Enabling a Healthier World

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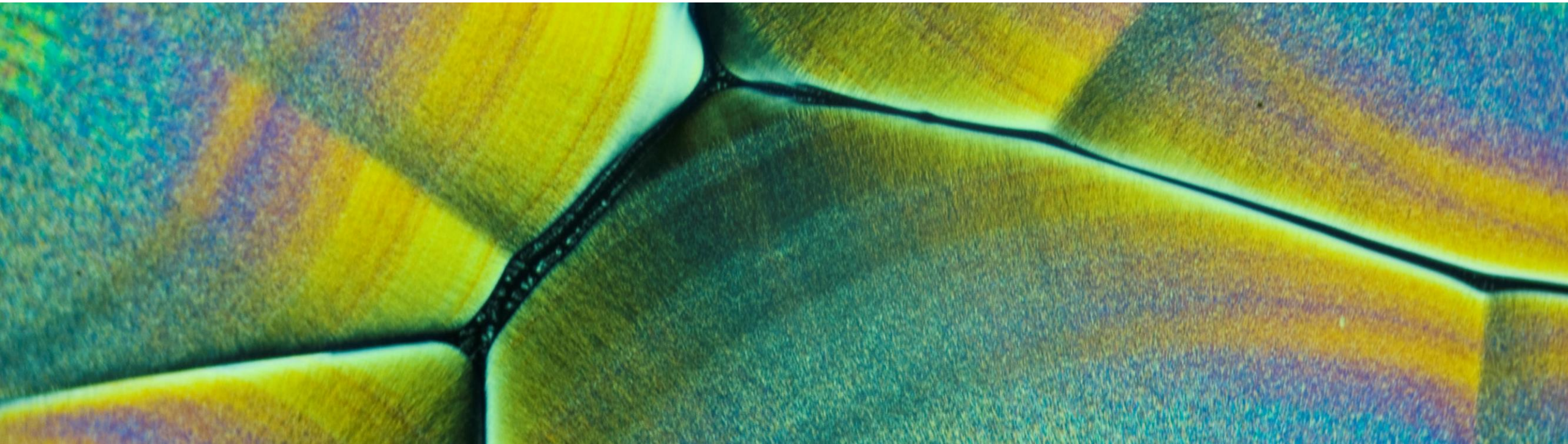
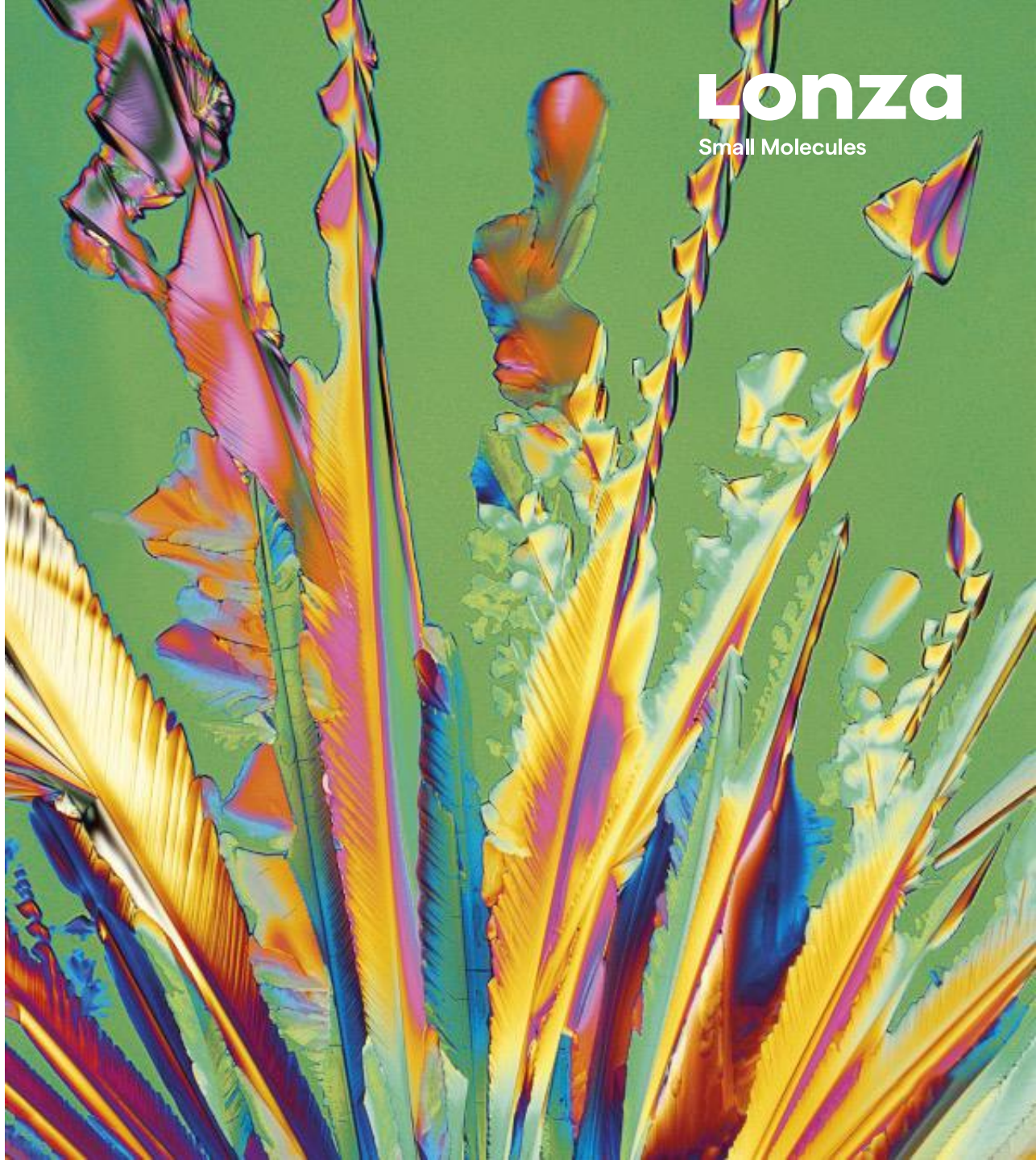
Solubility: From in vitro best practices to in vivo relevance

Deanna Mudie | PBBM 2023 Workshop | 29 Aug 2023



Agenda

- Factors impacting solubility and effects on bioperformance
- 3 Solubility Case Studies
- Summary - PBPK/PBBM + in vitro tools can drive understanding of solubility & bioperformance



Acknowledgments

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Aaron Stewart

Michael Grass

Jesus Rosales

Michael Morgen

David Vodak

Solubility – a fundamental driver of drug bioperformance

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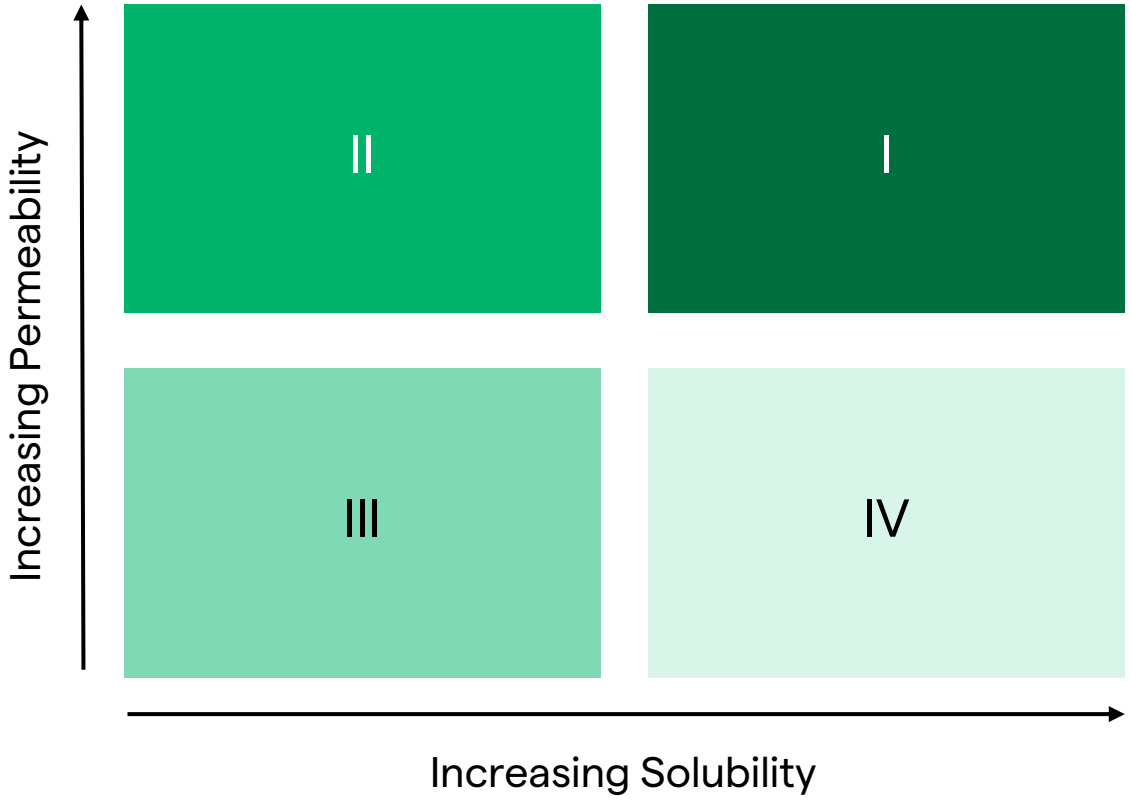
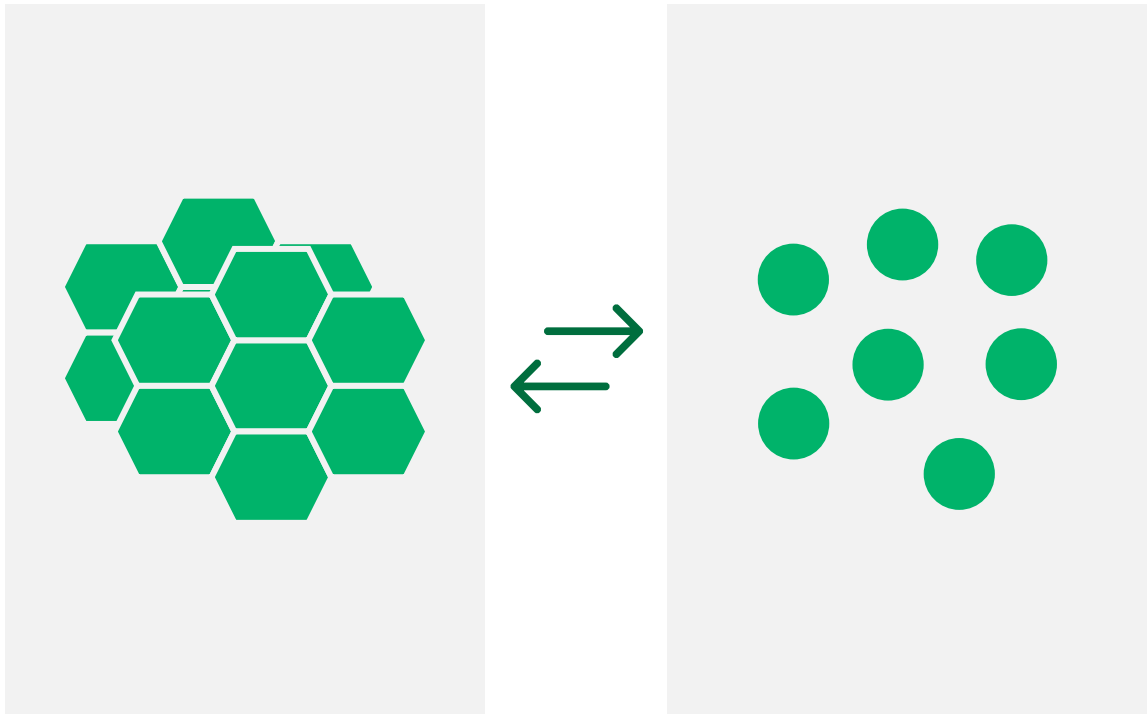
Biopharmaceutics Classification System (BCS)



Solubility = maximum concentration of drug in solution...



Solubility is Impacted by Drug Formulation – GI Fluid Property interplay

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- M.W.
- T_m
- log P
- pK_a

- pK_a
- Hydrophobicity
- CMC

- pH
- Buffer species
- Bile, fats
- Osmolality

Interplay impacts:

- Bulk solubility along GI tract
- Solid particle surface solubility
- Solubilization in bile, fats, excipients

Solubility Impacts on Oral Bioperformance

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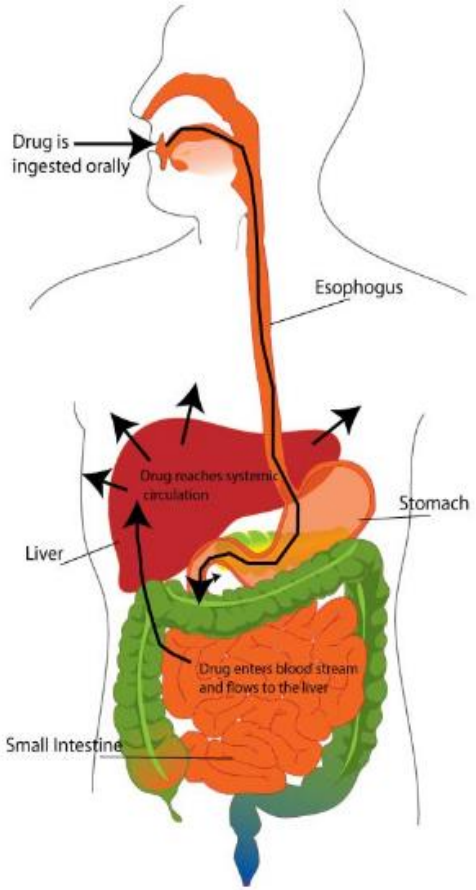
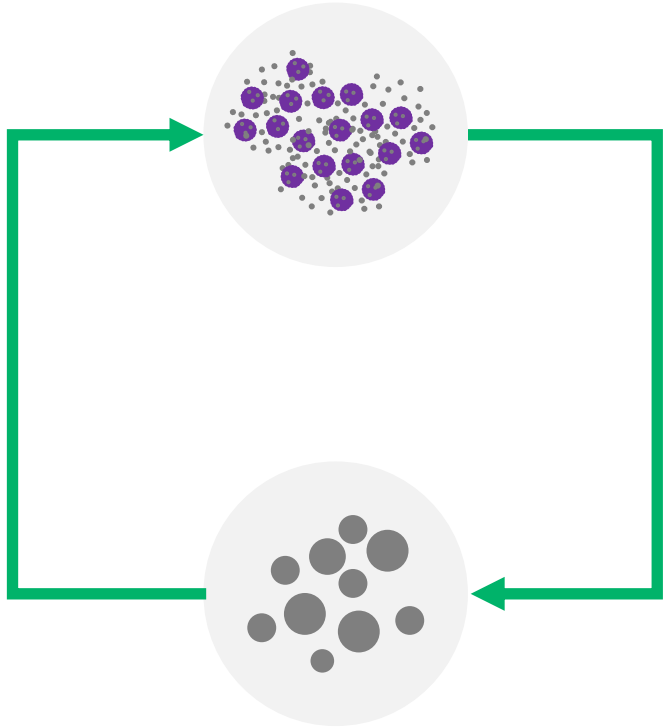


