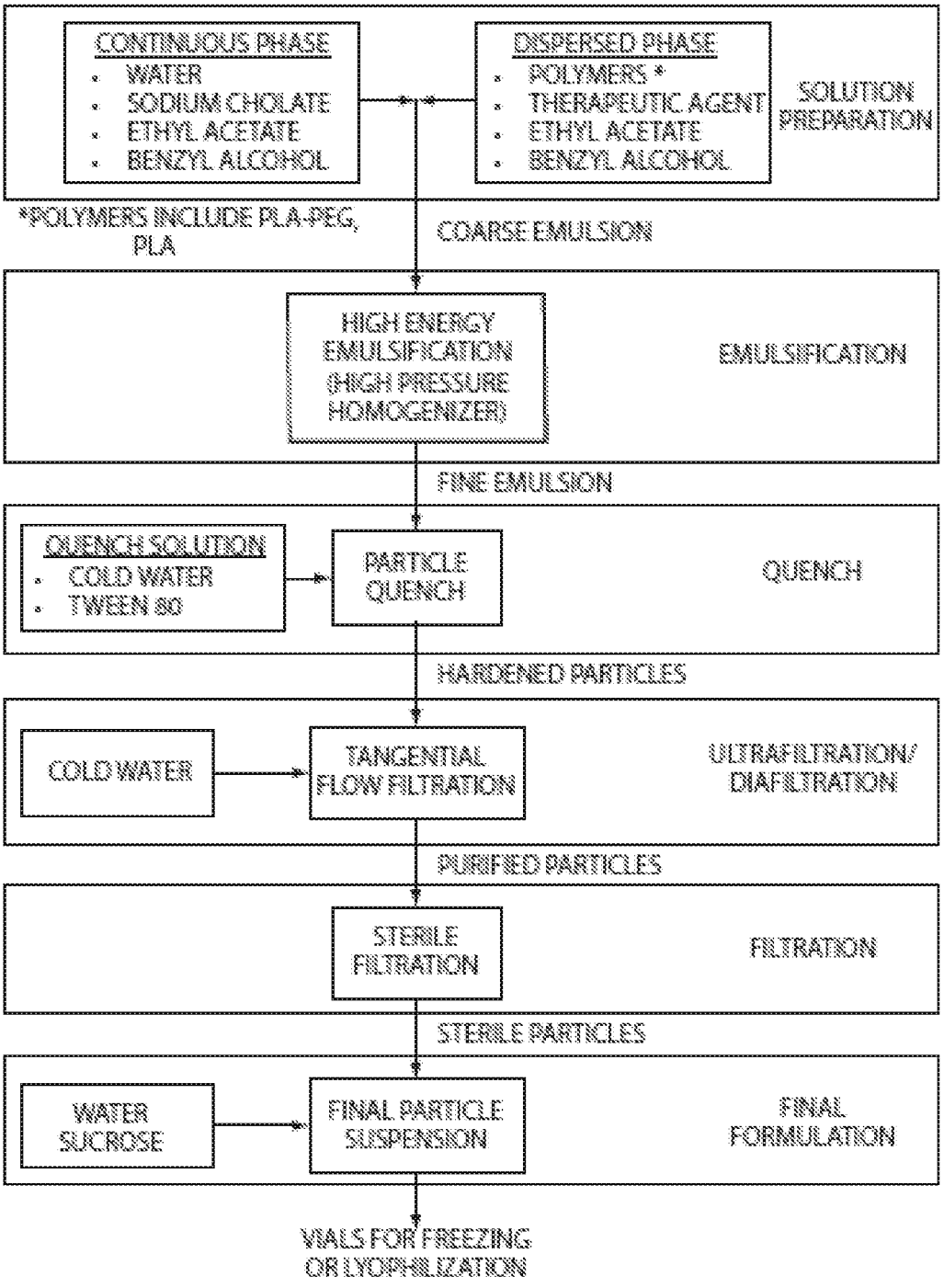

CONTINUOUS PHASE
WATER
SODIUM CHOLATE
ETHYL ACETATE
BENZYL ALCOHOL
DISPERSED PHASE
POLYMERS *
THERAPEUTIC AGENT
ETHYL ACETATE
BENZYL ALCOHOL
SOLUTION PREPARATION
*POLYMERS INCLUDE PLA-PEG, PLA
COARSE EMULSION
HIGH ENERGY EMULSIFICATION (HIGH PRESSURE HOMOGENIZER)
EMULSIFICATION
FINE EMULSION
QUENCH SOLUTION
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

Figure 1

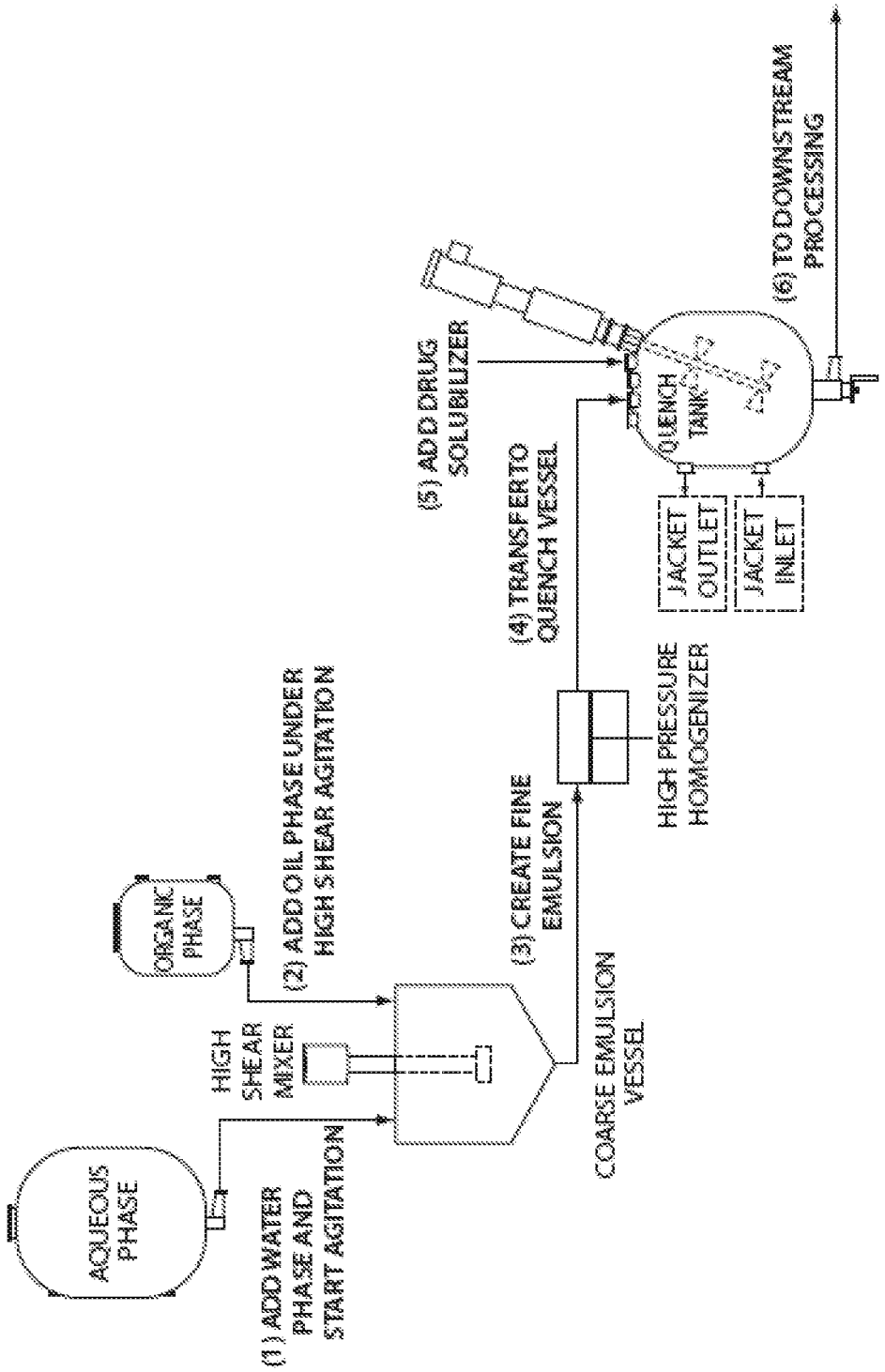

AQUEOUS PHASE
(1) ADD WATER PHASE AND START AGITATION
HIGH SHEAR MIXER
ORGANIC PHASE
(2) ADD OIL PHASE UNDER HIGH SHEAR AGITATION
COARSE EMULSION VESSEL
(3) CREATE FINE EMULSION
HIGH PRESSURE HOMOGENIZER
(4) TRANSFER TO QUENCH VESSEL
(5) ADD DRUG SOLUBILIZER
QUENCH TANK
JACKET OUTLET
JACKET INLET
(6)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

