



Application of Quality by Design in Blending Process for XLGB Capsule-Study on the Construction of Comprehensive Risk Management System for Medicine Industry

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Abstract

Improving the medical quality and guarantee the safety is the eternal theme of medical industry. Since the risk exists throughout the medical work, risk prediction and management have become an important part of industry management. The comprehensive risk management of industry has been a focus at present and could be a popular in the future. However, the study of comprehensive risk management for industries of Chinese Patent Medicine a used by manufacture organically and systematically.

Near Infrared (NIR) spectroscopy has become a widely used analytical technique in medicine industry due to its high speed acquisition and non-destructive nature, which can measure both physical and chemical properties with little or sample preparation. As NIR spectra are characterized by broad and overlapping absorption bands, assignment to specific chemical group vibrations may be rather difficult. To overcome these drawbacks, chemometrical tools such as multivariate data analysis are used to extract the useful information from NIR spectra and to correlate them with reference values.

Blending process is a mix operation resulting in a solid intermediate or API, commonly used in pharmaceutical processes. In order to obtain API products with desired and highly reproducible solid state properties (purity, polymorphism, size distribution, and density and flow ability), understanding and controlling the blending process are critical.

We present in this paper a systematic approach to apply a NIR method according to the QbD and PAT principles to both the pharmonic qualities and risk management of Chinese patent medicines Xian Ling Gu Bao Capsule (XLGB). Empirical experiments have been carried out in order to make a comprehensive comparison of these approaches. Experimental results show that they can effectively monitor the API contents during the blending process and enable an automated unequivocal decision once the predefined ending point is reached.

The outline of this paper is as follows. Section II presents a brief review of related works, before section III explains the chemo metric approaches used in our experiments together with different improvement techniques. The empirical experimental results and corresponding analysis are then presented in section IV, before some concluding remarks are made. CPM is still theoretical and lack of summary and communication of practical experience. To improve the quality of medical service and the management level of medical safety, this article summarized the innovation theory and practice on construction of comprehensive risk management of industries of Chinese Medicine; it provides prospective guidelines for future investigations that apply QbD to medicine industry. Employing the QbD concept in this way is a novel area in CPM quality.

Keywords: Near infrared; XLGB; Process analytical technology

Introduction

In China, herbs have been widely used to cure disease from ancient times which are used under the guidance of a special theory of Chinese medicine. However, the measurement of critical quality attributes of raw materials and intermediate which allowing process understanding and control is

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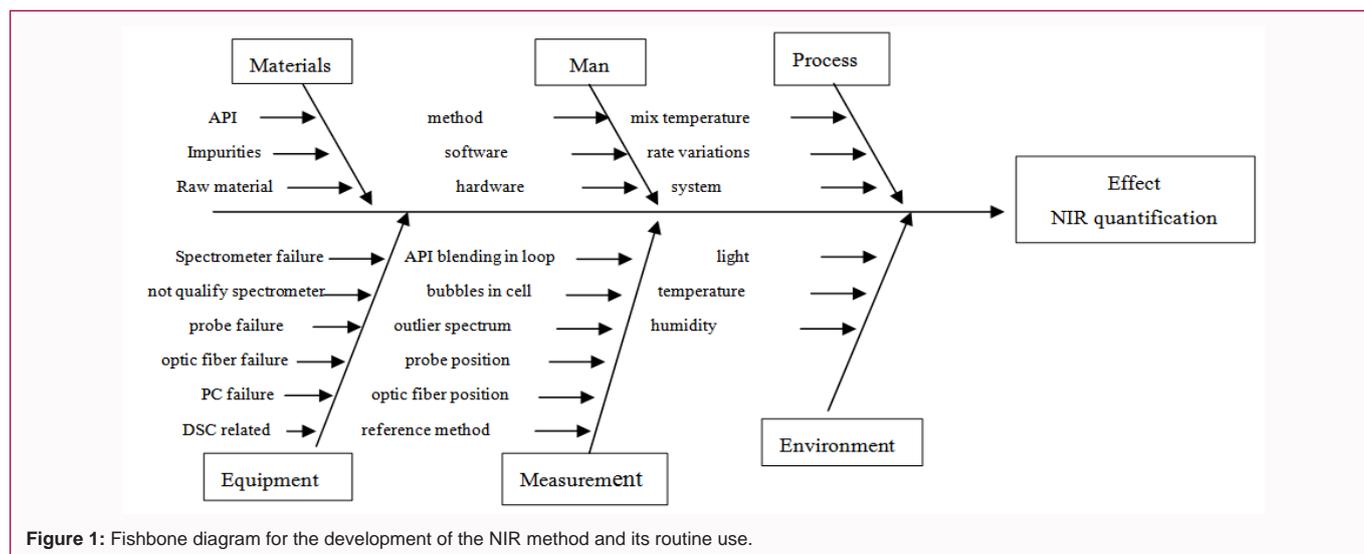


Figure 1: Fishbone diagram for the development of the NIR method and its routine use.