Dissolution

$$\frac{dM}{dt} = k_{pr}(t) \cdot \left(S_{s(t)} - C_{b(t)}\right)$$



Permeation

$$\frac{dM}{dt} = k_p(t) \cdot S_{b(t)}^{*}$$

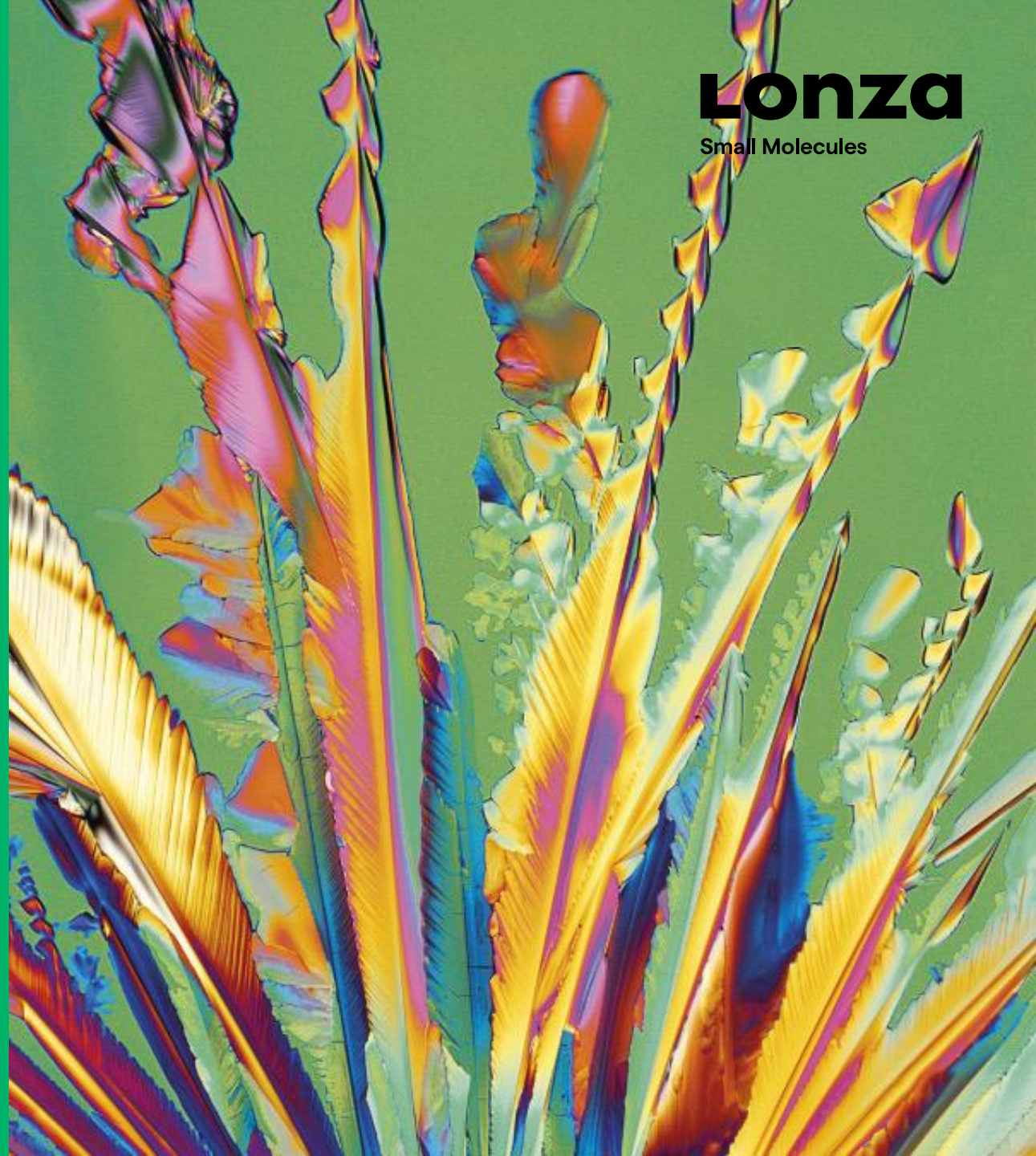
Precipitation

$$\frac{dM}{dt} = k_d(t) \cdot \left(C_{b(t)} - S_{b(t)}\right)$$

* at saturation, e.g. maximum absorbable dose

Belinostat Case Study

Amorphous solubility in presence of excipients and influence on rate and extent of dissolution of ASDs



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Belinostat is a BCS 2 Drug Formulated as Amorphous Solid Dispersions (ASDs) with 3 Different Dispersion Polymers

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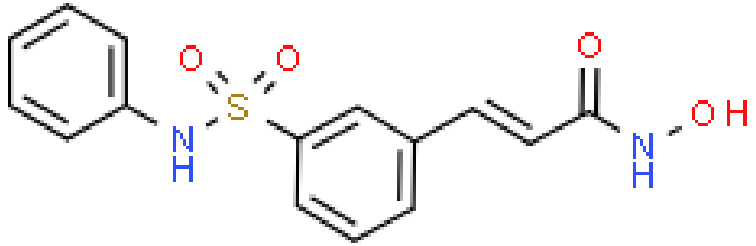
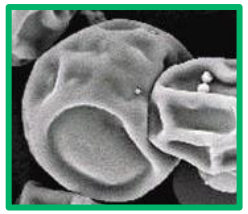
Belinostat

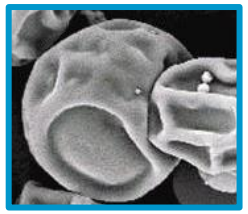
- BCS 2
- pK_a = ≥ 8 (acidic)
- Log P < 2



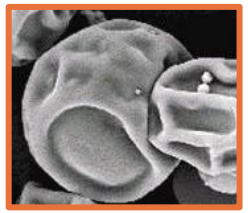
+



25% active HPMCAS-M ASD



25% active PVP K30 ASD



25% active PVP VA64 ASD

Goal: **match performance of oral solution in dog study**

Ref: Stewart et al., J Pharm Sci 108 (2019) 326-336

Belinostat ASDs Dissolve to the Amorphous Solubility

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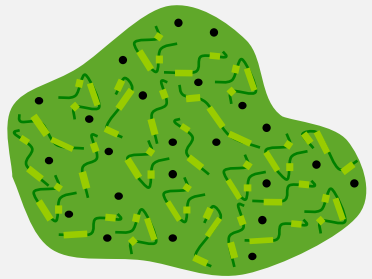
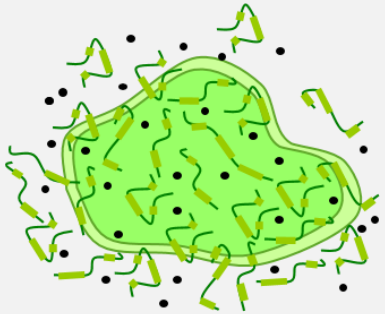
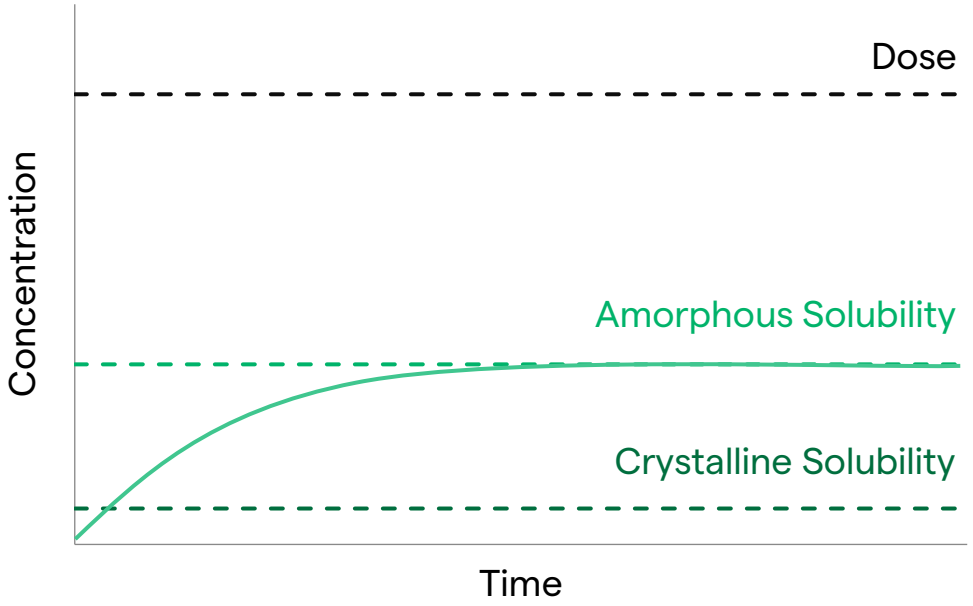
ASD particle







Amorphous solubility can depend on dispersion polymer

Amorphous Solubility can be Measured using a Solvent-Shift Test

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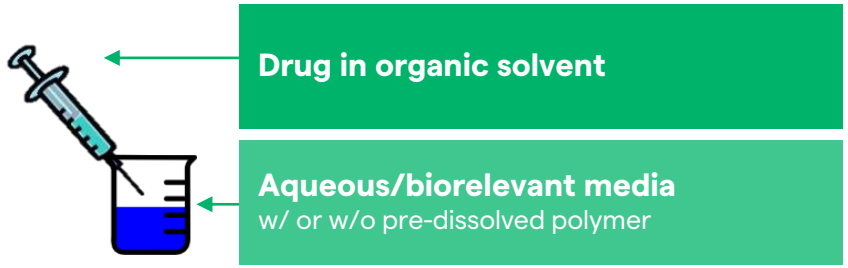

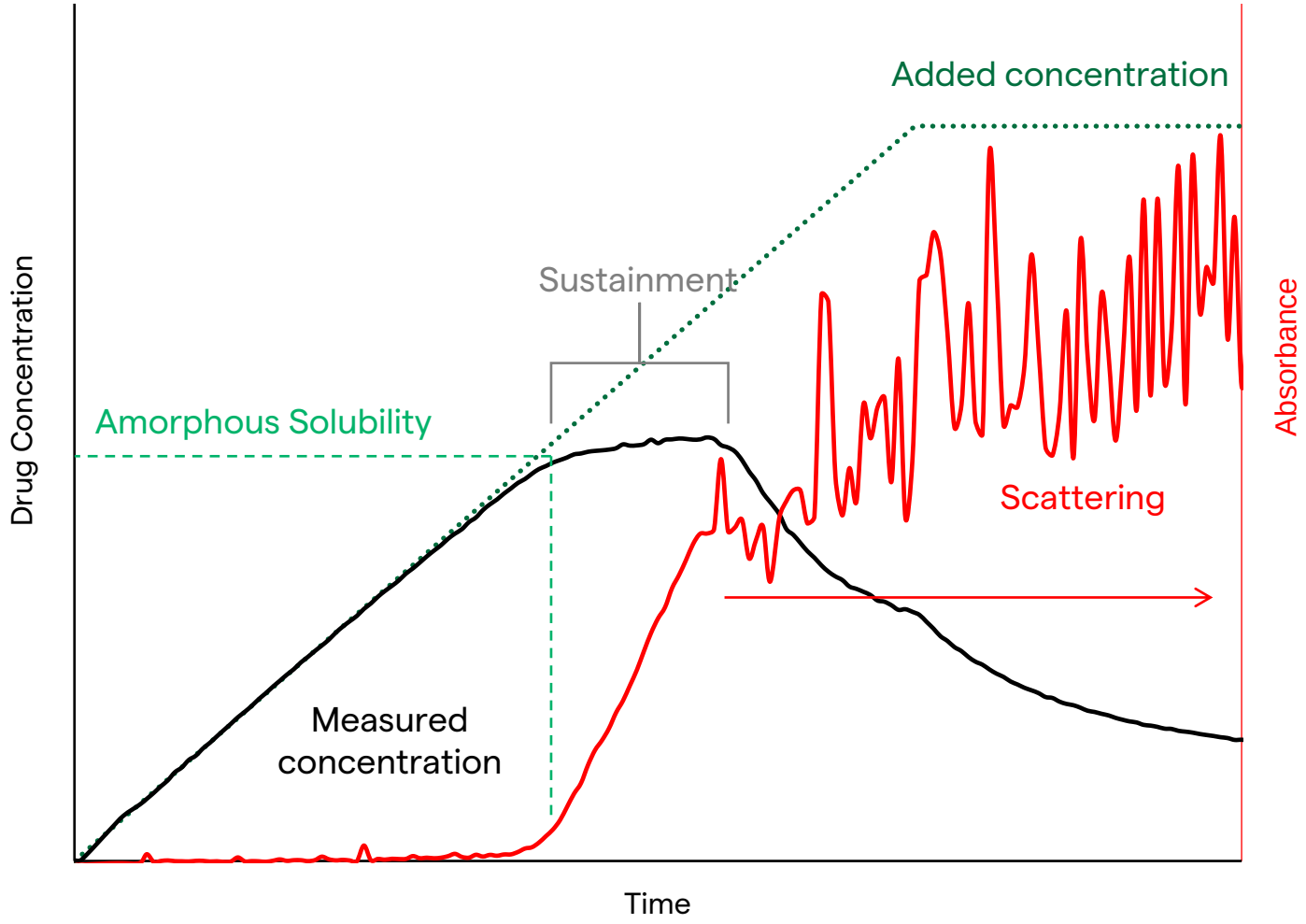

Ref: Murdande *et al. J Pharm Sci.* 99 (**2010**), 1254

Belinostat Amorphous Solubility is Depressed in the Presence of Polymer and Depends on Polymer Type

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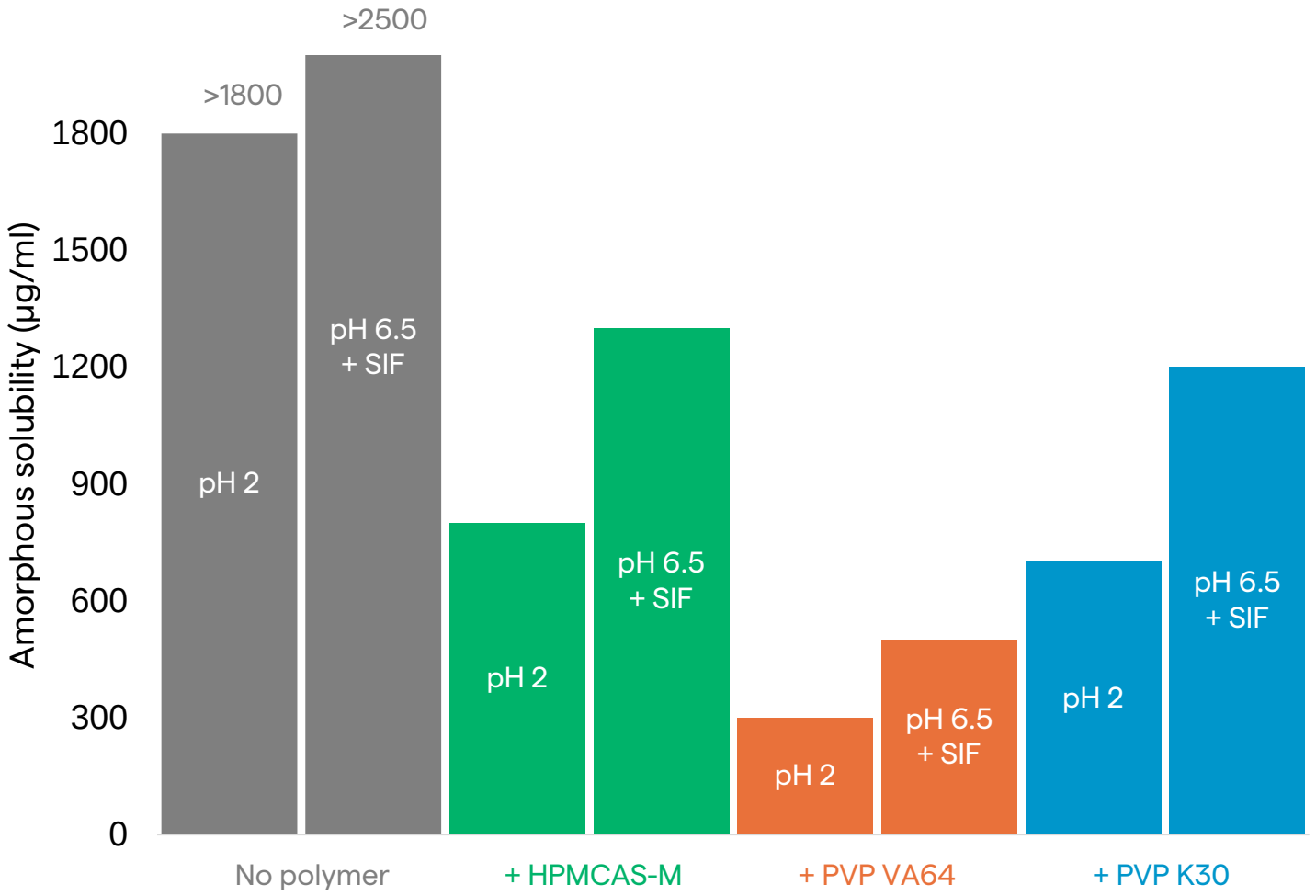
Belinostat dissolved in ethanol

