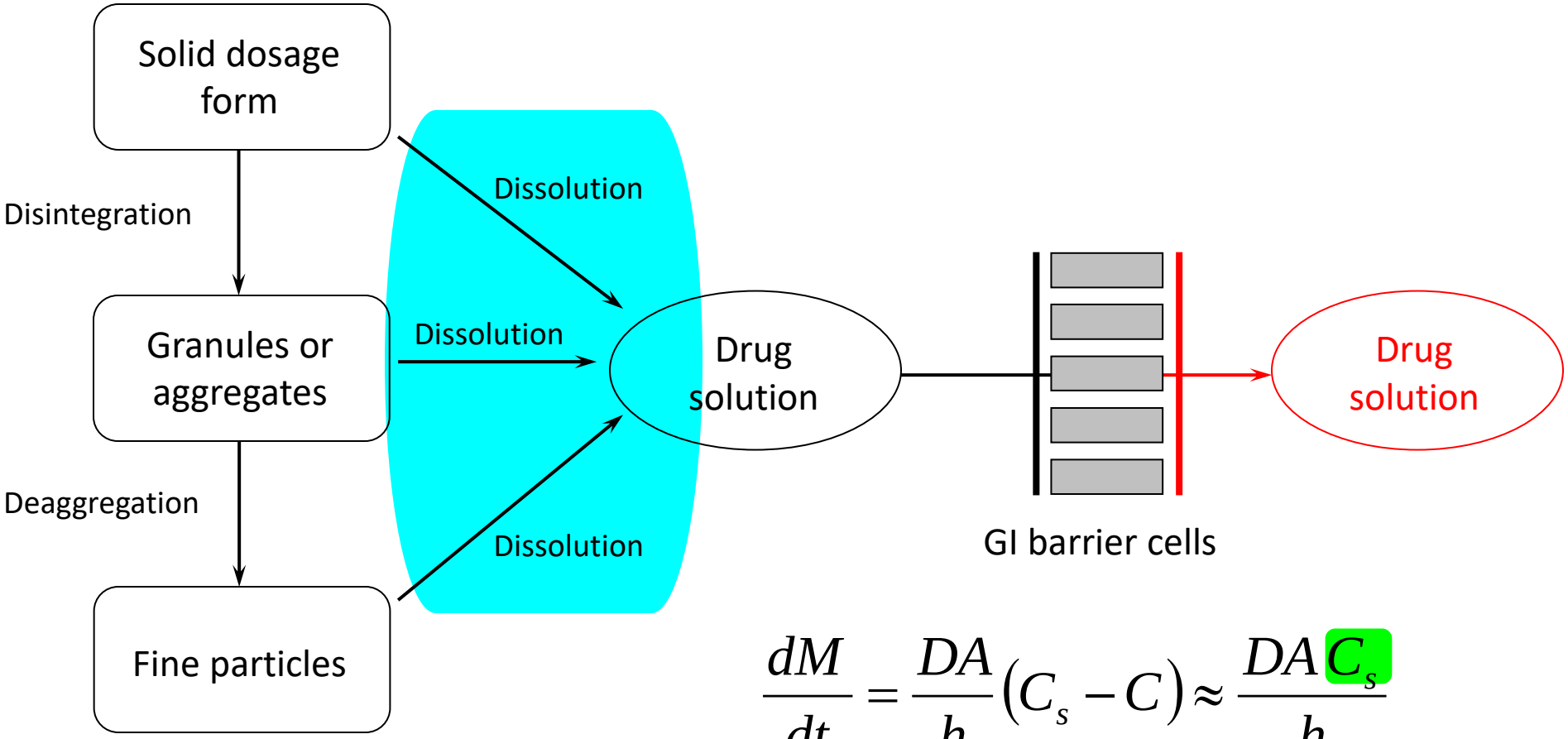
Release Mechanisms of Amorphous Solid Dispersions

Lynne S. Taylor

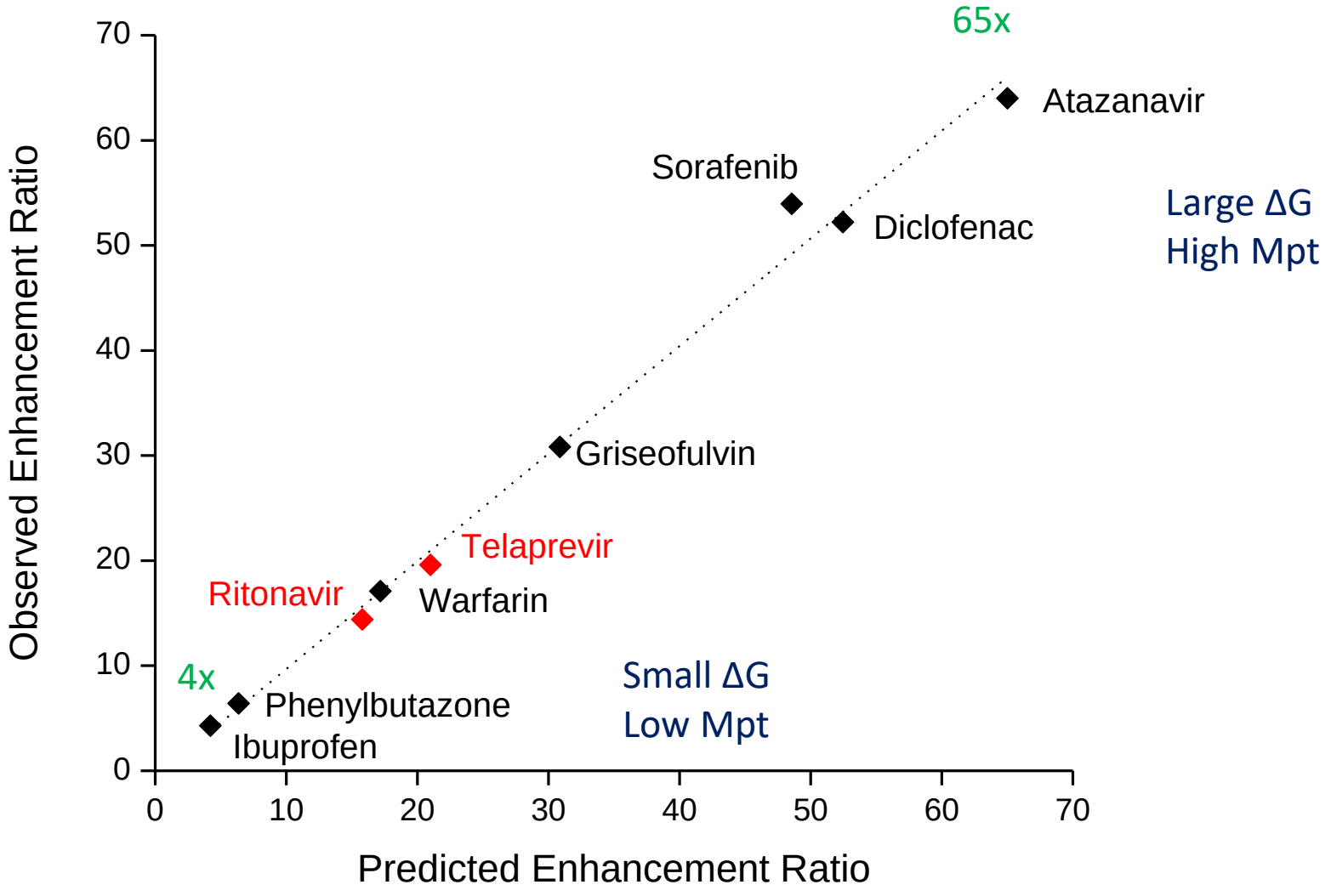
Purdue University

Solubility → Dissolution → Absorption



$$\frac{dM}{dt} = \frac{DA}{h}(C_s - C) \approx \frac{DAC_s}{h}$$

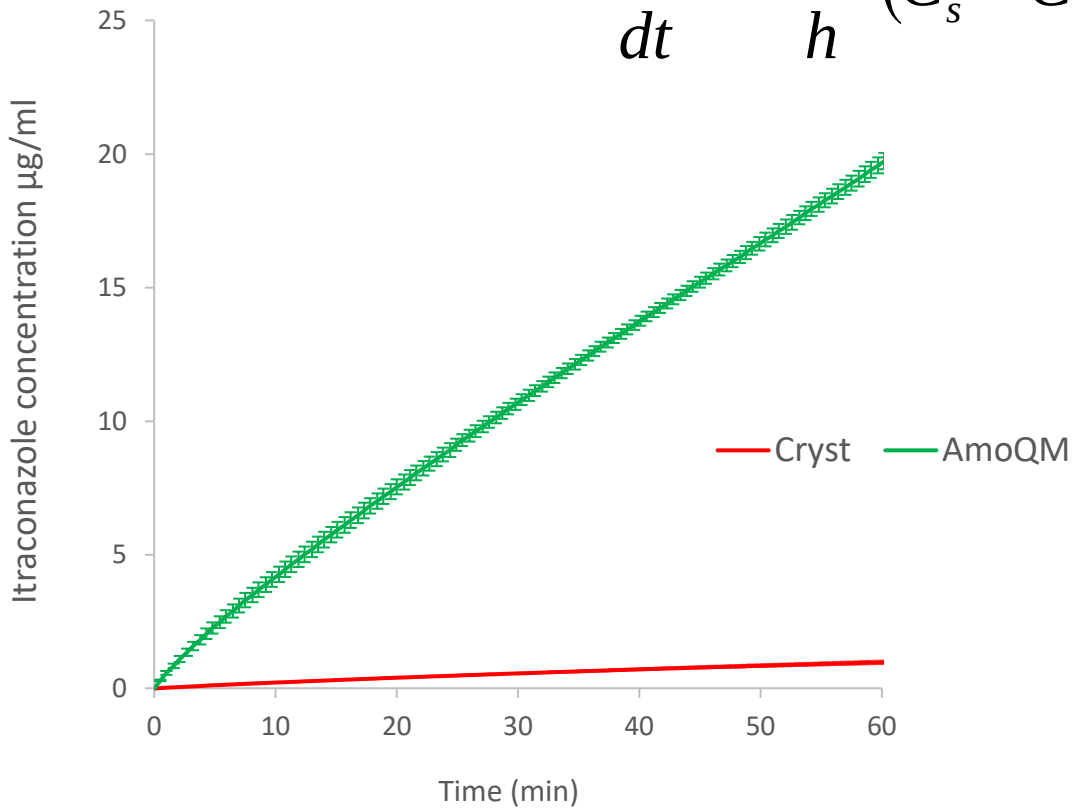
Amorphous:Crystalline Solubility Ratios



Taylor, L. S.; Zhang, G. G. Z., *ADDR*. 2016 doi:10.1016/j.addr.2016.03.006

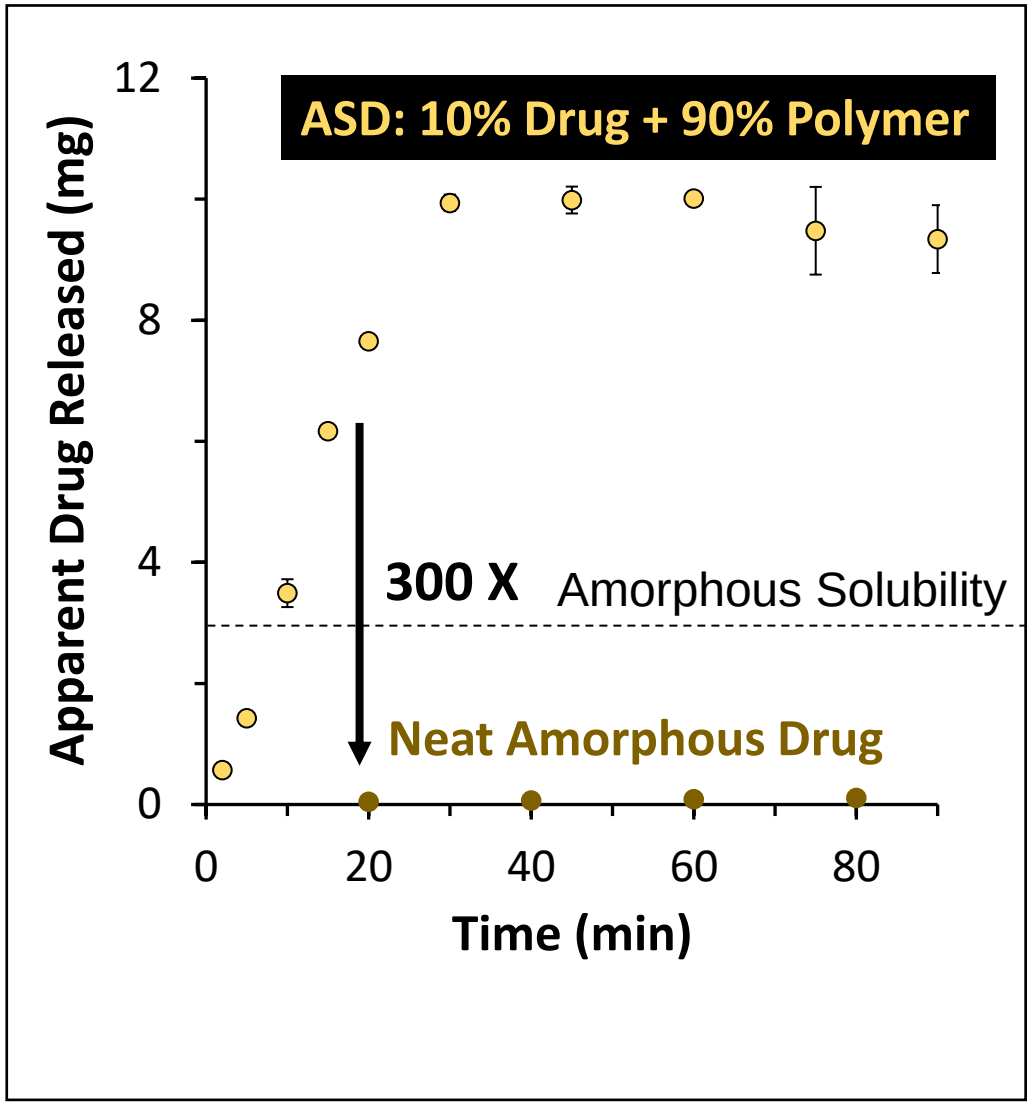
Amorphous Form has a Faster Dissolution Rate than Crystal

