International Journal of Pharmaceutics 471 (2014) 264–275

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

# Verification of model development technique for NIR-based real-time monitoring of ingredient concentration during blending

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ARTICLE INFO

*Article history:*
Received 4 December 2013
Received in revised form 9 April 2014
Accepted 9 May 2014
Available online 14 May 2014

*Keywords:*
Near infrared (NIR)
Locally weighted partial least squares (LW-PLS)
Process analytical technology (PAT)
Blending process
Real-time monitoring

ABSTRACT

There has been a considerable research on the process analytical technology (PAT) and real-time monitoring based on NIR, but the model development is still an important issue and persons in charge have difficulty in building good models. In this study, to realize efficient NIR-based real-time monitoring of ingredient concentration and establish a model development method, we investigated the effect of a calibration set, spectral preprocessing, wavelengths, and other factors on the prediction error through pilot and commercial scale blending experiments. The results confirmed that the small prediction error was realized by a calibration set, including dynamic measurement spectra acquired with the target blender. In addition, the results demonstrated that locally weighted partial least squares (LW-PLS) achieved the smaller prediction error than conventional PLS. The present study has also clarified that spectral preprocessing methods and wavelengths selected to build a model affect the prediction error of ingredient concentration interactively. A wide wavelength range should be selected when the spectral preprocessing does not lessen the effect of baseline variation, while a narrow wavelength range should be selected when it strongly decreases the effect.


## 1. Introduction

To ensure the content uniformity of drug products, the blend uniformity in the blending process needs to have the concentration of the active pharmaceutical ingredient (API) almost the same as the target value at representative points in the blender (e.g., the API concentration is not less than 90% at all points) and consistent (e.g., the relative standard deviation is not more than 5.0%) (FDA, 2003). In the past, manufacturing conditions to ensure blend uniformity were investigated through process development study, with three batches being validated by using commercial scale equipment. Even if the manufacturing conditions are well established in the validation, unexpected issues may occur due to various disturbances such as variations in the raw material properties and environments. For example, humidity affects the blending time needed to achieve the desired blend uniformity (El-Hagrasy et al., 2006).

To prevent such issues, it is useful to develop a real-time monitoring technique to control the blend uniformity in routine commercial manufacturing. Rapid measurement techniques, including real-time monitoring, have been studied with enthusiasm as a part of process analytical technology (PAT) (FDA, 2004). NIR spectrometers, which are popular PAT tools (Reich, 2005; Roggo et al., 2007; Jamrógiewicz, 2012), have been applied to rapid measurement and real-time monitoring of the blend uniformity of various components (Nakagawa et al., 2013). The studies on rapid measurement and real-time monitoring of the blend uniformity started from evaluating the blend uniformity of an API with a qualitative technique without chemometric model (Hailey et al., 1996; Sekulic et al., 1996). Thereafter, a large number of studies were performed to evaluate the blend uniformity of both APIs and excipients with quantitative techniques based on the chemometric models (Wu and Khan 2009a; Liew et al., 2010).

Quantitative techniques are preferable to qualitative in order to judge the blend uniformity with high accuracy. However, developing a robust quantitative calibration model to estimate the blend uniformity with NIR spectra requires enormous labor and time, because the effect of various physical properties such as granule particle size on NIR spectra needs to be considered. In addition, when a calibration model is used for real-time monitoring with an on-line NIR spectrometer, the effect of movement of a mixture in a blender on the prediction error needs to be evaluated carefully (Sulub et al., 2009, 2011). Karande et al. (2010) reported that the best prediction

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http://dx.doi.org/10.1016/j.ijpharm.2014.05.013
0378-5173/

performance for the concentration of API and excipients during blending was achieved by using a calibration set consisting of spectra acquired by dynamic sampling on real-time monitoring. Dynamic sampling or dynamic measurement means data acquisition is conducted with the rotating blender. However, to build a calibration model for real-time monitoring with the small prediction error and high robustness, not only a calibration set but also modeling parameters, such as spectral preprocessing, wavelengths, latent variables and manufacturing conditions including scales and equipment types, need to be investigated.

Spectral analysis techniques strongly affect the prediction error. Generally, partial least squares (PLS) is applied to the calibration model development with NIR spectra. Recently, locally weighted PLS (LW-PLS) has attracted attention because it can build more accurate models than the conventional PLS (Kim et al., 2011; Nakagawa et al., 2012). LW-PLS is a type of just-in-time modeling that has been successfully applied to various industrial processes (Kano and Fujiwara, 2013; Kim et al., 2013). In LW-PLS, all samples stored in a calibration set are weighted according to their distances from a query, for which sample output is predicted, and they are used to build a calibration model. Kim et al. (2011) reported that API concentration in granules for tableting was accurately predicted by using LW-PLS with spectra obtained through static measurement. Thus, LW-PLS was expected to have potential for improving the prediction error in the application of real-time monitoring of API concentration with NIR during blending.

