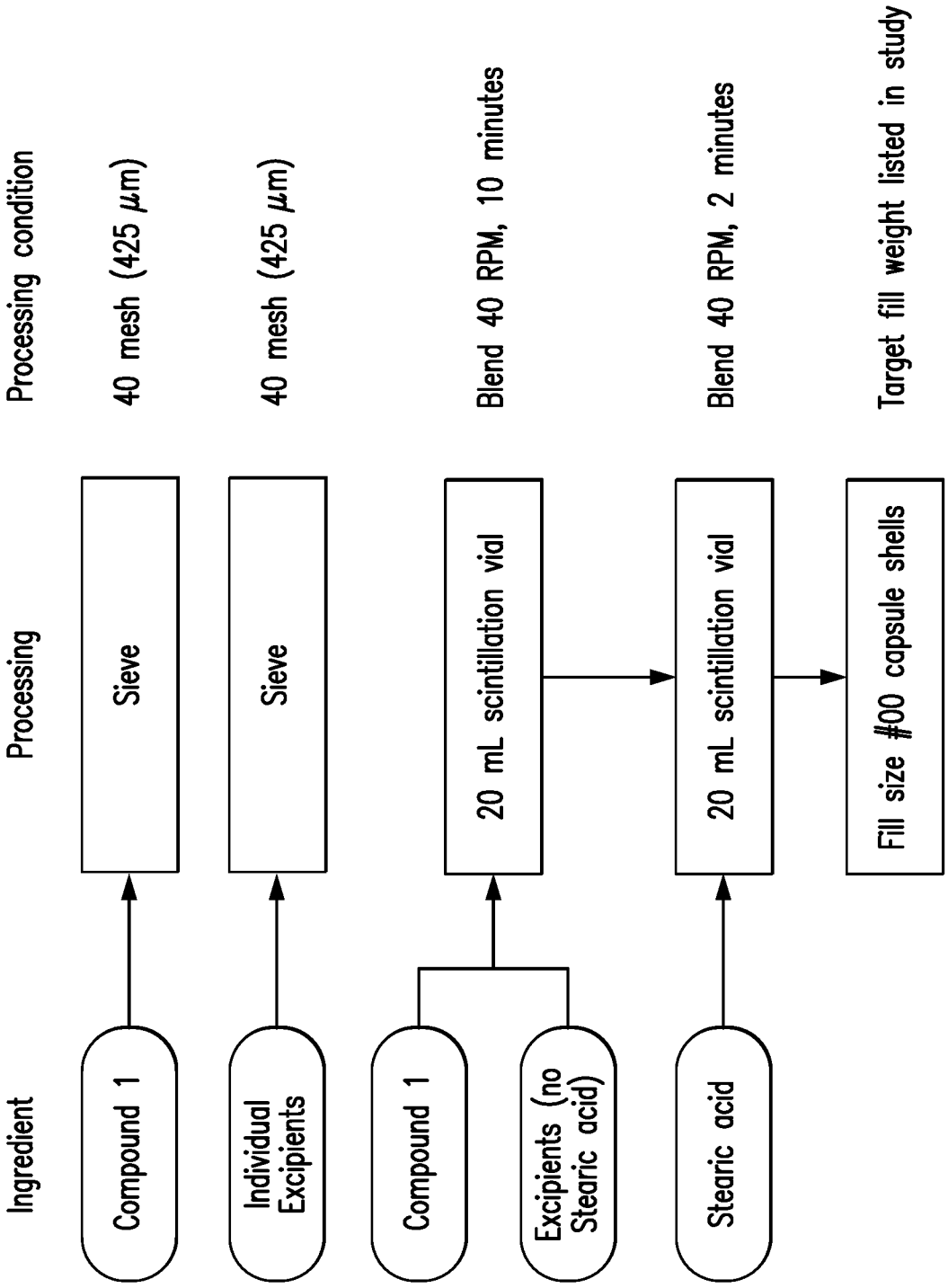

Ingredient
Processing
Processing condition
Compound 1
Sieve
40 mesh (425 μm)
Individual Excipients
Sieve
40 mesh (425 μm)
Compound 1
Excipients (no Stearic acid)
20 mL scintillation vial
Blend 40 RPM, 10 minutes
Stearic acid
20 mL scintillation vial
Blend 40 RPM, 2 minutes
Fill size #00 capsule shells
Target fill weight listed in study

FIG. 1

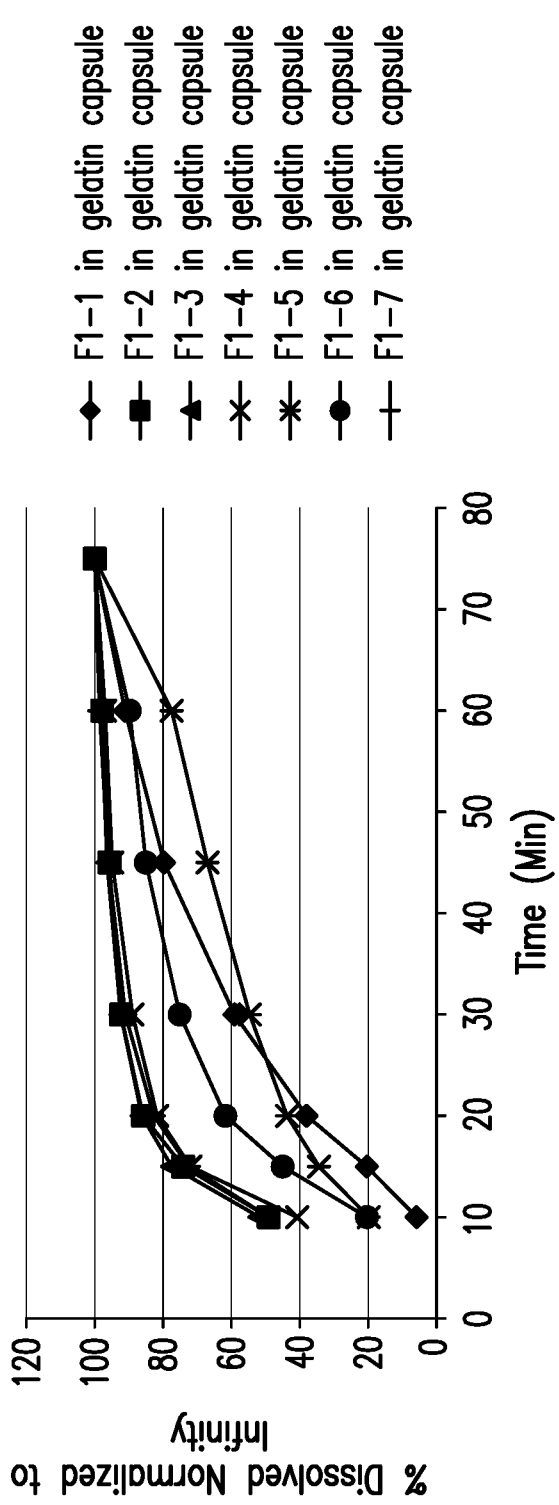

F1–1 in gelatin capsule
F1–2 in gelatin capsule
F1–3 in gelatin capsule
F1–4 in gelatin capsule
F1–5 in gelatin capsule
F1–6 in gelatin capsule
F1–7 in gelatin capsule
% Dissolved Normalized to Infinity
Time (Min)
0
20
40
60
80
100
120
0
10
20
30
40
50
60
70
80

FIG. 2

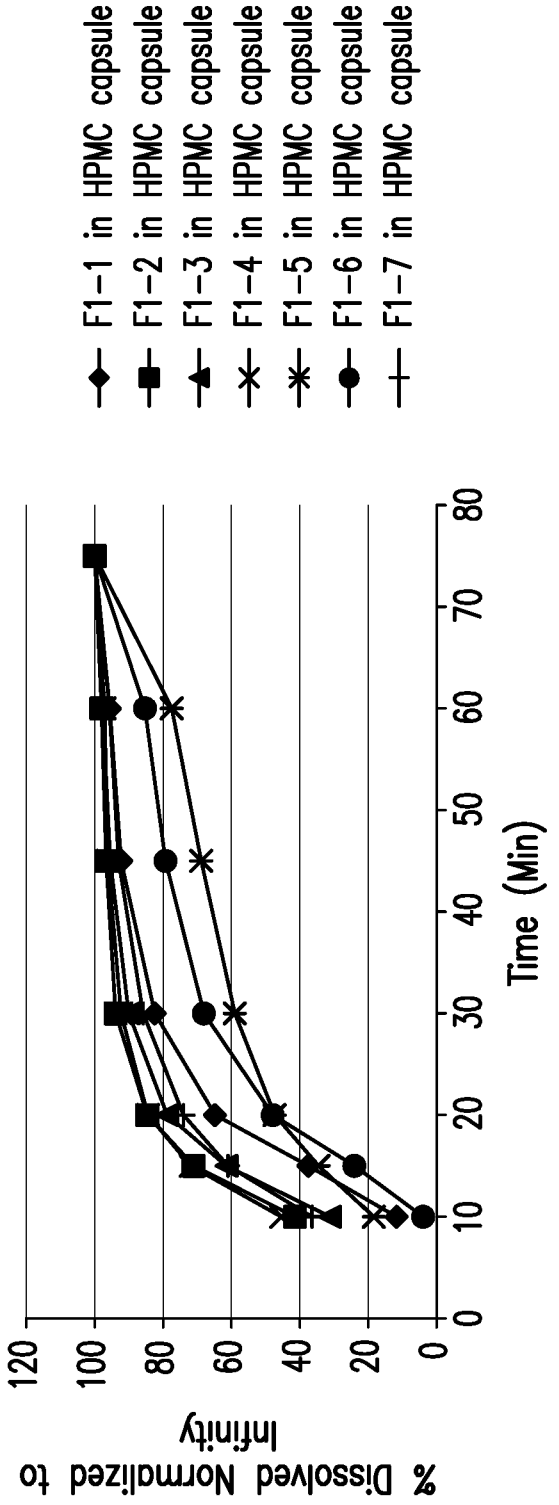

F1–1 in HPMC capsule
F1–2 in HPMC capsule
F1–3 in HPMC capsule
F1–4 in HPMC capsule
F1–5 in HPMC capsule
F1–6 in HPMC capsule
F1–7 in HPMC capsule
% Dissolved Normalized to Infinity
Time (Min)
0
20
40
60
80
100
120
0
10
20
30
40
50
60
70
80

FIG. 3

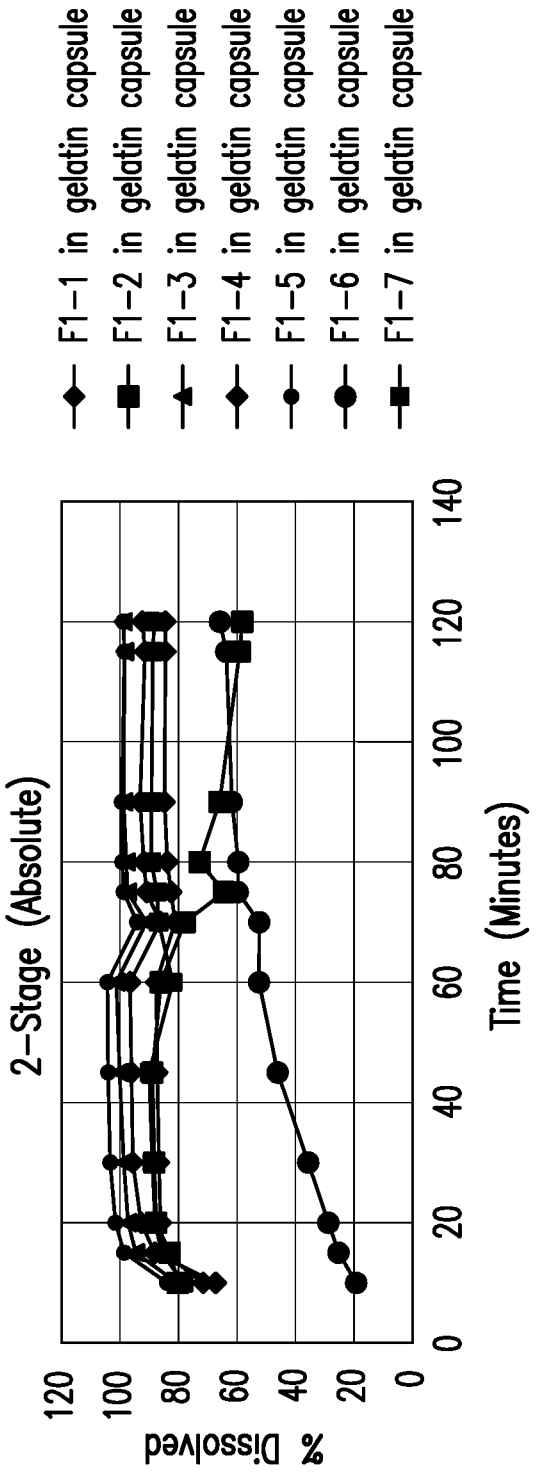

F1–1 in gelatin capsule
F1–2 in gelatin capsule
F1–3 in gelatin capsule
F1–4 in gelatin capsule
F1–5 in gelatin capsule
F1–6 in gelatin capsule
F1–7 in gelatin capsule
2–Stage (Absolute)
% Dissolved
Time (Minutes)
0
20
40
60
80
100
120
140

FIG. 4

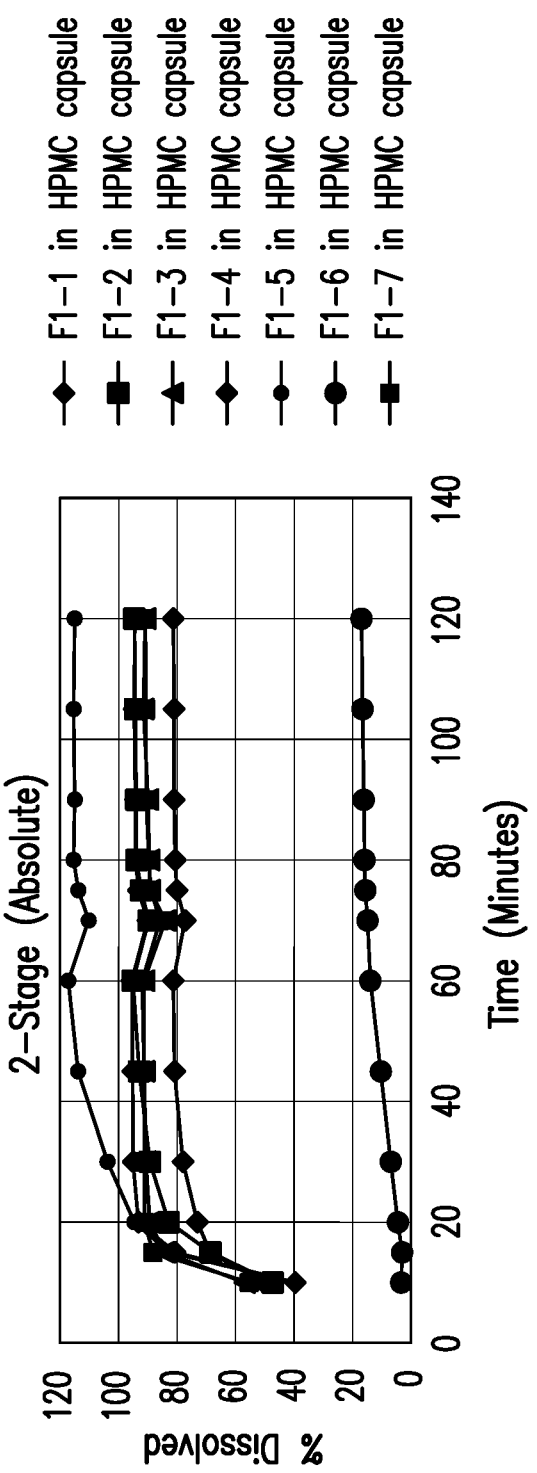

F1–1 in HPMC capsule
F1–2 in HPMC capsule
F1–3 in HPMC capsule
F1–4 in HPMC capsule
F1–5 in HPMC capsule
F1–6 in HPMC capsule
F1–7 in HPMC capsule
2–Stage (Absolute)
% Dissolved
Time (Minutes)
0
20
40
60
80
100
120
140

FIG. 5

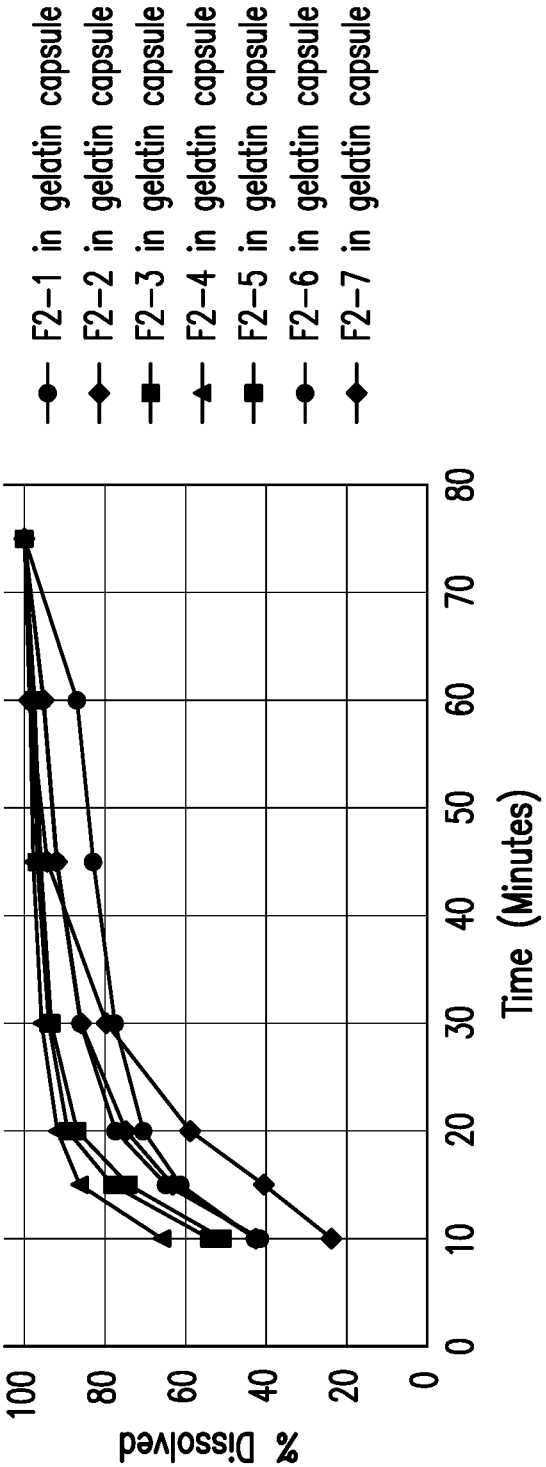

F2-1 in gelatin capsule
F2-2 in gelatin capsule
F2-3 in gelatin capsule
F2-4 in gelatin capsule
F2-5 in gelatin capsule
F2-6 in gelatin capsule
F2-7 in gelatin capsule
% Dissolved
0
20
40
60
80
100
Time (Minutes)
0
10
20
30
40
50
60
70
80

FIG. 6

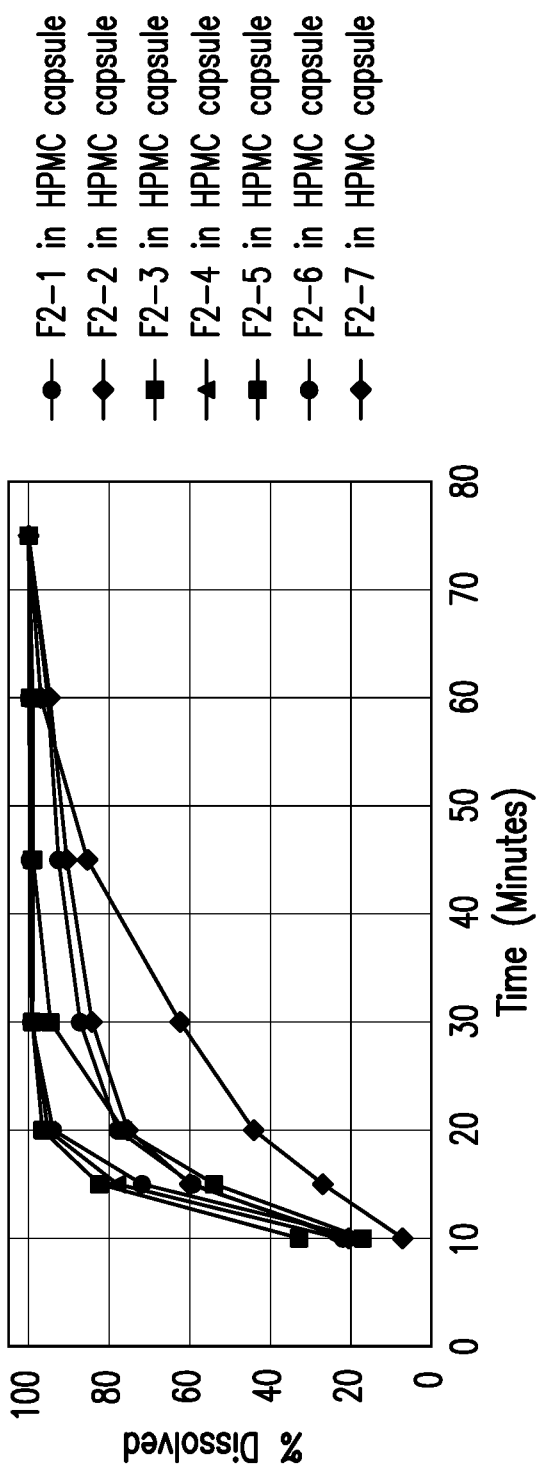

F2-1 in HPMC capsule
F2-2 in HPMC capsule
F2-3 in HPMC capsule
F2-4 in HPMC capsule
F2-5 in HPMC capsule
F2-6 in HPMC capsule
F2-7 in HPMC capsule
% Dissolved
0
20
40
60
80
100
Time (Minutes)
0
10
20
30
40
50
60
70
80

FIG. 7

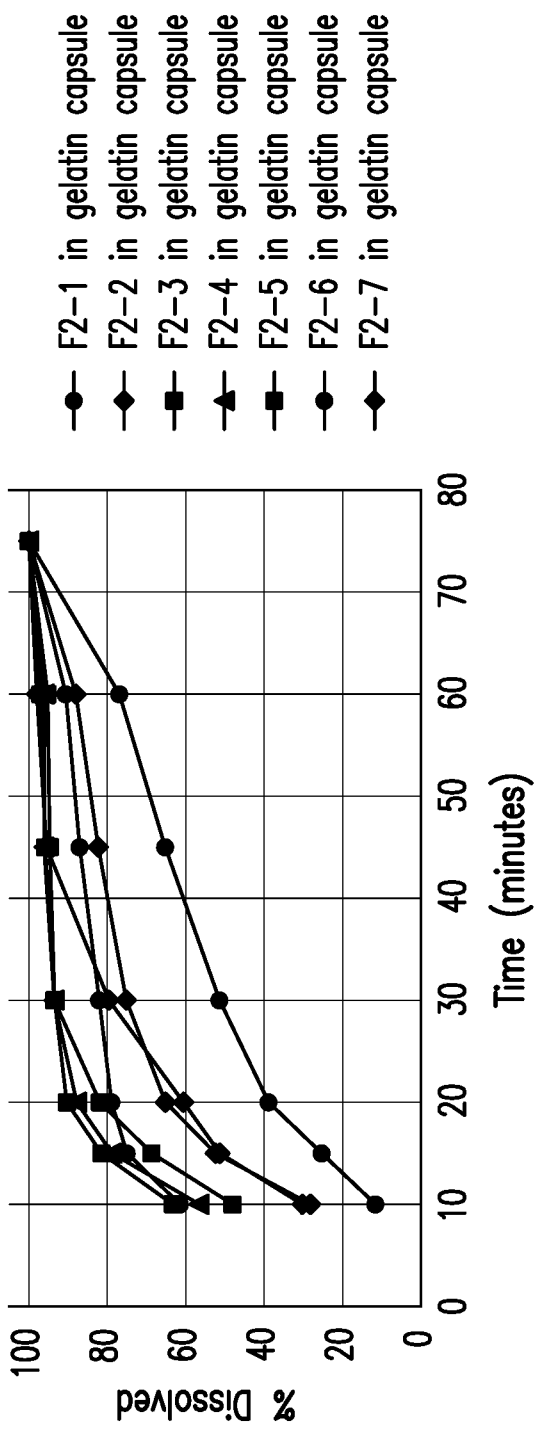

F2-1 in gelatin capsule
F2-2 in gelatin capsule
F2-3 in gelatin capsule
F2-4 in gelatin capsule
F2-5 in gelatin capsule
F2-6 in gelatin capsule
F2-7 in gelatin capsule
% Dissolved
0
20
40
60
80
100
0
10
20
30
40
50
60
70
80
Time (minutes)

