Quality by Design (QbD): Application of Comprehensive Risk Analysis in Blending Process for XLGB Capsule in Medicine Industry

Yamin Zuo 1#, Jie Huang 2#, Xuehua Deng 1, Yichun Sun 2*, Qing Wu 34*

1 School of Basic Medical Sciences, Hubei Key Laboratory of Wudang Local Chinese Medicine Research, Hubei University of Medicine, 30 Renmin South Rd, Shiyan, Hubei 442000, China
2 The Sinopharm Tongjitang (Guizhou) Pharmaceutical Co., Ltd., 99 Guihui Rd, Guiyang 551400, Guizhou, China.
3 Guizhou Key Laboratory for Information System of Mountainous Areas and Protection of Ecological Environment, Guizhou Normal University, 116 Baoshan North Rd, Guiyang, Guizhou 550001, China.
4 Innovation Laboratory, the Third Experiment Middle School in Guiyang, Guiyang, Guizhou 550001, China.
# the authors contribute equally
* Correspondence: 20170529@hbmu.edu.cn; wq0851@gznu.edu.cn.

Abstract: Intelligent development is becoming an inevitable choice for the development of green manufacturing enterprises, improving the medical quality and guaranteeing the safety is an important role player in the intelligent development of medical industry. Since the risk model prediction is crucial in many areas of medical work, risk management and communication are meaningful in industry management. The framework of comprehensive risk management of Chinese Patent Medicine (CPM) has been presented and constructed at present. To enhance the quality level and safety management of medical service, this article explored the different theory meanings of innovation and conducted a comprehensive risk evaluation of Chinese medicine industry. This paper provides a foundational reference for future research that how to apply quality-by-design (QbD) approach for the development of medicine industry. This study demonstrates that the application of the QbD concept is a novel area in CPM quality.

1. INTRODUCTION
In China, medicinal herbs have been used to cure various disease since ancient times which are guided according to the theory of Chinese medicine. However, in pharmaceutical experimental design, the measurement of feature quality parameters such as raw materials or intermediate, which is a basic requirement to ensure the efficacy for the medicine quality control.

The process analytical technology (PAT) firstly promoted by the Food and Drug Administration (FDA) is rooted in the Quality-by-Design (QbD) framework, then widely cited and developed by the ICH Q8(R2), Q9 and Q10 guidelines which provides basic product and process understanding for continuous improvement, in addition, based on the proper scientific background and risk management...
of quality, the objective was to meet the predefined criteria of final product quality. Risk is defined as a feature that things are unpredictable and uncontrollable. A risk assessment was conducted using an analysis approach, involving the process development, analytical development, active pharmaceutical ingredient (API) and manufacturing. Despite the research on the risk management of medicine manufacture started later in China, this aspect was quickly gaining wide attention in a variety of application. Medicine risk management is defined as a guidelines that eliminates or decrease the breakage and economic loss occurred accidentally or unavoidably.

Near infrared spectroscopy (NIRS) has become an indispensable analytical tool used in medicine industry attributed to its rapid, low-cost and non-destructive feature. Since the NIRS is overlap, this makes it rather difficult to assess specific chemical information to a spectrum. To overcome these drawbacks, advanced different multivariate data analysis is widely applied to estimate the vibrational NIR spectra contribution.

Blending process is an effective and convenient operation featured in forming a solid intermediate or API as an end point, which is widely used in pharmaceutical industry. To obtain API products with highly and unique properties (such as purity, polymorphism, size distribution, density and flow ability), defining the details of the blending process is critical.

In this paper, we apply NIRS to define the quality and management of Chinese patent medicines Xian Ling Gu Bao capsule (XLGB) according to the QbD and PAT concept. Several studies have been explored in order to address a systematic analysis of the approaches. Our experimental results demonstrated that proposed method could monitor the API contents effectively in the blending process and be able to make effective decision once reached the predefined ending point.

The paper outline is organized as following. The section II presents previous related works in order to establish a background for this research, section III describes the chemometric approaches of our proposed model and different improvement techniques. The results and discussion from the empirical experimental are then presented in section IV.

2. RELATED WORK

Undoubtedly, the framework is important, thus administrators in the industry should be able to predict proper responsibility for the risk and control management. Several modern analytical methods have been used to identify the quality and management of risk in Chinese patent medicines, which could be classified into two major categories roughly. Thus the first uses approaches as HPLC, GC and so on in order to define the active ingredient and content of the medicine. Alternatively, several other biological techniques are applied, which was aided by bio-chip or bio-chemistry etc, the main objective was to strengthen the scientific interpretation of the medicine. However, neither approach has its own benefits and drawbacks to makes a break-through.