Table 1: Risk assessment using FMEA methodology for the development and the routine use of the NIR method.

Risk	Risk nature	Risk priority	Evaluation
spectrometer failure	controlled	low	spectra quality check test/maintenance
probe position	noise	low	Ruggedness parameter
probe contamination	controlled	low	spectra quality check test/cleaning
optical fiber position	noise	low	Ruggedness parameter
flow rate	experimental	high	Ruggedness parameter
system scale	experimental	high	Ruggedness parameter
API content	experimental	high	experimental protocol parameter
impurities content	experimental	high	DOE factor
material temperature	experimental	high	experimental protocol parameter
raw material batch variation	noise	low	Ruggedness parameter
spectrometer temperature	controlled	low	the spectrometer was placed in a thermostatic box
optical fiber temperature	noise	high	Ruggedness parameter
reference methods and sampling	controlled	low	reference methods are validated.
model parameters	experimental	high	evaluated during the method development
outlier spectrum	controlled	low	outlier detection mechanisms

a basic requirement for the medicine quality control to ensure the efficacies.

The Process Analytical Technology (PAT) initiative promoted by the Food and Drug Administration (FDA) is embraced in the Quality-by-Design (QbD) framework, introduced and developed by the ICH Q8 (R2), Q9 and Q10 guidelines that aims product and process understanding and process control, based on the scientific background and quality risk management, with the goal of ensuring a predefined final product quality. Risk is defined as an objective and probabilistic status that people are unable to control and predict. A risk assessment was conducted by involving internal experts of the process development, analytical development, Active Pharmaceutical Ingredient (API) pilot plant and manufacturing. Though the research on medicine manufacture risk management conducted later in China, it has been received more and more attention. Medicine manufacture risk management is defined as an activity that eliminates or decrease the damage and economic loss caused by manufacture organically and systematically.

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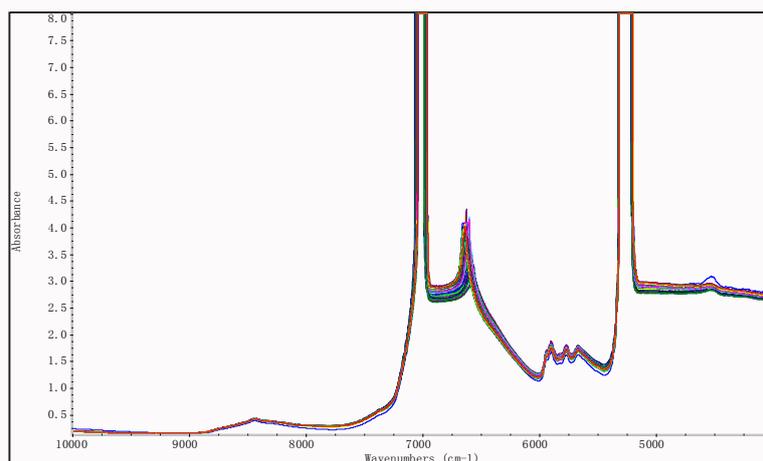


Figure 2: Overlay of the NIR spectra included in the calibration set.

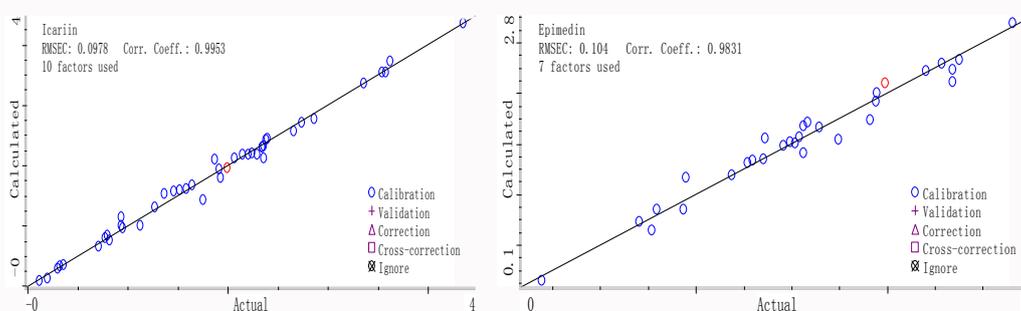


Figure 3: The NIR predictions and chromatographic reference values for the 2 analytes.

