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Pharmacokinetic study of three cardiovascular drugs by high-performance liquid chromatography using pre-column derivatization with 9,10-anthraquinone-2-sulfonyl chloride

Han Liu [a], Fang Feng [a,b,*], Ming Ma [a], Shuangjin Cui [a], Darong Xie [a], Sizhi Xu [a]

[a] *Department of Pharmaceutical Analysis, China Pharmaceutical University, Nanjing 210009, China*
[b] *Key Laboratory of Drug Quality Control and Pharmacovigilance (China Pharmaceutical University), Ministry of Education, Nanjing 210009, China*

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Abstract

A new method was developed to analyze three cardiovascular drugs in rat plasma, Mexiletine hydrochloride (MXL), Methoxamine hydrochloride (MTX), and Metaraminol bitartrate (MTR), by high-performance liquid chromatography (HPLC) using 9,10-anthraquinone-2-sulfonyl chloride (ASC) as the derivatization reagent. The derivatization modes and conditions for this method were optimized. The quantitative analysis was achieved using a C_{18} column at room temperature (25 °C), with various volume ratios of methanol–water as the mobile phase and a detection wavelength at 256 nm. Analytical linearity was obtained for the method over the concentration range of 0.04–8.0 μg mL^{-1} for all the three drugs. The lower limit of quantification (LLOQ) was 0.04 μg mL^{-1}. This method was successfully applied to the analysis of the three drugs in rat plasma and their pharmacokinetic studies. The $t_{1/2}$ values of the three drugs in rats were found to be 5.38 ± 0.61, 4.49 ± 0.53, and 3.70 ± 0.19 h for MXL, MTX, and MTR, respectively.

Keywords: High-performance liquid chromatography; 9,10-Anthraquinone-2-sulfonyl chloride; Derivatization; Mexiletine hydrochloride; Methoxamine hydrochloride; Metaraminol bitartrate; Rat pharmacokinetics

1. Introduction

Mexiletine hydrochloride (MXL), Methoxamine hydrochloride (MTX), and Metaraminol bitartrate (MTR) are cardiovascular drugs with a narrow therapeutic window [1,2]. When their concentrations in plasma exceeded the therapeutic window, serious side effects can occur [2,3]. It is thus important to monitor their concentrations in plasma.

Various methods have been reported for analyzing MXL, MTX, and MTR [4–16]. The previously published methods using gas chromatography (GC) [4,5], high-performance liquid chromatography (HPLC) [6–8], and high-performance capillary electrophoresis (HPCE) [9], however, were not sensitive enough, because their lower limit of quantification (LLOQ) was about 0.1 μg mL^{-1}. The methods using gas chromatography–mass spectrometry (GC–MS) [10,11] and liquid chromatography–mass spectrometry (LC–MS) [12] require the instrumentation that is not always available in common laboratories. Other methods, such as those by labeling drugs with ^{11}C [13,14] or ^{18}F [15,16], were unconventional and time-consuming.

Several derivatization reagents, such as 2,2,2-trichloroethyl chloroformate [16], perfluorooctanoyl chloride [17], dansyl chloride [18,19], fluram [20], and *o*-phthalaldehyde [21], have been applied for the analysis of MXL [17,18,20], MTX [19,21], and MTR [16,19]. The use of these agents, however, requires high reaction temperature [17], completion of the operation in dark [18,19], or complicated procedure [16,18,19].

An alternative derivatization agent, 9,10-anthraquinone-2-sulfonyl chloride (ASC), was synthesized in our laboratory [22]. This can react with the analyte rapidly at room temperature,

* Corresponding author. Tel.: +86 25 83271301.
E-mail address: fengfang1@126.com (F. Feng).

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without removal of light or a post-derivatization treatment to inactivate excessive reagents [22–24]. A considerable improvement was made of the polarity and UV absorption of the ASC derivatives [22–24], which are beneficial to the analysis of the trace drugs in biological fluids.

The purposes of this paper were to optimize the derivatization conditions and develop a specific, sensitive, and simple method for the analysis of the three drugs in biological samples and pharmacokinetic study in rat.

