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Particle-size distribution of a powder: comparison of three analytical techniques

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Abstract

The purpose of this study is to compare two diffraction techniques (particle in air, PIA and particle in liquid, PIL) to an image analysis (IA), on spherical standard powders, applied to two different samples as a matter of particle size distribution (P52 and P260). We show by a direct qualitative comparison of the distribution curves that PIA and PIL give the same results in all cases, and that IA and diffraction methods can be considered as similar, excepted for P52 number analysis. The statistical layout demonstrates that the two diffraction methods give very close results. IA and laser methods provide us with different results except in the case of P260 in volume. In IA, there is a critical number of particles to be counted; this number is influenced by the width of the distribution. PIA and PIL are also influenced by the breadth of the distribution, depending on the principle of working. We show the importance of choice and complementarity of these techniques to measure the distribution size. Copyright © 1996 Elsevier Science B.V.

Keywords: Image analysis; Laser light diffraction technique; Particle-size distribution

1. Introduction

At the present time, in european and international registered files, because of the automation of processes and the frequent changes of production sites, research/development departments have to deal with more and more precise knowledge on the particulate materials to be able to detect any variability of physical properties on the active drug as well as on the excipients. The final purpose is to determine particle size distribution to try obtaining better handle manufacturing processes.

From this point of view, preformulation is essential to define characteristics of the powder, in particular size, shape, and area, from molecular to particulate state, to draw up specifications and

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quality levels which can be acceptable for raw materials and final drug.

The aim of this work is first to compare, on spherical standard powders, three techniques (Brewer and Ramsland, 1995) (two laser light diffraction techniques (Merkku and Yliruusi, 1992a,b) and image analysis, which is commonly used as a standard method) to evaluate the viability of analysis for different particle sizes, from a few micrometers to several hundred micrometers. Image analysis gives a direct observation. PIA and PIL are indirect but rapid methods which allow to work on a large number of particles.

It is important to emphasize the influence of choice and complementarity of these techniques, according to chemical composition, real density and form of the analyzed powder (Washington, 1992).

First we study the three techniques, their advantages and their limitations and we apply them to two spherical standard powders of 52 and 260 μm mean diameter, showing a ratio close to 5.

2. Materials and methods

2.1. Raw materials (standard particles)

- Origin: Bang Laboratories Inc Carmel USA productor (particle specialists—certification),
- shape: spherical particles,
- chemical composition: styrene and divinylbenzene copolymer (92:8),
- material density: 1.050 g/ml,
- color: white,
- two types:
  - *P52: diameter distribution around 52 μm (Ref. P0520000PN), size range 10–100 μm,
  - *P260: diameter distribution around 260 μm (Ref. P2600000PN), size range 100–1000 μm.

2.2. Instruments and methods

2.2.1. Optical microscopy coupled with image analysis (IA)

This method consists in an optical microscope interfaced with an image analyzer, and allows a direct observation followed by a dimensional measure.

It is considered as a fundamental method, used to standardize other more rapid indirect methods (AFNOR, 1990).

The powder is put down on a glass plate and observed under an optical microscope (Nachet NS 400, objectives × 8 for P260 and × 16 for P52). It is then filmed with a video camera (Cohu, model 4712–5000, resolution 512 × 512 in 256 grey shades). The image is numerized by a computer and then treated in order to obtain a binary black and white image by changing the contrasts, filtration and binarization (computerized system VIDAS, Kontron).

The program allows to measure the area and to calculate the diameter of the circle (Ds) which has the same area as the image of the particle according to the following formula (Barber, 1993):

$$Ds = 2\sqrt{(S/\pi)}$$

the number of observed particles is close to 500 (Paine, 1993).

2.2.2. Laser light diffraction (Coulter LS 130, Coultronics)

Powder is translocated by a fluid (air or liquid). The particles in suspension are illuminated with a laser beam. The incident laser beam is diffracted on powder particles. The diffractive angle on one particle is correlated to its size. The whole particles produce diffraction of the laser beam, and the diffraction image is sampled through 126 photodiodes located in different angles.

Theoretical Fraunhofer model is used to provide size data. This model which is an approximation of Mie theory, can be applied to diffractive angles less than 8° generally valuable for particle diameter up to 5 μm. Furthermore this model does not require special knowledge about the analyzed product, especially on refractive indices.

