

M. de Matas<sup>1</sup>, S. Plakkot<sup>2</sup>, P. York<sup>1</sup>, M. Saunders<sup>3</sup>, and B. Sulaiman<sup>4</sup>

<sup>1</sup>Institute of Pharmaceutical Innovation, University of Bradford, <sup>2</sup>Lena Nanoceutics Ltd.,

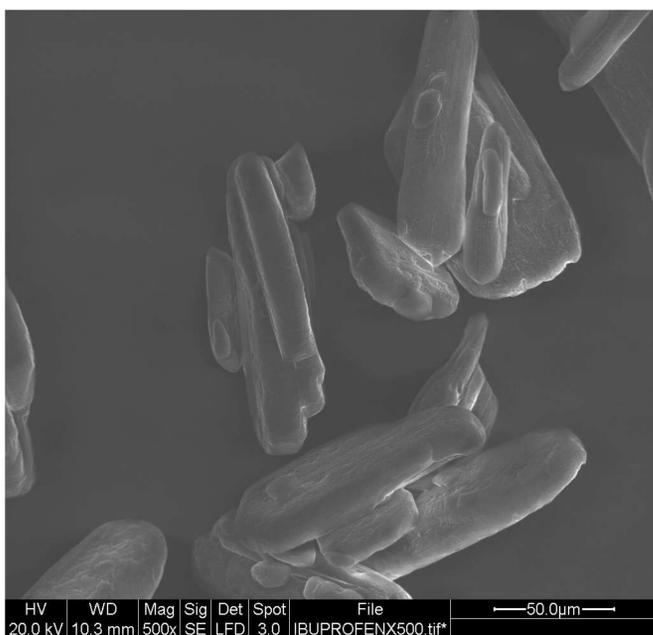
<sup>3</sup>Synectix Pharmaceutical Solutions Limited, <sup>4</sup>Dena Technology Ltd.

## Introduction

Low melting temperature (<100°C), ductile drugs can be difficult to handle and provide challenges to particle size reduction[1]. The purpose of this study was to evaluate the effectiveness of a new comminution technology for reducing the particle size of a challenging active pharmaceutical ingredient (API) to sub-micron levels. The intention of these studies was to improve the dissolution rate of the selected API.

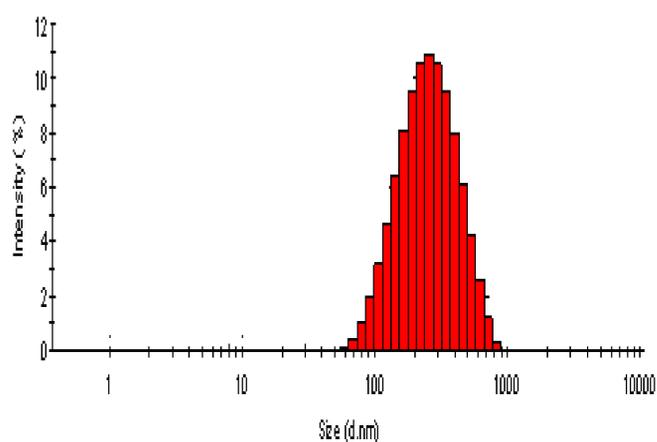
## Experimental Methods

Particle size reduction of a ductile API (brittle:ductile transition 850 μm, melting temperature 78°C) was performed using the DM100 process intensifier (Dena technology Ltd., UK)[2]. The drug was processed at a solids load of 15%w/w for 60 minutes in an aqueous suspension comprising water soluble polymers and an anion surfactant. At-line measurements of particle size were undertaken using dynamic light scattering (DLS) with subsequent evaluation of suspensions by Transmission Electron Microscopy (TEM). The initial size of elongated particles of drug X with aspect ratios of 4 to 6 was approximately in the range 20 μm to 30 μm by 80 μm to 120 μm as determined by Scanning Electron Microscopy (SEM) (Figure 1).



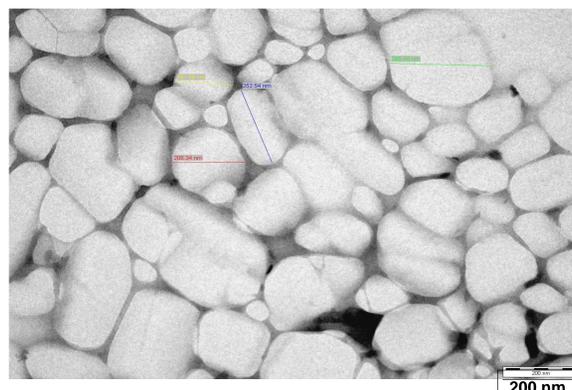
**Figure 1. SEM Image of the initial particle size of drug X**

Size Distribution by Intensity

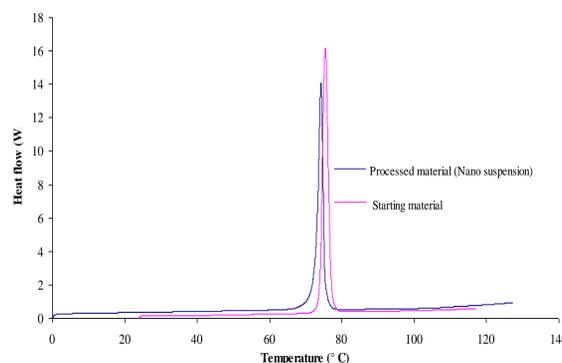


**Figure 2. Particle Size distribution by Dynamic light Scattering for particle produced after 60 minutes of processing**

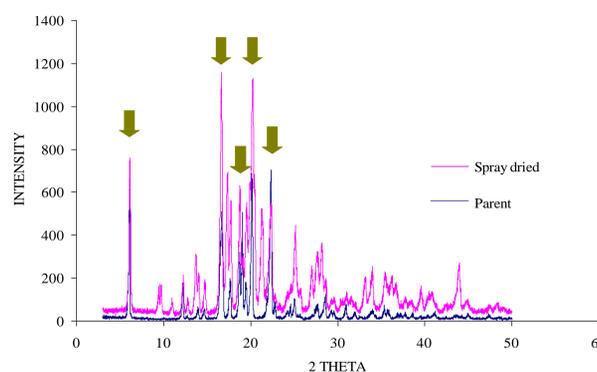
Processed suspensions were then spray-dried in the presence of a water soluble carrier with characterization of in-process materials and spray-dried powder by x-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), TEM and SEM.



