

S. Plakkot¹, M. de Matas², P. York², M. Saunders³ and B. Sulaiman⁴

¹Lena Nanoceutics Ltd., ²Institute of Pharmaceutical Innovation, University of Bradford, ³Synectix Pharmaceutical Solutions Limited, ⁴Dena Technology Ltd.

Introduction

- A critical problem associated with poorly soluble drugs is low and variable bioavailability derived from slow dissolution and absorption.
- A technology licensed to Lena Nanoceutics is based on process intensification using high speed, high efficiency processes that can rapidly generate nano-particles with rapid dissolution rate. [1]
- Nano-particles have the potential to enhance the rate and extent of drug absorption for compounds demonstrating limited aqueous solubility. A study was therefore undertaken to evaluate the impact of sub-micron particles on the dissolution rate of a Nonsteroidal Anti-inflammatory drug (NSAID).

Experimental Methods

- Particle size reduction of a poorly-water soluble NSAID was performed using the Dena DM100 processing system (Dena Technology Ltd, UK).
- The initial size of elongated particles of drug X with aspect ratios of 4 to 6 was approximately in the range 20µm to 30 µm by 80 µm to 120 µm as determined by Scanning Electron Microscopy (SEM) (Figure 1).

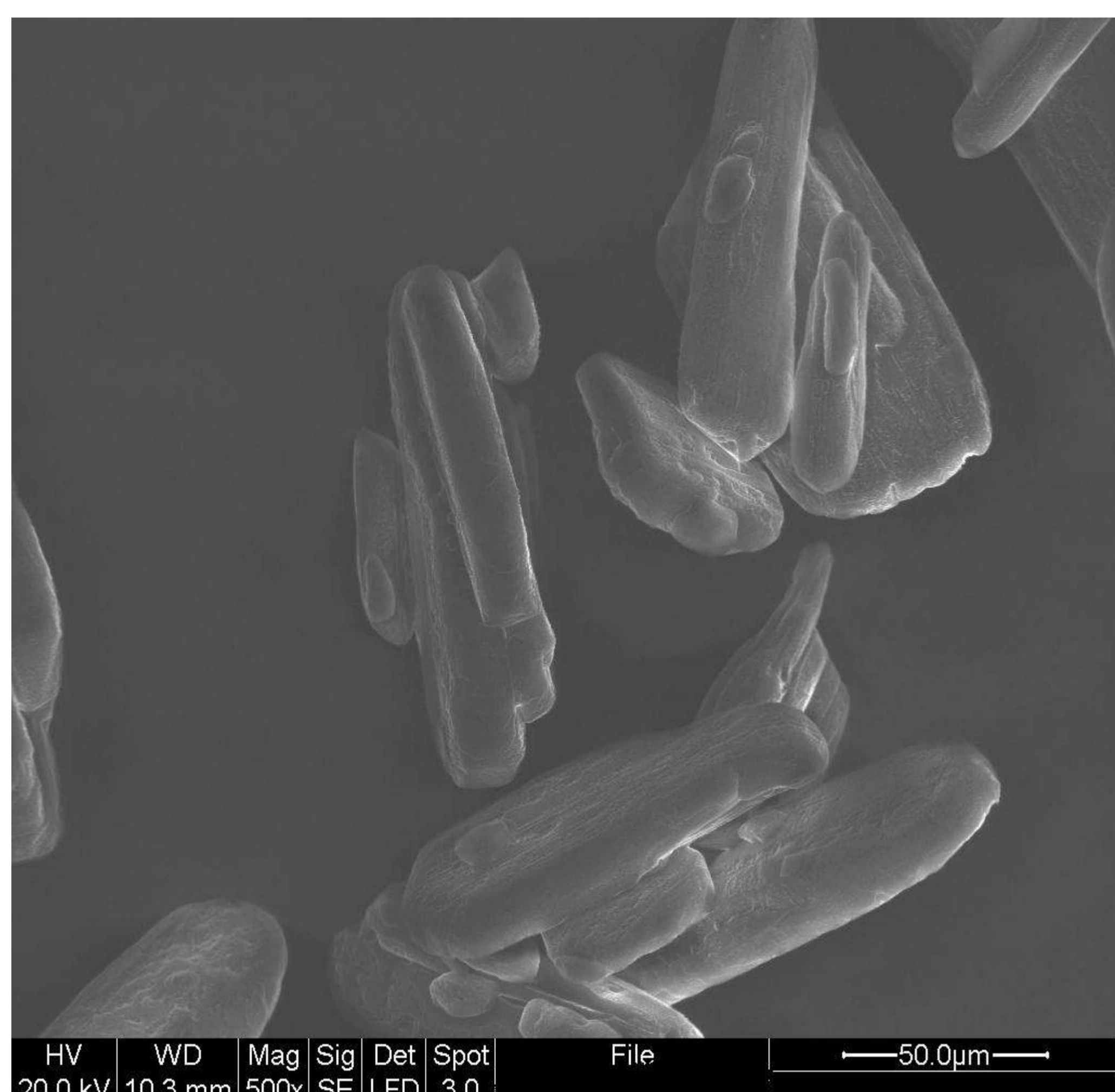


Figure 1. SEM Image of the initial particle size of drug X.

- 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).

