

Application of Pulsewave Technology to Biotechnology (Pharmaceutical, Functional Food, Nutraceutical, OTC)

PULSEWAVE MICRONIZATION MILL TECHNOLOGY

The Pulsewave resonance disintegration micronization mill is a fundamental and revolutionary change in the way that cominution of materials is accomplished. It operates on the novel principle of resonance disintegration, that reduces the particle size of various materials by the application of the physics of resonance, shock waves, and vortex-generated shearing forces, as opposed to the crushing and grinding processes of conventional milling. It is designed to reduce particle size along natural lines of cleavage, generating finished product with a very tight particle size distribution.

In addition to ability to reduce the particle size of materials, this technology also is capable of selective differential fragmentation of particles in complex multiphase materials. The throughput of the mill varies based on the size and composition of the starting material and the desired particle size, resulting in a more uniform, consistent, and predictable product.

Material can be run in several different media including atmospheric air, water, helium, or liquid nitrogen. This allows for the custom micronization of materials of various chemistry and volatility. And most uniquely, the direction of mill rotation can be easily changed from clockwise to counter-clockwise, producing an altered finished-product granulation and energy consumption. Rotational characteristics add significant dimension to the variables under operator control for producing target outcomes of material processing.

Reduced energy consumption, always a concern for any micronization process, is one of the many significant benefits of using the Pulsewave technology. It is expected that this technology will contribute to lower building costs, and maintenance costs, due to the relatively simplified processing system required to operate this technology.

Processing capability beneficial to biotech and pharma applications:

- 1• Mill can be operated at different speeds and directions, providing versatility in particle size reduction processing.
- 2• Mill is a continuous flow processor, taking material in at the top of the mill, and releasing processed material at the bottom. Passage time for the material flow is less than one second (<1 sec).
- 3• Most material does not come in contact with the machine; processing occurs within a powerful airflow (Coanda airflow). This process greatly reduces any contamination of processed material.

- 4• The mill can process 500-8000 pounds/hour, depending on type of material.
- 5• Heat generation can be controlled to desired levels.
- 6• Process does not destroy proteins and high molecular weight polymers.
- 7• Mill can accept materials with water content up to 20-30%.
- 8• Provides a basis for dry fractionation of plant or other complex materials.
- 9• Mill can quickly generate stable emulsions (water-oil, etc.)
- 10• Mill will perform cold processing. Material can be run in several different media including atmospheric air, water, helium, Co2 or liquid nitrogen. This allows for the custom micronization of materials of various chemistry and volatility.
- 11• Moisture is removed from material naturally while being processed. Conversely, the technology allows for the introduction of moisture and other liquids, providing even greater finished product moisture control.
- 12• It has been shown that the material compounds normally contributing to rancidity are relatively low, contributing to an expected long shelf life (meets or exceeds food industry standards). The mill is stainless steel, FDA conformance.

Specific criteria applicable to pharmaceutical processing includes but is not limited to:

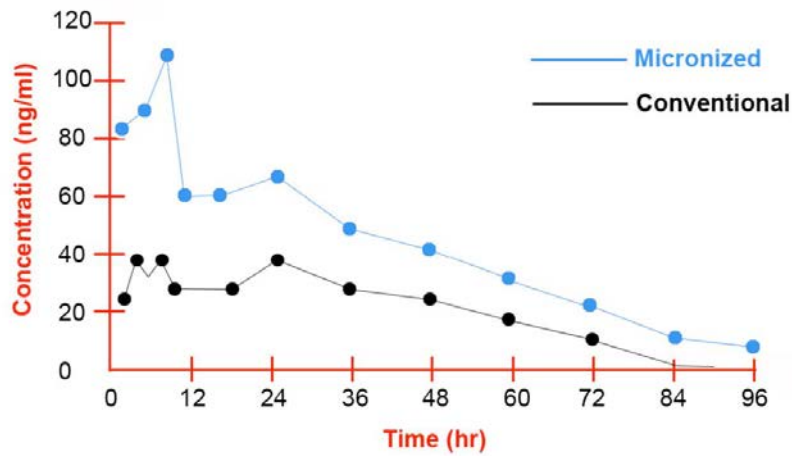
IMPROVED DISSOLUTION, SOLUBILITY, AND BIOAVAILABILITY

As a consequence of core benefits of processing material through the Pulsewave mill, materials prepared for pharmaceuticals will express increased characteristics supportive to high dissolution, leading to high solubility of product. This, and increased surface area, with clean surface faces and edging on product, will result in a greatly improved effect in efficacy.

