Challenges and Opportunities for Oral Delivery of Poorly Soluble Drugs

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Distinguished Scientist

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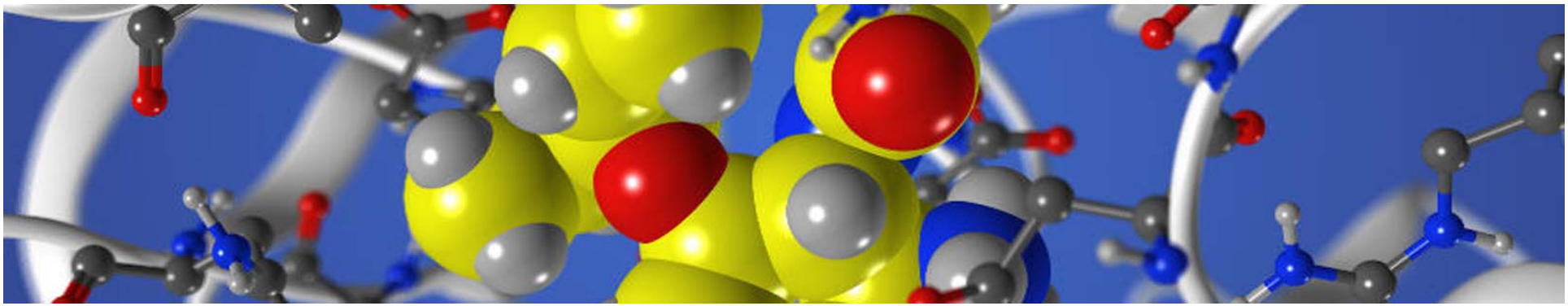


Outline

- Overview of Industry Today
  - Sources of Oral Bioavailability Limitations
  - Market Trends
- Challenges & Opportunities for Poorly Soluble APIs
  - Impact of low solubility in development
  - Case studies of successful development
- Technologies and Limitations for Handling Poorly Soluble Compounds
  - Emerging Opportunities to Improve Amorphous Development
- Future Direction and Concluding Comments

Sources of Bioavailability Limitations

Technological Intervention to improve solubility and dissolution rate

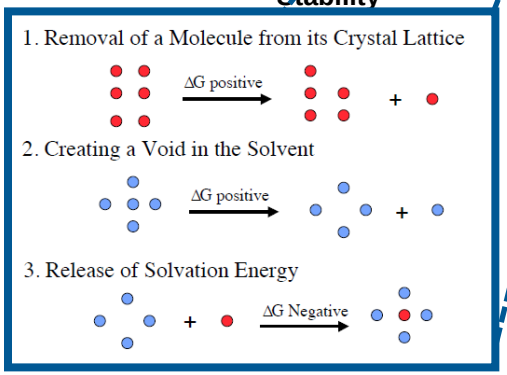
Tablet

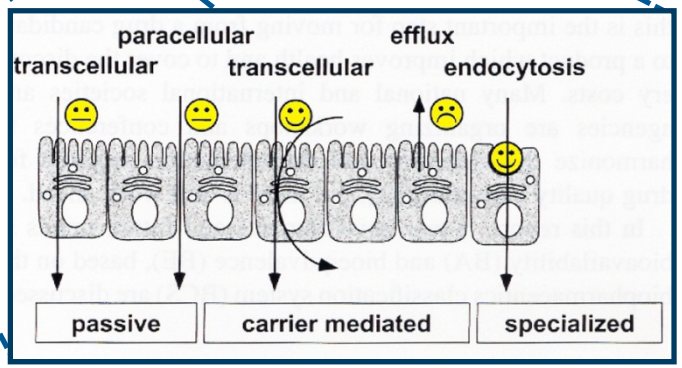
G. I. Tract
-Solubility/ dissolution
-Stability

Intestinal wall
- **Permeability**
- **Stability**

Systemic Circulation
- **First-pass**
- **Metabolism/clearance**

Target tissue





$$\frac{dW}{dt} = \frac{D \cdot A \cdot (C_s - C(t))}{L}$$

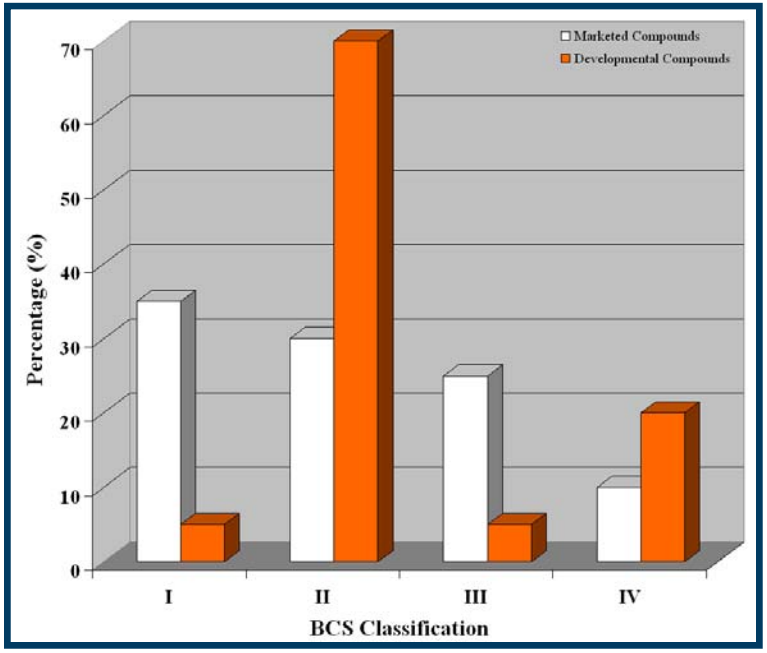
Noyes-Whitney Equation

$$MAD = K_a \cdot C(t) \cdot V_{SI} \cdot t$$

Maximum Absorbable Dose

Solubility Trends & Developmental Pipelines

Compound Trends



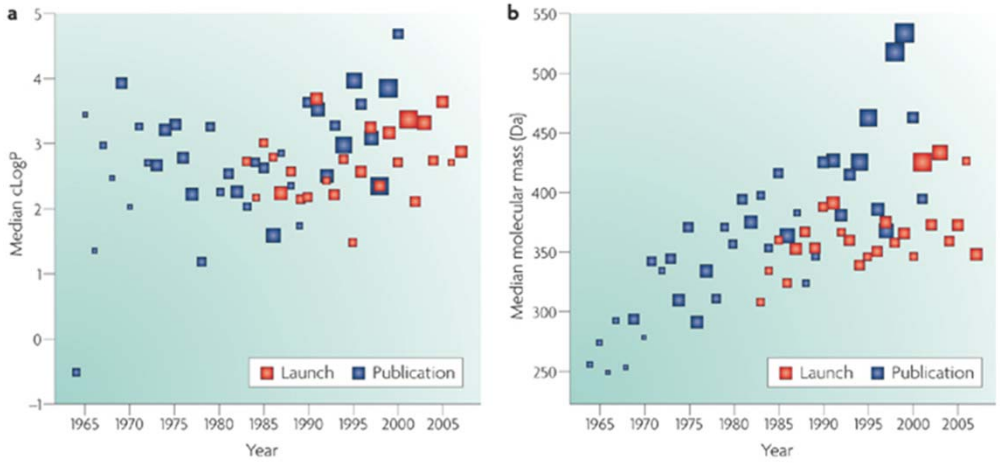
Lipinski's Rule of 5

- Predictor of Limited Oral Bioavailability
  - Molecular Weight > 500
  - Log P > 5
  - H-Bond Donors > 5
  - H-Bond Acceptors > 10

- Examples Meeting The Rule of 5
  - Cyclosporine
  - Itraconazole
  - Ritonavir
  - Lopinavir

592 oral drugs approved worldwide between 1983 and 2007

The size of the squares represents the mean Lipinski score



Nature Reviews | Drug Discovery

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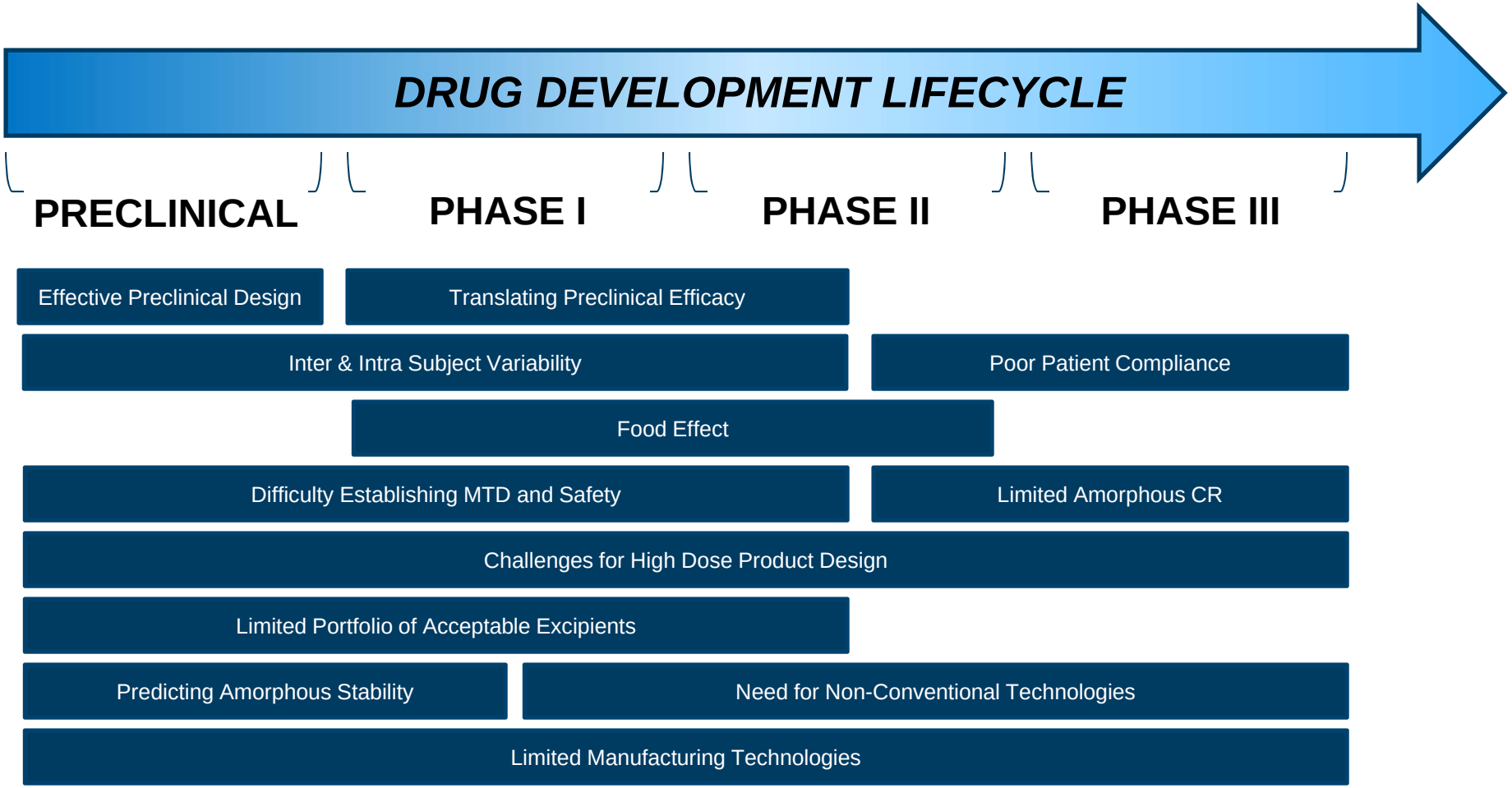
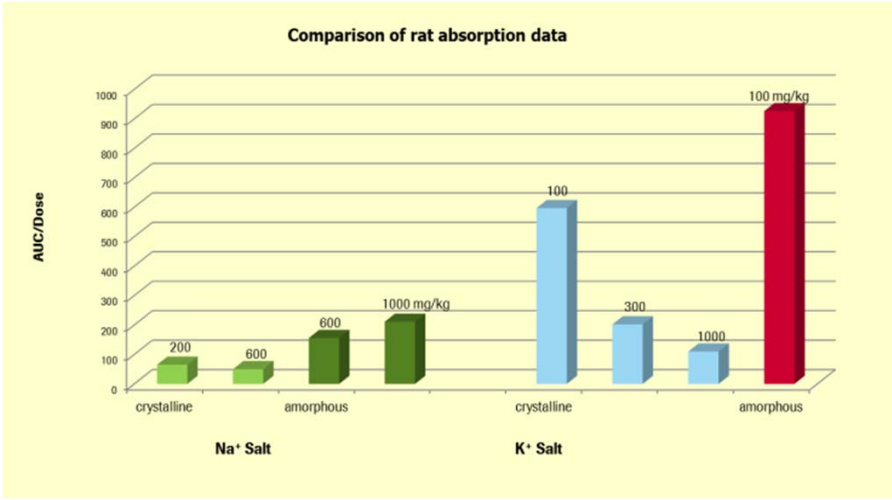
Low Solubility Drug Development Challenges



