

Review of 'Size distribution and particle morphology of analytes dried through the Evaporative Light Scattering Detector: Part A'

Overall: The paper estimates the size distribution of droplets produced by a nebuliser (used in an ELSD) for water and at one liquid and gas flow rate. It demonstrates that this is a challenge due to the submicron droplet sizes produced and therefore the need to use more than one method and perhaps should highlight that there is a lack of droplet size measurements for nebulisers in the literature due to this challenge. It's a shame this is not done for a range of flow rates, however it is appreciated that the ELSD runs at one flowrate. The area where this aspect of the paper could be improved is in giving the reader an understanding of the accuracy of the estimates that are made especially given that air atomiser size prediction models are known for their lack of universality across nozzle types.

The paper then uses this estimated drop size distribution in analysis of measurement of size distribution of solutions atomised and dried in the ELSD and measured using an SMPS. The discussion of the measured size versus predicted needs a bit more depth of analysis and discussion.

The morphologies of particles made in the ELSD are also reported via some high-quality SEMs, this is important for the analysis and good to see.

Overall this is an interesting study, and thorough analysis of the particle formation going on in this system. It would benefit from some of the analysis and discussions developing and some clarification in places. See comments below

(Some of this is interesting for those doing spray drying, especially of inhalable products, I wonder if there is the opportunity to change the title to make it more obvious that there might be something of interest to them.)

Comments:

P2 - L27 – These references are not appropriate. There is a huge amount of literature out there on particle morphology development in hundreds of systems in the spray drying literature. This include organic solutes (L28,29 incorrect). However these tend to focus on larger particles than produce in a nebuliser. However there is significant work on the production of particles for inhalable drug delivery and this focusses on smaller particles, of a size which is similar to the nebuliser.

It is also common to try and estimate droplet size distribution from particle size distribution in spray drying systems.

P2 – L37. I don't think you present results at different temperatures.

P2 -L44 – Bertrani reference, clarify – submitted or in preparation?

P3 – Table 1 – define symbols

P3 = L69 – Provide details of impingement diffuser.

ELSD – Please clarify: Is the whole thing heated to 25°C or just the evaporator section? What is the Y piece for? Is the total nitrogen flow into the Y-Piece -0.4 or 2l/min, if there is make-up nitrogen? How much nitrogen goes down each branch of Y? What is geometry of the nebuliser section?

Fig 3 – thanks for this clear diagram, could you also add tube diameters.

P6 - I13,14 please give details of liquid trap, what particle sizes are you aiming to remove?

P7 – I138 , ' f_l tends to 1' or equals 1 for $d_p > 2 \mu\text{m}$, in your analysis?

PDPA – can you give some details of the system and discuss the detection reliability and accuracy for the minimum particle size. Depends on wavelength, magnification, detection volume, beam angle, refractive index, focal distance etc. What is the minimum size that the system software reports?

P8- I162 The equation for the D_{32} , how universal is this equation. Typically these equations are not that accurate.

P9 equation (6) – looks like $n_{p,s}$ is an absolute number distribution not a pdf per unit concentration of gas? Make this clear.

Also can you discuss correction factor more.

P9_I181 replace 'detector' by 'ELSD' for clarity.

P9 – section 2.4 what was the expected size distribution? Is it cut off? How reproducible, why 90 seconds scans?

Results

A few things here,

Reproducibility – is the data presented in figure 6 a single experiment, or average of a number of experiments? (I don't think you say how long the experiment was done for, whether you see any drift over time or run to run, day to day variability in any of these set-ups. A reader would benefit from seeing some error estimates, to get a feel for the accuracy of the predictions you make

Graphs I believe the output of the PDPA will be in a histogram format, please plot points rather than a piecewise line. I expect it's the same for the AAC (just use small points if there is a lot of them). Plot fits as lines.

