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Research paper

Measurement of pharmaceutical particles using a time-of-flight particle sizer

Niklas Laitinen[a,*], Anne Mari Juppo[b]

[a]*Pharmaceutical Technology Division, University of Helsinki, Helsinki, Finland*
[b]*AstraZeneca R&D Mölndal, Mölndal, Sweden*

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Abstract

The Aerosizer® is an instrument for time-of-flight measurement, which is widely used in particle size determinations. The results of various studies indicate that there are still some problems related to the optimization of the analysis conditions. In this study, the behaviour of a set of different kinds of pharmaceutical particles during Aerosizer measurements was studied. An Aerosizer LD equipment with an AeroDisperser™ was validated with particle size standards. Volume particle size distributions of particles with different size and shape characteristics were determined (PVP, Celphere®, lactose, a drug substance, PHB microparticles). The aim was to investigate the effects of the shear force and deagglomeration levels during the dispersion of the particles on the particle size distributions that were obtained. The results of this study indicate that the ability of the instrument to disperse particles is highly dependent on the properties of the materials. According to the validation measurements, the instrument gives accurate results for spherical, uncohesive particles. The capability of the dispersing unit to separate particles aerodynamically was well observed with PVP. Time-of-flight measurements were uncomplicated for relatively large particles, such as Celphere®, which have little interaction with each other and with the instrument housing. For lactose, increasing shear force rates resulted in size distributions with larger particle sizes. In the case of the PHB microparticles the results indicated that the aggregates became smaller and particles were partly separated to primary particles with all shear force levels.

Keywords: Time-of-flight; Aerosizer; Particle size; Pharmaceutical particle; Shear force; Deagglomeration

1. Introduction

Instruments that are based on the aerodynamic time of flight of particles have increased in popularity in particle size analysis during the past decade. Dahneke first introduced time-of-flight aerosol beam spectrometry (TOFABS) [1]. Examples of commercially developed instruments include the APS33B (Aerodynamical Particle Sizer, TSI, St. Paul, MN, USA) and the Aerosizer® by TSI (TSI Inc., St. Paul, MN, USA, previously by API, Amherst Process Instruments, Hadley, MN, USA). The TOFABS method functions as follows: (a) a sample is dispersed in air, creating an aerosol beam, (b) individual suspended particles are accelerated in an air flow, (c) the particles are detected in the measurement zone, and (d) the measured time-of-flight of individual particles is converted to particle sizes.

The Aerosizer operates in the size range of 0.2–700 μm. A thorough technical description of the instrument and the system components has been given by Niven [2]. Many different accessories have been developed to optimize the sampling and handling of powders measured with the instrument, including the AeroDisperser™, an automatic particle feed system. This is a dry powder dispersion unit in which the sample is suspended in air by a pulse jet disperser. The force and the duration of the jet can be accurately controlled [3]. It is claimed that, using this controlled function, initial deagglomeration and powder sample fluidization, as well as the dispersion of the powder, is possible.

The instrument has become widely used in aerosol sciences because of its ability to measure small quantities and because it is a fast method compared with cascade impactors or liquid impingers, for example. Research groups have studied the use of the Aerosizer in characterizing a number of different aerosols from pressurized metered-dose inhalers. Mitchell and Nagel [4] stated that the performance of the Aerosizer may be somewhat drug specific. Mitchell et al. [5] found limitations to using the instrument when the concentration of the drug particles that were measured exceeded about 10^{10} particles/

* Corresponding author. Pharmaceutical Technology Division, University of Helsinki, P.O. Box 56, FIN-00014 Helsinki, Finland. Tel.: +358-9191-59746; fax: +358-9191-59144.
E-mail address: niklas.laitinen@helsinki.fi (N. Laitinen).

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m^3. They reasoned that the problems were primarily related to insensitivities in the signal correlation system in the measurement zone.

The Aerosizer is capable of counting up to 100 000 particles per second. The instrument has been shown to be easy to operate and easy to maintain. The required sample size is very small and this enables the measurement of materials that can only be used in small quantities or are very expensive. As the Aerosizer needs density information about the materials in order to calculate the particle sizes, some additional work is often required prior to analysis.