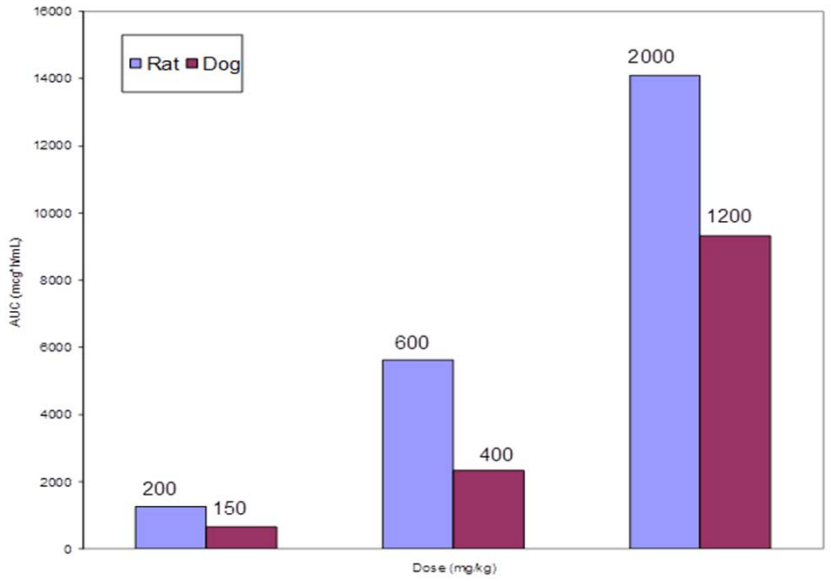
- Low solubility can present major challenges to the successful development of NCEs
- The nature of the challenges change as the program progresses through clinical development

Solubility Driven Challenges in Preclinical Development

- Adequate solubility needed for potency and safety assays and must be considered during design and execution of *in vitro* assays
  - Compounds with poor solubility have the potential to precipitate in assay media/buffer.
  - DMSO stock solutions of poorly soluble compounds have the potential to precipitate during freeze thaw cycles.
  - Assay media greatly impacts solubility



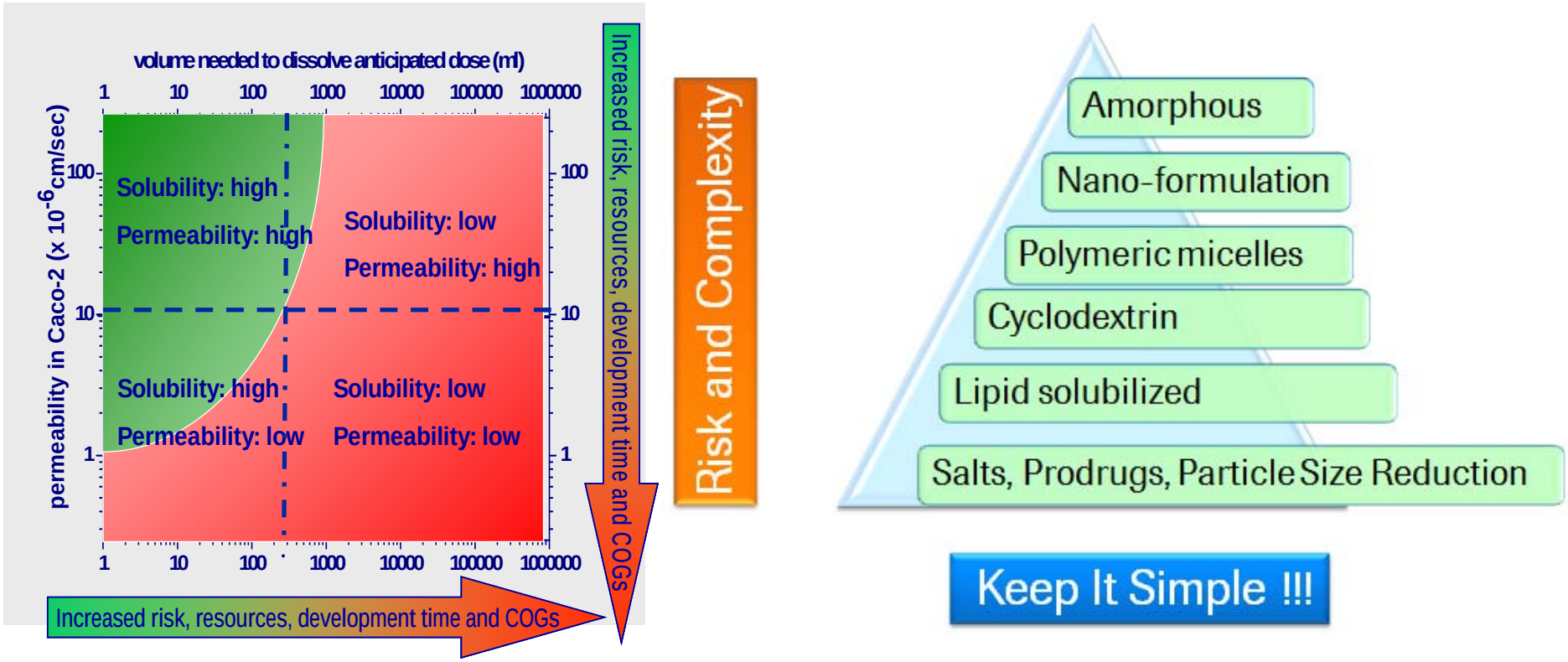
- Adequate solubility is needed for *in vivo* studies at all stages leading to EIH
  - To achieve optimal exposure in PK/PD studies to get proof of concept (POC) in appropriate animal models for project to move to the next stage
  - Multiple fold exposure is required for safety studies in preclinical tox species
  - Salt forms or special formulation are needed to achieve the desired exposure
  - To achieve the exposure in human studies



- Future Challenges
  - Design and development of technologies and compositions to support early development work with limited API supply
  - Optimization of in silico methods to improve computer based design
  - New materials for achieving maximum exposure (multiples over anticipated dose)

Options for Improving Solubility

Compound & Technology Risk Mapping



- Low solubility compounds are inherently more challenging to develop, raising the risk of failure
- Many technologies can address low solubility but also present trade-offs

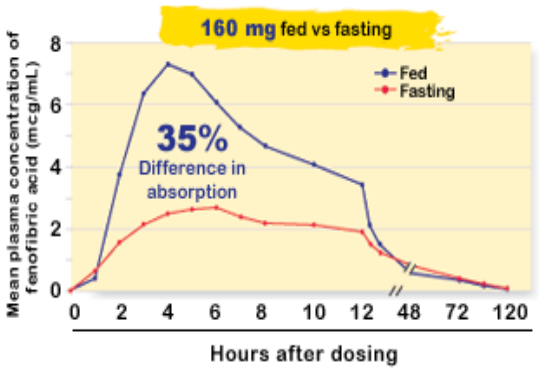
Current Success Stories

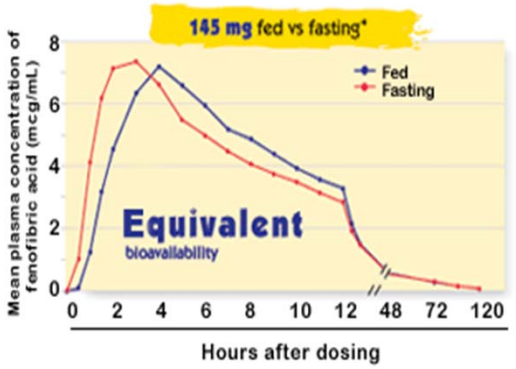
Tricor® - Formulation Intervention to Improve Delivery

