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Research Article

An Approach to Rapid Determination of Tween-80 for the Quality Control of Traditional Chinese Medicine Injection by Partial Least Squares Regression in Near-Infrared Spectral Modeling

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This study established an approach to rapidly determine the Tween-80 in traditional Chinese medicine (TCM) injection by using near-infrared (NIR) spectroscopy. Totally 133 standard solutions of Tween-80 were prepared and randomly divided into calibration set and validation set, containing 109 and 24 samples, respectively. Spectral data were preprocessed and then subjected to establish a predictive model using partial least-squares (PLS). The standard error of cross validation (SECV), standard deviation of calibration (SEC), and the determination coefficient (R) of the established model were 0.0561, 0.0526, and 0.9986, respectively. The model was successfully applied to determine Tween-80 contents in 25 *XBJ Injections* and 40 *FFSX Injections*, and it produced satisfactory quantitative analysis results with average relative deviations 0.60% and 0.16%, respectively, for 25 *XBJ Injections* and 40 *FFSX Injections*, and the maximum relative deviations 8.57% and 7.60%, respectively. This work shows that NIR model displayed quite good predictive ability for Tween-80 quantitative analysis, which could potentially be applied to rapid determination of Tween-80 in the production process of TCM injections and other TCM products.

1. Introduction

Traditional Chinese medicine (TCM) injection is a new dosage form developed in the modernization of TCM. It displays exact efficacy in clinical practice but raises a controversy either due to its possible adverse reactions [1–3]. TCM injections are generally produced from medicinal materials with sources of plants or animals, and both the complicated ingredients thereof and the production process may result in uncontrollable and random factors affecting the quality of TCM injections. Moreover, TCM injections are typically added with excipients, such as various solubilizers, which may also affect the quality of the products. Therefore, TCM injection is facing high-quality risks, and accordingly, more perfect means of quality control are urgently required [4–6].

However, the current quality control method of TCM injections is still at infancy. According to Chinese Pharmacopoeia (2015), quality control of TCM injection is mainly conducted via determining some active ingredients, while nonbioactive additives and excipients thereof were often ignored. A representative pharmaceutical excipient is Tween-80 (see its chemical structure in Figure 1).

As a common solubilizer, emulsifier, or stabilizer, Tween-80 is often used in a number of TCM injections, such as *XBJ Injection* and *FFSX Injection*. In general, nearly 2.5% Tween-80 [7] is commonly added to TCM injection, particularly in TCM injection with volatile components as the main active ingredients. Tween-80 is a nonbioactive adjuvant, but recent studies have found that drugs containing Tween-80 exhibit sensitization, hemolysis, hepatotoxicity, or peripheral neurotoxicity activities [8–10] and may even correlate with anaphylactic reaction [1–3]. Therefore, the FDA has issued a security warning for Tween-80 [11]. So far, adverse reactions of TCM injections have been frequently

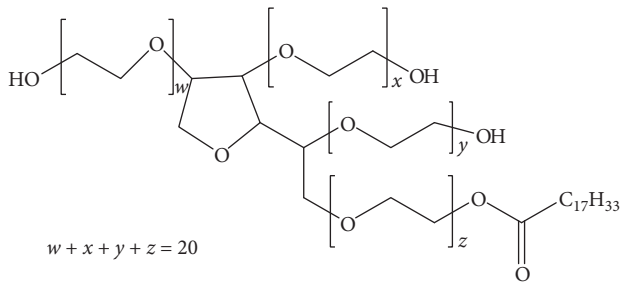

Figure 1: Chemical structural of Tween-80.

reported [1–3], and there are evidences indicating that Tween-80 might be, at least in part, responsible for those issues [12, 13]. So, Tween-80 should attract our more attention in the quality control of TCM injections.

Some routine analytical methods, such as gas chromatography and ultraviolet spectrophotometry, were widely used to determine Tween-80 content [14–17]. However, these methods are mostly cumbersome and time-consuming, and the determination process may suffer from slight deviations; as a result, sample quality cannot be ascertained in a timely manner. Thus, a rapid, efficient, and accurate quality control method is needed.

