TRANSFORM

pharmaceuticals

Enhancing Solid Dosage Bioavailability with Size, Crystal Form, and Formulation

Second U.S.-Korea Nano Forum

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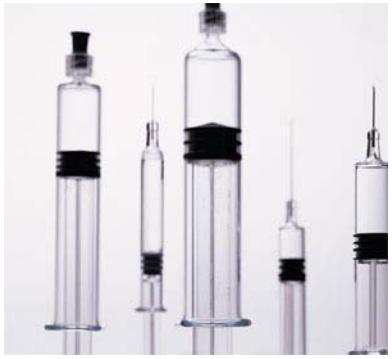
Drug Delivery Forms

parenteral



pulmonary

transdermal

oral

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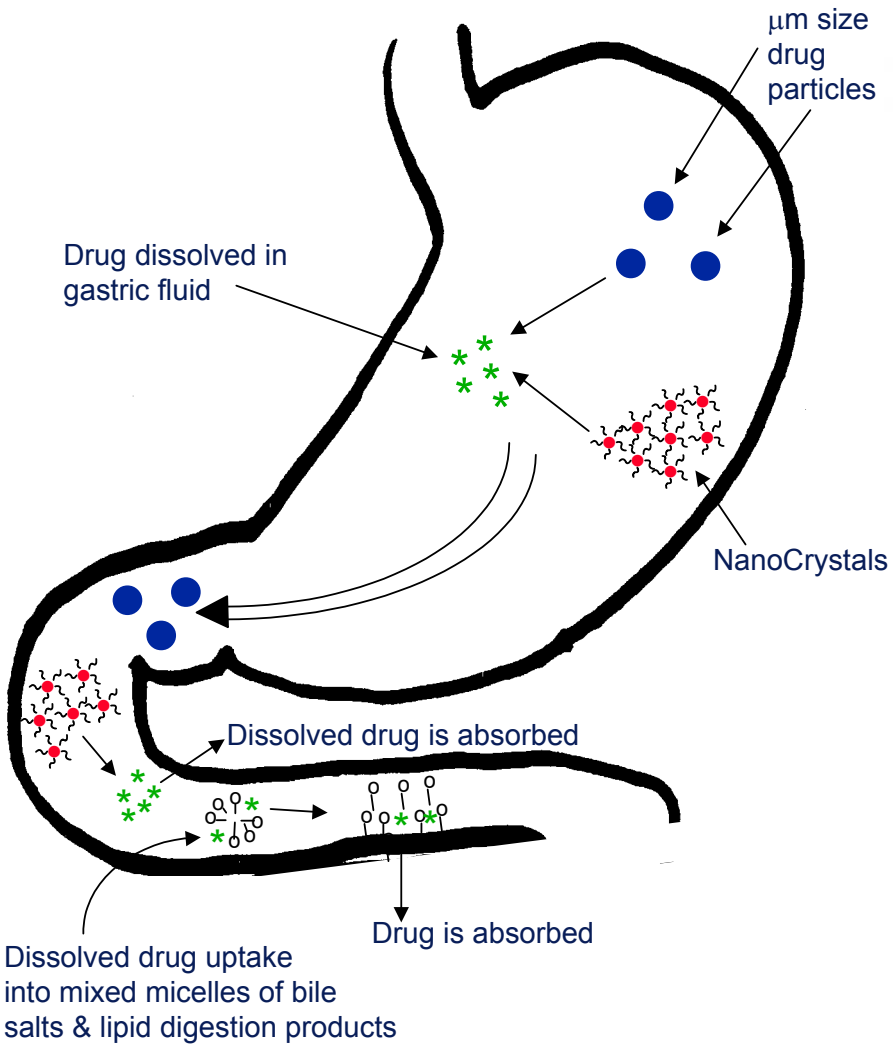
The Impact of Size on Efficacy



- Most drugs in solid form fall in the range of 10-500 microns
- Poor aqueous solubility may limit oral bioavailability or ability to deliver as a parenteral formulation
- Absorption may depend on rate of dissolution, which in turn is controlled by particle size, crystalline form, and aqueous environment

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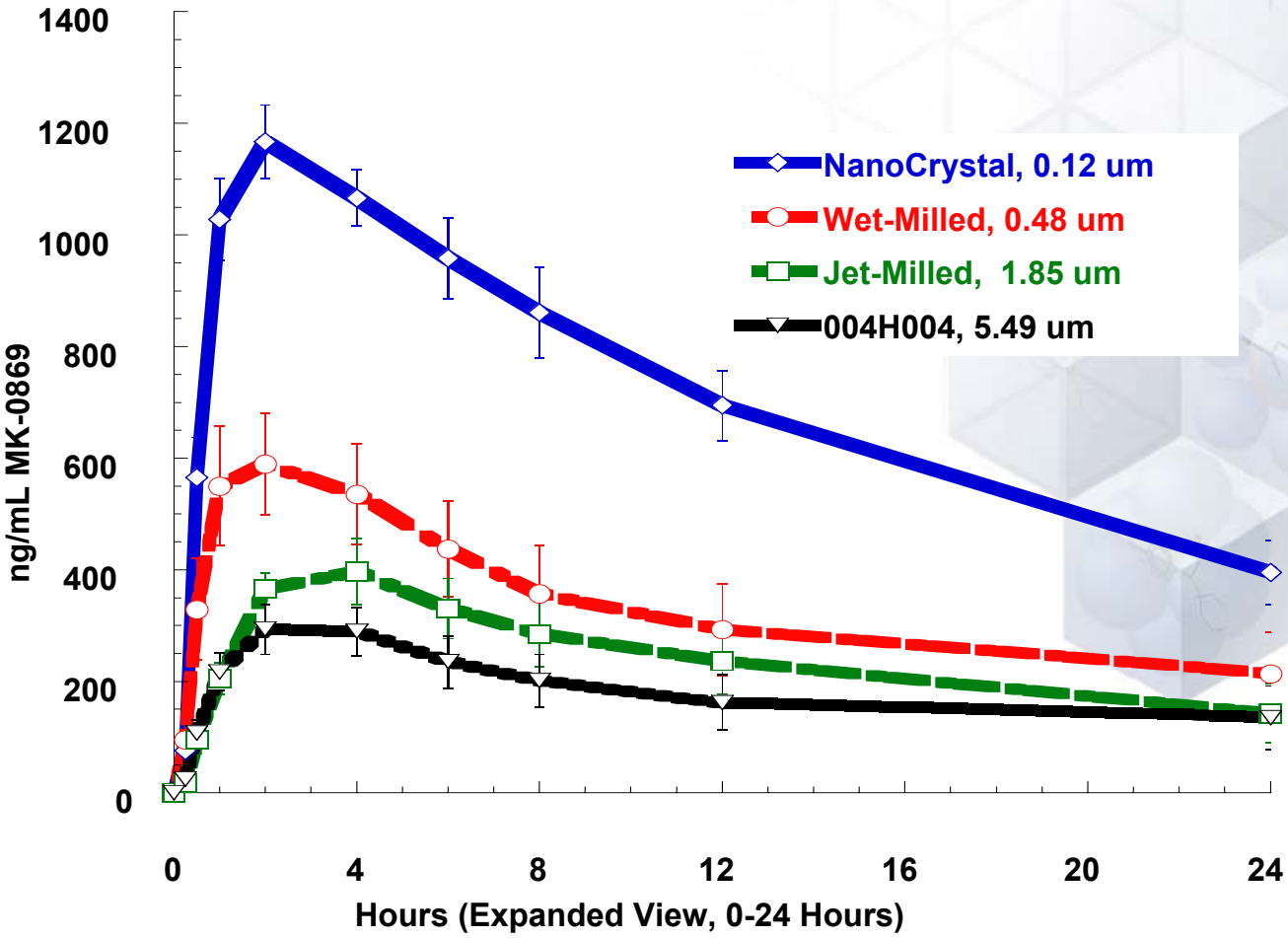
MK-869 Particle Size Effects in Dogs



