

Wet method development for laser diffraction measurements



Introduction

Particle size analysis using wet dispersion is by far the most widespread method for obtaining reproducible results using laser diffraction. Wet analysis provides a method of dispersion for samples across a wide particle size range, ranging from sub-micron pigments through to sands and sediments. In the case of large particles or polydisperse distributions the viscosity of wet dispersants ensures that bias-free measurements can be made, as the effects of particle sedimentation can be easily overcome. Dispersion can be readily achieved for diverse particulate systems due to the wide range of available wet dispersants available for laser diffraction measurements. The dispersion stability can also be optimized in a way that is not possible for dry measurements. This is due to the fact that the dispersion energy available when particles are wetted in a dispersant is much higher than that seen within a dry powder dispersion system. As such, wet analysis is often the only method available for the reproducible dispersion of sub-micron materials and is preferred for larger materials, especially in the case of sticky or strongly agglomerated powders. Particle friability is also not as much of an issue within wet analysis, as the method of dispersion is less aggressive compared to dry analysis.

Although it is possible to obtain good results using wet dispersion, this can only be achieved if the analyst first develops a robust method. This application note aims to provide users with an idea of the important parameters that should be considered

as part of method development when defining a Standard Operating Procedure (SOP) for measuring wet dispersions using laser diffraction. Laser diffraction measurements can appear to be easy to set up. However, it is important that the following factors associated with the sample are considered if realistic measurements are to be made:

- **Representative Sampling** of the material under test, such that the sub-sample is characteristic of the whole batch.
- **Dispersant selection** in terms of the type of liquid used to disperse the powder and any additives used to promote stabilization.

Users must also configure the instrument's sample dispersion unit in order to achieve reproducible results that actually relate to the physical properties of the powder itself, either in terms of the agglomerated state or in a well-dispersed state. This requires control of the:

- **Measurement Settings** and other analysis options, such as setting the correct obscuration.

- **Dispersion Energy** in terms of the application of sonication to cause deagglomeration of the sample.

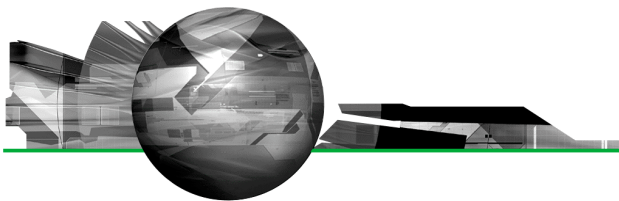
Within this document it is assumed that the user is familiar with the basic operation of a laser diffraction system. This guidance document relates specifically to the Mastersizer 2000 system using the Hydro 2000S, Hydro 2000G or Hydro 2000MU wet dispersion units, all of which allow the user to sonicate the sample within the Mastersizer 2000 system and follow the dispersion process in real-time. However, the method development steps described here can be applied to the wet dispersion units used with other Malvern diffraction systems. Note that guidance on the selection of optical properties is given elsewhere.

Representative Sampling

The way that the sample is withdrawn from the bulk material for analysis is one of the most important aspects of particle size analysis. This is particularly true if large particles (>70 microns in size) are present in the sample. Laser diffraction is a volume-

Table 1: Dispersants for laser diffraction measurements.

| Dispersant | Polarity |
|---|---|
| Water / Deionised Water | Very Polar Solvent ↓ Very Non-Polar Solvent |
| Organic Acids (e.g. Acetic Acid) | |
| Alcohols (e.g. Methanol / Ethanol / Isopropyl Alcohol) | |
| Simple alkanes (Hexane / Heptane / Iso-Octane / Cyclohexane) | |
| Long-chain alkanes and alkenes (Dodecane / Mineral Oils / Sunflower Oil / Palm Oil) | |



based measurement technique and is therefore sensitive to small changes in the amount of large material in the sample. This is because coarse particles occupy a large volume compared to smaller particles (one 100 micron particle has the same volume as one million 1 micron particles and will therefore give the same scattering response). A guide to how sampling can be controlled is given elsewhere^[1]. If sampling is controlled it should be easy to obtain a measurement-to-measurement reproducibility within the limits defined in ISO13320-1^[2], the ISO standard for laser diffraction measurements (within 3% at the $D(v,0.5)$ and within 5% at the $D(v,0.1)$ and $D(v,0.9)$). If sampling is not controlled then measurement-to-measurement variations of up to 20% can be observed.

