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# Single particle inductively coupled plasma mass spectrometry metrology: Revisiting the transport efficiency paradigm

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## ABSTRACT

Transport efficiency has become a critical parameter in single particle inductively coupled plasma mass spectrometry (SP-ICP-MS) since it is involved in the calibrations to determine different measurands (element mass per particle, particle size and particle number concentration). Specific methods for its determination based on the use of particle standards have been developed and widely applied (particle frequency and particle size methods). A refined indirect method not relying on particle standards is also available (dynamic mass flow method). A number of discrepancies on the accuracy of these methods and their adequacy have become evident, making a revision of the topic pertinent. In fact, the application of the particle frequency and particle size methods determine the transport efficiencies corresponding to the particles or the dissolved element respectively, whereas the solvent transport efficiency is actually measured by the dynamic mass flow method. The use of each of these methods requires assuming different conditions that must be considered. These conditions, together with the sources of bias associated to each method are critically discussed to provide a holistic and harmonized view of transport efficiency in the context of SP-ICP-MS metrology.

## 1. Introduction

Forty years ago, Browner and Boorn wondered in their seminal paper whether sample introduction was the Achilles' Heel of atomic spectroscopy [1]. To date, the efficiency of sample introduction in single particle inductively coupled plasma mass spectrometry (SP-ICP-MS) still remains a controversial topic.

Degueldre and Favarger mentioned in their first paper on SP-ICP-MS the *nebulisation yield* ( $\eta_{neb}$ ) of diluted suspensions that were sprayed and transported in an argon flow into the plasma torch [2], although their subsequent publications did not include any further estimation or application of this parameter. It was Pace et al. [3] who developed specific procedures for determining the transport efficiency with the purpose of counting and sizing nanoparticles by SP-ICP-MS. They developed the so-called particle frequency and particle size methods for determining *transport efficiency* ( $\eta_n$ ), methods that are extensively used in this field. More recently, Cuello-Núñez et al. [4] developed the dynamic mass flow method for determining *transport efficiency* ( $\eta$ ), based on the measurement of mass flows, with the aim of determining number concentrations.

The objectives of this article are to review critically the role of

transport efficiency in SP-ICP-MS as well as the available methods for its determination, a comparison between them, trying to give a holistic and harmonized view of their implications in the SP-ICP-MS metrology and paying special attention to their current limitations.

## 2. Harmonization of terminology

Both expressions *transport* [5–7] and *nebulization* [8,9] *efficiency* can be found in SP-ICP-MS and atomic spectrometry literature. Despite the term selected, what is relevant is the entity whose efficiency is measured. From the point of view of analytical performance, *analyte transport efficiency* is the relevant parameter, although the term *aerosol transport efficiency* has also been used with the same meaning [5,10], but also referring to the volume of solvent or sample nebulized [11–14]. In this regard, IUPAC publications refer to *nebulization efficiency* [15], being related to the amount of analyte and not to the amount of sample or solvent. Hence, in the context of ICP-MS, (analyte) transport efficiency would be defined as the ratio of the mass of analyte entering the plasma to the mass of analyte aspirated, typically expressed as a percentage [1,5].

Although the use of the terms “transport” or “nebulization” might

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not be particularly critical, excluding the object of the transport/nebulization (analyte, solvent) might be. However, whereas in atomic spectrometry the analyte is clearly identified as the element being determined, in SP-ICP-MS two types of analytes can be considered: particles and dissolved species related to specific elements under study. Therefore, the use of the expression “analyte transport efficiency”, although used in SP-ICP-MS, would not be recommended in this context and will not be used in this article in relation to SP-ICP-MS.

With respect to the symbols,  $\epsilon_n$  has been used in atomic spectrometry publications from early times and it is the symbol recommended by IUPAC for the nebulization efficiency [15]. However,  $\eta$  with different subscripts can be found in SP-ICP-MS publications when referring to nebulization/transport efficiency [3,4,12,16]. Here, the symbol  $\eta$  will be used along the text.

Although a revision of the terms and symbols used in the publications on the topic is out of the scope of this article, readers should be aware of this terminology and symbology when consulting the bibliography.

### 3. Calibration in SP-ICP-MS

In quantitative atomic spectrometry, mass concentration is the usual measurand and calibration overcomes analyte transport efficiency issues by the use of standards measured under the same conditions as the samples. In SP-ICP-MS, and focusing on particles, the primary measurands are the number concentration of particles and the mass of element per particle. In addition, when information about the shape, composition and density of the particles is available, the size of the particles can also be estimated from the mass of element determined (e.g., the diameter for spherical particles).

The different SP-ICP-MS measurands involve the corresponding calibrations, which require suitable standards in order to report the corresponding results. In the case of number concentration, direct calibration requires the use of one or more number concentration standards to obtain the coefficient  $K_N$  of the calibration function:

$$Y_N = K_N X^N \quad (1)$$

where  $Y_N$  is the number of particle events counted during an acquisition time ( $t_i$ ) and  $X^N$  the number concentration of particles.

In the case of size, the most straightforward approach is based on the use of one or more particle reference materials with known shape and size and same composition as the targeted particle to obtain directly the coefficient  $K_d$  of the calibration function:

$$S_p = K_d d^3 \quad (2)$$

where  $S_p$  is the net intensity of the particle events ( $S_p = \sum (Y_{p,i} - Y_B)$ ),  $Y_{p,i}$  is the gross intensity of the individual readings along a particle event and  $Y_B$  is the mean intensity of the baseline) and  $d$  is the diameter for spherical particles. Since monodisperse particles always show a more or less broad distribution, averaged intensities and diameters are used.

Eq. 2 arises from considering the relationship between the net intensity of each particle event and the number of atoms of the element monitored in each particle detected, and hence to the mass of element per particle ( $m_p$ ):

$$S_p = K_m m_p \quad (3)$$

where  $K_m$  is the slope obtained from a mass per particle calibration (net particle event intensity vs. element mass per particle).

