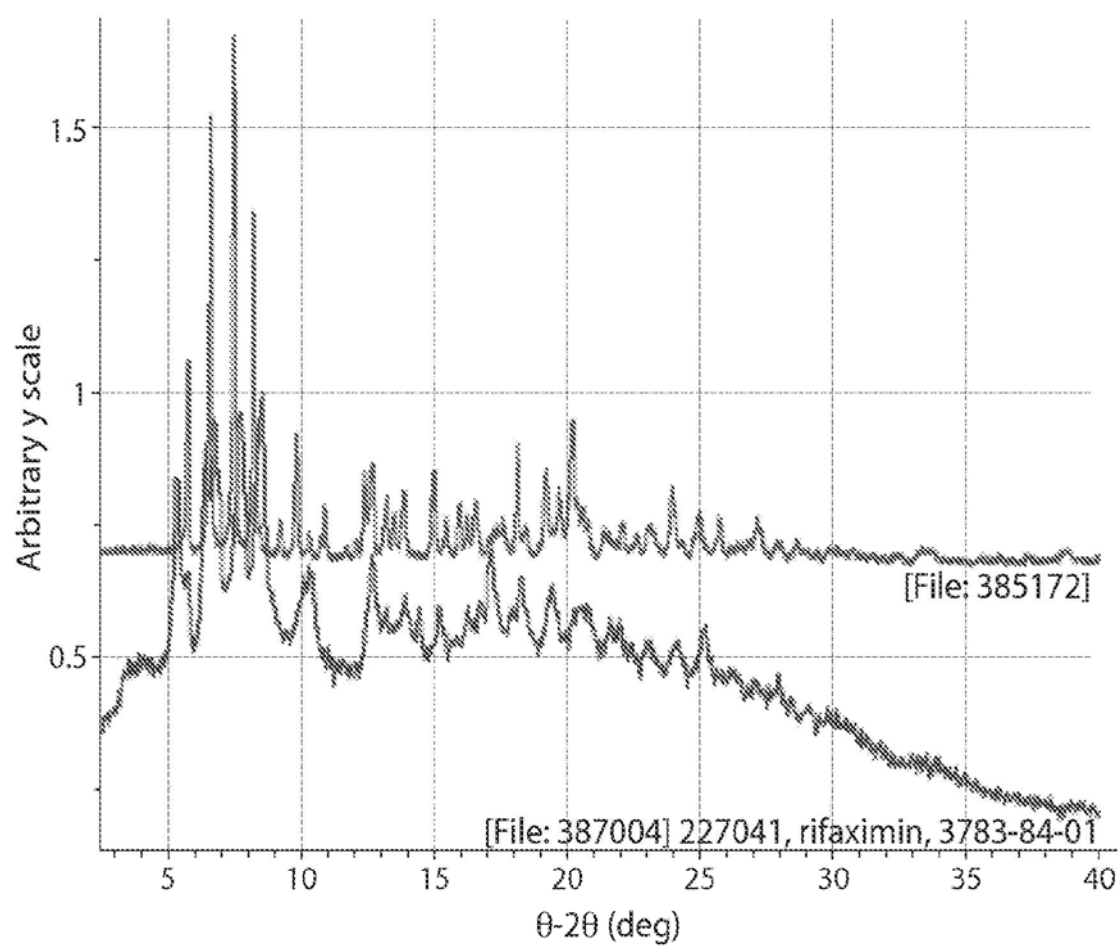


Fig. 30

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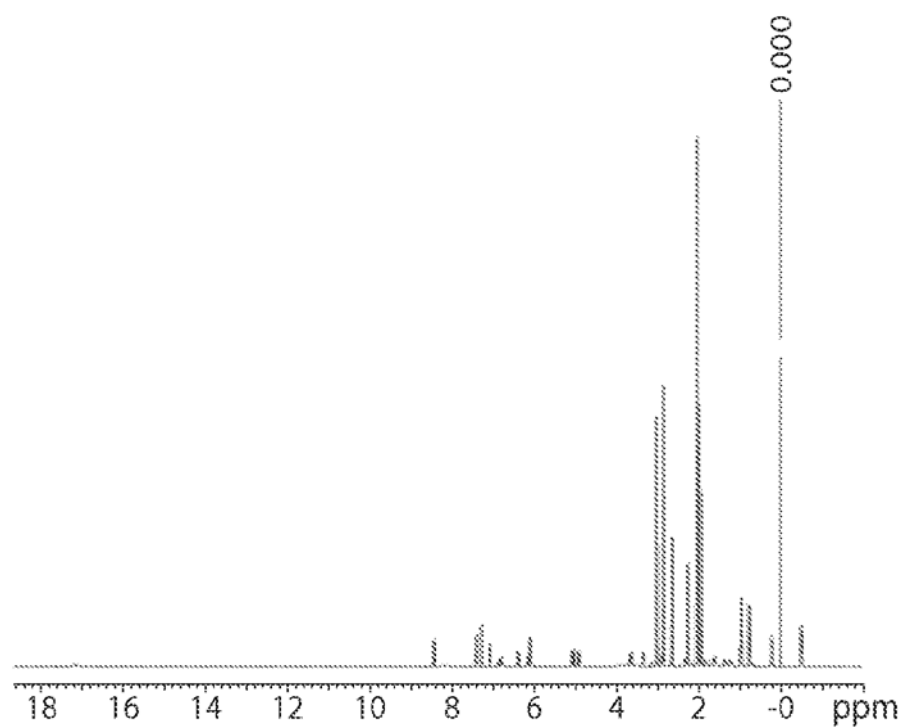


Fig. 31

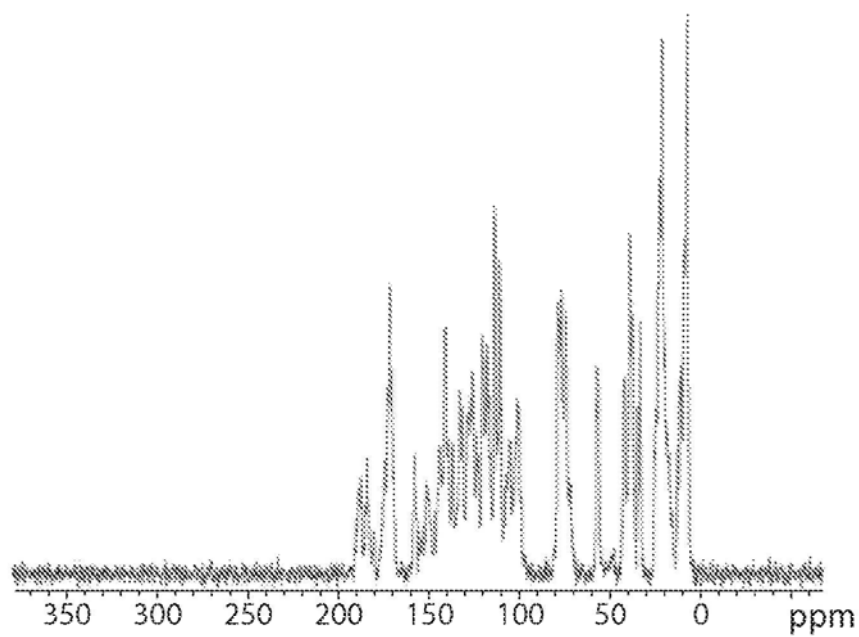


Fig. 32

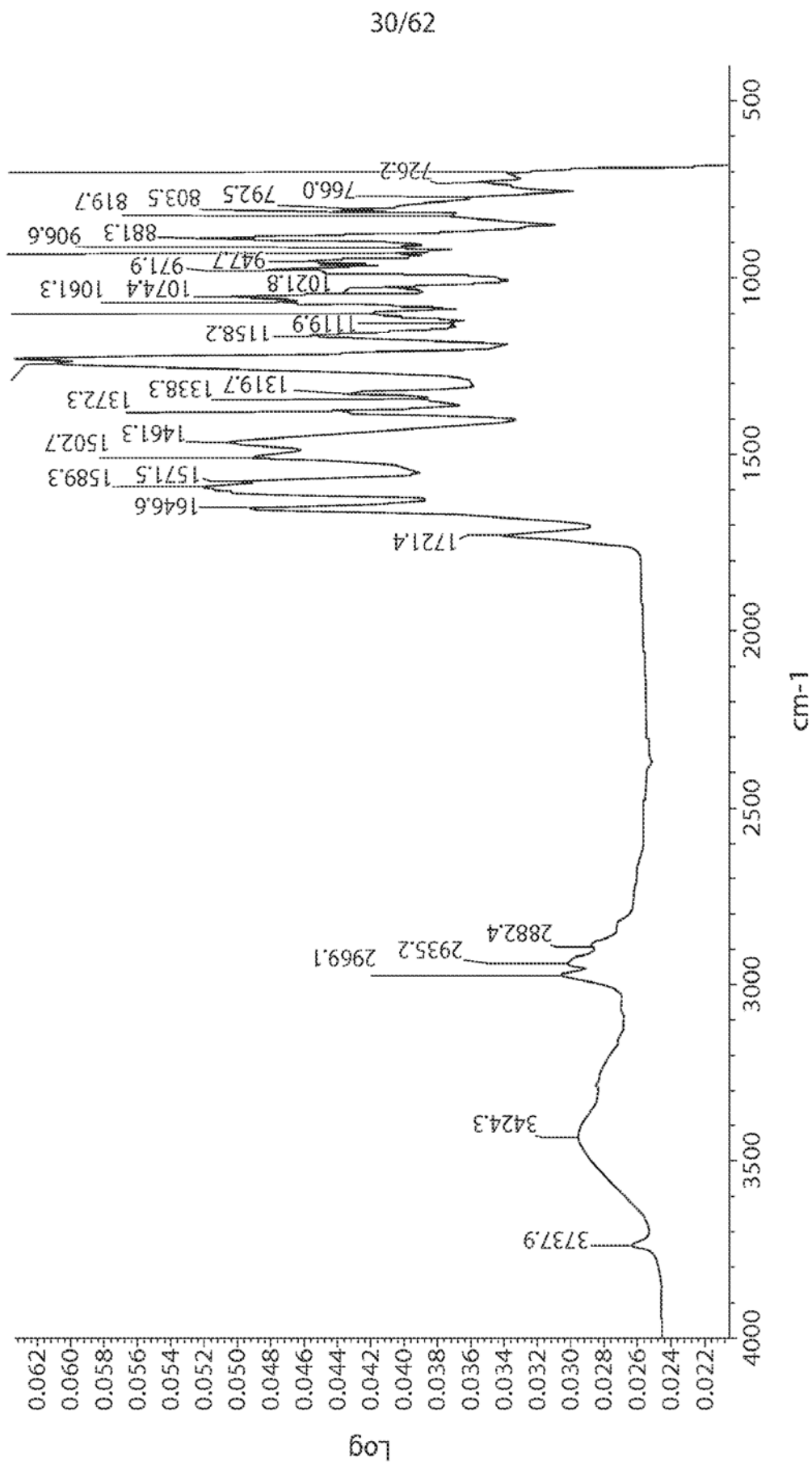


Fig. 33

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Observed IR peaks for Rifaximin:piperazine cocrystal 1

Region 4000.0 400.0

Absolute threshold: 0.0251

Sensitivity: 90

Observed Peak list (± 2 cm⁻¹):

