NIR Determination of Three Critical Quality Attributes in Alcohol Precipitation Process of Lonicerae Japonicae with Uncertainty Analysis

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***Abstract*—The aim of this study was to investigate the feasibility of near infrared (NIR) spectroscopy and multivariate calibration (MVC) techniques in monitoring and understanding of the alcohol precipitation process of water extract of Lonicerae Japonicae within the framework of ICH's Quality by Design (QbD) and FDA's process analytical technology (PAT). The contents of Chlorogenic acid, Luteoloside and soluble solid were identified as three critical quality attributes (CQAs) to be monitored. After a comparison of different spectra preprocessing methods, the raw NIR spectra were applied to multivariate modeling. By the interval PLS (iPLS) method, three characteristic wavebands, 8802~7605 cm^{-1}, 6001~6201 cm^{-1} and 7605~7308 cm^{-1}, were selected for Chlorogenic acid, Luteoloside and soluble solid, respectively. PLS quantitative models based on these wavebands showed much improved performance. Moreover, prediction uncertainty was denoted and visualized by both the PLS confidence interval and simple interval calculation (SIC) interval. And a new index—Extent of Uncertainty (E_u) is proposed to assess the magnitude of uncertainty for CQAs with different dimensions in the same scale. The overall results provided the useful understanding of and deep insight into the alcohol precipitation process of Chinese herbal medicine (CHM).**

Keywords- alcohol precipitation; near infrared; multivariate calibration; uncertainty; Quality by Design; process analytical technology; Chinese herbal medicine

I. INTRODUCTION

In 2005, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) defines Quality by Design (QbD) in the annex of ICH Q8 as "a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management" [1]. The QbD principles increase process knowledge and product understanding, usually by the application of new technologies such as Process Analytical Technology (PAT) initiated by the U.S. Food and Drug Administration (FDA) in 2004 [2]. These guidance documents are not regulatory but to encourage the pharmaceutical innovations and quality assurance.

The principles of QbD and PAT are originally employed only for chemical drugs. Nevertheless, the concept behind PAT and QbD is recently more and more introduced and applied to Chinese herbal medicine (CHM) preparations [3-4], because they are very appropriate for the CHM industry to facilitate the use of innovative technologies, reduce production cost, increase the efficiency of manufacturing process, improve the final products quality and assure the clinical safety.

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Alcohol precipitation is one of the most important purification techniques in preparation of Chinese herbal medicines, and is typically operated in a batch-wise manner. Through alcohol precipitation, the unwanted components such as inorganic acid salt, starch, proteins, polysaccharide, etc. which are poorly dissolved in ethanol are precipitated, while the effective chemicals with good solubility in both water and alcohol are preserved. The effect of alcohol precipitation is related to a number of critical process parameters (CPPs), like the temperature and density of water extract, speed of agitation and adding of ethanol, the final concentration of ethanol, etc. And the change of the starting materials and interaction of CPPs often result in the lot-to-lot variation. In order to enhance the batch reproducibility of alcohol precipitation, Huang [5] proposed the multivariate batch monitoring technique. However, until now, few studies have been focused on monitoring the multiple critical quality attributes (CQAs) during the process of alcohol precipitation.

In this article, near infrared (NIR) spectroscopy is investigated as a PAT tool to monitor the alcohol precipitation process of water extract of Lonicerae Japonicae, which is the key production unit of Qingkailing Injection specified in Chinese Pharmacopeia (Ch.P. 2010 edition, Volume I). The contents of Chlorogenic acid, Luteoloside and soluble solid are identified as the three CQAs, since Chlorogenic acid and Luteoloside are proved to be pharmacologically active [6,7] and soluble solid is linked with the intermediate purity.

The concept of "risk assessment" under the framework of QbD and PAT is realized in this study by the evaluation of NIR prediction uncertainty. Two types of prediction intervals, the confidence interval and simple interval calculation (SIC) interval whose assumptions are based on error normality and error finiteness [8], respectively, are compared and discussed. And a new index to indicate the level of prediction uncertainty for different CQAs in the same scale is proposed.

