

Hypothetical PK profiles of IR vs MR dosage forms

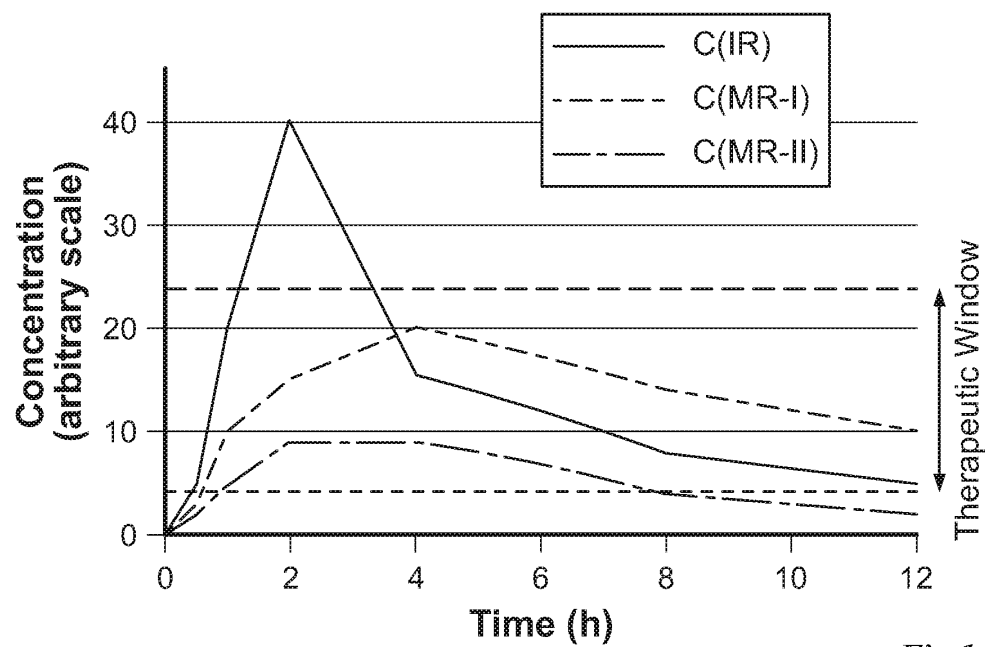


Fig 1

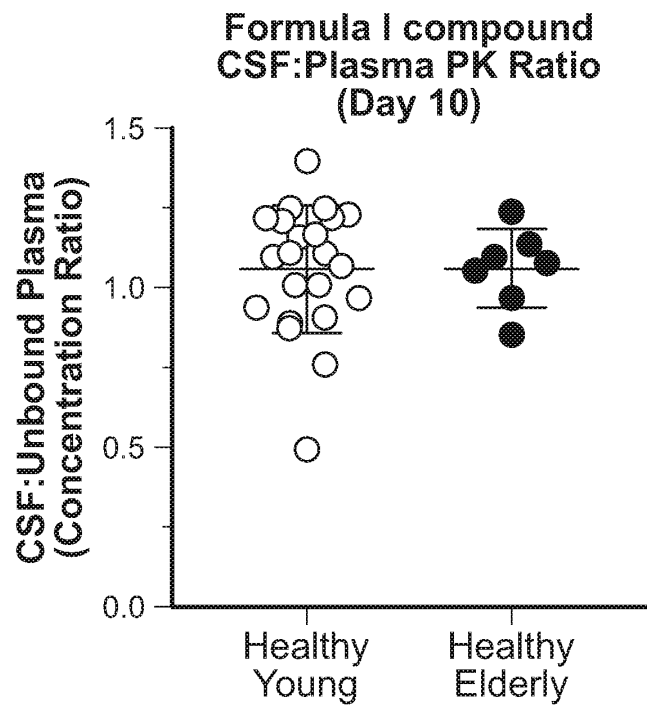
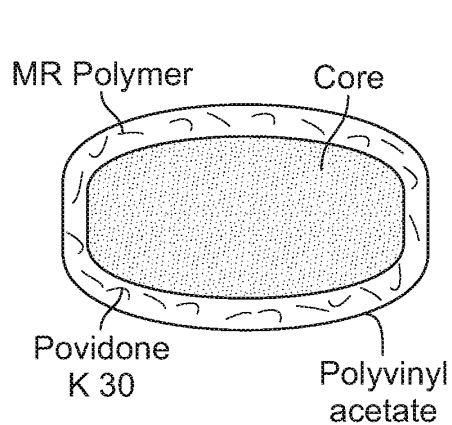
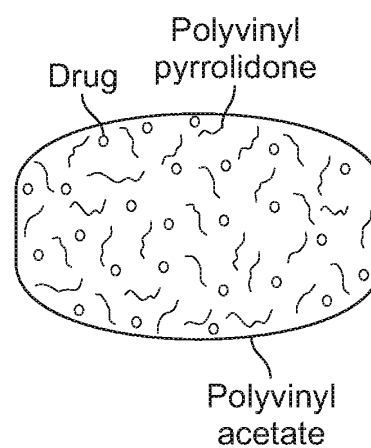
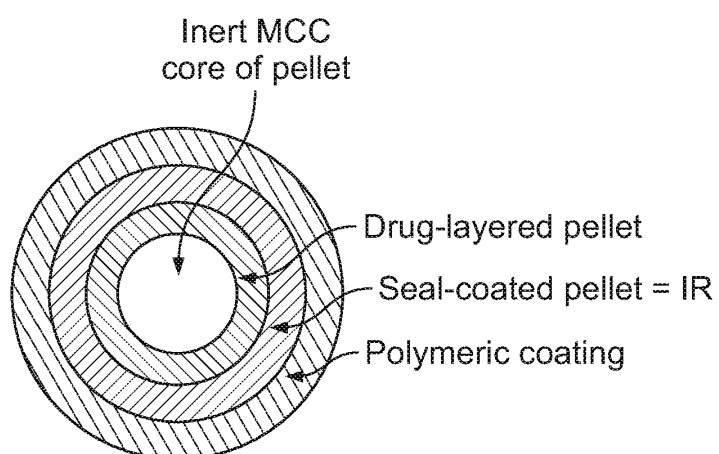


Fig 2

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*Fig 3**Fig 4**Fig 5*

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Comparative Formulas of Matrix Modified Release (MR), 80 mg tablets

Stage	Sr. No.	Batch Number		1		2		3	
		Ingredients		%w/w	mg/tab	%w/w	mg/tab	%w/w	mg/tab
Intra-granular Part (Pre-RC)	1	Formula I compound		20.00	80.00	20.00	80.00	20.00	80.00
	2	Microcrystalline Cellulose (Avicel PH 102)		43.00	172.00	33.00	132.00	23.00	92.00
	3	Polyvinyl Alcohol (Parteck SRP80)		30.00	120.00	40.00	160.00	50.00	200.00
	4	Povidone (Kollidon 30)		3.00	12.00	3.00	12.00	3.00	12.00
	5	Purified Talc		1.00	4.00	1.00	4.00	1.00	4.00
	6	Colloidal Silicon Dioxide (Aerosil 200Pharma)		0.50	2.00	0.50	2.00	0.50	2.00
	7	Magnesium Stearate		0.50	2.00	0.50	2.00	0.50	2.00
Extra-granular Part (Post RC)	Pre-RC Blend Weight			98.00	392.00	98.00	392.00	98.00	392.00
	8	Colloidal Silicon Dioxide (Aerosil 200Pharma)		0.50	2.000	0.50	2.000	0.50	2.000
	9	Purified Talc		1.00	4.000	1.00	4.000	1.00	4.000
	10	Magnesium Stearate		0.50	2.000	0.50	2.000	0.50	2.000
	Compressed Tablet Weight			100.00	400.000	100.00	400.000	100.00	400.000
Film-Coating (12%w/v Dispersion)	11	Opadry White		3.00	12.000	3.00	12.000	3.00	12.000
	12	Purified Water		-	Q.S.	-	Q.S.	-	Q.S.
	Film-Coated Tablet Weight			-	412.000	-	412.000	-	412.000

