FIGURE 1

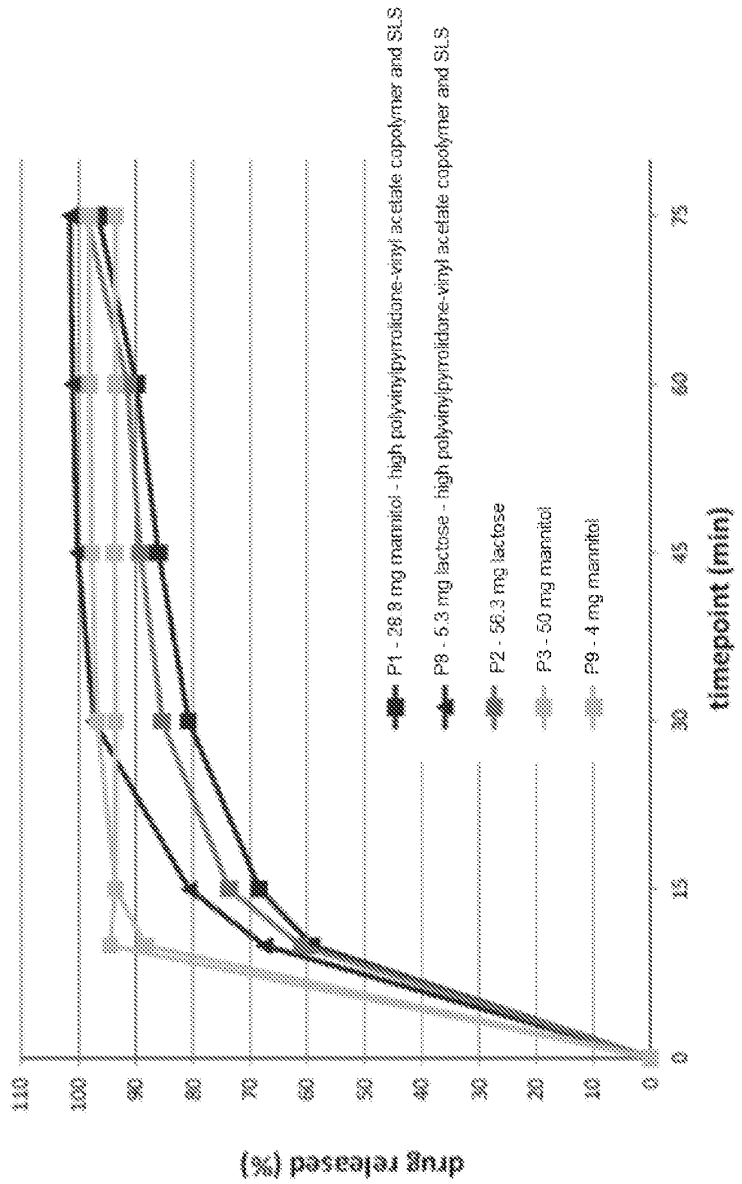

drug released (%)
timepoint (min)
P1 - 28.8 mg mannitol - high polyvinylpyrrolidone-vinyl acetate copolymer and SLS
P8 - 5.3 mg lactose - high polyvinylpyrrolidone-vinyl acetate copolymer and SLS
P2 - 56.3 mg lactose
P3 - 50 mg mannitol
P9 - 4 mg mannitol

FIGURE 2

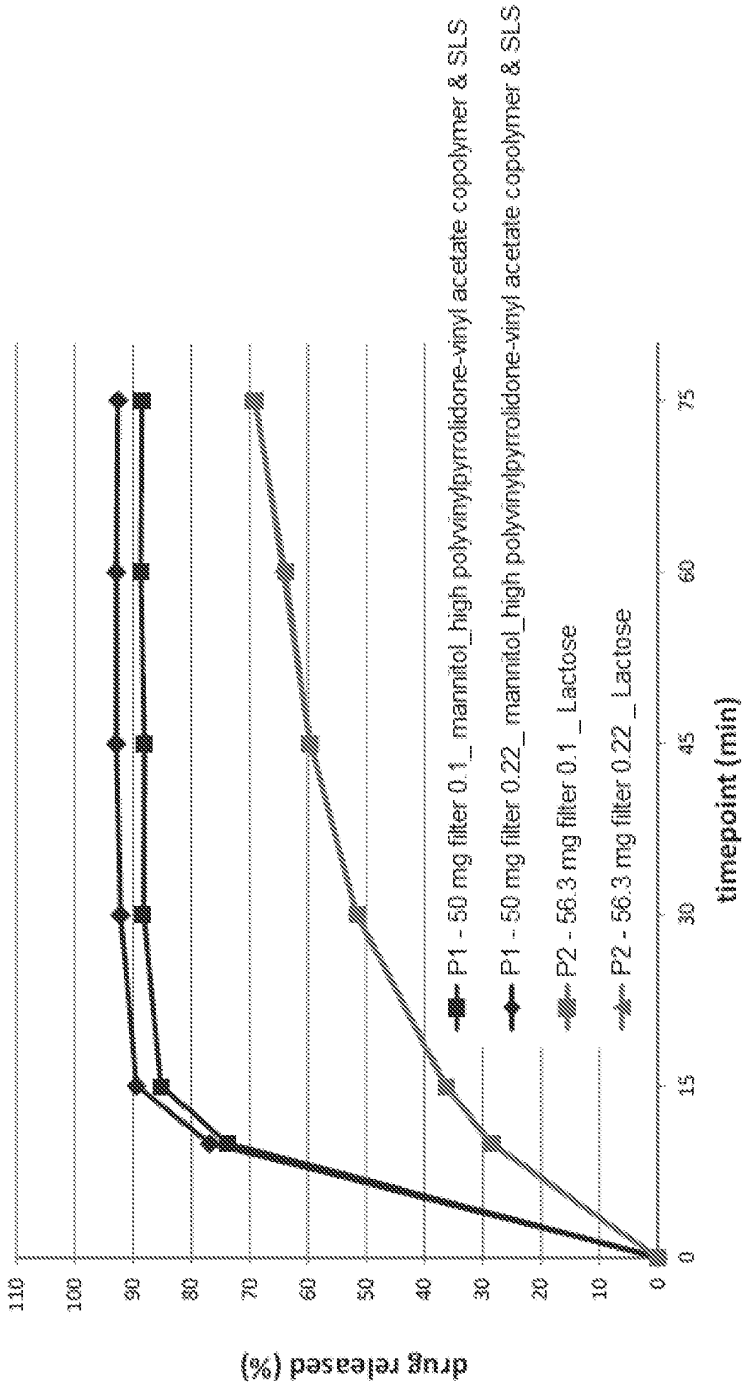

drug released (%)
timepoint (min)
P1 - 50 mg filter 0.1_ mannitol_high polyvinylpyrrolidone-vinyl acetate copolymer & SLS
P1 - 50 mg filter 0.22_ mannitol_high polyvinylpyrrolidone-vinyl acetate copolymer & SLS
P2 - 56.3 mg filter 0.1 _ Lactose
P2 - 56.3 mg filter 0.22 _ Lactose

FIGURE 3

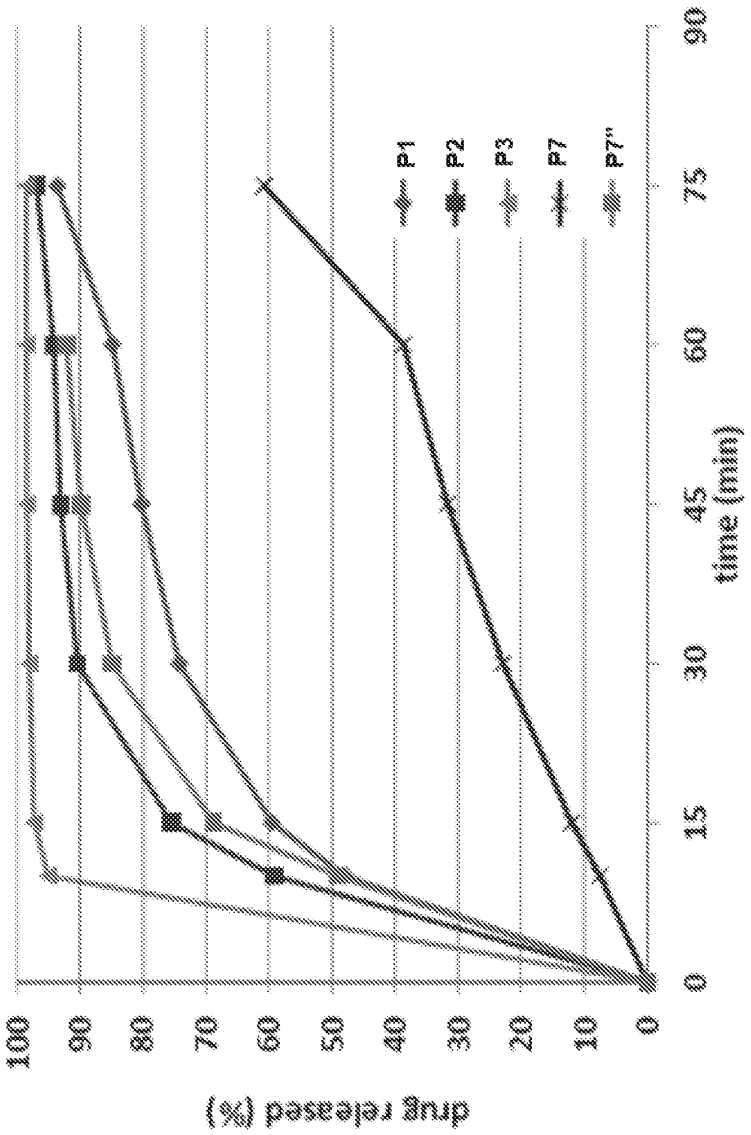

drug released (%)
100
90
80
70
60
50
40
30
20
10
0
0
15
30
45
60
75
90
time (min)
P1
P2
P3
P7
P7"

FIGURE 4

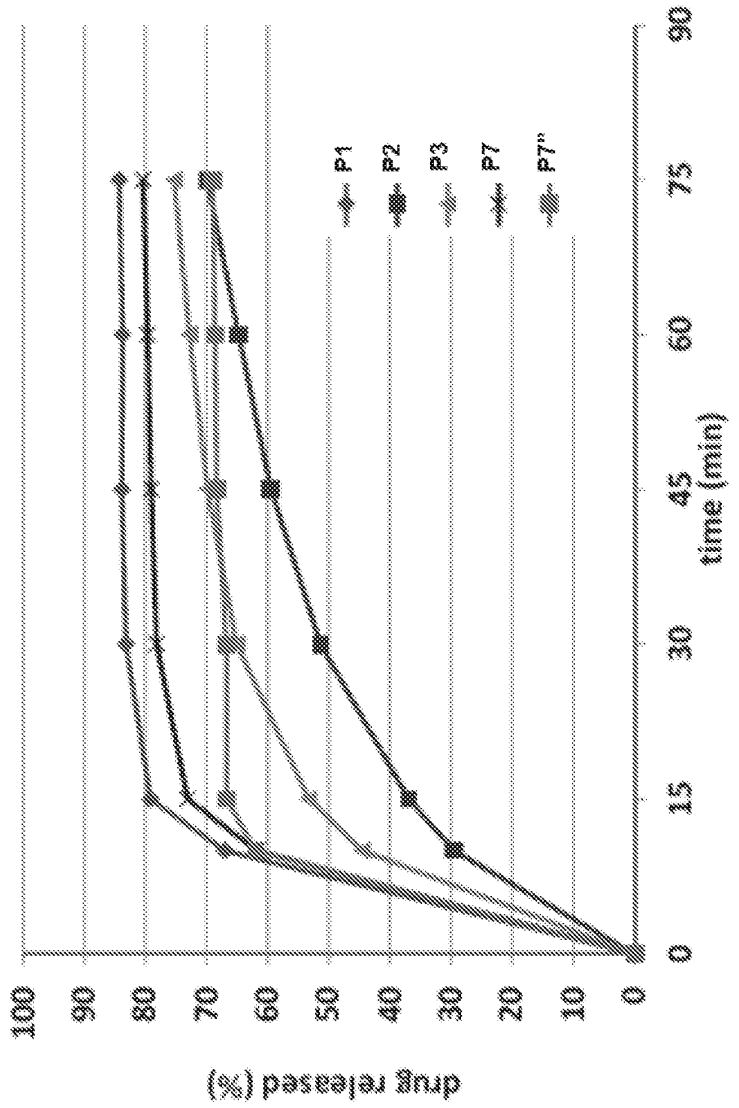

drug released (%)
100
90
80
70
60
50
40
30
20
10
0
0
15
30
45
60
75
90
time (min)
P1
P2
P3
P7
P7"

FIGURE 5

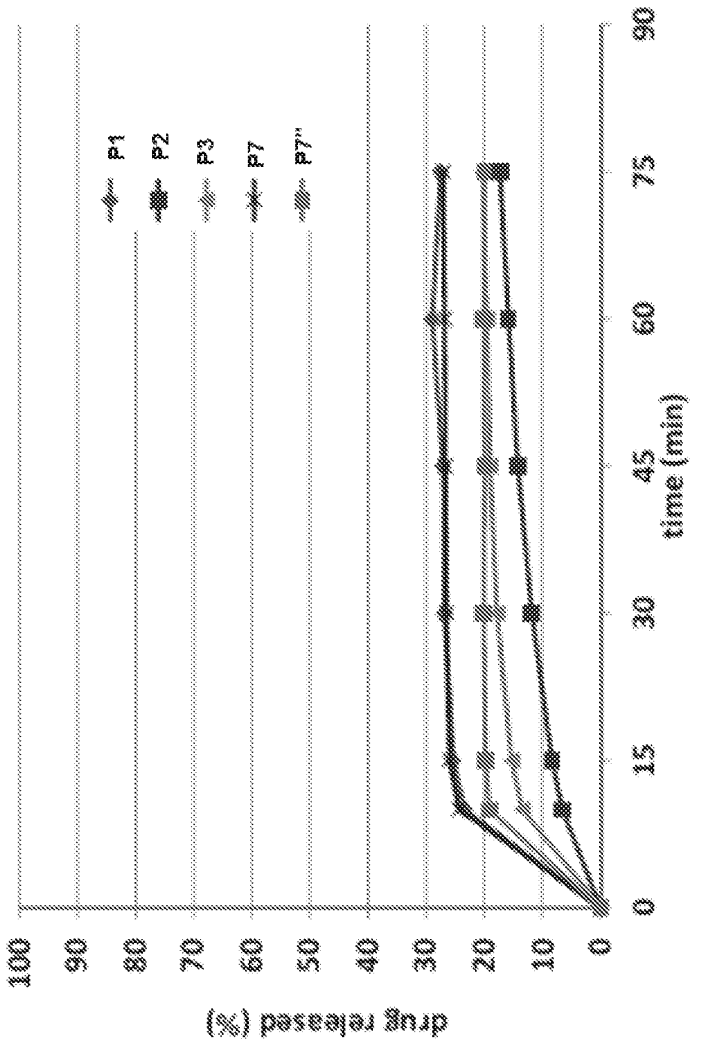

drug released (%)
100
90
80
70
60
50
40
30
20
10
0
0
15
30
45
60
75
90
time (min)
P1
P2
P3
P7
P7''

FIGURE 6

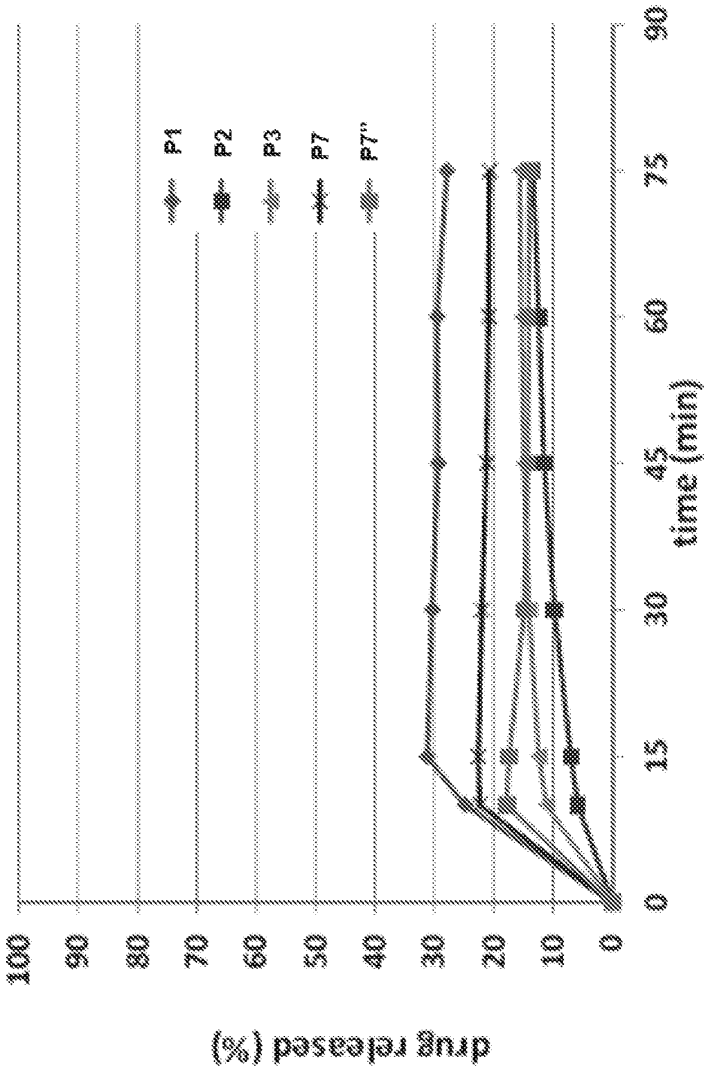

drug released (%)
100
90
80
70
60
50
40
30
20
10
0
0
15
30
45
60
75
90
time (min)
P1
P2
P3
P7
P7''

FIGURE 7

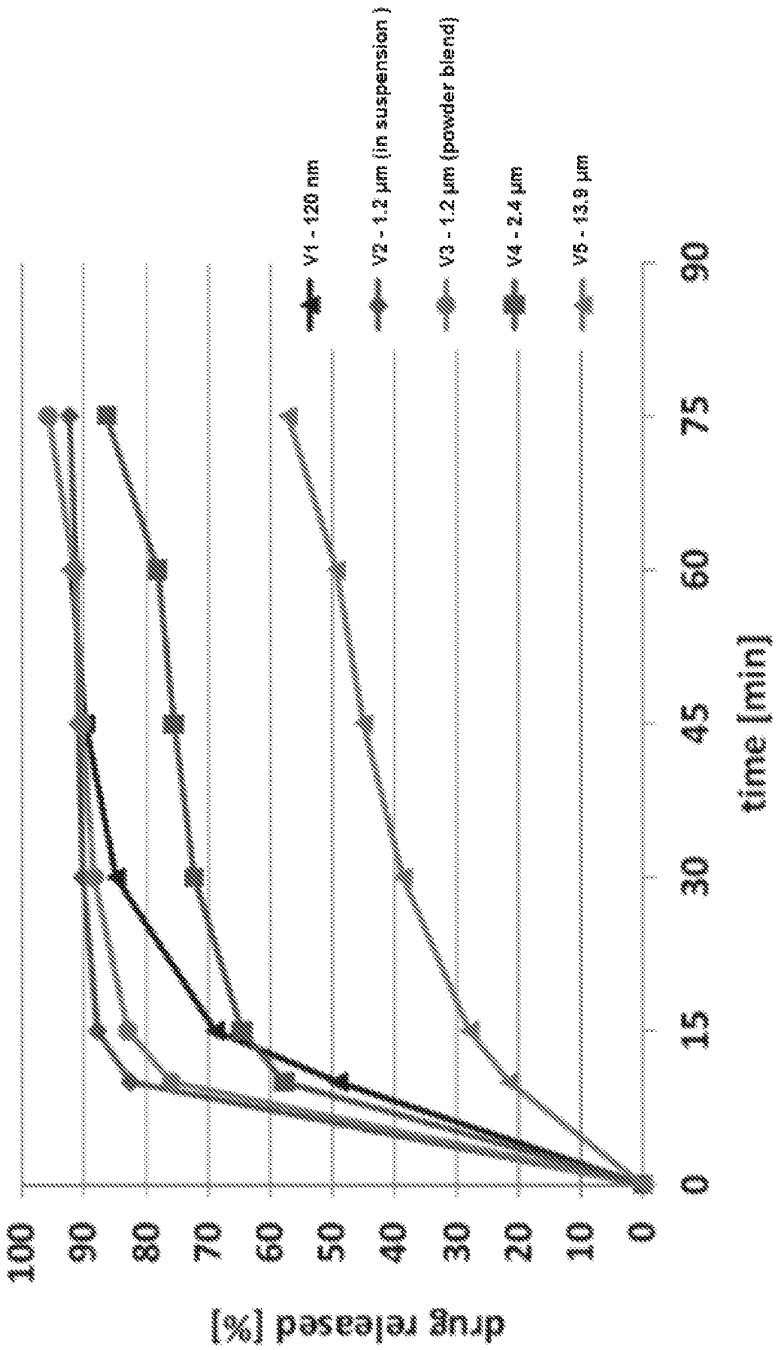

drug released [%]
100
90
80
70
60
50
40
30
20
10
0
time [min]
0
15
30
45
60
75
90
V1 - 128 nm
V2 - 1.2 µm (in suspension)
V3 - 1.2 µm (powder blend)
V4 - 2.4 µm
V5 - 13.9 µm

