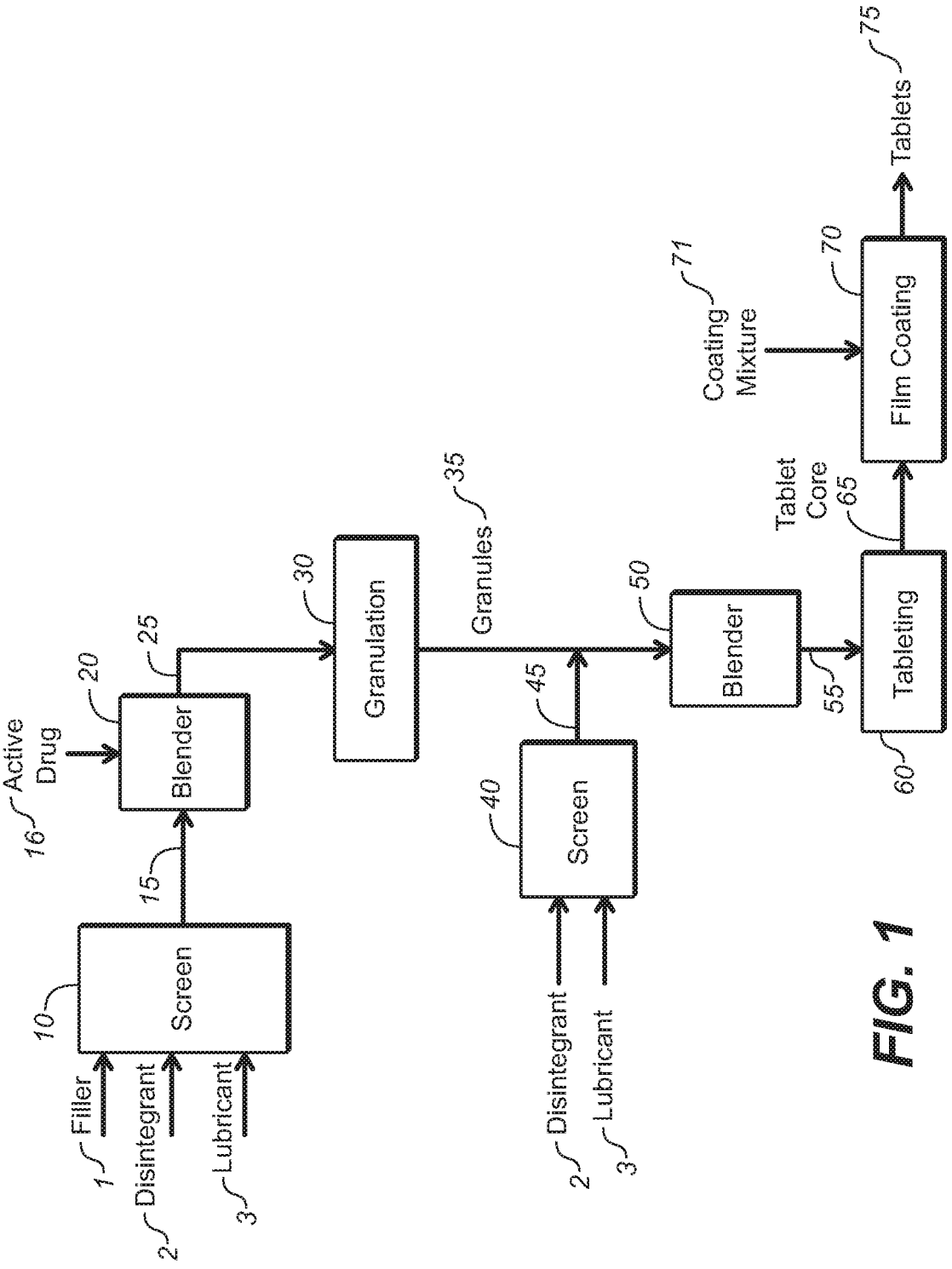

Filler
Disintegrant
Lubricant
Screen
Active Drug
Blender
Granulation
Granules
Screen
Disintegrant
Lubricant
Blender
Tablet Core
Tableting
Coating Mixture
Film Coating
Tablets
1
2
3
10
15
16
20
25
30
35
40
45
50
55
60
65
70
71
75

FIG. 1

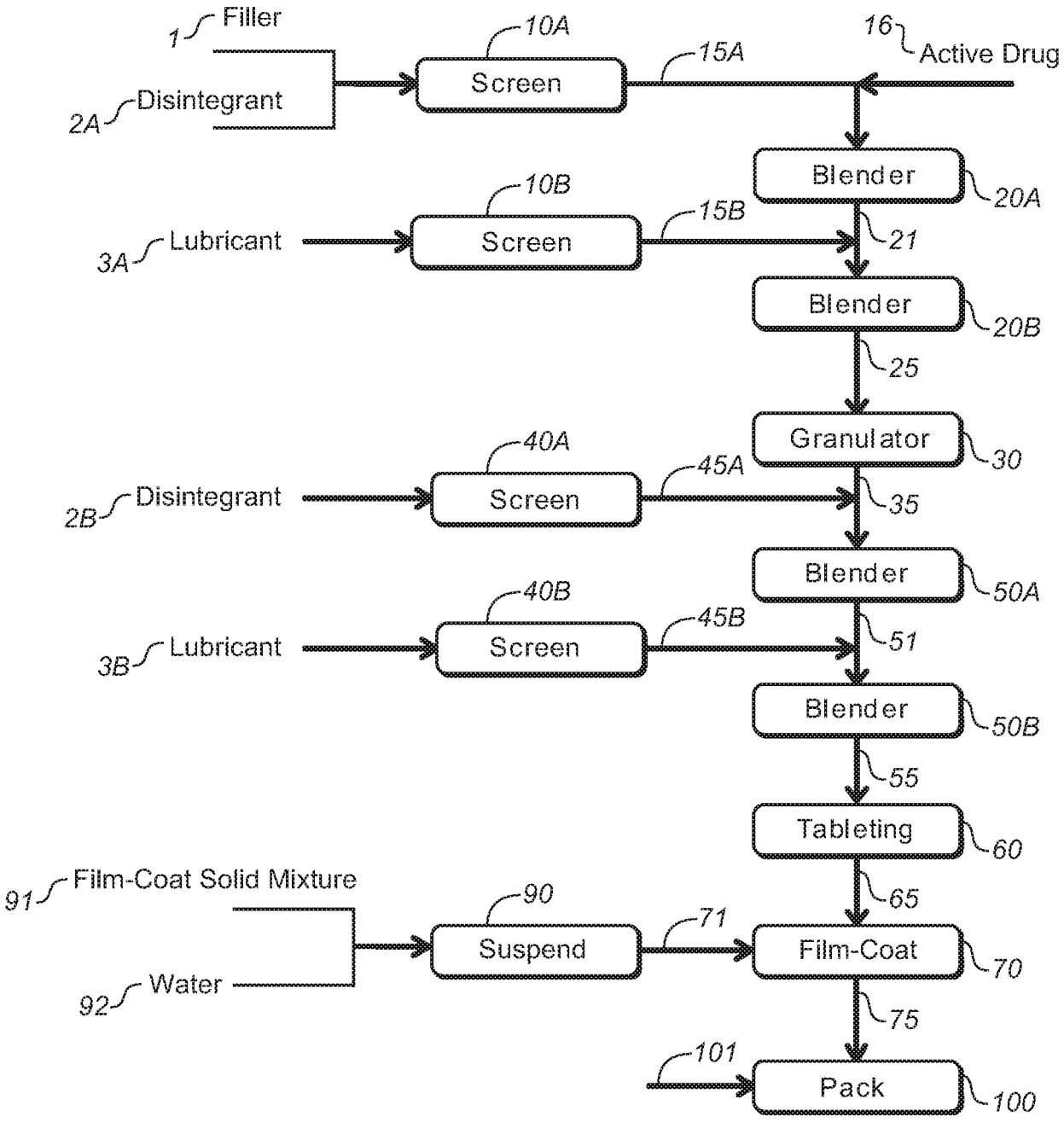

1
Filler
2A
Disintegrant
10A
Screen
15A
16
Active Drug
Blender
20A
3A
Lubricant
10B
Screen
15B
21
Blender
20B
25
Granulator
30
2B
Disintegrant
40A
Screen
45A
35
Blender
50A
3B
Lubricant
40B
Screen
45B
51
Blender
50B
55
Tableting
60
91
Film-Coat Solid Mixture
92
Water
90
Suspend
71
Film-Coat
70
65
75
101
Pack
100

