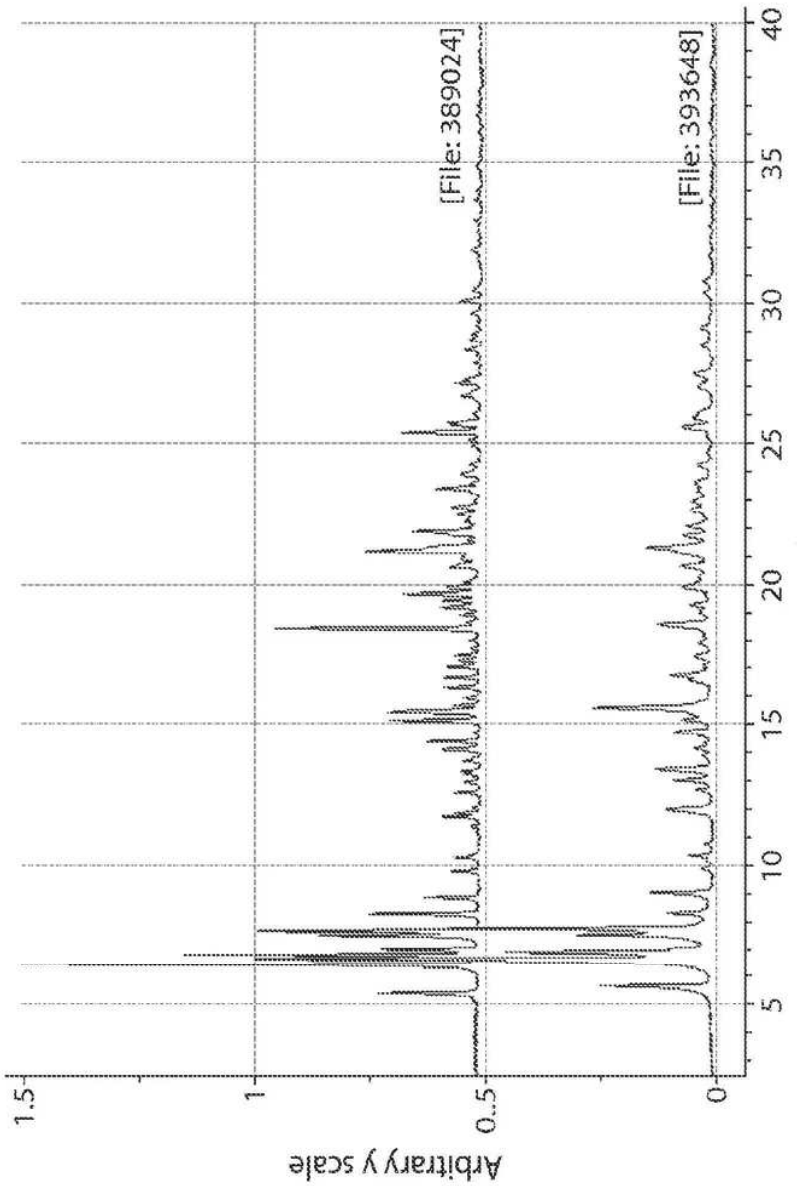

[File: 389024]
[File: 393648]
Arbitrary y scale
θ-2θ (deg)
0
0.5
1
1.5
5
10
15
20
25
30
35
40

Fig. 1

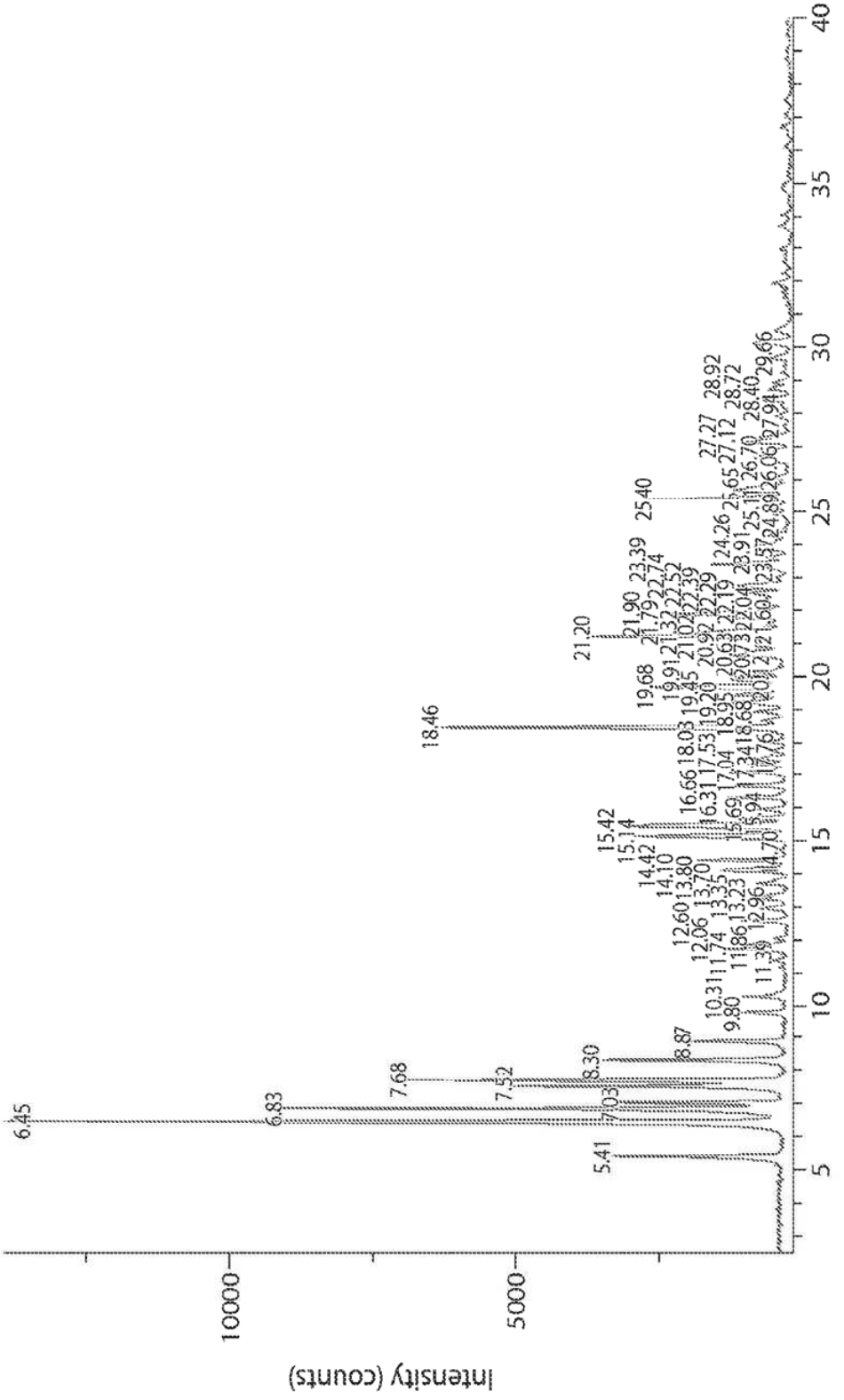

Intensity (counts)
10000
5000
θ-2θ (deg)
5
10
15
20
25
30
35
40
6.45
6.83
7.68
7.52
8.30
8.87
9.80
10.31
11.74
12.06
12.60
13.23
13.70
14.10
14.42
15.14
15.42
16.31
16.66
17.53
18.03
18.46
19.20
19.45
19.68
19.91
20.92
21.20
21.90
22.39
22.74
23.39
24.26
25.40
26.70
27.27
27.94
28.40
28.72
28.92
29.66

Fig. 2

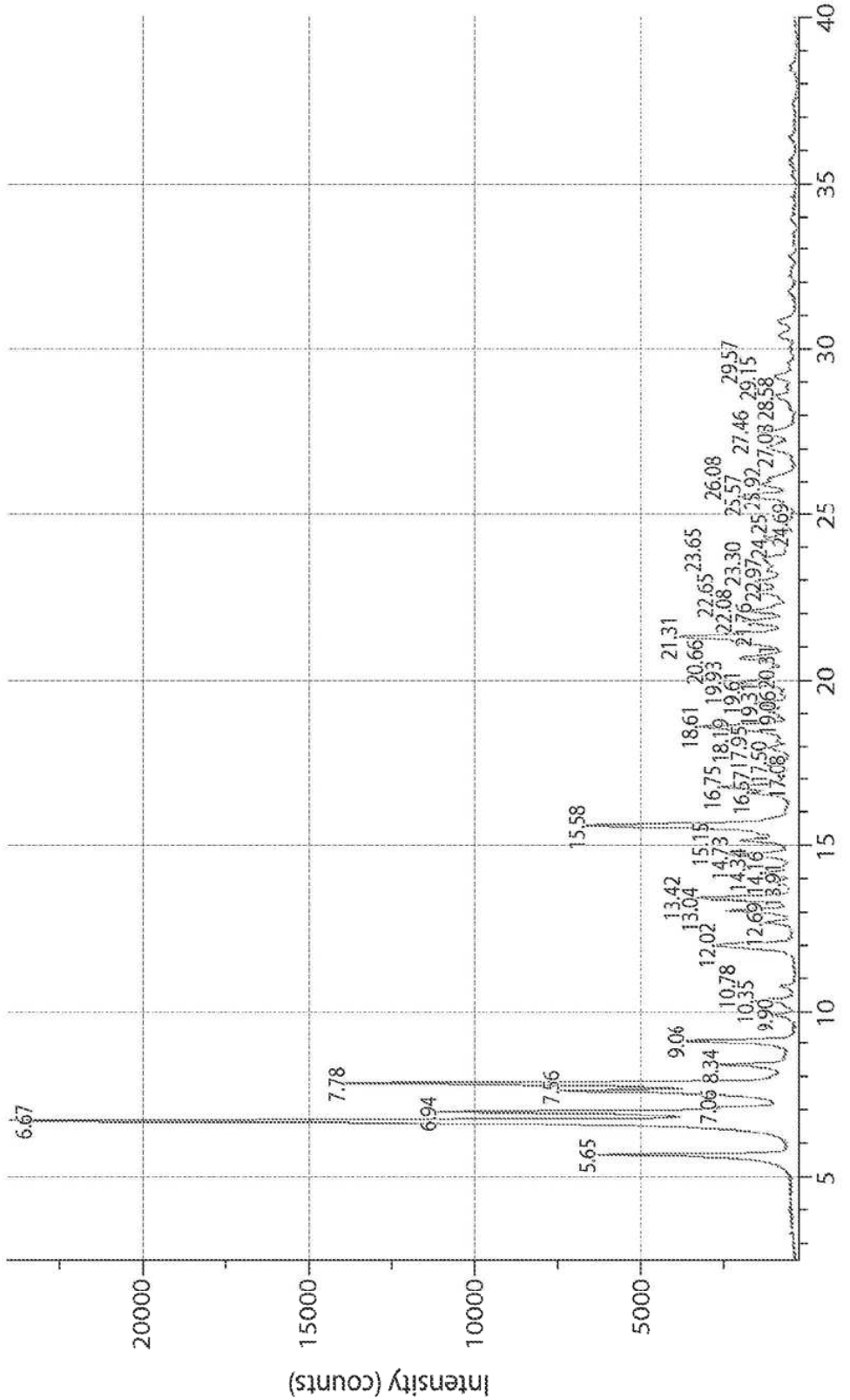

Intensity (counts)
20000
15000
10000
5000
θ-2θ (deg)
5
10
15
20
25
30
35
40
6.67
7.78
6.94
7.56
5.65
7.06
8.34
9.06
9.90
10.35
10.78
12.02
12.69
13.04
13.42
14.16
14.34
14.73
15.15
15.58
16.57
16.75
17.50
17.95
18.19
18.61
19.06
19.31
19.61
19.93
20.31
20.66
21.31
21.76
22.08
22.65
23.30
23.65
24.25
24.69
25.57
25.92
26.08
27.08
27.46
28.58
29.15
29.57

Fig. 3

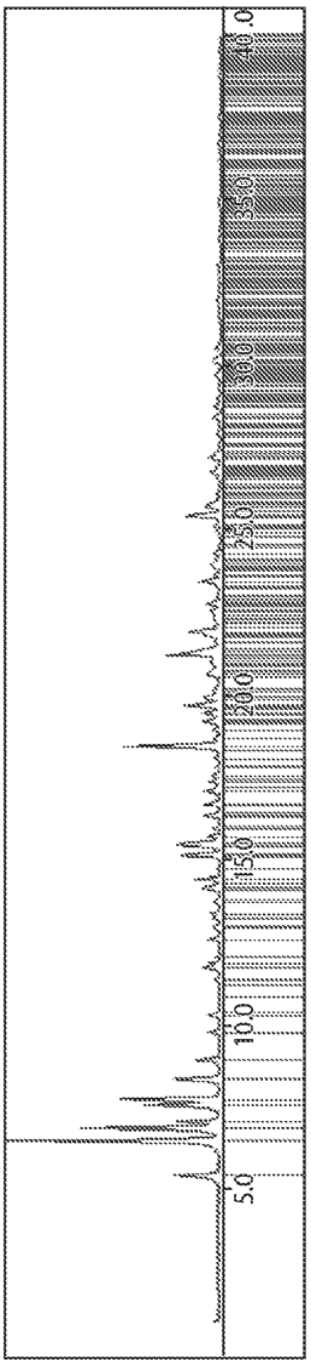


Fig. 4

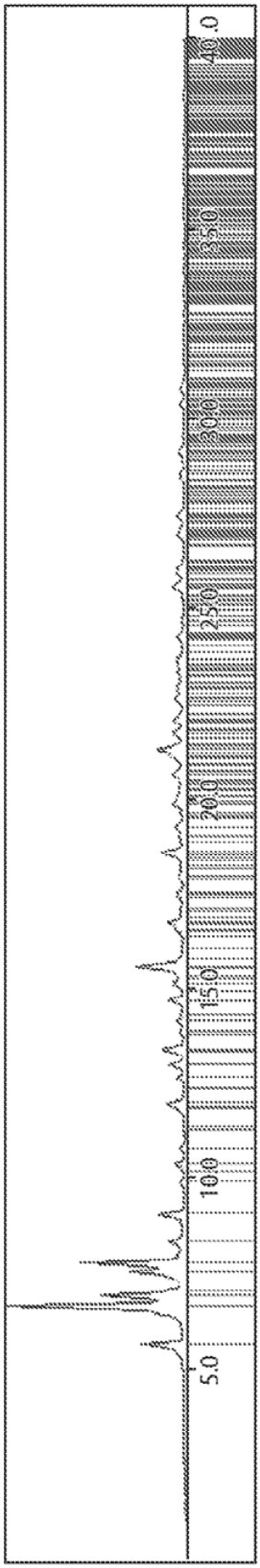


Fig. 5

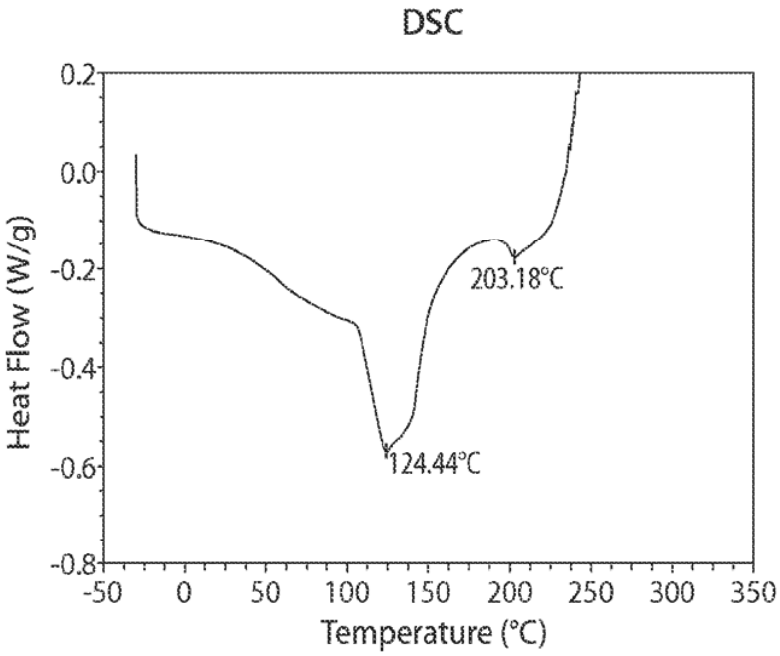

DSC
0.2
0.0
-0.2
-0.4
-0.6
-0.8
Heat Flow (W/g)
203.18°C
124.44°C
-50
0
50
100
150
200
250
300
350
Temperature (°C)

Fig. 6

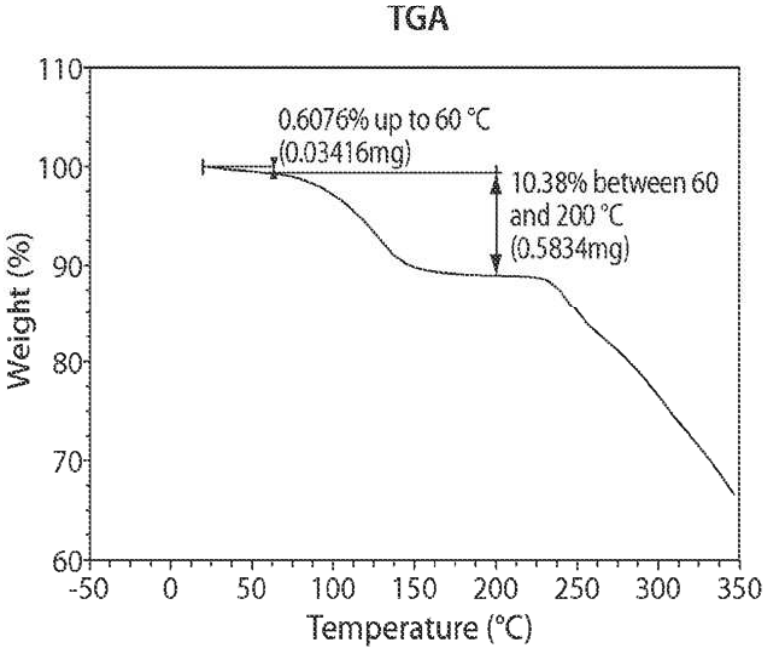

TGA
110
100
90
80
70
60
Weight (%)
0.6076% up to 60 °C
(0.03416mg)
10.38% between 60
and 200 °C
(0.5834mg)
-50
0
50
100
150
200
250
300
350
Temperature (°C)

Fig. 7

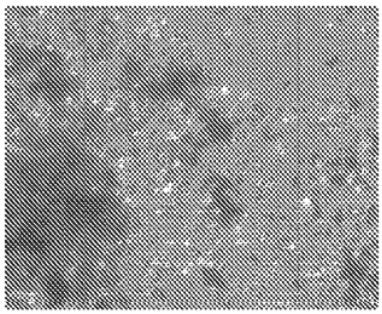


Fig. 8A

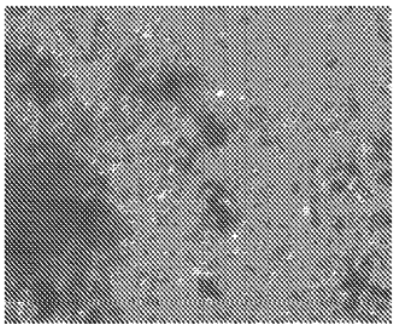


Fig. 8B

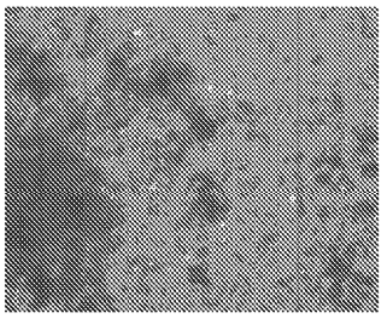


Fig. 8C

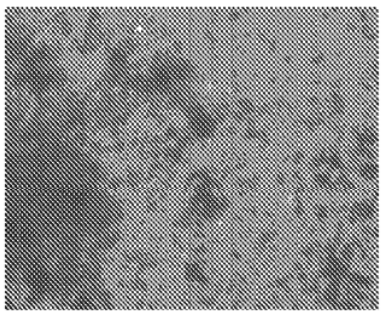


Fig. 8D

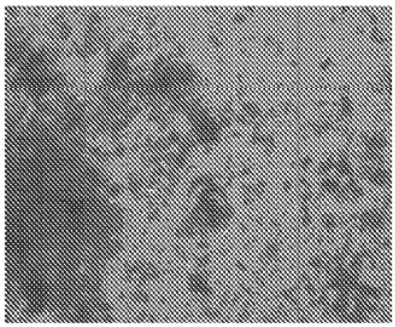


Fig. 8E

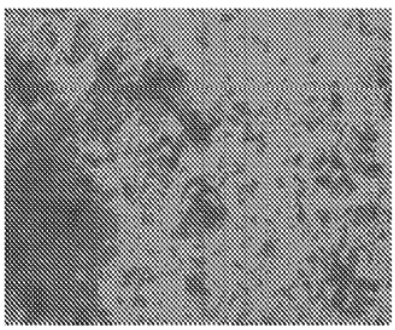


Fig. 8F

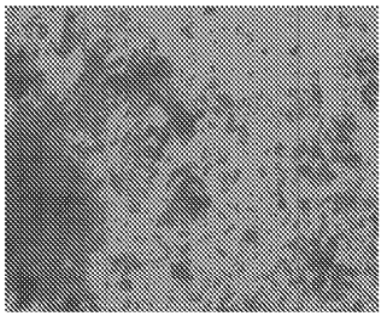


Fig. 8G

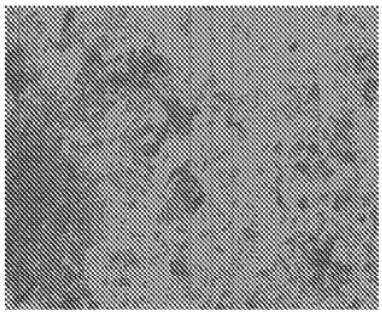


Fig. 8H

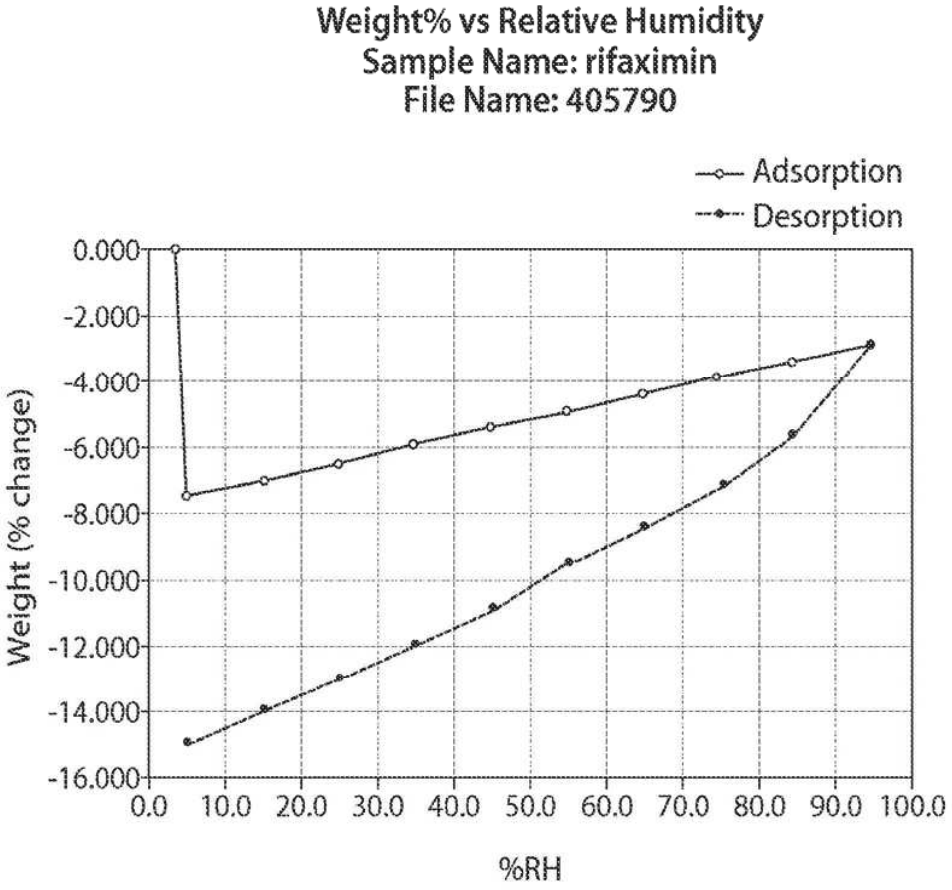

Weight% vs Relative Humidity
Sample Name: rifaximin
File Name: 405790
Adsorption
Desorption
0.000
-2.000
-4.000
-6.000
-8.000
-10.000
-12.000
-14.000
-16.000
Weight (% change)
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
%RH

