FIG. 1

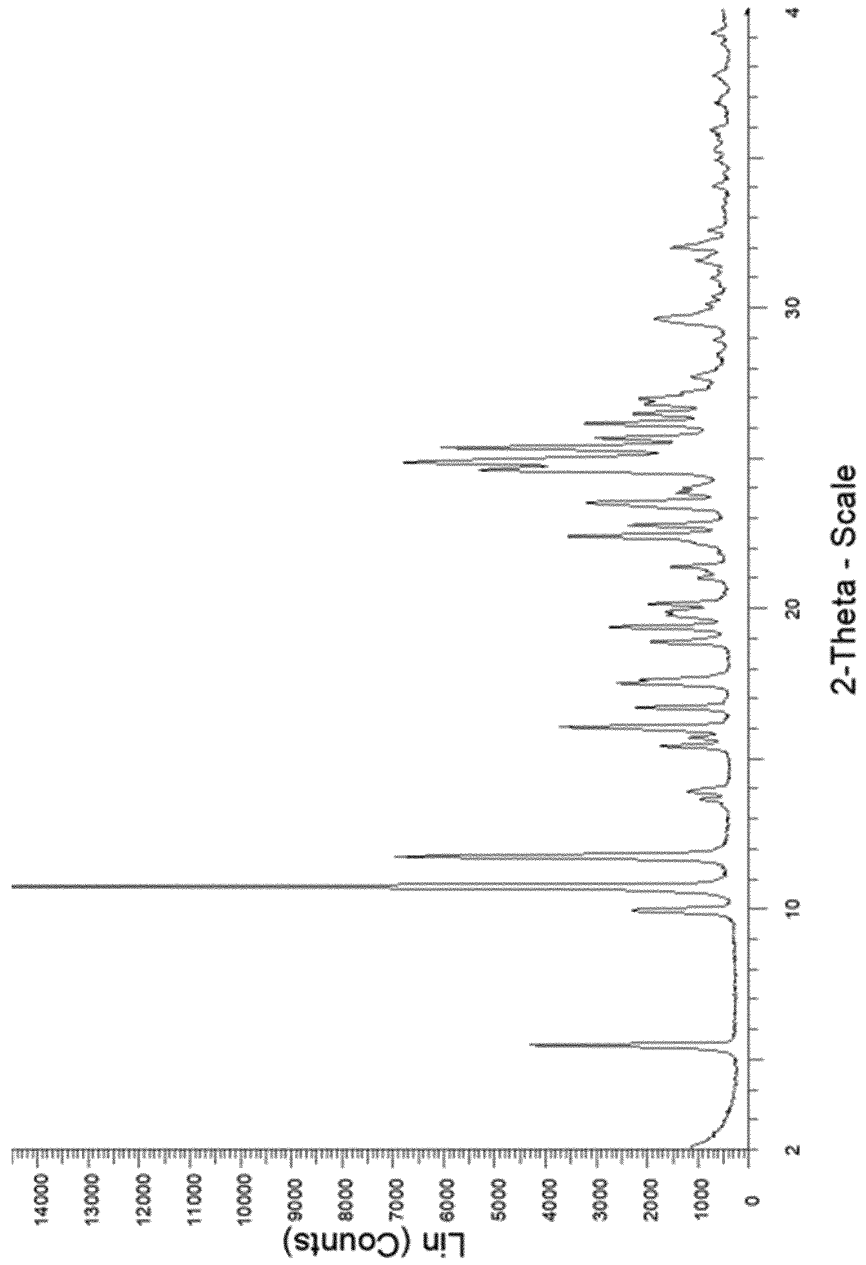

Lin (Counts)
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2
10
20
30
4
2-Theta - Scale

FIG. 2

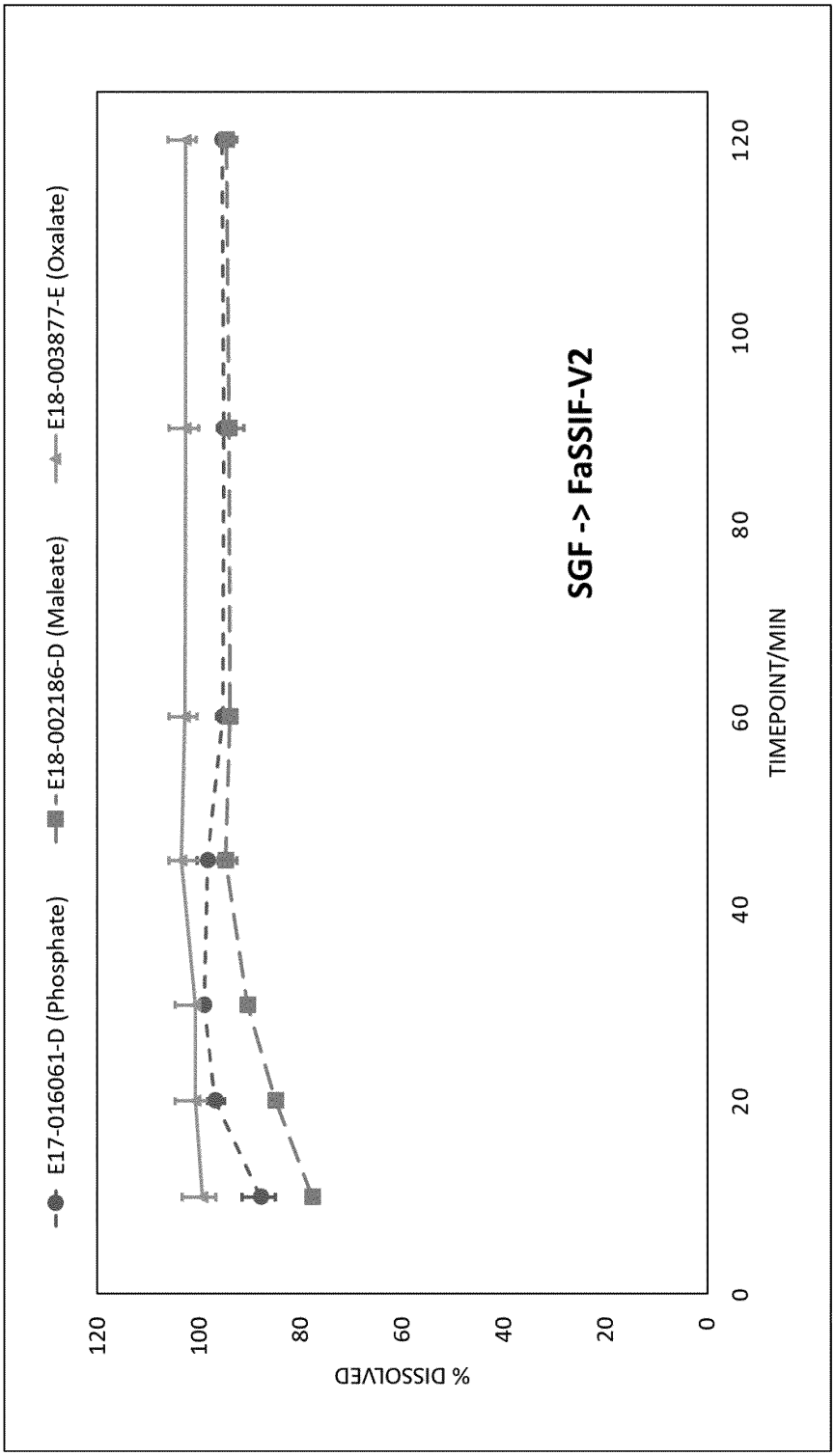

E17-016061-D (Phosphate)
E18-002186-D (Maleate)
E18-003877-E (Oxalate)
SGF -> FaSSIF-V2
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120

FIG. 3

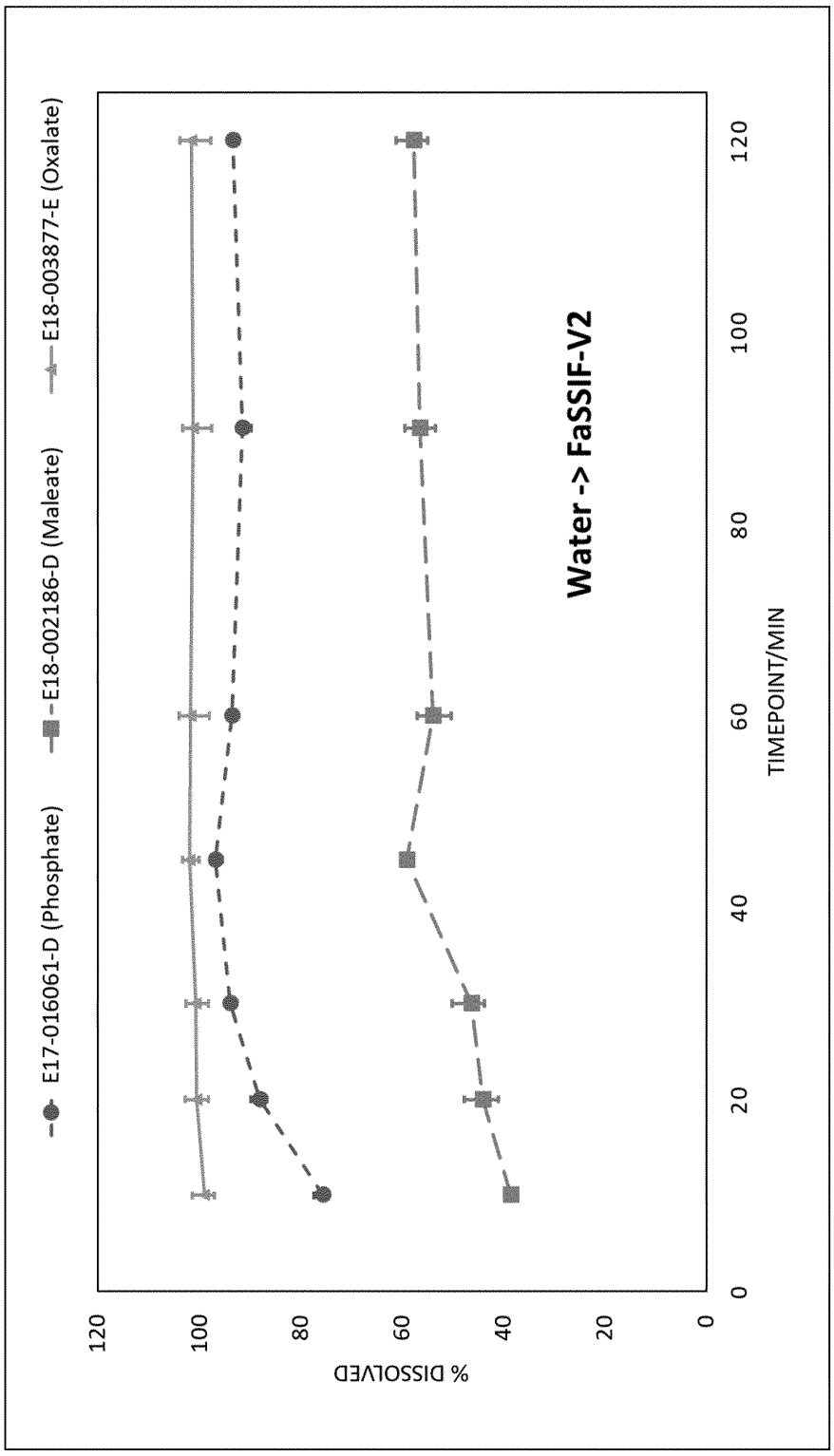

E17-016061-D (Phosphate)
E18-002186-D (Maleate)
E18-003877-E (Oxalate)
Water -> FaSSIF-V2
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120

FIG. 4

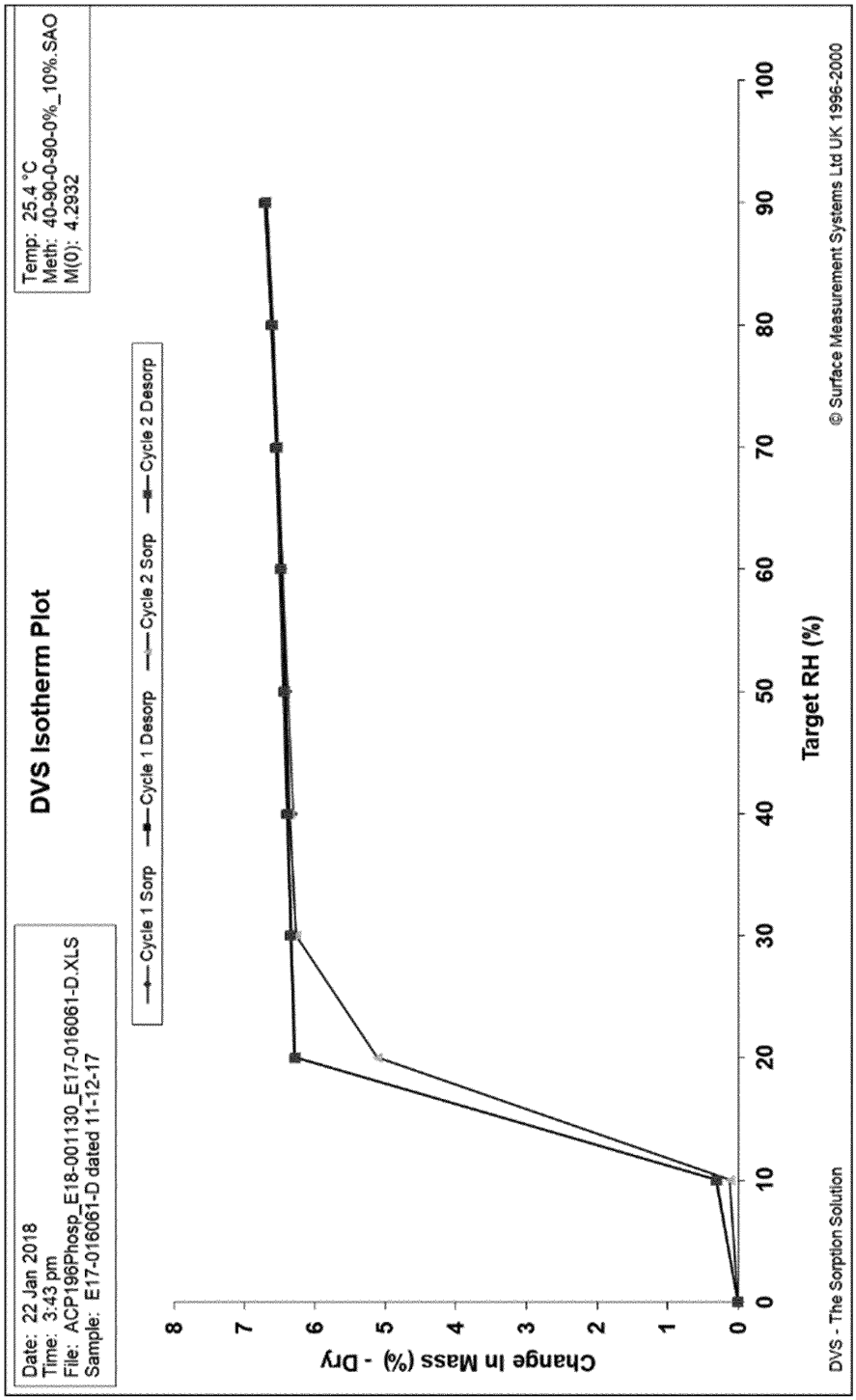

DVS Isotherm Plot
Date: 22 Jan 2018
Time: 3:43 pm
File: ACP196Phosp_E18-001130_E17-016061-D.XLS
Sample: E17-016061-D dated 11-12-17
Temp: 25.4 °C
Meth: 40-90-0-90-0%_10%.SAO
M(0): 4.2932
Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Sorp
Cycle 2 Desorp
Change In Mass (%) - Dry
Target RH (%)
0
1
2
3
4
5
6
7
8
0
10
20
30
40
50
60
70
80
90
100
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FIG. 5