FIG. 2

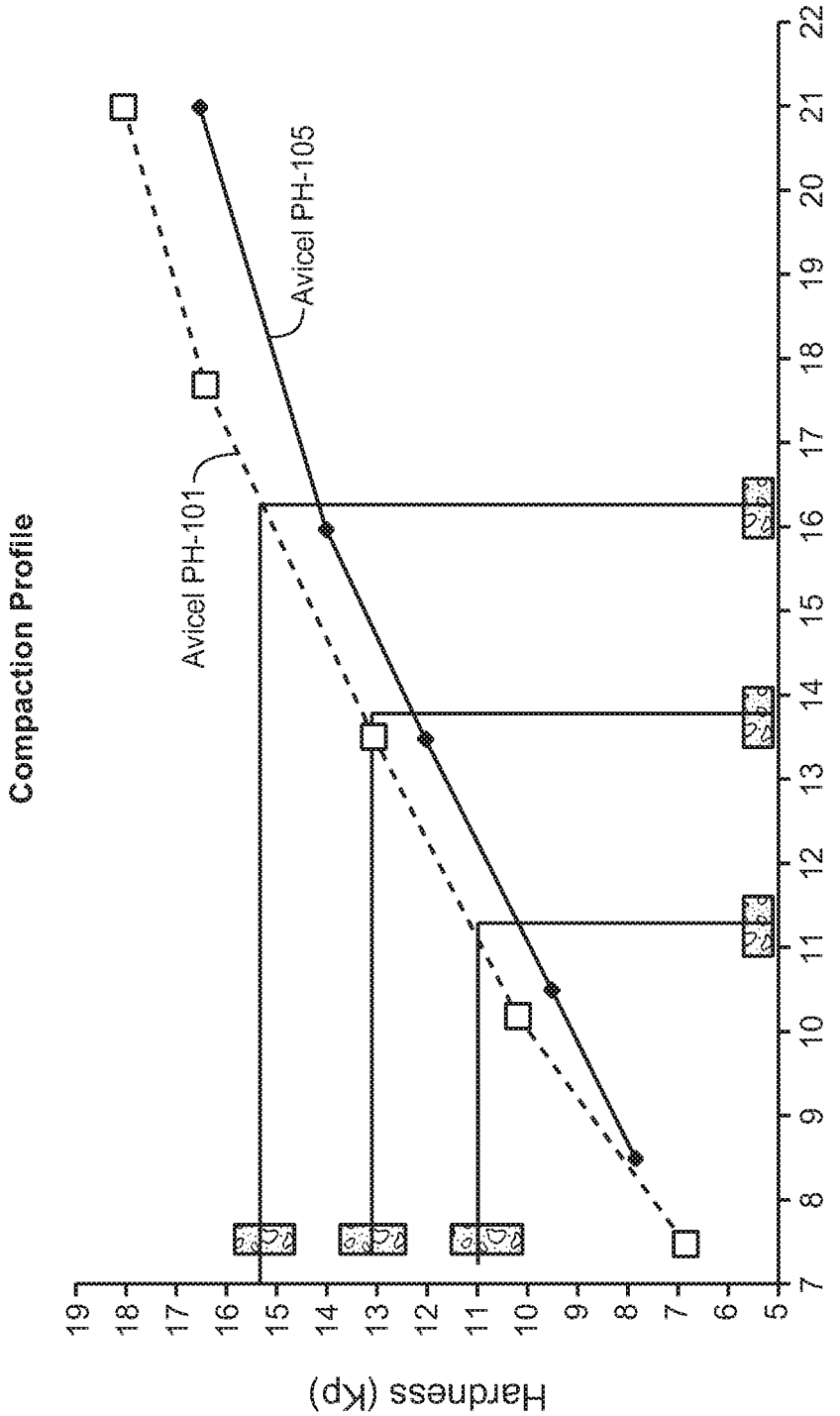

Compaction Profile
Avicel PH-101
Avicel PH-105
Hardness (kp)
Compaction Force (kN)
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

FIG. 3

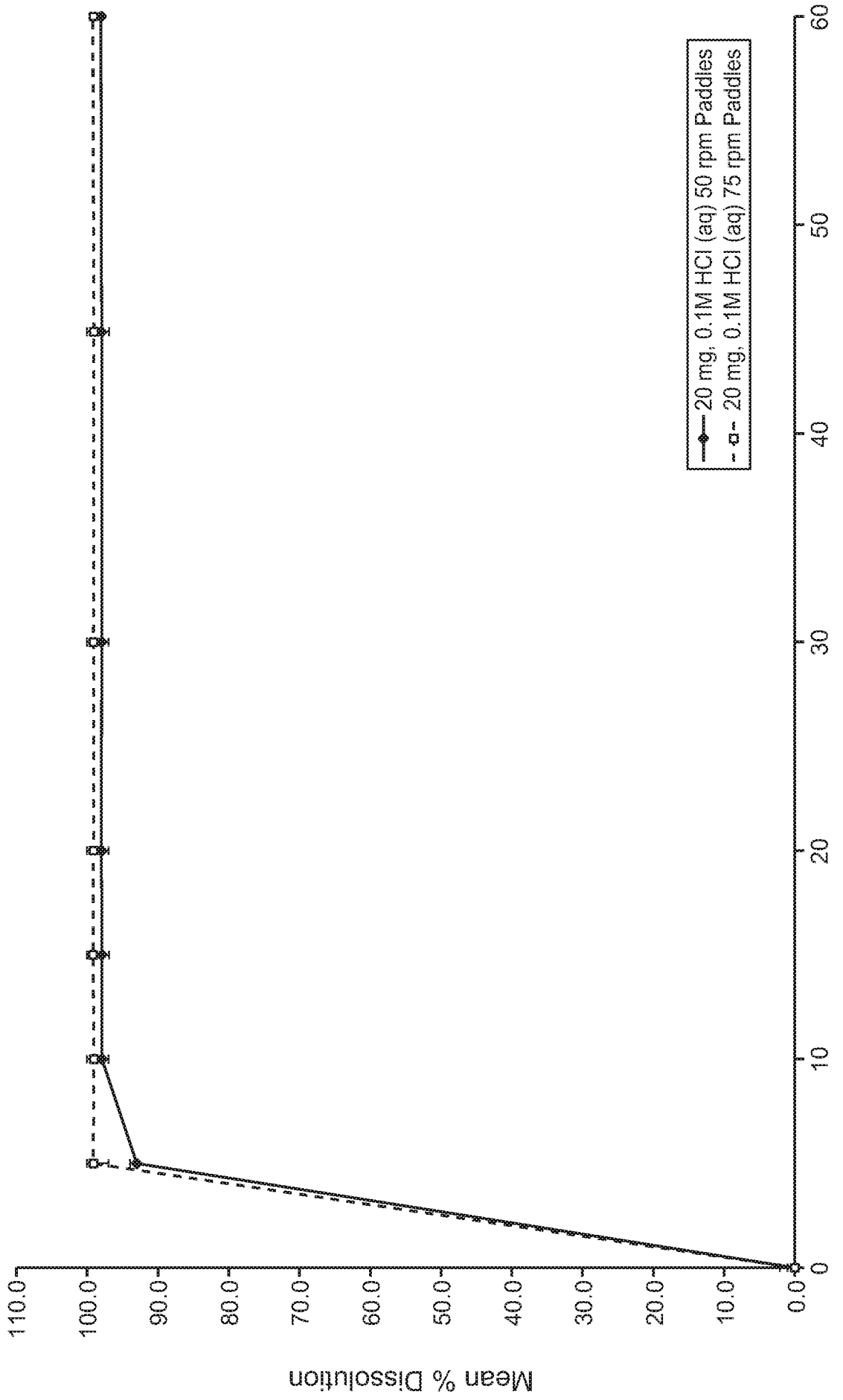

Mean % Dissolution
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
10
20
30
40
50
60
Time (Min)
20 mg, 0.1M HCl (aq) 50 rpm Paddles
20 mg, 0.1M HCl (aq) 75 rpm Paddles

FIG. 4

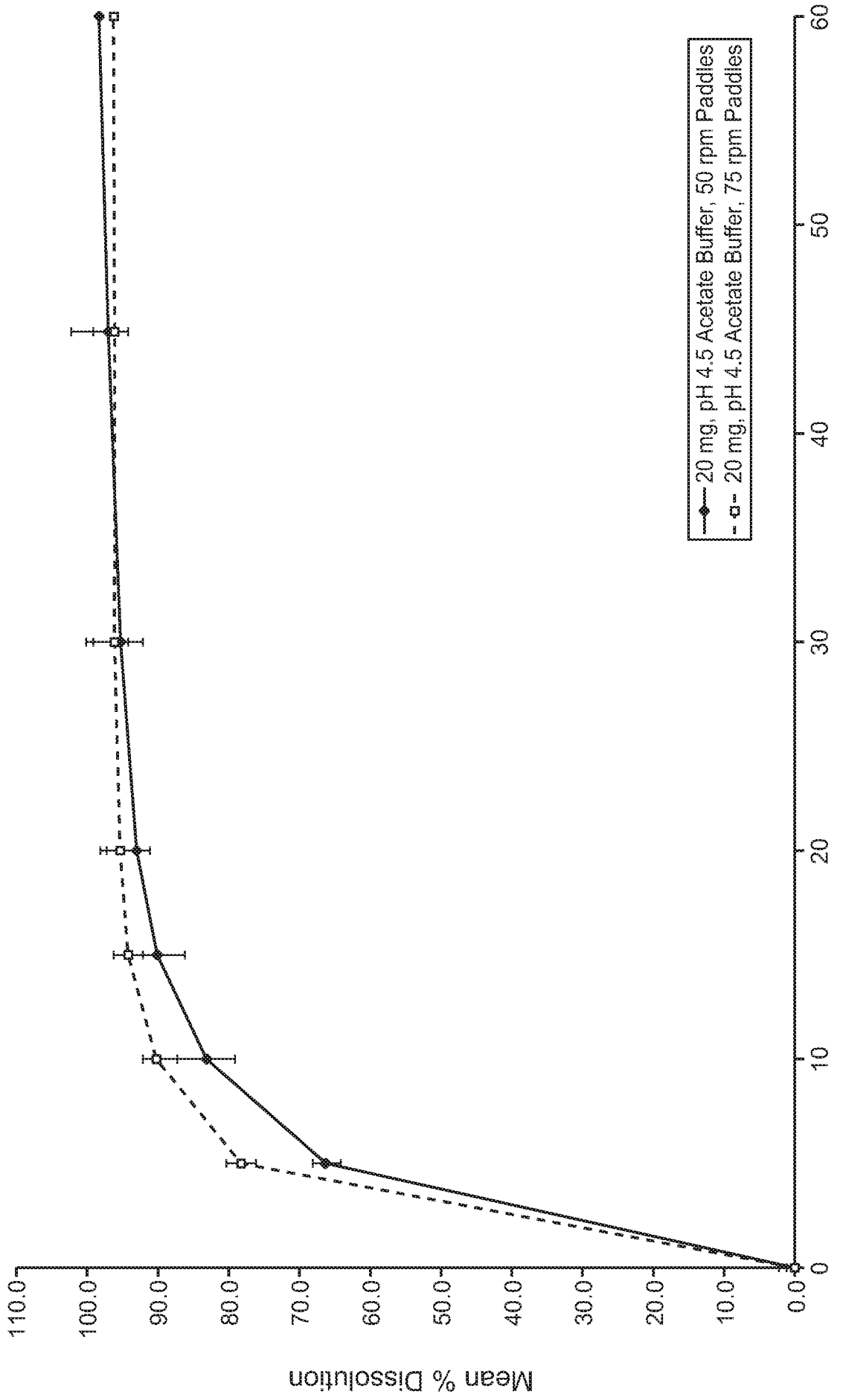

Mean % Dissolution
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
10
20
30
40
50
60
Time (Min)
20 mg, pH 4.5 Acetate Buffer, 50 rpm Paddles
20 mg, pH 4.5 Acetate Buffer, 75 rpm Paddles

