Author's rebuttal after Revision 2

We have further revised the document according to the reviewer's suggestions. The original revisions are marked in red, and the second revisions in blue.

Review after revision

The paper has been improved and highlighted aspects of clarity addressed. However the two key areas that need improvement, understanding the accuracy of the estimates and depth of analysis, have not been addressed. Please address these to give confidence in data, and a complete well analysed dataset for the record.

My original review is below with:
1> revolved comments removed
2> authors rebuttal in grey
3> further comments in bold.

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.

A: We thank the reviewer for the comments, as well as for the references further on. We added these references to the introduction, and particularised the study to the ELSD conditions

This issue remains – the references are both liquid metal systems, they are not solutions, they are not similar in particle size, the second one is a rotary atomiser! They are not appropriate. Give the reader a better understanding of the area, there are lots of far more relevant papers out there, with more similar systems and more similar particle sizes.

We have modified the introduction to both cover the range of reviews on spray drying, and once again explain the particular purpose of the present paper, *which is very specific to validation experiments for the ELSD nebulizer, and nothing else.*

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?

A: The system was geometrically arranged to probe a volume of approximately 2 mm length and the smallest possible diameter corresponding to the index of refraction of the fluids considered (water, DOS). This has been added to the text.

More details could still be shared and discussed in the context of accuracy and the 2 um limit you choose, how sensitive are the results to this 2um choice?

The 2 µm represents the lower detection limit of the technique, below which detection is not reliable, and lower than 100%. As stated in the paper, “, the PDPA has a lower detection limit of approximately 2 µm, below which droplets cannot be reliably sized

(Boutier, 2013)". The results are not sensitive to the limit. A comparison of different methods of particle sizing in the micrometer range is available in [R1], which has also been added to the manuscript.

[R1] Sijs, R. et al., "Drop size measurement techniques for sprays: Comparison of image analysis, phase Doppler particle analysis, and laser diffraction " *AIP Advances*, 21:1, 015315 (2021), https://doi.org/10.1063/5.0018667.

P8- l162 The equation for the D_{32}, how universal is this equation. Typically these equations are not that accurate.

> A: Indeed, the authors have not been able to find an available equation in the literature for the range of conditions and nebulisers used, and we acknowledge that there may be inaccuracies, even though the nebuliser is of the same type. This remains an outstanding problem in the field. This has been added as a footnote.

The Aliseda atomiser is a commercial two-fluid nozzle, it is distinctly different from the nebuliser used, and I suspect the operating conditions were a long way away from the nebuliser used. There appear to be correlations available, for similar nebulisers e.g. Kashani, Arash & Mostaghimi, Javad. (2010). Aerosol characterization of concentric pneumatic nebulizer used in inductively coupled plasma-mass spectrometry(ICP-MS). Atomization and Sprays. 20. 415-433. 10.1615/AtomizSpr.v20.i5.40. It would be useful to get some perspective on accuracy of translation of results from DOS to water which is all this equation is used for in this case.

Bertani's thesis (Bertani, goes through many available correlations, including the ones suggested above (see Chapter 2.3.6 of the thesis, Kashani specifically is eq. 2.66 in that work). The selection was restricted by the small liquid and gas flow conditions for which it was validated. Aliseda's correlation on the other hand, was not only well validated, it was also validated for a wide range of fluid of widely varying viscosity – Table 1 in Aliseda's paper. The transition from water to DOS is well covered in this surface-tension/density space. Although his flow rates were higher, his nozzle was also much bigger, and the non-dimensional numbers (We, Oh) were within the same order of magnitude which we were experimenting. We have added further detail to the relevant section in the manuscript.

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.

A: The measurements of size distribution (both SMPS and AAC) were each repeated 3 times and averaged, as stated. The peak concentration variability was negligible, even across multiple days; the averaging just reduced the noise of the data. Whereas the distributions out of the instruments are given as histograms, the fitted lines are much clearer when there are multiple lines on the plot.

Error estimates of the PDPA are harder to estimate. Calibration measurements were made with a standard aerosoliser unit before deployment. Variability was neglibible across multiple days.

Please add some data on accuracy and discuss errors in the paper.
With regard to plots, points representing the instrument data gives clarity on resolution and is actually the measured data. The line between these points are not what is measured and the reader is having to second guess the resolution of the instrument and positions of the points. (I am not suggesting plotting them as bar/column graphs which would be hard to do with many lines.)

The following statement has been added to the text, l. 215-218: "PDPA measurements are collected over 120 s, and averaged over three repeats are produced, with negligible variation between measurements. Likewise, well-mixed AAC measurements were collected as an average of 3 scans, with negligible variability. The estimated variability of the mode across runs was 5.2 nm. "The resolution is determined by the binning allowed by the different instruments; the points on the lines represent the bins. No smoothing has been applied. A statement to that effect has been added to Figure 6.

