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Achieving Bioavailability Enhancement for Poorly Soluble Compounds: Streamlining Technology Selection

Aaron Stewart — associate principal scientist, R&D

Small molecule technologies

Flexible model across the product development cycle

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DESIGN
Small / Lab-Scale (non-GMP) feasibility

DEVELOP *> 350Projects*
Clinical scale development, manufacture & packaging

MANUFACTURE *> 270 Products*
Commercial scale manufacture & packaging

Drug Substances
full range of API inclusive of GMP intermediates, HPAPI, cytotoxic payloads for ADC's

Particle-Engineering
micronization, amorphous solid dispersions, melt-spray-congealing

Drug Products
tablets (IR and MR), encapsulated powder & MP, soft gels, liquid-fill hard caps

SimpliFiH® Solutions – rapid first-in-human services

Designed for poorly soluble molecules and accelerated development

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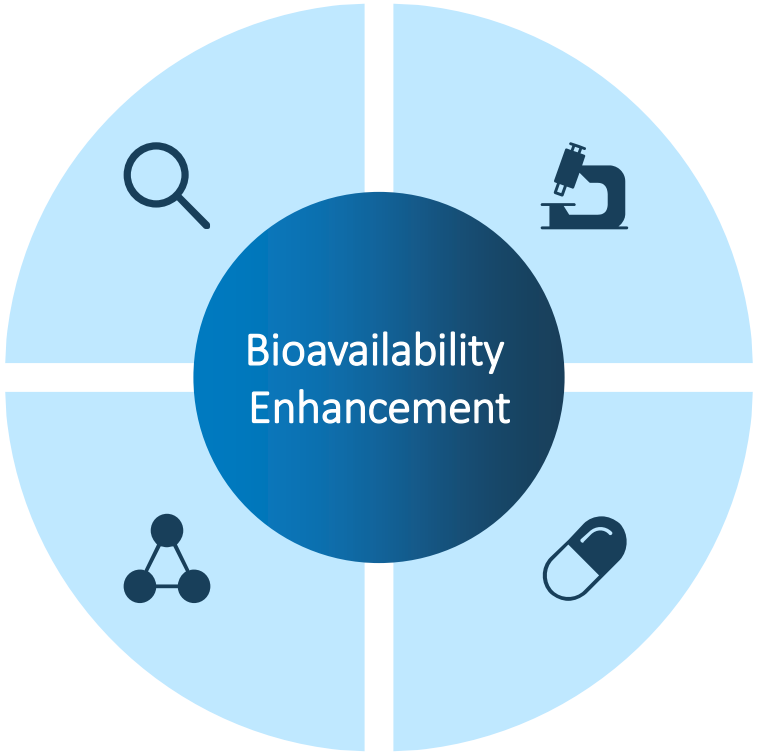
Solid State Characterization

- Salt screening
- Polymorph screen
- Chemical / physicochemical analyses

API Development & Supply

- Dedicated kilo-labs
- API / HPAPI (OEL 4)
- Toxicity study and first-in-human supply



Technology Selection

- Technology Review Board oversight
- Selection based on models, databases and reference maps
- Particle size reduction, spray dried dispersions (SDD), lipid based formulations (LBF)

Drug Product

- Powder (API)-in-capsule or bottle (PIC/PIB)
- Liquid-filled hard capsules (LFHC)
- Tablets

Our global footprint in small molecules…

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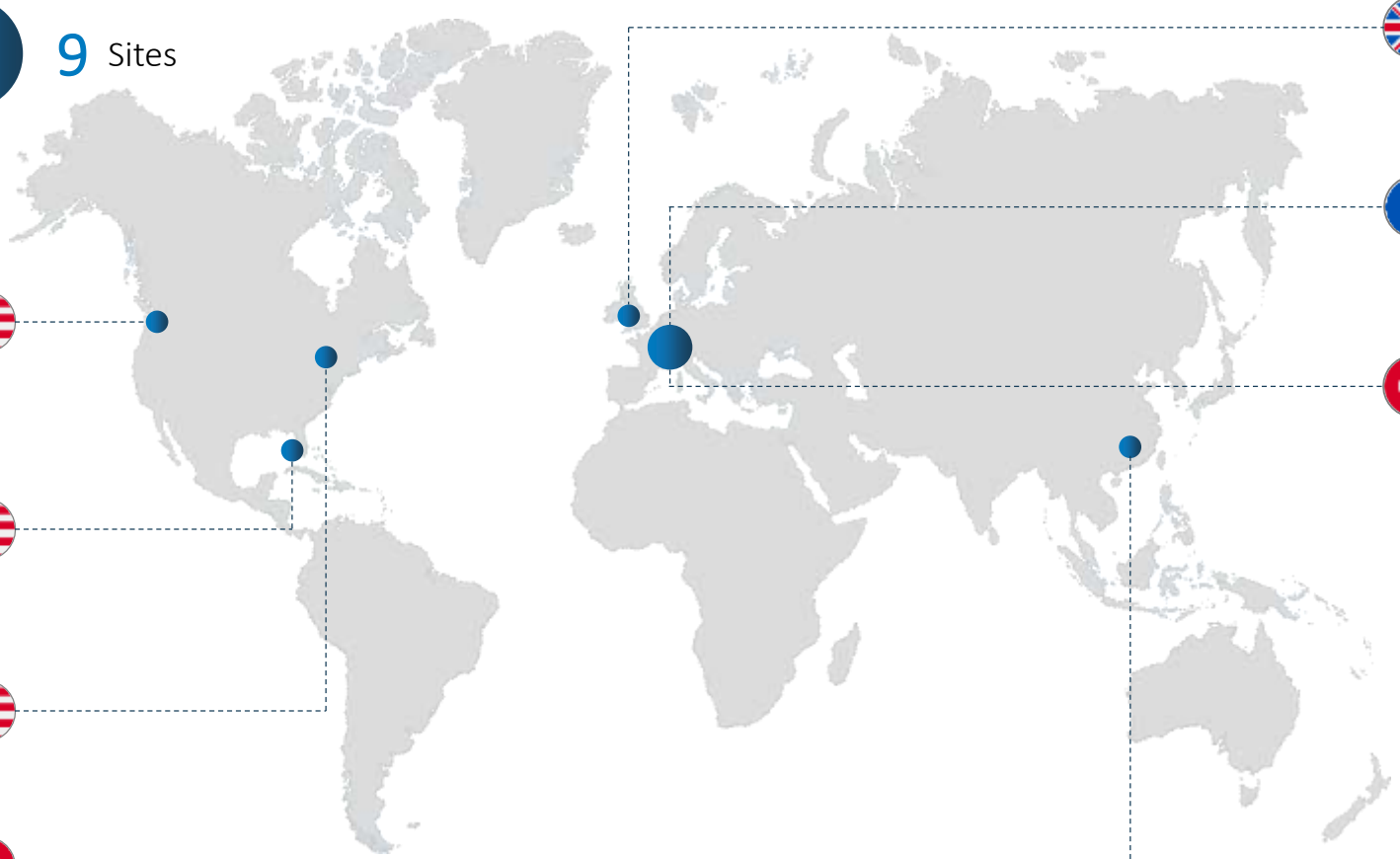
3 Regions

9 Sites



Bend, USA
Particle engineering / solid dispersions Drug product development & **manufacturing**

Tampa, USA
Drug product development and manufacturing
Clinical supply services

Quakertown, USA
Particle engineering / jet milling

Nansha, China
API development and manufacturing

Edinburgh, UK
Drug product development & manufacturing
Lipid-based formulations / liquid filled hard capsules

Ploermel, France
Drug product development & manufacturing
Lipid-based formulations, soft gels, liquid filled hard capsules

Visp, Switzerland
Drug Substance development and manufacturing
HPAPI and ADC capabilities

Monteggio, Switzerland
Particle engineering / jet milling

Basel, Switzerland
Drug product development & manufacturing
Parenteral / IV formulation and sterile fill/finish services

Outline

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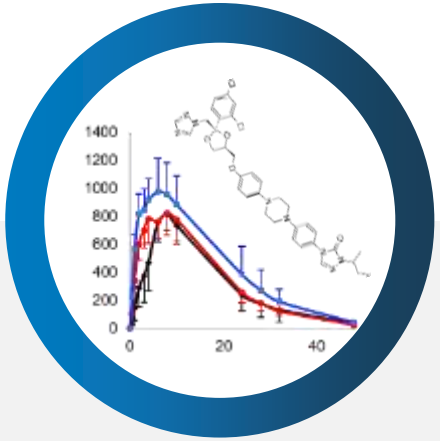
Identifying key barriers to absorption for a given compound leveraging historical guidance maps and in vitro/in silico tools