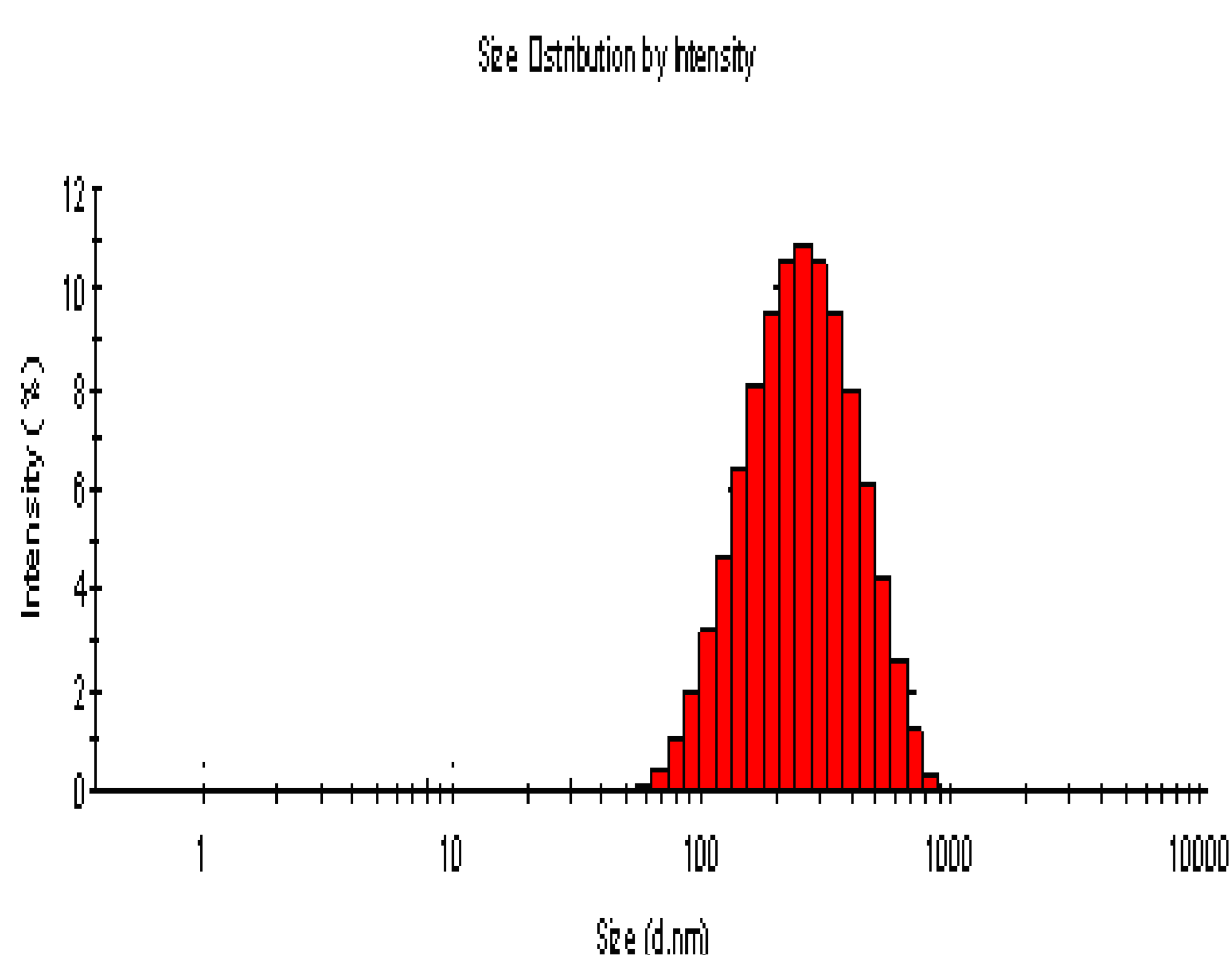


Figure 2. Particle Size distribution by Dynamic light Scattering.