Many results from various studies indicate that there are still many problems related to measurements with the Aerosizer. The present study investigates the behaviour of a set of different kinds of pharmaceutical particles in Aerosizer measurements. The study comprises validation measurements with particle size standards and measurements of particles with heterogeneous size and shape characteristics. The main objective was to investigate the effects of the shear force and deagglomeration levels on the dispersion of the particles.

2. Materials and methods

2.1. Particle size standards and pharmaceutical particles

The instrument validation measurements were made using certified NIST traceable particle size standards of borosilicate glass particles with given mean sizes of 2.5 and 19.9 μm and polystyrene divinylbenzene particles with mean sizes of 200 and 646 μm (Duke Scientific Corp., Palo Alto, USA).

Particle sizes were measured from biodegradable polyhydroxybutyrate (PHB) microparticles (AstraZeneca R&D Mölndal, Mölndal, Sweden), an active drug substance Drug Substance A (AstraZeneca R&D Mölndal), Celphere® 102 microcrystalline cellulose particles (FMC Biopolymer, Philadelphia, PA, USA), micronized polyvinylpyrrolidone, PVP (Kollidon®, BASF, Ludwigshafen, Germany) and lactose processed with a supercritical fluid crystallization technique called SEDS (Solution Enhanced Dispersion by Supercritical Fluids, Bradford Particle Design, Bradford, UK). Carbon dioxide was used as a supercritical fluid. The solution of lactose (10% w/v) in water was cointroduced with methanol and supercritical fluid in a three-component nozzle with an opening of 0.2 mm in diameter. The flow rates of carbon dioxide, solution and methanol were 9, 0.035 and 0.665 ml/min, respectively. Pressure used was 150 bar and temperature 45 °C.

2.2. Time-of-flight measurements

An Aerosizer LD (TSI Inc.), combined with the AeroDisperser with version 7.04 software, was used in time-of-flight measurements. In the first part of the study, validation measurements of the Aerosizer were made. The validation range for the equipment covered by the certified standards was 2.5–650 μm. The measurement accuracy and the confidence interval of the instrument were calculated according to Eqs. (1) and (2). Precision was determined as the relative standard deviation of mean volume particle size ($n = 6$).

$$\text{Accuracy} = \frac{\text{Measured mean size} - \text{mean size of standard}}{\text{mean size of standard}} \times 100\% \quad (1)$$

$$\text{Confidence interval} = \text{Measured mean size} \pm t_{0.025}(n-1)\frac{\text{standard deviation}}{\sqrt{n}} \quad (2)$$

where $t_{0.025}(n-1)$ is the 2.5% percentile in Student's t-distribution.

In the second part of this study, the Aerosizer was used for measurements of the materials mentioned above. The Aerosizer was equipped with an AeroDisperser dry powder dispersion unit. The effect of the shear force used in dispersing the particles was studied, as well as the effect of the level of deagglomeration force.

The numerical shear force values expresses the pressure drop across the annular gap between the disperser pin and

Table 1
Particle volume mean diameters (μm) of certified standards measured with the Aerosizer with different shear force and deagglomeration levels ($n = 6$)[a]

Shear force	Duke 4365 646 ± 13 μm		Duke 4320 200 ± 4.0 μm		Duke 9020 19.9 ± 1.4 μm		Duke 9002 2.5 ± 1.0 μm	
	Mean	RSD	Mean	RSD	Mean	RSD	Mean	RSD
Normal deagglomeration								
0.5	**638.1**	**2.9**	**199.0**	**1.0**	20.7	1.1	4.1	52.0
1.5	–	–	201.0	1.2	**20.6**	**0.2**	**3.0**	**13.6**
3.0	–	–	200.1	2.5	20.7	0.2	3.6	9.8
4.0	–	–	203.8	0.7	20.7	0.3	3.6	26.7
High deagglomeration								
0.5	–	–	199.7	0.4	20.8	2.6	4.0	50.5
3.0	–	–	202.9	1.2	20.4	2.5	3.6	32.8

[a] The values in bold were used for the calculations of accuracy and precision.