Fig. 9

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

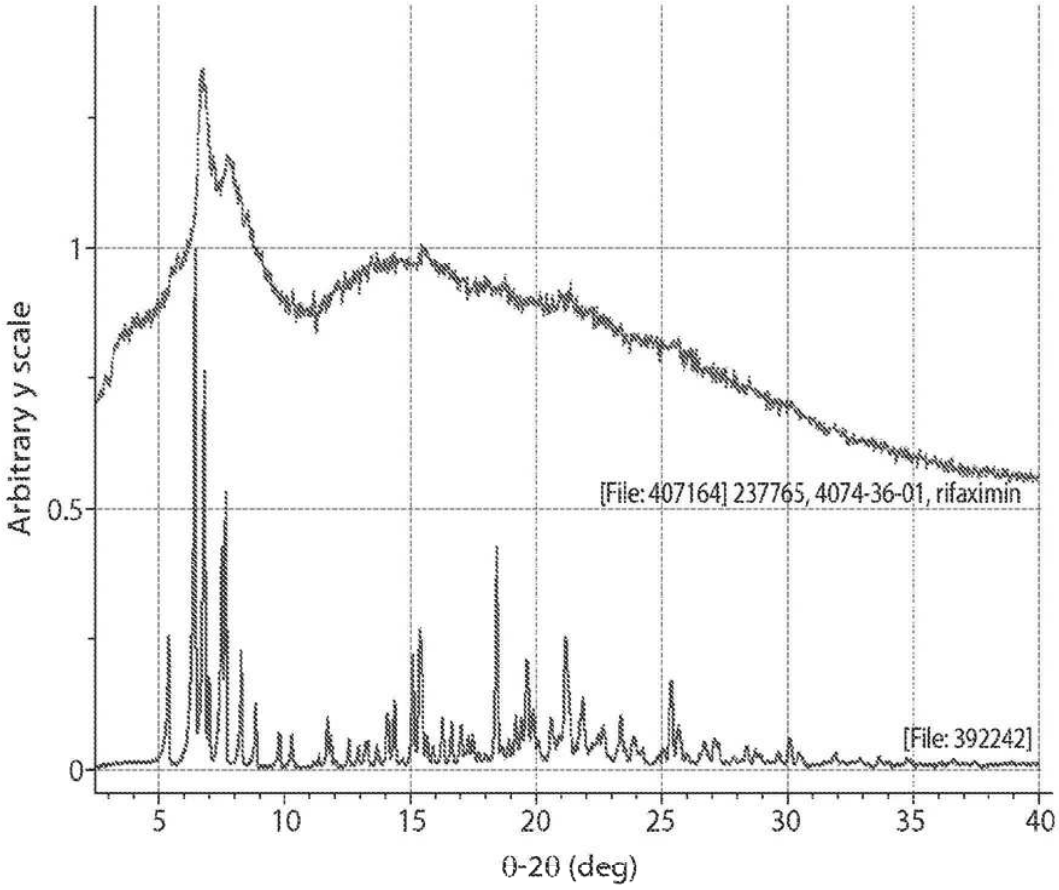

Arbitrary y scale
1
0.5
0
[File: 407164] 237765, 4074-36-01, rifaximin
[File: 392242]
5
10
15
20
25
30
35
40
0-20 (deg)

Fig. 10

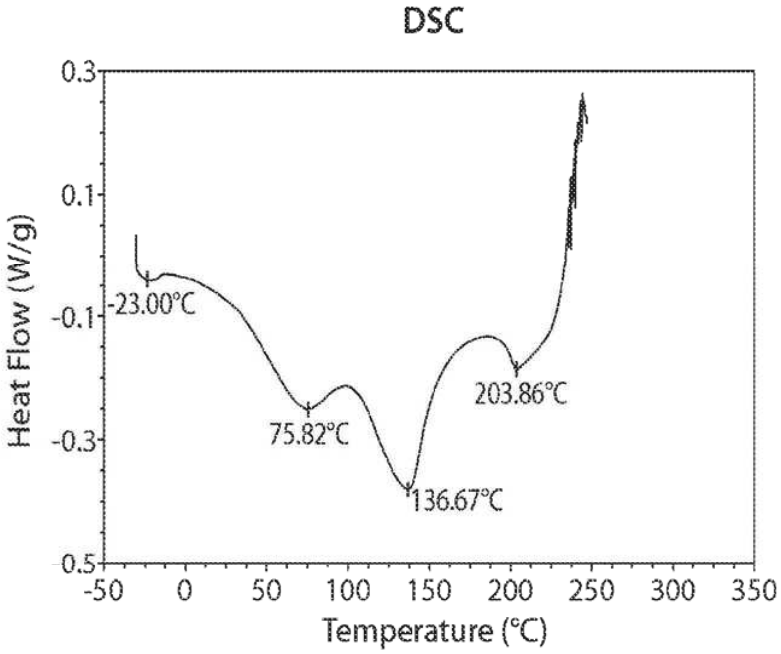

DSC
Heat Flow (W/g)
0.3
0.1
-0.1
-0.3
0.5
-23.00°C
75.82°C
136.67°C
203.86°C
-50
0
50
100
150
200
250
300
350
Temperature (°C)

Fig. 11

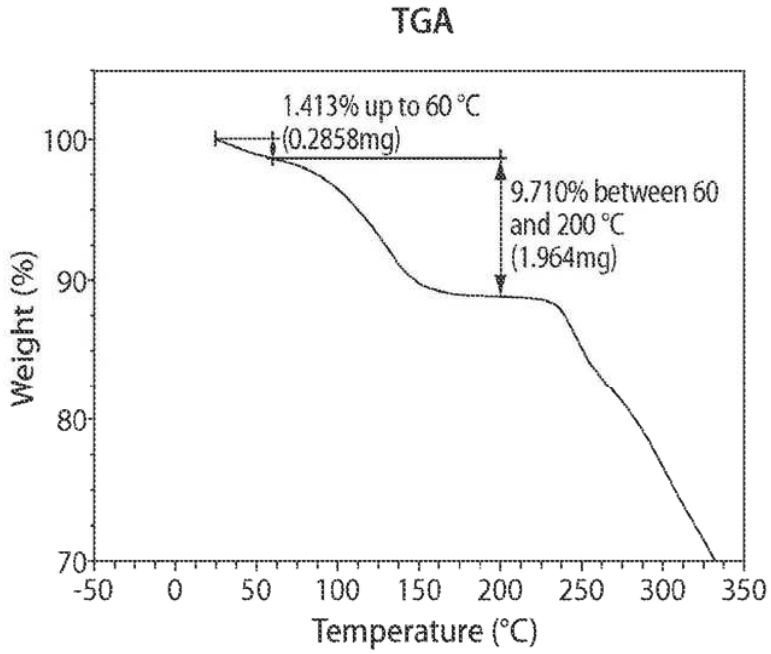

TGA
1.413% up to 60 °C
(0.2858mg)
9.710% between 60
and 200 °C
(1.964mg)
Weight (%)
100
90
80
70
-50
0
50
100
150
200
250
300
350
Temperature (°C)

Fig. 12

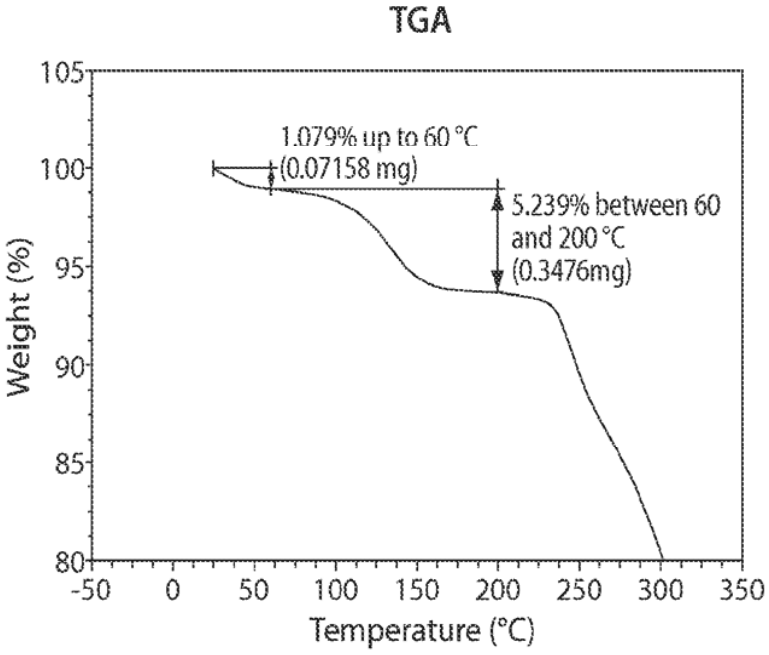

TGA
105
100
95
90
85
80
Weight (%)
1.079% up to 60 °C
(0.07158 mg)
5.239% between 60
and 200 °C
(0.3476mg)
-50
0
50
100
150
200
250
300
350
Temperature (°C)

Fig. 13

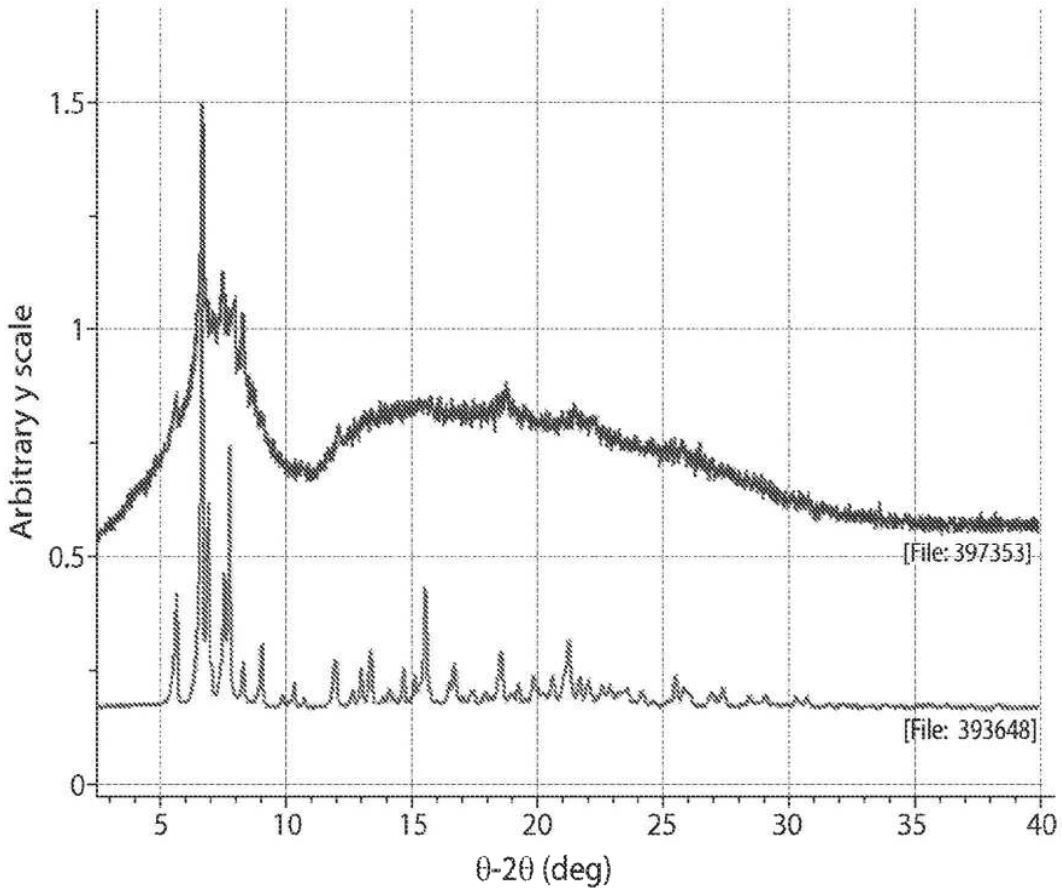

1.5
1
0.5
0
Arbitrary y scale
[File: 397353]
[File: 393648]
5
10
15
20
25
30
35
40
θ-2θ (deg)

Fig. 14

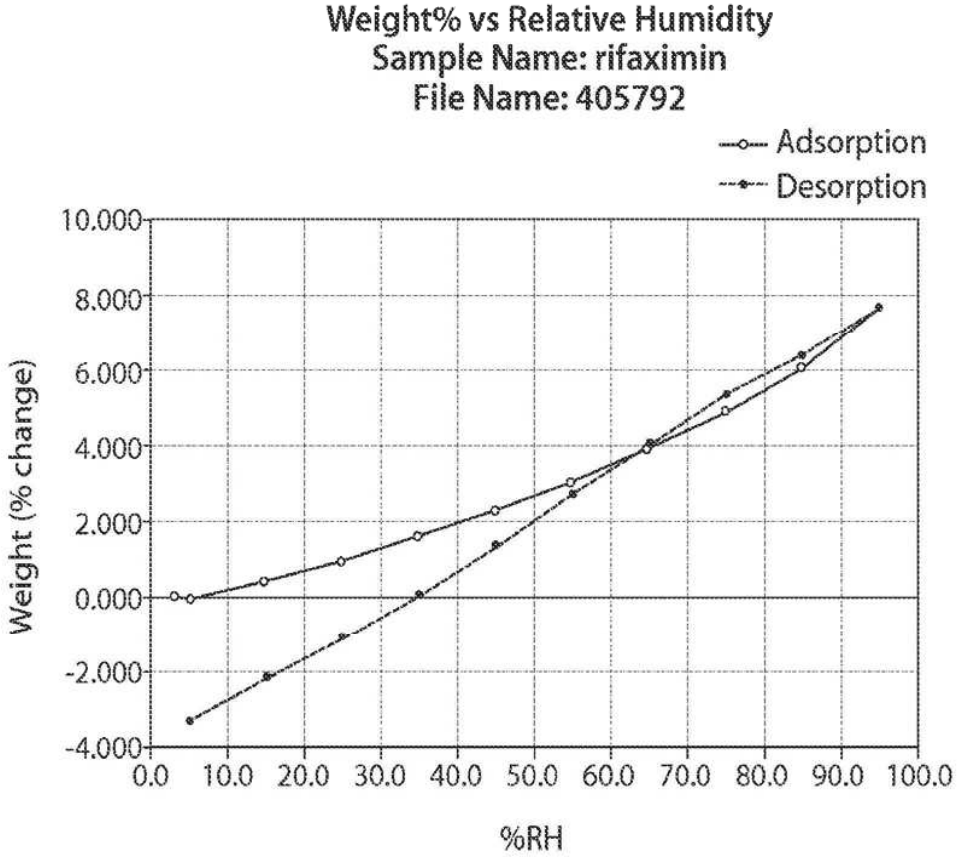

Weight% vs Relative Humidity
Sample Name: rifaximin
File Name: 405792
Adsorption
Desorption
Weight (% change)
10.000
8.000
6.000
4.000
2.000
0.000
-2.000
-4.000
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
%RH

Fig. 15

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

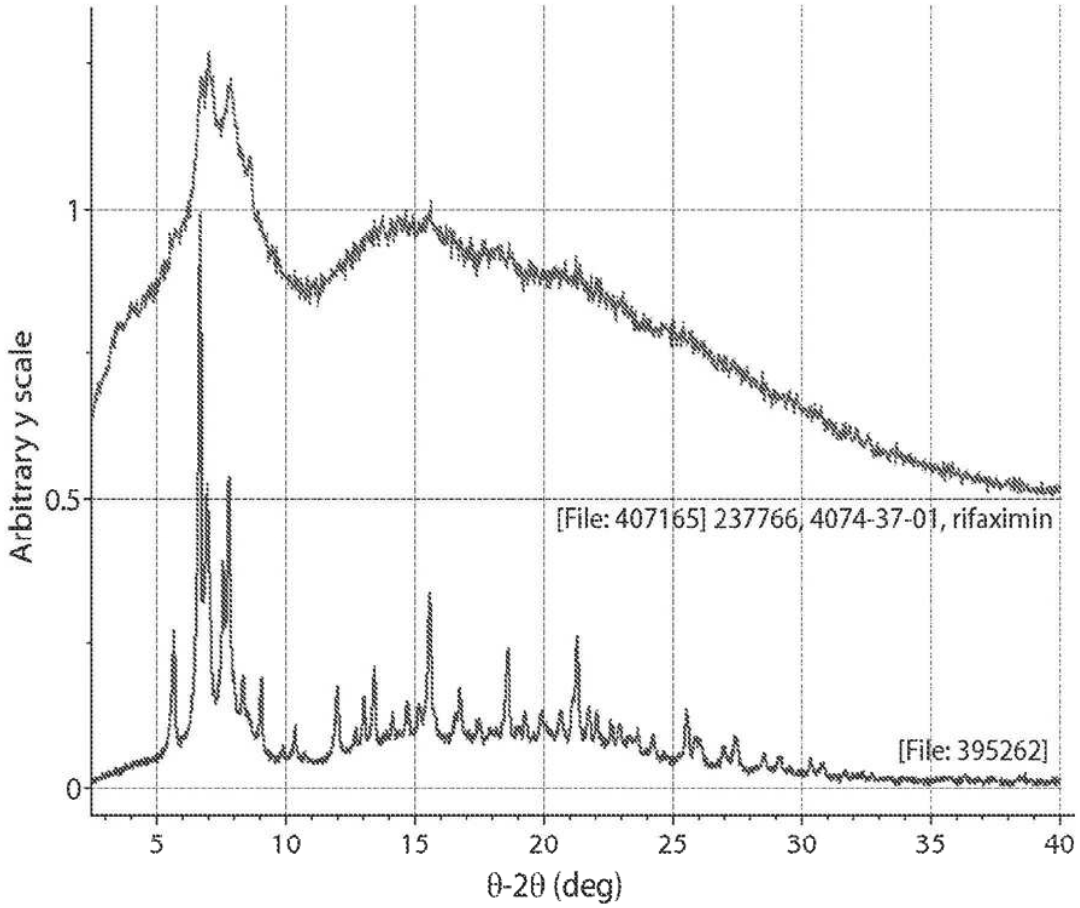

Arbitrary y scale
1
0.5
0
[File: 407165] 237766, 4074-37-01, rifaximin
[File: 395262]
5
10
15
20
25
30
35
40
θ-2θ (deg)

Fig. 16

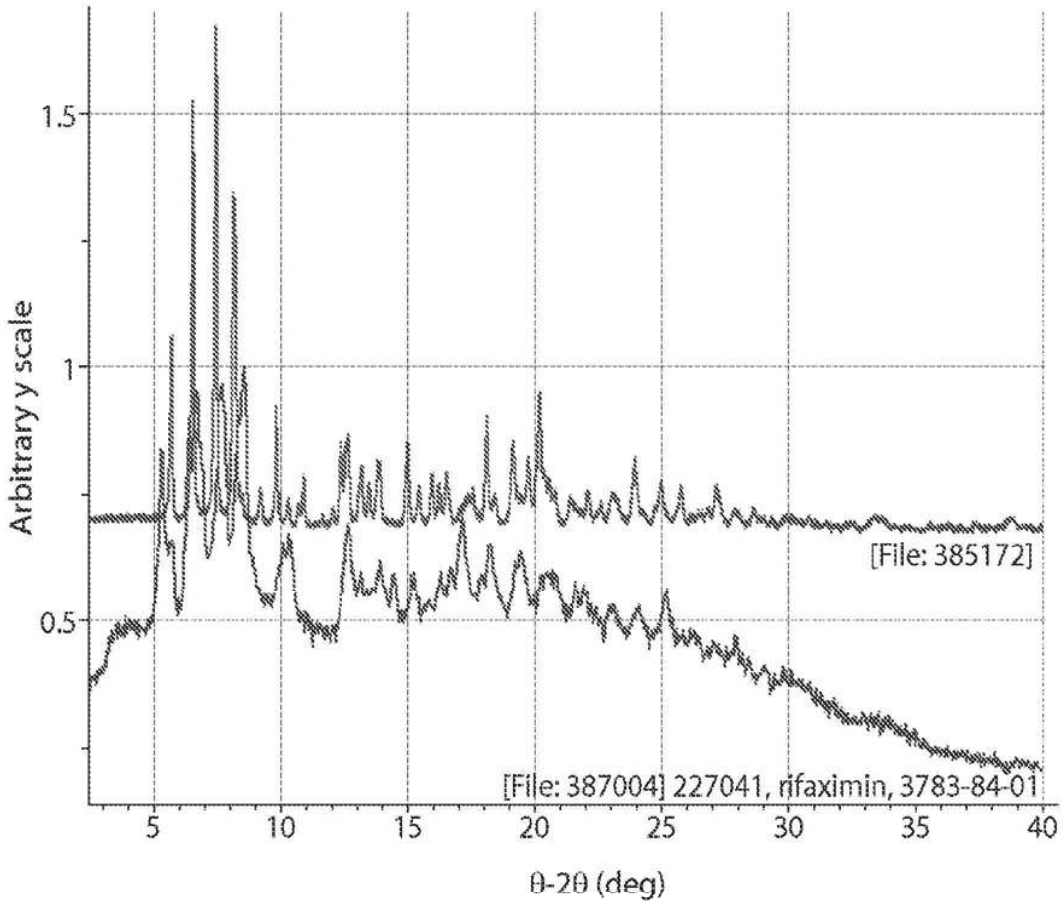

1.5
1
0.5
Arbitrary y scale
[File: 385172]
[File: 387004] 227041, rifaximin, 3783-84-01
5
10
15
20
25
30
35
40
θ-2θ (deg)