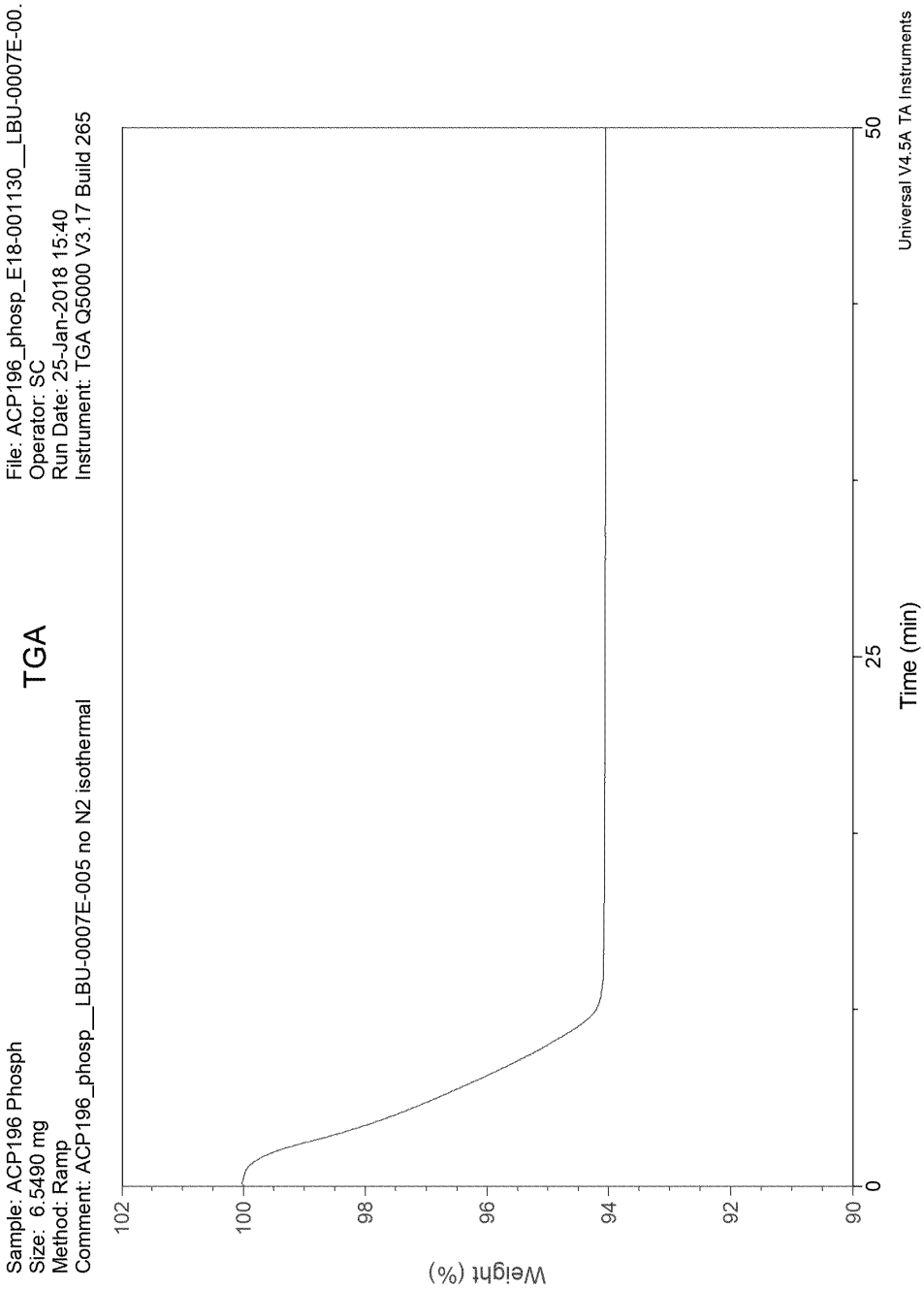

TGA
Sample: ACP196 Phosph
Size: 6.5490 mg
Method: Ramp
Comment: ACP196_phosp__LBU-0007E-005 no N2 isothermal
File: ACP196_phosp_E18-001130__LBU-0007E-00.
Operator: SC
Run Date: 25-Jan-2018 15:40
Instrument: TGA Q5000 V3.17 Build 265
Weight (%)
102
100
98
96
94
92
90
0
25
50
Time (min)
Universal V4.5A TA Instruments

FIG. 6

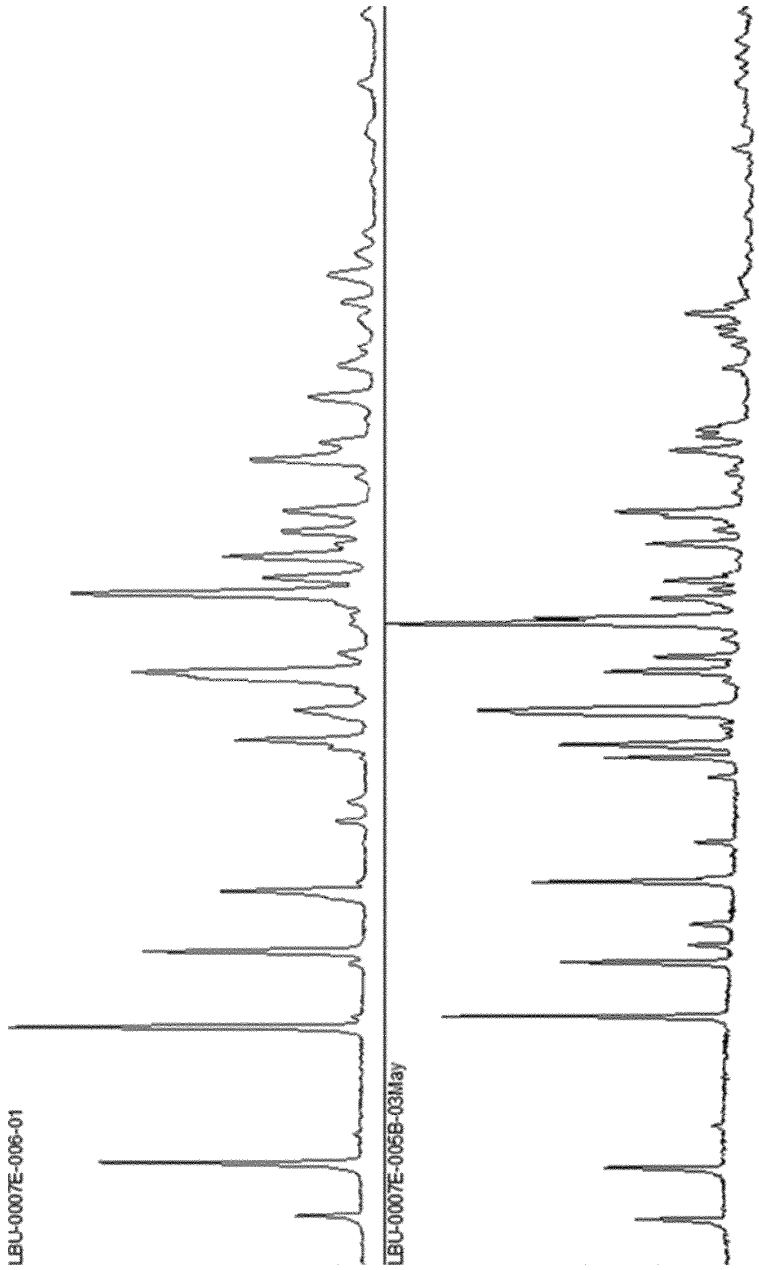


FIG. 7

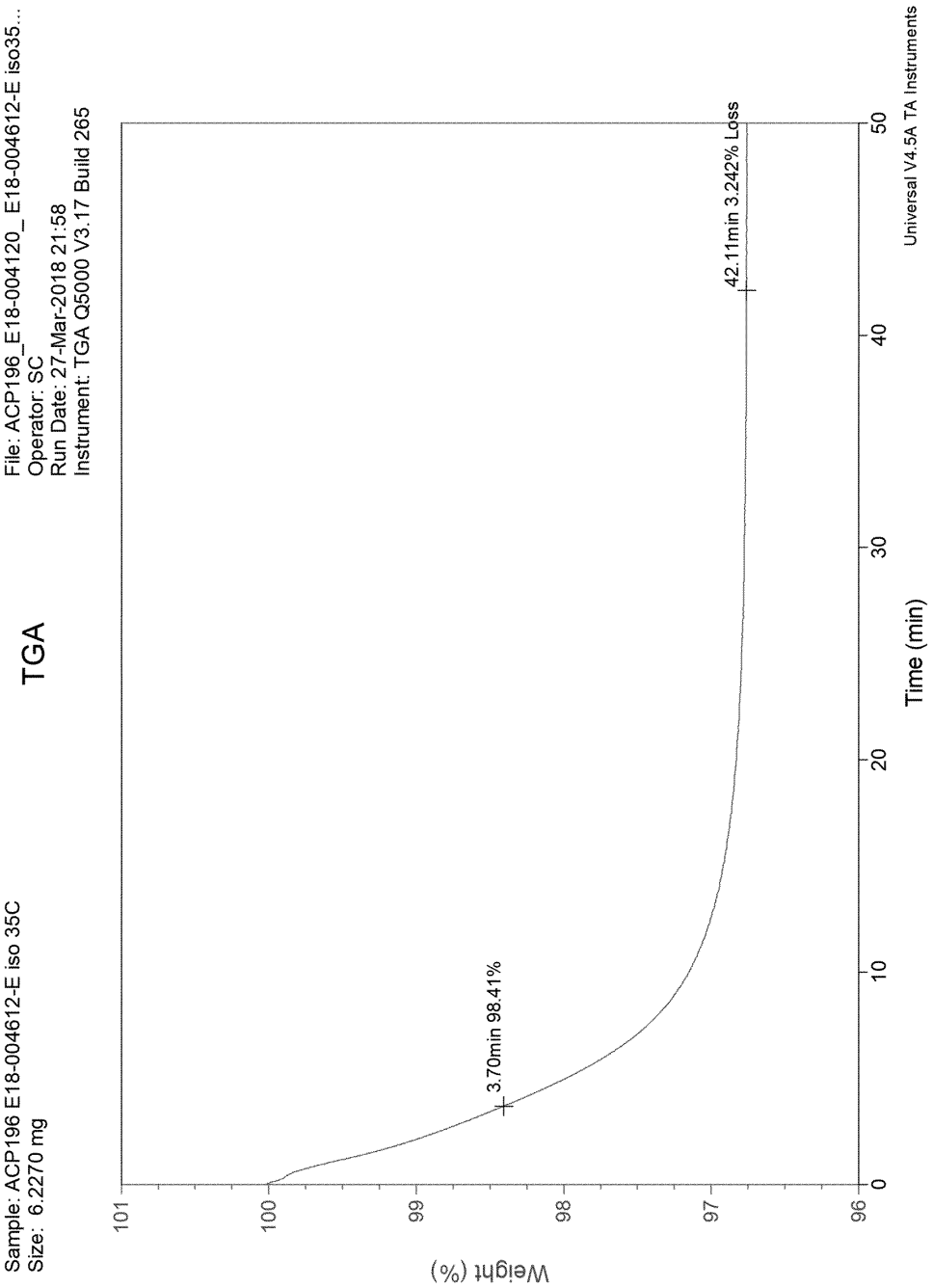

TGA
File: ACP196_E18-004120_ E18-004612-E iso35...
Operator: SC
Run Date: 27-Mar-2018 21:58
Instrument: TGA Q5000 V3.17 Build 265
Sample: ACP196 E18-004612-E iso 35C
Size: 6.2270 mg
3.70min 98.41%
42.11min 3.242% Loss
Weight (%)
Time (min)
Universal V4.5A TA Instruments

FIG. 8

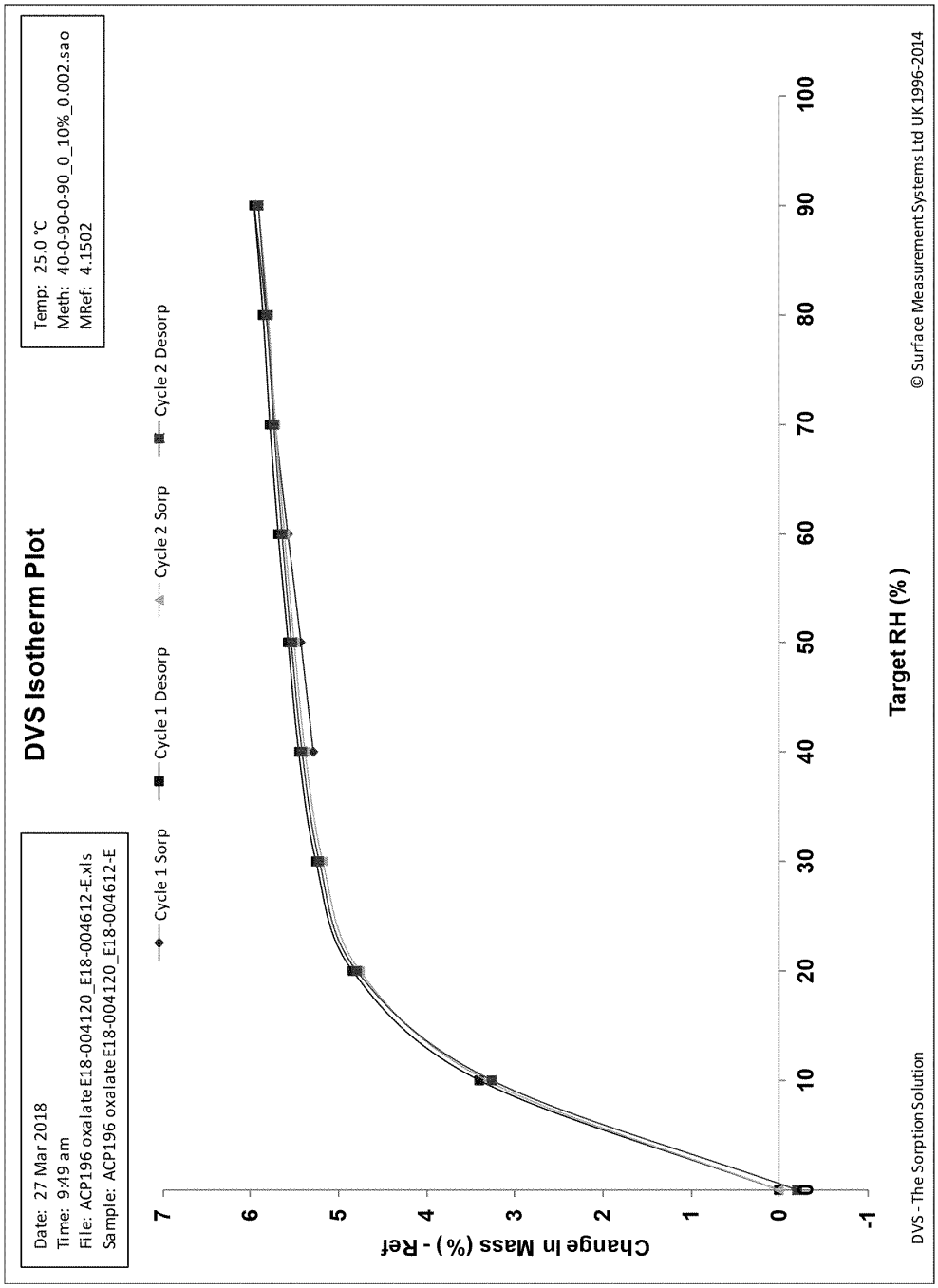

DVS Isotherm Plot
Date: 27 Mar 2018
Time: 9:49 am
File: ACP196 oxalate E18-004120_E18-004612-E.xls
Sample: ACP196 oxalate E18-004120_E18-004612-E
Temp: 25.0 °C
Meth: 40-0-90-0-90_0_10%_0.002.sao
MRef: 4.1502
Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Sorp
Cycle 2 Desorp
Change In Mass (%) - Ref
Target RH (%)
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FIG. 9A

