

Dissolution of PVPVA-Based Amorphous Solid Dispersions and Absorption of Poorly Soluble Drugs

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NCE drug discovery is shifting toward poorly water soluble compounds

		Solubility	
		High	Low
Permeability	High	Class 1 Marketed: 40% NCE: 18%	Class 2 Marketed: 33% NCE: 54%
	Low	Class 3 Marketed: 21% NCE: 22%	Class 4 Marketed: 6% NCE: 6%

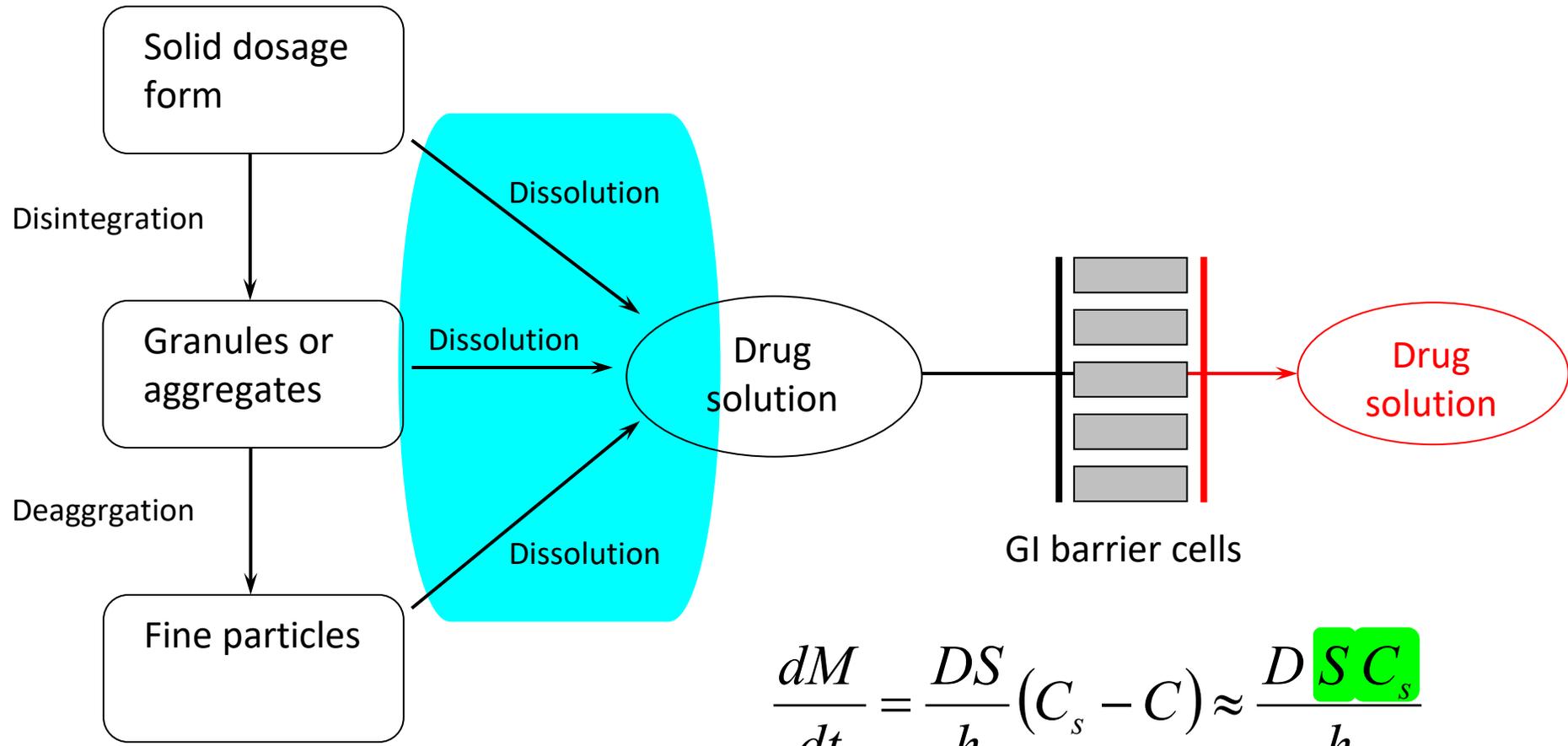
NCE

- From a data set of 28,912 medicinal chemistry compounds
- At least one target
- Having affinities at sub- μ M concentrations.

Benet et. al., 2011, AAPS J
Broccatelli et al., 2012, Mol Pharm



Solubility \longrightarrow Dissolution \longrightarrow Absorption



$$\frac{dM}{dt} = \frac{DS}{h} (C_s - C) \approx \frac{D S C_s}{h}$$



Enabling formulations have successfully delivered many insoluble compounds to human

- Solutions: pre-dissolved
 - Co-solvent
 - Lipid solutions
- Solids: dissolution rate enhancement
 - Salts and co-crystals
 - Complexes
 - Nano-crystals
 - Amorphous and amorphous solid dispersions
- Crystallization inhibition
 - In vivo pH changes or enhanced dissolution
 - Leading to supersaturation in the GI track



Solution process is a balance between solute-solute, solvent-solvent, and solute-solvent interactions

Crystalline Solids



Stage 1. Abstraction of a molecule from the solute.

Pair potential energy = u_{BB}

Energy change = $+u_{BB}$



Stage 2. Creation of a hole in the solvent.

Pair potential energy = u_{AA}

Energy change = $+u_{AA}$



Stage 3. Insertion of a solute molecule into the solvent.

Pair potential energy = u_{AB}

Energy change = $-2u_{AB}$

Amorphous Solids



- “Penalties” for Stages 1 and 2
- “Rewards” for Stage 3
- Comparing amorphous to crystalline
 - Much less “penalties” for Stage 1
 - Stages 2 and 3 are identical
 - Leading to higher apparent solubilities for amorphous solids

Figure 2.16 Hypothetical stages in the solution process.

Grant & Higuchi, 1990, Solubility Behavior of Organic Compounds

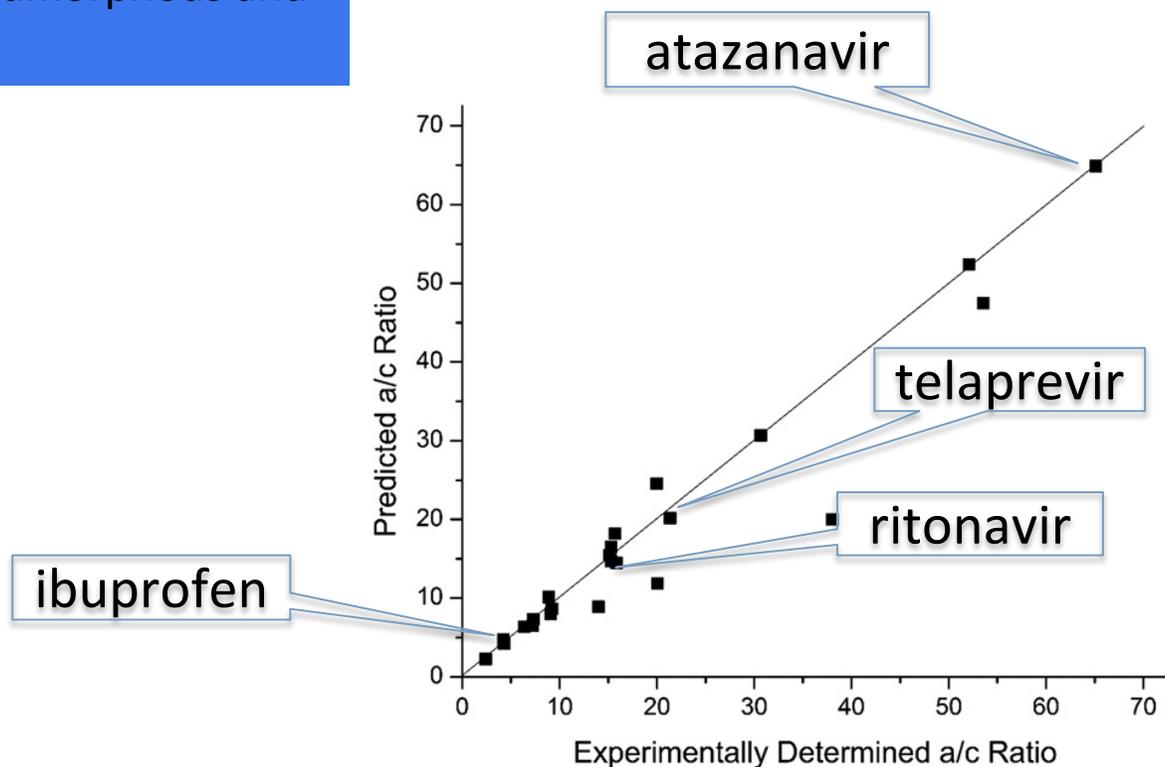


Amorphous solids, due to the lack of crystallinity, are more soluble than crystalline solids

$$\ln \frac{x_D^{L1(a)}}{x_D^{L1(c)}} = \frac{\mu_D^{0(a)} - \mu_D^{(c)}}{RT} + \ln(x_D^{L2(a)} \gamma_D^{L2(a)})$$

Free energy difference between dry amorphous and crystalline phases

Account for the decrease in drug activity due to water sorption into amorphous

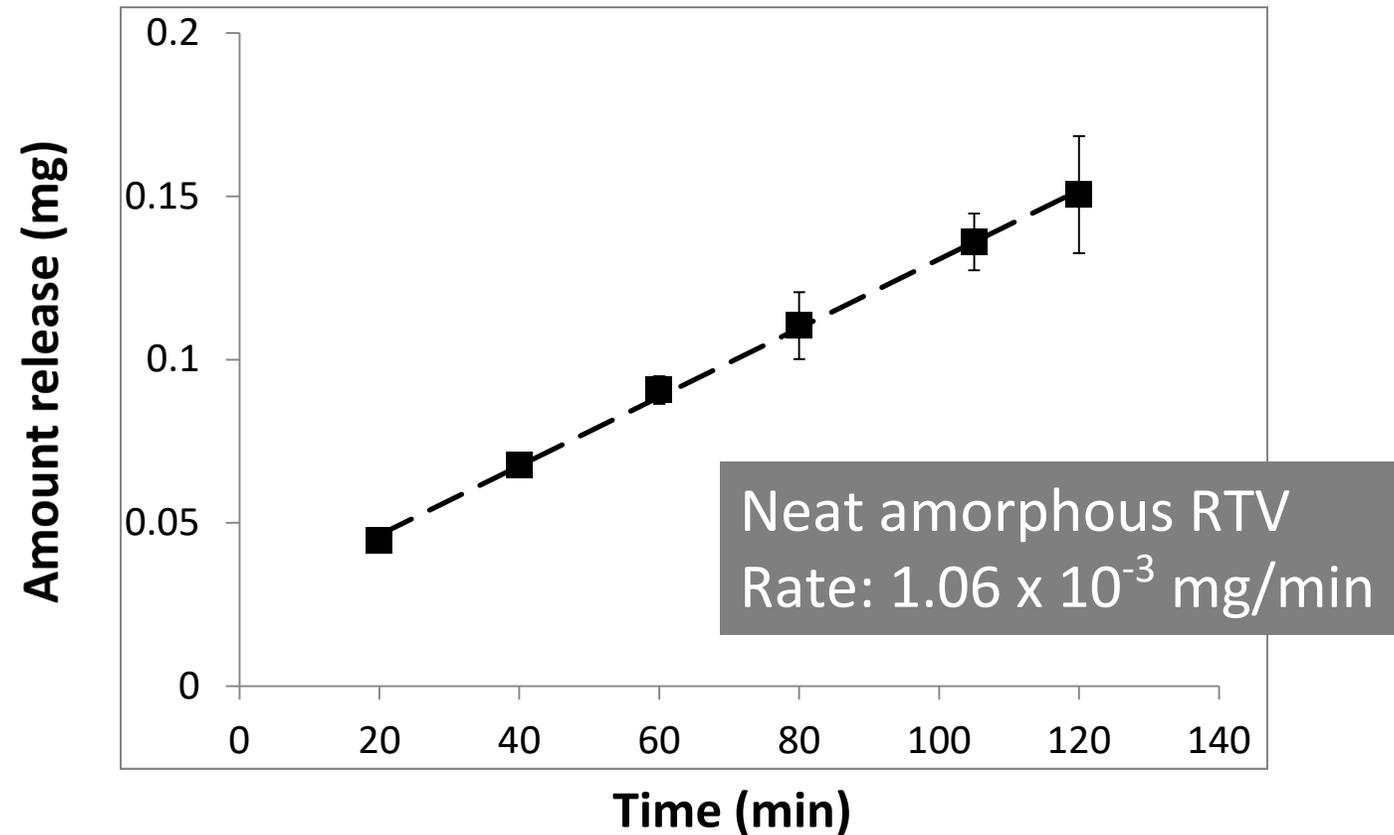


Taylor & Zhang, 2016, Adv Drug Del Rev



In reality, dissolution of ASD can be much faster than neat amorphous drug

pH 6.8 buffer; 100 mg tablet of 1 cm diameter

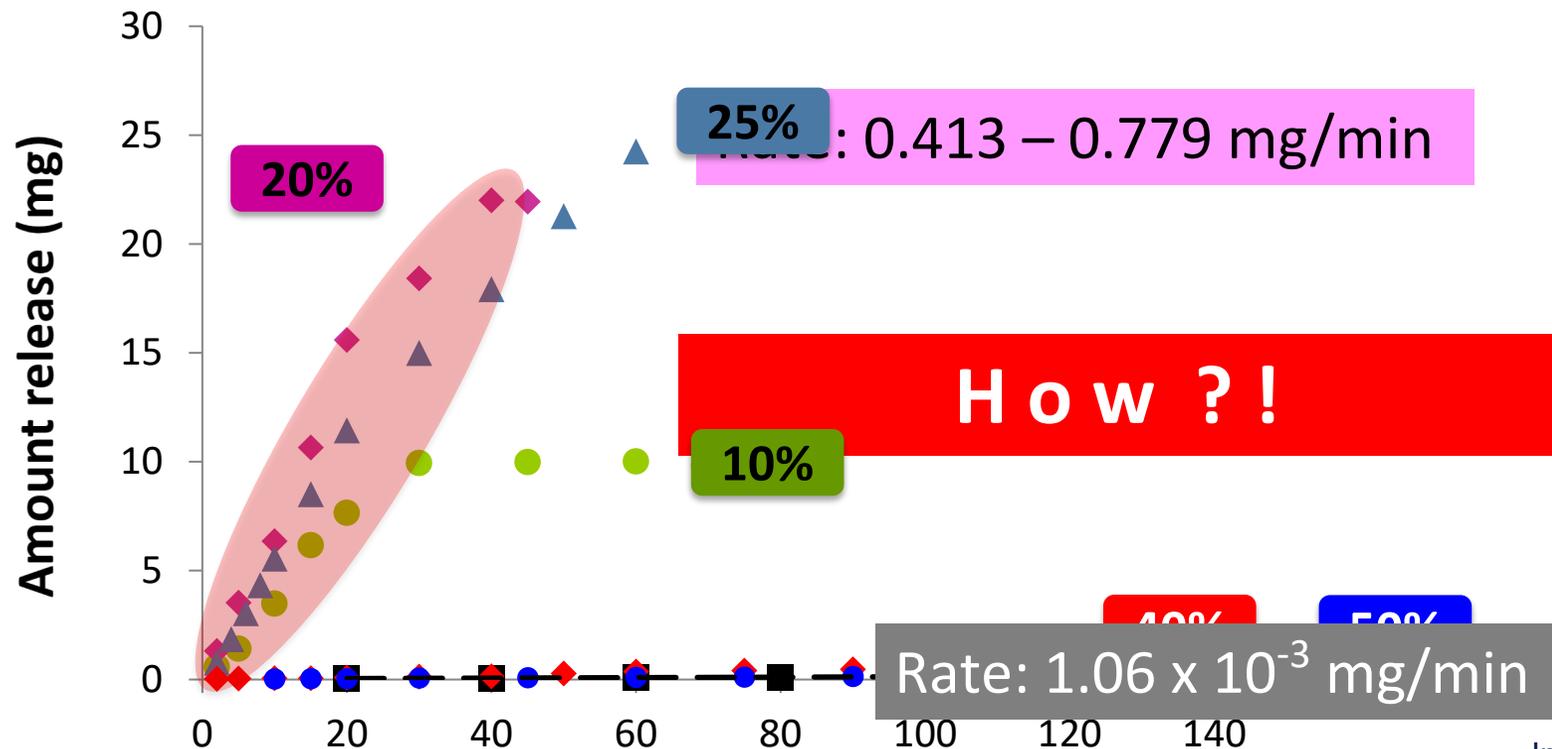


Indulkar et. al., 2019, Mol Pharm



In reality, dissolution of ASD can be much faster than neat amorphous drug, but slow at high drug loadings