2. Experiment

2.1. Materials and reagents

Mexiletine hydrochloride, Methoxamine hydrochloride, and Metaraminol bitartrate were kindly supplied by Changzhou Pharmaceutical Co. Ltd. (Changzhou, China), Yuan Da Pharmaceutical Co. Ltd. (Wuhan, China), and Tai Yang Pharmaceutical Co. Ltd. (Beijing, China), respectively. The purity of each drug was above 98%. ASC was synthesized in our laboratory [22].

Methanol and acetonitrile were HPLC-grade (Merck, Darmstadt, Germany). Analytical grade dichloromethane, chloroform, ethyl acetate, ethyl ether, toluene, sodium hydroxide, boracic acid, potassium chloride, and sodium carbonate were used (Nanjing Chemical Co., Nanjing, China). Doubly distilled water was used throughout this study.

2.2. Instrumentation

An HPLC-UV system was used for this work. This consisted of a Shimadzu LC-10Atvp HPLC and a Shimadzu SPD-10Avp UV detector (Shimadzu, Kyoto, Japan). A Thermo Electron TSQ quantum ultra tandem mass spectrometer equipped with an electrospray ionization (ESI) source (San Jose, CA, USA), and a Thermo Electron surveyor LC pump together with an autosampler were used for the analysis by LC–MS. A Shimadzu UV-260 spectrometer (Shimadzu, Kyoto, Japan) was used to record the UV absorption of the standard derivatives.

2.3. Chromatographic conditions

The chromatographic analysis was performed using a Lichrosper C_{18} column (250 mm × 4.6 mm, 5 μm; Hanbang Co., Huaian, China) with column temperature set at 25 °C. The detection wavelength was 256 nm and the flow rate was 1.0 mL min^{-1}. Methanol–water (80:20, v/v) was used as the mobile phase-I for the analysis of MXL, methanol–water (72:28, v/v) as mobile phase-II for MTX, methanol–water (70:30, v/v) as the mobile phase-III for MTR.

2.4. Mass spectrometry conditions

The mass spectrometer was operated in negative ion mode, using the full scan mode. The spray voltage was set at 5.0 kV. Nitrogen was used as the sheath gas (35 psi). The heated capillary temperature was set at 300 °C.

2.5. Preparation of solutions

The buffers of different pH ranged from 6.6 to 8.5 were prepared according to Atkins-Pantin buffer [25]. The ASC stock solution was prepared by dissolving ASC in acetonitrile to obtain a concentration of 500 μg mL^{-1}. The working solutions of ASC were obtained a by serial dilution of the stock solution. The stock solution of each drug was prepared by dissolving each drug in water to obtain a concentration of 80 μg mL^{-1}. The working solutions of each drug were obtained by a serial dilution of the stock solution. All the solutions prepared above were stored at 4 °C.

2.6. Calibration curves and quality control (QC) samples

To each drug, samples for plasma calibration curves (with concentration of 0.04–8.00 μg mL^{-1}) were prepared by adding 10 μL of its working solutions to 100 μL blank rat plasma. The QC samples (0.04, 0.40, and 4.00 μg mL^{-1} in plasma) were obtained in the same way.

2.7. Preparation of the standard derivatives

In a 50-mL three-necked flask, 1.2 mmol of each drug was dissolved with 5 mL of water. Then 1 mL of 2 mol L^{-1} NaOH solution and 8 mL of ethyl acetate were added successively to the flask with stirring. The ASC solution (1.0 mmol in 8 mL ethyl acetate) was added dropwise to the flask within 15 min. The mixture was stirred for 1.5 h. Then the aqueous phase was discarded. The organic phase was washed with 10 mL of water for three times, and then separated from the aqueous phase and dried over anhydrous Na_2SO_4. The ethyl acetate was then removed using a water-bath kept at 80 °C to obtain the derivatives. The three standard derivatives were identified by ESI-MS in the negative ion mode. The UV absorption charts of standard derivatives were obtained by the Shimadzu UV-260 spectrometer.