Fig. 17

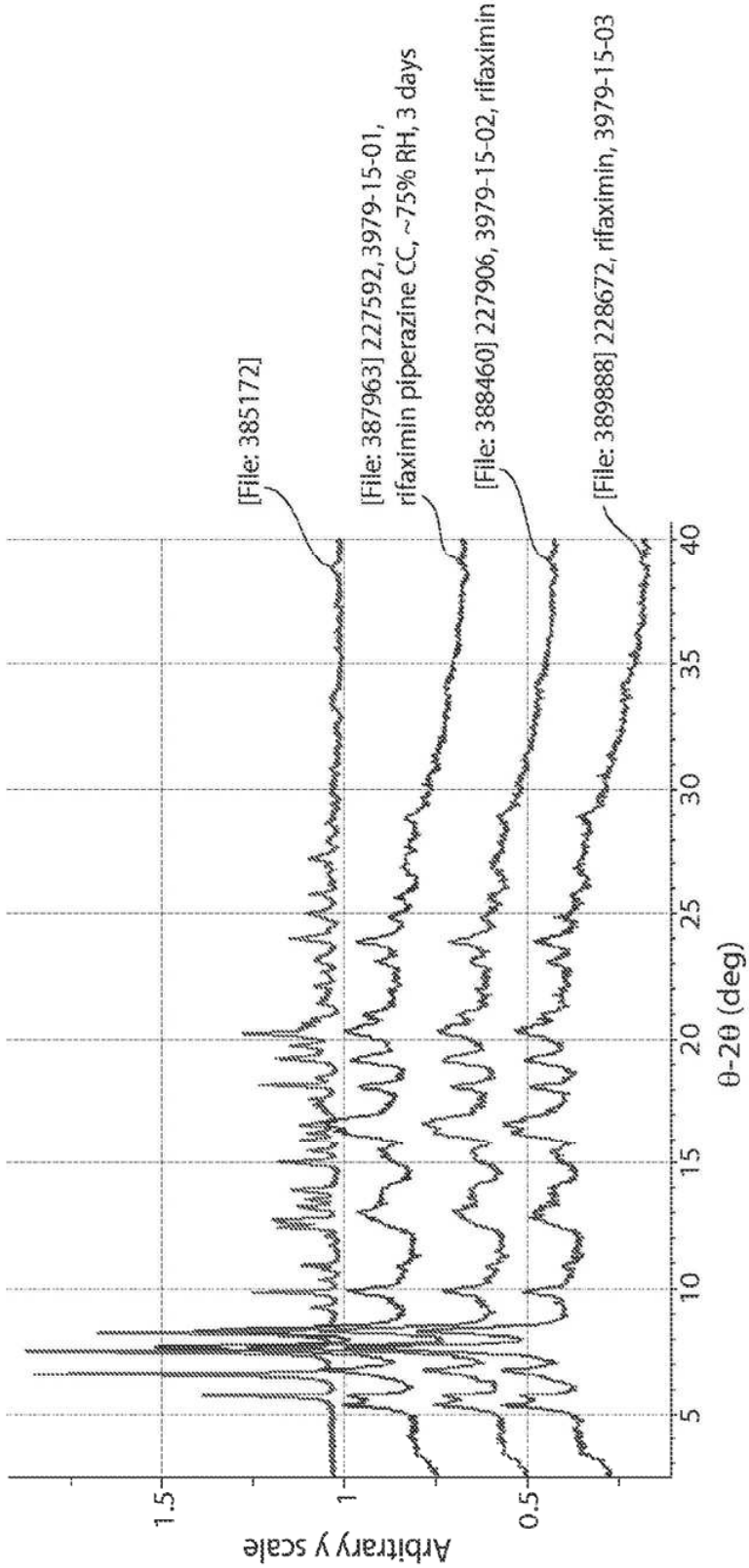

[File: 385172]
[File: 387963] 227592, 3979-15-01, rifaximin piperazine CC, ~75% RH, 3 days
[File: 388460] 227906, 3979-15-02, rifaximin
[File: 389888] 228672, rifaximin, 3979-15-03
Arbitrary y scale
0.5
1
1.5
θ-2θ (deg)
5
10
15
20
25
30
35
40

Fig. 18

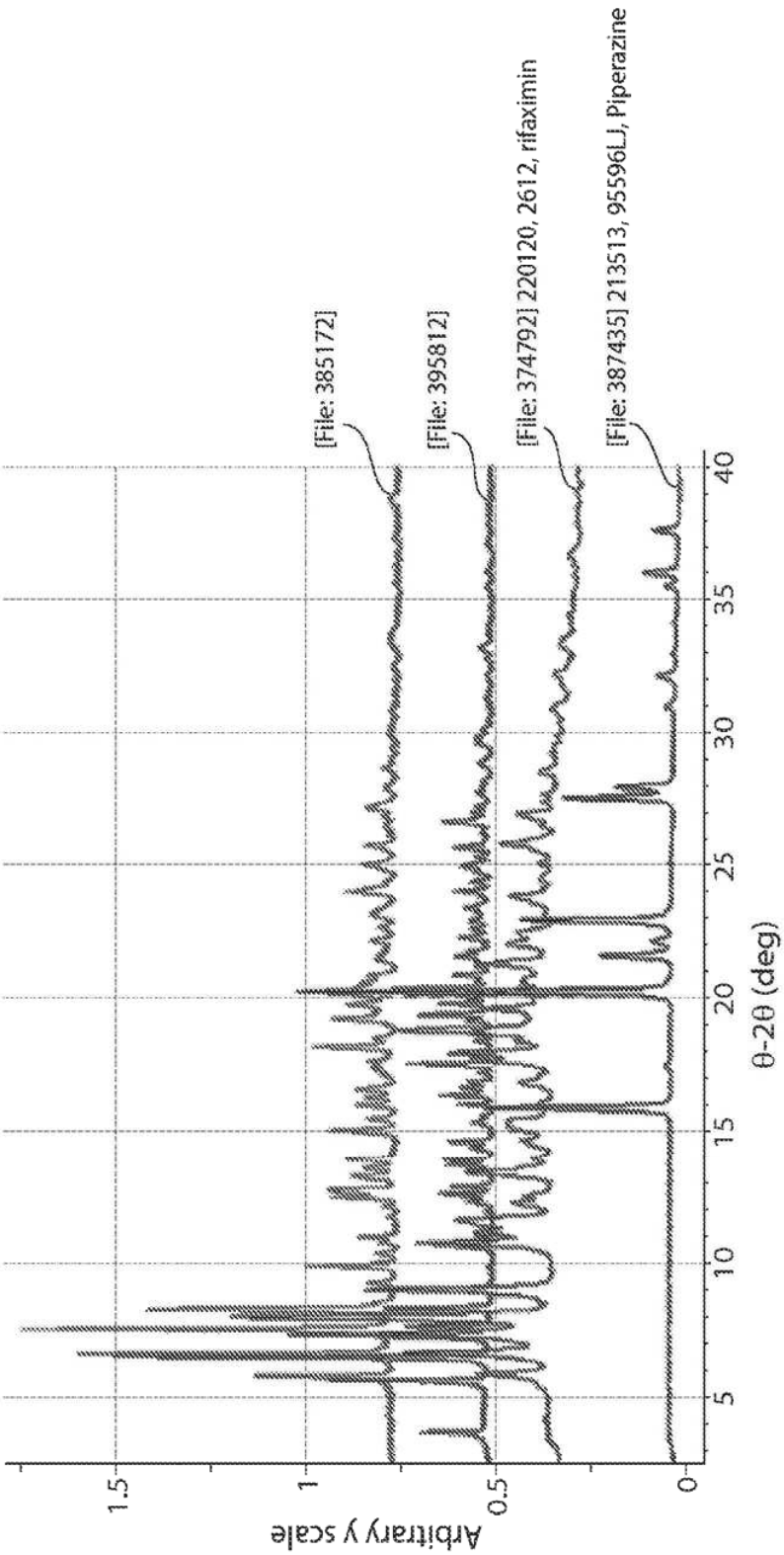

[File: 385172]
[File: 395812]
[File: 374792] 220120, 2612, rifaximin
[File: 387435] 213513, 95596LJ, Piperazine
Arbitrary y scale
0
0.5
1
1.5
θ-2θ (deg)
5
10
15
20
25
30
35
40

Fig. 19

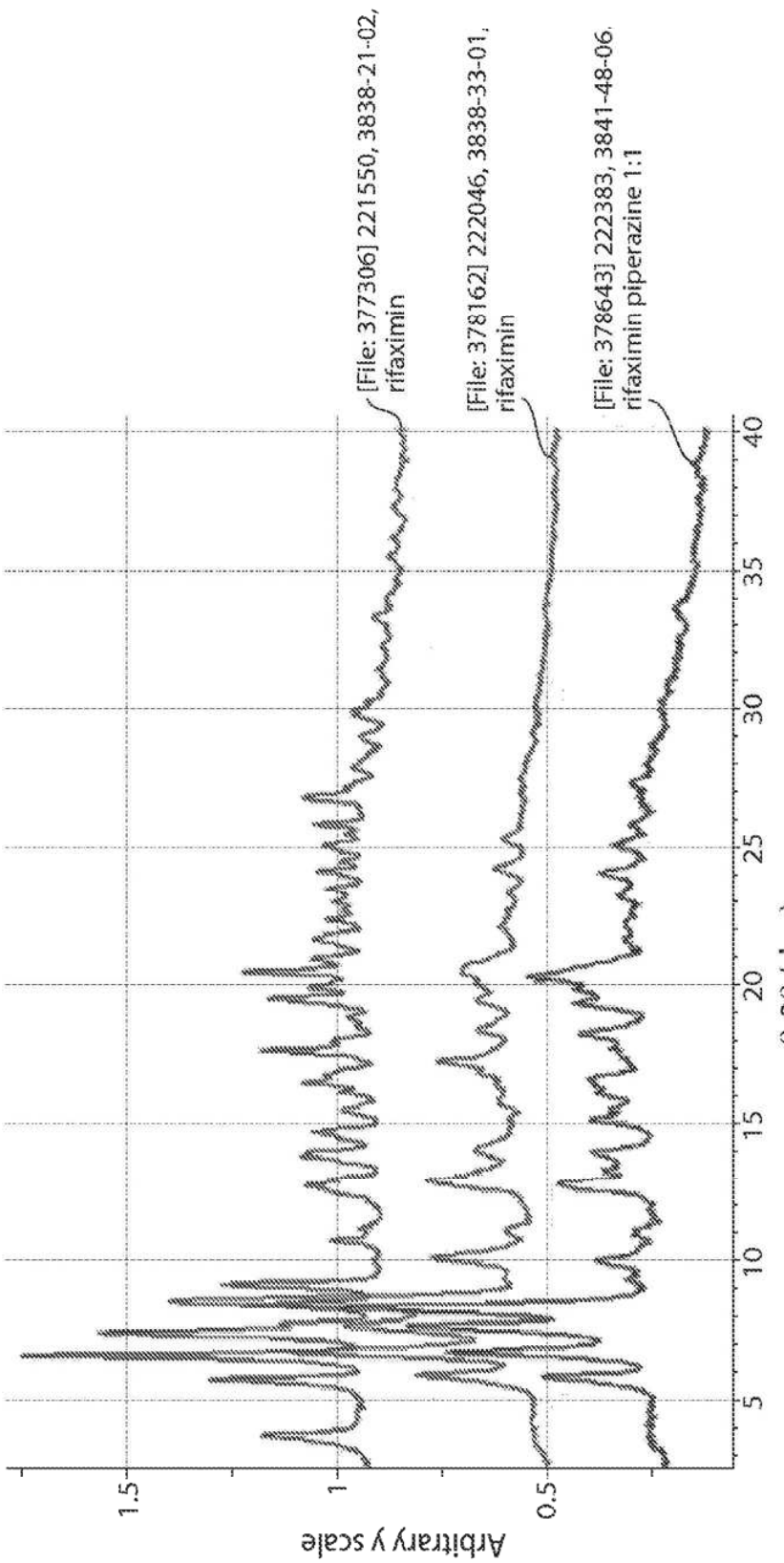

[File: 377306] 221550, 3838-21-02, rifaximin
[File: 378162] 222046, 3838-33-01, rifaximin
[File: 378643] 222383, 3841-48-06, rifaximin piperazine 1:1
Arbitrary y scale
0.5
1
1.5
θ-2θ (deg)
5
10
15
20
25
30
35
40

Fig. 20

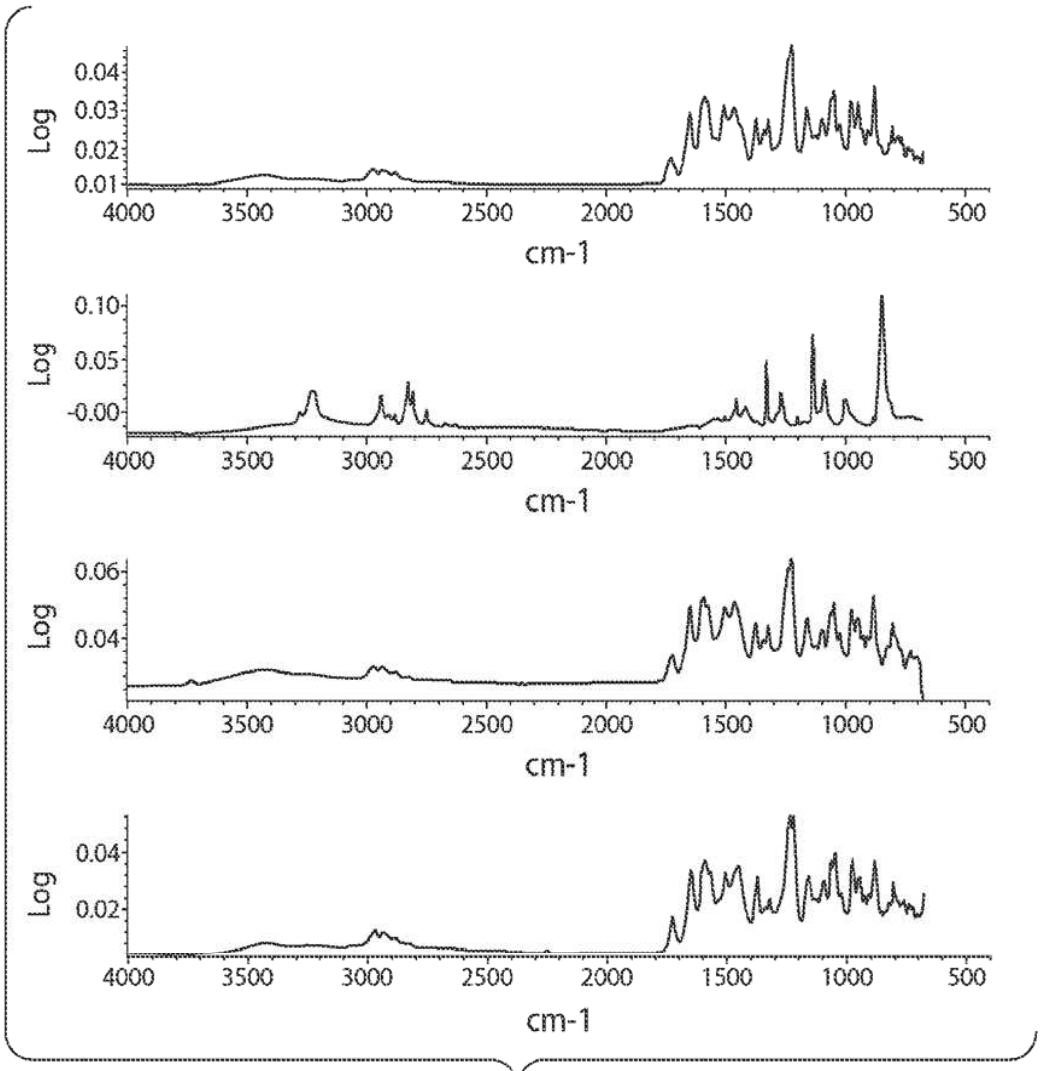

Log
0.04
0.03
0.02
0.01
4000 3500 3000 2500 2000 1500 1000 500
cm-1
Log
0.10
0.05
-0.00
4000 3500 3000 2500 2000 1500 1000 500
cm-1
Log
0.06
0.04
4000 3500 3000 2500 2000 1500 1000 500
cm-1
Log
0.04
0.02
4000 3500 3000 2500 2000 1500 1000 500
cm-1

Fig. 21

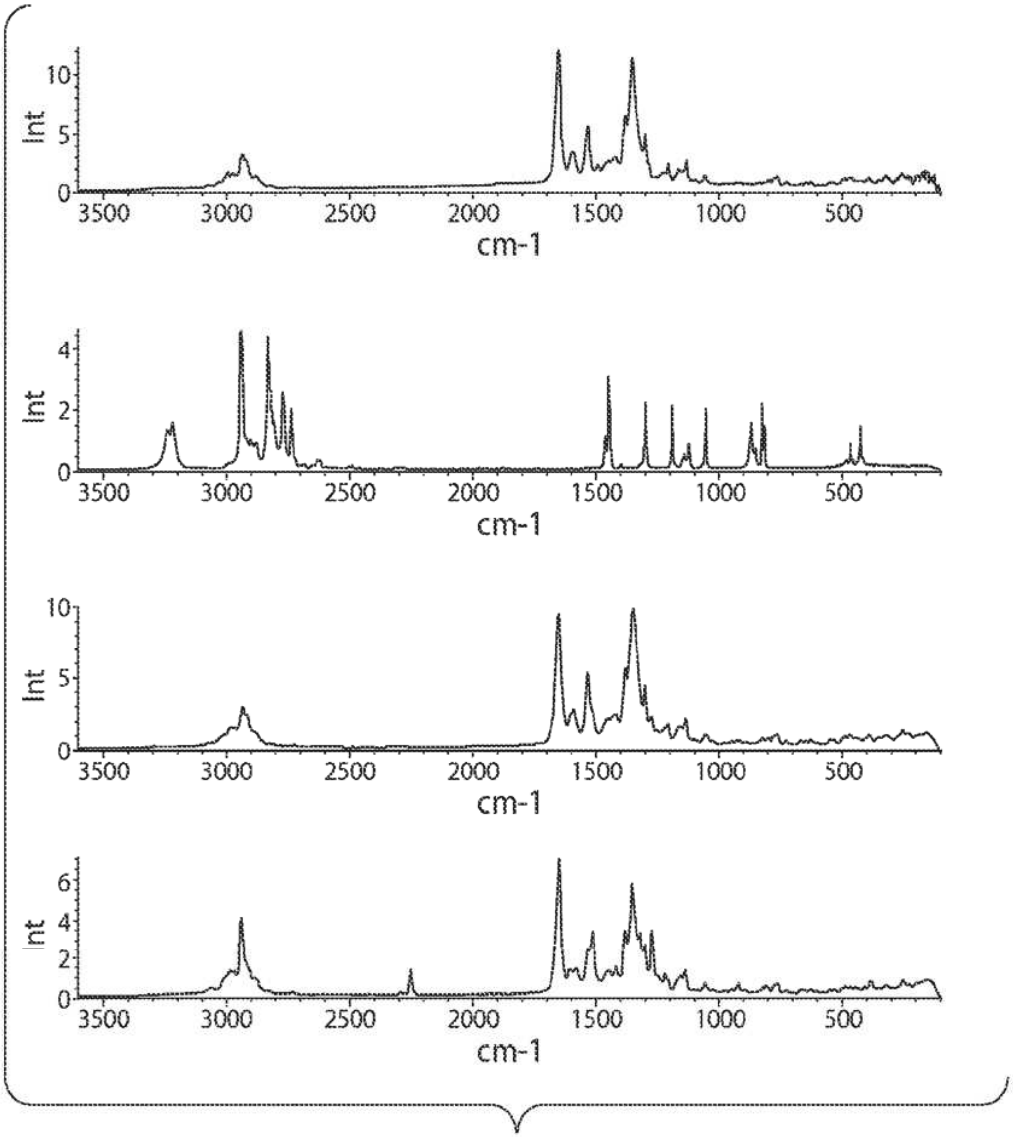

Int
10
5
0
3500
3000
2500
2000
1500
1000
500
cm-1
Int
4
2
0
3500
3000
2500
2000
1500
1000
500
cm-1
Int
10
5
0
3500
3000
2500
2000
1500
1000
500
cm-1
Int
6
4
2
0
3500
3000
2500
2000
1500
1000
500
cm-1