1. pH 2 HCl or
2. pH 6.5 phosphate buffer + 6.7 mM SIF

w/300 µg/ml pre-dissolved:

1. PVP K30
2. PVP VA64
3. HPMCAS-M
4. No polymer



Ref: Stewart et al., J Pharm Sci 108 (2019) 326-336

ASDs Reach Amorphous Solubilities Measured by Solvent-Shift in Non-Sink In Vitro Dissolution Test

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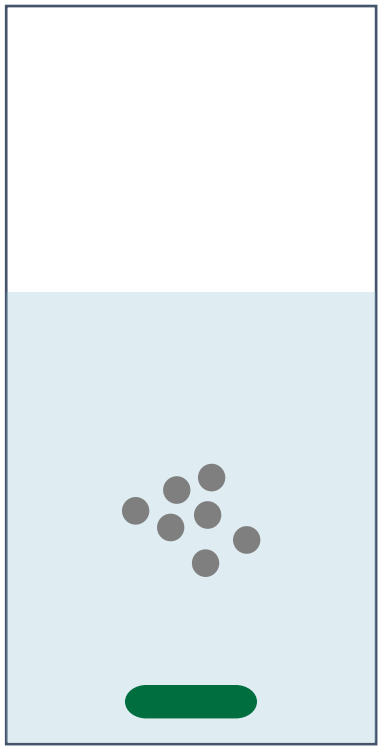
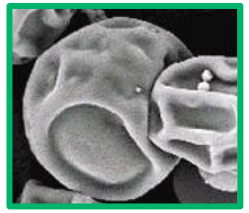
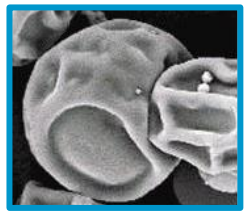
Intestinal pH test (pH 6.5, 6.7 mM SIF)
Non-sink test ('Do' > 1.5)

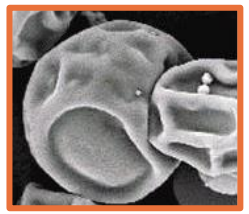




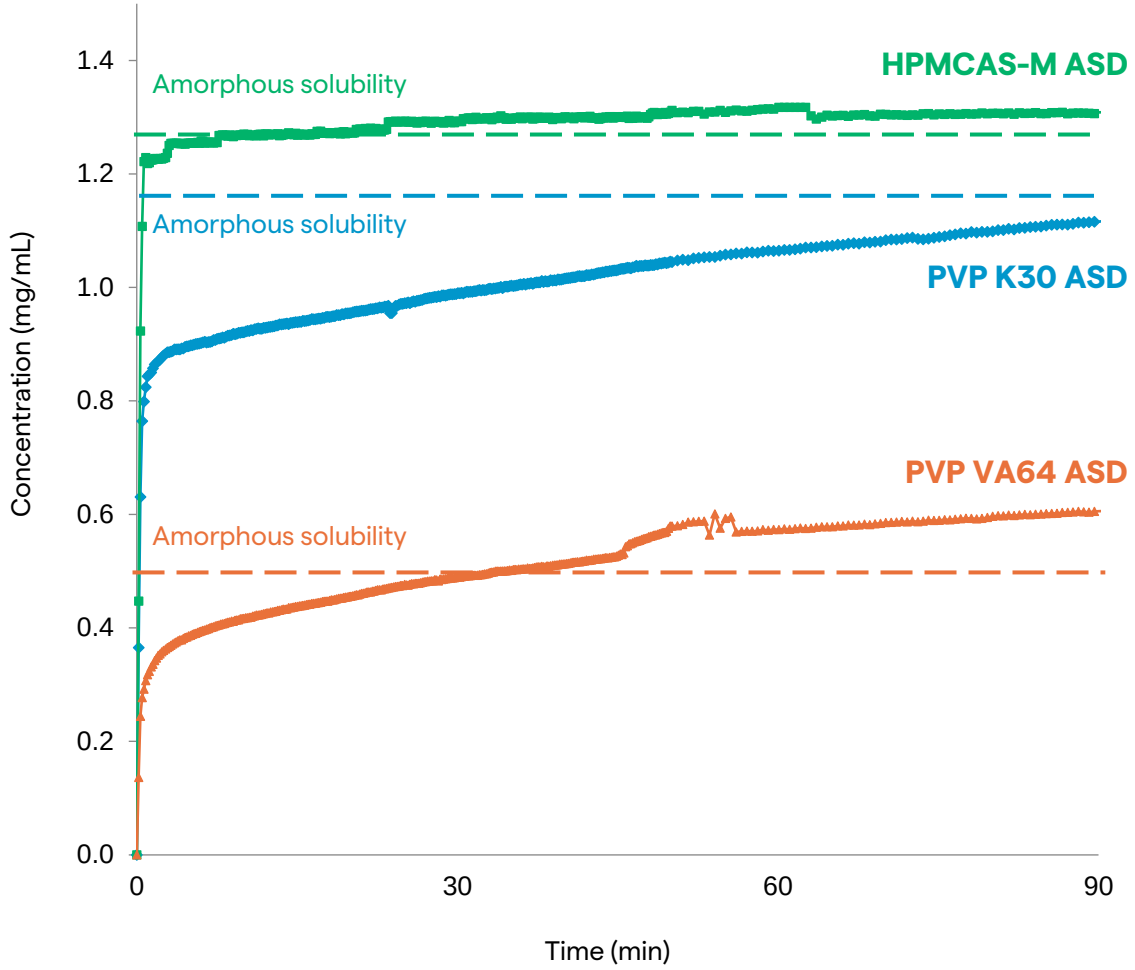
25% active HPMCAS-M ASD



25% active PVP K30 ASD



25% active PVP VA64 ASD



Ref: Stewart et al., J Pharm Sci 108 (2019) 326-336

HPMCAS-M ASD does not Reach Amorphous Solubility in Gastric Medium due to Aggregation

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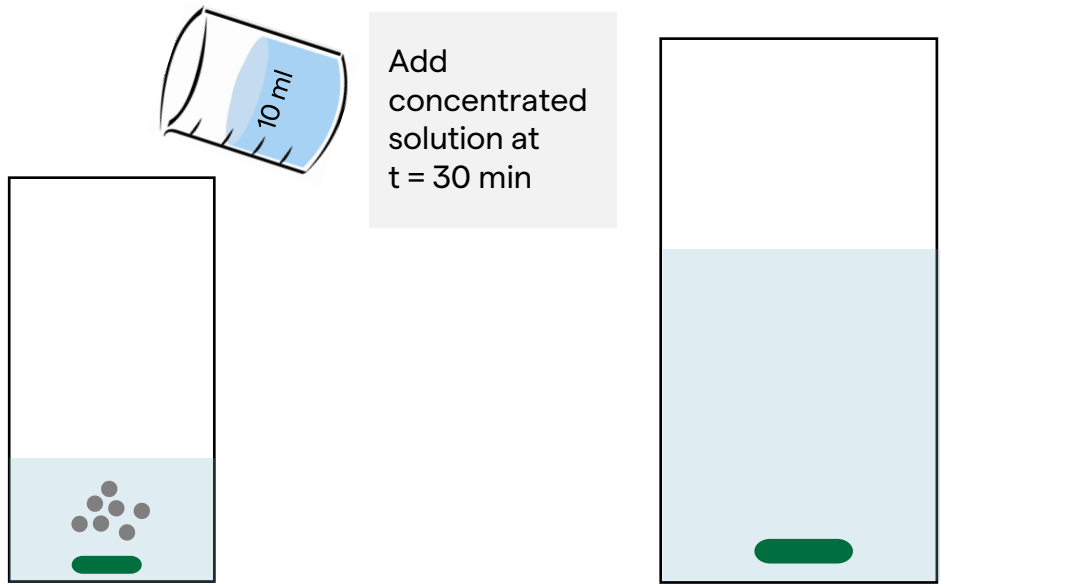
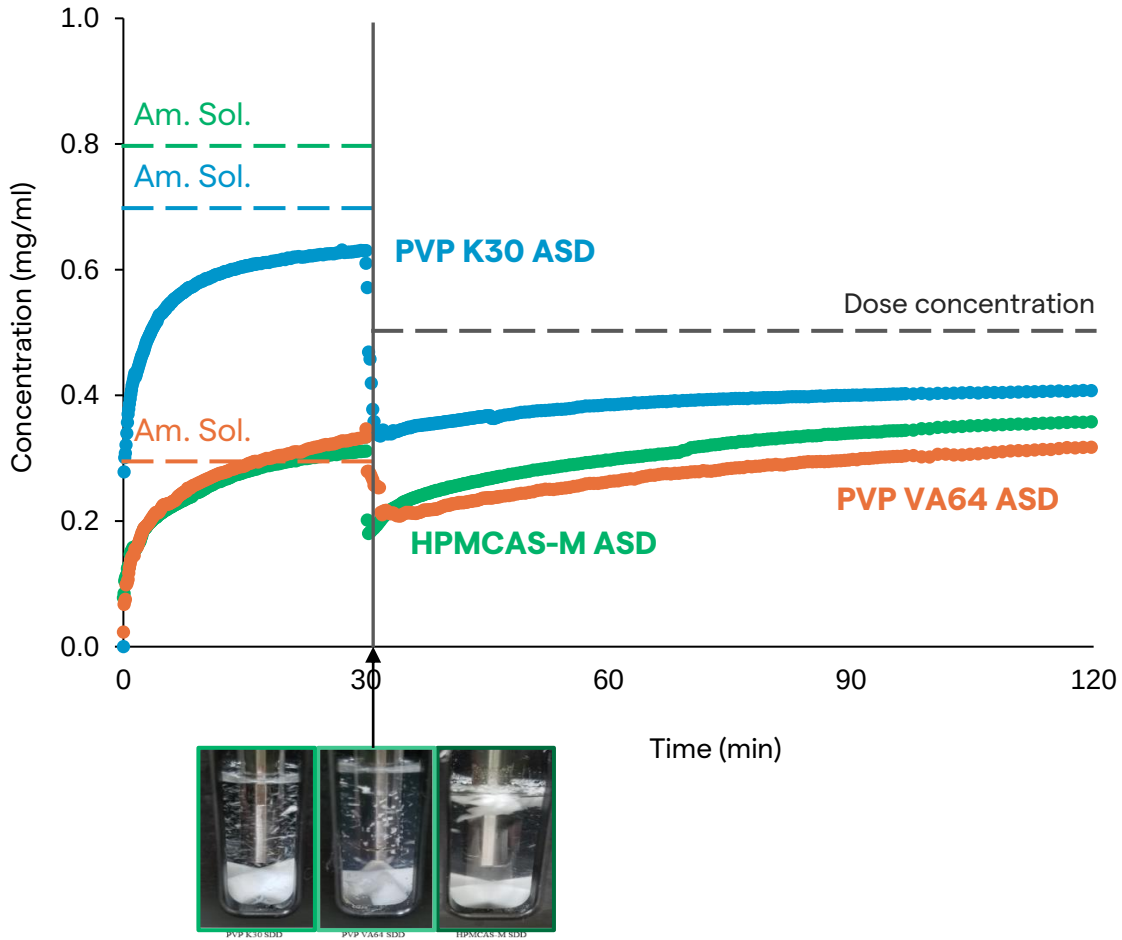
Gastric transfer test (pH 2 → 6.5, 6.7 mM SIF)
Gastric non-sink ('Do' > 1.3 → 'Do' ≤ 1)



pH 2
30 min

pH 6.5 + 6.7 mM SIF



Ref: Stewart et al., J Pharm Sci 108 (2019) 326-336

Modeling Strategy – Extract Z-Factor from In Vitro Dissolution Profiles and Amorphous Solubilities

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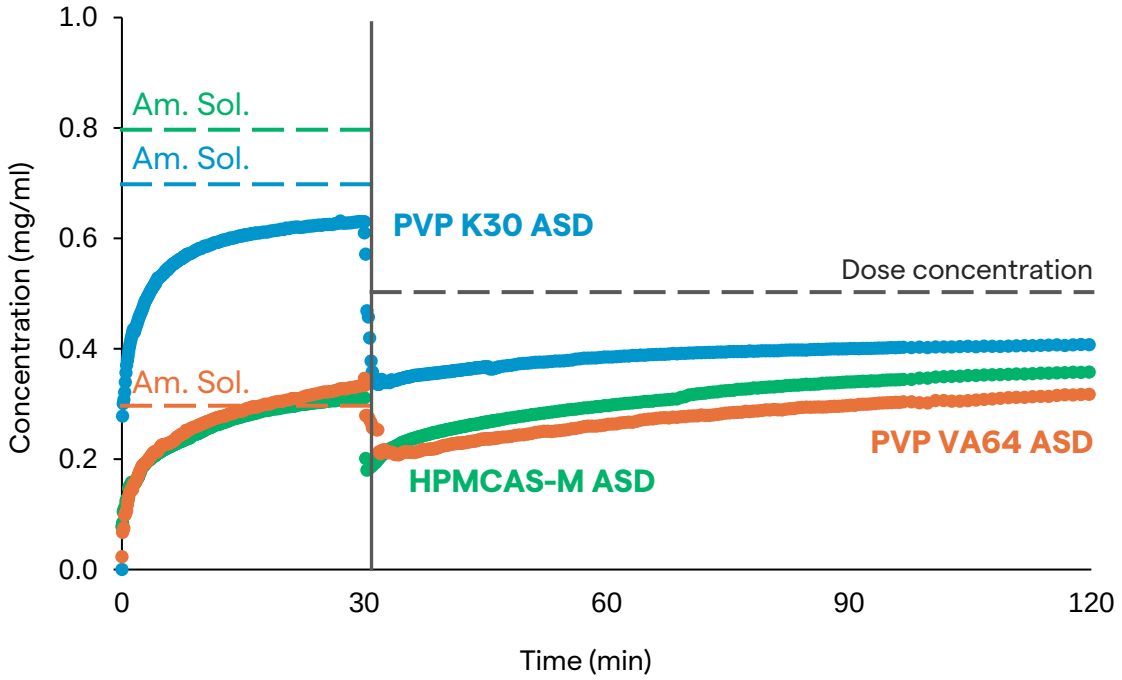
$$\frac{dM}{dt} = z \cdot M_{u,o} \left(\frac{M_{u,t}}{M_{u,o}}\right)^{2/3} (S_s - C_b)$$

$$z = \frac{3 \cdot D}{\rho \cdot r^2}$$



Ref: Stewart et al., J Pharm Sci 108 (2019) 326-336, Takano et al. Pharm Res, 2006

