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

Second U.S.-Korea Nano Forum

Tony Meehan, Ph.D.
Director, Pharmaceutical Development
February 17, 2005
Drug Delivery Forms

parenteral

oral

pulmonary

transdermal
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
MK-869 Particle Size Effects in Dogs

Hours (Expanded View, 0-24 Hours)

ng/mL MK-0869

- NanoCrystal, 0.12 um
- Wet-Milled, 0.48 um
- Jet-Milled, 1.85 um
- 004H004, 5.49 um
Total Exposure (AUC) in Humans

AUC, pg hr/mL vs Dose (mg)

- Nanocapsule, Fed
- NanoCrystal Suspension, Fasted
- NanoCapsule, Fasted
- Tablet, Fasted
- Tablet, Fed

Dose (mg) vs AUC, pg hr/mL

0 50 100 150 200 250 300 350
0 20 40 60 80 100 120

Transform Pharmaceuticals
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**
Jet Milling

- 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 to 1000 nm
- Particles stabilized via adsorbed GRAS excipients
- (Nanosystems’ technology)
- Enhances dissolution rate of oral drugs
- Enables parenteral forms of poorly soluble drugs

Asada
Other Methods of Size Reduction

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

Supercritical Fluid Extraction
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**
HTE in Pharmaceutical Formulations

TransForm Pharmaceuticals Platforms

Solid Oral Forms  Transdermal  Liquid/Injectable Formulations

CrystalMax™  DerMax™  FAST™/SFinX™
- Parallel experimentation: > 10,000 crystallizations/week
- Typically 0.25 - 2 mg of compound per test
- Cooling, evaporative, melt, anti-solvent, and other modes
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
Pharmaceutical Co-Crystals

A stable higher energy form

Can impact:
- Solubility
- Dissolution rate
- Hygroscopicity
- Stability
- Habit
- Processability

Co-crystal with new structure, properties

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

Broad potential applicability
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

Improved Dissolution of Itraconazole

- Co-crystals of itraconazole showed improved dissolution compared to the free base
- Enables alternative formulation options
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
**Precipitation Inhibition: Spring and Parachute**

**Problem:** API with poor solubility & low bioavailability

**Solution:** “Spring” and “parachute” concept

Diagram:
- Concentration axis
- Time axis
- New Form
- Free drug in equilibrium
- “Spring” and “Parachute” concepts
- Precipitation Inhibition
Precipitation: Celecoxib salt in water
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)

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

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

Marketed product TPI-213M

Transform Pharmaceuticals
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

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**Franz Diffusion Cell**
1 – 2 experiments / in² of skin

**TransForm Permeation Cell Array**
25 – 100 experiments / in² of skin
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