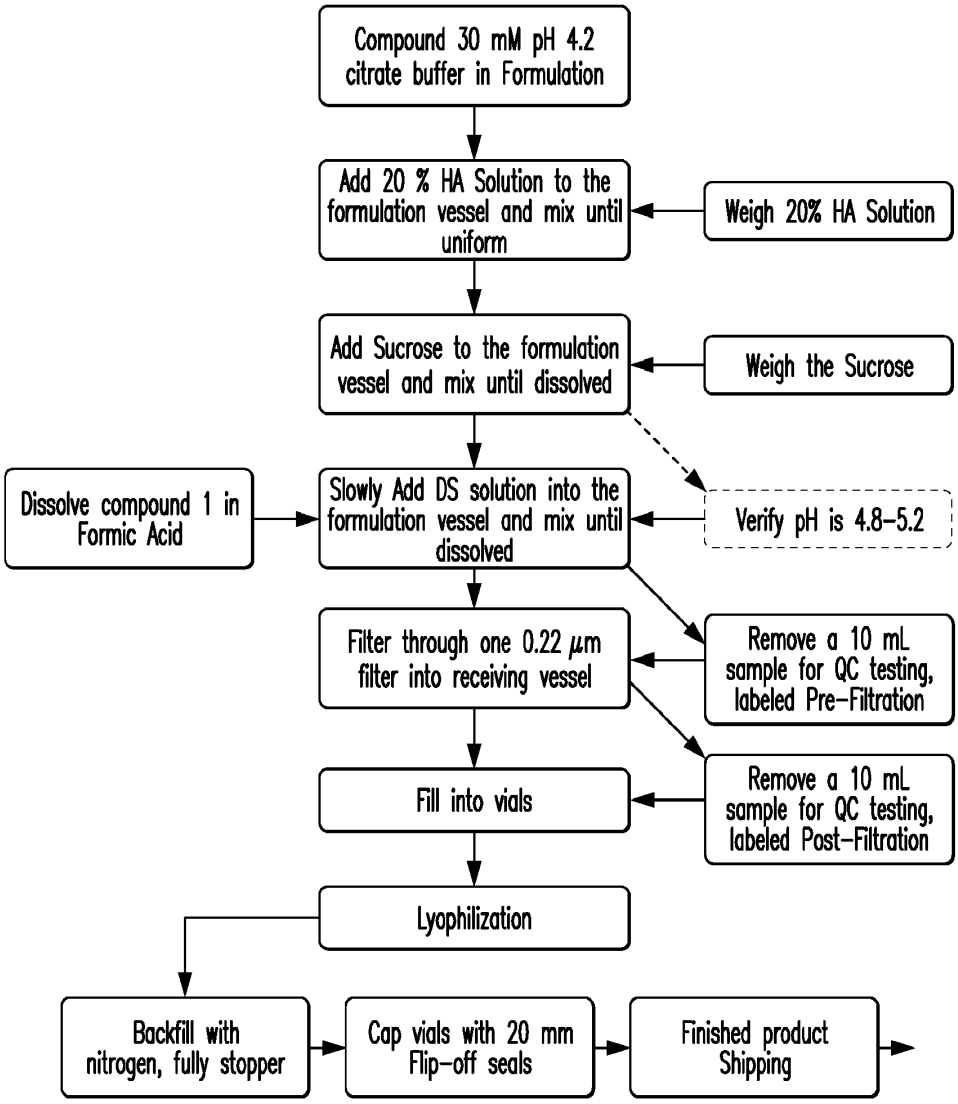

Compound 30 mM pH 4.2 citrate buffer in Formulation
Add 20 % HA Solution to the formulation vessel and mix until uniform
Weigh 20% HA Solution
Add Sucrose to the formulation vessel and mix until dissolved
Weigh the Sucrose
Dissolve compound 1 in Formic Acid
Slowly Add DS solution into the formulation vessel and mix until dissolved
Verify pH is 4.8–5.2
Filter through one 0.22 μm filter into receiving vessel
Remove a 10 mL sample for QC testing, labeled Pre-Filtration
Fill into vials
Remove a 10 mL sample for QC testing, labeled Post-Filtration
Lyophilization
Backfill with nitrogen, fully stopper
Cap vials with 20 mm Flip-off seals
Finished product Shipping

FIG. 1

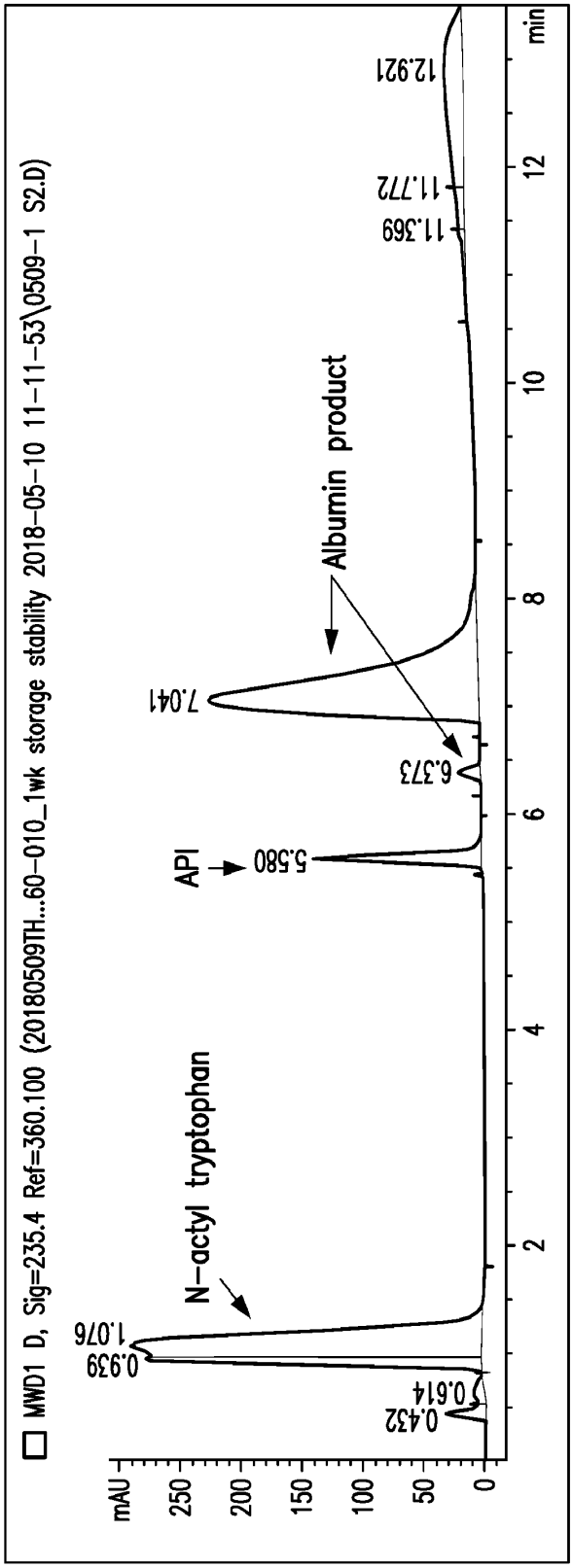

MWD1 D, Sig=235.4 Ref=360.100 (20180509TH...60-010_1wk storage stability 2018-05-10 11-11-53\0509-1 S2.D)
mAU
250
200
150
100
50
0
min
2
4
6
8
10
12
0.432
0.614
0.939
1.076
N-acetyl tryptophan
API
5.580
6.373
7.041
Albumin product
11.369
11.772
12.921

FIG. 2

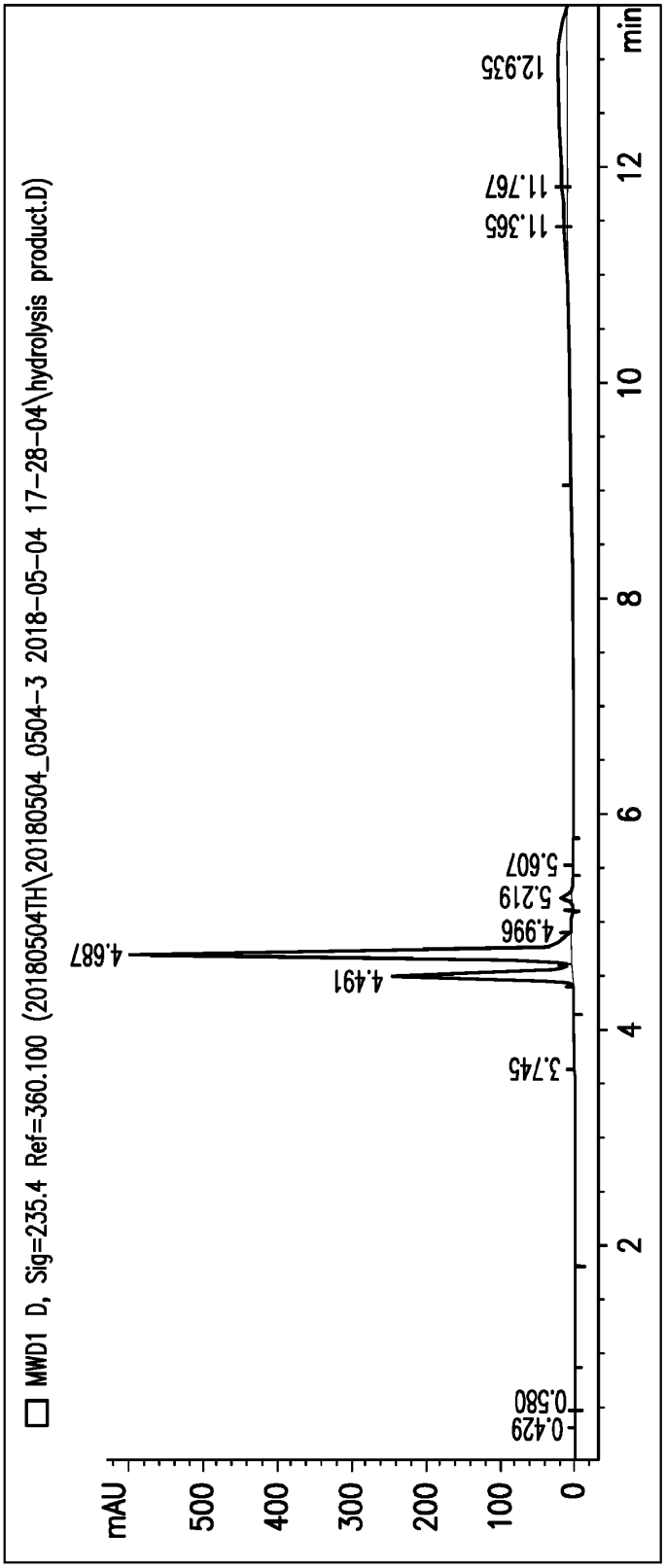

MWD1 D, Sig=235.4 Ref=360.100 (20180504TH\20180504_0504-3 2018-05-04 17-28-04\hydrolysis product.D)
mAU
500
400
300
200
100
0
min
2
4
6
8
10
12
0.429
0.580
3.745
4.491
4.687
4.996
5.219
5.607
11.365
11.767
12.935

