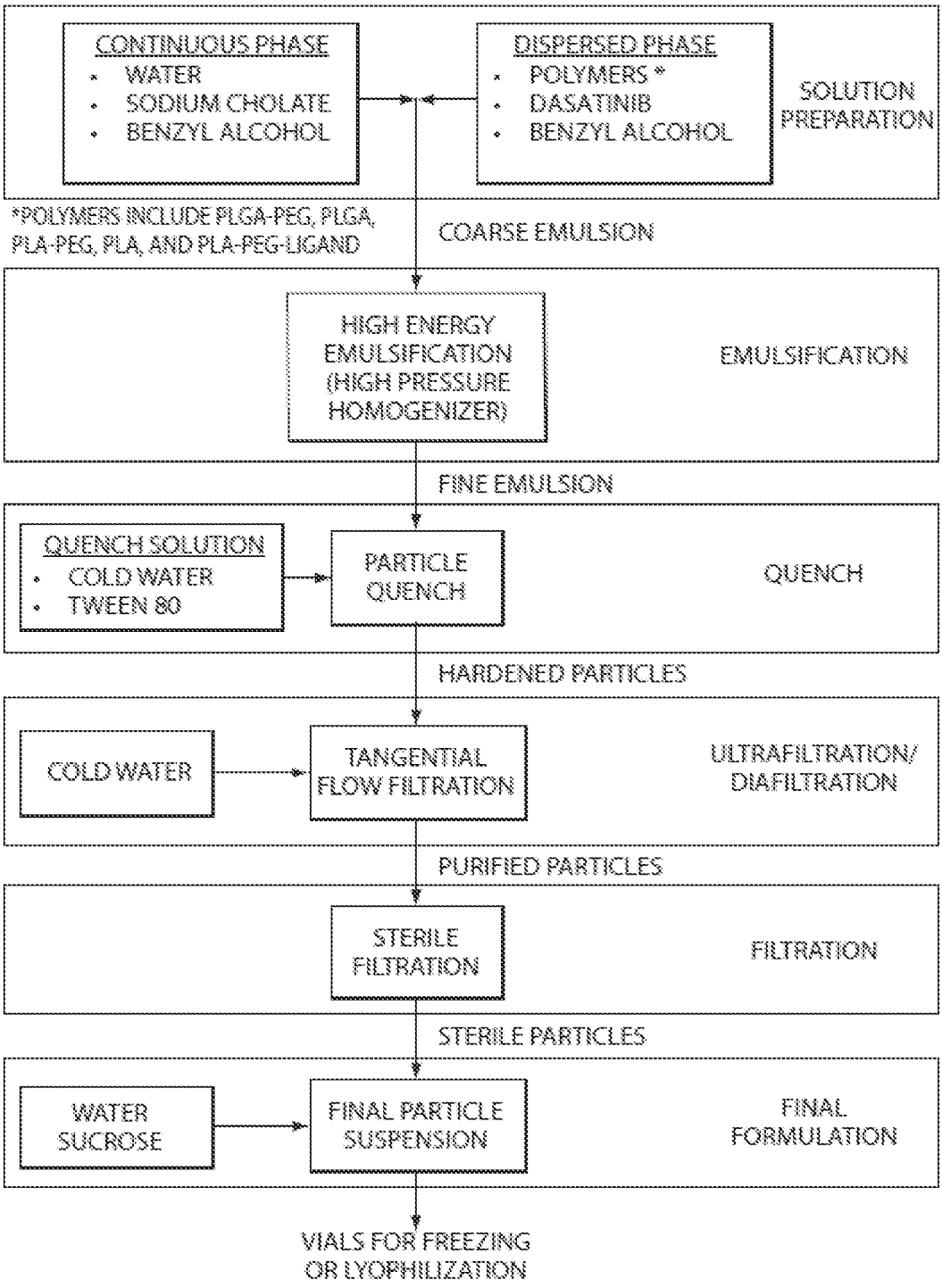

CONTINUOUS PHASE
WATER
SODIUM CHOLATE
BENZYL ALCOHOL
DISPERSED PHASE
POLYMERS *
DASATINIB
BENZYL ALCOHOL
SOLUTION PREPARATION
*POLYMERS INCLUDE PLGA-PEG, PLGA, PLA-PEG, PLA, AND PLA-PEG-LIGAND
COARSE EMULSION
HIGH ENERGY EMULSIFICATION (HIGH PRESSURE HOMOGENIZER)
EMULSIFICATION
FINE EMULSION
QUENCH SOLUTION
COLD WATER
TWEEN 80
PARTICLE QUENCH
QUENCH
HARDENED PARTICLES
COLD WATER
TANGENTIAL FLOW FILTRATION
ULTRAFILTRATION/ DIAFILTRATION
PURIFIED PARTICLES
STERILE FILTRATION
FILTRATION
STERILE PARTICLES
WATER SUCROSE
FINAL PARTICLE SUSPENSION
FINAL FORMULATION
VIALS FOR FREEZING OR LYOPHILIZATION

