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Development of an empirical method relating crystal size distributions and FBRM measurements

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HIGHLIGHTS

- A model relates focused beam reflectance measurements to crystal size distribution.
- The model is constructed empirically using known crystal size distributions.
- Experimental results demonstrate the practicality of the method.
- Two inversion methods estimating crystal size distribution are studied and applied.

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ABSTRACT

The empirical model developed in the present work allows estimation of crystal size distributions from focused beam reflectance measurements (FBRM) of chord length distributions. The model is constructed from purposely varied crystal size distributions and the corresponding measured chord length distributions, which allows construction of a transformation matrix relating the two distributions. Experimental results show advantages over more complex phenomenological models, presumably because the transformation matrix implicitly embodies such phenomena. The ability of the model to address varying crystal concentration and selectively added size fractions is demonstrated with experimental results. Finally, the simplicity of the approach allows rapid (of order 0.1 s) estimation of crystal size distributions from FBRM, which is a promising outcome for potentially using the approach in an on-line control scheme.

1. Introduction

The pharmaceutical industry has adopted the concept of process analytical technology (PAT), but implementation requires development of new methods that facilitate monitoring and control of critical operations in a process in order to ensure the quality of products (U.S. Food and Drug Administration, 2004). Appropriate measurement tools, such as with various spectroscopy and particle sizing methods, coupled with robust data analysis, are necessary for this paradigm to be successful. Since many pharmaceutical products are crystalline, implementation of real-time measurement of crystal size distribution (CSD) is a vital objective in designing and producing active pharmaceutical ingredients (APIs).

One particularly promising technique to achieve real-time CSD detection is focused beam reflectance measurement (FBRM), which uses a backscattered laser to detect particles as the laser scans across a segment of a crystal. The relationship between the chord length distribution (CLD) from FBRM and particle size distribution (PSD) has been investigated extensively (Barrett and Glennon, 1999; Heath et al., 2002; Yu et al., 2008), which revealed that more particles lead to more chord counts and large particles have longer mean chord lengths. Such properties provide the FBRM the ability to qualitatively detect the onset of nucleation, growth, and dissolution, and changes in the form of the CLD linked to crystal morphology (Barthe et al., 2008). Therefore, it has been used in several applications, such as studying nucleation kinetics and metastable zone width (Mitchell et al., 2011), and controlling crystallization with other tools (ATR-FTIR) (Fujiwara et al., 2002; Hermanto et al., 2010; Togkalidou et al., 2004; Worlitschek and Mazzotti, 2004) to limit the supersaturation rate inside the metastable zone. Moreover, it is also employed to study polymerization (Hukkanen and Braatz, 2003) and emulsions (Leba et al., 2010).

To make quantitative predictions, researchers have attempted to establish a mathematical model of FBRM measurements of CLD. What may be referred to as a geometric model defines

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chords as straight lines from the 2D projection of a particle. Hence, under assumptions of non-overlapping particle projections and non-expanding laser beam, the modeling can be realized by two steps: the first is to project the particles onto a 2D plane randomly and the second step is to sample chord length from the projection. The two-step algorithm can be fulfilled either by analytical calculation for spherical and ellipsoidal particles (Li and Wilkinson, 2005; Simmons et al., 1999; Tadayyon and Rohani, 1998; Wynn, 2003), or by Monte Carlo simulation (Nere et al., 2007; Ruf et al., 2000) for arbitrary shape. Agreements on CLD data between experimental measurements and model prediction are reported in various suspensions, especially those of opaque and sphere-like particle systems, such as ceramic beads, aluminum particles, glass beads, and polymer beads (Li and Wilkinson, 2005; Ruf et al., 2000; Tadayyon and Rohani, 1998).

In a crystallization process, the simple assumptions of the geometric model may be insufficient to estimate the CSD; e.g., the laser may not be backscattered completely because of the transparency of the crystals. In addition, the laser backscattered from the crystal surface is not as stable as from opaque particles, which causes chord splitting or chord concatenation (Kail et al., 2007). In actual measurements, such as of the CLD of glycine crystals in ethanol, the peaks of the CLD have no dependence on the size of the crystals and only the skewness of the CLD differs (Yu et al., 2008), which is not explained by the geometric model.

Kail et al. (2008, 2009) state such issues for the geometric model and build an optical model that has many physical subtleties, such as laser intensity profile, chord discrimination criteria, refractive indices, particle velocity and so on. Chords are identified if the simulated backscattered laser intensity is greater than a threshold value. The model predicts the FBRM measurement much better than the geometric model. The optical model can be applied to estimate the CSD, for example, in preferential crystallization (Czapla et al., 2010).

