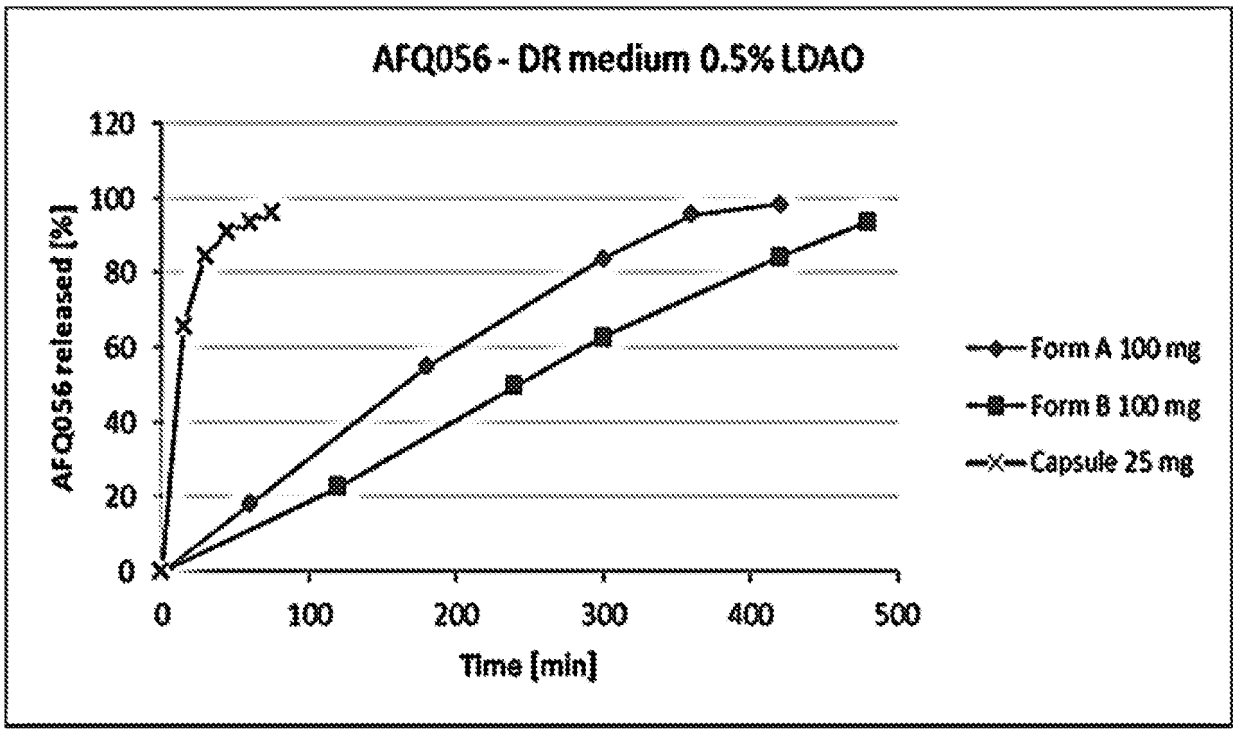
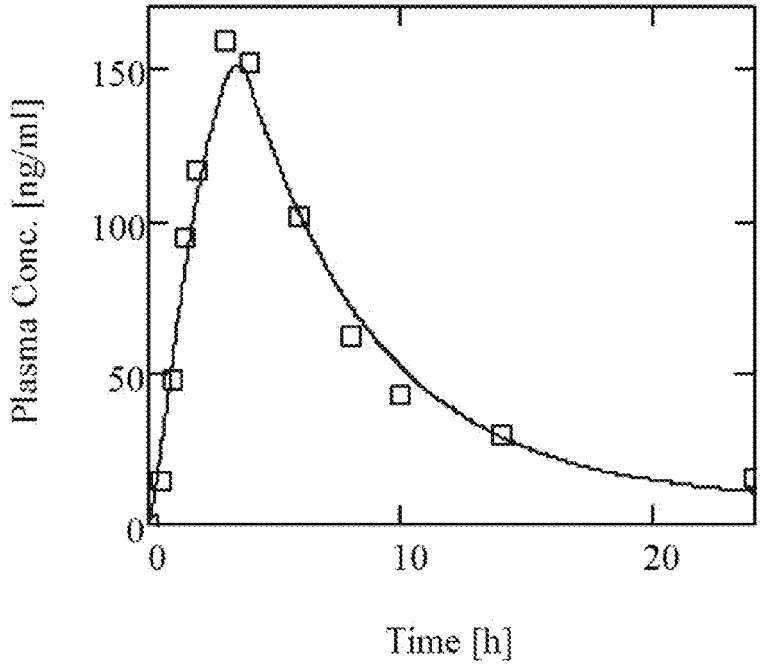
Figure 1