I suggest changing your graphs from Excel as it does not look professional. Add the np.m etc in the legend.

A: Graphs were produced with Matlab. The y-axis correctly and clearly represent what is being shown.

Agree they are understandable, would be useful to see the variable names np.m etc in the legend.

The names are not necessary in Figure 6, 7, as they represent different numbers depending on what instrument was used. The caption identifies each variable depending on the case, and avoids crowding the legened.

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 of have they been scaled at all? There is no discussion of the 'C' factor

A: The data on the figure are normalized by the peak of the concentrations measured with the well-mixed AAC. The correction factor C was obtained from the ratio in Eq. 1.

Normalisaition: If the values are not as measured np,m, np,s, na,m then clearly indicate the variable you are plotting to make the normalisation clear
State the calculated value of C in the text and discuss.

As stated in the original text, the constant C is obtained from the ratio in Eq. (1). The value is approximately unity for all cases in the range considered, above 2 um. The values were not logged, as the calculations were done to determine the intermediate value, to yield the final distributions in the bins in Figure 6.

Fig 7 a is fl a continuous function or purely based on a division of the two curved 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?

A: The factor f_L is determined from Eq. 1 as a function of diameter along with the factor C for the peak number. The factor f_L is shown on the same plot as the numbers for for clarity, but the numbers are the same as in Fig. 6.

It's not a central point to the paper, but same as before, if fl, and ft are not calculated as continuous functions, but rather from the division of dN/dlog(d) at specific diameter values, then for clarity they should be plotted as points.

Quantities have been calculated at each point. A statement to that effect has been added to Figs. 6 and 7. We believe that plotting every point as a symbol would clutter the plot.

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 that 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., Gorringe, 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

A: We thank the reviewer for the additional helpful references. Having examined these references, it is clear that they are generally relevant, but that the geometry of the nebuliser is quite different from the one used in this study. Therefore, we prefer to use the correlation generate in a study with an almost identical nebuliser.

Note: The atomiser in Aliseda 2008 is a commercial two-fluid nozzle, so not very similar to your nozzle. Kemp, Thybo nozzles are possible more similar in design but I suspect the liquid orifice is large, not sure you gave measurements of your nozzle? There are nebuliser correlations about see above.

As noted above in the discussion of choice of correlations, a large survey of relevant two-fluid nozzles was undertaken, and the closest analogs were used (Aliseda), for which similar We, Re ranges were available. Key dimensions of the of the nozzle used are now given in Fig. 1. These are different from the dimensions used by Aliseda 2008, but the range of We and Re are the same.

P12 l220 – 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.

A: Yes, the bulk density means the solid density, so that equations (7) and (8) can be used after drying.

It's a question of definition, in my book 'bulk' contains pores, 'true' no pores

Bulk density means the density of the relevant material in its compacted form, i.e. for a liquid, this is just the density of the liquid; in the case of solids, this means solids without pores.

Fig 9. Again what is accuracy of these measurements. Please give some metrics for these distributions, such as mean, median, d10, d90 etc.

A: The variability of the peak number measurements is within a less than one percent. The statistical properties are of limited interest for the present paper, compared to the full distribution, as these will be further used for comparison with a model of elastic scattering and signal in the companion paper.

Give data on accuracy in paper, if its less then 1 % say so, and some example data. I was interested, especially in modal values.

We believe that the data speaks for itself, because the means and modes are not used for any particular calculation. Note that the distributions are not log normal, so values of d10 or d90 are not very representative The modal values can be extracted

from the data if there were required. As seen from the graphs, and these vary with concentration.

P13 l247 – 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?

A: The distributions are not by log-normal, as can be seen in Fig. 9, RHS column, as the impingement changes the original droplet size and thus the final distribution. Only two analytes have well defined bulk densities in Table 1, (citric acid and caffeine), and the corresponding modes are cited on the text: "the mode diameters from the peaks of Fig. 9, yields final mode diameters of 46 nm and 52 nm for citric acid and caffeine respectively. The resulting values should be compared to the measured modes of 35 nm 65 nm, respectively according to values on Fig. Therefore, it does not make sense to compare the log normal means.

I was suggesting comparing the log-normal distributions of the particles predicted from the initial spray distribution (please state what you used for mode and sigma) and eqn 8, with the measured distribution in fig 9. This would show you how impingement changes the distribution clearly and clearly show any inconsistencies.

As mentioned above, the final distributions are clearly not log-normal, even if the initial droplet distributions may be so. This of course is a result of the impingement, as discussed in line 247. These are not inconsistencies, but expected physical effects.