Ritonavir release
pH 6.8 buffer; 100 mg tablet of 1 cm diameter

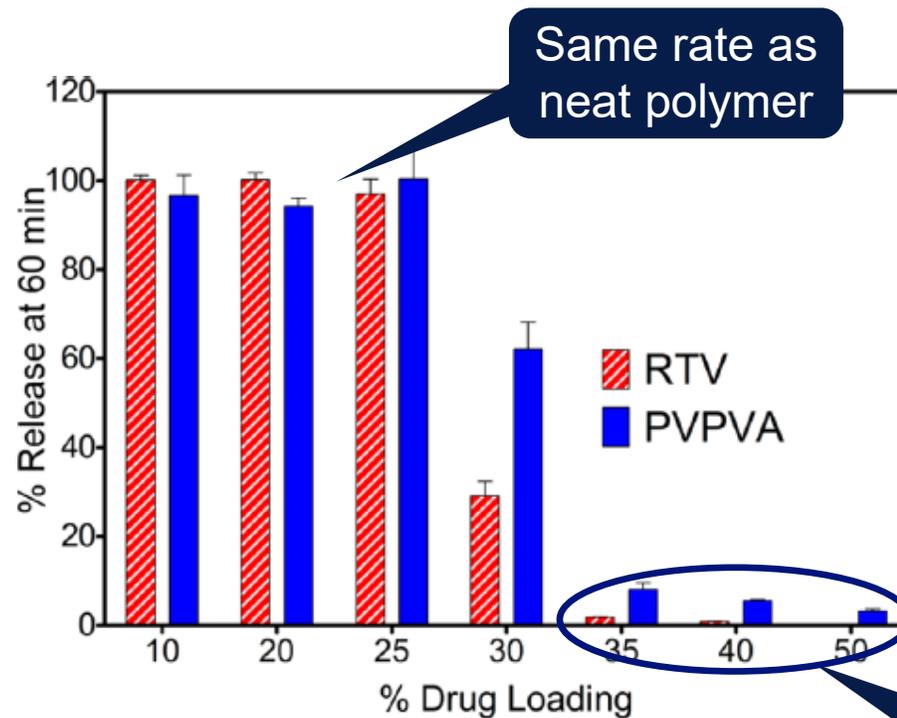
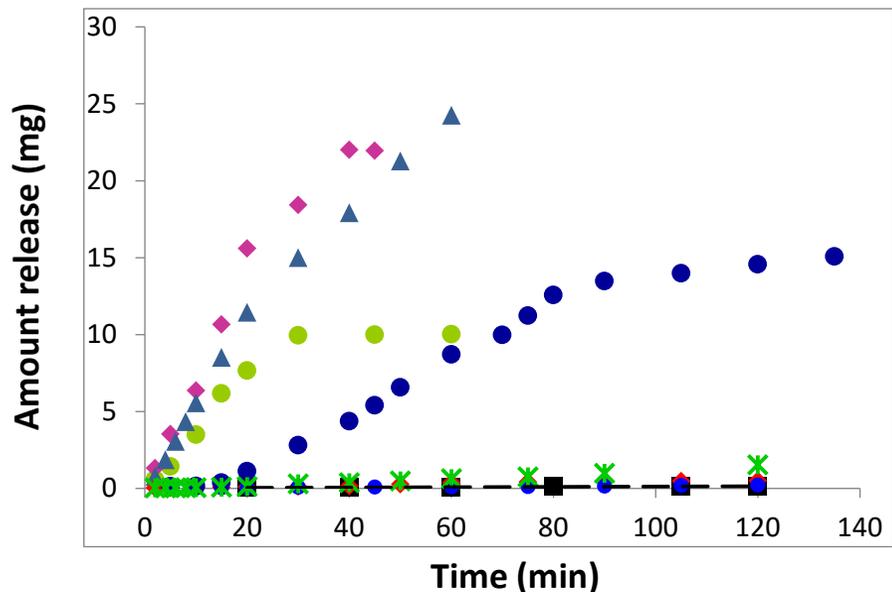


Indulkar et. al., 2019, Mol Pharm



ASD dissolution transitions from polymer controlled to drug controlled, around “Limit of Congruency”

Ritonavir release



New concept/term: Limit of Congruency (LoC)

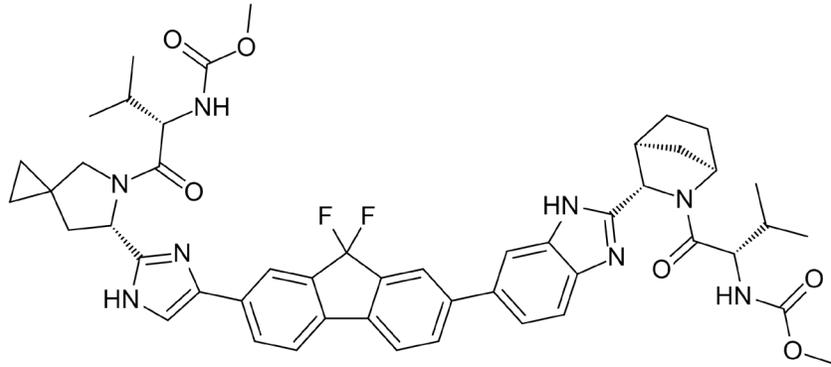
“Falling off the cliff” beyond certain drug loading

Rapid phase separation at the dissolution interface

Indulkar et. al., 2019, Mol Pharm

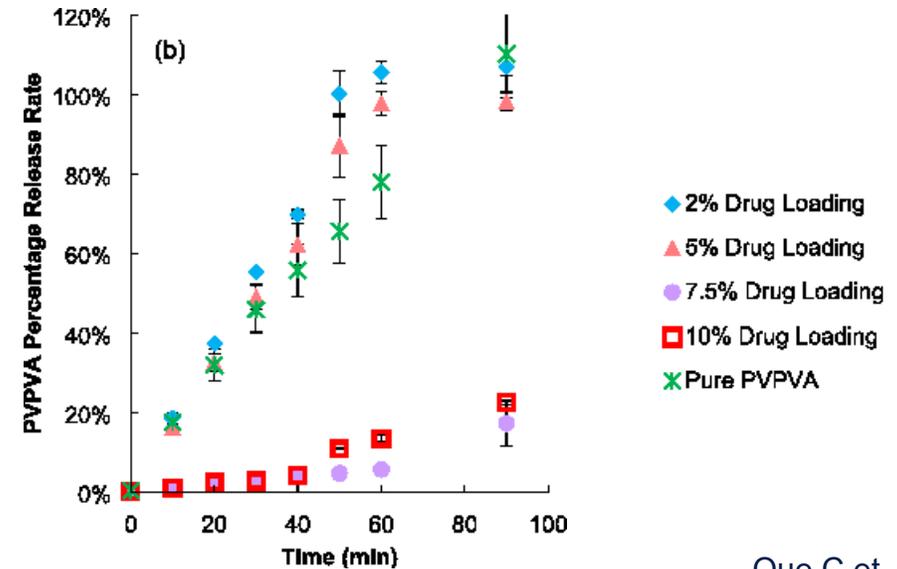
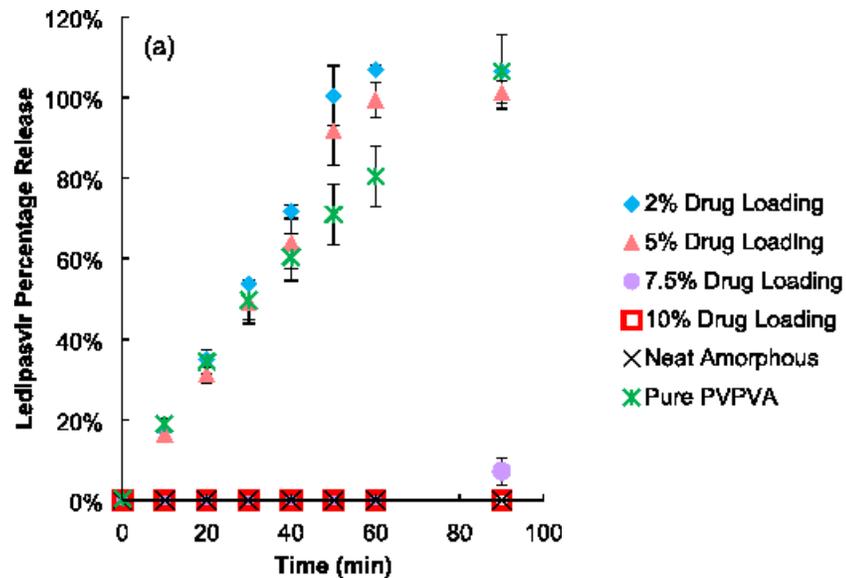


This phenomenon is general for PVPVA-based ASDs



Ledipasvir: Antiviral/HCV

LoC: ~ 5%

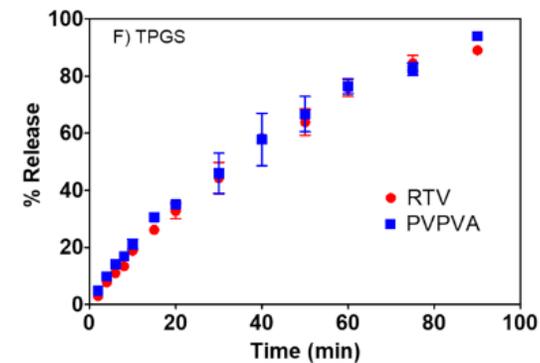
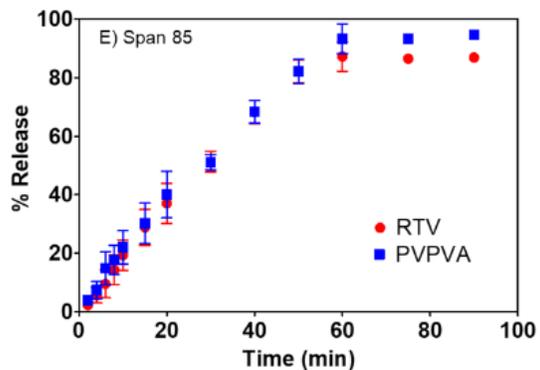
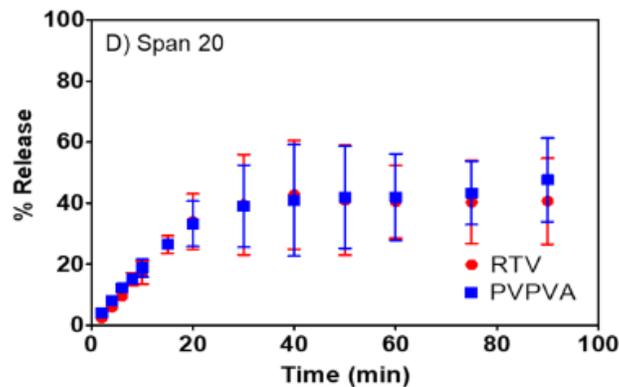
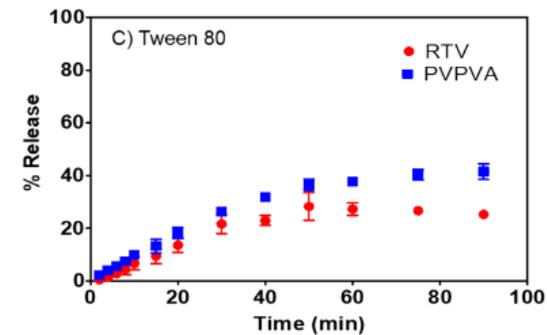
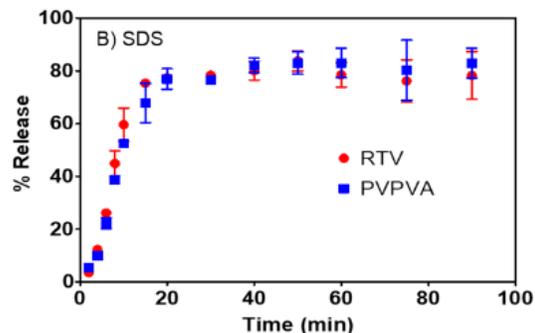
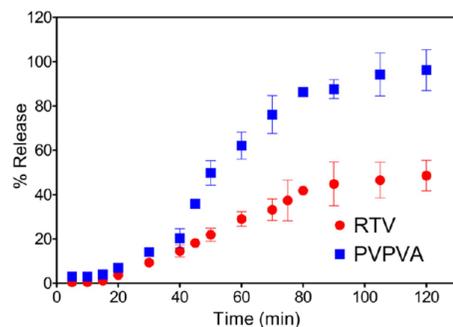


Que C et. al., 2019, Mol Pharm



Incorporation of surfactants can change LoC

Ritonavir:PVPVA 30:70 with additional 5% Surfactants

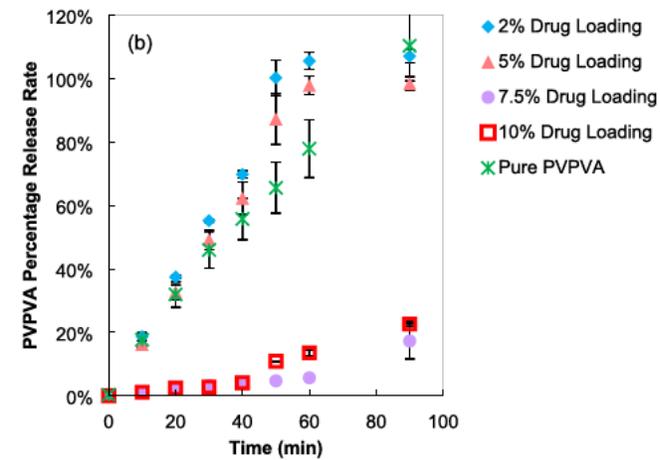
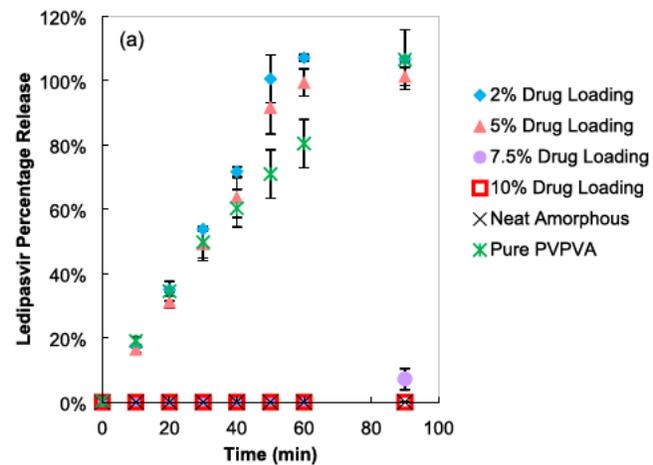


Indulkar C et. al., 2022, Pharm Res

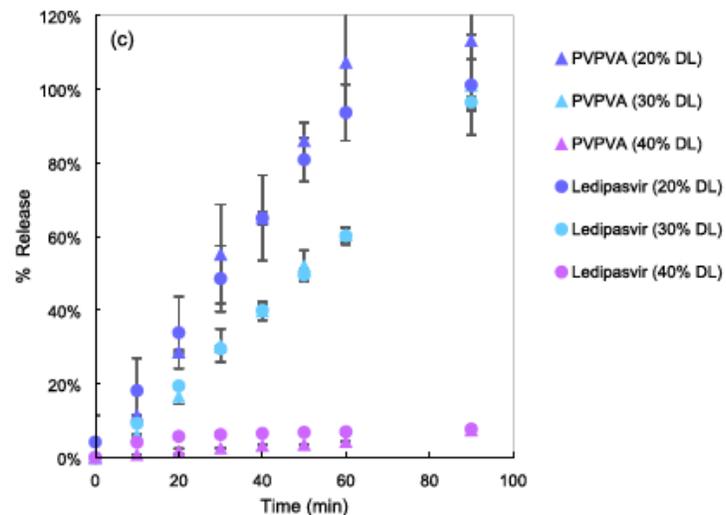


Incorporation of surfactants can change LoC

Ledipasvir
LoC ~ 5%



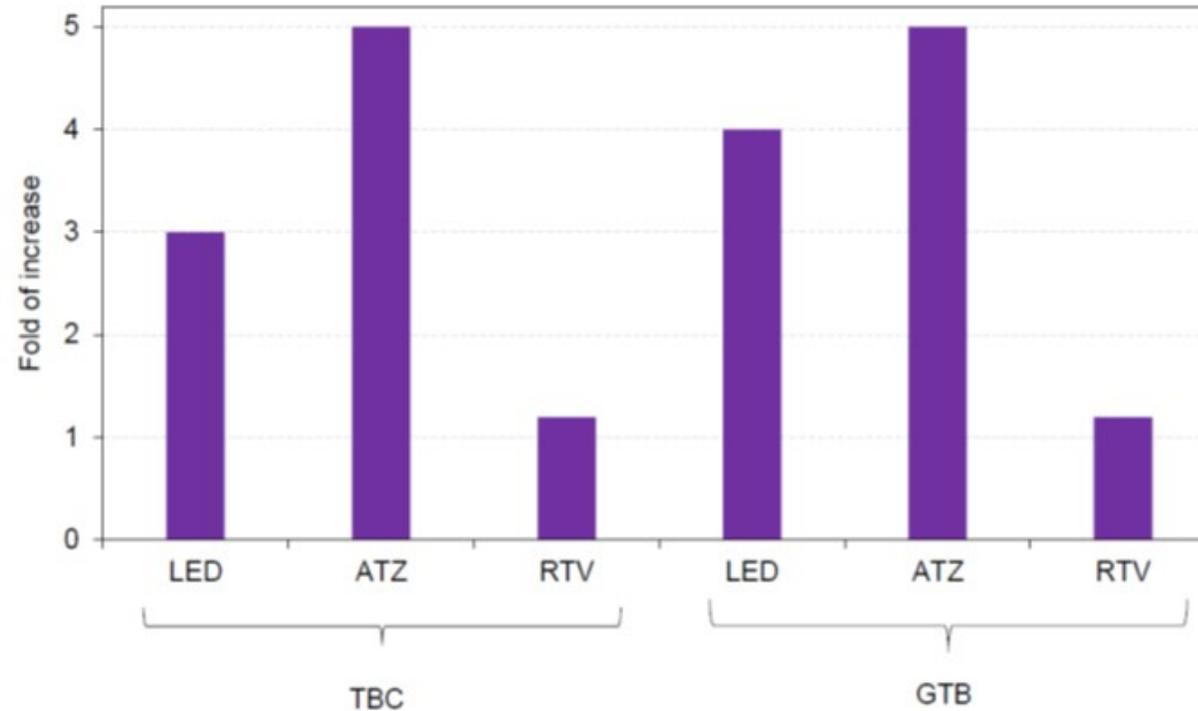
With 5% SDS
LoC increase to ~ 30%



Que et. al., 2019, Mol Pharm



Plasticizers can also change LoC



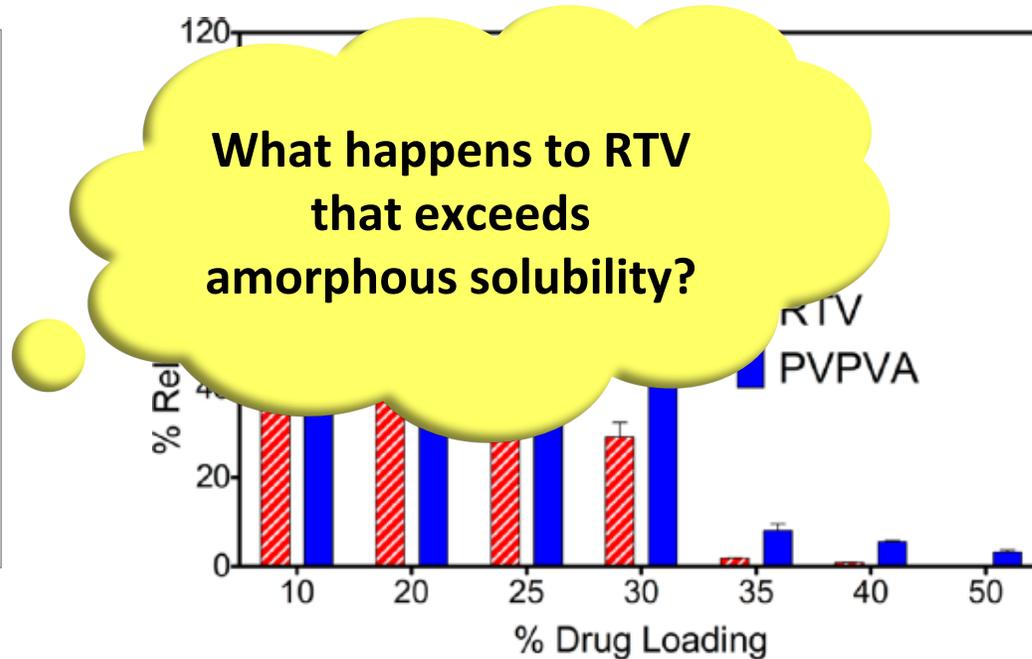
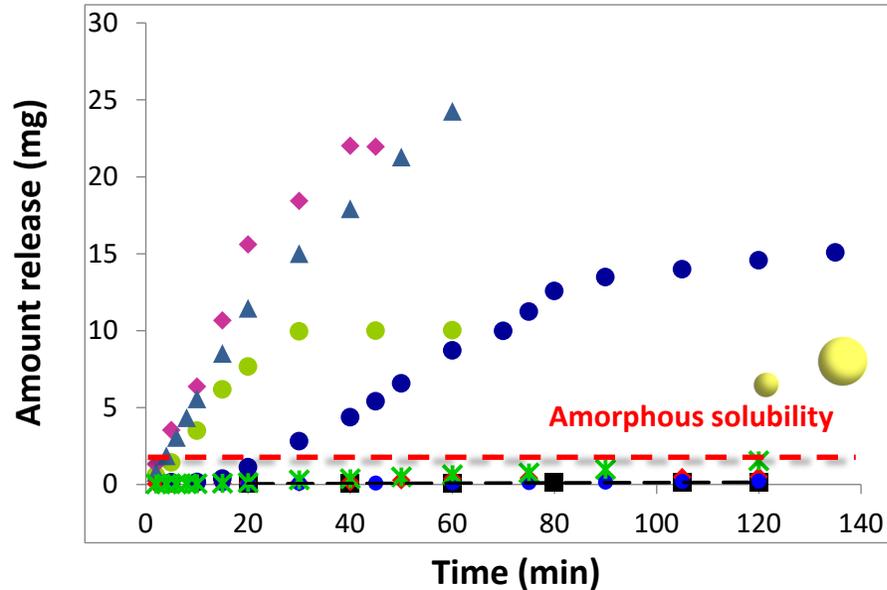
Drug	Max Enhancement in LoC	T _g , °C
ATZ (5%)	5X	105
LED (5%)	4X	160
RTV (25%)	1.2X	45

