A novel algorithm for blending process monitoring of Angong Niuhuang intermediate using Vector Operation Moving Block Standard Deviation

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Abstract

This study aimed to introduce a novel approach named Vector Operation Moving Block Standard Deviation (VO-MBSD) to characterize the original powder blend uniformity of Angong Nuihuang intermediate using NIR technology, including 400g *Rhizoma Coptidis*, 400g *Radix Scutellariae*, 400g *Radix Curcumae* and 400g *Fructus Gardeniae*. A novel blending evaluation method named VO-MBSD compared with Moving Block Standard Deviation (MBSD) was applied to characterize the blending of Chinese Materia Medica (CMM) original powder including Rhizoma Coptidis, Radix Scutellariae, Radix Curcumae and Fructus Gardeniae. HPLC (High Performance Liquid Chromatography) analysis demonstrated these observations perfectly. OV-MBSD is the rate of change by time, which not only represents the scalar change but also the vector change. The identification accuracy of blend uniformity and end-point via VO-MBSD was the same with classical HPLC method. This method is more accuracy than original MBSD method. Compared with classical MBSD, it is appropriate for the determination of blending end-point and could be successfully implemented as an on-line monitoring tool for blending process.

Keywords: Near-infrared spectroscopy; Blending; Vector Operation Moving Block Standard Deviation; Angong Niuhuang intermediate; Process analysis Technology

1 Introduction

Blending process is very common in the pharmaceutical industry and represents a critical unit operation of the production process of solid dosage forms. The formulation of Angong Niuhuang Wan is complex [1], in which, original powder blending is a key point in the production process. Near-Infrared (NIR) technology combining with chemometrics has been applied in pharmaceutical blending, coting and component distribution of tablet [2-8]. These tasks have been mainly performed by partial least-squares (PLS) [9-10], Classical least squares (CLS) [11], Partial least square discriminant analysis (PLS-DA) [12], Moving block standard deviation (MBSD) [13-15], Principal component scores distance analysis (PC-SDA) [16].

The most common approach for qualitative assessment of homogeneity is to calculate the MBSD between consecutive spectra. Momose et al [14] noted that homogeneity using MBSD is an important point in detecting

end-points for blending of nicaldipine hydrochloride. Our team [17] monitored the blending of Yinhuang powder using moving block macropixel relative standard deviation (MBMRSTDEV). Studies for in-line monitoring of blending process of Zhongsheng pill powder using MBSD were published by Jin et al [18].

However, MBSD is based on the absorbance value of spectrum, which is suitable for spectral absorption coefficient is bigger or content variable greatly. Spectral features in the NIR region (4000-12500 cm^{-1}) are overtones and combinations of vibrations observed in the mid-infrared (IR) region and are therefore much less intense than the parent absorptions [19]. The functional groups, C–H, N–H, O–H, S–H are almost exclusively involving the hydrogen atom. According to molecular vibrations, the NIR frequency range can be divided into four ranges: combination region (CR, 4000–4900 cm^{-1}), first combination-overtone (FCOT, 4900–7100 cm^{-1}), second combination-overtone (SCOT, 7100–10,000 cm^{-1}), and third overtone (TO, 10,000–12,500 cm^{-1}) [20]. In addition, the absorbance value is a scalar without direction for MBSD method.

In this work, a novel approach named VO-MBSD was used to characterize the original powder blend uniformity using NIR technology, including 400g Rhizoma Coptidis, 400g Radix Scutellariae, 400g Radix Curcumae and 400g Fructus Gardeniae. We then compared obtained results from MBSD and VO-MBSD, and validity of this method was confirmed by HPLC. Our tasks delineates the general steps of this novel method involved in the original powder blend uniformity and could thus also be used as practical guidance for blend process of Chinese Materia Medica.

2 Basic theory

Vector Operation Moving Block Standard Deviation was introduced based on NIR spectrum. Firstly, it was need to calculate the tan α, where

$$\alpha \equiv [a, b] \qquad (1)$$

a was defined as a line between two absorbance values under the corresponding wavenumber, b was defined as a line between adjacent wavenumber. α is the angle between the two lines.

