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Effect of dwell time on single particle inductively coupled plasma mass spectrometry data acquisition quality

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The characterization, sizing, and quantification of metal-based nanoparticles (NP) in a variety of matrices using single particle-inductively coupled plasma-mass spectrometry (SP-ICP-MS) is becoming increasingly popular due to the sensitive nature of the technique. Nanoparticle events in the plasma are less than 0.5 ms in duration; however current quadrupole-based ICP-MS instruments are limited to instrument dwell times in the millisecond range and have data acquisition overhead that adversely affects data quality. Novel instrument settings and data processing techniques can be used to explore the benefits of continuous data acquisition rates as fast as 10^5 Hz (or 10 μs dwell times). This paper provides data on the different effects data acquisition rate has on the quality of data that can be obtained by SP-ICP-MS. The effect of varying the dwell time and its influence on particle integration, particle counting, particle sizing, and background signal is discussed. This paper provides data on identifying the significant instrument settings and their implications on nanoparticle characterization.

Introduction

The characterization and quantification of metal-based nanoparticle (NP) suspensions utilizing ICP-MS is gaining momentum. The main advantage of using ICP-MS as a detector is its high sensitivity when compared to other particle characterization techniques, such as dynamic light scattering, differential centrifugal sedimentation, and field flow fractionation.[1] Avoiding dilution of environmental samples reduces the possibility of changing the sample chemistry affecting any NP determination due to transformation of the particles. In addition exposure concentrations of NPs in aqueous environments are speculated to be in the range of 10^3 to 10^5 particles per mL.[2,3] One of the limitations of many quadrupole-based ICP-MS instruments is that they have a minimum dwell times in the millisecond range and are designed to settle between each measurement, thereby missing parts of the transient signal. However, short transient signals generated by individual NP events in the ICP are less than about 0.5 ms in length.[4] Because the duration of transient signals generated by individual NPs are in the range of hundreds of microseconds, their detection involves the use of instruments capable of fast data acquisition at frequencies around 10^5 Hz (or 10 μs).[5]

The objective of this paper is to present experimental data in evaluating ICP-MS data acquisition speed on particle integration, particle counting, particle sizing, and the background signal-ultimately improving the counting and sizing of NPs using SP-ICP-MS. In that regard, the benefits of collecting data using dwell times as short as 10 μs, continuously without any settling is demonstrated, with data being provided as proof of concept.

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Theory

Single particle-inductively coupled plasma-mass spectrometry (SP-ICP-MS) is based on the assumptions that each transient peak or pulse represents a single particle event, and the difference in the continuous baseline signal of the blank and nanoparticle sample represents the dissolved concentration of the element. The frequency of the events is directly proportional to the number of particles (or agglomerates) entering the plasma, while the intensity of the event (*i.e.* transient event area) is proportional to the particle diameter or the mass of the element within the particle. Once the transport efficiency of the introduction system is determined, the particle concentration in the delivered suspension of NPs can then be calculated. There may be a background response on that mass due to contamination, spectral overlap ions or instrument background. The change in that continuous response (on top of which are the NP events) is directly proportional to the dissolved concentration of the element.

The number of particles entering the plasma is dependent on the particle concentration in the sample, the sample introduction system used (*i.e.* the transport efficiency to the plasma), the sample uptake rate, and the sample matrix. Although not specifically covered in this paper, Pace *et al.* present information and theory on how to establish the system transport

efficiency.[6] Following nebulization, the NPs randomly arrive in the plasma; therefore the number of particles must be low enough to separate the ion plumes produced from the ionization of individual NPs. The probability of more than one NP being measured within a dwell time (coincidence) can be estimated by Poisson statistics.[4] This probability of coincidence decreases by decreasing the dwell time as well as the concentration of NPs in the suspension.

Capture of the entire peak event has important implications on how to precisely and accurately determine particle concentration and the mass of the element in each particle. It has been established that the full width of a particle event is less than 0.5 ms;[4] therefore the choice of instrument dwell time will affect the maximum number of particles that can be introduced to the plasma within a given amount of time without signals from individual particles overlapping. If the dwell time is not short enough (*i.e.* equal to or less than the event width of ~0.5 ms), the instrument response will be the summation of the particles, resulting in an artificially larger event response and a reduced number of event counts, thus affecting particle mass and concentration calculations (Fig. 1). In most literature to date, dwell times between 3 and 10 ms are commonly used. With such long dwell times anywhere between 6 and 20 particle events can occur during each dwell time (assuming two particles never arrive in the plasma at the same time). However, if the system is limited to millisecond level dwell times or the particle concentration is too high then the sample can simply be diluted to reduce the probability of coincidence.