Table 2
Accuracy and precision of Aerosizer determined with certified standards

Standard/Batch	Material	Density (g/cm^3)	Certified particle size (μm)	Volume mean diameter (μm)	RSD/Precision (%)	Confidence interval 95% (μm)	Accuracy (%)
Duke 9002-001	Borosilicate glass	2.55	2.5 ± 1.0	3.0	13.6	2.0;4.0	+ 20
Duke 9020-002	Borosilicate glass	2.52	19.9 ± 1.4	20.6	0.2	20.5;20.7	+ 4
Duke 4320-004	Polystyrene divinylbentzene	1.05	200 ± 4.0	199.0	1.0	193.9;204.1	− 1
Duke 4365-003	Polystyrene divinylbentzene	1.05	646 ± 13	638.1	2.9	619.6;656.6	− 1

the pin bowl. The pressure drop produces a certain shear force. An increased pressure drop results from decreased gap dimensions, which also defines the maximum size of a particle that can pass the gap. The increased pressure drop also causes higher linear air velocity in the gap. The deagglomeration variable describes the two preset airflow patterns (high and low), which transport the powder from the sample cup to the disperser pin [6]. A diagram of the powder disperser is given in Ref. [3].

Three parallel measurements of each material were made ($n = 3$). The shear force levels that were used were 0.5, 1.5, 3.0 and 4.0 psi. A value of 0.5 psi was described as low, 1.5 psi as medium, 3.0 psi as high and 4.0 psi as the peak shear force in the Aerosizer User Manual. The effect of the deagglomeration force was studied using the low and high levels with two shear force levels (0.5 and 3.0 psi). The rest of the set parameters for the Aerosizer instrument were as follows: the PMT voltage was 850 V, the nozzle type was 700 μm and the feed rate was constant (5000 particles/s). After each measurement, the sample cup and the disperser unit were thoroughly cleaned. The densities of the standards were given by the supplier and the densities of the particles used were determined with helium pycnometry (Micromeritics Multivolume Pycnometer, Micromeritics Instruments Inc., Norcross, GA, USA). To assist with the interpretation of the results, scanning electron microscope (SEM) micrographs were taken of all the materials studied (Jeol JSM-5400, Tokyo, Japan). The span or the polydispersity of the particle size distributions was calculated in order to get a picture of the width of the distributions (Eq. (3)).

$$\text{Span} = (D(v,90\%) - D(v,10\%))/D(v,50\%) \quad (3)$$

where $D(v,90\%)$, $D(v,10\%)$ and $D(v,50\%)$ are the equivalent diameters at 90, 10 and 50% cumulative size. A small span indicates a narrow size distribution.

3. Results and discussion

3.1. Validation measurements

The results obtained from the Aerosizer measurements for the certified standards are presented in Table 1. The accuracy and precision values calculated from the results of analyses are presented in Table 2. According to the measurements, it can be concluded that, in the particle size range of < 20 μm, the precision of the Aerosizer was better than 15% and the accuracy better than +20%. In the particle size range of ≥ 20 μm, the precision of Aerosizer was better than 3% and the accuracy better than ±5%.

3.2. Time-of-flight measurements of the different particles

The measured mean volume diameters using different shear force and deagglomeration levels together with the calculations of the span are presented in Table 3. The densities (g/cm^3) for the particles were: 1.20 (PVP), 1.60 (Celphere), 1.32 (lactose), 1.29 (drug A), and 1.97 (PHB microparticles). In this study, the capability of the dispersing unit to separate particles aerodynamically was well observed with PVP (Fig. 1b). With the highest shear force levels (4.0 and 3.0 psi), the size distributions were unimodal and narrower than with the low shear forces. This tendency can also been seen from the mean size values (Table 3). The Aero-Disperser appeared to break apart the agglomerates

Table 3
Particle volume mean diameters (μm) measured with the Aerosizer with different shear force and deagglomeration levels ($n = 3$)

Shear force	PVP			Celphere			Lactose			Drug substance A			PHB Microparticles		
	Mean	RSD	Span	Mean	RSD	Span	Mean	RSD	Span	Mean	RSD	Span	Mean	RSD	Span
Normal deagglomeration															
0.5	12.6	15.7	1.1	150.3	0.5	0.5	4.7	0.8	1.1	6.9	5.9	0.9	6.4	0.5	1.2
1.5	–	–	–	146.8	3.3	0.4	16.0	7.5	1.1	7.9	1.0	0.8	6.4	0.3	1.3
3.0	2.8	0.1	1.1	160.2	0.5	0.4	13.0	4.4	1.2	6.6	0.8	0.8	6.6	0.5	1.4
4.0	2.8	0.2	1.8	–	–	–	14.0	5.7	1.2	8.6	0.8	1.2	6.9	0.3	1.3
High deagglomeration															
0.5	66.0	59.0	1.6	147.2	4.3	0.4	6.2	2.4	1.4	9.7	2.4	1.0	6.4	0.9	1.2
3.0	2.8	0.2	0.9	154.8	1.7	0.5	9.7	2.1	1.6	9.8	1.8	0.9	6.3	0.4	1.4