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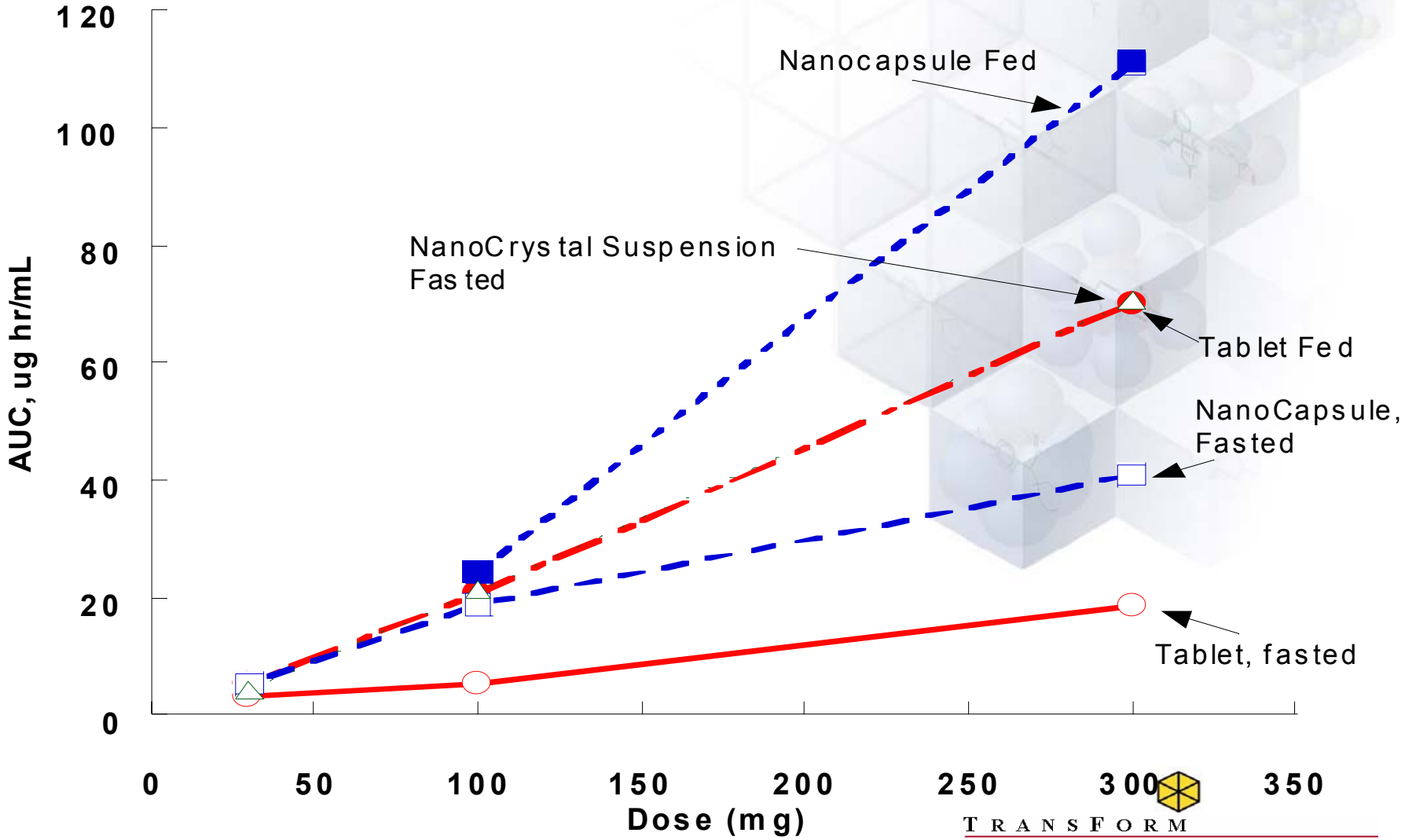
Total Exposure (AUC) in Humans



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Improving Oral Bioavailability

- **Particle Size Reduction**
  - Jet-milling, high energy ball milling
  - Spray drying
  - Super critical fluid extraction
  - High supersaturation crystallization
- **Solid Form Thermodynamics**
  - Amorphous
  - Salts
  - Higher Free Energy Polymorphs
- **Improve Solubility**