*Particles in air (PIA): dry powder device

Parameters of particle-size analysis are the following:

- acquisition time (30 s),

Table 1
Experimental conditions for the three methods

	AI	PIA	PIL
Samples	500 particles	10–20 g	2–5 g
Dispersion medium	Air	Air	Liquid: degased water
Dispersion technique	No cluster	Mecanical	Ultra sound
Optical analysis	Direct size and shape	Indirect size	Indirect size
Analysis range (μm)	Lens × 8: 1–600 Lens × 16: 0.5–300	0.4–900	0.1–900
Data processing	Well defined	Unknown	Unknown
Running time (h)	18	4	4

- auger speed, and
- vibrator frequency.

Following the manufacturer norms, the last two parameters are defined in order to obtain an obscuration of 8–12%.

* Particles in liquid (PIL): 'hazardous fluid' module

Parameters of particle-size analysis are the following:

- acquisition time (60 s)
- ultrasonic application: time, 30 s; intensity, 4, and
- pump speed: controlled to obtain an obscuration of 4–8%.

2.2.3. Interest and limitations of the methods: experimental conditions

Image analysis allows a direct observation and a verification of roundness, but it is tedious method. As shown in Table 1 laser methods enable work on a large number of particles which better represents the samples.

PIL will have limited applications as soon as the sample is soluble in most of the liquids (for example in case of a tensio-active powder). But on the other hand the study of a very cohesive powder will not be possible through PIA method (due to limit of disagglomeration in the air).

Concerning data treatment, it must be noticed that the algorithm used with Coulter LS 130 is not indicated by the manufacturer.

2.3. Statistical layout

Results of particle-size analysis obtained with each of the three techniques are expressed as ratio of the particles number or the particles volume as a function of diameter logarithm. The frequency distribution (number and volume) are studied by Pearson curves (CEMACEA, 1978). For each density function determined, Fisher coefficients are calculated (coefficient of sweekness and coefficient of kurtosis). For each powder these coefficients are statistically compared with a risk of 1%.

The whole computation is obtained through Microsoft Excel 5.0.

3. Results and discussion

It is uneasy to compare the three techniques results of a particle size analysis. In a first part will be presented and discussed the distribution curves as far as number and volume data are concerned, directly obtained by the different techniques (AI, PIL and PIA).

3.1. Comparison of distribution curves

3.1.1. Number distribution (Fig. 1(a, b))

P52: the results of PIA and PIL are almost similar, with very close particle geometric mean (Table 2) respectively 27.3 and 26.5 μm and closely related geometric standard deviation respectively 1.93 and 1.96.

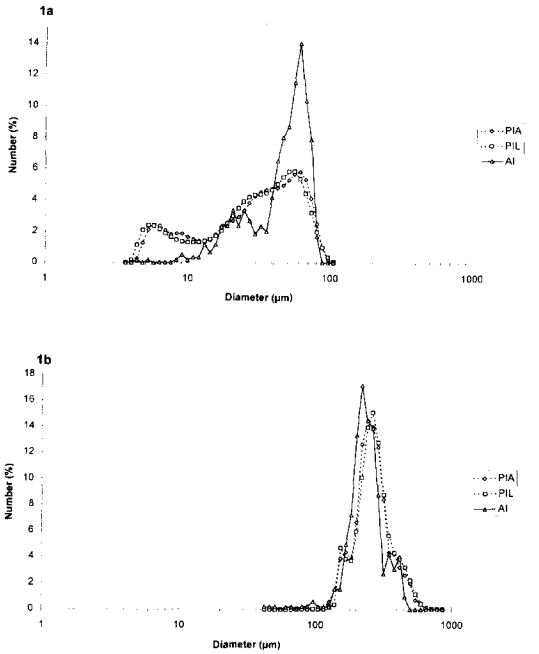

Fig. 1. Number distribution curves from AI, PIA and PIL methods for P52 powder (a) and P260 powder (b).

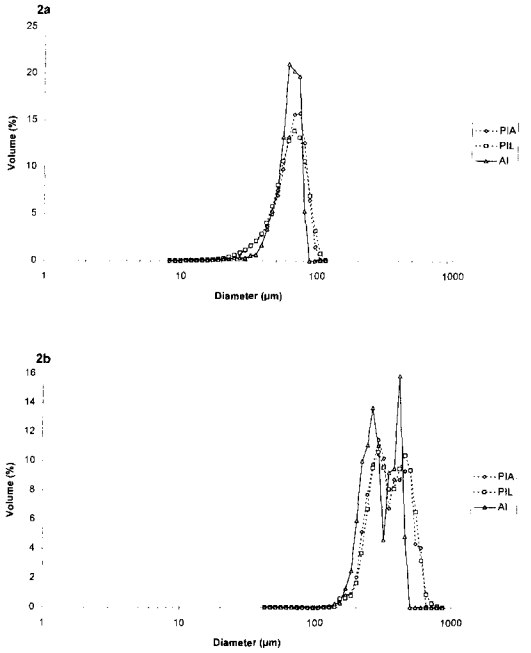

Fig. 2. Volume distribution curves from AI, PIA and PIL methods for P52 powder (a) and P260 powder (b).