II. THEORY

A. Multivariate Calibration (MVC)

In this paper, partial least squares (PLS) is applied to relate the reference analysis results of the three CQAs to the NIR spectra obtained from the alcohol precipitation process of Lonicerae Japonicae. The number of latent variables is optimized by leave-one-out (LOO) cross-validation method and the statistics of the root mean squared error of cross-validation (RMSECV) and predicted residual error sum square (PRESS) [9]. The quality of the PLS model built is

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evaluated in terms of correlation coefficient (r), the root mean squared error of calibration (RMSEC), RMSECV, the root mean squared error of prediction (RMSEP) and residual predictive deviation (RPD) [10,11].

B. Uncertainty Evaluation

1) PLS Confidence Interval (CI): PLS CI aims at indicating the PLS prediction uncertainty. However, until now, there are no generally accepted approaches to estimate the PLS CI. Bouckaert [12] compared different methods for estimating PLS CI, including the classic ordinary least squares (OLS) method, the U-deviation method and linearization method. Aji [13] proposed a bootstrap method to determine the PLS CI, and Boiret [14] adapted this method to the pharmaceutical environment. In this article, the most prevalent formulation (see Eq.1) to calculate the PLS CI in industrial applications [15] will be applied in the error estimation of the three CQAs.

$$[\hat{Y} - t_{\alpha/2,n-k-1}s, \hat{Y} + t_{\alpha/2,n-k-1}s,] \quad (1)$$

where $\hat{Y}$ is PLS prediction value from the NIR spectrum, t is the Student's t distribution, α is the significance level, n is the number of spectra used in the calibration set, k is the number of principal components selected for building the calibration model and s is denoted as follows:

$$s = RMSEC(1 + H_0)^{1/2} \quad (2)$$

where RMSEC is a measurement of how well spectra data correlates to the values of CQAs in model development and

$$H_0 = t(T'T)^{-1}t \quad (3)$$

where H_0 equals the PLS leverage and is proportional to the Hotelling T^2 statistic.

2) SIC interval: Different from the PLS CI method who assumes that the distribution of the estimated error is normal, the simple interval calculation (SIC) method is based on a single postulate that all errors involved in calibration problem are finite [16].

Consider the PLS model in our case as

$$Y = Xa + \varepsilon \quad (4)$$

where X represents the matrix of NIR spectra, a is the vector of regression coefficient and ε is the vector of error.

Error finiteness means that there is a maximum error deviation (MED, represented by β) of ε. MED is usually unknown. In this work, only the upper limit of β (β_{SIC}) that approximates four times of RMSEC [17] is utilized. Then, for a given calibration set (X, Y), the following inequation is established:

$$Y_i^- < X_i^T b < Y_i^+ \quad (5)$$

where $Y_i^- = Y_i - \beta$, $Y_i^+ = Y_i + \beta$, i = 1, 2, ···, n

In Eq.5, b is the region of possible values (RPV) that stands for the parameter's space, and n is the number of samples in X. When a new sample's spectrum (x) is obtained, the predicted value $y = x^t b$ belongs to the interval:

$$V = [v^-, v^+], \text{ where } v^- = \min(x^t b), v^+ = \max(x^t b) \quad (6)$$

V in Eq.6 is the SIC prediction interval. v^- and v^+ are calculated by linear programming algorithm.

III. Materials and Methods

A. Materials

Chlorogenic acid and Luteoloside were obtained from National Institute for the Control of Pharmaceutical and Biological Products (NICPBP, Beijing, P. R. China). Flos Lonicerae Japonicae was purchased from Beijing Ben Cao Fang Yuan Medicine Co. LTD. (Beijing, P. R. China). Methanol (Fisher Scientific, USA), acetonitrile (Fisher Scientific, USA), formic acid (Sigma-Aldrich Co. LLC, USA), glacial acetic acid (Beijing Chemical Works, P. R. China), and distilled water (A.S. Watson Group Ltd, Hong Kong of China) were of HPLC grade and all other reagents were of analytical grade.