• Why improve bioavailability?

- Intravenous drugs may be orally administered
- Dose of orally administered drug may be lowered
 - Lower cost
 - Safer
- Variability of effective dose is reduced
- Provide patient with most convenient and consistent dose possible.

Enhancing Oral Bioavailability (Increased Absorption with Micronization)



Mean plasma concentration-vs-time profiles,
for both products.

- **Nanonization:** nanoparticles can be expected to improve all common drug administration techniques:
 - Oral
 - Transmucosal
 - Ocular
 - Injection
 - Pulmonary
 - Implant
 - Transdermal
- More than 300 companies in the U.S. alone are involved in developing drug delivery mechanisms using nanotechnology.
- PW mill consistently matches or exceeds existing technology in materials processed to date.

THREE EXAMPLES OF ACTUAL MATERIALS PROCESS THROUGH THE MILL

1. GLUCOSAMINE SULFATE: a widely used supplement that may ease pain in knee osteoarthritis (cartilage breakdown causing joint pain).

Glucosamine sulfate, run through PW mill one time (1X), illustrates:

- (a) Start-size for material: 50% of processed material = 350 μ m (micron) size.
- (b) Run thru mill 1X: 50% of processed material = 7.437 μ m (micron) size.

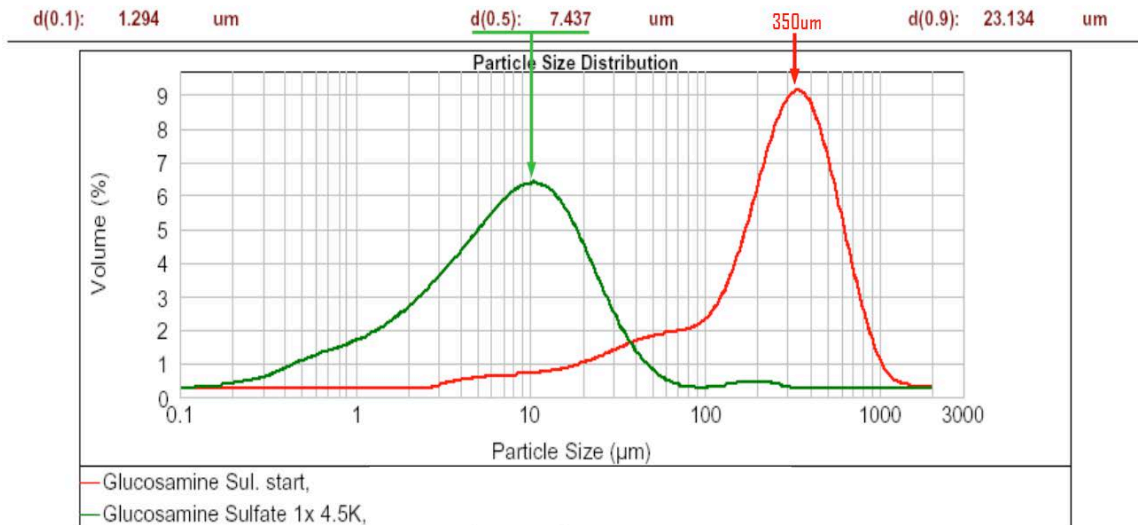
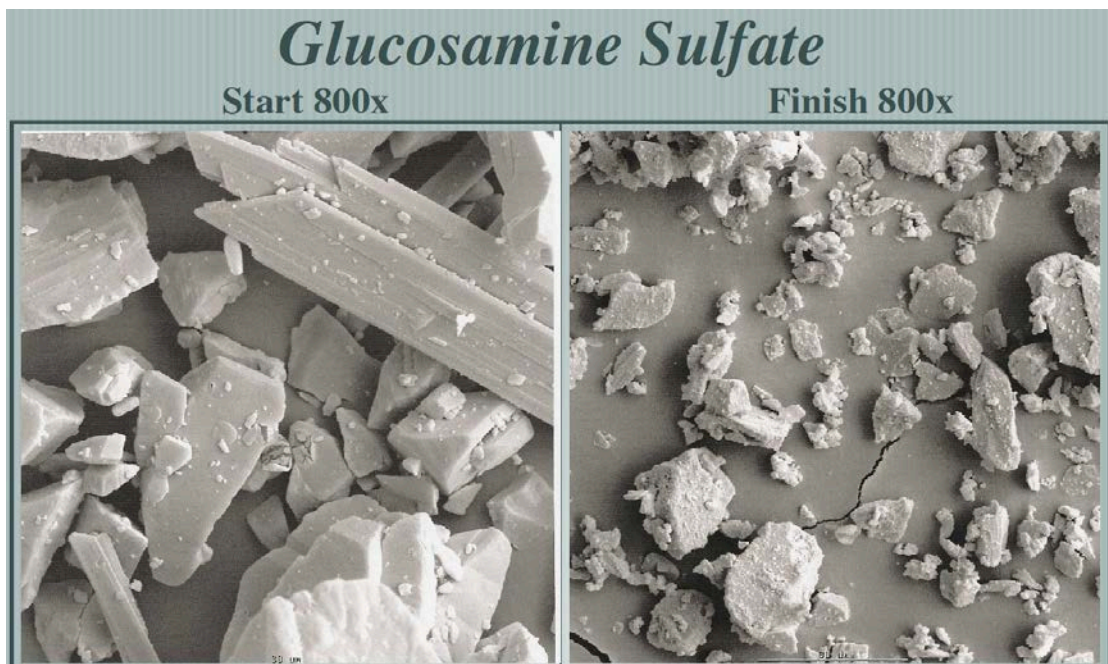
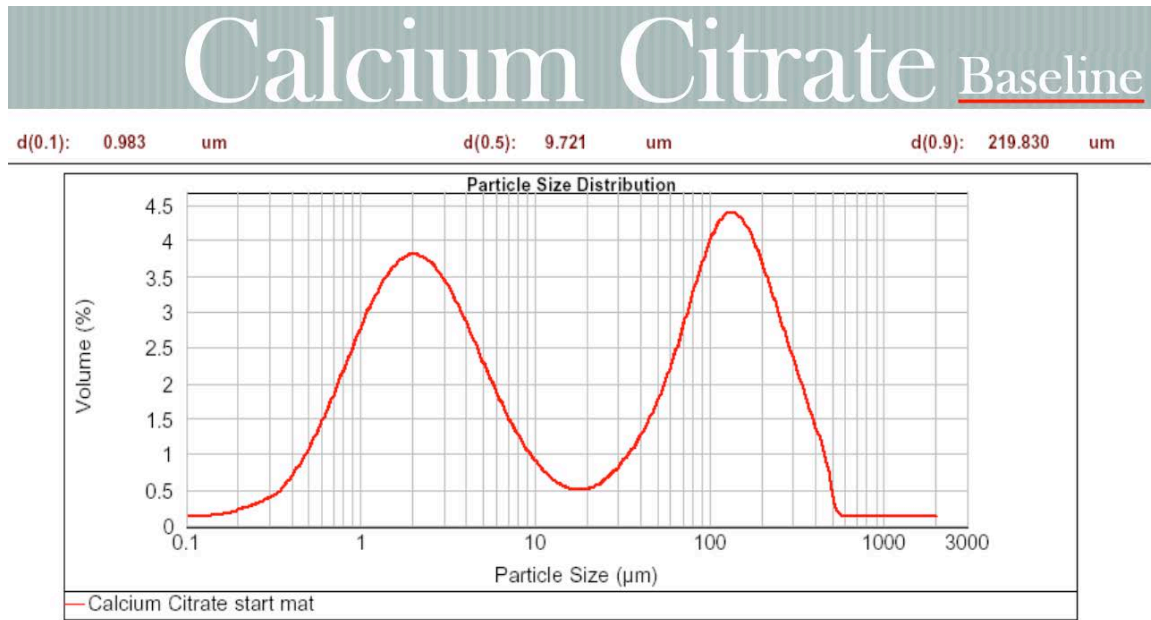


Image: Scanning Electron Microscope showing visual size of starting material, and comparative size of reduction after 1X pass through PW mill.

