USE OF 3D-PRINTED ‘TABLETS’ AS A BIOPHARMACEUTICS INVESTIGATION TOOL

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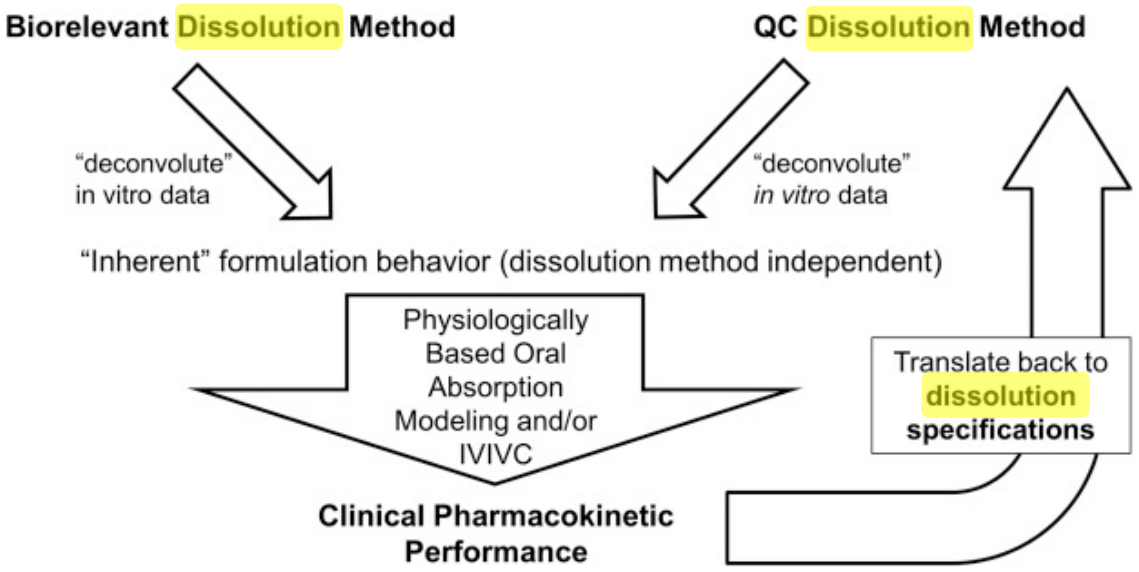
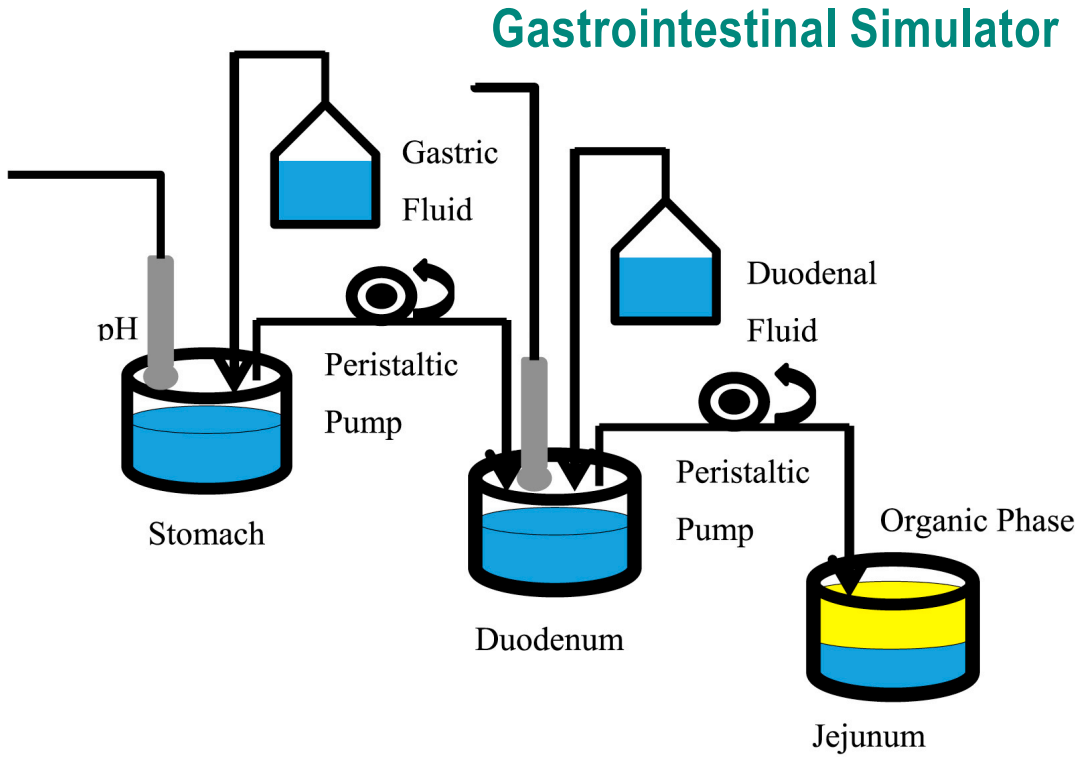
Adam T. Procopio, Derrick Smith, Yash Kapoor, Melanie Marota, Andre Hermans, Rebecca Nofsinger, Filippos Kesisoglou, Seth Forster, Jerry Klinzing, Ron Smith, Allen Templeton

Goal: to develop pre-clinical and clinical tools and approaches that improve the quality and timeliness of Oral Drug Product development

Biopharmaceutical Tools and Approaches



F. Kesisoglou - *J. Pharm. Sci. 106 (2017)*



Y. Tsume, N. Igawa, A.J.Drelich, H. Ruan, G.E.Amidon, G.L. Amidon
*Journal of Drug Delivery Science and Technology (*2019)

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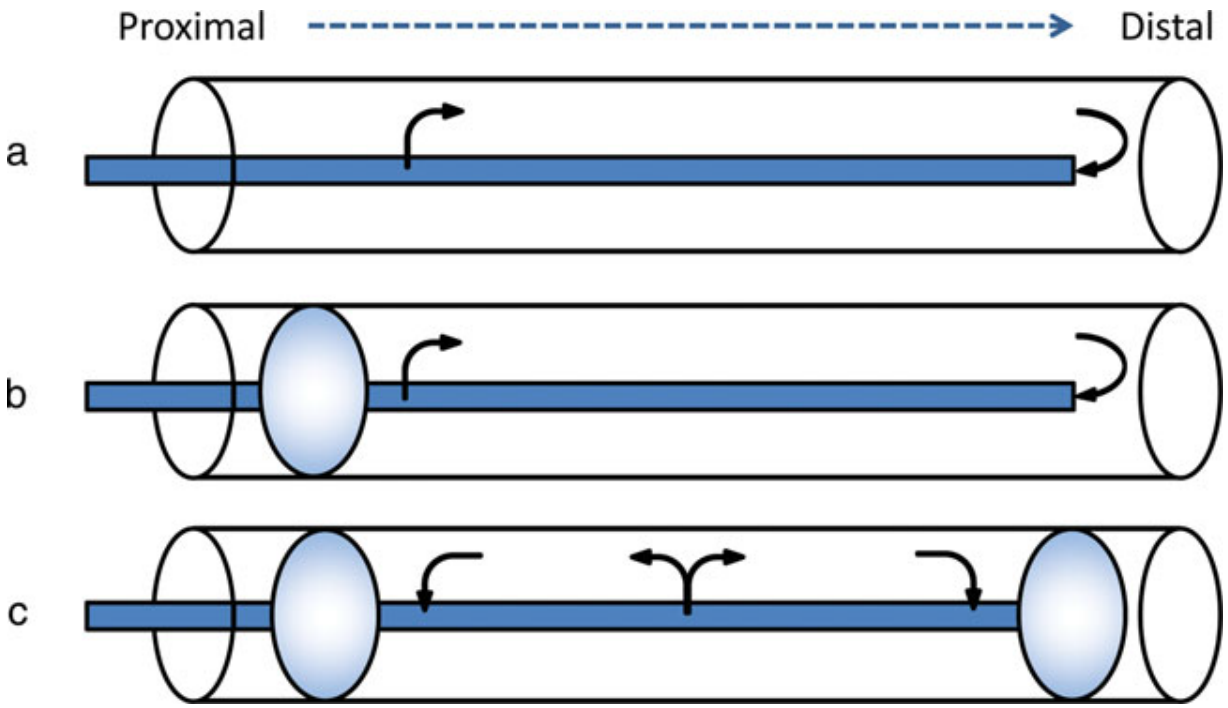
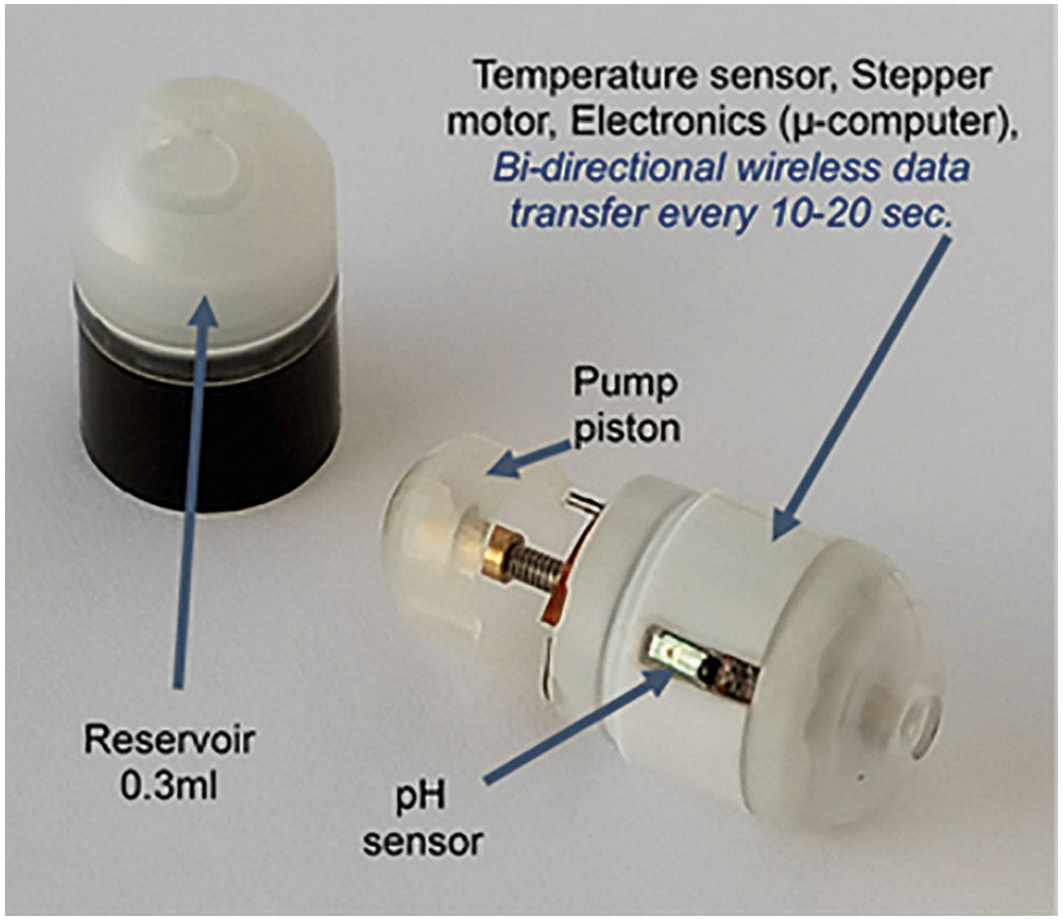
Regional Absorption Challenges



Dahlgren, Roos, Sjögren, Lennernäs; *Direct in vivo human intestinal permeability determined with different clinical perfusion intubation methods,* **2014** J Pharm Sci, 104



Becker et al, *Novel orally swallowable Intellicap device,* **2014** AAPS PharmSiTech, 15

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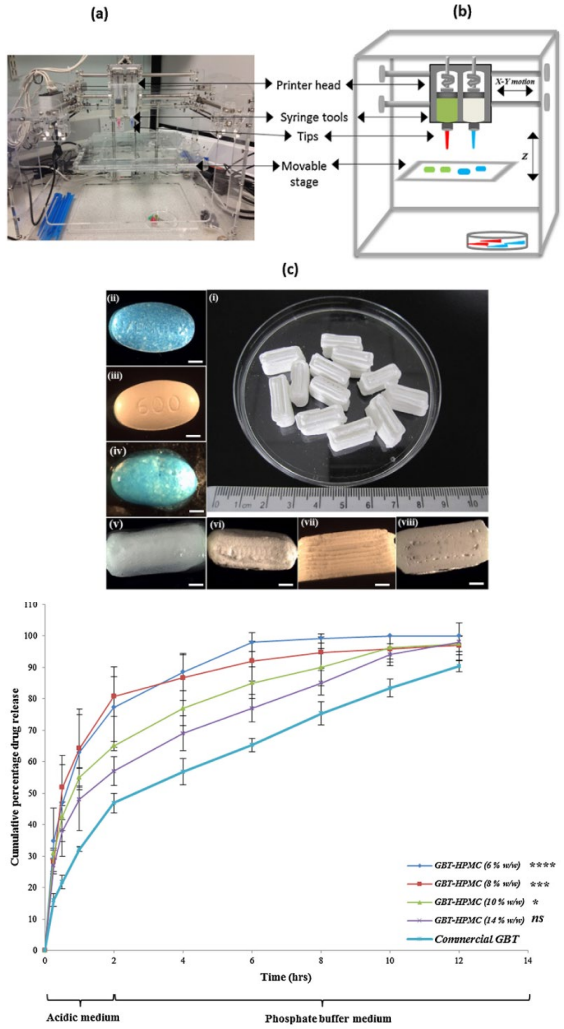
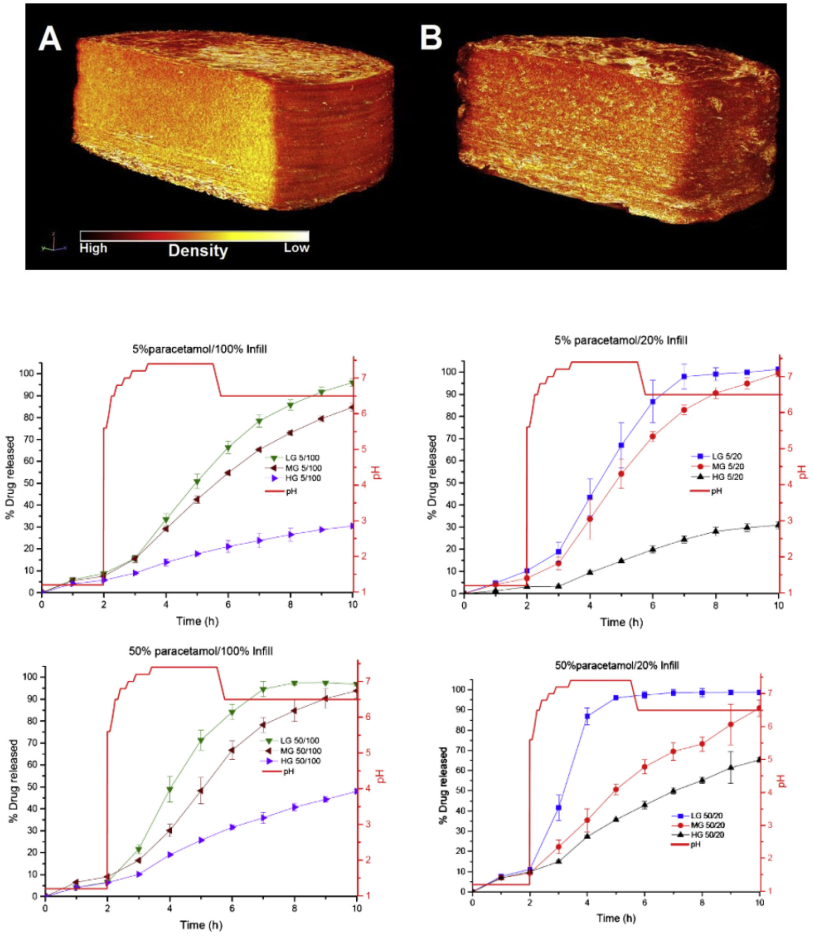
Select Examples of 3D Printing to Control Drug Release Rate

