# PROCESSING OF SPHERICAL CRYSTALLINE PARTICLES VIA A NOVEL SOLUTION ATOMISATION AND XTALLISATION BY SONICATION (SAXS) TECHNIQUE

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## Introduction

The limitations of conventional crystallisation techniques in the processing of active pharmaceutical ingredients for inhalation formulations typically requires the need for an additional micronisation step in fine-tuning the particle size characteristics. These destructive based techniques have been shown to adversely affect a range of highly important physicochemical properties (1). Alternative processes for the production of drug particles within an optimum particle size range have shown significant interest and potential. However, there continues to remain the need to engineer particles with an even greater control of the surface characteristics and surface geometry of respirable sized particles while maintaining high throughput, low cost and industrial scalability. This study reports the novel design of a single-step (solution to particle) technique able to produce particles within a well-defined particle size range while controlling their macroscopic morphology and mesoscopic surface topography.

## Materials and Methods

***Particle Formation by Solution Atomisation and Xtallisation by Sonication (SAXS) process***

The SAXS process is described in detail elsewhere (2). The technique consists of three inter-dependant processes:

(i) the production of aerosol droplets of the solute from a carrier solvent using a suitable aerosol generator;

(ii) the collection of the highly supersaturated droplets in a crystallisation vessel containing a non-solvent of the drug;

(iii) the application of ultrasonic waves to a crystallisation vessel to controllably induce homogeneous nucleation and crystal growth.

By combining these processes and controlling relevant parameters, high purity micron-sized crystalline particles could be readily produced in a single-step operation. A schematic representation of the SAXS system is illustrated in Figure 1.

A 4% w/w budesonide solution in methanol was sprayed at a constant flow rate of 16 ml/h. Solutions were sprayed from a conventional high pressure atomiser via a 0.7 mm orifice with a supporting air flow rate of 600 l/h. The separation distance between atomising nozzle and collecting non-solvent was held constant at 15 cm. The highly supersaturated droplets were crystallised in the 35-45kHz ultrasonic frequency range.

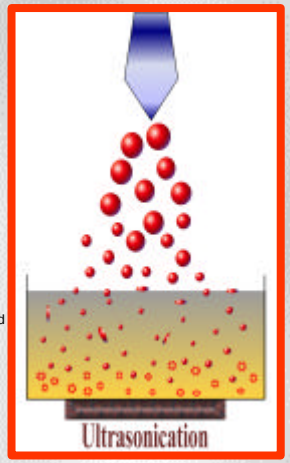


**Fig. 1. Schematic representation of the SAXS process**

**In vitro aerolisation performance**

The in vitro aerolisation performance of carrier free dry powder formulations of micronised and SAXS processed budesonide particles were tested with an Andersen cascade impactor (ACI). Approximately 800µg of sample was weighed into a Turbuhaler reservoir device, and immediately tested upon filling. The amount of drug on each stage was determined by HPLC.

**Settling behavior in pressurised metered dose inhaler formulations**

The influence of possible variations in the dispersive and surface free energies and morphology of micronised and SAXS processes budesonide particles was studied by relating the dispersion stability of the two formulations in a model HFA-pMDI formulation (3). Pressurised metered-dose inhaler formulations of micronised and SAXS processed budesonide were prepared and left to stabilise for 7 days. The dispersion stability was investigated by shaking the glass cans for 10 seconds and subsequently imaging at well-defined time intervals.

## Results and discussion

Variations in the particle morphology of micronised and SAXS processed budesonide particles are shown in Fig. 2A and B, respectively. The SAXS particles appear to be more reproducible in both shape and size. The aerodynamic size distribution and fine particle fraction data for carrier free formulations of micronised and SAXS processed budesonide particles are shown in figure 3. These data illustrated a marked improvement in fine particle delivery characteristics of SAXS processed budesonide. The significant increase in the emitted dose for sprayed-sonocrystallised budesonide (SAXS - 827.1 ± 53.0 µg, micronised budesonide - 691.8 ± 98.5 µg) indicated a dramatic decrease in the adhesive interactions of the SAXS particles within the Turbuhlaer device. The difference in the settling behaviour of micronised and SAXS processed budesonide particles are shown in Figures 4A and 4B, respectively. The micronised particles were shown to flocculate almost instantaneously upon re-dispersion. Meanwhile, budesonide particles remained freely dispersed in the propellant for up to 45 minutes. The apparent increase in stability may be a result of a reduction in surface free energy components and/or the morphological characteristics of the SAXS produced budesonide particles.

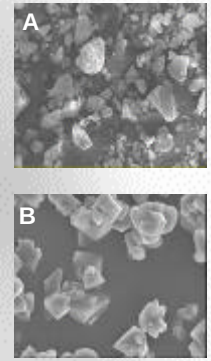


**Fig. 2. SEM micrographs of (A) micronised and (B) SAXS budesonide particles**

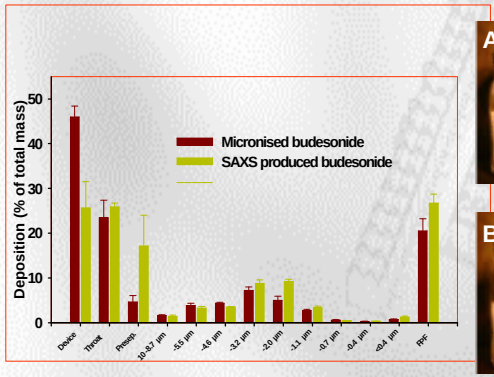


**Fig. 3. Aerodynamic size distribution and deposition profile of carrier free formulations of micronised and SAXS produced budesonide particles.**

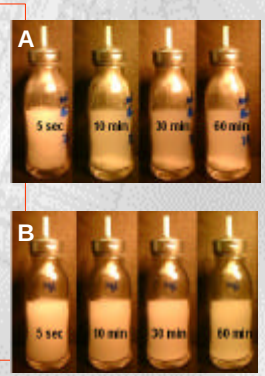


**Fig. 4. Suspension stability of (A) micronised and (B) SAXS budesonide particles in a model HFA-pMDI formulation**

## Conclusions

*In-vitro* aerolisation studies suggested a significant improvement in device clearance and dispersion behaviour of SAXS processed budesonide particles in a carrier free dry powder formulation. Furthermore, the apparent increase resistance to flocculation in a model HFA pMDI formulation suggested a significant alteration to the physicochemical properties of budesonide particle produced by the novel SAXS process.

## References

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3. Wu, W., Giese, R.F., and van Oss, C.J. (1999), "Stability versus flocculation of particle suspensions in water,". *Colloid Surf. B –Biointerfaces*, 14, 47-55.

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