Listen to a recording of this issue

The Altascientist

SCIENTIFIC JOURNAL

ISSUE NO. 22

# NANOMILLING

## For better solubility and improved bioavailability

A crucial feature of drug development is bioavailability, defined as "the ability of a drug to be absorbed and used by the body." For a drug to be bioavailable, it must first be soluble, meaning able to be dissolved, especially in water. Many drugs on the market today are poorly water soluble, and patent extensions or 505(b)(2) new patents become possible for formulation improvements delivered via nanomilling.

**Figure 1.** USP and BP solubility criteria.

# SOLUBILITY CLASSIFICATIONS

The Biopharmaceutics Classification System (BCS) is a guide provided by the U.S. FDA for predicting a drug's intestinal absorption. This system develops a prediction using the parameters of solubility and intestinal permeability.

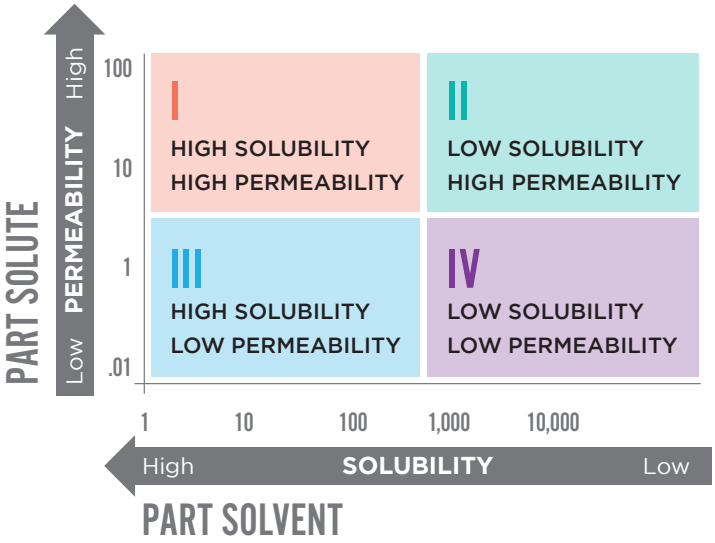
**Table 1.** Human pharmaceuticals are classified according to the following four BCS categories.

| | CLASS I | CLASS II | CLASS III | CLASS IV |
|---|---|---|---|---|
| Solubility | High | Low | High | Low |
| Intestinal Permeability | High | High | Low | Low |
| General Characteristics | Generally, very well-absorbed | Exhibits dissolution rate-limited absorption | Exhibits permeability-limited absorption | Very poor oral bioavailability |

Forty percent of marketed drugs and 90% of active pharmaceutical ingredients (APIs) are poorly water-soluble, BCS Class II or IV. APIs that fall into BCS Class II are optimal candidates for particle size reduction as their dissolution is the rate-determining factor in drug absorption.

The BCS classes are depicted in Figure 2.

**Figure 2.** BCS Classes I-IV




A complementary classification system to the BCS is the Biopharmaceutical Drug Disposition Classification System (BDDCS). The BDDCS recognizes that drugs with high permeability are generally very well metabolized, while the low permeability APIs are primarily eliminated via urine and bile as unchanged drug. While the solubility criteria in the BCS and BDDCS are the same, the second variable considered to determine permeability, is not.

In the BDDCS, the second variable is related to the assessment of drug metabolism, whereas in the BCS, permeability is assessed based on the extent of intestinal absorption. For a drug to be rated as highly permeable, the systemic absorption of parent drug and its metabolites must be at least 90% of the administered dose, relative to an intravenous reference dose or based on a mass balance determination. Therefore, the BCS and BDDCS classification of a drug may differ.

# OVERCOMING SOLUBILITY CHALLENGES

Promising therapeutic molecules, even if classified as poorly soluble, can be developed successfully. There are multiple technologies available to increase the solubility and oral bioavailability of poorly soluble molecules being developed as APIs by reducing their particle size.

