Enabling a Healthier World

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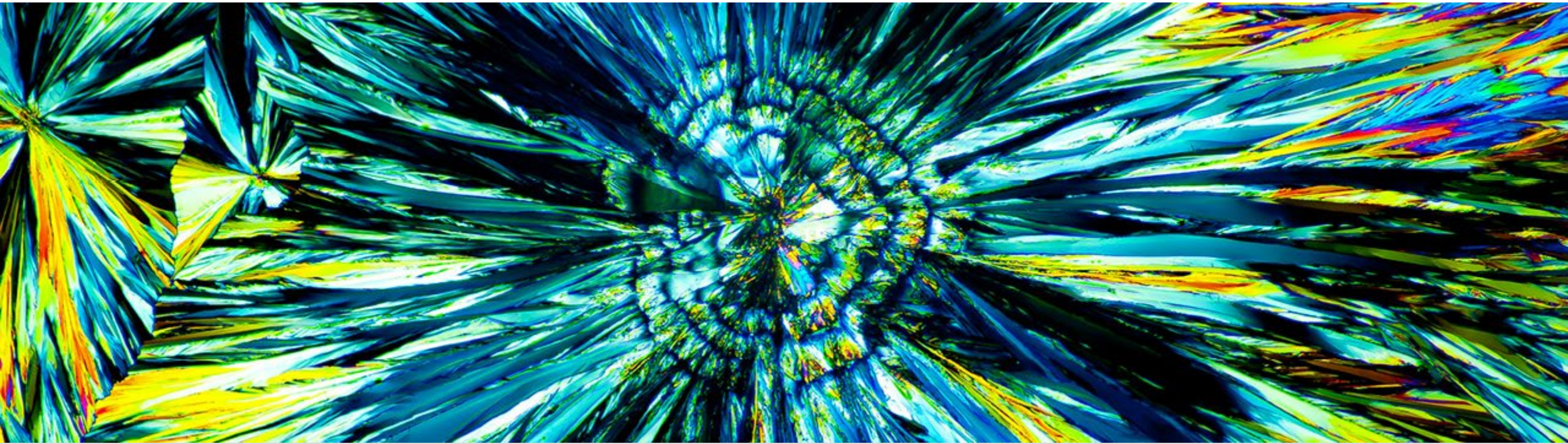
Using In Silico PK Simulations for Early Formulation Development of Amorphous Solid Dispersions

Deanna Mudie

February 15, 2023

Business Use Only



Outline

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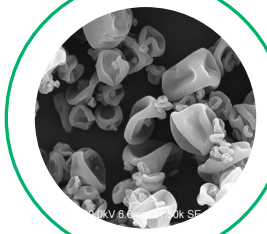
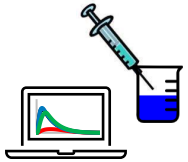


Key design considerations for Amorphous Solid Dispersions

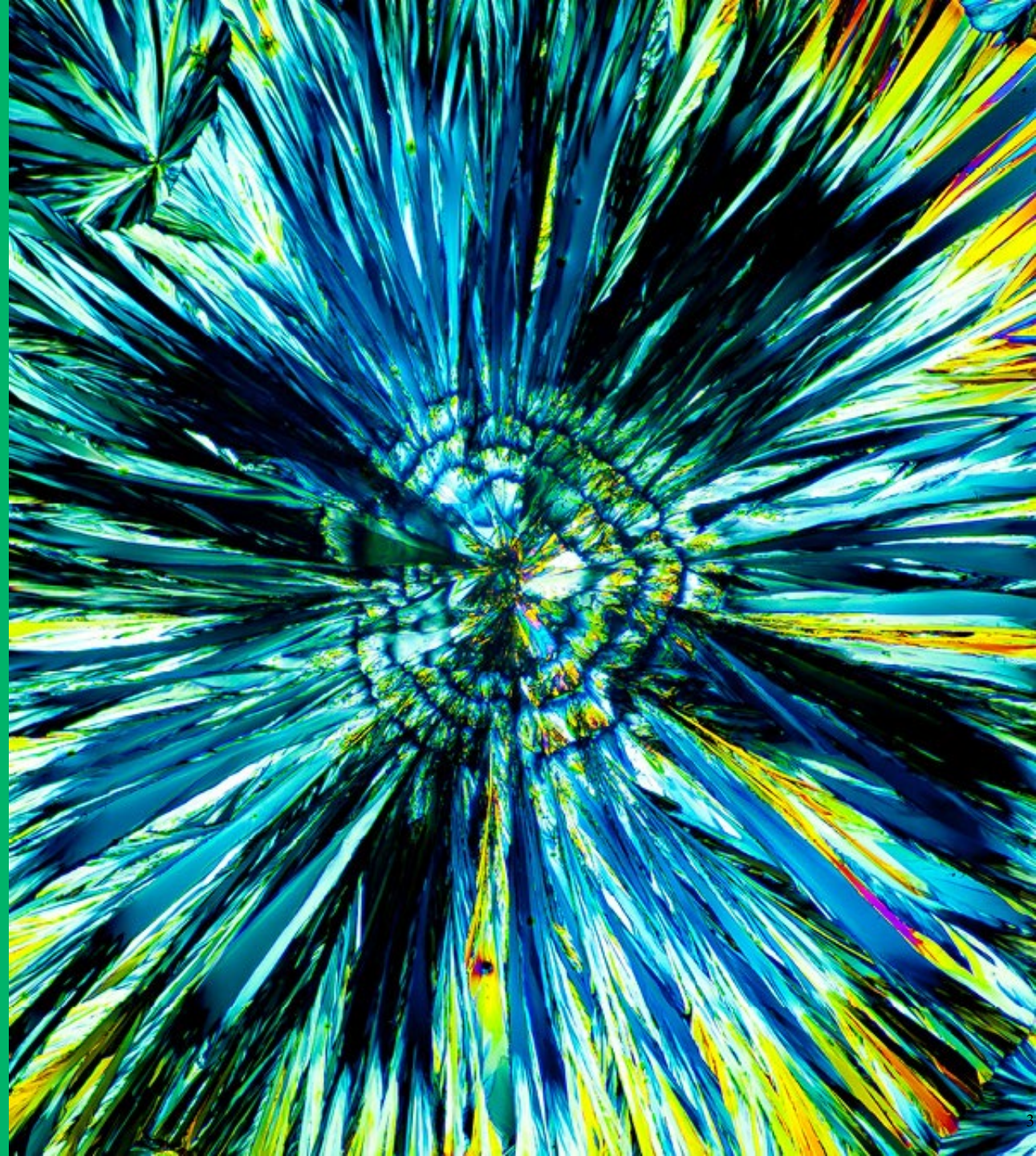


ASD bioperformance assessment

Case study: acalabrutinib ASD tablets overcome pH effect

Summary: In silico PK simulations can de-risk ASD formulation development

Key Design Considerations for Amorphous Solid Dispersions



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Amorphous Solid Dispersions (ASDs) Can Enhance Bioavailability of Poorly Soluble Drugs