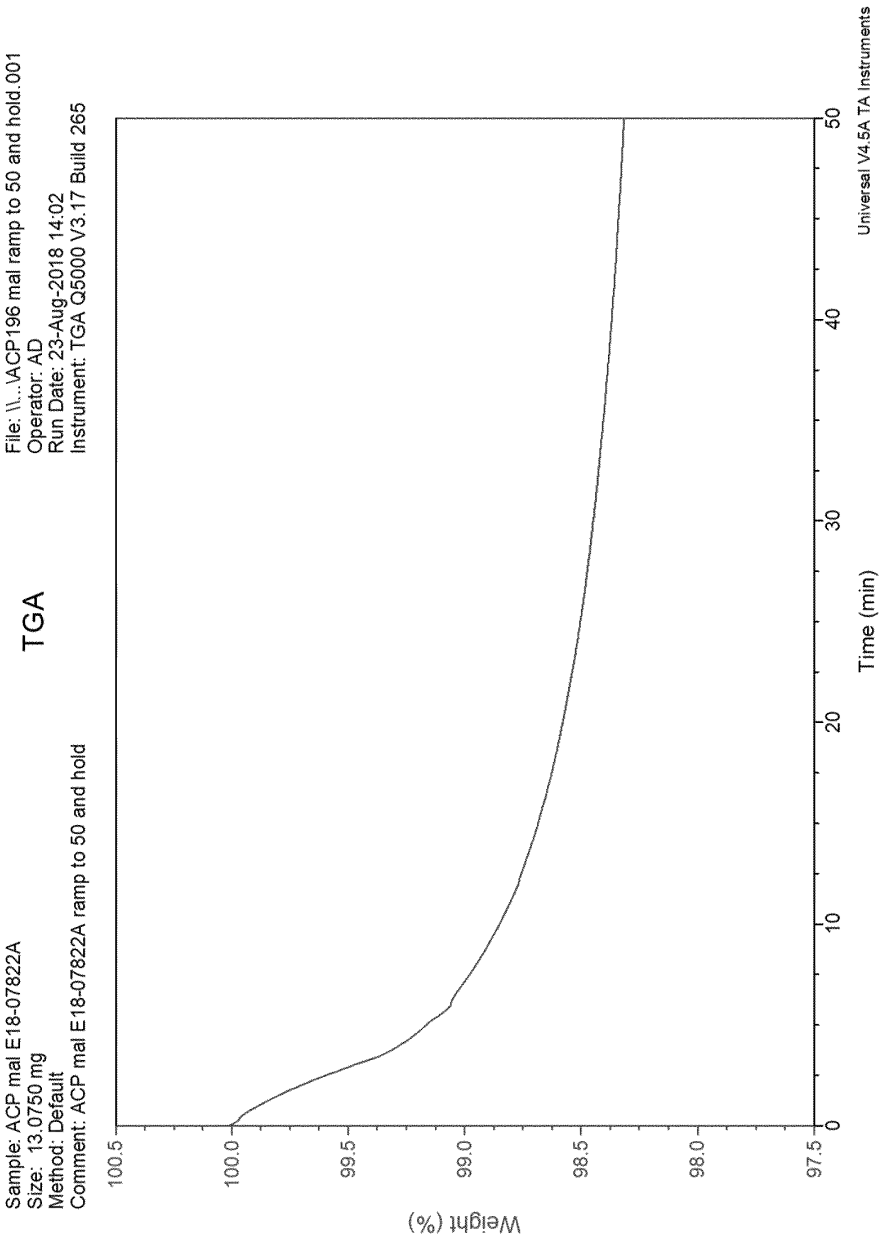

TGA
Sample: ACP mal E18-07822A
Size: 13.0750 mg
Method: Default
Comment: ACP mal E18-07822A ramp to 50 and hold
File: \\...\ACP196 mal ramp to 50 and hold.001
Operator: AD
Run Date: 23-Aug-2018 14:02
Instrument: TGA Q5000 V3.17 Build 265
Weight (%)
100.5
100.0
99.5
99.0
98.5
98.0
97.5
Time (min)
0
10
20
30
40
50
Universal V4.5A TA Instruments

FIG. 9B

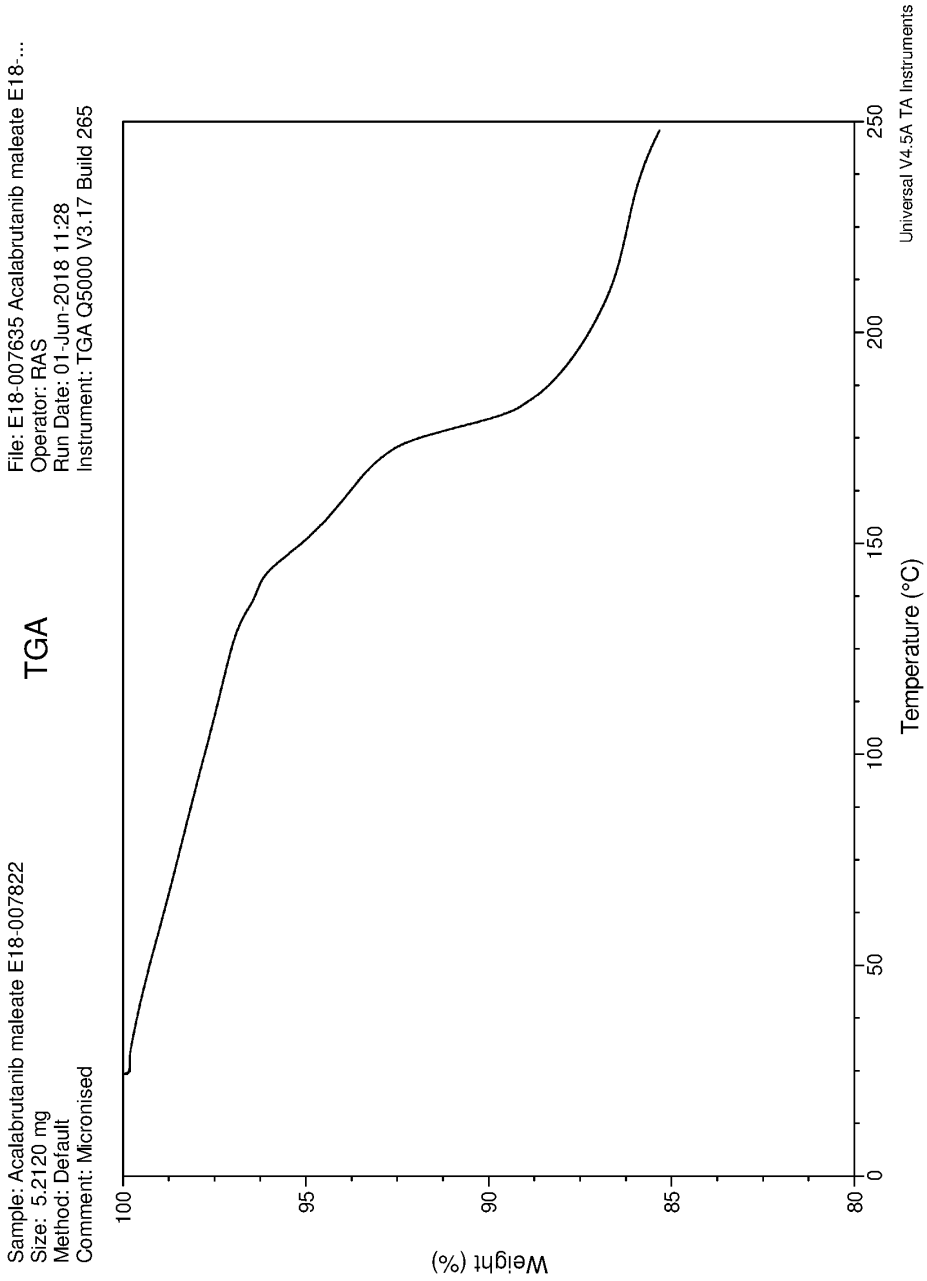

TGA
Sample: Acalabrutanib maleate E18-007822
Size: 5.2120 mg
Method: Default
Comment: Micronised
File: E18-007635 Acalabrutanib maleate E18-...
Operator: RAS
Run Date: 01-Jun-2018 11:28
Instrument: TGA Q5000 V3.17 Build 265
Universal V4.5A TA Instruments
Weight (%)
Temperature (°C)
100
95
90
85
80
0
50
100
150
200
250

FIG. 10A

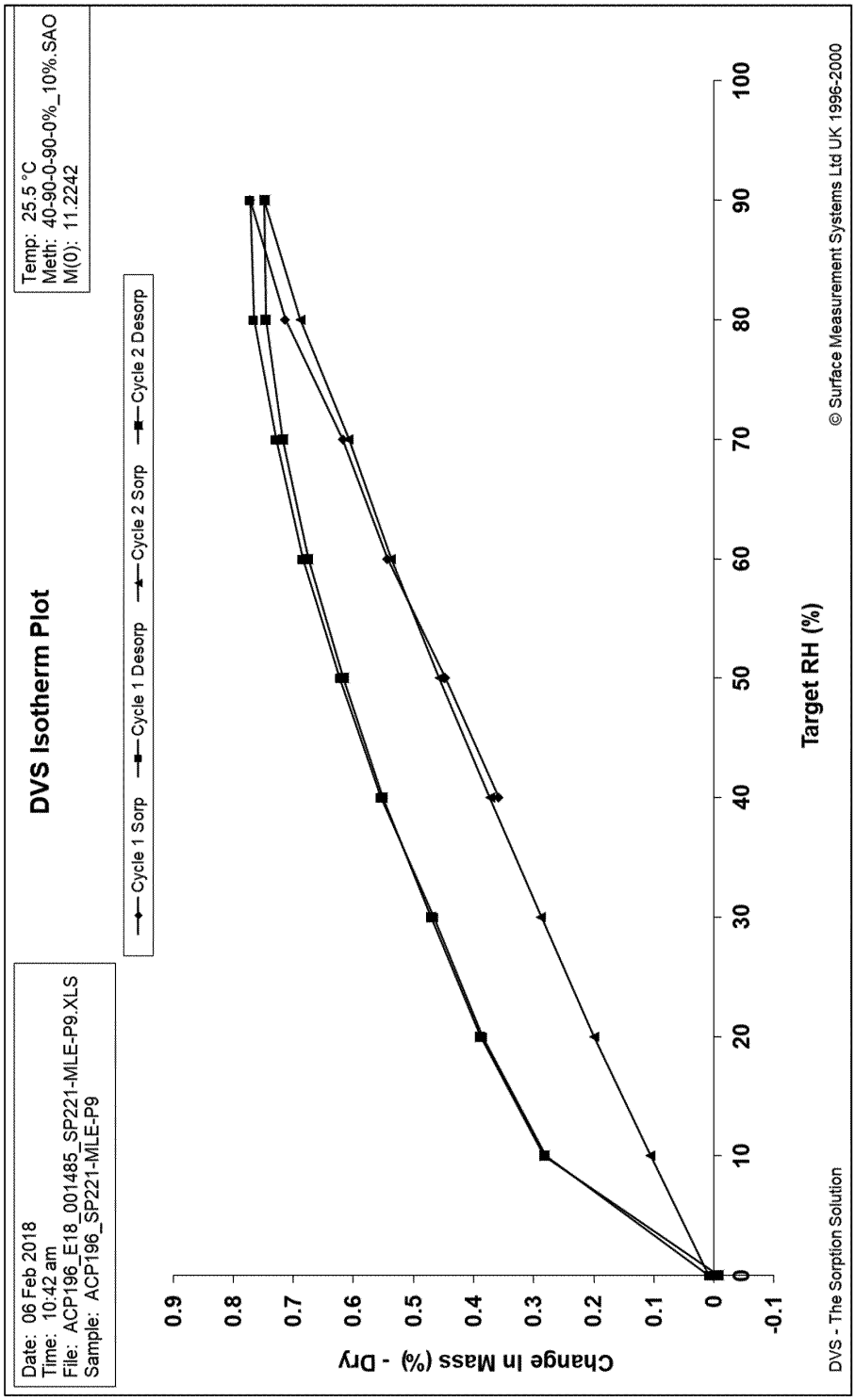

DVS Isotherm Plot
Date: 06 Feb 2018
Time: 10:42 am
File: ACP196_E18_001485_SP221-MLE-P9.XLS
Sample: ACP196_SP221-MLE-P9
Temp: 25.5 °C
Meth: 40-90-0-90-0%_10%.SAO
M(0): 11.2242
Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Sorp
Cycle 2 Desorp
Change In Mass (%) - Dry
Target RH (%)
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
0
10
20
30
40
50
60
70
80
90
100
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FIG. 10B

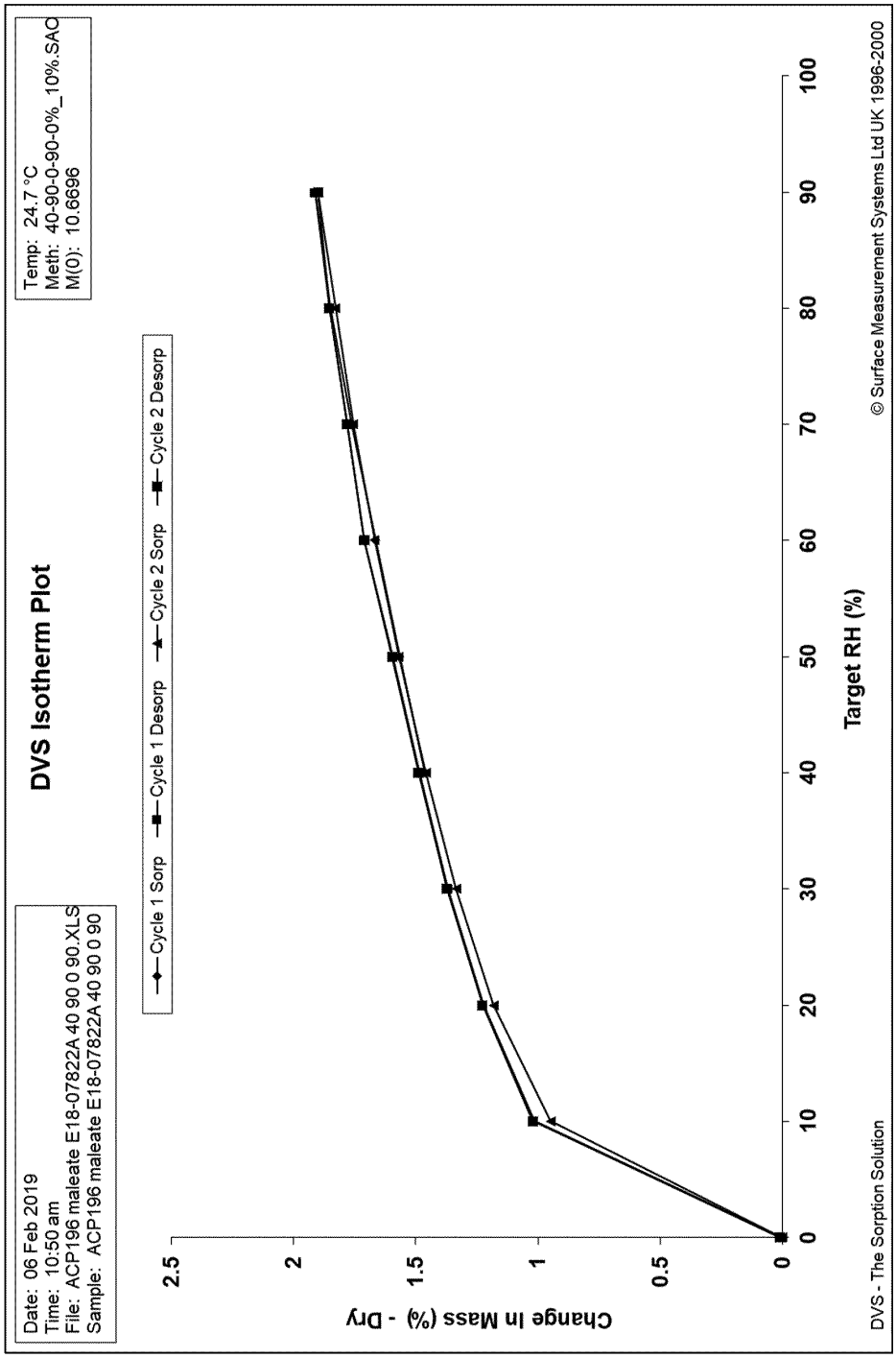

DVS Isotherm Plot
Date: 06 Feb 2019
Time: 10:50 am
File: ACP196 maleate E18-07822A 40 90 0 90.XLS
Sample: ACP196 maleate E18-07822A 40 90 0 90
Temp: 24.7 °C
Meth: 40-90-0-90-0%_10%.SAO
M(0): 10.6696
Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Sorp
Cycle 2 Desorp
Change In Mass (%) - Dry
Target RH (%)
0
0.5
1
1.5
2
2.5
10
20
30
40
50
60
70
80
90
100
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FIG. 11

