**Maximising MDI suspension product performance via sonic probe processing**

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## Summary

Most Metered Dose Inhaler (MDI) products are formulated as suspensions rather than solutions and this is primarily due to solubility constraints of the active pharmaceutical ingredient/s (API/s) in the hydrofluoroalkane (HFA) based formulations.[1] In order to achieve the desired respirable performance of the product, the input API/s need to be reduced in particle size. This is typically performed by air jet milling, commonly referred to as micronisation. However, micronisation, in addition to the creation of particles of the target size; typically <5µm in diameter, also creates many sub-micron particles as well as amorphous crystal regions. The latter, upon storage, can give rise to agglomerated particles which, if not effectively broken up during MDI manufacture, may adversely affect product performance. The agglomerated particle clusters behave aerodynamically as larger particles and can deposit in the throat instead of being inhaled. Hence formulations in which agglomerates are not properly broken up will exhibit sub-optimal performance which may be manifest in terms of both lowered respirability and more variable dosing behaviour.

This paper compares the use of conventional high shear mixing processing employing the rotor/stator principle, with a new process using powerful ultrasonic probes to effect de-agglomeration during MDI formulation manufacture. Malvern laser diffraction and Andersen Cascade impactor data are presented to show that ultrasonic probe processing can give rise to MDI product with a greater degree of dispersion and higher respirability than product made using conventional high shear mixing.[2]

Finally, data demonstrating successful employment of the sonic probe approach at the pilot manufacturing scale are shown, where a bulk concentrate was processed and monitored over time until full dispersion was complete.

## Background

Agglomeration of the APIs employed in MDIs may occur both during and post manufacture of the powders and is a process driven by thermodynamics with the tendency of adjacent particles to fuse to one another to achieve a lower energy state. Sometimes agglomeration can be mitigated by careful control of storage conditions, for example by employing temperature and humidity control, when different APIs exhibit different tendencies to form agglomerates depending on factors such as hygroscopicity and crystal properties. The method of preparation of the powders is also a critical factor in the tendency for agglomerate formation, with conventional micronisation being particularly problematic due to the formation of a large population of sub-micron particles and crystal surface amorphicity, both of which may lead to the formation of agglomerates. Particle engineering of APIs using liquid phase processing can lower the tendency for agglomerate formation by removing amorphicity and creating rounder particles, although the spray drying typically used to yield the powders from this approach can be a problem area in terms of agglomerate generation. There is therefore an ongoing need to both minimise the formation of agglomerates in input APIs and also to ensure that should any agglomerates be present, that they are effectively broken down into primary particles during suspension manufacturing operations.

High shear mixers based on the rotor/stator principle have been used for many years in suspension MDI manufacture at all processing scales to achieve formulation dispersion.[3] Using a validated, Malvern laser diffraction particle sizing method employing medium followed by high power sonication,[4] it was found that sonic probe treatment of suspensions, that were thought to be fully dispersed, resulted in further dispersion as evidenced by a reduction in measured particle size at the 30W high power level. Experiments were planned to explore in more detail, the dispersion of API suspensions using ultrasonic probes and particle size data were compared to data achieved using the standard high shear mixing approach.

## Experimental

Experiment 1

Micronised API (70 mg, of producer lot known to contain agglomerates, Fig 1.) was weighed into each of 5 glass sample vials. Model propellant dispersant (1% ethanol in a mixture of isooctane and decafluoropentane in a ratio by weight of 52:48) (25 ml) was then added to each vial. Each vial was then subjected to a specific dispersion regime detailed in Table 1, using either a high shear mixer (model IKA T25 Ultra Turrax), or a sonic probe (model Hielscher UIP 100H) with 7 mm sonotrode; 100 W rating. The processing duration for each sample was 2 minutes.

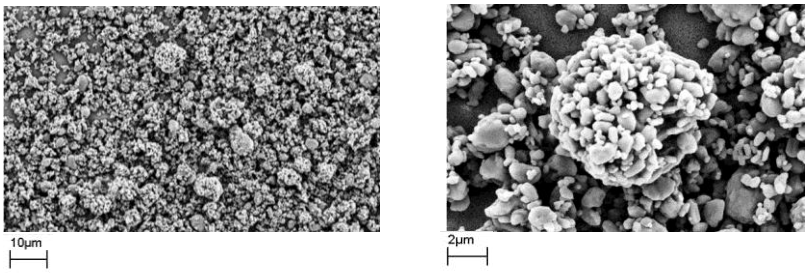


**Fig 1. Scanning Electron Micrographs showing agglomerates in input micronised API**

**Table 1. Dispersion regimes Employed in Experiment 1**

| Sample | Dispersion Regime | Specific Conditions |
|---|---|---|
| 1 | Hielscher UIP100H 7 mm sonotrode submersed in dispersion | 100W, Amplitude setting 100% with 0.5 seconds pulse width |
| 2 | High shear mixing – medium intensity | 10,000 RPM |
| 3 | High shear mixing – high intensity | 20,000 RPM |