FIG. 5

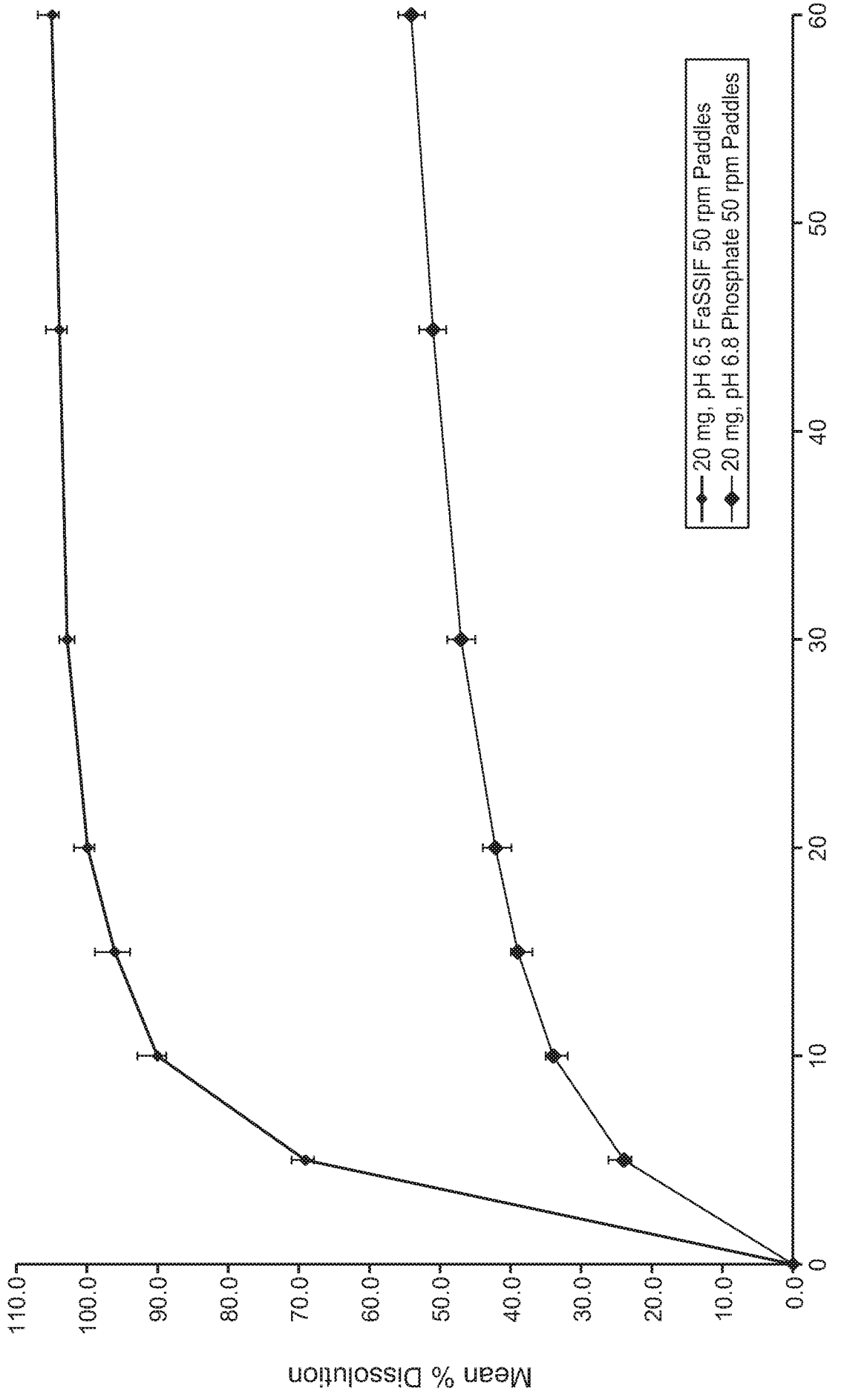

Mean % Dissolution
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
10
20
30
40
50
60
Time (Min)
20 mg, pH 6.5 FaSSIF 50 rpm Paddles
20 mg, pH 6.8 Phosphate 50 rpm Paddles

FIG. 6

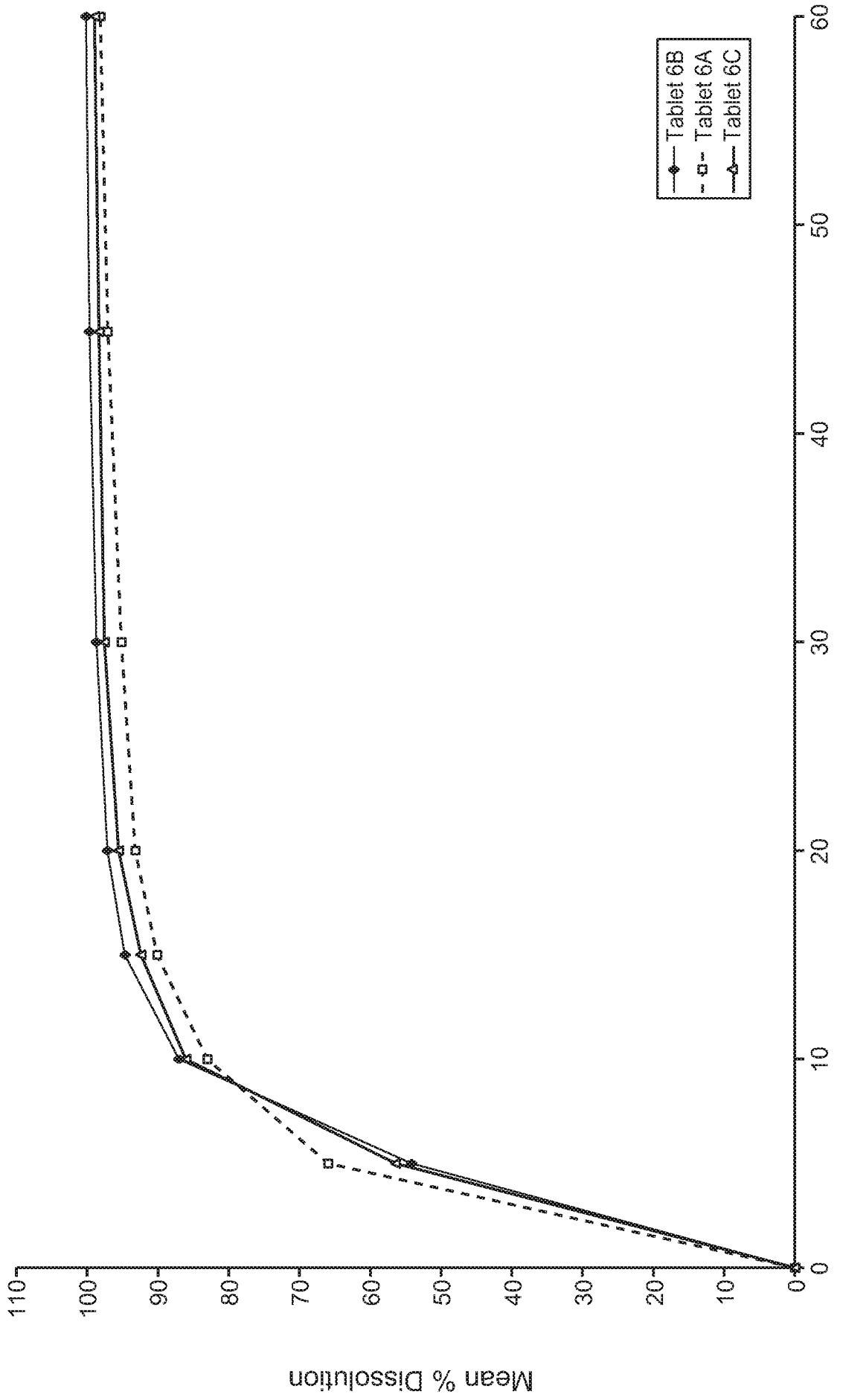

Mean % Dissolution
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
Time (Min)
Tablet 6B
Tablet 6A
Tablet 6C

FIG. 7

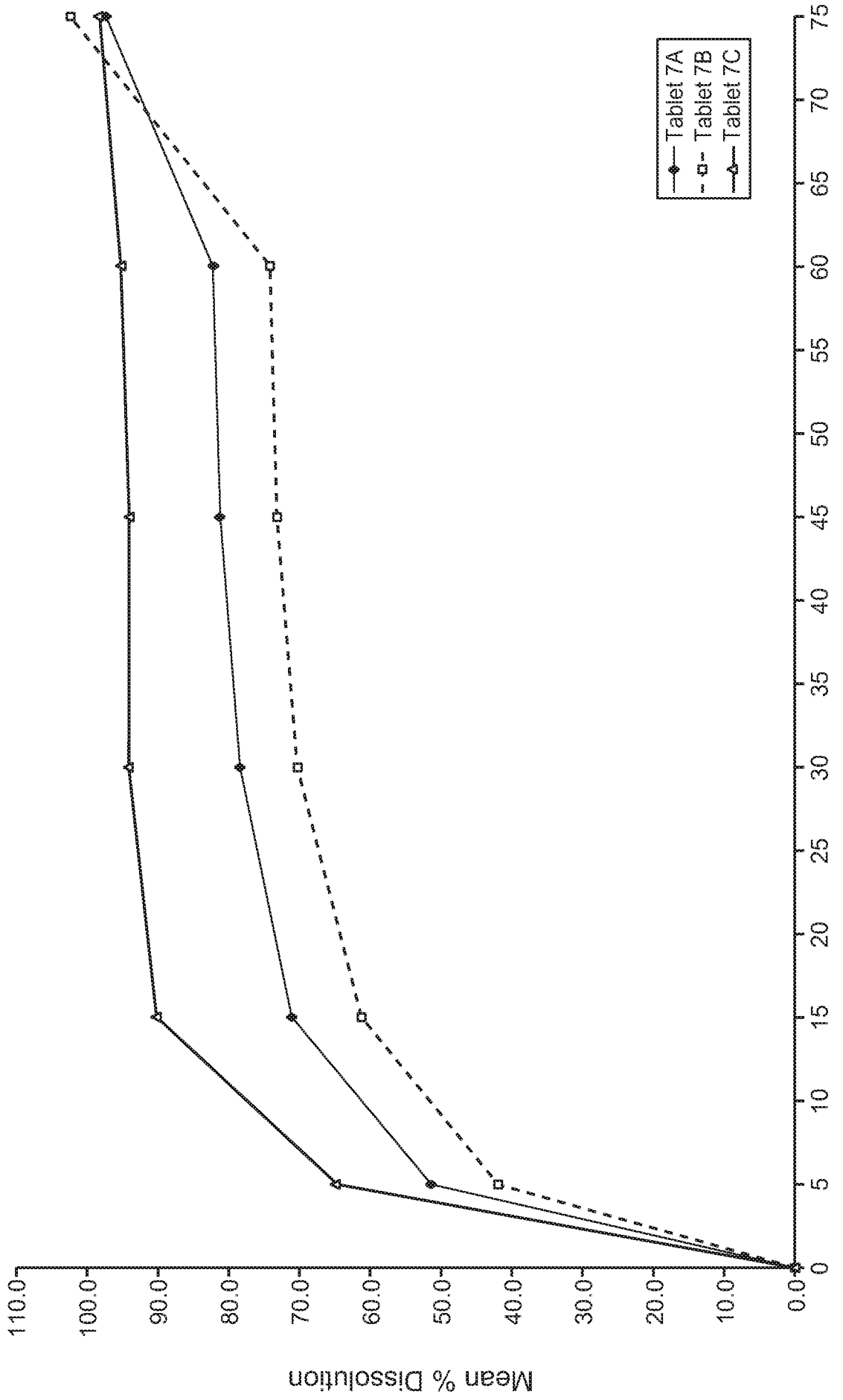

Tablet 7A
Tablet 7B
Tablet 7C
Mean % Dissolution
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
Time (Min)

