A Quadro Engineering White Paper

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Improving API Particle Size Distribution Targets
Is There a Better Way?

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Improving API Particle Size Distribution Targets - Is There a Better Way?

Milling is an integral step in API production; however, not all size reduction methodologies offer the same level of narrow particle size distribution spans, nor an easy, repeatable and accurate ability to control particle size range outputs. As companies strive for better manufacturing efficiencies – selection of the most suitable equipment for the application, needs to be paired with options offering the greatest return-on-investment. This Paper explores the background of API milling from a technology perspective – reviewing traditional comminuting methodologies, and exploring new, innovative breakthroughs in conical milling size reduction.

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Active Pharmaceutical Ingredients (API) Milling Trends:

It is well known, and widely documented, that API production is one of the fastest growing segments within the pharmaceutical industry; with manufacturing production expected to grow at a 7.9% CAGR through 2016.[1]

Partly fuelled by the world's increased need for "secondary care" small molecules – integral in prescription drugs issued by specialists such as oncologists[2], and partly driven by a concurrent increased demand of well-established drugs in both mature and emerging markets[3]; API manufacturers have been challenged to look for the most efficient processing equipment available, without sacrificing product quality or operator safety.

The most appropriate equipment selection begins in the early stages of a Drug Discovery Process – usually between pre-clinical and Phase II[4], before submitting a New Drug Application (NDA). It is at these stages that formulators consider a vast number of ingredient properties and characteristics in their decision as to how best to commercially produce and launch their product.

After what is often a costly and lengthy new molecule development period, an optimized API particle size distribution target is reached - where the new drug will offer the best bioavailability, stability, granule properties and technical feasibility.[5] [6] It is at this stage, that powder milling or comminuting technologies are investigated and selected according to their ability to duplicate lab results on a larger scale.[7]

Over the last century, powder milling equipment has progressed to meet the changing "needs" of APIs, growing safety requirements (of both product and operators), and increasing production volumes - to name but a few of the many drivers that the API industry has seen. However, accelerated changes in the last few decades are trending towards smaller and smaller particle size distributions as potencies increase, and drug delivery methods change.[8]

Most milling technologies use varying forms of impact, grinding, crushing or attrition to convert energy into size reduction – whether generated by gyrating impellers or rotors, or by pneumatic means. Since the amount of size reduction is directly proportional to the "energy" being generated within the milling chamber[10], the right equipment selection becomes increasingly important (Figure 1).

Particle sizing, homogeneous dispersion and calibration are of course key functions of a milling device; however, in addition to size reduction steps, API manufacturing requires attention to equipment design, industrial hygiene and safety.[9]

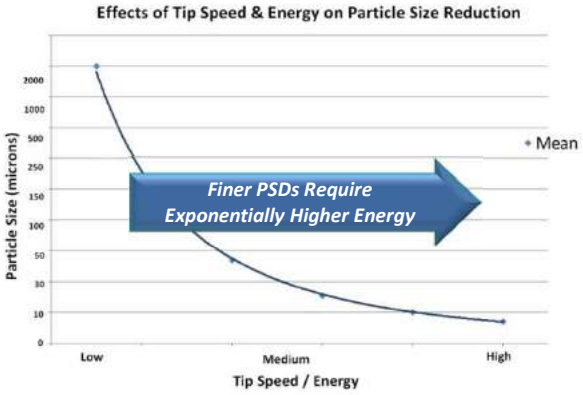

Figure 1: Relationship Between Particle Size Distribution vs. Amount of Energy Imparted

Size Reduction Equipment Alternatives:

Traditionally, API size reduction technologies are selected based on a number of product-specific, and equipment compliant parameters. One of these parameters typically being attainable PSDs .

For comparison purposes, this Paper groups API comminuting technologies into five PSD targets, ranging from "coarser" to "finer" distributions. Oscillators are sometimes utilized at the coarser end of the distribution spectrum (d50s >300 µm), followed by conical mills (typical d50s in the 150-300 µm range), then by hammermills and pin mills in the mid-to-fine-range (d50s ≈ 75-150 µm and 15-150 µm respectively), and finally jet mills for finer PSDs (common d50s < 15 µm).[11]

Focusing on the mid-to-fine-range PSD target (d50s ≈ 15-150 µm), hammermills and pin mills have provided adequate results over the last several decades, albeit at times at a trade-off in excess product loses, overheating and/or plugging of internal components. For example, pin mills can lead to very extensive cleaning cycles due to their propensity to pin plugging[12], which in turn results in higher percentages of product waste. Additional challenges of these traditional mills include the amount of milled product outside the desired particle size distribution or the difficulty to easily control and shift PSD targets to accommodate varying API characteristics. Furthermore, when looking at pin mills in particular, the need for air handling systems adds to the complexity of the process; with increased product losses, as well as higher production and maintenance costs.