2.8. Pre-column derivatization procedure

To 0.1 mL of plasma, 0.05 mL of 0.5 mol L^{-1} NaOH solution and 0.5 mL of ethyl acetate were added successively. The mixture was vortex-mixed for 3 min and then centrifuged at 1500 × *g* for 10 min. 0.4 mL of the supernatant was transferred to a glass tube and evaporated to dryness at 37 °C under a gentle nitrogen stream. The dry residue was dissolved with 75 μL of the buffer (pH 7.9 for MXL and MTX, pH 7.2 for MTR), and then mixed with 25 μL of ASC solution (300 μg mL^{-1}) by vortex-mixing for 15 min at room temperature. Twenty microliters of the solution was injected into the HPLC-UV system.

2.9. Method validation

To evaluate linearity, plasma calibration curves were prepared and assayed repeatedly on five separate days. The peak areas (*A*) of each derivative were plotted against the theoretical concentrations (*C*) in plasma. Regression parameters of the slope, intercept, standard derivations of the slope and intercept and cor-

relation coefficient (r) were calculated. Precision and accuracy were determined repeatedly on three separate days by using QC samples replicates ($n = 5$) at three concentrations. The precision was defined as the relative standard deviation (RSD) calculated using QC samples ($n = 5$). The accuracy was defined as the relative error (RE) of the mean of QC samples ($n = 5$) from the theoretical concentrations. The stability of the three drugs in plasma was evaluated by analyzing QC samples ($n = 3$) under various conditions in terms of temperature and duration (room temperature storage for 12 h, long-term storage at −20 °C for 5 days, and freezing-thawing for five cycles). The stability of the extraction was assessed by storing the extracted QC samples at −20 °C for 5 days, followed by analysis. The resulting concentrations were compared with their theoretical concentrations, and the relative error (RE) was calculated. The evaluation of the stability of the derivatives in derivatization mixture was conducted after derivatization by storing the mixture at room temperature over a period of 48 h, followed by analysis.

2.10. Pharmacokinetic study

2.10.1. Animal

Sprague-Dawley male rats (180–220 g) were supplied by the Laboratory Animal Center of China Pharmaceutical University (Nanjing, China). The rats were housed under controlled environmental conditions (temperature at 23 ± 1 °C; humidity at 55% ± 5%) with a commercial food diet and water free. The studies were approved by the Animal Ethics Committee of China Pharmaceutical University.

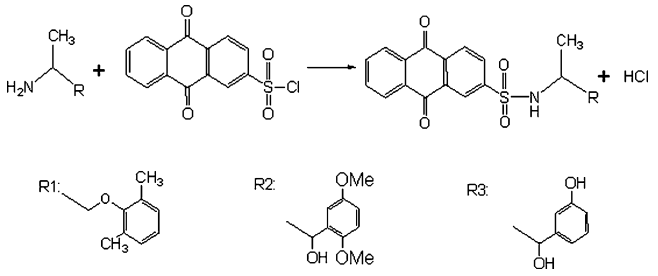
2.10.2. Animal administration

The rats were fasted overnight with a free access to water for at least 12 h before the experiment. The drugs were administered to the rats following the clinical administration, respectively.

MXL aqueous solution was orally administrated to the rats at the level of 50 mg kg^{-1}. After administration, 0.2 mL of blood was collected at the time intervals of 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 h. MTX and MTR solutions were intravenously administrated to the rats at the level of 1 mg kg^{-1}, respectively. 0.2 mL of blood was collected at the time intervals of 0.05, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, and 12 h post-dosing. The plasma was immediately separated by centrifugation at 5000 × g for 10 min and stored at −20 °C until analyzed.