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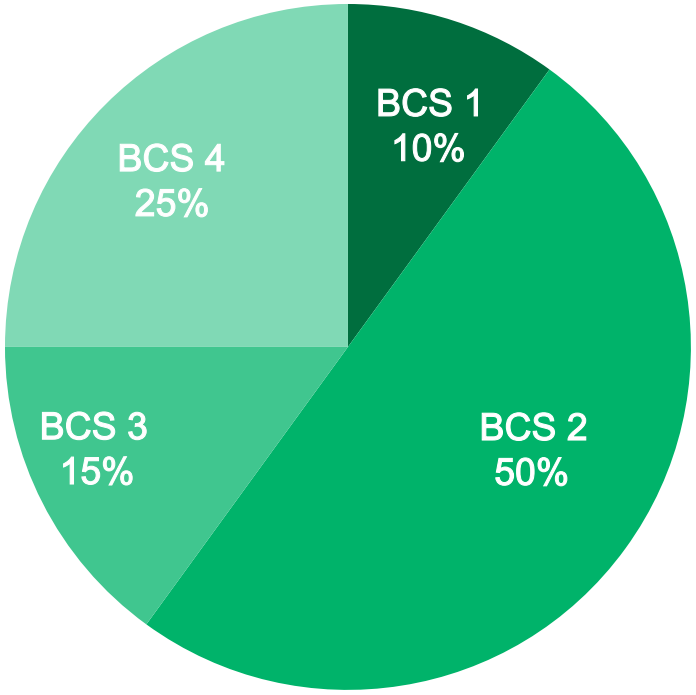
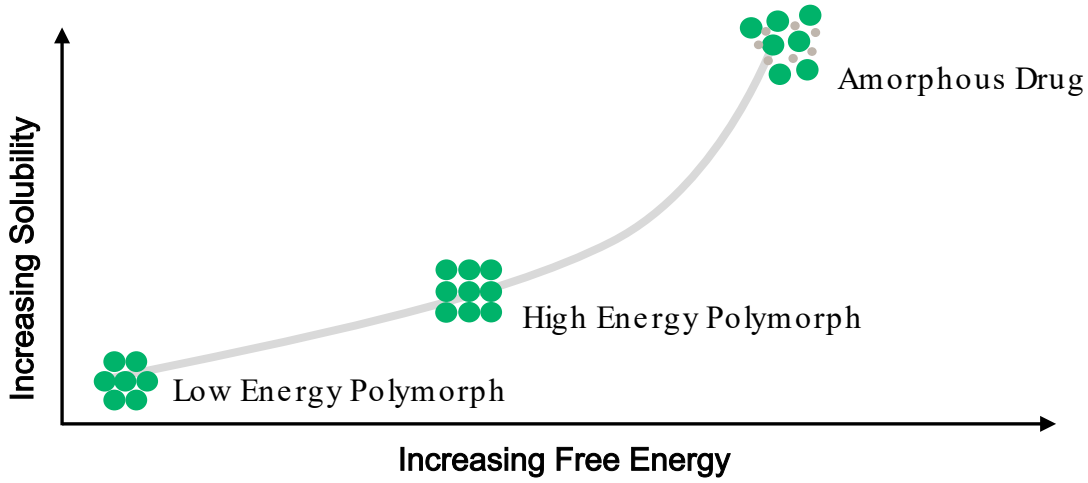


Drug-Like Property Concepts in Pharmaceutical Design, Di, Li et al. In Current Pharmaceutical Design, Volume 15, Number 19, 2009, pp. 2184-2194(11)



- **Amorphous form provides solubility enhancement over crystalline form**
  Can boost dissolution rate and maintain supersaturation
- **Amorphous form is thermodynamically unstable**
  Formulate as ASD to stabilize high energy state

ASD Dosage Forms Can be Designed to Maximize Unit Dosage Strength and Achieve Key Attributes

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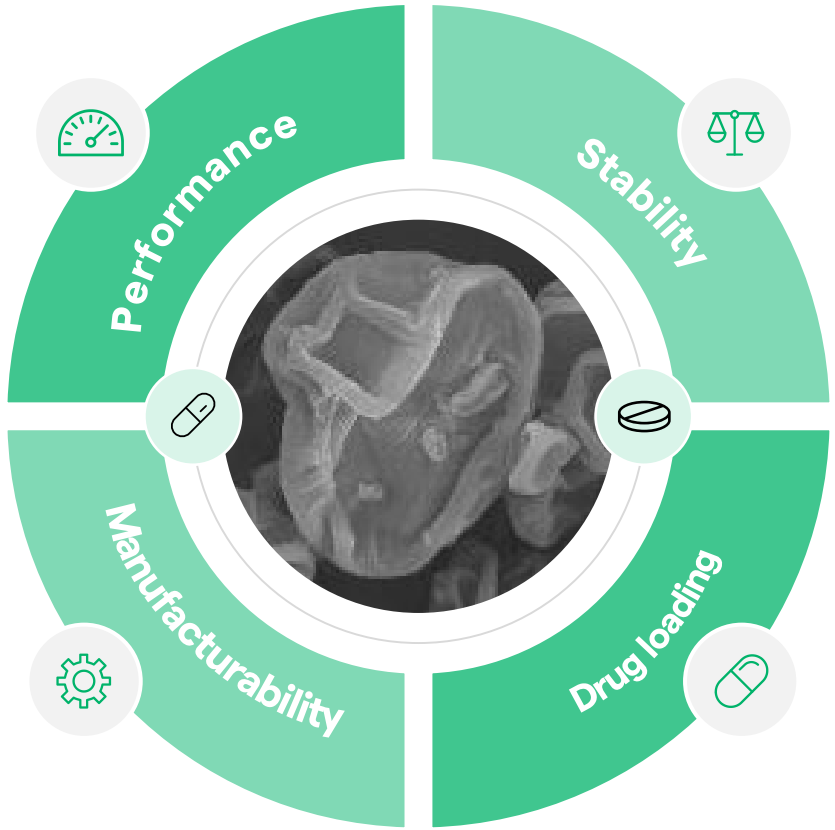
ASDs dosage forms

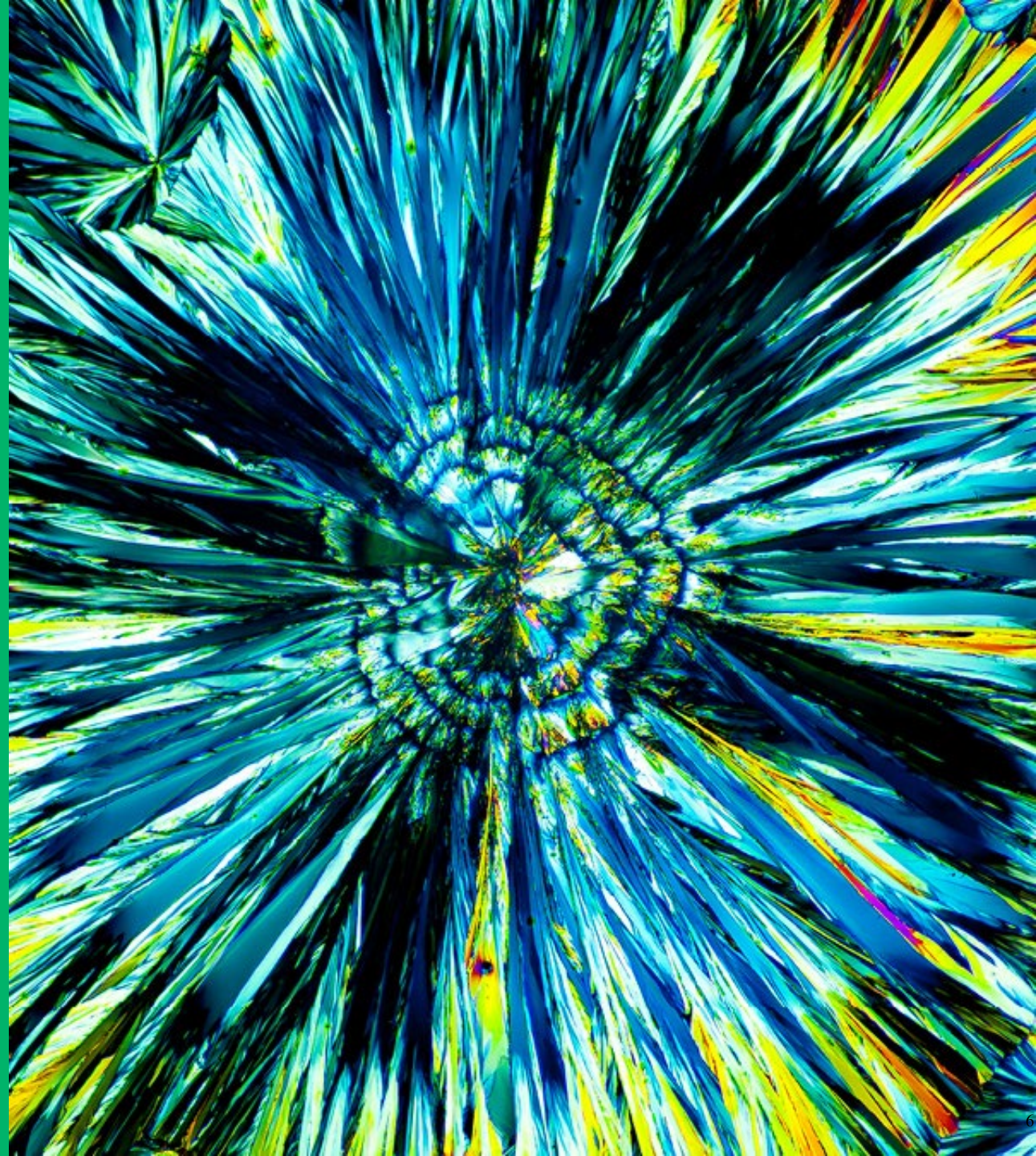
- Tablets
- Capsules
- Suspensions
- Sachets
- Powder in bottle