Correa-Soto et. al., 2023, Pharm Res



ASD dissolution transitions from polymer controlled to drug controlled, around “Limit of Congruency”

Ritonavir release



What happens to RTV that exceeds amorphous solubility?

New concept/term: Limit of Congruency (LoC)

“Falling off the cliff” beyond certain drug loading

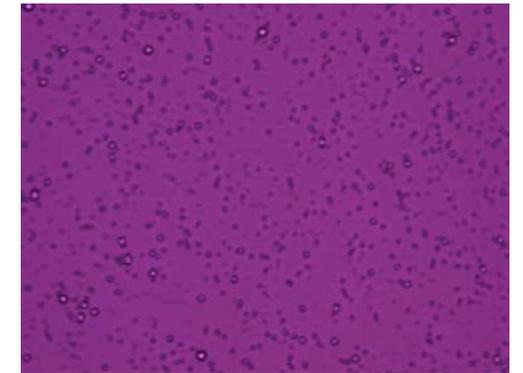
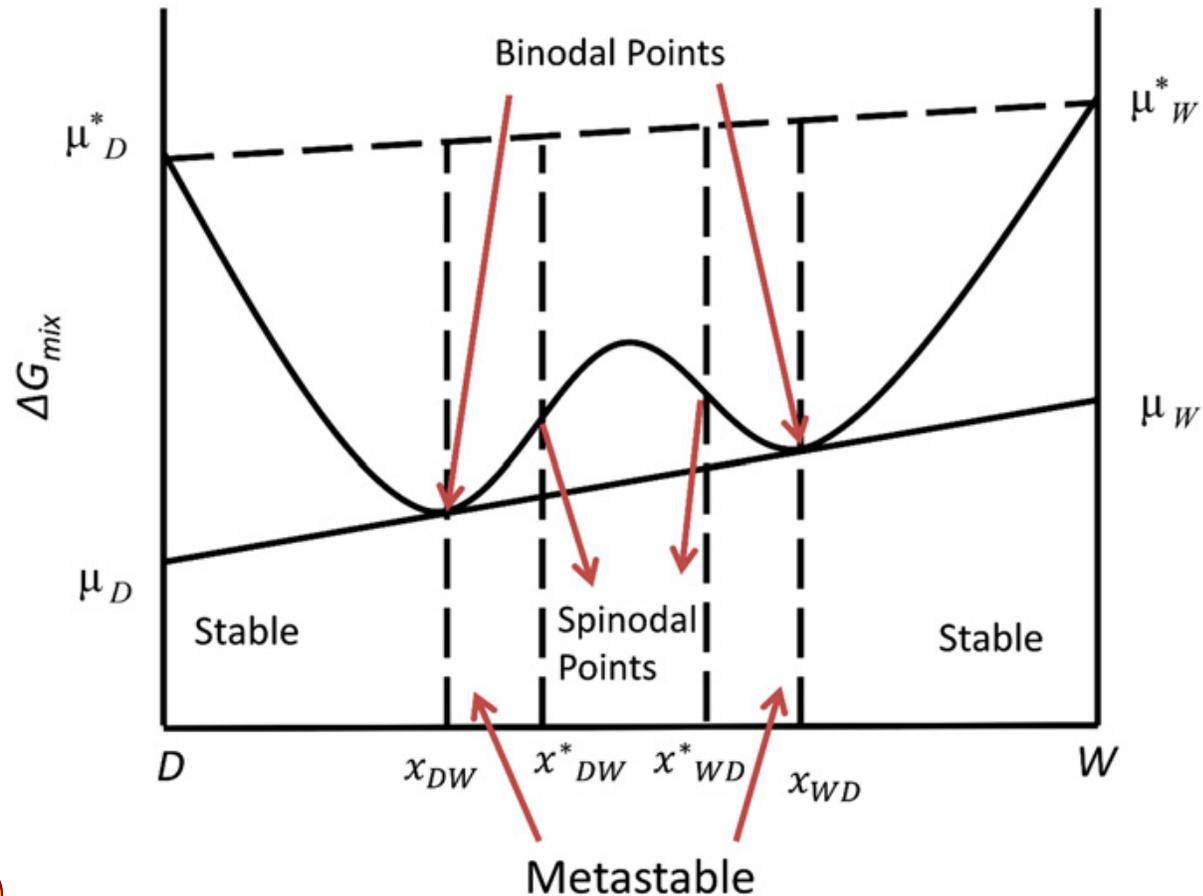


Indulkar et. al., 2019, Mol Pharm



Excess drug that exceeds amorphous solubility exists as liquid/glass droplets (LLPS/GLPS)

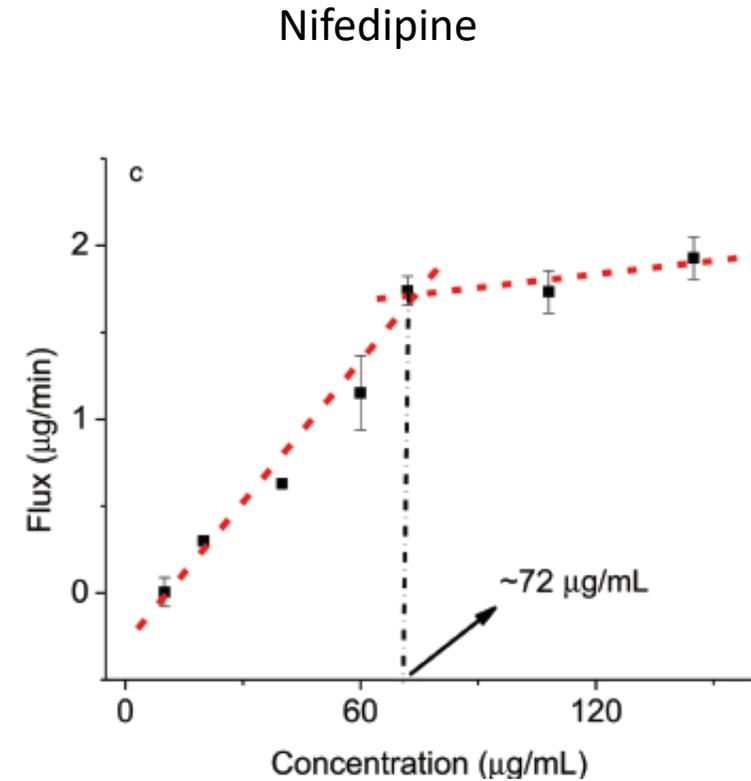
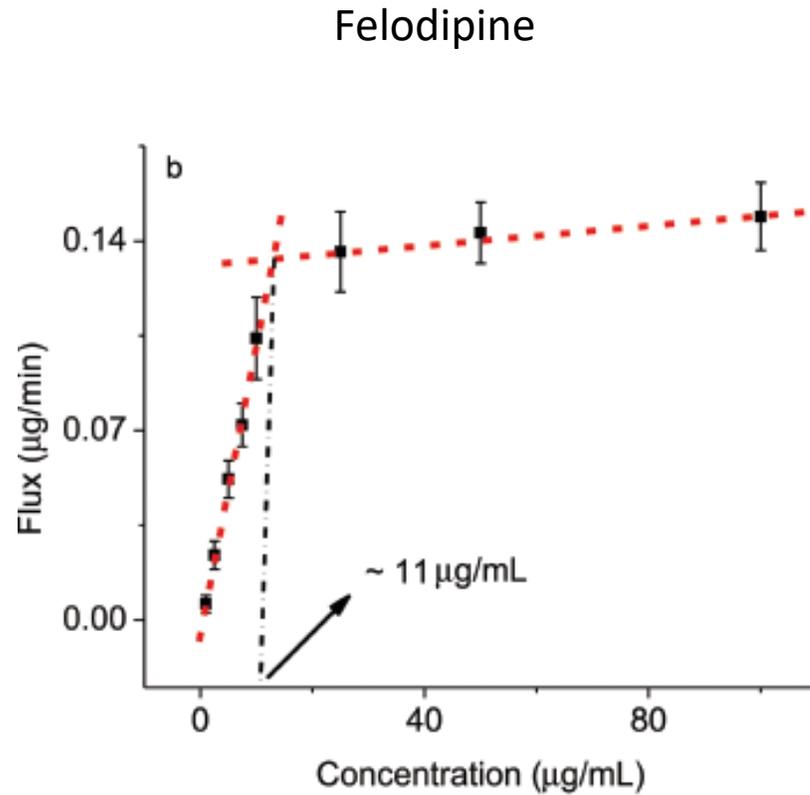
Free Energy Diagram for Miscibility of Two Phases – Liquid Liquid Phase Separation



Taylor & Zhang, 2016, Adv Drug Del Rev



Thus, mass transport will be limited at certain “apparent” concentration



Corresponds to amorphous solubility

Raina et al, 2014, J Pharm Sci



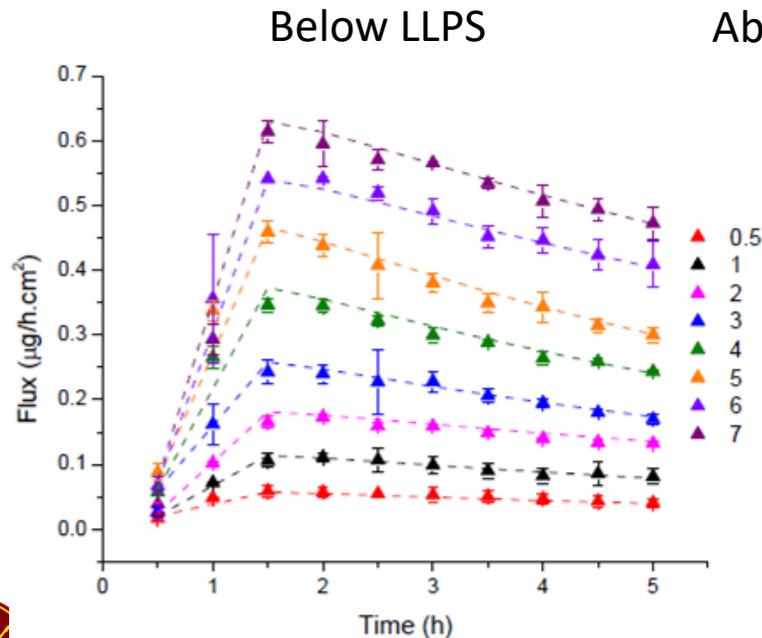
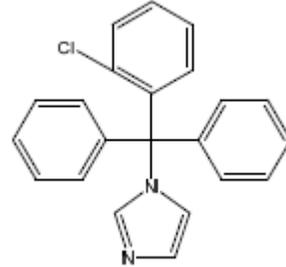
Droplets serve as a drug reservoir, driving sustained, enhanced diffusive absorption

Clotrimazole

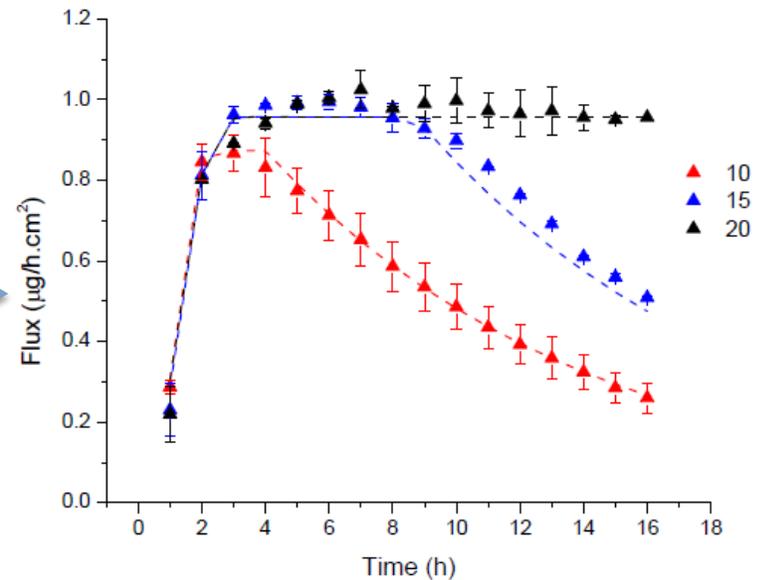
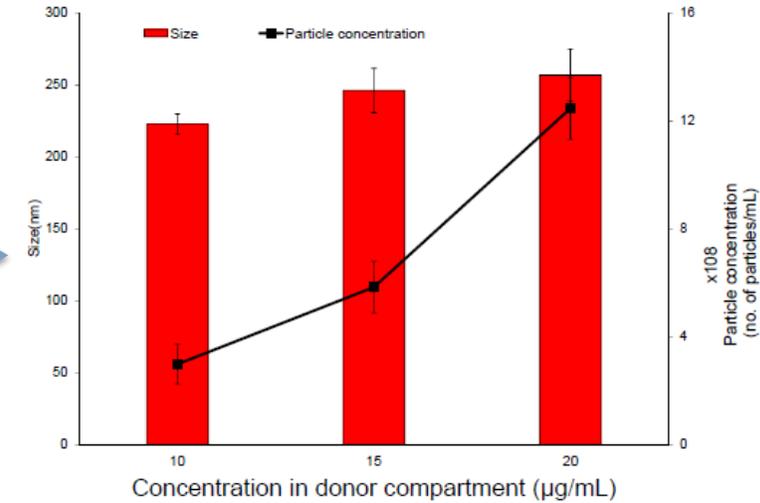
Weak base, $pK_a \sim 5.9$