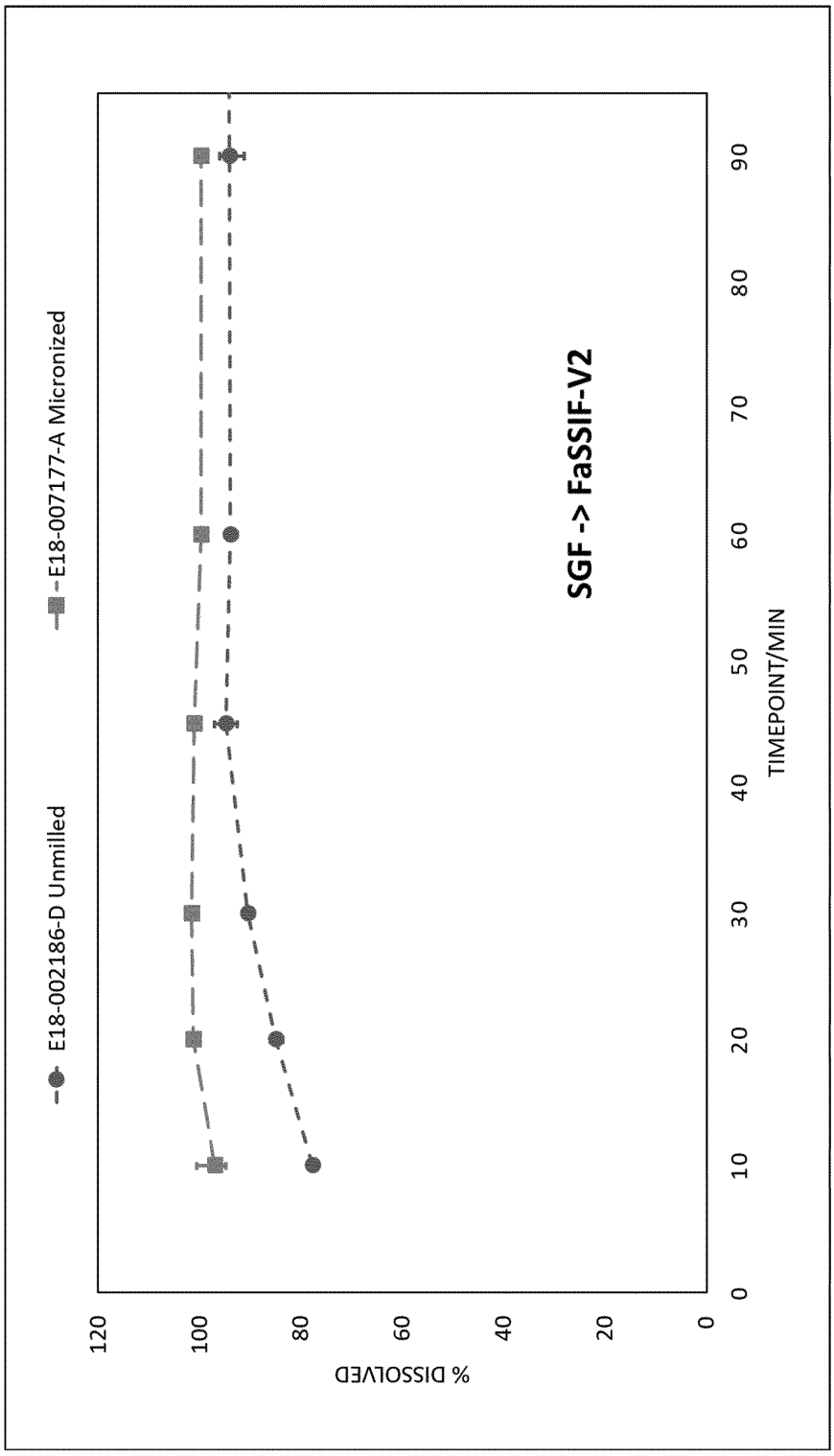

E18-002186-D Unmilled
E18-007177-A Micronized
SGF -> FaSSIF-V2
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120
0
10
20
30
40
50
60
70
80
90

FIG. 12

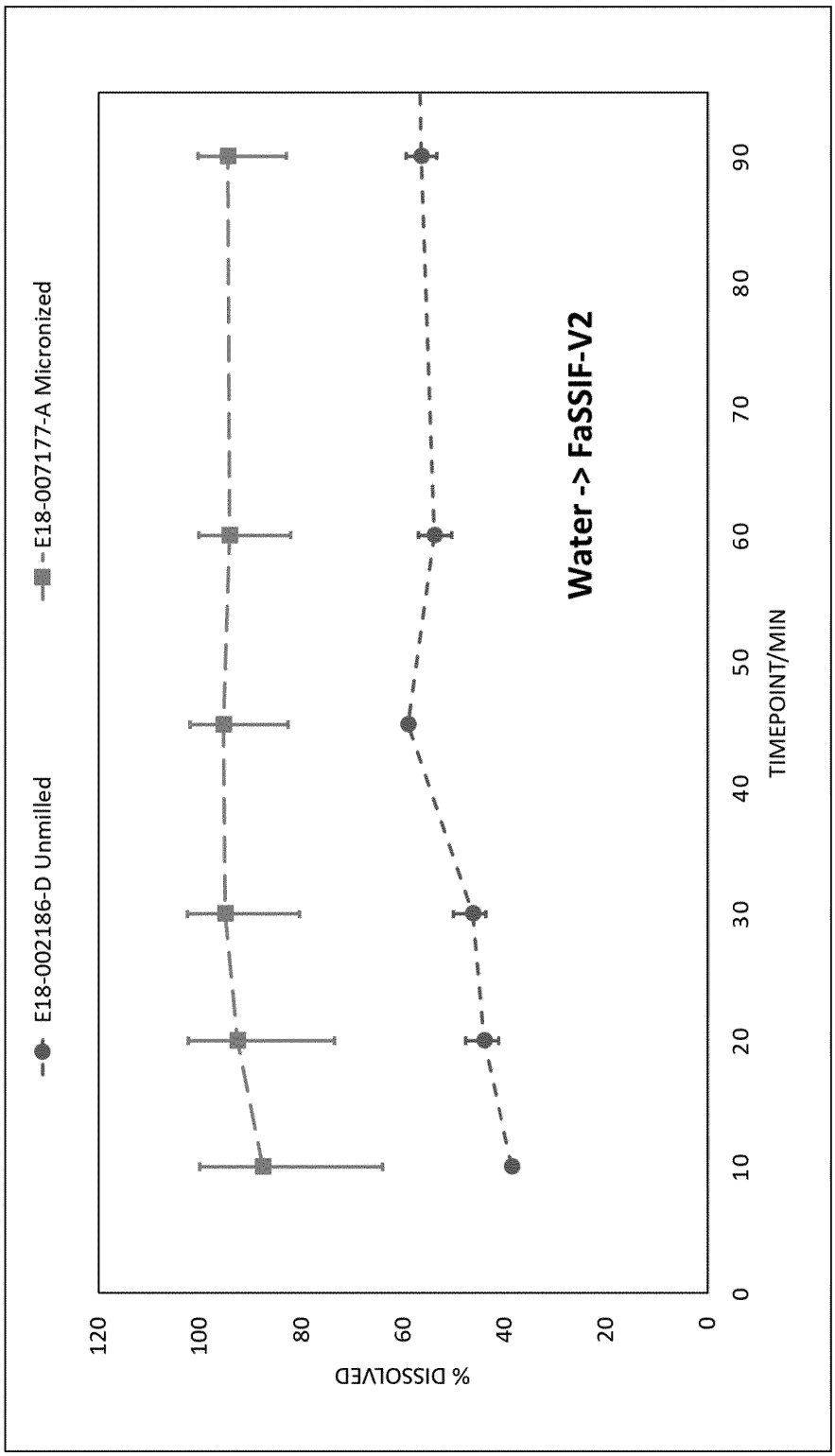

E18-002186-D Unmilled
E18-007177-A Micronized
Water -> FaSSIF-V2
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120
0
10
20
30
40
50
60
70
80
90

FIG. 13

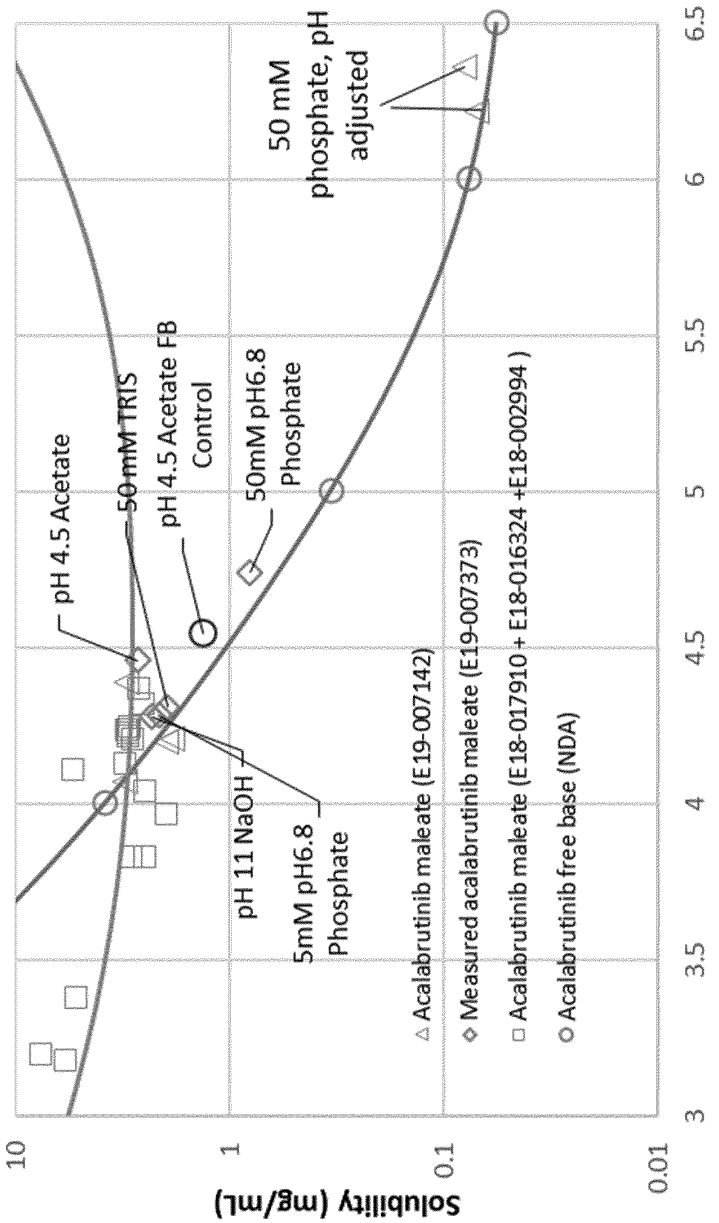

Solubility (mg/mL)
10
1
0.1
0.01
3
3.5
4
4.5
5
5.5
6
6.5
Final pH
pH 4.5 Acetate
50 mM TRIS
pH 4.5 Acetate FB Control
50mM pH6.8 Phosphate
50 mM phosphate, pH adjusted
pH 11 NaOH
5mM pH6.8 Phosphate
Acalabrutinib maleate (E19-007142)
Measured acalabrutinib maleate (E19-007373)
Acalabrutinib maleate (E18-017910 + E18-016324 +E18-002994)
Acalabrutinib free base (NDA)

FIG. 14

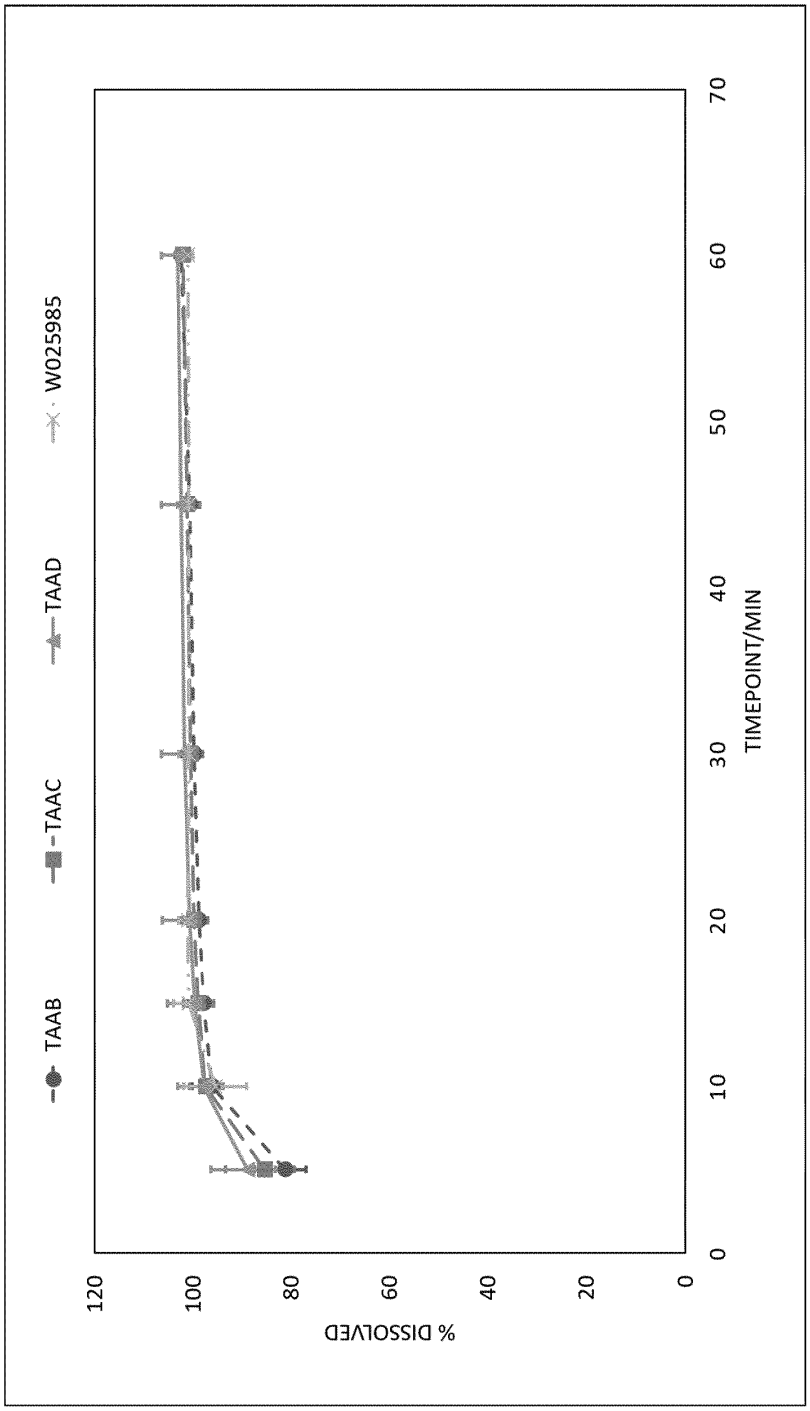

TAAB
TAAC
TAAD
W025985
% DISSOLVED
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
TIMEPOINT/MIN

