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Simultaneous determination of eight active components in Chinese medicine 'YIQING' capsule using high-performance liquid chromatography

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Abstract

An effective, accurate and reliable method for the simultaneous separation and determination of eight active components (berberine, aloe-emodin, rhein, emodin, chrysophanol, baicalin, baicalein and wogonin) in Chinese medicine 'YIQING' capsule was developed using reverse phase high-performance liquid chromatography (RP-HPLC) coupled with diode array detection. The chromatographic separation was performed on a Lichrospher C_{18} column (250 mm × 4.6 mm i.d. with 5.0 μm particle size) with a simple linear gradient elution programme. Due to the different UV characteristic of these components, three detection wavelengths were utilized for the quantitative analysis (UV wavelength 254 nm for anthraquinone derivatives, 278 nm for flavones compounds, and 345 nm for protoberberine alkaloids, respectively). Excellent linear behaviors over the investigated concentration ranges were observed with the values of R^2 higher than 0.99 for all the analytes. The recoveries, measured at three concentration levels, varied from 94.9% to 105.3%. The validated method was successfully applied to the simultaneously determination of these active components in 'YIQING' capsules from different production batches.

Keywords: High-performance liquid chromatography; Quantitative analysis; Active components; Chinese medicine; 'YIQING' capsule; Quality control

1. Introduction

Traditional Chinese medicine (TCM) has a robust history with roots dating back thousands of years for the medicinal practice in China and some East Asian countries [1,2]. 'YIQING' capsule, derived from the well-known TCM formula named 'San-Huang-Xie-Xin-Tang' and composed of three commonly used Chinese herbs *Rhizoma Coptidis*, *Radix et Rhizoma Rhei* and *Radix Scutellariae*, has been officially listed in the Chinese Pharmacopoeia for a long time [3]. 'San-Huang-Xie-Xin-Tang' has therapeutic effects on purging fire for removing toxin, eliminating phlegm and hemostasis, eliminating the wetness-evil from the upper warmer, clearing away the heat-evil and expelling superficial evils. Accordingly, the derived botanical drug 'YIQING' capsule is used for the treatment of intense heat in the body, inflammation and painful swelling of the eyes, sore throat, gingival bleeding, reddish urine, constipation and also effective for the treatment of pharyngitis and amygdalitis [3].

By now, some analytical methods have been developed for the quantitative analysis of the target components in the final products derived from 'San-Huang-Xie-Xin-Tang' [3–6]. However, most of the current studies concentrate on the determination of the target components from only one medicinal plant, and are lack of the quantitative information about the other two medicinal compositions. Generally, all the medicinal plants composing 'San-Huang-Xie-Xin-Tang' play the important roles for the therapeutic effects, according to the theory of TCM and thousands of years of medicinal practice. The modern pharmacology studies have also revealed that the protoberberine alkaloids from *Rhizoma Coptidis*, anthraquinone derivatives from Rhubarb, and flavones from *Radix Scutellariae* are the active components contained in these herbs [7–15]. Although the methods for the determination of the target components in the medicinal plants, such as *Rhizoma Coptidis*, *Radix et Rhizoma Rhei*, *Radix Scutellariae* and other chemical matrices, have been well reported using different analytical techniques [16–22], the meth-

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ods about the simultaneous separation and determination of multiple active components (including the protoberberine alkaloids, anthraquinone derivatives and flavones compounds) in a single running are not available in the literatures. It is in common thought that taking into account the direct quantification of as many as possible components will provide much valuable qualitative and quantitative information for the quality control of the TCM-derived botanical drugs made by multiple medicinal plants. Therefore, the development of an analytical method for the simultaneous determination of protoberberine alkaloids, anthraquinone derivatives, and flavones compounds is in urgent need to improve the quality control of 'YIQING' capsule and the other related botanical drugs.