'Substituting the values for effective density values for the bulk density values given on Tables 1 and Tables 3, and using the mode diameters from the peaks of Fig. 9 for an analyte concentration of 1g/L, yields final mode diameters of 46 nm and 52 nm for citric acid and caffeine respectively. The resulting values should be compared to the measured modes of 35 nm 65nm, respectively, according to values on Fig. 9.' The sentence does not make sense, I think you are using bulk density (table 1), in eqn 8 and initial mode of 550 nm from fig8 to calculate a predicted mode.

We are not entirely sure what is requested here. The exercise is simply to consider mass conservation for a representative diameter of the wet and dry particles. This involves using the mode diameter (of course, if the distribution is not log-normal, this would not be exact) and use Eq. 8 for the determination of the final diameter of the dried particle. The densities used are those of the initial and final substances (caffeine and citric acid). Calculations are not possible for dextran, as density values are uncertain.

Please add table of predicted and measured modal values, for all experiments, and discuss. This is of significant value as it shows if impingement is consistent and gives confidence or otherwise in the initial droplet size distributions.

We do not understand how the reviewer believes that adding a table of the measured modal values (shown clearly in Fig. 9) improves the confidence of the initial droplet size distributions. The comparison of the modal values shown above for the cases of caffeine and citric acid show that the values of the before and after drying modes are well compatible. Given that the distributions are not log-normal, further comparisons for different concentrations are possible, but not particularly enlightening.

On the other hand, the reviewer may be interested in reading the companion paper (Bertani, 2026) on the numerical modelling of the evaporation and scattering processes, which are exactly the point of the present experiments. In that paper, we show that there is good agreement of the signal, and the final particle distributions obtained using the initial particle droplet size distributions.

P13 l246-255 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/cubic root density.

A: All particles are measured using the electrical mobility diameter as usual per SMPS. The SMPS is calibrated with spherical particles. Estimates of error are determined from repeatability, as discussed above. Estimates of wall losses through the detector past impingement section are negligible (see Bertani, 2024). The state in flight is not known, but it can be assumed that all particles are solid after drying, and the densities for the corresponding dried solid.

Include this and its implications in the discussion in the paper. Discuss all the 4 concentrations for all 3 materials.

As discussed above, the calculation using Eq. (8) is possible but not very enlightening or accurate. The diameters should in general increase with the 1/3 power of concentration. Nevertheless, an extra figure has been added (new Fig. 10) to address the issue, by plotting the estimated values using Eq. 8 vs concentration, and the measured mode (rather than the mass mean) diameters from Fig. 9.

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.

A: The nitrogen dilution is sufficiently large that the total mass evaporated does

not affect the concentration of water in the bulk mixture significantly. See the modelling paper (Bertani et al., 2026) and the PhD thesis (Bertani, 2024).

Good, state this and add the calculated humidity to the paper.

The value is negligible, and therefore it is immaterial.

P13 l254 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?

A: Unclear which equation is being referred to, but the mode diameter in the section is only calculated from a mass balance, for which surface tension is irrelevant.

You suggest the surface tension is playing a role in the droplet size. Eqn 5 captures this effect, so can be used to support your hypothesis or otherwise. My feeling it is likely to be a negligible effect, but you can show otherwise.

Surface tension plays a role in the atomisation, but not in the evaporation or mass balance, so we do not understand the question. Perhaps the questions is whether there is a Kelvin effect to the evaporation, but this is not the case for the present conditions.

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.

A: We thank the reviewer for the suggestion, but this is beyond the scope of the study for the operation of the ELSD.

I would suggest that given it is critical to particle structure it is important to particle properties and therefore performance and a few sentences should be added to cover this. It is also misleading to use bulk solution crystallisation references without highlighting this.

We do not have further comments beyond our original statement. The bulk densityid here defined as the density of the condensed phase density as listed on Table 2, and there is nothing to add.

P15 l282 ‘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.

A: We agree that the crystallisation process leads to different morphologies. Volatility is discussed in the companion modelling paper (Bertani et al., 2025), rather than the present paper where only the measurement results are presented.

This statement 'Down- stream measurements reveal that analyte properties, particularly volatility and bulk density, significantly influence final particle size distributions.' Is not supported by your data. All the solutes are essentially non-volatile. The particle morphology is more important than true density, and morphology is driven by solidification/crystallisation behaviour which may be a function of drying conditions where true density is only a function of polymorph/amorphous.

The statement regarding the concentration is a reflection of equation 8 regarding the bulk density of the condensed phase. The analyte volatility and the corresponding rate of evaporation affects the crystallisation, which in turns changes the bulk density and the final particle diameter. The reviewer should be aware that the SMPS measures the electrical mobility diameter, which can differ from the the spherical assumption regarding equation 8.

Nevertheless, we have modified the statement to: "Measurements of the electrical mobility distribution of the dried particles downstream of the evaporator shows that morphological changes associated with the analyte characteristics affect the bulk density, thus influencing final particle size distributions."