Nanomilling is a universal technique that can be applied to almost any API with water solubility below 200 µg/mL. It is a very adaptable drug delivery platform suitable for oral, injectable, inhalable, and buccal applications, for which fine drug particulates are especially desired in formulations.

Nanomilling is a unit operation where mechanical energy is applied to physically break down coarse particles to finer ones. It has wide commercial and industrial applications, as every drug can be ground to finer particles, whether aqueous or non-aqueous soluble. Decreasing the size of the API molecule increases the size of the specific surface area; the larger surface area allows for greater contact with water, increasing the API's dissolution rate and bioavailability.

**Figure 3.** The Noyes-Whitney Equation and Impact of Particle Size on Surface Area

## Noyes-Whitney Equation

$$\frac{dm}{dt} = A \cdot \left(\frac{D}{h}\right) \cdot (C_s - C)$$

Where:

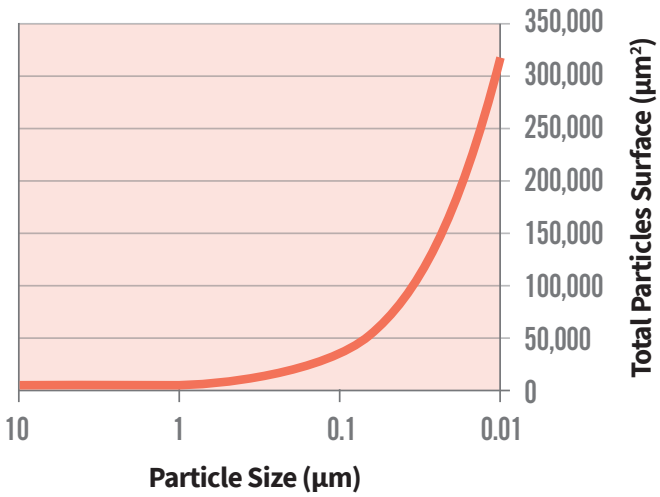
- **m** = mass (mol)
- **t** = time (s)
- **C** = concentration of solute dissolved at a particular time ($mol \cdot cm^{-3}$)
- **D** = diffusivity ($cm^2 \cdot s^{-1}$)
- **h** = apparent thickness (cm) of the aqueous boundary layer (depends on rate of stirring and the temperature)
- **A** = surface area available for dissolution ($cm^2$).

**Small particle size - greater surface area**

**Fast rate of dissolution**

**Rapid drug absorption**

**Impact of Particle Size on Surface Area**




Consult our webinar titled **The Development of Nanosuspension Formulations for Poorly Soluble Drugs** at timestamp 10:00, for a detailed explanation of the equation.

# NANOMILLING BENEFITS

Benefits of particle size reduction for the parenteral route include small dose volumes (resulting from high drug loading) and avoidance of harsh solvents and/or extreme pH conditions. Advantages for the pulmonary route include the ability to use inhalers intended for solutions, as well as the ability to produce spray-dried powders whose particle sizes are optimized for deep lung delivery.

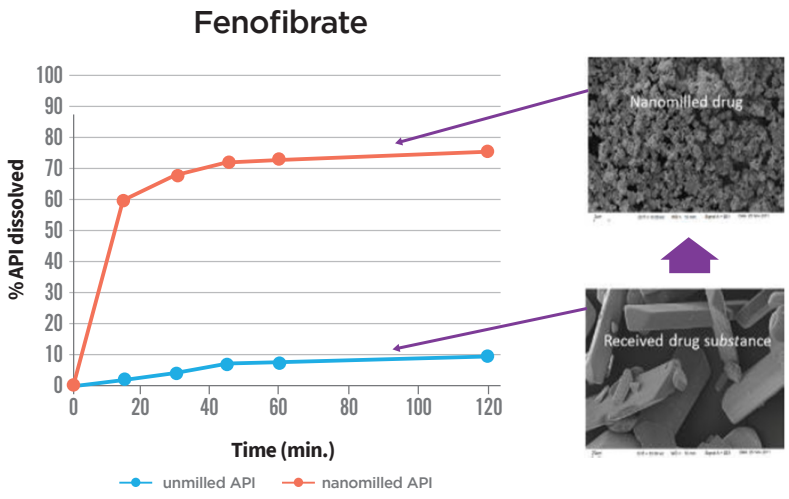
Other advantages include reduced fed/fasted variability in both liquid and solid dosage forms, faster onset of therapeutic action, low excipient side effects, and the ability to run continuously.