Key formulation factors

- Drug &polymer properties
- ASD particle properties
- Excipient types &composition
- Processing parameters
- Drug loading in ASD
- ASD loading in dosage form

Amorphous Solid Dispersion Bioperformance Assessment



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To Perform Well in Vivo ASDs Must Dissolve Adequately and Maintain Supersaturation

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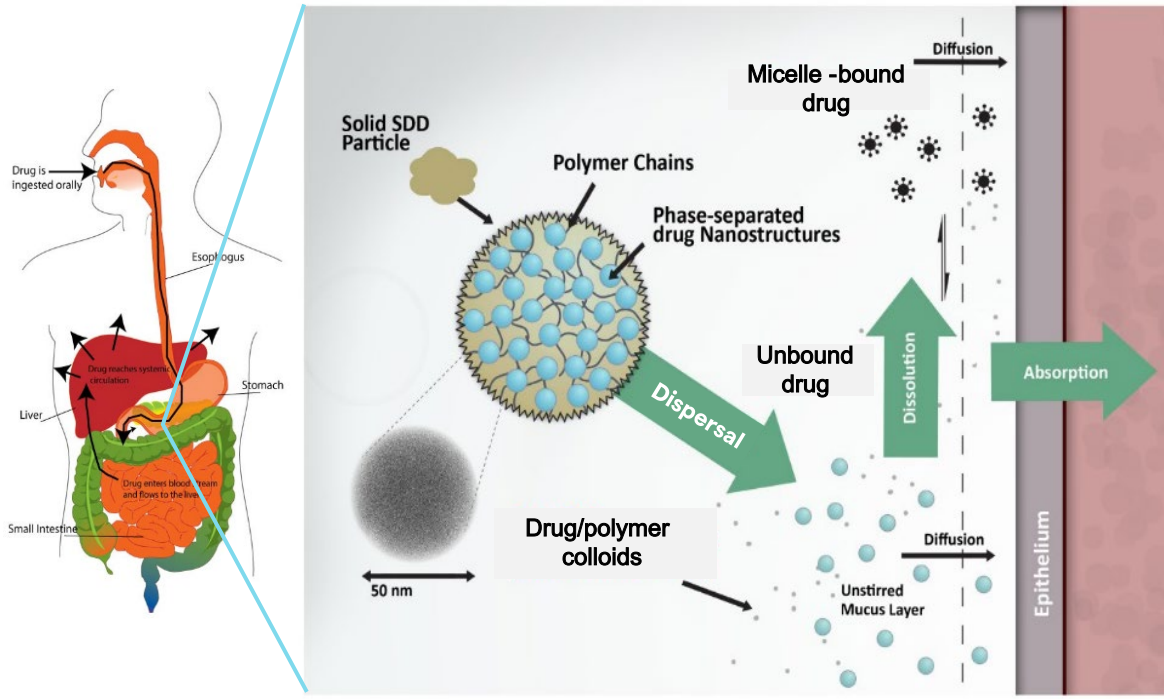

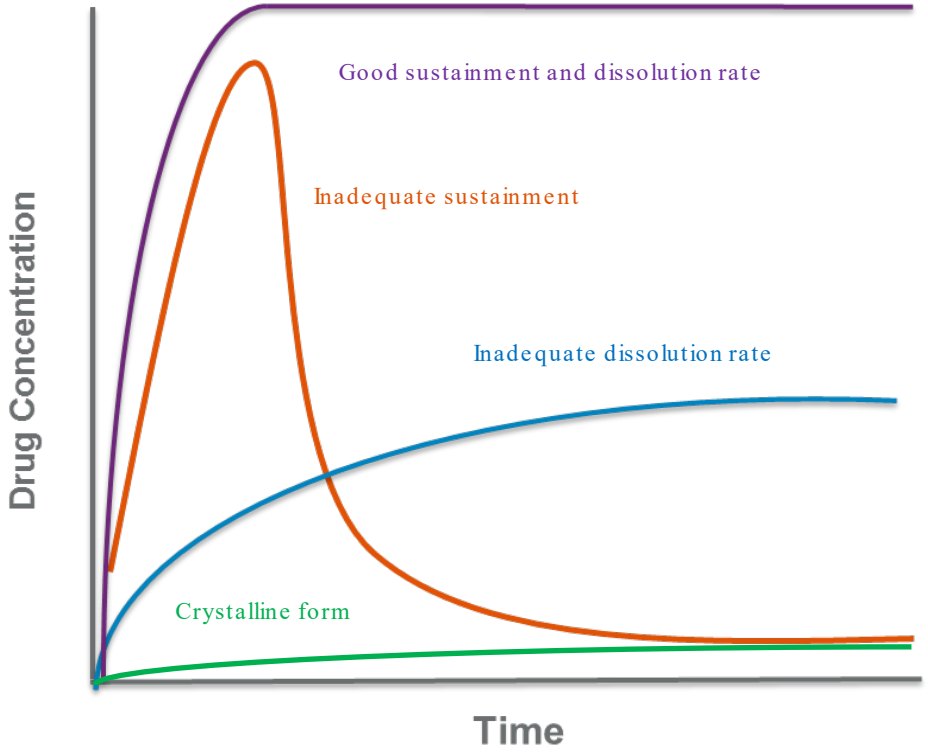

Brewster, ME et al. Pharmazie. 2008 Mar;63(3):217-20.

In Vivo Performance Depends Upon Physiological, Drug Substance, and Formulation Properties

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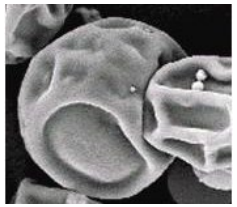
Gastrointestinal fluid

- pH
- Buffer capacity &species
- Bile salts and lipids
- Fluid volumes &transit
- Shear rates, mixing

Drug substance

- Intrinsic solubility
  - Crystalline, amorphous
- Acid/base character &pK_a
- log P/ log D



Particle & dosage form

- Size distribution
- Porosity
- Tablet, capsule, suspension

Polymer (ASDs)

- Solubility vs. pH
  - Ionizable, non-ionizable
- Polymer to drug ratio

Drug formulation – GI interplay impacts:

- Rate, extent and location of drug release along GIT
- Degree of supersaturation &tendency to crystallize →key consideration for ASDs

Traditional Methods may be Limited For Predicting Bioperformance of Some ASD Drug Products

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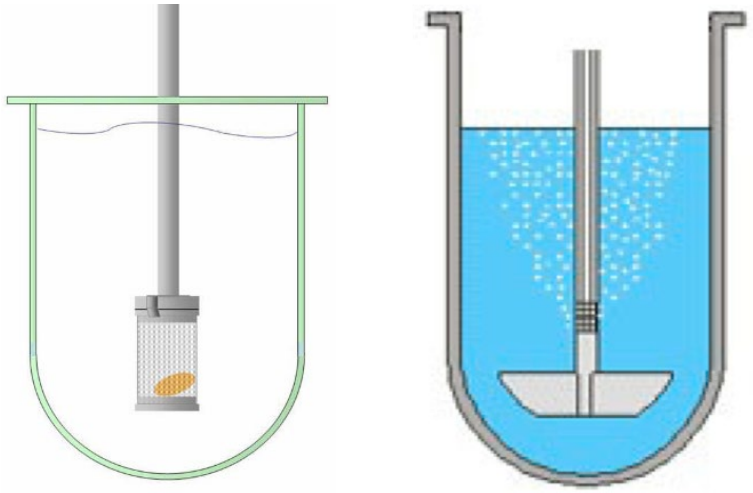

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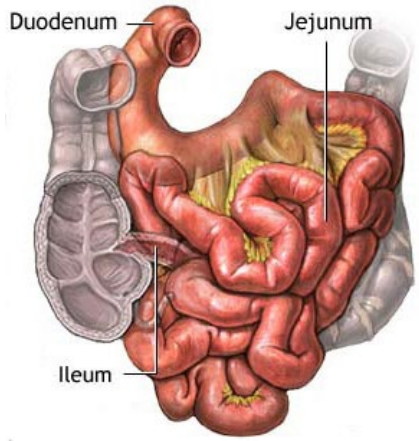

source: daviddarling.info

- How can we use traditional methods and new methods to understand bioperformance of oral drug products?
- Use in vitro – in silico toolkit and mechanistic approach to methodology selection and design

In Vitro Performance Toolkit for Assessing ASD Bioperformance

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Solvent -shift polymer screen