Secondly, the standard deviation (SD) at an individual wavenumber was calculated using the tan α of three consecutive spectra; The third step is to select the wavelength range, in which the value of SD changed greatly; At last, mean value of SD across the whole selected wavenumber range was then calculated to represent the spectral variation within the time window. Each successive value was determined by shifting the window (in time) by one sample until all acquired spectra were utilized. As a result, the end-point of blending is complete with the small OV-MBSD value and fluctuation within a narrow range. OV-MBSD is the rate of change in absorbance by time, which not only represents the scalar change but also the vector change.

3 Materials and Methods

3.1 Materials

The *Rhizoma Coptidis*, *Radix Scutellariae, Radix Curcumae* and *Fructus Gardeniae* powder was purchased from Tong Ren Tang Technologies Co., Ltd. (Beijing China). Geniposide reference standard (lot number: 110749–201115), baicalin (lot number: 110715–201117), beberine hydrochloride reference standard (lot number: 110713–201212) were supplied by the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). HPLC-grade acetonitrile (MeCN) were purchased from E. Merck (Darmstadt, Germany) and phosphoric acid (AR grade) was obtained from Beihua Fine Chemicals Co., Ltd. (Beijing, China). The water used for HPLC was purified by Milli-Q system (Millipore, Milford, MA, USA.).

3.2 The Mixing and sampling steps

The powders were mixed in a 5L stainless steel non-symmetric V-blender from Zhong Xi Yuan Da Technologies (Beijing China). The blender rotational speed was 20 rpm. The V-blender was filled by loading 1.6 kg of powder into the

blender arm, which corresponds approximately to a 60% fill level.

The sampling operation was carried out at predefined periods (0, 2, 4, 6, 8, 10, 8, 10, 16, 20, 25, 30, 32, 34, 36, 38, 40, 45, 50, 55, 60, 65, 70 min). For each sampling period, the V-blender was stopped and five samples of approximately 2 g were collected using a pocket thief sampler at the positions shown in Figure 1, that is at the top of the right arm, top of the left arm, middle of the right arm, middle of the left arm and bottom of the blender. The samples were then saved for future data analysis.
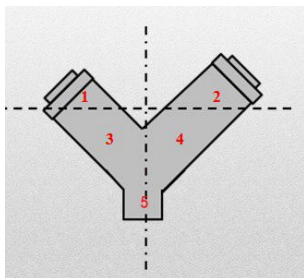

Figure 1.   The sampling position

3.3 NIR equipment and data pretreatmeat software

The NIR spectra were collected with the reflectance mode using the AntarisⅡ Near-infrared spectrophotometer (Thermo Electron Co., USA). Each spectrum was scanned for 64 times with 8 cm^{-1} resolution. The range of spectra was from 10,000 cm^{-1} to 4000 cm^{-1}. Each sample was collected three times and the mean of three spectra was used for the future analysis. The sample was hold in a circular liquid cuvette with plastic cap (Optical path is 8 mm). Data analysis was performed by the Unscrambler 7.8 (CAMO Software Inc., Norway).

3.4 The method of HPLC analysis

A Shimadzu LC-20AT system consisting of two pumps, DAD detector, and an auto sampler was used throughout this study. Samples were separated on an Agilent SB C18 column (150 mm × 4.6 mm I.D., 5 μm). The mobile phase consisted of acetonitrile (A) and water containing 0.5% (v/v) phosphoric acid (B). A gradient program was used as follows: 0min, 9: 91 (A : B, v/v), The flow rate was 1 mL/min; 16 min, 18 : 82, The flow rate was 1 mL/min; 52 min, 40 : 60, The flow rate was 1 mL/min. The column temperature was 35℃. The samples were detected at 254 nm.

4 Results and Discussion

4.1 Raw spectra of mixing powder in blending process

Fig. 2 showed raw spectra of Angong Nuihuang intermediate in blending process. According to the theory of four frequency range of NIR [20], the reflectance intensities varied obviously in combination region (CR, 4000-4900 cm^{-1}) and first combination-overtone (FCOT, 4900-7100 cm^{-1}). Furthermore, there are differences between four types of Chinese herbal medicines, which were layered into the mixer before blending. As the blending process, their difference is getting smaller and smaller. More absorption characteristics of Angong Nuihuang intermediate are under investigation.
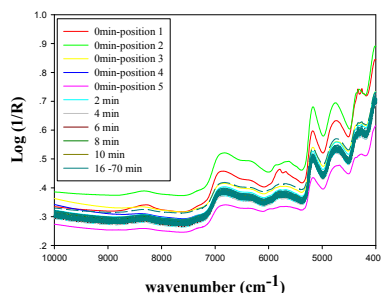

Figure 2. Typical NIR raw spectra collected for an blending process of Angong Nuihuang intermediate.

