

Transitioning from a lab-scale PLGA microparticle formulation to pilot-scale manufacturing

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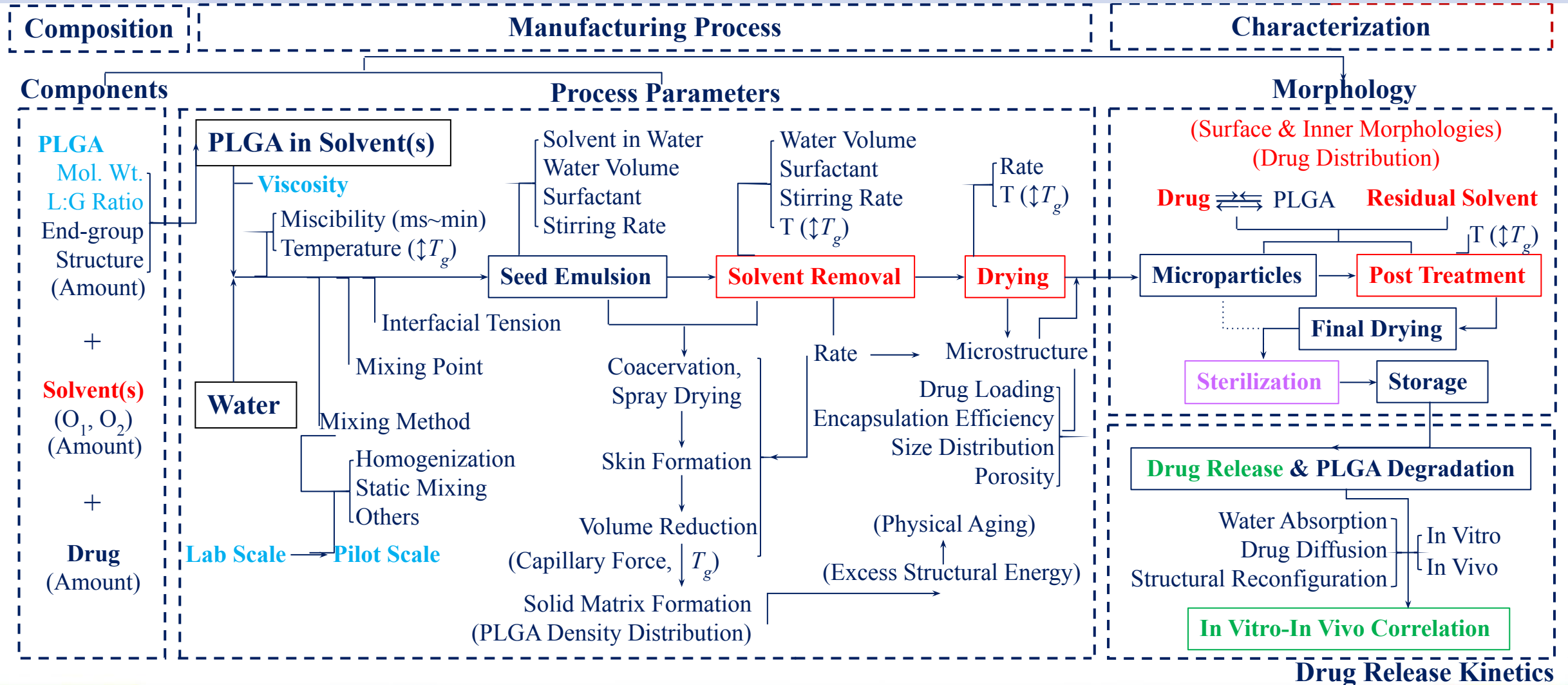
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PLGA Formulation Development Complexity