Dissolution Profile

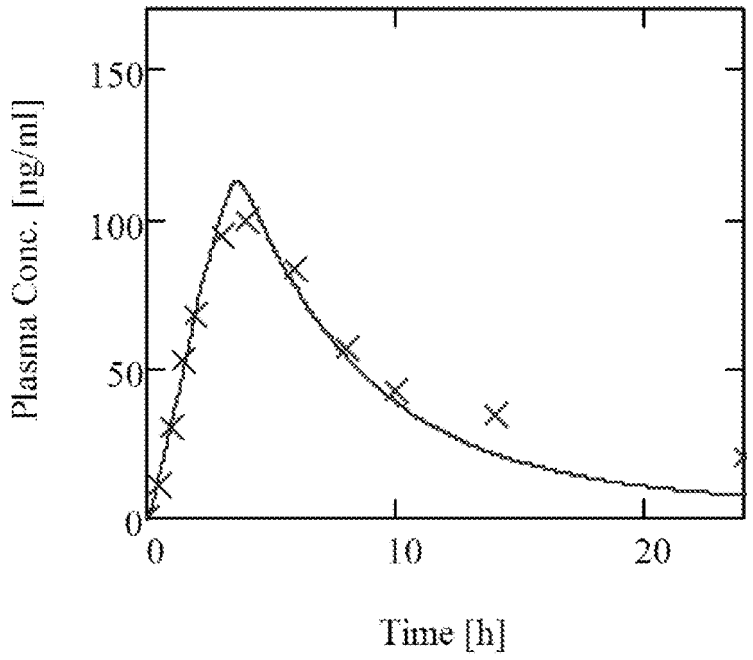


In Vitro – In Vivo Correleation (IVIVC): mechanistic PK model

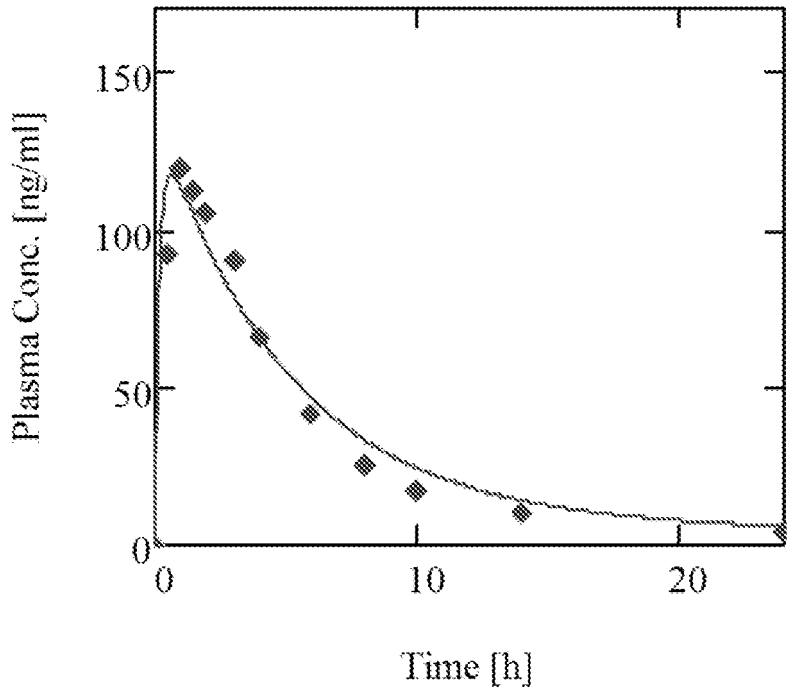
Form A 100 mg



Form B 100 mg



Capsules 50 mg

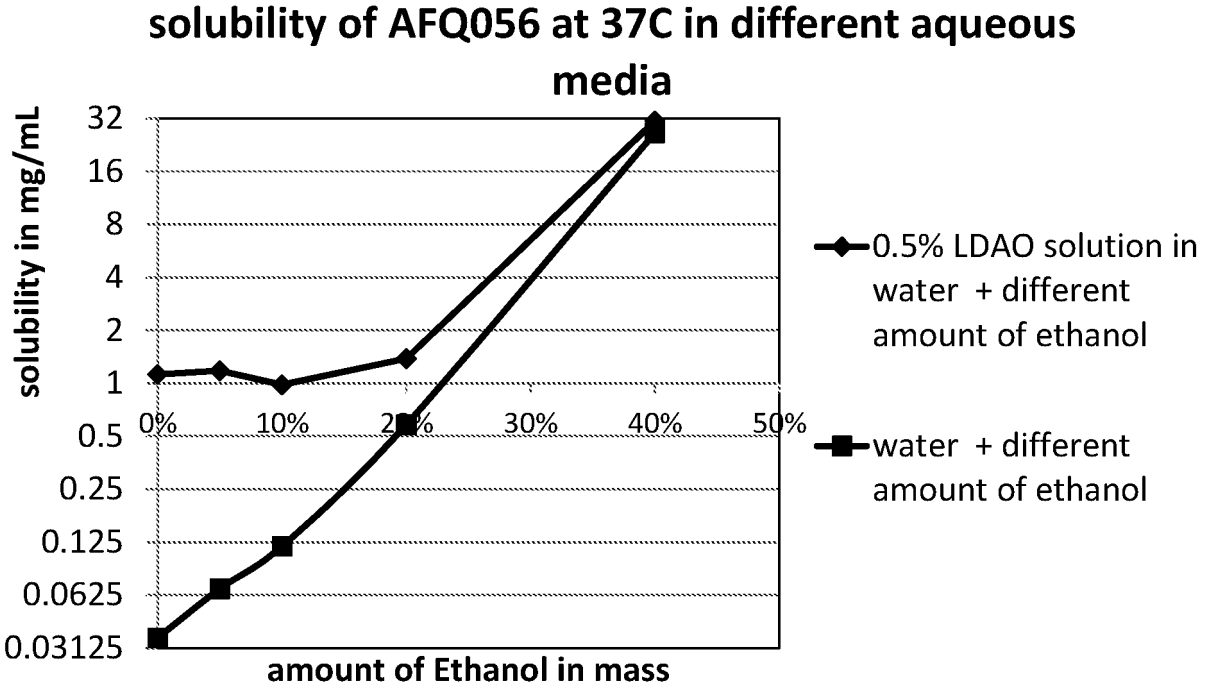


Calculated (symbols) versus observed (lines) plasma concentration

PK parameters:

	AUC_{48h} [h*ng/mL] (observed)	**C_{max} [ng/mL] (observed)**
Form A 100 mg	1440 (1438)	145.2 (159.3)
Form B 100 mg	1046 (1317)	109.3 (99.5)
Capsule 50 mg	865 (745)	115.9 (119.7)

Figure 2



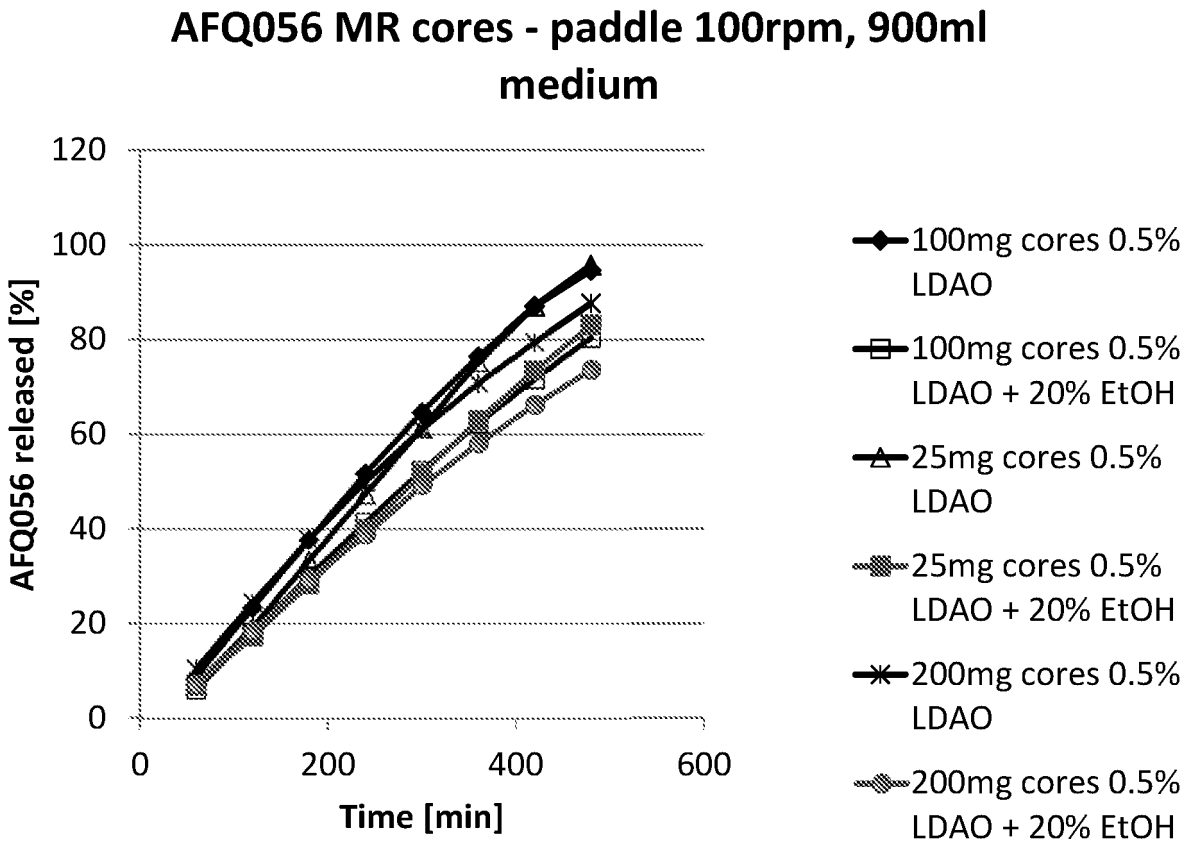
0.5% LDAO (Lauryldimethylamine *N*-oxide) is the medium for testing the dissolution rate