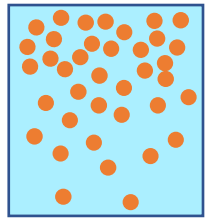
$$\frac{dM}{dt} = \frac{DA}{h}(C_s - C) \approx \frac{DA\,C_s}{h}$$

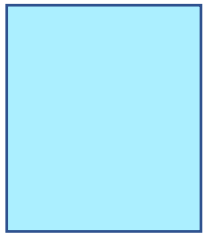


Amorphous Solid Dispersion Release Drug Faster than Neat Amorphous Drug

$$\frac{dM}{dt} = \frac{DA}{h}(C - C) \approx \frac{DAC_s}{h}$$

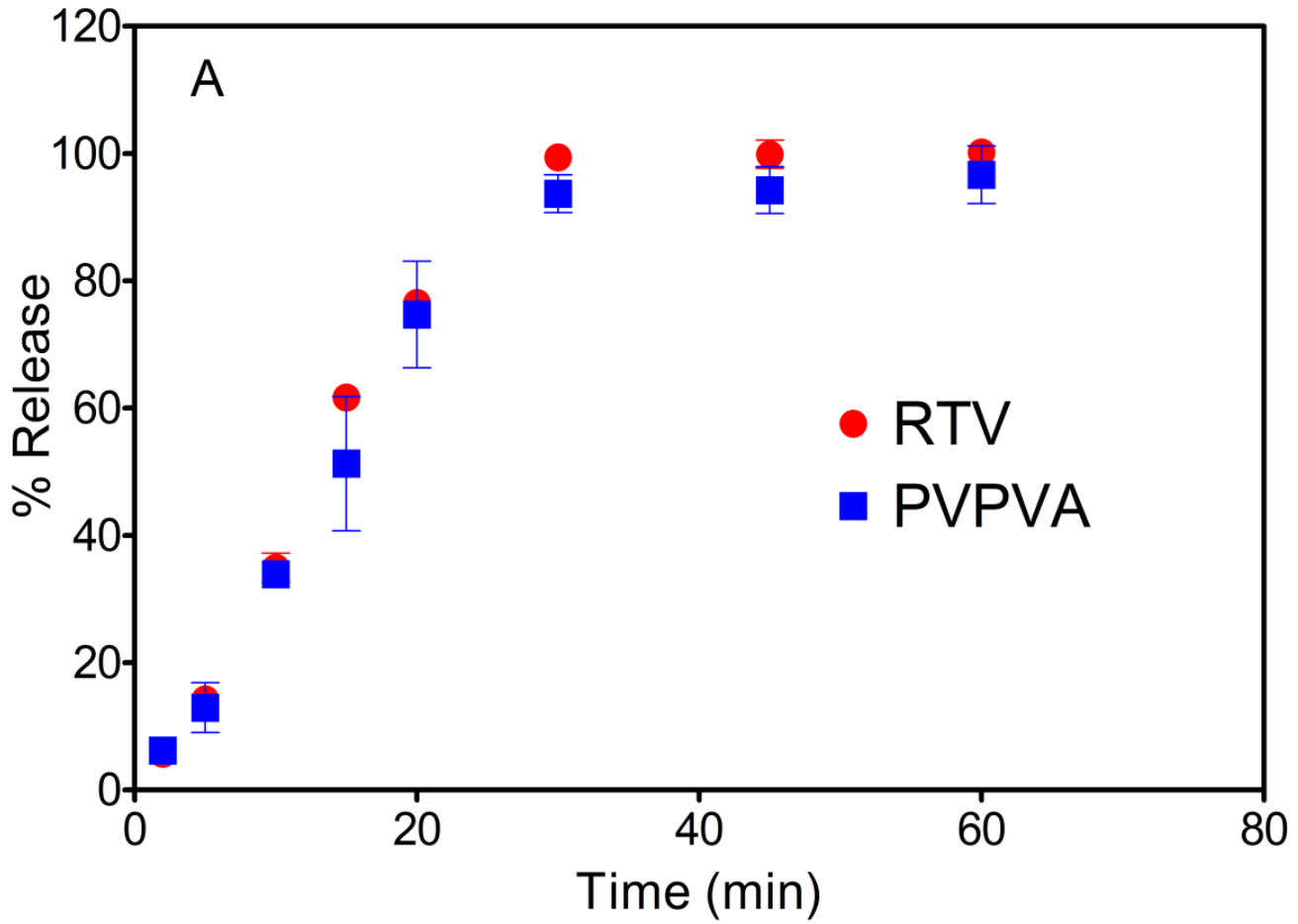






Indulkar et al. (2019). *Molecular Pharmaceutics*, *16*(3), 1327-1339.

Comparison of Drug and Polymer Release Rates (10% DL)- Drug Release is Controlled by Polymer

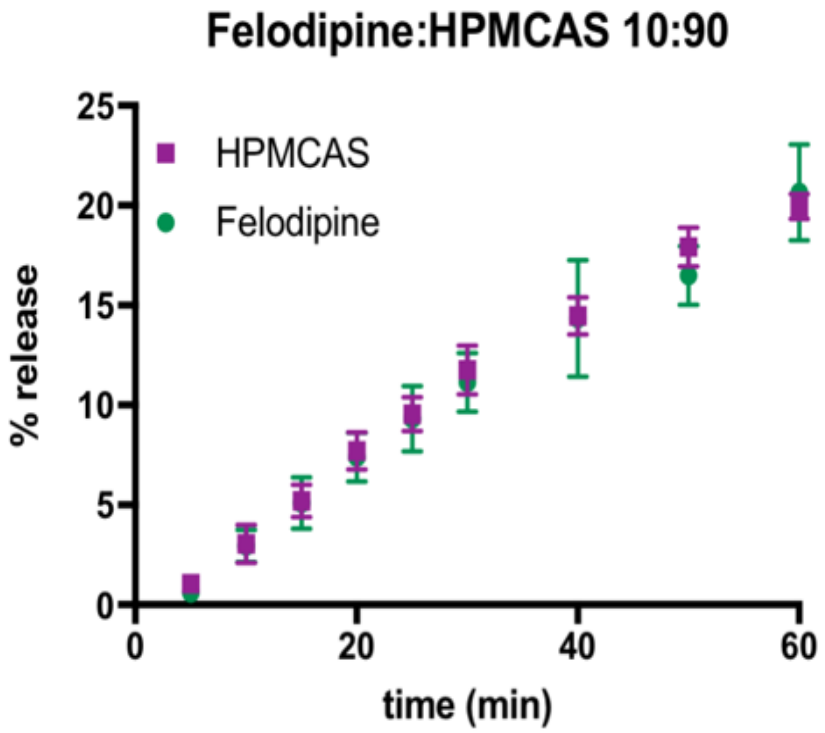


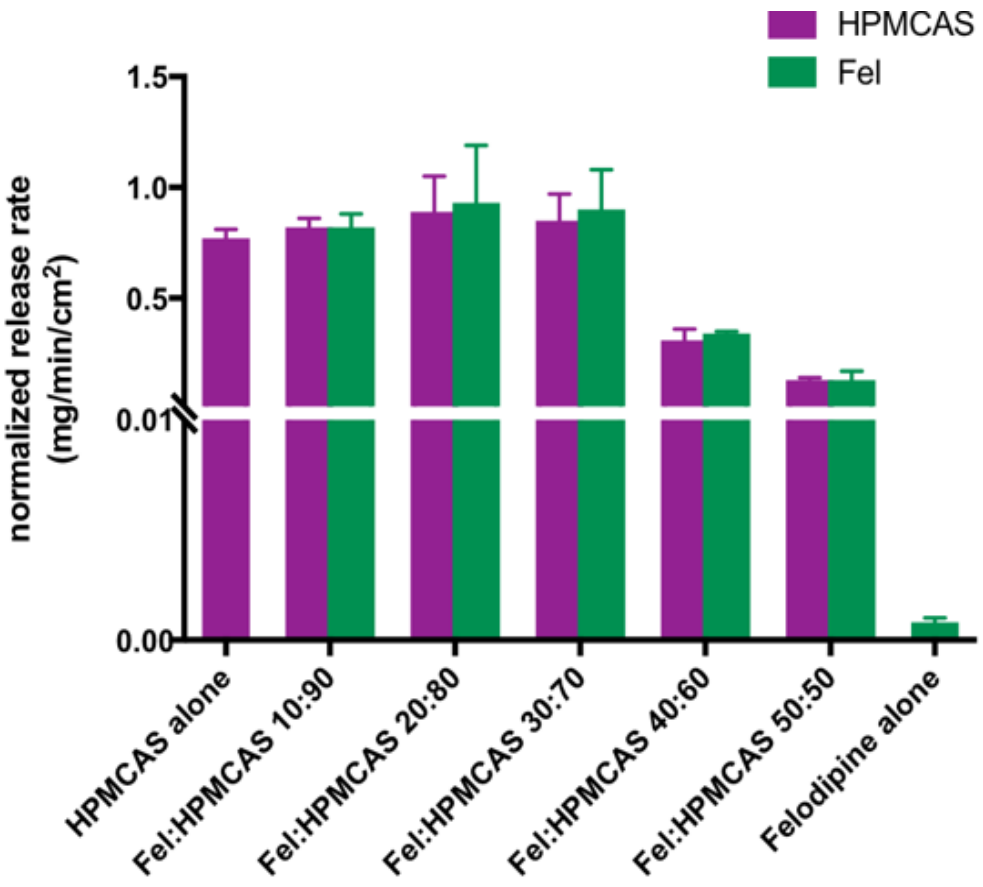
Congruent release

10% drug loading

Indulkar et al. (2019). *Molecular Pharmaceutics*, *16*(3), 1327-1339.

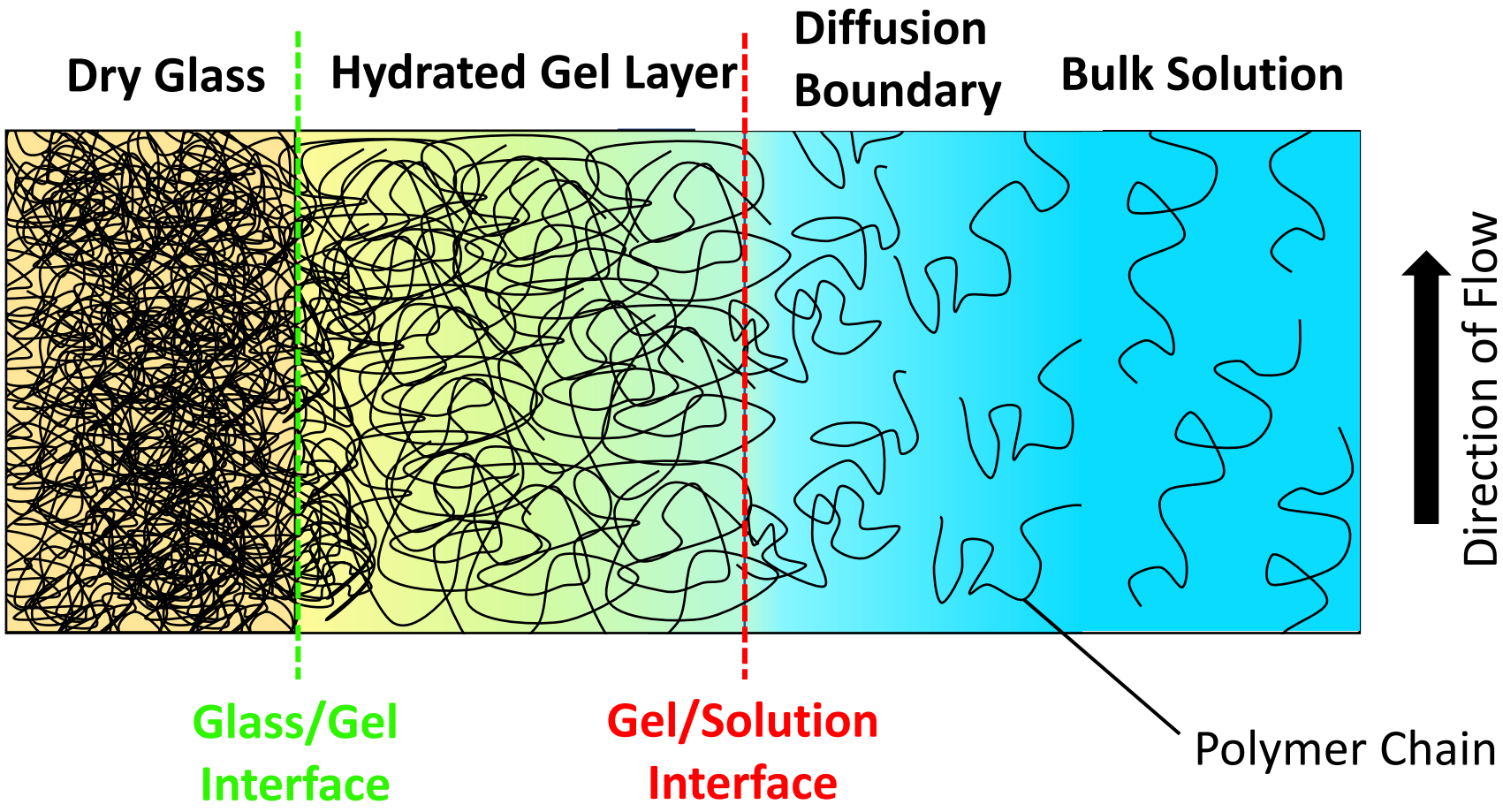
Similar Observation for HPMCAS-Based ASDs





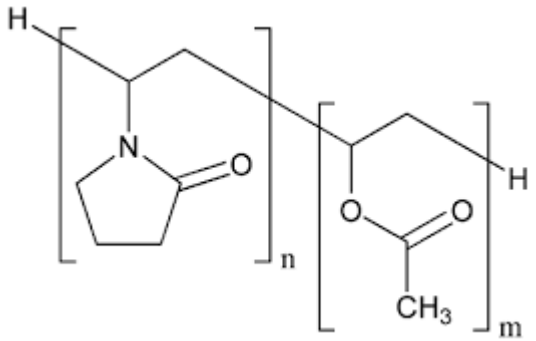
Saboo, S., Moseson, D.E., Kestur, U.S. and Taylor, L.S., 2020. *Eur J Pharm Sci*, *155*, 105514.