Xian Ling Gu Bao capsule (XLGB). Empirical experiments have been carried out in order to make a comprehensive comparison of these approaches. Experimental results show that they can effectively monitor the API contents during the blending process and enable an automated unequivocal decision once the predefined ending point is reached.

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Related Work

The construction of the framework is the most important things, thus industry administrators should assume the responsibility for risk management and control. Various modern approaches have been applied to investigate the pharmonic qualities and risk management of Chinese patent medicines. They can be roughly classified into two major categories. The first uses approaches as HPLC, GC and so on in order to unveil the ingredient and content of the medicine. Alternatively, modern biological techniques are applied, aided by bio-chip or bio-chemistry etc, in order to give a scientific interpretation of the medicine. However, neither approach makes a break-through because of its own hindrance in various aspects.

Several NIR spectroscopy applications in the pharmaceutical field concerning the monitoring of analyte solute concentration

were reported. Naidu et al. [1] developed correlation between the NIR spectra and cellulose content which is useful in precise at-line prediction of functional coat value and can be used for monitoring the Wurster coating process. However, it does not give an in-depth discussion about pros and cons of various chemometrics in their applications, and therefore provide little useful hints to real works. Similarly, Grassi et al. [2] investigated the capability of Fourier Transform-Near Infrared (FT-NIR) spectroscopy to monitor and assess process parameters in beer fermentation at different operative conditions, but provides little insight of how to apply this technique in practice.

Rosas et al. [3] monitored physicochemical changes of the formulation during freeze-drying by NIR spectroscopy, several spectral pre-processing techniques and spectral data analysis techniques such as the mean of selected wave numbers (Mws), the correlation coefficient (CorrCoef) and Principal Component Analysis (PCA) have been evaluated and compared. We evaluate alternative chemometric techniques in our work. Khorasani et al. [4] studied the application of Near Infrared-Chemical Imaging (NIR-CI) supported by chemometric modeling as non-destructive tool for monitoring and assessing the roller compaction and tableting processes. In this study, the critical process parameter and critical quality attributes were identified and a design space was established.

Mirschel et al. [5] demonstrated for the first time that Near Infrared (NIR) chemical imaging can be used for in-line analysis of textile finishing processes based on impregnation. It was shown that this method is able to detect and visualize various inhomogeneities on

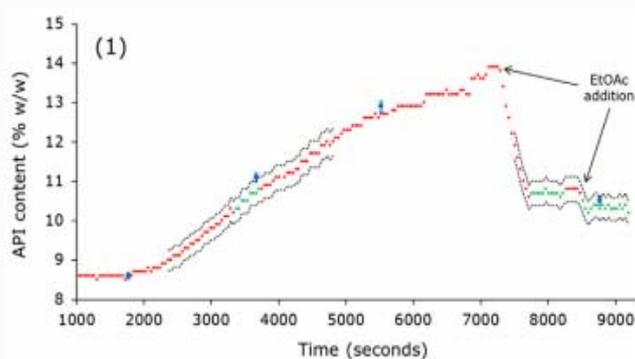


Figure 4: Real-time monitoring of the API content performed by the NIR method during the blending process, the green triangles represent the predictions in the range of the seeding acceptance criterion whereas the red points represent the predictions out of this range. The dashed lines represent the uncertainty of the method over the range of validation.

Table 2: PLS model characteristics for the API content.

model feature	model		
	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			
R ² _c	0.9453	0.9678	0.9831
R ² _{cv}	0.167	0.124	0.159
RMSEC(% W/W)	0.198	0.189	0.104
RMSECV(% W/W)	0.0056	0.0057	0.0023

the finished textiles resulting from processing defects or from various technical effects that may influence the drying process and consequently the spatial distribution of the finish. However, their works mainly focus on the development methodology and software architecture aspects of the system instead of the chemometrics used.