which were seen in the SEM micrograph (Fig. 1a). Measurements of micronized salbutamol powder at three different shear levels also showed clear effects with increasing shear forces [3]; the size distributions shifted to smaller sizes. The question whether the increasing shear force level caused milling of the drug or if it separated particles by deagglomeration was not discussed. However, both these mechanisms could be possible and, in the case of PVP, the latter appears to hold true according to the primary particle sizes observed in the SEM micrographs.

The results show that the different shear forces had no evident effect on the size distribution for Celphere particles (Fig. 2b and Table 3). The distribution shows that the majority of the particles are around 200 μm. The Celphere particles are visualized in Fig. 2a. According to these results for Celphere, time-of-flight measurements are uncomplicated for relatively large particles which have little interaction with each other and with the instrument housing. However, high shear forces cannot be used for large particles, since the gap between the pin bowl and the disperser pin, which controls the pressure between the detection chamber and the disperser, becomes too small for particles to fit in the gap.

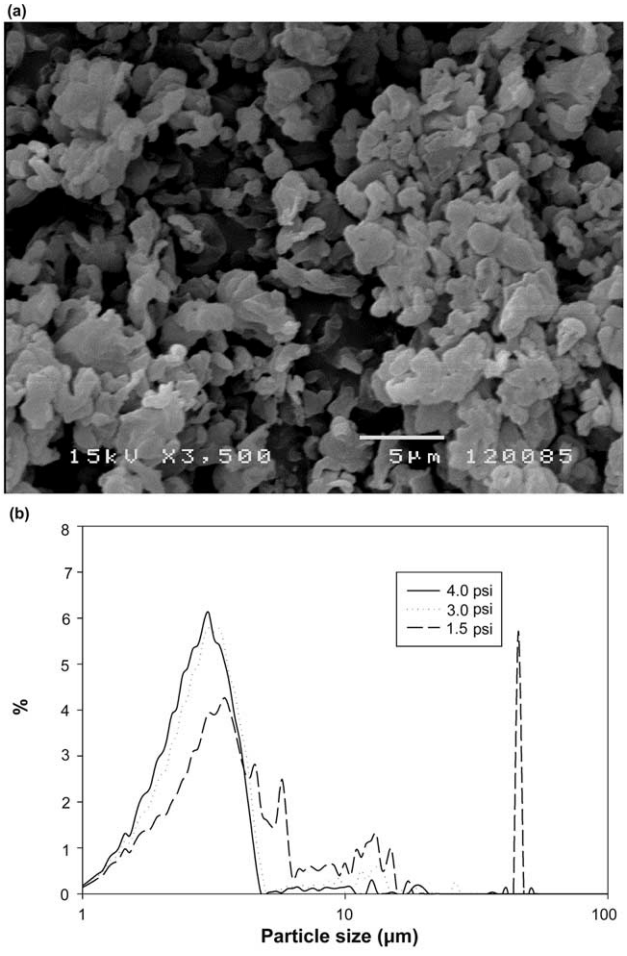

Fig. 1. (a) SEM micrograph of PVP. (b) Particle volume size distributions measured with the Aerosizer from PVP using different shear forces ($n = 3$).