Gel printing



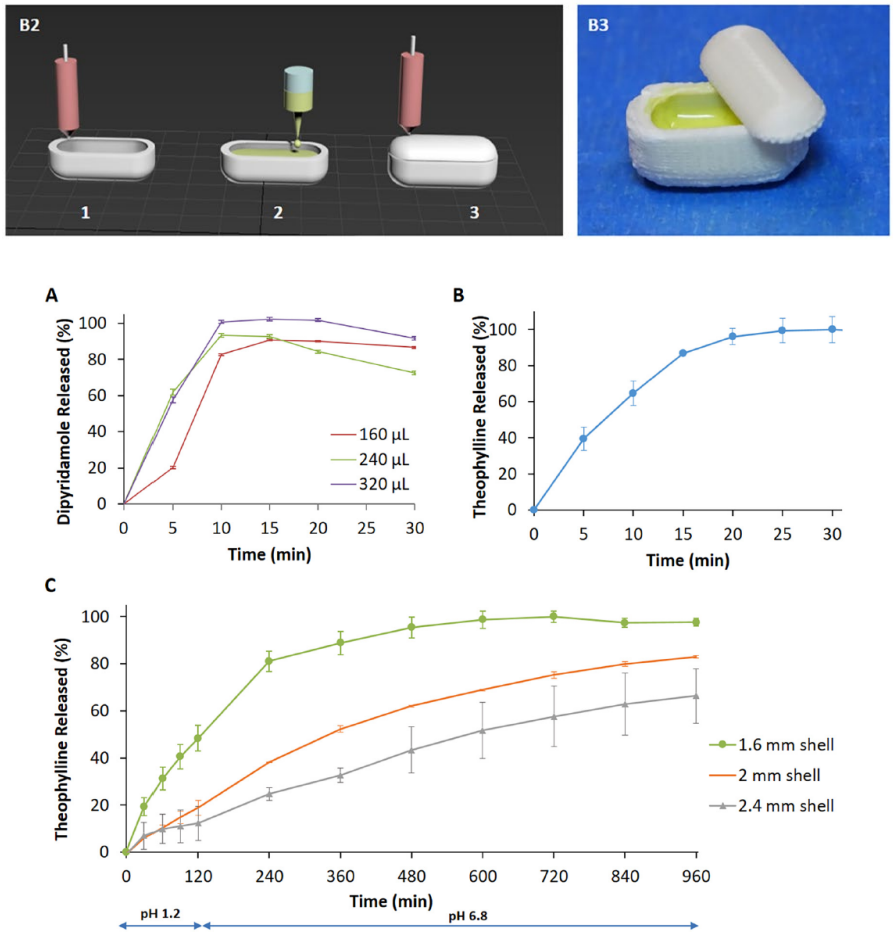
S.A. Khaled et al. Int. J. Pharm., 462 (2016)

HME Matrix



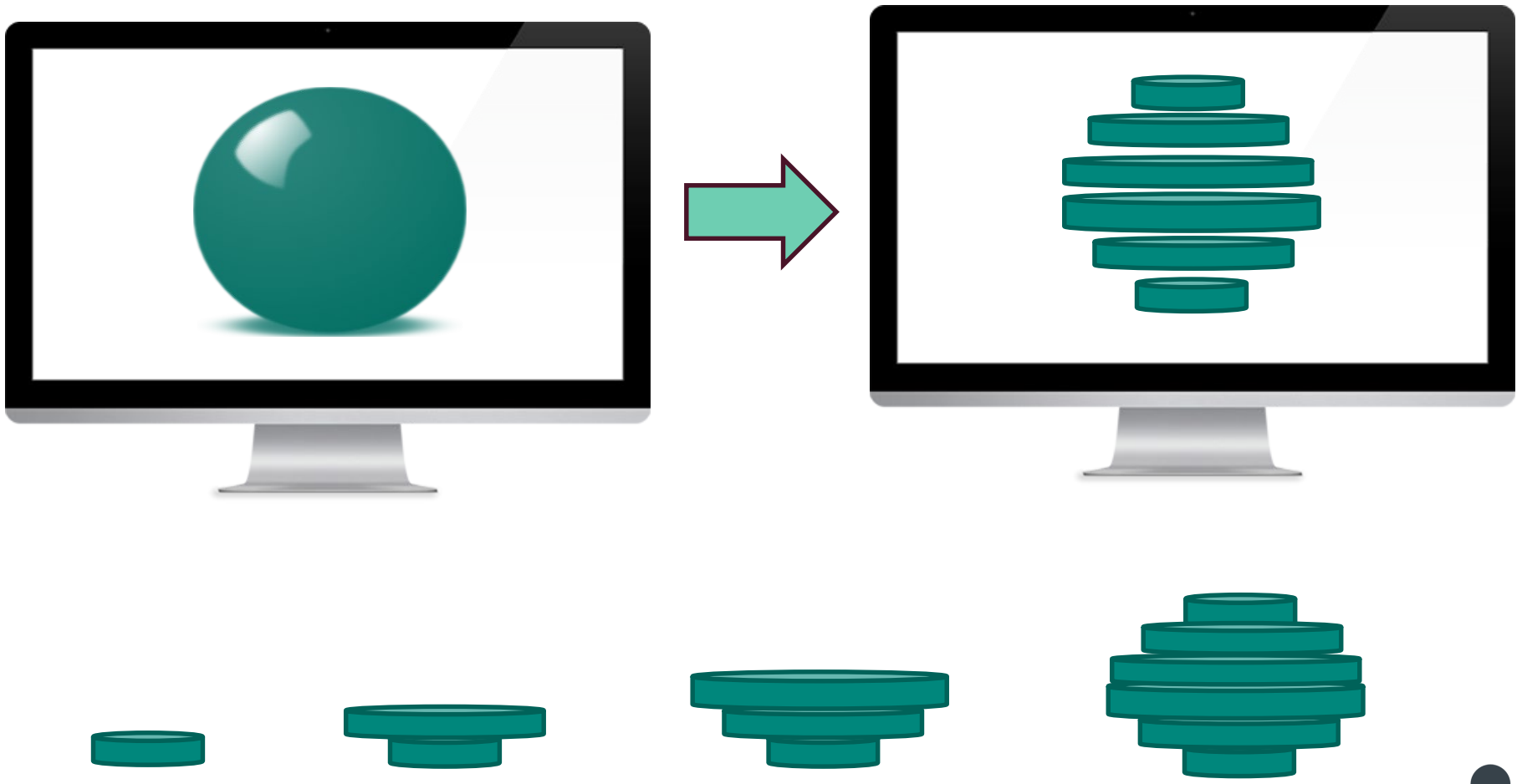
A. Goyanes et al. Int. J. Pharm., 527 (2017)

Core-Shell



T.C. Okwuosa et al. Euro. J. Pharm Sci., 118 (2018)

What is 3D Printing (3DP)?



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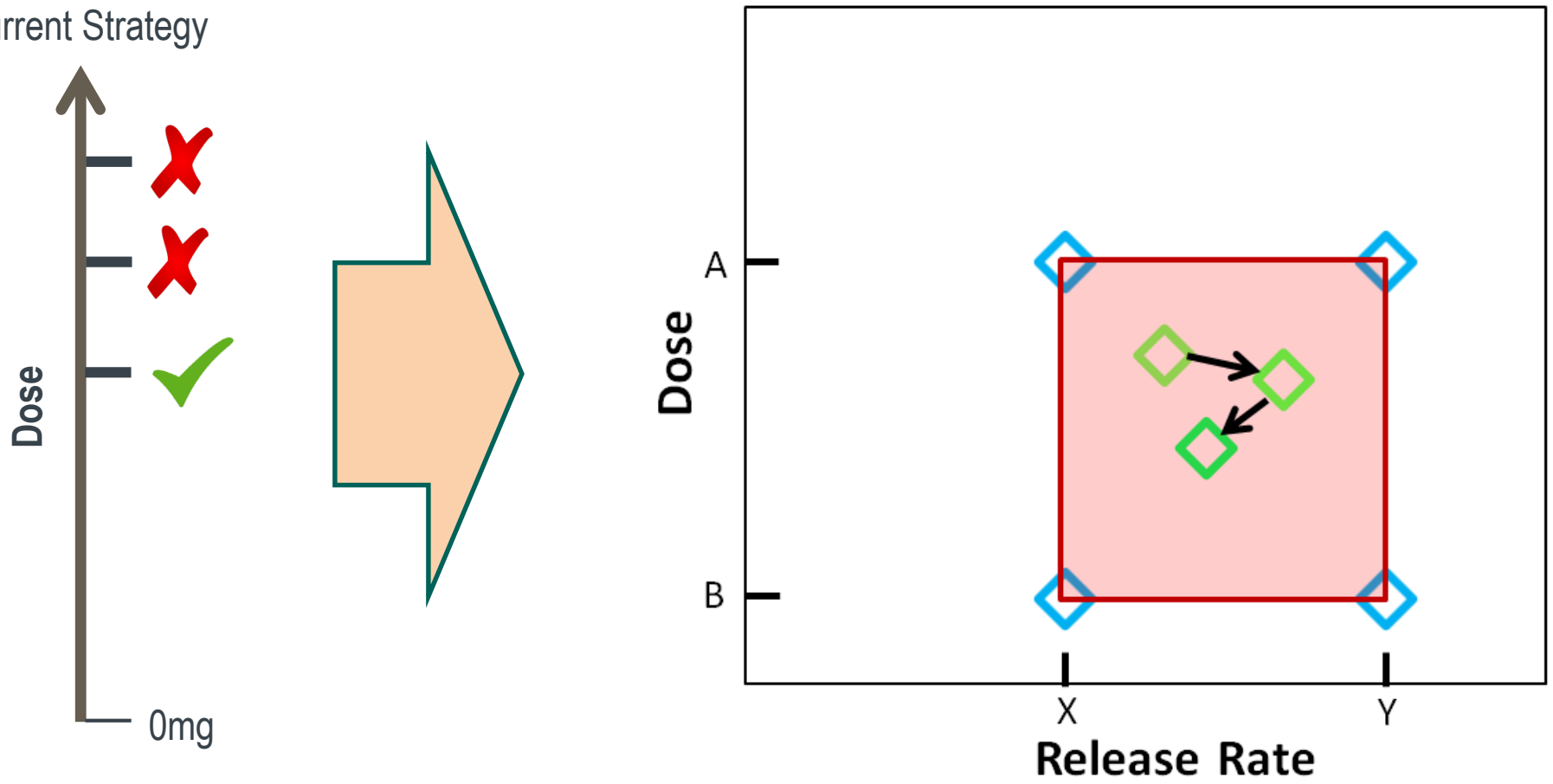
Expanding Formulation Design Space for Ph1-Ph2a Clinical Trials



- Feedback during the dosing cycle allows iterations of the formulation to be dosed in subsequent panels
- Increased POS of meeting the PK target compared to the standard paradigm