$S_{cryst} \sim 0.55 \mu\text{g/mL}$

$S_{amor} \sim 7.5 \mu\text{g/mL}$



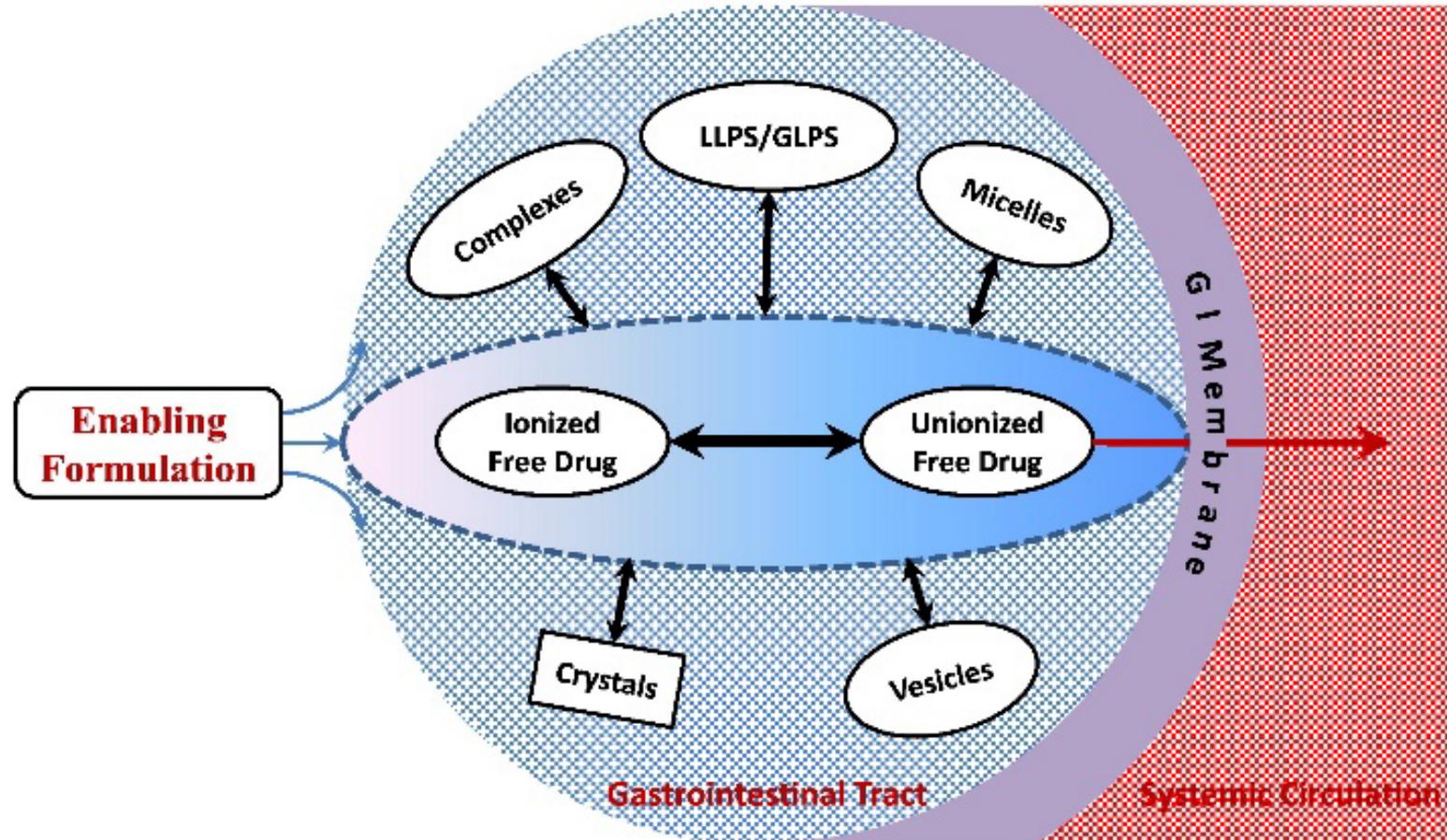
Above LLPS



Indulkar et. al., 2016, Mol Pharm



Compartments in GI track and absorption



Taylor & Zhang, 2016, Adv Drug Del Rev

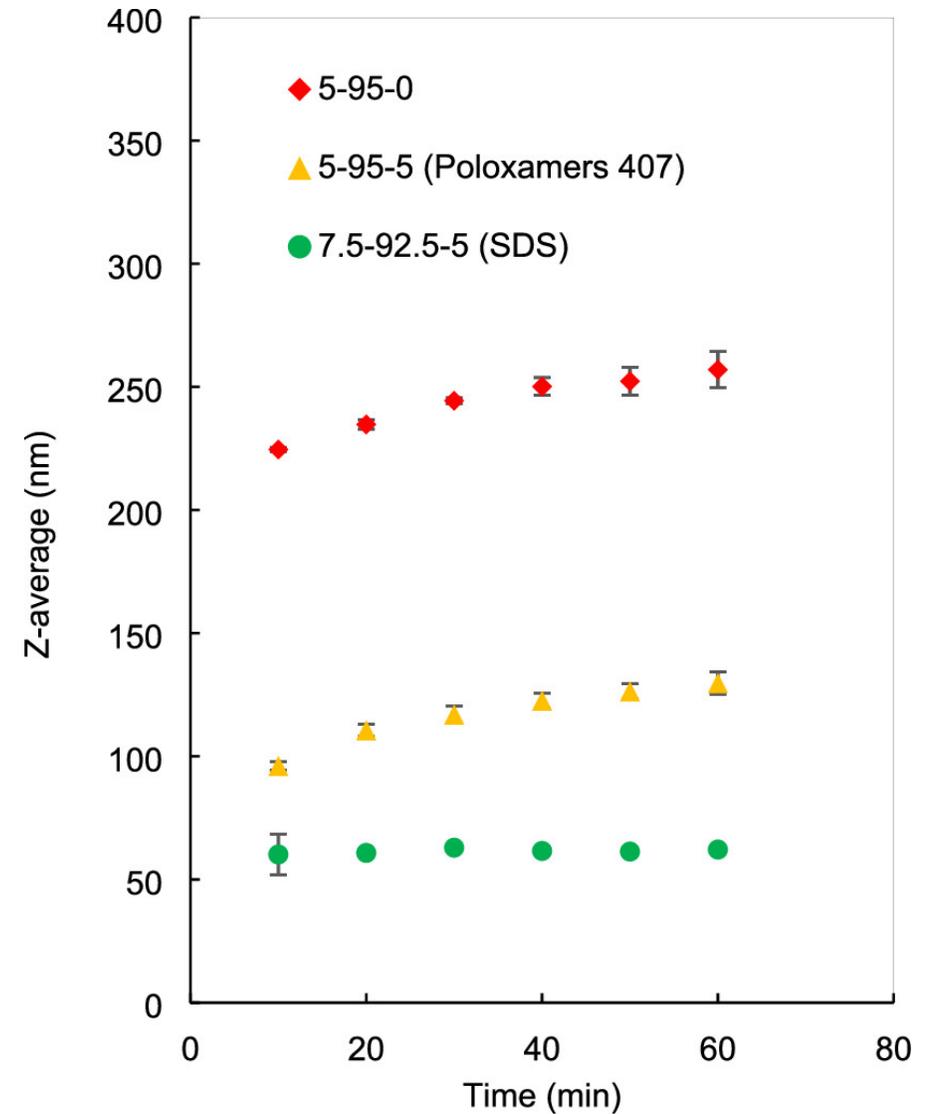
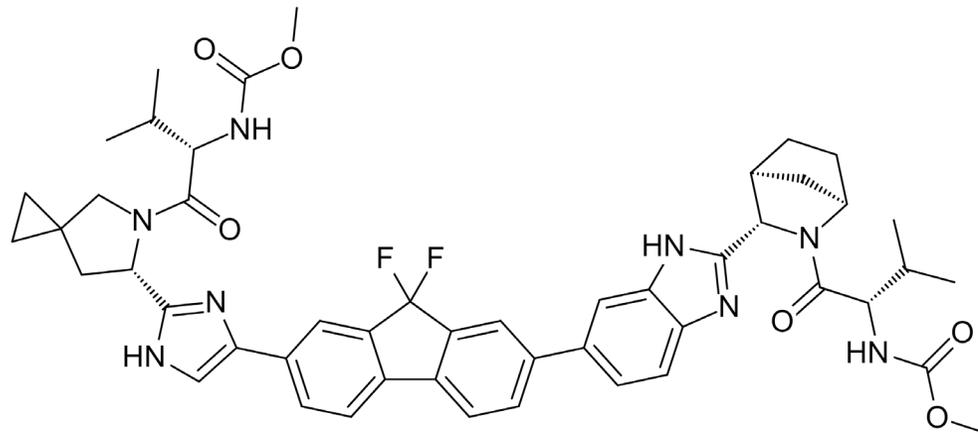


Several more critical points

- Droplet/particle size as a function of formulation composition

Ledipasvir: Antiviral/HCV

LoC: ~ 5%

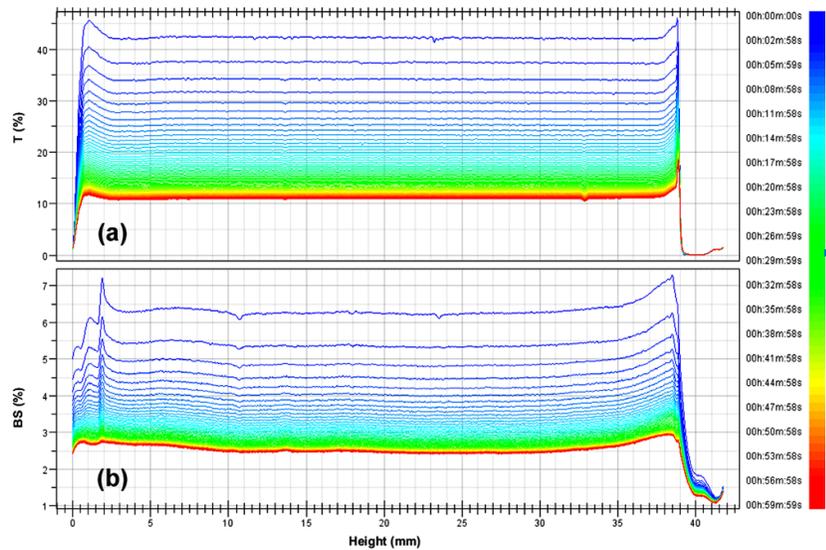


Que C et. al., 2019, Mol Pharm



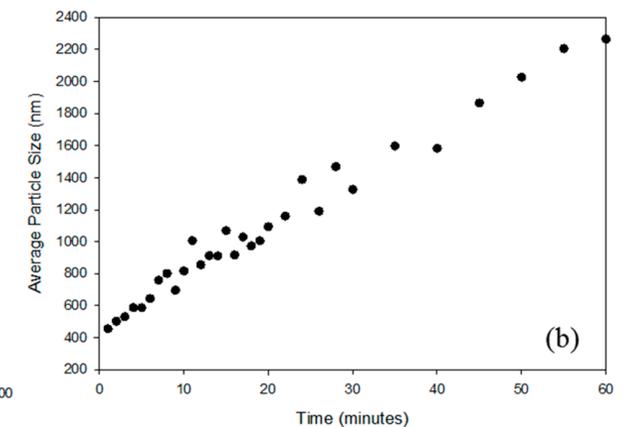
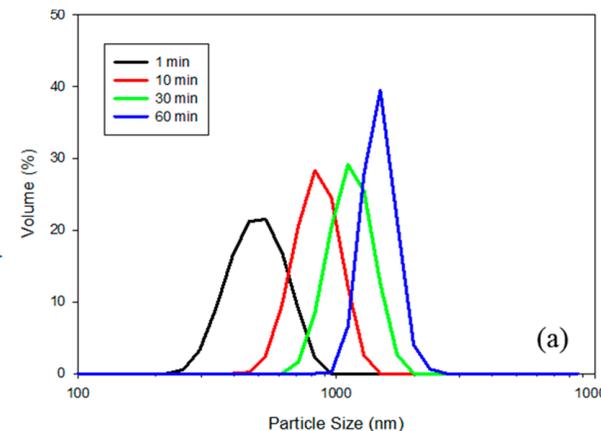
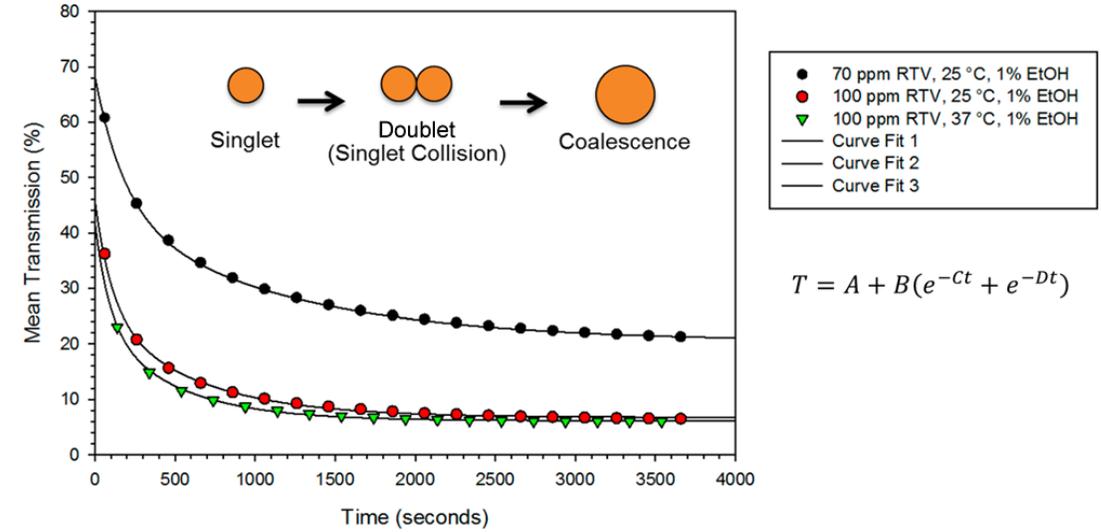
Several more critical points

- Physical stability of droplets/particles
 - Against crystallization
 - Against coalescence/aggregation



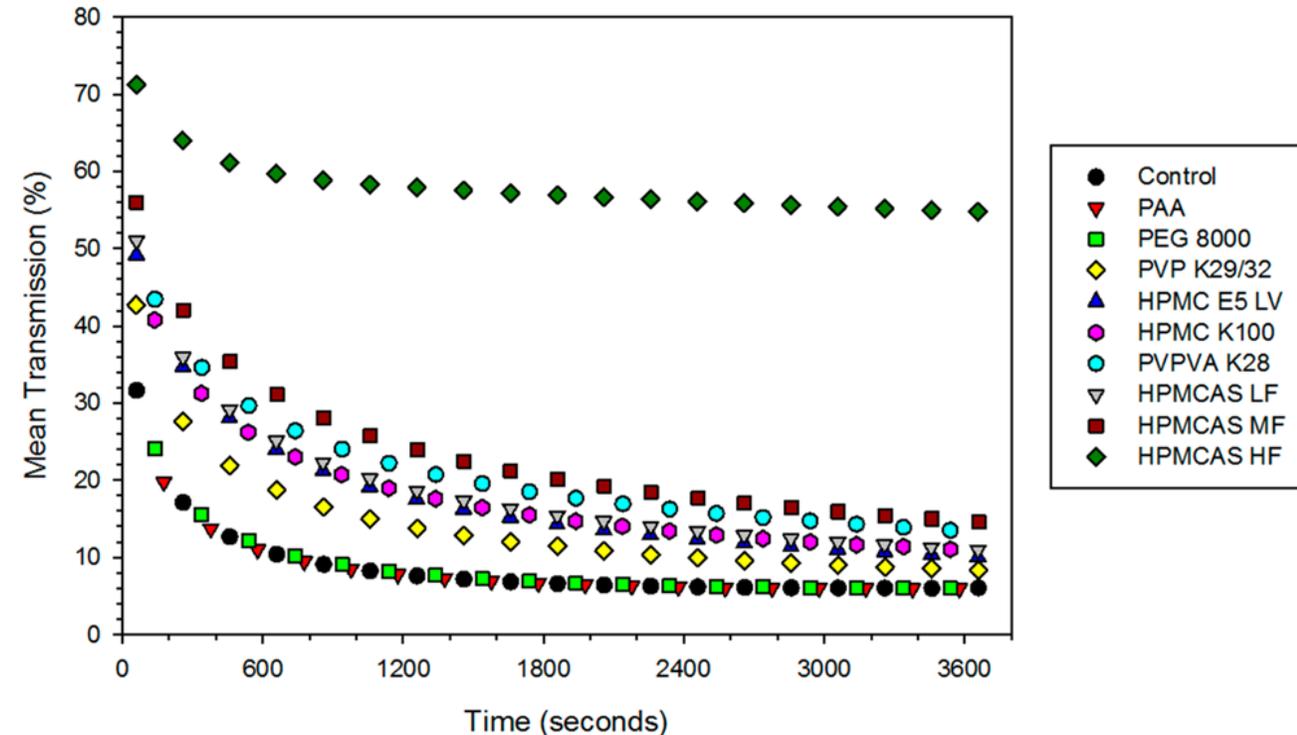
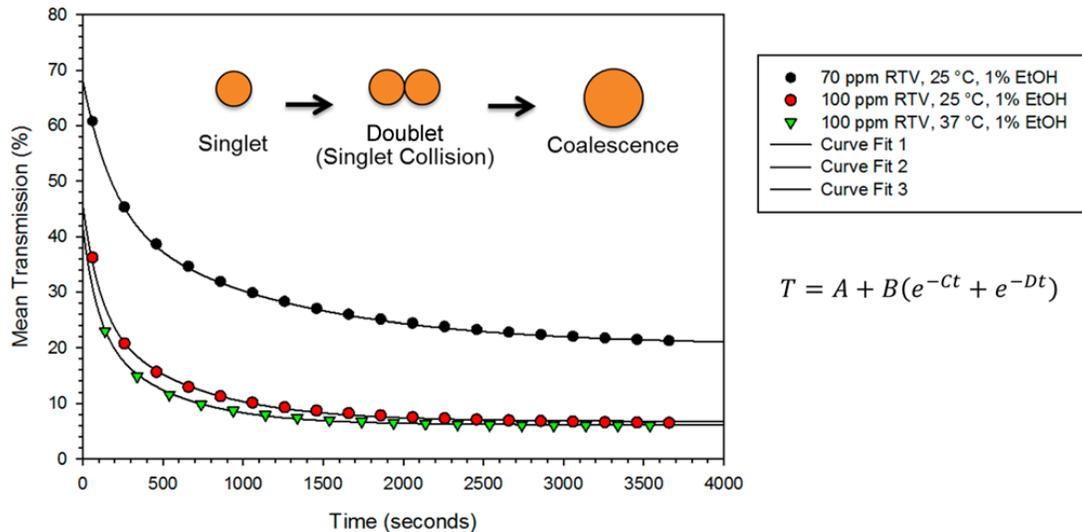
(a) Transmission; (b) Back scattering

Sun et. al., 2019. Mol Pharm



Several more critical points

- Physical stability of droplets/particles
 - Against crystallization
 - Against coalescence/aggregation



