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INVESTIGATING THE DE-AGGLOMERATION PROFILES OF DPI FORMULATIONS

In this paper, Srinivas Ravindra Babu Behara, PhD, Researcher; David Morton, PhD, Associate Professor; Ian Larson, PhD, Senior Lecturer; and Peter Stewart, PhD, Deputy Dean & Professor of Pharmaceutical Sciences, all of Monash University; and Paul Kippax, PhD, Product Group Manager, Malvern Instruments, describe the use of laser diffraction to analyse dry powder behaviour. The authors introduce relative de-agglomeration versus flow rate profiles, which represent an effective graphical means to summarise the outcome of the complex interplay between the applied aerosolisation energy and the cohesive forces opposing dispersion in different powder formulations emitted from different inhalation devices. The resulting data can be used as a screening method for developing a formulation strategy for a particular active substance.

Despite extensive research efforts, the relative efficiency with which current dry-powder inhaler (DPI) products deliver drugs remains relatively low. Estimates suggest that most commercial products deliver less than 20% of the emitted dose to the lung during routine use.[1] The key to better performance is achieving more informed control of the powder aerosolisation and dispersion processes, as driven by the inhalation effort of the patient. This should ensure that the device and formulation are well matched and optimised. Analytical techniques that support these goals are essential.

> "Potential strategies to improve drug delivery include reducing the strength of particle-particle interactions or increasing the intensity of the dispersion process for higher energy impaction. One way to support research in this area is to look at the strength of individual particle-particle interactions"

DPI formulations have, by necessity, relatively fine drug particle sizes, since only particles of around 5 µm or smaller will penetrate to the lung. Rather than existing as dispersed particles, within the DPI device these micronised, cohesive particles form a continuous networked structure. Packing fractions and interactive forces vary throughout the powder bed and may change during the aerosolisation process. For these reasons analysing the behaviour of the bulk powder bed is a logical approach, and more realistic than investigating and modelling individual particles.

Using the technique of laser diffraction (see Box 1), particle size can be measured in real-time during a DPI actuation. In recent work [2,3] laser diffraction has been used to measure the de-agglomeration behaviour of model DPI formulations over a very broad range of flow rates (30-180 L/min), during dispersion with a commercial device. The resulting data aid understanding of the process and quantify the extent of powder de-agglomeration, providing a new tool for characterising bulk powders and passive DPI performance better.[4,5,6]

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	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)	FPF
Salbutamol Sulphate	0.3	3.4	7.8	75.10%
Lactohale 300	0.2	4.1	9.1	64.80%

Figure 1: Primary particle size data obtained for each of the model formulations. The FPF in this case is defined as the volume% below 5.4 µm in size.

THE MECHANISMS OF DISPERSION

The particle-particle interactions between particles in the sub-5 µm region can be very strong, being driven by electrostatic forces, contact potentials, and intermolecular and capillary interactions.[7] Loaded into a capsule or device, these particles will therefore form a powder bed network, with the strength of interactions being influenced by physical properties such as the particle morphology,[8] surface energy and surface composition.[9] Variations in crystallinity [9] and adsorbed impurities will introduce non-homogeneity into the drug particle population, which may also influence the strength of particle-particle interactions across the network. The microstructures that result range from loosely adhered groups of particles to tightly bound agglomerates.

Delivery of a DPI dose involves two steps: entrainment of the air into the powder bed and then dispersion (i.e. de-agglomeration) of the active drug particles to approach their primary particle size. Achieving efficient powder entrainment, and as a result close to complete device emptying, is important to ensure the delivery of a consistent therapeutic dose. De-agglomeration to a fine, respirable particle size, on the other hand, ensures that the drug is delivered to the target region of the respiratory tract, and that a suitable bioavailability is therefore achieved. For the majority of DPIs (which are passive devices) these twin goals must be achieved by controlling particle-particle interactions such that the inhalation effort of the patient provides sufficient energy via the airflows in the device for dispersion/aerosolisation processes to proceed to a clinically effective conclusion.

As air is drawn through a DPI by the patient, the powder bed is subjected to an aerodynamic drag force and an applied velocity gradient. These parameters influence the rate of acceleration of the particles, and the energy of impact collisions between particles and between particles and the device.[10] De-agglomeration may result from fractures caused by these collisions and from the more gradual process of erosion from the bed.[10] Increasing the flow velocity increases the pressure drop across,[6] and turbulent kinetic energy within,[10] the device, driving up the energy potentially available for dispersion.

