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A Rapid and Simple Quantitative Method for the Active Ingredients of Aescin in the Extraction Process Using Near Infrared Spectroscopy

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Abstract

To achieve a rapid and simple detection for the active ingredients of Aescin in the extraction process using near-infrared spectroscopy (NIR) and to realize the state monitoring and quality control of the extraction process. Partial least square regression (PLS) was applied to build the near-infrared calibration models, and the applicability of the model was investigated by predicting the unknown samples in the extraction process. The correlation coefficients of the established Aescin models (A, B, C, D) were 0.9836, 0.9831, 0.9833, 0.9824, and the prediction standard deviations (SEP) were 0.05636, 0.05043, 0.02412, 0.05636, respectively. This study suggests that the proposed model has superior stability and accuracy. NIR spectroscopy technique provides a novel efficient and environmentally friendly approach to the rapid determination of four Aescin key quality indicators (A, B, C, D) in the extraction, which was solved the problem that the lack of state monitoring during the extraction of Aescin, thereby improved the quality of Aescin.

Keywords

NIR Spectroscopy, Aescin, Extraction Process, State Monitoring, Quality Control

1. Introduction

Aescin is the main active mixture of extract from the seeds of *Aesculus chinensis Bunge* or *Aesculus hippocastanum*. Which is a natural compound of acylation

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triterpene glycosides, consisting of A, B, C and D Aescin [1] (**Figure 1**). Previous studies had proved that Aescin has effective because of its anti-inflammation, antiedema, anti-exudation, and anti-tumor effects, as well as in aiding ischemia injuries and providing blood capillary protection [2]-[7], which is mainly applied in the form of sodium salt to treat diseases such as postoperative edema, phlebitis, haemorrhoids, etc [8]-[16]. However, the lack of simple and rapid quantitative methods in the extraction process of *Aesculus chinensis* results in low extraction efficiency and may lead to more impurities. At present, the extraction effect is evaluated by HPLC. However, HPLC cannot monitor the extraction process in real time, which may lead to more impurities in the final product.

The stability of the extraction process influences the quality of the Aescin, which severely limit its clinical effect [17] [18] [19] [20]. HPLC has been extensively applied to determine the content of Aescin A-D [16] [21]. In this method, the medicinal material is first subjected to methanol extraction, followed by ungrease treatment with petroleum ether to remove the interfering grease, and then the content of Aescin A-D in extractive can be established by HPLC. The processing step of test solution in this method is complicated and time consuming. In addition, to obtain satisfactory separation degree of component during HPLC, the holding time is relatively long, which cannot meet the requirements of rapid detection of *Aesculus chinensis Bunge* extractive.

NIR spectroscopy is an environmentally friendly rapid process analysis technology [22] [23], which can realize simultaneous determination of multiple components without requiring pretreatment for samples [24] [25] [26] and has been extensively used in various scientific fields [27]-[36]. Currently, there have been no reports on the application of NIR spectroscopy in quality control during extraction of *Aesculus chinensis Bunge*. In this study, the extraction process of *Aesculus chinensis Bunge* medicine material was regarded as research objects. NIRS was adopted to determine the analytical values of Aescin A, B, C, D in *Aesculus chinensis Bunge*. A rapid and simple quality control method during *Aesculus chinensis Bunge* extraction process was established using PLS, which is of great research significance and application prospect to quality control during *Aesculus chinensis Bunge* extraction process.

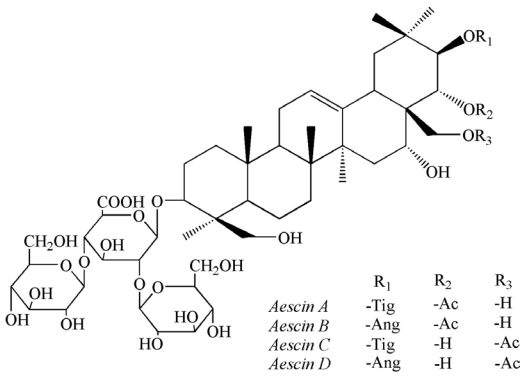


Figure 1. The structure of Aescin [18].