Experiment 1 – Results

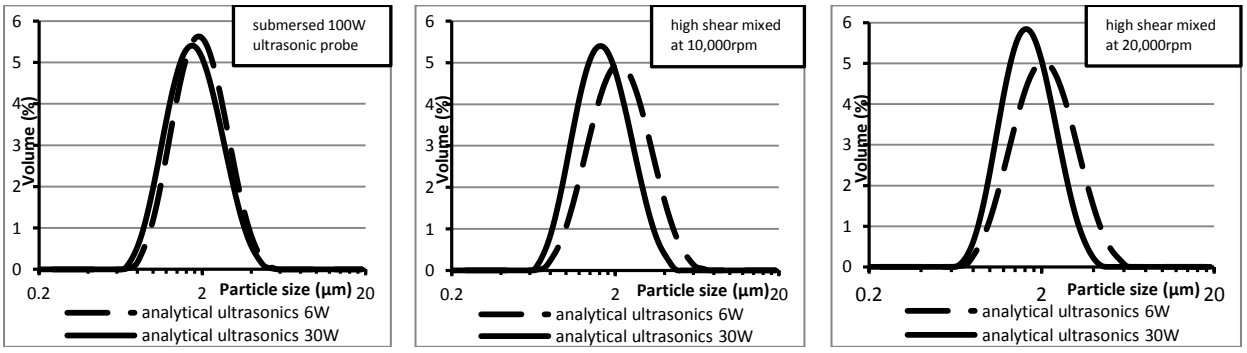


**Fig 2. Malvern analysis of different dispersion processing regimes; submersed 100W ultrasonic probe (left), high shear mixed at 10,000 RPM (centre) and high shear mixed at 20,000 RPM (right). Charted data are for individual samples but are representative of a larger data set.**

Experiment 1 – Discussion

The model dispersant was chosen to with the aim of matching closely the behaviour of the final pressurised formulation and hence contained a low percentage of ethanol. Malvern Mastersizer 2000 suspension particle size measurements were then performed employing the instrument-based sonic probe at a level of 6W power followed by 30W power. Figure 2 shows the particle size distribution of Samples 1 to 3, respectively. Each chart shows two traces; a first trace showing the particle size distribution after instrument-based sonication at 6W power (dashed line) and a second showing the particle size distribution after instrument-based sonication at 30W power (full line). It will be appreciated that for the samples produced using the submersed ultrasonic probe, that the 6W and 30W Malvern particle size distribution (PSD) measurements essentially overlap demonstrating that the ultra sonic probe mixing employed at the processing stage was successful in removing nearly all primary agglomerates. The PSDs for the samples where high shear mixing was employed, show a significantly larger particle size in the 6W instrument-based sonication measurements, pointing to more agglomerates remaining in those dispersions post processing.

Experiment 2

Ethanol (12.02g) was weighed into a 1 litre stainless steel vessel which was cooled to -70°C. Liquefied HFA134a (~600g) was transferred to the vessel. The temperature was adjusted to -55°C, during which the vessel was lightly sealed with PARAFILM$^{TM}$ to protect against ingress of moisture. An ultrasonic apparatus consisting of a Hielscher UIP1000 1000W ultrasonic processor with a 40 mm diameter sonotrode probe was manoeuvred over the vessel and the probe tip was submersed to a depth of approximately 4 cm into the chilled propellant mix. The probe was switched on to half power (50% amplitude; 500W) for about 30 to 45 seconds and micronised API 1 (2.156 g) followed by micronized API 2 (0.629 g), both from producer lots known to contain primary agglomerates, were added to the vessel by momentarily raising the shroud. The ultrasonic processor

was then turned up to full power, 1000W (100% amplitude) and operated for 5 minutes with occasional swirling of the vessel, to ensure effective bulk flow of particles in the propellant mix. The mixture thus prepared was weighed and then added to a 2 litre batching vessel of a cold filling apparatus with refrigeration. Liquefied HFA134a was added such that the resulting total weight of HFA134a allowing for evaporation during the aforementioned processing was 1187 g. The resulting test dispersion was filled in 12 g aliquots into 10 ml aluminium cans having a fluoropolymer internal coating, which were then sealed with 63 µl metering valves. To produce a control reference dispersion product, the procedure of Experiment 1 was repeated using a Silverson Model L4R high shear mixer applied at 7000 RPM in place of the ultrasonic probe.

