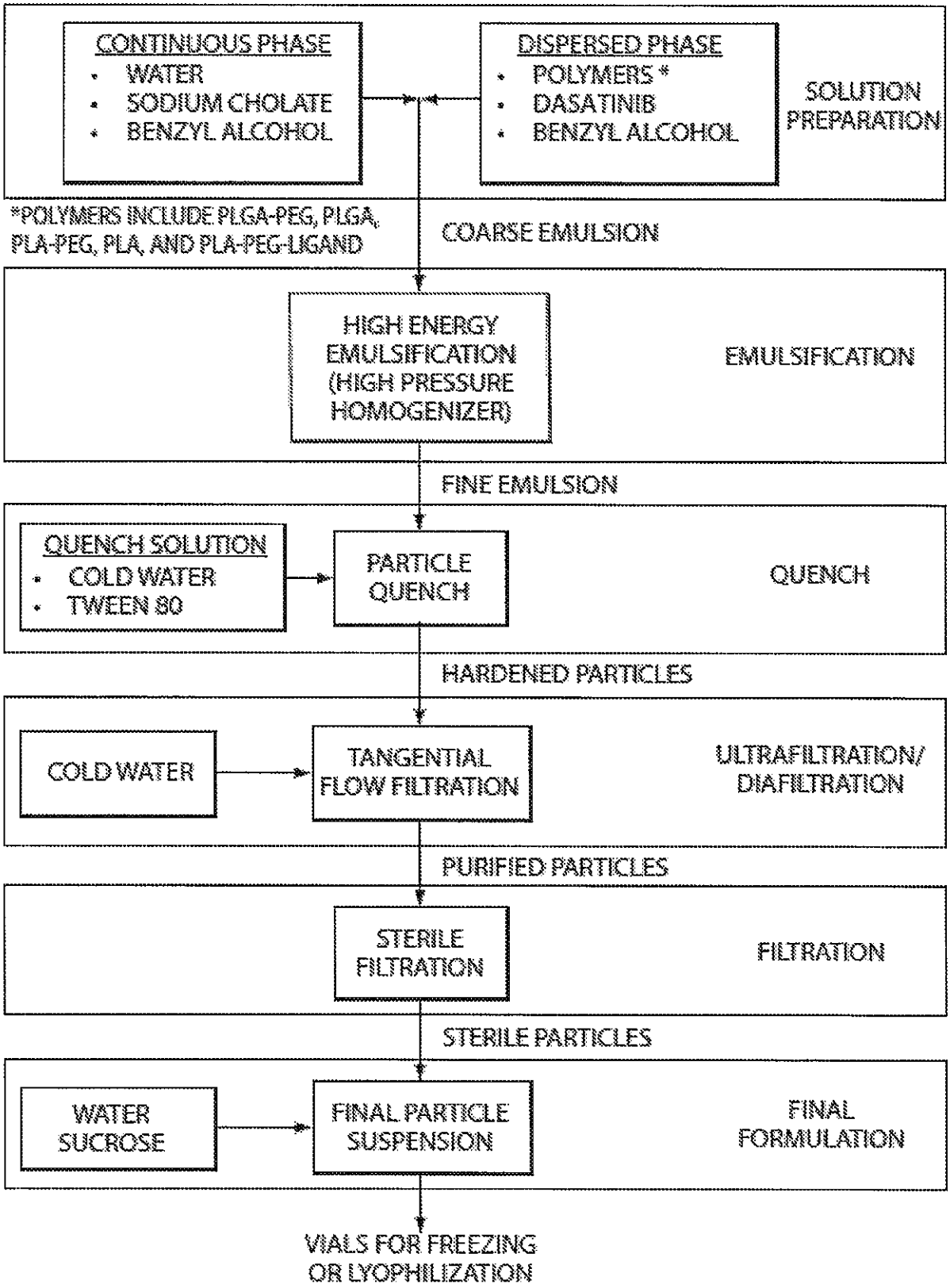

CONTINUOUS PHASE
WATER
SODIUM CHOLATE
BENZYL ALCOHOL
DISPERSED PHASE
POLYMERS *
DASATINIB
BENZYL ALCOHOL
SOLUTION PREPARATION
*POLYMERS INCLUDE PLGA-PEG, PLGA, PLA-PEG, PLA, AND PLA-PEG-LIGAND
COARSE EMULSION
HIGH ENERGY EMULSIFICATION (HIGH PRESSURE HOMOGENIZER)
EMULSIFICATION
FINE EMULSION
QUENCH SOLUTION
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