Dispersant selection

Selection of an appropriate dispersant is the next stage when making wet laser diffraction measurements. It is important that the chosen dispersant:

- Is transparent to the laser beam, ensuring light scattering measurements can be made.
- Has a different refractive index to the particles being measured, as it is the refractive index difference which defines the intensity of scattering observed.
- Does not dissolve the material under test during the measurement.
- Can wet the particles being measured, ensuring agglomerate dispersion.
- Can stabilize the particles following dispersion such that re-agglomeration does not occur.
- Is not too viscous as otherwise bubble formation may occur during measurements.

Water is normally the first choice of solvent as it is transparent and inexpensive. For large particles it is possible to use normal tap water, although when setting SOPs the fact that tap water quality can vary between locations needs to be considered. Where possible, measurements should be made in deionised water, especially where there is a significant amount of material below $20\mu\text{m}$ in size, as the salts present in tap water can lead to particle agglomeration. It may also be necessary to add surfactants and other stabilizers to prevent agglomeration of fine particles.

Many materials, especially pharmaceuticals actives, are soluble in water. For such materials it will be necessary to use a less polar dispersant (table 1). The choice of dispersant will in this case depend on the polarity of the material under test. The cost of disposal of some non-aqueous dispersants is also an important consideration.

Surfactants

The first stage of dispersion during a wet measurement is the wetting of the particle surface by the chosen dispersant. In some cases it may be necessary to use a surfactant to cause wetting to occur. Surfactants (Surface Active Agents) work by lowering the surface tension of the dispersant. This reduces the contact angle between the dispersant and the particle surface, aiding dispersion. The choice of surfactant depends on the particle surface chemistry and the nature of the dispersant. Non-ionic surfactants (e.g. Tween 20 / 80; Span 20 / 80) are generally considered safe for use within pharmaceuticals or food applications. In some applications anionic surfactants (e.g. SDS (sodium dodecylsulfate) or cationic surfactants (e.g. CTAB) can be used to not only improve wetting but also stabilize the particles by absorbing to the particle surface, thus providing a barrier to agglomeration. A guide to different surfactants for use

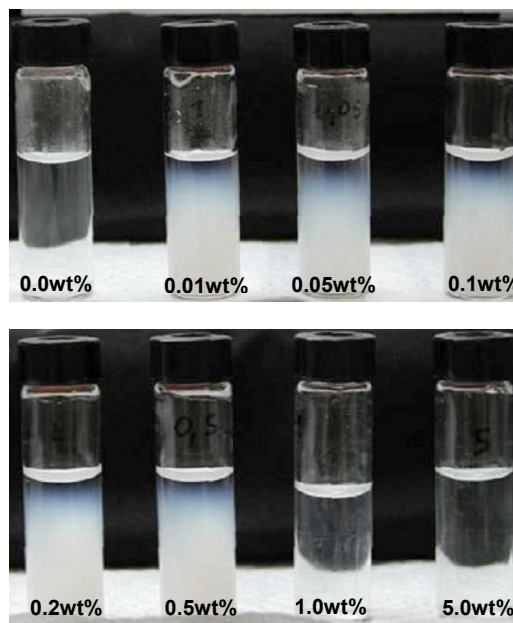
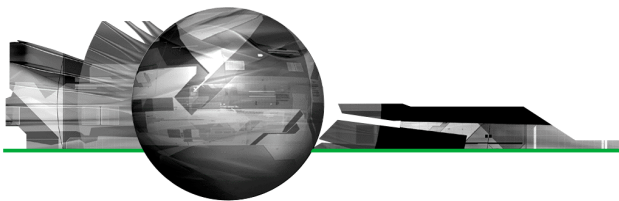


Figure 1: Cerium Oxide Suspensions containing different concentrations of Sodium Hexametaphosphate. In this case 0.1wt% represents the optimum concentration for dispersion.



with different particle and dispersant types can found in ISO14887^[3].