200 mg Capsule
- Milled fenofibrate

160 mg Tablet
- Micronized fenofibrate

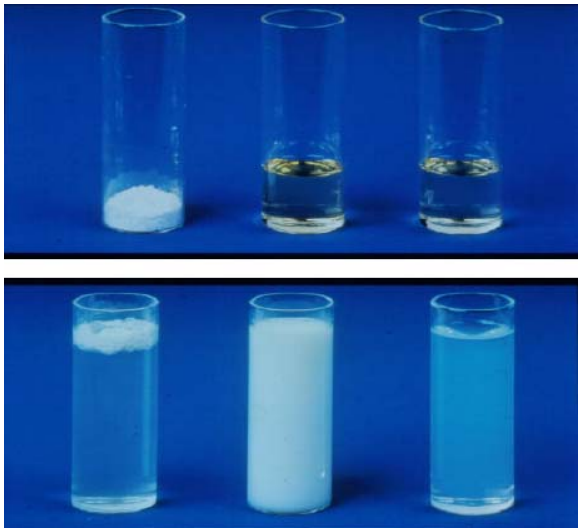
145 mg Tablet
- NanoCrystal fenofibrate



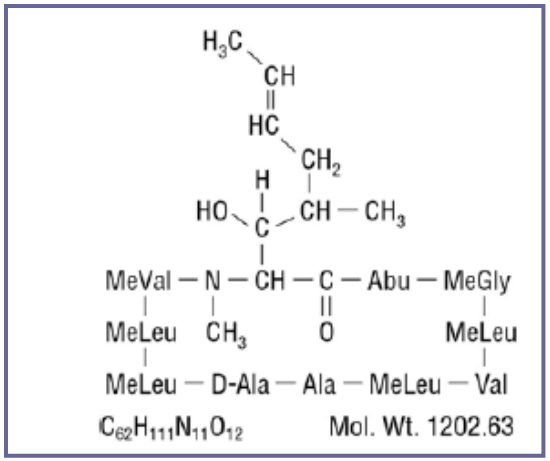


Current Success Stories

Neoral® - Formulation Intervention to Improve Delivery and Extend Market Protection



API | Sandimmune™ | Neoral™



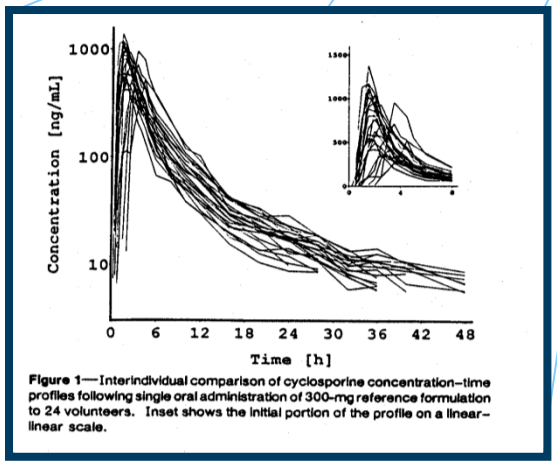


Figure 1—Interindividual comparison of cyclosporine concentration–time profiles following single oral administration of 300-mg reference formulation to 24 volunteers. Inset shows the initial portion of the profile on a linear–linear scale.

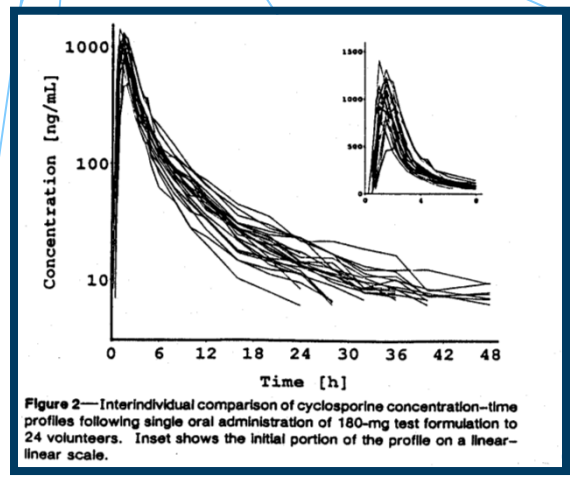
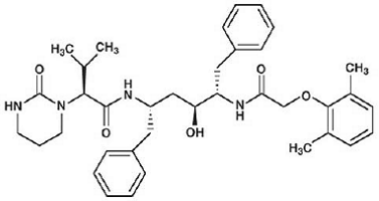
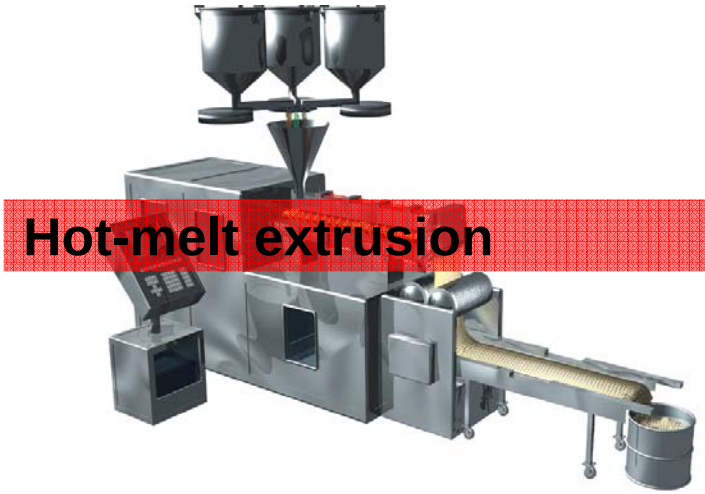


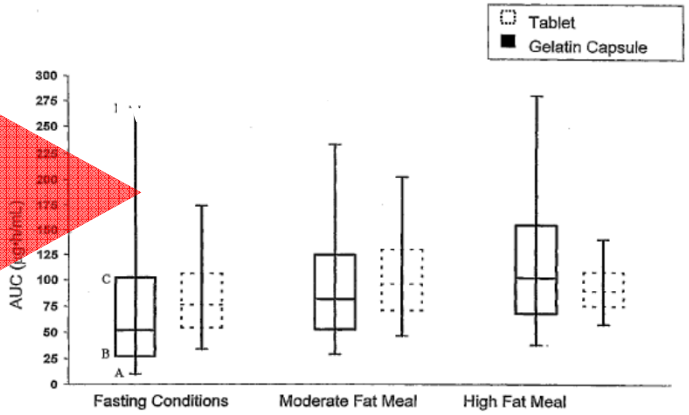
Figure 2—Interindividual comparison of cyclosporine concentration–time profiles following single oral administration of 180-mg test formulation to 24 volunteers. Inset shows the initial portion of the profile on a linear–linear scale.

Current Success Stories

Kaletra® - Amorphous Dispersion for Improve Delivery



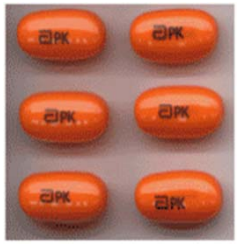




Rosenberg et al. Patent # WO 2006/091529 A2

Kaletra Soft Gelatin Capsule

- Dose per unit:
  - 133 mg lopinavir/33 mg ritonavir
- Dose administration:
  - t.i.d. with food
- Refrigerated storage required

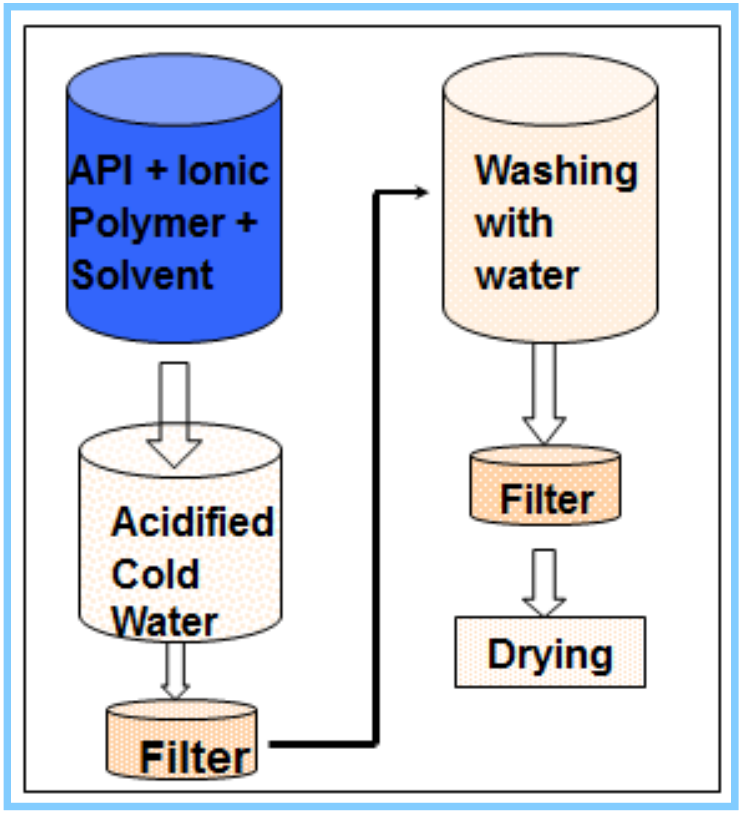


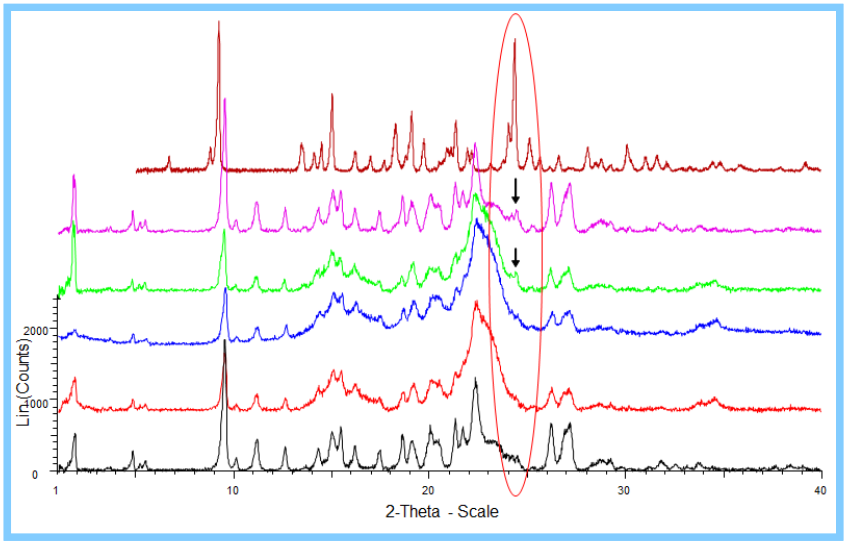
Kaletra Tablet

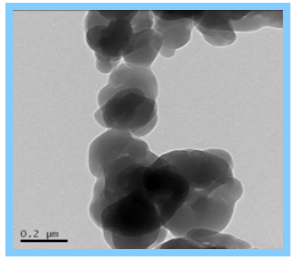
- Dose per unit:
  - 200 mg lopinavir/50 mg ritonavir
- Dose administration:
  - b.i.d. independent of food
- Store at ambient conditions