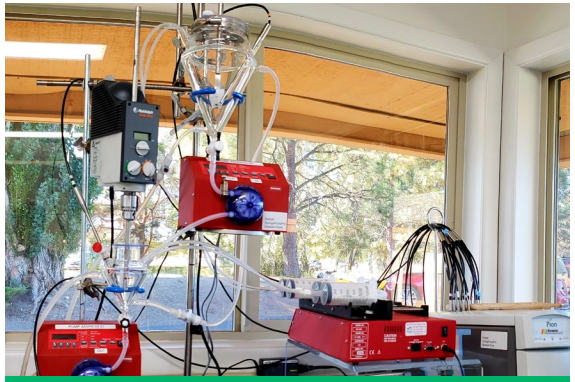
- Amorphous “solubility”
- Precipitation risk
- Polymer selection
- Drug/polymer interaction

ASD dissolution

- Precipitation rate
- Maximum apparent concentration

Tablet dissolution - USP

- Precipitation rate of tablet – static bulk transfer



Controlled transfer dissolution

- Precipitation rate vs. emptying rate of tablet – dynamic fluid movement
- “Book-end” for formulation performance

in vitro dissolution test and parameters selected based upon *in vivo* problem statement

Assembling All the Pieces Using in Silico Tools

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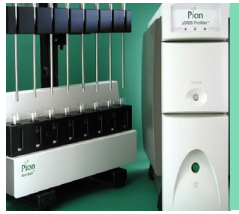
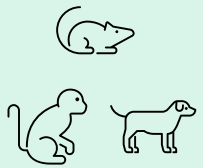
Inputs

Calculated & measured drug properties



In vitro data



In vivo PK

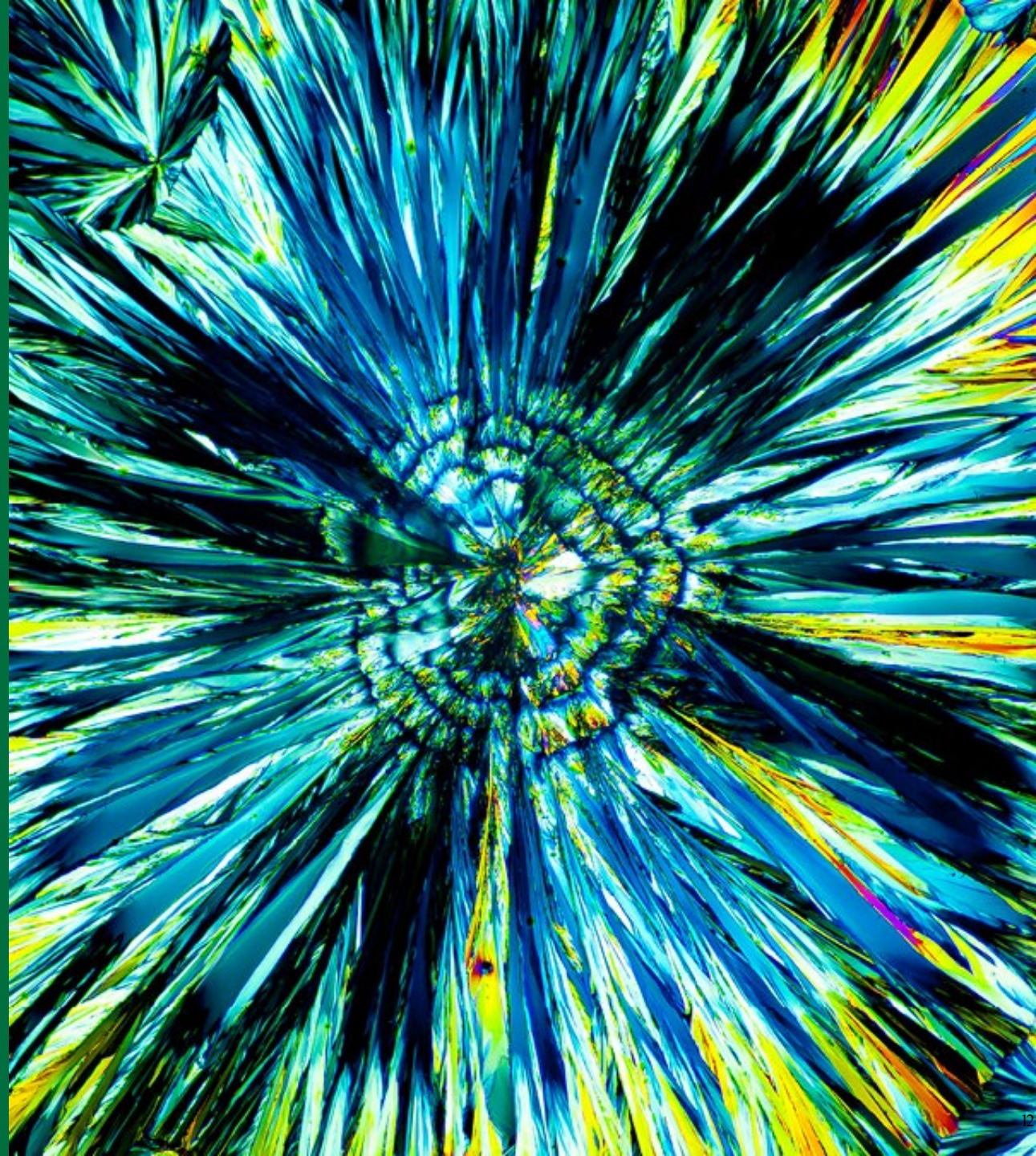
In silico absorption predictions

Hypothesis/"What if" Questions

Outputs

- Parameter sensitivity assessment
- Identified physiological barriers to absorption
- Technology and formulation selection
- Guidance for additional *in vitro* testing

Case study: Acalabrutinib ASD Tablets Overcome pH Effect



Calquence® (Crystalline Acalabrutinib) Shows Reduced Performance with ARAs

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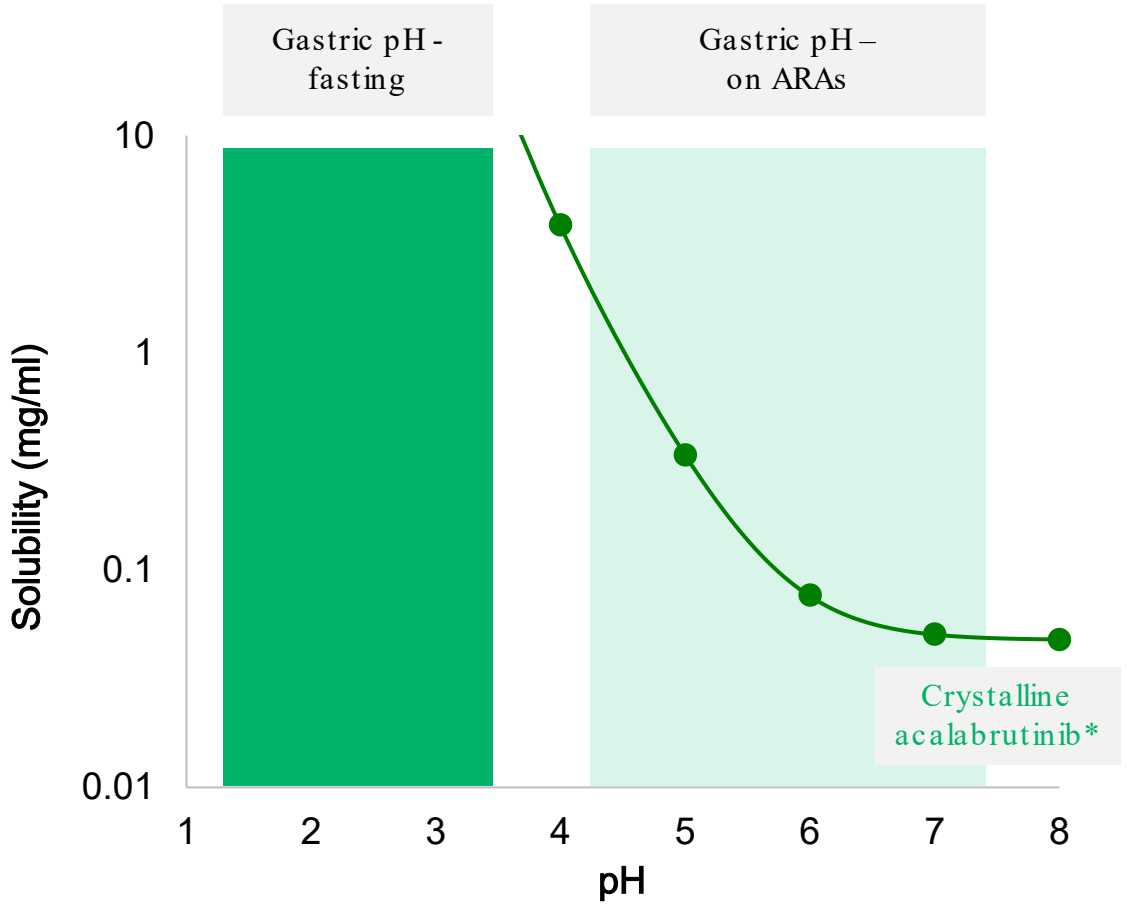
- Bruton tyrosine kinase inhibitor indicated for oncology
- Plasma AUC reduced by 43% when taken with PPI*
- Patients must avoid taking with PPIs or other ARAs