In this study, a simple, accurate and reliable analytical method for the simultaneous determination of eight active components including berberine, aloe-emodin, rhein, emodin, chrysophanol, baicalin, baicalein and wogonin (their chemical structures were shown in Fig. 1) contained in 'YIQING' capsule was developed using reverse phase high-performance liquid chromatography coupled with diode array detection. The baseline separation of the target components was achieved within 50 min using a simple gradient elution programme. To improve the sensitivity and selectivity of the separation, the detections at three different wavelengths were employed for the quantitative analysis because of the different UV characteristic of the investigated compounds. The validated method was successfully applied to the quantitative analysis of these eight active components contained in 'YIQING' capsules from different production batches. As a result, the developed HPLC method is particularly suitable for the routine analysis of 'YIQING' capsule and the other related botanical drugs.

2. Experimental

2.1. Chemicals and reagents

Botanical drug 'YIQING' capsule was supplied by a Chinese pharmaceutical manufacturer (Kanghong, Sichuan, China).

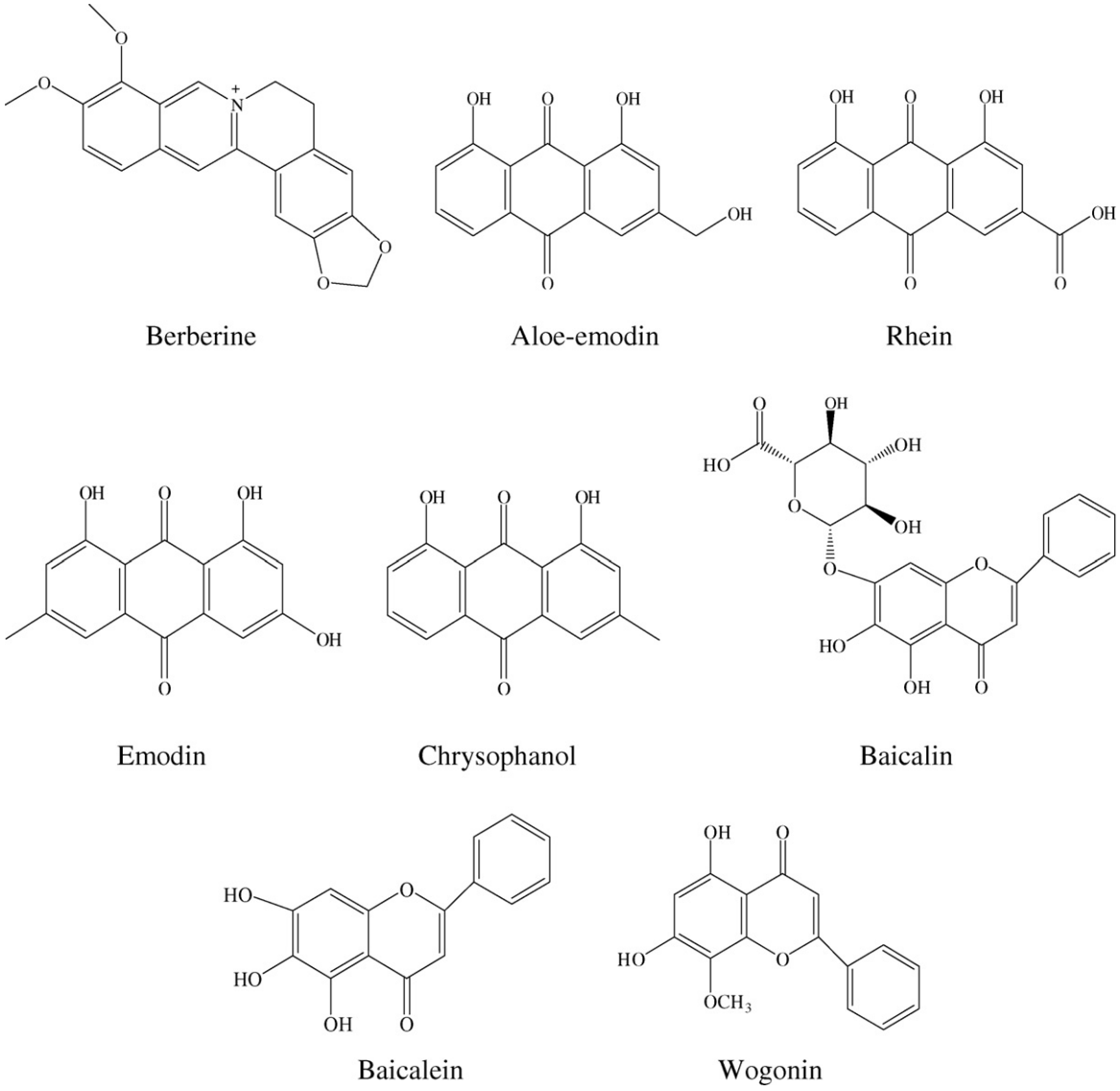

Fig. 1. The chemical structures of the investigated eight active components.