FIG. 8

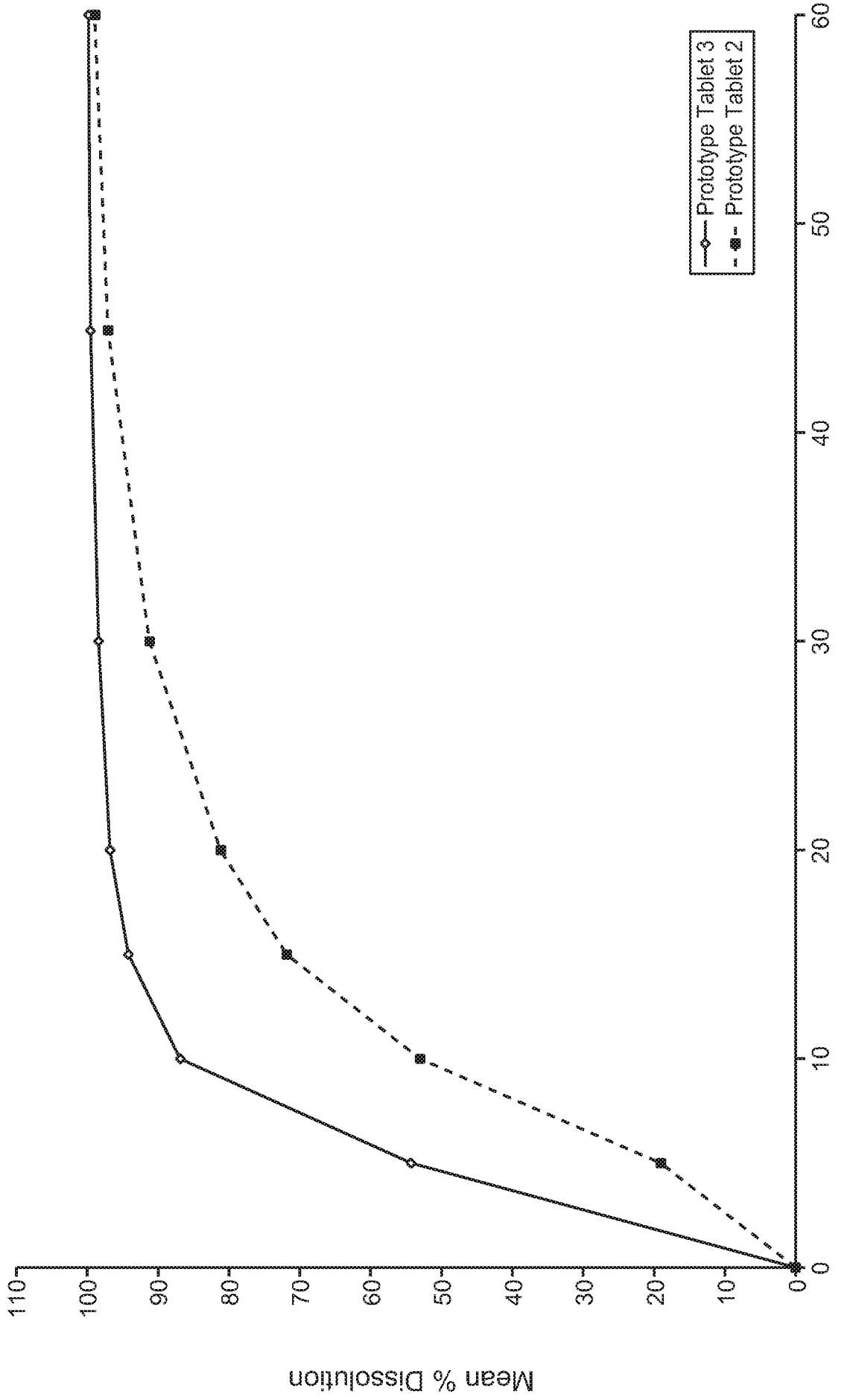

Mean % Dissolution
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
Time (Min)
Prototype Tablet 3
Prototype Tablet 2

FIG. 9

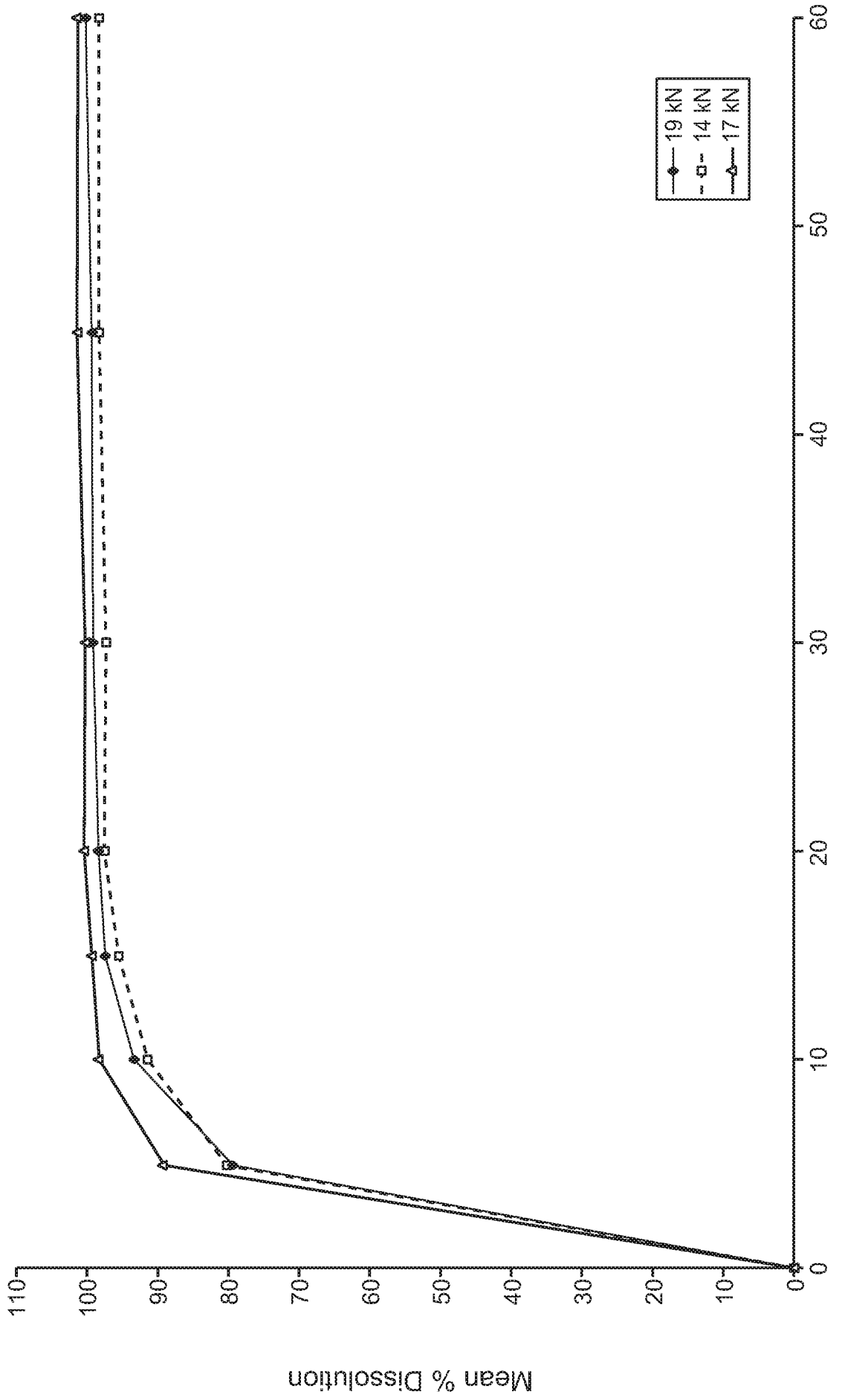

Mean % Dissolution
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
Time (Min)
19 kN
14 kN
17 kN