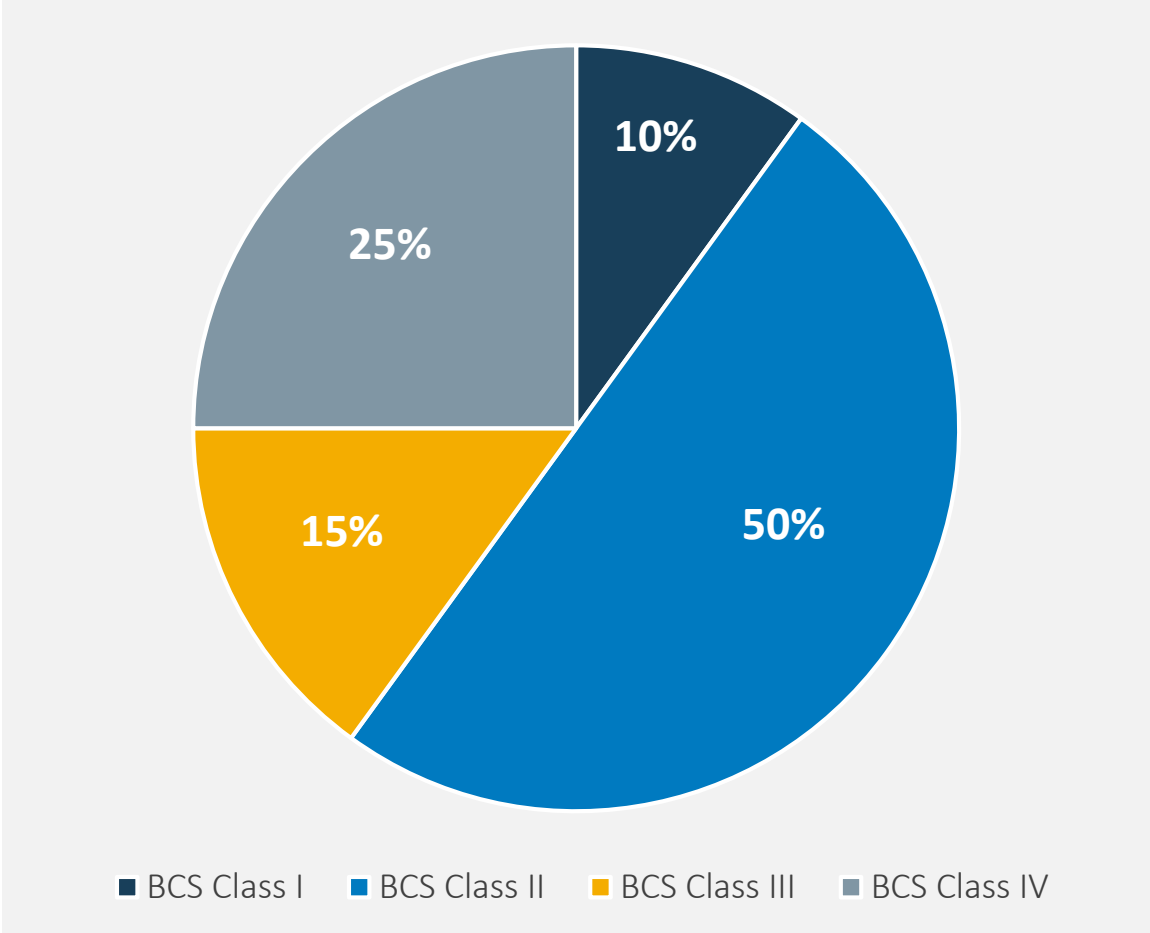
Overview of common bioavailability enhancing technologies



Case Study – Improving oral absorption for a BCS Class II compound: Itraconazole

The ongoing issue

Low solubility continues to plague development pipelines



Reference:

- *Drug-Like Property Concepts in Pharmaceutical Design, Di, Li; Kerns, Edward H.; Carter, Guy T. In Current Pharmaceutical Design, Volume 15, Number 19, 2009, pp. 2184-2194(11)*

Compound qualification and technology mapping

A science-based approach to selecting a technology for your compound

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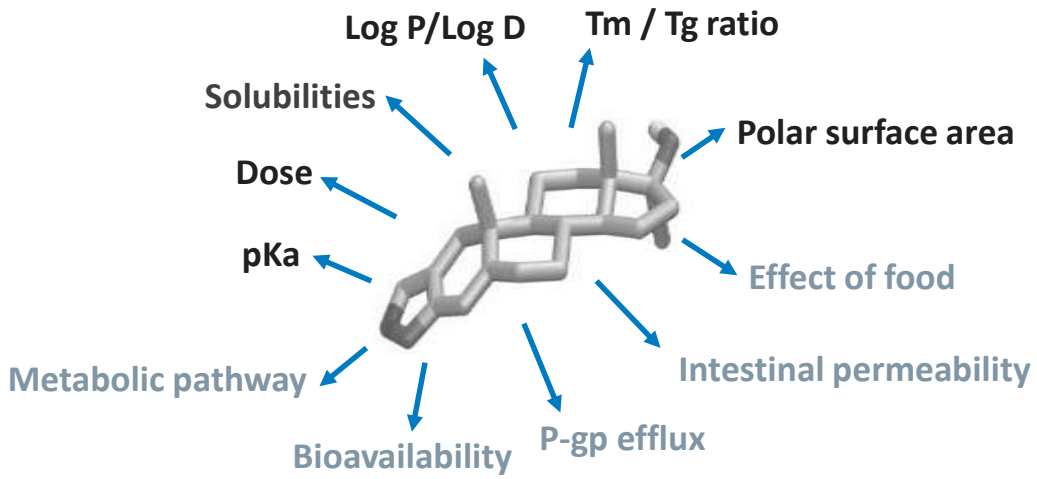

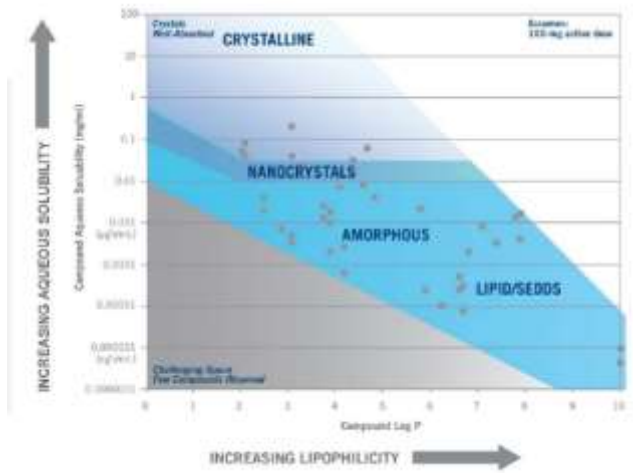

- Broad, in-depth review considers physical and biological barriers to drug absorption
- Drawbacks: Qualitative assessment. Does not factor in experience and technology precedence
- Leverages large compound in vivo datasets and based on data collected during preformulation
- Drawbacks: Data does not include head-to-head comparisons. Would another technology have been better?

A streamlined approach to tech selection leverages both first principles as well as historical experience/data

In vitro and *in silico* tools can be used to predict or assess the rate-determining steps to absorption

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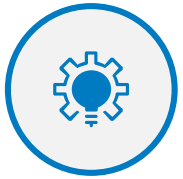

Basic property prediction

- HBD, HBA, PSA
- Acid/base/neutral
- pK_a
- LogP/LogD
- pH-solubility
- Tm
- Provisional BCS

In vitro assessment

- pH-solubility
- LogP/LogD
- Tm & Tg
- Micelle partition coeff.
- Caco2 permeability
- PAMPA permeability

Dimensionless numbers/simple calculations

- Dose Number
- Dissolution Number
- Permeation Number
- FaCS

PBPK Modeling

- Hypothesis testing
- ID key performance Attributes
- Managing expectations/risk in vivo

Dimensionless numbers

FaCS classification

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Key Inputs:

- Crystalline Aqueous Solubility
- Amorphous Aqueous Solubility
- Projected Dose (or range)
- Physiology
- Log P/Micelle Partition
- Effective Permeability

Outputs:

Dose Number

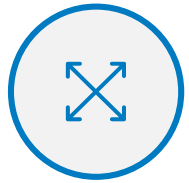
$$Do = \frac{Dose/Vol}{C_s}$$

How many GI fluid volumes are required to dissolve the dose ?

Permeation Number

$$Pn = k_{abs} \cdot t_{abs}$$

How many times can the drug permeate over the course of GI transit ?



Dissolution Number

$$Dn = k_{diss} \cdot t_{abs}$$

How many times can the drug dissolve over the course of GI transit ?

Sugano and Terada, Journal of Pharmaceutical Sciences 104:2777-2788, 2015

Fraction absorbed classification system (FaCS)

Three limiting cases

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Dose Number

$$Do = \frac{Dose/Vol}{C_s}$$

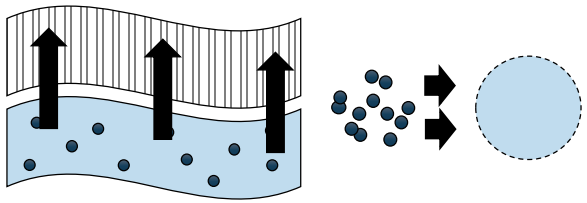
Permeation Number

$$Pn = k_{abs} \cdot t_{abs}$$

Dissolution Number

$$Dn = k_{diss} \cdot t_{abs}$$

Case 1: Dissolution Rate Limited (DRL)



$$Dn < Pn/Do$$

Cases where this occurs:

- High permeability relative to dose and solubility
- Dissolution rate is slow

Sugano and Terada, Journal of Pharmaceutical Sciences 104:2777-2788, 2015

Fraction absorbed classification system (FaCS)

Three limiting cases

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Dose Number

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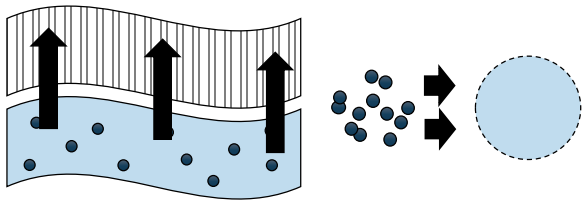
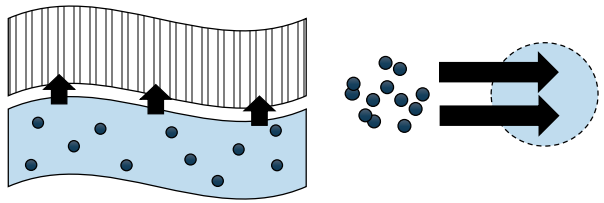


$$Dn < Pn/Do$$

Cases where this occurs:

- High permeability relative to dose and solubility
- **Dissolution rate is slow**

Case 2: Permeability limited (PL)



$$Pn < Dn \ \& \ Do < 1$$

Cases where this occurs:

- Dissolution rate is fast relative to permeability
- **Dose is low relative to solubility**

Sugano and Terada, Journal of Pharmaceutical Sciences 104:2777-2788, 2015

Fraction absorbed classification system (FaCS)

Three limiting cases

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Dose Number

$$Do = \frac{Dose/Vol}{C_s}$$

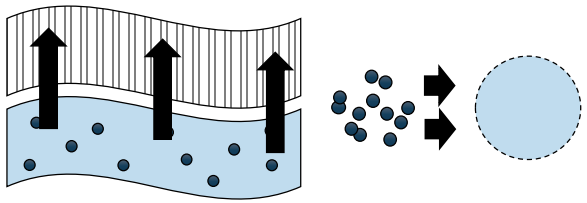
Permeation Number

$$Pn = k_{abs} \cdot t_{abs}$$

Dissolution Number

$$Dn = k_{diss} \cdot t_{abs}$$

Case 1: Dissolution Rate Limited (DRL)



$$Dn < Pn/Do$$

Cases where this occurs:

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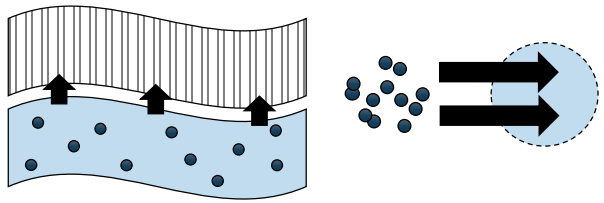
Case 2: Permeability limited (PL)

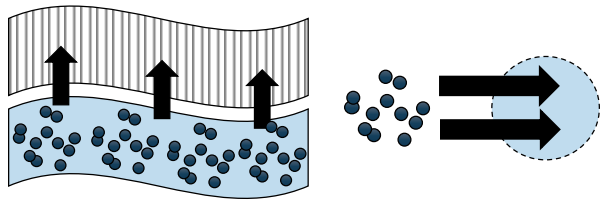


$$Pn < Dn \ \& Do < 1$$

Cases where this occurs:

- Dissolution rate is fast relative to permeability
- **Dose is low relative to solubility**

Case 3: Solubility-permeability limited (SL)



$$Pn/Do < Dn \ \& \ Do > 1$$

Cases where this occurs:

- Low permeability relative to dose and solubility
- **Dose is high relative to solubility**

Sugano and Terada, Journal of Pharmaceutical Sciences 104:2777-2788, 2015

Multiple problem statement-specific bioperformance *in vitro* tools using fiber optics

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Amorphous solubility

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

Dissolution

- Dissolution rate
- Precipitation rate
- Maximum apparent concentration
- Speciation

Flux

- Clean measurement of “effective” concentration
- Able to properly account for micelle, colloid, and particle contribution to boundary layer diffusion and dissolution rate
- Can corroborate rate-limiting step to absorption in vivo

Controlled transfer dissolution

- Dissolution rate
- Precipitation rate vs. emptying rate
- Gastric precipitation
- “Book-end” for formulation performance

Assembling all the pieces using *in silico* absorption modeling

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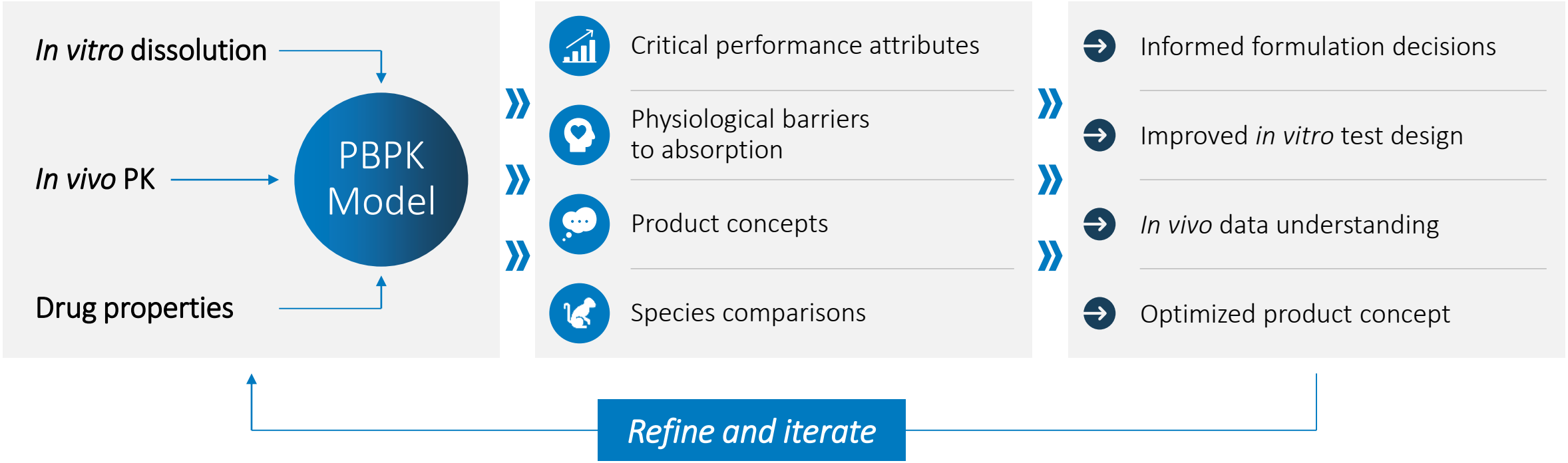
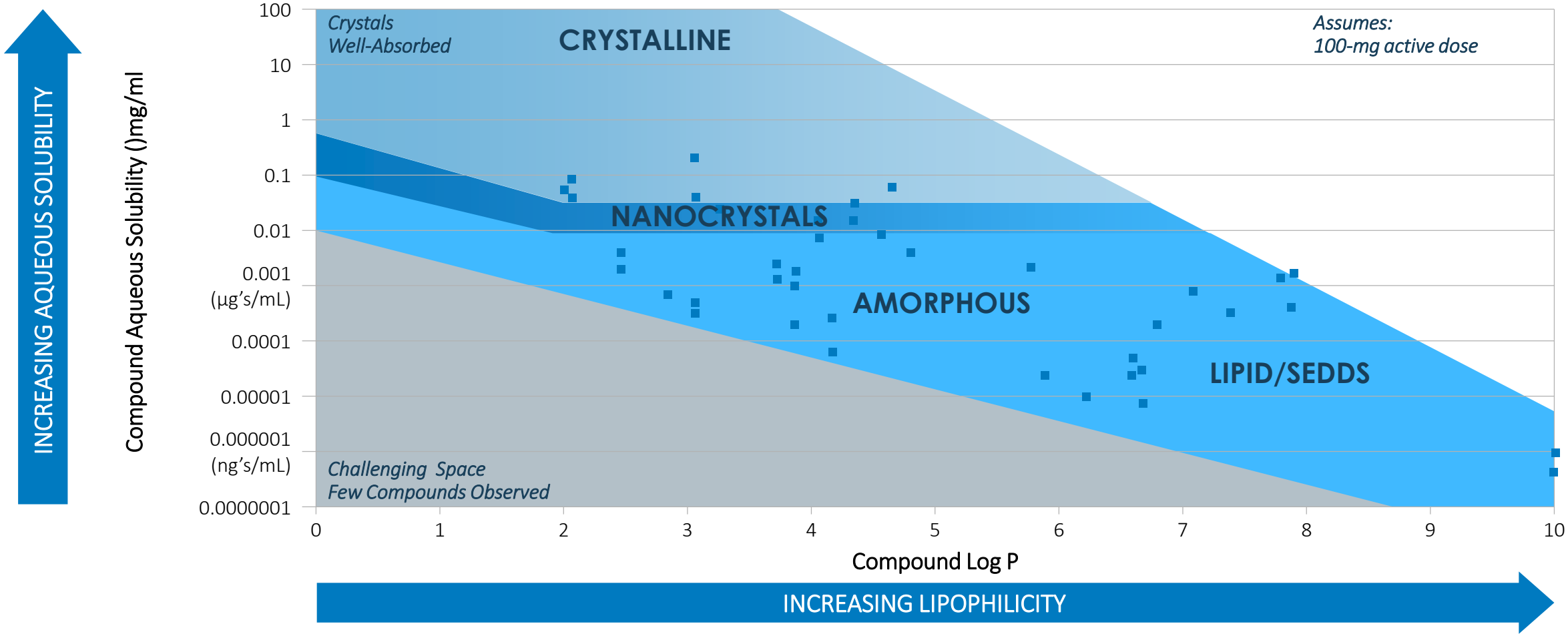


Absorption modeling should be a hypothesis-driven exercise, with the outcome being assessed risk and managed expectations with respect to drug performance. Doing so can lead to an optimized formulation sooner and with less resources.

Common Bioavailability-Enhancing Technologies

Conceptual guidance map for technology selection based on molecular properties and dose



H.D. Williams et al. "Strategies to Address Low Solubility in Discovery and Development," *Pharmacol. Rev.*, 65(2013), 315-499

Salts, Polymorphs, Co-crystals

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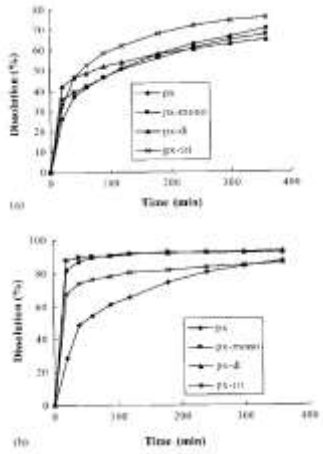
Compound properties

- DCS II or IV
- Ionizable (for salts)
- Crystalline

In Vitro Dissolution



In Vivo PK Data

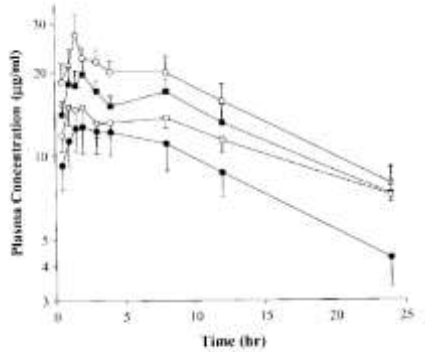


Fig. 2. Plasma concentration profiles of piroxicam after the oral administration of: (●) PX, (□) PX-MEA, (■) PX-DEA, and (○) PX-TEA. The data is expressed as a mean ± S.E. ($n = 6$).

Potential Advantages

- Potential for solubility and dissolution rate enhancement (K_{sp} dependent)
- High-dose potential
- Few enabling excipients required
- High precedence
- Few manufacturing unit ops
- Solid dosage form

Potential Challenges

- Common-ion effect
- Precipitation in small intestine
- Salt or co-former factor
- Stability upon storage

Serajuddin, A.T.M., and M. Pudipeddi in *Handbook of Pharmaceutical Salts*, IUPAC, 2002; Gwak, H.S., J.S. Choi, and H.K. Choi, *Int J Pharm Sci*, 297(2005)156-161; Tong, W.Q., "Salt Form Screening and Selection," Integrated Drug Product Development Process, University of Utah, Salt Lake City Utah, July 17-19, 2006.

