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Modelling of artefacts in estimations of particle size of needle-like particles from laser diffraction measurements

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ABSTRACT

Manufacturing of particulate products across many industries relies on accurate measurements of particle size distributions in dispersions or powders. Laser diffraction (or small angle light scattering) is commonly used, usually off-line, for particle size measurements. The estimation of particle sizes by this method requires the solution of an inverse problem using a suitable scattering model that takes into account size, shape and optical properties of the particles. However, laser diffraction instruments are usually accompanied by software that employs a default scattering model for spherical particles, which is then used to solve the inverse problem even though a significant number of particulate products occur in strongly non-spherical shapes such as needles. In this work, we demonstrate that using the spherical model for the estimation of sizes of needle-like particles can lead to the appearance of artefacts in the form of multimodal populations of particles with size modes much smaller than those actually present in the sample. This effect can result in a significant under-estimation of the mean particle size and in false modes in estimated particles size distributions.

1. Introduction

Particle size measurements are crucial across many industries in the manufacturing of particulate products, such as pharmaceuticals, agrochemicals, detergents, pigments and food. Particle size and shape have a profound influence on downstream processing as well as on final product properties through a variety of product attributes, such as solubility, dissolution kinetics, flowability, etc. There are various particles sizing methods commonly employed in practice, some of them online and others offline (Washington, 1992; Shekunov et al., 2007; Abbireddy and Clayton, 2009). One of the widely used techniques for measuring of particle size distribution (PSD) in dispersions is laser diffraction (Black et al., 1996) which is typically arranged in a flow-through setting but is most often used off line as there are limits on dispersion densities due to multiple scattering. Laser diffraction measurement involves the collection of scattered light from a dilute dispersion of particles by an array of detectors placed at different spatial locations so that they cover a certain span of scattering angles θ. Since the angular dependence of the scattered light intensity originating from a particle is a function of the size and shape of the particle, as well as the orientation of the particle with respect to the incident laser beam, the particle size and shape can be inferred from the corresponding scattering intensity pattern. However, as there is typically a distribution of particle sizes across a population, the intensity pattern measured by the detectors will be a convolution of the intensity patterns from all the particles of different sizes in the dispersion.

The estimation of the PSD from the measured scattering intensity pattern (scattering intensity as a function of scattering angle) involves solving an inverse problem using a suitable scattering model which describes the scattering intensity for particles of a given shape, size and optical properties. The inversion is implemented in the software accompanying laser diffraction instruments, typically using the Mie scattering model (Bohren and Huffman, 1983) for spherical particles as a default, regardless of the shape of particles in the measured sample. This can lead to various artefacts, such as apparently multimodal distributions in PSD estimates (e.g., Hamilton et al., 2012; Polakowski et al., 2014) when the shape of the particles in the sample deviates significantly from spherical. This could result in misleading estimates of mean particles sizes with severe consequences for applications where the process is very sensitive to the particle sizes. This is particularly important in the pharmaceutical industry where many of the active pharmaceutical ingredients are crystallised in needle-like habits.

In this paper, we demonstrate that multimodal PSDs can be obtained from the inversion process even when the true particle size

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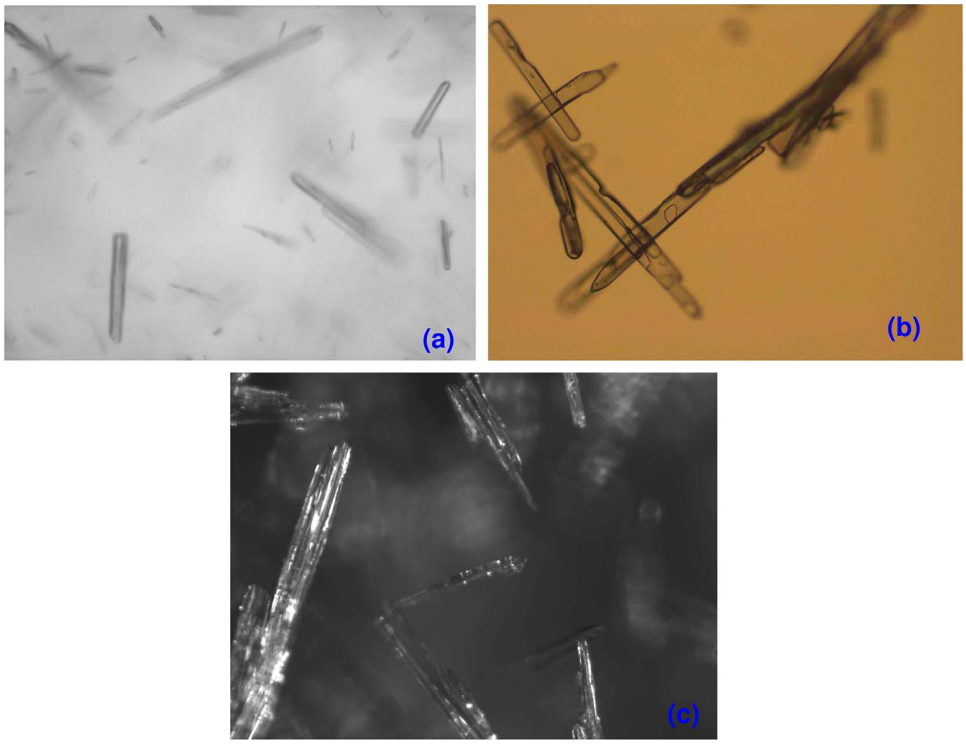