Potential strategies to improve drug delivery include reducing the strength of particle-particle interactions [2] or increasing the intensity of the dispersion process for higher energy impaction. One way to support research in this area is to look at the strength of individual particle-particle interactions, using, for example, atomic force microscopy (AFM) measurements. An alternative is to look at the behaviour of the powder bed in its entirety and its response to airflow rate: this latter approach is explored here.

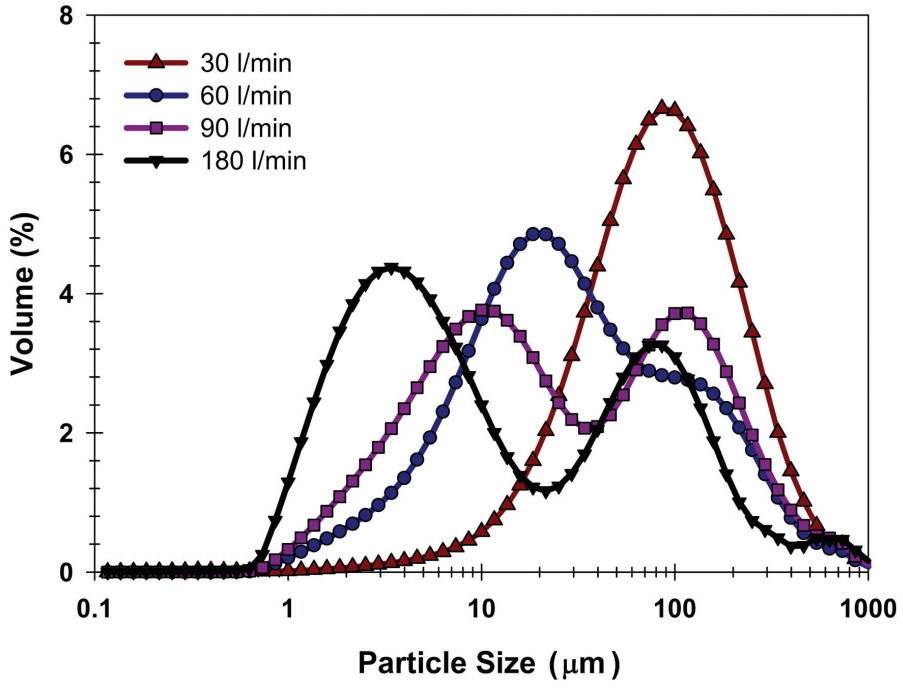

Figure 2: Particle size distributions for salbutamol sulphate measured at flow rates in the range 30-180 L/min.

INVESTIGATING DISPERSION AS A FUNCTION OF AIRFLOW RATE FOR MODEL DPI COMPOUNDS

Experiments were carried out to investigate the dispersion behaviour of two model compounds: Lactohale 300 (LH300) (DFE Pharma, Goch, Germany) and salbutamol sulphate (SS). The particle size of aerosols produced using a Rotahaler® (GSK, London, UK) commercial DPI were measured at airflows in the range 30-180 L/min using the Spraytec laser diffraction analyser (Malvern Instruments, Malvern UK). This upper limit is well above the maximum figure specified for DPI testing (100 L/min) within pharmacopoeia guidelines but reflects the peak inspiratory flow achieved by some patients with certain inhaler devices; the lower limit lies within the accepted range for routine testing. The samples were also measured as liquid dispersions in order to establish a primary particle size distribution against which the degree of dispersion achieved using the DPI could be benchmarked.

Figure 1 shows primary particle size distribution data for the two samples. No evidence of agglomerates was observed, and the Dv50 values for both compounds lie below 5 µm. These results set a baseline for optimal de-agglomeration, suggesting a maximum Fine Particle Fraction (FPF) of around 65% for the LH 300 and 75% for the SS.

The average particle size distributions reported for the SS formulation during dispersion using the Rotahaler at different flow rates are reported in Figure 2.

At low airflow rates, dispersion of the SS produces a monomodal particle size distribution with a Dv50 that falls from 85 µm at 30 L/min to around 19 µm at 60 L/min. However, at 60 L/min a shoulder appears at around 60 µm, suggesting the evolution of a second, smaller particle size mode within the distribution. A bimodal distribution is very much in evidence at all flow rates in the range 90-180 L/min, where the mode