In all cases the concentration of surfactant should be carefully controlled. Surfactants are active at very low concentrations (>0.001 g/l). Generally 1-2 drops of a diluted surfactant solution (10% concentration) is sufficient to improve particle wetting. Using higher concentrations can lead to bubble formation within the dispersion unit, causing the reporting of large particles that are not present in the sample.

Stabilizers

Once the particles are dispersed within the chosen dispersant it is important to ensure that re-agglomeration is prevented. Within aqueous dispersants controlling the conductivity of the suspension can ensure stability. This can simply involve using deionised water as a dispersant rather than tap water. It is also possible to use charge-stabilizing agents such as Sodium Hexametaphosphate (Calgon), Ammonium Citrate or Sodium Pyrophosphate. Each of these increases the stability of a suspension

by increasing the zeta-potential (this is related to the particle charge). However, just as with surfactants, adding too much of these stabilizing agents can cause dispersion problems. Typically the concentration of these species should not be higher than 1w/v% otherwise the conductivity of the solution will be too high, causing agglomeration to occur. A good example of dispersion optimization using these stabilizers is given elsewhere^[4].

Optimizing Dispersant Selection

It is possible to choose the correct dispersion conditions without the need for carrying out particle size measurements. The sample under test can be dispersed in a series of vials containing different dispersants. If the particles float on the top of the dispersant this suggests that wetting is poor – this can be improved by either adding surfactants or by moving to a dispersant with a lower surface tension. If the particles are wetted by the dispersant then the user should sonicate the sample and then observe the settling behaviour. An example of this is shown in figure 1, where

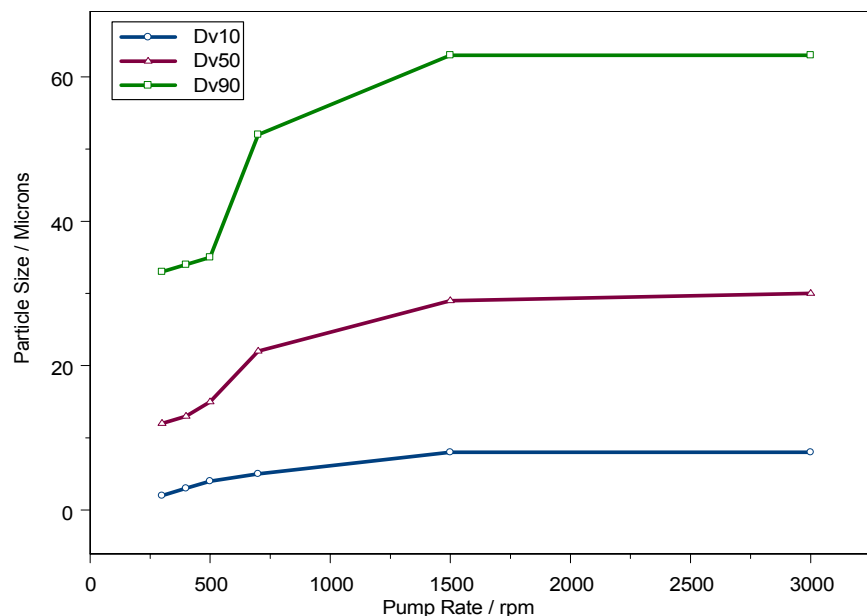


Figure 2: Particle size as a function of pump/stirrer rate.

sodium hexametaphosphate has been used to stabilize a cerium oxide suspension. As can be seen, at low concentrations the suspension is unstable and has completely settled out. Between 0.01wt% and 0.5wt% the suspension is stable – this suggests that a concentration of around 0.25wt% would provide a robust means of ensuring dispersion stability. Finally, the suspension becomes unstable when the concentration of sodium hexametaphosphate is increased beyond 0.5wt%. This is due to the increase in the solution ionic strength.