Fig. 22

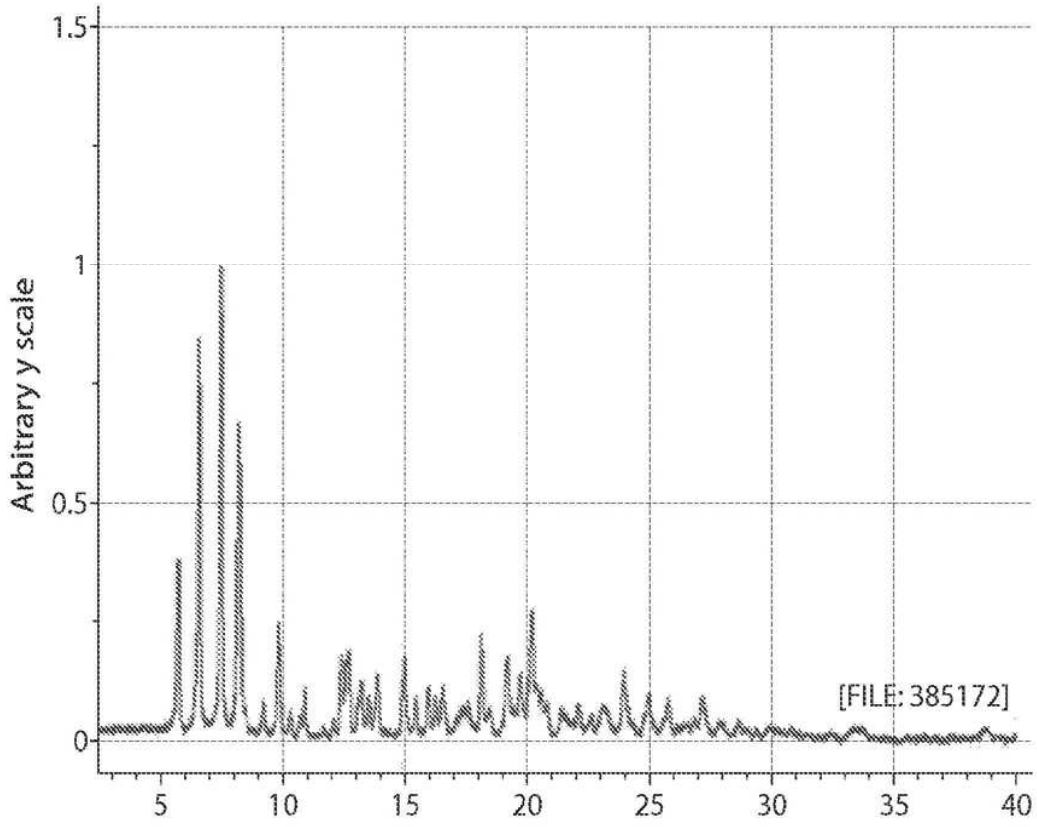


Fig. 23

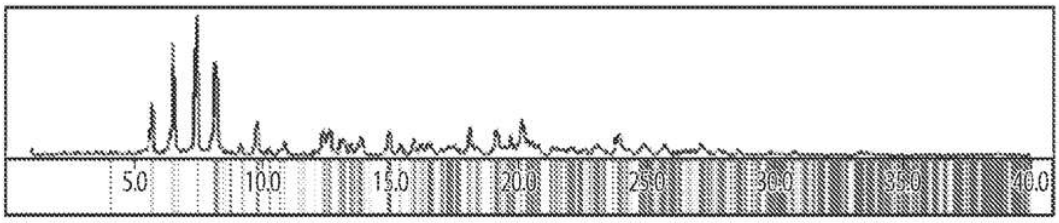


Fig. 24

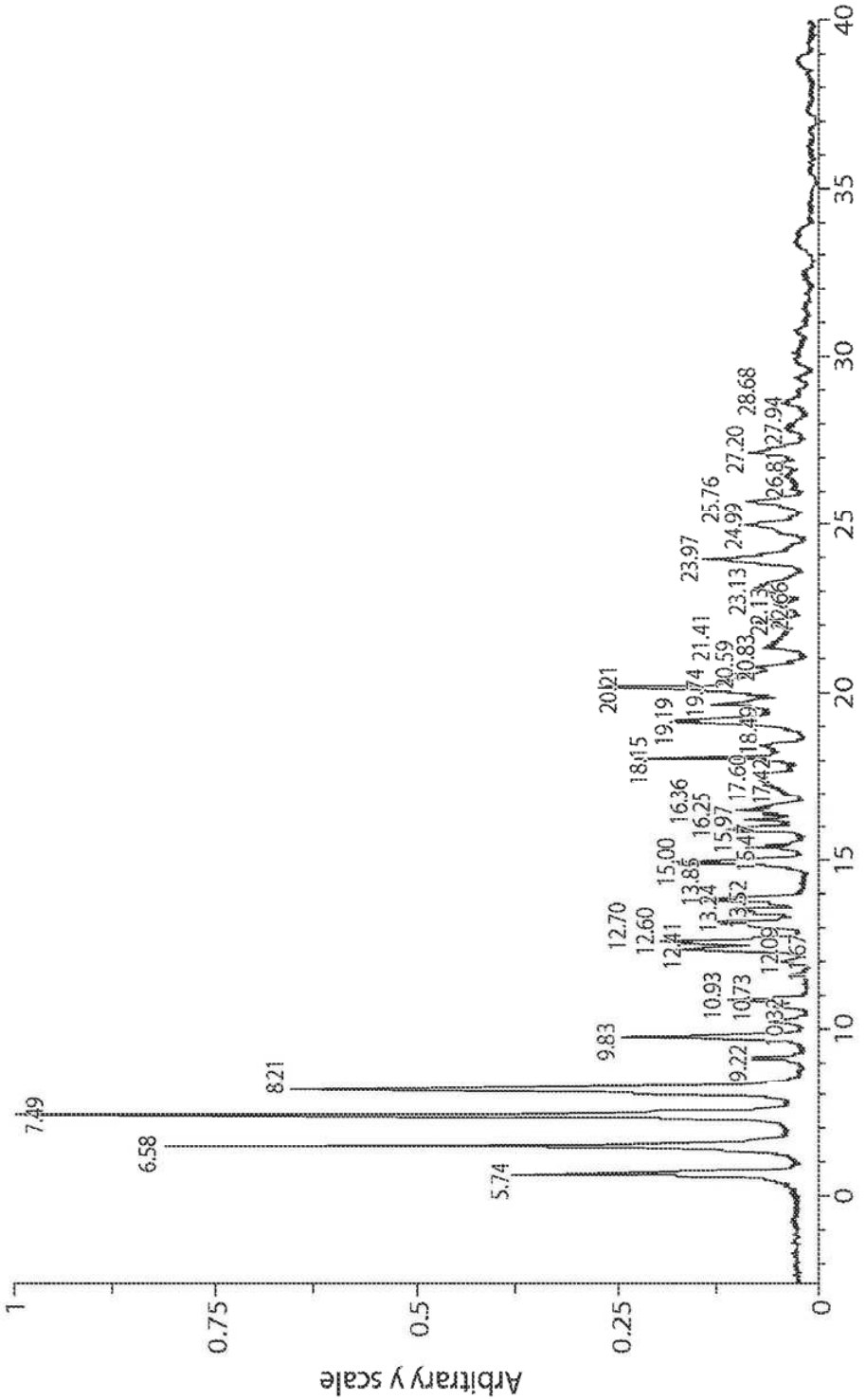

Arbitrary y scale
θ-2θ (deg)
7.49
8.21
6.58
5.74
9.83
9.22
10.93
10.73
12.70
12.60
12.41
13.24
13.85
15.00
15.97
16.36
16.25
17.60
18.15
19.19
19.74
20.21
21.41
23.97
25.76
27.20
28.68
27.94

Fig. 25

°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

°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
9.83 ± 0.10	8.999 ± 0.092	25

Fig. 27

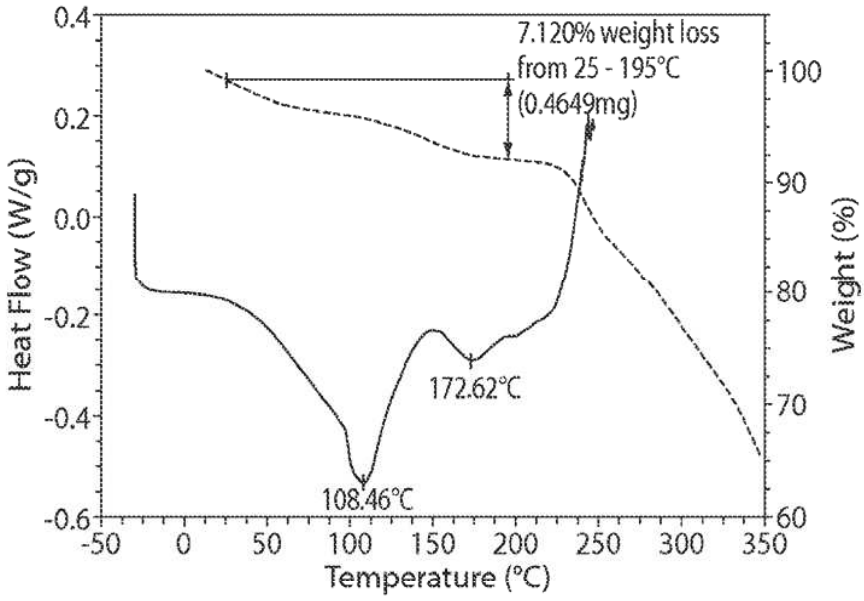


Fig. 28

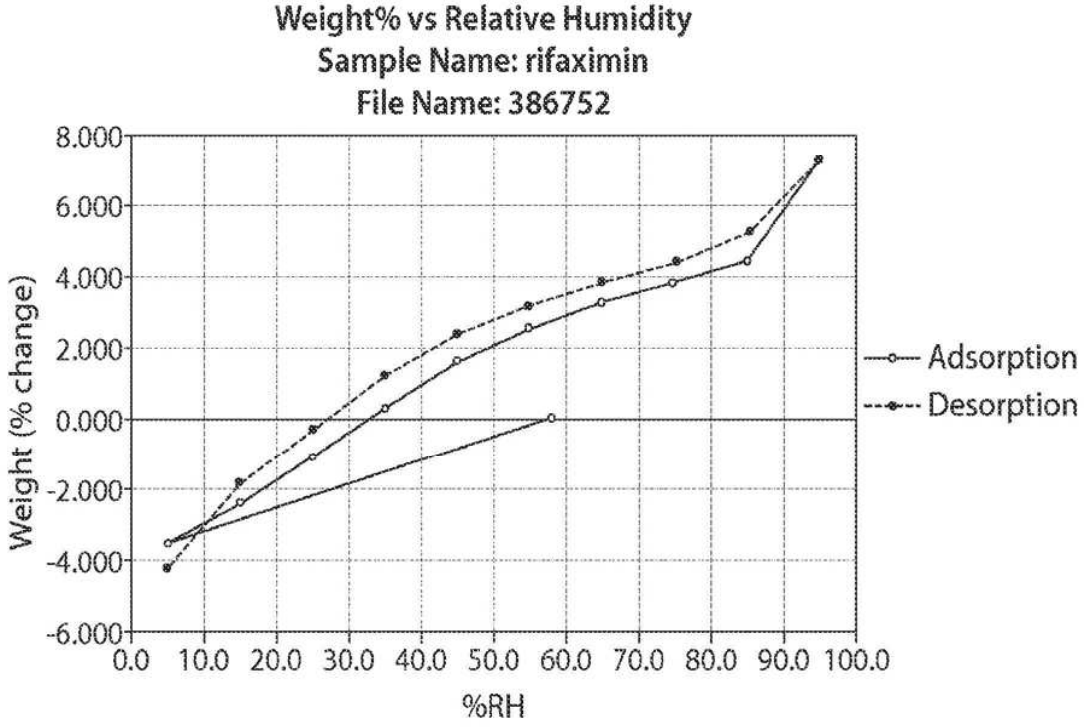

Weight% vs Relative Humidity
Sample Name: rifaximin
File Name: 386752
8.000
6.000
4.000
2.000
0.000
-2.000
-4.000
-6.000
Weight (% change)
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
%RH
Adsorption
Desorption

Fig. 29

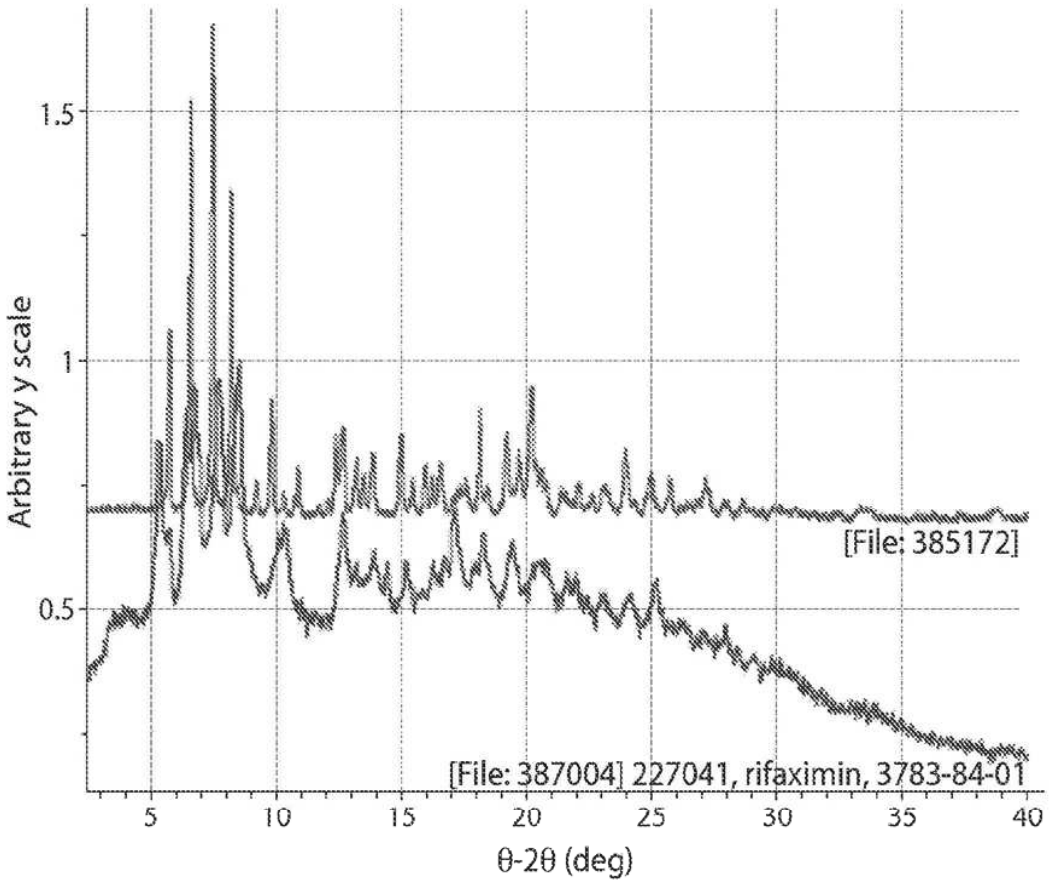

1.5
1
0.5
Arbitrary y scale
[File: 385172]
[File: 387004] 227041, rifaximin, 3783-84-01
5
10
15
20
25
30
35
40
θ-2θ (deg)

Fig. 30

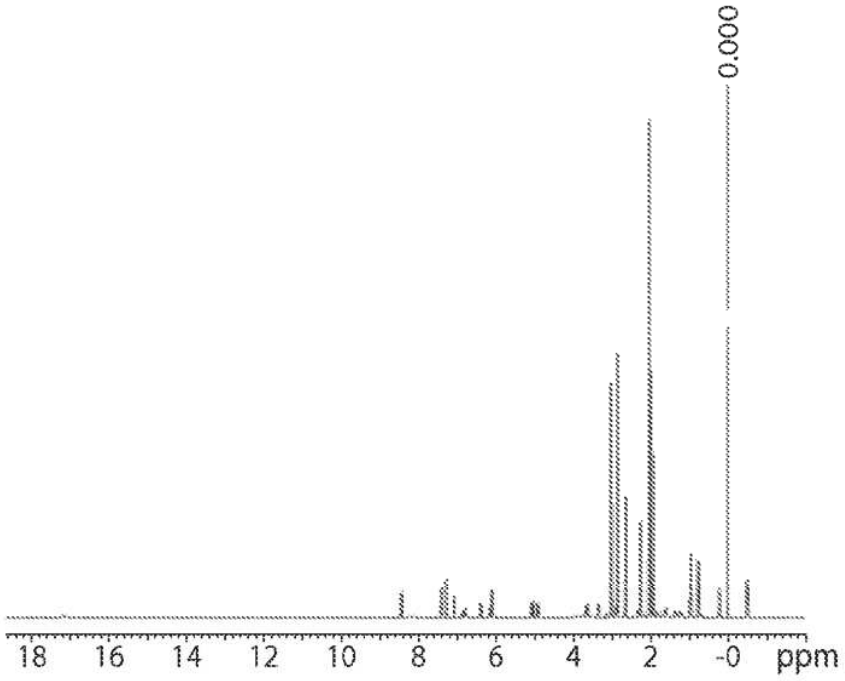


Fig. 31

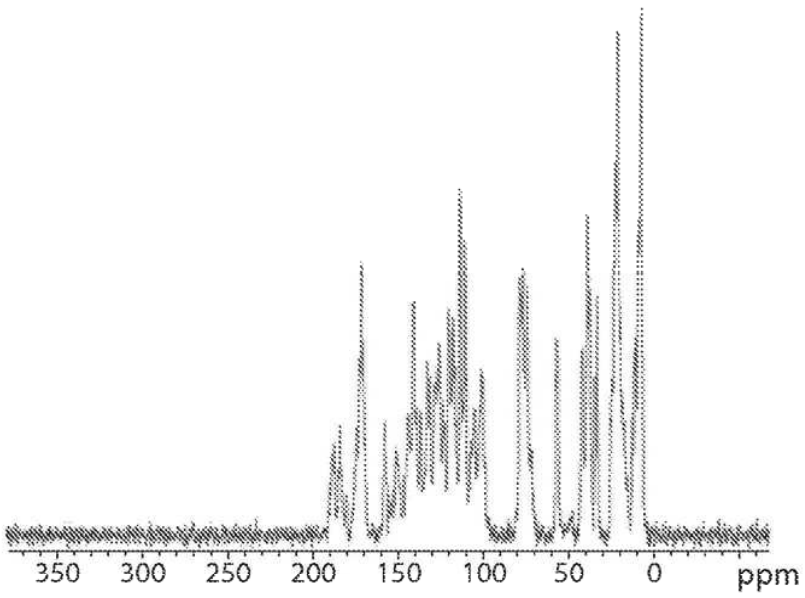


Fig. 32

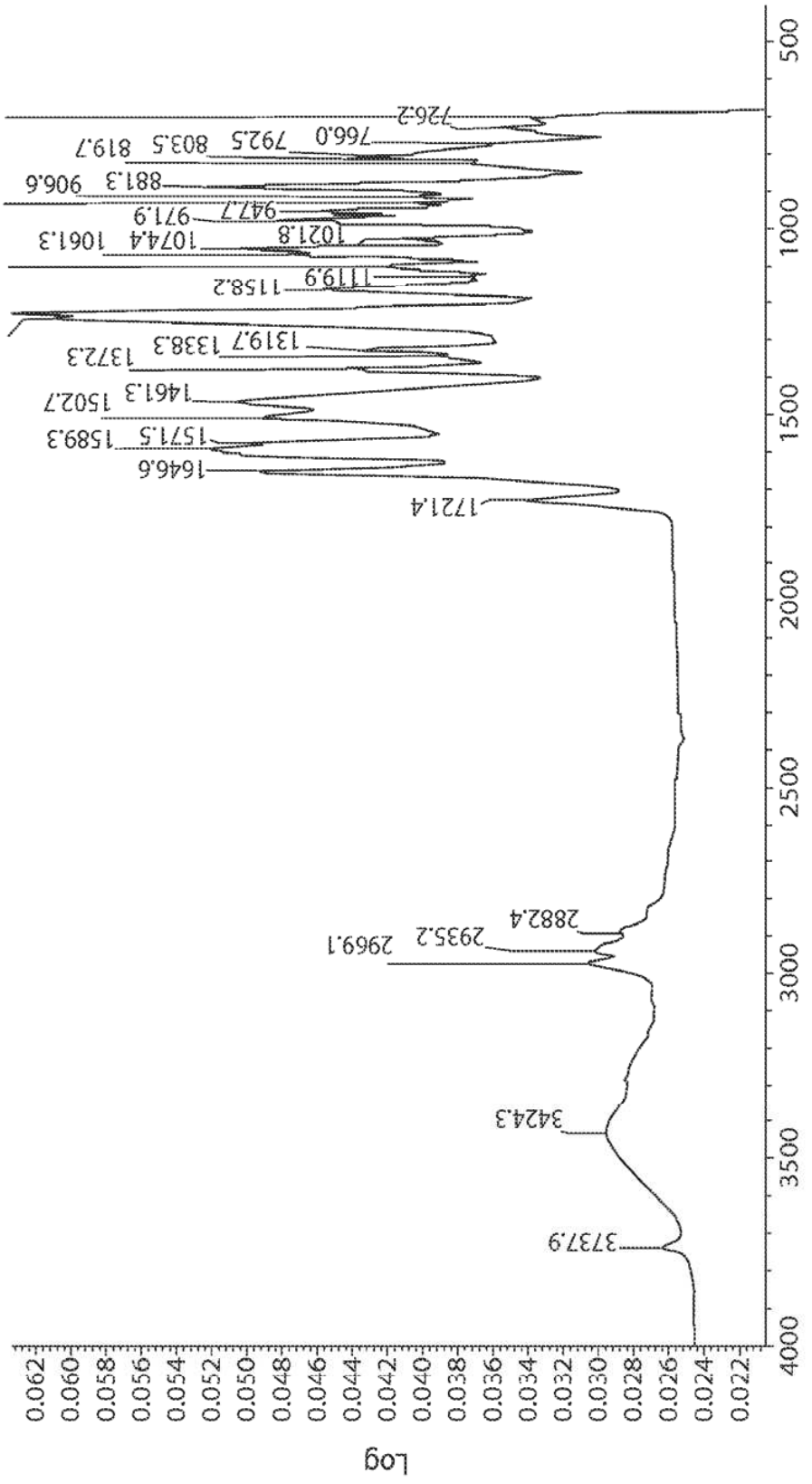

Log
0.062
0.060
0.058
0.056
0.054
0.052
0.050
0.048
0.046
0.044
0.042
0.040
0.038
0.036
0.034
0.032
0.030
0.028
0.026
0.024
0.022
4000
3500
3000
2500
2000
1500
1000
500
cm-1
3737.9
3424.3
2969.1
2935.2
2882.4
1721.4
1646.6
1589.3
1571.5
1502.7
1461.3
1372.3
1338.3
1319.7
1158.2
1119.9
1074.4
1061.3
1021.8
971.9
947.7
906.6
881.3
819.7
803.5
792.5
766.0
726.2