FIG. 10

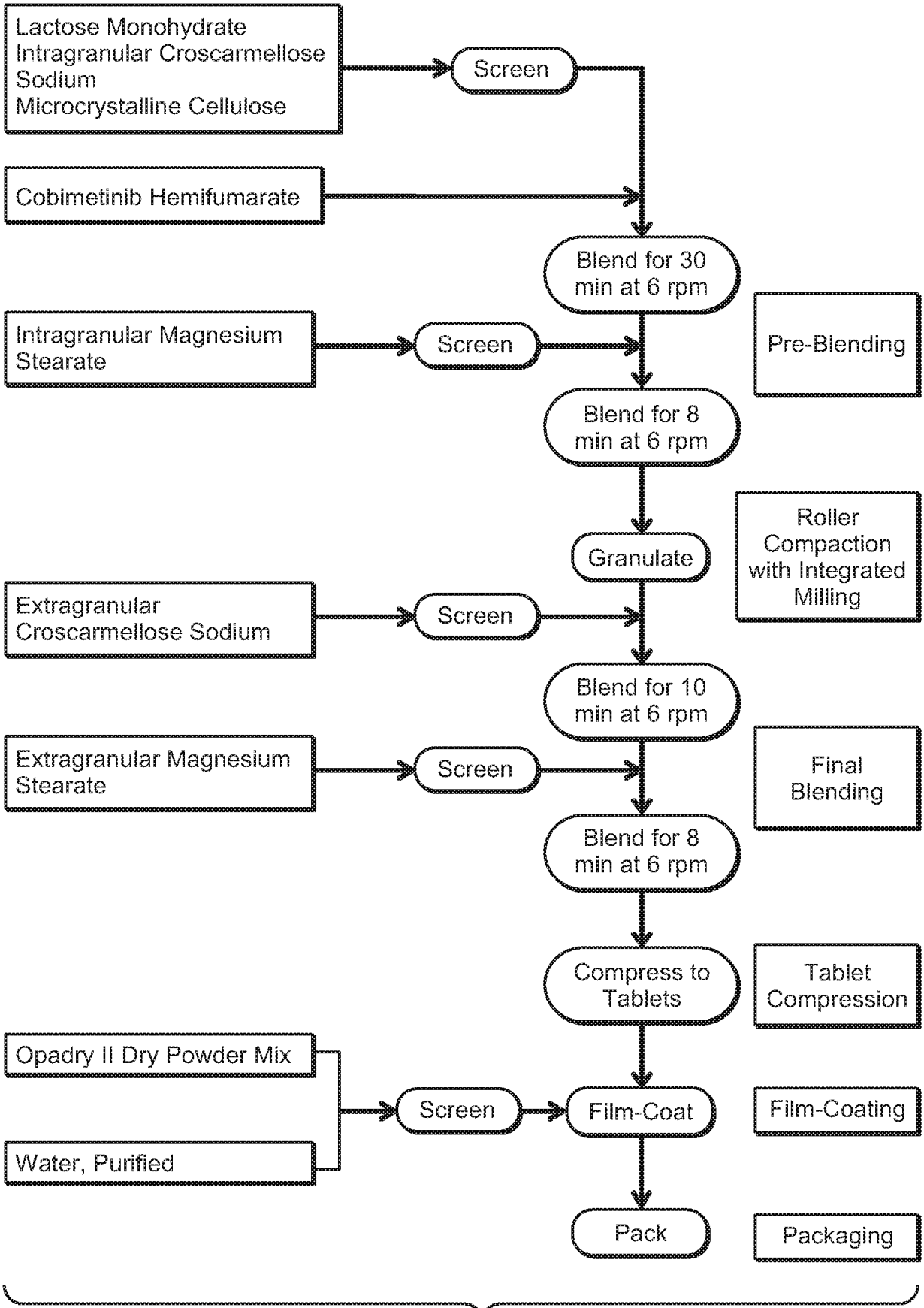

Lactose Monohydrate
Intragranular Croscarmellose Sodium
Microcrystalline Cellulose
Screen
Cobimetinib Hemifumarate
Blend for 30 min at 6 rpm
Intragranular Magnesium Stearate
Screen
Pre-Blending
Blend for 8 min at 6 rpm
Granulate
Roller Compaction with Integrated Milling
Extragranular Croscarmellose Sodium
Screen
Blend for 10 min at 6 rpm
Extragranular Magnesium Stearate
Screen
Final Blending
Blend for 8 min at 6 rpm
Compress to Tablets
Tablet Compression
Opadry II Dry Powder Mix
Water, Purified
Screen
Film-Coat
Film-Coating
Pack
Packaging

FIG. 11

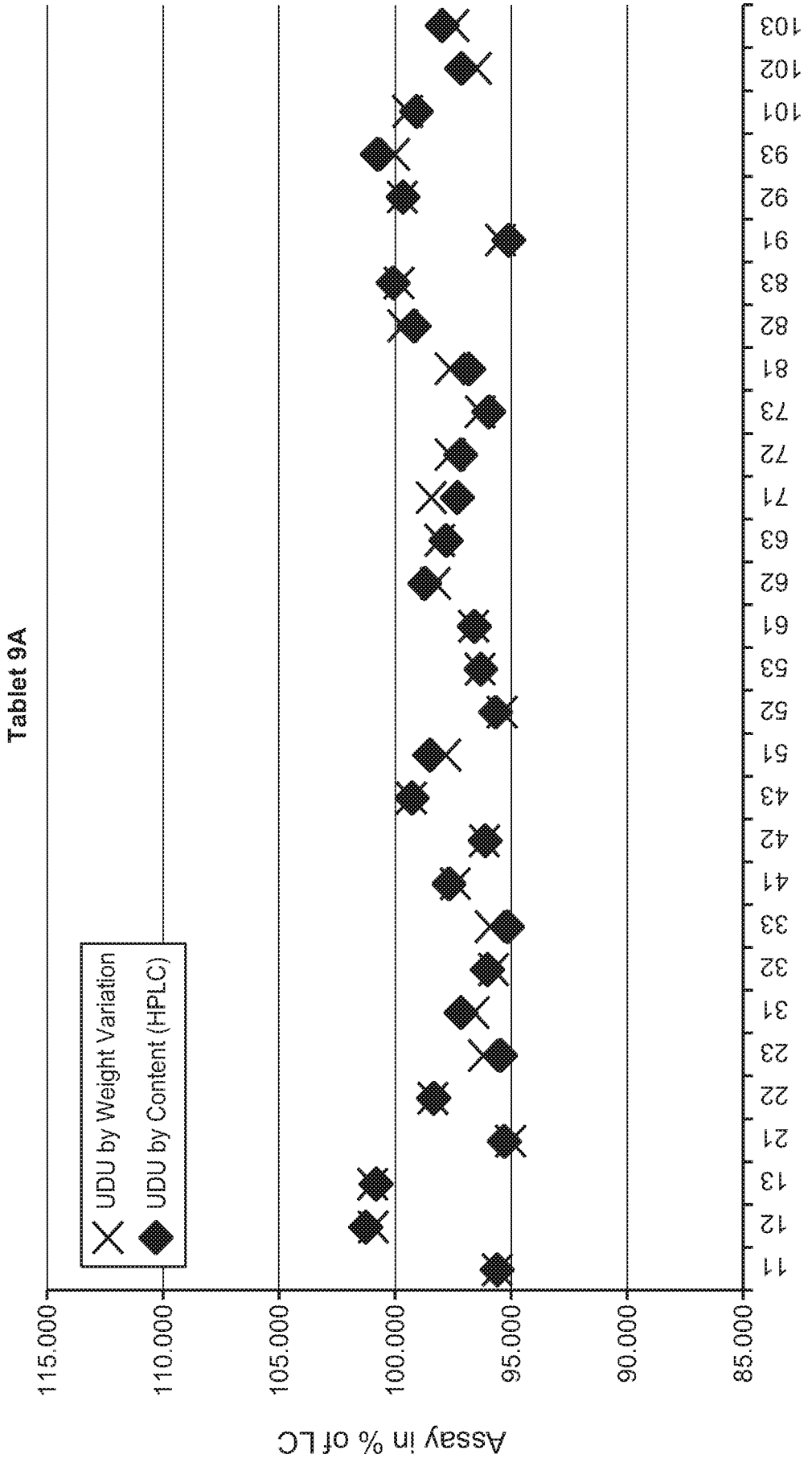

Tablet 9A
UDU by Weight Variation
UDU by Content (HPLC)
Assay in % of LC
115.000
110.000
105.000
100.000
95.000
90.000
85.000
11
12
13
21
22
23
31
32
33
41
42
43
51
52
53
61
62
63
71
72
73
81
82
83
91
92
93
101
102
103

FIG. 12A

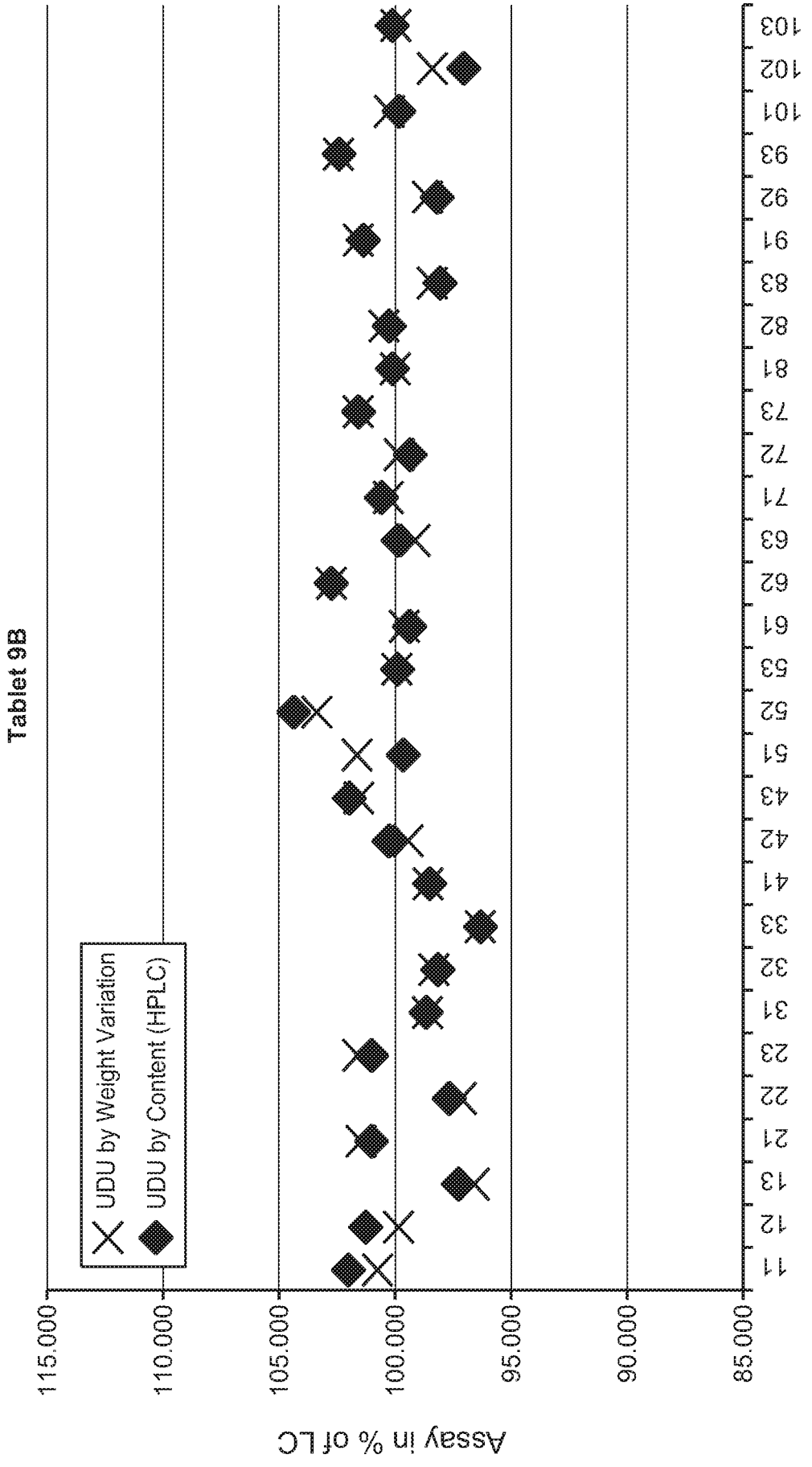

Tablet 9B
UDU by Weight Variation
UDU by Content (HPLC)
Assay in % of LC
115.000
110.000
105.000
100.000
95.000
90.000
85.000
11
12
13
21
22
23
31
32
33
41
42
43
51
52
53
61
62
63
71
72
73
81
82
83
91
92
93
101
102
103