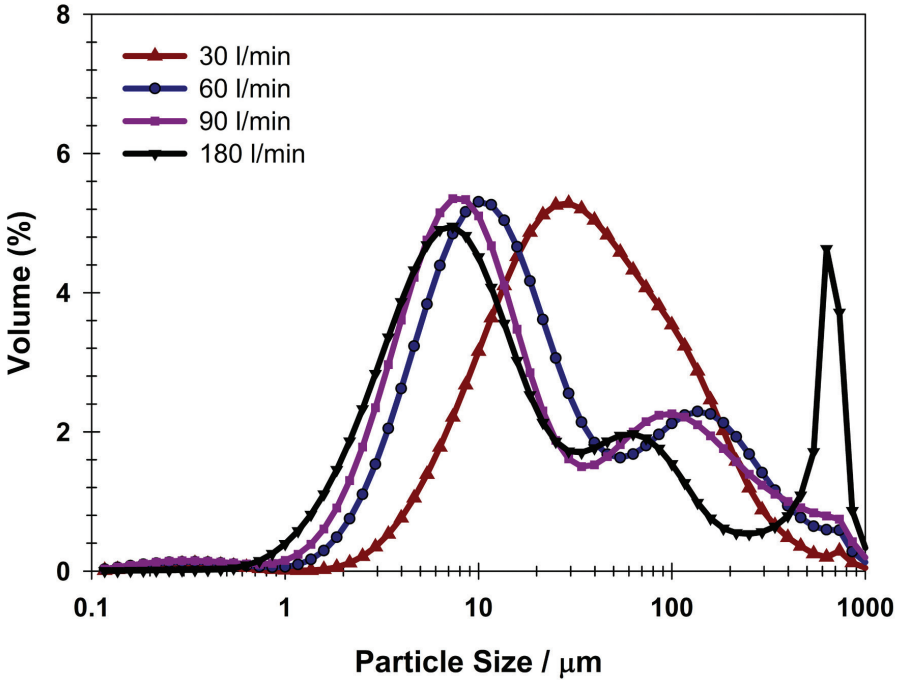

Figure 3: Particle size distributions for Lactohale 300 measured at flow rates in the range 30-180 L/min.

for the finer particle population is seen to shift towards smaller sizes as the applied flow rate increases. Furthermore, as flow rate increases, the area under the curve of the coarser particle population gradually decreases while that of the finer population increases, illustrating the continuing de-agglomeration.

The equivalent data for LH300 show quite different behaviour (see Figure 3). A monomodal distribution is observed at an airflow rate of 30 L/min but a well-defined bimodal distribution establishes at 45 L/min which persists at all higher flow rates. The finer population is centred on a particle diameter of around 7-8 µm at all flow rates, and the coarser population is similarly constant. The area under the fine and coarse parts of the bimodal curve are also, to a significant extent, flow rate independent. At very high flows there is evidence of extremely coarse material exiting the device; this is attributed to the entrainment of solid plugs of undispersed powder.

Emitted dose data (expressed as a percentage of loaded dose) for both compounds (see Figure 4) provide complementary information, indicating the extent of powder entrainment, rather than dispersion. These results suggest that for SS little improvement in emitted dose is achieved by increasing flow rate above 60 L/min, at which point emitted dose is 63.4%. In contrast, LH300 exhibits a steadier rise, from a lower base point (23.7% at 30 L/min) to a much higher upper figure (81.9% at 90 L/min).

Flow rate (L min^{-1})	Salbutamol Sulphate	Lactohale 300
30	32.6 (15.4)	23.7 (10.5)
45	49.6 (15.1)	66.5 (6.4)
60	63.4 (4.6)	74.0 (2.7)
90	60.8 (4.8)	81.9 (2.5)
120	67.4 (5.4)	85.1 (2.2)
150	66.5 (7.8)	85.9 (4.9)
180	68.9 (5.9)	86.4 (1.4)

Figure 4: Emitted doses of processed salbutamol sulphate and Lactohale 300 (expressed as a percentage of loaded dose) dispersed from the Rotahaler® at different flow rates (L/min).

INTRODUCING THE RELATIVE DE-AGGLOMERATION VERSUS FLOW RATE PROFILE

The measured dispersion data can be displayed in a number of different ways. There are, however, obvious benefits in tracking how the FPF (defined as the sub-5.4 µm fraction in this case) changes as a function of flow rate, since this parameter is indicative of the amount of material likely to deposit in the lung. 5.4 µm was selected as the FPF cut-off diameter in this case, as this represented the upper boundary of the size band reported by Spraytec which included data at 5 µm. Normalisation of these results against the primary particle size data for each compound removes a confounding influence from this analysis. With the SS and LH300, 'perfect' de-agglomeration would yield different FPFS – around 75% and 65%, respectively – because these two formulations have different primary particle size distributions.