Figure 2A

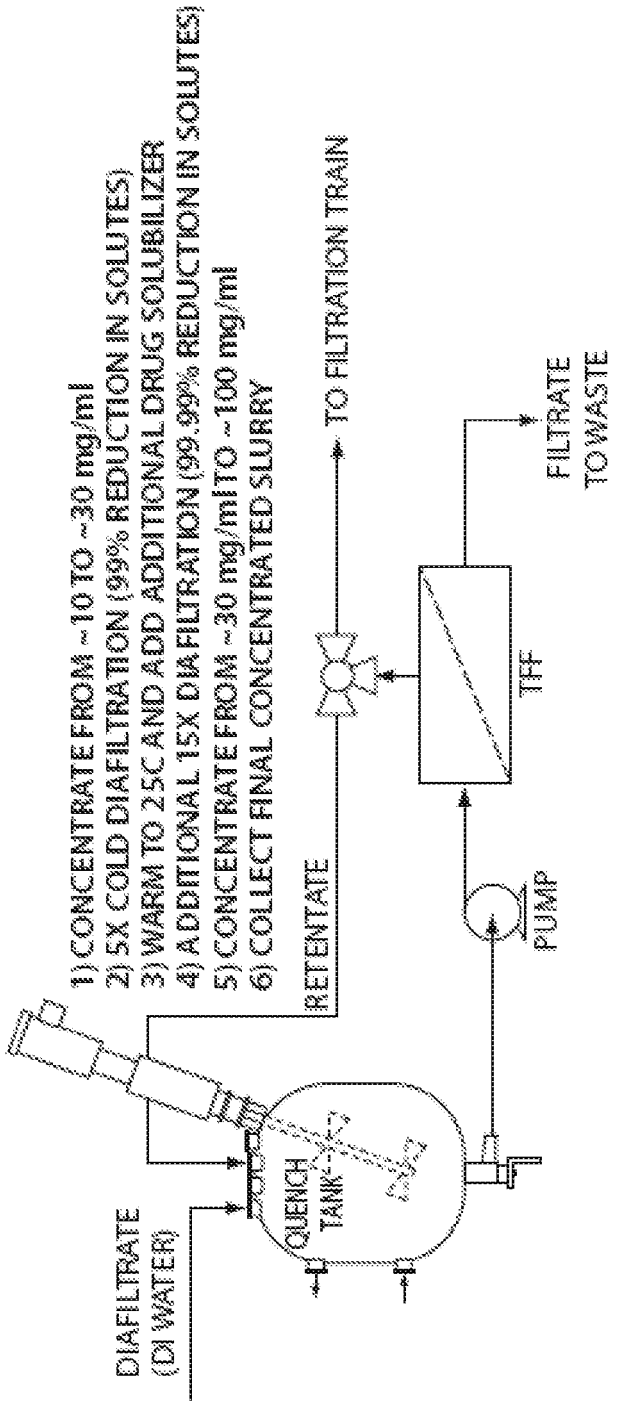

1) CONCENTRATE FROM ~10 TO ~30 mg/ml
2) 5X COLD DIAFILTRATION (99% REDUCTION IN SOLUTES)
3) WARM TO 25C AND ADD ADDITIONAL DRUG SOLUBILIZER
4) ADDITIONAL 15X DIAFILTRATION (99.99% REDUCTION IN SOLUTES)
5) CONCENTRATE FROM ~30 mg/ml TO ~100 mg/ml
6) COLLECT FINAL CONCENTRATED SLURRY
RETENTATE
TO FILTRATION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

Figure 2B

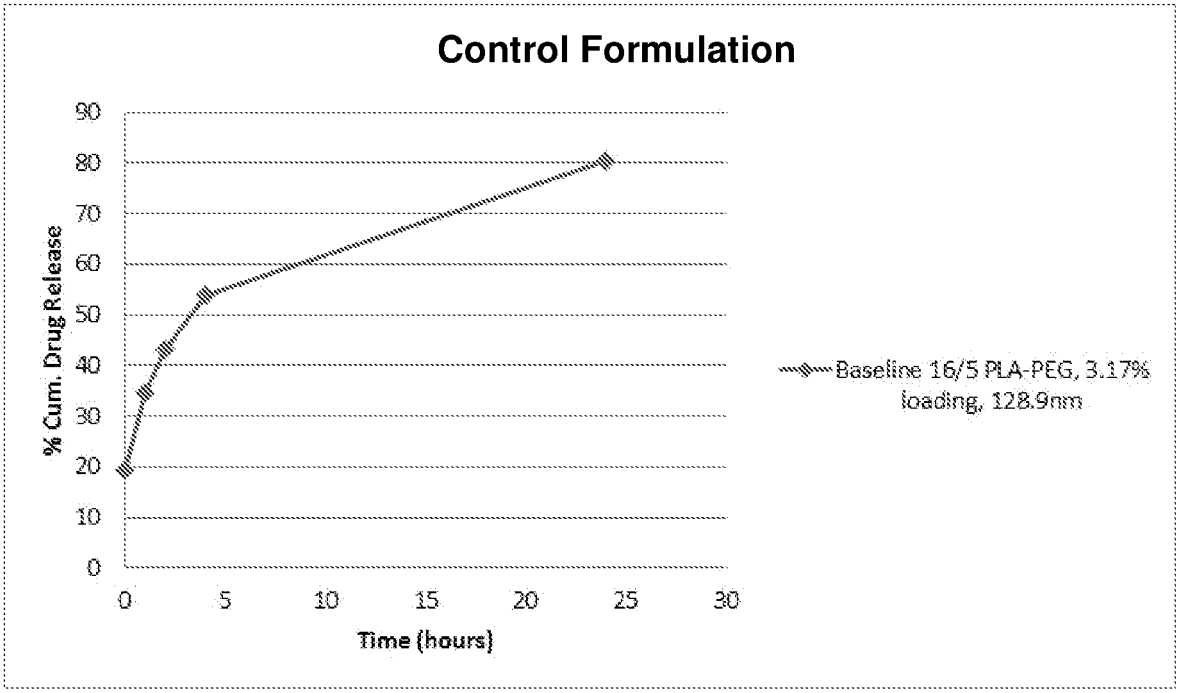

Control Formulation
% Cum. Drug Release
0
10
20
30
40
50
60
70
80
90
0
5
10
15
20
25
30
Time (hours)
Baseline 16/5 PLA-PEG, 3.17% loading, 128.9nm

Figure 3

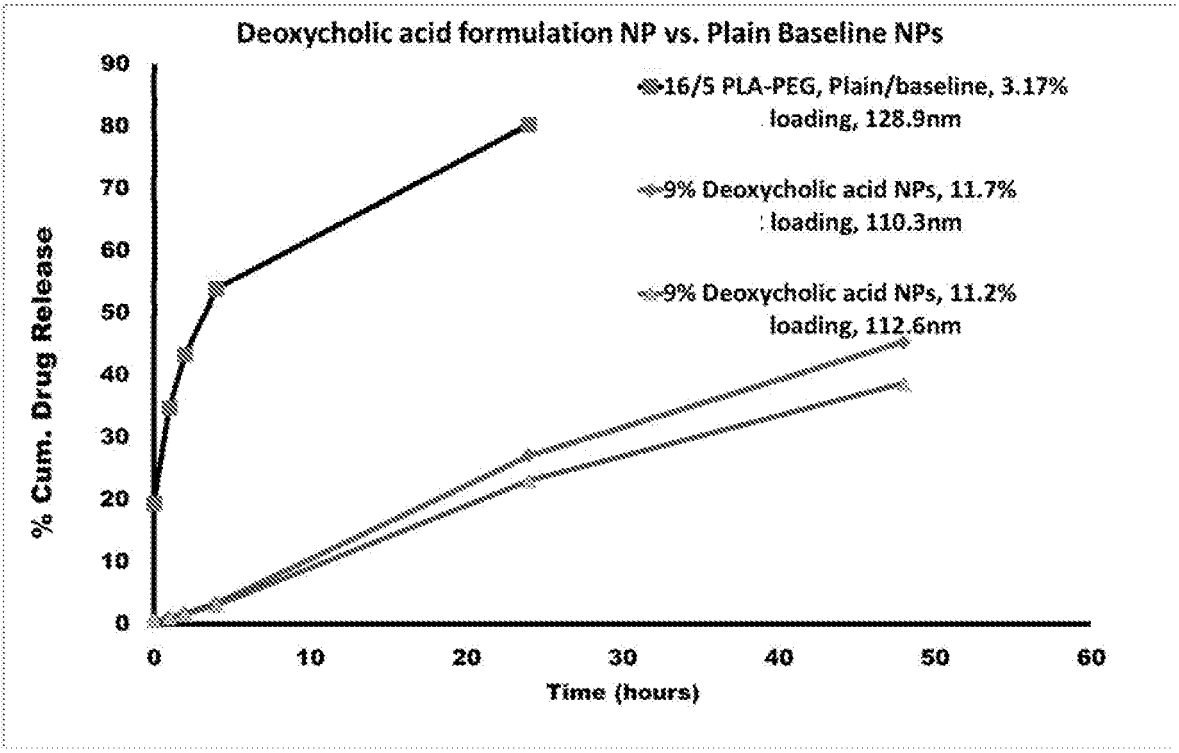

Deoxycholic acid formulation NP vs. Plain Baseline NPs
% Cum. Drug Release
Time (hours)
16/5 PLA-PEG, Plain/baseline, 3.17% loading, 128.9nm
9% Deoxycholic acid NPs, 11.7% loading, 110.3nm
9% Deoxycholic acid NPs, 11.2% loading, 112.6nm
0
10
20
30
40
50
60
70
80
90

Figure 4

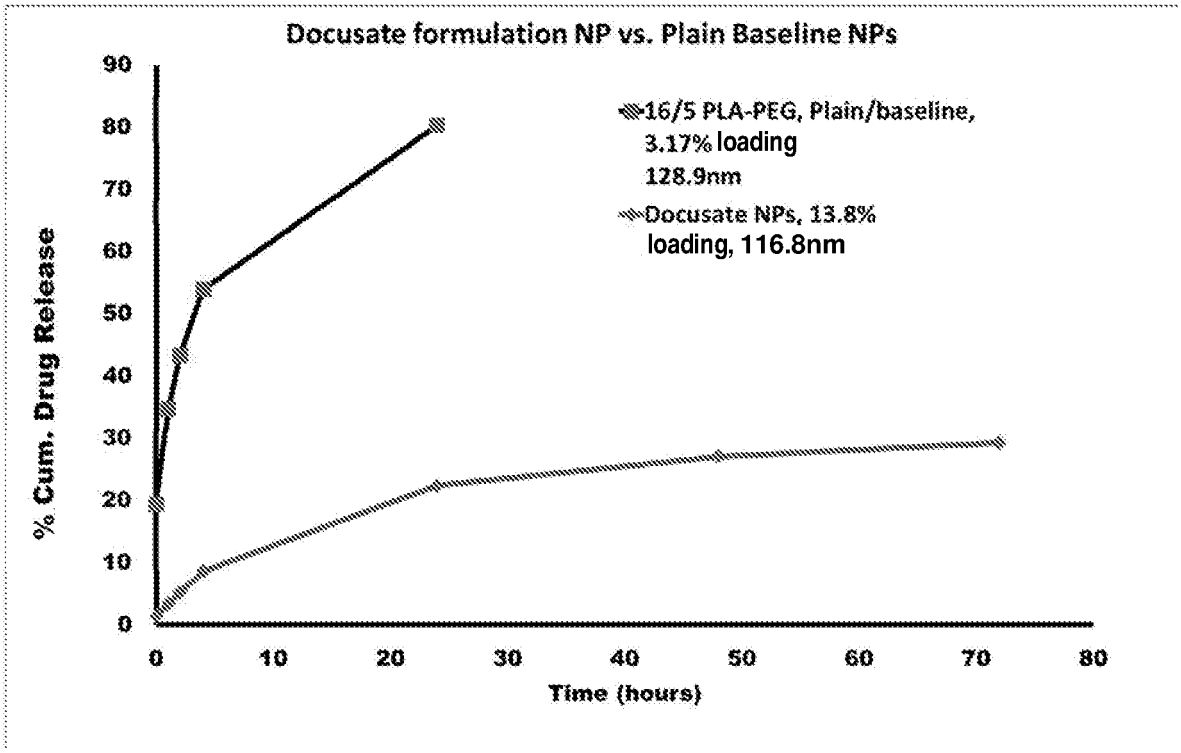

Docusate formulation NP vs. Plain Baseline NPs
% Cum. Drug Release
Time (hours)
16/5 PLA-PEG, Plain/baseline, 3.17% loading 128.9nm
Docusate NPs, 13.8% loading, 116.8nm
0
10
20
30
40
50
60
70
80
90