B. Description of Alcohol Precipitation Process

Before alcohol precipitation, the water extract of Flos Lonicerae Japonicae with required densities was prepared according to the procedure of Qingkailing Injection specified in Ch.P. (2010 edition, Volume I). The alcohol precipitation process was carried out in a cylindrical glass reactor with a volume of about 3L. Reactor agitation was provided by RW20 digital overhead stirrer (IKA Works, Germany). The stirring speed was maintained at 500 rpm. 95% alcohol was pumped into the reactor form the alcohol storage tank with a constant flow rate of 75 mL·min^{-1}. At the beginning of each batch of the alcohol precipitation process, the agitator and the pump were turned on simultaneously soon after 0.4 L concentrated water extract was added into the reactor. The alcohol precipitation process was lasted for 30 min. During the process, when the predefined amount of ethanol was added, the pump was turned off to stop the adding of alcohol.

C. Experimental Setup

To determine the three CQAs, 12 batches of alcohol precipitation were performed as arranged in Table I. The 12 batches were divided into three groups in connection with three CQAs. For example, Group 2 of Batches 5 to 8 was used to build the NIR quantitative model to determine the content of Luteoloside. In each group, the calibration set was constructed with one normal batch and two fault batches, and the left one normal batch was treated as the validation set. The fault batches, by changing the densities of the starting material and volume of the 95% alcohol added, were used to expand the variation coverage of the calibration set.

During each precipitation process, 1.5 mL suspension liquid was drawn by a pipette gun at the fixed position in the reactor every 0.5 min, and 61 samples including the one sampled at 0 min were hence prepared. All samples were treated by centrifugation at 5976 × g for 10 min before a further analysis.

TABLE I. EXPERIMENTAL RUNS

No. of Group	CQA	No. of Batch	Normal / Fault batches	Calibration / Validation set	Densities of water extract	alcohol added (L)
1	CA	1	N	Val.	1.10	1.50
		2	N	Cal.	1.10	1.50
		3	F	Cal.	1.05	1.71
		4	F	Cal.	1.15	1.71
2	LU	5	N	Val.	1.10	1.50
		6	N	Cal.	1.10	1.50
		7	F	Cal.	1.15	1.50
		8	F	Cal.	1.05	1.50
3	SS	9	N	Val.	1.10	1.50
		10	N	Cal.	1.10	1.50
		11	F	Cal.	1.15	1.33
		12	F	Cal.	1.05	1.33

D. NIR Spectroscopy

The sample after centrifugation was filled into a quartz cuvette (8 mm in diameter) covered with a plastic cap. Then, an Antaris Nicolet FT-NIR system (Thermo Fisher Scientific Inc., USA) was utilized to collect the spectra in transmittance mode. Each spectrum was the result of averaging 16 scans of 4 cm^{-1} resolution in the 10000 to 4000 cm^{-1} region. For every sample, triplicate spectra were obtained and the 3 spectra were averaged for use in the calibration model. All NIR data were collected and archived using the Thermo Scientific RESULT software.

E. Reference Analysis

1) HPLC Determination: HPLC separations were performed on Agilent 1100 HPLC system with integrated four gradient systems, vacuum degasser, autosampler, temperature controlled column compartment and diode array detector (DAD) detector (Agilent Technologies, USA).

a) To assay the Clorogenic acid, an Agilent XDB C18 column (250 × 4.6 mm, 5 μm) was utilized with a mixture of methanol and 0.1% formic acid water solution (20:80, v/v) as the mobile phase. The column temperature was controlled at 30℃. The spectrometer was set at 327 nm. The flow rate was maintained at 1 $mL \cdot min^{-1}$. The samples of Group 1 after NIR scanning were diluted by 50% methanol water solution appropriately. Then the diluent was filtered through a 0.45 μm Millipore filter membrane, and 10 μL aliquot of filtrate was injected into the HPLC system for analysis.

b) For the determination of Luteoloside, the separation was performed on Agilent ZOBAX SB-Phenyl column (250×4.6 mm, 5 μm) controlled at 30℃. Acetonitrile (A) and 0.5% glacial acetic acid solution (B) were the mobile phase. The gradient program was as follows: initial 10% (A); at 0–30 min, linear change from 10% to 30% (A). The signal was recorded at 350 nm and the flow rate was 1 $mL \cdot min^{-1}$. The samples of Group 2 after NIR scanning were directly filtered by 0.45 μm membrane filter, and 5 μL of filtrate was injected into the HPLC system for analysis.