2. Materials and Methods

2.1. Materials

Sodium aescinate as reference substance (National Institutes for Food and Drug Control, batch No.: 100346-200402);

Acetonitrile (chromatographically pure, Merck);

Methyl alcohol (analytically pure, Guangzhou Chemical Reagent Factory);

95% ethyl alcohol (Pharmaceutical grade, Guangzhou Chemical Reagent Factory).

2.2. Methods

2.2.1. HPLC Method

The four key quality-indicative ingredients of *Aesculus chinensis Bunge* were assayed using UltiMate 3000 HPLC instrument (ThermoFisher Scientific Inc., including gradient pump SR-3000, automatic sampler WPS-3000, column thermostat TCC-3000, ultraviolet detector VWD-3100, chromatograph workstation Chameleon 7.2). The chromatographic conditions were set as follows: Kromasil C_{18} (4.6 mm × 250 mm, 5 μm) was adopted at a temperature of 30˚C. A isocratic elution program was run at a flow rate of 1.000 mL/min using the mobile phase acetonitrile-0.2% phosphoric acid solution (36:64). Detecting wavelength was set to 220 nm for Aescin. The standard and sample solutions were filtered using a 0.45-μm-milipore filter and 10 μL was and subjected to HPLC analysis [37] [38].

2.2.2. Preparation of Sodium Aescinate as Reference Substance

20.40 mg of standard sample of Sodium aescinate was weighed and placed in a 5mL volumetric flask, dissolved with 36% methyl alcohol, and then diluted to constant volume to prepare 1mL of stock solution containing 1.5830 mg of Aescin A, 1.1546 mg of Aescin B, 0.5040 mg of Aescin C, 0.3006 mg of Aescin D. Then, using the prepared stock solution, a series of control solutions of different concentrations was prepared.

2.2.3. Preparation of Extracting Solution

3750 ml of 70% ethyl alcohol was weighed and placed in a 5 L conical flask, heated to 60˚C in water bath. Then, 150 g of *Aesculus chinensis Bunge* medicine material (smashed and screened by a 60-mesh sieve). Stirring extraction was performed for 2 h, 10 ml of extracting solution was collected every 4 min. A total of 210 samples were collected in 7 batches, the first 70 samples were regarded as modeling set (calibration set), while the remaining 140 samples were regarded as a validation set.

2.2.4. Sample Measurement

The extracted solution was filtered by 0.45-μm-milipore filter, the filtrate and control solution was measured according to chromatographic condition prescribed in section "2.2.1".

2.2.5. NIR Spectroscopy Collecting

NIR spectroscopy for the extracting solution of *Aesculus chinensis Bunge* was conducted utilizing an NIR spectroscopy instrument (NGD-U10, Guangzhou SonDon Network & Technology Co., Ltd., Guangzhou, China). The extracting solution of *Aesculus chinensis Bunge* was placed in a 1mm quartz cell. The spectrum scanning was performed with a transmission detector, with scanning wavelength varying between 950 and 1650 nm, scan times of 100, resolution ratio of 2 nm. Each extracting solution was repeatedly scanned for 3 times, and the averaged spectrum was obtained, as showed in Figure 2. The data was processed and calculated using data analysis software Matlab2012a (MathWorks, America).