The process and equipment are easy to scale. Once the formulation and the process are optimized, very little batch-to-batch variation is observed in the quality of the dispersion.[23]

The closed system allows for control of the milling environment as well as protection of the operators from exposure to potent drugs.

A real-world example of the significant change in fenofibrate particle size achieved via nanomilling is demonstrated in Figure 4.

**Figure 4.** Particle Size Reduction via Nanomilling




**Your API is a good candidate for nanomilling if it has the following characteristics:**

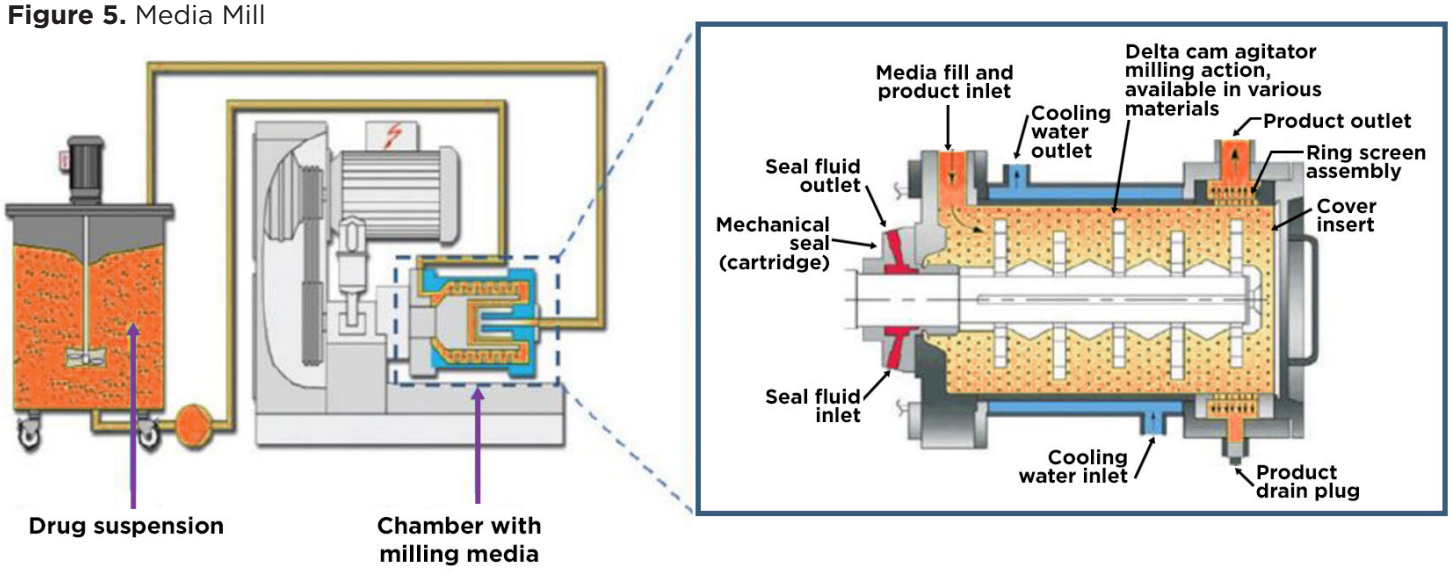
- ☐ Small molecule
- ☐ Low aqueous solubility (>0.2mg/mL)
- ☐ High melting point
- ☐ Stable in aqueous solutions
- ☐ Poor bioavailability
- ☐ BSC Class II/IV
- ☐ Dosage form – can be any, but most often the following:
  - Injectable
  - Topical
  - Oral

# HOW NANOMILLING WORKS

Nanomilling uses a high-energy wet mill to physically break down coarse particles, reducing their size to less than 1,000 nm (usually in the 100 to 200 nm range, sometimes even smaller when a smaller milling media is used). High energy and shear forces are generated through the impact of the milling medium with the drug. This further disintegrates microparticulate drug into nanosized particles. With modern mills, the milling times may be only a few minutes, making it a very efficient technique.