Raising ethanol levels in the pure aqueous solution leads to a steadily increasing solubility of AFQ056

Aqueous 0.5% LDAO solution:

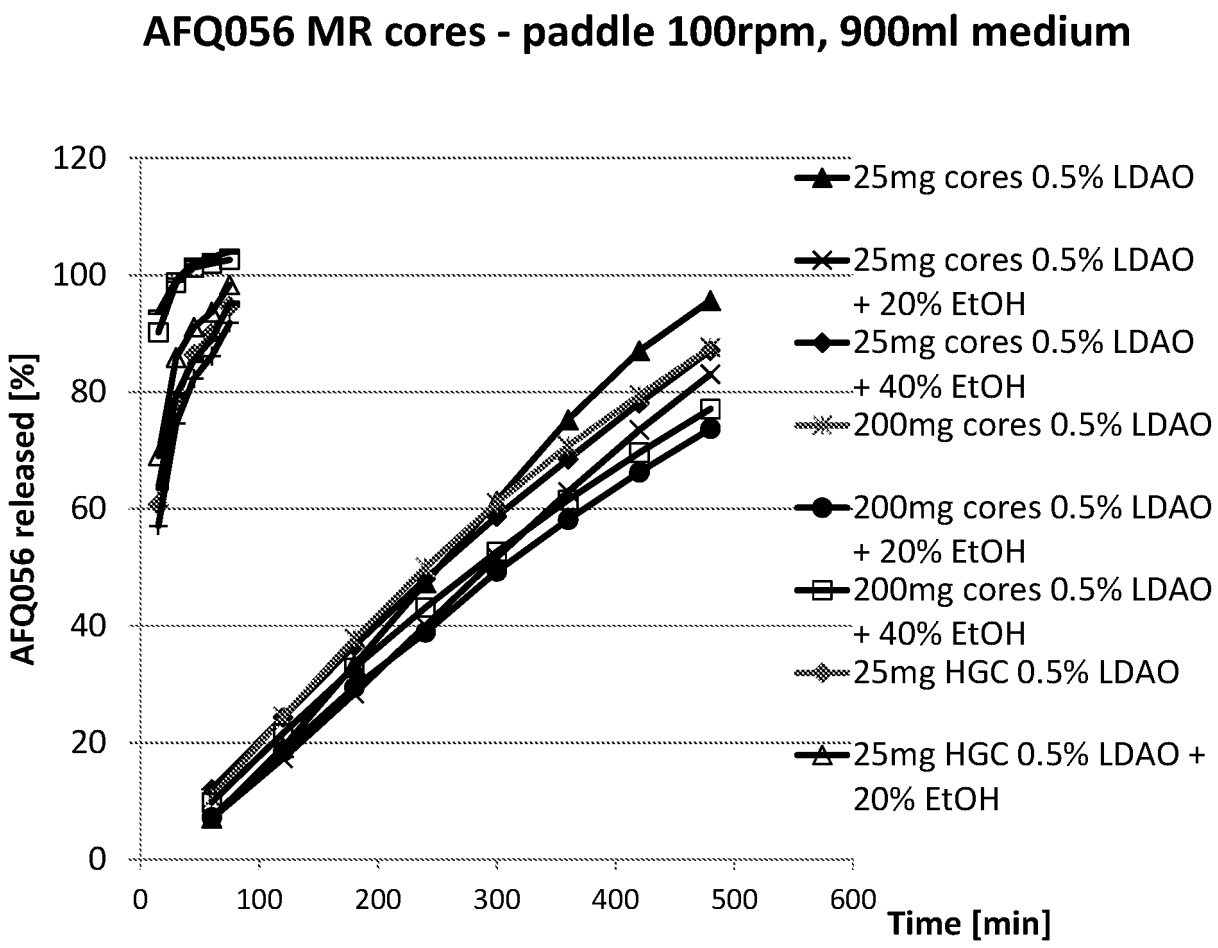
- **Up to 20% of ethanol the solubility of AFQ056 remains comparable.**
- **in the presence of 40% ethanol the solubility with/without LDAO is dominated by the presence of the ethanol**

Figure 3



When tested with a biorelevant dissolution rate method all modified release dosage strengths show consistently a lower dissolution rate in the presence of 20% ethanol. Based on the solubilities one would have expected rather the same dissolution rate.