701.5

726.2

766.0

792.5

803.5

819.7

881.3

906.6

925.2

947.7

971.9

1021.8

1047.4

1061.3

1094.2

1119.9

1158.2

1223.2

1237.3

1319.7

1338.3

1372.3

1461.3

1502.7

1571.5

1589.3

1646.6

1721.4

2882.4

2935.2

2969.1

3424.3

3737.9

Fig. 34

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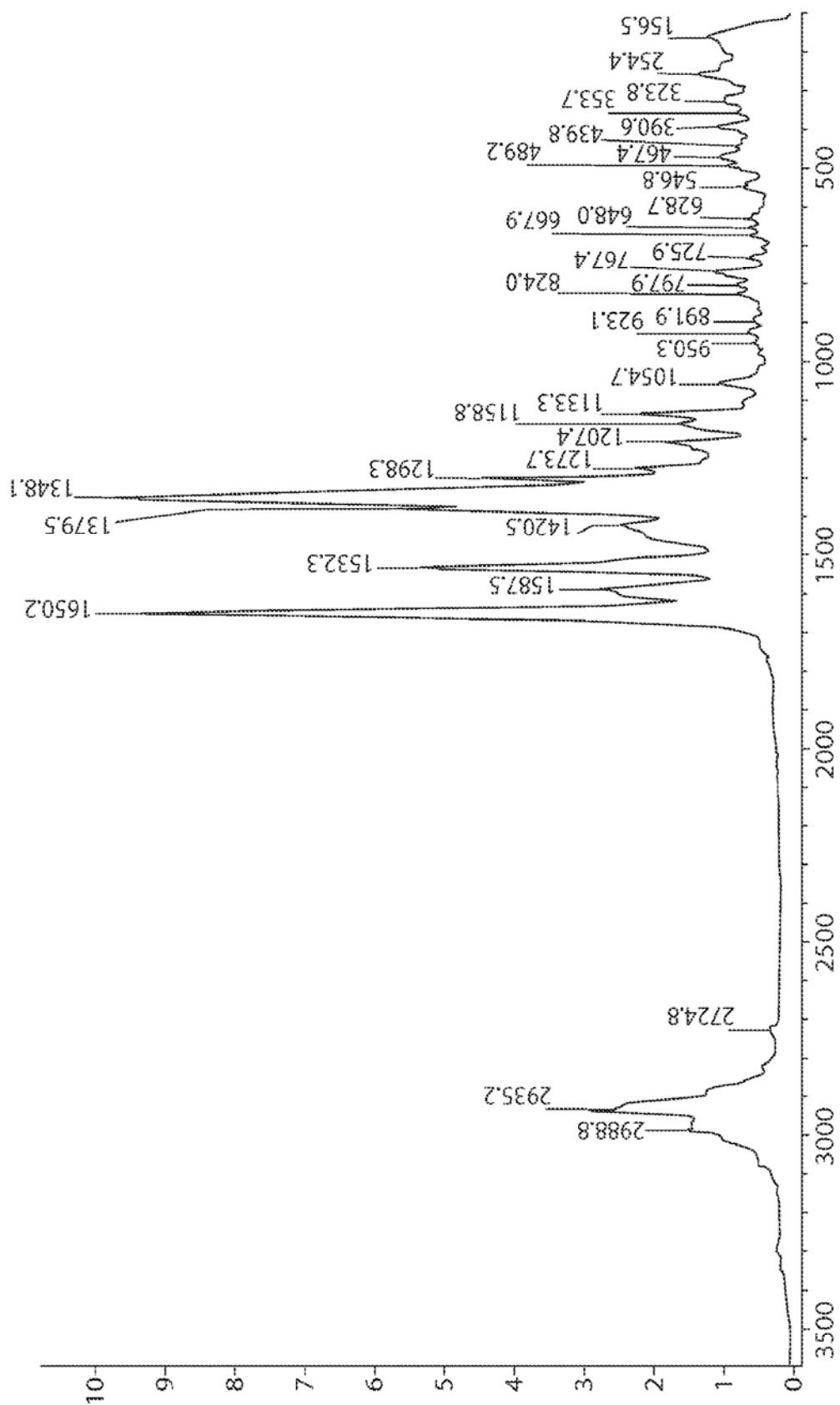


Fig. 35

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Observed Raman peaks for Rifaximin:piperazine cocrystal 1

Spectrum: rifaximin
Region: 3600.4 98.3
Absolute threshold: 0.165
Sensitivity: 80
Peak list (± 2 cm⁻¹):

156.5
254.4
323.8
353.7
390.6
439.8
467.4
489.2
546.8
628.7
648.0
667.9
725.9
767.4
797.9
824.0
891.9
923.1
950.3
1054.7
1133.3
1158.8
1207.4
1273.7
1298.3
1348.6
1379.5
1420.5
1532.3
1587.5
1650.2
2724.8
2935.2
2988.8

Fig. 36

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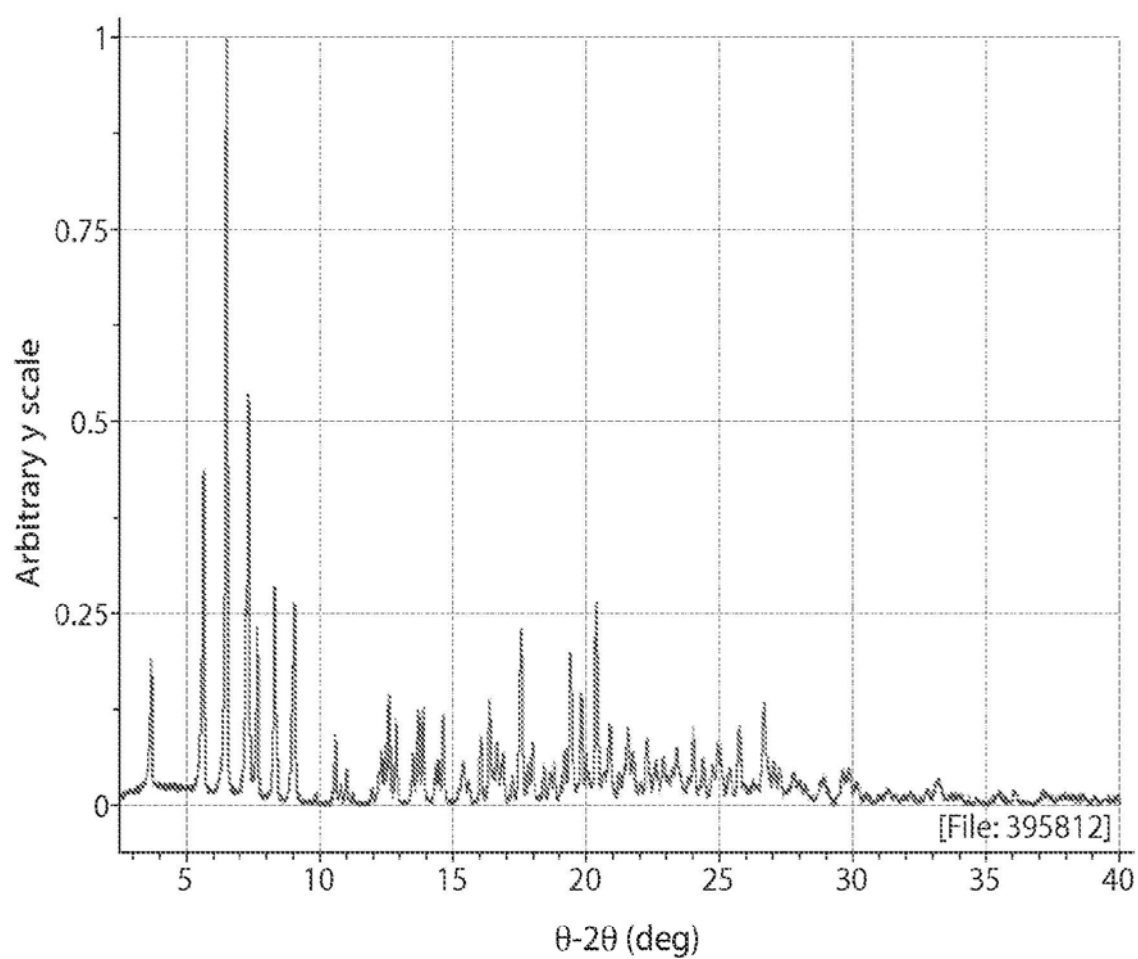


Fig. 37

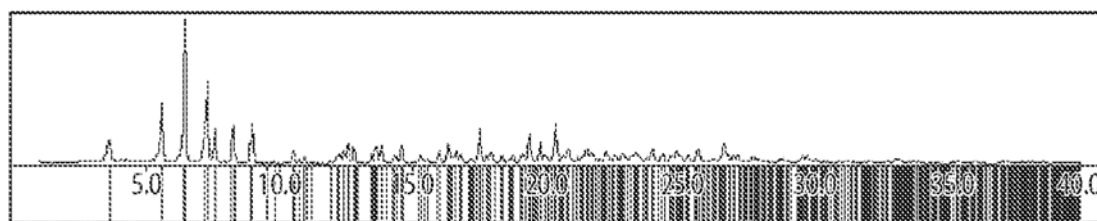
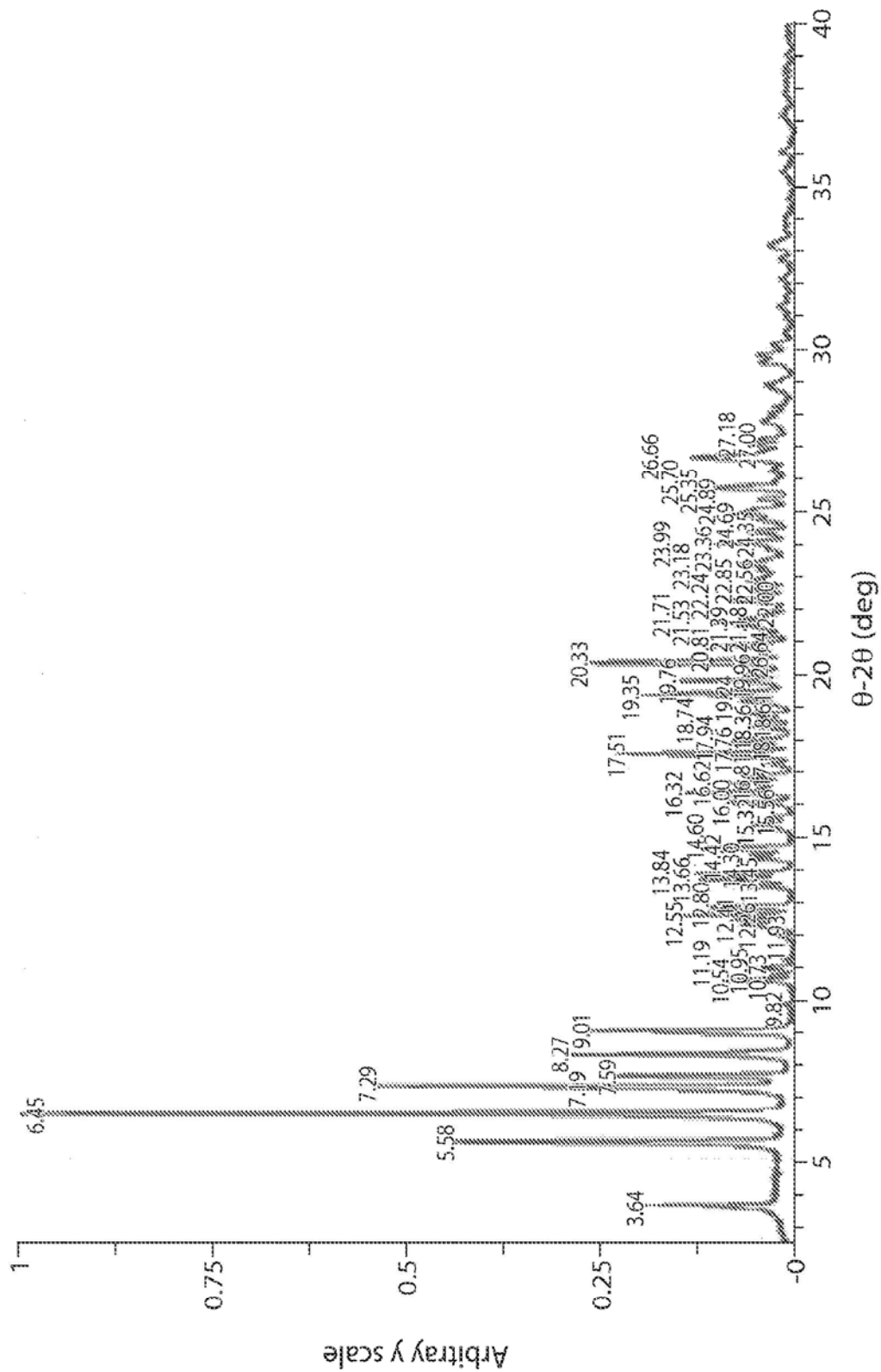