Fig. 6

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Comparative Dissolution Data of Formula I compound MR tablets

Media & Conditions		900 mL pH 3.0 McIlvaine Buffer, USP Apparatus II, 50 rpm, n=3					
Batch No.	1		2		3		
Formulation Details	30% Parteck Conc.		40% Parteck Conc.		50% Parteck Conc.		
Time Points	% Drug Release	%RSD	% Drug Release	%RSD	% Drug Release	%RSD	
0h (Initial)	0	0	0	0	0	0	0
0.5h	8	12.5	7	8.7	6	9.1	9.1
1h	15	10.4	14	15.2	13	7.7	7.7
2h	26	13.7	26	13.9	25	6.2	6.2
4h	43	14.1	47	14.4	45	6.7	6.7
6h	62	13.8	65	14.5	64	6.5	6.5
8h	80	12.8	80	14.7	79	6.7	6.7
10h	97	3.1	91	12.4	90	5.2	5.2
12h	101	1.0	97	9.0	97	3.9	3.9
18h	105	2.5	101	7.2	100	3.5	3.5
24h	107	2.5	103	7.3	101	4.5	4.5
25h (Recovery)	105	2.7	102	6.7	100	3.2	3.2

Fig 7

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MR matrix Tablets with HPMC K-15M (intra-granular)

Stage	Sr. No.	Batch Number		1		2		3	
		Ingredients		%w/w	mg/tab	%w/w	mg/tab	%w/w	mg/tab
Intra-granular Part (Pre-RC)	1	Formula I compound		20.00	80.00	20.00	80.00	20.00	80.00
	2	Microcrystalline Cellulose (Avicel PH 200)		63.00	252.00	58.00	232.00	53.00	212.00
	3	HPMC (Methocel K-15M CR)		10.00	40.00	15.00	60.00	20.00	80.00
	4	Povidone (Kollidon 30)		3.00	12.00	3.00	12.00	3.00	12.00
	5	Purified Talc		2.00	8.00	2.00	8.00	2.00	8.00
	6	Colloidal Silicon Dioxide (Aerosil 200Pharma)		1.00	4.00	1.00	4.00	1.00	4.00
	7	Magnesium Stearate		1.00	4.00	1.00	4.00	1.00	4.00
Total Weight of Tablet				100.00	400.00	100.00	400.00	100.00	400.00

Fig 8

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Comparative Dissolution Data of MR Matrix Tablets with HPMC K-15M (intra-granular)

Media & Conditions	900 mL pH 3.0 McIlvaine Buffer, USP Apparatus II, 50 rpm, n=3					
Batch No.	1		2		3	
Formulation Details	10% HPMC K-15M		15% HPMC K-15M		20% HPMC K-15M	
Time Points	% Drug Release	%RSD	% Drug Release	%RSD	% Drug Release	%RSD
0h (Initial)	0	0	0	0	0	0
0.5h	29	14.1	15	6.7	8	7.5
1h	37	14.0	20	7.5	10	0.0
2h	46	11.5	28	8.9	15	3.8
4h	62	9.1	40	5.2	24	8.8
6h	75	6.1	49	5.1	32	6.6
8h	84	5.6	57	5.6	39	6.8
10h	91	5.2	65	5.9	45	7.1
12h	97	4.9	71	6.1	52	7.3
18h	106	4.1	91	4.4	73	5.7
24h	107	5.1	99	4.6	83	6.0
25h (Recovery)	108	4.8	101	4.1	85	5.9

Fig 9

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MR matrix Tablets with Parteck SRP80 (extra-granular)

Stage	Sr. No.	Batch Number		1		2		3		4	
		Ingredients	%w/w	mg/tab	%w/w	mg/tab	%w/w	mg/tab	%w/w	mg/tab	%w/w
Intra-granular Part (Pre-RC)	1	Formula I compound	20.00	80.0	20.0	80.0	20.0	80.0	20.0	80.0	20.0
	2	Microcrystalline Cellulose (Avicel PH 102)	43.0	172.0	43.0	172.0	43.0	172.0	43.0	172.0	43.0
	3	Povidone (Kollidon 30)	3.0	12.0	3.0	12.0	3.0	12.0	3.0	12.0	3.0
	5	Colloidal Silicon Dioxide (Aerosil 200Pharma)	0.5	2.0	0.5	2.0	0.5	2.0	0.5	2.0	0.5
	6	Talc	1.0	4.0	1.0	4.0	1.0	4.0	1.0	4.0	1.0
	7	Magnesium stearate	0.5	2.0	0.5	2.0	0.5	2.0	0.5	2.0	0.5
	Pre-RC Blend Weight		68.0	272.0	68.0	272.0	68.0	272.0	68.0	272.0	68.0
Extra-granular Part (Post RC)	7	Polyvinyl Alcohol (Parteck SRP 80)	22.2	80.0	30.0	120.0	36.4	160.0	41.70	200.0	41.70
	8	Colloidal Silicon Dioxide (Aerosil 200Pharma)	0.6	2.0	0.5	2.0	0.5	2.0	0.4	2.0	0.4
	9	Purified Talc	1.1	4.0	1.0	4.0	0.9	4.0	0.8	4.0	0.8
	10	Magnesium Stearate (Vegetable Grade)	0.6	2.0	0.5	2.0	0.5	2.0	0.4	2.0	0.4
	Compressed Tablet Weight		100.0	360.0	100.00	400.000	100.0	440.000	100.0	480.000	100.0

Fig 10

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Comparative Dissolution Data of MR matrix Tablets with Parteck SRP80 (extra-granular)

Media & Conditions		900 mL pH 3.0 McIlvaine Buffer, USP Apparatus II, 50 rpm, n=3							
Batch No.		1		2		3		4	
Formulation Details		Parteck SRP 80 -- 80 mg		Parteck SRP 80 -- 120 mg		Parteck SRP 80 -- 160 mg		Parteck SRP 80 -- 200 mg	
Time Points	% Drug Release	%RSD	% Drug Release	%RSD	% Drug Release	%RSD	% Drug Release	%RSD	
	0	0	0	0	0	0	0	0	
	8	14.5	7	0	6	20.4	6	10.2	
	16	12.9	14	0	12	26.1	11	14.3	
	29	13.3	28	0	25	25.0	21	14.3	
	49	11.9	51	2	47	24.1	42	14.9	
	71	8.9	70	2.2	64	22.5	60	15.0	
92	12.9	86	2.3	78	19.7	75	14.2		
98	12.2	98	1	87	14.5	86	12.4		
100	10.1	102	2.9	94	10.1	95	10.0		
103	8.2	105	6.5	101	3.5	103	2.8		
105	7.0	105	5.8	104	3.9	106	1.4		
25h (Recovery)			108	4.8	101	4.1	85	5.9	