FIGURE 8

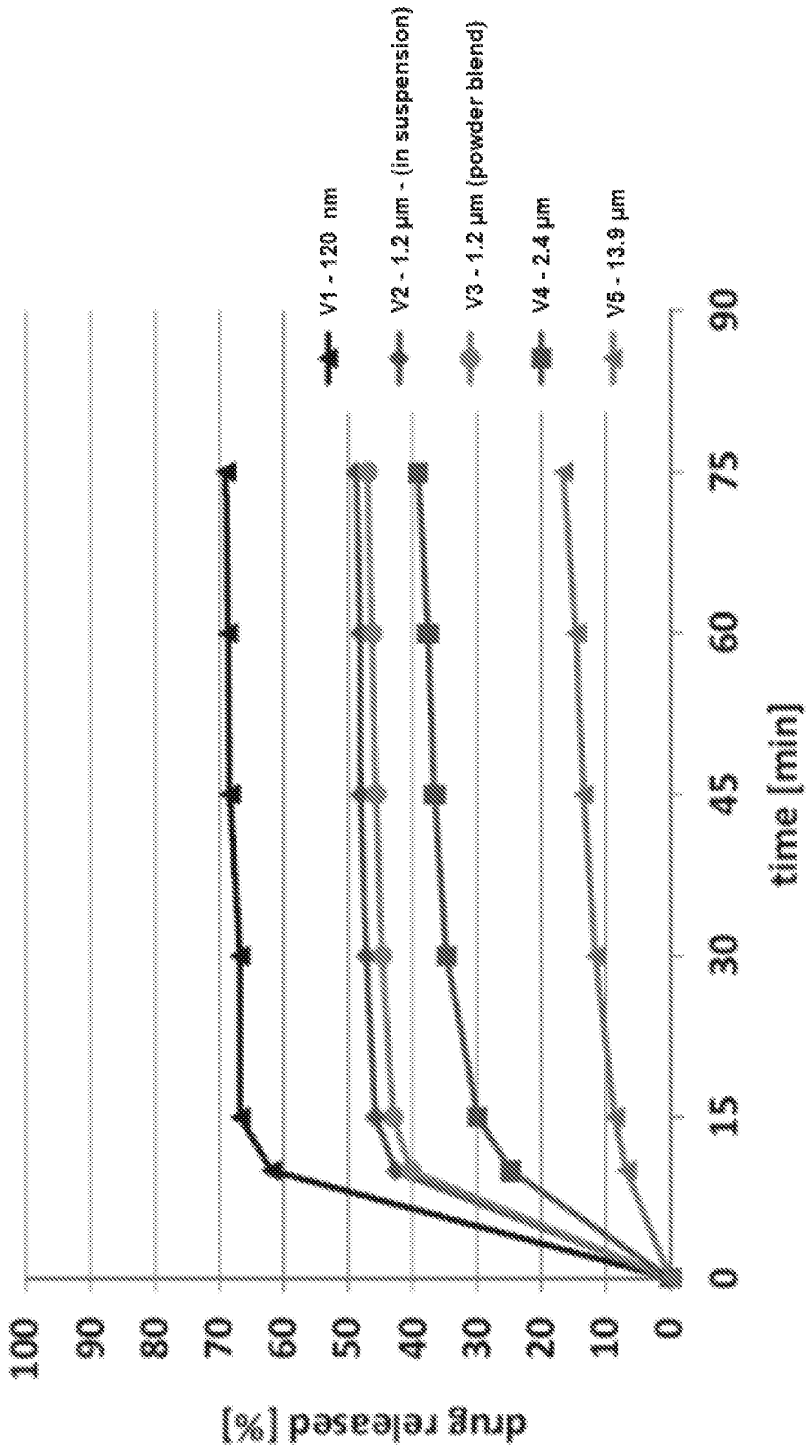

V1 - 120 nm
V2 - 1.2 µm - (in suspension)
V3 - 1.2 µm (powder blend)
V4 - 2.4 µm
V5 - 13.9 µm
drug released [%]
time [min]
0
10
20
30
40
50
60
70
80
90
100
0
15
30
45
60
75
90

FIGURE 9

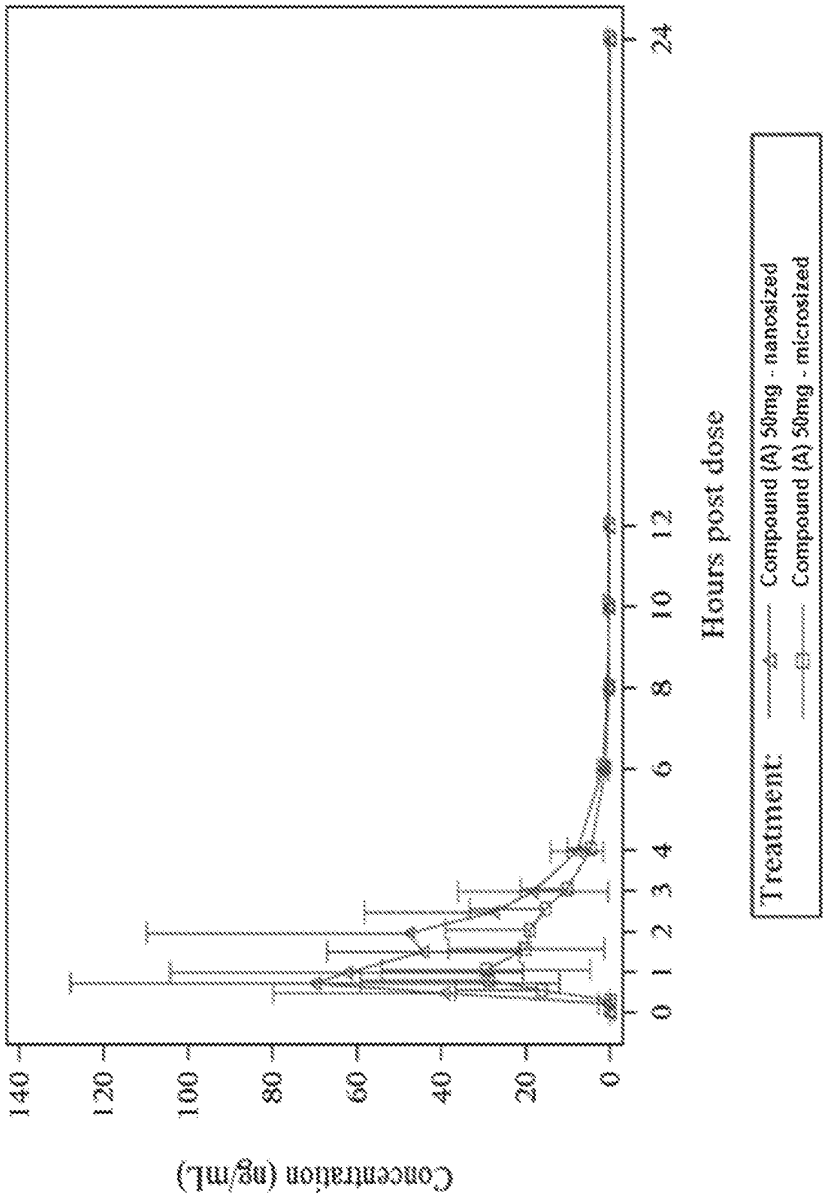

Concentration (pg/mL)
140
120
100
80
60
40
20
0
0 1 2 3 4 6 8 10 12 24
Hours post dose
Treatment:
Compound (A) 50mg - nanosized
Compound (A) 50mg - microsized

FIGURE 10

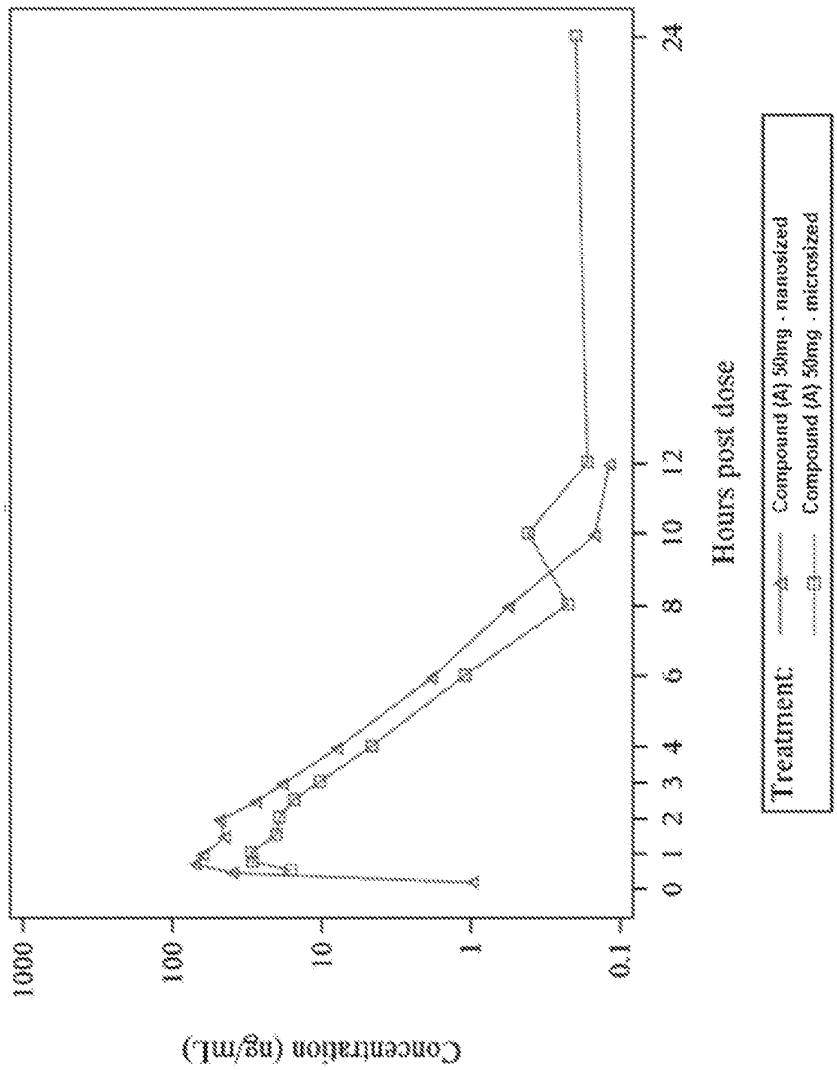

Concentration (ng/mL)
1000
100
10
1
0.1
0 1 2 3 4 6 8 10 12 24
Hours post dose
Treatment:
Compound (A) 50mg - nanosized
Compound (A) 50mg - microsized

FIGURE 11

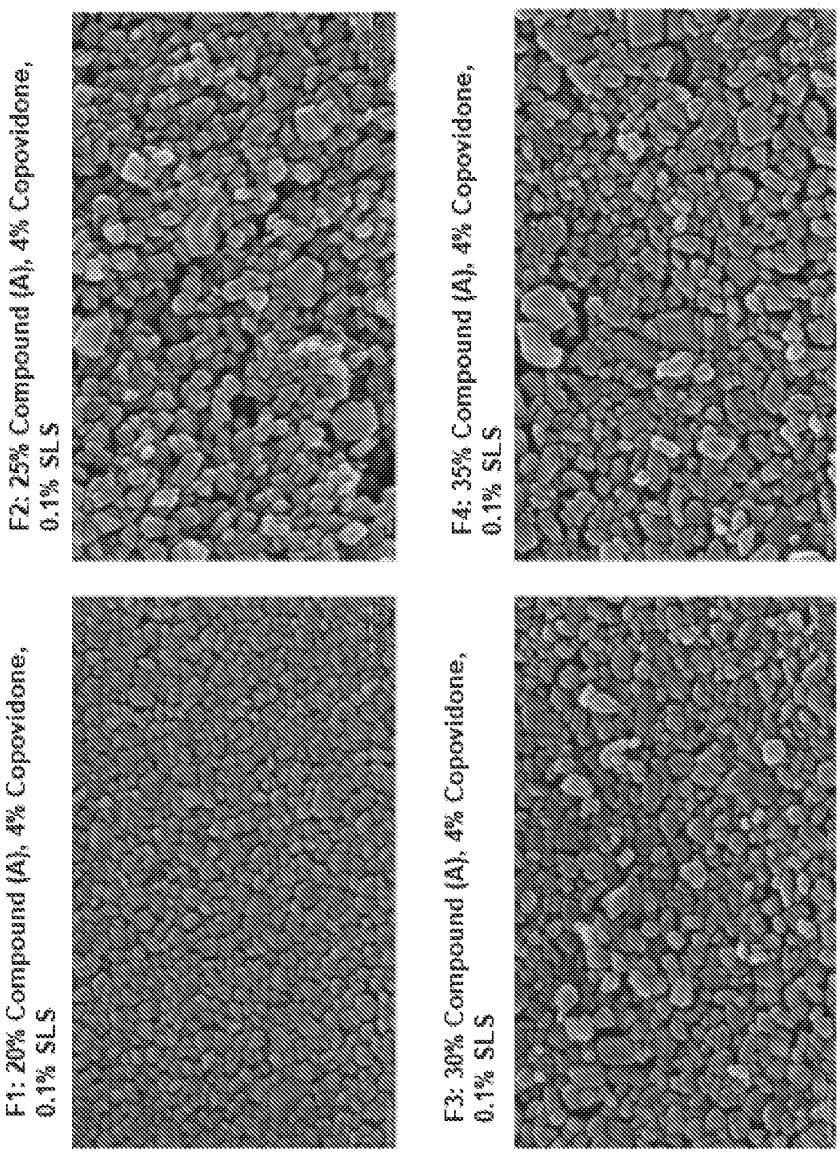

F1: 20% Compound (A), 4% Copovidone, 0.1% SLS
F2: 25% Compound (A), 4% Copovidone, 0.1% SLS
F3: 30% Compound (A), 4% Copovidone, 0.1% SLS
F4: 35% Compound (A), 4% Copovidone, 0.1% SLS

FIGURE 12

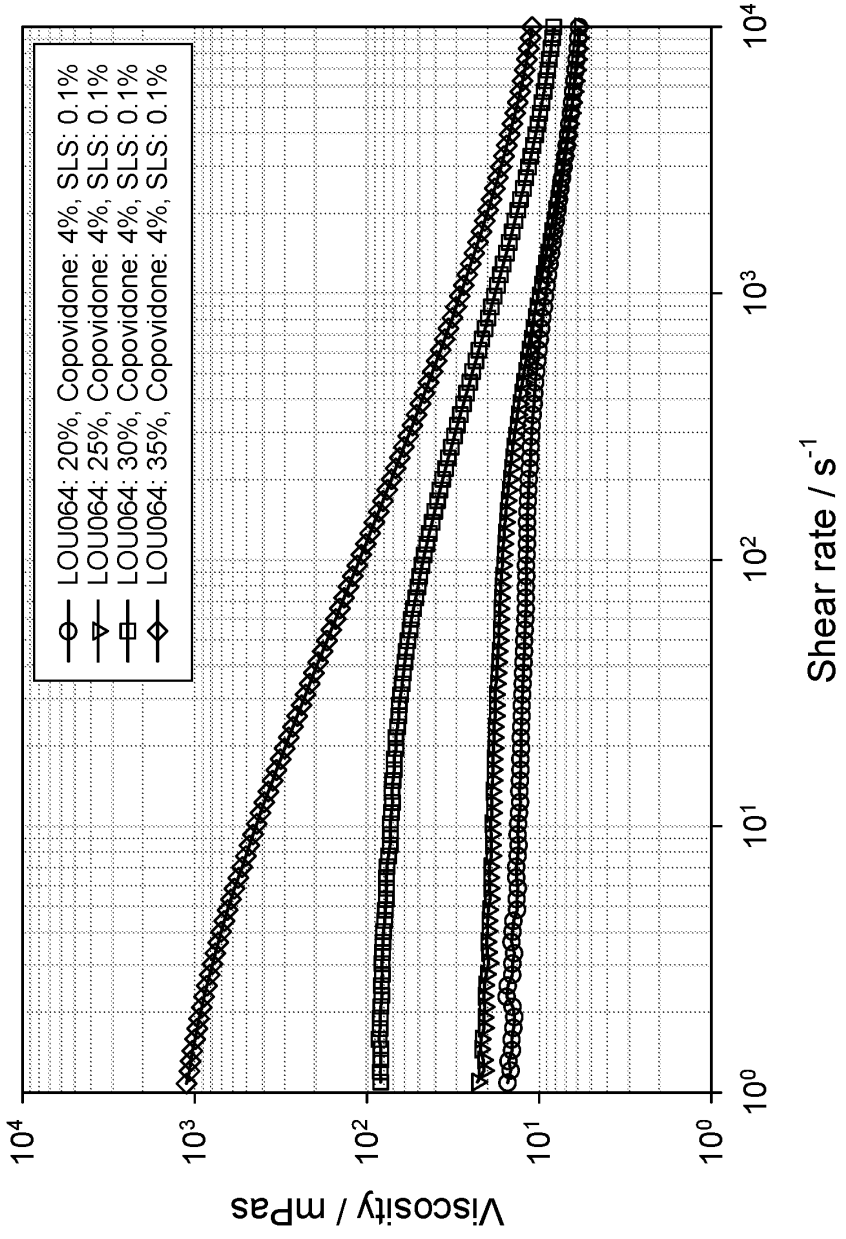

LOU064: 20%, Copovidone: 4%, SLS: 0.1%
LOU064: 25%, Copovidone: 4%, SLS: 0.1%
LOU064: 30%, Copovidone: 4%, SLS: 0.1%
LOU064: 35%, Copovidone: 4%, SLS: 0.1%
Viscosity / mPas
Shear rate / s-1
10^0
10^1
10^2
10^3
10^4

FIGURE 13

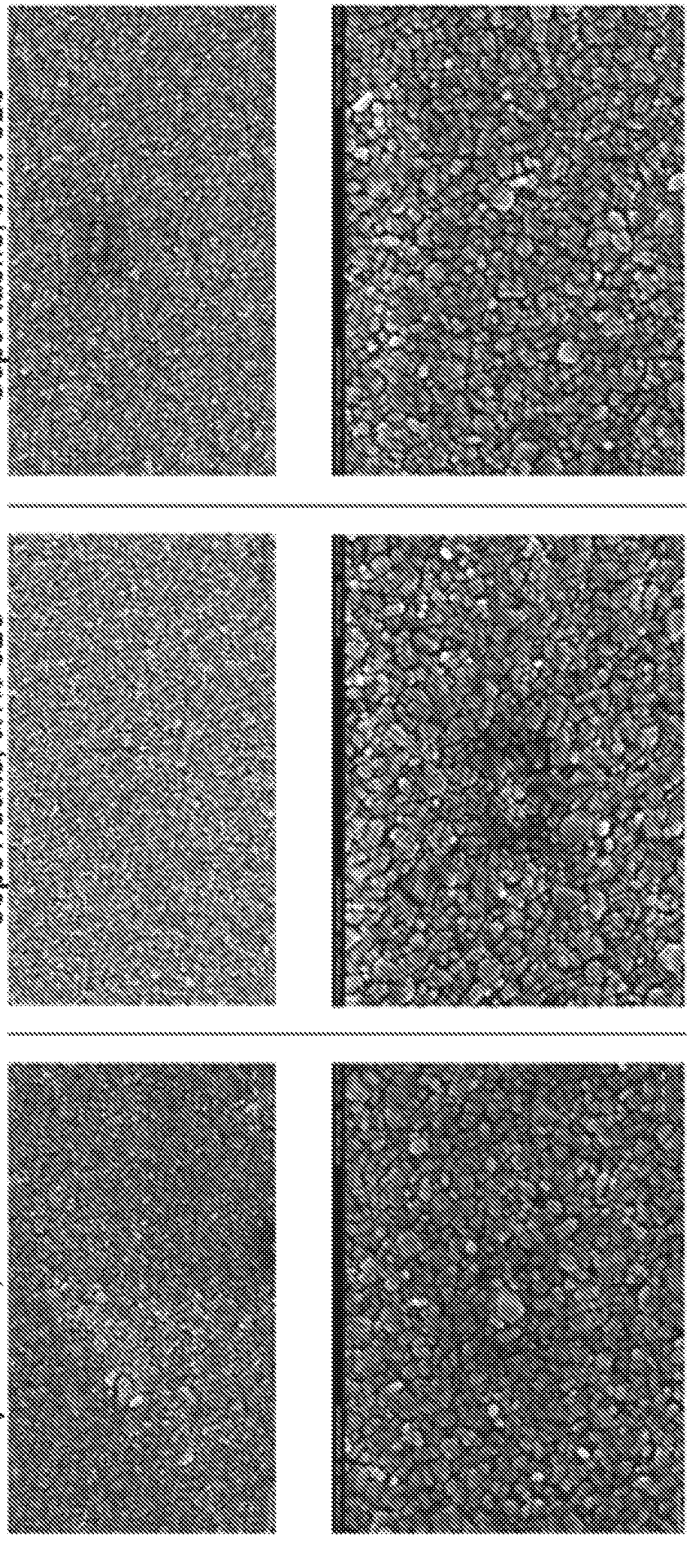

F2: 25% Compound (A), 4% Copovidone, 0.1% SLS
F6: 25% Compound (A), 3.5% Copovidone, 0.1% SLS
F5: 25% Compound (A), 3% Copovidone, 0.1% SLS