Comparing the proportion of the dose dispersed to below 5.4 µm with the baseline figure provided by the wet dispersion measurements yields 'relative de-agglomeration', which takes into account this difference. The relative de-agglomeration-flow rate

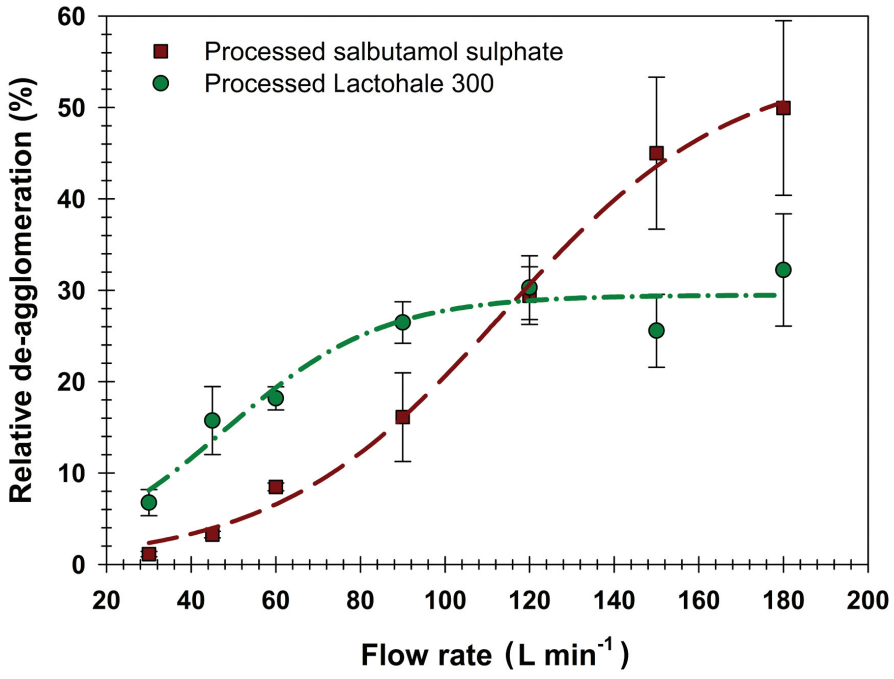

Figure 5: Relative de-agglomeration versus flow rate profiles for salbutamol sulphate and Lactohale 300, including empirical model curves.

	Maximum extent of de-agglomeration (*a*)	Change in de-agglomeration with flow rate (*b*)	Flow rate required to achieve 50% de-agglomeration (*X0*)
Salbutamol sulphate	54.92	26.94	113.77
Lactohale 300	29.48	18.6	48.01

Figure 6: Relative de-agglomeration profile parameters for salbutamol and Lactohale 300.

profile (see Figure 5) shows the progression of dispersion towards the ideal as the applied flow rate is increased.

The relative de-agglomeration profiles for SS and LH300 provide a graphical summary of the very different dispersion behaviour observed with SS and LH300. With SS, relative de-agglomeration rises steadily with flow rate to reach around 50% at 180 L/min. In sharp contrast, with LH300 the relative de-agglomeration value reaches a plateau of around 30% at a flow rate of 90 L/min. Beyond this, the degree of de-agglomeration achieved appears to be independent of flow rate.

Empirical modelling was carried out to represent the developed de-agglomeration profiles in terms of specific parameters. Performing a non-linear least squares regression produced a good fit using a three-parameter sigmoidal equation of the form (see Figure 5):

$$y = \frac{a}{1 + e^{-\left(\frac{x-x0}{b}\right)}}$$

Where parameters *a* and *b* are the maximum extent of de-agglomeration of the powder and the change in de-agglomeration with flow rate respectively, and $\chi 0$ is the flow rate required to achieve 50% de-agglomeration. Values of these parameters for SS and LH300 are shown in Figure 6.

RELATIVE DE-AGGLOMERATION PROFILES TO COMPARE DISPERSION PERFORMANCE

Values for the three parameters derived from the relative de-agglomeration profile efficiently characterise the unique dispersion behaviour of the different compounds. Taken together these data summarise the outcome of the complex interplay between the applied aerosolisation energy and the cohesive forces opposing dispersion. More practically, they provide valuable screening information for devising a formulation strategy for a particular drug.

The maximum extent of relative de-agglomeration is indicative of the optimal achievable performance within the flow field of the device, while the flow rate to achieve 50% relative de-agglomeration suggests how easy or difficult dispersion will be. The change in relative de-agglomeration with flow rate reflects the likely dependence of drug delivery on patient inhalation characteristics. These are all pertinent inputs to the decision-making process surrounding formulation development and its matching to a device system.