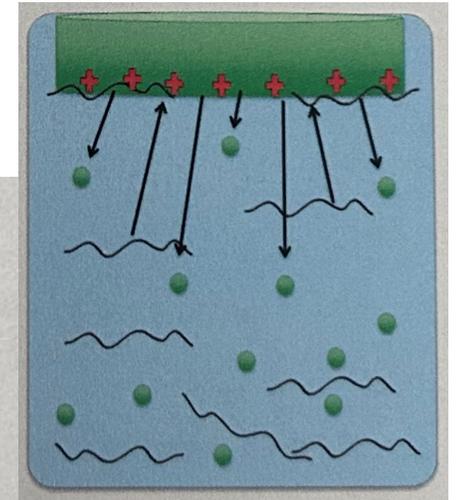
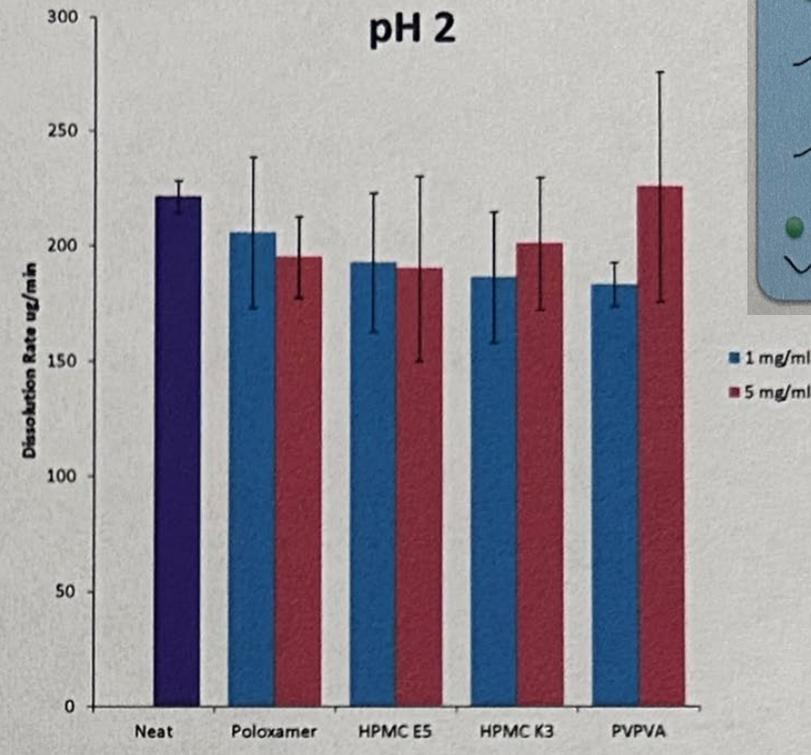
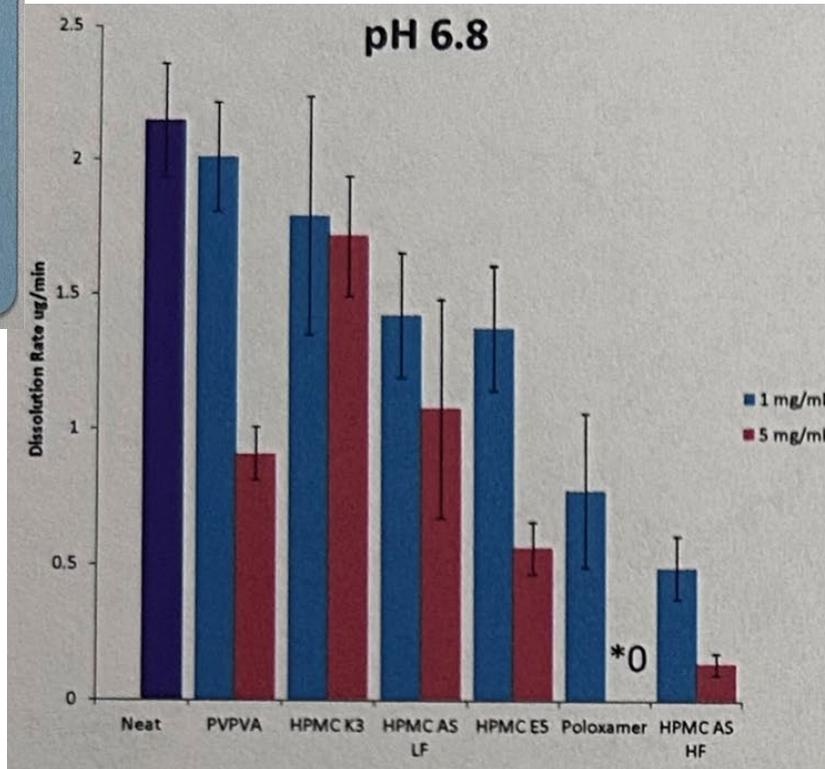
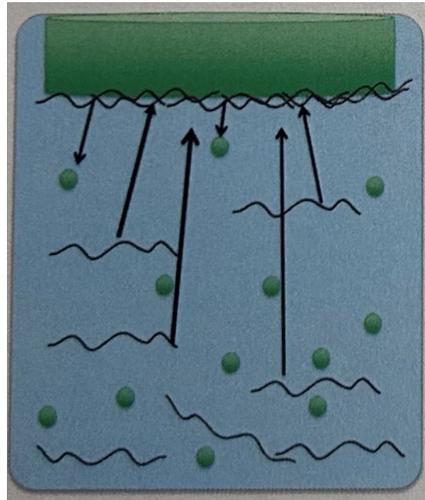
Sun et. al., 2019. Mol Pharm



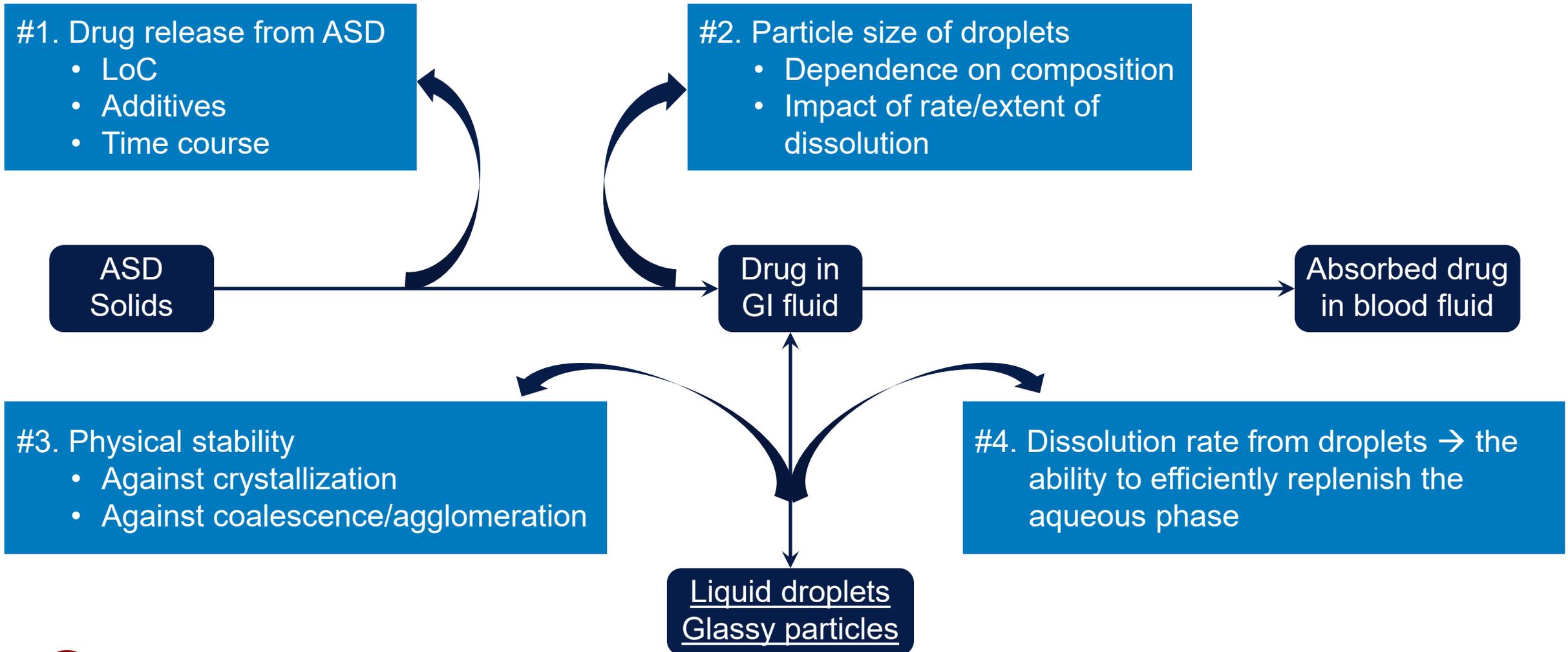
Several more critical points

- Reduced rate of dissolution/equilibration

Atazanavir IDR



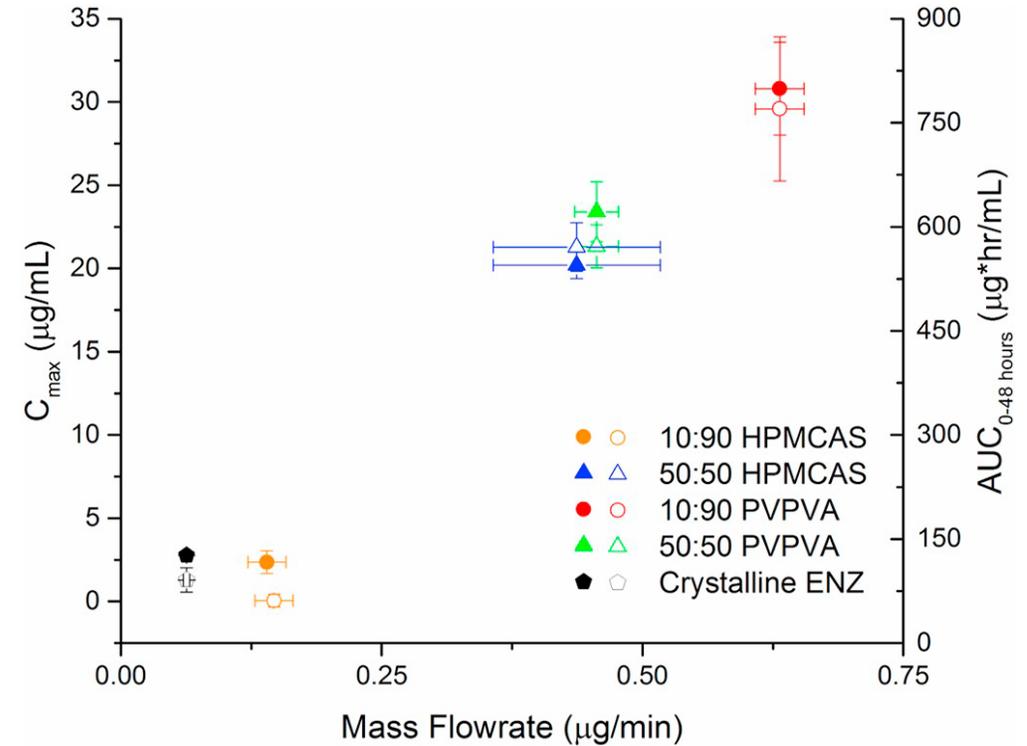
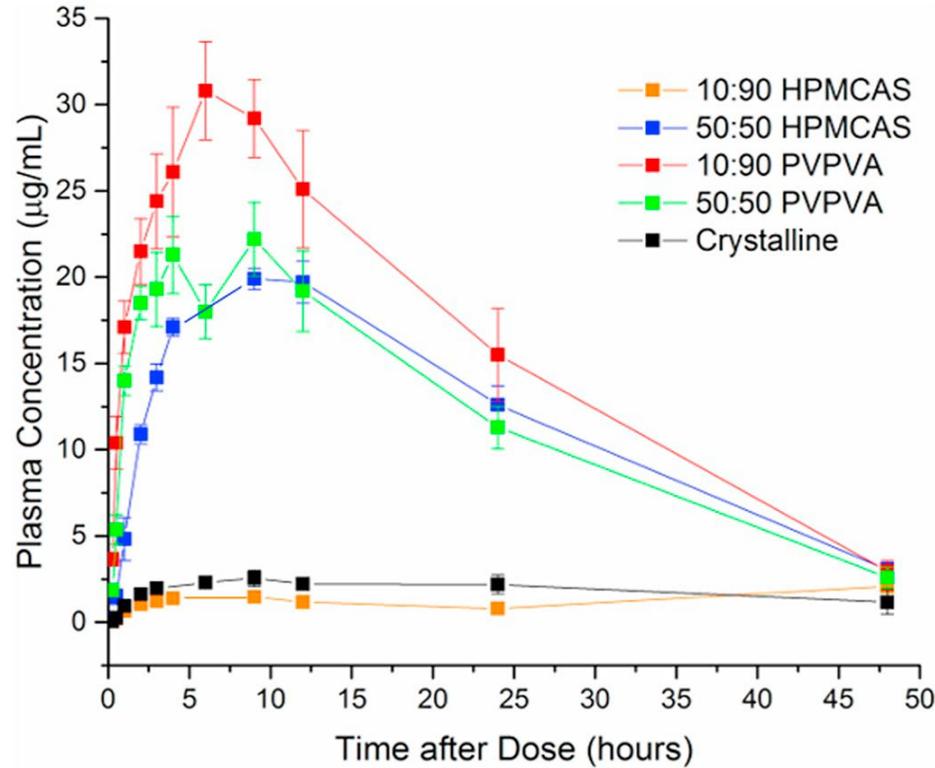
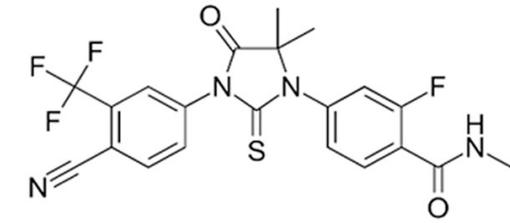
Design principle: Four aspects of technical considerations



Gaps/questions/knowledge to gain

- Critical role of nanodroplets in absorption: is it a must?

Enzalutamide



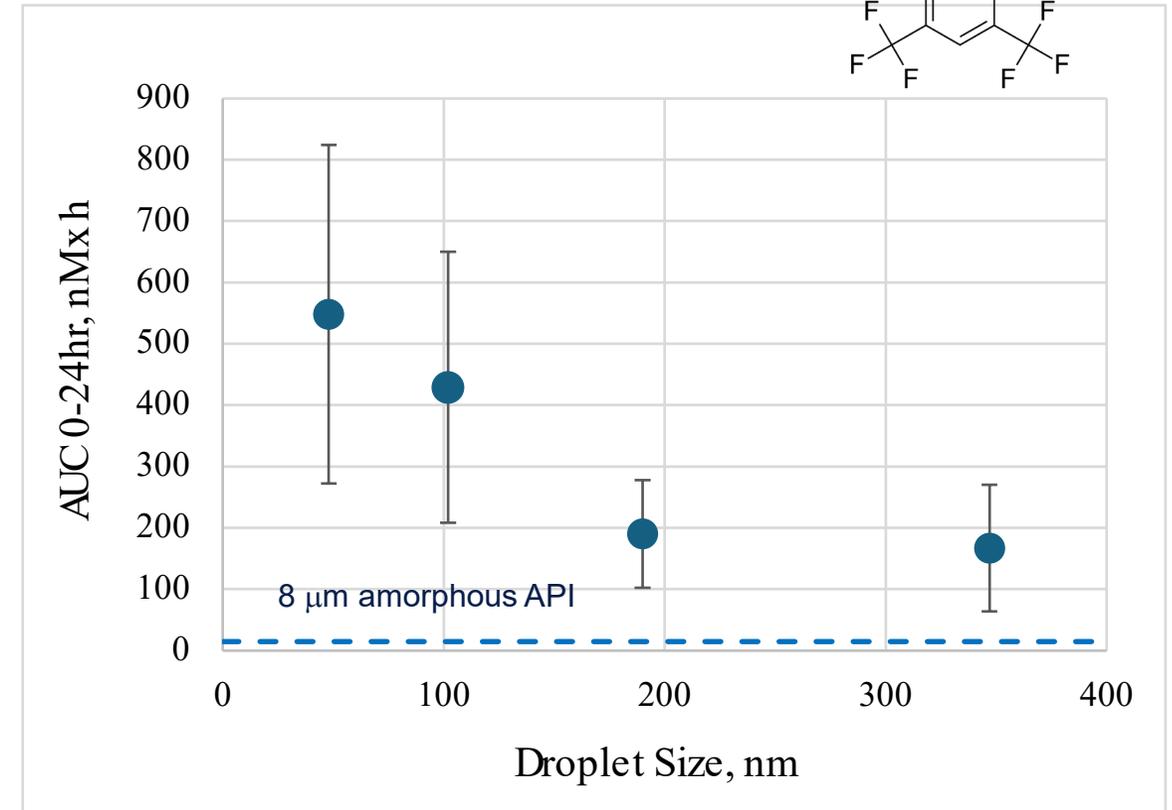
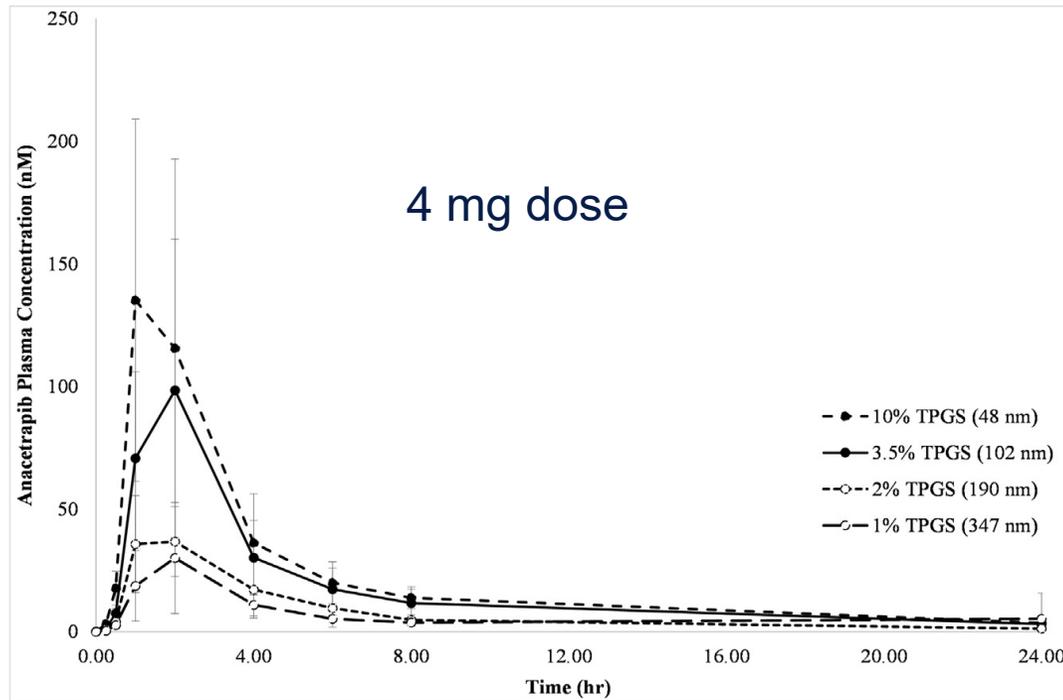
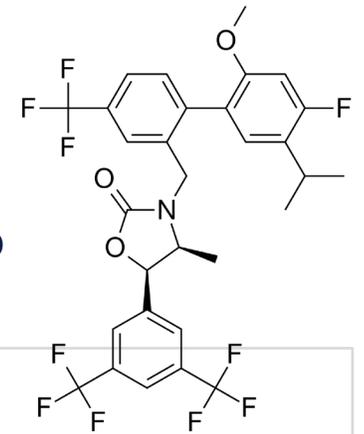
Wilson et al, 2018, J Control Rel



Gaps/questions/knowledge to gain

- Critical role of nanodroplets in absorption: Is it a must?

