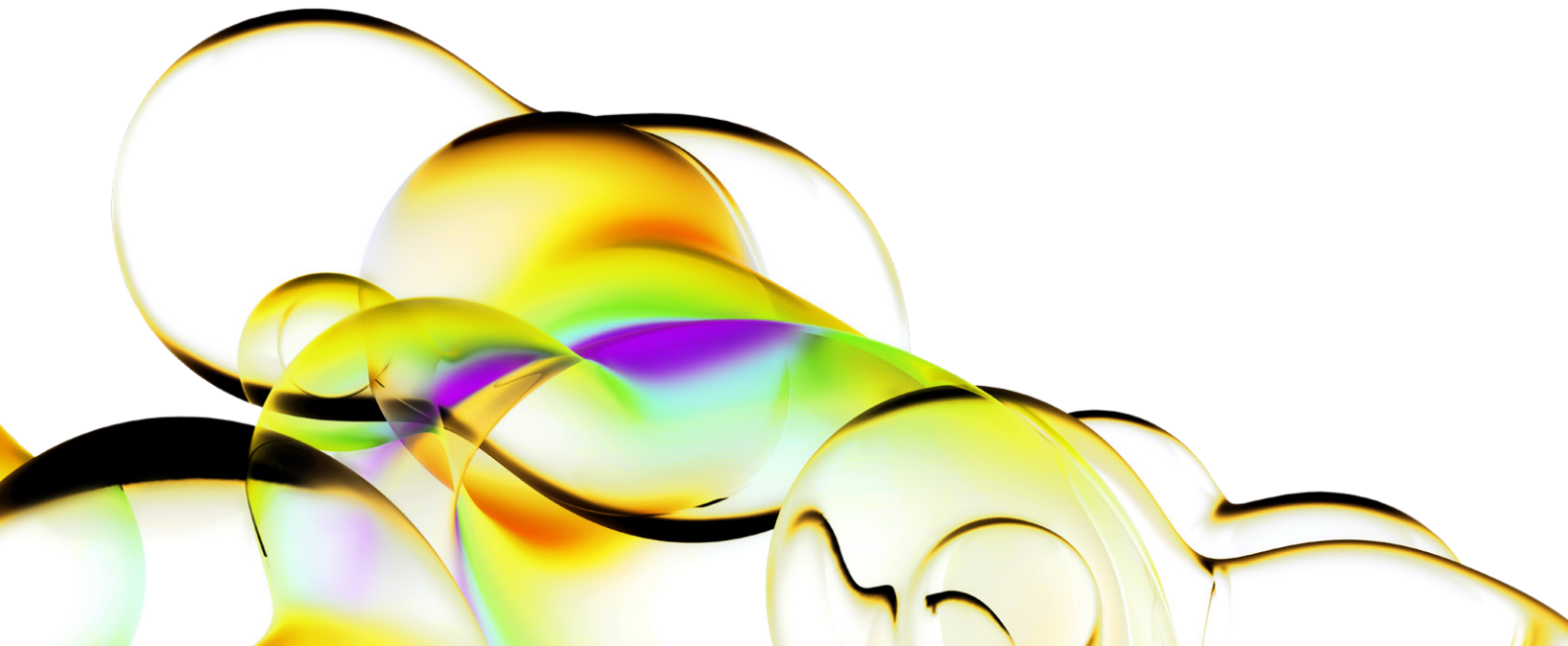
APPLICATION NOTE

Dry milling of analgesics for particle size reduction on the Omni Bead Ruptor 96.

Introduction

Milling processes are widely employed in pharmaceutical production and testing to reduce particle size to increase solubility or stabilization and for component analysis [1-2]. As most drugs compounds must be comminuted at some point in the production or QC process, optimization of milling parameters and the correlation of these parameters with effective particle size distributions is critical. While the milling process is operable under dry and wet conditions, physio-chemical properties of the particle during dry milling are affected by parameters both easily attainable and manipulated (type of milling equipment, milling energy, processing time, ball-powder ratio, and particle rigidity) [3]. While milling wet suspensions will achieve smaller particle diameters across multiple concentrations when compared with the corresponding dry-milled samples [4], dry milling is preferred as it maintains product integrity and easier to scale in a production environment.

In this investigation, the efficacy of the dry milling protocol in the reduction of analgesics was examined, in part, as a feasibility study to determine an adequate range of sample composition over which the Omni Bead Ruptor 96 can operate. Herein, we evaluate the time course over which the milling frequency of samples of consistent mass produced a reduction in particle size. The average particle diameter was measured via 1:1 (mg:mL) dilution in a cuvette prepared for a Particle Size Analyzer (Shimadzu SALD-7500nano).