Fig. 38

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$^{\circ}2\theta$	d space (Å)	Intensity (%)	$^{\circ}2\theta$	d space (Å)	Intensity (%)
3.64 $\pm$ 0.10	24.288 $\pm$ 0.686	19	17.76 $\pm$ 0.10	4.995 $\pm$ 0.028	5
5.58 $\pm$ 0.10	15.825 $\pm$ 0.288	44	17.94 $\pm$ 0.10	4.944 $\pm$ 0.027	8
6.45 $\pm$ 0.10	13.696 $\pm$ 0.215	100	18.36 $\pm$ 0.10	4.832 $\pm$ 0.026	6
7.19 $\pm$ 0.10	12.297 $\pm$ 0.173	28	18.61 $\pm$ 0.10	4.768 $\pm$ 0.026	4
7.29 $\pm$ 0.10	12.128 $\pm$ 0.168	54	18.74 $\pm$ 0.10	4.734 $\pm$ 0.025	6
7.60 $\pm$ 0.10	11.635 $\pm$ 0.155	23	19.14 $\pm$ 0.10	4.638 $\pm$ 0.024	7
8.27 $\pm$ 0.10	10.696 $\pm$ 0.131	29	19.35 $\pm$ 0.10	4.586 $\pm$ 0.024	20
9.01 $\pm$ 0.10	9.815 $\pm$ 0.110	26	19.76 $\pm$ 0.10	4.492 $\pm$ 0.023	15
9.82 $\pm$ 0.10	9.006 $\pm$ 0.092	2	19.96 $\pm$ 0.10	4.449 $\pm$ 0.022	7
10.54 $\pm$ 0.10	8.394 $\pm$ 0.080	9	20.33 $\pm$ 0.10	4.368 $\pm$ 0.021	27
10.73 $\pm$ 0.10	8.244 $\pm$ 0.077	3	20.64 $\pm$ 0.10	4.303 $\pm$ 0.021	5
10.95 $\pm$ 0.10	8.081 $\pm$ 0.074	4	20.83 $\pm$ 0.10	4.264 $\pm$ 0.020	11
11.19 $\pm$ 0.10	7.906 $\pm$ 0.071	2	21.18 $\pm$ 0.10	4.194 $\pm$ 0.020	5
11.93 $\pm$ 0.10	7.421 $\pm$ 0.063	2	21.39 $\pm$ 0.10	4.155 $\pm$ 0.019	5
12.26 $\pm$ 0.10	7.219 $\pm$ 0.059	6	21.53 $\pm$ 0.10	4.128 $\pm$ 0.019	10
12.41 $\pm$ 0.10	7.132 $\pm$ 0.058	8	21.71 $\pm$ 0.10	4.093 $\pm$ 0.019	7
12.55 $\pm$ 0.10	7.052 $\pm$ 0.056	15	22.00 $\pm$ 0.10	4.040 $\pm$ 0.018	3
12.80 $\pm$ 0.10	6.914 $\pm$ 0.054	11	22.24 $\pm$ 0.10	3.998 $\pm$ 0.018	8
13.45 $\pm$ 0.10	6.585 $\pm$ 0.049	7	22.56 $\pm$ 0.10	3.941 $\pm$ 0.017	6
13.66 $\pm$ 0.10	6.484 $\pm$ 0.048	13	22.85 $\pm$ 0.10	3.892 $\pm$ 0.017	6
13.84 $\pm$ 0.10	6.399 $\pm$ 0.046	13	23.18 $\pm$ 0.10	3.837 $\pm$ 0.016	5
14.30 $\pm$ 0.10	6.194 $\pm$ 0.043	5	23.36 $\pm$ 0.10	3.809 $\pm$ 0.016	7
14.42 $\pm$ 0.10	6.141 $\pm$ 0.043	6	23.99 $\pm$ 0.10	3.709 $\pm$ 0.015	10
14.60 $\pm$ 0.10	6.067 $\pm$ 0.042	12	24.35 $\pm$ 0.10	3.655 $\pm$ 0.015	6
15.32 $\pm$ 0.10	5.784 $\pm$ 0.038	5	24.69 $\pm$ 0.10	3.605 $\pm$ 0.014	6
15.56 $\pm$ 0.10	5.695 $\pm$ 0.037	4	24.89 $\pm$ 0.10	3.578 $\pm$ 0.014	9
16.00 $\pm$ 0.10	5.538 $\pm$ 0.035	9	25.35 $\pm$ 0.10	3.514 $\pm$ 0.014	5
16.32 $\pm$ 0.10	5.431 $\pm$ 0.033	14	25.70 $\pm$ 0.10	3.467 $\pm$ 0.013	11
16.62 $\pm$ 0.10	5.333 $\pm$ 0.032	9	26.66 $\pm$ 0.10	3.344 $\pm$ 0.012	13
16.81 $\pm$ 0.10	5.273 $\pm$ 0.031	6	27.00 $\pm$ 0.10	3.302 $\pm$ 0.012	6
17.18 $\pm$ 0.10	5.161 $\pm$ 0.030	4	27.18 $\pm$ 0.10	3.280 $\pm$ 0.012	5
17.51 $\pm$ 0.10	5.065 $\pm$ 0.029	22			

Fig. 40

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2θ	d space ($\text{\AA}$)	Intensity (%)
3.64 ± 0.10	24.288 ± 0.686	19
5.58 ± 0.10	15.825 ± 0.288	44
6.45 ± 0.10	13.696 ± 0.215	100
7.29 ± 0.10	12.128 ± 0.168	54
7.60 ± 0.10	11.635 ± 0.155	23
8.27 ± 0.10	10.696 ± 0.131	29
9.01 ± 0.10	9.815 ± 0.110	26

Fig. 41

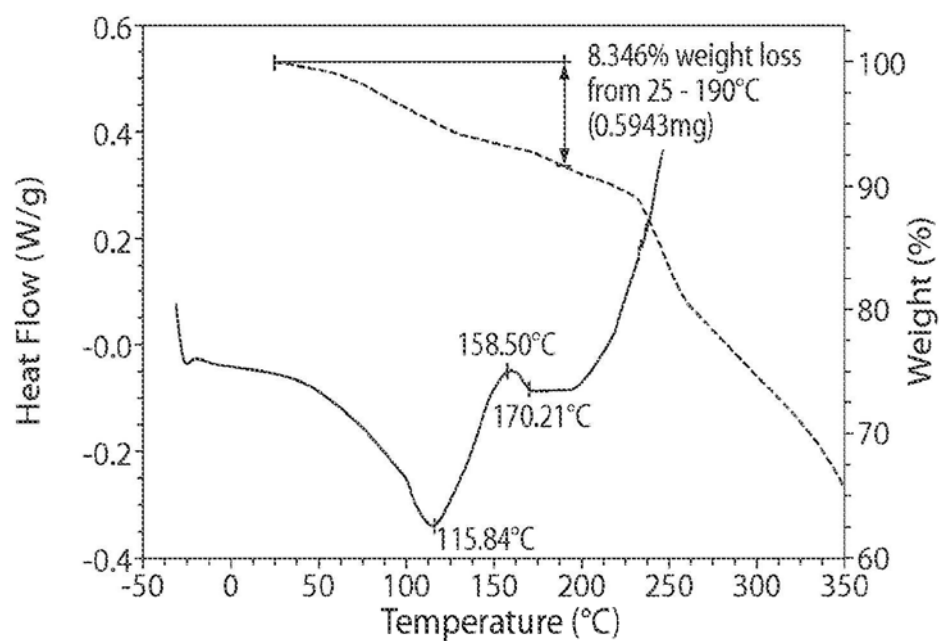


Fig. 42

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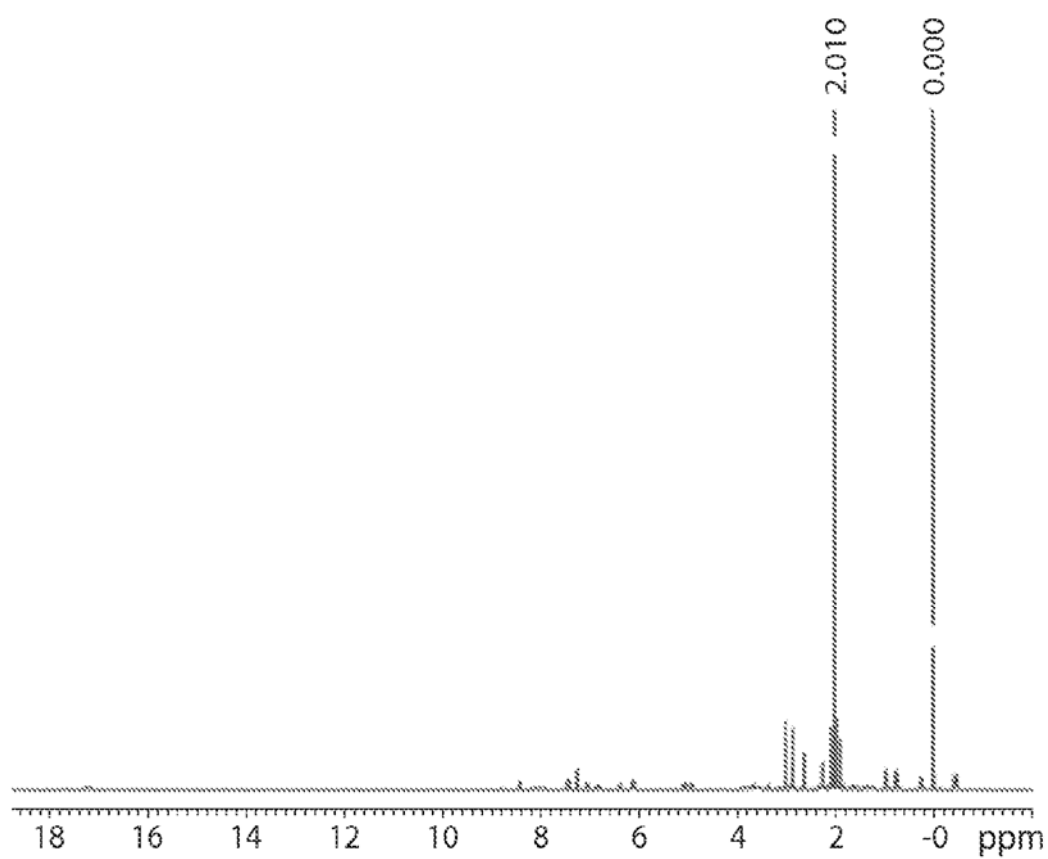


Fig. 43

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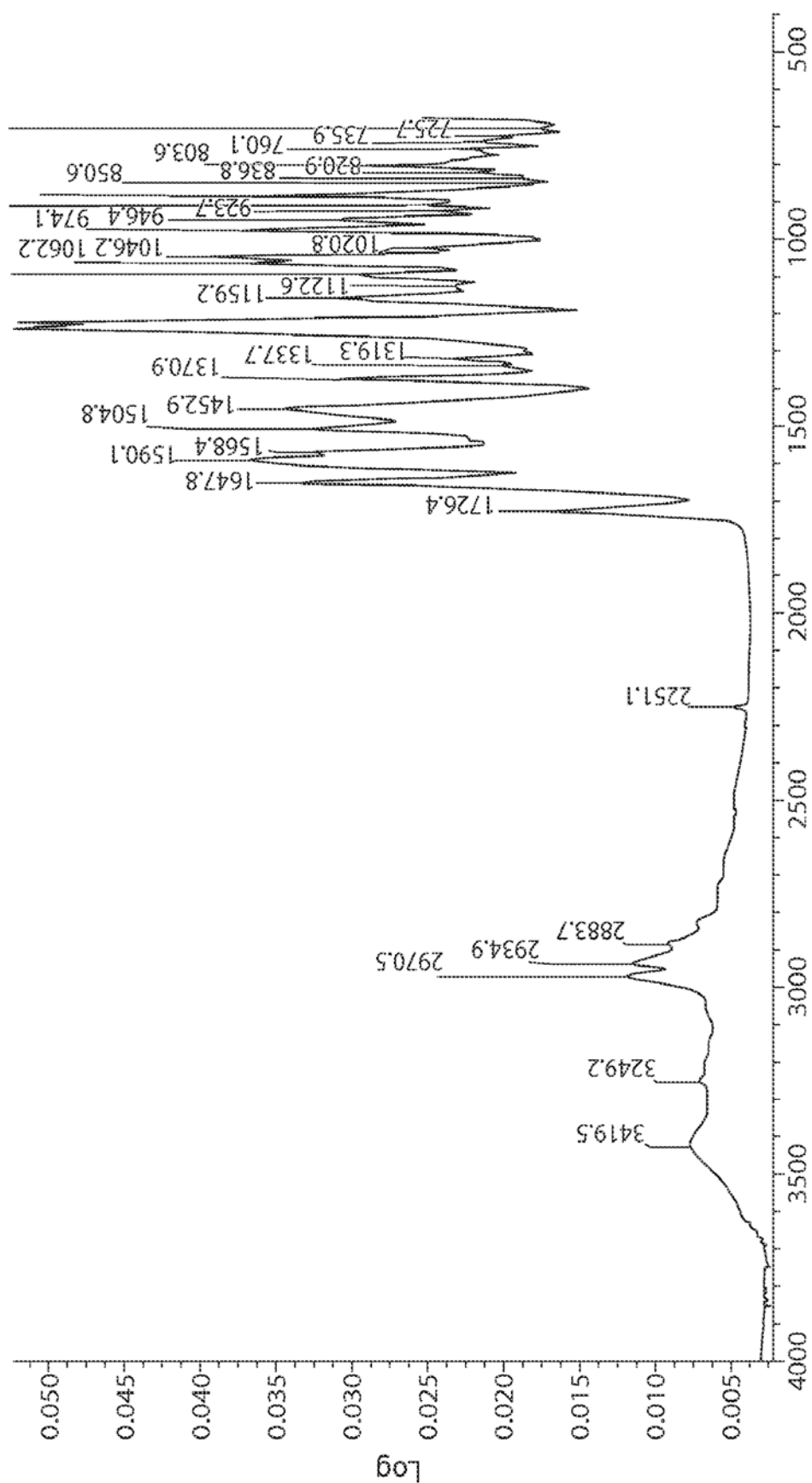