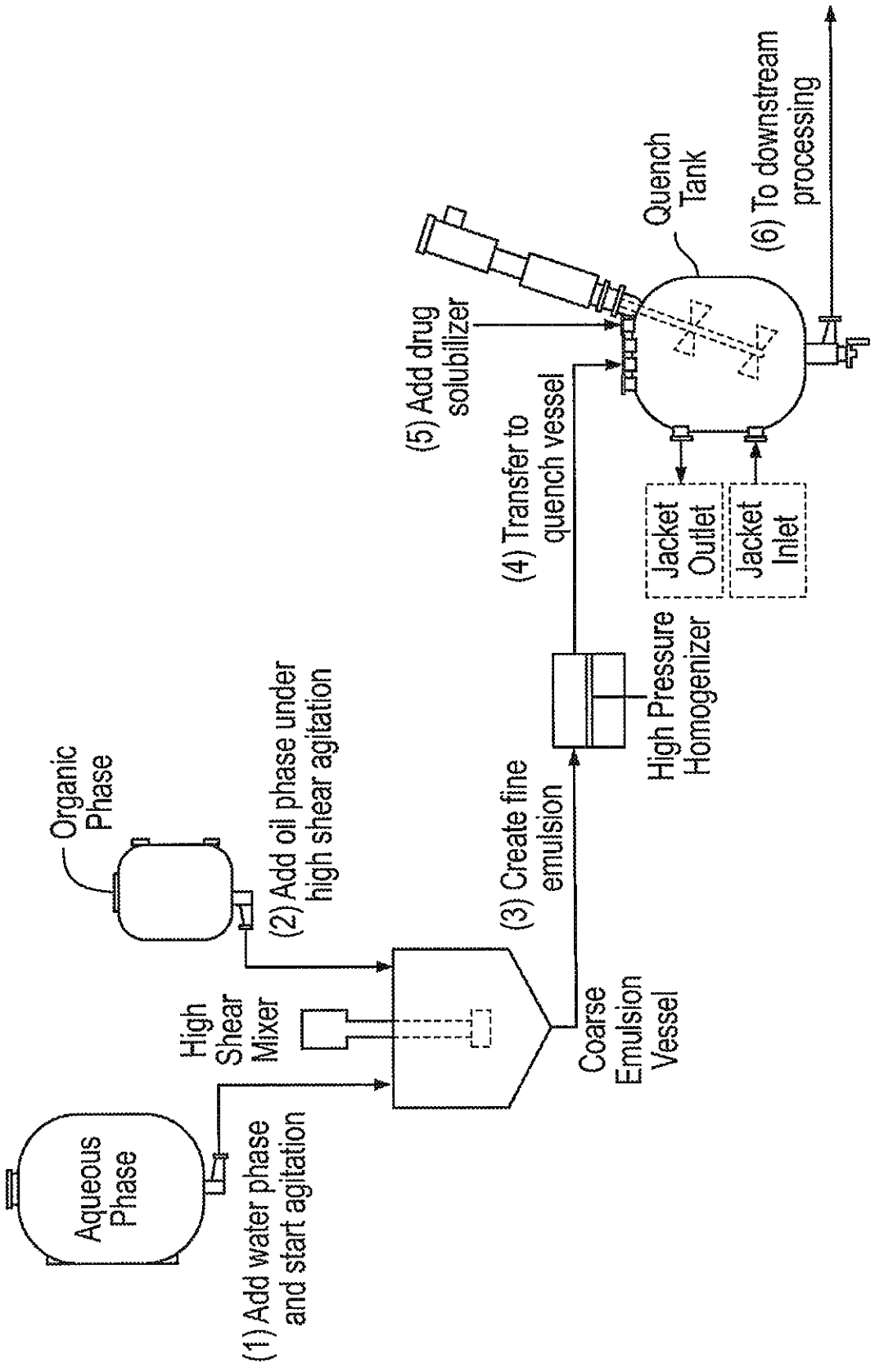

Aqueous Phase
(1) Add water phase and start agitation
Organic Phase
(2) Add oil phase under high shear agitation
High Shear Mixer
Coarse Emulsion Vessel
(3) Create fine emulsion
High Pressure Homogenizer
(4) Transfer to quench vessel
(5) Add drug solubilizer
Quench Tank
Jacket Outlet
Jacket Inlet
(6) To downstream processing

FIG. 2A

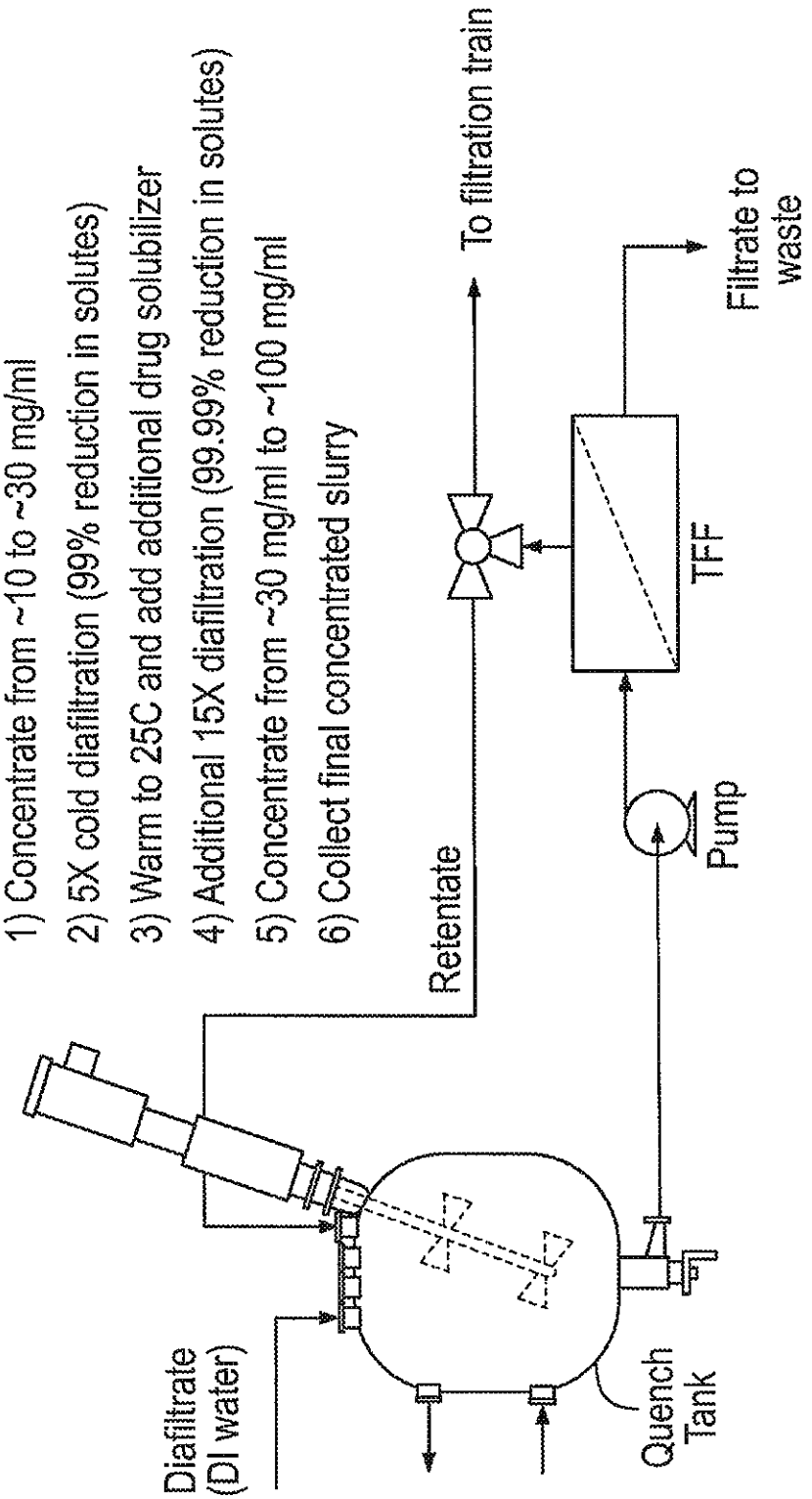

1) Concentrate from ~10 to ~30 mg/ml
2) 5X cold diafiltration (99% reduction in solutes)
3) Warm to 25C and add additional drug solubilizer
4) Additional 15X diafiltration (99.99% reduction in solutes)
5) Concentrate from ~30 mg/ml to ~100 mg/ml
6) Collect final concentrated slurry
Retentate
To filtration train
Filtrate to waste
TFF
Pump
Diafiltrate (DI water)
Quench Tank