Fig. 1. Images of typical needle-like crystals of (a) cellobiose octaacetate, (b) benzoic acid and (c) metformin hydrochloride.

is monodisperse, i.e., all particles are of the same size. We simulate the scattering intensity patterns for monodisperse population of needle-like particles to explain how multimodal PSD artefacts arise due to solving the inverse problem using a scattering model for spherical particles. We compute the angularly dependent scattering intensity for needle-like particles of specified optical properties using a model for infinitely long cylinders with diameters ranging from 1 to 100 micrometres. Then we solve the inverse problem of estimating PSD from the angularly dependent scattering intensity pattern using the Mie theory for spherical particles, mimicking the analysis performed when using commercial laser diffraction instruments. Since the PSD of needle-like particles is exactly specified here, the estimated PSD from the inversion can be directly compared with the actual PSD. We consider two limiting cases, when needle-like particles are assumed to perfectly aligned with flow which is perpendicular to the incident laser beam and when they adopt random orientations. We show that in either case the inversion results in estimated PSD that are multimodal where smaller modes are mathematical artefacts due to inversion and we explain how these are related to different shapes of intensity scattering patterns for needle-like particles compared to those of spheres.

2. Calculating scattering intensity

The scattering intensity patterns for needle-like particles will be simulated using the scattering theory for infinitely long cylinders (Bohren and Huffman, 1983). Even though the theory was developed for infinitely long cylinders, it is applicable for needle-like particles with lengths significantly larger than their diameters (Wickramasinghe, 1973). Such long thin particles of approximately cylindrical shape are similar to needle-like particles often encountered in pharmaceutical and chemical manufacturing. For example, in Fig. 1 we show typical particles of cellobiose octaacetate, benzoic acid and metformin hydrochloride. As needle-like particles are modelled as infinitely long cylinders in this work, the circular cross-sectional diameters of these cylinders will be used to represent the size of needle-like particles as their length cannot be specified. The scattering intensity pattern for spherical particles will be simulated using the Mie theory (see Bohren and Huffman, 1983 and Section 1 of the supplementary information for details). The procedure for performing the calculations is described below.

Consider a detector system (Fig. 2(a)) in which a monochromatic light with wave vector $\mathbf{k}_i$ is incident on a particle of arbitrary size and shape. The scattered light with wave vector $\mathbf{k}_s$ is then collected at different angles θ to the direction of propagation of the incident light by an array of detectors as depicted in Fig. 2(a). Both the incident and scattered light have components parallel and perpendicular to the scattering plane (the plane containing the incident and scattered light) (Bohren and Huffman, 1983). The scattering wave vector $\mathbf{q}$ is the difference between the incident and scattered wave vectors as sketched in Fig. 2(b). The magnitude of the scattering wave vector is a function of the scattering angle θ, and it is given by Sorensen (2001)

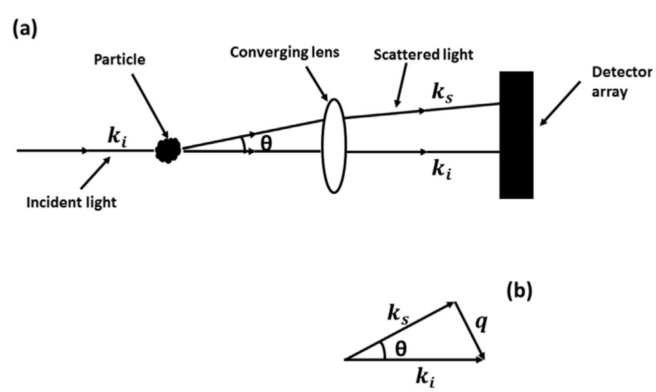

Fig. 2. (a) Schematic of the setup of typical laser diffraction instruments. (b) Illustration of the scattering wave vector.