3. Results and Discussion

3.1. The Standard Curves of Aescin Components

The working curves were plotted using Aescin concentration as abscissa and peak area as ordinate as showed in Figure 3. The regression equation for Aescin A is $Y = 44.861X - 0.0229$ ($r = 1.0000$), linear range was 0.007915 - 1.5830 mg/mL; The regression equation for Aescin B is $Y = 36.370X + 0.0094$ ($r = 1.0000$), linear range was 0.005773 - 1.1546 mg/mL; The regression equation for Aescin C is $Y = 44.943X - 0.0075$ ($r = 1.0000$), linear range was 0.002520 - 0.5040 mg/mL; The regression equation for Aescin D is $Y = 44.949X - 0.0055$ ($r = 1.0000$), linear range was 0.001503 - 0.3006 mg/mL.

3.2. Establishment of Quantitative Analysis Model of Aescin

According to the concentrations of Aescin components measured by HPLC, the first 70 samples were regarded as the calibration set, and the calibration model was constructed using PLS; the last 140 samples were regarded as validation set to validate the predictive performance of the calibration model. Concentrations of Aescin components in calibration set and validation set are shown in Table 1. The correlation coefficient(R), root mean square error of cross validation

Table 1. The concentrations of Aescin components in calibration set and validation set.

Component	Group	Number of sample	Max value	Min value	Average value	Standard deviation
Aescin A	Modeling set	70	0.3659	0.1162	0.2024	0.05520
	Prediction set	140	0.3016	0.1183	0.1965	0.05484
Aescin B	Modeling set	70	0.3190	0.1009	0.1778	0.04945
	Prediction set	140	0.02689	0.1020	0.1724	0.04917
Aescin C	Modeling set	70	0.1433	0.04263	0.07746	0.02254
	Prediction set	140	0.1191	0.04260	0.07631	0.02295
Aescin D	Modeling set	70	0.09611	0.03068	0.05329	0.01523
	Prediction set	140	0.08157	0.02958	0.05361	0.01575

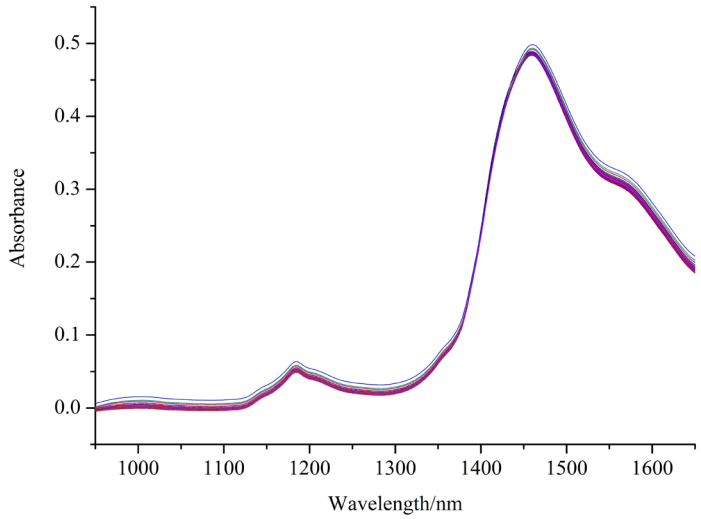
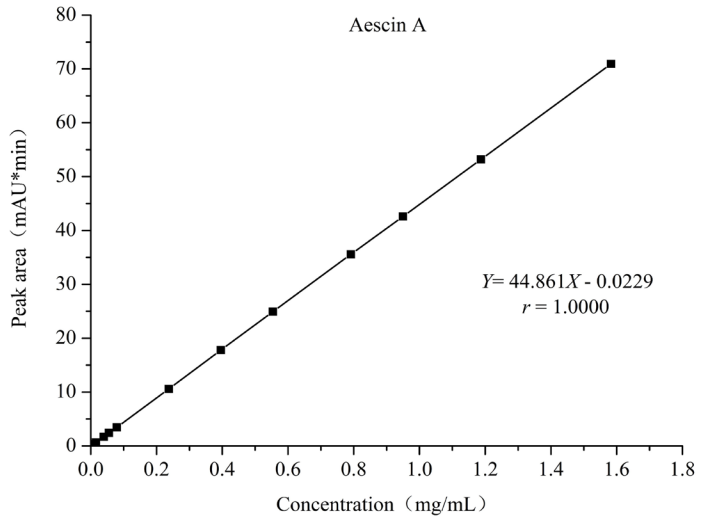
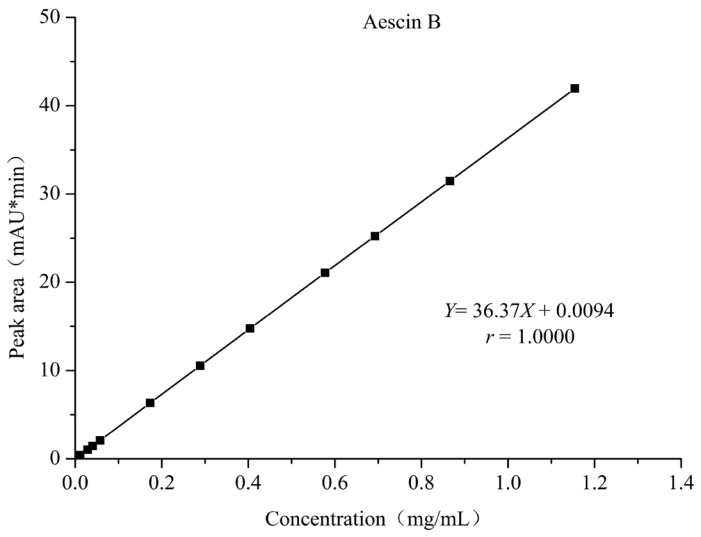