FIGURE 14

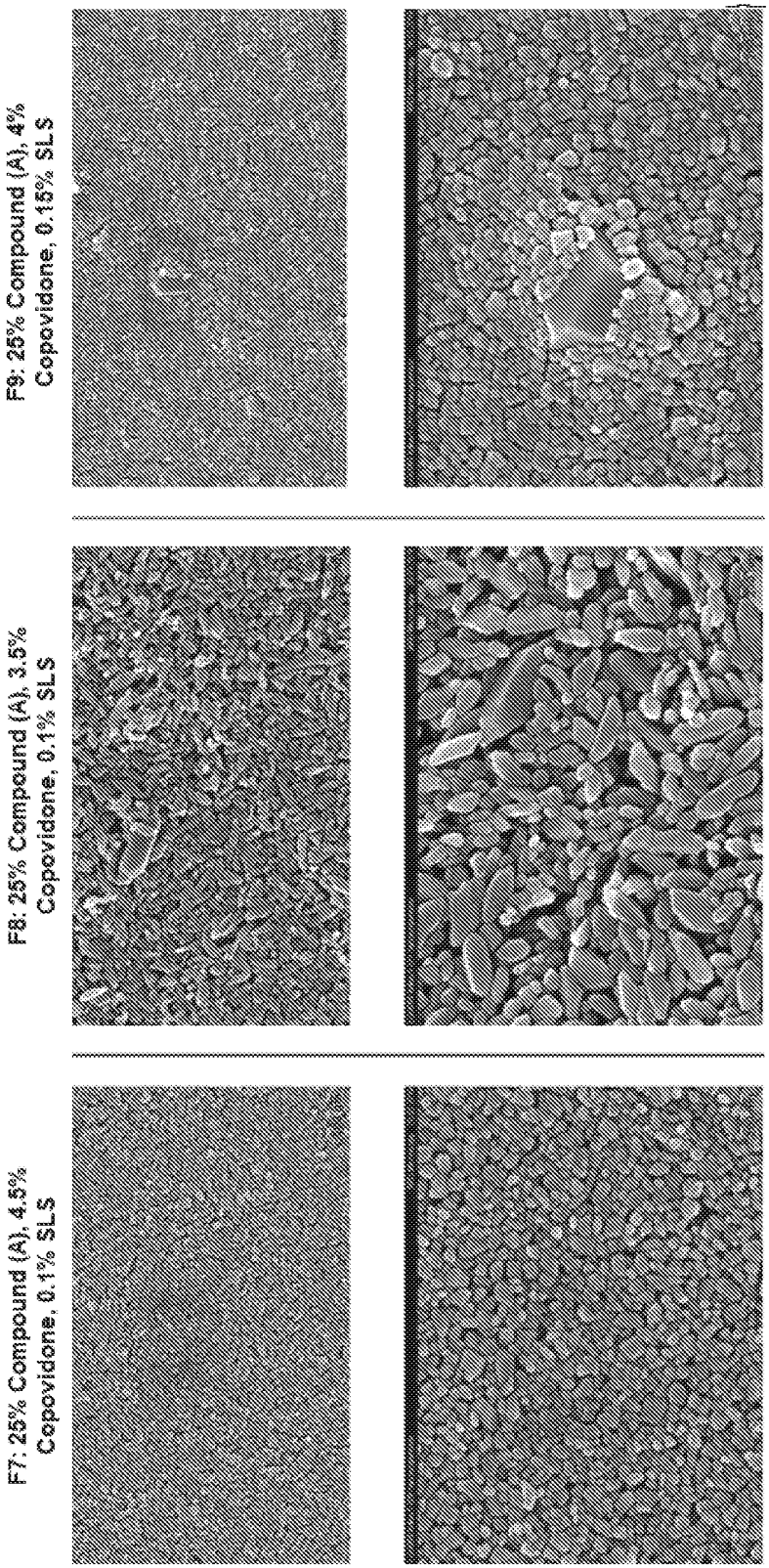

F9: 25% Compound (A), 4%
Copovidone, 0.15% SLS
F8: 25% Compound (A), 3.5%
Copovidone, 0.1% SLS
F7: 25% Compound (A), 4.5%
Copovidone, 0.1% SLS

FIGURE 15a

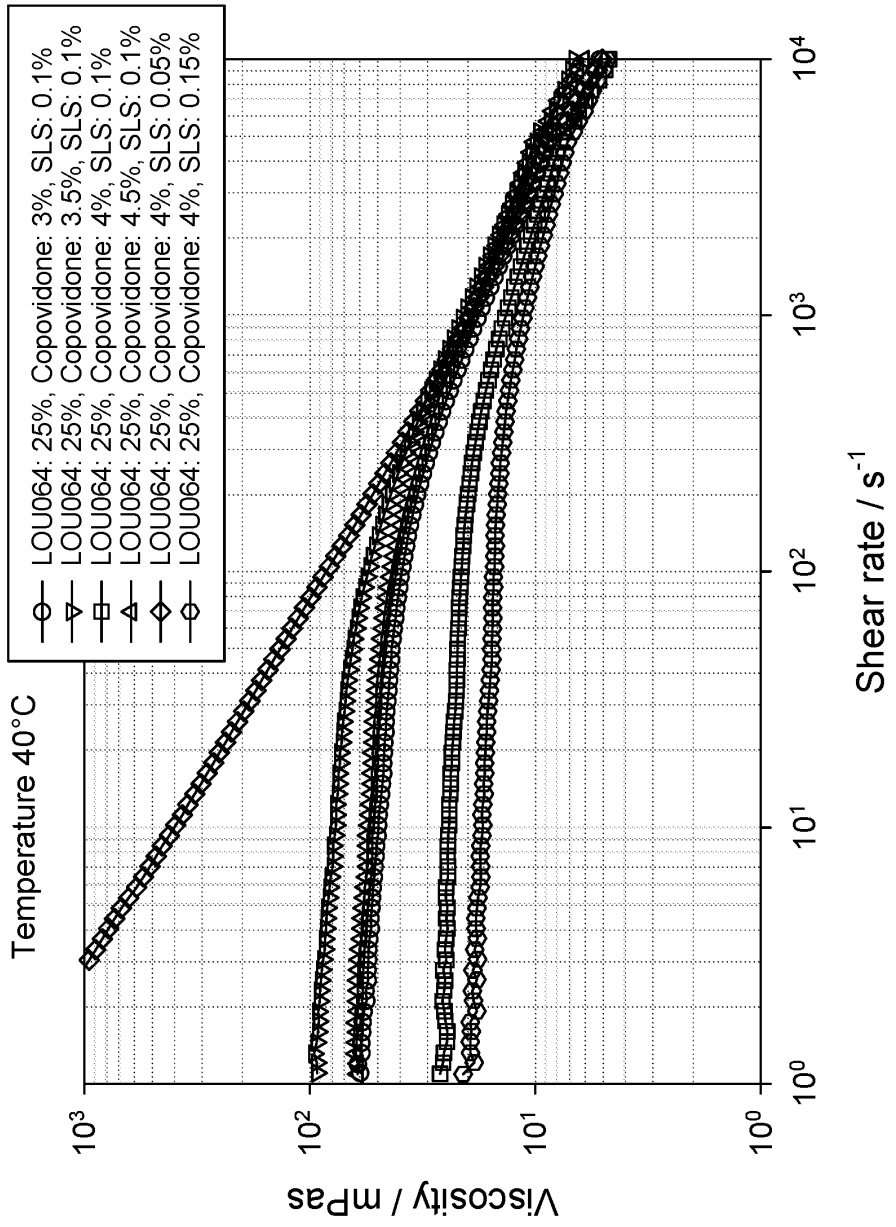

Temperature 40°C
LOU064: 25%, Copovidone: 3%, SLS: 0.1%
LOU064: 25%, Copovidone: 3.5%, SLS: 0.1%
LOU064: 25%, Copovidone: 4%, SLS: 0.1%
LOU064: 25%, Copovidone: 4.5%, SLS: 0.1%
LOU064: 25%, Copovidone: 4%, SLS: 0.05%
LOU064: 25%, Copovidone: 4%, SLS: 0.15%
Viscosity / mPas
10^3
10^2
10^1
10^0
10^0
10^1
10^2
10^3
10^4
Shear rate / s^{-1}

FIGURE 15b

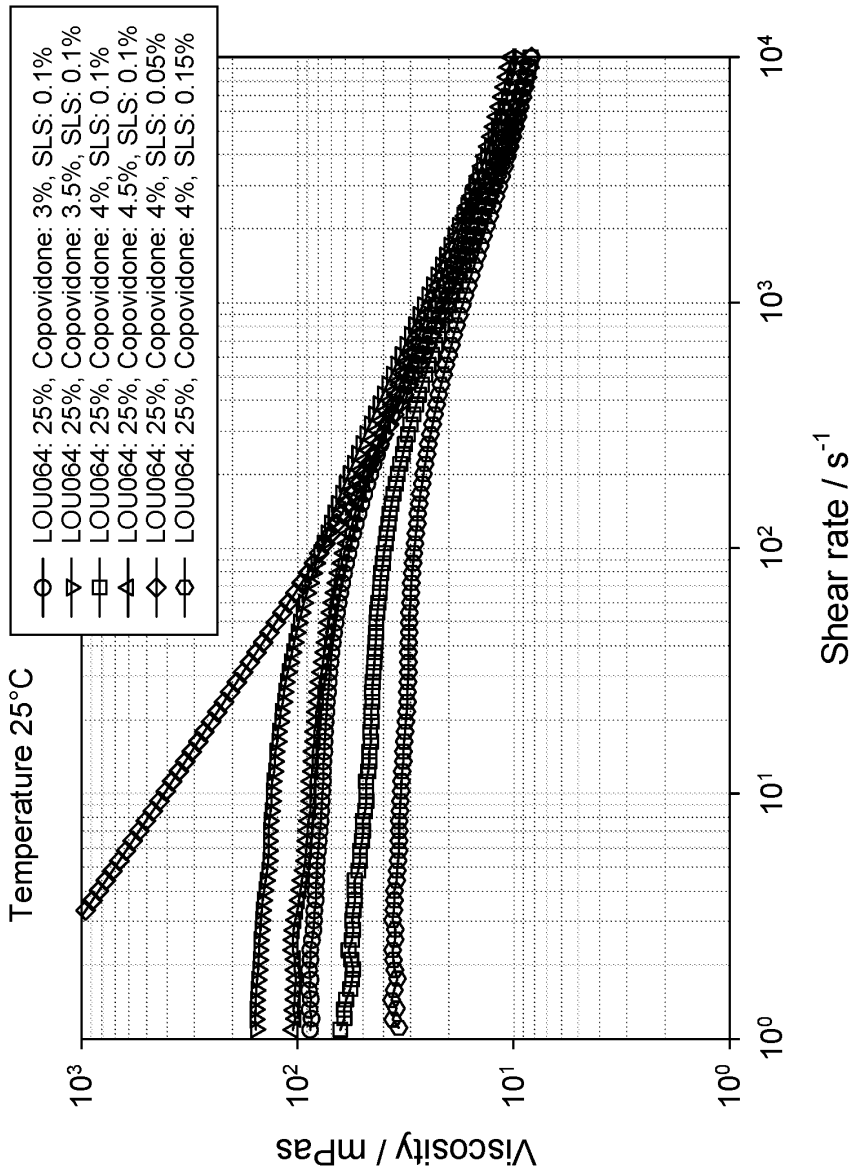

LOU064: 25%, Copovidone: 3%, SLS: 0.1%
LOU064: 25%, Copovidone: 3.5%, SLS: 0.1%
LOU064: 25%, Copovidone: 4%, SLS: 0.1%
LOU064: 25%, Copovidone: 4.5%, SLS: 0.1%
LOU064: 25%, Copovidone: 4%, SLS: 0.05%
LOU064: 25%, Copovidone: 4%, SLS: 0.15%
Temperature 25°C
Viscosity / mPas
Shear rate / s-1
10^3
10^2
10^1
10^0
10^0
10^1
10^2
10^3
10^4

FIGURE 15c

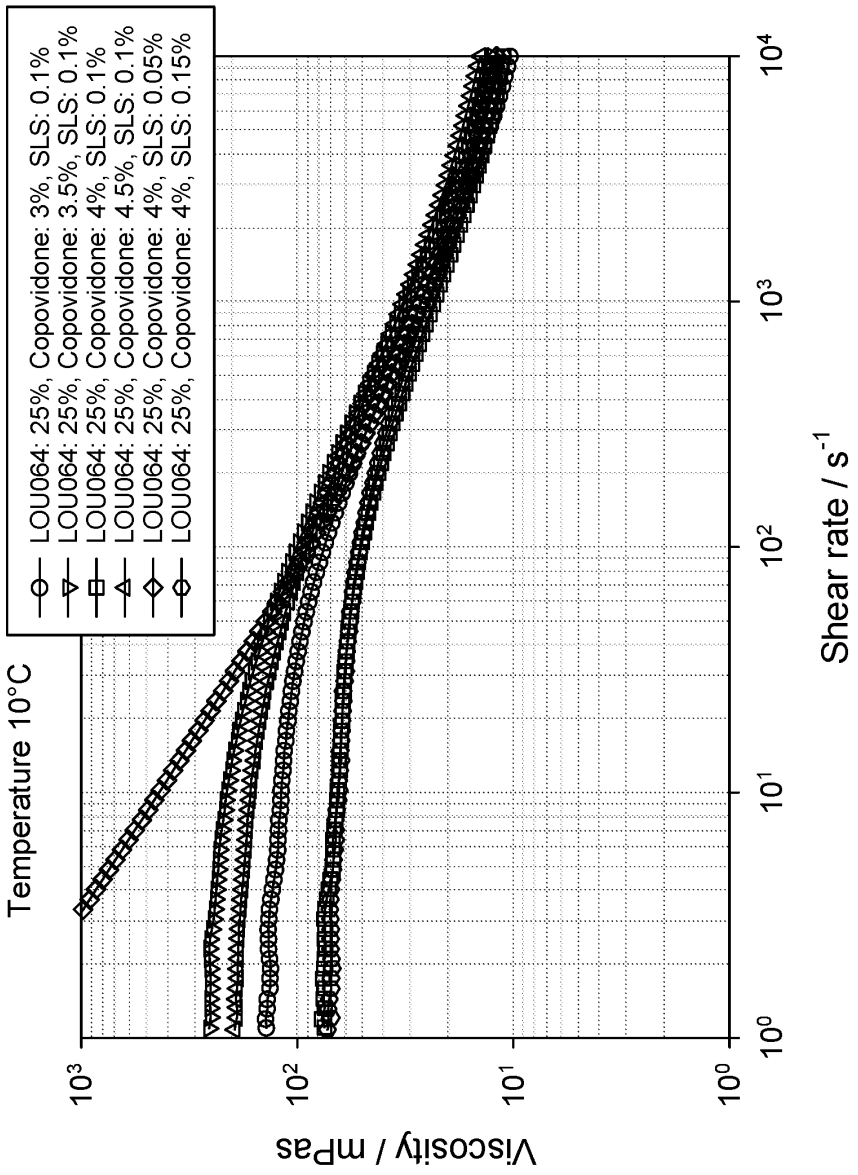

LOU064: 25%, Copovidone: 3%, SLS: 0.1%
LOU064: 25%, Copovidone: 3.5%, SLS: 0.1%
LOU064: 25%, Copovidone: 4%, SLS: 0.1%
LOU064: 25%, Copovidone: 4.5%, SLS: 0.1%
LOU064: 25%, Copovidone: 4%, SLS: 0.05%
LOU064: 25%, Copovidone: 4%, SLS: 0.15%
Temperature 10°C
Viscosity / mPas
Shear rate / s-1
10^3
10^2
10^1
10^0
10^0
10^1
10^2
10^3
10^4

FIGURE 16A

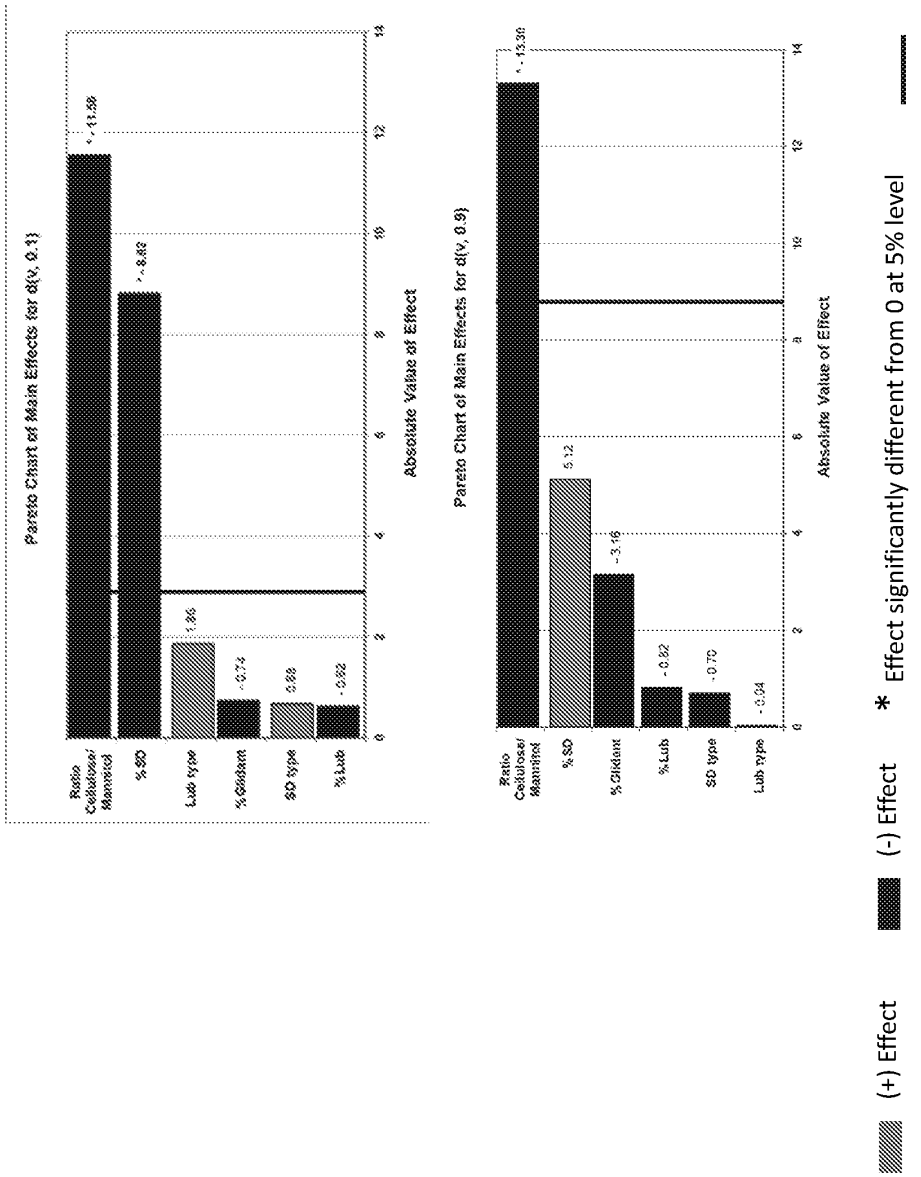

Pareto Chart of Main Effects for d(v, 0.1)
Ratio Cellulose/ Mannitol
%SD
Lub type
%Glidant
SD type
%Lub
Absolute Value of Effect
Pareto Chart of Main Effects for d(v, 0.9)
Ratio Cellulose/ Mannitol
%SD
%Glidant
%Lub
SD type
Lub type
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 16B

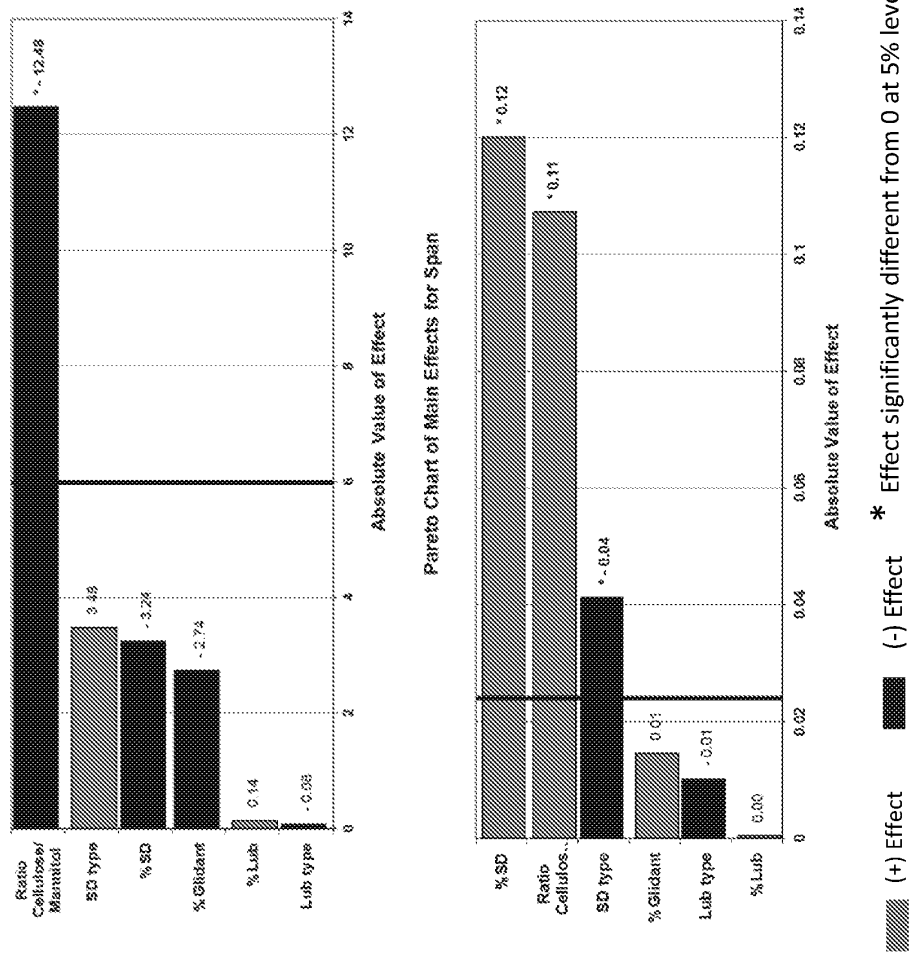

Pareto Chart of Main Effects for d(x, 0.5)
Ratio Cellulose/ Mannitol
SD type
% SD
% Glidant
% Lub
Lub type
* - 12.48
3.48
- 3.26
- 2.74
0.14
- 0.08
Absolute Value of Effect
Pareto Chart of Main Effects for Span
% SD
Ratio Cellulos...
SD type
% Glidant
Lub type
% Lub
* 0.12
* 0.11
* - 0.04
0.01
- 0.01
0.00
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 17