Near-infrared (NIR) spectroscopy has been ever increasingly accepted as a fast and green process analysis technology in chemical industry, agriculture, food, medicine, tobacco, and some other fields [18–22]. The frequency doubling of the stretching vibration of compounds X-H (X = C, O, N, etc.) causes absorption in NIR spectroscopy. NIR combined with chemometrics algorithms can qualitatively and quantitatively determine unknown samples [23, 24], thereby achieving the purpose of quality control. Researchers have used different concentrations of ethanol solution to quickly determine the alcoholicity of liquor and have found good application prospect [25].

This work intends to use the NIR spectrum of different concentrations of Tween-80 standard solutions to establish an optimized PLS model. By using the proposed model, Tween-80 contents can be predicted in TCM injections (see Figure 2). This work is expected to provide a promising method for the quality control of TCM injection and gain further insight into the preparation of medicines containing Tween-80.

2. Materials and Methods

2.1. Materials. Tween-80 (batch number 20120201) was obtained from Nanjing Well Chemical Co., Ltd. (Nanjing, China). 25.0 g Tween-80 was accurately weighted and completely dissolved in pure water to a final volume of 500 mL. Then, 133 Tween-80 standard solutions were then prepared by stock solution dilution, with concentrations uniformly distributed at the range of 0.1~5% (g/g).

25 *XBJ Injection* samples (Tween-80 labeled amount 0.14%, g/g) were provided by the manufacturer A (Tianjin, China). These samples involve nine batches, with batch numbers as follows: 1212051, 1212151, 1212211, 1212231, 1301061, 1301121, 1301151, 1301161, and 1303171. 40 *FFSX Injection* samples (Tween-80 labeled amount 2.00%, g/g) were provided by the manufacturer B (Shijiazhuang, China). These samples involve eight batches, with batch numbers as follows: 12021031, 12021131, 12021141, 12022041, 12022441, 12022941, 12022942, and 12022942.

2.2. NIR Apparatus and Software. A Bruker spectrometer (Bruker Optics, Germany) was used for spectral acquisition. Transmission spectra of samples were scanned in a 2 mm light path. Each spectrum was acquired as the average of 32 scans on the same sample in the wavelength range of 12,000 to 4000 cm^{-1}. The spectral resolution was kept to 8.0 cm^{-1}.

Processes of spectral wavebands selection, spectral pretreatment, and PLS modeling were performed using THUNIR software (Tsinghua University version 3.0, Beijing) [26–29].

2.3. Spectral Data Pretreatment. In order to obtain reliable, accurate, and stable calibration models, it is necessary to preprocess the spectral data before modeling. Spectral pretreatment was performed using Savitsky–Golay (SG) smoothing, first-order and second-order convolutional derivation, multiplicative scatter correction (MSC), standard normal variant (SNV), and normalization. The effects of different pretreatment methods were compared, and the optimized combination was selected.

2.4. Calibration of Models. The predictive model was constructed based on NIR data of 133 Tween-80 standard solution samples. Partial least squares (PLS) combines data matrix decomposition with regression interaction. The PLS model is robust and reduces the interference caused by light scattering and other components. PLS can eliminate noises to establish a well-stabilized model with prediction ability, thereby solving the model's overfitting and variable collinearity. In NIR-based modeling, PLS is the most commonly used linear regression method [30–32]. In this study, the PLS method was thus used to extract valid information from the NIR spectrum and a quantitative calibration model was established. The performance of the established model was evaluated via indicators of standard error of cross validation (SECV), the standard error of calibration (SEC), the primary factor (LV), and the determination coefficient (R) [28, 33–35].

The established quantitative calibration model was used to predict the Tween-80 content in 25 *XBJ Injection* samples and 40 *FFSX Injection* samples.