FIG. 2B

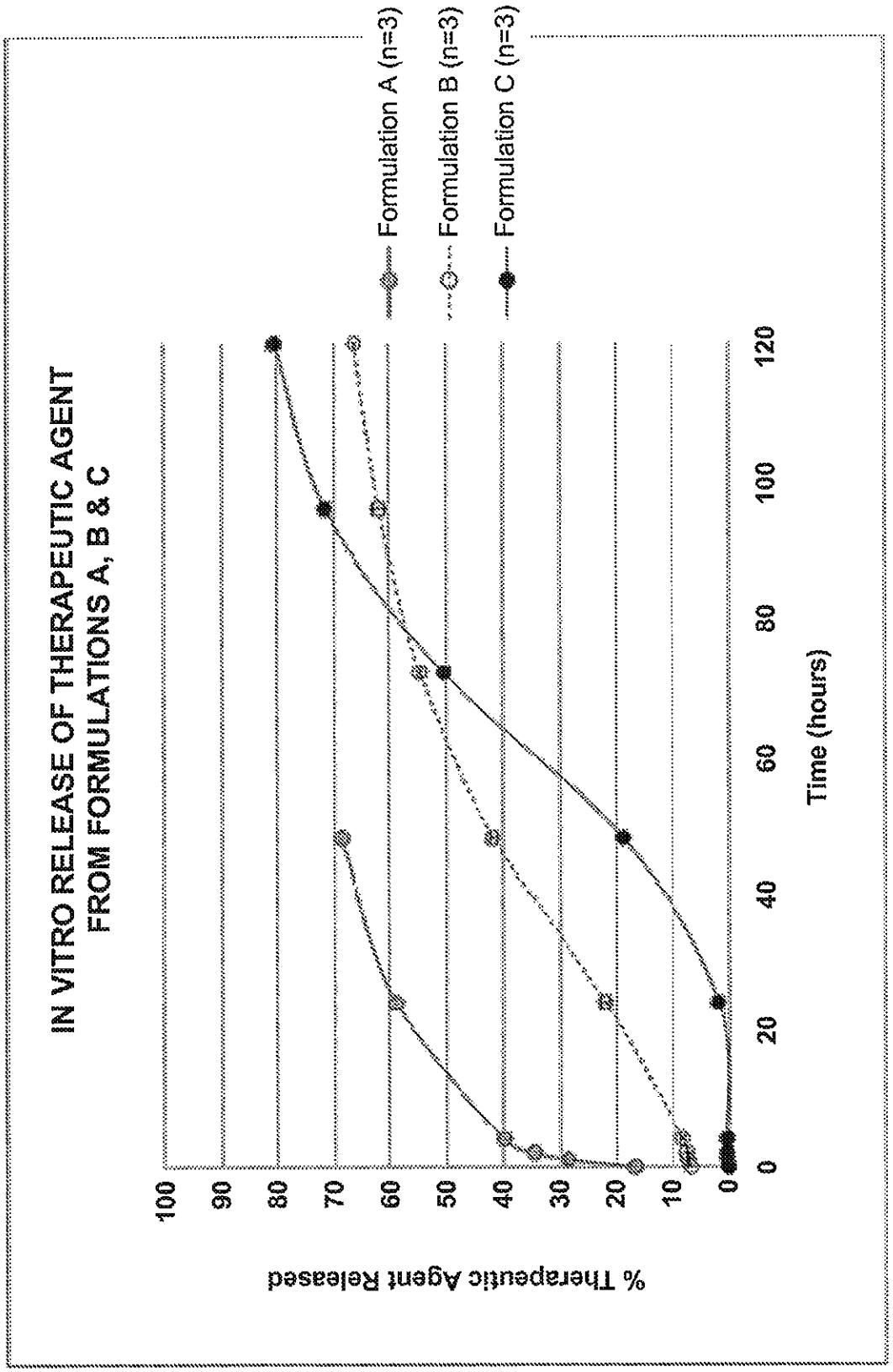

IN VITRO RELEASE OF THERAPEUTIC AGENT
FROM FORMULATIONS A, B & C
Formulation A (n=3)
Formulation B (n=3)
Formulation C (n=3)
% Therapeutic Agent Released
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
Time (hours)

FIG. 3

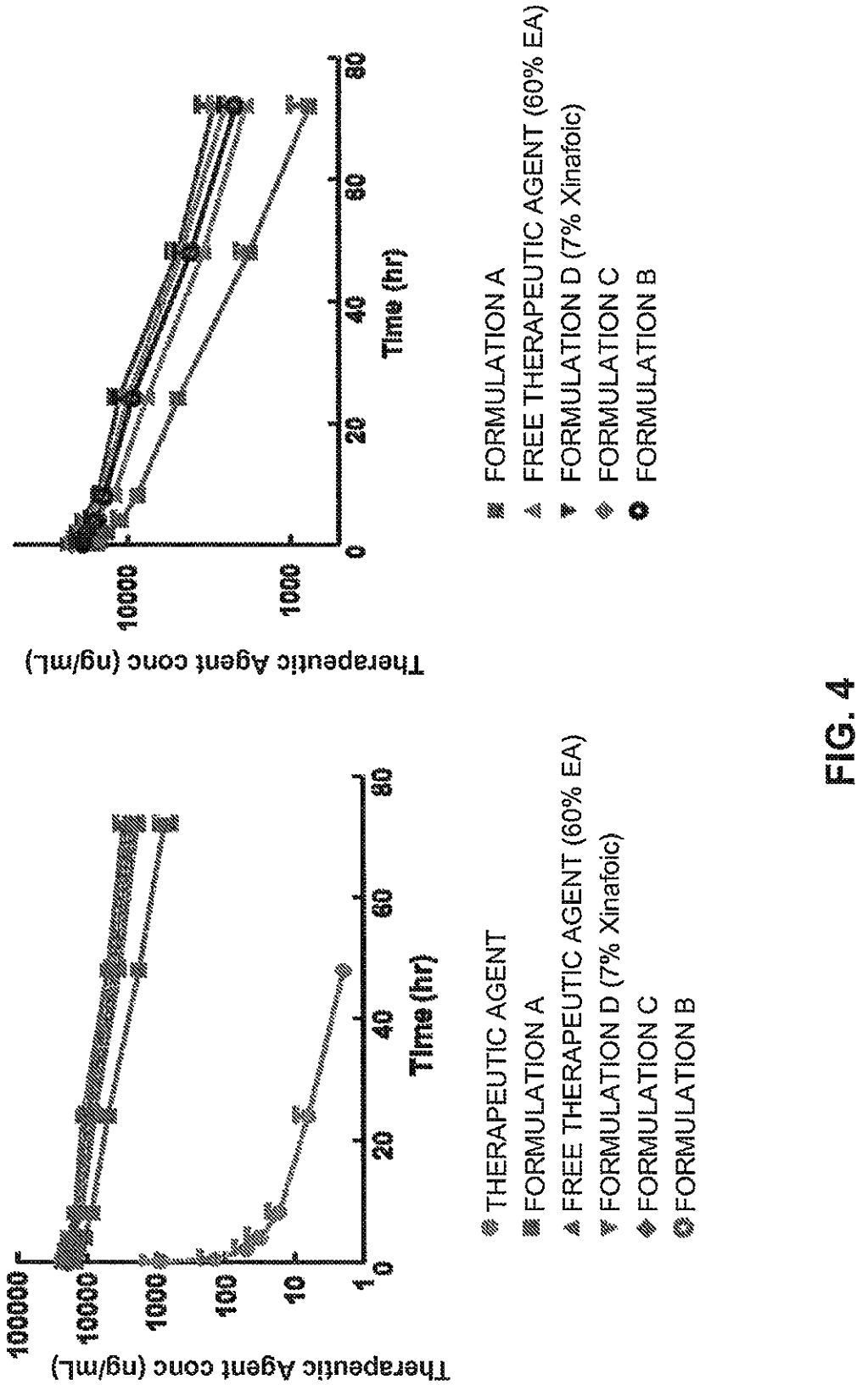

Therapeutic Agent conc (ng/mL)
100000
10000
1000
100
10
1
0
20
40
60
80
Time (hr)
THERAPEUTIC AGENT
FORMULATION A
FREE THERAPEUTIC AGENT (60% EA)
FORMULATION D (7% Xinafoic)
FORMULATION C
FORMULATION B
Therapeutic Agent conc (ng/mL)
10000
1000
0
20
40
60
80
Time (hr)
FORMULATION A
FREE THERAPEUTIC AGENT (60% EA)
FORMULATION D (7% Xinafoic)
FORMULATION C
FORMULATION B