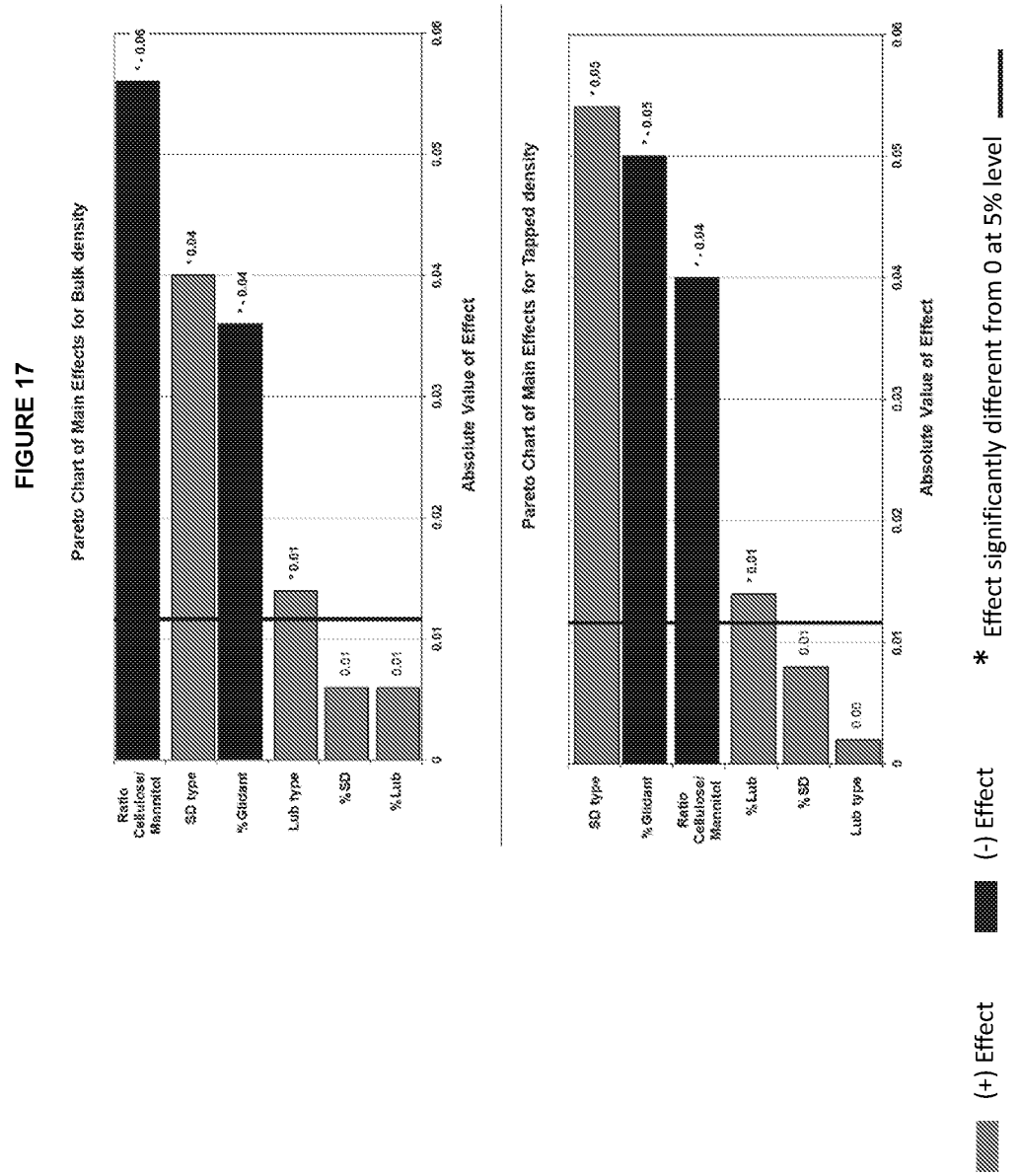

Pareto Chart of Main Effects for Bulk density
Ratio Cellulose/ Mannitol
SD type
% Glidant
Lub type
% SD
% Lub
Absolute Value of Effect
Pareto Chart of Main Effects for Tapped density
SD type
% Glidant
Ratio Cellulose/ Mannitol
% Lub
% SD
Lub type
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 18

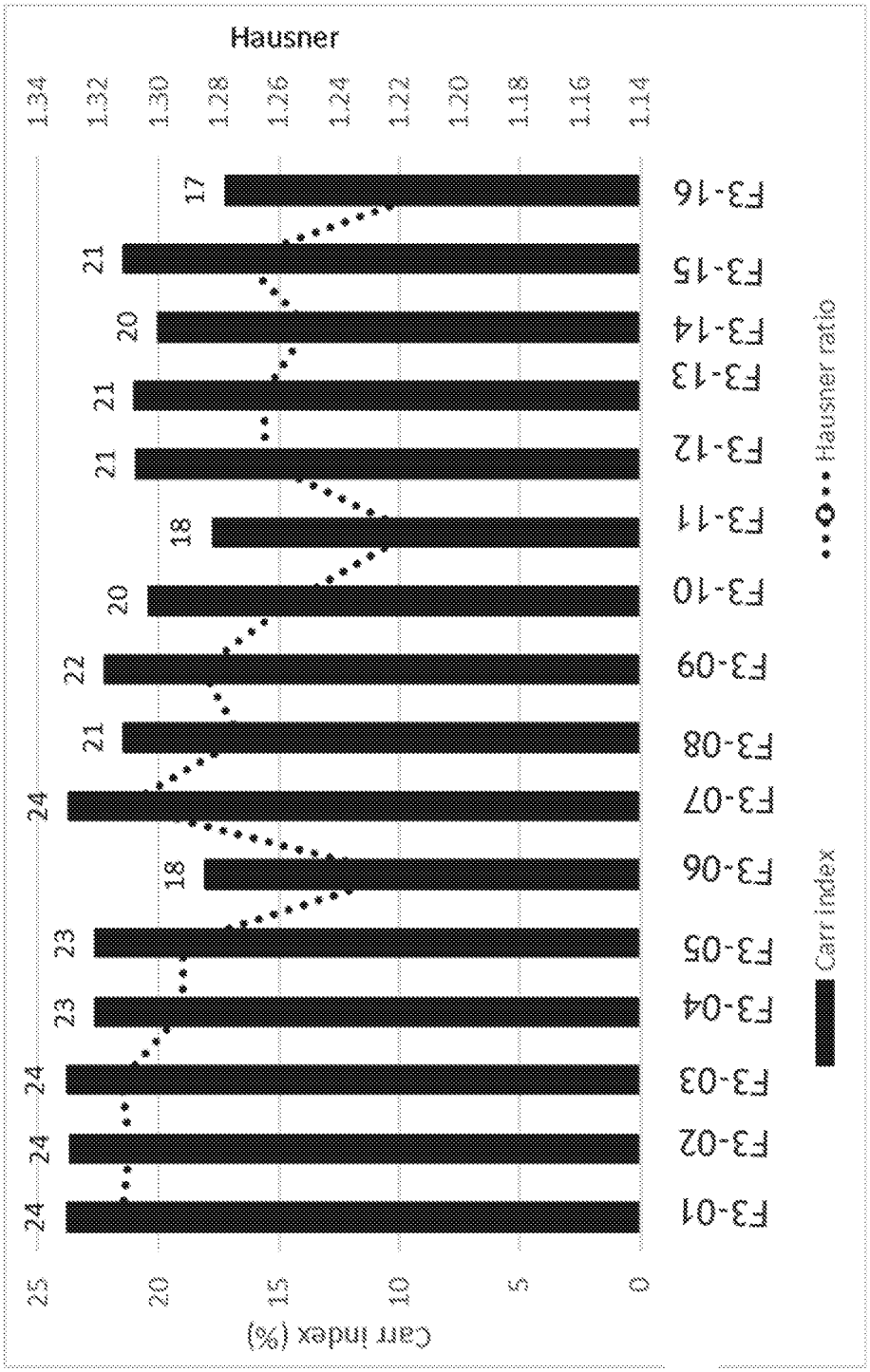

Hausner
1.34
1.32
1.30
1.28
1.26
1.24
1.22
1.20
1.18
1.16
1.14
F3-16
F3-15
F3-14
F3-13
F3-12
F3-11
F3-10
F3-09
F3-08
F3-07
F3-06
F3-05
F3-04
F3-03
F3-02
F3-01
17
21
20
21
21
18
20
22
21
24
18
23
23
24
24
24
25
20
15
10
5
0
Carr index (%)
Carr index
Hausner ratio

FIGURE 19

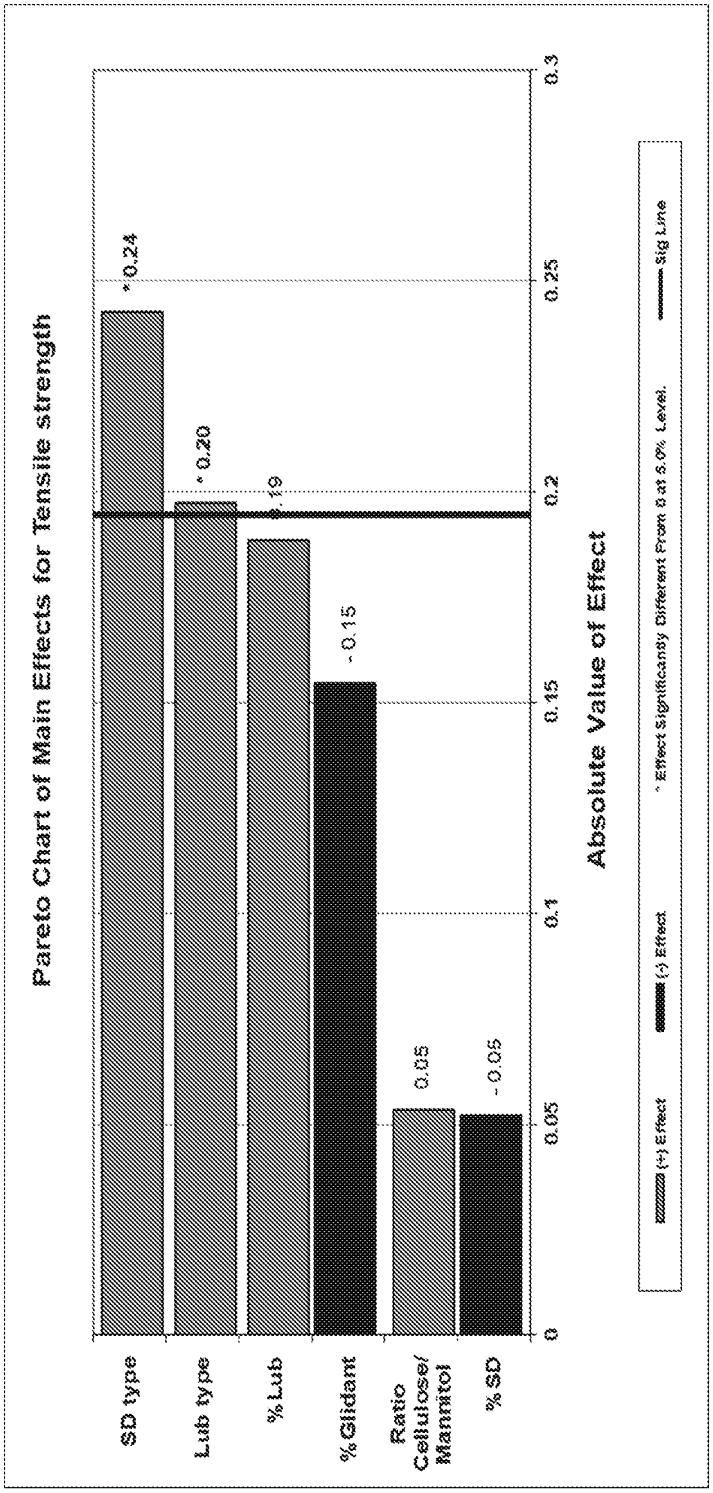

Pareto Chart of Main Effects for Tensile strength
SD type
Lub type
% Lub
% Glidant
Ratio Cellulose/ Mannitol
% SD
0.24
0.20
0.19
-0.15
0.05
-0.05
0
0.05
0.1
0.15
0.2
0.25
0.3
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect Significantly Different From 0 at 5.0% Level.
Sig Line

FIGURE 20

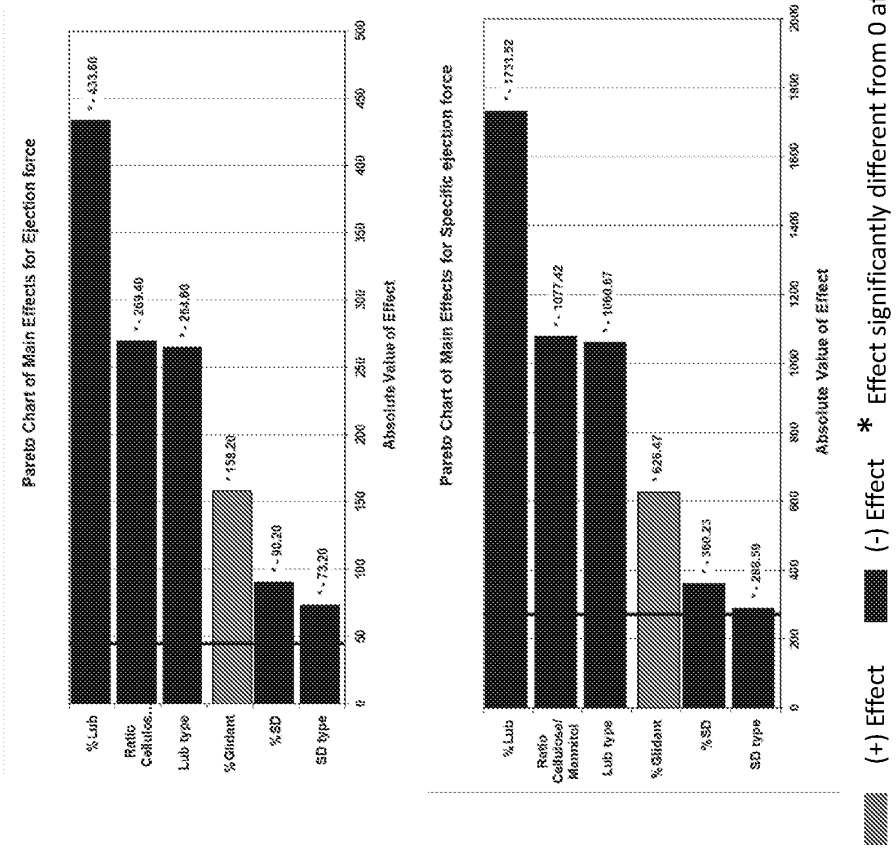

Pareto Chart of Main Effects for Ejection force
% Lub
Ratio Cellulose...
Lub type
% Glidant
% SD
SD type
Absolute Value of Effect
Pareto Chart of Main Effects for Specific ejection force
% Lub
Ratio Cellulose/ Mannitol
Lub type
% Glidant
% SD
SD type
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 21

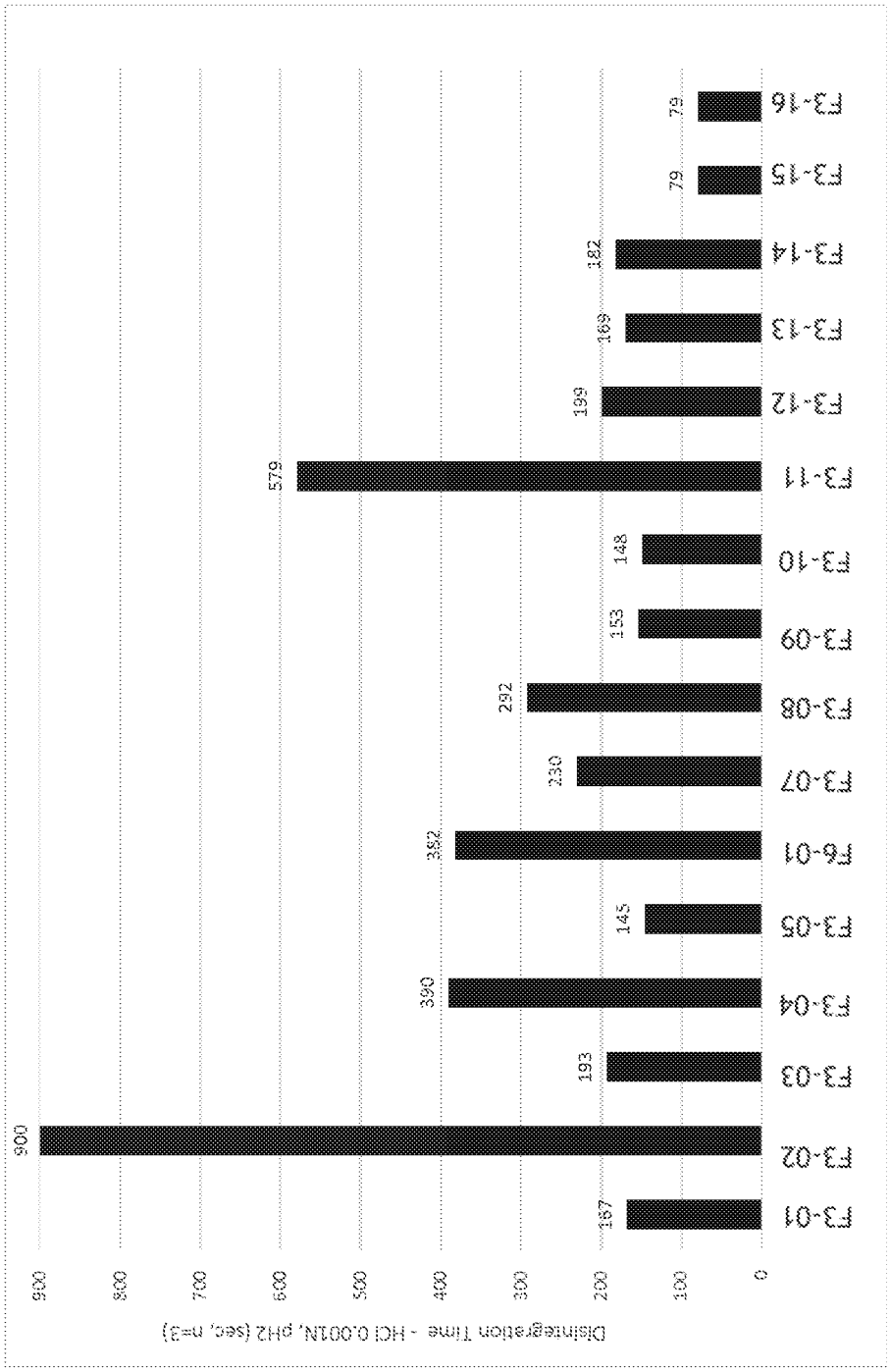

Disintegration Time - HCl 0.001N, pH2 (sec, n=3)
0
100
200
300
400
500
600
700
800
900
F3-01
187
F3-02
900
F3-03
193
F3-04
390
F3-05
145
F6-01
392
F3-07
230
F3-08
292
F3-09
153
F3-10
148
F3-11
579
F3-12
199
F3-13
169
F3-14
182
F3-15
79
F3-16
79