2) Soluble Solid Content Measurement: After NIR analysis, 0.5 mL of one sample in Group 3 was drawn into a penicillin bottle. The penicillin bottle with liquid was weighted and then was oven dried at 110℃ to the constant weight. Then, the soluble solid content (S %) could be calculated by the Eq.7:

$$S\% = \frac{W_{bottle+solid} - W_{bottle}}{W_{bottle+liquid} - W_{bottle}} \times 100\% \quad (7)$$

Where W_{bottle} means the weight of the penicillin bottle; $W_{bottle+liquid}$ is the weight of penicillin bottle with 0.5mL liquid; $W_{bottle+solid}$ is the constant weight of penicillin bottle with soluble solid.

F. Software and Computing

The software Matlab 7.0 (MathWorks Inc., USA) combined with PLS_Toolbox 2.1 (Eigenvector Research Inc., USA) was used in PLS regression. SIMCA P + 11.5 (Umetrics, Sweden) served as chemometric tool for data preprocessing, and iToolbox (The Royal Veterinary and Agricultural University, Denmark) for variable selection. SIC interval V and β_{sic} were computed using the SIC Toolbox (Semenov Institute of Chemical Physics, Russia).

IV. RESULTS AND DISSCUSSION

A. Results of Reference Analysis

Since the HPLC methods used here are recommended by the Ch.P. (2010 Edition, Volume I), the accuracy and reproducibility of the methods have already been approved officially. The linearity tests for the quantitation of Clorogenic acid and Luteoloside were carried out over the range 2.01 - 80.4 $\mu g \cdot mL^{-1}$ and 2.014 - 80.56 $\mu g \cdot mL^{-1}$, respectively. The parameters of the calibration curves y = 16.446x - 2.6209 (r = 0.9998) and y = 12.168x - 1.5585 (r = 0.9999) for Clorogenic acid and Luteoloside, respectively, demonstrate the good linear relationship between peak area (y) and concentration (x) of equivalent components. A summary of HPLC analysis and soluble solid content measurement can be found in Table II. All the reference values in the validation sets are within the ranges of the calibration sets, indicating that the established calibration sets cover a suitable wide range of variability.

B. Preprocessing of NIR Spectra

The profile of the original process NIR spectra are exemplified by three time points from Bacth 2 shown in Fig.1. Before the calibration model development, the most prevalently used preprocessing methods or the chained combination of them, such as Savitzky-Golay (S-G) smoothing, derivatives, multiplicative scatter correction (MSC), standard normal variate transformation (SNV), wavelet de-nosing of spectra (WDS), etc. were compared and investigated (results not listed).

The preprocessing effects for the three CQAs were similar. The S-G smoothing, WDS and no pretreatment to the original spectra outperform other methods in both the model calibration and prediction denoted by the relatively low RMSEC, RMSECV, RMSEP and high RPD. Since the three methods have almost the same preprocessing abilities, considering for the actual application, the original spectra without any pretreatment are employed in quantitative model development to save the computing time.

TABLE II. A SUMMARY OF REFERENCE ANALYSIS

CQA	Calibration set		Validation set	
	Lower bound	*Upper bound*	*Lower bound*	*Upper bound*
CA (mg·mL^{-1})	0.9319	9.8842	1.4103	7.0962
LU(μg·mL^{-1})	22.56	154.55	28.87	133.88
SS (g·mL^{-1})	0.0284	0.2318	0.0299	0.2226

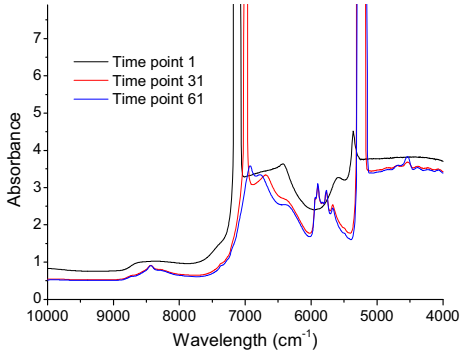

Figure 1. Raw NIR spectra selected at three time points of Batch 2. (Time point 1 corresponds to 0 min; Time point 31 corresponds to 15 min. Time point 61 corresponds to 30 min.)