An ideal formulation for respiratory delivery would have a high maximum percentage de-agglomeration (*a*), a low change in de-agglomeration with flow rate value (*b*) and require a low flow rate to achieve 50% de-agglomeration ($\chi 0$). Such formulations might be expected to deliver a high proportion of the loaded dose successfully and consistently, even for physically weak patient groups.

In combination with the emitted dose and particle size distribution data, the relative de-agglomeration curve also supports a more detailed analysis of the possible mechanisms of entrainment and dispersion. With SS, increasing flow rate fails to increase emitted dose above a plateau of around 65%, reached at around 60 L/min. However, the relative de-agglomeration curve shows that flow rates in excess of this figure are beneficial in terms of dispersion. Although higher flow rates drive no more material from the device, they promote the dispersion of larger emitted agglomerates to a respirable size (Figure 5), and the continued dispersion of smaller particles (Figure 2).

Interestingly, even though the mode of the finer SS population shifts towards a smaller particle size with increasing flow rate, the size of the larger population remains constant. This suggests that break-up is not a step-wise process but rather that certain agglomerates in the 30 to 600 µm range break up almost completely while others remain intact. Reasons for this are still speculative, but one explanation could be that higher flow rates increase the incidence of impaction. If impaction-based dispersion results in a dramatic reduction in particle size then this would rationalise the observed behaviour.

With the LH300, a larger proportion of the dose is entrained (Figure 4), but the dispersion of this delivered dose plateaus at a low level (Figure 5). Neither result suggests any benefits to increasing flow rate above

BOX 1: LASER DIFFRACTION: REAL-TIME MEASUREMENT OF THE DPI AEROSOL

Uptake of the technique of laser diffraction by DPI researchers is largely attributable to the capability it offers for real-time particle size measurement of the emitted aerosol. With measurement rates in excess of 2.5 kHz, laser diffraction systems track changes in particle size which occur as a result of dispersion during a device actuation. Concentration is also measured as a function of time, making it a suitable technique for studying entrainment.

Particles illuminated in a collimated laser beam scatter light over a range of angles. Large particles generate a high scattering intensity at relatively narrow angles to the incident beam, while smaller particles produce a lower intensity signal but at much wider angles. Laser diffraction particle size analysers record the pattern of scattered light using an array of detectors and then calculate particle size distribution from this, for the entire sample, using an appropriate light scattering model.

The technique can be used to measure both wet and dry samples, including sprays from 0.1-2000 µm in size, comfortably covering the range of interest for DPIs; from primary particles through to agglomerates. Instruments configured for DPI analysis can be set up, in terms of test flow rate, in accordance with pharmacopoeia guidelines for aerodynamic particle size measurement by cascade impaction. However, since measurement is unaffected by airflow, results can also be gathered outside this range, a prerequisite for this study.

around 90 L/min, but ultimate performance is relatively limited in terms of the likely success of drug delivery, with only around 25% of the dose being delivered in a respirable form.

The data here suggest there are relatively weakly bound particulate structures within the powder bed that are easily detached, but that these are present alongside strongly bound agglomerates that cannot be dispersed even when the available dispersion energy is high (high flow rates).

Powders with a high value of *a*, and low values of both *b* and $\chi 0$ are superior in terms of drug delivery performance, dispersing easily and consistently to a high respirable fraction.

Deriving these parameters from the relative de-agglomeration profile is consequently a powerful way of characterising the behaviour of the powder bed in a way that will reflect in-use performance. The approach allows researchers to screen new powder/device combinations rapidly and to summarise dose performance in an efficient and informative way, supporting the swifter development of more successful DPI solutions.

> "In combination with the emitted dose and particle size distribution data, the relative de-agglomeration curve also supports a more detailed analysis of the possible mechanisms of entrainment and dispersion"

IN CONCLUSION

The relative de-agglomeration *versus* flow rate profile provides a tool for contrasting and comparing the performance of DPI formulations in a given device. Derived from laser diffraction measurements of dispersed particle size at flow rates across and beyond the range routinely adopted for DPI characterisation, it quantifies and summarises the dispersive behaviour of a formulation dose. Empirical modelling indicates that the shape of the de-agglomeration profile can be understood using three parameters:

- Maximum extent of de-agglomeration of the powder (*a*)
- Change in de-agglomeration with flow rate (*b*)
- Flow rate required to achieve 50% de-agglomeration ($\chi 0$)

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