FIG. 8

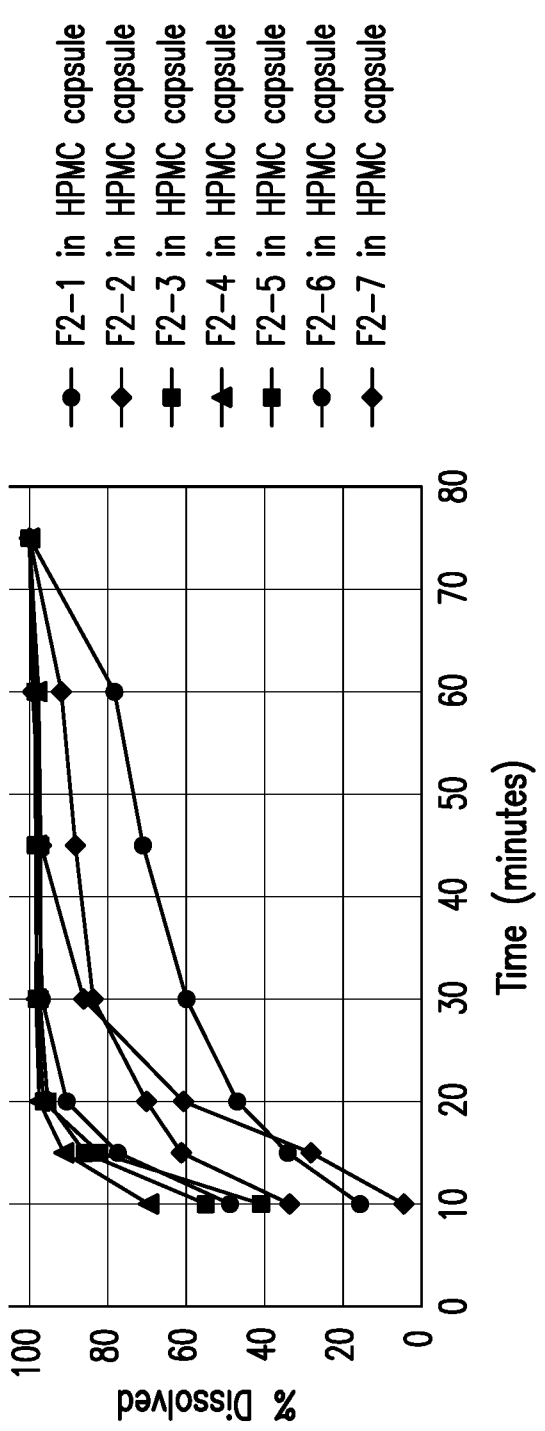

F2-1 in HPMC capsule
F2-2 in HPMC capsule
F2-3 in HPMC capsule
F2-4 in HPMC capsule
F2-5 in HPMC capsule
F2-6 in HPMC capsule
F2-7 in HPMC capsule
% Dissolved
0
20
40
60
80
100
0
10
20
30
40
50
60
70
80
Time (minutes)

FIG. 9

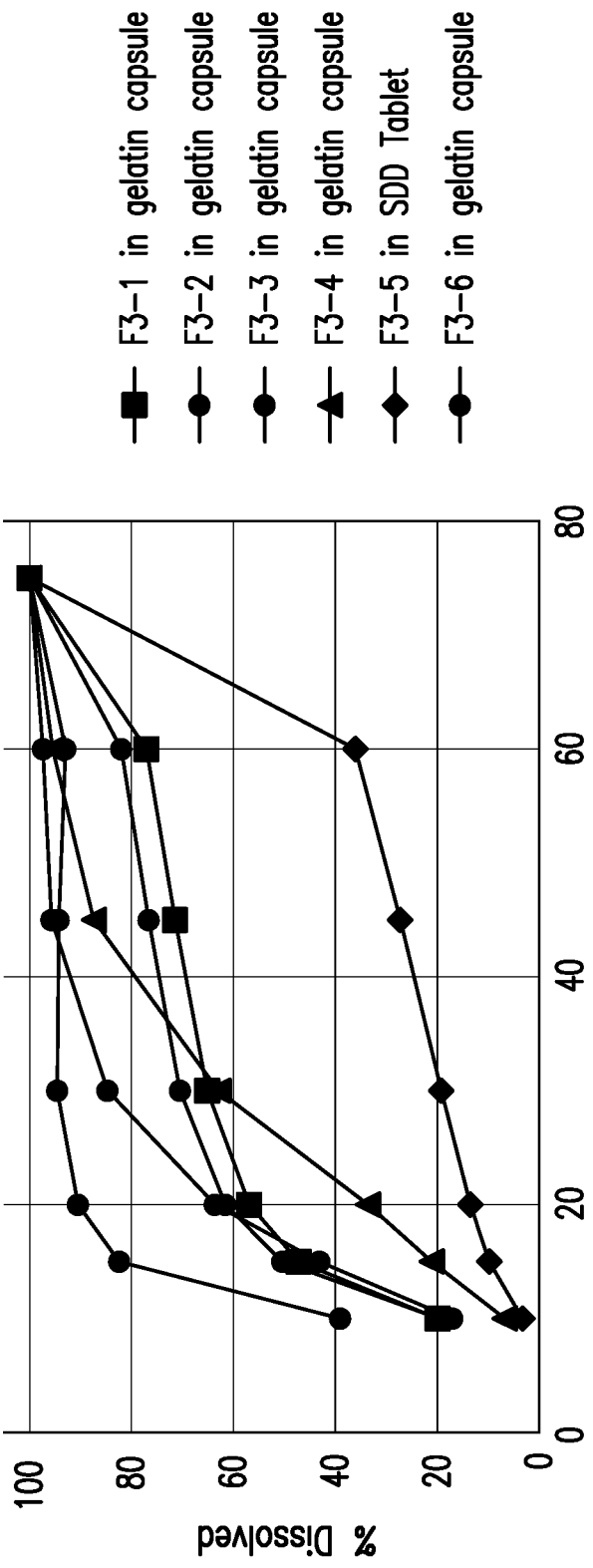

F3-1 in gelatin capsule
F3-2 in gelatin capsule
F3-3 in gelatin capsule
F3-4 in gelatin capsule
F3-5 in SDD Tablet
F3-6 in gelatin capsule
% Dissolved
0
20
40
60
80
100
Time (Minutes)
0
20
40
60
80

FIG. 10

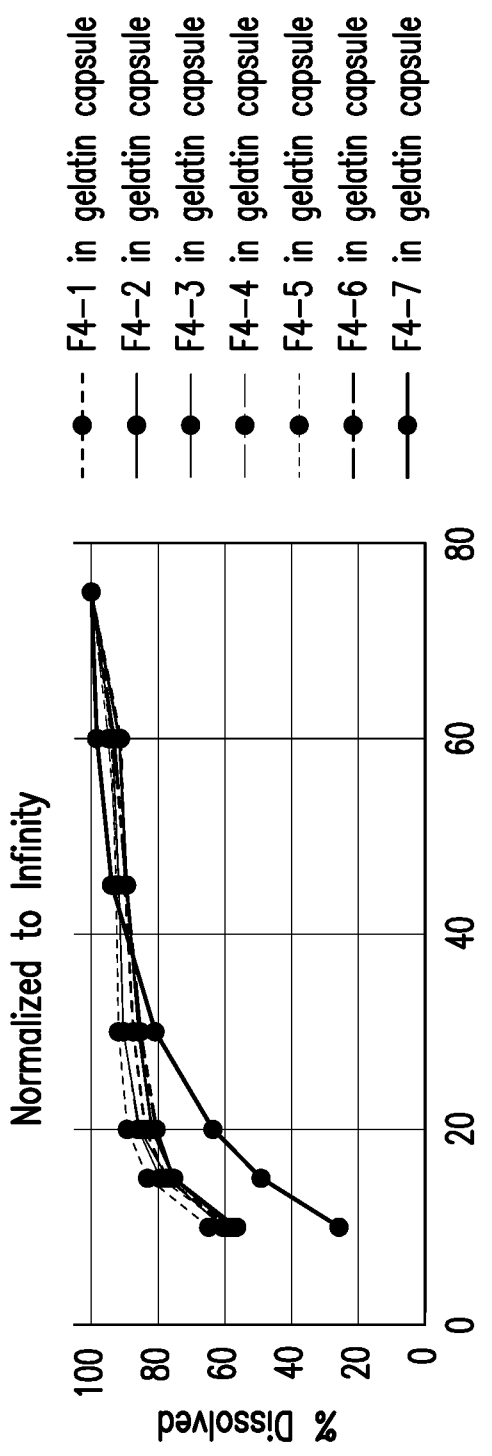

F4–1 in gelatin capsule
F4–2 in gelatin capsule
F4–3 in gelatin capsule
F4–4 in gelatin capsule
F4–5 in gelatin capsule
F4–6 in gelatin capsule
F4–7 in gelatin capsule
Normalized to Infinity
% Dissolved
0
20
40
60
80
100
0
20
40
60
80
Time (Minutes)

FIG. 11

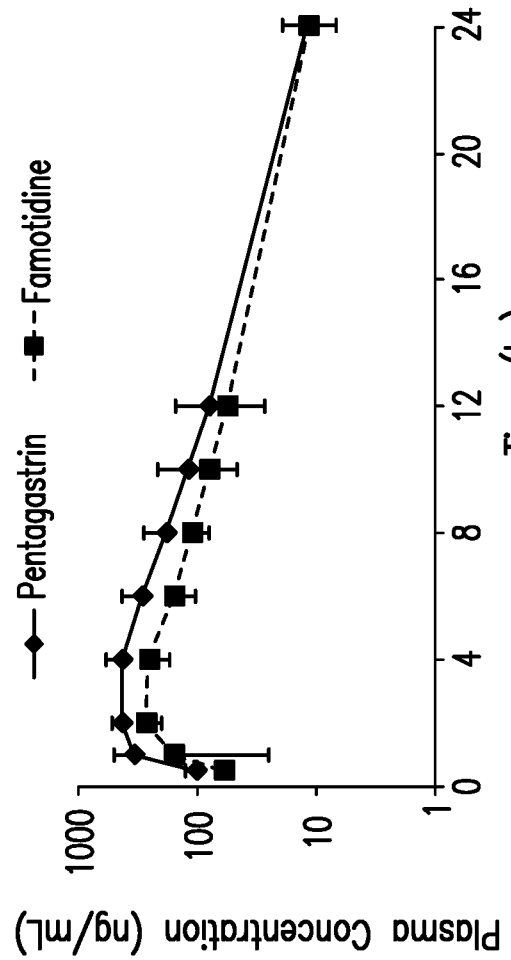

Pentagastrin
Famotidine
Plasma Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (hr)

FIG. 12

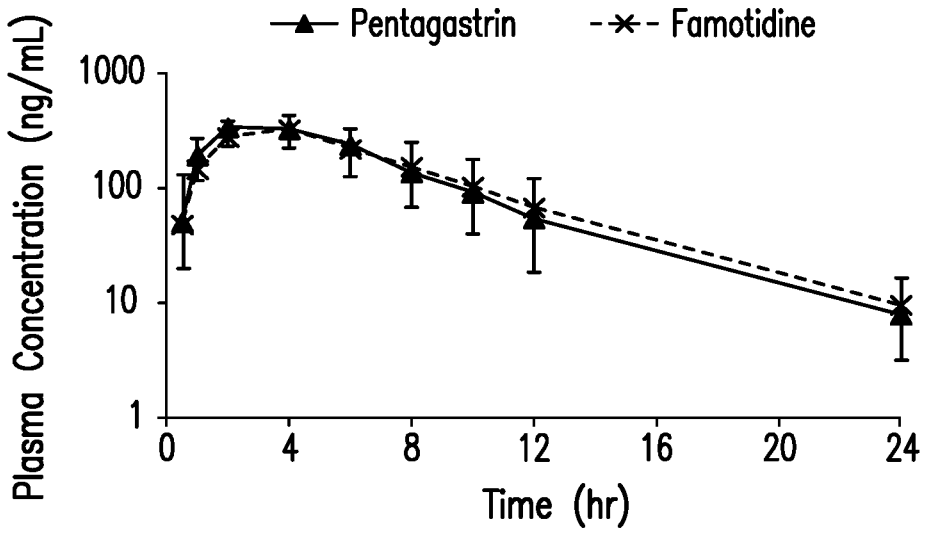

Pentagastrin
Famotidine
Plasma Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (hr)

FIG. 13

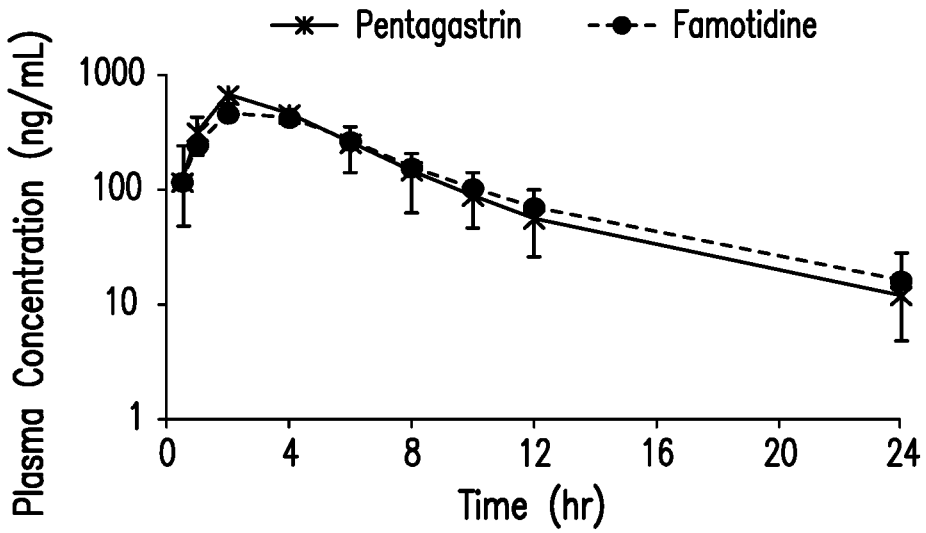

Pentagastrin
Famotidine
Plasma Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (hr)

FIG. 14

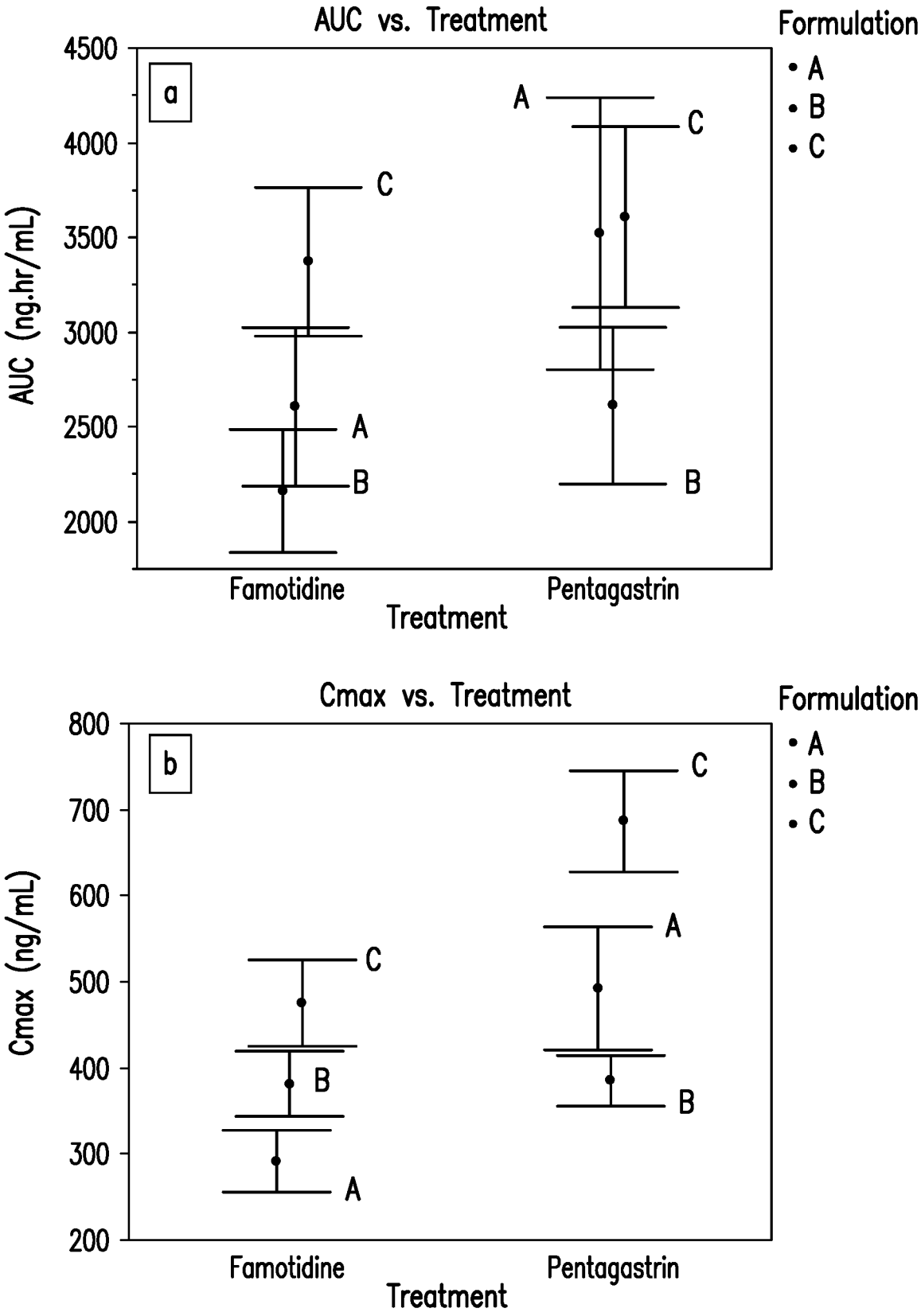

AUC vs. Treatment
Formulation
• A
• B
• C
a
AUC (ng.hr/mL)
4500
4000
3500
3000
2500
2000
C
A
B
A
C
B
Famotidine
Pentagastrin
Treatment
Cmax vs. Treatment
Formulation
• A
• B
• C
b
Cmax (ng/mL)
800
700
600
500
400
300
200
C
B
A
C
A
B
Famotidine
Pentagastrin
Treatment

FIG. 15

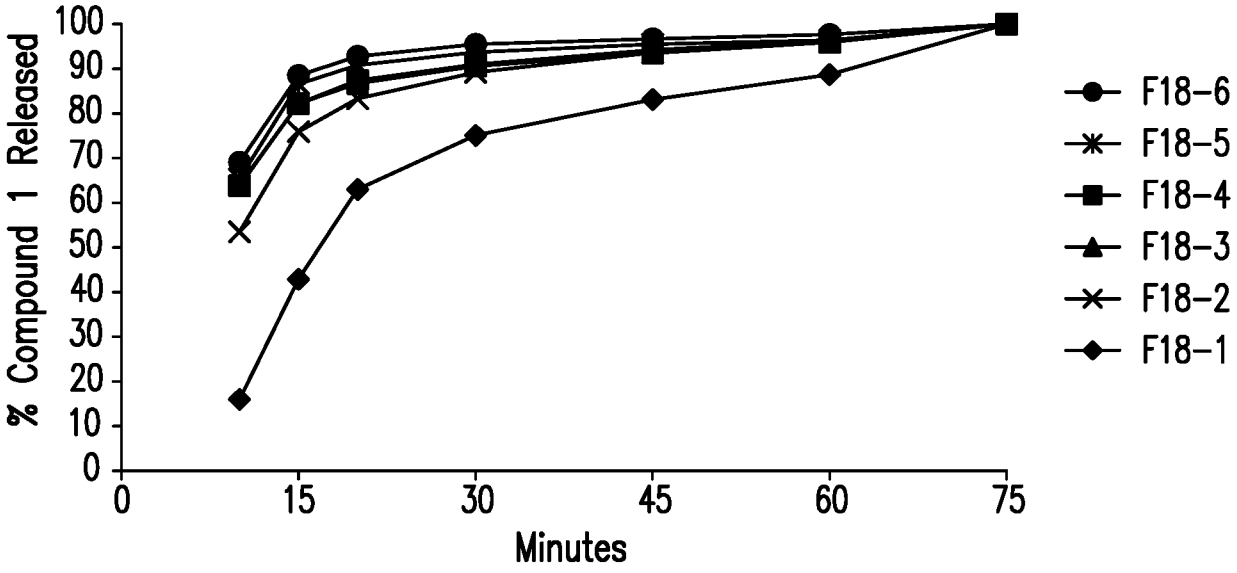

% Compound 1 Released
100
90
80
70
60
50
40
30
20
10
0
0
15
30
45
60
75
Minutes
F18-6
F18-5
F18-4
F18-3
F18-2
F18-1

FIG. 16

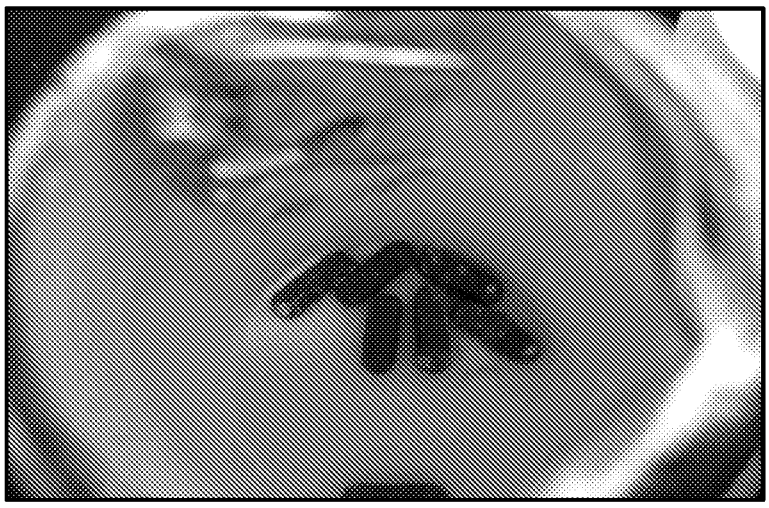


FIG. 17

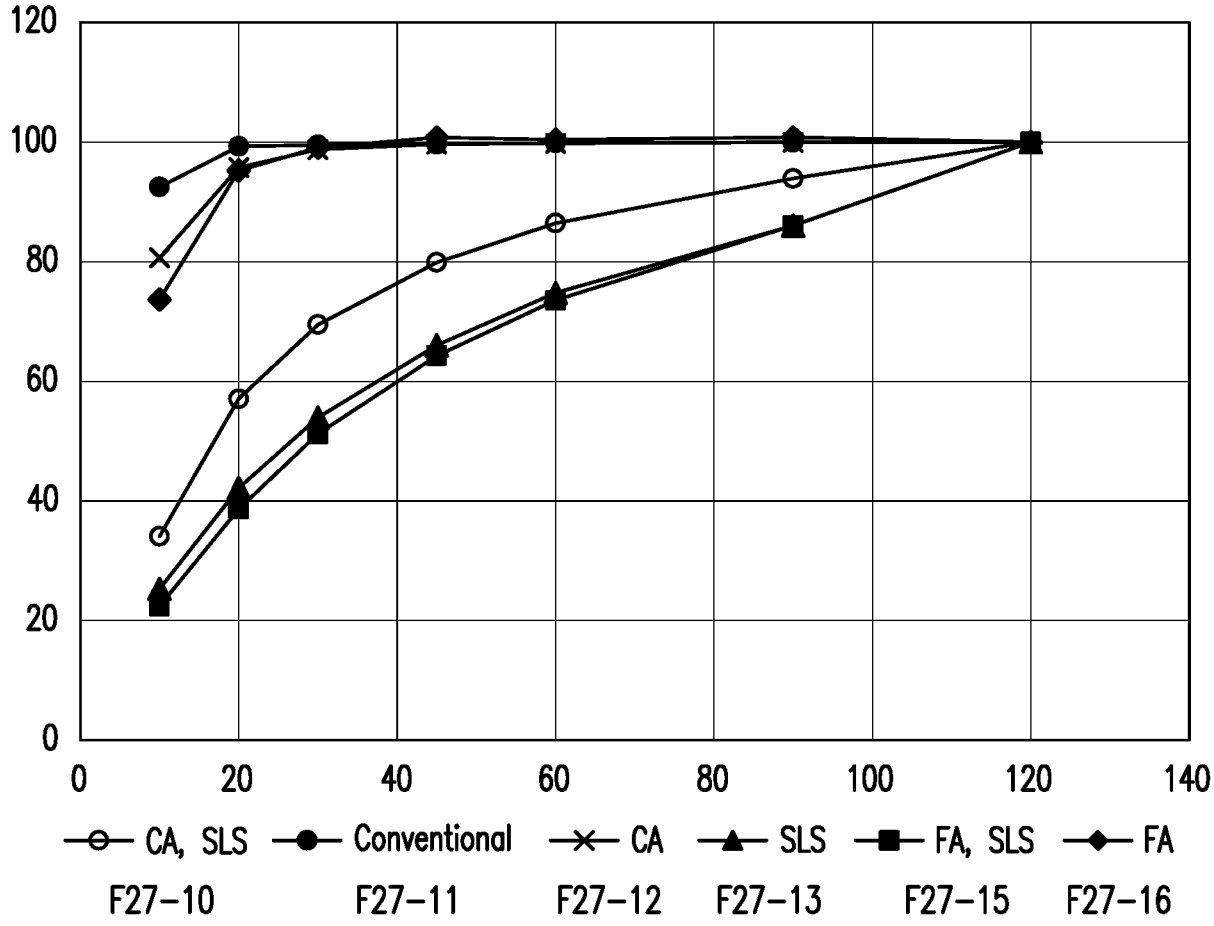

120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
CA, SLS
Conventional
CA
SLS
FA, SLS
FA
F27-10
F27-11
F27-12
F27-13
F27-15
F27-16