Another important consideration of the ICP-MS data acquisition is that it is not interrupted for data processing or other hardware operations. Most commercial instruments invoke a settling time during data acquisition. During this settling time, events are missed or partial events are captured (Fig. 1). Missing events lead to the requirement that the users increase their total acquisition time so that counting statistics improve. For example, if the settling time equalled the dwell time it would take twice as long to obtain the same number of data points (or events) compared to a system that did not require any settling.

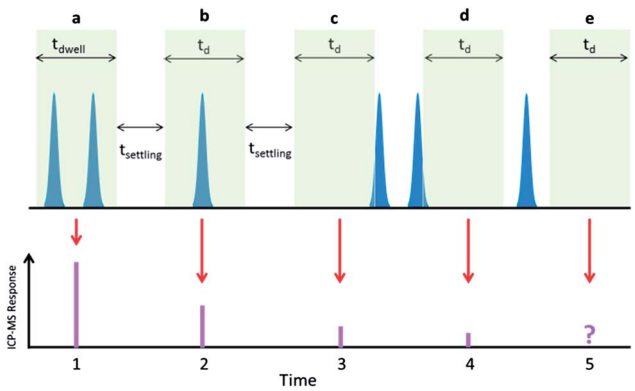

Fig. 1 Effect of dwell and settling times on single particle measurements. (a) 2 particles detected (b) 1 single particle detected (c) the leading edge of 1 particle detected (d) the trailing edge of 1 particle detected (e) no particles detected.

In the case of partial event capture, a low bias in the event intensities can be created resulting in a low-biased particle size distribution.

Instrumental

All data in this work was acquired with a PerkinElmer NexION series ICP-MS (Shelton, CT) operating in single particle mode, a mode optimized for collection of NP event data, using the Syngistix Nano Application Module. Based on the challenges described above relating to single particle analysis, optimal data acquisition requires extremely fast data acquisition rates. This is accomplished by eliminating system settling time and allowing data acquisition rates as fast as 10^5 Hz (10 μs dwell times). The elimination of the settling time avoids the issues due to partial event capture as illustrated in Fig. 1. The fast rate of data acquisition enables the user to capture up to 6 million data points per minute, thereby allowing for baseline (or down to the dissolved background response) resolution of multiple events. These capabilities are demonstrated in Fig. 2 and 3. Fig. 2 is a screen capture of a zoomed in portion of the raw data collected at a dwell time of 50 μs when analysing a suspension of NIST 8013 60 nm gold NPs with a particle concentration of approximately 250 000 particles per mL of solution. Despite the high particle concentration, baseline separation of the events is

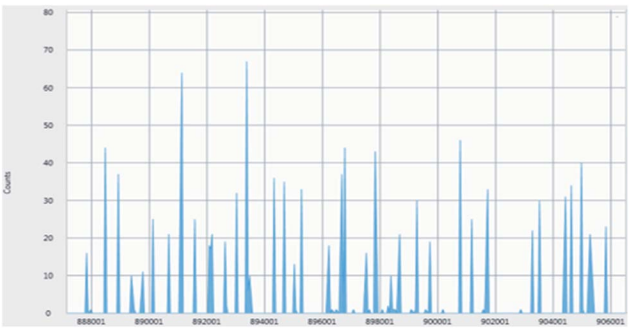

Fig. 2 Zoomed in trace of NIST SRM 8013 60 nm gold nanoparticle standard at a dwell time of 50 μs. Particle concentration of 250 000 particles per mL.

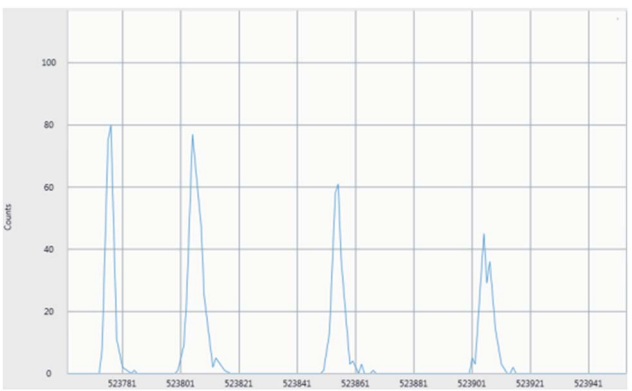

Fig. 3 Zoomed in of four NP events at a dwell time of 50 μs. Particle concentration of 250 000 particles per mL.

easily achieved, thus reducing the probability of coincidence. In Fig. 3 the graph is further zoomed in, demonstrating the resolving power of the single particle mode analysis.

