The inventor of Laser Particle Size Technology

Particle Size and Shape Analysis in

PHARMACEUTICAL INDUSTRY

Generalities

Many analytical methods exist for the characterization of products manufactured in the pharmaceutical industry. Measuring the size and shape of particles or emulsions is undoubtedly one of the simplest and quickest methods, but provides indispensable qualitative data to assess the feasibility of a manufacturing process or the final effectiveness of a formulation.

Measuring size and shape is part of the precise requirements of the standards taken as the basis for the assessment of the possibilities for particle size analysis techniques and the benefits of morphological analysis for this application.

Standards USP <429>, USP <776> and <1058>

The first two USP standards [1-2] include the content of the above ISO standards.

Standard USP <1058> [3] covers IQ (Installation Qualification), OQ (Operational Qualification) and PQ (Performance Qualification) processes.

The IQ-OQ-PQ validation plans provided by CILAS (figure 1) are used to install and maintain instruments in accordance with the GMP (Good Manufacturing Practices) required by the WHO (World Health Organization).

Figure 1: IQ-OQ-PQ Qualification Workbook

Standard 21 CFR Part 11

Regulation 21 CFR Part 11 defines the bases for the electronic signatures on documents transmitted to the FDA (Food and Drug Administration) (figure 2).

FDA U.S. Food and Drug Administration

SizeExpert software meets the requirements of the standards and mainly manages multi-level access.

This standard:

-Speeds up the exchange of information
-Improves data searches
-Reduces errors and variability
-Reduces data storage costs

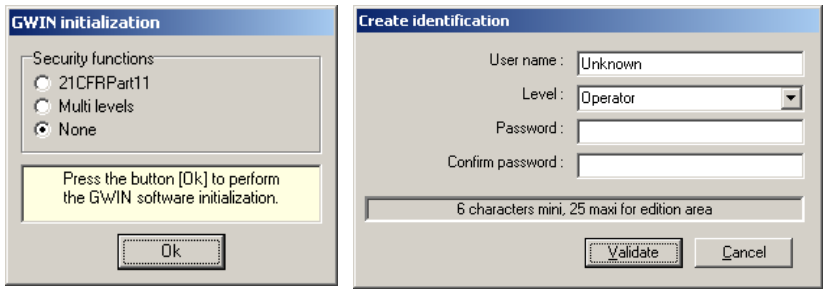


Figure 2: Multi-Level access with SizeExpert software

[1] United State of Pharmacopeia : USP <429> Light Diffraction Measurement of Particle Size

[2] United State of Pharmacopeia : USP <776> Optical Microscopy

[3] United State of Pharmacopeia : USP <1058> Analytical Instrument Qualification

Why analyse particle size and shape ?

Particle size anlaysis

Most compounds used for their pharmaceutical properties, active ingredients or excipients, are in powder or emulsion form.
Depending on the circumstances, the particle size distributions obtained by diffraction laser can be measured using dry or wet modes.

Figure 3 and figure 4 show the particle size distributions of an active ingredient, domperidone, and excipients, aluminum and silicon oxides (alumina and silica) and magnesium carbonate.

