INTERNATIONAL STANDARD

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13319-1

First edition

Determination of particle size distribution — Electrical sensing zone method —

Part 1:
Aperture/orifice tube method

Détermination de la distribution granulométrique — Méthode de détection de zones électrosensibles —
Partie 1: Méthode d'ouverture/d'orifice du tube

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 24 *Particle characterization including sieving*, Subcommittee SC 4, *Particle characterization*.

This first edition of ISO 13319-1 cancels and replaces ISO 13319:2007, which has been technically revised. The main changes compared to the previous edition are as follows:

— a general update to reflect the needs of modern quality assurance;

— the section on repeatability and inter system variation has been expanded;

— many instruments of this type are under strict controls within the pharmaceutical and related industries, therefore a new annex has been prepared with details of the factors which should be considered when developing a validated method in this arena;

— Clause 10 now gives details of the exact parameters which should be reported, in order to present the method and the key parameters of the result.

A list of all parts in the ISO 13319 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

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Determination of particle size distribution — Electrical sensing zone method —

Part 1:
Aperture/orifice tube method

1 Scope

This document specifies the measurement of the size distribution of particles dispersed in an electrolyte solution using the electrical sensing zone method. This can include biologics such as cells, but also industrial particles such as carbon, cement, ceramic powders, metal powders, pigments and polymer powders. The method measures pulse heights and their relationship to particle volumes or diameters, and is applicable over the range (implementation dependant) from approximately 0,5 μm to above 1 mm. This document does not address the specific requirements of the measurement of specific materials.

2 Normative references

There are no normative references in this document.

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3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

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https://standards.iteh.ai/catalog/standards/sist/8210e85f-0422-4e3f-b221-
813a1e637dc5/iso-prf-13319-1

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
dead time
time during which the electronics are not able to detect particles due to the signal processing of a previous pulse

3.2
aperture
small diameter hole through which suspension is drawn

3.3
sensing zone
volume of electrolyte solution within, and around, the aperture in which a particle is detected

3.4
analysis volume
volume of suspension that is analysed

3.5
size bin
size interval to distinguish particle size for size distribution measurement

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3.6
envelope size
external size of a particle as seen in a microscope

3.7
envelope volume
volume of the envelope given by the three-dimensional boundary of the particle to the surrounding medium

3.8
effective density
density of a porous particle where open pores are filled with liquid and closed pores are not (so included in the density)

4 Symbols

For the purposes of this document, the following symbols apply.

A_p amplitude of the most frequent pulse

A_x amplitude of the electrical pulse generated by an arbitrary particle

D aperture diameter

d_m certified mean diameter of the microspheres used for primary calibration

d_{micr} mean diameter of the sieved fraction as determined using microscopy

d_{ESZ} mean diameter of the sieved fraction as determined using the ESZ instrument

df   degrees of freedom

d_L particle diameter at the lower boundary of a size interval or channel

d_p modal diameter of a certified particle size reference material

d_{ref} reference diameter of the microspheres

d_U particle diameter at the upper boundary of a size interval or channel

f_{resp} response factor

K_d calibration constant of diameter

K_{da} arbitrary calibration constant of diameter of any value to start the mass calibration procedure

m mass of sample

M_b mass balance, percentage of particles accounted for in a measurement in comparison to input particle mass

M_m mass of particles measured by the instrument

n number used to signify the maximum of an integral be it channel number [(in Formula (D.1)] or number of repeat measurements [in Formulae (G.1) and (G.2)]

n_c counted particle number

N_c mean of a Poisson distribution, used to describe the temporal spread of counts within a size bin

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N_{c5}	count for 5 % coincidence
N_i	total number of counts across all size intervals
ΔN_i	number of counts in a size interval i
$\overline{N}$	mean of particles in counts N_i (i = 1, 2, 3...n)
p	significance level of statistical test
V_m	analysis volume
V_T	volume of electrolyte solution in which a mass, m is dispersed
$\overline{V}_i$	arithmetic mean volume for a particular size interval i
x	diameter of a sphere with volume equivalent to that of the particle
x_{max}	maximum particle size that can be obtained on a specific aperture
x_{min}	minimum particle size that can be obtained on a specific aperture
ρ	immersed density/effective density (solid density including eventual closed pores, but excluding open pores within the particles)
χ^2	chi-squared statistical distribution

5 Principle

A dilute suspension of particles dispersed in an electrolyte solution is stirred to provide a homogeneous mixture and is drawn through an aperture in an insulating wall. An electric current applied across two electrodes, placed on each side of the aperture, enables the particles to be sensed by the electrical impedance changes as they pass through the aperture. The impedance pulses generated by particle passage are amplified and digitally captured, and the pulse height and shape is analysed, yielding particle count data. The pulse height is regarded directly proportional to particle volume. After employing a calibration factor, a distribution of the number of particles against the volume-equivalent diameter is obtained. The size range of particles to be measured depends upon the size of the aperture.