Figure 5

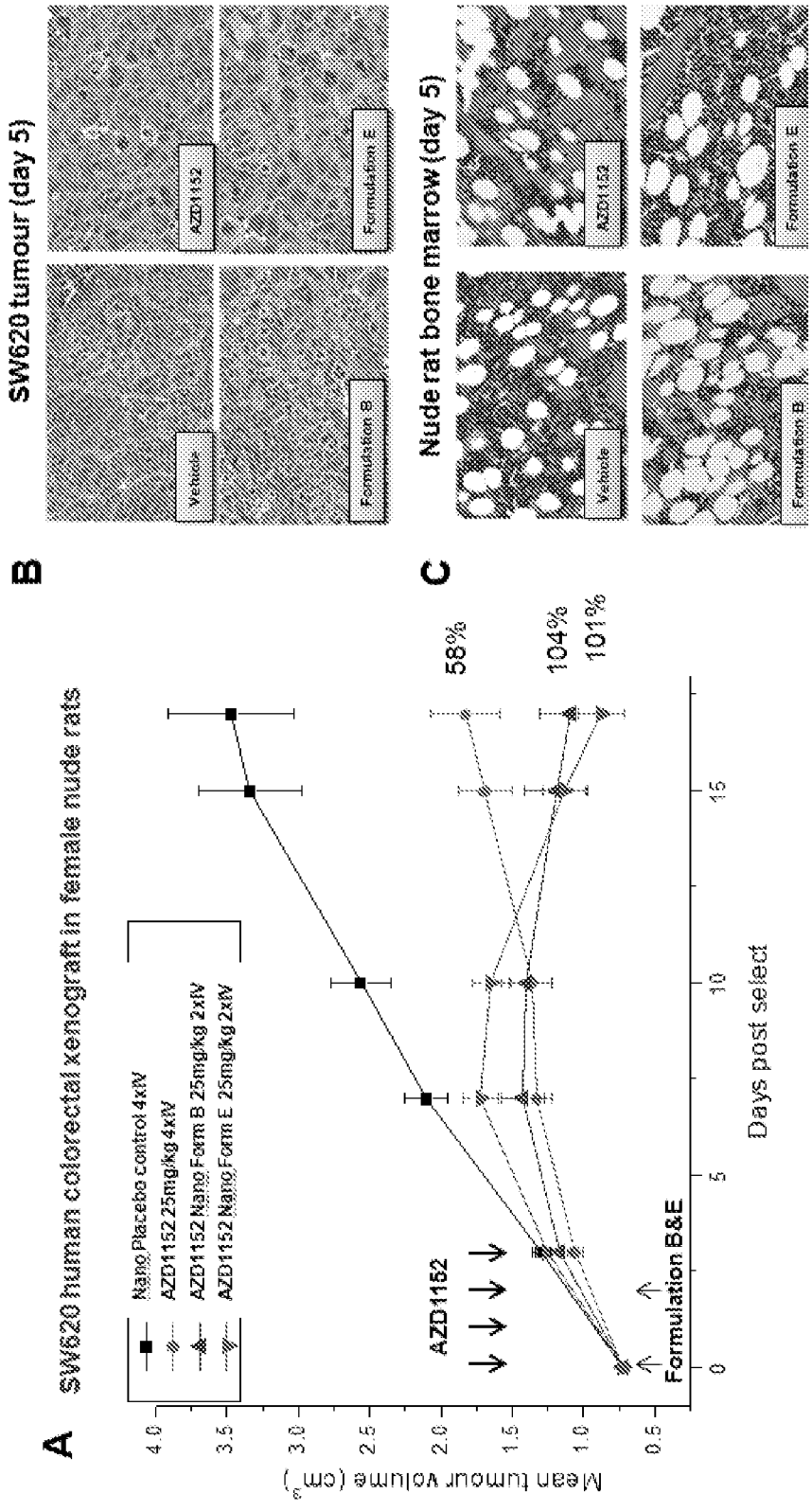
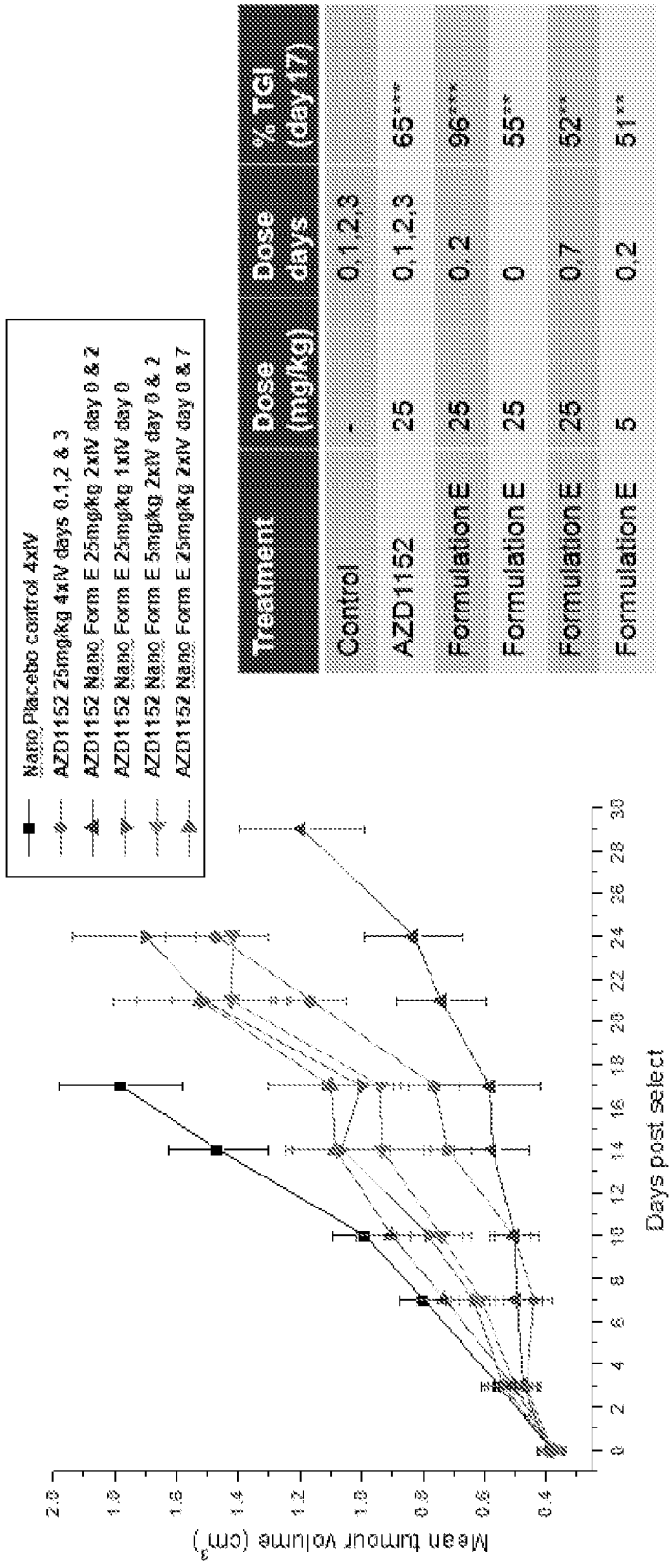

A
SW620 human colorectal xenograft in female nude rats
Nano Placebo control 4x/W
AZD1152 25mg/kg 4x/W
AZD1152 Nano Form B 25mg/kg 2x/W
AZD1152 Nano Form E 25mg/kg 2x/W
AZD1152
Formulation B&E
Mean tumour volume (cm³)
Days post select
B
SW620 tumour (day 5)
Vehicle
AZD1152
Formulation B
Formulation E
C
Nude rat bone marrow (day 5)
Vehicle
AZD1152
Formulation B
Formulation E
58%
104%
101%

Figure 6



Treatment	Dose (mg/kg)	Dose days	% TGI (day 17)
Control	-	0,1,2,3	
AZD1152	25	0,1,2,3	65***
Formulation E	25	0,2	96***
Formulation E	25	0	55**
Formulation E	25	0,7	52**
Formulation E	5	0,2	51**