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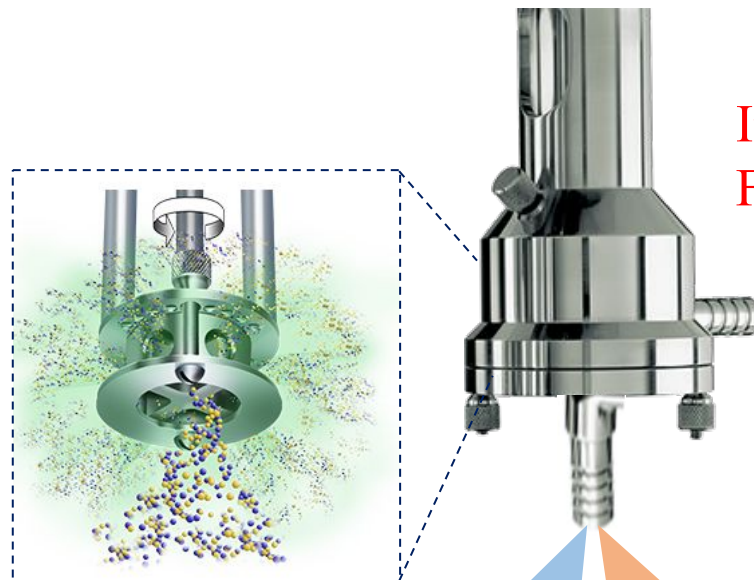
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Transition from Lab to Pilot Scale

Lab Scale (0.25~1 g/Batch)

Pilot Scale (25 g)



Microparticle Seed Emulsion

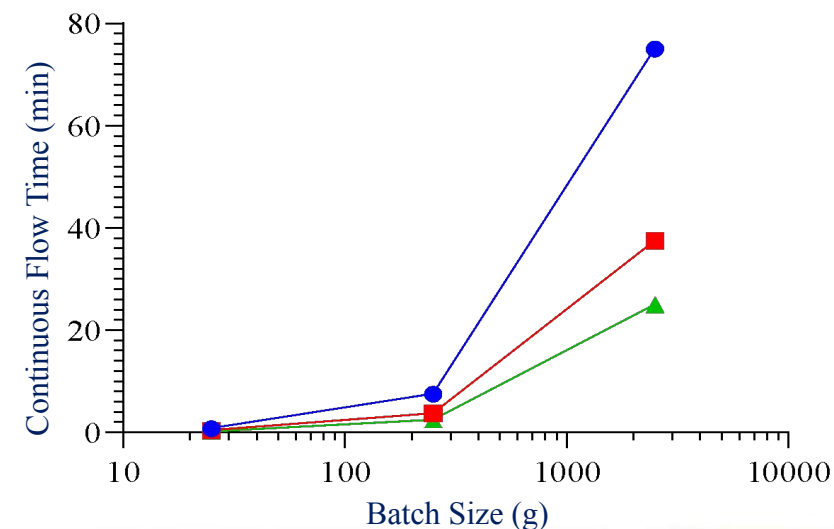
Aqueous Extraction

Aqueous Phase (AP)

Organic Phase (OP)

CP:DP Flow Rates (mL/min)