Anacetrapib



Kesisoglou et al, 2019, J Pharm Sci



Gaps/questions to answer/knowledge to gain

- Dependence of nanodroplet formation on formulation compositions
 - Especially the “minor” excipients, such as surfactants: Which one works the best? Variations from different sources; Lot-to-lot variation
- *In vitro/in vivo* differences
 - Media
 - Agitation
 - Close/open system: effective and adequate removal of drug to simulate absorption
- Continued performance (dissolution/absorption) upon long term storage
- Structures in ASDs that lead to the better dissolution/release performance, and analytical tools in probing the structures
-





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On behalf of
Propelling
Professional*



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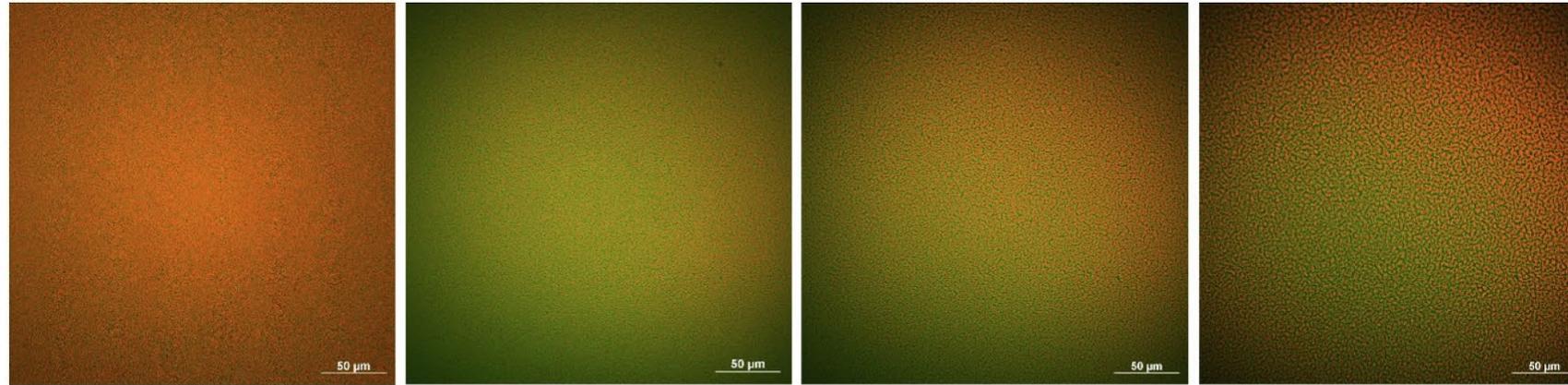
AAPS on the surface of tablet is responsible: Time-lapse confocal fluorescence microscope images

0 min

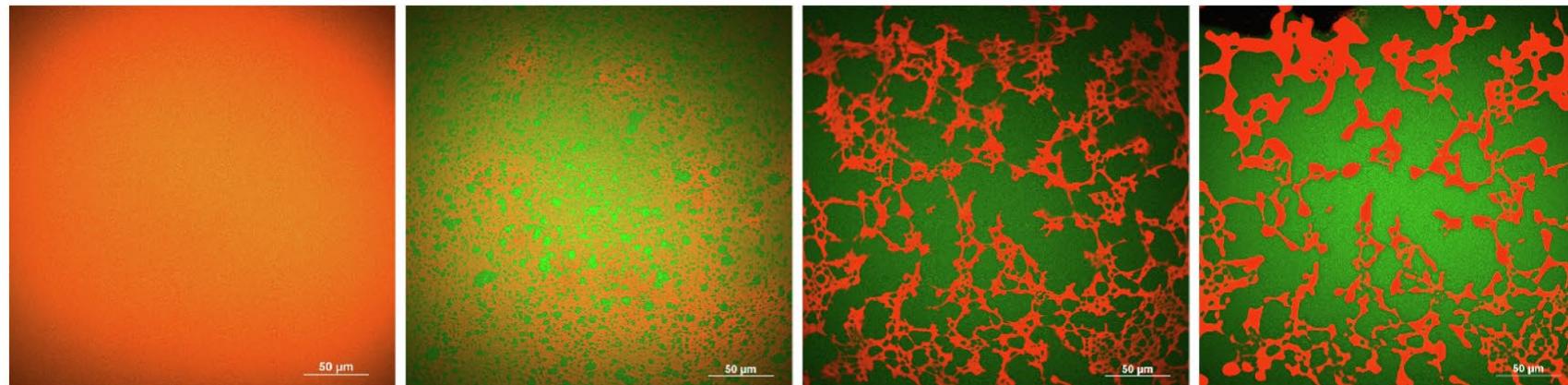
5 min

10 min

30 min



RTV-PVPVA 20-80

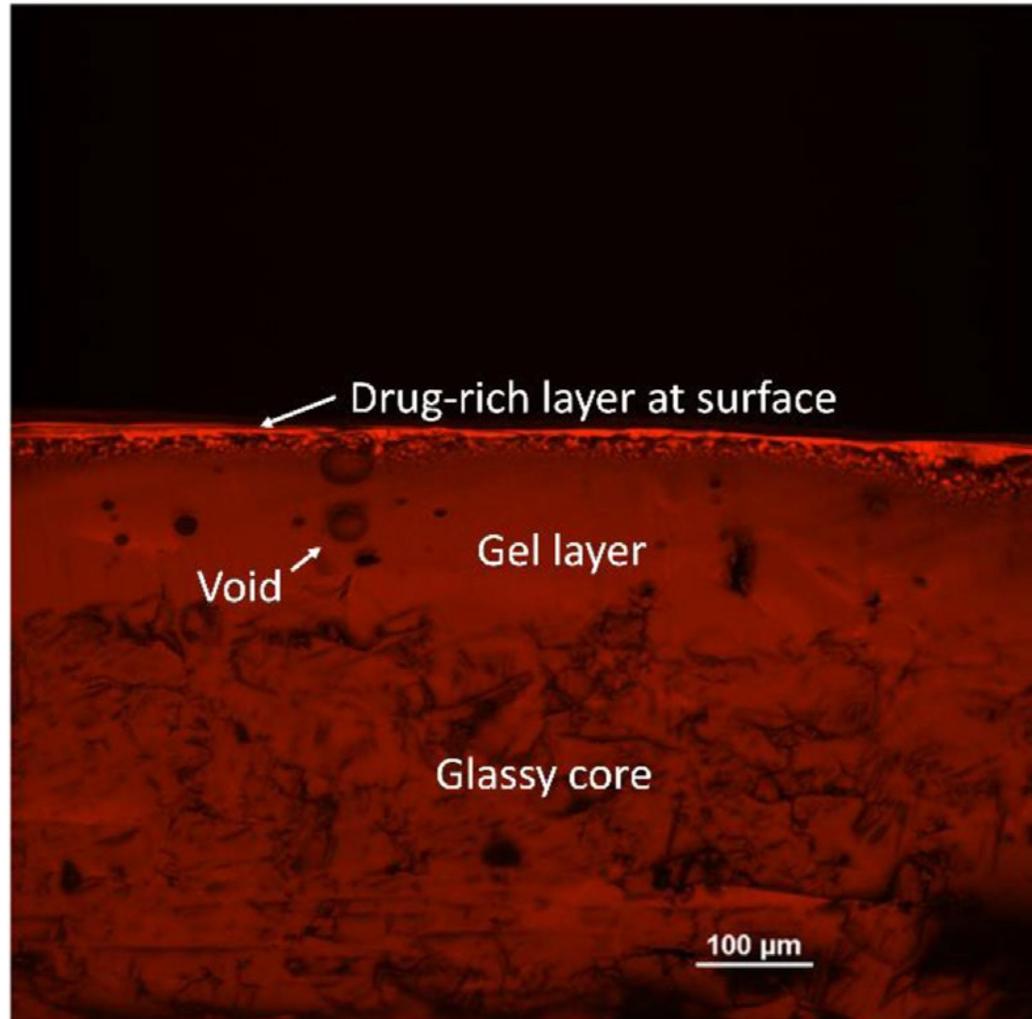


RTV-PVPVA 30-70

Yang et. al., 2022, Int J Pharm



AAPS on the surface of tablet is responsible: Cross section after 5 min of exposure, RTV-PVPVA 30-70



[Back](#)

Yang et. al., 2023, J Pharm sci

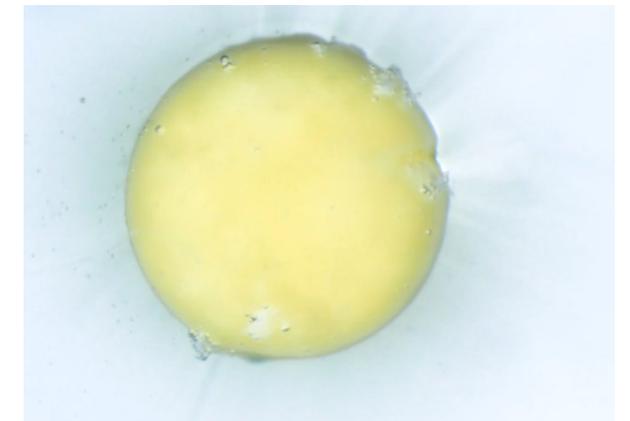
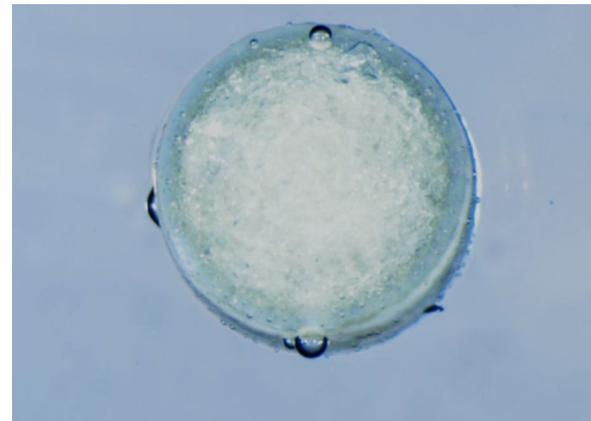


Videos

Stereomicroscope



12.5% Drug loading



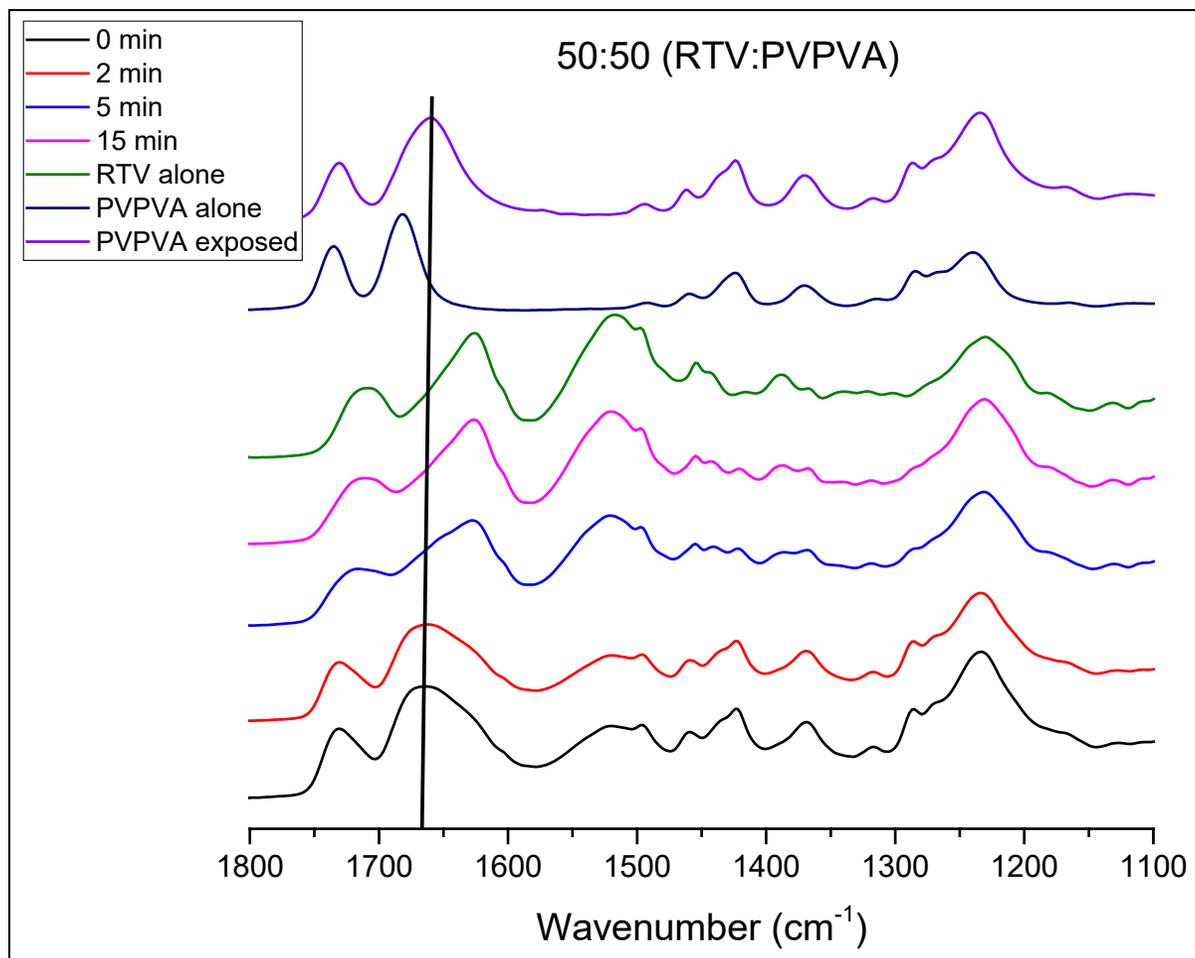
All tablets have the same size (3mm diameter)
Tablets are pressed with ~20mg of ASD

[Back](#)