Figure 7

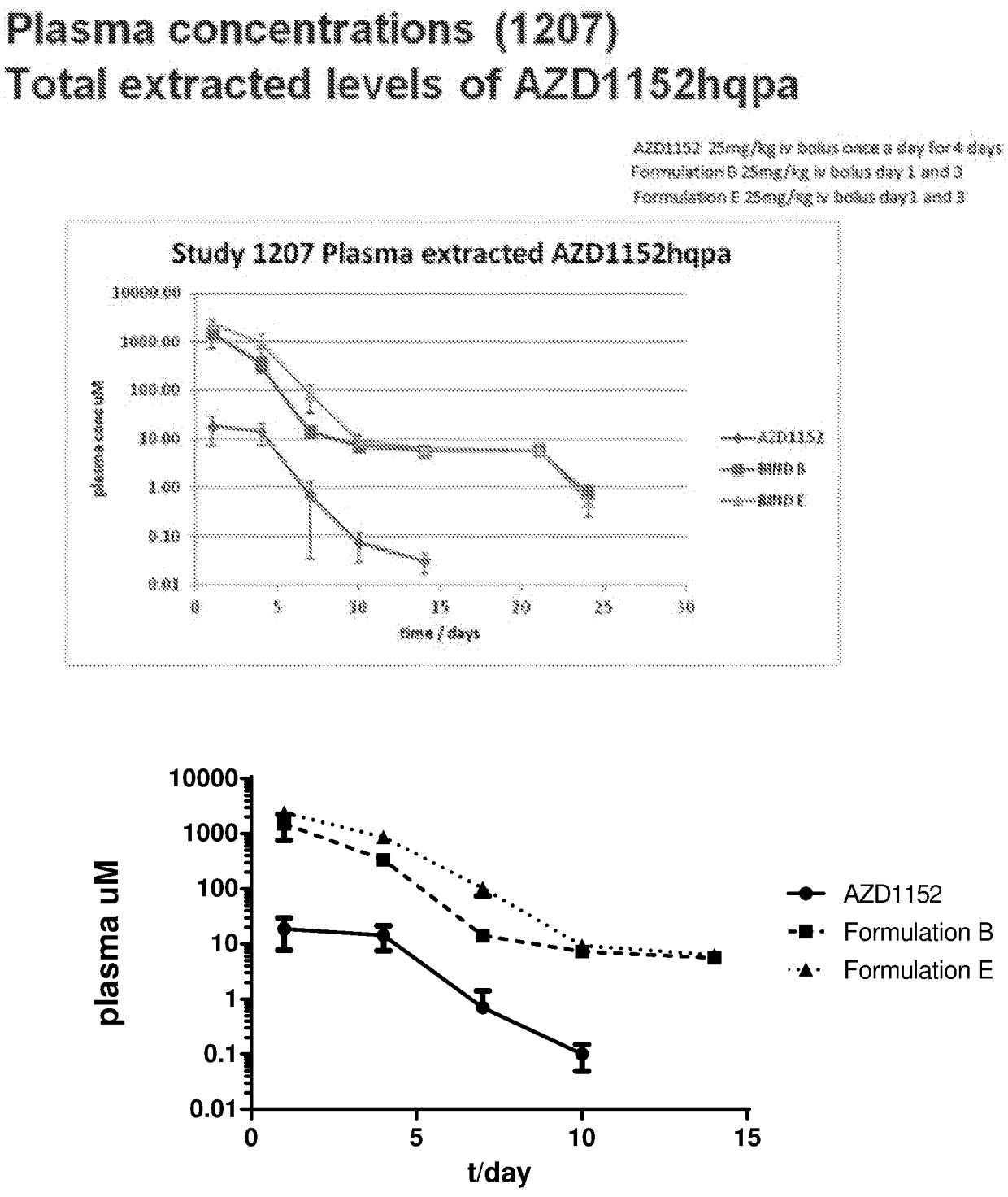


Figure 8

Two representations showing in-vivo exposure results from Example 6

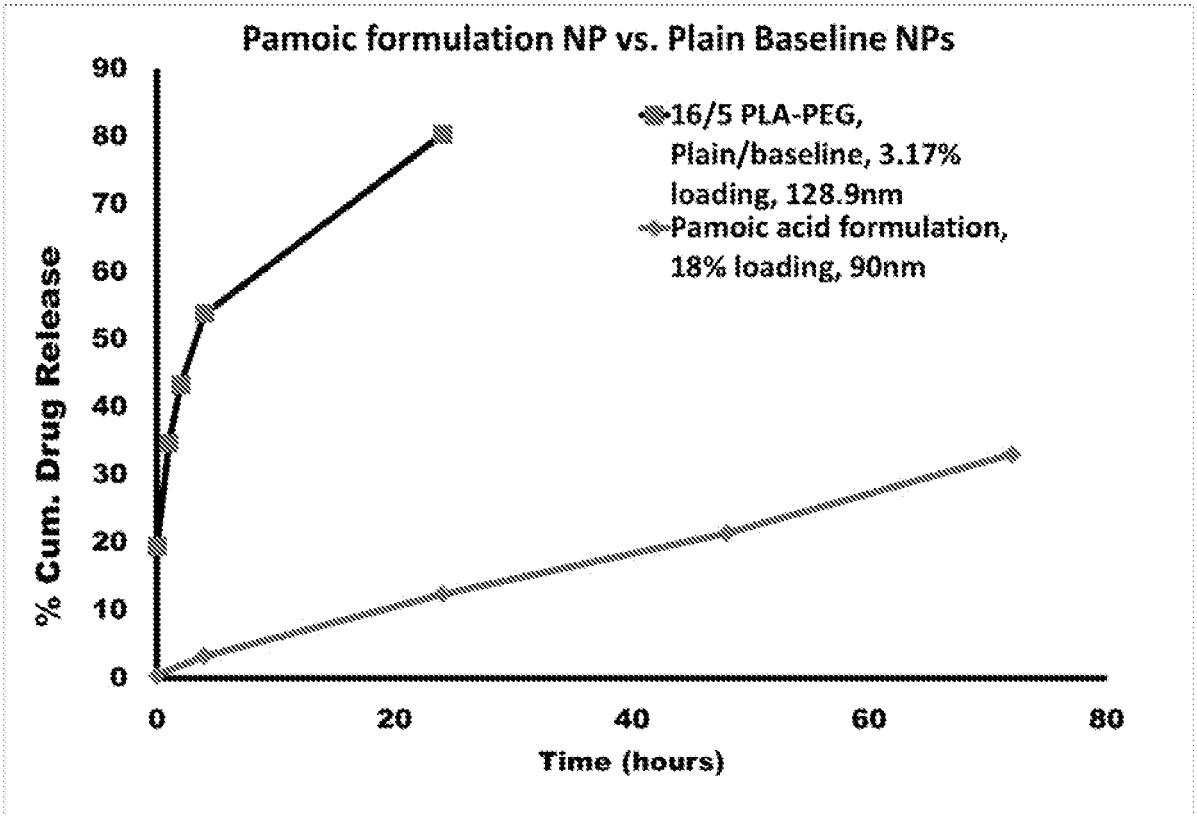

Pamoic formulation NP vs. Plain Baseline NPs
16/5 PLA-PEG, Plain/baseline, 3.17% loading, 128.9nm
Pamoic acid formulation, 18% loading, 90nm
% Cum. Drug Release
0
10
20
30
40
50
60
70
80
90
0
20
40
60
80
Time (hours)

Figure 9

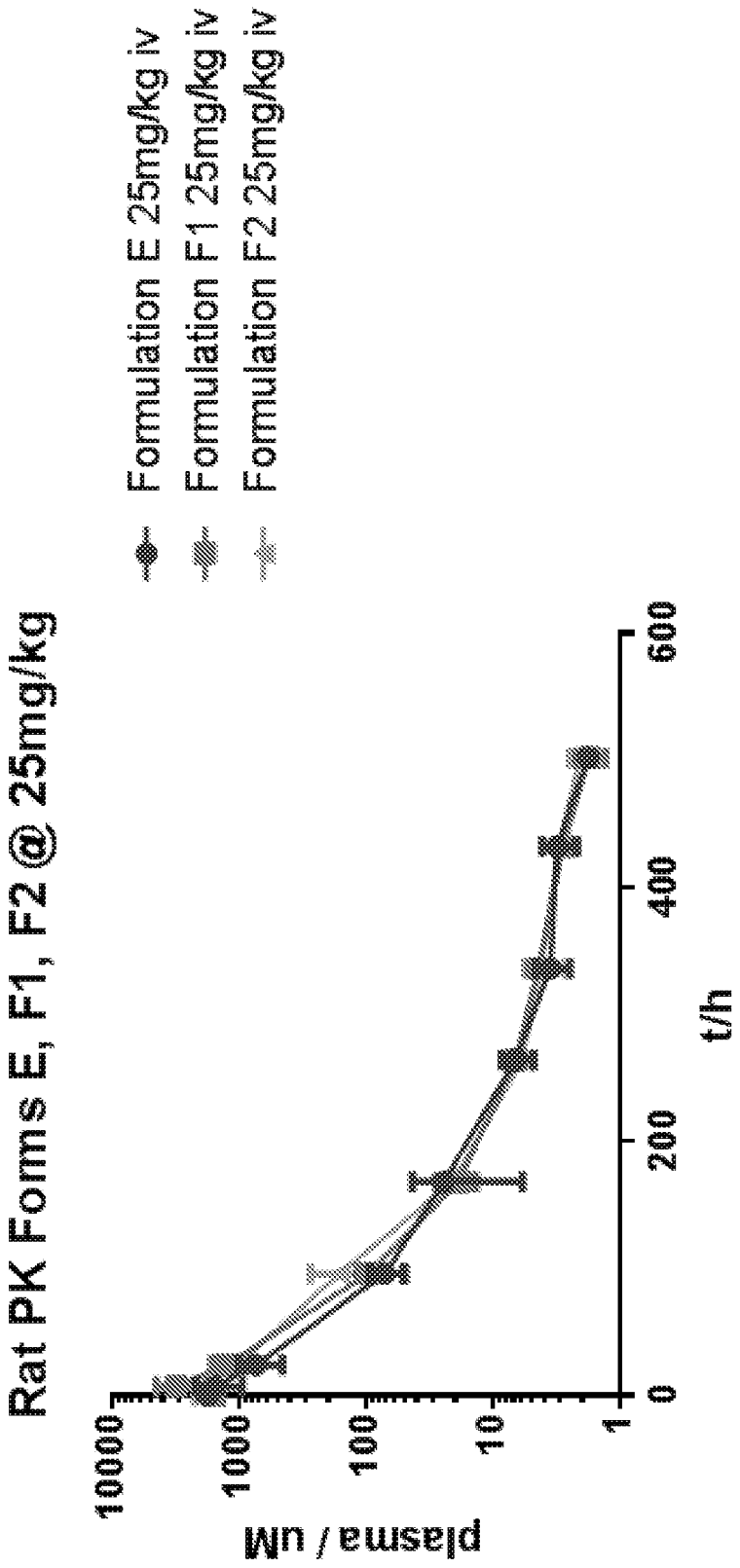

Rat PK Foms E, F1, F2 @ 25mg/kg
Formulation E 25mg/kg iv
Formulation F1 25mg/kg iv
Formulation F2 25mg/kg iv
plasma / uM
10000
1000
100
10
1
0
200
400
600
t/h