Measurement Settings

During SOP development, it is important to consider how the amount of sample and the dispersion unit settings affect the measured particle size.

Pump and Stirrer Settings

Optimization of the pump / stirrer rate can be simply be achieved by determining how the reported particle size changes as the pump speed is increased. An example of this is shown in figure 2. At low speeds the reported particle size is too low as the pump rate is not fast enough to suspend the large particles within the sample. At higher pump rates (1500 – 3000 rpm) the reported particle size reaches a plateau value where the particle size remains constant. It is at this point that the particles are correctly presented to the measurement cell. The pump rate should be set at a value at the centre of this range (i.e. at around 2250 rpm for this example). Note that users should not default to using the fastest possible pump rate as this may lead to bubble formation in some dispersants. High pump speeds can also cause particle break-up, especially for emulsion samples.

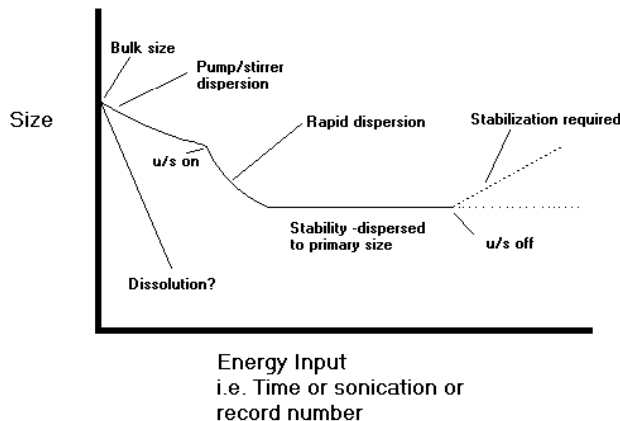
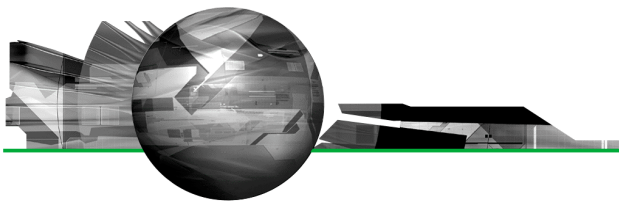


Figure 3: Theoretical plot showing the process of particle dispersion.

Sample Concentration

The sample concentration used for wet laser diffraction measurements must be set so as to allow reproducible scattering data to be obtained without observing multiple scattering [2]. For fine particle measurements (<10 microns in size) this will require users to measure at no more than 10% obscuration. For coarser materials measurement obscurations of up to 20% can be used in order to maximize the single-to-nose ratio. The concentration at which multiple scattering occurs can be assessed by measuring the particle size of a stable dispersion as a function of the measurement obscuration. At low obscurations the reported particle size will be constant – this is where the correct result is obtained. The reported size will shift towards the finer particle sizes at higher obscurations as multiple scattering starts to occur.

Sonication Energy

Once the material being measured has been wetted by the chosen dispersant it is important to ensure that full particle dispersion is

achieved. ISO13320-1 provides guidance concerning the process by which the state of dispersion can be optimized. It suggests that users must understand how the input of dispersion energy affects the particle size. For wet measurements this involves determining how the dispersion is affected by the application of ultrasound.

Solid Particle Measurements

The process of wet method development for the measurement of solid particles is as follows:

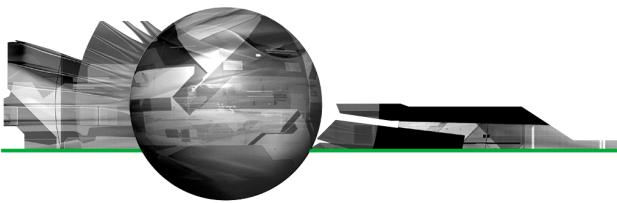
1. The particle size of the sample should be measured following initial wetting of the particles.
2. The particle size should be measured during the application of ultrasound. This allows the dispersion of the sample to be understood.
3. The ultrasound probe should be switched off and the particle size monitored to ensure that the dispersion is stable.