Results & discussion

Effect of dwell time on particle integration

A major benefit of the instrument's single particle mode is that multiple points can be measured to define a single particle event, and the area of the peak can be related to the mass of the element within the NP. The ability to view the full event provides the user with insight into the quality of the data by displaying a visual confirmation of NP event separation. Fig. 4–6 show NP events using dwell times of 50 μs, 30 μs, and 10 μs, respectively. Each of these figures displays an event of approximately 300–400 μs in duration indicating consistent system performance regardless of the data acquisition rate. Since there is a normal distribution around the nominal size of the particle, the event response and duration will vary slightly from event to event. However by reviewing the number of points per peak in Fig. 4–6, the advantage of shorter dwell times is emphasized in the resulting single event profile. The number of points per peak is summarized in Table 1.

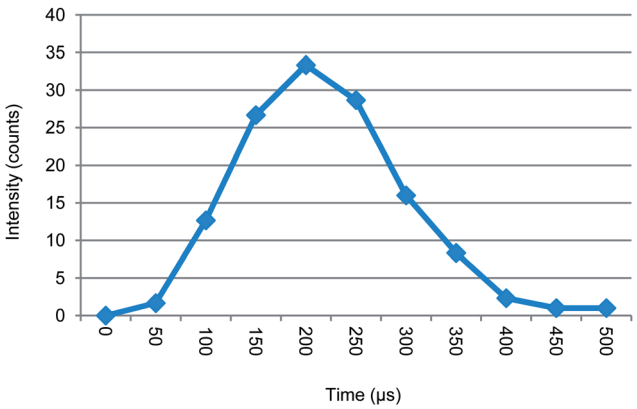

Fig. 4 Raw data of a NIST SRM 8013 60 nm gold nanoparticle acquired at a dwell time of 50 μs.

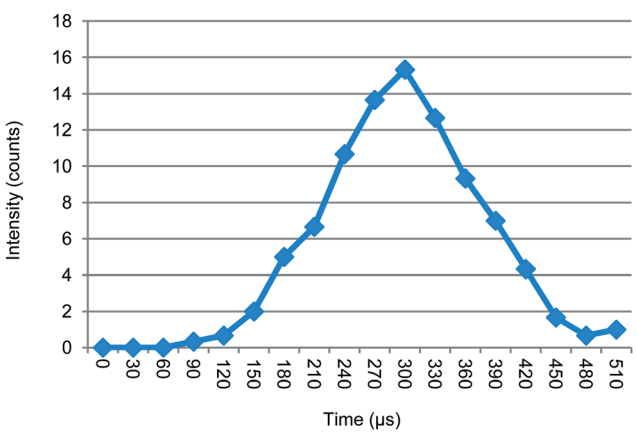

Fig. 5 Raw data of a NIST SRM 8013 60 nm gold nanoparticle acquired at a dwell time of 30 μs.

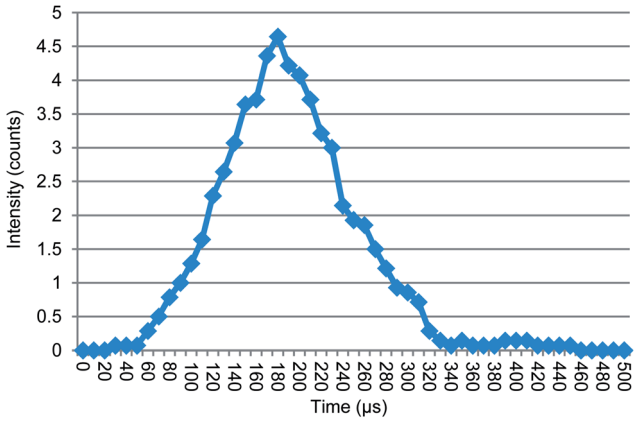

Fig. 6 Raw data of a NIST SRM 8013 60 nm gold nanoparticle acquired at a dwell time of 10 μs.