FIG. 12B

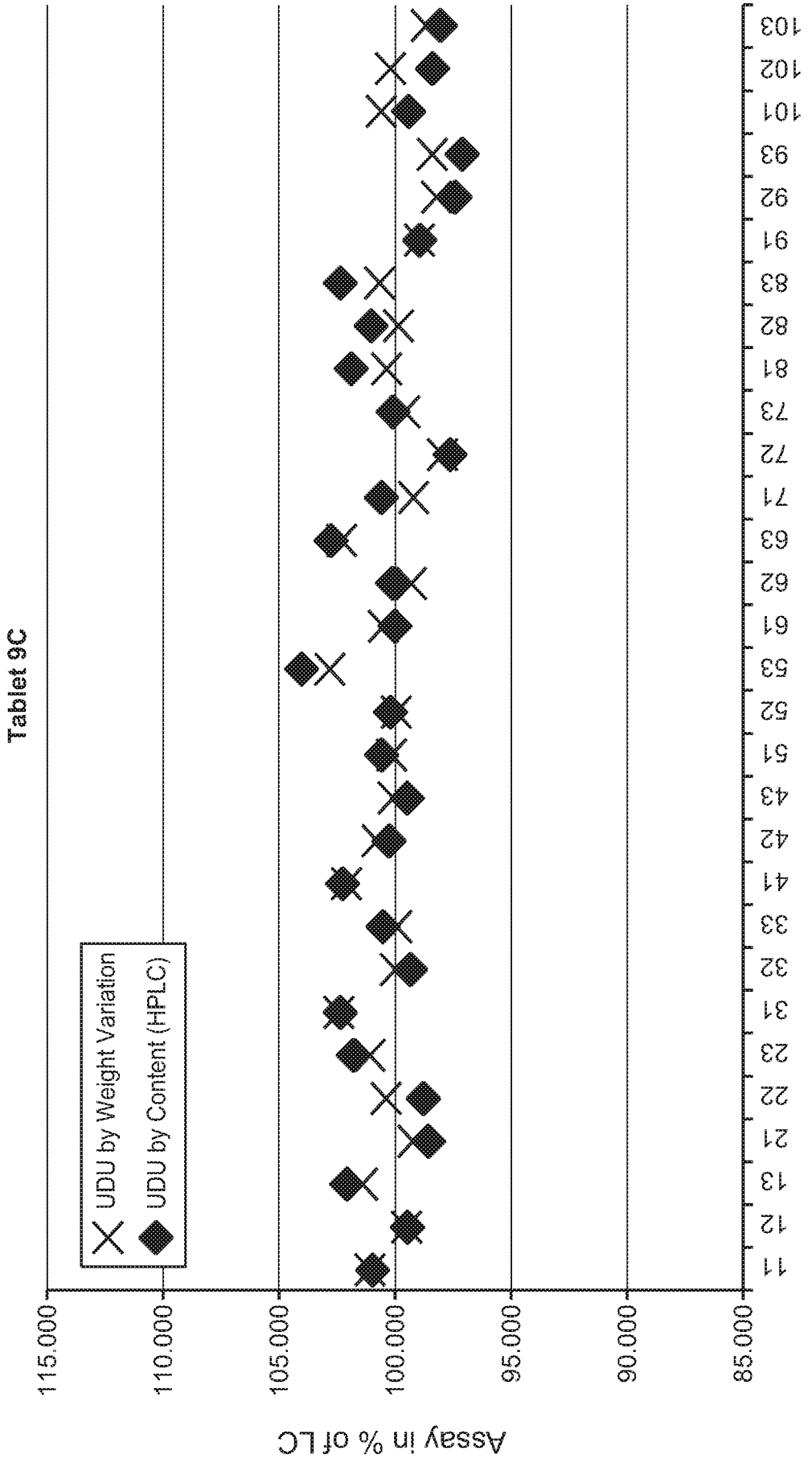
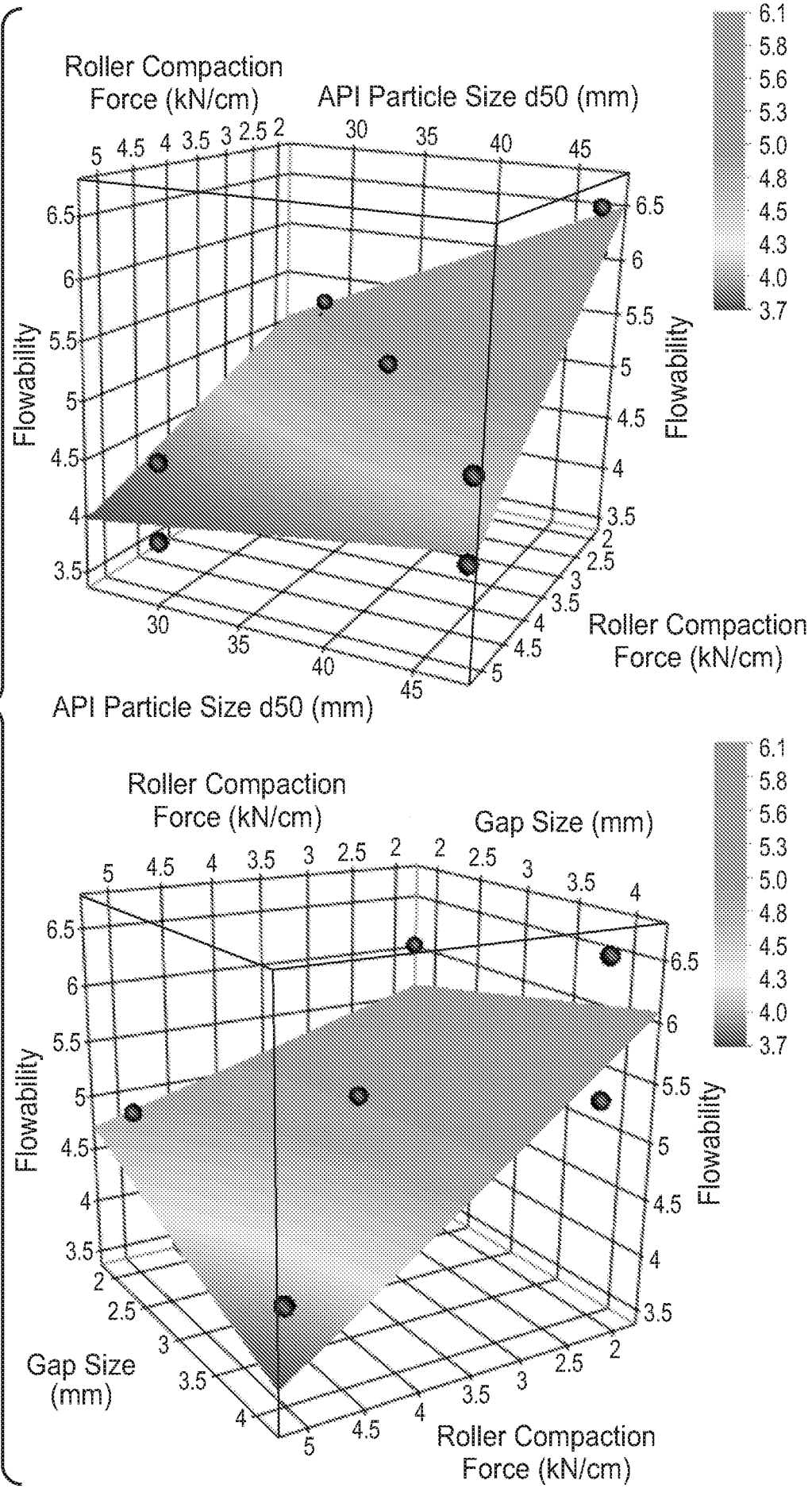

Tablet 9C
UDU by Weight Variation
UDU by Content (HPLC)
Assay in % of LC
115.000
110.000
105.000
100.000
95.000
90.000
85.000
11
12
13
21
22
23
31
32
33
41
42
43
51
52
53
61
62
63
71
72
73
81
82
83
91
92
93
101
102
103

FIG. 12C

FIG. 13


Roller Compaction Force (kN/cm)
API Particle Size d50 (mm)
Flowability
6.1
5.8
5.6
5.3
5.0
4.8
4.5
4.3
4.0
3.7
Roller Compaction Force (kN/cm)
API Particle Size d50 (mm)
Roller Compaction Force (kN/cm)
Gap Size (mm)
Flowability
Gap Size (mm)
Roller Compaction Force (kN/cm)

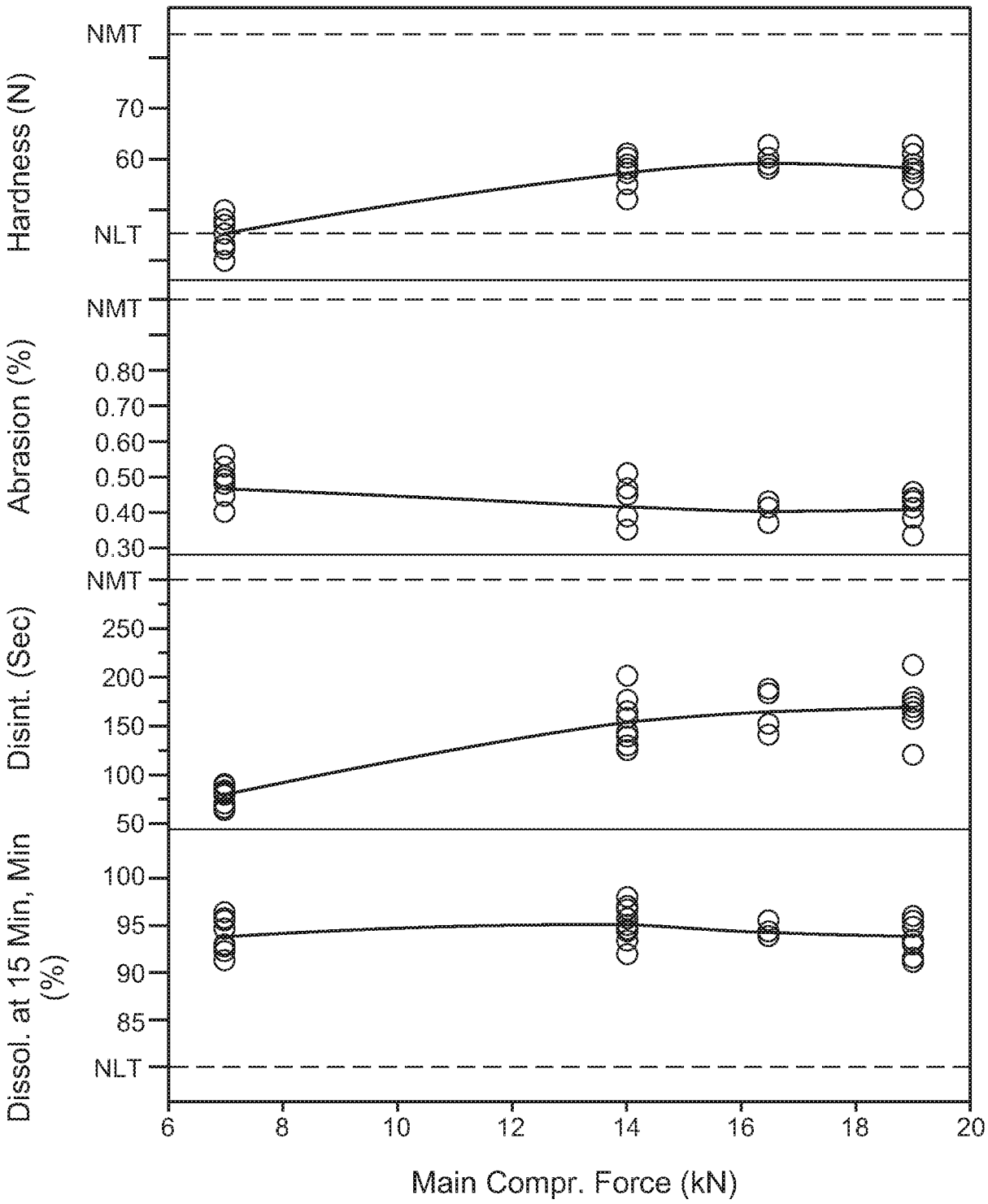

Hardness (N)
NMT
70
60
NLT
Abrasion (%)
NMT
0.80
0.70
0.60
0.50
0.40
0.30
Disint. (Sec)
NMT
250
200
150
100
50
Dissol. at 15 Min, Min (%)
100
95
90
85
NLT
6
8
10
12
14
16
18
20
Main Compr. Force (kN)