Fig. 44

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Observed and Characteristic IR peaks for Rifaximin: piperazine cocrystal 2

Spectrum: rifaximin

Region 4000.0 400.0

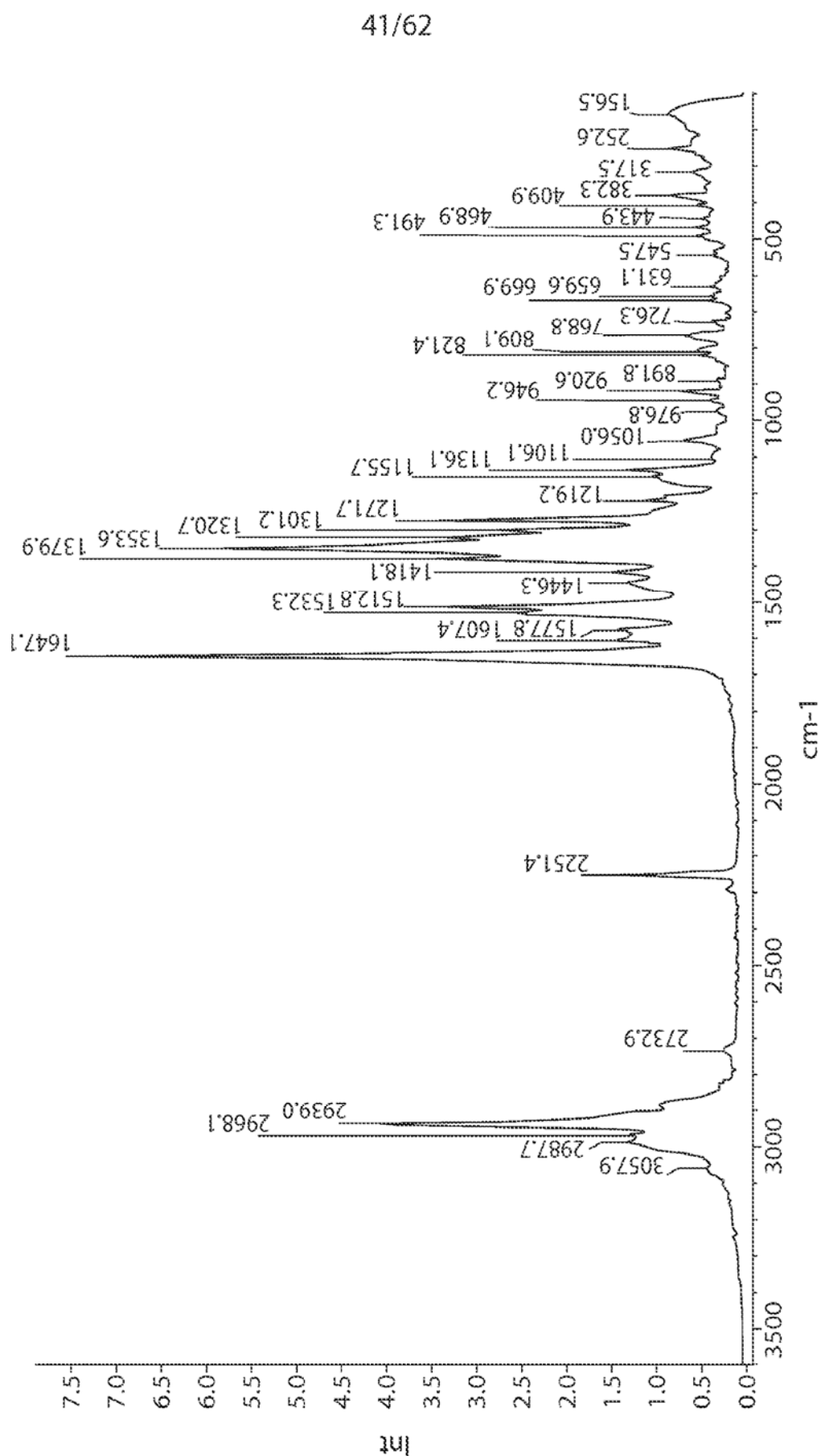
Absolute threshold: 0.0040

Sensitivity: 90

Observed Peak list ($\pm 2 \text{ cm}^{-1}$): Characteristic Peaks ($\pm 2 \text{ cm}^{-1}$):

704.0	1452.9
725.7	2251.1
735.9	
760.1	
803.6	
820.9	
836.8	
850.6	
880.6	
906.5	
923.7	
946.4	
974.1	
1020.8	
1046.2	
1062.2	
1091.7	
1122.6	
1159.2	
1221.4	
1237.3	
1319.3	
1337.7	
1370.9	
1452.9	
1504.8	
1568.4	
1590.1	
1647.8	
1726.4	
2251.1	
2883.7	
2934.9	
2970.5	
3249.2	
3419.5	

Fig. 45



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Observed and Characteristic Raman peaks for Rifaximin:piperazine cocrystal 2

Spectrum: rifaximin

Region: 3600.4 98.3

Absolute threshold: 0.209

Sensitivity: 80

Peak lists ($\pm 2 \text{ cm}^{-1}$):

Observed Peaks:

156.5
252.6
317.5
382.3
409.9
443.9
468.9
491.3
547.5
631.1
659.6
669.9
726.3
768.8
809.1
821.4
891.8
920.6
946.2
976.8
1056.0
1106.1
1136.1
1155.7
1219.2
1271.7
1301.2
1320.7
1353.6
1379.9
1418.1
1446.3
1512.8
1532.3
1577.8
1607.4
1647.7
2251.4
2732.9
2939.0
2968.1
2987.7
3057.9

Characteristic Peaks:

920.6
1219.2
1320.7
1577.8
1607.4
2251.4

Fig. 47

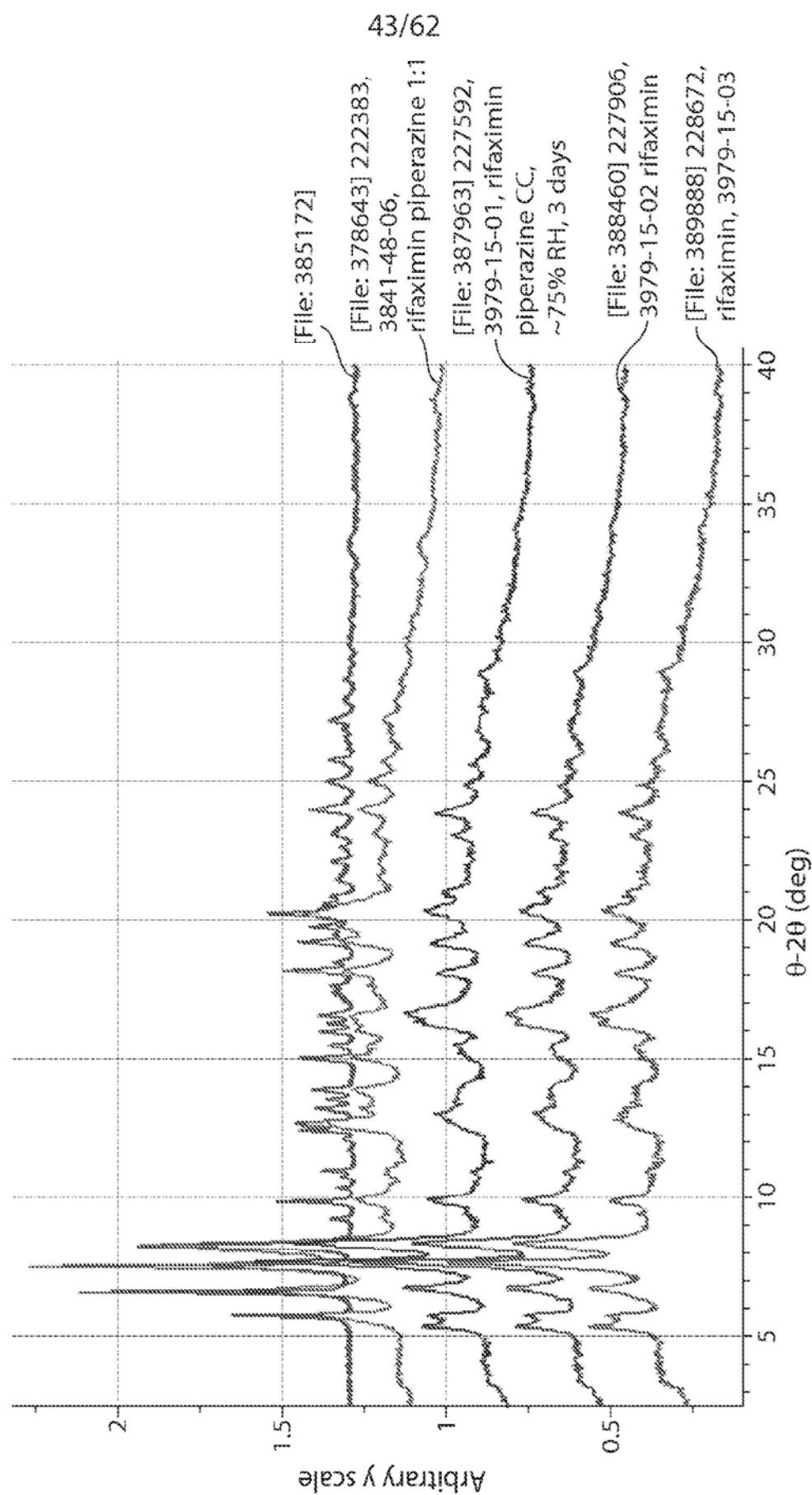


Fig. 48

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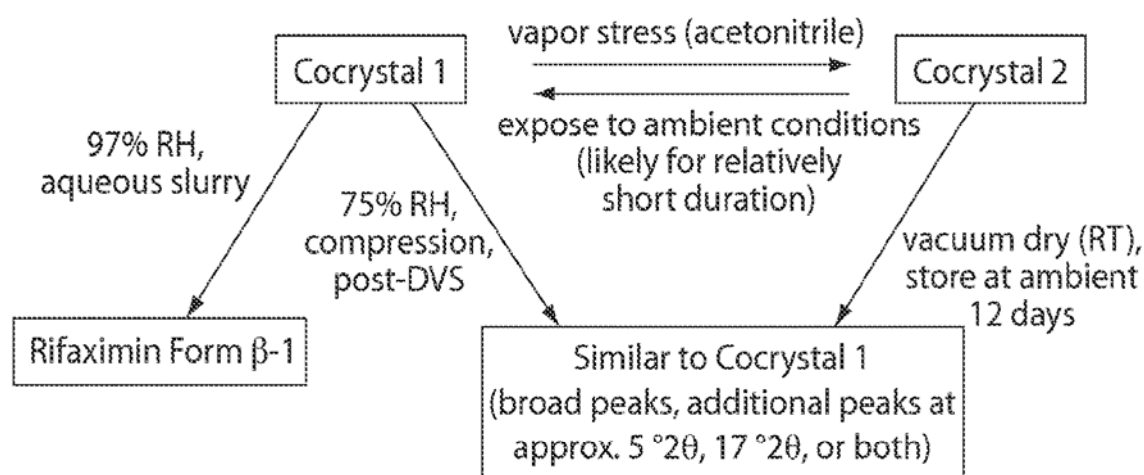