Conventionally, particles having a size greater than around 0,5 µm are measured by the technique. A schematic of the instrumentation is given in Figure 1.
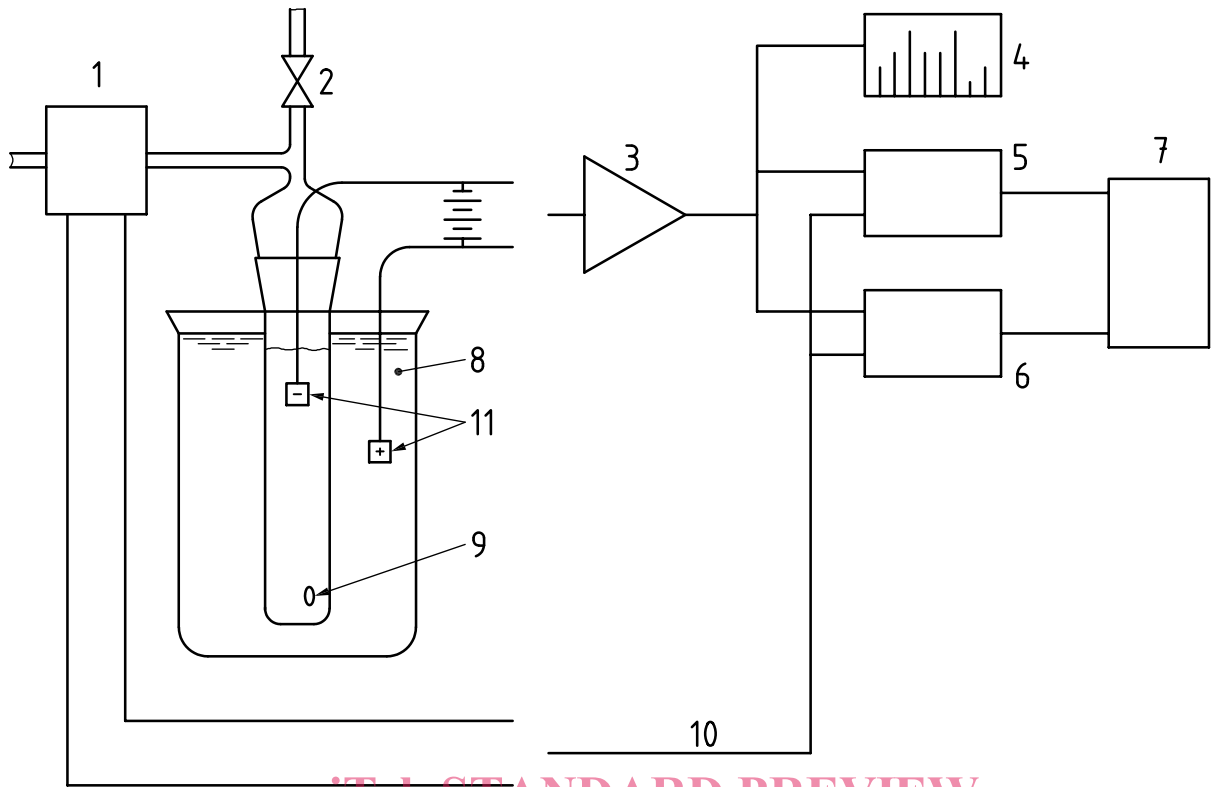
Key

1   volumetric metering device
2   valve
3   pulse amplifier
4   oscilloscope pulse display
5   counting circuit
6   pulse-height analyser
7   output
8   stirred suspension of particles in electrolyte solution
9   aperture
10 counter start/stop triggered by the volumetric device
11 electrodes

Figure 1 — Diagram illustrating the principle of the electrical sensing zone orifice/tube method

6   General operation

6.1   Response

The response (i.e. the electrical pulse height generated when a particle passes through the aperture) has been found both experimentally and theoretically to be proportional to the particle volume if the particles are spherical [1]-[3]. This has also been shown to be true for particles of other shapes; however, the constant of proportionality (i.e. the instrument's calibration constant) may be different [4]. In general, particles should have a low conductivity with respect to the electrolyte solution, but particles with high conductivity can be measured e.g. metals [5], carbon [6], silicon and many types of cells and organisms, such as blood cells [7],[8]. For porous particles, the response may vary with the porosity [9],[10]. Recommendations for the measurement of conducting particles and porous particles are given in Annex D.