FIG. 18

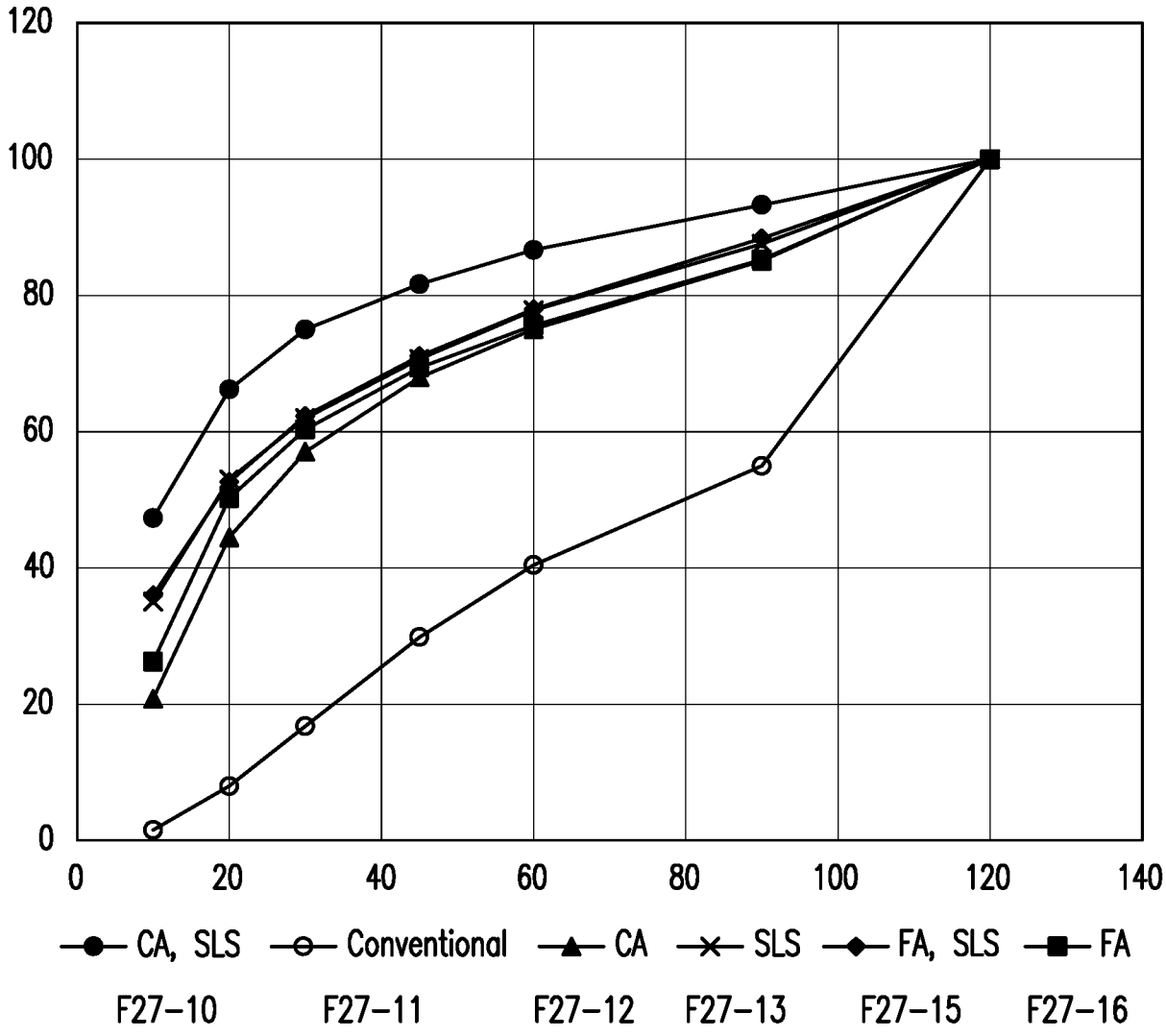

120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
CA, SLS
Conventional
CA
SLS
FA, SLS
FA
F27-10
F27-11
F27-12
F27-13
F27-15
F27-16

FIG. 19

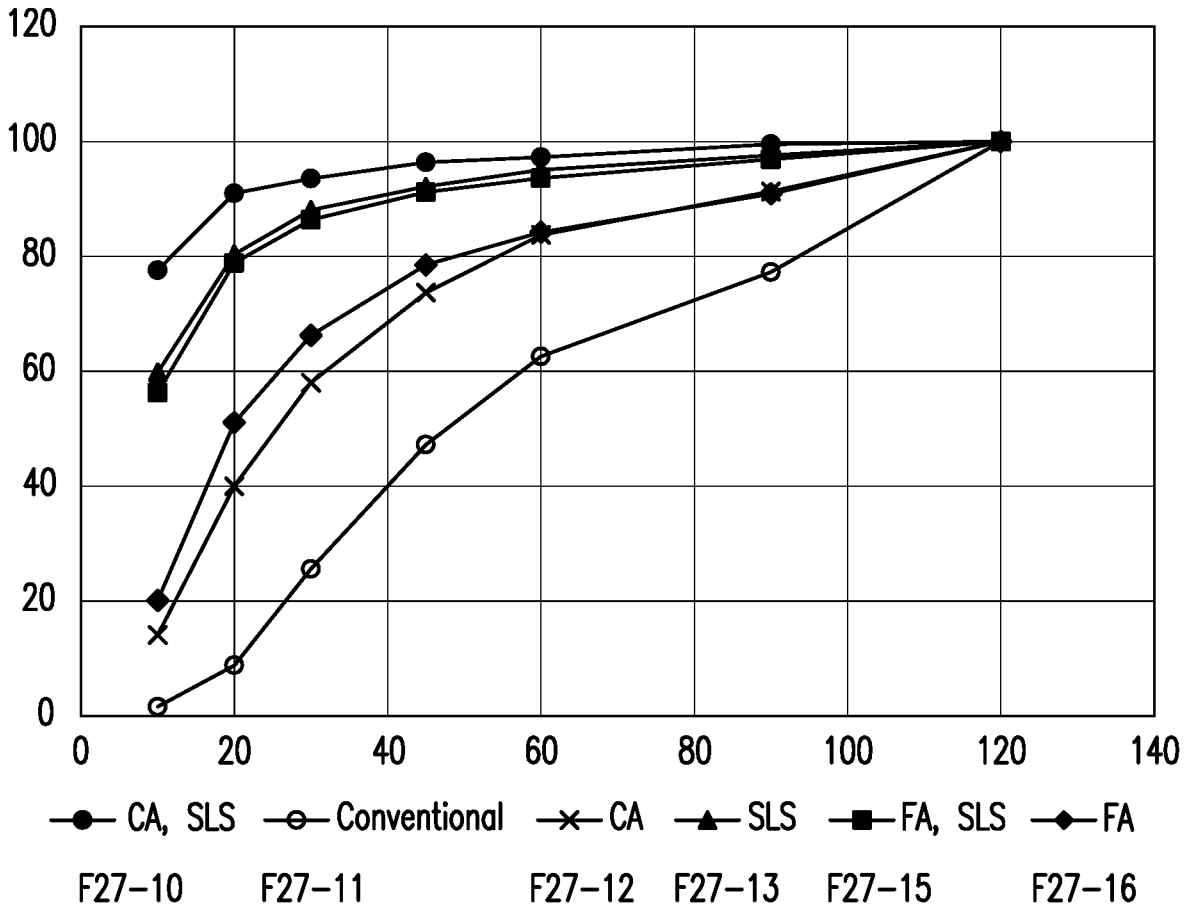

120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
CA, SLS F27-10
Conventional F27-11
CA F27-12
SLS F27-13
FA, SLS F27-15
FA F27-16

FIG. 20

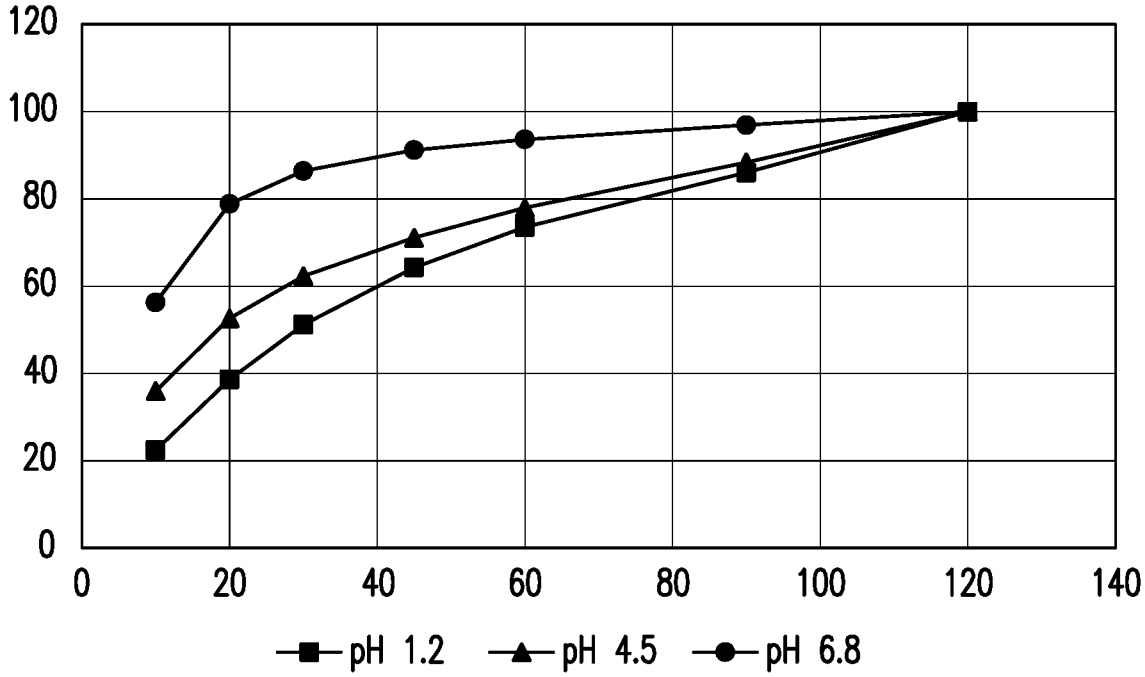

120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
pH 1.2
pH 4.5
pH 6.8

FIG. 21

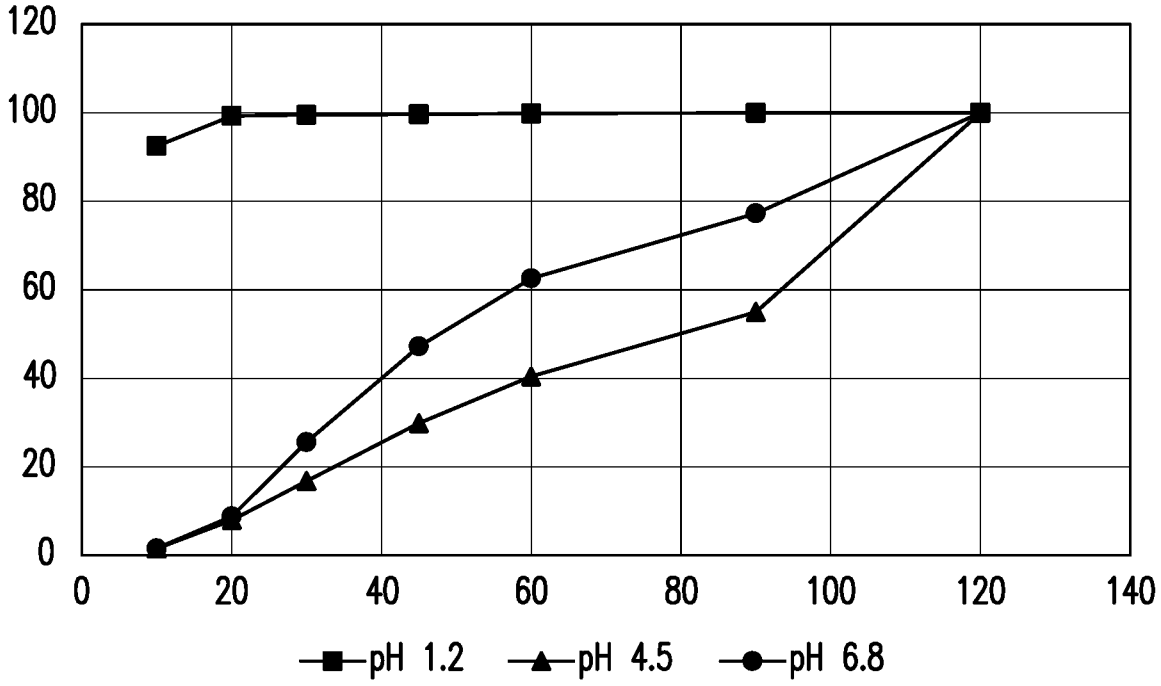

120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
pH 1.2
pH 4.5
pH 6.8

FIG. 22

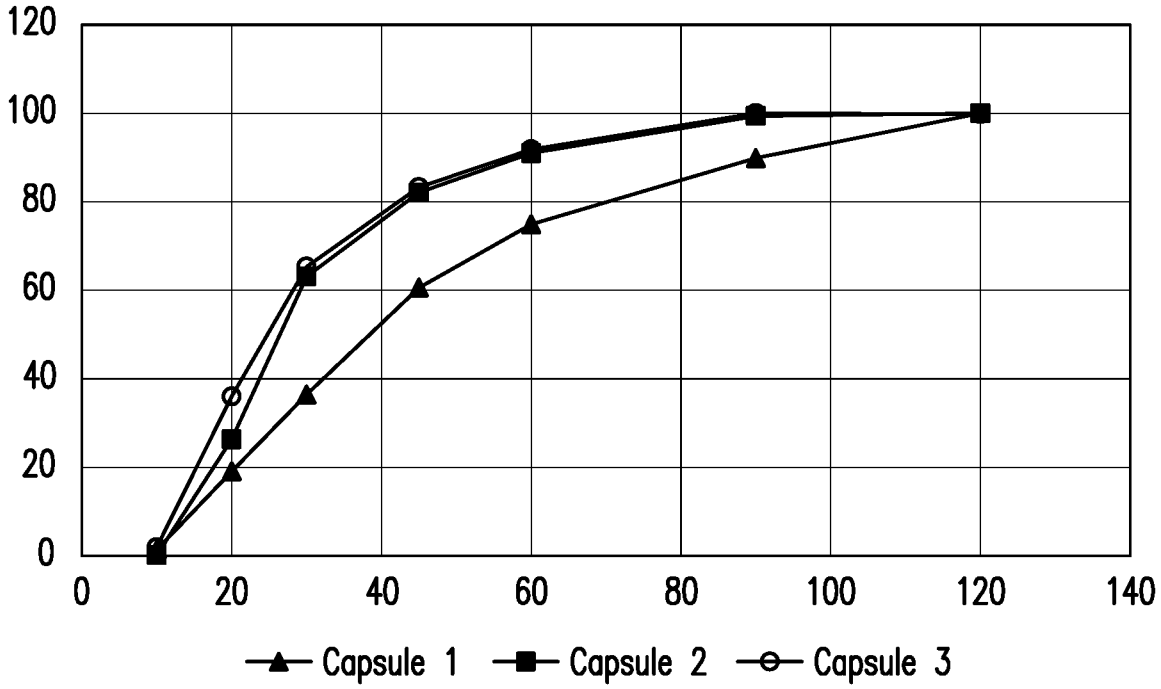

120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Capsule 1
Capsule 2
Capsule 3

FIG. 23

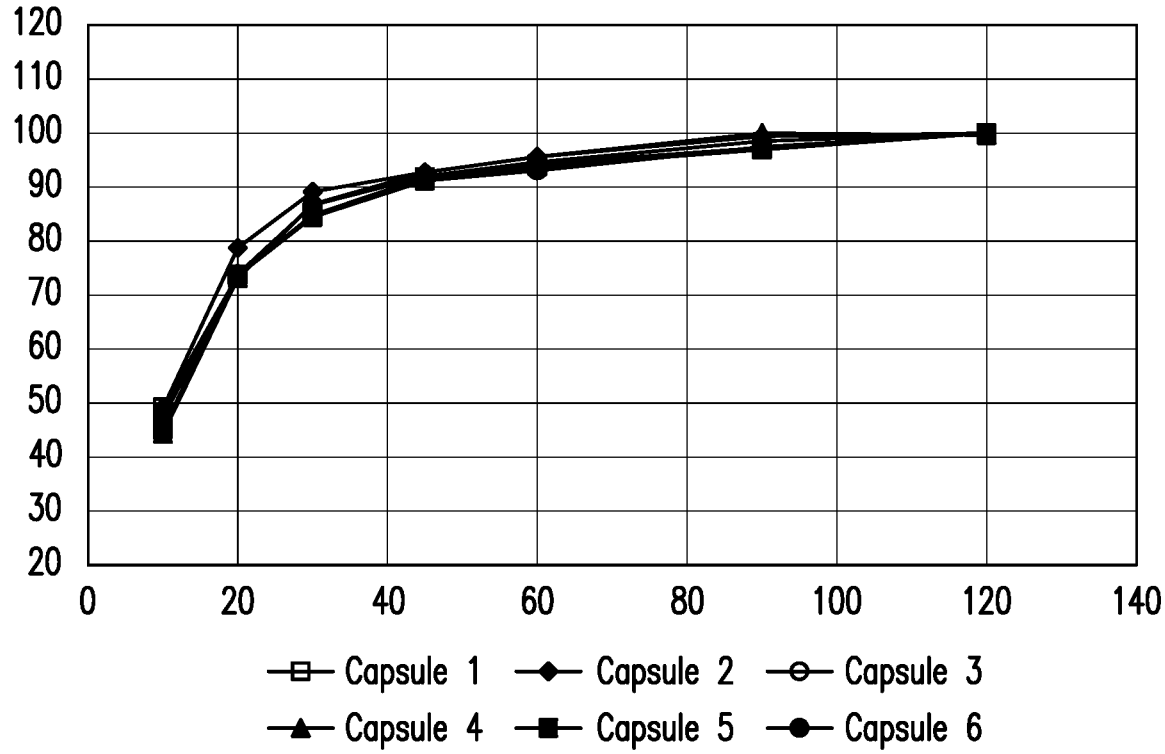

120
110
100
90
80
70
60
50
40
30
20
0
20
40
60
80
100
120
140
Capsule 1
Capsule 2
Capsule 3
Capsule 4
Capsule 5
Capsule 6

FIG. 24

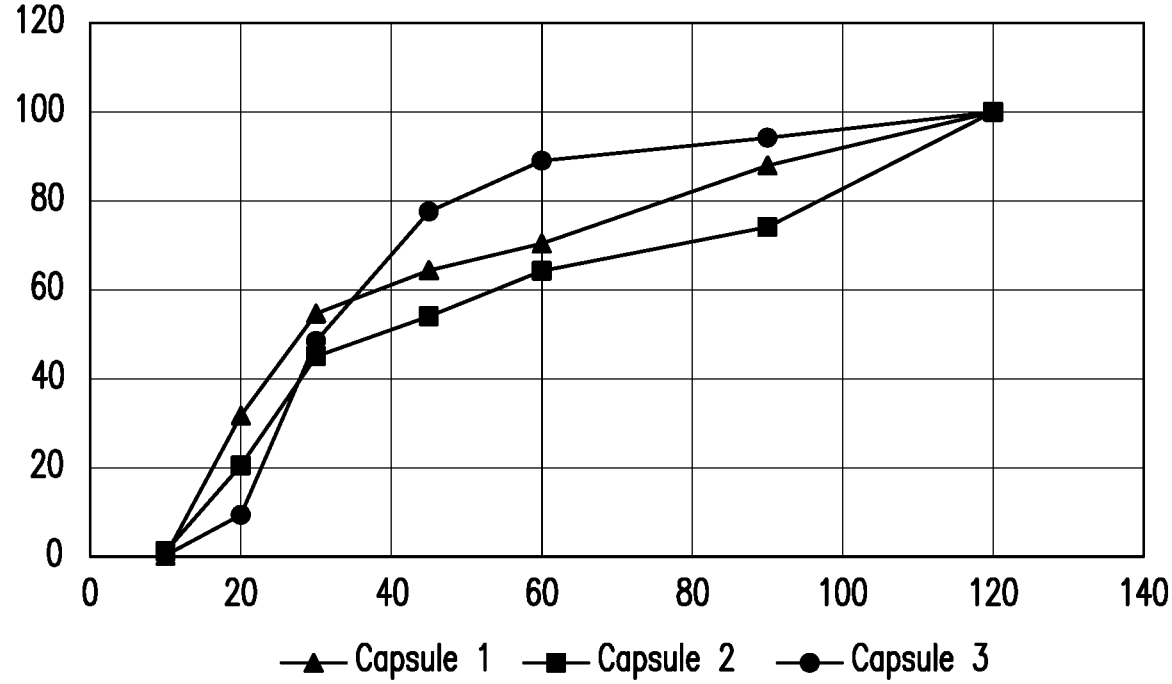

120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Capsule 1
Capsule 2
Capsule 3

FIG. 25

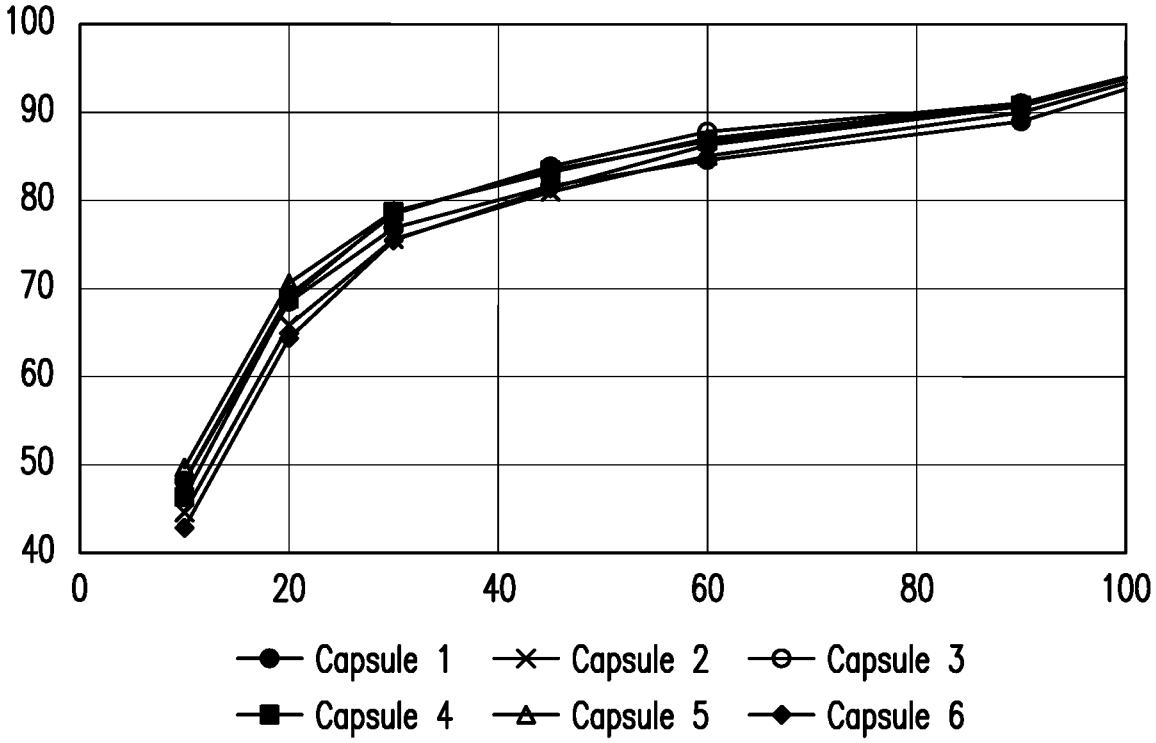

100
90
80
70
60
50
40
0
20
40
60
80
100
Capsule 1
Capsule 2
Capsule 3
Capsule 4
Capsule 5
Capsule 6

FIG. 26

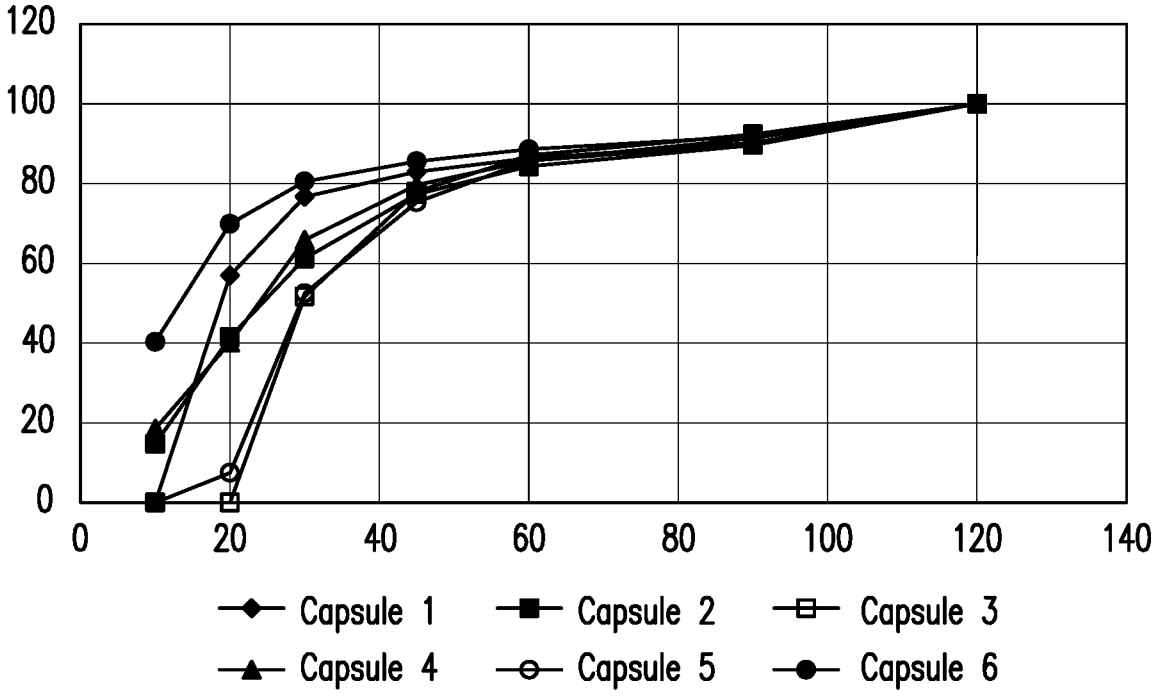

120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Capsule 1
Capsule 2
Capsule 3
Capsule 4
Capsule 5
Capsule 6

FIG. 27

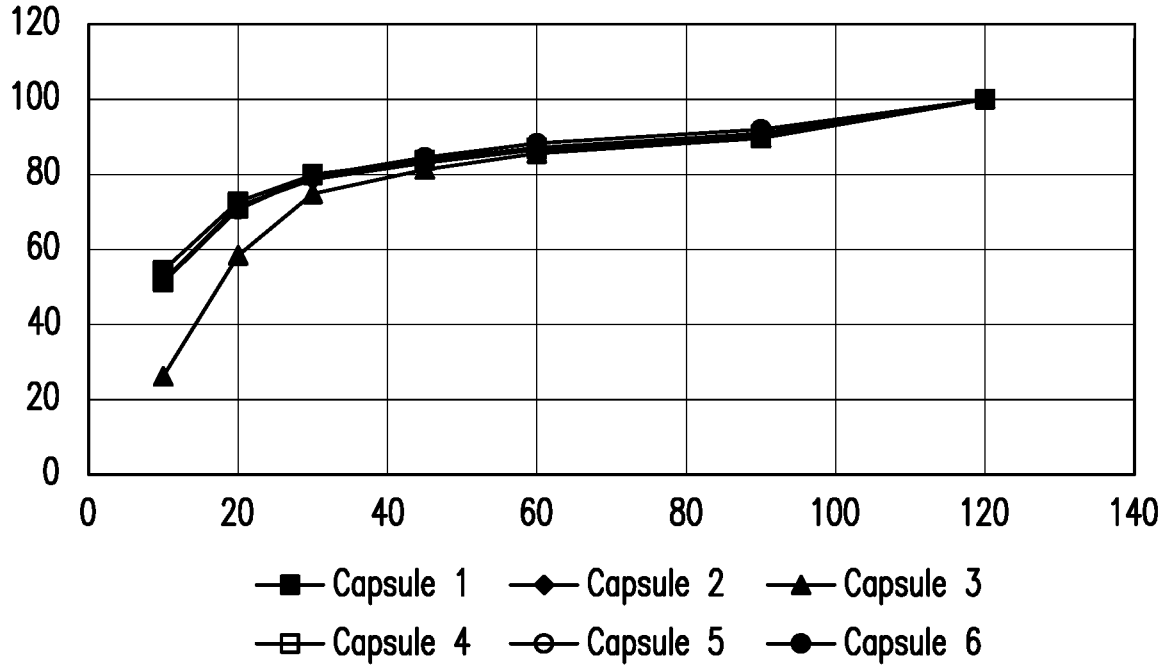

120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Capsule 1
Capsule 2
Capsule 3
Capsule 4
Capsule 5
Capsule 6