FIGURE 22

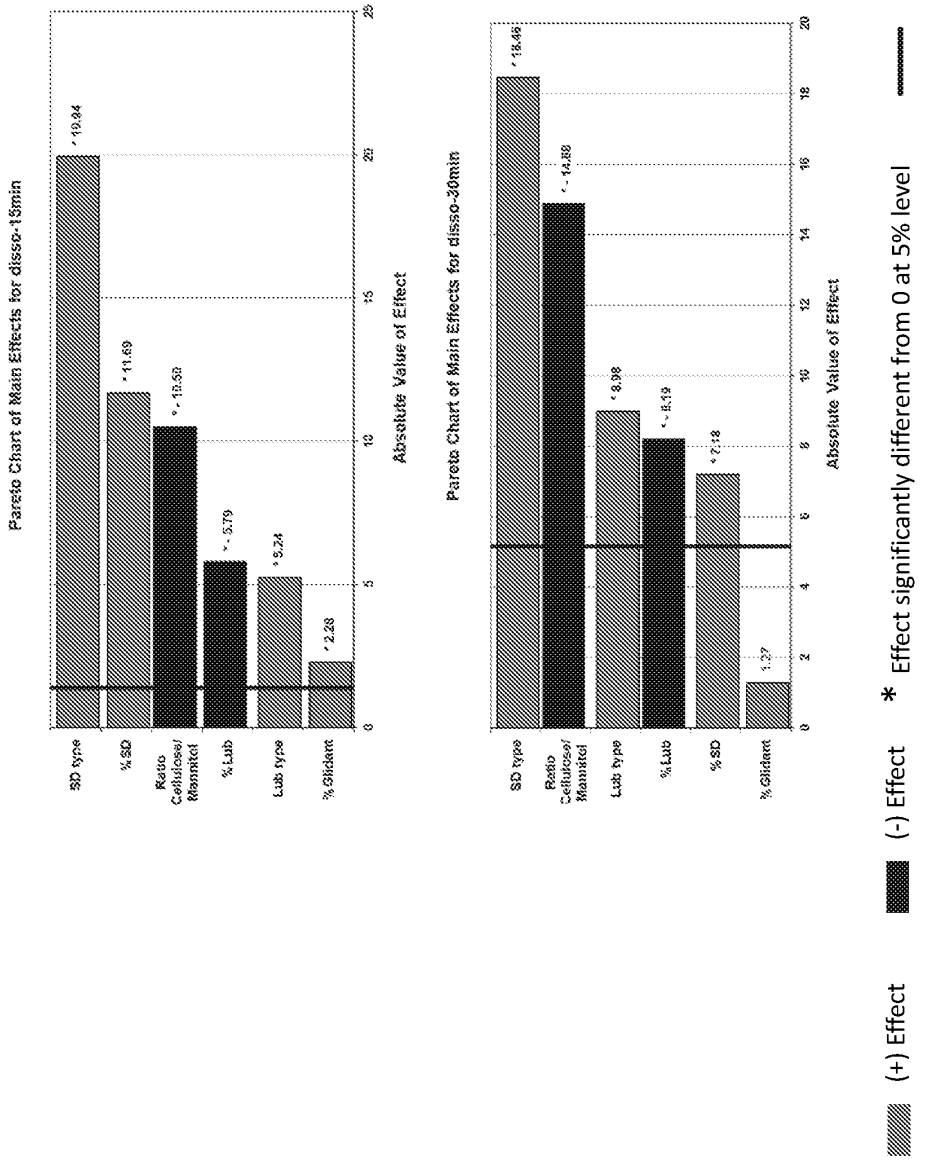

Pareto Chart of Main Effects for disso-15min
SD type
% SD
Ratio Cellulose/ Mannitol
% Lub
Lub type
% Glidant
Absolute Value of Effect
Pareto Chart of Main Effects for disso-30min
SD type
Ratio Cellulose/ Mannitol
Lub type
% Lub
% SD
% Glidant
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 23A

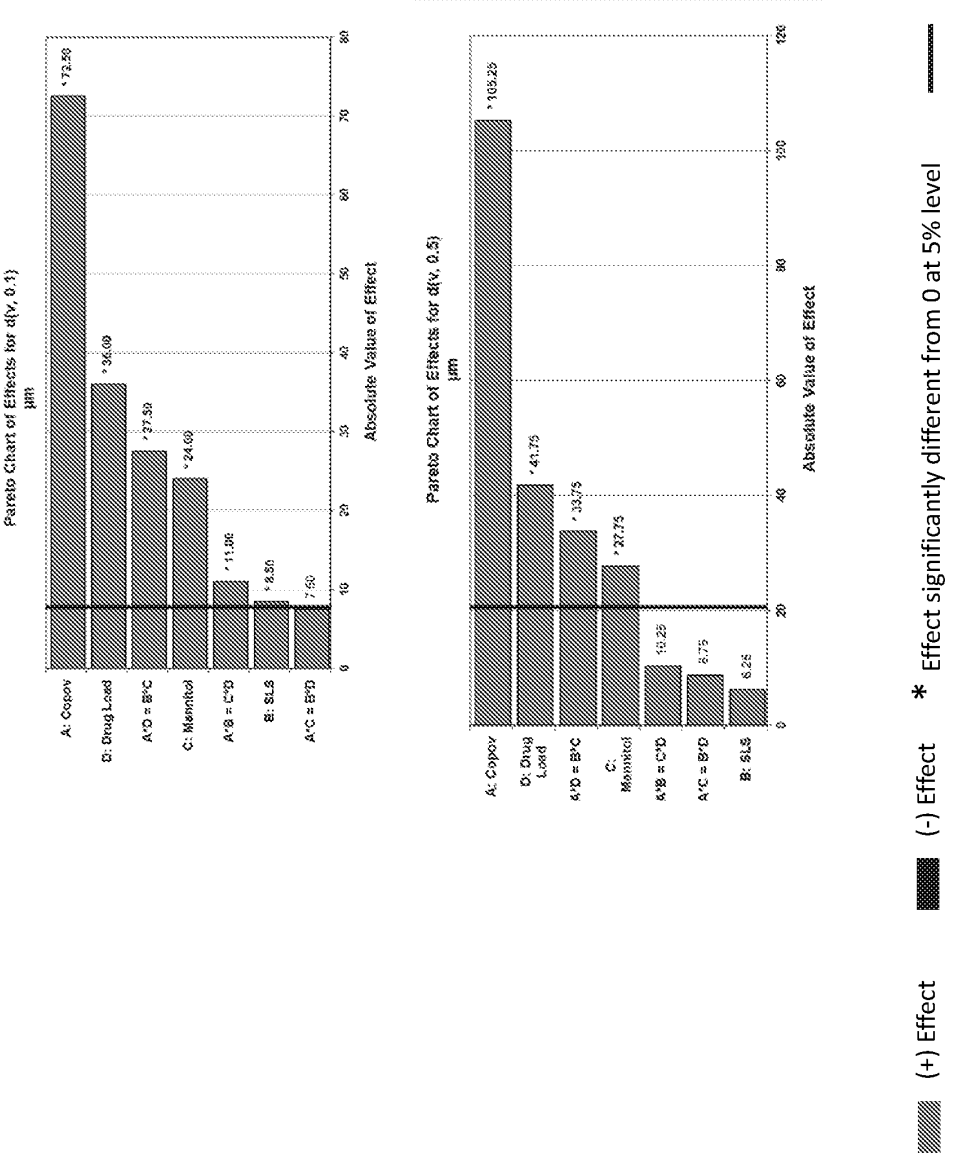

Pareto Chart of Effects for d(v, 0.1)
μm
A: Copov
D: Drug Load
A*D = B*C
C: Mannitol
A*B = C*D
B: SLS
A*C = B*D
72.50
36.69
27.50
24.69
11.06
8.56
7.50
Absolute Value of Effect
Pareto Chart of Effects for d(v, 0.5)
μm
A: Copov
D: Drug Load
A*D = B*C
C: Mannitol
A*B = C*D
A*C = B*D
B: SLS
105.25
41.75
33.75
27.75
13.25
8.75
6.25
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 23B

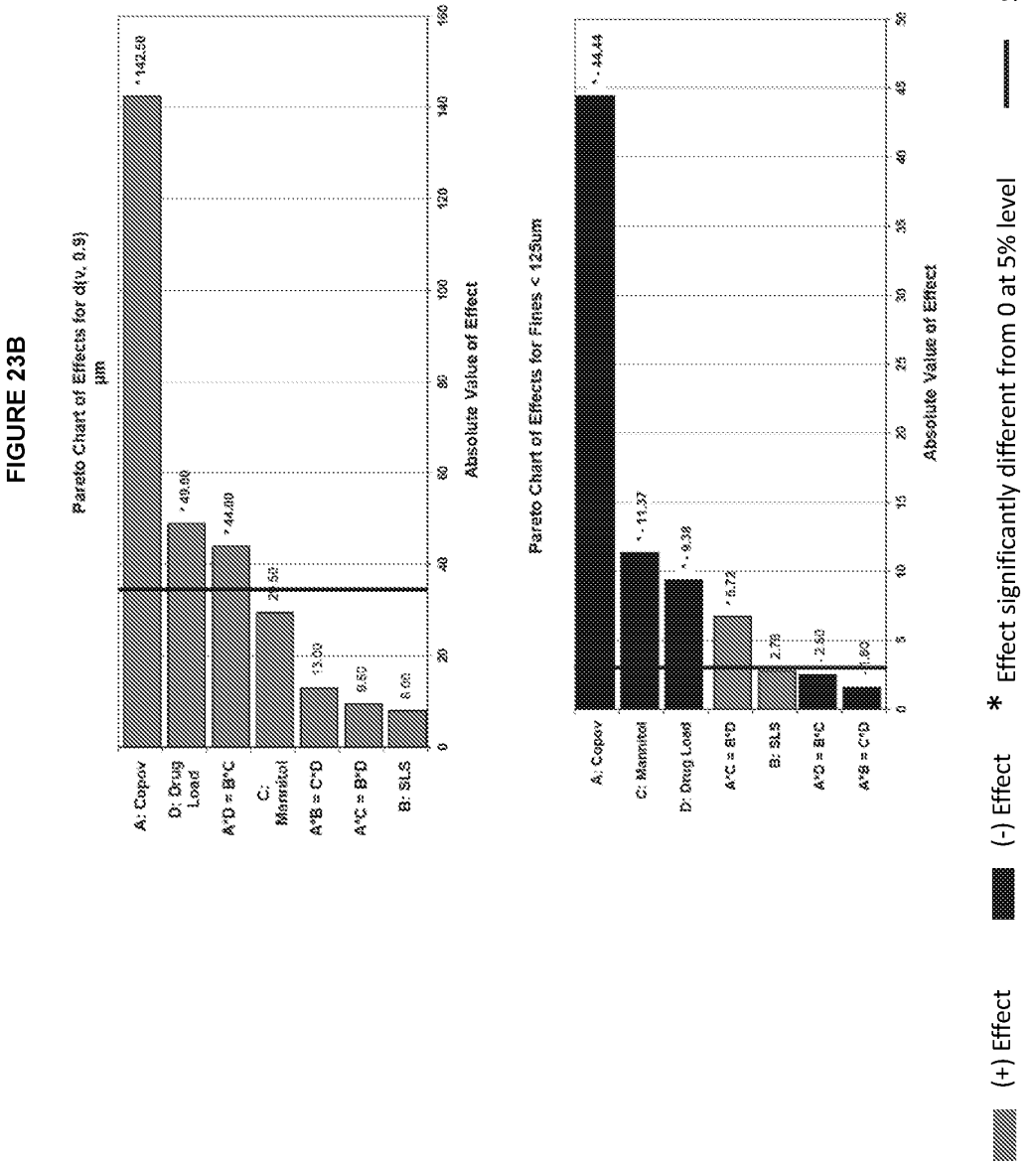

Pareto Chart of Effects for d(v, 0.9)
µm
A: Copov
D: Drug Load
A*D = B*C
C: Mannitol
A*B = C*D
A*C = B*D
B: SLS
142.58
49.80
44.80
25.62
13.50
9.52
8.66
Absolute Value of Effect
Pareto Chart of Effects for Fines < 125um
A: Copov
C: Mannitol
D: Drug Load
A*C = B*D
B: SLS
A*D = B*C
A*B = C*D
44.44
11.37
9.38
6.72
2.78
2.62
1.80
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 24

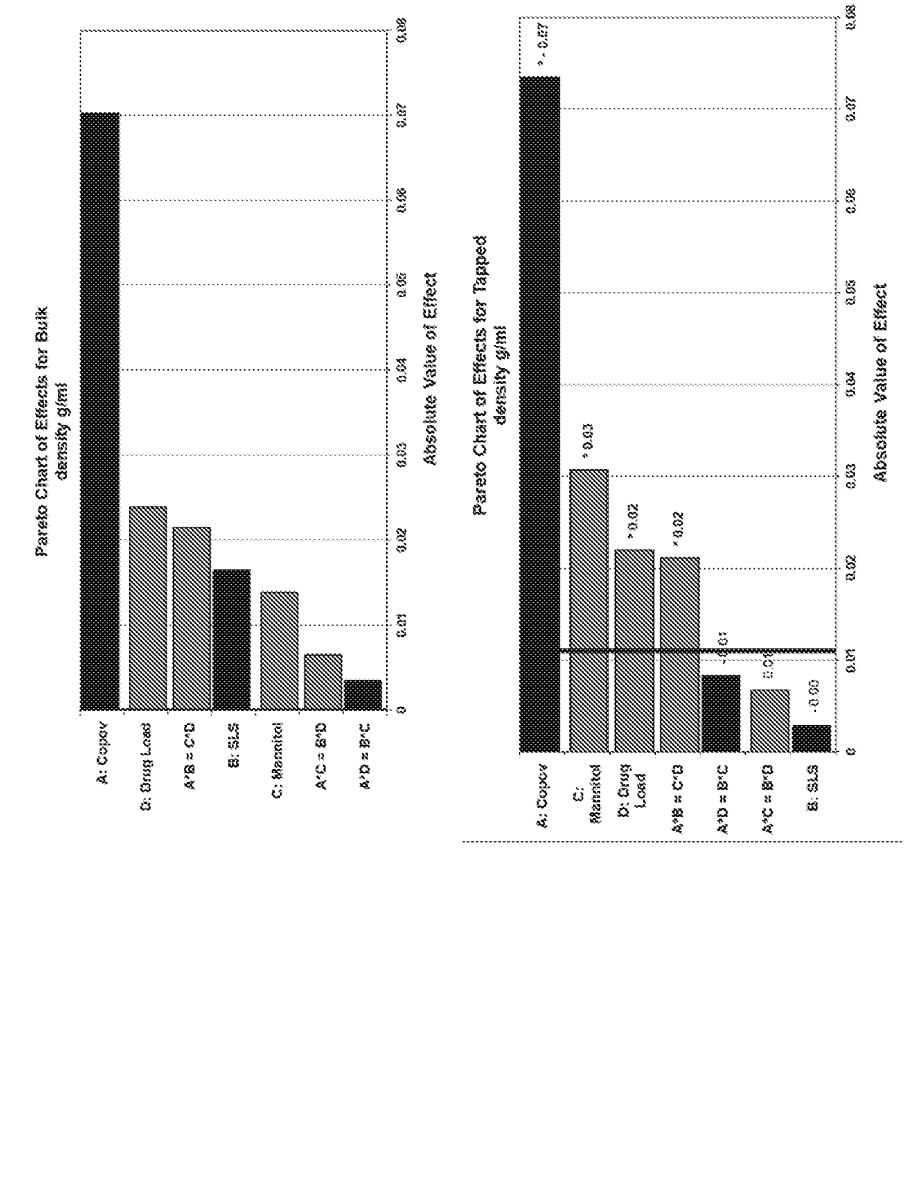

Pareto Chart of Effects for Bulk density g/ml
A: Copov
D: Drug Load
A*B = C*D
B: SLS
C: Mannitol
A*C = B*D
A*D = B*C
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
Absolute Value of Effect
Pareto Chart of Effects for Tapped density g/ml
A: Copov
C: Mannitol
D: Drug Load
A*B = C*D
A*D = B*C
A*C = B*D
B: SLS
0.07
0.03
0.02
0.02
0.01
0.01
0.00
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 25

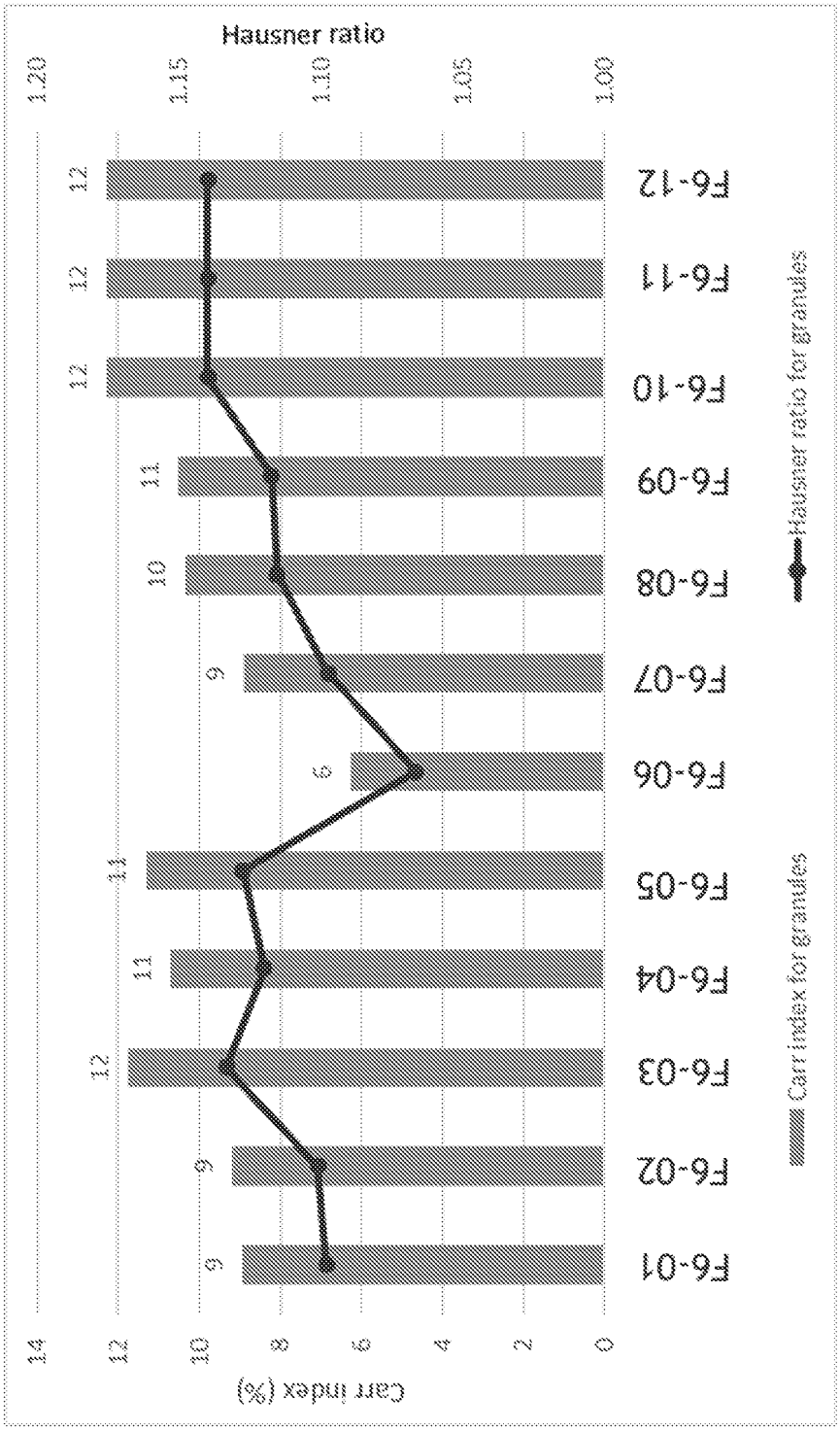

Hausner ratio
1.20
1.15
1.10
1.05
1.00
F6-12
F6-11
F6-10
F6-09
F6-08
F6-07
F6-06
F6-05
F6-04
F6-03
F6-02
F6-01
12
12
12
11
10
9
9
11
11
12
9
9
Carr index (%)
14
12
10
8
6
4
2
0
Carr index for granules
Hausner ratio for granules