Regarding number concentration standards, there is only one quality control material currently available reporting nanoparticle number concentrations (LGCQC5050), consisting of gold nanoparticles of 30 nm diameter in citrate medium. Hence, commercial suspensions of known element mass concentration and mean size are often used as an alternative. In principle, the composition, size and shape of the particles used for number concentration calibration would not be relevant, if they

behave in the nebulization system as the particles from the sample; hence, the same number concentration calibration could be used for different types of particles in such case.

With respect to particle size standards, the number of certified reference materials is limited, although particle standards covering different sizes, compositions and shapes are commercially available from different companies. When these particles are non-porous solids, they are also used as element mass per particle standards by considering the density of the bulk material. However, very often size standards of specific compositions are not available or multicomponent particles with complex compositions are measured. In such cases, instead of calibrating directly by using particle size standards it can be performed from calibrations with dissolved element standards.

### 4. Basis of size calibration from dissolved standards in SP-ICP-MS

Mass concentration calibration in standard-mode ICP-MS involves the continuous introduction through the nebulization system and the measurement of a number of dissolved standards in the same conditions as the analyzed samples. Although this is also the approach most commonly applied in SP-ICP-MS (Fig. 1.a), an alternative on-line microdroplet calibration approach has been proposed recently [17,18] (Fig. 1.b). This approach is based on the introduction of discrete amounts of elements in individual monodisperse microdroplets of dissolved mass concentration standards and known volume. The microdroplets are desolvated along a falling tube prior to mixing with the aerosol of the sample, which is delivered by a conventional nebulization system upstream of the plasma torch. Since the microdroplets can be introduced into the plasma simultaneously with the sample, any interference produced by the sample matrix would also affect the standards,

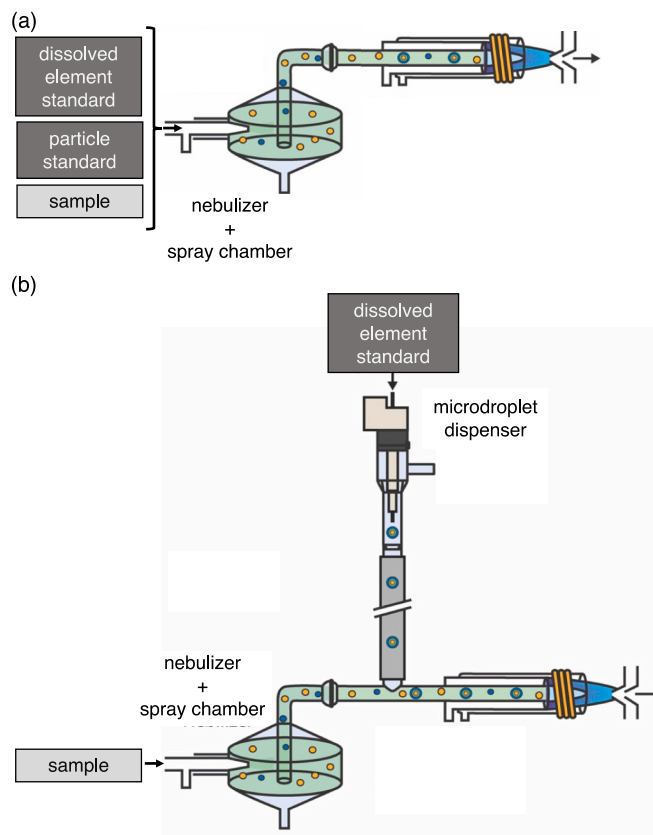


Fig. 1. Introduction modes of standards in SP-ICP-MS: (a) continuous direct nebulization, (b) on-line microdroplet. Adapted from [21] with permission from ACS.

compensating their effect [19,20].

In standard-mode ICP-MS, when a solution of an element M of mass concentration  $X^M$  is nebulized into the instrument (Fig. 1.a), the relationship between the signal  $Y_R$  (ions counted per time unit) and the mass concentration can be expressed as [16]:

$$Y_R = K_R X^M = K_{intro} K_{ICPMS} K_M X^M \quad (4)$$

where  $K_R$  is the analytical sensitivity obtained from a standard-mode calibration (signal intensity in cps vs. element mass concentration),  $K_{intro}$  ( $= \eta Q_{sam}$ ) is a factor related to the sample introduction, where  $\eta$  is the transport efficiency and  $Q_{sam}$  the sample introduction flow rate,  $K_{ICPMS}$  is the detection efficiency, which represents the ratio of the number of ions detected versus the number of atoms of the measured isotope introduced into the ICP; and  $K_M$  ( $= AN_{Av}/M_M$ ) is a factor related to the element measured, where  $A$  is the atomic abundance of the isotope considered,  $N_{Av}$  the Avogadro number, and  $M_M$  the atomic mass of the element.

On the other hand, for solid, homogeneous and spherical particles, eqs. 2 and 3 can be expanded respectively as [16]:

$$S_P = \frac{1}{6} \pi \rho F_P K_{ICPMS} K_M d^3 \quad (5)$$

where  $\rho$  is the density and  $F_P$  the mass fraction of the element in the particle, and

$$S_P = K_{ICPMS} K_M m_P \quad (6)$$

The slopes of both equations are independent of the nebulization process, since only those particles reaching the plasma are measured, and only depends on the element and the nature of the particles. On the other hand, both equations require knowing the detection efficiency of the element measured.

When working in continuous direct nebulization mode, the detection efficiency can be obtained from a calibration with dissolved standards and eq. 4 if  $\eta$  and  $Q_{sam}$  are known:

$$K_{ICPMS} = \frac{K_R M_M}{\eta Q_{sam} A N_{Av}} \quad (7)$$

In their paper, Pace et al. [3] determined the mass of element per particle from a transformed calibration with dissolved standards, where the x-axis, corresponding to the element mass concentration, is transformed to element mass per event ( $W$ ) through:

$$W = \eta Q_{sam} t_{dwell} X^M \quad (8)$$

where  $W$  corresponds to the mass of dissolved element introduced into the plasma during a time  $t_{dwell}$ . The net intensity  $S_P$  of a particle event would be interpolated in the transformed calibration to obtain the element mass in the particle, and from it the diameter for a spherical, solid and homogeneous particle:

$$d = \left( \frac{6 m_P}{\pi \rho F_P} \right)^{1/3} \quad (9)$$

Both approaches are equivalent, and both rely on the fact that the element both in dissolved and particulate forms behaves in the ICP-MS in the same way. That is, the efficiency of the processes occurring in the plasma (desolvation of the nebulized droplets, volatilization of the resulting/present particles, their atomization and ionization of the resulting atoms), the interface, the spectrometer and the detector are the same. All these processes are included in  $K_{ICPMS}$ , whereas Pace et al. summarized them as a "particle ionization efficiency" to be estimated from the ratio between the element mass concentration determined by conventional ICP-MS directly from the particles and after dissolution under the same experimental conditions applied in SP-ICP-MS.