FIG. 3

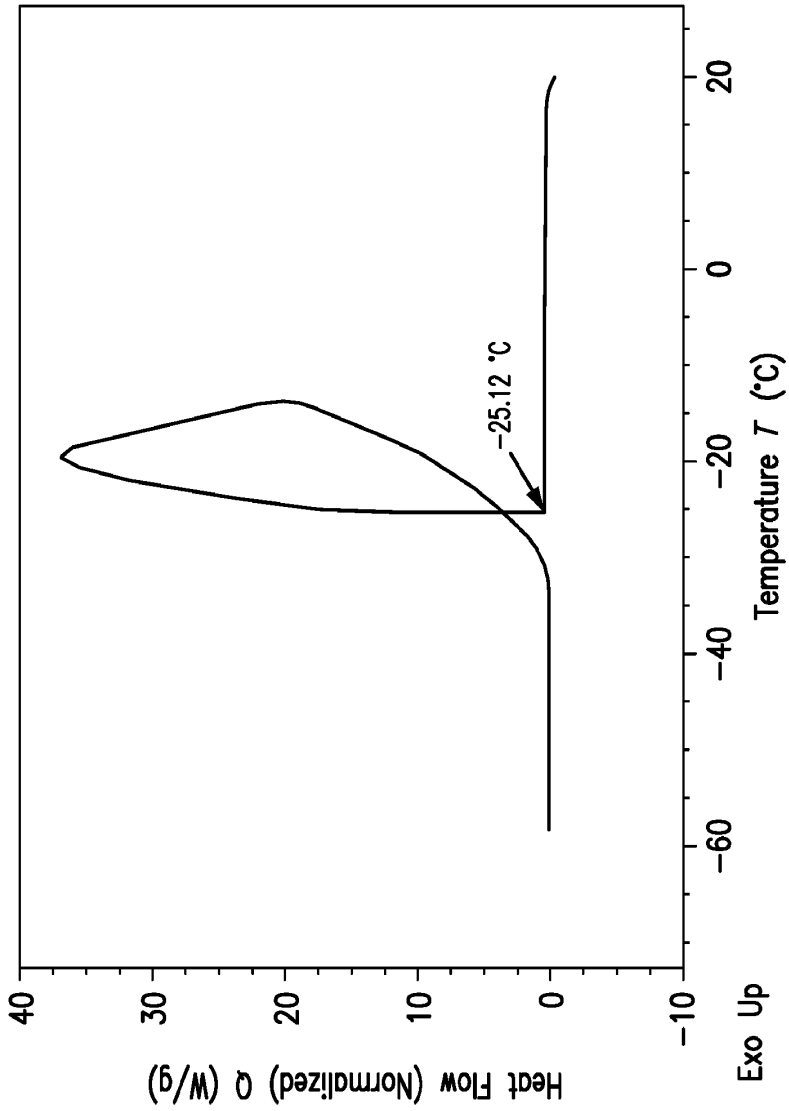

Heat Flow (Normalized) Q (W/g)
40
30
20
10
0
−10
Exo Up
−25.12 °C
20
0
−20
−40
−60
Temperature T (°C)

FIG. 4

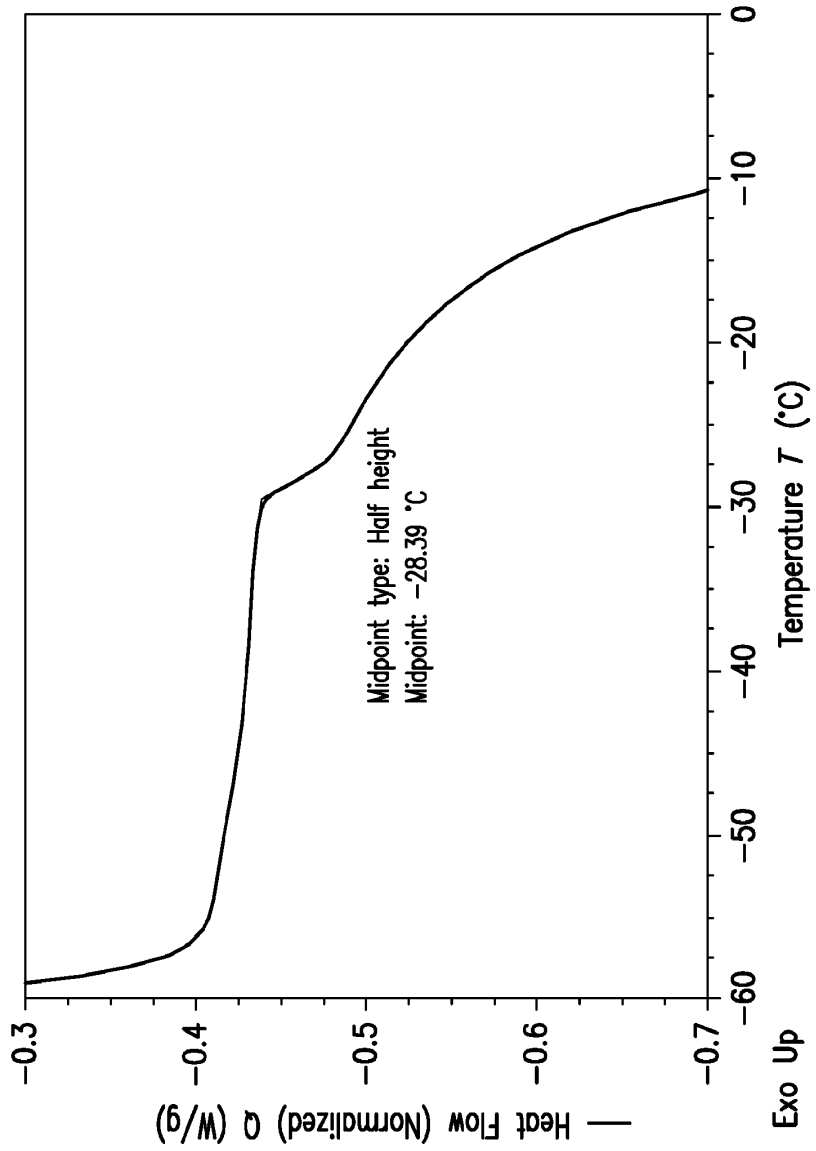

Midpoint type: Half height
Midpoint: −28.39 °C
Temperature T (°C)
0
−10
−20
−30
−40
−50
−60
−0.3
−0.4
−0.5
−0.6
−0.7
Heat Flow (Normalized) Q (W/g)
Exo Up

FIG. 5

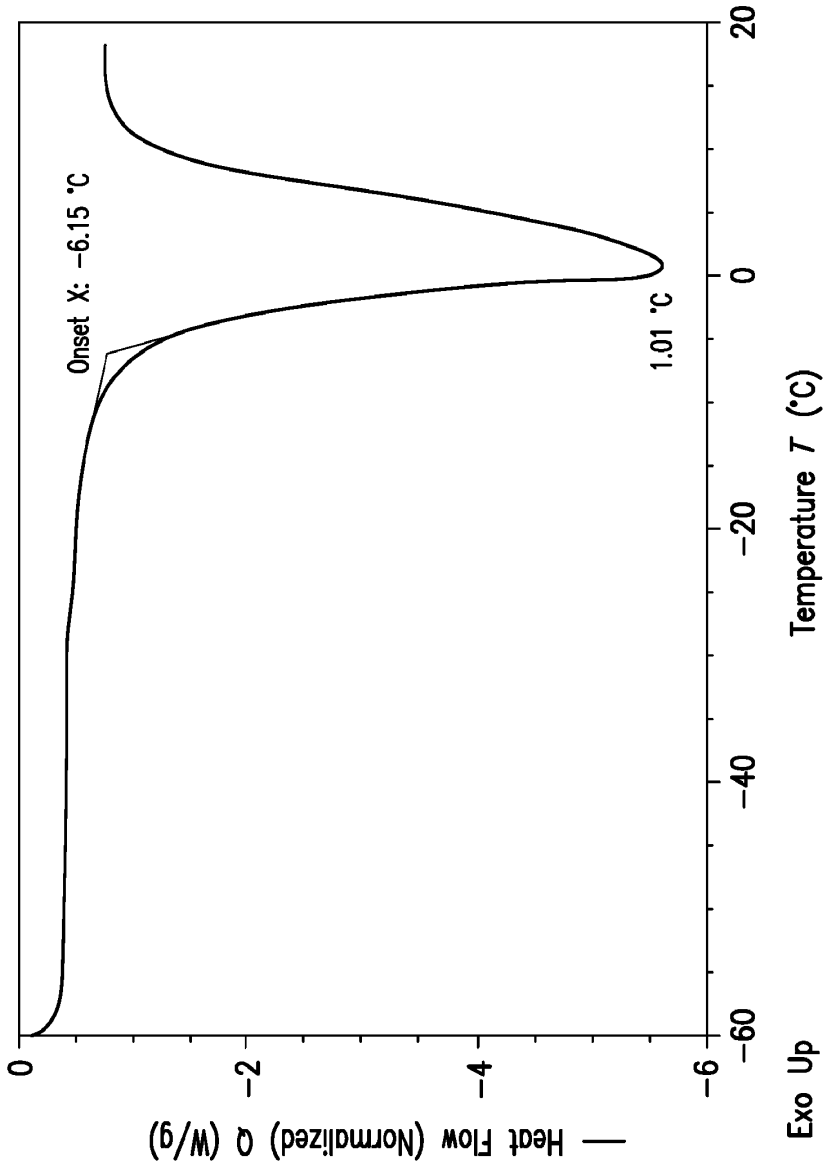

Onset X: −6.15 °C
1.01 °C
Heat Flow (Normalized) Q (W/g)
Exo Up
Temperature T (°C)
0
−2
−4
−6
20
0
−20
−40
−60