Because the surface quickly converts to neat amorphous drug

FTIR of tablet surface



Wet PVPVA

Dry PVPVA

Neat amorphous RTV

15 min

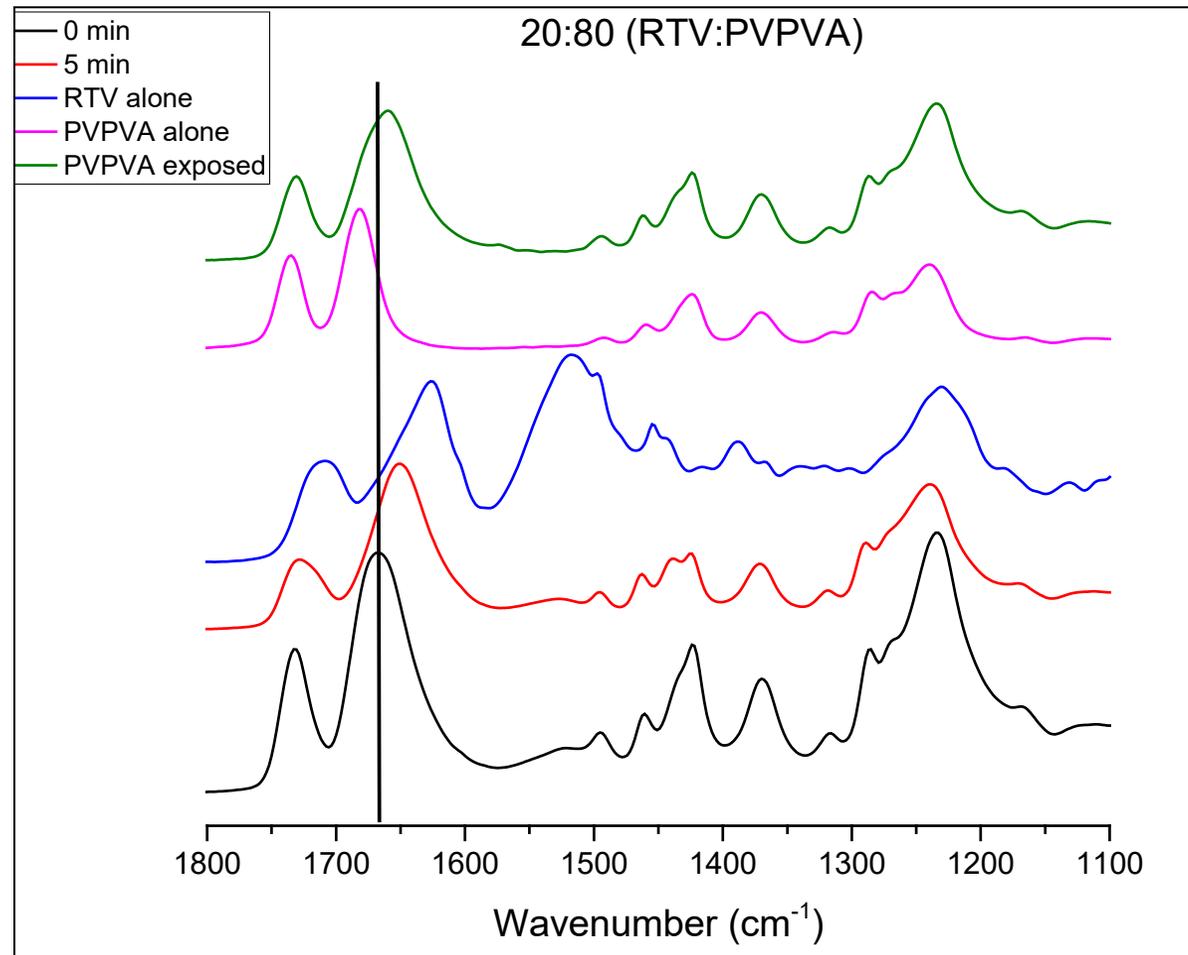
5 min

2 min

Dry tablet



In comparison, lower drug loading ASDs do not convert to neat amorphous drug



Wet PVPVA

Dry PVPVA

Neat amorphous RTV

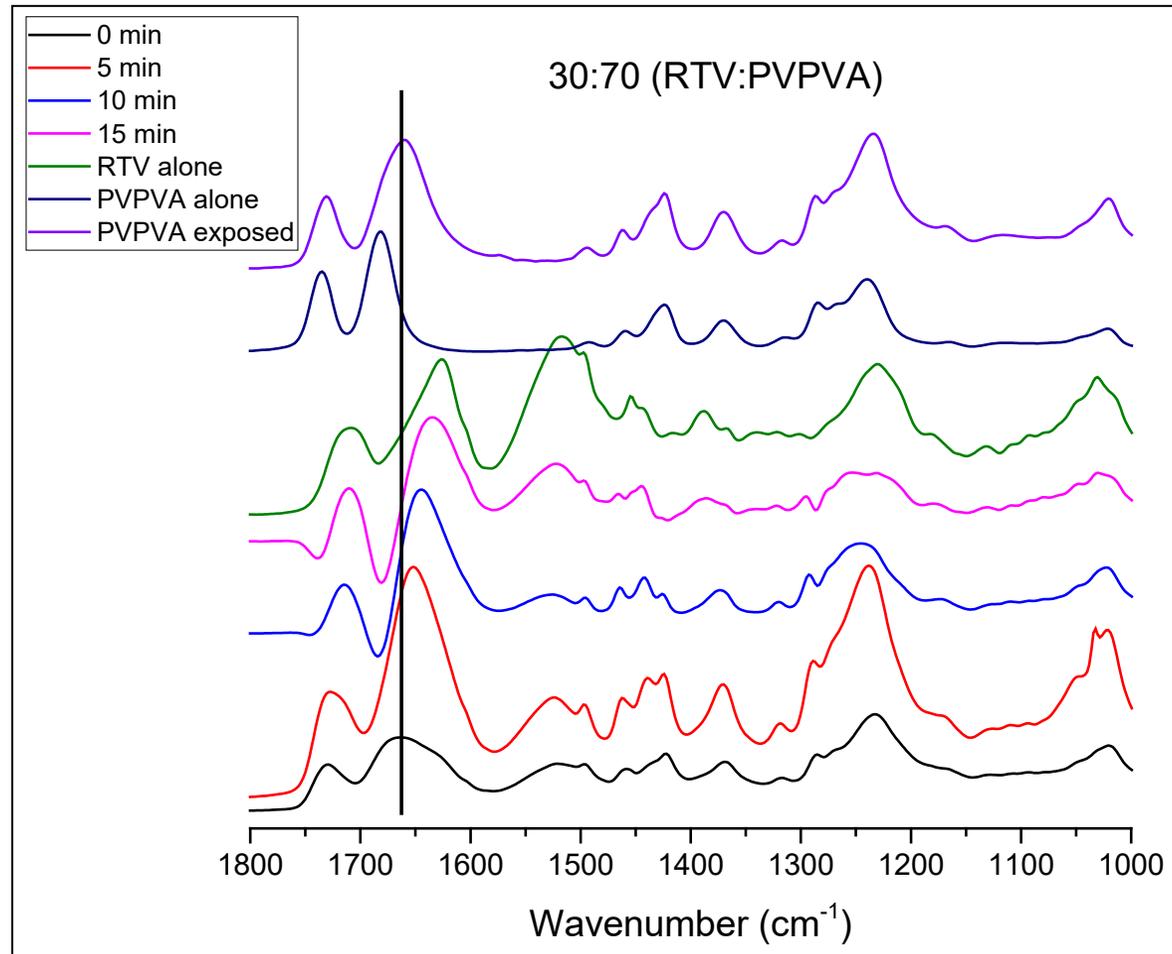
5 min

Dry tablet

[Back](#)



IR spectrum of the surface is also transitioning from ASD to neat amorphous drug



Wet PVPVA

Dry PVPVA

Neat amorphous RTV

15 min

10 min

5 min

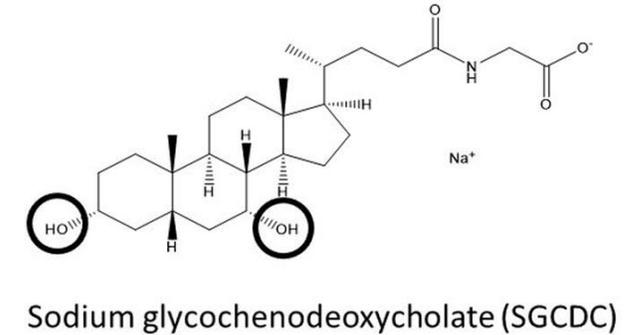
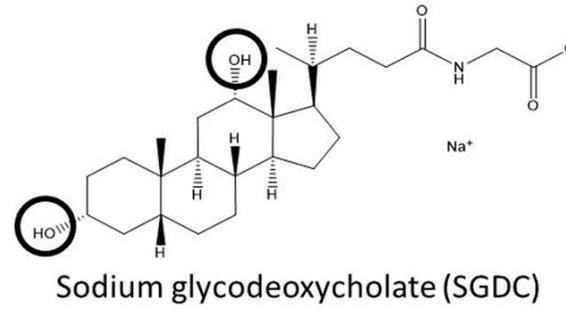
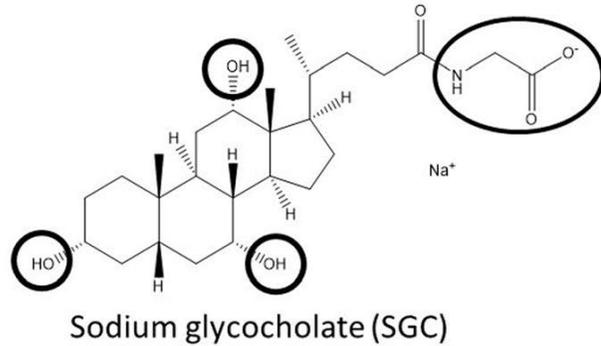
Dry tablet

[Back](#)

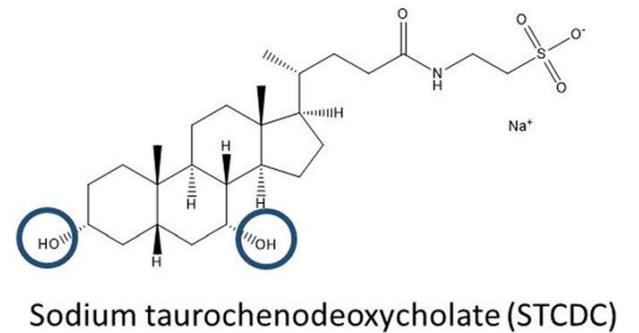
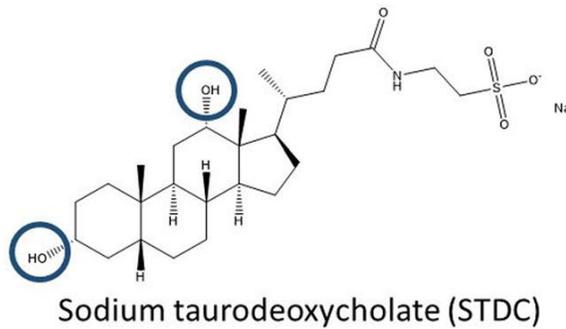
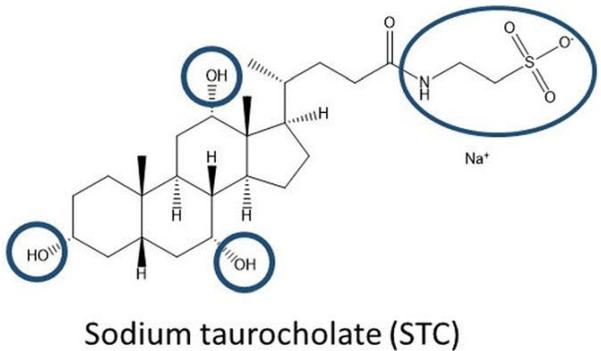


Bile salts abundant in human intestinal fluid (HIF)

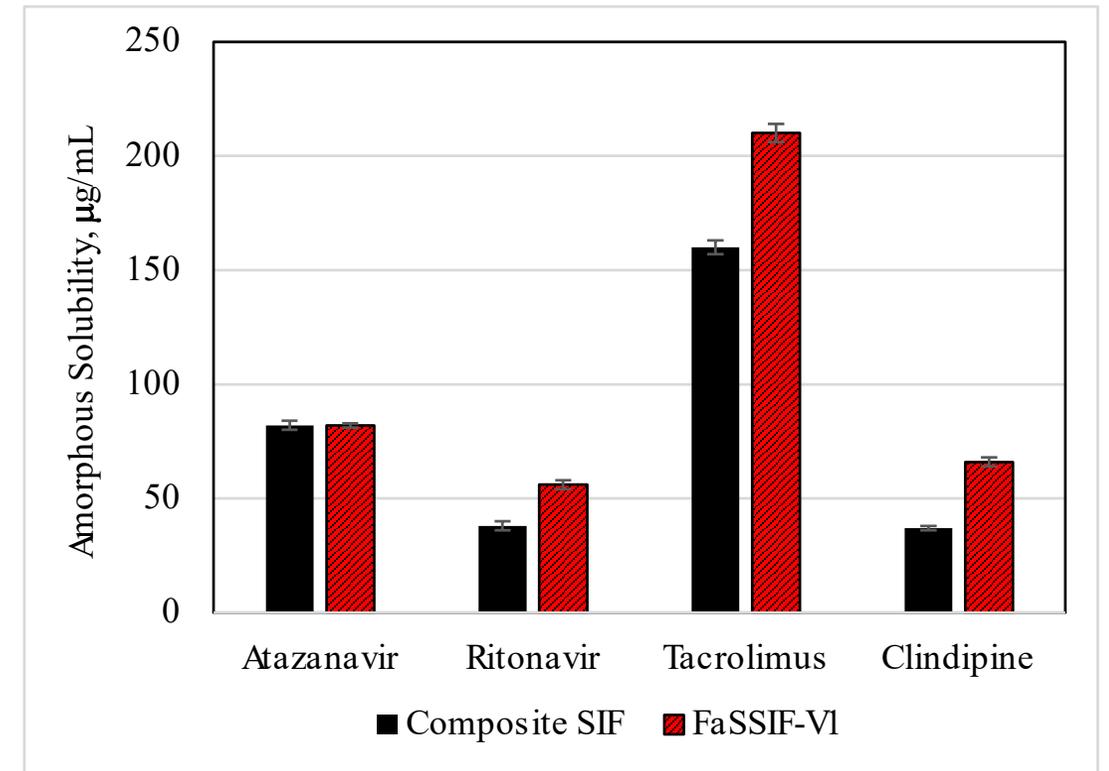
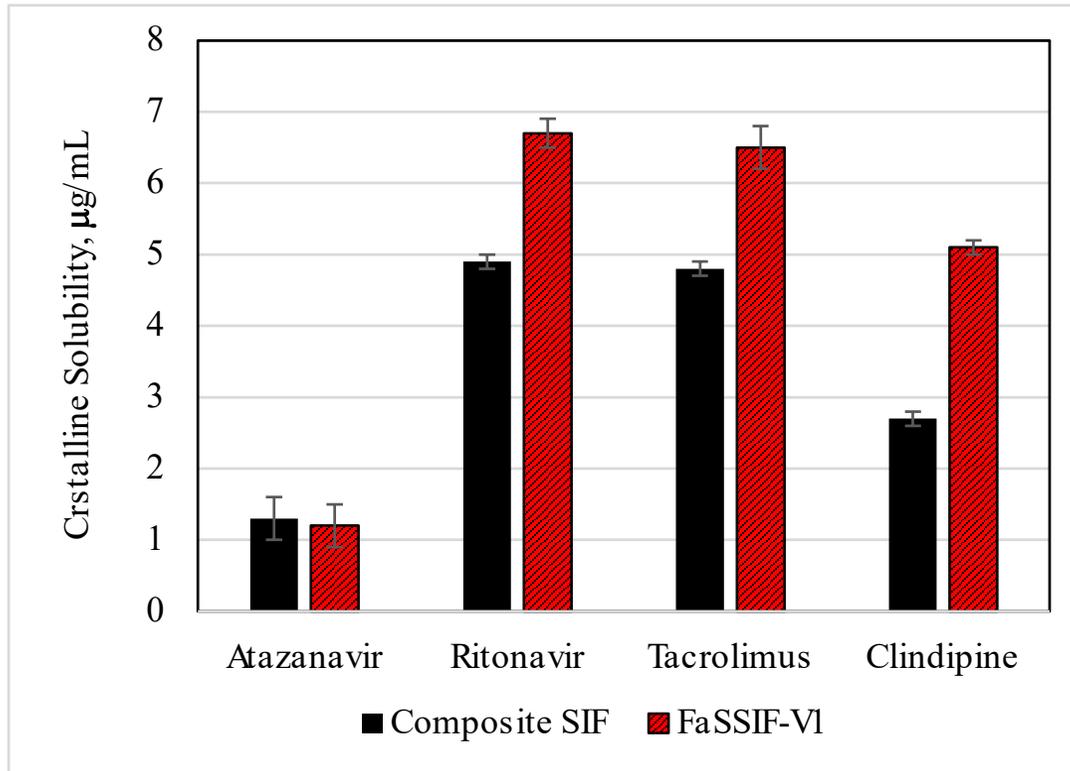
Glycine conjugated



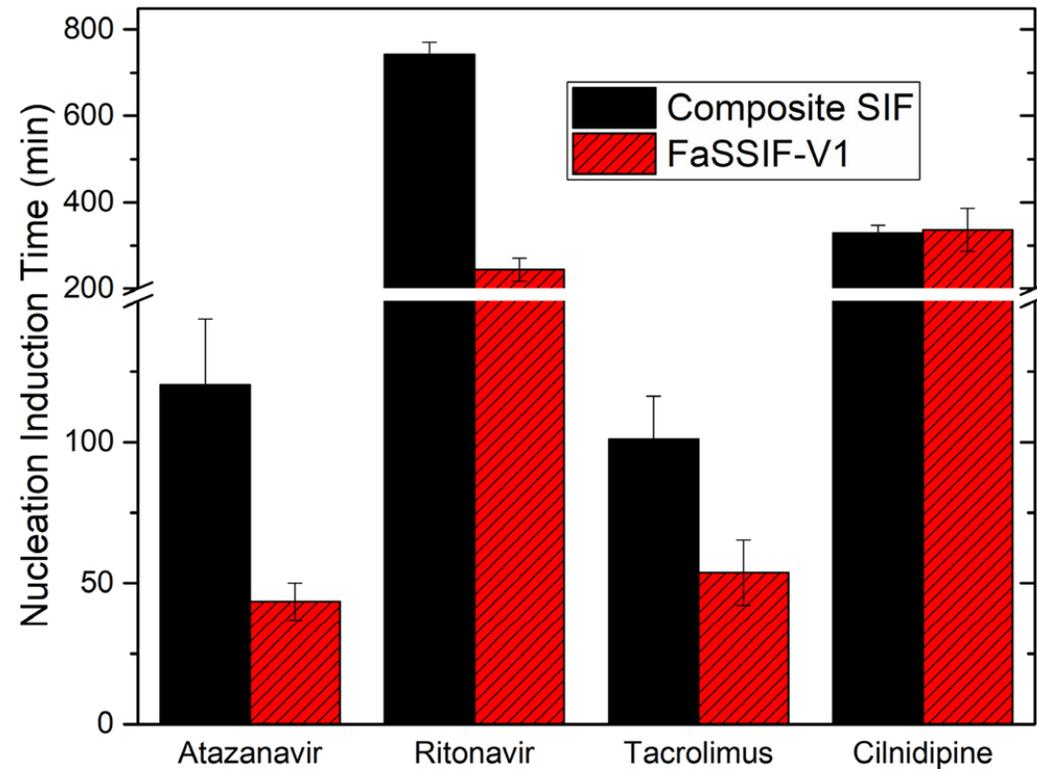
Taurine conjugated



Difference between FaSSIF-V1 and Composite-SIF Solubility



Difference between FaSSiF-V1 and Composite-SiF Crystallization



[Back](#)



Back to the thermodynamic origin of dissolution, and Noyes-Whitney dissolution equation

Noyes-Whitney equation:
$$\frac{dM}{dt} = \frac{DA}{h}(C_s - C) \approx \frac{DA}{h} C_s$$

Iopanoic acid

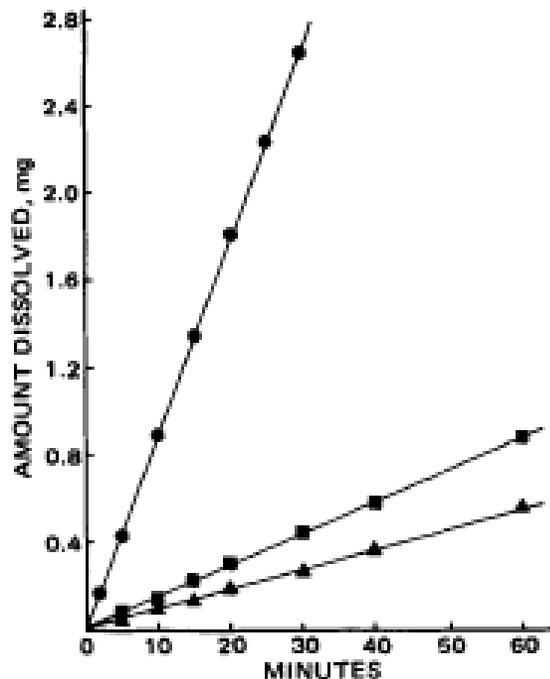
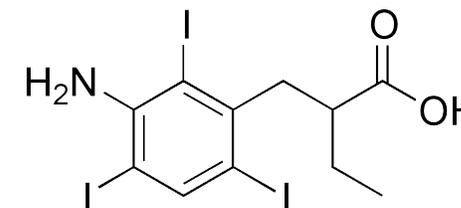


Figure 5—Intrinsic dissolution of Form I (▲), Form II (■), and the amorphous form (●) of iopanoic acid.