Effect of dwell time on particle counting: number of particles per mL

In theory the upper limit to the number of particles that can be measured within a given time frame is limited by the duration of the NP event. Assuming the entire signal from one particle lasts no more than 0.5 ms (see Fig. 4–6), then the maximum number of particles per second that could be measured would be 2000 (1 per 0.0005 s).[4] However this assumes that the particles are not arriving randomly. In actuality, particles arrive randomly, the result of introducing heterogeneous suspensions with a pneumatic nebulizer. This must be taken into consideration when choosing sample introduction parameters.

As an example, two experiments were conducted where the rate of sample introduction was changed while the number of particles in the solution was kept constant at 250 000 particles per mL. Fig. 7 displays the two sets of data where the number of particle events is plotted *vs.* the dwell time used for data acquisition. Note that the transport efficiencies of the two flow rates were different. As illustrated, increasing the flow rate increases the event rate (peaks per min^{-1}), which in turn increases coincidence. When comparing the two sets of data, the reduced flow rate (300 μL min^{-1}) allows for longer dwell times to be used without any significant amount of coincidence occurring. A closer look at the two datasets shows that a significant increase in coincidence can be seen earlier in the higher flow rate (450 μL min^{-1}) data (around 100 μs) than in the

Table 1 Summary of points per peak and event duration for different dwell times of single nanoparticle events

Dwell time (μs)	Points integrated	Event duration (μs)
50	8	400
30	13	390
10	31	310

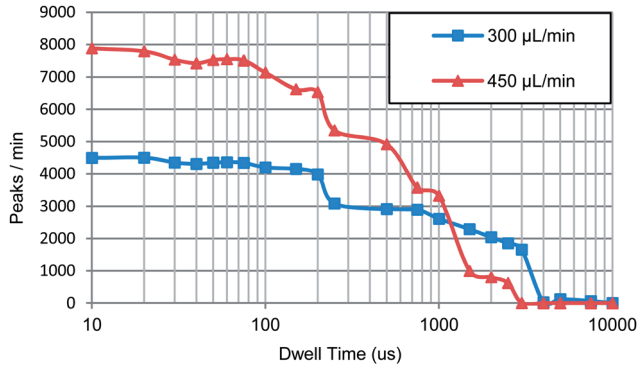

Fig. 7 Particle events *vs.* dwell time for 250 000 particles per mL of 60 nm Au NPs nebulized at different flow rates.

300 µL min^{-1} data (around 200 µs). Another important consideration is that no peaks will be measured if the dwell time is increased to the point where the NP events begin to form a continuum response. Upon review of the data represented by Fig. 7, this event effectively occurs at 3 ms and 4 ms for the sample flow rates of 450 µL min^{-1} and 300 µL min^{-1}, respectively. The most noteworthy finding resulting from this study is that with fast acquisition (less than 100 µs) the system is more easily able to resolve a greater number of NP events per second, reducing the need for excessive dilution and further changes in the sample matrix.

The effect of dwell time on particle counting was further investigated by processing each of the size histograms generated during this study, with the objective of excluding events outside the primary Gaussian distribution. Fig. 8 below shows an example of a size histogram from the analysis of NIST SRM 8013 60 nm gold nanoparticles at a concentration of 250 000 particles per mL acquired at a dwell time of 50 µs. The data derived from each histogram is the number of particle events, mean particle counts and the corresponding mean particle diameter. The particle size histograms were then divided into the primary distribution of the particles and the remainder of events greater than and outside the primary distribution. Each section of the histogram will then have the associated the number of particle events, mean particle counts and the corresponding mean particle diameter. It can be then assumed that for the particle responses greater than the primary distribution are due to coincidence and/or any agglomerates in the solution.

This treatment of the data allows for further investigation of the effect of dwell time on particle counting. Fig. 9 shows the data from the 300 µL min^{-1} flow rate processed to view the total number of events, events within the primary distribution and the remaining particle events (coincidence and/or agglomeration).

As displayed, the number of particle events in the primary distribution and the total number of particle events decrease as the dwell time increases, restating our earlier finding about the increased rate of coincidence with longer dwell time. This effect can also be represented by ratioing the number of remaining particle events to the total number of events at each dwell time, (Fig. 10). This shows that at dwell times above 100 µs, the number of events outside the primary distribution is greater than 10% of the total events under the above stated data acquisition conditions.