FIG. 6

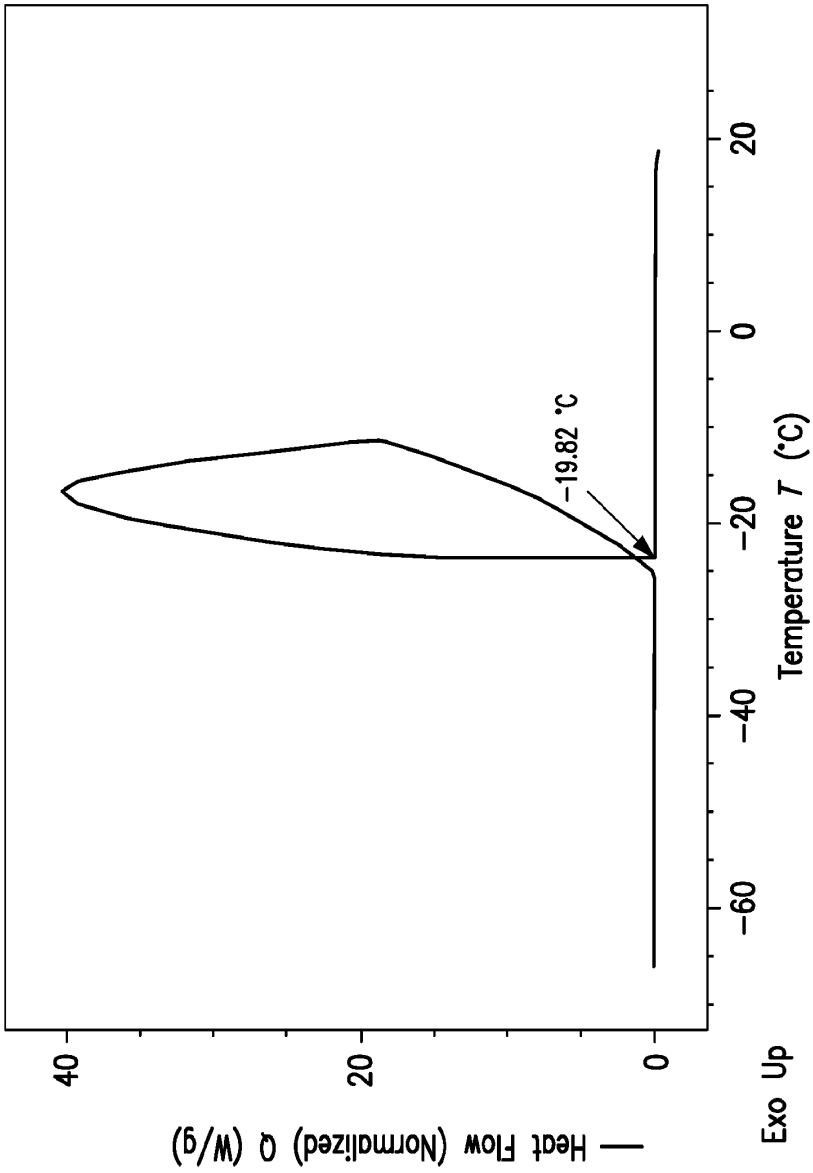

−19.82 °C
Temperature T (°C)
20
0
−20
−40
−60
Exo Up
— Heat Flow (Normalized) Q (W/g)
40
20
0

FIG. 7

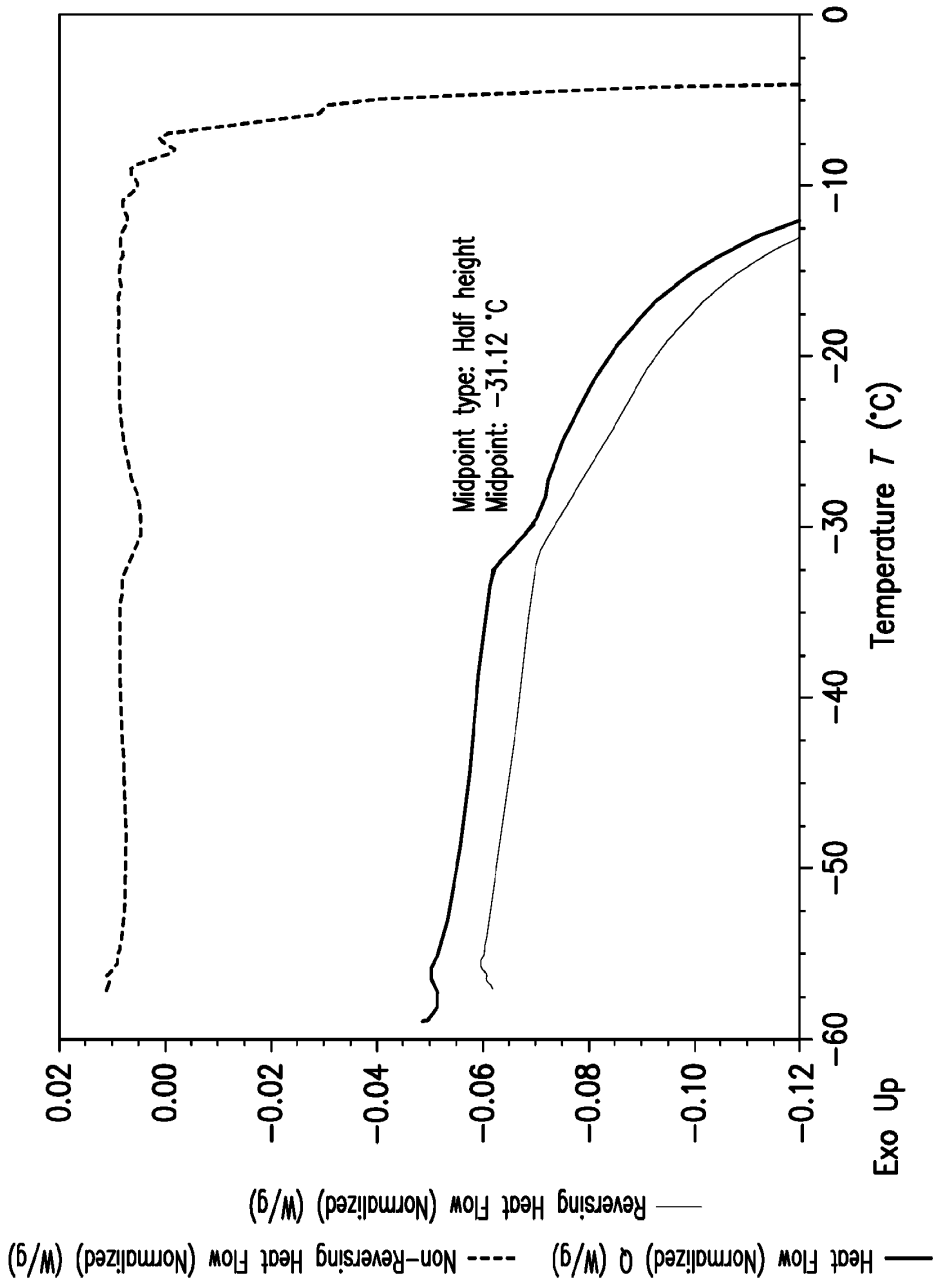

Heat Flow (Normalized) Q (W/g)
Non-Reversing Heat Flow (Normalized) (W/g)
Reversing Heat Flow (Normalized) (W/g)
Midpoint type: Half height
Midpoint: -31.12 °C
Temperature T (°C)
Exo Up
0.02
0.00
-0.02
-0.04
-0.06
-0.08
-0.10
-0.12
0
-10
-20
-30
-40
-50
-60

FIG. 8

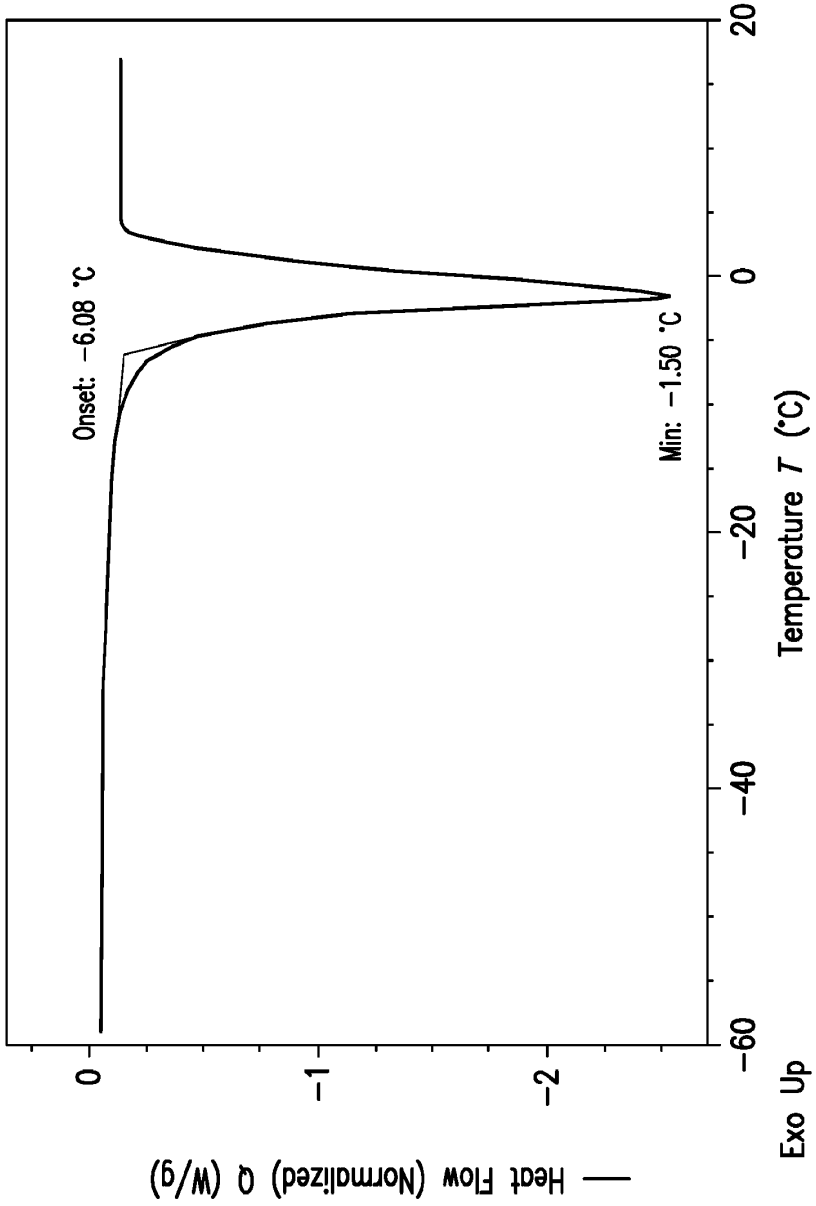

Onset: −6.08 °C
Min: −1.50 °C
Temperature T (°C)
20
0
−20
−40
−60
Exo Up
0
−1
−2
Heat Flow (Normalized) Q (W/g)