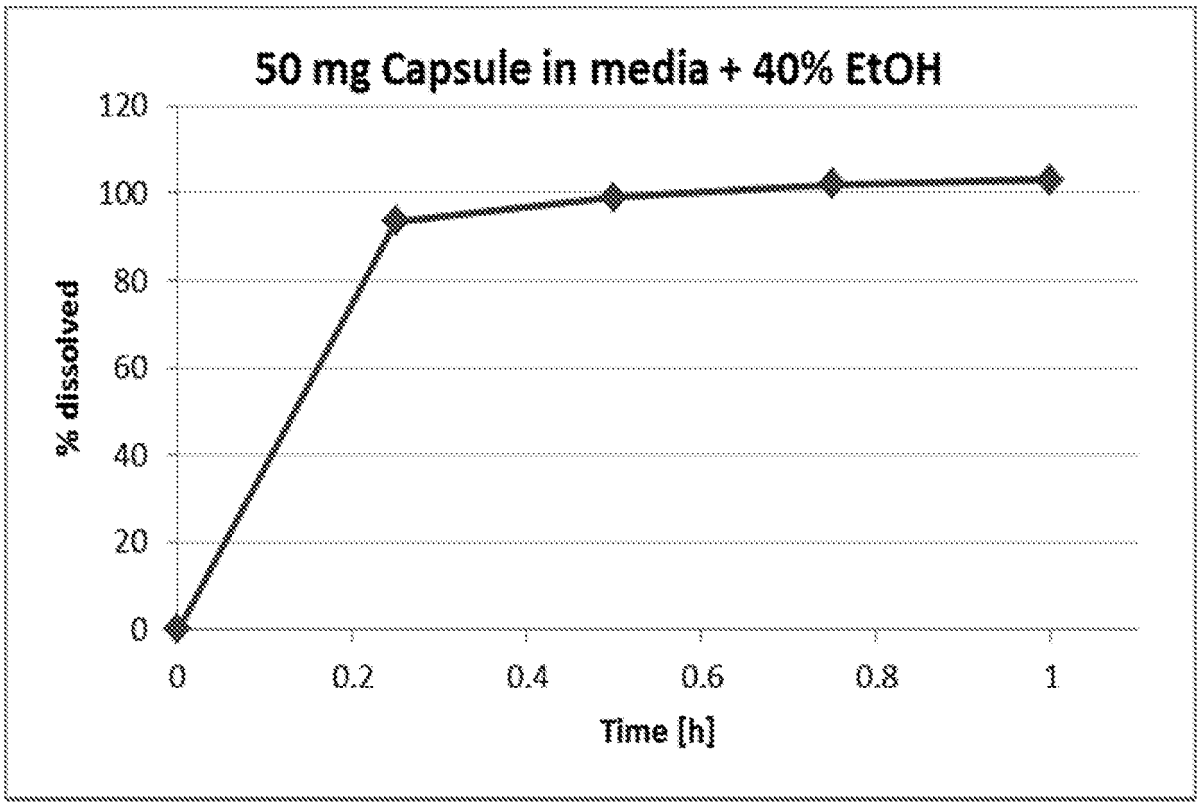
Figure 4

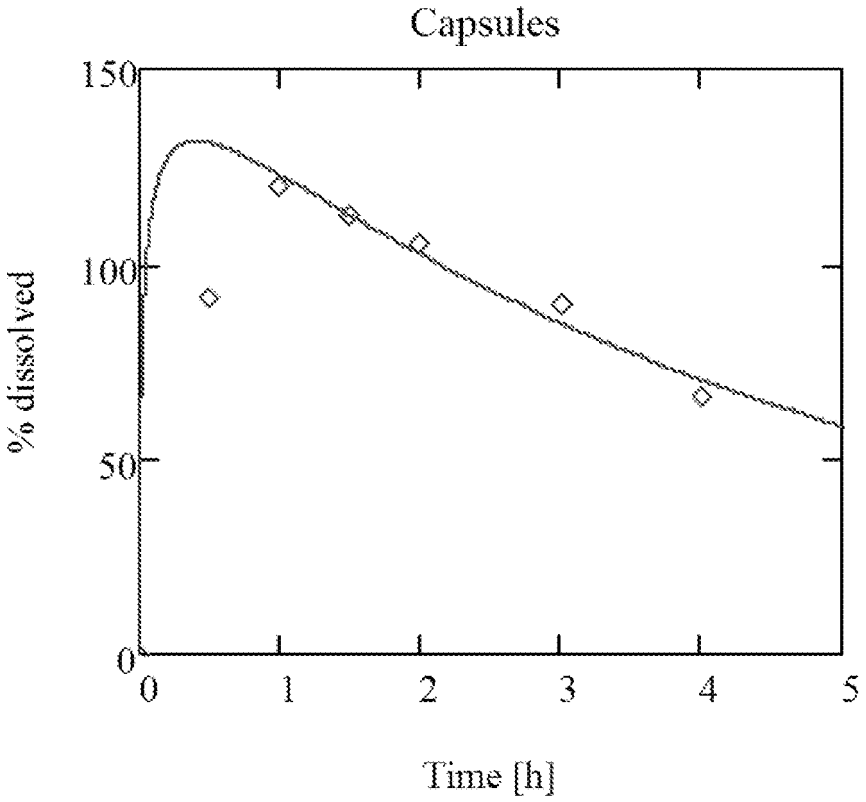


When tested with a biorelevant dissolution rate method immediate release (IR) dosage strengths show consistently a trend to faster dissolution rate in the presence of 20% and 40% ethanol which is expected. However, the modified release (MR) forms independent of their strengths are dissolving similarly or at a slower rate in the presence of ethanol. Even in the presence of 40% ethanol despite the high solubility an increase of the dissolution rate is not noted.

Figure 5

Dissolution profile: Immediate release Form (IR) Capsule 50 mg





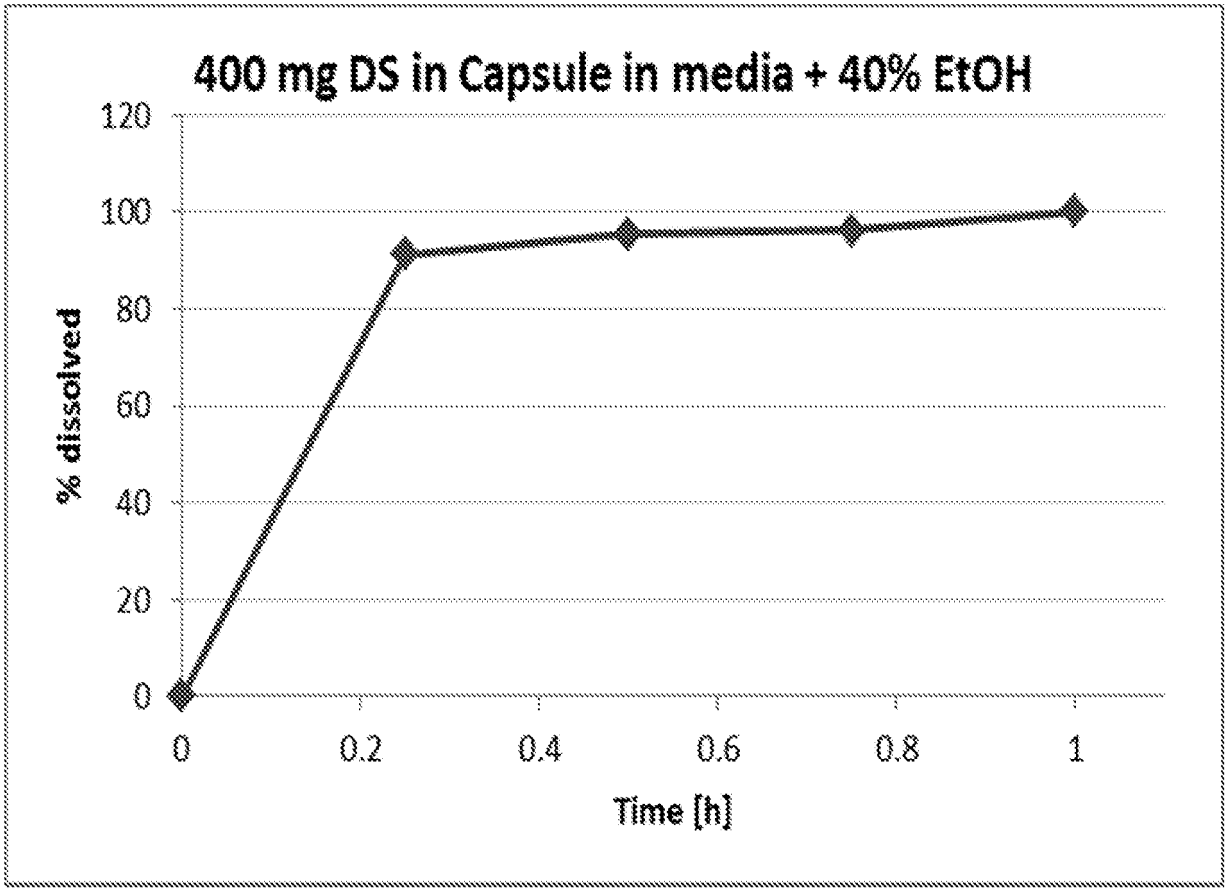
Simulated (line) plasma concentration profile is compared to the observed plasma concentration profile of the 50 mg capsule (symbols)