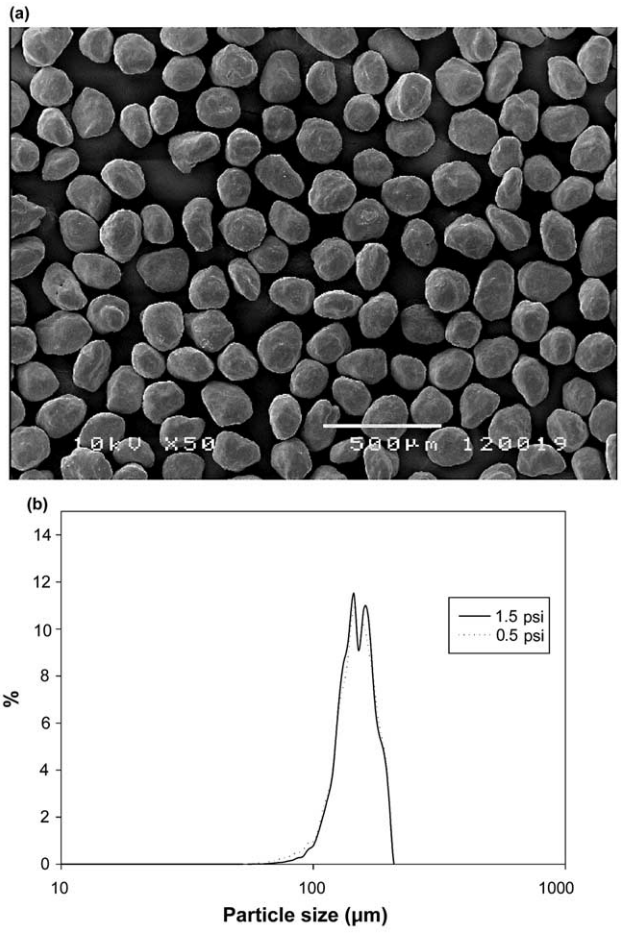

Fig. 2. (a) SEM micrograph of Celphere. (b) Particle volume size distributions measured with the Aerosizer from Celphere using different shear forces ($n = 3$).

In the case of lactose (Fig. 3a), increasing shear force rates resulted in size distributions with larger particle sizes. This is illustrated in Fig. 3b with shear force levels of 0.5, 1.5 and 3.0 psi. The use of the two highest shear forces considerably changes the size distribution. This can also be seen as a change in the particle mean size. With a high deagglomeration level and a shear level of 3.0 psi, deagglomeration increased slightly (Table 3). Before the analysis, the material produced with supercritical fluid crystallization was very loose and fluffy but, when handling the powder and by turning the sample container, a spontaneous aggregation of particles occurred. In other words, when some energy was brought to the powder system, the particle cohesion increased. This could also be the explanation for the results that were obtained; with an increasing energy level of powder dispersion and with higher shear force levels, more particle agglomeration take place. However, Hindle and Byron [6] report an opposite kind of behaviour for a cohesive, micronized, terbutaline sulphate powder. When peak shear was used, there was a clear decrease in the number of large agglomerates measured, as compared to the low shear rates. These contradictory results indicate that

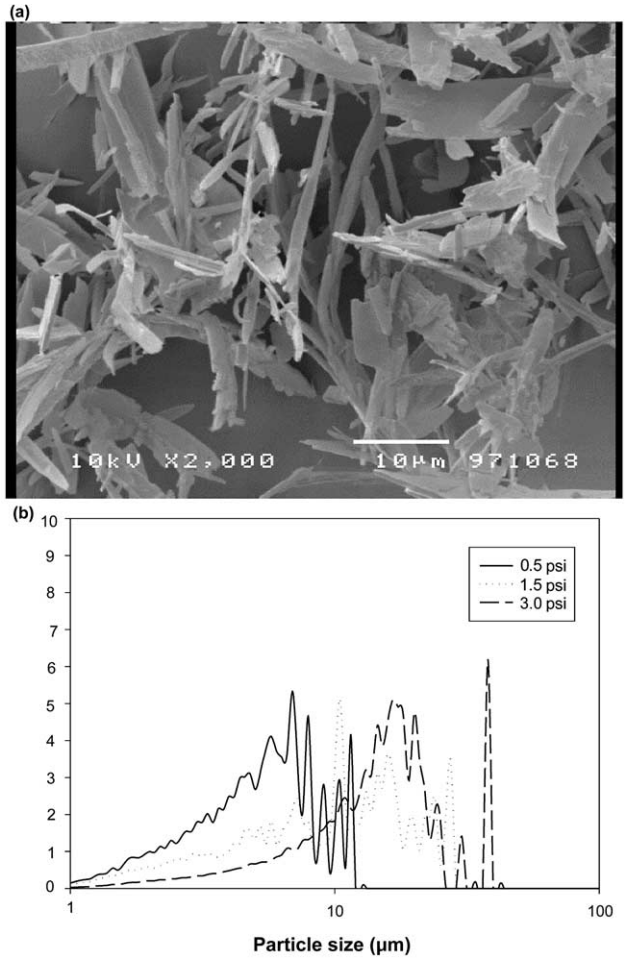

Fig. 3. (a) SEM micrograph of lactose. (b) Particle volume size distributions measured with the Aerosizer from lactose using different shear forces ($n = 3$).