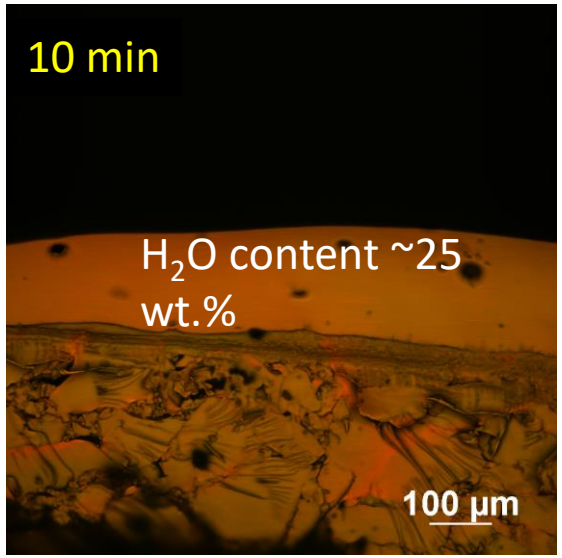
Neutral Polymer Dissolution Overview



Gel Layer = High viscosity region; Polymer diffusion <<< water diffusion

Copovidone





Gel

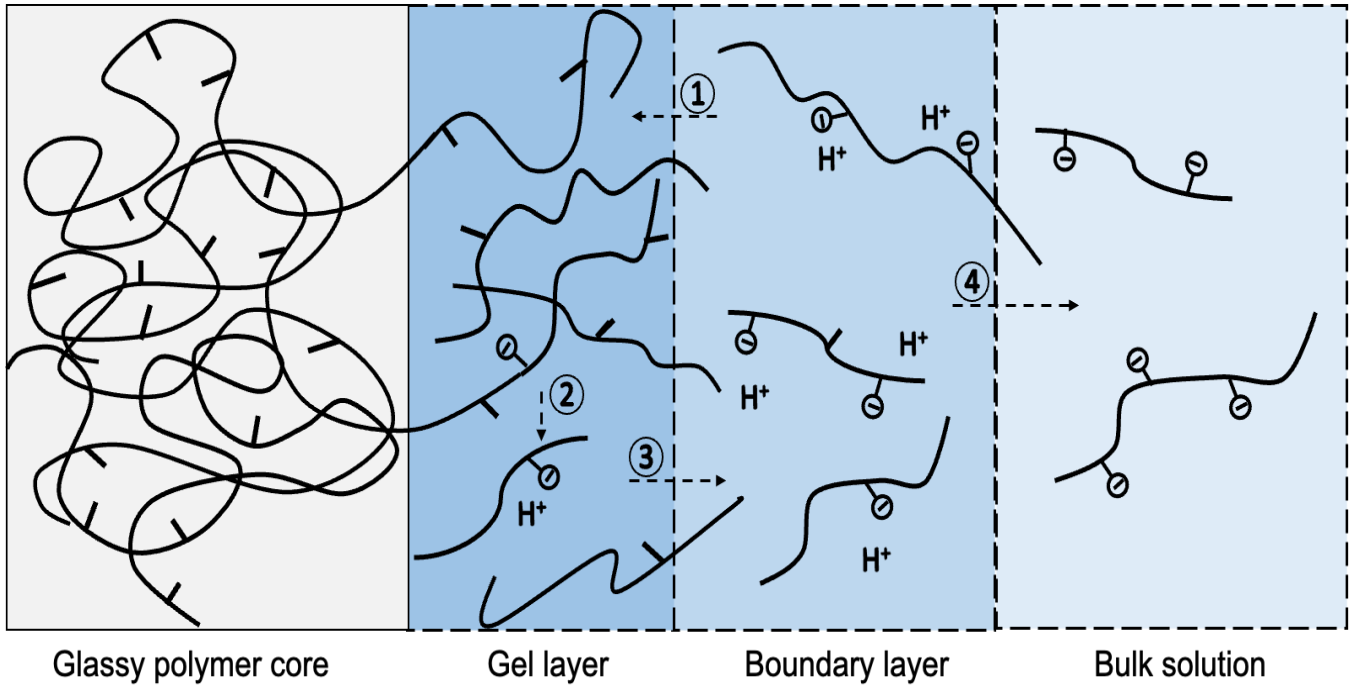
Glass

<u>Overview</u>
Tg ~ 110°C
MW ~70,000
Spray drying, HME

<u>Pros</u>
Highly soluble
Not pH-dependent
Extrudable
Soluble in multiple solvents

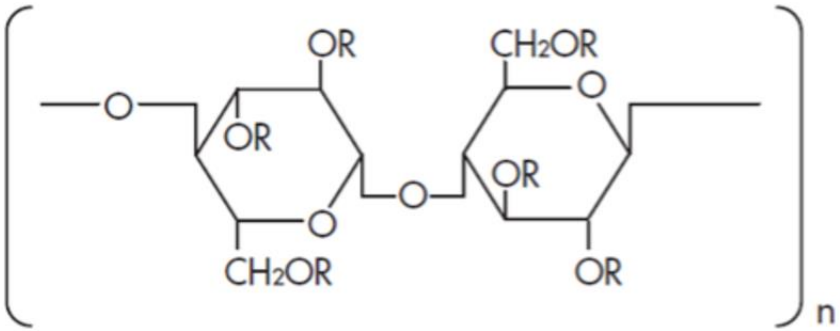
<u>Cons</u>
Gel formation
Often not good for high
Crystallization-tendency drugs
Hygroscopic

Ionic Polymer Dissolution Overview

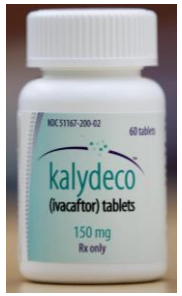


1. H_2O and base diffusion to polymer
2. Ionization of acid groups
3. Polymer movement into boundary layer
4. Polymer and proton diffusion to bulk

HPMCAS



R = -H
-CH3
-CH2CH(CH3)OH
-COCH3
-COCH2CH2COOH
-CH2CH(CH3)OCOCH3
-CH2CH(CH3)OCOCH2CH2COOH



Overview
Available as 3 grades
Tg ~ 120°C
MW ~18,000
Spray drying, HME, Co-precipitation

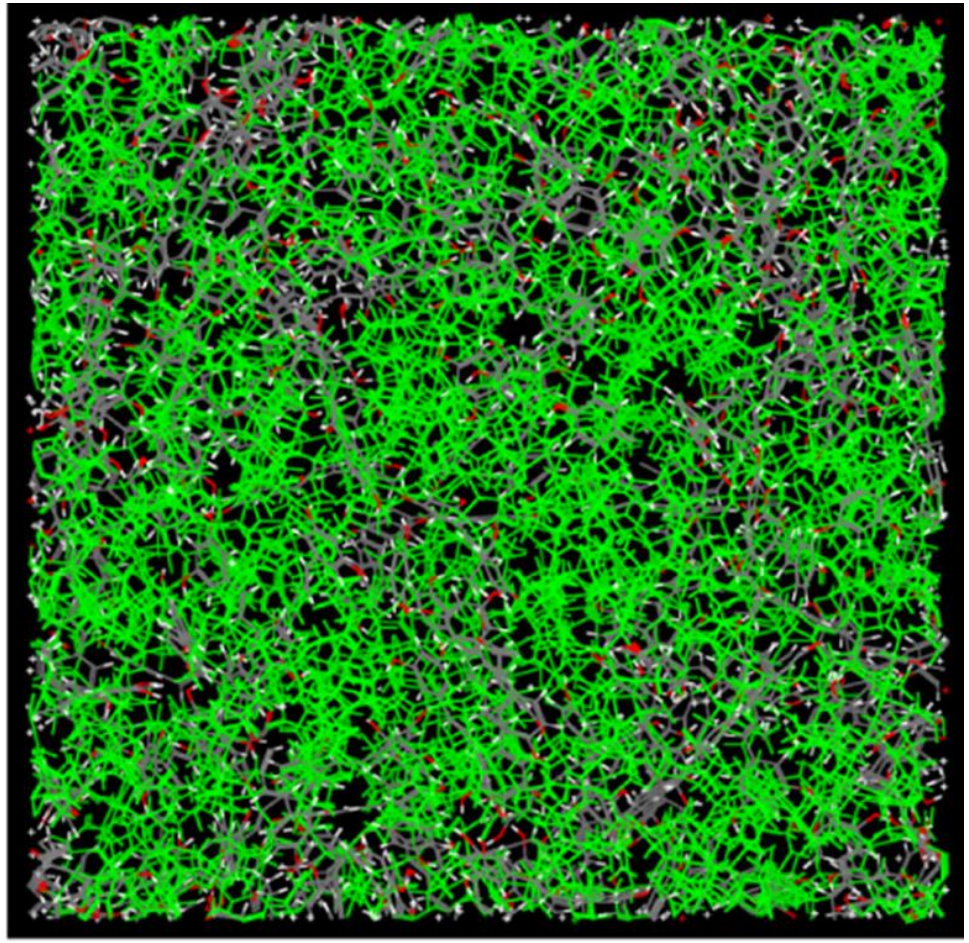
Grade	Acetyl [%]	Succinoyl [%]	Dissolution pH
AS-LF/LG	5-9	14-18	> 5.5
AS-MF/MG	7-11	10-14	> 6.0
AS-HF/HG	10-14	4-8	> 6.5

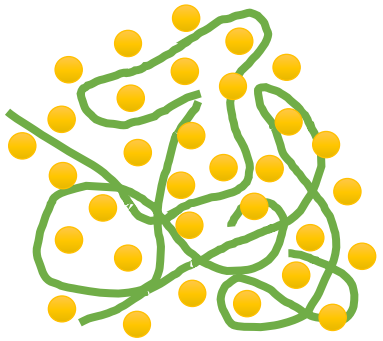
Pros
Excellent crystallization inhibitor
Low hygroscopicity
pH dependent solubility
Disintegration

Cons
pH-sensitive dissolution
Harder to extrude than copovidone
Reactivity
Degradation

Amorphous Solid Dispersions – Molecular Level Structure

MD simulation of PVP and resveratrol ASD



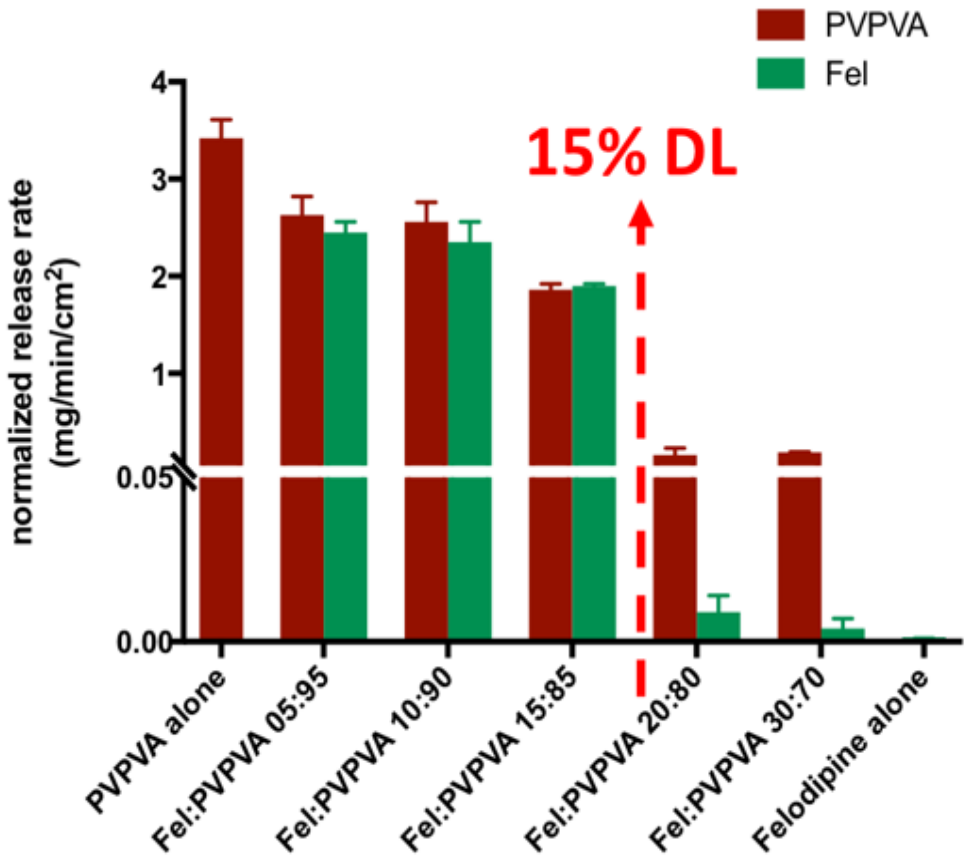


Considerations

1) Polymer dissolution rate
2) Impact of drug on polymer dissolution
3) Impact of polymer on drug dissolution
4) Phase behavior

Pajzderska, A., & Gonzalez, M. A. (2023). Molecular Dynamics Simulations of Selected Amorphous Stilbenoids and Their Amorphous Solid Dispersions with Poly (Vinylpyrrolidone). *Journal of Pharmaceutical Sciences*.