Fig. 33

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

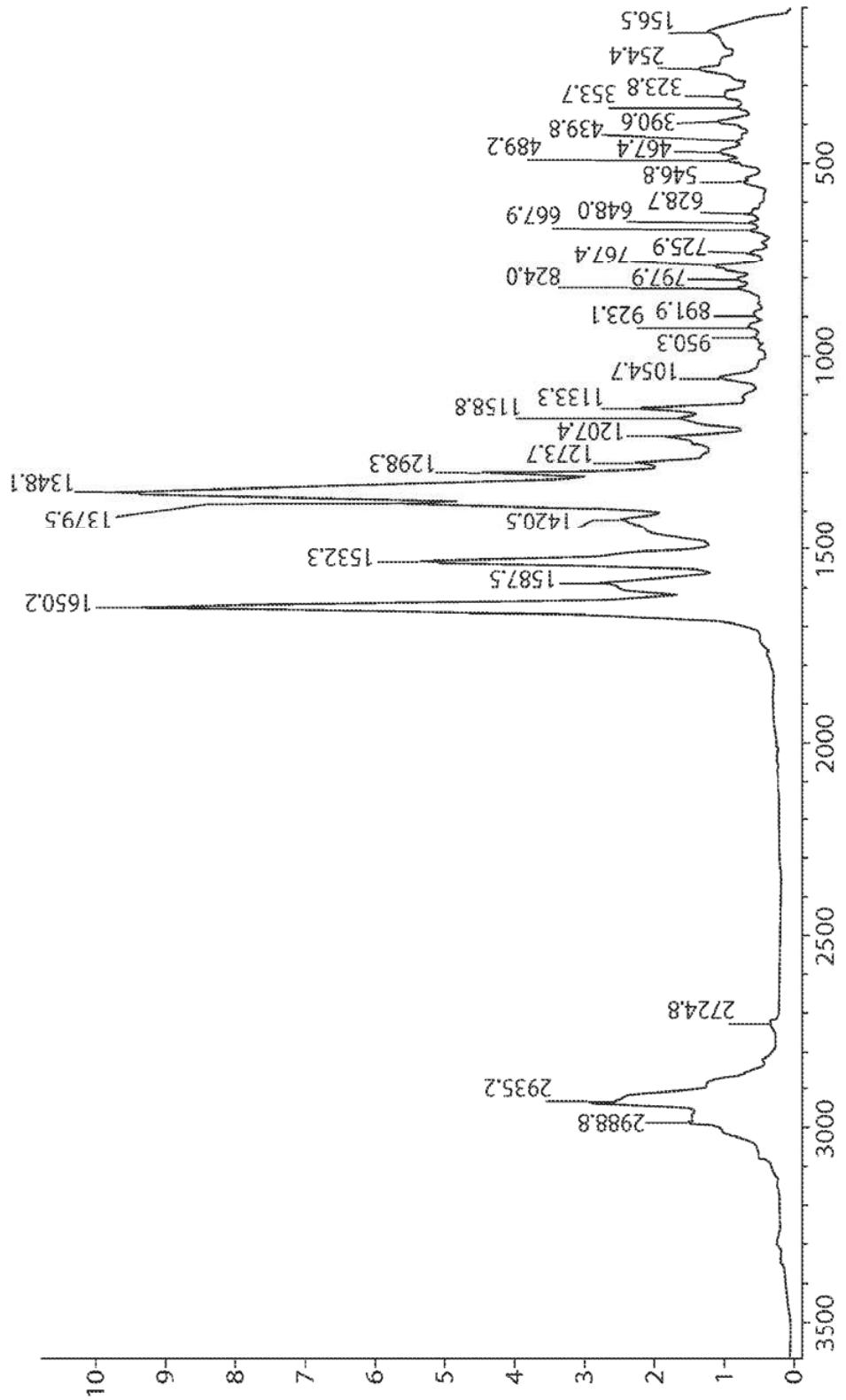

156.5
254.4
323.8
353.7
390.6
439.8
467.4
489.2
546.8
628.7
648.0
667.9
725.9
767.4
797.9
824.0
891.9
923.1
950.3
1054.7
1133.3
1158.8
1207.4
1273.7
1298.3
1348.1
1379.5
1420.5
1532.3
1587.5
1650.2
2724.8
2935.2
2988.8
3500
3000
2500
2000
1500
1000
500
0
1
2
3
4
5
6
7
8
9
10

Fig. 35

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

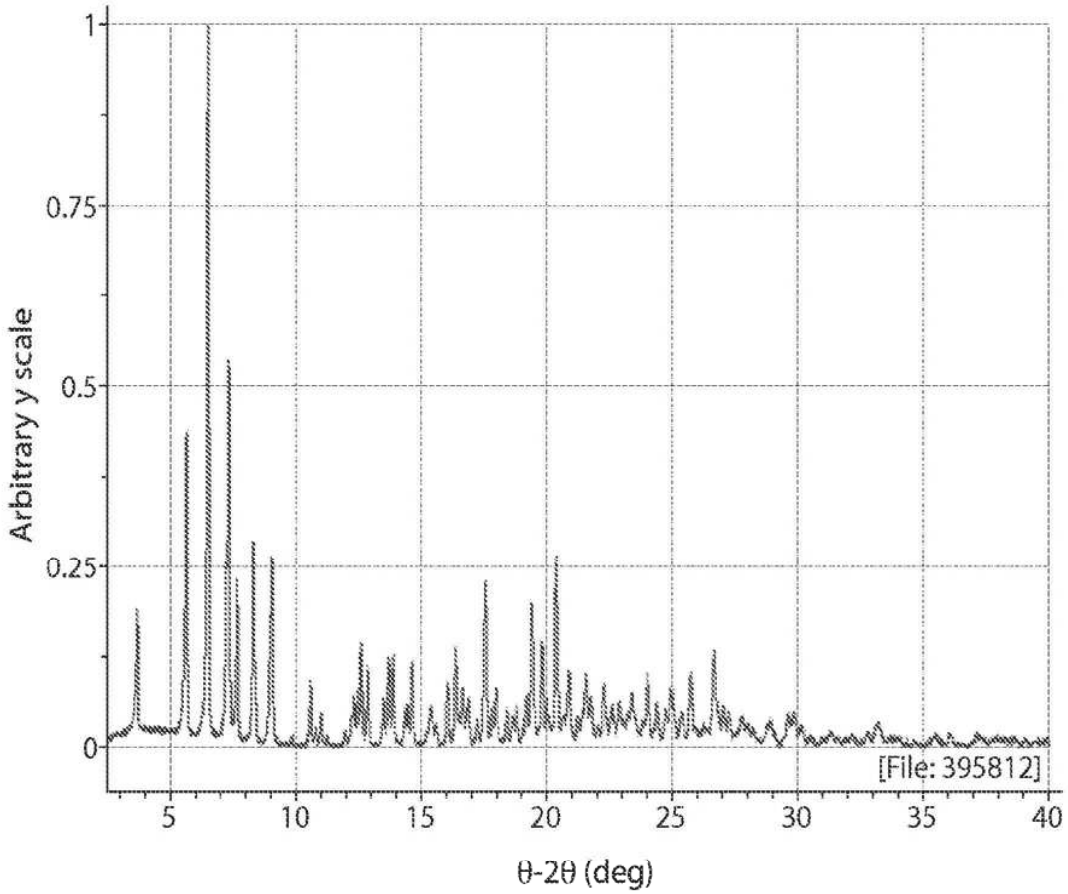

1
0.75
0.5
0.25
0
Arbitrary y scale
[File: 395812]
5
10
15
20
25
30
35
40
θ-2θ (deg)

Fig. 37

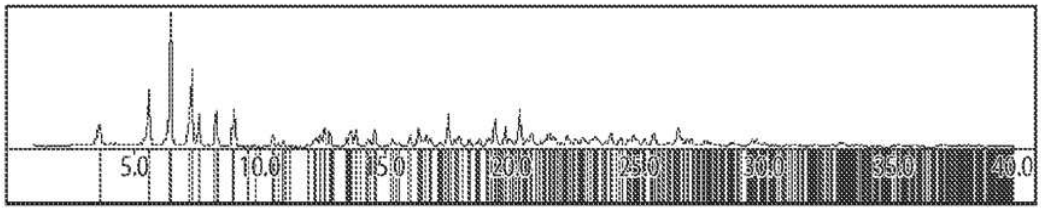

5.0
10.0
15.0
20.0
25.0
30.0
35.0
40.0

Fig. 38

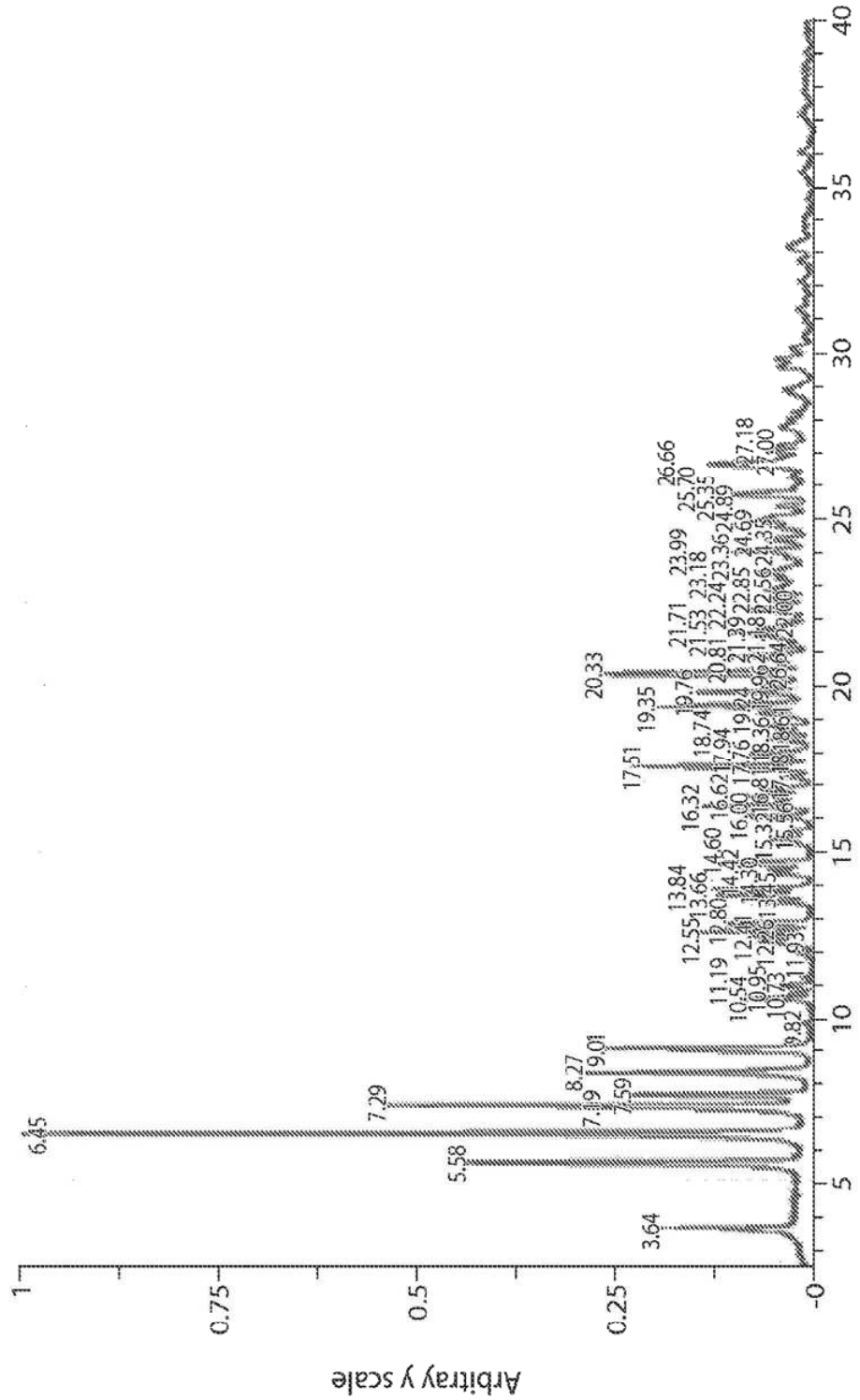

Arbitrary y scale
θ-2θ (deg)
6.45
7.29
5.58
3.64
8.27
9.01
7.59
17.51
20.33
19.35
16.32
13.84
26.66
25.70
27.18

Fig. 39

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

Fig. 40

°20	*d* space (Å)	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

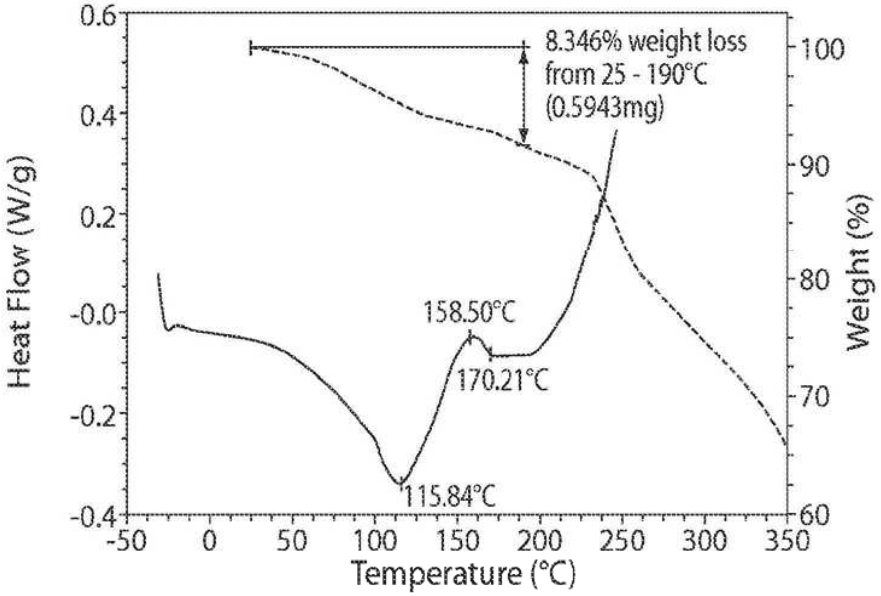


Fig. 42

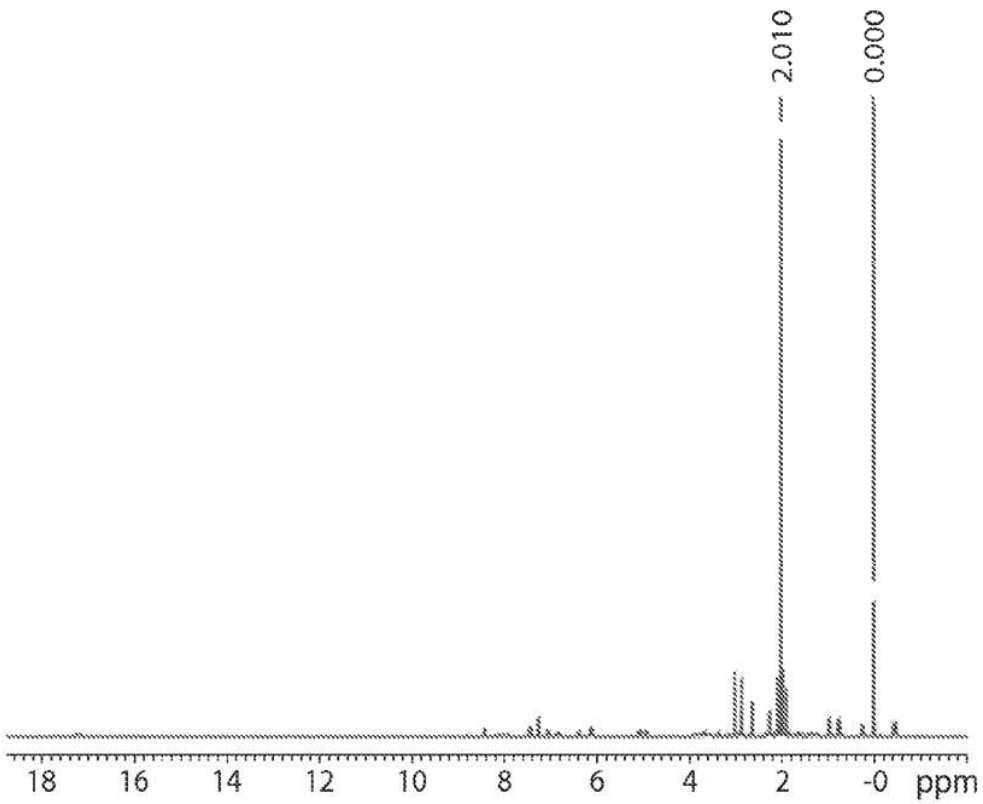


Fig. 43

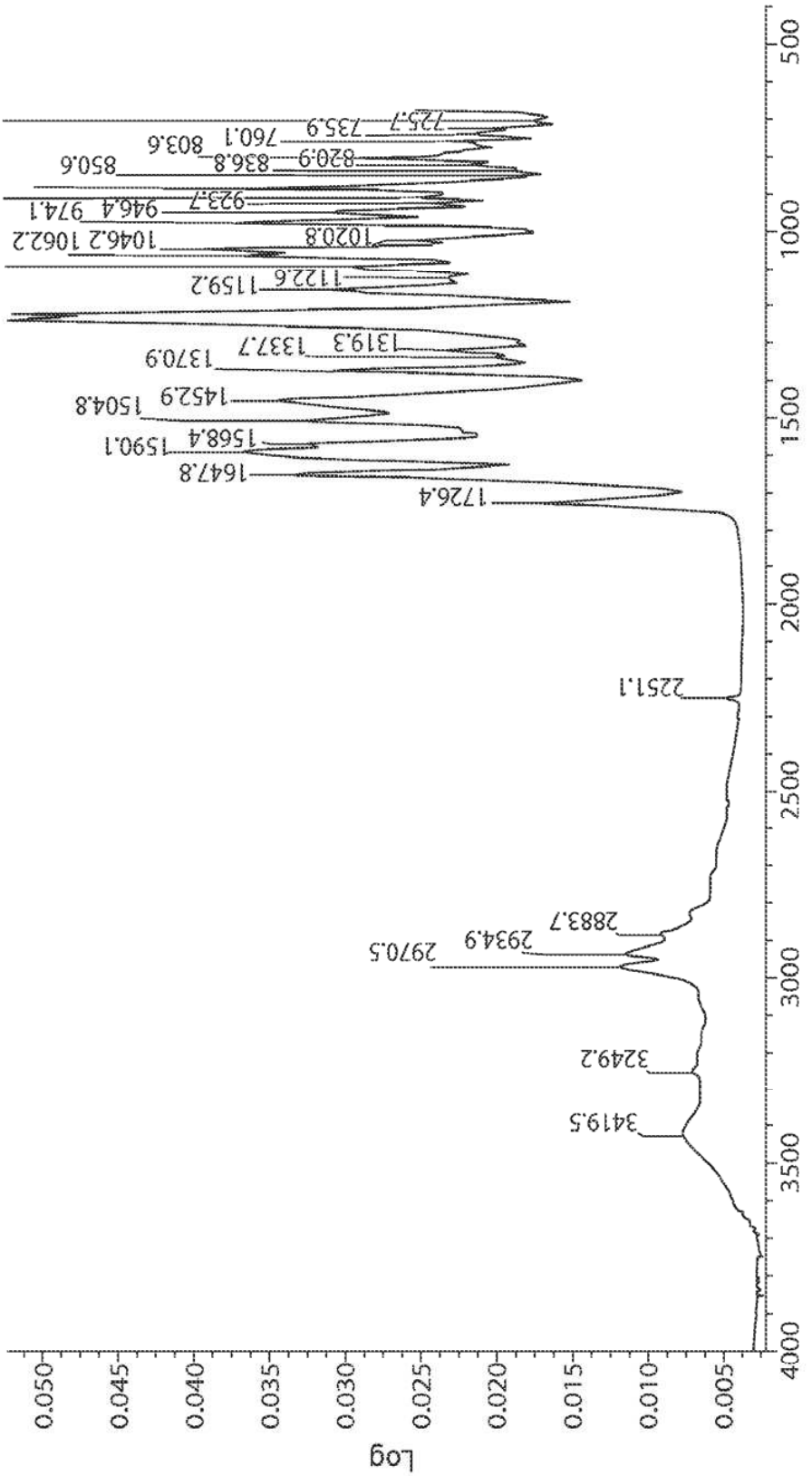

Log
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
4000
3500
3000
2500
2000
1500
1000
500
3419.5
3249.2
2970.5
2934.9
2883.7
2251.1
1726.4
1647.8
1590.1
1568.4
1504.8
1452.9
1370.9
1337.7
1319.3
1159.2
1122.6
1062.2
1046.2
1020.8
974.1
946.4
923.7
850.6
836.8
820.9
803.6
760.1
735.9
725.7

Fig. 44

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 (+/-2 cm^{-1}):	Characteristic Peaks (+/- 2 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

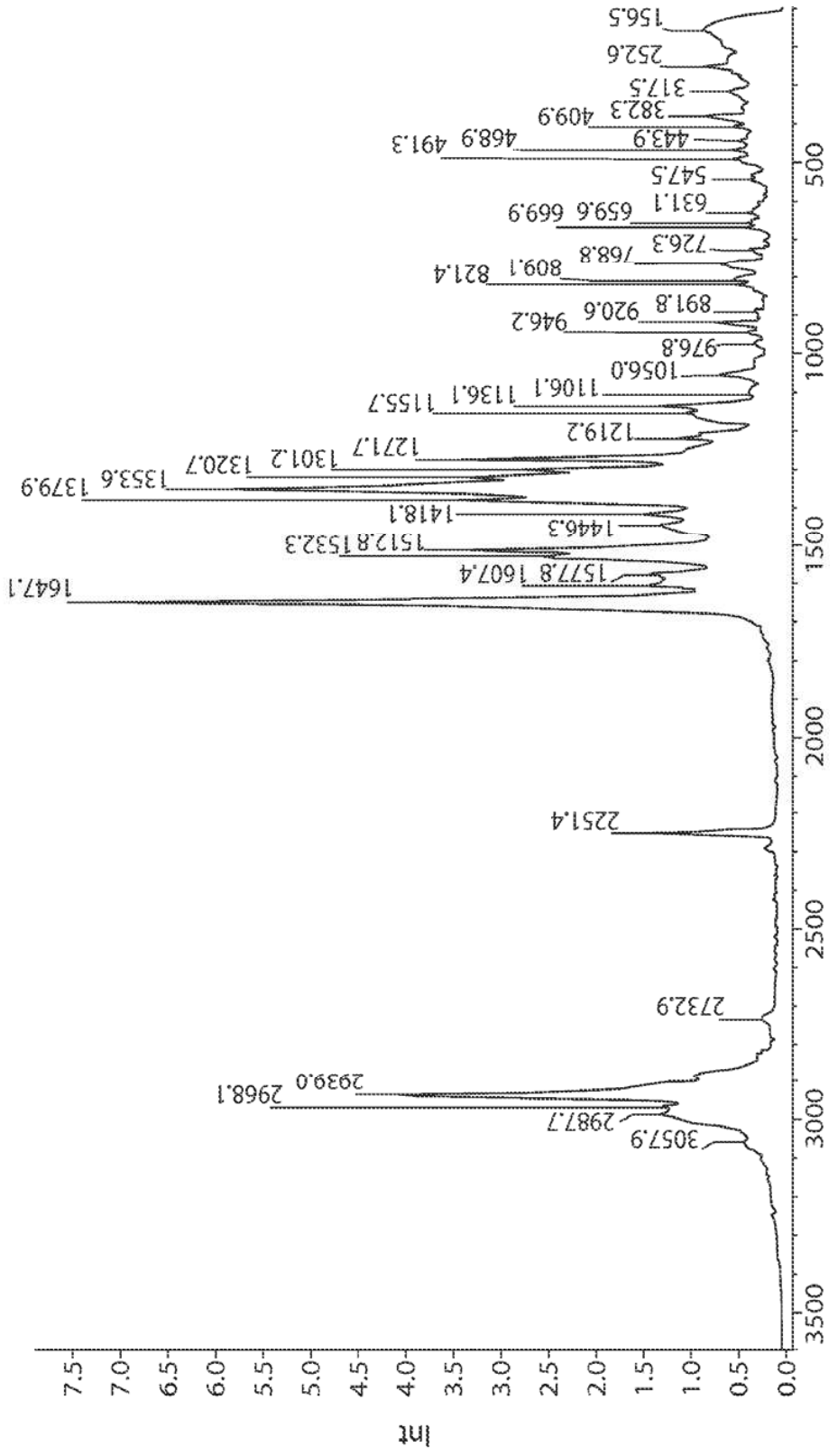

Int
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3500
3000
2500
2000
1500
1000
500
cm-1
3057.9
2987.7
2939.0
2968.1
2732.9
2251.4
1647.1
1577.8
1607.4
1512.8
1532.3
1446.3
1418.1
1379.9
1353.6
1320.7
1301.2
1271.7
1219.2
1155.7
1136.1
1106.1
1056.0
976.8
946.2
920.6
891.8
821.4
809.1
768.8
726.3
669.9
659.6
631.1
547.5
491.3
468.9
443.9
409.9
382.3
317.5
252.6
156.5