3. Results and Discussion

3.1. NIR Spectral Features. The selected spectral scanning range was 12000–4000 cm^{-1}, and the measured characteristics were the fundamental frequencies of molecular vibration, particularly the frequency doubling and combined frequency absorption bands of the stretching and bending vibration [36–39]. The original and pretreated spectra of Tween-80 are shown in Figure 3. In the original spectra, 5500–5800 cm^{-1} and 6500–7300 cm^{-1} had significant

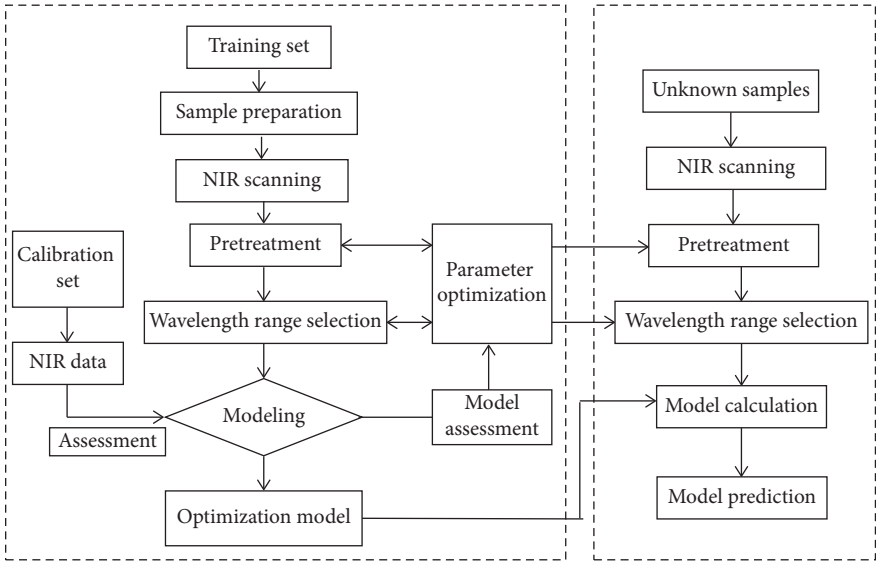

Figure 2: Experimental flow chart.

responses, which were related to the second-order frequency doubling of -CH_2 and -CH and the three-stage frequency doubling of C=O [40–43]. Figure 4(a) summarizes the shifts in the NIR spectrum baseline. These three bonds are widespread in the target molecules, so their concentration information can be reflected in the NIR spectra and this can be viewed as the foundation of NIR quantitative analysis of the Tween-80.

3.2. Calibration of the Model

3.2.1. Calibration and Validation Sets. 133 samples were randomly divided into calibration and validation sets, which contained, respectively, 109 and 24 samples. The calibration set was used to construct a predictive model for quantitative determination of Tween-80 in TCM injections, and the validation set was applied as blind samples to investigate the accuracy of the proposed method.

3.2.2. Data Pretreatment. NIR spectroscopy inevitably contains noises that are independent of the nature of the sample. Pretreatment of the spectral data can effectively filter the noise of the NIR spectrum, thereby ensuring a good correlation between the spectral data and the components, reducing the complexity of the quantitative model, and improving the accuracy of the model [22]. We investigated different spectral preprocessing methods and compared their SEC, SECV, and R values, as listed in Table 1. After SG smoothing on spectra, the SEC and SECV values obviously decreased and R values were close to 1, which suggested pretreatment of convolution smoothing allows a superior model performance.

3.2.3. Waveband Selection. The band of near-infrared spectrum was 14286–4000 cm^{-1}, which was divided into short-wave and long-wave near-infrared regions. The short-wave near-infrared region was a high-frequency absorption band, and the long-wave near-infrared region was a first- and second-order frequency doubling absorption band [44]. To obtain more information, the available area was covered up to the entire near-infrared band, which had a wider spectral range than that of the short-wave or long-wave near-infrared alone. As shown in Figure 3, most of the spectral regions were smooth. However, noise was detected in the spectra of 5300–4800 and 420–4000 cm^{-1}, which were discarded during the calibration process. In this research, the selected wavelength range was 5780–5870.7 cm^{-1}. To verify the correctness of the band selection, the relevant coefficients of the spectrum in this band were studied. As shown in Figure 4(b), the variables with higher coefficients (>0.4) were mostly distributed in the selected region. Therefore, the selected band (5780–5870.7 cm^{-1}) was the best modeling band.

3.2.4. Optimum LVs. Selection of the primary factors directly affects the prediction ability of calibration model. For instance, if the selected primary factor is excessively small, the useful information of the original spectrum will be lost and may result in insufficient fitting, while the primary factor is excessively large, it will include excessive measured noise, leading to an overfitting phenomenon and a significant increase in the prediction error of the built model. To avoid "under-fitting" and "overfitting," the optimal LV values must be used to establish the appropriate model [45–48]. In this study, we acquire optimum LVs by comparing the correlation diagram of the SECV and LV values. The SECV value is observed decreasing as the LV increasing, and LV reaches the optimal value when the SECV approached a constant value, as shown in Figure 4(c).