it can be difficult to evaluate the complex behaviours of materials in Aerosizer measurements. The results should therefore be interpreted with care.

A similar effect was noted with drug substance A (Fig. 4a). The lowest shear force level (0.5 psi) resulted in a distribution with the smallest particles. At the higher levels, the particle size distributions were relatively close to each other. When using the 4.0 psi shear force, peaks in the largest particle size range of the size distribution curve can be seen (Fig. 4b). The reason for this might also be the agglomeration of particles. However, the particle mean sizes of all the measurements overlap (Table 3). It is difficult to understand exactly what takes place when these flaky particles accelerate through the dispersing and detection unit of the instrument. It might even be expected that brittle, elongated, flaky particles would actually break apart and be micronized, making the particle size smaller. Nevertheless, this does not occur in the case of the drug substance used. Distribution peaks in results that do not correlate with the expected size distribution are difficult to interpret. Heitbrink et al. [7] and Niven [3] have previously presented the existence of phantom peaks, which are associated with problems in the particle detection area in the measurement zone of the Aerosizer. Problems arise due to timer insensitivity in the signal correlation system. According to Mitchell et al. [5], the reason for the phantom peaks is the high concentration of particles in the detection area, causing overloading together with the autocombine function in the software, which combines the data from the two sensitivity ranges of photomultipliers. Thornburg et al. [8] have also reported false peaks. They examined the counting efficiency of the equipment and found that particle diameter, aerosol concentration, Aerosizer model and PMT voltage influenced the counting efficiency. An increase in PMT voltage increased the counting efficiency for smaller particles (<0.45 µm), but created false, larger particles. In our pretests, we did not observe any effect from the PMT voltage.

The volume size distributions of the PHB microspheres measured with two shear force levels are shown in Fig. 5b. As shown in Fig. 5a, the material is highly agglomerated. The Aerosizer results indicate that the aggregates have at least partly been separated to primary particles. As the results are equal with all shear force levels the agglomera-

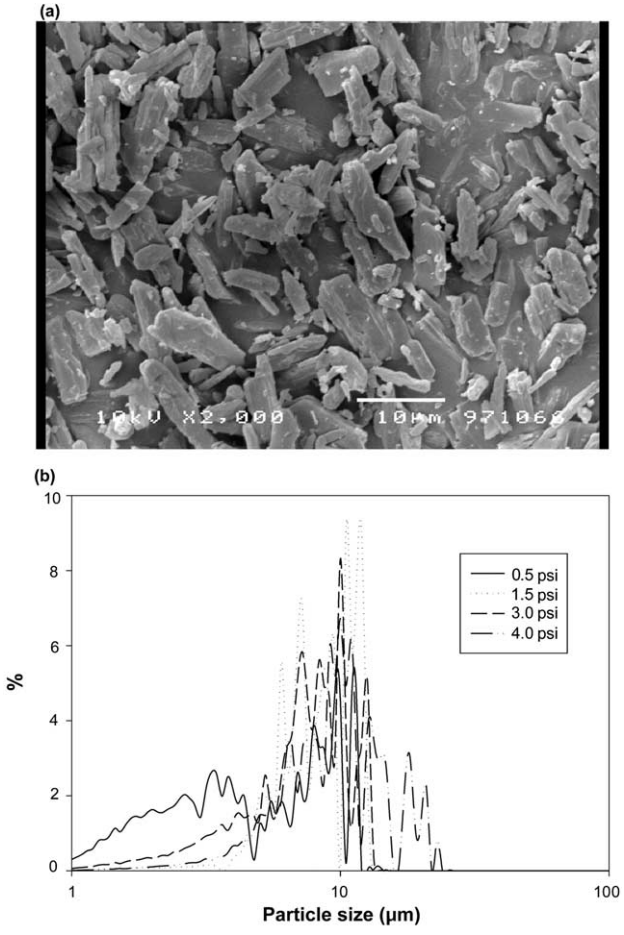

Fig. 4. (a) SEM micrograph of drug substance A. (b) Particle volume size distributions measured with the Aerosizer from drug substance A using different shear forces ($n = 3$).