Fig. 46

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 (+/-2 cm^{-1}):

Observed Peaks:	Characteristic Peaks:
156.5	920.6
252.6	1219.2
317.5	1320.7
382.3	1577.8
409.9	1607.4
443.9	2251.4
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	

Fig. 47

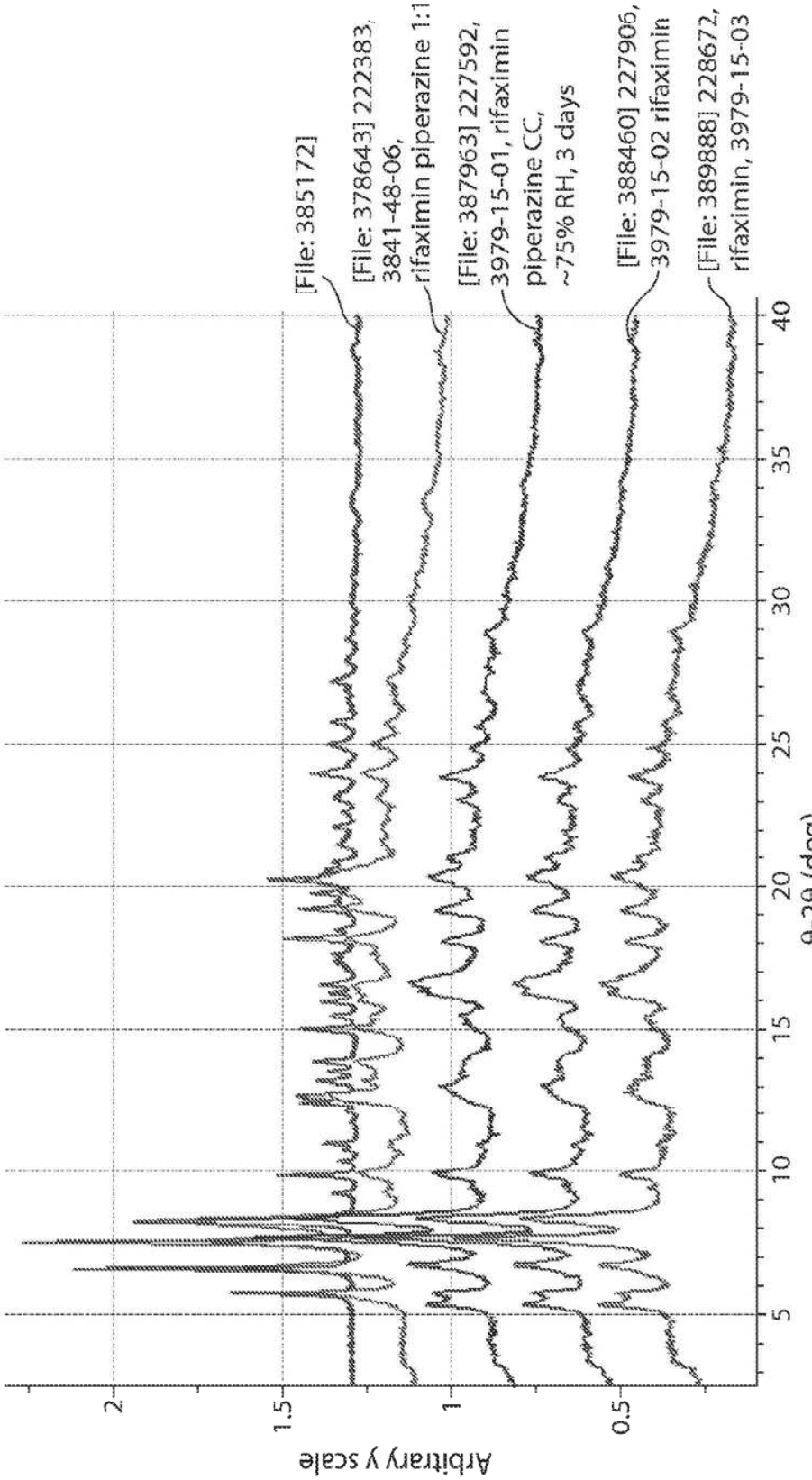

[File: 385172]
[File: 378643] 222383, 3841-48-06, rifaximin piperazine 1:1
[File: 387963] 227592, 3979-15-01, rifaximin piperazine CC, ~75% RH, 3 days
[File: 388460] 227905, 3979-15-02 rifaximin
[File: 389888] 228672, rifaximin, 3979-15-03
Arbitrary y scale
0.5
1
1.5
2
5
10
15
20
25
30
35
40
θ-2θ (deg)

Fig. 48

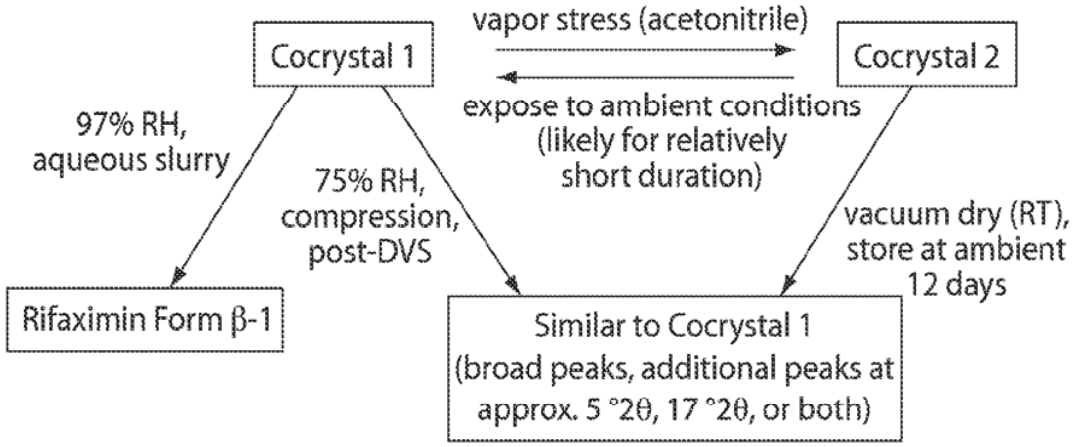

Cocrystal 1
vapor stress (acetonitrile)
Cocrystal 2
expose to ambient conditions
(likely for relatively
short duration)
97% RH,
aqueous slurry
75% RH,
compression,
post-DVS
vacuum dry (RT),
store at ambient
12 days
Rifaximin Form β-1
Similar to Cocrystal 1
(broad peaks, additional peaks at
approx. 5 °2θ, 17 °2θ, or both)

Fig. 49

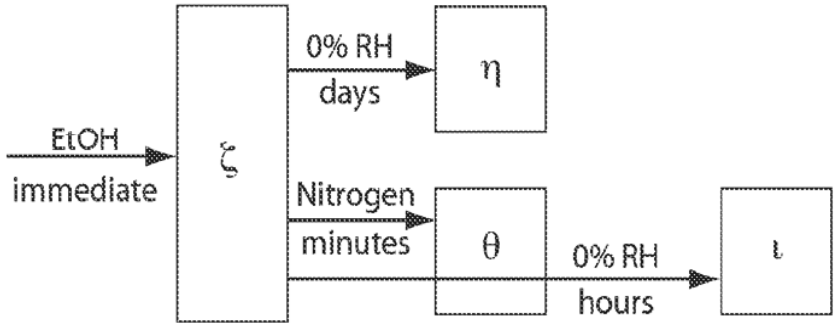

EtOH
immediate
ζ
0% RH
days
η
Nitrogen
minutes
θ
0% RH
hours
ι

Fig. 50

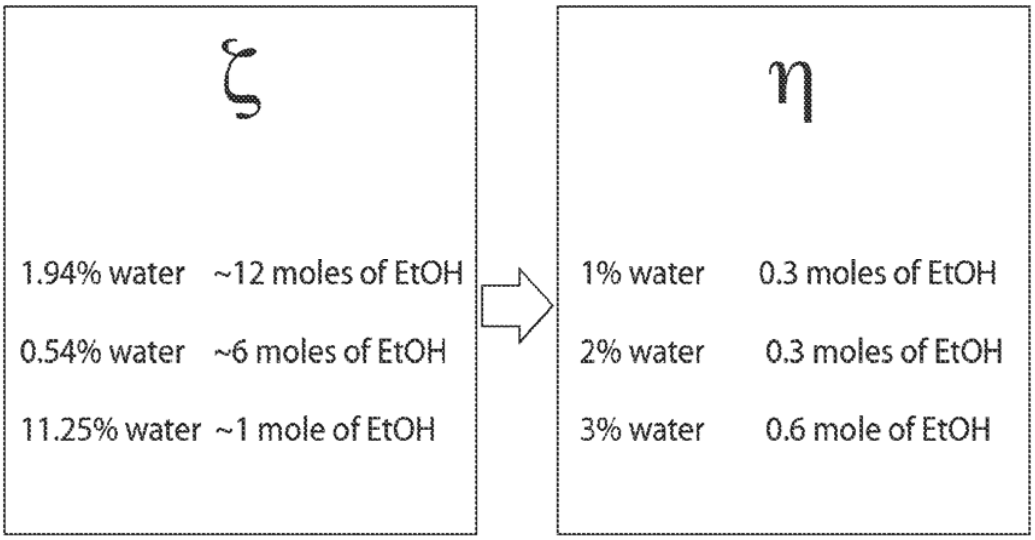

ζ
1.94% water ~12 moles of EtOH
0.54% water ~6 moles of EtOH
11.25% water ~1 mole of EtOH
η
1% water 0.3 moles of EtOH
2% water 0.3 moles of EtOH
3% water 0.6 mole of EtOH

Fig. 51

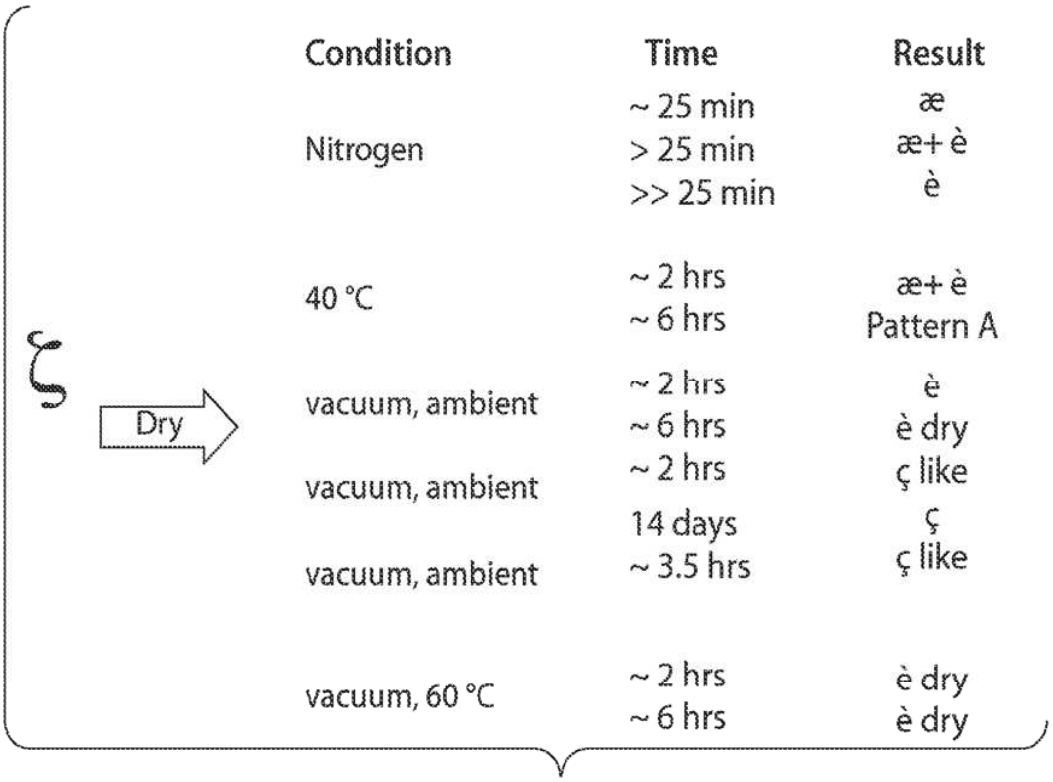

ζ
Dry
Condition
Time
Result
Nitrogen
~ 25 min
æ
> 25 min
æ+ è
>> 25 min
è
40 °C
~ 2 hrs
æ+ è
~ 6 hrs
Pattern A
vacuum, ambient
~ 2 hrs
è
~ 6 hrs
è dry
vacuum, ambient
~ 2 hrs
ç like
14 days
ç
vacuum, ambient
~ 3.5 hrs
ç like
vacuum, 60 °C
~ 2 hrs
è dry
~ 6 hrs
è dry

Fig. 52

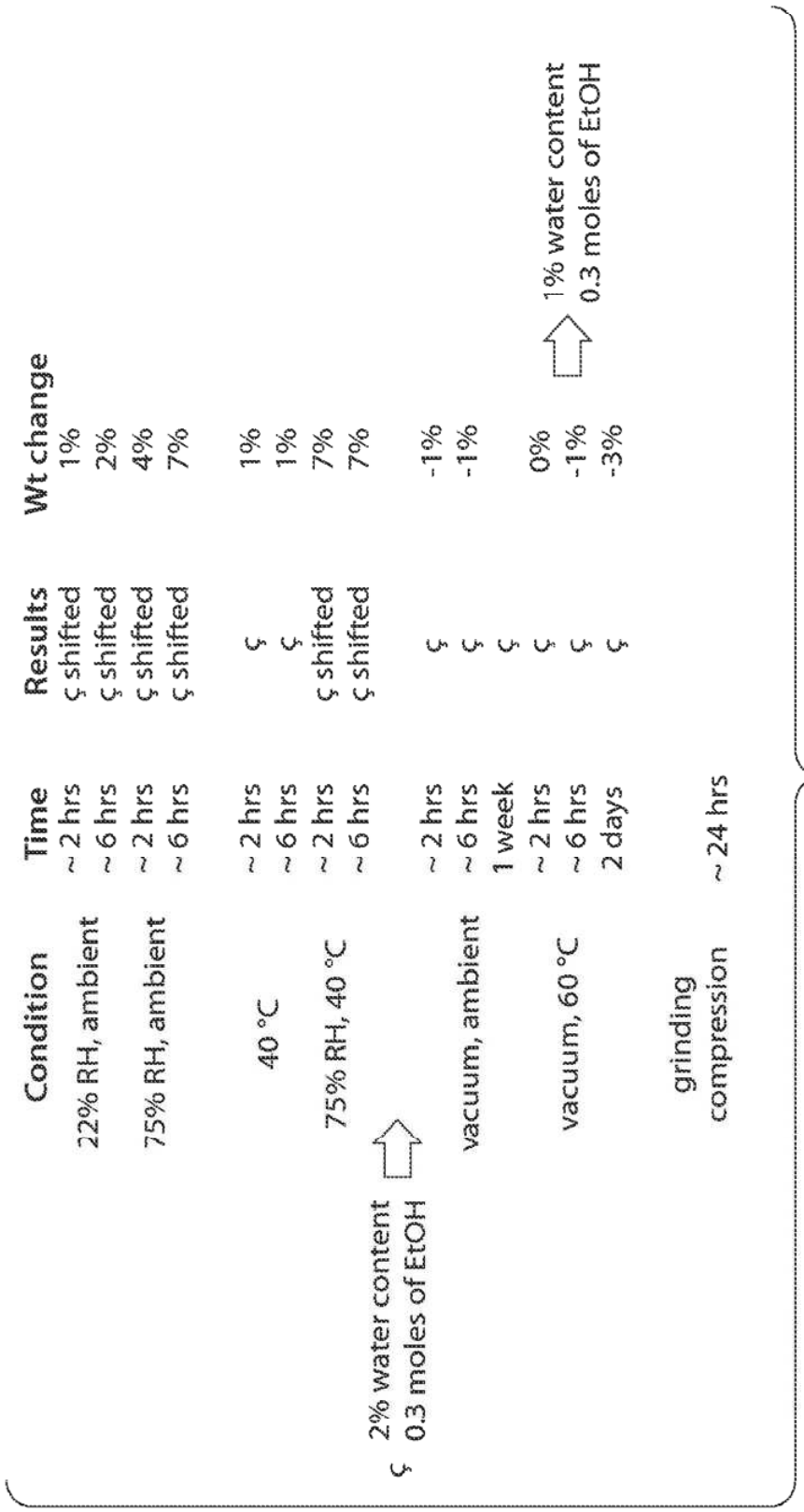

Condition
Time
Results
Wt change
22% RH, ambient
~ 2 hrs
ç shifted
1%
~ 6 hrs
ç shifted
2%
75% RH, ambient
~ 2 hrs
ç shifted
4%
~ 6 hrs
ç shifted
7%
40 °C
~ 2 hrs
ç
1%
~ 6 hrs
ç
1%
75% RH, 40 °C
~ 2 hrs
ç shifted
7%
~ 6 hrs
ç shifted
7%
2% water content
0.3 moles of EtOH
ç
vacuum, ambient
~ 2 hrs
ç
-1%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

Fig. 53

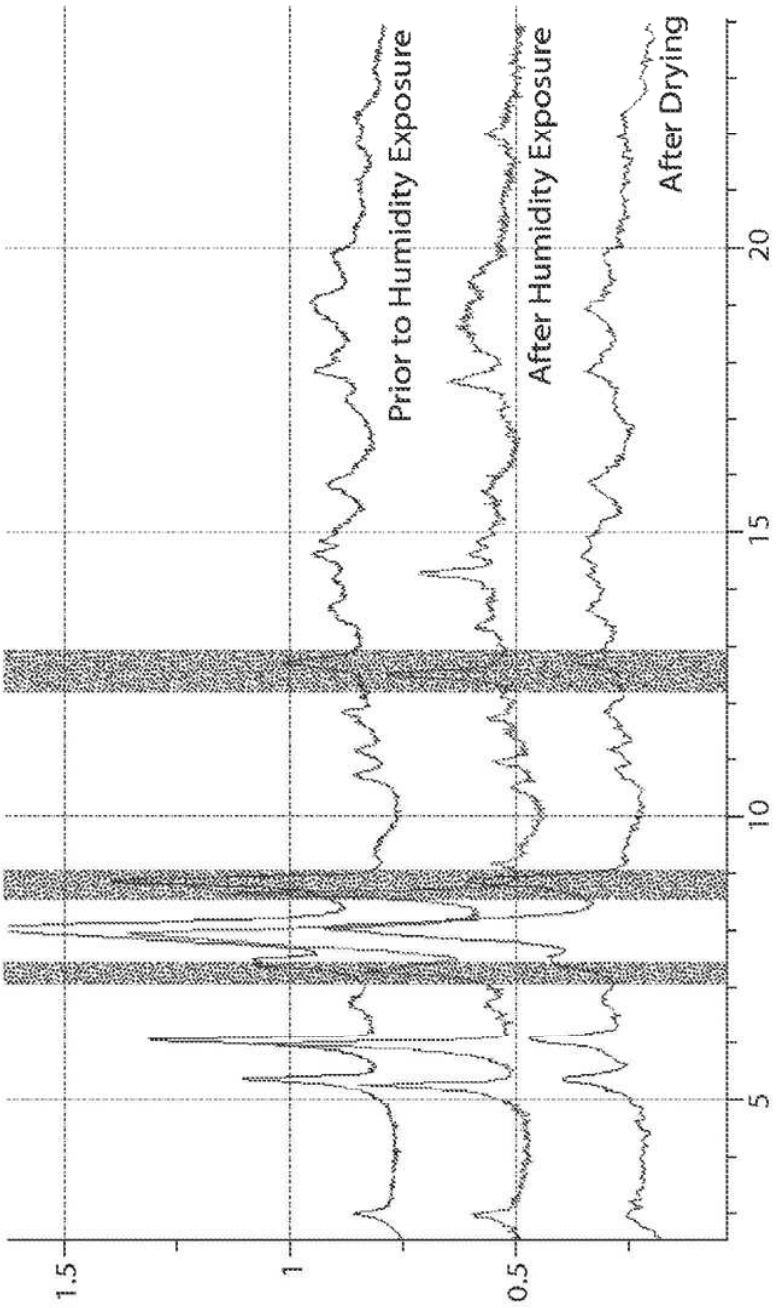

Prior to Humidity Exposure
After Humidity Exposure
After Drying
1.5
1
0.5
5
10
15
20
θ-2θ (deg)