FIG. 9

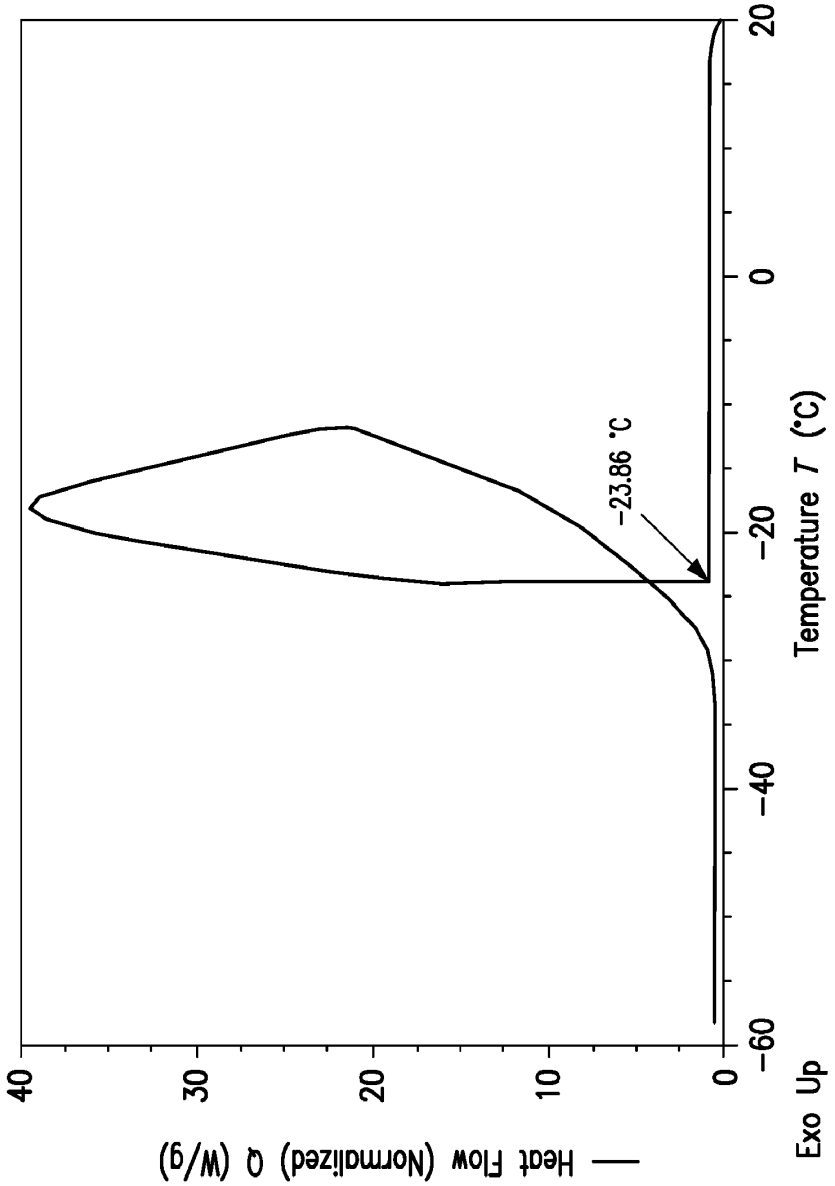

Heat Flow (Normalized) Q (W/g)
40
30
20
10
0
Exo Up
−60
−40
−20
0
20
Temperature T (°C)
−23.86 °C

FIG. 10

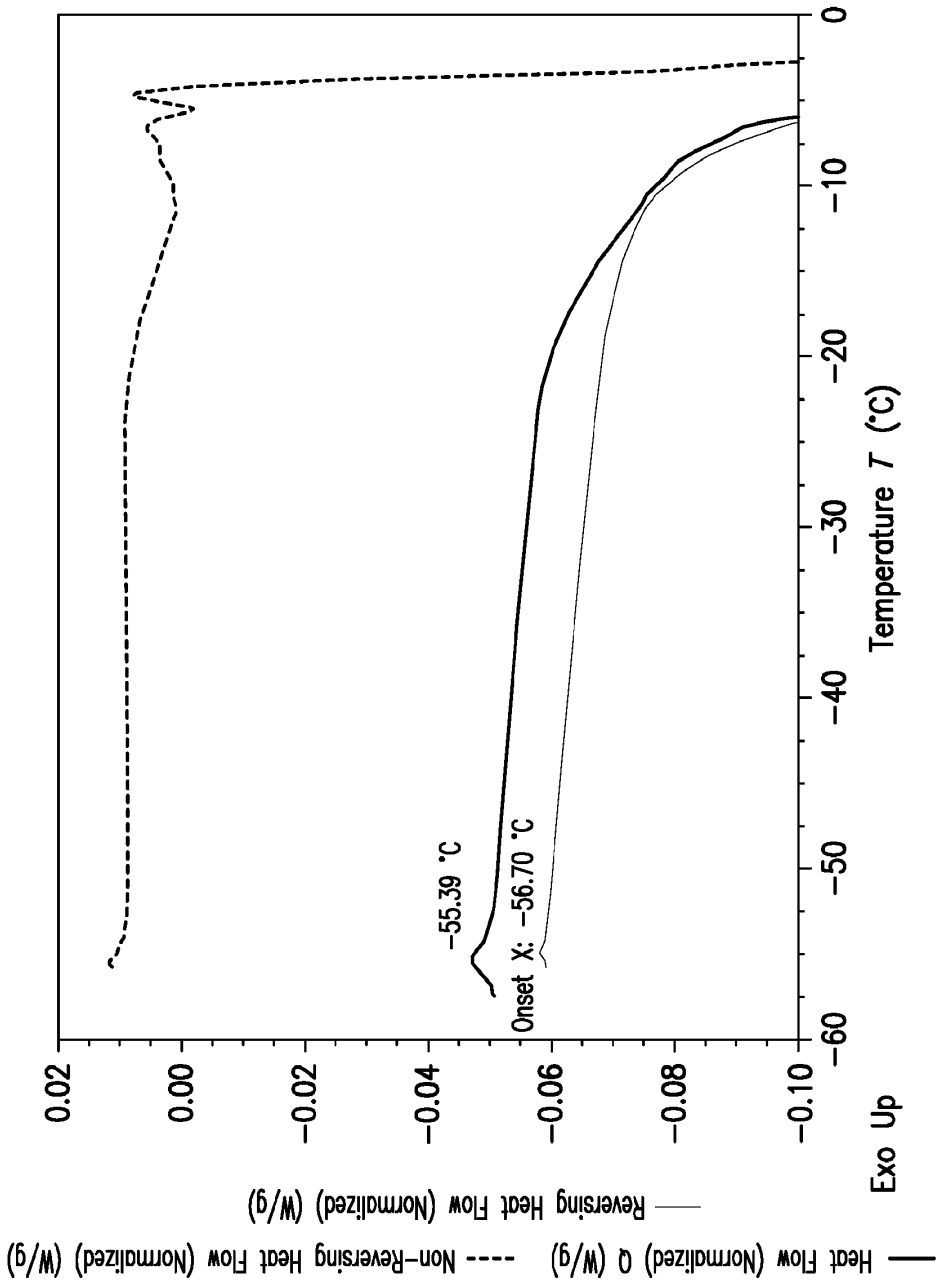

Heat Flow (Normalized) Q (W/g)
Non-Reversing Heat Flow (Normalized) (W/g)
Reversing Heat Flow (Normalized) (W/g)
Exo Up
0.02
0.00
-0.02
-0.04
-0.06
-0.08
-0.10
0
-10
-20
-30
-40
-50
-60
Temperature T (°C)
Onset X: -56.70 °C
-55.39 °C

FIG. 11

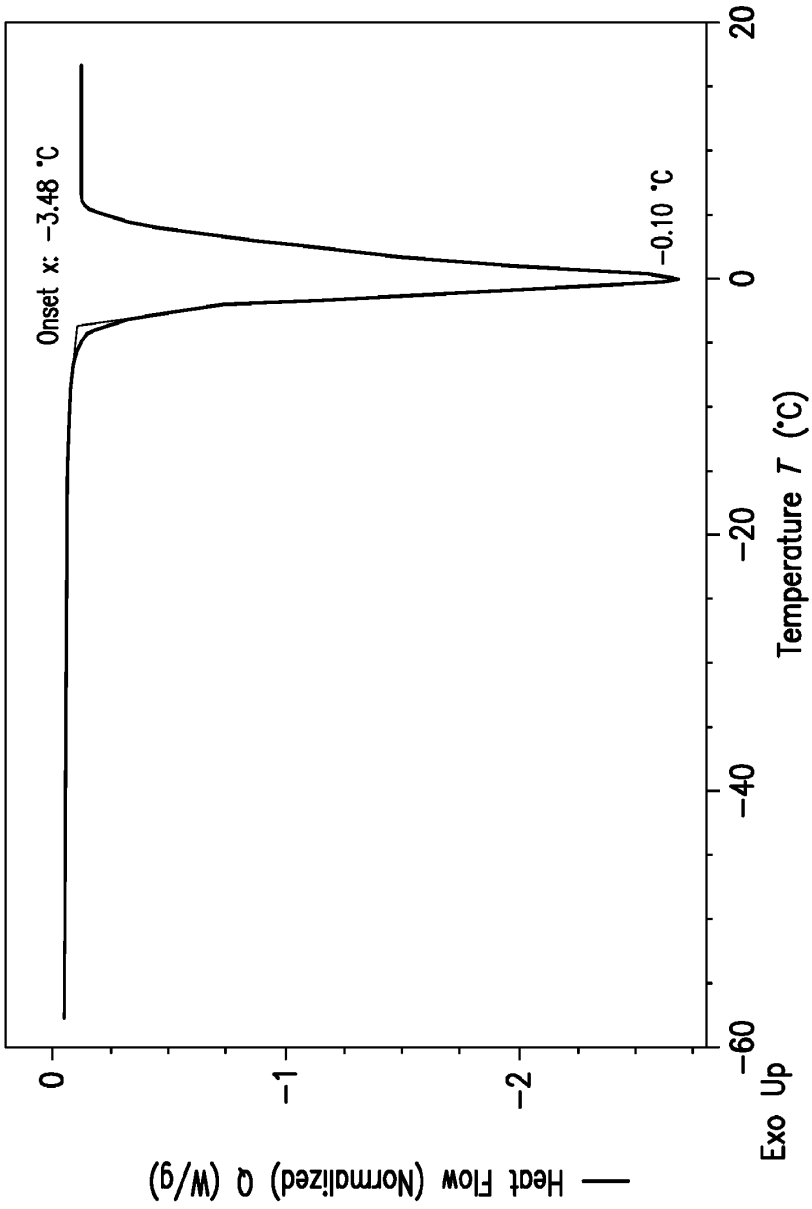

Onset x: −3.48 °C
−0.10 °C
Heat Flow (Normalized) Q (W/g)
Exo Up
Temperature T (°C)
0
−1
−2
20
0
−20
−40
−60