Fig 11

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Composition of MR Pellets, 80 mg

Pore Former		3 % Povidone		30 % Povidone		25 % Povidone		20 % Povidone	
Sr. No.	Ingredients	%w/w	mg/unit	%w/w	mg/unit	%w/w	mg/unit	%w/w	mg/unit
Drug Layering Stage									
1	Microcrystalline Cellulose (Celphere CP-305)	55.33	160	55.33	160	55.33	160	55.33	160
2	Formula I compound	27.67	80	27.67	80	27.67	80	27.67	80
3	Hypromellose (HPMC 5 cps)	5.19	15	5.19	15	5.19	15	5.19	15
4	Povidone (Kollidon 30)	2.59	7.5	2.59	7.5	2.59	7.5	2.59	7.5
5	Purified Water (For 15%w/w Dispersion)	NA	580.83	NA	580.83	NA	580.83	NA	580.83
Drug Layered Pellets Weight		90.78	262.5	90.78	262.5	90.78	262.5	90.78	262.5
IR Pellet Stage									
Drug Layered Pellets		90.78	262.5	90.78	262.5	90.78	262.5	90.78	262.5
6	Hypromellose (HPMC 5 cps)	1.64	4.73	1.64	4.73	1.64	4.73	1.64	4.73
7	Polyethylene Glycol (PEG6000)	0.18	0.52	0.18	0.52	0.18	0.52	0.18	0.52
8	Purified Water (For 10%w/w Solution)	NA	47.25	NA	47.25	NA	47.25	NA	47.25
IR Pellet Weight		92.59	267.75	92.59	267.75	92.59	267.75	92.59	267.75
MR Coating Stage (8 % weight gain on IR Pellets)									
IR Pellets		92.59	267.75	92.59	267.75	92.59	267.75	92.59	267.75
9	Polyvinyl Acetate Dispersion (Kollicoat SR 30 D) (Solid Content)	6.22	18	5.07	14.67	5.25	15.19	5.45	15.75
10	Polyethylene Glycol (PEG 6000)	0.5	1.44	0.40	1.17	0.42	1.22	0.44	1.26
11	Talc (micronized)	0.5	1.44	0.40	1.17	0.42	1.22	0.44	1.26
12	Povidone (Kollidon 30)	0.19	0.54	1.52	4.40	1.31	3.80	1.09	3.15
13	Purified Water (For 15%w/w Dispersion)	NA	79.38	NA	121.32	NA	121.32	NA	121.32
MR Pellet Weight		100	289.17	100.00	289.16	100.00	289.18	100.00	289.17

Fig 12

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Comparative Drug Release Data of Batches with Different Pore Former Levels

Time (h)	2.38%w/w 3% Pore Former	5.03%w/w 20% Pore Former	4.85 %w/w 20% Pore Former	5.20%w/w 3% Pore Former	7.92%w/w 20% Pore Former	7.50 %w/w 20% Pore Former	8.20%w/w 3% Pore Former	9.49%w/w 20% Pore Former	8.97 %w/w 20% Pore Former
0	0	0	0	0	0	0	0	0	0
0.5	22	25	19	15	10	5	3	3	2
1	42	31	34	28	11	11	7	6	5
2	66	50	55	40	23	19	15	11	11
4	87	75	79	57	42	33	29	21	20
6	96	90	92	67	55	44	40	29	28
8	100	97	99	74	64	55	48	36	36
10	102	100	102	79	75	63	55	43	43
12	103	102	104	83	84	70	62	49	49
18	104	102	106	91	94	86	75	63	65
24	106	102	108	96	102	96	85	74	78

Fig 13

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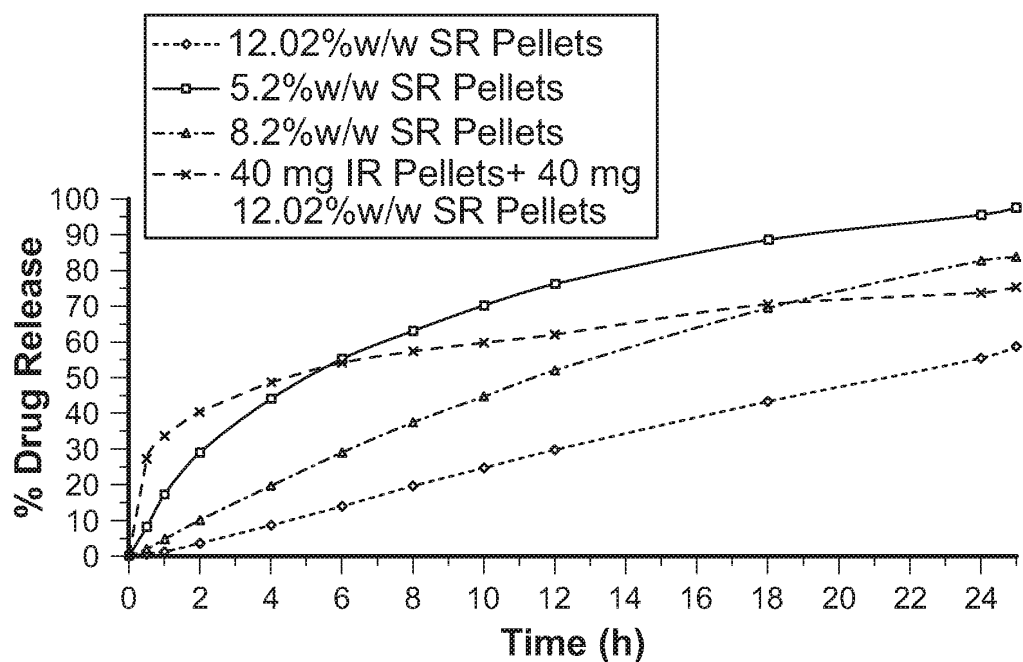


Fig 14

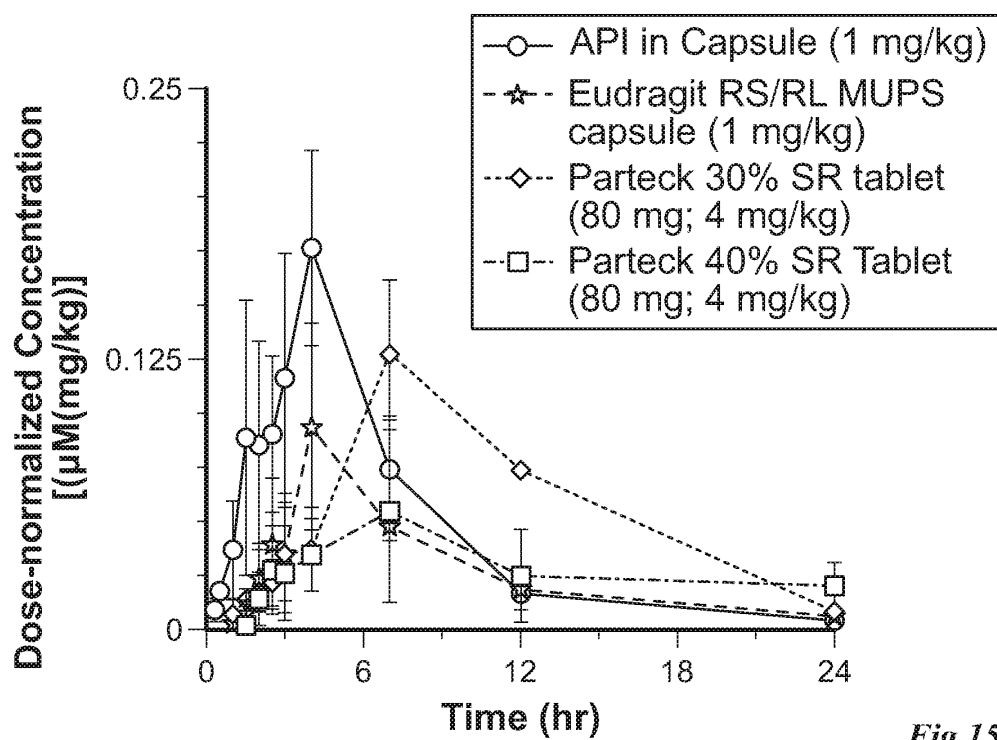


Fig 15

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Dose-Normalized Data summary for Formulations 1-5 in Minipig