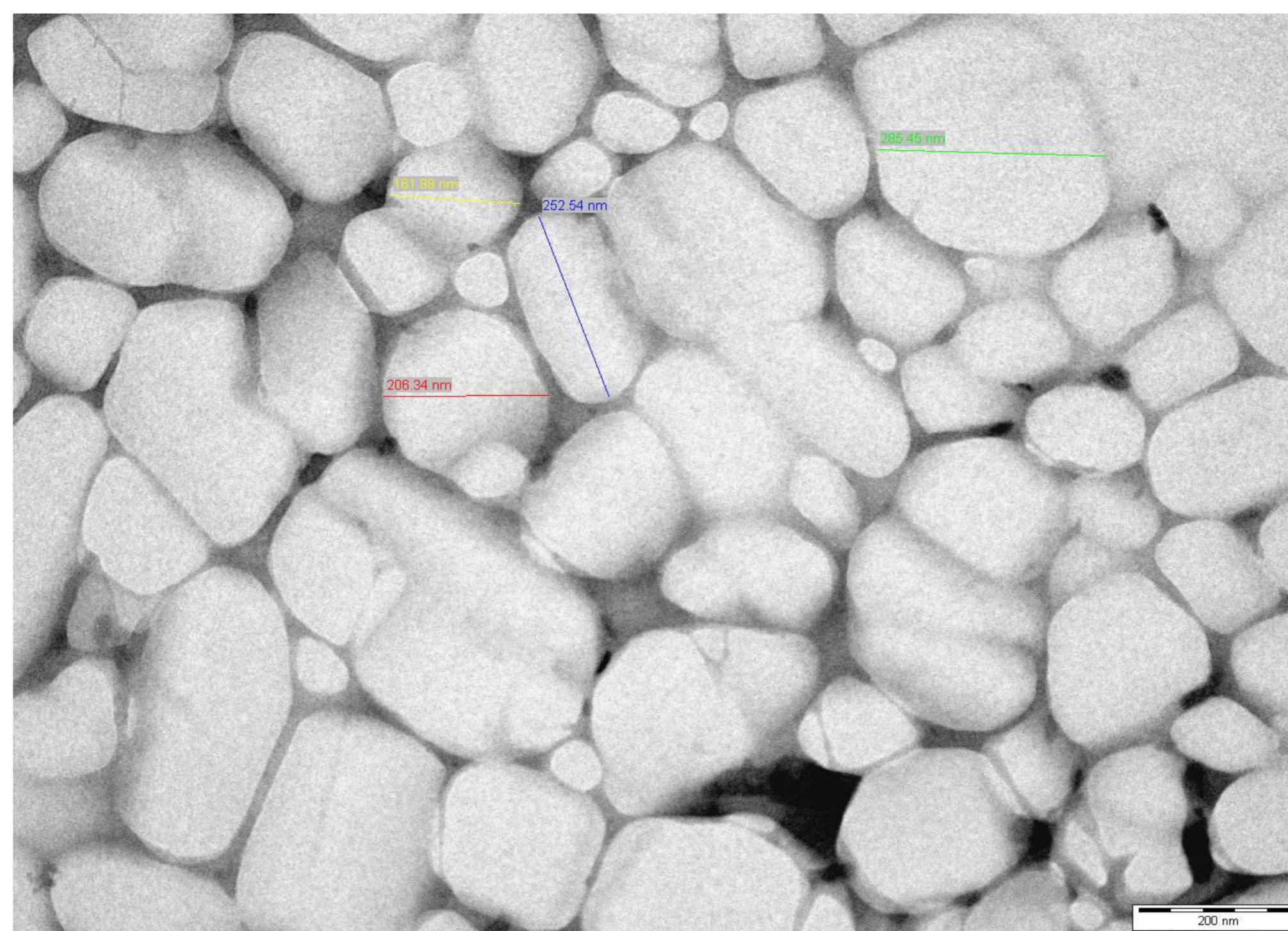


Figure 3. TEM image showing the particle size of drug X after processing.

- The resultant nano-suspension was then spray dried in the presence of a water soluble carrier to obtain a free flowing solid which was evaluated by x-ray powder diffraction (XRPD) and SEM to assess crystallinity and solid form prior to evaluation of dissolution rate.