Several applications of NIRS in the pharmaceutical field that concerning the concentration has been reported. Naidu VR [1] et al developed the linkage between NIRS and content of cellulose which could be useful in the functional coat value prediction and the long-term monitoring of the Wurster coating process. However, the analysis was not in-depth in the pros and cons of each chemometric in their applications, and therefore no comprehensive real works were included. Similarly, Grassi S [2] et al explored the usage of Fourier-Transform near infrared (FT-NIR) spectroscopy to define process parameters in the fermentation process of beer at different point in operation but there was little insight on how to translate this technique into practice.

Rosas JG [3] et al monitored changes in physicochemical properties and the formulation during freeze-drying by NIR spectroscopy, meanwhile, several different spectral transformation tools such as the means of selected wavenumbers, principal component analysis and the correlation coefficient have been compared. We also explored alternative chemometric techniques in our work. Khorasani M [4] et al studied the usage of near-infrared chemical imaging (NIR-CI) coupled with different chemometric modeling as a highly versatile and a non-destructive equipment for the roller compaction assessment and monitoring the tableting processes. In this study, the linkage between the attributed process and quality parameters were explored, and the experimental design space was calculated.
Mirschel et al. demonstrated firstly that near-infrared (NIR) chemical imaging was to be much more useful during the in-line textile finishing processes analysis. One of the advantages of this method was that it can effectively measure and visualize different inhomogeneities, which may influence the drying process and the spatial of the finish distribution consequently. However, their work mainly focuses on the aspects of development methodology and software architecture.

In comparison with previous research, our research focuses mainly on more heavily comparison of various chemometrics, as well as their pros and cons. We will create a predictive variable map which can have an important impact on the quality attributes of NIR method that could summarize the risks.

### 3. CHEMOMETRIC TECHNIQUES

Different chemometric approaches have been created and characterized for on-line real-time process monitoring purpose. To obtain objective results, we choose a small fraction of the most popular items in our experiments. As Chinese patent medicine is a complex drug-containing system, so a single quality-marker is found to be difficult to reflect its security. So comprehensive risk of bias assessment is becoming the tendency of quality control on Chinese patent medicine.

a. **Clustering analysis**

Clustering analysis can clear classify the metabolites with the same and different quantitative character between the sample groups. As such, it can be widely used in the fields such as medicine, biology and so on. In addition, it is also used in the quality control of Chinese traditional medicine.

b. **Discriminant analysis**

The object of discriminant analysis is obtained and classified several known samples of the observation data, then apply these discriminant classification models to other unknown sample. This model concludes four different types: maximum likelihood, Fisher’s discriminant analysis, discriminant analysis of Bayer’s and logistic regression method.

c. **Analysis of principal component**

This analysis is to choose best characteristic related to the question to be sort. We can use the method to discover one or several better indicators which can independently represent one aspect.

d. **Artificial neural networks**

This method is a processing system of simulating the human brain working function. Thus, it is characterized by the integration of processing information, function of self-organization and self-studying.

### 4. EXPERIMENTAL RESULTS AND ANALYSIS

A Fourier Transform Process Analyses Near Infrared spectrometer equipped with In GaAs detectors and an immersion transmission probe was explored to record the data of in and on-line measurement at laboratory.

a. **Risk assessment**

The ICH Q9 guideline has implemented the principles of different quality assessment instruments to identify the risk. A fishbone diagram map was illustrated to create the variables that would have a potential impact on the quality of NIR method, which was shown in Fig1. About six categories were illustrated in total: i.e., equipment, environment, measurement, materials, man, and process. Subsequently the risk assessment of bias and quality was performed according to the Failure Mode Effects Analysis (FMEA) principle, which allowed management and mitigation of risk to bring the NIR measurement into dynamics.

The key risks were summarized in table 1, which had a significant impact on the model’s development, validation, or future application. The risks were first categorized as controlled, noise and experimental aspects. For every risk, the aspects of probability, severity and detectability were evaluated, then the risk priority level was categorized as low, medium or high aspect. High-risk factor priority was contained both in development and validation.
Fig 1. Fishbone diagram for the NIR method developed and its routine usage.

Table 1. The risk assessment of the NIR method using FMEA methodology for its development and the routine usage.

| Risk origin                                      | Risk nature | Risk priority | Evaluation                                  |
|--------------------------------------------------|-------------|---------------|---------------------------------------------|
| spectrometer failure operation                   | controlled  | low           | spectra quality check test or maintenance   |
| probe position                                   | noise       | low           | Ruggedness parameter                        |
| optical fiber position                           | noise       | low           | Ruggedness parameter                        |
| flow rate                                        | experimental| high          | Ruggedness parameter                        |
| API content                                      | experimental| high          | experimental protocol                       |
| impurities content                               | experimental| high          | DOE factor                                  |
| raw batch variation in material                  | noise       | low           | Ruggedness parameter                        |
| optical fiber temperature                        | noise       | high          | Ruggedness parameter                        |
| The outlier spectrum                             | controlled  | low           | outlier detection mechanisms                |

b. NIR method development

(1) NIR spectra

The overlay plots of the raw NIR spectra in the range 4000-12000 cm⁻¹ were shown in Fig 2. The specific chemicals group of bands was difficult for assignment. However, the bands identification of API was explored. Such as the encompasses of N-H and O-H combination were shown in the range 5000-5200cm⁻¹, the O-H 1st overtone band was shown in the range 7000-7200 cm⁻¹. Moreover, the 1st overtone of -CH, -CH₃,-CH₃ bonds corresponding to the ranges 5200-6000 cm⁻¹, which could be explained by the organic solvents predominantly.
(2) The building of qualitative models