Images from www.Calquence.com (accessed June 8, 2021)

*Calquence FDA label



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

Amorphous Solid Dispersion (ASD) Tablets to Overcome pH Effect

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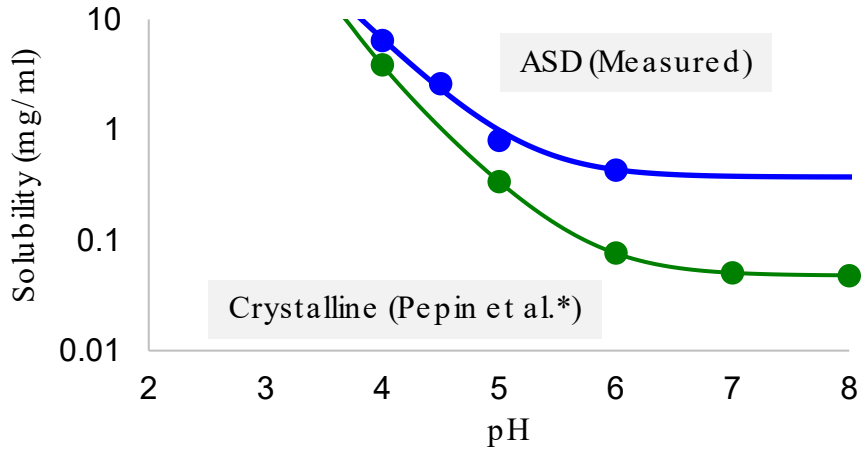
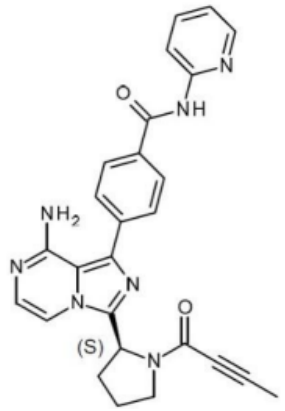
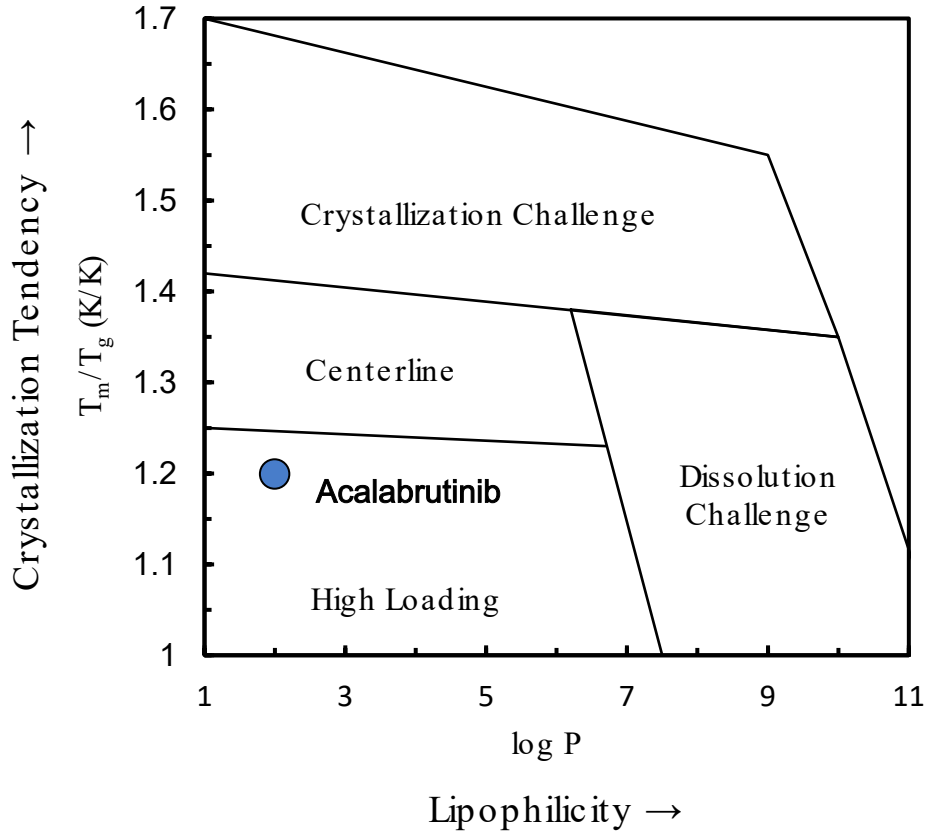
- BCS 2
- S+ P_{eff}: 5.4 X 10^{-4} cm/s*
- pK_a: 3.5, 5.8 (basic)*
- Melting point: 214° C†
- Intrinsic sol.: 48 µg/ml*
- Glass transition: 133° C†







*Pepin et al. *Eur J Pharm Biopharm* 2019 Sep;142, † Mudie et al. *Pharmaceutics* 2021, *13*(4), 557

Friesen et al. *Mol Pharm.*, 2008, 2008 Nov-Dec;5(6)

In Vitro – in Silico ASD Development Strategy

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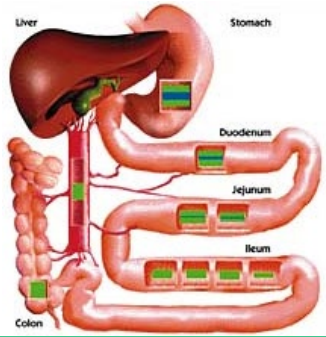
Polymer screen

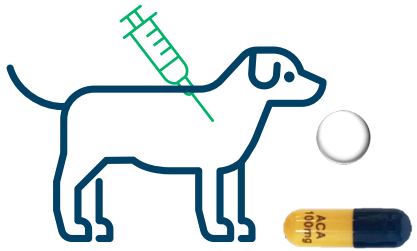
ASD manufacture

ASD dissolution

Tablet dissolution



In silico prediction



In vivo study

Streamlined approach based upon drug, polymer, & physiological properties

Mudie et al. *Pharmaceutics* 2021, *13*, 1257

ASD Tablet Design and Performance Goals

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ASD tablet design

- 50/50 acalabrutinib/HPMCAS-H ASD in IR tablet
- Good stability
- 60% smaller than Calquence capsules

In vivo study goals

- Mitigate pH effect using ASD tablet
- Match plasma exposure of fasted Calquence using ASD tablet
- Show pH effect with Calquence