C. *Waveband Selection*

After the comprehensive study of preprocessing methods, however, little improving of the calibration model was observed. This phenomenon may be related to the noisy or redundant information carried by the full length NIR spectra. Therefore, the interval PLS (iPLS) was applied to select the useful waveband and could also be helpful in interpretation of the NIR data.

In the iPLS method, the spectra were first split into a number of non-overlapping intervals. Then, each interval underwent a separate PLS modeling and the RMSECV was minimized to detect the optimal intervals. In this paper, for the three CQAs, the numbers of intervals were all optimized in the range between 2 and 100 at an increment of 2. The optimal numbers of interval were 5, 30 and 20 for Chlorogenic acid, Luteoloside and soluble solid, respectively. The corresponding results of iPLS regression are presented in Fig.2 The three wavebands selected by iPLS method are 8802~7605 cm^{-1}, 6001~6201 cm^{-1} and 7605~7308 cm^{-1} for Chlorogenic acid, Luteoloside and soluble solid, respectively.

D. *Model Calibration and Validation*

With the potential wavebands we explored, PLS models were built to determine the three CQAs. In each group, there were 183 samples in the calibration set and 61samples in the validation set. For each individual PLS model, the number of PLS latent factor was optimized and chosen mainly according to the RMSECV and PRESS statistics. Taking soluble solid content for instance, 7 factors were adequate to perform both the model calibration and validation based on the waveband of 7605~7308 cm^{-1} (see Fig.3).

Table III shows the summary of modeling statistics. From the calibration point of view, the low RMSEC and RMSECV demonstrated the success of the waveband selection. From the validation point of view, the models built on the iPLS selected wavebands also exert good prediction capability.

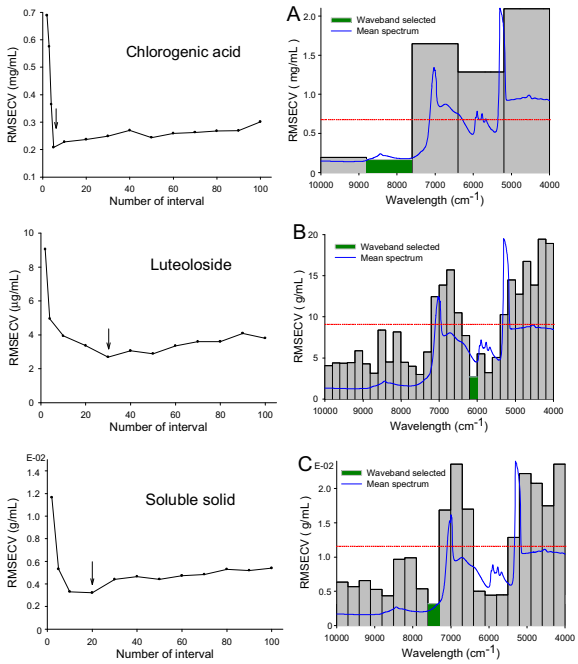

Figure 2. iPLS regression. Bars represent the optimized RMSECV for each interval. Green bar is the optimal waveband selected. Blue line is the mean spectrum scaled by the Y axis. The red dotted line is RMSECV for the global model using 4, 4 and 7 latent factors for Chlorogenic acid (A), Luteoloside (B) and soluble solid (C), respectively.

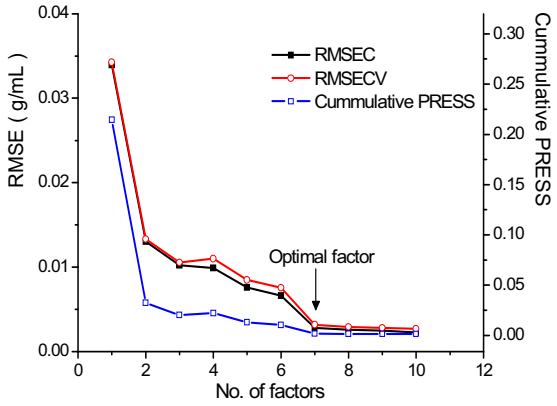

Figure 3. The optimal latent factor selected for soluble solid content based on the waveband of 7605~7308 cm^{-1}.