- 300:100
- 600:200
- ▲ 900:300



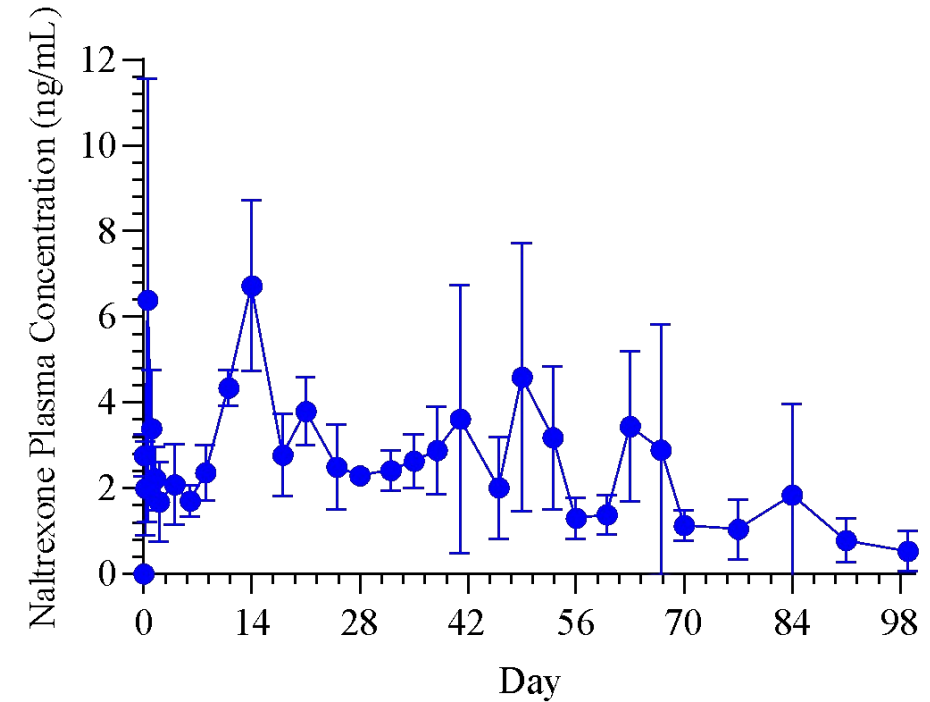
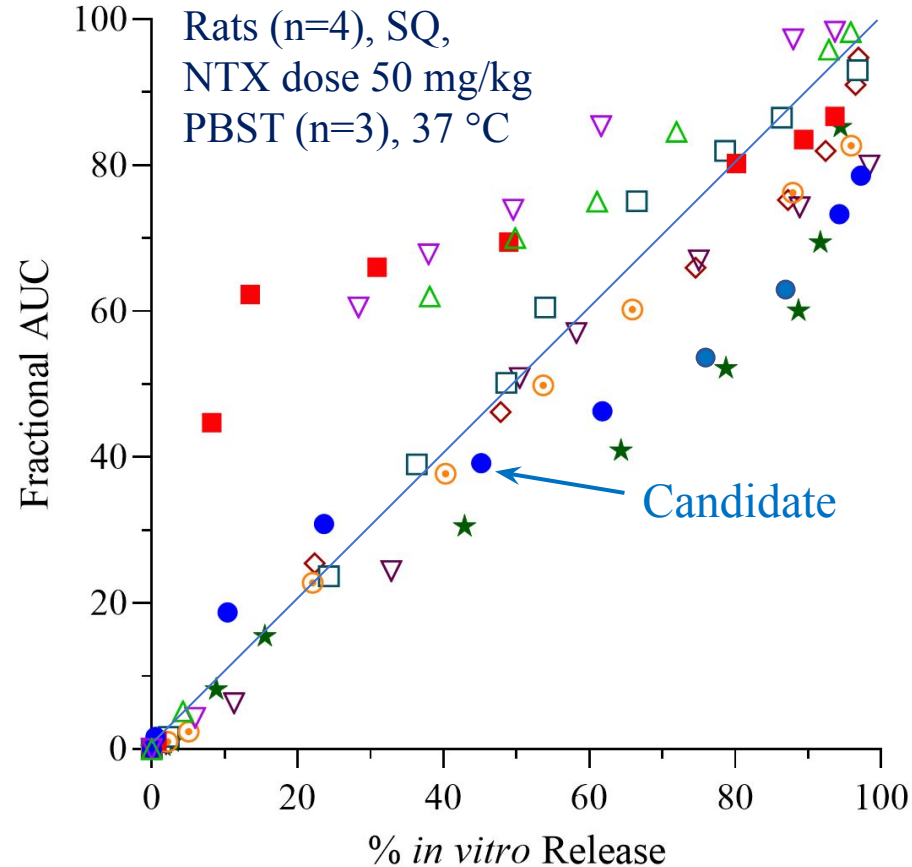
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Candidate Lab Scale Formulation

1. High Naltrexone loading (33-35%).
2. The naltrexone concentrations in the blood remain within the Vivitrol range.
3. Scalable formulation (e.g., low η).



Plasma concentration profile of the candidate long-acting naltrexone benchtop formulation (rats, n=4, SC, 50 mg/kg).