In comparison, our work focuses on in-depth comparison and analysis of various chemometrics available, as well as their pros and cons. We will create a potential variable map that can have an impact on the desired NIR method quality attributes to summarize the risks.

Chemometric Techniques

Various chemometric approaches have been developed for on-line process monitor purpose. We choose some of the most popular and successful approaches in our experiments. Mathematical statistics is a kind of quantitative analysis method that is adapt to analysis, judgment, and evaluation. As Chinese patent medicine is a complex chemical system, a single index is difficult to reflect security, validity and operation marks. Many indexes comprehensive assessment is becoming the developmental tendency of quality assessment and control of Chinese patent medicine, recently it is extensively applied.

Clustering analysis

The clustering analysis is a method of mathematics statistics that study "birds of a feather flock together". The clustering analysis can classify some objects of observation according to some quantitative character, and it is widely used in the fields such as biology, medicine and so on. And it is also often used in the quality of Chinese traditional medicine now a day.

Fuzzy clustering analysis is common used in the quality of Chinese traditional medicine. When using Fuzzy clustering analysis, firstly, standardization of the data, then choosing desirable qualities classification of medicine as the sample set, regard some indexed that the sample measured as the initial data. Because initial data may have different dimensions it may be not in [0,1], we must make standardization change according to the formula of standardization, i.e., compressing the data into [0,1] according to the fuzzy theory, and thus we can compare the medicine with each other, building fuzzy similar matrix which concluded subjective evaluation and equation. Then classifying the quality according to the fuzzy matrix R, the classifying the quality according to the fuzzy matrix R, the method such as netting method, Boole matrix method, transitive closure method, step-wise partitioning method.

Discriminant analysis

Discriminant analysis is a definite classifies technology. It classified object according to some indexes which we observed. Discriminant analysis is that the object studied is classified and obtains a number of various known samples of the observation data, establishes the discriminant in this foundation, then carries on the discriminant classification to the unknown type sample. Using discriminant analysis method, through some recognition index (for example: Active constituent quantity), conducting multiple regression for some simple measurable physical and chemical indexes, using variance analysis return and examination technology, we may screen out from these index and finally give the discriminant function. This method concludes four types: maximum likelihood method, which is based on the theory of probability in the multiplication law about independent event and is suitable in various indexes that is qualitative or the semi-quantitative situation; discriminant analysis of Fisher's method, which is used between two or more than two types, but commonly used in the condition of two kinds; discriminant analysis of Bayer's method, which carries on the evaluation quality about new sample that is out of "class" and request each kind class to subject to multivariate normal distribution; logistic regression method, which doesn't request the multivariate normal distribution and use two types of discriminant, so we can use it in various indexed that are two-valued variable or semi-quantitative situation.

Analysis of principal component

We made many observations on the same individual referring to many random variables all of that are reflection to individual nature. Apparently they are identified with each other, substantially, amount

of information is irregularity and it is hard to colligate. We can use the method of analysis of principal component to set down one or several better aggregative indicators that independently represent one of numerous aspects. The method of analysis of principal component is to choose characteristic best related to the question to take part in sorting. In recent years, the method of analysis of principal component is widely applied in the discriminatory analysis of quality traditional and herbal drugs.

Artificial neural networks

Artificial neural network is a nonlinear science emerging rapidly in the middle of 20C 80S that is applied in the area of pattern recognition, data processing and automation controlling and so on, and get satisfactory results. Artificial neural network is an information processing system of simulating working function of human brain. It builds on human brain nervous system processing the information, and is on the theoretical basis of mathematic network topology, and is characterized by jillion parallelism, altitudinal ability of fault tolerance, integration of processing and storing information, and function of self-organization and self-studying. At the moment, it is BP (back propagation) that is an artificial neural network extensively adopted. It is characterized by strong nonlinear capability, and the capability of self-organization, adapting and self-studying, altitudinal fault tolerance and robustness. This network has three layers that are input layer, output layer and hidden layer corresponded to input, transition and output. Artificial neural network applies cross-correlation technique to get electrical signals or image that is full reflection of inner quality of traditional and herbal drugs, makes a comprehensive assessment of traditional and herbal drugs, and quality control for it.

With gradual penetration of traditional and herbal drugs complex system certification, many kinds of mathematics statistics method will be further applied in the traditional and herbal drugs quality assessment. Moreover, make fundamental action characteristic of medicative material of traditional and herbal drugs be best characterized, and reflect the quality of traditional and herbal drugs more objectively to embrace control quality of that.