2.10.3. Analysis of rat plasma samples and calculation of pharmacokinetic parameters

The rat plasma samples were analyzed following the procedures previously described in Section 2.8. Pharmacokinetic parameters were calculated from the plasma concentration–time data. The elimination half-life time ($t_{1/2}$) and elimination rate constant (k_e) were calculated by linear regression of the terminal portion of the plasma concentration–time curve. The peak plasma concentration (C_{max}) was the observed value obtained from the experimental data. The area under the plasma concentration–time curve from zero to the last measurable concentration point ($AUC_{0-\tau}$), the area under the plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$), mean residence time (MRT), apparent volume of distribution (V_d), and total plasma clearance (Cl) were calculated according to non-compartmental model.



Scheme 1. The synthesis reaction between ASC and MXL (R1), MTX (R2), and MTR (R3).

3. Results and discussion

3.1. Identification of the standard derivatization products

The reaction of ASC with MXL, MTX, and MTR is shown in Scheme 1. Three derivatives, MXL–ASC (yellow solid), MTX–ASC (orange solid), and MTR–ASC (yellow solid) were obtained following the procedures in Section 2.7. These all had UV absorptions at 256 and 325 nm, which were similar to those of ASC derivatives previously reported [22–24]. The absorption at 256 nm was much greater than that at 325 nm, and consequently 256 nm was selected as detection wavelength. The mass spectra of each derivative were obtained by ESI-MS in negative ion mode, using full scan mode. The base peaks in the mass spectra were attributed to the $[M–H]^-$ ions of the three derivatives with m/z 448, 480, and 436 for MXL, MTX, and MTR, respectively.

3.2. Optimization of the derivatization mode and conditions

3.2.1. Derivatization mode

Previous applications of ASC [22–24] were all performed in a two-phase (aqueous–organic) system while a one-phase system was also a common derivatization mode [26,27]. In this study, both the two-phase system and one-phase system were studied and compared with each other.

3.2.1.1. Two-phase mode. The solution of each drug was mixed with NaOH solution and ASC solution prepared by different organic solvents. The mixture was vortex-mixed and centrifuged. The organic phase was separated and evaporated to dryness. The residue was dissolved by mobile phase and analyzed by HPLC-UV.

3.2.1.2. One-phase mode. The ASC solution prepared by acetone or acetonitrile was added to the solution of each drug (prepared in the buffers with various pHs). The mixture was vortex-mixed. Twenty microliters of the mixture was injected into HPLC-UV system.

The one-phase system was found to exhibit certain advantages over the two-phase one. First, the derivatization efficiency

of the one-phase system was much higher. Second, the procedure of the one-phase system was much simpler. As a result, the one-phase system was selected. The derivatization using ASC acetonitrile solution led to a better peak shape than that using acetone, and consequently acetonitrile was selected as the reaction solvent.

3.2.2. Derivatization conditions

The influence of the buffer pH, ASC volume, ASC concentration, and reaction time were investigated.

3.2.2.1. Buffer pH. The buffer was used to keep the drugs in dissociative form in order to retain their nucleophilic character. The effect of the buffer pH was investigated in the pH range from 6.6 to 8.5. The derivatization efficiency was found to reach maximum when the buffer pH was at 7.9 for MXL and MTX, and 7.2 for MTR.

3.2.2.2. ASC volume. When the aqueous volume ($V_{aqueous}$) was fixed, the volume of the ASC solution (V_{ASC}) was one of the important factors. The ratio of $V_{ASC}/V_{aqueous}$ was varied from 1/5 to 3/1, and the ratio of 1/3 was found to be the optimum.

3.2.2.3. ASC concentration. The influence of ASC concentration was examined over a range of 20–500 μg mL^{-1}. The analytical responses of the three drugs were all found to reach the maximum when ASC concentration was 300 μg mL^{-1}.

3.2.2.4. Reaction time. The effect of reaction time was tested over the range from 3 to 20 min. When reaction time was more than 10 min, the derivatization efficiency was found to arrive at the maximum. Fifteen minutes ware adopted to guarantee complete reaction.