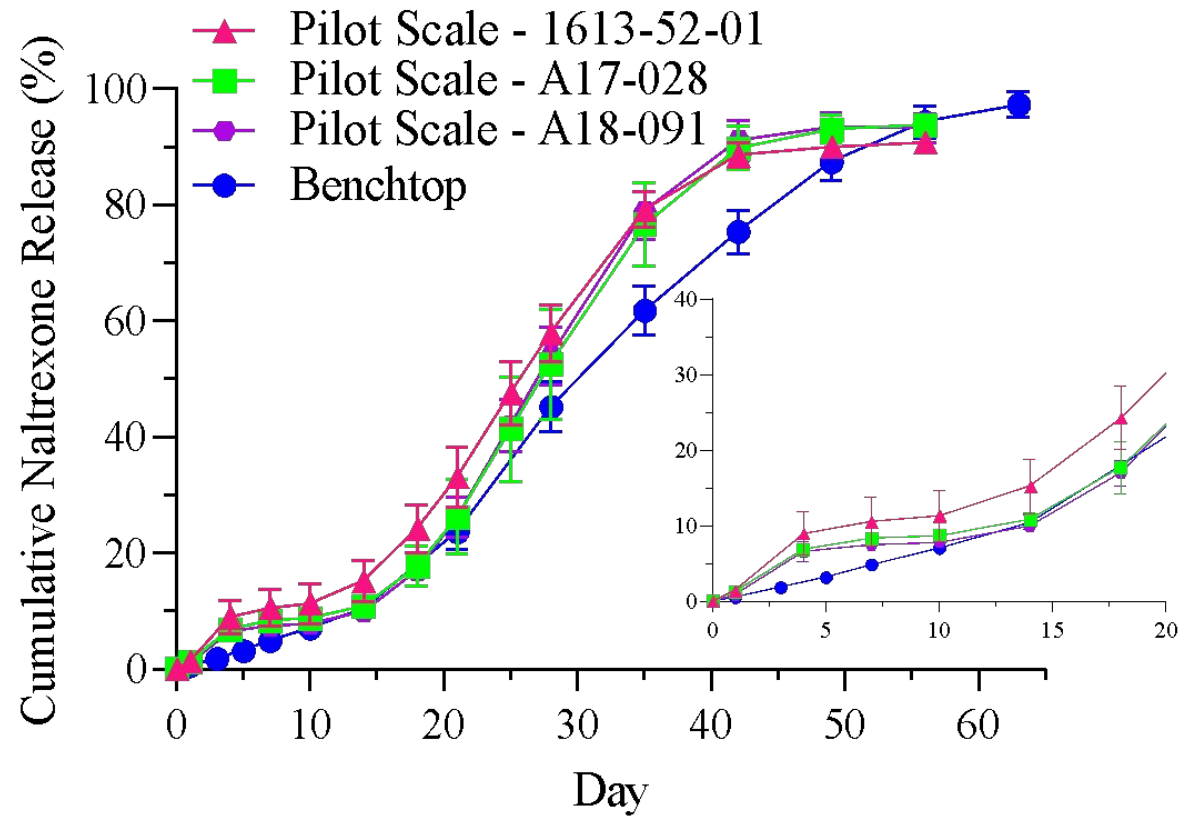


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Lab to Pilot Comparison – Loading, Release, & Size



Lot#	Scale	NTX Loading (%)	EE (%)	Residual BA (%)
A18-091	Benchtop	34.7 (0.8)	86.8	0.73 (0.01)
A18-091	Pilot	35.9 (1.0)	89.9	1.22 (0.03)*
A17-028	Pilot	36.2 (0.1)	90.6	1.12 (0.03)*
1613-52-01	Pilot	36.4 (0.7)	91.1	1.11 (0.02)*

Lot#	Scale	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
A18-091	Benchtop	38.5 (1.1)	69.1 (1.6)	106.4 (3.1)
A18-091	Pilot	35.0 (0.7)*	68.3 (2.3)	111.4 (4.1)
A17-028	Pilot	35.5 (1.3)	65.6 (1.5)	106.8 (3.9)
1613-52-01	Pilot	32.8 (1.2)*	62.3 (0.3)*	101.5 (1.3)