ASD Tablets Achieve Performance Goals In Vitro

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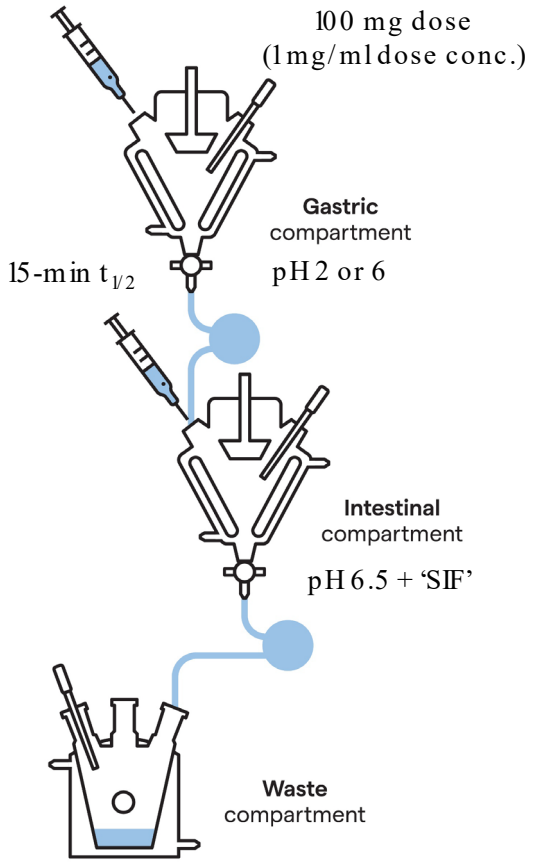
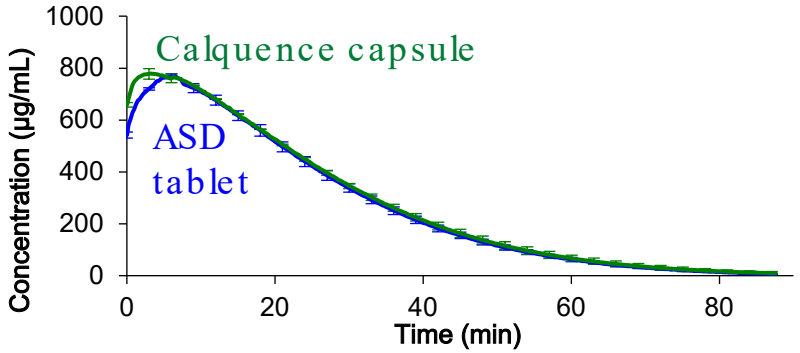
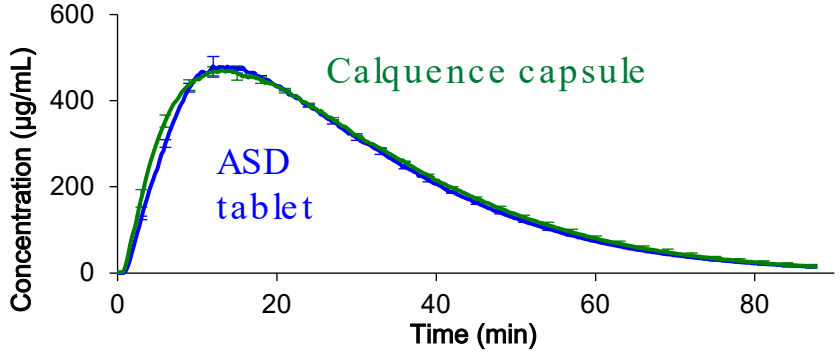


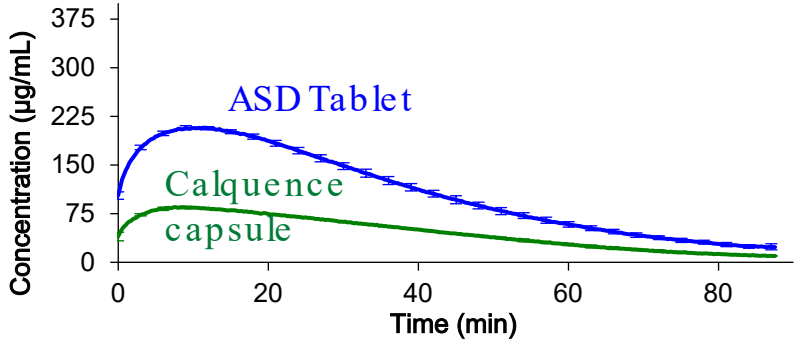
Gastric Compartment, pH 2



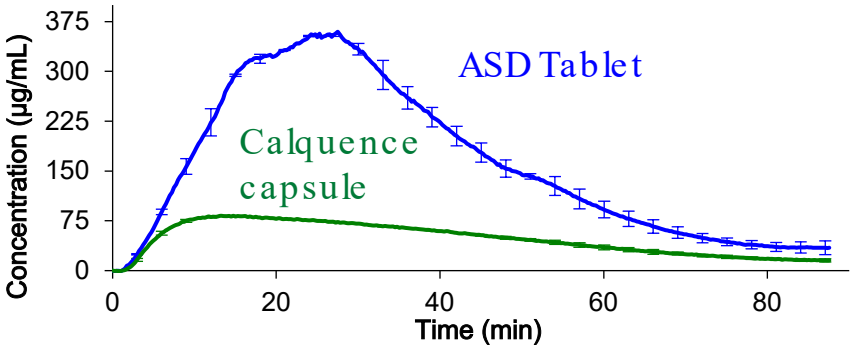
Intestinal Compartment



Gastric Compartment, pH 6



Intestinal Compartment



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

In Silico Predictions – Gain Confidence in Formulation Identified From in Vitro Testing

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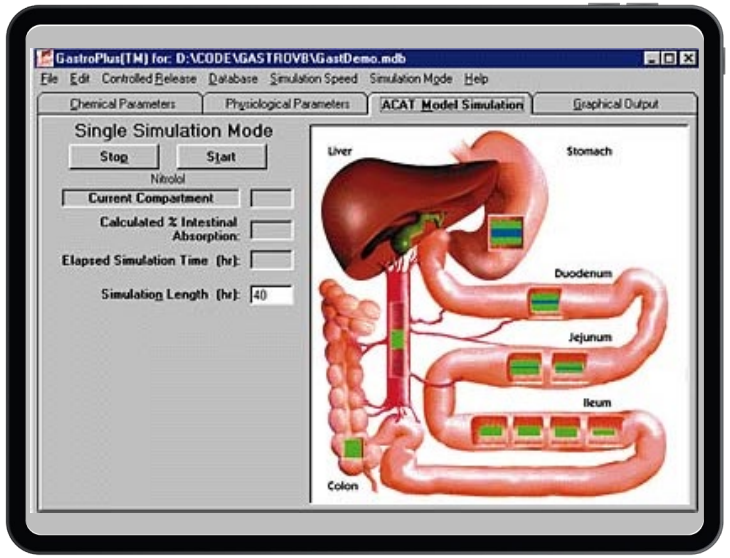
GastroPlus® v9.8 (Simulations Plus, Inc.)



- Bottom – up predictions
- No optimization

- Fasted beagle dog physiology
- **Gastric pH adjusted** to reflect pentagastrin (bulk pH ~2) or famotidine pretreatments (bulk pH ~6) and adjusted for surface pH effects
- Single compartment PK parameters derived from published oral solution data in dogs
- **Physicochemical properties measured or calculated** from Pepin et al.*, FDA documentation, ADMET Predictor® v9.5
- **Solubility vs. pH measured** in house for ASD or by Pepin et al. (Calquence)*
- **Dissolution rates derived from USP 2 transfer test data** ('low dose' test)
- Negligible precipitation assumed

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

In Silico Input - Solubility vs. pH and Surface vs. bulk pH

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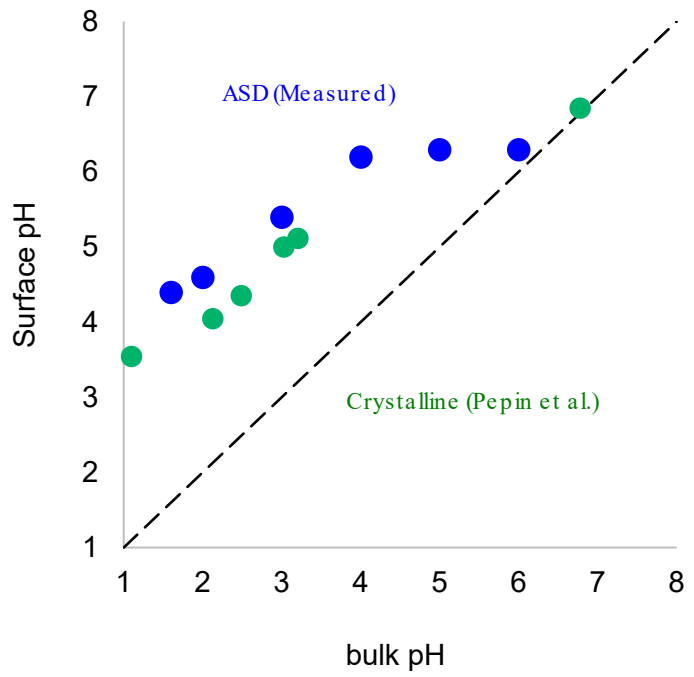
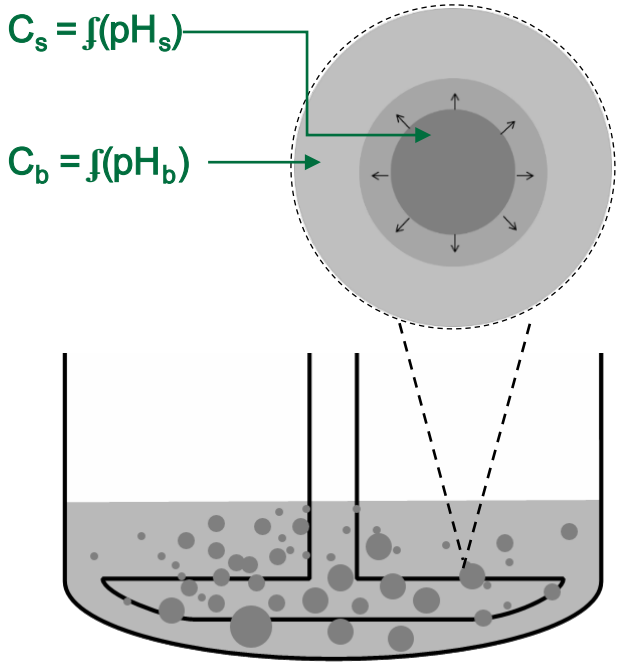
Surface pH vs. bulk pH