FIG. 28

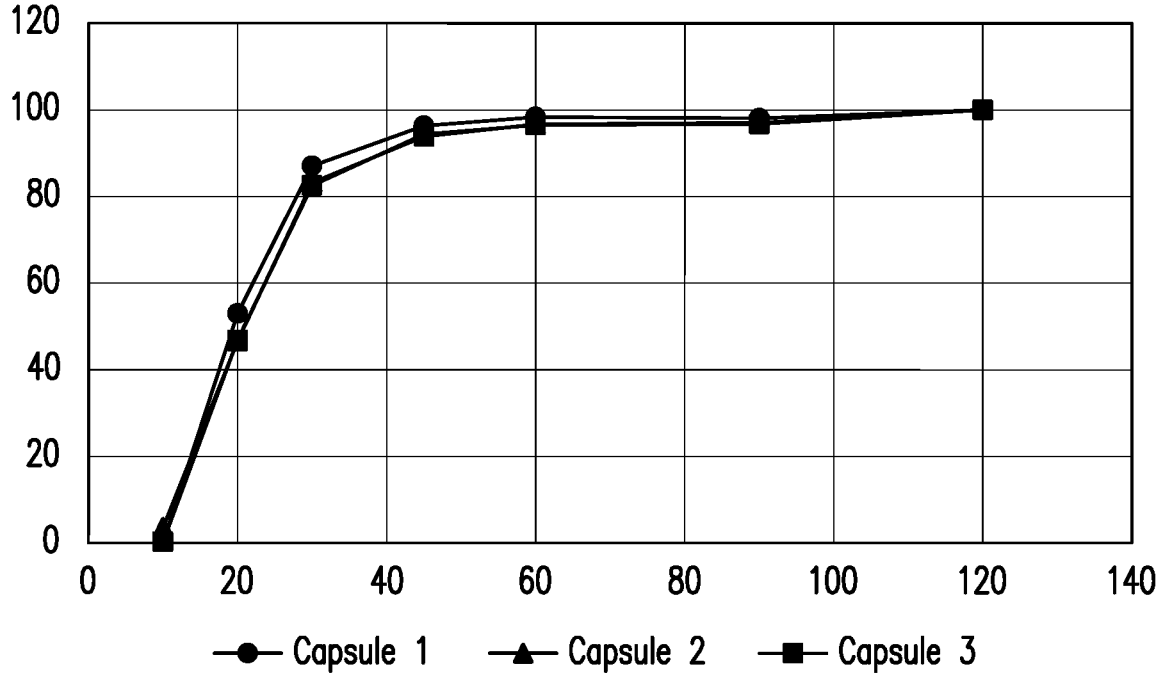

120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Capsule 1
Capsule 2
Capsule 3

FIG. 29

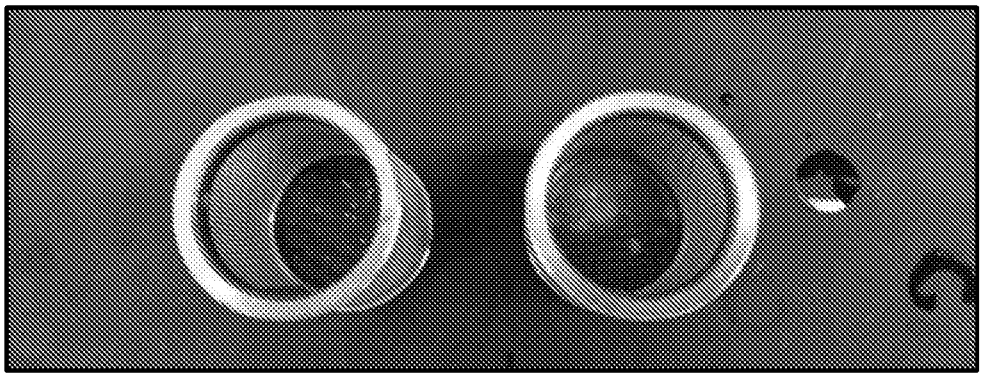


FIG. 30

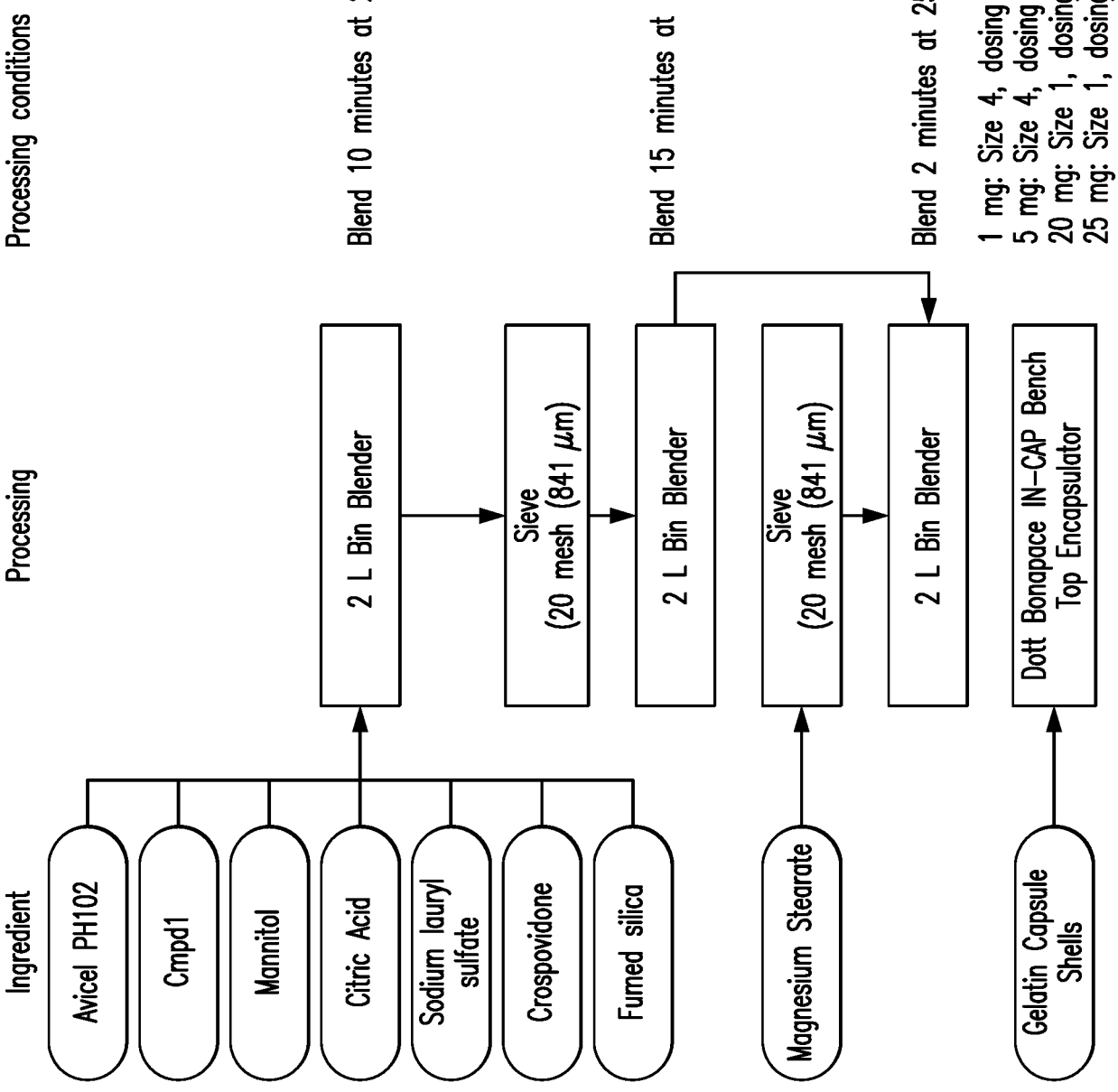

Ingredient
Processing
Processing conditions
Avicel PH102
Cmpd1
Mannitol
Citric Acid
Sodium lauryl sulfate
Crospovidone
Fumed silica
Magnesium Stearate
Gelatin Capsule Shells
2 L Bin Blender
Blend 10 minutes at 25 rpm
Sieve (20 mesh (841 μm)
2 L Bin Blender
Blend 15 minutes at 15 rpm
Sieve (20 mesh (841 μm)
2 L Bin Blender
Blend 2 minutes at 25 rpm
Dott Bonapace IN-CAP Bench Top Encapsulator
1 mg: Size 4, dosing disk 7 mm (Fixed)
5 mg: Size 4, dosing disk 12 mm (Adjustable)
20 mg: Size 1, dosing disk 19.5 mm (Adjustable)
25 mg: Size 1, dosing disk 19.5 mm (Adjustable)

FIG. 31

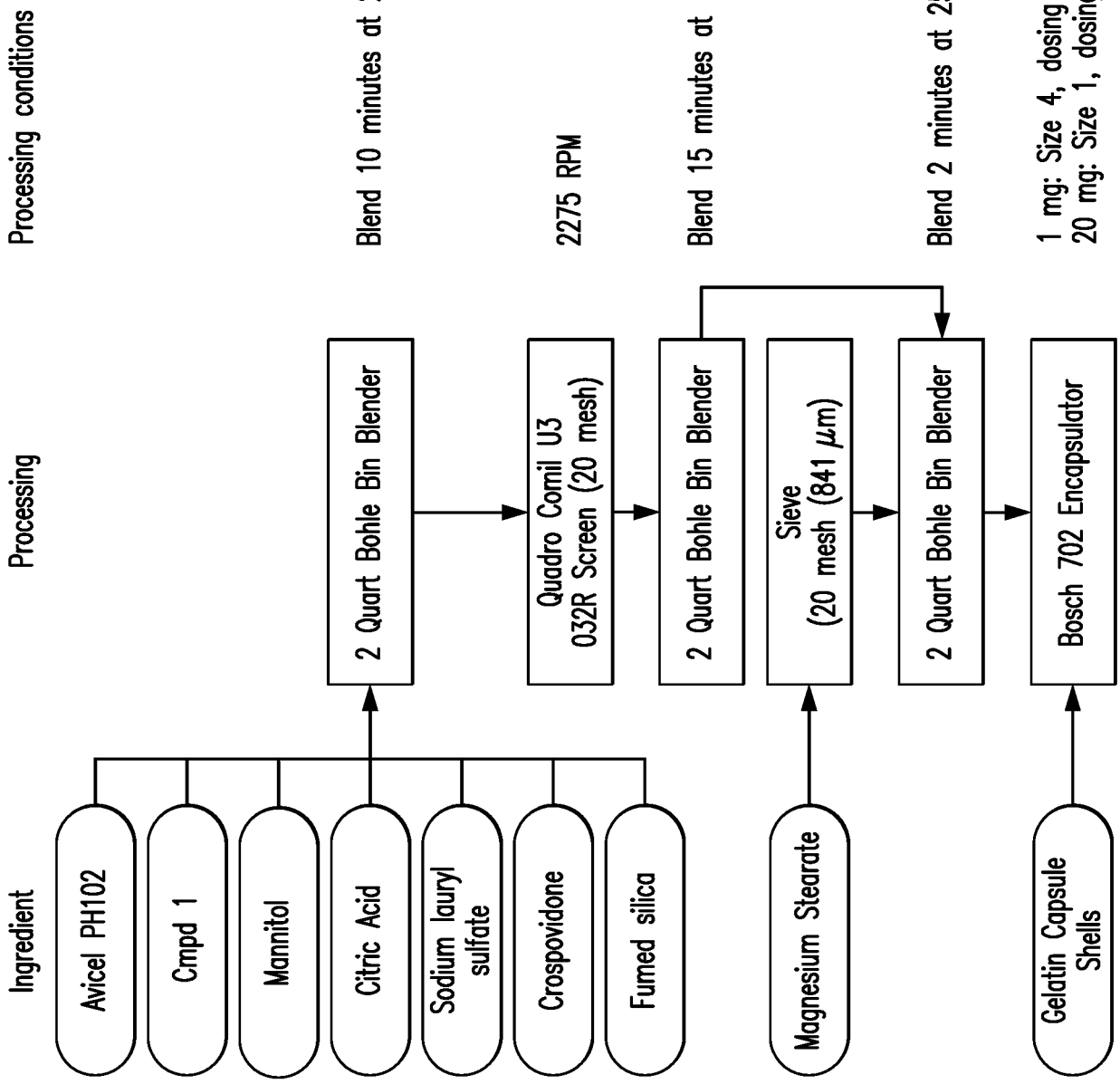

Ingredient
Avicel PH102
Cmpd 1
Mannitol
Citric Acid
Sodium lauryl sulfate
Crospovidone
Fumed silica
Magnesium Stearate
Gelatin Capsule Shells
Processing
2 Quart Bohle Bin Blender
Quadro Comil U3 032R Screen (20 mesh)
2 Quart Bohle Bin Blender
Sieve (20 mesh (841 μm)
2 Quart Bohle Bin Blender
Bosch 702 Encapsulator
Processing conditions
Blend 10 minutes at 25 rpm
2275 RPM
Blend 15 minutes at 15 rpm
Blend 2 minutes at 25 rpm
1 mg: Size 4, dosing disk 7 mm (Fixed)
20 mg: Size 1, dosing disk 19.5 mm (Adjustable)

FIG. 32

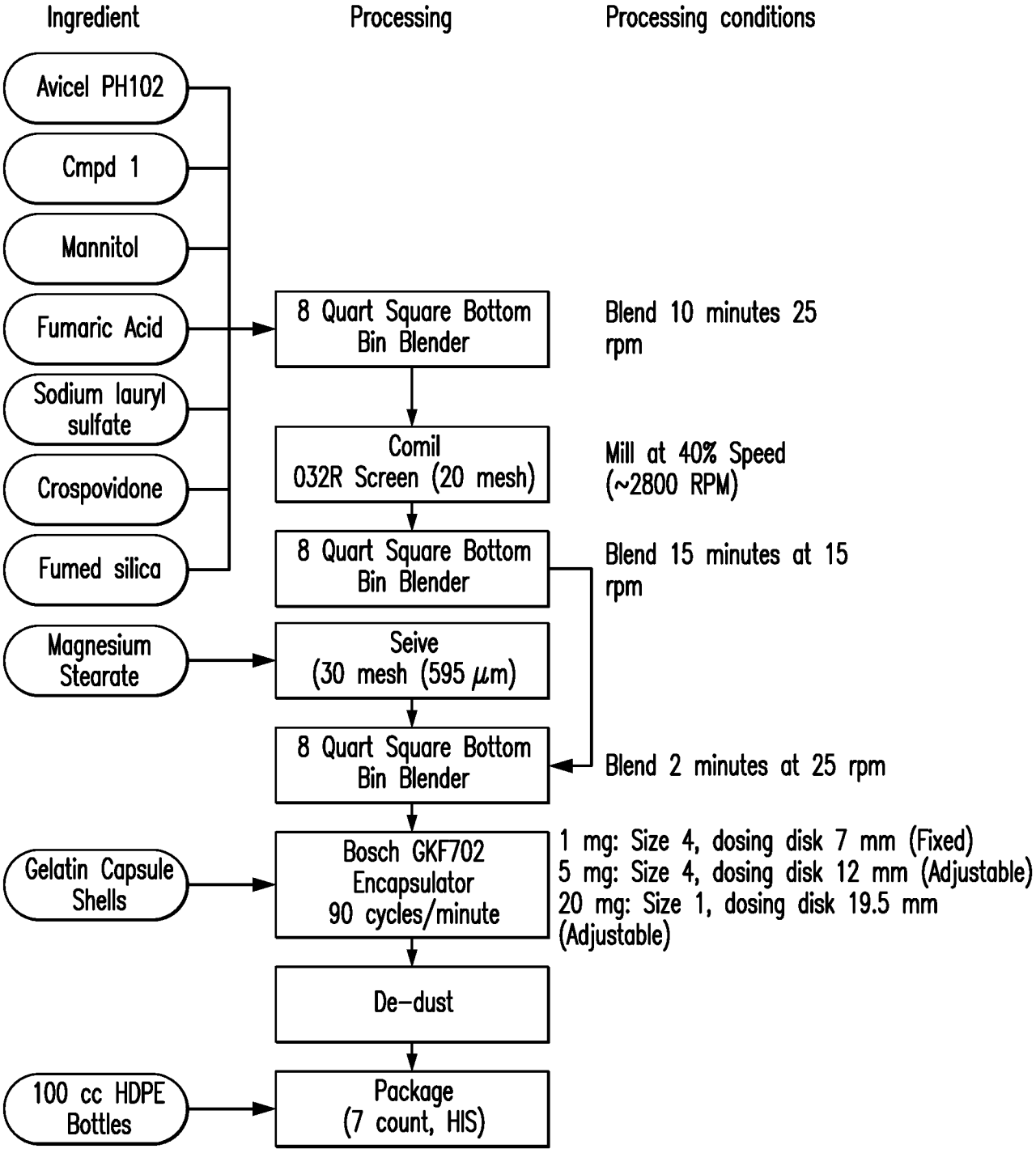

Ingredient
Processing
Processing conditions
Avicel PH102
Cmpd 1
Mannitol
Fumaric Acid
Sodium lauryl sulfate
Crospovidone
Fumed silica
Magnesium Stearate
Gelatin Capsule Shells
100 cc HDPE Bottles
8 Quart Square Bottom Bin Blender
Blend 10 minutes 25 rpm
Comil 032R Screen (20 mesh)
Mill at 40% Speed (~2800 RPM)
8 Quart Square Bottom Bin Blender
Blend 15 minutes at 15 rpm
Seive (30 mesh (595 μm)
8 Quart Square Bottom Bin Blender
Blend 2 minutes at 25 rpm
Bosch GKF702 Encapsulator 90 cycles/minute
1 mg: Size 4, dosing disk 7 mm (Fixed)
5 mg: Size 4, dosing disk 12 mm (Adjustable)
20 mg: Size 1, dosing disk 19.5 mm (Adjustable)
De-dust
Package (7 count, HIS)

FIG. 33

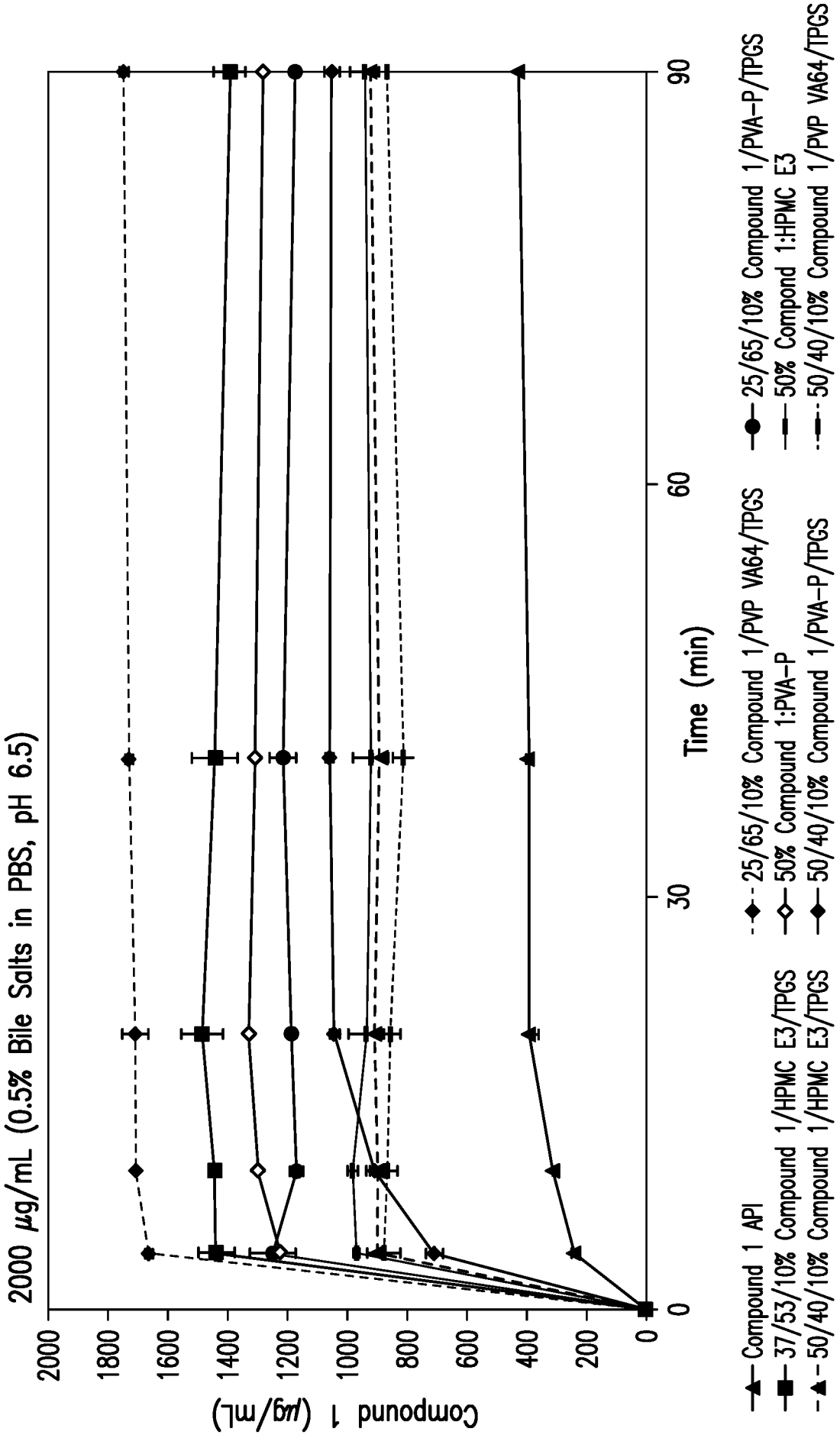

2000 µg/mL (0.5% Bile Salts in PBS, pH 6.5)
Compound 1 (µg/mL)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
30
60
90
Time (min)
Compound 1 API
37/53/10% Compound 1/HPMC E3/TPGS
50/40/10% Compound 1/HPMC E3/TPGS
25/65/10% Compound 1/PVP VA64/TPGS
50% Compound 1:PVA-P
50/40/10% Compound 1/PVA-P/TPGS
25/65/10% Compound 1/PVA-P/TPGS
50% Compound 1:HPMC E3
50/40/10% Compound 1/PVP VA64/TPGS

FIG. 34

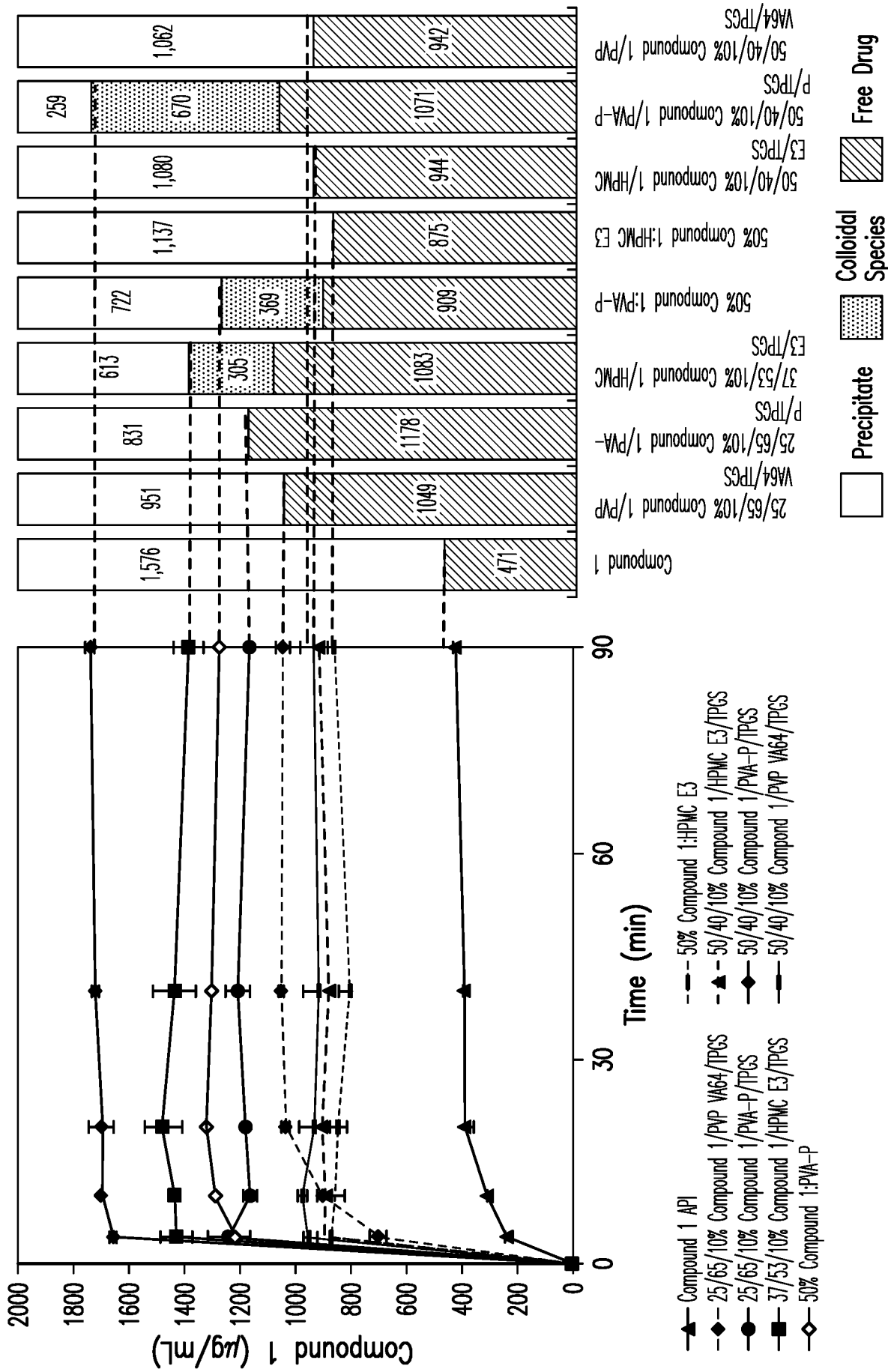

Compound 1 (µg/mL)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
30
60
90
Time (min)
Compound 1 API
25/65/10% Compound 1/PVP VA64/TPGS
25/65/10% Compound 1/PVA-P/TPGS
37/53/10% Compound 1/HPMC E3/TPGS
50% Compound 1:PVA-P
50% Compound 1:HPMC E3
50/40/10% Compound 1/HPMC E3
50/40/10% Compound 1/PVA-P/TPGS
50/40/10% Compound 1/PVP VA64/TPGS
Precipitate
Colloidal Species
Free Drug
Compound 1
25/65/10% Compound 1/PVP VA64/TPGS
25/65/10% Compound 1/PVA-P/TPGS
37/53/10% Compound 1/HPMC E3/TPGS
50% Compound 1:PVA-P
50% Compound 1:HPMC E3
50/40/10% Compound 1/HPMC E3/TPGS
50/40/10% Compound 1/PVA-P/TPGS
50/40/10% Compound 1/PVP VA64/TPGS
1,576
951
831
613
722
1,137
1,080
259
1,062
471
1049
1178
1083
909
875
944
1071
942
670
369
305