FIG. 12

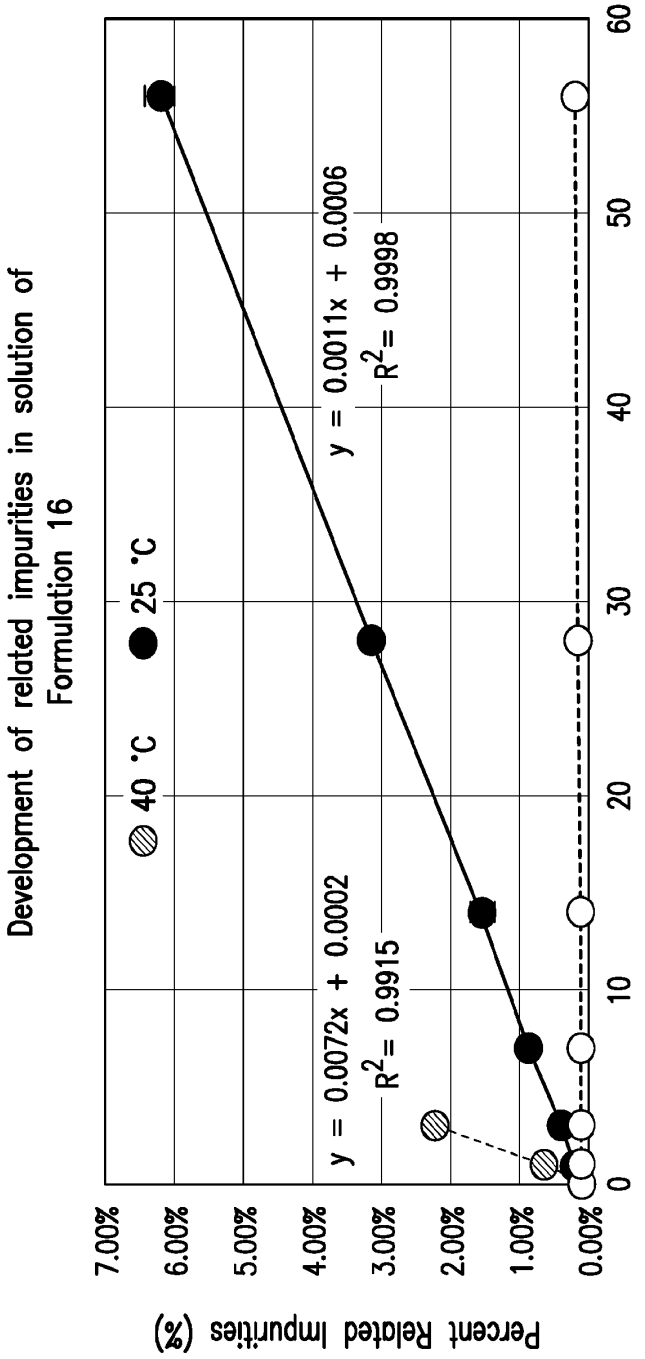

Development of related impurities in solution of Formulation 16
40 °C
25 °C
y = 0.0072x + 0.0002
R2= 0.9915
y = 0.0011x + 0.0006
R2= 0.9998
Percent Related Impurities (%)
7.00%
6.00%
5.00%
4.00%
3.00%
2.00%
1.00%
0.00%
0
10
20
30
40
50
60
Time (Days)

FIG. 13

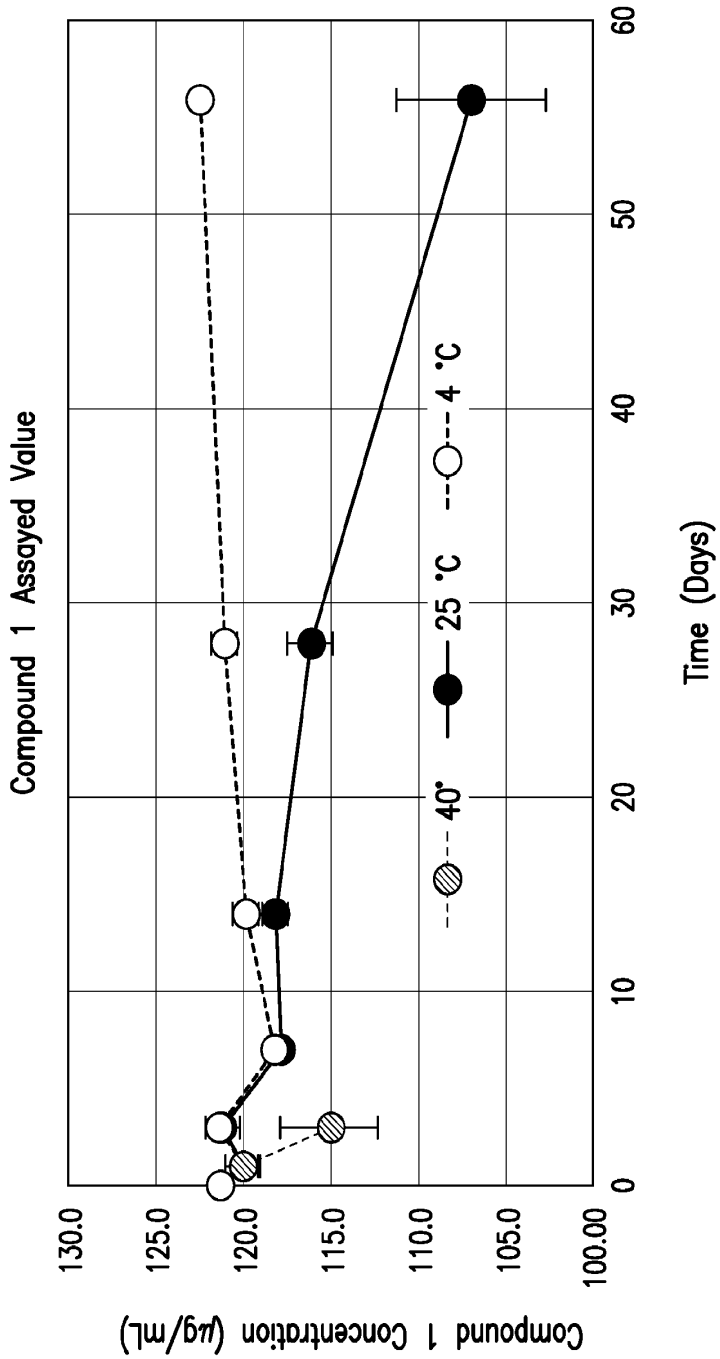

Compound 1 Assayed Value
Compound 1 Concentration (µg/mL)
130.0
125.0
120.0
115.0
110.0
105.0
100.00
0
10
20
30
40
50
60
Time (Days)
4 °C
25 °C
40°