Nanocrystals: top down (attrition) or bottom up (nucleation)

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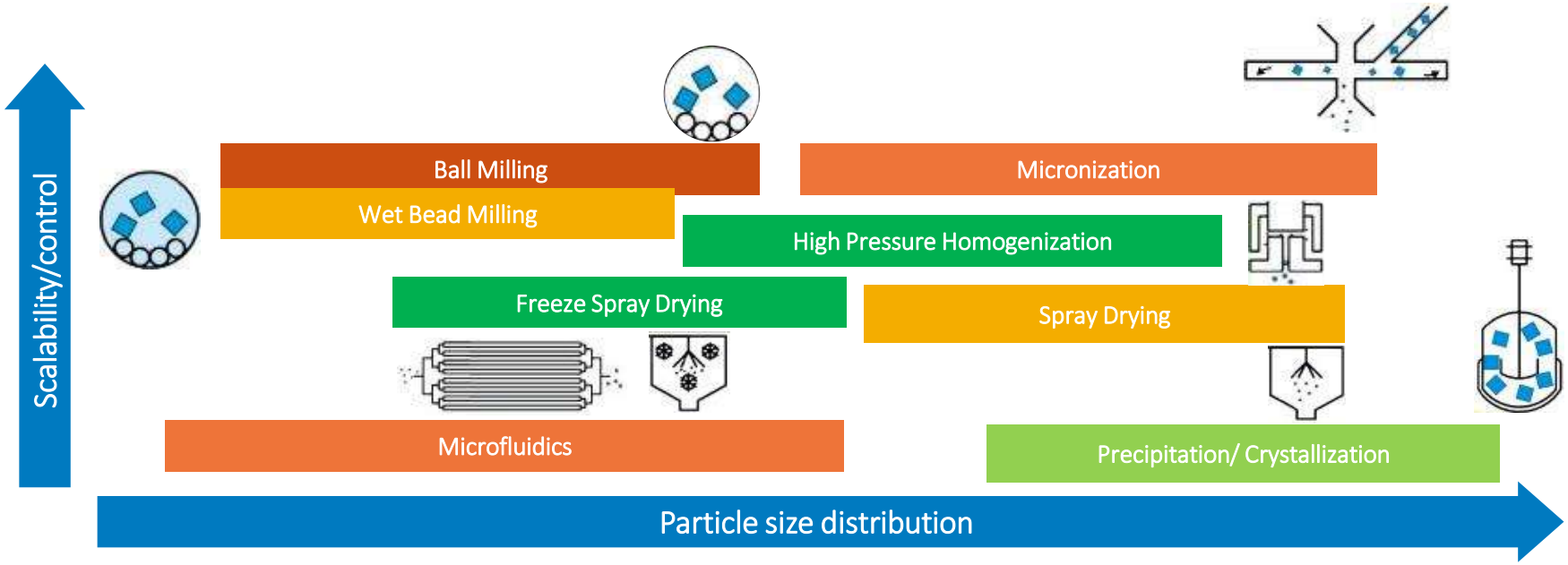
Compound properties

- DCS IIa
- Low solubility in milling media
- Crystalline

Wang et al. *Current Opinion in Chemical Eng.*

2012, 1, 102-107



Potential Advantages

- Dissolution rate enhancement
- High dose potential
- High precedence
- Solid or liquid dosage form

Potential Challenges

- Stability – ripening
- Little to no solubility enhancement
- Form changes
- Cost of production

Amorphous solid dispersions: Hot-Melt-Extrusion (HME)

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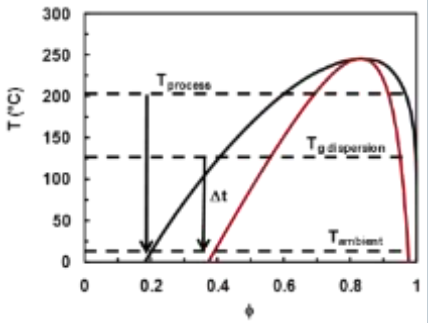
Compound properties

- DCS IIa/b and IV
- Thermal stability
- Low/moderate melting point

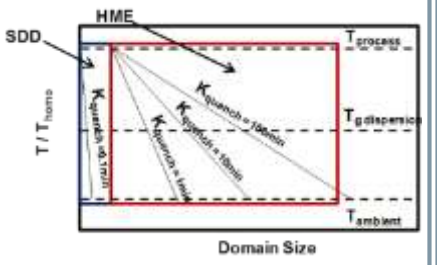
DiNunzio, J.C., Melt Extrusion: Case Studies

Delivery Systems. 2010

Formulation Considerations



Process Considerations



Extrudate

Chopped

Potential Advantages

- Solubility and dissolution rate enhancement
- High throughput
- Precedence
- Solid dosage form
- Small process footprint

Potential Challenges

- Drug loading
- Physical stability - perception
- High-T_m compounds not applicable
- Thermally sensitive molecules
- Scale down of process – perception

Amorphous solid dispersion: spray drying

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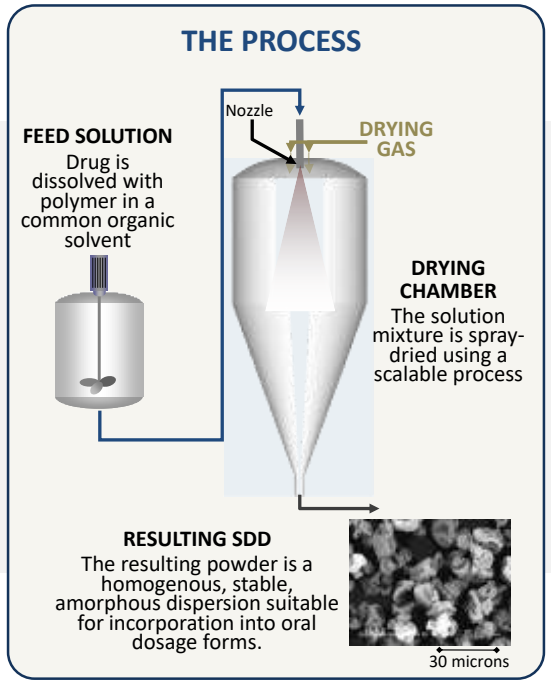
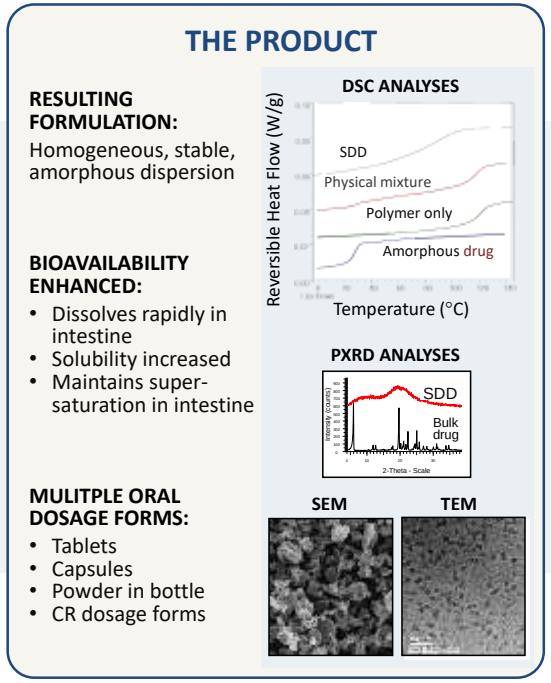
Compound properties

- DCS IIa/b and IV
- Solvent soluble

Friesen, D.T., et al., *Mol. Pharm.*, 5:6(2008)1003-1019





Potential Advantages

- Solubility and dissolution rate enhancement
- Process scalability
- Precedence
- Solid dosage form
- Applicable to large compound property space

Potential Challenges

- Drug loading – kinetically stable
- Solvent-based process
- Organic solvent solubility may be limiting
- Physical stability – perception

Lipid-Based Formulations (LBF)

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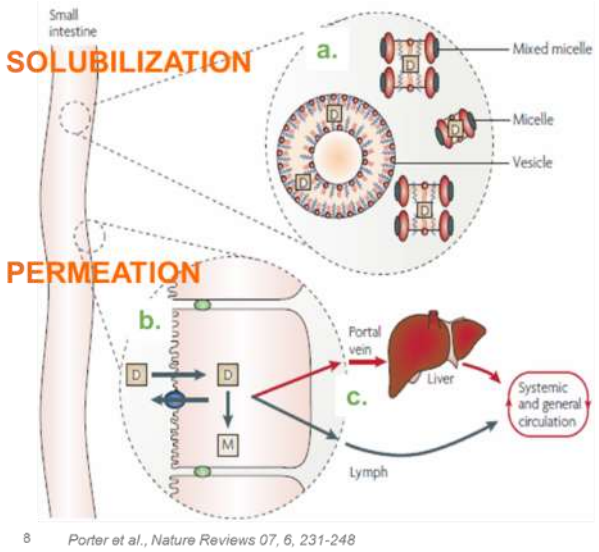
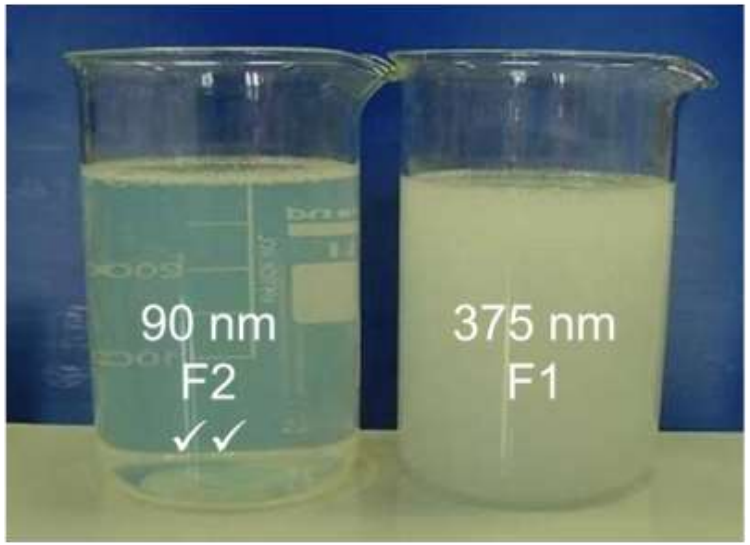
Compound properties

- DCS IIa/b and IV, sometimes III
- Adequate lipid solubility
  - high logP
  - Low T_m





Potential Advantages

- Solubility enhancement
- Bypasses dissolution if a solution
- Process scalable
- Precedence
- Induce fed state
- Increase lymphatic uptake