A theoretical plot of how the particle size may vary during dispersion is given in figure 3. Following initial

wetting of the sample in the dispersion unit the particle size may slowly decrease – this is due to the dispersion of loosely bound agglomerates under the action of the pump and stirrer. If the obscuration reduces rapidly at this point it may suggest that the material under test is soluble in the chosen dispersant. If this is the case the obscuration drop will often be associated with an increase in the measured particle size, as the fines present in the sample will be dissolved most rapidly. If this is observed a different dispersant should be used.

Following the initial stage of dispersion, ultrasound should be applied and the particle size followed in real-time. Rapid dispersion is normally observed at this stage as strongly bound agglomerates are dispersed. As the time of sonication is increased the particle size should reach a plateau where the particle size becomes stable – this represents the fully dispersed state. If the particle size continues to reduce over time this may suggest that particle break-up occurs during sonication. Sonication may also cause agglomeration to occur – this would suggest that the dispersion is unstable, requiring the analyst to adjust the dispersion conditions.

Finally, the particle size should be monitored with the ultrasound probe switched off once full dispersion is achieved. If the particle size remains stable when this occurs then the dispersion conditions are optimized. If the particle size increases the dispersion conditions will need to be adjusted, for example by moving to higher stabilizer concentrations or by using deionised water rather than tap water. Note that it is also possible to make measurements under continuous sonication in order to prevent re-agglomeration.



Emulsion Measurements

The dilution of emulsions for laser diffraction measurements can lead to particle coalescence if the dispersion conditions are not optimized. If possible, the choice of surfactants and stabilizers should mimic those present in the product being tested. If the composition of the emulsion is unknown then measurements should be made in deionised water buffered with non-ionic surfactant. Dispersion stability should be assessed by making repeat measurements over time. Sonication should never be used for emulsion samples, as this will cause further emulsification. High pump and stirrer rates should also be avoided as high shear can cause droplet break-up.

Method Development Examples

The following examples show how the dispersion of materials can be optimized following the guidance given above.

Silica

Figure 4 shows the dispersion process for a silica catalyst support material. Initially the particle size was measured during dispersion under the action of the pump and stirrer within the dispersion unit. As can be seen, the coarse particle fraction (Dv90) reduces during this process, as loose agglomerates are dispersed. Following this the ultrasound probe within the dispersion unit was switched on, causing further rapid dispersion. This continued until a stable particle size was obtained. The fact that the particle size stabilized shows that full dispersion was achieved without particle break-up (the size would continue to reduce if break-up occurred). At this point the ultrasound was switched off in order to assess if the dispersion was stable. In this case the particle size remained constant, showing that the dispersion is indeed stable.

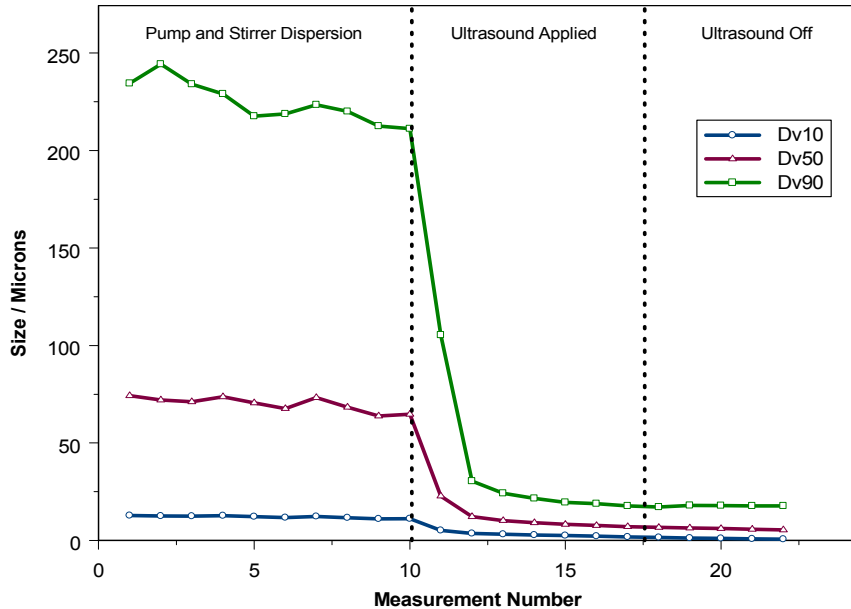


Figure 4: Particle size distribution statistics obtained during the dispersion of a silica catalyst support material.