3.2.5. Model Establishment. The PLS method has been most commonly used in NIR spectroscopy-based quantitative

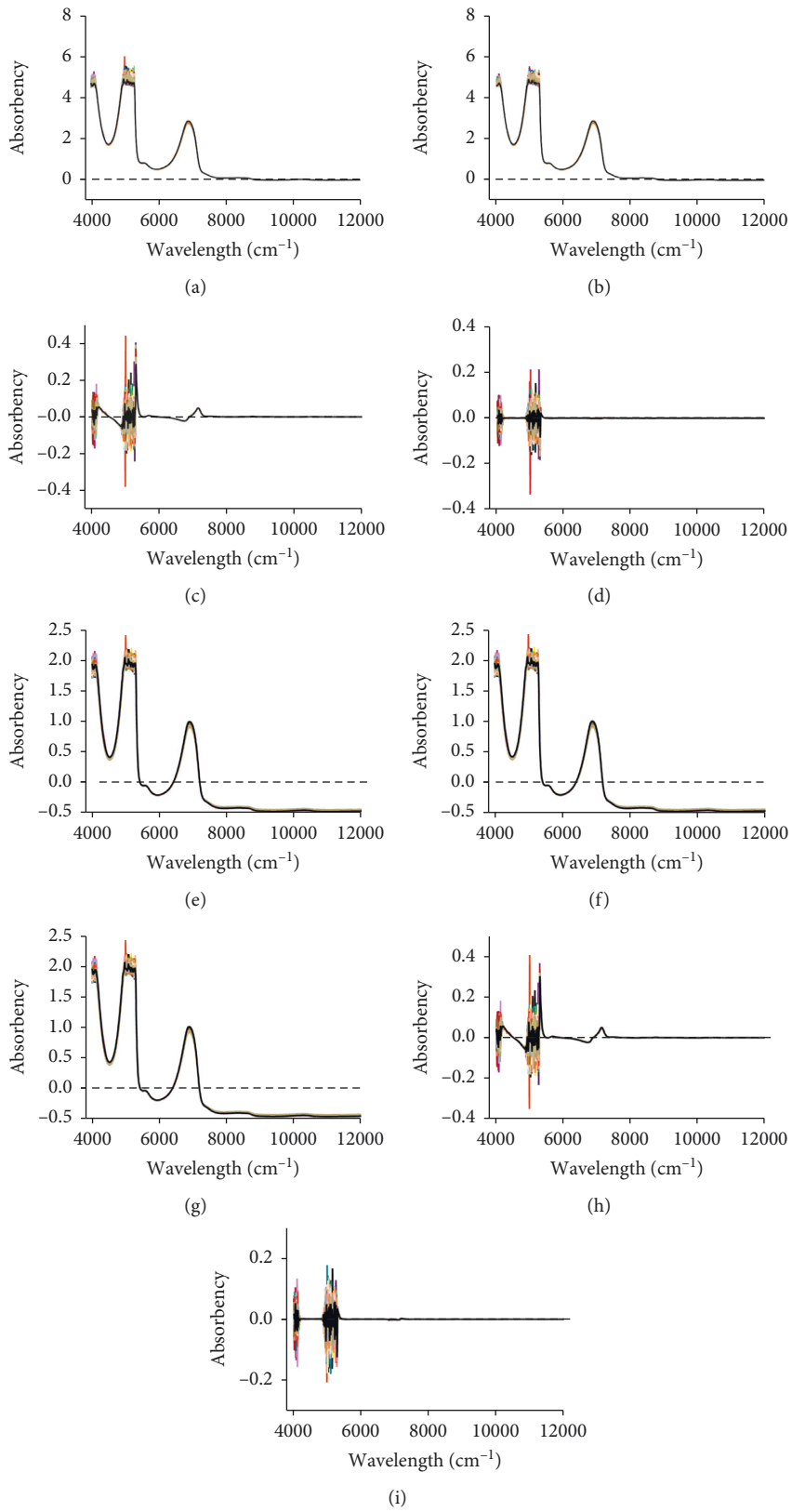

Figure 3: Comparison of the spectrum pretreatment results of Tween-80. Raw NIR spectra of full wavelength (a) and spectra preprocessed using SG smoothing (b) and one-dimensional convolution (c), two-dimensional convolution (d), multiplicative scatter correction (e), standard normal variable transformation (f), normalization method (g), one-order derivative convolution + multiplicative scatter correction (h) and two-dimensional convolution + multiplicative scatter correction (i).