FIGURE 26

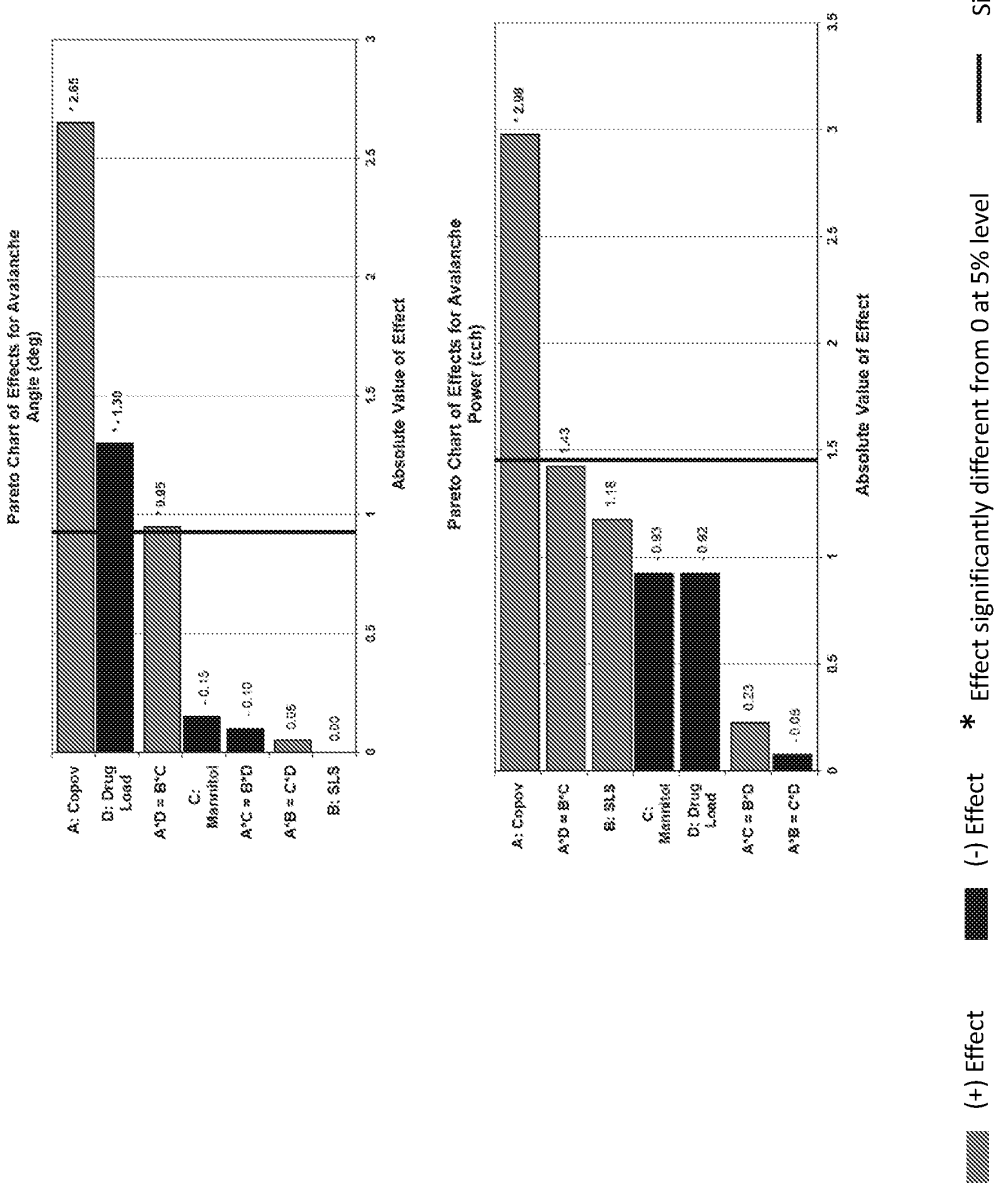

Pareto Chart of Effects for Avalanche
Angle (deg)
A: Copov
B: Drug Load
A*D = B*C
C: Mannitol
A*C = B*D
A*B = C*D
B: SLS
2.65
-1.30
0.95
-0.15
-0.10
0.05
0.00
0
0.5
1
1.5
2
2.5
3
Absolute Value of Effect
Pareto Chart of Effects for Avalanche
Power (cch)
A: Copov
A*D = B*C
B: SLS
C: Mannitol
D: Drug Load
A*C = B*D
A*B = C*D
2.88
1.43
1.18
0.93
0.92
0.23
-0.09
0
0.5
1
1.5
2
2.5
3
3.5
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 27

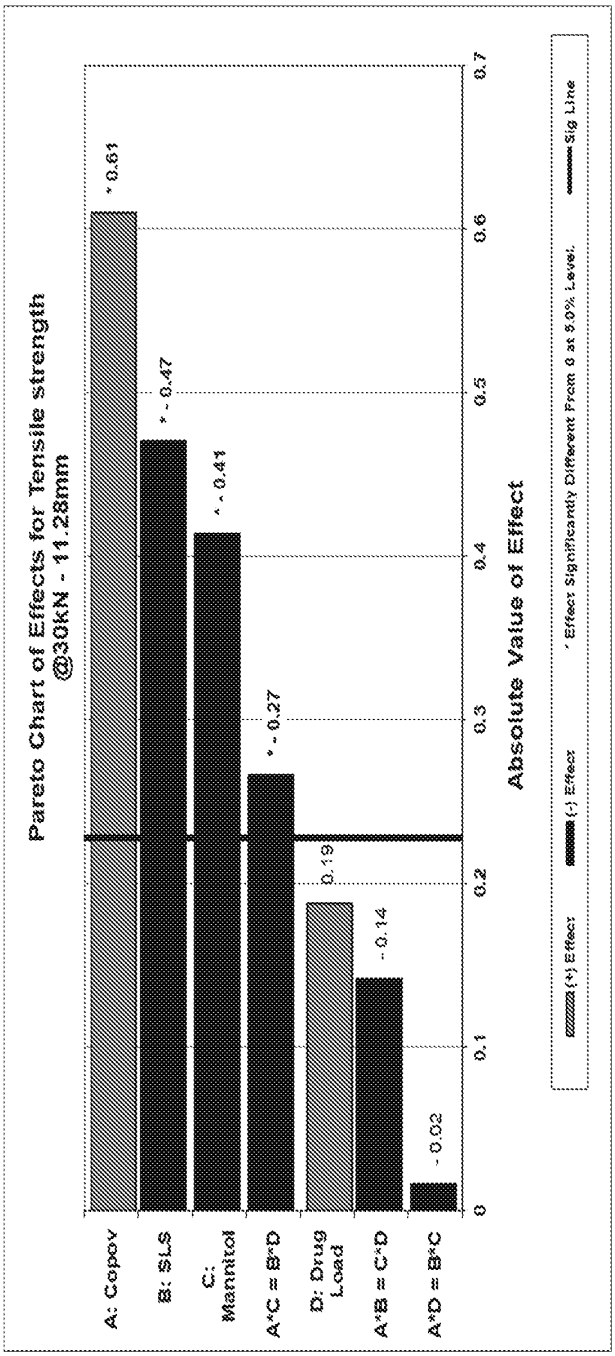

Pareto Chart of Effects for Tensile strength
@30kN - 11.28mm
A: Copov
B: SLS
C: Mannitol
A*C = B*D
D: Drug Load
A*B = C*D
A*D = B*C
0.61
0.47
0.41
0.27
0.19
0.14
0.02
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Absolute Value of Effect
(+) Effect
(-) Effect
Effect Significantly Different From 0 at 5.0% Level.
Sig Line

FIGURE 28

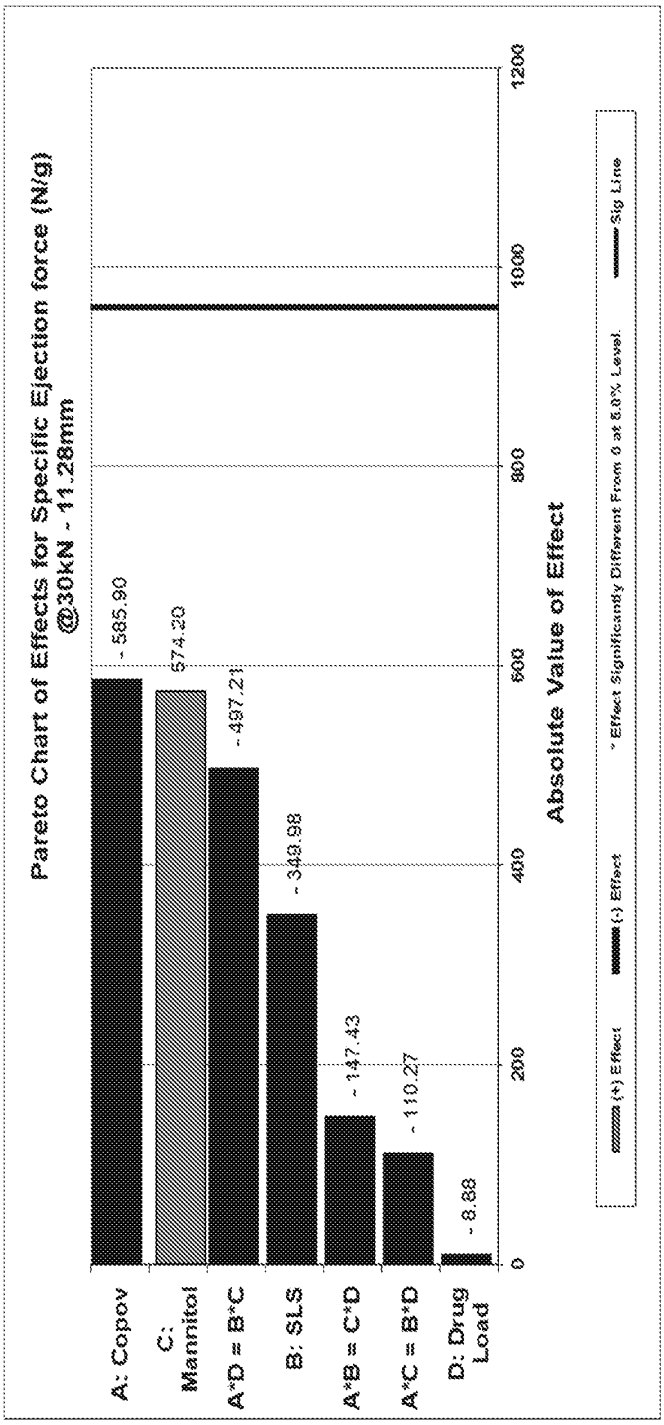

Pareto Chart of Effects for Specific Ejection force (N/g)
@30kN - 11.28mm
A: Copov
C: Mannitol
A*D = B*C
B: SLS
A*B = C*D
A*C = B*D
D: Drug Load
- 585.90
574.20
- 497.21
- 348.98
- 147.43
- 110.27
- 8.88
0
200
400
600
800
1000
1200
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect Significantly Different From 0 at 5.0% Level
Sig Line

FIGURE 29A

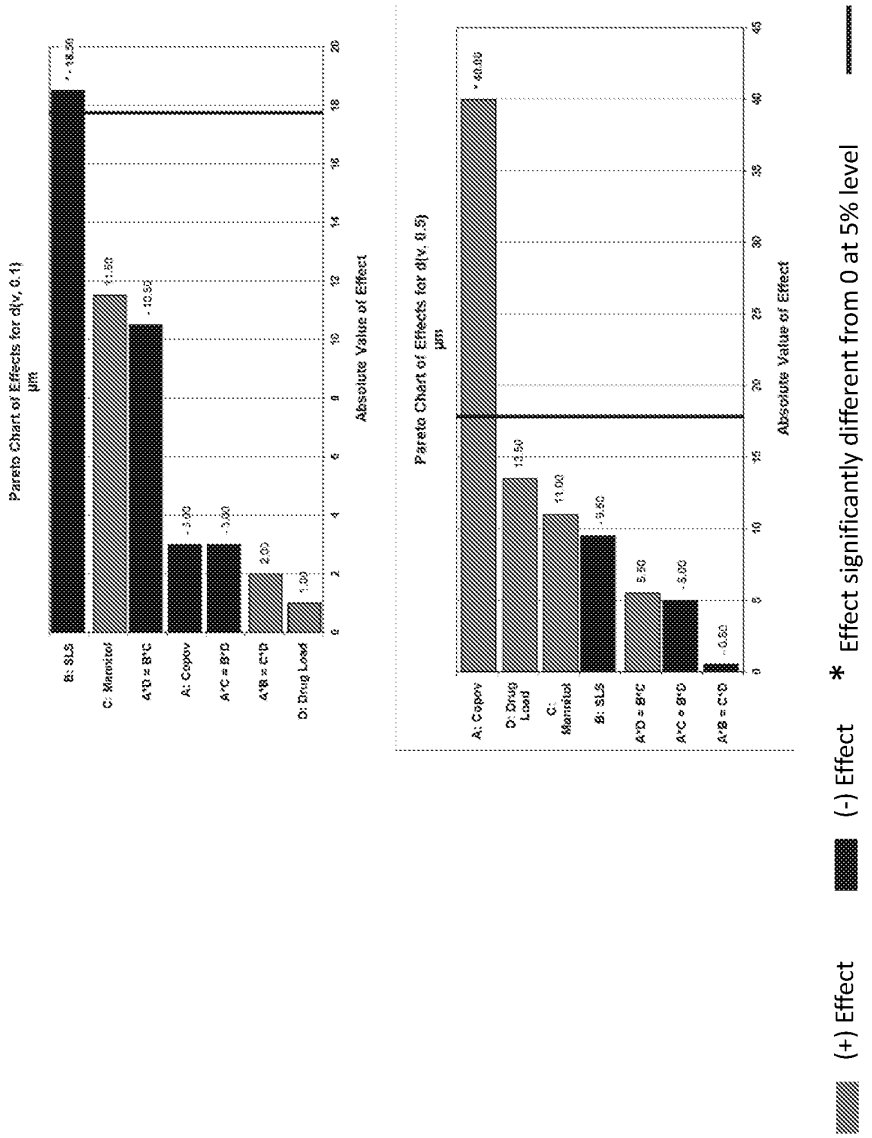

Pareto Chart of Effects for d(v, 0.1)
μm
B: SLS
C: Mannitol
A*D = B*C
A: Copov
A*C = B*D
A*B = C*D
D: Drug Load
Absolute Value of Effect
Pareto Chart of Effects for d(v, 0.5)
μm
A: Copov
D: Drug Load
C: Mannitol
B: SLS
A*D = B*C
A*C = B*D
A*B = C*D
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 29B

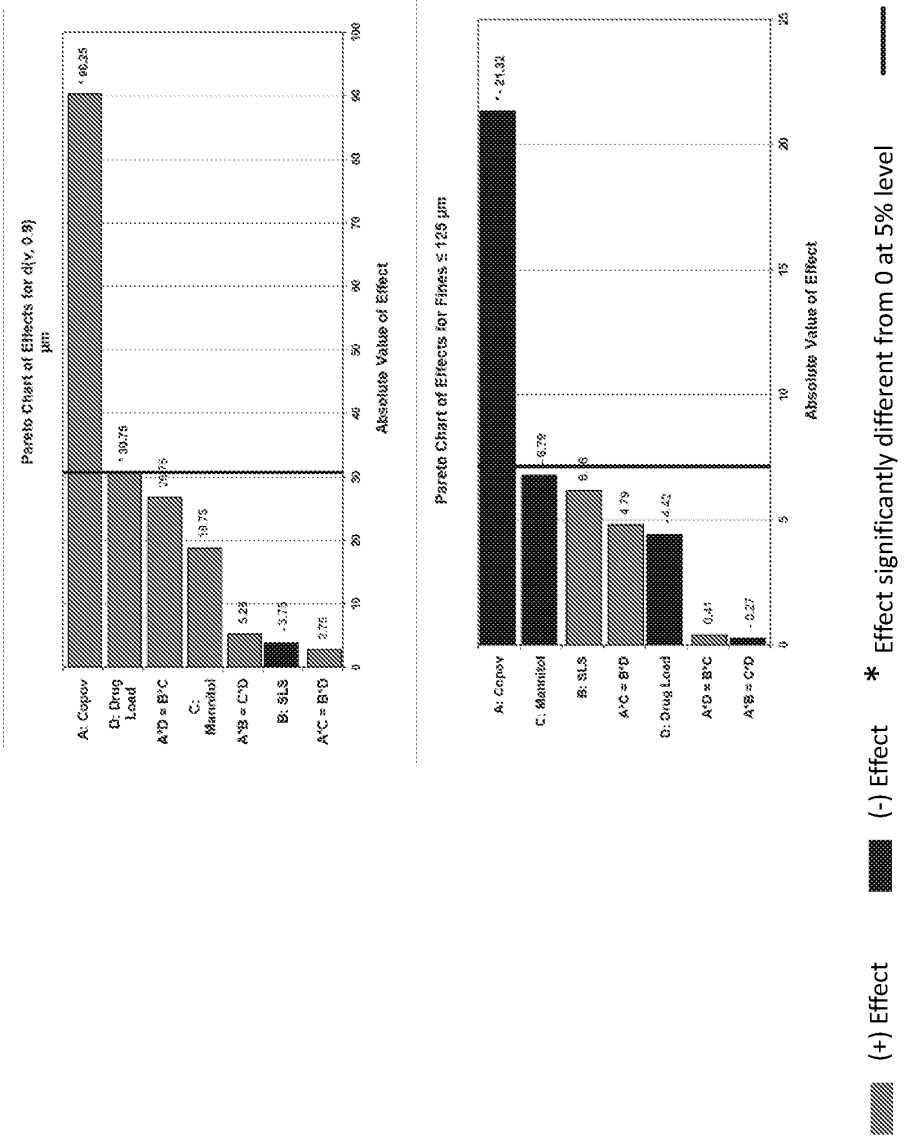

Pareto Chart of Effects for d(v, 0.9) µm
A: Copov
D: Drug Load
A*D = B*C
C: Mannitol
A*B = C*D
B: SLS
A*C = B*D
Absolute Value of Effect
Pareto Chart of Effects for Fines ≤ 126 µm
A: Copov
C: Mannitol
B: SLS
A*C = B*D
D: Drug Load
A*D = B*C
A*B = C*D
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 30

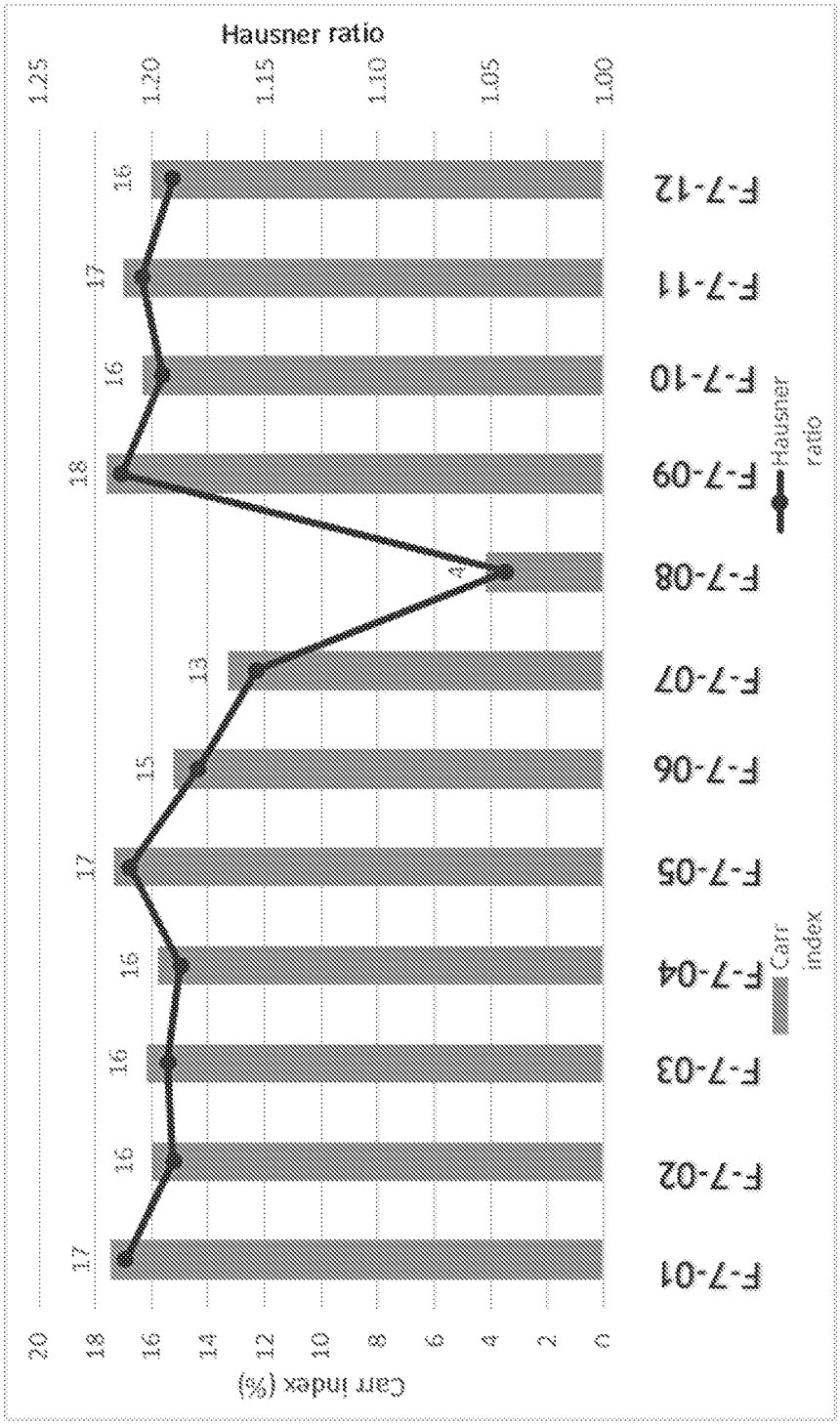

Hausner ratio
1.25
1.20
1.15
1.10
1.05
1.00
Carr index (%)
20
18
16
14
12
10
8
6
4
2
0
F-7-01
F-7-02
F-7-03
F-7-04
F-7-05
F-7-06
F-7-07
F-7-08
F-7-09
F-7-10
F-7-11
F-7-12
17
16
16
16
17
15
13
4
18
16
17
16
Carr index
Hausner ratio