As the response is proportional to the volume of particles, the pulse amplitude provides a relative scale of particle volumes. By calibration, this scale may be converted to spherical diameter. The calibration constant based on diameter may be calculated by Formula (1):

$$K_d = \frac{d_p}{\sqrt[3]{A_p}}$$

(1)

The size, x, of any particle can be calculated by Formula (2):

$$x = K_d \cdot \sqrt[3]{A_x}$$

(2)

Typical apertures have a length to diameter ratio of 0,75. This causes some variation in the electrical field within the aperture, which leads in turn to some deviations in the particle sizes measured. This can be countered by increasing the aperture length.

6.2   Size limits

The lower size limit of the electrical sensing zone method is generally considered to be restricted only by thermal and electronic noise. It is normally stated to be about 0,6 μm but, under favourable conditions, 0,4 μm is possible. There is no theoretical upper size limit, and for particles having a density similar to that of the electrolyte solution, the largest aperture available (normally 2 000 μm) may be used. The practical upper size limit is about 1 200 μm, limited by particle density.

The size range for a single aperture is related to the aperture diameter, D. The response has been found to depend linearly in volume on D, within about 5 % under optimum conditions, over a range from 0,015 D to 0,8 D (i.e. 1,5 μm to 80 μm for a 100 μm aperture) although the aperture may become prone to blockage at particle sizes below the maximum size where the particles are non-spherical. In practice, the lower limitation is due to thermal and electronic noise and the upper limitation is due to non-spherical particles passing through the aperture. This restricts the operating range to be within 2 % to 60 % of the aperture size. This size range can be extended by using two or more apertures (see Annex B). In practice, this procedure can be avoided by the careful selection of the diameter of one aperture, to achieve an acceptable range.

Sedimentation of particles becomes important when the particles are large and have a high density (for example, 100 μm quartz particles have a sedimentation rate in water of about 1 cm/s). Large apertures are available, up to 2 000 μm. In such applications, the viscosity and the density of the electrolyte solution should be increased, for example, by addition of glycerol or sucrose, in order to prevent particle sedimentation and to increase the possibility of keeping the particles in homogeneous suspension. The homogeneity may be checked by repeated analyses at a range of stirrer speeds. The results of this should be compared to establish the lowest stirrer speed at which recovery of the largest particles is maintained.

6.3   Effect of coincident particle passage

Ideal data would result if all particles traversed the aperture singly and, thus, would produce single pulses. However the opportunity exists, especially at increased concentrations, that two or more particles arrive in the sensing zone more or less together, which would result in a complex pulse.

Several possibilities exist, i.e (a) two particles pass the sensing zone at the same time, leading to a pulse height equal to the sum of both pulse heights, and to a loss of counts; (b) two particles pass the sensing zone at slightly different times but within the same measurement period of the larger particle, leading to the same pulse height for the larger particle but a distorted pulse shape, and to a loss of counts; (c) two particles, which are individually too small for measurement but have together sufficient volume, pass the sensing zone at the same time, leading to an extra pulse of measurable height, and to an increase of counts. This occurrence is named coincidence. Its effects will distort the size distribution obtained but can be minimized by using low particle concentrations. The probability of coincidence may be described by a Poisson distribution (see Annex A). Table 1 shows counts per millilitre for the

coincidence probability to be 5 % as well as the corresponding analysis volumes to count 100 000 particles.

Table 1 — Counts for 5 % coincidence probability and analysis volumes for 100 000 counts

Aperture diameter D μm	Maximum counts for 5 % coincidence[a] $N_{5\%}$ #/ml	Analysis volume for 10^5 counts[b] V_a ml
1 000	5,0E + 01	2 000
560	2,8E + 02	351
400	7,8E + 02	128
280	2,3E + 03	44
200	6,3E + 03	16
140	1,8E + 04	5,5
100	5,0E + 04	2
70	1,5E + 05	0,69
50	4,0E + 05	0,25
30	1,0E + 06	5,4E - 02
20	6,3E + 06	1,6E - 02
10	5,0E + 07	2,0E - 03
[a] Calculated using formula $N_{5\%} = 5 \cdot 10^{10}/D^3$ particles per ml.		
[b] Use pro rata values for other analysis volumes and count numbers.		

