Nanoparticle Technology: Leveraging Rapid Dissolution to Improve Performance of Poorly Water-Soluble Drugs

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What are Engineered Nanoparticles?

Nanoscale particles of API:

- characterized by an extremely high surface-area to mass ratio and stabilized against agglomeration using surface modifiers
- not naturally occurring; prepared by:
  - molecular deposition/complexation ("bottom up")
  - attrition of larger non-nanoscale materials ("top down")
- range in size from ca. 80 to 1000 nm for many pharmaceutical applications
Schematic of an Aqueous Nanoparticle Dispersion

- drug particle
- primary stabilizer
- secondary stabilizer (optional)
- aqueous phase
- adsorbed stabilizer

80 - 1000 nm
Rationale for Engineered Nanoparticles in Drug Delivery

\[ \frac{dC}{dt} = \frac{DS}{Vh} (C_s - C) \]  \hspace{1cm} (1)

\[ \frac{dC}{dt} = \frac{DS}{Vh} (C_s) \]  \hspace{1cm} (2)

\[ \frac{dC}{dt} = kS \]  \hspace{1cm} (3)

- For a freely soluble drug, \( S \) is not critical: large \( C_s \) \( \Rightarrow \) large \( k \) \( \Rightarrow \) large \( dC/dt \)

- For a poorly soluble drug, \( k \) is small \( \Rightarrow \) \( dC/dt \) is highly responsive to \( S \)
To What Extent Can We Increase Surface Area?

2.0 cm³ of material - single cube with side length of ca. 1.25 cm - divided 24 times will produce enough 1 nm-sized cubes to completely cover a rugby field in a single layer.

Source: Adapted from work of Clayton Teague, National Nanotechnology Initiative (www.nano.gov)

Source: http://flickr.com/photos/learza/114576761/, This image is licensed under Creative Commons Attribution ShareAlike 2.0 License.
Applicability of Engineered Nanoparticles for Oral Delivery

- It is estimated that approximately 40% of all new drugs are insoluble, many of which suffer from poor oral bioavailability*

- For readily permeable compounds (BCS Class 2), a reduction in particle size can translate to substantial improvement in the rate and extent of oral absorption

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<th>SOLUBILITY</th>
<th>PERMEABILITY</th>
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<td>High</td>
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Benefits of Engineered Nanoparticles in Oral Drug Delivery

- Increased bioavailability
- Increased rate of absorption
- Reduced fed/fasted variable absorption
- Improved dose proportionality
- Avoidance of uncontrolled precipitation after dosing
Overcoming the Gastrointestinal “Window of Absorption”

Large API Particles
dissolution time >> GI transit time

API Nanoparticles
dissolution time < GI transit time
Example: Particle-Size Dependence of MK-0869

Benefits of Engineered Nanoparticles in Parenteral Delivery

- High drug loading in aqueous formulations (up to 45% w/w)
- Avoidance of harsh vehicles (e.g., cosolvents, solubilizers, pH extremes)
- Readily syringable formulations facilitate use of traditional small-bore needles
- Safety established for IV*, IM and SC routes of administration

Example: Preclinical Pharmacokinetics of Compound X Following Intravenous and Intramuscular Administration

![Graph showing mean plasma concentration over time for different administration routes.]

- Commercial product (solution), IV
- Nanoparticle dispersion, IV
- Nanoparticle dispersion, IM
Benefits of Engineered Nanoparticles in Pulmonary Delivery

- Precision delivery to target site
- Increased uniformity of surface coverage
- Shorter nebulization times

Therapeutic quantities of drug can be delivered rapidly using ultrasonic nebulizers

A much greater portion of the emitted dose can be deposited in the lung

Source: www.elan.com
How are Engineered Nanoparticles Produced?

- Spray freezing into liquid (SFL)
- Emulsification
- Precipitation with a compressed fluid antisolvent (PCA)
- Rapid expansion from a liquefied-gas solution (RESS)
- Evaporative precipitation into aqueous solution (EPAS)
- High-pressure homogenization
- Microfluidization
- High-energy wet milling

Preparation of Engineered Nanoparticles by Wet Milling

PolyMill® is a registered trademark of Elan Pharma International Limited.
NanoMill®–2 Manufacturing Platform

NanoMill® is a registered trademark of Elan Pharma International Limited.
Morphology of Unmilled and Milled Drug Particles

before milling

after milling
Time Dependence of Particle Size Reduction by Wet Milling

Particle Size Determination by Laser Diffraction

- Time Dependence of Particle Size Reduction by Wet Milling
Scalability of Wet Milling Process

![Graph showing particle size distribution for different NanoMill processes.](image)

- NanoMill-2 (4 kg)
- NanoMill-10 (33 kg)
- NanoMill-10 (131 Kg)
- NanoMill-60 (299 Kg)
Reproducibility of Wet Milling Process
Commercial Example:
Megace® ES (megestrol acetate oral suspension)

- 16-fold reduction in viscosity
- 75% reduction in dose volume
- elimination of fed/fasted variability

Megace® is a registered trademark of Bristol-Myers Squibb Company licensed to Par Pharmaceutical, Inc.
Mean plasma concentration of fenofibric acid after administration of one 160-mg fenofibrate tablet in low-fat fed (n=36) and fasting (n=36) conditions.

Mean plasma concentration of fenofibric acid after a single administration of one 145-mg fenofibrate tablet in low-fat fed and fasting conditions (n=44).

*The two regimens high-fat fed and fasting were found to be bioequivalent, as were the two regimens low-fat fed and fasting. 

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Potential Challenges in Developing Nanoparticle Products

- Particle agglomeration
- Particle size growth (Ostwald ripening)
- Changes in particle morphology
- Changes in polymorphic form
- Process-related impurities (e.g., residual solvents, media attrition)
- Process scalability and reproducibility
- Lack of a universal particle sizing method
Key Characterization Needs for Nanoparticle Applications

- Particle size distribution
- Solid-state properties
- Dissolution behavior
- Microbial limits testing (for aqueous products or product intermediates)
- Application specific methods (e.g., route of administration)
- Technology specific methods (i.e., novel, unique to formulation/process)
Concluding Remarks

• Nanoparticle engineering offers significant potential to improve the delivery performance of poorly water-soluble drugs, and hence the treatment outcomes of patients who will benefit from these novel drug products.

• A number of commercial drug products employing nanoparticle technology have already been approved by FDA.

• FDA’s current requirements for assessing drug product safety, efficacy and quality appear adequate for evaluation of nanoparticle-based drug products.

• Future evolution of more complex nanotechnologies (e.g., drug targeting, intracellular delivery, etc.) will likely drive the need for periodic evaluation of FDA policy and procedures for regulating nanotechnology based drug products.