Figure 10

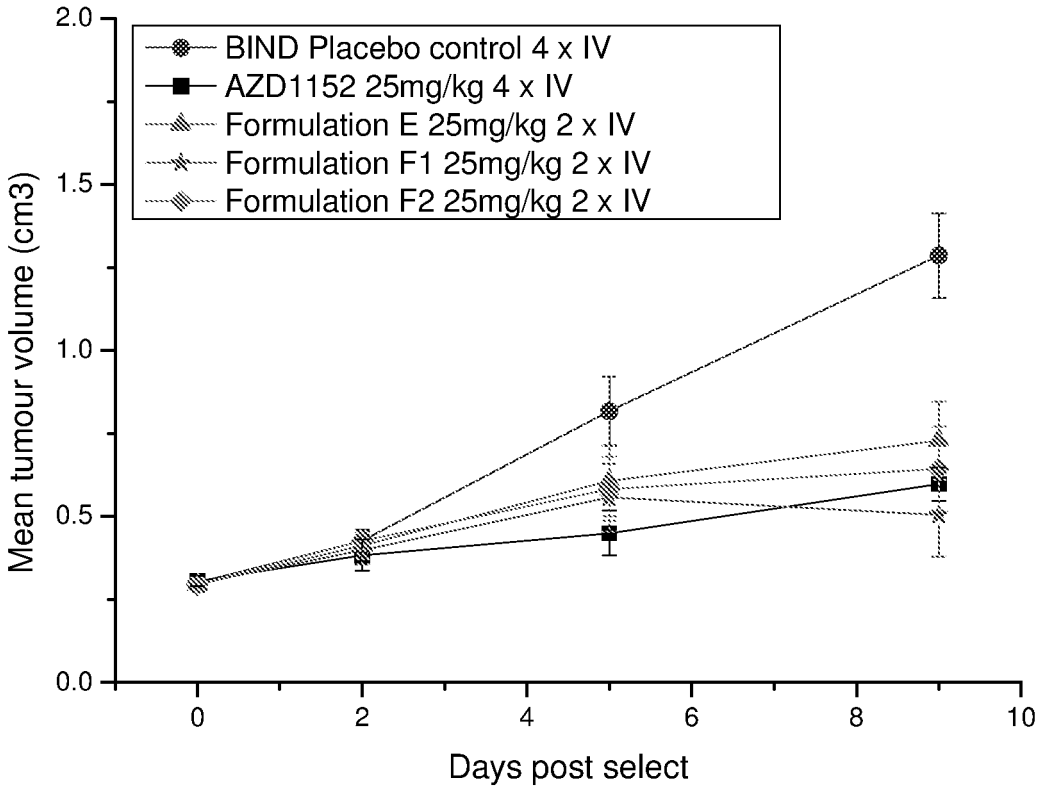


Figure 11

Formulation F1 and F2 give equivalent tumour control to Formulation E in rats bearing SW620 tumours. Mean tumour size for each group is represented. Bars represent standard error of mean.

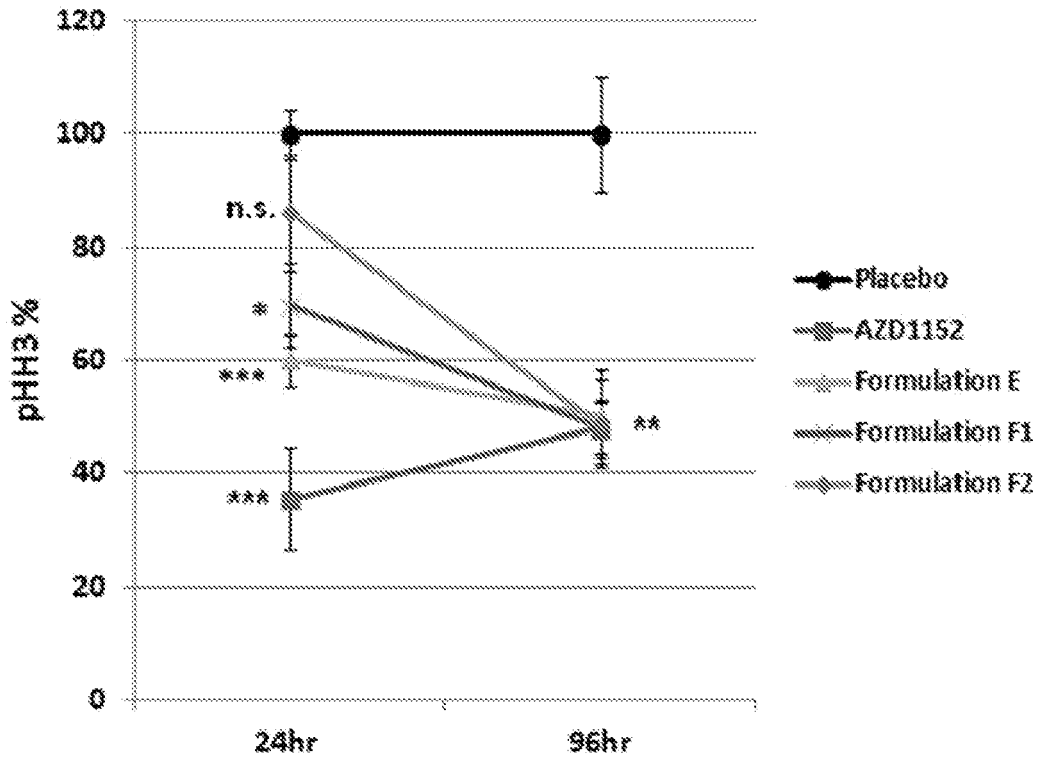


Figure 12

In vivo activity of AZD1152 and AZD1152- HQPA nanoparticle Formulations E/F1/F2

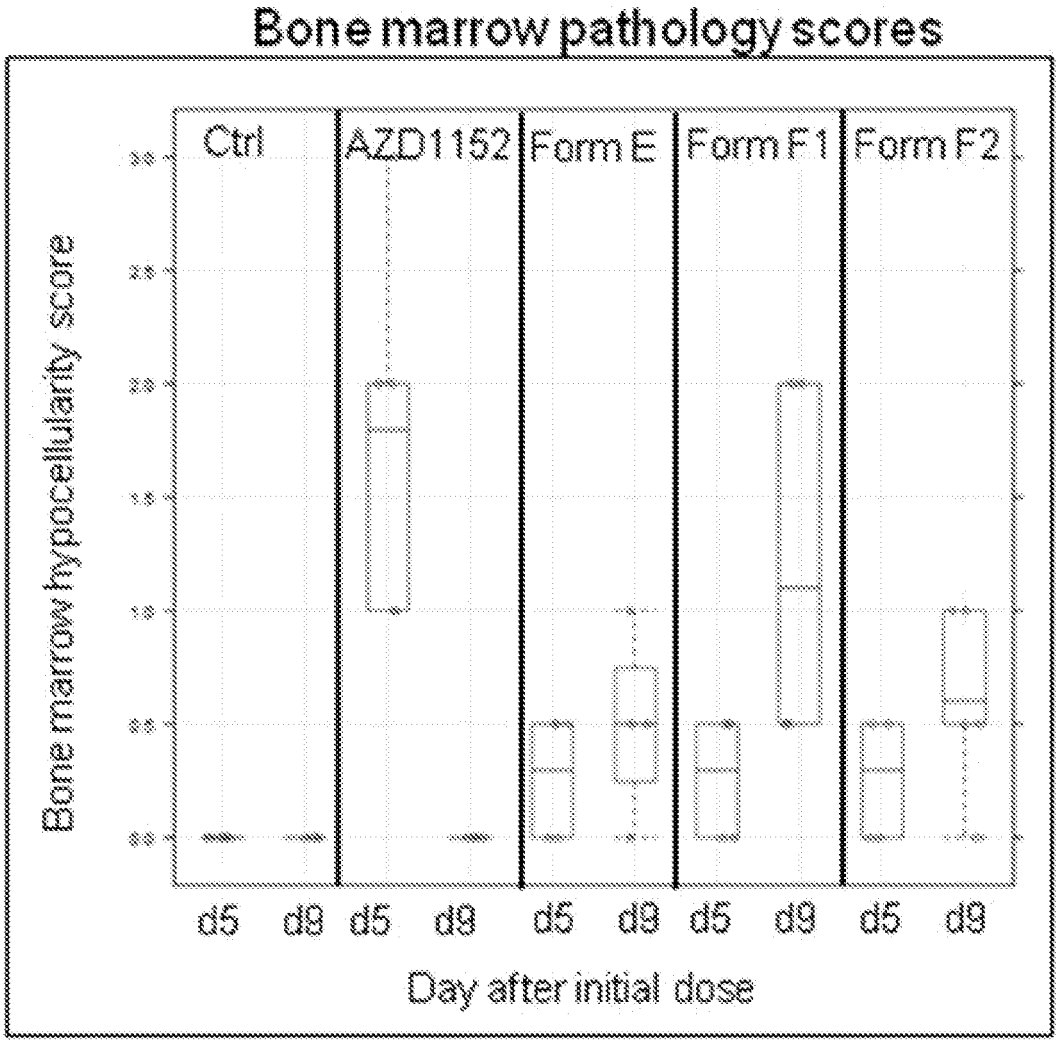


Figure 13

Effects of Formulations E, F1, F2 on Bone marrow integrity.

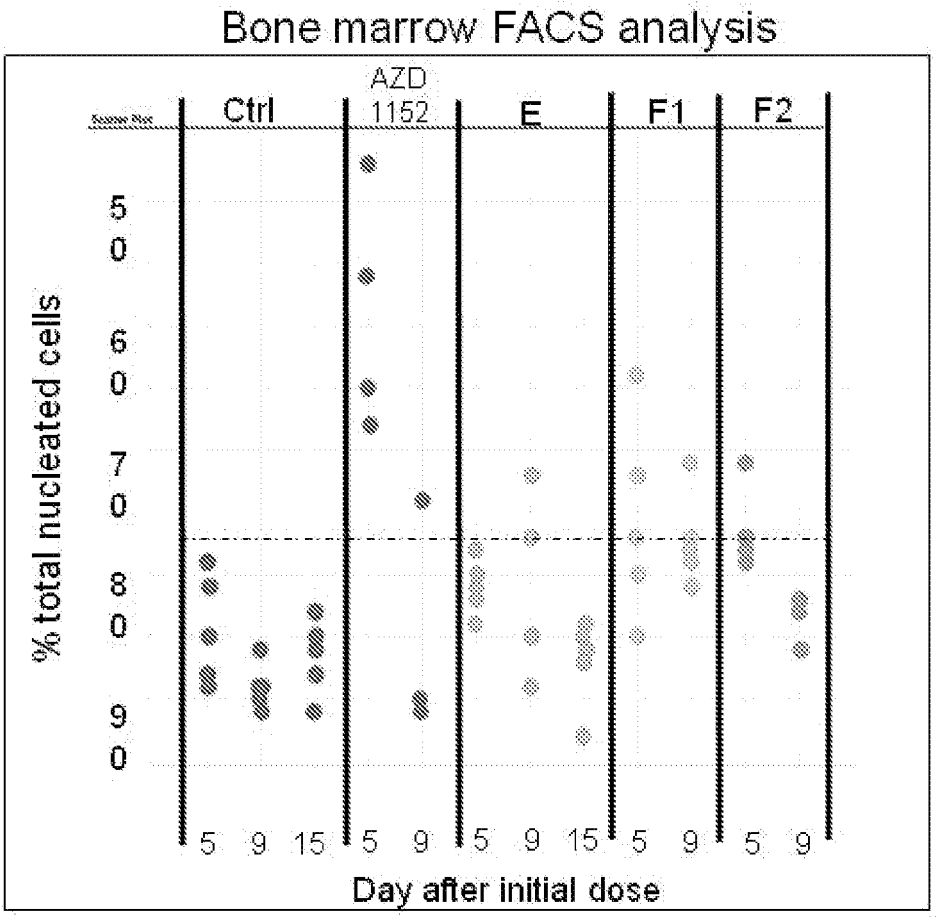


Figure 14

Effects of Formulations E, F1, F2 on Bone marrow integrity.