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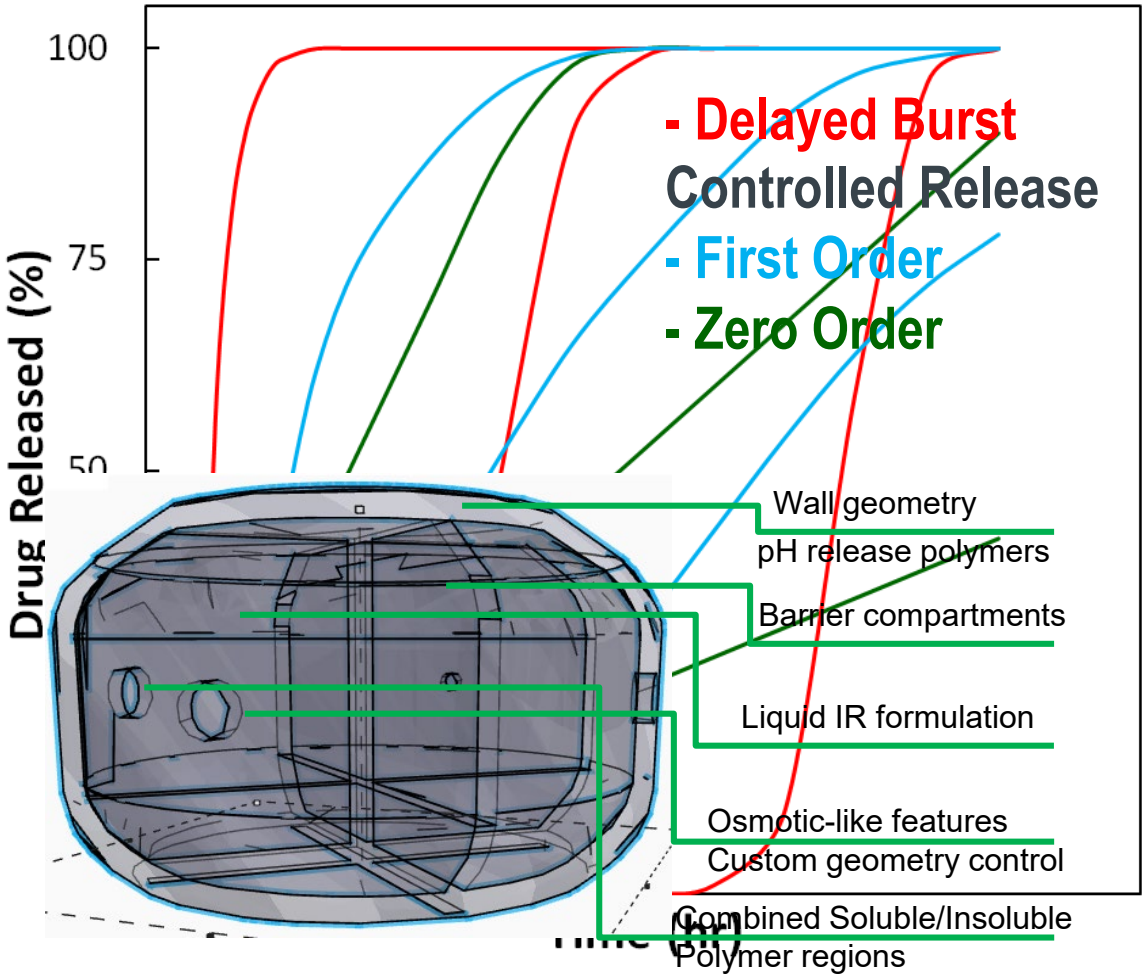
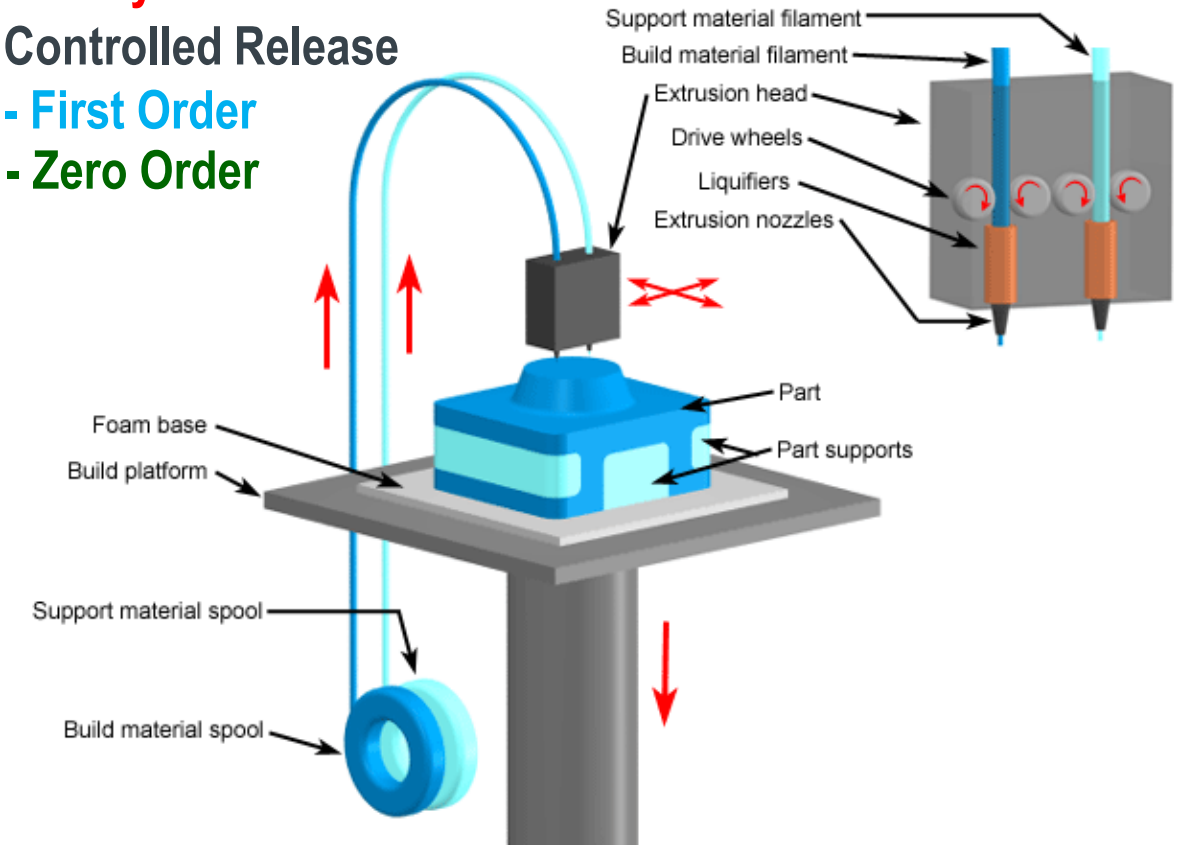
Expanding Formulation Design Space for Ph1-Ph2a Clinical Trials



Fused Deposition Modeling

- Delayed Burst
Controlled Release
- First Order
- Zero Order



*** All without modifications to API formulation composition**

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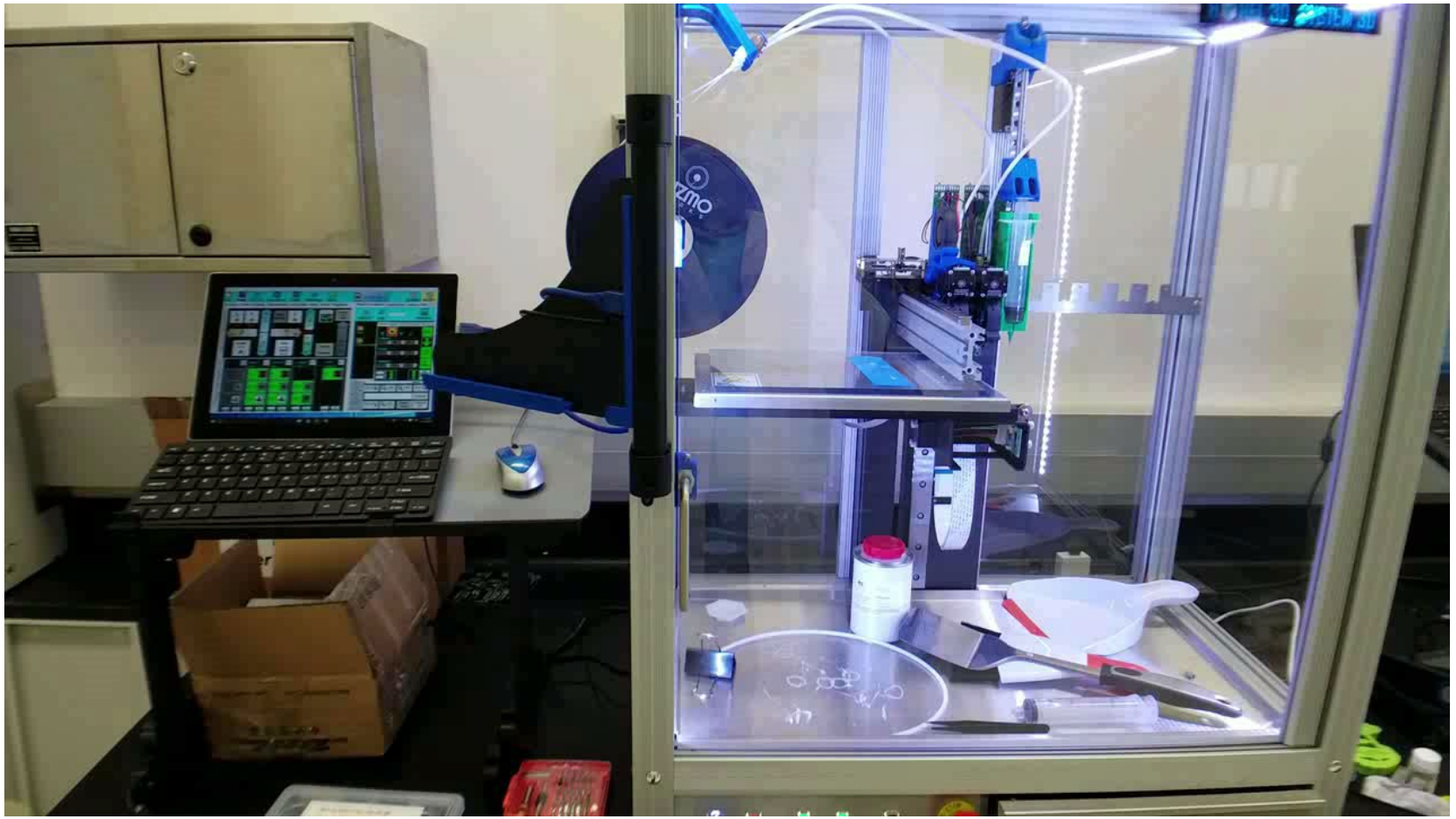
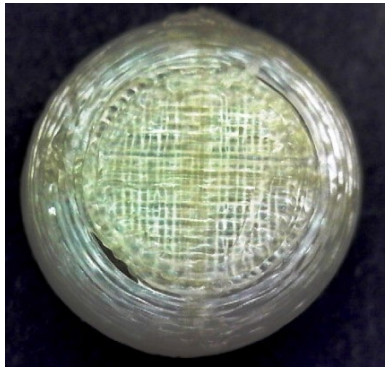
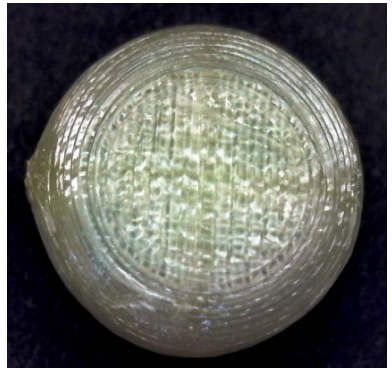
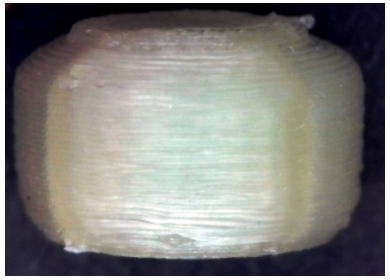
Capsule Strategy – Delayed Release

Print Conditions:
180°C Temp
10mm/s Speed
10% Fan Speed









Optimized Settings
"As Sliced"

Zoned

Polyvinyl alcohol (PVA) capsule shell with Metformin gel filling

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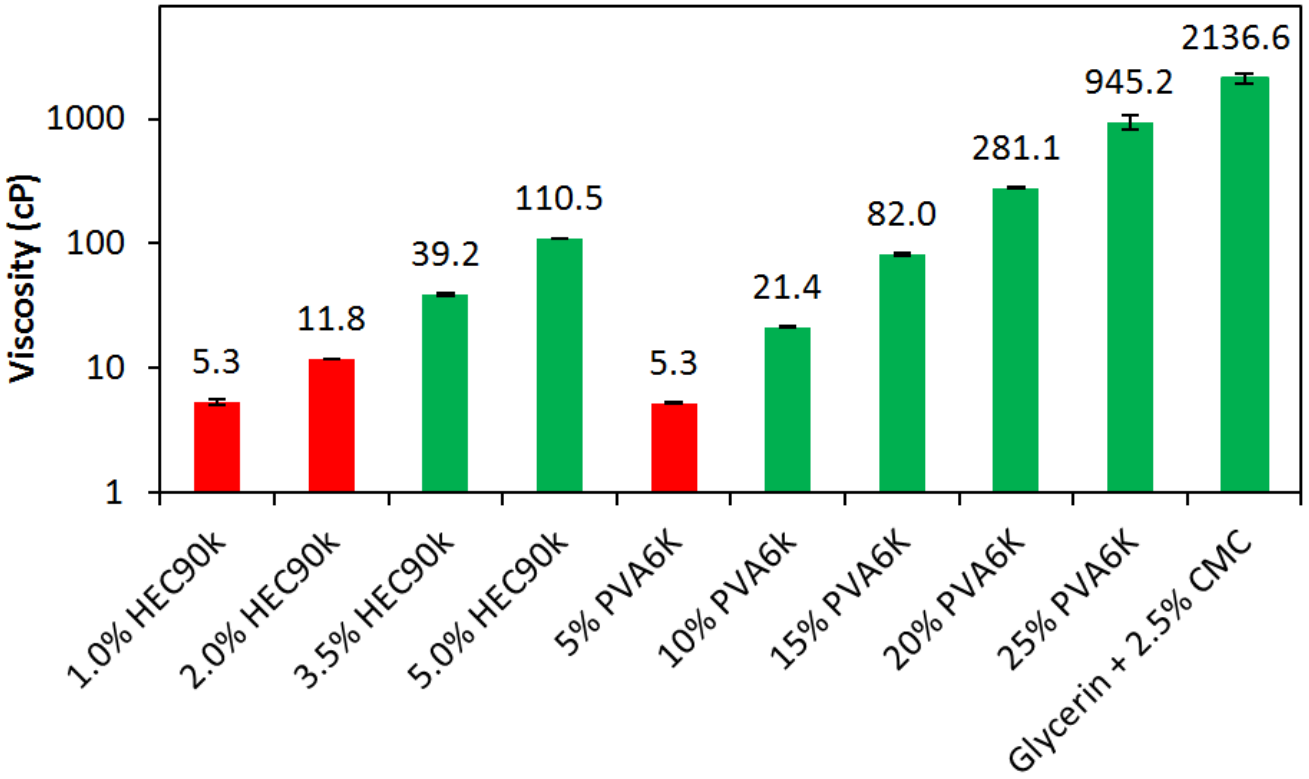
Initial Qualifications

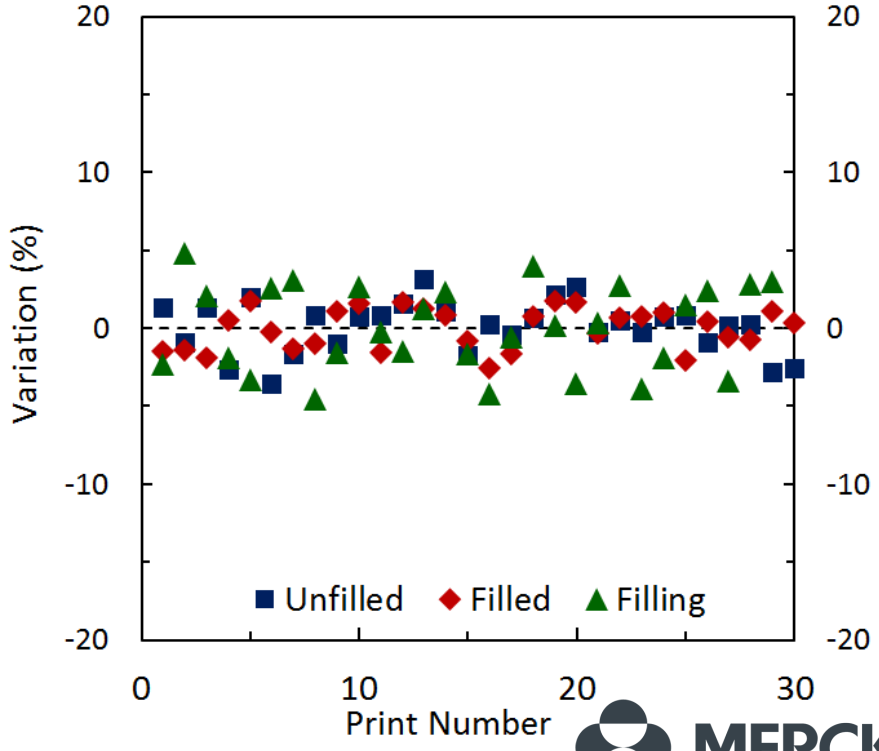
Non-Flow Control:

Liquids/Gels require > 20 cP to not drip during capsule printing



Flow Control:

Less than 5 wt% variability for prints: 1.31% RSD for filled capsules



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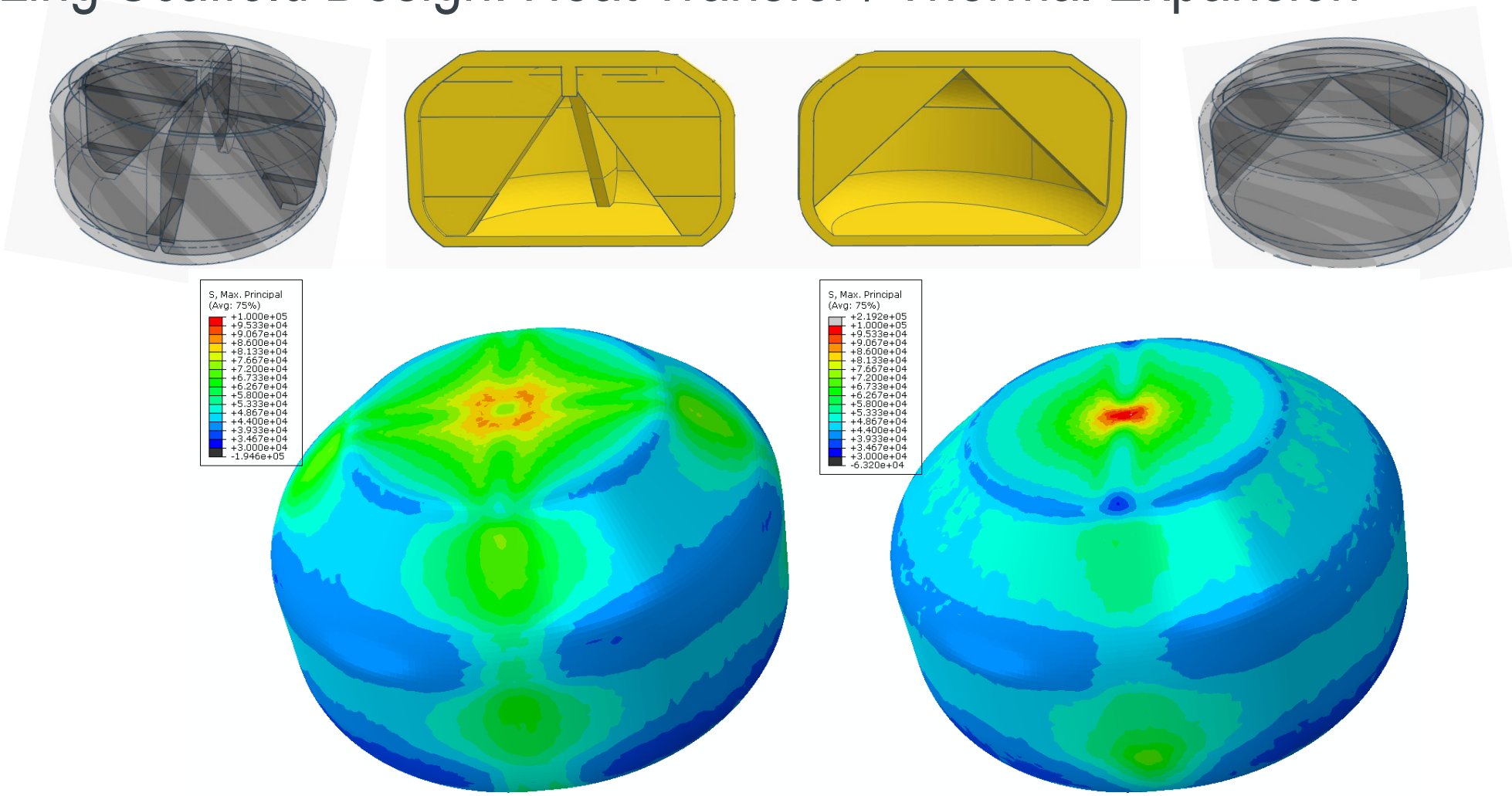
Optimizing Scaffold Design: Heat Transfer / Thermal Expansion



2 fin design reduces internal stresses from expansion by a factor of 2-3

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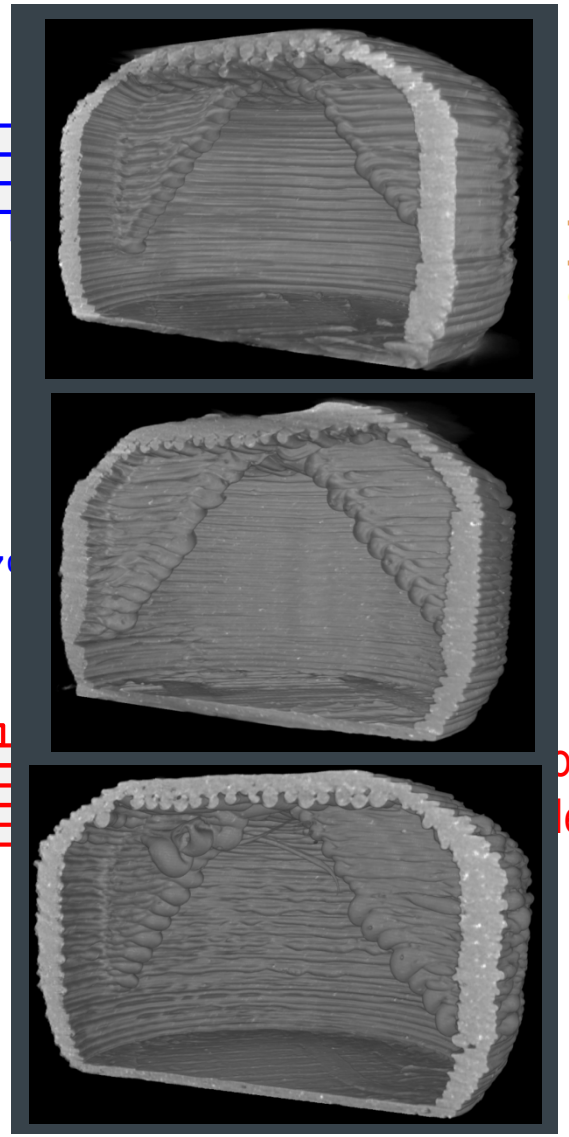
D.M. Smith et al. Int. J. Pharm., 544 (2018)

Optimizing Mechanical Properties

Minimum Layer-Layer Overlap



0.35 mm nozzle,
10.0 mm/s

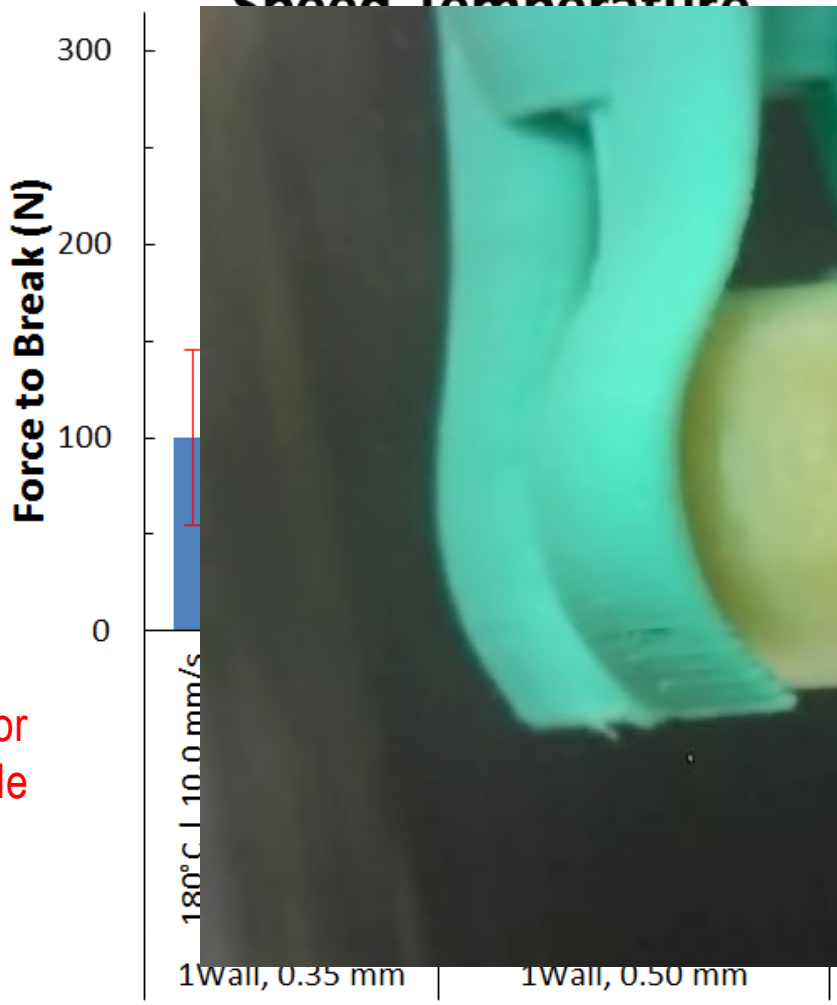
0.15 mm layers

0.35 mm nozzle,
16.0 mm/s

~67°

0.10 mm layer top

0.35 mm nozzle,
22.0 mm/s



Minimum Welding Temperature

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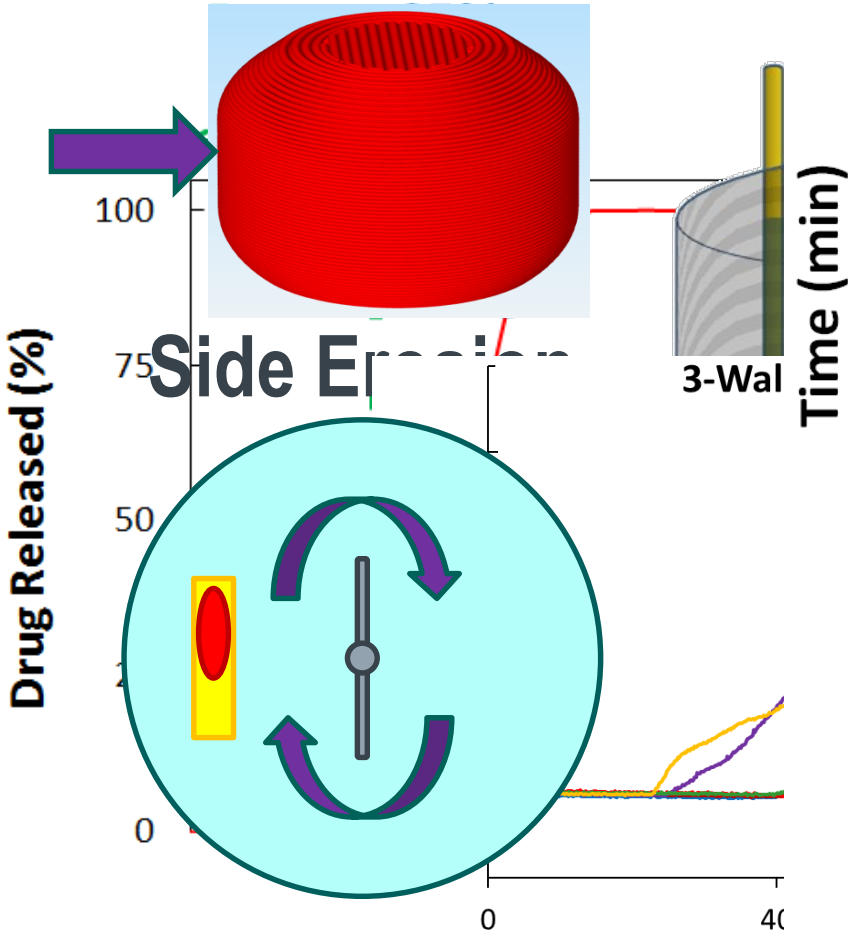
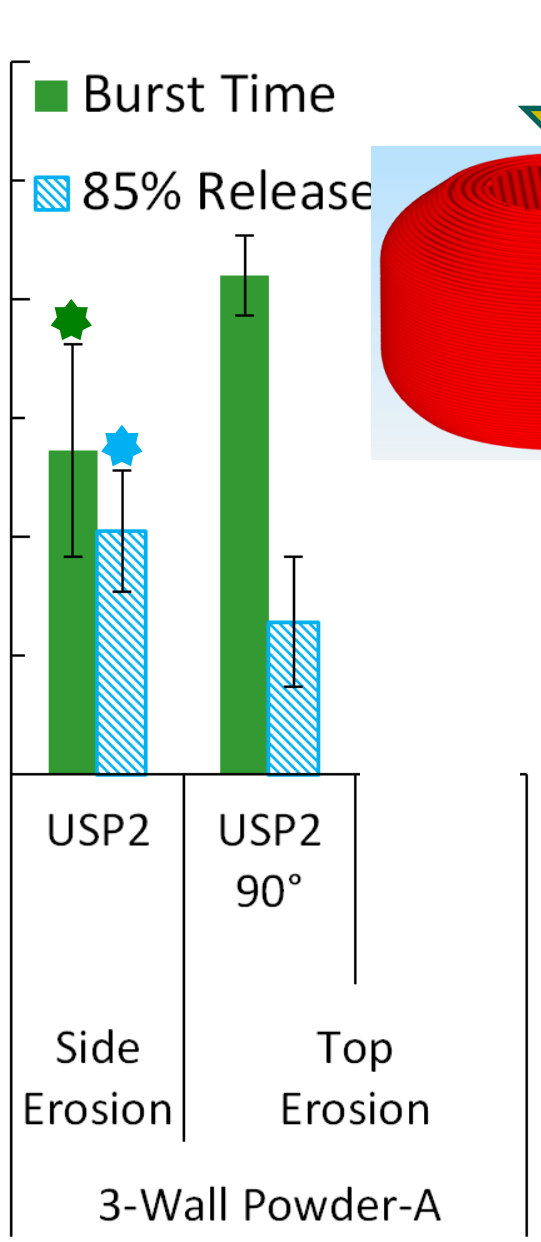
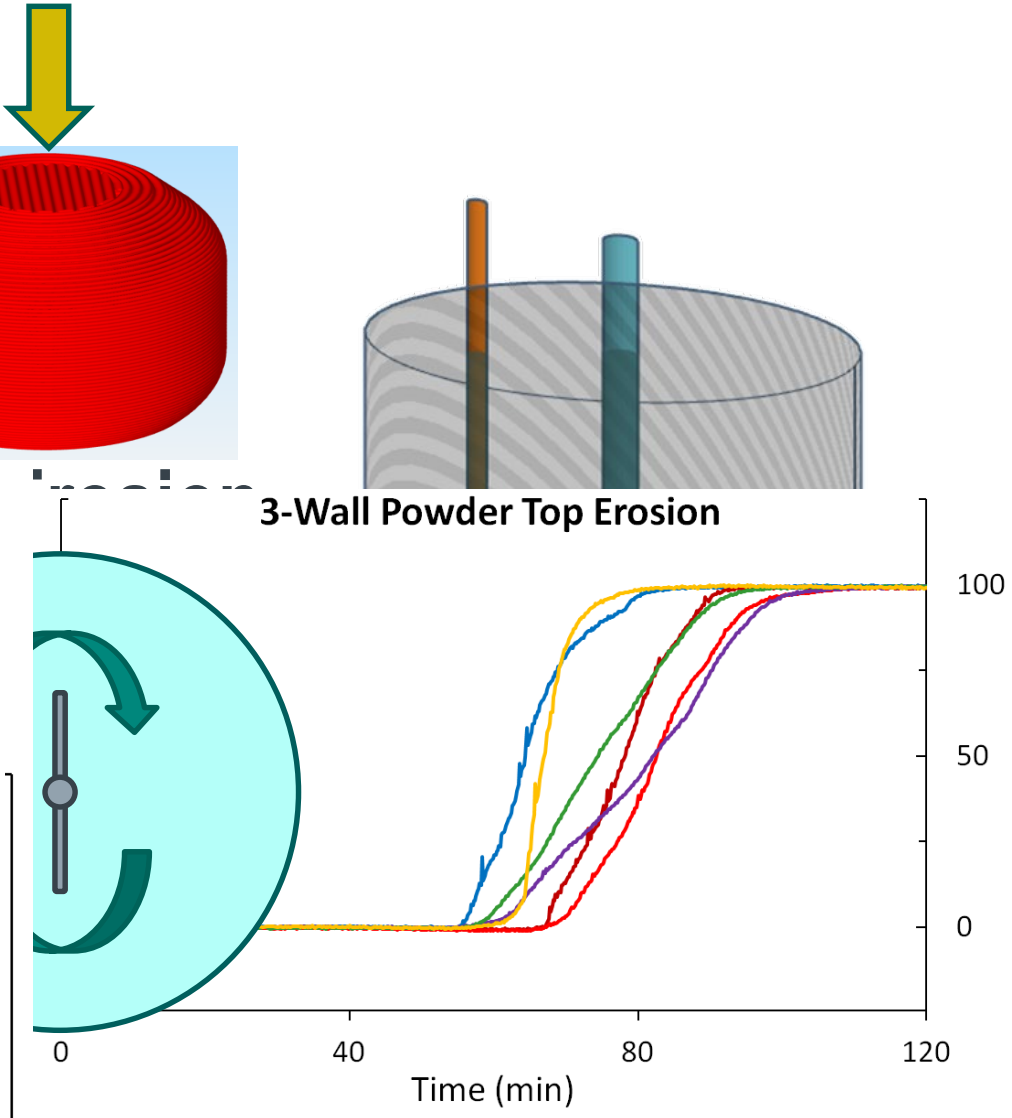
D.M. Smith et al. Int. J. Pharm., 544 (2018)