Drug Loading and Release – PVPVA-ASDs



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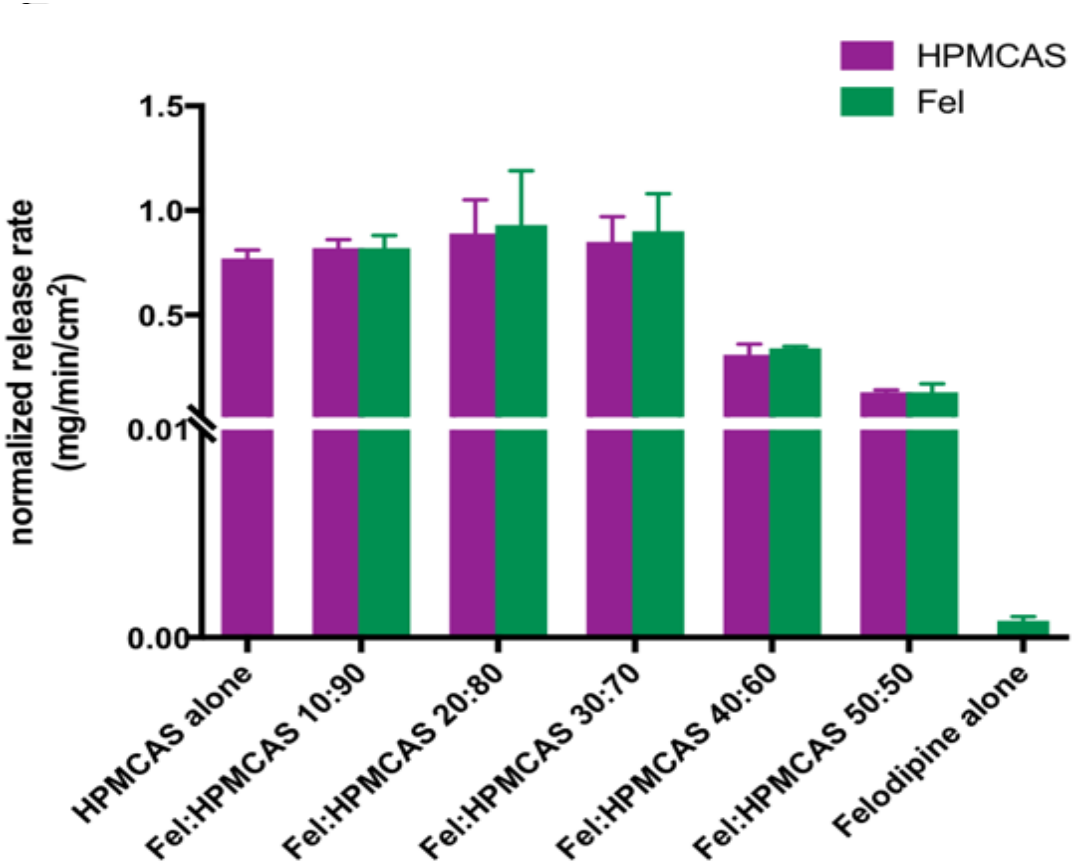
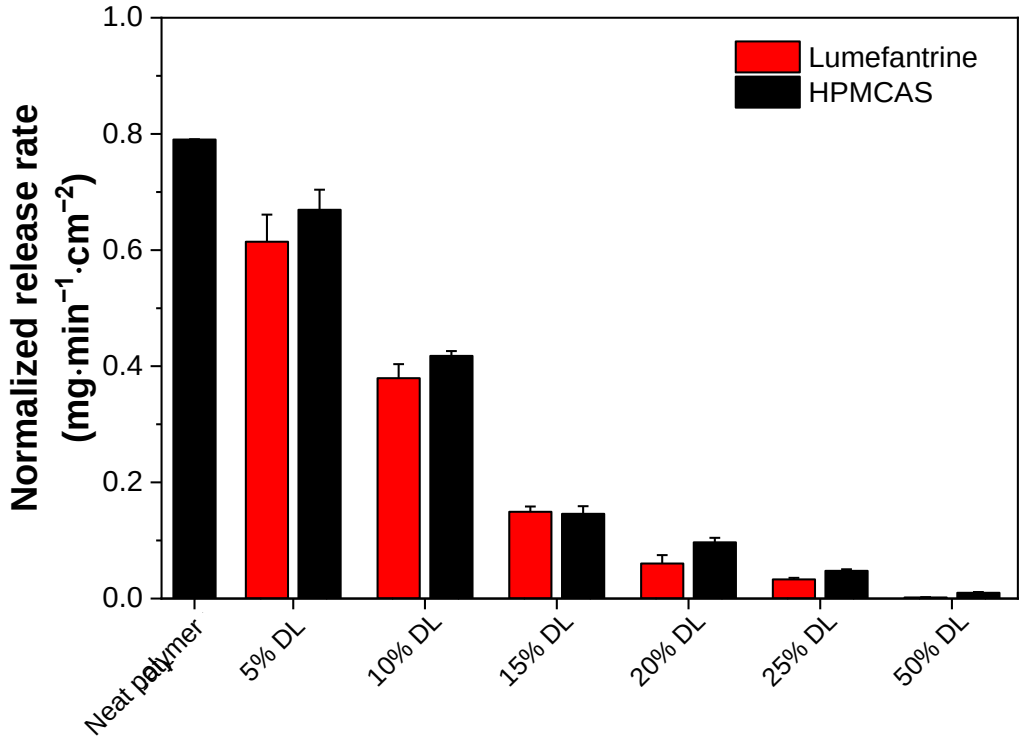
Drug Loading and Release – HPMCAS-ASDs

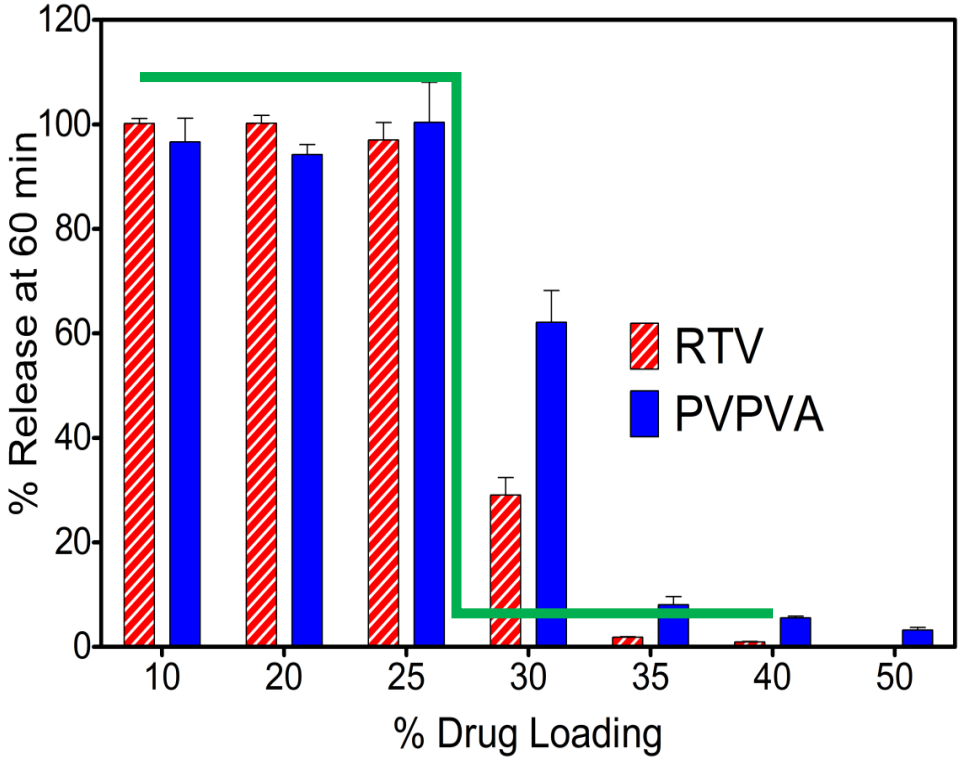


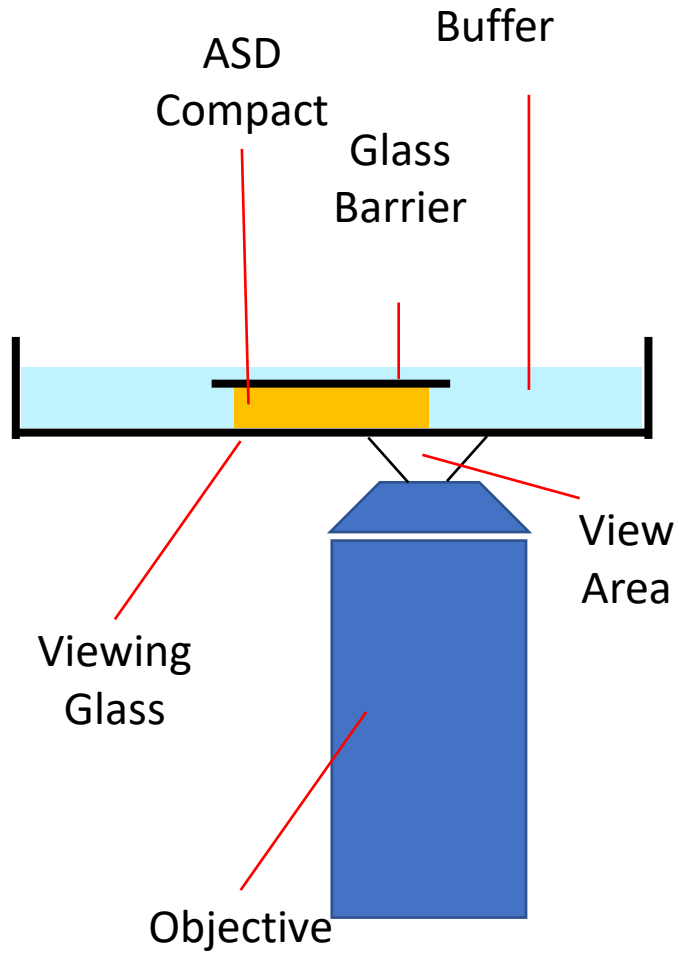
Saboo, S., Moseson, D.E., Kestur, U.S. and Taylor, L.S., 2020. *Eur J Pharm Sci*, *155*, 105514.

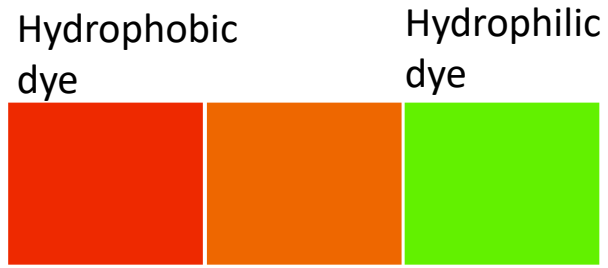


Hiew, T. N., Zemlyanov, D. Y., & Taylor, L. S. (2021). *Molecular Pharmaceutics*, *19*(2), 392-413.

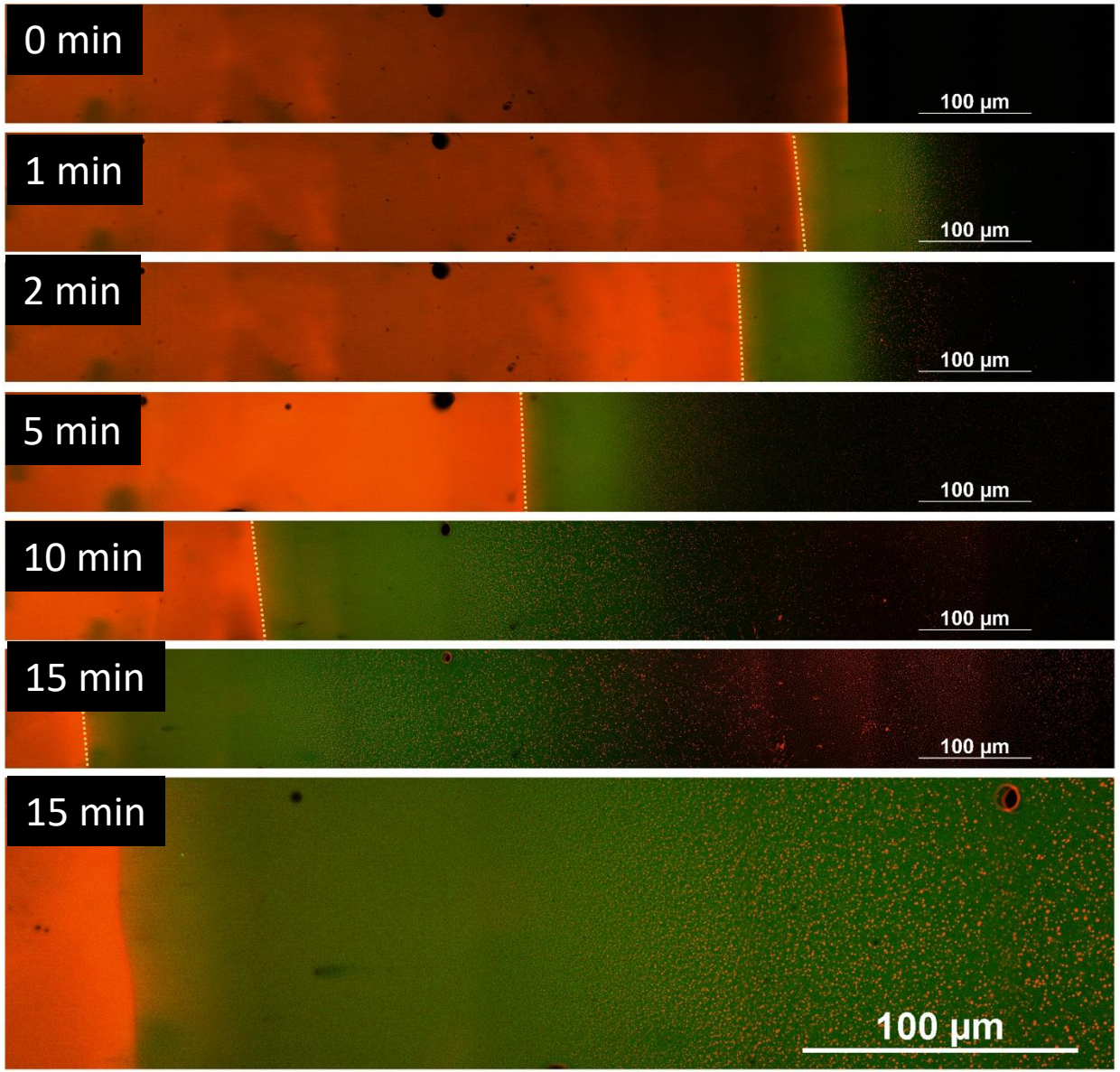
Probing the “falling-off-a-cliff” effect in PVPVA-ASDs