Standard substances including berberine, aloe-emodin, rhein, emodin, chrysophanol, baicalin, baicalein and wogonin were all purchased from National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Methanol and acetonitrile were of HPLC grade, and both were purchased from Merck (Darmstadt, Germany). Phosphoric acid and potassium dihydrogen phosphate were analytical reagents, and both were purchased from Sanying chemical reagent company (Shanghai, China). Other reagents were all of analytical grade. Deionized water used throughout the experiments was generated by a Milli-Q academic water purification system (Milford, MA, USA).

2.2. Instrumentation and analytical conditions

The HPLC system HP 1100 series (Agilent Technologies, Waldbronn, Germany), equipped with the ChemStation software (Agilent Technologies) and comprised a quaternary pump, an online vacuum degasser, an autosampler, a thermostated column compartment and a diode array detector, was used for the chromatographic analysis. All separations were carried out on a Lichrospher C_{18} column (250 mm × 4.6 mm i.d., 5.0 μm particle size) from Hanbang Science & Technology (Jiangsu, China). A linear gradient elution of eluents A (10 mM KH_2PO_4, 0.02% (v/v) H_3PO_4 in water, pH 3.0) and B (methanol) was used to run the separation. The elution programme was well optimized and conducted as follows: an isocratic elution of 40% B with the first 10 min, a linear gradient of 40–90% B with the range of 10–42 min, and then an isocratic elution of 90% B for the next 10 min. After holding the solvent composition of 90% B for a further minute the column was returned to its starting condition. The solvent flow rate was 0.8 ml/min, the injection volume was 20 μl, and the column temperature was maintained at 30 °C.

2.3. Standard solution preparation

The standard stock solutions of berberine (0.880 mg/ml), baicalin (0.896 mg/ml), baicalein (0.307 mg/ml) and wogonin (0.144 mg/ml), aloe-emodin (0.075 mg/ml), rhein (0.079 mg/ml), emodin (0.060 mg/ml) and chrysophanol (0.052 mg/ml) were prepared in methanol and stored away from light at 4 °C. Working solutions of the lower concentration were prepared by appropriate dilution of the stock solution.

2.4. Sample solution preparation

The powder of 'YIQING' capsule (about 0.10 g) was extracted with 25 ml solvent composed of 0.1 M HCl aqueous solution and methanol (1:100, v/v) for 60 min in an ultrasonic bath. The addition of HCl solution into the solvent was to improve the extractability for anthraquinone derivatives contained in this botanical drug [3]. The extracted solution was prepared by the method of weight relief, by which the weight lost in the extraction procedure was compensated. After the centrifugation at 10,000 rpm for 10 min, the supernatant was injected into HPLC system after filtering through a 0.45 μm syringe filter.

3. Results and discussion

3.1. Chromatographic separation

Due to the complex composition of the sample solution, different mobile phases (such as H_3PO_4–H_2O–CH_3OH, H_3PO_4–KH_2PO_4–H_2O–CH_3OH, H_3PO_4–NaH_2PO_4–H_2O–CH_3OH, H_3PO_4–KH_2PO_4–H_2O–CH_3CN, and H_3PO_4–KH_2PO_4–H_2O–CH_3OH–CH_3CN) were attempted to elute the investigated eight components. Since some alkaloids were contained in the sample solution, the ion-pair agents such as triethylamine and SDS were also tried to improve the separation of these components. Considering the total resolution of the chromatographic separation, the running time and solvent/reagent consumption, the mobile phase H_3PO_4–KH_2PO_4–H_2O–CH_3OH was chosen for the separation. The typical chromatographic profiles of the blank, standard solution and the real sample solution were shown in Fig. 2. The blank sample used here was the mixture of 0.1 M HCl aqueous solution and methanol (1:100, v/v), which was applied in the extraction procedure. Almost no interference was presented in the chromatographic separation, and each target peak had a good resolution. Because of the different UV characteristic of these three categories compounds investigated, the detections at three wavelengths (254 nm for anthraquinone derivatives, 278 nm for flavones compounds, and 345 nm for protoberberine alkaloids, respectively) were carried out to improve the sensitivity and selectivity for the quantitative analysis. The chromatograms of the standard solution at three different detec-