A typical large-scale mill is depicted in Figure 5 (components not shown to scale).

**Figure 5.** Media Mill




The suspending medium is water containing a surface-active agent, which becomes a colloid suspension during the milling process, with the surface-active agents working to stabilize the particle size of the drug during milling. The surface-active agents can be polymers, or ionic or non-ionic surfactants. The surface-active agent coats the surface of the particles and inhibits particle aggregation, agglomeration, and a natural process called Ostwald ripening.

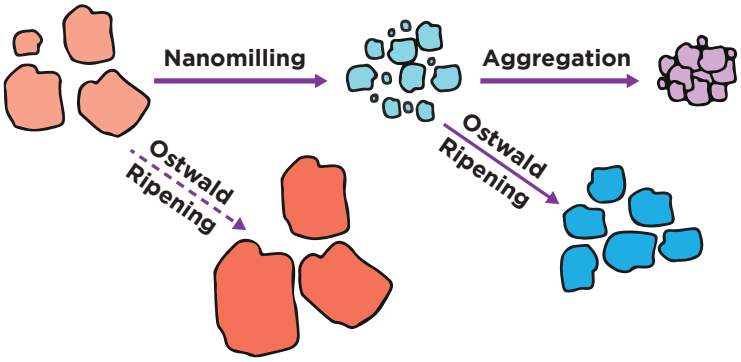
# MAXIMIZING FORMULATION

To manufacture a drug nanosuspension with desired particle size and appropriate storage stability, selecting the optimal program parameters (stabilizer formulation and process/equipment framework) for the wet media milling process is essential.

A poorly formulated drug nanosuspension may undergo aggregation, Ostwald ripening, fast sedimentation of particles, and cake formation during milling/storage, any of which will lead to problems later in the manufacturing process, and poor product performance/slow dissolution from the final dosages. The high surface area associated with the drug nanoparticles can be compromised by potential particle size increase/growth during milling and storage, which minimizes the significant benefits that should be realized from the nanomilling process.

Possible issues that may arise during the wet media milling of drugs are shown in Figure 6.

**Figure 6.** Particle Size Reduction via NanomillingArea




The efficiency of stabilizers depends on several factors. The affinity of the stabilizer to hydrophobic surfaces, which is related to the hydrophobicity of the material, is important. In addition, the difference in surface energy between the drug and stabilizer has an important role. Higher viscosity results in a more stable end product, but highly viscous materials are difficult to mill, so the appropriate balance needs to be struck.

# ALTASCIENCES' CASE STUDY

## Overview

A client entrusted Altasciences' CDMO with a highly active compound which was headed towards clinical trials based on excellent in vitro activity and a good toxicity profile. However, due to very poor aqueous solubility and less than desirable bioavailability, improvements to the formulation were required to realize all the benefits of the drug's inherent activity. The solution suggested was a nanosuspension prepared by aqueous nanomilling, for a significant increase in dissolution rate and an increase in bioavailability.

## Purpose

To determine the suitability of nanomilling for a client's drug, and to develop a stable, nanoparticulate suspension formulation of the API that would improve bioavailability.

## Details

- Drug development phase: preclinical
- Class of drug: small molecule, BCS Class II/IV
- Routes of administration: oral and injectable

## Methods

- Standard nanomilling conditions for screening in a jar mill (roller milling)
- Drug concentration: 20-30%
- Milling media: ceramic yttria-stabilized zirconia beads (YTZ), 0.5-2mm, 50% v/v
- Aqueous phase: 6 aqueous phases, each containing a different stabilizer
- Volume: 1-100 mL
- Drug requirement/jar: 0.02-2g
- Roller mill speed (RPM): 60-200 RPM
- Sampling timepoints: 1, 2, 4, 8, 24 hours
- Particle size distribution (PSD) method: D50 determined by laser diffraction (LD) on a Horiba LA-950