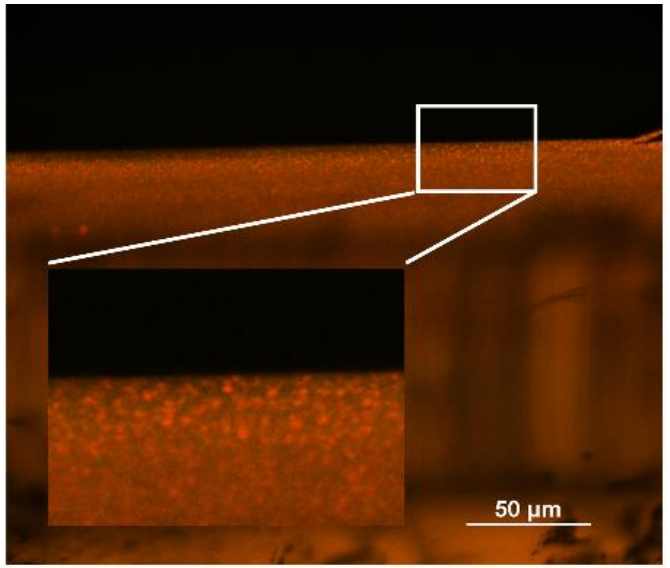




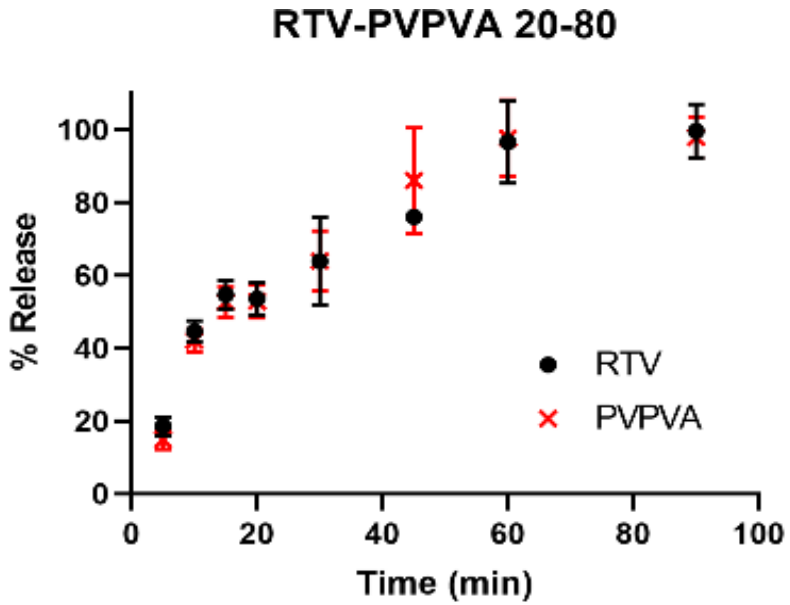


Ritonavir-PVPVA “Low” Drug Loading ASD





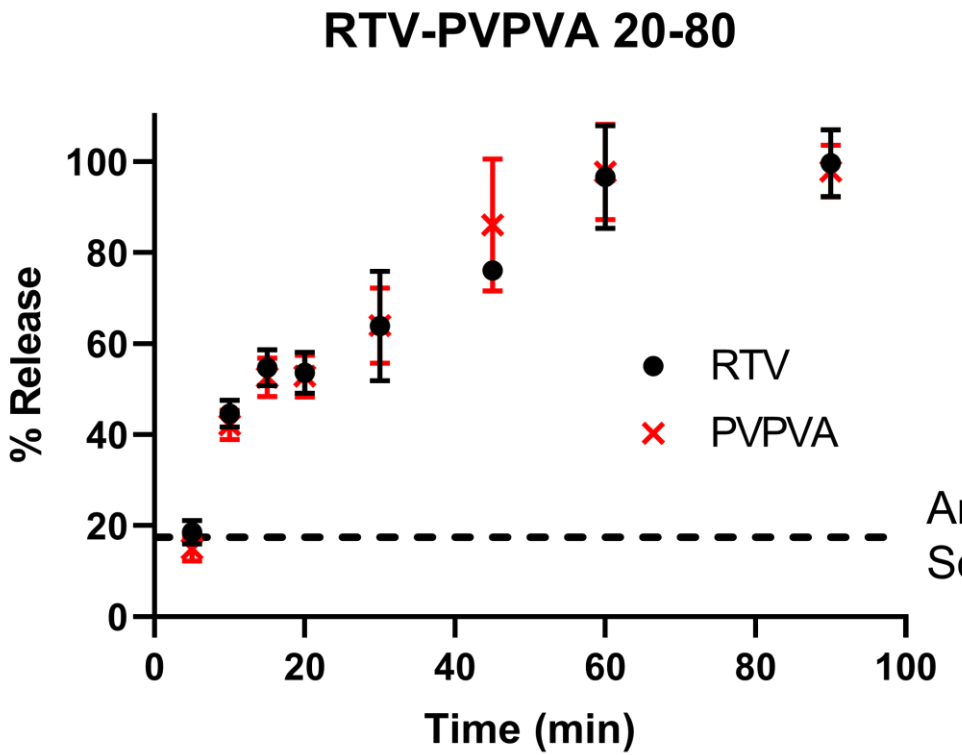
Congruent release – drug and polymer release together



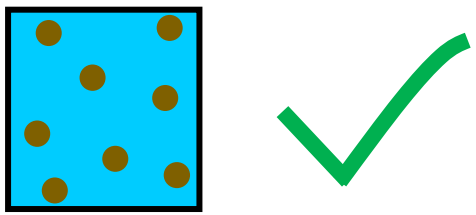
Yang, R., Zhang, G.G., Zemlyanov, D.Y., Purohit, H.S. and Taylor, L.S., 2023. *J. Pharm. Sci.*, *112*(1), 304-317.