Phase	Formulation	Animal ID	Terminal t1/2 (hr)	Tmax (hr)	Cmax/Dose $\mu\text{M}/(\text{mg}/\text{kg})$	AUC _{0-24hr} /Dose (hr* $\mu\text{M})/(\text{mg}/\text{kg})$	AUC _{0-inf} /Dose (hr* $\mu\text{M})/(\text{mg}/\text{kg})$	Bioavailability (%)
1	API in Gelatin Capsule {1 mg/kg}	Mean	2.88	4	0.176	0.944	0.954	53.1
		SD	1.44	0	0.045	0.250	0.249	14.9
		CV%	50.1	0	25.6	26.5	26.1	28.0
2	IR Tablet 80 mg; (4 mg/kg)	Mean	11.6	1.83	0.0513	0.480	0.848	26.6
		SD	12.7	1.04	0.0482	0.445	1.01	23.4
		CV%	110	56.8	94.0	92.7	120	88.1
3	Parteck 40% MR Tablet {80 mg; 4 mg/kg}	Mean	19.6	11.7	0.0574	0.623	1.40	34.1
		SD	21.4	10.8	0.0390	0.303	NA	15.4
		CV%	109	92.4	68.0	48.6	NA	45.2
4	Parteck 30% MR tablet {80 mg; 4 mg/kg}	Mean	3.81	7	0.127	1.17	1.25	67.6
		SD	0.232	0	0.035	0.06	NA	7.6
		CV%	6.08	0	27.3	5.45	NA	11.3
5	Eudragit RS/RL MUPS capsule (1 mg/kg)	Mean	5.01	4.75	0.0950	0.146	0.156	35.4
		SD	2.30	1.50	0.0449	0.039	0.042	10.3
		CV%	45.9	31.6	47.3	26.9	27	29.2

Fig 16

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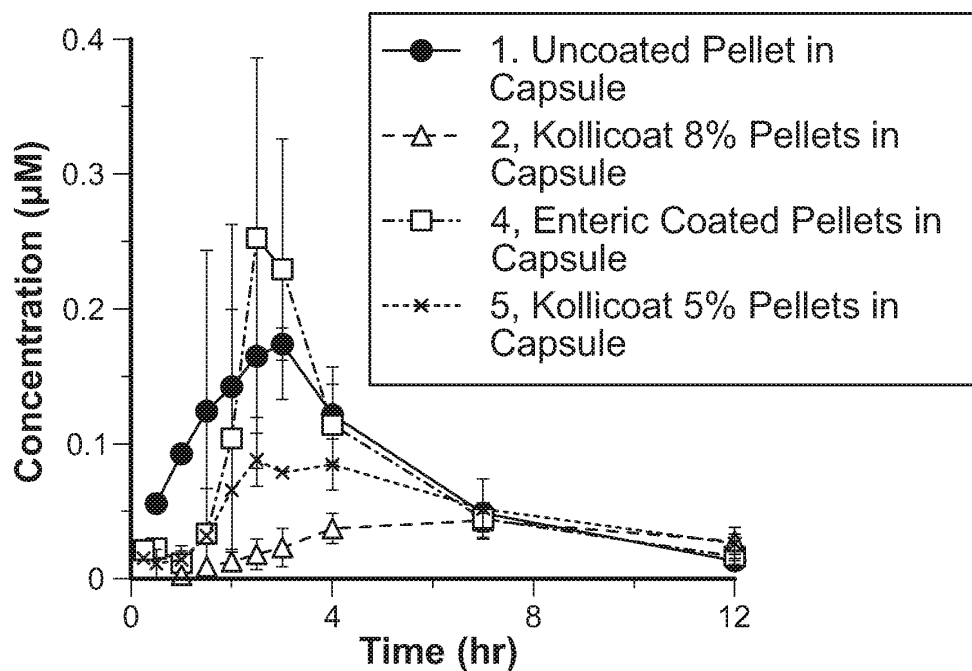


Fig 17A

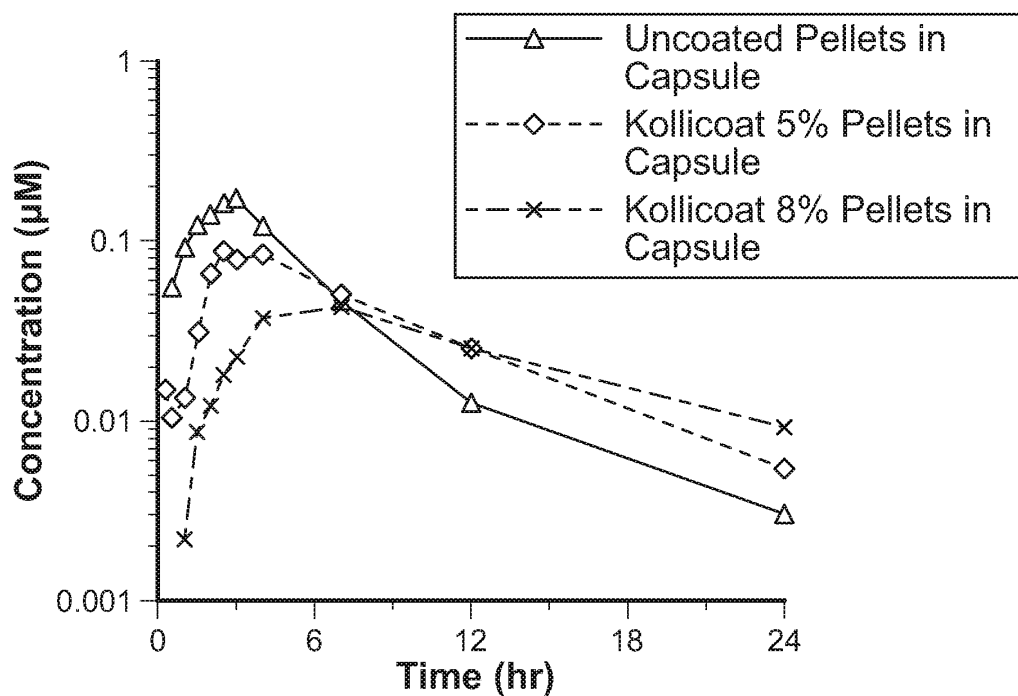


Fig 17B

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Minipig PK: Modified Release Formulations @ 1 mg/kg