**Figure 3. TEM image showing the particle size of drug X after processing.**



**Figure 4. DSC plot for starting material Vs processed material**

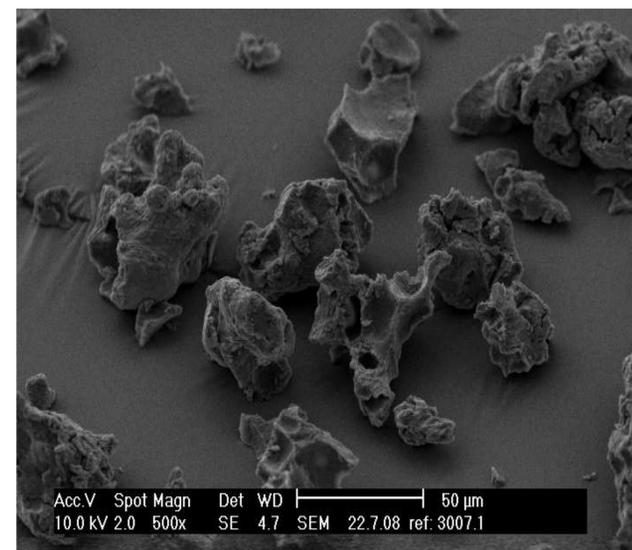


**Figure 5. X-ray powder diffraction for spray dried powder and starting materials (additional peaks are derived from the inert carrier).**

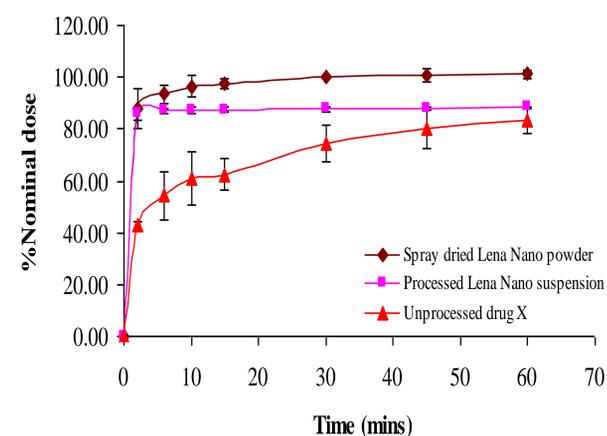
Dissolution behavior of nano-sized formulations was compared to that of commercial drug substance at pH 7.2. Phosphate buffer pH 7.2 was used as the dissolution media at a volume of 900 ml. The temperature of the dissolution bath was set to 37°C. 5mL aliquots of the dissolution media were collected at 0, 2, 6, 10, 15, 30, 45 and 60 minutes and were replaced with equivalent volumes of fresh media. Aliquots were then centrifuged at 14700 rpm for 30 minutes. The supernatant was collected and analysed for the levels of drug using a suitable HPLC method.

## Results and Discussion

DLS and TEM showed that particles of average diameter of approximately 250 nm were produced after 60 minutes of processing (see Figures 2 and 3). DSC and X-ray powder diffraction showed that drug X had maintained its crystallinity and physical form following size reduction and spray drying respectively (see Figures 4 and 5). SEM showed that the spray dried powder had particle size in the range >1 μ (see Figure 6). The dissolution data for the unprocessed drug X, processed Lena nano suspension and spray dried Lena nano powder, showed that the formulation gave more rapid dissolution at the early time points than the unprocessed API (Figure 7). This suggests that no marked particle growth or agglomeration had occurred during spray drying.



**Figure 6. SEM image showing the spray dried powder**



**Figure 7. Comparative dissolution of spray dried Lena nano powder & nano suspension vs unprocessed drug X.**

The spray dried nano powder when re-dispersed in saturated aqueous solution of drug X gave average particle size less than 600 nm. These results provide further confirmation that sub-micron particulates of drug X had been maintained within the water soluble matrix after spray-drying.

## Conclusion

The studies have shown that sub-micron sized crystalline particles of a ductile drug can be produced using a novel comminution technique. These particles can be isolated as a fast dissolving solid form, which maintains a high level of crystallinity after processing and dissolves more rapidly than commercially available forms of the API.

## References

- [1] Larsson, I.; Kristensen, H.G. Powder Technology (2000), 107(1-2), 175-178. Comminution of a brittle ductile material in a micros Ring Mill.
- [2] "The Milling System", Sulaiman, Brian, Patent no.:WO/2007/020407, 2007.

## Acknowledgements

Support was given by Institute of Pharmaceutical Innovation, University of Bradford. Spray drying was carried out by Synectix Pharmaceutical Solutions Limited at King's College London.

## For further information

Please contact [M.Dematas1@Bradford.ac.uk](mailto:M.Dematas1@Bradford.ac.uk). More information on this and related projects can be obtained at [www.lenanano.com](http://www.lenanano.com).