In microdroplet calibration,  $K_m$  (and hence  $K_{ICPMS}$ ) is estimated from the net particle event intensity and the mass of element in the droplets

(eq. 3), where the latter is calculated from the mass concentration of the dissolved standard and the volume of the droplets, whose size is measured with a camera assuming the droplets are spherical.

In summary, when dissolved standards are introduced through the nebulization system, the transport efficiency and the sample flow rate must be known. Whereas the sample flow rate is easily measured gravimetrically, by weighting the amount of solvent introduced through the nebulization system during a fixed time interval, the determination of the transport efficiency is not so straightforward. This is not the case when the dissolved standards are introduced as microdroplets, since they behave as a proxy for particle standards.

## 5. Determination of transport efficiency

Analyte transport efficiency has been measured from the early times of atomic spectrometry to study the performance of the nebulization systems used for sample introduction [10]. Traditionally, methods used to determine analyte transport efficiency have been based on the collection of the nebulized aerosol itself or the liquid going to waste, followed by the determination of the content of the element in the collected liquid, being classified as *direct* and *indirect* methods, respectively. With the emergence of SP-ICP-MS, Pace et al. [3] proposed two new methods for determination of transport efficiency based on the use of nanoparticle standards, referred to as particle frequency and particle size methods. The first one requires the use of nanoparticle standards of known number concentration, whereas the second is based on the use of particle size and dissolved element standards.

The particle frequency method is in fact a one-point number concentration calibration, since eq. 1 can be expressed as:

$$Y_N = K_N X^N = K_{intro} t_i X^N = \eta Q_{sam} t_i X^N \quad (10)$$

and  $\eta$  can be determined once the slope of the calibration and the sample flow rate are known.

The particle size method is based on the use of eq. 3 and 4, and the ratio of their slopes:

$$\frac{K_R}{K_m} = K_{intro} = \eta Q_{sam} \quad (11)$$

where  $K_R$  is obtained from the slope of the calibration with dissolved standards of the element selected (e.g.,  $Au^{3+}$ ), and  $K_m$  from the calibration with size standards of nanoparticles including the same element in their composition (e.g., Au nanoparticles). With microdroplet calibration, transport efficiency is only required for determination of number concentrations, but it has been proposed its determination by using the particle size method. In this case, the estimation of  $K_m$  and  $K_R$  are performed by measuring a dissolved standard (typically caesium) introduced as droplets through the microdroplet dispenser and continuously through the nebulization system, respectively. Mehrabi et al. [17,18] determined this transport efficiency as the ratio of the so-called plasma uptake rate (volume of sample reaching the plasma per time unit) and the sample flow rate, since the plasma uptake rate is in fact  $K_{intro}$  described above.

The dynamic mass flow method is based on the continuous measurement of the sample mass flow reaching the plasma and the mass flow of the sample uptake by the ICP-MS nebulization system [4]. The ratio of the sample mass flow reaching the plasma to the mass flow of the sample uptake is equal to the transport efficiency of the sample, that it is of the solvent. Since this method does not involve the direct measurement of the aerosol reaching the plasma, it should be classified as an *indirect* method, but its application in SP-ICP-MS implies that this transport efficiency determined for the solvent is equal to that of the particles. This condition was achieved by using a nebulization system thermostated at low temperature (2°C), that minimized the vaporization of water from the aerosol droplets during nebulization. Under such conditions the transport efficiency was in agreement with the one determined by the

frequency method using Au nanoparticles (NIST RM 8013) in citrate medium. Unlike the frequency or the size method, the DMF method does not require any reference material and weighing operations are traceable to the SI through the use of calibrated weights traceable to national primary standards of mass [4]. Table 1 summarizes the different standards (apart from calibrated weights) required for implementing the different methods for determination of transport efficiency described above.

## 6. The paradigm of transport efficiency in SP-ICP-MS

From the work by Pace et al. [3], the determination of the transport efficiency has been considered a metrological cornerstone in SP-ICP-MS. It allows the determination of the element mass content (and particle size under the conditions discussed above), even if the corresponding particle standards are not available, by the use of dissolved standards. In a similar way, particle number concentrations can be determined from eq. 10 by using the transport efficiency, although this should be considered a redundant action, since the particle frequency method is in fact a number concentration calibration itself. Besides, the use of nebulization systems with 100% transport efficiency [22,23] would circumvent this determination. Such efficiencies can be achieved by using direct injection devices or specially designed spray chambers working at flow rates in the few  $\mu\text{L min}^{-1}$  range. However, although the feasibility of these systems has been reported, they are not routinely used. Alternatively, knowing the transport efficiency is neither required to obtain size/element mass per particle information when using on line microdroplet calibration.

Table 1 summarizes the conditions that are assumed to be met by the different methods to provide accurate transport efficiencies. Issues related to the effect of the sample matrix have not been considered, since they could be circumvented by using matrix-matched standards [24,25], standard addition calibration [26] or internal standardization [27], apart from the use of the on line microdroplet calibration approach describe above [19,20].

The dynamic mass flow approach is a method for determination of the solvent transport efficiency and hence, it is the method with more critical requirements for applying this efficiency to the particles. As it has been stated above, vaporization of the solvent must be avoided.