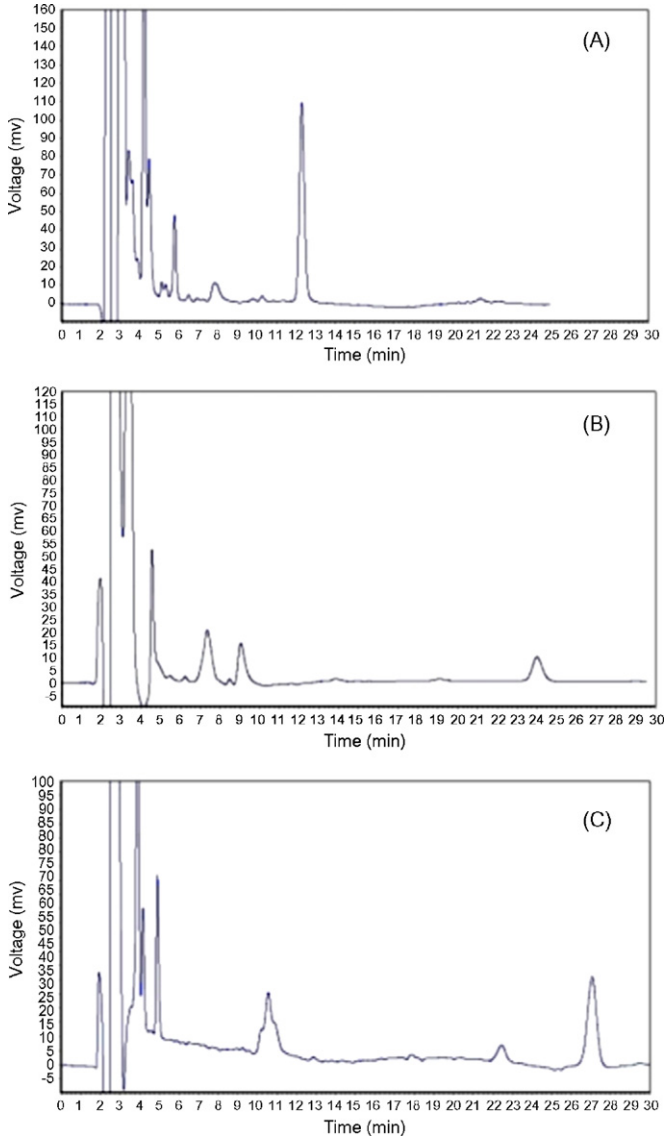


Fig. 1. Derivatization chromatograms of blank rat plasma by the method of MXL (A), MTX (B), and MTR (C).