Gastric medium				
	S_s (mg/ml)	z (mL/g/s)	Ss · z (h^{-1})	r (µm)
PVP K30	0.7	32	80.6	8
PVP VA64	0.3	0.2	0.2	104
HPMCAS-M	0.8	0.06	0.2	169

Intestinal medium				
	S_s (mg/ml)	z (mL/g/s)	Ss · z (h^{-1})	r (µm)
PVP K30	1.1	3	11.6	25
PVP VA64	0.5	0.3	0.6	73
HPMCAS-M	1.2	0.7	3.1	50

PVP K30 ASD Performed Best In Vivo and Model Predictive of Average Plasma Profiles

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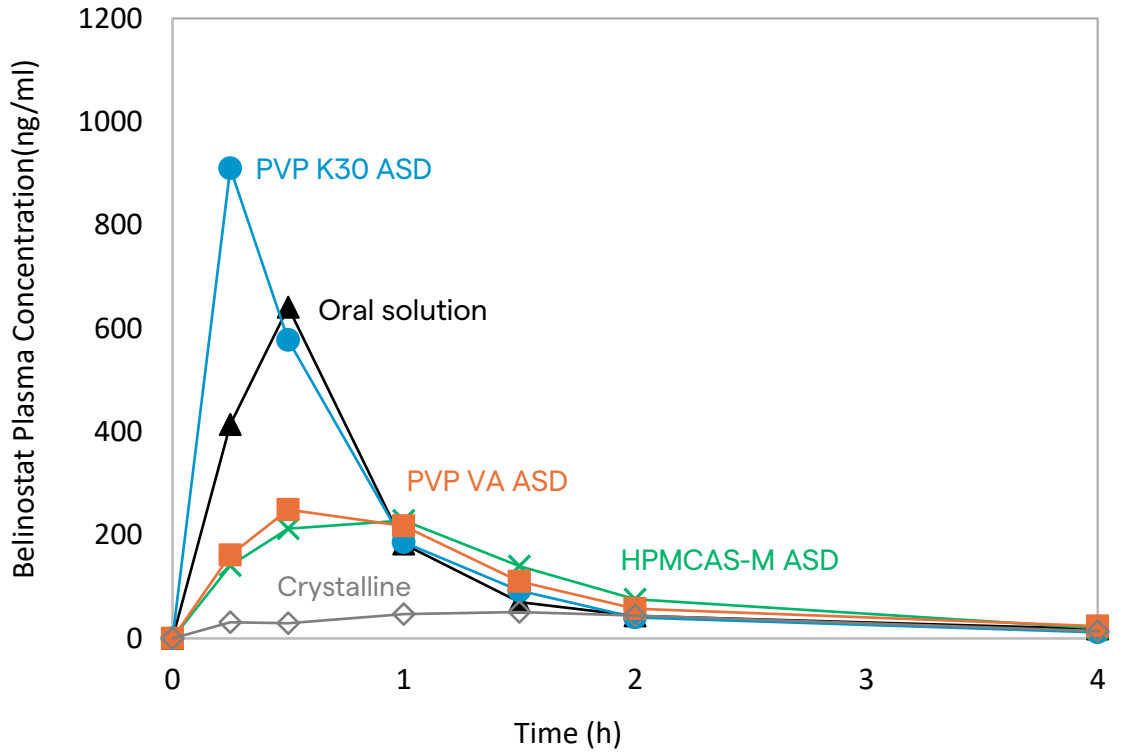
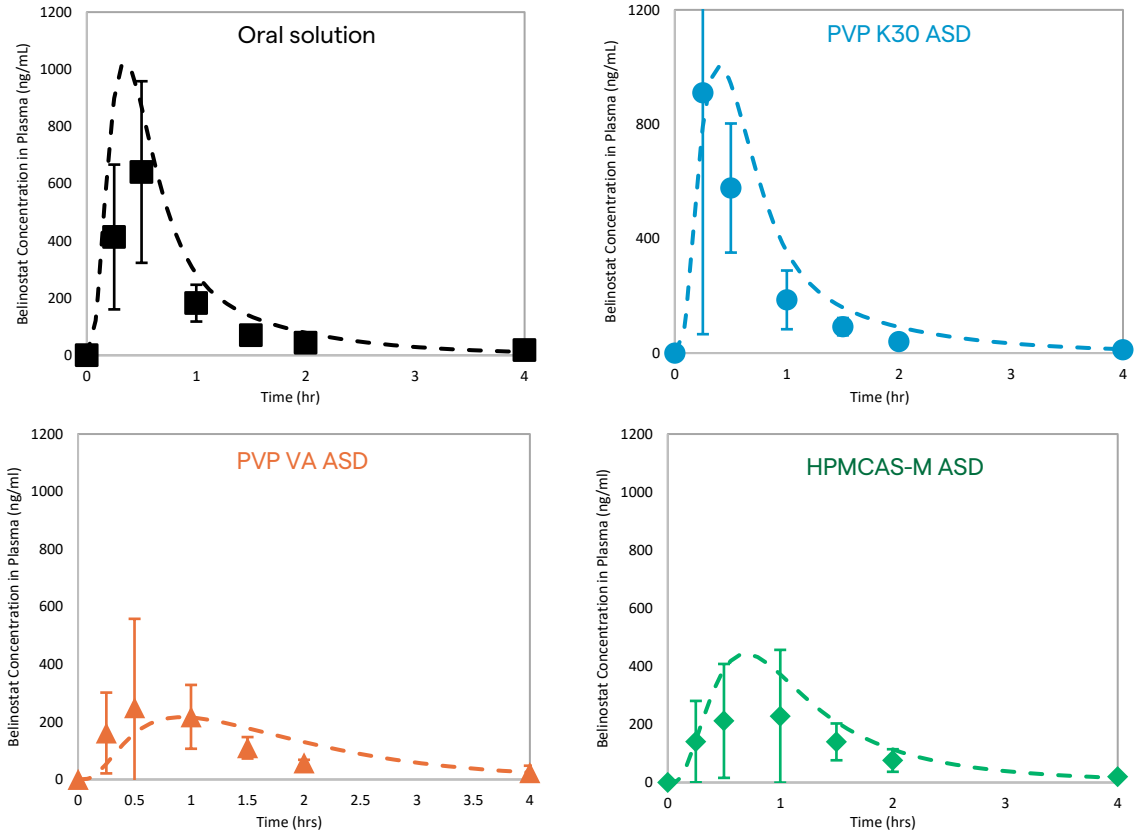
Fasted beagle dogs (n=4), 50 mg dose



Modeled using GastroPlus® version 9.0



Ref: Stewart et al., J Pharm Sci 108 (2019) 326-336

Belinostat Case Study Conclusions

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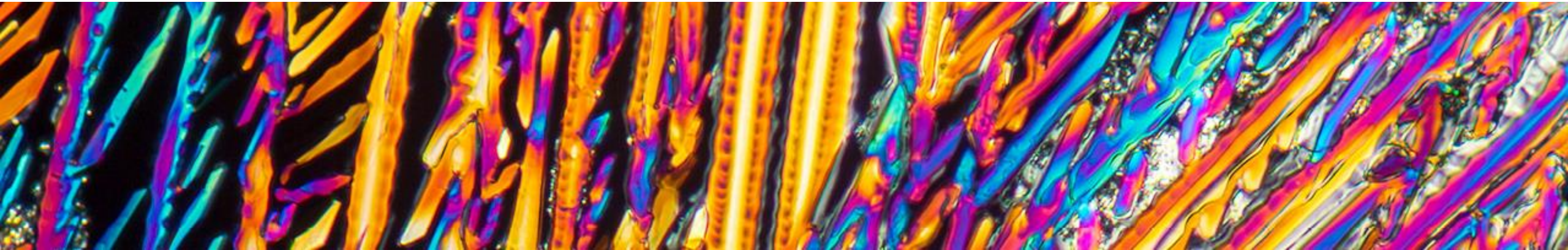
Amorphous solubility and effective particle size drive Belinostat ASD dissolution

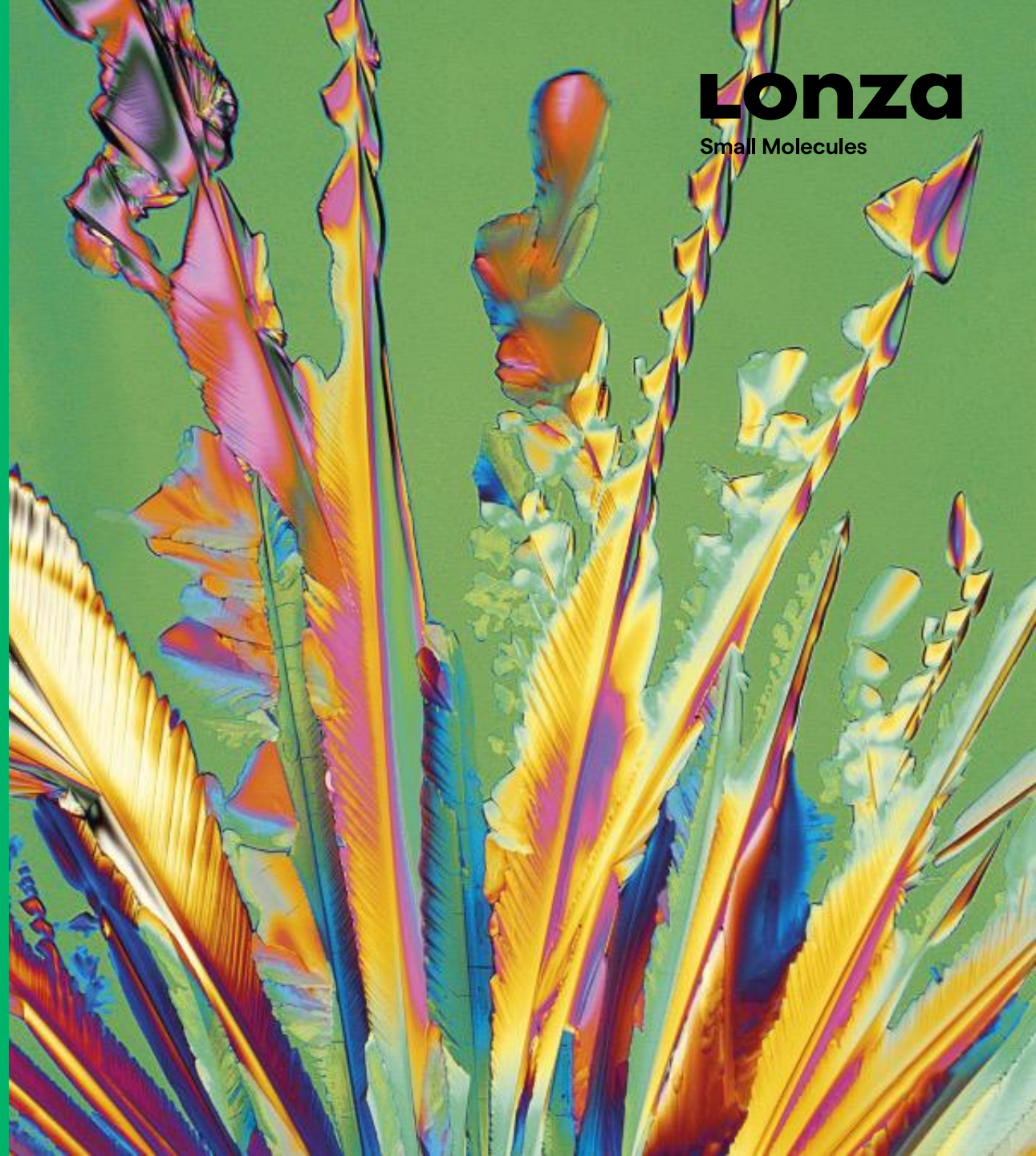
Amorphous solubility can be effectively measured using a pH-shift test

It’s important to test solubility in the presence and absence of formulation excipients



Itraconazole Case Study

Drug-polymer colloids drives performance by impacting maximum concentration driving force for absorption



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Itraconazole is a BCS 2 Drug Formulated as ASDs using Different Grades of HPMCAS

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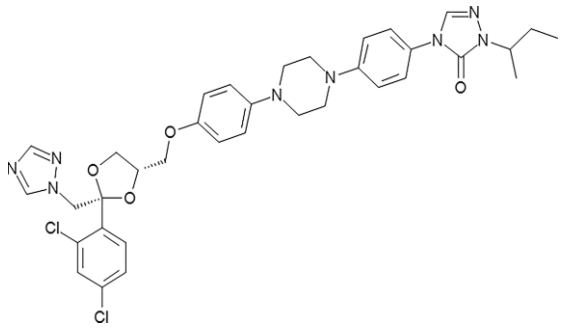
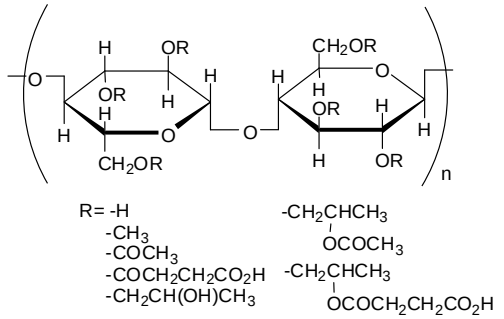
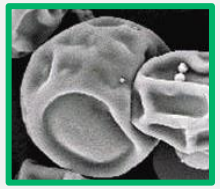
Itraconazole
- BCS 2
- pK_a = 3.7
- log P = 6.3



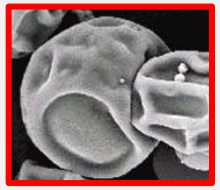
Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS)





25% active
Hydrophilic SDD
Affinisol 716HP ('L grade')

or



25% active
Hydrophobic SDD
Affinisol 126HP ('H grade')

Goal:

exceed performance of marketed formulation* in rat study
*Sporanox® spray-layered amorphous dispersion

Stewart et al. Mol. Pharm. 14, 2437–2449 (2017)