FIG. 14

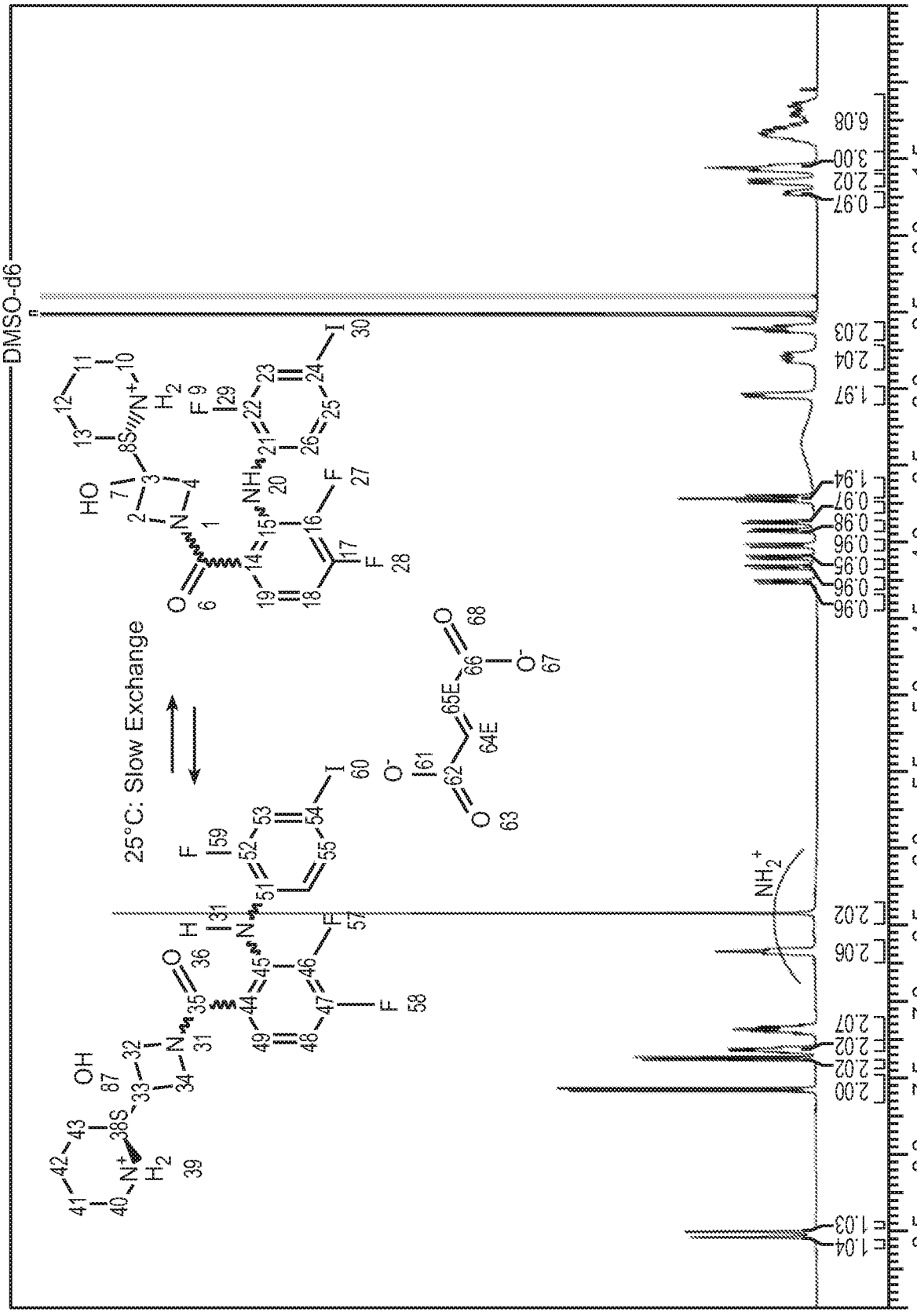

DMSO-d6
25°C: Slow Exchange
Chemical Shift (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.03
1.04
2.00
2.02
2.02
2.07
2.06
2.02
0.96
0.96
0.95
0.96
0.98
0.97
1.94
1.97
2.04
2.03
0.97
2.02
3.00
6.08