Potential Challenges

- Drug loading – lipid solubility
- Liquid formulation
- Physical stability – unknown crystal forms?
- High excipient (surfactant, lipid) loading (Esp. for toxicology studies)

Representative technology options relative to problem statement

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Technology	Dissolution Rate Limited	Solubility Limited	Permeability Limited	Solubility and Permeability Limited
Salt, Polymorph, Cocrystal	X	X		x
Nanocrystals	XX			
Amorphous	XX	XX		X
Lipids	XX	XX	X	XX

H.D. Williams et al. "Strategies to Address Low Solubility in Discovery and Development," *Pharmacol. Rev.*, 65(2013), 315-499

Case Study – Improving Itraconazole Oral Absorption

Itraconazole Physicochemical Properties

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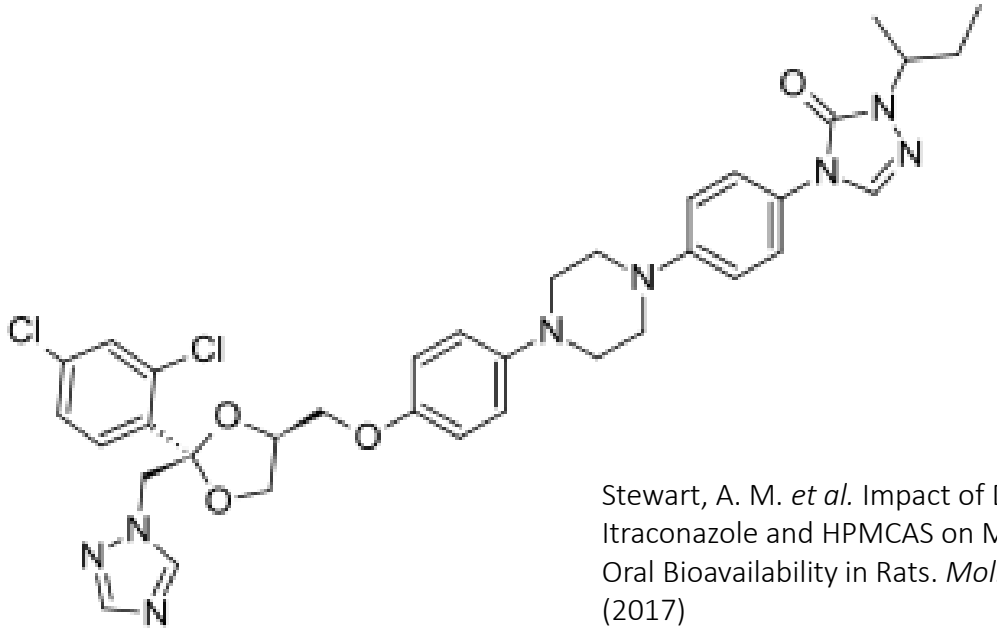
Indication: Serious fungal infections

Marketed formulation is coated beads of an amorphous dispersion of ITZ and HPMC Sporanox®

MW	706
pKa	3.7
logP	5.9
Solubility (µg/mL)	
Water	$< 10^{-3}$
6.7 mM SIF	0.07



Stewart, A. M. *et al.* Impact of Drug-rich Colloids of Itraconazole and HPMCAS on Membrane Flux In Vitro and Oral Bioavailability in Rats. *Mol. Pharm.* **14**, 2437–2449 (2017)

Itraconazole is Solubility-permeability limited in vivo

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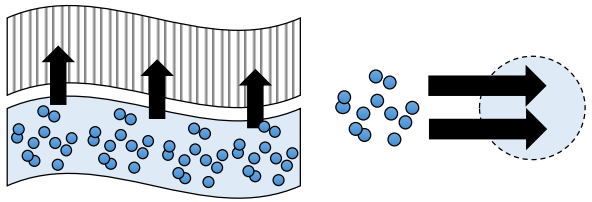
BCS	Ref: Amidon, G.L., et al. *Pharm Res.* (1995), 12 (3), 413-420	FaCS	Ref: Sugano, K., et al., J Pharm Sci. (2015), 104, 2777-2788

Dose Number

$$Do = \frac{Dose/_{Vol}}{C_s}$$

Solubility-permeability limited



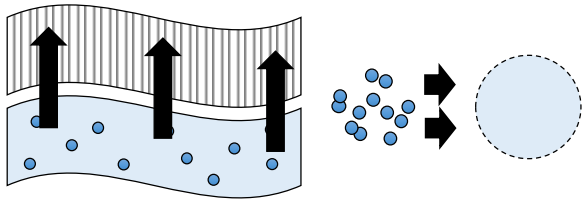
$Pn/Do < Dn \ \& \ Do > 1$

ITZ SDDs in rats

Dissolution Number

$$Dn = k_{diss} \cdot t_{abs}$$

Dissolution-limited

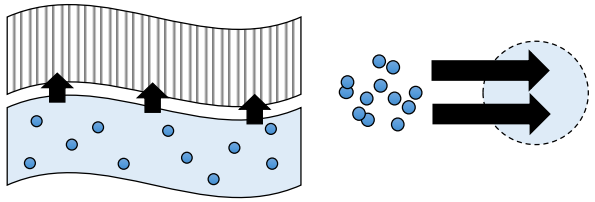


$Dn < Pn/Do$

Permeation Number

$$Pn = k_{abs} \cdot t_{abs}$$

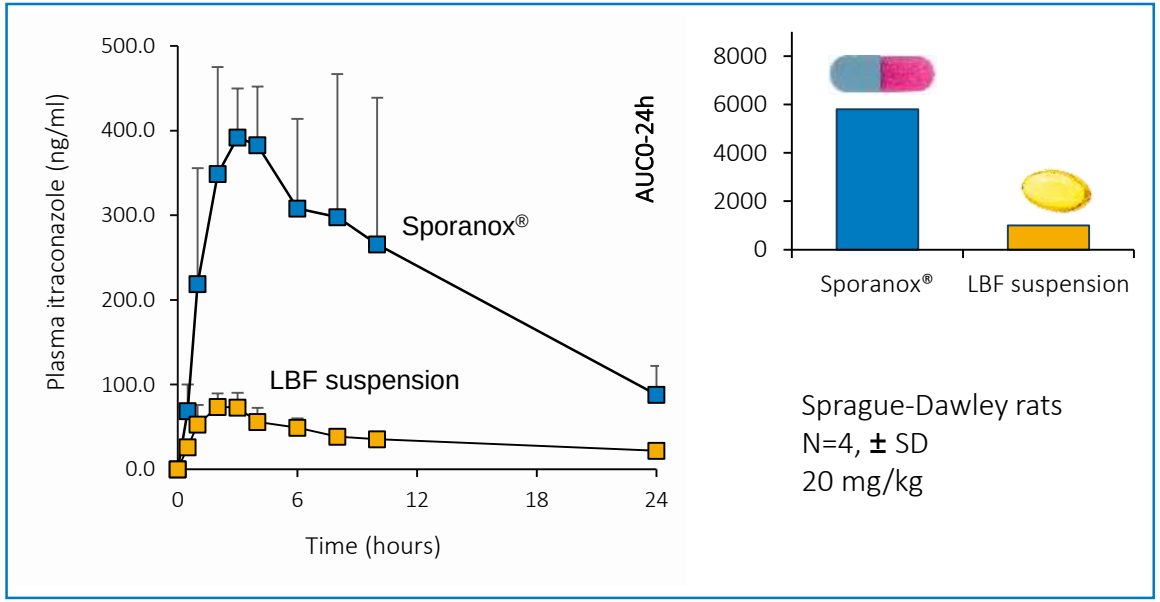
Permeability -limited



$Pn < Dn \ \& Do < 1$

In Vivo Head-to-Head Technology Comparison

Itraconazole absorption from solid dispersions and LBFs in rats



- Itraconazole solubility in LBFs is low (<10 mg/g) = only suspensions can be developed

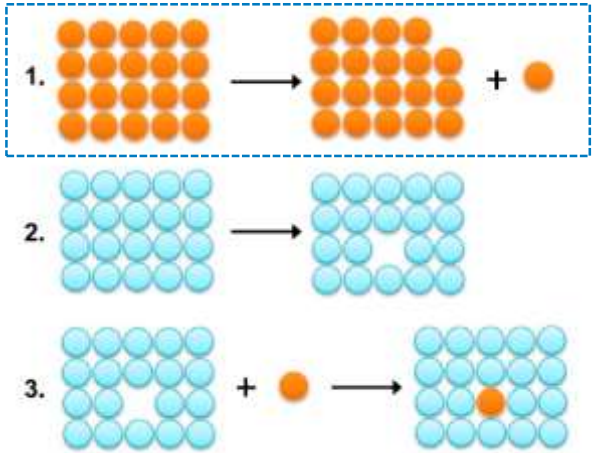
- *In vivo*, LBF suspension performance is **significantly out performed by the amorphous solid dispersion product (Sporanox®)**

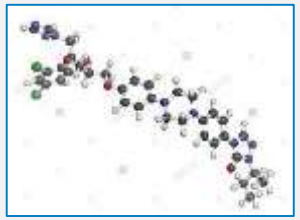
Sahbaz Y et al. (2015) Molecular Pharmaceutics 12 pp 1980-1991

Underlying mechanisms:

- ITZ affinity for lipids / lipid colloids **(3)** is too little to off-set the energy requirement to break bonds in crystalline lattice **(1)**

- Solid-state barrier to ITZ solubility predominates





Itraconazole

✓ Brick dust

Develop using ASD

Amorphous is good…can we do better?