I suggest changing your graphs from Excel as it does not look professional. Add the $n_{p,m}$ etc in the legend

Fig 6. In figure title says 'normalised', what do you mean by this as they do not appear to be pdfs. Are they the straight data or have they been scaled at all? There is no discussion of the 'C' factor

Fig 7 a is it a continuous function or purely based on a division of the two curves at points? Clarify in text. And plot as points if it is, or equation that you have. Would it not be better to plot $n_{p,m}$ calculated from $n_{A,m}$ by equation (1) so the fit can be seen rather than replotting the curves from Fig 6?

Fig 7b you have cut this off at 1 μm , what range is f_t defined over? Is the impact of f_t on the mode taken into account? Comment on accuracy at small R. Adding error bars to PDPA results would be of value.

The validity of equation 5 needs some discussion and its validity in these circumstances justified. It looks to be based on experiments on a commercial two fluid nozzle which produces droplets that are of a considerably larger size than produced by a nebuliser. The work of Kemp, see below, as I recall discusses the validity of the droplet-size correlation between sizes. I think they use the correlation by Thybo, which appears to be for smaller droplet sizes.

Thybo, P., Hovgaard, L., Andersen, S. K., & Lindeløv, J. S. (2008). Droplet Size Measurements for Spray Dryer Scale-Up. *Pharmaceutical Development and Technology*, 13(2), 93–104. <https://doi.org/10.1080/10837450701830957>

Kemp, I. C., Wadley, R., Hartwig, T., Cocchini, U., See-Toh, Y., Gorringer, L., ... Ricard, F. (2013). Experimental Study of Spray Drying and Atomization with a Two-Fluid Nozzle to Produce Inhalable Particles. *Drying Technology*, 31(8), 930–941. <https://doi.org/10.1080/07373937.2012.710693>

Kemp, I. C., Hartwig, T., Herdman, R., Hamilton, P., Bisten, A., & Bermingham, S. (2016). Spray drying with a two-fluid nozzle to produce fine particles: Atomization, scale-up, and modeling. *Drying Technology*, 34(10), 1243–1252. <https://doi.org/10.1080/07373937.2015.1103748>

P12 I220 – bulk density? Do you mean absolute/true density of solid. Bulk density of powder is not important. And bulk density of liquid is essentially the same as water.

Fig 9. Again what is accuracy of these measurements. Please give some metrics for these distributions, such as mean, median, d_{10} , d_{90} etc.

P13 I247 – the estimated modal sizes are for what concentrations, I suggest a table, comparing these, and a graph comparing a predicted log-normal distribution to the measured might be of value?

P13 I246-255 This argument needs development and refinement: You are giving one number when you have data for 4 concentrations, so why not present all the data? Let's have some error estimates for the size estimated from the droplet size distribution

(assuming spherical particle with no porosity). Caffeine particles are not spherical, SMPS measurement makes this assumption so what size/diameter are we comparing, is there data on how shape changes SMPS measurements. Shape may also affect the losses in the ELSD comment on this? Absolute densities used are for what form of solid: polymorph, hydrate, amorphous? Include dextran data, estimate density if not measured, it does not have big impact on result as it is proportional to $1/\text{cubic root density}$.

Also you are assuming the particles are dry leaving the ELSD, but all evaporated water ends up in nitrogen stream so will increase humidity, please estimate this humidity.

P13 I254 I believe these dilute solutions will have surface tension very close to water, so unlikely to be important, why not look up and use in the equation?

P14 Good clear images

P14 -15 It would be nice to see this discussion discuss crystallisation, or lack of, of these systems in a little more detail, and draw on the spray drying literature. Crystallisation in bulk solutions is a very different process, and can lead to a very different particle morphology. The references for citric for example are all solution crystallisation so we would expect their morphology to be quite different.

P15 I282 'Down- stream measurements reveal that analyte properties, particularly volatility and bulk density, significantly influence final particle size distributions.' This is really the solidification and crystallisation behaviour, which leads to different morphologies. You mention volatility of the solute, if this is important you should estimate how much of the solute will evaporate and if this will change particle size estimate.

General:

Throughout avoid 'ELSD detector' and just ELSD, after all the 'D' is detector.