FIG. 14

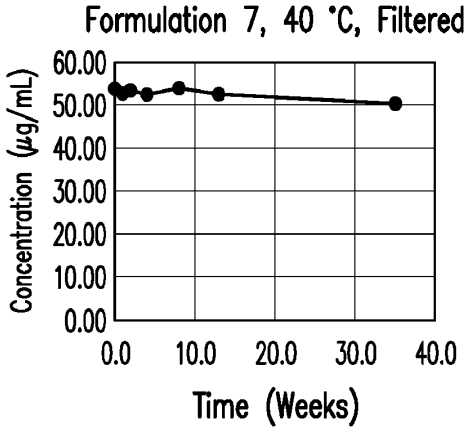


FIG. 15A

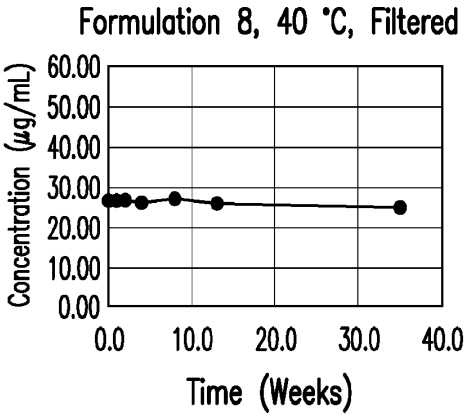


FIG. 15B

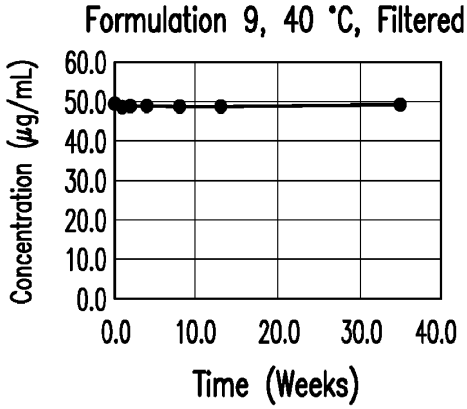


FIG. 15C

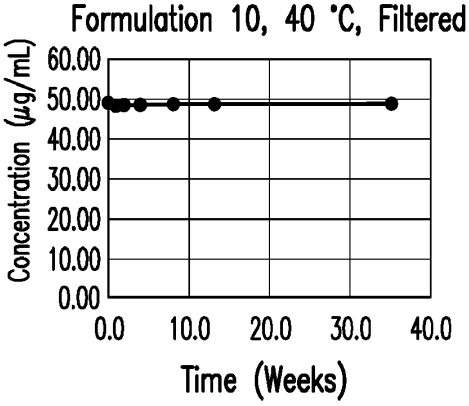


FIG. 15D

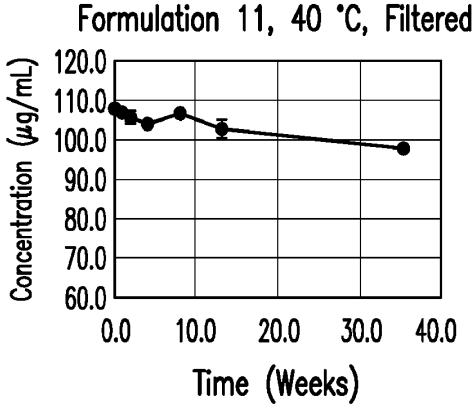


FIG. 15E

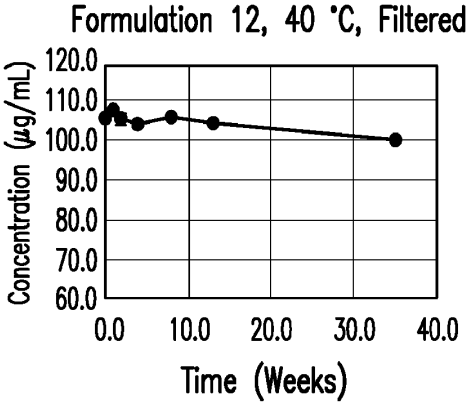


FIG. 15F

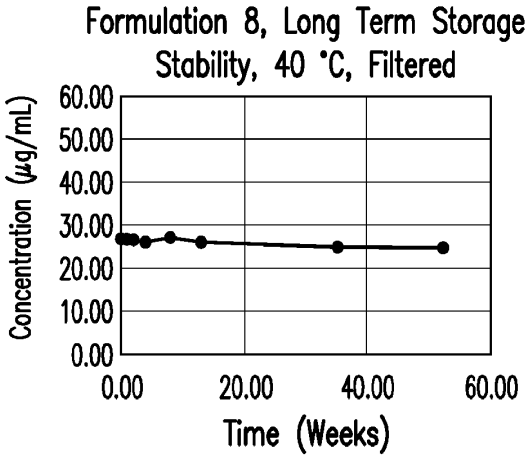


FIG. 16A

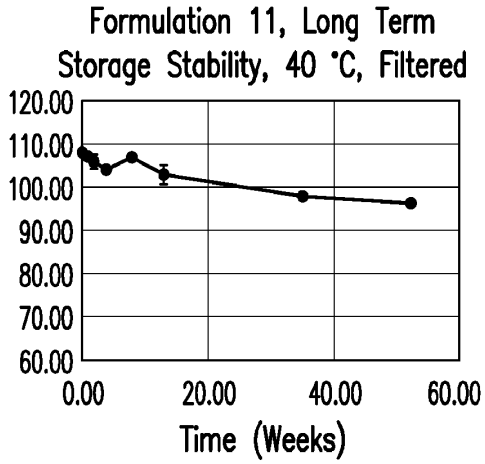


FIG. 16B

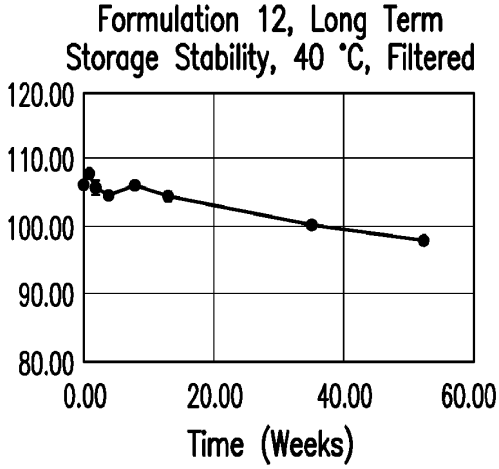
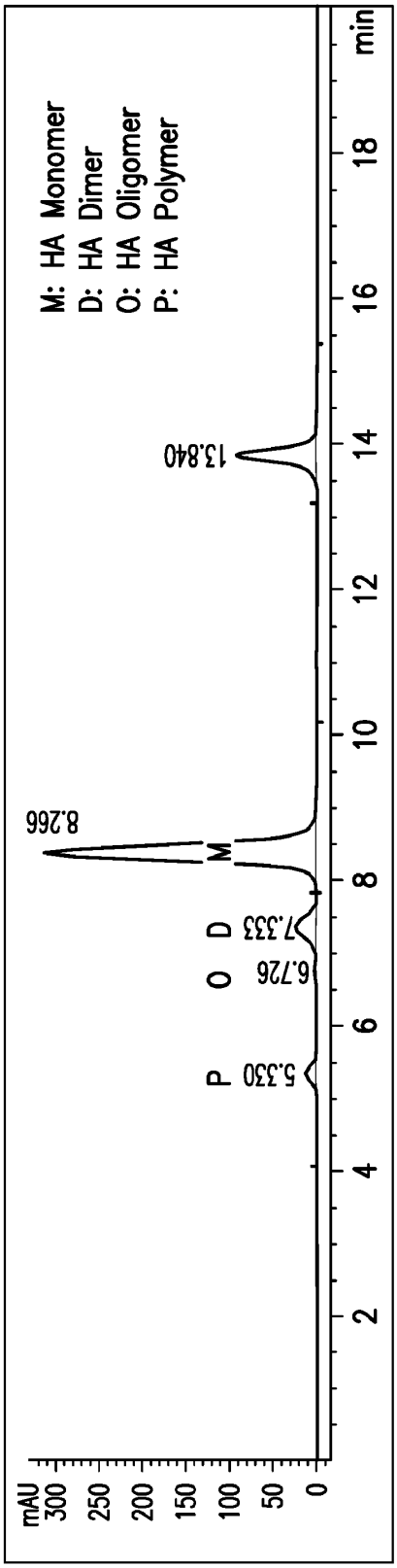


FIG. 16C



Analytical Method:
Column: TOSOH Bioscience, LLC TSKgel G300SW 7.8 mm ID x 30 cm, 5 μm column #S7363-06R
Mobile Phase: 0.10 M K_2HPO_4
Flow Rate: 1.0 mL/min
Column Temp: Ambient
UV Detection: 228 nm
Injection Volume: 10 μL
Needle Wash: Water
Run Time: 20 minutes

FIG. 17

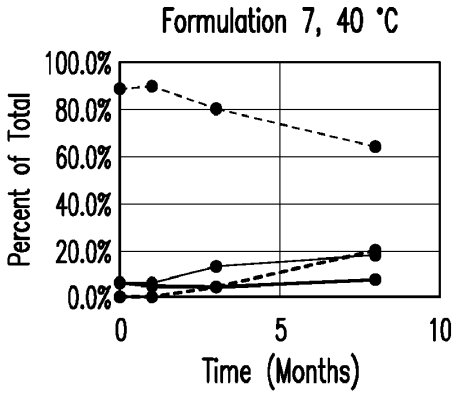


FIG. 18A

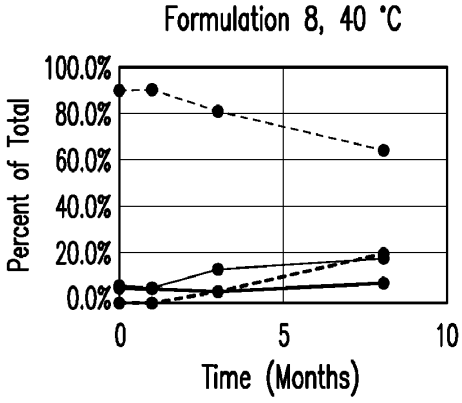


FIG. 18B

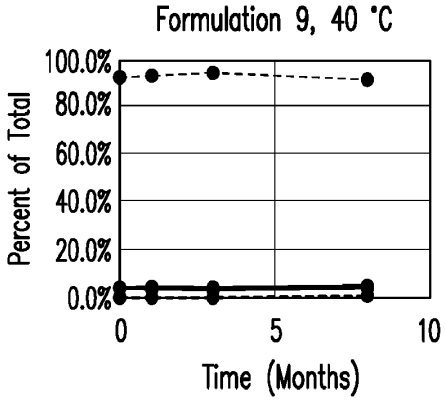


FIG. 18C

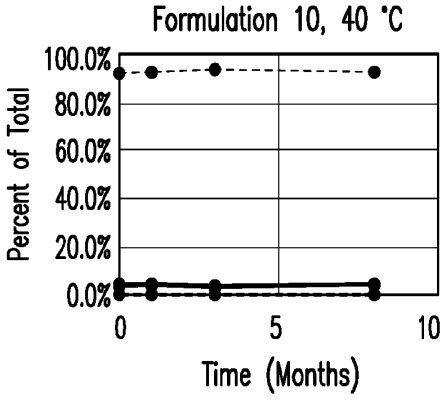


FIG. 18D

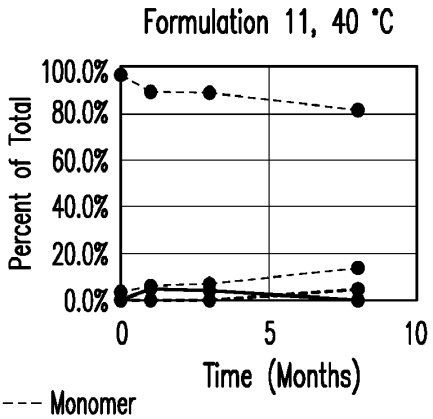


FIG. 18E

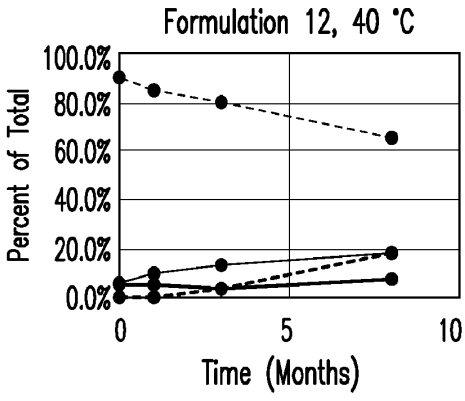
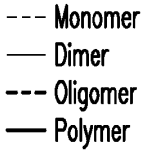