FIG. 4

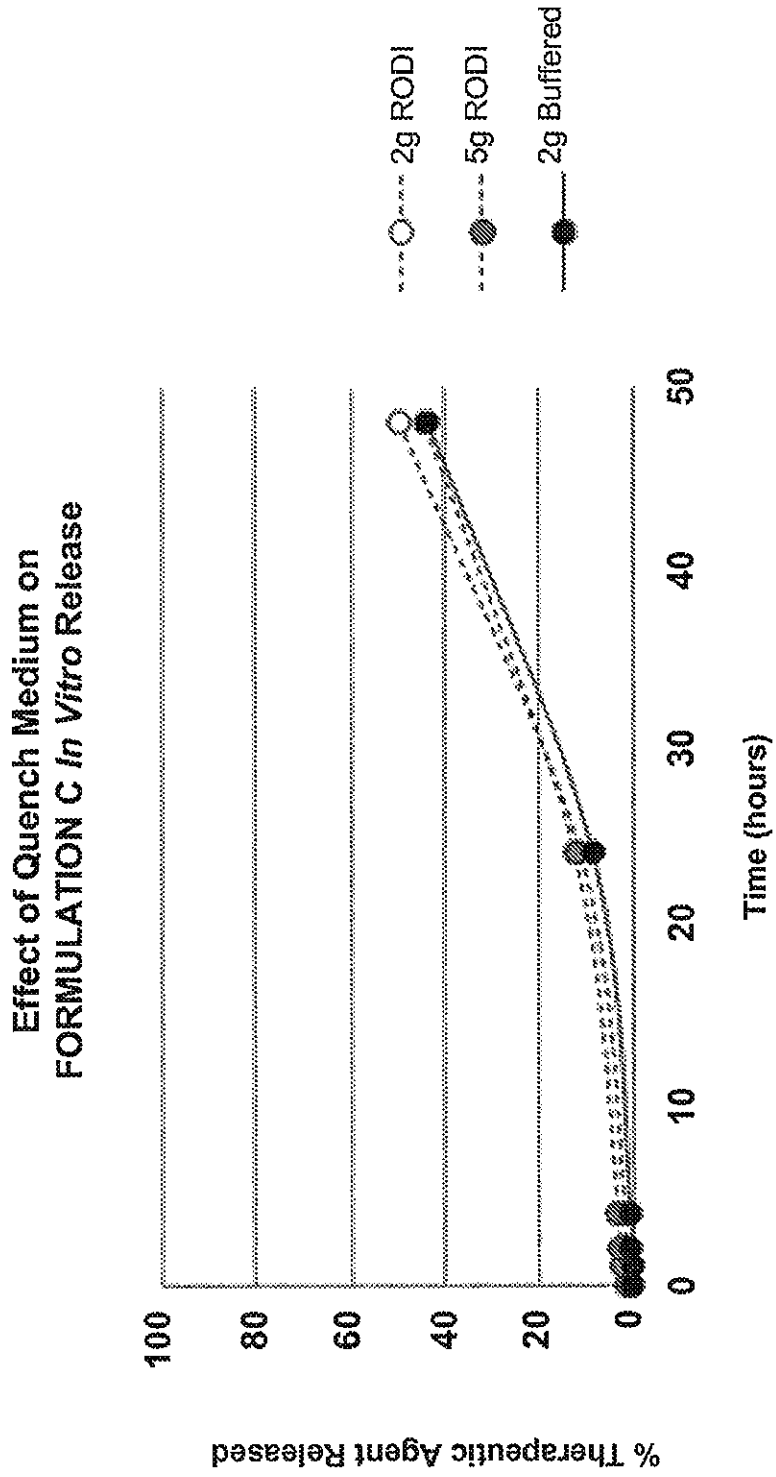

Effect of Quench Medium on
FORMULATION C *In Vitro* Release
% Therapeutic Agent Released
100
80
60
40
20
0
0
10
20
30
40
50
Time (hours)
2g RODI
5g RODI
2g Buffered

FIG. 5

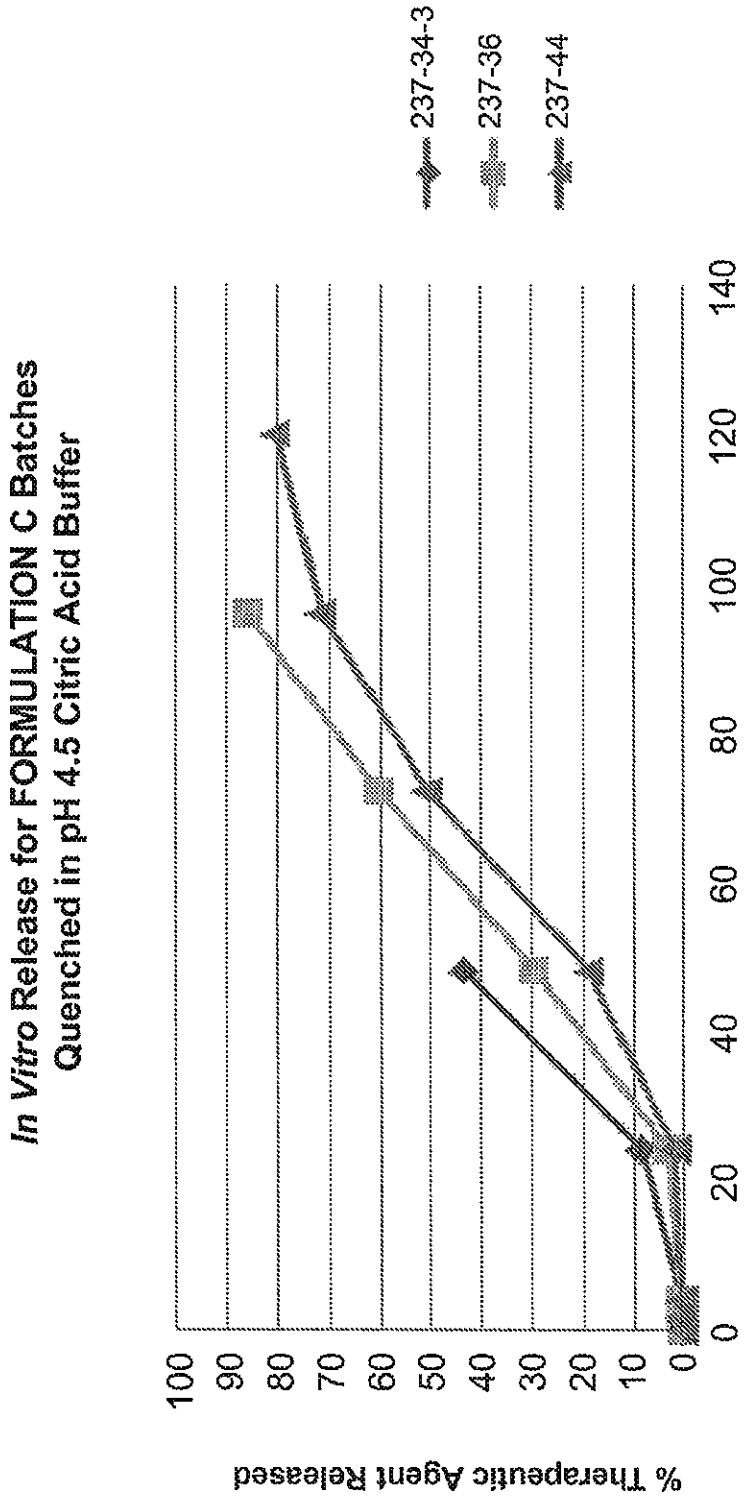

In Vitro Release for FORMULATION C Batches
Quenched in pH 4.5 Citric Acid Buffer
237-34-3
237-36
237-44
% Therapeutic Agent Released
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
140
Time (hours)