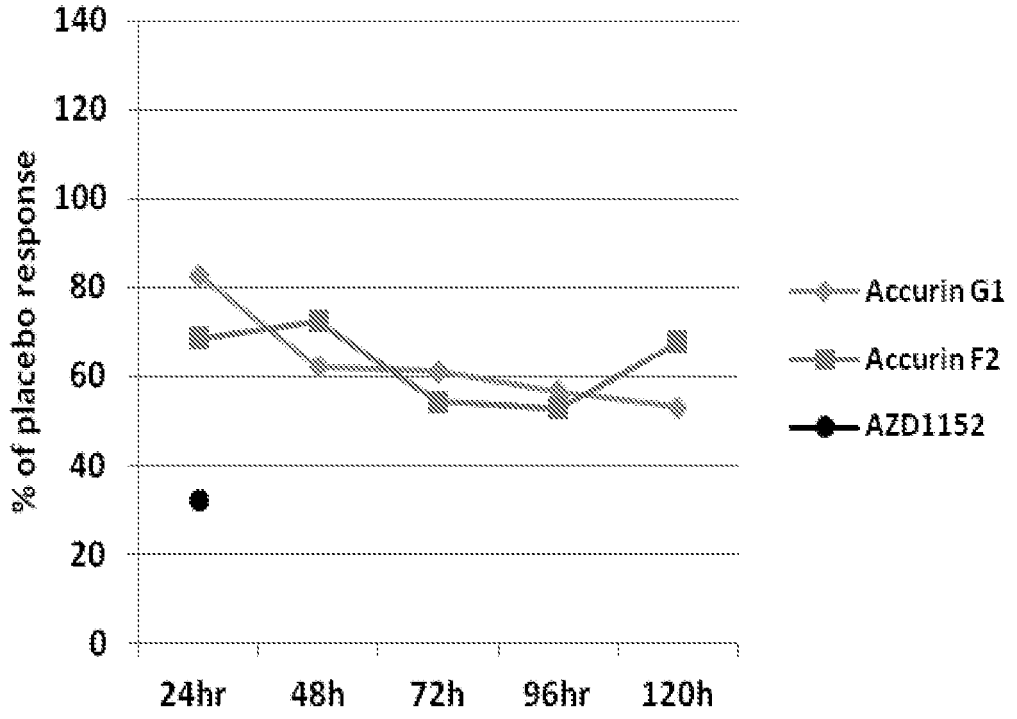


Figure 15

In vivo activity of AZD1152 and AZD1152- HQPA nanoparticle Formulations G1 and G2

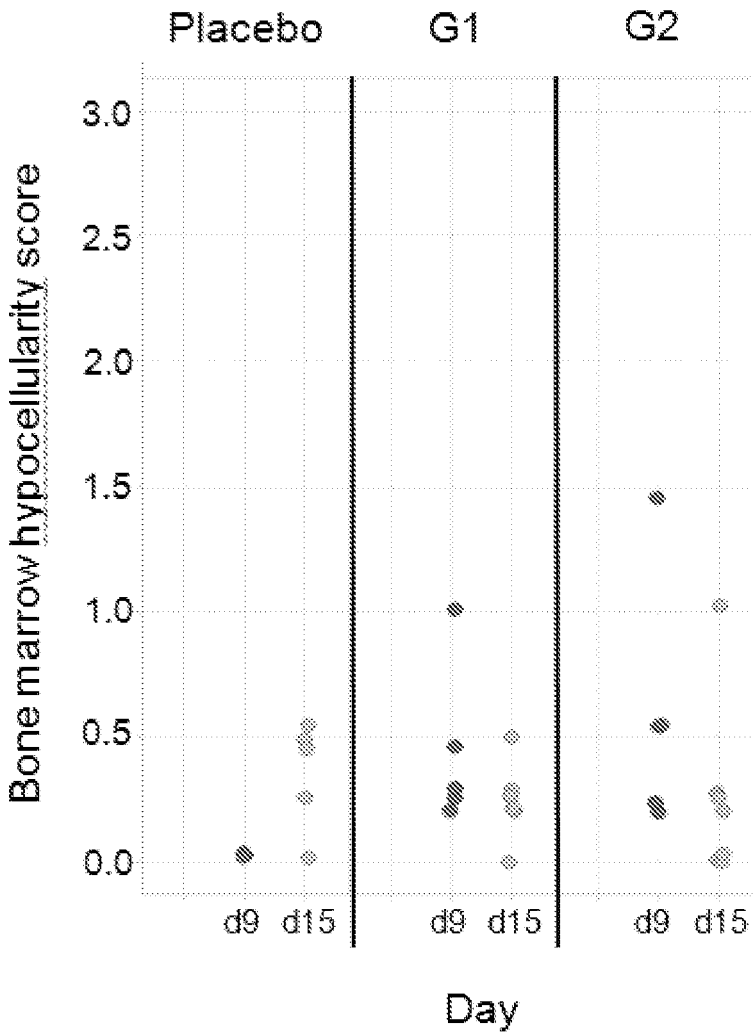


Figure 16

Effects of Formulations G1 and G2 on Bone marrow integrity.

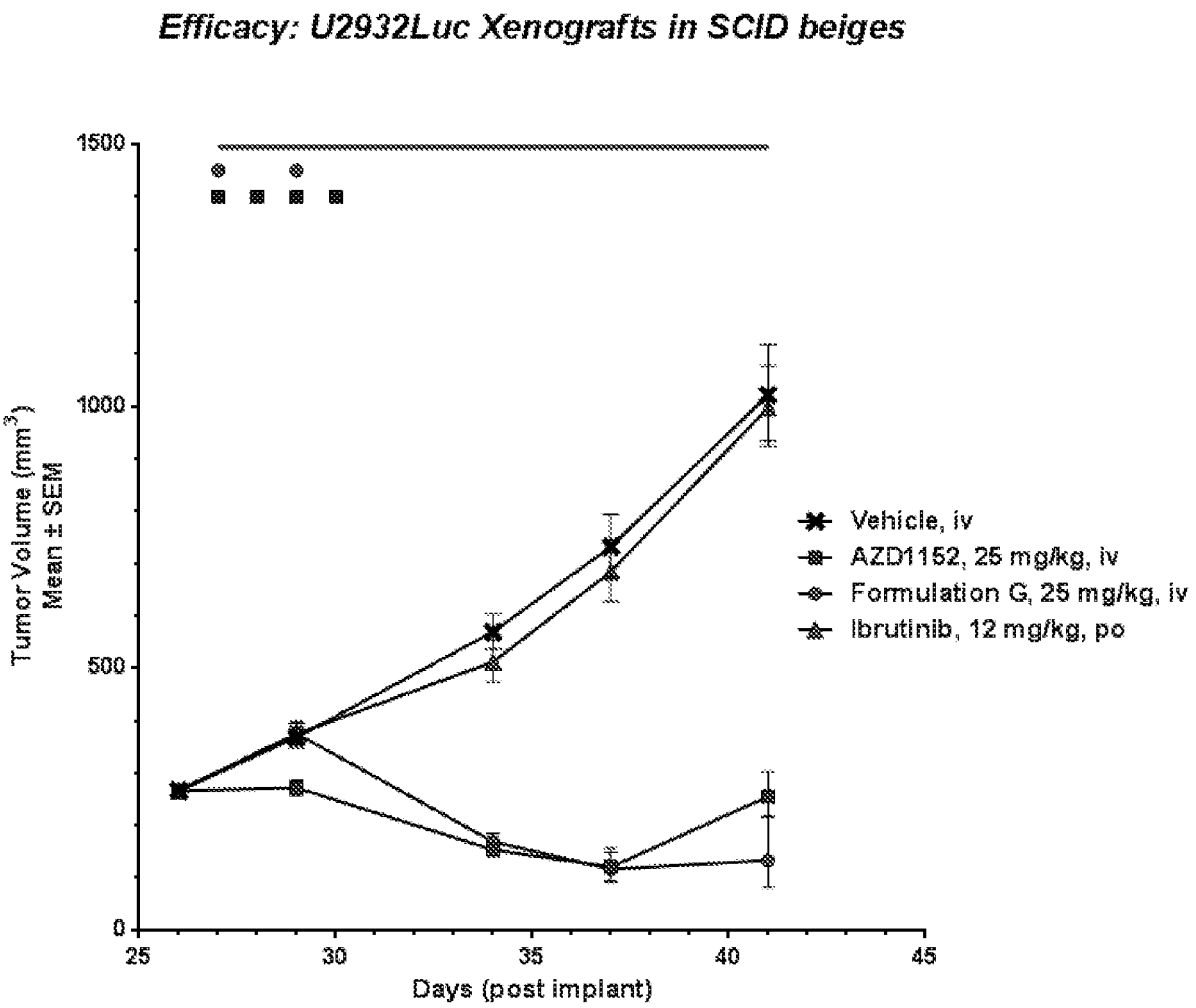


Figure 17

Formulation G1 gives equivalent tumour control to AZD1152 in mice bearing U2932 tumours. Mean tumour size for each group is represented. Bars represent standard error of mean.