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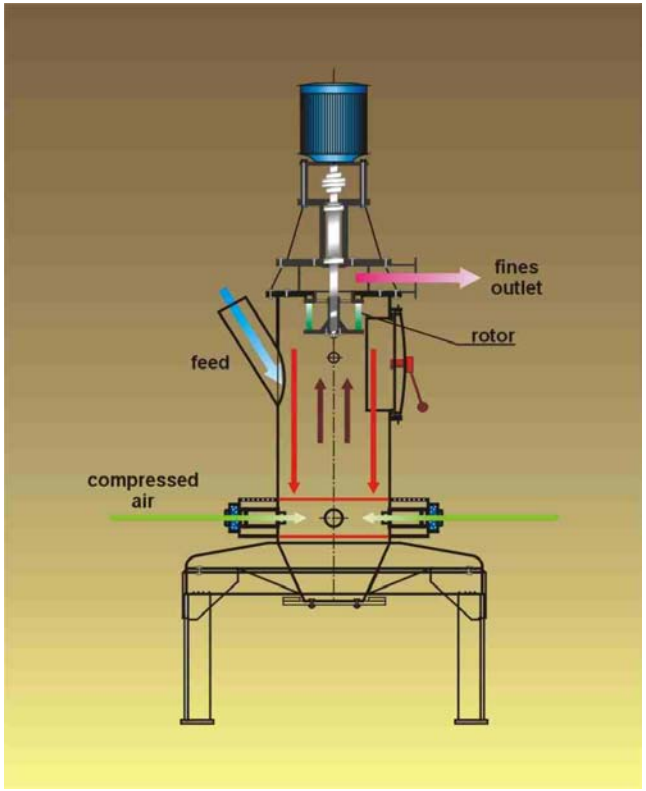
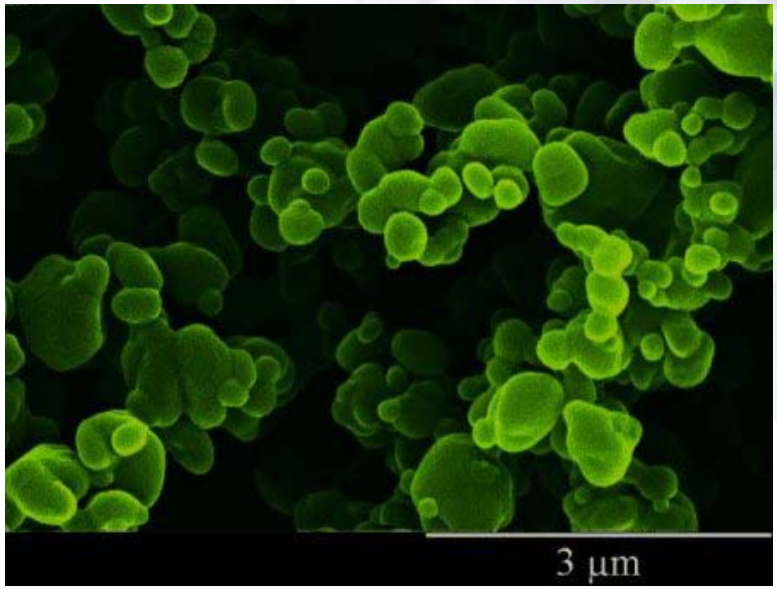
Jet Milling



www.comex-group.com

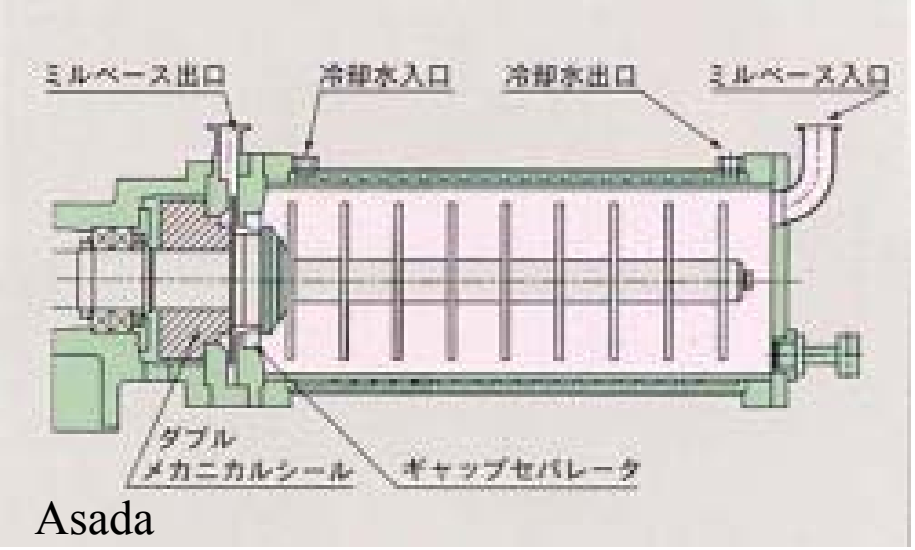
- Relies on particle-particle interaction
- Narrow size distribution
- Minimal heating
- Mean size 1-10 microns



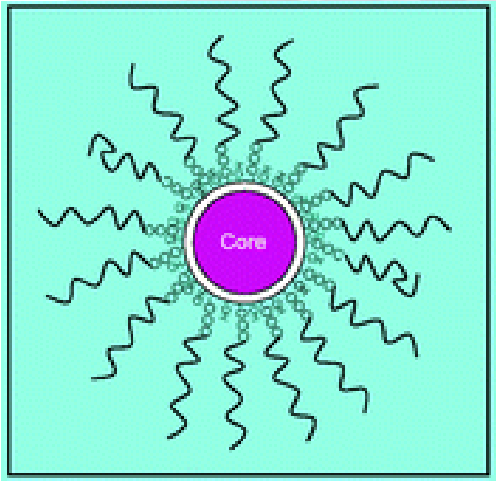
Beclomethasone Dipropionate (after micronization), www.hovione.com

High Energy Ball Milling

- Mean size range from 100 o 1000 nm
- Particles stabilized via adsorbed GRAS excipients
- (Nanosystems' technology)
- Enhances dissolution rate of oral drugs
- Enables parenteral forms of poorly soluble drugs



Asada



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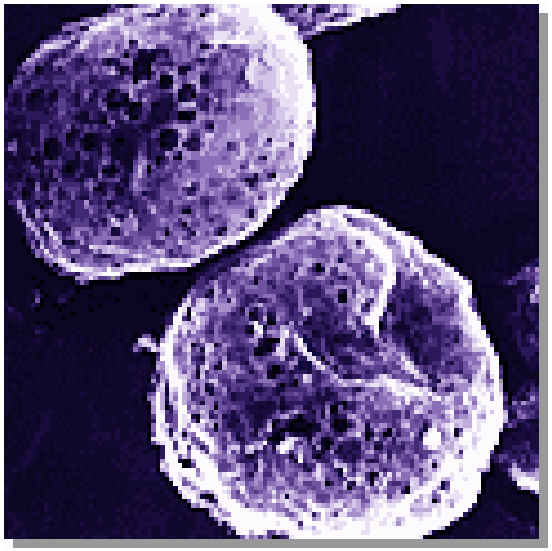
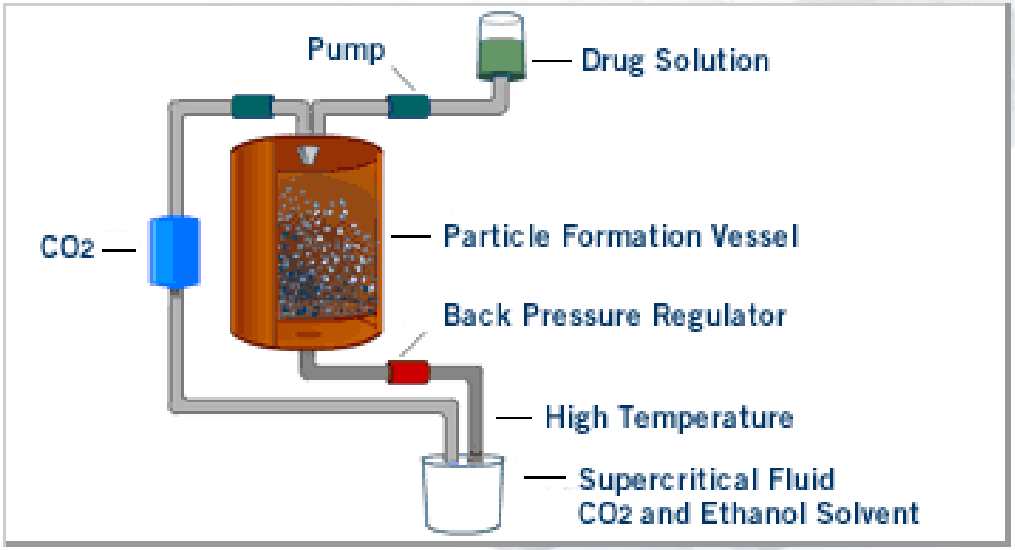
Other Methods of Size Reduction