Fig. 54

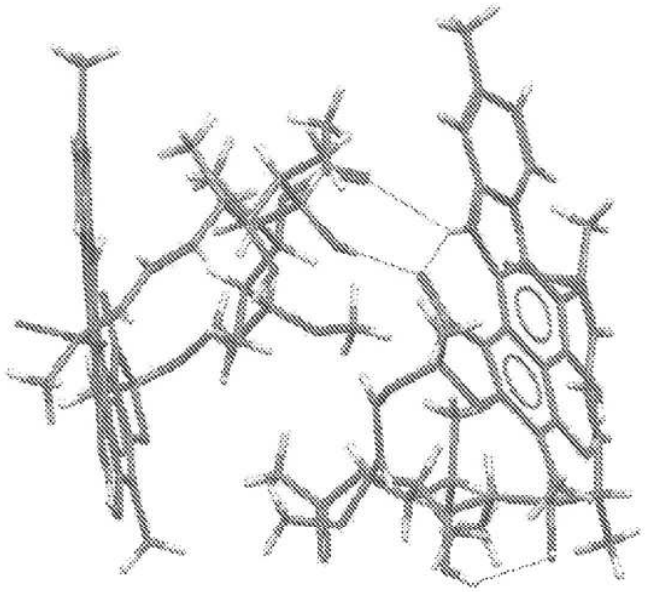


Fig. 55

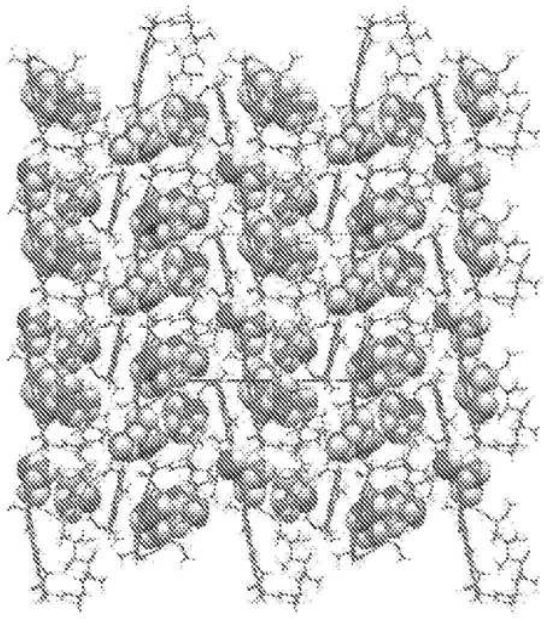


Fig. 56

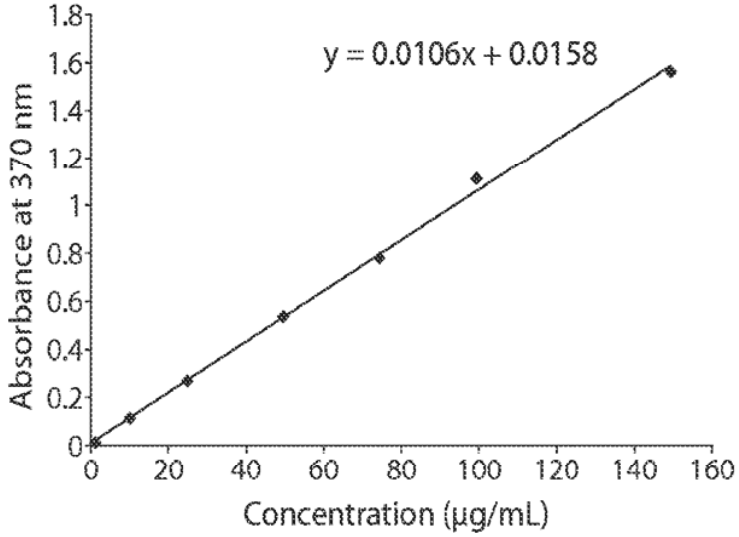

y = 0.0106x + 0.0158
Absorbance at 370 nm
Concentration (µg/mL)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
0
20
40
60
80
100
120
140
160

Fig. 57

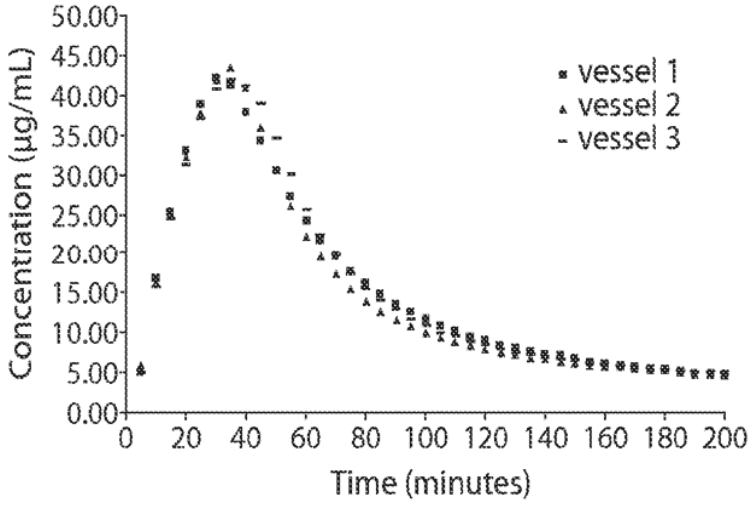

vessel 1
vessel 2
vessel 3
Concentration (µg/mL)
Time (minutes)
0.00
5.00
10.00
15.00
20.00
25.00
30.00
35.00
40.00
45.00
50.00
0
20
40
60
80
100
120
140
160
180
200

Fig. 58

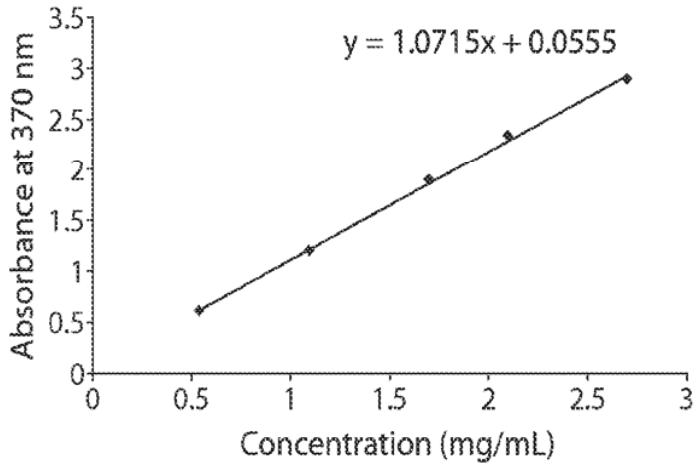

y = 1.0715x + 0.0555
Absorbance at 370 nm
Concentration (mg/mL)
0
0.5
1
1.5
2
2.5
3
3.5

Fig. 59

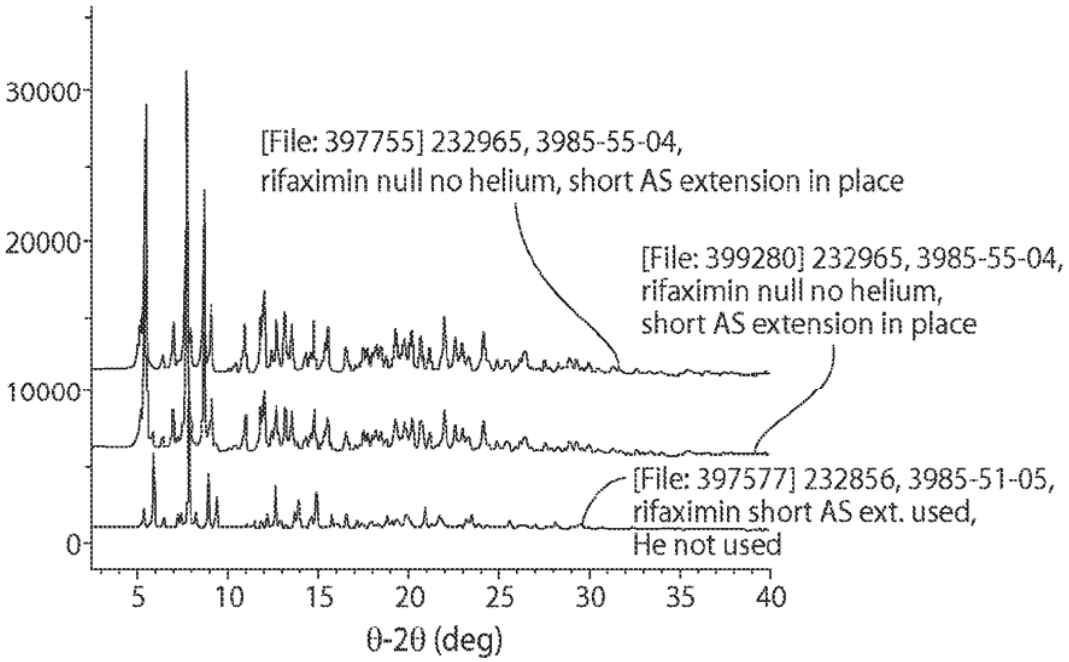
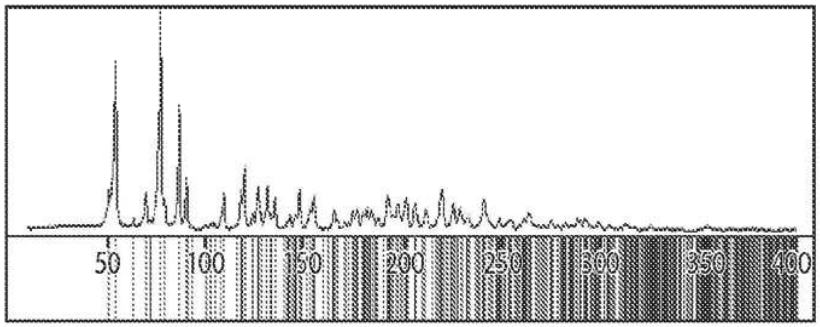

[File: 397755] 232965, 3985-55-04,
rifaximin null no helium, short AS extension in place
[File: 399280] 232965, 3985-55-04,
rifaximin null no helium,
short AS extension in place
[File: 397577] 232856, 3985-51-05,
rifaximin short AS ext. used,
He not used
30000
20000
10000
0
5
10
15
20
25
30
35
40
θ-2θ (deg)

Fig. 60



Indexing solution and derived quantities

Form / Pattern	Rifaximin Form θ
Family and Space Group	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]	$C_{43}H_{51}N_3O_{11}$, xC_2H_6O $0 \le x \le 4$
Density (g/cm^3)[a]	$1.05 \le y \le 1.29$
Weight Fraction Solvent (%)[a]	$0 \le z \le 19.0$

[a]Density and weight fraction solvent are based on the assumed composition

Fig. 61

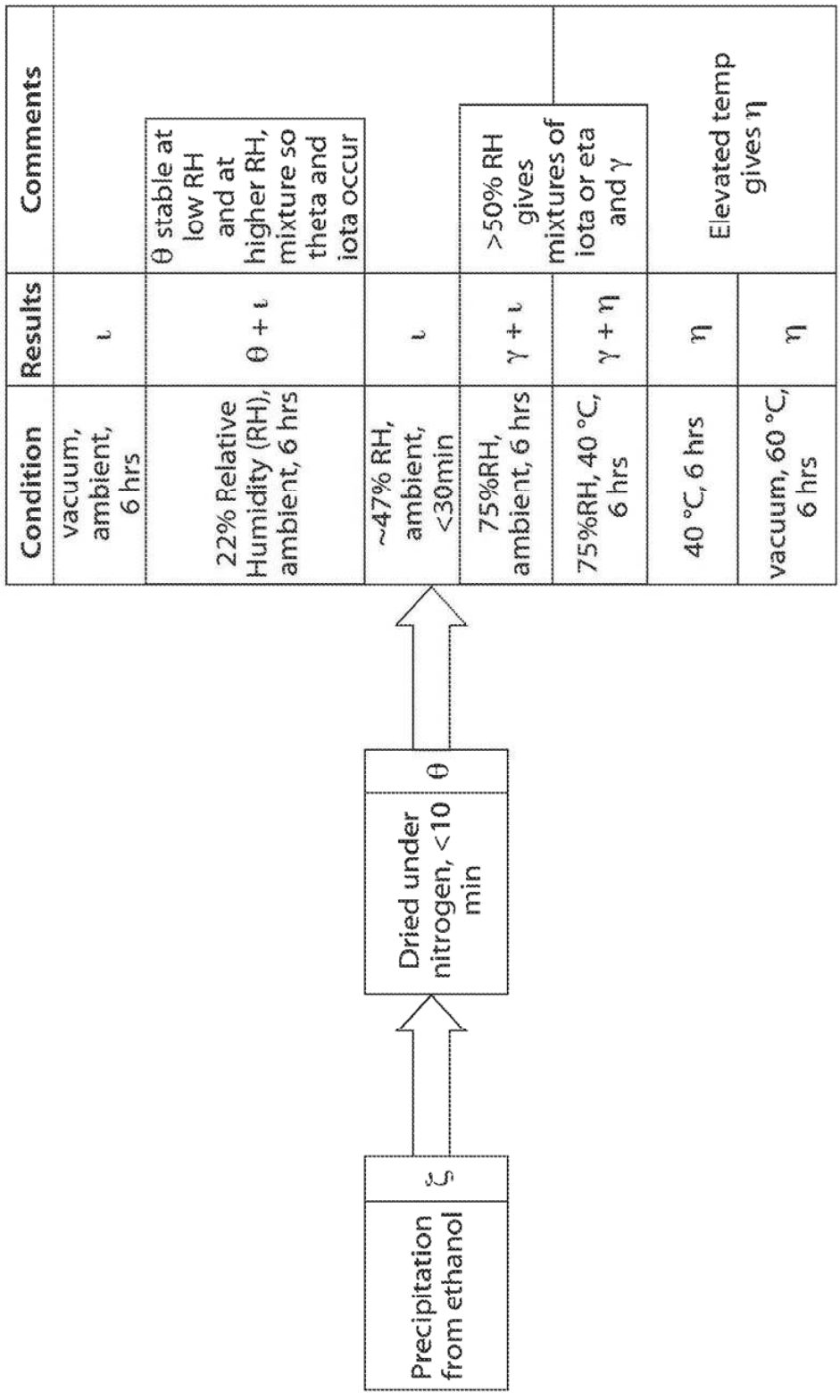
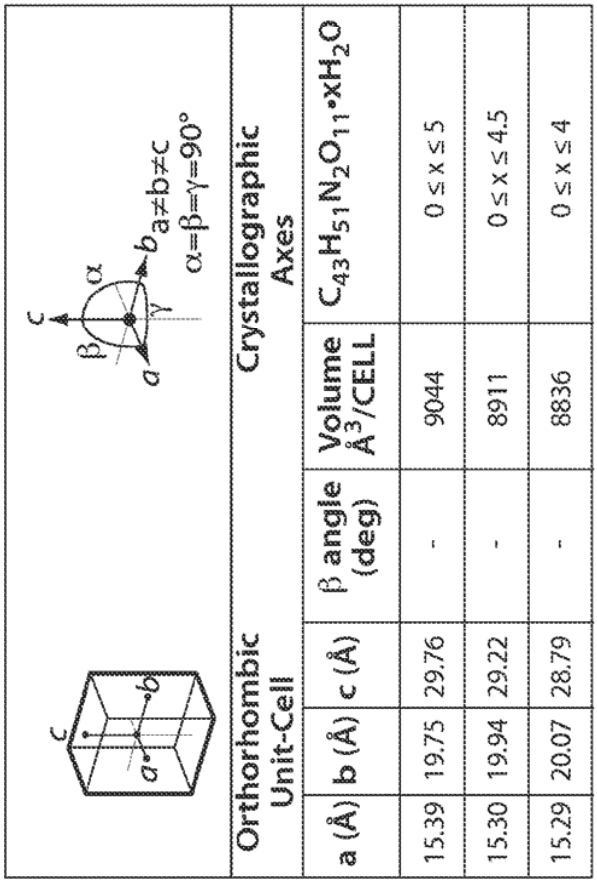

Precipitation from ethanol
ζ
Dried under nitrogen, <10 min
θ
Condition
Results
Comments
vacuum, ambient, 6 hrs
ι
22% Relative Humidity (RH), ambient, 6 hrs
θ + ι
θ stable at low RH and at higher RH, mixture so theta and iota occur
~47% RH, ambient, <30min
ι
75%RH, ambient, 6 hrs
γ + ι
>50% RH gives mixtures of iota or eta and γ
75%RH, 40 °C, 6 hrs
γ + η
40 °C, 6 hrs
η
Elevated temp gives η
vacuum, 60 °C, 6 hrs
η

Fig. 62



Orthorhombic Unit-Cell				Crystallographic Axes		$C_{43}H_{51}N_2O_{11}\cdot xH_2O$
a (Å)	b (Å)	c (Å)	β angle (deg)	Volume Å^3/CELL		
15.39	19.75	29.76	-	9044		$0 \le x \le 5$
15.30	19.94	29.22	-	8911		$0 \le x \le 4.5$
15.29	20.07	28.79	-	8836		$0 \le x \le 4$

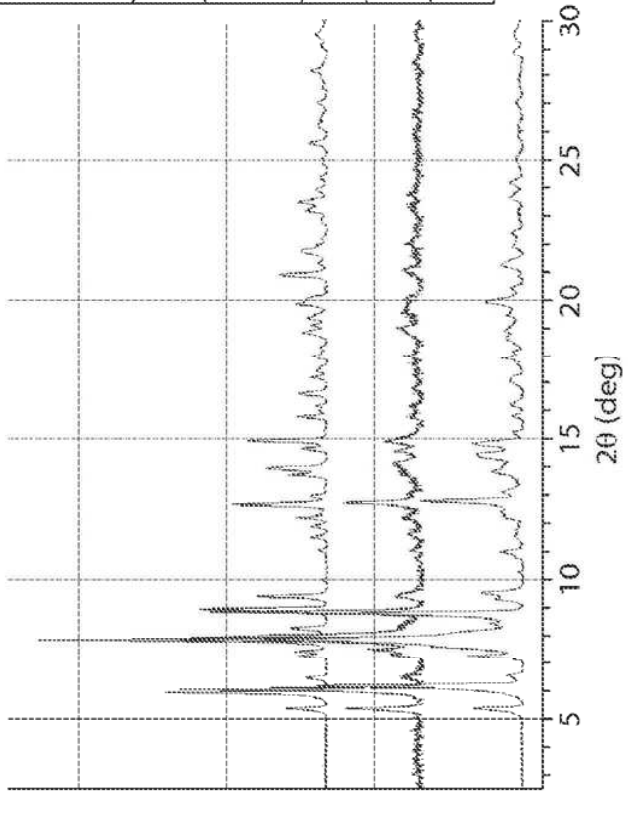


Fig. 63

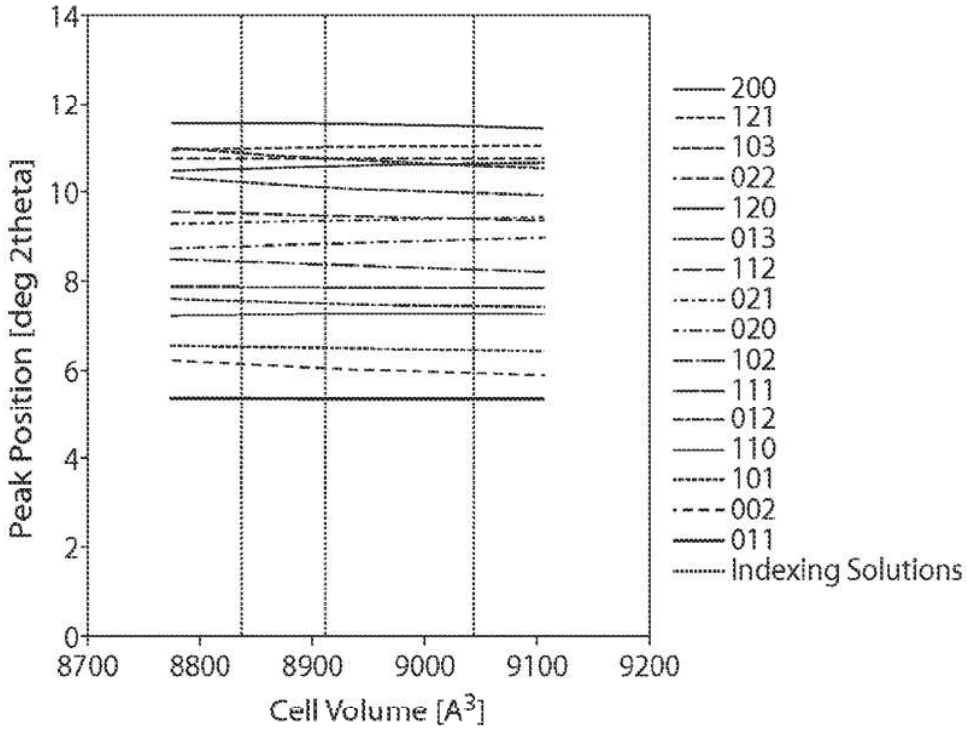
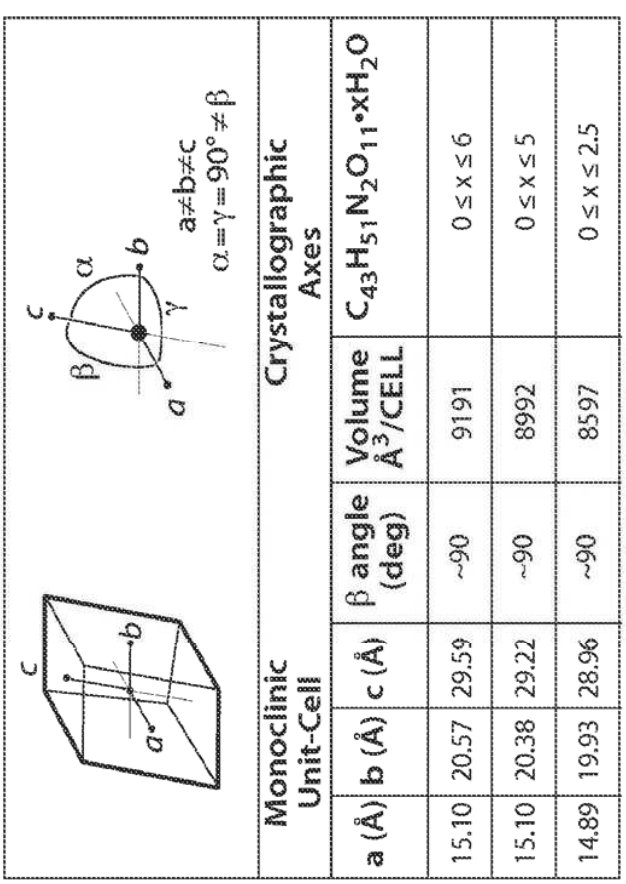