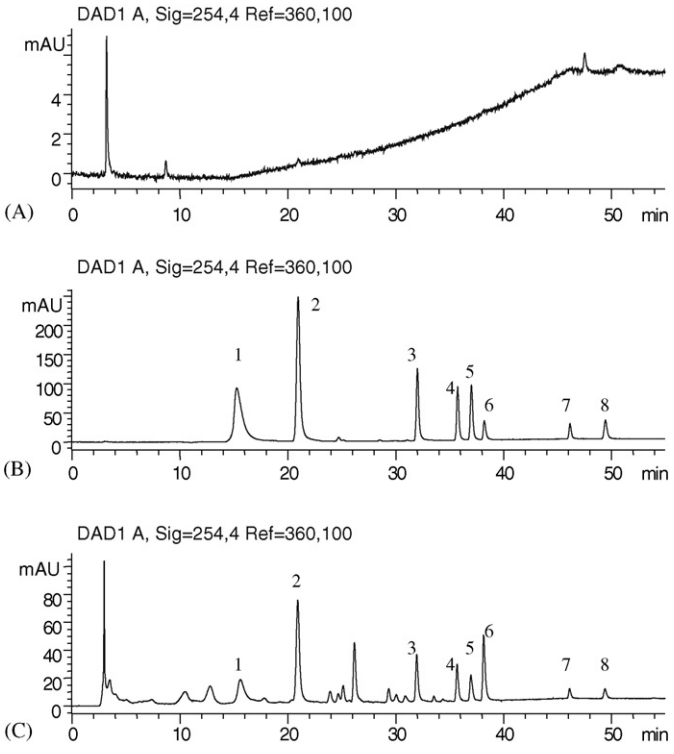

Fig. 2. The typical chromatographic profiles of the blank (A), standard solution (B) and the real sample solution (C). The peaks marked with 1–8 are berberine, baicalin, baicalein, wogonin, aloe-emodin, rhein, emodin and chrysophanol, respectively. The separation condition was described in Section 2.2.

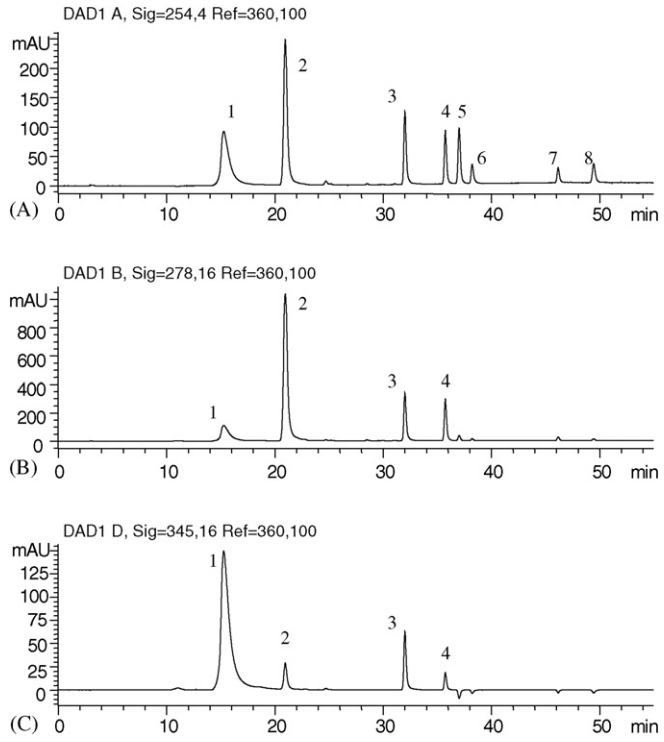

Fig. 3. Representative chromatograms of the mixture standard solution at three different detection wavelengths. The peaks marked with 1–8 are berberine, baicalin, baicalein, wogonin, aloe-emodin, rhein, emodin and chrysophanol, respectively. The separation condition was described in Section 2.2.