Spray Drying



Supercritical Fluid Extraction

- PSD < 1,000 nm
- Applicable for pulmonary, oral, or parenteral delivery.
- Generally amorphous; may agglomerate or pick up moisture; less chemically stable

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Particle Size Reduction Summary

- **Particle size reduction generally successful in improving oral, pulmonary, and parenteral bioavailability**
- **However, problems exist…**
  - Downstream processing, material handling
  - Chemical and physical stability
- **Manufacturing processes for crystalline particles < 100 nm really don't yet exist, but could present an opportunity for improving drug delivery efficacy**

Improving Oral Bioavailability

- **Particle Size Reduction**
  - Jet-milling, high energy ball milling
  - Spray drying
  - Super critical fluid extraction
  - High supersaturation crystallization
- **Solid Form Thermodynamics**
  - Amorphous
  - Salts
  - Higher Free Energy Polymorphs
- **Improve Short Term Solubility**

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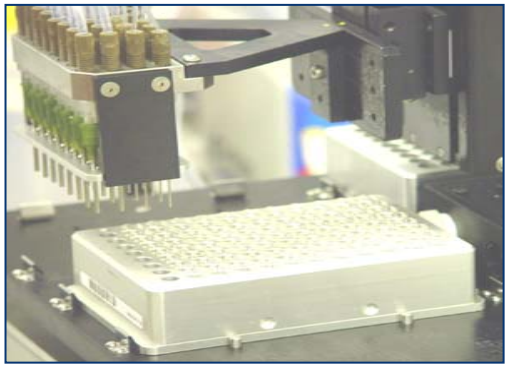
HTE in Pharmaceutical Formulations

TransForm Pharmaceuticals Platforms

Solid Oral Forms

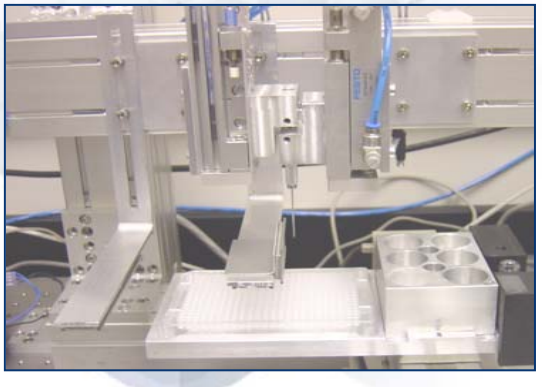
CrystalMax™

Transdermal



DerMax™

Liquid/Injectable Formulations



FAST™/SFinX™

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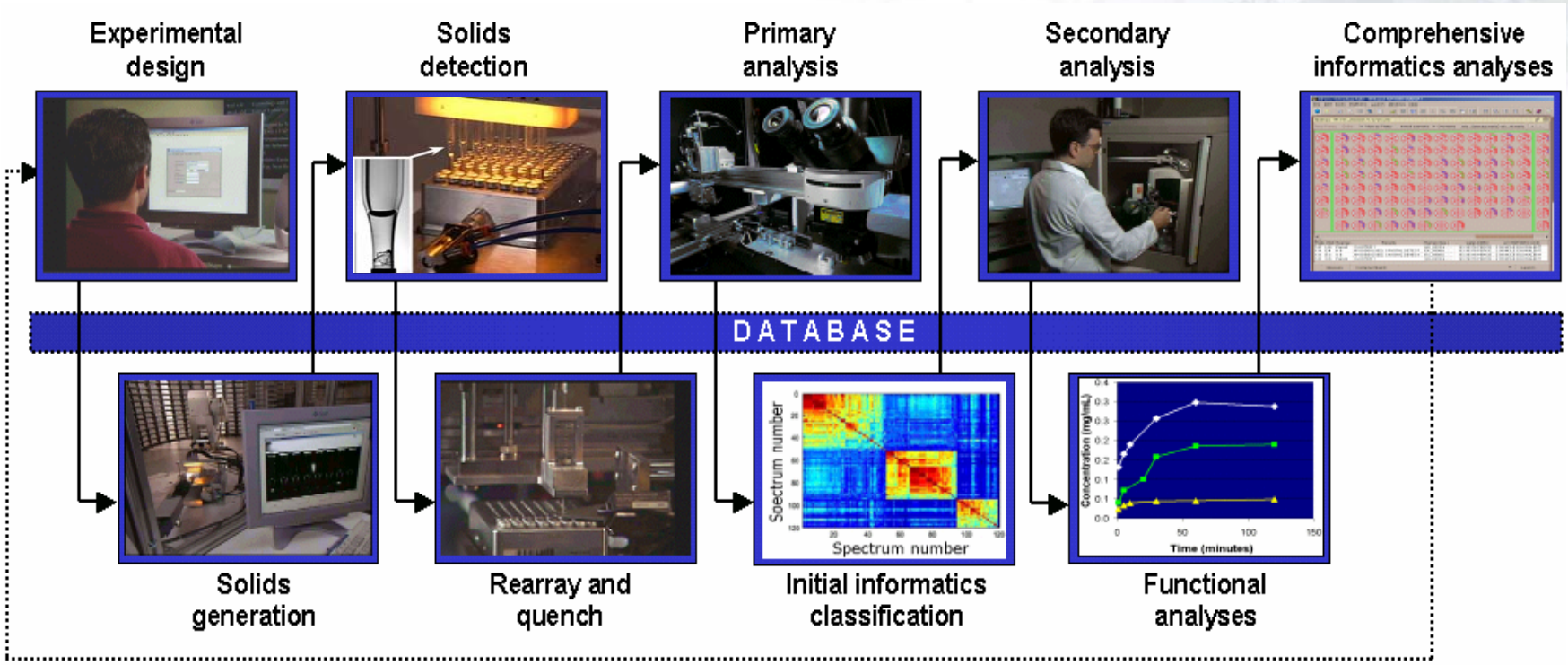
CrystalMax™ Process Flow