FIG. 6

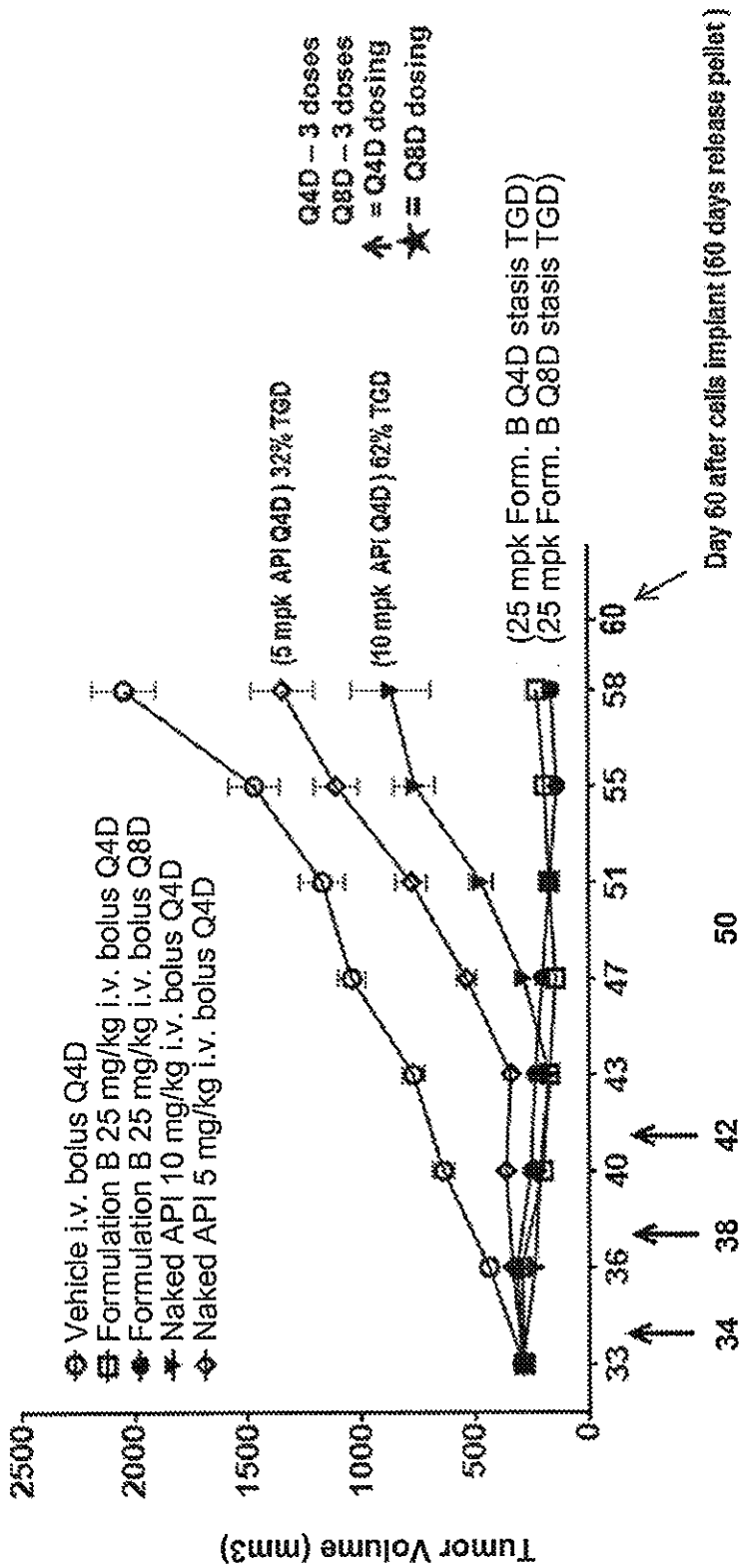

Tumor Volume (mm3)
2500
2000
1500
1000
500
0
Vehicle i.v. bolus Q4D
Formulation B 25 mg/kg i.v. bolus Q4D
Formulation B 25 mg/kg i.v. bolus Q8D
Naked API 10 mg/kg i.v. bolus Q4D
Naked API 5 mg/kg i.v. bolus Q4D
(5 mpk API Q4D) 32% TGD
(10 mpk API Q4D) 62% TGD
(25 mpk Form. B Q4D stasis TGD)
(25 mpk Form. B Q8D stasis TGD)
Q4D -- 3 doses
Q8D -- 3 doses
= Q4D dosing
= Q8D dosing
Day 60 after cells implant (60 days release pellet)
33
34
36
38
40
42
43
47
50
51
55
58
60