Figure 2. NIR spectroscopy of extracting solution of Aesculus chinensis Bunge.



(a)



(b)

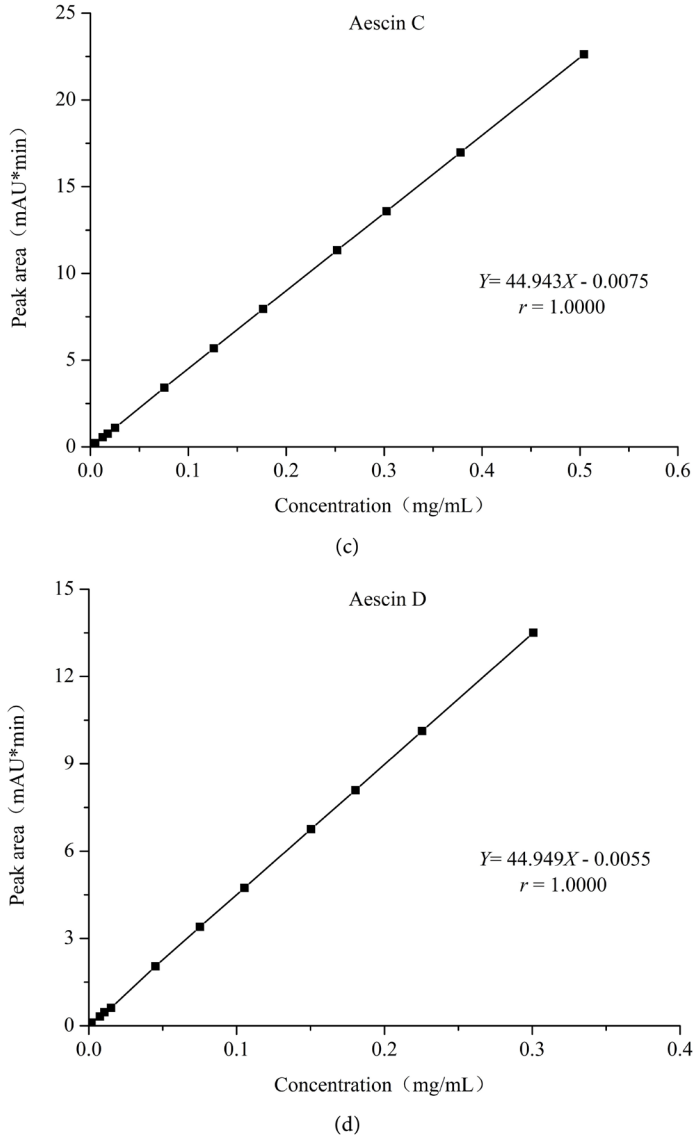


Figure 3. Standard curves of Aescin components. (a) Aescin A; (b) Aescin B; (c) Aescin C; (d) Aescin D.