- **Parallel experimentation: > 10,000 crystallizations/week**
- **Typically 0.25 - 2 mg of compound per test**
- **Cooling, evaporative, melt, anti-solvent, and other modes**

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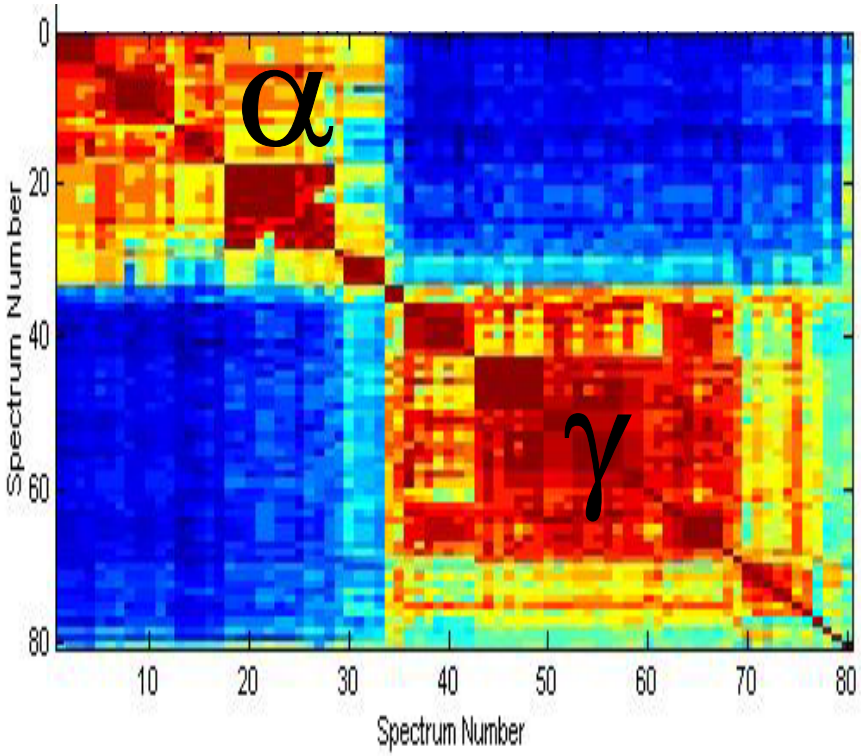
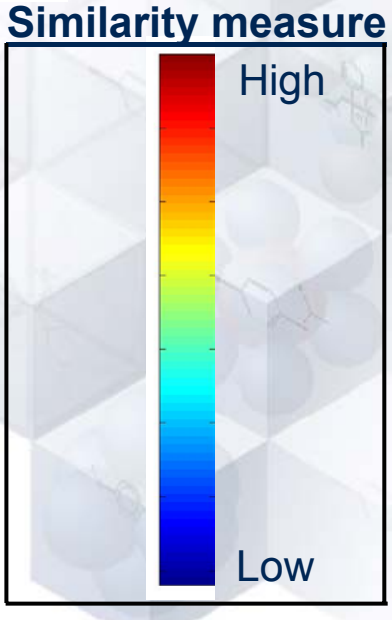
Clustering of Glycine Polymorph Raman Spectra

- Each dot = value of ‘similarity’ for a pair of spectra





- Rapid, automated crystal form classification
- Method can be used with other types of data

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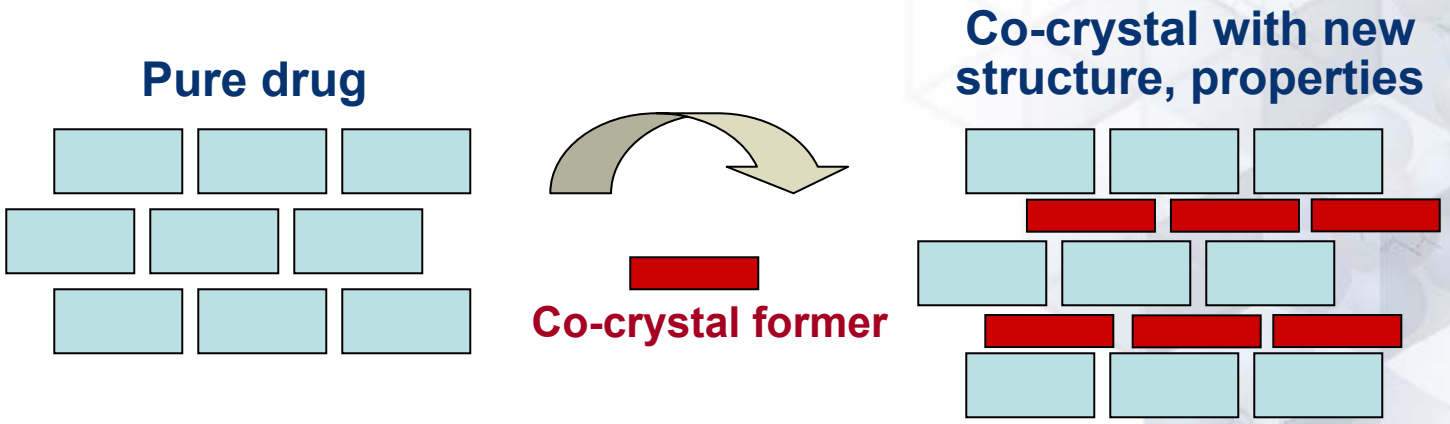
Pharmaceutical Co-Crystals

A stable higher energy form



Can impact:

- Solubility
- Dissolution rate
- Hygroscopicity
- Stability
- Habit
- Processability

- **Many of the potential benefits of a salt, without the limitations**
  - > 30% of compounds lack “saltable” functional groups
- **Broad potential applicability**

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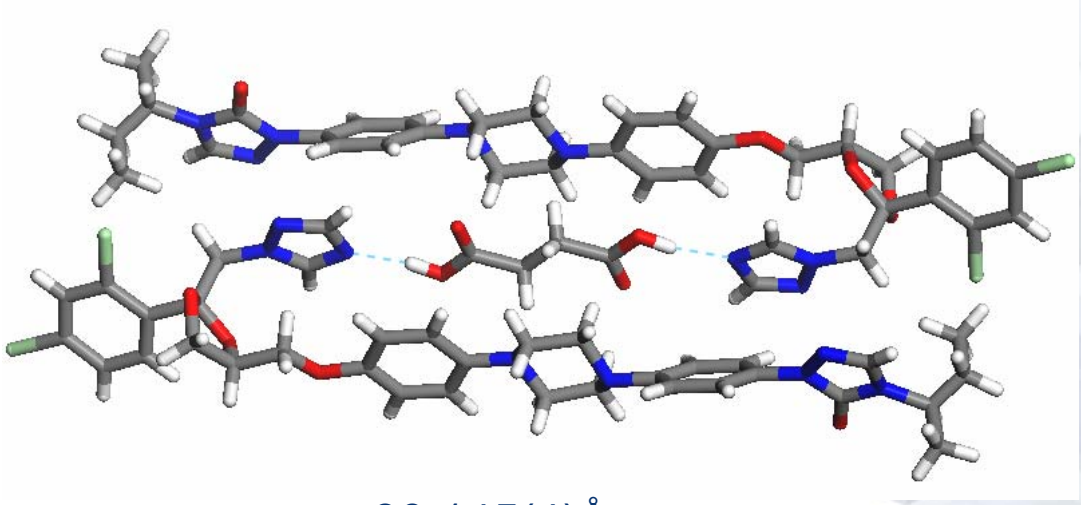
Itraconazole: Succinic Acid Co-Crystal