To further investigate the effect of dwell time on the rate of coincidence and its effect on particle counting, we posed that

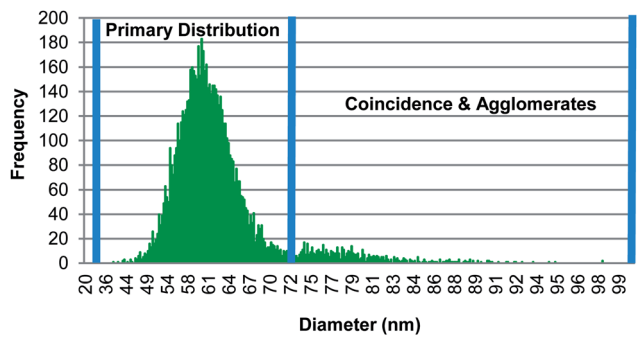

Fig. 8 Size histogram of NIST SRM 8013 60 nm gold nanoparticles at a concentration of 250 000 particles per mL acquired at a dwell time of 50 µs.

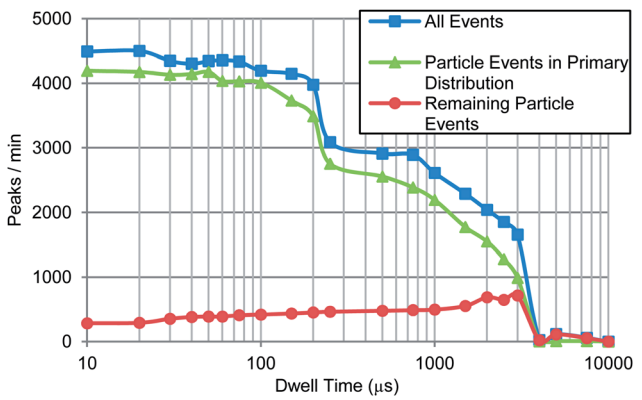

Fig. 9 Particle events *vs.* dwell time for 250 000 particles per mL of 60 nm Au NPs nebulized at 300 µL min^{-1}. Data separated by grouping events in the primary distribution.

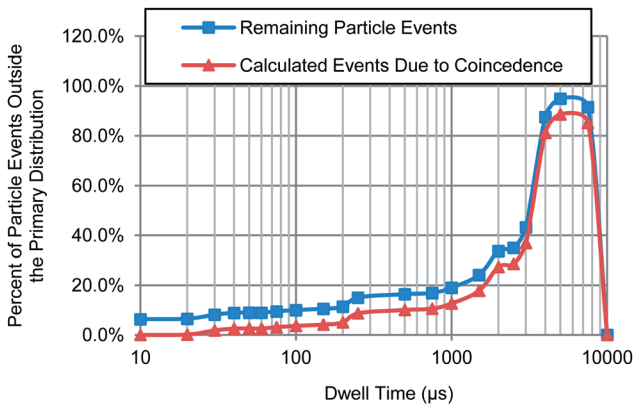

Fig. 10 Percent of particle events outside the primary distribution *vs.* dwell time for 250 000 particles per mL of 60 nm Au NPs nebulized at 300 µL min^{-1}.

the number of remaining particle events under the minimum dwell time of 10 μs was completely due to agglomeration (*i.e.* no coincidence at all). Under this assumption, the relative number of events due to agglomeration was subtracted from the remaining particle events to give the number of events that had a greater probability of being due to coincidence. Under this assumption, the amount of events most likely due to coincidence is greater than 10% at dwell times above 500 μs in agreement with what it was demonstrated earlier with regard to the duration of single particle transient signal. Using a dwell time that is greater than the individual nanoparticle transient signal will inevitably increase the rate of particle coincidences leading to inaccurate particle counting and sizing.

Effect of dwell time on particle sizing

To evaluate the effects of dwell time on particle size calculation and coincidence counting, a two point particle size calibration was performed using NIST RM 8012 and NIST RM 8013 gold nanoparticles with nominal diameters of 30 nm and 60 nm, respectively. Both Au NPs standards were prepared at a concentration of approximately 250 000 particles per mL. The calibration was constructed using 50 μs dwell time at an aspiration rate of 300 μL min^{-1}. Once the calibration was obtained, the same RM 8013 standard was continuously aspirated as the dwell time was varied from 10 μs to 10 000 μs. Fig. 11 shows the effect of dwell time on the mean particle intensity. As expected, with longer dwell time more coincidences occur. The rate of coincidence increases steadily as the dwell time increase where an exponential increase is noticed once the dwell time reaches 3000 μs. Therefore one can state at 3000 μs, with the sample introduction conditions used and particle concentration of the solution, the NP responses begin to form a continuum and cannot be differentiated from background signal.