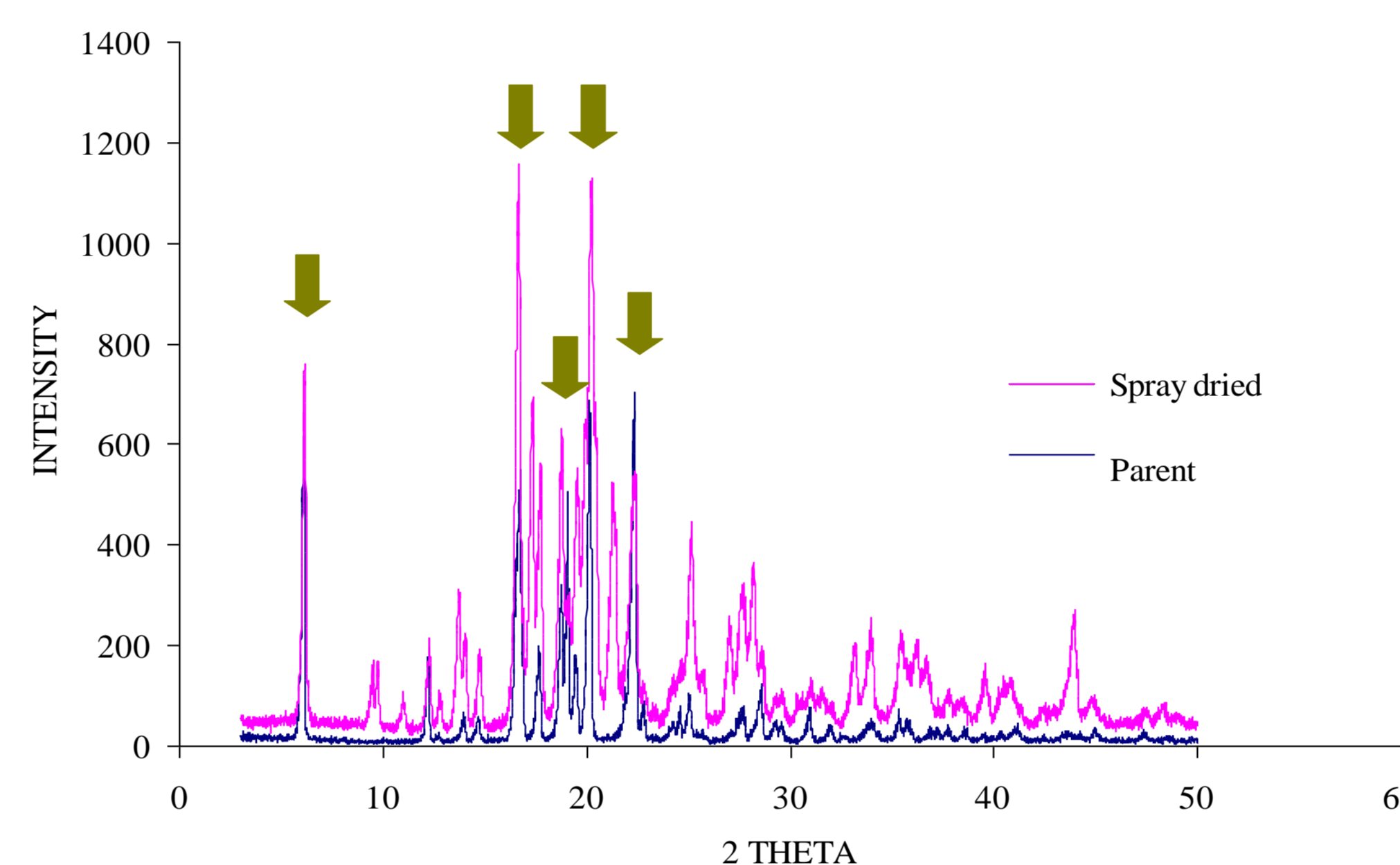


Figure 4. X-ray powder diffraction patterns for spray dried powder and starting materials (additional peaks are derived from the inert carrier).