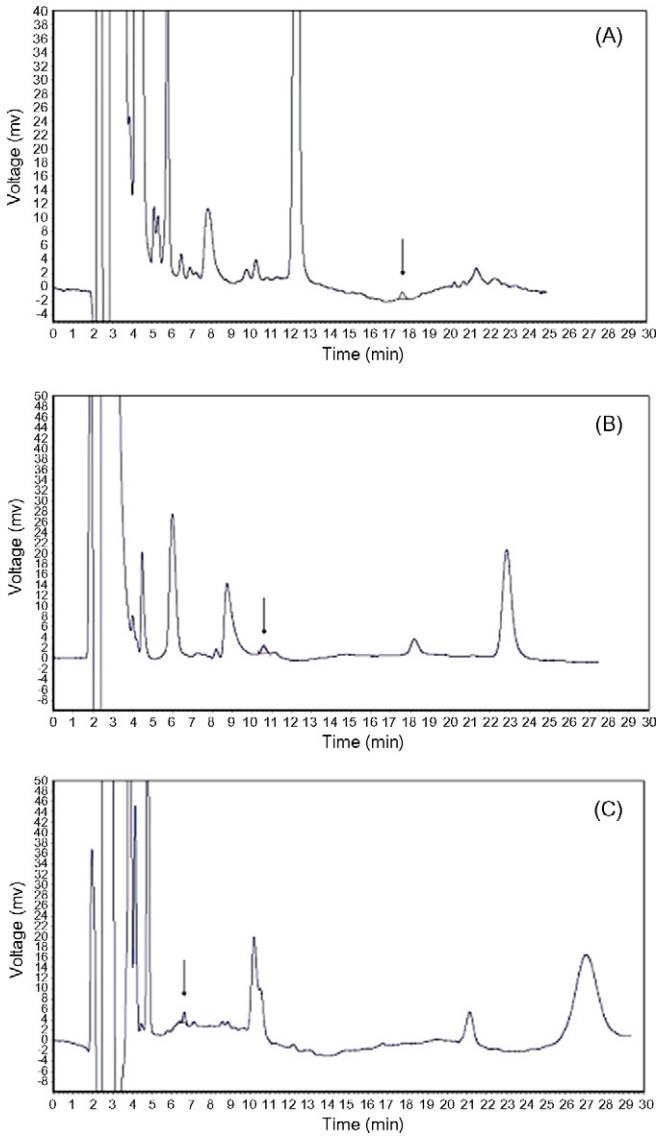


Fig. 2. Derivatization chromatograms of rat plasma added with MXL (A), MTX (B), and MTR (C) (0.04 μg mL^{-1}).

Table 1
The precision of the derivatization method ($n = 5$)

		Added concentration ($\mu g\,mL^{-1}$)					
		0.04		0.40		4.00	
		Mean	RSD (%)	Mean	RSD (%)	Mean	RSD (%)
MXL	Intra-batch	0.037	7.9	0.408	5.6	4.017	3.0
	Inter-batch	0.038	8.6	0.411	7.1	4.023	5.4
MTX	Intra-batch	0.039	8.3	0.407	5.9	4.021	3.2
	Inter-batch	0.038	8.7	0.405	7.2	4.025	6.3
MTR	Intra-batch	0.042	8.0	0.409	5.3	4.021	3.4
	Inter-batch	0.041	8.7	0.406	7.6	4.019	5.4

3.3. Method validation

3.3.1. Specificity

Fig. 1 presents the chromatograms of blank rat plasma by the method of MXL, MTX, and MTR. No significant interference was observed at the retention time of 17.6 min, 10.7 min, and 6.8 min for MXL–ASC, MTX–ASC, and MTR–ASC, respectively.

3.3.2. Linearity of calibration curves and lower limits of quantification

Analytical linearity was obtained for the method over the plasma concentration from 0.04 to 8.0 $\mu g\,mL^{-1}$ for all the three drugs. The linear equations for MXL, MTX, and MTR were as follows: $A = (451608.6 \pm 9051.1) \times C + (1862.6 \pm 84.2)$, $A = (535999.8 \pm 11767.5) \times C + (3480.8 \pm 107.5)$, and $A = (491736.2 \pm 8961.4) \times C - (5485 \pm 124.6)$, respectively, with correlation coefficients (r) equal to or greater than 0.9993.

Table 2
The accuracy of the derivatization method ($n = 5$)

	Relative error (%)		
	0.04[a]	0.40[a]	4.00[a]
MXL	−3.9	2.4	0.9
MTX	−3.6	1.4	0.8
MTR	2.8	2.5	2.1

[a] Added concentration ($\mu g\,mL^{-1}$).

Table 3
The stability of three drugs in plasma ($n = 3$)

Conditions	Drugs	Added concentration ($\mu g\,mL^{-1}$)					
		0.40		4.00		4.00	
		Mean	RE (%)	Mean	RE (%)	Mean	RE (%)
Room temperature storage for 12 h	MXL	0.038	−4.5	0.42	5.2	4.12	3.0
	MTX	0.043	6.8	0.39	−3.5	3.88	−3.0
	MTR	0.037	−8.5	0.38	−5.8	3.91	−2.3
Long-term storage at −20 °C for 5 days	MXL	0.042	5.7	0.37	−7.0	4.18	4.5
	MTX	0.037	−8.0	0.38	−4.8	3.89	−2.8
	MTR	0.042	4.8	0.43	7.0	3.86	−3.5
Freeze-thaw for five cycles	MXL	0.044	9.3	0.39	−2.0	4.15	3.8
	MTX	0.038	−5.8	0.42	4.2	4.21	5.3
	MTR	0.038	−6.0	0.42	5.2	3.81	−4.8
Extraction storage for 5 days	MXL	0.037	−7.3	0.43	6.2	4.10	2.5
	MTX	0.043	7.8	0.42	5.5	3.79	−5.3
	MTR	0.042	4.5	0.42	4.0	4.09	2.3