FIG. 35

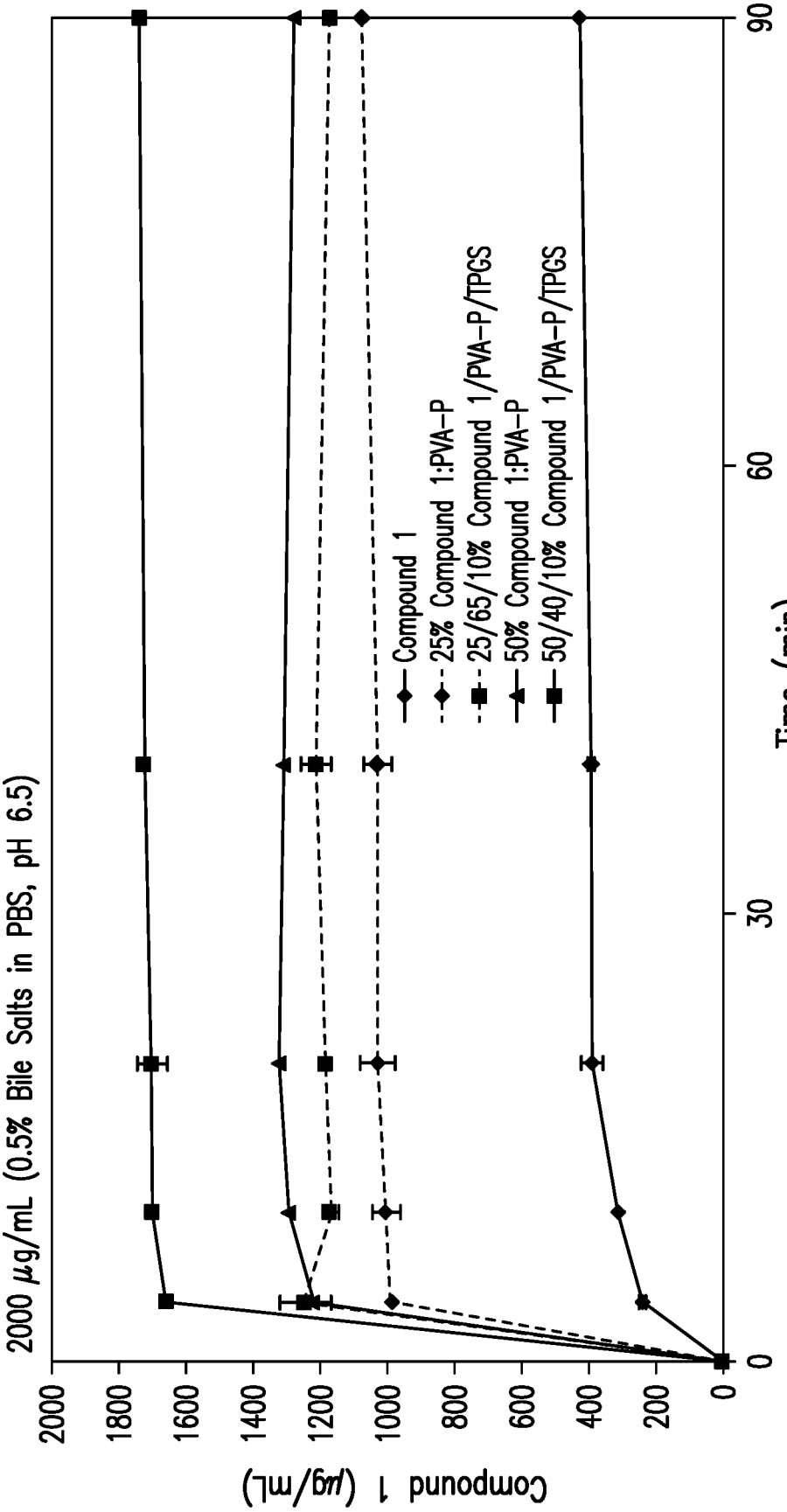

2000 µg/mL (0.5% Bile Salts in PBS, pH 6.5)
Compound 1 (µg/mL)
0
200
400
600
800
1000
1200
1400
1600
1800
2000
0
30
60
90
Time (min)
Compound 1
25% Compound 1:PVA-P
25/65/10% Compound 1/PVA-P/TPGS
50% Compound 1:PVA-P
50/40/10% Compound 1/PVA-P/TPGS

FIG. 36

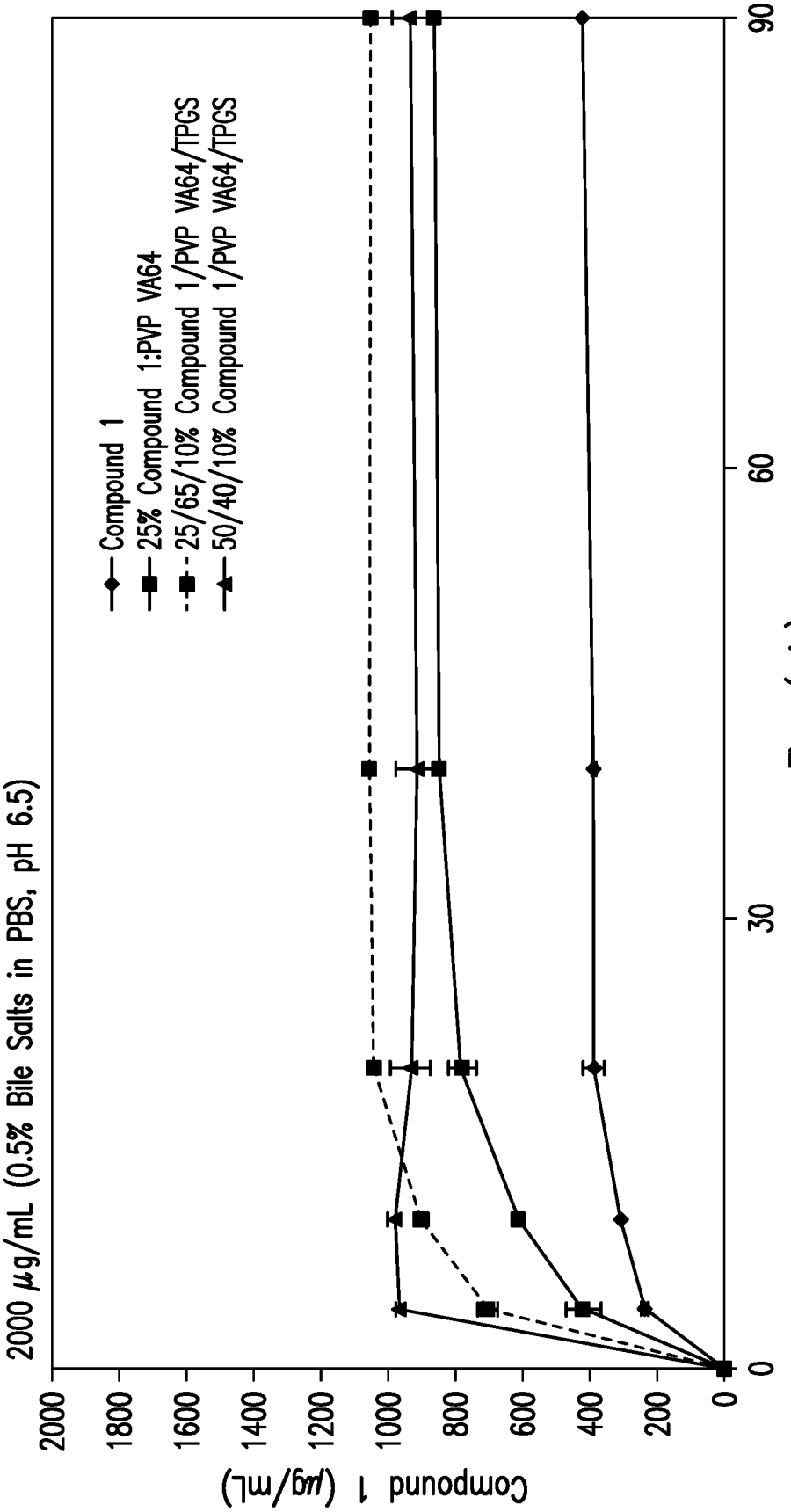

2000 µg/mL (0.5% Bile Salts in PBS, pH 6.5)
Compound 1 (µg/mL)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
30
60
90
Time (min)
Compound 1
25% Compound 1:PVP VA64
25/65/10% Compound 1/PVP VA64/TPGS
50/40/10% Compound 1/PVP VA64/TPGS

FIG. 37

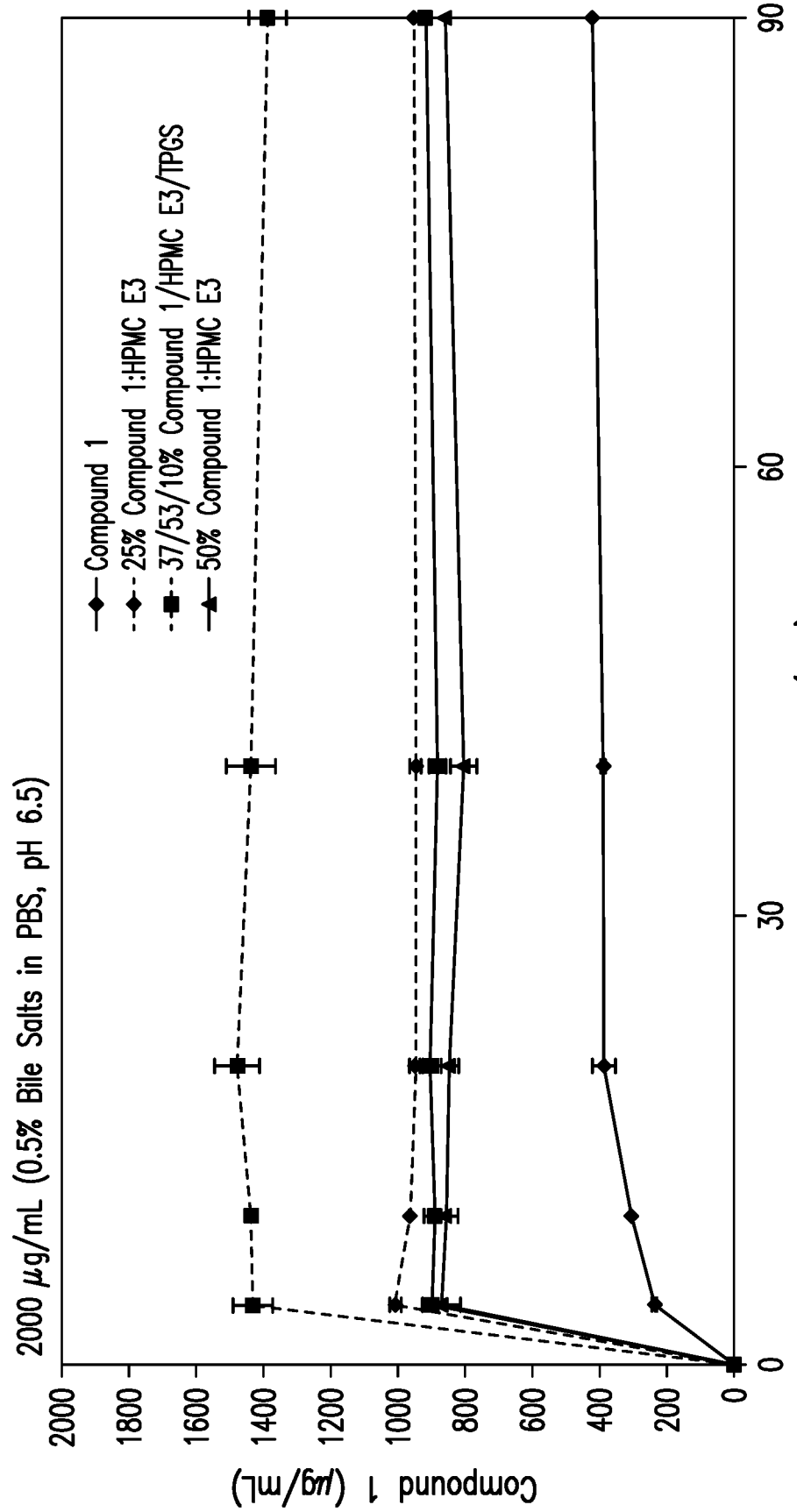

2000 µg/mL (0.5% Bile Salts in PBS, pH 6.5)
Compound 1
25% Compound 1:HPMC E3
37/53/10% Compound 1/HPMC E3/TPGS
50% Compound 1:HPMC E3
Compound 1 (µg/mL)
Time (min)
0
200
400
600
800
1000
1200
1400
1600
1800
2000
0
30
60
90

FIG. 38

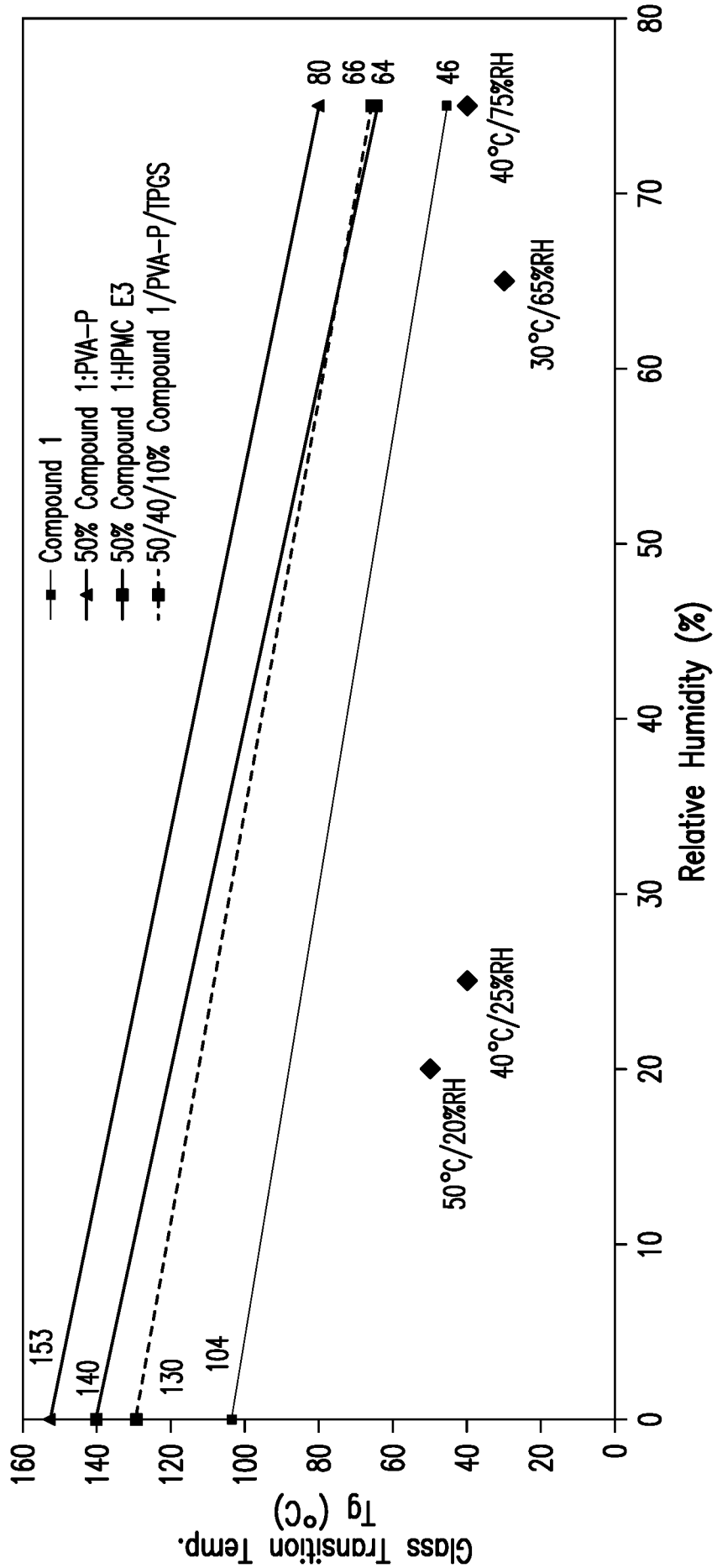

Glass Transition Temp.
Tg (°C)
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
Relative Humidity (%)
Compound 1
50% Compound 1:PVA-P
50% Compound 1:HPMC E3
50/40/10% Compound 1/PVA-P/TPGS
153
140
130
104
80
66
64
46
50°C/20%RH
40°C/25%RH
30°C/65%RH
40°C/75%RH

FIG. 39

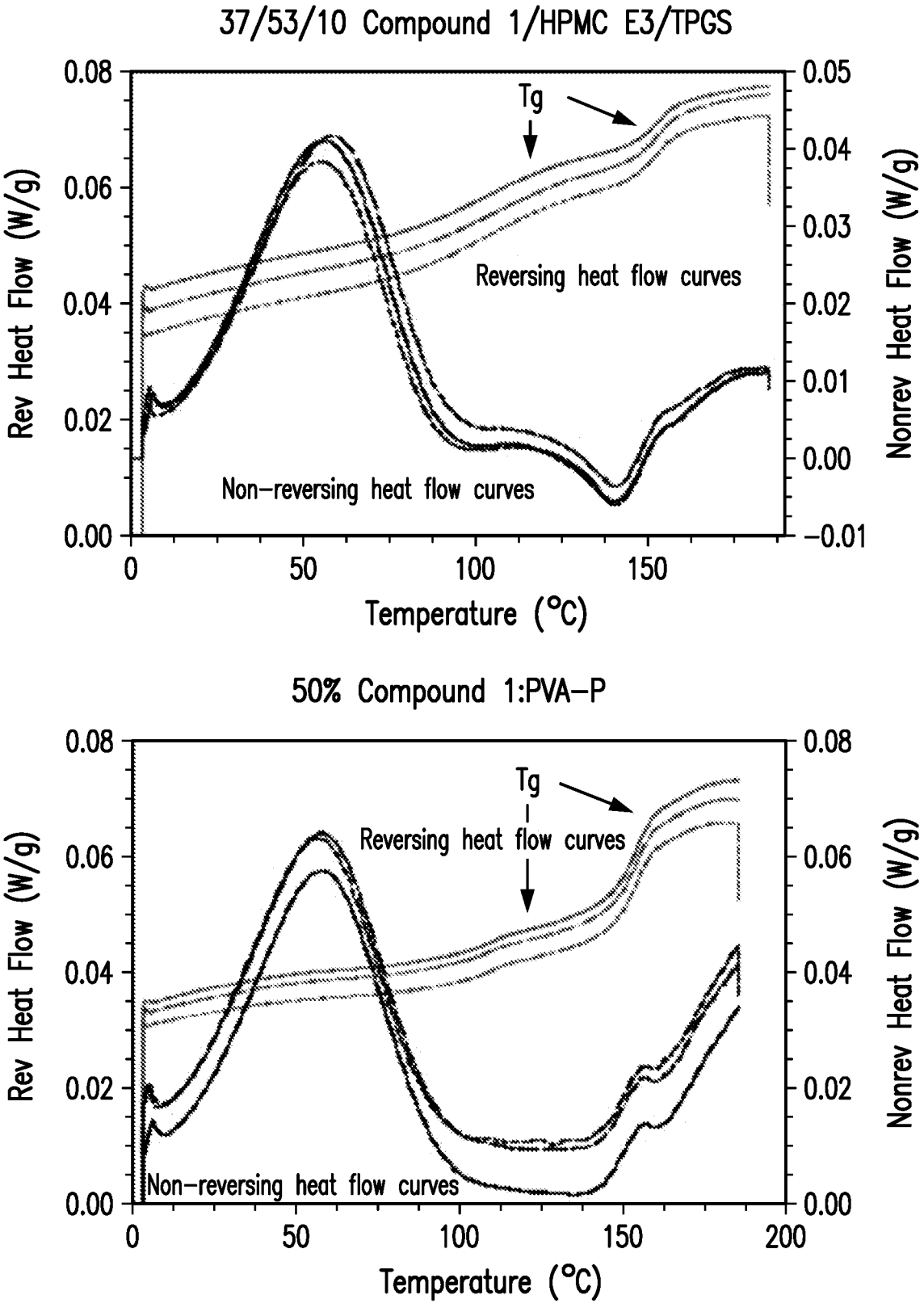

37/53/10 Compound 1/HPMC E3/TPGS
Rev Heat Flow (W/g)
Nonrev Heat Flow (W/g)
Tg
Reversing heat flow curves
Non-reversing heat flow curves
Temperature (°C)
50% Compound 1:PVA-P
Rev Heat Flow (W/g)
Nonrev Heat Flow (W/g)
Tg
Reversing heat flow curves
Non-reversing heat flow curves
Temperature (°C)

FIG. 40

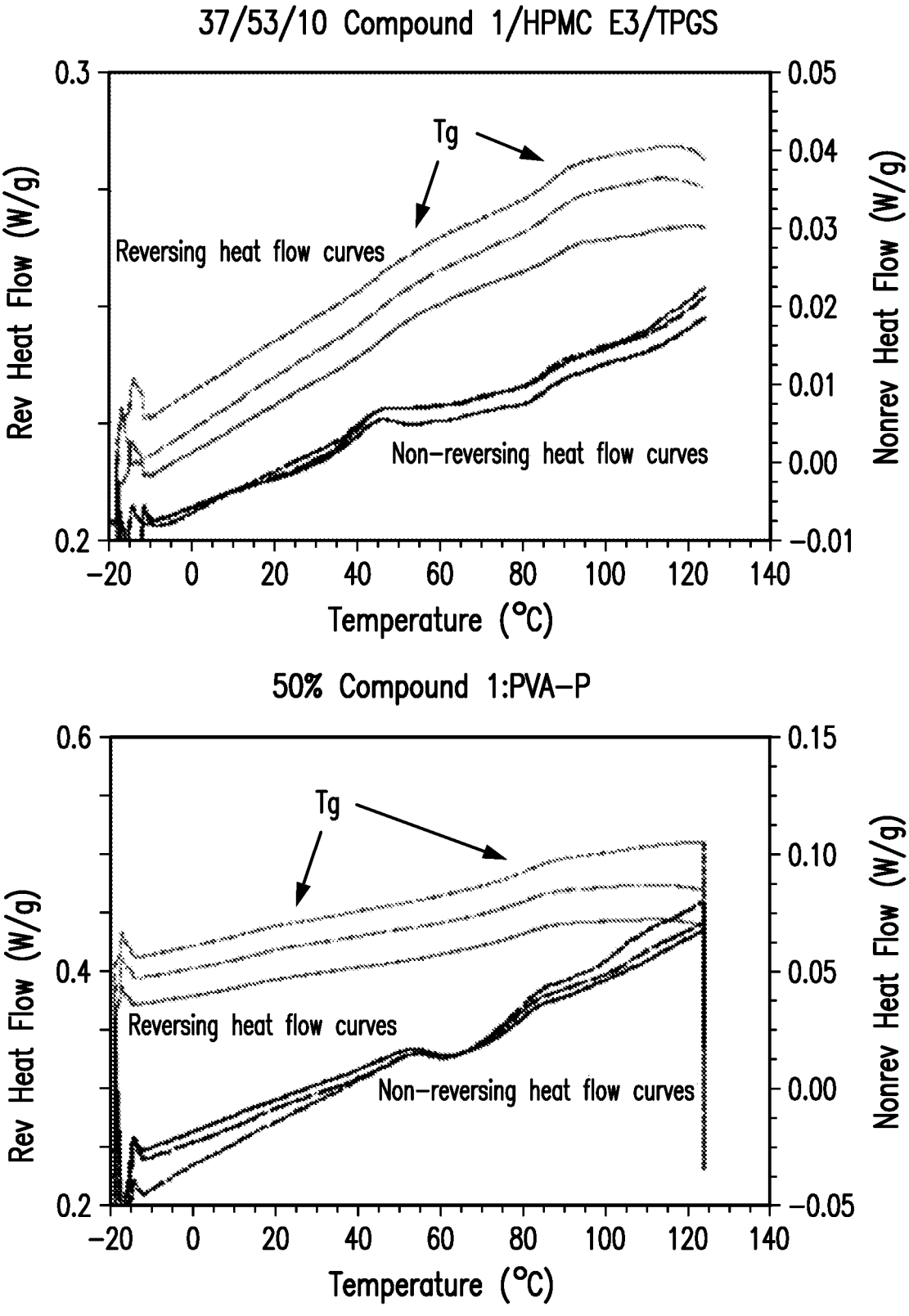

37/53/10 Compound 1/HPMC E3/TPGS
Tg
Reversing heat flow curves
Non-reversing heat flow curves
Rev Heat Flow (W/g)
Nonrev Heat Flow (W/g)
Temperature (°C)
50% Compound 1:PVA-P
Tg
Reversing heat flow curves
Non-reversing heat flow curves
Rev Heat Flow (W/g)
Nonrev Heat Flow (W/g)
Temperature (°C)
75% RH