*statistically significant difference relative to the benchtop formulation



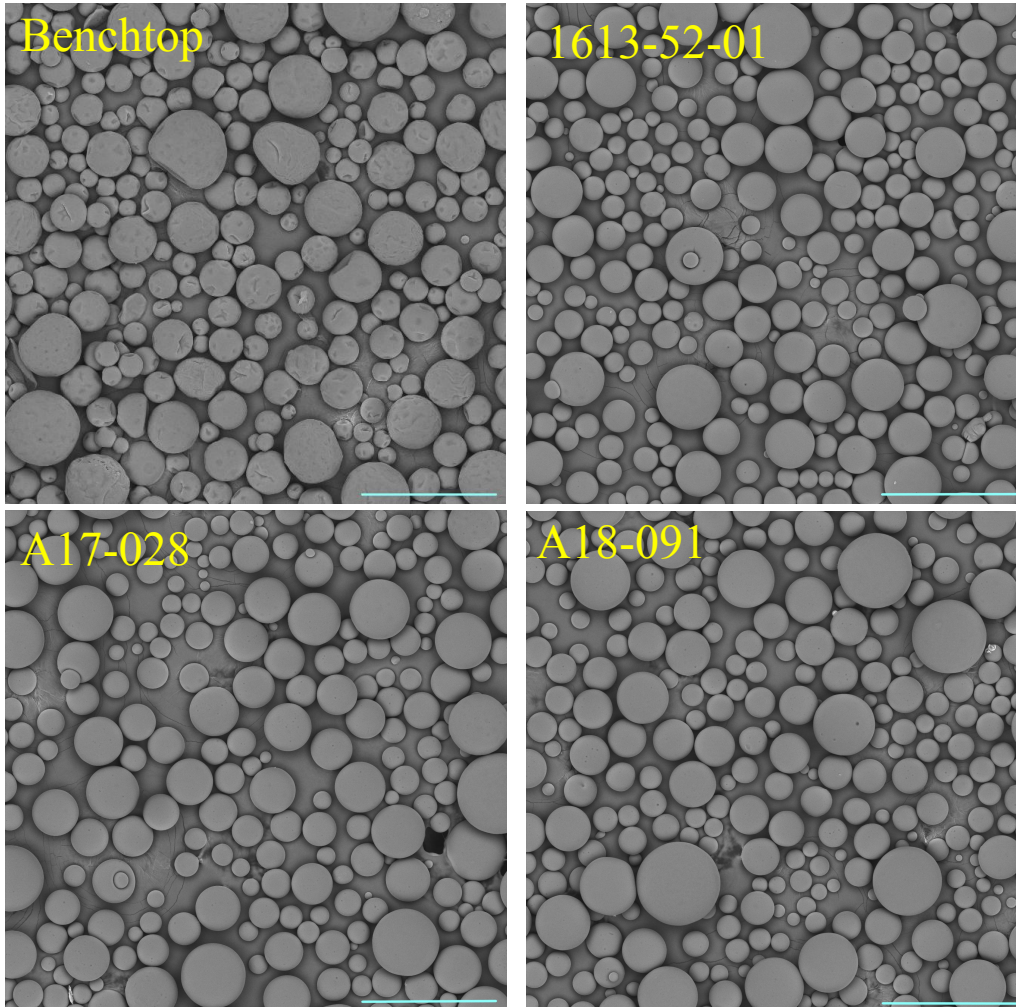
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Lab to Pilot Comparison – Morphology & Mw



Molecular weights of PLGA as received.

PLGA	Lot #	M_n (kDa) ($\pm$ SD)	M_w (kDa) ($\pm$ SD)	M_z (kDa) ($\pm$ SD)	MHS slope*
Lactel B6006-2P	A17-028	66.016 ± 0.377	78.198 ± 0.456	94.406 ± 1.107	0.648
	A18-091	66.038 ± 0.250	79.689 ± 0.114	96.626 ± 0.507	0.652
	1613-52-01 (R&D Only)	58.277 ± 0.279	74.102 ± 0.259	93.901 ± 0.738	0.637

Molecular weights of Pilot Scale Batches.