Materials and methods

- Omni Bead Ruptor 96 (Cat# 27-0001)
- 50 mL Milling jars (Cat# 27-006)
- 25 mm Milling balls (Cat# 27-206)

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50 mL Milling jars
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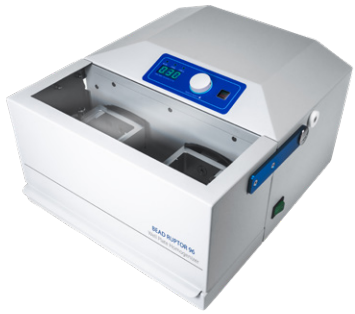

Omni Bead Ruptor 96
Cat# 27-0001

Sample selection and preparation

Aspirin (regular, 325 mg; enteric-coated, 81 mg) and Excedrin (250 mg Acetominophen, 250 mg Aspirin, 65 mg Caffeine), were used to examine processing capabilities over varying frequencies and duration. Approximately 5 grams of the sample was isolated to place into a 50 mL milling jar containing one 25mm milling ball. With the jar firmly tightened, each individual sample was processed at either 15, 20, 25, or 30 Hz for 30 seconds, for 1, 2, or 5 minutes.

Sample analysis

Particle size was monitored through analysis (PSA) on a Shimadzu SALD-7500 nano laser diffraction spectrometer. Each measurement was obtained from a 10-15 mg sample removed from the processed material (a range was established in order to maintain an absorbance of 0.1 - 0.2 across varying refractive indices, and diluted to 1:1 (mg:mL) with a 4:1 solution of ddH2O and acetonitrile. Since the samples were primarily water-soluble, this solution was used to disperse the homogenized powder and delay the dissolution of the sample enough to acquire an accurate particle size distribution.

Particle size analysis

Refraction indices used for Aspirin (both normal and enteric) and Excedrin were 1.55 ± 0.2 and 1.60 ± 0.2, respectively. Acquisition time was taken as 256 signal averages over 1 second.

Results

In this study, we investigated the evolution of droplet size resulting from increased milling force and time for comminuted analgesic samples. A consistent sample mass was used to conserve the total mass fraction across different processing intensities and durations. 10-15 mg samples were then removed after the milling process and analyzed via PSA. Data is presented in a step-wise manner by which we first determine an ideal frequency (avoiding the maximum specification of 30 Hz to reduce ambient heat formation unless minimum particle size was reached at that frequency) and subsequently display the time course of the particle size reduction at the given frequency.

Table 1: Sample Processing at 30 seconds.

Aspirin (regular)		Aspirin (enteric)		Excedrin	
Frequency (Hz)	Mean particle diameter (µm)	Frequency (Hz)	Mean particle diameter (µm)	Frequency (Hz)	Mean particle diameter (µm)
15	20.395	15	162.922	15	57.634
20	29.022	20	37.653	20	36.196
25	19.650	25	37.184	25	39.641
30	16.759	30	N/A	30	33.807

The data in Table 1 indicates that processing frequency is correlated to resulting particle size distribution up to the ideal frequency at which there is no detectable change in the sample particle size distribution. Based on the results in table one it was determined that the ideal frequency for processing Aspirin was 30 Hz and 25 Hz respectively. Optimal frequency for reduction of particle size from the Excedrin tables was 30 Hz. This initial duration selection ensures that, over a short burst, milling frequency is the dominant parameter affecting particle size. Thus, ideal particle size reduction occurs at the optimal powdering force applied to the sample.

All samples were then milled at the "optimal frequency" for increasing time periods of 1, 2, and 5 minutes. Figures 1-3 show the resulting particle size distributions.

Figures 1-3 indicates that mean particle size decreases as a function of milling time. However, particle size reduction rate slows as milling times are extended. It was observed that negligible reductions in mean particle size were achieved if milling durations were extended past five minutes. The greatest particle size reduction occurred in the first sixty seconds of milling. Table 2 displays the mean particle size achieved after 5 minutes of milling for all three sample types.

