

# The influence of crystallization processes on the nano-mechanical properties of fluticasone propionate

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## Summary

In producing a formulation for pulmonary drug delivery, particle size reduction of the active ingredient is often a necessary but detrimental step. Previous studies have investigated the effect of micronization on dry powder inhaler (DPI) performance. However, the effect of mechanical properties of materials upon crystallisation and their resultant micronization properties are not fully understood. Furthermore, there remains a paucity of data relating the mechanical properties of crystals and the subsequent properties once they have been micronized. This study highlights the changes in Young's modulus of crystalline materials as a function of crystallization process. Using an AFM based approach, the mechanical properties of six crystalline fluticasone propionate batches prepared using batch antisolvent precipitation are evaluated using Hertzian mechanics. The Young's modulus values varied between 0.1-2.5 GPa and suggested that rate of antisolvent addition had a greater effect on the Young's modulus of the crystals.

## Background

To enable active pharmaceutical ingredients (APIs) to be delivered to the lungs, particles are generally required to be less than 5  $\mu\text{m}$ . Though novel techniques of directly producing material within this range have been proposed [1,2,3], conventional methods are still dominant within industry [4]. Subsequently, to achieve the particle size requirement for API lung delivery, high energy processing techniques such as micronization, are employed to reduce particle size of input materials produced from batch crystallisation processes. Such high shear mechanical processing techniques result in significant particle fragmentation, which contributes to reducing particle size. The high energy inputs and relative inefficiency of these processes [5] highlight the importance of using optimum operating conditions.

The use of ultrasound in pharmaceutical manufacturing during the crystallisation process has been indicated as a future means of obtaining defined crystalline material within specified parameters [6]. The collapse of cavitation bubbles produced during fluctuations of ultrasound waves through liquid media release large amounts of energy that in turn causes rapidly dissipated changes in temperature and pressure. These kinetic responses, at a macromolecular level, are known to change crystallization kinetics within a defined system. The effect of sonocrystallization on the mechanical properties of these materials is however, not currently known.

A key parameter that plays a pivotal role in determining the efficiency of the micronization process and quality of the resultant micronized product is the Young's modulus of the input crystalline material [7]. The Young's modulus represents the resistance of a material to elastic deformation. Hence, understanding the relationship between crystallisation processes and Young's modulus of resultant crystals should, therefore, aid development of operating parameters that lead to consistent processing and therefore, generate micronized products of defined quality and functionality.

## Aims

The aim of this current study was to determine the relationship between different crystallization processes and the Young's modulus of the resultant crystalline products using an AFM based nano-indentation approach.

## Experimental

To produce crystalline material of fluticasone propionate (FP), acetone was used as the solvent and water as the antisolvent. Six crystalline batches were prepared in total, each with a different rate of antisolvent/solvent ratio addition, with and without the influence of ultrasound (P100, Sonic Systems, Somerset, UK). The resulting crystals were collected by vacuum filtration and then dried at 40°C under vacuum.

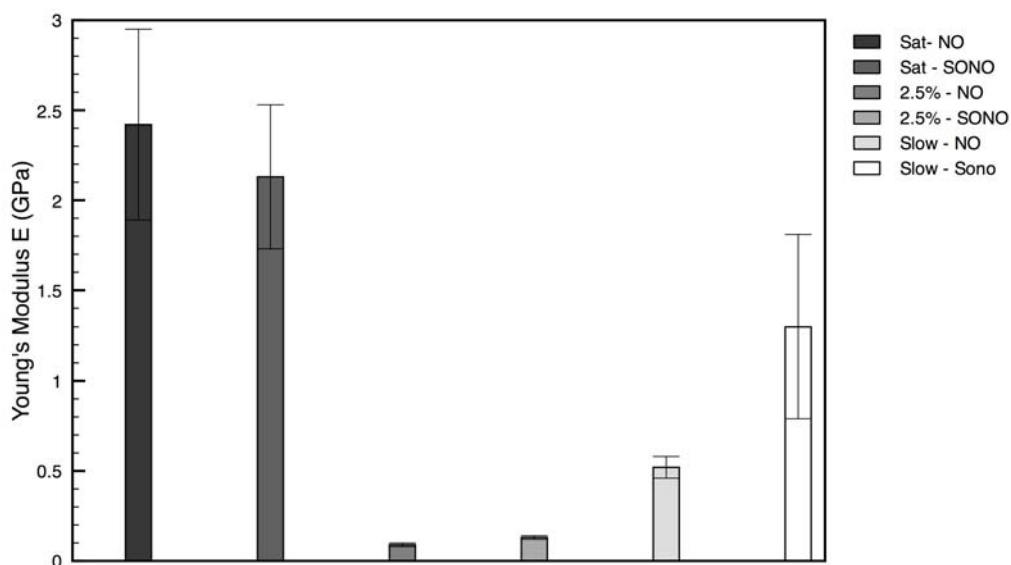
Sample Name	Drug/Solvent Concentration (% w/v)	Solvent/Antisolvent Ratio (v/v)	Antisolvent Addition Rate (mL/hr)	Ultrasound
Sat - NO	Saturated	5:2	300	No
Sat - SONO	Saturated	5:2	300	Yes
2.5 % - NO	2.5	5:3	300	No
2.5% - SONO	2.5	5:3	300	Yes
Slow - NO	2.5	5:3	10	No
Slow - SONO	2.5	5:3	10	Yes

**Table 1.** Details of the batches of fluticasone propionate crystallised using different operating conditions.

Nano-indentation tests were performed using a Nanoscope IIIa and J-scanner (Digital Instruments, Cambridge, UK) using a silicon AFM probe with a nominal spring constant of 36.5 N/m. Repeated indentations (n = 4) of a single crystal were performed on a the dominant crystal face and using the Hertzian model of deformation, the cantilever deflection and piezo displacement were derived into Young's modulus values.

### Results and Discussion

Nano-indentation results from the different samples shows significant mechanical variation in the values of Young's Modulus. It is clear from the data that the rate of antisolvent addition has changed the elasticity and plasticity of the API's Young's modulus, ranging from 0.1 – 2.5 GPa.



**Figure 1.** Results obtained from nano-indentation of individual fluticasone propionate crystals of different batches using an AFM approach.

The data suggests that the rate of antisolvent addition has a greater effect on the subsequent Young's modulus of the material than ultrasound though the large standard deviation for slowly crystallised FP with sonication did reveal possible influences of ultrasound on the mechanical properties.

### Conclusion

This study has demonstrated the change in the mechanical nature of pharmaceutical materials when crystallization conditions have been altered. Future studies with these materials will investigate the micronization efficiency and their relative functionality as pulmonary formulations.

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