(RMSECV), SEP was regarded as evaluation indexes for the model. The larger the *r* value is, the smaller the RMSECV value is, and the more reasonable the calibration model construction is. The smaller the SEP value is, the better the predictive performance of the model is [39] [40] [41] [42].

3.3. Selection of the Number of Model Primary Factors

During modeling construction, the predictive performance of the PLS model is closely related to the number of primary factors (principal components, PCs). In the case that the samples calibration set are given, a too small number of PCs will lead to incomplete information of modeling and reduced predictive performance of model; in contrast, a over-large number of PCs will lead to complex model and introduction of excessive measurement noise, resulting in over-fitting,

which means that the model suits the calibration set better but reduces the predictive power of the prediction set. Therefore, an appropriate number of PCs is of direct influence on the predictive performance of the model [43] [44] [45]. Every PLS calibration model involves an optimal number of PCs. The RMSECV value varied with the number of PCs, as showed in **Figure 4**. The minimum RMSECV value corresponds to optimal number of PCs, so the optimal numbers of PCs for Aescin A, Aescin B, Aescin C, Aescin D were 7, 7, 7, 6, respectively.

3.4. Model Construction and Evaluation

After sample processing, the near infrared spectra of 70 samples in calibration set were associated with the concentrations of Aescin components (with optimal numbers of primary factors of 7, 7, 7, 6) measured by HPLC using PLS within wavelength range of 950 nm - 1650 nm. The near infrared quantitative calibration models of Aescin A, Aescin B, Aescin C, Aescin D were constructed and analyzed. The correlation coefficients (R) of Aescin A, Aescin B, Aescin C, Aescin D were 0.9836, 0.9831, 0.9833, 0.9824, and RMSECV values were 0.0099, 0.0090, 0.0041, 0.0029, respectively. **Figure 5** indicates the relation between prediction value and measured value of Aescin components. It can be seen that the R values of the four key indicators are all greater than 98%, which has a good linear relationship, which means that the NIR spectroscopy has a good prediction effect and can be used for the prediction of the Aescin extraction process. During the modeling process, two exceptional data points (No. 20 and No. 68) were eliminated using automatic optimization function of Software.

3.5. Prediction Effect and Evaluation

The near infrared spectra of remaining 140 samples in validation set were input in calibration model to predict the concentration of Aescin components, and the prediction results were compared with the values measured by HPLC to validated the correctness of calibration model, as shown in **Figure 6**. The RMSECV values of four models were 0.0099, 0.0090, 0.0041, 0.0029, and their SEP values