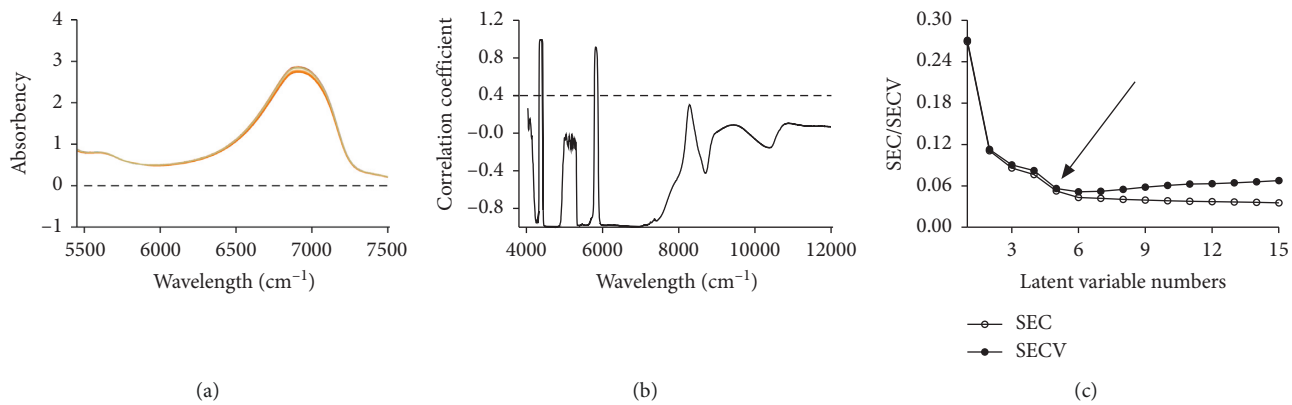

Figure 4: Enlarged view of the shifts in the NIR spectrum baseline (a). Correlogram of the NIR spectra and Tween-80 concentration (b). Relational graph of LV numbers and SECV of Tween-80 (c).

Table 1: Comparison of different calibration models of Tween-80 content developed with different spectral preprocessing methods.

No.	Pretreatment methods	LVs	Calibration		Cross validation	
			R	SEC	R	SECV[c]
B	SG smoothing	5	0.9986	0.0526	0.9984	0.0561
C	One DC	5	0.9985	0.0523	0.9980	0.0635
D	Two DC	5	0.9985	0.0523	0.9984	0.0561
E	MSC	5	0.9983	0.0571	0.9981	0.0615
F	SNV	5	0.9980	0.0614	0.9978	0.0660
G	Normalization	5	0.9985	0.0523	0.9984	0.0561
H	One DC + MSC	4	0.9964	0.0834	0.9958	0.8840
I	Two DC + MSC	4	0.9964	0.834	0.9981	0.8840

LV: latent variable number; SEC: standard error of calibration; SECV: standard error of cross validation; DC: dimension convolution; MSC: multiple scatter correction; SNV: standard normal variate.

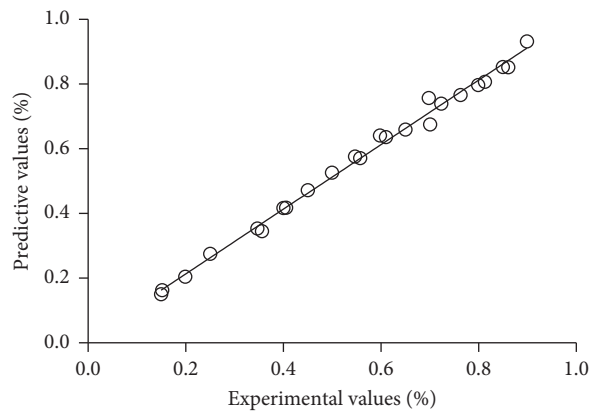

Figure 5: Fitting trend diagram of Tween 80 verification set.

