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Near infrared spectroscopy based monitoring of extraction processes of raw material with the help of dynamic predictive modeling

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ABSTRACT

The control of batch-to-batch quality variations remains a challenging task for pharmaceutical industries, e.g., traditional Chinese medicine (TCM) manufacturing. One difficult problem is to produce pharmaceutical products with consistent quality from raw material of large quality variations. In this paper, an integrated methodology combining the near infrared spectroscopy (NIRS) and dynamic predictive modeling is developed for the monitoring and control of the batch extraction process of *licorice*. With the spectra data in hand, the initial state of the process is firstly estimated with a state-space model to construct a process monitoring strategy for the early detection of variations induced by the initial process inputs such as raw materials. Secondly, the quality property of the end product is predicted at the mid-course during the extraction process with a partial least squares (PLS) model. The batch-end-time (BET) is then adjusted accordingly to minimize the quality variations. In conclusion, our study shows that with the help of the dynamic predictive modeling, NIRS can offer the past and future information of the process, which enables more accurate monitoring and control of process performance and product quality.

1. Introduction

Consistency has long been an important requirement for any industrial product, and is even more significant for pharmaceutical manufacturing to obtain drugs with reliable performance. In the mean time, however, the production of pharmaceuticals is often accompanied with batch processes, which brings difficulties to the process monitoring due to the presence of significant non-linearity, the absence of steady-state operation, etc. [1]. It becomes even worse when we have to face raw materials, such as the extraction process used widely in the manufacturing of traditional Chinese medicine (TCM), which aims to extract active pharmaceutical ingredients from herbs, animal tissues, and so on. Although it is necessary to follow target process trajectories and achieve tight final drug product quality specifications, quality tracking is difficult to achieve for the extraction processes in practice because of the fluctuation in raw material properties [2,3]. In reality, the quality of raw materials (herbs, fungi, animal tissues, etc.) depends on a number of less controllable factors such as cultivating location, climate, harvest time, which often result in large quality variations even after restrict material selection procedures [4]. Consequently, one great challenge faced here is how to produce products with consistent quality from the raw materials of large quality fluctuation. Currently, the control of batch-to-batch quality variations remains a challenging task for TCM manufacturing or other process with raw materials, while the quality control by only analyzing the samples does not solve this problem due to the inherent non-uniform quality distribution within the bulk of raw materials [5]. Since such quality risk enters the process from the very beginning, it is necessary to identify the initial state of the manufacturing, as well as recognizing the current state and predicting the future state, in order to obtain integrated knowledge about the process, based on which reliable control strategies can be developed. Technically, this further relies on the data mining of appropriate online process measurements.

In this study, we take the extraction process of *licorice* as a typical case to practice the above consideration. The control objective is to minimize the fluctuation in the final quality of the extract, with the main disturbances from the changes in the raw *licorice* roots (which is usually unknown). We utilize near infrared spectroscopy (NIRS) as the primary tool for the data collection during the process, which is getting more and more applications in the pharmaceutical manufacturing (including TCM production) as a process analytical technology (PAT) tool for quality control [4–12]. We reason that the NIRS measurements may contain complete information about the state of the instantaneous extraction process, which not only reflects

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the disturbance from the feed-stock raw materials but can also imply the final quality properties due to the inherent correlation between different measurements. Therefore, our first objective is to infer the initial state of each batch from the first N time points of NIRS measurements and to investigate how informative the inferred initial state values are. For example, can they provide information on the process performance and product quality? To answer such a question, a state-space model is constructed with the subspace approach using the data from 10 normal batches of *licorice* extraction [13,14]. The results indicate that the inferred initial states can give early warning of disturbance occurred in the initial stage of the extraction process. The monitoring program developed under the normal conditions is then applied to the abnormal batches with artificially induced disturbance of solvent volume variations and shows good fault detection capability.

Our second objective is to develop a model predictive control (MPC) strategy to minimize the end product quality variations of the extraction process. We investigate here how to compensate the disturbance induced from the raw materials by adjusting the process parameters. A partial least squares (PLS) regression model is constructed to predict the final product quality based upon the NIRS data measured up to the mid-course time point T [15]. The process parameter such as the batch-end-time (BET) is then adjusted according to the prediction, so as to minimize the quality deviations in the extracts. The results indicate that the strategy is effective for improving the product quality consistency.

The main contribution of this paper lies in how to utilize the process measurements to infer the past process states and predict the future product quality of the extraction process, as illustrated in Fig. 1. The extracted information provides knowledge for an adaptive process adjustment to "ensure the acceptable quality of in-process and/or final products based on process data" [16]. This model-based approach provides an example of quality by design (QbD) with process modeling and can be applied to other processes in pharmaceutical manufacturing [17].