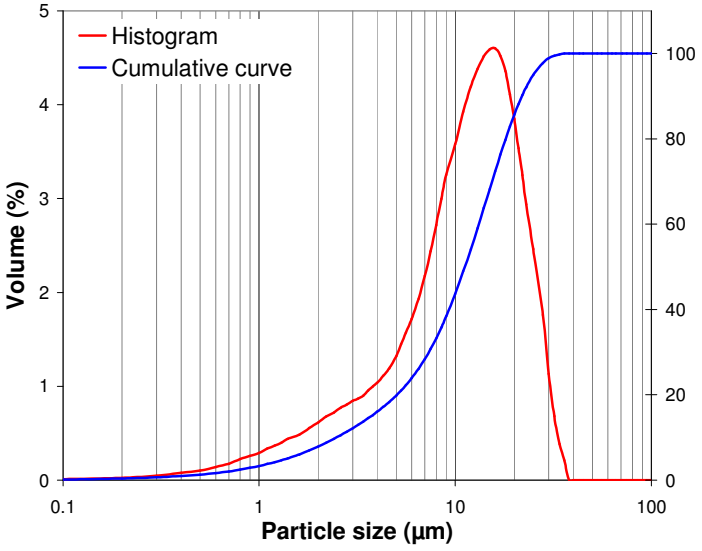


Figure 3: Particle size distributions for an active ingredient

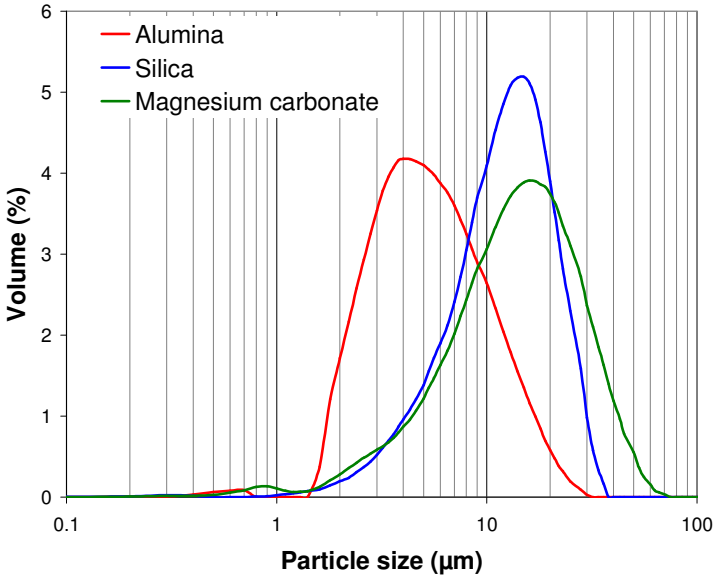
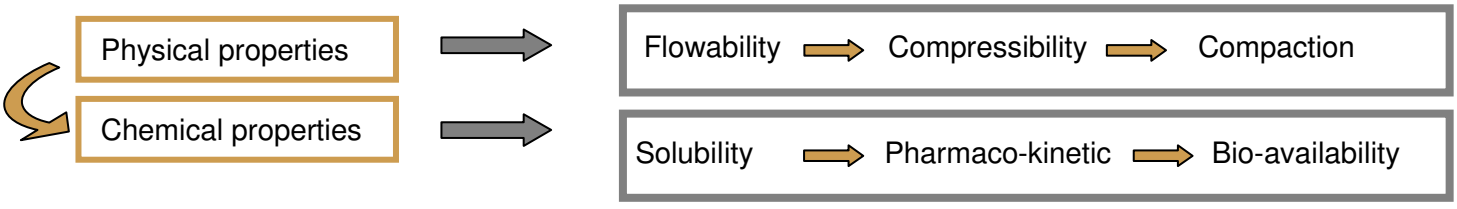


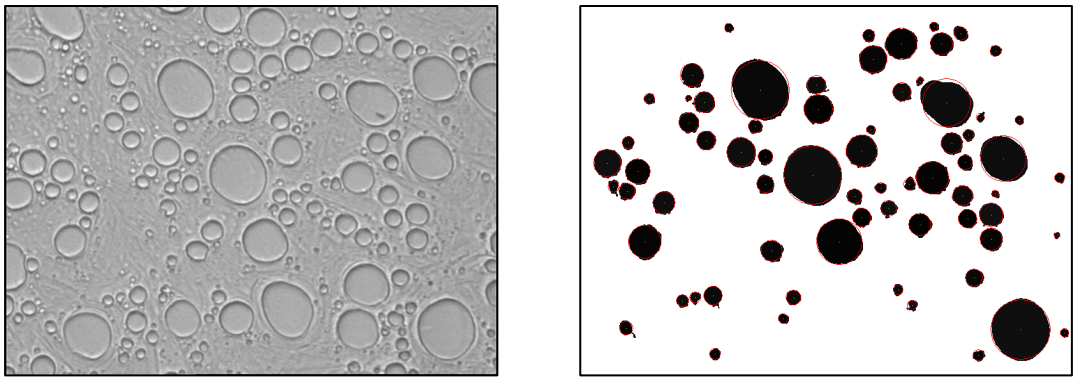
Figure 4: Particle size distributions for excipients



- Particle testing is specifically required during stability testing, prior to release of the drug into the market
- A decrease in particle size during stability testing resulting in higher weight as humidity adsorption increased
- Prolonged storage:
  - influenced crystal growth and modification of the active ingredient
  - caused a decrease in particle size resulting in increasing agglutination
  - caused a change in particle size of a drug, negatively impacting content uniformity