FIGURE 31

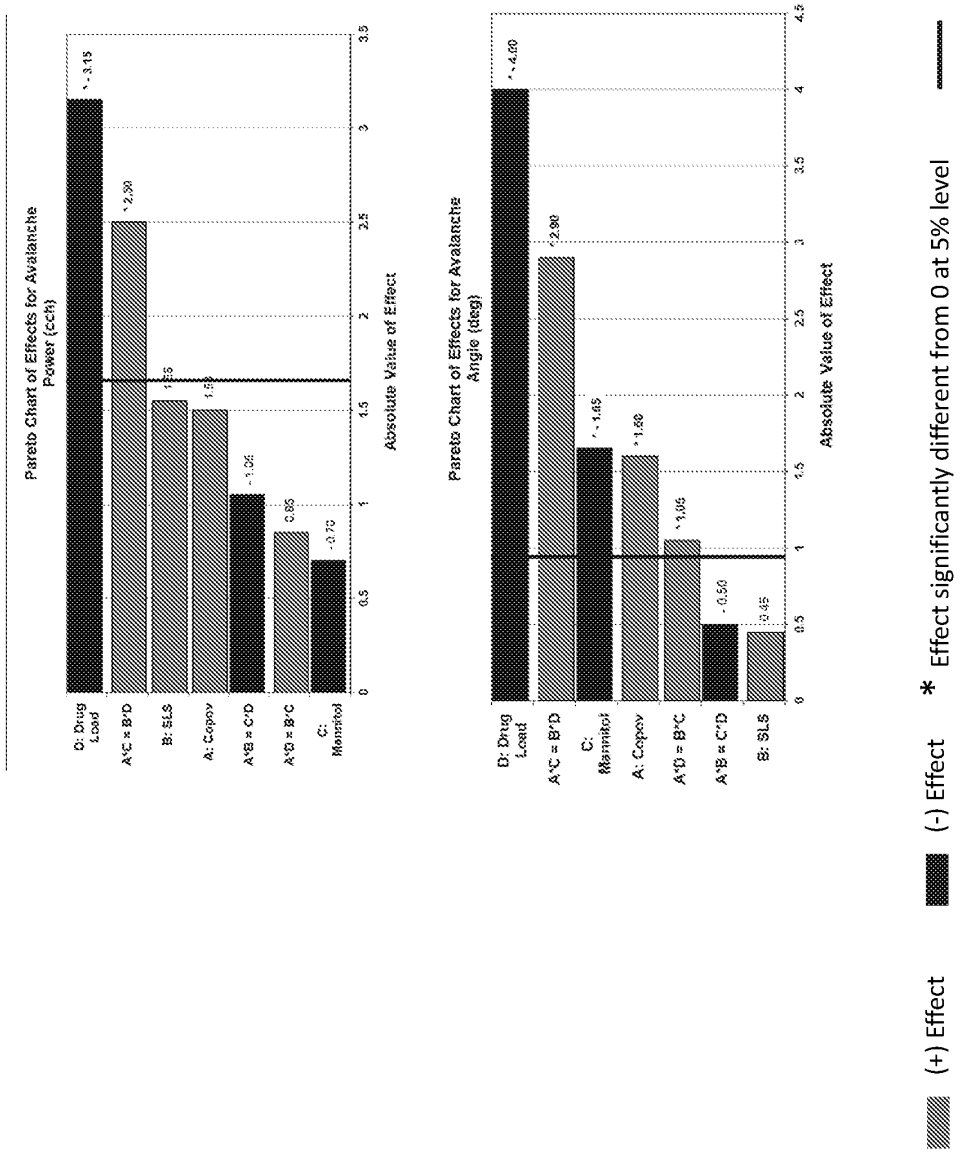

Pareto Chart of Effects for Avalanche
Power (cck)
D: Drug Load
A*C = B*D
B: SLS
A: Copov
A*B = C*D
A*D = B*C
C: Mannitol
Absolute Value of Effect
Pareto Chart of Effects for Avalanche
Angle (deg)
D: Drug Load
A*C = B*D
C: Mannitol
A: Copov
A*D = B*C
A*B = C*D
B: SLS
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 32

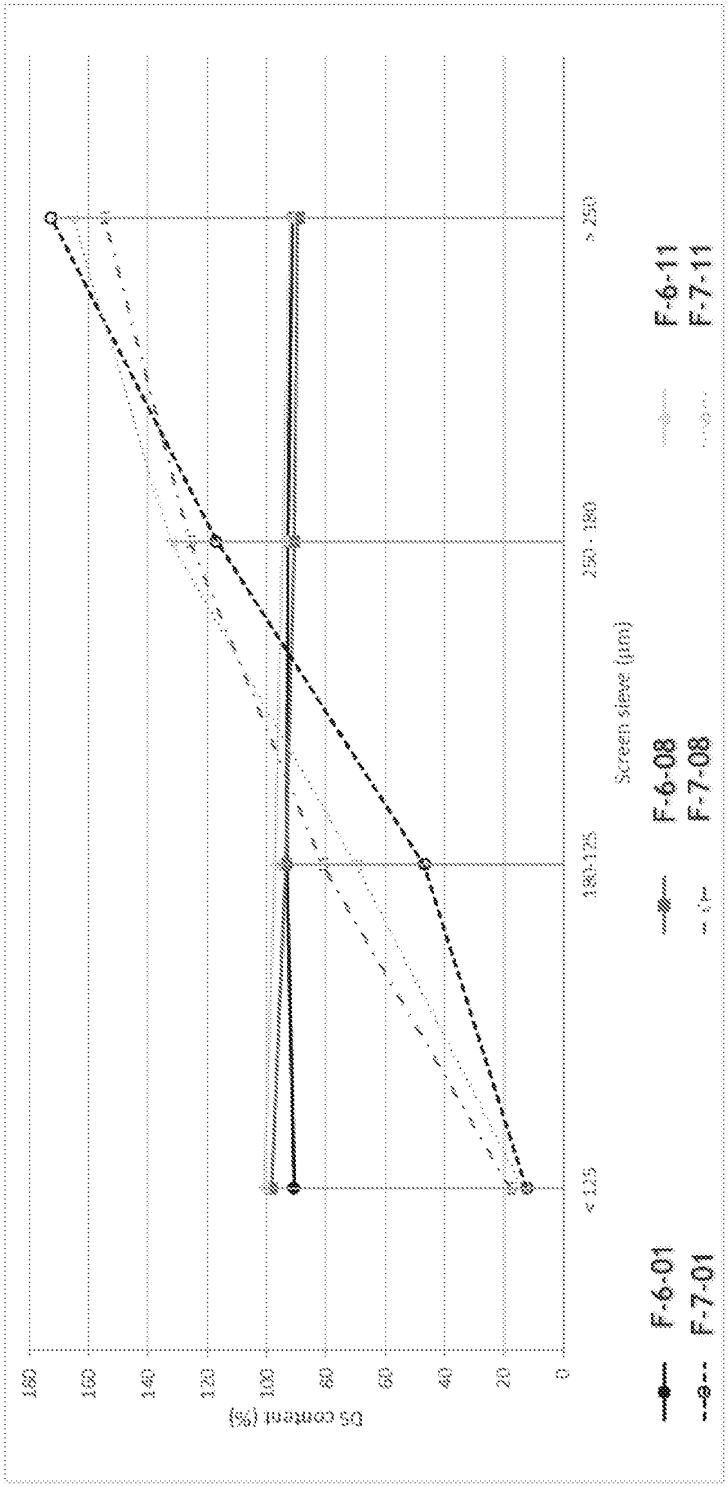

DS content (%)
0
20
40
60
80
100
120
140
160
180
< 125
180-125
250 - 180
> 250
Screen sieve (µm)
F-6-01
F-7-01
F-6-08
F-7-08
F-6-11
F-7-11

FIGURE 33

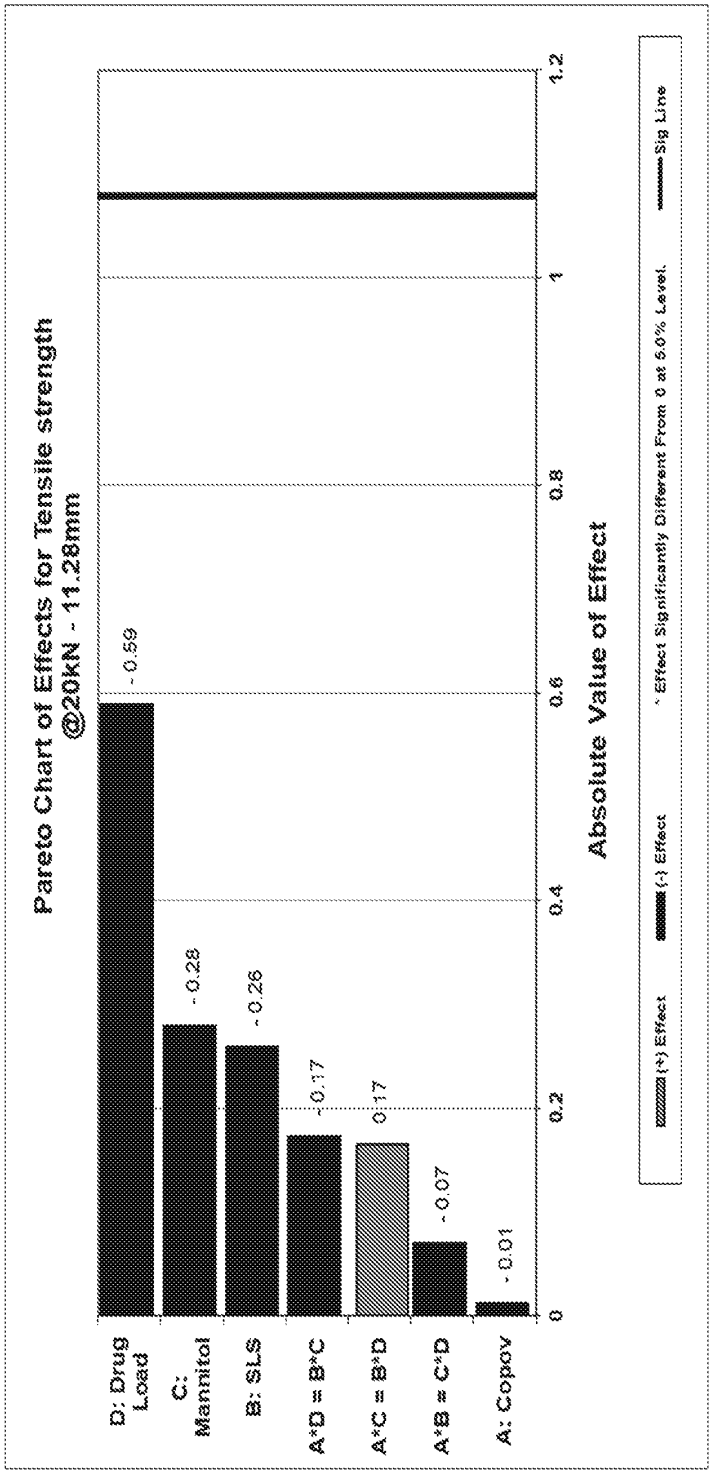

Pareto Chart of Effects for Tensile strength
@20kN - 11.28mm
D: Drug Load
C: Mannitol
B: SLS
A*D = B*C
A*C = B*D
A*B = C*D
A: Copov
0.59
0.28
0.26
0.17
0.17
0.07
0.01
0
0.2
0.4
0.6
0.8
1
1.2
Absolute Value of Effect
(+) Effect
(-) Effect
Effect Significantly Different From 0 at 5.0% Level.
Sig Line

FIGURE 34

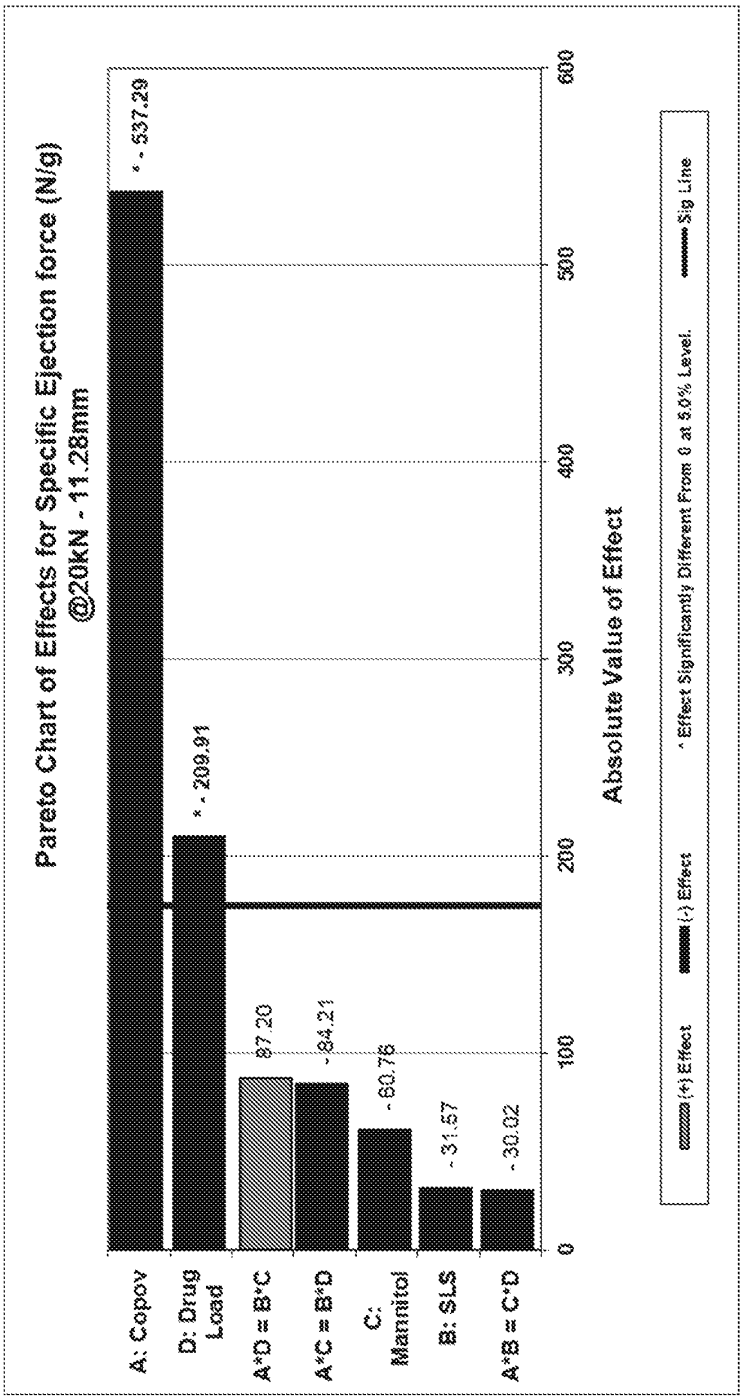

Pareto Chart of Effects for Specific Ejection force (N/g)
@20kN - 11.28mm
A: Copov
D: Drug Load
A*D = B*C
A*C = B*D
C: Mannitol
B: SLS
A*B = C*D
* - 537.29
* - 209.91
87.20
84.21
- 60.76
- 31.57
- 30.02
0
100
200
300
400
500
600
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect Significantly Different From 0 at 5.0% Level.
Sig Line

FIGURE 35

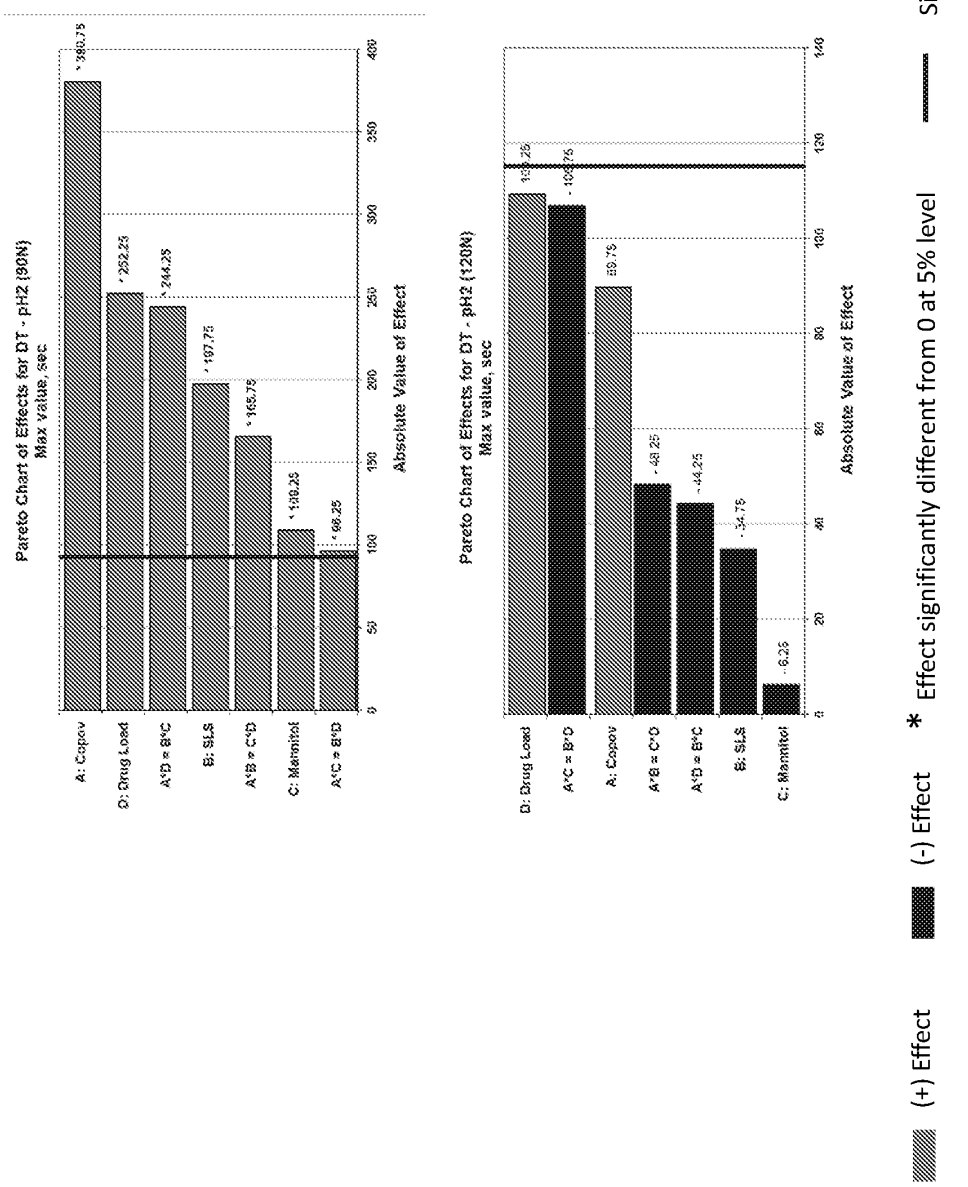

Pareto Chart of Effects for DT - pH2 (90N)
Max value, sec
A: Copov
D: Drug Load
A*D = B*C
B: SLS
A*B = C*D
C: Mannitol
A*C = B*D
Absolute Value of Effect
Pareto Chart of Effects for DT - pH2 (120N)
Max value, sec
D: Drug Load
A*C = B*D
A: Copov
A*B = C*D
A*D = B*C
B: SLS
C: Mannitol
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 36

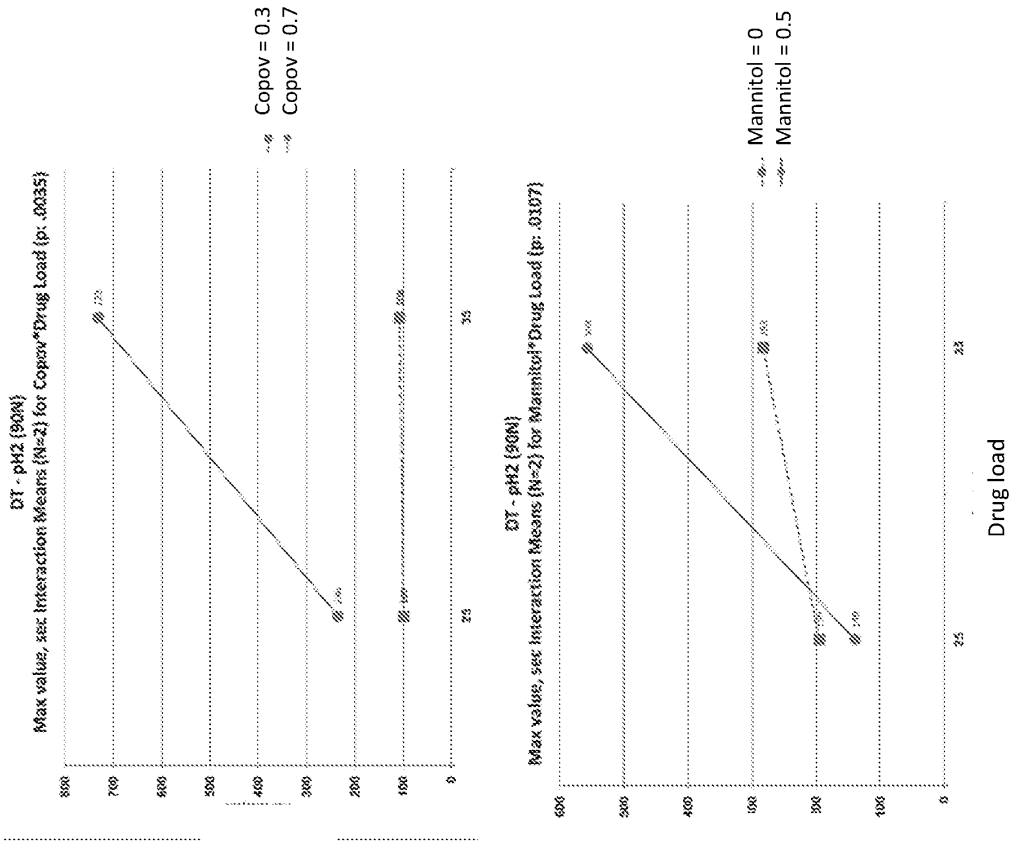

DT - pH2 (90N)
Max value, sec Interaction Means (N=2) for Copov*Drug Load (p: .0035)
Copov = 0.3
Copov = 0.7
DT - pH2 (90N)
Max value, sec Interaction Means (N=2) for Mannitol*Drug Load (p: .0107)
Mannitol = 0
Mannitol = 0.5
Drug load