Table 4
The pharmacokinetic parameters of MXL, MTX and MTR

Drugs		C_{max}[a] ($\mu g\,mL^{-1}$)	$t_{1/2}$ (h)	k_e (h^{-1})	k_a[a] (h^{-1})	MRT (h)	V_d (L)	Cl ($mL\,min^{-1}$)	$AUC_{0-\tau}$ ($\mu g\,h\,mL^{-1}$)	$AUC_{0-\infty}$ ($\mu g\,h\,mL^{-1}$)
MXL	Mean	3.86	5.38	0.13	0.36	5.53	2.68	5.71	12.36	12.96
	±s	1.26	0.61	0.01	0.06	1.15	0.51	0.49	3.51	3.34
MTX	Mean		4.49	0.16		6.24	0.28	0.73	1.75	2.06
	±s		0.53	0.02		0.66	0.04	0.13	0.04	0.07
MTR	Mean		3.70	0.19		4.73	0.13	0.41	2.79	3.10
	±s		0.19	0.01		0.19	0.02	0.08	0.27	0.32

[a] MTX and MTR were administered to rat intravenous. Since there were no "C_{max}" or "k_a" in intravenous model, C_{max} and k_a of MTX and MTR were not listed.

The limit of detection (LOD) for MXL, MTX, and MTR were 0.01 μg mL^{-1} with a signal-to-noise ratio (S/N) of 3. The lower limit of quantification (LLOQ) was defined as the lowest concentration on the calibration curve. The LLOQ of MXL, MTX, and MTR were 0.04 μg mL^{-1} (Fig. 2).

3.3.3. Precision and accuracy

Precision of the assay was determined by repeatedly analyzing the QC replicates ($n = 5$) at three concentration levels on three separate days. The intra-batch and inter-batch precisions were less than 9% for each drug at the three concentrations tested. The accuracy of the method ranged from −3.9% to 2.8%. All intra-batch precision, inter-batch precision, and accuracy values were acceptable over the entire concentration range tested. The results of the precision and accuracy are presented in Tables 1 and 2, respectively.