Phase	Formulation	Tmax (hr)	Cmax (μM)	Tlast (hr)	AUC, 0-inf (hr*μM)	AUC, 0-24 hr (hr*μM)	Absolute Bioavailability (%)
1	Uncoated Pellets in Capsule	Mean	3	0.197	20	0.894	51.7
2	Kollicoat 8% Pellets in Capsule	Mean	5	0.0469	24	0.658	37.6
4	Enteric Coated Pellets in Capsule	Mean	3	0.256	24	0.927	53.5
5	Kollicoat 5% Pellets in Capsule	Mean	3	0.094	24	0.777	44.7

Fig 18

Cyno PK: Modified Release Formulations @2 mg/kg

Phase	Formulation	Terminal t _{1/2} (hr)	Tmax (hr)	Cmax (μM)	AUC, 0-last (hr*μM)	AUC, 0-inf (hr*μM)	AUC, 0-12 hr (hr*μM)
1	Uncoated Pellets in Capsule	Mean	2.36	1.5	1.42	2.71	2.66
2	Kollicoat 8% Pellets in Capsule	Mean	2.95	7.5	0.0660	0.626	0.467
3	Neat API in Capsule	Mean	2.56	1.2	1.14	2.37	2.29
4	Enteric Coated Pellets in Capsule	Mean	2.23	1.5	1.82	3.45	3.40
5	Kollicoat 5% Pellets in Capsule	Mean	3.37	2.0	0.190	1.04	0.922
6	Kollicoat 3% Pellets in Capsule	Mean	2.67	2.1	0.585	2.03	1.93

Fig 19

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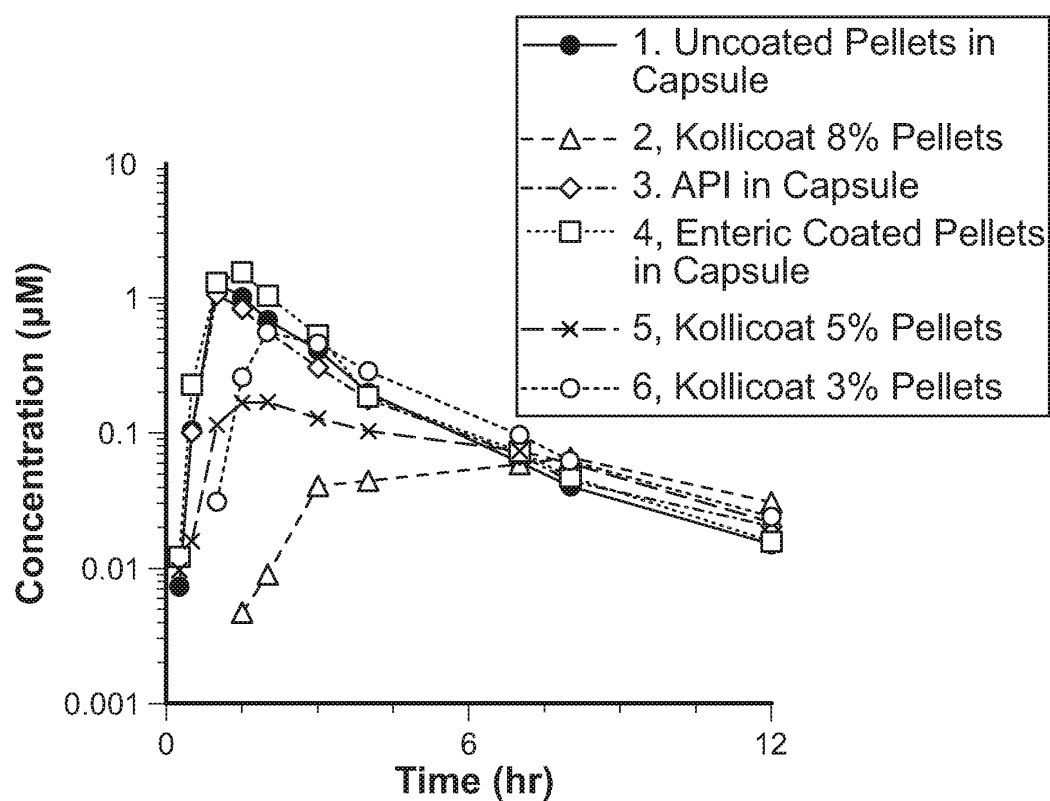


Fig 20A

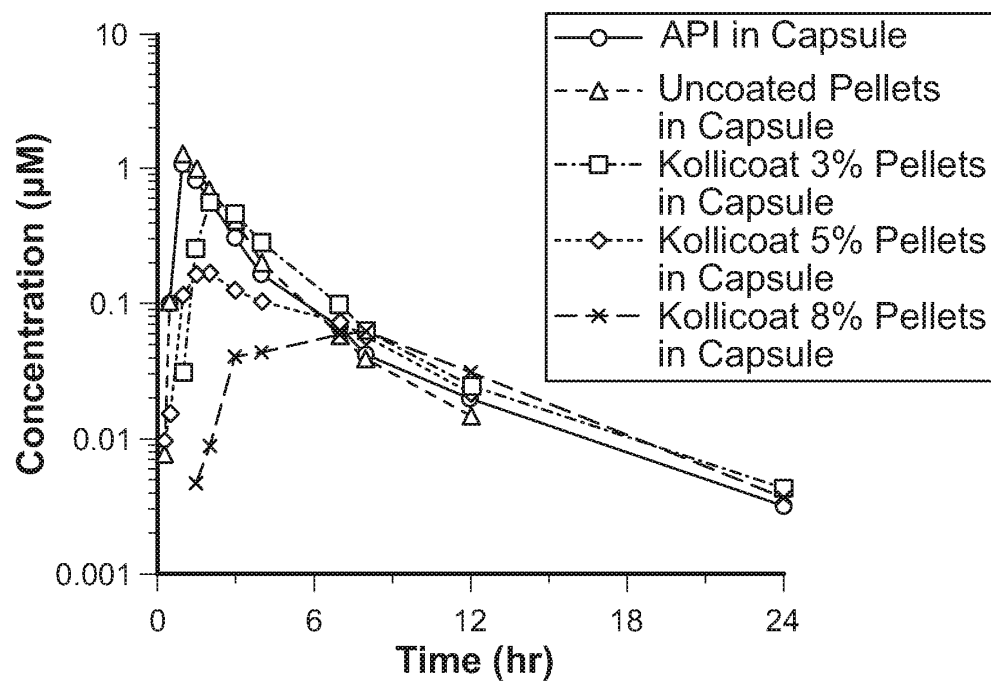


Fig 20B

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MR Pellets in Capsule - Eudragit L30D55 + Carbopol

Sr. No.	Ingredients	%w/w	mg/tablet
Drug Loading Stage			
1	Celphere CP-305 (#35-#50)	56.35	160.00
2	Formula I compound	28.17	80.00
3	HPMC 5 cps	5.28	15.00
4	Povidone (Kollidon 30)	2.64	7.50
5	Purified Water (For 15%w/w Dispersion)	NA	580.83
Drug Loaded Pellets Weight			
	Seal Coating Stage (2% weight gain on Drug Loaded Pellets)	92.45	262.50
Seal Coated Pellets			
6	HPMC 5 cps	1.67	4.73
7	PEG6000	0.18	0.52
8	Purified Water (For 10%w/w Solution)	NA	47.25
Seal Coated Pellet Weight			
	MR Coating Stage (5% weight gain on Seal Coated Pellets)	94.30	267.75
Seal Coated Pellets			
9	Eudragit L30D55	1.39	3.94
10	Carbopol 971P	0.83	2.36
11	Triethyl Citrate (TEC)	0.14	0.39
12	Talc (Micronized)	2.36	6.69
13	Purified Water (For 15%w/w Dispersion)	NA	75.84
MR Pellet Weight			
	Lubrication Stage (0.99%w/w on MR Coated Pellets)	99.01	281.13
MR Coated Pellets			
13	Purified Talc (Micronized)	0.99	2.81
Lubricated MR Pellet Weight			
		100.00	283.95