tion wavelengths were shown in Fig. 3. The representative UV spectra of three categories compounds were shown in Fig. 4. The target components in the chromatographic profile of the real sample solution were identified by comparing the retention times and the characteristic of the UV spectra of these peaks with those presented in the chromatogram of the mixture standard solution.

3.2. Linearity, work range and limits of detection

Integrated chromatographic peak areas were plotted against the corresponding concentration of the injected standard solutions to obtain the calibration curves. The injection concentration, which could be detected at the signal-to-noise ratio of 3, was considered to be the limit of detection (LOD). Limit of quantification (LOQ) was the injection concentration corresponding to the peak heights with signal-to-noise ratio of 10. The regression equations were established using seven concentration levels on the consecutive 6 days. The detailed descriptions of the regression curves were presented in Table 1. The good linearity (Coefficient of determination $R^2 > 0.99$) was achieved in the investigated ranges for all the analytes. Moreover, the developed calibration curves were considerable stable because the relative standard derivation (R.S.D.) values of the slope were all less than 5.0%. Although the R.S.D. values of intercept were a little higher, the quantification results were still stable, due to the fact that the values of intercept were not in the same order of magnitude of the corresponding values of peak area.

3.3. Repeatability, precision and stability

The injection repeatability was determined by the injection of continuous six times using the same sample, while the analysis repeatability was examined by the injection of six different samples, which were prepared with the same sample preparation procedure. The mixture standard solutions at three concentration levels were used for the test of injection repeatability, while the real sample solution was used for the test of analysis repeatability. The results of injection repeatability of the solution at medium concentration (berberine, 0.098 mg/ml; baicalin, 0.288 mg/ml; baicalein, 0.031 mg/ml; wogonin, 0.018 mg/ml; aloe-emodin, 0.008 mg/ml; rhein, 0.004 mg/ml; emodin, 0.003 mg/ml; chrysophanol, 0.097 mg/ml) were shown in Table 2, and all the R.S.D. values were lower than 1.0%. Meanwhile, the R.S.D. values of the analysis repeatability were lower than 2.0% both for the retention time and peak area.

The instrument precision was examined by performing the intra-day and inter-day assays by six replicate injections of the mixture standard solutions used above. The intra-assay precision was performed with the interval of 4 h in 1 day, while the inter-assay precision was performed over 6 days. The precision result of the solution at medium concentration was presented in Table 3, and it was shown that the R.S.D. values of retention time were lower than 1.0%, while the R.S.D. values of peak area were lower than 4.0% both for the intra-assay and inter-assay precision. For the stability test, the same real sample was analyzed within 24 h at the room temperature, and the solution was

Table 1
Results of regression analysis on calibration curves and detection limits

Components	Regression equation ($y = ax + b$)[a]	R^2	Linear range (mg/l)	LOD (mg/l)	LOQ (mg/l)
Berberine	$y = (45.20 \pm 0.46)x + (-65.44 \pm 10.67)$	0.9999	9.75–293.0	0.24	0.49
Baicalin	$y = (49.81 \pm 0.26)x + (280.95 \pm 28.88)$	0.9982	7.20–576.0	0.72	1.44
Baicalein	$y = (90.14 \pm 0.95)x + (-81.09 \pm 37.55)$	0.9999	1.55–153.5	0.15	0.31
Wogonin	$y = (129.79 \pm 2.71)x + (-24.21 \pm 20.66)$	0.9999	0.90–90.0	0.09	0.18
Aloe-emodin	$y = (105.02 \pm 2.85)x + (-19.95 \pm 7.09)$	0.9999	0.75–75.0	0.19	0.38
Rhein	$y = (66.09 \pm 2.67)x + (-10.99 \pm 5.01)$	0.9993	0.80–39.5	0.40	0.79
Emodin	$y = (65.44 \pm 1.41)x + (-2.34 \pm 1.69)$	0.9999	0.60–30.0	0.30	0.60
Chrysophanol	$y = (124.40 \pm 2.52)x + (-9.54 \pm 3.29)$	0.9999	0.50–26.0	0.26	0.52

[a] y is the peak area, x the corresponding injection concentration, a the slope and b is the intercept of the regression line, respectively. Both values of a and b are given as the form of mean ± S.D.