When applying the particle frequency method, transport efficiency is considered independent of the characteristics of the particles used based on considering that particles within a range of sizes with different compositions and densities, nebulize in a specific nebulization system in

the same way. Although this issue has not been investigated in depth, Geiss et al. [28] obtained similar transport efficiencies when using gold and silver nanoparticle standards. Moreover, results obtained using transport efficiencies determined by the particle size method do not suggest different behaviours in the nanometre range, and gold nanoparticle standards are typically used for this purpose [28]. On the contrary, different behaviours have been reported for particles over ca. 100 nm depending on their nature. Bucher and Auger [29] obtained similar efficiencies for  $\text{SiO}_2$  particles up to 500 nm, in agreement with those obtained with 60 nm Au nanoparticles, whereas the efficiency was lower for 1000  $\mu\text{m}$  particles. In a similar way, Laborda et al. [30] obtained similar transport efficiencies for 50 nm Au and polystyrene standards of sizes up to 2  $\mu\text{m}$ , but not for 5  $\mu\text{m}$ .

In the case of the particle size method, the fact of using particle size and dissolved element standards would require that the element behaves in the plasma in the same way, regardless of the form in which it is introduced (same  $K_{ICPMS}$ ). In general, this behaviour is assumed for nanoparticles (<100 nm) of most metals and metal oxides, although it is not always the case, as it has been demonstrated for refractory oxides like cerium oxide [27,31,32]. Another condition that has been considered fulfilled is that nanoparticles and dissolved element are nebulized with the same efficiency. However, Torregrosa et al. [33] have recently studied transport efficiencies of nanoparticles and dissolved elements by using a conventional direct method, based on the collection of the aerosol in a quartz filter followed by the quantitative release of the nanoparticles with diluted ammonia and the dissolved element with diluted nitric acid [34]. They observed higher transport efficiencies for the dissolved element compared to those for nanoparticles, which questions the approach proposed by Pace et al. [3]. These results suggest that aerosol ion redistribution (AIR) [5] could play a relevant role on the enrichment of the aerosol on dissolved species in comparison to the particles, although this issue should be studied in more detail.

Therefore, as long as nebulization of nanoparticles differs from that of dissolved species, the application of the particle size method could be considered no longer valid. However, it should be noted that the transport efficiency calculated by the particle size method is not actually the particle transport efficiency, but that of the dissolved element, since the ratio involved in the calculation (eq. 11) requires that all the processes involved once a particle reaches the plasma would be eventually the same that the ones from the dissolved element, so differences are just due to the transport of the dissolved element (the transport efficiency for a particle that reaches the plasma is 100%). Moreover, it is the transport efficiency of the dissolved element the one required to transform the

**Table 1**  
Methods for determination of transport efficiency in SP-ICP-MS: Standards required, conditions and sources of bias.

Method	Standards*	Conditions	Sources of bias
Particle frequency	<ul style="list-style-type: none"> <li>Particle number concentration</li> </ul>	<ul style="list-style-type: none"> <li>Same behaviour in the nebulization system of the particles in the standard and the sample</li> </ul>	(–) Losses of particles in containers, nebulization system, tubing...  (–) High concentration of standards (occurrence of 2-particle events) (–) Lower part of the size distribution of the standard below the size critical value (+) Counting of baseline readings as particle events (false positives) (+/–) Calculation of number concentrations from density, size and element mass concentration of a size particle standard
Particle size (continuous nebulization)	<ul style="list-style-type: none"> <li>Particle size</li> <li>Dissolved element</li> </ul>	<ul style="list-style-type: none"> <li>Same behaviour in the plasma of dissolved and particulate element</li> <li>Same transport efficiency of dissolved and particulate element, regardless of the element (Same as above)</li> </ul>	(+) Particle density lower than bulk material (porosity)  (+/–) Asymmetrical particle size distribution (–) Use of too large particle standards (incomplete atomization) (Same as above)
Particle size (on line microdroplet)	<ul style="list-style-type: none"> <li>Dissolved element</li> </ul>	<ul style="list-style-type: none"> <li>(Same as above)</li> </ul>	(Same as above)
Dynamic mass flow	<ul style="list-style-type: none"> <li>None</li> </ul>	<ul style="list-style-type: none"> <li>No vaporization of the solvent during nebulization (cooled spray chamber at 2°C)</li> <li>Same transport efficiency of solvent and particles</li> </ul>	(+) Nebulization at room temperature

\* Apart from calibrated weights.

dissolved element mass concentration calibration into the corresponding mass per event calibration through eq. 8, as proposed by Pace et al. [3], or alternatively calculate  $K_{ICPMS}$  from the slope of a dissolved element mass concentration calibration ( $K_R$ ) by using eq. 7. In both cases, the use of dissolved standards, which are nebulized with a specific efficiency, is required to convert the signal produced by individual particles into the mass of element in such particles. Thus, the particle size method is in fact a method for the determination of the transport efficiency of dissolved elements (through the use of suspension of particles with known size), whereas the particle frequency method is a method for the determination of the transport efficiency of particles, despite the limitations and constraints discussed above.

Whereas the particle transport efficiency, determined by the particle frequency method using a generic particle standard (e.g., Au nanoparticles) can be used for determination of the number concentration of a suspension containing unknown particles through eq. 10, the determination of the mass content of a specific element through eq. 6 requires knowing  $K_{ICPMS}$  when using the conventional continuous nebulization. Estimation of  $K_{ICPMS}$  from eq. 7 involves  $K_R$ , that can be known from a calibration with dissolved standards, and their transport efficiency, which must be assumed that is the same as for a generic dissolved standard (e.g.,  $Au^{3+}$ ) which should be used for determination of the transport efficiency by the particle size method.

## 7. Limitations of the methods for determination of transport efficiency

Although Pace et al. [3] reported similar values for the transport efficiency measured using either the frequency or the size method, other authors have observed relevant differences [12,35]. Liu et al. [35] obtained lower transport efficiencies by using the frequency method and citrate stabilized 60-nm gold nanoparticles (RM 8013, NIST), whereas similar efficiencies were obtained by both methods when using PVP stabilized silver nanoparticles (RM 8017, NIST), in agreement with the value obtained by the size method with RM 8013. On the contrary, Geertsen et al. [36] reported similar transport efficiencies by using both methods for gold nanoparticles stabilized with chitosan in the range of 30–150 nm. An interlaboratory study [28], involving seven expert laboratories using a variety of Au nanoparticle standards, concluded that, comparing absolute differences between these two methods, when transport efficiency values deviated, those obtained by the frequency method were lower than using the size method. However, when the upper and lower uncertainty limits were considered, there were no significant differences between both methods in most of the laboratories involved in the study.