## Methods and Results

Solid API was milled on a roller mill in a glass jar containing the drug (20% w/w), a series of pharmaceutically acceptable stabilizers, and YTZ ceramic milling media. The suspension was sampled at different timepoints for particle size measurements until the D50 plateaued. Each of the six stabilizers were found to be compatible with the process, which provided significant reduction in particle size from a D50 of ≈ 30µm to < 300nm; three stabilizers promoted particle size reduction to < 200nm. These three also appeared to sufficiently stabilize the nanosuspension after milling, as determined by LD measurements following incubation at ambient conditions for 24 hours.

These three promising stabilizers were further investigated by repeating the milling at different drug loadings (10-40%), milling media sizes (0.5-2mm), and milling speeds (60-200 RPM) to determine the best conditions for scale-up for high-energy media milling. Each unique combination was monitored for particle size distribution by LD, with sampling times of 1, 2, 4, 8, and 24 hours.

Several of the conditions investigated were able to reach the minimum D50 of about 170nm. The suspensions were separated from the media and allowed to sit at ambient temperature for a week with daily sampling for evaluation of PSD stability. Two of these were shown to maintain the PSD over that time and one was selected for further scale-up.

Initial conditions for scale-up in a high-energy media mill (NETZSCH DeltaVita) were as determined for the experiments above for milling media loading and size, stabilizer type and concentration, and drug loading. The only variables during initial scale-up and process development were milling speed and milling time.

The optimized conditions determined during roller milling translated smoothly to high-energy milling and allowed for selection of optimized times and speeds to provide a stable nanosuspension for use in preclinical pharmacokinetic (PK) and toxicity studies.

## Conclusion

It is possible to screen a panel of nanoparticle stabilizers at small scale in a simple and quick process, providing reliable data to determine the feasibility of nanomilling for the drug of interest. The protocol also identified suitable conditions for scale-up on a high-energy media mill for both preclinical and clinical batches. The combination of speed and affordability makes roller milling and nanosuspension formulation an excellent option for compounds with aqueous solubility issues.

# EXPERIENCE YOU CAN TRUST

Nanomilling is a highly complex process requiring a unique level of CDMO expertise that can only be gained through extensive experience with developing a broad range of APIs.

The experts at Altasciences can take your API from formulation to commercialization. We have the necessary procedures, equipment, and experience to work with any formulation. Our highly skilled teams work with the latest equipment, including the Netzsch DeltaVita 15-300 mill, that can reduce particles to nanometer size with our wet milling options, fill vials in a range of sizes (from 0.3 ml to 500 ml), and package them.

## REFERENCE


F. Thomas, Looking Beyond the Solubility Horizon, Pharmaceutical Technology 43 (6) 2019.

M. Li et al, Nanomilling of Drugs for Bioavailability Enhancement: A Holistic Formulation-Process Perspective Pharmaceutics 2016, 8, 17; doi:10.3390/pharmaceutics8020017

L. Peltonen et al, Pharmaceutical nanocrystals by nanomilling: critical process parameters, particle fracturing and stabilization methods Journal of Pharmacy and Pharmacology 2010; 62: 1569–1579

Y. Golfar et al, Prediction of Biopharmaceutical Drug Disposition Classification System (BDDCS) by Structural Parameters, J Pharm Pharm Sci (www.cspsCanada.org) 22, 247 - 269, 2019


# ALTASCIENCES' RESOURCES

**Webinar**

The Development of Nanosuspension Formulations for Poorly Soluble Drugs

**Blog**

Improving Solubility of Molecules via Nanomilling

**Article Featured in Biopharma Dive**

Nanomilling: an Optimal Solution for Poorly Soluble, Challenging APIs

**White Paper**

Utilizing Nano Particular Formulations in the Delivery of Poorly Soluble Drugs

## ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.



ALTASCIENCES

CONTACT US

altasciences.com | contact@altasciences.com | Tel: 514 246-4191

Follow us on LinkedIn