Peak Position [deg 2theta]
Cell Volume [A3]
0
2
4
6
8
10
12
14
8700
8800
8900
9000
9100
9200
200
121
103
022
120
013
112
021
020
102
111
012
110
101
002
011
Indexing Solutions

Fig. 64



Monoclinic Unit-Cell			Crystallographic Axes		
a (Å)	b (Å)	c (Å)	β angle (deg)	Volume Å^3/CELL	$C_{43}H_{51}N_2O_{11}\cdot xH_2O$
15.10	20.57	29.59	~90	9191	$0 \le x \le 6$
15.10	20.38	29.22	~90	8992	$0 \le x \le 5$
14.89	19.93	28.96	~90	8597	$0 \le x \le 2.5$

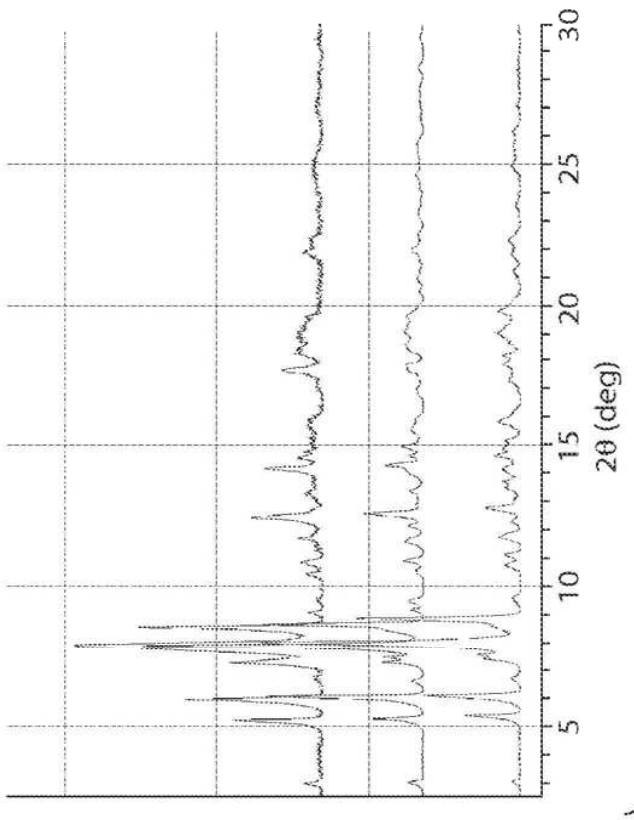


Fig. 65

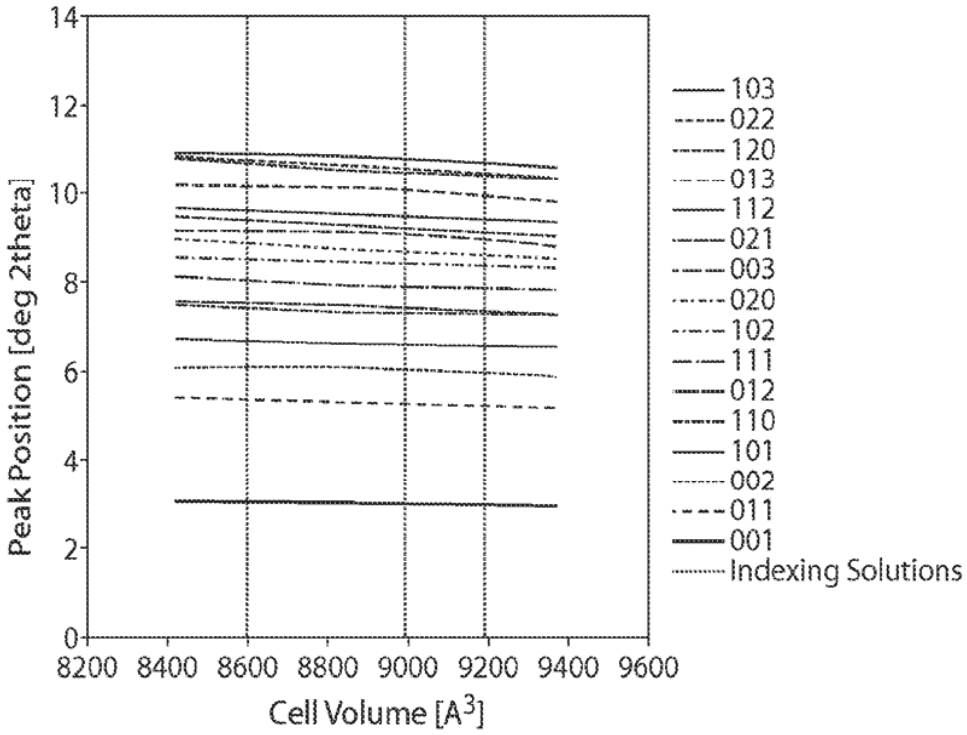

Peak Position [deg 2theta]
Cell Volume [A3]
0
2
4
6
8
10
12
14
8200
8400
8600
8800
9000
9200
9400
9600
103
022
120
013
112
021
003
020
102
111
012
110
101
002
011
001
Indexing Solutions

Fig. 66

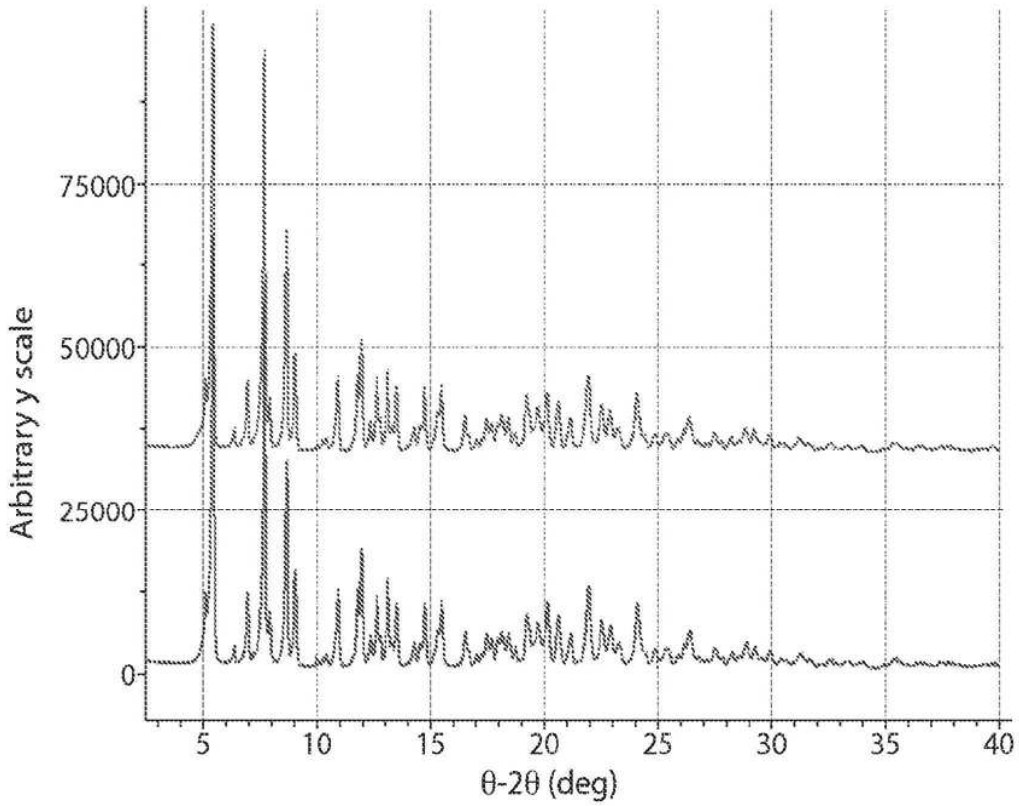

75000
50000
25000
0
Arbitrary y scale
5
10
15
20
25
30
35
40
θ-2θ (deg)

Fig. 67

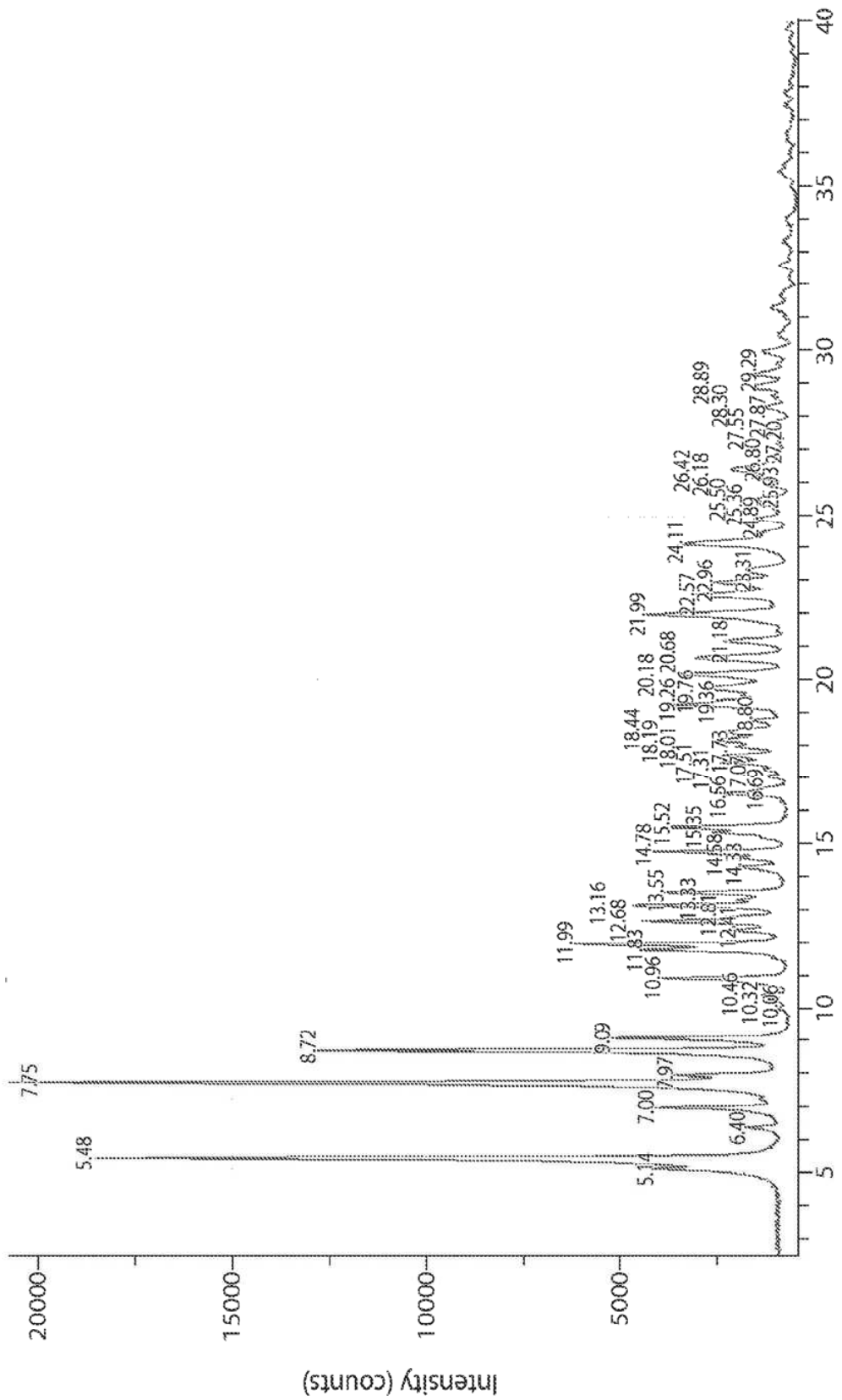

Intensity (counts)
20000
15000
10000
5000
θ-2θ (deg)
5
10
15
20
25
30
35
40
7.75
5.48
8.72
9.09
7.00
7.97
6.40
5.14
10.46
10.32
10.06
11.99
13.16
12.68
11.83
10.96
13.55
13.33
12.81
12.41
14.78
15.52
15.35
14.68
14.33
16.56
17.07
16.69
17.51
17.31
17.73
18.44
18.19
18.01
18.80
19.36
19.76
19.26
20.18
20.68
21.18
21.99
22.57
22.96
23.31
24.11
24.89
25.36
25.50
26.42
26.18
26.80
27.87
27.55
28.89
28.30
29.29

Fig. 68

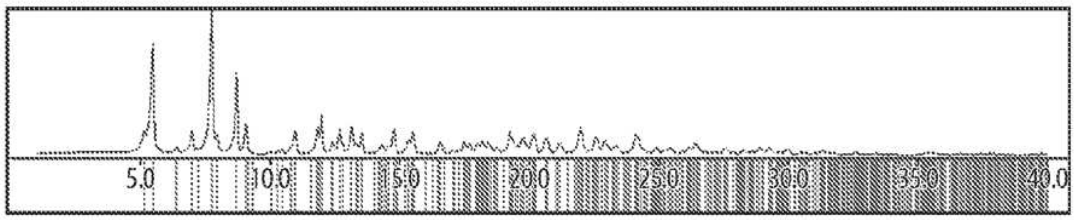


Fig. 69

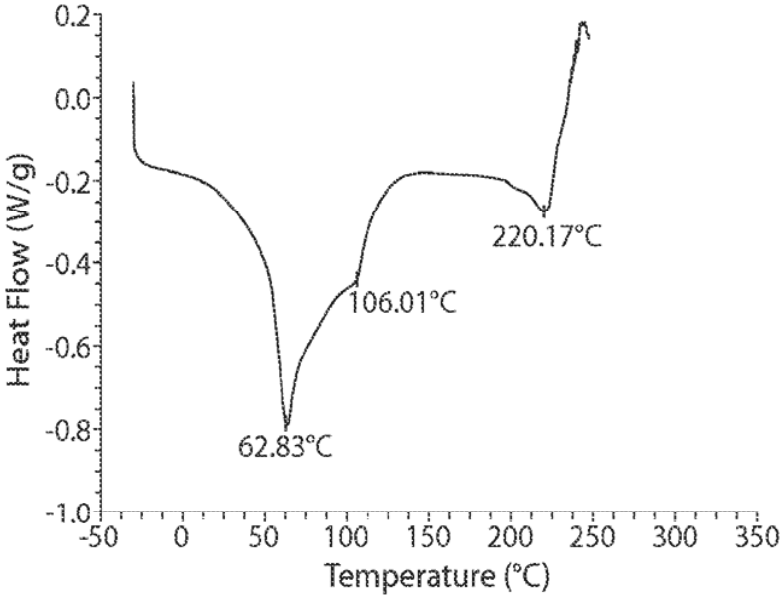


Fig. 70A

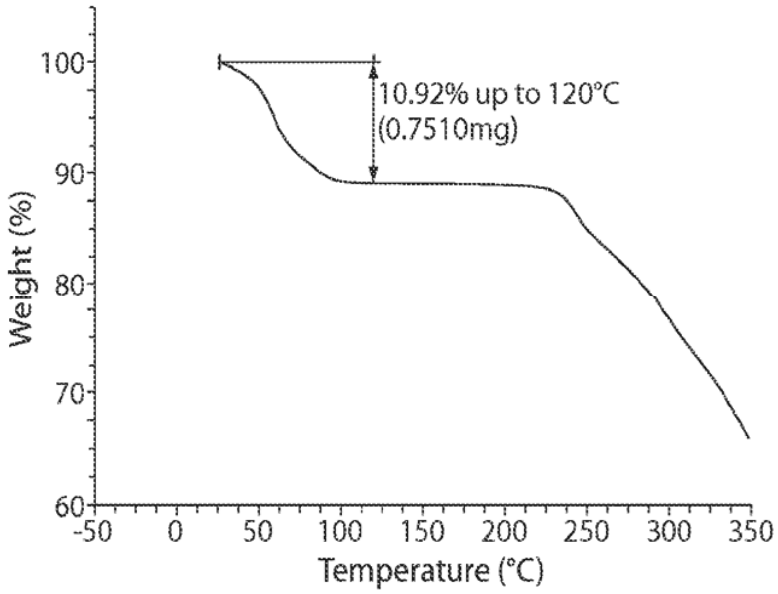


Fig. 70B

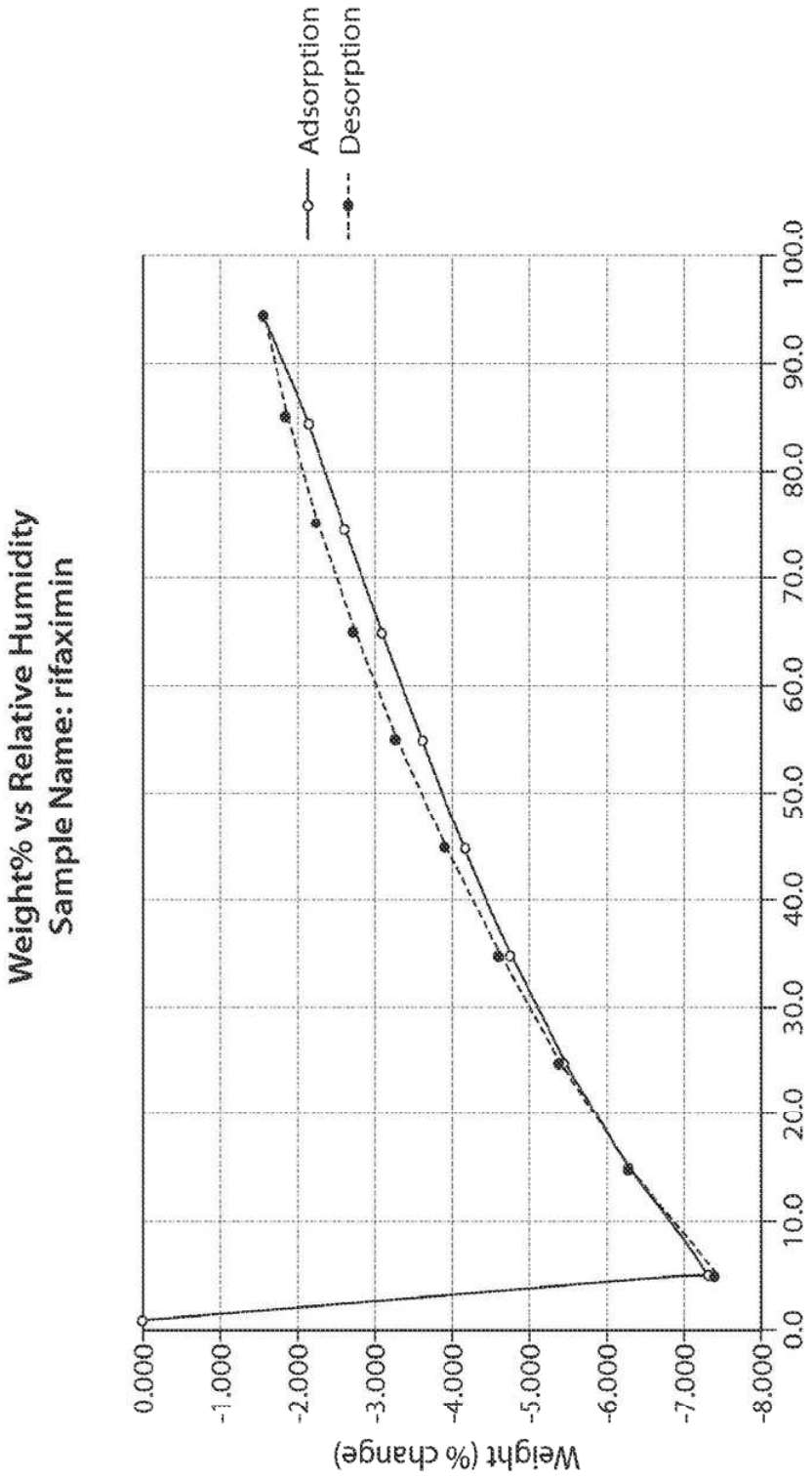

Weight% vs Relative Humidity
Sample Name: rifaximin
Adsorption
Desorption
Weight (% change)
0.000
-1.000
-2.000
-3.000
-4.000
-5.000
-6.000
-7.000
-8.000
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
%RH

Fig. 71

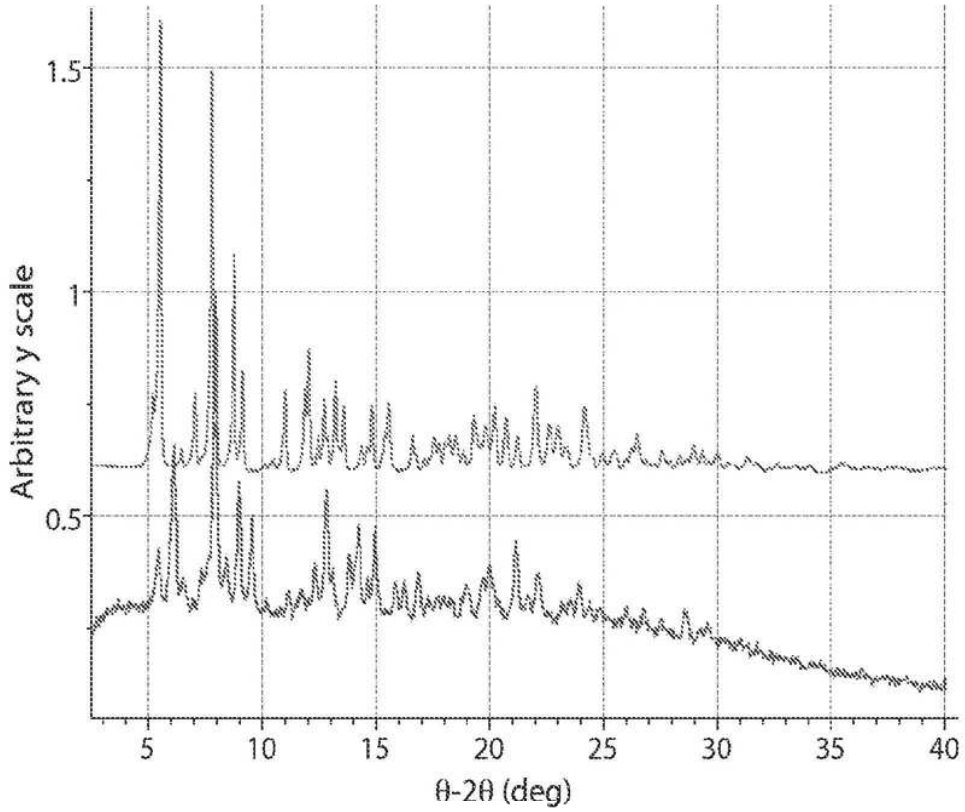


Fig. 72