The aerodynamic PSDs were determined for both the test (ultrasonic probe dispersion) and the reference (high shear mix dispersion) MDI products using the Andersen Mark II Cascade Impactor (ACI) (Thermo Fisher Scientific, Waltham, Massachusetts). Three ACI tests were conducted on each product by coupling the MDI to a USP inlet ('Throat') and actuating 6 times into the ACI setup. The flow rate during testing was 28.3 litres per minute (lpm). The API collected on the valve stem, actuator, throat, ACI Stage 0 jet, ACI impaction plates 0 to 7 and the filter was determined by rinsing each individual section with a known volume of solvent (85% Methanol and 15% Ammonium Acetate solution). The recovered samples were analysed using an HPLC assay. The ACI impaction plates were not coated for any of the tests.

Experiment 2 Results

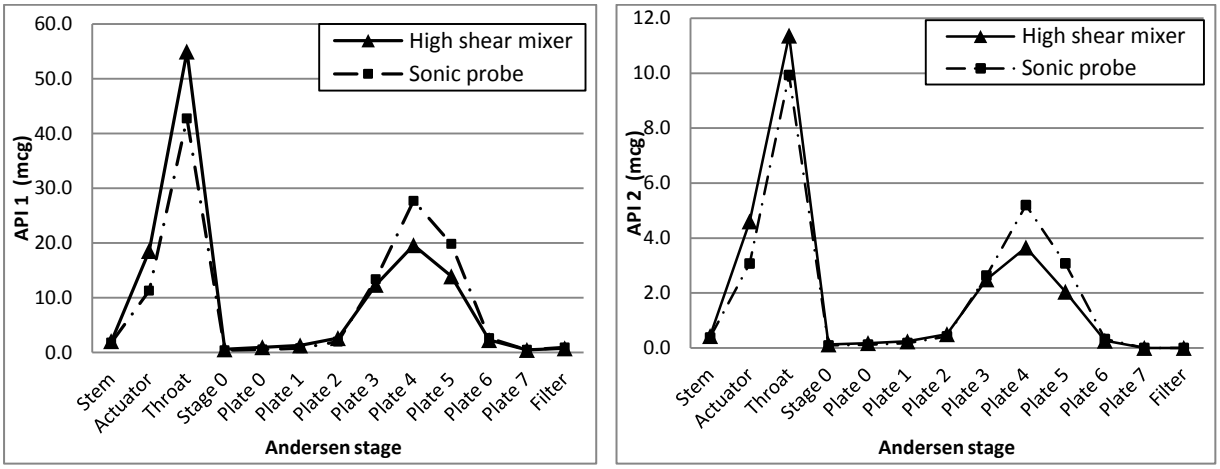


**Fig 3. ACI profile of agglomerated API 1 (left) and agglomerated API 2 (right) (results are an average of 3 separate determinations - one on each of 3 MDIs)**

Experiment 2 Discussion

The averaged results from each population are shown in Fig. 3 with respect to both API 1 and API 2 content. From the charts it can be observed that processing with a submersed, powered ultrasonic probe instead of a conventional high shear mixer, resulted in a reduction in deposition within the actuator and throat, as well as a corresponding increase in deposition on plates 4 and 5 for both APIs.

Experiment 3

This experiment involved the monitoring of the ultrasonic probe dispersion process in a chilled API concentrate at pilot scale, with the aim of determining the minimum processing time to achieve full de-agglomeration of the input APIs. The experiment involved taking samples for particle size analysis from the concentrate at timed intervals during the dispersion process. It was hypothesised that when the concentrate had been processed enough to reach full de-agglomeration, the particle size values of the APIs recovered from the concentrate would be expected to plateau to a minimum value.

Cold concentrates were manufactured using two API lots with distinctly different PSDs which spanned a typical micronised MDI product specification range. The reason for the latter selection was due to the fact that lower PSD values are typically found to correlate with a higher tendency for agglomeration of the API. Two 5 kg concentrates consisting of a mixture of liquefied HFA134a (4420.1g), Ethanol (469.7g), micronised API 1 (85.4g) and micronised API 2 (24.8g) were prepared. The concentrate temperature was maintained at approximately -55°C and preparation occurred within a dry environment to minimise moisture ingress. A Hielscher UIP1000 1000W ultrasonic processor with a 40 mm diameter sonotrode probe was used to process the contents of the concentrates for a total period of 60 to 70 minutes at full power (100% amplitude). The concentrate suspensions were also intermittently dispersed using a high shear mixer at 5500 rpm. The processing of the concentrates was monitored by removing a 1 ml sample via a pre-chilled pipette at regular intervals and transferring the sample directly to the Malvern dispersion medium. Malvern particle size analysis of the concentrate samples was

performed at low (6W) instrument ultrasonic probe dispersion energy, to limit further de-agglomeration in-situ during the analysis.