Fig. 1

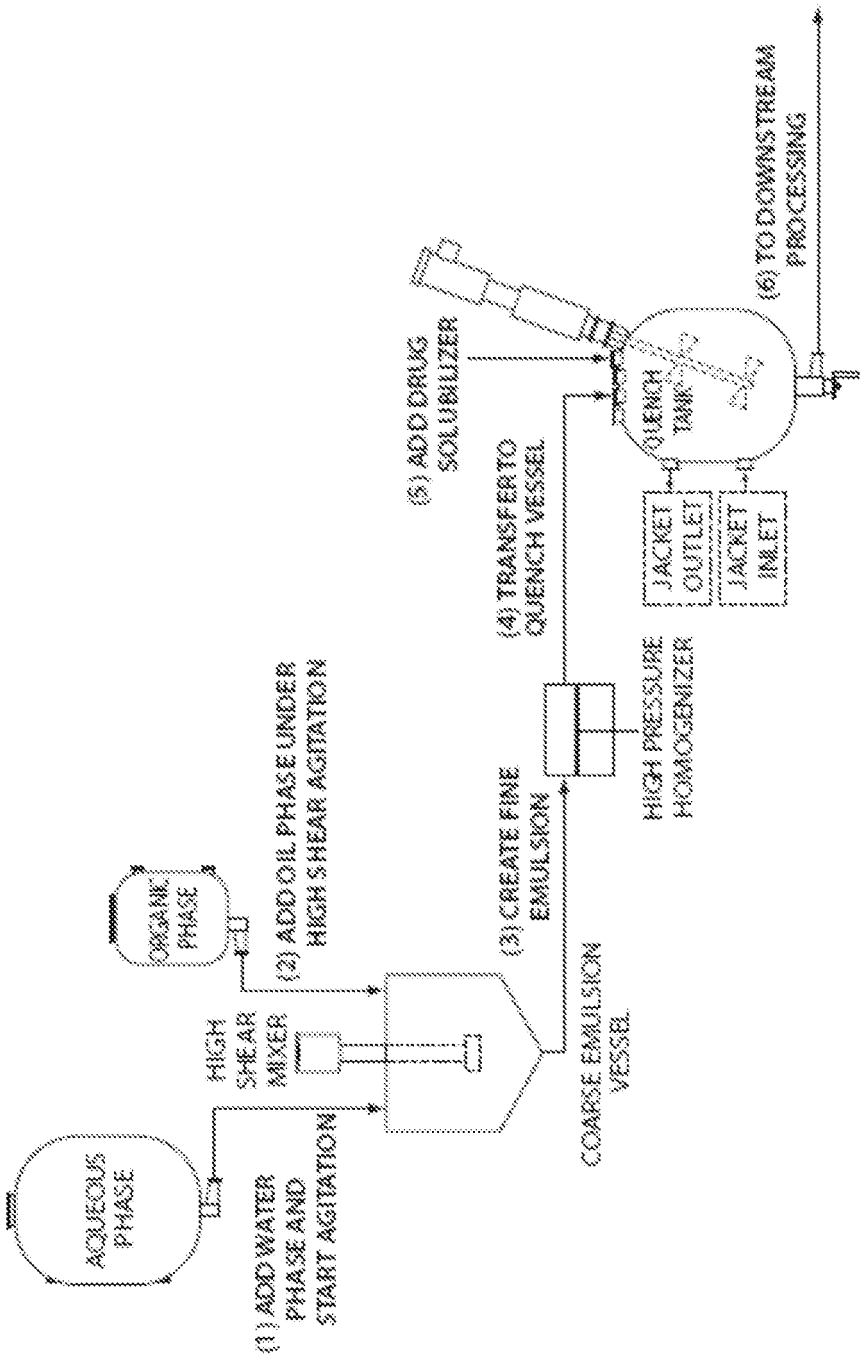

AQUEOUS PHASE
(1) ADD WATER PHASE AND START AGITATION
HIGH SHEAR MIXER
ORGANIC PHASE
(2) ADD OIL PHASE UNDER HIGH SHEAR AGITATION
COARSE EMULSION VESSEL
(3) CREATE FINE EMULSION
HIGH PRESSURE HOMOGENIZER
(4) TRANSFER TO QUENCH VESSEL
(5) ADD DRUG SOLUBILIZER
QUENCH TANK
JACKET OUTLET
JACKET INLET
(6) TO DOWNSTREAM PROCESSING