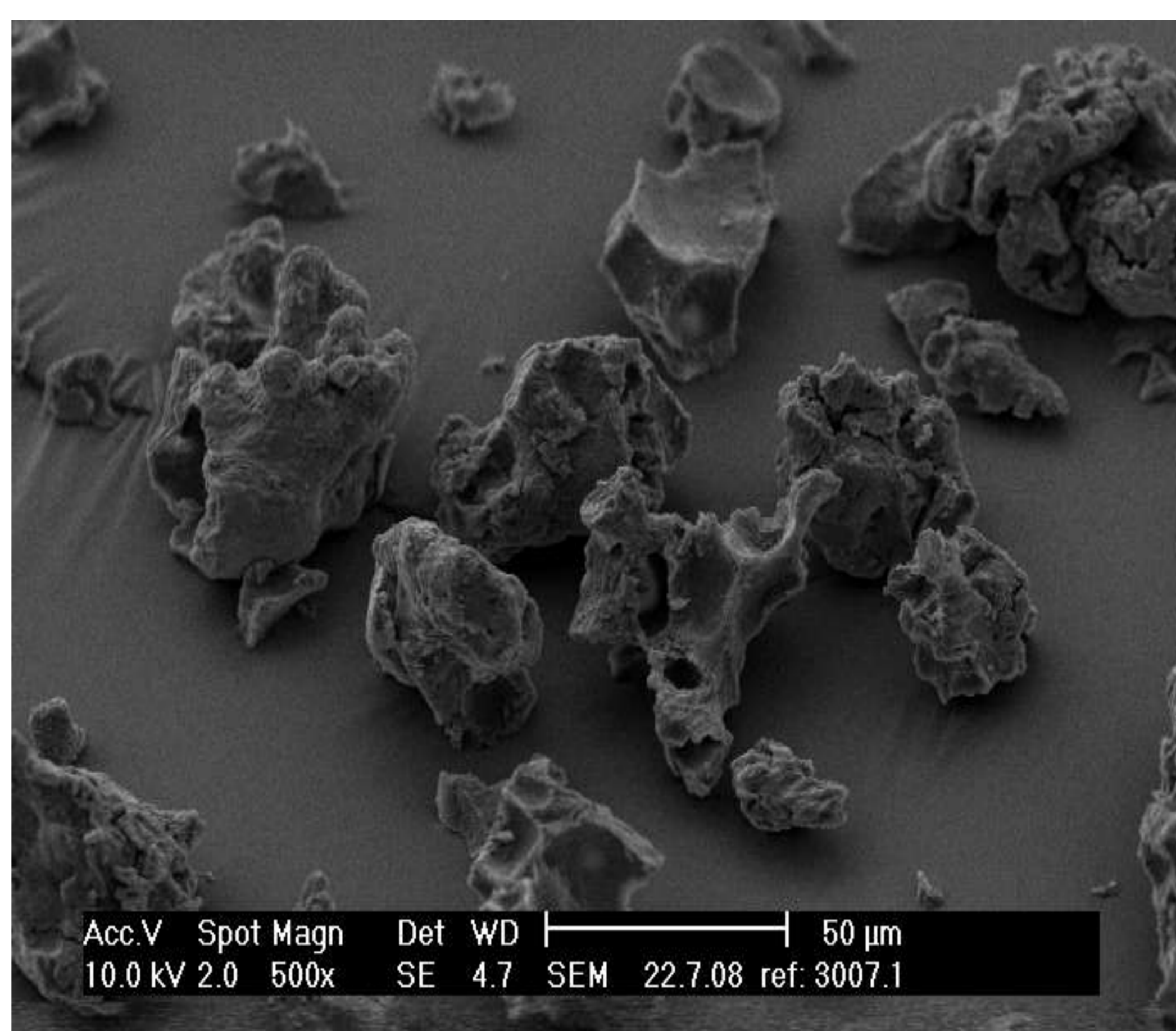


Figure 5. SEM image of spray dried powder.

- Dissolution testing (n = 6), was performed with the USP apparatus 2 [2], with paddle rotations of 50 rpm, for the unprocessed drug, processed nano-suspension and spray dried powder all at a dose of 200 mg. 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 were collected at 0, 2, 6, 10, 15, 30, 45 and 60 minutes after addition of formulations to the dissolution vessels, and were replaced with equivalent volumes of fresh media.
- Aliquots were then centrifuged at 14800 rpm for 30 minutes.
- The supernatant was collected and analysed for the levels of drug using a suitable reverse phase high performance liquid chromatography (RP-HPLC) method.

Results and Discussion

- DLS (Figure 2) and TEM (Figure 3) showed that particles of average diameter of approximately 250 nm were produced after 60 minutes of processing.
- X-ray powder diffraction showed that drug X had maintained its crystallinity following size reduction and spray drying (see figure 4).
- SEM showed that the spray dried powder had irregular morphology with the size typically about 25µm (see Figure 5).
- The dissolution data for nano suspension and the nano powder gave more rapid dissolution at the early time points when compared with the unprocessed drug (Figure 6).
- This suggests that no notable particle growth or agglomeration had occurred during spray drying.