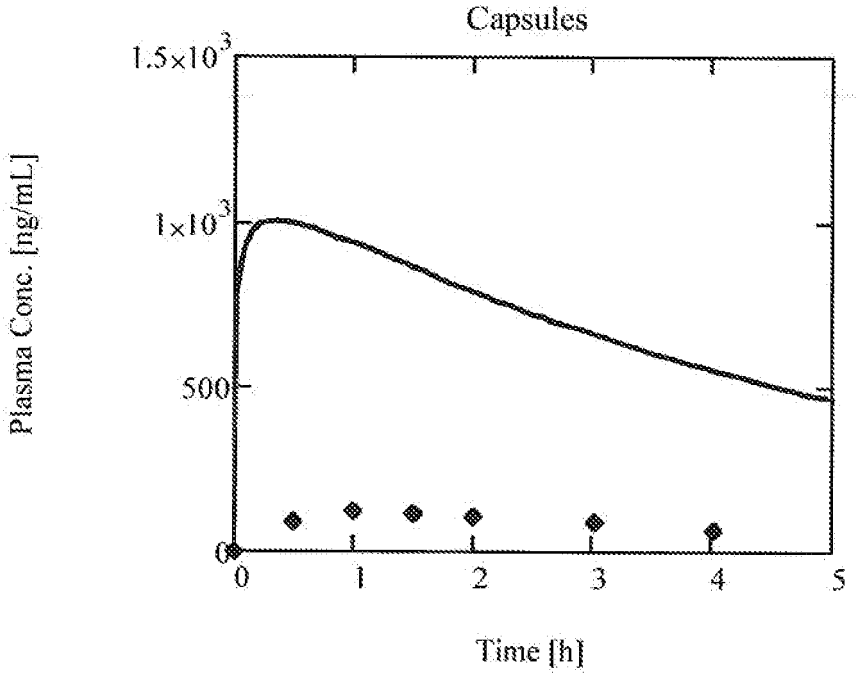
	Tmax [h]	**Cmax [ng/mL]**	**AUC_{48h} [h*ng/mL]**
Capsule 50 mg in study X2167	1.0	115.9	865
Simulation hPK from Capsule 50 mg in dissolution medium + 40% EtOH	0.4 (faster)	130.1 (higher)	947 (higher)

Simulated PK parameters compared to human data

Figure 6

Dissolution profile: Immediate release Form (IR) Capsule 400 mg





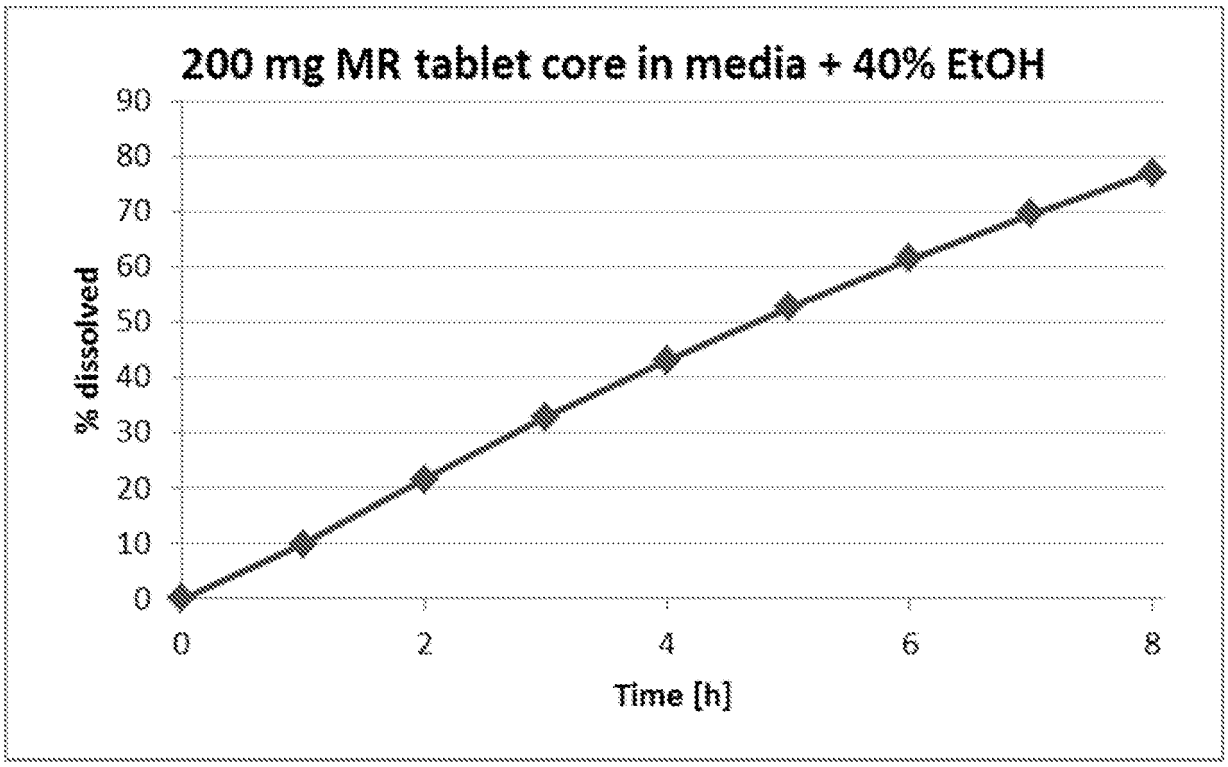
Simulated (line) plasma concentration profile is compared to the observed plasma concentration profile of the 400 mg capsule (symbols)