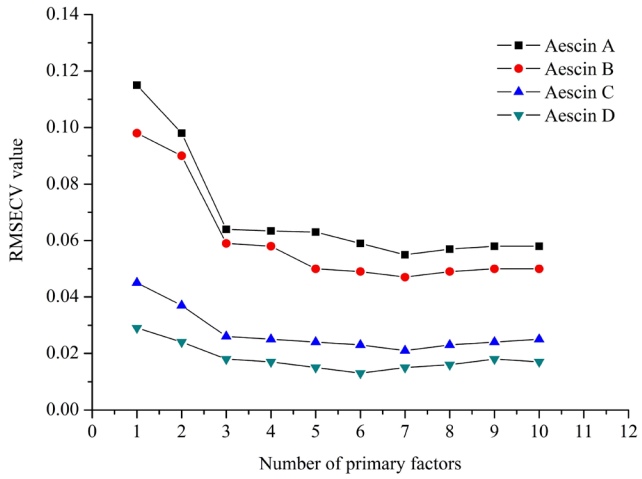
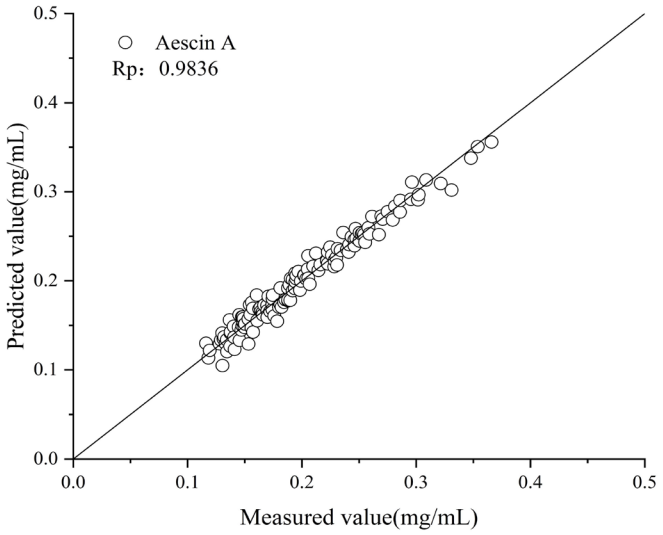
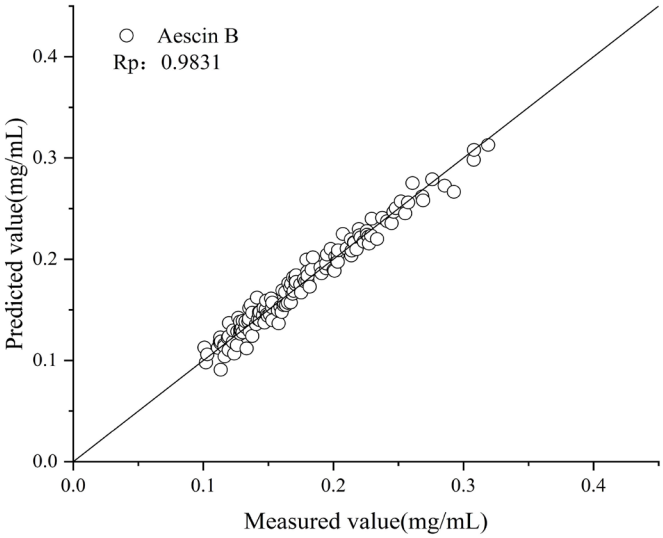


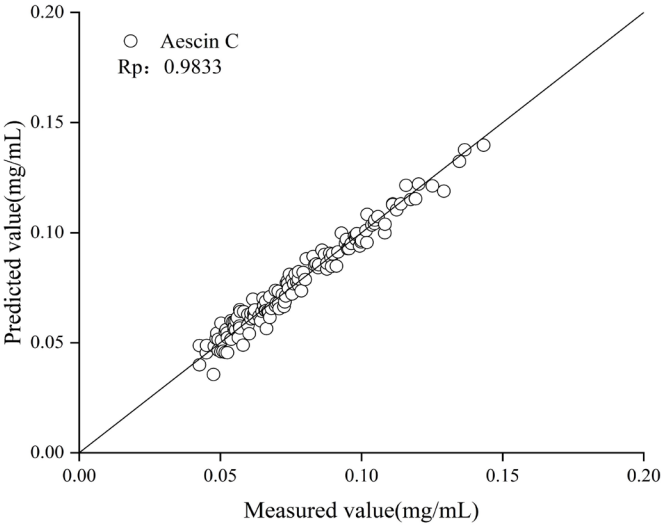
Figure 4. Variation of RMSECV value with number of primary factors.