Fig. 2A

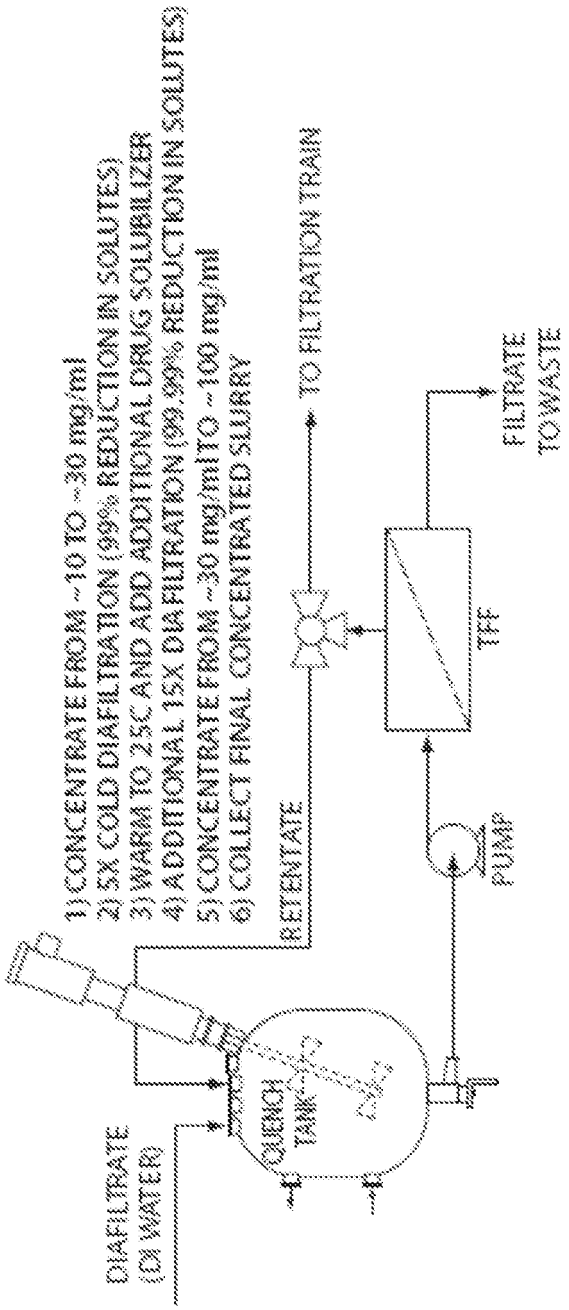

1) CONCENTRATE FROM ~10 TO ~30 mg/ml
2) 5X COLD DIAFILTRATION (99% REDUCTION IN SOLUTES)
3) WARM TO 25C AND ADD ADDITIONAL DRUG SOLUBILIZER
4) ADDITIONAL 15X DIAFILTRATION (99.99% REDUCTION IN SOLUTES)
5) CONCENTRATE FROM ~30 mg/ml TO ~100 mg/ml
6) COLLECT FINAL CONCENTRATED SLURRY
RETENTATE
TO FILTRATION TRAIN
TFF
FILTRATE TO WASTE
PUMP
QUENCH TANK
DIAFILTRATE (DI WATER)

Fig. 2B

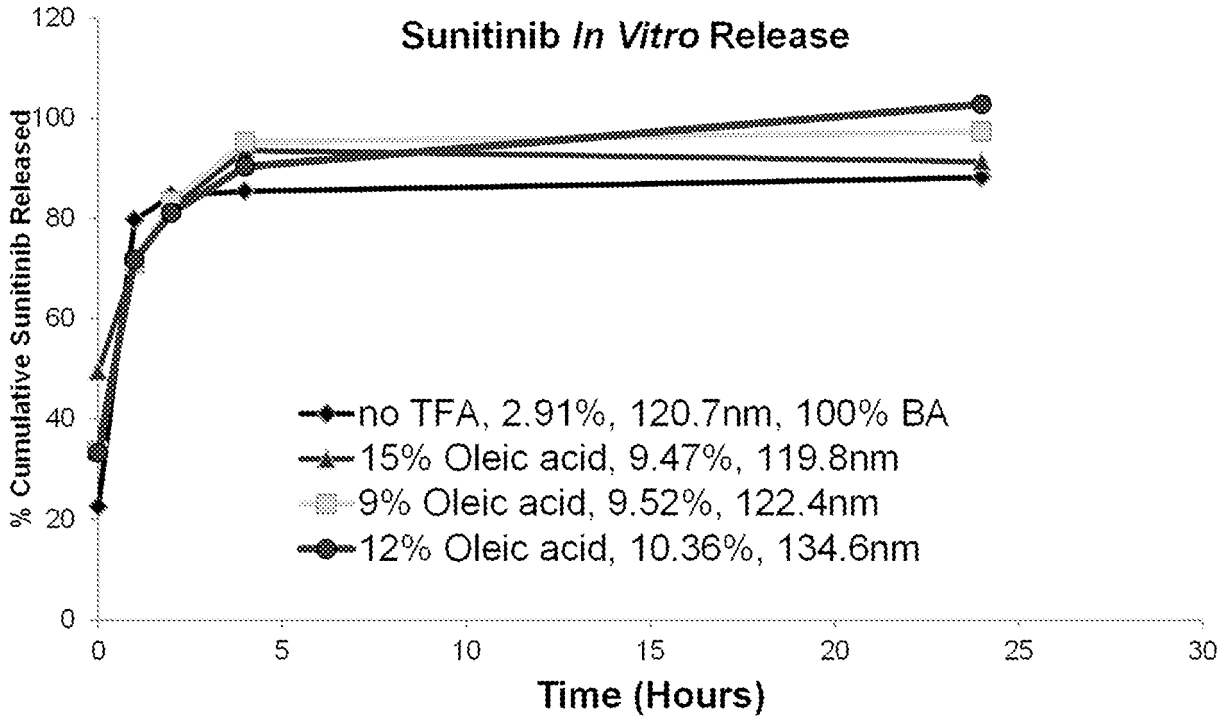

Sunitinib *In Vitro* Release
% Cumulative Sunitinib Released
120
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (Hours)
no TFA, 2.91%, 120.7nm, 100% BA
15% Oleic acid, 9.47%, 119.8nm
9% Oleic acid, 9.52%, 122.4nm
12% Oleic acid, 10.36%, 134.6nm