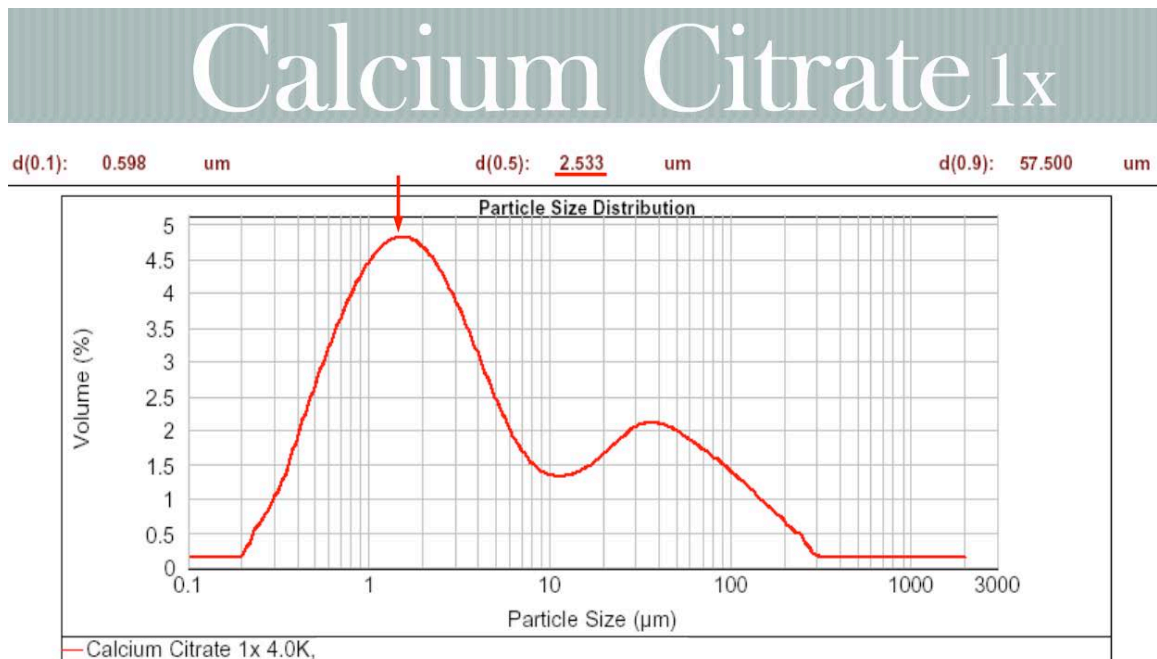


2. CALCIUM CITRATE (Medication used to prevent or treat low blood calcium levels). Calcium is a high-demand pharmaceutical for which increased bioavailability is expected to significantly improve efficacy of product.

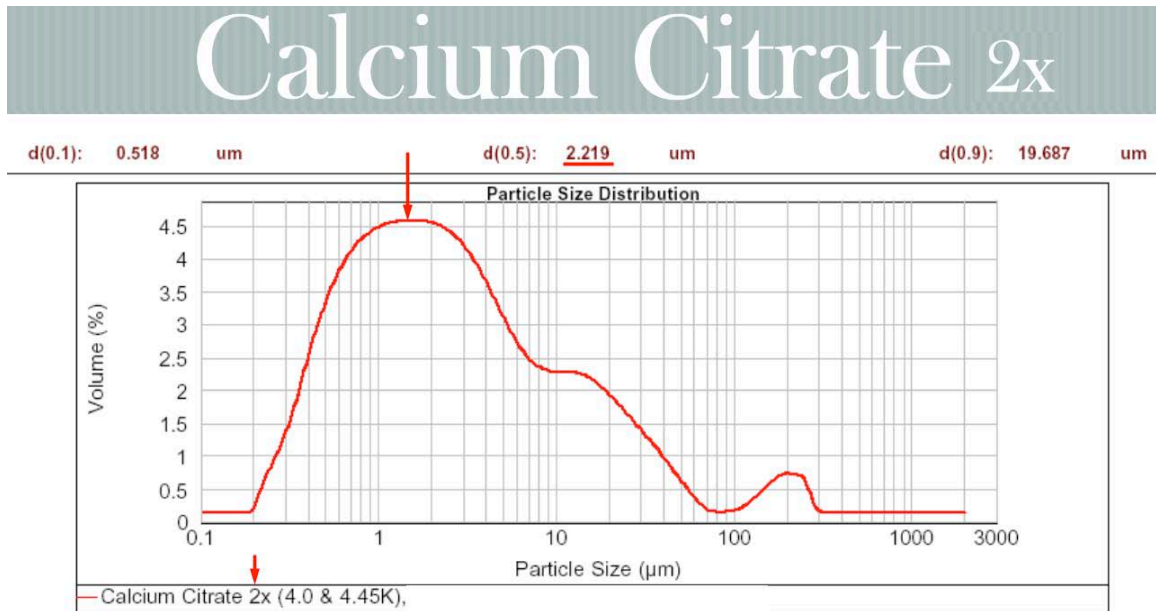
The starting, raw material (baseline) results in 90% being below 219 μ m.



With material run through PW mill once (1X), 50% of material dropped to below 2.533 μ m, with 90% of material being below 57.5 μ m.