Fig 21

MR Pellets in Capsule - Aquacoat + Carbopol

Sr. No.	Ingredients	%w/w	mg/tablet
	Drug Loading Stage		
1	Celphere CP-305 (#35-#50)	53.78	160.00
2	Formula I compound	26.89	80.00
3	HPMC 5 cps	5.04	15.00
4	Povidone (Kollidon 30)	2.52	7.50
5	Purified Water (For 15%w/w Dispersion)	NA	580.83
	Drug Loaded Pellets Weight	88.24	262.50
	Seal Coating Stage (2% weight gain on Drug Loaded Pellets)		
	Drug Loaded Pellets	88.24	262.50
6	HPMC 5 cps	1.59	4.73
7	PEG6000	0.17	0.52
8	Purified Water (For 10%w/w Solution)	NA	47.25
	Seal Coated Pellet Weight	90.00	267.75
	MR Coating Stage (10% weight gain on Seal Coated Pellets)		
	Seal Coated Pellets	90.00	267.75
9	Aquacoat ECD 30 (Solid Content)	4.50	13.39
10	Carbopol 971P	2.25	6.70
11	Acetyltributyl Citrate (ATBC)	1.50	4.47
12	Talc	0.75	2.23
13	Purified Water (For 15%w/w Dispersion)	NA	151.81
	MR Pellet Weight	99.01	294.54
	Lubrication Stage (0.99%w/w on MR Coated Pellets)		
	MR Coated Pellets	99.01	294.54
14	Purified Talc	0.99	2.95
	Lubricated MR Pellet Weight	100.00	297.49

Fig 22

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MR Pellets in Capsule - Kollicoat Strategy

Sr. No.	Ingredients	%w/w	mg/tablet
Drug Loading Stage			
1	Celphere CP-305 (#35-#50)	56.35	160.00
2	Formula I compound	28.17	80.00
3	HPMC 5 cps	5.28	15.00
4	Povidone (Kollidon 30)	2.64	7.50
5	Purified Water (For 15%w/w Dispersion)	NA	580.83
Drug Loaded Pellets Weight			
	Seal Coating Stage (2% weight gain on Drug Loaded Pellets)	92.45	262.50
Seal Coated Pellet Weight			
6	Drug Loaded Pellets	92.45	262.50
	HPMC 5 cps	1.67	4.73
7	PEG6000	0.18	0.52
8	Purified Water (For 10%w/w Solution)	NA	47.25
Seal Coated Pellet Weight			
	MR Coating Stage (5% weight gain on Seal Coated Pellets)	94.29	267.75
MR Coated Pellets			
9	Kollicoat SR 30 D (Solid Content)	94.29	267.75
10	Carbopol 971P	2.36	6.69
11	Polyethylene Glycol (PEG 6000)	1.18	3.34
12	Talc	0.79	2.24
13	Purified Water (For 15%w/w Dispersion)	0.39	1.12
MR Pellet Weight			
	MR Pellet Weight	NA	116.29
MR Pellet Weight			
	Lubrication Stage (0.99%w/w on MR Coated Pellets)	99.01	281.14
MR Coated Pellets			
14	MR Coated Pellets	99.01	281.14
	Purified Talc	0.99	2.81
Lubricated MR Pellet Weight			
	Lubricated MR Pellet Weight	100.00	283.95

Fig 23

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Compositions of Formula I MR tablets

Stage	Sr. No.	Strength		80 mg		160 mg		106.68 mg		40 mg		100mg	
		Ingredients		%w/w	mg/tab	%w/w	mg/tab	%w/w	mg/tab	%w/w	mg/tab	%w/w	mg/tab
Intra-granular Part (Pre-RC)	Dry Granulation Process												
	1	Formula i compound		20.00	80.00	40.00	160.00	26.67	106.68	10.00	40.00	25.00	100.00
	2	Microcrystalline Cellulose (Avicel PH 102)		68.00	272.00	48.00	192.00	61.33	245.32	78.00	312.00	63.00	252.00
	3	Povidone (Kollidon 30)		3.00	12.00	3.00	12.00	3.00	12.00	3.00	12.00	3.00	12.00
	4	Croscarmellose Sodium (Ac-Di-Sol)		2.50	10.00	2.50	10.00	2.50	10.00	2.50	10.00	2.50	10.00
	5	Talc		0.50	2.00	0.50	2.00	1.00	4.00	1.00	4.00	0.50	2.00
	6	Colloidal Silicon Dioxide (Aerosil 200Pharma)		1.00	4.00	1.00	4.00	0.50	2.00	0.50	2.00	1.00	4.00
	7	Magnesium Stearate		0.50	2.00	0.50	2.00	0.50	2.00	0.50	2.00	0.50	2.00
	8	Croscarmellose Sodium (Ac-Di-Sol)		2.50	10.00	2.50	10.00	2.50	10.00	2.50	10.00	2.50	10.00
	9	Colloidal Silicon Dioxide (Aerosil 200Pharma)		0.50	2.00	0.50	2.00	0.50	2.00	0.50	2.00	0.50	2.00
	10	Talc		1.00	4.00	1.00	4.00	1.000	4.00	1.00	4.00	1.00	4.00
Extra-granular Part (Post RC)	11	Magnesium Stearate		0.50	2.00	0.50	2.00	0.50	2.00	0.50	2.00	0.50	2.00
	Total Compressed Tablet Weight			100.00	400.00	100.00	400.00	100.00	400.00	100.00	400.00	100.00	400.00
	12	Opadry White 03F580030		3.00	12.00	3.00	12.00	3.00	12.00	3.00	12.00	3.00	12.00
	13	Purified Water		-	Q.S.	-	Q.S.	-	Q.S.	-	Q.S.	-	Q.S.
Film-Coating (12%w/v Dispersion)	Total Film-Coated Tablet Weight			-	412.00	-	412.00	-	412.00	-	412.00	-	412.00

Fig 24

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Manufacturing Process Steps of Formula I compound tablets