TABLE III. MODELING STATISTICS FOR DETERMINATION OF CHLOROGENIC ACID (CA), LUTEOLOSIDE (LU) AND SOLUBLE SOLID (SS)

CQA	Waveband	LVs	Calibration set			Validation set		
			r_{cal}	*RMSEC*	*RMSECV*	r_{val}	*RMSEP*	*RPD*
CA	8802~7605 cm^{-1}	7	0.9928	0.181	0.204	0.9943	0.290	4.97
LU	6001~6201 cm^{-1}	6	0.9968	2.35	2.68	0.9975	3.64	7.69
SS	7605~7308 cm^{-1}	7	0.9979	2.80E-03	3.16 E-03	0.9990	2.16E-03	20.46

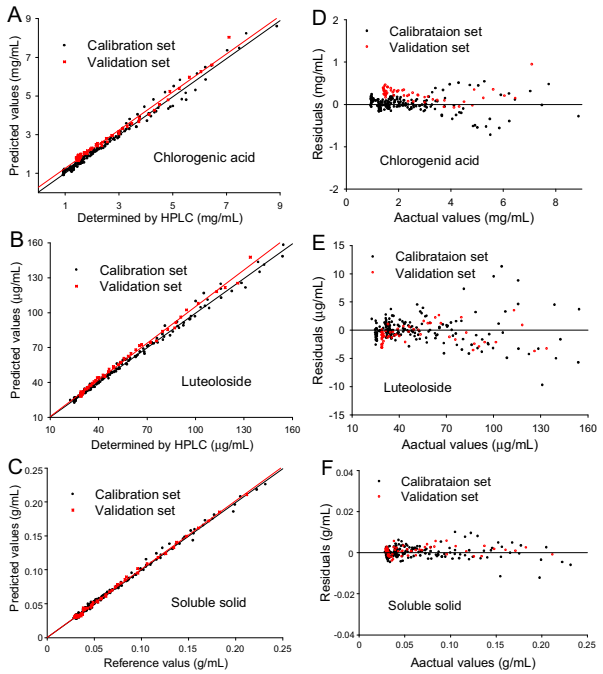

Figure 4. The correlation diagrams and residual plots.

Finally, the correlation plots of actual values determined by reference methods and values predicted by NIR spectra are plotted (see the correlation diagrams in Fig.4A, B and C). The prediction residuals for both the calibration sets and validation sets of the three CQAs are shown in Fig.4D, E and F. The linearity of the regression lines is favorable. The mean percent errors (ratios of residuals to actual values) are about 13.33%, 2.96% and 3.58% for Chlorogenic acid, Luteoloside and soluble solid, respectively, demonstrating that the models developed are satisfying.

E. Uncertainty Analysis

Prediction Interval: There is a practical need to assess the uncertainty of the PLS predicted results, because such prediction could be related with the quality, efficacy and even patient safety of the final products. As illustrated in Section II.B in this article, two kinds of uncertainty indexes, the PLS confidence interval (CI, α=0.95) and SIC interval (SI), are calculated and plotted for the three validation sets (Batch 1, 5 and 9 in Table 1) of the three CQAs.

Seen from Fig.5, CI and SI are quite different for the uncertainty analysis. The PLS CI seems unchanged during the precipitation process, whereas the SI varies for each individual sample. Generally, the mean width of SI in one batch approximates twice that of CI (see Table IV), which can be mainly attributed to the values of student t (1.9735 in our case, with α=0.95) in Eq.1 and β_{SIC} (about four times of RMSEC) in Eq.5. For the particular time points in the alcohol precipitation process, such as the time point when the adding of alcohol is stopped, the final time point, etc. prediction with individual uncertainty interval is sometimes more helpful in practice. Therefore, a combination use of SI and traditional CI could help the operator make the right judgment.