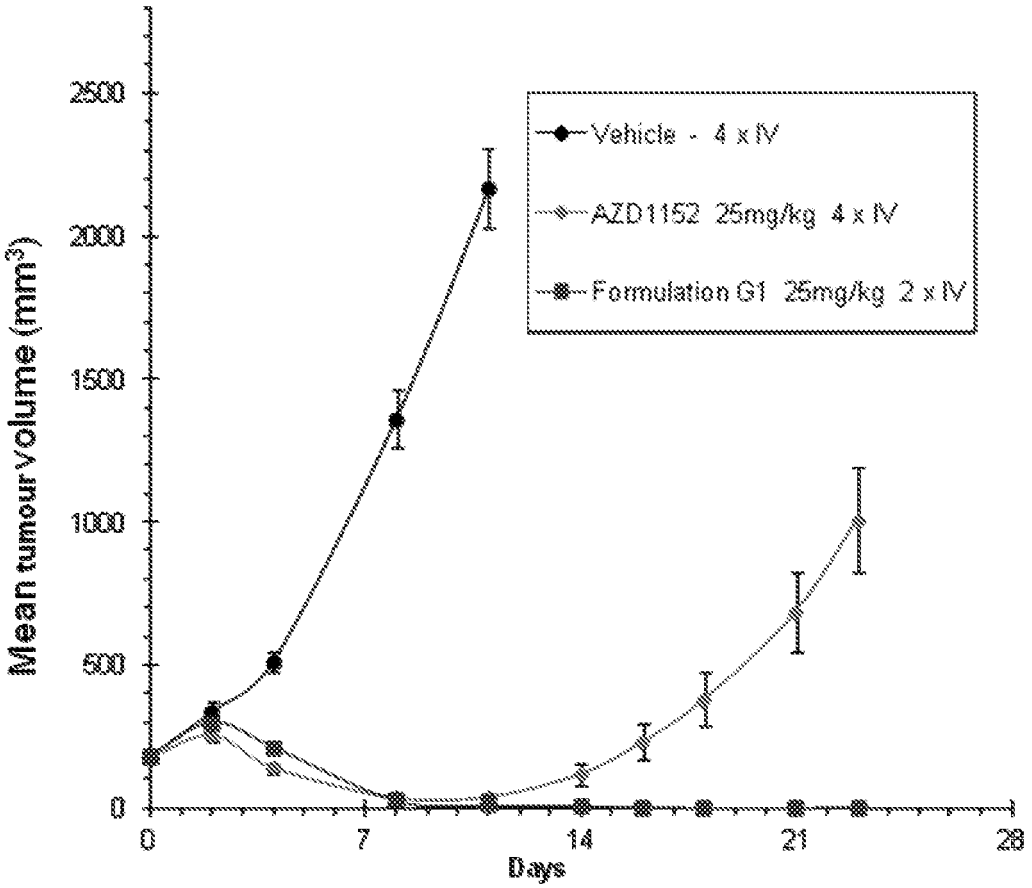


Figure 18

Formulation G1 gives longer tumour control than AZD1152 in mice bearing SC-61 primary tumours. Mean tumour size for each group is represented in mm^3. Bars represent standard error of mean (SEM)