Processing Steps	Process Details
Step 1	Co-sifting of Formula I compound with Povidone, Croscarmellose Sodium, Colloidal Silicon Dioxide and Talc through #40 sieve.
Step 2	Blending of Step 1 in conta blender for 5 minutes at 20 rpm
Step 3	Sifting of Microcrystalline Cellulose through #40 sieve and divide it in 2 equal lots.
Step 4	Add lot-1 MCC from Step 3 in conta blender (step 2) and blend for 5 minutes at 20 rpm
Step 5	Blend lot-2 MCC from Step 3 in conta blender (step 4) for 5 minutes at 20 rpm
Step 6	Sifting of Magnesium Stearate through #60 sieve
Step 7	Addition of Step 6 to Step 5 in conta blender and mix for 3 minutes at 20 rpm
Step 8	Dry-granulation of Step 7 blend using Roller Compactor
Step 9	Mill the granules using Oscillating Granulator 0.8mm or 1.0mm
Step 10	Addition of Step 9 granules in conta blender and mix it for 5 minutes
Step 11	Sifting of Croscarmellose Sodium, Colloidal Silicon Dioxide and Talc through #40 sieve
Step 12	Addition of Step 11 to Step 10 in conta blender and mix for 5 minutes at 20 rpm
Step 13	Sifting of Magnesium Stearate through #60 sieve
Step 14	Addition of Step 13 to Step 12 in conta blender and mix for 2 minutes at 20 rpm
Step 15	Tablet compression using appropriate oval punches in Korsch/Cadmach machine. Tapping to hopper was done to get proper flow of blend.
Step 16	Film Coating using Opadry White to achieve 3.00%w/w weight gain

Fig 25

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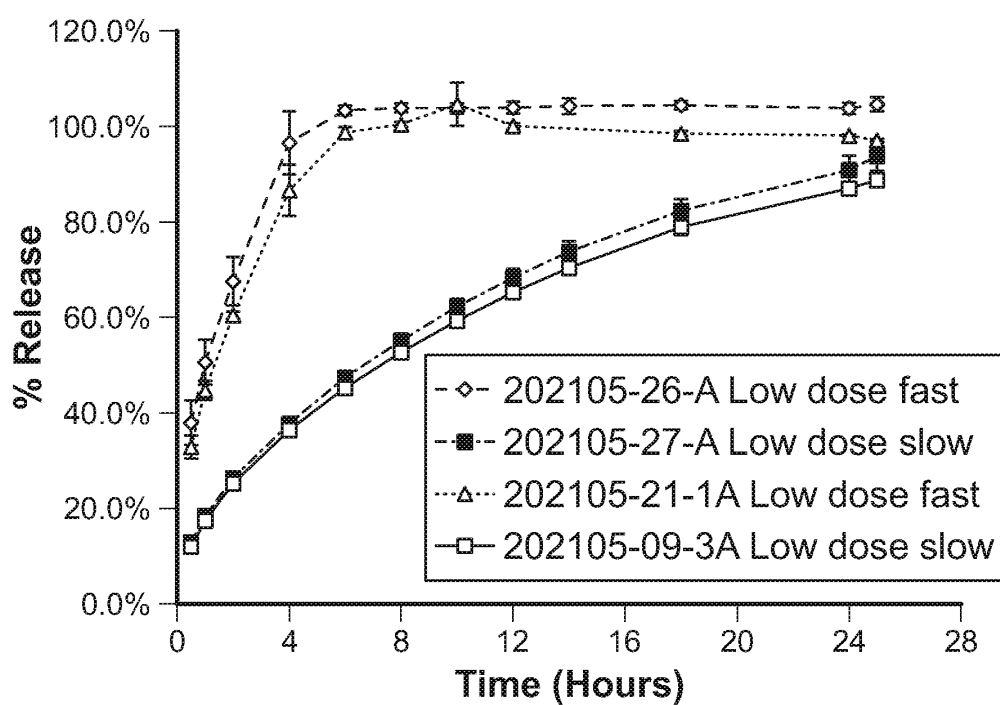
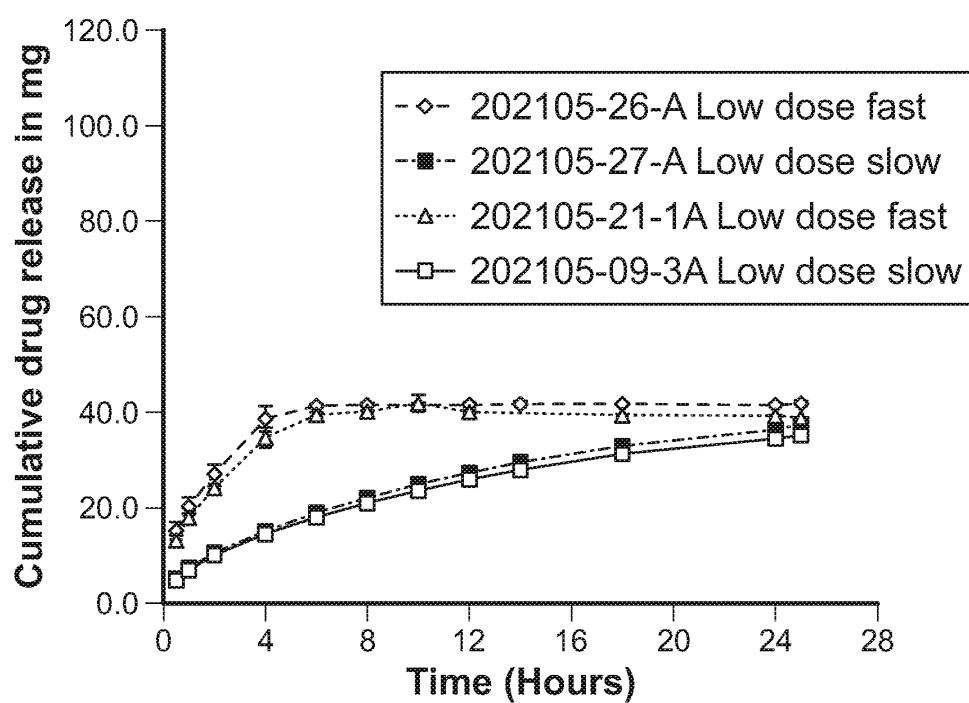
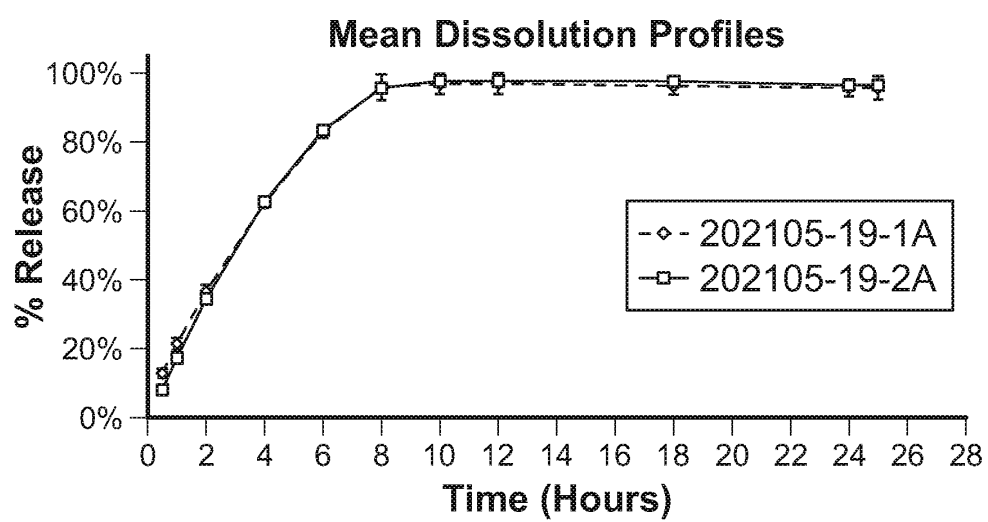