The lower transport efficiency measured by using the frequency method could be explained by the loss of particles on the walls of containers and/or the sample introduction system, which can occur in the diluted suspensions used for the measurements, but also in the stock suspension during storage. Although the nature of the surface coating might play a role on the stabilization and losses of the particles, no definitive conclusions can be drawn from the available studies [28,36].

Regarding the number concentration of the standards, the use of high concentrations may result in too high fluxes of nanoparticles in the plasma, increasing the detection of particle events corresponding to more than one particle and hence underestimating the counting of particles events. In fact, optimal number concentrations should be selected to minimize this source of bias without compromising precision due to counting statistics [37], since using too diluted suspensions would involve counting less particle events, and hence reducing the precision of the measurements, unless the analysis time is increased.

Despite the transport efficiency does not depend on the size of the particles in the nanometres range, the use of standards prepared from too small nanoparticles can lead to the partial detection of the particle distribution and the underestimation of the actual number concentration, as it happened in some laboratories with the 30 nm Au standard in

the interlaboratory study described in [28], due to the size critical values achievable with some of the instruments used. A similar effect could be produced if the threshold criterion applied for the discrimination of particle events from the baseline was too high. Alternatively, if the threshold criterion is too low, the number of particles can be overestimated due to the counting of false positives from the baseline [16].

Since only one number concentration particle standard is currently available, size standards of spherical and solid nanoparticles from pure metals are frequently used, being the number concentration calculated by the following equation:

$$X^N = \frac{6 \times 10^{21}}{\pi \rho d^3} X^M \quad (12)$$

where the density of the particles ( $\rho$ ) is expressed in  $g\ cm^{-3}$ , the particle diameter ( $d$ ) in nm and  $X^M$  in  $g\ L^{-1}$ . Calculation of  $X^N$  from eq. 12 requires to know accurately both the diameter and the element mass concentration. Since mean diameters are used in such calculations, polydisperse suspensions must be avoided as size standards to minimize bias between the calculated and actual number concentrations [38]. Moreover, the suspension should not contain dissolved forms of the element, whose content should be determined separately and subtracted from the total content. Due to these constraints, both size and element mass concentration of standards use to be verified by in-house measurements, especially when using non-reference materials [14,28,38]. In any case, reported expanded uncertainties for number concentrations calculated from size particle standards were in the range of 6–27% [14], in the same range than the available number concentration particle standard (19%) [39]. Finally, the density of the particles must be the same as the bulk metal, which is not the case for porous particles, like the platinum nanoparticles tested in [28].

Systematic errors associated to the particle size method are related to the estimation of the mean element mass of the particle size standard used if the density of the particles is lower than the bulk metal, due to the porosity of the particles, as it has been commented above for platinum nanoparticles. Another source of bias can arise from the estimation of the mean intensity of the particle events ( $S_p$ ), required for calculation of  $K_m$  from eq. 5.  $S_p$  can be estimated from individual particle events recorded for the standard, but also from the corresponding signal distribution, that can be fitted to Gaussian or lognormal distributions. Since the approach followed will depend on the software/instrument used, the potential bias is not easily predictable. Although harmonization of these procedures would be desirable, given its impact on the transport efficiency estimation, there is not a common agreement, and most users follow procedures according to the proprietary software of the ICP-MS manufacturers for data processing. A deeper discussion about this topic can be found in [40]. In any case, the use of monodisperse standard with narrow and Gaussian size distribution minimizes this error [28]. Finally, the use of too large particle standards can lead to the underestimation of  $K_m$  because the particles are not fully volatilized and atomized in the plasma, as it has been the case for Au particles of 250 nm [41] or for  $SiO_2$  particles over 1.8  $\mu m$  [6]. This underestimation of  $K_m$  can also be due to the limited dynamic range of pulse counting detectors [41], which may be extended by reducing the sensitivity (e.g., use of less abundant isotopes [29,30] or defocusing the ion beam [42]).

In the case of the dynamic mass flow method, the main source of bias is related to the nebulization systems used, since cooled spray chambers are required to avoid solvent vaporization when using aqueous suspensions [4,28]. However, overestimated transport efficiencies have been reported using organic solvents despite controlling the nebulization temperature [43]. Other sources of bias have been considered by Murphy et al. [14] related to aerosol ion redistribution [5], although they should not be relevant since dissolved species are involved in aerosol ion redistribution and the dynamic mass flow method is only applied in relation to transport of particles.

Regarding the uncertainty associated to the different methods,

Murphy et al. [12] estimated the relative expanded uncertainties for the determination of the transport efficiency by the particle frequency and the particle size methods as 11.5 and 7.9%. Considering the same reference material (RM 8013), Cuello et al. [4] estimated a relative expanded uncertainty for the dynamic mass flow method of 11.4%. In a more recent publication using three different nebulization systems, Murphy et al. [14] reported representative uncertainty values in the range of 4–11 and 5–8% for the particle frequency and the particle size methods, respectively, as well as 3–5% for the dynamic mass flow method, although an anomalous value of 38% was also reported under the same conditions.

## 8. Conclusions

After more than ten years of steady development of SP-ICP-MS, it is time to harmonize a number of issues in relation to the technique, and transport efficiency is one of them. Pace et al. [3] made a great work by developing two novel methods for the determination of transport efficiencies, as they allowed SP-ICP-MS to be applied to unknown particles, even if no standards of those particles were available. However, the extensive use of these methods, together with a comprehensive inter-laboratory comparison study and some additional studies on the topic published recently, makes necessary to revise and reconsider a widely accepted paradigm.