Anisotropic Dissolution







Powder A : proprietary API,
40mg, BCS Class I

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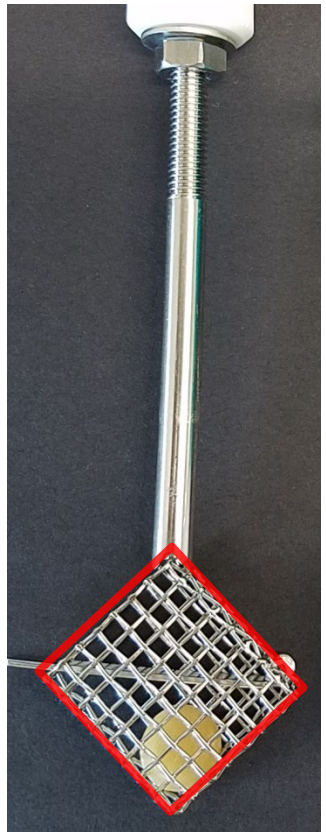
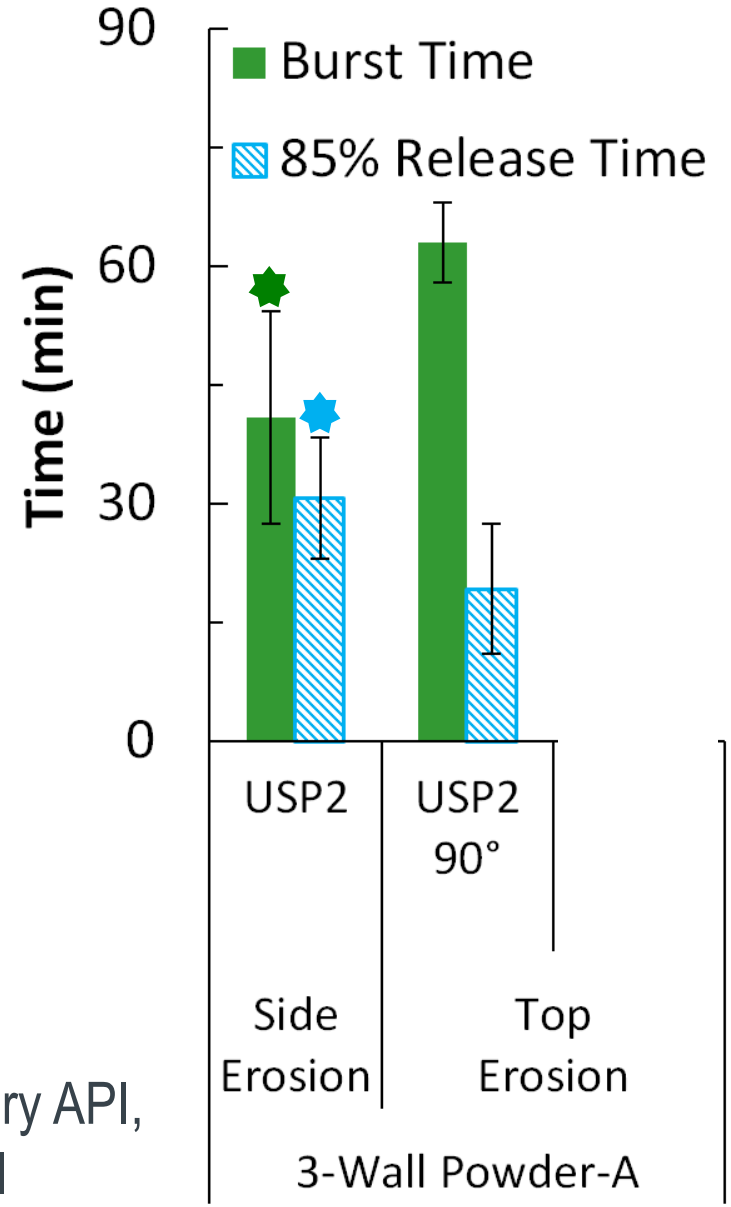
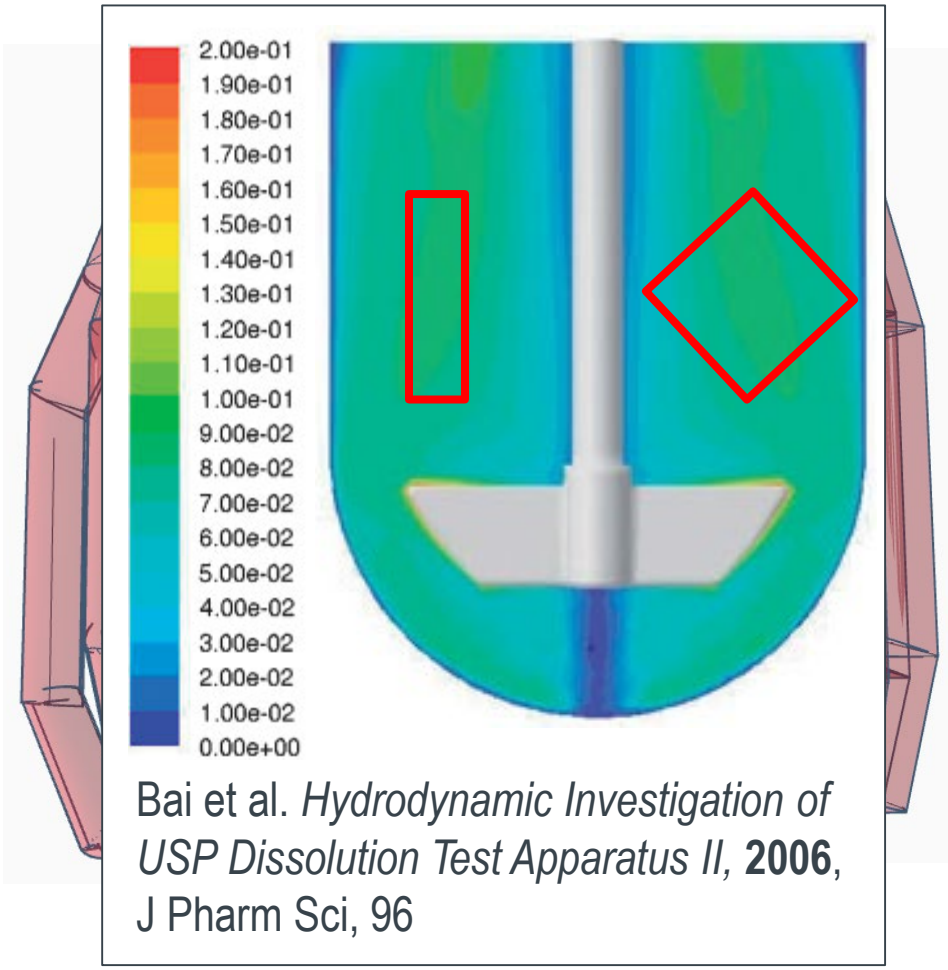
Anisotropic Dissolution







Bai et al. *Hydrodynamic Investigation of USP Dissolution Test Apparatus II,* **2006**, J Pharm Sci, 96

Powder A : proprietary API, 40mg, BCS Class I

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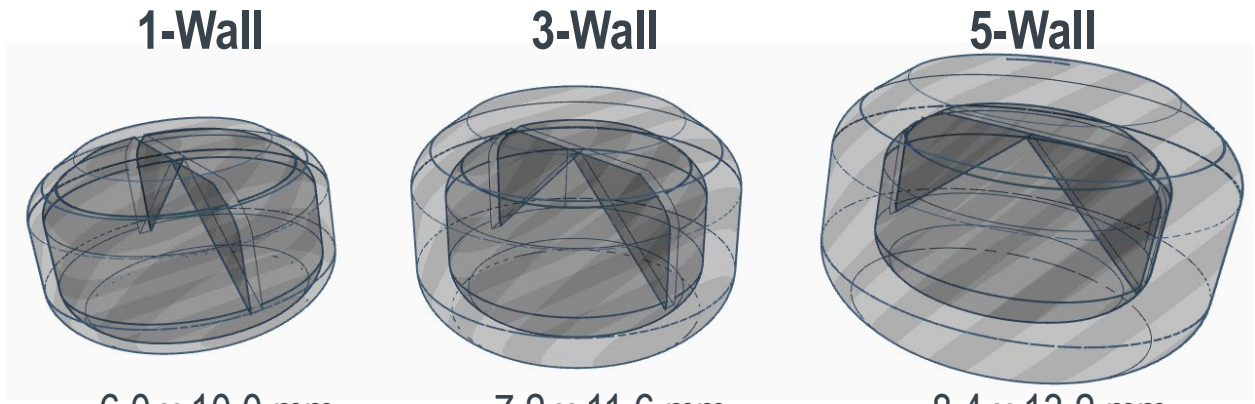
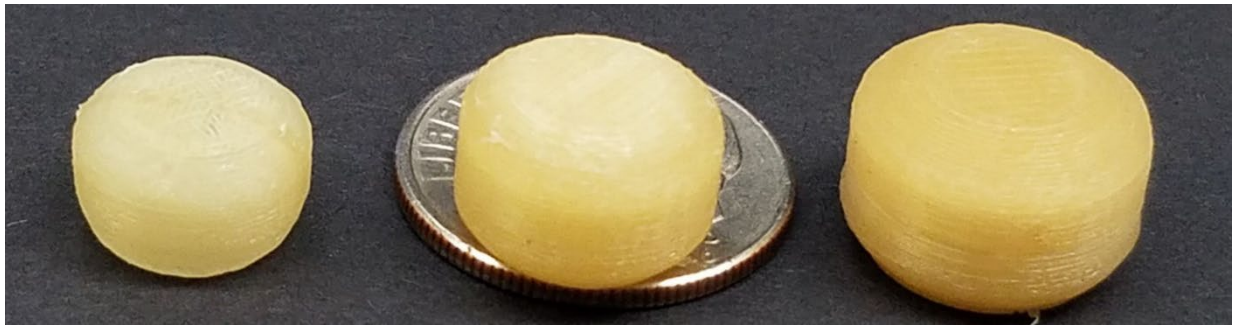
Burst Time Control Strategy