1) Extent of Uncertainty: In order to evaluate the magnitude of prediction uncertainty, a new index—Extent of uncertainty (E_u) is proposed:

$$E_u = \frac{W_{\text{interval},i}}{Y_{predict,i}} \quad i = 1,2,\cdots,n \tag{8}$$

where $W_{interval}$ is the width of prediction interval (CI for calculating E_u-CI; SI for E_u-SI); $Y_{predict}$ is value of CQA predicted by NIR spectra; i is the number of time point. By E_u, the uncertainty will be assessed in the same scale for different CQAs or different time points in the whole process.

Values of E_u for the three CQAs in the validation sets are calculated and plotted in Fig.5. As the width of CI is almost the same in the process, the trend of E_u-CI is opposite to change of content of the CQA. Nevertheless, there is no regular form for E_u-SI. Taking Chlorogenic acid for example, it can be deduced that the prediction with large values of E_u-SI is weaker from time point 25 to 50 than other time points.

To compare the extent of prediction uncertainty of the three CQAs, the mean of Eu is computed shown in Table IV. The smallest uncertainty is observed for the prediction of Luteoloside. What's more, there is a good correlation between the mean of E_u and the mean of percent errors, approving that the new index E_u is very useful in evaluating the prediction uncertainty.

V. CONCLUSIONS

In this paper, Three PLS models were successfully constructed to determine the three CQAs during the process of alcohol precipitation of Lonicerae Japonicae. The original spectra without any pretreatment were capable to perform the multivariate modeling. By using iPLS method, three distinct wavebands of 8802~7605 cm^{-1}, 6001~6201 cm^{-1} and 7605~7308 cm^{-1} were selected for Chlorogenic acid, Luteoloside and soluble solid, respectively, and significantly improved the performance of PLS models compared to that without variable selection. Moreover, the PLS prediction uncertainty was denoted by the SIC interval as well as conventional confidence interval. And SIC interval was more sensitive to estimate the individual prediction error. The proposed new index, Extent of Uncertainty (E_u) provided a useful insight into the uncertainty level of CQAs with different dimensions.

TABLE IV. A SUMMARY OF REFERENCE ANALYSIS

CQA	Mean width of prediction interval		Mean of E_u	
	CI	*SI*	*CI*	*SI*
Chlorogenic acid ($mg \cdot mL^{-1}$)	0.78	1.68	0.38	0.79
Luteoloside ($\mu g \cdot mL^{-1}$)	9.43	21.56	0.22	0.43
Soluble solid ($g \cdot mL^{-1}$)	1.15 E-02	2.56 E-02	0.25	0.54

CI represents the confidence interval; SI represents the SIC interval.

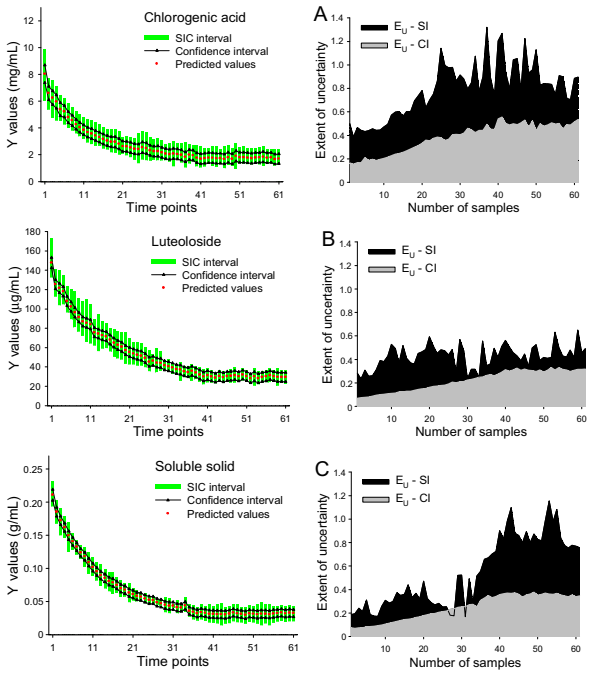

Figure 5. Visualization of the prediction intervals and extent of uncertainty at different time points of the ethanol precipitation process. SI represents the SIC interval; CI represents the confidence interval. Chlorogenic acid (A), Luteolosideand (B) and soluble solid (C).

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