modeling. Data of Tween-80 NIR spectrum were pretreated and then used to establish a calibration model. The SECV, SEC, LV, and R values were investigated to evaluate the model performance, and the result showed that the models had low SEC and SECV values and R value close to 1. The best modeling band (5780–5870.7 cm^{-1}) was selected, which allowed acceptable model performance of the Tween-80 calibration model, with parameters as follows: LVs 5, SECV values 0.0561, SEP values of 0.0526, and the R value 0.9984.

3.2.6. Model Validation. The established calibration model should take an external validation to verify its accuracy. Samples of validation set were tested as blind samples using the established model, and the result indicates that the correlation of the prediction values and factual values R is most close to 1 ($R = 0.9968$). Figure 5 indicates that the calibration model was acceptable.

3.2.7. Model Application. The Tween-80 labeled amounts in *XBJ Injection and FFSX Injection* were 0.14% and 2.00%, respectively. The established Tween-80 calibration model was used to predict the Tween-80 content in 25 samples of *XBJ Injection* and 40 samples of *FFSX Injection*. Table 2 lists the predicted value and the labeled value. The results showed that in samples of both *XBJ Injection* and *FFSX Injection*, the predicted values of the Tween-80 calibration model strongly matched with the true value. For *XBJ Injection* and *FFSX Injection*, the average relative deviations were 0.60% and 0.16%, respectively, and the maximum relative deviations were 8.57% and 7.60%, respectively.

4. Discussion

In the past decade, process analysis technology (PAT) gradually became an important technology for production process controlling in chemical engineering, environmental, agricultural, food, and other fields, along with the acceptance of concept of "*quality by design*." As one of the most common PAT technologies, NIR is now widely applied in these fields. However, either for TCM products or production process, the mainstream quality control method is still an offline analysis approach. In recent years, people come to recognize the advantages of the NIR-based method, i.e., fast, real-time, in situ, nondestructive, and accurate, and NIR shows great expectation in the quality control for TCM injections. Moreover, presently most quality control methods focus on the so-called bioactive components of TCM, while nearly take no consideration on other additive

Table 2: Experimental vs. predictive values of Tween-80 in *XBJ Injection* and *FFSX Injection*.