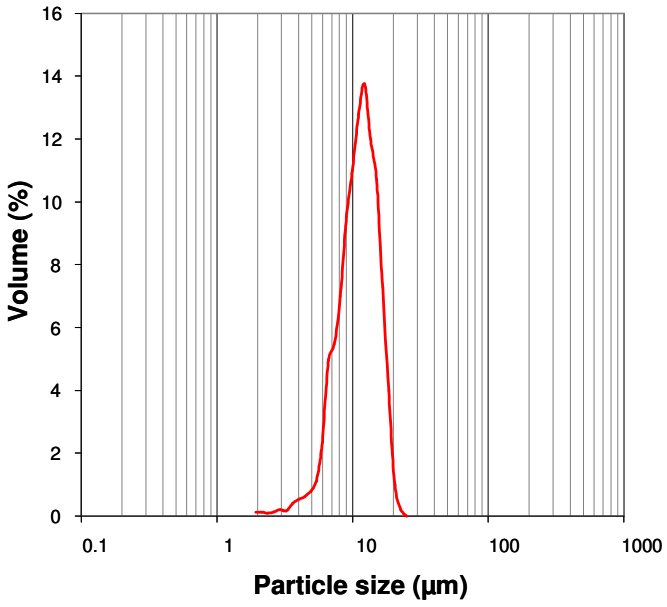
In special cases, it is also possible to measure the particle size thanks to optical microscopy and image analysis
In the case shown in figure 5.a, a concentrated emulsion has been placed on a microscope plate. The specimen was carefully prepared in view of obtaining fully separated drops and ensuring optimal conditions for the analysis.

For this type of image, digital processing (figure 5.b) involves thresholding to convert the image into black and white. A selection filter was then applied to select isolated particles and exclude agglomerates. In the example shown, the filter applied allowed the most spherical particles to be selected.



a) b)

Figure 5: Processing of an image of a micro-emulsion used in cosmetics
a) original image b) processed image



The size of the drops of this emulsion was determined on the basis of the analysis of 1049 particles. The corresponding particle size distribution is shown in figure 6.

The typical diameters of this monomode and monodisperse distribution are as follows:

D_{10} = 7.1 µm, D_{50} = 11.7 µm, D_{90} = 16.6 µm

Figure 6: Particle size distribution of a micro-emulsion

[2] Rheology modification in mixed shape colloidal dispersions. Part I: Pure components
Soft Matter, Volume 3, p. 1145–1162, (2007)
[3] Rheology modification in mixed shape colloidal dispersions. Part II: Mixtures
Soft Matter Volume 4, p. 337–348, (2008)
[4] The influence of pigment particle shape on the in-plane tensile strenth properties of kaolin-based coating layers
Tappi Journal Volume 5, N°12 (2006)

Morphological analysis

The importance of the morphology of particles can, for example, be demonstrated by the representation of the intrinsic viscosity of the solution, which influences the thixotropic behavior of a viscous solution [6].

Figure 7 shows changes to this size based on aspect ratio for particles at constant concentrations and volumes. This representation demonstrates a rapid increase in intrinsic viscosity when the particles have a strong shape anisotropy. This property can have a significant impact on the cream or pomade formulation.

Compactation phenomena are directly related to size and shape parameters (figure 8). The control of these parameters therefore enables improvements to manufacturing and compacting processes [7-9].