Fig. 49

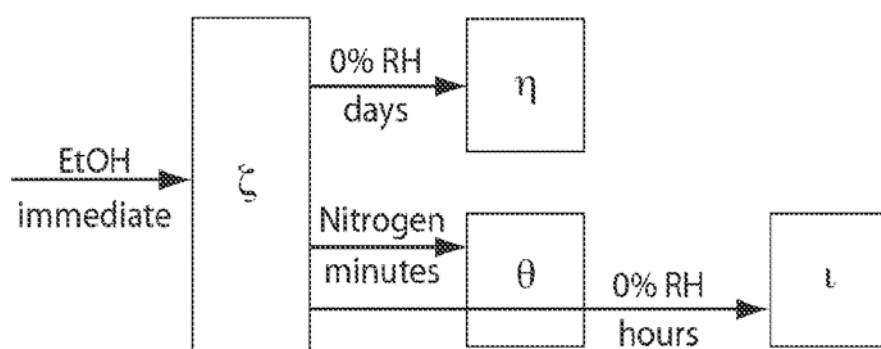


Fig. 50

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ξ	η
1.94% water ~12 moles of EtOH	1% water 0.3 moles of EtOH
0.54% water ~6 moles of EtOH	2% water 0.3 moles of EtOH
11.25% water ~1 mole of EtOH	3% water 0.6 mole of EtOH

Fig. 51

Condition	Time	Result
Nitrogen	~ 25 min	æ
	> 25 min	æ+ è
	>> 25 min	è
40 °C	~ 2 hrs	æ+ è
	~ 6 hrs	Pattern A
vacuum, ambient	~ 2 hrs	è
	~ 6 hrs	è dry
vacuum, ambient	~ 2 hrs	ç like
	14 days	ç
vacuum, ambient	~ 3.5 hrs	ç like
	~ 2 hrs	è dry
vacuum, 60 °C	~ 6 hrs	è dry

Fig. 52

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Condition	Time	Results	Wt change
22% RH, ambient	~ 2 hrs	ζ shifted	1%
	~ 6 hrs	ζ shifted	2%
75% RH, ambient	~ 2 hrs	ζ shifted	4%
	~ 6 hrs	ζ shifted	7%
40 °C	~ 2 hrs	ζ	1%
	~ 6 hrs	ζ	1%
75% RH, 40 °C	~ 2 hrs	ζ shifted	7%
	~ 6 hrs	ζ shifted	7%
vacuum, ambient	~ 2 hrs	ζ	-1%
	~ 6 hrs	ζ	-1%
	1 week	ζ	
vacuum, 60 °C	~ 2 hrs	ζ	0%
	~ 6 hrs	ζ	-1%
	2 days	ζ	-3%
grinding compression	~ 24 hrs		

2% water content
 ζ 0.3 moles of EtOH

1% water content
 0.3 moles of EtOH

Fig. 53

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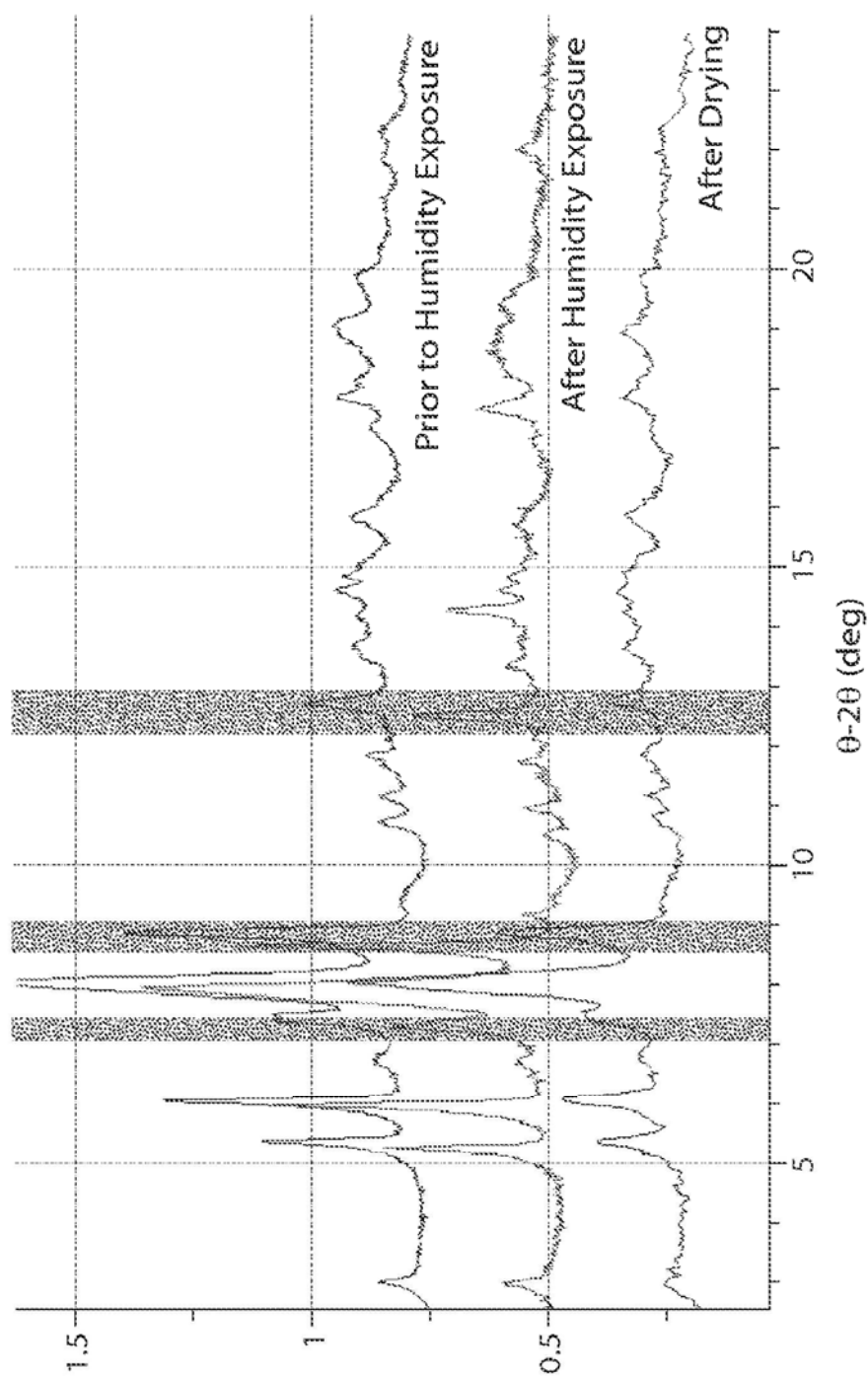


Fig. 54

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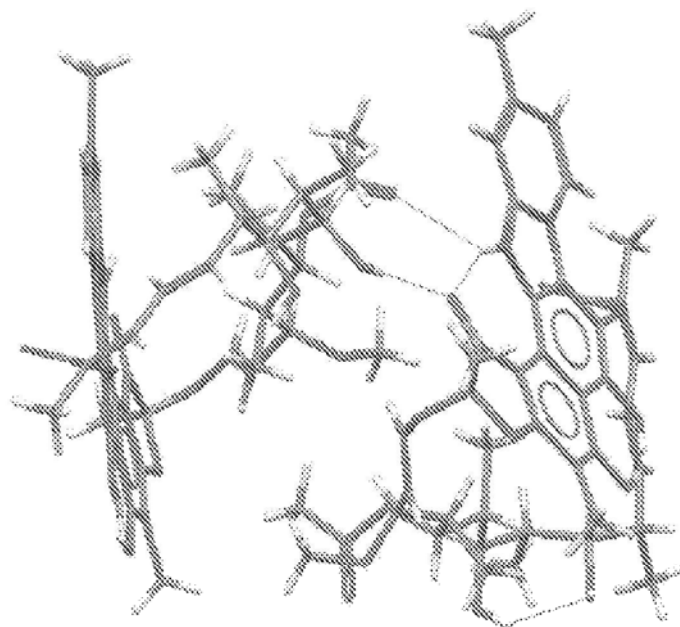


Fig. 55

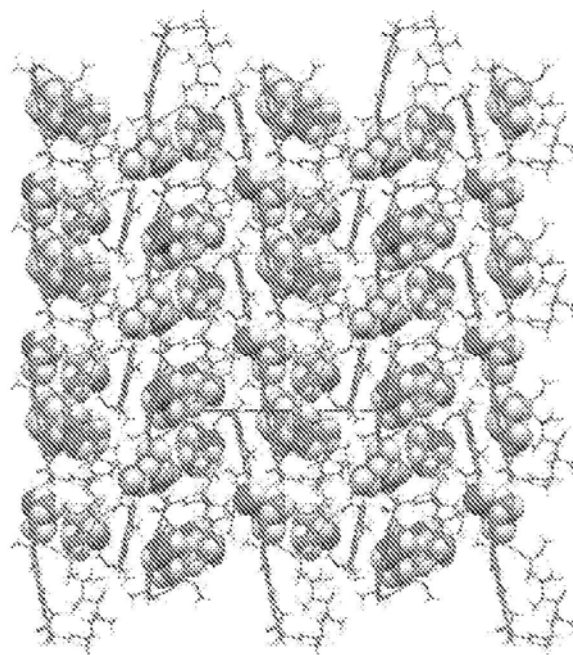


Fig. 56

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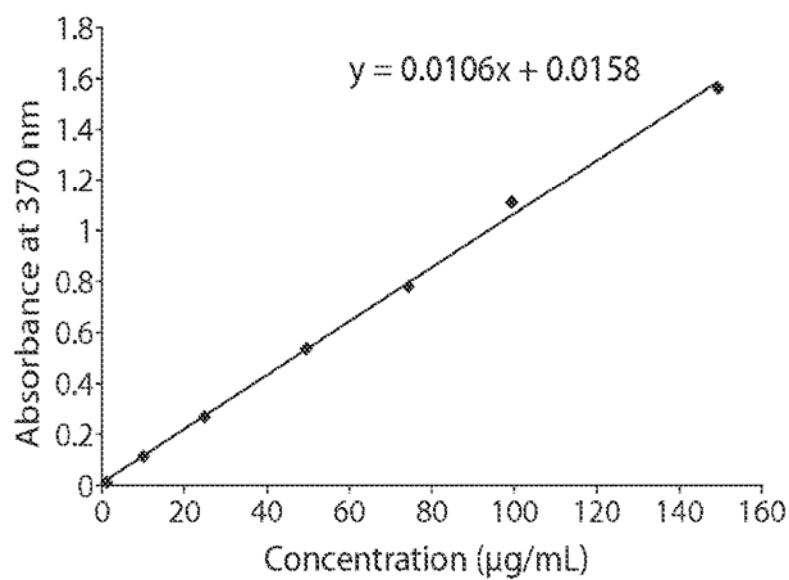


Fig. 57

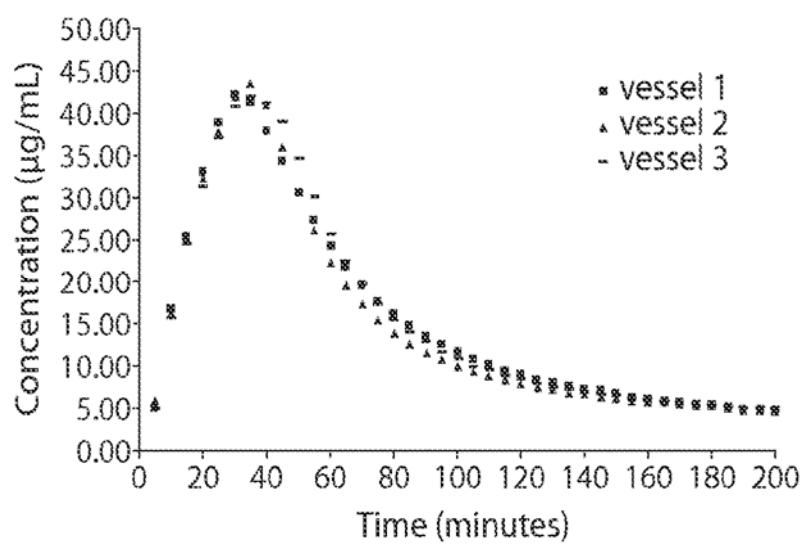


Fig. 58

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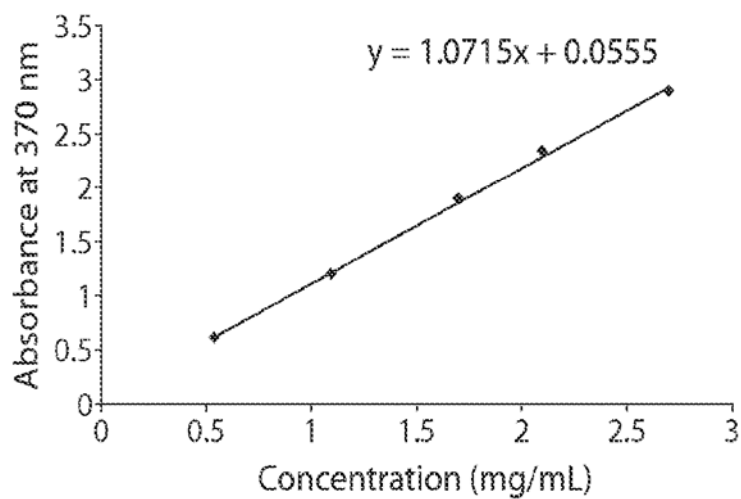


