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Factors affecting on-line estimation of diastereomer composition using Raman spectroscopy

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Abstract

This paper addresses the estimation of fractional solid composition of two diastereomers during crystallization. The estimation is obtained through a Partial Least Square (PLS) model that utilizes on-line Raman spectroscopy and additional process information such as temperature and slurry density. Several PLS models are developed that incorporate conditions that either neglect or account for variability in the additional process variables. It is shown that the model that incorporates both temperature and slurry density is the most accurate.

Keywords: Calibration; Estimation; Prediction method; Regression analysis; Spectra correlation

1. Introduction

The manufacturing of pharmaceuticals often involves separation of enantiomers, which are chiral molecules that are mirror images of each other. Since the physical properties of both enantiomers ($R =$ right handed and $S =$ left handed) are the same, a traditional separation method such as crystallization by seeding is feasible but it becomes very sensitive to the experimental conditions (Elsner, Menendez, Muslera, & Seidel-Morgenstern, 2005; Qian & Botsaris, 1997). Thus, the pharmaceutical industry usually relies on the achiral synthesis of the enantiopure product or the reaction between the enantiomer with a chiral acid/base to form different diastereomers. Diastereomers are molecules that have two or more chiral centres and are not mirror images of each other. The resulting diastereomers have different physical properties such as solubility and often crystallize into different crystal structures. With these differences, crystallization can effectively separate the desired product with very high purity (Jacques, Collet, & Wilen, 1981; Wilen, Collet, & Jacques, 1977).

To meet government regulations, the purity of the final product is of crucial importance. Thus, the capability of on-line monitoring of the optical purity of the crystals present at a given time will help develop a robust crystallization process. The traditional methods used to determine the diastereomer composition in both solid and/or liquid phase are by chiral HPLC method or with the use of polarimeter to determine the chirality in solution phase. However, both of the analytical methods cannot be conducted on-line and required sample preparation. On-line Raman spectroscopy is suitable for this application since Raman can detect the lattice vibrations corresponding to the translational and rotational motion of the entire molecule within the lattice structure of the crystal (Ferraro, 1971). As a result, Raman spectroscopy is capable of differentiating similar molecules with different crystal lattice structures. To the best of the authors' ability, there was no pervious work with Raman differentiating the composition of the diastereomer in crystallization. However, several authors have demonstrated the ability of monitoring the changing compositions of two different

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crystals on-line during a solvent-mediated polymorphic transformation with Raman (Berglund, Wang, Wachter, & Antosz, 2000; Hu, Liang, Myerson, & Taylor, 2005; Ono, Horst, & Jansens, 2004; O'Sullivan, Barrett, Hsiao, Carr, & Glennon, 2003; Scholl, Bonalumi, Vicum, Mazzotti, & Muller, 2006). In addition, chemometric techniques can be applied to the Raman spectra to differentiate slight peak shifts and to remove noise from the signals off-line (Falcon & Berglund, 2004; Rades, Pratiwi, Fawcett, & Gordon, 2002; Starbuck et al., 2002).

The collection of data through an immersion probe and its connection to the detector via a fiber optic cable, allows analysis of solid phase composition in real-time. The returned Raman signal depends on the amount of inelastic scattering from the solids detected by the analyzer within the detection zone. As a result, the relative Raman intensity corresponding to the diastereomers in the slurry will be impacted by a number of other solid-state factors besides the primary one of particle characteristics. Several authors have hypothesized that the intensity of the returned Raman signal during crystallization of different polymorphs may be a function of particle size and shape (O'Sullivan et al., 2003; Zhou, Wang, Ge, & Sun, 2002). This is based on the assumption that the returned Raman signal primarily comes from a volume close to the surface of the crystal. Additionally, slurry density defined as the total mass of crystals per unit volume (mg/mL), may be another solid-state factor since the number of crystals inside the detection zone will influence the intensity of the returned Raman signal. Furthermore, the Raman spectrum will be affected by the relative amount of solvent and solids in its path. Consequently, slurry density should impact the returned Raman signal intensity. A recent study showed that Raman spectra along with multivariate analysis were capable in predicting both the slurry density and percent composition of an anhydrous/monohydrate system (Caillet, Puel, & Fevotte, 2006). However, the authors did not investigate whether temperature has any effects, as all the experiments were run isothermally.

For a batch cooling crystallization process, temperature changes constantly and affects slurry density directly since the solubility of the solute is a function of temperature. In addition, temperature can alter Raman band areas by changing the sample density and therefore the number of analyte molecules in the sampled volume (Pelletier, 2003). Hence, in the present work, we examine whether the information provided by Raman spectroscopy is sufficient or whether it needs to be complemented by additional process measurements in order to provide an accurate estimation, through a Partial Least Square (PLS) model, of the solid composition of one of the two diastereomers involved in the production of an active pharmaceutical ingredient, denoted here as compound *A*. A previous study showed that the incorporation of temperature into a single chemometrics calibration improves model accuracy in predicting solute concentration with the use of IR (Togkalidou, Fujiwara, Patel, & Braatz, 2001). In this study, temperature, slurry density, and the entire Raman spectrum were used in the modeling task. PLS regression was used to quantify the composition of the diastereomeric mixture. Four different models are examined and compared for their prediction/estimation accuracy.

2. Experimental section

2.1. Materials

HPLC grade solvents were used as received from commercial suppliers without further purification. The starting materials (racemic mixture of compound *A* and a pure enantiomer of a chiral acid, denoted here as *D*) that met the specifications were used as received from qualified suppliers without further purification.

2.2. Preparation of pure *S*-*D* diastereomer

A racemic mixture of compound *A* was reacted with a pure enantiomer of a chiral acid (denoted here as *D*) in a solvent mixture of well defined composition and the solution was heated and held at 5° above the saturation point to ensure complete dissolution. The solution was then slowly cooled and seeded with 2% by weight of the *S*-*D* diastereomer (desired product) at specific seeding temperature. The seeded slurry was cooled to a target solid recovery temperature. It was then followed by a filtration wash and drying step. The end product was analyzed by a chiral HPLC method resulting in optical purity of at least 97% of the *S*-*D* diastereomer.

2.3. Preparation of pure *R*-*D* diastereomer

The preparation of pure *R*-*D* diastereomer needed, for the calibration process, first involved the purification of the *R* enantiomer from the racemic mixture of compound *A*, followed by reaction with *D* to form the *R*-*D* diastereomer. Since the crystallization kinetic of the *R*-*D* diastereomer is slow compared with the *S*-*D* diastereomer, the purification step of the *R* enantiomers would ensure the optical purity of the *R*-*D* diastereomer. For the purification step, racemic free base of compound *A* was reacted with a pure enantiomer of another chiral acid, denoted as *L*, in solvent and the solution was heated and held at 5° above the saturated temperature to allow for complete dissolution. The solution was then slowly cooled and seeded with 2% by weight of the *R*-*L* diastereomer at a specified seeding temperature. The seeded slurry was cooled to a target isolation temperature and then followed by a filtration and drying step. The dry *R*-*L* crystals would then go through a free basing step to obtain the pure *R* enantiomer. Finally, the pure *R* enantiomer reacted with *D* and crystallized to form *R*-*D* diastereomer. The product was analyzed by a chiral HPLC method, resulting in optical purity greater than 98%.