FIG. 15

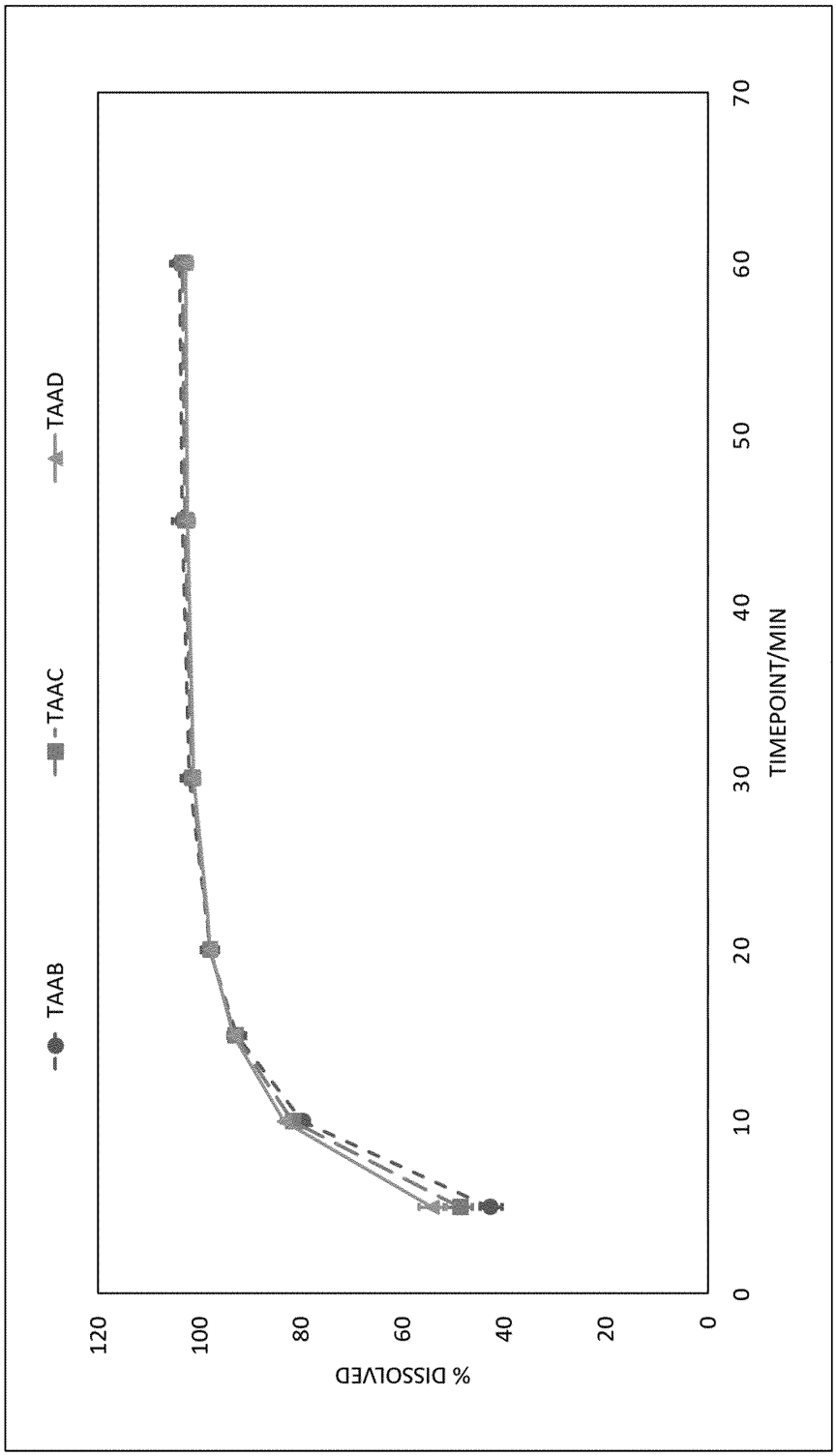

TAAB
TAAC
TAAD
% DISSOLVED
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
TIMEPOINT/MIN

FIG. 16

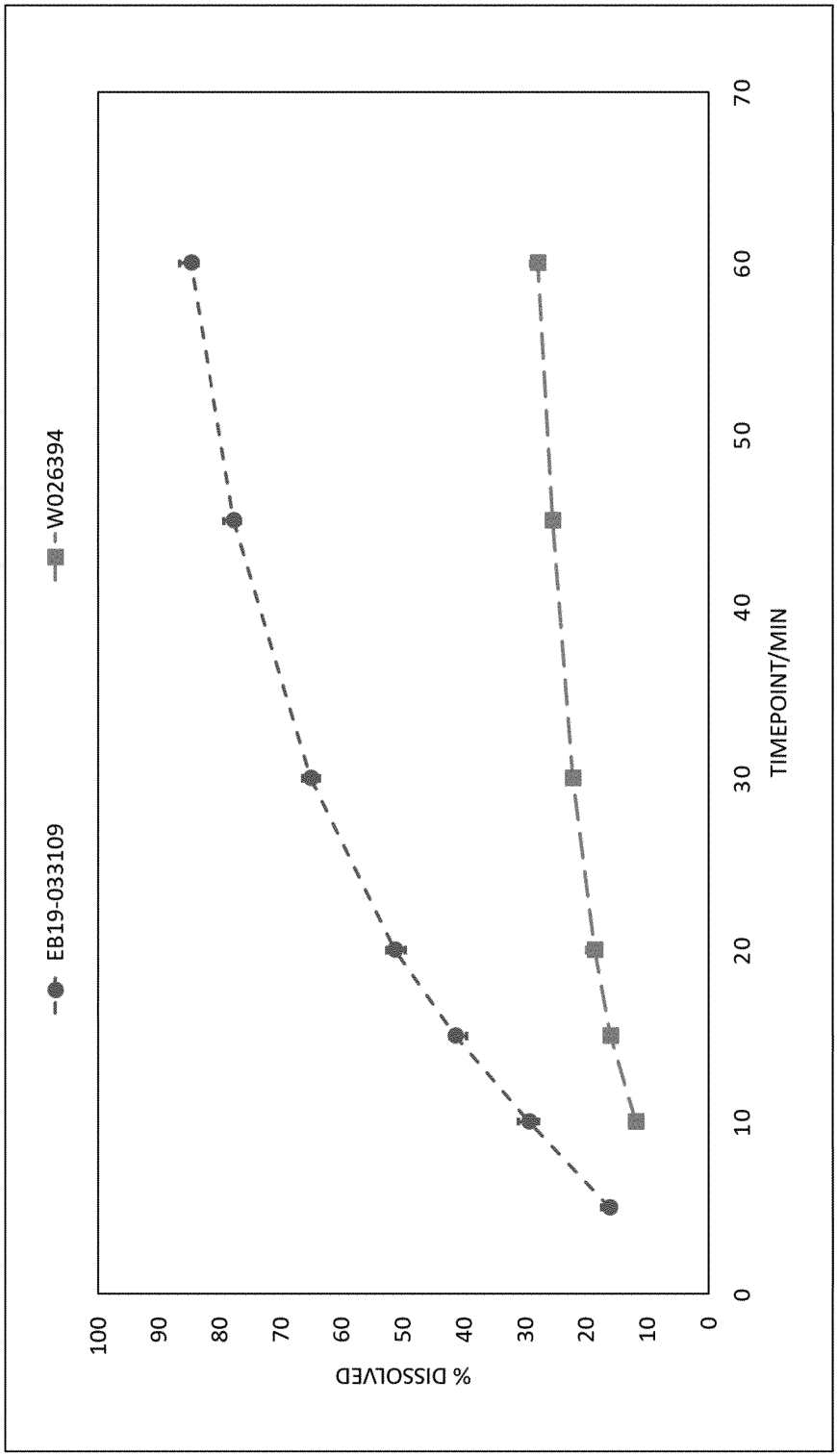

EB19-033109
W026394
% DISSOLVED
TIMEPOINT/MIN
0
10
20
30
40
50
60
70
80
90
100

FIG. 17

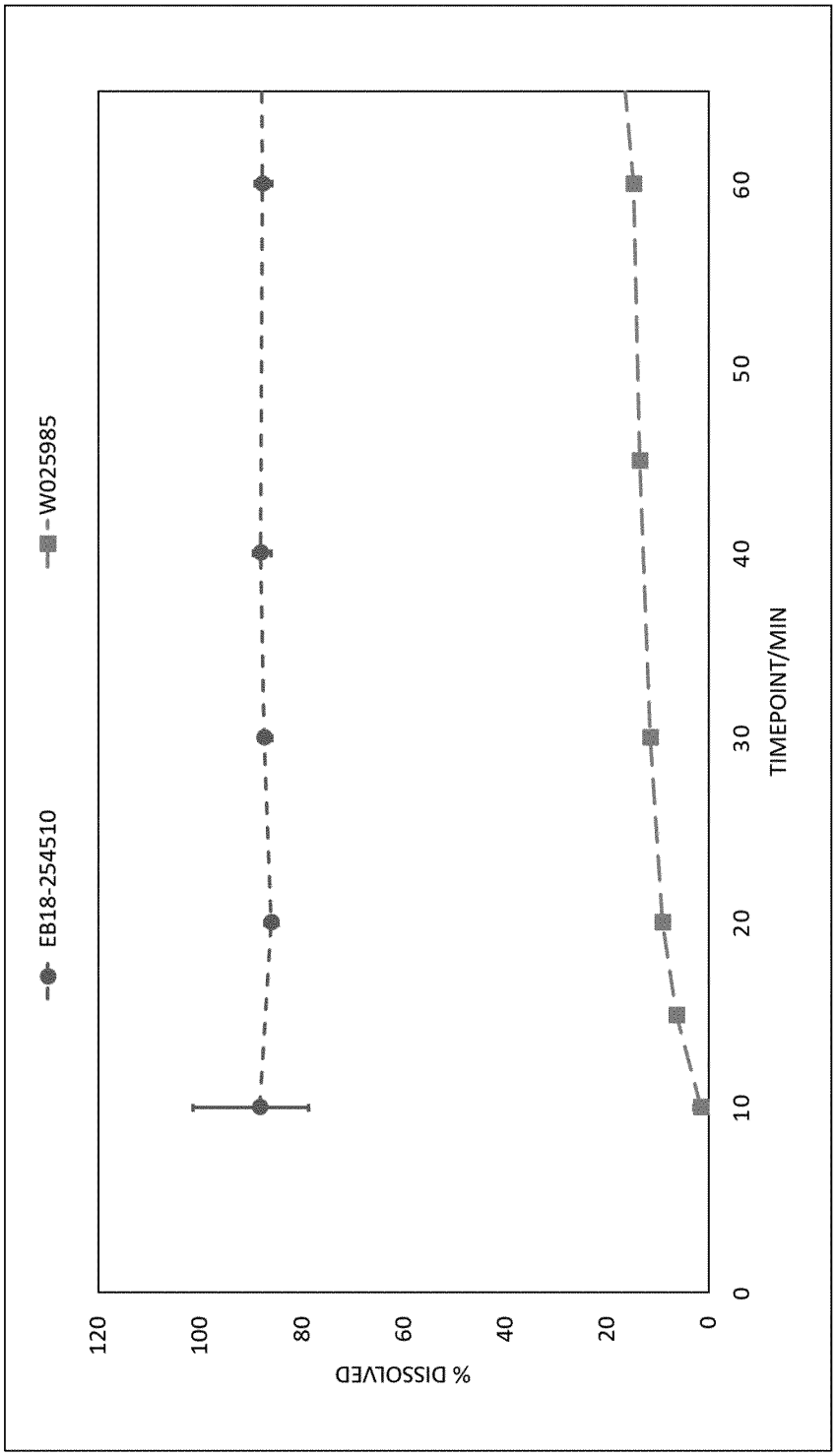

EB18-254510
W025985
% DISSOLVED
120
100
80
60
40
20
0
0
10
20
30
40
50
60
TIMEPOINT/MIN

FIG. 18

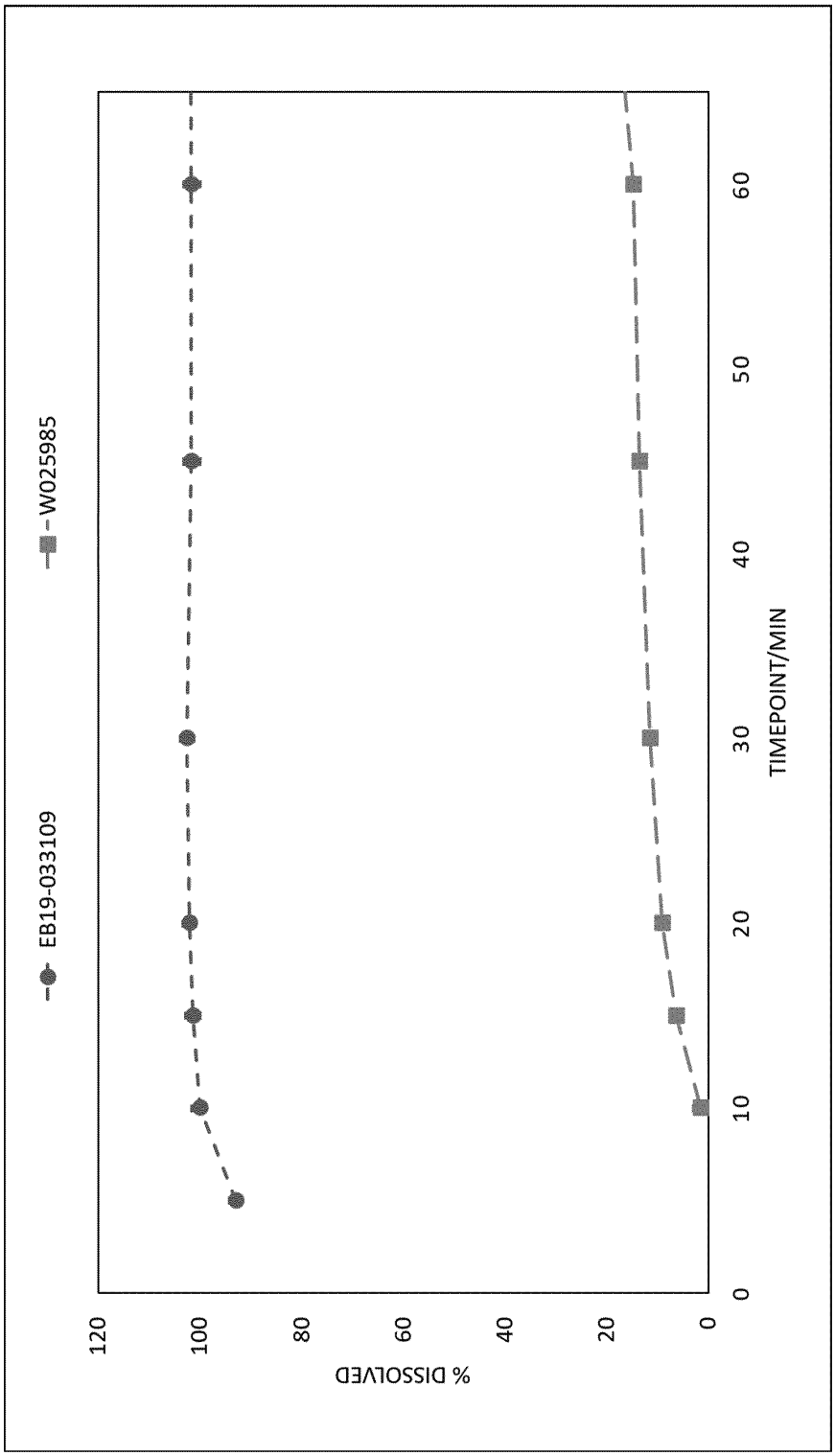

EB19-033109
W025985
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120
0
10
20
30
40
50
60