Predictive NIR models were established to quantify the two analytes calculated by the PLS regression. The calibration model included the following steps: outlier’s data detection and elimination, the spectral range and pre-treatment method selection, number of PLS factors determination. Internal validation was carried out by a random subsets cross-validation to estimate model’s performance. The PLS factors number was chosen for which had no significant variation of the RMSECV value.

Different spectral transformation was explored to improve the model’s ability on content prediction. Three data pre-transformation were selected: the correction of linear baseline, 1st and 2nd derivative. So, the linear baseline correction was chosen between 2 points at 5400-6000cm⁻¹ and 7100-7300cm⁻¹, to reduce spectral drift. Then the 1st and 2nd derivatives were respectively computed according to the Savitsky-Golay algorithm based on 7 smoothing points and a second order polynomial, as shown in Table 2.

| model feature     | a                  | b                  | c                  |
|-------------------|--------------------|--------------------|--------------------|
| pre-treatment     | Linear baseline correction | 1st derivative | 2nd derivative |
| range(cm⁻¹)       | 5400-6000cm⁻¹      | 5400-6000cm⁻¹      | 5400-6000cm⁻¹      |
|                   | 7100-7300cm⁻¹      | 7100-7300cm⁻¹      | 7100-7300cm⁻¹      |
| PLS factor number | 5                  | 6                  | 7                  |
| Development       | R²C                | 0.9453             | 0.9678             | 0.9831             |
|                   | R²CV               | 0.167              | 0.124              | 0.159              |
|                   | RMSEC(\% W/W)      | 0.198              | 0.189              | 0.104              |
|                   | RMSECV(\% W/W)     | 0.0056             | 0.0057             | 0.0023             |

As illustrated in Fig3, a good linear relationship was obtained between the NIR model predictions and reference chromatographic values for the 2 analytes both during calibration and validation. The models’ candidates both have a small PLS factors Otherwise, for each analyte model, the values of RMSEC and RMSECV were low. In conclusion, these results demonstrated a good predictive performance for both analytes.
6

(3) Real-time monitoring and the predefined point detection

The ability of NIRS to monitor real-time and simultaneously calculate the 2 analytes contents, otherwise, the probability to detect the predefined point, was assessed by the blending process at laboratory scale. As shown in Fig 4, it could be concluded that the two analytes present good agreement between NIRS and the reference values included the uncertainty of the NIR method.

5. CONCLUSION

This paper presents our initial research on applying the quality by design principle in blending process for XLGB capsule to research the Chinese patent medicines. The aim was to unveil the underlying linkage between API of the medicine and an automated unequivocal decision once the target composition was reached the predefined point.

ACKNOWLEDGMENT

This work is supported by the XLGB capsule Standardization (the National Traditional Chinese Medicine Standardization project ZYBZHOC-GG2-10; the Science and Technology Support Plan of Guizhou Provincial (Grant No.[2019]2778)).

REFERENCES

[1] Naidu VR1, Deshpande RS2, Syed MR2, Deoghare P2, Singh D2, Wakte PS3. PAT-Based Control of Fluid Bed Coating Process Using NIR Spectroscopy to Monitor the Cellulose Coating on Pharmaceutical Pellets[J]. AAPS PharmSciTech. 2017 Aug;18(6):2045-2054.
[2] Grassi S1, Amigo JM2, Lynggaard CB3, Foschino R1, Casiraghi E1. Beer fermentation: monitoring of process parameters by FT-NIR and multivariate data analysis. Food Chem. 2014 Jul 15;155:279-86.
[3] Rosas JG1, de Waard H2, De Beer T3, Vervaet C4, Remon JP4, Hinrichs WL2, Frijlink HW2, Blanco M5. NIR spectroscopy for the in-line monitoring of a multicomponent formulation during the entire freeze-drying process. J Pharm Biomed Anal. 2014 Aug;97:39-46.

[4] Khorasani M1, Amigo JM2, Sun CC3, Bertelsen P4, Rantanen J5. Near-infrared chemical imaging (NIR-CI) as a process monitoring solution for a production line of roll compaction and tableting. Eur J Pharm Biopharm. 2015 Jun;93:293-302.

[5] Mirschel G1, Daikos O1, Scherzer T2, Steckert C3. Near-infrared chemical imaging used for in-line analysis of functional finishes on textiles. Talanta. 2018 Oct 1;188:91-98.