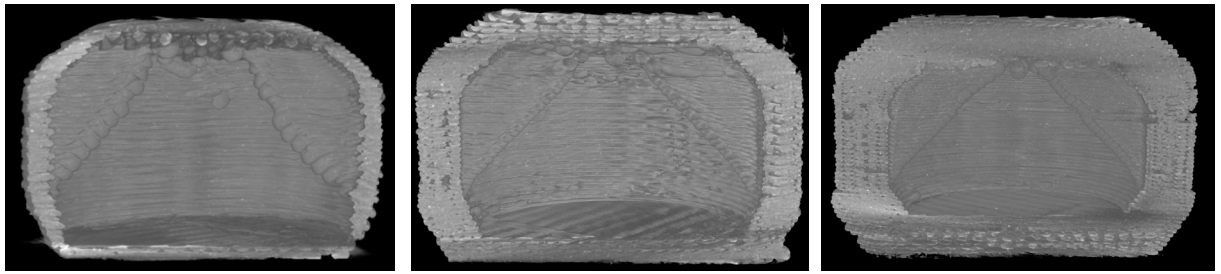


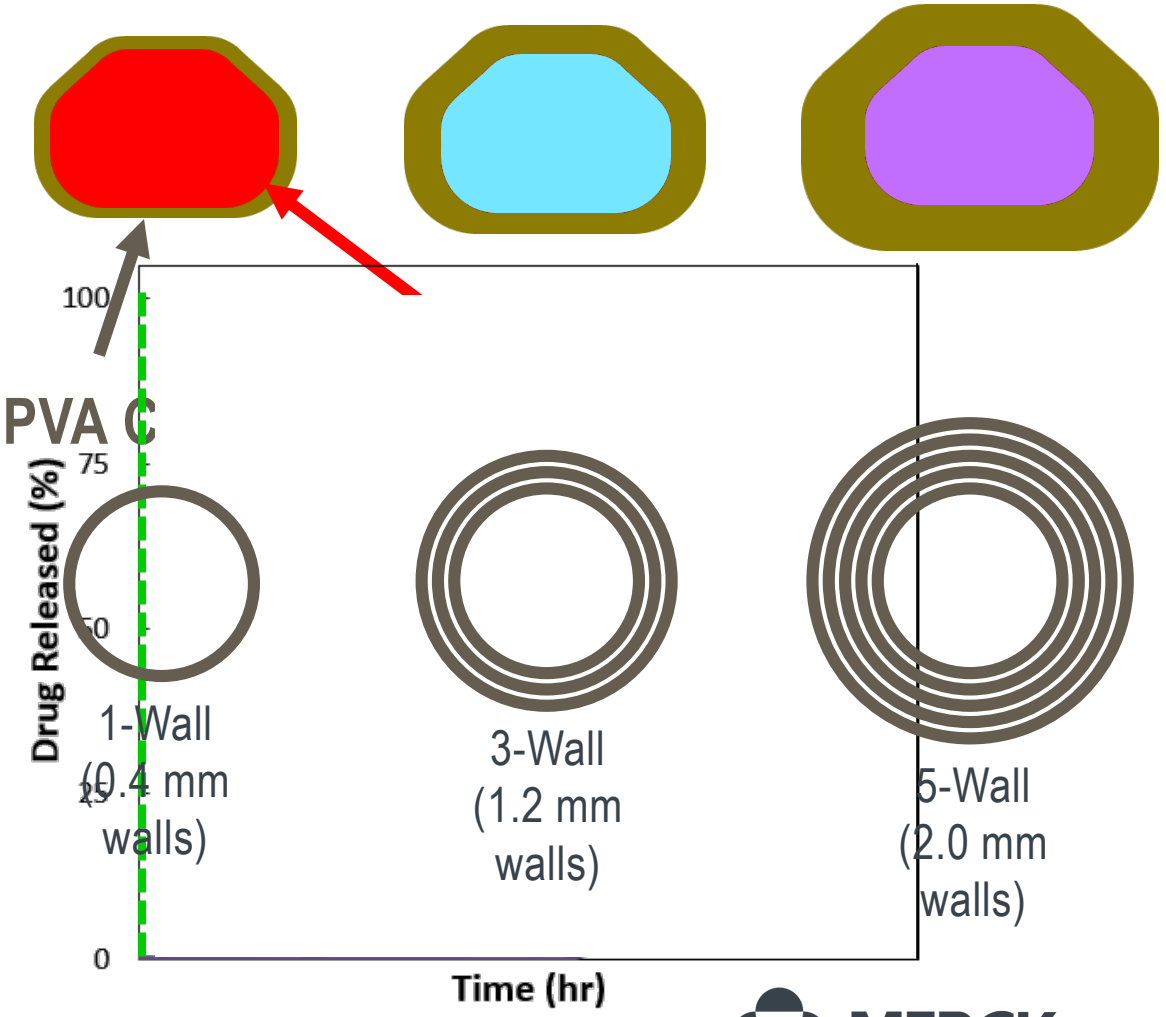
6.0 x 10.0 mm
0.4 mm Walls

7.2 x 11.6 mm
1.2 mm Walls

8.4 x 13.2 mm
2.0 mm Walls







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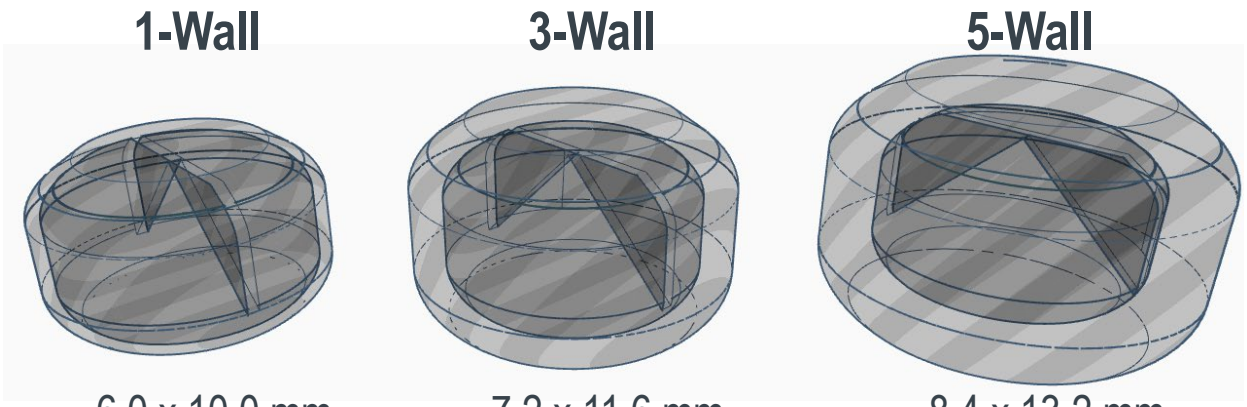
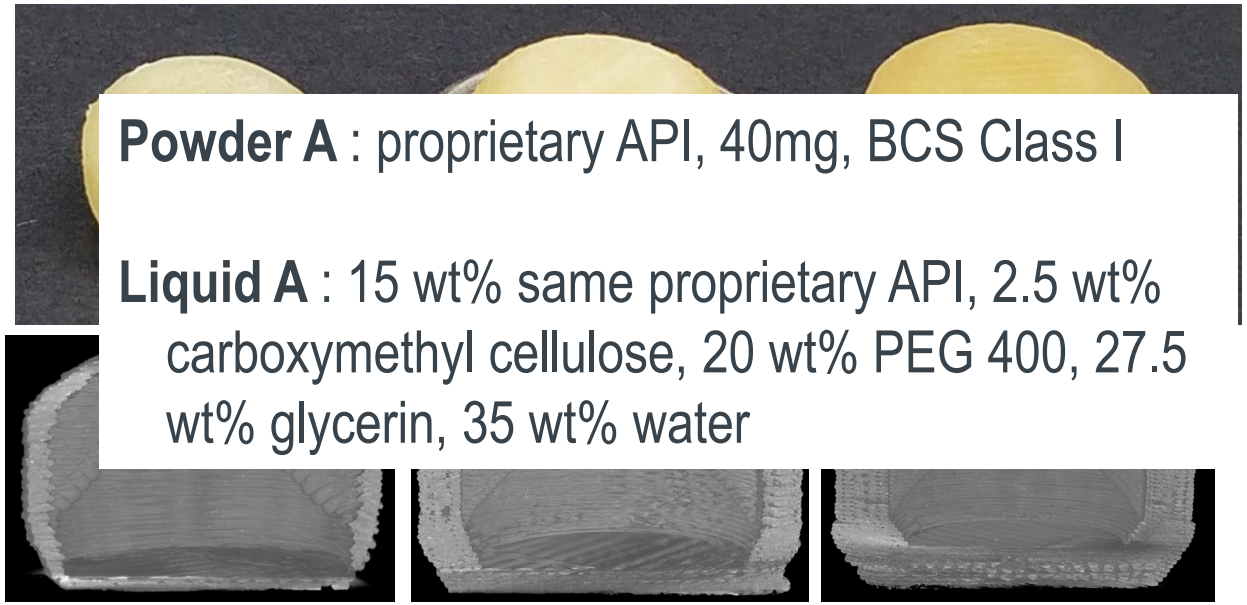
D.M. Smith et al. Int. J. Pharm., 550 (2018)

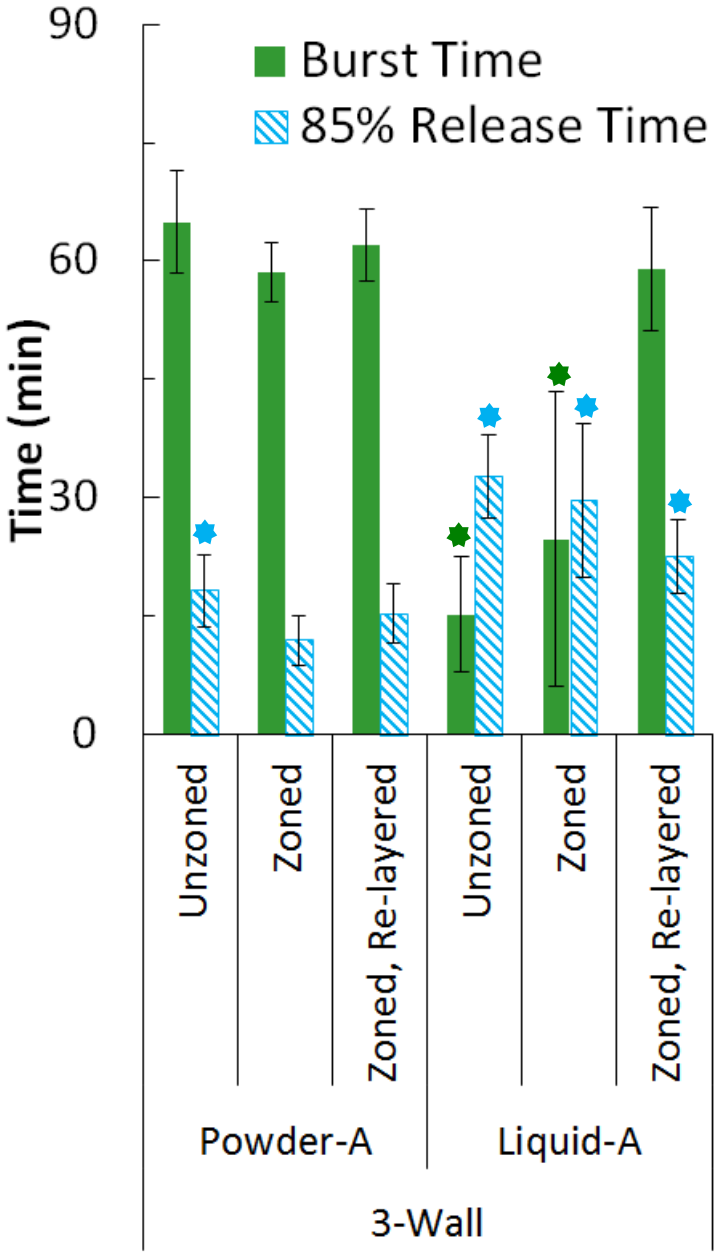
Burst Time Control Strategy





Powder A : proprietary API, 40mg, BCS Class I

Liquid A : 15 wt% same proprietary API, 2.5 wt% carboxymethyl cellulose, 20 wt% PEG 400, 27.5 wt% glycerin, 35 wt% water



Unzoned = raw sliced
Zoned = no macro defects
Zones Re-layered = enhanced mechanical proprties

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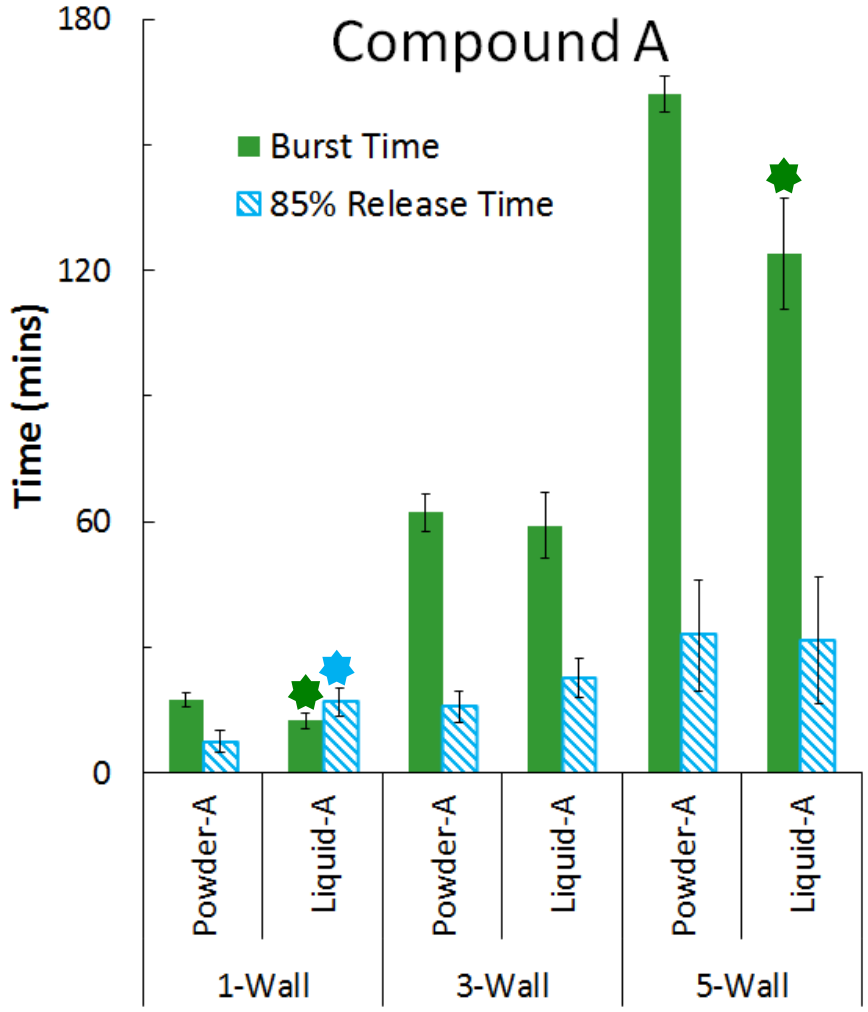
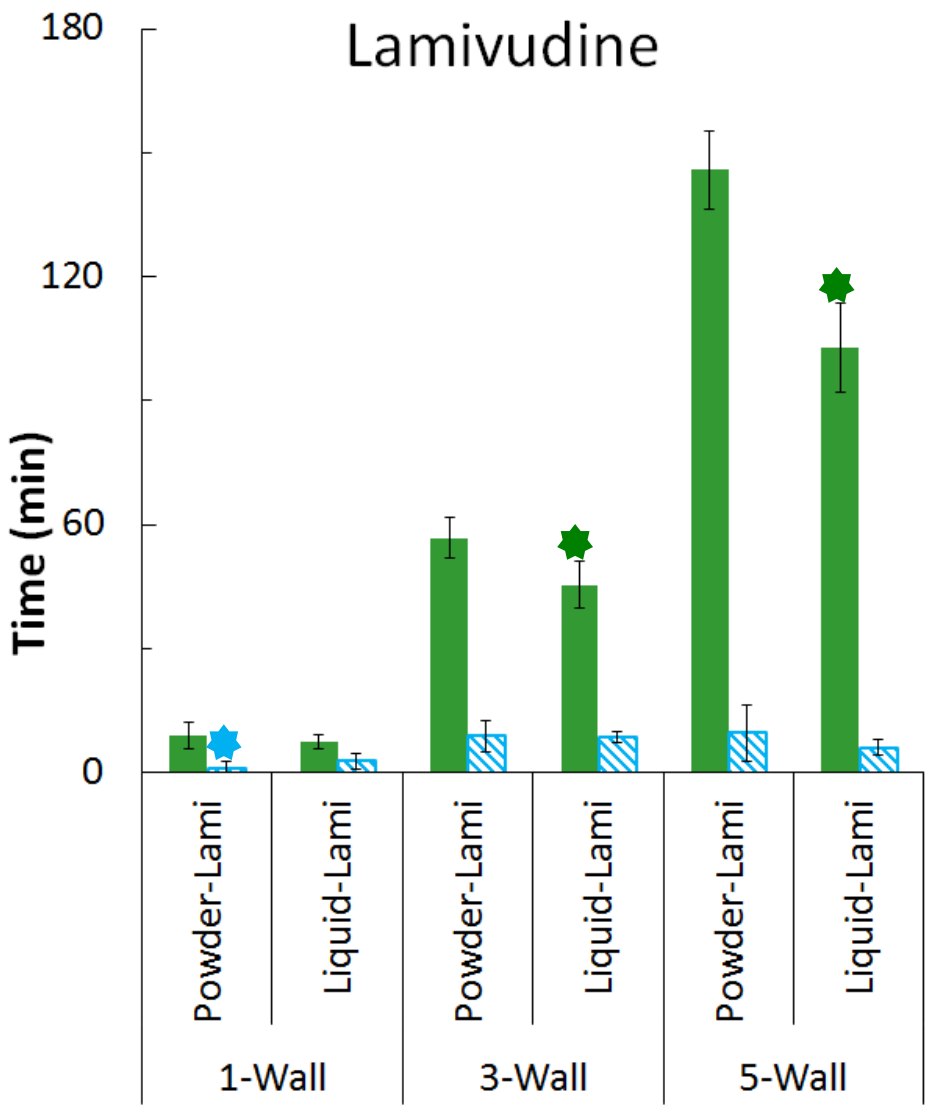
Liquid vs. Solid Fills