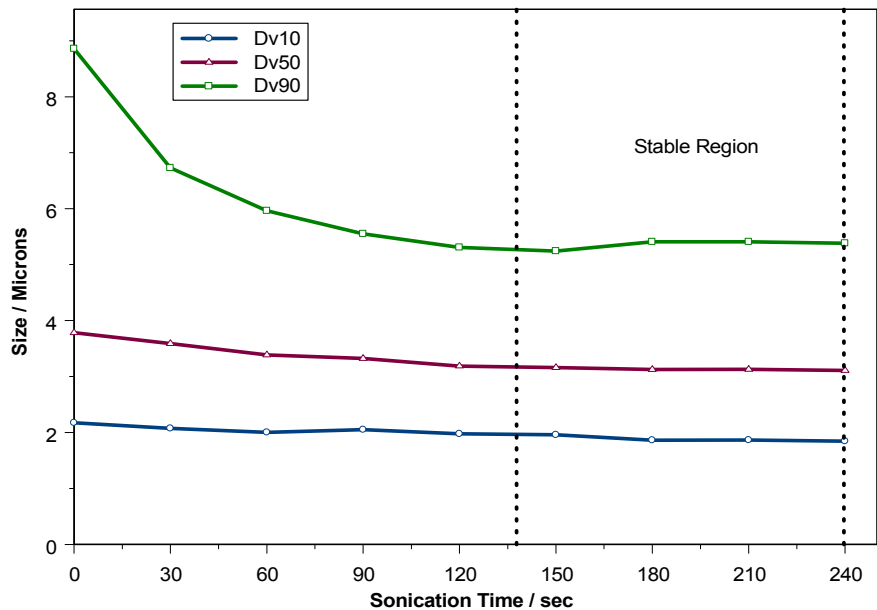
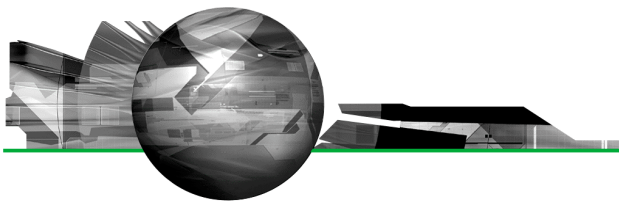


Figure 5: Particle size distribution statistics obtained during the dispersion of a pharmaceutical powder.



Pharmaceutical Powder

A similar dispersion process can be observed for other materials. Figure 5 shows how the particle size varies with sonication time for a pharmaceutical powder. In this case the powder was dispersed in Isopropyl Alcohol, as it was found to be soluble in water. Sonication of the sample showed an initial decrease in the particle size until a plateau was

reached at between 120sec and 240sec of sonication. In this case a sonication time of 180sec was chosen as a robust way of dispersing the powder. Table 2 shows the batch-to-batch variation in the results obtained using an SOP set for this sonication time, confirming that this provides a reproducible dispersion method.