Aescin A
Rp：0.9836
Predicted value(mg/mL)
Measured value(mg/mL)
0.0
0.1
0.2
0.3
0.4
0.5

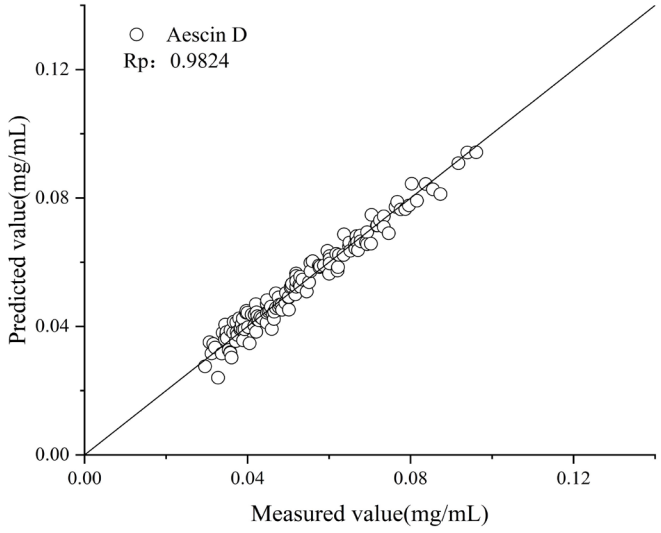
(a)


Aescin B
Rp：0.9831
Predicted value(mg/mL)
Measured value(mg/mL)
0.0
0.1
0.2
0.3
0.4

(b)

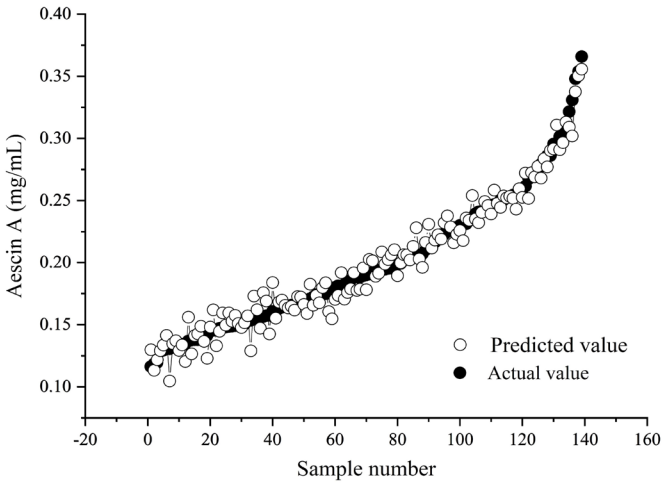

Aescin C
Rp：0.9833
Predicted value(mg/mL)
Measured value(mg/mL)
0.00
0.05
0.10
0.15
0.20

(c)

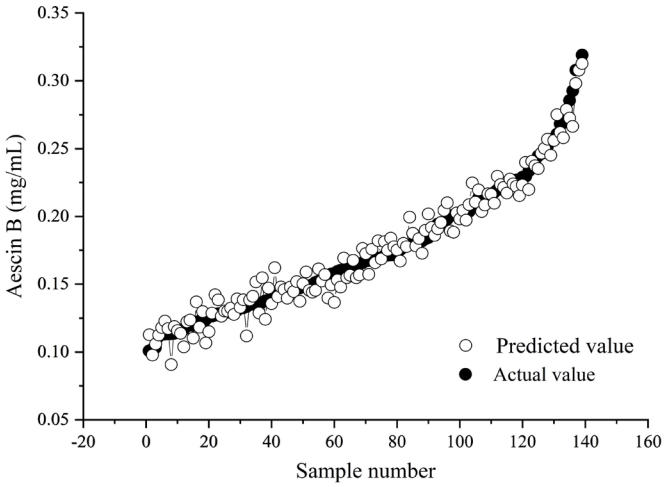


(d)