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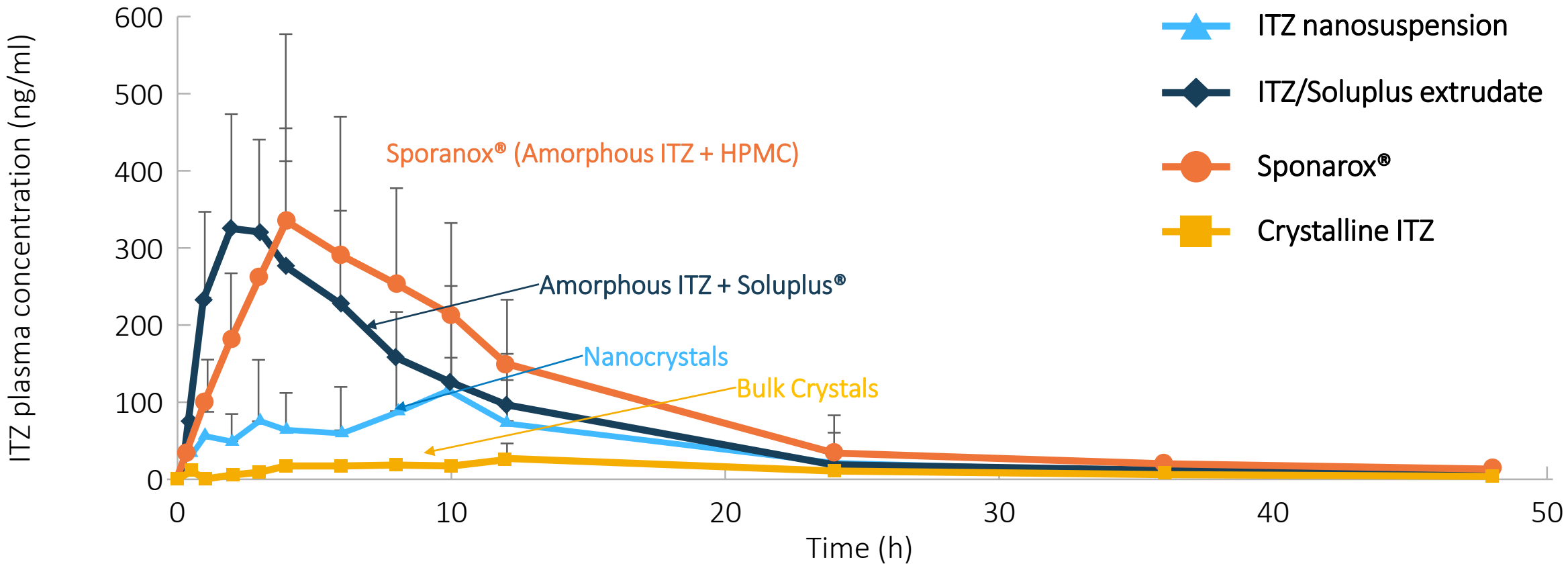

Zhang *et al*. *Eur J Pharmaceutics Biopharmaceutics* (2013) 85 (3), 1285-1292

Evaluating ASD formulations in rats

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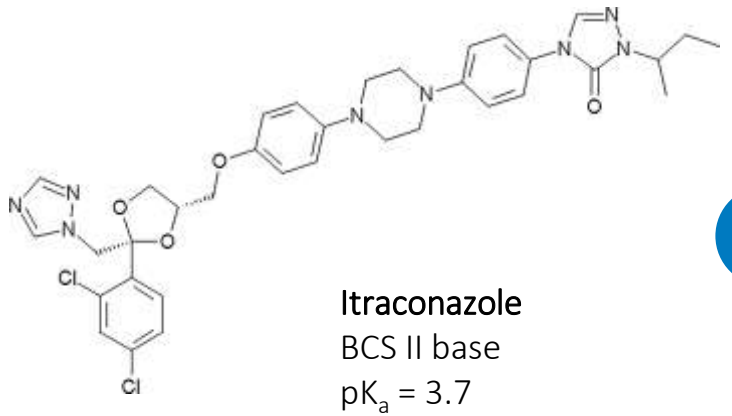
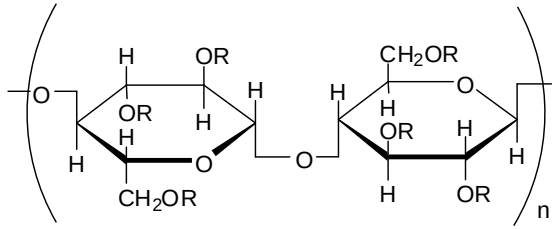


Itraconazole
BCS II base
pK_a = 3.7
cLogP = 6.3

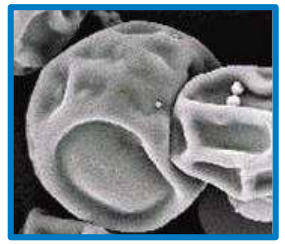
Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS)



R= -H
-CH_3
-$COCH_3$
-$COCH_2CH_2CO_2H$
-$CH_2CH(OH)CH_3$

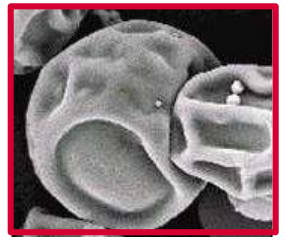
-CH_2CHCH_3 (OCOCH$_3$)
-CH_2CHCH_3 (OCOCH$_2$CH$_2$CO$_2$H)

25% active
Hydrophilic SDD
Affinisol 716HP



OR

25% active
Hydrophobic SDD
Affinisol 126HP



Formulations dosed to rats

Sprague-Dawley (n=6), fasted
Dose: 50 mg/kg
Dosing vehicle: 0.5% Methocel A4M in H2O
Dosing route: oral gavage

Ref: Stewart, A.M., et al. *Mol Pharm* (2017), 14 (7), 2437-2449

Itraconazole/HPMCAS ASDs form nanoparticles upon dissolution

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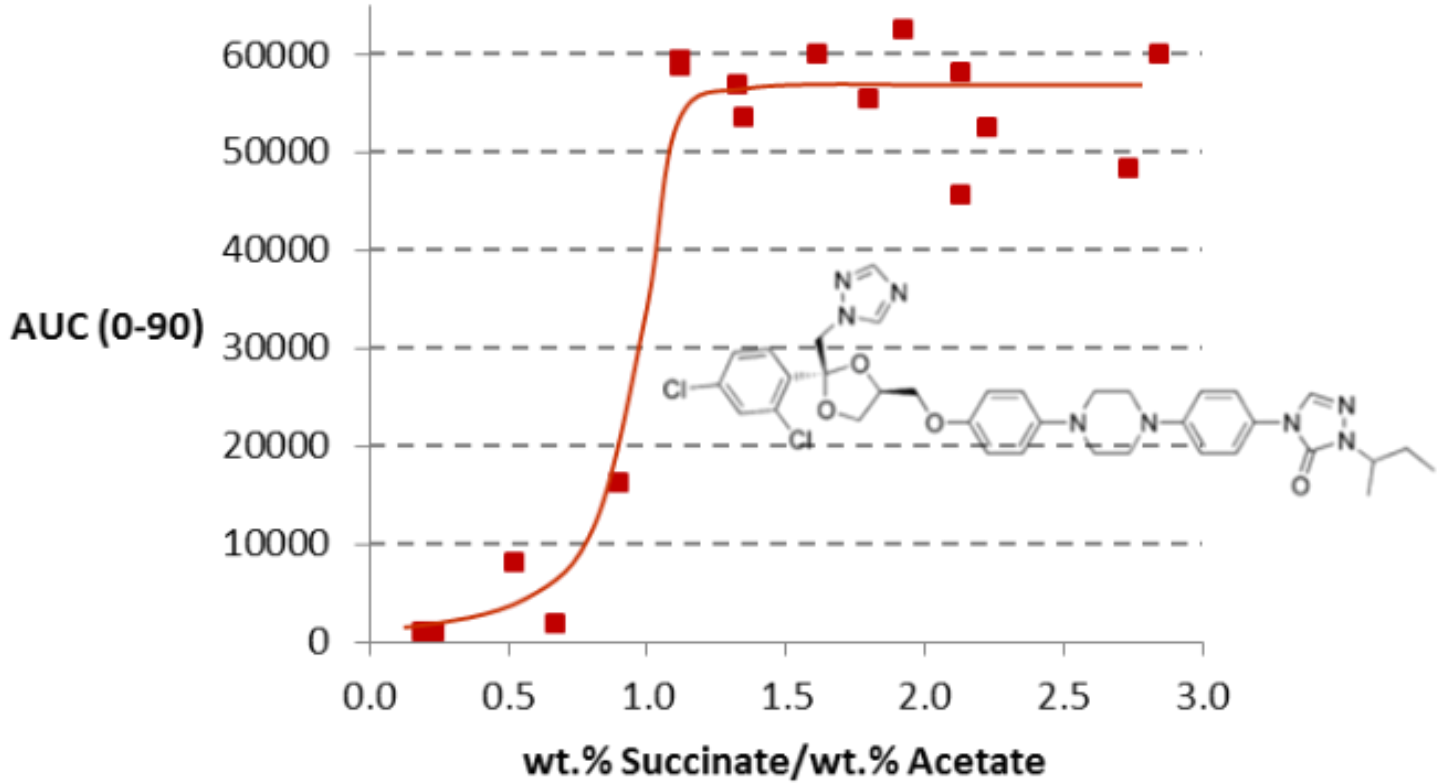
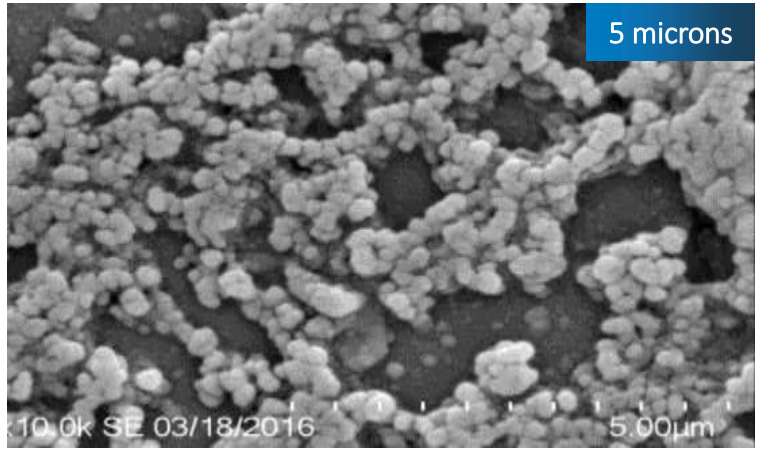
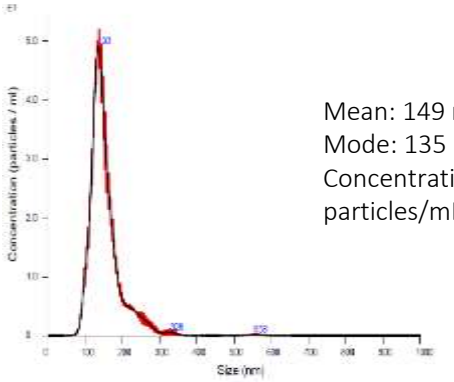
25% Itraconazole/75% HPMCAS