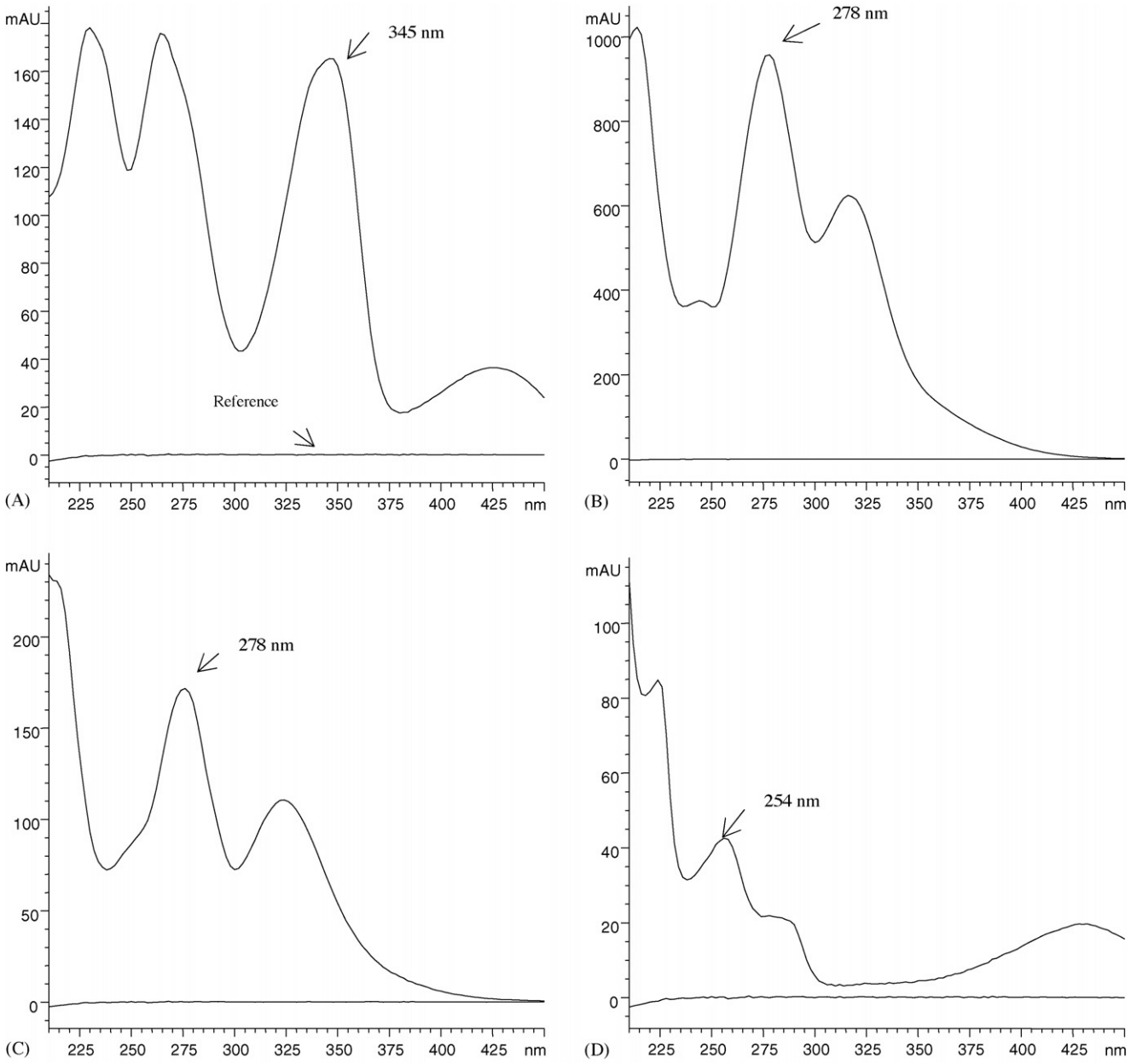

Fig. 4. The representative UV spectra of three categories compounds (A, berberine; B, baicalin; C, baicalein; D, aloe-emodin).