FIG. 18F



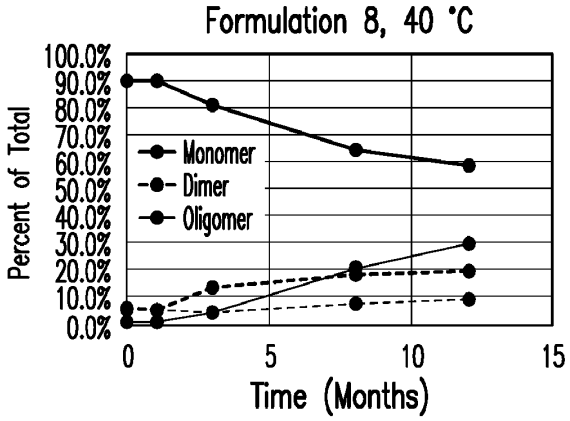


FIG. 19A

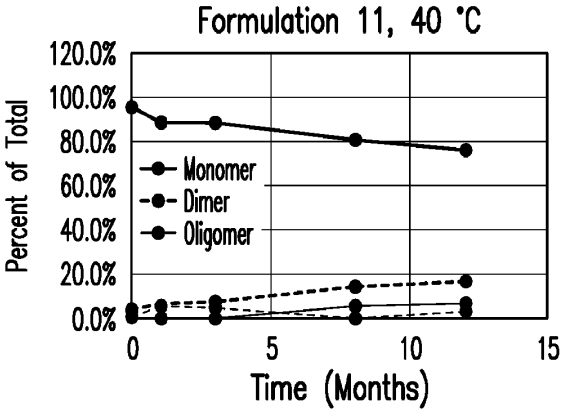


FIG. 19B

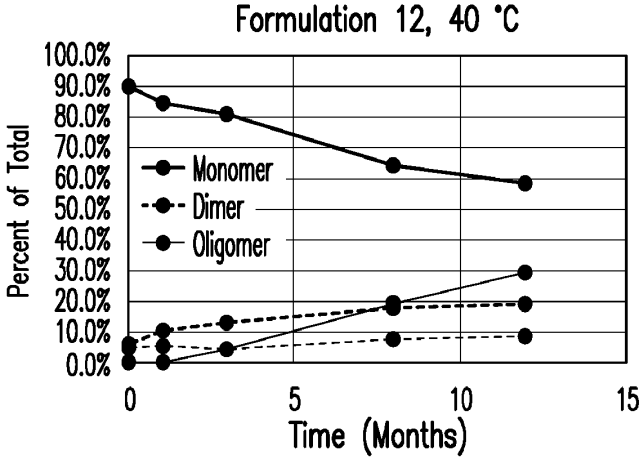


FIG. 19C

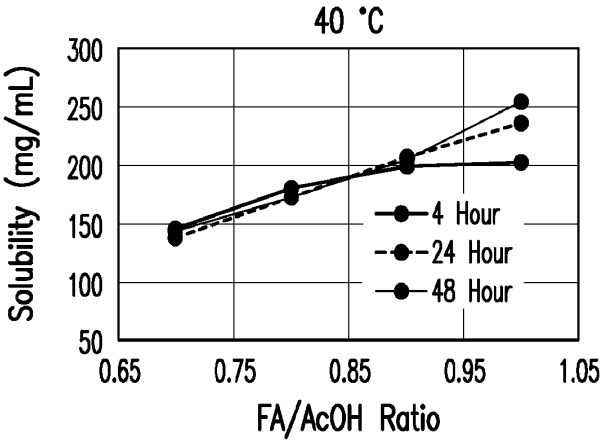


FIG. 20A

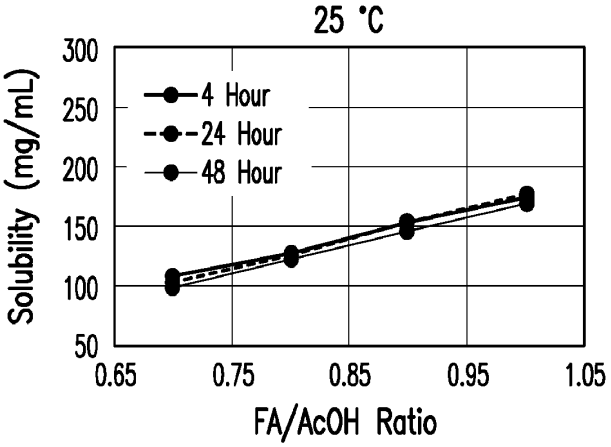


FIG. 20B

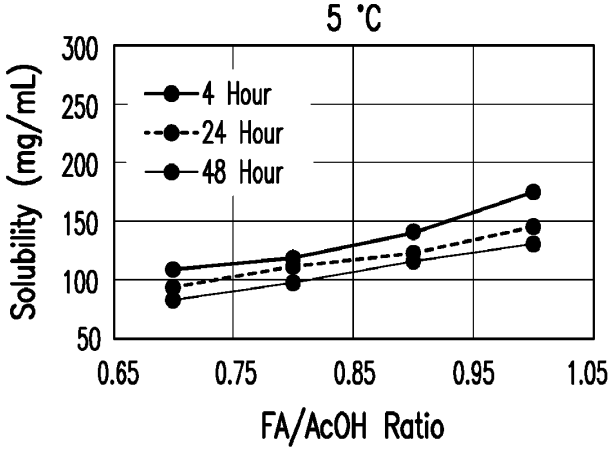


FIG. 20C

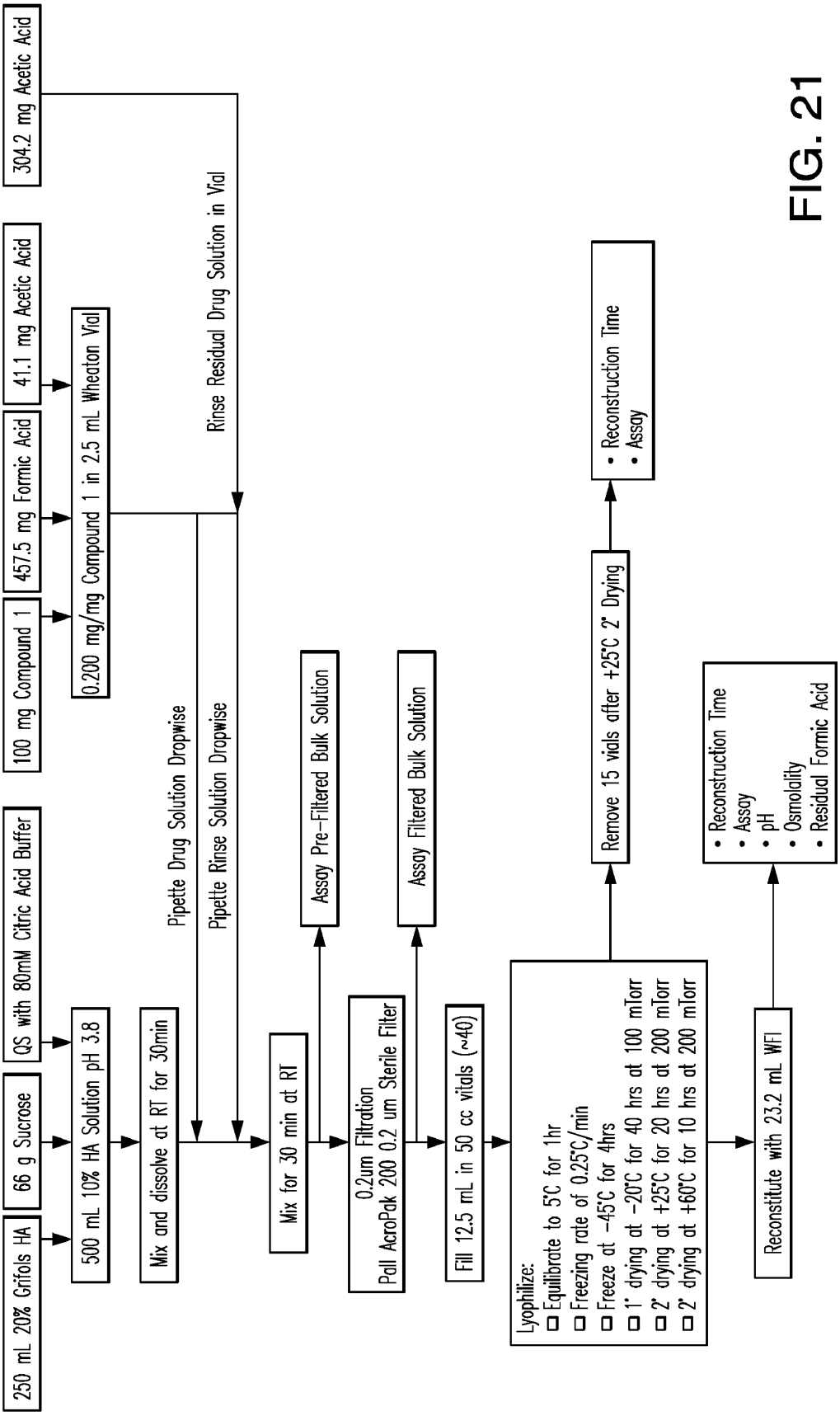

250 mL 20% Grifols HA
66 g Sucrose
QS with 80mM Citric Acid Buffer
500 mL 10% HA Solution pH 3.8
Mix and dissolve at RT for 30min
100 mg Compound 1
457.5 mg Formic Acid
41.1 mg Acetic Acid
304.2 mg Acetic Acid
0.200 mg/mg Compound 1 in 2.5 mL Wheaton Vial
Pipette Drug Solution Dropwise
Pipette Rinse Solution Dropwise
Rinse Residual Drug Solution in Vial
Mix for 30 min at RT
Assay Pre-Filtered Bulk Solution
0.2um Filtration
Pall AcroPak 200 0.2 um Sterile Filter
Assay Filtered Bulk Solution
Fill 12.5 mL in 50 cc vitals (~40)
Lyophilize:
Equilibrate to 5°C for 1hr
Freezing rate of 0.25°C/min
Freeze at -45°C for 4hrs
1° drying at -20°C for 40 hrs at 100 mTorr
2° drying at +25°C for 20 hrs at 200 mTorr
2° drying at +60°C for 10 hrs at 200 mTorr
Remove 15 vials after +25°C 2° Drying
• Reconstruction Time
• Assay
Reconstitute with 23.2 mL WFI
• Reconstruction Time
• Assay
• pH
• Osmolality
• Residual Formic Acid