$P2_1/c$

a=30.145(4)Å
b=5.7435(7)Å
c=21.580(3)Å

β=105.133(2)°

- **The acid groups of the co-crystal former do not interact with the strongest base on itraconazole**
- **Geometry of co-crystal former drives crystal formation**

Remenar, J. F. et al. *J. Am. Chem. Soc.* 125, 8456 (2003)

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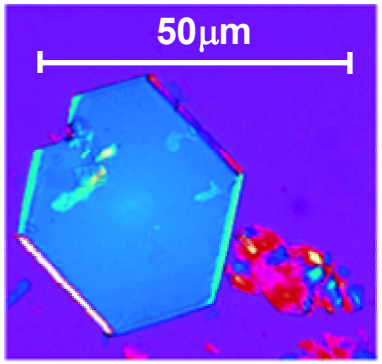
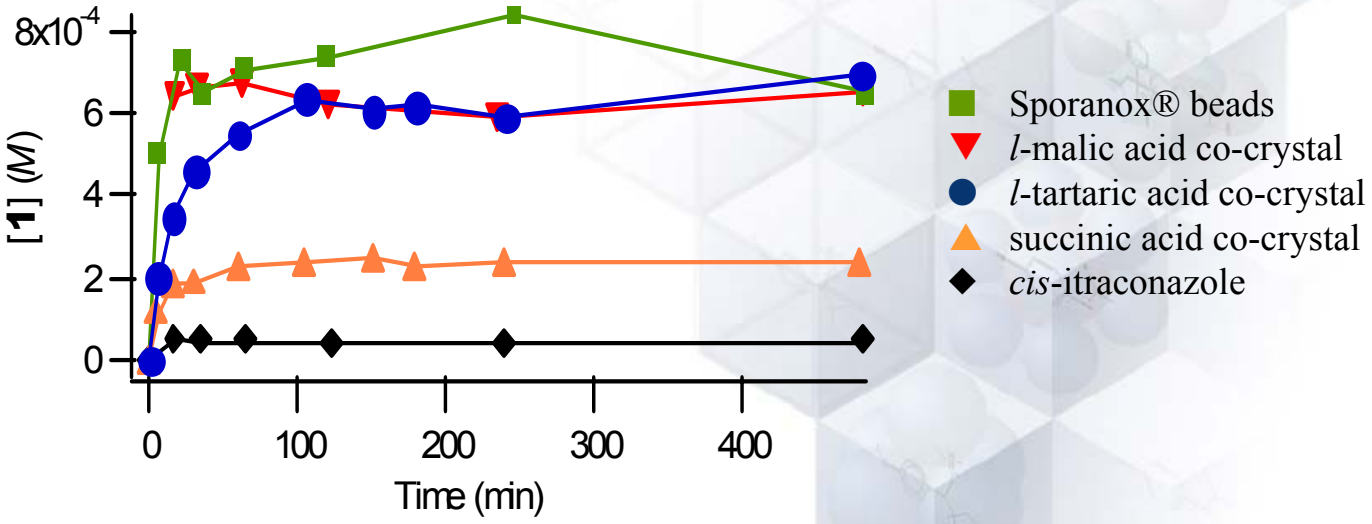
Improved Dissolution of Itraconazole





- Co-crystals of itraconazole showed improved dissolution compared to the free base
- Enables alternative formulation options

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New Crystal Form of Celecoxib

Issues

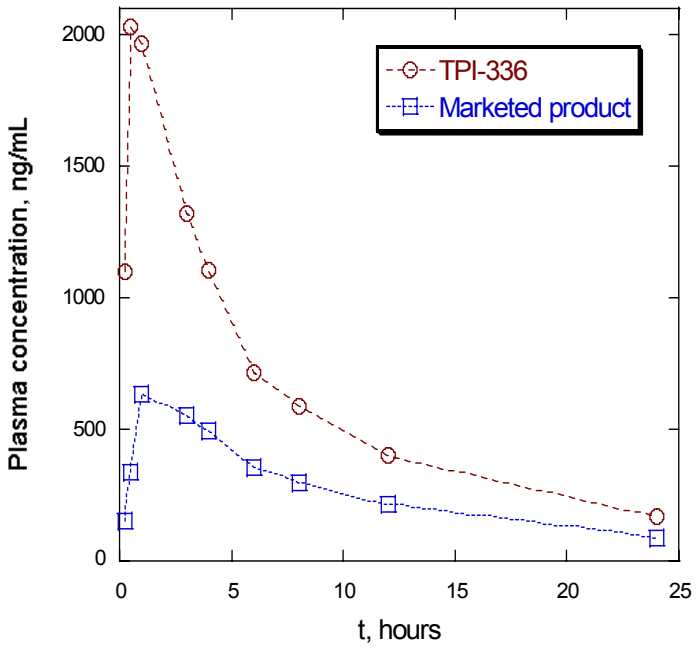
40% bioavailable
Slow onset
Non-linear PK