- Comparison of intrinsic dissolution rates of three solid forms: two polymorphs and amorphous solid
- IDRs are reflecting (apparent) solubility values of the solids

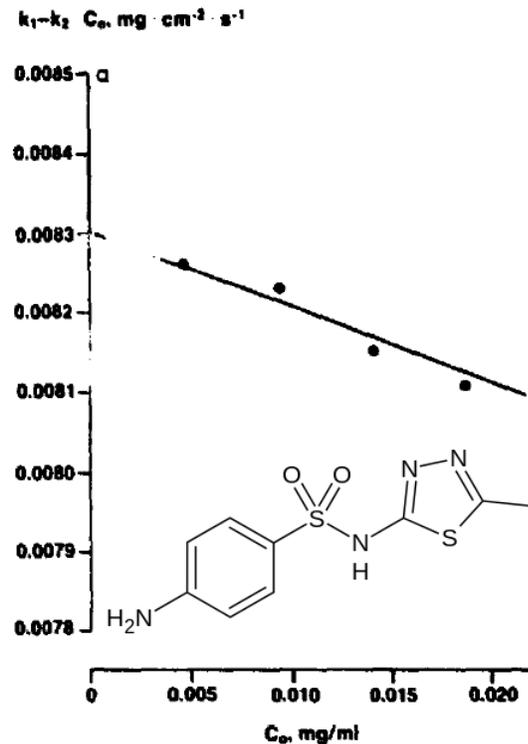
Stagner & Guillory, 1979, J Pharm Sci



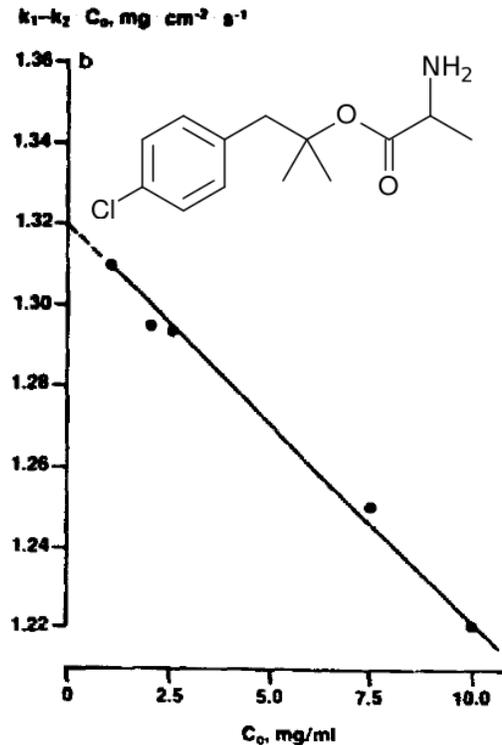
Back to the thermodynamic origin of dissolution, and Noyes-Whitney dissolution equation

Noyes-Whitney equation:
$$\frac{dM}{dt} = \frac{DA}{h}(C_s - C)$$

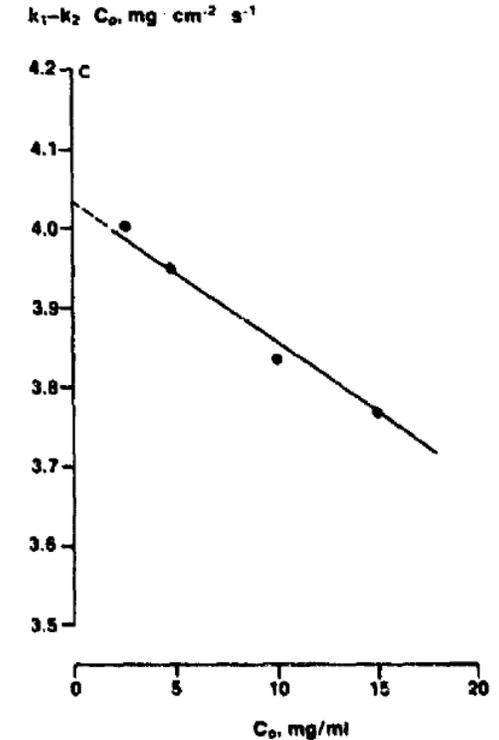
Sulfamethizole



Alaproclate-HCl



FLA 731-HCl



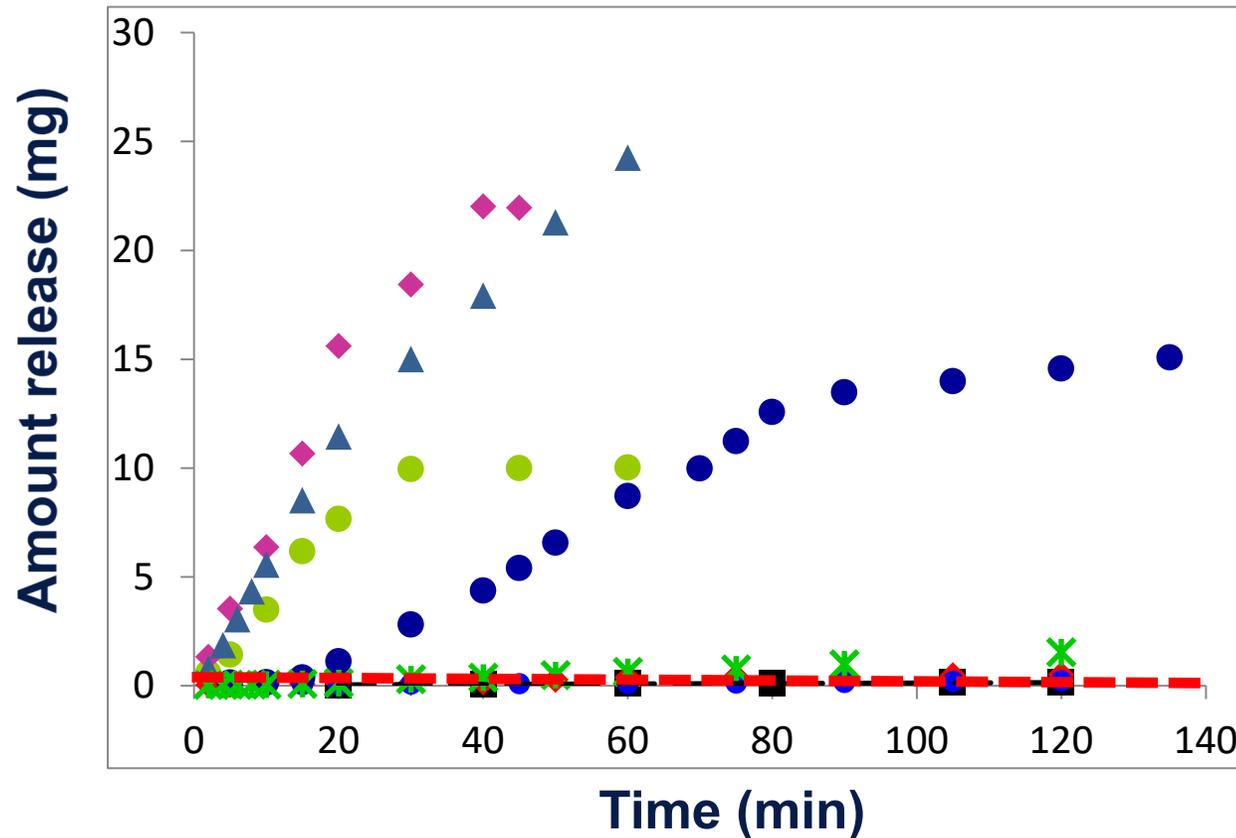
Dissolved solutes reduce the dissolution rates from solid surfaces

Nicklasson et al, 1983, Int J Pharm;



Release will be zero for all ASDs, when initial conc. in the medium is at amorphous solubility

Noyes-Whitney equation: $\frac{dM}{dt} = \frac{DA}{h} (C_s - C) \rightarrow C_{\text{Amorphous}}$



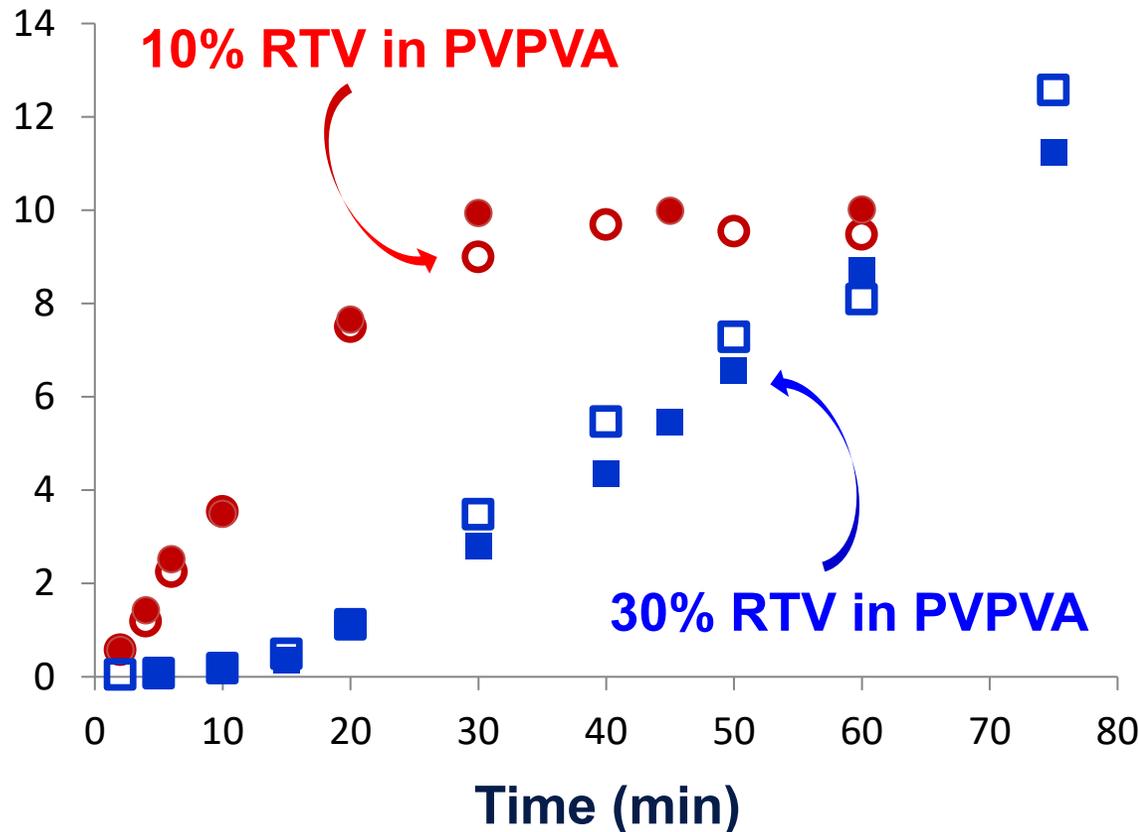
Indulkar et. al., 2019, Mol Pharm



50%: Yes, no release
10% & 30%: No, no impact!

} **Different controlling surfaces**

Noyes-Whitney equation:
$$\frac{dM}{dt} = \frac{DA}{h} (C_s - C) \rightarrow C_{\text{Amorphous}}$$

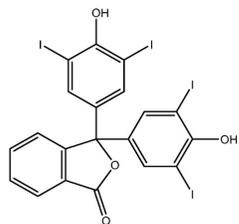


Solid symbol: pH buffer

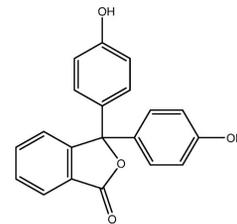
Open symbol: pH buffer saturated with amorphous RTV



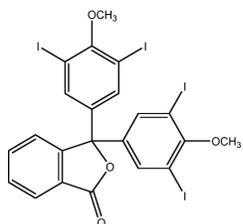
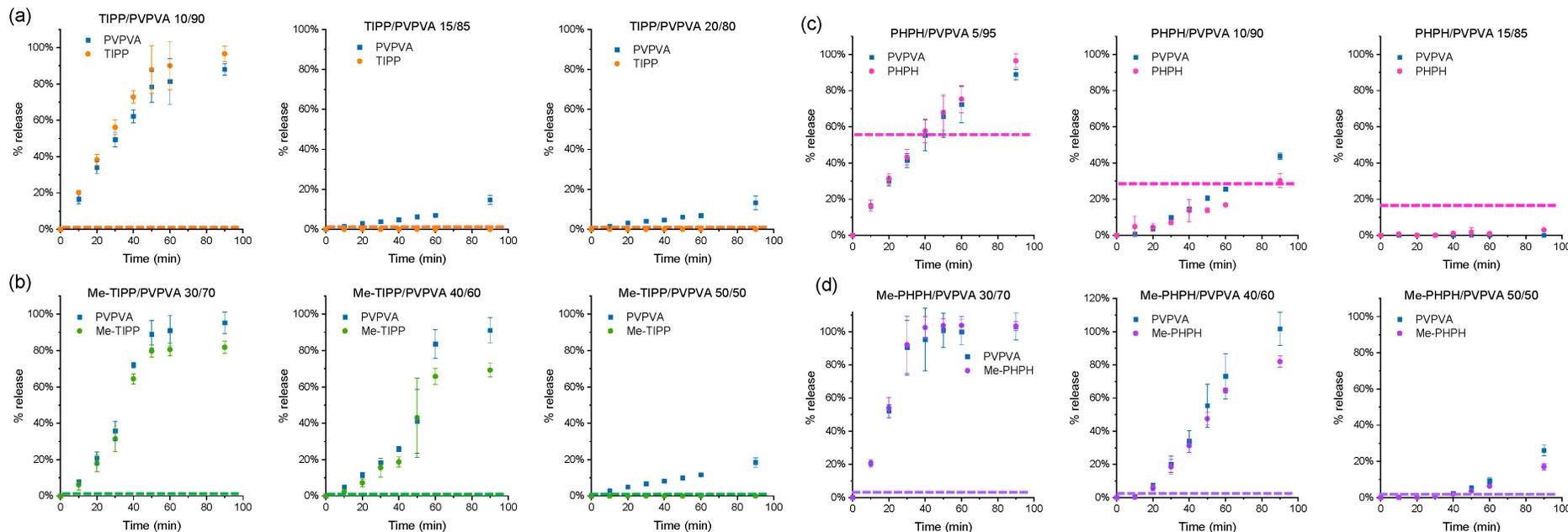
Strength of molecular interactions impact LoC



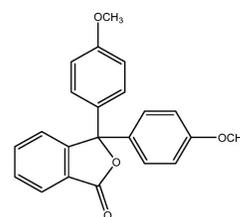
TIPP, 10%
 HB ✓
 XB ✓



PHPH: 5%
 HB ✓
 XB ✗



Me-TIPP: 30%
 HB ✗
 XB ✓

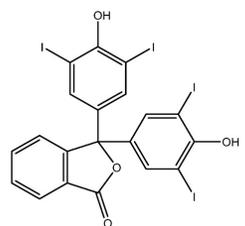


Me-PHPH: 40%
 HB ✗
 XB ✗

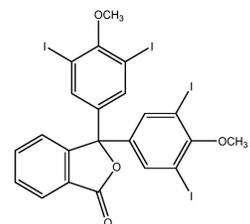
Que C et. al., 2021, Mol Pharm



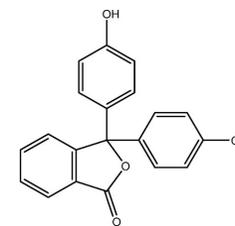
Strength of molecular interactions impact LoC



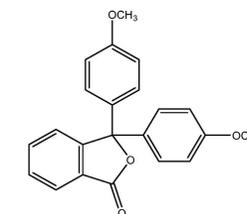
TIPP, 10%
 HB ✓
 XB ✓



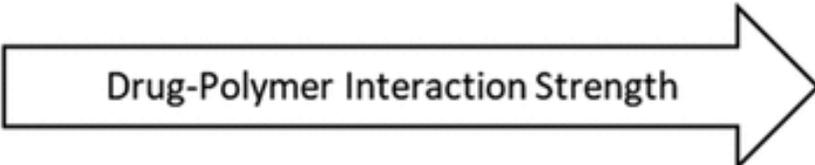
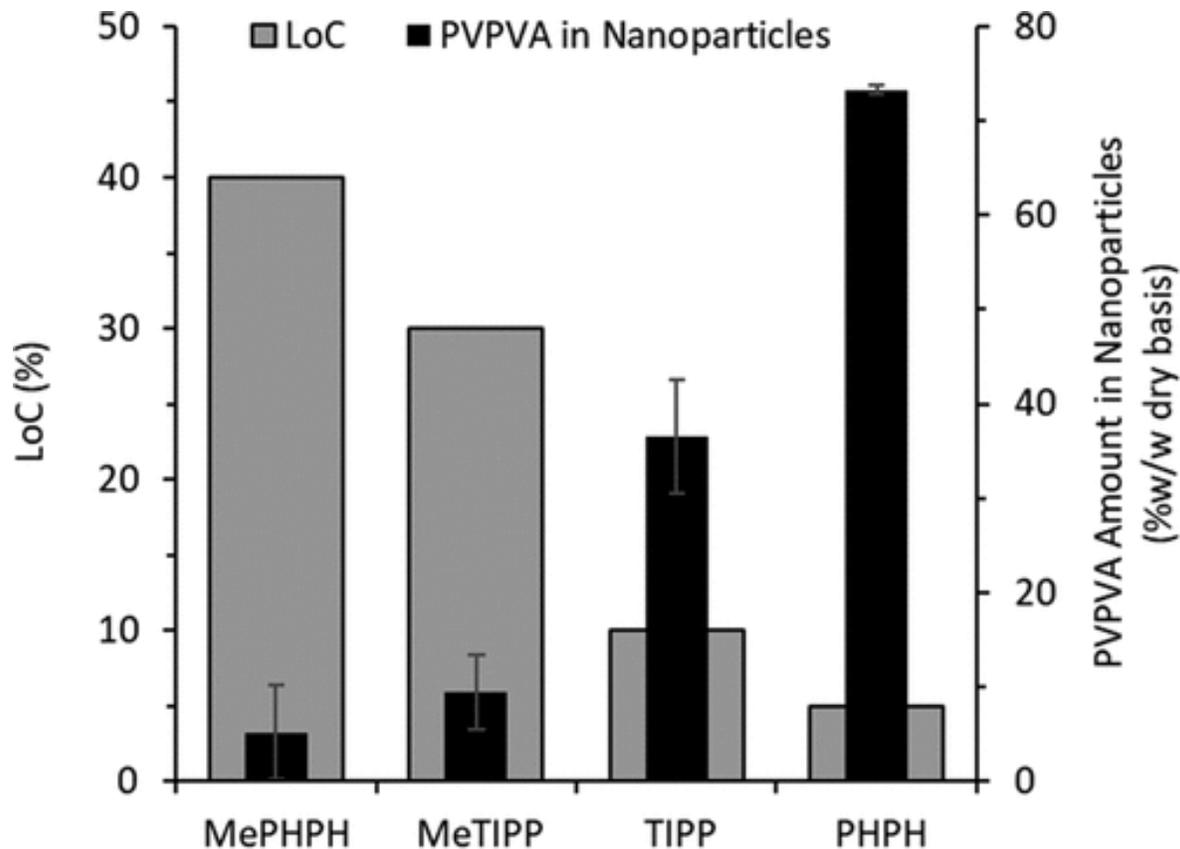
Me-TIPP: 30%
 HB ✗
 XB ✓



PHPH: 5%
 HB ✓
 XB ✗



Me-PHPH: 40%
 HB ✗
 XB ✗



Deac et al, 2023. Mol Pharm