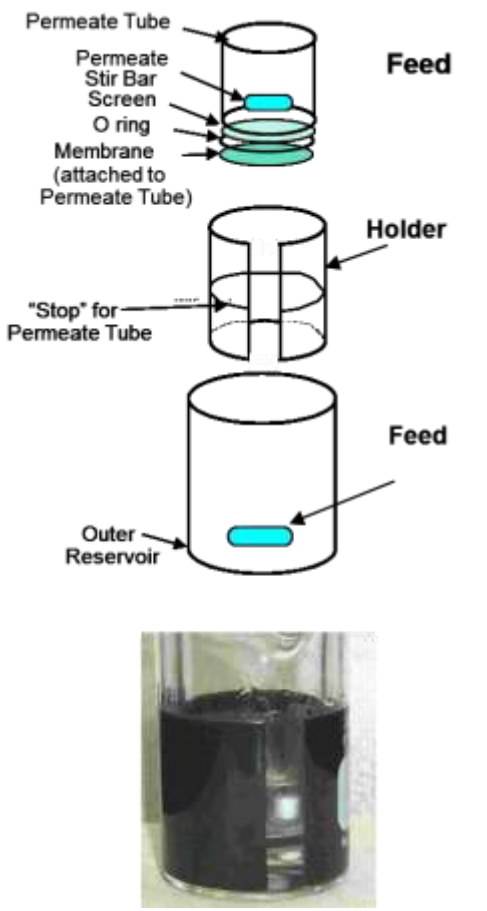


Nanoparticle Tracking Analysis (NTA)



Mean: 149 nm
Mode: 135 nm
Concentration: 3 x 10^{10} particles/mL

Membrane flux can help us determine significance of nanoparticles in vitro



Feed Volume: 5 mL

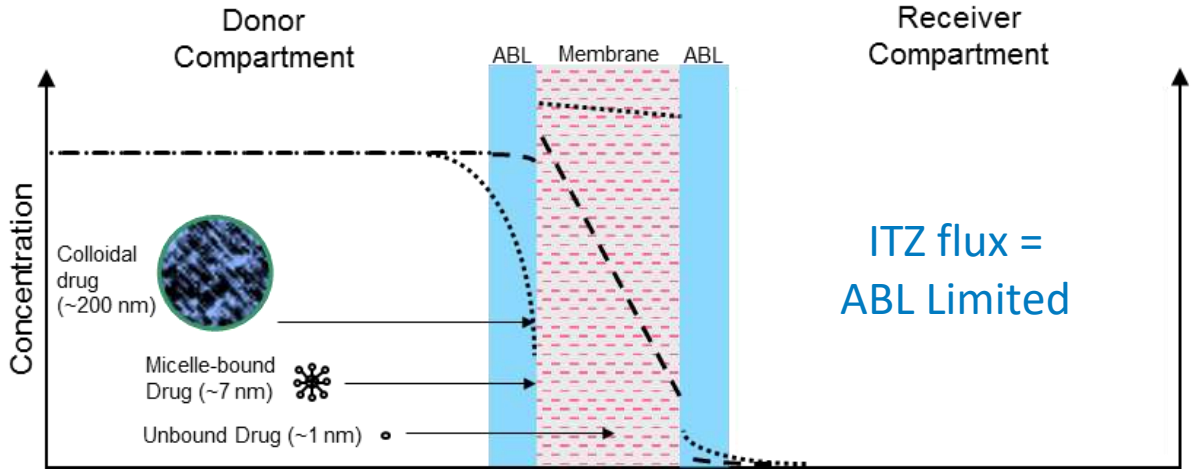
Receiver Volume: 10 mL

SA: 4.9 cm^2

SA/V = 1.0 cm^{-1}

Accurel PP 1E membrane (55% porous, 100 µm thickness)

50 µL lipid (20% phospholipid in dodecane)



In vitro test parameters designed to reflect *in vivo* situation

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	Solubility-permeability limited	Intestinal fluid composition
***In Vivo* - rats**	➔ Pn/Do: 0.03 (<< Dn) ➔ k_a << k_d ➔ Do: 180	➔ Bile salts: 10-100 mM ➔ pH 6 (ITZ <1% ionized)

	Solubility-permeability limited	Fluid composition
***In Vitro* - flux test**	➔ Pn/Do: 0.005 (<< Dn) ➔ k_a << k_d ➔ Do: 10	➔ Bile salts: 27 mM NaTC (4:1 NaTC:PC) ➔ pH 6.5 (ITZ < 1% ionized)

Hydrophilic SDD has the highest flux *in vitro* driven by nanoparticle concentration

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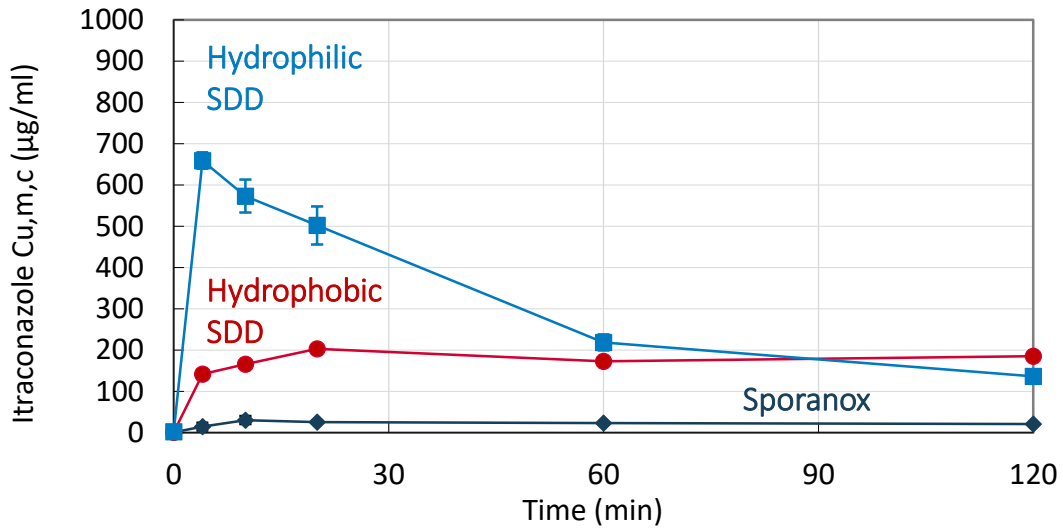
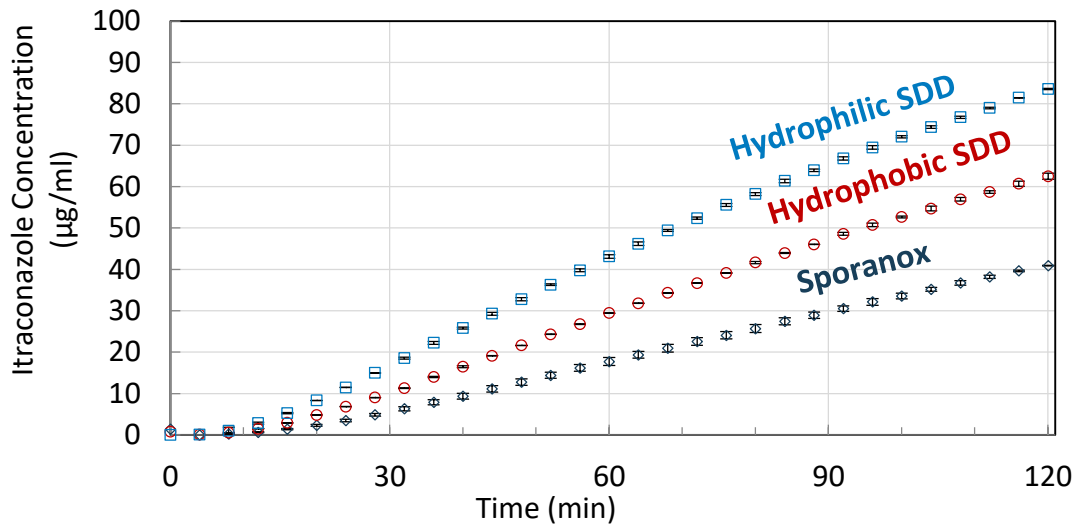
Donor



Receiver



No.	Formulation	Dispersion polymer	Flux (µg/min/cm²)	Nano Conc (µg/ml)
1 ■	25% ITZ/75% HPMCAS SDD	AFFINISOL 716HP	1.18	602
2 ●	25% ITZ/75% HPMCAS SDD	AFFINISOL 126HP	0.85	150
3 ◆	Sporanox® spray layered dispersion	HPMC	0.53	0

In-vitro flux is readily predicted: What about in vivo?