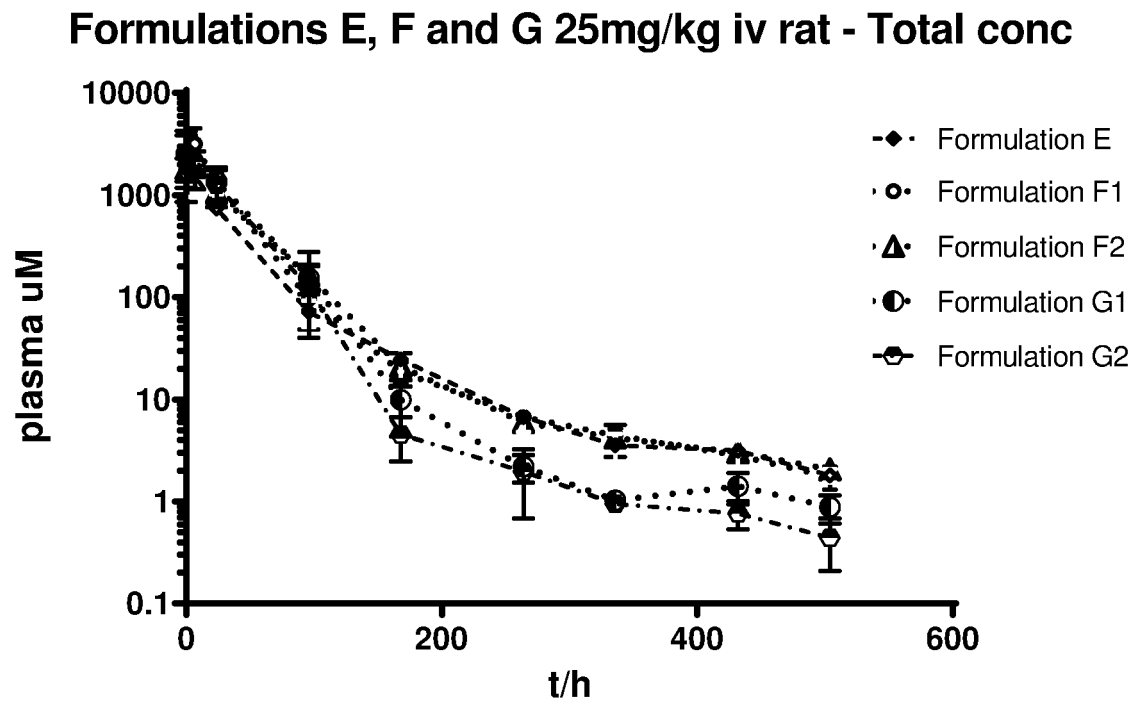


Figure 19

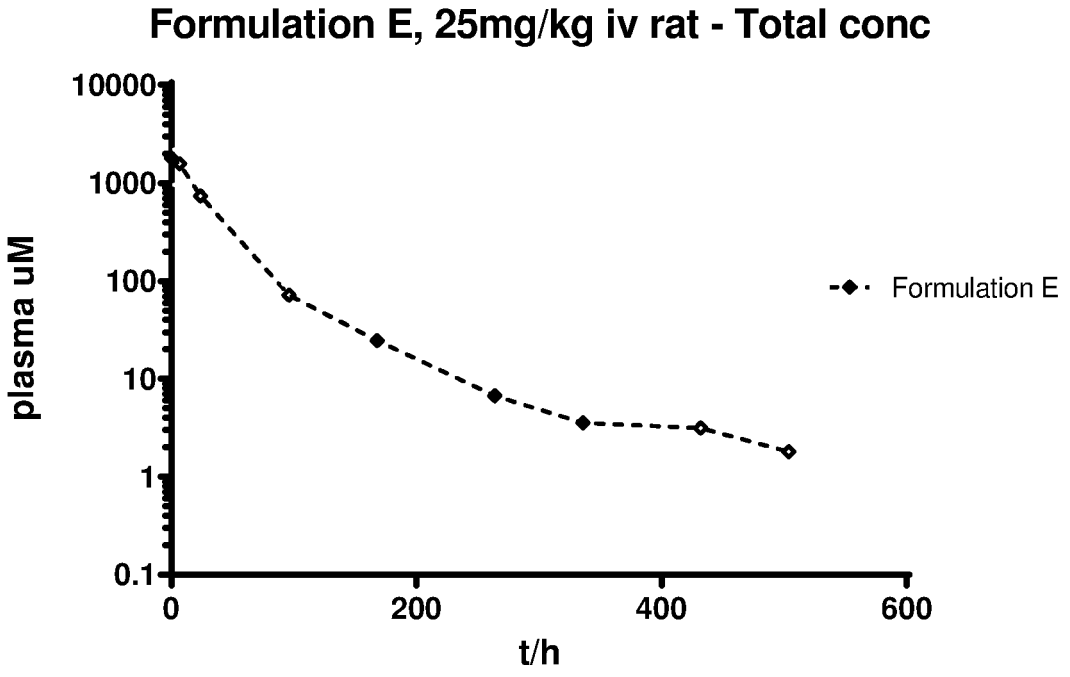


Figure 19a

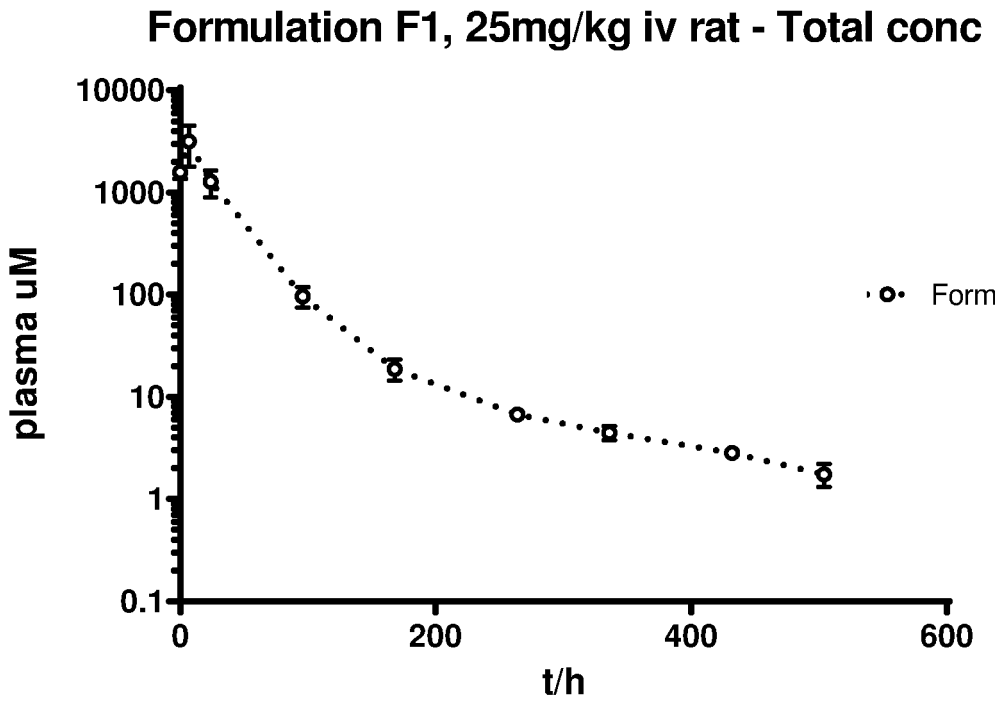


Figure 19b

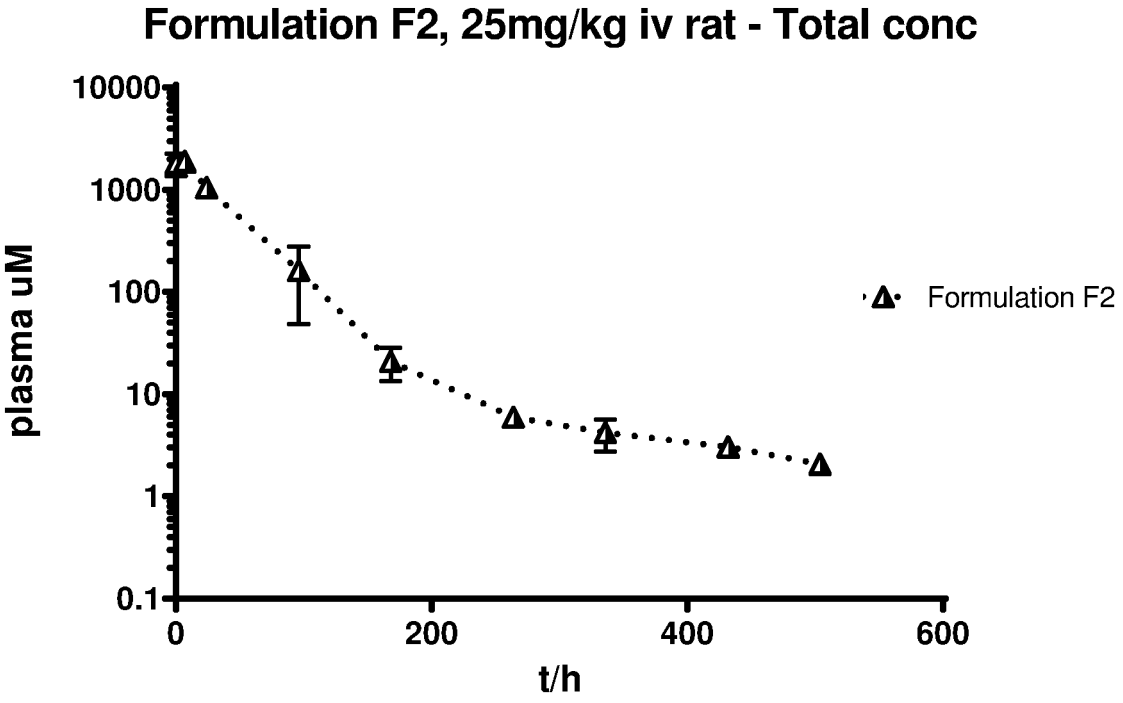


Figure 19c

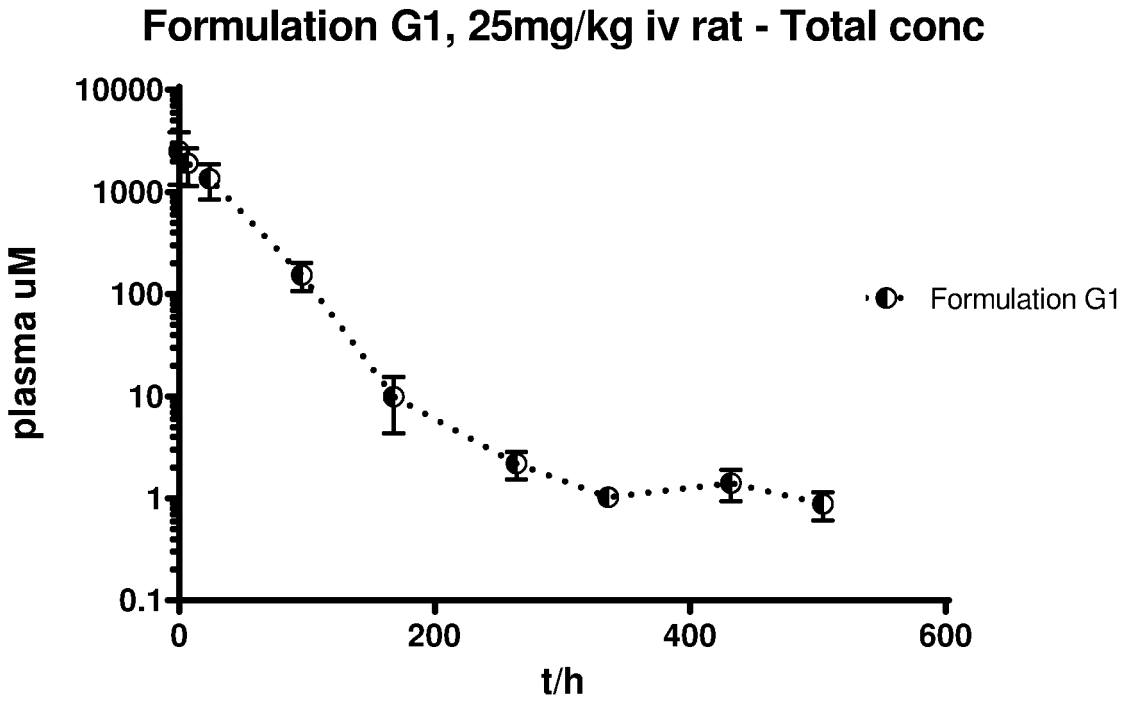


Figure 19d

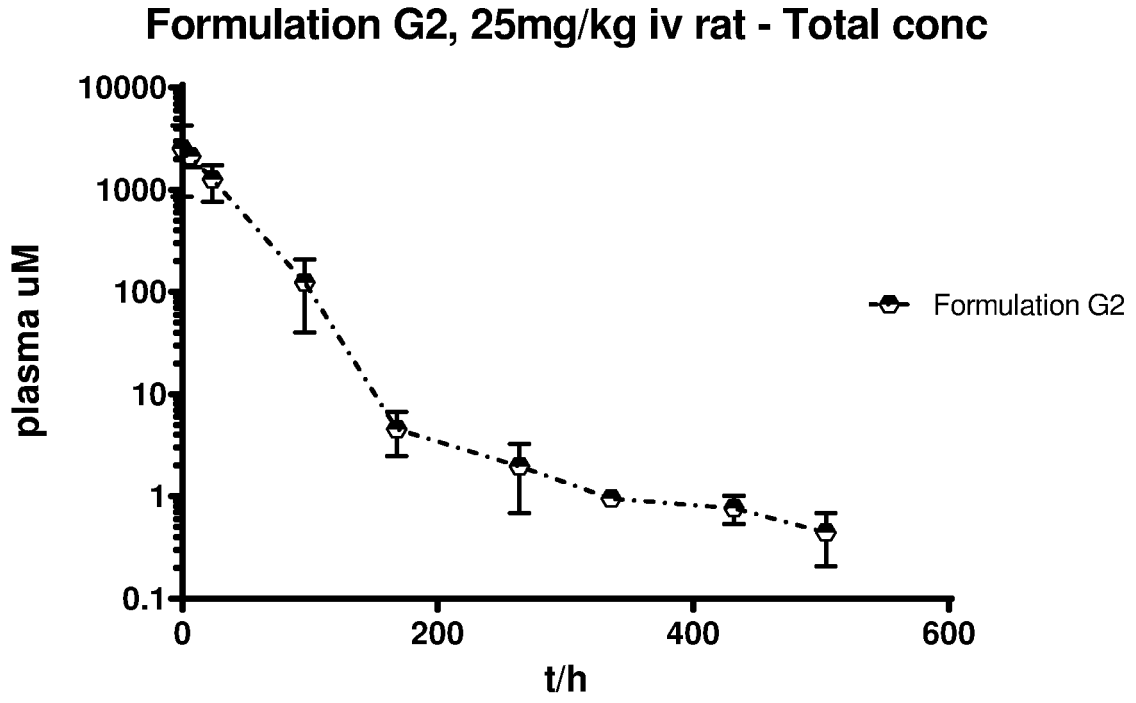


Figure 19e

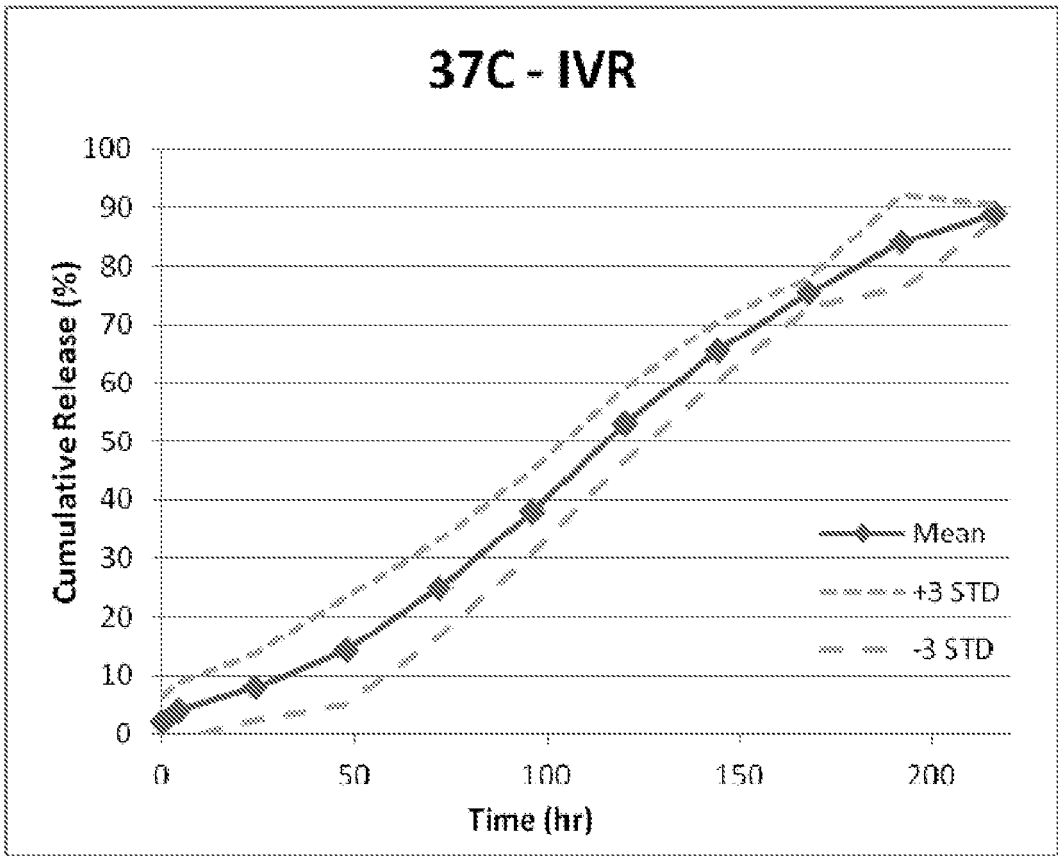


Figure 20

In-vitro release at 37 ºC of batches shown in Example 11.