As a result, the event response increases which correlates to a greater mass of the element, resulting in a bias on particle size (Fig. 12). Note that the NIST certified value[7] of the particle size is approximately 56 nm as determined by TEM which is reflected in the results presented in Fig. 12 up to the 500 μs dwell time. Using the data reduction techniques (described in the previous section) one can alleviate the effect of dwell time on particle sizing. However at longer dwell times, greater than 3 ms, this data reduction technique reaches its limitation due to the increased level of coincidence encountered.

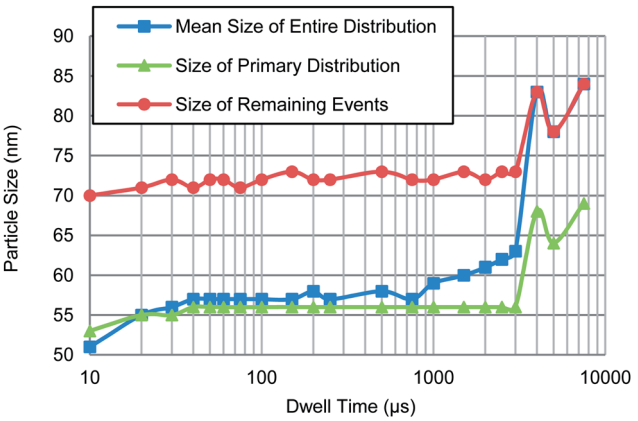

Fig. 12 Effect of dwell time on mean particle size calculation for 250 000 particles per mL of 60 nm Au NPs nebulized at 300 μL min^{-1}.

Effect of dwell time for various particle concentrations

As discussed in the previous sections, the rate of coincidence increases with increased particle concentration and increased dwell times. To further investigate this fact and its implications on various particle concentrations, another experiment was conducted where solutions of 50 nm gold NP concentrations ranging from 100 000 to 500 000 particles per mL were prepared and analysed at dwell times of 50, 100, 500, 1500, and 3000 μs. In order to calculate particle concentration for each analysis, the system transport efficiency was established using the 100 000 particles per mL solution at a dwell time of 50 μs. The flow rate was held constant at approximately 300 μL min^{-1}. The effect of dwell time on the particle counting efficiency of this experiment is summarized in Fig. 13. The particle counting efficiency was calculated from the events in the primary distribution by comparing the determined particle concentration to the target concentration of each prepared solution. The data obtained supports the data in Fig. 10 that displays increasing the dwell time increases coincidence and, in addition, provides

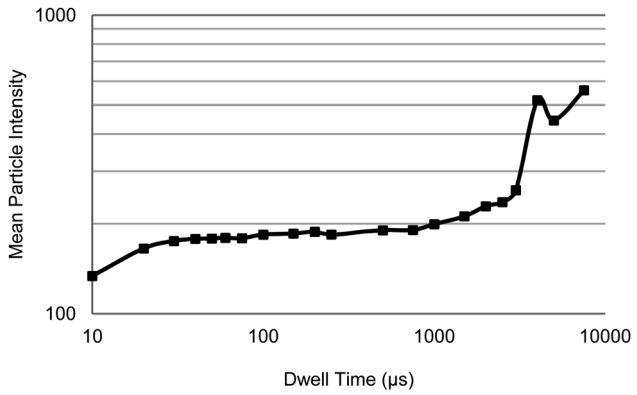

Fig. 11 Effect of dwell time on mean particle intensity for 250 000 particles per mL of 60 nm Au NPs nebulized at 300 μL min^{-1}.

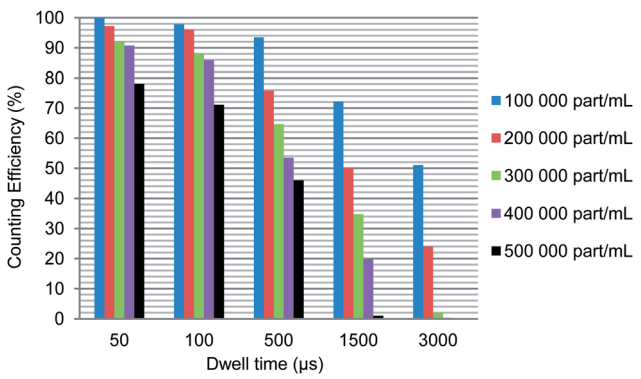

Fig. 13 The effect of dwell time and NP concentration on particle counting.