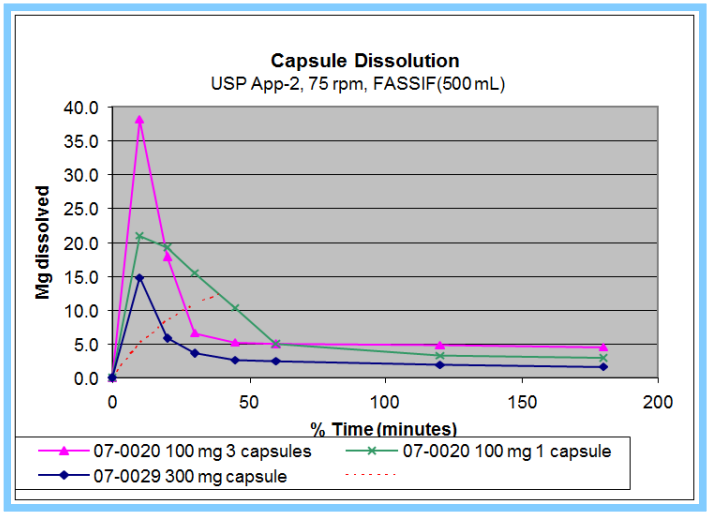
Current Success Stories

Zelboraf® - Molecule to Medicine with Novel Technology







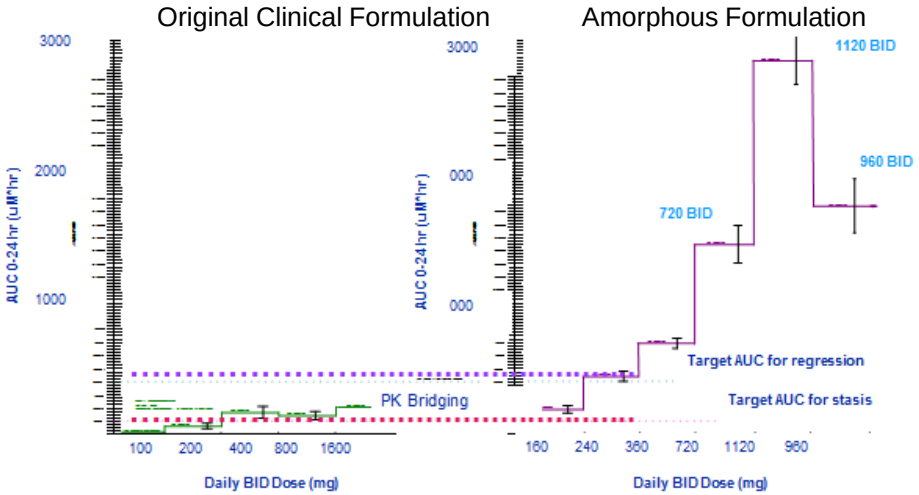


- **Poor Solubility >>>>> Poor Bioavailability**
- Polymorphic Transformation (metastable Form I to stable Form II) **>>>>** Clinical Supply Stock-out Situation
- High Dose **>>>>** Patient Dosing Convenience

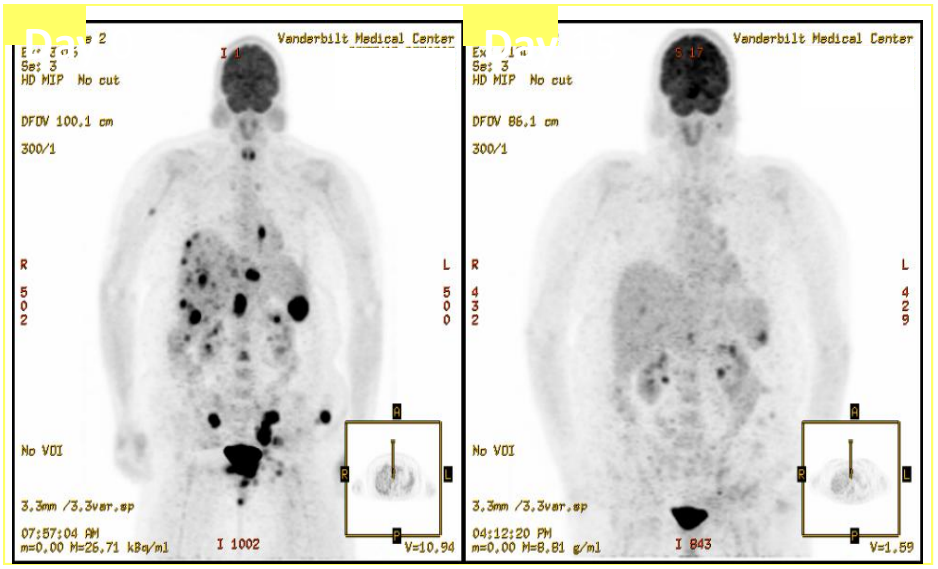
Current Success Stories

Zelboraf® - Making a Difference in Therapy

Bioavailability Comparison



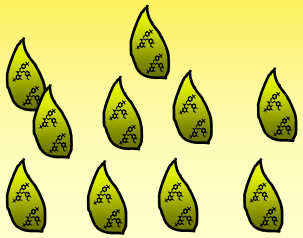
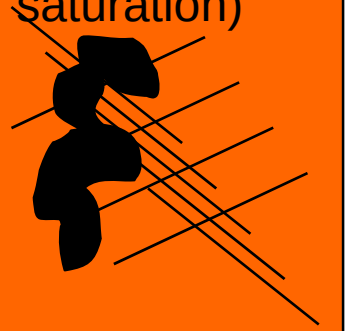
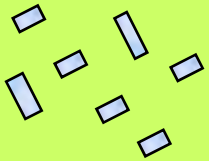
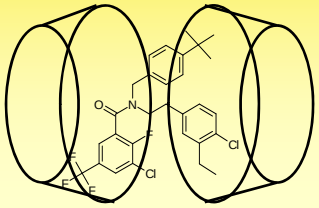
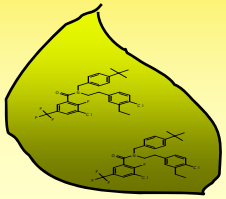
Treatment Results in Tumor Regression



- Development of an amorphous formulation enabled a molecule which could otherwise not be delivered → Life saving benefit to patients in need
- Successful implementation of new technology led to commercial product

Oral Formulations Approaches for Poorly Water Soluble Compounds (BCS 2/4 compounds)

Conventional → No-Conventional: Risk and complexity

Salts Pro-drug 	SEDDS/SMEDDS 	Nanoparticles Polymeric micelles Dendrimers	Amorphous (high dissolution rate and super saturation) 
Particle size reduction 	Complexes Co-crystals 	Crystalline Solid Dispersion 	

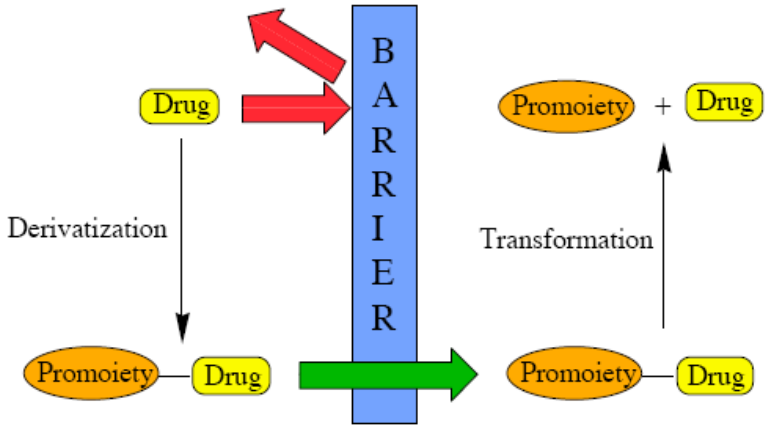
Need for amorphous formulation has significantly increased

Technologies to Improve Solubility

PRODRUGS

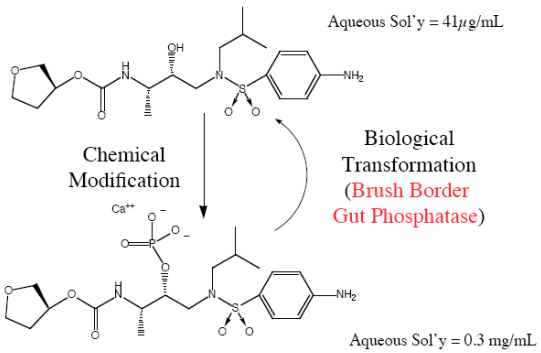
Chemical approach using reversible derivatives that is pharmacologically inert

Successfully applied to a number of commercially marketed products



Prodrugs represents a Chemical/Biochemical approach to the Optimization of Drug Delivery

VX-175/GW 908
(A Phosphate Prodrug of Amprenavir)



7 fold increase in solubility

Advantages

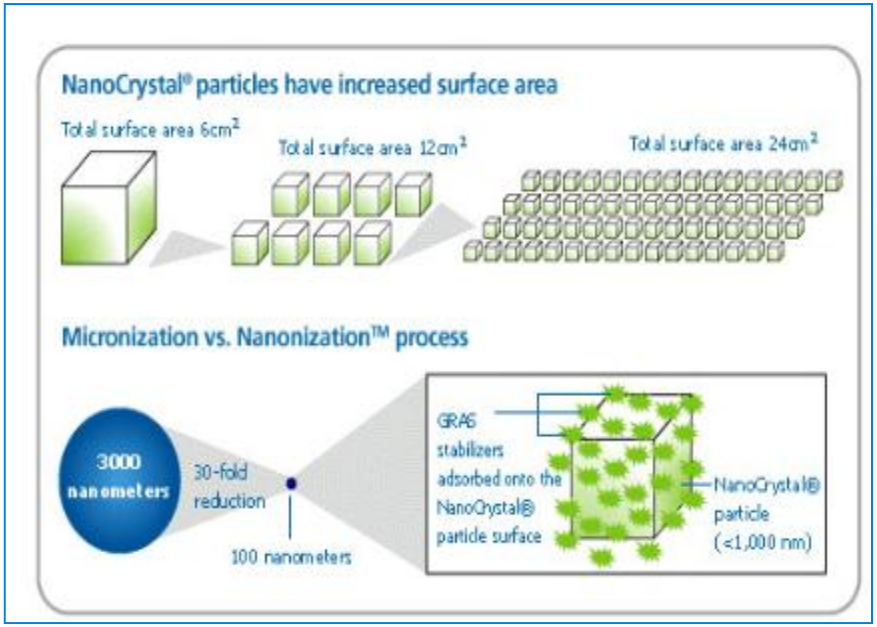
- NCE, Patentable
- Enhanced biopharmaceutical performance