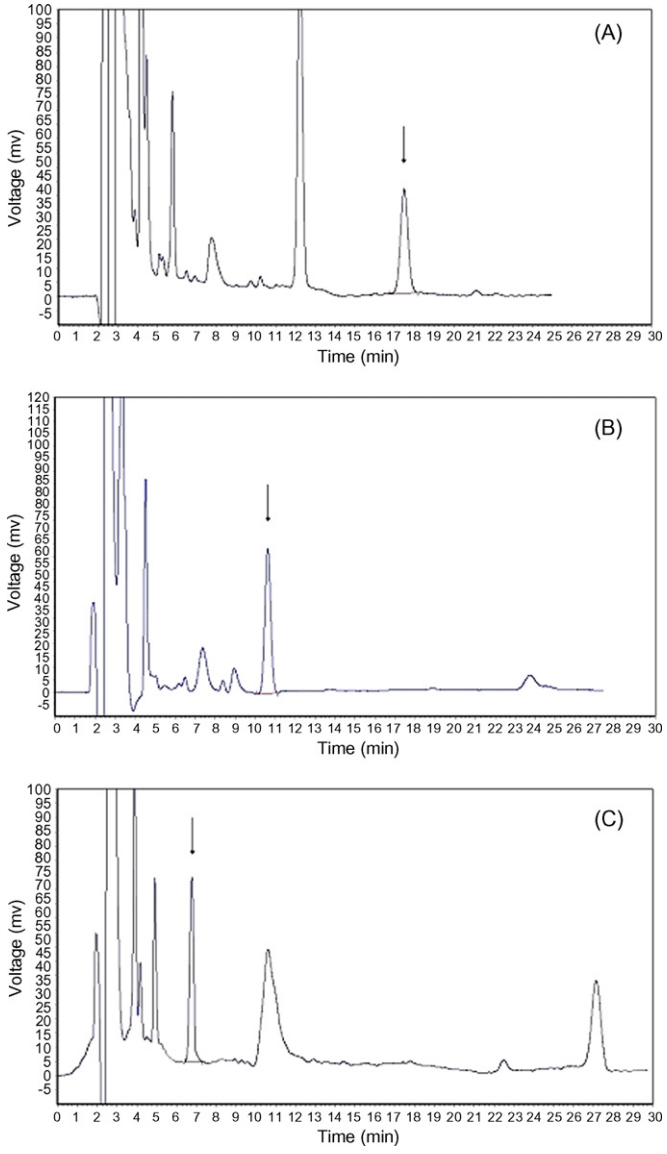


Fig. 3. Derivatization chromatograms of rat plasma samples of MXL (A), MTX (B), and MTR (C).

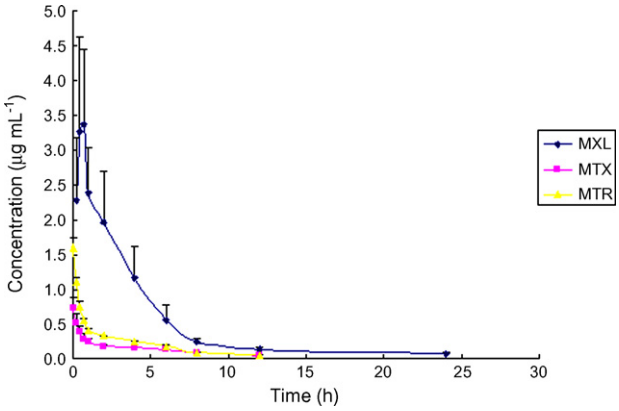


Fig. 4. Plasma concentration–time curves of MXL, MTX, and MTR.

3.3.4. Stability

The stability experiments were designed to cover the anticipated conditions that the authentic samples may encounter (e.g., room temperature storage for 12 h, long-term storage at −20 °C for 5 days, freezing-thawing for five cycles, and extraction storage for 5 days). The results are summarized in Table 3. For each stability condition tested, the relative error was less than ±10%, indicating no significant degradation. The stability of the MXL, MTX, and MTR derivatives in the mixture after derivatization at room temperature was tested over a period of 48 h. Compared with the derivatization samples prepared freshly, no significant degradation was found by inspecting the peak areas of the derivatives. This indicates that the derivatives were sufficiently stable during the time required for analysis.

3.4. Pharmacokinetic results

Fig. 3 presents the typical chromatograms of the plasma samples obtained from the rats after administration of MXL, MTX, and MTR, respectively. The plasma concentration–time curves for the three drugs are provided in Fig. 4. The pharmacokinetic parameters were calculated according to the concentration–time curves and are listed in Table 4. The $t_{1/2}$ of the three drugs in rat were 5.38 ± 0.61, 4.49 ± 0.53, and 3.70 ± 0.19 h, respectively. $AUC_{0-\tau}$ of the three drugs in rat were 12.86 ± 3.51, 1.75 ± 0.04, and 2.79 ± 0.27 μg h mL^{-1}, respectively.

4. Conclusions

An HPLC method with a new pre-column derivatization was developed using 9,10-anthraquinone-2-sulfonyl chloride (ASC) as derivatization reagent for the determination of MXL, MTX, and MTR in rat plasma. After a pre-column derivatization, both the detection limit and the chromatographic behavior of each drug were improved significantly. Compared to the other methods [4–19] reported previously, this method was accurate, sensitive, and simple. It has been successfully applied to the pharmacokinetic study of three drugs in rats, and the pharmacokinetic characteristics were revealed.

The derivatization with ASC was first time accomplished in one-phase system, and it was completed rapidly at room temper-

ature and without protection from light. This new derivatization mode can help to understand the characteristics of ASC and should be of value for its further application.

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