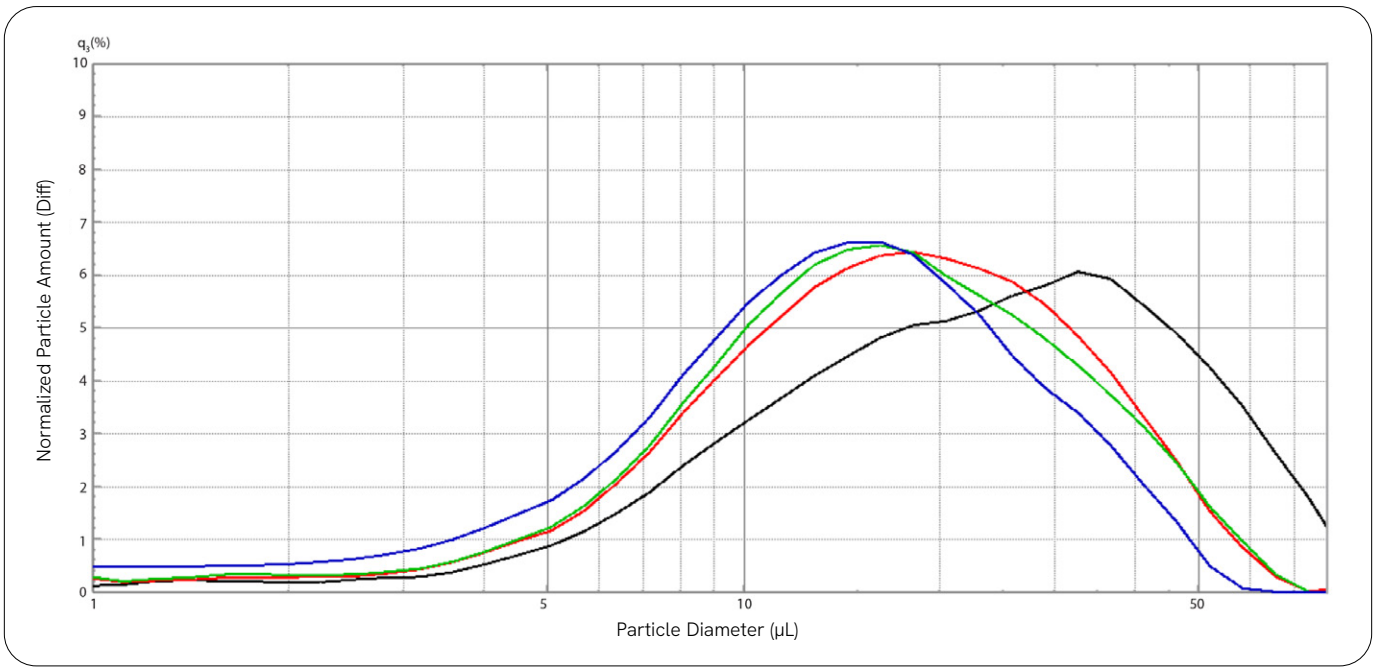

Figure 1: PSA of Aspirin (regular) sample at 25Hz

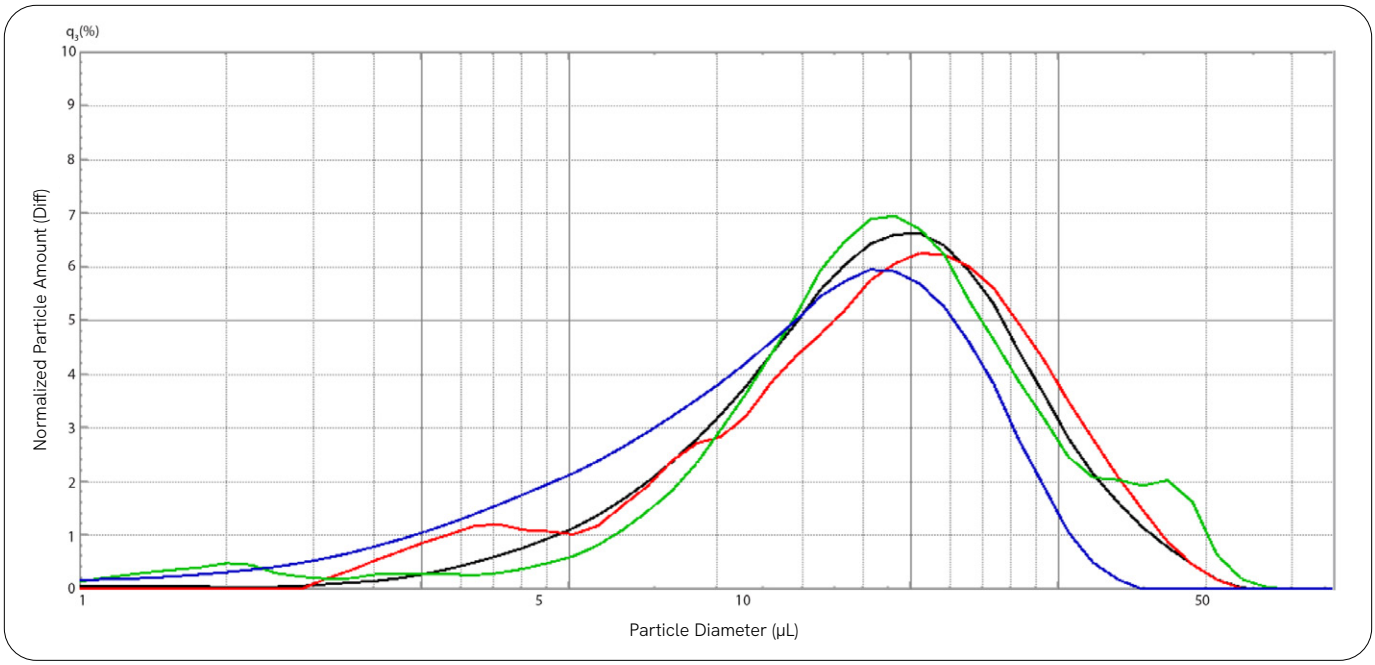

Figure 2: PSA of Aspirin (enteric-coated) sample at 25Hz

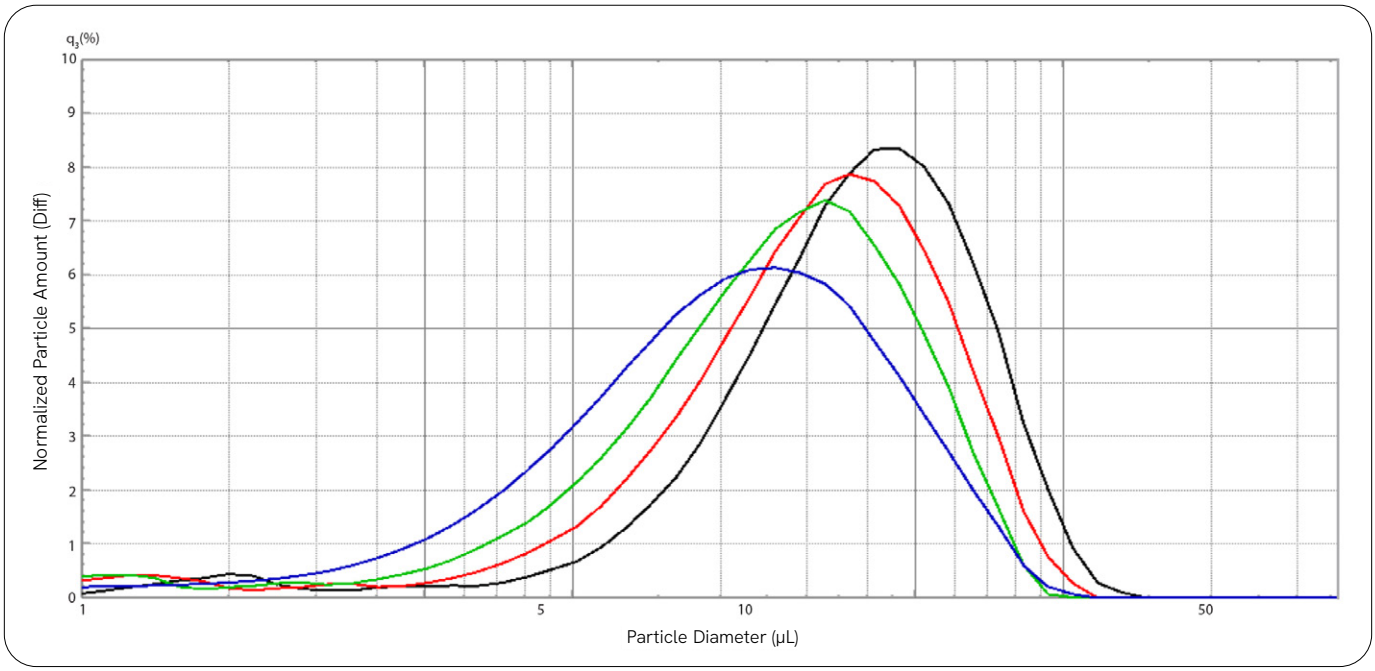

Figure 3: PSA of Excedrin sample at 30Hz

Table 2: Particle size as a function of processing time

Aspirin (regular) 25 Hz		Aspirin (enteric) 25 Hz		Excedrin 30 Hz	
Time (sec)	Mean particle diameter (µm)	Time (sec)	Mean particle diameter (µm)	Time (sec)	Mean particle diameter (µm)
30	19.65	30	37.18	30	33.80
60	14.36	60	38.77	60	27.07
120	13.68	120	29.01	120	22.25
300	11.19	300	23.79	300	18.37

Conclusion

Particle size distributions of samples processed at a fixed frequency over increasing durations revealed that, at the initially selected frequency, there was a trend in diameter reduction that ultimately reached a minimal value at the longest time step. This observation tells us that the inertia of the grinding ball causes moments of impact at an optimal energy and powder dissipation throughout the jar to consistently reduce particle diameter over extended periods of time. The optimal frequency for this phenomenon to occur with Aspirin and Excedrin was recorded to be 25Hz and 30Hz for the selected analgesics, where increasing time steps will further improve particle size reduction.

References

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