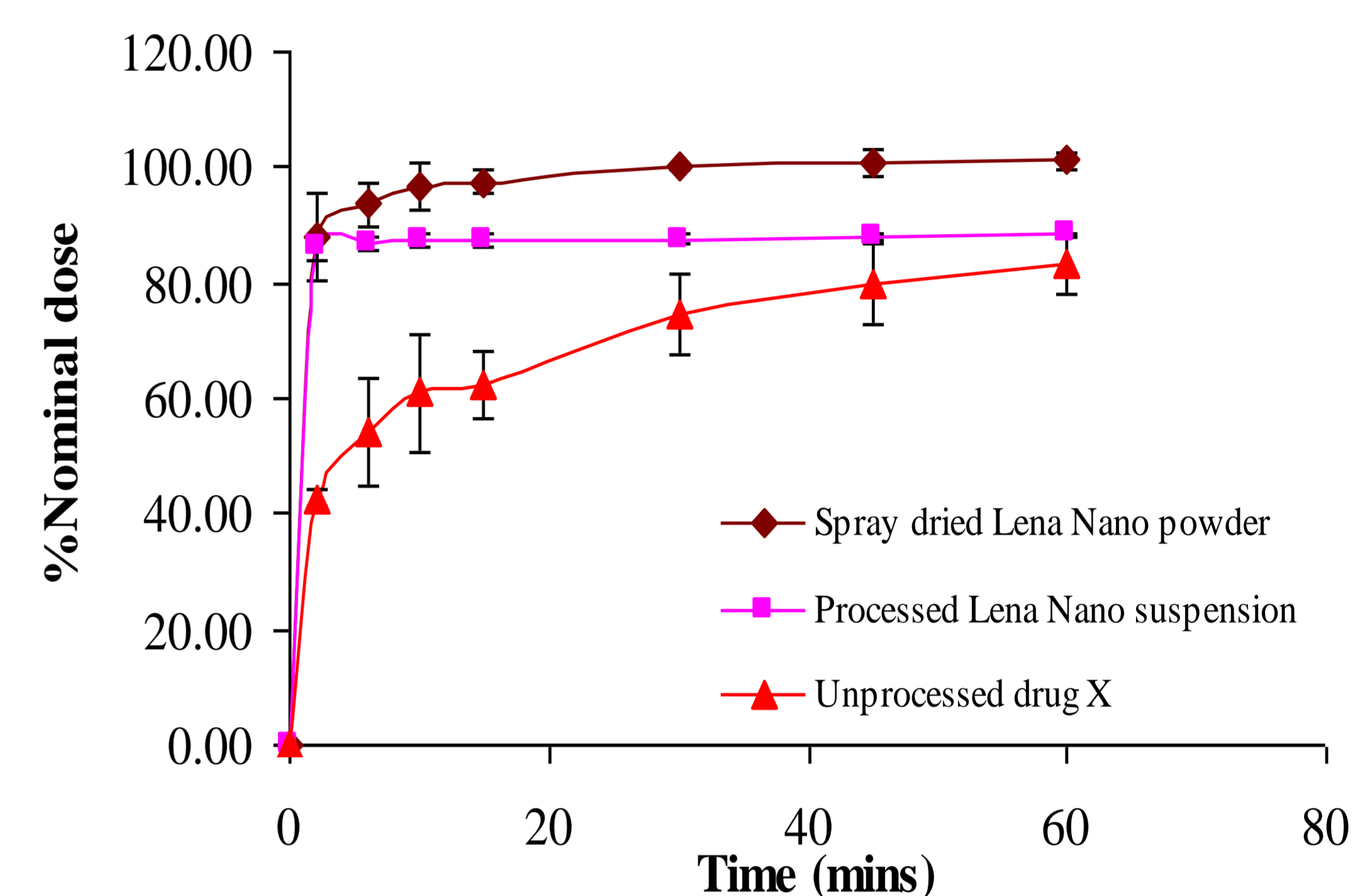


Figure 6. Comparative dissolution of spray dried nano powder, nano suspension vs unprocessed drug X.

- These results provide further confirmation that sub-micron particulates of drug X had been maintained within the water soluble matrix after spray-drying.

Conclusion

- Processing of drug X reduced size from 20 x 120 µm to an average size of approximately 250 nm.
- With a relatively short processing time, it was possible to produce nano-particles which demonstrated more rapid dissolution than the unprocessed material.
- These particles can be isolated as a fast dissolving solid form, which maintains a high level of crystallinity after processing.

References

- [1] "The Milling System", Sulaiman, Brian, Patent no.:WO/2007/020407, 2007.
- [2] The United states Pharmacopeia, 2008.

Acknowledgements

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For further information

Please contact M.Dematas1@Bradford.ac.uk. More information on this and related projects can be obtained at www.lenanano.com