Fig. 59

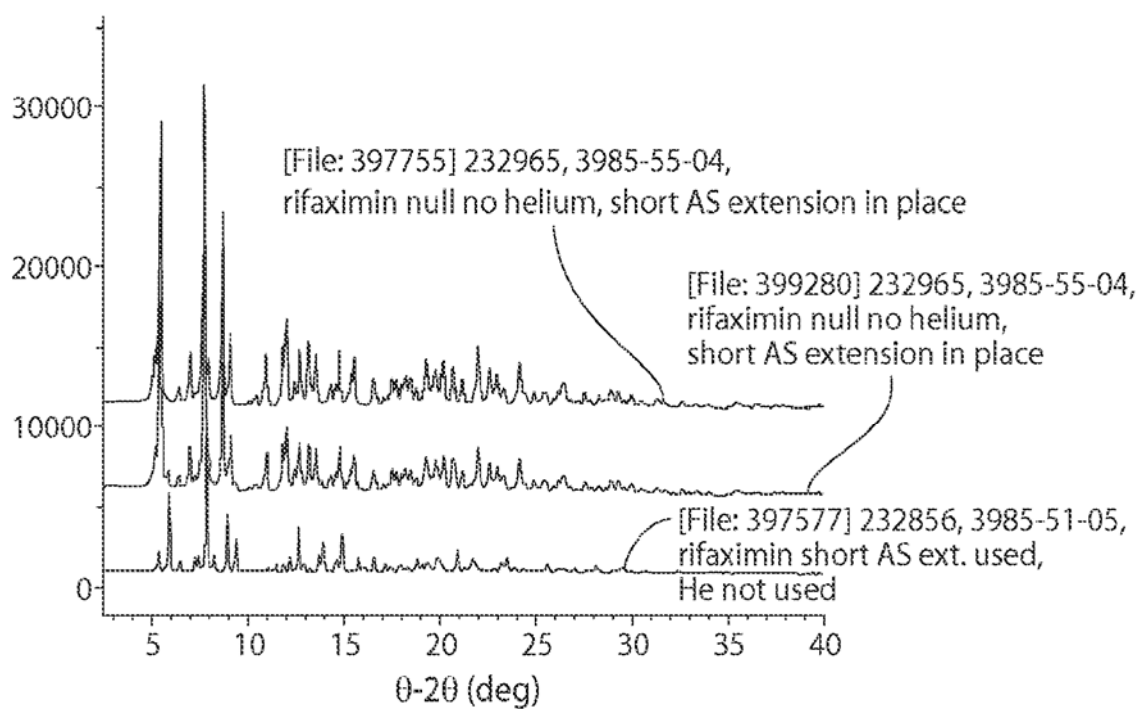
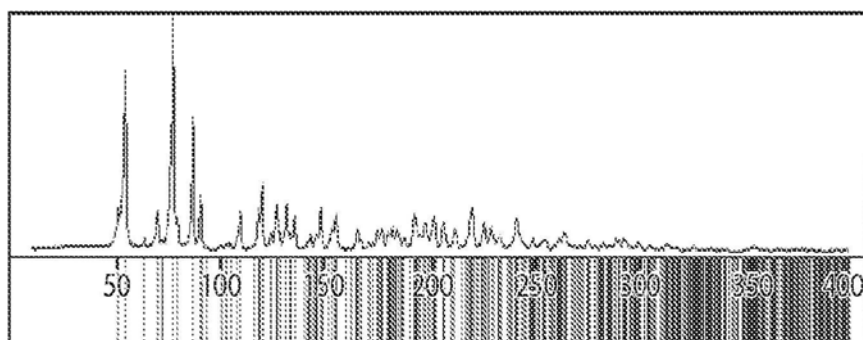


Fig. 60

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Indexing solution and derived quantities

<i>Form / Pattern</i>	Rifaximin Form θ
<i>Family and Space Group</i>	Orthorhombic $P2_12_12_1$ (#19)
Z'/Z	2 / 8
a (Å)	15.274
b (Å)	20.277
c (Å)	32.231
α (deg)	90
β (deg)	90
γ (deg)	90
Volume (Å ³ /cell)	9982.3
V/Z (Å ³ /asym, unit)	1247.8
Assumed Composition ^a	$C_{43}H_{51}N_3O_{11} \cdot xC_2H_6O$ $0 \leq x \leq 4$
Density (g/cm ³) ^a	$1.05 \leq \rho \leq 1.29$
Weight Fraction Solvent (%) ^a	$0 \leq z \leq 19.0$

^aDensity and weight fraction solvent are based on the assumed composition

Fig. 61

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Condition	Results	Comments
vacuum, ambient, 6 hrs	ι	
22% Relative Humidity (RH), ambient, 6 hrs	$\theta + \iota$	θ stable at low RH and at higher RH, mixture so theta and iota occur
~47% RH, ambient, <30min	ι	
75%RH, ambient, 6 hrs	$\gamma + \iota$	>50% RH gives mixtures of iota or eta and γ
75%RH, 40 °C, 6 hrs	$\gamma + \eta$	
40 °C, 6 hrs	η	Elevated temp gives η
vacuum, 60 °C, 6 hrs	η	

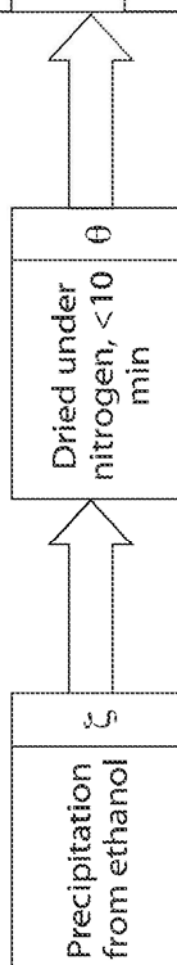


Fig. 62

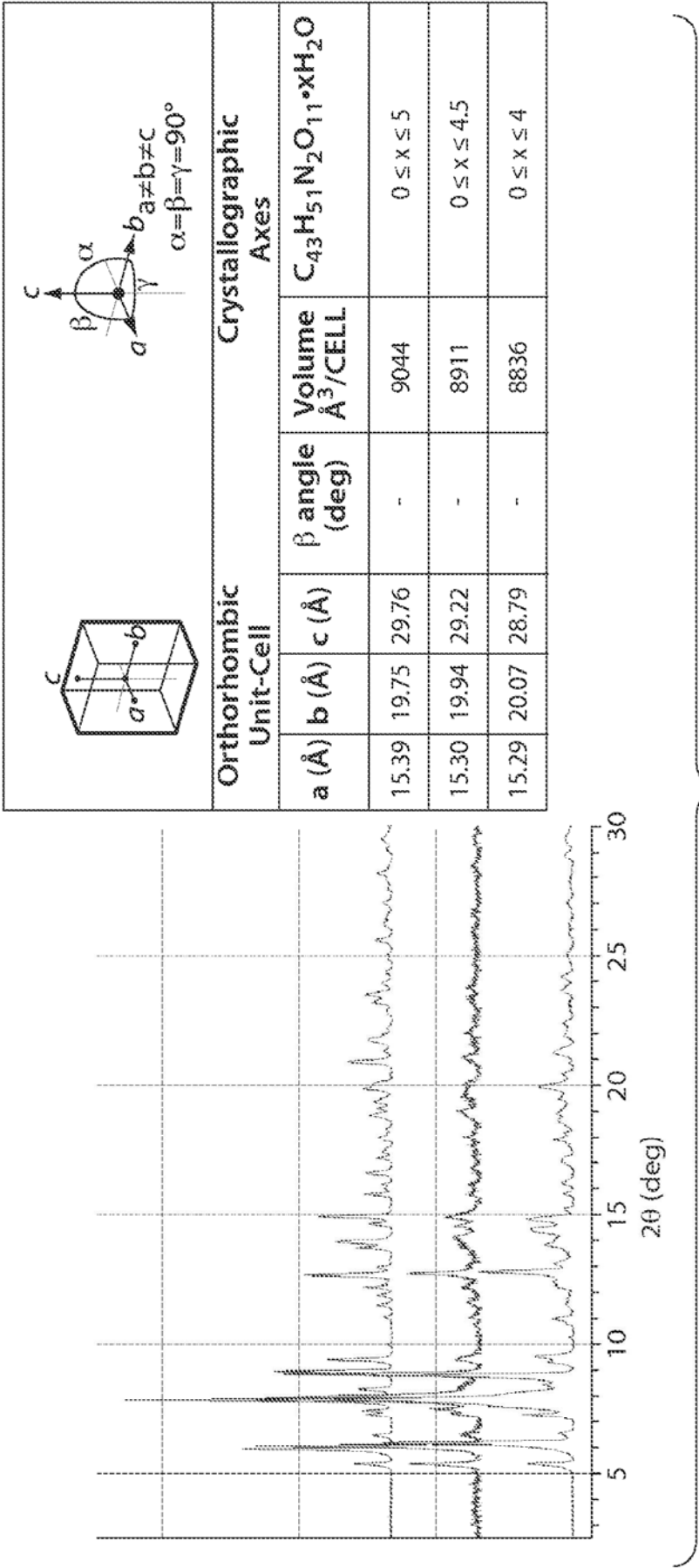


Fig. 63

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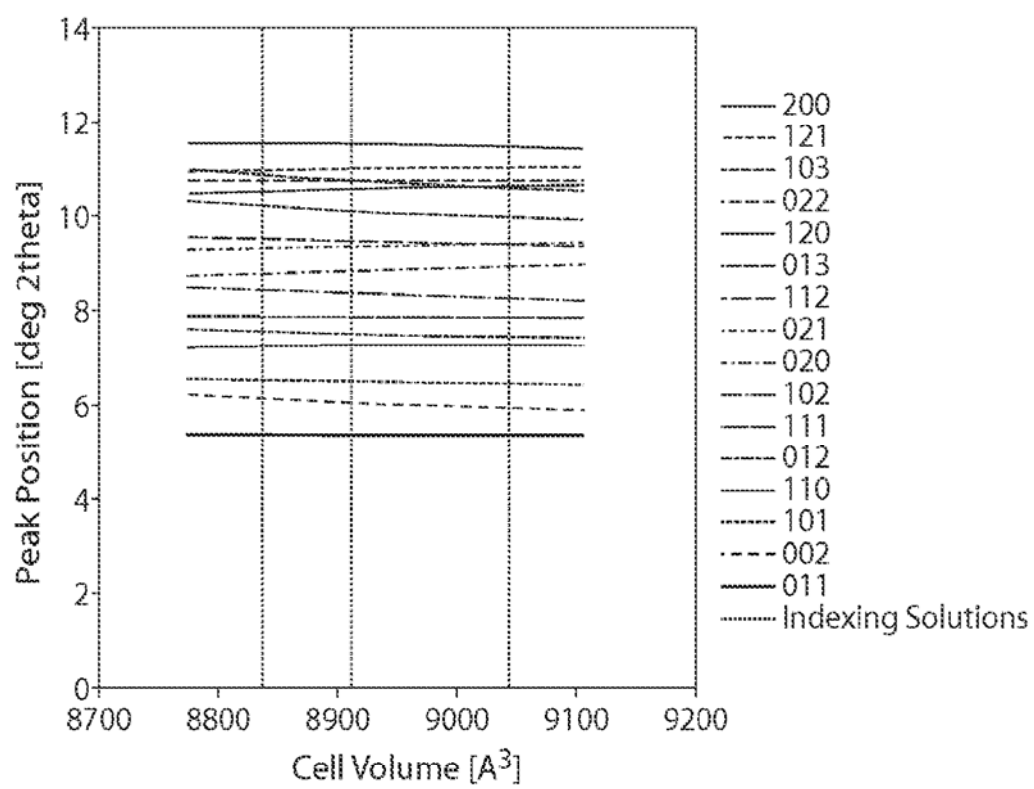