First of all, transport efficiencies involved in SP-ICP-MS are directly related to the method applied for their determination. Hence, by using the particle frequency method, the *particle transport efficiency* is determined, whereas the *dissolved element transport efficiency* is determined by the particle size method. Regarding the dynamic mass flow method, it allows to determine the *solvent transport efficiency*, which under specific conditions (cooled and equilibrated nebulization system) can be equivalent to the particle transport efficiency, at least in aqueous suspensions.

Both direct and indirect methods for determination of transport efficiencies developed in the early times of atomic spectrometry were oriented to fundamental studies and their complexity prevents their routine use as part of a typical SP-ICP-MS workflow, where the determination of transport efficiency is linked to the different calibrations involved in SP-ICP-MS analysis. In this context, the dynamic mass flow method also shares practical limitations that restrict its use, as evidenced by its reduced application [4,43,44].

Although no statistically significant differences have been demonstrated between the particle frequency and the particle size methods, there is a general consensus about the robustness of the latter [12,28,35,36], mainly because it is not affected by particle losses, being more frequently used in most publications. In any case, the recommendation of applying the particle size method when the objective of the measurements is the determination of the particle size or the element mass per particle, whereas applying the particle frequency method for the determination of particle number concentrations, is a fair option to minimize bias in SP-ICP-MS analysis [28]. However, this approach does not compensate either the different level of losses in standards and samples or the different behaviour of dissolved and particulate forms, but it may be considered the least bad option especially in the most complex cases. From a practical point of view, the main use of the dynamic mass flow method can be the assignment of a SI traceable number concentration value to commercial nanomaterials to be used as quality control materials in SP-ICP-MS [45]. Regarding uncertainty, all three methods show similar values under optimal conditions, being the uncertainty associated to the use of a reference material the main contribution in both frequency and size methods.

Since reference materials for different types of particles are not expected to be available in the short term, aqueous suspensions of inert particles (e.g., Au), detectable in most instruments (40–60 nm), with narrow, gaussian and monodisperse distributions, stabilized with some organic coating (e.g., pegylated) and accurately characterized with

respect to size, number and mass concentration would be good candidates as standards for generic SP-ICP-MS analysis.

## CRediT authorship contribution statement

**Eduardo Bolea:** Writing – review & editing, Funding acquisition.  
**Francisco Laborda:** Writing – original draft, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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## References

- [1] R.F. Browner, A.W. Boorn, Sample introduction: the Achilles' heel of atomic spectroscopy? *Anal. Chem.* 56 (1984) 786A–798A, <https://doi.org/10.1021/ac00271a718>.
- [2] C. Degueldre, P.-Y. Favarger, Colloid analysis by single particle inductively coupled plasma-mass spectroscopy: a feasibility study, *Colloids Surfaces A Physicochem. Eng. Asp.* 217 (2003) 137–142, [https://doi.org/10.1016/S0927-7757\(02\)00568-X](https://doi.org/10.1016/S0927-7757(02)00568-X).
- [3] H.E. Pace, N.J. Rogers, C. Jarolimik, V.A. Coleman, C.P. Higgins, J.F. Ranville, Determining transport efficiency for the purpose of counting and sizing nanoparticles via single particle inductively coupled plasma mass spectrometry, *Anal. Chem.* 83 (2011) 9361–9369, <https://doi.org/10.1021/ac201952t>.
- [4] S. Cuello-Nuñez, I. Abad-Álvarez, D. Bartzak, M.E. del Castillo Busto, D.A. Ramsay, F. Pellegrino, H. Goenaga-Infante, The accurate determination of number concentration of inorganic nanoparticles using spICP-MS with the dynamic mass flow approach, *J. Anal. At. Spectrom.* 35 (2020) 1832–1839, <https://doi.org/10.1039/C9JA00415G>.
- [5] A. Montaser, M.G. Minnich, H. Liu, A.G.T. Gustavsson, R.F. Browner, *Fundamental aspects of sample introduction in ICP spectrometry*, in: A. Montaser (Ed.), *Inductively Coupled Plasma Mass Spectrometry*, Wiley-VCH, New York, 1998, p. 335.
- [6] J.W. Olesik, P.J. Gray, Considerations for measurement of individual nanoparticles or microparticles by ICP-MS: determination of the number of particles and the analyte mass in each particle, *J. Anal. At. Spectrom.* 27 (2012) 1143–1155, <https://doi.org/10.1039/c2ja30073g>.
- [7] F. Laborda, J. Jiménez-Lamana, E. Bolea, J.R. Castillo, Critical considerations for the determination of nanoparticle number concentrations, size and number size distributions by single particle ICP-MS, *J. Anal. At. Spectrom.* 28 (2013), <https://doi.org/10.1039/c3ja50100k>.
- [8] R. Herrmann, C. Onkelinx, Quantities and units in clinical chemistry: Nebulizer and flame properties in flame emission and absorption spectrometry (Recommendations 1986), *Pure Appl. Chem.* 58 (1986) 1737–1742, <https://doi.org/10.1351/pac198658121737>.
- [9] J. Tuoriniemi, G. Cornelis, M. Hasselöv, Size discrimination and detection capabilities of single-particle ICPMS for environmental analysis of silver nanoparticles, *Anal. Chem.* 84 (2012) 3965–3972, <https://doi.org/10.1021/ac203005r>.
- [10] D.D. Smith, R.F. Browner, Measurement of aerosol transport efficiency in atomic spectrometry, *Anal. Chem.* 54 (1982) 533–537, <https://doi.org/10.1021/ac00240a041>.
- [11] S. Gschwind, M.D.L. Aja Montes, D. Günther, Comparison of sp-ICP-MS and MDG-ICP-MS for the determination of particle number concentration, *Anal. Bioanal. Chem.* (2015) 4035–4044, <https://doi.org/10.1007/s00216-015-8620-7>.
- [12] K.E. Murphy, J. Liu, A.R. Montoro Bustos, M.E. Johnson, M.R. Winchester, *Characterization of Nanoparticle Suspensions Using Single Particle Inductively Coupled Plasma Mass Spectrometry*, Gaithersburg, MD, 2016, <https://doi.org/10.6028/NIST.SP.1200-21>.
- [13] M. Loula, A. Kaña, R. Koplík, J. Hanuš, M. Vosmanská, O. Mestek, Analysis of Silver Nanoparticles Using Single-Particle Inductively Coupled Plasma–Mass Spectrometry (ICP-MS): Parameters Affecting the Quality of Results, *Anal. Lett.* 52 (2019) 288–307, <https://doi.org/10.1080/00032719.2018.1459657>.