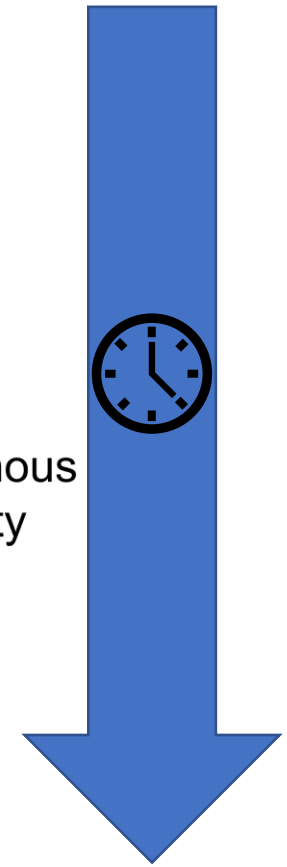
Mechanism for Congruent Release

Congruent



Amorphous Solubility





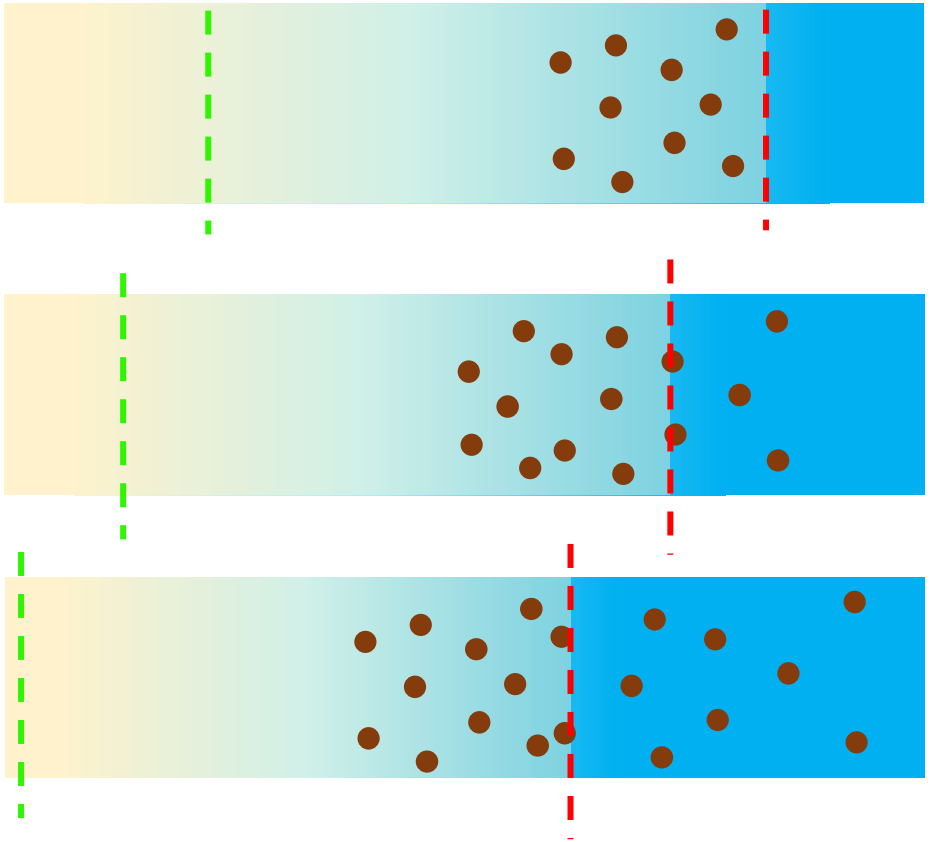
Hydrophilic Phase

Hydrophobic Phase

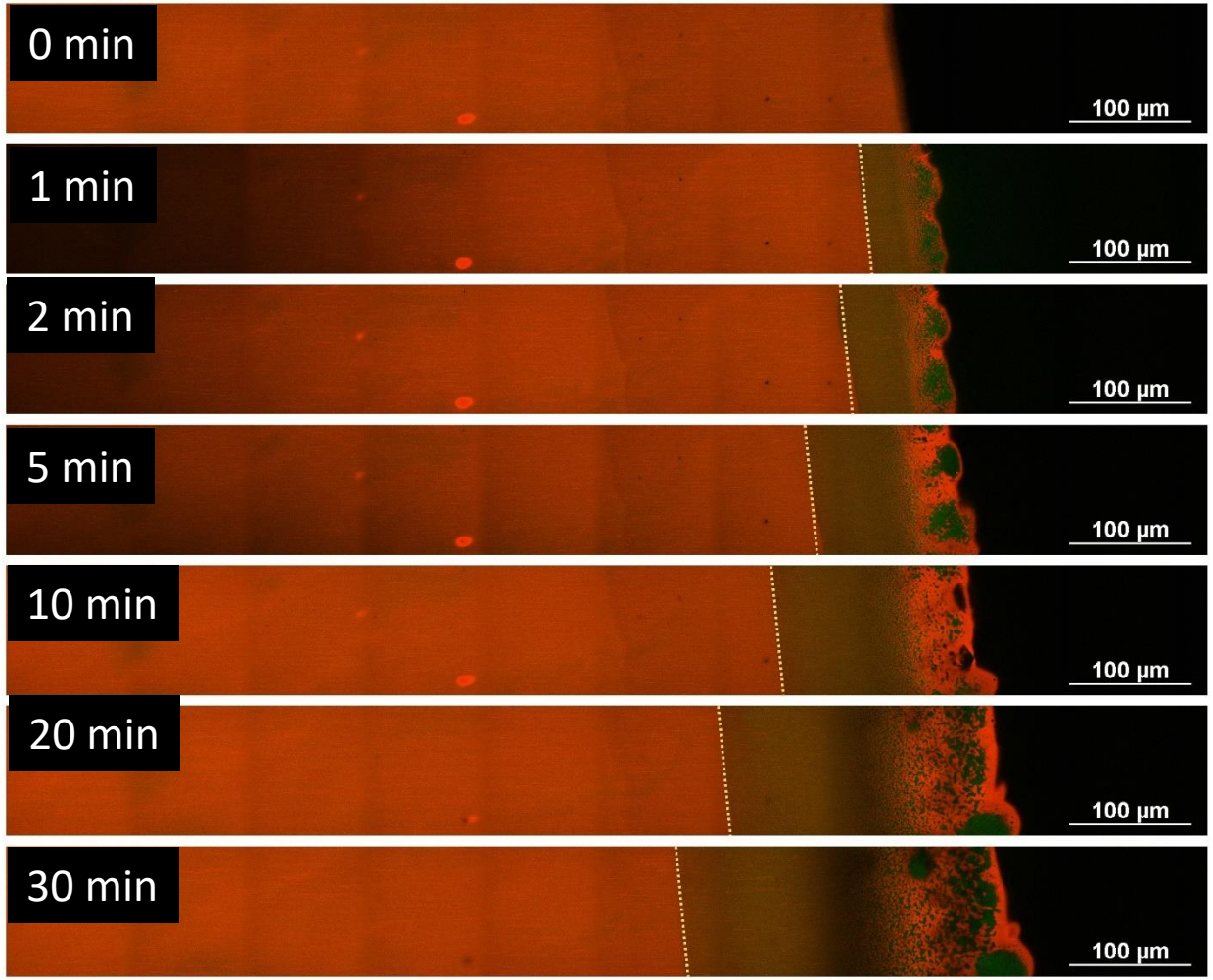
Dry ASD

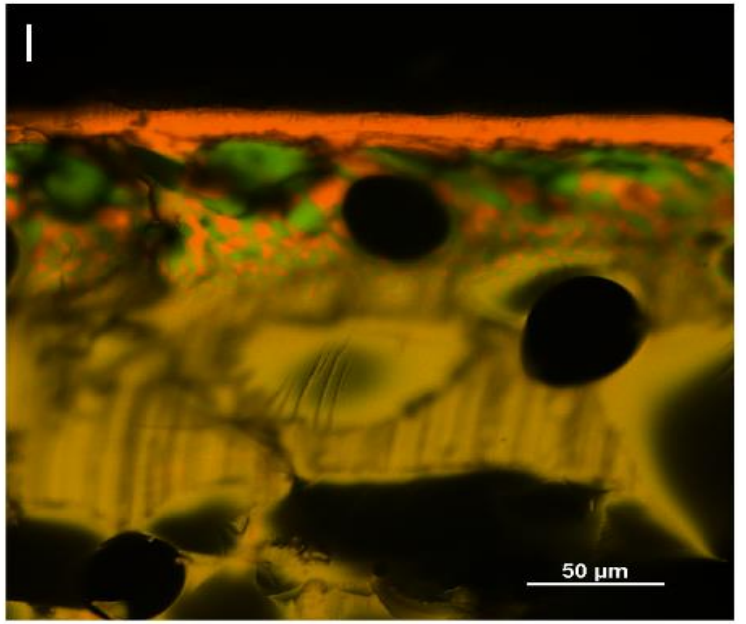
Hydrated Gel Layer

Water

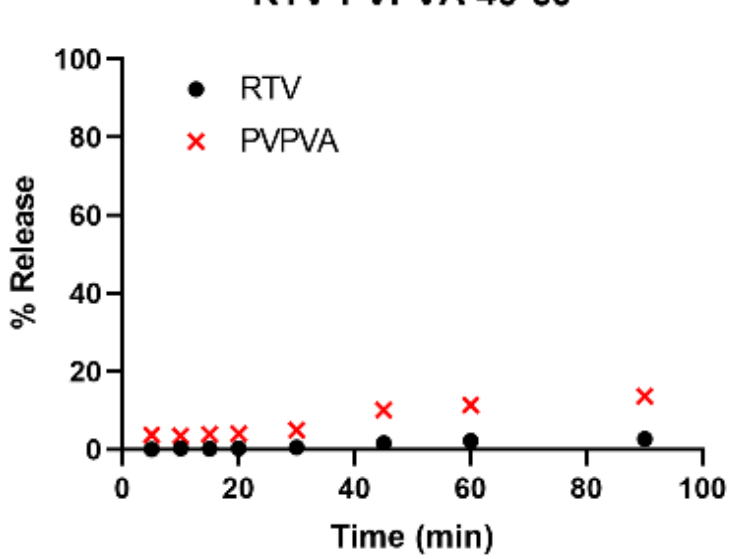


Ritonavir-PVPVA “High” Drug Loading ASD





Incongruent release – some polymer release, no drug release



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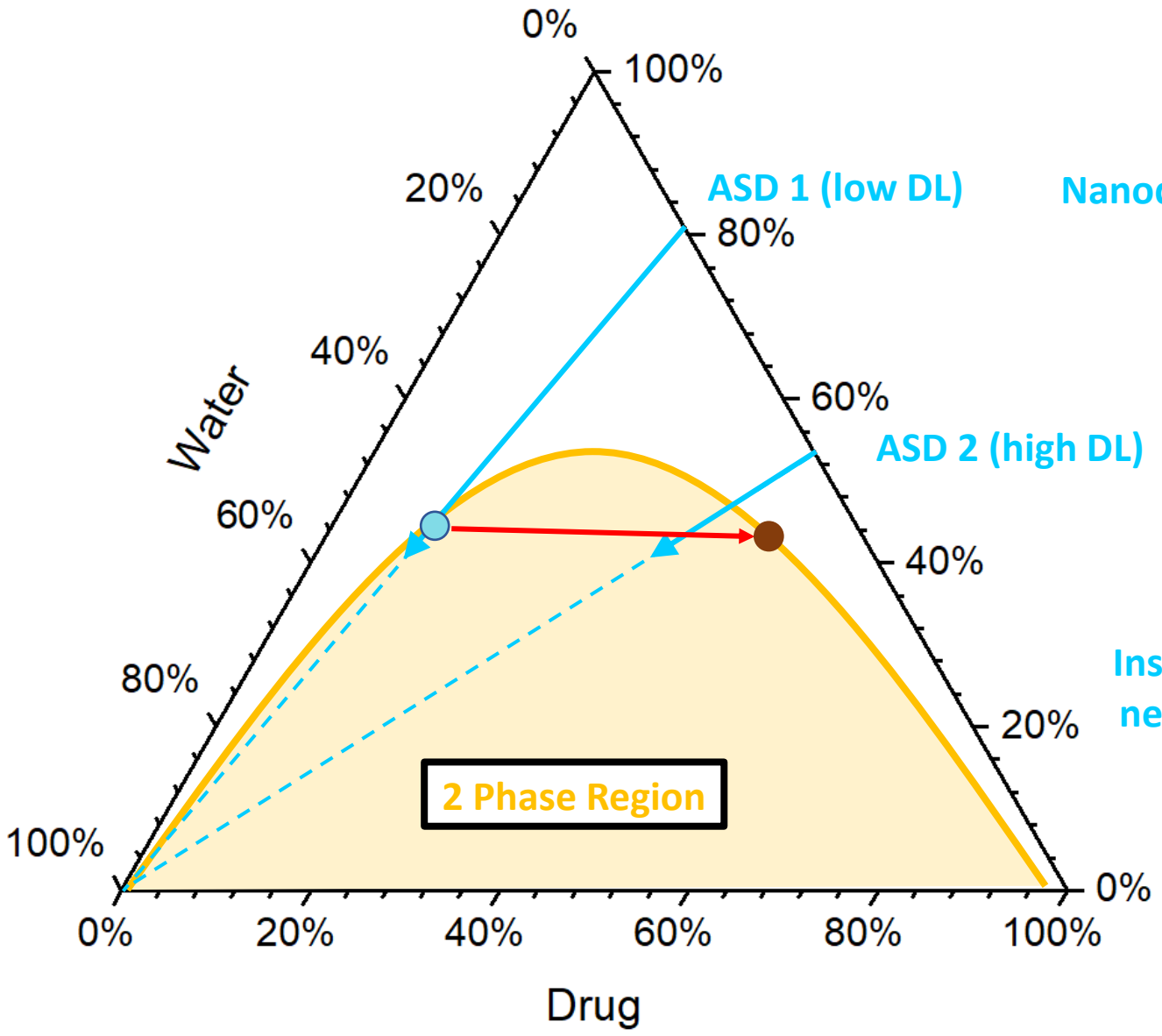
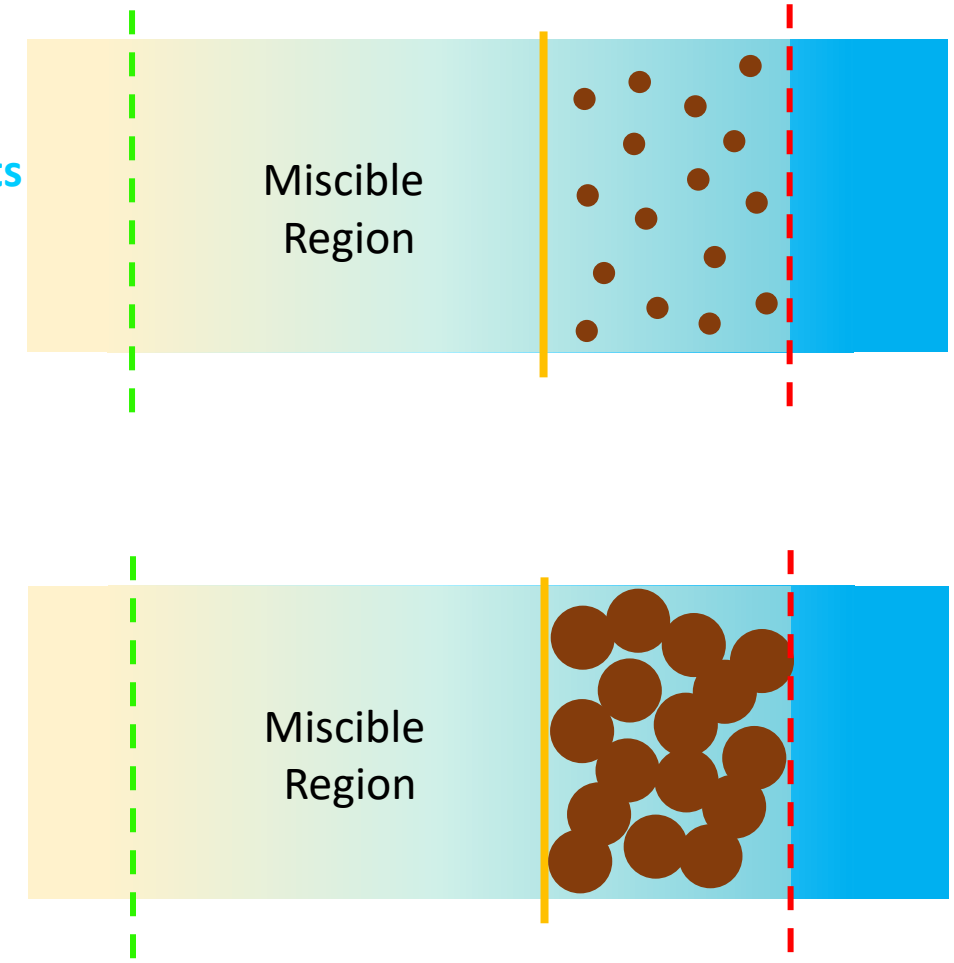
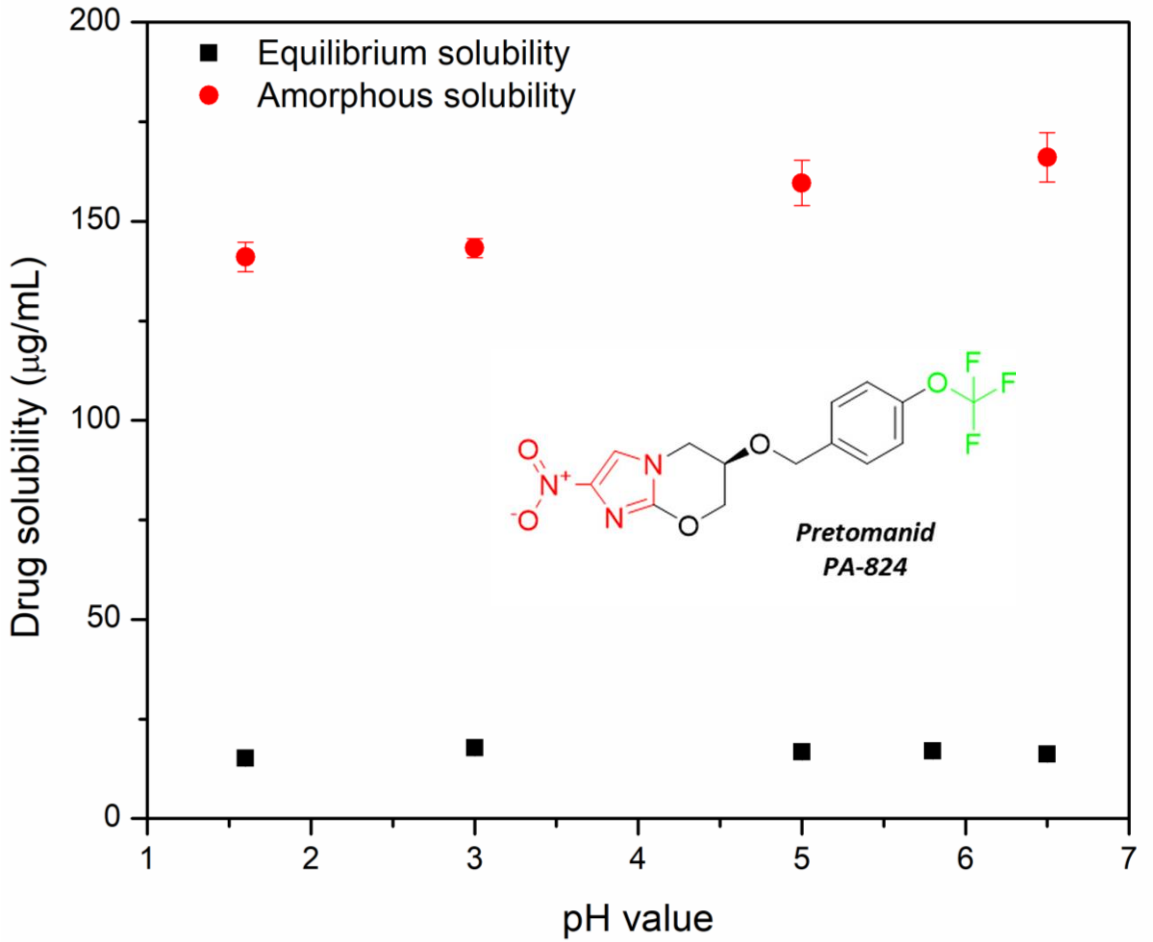
Phase Morphology with Drug Loading