PLGA	Lot #	M_n (kDa) ($\pm$ SD)	M_w (kDa) ($\pm$ SD)	M_z (kDa) ($\pm$ SD)	MHS slope
Lactel B6006-2P	A17-028	43.470 ± 0.149	57.072 ± 0.181	75.053 ± 0.547	0.622
	A18-091	43.607 ± 0.174	57.292 ± 0.184	75.108 ± 0.540	0.630
	1613-52-01 (R&D Only)	42.329 ± 0.193	55.729 ± 0.200	73.463 ± 0.579	0.620

*MHS slope: The slope a of the Mark-Houwink-Sakurada equation, $[\eta] = KM^a$



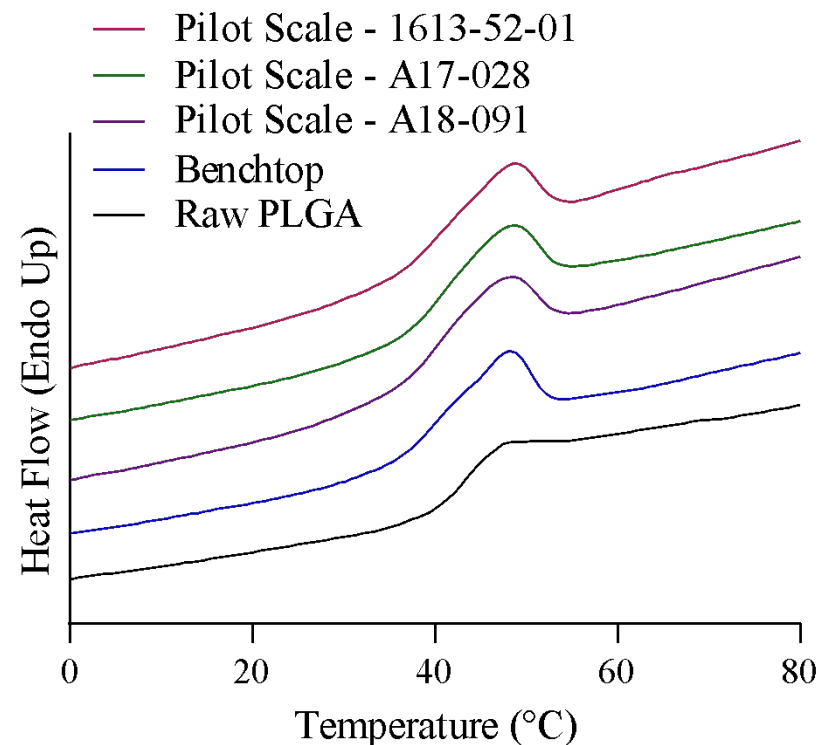
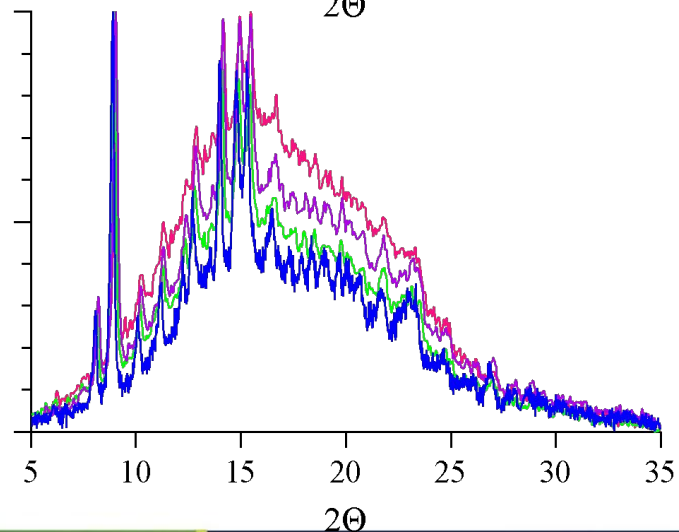
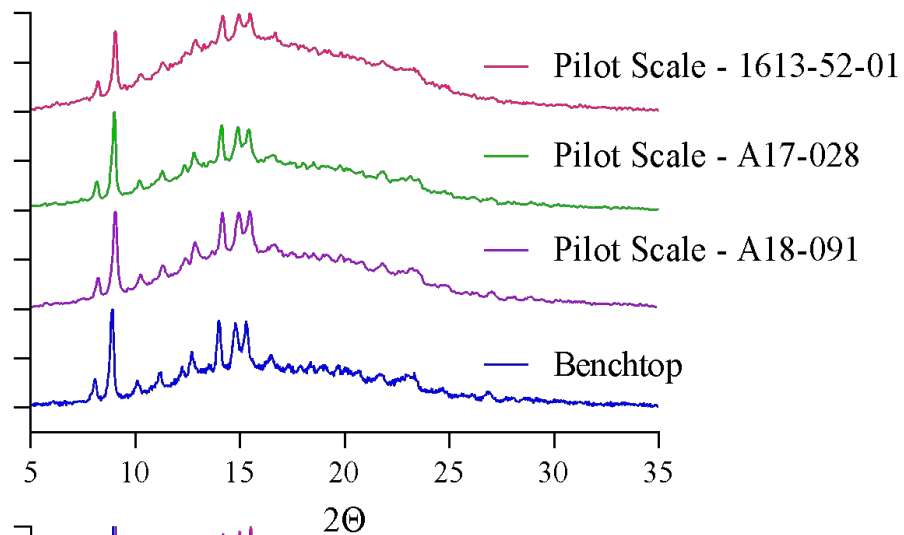
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Lab to Pilot Comparison – Solid State