Counts per millilitre should always be less than these quoted values. Since particle size distributions should not be a function of concentration, the effect of coincidence can be tested by obtaining a distribution at one concentration and comparing it with that obtained when the concentration is halved. In such a test, repeat such dilutions until the reduction in count in a channel with the largest number decreases in proportion to the dilution. This should always be done when analysing very narrow size distributions, as this is where the effect of coincidence is most noticeable.

6.4 Dead time

In instruments using digital pulse processing routines, the signal is scanned at high frequency. Information on pulse parameters, such as maximum pulse height, maximum pulse width, mid-pulse height, mid-pulse width and pulse area is stored for subsequent analysis. In this case, analogue-to-digital conversion of the pulse with storage of the size value for the pulse is not performed in real time and dead time losses are avoided.

To minimize the effect of dead time, the analyser should be used with the lower threshold set to exclude thermal and electronic noise, as indicated at A in Figure 2. Additionally, the concentration of particles should be maintained below 5 % coincidence levels.
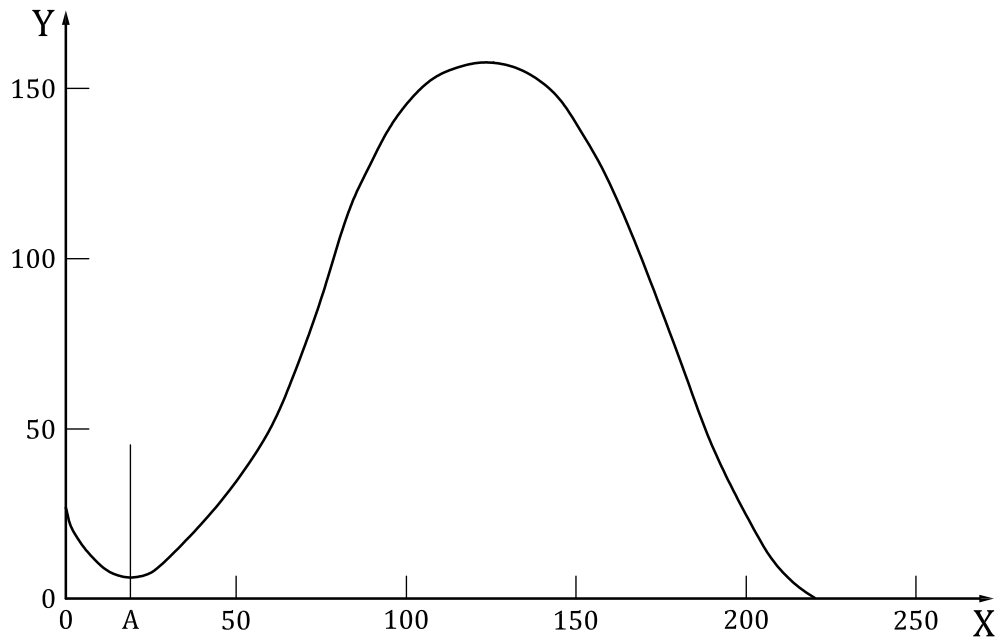
Key

X   channels

Y   counts

NOTE   Counts at channels below A are noise counts. True particle counts are at the higher channels.

Figure 2 — Typical results

6.5 Analysis volume

The analysis volume should be chosen based on the following requirements:

a)   allow a representative sample of the suspension;

b)   allow a sufficient number of particles to be counted and measured in relation to the required quality of the size distribution; and

c)   have sufficient precision for the number of particles to be counted if particle concentration is of interest.

Typical values of the analysis volume are given in Table 1.

Table 1 shows that the analysis volumes become excessive for counting this particle number when the aperture diameter becomes greater than 140 µm. Then, counting less particles means that less information on the size distribution will become available, so consideration should be taken into taking a representative sample.

7   Repeatability and reproducibility of counts

7.1   Instrument repeatability

In a correctly performed analysis, the number of counts in a size interval is a random variable which follows a Poisson distribution. In this, the variance is equal to the expected (mean) value. This indicates that the standard deviation of a number of counts, n_c, with mean, N_c, approximates to $\sqrt{N}_c$. Both the variance and the standard deviation can be used in statistical tests on the correctness of instrument operation or sample preparation. The statistical chi-squared test can be used to test whether obtained

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