Itraconazole ASDs Form Drug-Polymer Colloids in Aqueous Media

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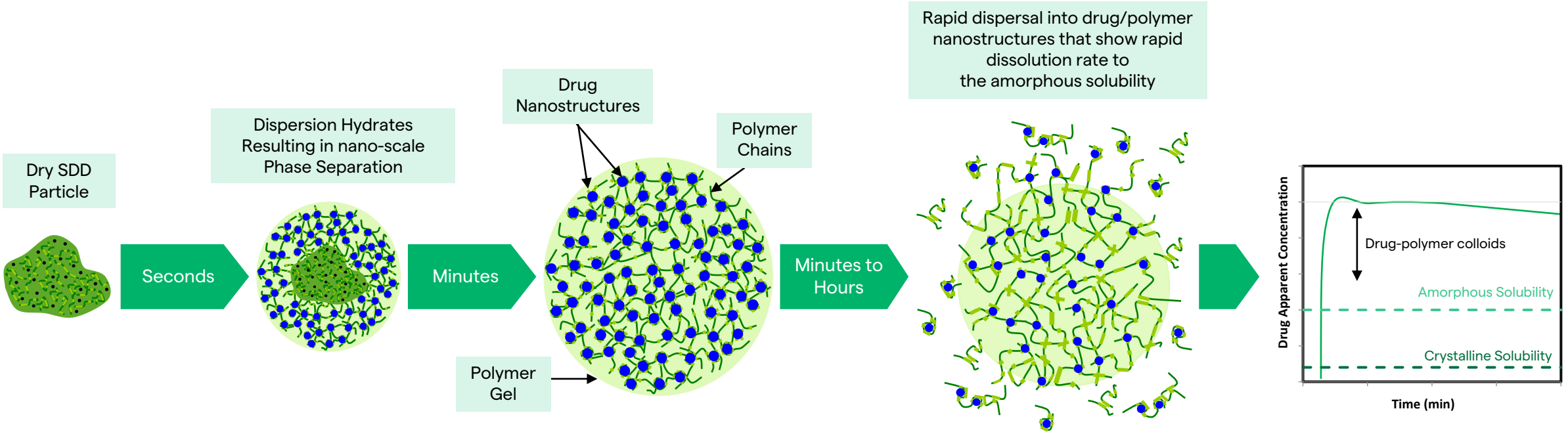

Colloids and Drug Speciation can be Measured using Non-Sink In Vitro Test

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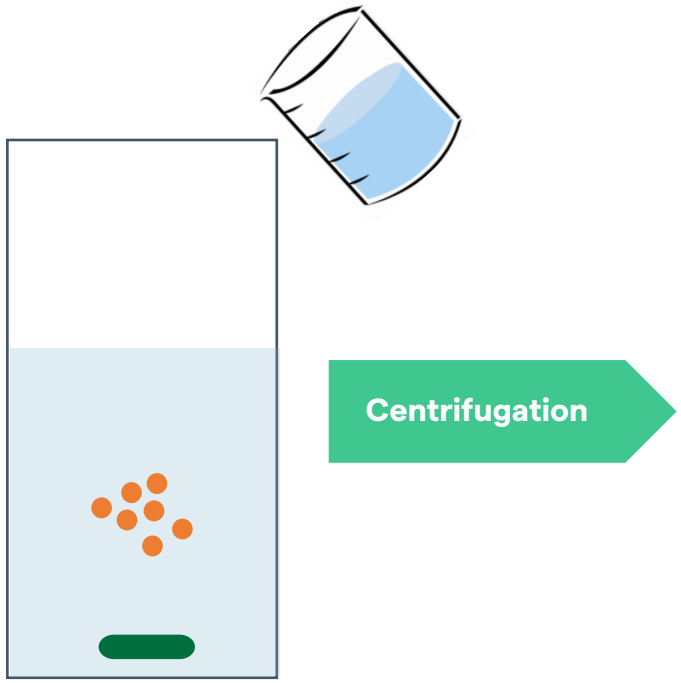
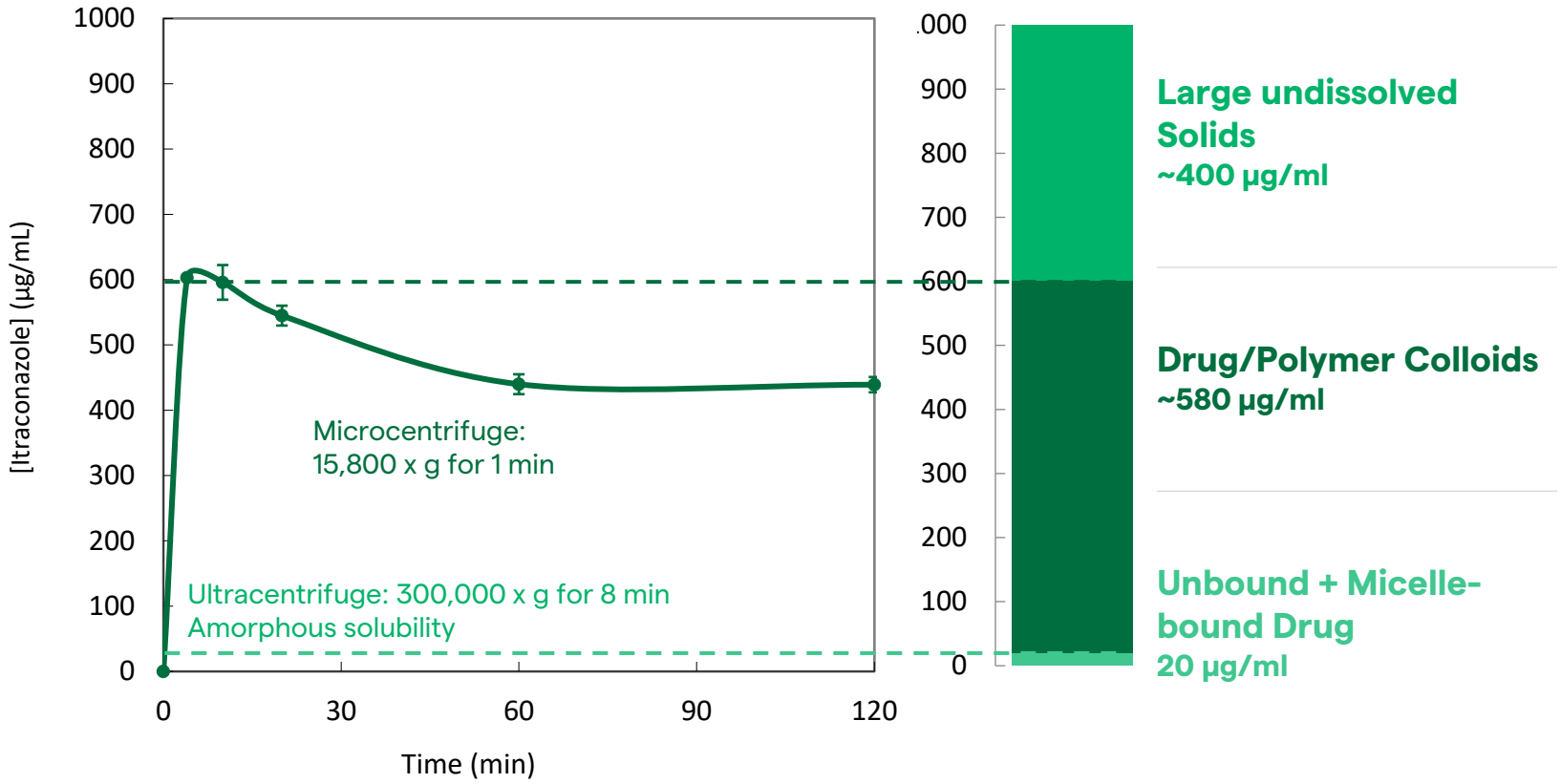


Centrifugation

25% Itraconazole:HPMCAS-L ASD
pH 6.5, 27 mM bile salts



+ Dynamic Light Scattering (DLS) to confirm/determine size of species

Colloid Concentration is Influenced by Polymer Type and Impacts Permeation Rate in a Membrane Flux Assay

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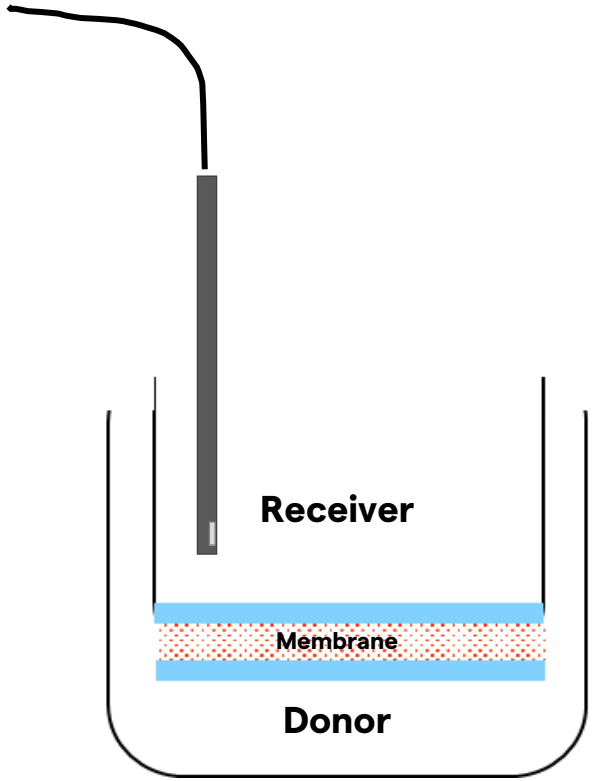
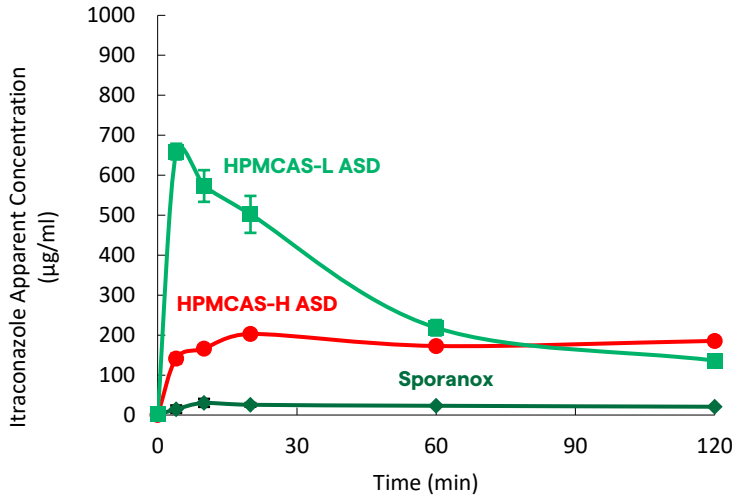
Membrane Flux Assay

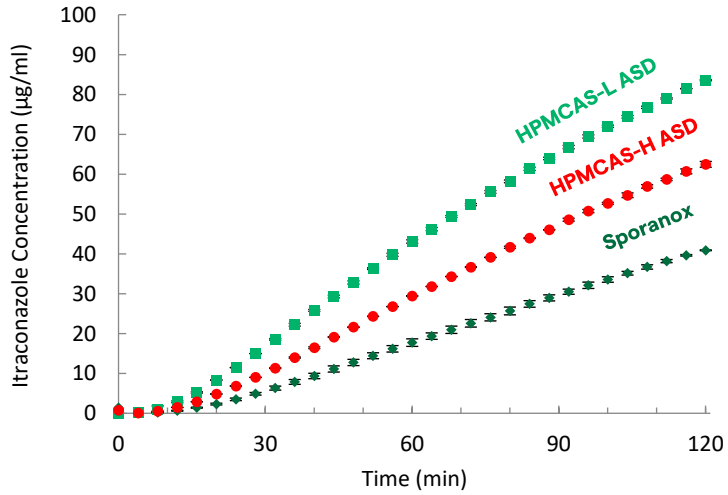


Stewart et al. Mol. Pharm. 14, 2437–2449 (2017)

Donor



Receiver



No.	Formulation	Flux (µg/min/cm2)	Colloid (µg/ml)
1 ■	25% ITZ/75% HPMCAS-L SDD	1.18	602
2 ●	25% ITZ/75% HPMCAS-H SDD	0.85	150
3 ◆	Sporanox® spray layered dispersion	0.53	0

Increased Flux Mechanism – Colloids Help Shuttle Drug Across the Unstirred Water Layer (UWL)

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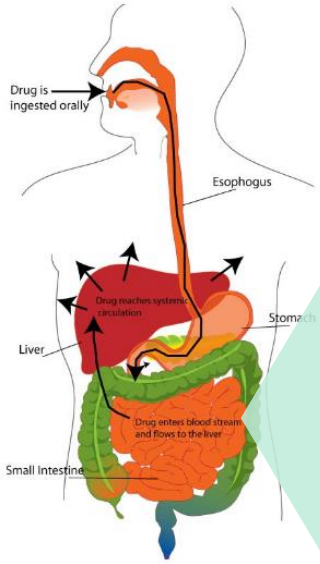
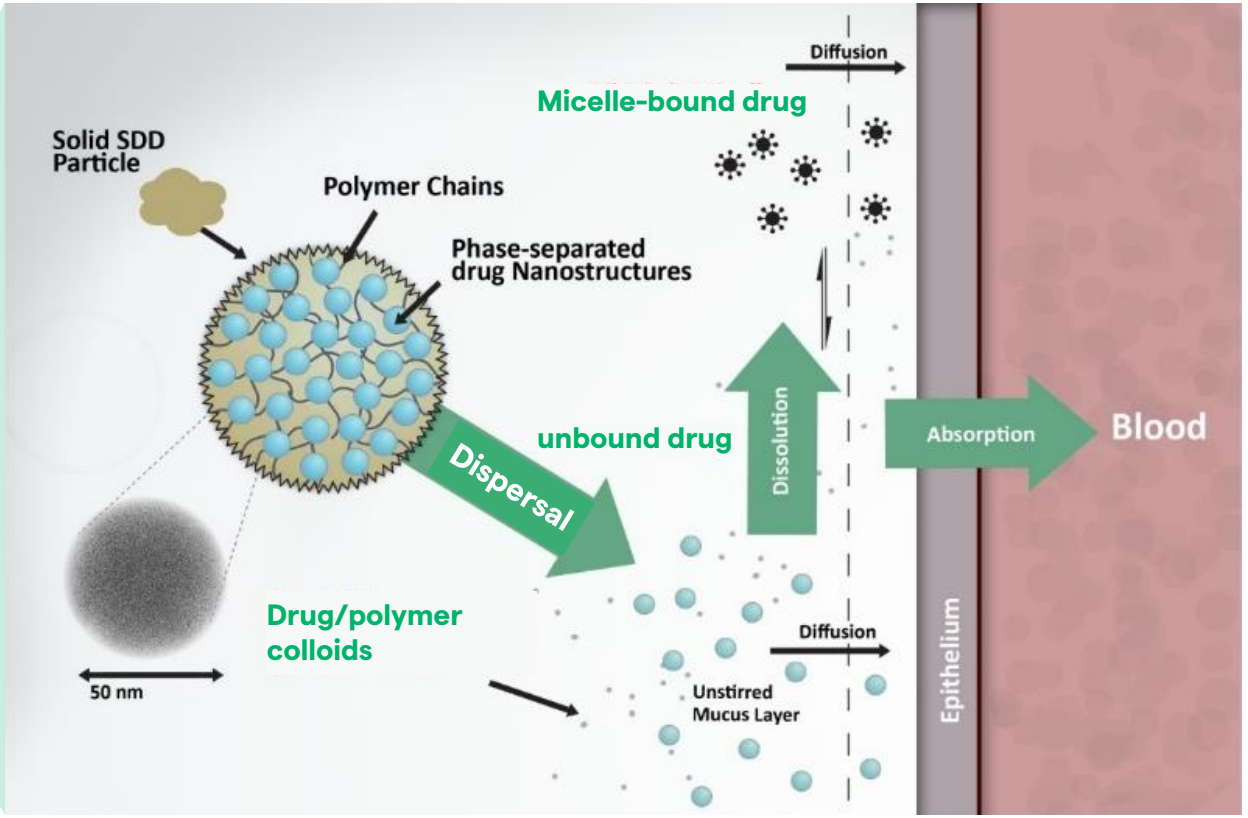
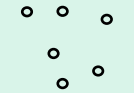
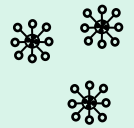
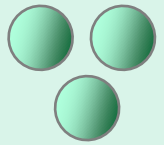
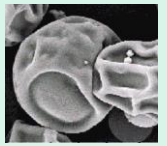