Fig. 3

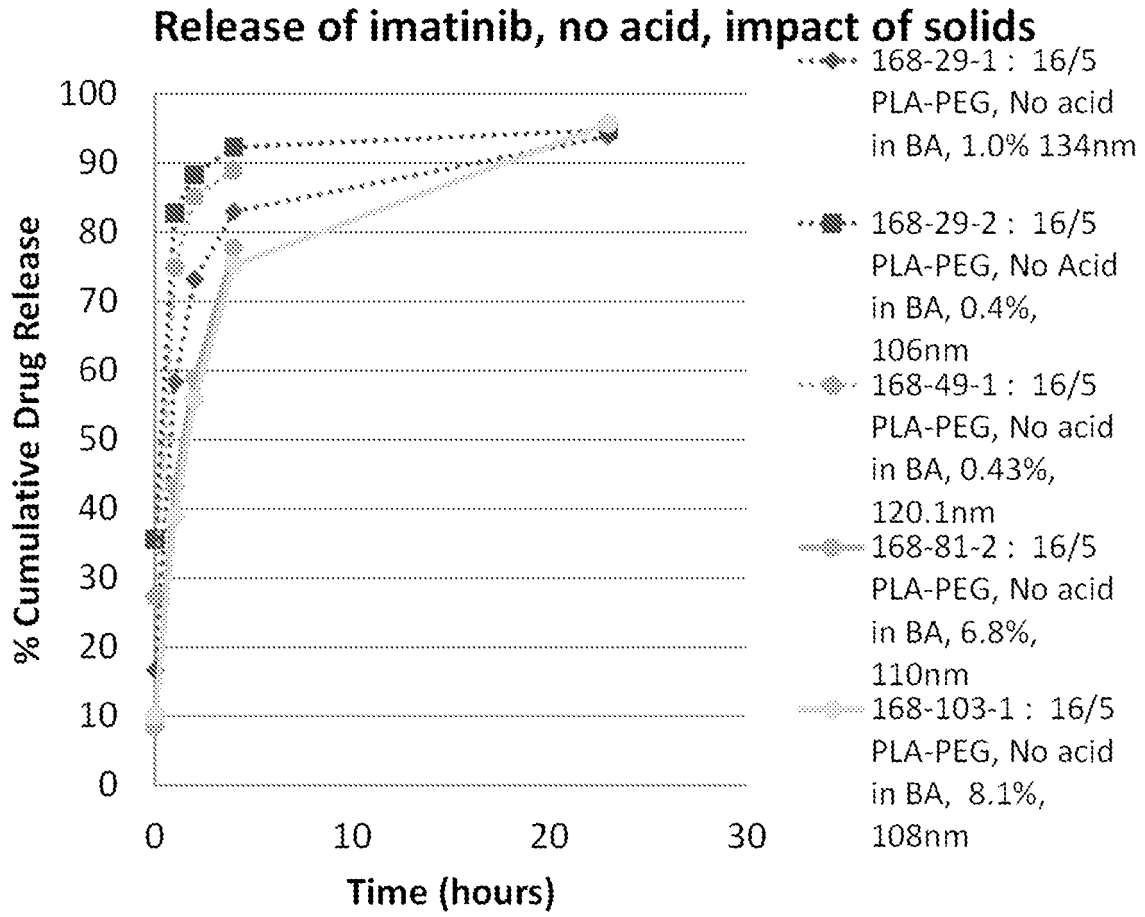

Release of imatinib, no acid, impact of solids
% Cumulative Drug Release
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
Time (hours)
168-29-1 : 16/5 PLA-PEG, No acid in BA, 1.0% 134nm
168-29-2 : 16/5 PLA-PEG, No Acid in BA, 0.4%, 106nm
168-49-1 : 16/5 PLA-PEG, No acid in BA, 0.43%, 120.1nm
168-81-2 : 16/5 PLA-PEG, No acid in BA, 6.8%, 110nm
168-103-1 : 16/5 PLA-PEG, No acid in BA, 8.1%, 108nm