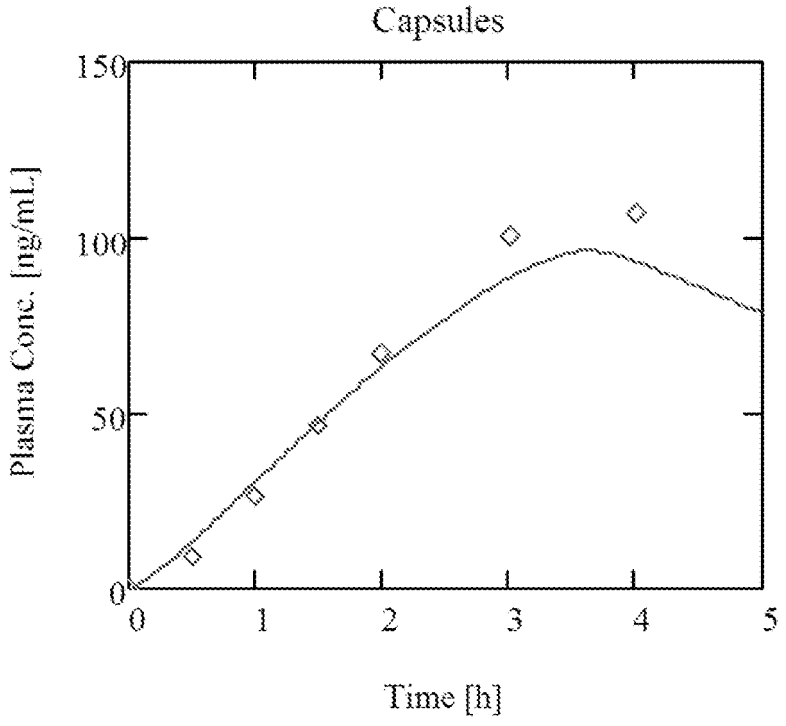
	Tmax [h]	Cmax [ng/mL]	AUC_{48h} [h*ng/mL]
Capsule 400 mg in study X2101	3.48	315	1980
Simulation h-PK from Capsule 400 mg in dissolution medium + 40% EtOH	0.4 (faster)	997.1 (higher)	7249 (higher)

Simulated PK parameters

Figure 7

Dissolution Profile: Modified Release (MR) tablet cores of 200 mg



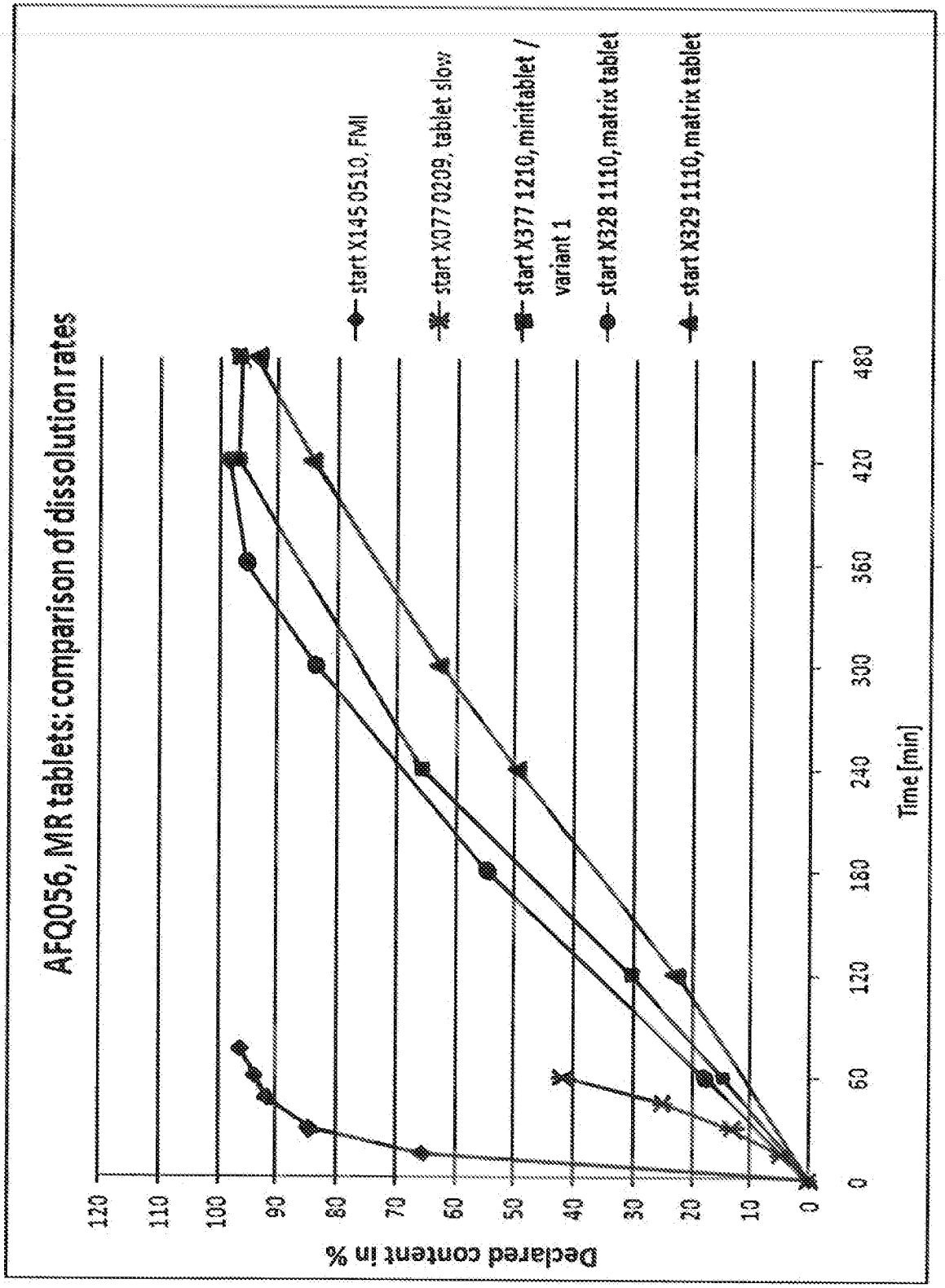


Simulated (line) plasma concentration profile compared to human PK data of MR Form B (symbols) observed

	Tmax [h]	**Cmax [ng/mL]**	**AUC_{48h} [h*ng/mL]**
MR tablet Form B 100mg in study X2167	4.0	99.5	1046
Simulation h-PK fromMR tablet 200 mg in dissolution medium + 40% EtOH (normalized to 100 mg)	3.5 (almost equal)	95.6 (almost equal)	905 (lower)

Simulated PK parameters compared to human data

Figure 8


AFQ056, MR tablets: comparison of dissolution rates
start X145 0510, FMI
start X077 0209, tablet slow
start X377 1210, minitablet / variant 1
start X328 1110, matrix tablet
start X329 1110, matrix tablet
Declared content in %
Time [min]
0
10
20
30
40
50
60
70
80
90
100
110
120
0
60
120
180
240
300
360
420
480