FIG. 19

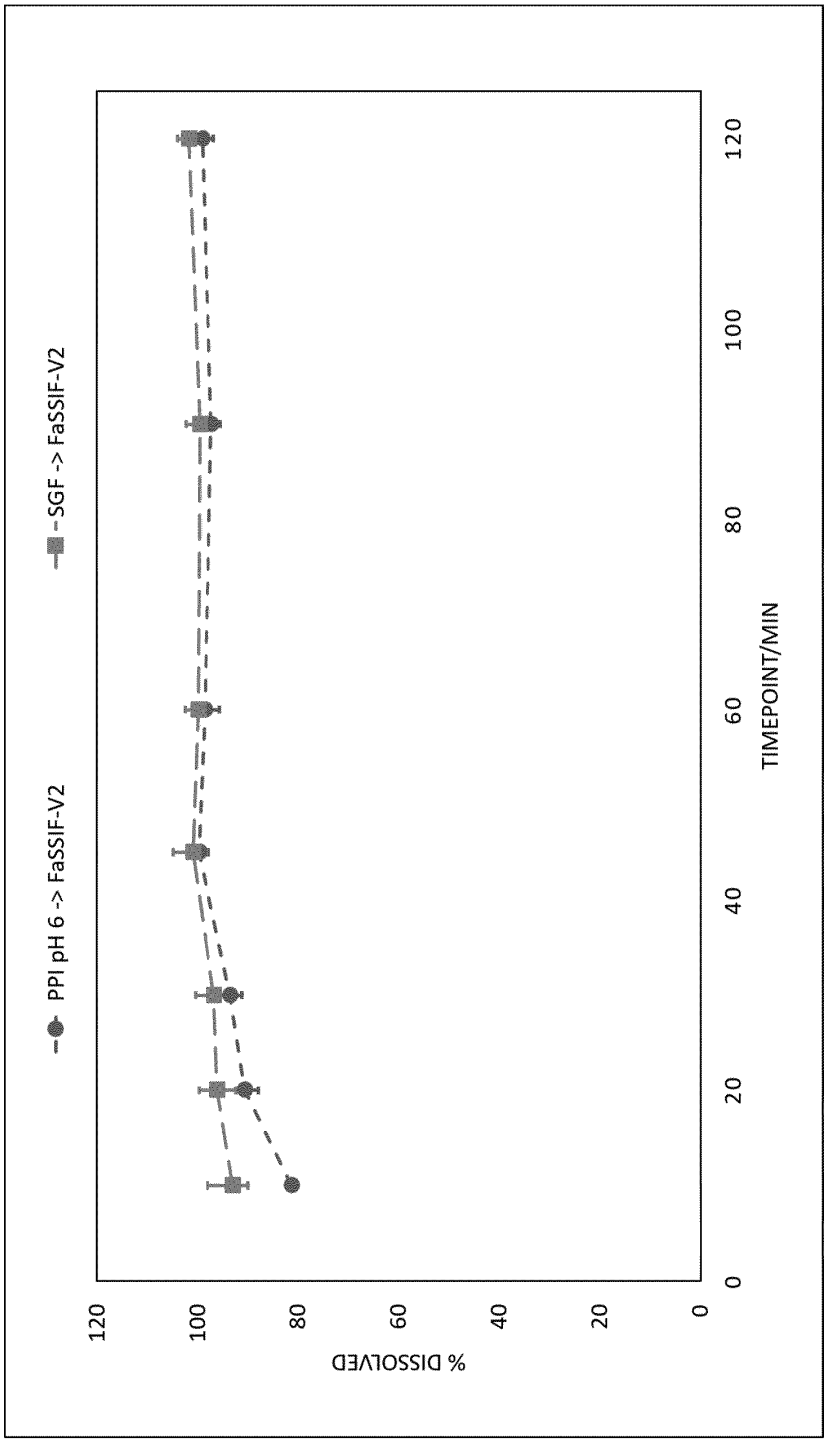

PPI pH 6 -> FaSSIF-V2
SGF -> FaSSIF-V2
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120
0
20
40
60
80
100
120

FIG. 20

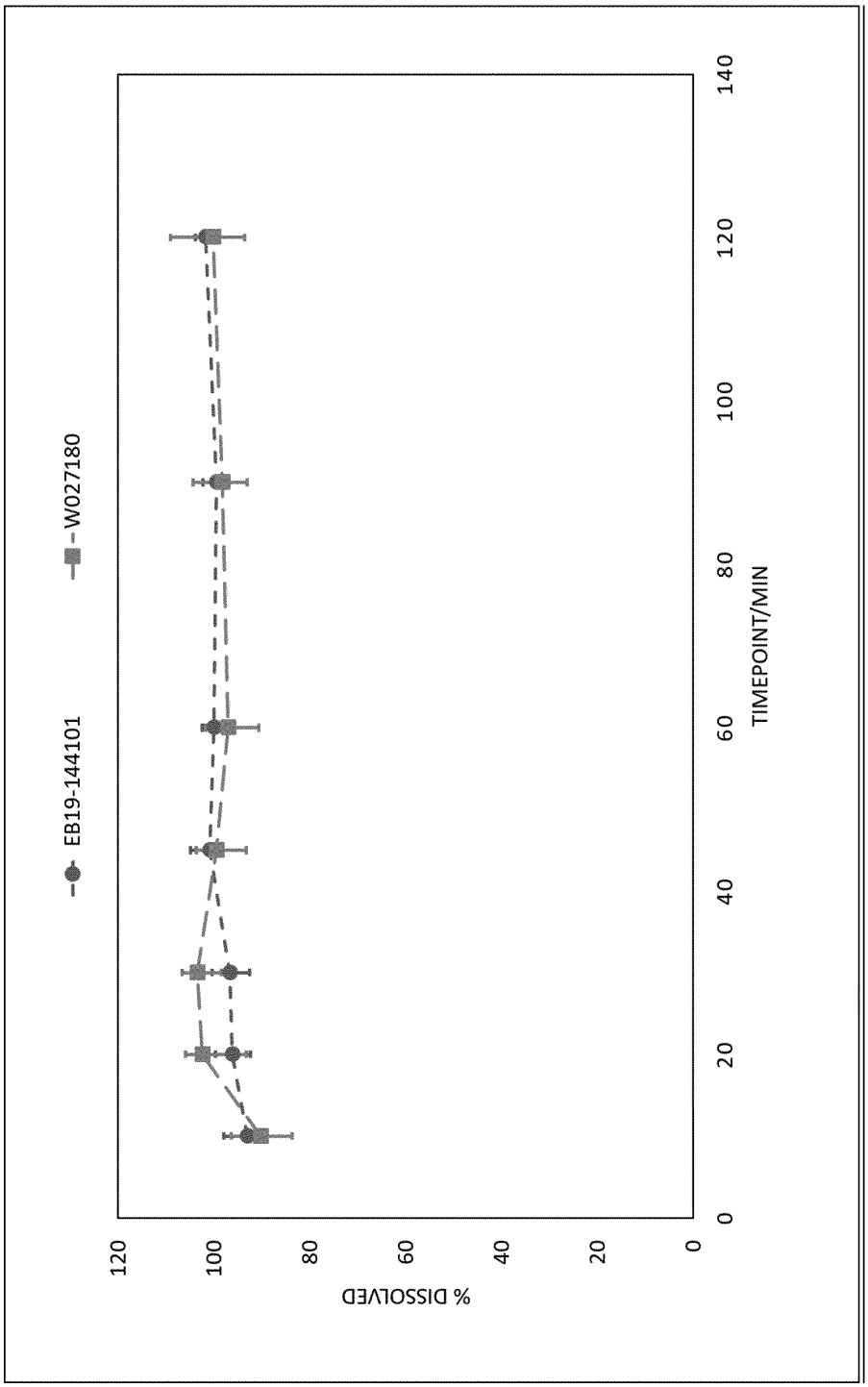

EB19-144101
W027180
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120
140

FIG. 21

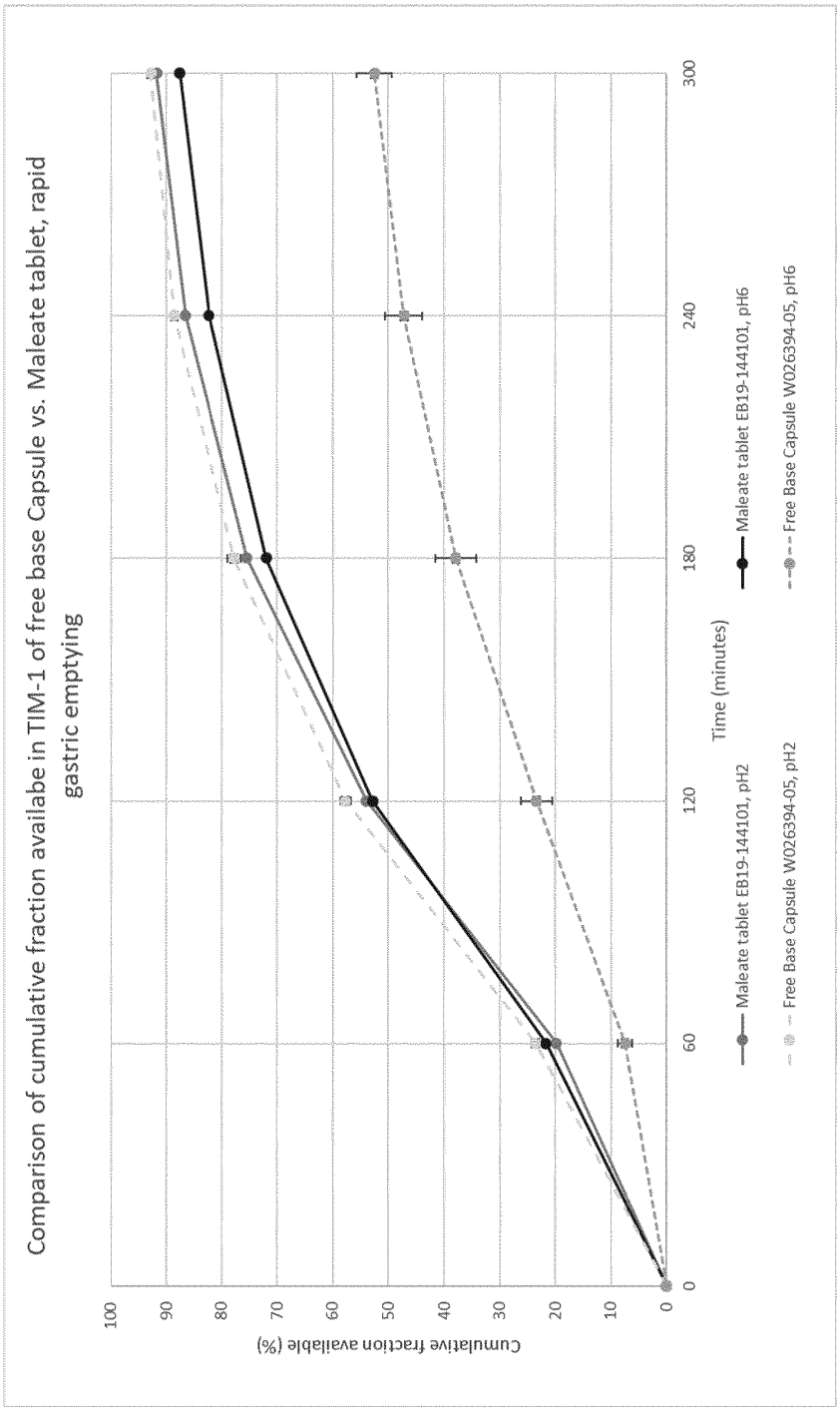

Comparison of cumulative fraction availabe in TIM-1 of free base Capsule vs. Maleate tablet, rapid gastric emptying
Cumulative fraction available (%)
0
10
20
30
40
50
60
70
80
90
100
0
60
120
180
240
300
Time (minutes)
Maleate tablet EB19-144101, pH2
Free Base Capsule W026394-05, pH2
Maleate tablet EB19-144101, pH6
Free Base Capsule W026394-05, pH6

FIG. 22

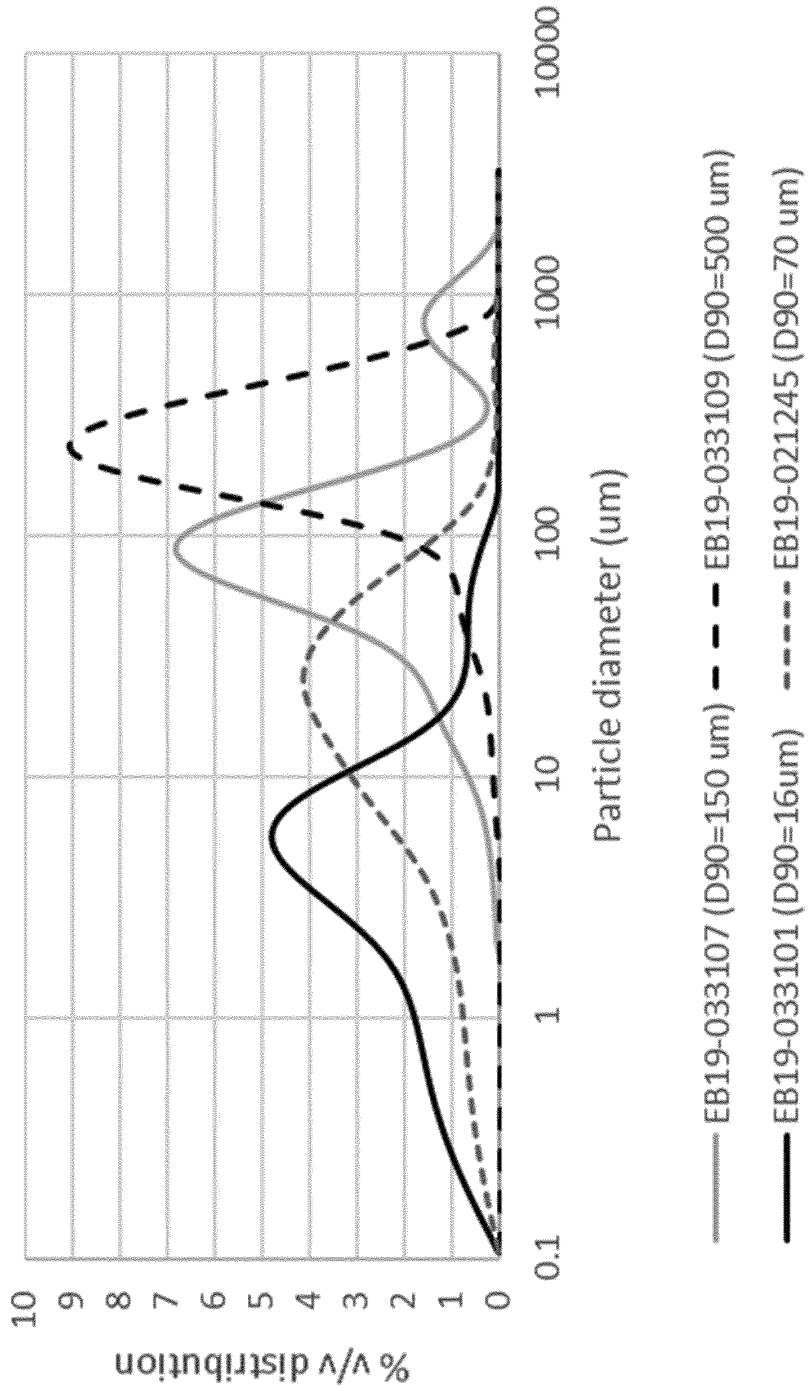

% v/v distribution
0
1
2
3
4
5
6
7
8
9
10
0.1
1
10
100
1000
10000
Particle diameter (um)
EB19-033107 (D90=150 um)
EB19-033109 (D90=500 um)
EB19-033101 (D90=16um)
EB19-021245 (D90=70 um)

FIG. 23

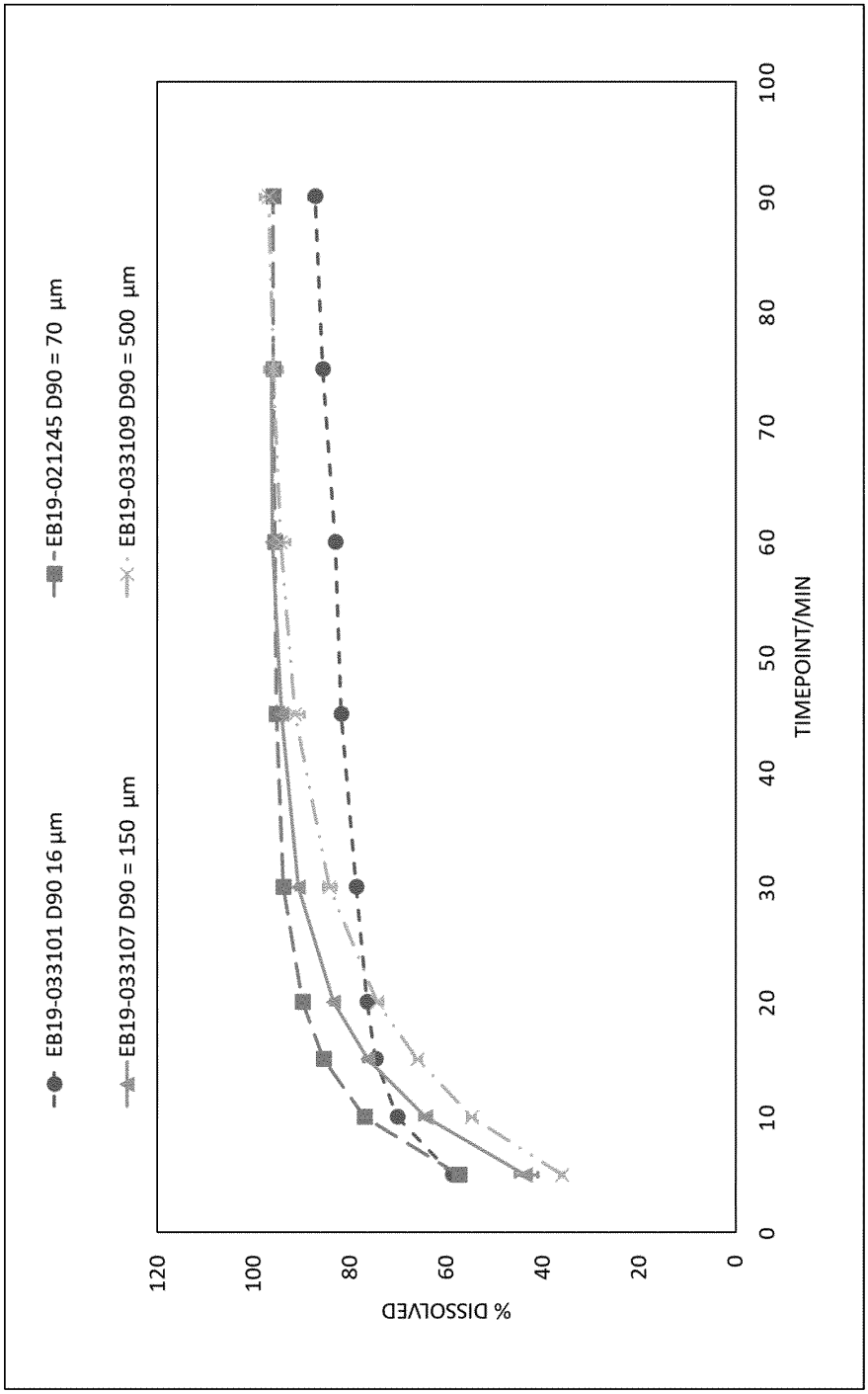

EB19-033101 D90 16 µm
EB19-021245 D90 = 70 µm
EB19-033107 D90 = 150 µm
EB19-033109 D90 = 500 µm
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120
0
10
20
30
40
50
60
70
80
90
100