Experimental Results and Analysis

A Fourier transforms process analyzer near infrared spectrometer with InGaAs detectors and equipped with an immersion transmission probe was used to record in and on-line data at laboratory.

Risk assessment

The ICH Q9 guideline describes the principles and tools of quality risk management to guide development efforts. A fishbone diagram, as shown in Figure 1 was created to map potential variables that have an impact on the desired NIR method quality attributes. In total 6 categories were identified: equipment, measurement, environment, materials, man and process. Subsequently a risk assessment was performed according to the Failure Mode Effects Analysis (FMEA) method, which allowed risk mitigation and brought into focus the main process variables or high risk variables of the NIR measurement dynamics.

Table 1 summarizes the risks, either identified as having a key influence on the models development, on the method validation or on the future routine application. Risks were first categorized as controlled, noise or experimental. For each risk, severity, probability and detectability were evaluated, resulting in a risk priority level

categorized as low, medium or high. Factors with high risk priority were included in the experimental design both in development and validation.

NIR method development

NIR spectra: Figure 2 plots an overlay of the raw NIR spectra recorded forming the calibration set in the range 4000 cm^{-1} to 12000 cm^{-1} . Band assignment to specific chemicals group is difficult. However the bands of interest of API were identified using NIR bands correlation table. The range 5000 cm^{-1} to 5200 cm^{-1} encompasses N-H and O-H combination bands. The range 7000 cm^{-1} to 7200 cm^{-1} contains the O-H 1st overtone band and combinations of this band. Moreover, the ranges 5200 cm^{-1} to 6000 cm^{-1} corresponding to the 1st overtone of -CH, -CH₂, -CH₃ bonds, can be attributed predominantly to the organic solvents.

Qualitative models building: Predictive NIR models based on PLS regression were computed to quantify the 2 analytes using the data from the calibration set. The calibration model optimization encompassed the following steps: number of PLS factors selection, outlier's detection and elimination, spectral range and spectral pre-treatment selection. Internal validation using a random subsets cross-validation was carried out to estimate models performance. The number of PLS factors was chosen such as the prime factor for which no significant variation of the RMSECV value was observed.

Different spectral pretreatments were investigated in order to improve the models prediction ability. Three pre-treatments were selected: linear baseline correction, 1st and 2nd derivative. The linear baseline correction was performed between 2 points at 5400 cm^{-1} to 6000 cm^{-1} and 7100 cm^{-1} to 7300 cm^{-1} , with the aim to reduce spectral drift. The 1st and 2nd derivatives were computed according to the Savitsky-Golay algorithm based on 7 smoothing points and a second order polynomial, in order to improve the resolution of overlapped bands and attenuate baseline offsets as shown in Table 2.

As shown in Figure3, a good agreement between the NIR predictions and chromatographic reference values both during calibration and validation for the 2 analytes. All model candidates have a small number of PLS factors. For each analyte model, the RMSEC and RMSECV values as well as their difference values are low. These results demonstrate a good global predictive performance and robustness of the candidate models for both analytes.

Real-time monitoring of the API and detection of the seeding point: The ability of the NIR method to monitor in real-time and simultaneously the 2 analytes contents, and consequently to detect the seeding point, was assessed by mimicking the blending process at laboratory scale. Out of Figure 4, it can be noticed that the NIR predictions of the two analytes present good agreement with the reference values taking into account the uncertainty of the NIR method.

Conclusion

This paper presents our works on applying quality by design in blending process for XLGB capsule to research on Chinese patent medicines. This is aim to unveil the underlying associations between API of the medicine and an automated unequivocal decision once the target composition to initiate the seeding was reached.

In our study, an analytical method based on NIR spectroscopy was developed as a PAT tool in order to determine on-line the API

during the blending process. Various chemometrics methods have been evaluated independently in order to ensure that it is fitted for its intended use. We identify PLS model as the most accurate one among all these models. A real-time process monitoring was performed following the validation phase to prove and document that the method is fitted for purpose.

Our results can be used as a guideline for future researches on Chinese patent medicine, particularly in the manufacturing process of new medicines. Its use as a primary method to control the blending step will enable several valuable benefits including reduction of process time, suppression of a particular difficult sampling and tedious off-line analyses.

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