Table 2
Repeatability of the developed method ($n = 6$)

Components	Retention time (min)				Peak area (mAu s)			
	Injection repeatability		Analysis repeatability		Injection repeatability		Analysis repeatability	
	Average	R.S.D. (%)	Average	R.S.D. (%)	Average	R.S.D. (%)	Average	R.S.D. (%)
Berberine	15.47	0.09	15.46	0.04	4461.30	0.82	2928.48	1.58
Baicalin	21.01	0.08	21.00	0.08	15418.38	0.20	15073.63	1.08
Baicalein	32.03	0.04	32.03	0.11	2877.52	0.58	1259.72	1.63
Wogonin	35.78	0.05	35.76	0.05	2344.52	0.31	1067.43	0.77
Aloe-emodin	37.05	0.09	37.06	0.05	756.77	0.54	242.85	1.92
Rhein	38.32	0.01	38.25	0.04	231.27	0.95	571.73	1.12
Emodin	46.22	0.05	46.20	0.03	193.82	0.60	83.37	1.75
Chrysophanol	49.51	0.05	49.47	0.04	315.57	0.71	101.45	1.99

Table 3
Intra-assay and inter-assay precision of the developed method ($n = 6$)

Components	Retention time (min)		Peak area	
	Average	R.S.D. (%)	Average	R.S.D. (%)
Intra-assay				
Berberine	15.47	0.27	4459.78	0.98
Baicalin	21.01	0.15	15603.20	1.39
Baicalein	32.02	0.06	2899.23	0.92
Wogonin	35.76	0.04	2346.22	0.60
Aloe-emodin	37.03	0.06	760.70	0.61
Rhein	38.32	0.04	232.22	0.42
Emodin	46.20	0.03	194.00	0.43
Chrysophanol	49.49	0.03	316.57	1.00
Inter-assay				
Berberine	15.43	0.43	4365.92	1.33
Baicalin	20.93	0.25	15102.90	0.45
Baicalein	31.99	0.08	2590.98	3.64
Wogonin	35.72	0.07	2327.75	0.89
Aloe-emodin	36.98	0.16	775.25	1.56
Rhein	38.19	0.15	260.70	1.35
Emodin	46.15	0.05	191.55	0.97
Chrysophanol	49.43	0.04	309.52	1.12

found to be rather stable (R.S.D. values of the retention time and peak area were both lower than 2.0%).

3.4. Recovery test

Because of the complexity of Chinese medicines, there has neither a standard method for the determination of these active components nor a standard reference. Therefore, recovery of the standard from samples is generally used to evaluate the accuracy of the newly developed analytical method. Three different quantities (low, medium and high) of the authentic standards were added into the known real sample. The mixtures were extracted as described in Section 2.4, and was analyzed using the developed HPLC method mentioned above. Then, the quantity of each component was subsequently achieved from the corresponding calibration curves. As was shown in Table 4, the recovery of the investigated components ranged from 94.9% to 105.3%, and their R.S.D. values were all less than 5.0%. It was known from the recovery tests that the developed method manifested the reliability and accuracy for the measurement of these components.