Approach

Novel crystal forms enable new formulation technique

Impact

~95% bioavailable
Faster onset
Linear PK



Potential implication

Lower dose
New indication
7+ years add'l patent life

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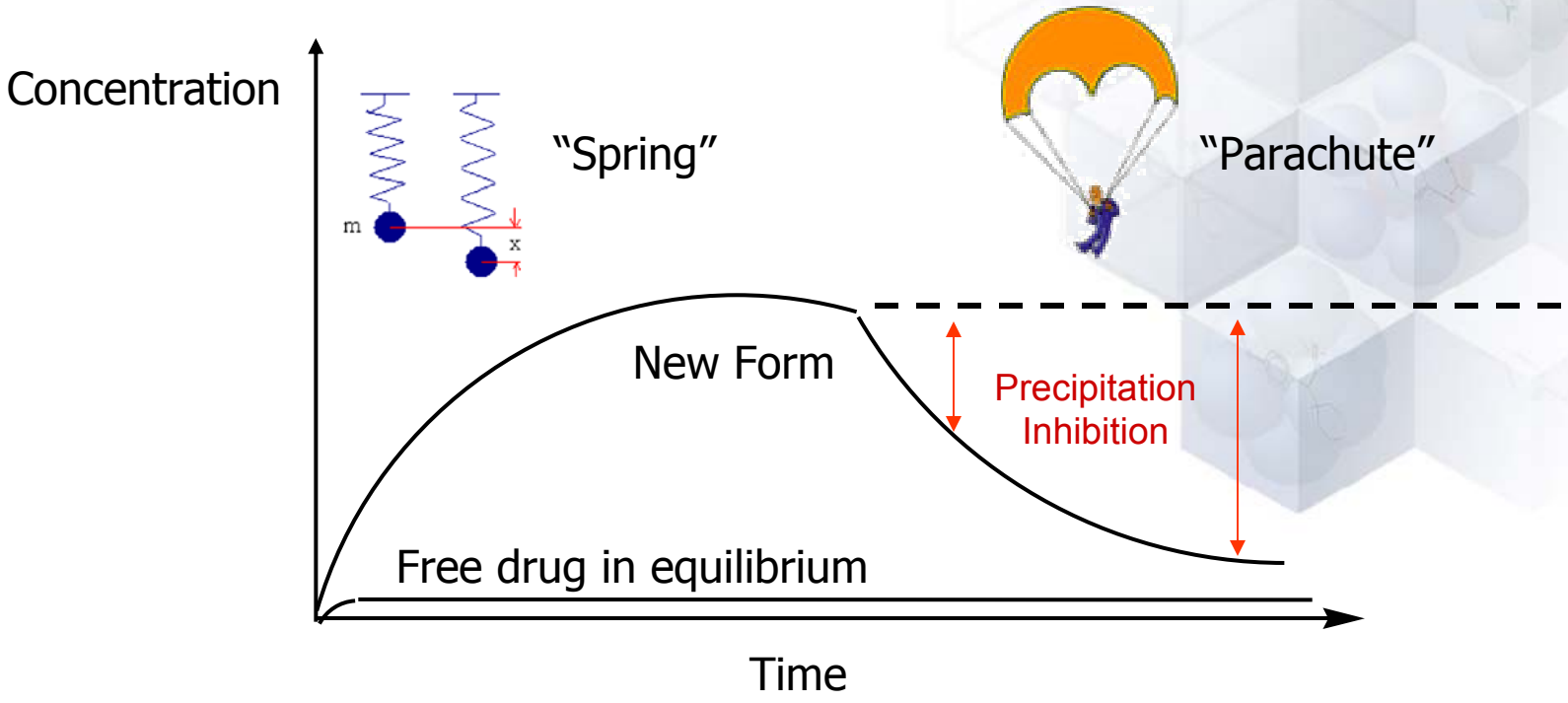
Precipitation Inhibition: Spring and Parachute

Problem: API with poor solubility & low bioavailability

Solution: "Spring" and "parachute" concept



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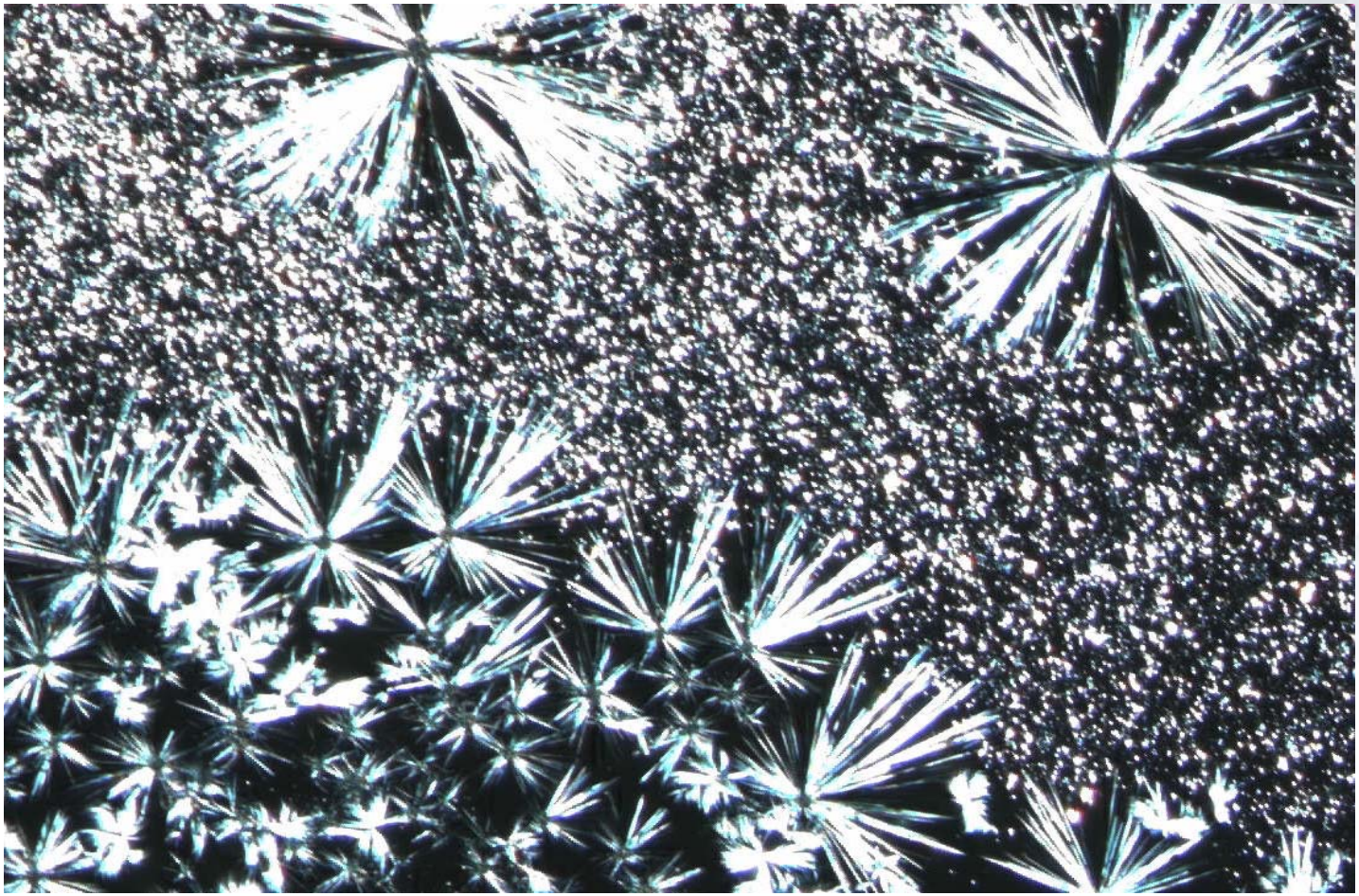
Precipitation: Celecoxib salt in water