**Table 2. Input API Particle Sizes used in Cold Concentrates (Malvern 30W de-agglomerated particle size)**

| API | API characteristics | Cold Conc. | d10 (µm) | d50 (µm) | d90 (µm) |
|---|---|---|---|---|---|
| API 1 | Less agglomerated but coarser primary size | 1 | 1.1 | 1.9 | 3.7 |
| API 2 | | | 1.2 | 2.0 | 3.6 |
| API 1 | More agglomerated but finer primary size | 2 | ~0.9 | ~1.5 | ~2.5 |
| API 2 | | | 0.9 | 1.6 | 2.9 |

Experiment 3 Results

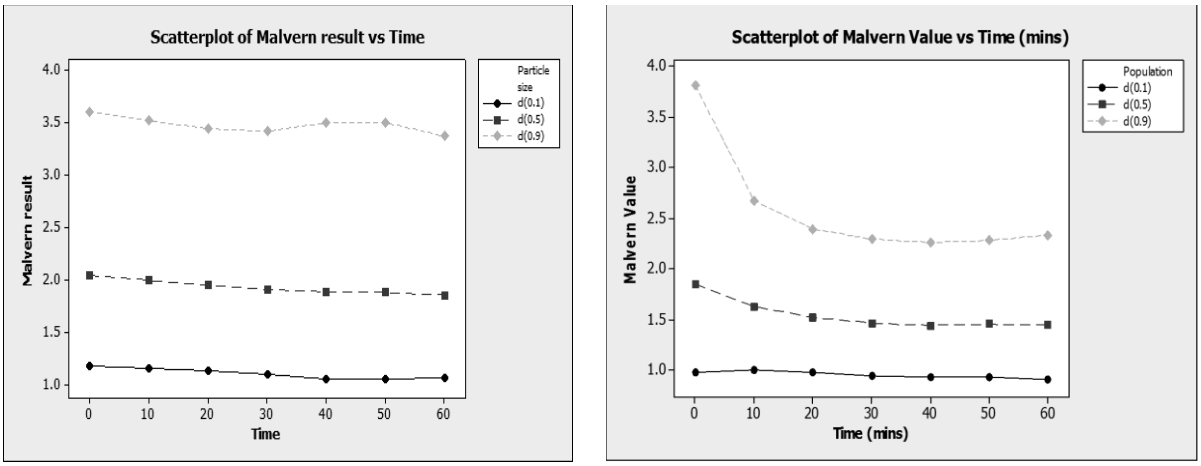


**Fig 4. Malvern (6W) particle size analysis versus processing time for Conc.1 (left) and Conc.2 (right)**

Experiment 3 Discussion

Table 2 shows the Malvern PSDs of the 4 input API lots using the Malvern instrument sonic probe at a setting of 30W. These data represent the reference PSDs of the APIs after full de-agglomeration. Fig 4 shows the PSDs of the samples taken from the Conc.1 and Conc.2 process sonication runs. The profiles are distinctly different. Conc.1, employing coarser, less agglomerated API, shows minimal particle size reduction over the time course of the experiment, whereas Conc.2, employing finer, more-agglomerated API, shows a distinct particle size reduction during the processing run due to the effective de-agglomeration of primary agglomerates by ultrasonic probe processing. The data suggest that an ultrasonic probe dispersion time of around 30 minutes was sufficient to effect complete de-agglomeration. Ultrasonic probe dispersion times of less than this could result in partially agglomerated API remaining in the product, the consequence of which could be variable and sub-optimal product performance. The data suggest that further sonic probe processing beyond the fully de-agglomerated stage, might result in some degree of primary particle break up leading to a slight further fall in measured PSD.

**Conclusions**

The use of ultrasonic probe dispersion was shown to provide a means of removing the primary agglomerates found in certain input API materials, which would otherwise remain using the standard dispersion process of high shear mixing. Ultrasonic probe dispersion therefore provides a means of maximising the respirable potential of an agglomerated input API which might otherwise remain agglomerated.

Ultrasonic probe dispersion was shown to be an effective process to fully de-agglomerate input API in a cold concentrate at the pilot scale. In order to achieve the most efficient processing regime and optimal MDI product performance, careful optimisation of the dispersion processing time is required on a case by case basis to address differences in the particle size and agglomeration levels of APIs.

**References**


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