FIG. 7

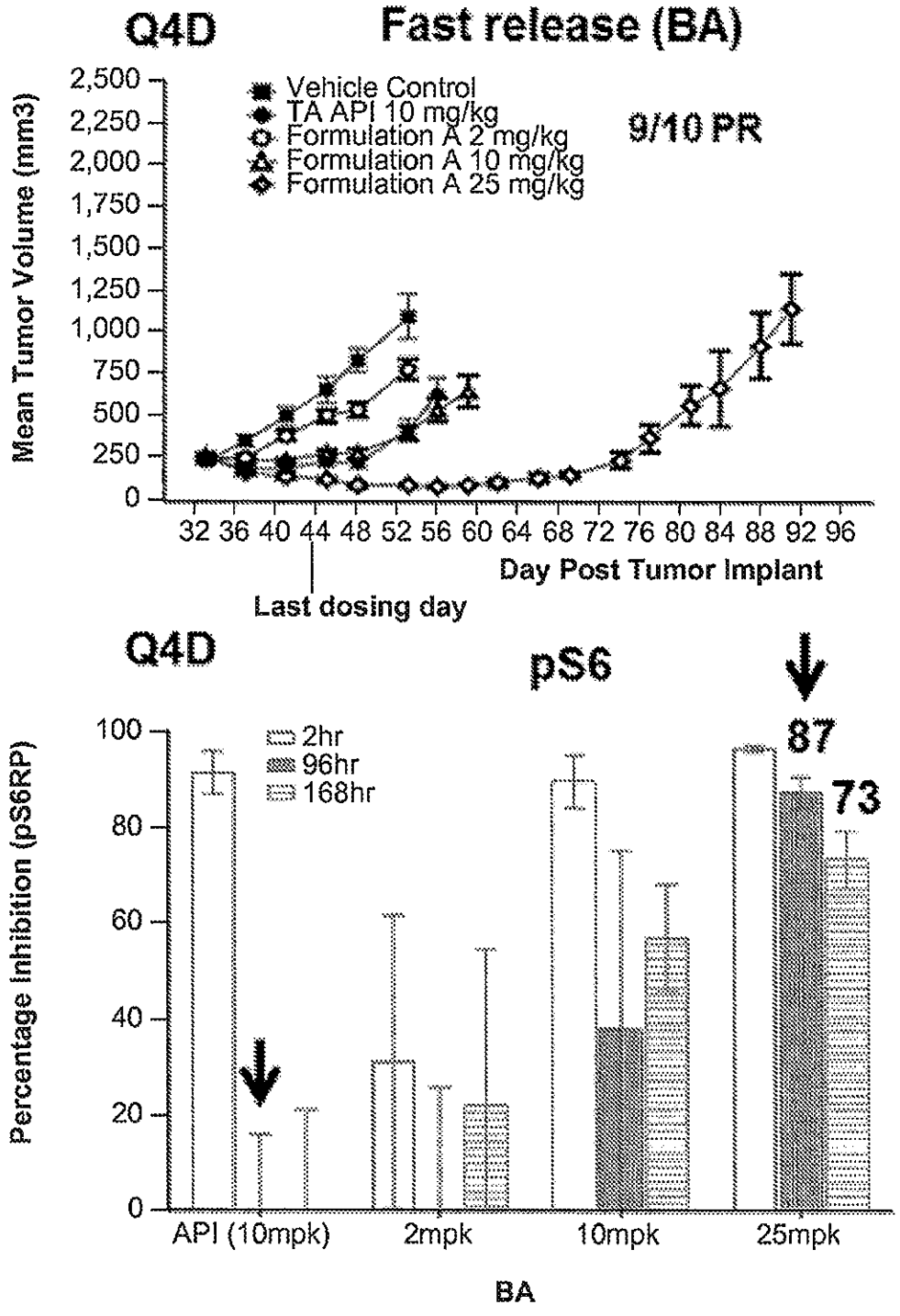

Q4D
Fast release (BA)
Vehicle Control
TA API 10 mg/kg
Formulation A 2 mg/kg
Formulation A 10 mg/kg
Formulation A 25 mg/kg
9/10 PR
Mean Tumor Volume (mm3)
2,500
2,250
2,000
1,750
1,500
1,250
1,000
750
500
250
0
32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
Day Post Tumor Implant
Last dosing day
Q4D
pS6
87
73
2hr
96hr
168hr
Percentage Inhibition (pS6RP)
100
80
60
40
20
0
API (10mpk)
2mpk
10mpk
25mpk
BA

FIG. 8A

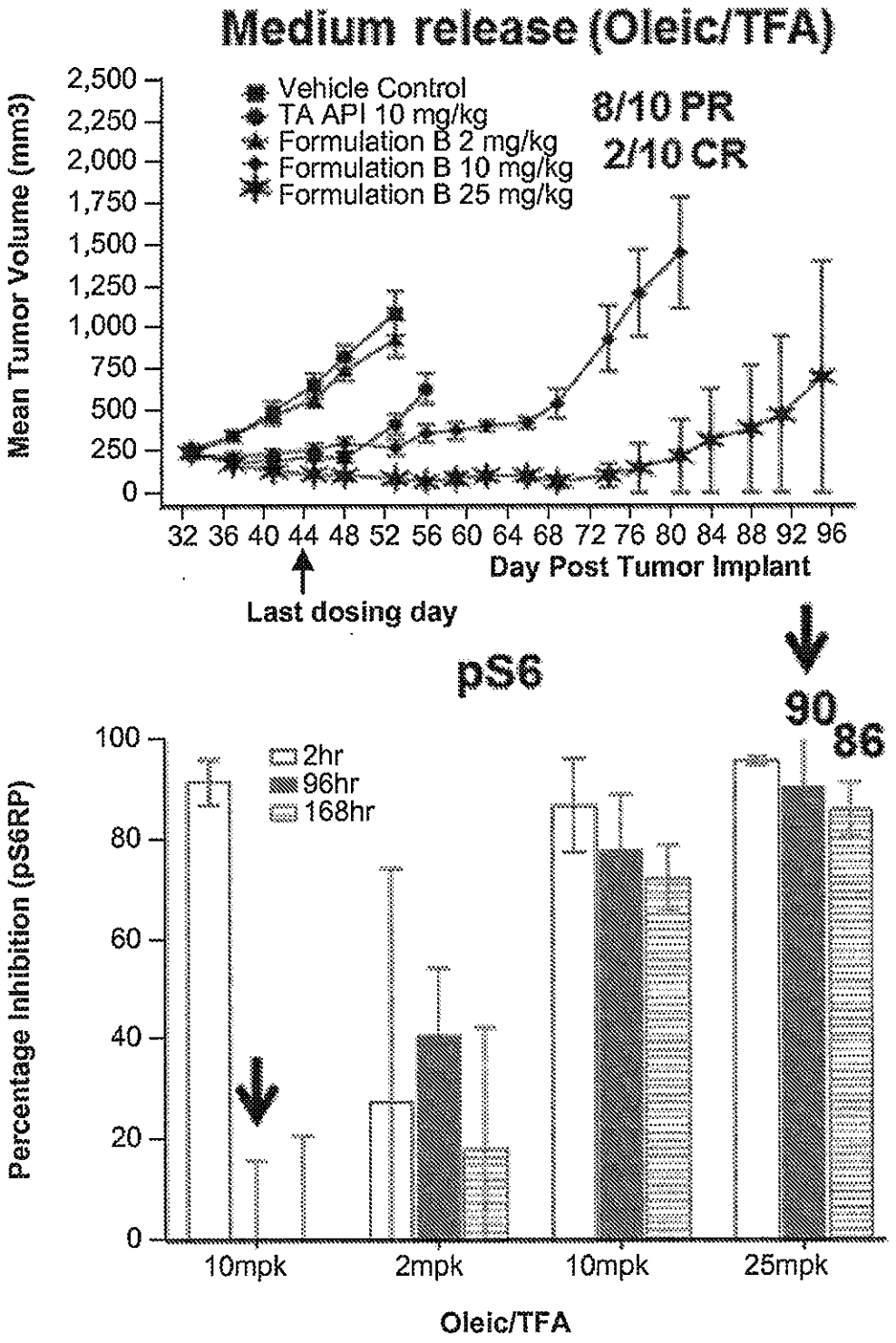

Medium release (Oleic/TFA)
Vehicle Control
TA API 10 mg/kg
Formulation B 2 mg/kg
Formulation B 10 mg/kg
Formulation B 25 mg/kg
8/10 PR
2/10 CR
Mean Tumor Volume (mm3)
2,500
2,250
2,000
1,750
1,500
1,250
1,000
750
500
250
0
32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
Day Post Tumor Implant
Last dosing day
pS6
90
86
2hr
96hr
168hr
Percentage Inhibition (pS6RP)
100
80
60
40
20
0
10mpk
2mpk
10mpk
25mpk
Oleic/TFA