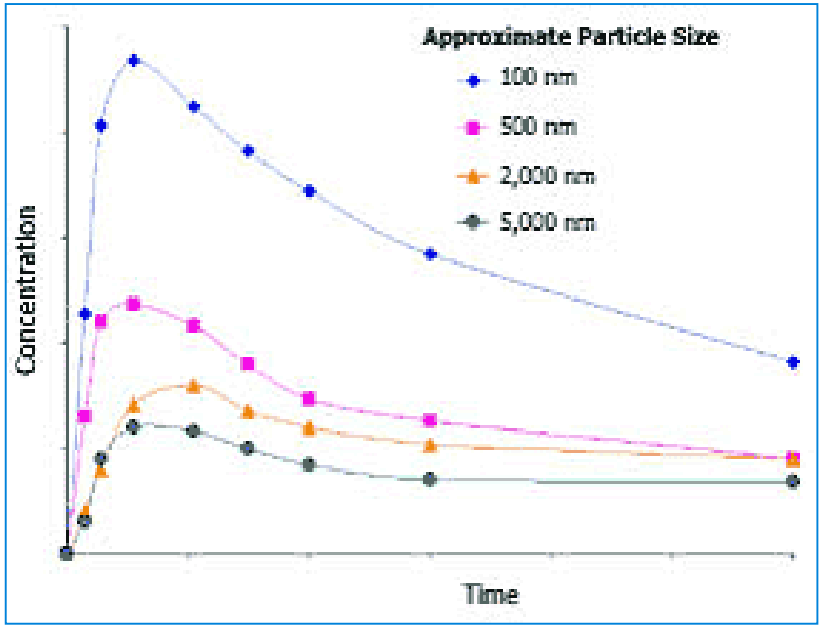
Opportunities

- Reducing development cost
- Site targeted prodrug design
- Expanding chemistries

Technologies to Improve Solubility

PARTICLE SIZE REDUCTION





Advantages

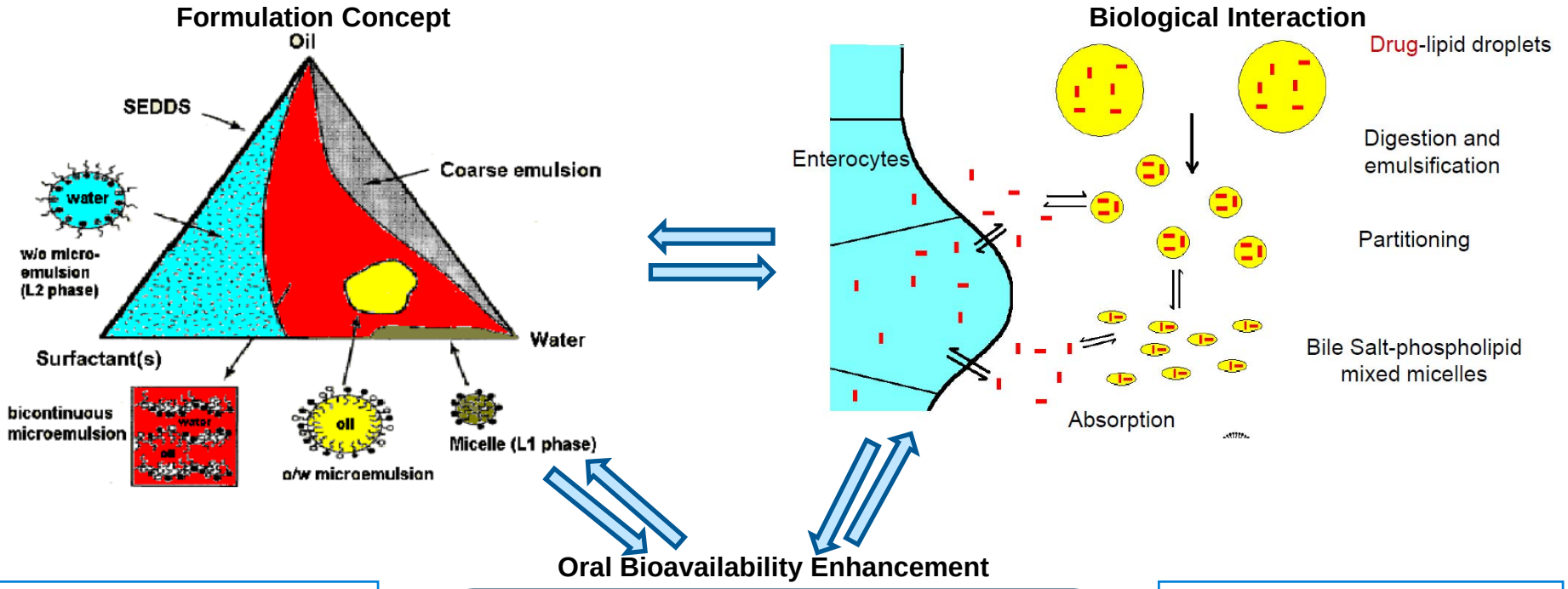
- **Improve exposure –** reduce dose
- **Faster onset of action –** improve efficacy
- **Minimize variability –** improve efficacy and decrease toxicity
- **Reduce/eliminate food effect –** improve convenience and compliance

Opportunities

- **Need for more advanced MFG technologies –** Imprinting, Templating, etc…
- **Expansion of nanotechnology into drug-device hybrid products –** MEMs technology
- **Lower cost of goods for manufacturing –** Current technologies are expensive, proprietary and time consuming

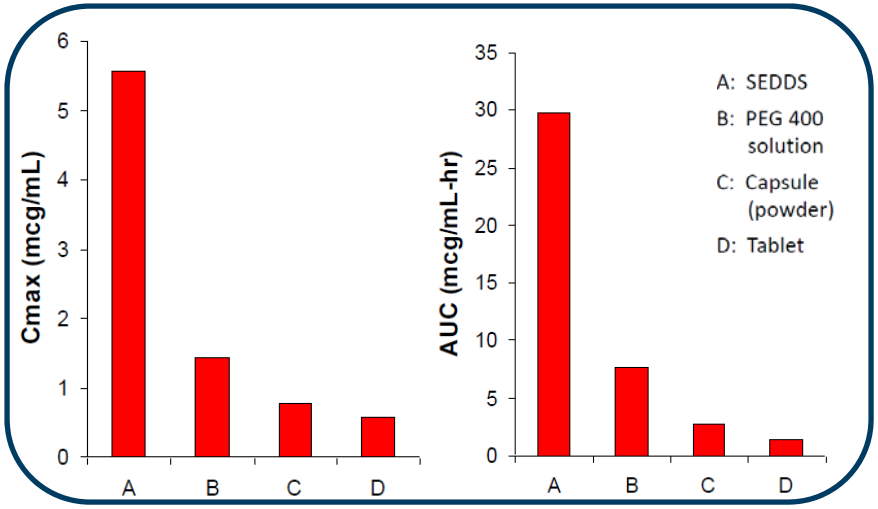
Technologies to Improve Solubility

LIPID FORMULATIONS



Advantages

- Reduced food effect
- Permeability enhancement
- Liquid nature provides for ease of scale-up



Opportunities

- Expansion of materials to support formulation development
- New technologies to improve manufacturability

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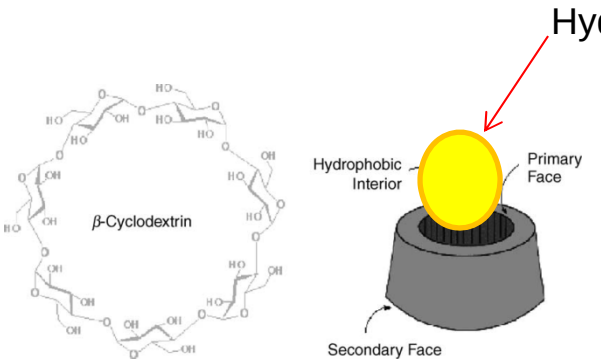
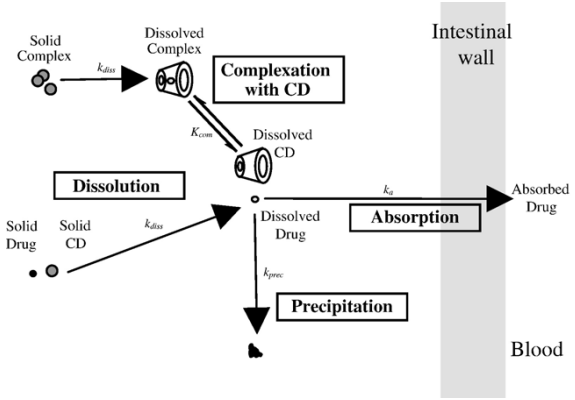
Technologies to Improve Solubility
CYCLODEXTRINS

Cyclodextrins

Oligosaccharides (6 or

more glucopyranose units)



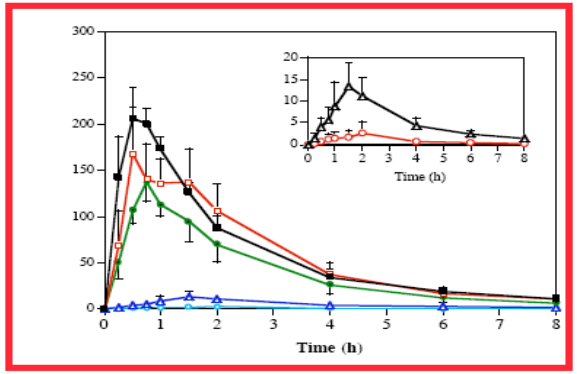


Forms inclusion complexes with drugs

- Steric
- Thermodynamic interactions

Advantages

- Enhanced drug delivery through biological membranes
- Increased stability



Plasma Concentration (±S.E.) Versus Time Profile of Cinnarizine After a 25 mg Dose to Male Beagle Dogs (n=4), SBE4-β-CD, pH 4.5 Solution (❑); HP-β-CD, pH 4.5 Solution (■)); SBE4-β-CD, Capsule (●); pH 4.5 Aqueous Suspension (Δ); Plain Capsule - No SBE4-β-CD (O)

Opportunities

- Improve stability of cyclodextrin in the intestinal environment

From: Javinen et al. *J. Pharm. Sci*., 84, 295-299 (1995)
Del Valle et al., *Process Biochem*,. (2003) Carrier et al. *J. Control. Release.* 123, 78-99. (2007)