Time	Declared content in %											
X145	X377 time		X328 time		X329 time		X077 time					
[min]	start	[min]	start	[min]	start	[min]	start	[min]	start	[min]	start	[min]	start
0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	65.6	60	14.7	60	17.9	120	22.7	15	4.5				
30	84.5	120	30.2	160	54.7	240	49.6	30	13.1				
45	90.8	240	65.7	300	83.7	300	62.6	45	24.9				
60	93.5	420	96.8	360	95.5	420	84.0	60	41.9				
75	96.0	480	96.5	420	98.2	480	93.5						

Method: - paddle, 0.5% LDAO in water, 900 ml, 100 rpm (X377, X328, X329)
- paddle, 0.5% LDAO in water, 900 ml, 75 rpm (X145)
- paddle, 0.5% SDS in water, 1000 ml, 50 rpm (X077)

Figure 9

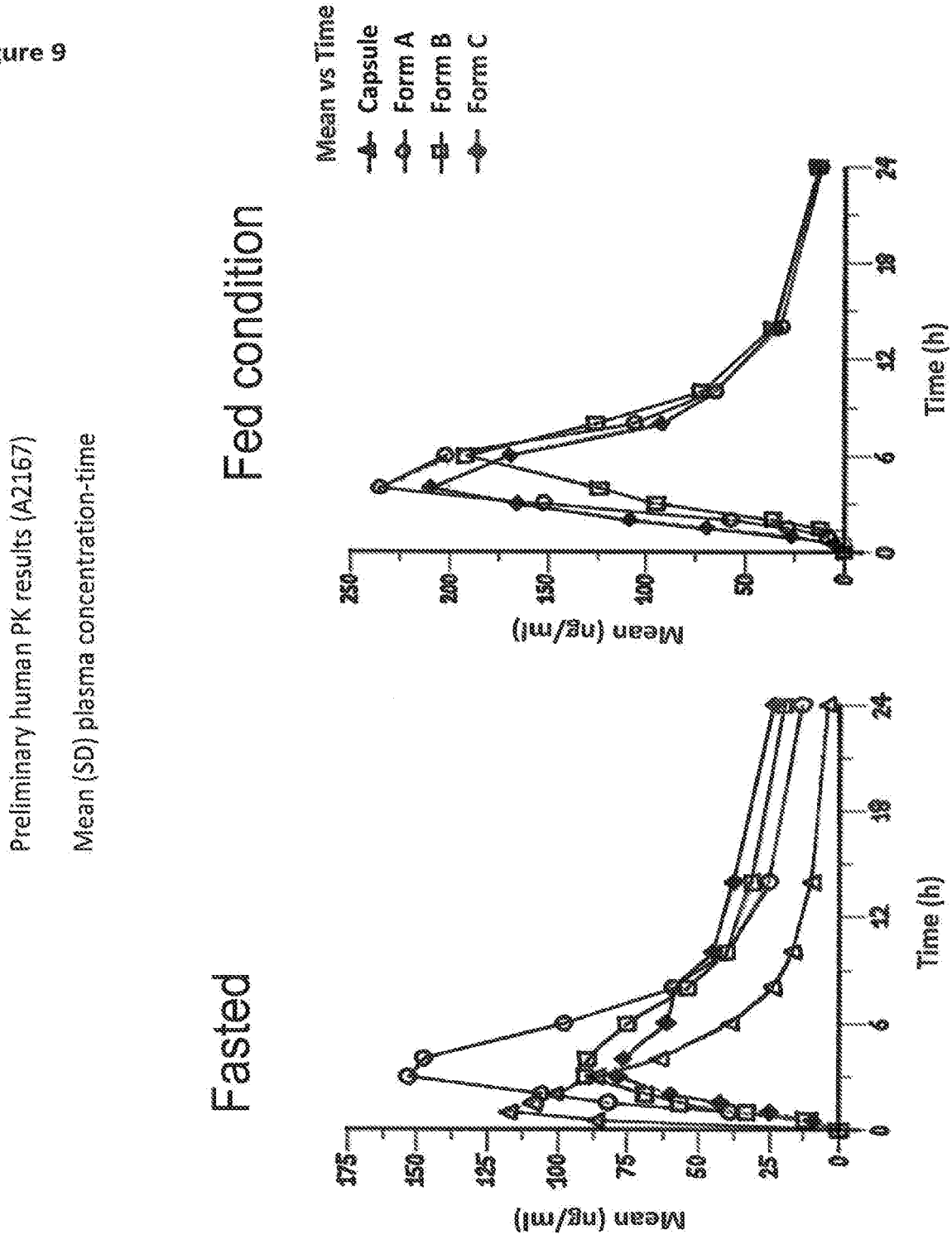

Preliminary human PK results (A2167)
Mean (SD) plasma concentration-time
Fasted
Fed condition
Mean vs Time
Capsule
Form A
Form B
Form C
Mean (ng/ml)
Time (h)
0
25
50
75
100
125
150
175
6
12
18
24
50
100
150
200
250