FIG. 8B

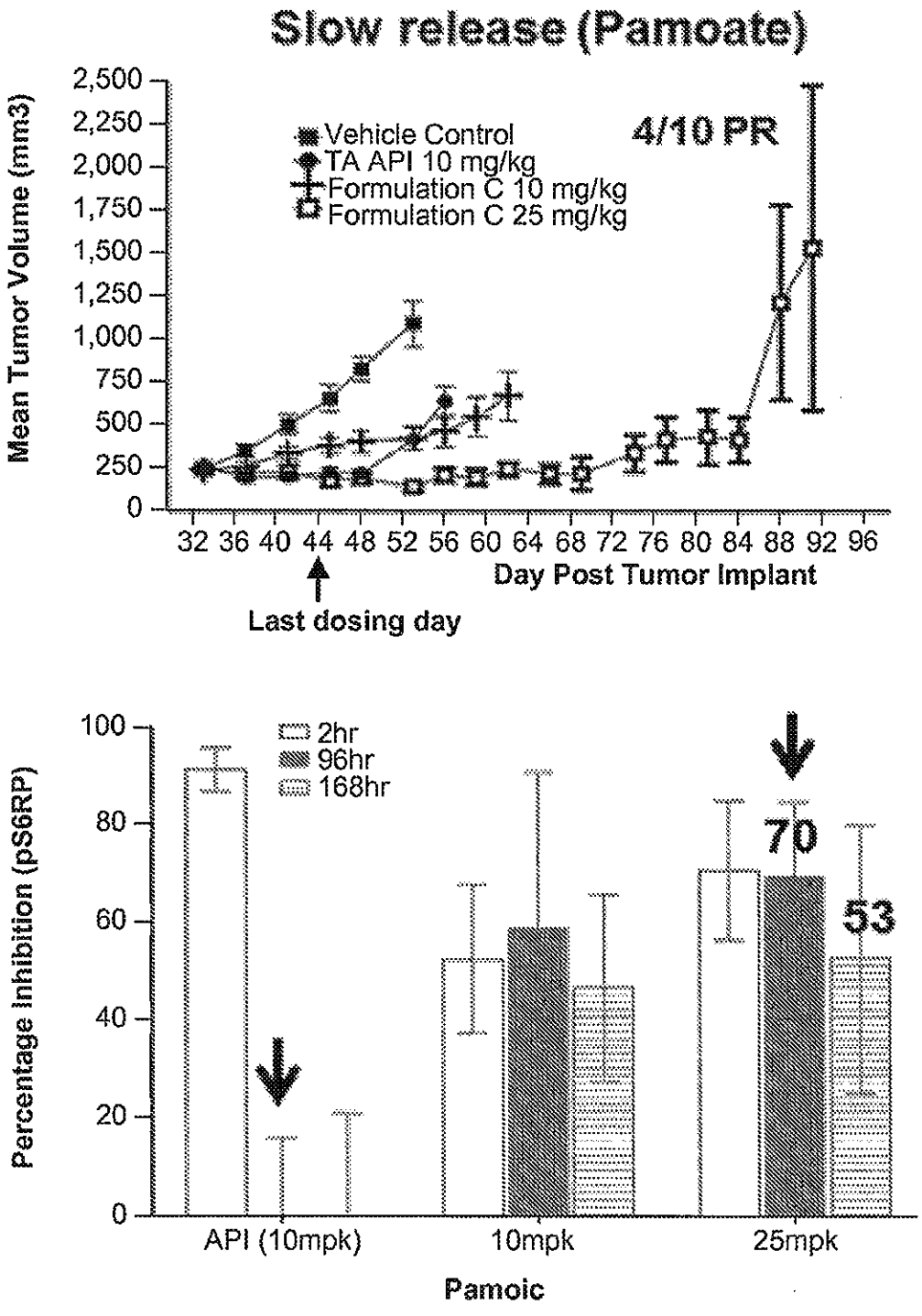
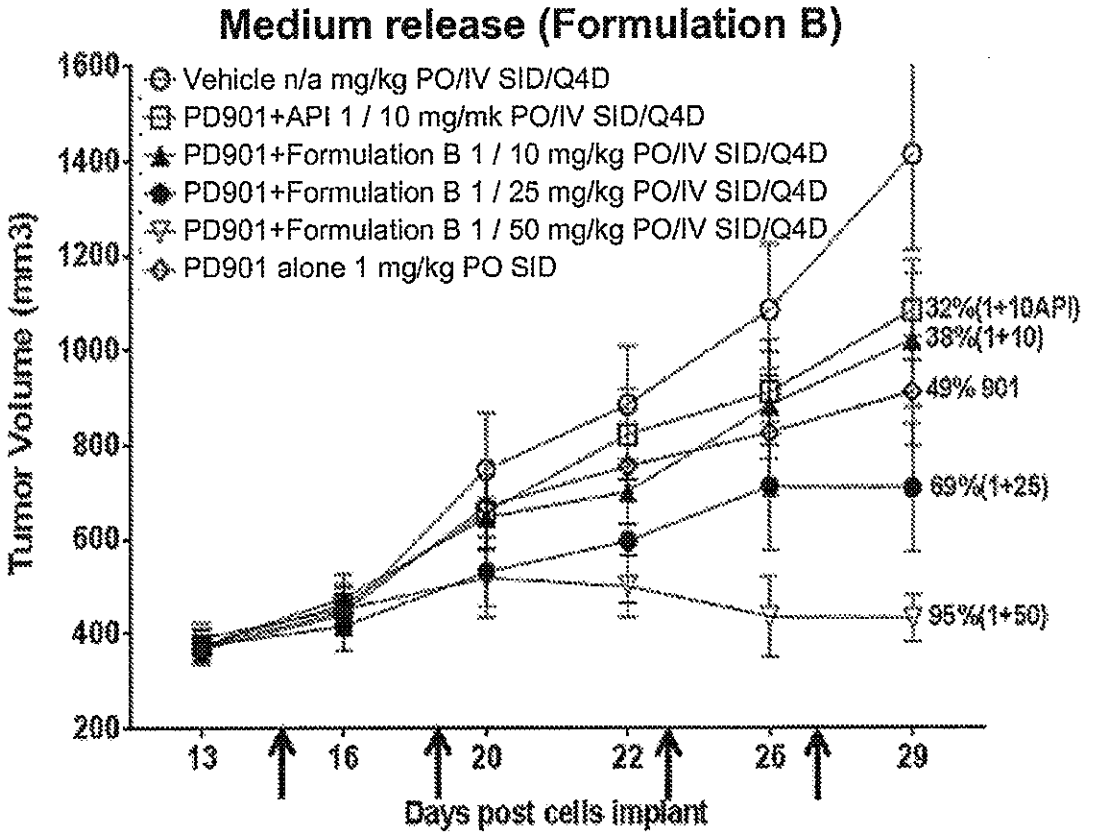

Slow release (Pamoate)
Mean Tumor Volume (mm3)
2,500
2,250
2,000
1,750
1,500
1,250
1,000
750
500
250
0
Vehicle Control
TA API 10 mg/kg
Formulation C 10 mg/kg
Formulation C 25 mg/kg
4/10 PR
32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
Day Post Tumor Implant
Last dosing day
Percentage Inhibition (pS6RP)
100
80
60
40
20
0
2hr
96hr
168hr
70
53
API (10mpk)
10mpk
25mpk
Pamoic

FIG. 8C


Medium release (Formulation B)
Vehicle n/a mg/kg PO/IV SID/Q4D
PD901+API 1 / 10 mg/mk PO/IV SID/Q4D
PD901+Formulation B 1 / 10 mg/kg PO/IV SID/Q4D
PD901+Formulation B 1 / 25 mg/kg PO/IV SID/Q4D
PD901+Formulation B 1 / 50 mg/kg PO/IV SID/Q4D
PD901 alone 1 mg/kg PO SID
Tumor Volume (mm3)
1600
1400
1200
1000
800
600
400
200
32%(1+10API)
38%(1+10)
49% 901
69%(1+25)
95%(1+50)
13
16
20
22
26
29
Days post cells implant