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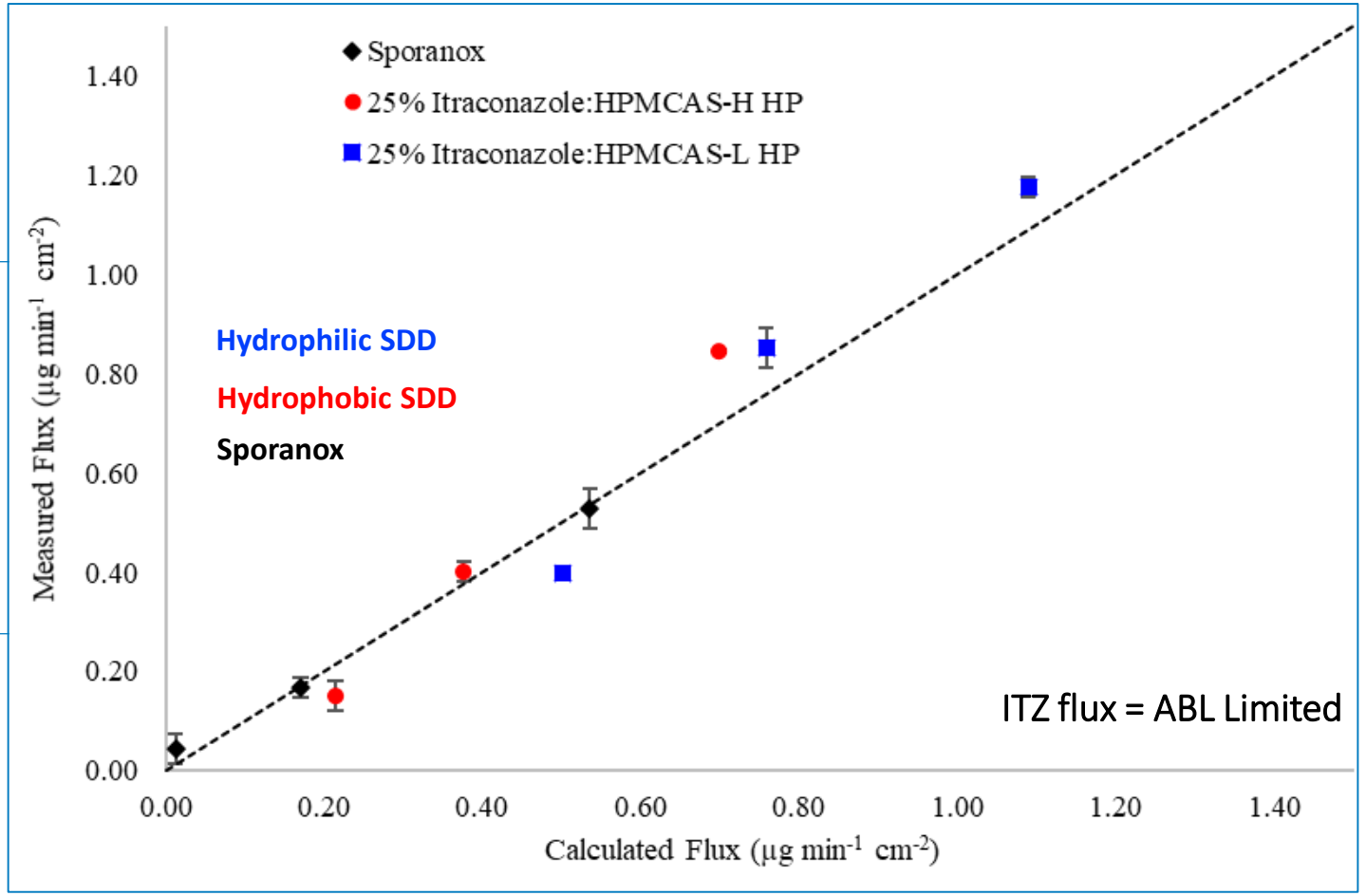
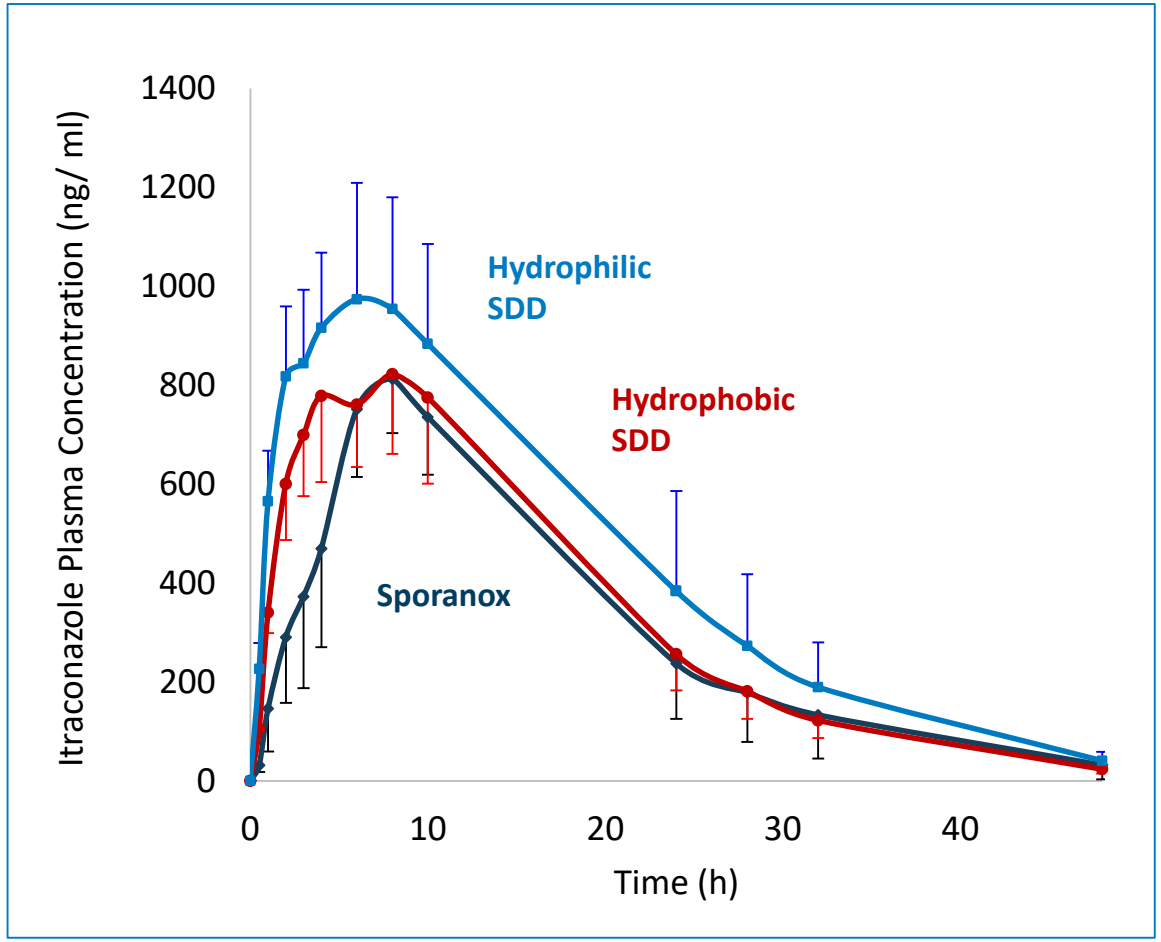
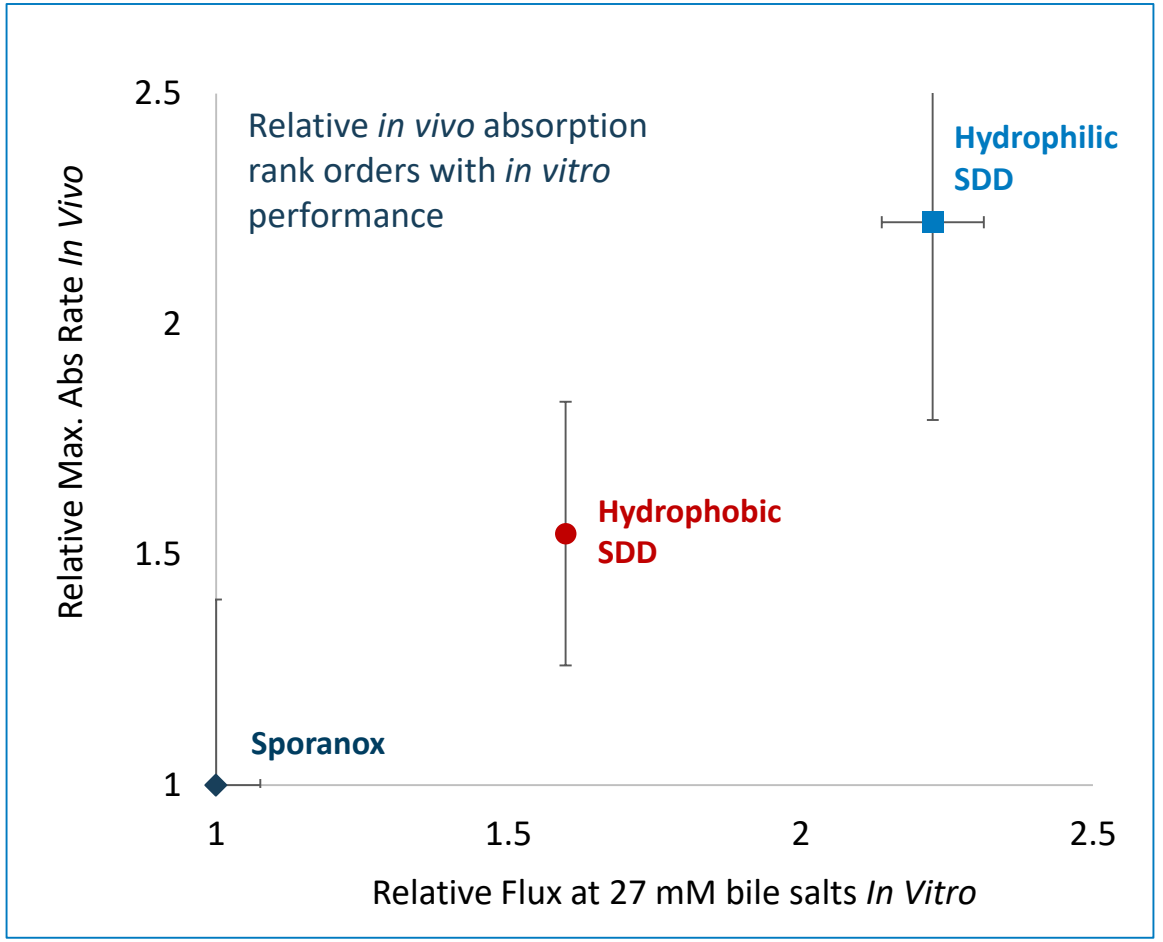
$$j = \frac{F_{ub} \cdot D_{ub} + F_{mb} \cdot D_{mb} + F_{coll} \cdot D_{coll}}{h_{ABL}} \cdot c_{total}$$



Hydrophilic SDD shows the fastest absorption in rats – rank orders with *in vitro* performance





Summary and thoughts

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BCS II/IV compounds continue to dominate the drug development pipeline

Compounds are getting more difficult to solubilize → streamlined tech selection increasingly required

Enabling technologies are specifically designed to accommodate BCS II/IV compounds across a diverse physicochemical space

in silico tools, *in vitro* tools, and historical experience can be used to focus on formulations and manufacturing processes with highest possibility of success

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- Michael E. Grass
- David Lyon

Three Sisters Mountains near Lonza in Bend, Oregon

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