Unbound drug
~1 nm


Micelle-bound drug (5-500 nm)


Drug/Polymer colloids
(10 – 400 nm)


Undissolved solids
(10-100 µm)

Contribution to absorption

Modeling Strategy – Modify P_{eff} to Account for Increased Permeation Rate for Colloid-Forming Formulations

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Small Molecules

$$P_{eff,nano} = P_{eff}\left(1 + \frac{D_{nano}}{D_{SIF}} \cdot \frac{c_{nano}}{c_{SIF}}\right)$$

Solubility model inputs:

- Amorphous solubility of free drug
- Biorelevant solubility

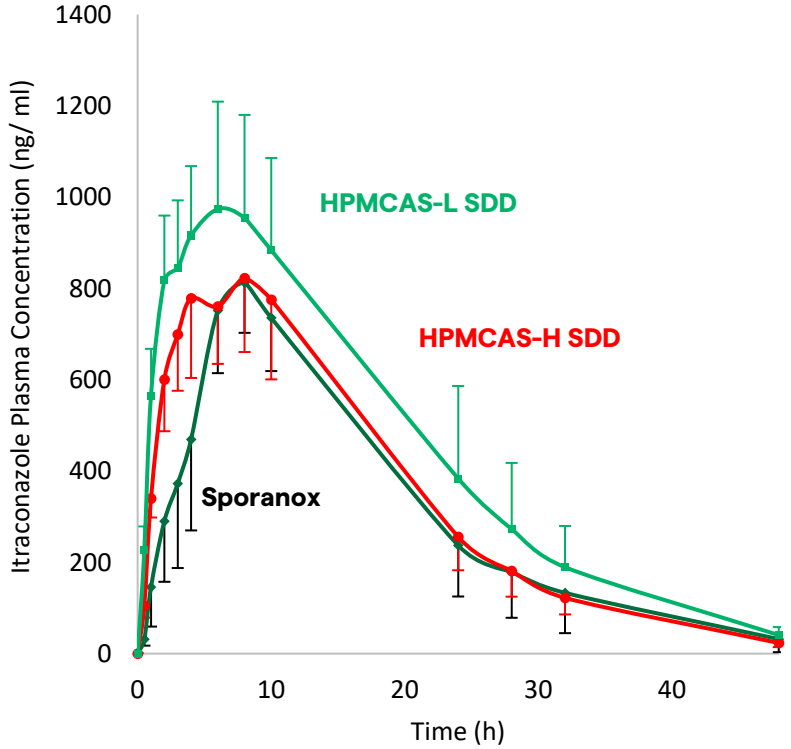
In Vitro Data	Notation	Analytical
Concentration of colloids	c_{nano}	Centrifuge + HPLC in media of interest
Concentration of bile micelle-bound drug	c_{SIF}	Ultracentrifuge + HPLC in biorelevant media
Concentration of free drug	c_{u}	Ultracentrifuge + HPLC in blank buffer
Size of colloids	d_{nano}	Dynamic Light Scattering
Size of bile salt micelles	d_{SIF}	

Stewart & Grass, Mol. Pharm. 17, 1, 180-189 (2019)

Colloids Influence In Vivo Absorption and Nano-Modified Peff Strategy Predicted Exposure in Rats

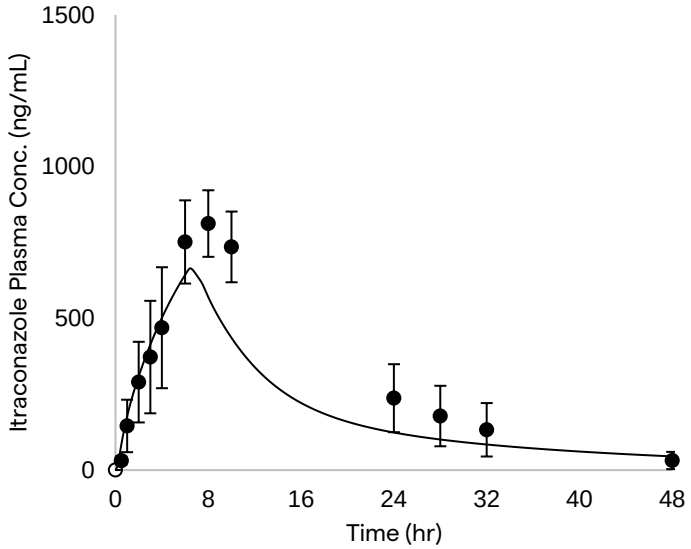
Lonza
Small Molecules

Fasted Sprague-Dawley rats (n=6), 50 mg/kg

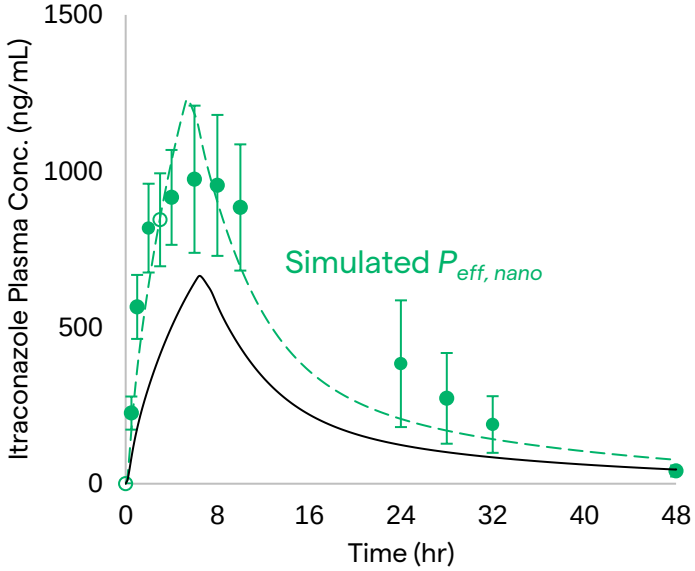


Modeled using GastroPlus version 9.6

Sporanox – No colloids



HPMCAS-L ASD

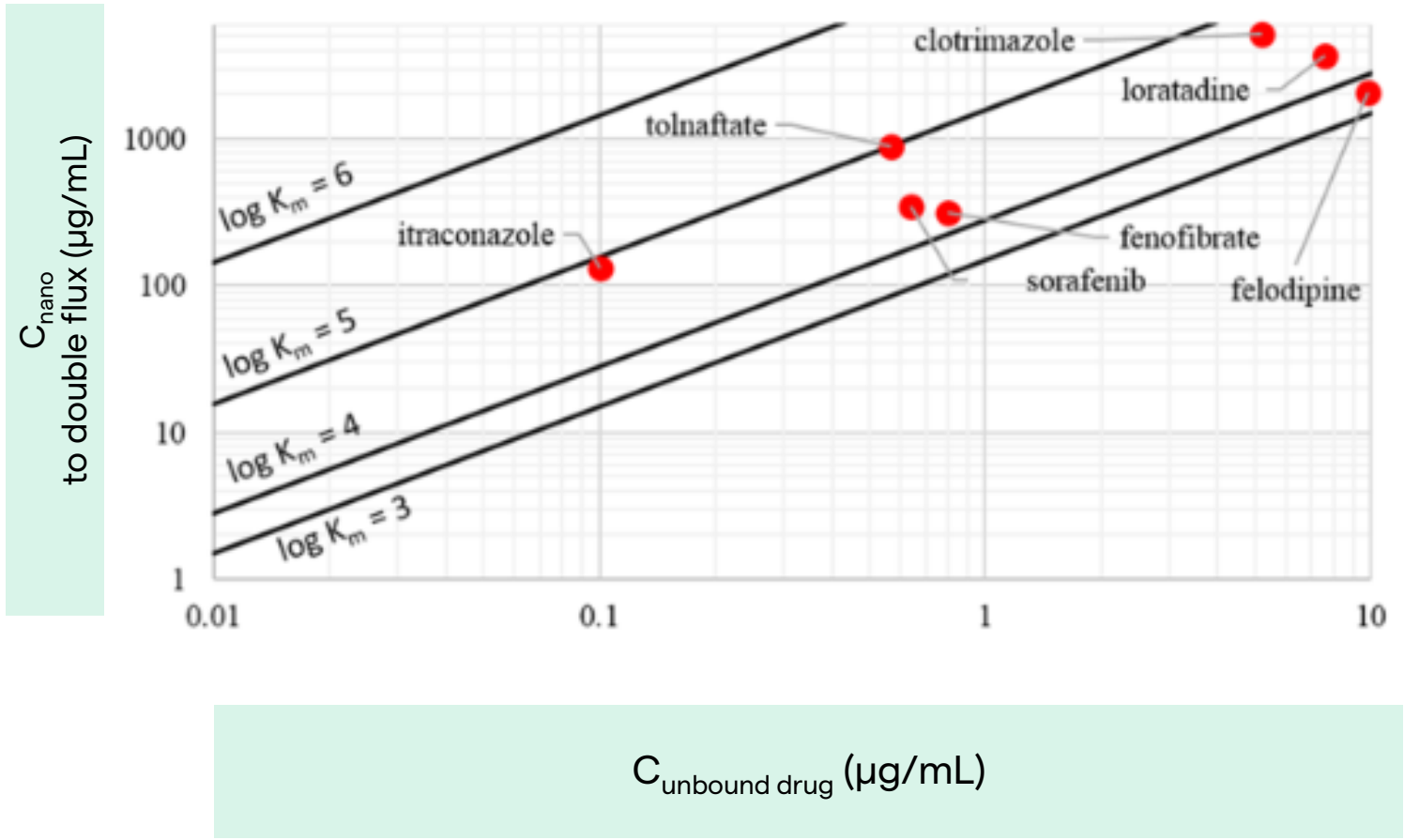


Stewart et al. Mol. Pharm. 14, 2437–2449 (2017), Stewart & Grass, Mol. Pharm. 17, 1, 180-189 (2019)

When do Drug-Polymer Colloids Tend to Improve Absorption?

Lonza
Small Molecules

- Solubility-permeability limited absorption
- Permeation is UWL limited
- $C_{nano} >> C_{unbound} + C_{SIF}$
  - As bile micelles ↓
  - As K_{bm} ↓
- Calculate $P_{eff, nano}$ vs. P_{eff} & run PSA



Stewart et al. Mol. Pharm. 14, 2437–2449 (2017)

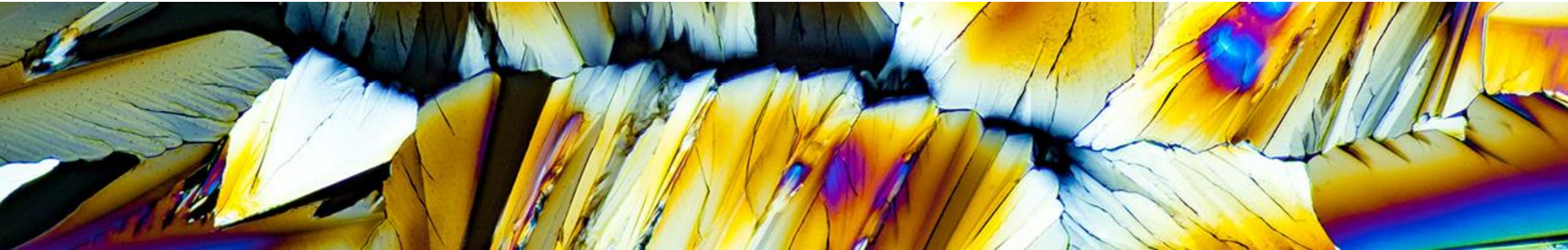
Itraconazole Case Study Conclusions

Lonza
Small Molecules

Drug-polymer colloids drive absorption of itraconazole ASDs

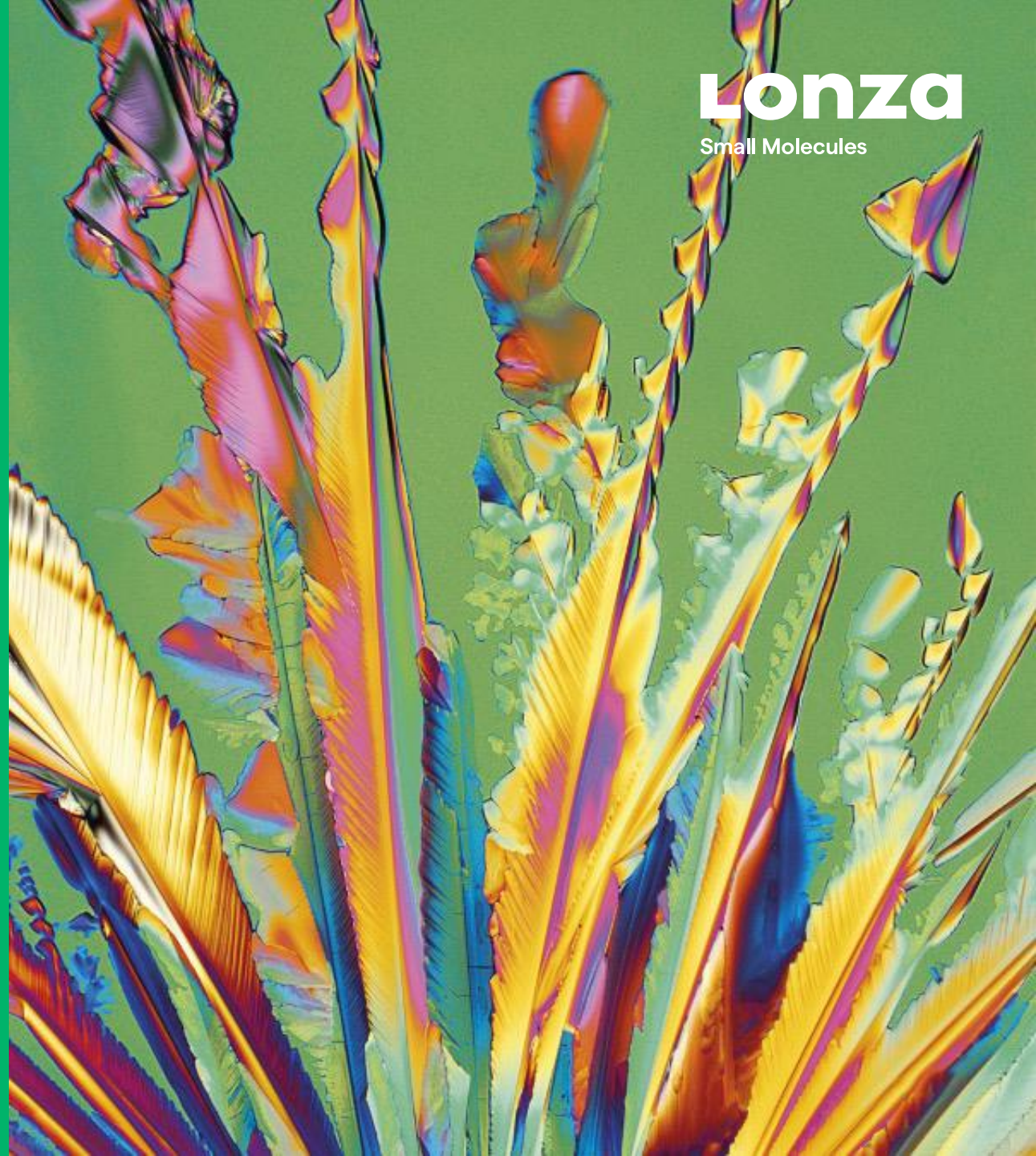
Colloid concentration and drug ‘speciation’ can be measured in vitro

