On-Line Monitoring of Pharmaceutical Production Processes Using Hidden Markov Model

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ABSTRACT: This article presents a new method for on-line monitoring of pharmaceutical production process, especially the powder blending process. The new method consists of two parts: extracting features from the Near Infrared (NIR) spectroscopy signals and recognizing patterns from the features. Features are extracted from spectra by using Partial Least Squares method (PLS). The pattern recognition is done by using Hidden Markov Model (HMM). A series of experiments are conducted to evaluate the effectiveness of this new method. In the experiments, wheat powder and corn powder are blended together at a set concentration. The proposed method can effectively detect the blending uniformity (the success rate is 99.6%). In comparison to the conventional Moving Block of Standard Deviation (MBSD), the proposed method has a number of advantages, including higher reliability, higher robustness and more transparent decision making. It can be used for effective on-line monitoring of pharmaceutical production processes. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:1487–1498, 2009

Keywords: pharmaceutical production; process on-line monitoring; Near Infrared (NIR) spectroscopy; Partial Least Squares (PLS); Hidden Markov Model (HMM); Moving Block of Standard Deviation (MBSD)

INTRODUCTION

It is well known that the modern life depends on pharmaceutical products. Needless to say, the quality of these products is important. In general, pharmaceutical production may consist of many steps, such as blending, drying, and crystallization. Among them, blending is an essential step, in which different ingredients are joined together physically and/or chemically to form a new product. In the blending process, Blend Uniformity Analysis (BUA) is a crucial technique and has been the subject of many discussions by the industry and government regulators.[1,2] Traditionally, BUA is done by collecting samples from the process and analyzing the samples off-line. This method could suffer from a number of drawbacks, time wasting, cost wasting and poor quality, as addressed in the reports.[3–5] Recently, the Near Infrared (NIR) spectroscopy has gained much attention, as it is reliable, noncontact and fast. In Ref. 6, NIR spectroscopy is used for the blend homogeneity assessment from thieved

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powder samples. The NIR spectra can be acquired from a single or several observation points,[7] or through multiple optical ports mounted on the blender.[8] It can also be used for on-line process control as discussed in Refs. 9–11.

In order to conduct *real-time* monitoring and quality control, however, simply using NIR spectroscopy is not enough. This is because the sample data only shows the local and instantaneous content of the blending. Thus, it is necessary to combine the NIR spectroscopy with other on-line monitoring techniques.

A simple method applied to calculate the variety of spectra which is used to control mixture uniformity is the Moving Block of Standard Deviation (MBSD) method,[12] which involves selecting a set of n consecutively recorded spectra and calculating the standard deviation at each wavelength, S_l,

$$S_l = \sqrt{\frac{\sum_{k=1}^{n} (A_{lk} - \overline{A}_l)^2}{n-1}} \quad (1)$$

where A_{lk} is the absorbance at wavelength l in spectrum k and $\overline{A}_l$ is the mean absorbance for the n spectra at wavelength l. Eq. (1) provides a vector made of S_l, $l = 1, 2, \ldots, m$. Accordingly, the mean standard deviation, $\overline{S}$, can be calculated by Eq. (2):

$$\overline{S} = \frac{\sum_{l=1}^{m} S_l}{m} \quad (2)$$

Next, the spectral set is shifted by one step in time and the same calculations are repeated. The variation of the values of $\overline{S}$, as a function of time, would be a measure of mixture uniformity in the samples. This process is depicted graphically in Figure 1.[13] While this method is effective, it is not very robust because small variations in the data may cause significant changes.

From a theoretical point of view, on-line monitoring can be considered as a pattern classification problem. According to literatures, a large number of pattern classification methods have been developed. These methods can be roughly classified into two categories: statistics methods and machine learning methods. The former includes conventional pattern classification methods, such as Bayesian classification and linear discriminate function analysis.[14] The latter includes Artificial Neural Network (ANN), decision tree induction, etc.[15,16] Since the pharmaceutical blending process is a dynamic process, in this article the Hidden Markov Model (HMM) was adopted. HMM is a machine learning method developed in early 1980s. It was first applied to speech recognition, in which HMM is used to handle the spatial and temporal pattern recognition problems. Recently, HMM has been successfully extended to pattern learning,[17,18] condition monitoring,[16,19] fault diagnosis,[20] and gene sequences analyses.[21] The application of HMM for on-line monitoring is of great interest because of its strong capability in capturing time-variant nonstationary features. Furthermore, it can effectively deal with uncertainty, randomness

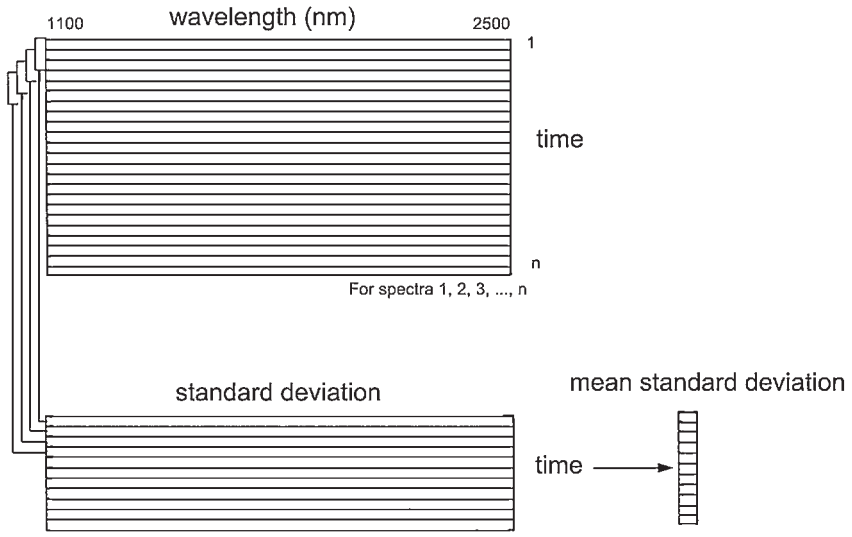

Figure 1. Illustration of the MBSD method for blend homogeneity evaluation.