To achieve accurate CSD estimation in crystallization, first-principles models must be very sophisticated. Yet they may still neglect some factors that influence the lengths of chords: for example, the surface roughness of crystals may develop when crystals are growing. As a result, the backscattering intensity varies as the laser scans across a crystal. Such microscopic features are difficult to model, especially, when the crystal surface is changing due to crystal growth. In batch crystallization, where small crystals grow significantly over time, the CSD estimation will be greatly affected by such phenomenon.

The present work proposes an effective empirical model from measured responses to different crystal sizes, which reduces the complexity of constructing the transformation matrix that relates CLD to CSD. Our experiments use paracetamol crystals, but the methodology is not directly related to the identity of the species. We assume that the measured CLD is constant and unique for crystals at a specific size. Such measurements were obtained by adding crystals from a specific sieve tray in a sieve nest to a nonsolvent (toluene) and defining the recorded CLD as the fingerprint vector for that size fraction.

The linearity and additivity of the fingerprint vectors validated between different size ranges of crystals and, accordingly, a linear transformation matrix was constructed. This model was then used in CSD estimation by minimizing the deviation of the predicted CLD from the measurements. Such minimization can be accomplished in less than a second since the transformation matrix is better conditioned than those matrices built by first-principles models, which usually require some tailored algorithms to invert (Grover et al., 2009; Li and Wilkinson, 2005; Worlitschek et al., 2005). In short, the empirical model can be easily established from experimental results and its rapid inversion offers a promising potential of real-time CSD monitoring.

2. Method and material

2.1. Method

The empirical model is generated from a discretized equation for modeling the CLD–CSD relationship. Then we use the experimental data to estimate the values of every entry in the transformation matrix.

Chord length distribution $q(s)$ is a density function, deduced as a convolution form (Worlitschek et al., 2005). Define $n(L_0)$ as the number density of crystals per unit volume of solvent at an infinitely small size interval around L_0 in the sampling volume of the FBRM. Such crystals at L_0 lead to a certain CLD $q^{L_0}(s)$ by a transformation function $q_p(s,L_0)$

$$q^{L_0}(s) = q_p(s,L_0)n(L_0)\,dL \tag{1}$$

The resulting $q^{L_0}(s)$ also depends on FBRM settings, for instance, the sampling time, but all those factors are incorporated in $q_p(s,L_0)$ as long as they are kept unchanged. Notice that both sides of Eq. (1) are distribution density functions and $n(L_0)\,dL$ is a scalar, so $q_p(s,L_0)$ stands for the CLD induced by crystals at size L_0. If such equations of crystal size from zero to infinity are summed up, we have the following equation:

$$q(s) = \int_0^{\infty} q_p(s,L)n(L)\,dL \tag{2}$$

where $q(s)$ [no./μm] is the total CLD as a function of chord length s. $n(L)$ [no./(μm mL)] is the CSD function, and $q_p(s,L)$ is the CLD for a single crystal CLD at size L. Thus, the unit of $q_p(s,L)$ is mL/μm.

We define the chord length distribution b_i and crystal size distribution x_j as follows:

$$b_i = \int_{s_i}^{s_{i+1}} q(s)\,ds \tag{3}$$

$$x_j = \int_{L_j}^{L_{j+1}} n(L)\,dL \tag{4}$$

From (2) and (3)

$$b_i = \int_{s_i}^{s_{i+1}} \int_0^{\infty} q_p(s,L)n(L)\,dL\,ds \tag{5}$$

Here, the square root of L_jL_{j+1} is assumed to be the representative size for the jth bin. If $q_p(s,L)$ is constant over a size bin $[L_j,L_{j+1}]$, the inner integral of Eq. (5) can be transformed into a summation, and we obtain

$$b_i = \int_{s_i}^{s_{i+1}} \sum_{j=1}^{\infty} \left(q_p(s,\sqrt{L_jL_{j+1}})x_j\right) ds \tag{6}$$

Eq. (6) indicates a matrix multiplication

$$\mathbf{b} = U\mathbf{x} \tag{7}$$

where

$$U_{i,j} = \int_{s_i}^{s_{i+1}} q_p(s,\sqrt{L_jL_{j+1}})\,ds \tag{8}$$

To construct the empirical model for FBRM and CSD, **b** and **x** are vectors that stand for histograms of CLD and CSD, respectively, in which each element is the number in a particular bin. Thus, **b** has the same format as the data structure of the FBRM (chord count no.) so that the FBRM measurement can be used directly. Similarly, **x** represents the crystal size population histogram, containing the volumetric concentrations of crystals in each size interval [no. of crystal/mL]. Therefore, matrix U relates the CLH **b** and CSH **x**.

In this work, we determine U from experimental results instead of a first-principles model, since there are many factors