Technologies to Improve Solubility

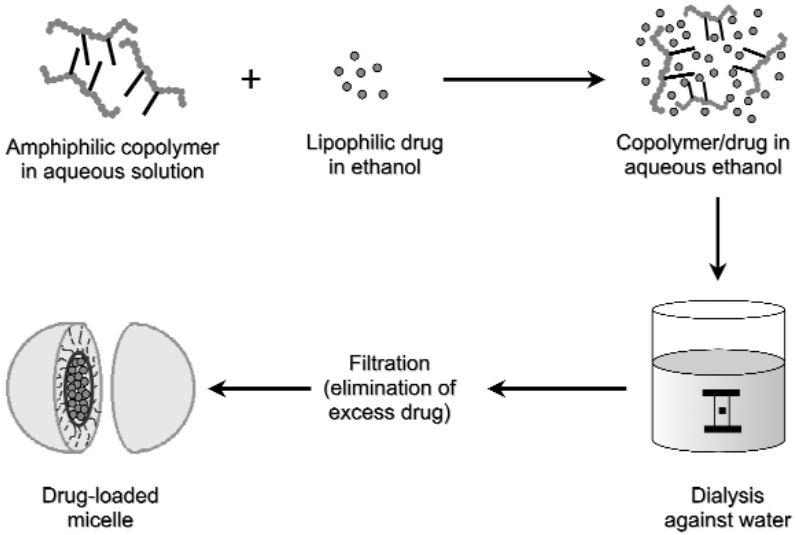
POLYMERIC MICELLES

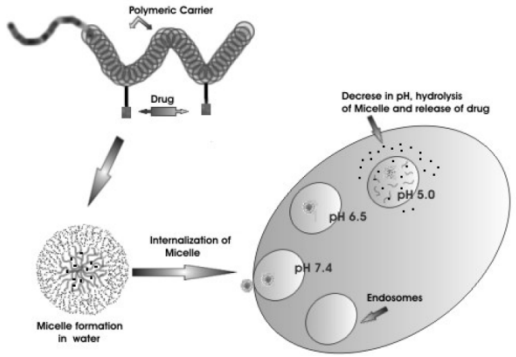
Self-assembling amphiphilic polymer

(i.g. poly(ethylene oxide)-*b*-poly(L-amino acid)

(PEO-*b*-PLAA)) forms micelles (< 100 nm)

- Provides sites for attachment of drugs
- Better kinetic and thermodynamic stability than surfactant based micelles





Advantages

- Stays unrecognized during blood circulations
- Extended circulation time
- Lower toxicity

Opportunities

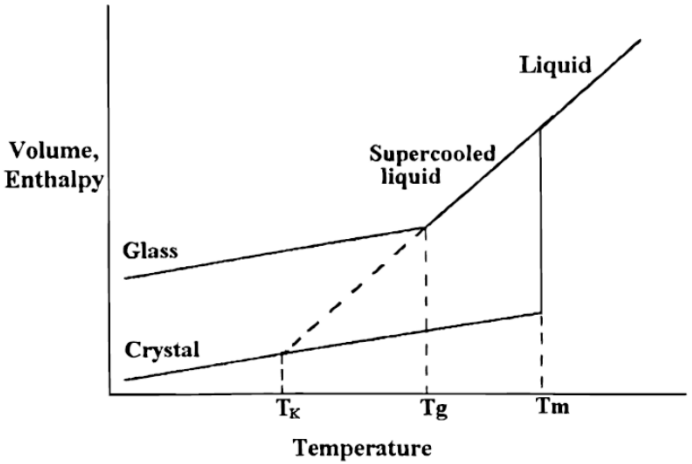
- Loading efficiency

Lavasanifar et al. *Adv. Drug Deliv. Rev.* 54, 169-190 (2002)
Francis, et al. *Pure Appl. Chem*. 76, 1321-1335, (2004).

Technologies to Improve Solubility

AMORPHOUS TECHNOLOGIES

THERMODYNAMIC PROPERTIES



SOLUBILITY ADVANTAGE

ACHIEVING SUPERSATURATION

PARTICLE SIZE REDUCTION

$S = S_\infty e^{\left(\frac{2\gamma M}{rpRT}\right)}$

THERMODYNAMIC CONTROL

$\Delta G = \Delta H - T\Delta S$

STABILIZING SUPERSATURATION

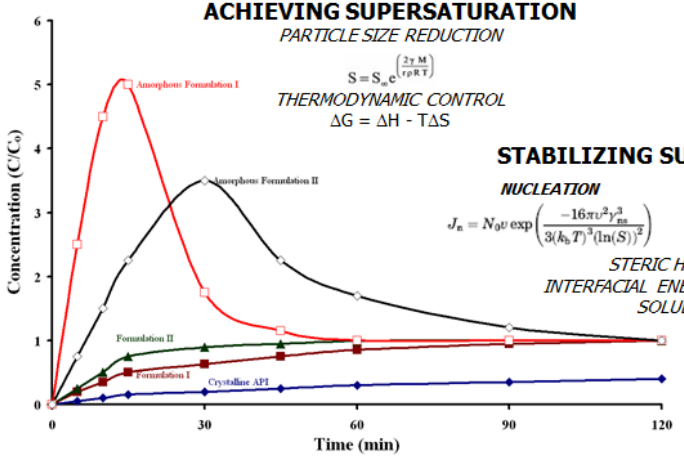
NUCLEATION

$J_n = N_0 \upsilon \exp\left(\frac{-16\pi\upsilon^2\gamma_{ns}^3}{3(k_bT)^3(\ln(S))^2}\right)$

GROWTH

$\frac{dr}{dt} = \frac{D\upsilon N_A}{r + D/k_+}(C - C_{eq})$

STERIC HINDERANCE
INTERFACIAL ENERGY MODIFICATION
SOLUBILIZERS

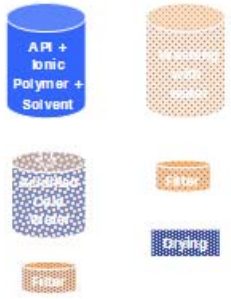


Advantages

- Supports solid dosage form
- Continuous manufacturing
- Potential for greater exposure than other technologies

AMORPHOUS MANUFACTURING

Spray Drying (SDD)
- Solvent evaporation
- Low boiling solvent



Microprecipitation (MBP)
- Solvent/Antisolvent
- Enables high BP solvent

Hot Melt Extrusion (HME)
- Temp. and shear
- Non-solvent

Fluid-bed layering (FBL)
- Drug/polymer layering
- Solvent evaporation
- Low boiling solvent

Opportunities

- Develop predictive tools for dispersions
- New materials to improve exposure and drug loading
- New technologies to improve manufacturing

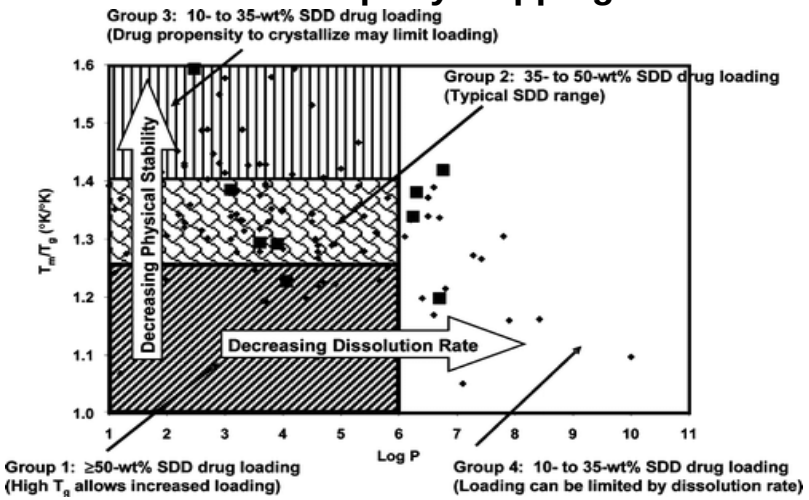
Examples of Commercial Products Using Amorphous API or ASD

Product	Form	Mol.Wt	Tm	Tg	Tm/Tg (C/C)	Tm/Tg (K/K)	Log P	Marketed Name
Zafiralukast	Amo. API	575.7	139	98	1.4	1.1	4.8	Accolate (GSK)
Rosuvastatin Ca	Amo. API	481.5	135	102	1.3	1.1	1.5	Crestor (AZ)
Quniapril HCl	Amo. API	474.9	125	91	1.4	1.1	0.9	Accupril (Pfizer)
Nelfinavir Mes.	Amo. API	663.9	133	105	1.3	1.1	4.1	Viracept (Pfizer)
Itraconazole	ASD	705.6	166	59	2.8	1.3	5.6	Sporanox (Jansen)
Ritonavir	ASD	720.3	123	87	1.4	1.1	4.9	Norvir (Abbott)
Lopinavir	ASD	628.8	125	101	1.2	1.1	~4.3	Kaletra* (Abbott)
Telaprevir	ASD	679.9	246	105	2.3	1.4	3.5	Incivek (Vertex)
Vemurafenib	ASD	489.9	270	109	2.5	1.4	3.8	Zelboraf (Roche)

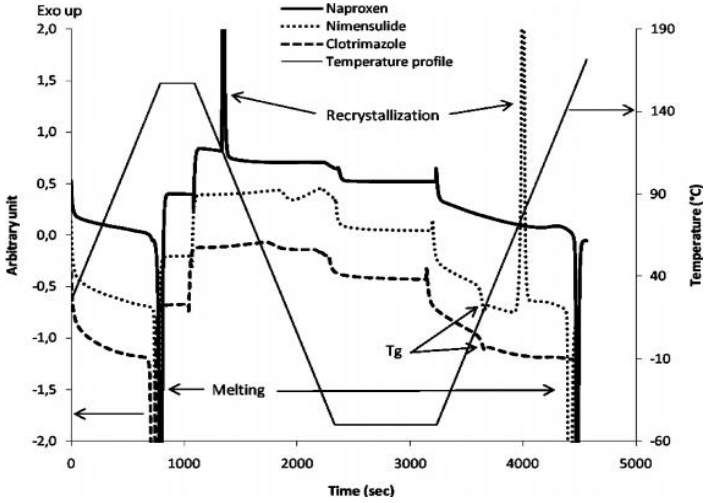
- Pure amorphous API poses much higher risk compared to ASD
- Development of stabilized ASD is preferred
- Successful commercialization of ASDs has been achieved with multiple technologies