	$T_{g, onset}$ (°C) ($\pm$ SD)
PLGA - A18-091	41.3 $\pm$ 1.1
PLGA - A17-028	42.8 $\pm$ 1.6
PLGA - 1613-52-01	42.3 $\pm$ 1.4
Benchtop	34.5 $\pm$ 0.2
Pilot Scale - A18-091	34.3 $\pm$ 0.7
Pilot Scale - A17-028	34.9 $\pm$ 0.6
Pilot Scale - 1613-52-01	34.8 $\pm$ 0.4



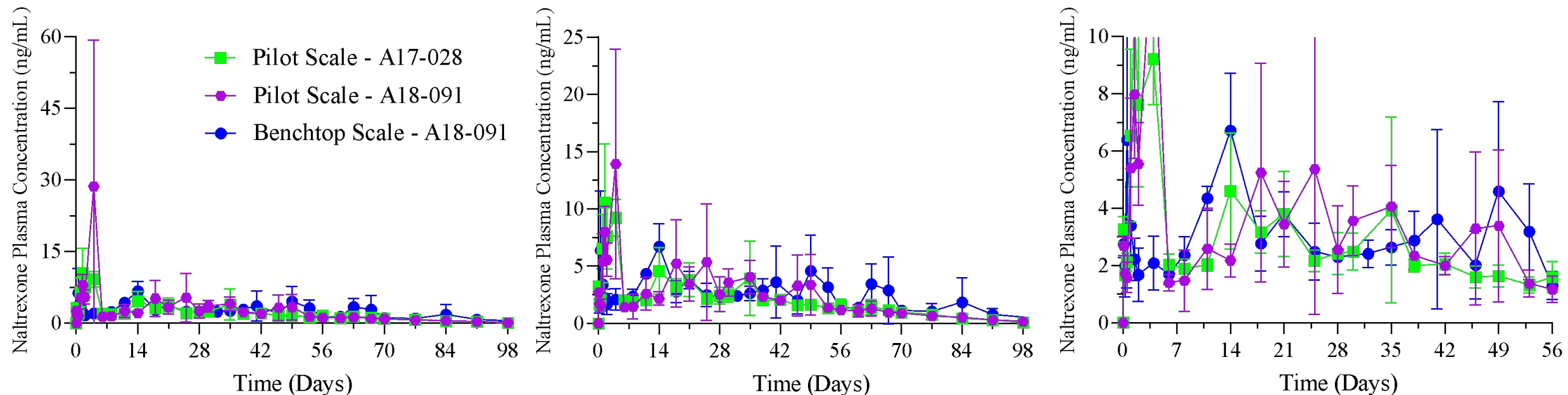
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Lab to Pilot Comparison – Pharmacokinetics



Formulation	AUC_{0-98} (ng•d/mL) $\pm$ SEM	C_{max} (ng/mL) $\pm$ SEM	T_{max} (day) $\pm$ SEM
Benchtop Scale A18-091	238.1 ± 21.0	9.98 ± 1.41	26.13 ± 11.36
Pilot Scale A18-091	224.1 ± 25.1	13.60 ± 4.12	9.25 ± 5.25
Pilot Scale A17-028	196.9 ± 13.0	11.49 ± 1.92	2.00 ± 0.68



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