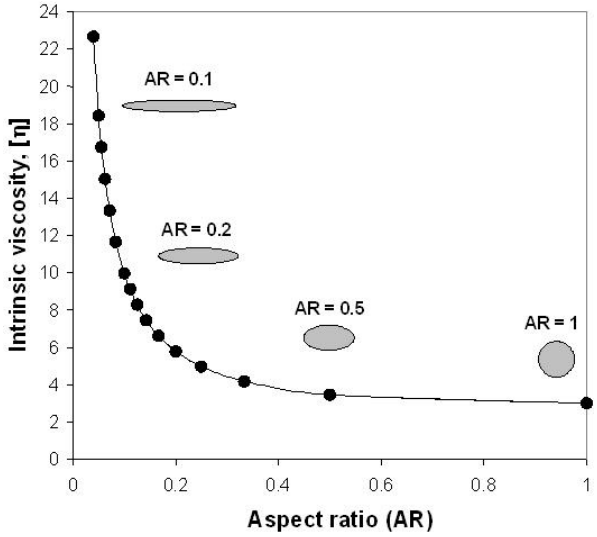
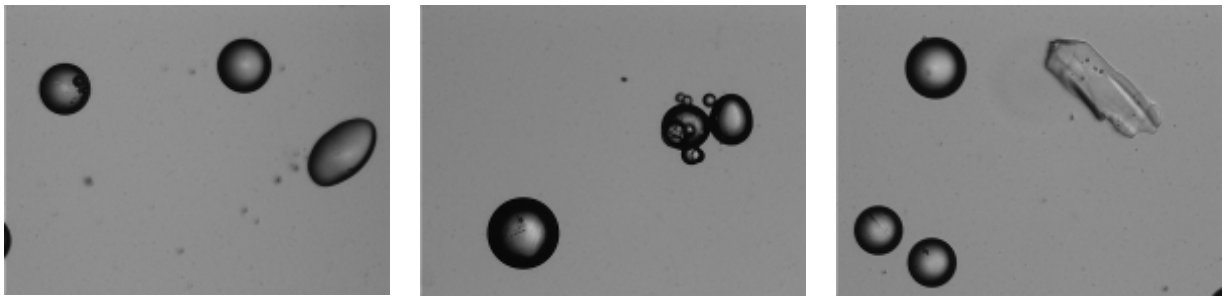


Figure 7: Influence of the shape on intrinsic viscosity



a) b) c)

Figure 8: Microscopic observations of a sample with an inhomogeneous shape

How to analyse ?

Particle size range

Particle size distribution generally between 0.1 et 50 µm.
The D_{50} is generally situated between 1 and 500 µm.

Liquid mode

Carried liquid : Water
Dispersing agent : Igepal
Ultrasons : 60s during dispersion
Mathematical model : Fraunhofer

Dry mode

Vibration frequency : 45 - 55 Hz
Cyclical ratio amplitude : 45 - 55 %
Air pressure : 100 - 500 bars

Particle size analysis in liquid mode

Carried liquid : Water
Dispersing agent : Igepal
Ultrasoudns : 60s

Special diameter of the particle size distribution shown in figure 9 :