FIG. 41

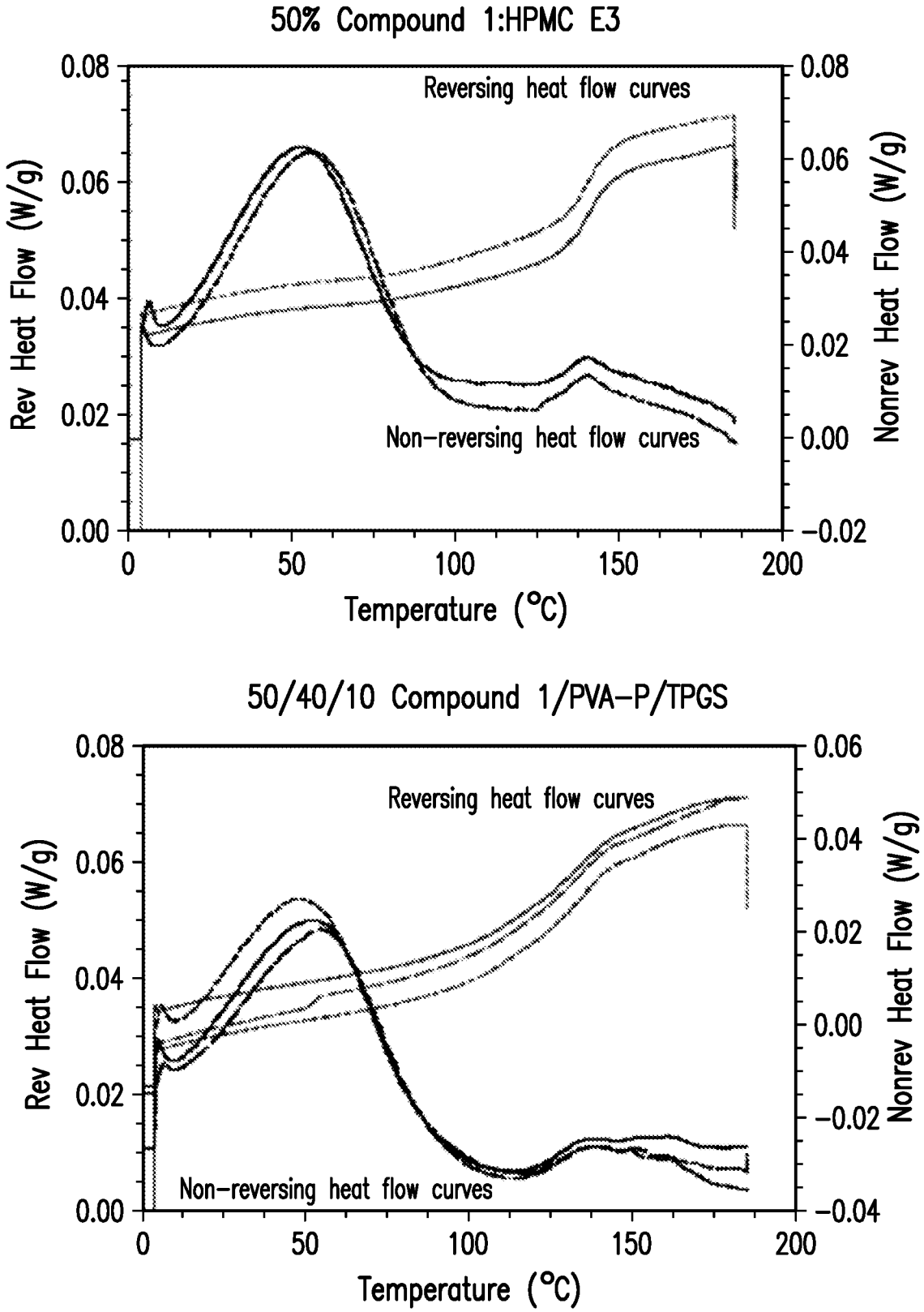

50% Compound 1:HPMC E3
Reversing heat flow curves
Non-reversing heat flow curves
Rev Heat Flow (W/g)
Nonrev Heat Flow (W/g)
Temperature (°C)
0.08
0.06
0.04
0.02
0.00
-0.02
0
50
100
150
200
50/40/10 Compound 1/PVA-P/TPGS
Reversing heat flow curves
Non-reversing heat flow curves
Rev Heat Flow (W/g)
Nonrev Heat Flow (W/g)
Temperature (°C)
0.08
0.06
0.04
0.02
0.00
-0.02
-0.04
0
50
100
150
200

FIG. 42

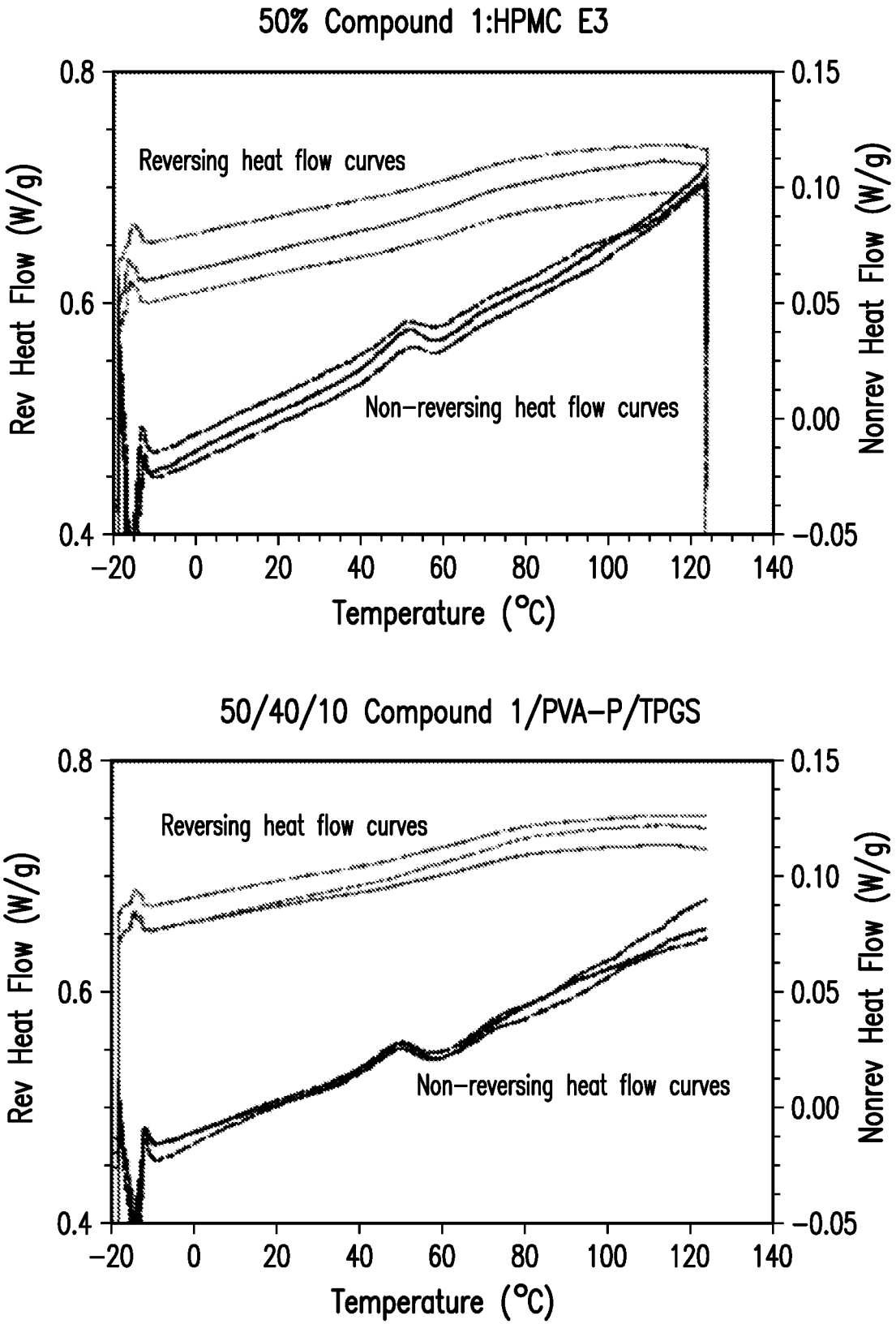

50% Compound 1:HPMC E3
Reversing heat flow curves
Non-reversing heat flow curves
Rev Heat Flow (W/g)
Nonrev Heat Flow (W/g)
Temperature (°C)
0.8
0.6
0.4
0.15
0.10
0.05
0.00
-0.05
-20
0
20
40
60
80
100
120
140
50/40/10 Compound 1/PVA-P/TPGS
Reversing heat flow curves
Non-reversing heat flow curves
Rev Heat Flow (W/g)
Nonrev Heat Flow (W/g)
Temperature (°C)

FIG. 43

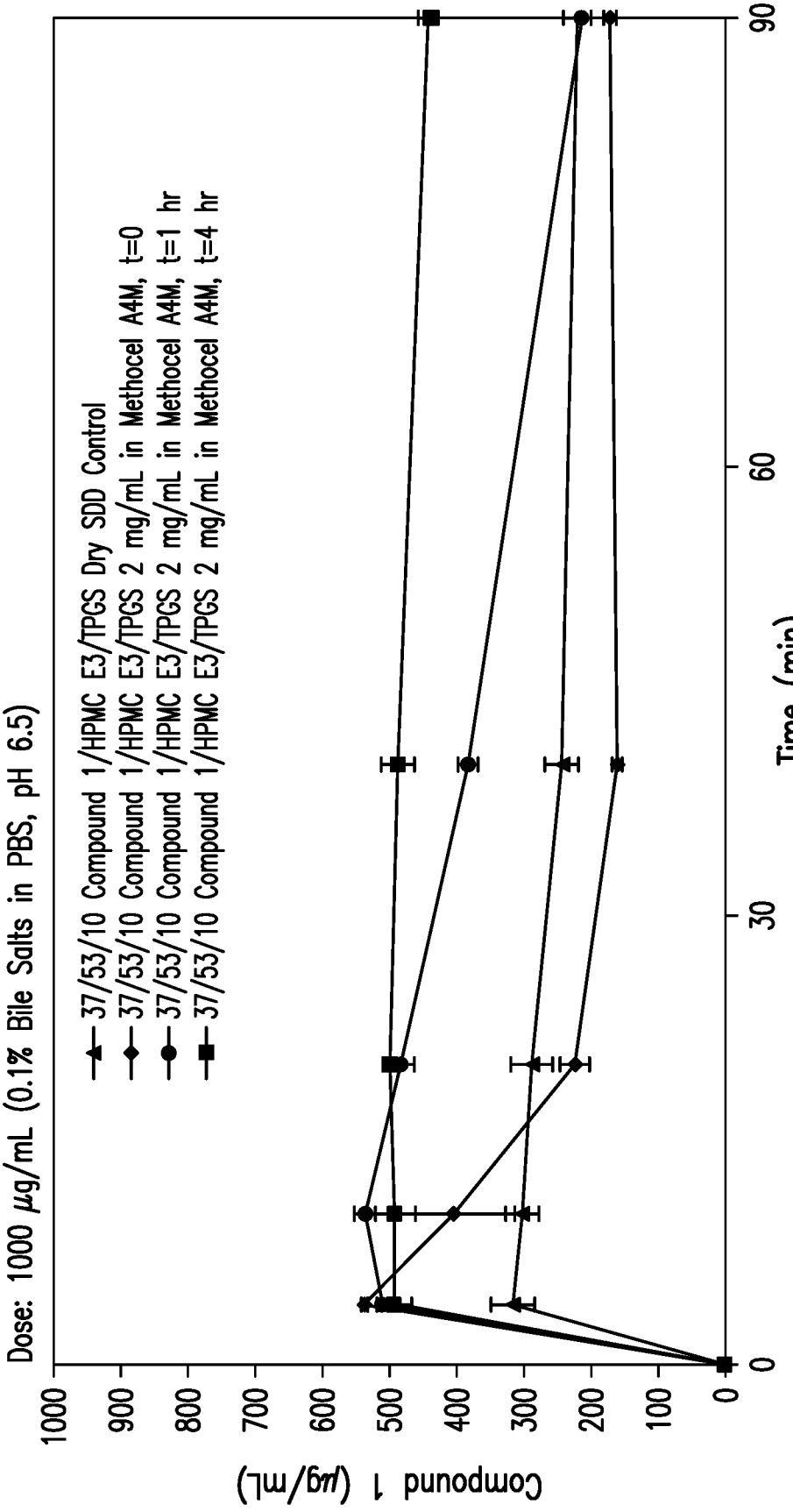

Dose: 1000 µg/mL (0.1% Bile Salts in PBS, pH 6.5)
37/53/10 Compound 1/HPMC E3/TPGS Dry SDD Control
37/53/10 Compound 1/HPMC E3/TPGS 2 mg/mL in Methocel A4M, t=0
37/53/10 Compound 1/HPMC E3/TPGS 2 mg/mL in Methocel A4M, t=1 hr
37/53/10 Compound 1/HPMC E3/TPGS 2 mg/mL in Methocel A4M, t=4 hr
Compound 1 (µg/mL)
1000
900
800
700
600
500
400
300
200
100
0
0
30
60
90
Time (min)

FIG. 44

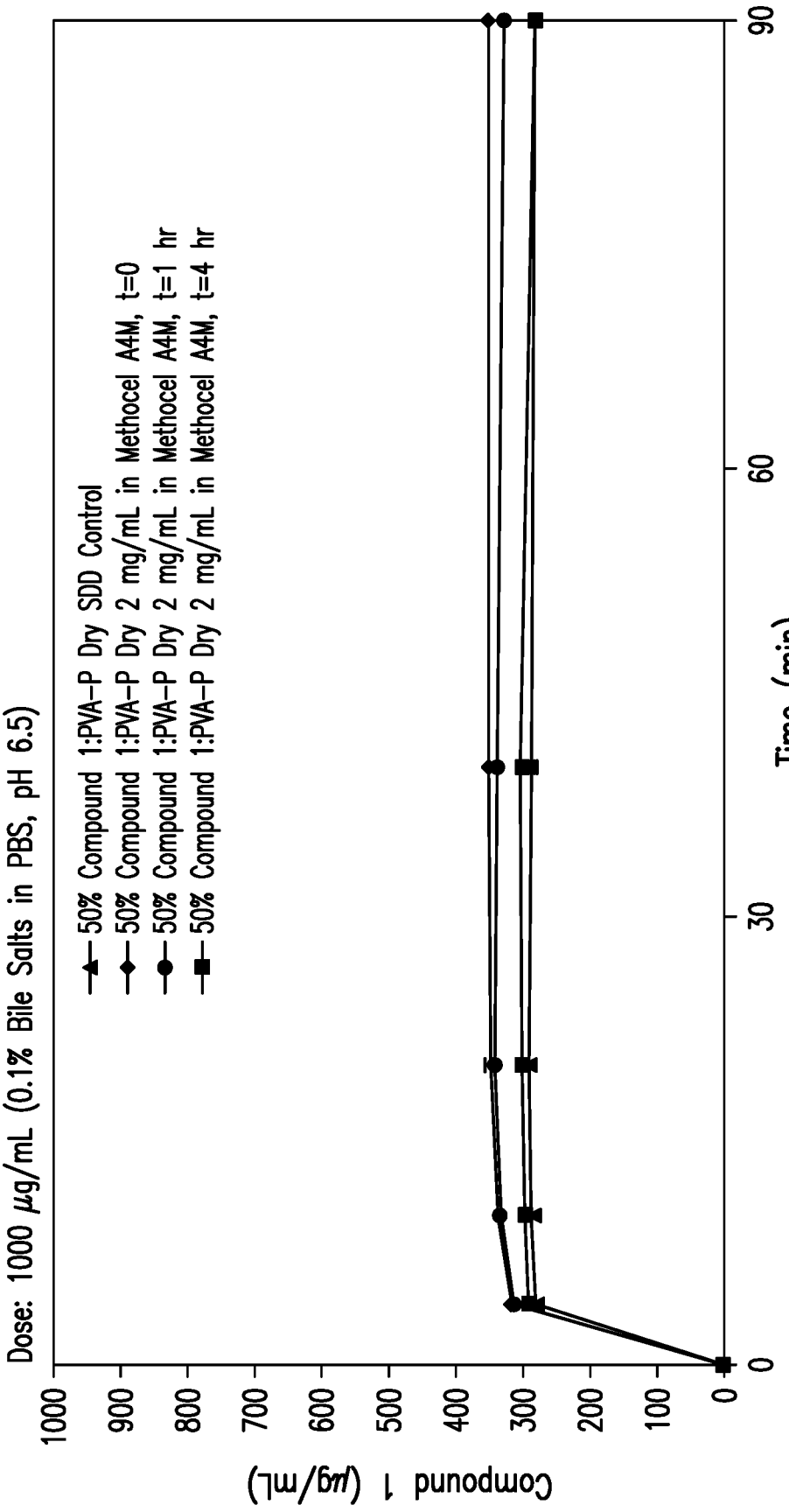

Dose: 1000 µg/mL (0.1% Bile Salts in PBS, pH 6.5)
50% Compound 1:PVA-P Dry SDD Control
50% Compound 1:PVA-P Dry 2 mg/mL in Methocel A4M, t=0
50% Compound 1:PVA-P Dry 2 mg/mL in Methocel A4M, t=1 hr
50% Compound 1:PVA-P Dry 2 mg/mL in Methocel A4M, t=4 hr
Compound 1 (µg/mL)
1000
900
800
700
600
500
400
300
200
100
0
0
30
60
90
Time (min)

FIG. 45

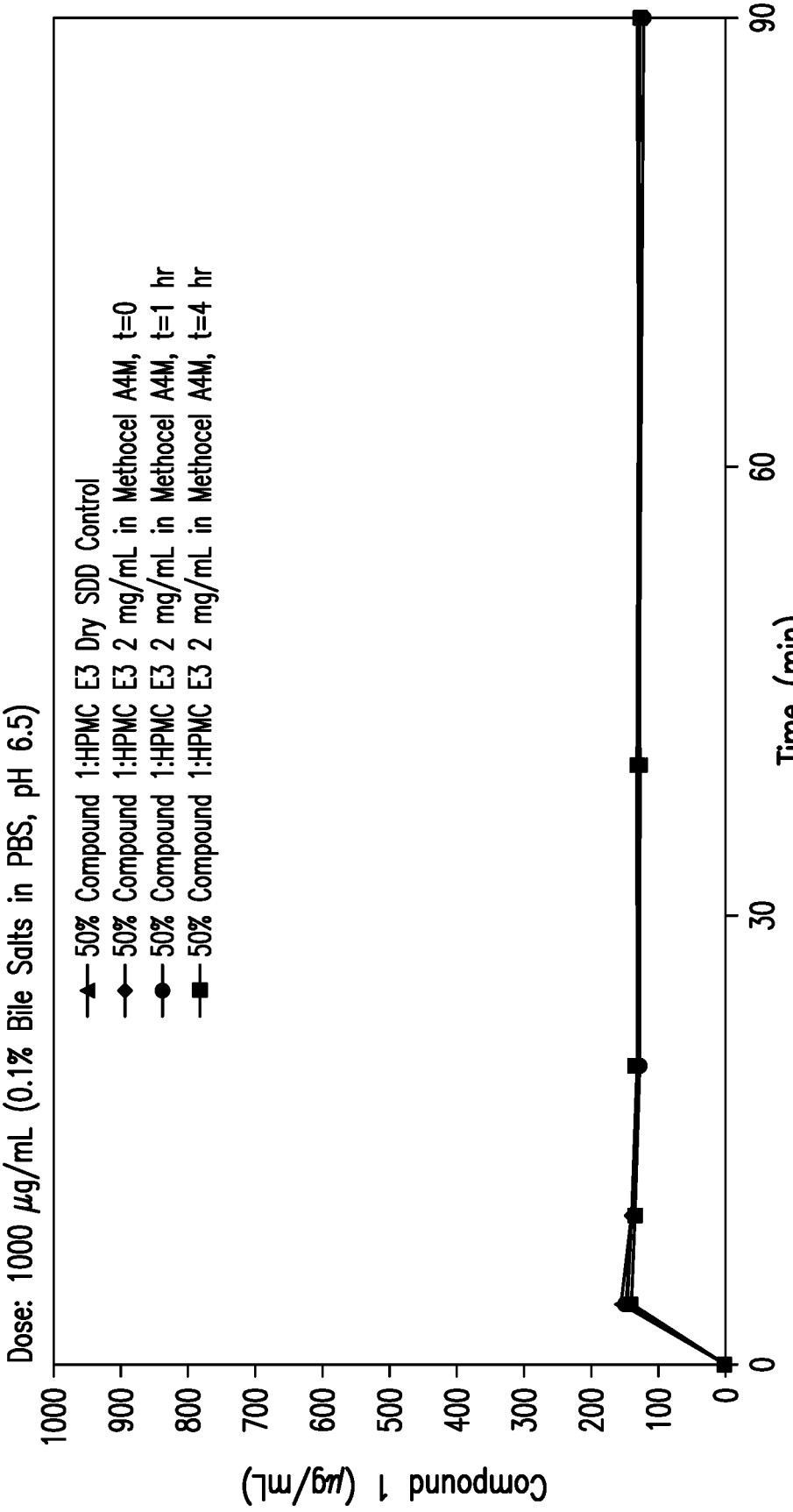

Dose: 1000 µg/mL (0.1% Bile Salts in PBS, pH 6.5)
50% Compound 1:HPMC E3 Dry SDD Control
50% Compound 1:HPMC E3 2 mg/mL in Methocel A4M, t=0
50% Compound 1:HPMC E3 2 mg/mL in Methocel A4M, t=1 hr
50% Compound 1:HPMC E3 2 mg/mL in Methocel A4M, t=4 hr
Compound 1 (µg/mL)
1000
900
800
700
600
500
400
300
200
100
0
0
30
60
90
Time (min)

FIG. 46

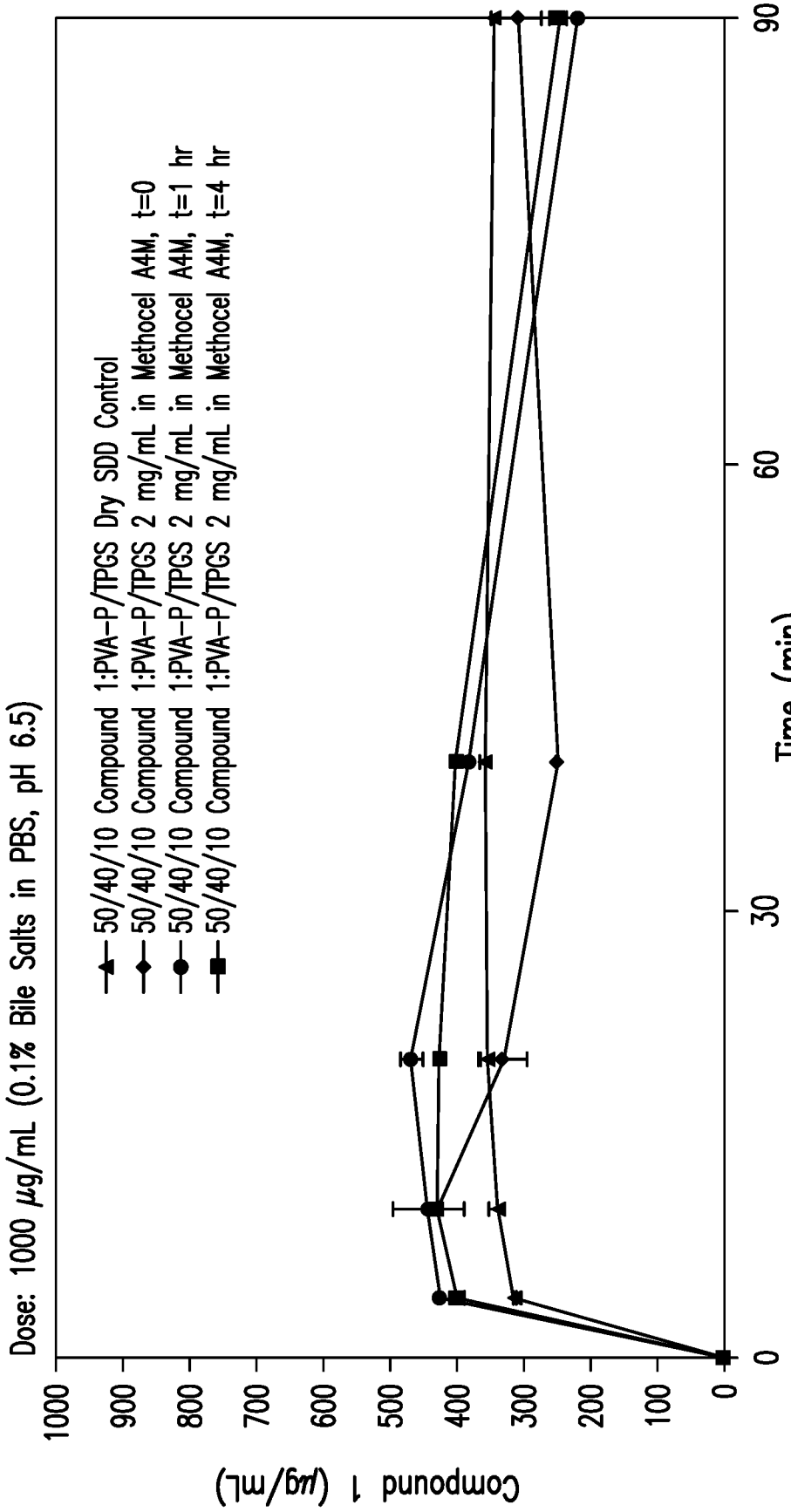

Dose: 1000 µg/mL (0.1% Bile Salts in PBS, pH 6.5)
50/40/10 Compound 1:PVA-P/TPGS Dry SDD Control
50/40/10 Compound 1:PVA-P/TPGS 2 mg/mL in Methocel A4M, t=0
50/40/10 Compound 1:PVA-P/TPGS 2 mg/mL in Methocel A4M, t=1 hr
50/40/10 Compound 1:PVA-P/TPGS 2 mg/mL in Methocel A4M, t=4 hr
Compound 1 (µg/mL)
1000
900
800
700
600
500
400
300
200
100
0
0
30
60
90
Time (min)