Fig. 4

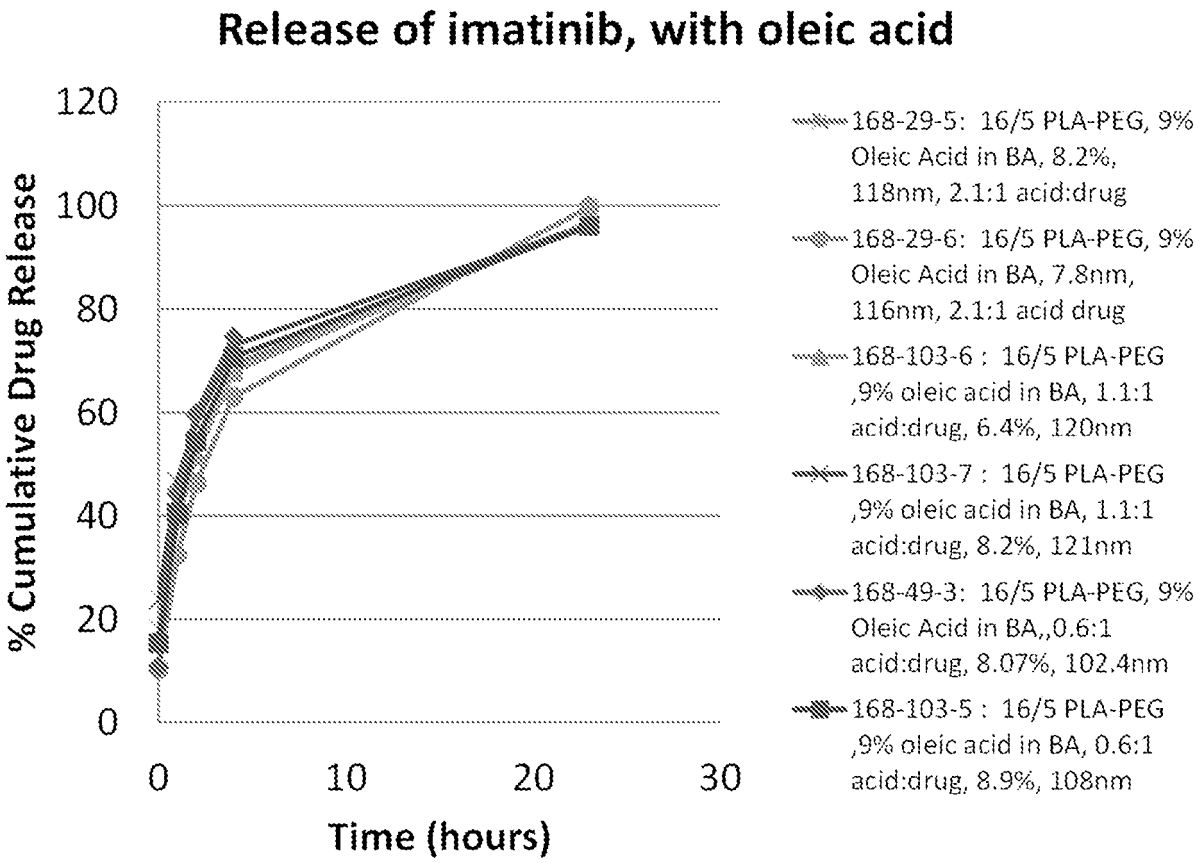

Release of imatinib, with oleic acid
% Cumulative Drug Release
120
100
80
60
40
20
0
0
10
20
30
Time (hours)
168-29-5: 16/5 PLA-PEG, 9% Oleic Acid in BA, 8.2%, 118nm, 2.1:1 acid:drug
168-29-6: 16/5 PLA-PEG, 9% Oleic Acid in BA, 7.8nm, 116nm, 2.1:1 acid drug
168-103-6 : 16/5 PLA-PEG ,9% oleic acid in BA, 1.1:1 acid:drug, 6.4%, 120nm
168-103-7 : 16/5 PLA-PEG ,9% oleic acid in BA, 1.1:1 acid:drug, 8.2%, 121nm
168-49-3: 16/5 PLA-PEG, 9% Oleic Acid in BA,,0.6:1 acid:drug, 8.07%, 102.4nm
168-103-5 : 16/5 PLA-PEG ,9% oleic acid in BA, 0.6:1 acid:drug, 8.9%, 108nm