No.	Batch	EV	PV	Ea	RD	No.	Batch	EV	PV	Ea	RD
1	1212051	0.140	0.151	0.011	7.857	34	12021131	2.000	2.001	0.001	0.050
2		0.140	0.143	0.003	2.143	35		2.000	2.016	0.016	0.800
3	1212151	0.140	0.133	−0.007	−5.000	36		2.000	1.987	−0.013	−0.650
4		0.140	0.140	0.000	0.000	37		2.000	2.009	0.009	0.450
5		0.140	0.152	0.012	8.571	38	12021141	2.000	1.987	−0.013	−0.650
6	1212211	0.140	0.150	0.010	7.143	39		2.000	1.968	−0.032	−1.600
7		0.140	0.149	0.009	6.429	40		2.000	1.965	−0.035	−1.750
8		0.140	0.151	0.011	7.857	41		2.000	1.936	−0.064	−3.200
9	1212231	0.140	0.144	0.004	2.857	42		2.000	1.940	−0.060	−3.000
10		0.140	0.142	0.002	1.429	43	12022041	2.000	1.929	−0.071	−3.550
11		0.140	0.137	−0.003	−2.143	44		2.000	1.943	−0.057	−2.850
12	1301061	0.140	0.138	−0.002	−1.429	45		2.000	1.957	−0.043	−2.150
13		0.140	0.149	0.009	6.429	46		2.000	2.152	0.152	7.600
14		0.140	0.136	−0.004	−2.857	47		2.000	2.130	0.130	6.500
15	1301121	0.140	0.135	−0.005	−3.571	48	12022441	2.000	2.132	0.132	6.600
16		0.140	0.136	−0.004	−2.857	49		2.000	2.126	0.126	6.300
17		0.140	0.134	−0.006	−4.286	50		2.000	2.110	0.110	5.500
18	1301151	0.140	0.139	−0.001	−0.714	51		2.000	2.003	0.003	0.150
19		0.140	0.140	0.000	0.000	52		2.000	2.002	0.002	0.100
20		0.140	0.133	−0.007	−5.000	53	12022941	2.000	1.992	−0.008	−0.400
21	1301161	0.140	0.132	−0.008	−5.714	54		2.000	2.000	0.000	0.000
22		0.140	0.135	−0.005	−3.571	55		2.000	1.984	−0.016	−0.800
23		0.140	0.136	−0.004	−2.857	56		2.000	1.977	−0.023	−1.150
24	1303171	0.140	0.144	0.004	2.857	57		2.000	1.995	−0.005	−0.250
25		0.140	0.142	0.002	1.429	58	12022942	2.000	1.998	−0.002	−0.100
26		2.000	1.982	−0.018	−0.900	59		2.000	1.961	−0.039	−1.950
27		2.000	1.999	−0.001	−0.050	60		2.000	1.974	−0.026	−1.300
28	12021031	2.000	1.984	−0.016	−0.800	61		2.000	1.944	−0.056	−2.800
29		2.000	1.973	−0.027	−1.350	62		2.000	1.949	−0.051	−2.550
30		2.000	1.976	−0.024	−1.200	63	12022943	2.000	1.933	−0.067	−3.350
31		2.000	2.035	0.035	1.750	64		2.000	1.911	−0.089	−4.450
32	12021131	2.000	2.041	0.041	2.050	65		2.000	1.927	−0.073	−3.650
33		2.000	2.041	0.041	2.050	—	—	—	—	—	—
		EV	[a]PV	[b]Ea	RD			EV	PV	Ea	RD
Mean (no. 1–25, *XBJ Injection*)		0.140	0.141	0.001	0.600	Mean (no. 26–65, *FFSX Injection*)		2.000	1.997	−0.003	−0.164
SEP (no. 1–25, *XBJ Injection*)		0.006				SEP (no. 26–65, *FFSX Injection*)		0.059			

PV: predicted values; Ea: absolute error; SEP: standard error of prediction; RD: relative deviation.

nonactive ingredients. For instance, Tween-80, as one of the most commonly used additives in TCM injection, might lead to potential quality risks of products, whereas it has not been paid much attention to the quality control. This work established a NIR-based quality control approach for Tween-80 in TCM injection, which can be used not only for the fast quality detection of Tween-80 in the terminal product of TCM injection but for the real-time detection of Tween-80 in the production process, due to its characteristics of rapid, in situ, and nondestructive. Moreover, the proposed method also can be used PAT technology with good adaptability in other TCM products and produce process.

For NIR modeling, the commonly used algorisms include multivariate linear regression (MLR), principal component regression (PCR), and partial least squares regression (PLSR). MLR often produces unsatisfactory prediction performance due to the problem of collinearity of spectral variables; PCR only decomposes the spectral array to eliminate the noise while PLSR decomposes both the spectral array and the concentration array simultaneously, which not only overcomes the disadvantage of the PCR with only data of spectra decomposed but resolves problems of variable collinearity and model overfitting. Therefore, the PLS modeling method is used in this study to construct calibration model.

This work concerned the quality control of Tween-80 in TCM injection but did not promote the method in the application for other TCM dosage forms containing Tween-80. In our further study, the proposed NIR-based Tween-80 quality control method would be improved and developed to be applied in other TCM, and even in food, cosmetics, and other industries.

5. Conclusions

In this study, a method for rapidly determining the Tween-80 in TCM injection by NIR spectroscopy was established for the first time. The proposed method is simple and

accurate, which may be suitable for application in the inspection in production processes and in final product quality assessment for TCM injection, thereby may promote the quality control of TCM injection and even expand the strategy for the quality control of the production process in the pharmaceutical industry.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Additional Points

Highlights. Rapid determination of Tween-80 in TCM injection by using near-infrared spectroscopy was established. This work could promote the quality control of TCM injection and expand the strategies for the quality control of the production process in the pharmaceutical industry.

Disclosure

Jin-Fang Ma and Tian-Ling Chen are the co-first authors.

Conflicts of Interest

The authors declare there are no conflicts of interest.

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