‘Nano-modified P_{eff}’ can model influence on in vivo performance



Acalabrutinib Case Study

Solubility at solid particle surface drives performance by impacting dissolution rate



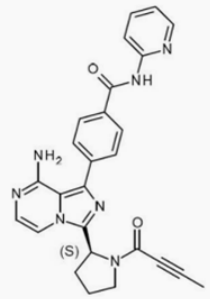
Deanna Mudie | PBBM 2023 Workshop | 29 Aug 2023

Acalabrutinib is a BCS 2 Drug Formulated as Crystalline Drug in Capsule or Tablet (CALQUENCE®)

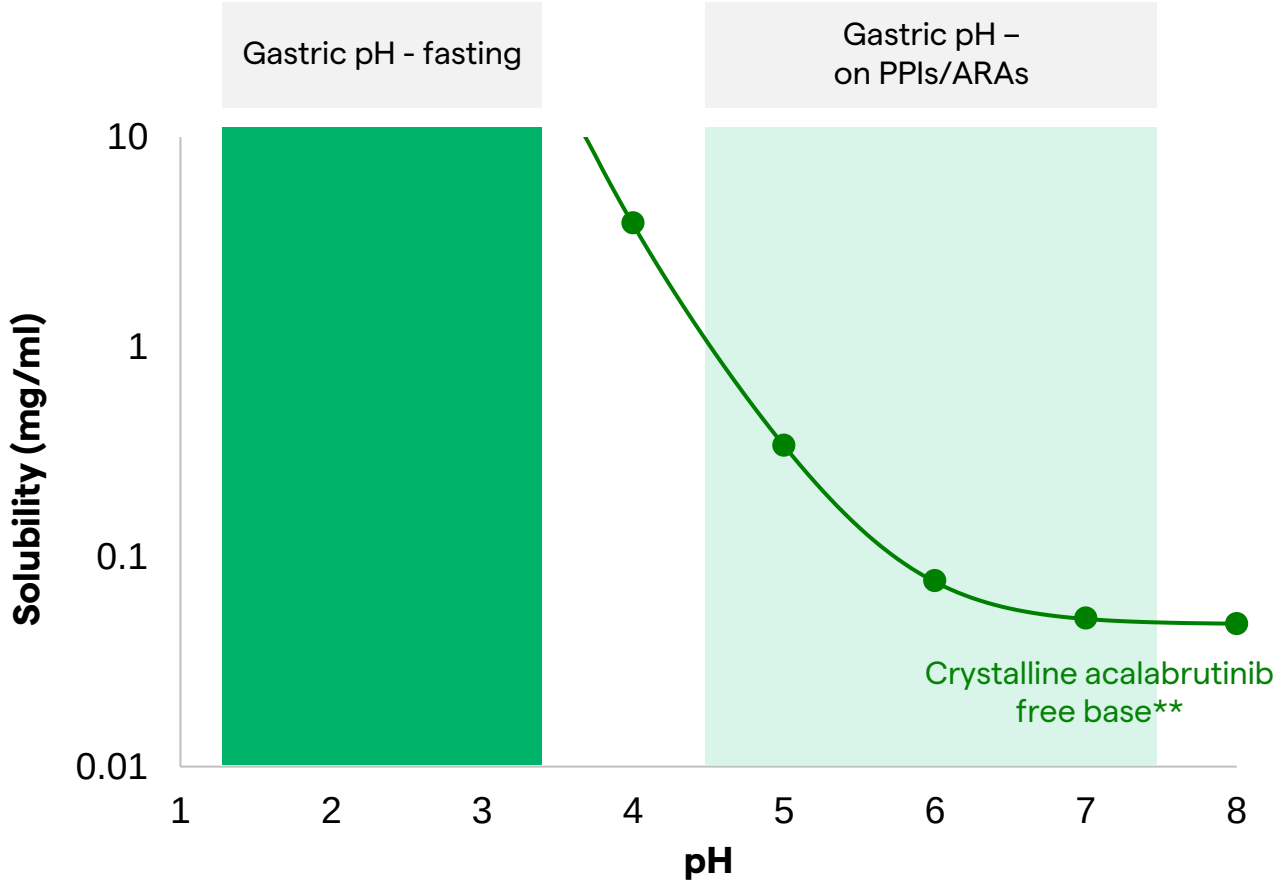
Lonza
Small Molecules

Acalabrutinib

- BCS 2b
- pK_a = 3.5, 5.8
- log P = 2



- Plasma AUC of free base ↓ 43% with PPI*
- Acalabrutinib maleate overcomes PPI effect
- Current case study evaluates ASD tablet

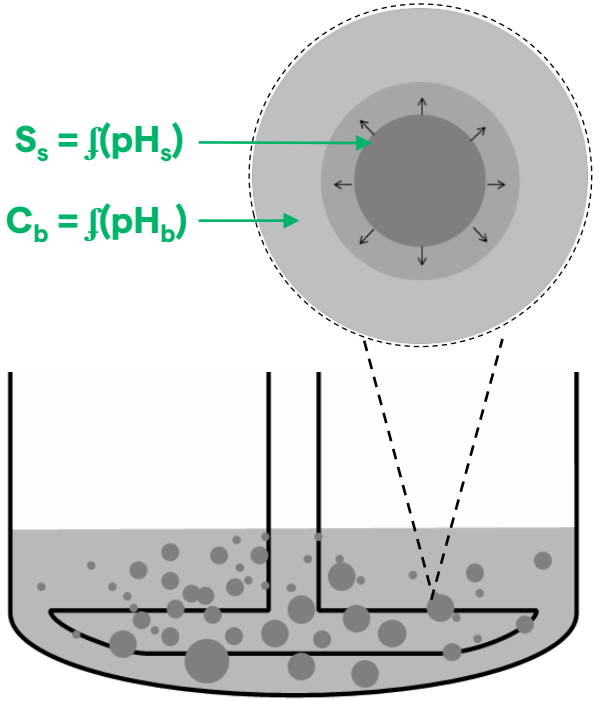


*Calquence FDA label
**Pepin et al. Eur J Pharm Biopharm. 2019 Sep;142

Modeling Rate and Extent of Gastric Release Relies On Estimating Surface Solubility

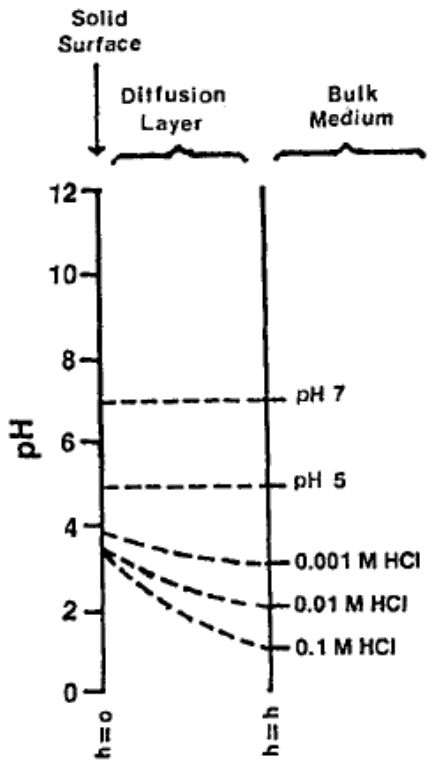
Lonza
Small Molecules

$$\frac{dM_{diss}}{dt} = k_{pr}(t) \cdot \left(S_{s(t)} - C_{b(t)}\right)$$

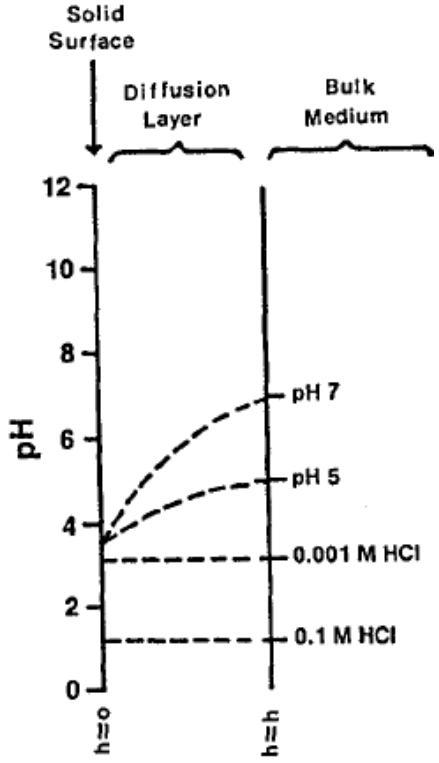


$pH_s \neq pH_b$ for some weak acids & bases

Mudie et al. AAPS J. 2020 Jan 27;22(2):34



Phenazopyridine (weak base)



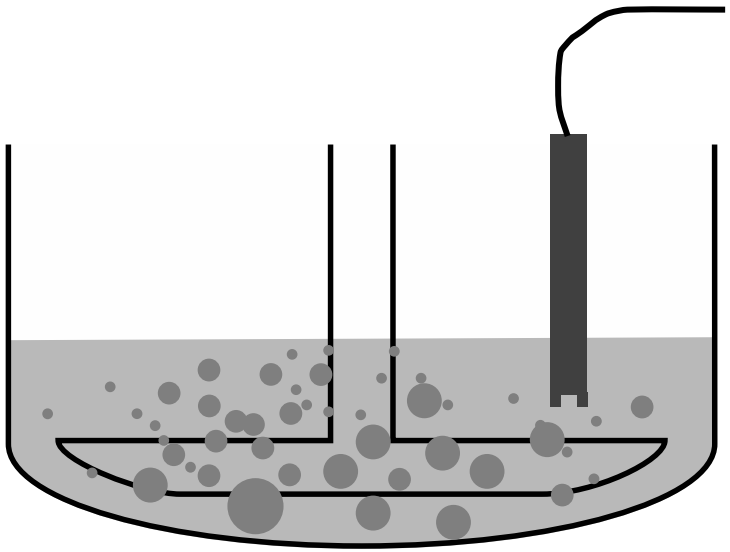
Phenazopyridine HCl

Example from Serajuddin & Jarowski, J Pharm Sci, 1985, 74, 2

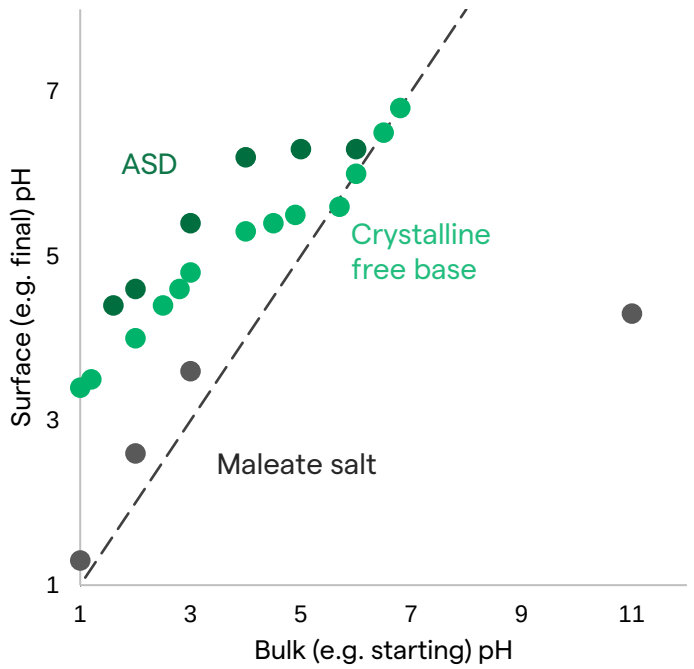
Measured Surface pH by Measuring pH of a Saturated Solution

Lonza
Small Molecules

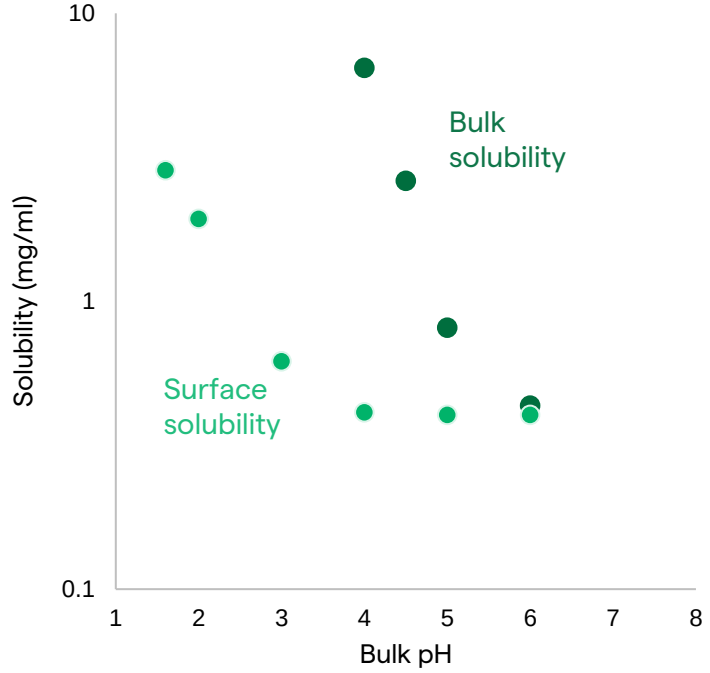
Measure pH of a saturated solution of drug in e.g. HCl



Results for acalabrutinib in HCl or NaOH



Bulk vs. Surface Solubility for ASD



Refs: Pepin et al. Eur J Pharm Biopharm. 2019 Sep;142, Pepin et al. Mol Pharm. 2023, 20, 4, Mudie et al. Pharmaceutics 2021, 13, 1257

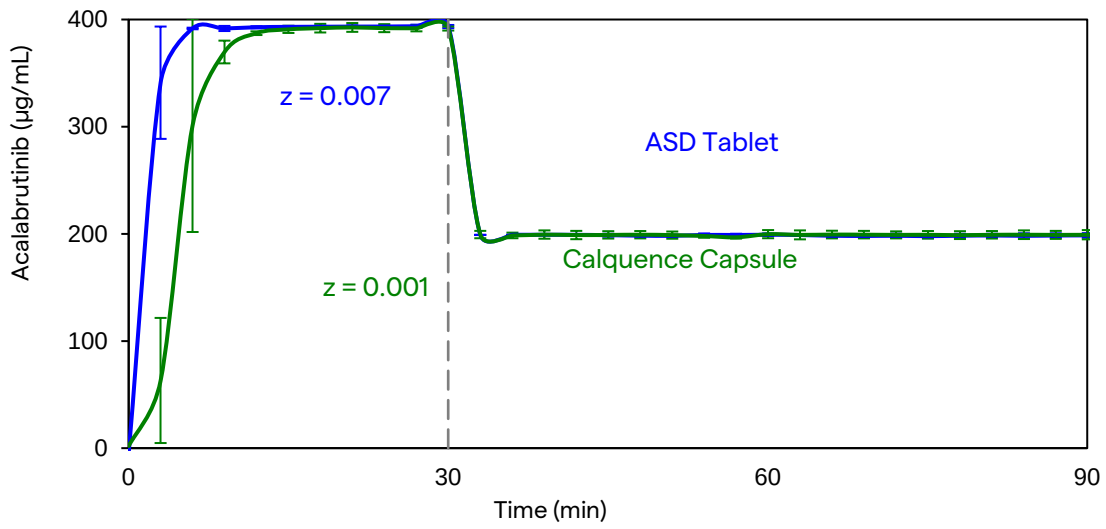
Modeling Strategy – Adjust Bulk pH to Surface pH and Extract Z-Factor from In Vitro Dissolution Profiles