Fig. 5

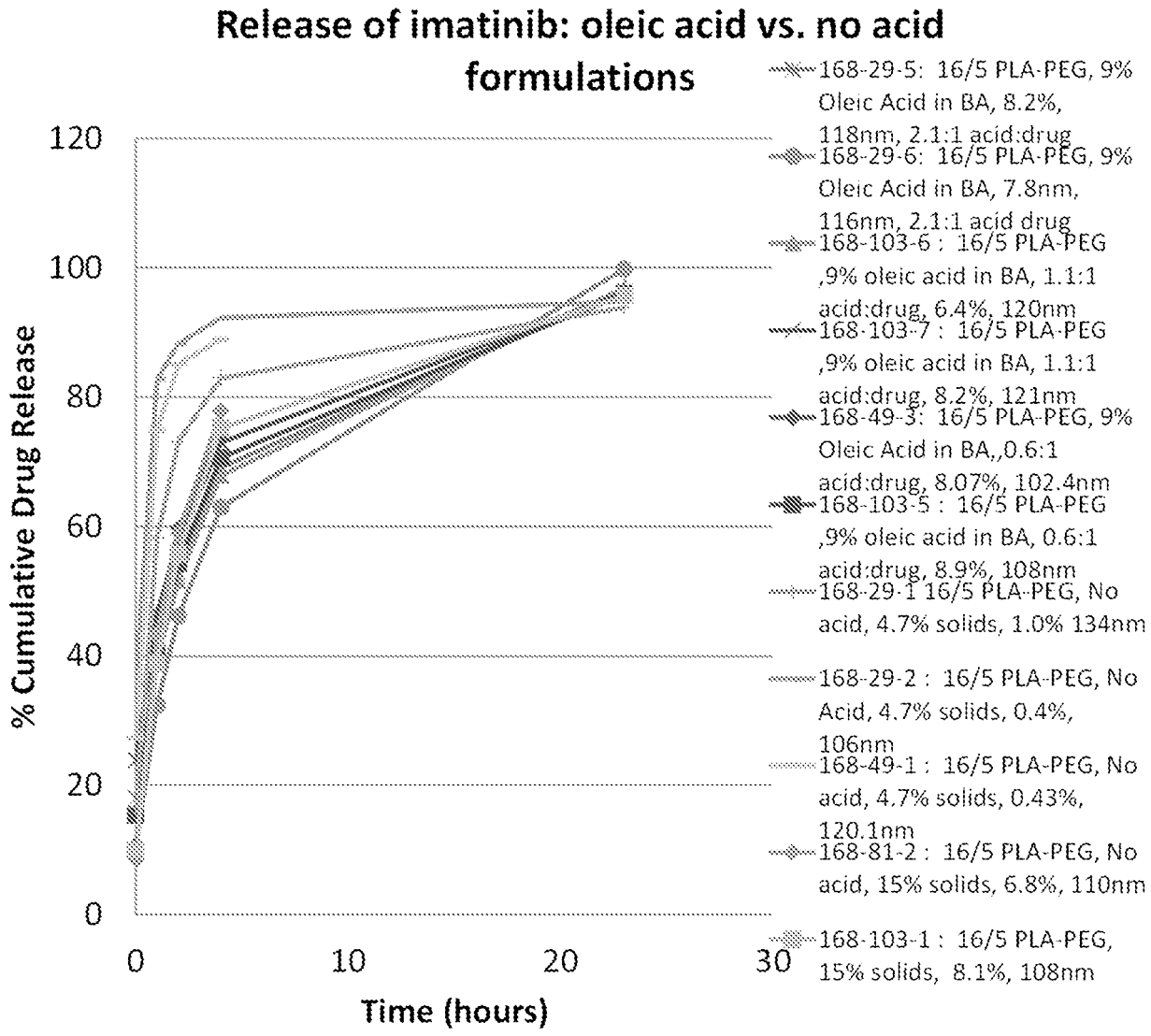

Release of imatinib: oleic acid vs. no acid formulations
% Cumulative Drug Release
120
100
80
60
40
20
0
0
10
20
30
Time (hours)
168-29-5: 16/5 PLA-PEG, 9% Oleic Acid in BA, 8.2%, 118nm, 2.1:1 acid:drug
168-29-6: 16/5 PLA-PEG, 9% Oleic Acid in BA, 7.8nm, 116nm, 2.1:1 acid drug
168-103-6 : 16/5 PLA-PEG ,9% oleic acid in BA, 1.1:1 acid:drug, 6.4%, 120nm
168-103-7 : 16/5 PLA-PEG ,9% oleic acid in BA, 1.1:1 acid:drug, 8.2%, 121nm
168-49-3: 16/5 PLA-PEG, 9% Oleic Acid in BA,,0.6:1 acid:drug, 8.07%, 102.4nm
168-103-5 : 16/5 PLA-PEG ,9% oleic acid in BA, 0.6:1 acid:drug, 8.9%, 108nm
168-29-1 16/5 PLA-PEG, No acid, 4.7% solids, 1.0% 134nm
168-29-2 : 16/5 PLA-PEG, No Acid, 4.7% solids, 0.4%, 106nm
168-49-1 : 16/5 PLA-PEG, No acid, 4.7% solids, 0.43%, 120.1nm
168-81-2 : 16/5 PLA-PEG, No acid, 15% solids, 6.8%, 110nm
168-103-1 : 16/5 PLA-PEG, 15% solids, 8.1%, 108nm