4.2 Absorption characteristics of First-derivative spectra

The First-derivative spectra of Radix Scutellariae, Rhizoma Coptidis, Fructus Gardeniae and Radix Curcumae were illustrated in Fig. 3. It can be seen clearly that the First-derivative spectra of four Chinese herbal medicines were different from each other over the wavenumber range 6076-4000 cm^{-1} and it have disparate intensities in 7601-6999 cm^{-1}. Therefore, the wavenumber range 6076-4000 cm^{-1} and 7601-6999 cm^{-1} were selected to future data analysis.
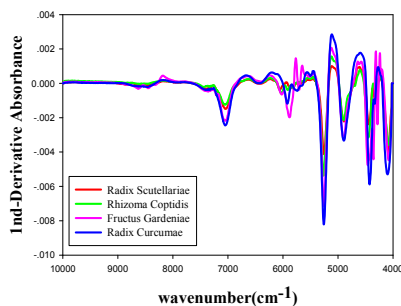

Figure 3. First-derivative spectra of Radix Scutellariae, Rhizoma Coptidis, Fructus Gardeniae and Radix Curcumae

4.3 Blend monitoring using MBSD and VO-MBSD

Fig. 4 exhibited that the trend of MBSD are approximately equal between different sampling positions. MBSD values were decreased from 0 min to 10 min, and then it changed greatly between 10 min and 34 min, the sampling position 2 is especially so. After 32 min, MBSD values appeared to have been leveling off. The smallest change can be seen from 40 min to 55 min, with the MBSD values of sampling position 1 varied between 0.0009 and 0.0015, position 2 varied between 0.0019 and 0.0009, position 3 varied between 0.0016 and 0.0019, position 4 varied between 0.0016 and 0.0019, position 5 varied between 0.0020 and 0.0029. This result showed that blending had already finished by 40 min. In reality, the bending end-point with smallest values of five sampling position were different from each other. Therefore, it was difficult in reliably determining the end-point using MBSD method.
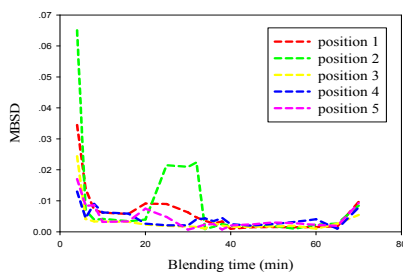

Figure 4. Moving Block Standard Deviation as a function of mixing time a mixture consisting of Rhizoma Coptidis (25%, w/w) Radix Scutellariae (25%, w/w), Radix Curcumae (25%, w/w) and Fructus Gardeniae (25%, w/w)

Fig. 5 showed the VO-MBSD trend of powder blending process over the wavenumber range 6076-4000 cm^{-1} and 7601-6999 cm^{-1}, in which the VO-MBSD value changes greatly. It can be seen clearly that different sampling positions had similar variation tendency, but there is a little differences in sampling position 2, compared with position 4 and other sampling positions in 10-36 minutes. From 0 min to 34 min, the VO-MBSD value was large and significant fluctuation. Five sampling positions showed the first smallest value simultaneously at 36 min, but it heighten quickly between 38min and 40 min. The smallest change were seen from 45 min to 60 min, with the VO-MBSD values of sampling position 1 varied between 5.81388×10^{-6} and 9.32009×10^{-6}, position 2 varied between 4.20196×10^{-6} and 9.11898×10^{-6}, position 3 varied between 6.7365×10^{-6} and 7.5427×10^{-6}, position 4 varied between 4.58391×10^{-6} and 7.88996×10^{-6}, position 5

varied between 5.91751×10^{-6} and 8.52786×10^{-6}. The process end-point with smallest VO-MBSD value of sampling position 1 and 2 appear at 50 min and 45 min respectively, sampling position 3, 4 and 5 appear at 60 min. As a result, a process endpoint is not a fixed time. The powder was uniformity at range of 45-60 min, which happened to coincide with HPLC method in next context. It comes to the conclusion that the VO-MBSD method can evaluate the process end-point more accurately than MBSD method.
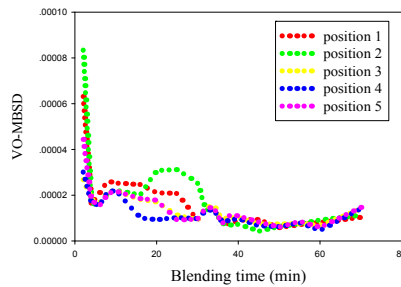