- [14] K.E. Murphy, A.R. Montoro Bustos, L.L. Yu, M.E. Johnson, M.R. Winchester, Comparison of direct and indirect measures of transport efficiency in single particle inductively coupled plasma mass spectrometry, *Spectrochim. Acta part B, At. Spectrosc.* 212 (2024) 106841, <https://doi.org/10.1016/j.sab.2023.106841>.
- [15] Efficiency of nebulization, in: IUPAC Compend. Chem. Terminol, International Union of Pure and Applied Chemistry (IUPAC), Research Triangle Park, NC, 2014, <https://doi.org/10.1351/goldbook.E01907>.
- [16] F. Laborda, A.C. Gimenez-Ingalature, E. Bolea, J.R. Castillo, About detectability and limits of detection in single particle inductively coupled plasma mass spectrometry, *Spectrochim. Acta Part B At. Spectrosc.* 169 (2020) 105883, <https://doi.org/10.1016/j.sab.2020.105883>.
- [17] K. Mehrabi, D. Günther, A. Gundlach-Graham, Single-particle ICP-TOFMS with online microdroplet calibration for the simultaneous quantification of diverse nanoparticles in complex matrices, *Environ. Sci. Nano.* 6 (2019) 3349–3358, <https://doi.org/10.1039/C9EN00620F>.
- [18] A. Gundlach-Graham, K. Mehrabi, Monodisperse microdroplets: a tool that advances single-particle ICP-MS measurements, *J. Anal. At. Spectrom.* 35 (2020) 1727–1739, <https://doi.org/10.1039/D0JA00213E>.
- [19] L. Hendriks, B. Ramkorun-Schmidt, A. Gundlach-Graham, J. Koch, R.N. Grass, N. Jakubowski, D. Günther, Single-particle ICP-MS with online microdroplet calibration: toward matrix independent nanoparticle sizing, *J. Anal. At. Spectrom.* 34 (2019) 716–728, <https://doi.org/10.1039/C8JA00397A>.
- [20] S. Harycki, A. Gundlach-Graham, Online microdroplet calibration for accurate nanoparticle quantification in organic matrices, *Anal. Bioanal. Chem.* 414 (2022) 7543–7551, <https://doi.org/10.1007/s00216-022-04115-2>.
- [21] S. Harycki, A. Gundlach-Graham, Single-particle ICP-TOFMS with online microdroplet calibration: a versatile approach for accurate quantification of nanoparticles, submicron particles, and microplastics in seawater, *Anal. Chem.* 95 (2023) 15318–15324, <https://doi.org/10.1021/acs.analchem.3c02785>.
- [22] M. Tharaud, P. Louvat, M.F. Benedetti, Detection of nanoparticles by single-particle ICP-MS with complete transport efficiency through direct nebulization at few-microlitres-per-minute uptake rates, *Anal. Bioanal. Chem.* (2020), <https://doi.org/10.1007/s00216-020-03048-y>.
- [23] S. Miyashita, H. Mitsuhashi, S. Fujii, A. Takatsu, K. Inagaki, T. Fujimoto, High transport efficiency of nanoparticles through a total-consumption sample introduction system and its beneficial application for particle size evaluation in single-particle ICP-MS, *Anal. Bioanal. Chem.* 409 (2017) 1531–1545, <https://doi.org/10.1007/s00216-016-0089-5>.
- [24] R.J.B. Peters, Z.H. Rivera, G. van Bommel, H.J.P. Marvin, S. Weigel, H. Bouwmeester, Development and validation of single particle ICP-MS for sizing and quantitative determination of nano-silver in chicken meat, *Anal. Bioanal. Chem.* 406 (2014) 3875–3885, <https://doi.org/10.1007/s00216-013-7571-0>.
- [25] I. Abad-Alvaro, D. Leite, D. Bartczak, S. Cuello-Nunez, B. Gomez-Gomez, Y. Madrid, M. Aramendia, M. Resano, H. Goenaga-Infante, An insight into the determination of size and number concentration of silver nanoparticles in blood using single particle ICP-MS (spICP-MS): feasibility of application to samples relevant to in vivo toxicology studies, *J. Anal. At. Spectrom.* 36 (2021) 1180–1192, <https://doi.org/10.1039/d1ja00068c>.
- [26] M. Aramendia, J.C. Garcia-Mesa, E.V. Alonso, R. Garde, A. Bazo, J. Resano, M. Resano, A novel approach for adapting the standard addition method to single particle-ICP-MS for the accurate determination of NP size and number concentration in complex matrices, *Anal. Chim. Acta* 1205 (2022) 339738, <https://doi.org/10.1016/j.aca.2022.339738>.
- [27] Y. Huang, J. Tsz-Shan Lum, K. Sze-Yin Leung, Single particle ICP-MS combined with internal standardization for accurate characterization of polydisperse nanoparticles in complex matrices, *J. Anal. At. Spectrom.* 35 (2020) 2148–2155, <https://doi.org/10.1039/d0ja00180e>.
- [28] O. Geiss, I. Bianchi, G. Bucher, E. Verleysen, F. Brassinne, J. Mast, K. Loeschner, L. Givélet, F. Cubadda, F. Ferraris, A. Raggi, F. Iacoponi, R. Peters, A. Undas, A. Müller, A.-K. Meinhardt, B. Hetzer, V. Gräf, A.R. Montoro Bustos, J. Barrero-Moreno, Determination of the transport efficiency in spICP-MS analysis using conventional sample introduction systems: an Interlaboratory comparison study, *Nanomaterials* 12 (2022) 725, <https://doi.org/10.3390/nano12040725>.
- [29] G. Bucher, F. Auger, Combination of 47Ti and 48Ti for the determination of highly polydisperse TiO<sub>2</sub> particle size distributions by spICP-MS, *J. Anal. At. Spectrom.* 34 (2019) 1380–1386, <https://doi.org/10.1039/c9ja00101h>.