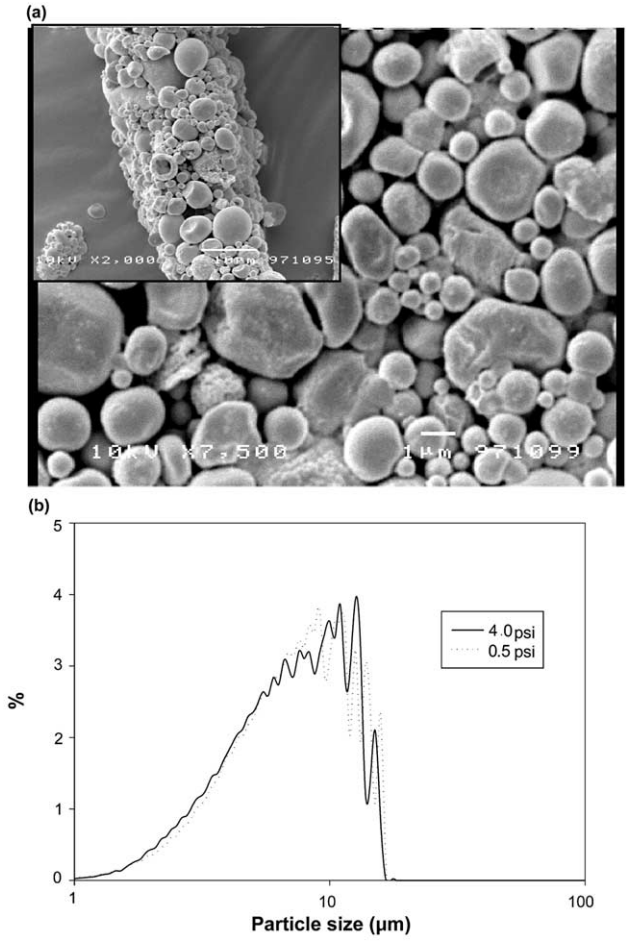

Fig. 5. (a) SEM micrographs of PHB microparticles. Agglomerates are visualized in the top left corner and the larger image shows a close-up of the agglomerate in question. (b) Particle volume size distributions measured with the Aerosizer from PHB microparticles using different shear forces ($n = 3$).

tion grade of the material has not been affected with rising shear force levels. The maximum size at over 10 μm can be due to the fact that there indeed are such large particles in the sample or that agglomerates still exist. The particle mean sizes for all shear levels are alike (Table 3). The ability of the dispersing unit to separate particles has been presented in a number of studies [3,7,9].

Some consideration should be given to the feed rate of particles during measurement. An effective experimental range should be within 500–10 000 particles/s. It has been reported that lowering the feed rate has an effect on the more efficient deaggregation of micronized terbutaline sulphate [8]. In the present study, the feed rate of 5000 particles/s was chosen because no systematic effect using other rates was found.

This study revealed that the effect of the shear force on particle size distribution was very complex for the particles investigated here. The Aero Disperser has been designed to disperse particles by varying the energy level for powder dispersion. Agglomerated powders should be dispersed and deagglomerated by using higher shear forces. It is expected that the mean size of particles would be smaller with higher shear force levels than with lower ones [3].

The results of the present investigation indicate that the ability of the instrument to disperse particles appears to be very dependent on the properties of the materials. According to the validation measurements, the instrument produces accurate results for spherical uncohesive particles. In the case of Celphere, the instrument was capable of dispersing the materials to primary particles at all shear force levels. In other words, in this study, the larger, regularly-shaped, compact particles were measured successfully by the Aerosizer. PVP behaved as expected: the introduction of higher shear forces dispersed the particles more efficiently. With other materials, the increasing shear force shifted the size distributions towards larger particle sizes for different reasons.

As complex particle interactions may occur during measurements with the instrument, the characteristics of the particles and the materials should be known when optimizing the settings of the equipment for each material that is measured.

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