- D_{10} = 1.99 µm
- D_{50} = 11.39 µm
- D_{90} = 26.12 µm

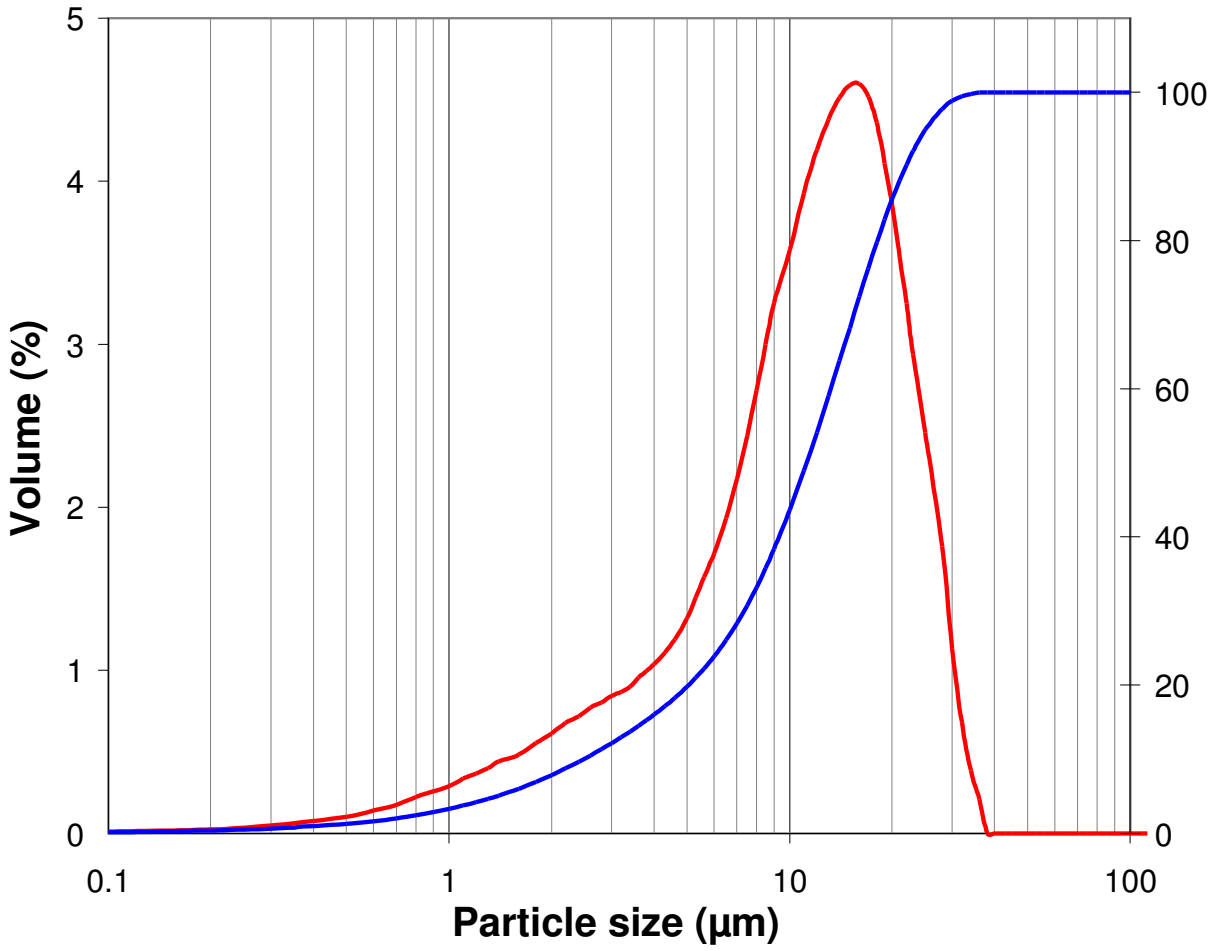


Figure 9: Particle size distribution obtained in liquid mode

Particle size analysis in dry mode

Vibration frequency = 50 Hz
Cyclical ratio amplitude = 50 %
Air pressure : 250 mbars

Special diameter of the particle size distribution shown in figure 10 :