In the present work, to verify model development techniques in their applications to real-time monitoring of ingredient concentration with NIR during blending, we evaluated the effect of calibration sets, spectral analysis techniques, modeling parameters and manufacturing conditions on the prediction. Then, we proposed a model development procedure on the basis of the evaluation results. The analytical performance of the developed models under various conditions was evaluated on the basis of the fitting performance to the calibration set, the prediction error for data sets acquired with various blending equipment, and the analytical validation according to the United States pharmacopeia (USP) and draft guideline on the use of NIR (EMA, 2012).

## 2. Materials and methods

### 2.1. Materials and equipment

#### 2.1.1. Sample

Granules including the API (Daiichi-Sankyo, Japan), which was under development, were used in this work. The granules were manufactured with fluid-bed granulators and diffusion mixers with V-blender and bin blenders. Table 1 summarizes the blending scale and conditions of samples used in model development. The samples with nine different API concentrations (70%, 75%, 85%, 90%, 100%, 110%, 115%, 125%, and 130%) were manufactured with the 1 kg scale blender. Symbols C, P, Te and A in Table 1 indicate that samples are used as a calibration set for model development, a parameter tuning set for optimizing model parameters, a test set for confirming the prediction error of developed models, and an analytical validation set for evaluating the prediction performance of developed models, respectively. Regarding the samples with 100% API concentration manufactured at 1 kg scale, different batches were used to prepare calibration sets and parameter tuning sets. In addition, samples with five different API concentrations of 70%, 85%, 100%, 115%, and, 130% were used as analytical validation set; these samples were manufactured in different batches from those for preparing calibration sets and parameter tuning sets. The following spectra were used as a calibration set and a test set: (1) spectra of samples manufactured at various scales (50 kg, 200 kg, 400 kg, and 500 kg) through static measurement, (2) spectra acquired during blending at various scales through dynamic measurement, and (3) spectra of samples manufactured with different particle sizes (11 μm and 89 μm) in the diluent (Mannitol; Roquette, France) through static measurement. The API concentration of the samples manufactured at various scales except 1 kg scale was 100%, and the standard particle size of diluent was 38 μm.

#### 2.1.2. Equipment and experimental condition

Corona (type: remote NIR-HR, Carl Zeiss, Germany), which has a diode array type NIR spectrometer with 3 nm resolution, was used for real-time monitoring (dynamic measurement). An NIR spectrum in the wavelength range of 1050–1680 nm, which is the standard measurement range of Corona, was obtained by averaging three spectra measured on every rotation of the blender. The example of obtained spectra is shown in Fig. 1: API, granules for tableting that include API, and granules for tableting that do not include API (placebo). Blending experiments with the various blenders, scales, and manufacturing conditions were conducted to acquire spectra by dynamic measurement based on the diffuse reflectance method. The dynamic measurement is defined as the measurement method in which the samples are measured during blending in real time as shown in Fig. 2(1) where Corona is mounted on V-blender. Static measurement with Corona was conducted under the same measurement conditions as dynamic measurement. The static measurement is defined as the measurement method in which the samples do not move on the detector of Corona as shown in Fig. 2(2). Ten spectra were obtained from ten different samples of one batch by static measurement.

**Table 1**
Manufacturing conditions of samples used in calibration (C), parameter tuning (P), test (Te), and analytical validation (A).[a]

| Manufacturing scale (kg) | Blender type | Rotation speed (rpm) | Measurement method | API concentration (%)[b] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 70 | 75 | 85 | 90 | 100 | 110 | 115 | 125 | 130 |
| 1 | V | 50 | Static | C | P/A | C | P/A | C/P/A | P/A | C | P/A | C |
| 5 | V | 37 | Static | – | – | – | – | C | – | – | – | – |
| 50 | V | 23 | Static, dynamic | – | – | – | – | C/Te | – | – | – | – |
| 200 | Bin[c] | 17 | Dynamic | – | – | – | – | C/Te | – | – | – | – |
| 400 | Bin[c] | 17 | Dynamic | – | – | – | – | C/Te | – | – | – | – |
| 500 | Bin[d] | 10 | Dynamic | – | – | – | – | C/Te | – | – | – | – |

[a] Some objectives of samples with same API concentration (though different batches) are represented with a slash. (e.g., P/A means that the API concentration is used for parameter tuning and analytical validation).
[b] The API concentration of 100% means the target concentration of this drug product.
[c] Tote blender.
[d] Bohle blender.