Fig 26

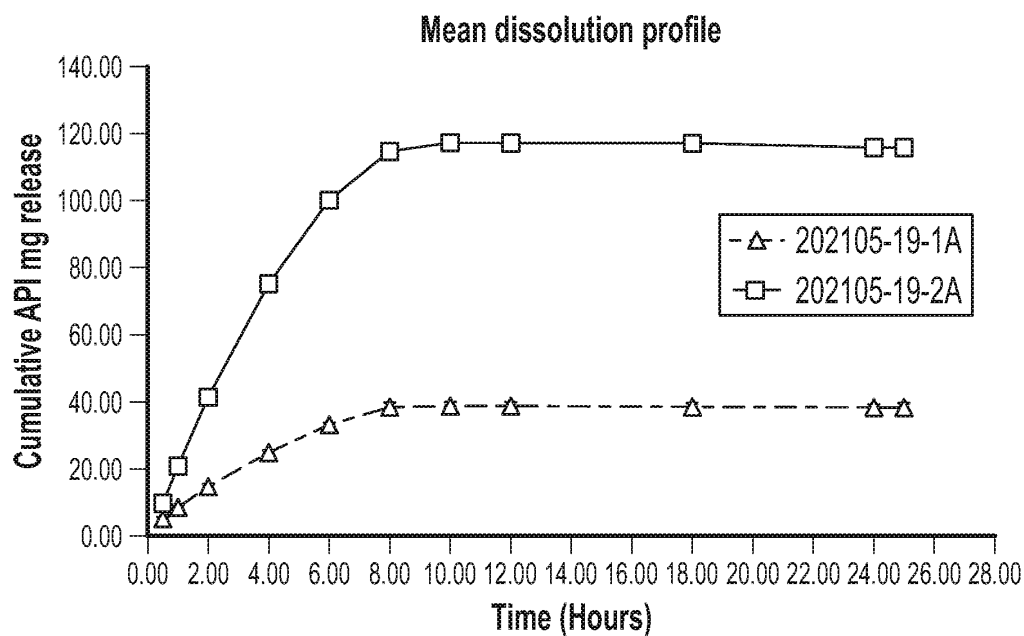
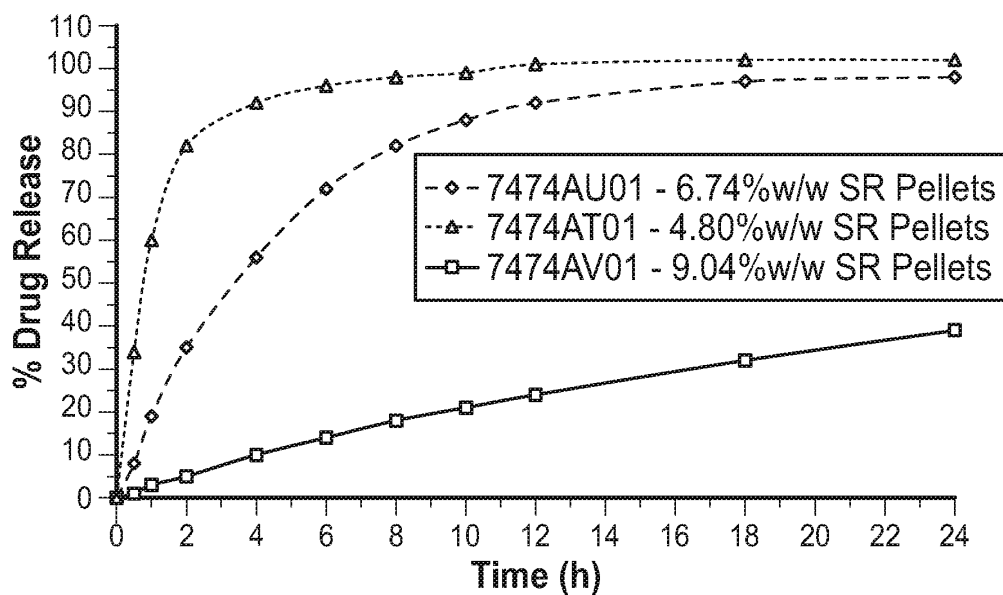
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*Fig 27*

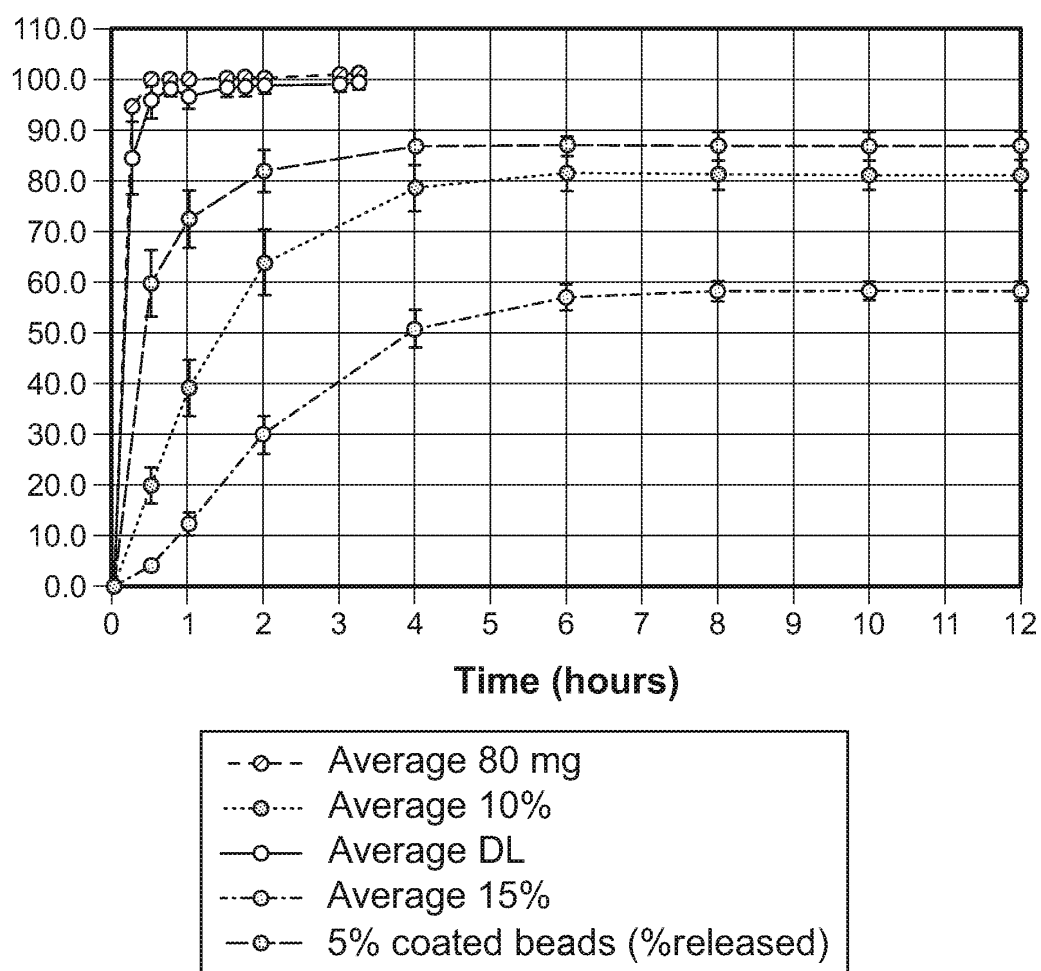
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*Fig 28*

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*Fig 29**Fig 30*

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*Fig 31*