2. Experimental and Methods

2.1. Materials

Raw *licorice* root (batch number 1403008) was supplied by Qiyitang pharmaceutical Co., Ltd. (Hebei, China). Liquiritin (batch number 111610) standard substance was obtained from the National Institutes for Food and Drug Control (Beijing, China). Ultra-pure water obtained from a Mill-Q water purification system (Millipore, USA) was used for ultra performance liquid chromatography (UPLC) analyses. The HPLC-grade acetonitrile and methyl alcohol were purchased from Fisher Scientific Ltd. (Leicestershire, UK). Pharmaceutical grade water used for *licorice* extraction was produced by a purification system of Huitong Environment Protection Recycle Ltd. (Tianjin, China).

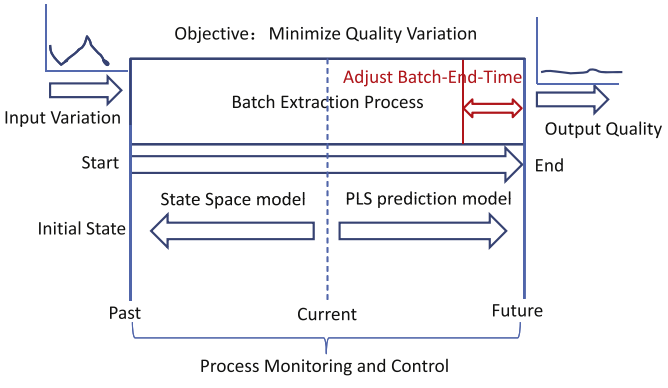

Fig. 1. The scheme of dynamic predictive model based process monitoring and control Strategy. The objective of the proposed approach is to minimize the product quality variations by adjusting the process to compensate the disturbances induced by factors like the quality fluctuation in raw materials. State-space model is used to infer the initial quality state from the process measurements (such as NIRS data), and PLS quality prediction model is applied to estimate the final product quality and adjust the process accordingly. Combining the past, current and future process information enables better quality monitoring and control for TCM extraction process.

2.2. Experiment Setup and the Extraction Process

Raw *licorice* root (50 g) and pharmaceutical grade water are placed into a flask for reflux extraction about 3 h. The *licorice* extracts at every 6 min(6, 12, 18, …, 180 min, 30 time points in total) are obtained by a peristaltic pump for the analysis. All the *licorice* extraction experiments are listed in Table 1. The first group is carried out ten times under normal operating conditions (NOC) in this study. Other groups are performed under abnormal operating conditions (AOC). Specifically, AOC1–AOC3 are carried out with abnormal solvent consumption (characterized by the mass ratio between solid and liquid, MR_{sl}), and AOC4–AOC5 are performed under lower temperatures than the NOC group. Each AOC group is repeated 3 times.

2.3. NIRS and UPLC Measurement

NIRS analysis is performed by an Antaris®II Fourier-Transform NIR spectrometer (Thermo Electron, USA) equipped with a SabIR fiber optic transflectance probe. The NIRS spectra of the *licorice* extraction are recorded on-line by the transflectance probe in the region of 10,000–4000 cm^{-1} with a resolution of 8 cm^{-1} and 64 scans per spectrum. The optical path length of the probe is set to be 3 mm.

UPLC measurement is carried out by a Waters Acquity UPLC I-Class series equipped with ACQUITY UPLC BEH C18 column (2.1 mm × 50 mm, 1.7 μm), PDA detector, binary solvent manager and sample manager-FTN. The mobile phase is composed of solvent A (formic acid – water, 1:1000, v/v) and solvent B (acetonitrile). The flow rate is 0.45 mL ·min^{-1}, the injection volume is 0.5 μL, and the column temperature is set at 35 °C. The gradient elution conditions are summarized in Table 2.

The samples used for the UPLC measurement are prepared as follows: all of the *licorice* extraction samples are stationary for stratification, and 500 μL supernatant is diluted by 1 mL methyl alcohol. After centrifugation, the obtained supernatant is sterilized by ultrafiltration (0.22 μm filters). Then, the filtrate is used for the final UPLC determination by a reversed-phase column with detection at 254 nm. The quantification methodology follows the instruction from [18]. Specifically, a calibration curve is established upon nine consecutive injections of different concentrations of liquiritin. Regression equation calibrated is $y = 2702166.9930x - 10687.8886$ ($r = 0.9999$, $n = 9$) with y being the peak area in the unit of mAU·s and x being the concentration (mg·mL^{-1}). Quantification results show that the linear region of the calibration curve is from 0.0185 mg ·mL^{-1} to 0.3694 mg ·mL^{-1}. Considering that each sample is diluted by 3 times, such linear region is adequate for our analysis.

Table 1
The experimental design for *licorice* extraction process.

Group no.	Repeated times	MR_{sl}	Heating temperature (°C)
NOC	10	1:8	105
AOC1	3	1:12	105
AOC2	3	1:7	105
AOC3	3	1:5	105
AOC4	3	1:8	75
AOC5	3	1:8	95