- [30] F. Laborda, C. Trujillo, R. Lobinski, Analysis of microplastics in consumer products by single particle-inductively coupled plasma mass spectrometry using the carbon-13 isotope, *Talanta* 221 (2021) 121486, <https://doi.org/10.1016/j.talanta.2020.121486>.
- [31] L. Sánchez-García, E. Bolea, F. Laborda, C. Cubel, P. Ferrer, D. Gianolio, I. da Silva, J.R. Castillo, Size determination and quantification of engineered cerium oxide nanoparticles by flow field-flow fractionation coupled to inductively coupled plasma mass spectrometry, *J. Chromatogr. A* 1438 (2016) 205–215, <https://doi.org/10.1016/j.chroma.2016.02.036>.
- [32] J. Wojcieszek, J. Jiménez-Lamana, K. Bierla, L. Ruzik, M. Asztemborska, M. Jarosz, J. Szpunar, Uptake, translocation, size characterization and localization of cerium oxide nanoparticles in radish (*Raphanus sativus* L.), *Sci. Total Environ.* 683 (2019) 284–292, <https://doi.org/10.1016/j.scitotenv.2019.05.265>.
- [33] D. Torregrosa, G. Grindlay, L. Gras, J. Mora, Unraveling the role of aerosol transport on nanomaterial characterization by means single particle inductively coupled plasma mass spectrometry, *J. Anal. At. Spectrom.* 38 (2023) 1874–1884, <https://doi.org/10.1039/D3JA00134B>.
- [34] D. Torregrosa, G. Grindlay, M. de la Guardia, L. Gras, J. Mora, Determination of metallic nanoparticles in air filters by means single particle inductively coupled plasma mass spectrometry, *Talanta* 252 (2023) 123818, <https://doi.org/10.1016/j.talanta.2022.123818>.
- [35] J. Liu, K.E. Murphy, M.R. Winchester, V.A. Hackley, Overcoming challenges in single particle inductively coupled plasma mass spectrometry measurement of silver nanoparticles, *Anal. Bioanal. Chem.* 409 (2017) 6027–6039, <https://doi.org/10.1007/s00216-017-0530-4>.
- [36] V. Geertsen, E. Barruet, F. Gobeaux, J.-L. Lacour, O. Taché, Contribution to accurate spherical gold nanoparticle size determination by single-particle inductively coupled mass spectrometry: a comparison with small-angle X-ray scattering, *Anal. Chem.* 90 (2018) 9742–9750, <https://doi.org/10.1021/acs.analchem.8b01167>.
- [37] I. Abad-Alvaro, E. Peña-Vázquez, E. Bolea, P. Bermejo-Barrera, J.R. Castillo, F. Laborda, Evaluation of number concentration quantification by single-particle inductively coupled plasma mass spectrometry: microsecond vs. millisecond dwell times, *Anal. Bioanal. Chem.* 408 (2016) 5089–5097, <https://doi.org/10.1007/s00216-016-9515-y>.
- [38] A.R. Montoro Bustos, K.E. Murphy, M.R. Winchester, Evaluation of the potential of single particle ICP-MS for the accurate measurement of the number concentration of AuNPs of different sizes and coatings, *Anal. Chem.* 94 (2022) 3091–3102, <https://doi.org/10.1021/acs.analchem.1c04140>.
- [39] LGC, Colloidal gold NPs – nominal diameter 30 nm quality control material LGCQC5050. [https://www.lgcstandards.com/medias/sys\\_master/root/h84/h04/10435846012958/LGCQC5050.pdf](https://www.lgcstandards.com/medias/sys_master/root/h84/h04/10435846012958/LGCQC5050.pdf), 2019.
- [40] F. Laborda, I. Abad-Alvaro, M.S. Jiménez, E. Bolea, Catching particles by atomic spectrometry: benefits and limitations of single particle - inductively coupled plasma mass spectrometry, *Spectrochim. Acta Part B At. Spectrosc.* 199 (2023) 106570, <https://doi.org/10.1016/j.sab.2022.106570>.
- [41] W.-W. Lee, W.-T. Chan, Calibration of single-particle inductively coupled plasma mass spectrometry (SP-ICP-MS), *J. Anal. At. Spectrom.* 30 (2015) 1245–1254, <https://doi.org/10.1039/C4JA00408F>.
- [42] I. Strenge, C. Engelhard, Single particle inductively coupled plasma mass spectrometry: investigating nonlinear response observed in pulse counting mode and extending the linear dynamic range by compensating for dead time related count losses on a microsecond timescale, *J. Anal. At. Spectrom.* 35 (2020) 84–99, <https://doi.org/10.1039/C9JA00327D>.
- [43] Z. Gajdosechova, J. Marleau-Gillette, Single particle analysis of polydisperse metal-bearing particles in cannabis vape liquids by organic mode ICP-MS, *J. Anal. At. Spectrom.* (2024), <https://doi.org/10.1039/d4ja00045e>.
- [44] A. Schavkan, C. Gollwitzer, R. Garcia-Diez, M. Krumrey, C. Minelli, D. Bartczak, S. Cuello-Núñez, H. Goenaga-Infante, J. Rissler, E. Sjöström, G.B. Baur, K. Vasilatou, A.G. Shard, Number concentration of gold nanoparticles in suspension: SAXS and spICPMS as traceable methods compared to laboratory methods, *Nanomaterials* 9 (2019), <https://doi.org/10.3390/nano9040502>.
- [45] H. Goenaga-Infante, Comment on “Comparison of direct and indirect measures of transport efficiency in single particle inductively coupled plasma mass spectrometry” by K. E. Murphy, A. R. Montoro Bustos, L. L. Yu, M. E. Johnson, M. R. Winchester, *Spectrochim. Acta Part B At. Spectrosc.* 106876 (2024), <https://doi.org/10.1016/j.sab.2024.106876>.