FIG. 47

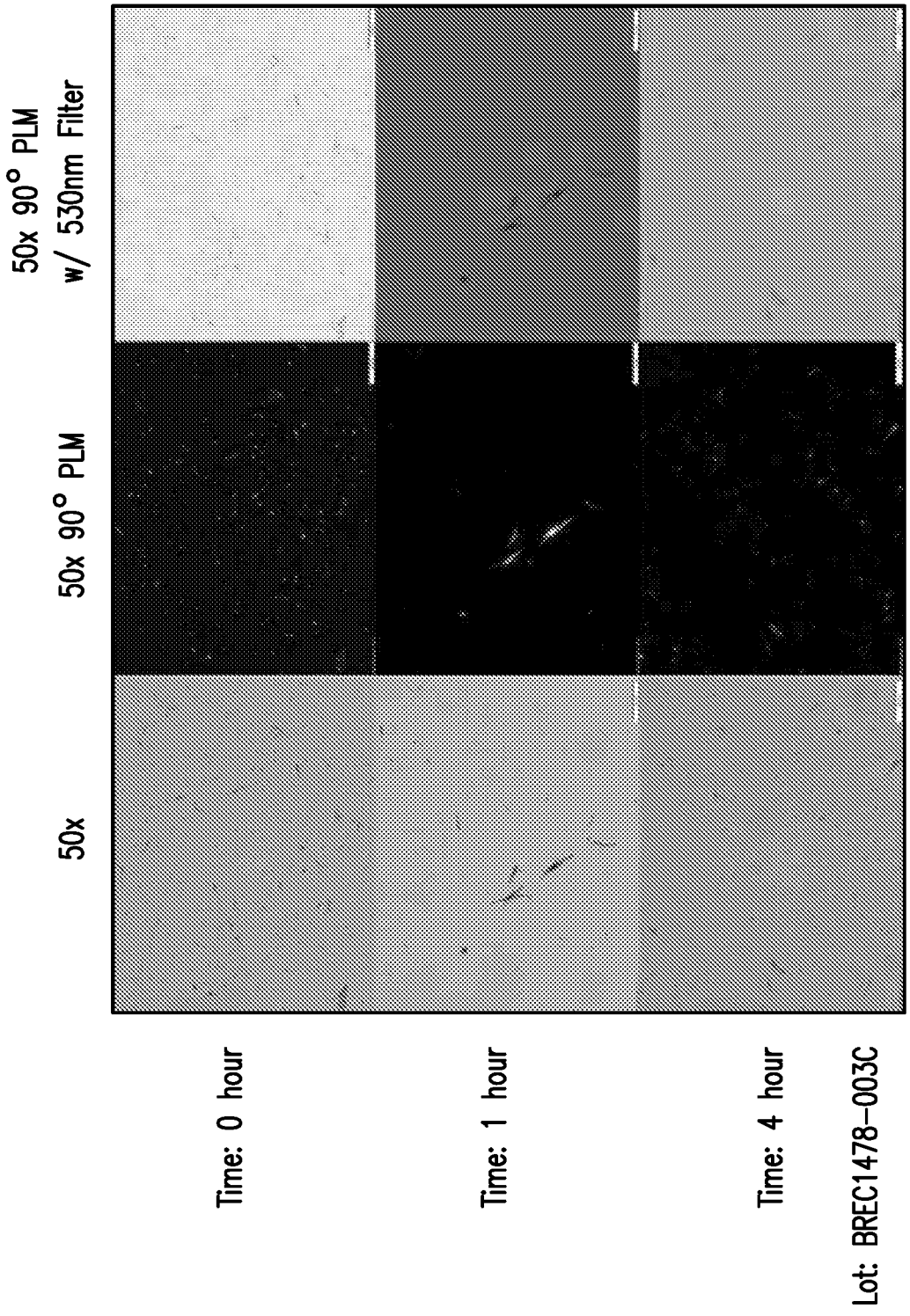

50x
50x 90° PLM
50x 90° PLM
w/ 530nm Filter
Time: 0 hour
Time: 1 hour
Time: 4 hour
Lot: BREC1478-003C

FIG. 48

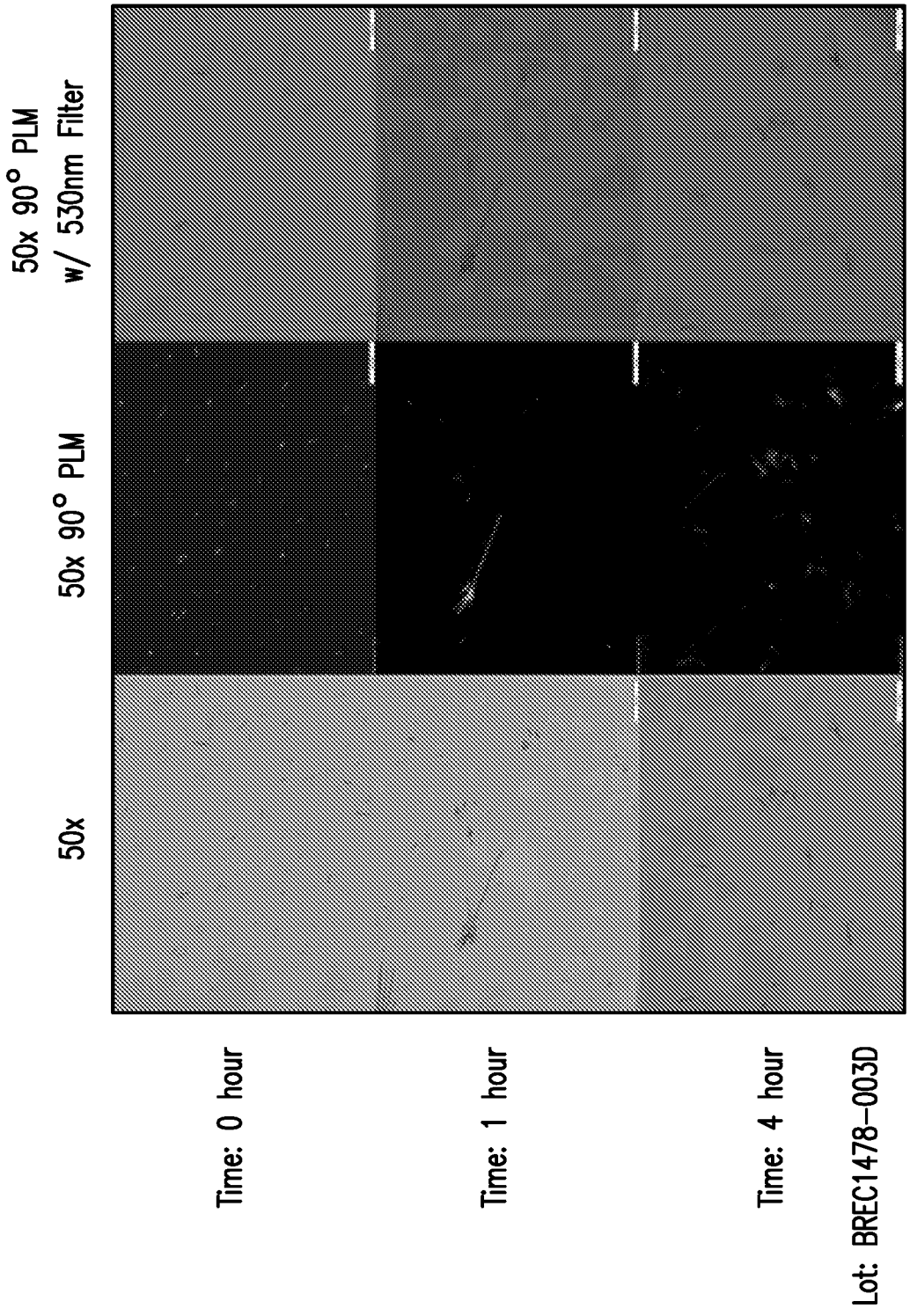

50x
50x 90° PLM
50x 90° PLM
w/ 530nm Filter
Time: 0 hour
Time: 1 hour
Time: 4 hour
Lot: BREC1478-003D

FIG. 49

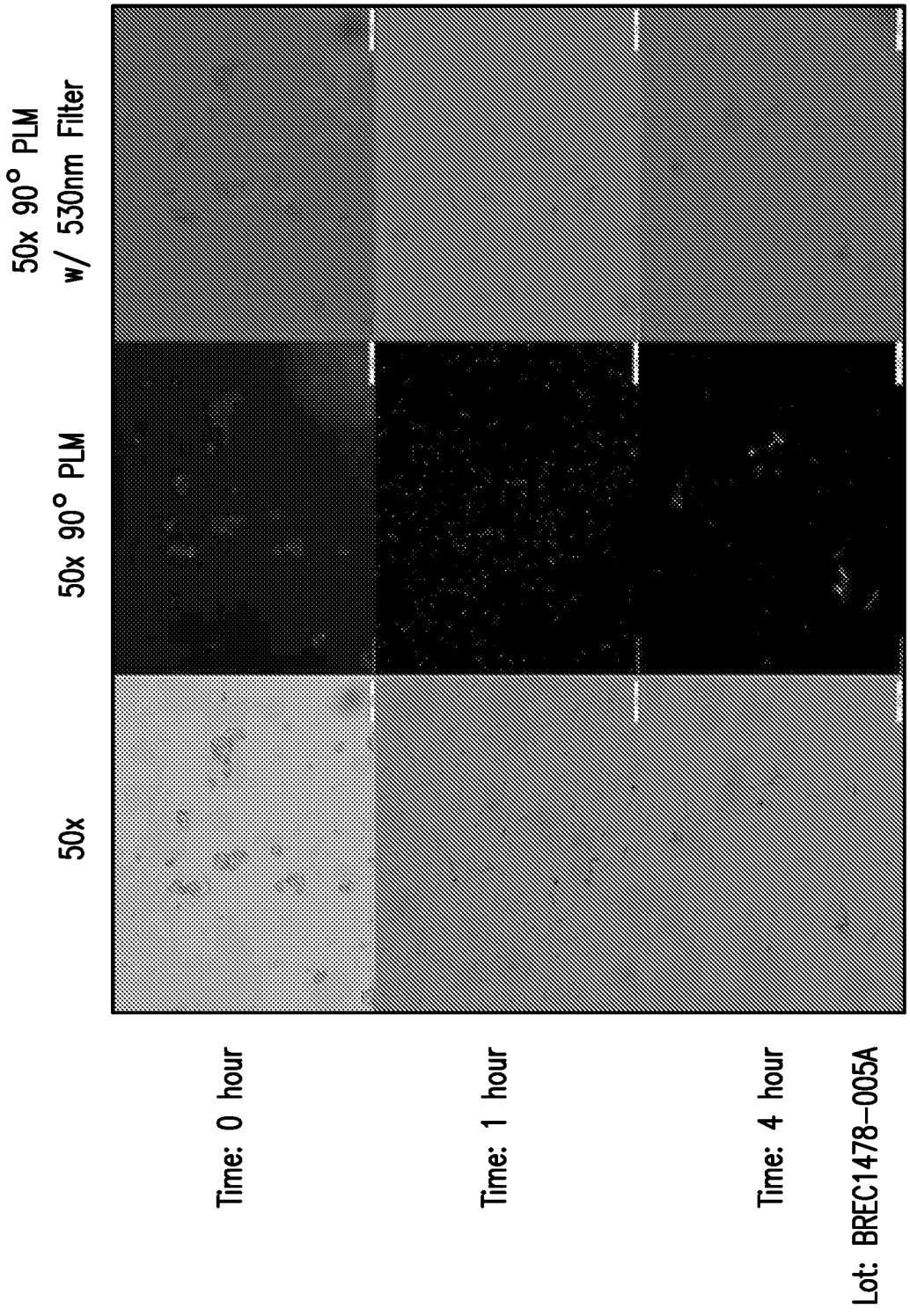

50x
50x 90° PLM
50x 90° PLM
w/ 530nm Filter
Time: 0 hour
Time: 1 hour
Time: 4 hour
Lot: BREC1478-005A

FIG. 50

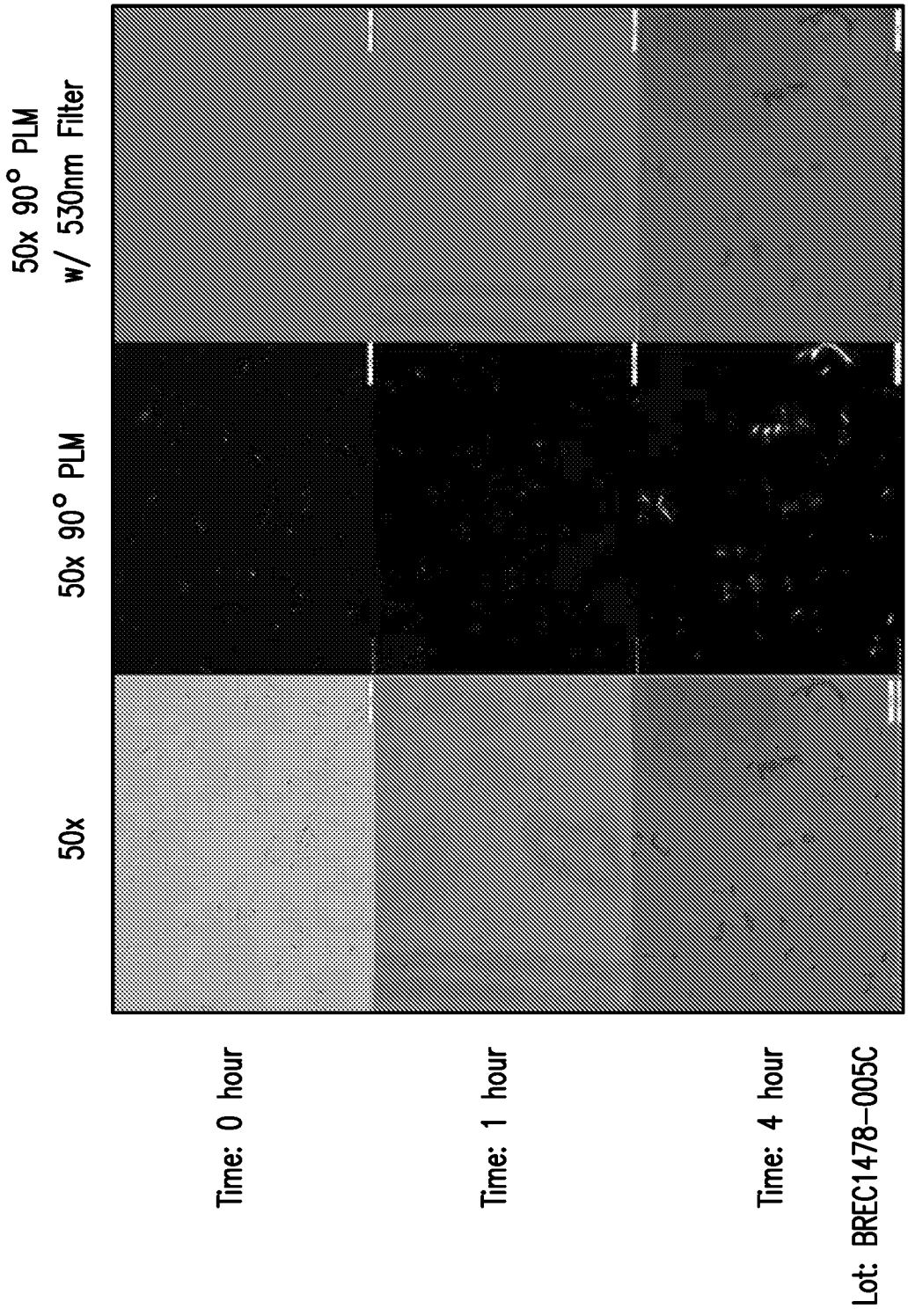

50x
50x 90° PLM
50x 90° PLM
w/ 530nm Filter
Time: 0 hour
Time: 1 hour
Time: 4 hour
Lot: BREC1478-005C

FIG. 51

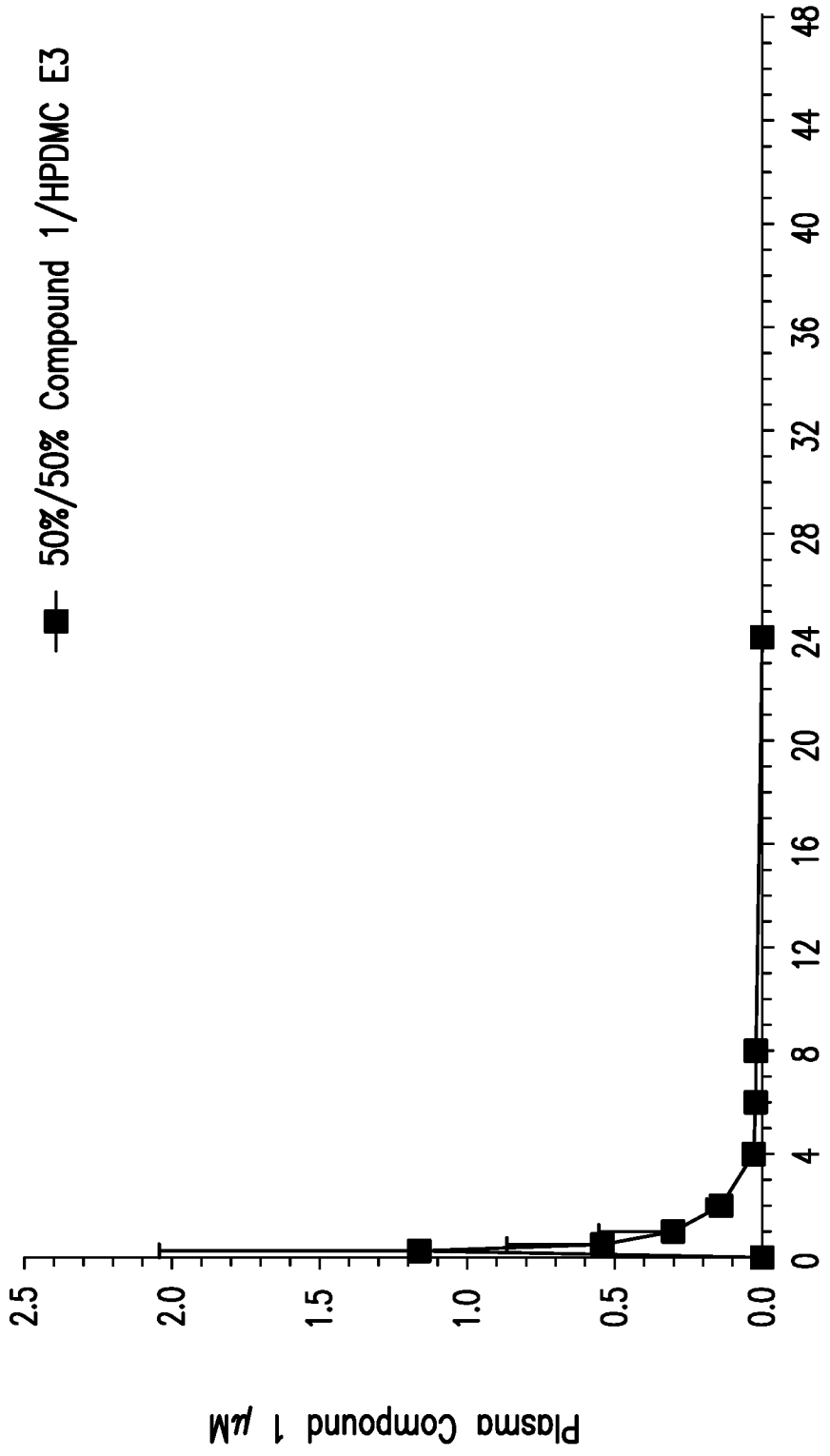

50%/50% Compound 1/HPDMC E3
Plasma Compound 1 μM
Time (hr)
0.0
0.5
1.0
1.5
2.0
2.5
0
4
8
12
16
20
24
28
32
36
40
44
48

FIG. 52

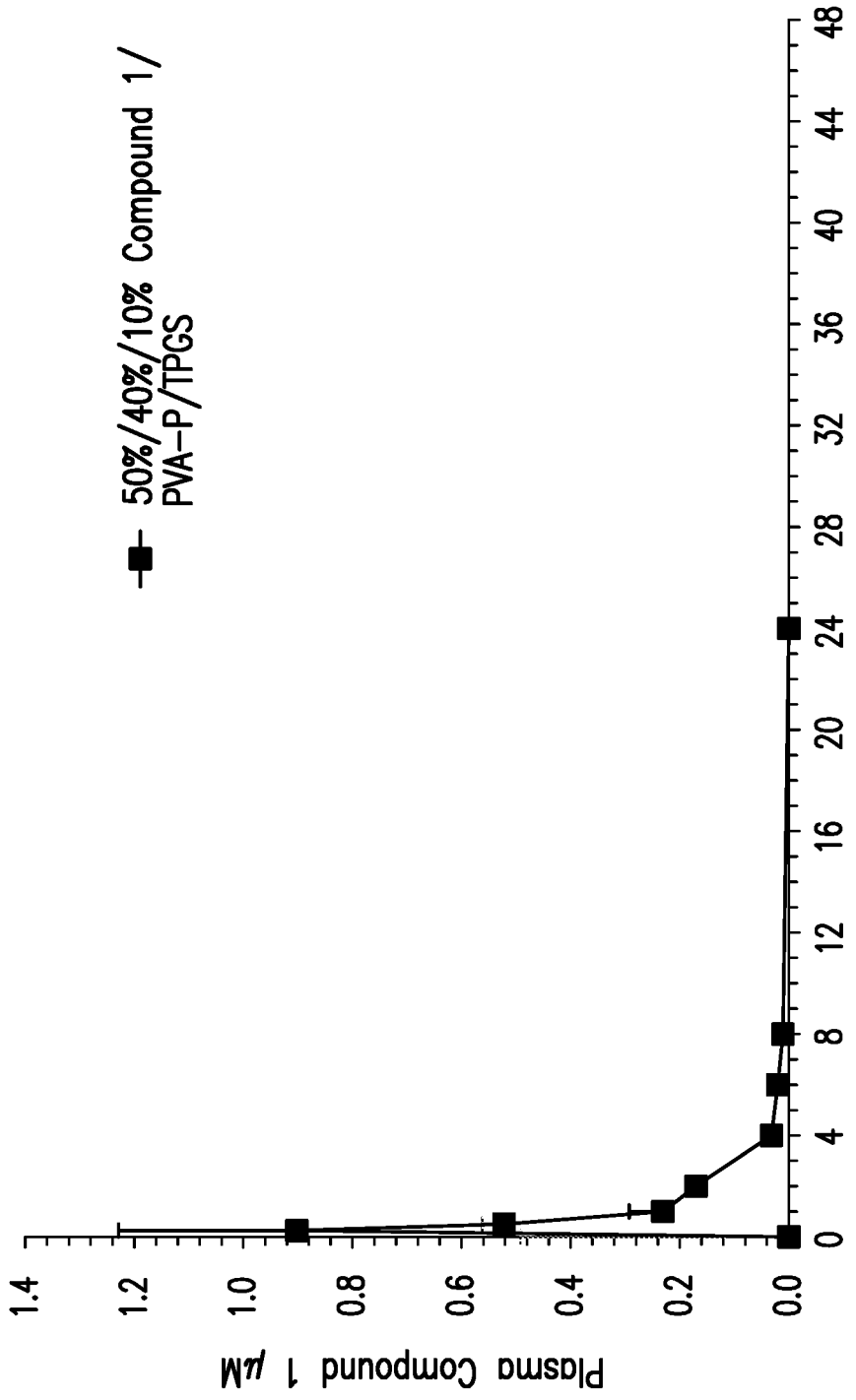

50%/40%/10% Compound 1/
PVA-P/TPGS
Plasma Compound 1 μM
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
4
8
12
16
20
24
28
32
36
40
44
48
Time (hr)

FIG. 53

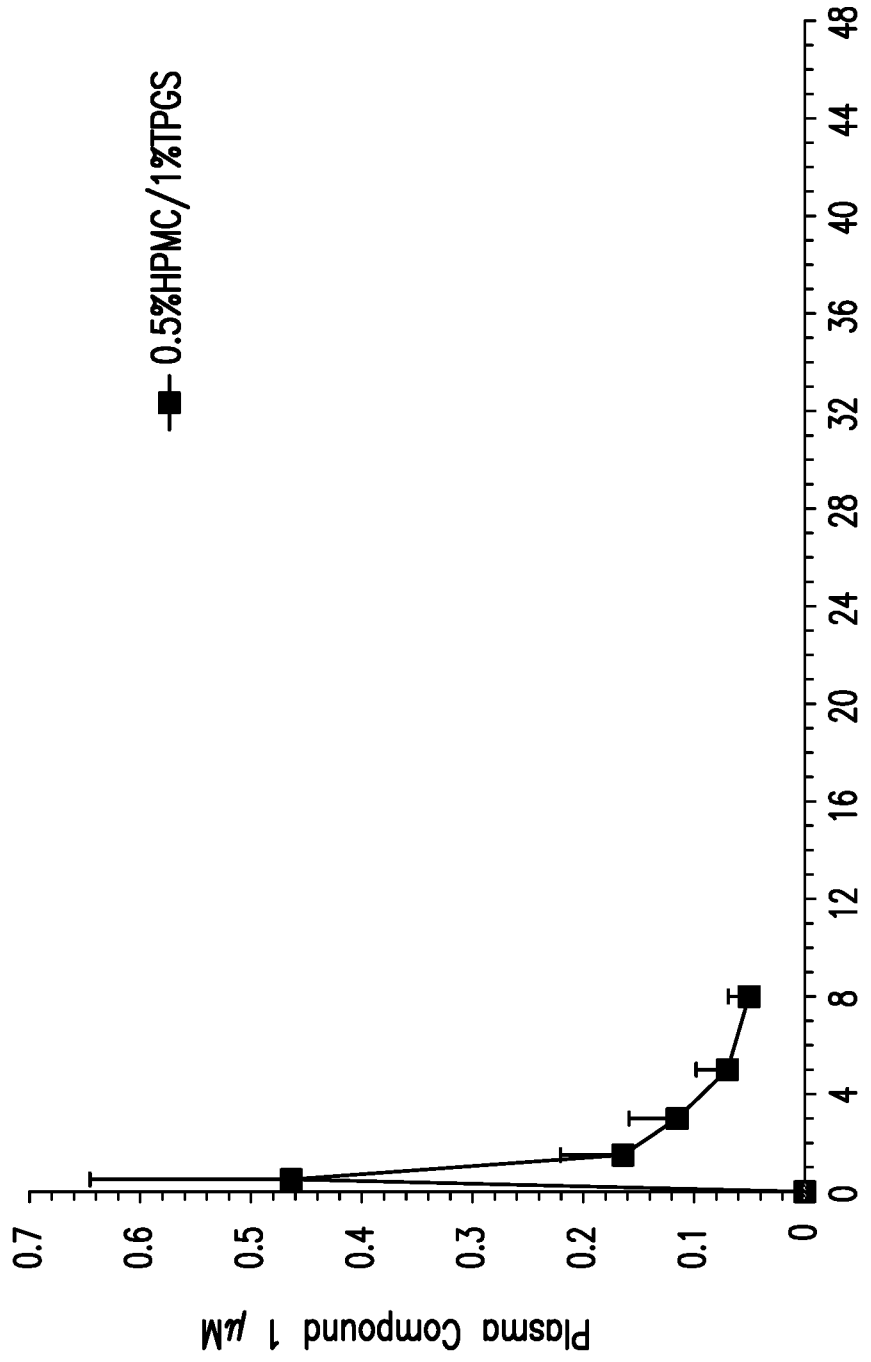

0.5%HPMC/1%TPGS
Plasma Compound 1 μM
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
4
8
12
16
20
24
28
32
36
40
44
48
Time (hr)