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Poor Solubility Problem

Challenge: Poorly soluble drug crashes out instantly upon dilution, limiting bioavailability

- Compound Properties
  - **Crystalline**
  - **Very low aqueous solubility**
  - **Unstable salts (pK_a compound 0.9, 14.6)**

Room Temperature Solubility

Vehicle	Solubility (mg/ml)
Water, pH 3-7	0.000060
PEG 400	71
Ethanol	28
triglycerides	< 25

Approach:

HT formulation studies to identify excipient combinations that delay precipitation or accelerate resolubilization in SGF

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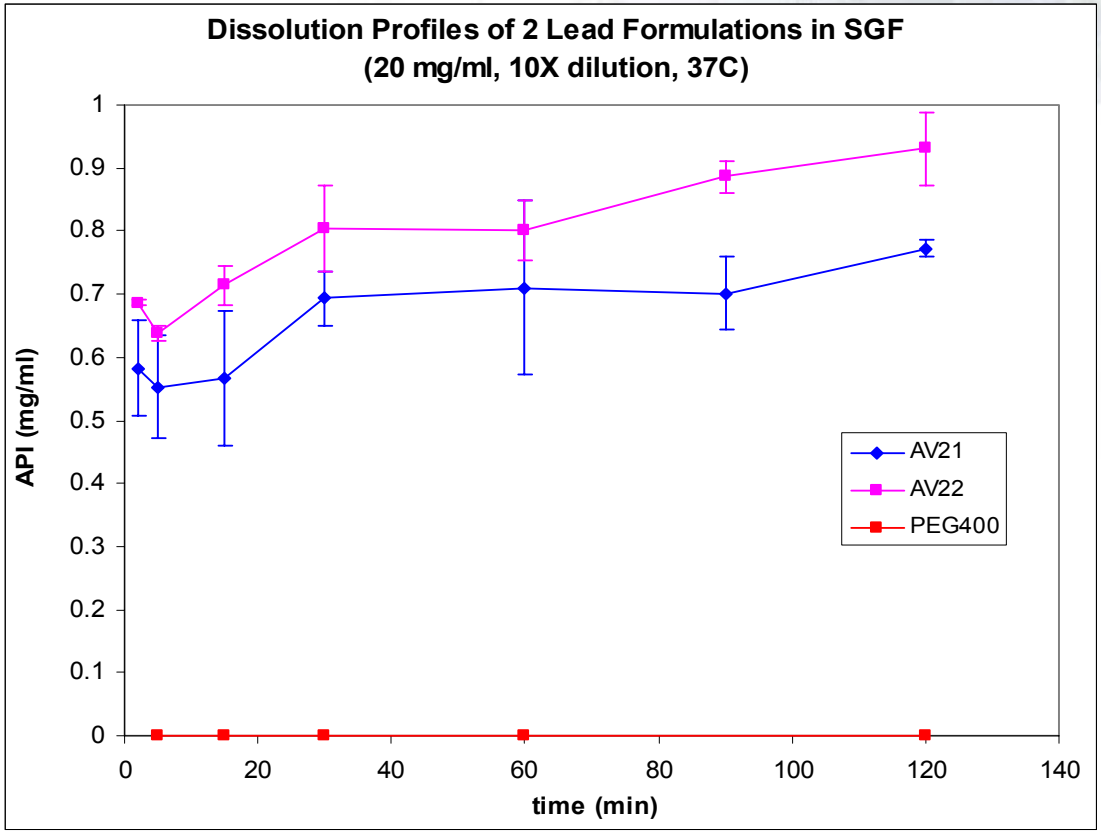
Precipitation Inhibition Solution

- Compound used: <5 g
- Project duration: 8 weeks
- >4,500 experiments
  - 2 HT studies
  - Optimization



- Solubility improvement vs. diluted PEG400: > 19,000X at 2 hours
- Enabled > 50% improvement in bioavailability

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Parenteral Reformulation: Propofol

- **Very effective I.V. anesthetic**
- **Formulated as a lipid emulsion**
  - Complex / expensive manufacturing process
  - Thermodynamically metastable
  - Difficult to handle aseptically
  - Risk of contamination
- **Opportunity for improved product**

Marketed product

TPI-213M

- **Lipid-free, preserved formulation**
- **Thermodynamically stable pluronic based colloidal self assembly**
- **Equivalent PK to Diprivan**
- **Enables multi-dose vials**

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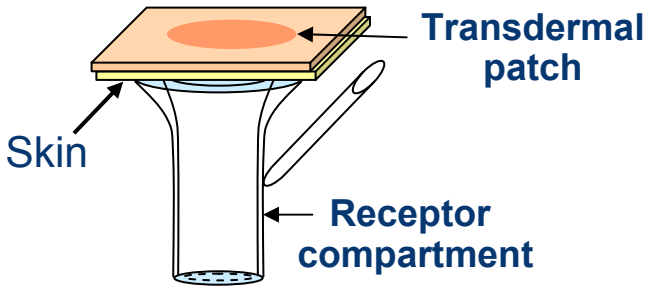
Enabling Transdermal Technology

ALZA in 2002

- Limited screening capacity
- Few transdermal candidates
- Slow formulation development

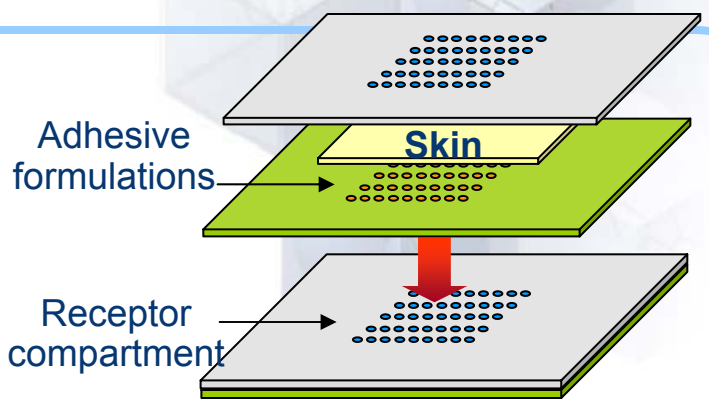
TransForm + ALZA in 2004

- 100x conventional capabilities
- Improved/enabled transdermal products with broad IP



Franz Diffusion Cell

1 – 2 experiments / in^2 of skin



TransForm Permeation Cell Array

25 – 100 experiments / in^2 of skin

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Summary

- Form, size, and environment impact the rate and extent of drug bioavailability
- Manufacturing processes for creating crystalline pharmaceuticals actives < 100 nm do not exist, yet may represent the next tool to improve drug delivery
- High throughput experimental methods present new opportunities to enable effective but poor performing molecules with new crystalline forms and formulations