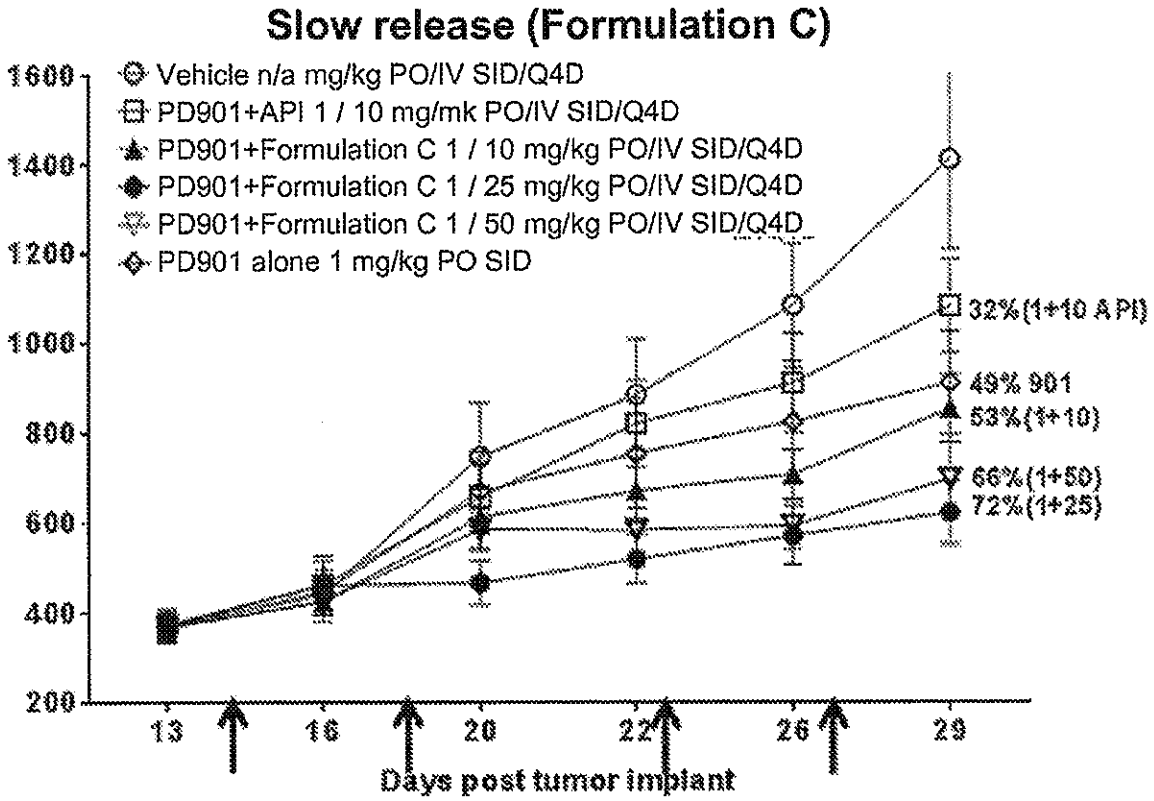

Slow release (Formulation C)
Vehicle n/a mg/kg PO/IV SID/Q4D
PD901+API 1 / 10 mg/mk PO/IV SID/Q4D
PD901+Formulation C 1 / 10 mg/kg PO/IV SID/Q4D
PD901+Formulation C 1 / 25 mg/kg PO/IV SID/Q4D
PD901+Formulation C 1 / 50 mg/kg PO/IV SID/Q4D
PD901 alone 1 mg/kg PO SID
1600
1400
1200
1000
800
600
400
200
32% (1+10 API)
49% 901
53%(1+10)
66%(1+50)
72%(1+25)
13
16
20
22
26
29
Days post tumor implant

FIG. 9

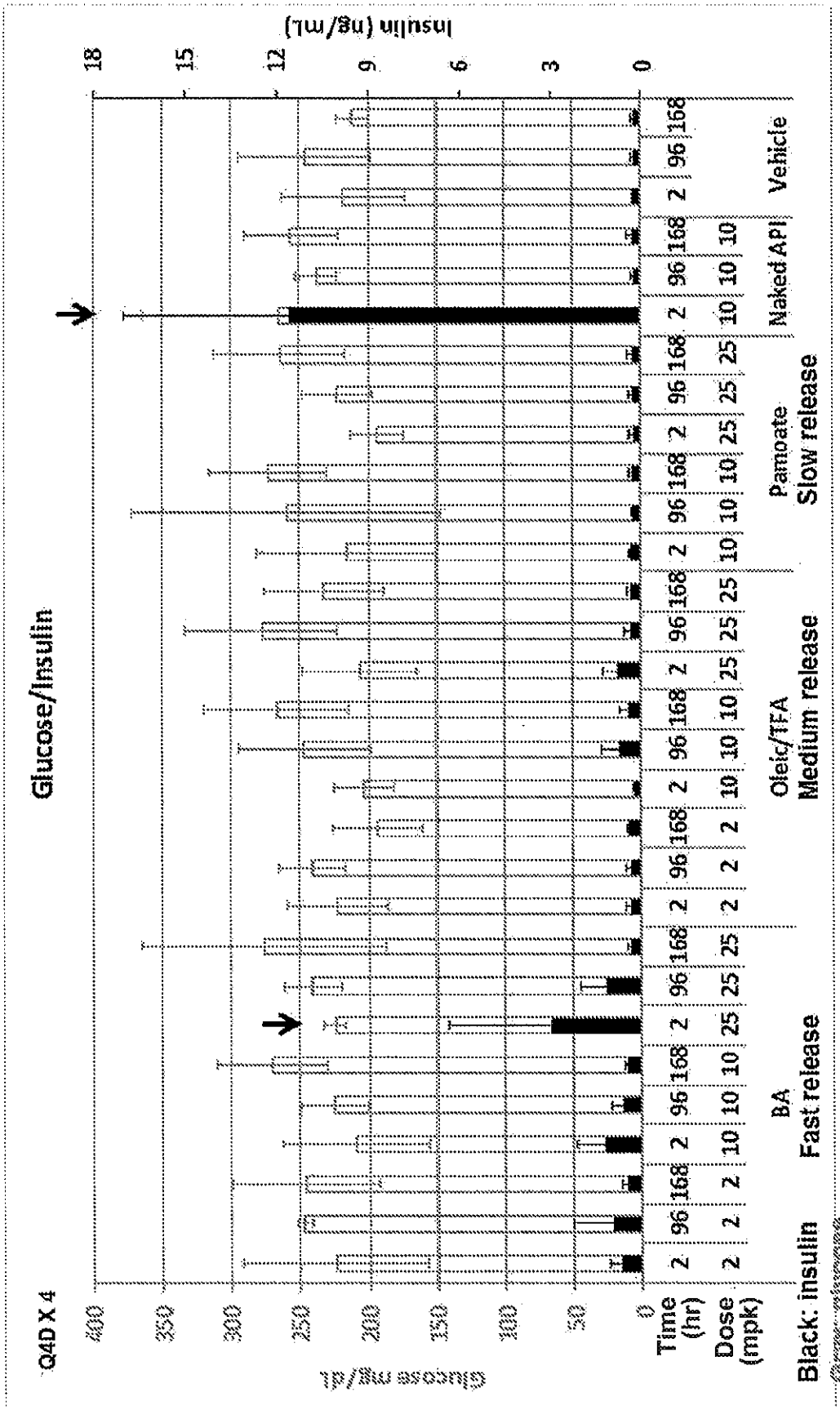

Glucose/Insulin
Q4D X 4
Insulin (ng/mL)
Glucose mg/dL
Time (hr)
Dose (mpk)
Black: insulin
Gray: glucose
BA
Fast release
Oleic/TFA
Medium release
Pamoate
Slow release
Naked API
Vehicle

FIG. 10