	Simulated bulk pH	Adjusted (surface) pH ASD Tablet	Adjusted (surface) pH Calquence capsule
Stomach (fasted)	2.0	4.6	4.0
Stomach (ARA)	6.0	6.3	6.0

$$\frac{dM}{dt} = \frac{D_{eff}}{R} \cdot A_s\,(t) \cdot \left(C_s - C_{b(t)}\right)$$



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

In Silico Input - in vitro Dissolution Rates

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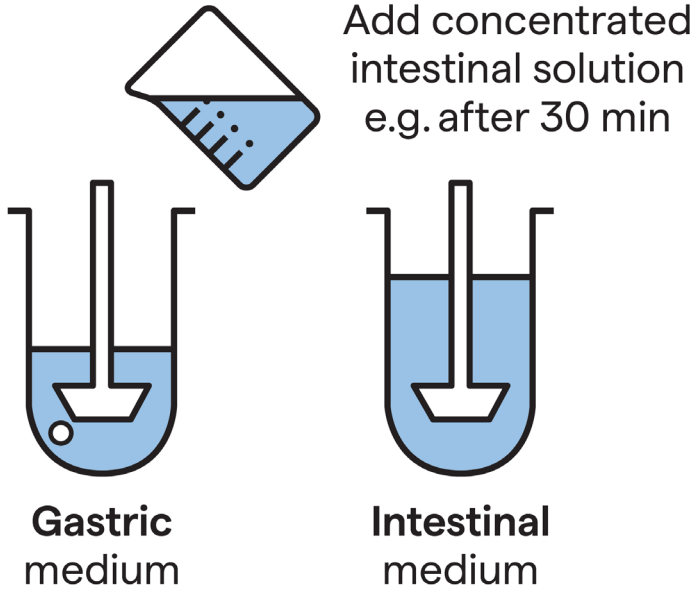
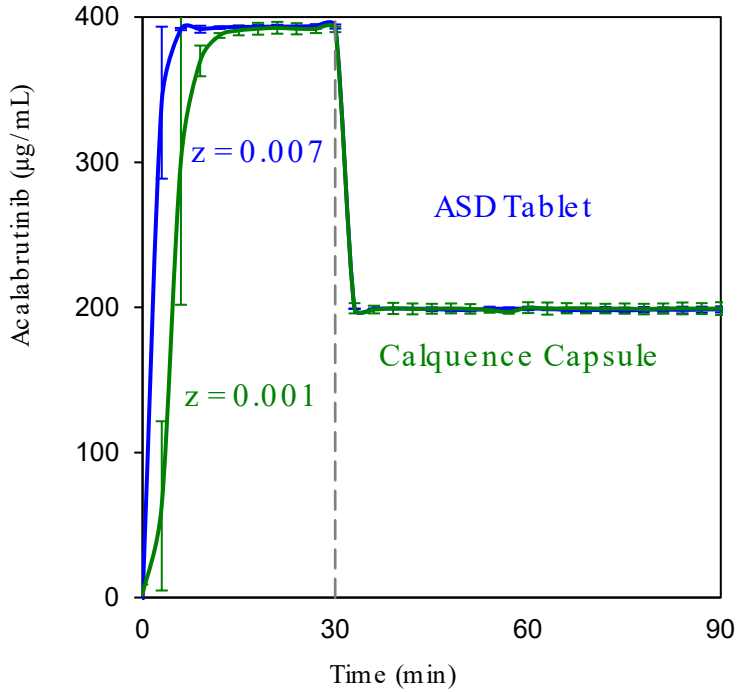
USP 2transfer test



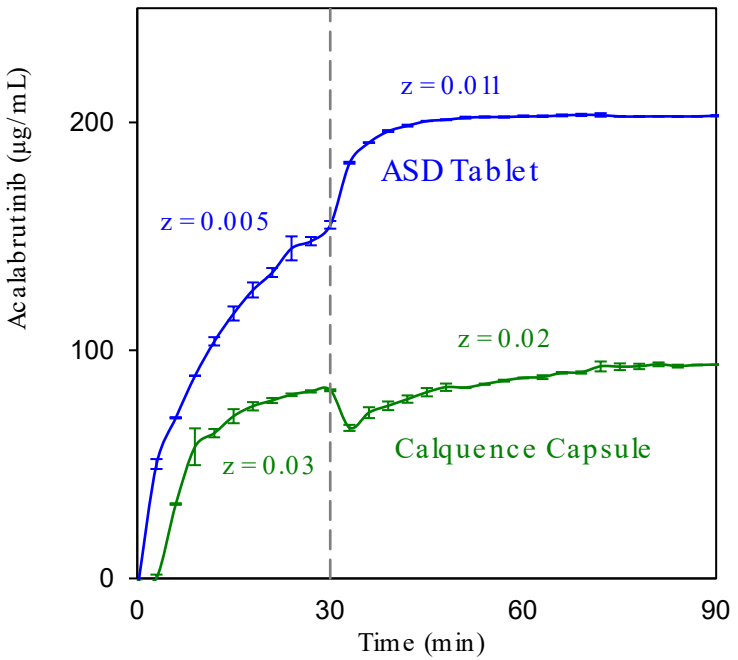
$$\frac{dM}{dt} = z \cdot M_{u,o}\left(\frac{M_{u,t}}{M_{u,o}}\right)^{2/3}(C_s - C_b)$$

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

pH 2 gastric test



pH 6 gastric test



Mudie et al. *Pharmaceutics* 2021, *13*, 1257, Takano et al. *Pharm Res*, 2006

In Silico Predictions Suggest ASD Tablets Will Overcome pH Effect in Dogs

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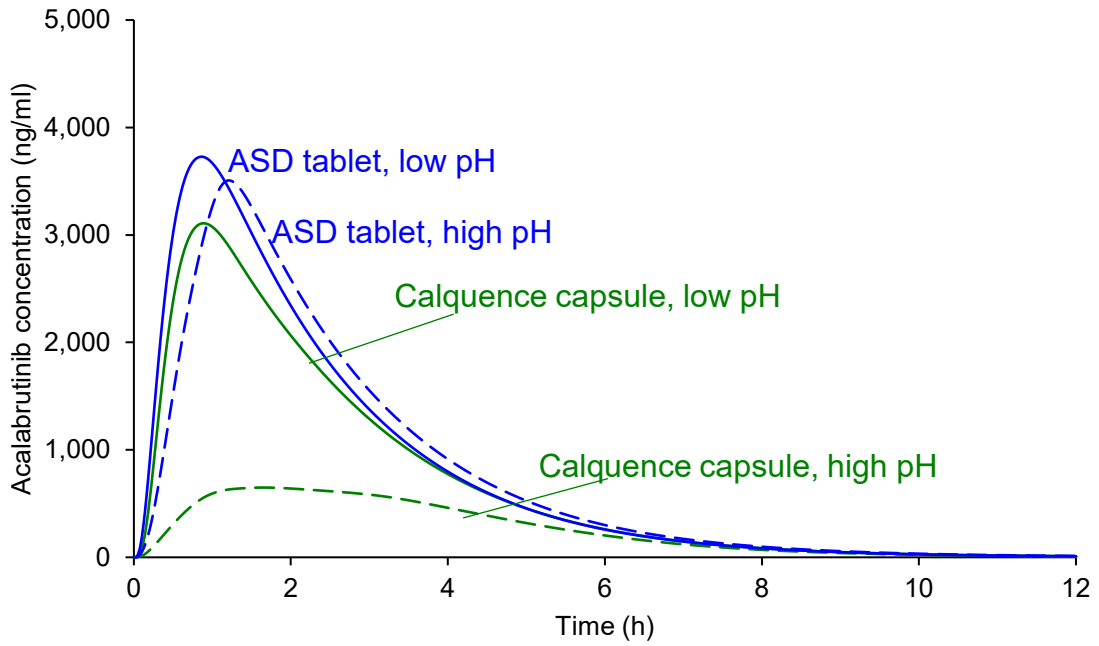
100 mg dose