Table 4
Recovery test of the developed method ($n = 3$)

Components	Quantity added (mg/l)	Quantity found (mg/l)	Recovery (%)	R.S.D. (%)
Berberine	23.76	24.85	104.6	0.92
	47.52	48.57	102.2	3.26
	71.28	71.35	100.1	1.10
Baicalin	89.60	93.27	104.1	4.30
	179.20	187.62	104.7	3.20
	268.80	263.96	98.2	0.63
Baicalein	3.32	3.21	96.8	2.30
	6.64	6.54	98.5	1.83
	9.96	10.13	101.7	2.17
Wogonin	2.13	2.15	100.8	2.00
	4.26	4.28	100.5	3.56
	6.39	6.06	94.9	1.45
Aloe-emodin	0.63	0.64	100.8	3.64
	1.26	1.25	99.4	4.70
	1.89	1.88	99.5	3.09
Rhein	2.53	2.66	105.3	2.98
	5.06	5.12	101.2	3.43
	7.59	7.40	97.5	3.07
Emodin	0.34	0.34	101.1	2.27
	0.68	0.67	98.3	4.33
	1.02	1.00	98.4	3.10
Chrysophanol	0.23	0.23	101.9	4.06
	0.46	0.46	100.6	3.77
	0.69	0.69	99.7	3.09

3.5. Application

The developed HPLC method was applied to the simultaneous determination of berberine, aloe-emodin, rhein, emodin, chrysophanol, baicalin, baicalein and wogonin in Chinese medicine 'YIQING' capsules from different production batches, and the results were presented in Table 5. It was shown that the content of baicalin was quite stable, because it was the target component for the quality control of 'YIQING' capsule by the

Table 5
Determination of the active components in 'YIQING' capsule by the developed HPLC method

No. of batches	Content ($n = 5$, mean ± S.D., mg/g)							
	Berberine	Baicalin	Baicalein	Wogonin	Aloe-emodin	Rhein	Emodin	Chrysophanol
20050803	13.20 ± 0.16	74.20 ± 1.55	3.80 ± 0.05	2.21 ± 0.03	0.65 ± 0.02	2.59 ± 0.04	0.38 ± 0.00	0.23 ± 0.00
20050920	14.08 ± 0.17	71.62 ± 0.67	4.06 ± 0.04	2.23 ± 0.02	0.64 ± 0.02	2.71 ± 0.02	0.35 ± 0.01	0.24 ± 0.00
20051012	16.58 ± 0.28	74.11 ± 0.83	3.73 ± 0.05	2.10 ± 0.02	0.62 ± 0.01	2.21 ± 0.03	0.33 ± 0.01	0.22 ± 0.00
20051103	17.71 ± 0.74	71.48 ± 3.07	3.63 ± 0.07	2.21 ± 0.04	0.65 ± 0.01	2.18 ± 0.04	0.34 ± 0.01	0.22 ± 0.00
20051124	15.48 ± 0.58	72.80 ± 2.30	3.24 ± 0.02	1.95 ± 0.03	0.62 ± 0.02	2.14 ± 0.04	0.31 ± 0.01	0.23 ± 0.00
20051125	14.91 ± 0.29	75.92 ± 0.74	3.35 ± 0.03	1.97 ± 0.01	0.63 ± 0.01	2.13 ± 0.02	0.30 ± 0.01	0.22 ± 0.00
20060106	13.38 ± 0.26	77.75 ± 1.24	3.63 ± 0.06	2.14 ± 0.02	0.71 ± 0.01	3.07 ± 0.03	0.40 ± 0.00	0.29 ± 0.01
Average	15.05	73.98	3.63	2.12	0.65	2.43	0.34	0.24
R.S.D. (%)	11.11	3.09	7.57	5.47	4.61	15.00	10.45	10.64

current method accepted by Chinese Pharmacopoeia [3]. However, the content of some important components such as berberine, rhein, emodin and chrysophanol had a fluctuation with the R.S.D. values higher than 10%, which would significantly influence the quality stability of this botanical drug. Therefore, the simultaneous determination of all these active components contained in 'YIQING' capsule is necessary to improve the quality control level of this botanical drug.

4. Conclusion

In the present study, an accurate and reliable analytical method for the simultaneous determination of eight active components (berberine, aloe-emodin, rhein, emodin, chrysophanol, baicalin, baicalein and wogonin) in Chinese medicine 'YIQING' capsule was developed using reverse phase high-performance liquid chromatography coupled with diode array detection. High linearity, repeatability, intra-day and inter-day precision, accuracy and reliability were presented in the method validation procedure. The proposed method is promising to improve the quality control of 'YIQING' capsule and other related botanical drugs.

Acknowledgements

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