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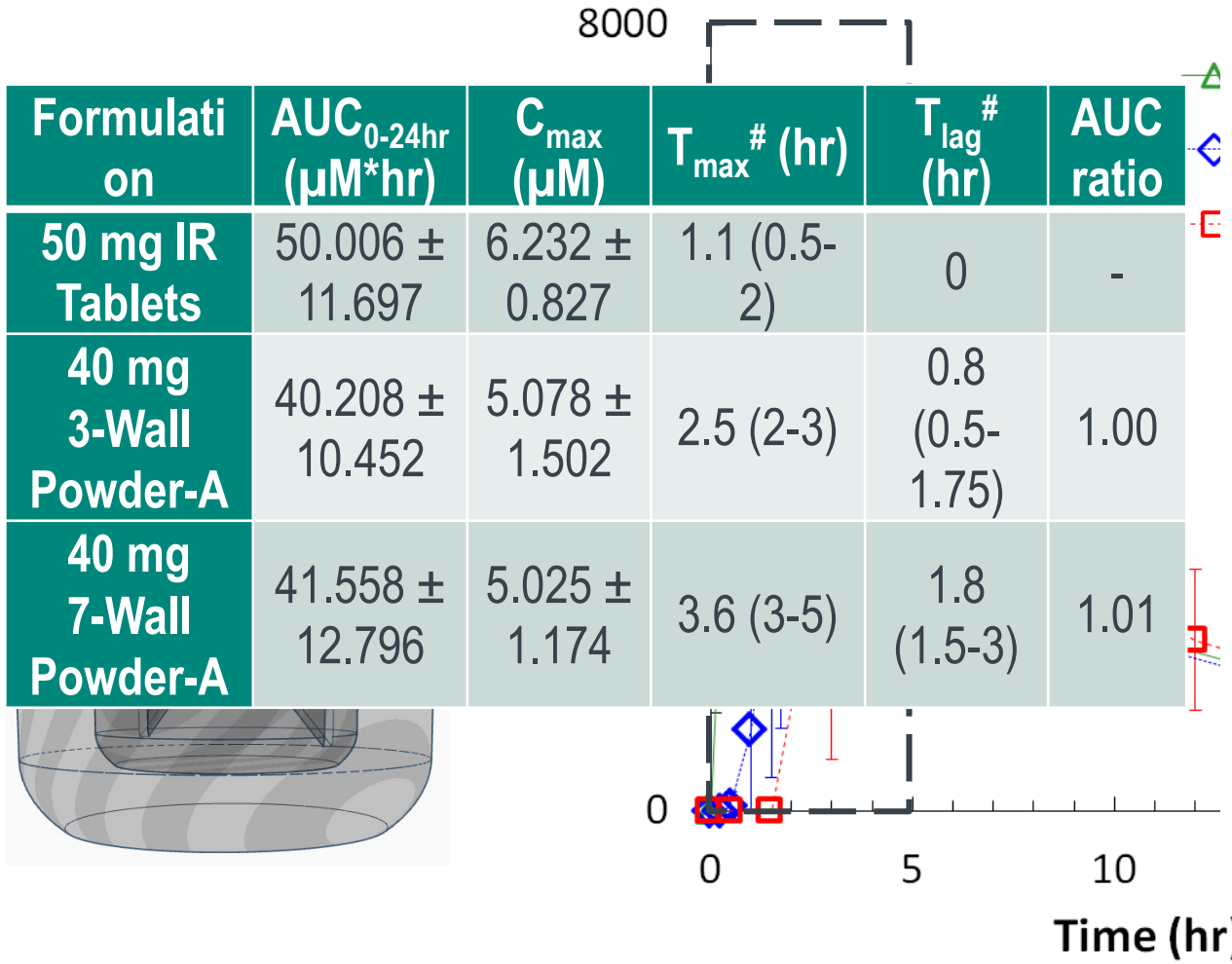
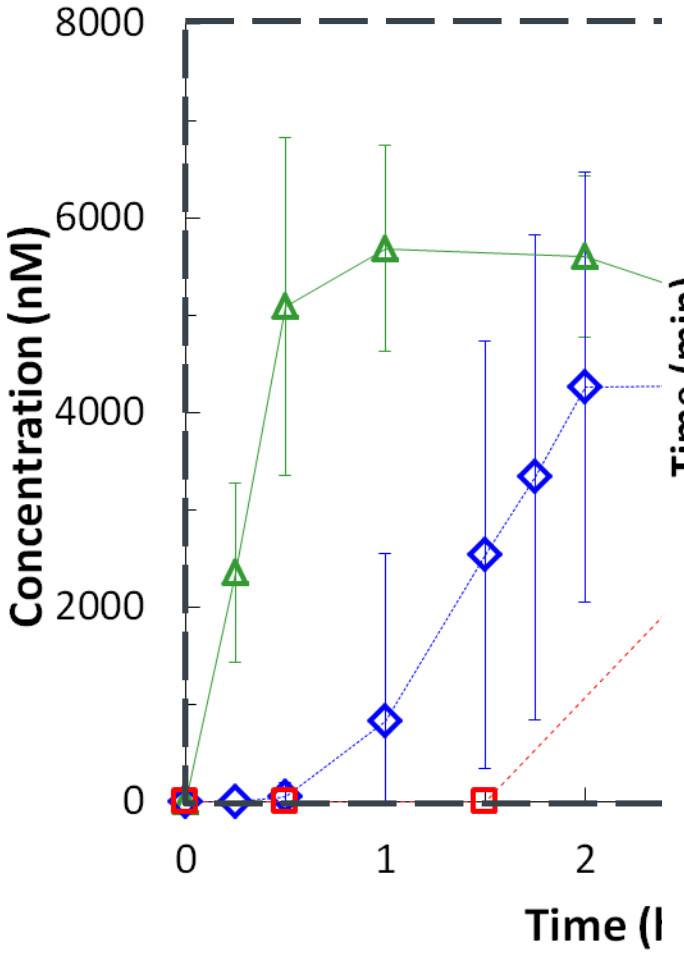
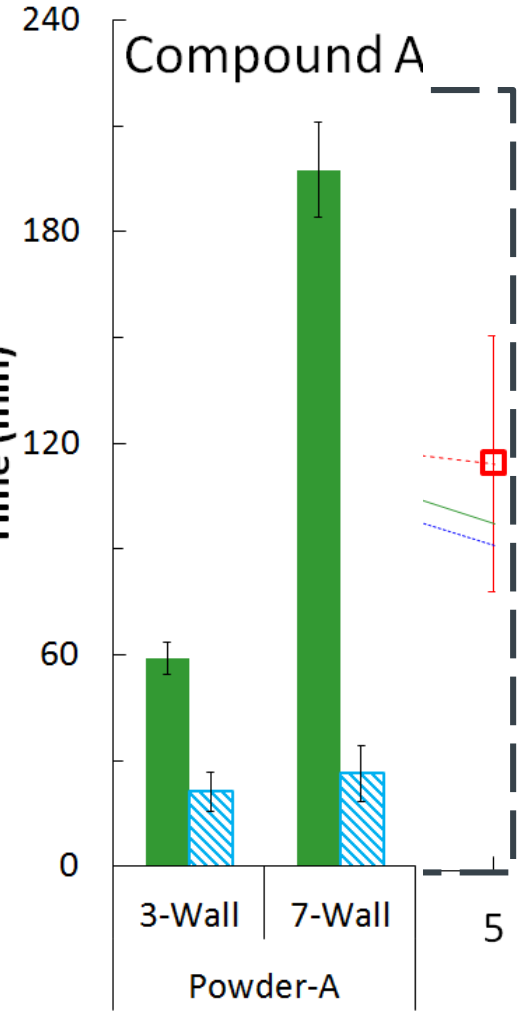
In Vivo Study (Beagle Dogs)

Formulation	AUC_{0-24hr} (μM*hr)	C_{max} (μM)	T_{max} # (hr)	T_{lag} # (hr)	AUC ratio
50 mg IR Tablets	50.006 ± 11.697	6.232 ± 0.827	1.1 (0.5-2)	0	-
40 mg 3-Wall Powder-A	40.208 ± 10.452	5.078 ± 1.502	2.5 (2-3)	0.8 (0.5-1.75)	1.00
40 mg 7-Wall Powder-A	41.558 ± 12.796	5.025 ± 1.174	3.6 (3-5)	1.8 (1.5-3)	1.01







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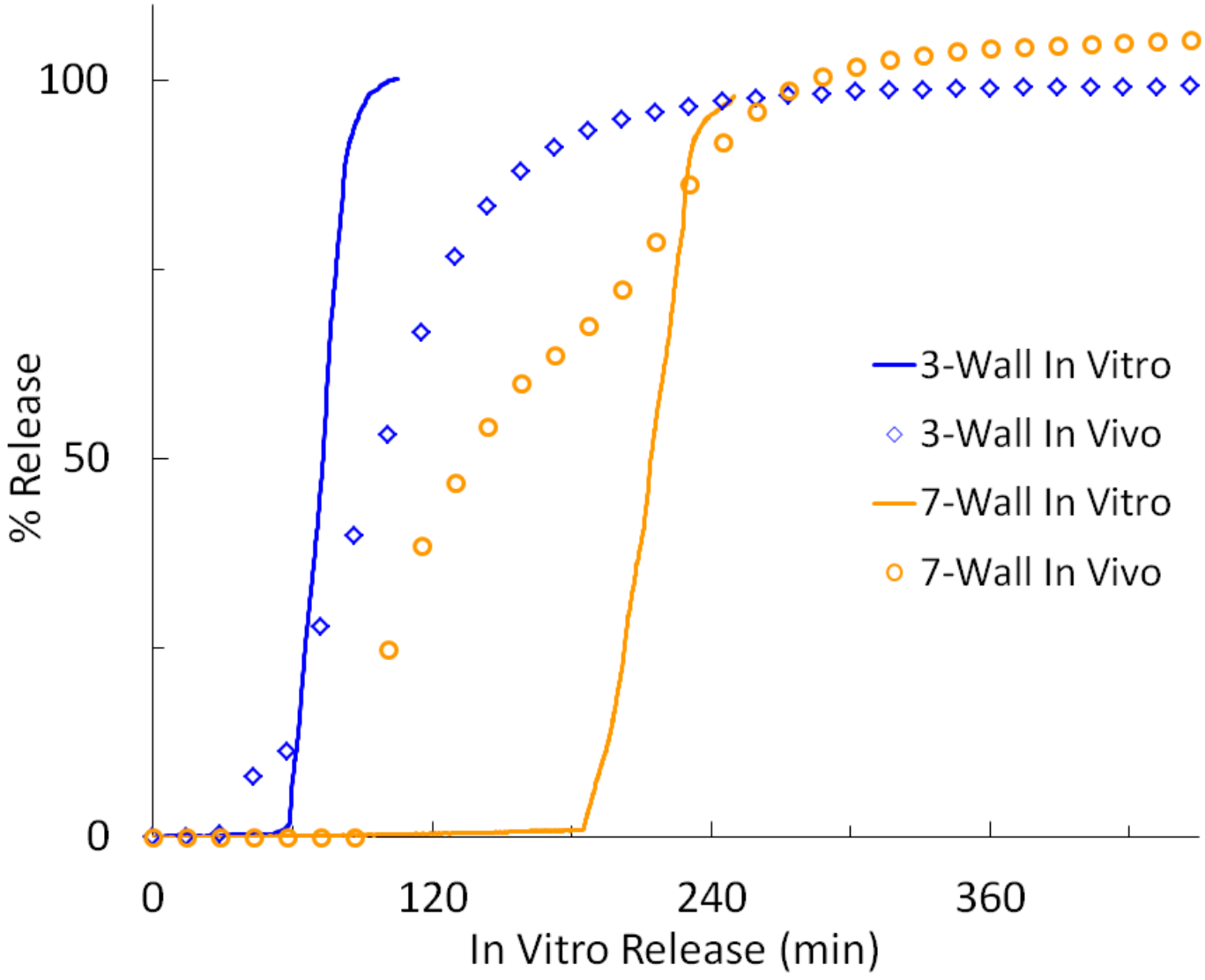
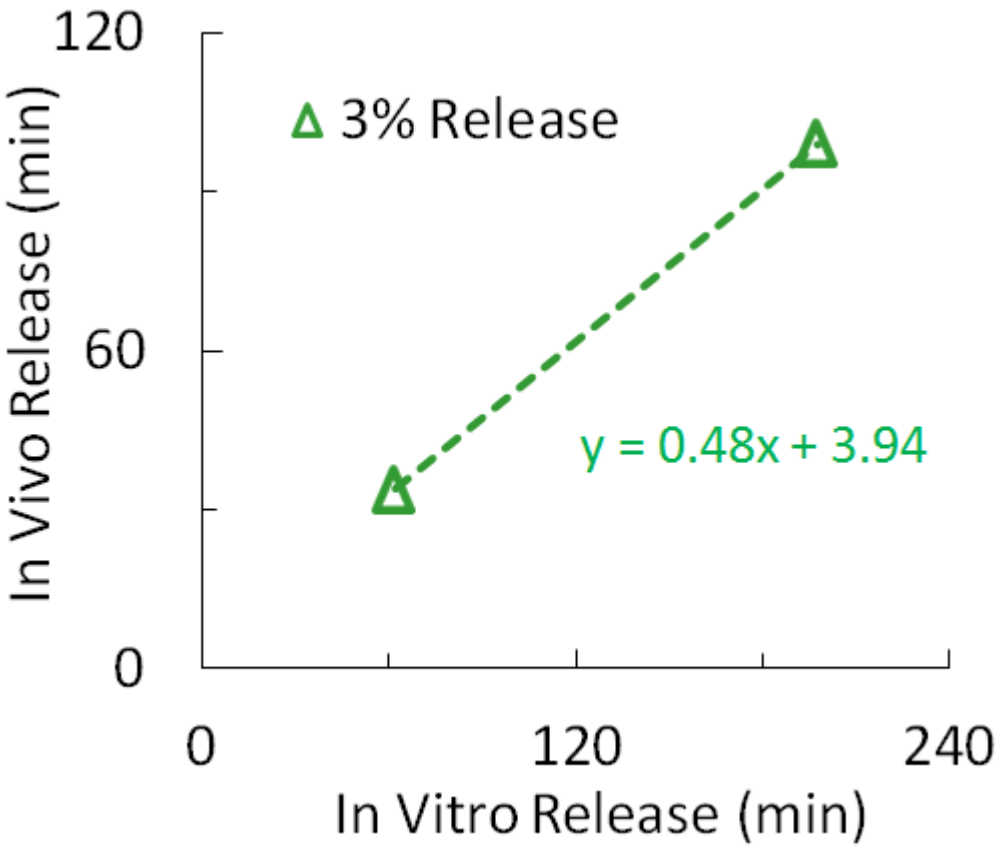
In Vitro – In Vivo Relationship