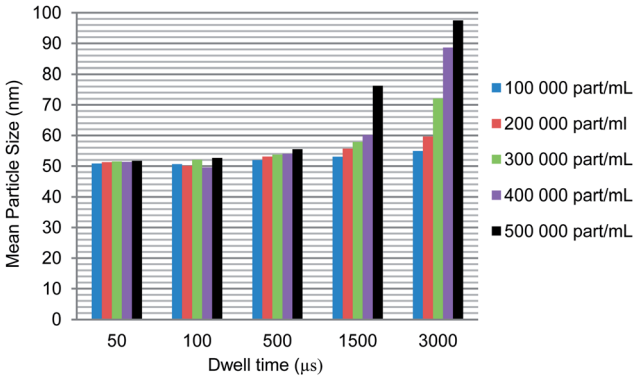

Fig. 14 The effect of dwell time and NP concentration on particle sizing.

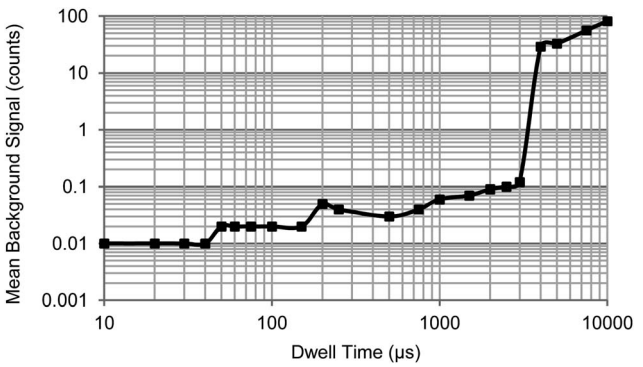

Fig. 15 Effect of dwell time on background signal.

insight into the fact that increasing the particle concentration will also increase the rate of coincidence.

The effect of dwell time on particle sizing of this experiment is shown in Fig. 14. The mean particle size is calculated from the mean event response from the primary distribution. When the primary distribution is selected, the error in sizing was not as large as counting since the mean particle response, even when including responses due to coincidence, will remain closer to the true value until the rate of coincidence becomes too high and biases the mean. The data obtained supports the data in Fig. 12 that displays increasing the dwell time slightly increases the particle size of the primary distribution until the mean response is obtained mostly from coincident events creating a significant bias in the calculated size as what is seen at 3000 µs.

Effect of dwell time on the background signal

The signal from the dissolved component of the element in the solution is directly proportional to the difference between the continuous background in the blank and nanoparticle sample. Therefore another consequence of using too long a dwell time is that it becomes increasingly difficult to differentiate the particles from the background since the continuous background signal increases with dwell time while the signal from a single particle does not. As shown in Fig. 15, the background response increases proportionally to the dwell time. However, the signal due to a single NP is independent of the dwell time as long as only one particle is present within the dwell time window and the signal resulting from each single particle is completely within the dwell time.[4] This change in the apparent continuous background signal will adversely affect the minimum size particle that can be detected since the background response must be subtracted from the NP response creating greater error in the NP size determination due to the greater noise amplitude in the elevated background. Therefore faster data acquisition (dwell times of 100 µs or less) allows smaller particles to be measured compared to data obtained with longer dwell times. The large increase in background signal at 3000 µs in Fig. 15 indicates that more coincidence is occurring (at this particle concentration) and where the NPs cannot be differentiated from background signal. This effect was similarly illustrated in Fig. 7 and Fig. 9–14 where the particle counting approached one because the system was at the point where the NP events begin to form a continuum response due to the longer dwell times.

Conclusion

This paper summarizes the different effects that data acquisition rate (dwell time + settling time) have on the quality of data that can be obtained by SP-ICP-MS. The single particle mode of the NexION, with no settling time and dwell times as low as 10 µs, has the ability to provide the user with data on the particle concentration, particle size, and the dissolved concentration of the elements in solution. To avoid errors due to partial NP event integration and coincidence with long dwell times, concentrated nanoparticle solutions have to be diluted significantly. Excessive sample dilution is to be avoided, as it may create greater uncertainty in NP counting due to subsequent manipulation and changes to the sample chemistry affecting nanoparticle transformation (dissolution, agglomeration, *etc.*).

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