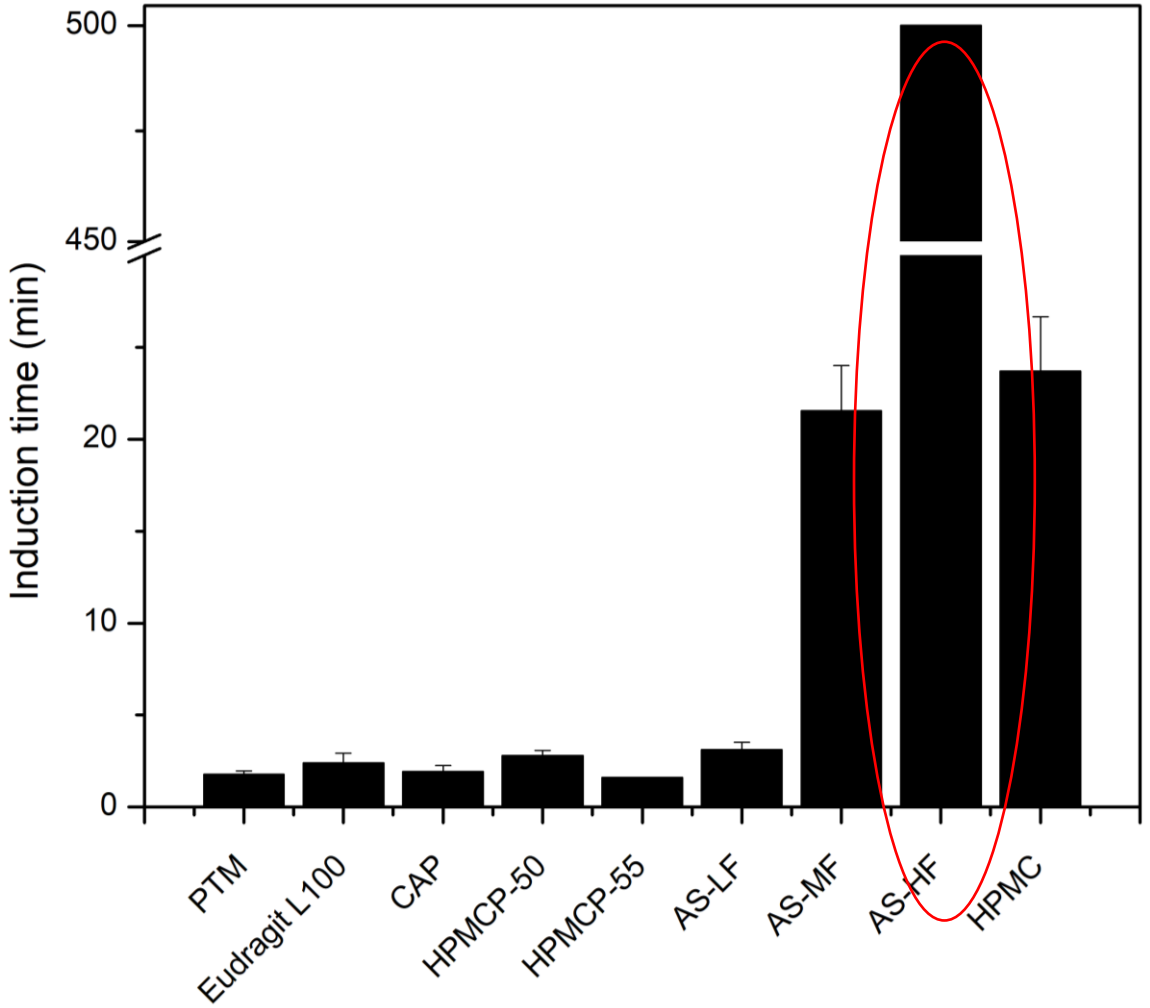


HPMCAS-based ASDs

pH independent drug solubility

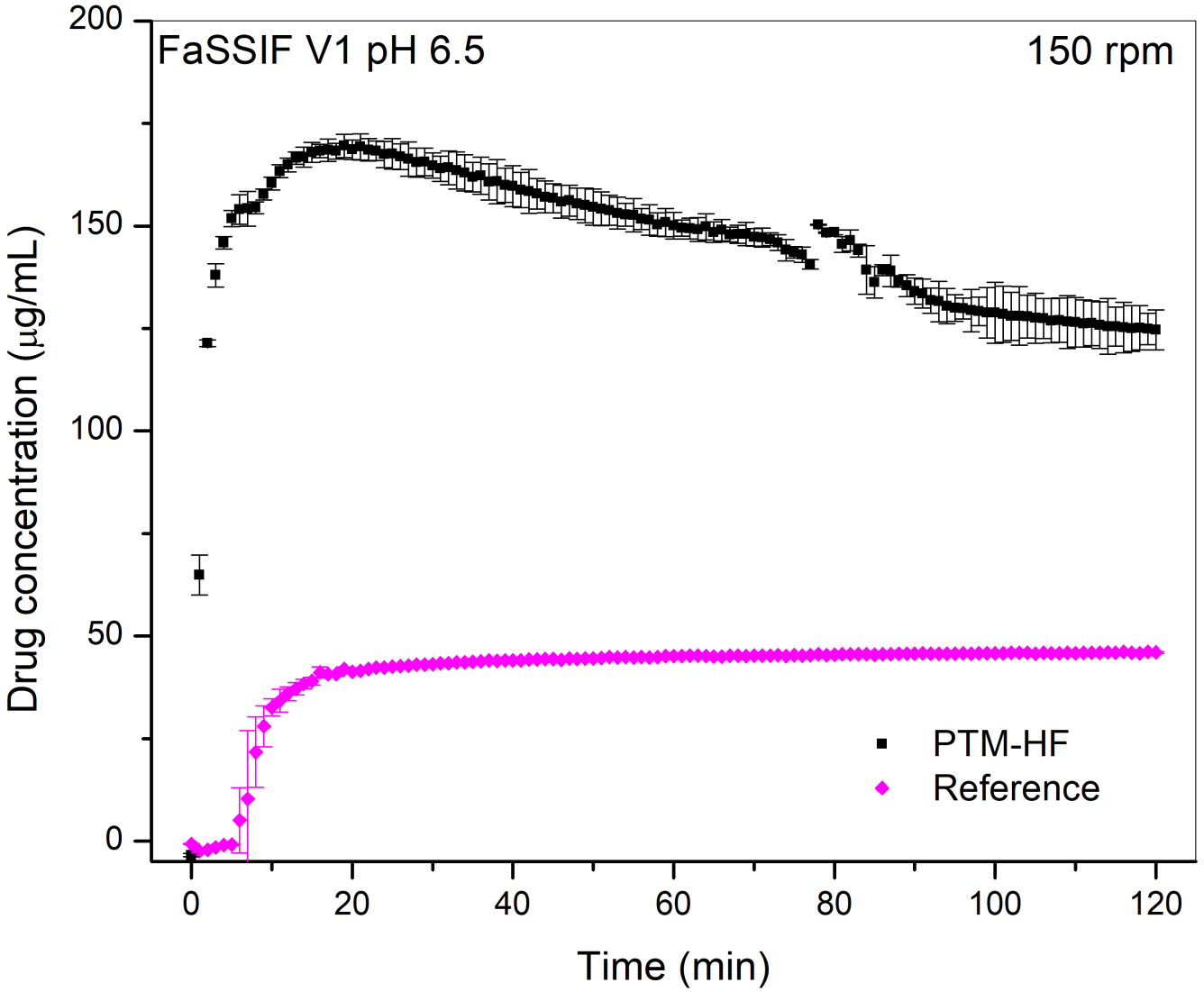


High crystallization tendency



HPMCAS-HF only viable choice for polymer

Improved PTM Dissolution from ASD in FASTED state conditions



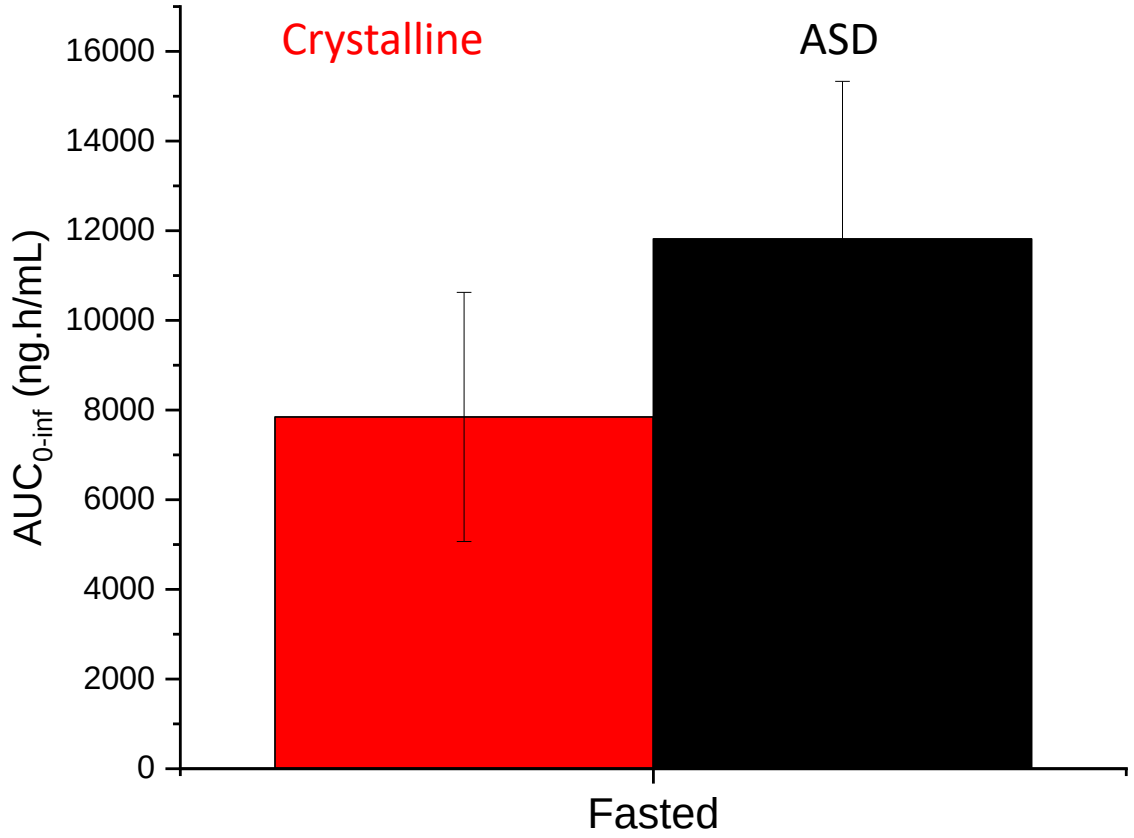
Complete release ~ 200 µg/mL

Binary ASD: PTM-HF 20-80 %w/w

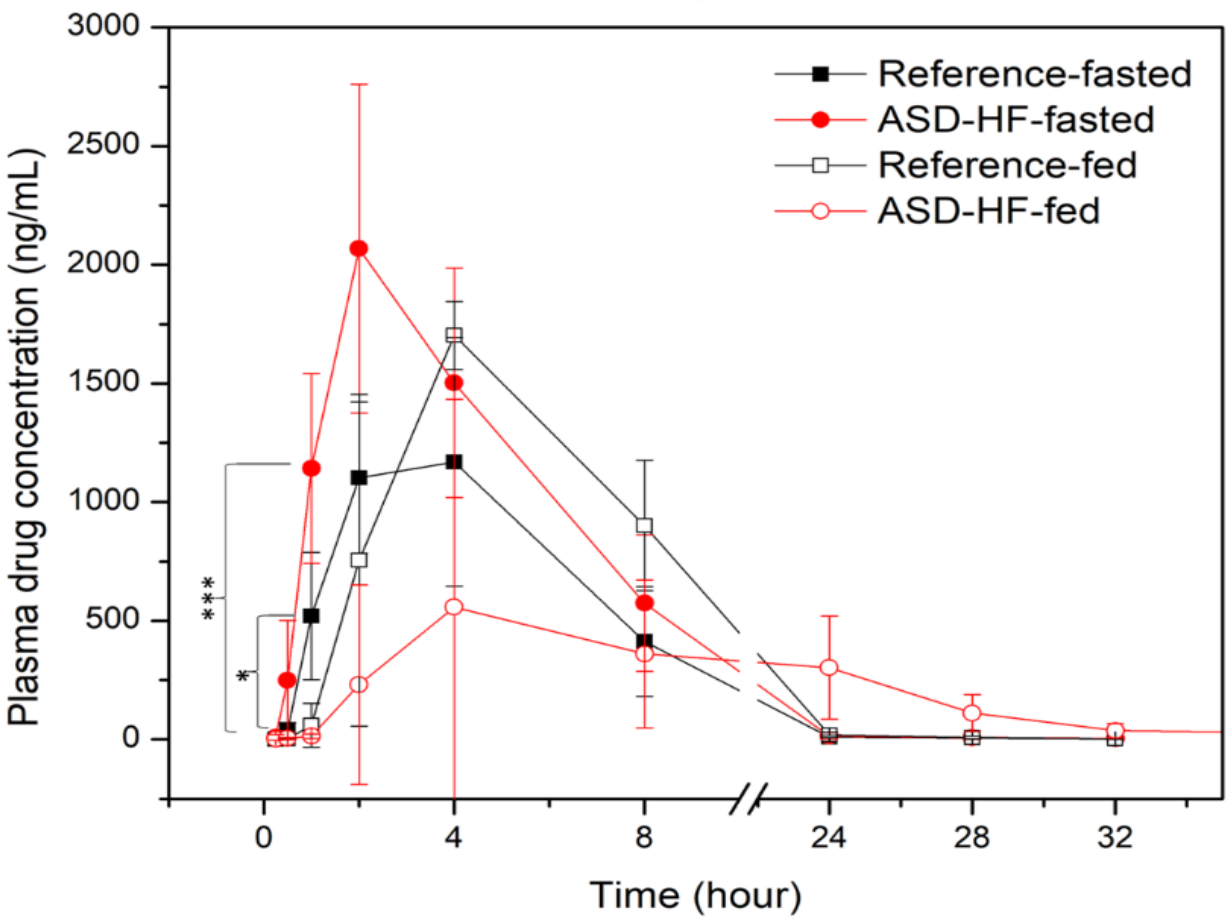
Dissolution testing:

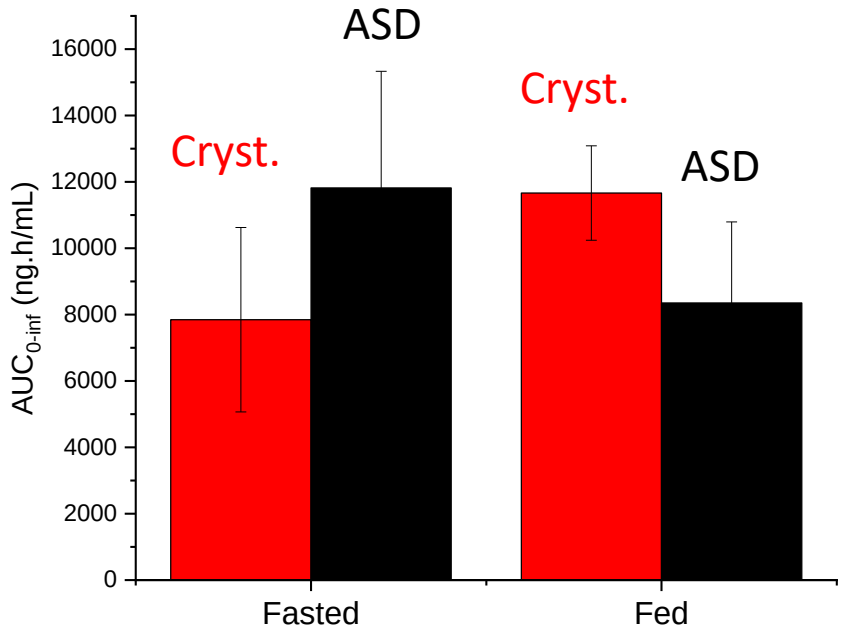
- ASD tablet (30 mg)
- Media: FaSSIF V1 (150 mL)
- 37°C, 150 rpm, USP apparatus II