Figure 5. Vector Operation Moving Block Standard Deviation as a function of mixing time a mixture consisting of Rhizoma Coptidis (25%, w/w) Radix Scutellariae (25%, w/w), Radix Curcumae (25%, w/w) and Fructus Gardeniae (25%, w/w)

4.6 Confirmation of validity for NIR condition by using HPLC analysis

HPLC method was investigated to determine geniposide, baicalin, and beberine hydrochloride. Fig. 6 showed the chromatograms of geniposide, baicalin, and beberine hydrochloride reference standard and the powder sample. The retention time of the geniposide, baicalin, and beberine hydrochloride in sample was equally to the reference standard. The calibration curve of the HPLC method was investigated before the samples analysis. The calibration curve of three reference standards showed good linearity respectively (R= 0.9999), within the geniposide range from 0.0599μg to 0.5985μg, the baicalin range from 0.0868μg to 1.7364μg, and the beberine hydrochloride range from 0.0252μg to 0.5048μg. It demonstrated that HPLC method can satisfy require of quantitative analysis.
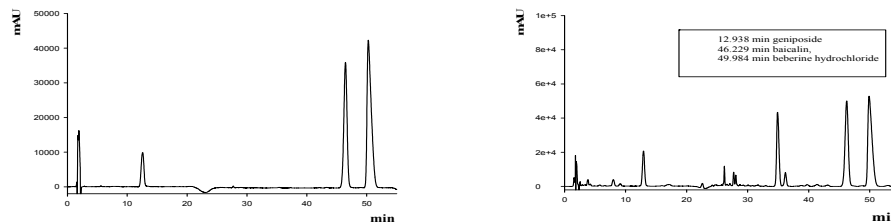

Figure 6. Chromatograms of geniposide, baicalin, and beberine hydrochloride reference standard and sample

In this study, HPLC analysis was conducted to confirm accuracy of end-point via NIR. Fig. 7 displayed that the relative standard deviation (RSD) of geniposide, baicalin, and beberine hydrochloride varied greatly from 0 min to 40 min, but three active components of blending powder showed the first smallest RSD value 3.70%, 2.27% and 0.93% at 36 min. Between 40 and 50 minutes, the changes were minor, with the RSD of baicalin, beberine hydrochloride ranging from 2.91% to 1.33%, and the RSD of beberine hydrochloride ranging from 0.28% to 1.12%. At 45 minute, the RSD of geniposide was 2.17%. Based on the recommendations from the FDA [21], the original powder was deemed homogenous. It comes to the conclusion that identifying the blend uniformity and end-point via VO-MBSD was the same with classical HPLC method. These results clearly demonstrate the accuracy of VO-MBSD to determine the blend uniformity and end-point via NIR. This method is more precise than original MBSD method.
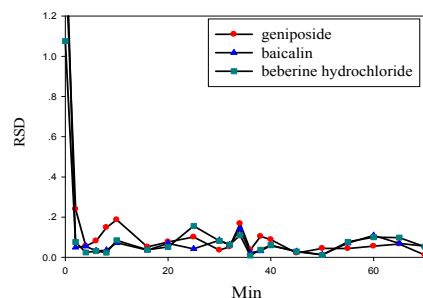
Figure 7. Identify the blend uniformity and end-point via HPLC method

5 Conclusions

Adequate and nondestructive estimation of blend uniformity for original powder is becoming increasingly indispensable for CMM production. Results in this study clearly demonstrate the accuracy of blend uniformity by VO-MBSD method, which is an unsupervised method without calibration model. It is more precise than MBSD since it not only represents the scalar change but also the vector change. As a result, it is suitable for in-line and on-line blending process. For within a process analytical technology (PAT) framework, a process endpoint is not a fixed time, but this does not mean that blending time is not to be considered. A range of acceptable process times is likely to be achieved during the manufacturing phase and should be evaluated [22]. According to quality-by-design principles, more novel methods should be developed to describe the process of CMM original powder blending.

Acknowledgments

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