Challenges for Predicting Suitability & Stability of Amorphous Dispersions

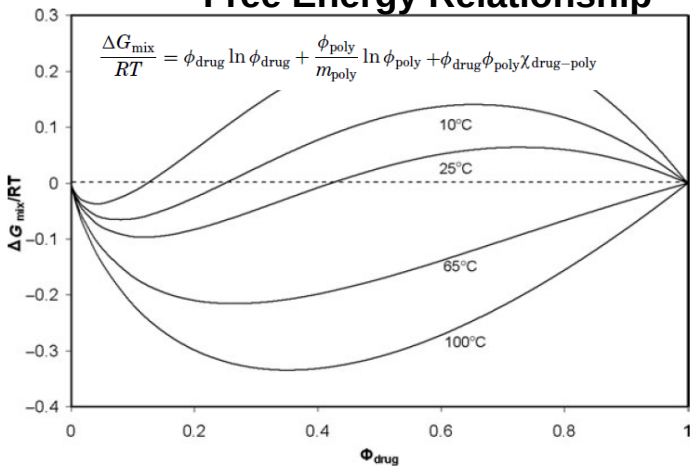
API Property Mapping



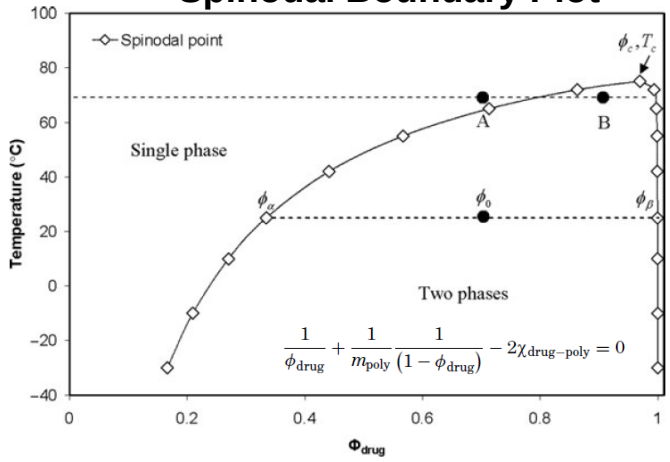
Thermal Characterization



Free Energy Relationship



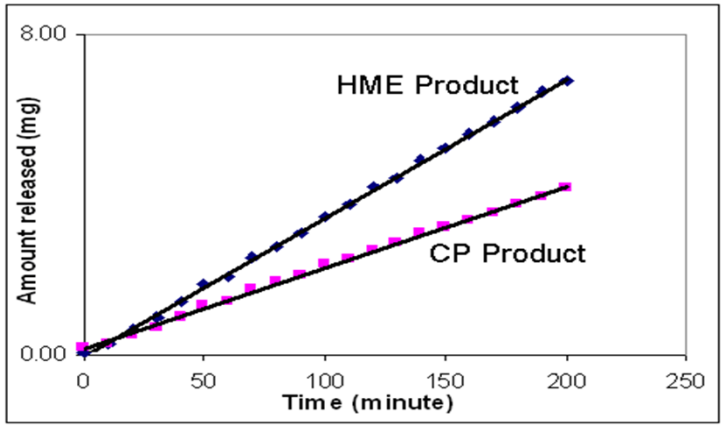
Spinodal Boundary Plot

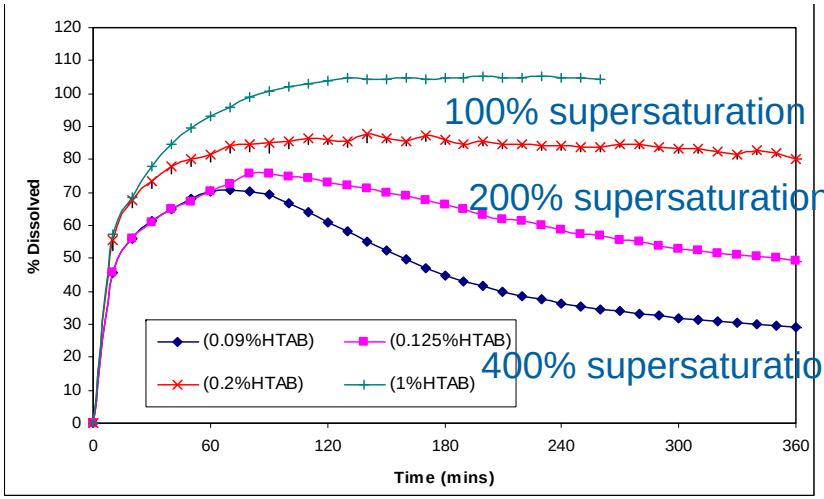


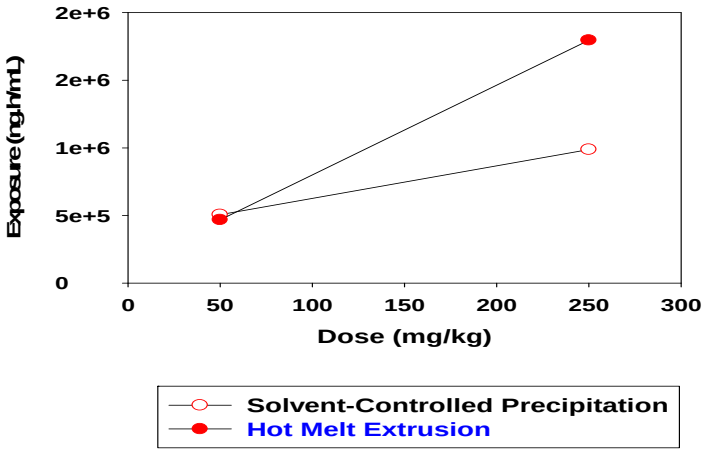
- Heating & Cooling method has an issue of decomposition of the compound with high melting point
- The compound of "easy amorphous" can be categorized into non-crystallizing compounds and has low Tm/Tg ratio
- Even if a compound has low Tm/Tg ratio and categorized as "easy amorphous", the compound can still be difficult to make amorphous

Dissolution Methods and Challenges

- High energy systems prone to crystallize during dissolution
- Crystallization kinetics depend on Temperature, Sink Condition and Media Composition
- Drug may be associated with polymer (free drug vs. bound drug)
- Higher supersaturation generally causes faster precipitation (lower recovery)

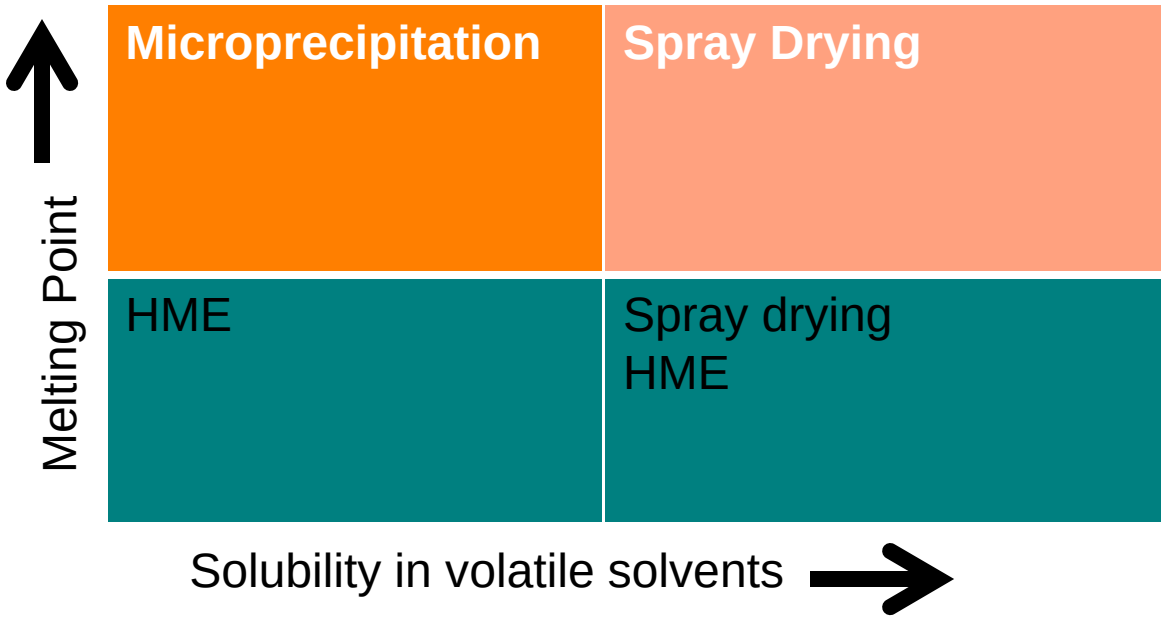






Judicious selection of dissolution condition is critical for " meaningful" interpretation of data

Amorphous Processing Technology Selection Guide



Compounds with melting point < 200°C could be suitable for HME and compounds with solubility > 50 mg/mL in low boiling point volatile solvent are suitable for SD

Pros & Cons of Amorphous Technologies

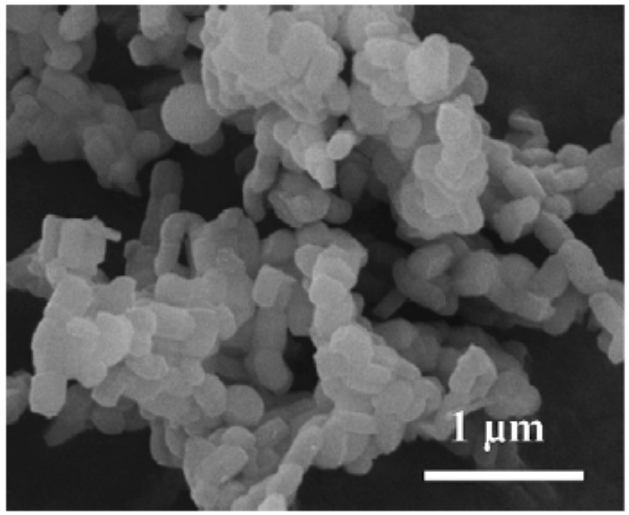
Technology	Pros	Cons
Melt Extrusion	Non-solvent based Short exposure to high temperature Modular design provides flexibility Extrudate density helps improve stability Continuous process Established scale-up and commercial feasibility	Thermal degradation Limited application for high T_m compounds Dissolution (erosion) Reduced compactability
Spray Drying	Rapid removal of solvent Established scale-up and commercial feasibility Processing occurs below Tg Applicable for low boiling point, low toxicity solvents (i.e. ethanol, acetone)	Requires adequate solubility in volatile solvent Residual solvent levels must be tested Phase separation may occur based on solubilities Low bulk density requires densification
Microprecipitation	Useful for compounds not amenable to HME or SD Provides high degree of super-saturation (ionic interaction) Modulated plasma profile due to enteric polymer Semi-continuous processing	Require ionic polymers Not suitable for weakly basic drugs Solvent extraction may require multiple washings Downstream processing required Scale-up challenges exist