Fig. 64

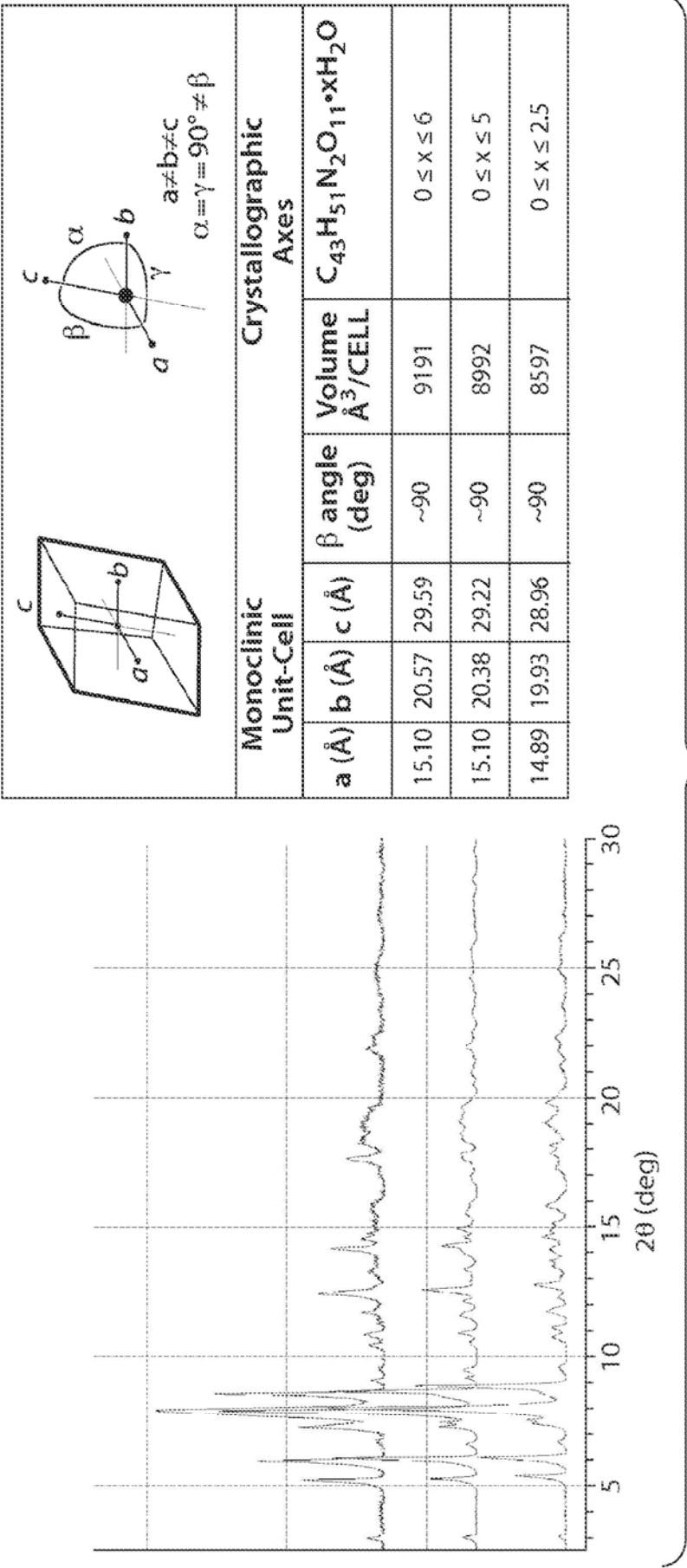


Fig. 65

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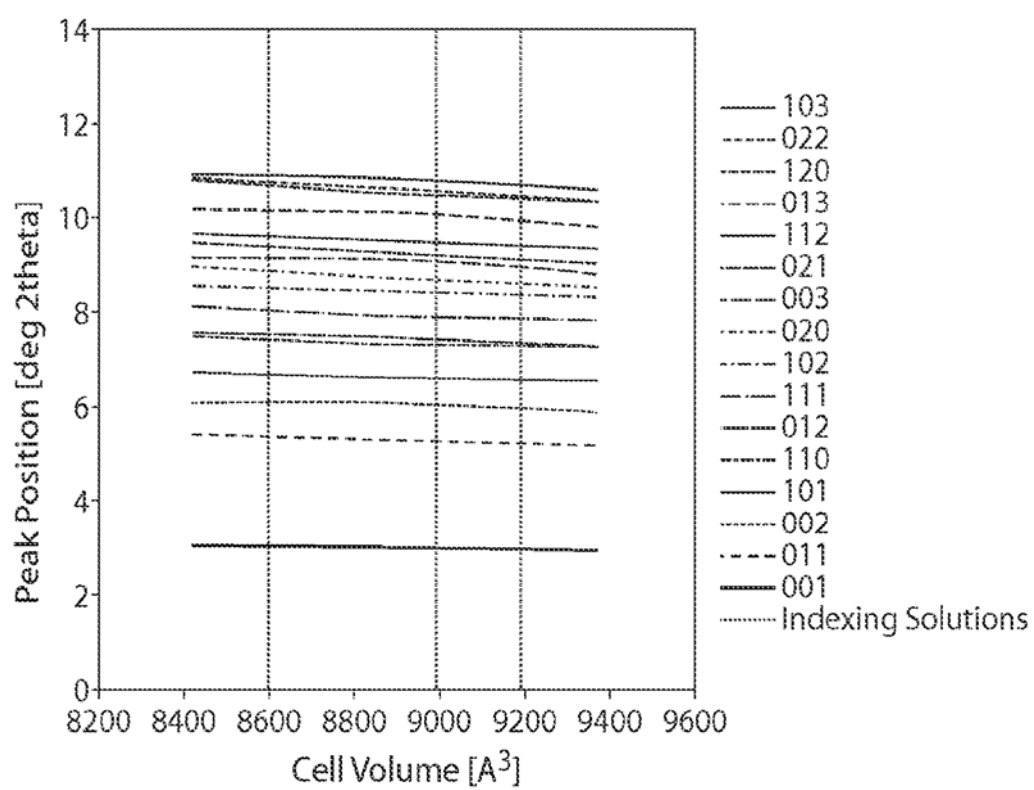


Fig. 66

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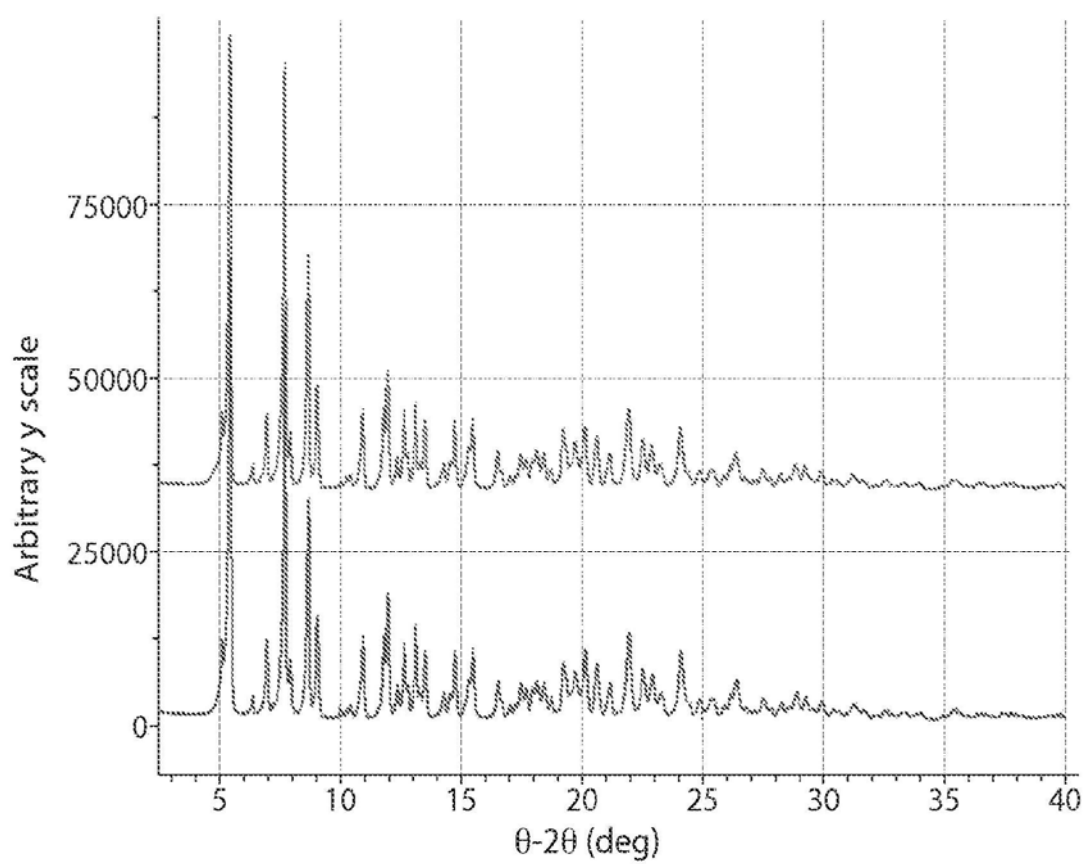


Fig. 67

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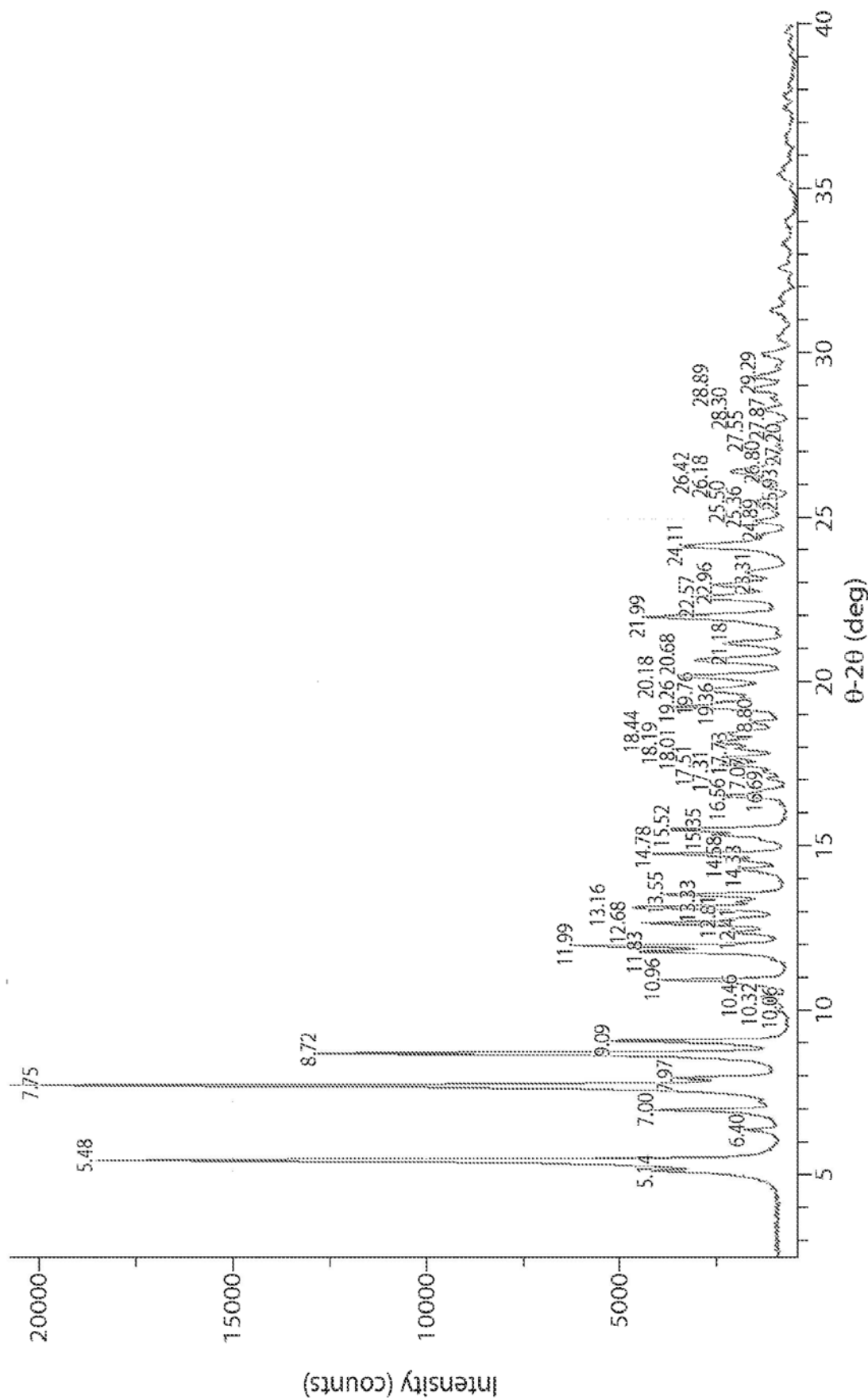