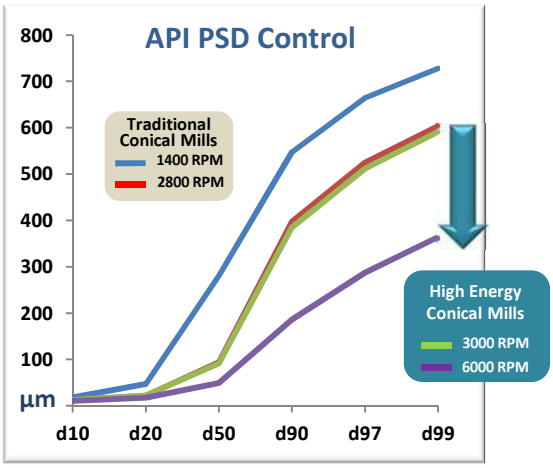

Figure 2: PSD Comparison Between Traditional Conical Mills and High Energy Conical Mills

To address some of these processing challenges, recent innovations in conical milling technology have resulted in the ability to produce finer API particle sizes (capable of shifting PSDs targets by 30-70%), taking cone milling performance from d50s of 150-300 µm, down to a sub 150 µm range (Figure 2).

These new, high energy conical mills, not only lower the PSD threshold of conventional cone mills, but also address one of Pharma's primary concerns: the production of narrower (tighter) particle size distribution spans, thus improving on-target milling by 30-60% (Figure 3).

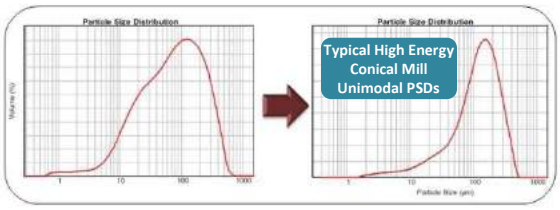

Figure 3: High Energy Cone Mill Capable of Narrower Particle Size Distributions

Furthermore, these high energy conical mills, provide the ability to control and shift PSDs, allowing manufacturers to maximize the amount of milled product within the desired target – reducing (and potentially eliminating) the need for screening over/undersized particles; resulting in less waste (Figure 4).

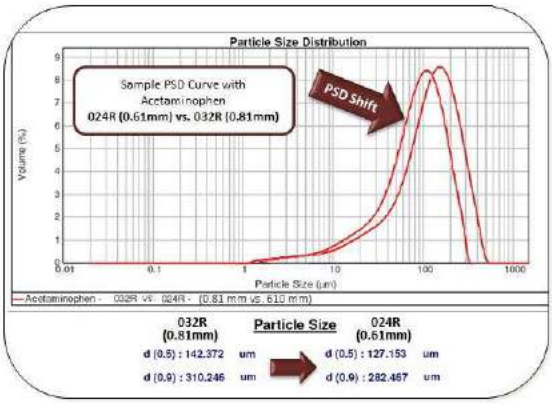

Figure 4: Controllability and PSD Shift Capabilities of High Energy Cone Mills

Containment:

Although it is not within the scope of this Paper to cover in detail product and operator safety/containment trends, they nevertheless continue to be one of Pharma's leading priorities.

Most API milling technologies address this industry pull with a variety of engineered solutions such as pneumatic handling equipment or product collectors for less stringent conditions; to cross-flow booths and isolators for more rigorous applications. Unfortunately, many of these solutions require costly capital investments and result in continually high operating costs. Finding ways to reduce the use of ancillary equipment– while still ensuring containment OEL levels below 1 µ/m^3 adds another variable or criteria to be considered during milling equipment selection.

Conclusion:

API producers live in a global environment, steered by the strictest of manufacturing guidelines, quality and safety requirements; and under profitability pressure from increased competition.[13]

Over the decades, milling technologies have improved and adapted to changing standards and customer needs – with varying levels of strengths and weaknesses. Choosing the right or optimum milling solution for each API size reduction application can be a critical and laborious balancing act.

Figure 4: In-line Tri-Clamp Designed High Energy Cone Mill

On one hand, the properties and characteristics of APIs must be retained; on the other hand, production efficiencies must be maximized.

API manufacturers have an increased number of size reduction equipment choices[14], including new developments in conical mills. When taking into account efficiency savings from tighter PSD spans (less out-of-spec waste), the ability to control/shift PSD targets (closer to the objective) while still ensuring sub 1 µ/m^3 OEL levels – finding a milling solution that delivers "everything" may appear daunting at first. However, new size reduction innovations enable impactful productivity improvements, enviable return-on-investment and an overall improvement in API particle size distribution targets.

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