With material run through mill a second time (2X), 50% of material dropped to below 2.219 μ m, with 90% of material being below 19.687 μ m.

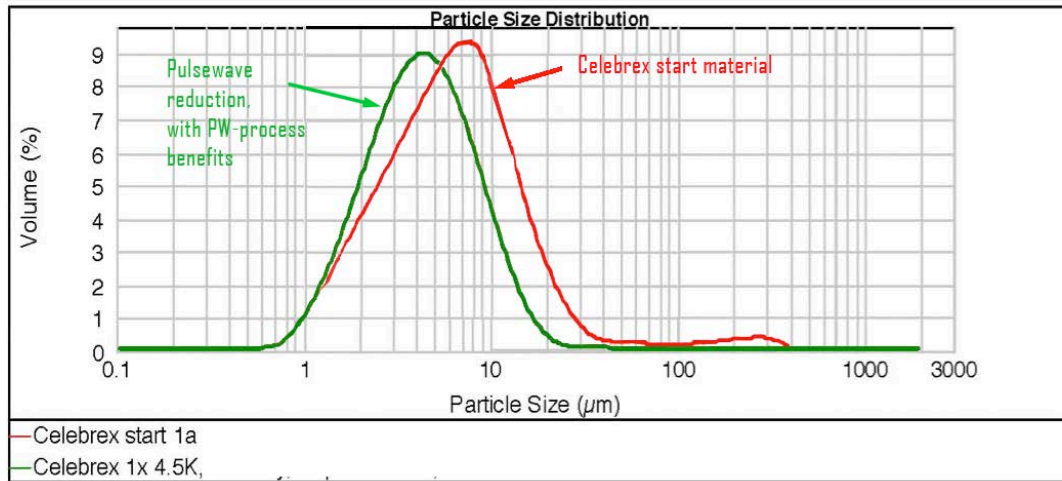


The biggest reduction will occur between original material size and 1X process through the mill; subsequent processing will make reductions in size, but not as large as the first run because of the physics and energy required to reduce micro-to-nano sized particles.

3. CELEBREX. (A nonsteroidal anti-inflammatory drug (NSAID) which relieves pain and swelling.)

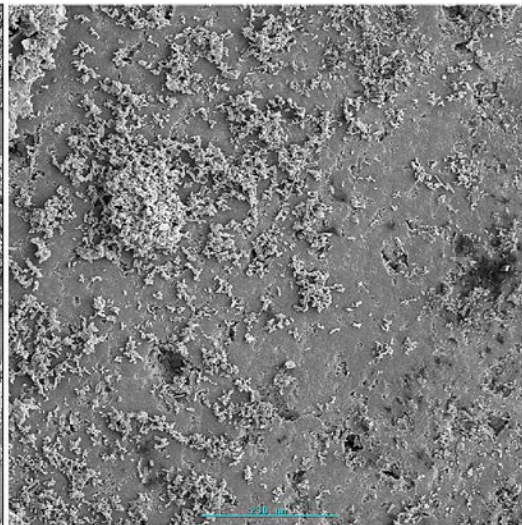
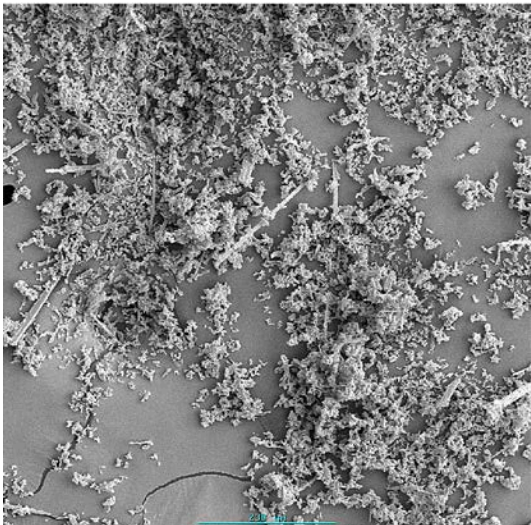
Starting, raw material represents final output from non-Pulsewave size reduction technology. This information reflects a one time pass (1X) through the PW mill, illustrating that the material can be taken down even further than product size used in contemporary milling. Scanning Electron Microscope images show same material viewed at 100X and 800X enlargements (start material vs. Pulsewave milled material).

d(0.1): 1.766 um d(0.5): 4.216 um d(0.9): 9.677 um



Celebrex - Start 100x

Celebrex - Finish 100x



Celebrex - 800x Start-Finish 1x