On the other hand, the results obtained with IA are clearly different with mean diameter of 47.4 μm and geometrical standard deviation of 1.28 and with indication of a bimodal distribution.

P260: in this case the three techniques give the same results, showing a nearly symmetrical monomodal distribution.

Table 2
Geometric mean and geometric standard deviation of number and volume distributions for P52 and P260

		Geometric mean (μm)	Geometric standard deviation
Number			
P52	AI	47.4	1.28
	PIA	27.3	1.93
	PIL	26.5	1.96
P260	AI	256.2	1.10
	PIA	258.2	1.10
	PIL	266.5	1.09
Volume			
P52	AI	66.5	1.05
	PIA	61.0	1.10
	PIL	60.4	1.10
P260	AI	323.1	1.08
	PIA	342.0	1.10
	PIL	354.1	1.10

3.1.2. Volume distribution (Fig. 2(a, b))

P52: results are similar for the three techniques considering geometric mean diameter and geometric standard deviation. The distribution is monomodal dissymmetrical type.

P260: we also observe a large similarity between the three techniques. In this case all of them indicate a bimodal distribution.

For P52, a difference between the measured means through laser techniques and AI can be pointed out in the case of a number distribution, but this deviation is not observed with a volume distribution.

We can conclude that there is a difference between AI and laser methods, precisely in the case of the highest standard deviation values showing a higher dispersion of distribution.

Table 3
Statistical comparison between PIA and PIL results for P52 and P260 powders

	P52 (No.)	P260 (No.)	P52 (Volume)	P260 (Volume)
Skewness	=	=	=	=
Kurtosis	=	=	≠	=
Variance	=	=	=	=
Mean	=	=	=	=

3.2. Statistical comparison of particle-size data

We will first discuss the results in words of statistical comparison of diffractometric laser methods (Table 3).

The two techniques, PIA and PIL, give the same results for P52 and P260 distribution, either in number or in volume.

This equivalence proves that for this kind of product and considering the analyzed size range, the preparation of the sample, either in the air or in liquid, does not show any difference, especially for disagglomeration phenomenon.

An equivalence of the results between laser diffractometry and IA can be admitted only concerning volume analysis of P260 powder (Table 4). In all the other cases there is no statistical equivalence between the laser methods and IA.

The result of a particle-size analysis appearing in a frequency table, is difficult to use as a matter of comparison. That is the reason why the investigator will attempt:

- to consider a direct qualitative comparison of the distribution curves, and
- to use statistical parameters of the particle-size distribution such as position or dispersion parameters and parameters of distribution forms.

We intentionally worked on these two methodologies since the second method is better codified and utilizes the whole information. Furthermore in the first approach, only the particle-size valuation can really estimate the margin limitations in relation to the technological purpose.

The statistical layout demonstrates that:

- the two laser methods (PIA and PIL) give very close results, and
- the laser methods and the image analysis which have very different measuring principles can in no case give precisely the same result, even on spherical particles.

4. Conclusion

We compared two laser techniques to an image analysis (standard method) in an ideal case (spherical particles) but on two different populations (P52 and P260).

A direct qualitative comparison of the distribution curves shows that PIA and PIL give the same results in all cases and that IA and laser methods can be considered as similar, excepted for P52 number analysis.

The statistical layout demonstrates that the two laser methods (PIA and PIL) give very close

Table 4
Statistical comparison between laser technique and AI results for P52 and P260 powders

	P52 (No.)	P260 (No.)	P52 (Volume)	P260 (Volume)
Skewness	=	≠	=	=
Kurtosis	≠	≠	≠	=
Variance	≠	=	=	=
Mean	≠	=	≠	=

results. But IA and laser methods provide us with different results except in the case of P260 in volume.

In IA there is a critical number of particles, depending on the width of the distribution, to be counted. In PIA and PIL, results are also influenced by the extent of particles population.

As a general rule, it is advisable to measure a particle by a method and in a medium, both depending on the purpose which is carried out, either better knowledge of a powder at preformulation step, or simple quality control during manufacturing process. As final drug control, the choice of the technique will not be based on the same criterion.

In the future, we propose to achieve this project, especially on the P52 powder, with measures of specific surface area.

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