FIG. 24

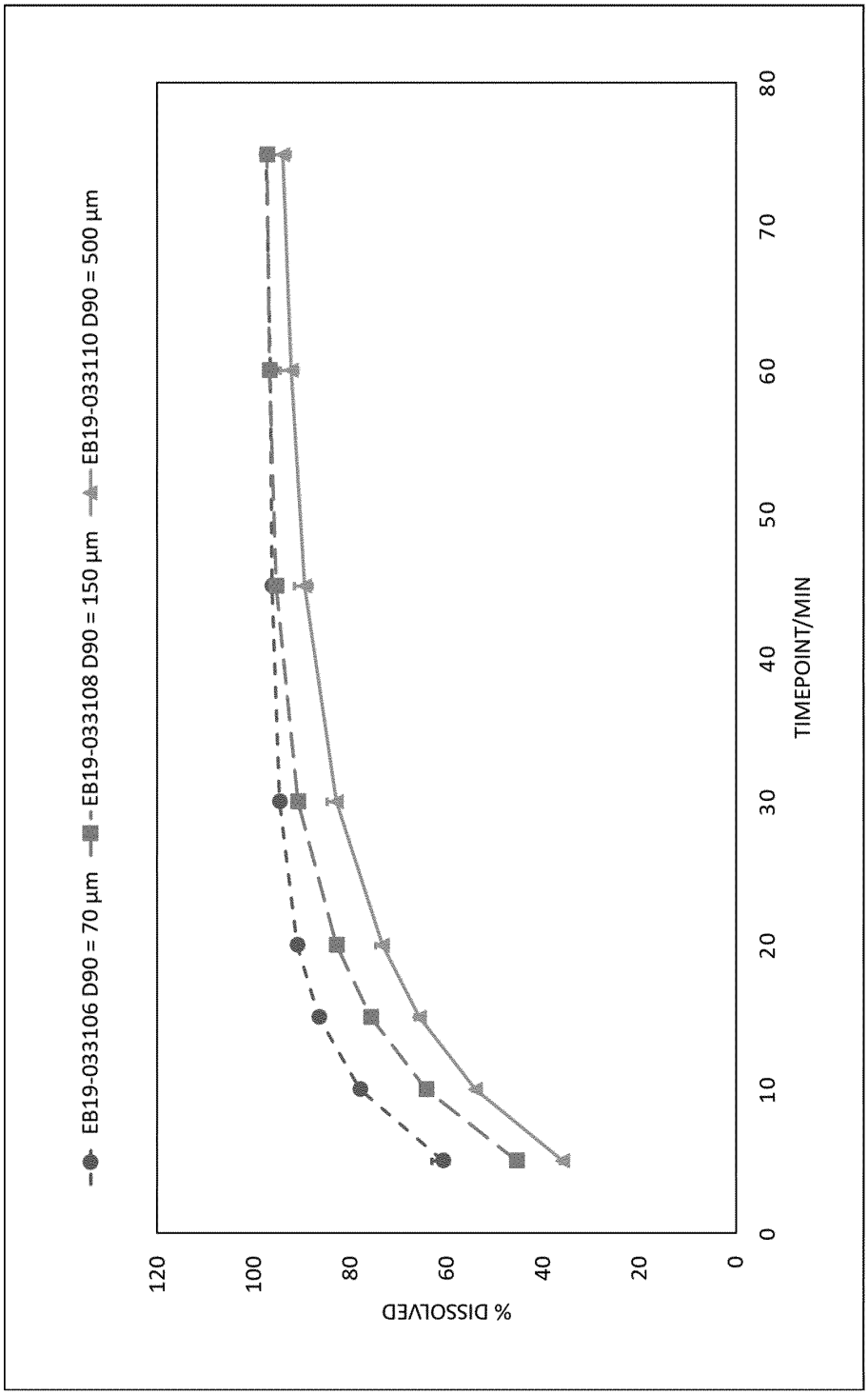

EB19-033106 D90 = 70 µm
EB19-033108 D90 = 150 µm
EB19-033110 D90 = 500 µm
% DISSOLVED
0
20
40
60
80
100
120
TIMEPOINT/MIN
0
10
20
30
40
50
60
70
80

FIG. 25

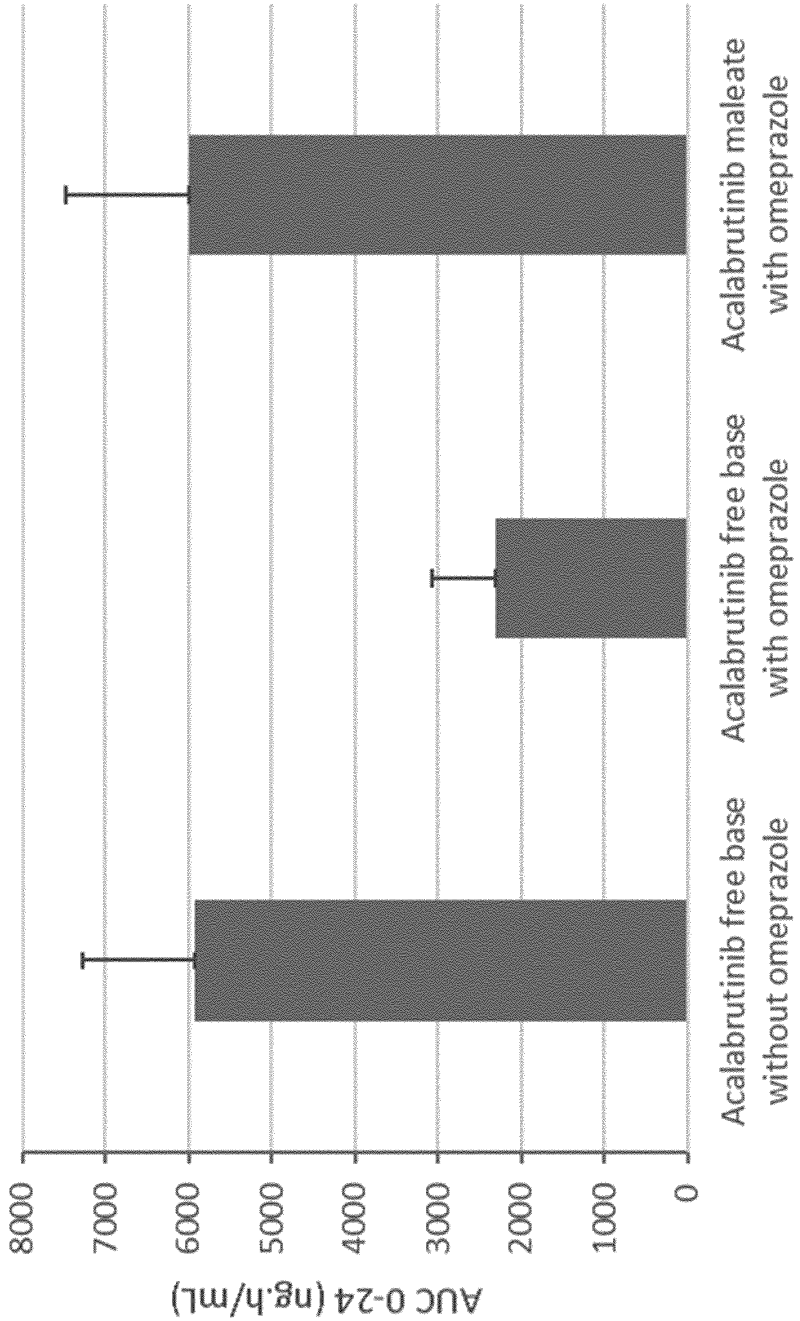

AUC 0-24 (ng.h/mL)
8000
7000
6000
5000
4000
3000
2000
1000
0
Acalabrutinib free base without omeprazole
Acalabrutinib free base with omeprazole
Acalabrutinib maleate with omeprazole

FIG. 26

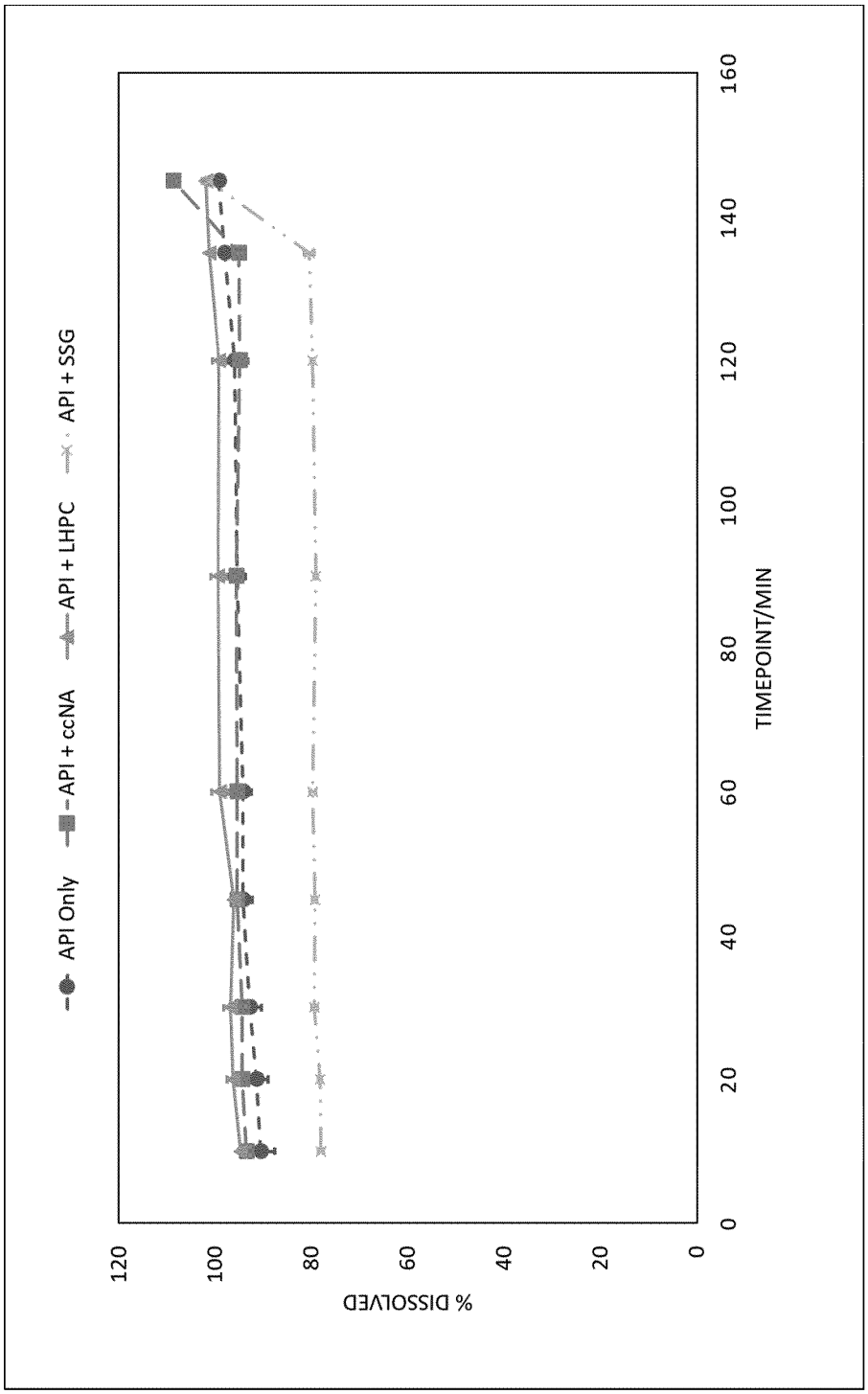

API Only
API + ccNA
API + LHPC
API + SSG
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120
0
20
40
60
80
100
120
140
160

FIG. 27

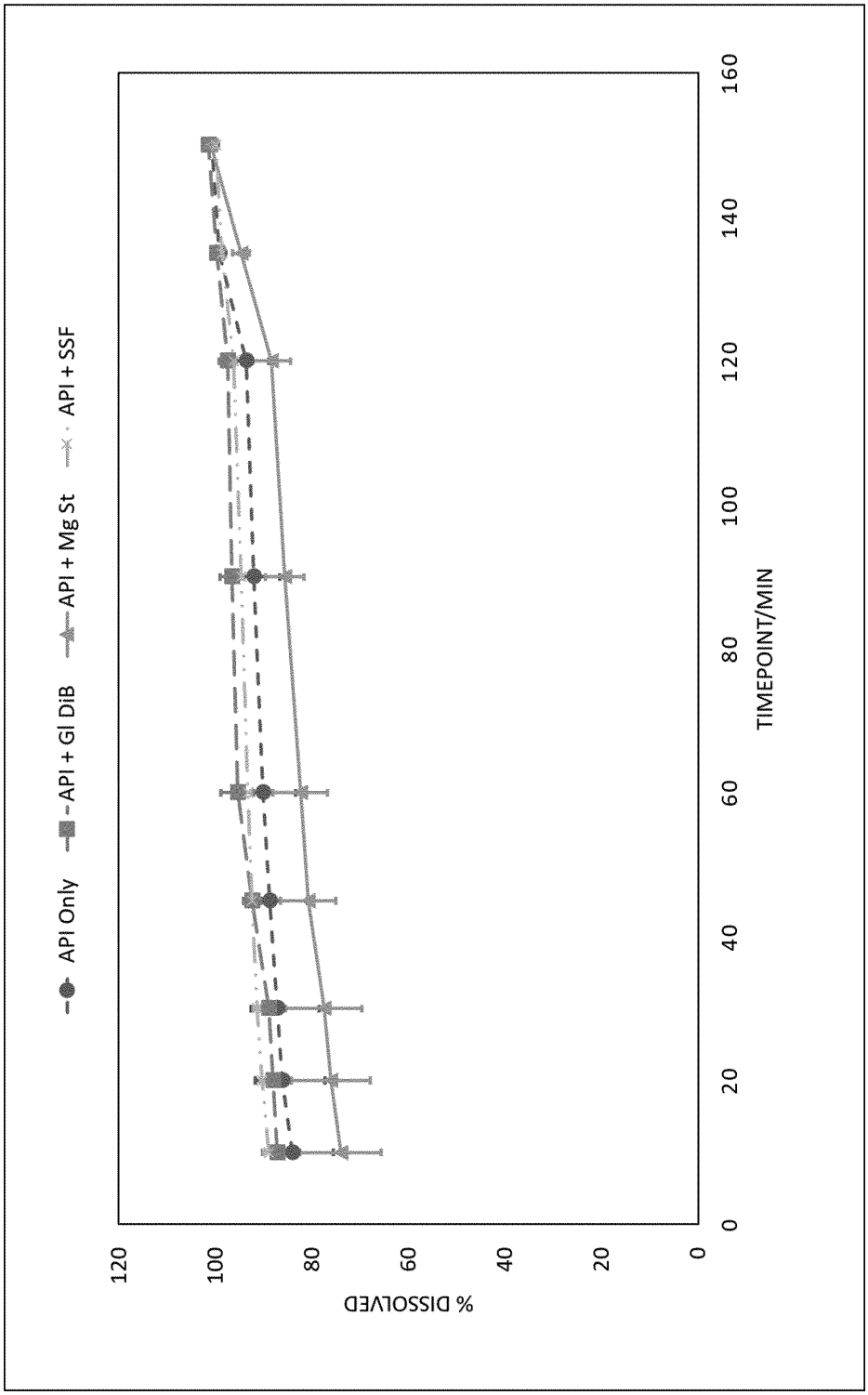

API Only
API + Gl DiB
API + Mg St
API + SSF
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120
0
20
40
60
80
100
120
140
160