Fig. 68

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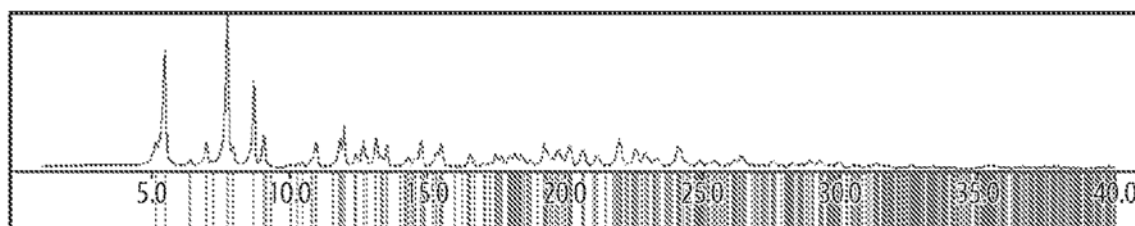


Fig. 69

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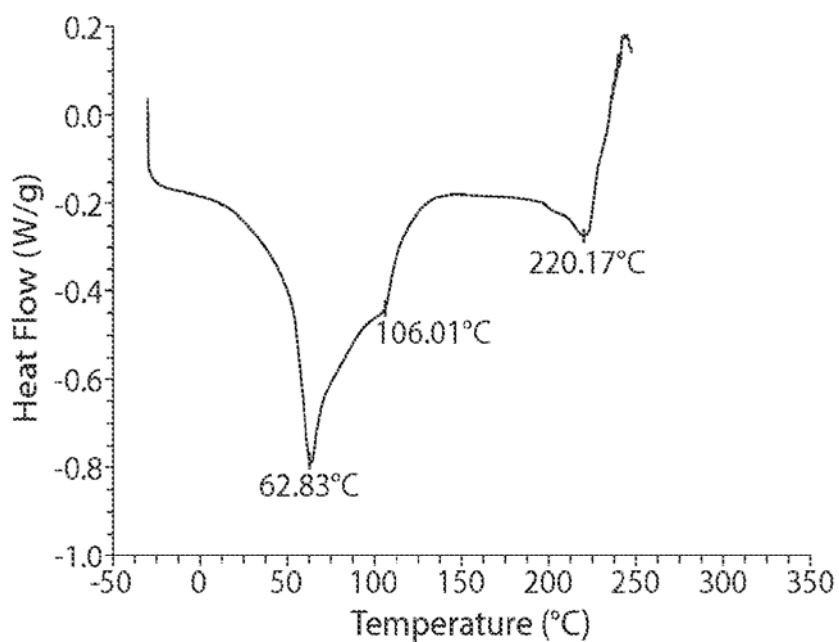


Fig. 70A

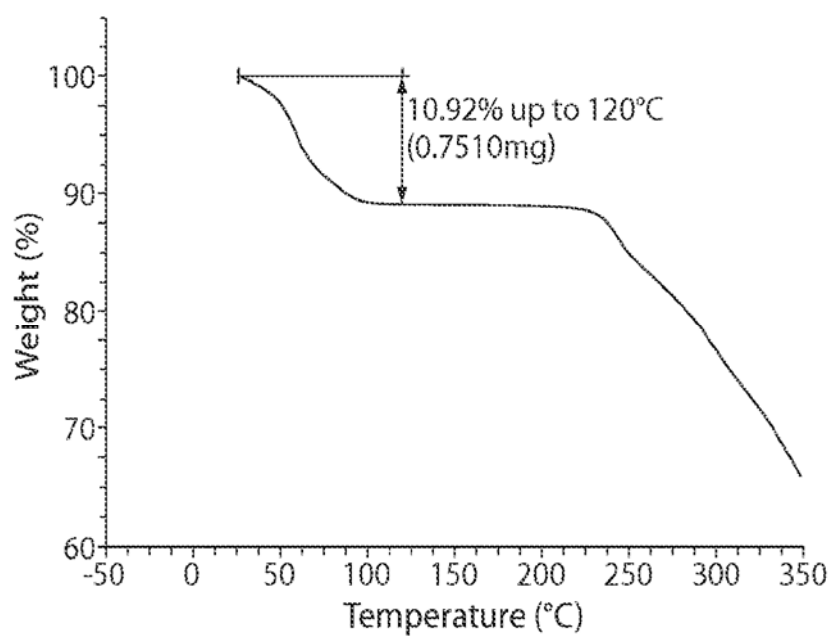


Fig. 70B

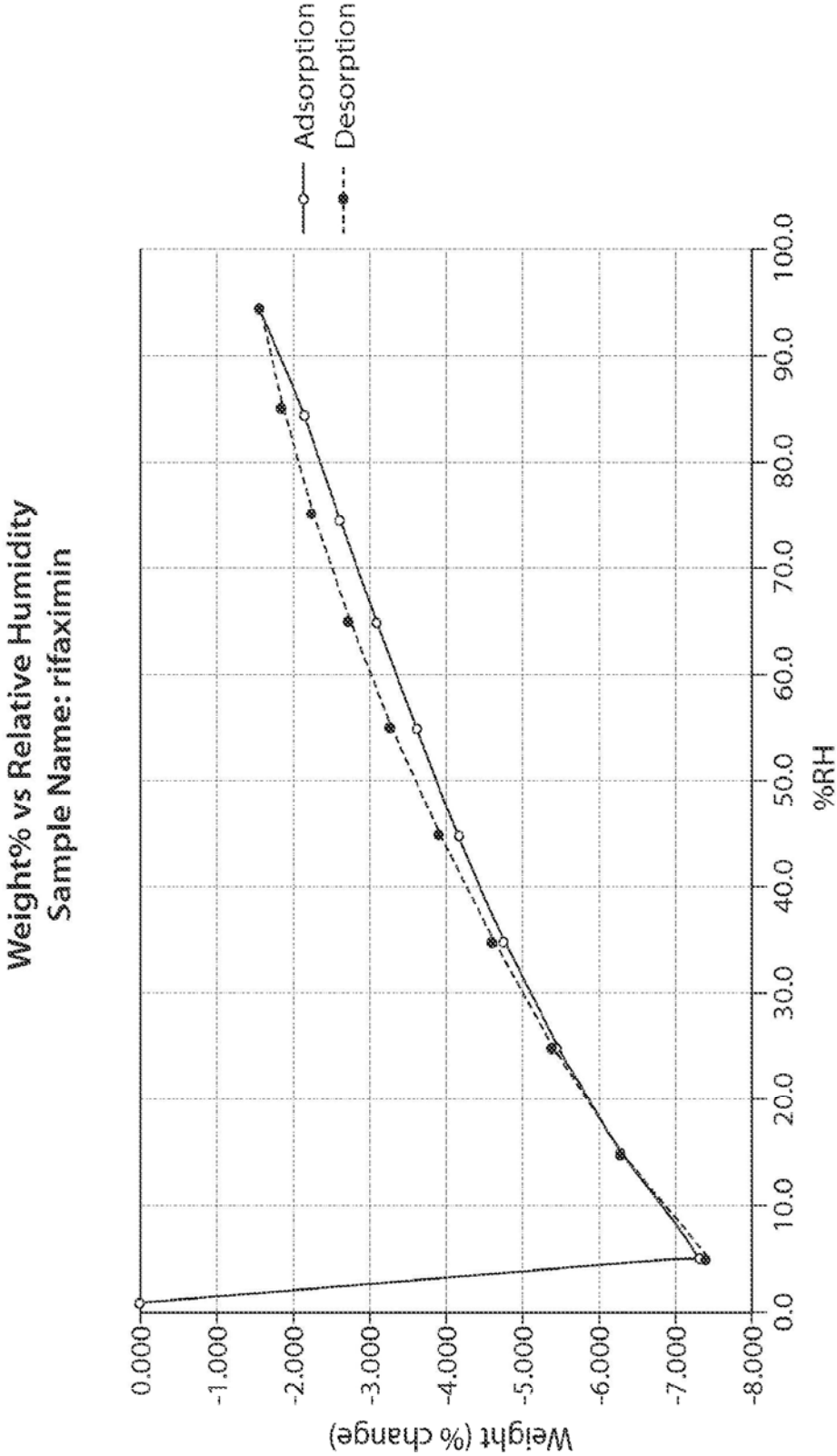


Fig. 71

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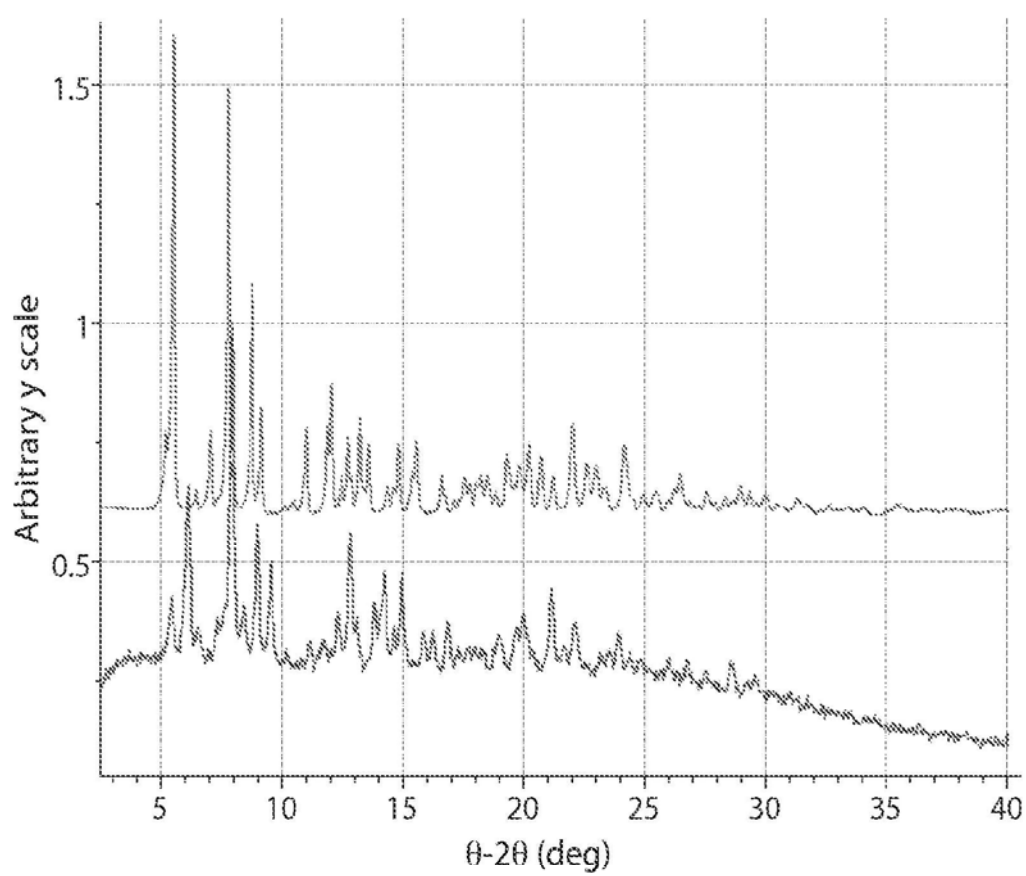


Fig. 72