Table 2: Results obtained for different pharmaceutical powder batches.

| Measurement | Dv10 / Microns | Dv50 / Microns | Dv90 / Microns |
|----------------------|----------------|----------------|----------------|
| 1 | 1.86 | 3.13 | 5.41 |
| 2 | 1.87 | 3.13 | 5.41 |
| 3 | 1.87 | 3.14 | 5.44 |
| 4 | 1.85 | 3.12 | 5.40 |
| 5 | 1.90 | 3.16 | 5.29 |
| Average | 1.87 | 3.13 | 5.39 |
| Variation (%) | 0.97 | 0.45 | 1.10 |

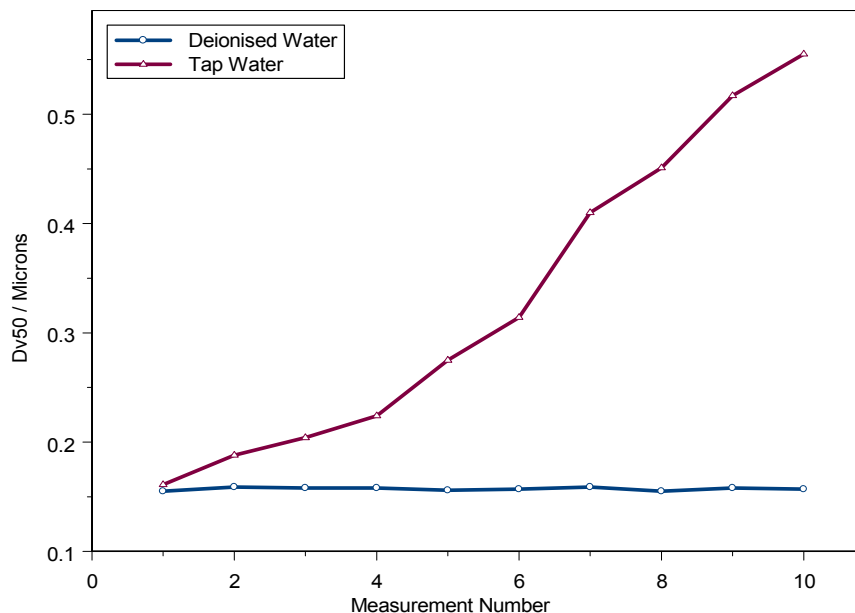


Figure 5: Dv50 reported for emulsion measurements in deionised water and tap water.

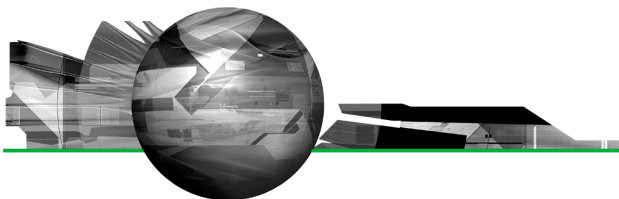
Emulsion Measurements

The importance of setting the correct dispersion conditions for emulsion measurements is shown in figure 5. Here the Dv50 reported for a series of food emulsion measurements is shown for two different dispersants. In each case the dispersion medium was buffered with a low concentration of non-ionic surfactant. However, one set of measurements was carried out in tap water that contained a high concentration of electrolytes whereas the other measurements were carried out in deionised water. As can be seen, the high electrolyte concentration in the tap water caused the emulsion to flocculate, leading to the reporting of a much larger particle size than expected. Moving to deionised water allowed stable measurements to be achieved.

Note that in this case making single measurements would not have allowed the dispersion process to be understood. Both dispersion methods yielded a similar particle size at the start of the measurement process. Only by making repeat measurement can the dispersion process followed, revealing the instability of the dispersion when using tap water as a dispersant. This then allows a possible source of result variability to be understood and isolated.

Summary

The development of a wet measurement method requires the user to explore and understand the way in which the material is sampled, the choice of dispersant and how the sample reacts to the application of ultrasound. By controlling each of these a robust method can be developed, ensuring good batch-to-batch reproducibility. This, in turn, increases the sensitivity of the size measurement to changes in the material properties.



References

[1] Sampling for Particle Size Analysis. Malvern Application Note: MRK456.

[2] ISO13320 (1999). Particle Size Analysis - Laser Diffraction Methods. Part 1: General Principles.

[3] ISO14887 (2000). Sample Preparation – Dispersing procedures for powders in liquids.

[4] The use of zeta potential measurements for improving dispersion during particle size determination. Malvern Application Note: MRK373.

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