FIGURE 37A

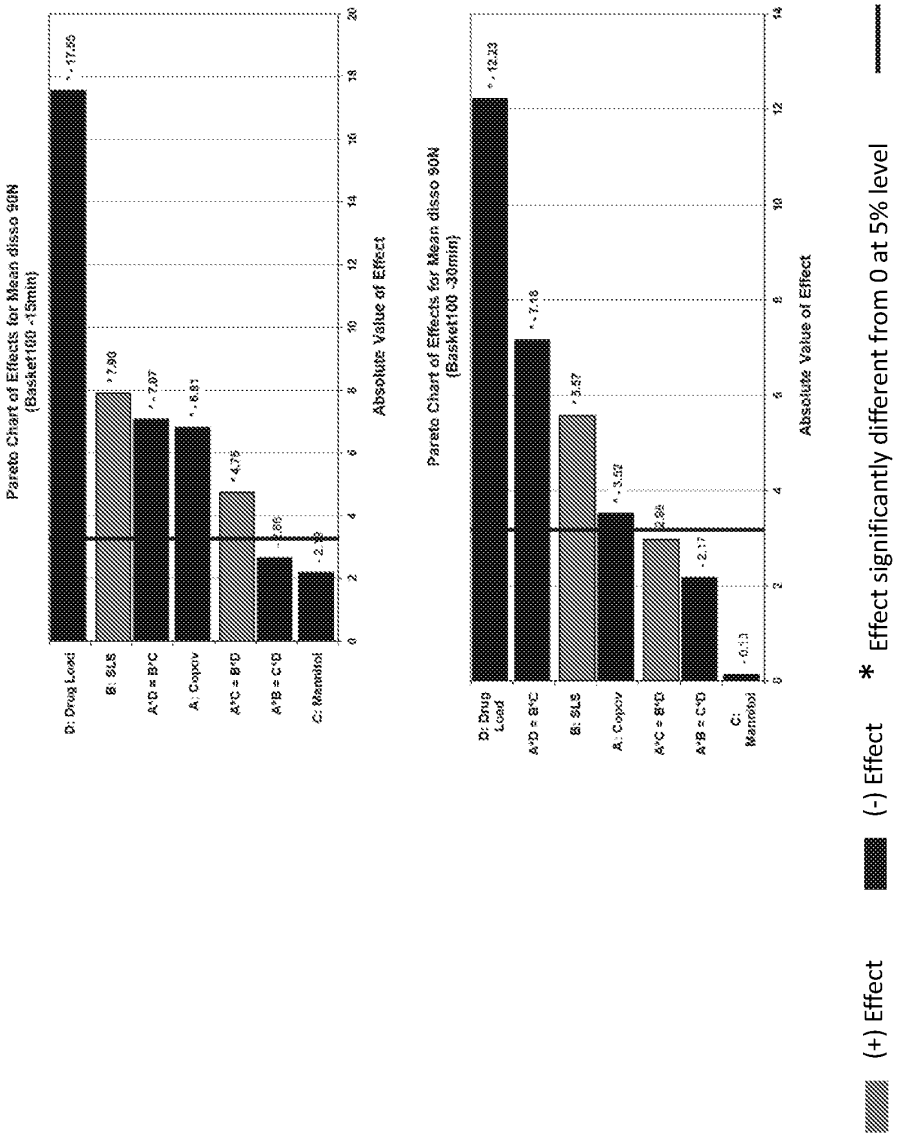

Pareto Chart of Effects for Mean disso 90N
(Basket100 -15min)
Absolute Value of Effect
D: Drug Load
B: SLS
A*D = B*C
A: Copov
A*C = B*D
A*B = C*D
C: Mannitol
Pareto Chart of Effects for Mean disso 90N
(Basket100 -30min)
Absolute Value of Effect
D: Drug Load
A*D = B*C
B: SLS
A: Copov
A*C = B*D
A*B = C*D
C: Mannitol
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 37B

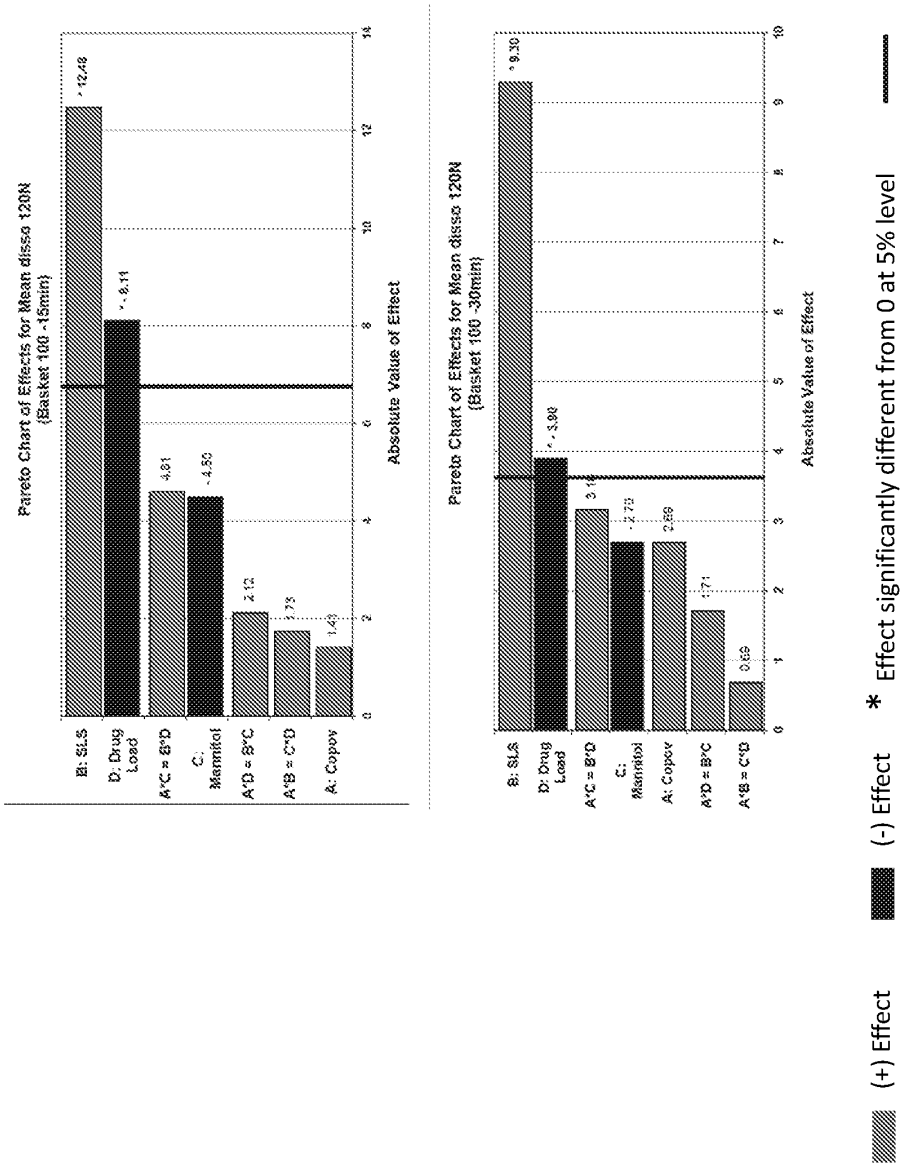

Pareto Chart of Effects for Mean disso 120N
(Basket 100 -15min)
B: SLS
D: Drug Load
A*C = B*D
C: Mannitol
A*D = B*C
A*B = C*D
A: Copov
12.48
8.11
4.81
4.56
2.12
1.78
1.49
Absolute Value of Effect
Pareto Chart of Effects for Mean disso 120N
(Basket 100 -30min)
B: SLS
D: Drug Load
A*C = B*D
C: Mannitol
A: Copov
A*D = B*C
A*B = C*D
9.30
3.90
3.14
2.78
2.69
1.71
0.89
Absolute Value of Effect
(+) Effect
(-) Effect
* Effect significantly different from 0 at 5% level
Sig Line

FIGURE 38

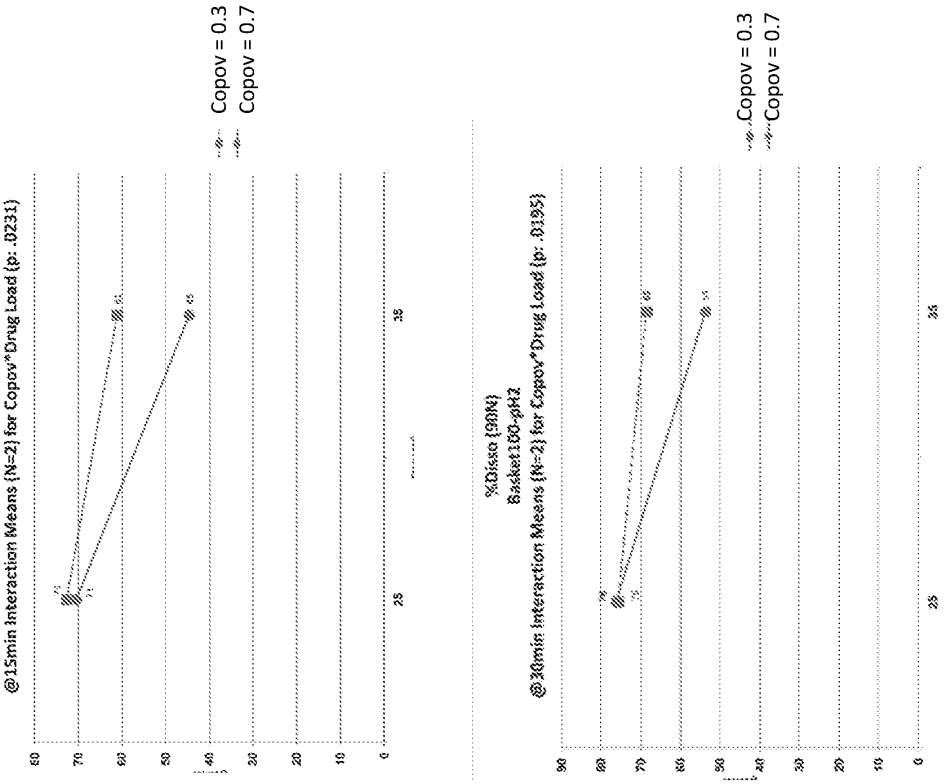

%Disso (90N)
Basket100-pH2
@15min Interaction Means (N=2) for Copov*Drug Load (p: .0231)
Copov = 0.3
Copov = 0.7
%Disso (90N)
Basket100-pH2
@30min Interaction Means (N=2) for Copov*Drug Load (p: .0185)
Copov = 0.3
Copov = 0.7
Drug load

FIGURE 39

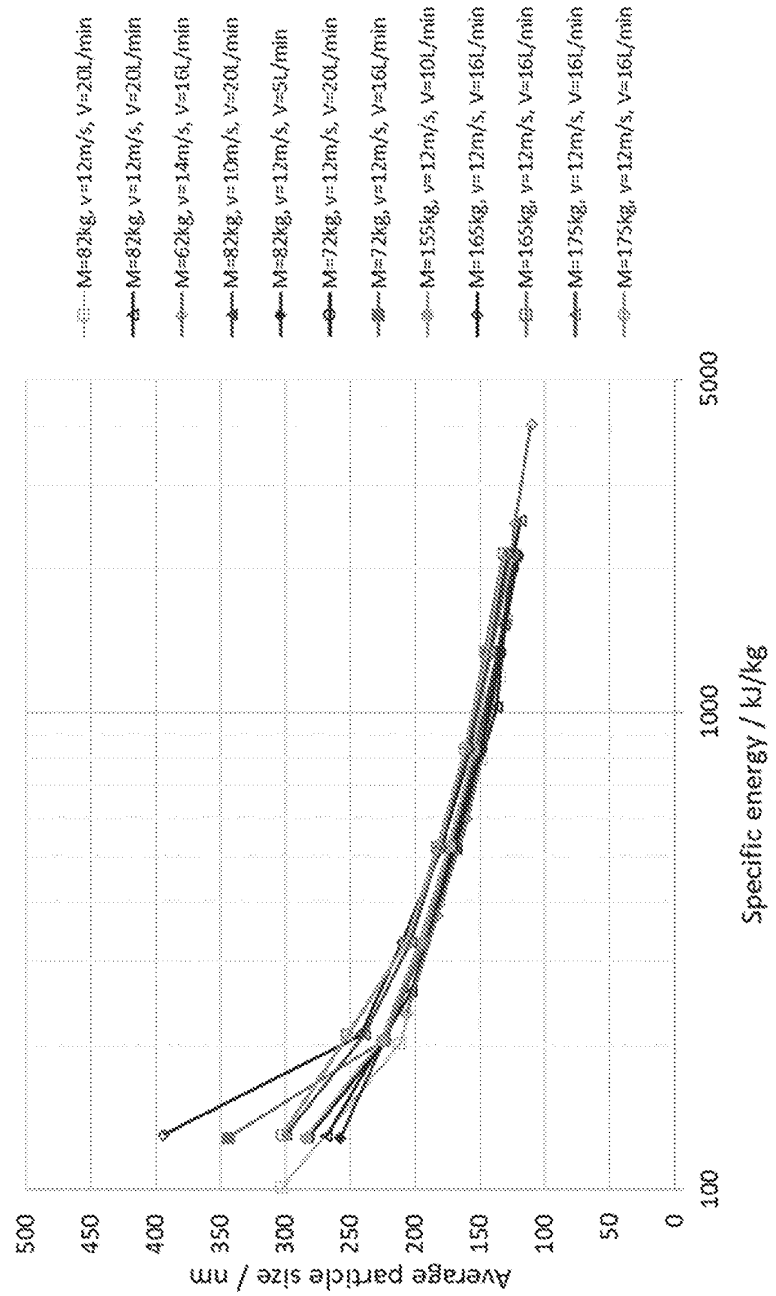

M=82kg, v=12m/s, V=20L/min
M=82kg, v=12m/s, V=20L/min
M=62kg, v=14m/s, V=16L/min
M=82kg, v=10m/s, V=20L/min
M=82kg, v=12m/s, V=5L/min
M=72kg, v=12m/s, V=20L/min
M=72kg, v=12m/s, V=16L/min
M=155kg, v=12m/s, V=10L/min
M=165kg, v=12m/s, V=16L/min
M=165kg, v=12m/s, V=16L/min
M=175kg, v=12m/s, V=16L/min
M=175kg, v=12m/s, V=16L/min
Average particle size / nm
500
450
400
350
300
250
200
150
100
50
0
100
1000
5000
Specific energy / kJ/kg

FIGURE 40

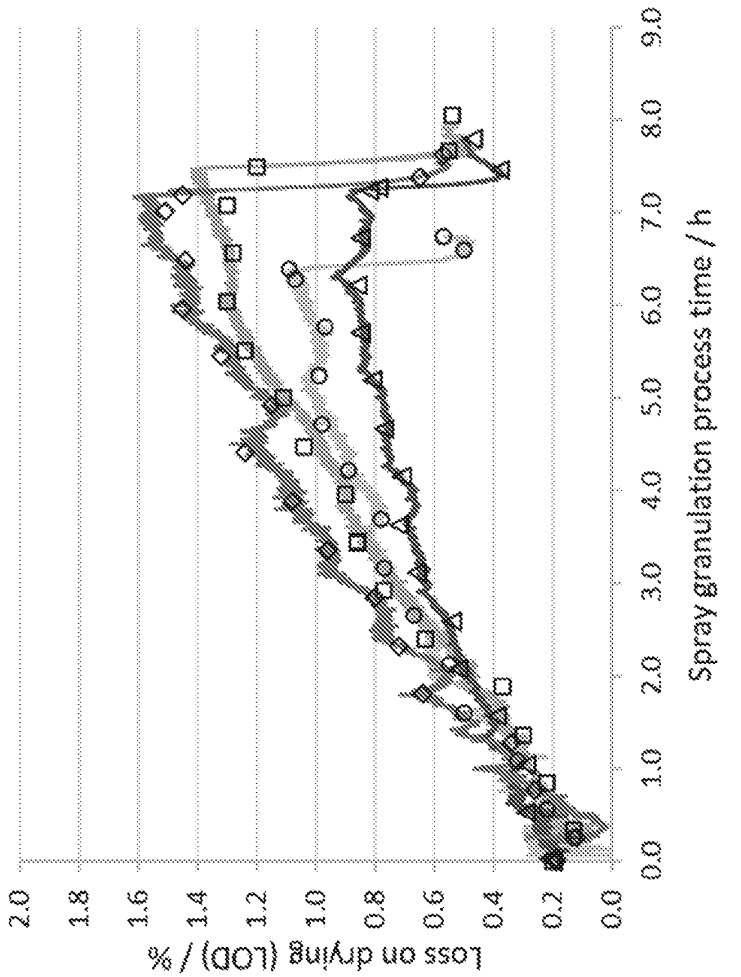
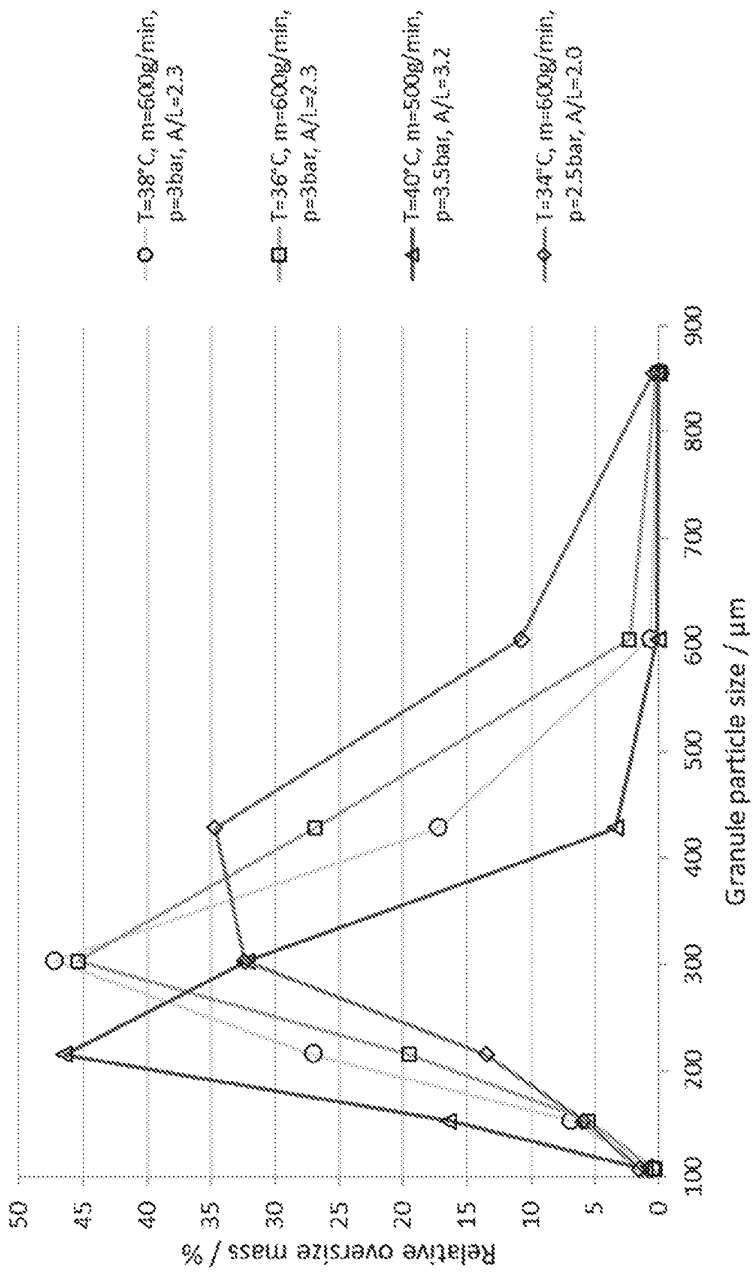

online LOD, T=38°C, m=600g/min, p=3bar, A/L=2.3
offline LOD, T=38°C, m=600g/min, p=3bar, A/L=2.3
online LOD, T=36°C, m=600g/min, p=3bar, A/L=2.3
offline LOD, T=36°C, m=600g/min, p=3bar, A/L=2.3
online LOD, T=40°C, m=500g/min, p=3.5bar, A/L=3.2
offline LOD, T=40°C, m=500g/min, p=3.5bar, A/L=3.2
online LOD, T=34°C, m=600g/min, p=2.5bar, A/L=2.0
offline LOD, T=34°C, m=600g/min, p=2.5bar, A/L=2.0
Loss on drying (LOD) / %
Spray granulation process time / h
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0

FIGURE 41


T=38°C, m=600g/min, p=3bar, A/L=2.3
T=36°C, m=600g/min, p=3bar, A/L=2.3
T=40°C, m=500g/min, p=3.5bar, A/L=3.2
T=34°C, m=600g/min, p=2.5bar, A/L=2.0
Relative oversize mass / %
Granule particle size / µm
0
5
10
15
20
25
30
35
40
45
50
100
200
300
400
500
600
700
800
900