FIG. 21

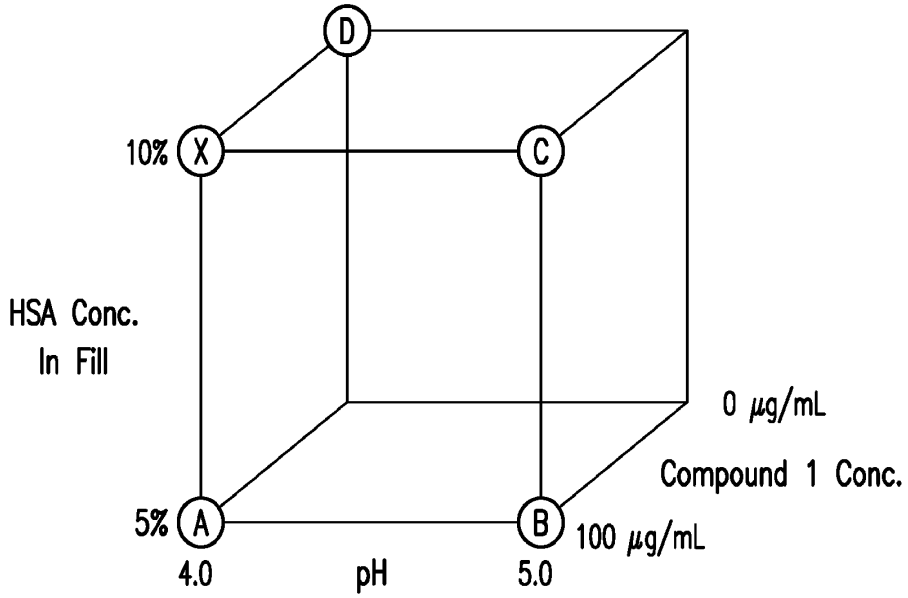

D
10%
X
C
HSA Conc.
In Fill
0 µg/mL
Compound 1 Conc.
5%
A
B
100 µg/mL
4.0
pH
5.0

FIG. 22

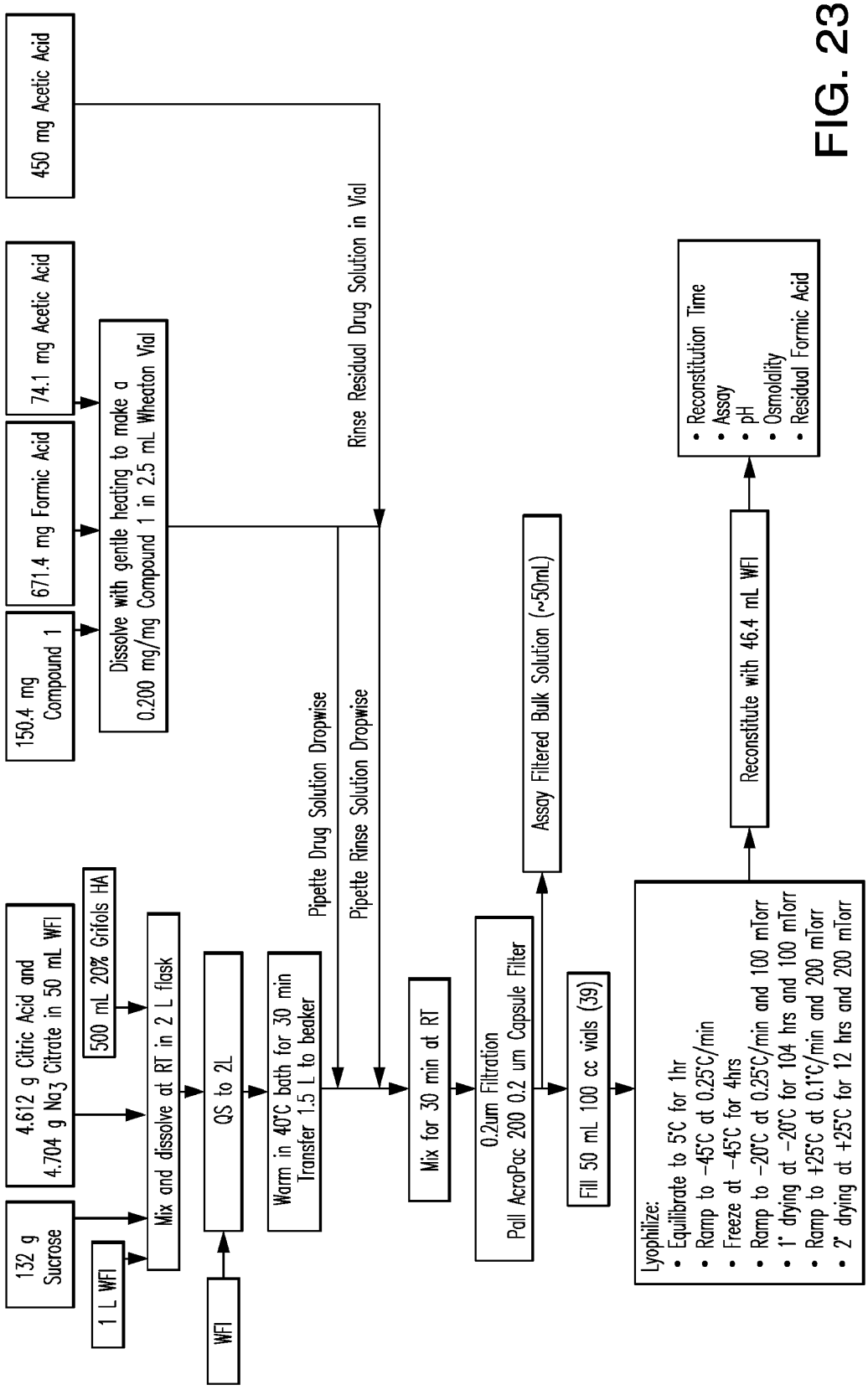

132 g Sucrose
1 L WFI
4.612 g Citric Acid and 4.704 g Na3 Citrate in 50 mL WFI
500 mL 20% Grifols HA
Mix and dissolve at RT in 2 L flask
WFI
QS to 2L
Warm in 40°C bath for 30 min
Transfer 1.5 L to beaker
150.4 mg Compound 1
671.4 mg Formic Acid
74.1 mg Acetic Acid
Dissolve with gentle heating to make a 0.200 mg/mg Compound 1 in 2.5 mL Wheaton Vial
450 mg Acetic Acid
Pipette Drug Solution Dropwise
Pipette Rinse Solution Dropwise
Rinse Residual Drug Solution in Vial
Mix for 30 min at RT
0.2um Filtration
Pall AcroPac 200 0.2 um Capsule Filter
Assay Filtered Bulk Solution (~50mL)
Fill 50 mL 100 cc vials (39)
Lyophilize:
• Equilibrate to 5°C for 1hr
• Ramp to -45°C at 0.25°C/min
• Freeze at -45°C for 4hrs
• Ramp to -20°C at 0.25°C/min and 100 mTorr
• 1° drying at -20°C for 104 hrs and 100 mTorr
• Ramp to +25°C at 0.1°C/min and 200 mTorr
• 2° drying at +25°C for 12 hrs and 200 mTorr
Reconstitute with 46.4 mL WFI
• Reconstitution Time
• Assay
• pH
• Osmolality
• Residual Formic Acid

FIG. 23

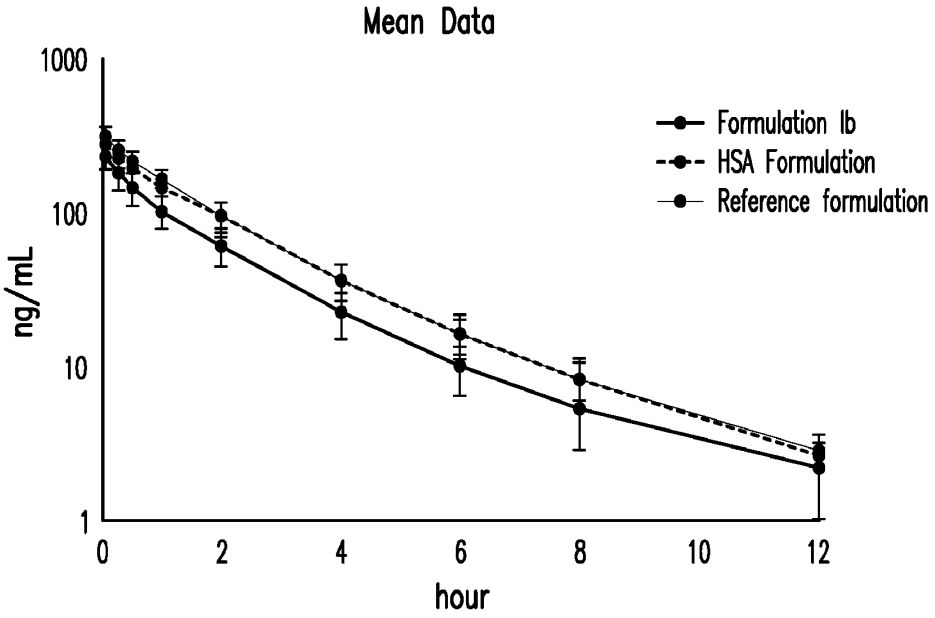

Mean Data
1000
100
10
1
ng/mL
0
2
4
6
8
10
12
hour
Formulation Ib
HSA Formulation
Reference formulation

FIG. 24

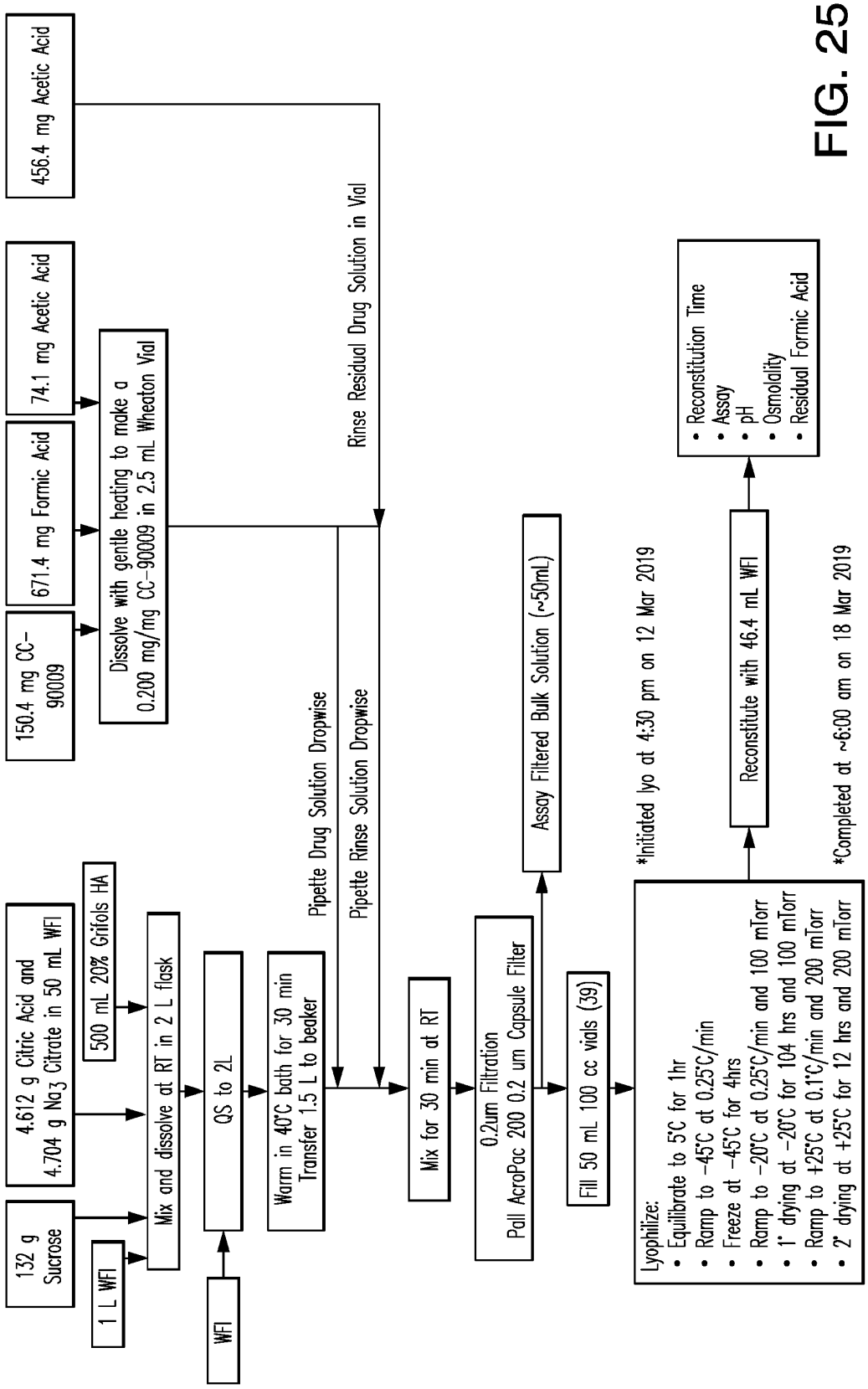

132 g Sucrose
1 L WFI
4.612 g Citric Acid and 4.704 g Na_3 Citrate in 50 mL WFI
500 mL 20% Grifols HA
Mix and dissolve at RT in 2 L flask
WFI
QS to 2L
Warm in 40°C bath for 30 min
Transfer 1.5 L to beaker
Pipette Drug Solution Dropwise
Pipette Rinse Solution Dropwise
Mix for 30 min at RT
0.2um Filtration
Pall AcroPac 200 0.2 um Capsule Filter
Assay Filtered Bulk Solution (~50mL)
Fill 50 mL 100 cc vials (39)
Lyophilize:
• Equilibrate to 5°C for 1hr
• Ramp to -45°C at 0.25°C/min
• Freeze at -45°C for 4hrs
• Ramp to -20°C at 0.25°C/min and 100 mTorr
• 1° drying at -20°C for 104 hrs and 100 mTorr
• Ramp to +25°C at 0.1°C/min and 200 mTorr
• 2° drying at +25°C for 12 hrs and 200 mTorr
*Initiated lyo at 4:30 pm on 12 Mar 2019
*Completed at ~6:00 am on 18 Mar 2019
Reconstitute with 46.4 mL WFI
• Reconstitution Time
• Assay
• pH
• Osmolality
• Residual Formic Acid
150.4 mg CC-90009
671.4 mg Formic Acid
74.1 mg Acetic Acid
Dissolve with gentle heating to make a 0.200 mg/mg CC-90009 in 2.5 mL Wheaton Vial
Rinse Residual Drug Solution in Vial
456.4 mg Acetic Acid

FIG. 25