Figure 10

PK Results

Mean (SD) plasma concentration-time profile of MR form B fasted versus fed

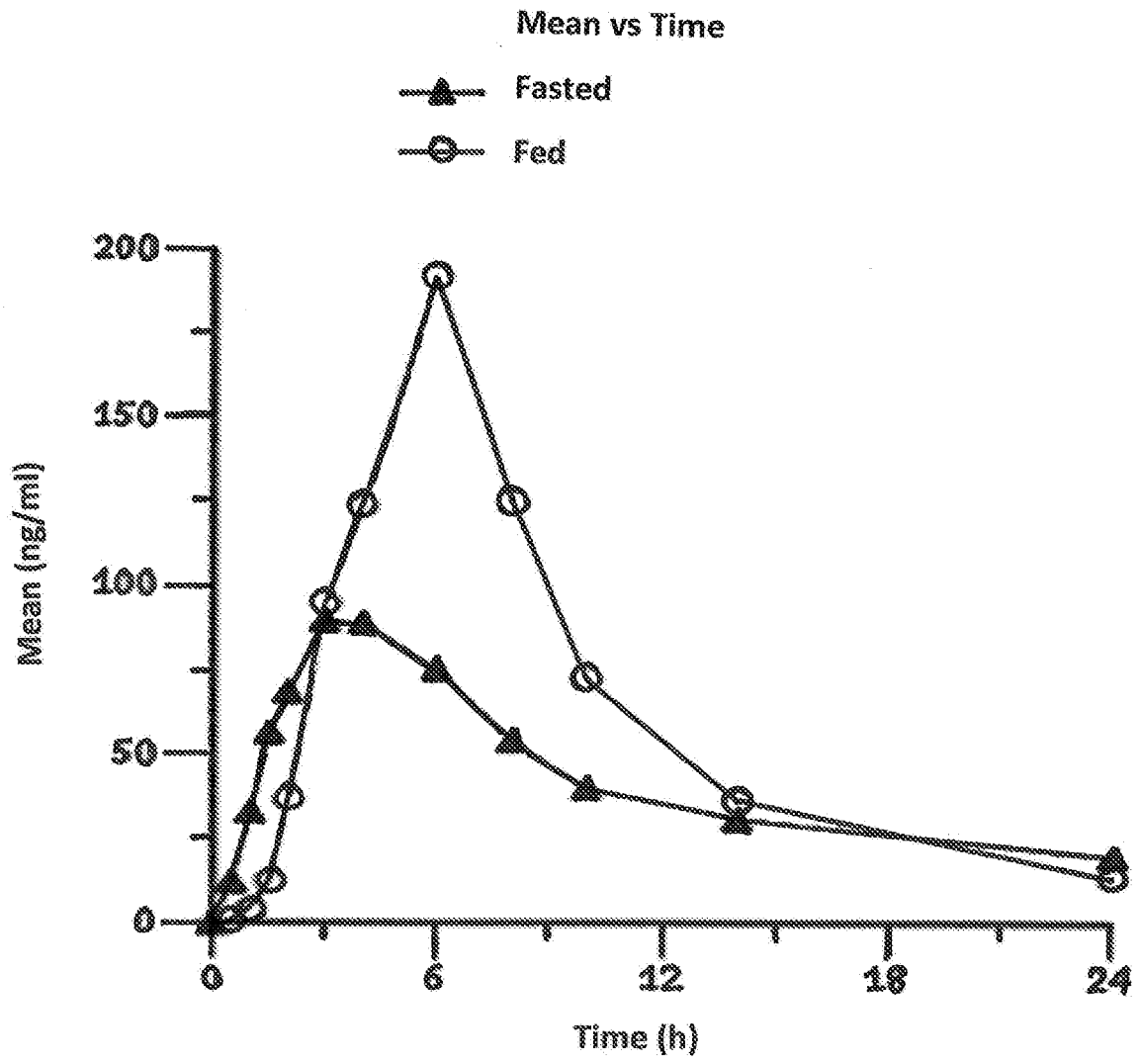
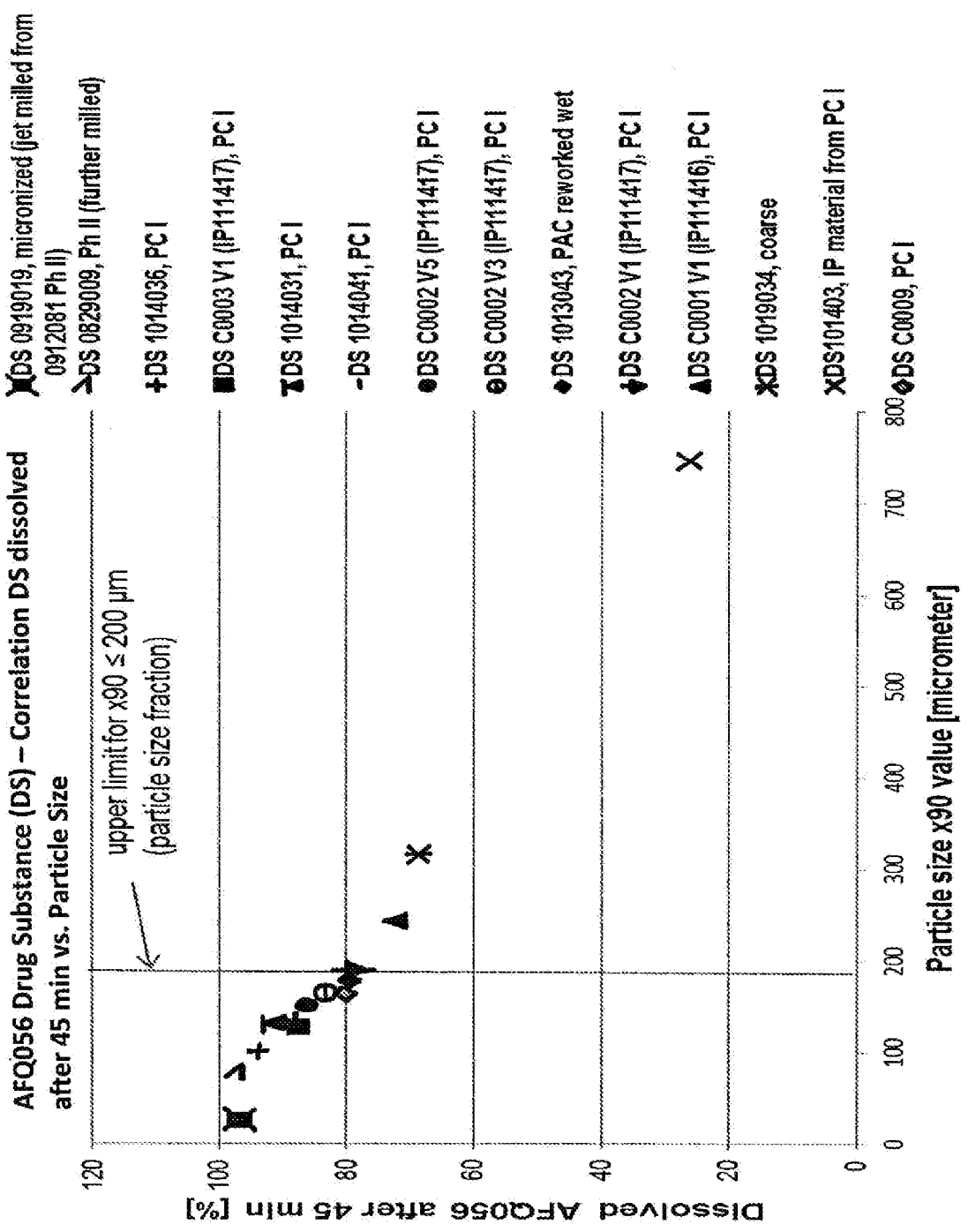


Figure 11


AFQ056 Drug Substance (DS) – Correlation DS dissolved after 45 min vs. Particle Size
upper limit for x90 ≤ 200 µm (particle size fraction)
DS 0919019, micronized (jet milled from 0912081 Ph II)
DS 0829009, Ph II (further milled)
DS 1014036, PC I
DS C0003 V1 (IP111417), PC I
DS 1014031, PC I
DS 1014041, PC I
DS C0002 V5 (IP111417), PC I
DS C0002 V3 (IP111417), PC I
DS 1013043, PAC reworked wet
DS C0002 V1 (IP111417), PC I
DS C0001 V1 (IP111416), PC I
DS 1019034, coarse
DS1101403, IP material from PC I
DS C0009, PC I
Dissolved AFQ056 after 45 min [%]
Particle size x90 value [micrometer]
0
20
40
60
80
100
120
0
100
200
300
400
500
600
700
800

Particle size distribution

	x10	x50	x90
0919019	2	7	26
0829009	8	33	77
1014036	8	40	101
C0003 V1	5	37	128
1014031	9	50	132
1014041	10	50	135
C0002 V5	6	40	151
C0009	12	66	164
C0002 V3	7	44	165
1013043	6	43	180
C0002 V1	8	53	191
C0001 V1	12	77	243
1019034	26	123	317
101403	285	515	747