Fig. 6

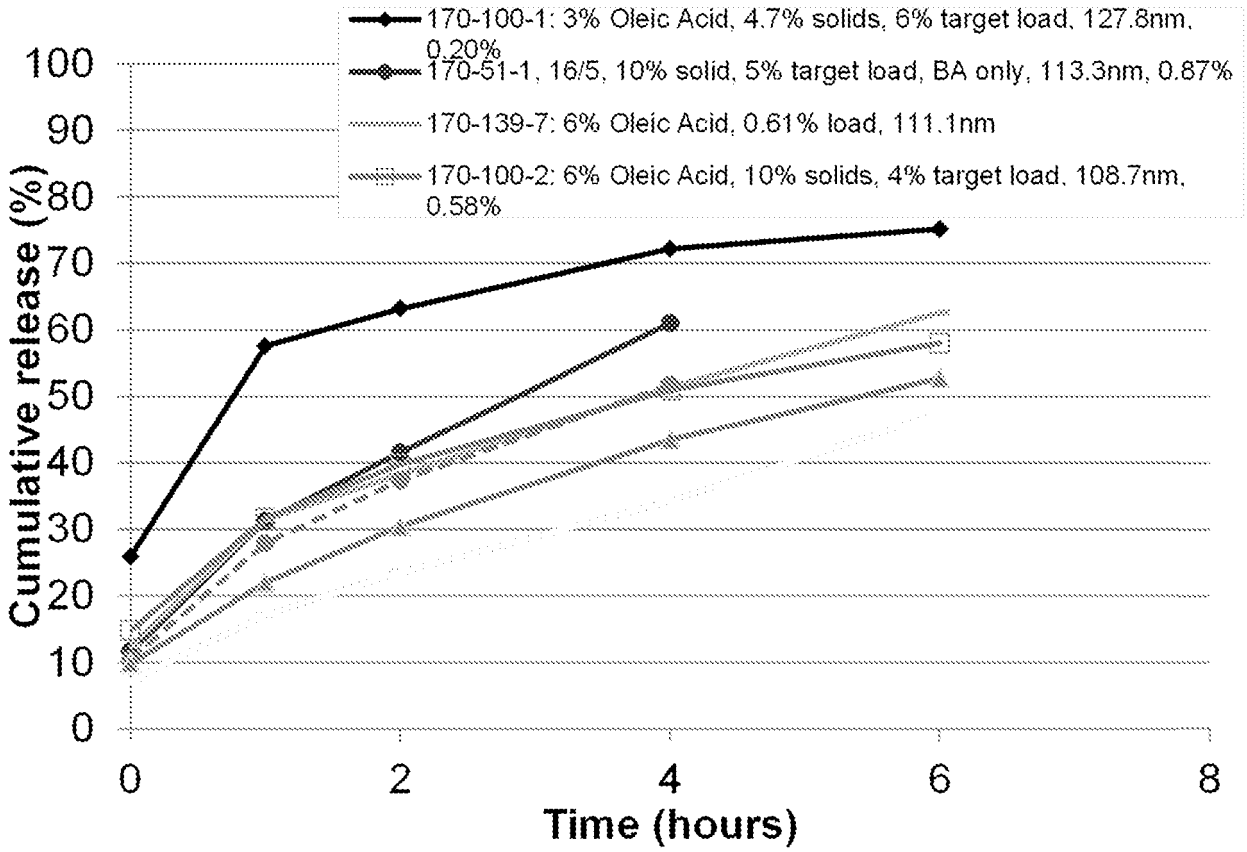

170-100-1: 3% Oleic Acid, 4.7% solids, 6% target load, 127.8nm, 0.20%
170-51-1, 16/5, 10% solid, 5% target load, BA only, 113.3nm, 0.87%
170-139-7: 6% Oleic Acid, 0.61% load, 111.1nm
170-100-2: 6% Oleic Acid, 10% solids, 4% target load, 108.7nm, 0.58%
Cumulative release (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
Time (hours)