- Mitigate pH effect (AUCs within 2%)
- Match exposure of Calquence at low pH (AUCs within ~10%)
- Show Calquence pH effect (~3-fold difference in AUC)

Mudie et al. *Pharmaceutics* 2021, *13*, 1257

In Vivo Outcome Matches Bottom – up in Silico Predictions

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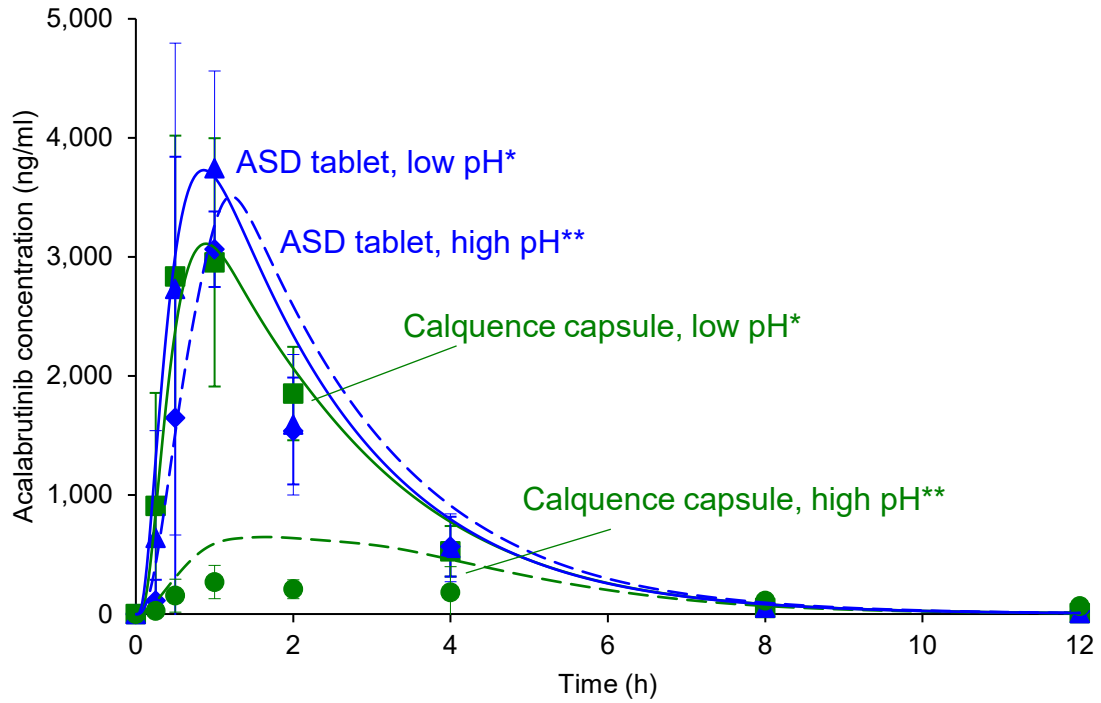
100 mg dose | Overnight fast, n = 6, crossover study, 1 – wk washout



	$AUC_{0\text{-inf}}$ (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

* 6 µg/kg subcutaneous pentagastrin, ** 40 mg oral famotidine

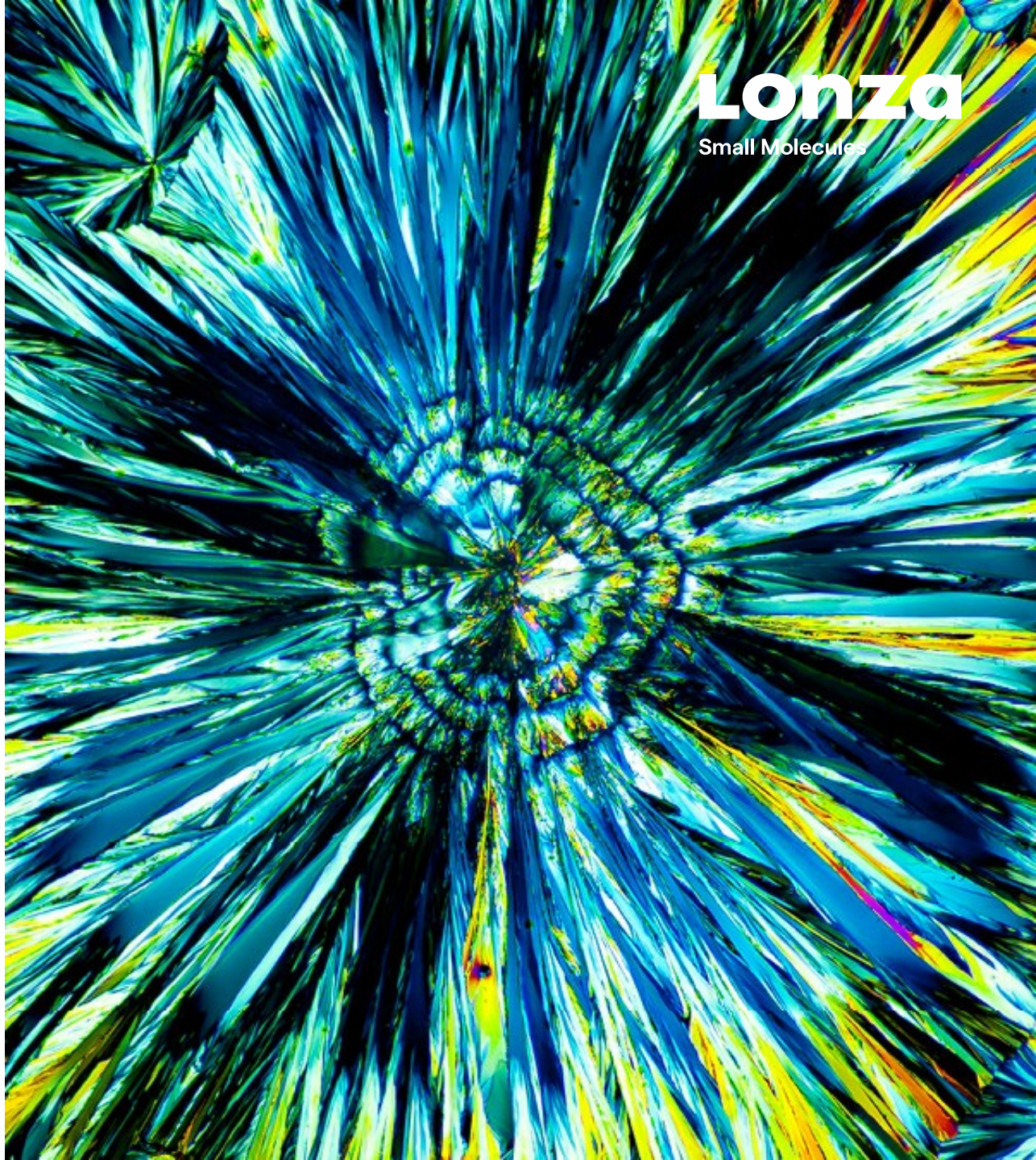
Mudie et al. *Pharmaceutics* 2021, *13*(4), 557 & Mudie et al. *Pharmaceutics* 2021, *13*, 1257

Summary

ASD tablets overcame acalabrutinib pH effect on the first try using in vitro – in silico development approach

In silico PK simulations successfully predicted in vivo study results using 'bottom up' approach

In silico PK simulations can accelerate ASD formulation optimization and reduce costs



References

- Mudie DM, Stewart AM, Rosales JA, Biswas N, Adam MS, Smith A, Craig CD, Morgen MM, Vodak DT. Amorphous Solid Dispersion Tablets Overcome Acalabrutinib pH Effect in Dogs. *Pharmaceutics*. 2021 Apr 15;13(4):557. https://doi.org/10.3390/pharmaceutics13040557

- Mudie, D.M.; Stewart, A.M.; Rosales, J.A.; Adam, M.S.; Morgen, M.M.; Vodak, D.T. In Vitro-In Silico Tools for Streamlined Development of Acalabrutinib Amorphous Solid Dispersion Tablets. *Pharmaceutics* 2021, 13, 1257. https://doi.org/10.3390/pharmaceutics13081257

Acknowledgments

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Questions

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