FIG. 15

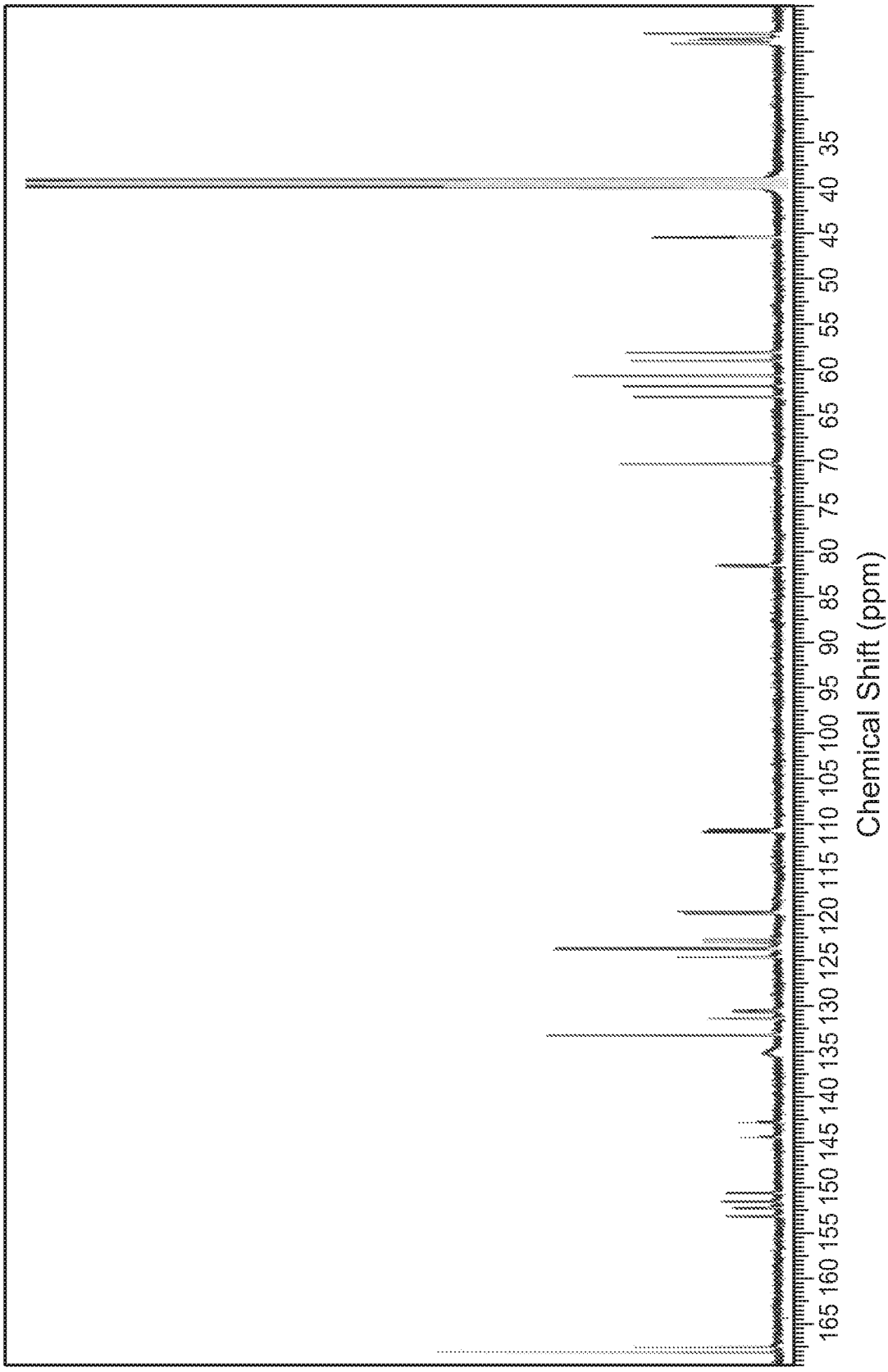

Chemical Shift (ppm)
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35

FIG. 16

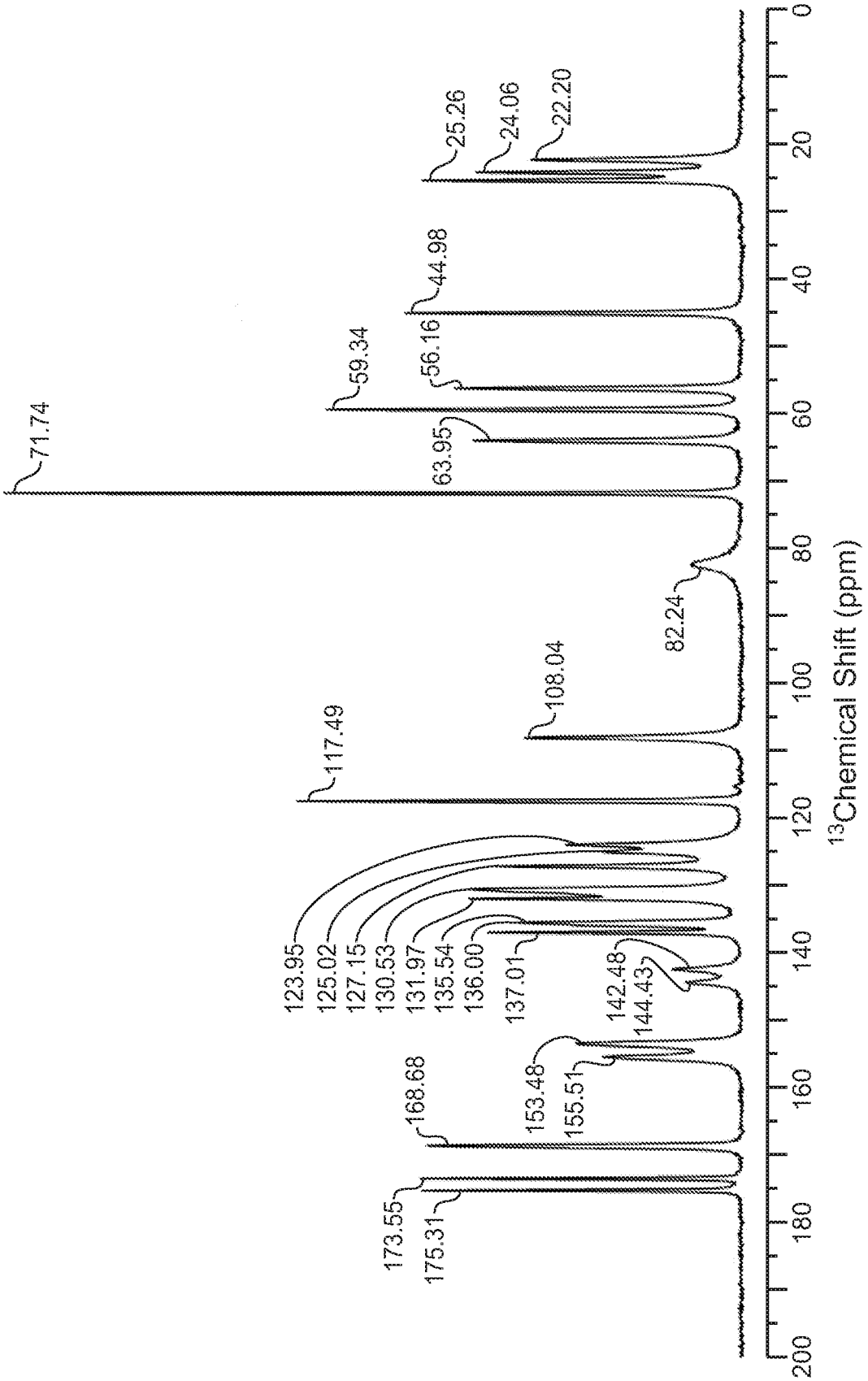

71.74
59.34
56.16
44.98
63.95
25.26
24.06
22.20
117.49
108.04
82.24
123.95
125.02
127.15
130.53
131.97
135.54
136.00
137.01
142.48
144.43
153.48
155.51
168.68
173.55
175.31
0
20
40
60
80
100
120
140
160
180
200
13Chemical Shift (ppm)

FIG. 17

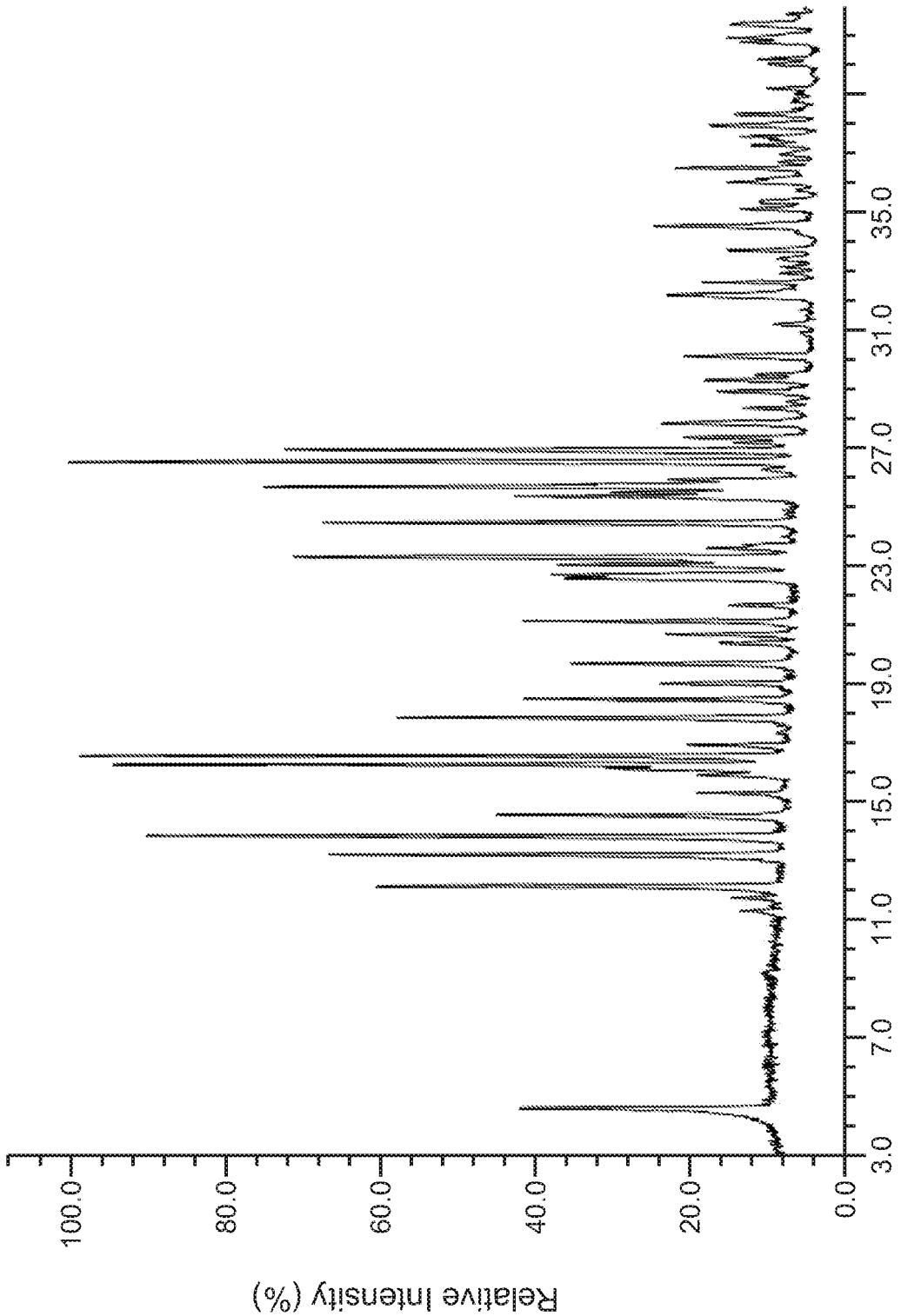

Relative Intensity (%)
100.0
80.0
60.0
40.0
20.0
0.0
3.0
7.0
11.0
15.0
19.0
23.0
27.0
31.0
35.0
2Theta

FIG. 18

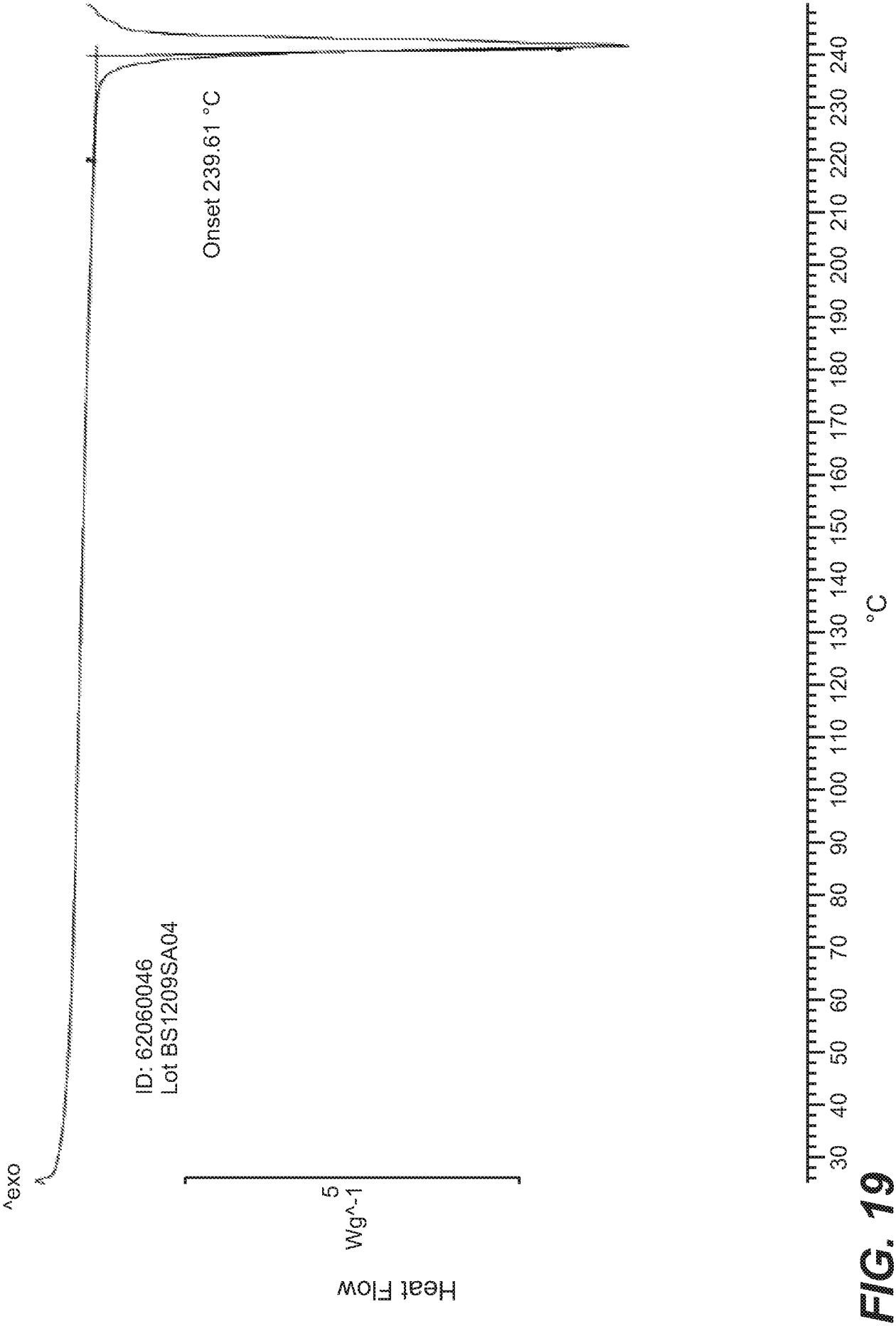

Onset 239.61 °C
ID: 62060046
Lot BS1209SA04
^exo
Heat Flow
5
Wg^-1
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240
°C

FIG. 19