Fig. 7

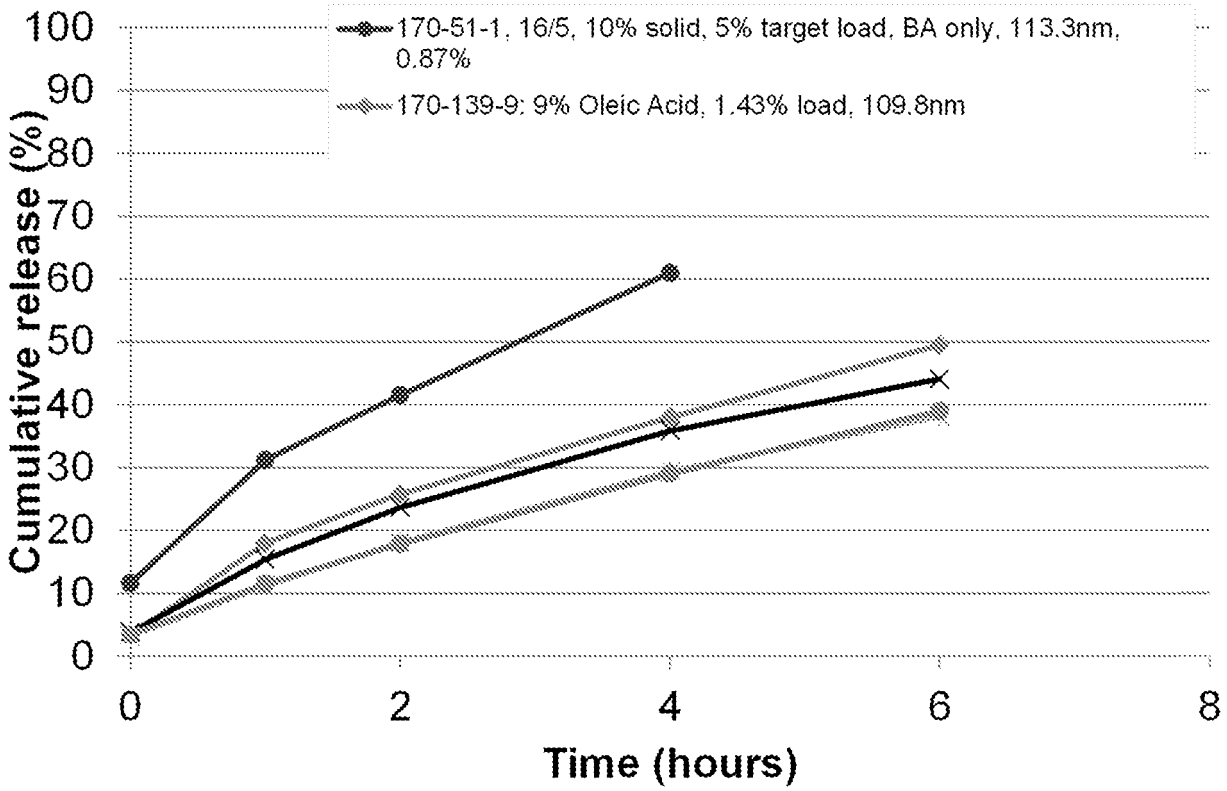

170-51-1, 16/5, 10% solid, 5% target load, BA only, 113.3nm, 0.87%
170-139-9: 9% Oleic Acid, 1.43% load, 109.8nm
Cumulative release (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
Time (hours)

Fig. 8

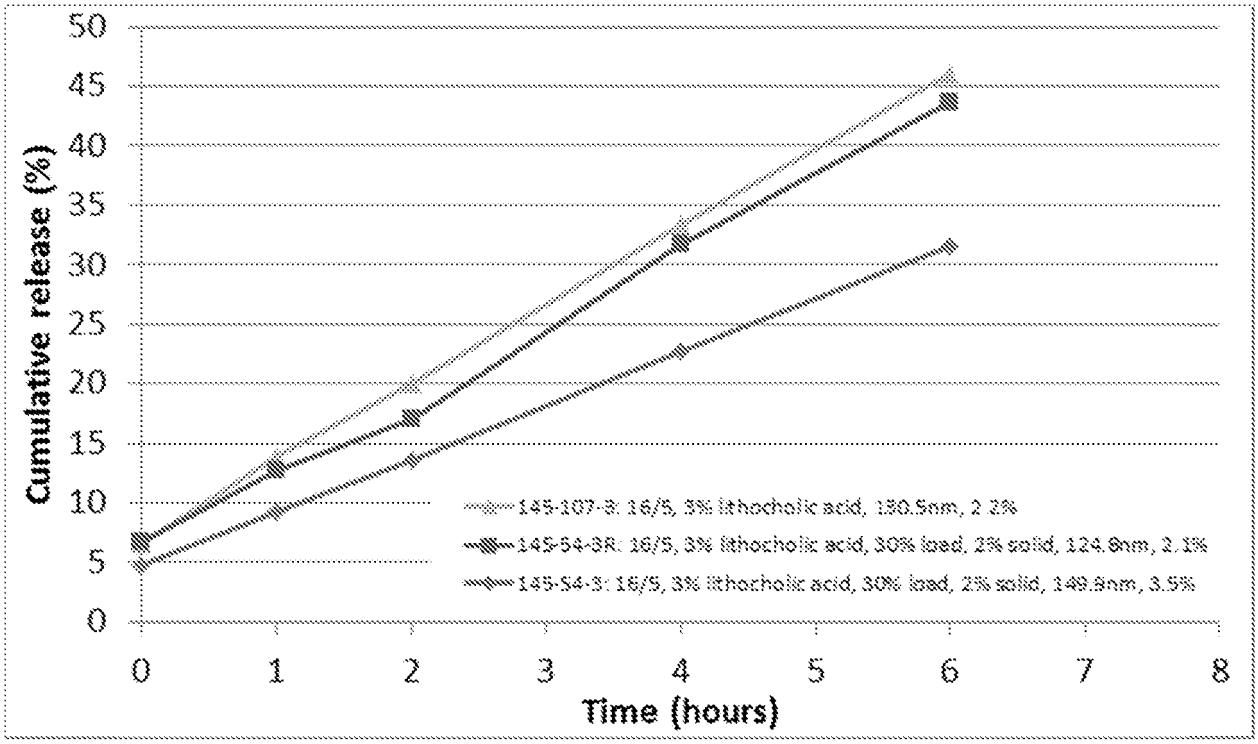

Cumulative release (%)
50
45
40
35
30
25
20
15
10
5
0
0
1
2
3
4
5
6
7
8
Time (hours)
145-107-3: 16/5, 3% lithocholic acid, 130.5nm, 2.2%
145-54-3R: 16/5, 3% lithocholic acid, 30% load, 2% solid, 124.9nm, 2.1%
145-54-3: 16/5, 3% lithocholic acid, 30% load, 2% solid, 149.9nm, 3.5%

Fig. 9