Improved Absorption in Vivo in Fasted State from ASD

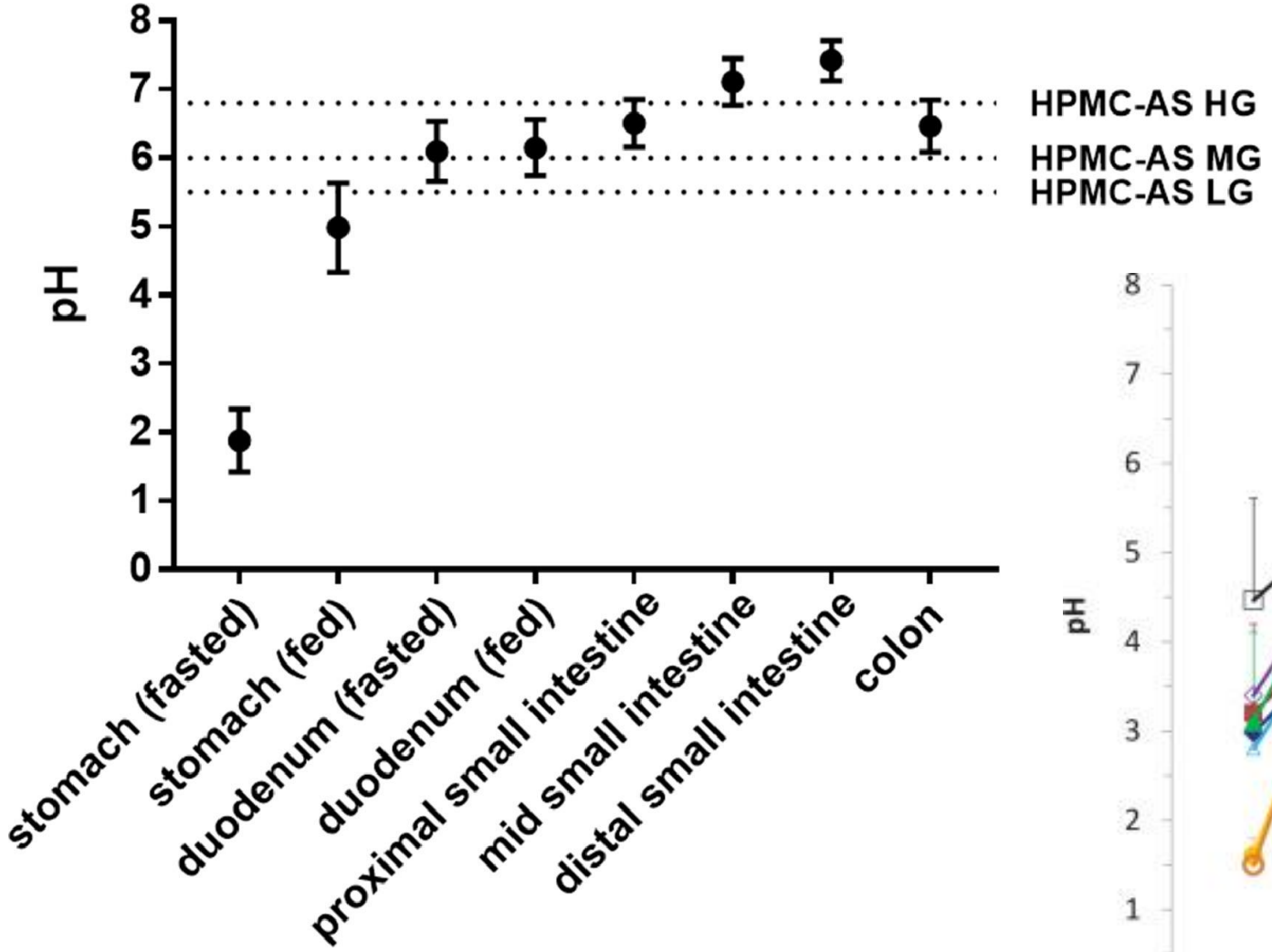


But – Negative Food Effect

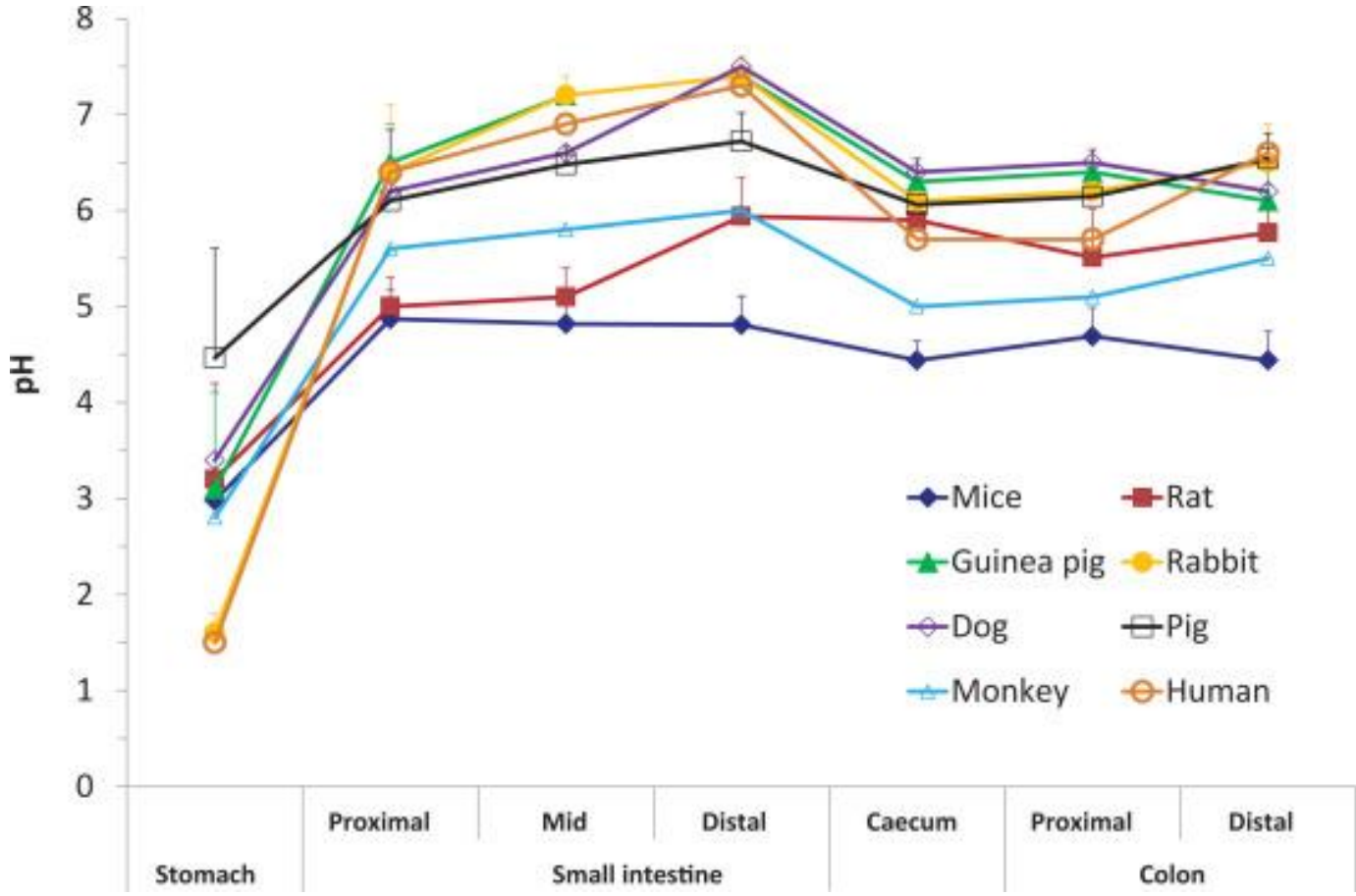




A Closer Look at pH

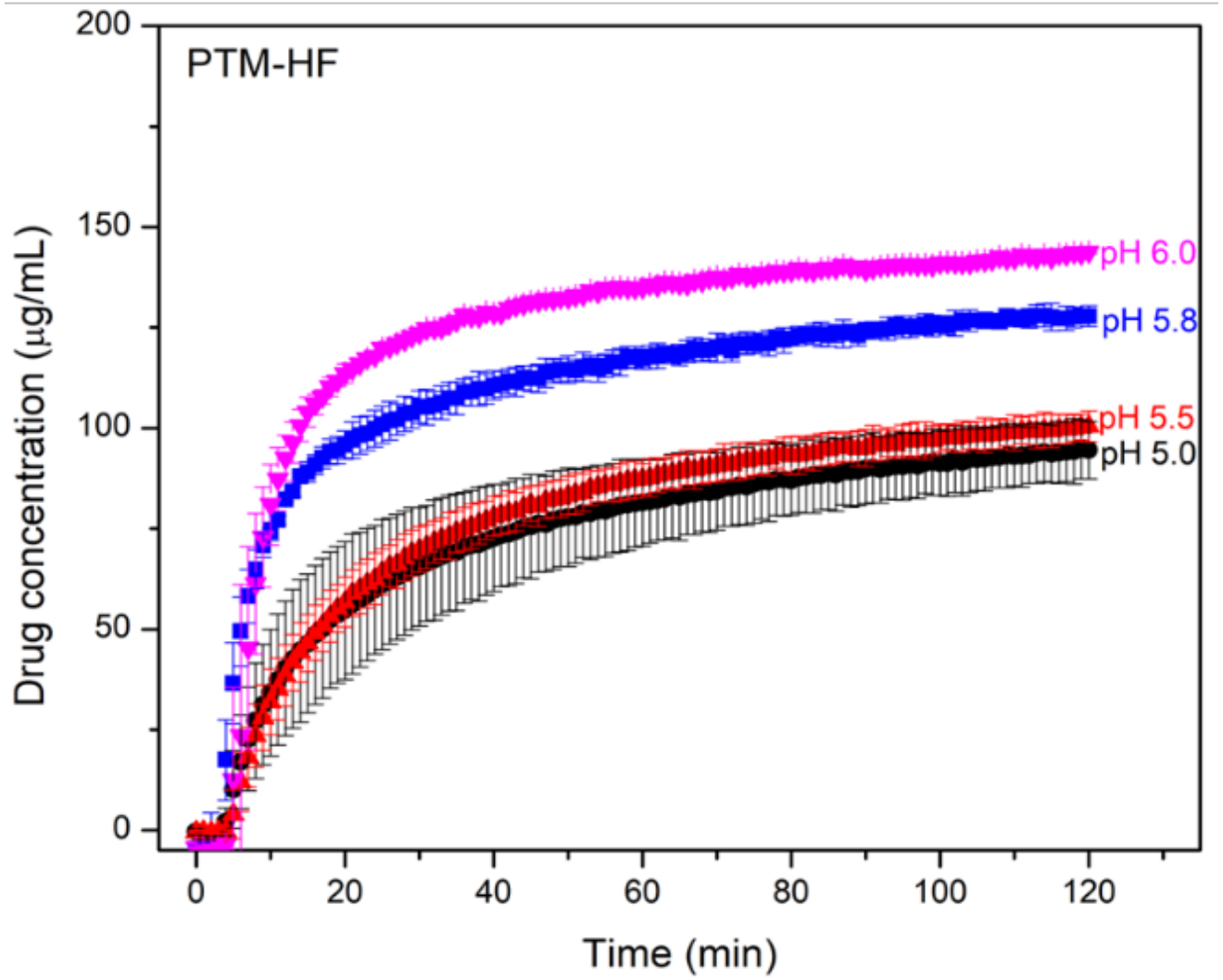


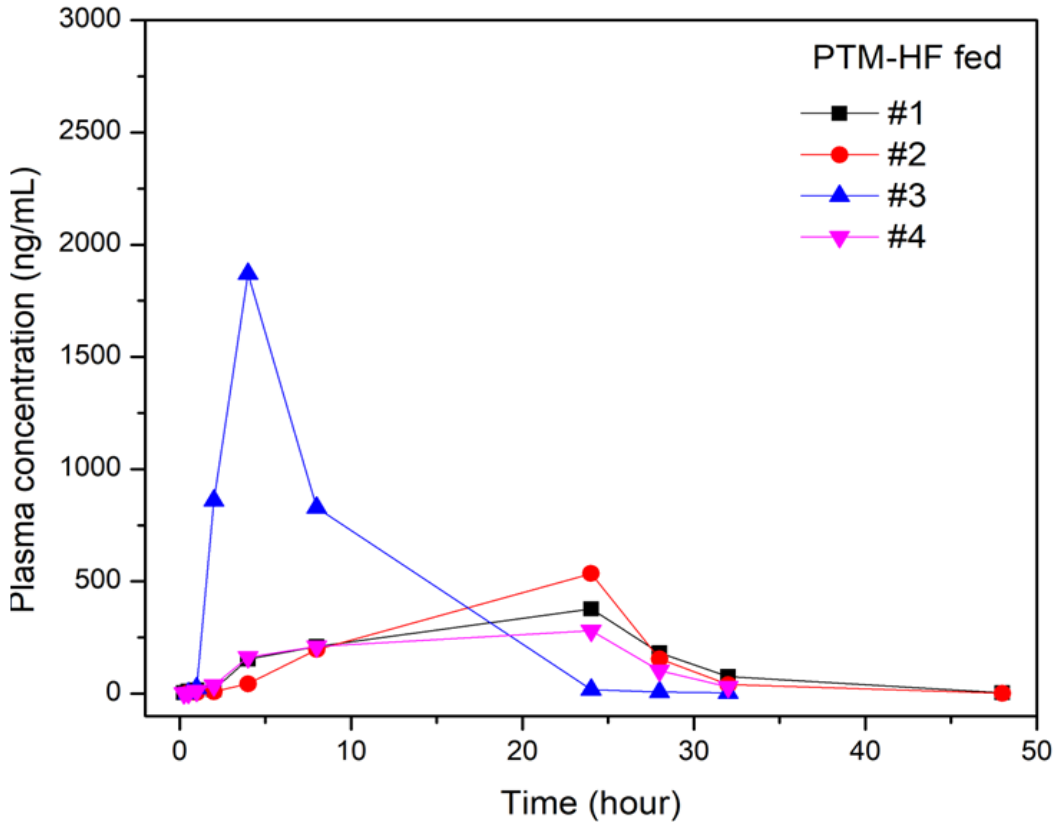
Vinarov, Zahari, *et al*. European Journal of Pharmaceutical Sciences 162 (2021): 105812.



Hatton, Grace B., *et al*. Journal of Pharmaceutical Sciences 104.9 (2015): 2747-2776.

Importance of pH for HPMCAS-based ASDs





Summary

- Release from ASDs is likely to be controlled by polymer release rate
- Polymer release is impacted by external factors (pH, hydrodynamics) and formulation factors (drug properties and loading, additional excipients)
- Release testing approaches are in their infancy for ASD formulations and will evolve as more is revealed about release mechanisms

Acknowledgements

- Ruochen Yang
- Alex Deac
- Tu Van Duong
- Thuy Nguyen
- Anura Indulkar
- BMGF
- TB Alliance
- AbbVie