Lonza
Small Molecules

	Simulated bulk pH	Adjusted (surface) pH ASD Tablet	Adjusted (surface) pH Calquence capsule
Dog stomach Low pH (e.g. pentagastrin)	**2.0**	**4.6**	**4.0**
Dog stomach High pH (e.g. famotidine)	**6.0**	**6.3**	**6.0**

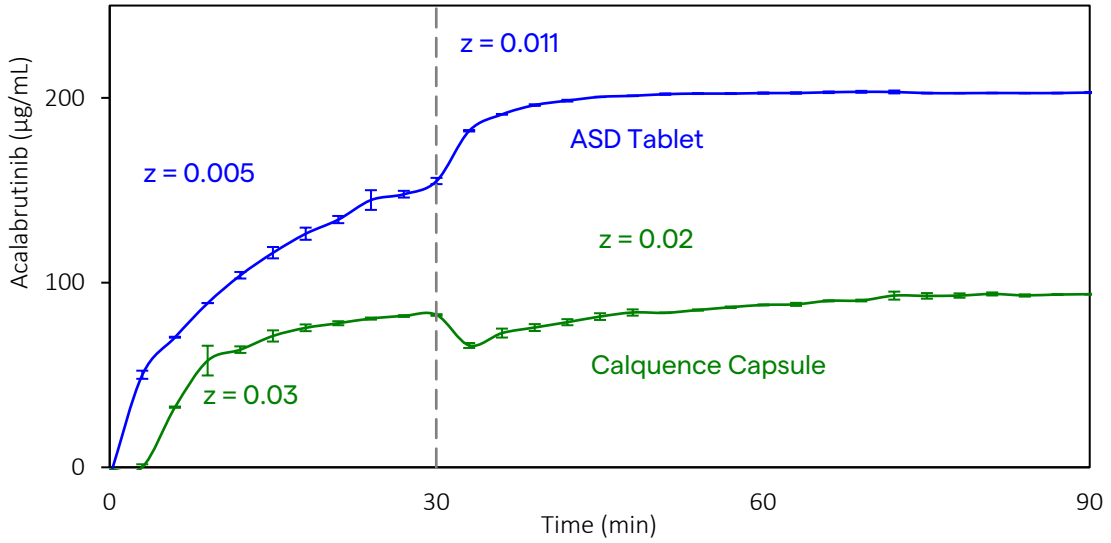
$$\frac{dM}{dt} = z \cdot M_{u,o}\left(\frac{M_{u,t}}{M_{u,o}}\right)^{2/3}(C_s - C_b)$$

pH 2 gastric test



$$\frac{dM}{dt} = z \cdot M_{u,o}\left(\frac{M_{u,t}}{M_{u,o}}\right)^{2/3}(C_s - C_b)$$

pH 6 gastric test

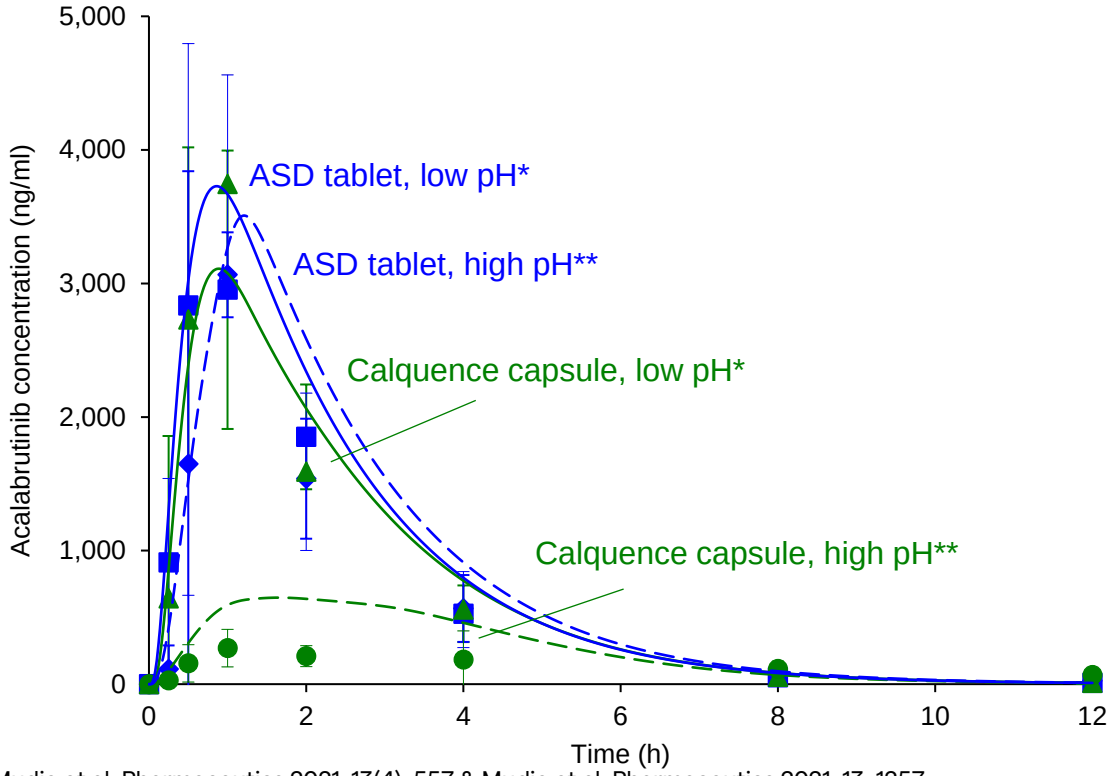


Mudie et al. Pharmaceutics 2021, 13, 1257

Bottom-Up Model was Predictive of In Vivo Dog Study Results

Lonza
Small Molecules

Fasted Beagle dogs (n=6), 100 mg



Modeled using GastroPlus version 9.8

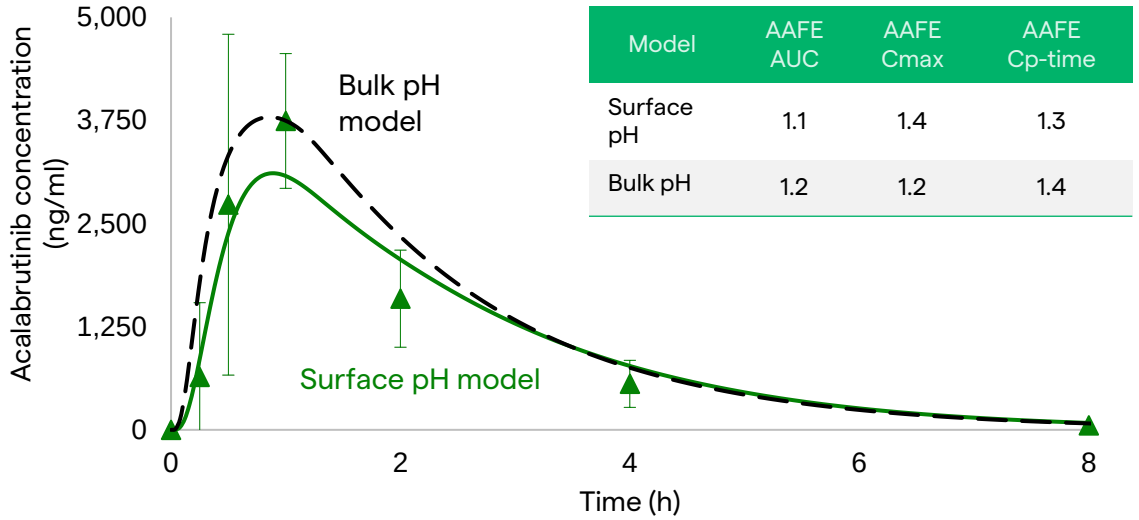
	$AUC_{0\text{-inf}}$ (ng h/mL)		Absolute average fold error (AAFE)	
	Obs	Sim	$AUC_{0\text{-inf}}$	C_p vs. time
ASD tablet, low pH	8161	9766	1.2	1.3
ASD tablet, high pH	7579	9555	1.3	1.6
Calquence capsule, low pH	8365	8607	1.1	1.3
Calquence capsule, high pH	3112	3096	1.6	3.0

Mudie et al. Pharmaceutics 2021, 13(4), 557 & Mudie et al. Pharmaceutics 2021, 13, 1257

Not Accounting for Surface pH Has Modest Impact on Predictions for Current Model

Lonza
Small Molecules

- 15% ↑ AUC & 22% ↑ Cmax Calquence capsule (bulk pH 2)



Model	AAFE AUC	AAFE Cmax	AAFE Cp-time
Surface pH	1.1	1.4	1.3
Bulk pH	1.2	1.2	1.4

- ↔ ASD tablet (bulk pH 2 & 6)
- ↔ Calquence capsule (bulk pH 6)

- Why???
  - Dissolution rate is already fast at bulk pH 2
  - Surface = bulk pH at pH 6
- Large overprediction of dissolution data for Pepin et al. model
  - "Use of bulk solubility instead of surface solubility led to an overall 48% overprediction…"
  - Prediction error highest at pH 4.5 (up to 250%)

Refs: Mudie et al. *Pharmaceutics* 2021, *13*, 1257, Pepin et al. *Eur J Pharm Biopharm*. 2019 Sep;142,

When does Drug/Formulation Impact Surface pH & Dissolution?

Lonza
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- Some weak acids & bases

Weak Acid	pK_a ↓	S_0 ↑
Weak Base	pK_a ↑	S_0 ↑

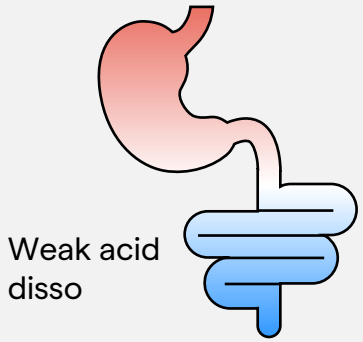
- Rule of thumb when surface pH ≠ bulk pH*

Weak acids	Weak bases
$pK_a < 6$ & $pK_a - \log S_o < 10$	$pK_a > 7$ & $pK_w - pK_a - \log S_o < 11$

Free form , sink conditions buffered media pH 5-7

- Predict using published calculations/software‡

- Most relevant for weak acids in intestine & weak bases in stomach



- Potential impact on absorption when dissolution is rate-limiting

- Conduct PSA

*Mudie et al. AAPS J. 2020 Jan 27;22(2):34 ‡ Mooney et al. J Pharm Sci, 1981, 70
‡ Ozturk et al. Pharm Res. 1998, 5, ‡ Al-Gousous et al. Mol Pharm. 2019, 16
‡ Pepin et al. Eur J Pharm Biopharm. 2019, 142 ‡ Pepin et al. Mol Pharm. 2023, 20

Acalabrutinib Case Study Conclusions

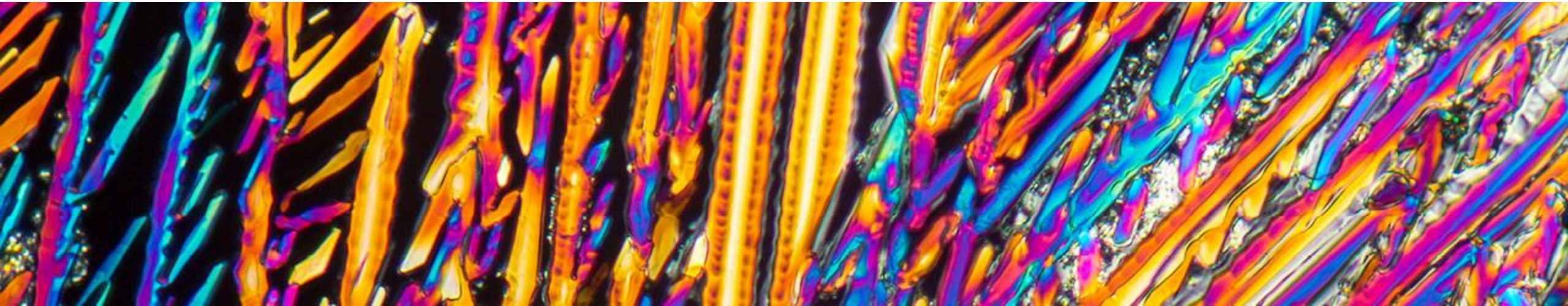
Lonza
Small Molecules

Acalabrutinib dissolution impacted by surface pH & surface solubility (≠ bulk solubility)

Surface pH can be estimated in vitro or predicted in silico

Importance of accounting for surface pH depends on

- Rate-determining step to absorption
- Drug, formulation, and GI fluid properties



Overall Summary

Lonza
Small Molecules

Solubility drives oral bioperformance through:

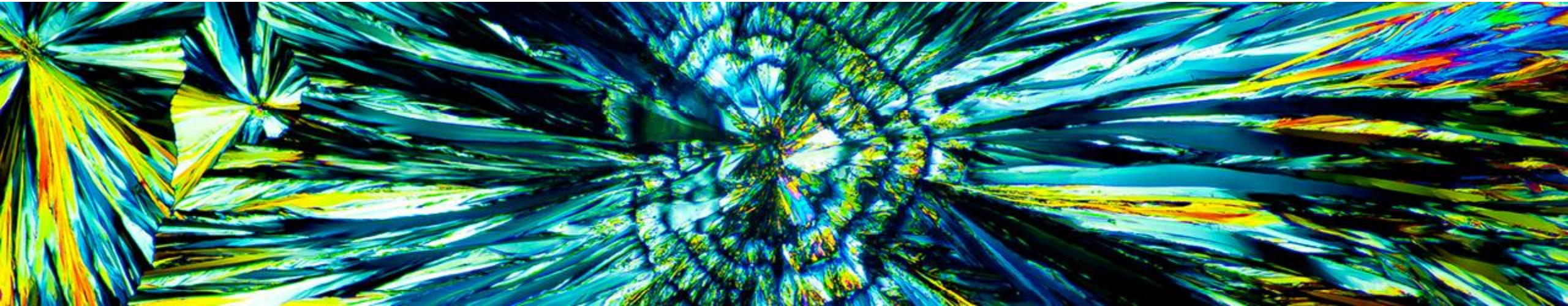
- Dissolution
- Precipitation
- Permeation

Solubility is influenced by interplay between:

- Drug
- Formulation
- GI fluids

Solubility & bioperformance can be understood/predicted using

- Targeted in vitro tools
- PBPK/PBBM



Lonza
Small Molecules

Mechanistic Study of Belinostat Oral Absorption From Spray-Dried Dispersions

Practical Approach to Modeling the Impact of Amorphous Drug Nanoparticles on the Oral Absorption of Poorly Soluble Drugs

Impact of Drug-Rich Colloids of Itraconazole and HPMCAS on Membrane Flux in Vitro and Oral Bioavailability in Rats

In Vitro-In Silico Tools for Streamlined Development of Acalabrutinib Amorphous Solid Dispersion Tablets

Selection of In Vivo Predictive Dissolution Media Using Drug Substance and Physiological Properties

Thanks!