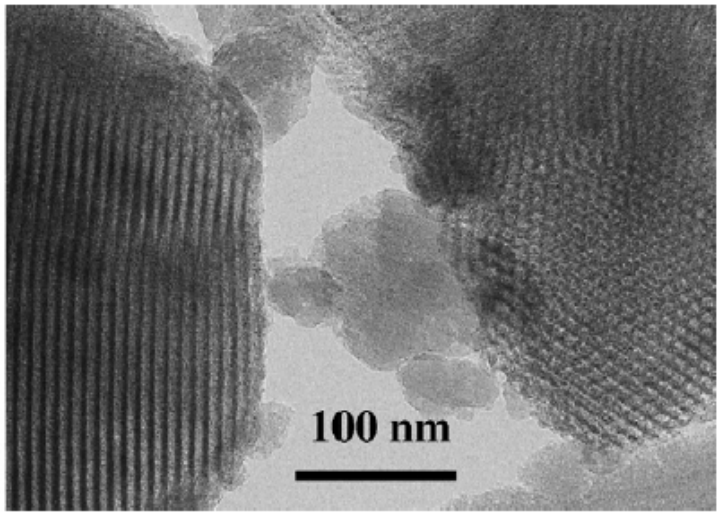
t is important to select the right process for the molecule, not force a process onto the compound

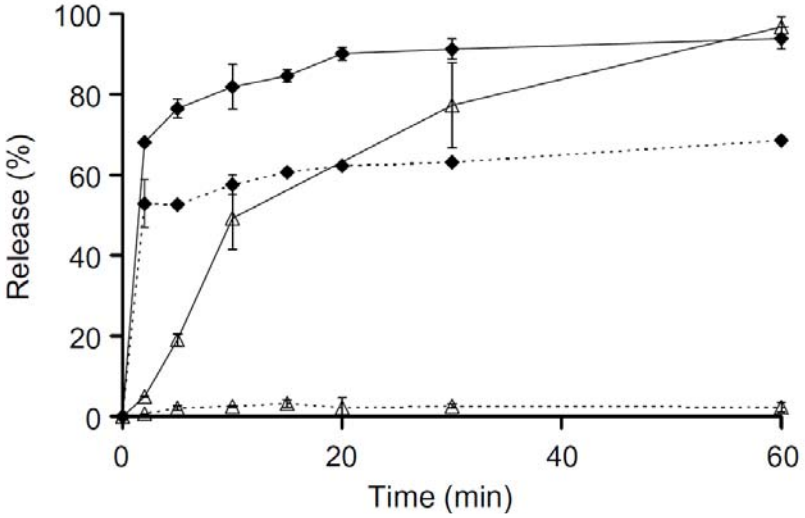
If necessary consider other novel technologies (i.e. mesoporous silica, KinetiSol)

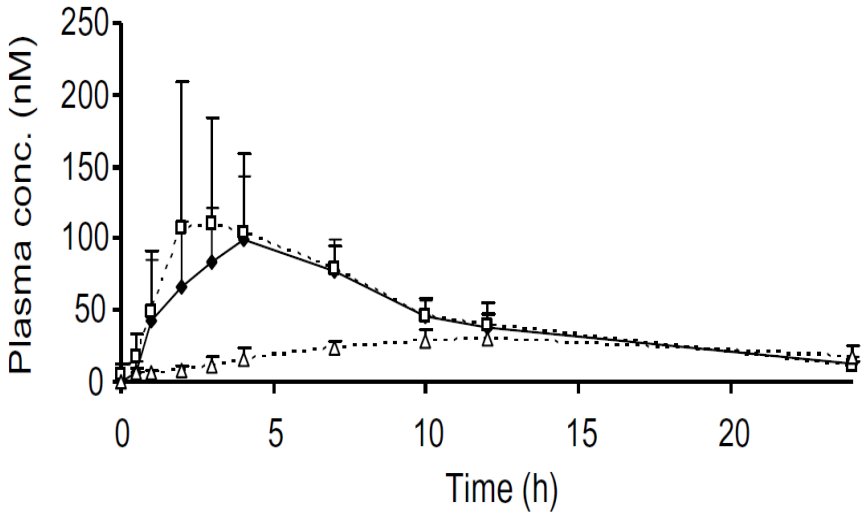
Opportunities for New Technologies

Case Study with Mesoporous Silica









- Mesoporous silica can improve dissolution rates and exposure of poorly soluble compounds

Mellaerts et al., EJPB. 69 2008, p. 223

Opportunities for New Technologies

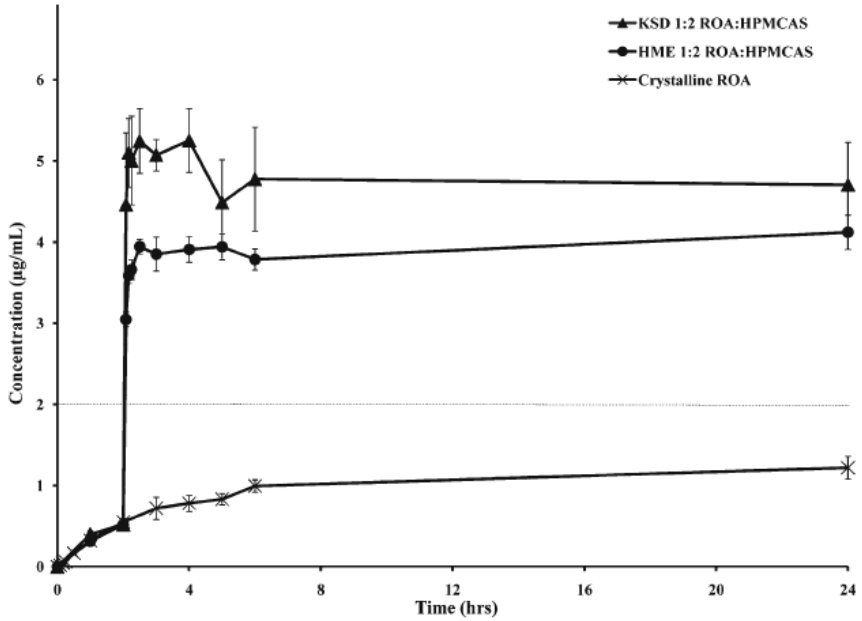
Case Study with KinetiSol

Melt Extrusion

Polymer	Particle size	Temperature (°C)	Screw speed (rpm)	Recirculation time (min)	Recovery (%)	Impurities (%)
Eudragit® L100-55	Unmicronized	140	300	2	22.7±0.5	55.9
Eudragit® L100-55	Micronized	140	300	0	69.1±0.5	17.3
HPMCAS	Unmicronized	170	300	2	70.9±0.3	10.2
HPMCAS	Micronized	170	300	0	78.4±0.1	8.9

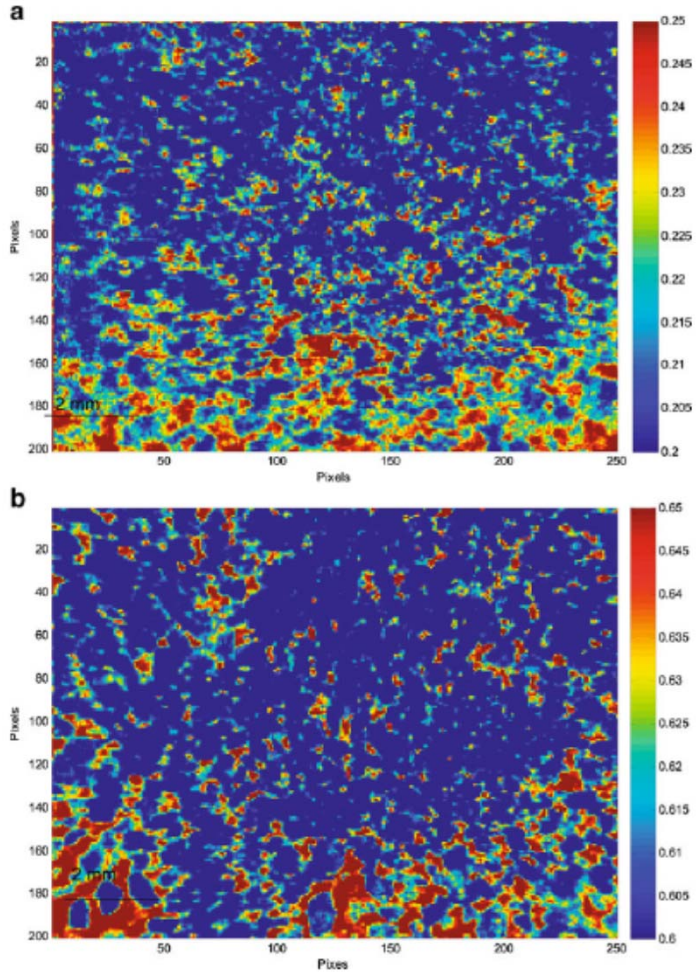
KinetiSol

Polymer	Particle size	Speed (rpm)	Temp. (°C)	Recovery (%)	Impurities (%)
Eudragit® L100-55	Unmicronized	1,450	100	70.9±0.8	12.9
HPMCAS	Unmicronized	2,400	112	99.4±1.2	1.6



Melt Extrusion

KinetiSol®



- Application of new technologies offers the possibility to significantly expand manufacturing window

Hughey et al., AAPS Pharm. Sci. Tech. 11 (2) June 2010

Future Directions

TODAY		TOMORROW
Many industrial pipelines have solubility limitations	ACTIVES	Chemistry of compounds becomes highly engineered to reduce solubility liabilities
Limited number of approved excipients for solubility enhancement	EXCIPIENTS	Pharma companies and excipient manufacturers work jointly to develop excipients with unique advantages
Simple models and descriptors predict stability and performance of advanced systems	MODELING	*In silico* methods advance to provide computer aided design and a priori prediction
Batch manufacturing processes with a limited portfolio of techniques to prepare advanced systems	MANUFACTURING	Continuous manufacturing and new technologies provide advantages to poorly soluble compounds

Summary Remarks

- Even today, poorly soluble compounds present major development challenges that may limit or even prevent a life saving medication from reaching the market
    - *Drives substantial investments in new technologies and products*

- Limitations of materials and technologies present unique opportunities for partnerships and collaborations to develop these areas
    - *Will generate new models for conducting business and developing therapies*

- True innovation allows a molecule to become a medicine

Acknowledgements

We Innovate Healthcare

- Dr. Dharmendra Singhal
  Hoffmann-La Roche, Inc.
- Dr. Harpreet Sandhu
  Hoffmann-La Roche, Inc.
- Dr. Waseem Malick
  Hoffmann-La Roche, Inc.
- Dr. James DiNunzio
  Hoffmann-La Roche, Inc.
- Dr. Raman Iyer
  Hoffmann-La Roche, Inc.
- Ms. Kaoru Tominaga
  Hoffmann-La Roche, Inc.

Questions