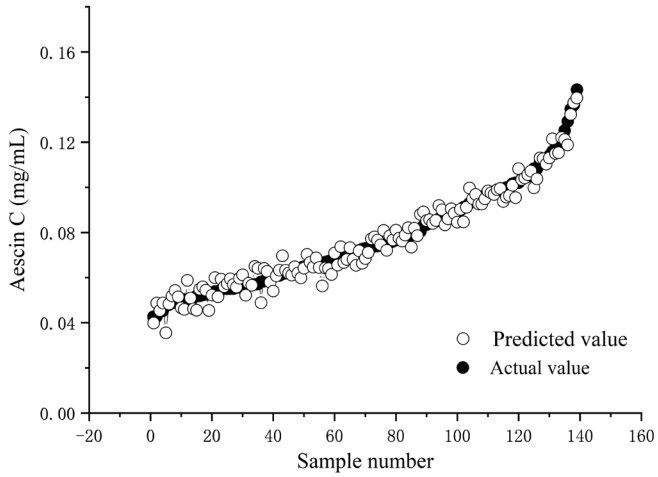
Figure 5. Relation between prediction value and measured value of Aescin components in calibration set.



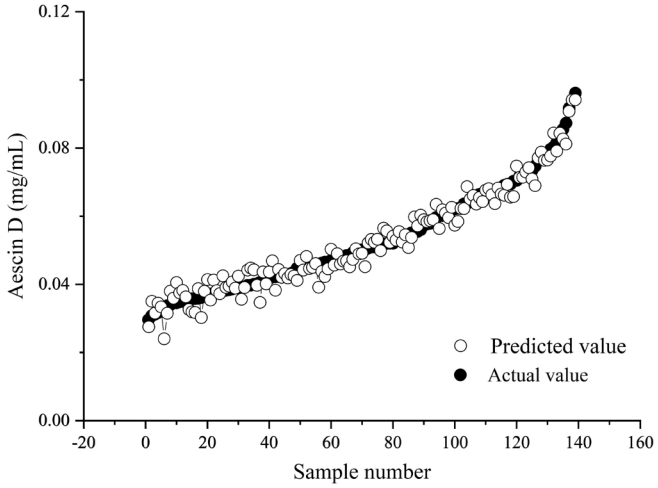
(a)



(b)



(c)



(d)

Figure 6. Relation between prediction value and measured value of Aescin components in validation set.

were 0.05636, 0.05043, 0.02412, 0.01659, respectively. The correlation coefficients (R) of the four Aescin in the verification set were 0.9790, 0.9759, 0.9783 and 0.9785, indicating that the prediction results were consistent with the measured values. The model constructed has good prediction ability and can be used for the rapid quantitative analysis of Aescin in the extraction process.

4. Conclusion

Regarding the 4 Aescin components in extraction of *Aesculus chinensis Bunge*, quantitative calibration models were constructed and analyzed using PLS within wavelength range from 950 nm to 1650 nm. The RMSECV of constructed models were 0.0099, 0.0090, 0.0041, 0.0029, the Rp values were 0.9836, 0.9831, 0.9833, 0.9824, and the optimal number of primary factors was set to 7, 7, 7, 6, respectively. The constructed calibration models were used to predict the concentrations of 4 Aescin components in 140 extracting solution of *Aesculus chinensis*

Bunge, and the SEP values were 0.05636, 0.05043, 0.02412, 0.01659, respectively. Using such near infrared method, it only takes 25s to measure an extracting solution of *Aesculus chinensis Bunge* (scanning for 32 times); while it takes at least 50 min to fulfill the same task using the HPLC method. The proposed method is fast, convenient, accurate, without requiring pretreatment for sample, which can be applied to status monitoring and quality control during *Aesculus chinensis Bunge* extraction and has a great application prospect.

Compliance with Ethical Standards

Funding

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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