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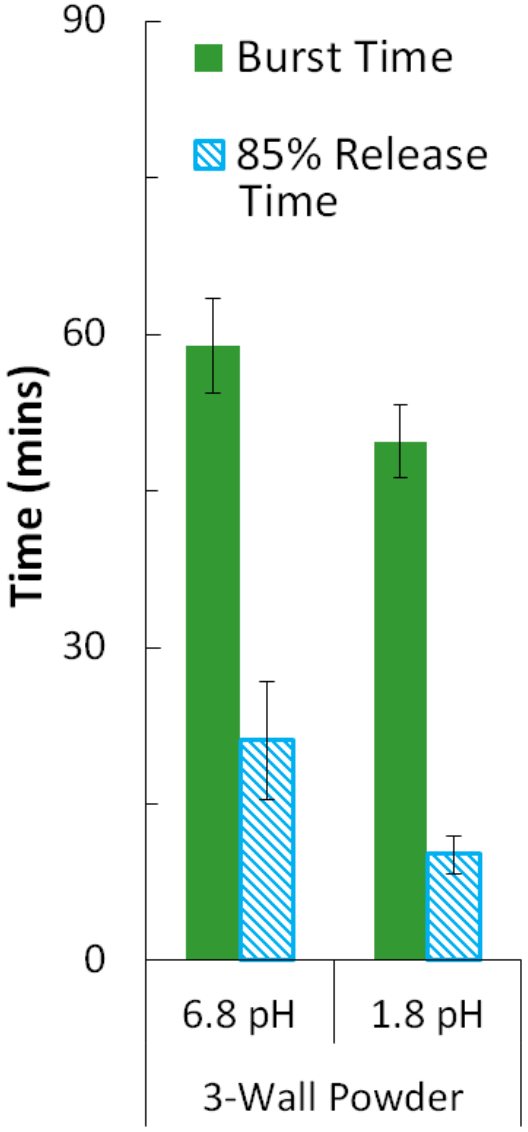
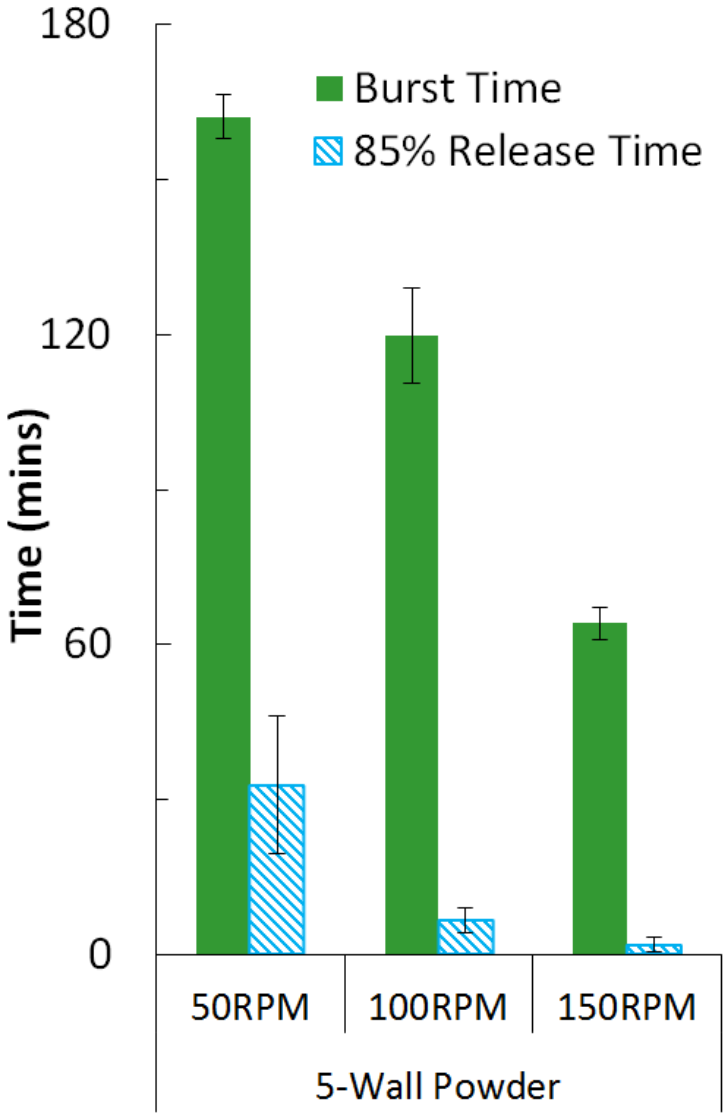
Manipulating Dissolution Conditions





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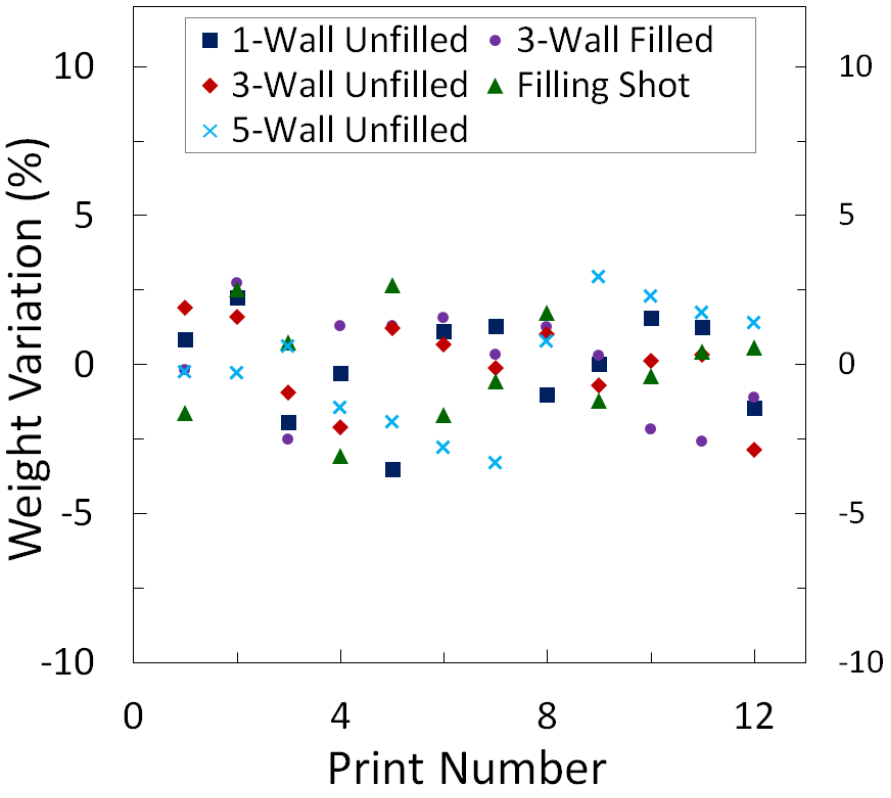
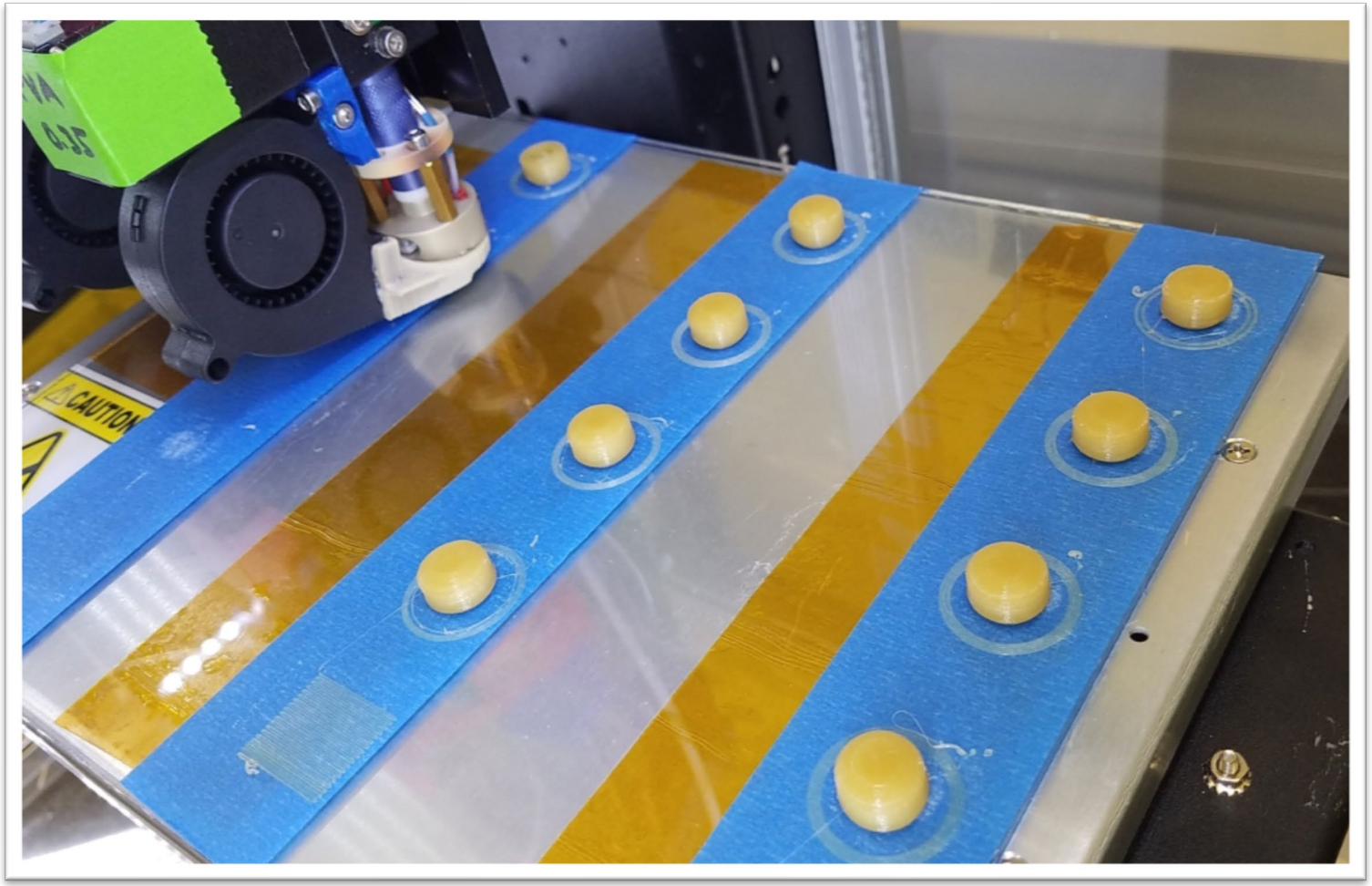
“Scaleup” for Early Clinical Studies





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Key takeaways

3DP

- 3D printing (3DP), offers R&D a new tool in the biopharmaceutical toolbox to improve the quality and timeliness of oral drug product development
- This technology is gaining significant academic acceptance as well as industrial interest and commercial implementation due to its ability to create complex geometries along with customizable material properties.
- We believe there is a potential to enhance our understanding of PK through both dose and dissolution flexibility in early clinical programs through the creation of complex and custom drug products.

Clinical 3D Printer

- Our Team has worked towards designing novel shell dosage forms with various fill options and studied the impact of in-vitro and in vivo release with various combinations
- Controlled and delayed release concept oral dosage forms have been demonstrated successfully with Metformin and other proprietary Merck compounds

Issues:

- Dissolution variability root cause has been identified as the anisotropic nature of both the dosage form and the dissolution media flow field

THANK YOU