- D_{10} = 52.43 µm
- D_{50} = 146.42 µm
- D_{90} = 286.75 µm

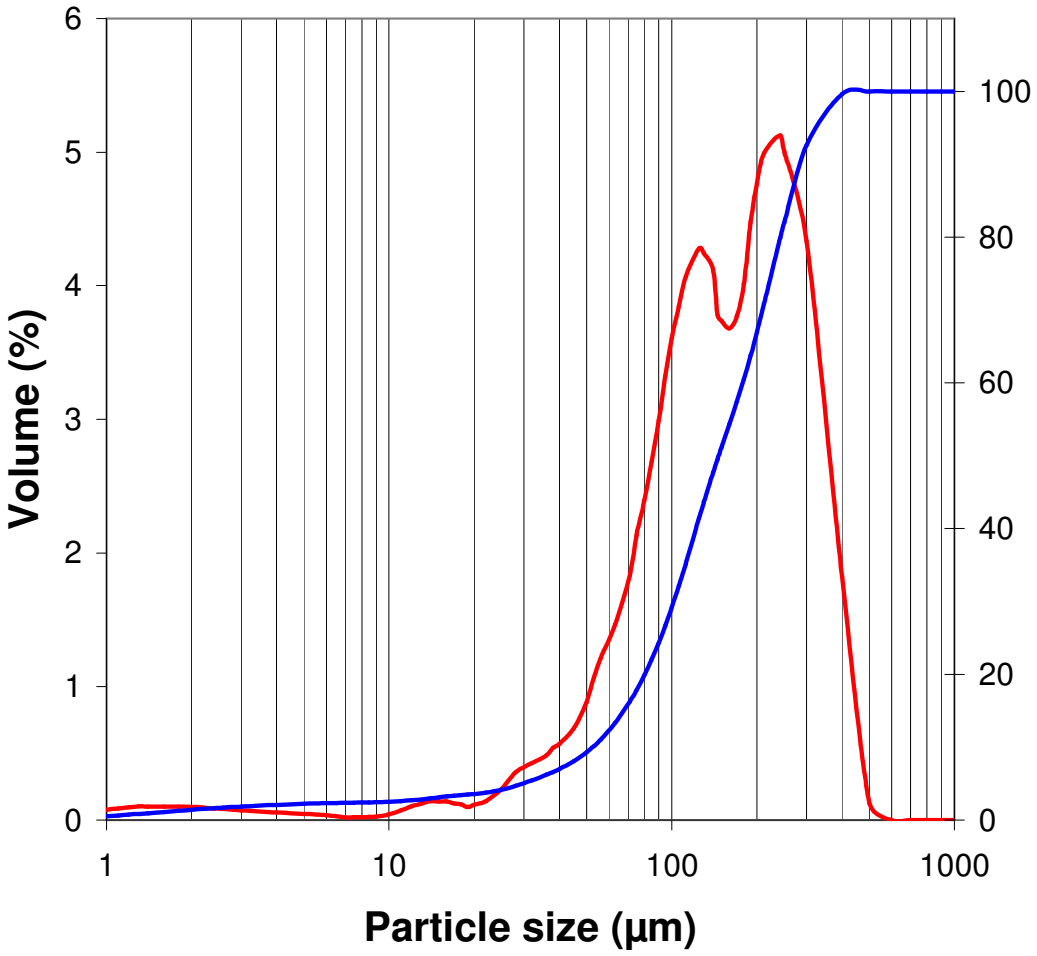


Figure 10: Particle size distribution obtained in dry mode

Shape parameter adapted for morphological analysis

An example of characteristic image is shown is figure 11. This image was obtained by optical microscopy with x40 magnification.

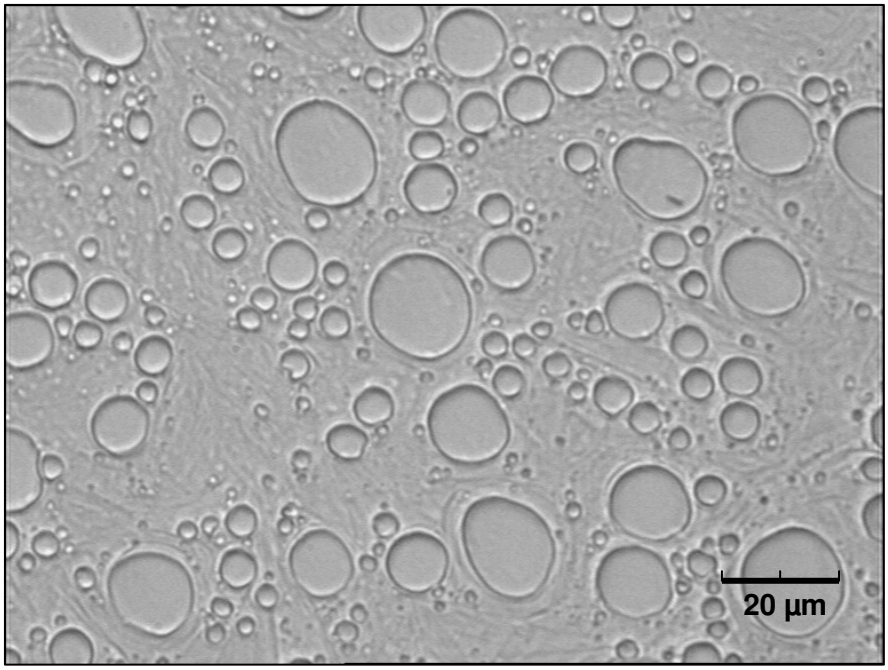
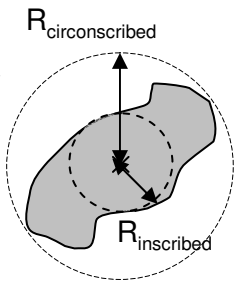


Figure 11: Characteristic image of a microemulsion used in cosmetic industry

The morphological parameters that may be used for this application are:

Sphericity

$$\text{Sphericity} = \frac{R_{inscribed}}{R_{circonscribed}}$$



Ratio of the radiuses of the inscribed and circumscribed circles.

In the case presented, Sphericity = 0.92
This parameter enables the deviation from circularity to be quantified.

Note

Agglomerates are not spherical. In case of spherical particles, a special selection filter can be applied. For example, a selection filter with a sphericity value comprised between 0.8 and 1 permits to remove all non spherical particle from the list of particles measured.