FIG. 28

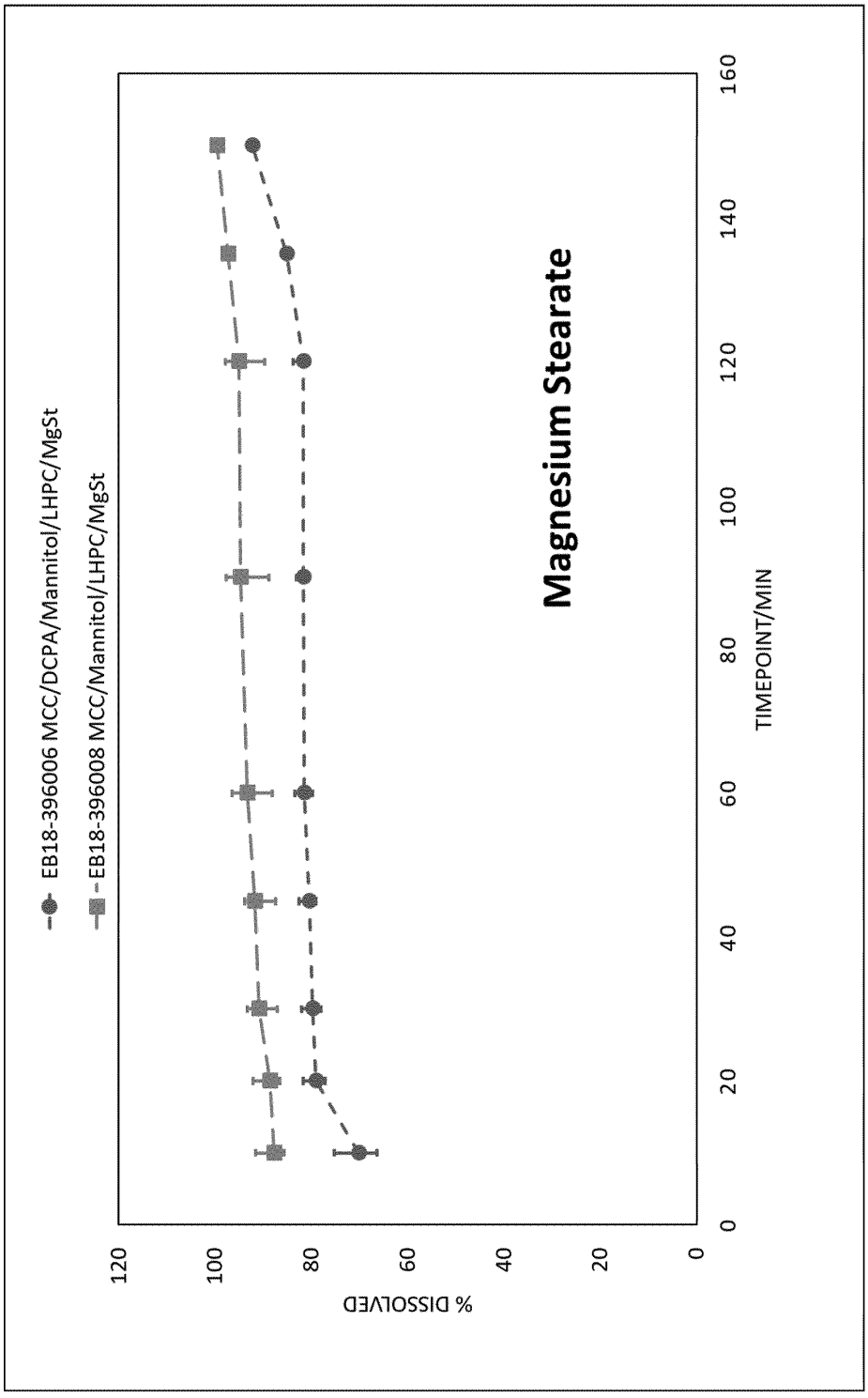

EB18-396006 MCC/DCPA/Mannitol/LHPC/MgSt
EB18-396008 MCC/Mannitol/LHPC/MgSt
Magnesium Stearate
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120
0
20
40
60
80
100
120
140
160

FIG. 29

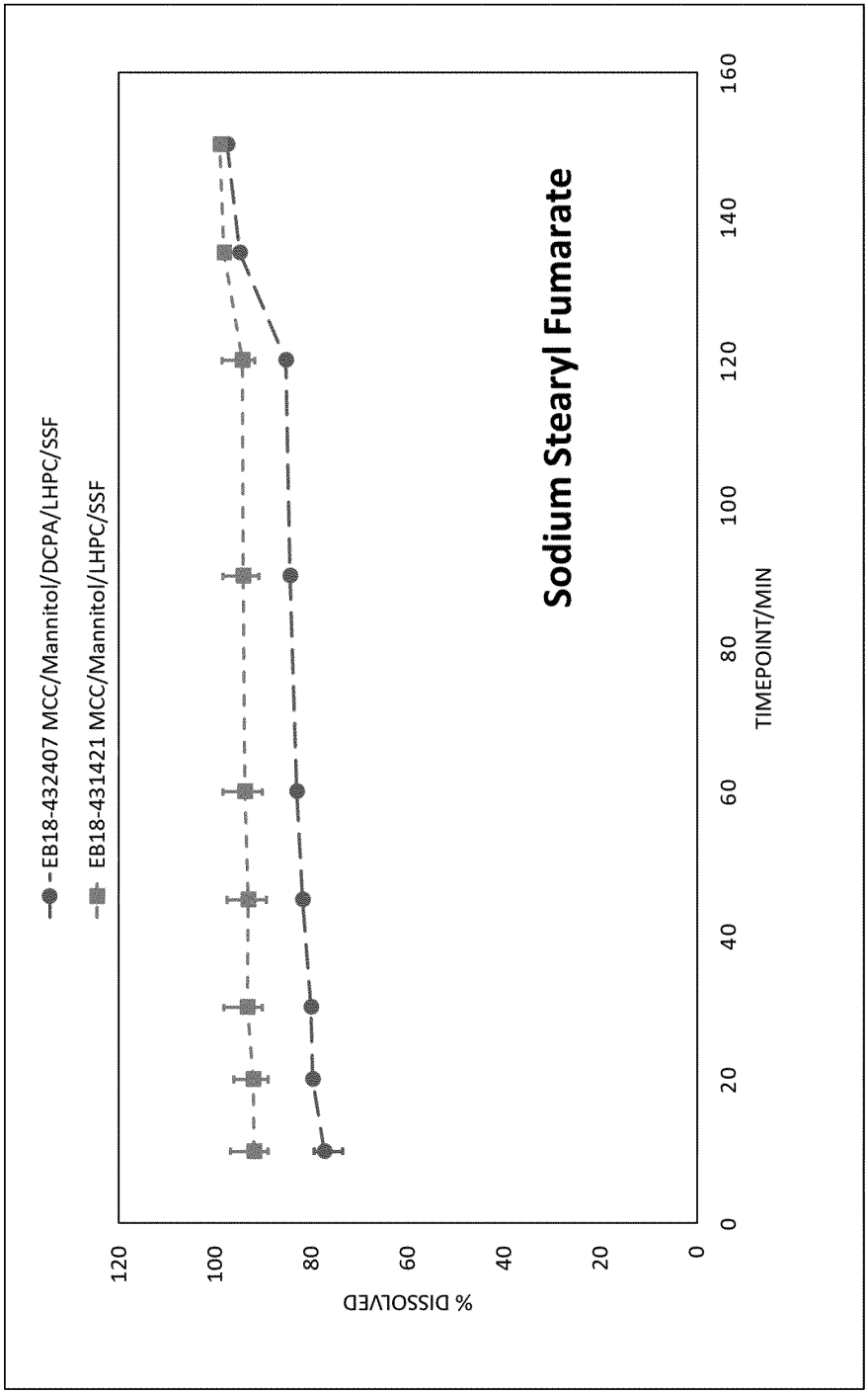

EB18-432407 MCC/Mannitol/DCPA/LHPC/SSF
EB18-431421 MCC/Mannitol/LHPC/SSF
Sodium Stearyl Fumarate
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120
140
160

FIG. 30

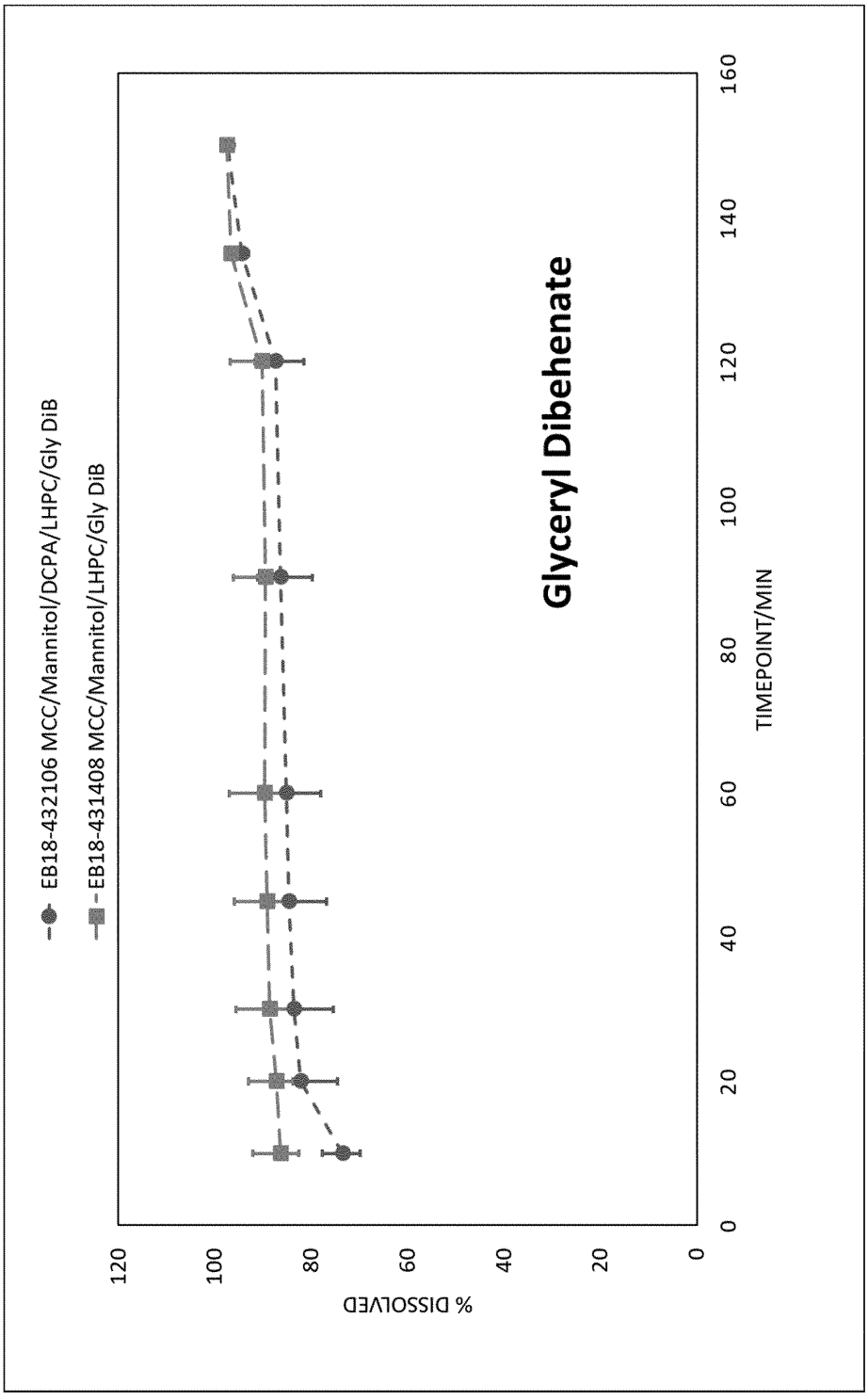
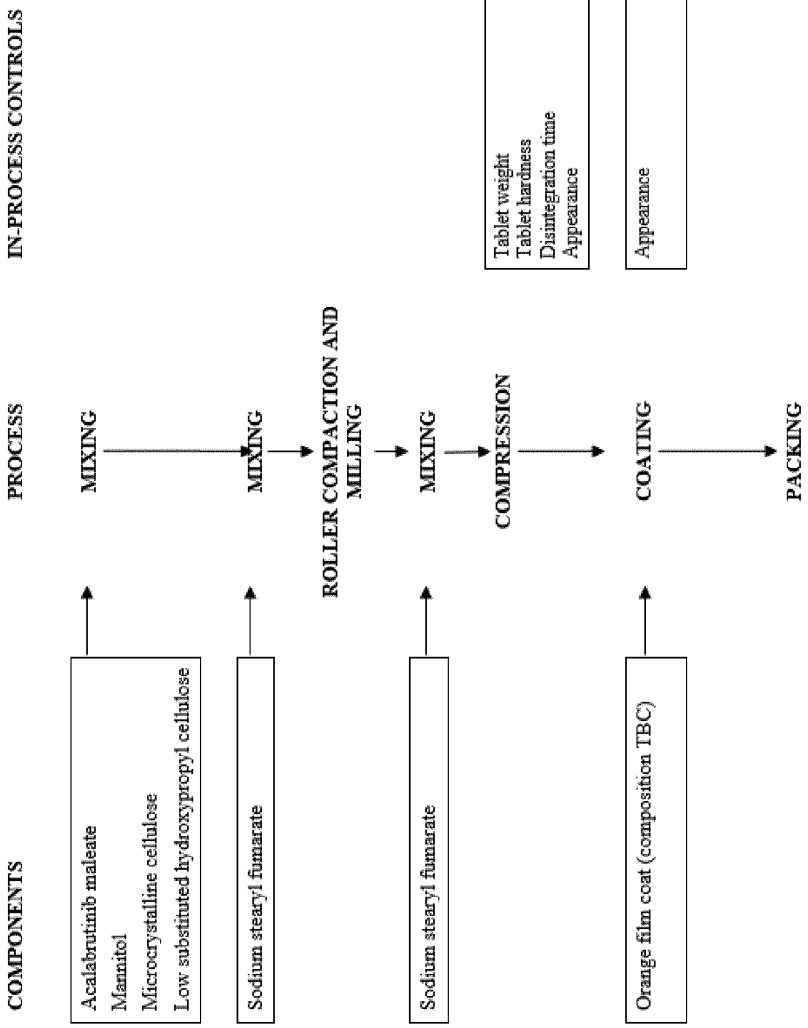

EB18-432106 MCC/Mannitol/DCPA/LHPC/Gly DiB
EB18-431408 MCC/Mannitol/LHPC/Gly DiB
Glyceryl Dibehenate
% DISSOLVED
TIMEPOINT/MIN
0
20
40
60
80
100
120
140
160

FIG. 31


COMPONENTS
PROCESS
IN-PROCESS CONTROLS
Acalabrutinib maleate
Mannitol
Microcrystalline cellulose
Low substituted hydroxypropyl cellulose
MIXING
Sodium stearyl fumarate
MIXING
ROLLER COMPACTION AND MILLING
Sodium stearyl fumarate
MIXING
COMPRESSION
Tablet weight
Tablet hardness
Disintegration time
Appearance
Orange film coat (composition TBC)
COATING
Appearance
PACKING