FIG. 54

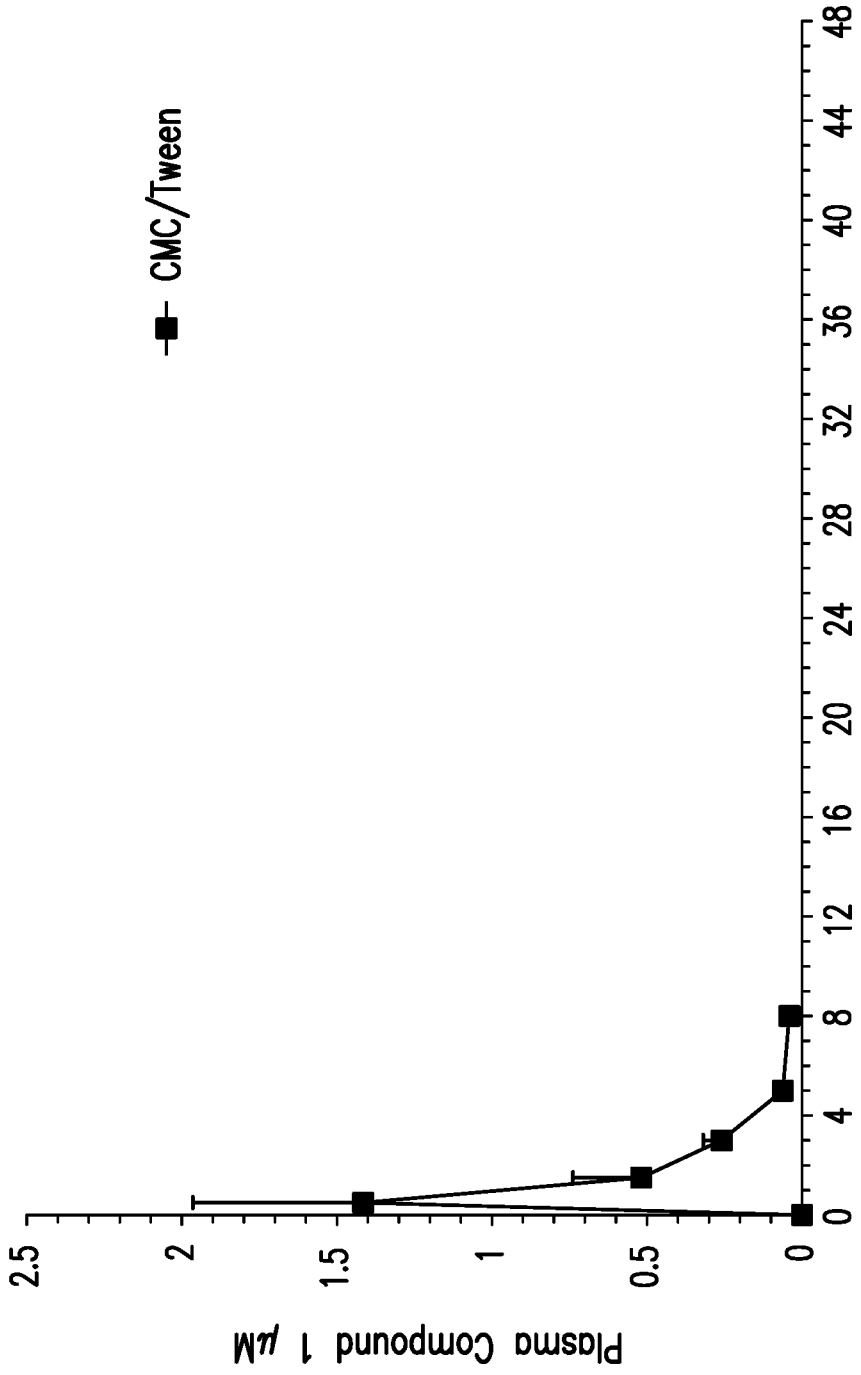

CMC/Tween
Plasma Compound 1 μM
2.5
2
1.5
1
0.5
0
0
4
8
12
16
20
24
28
32
36
40
44
48
Time (hr)

FIG. 55

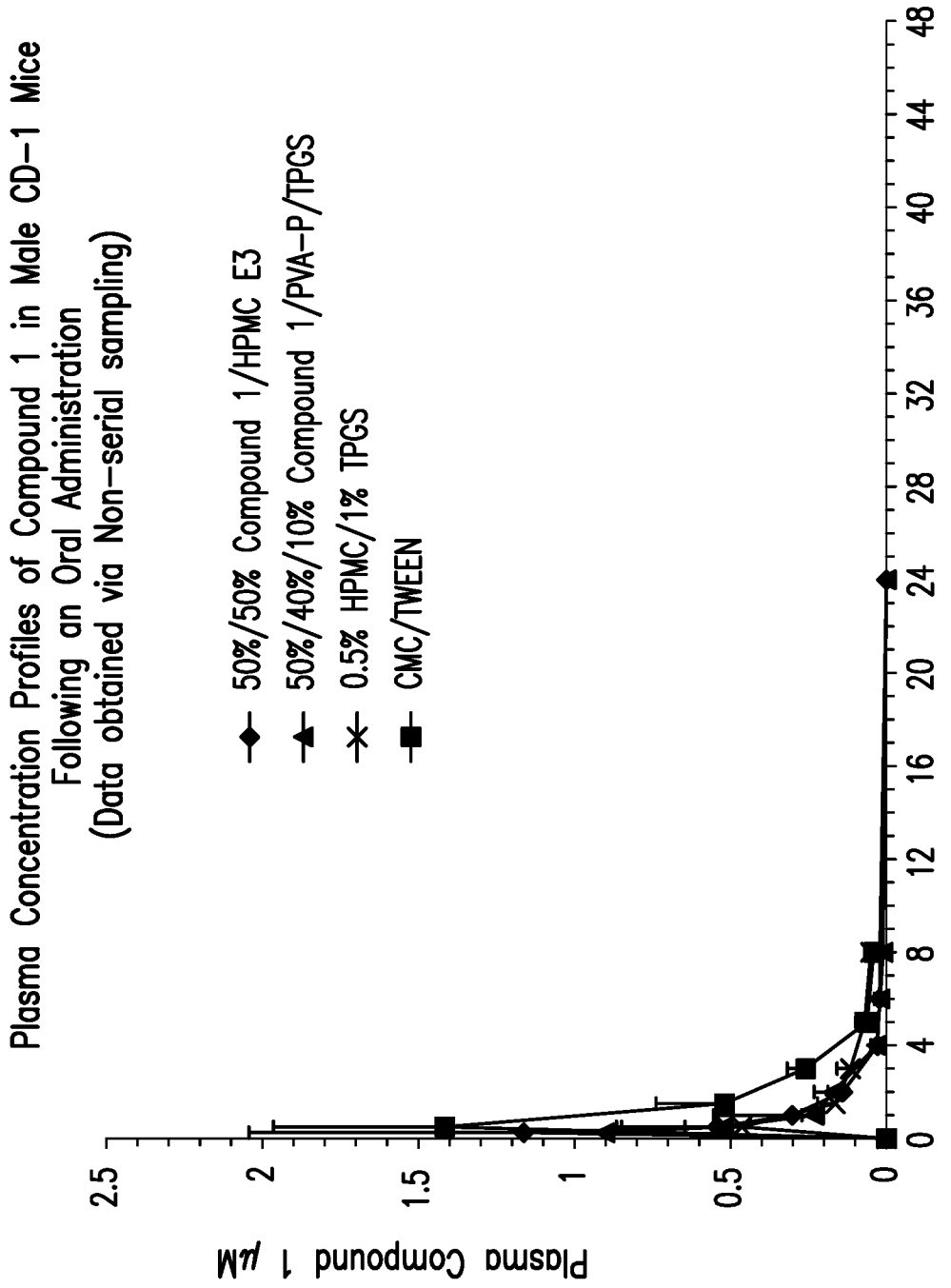

Plasma Concentration Profiles of Compound 1 in Male CD-1 Mice
Following an Oral Administration
(Data obtained via Non-serial sampling)
50%/50% Compound 1/HPMC E3
50%/40%/10% Compound 1/PVA-P/TPGS
0.5% HPMC/1% TPGS
CMC/TWEEN
Plasma Compound 1 μM
Time (hr)
0
0.5
1
1.5
2
2.5
0
4
8
12
16
20
24
28
32
36
40
44
48

FIG. 56

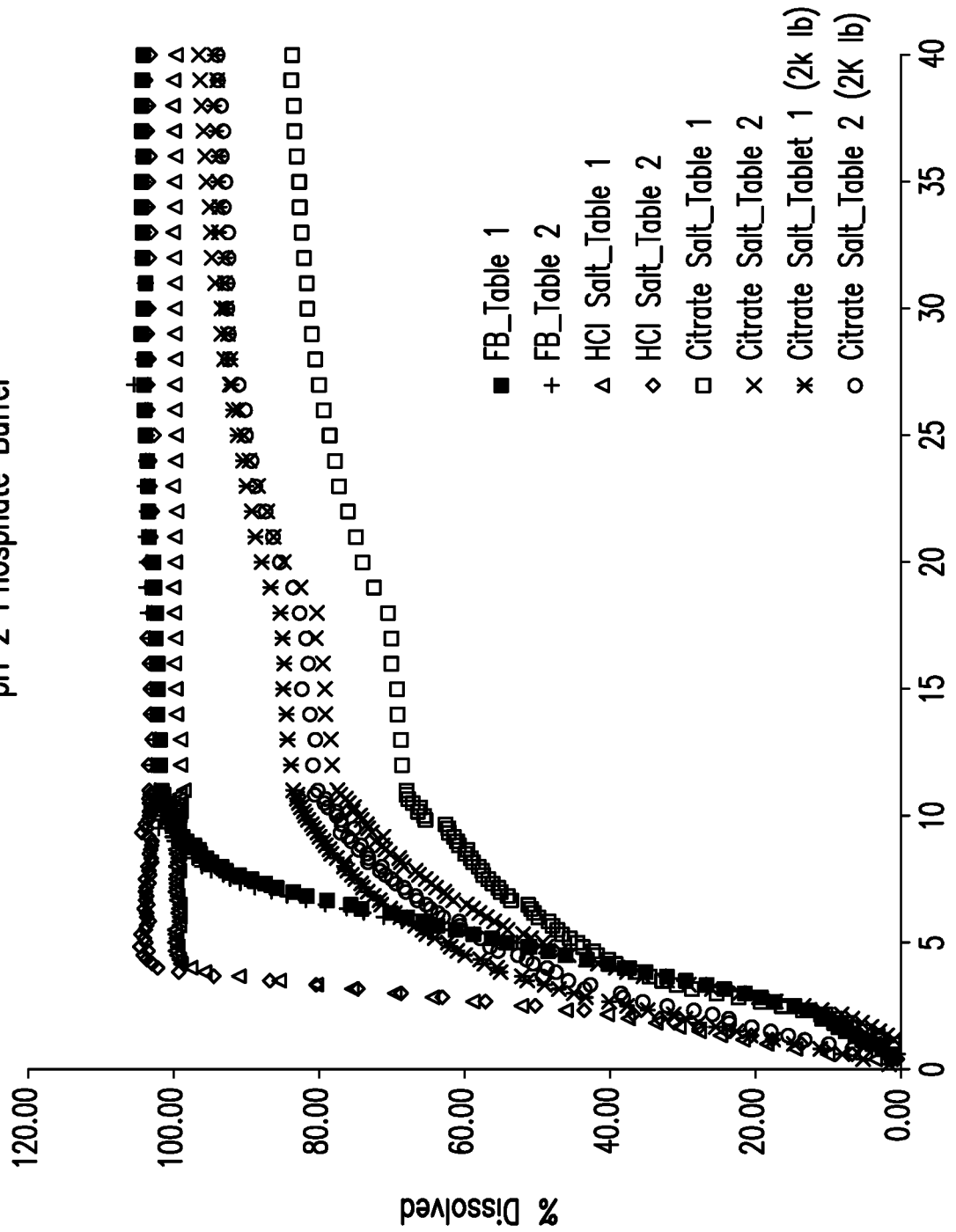

pH 2 Phosphate Buffer
% Dissolved
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0
5
10
15
20
25
30
35
40
Time (minute)
FB_Table 1
FB_Table 2
HCl Salt_Table 1
HCl Salt_Table 2
Citrate Salt_Table 1
Citrate Salt_Table 2
Citrate Salt_Tablet 1 (2k lb)
Citrate Salt_Table 2 (2K lb)

FIG. 57

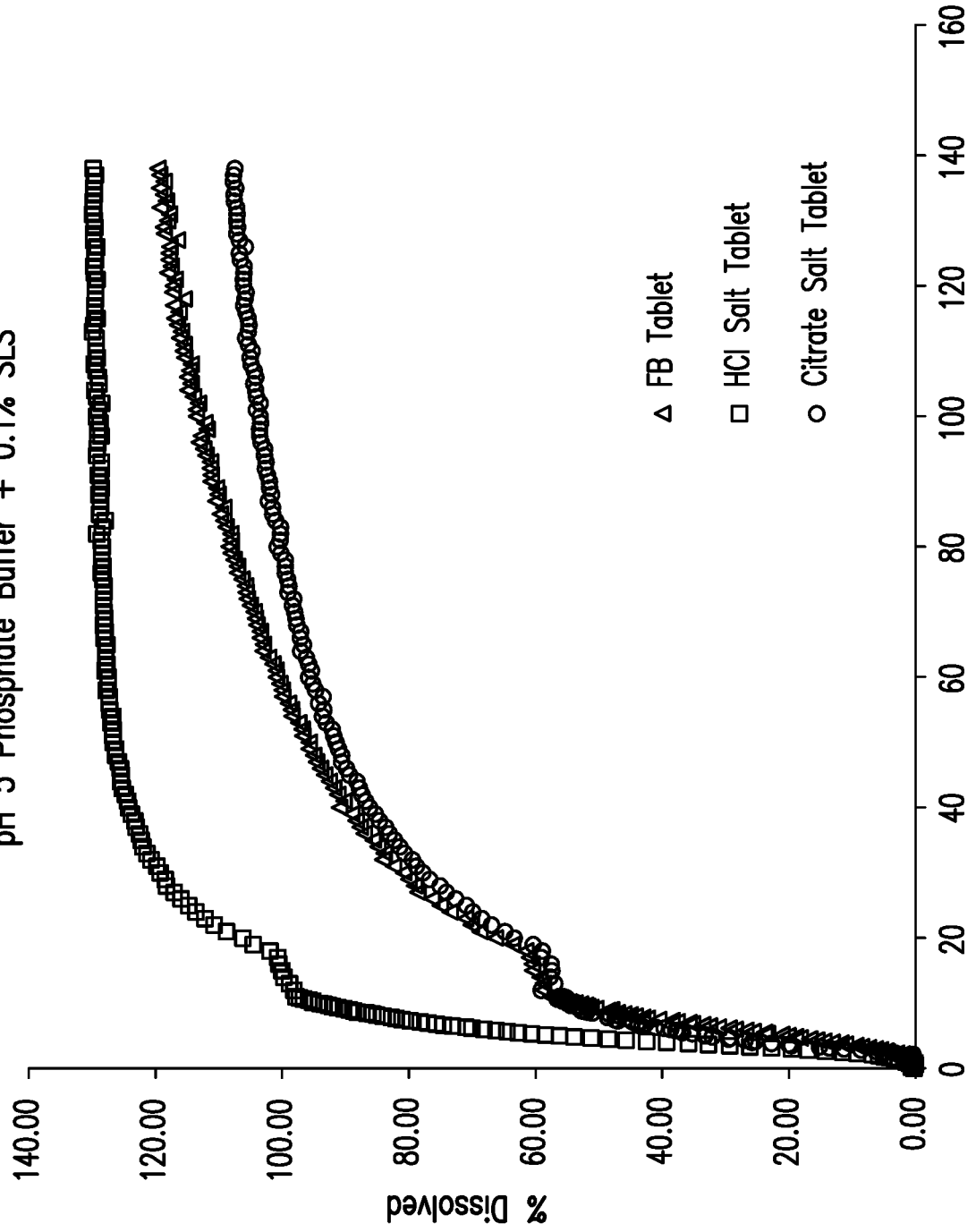

pH 5 Phosphate Buffer + 0.1% SLS
% Dissolved
140.00
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0
20
40
60
80
100
120
140
160
Time (minute)
Δ FB Tablet
□ HCl Salt Tablet
○ Citrate Salt Tablet

FIG. 58

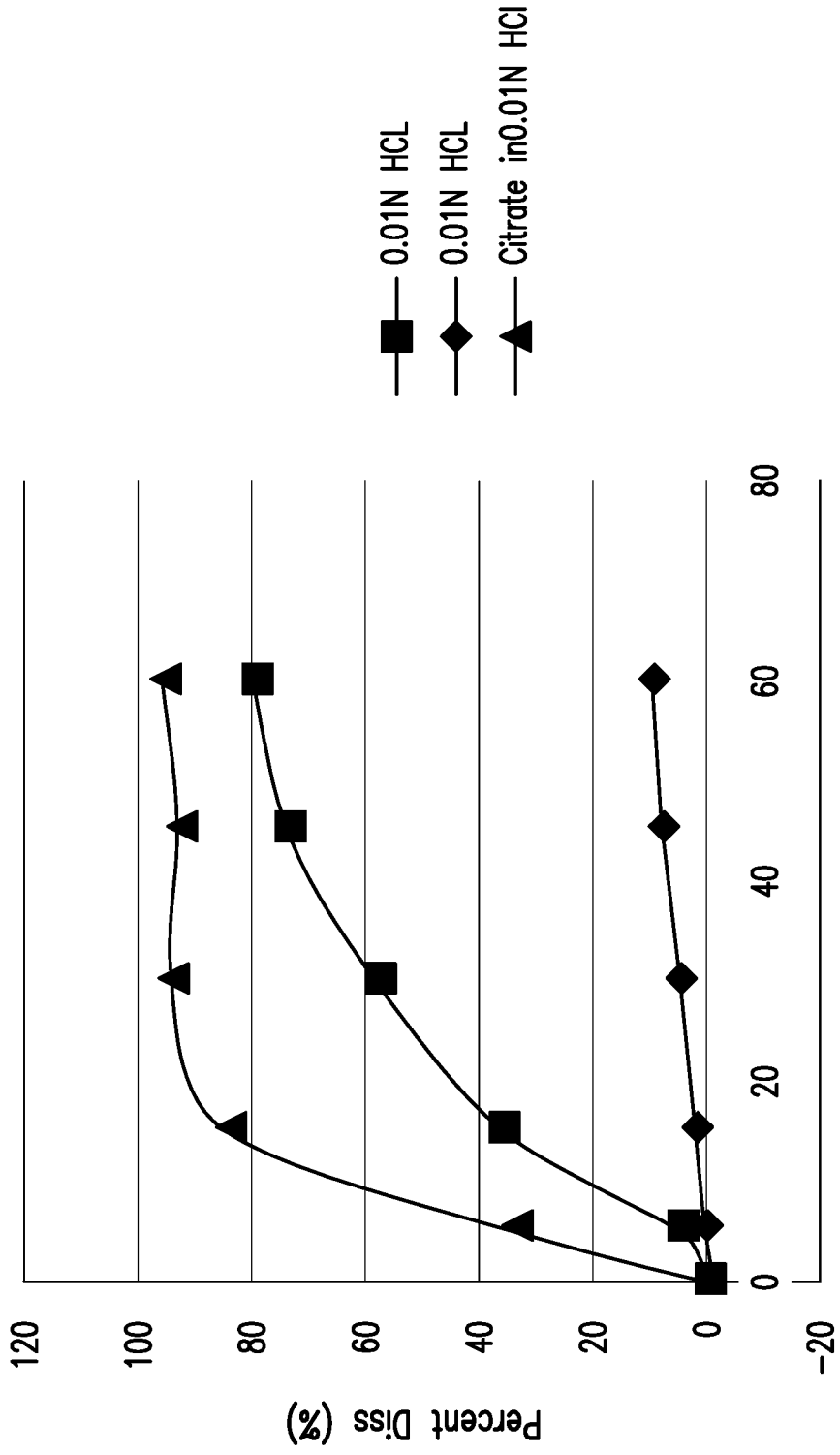

0.01N HCL
0.01N HCL
Citrate in0.01N HCl
Percent Diss (%)
120
100
80
60
40
20
0
-20
0
20
40
60
80
Time (min)

FIG. 59

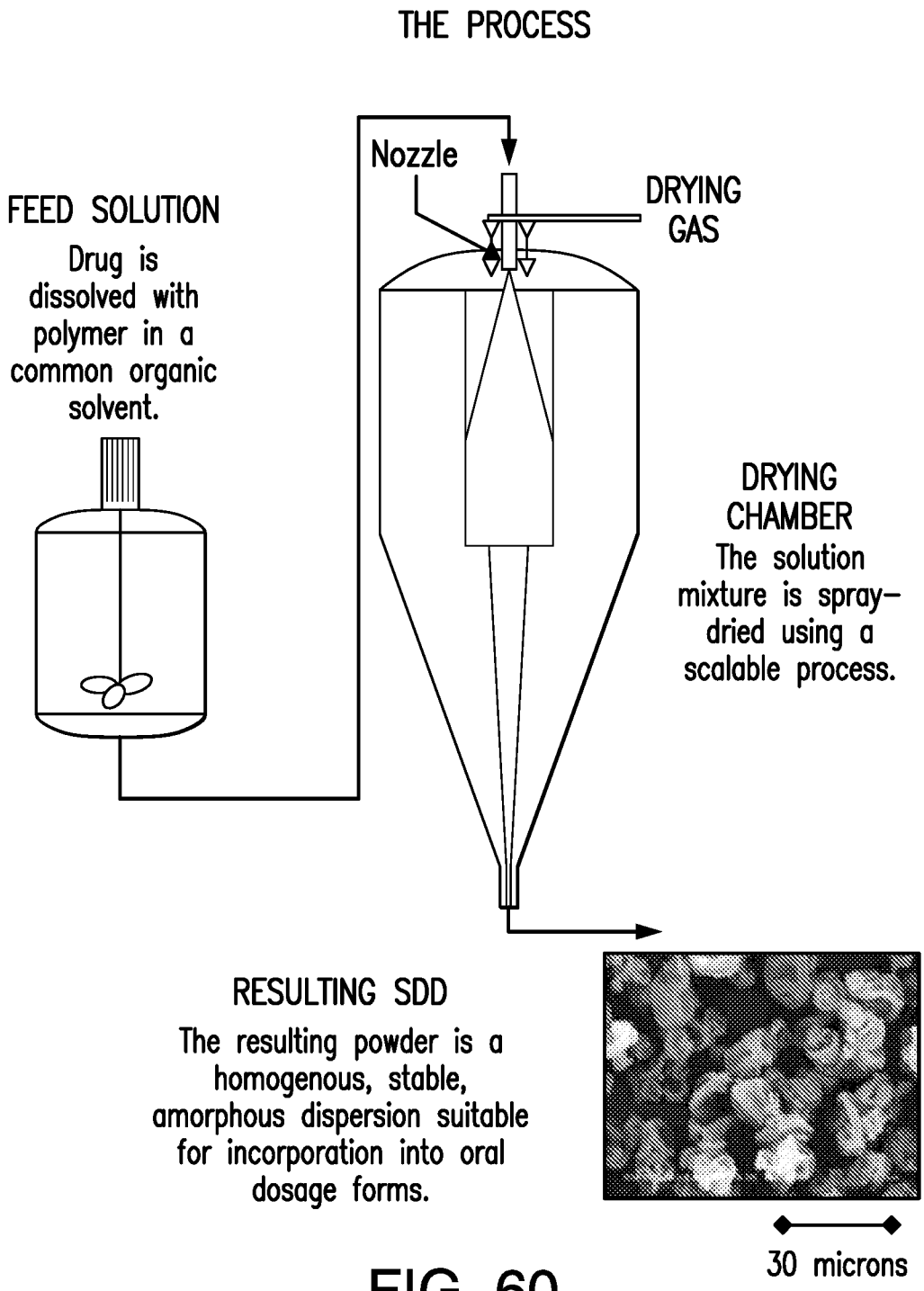

THE PROCESS
Nozzle
DRYING GAS
FEED SOLUTION
Drug is dissolved with polymer in a common organic solvent.
DRYING CHAMBER
The solution mixture is spray-dried using a scalable process.
RESULTING SDD
The resulting powder is a homogenous, stable, amorphous dispersion suitable for incorporation into oral dosage forms.
30 microns

FIG. 60