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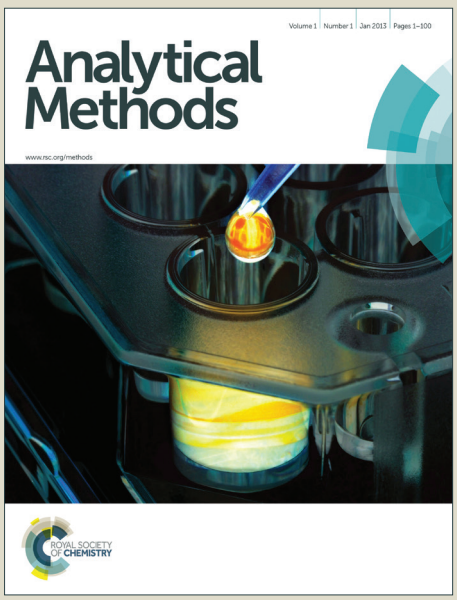

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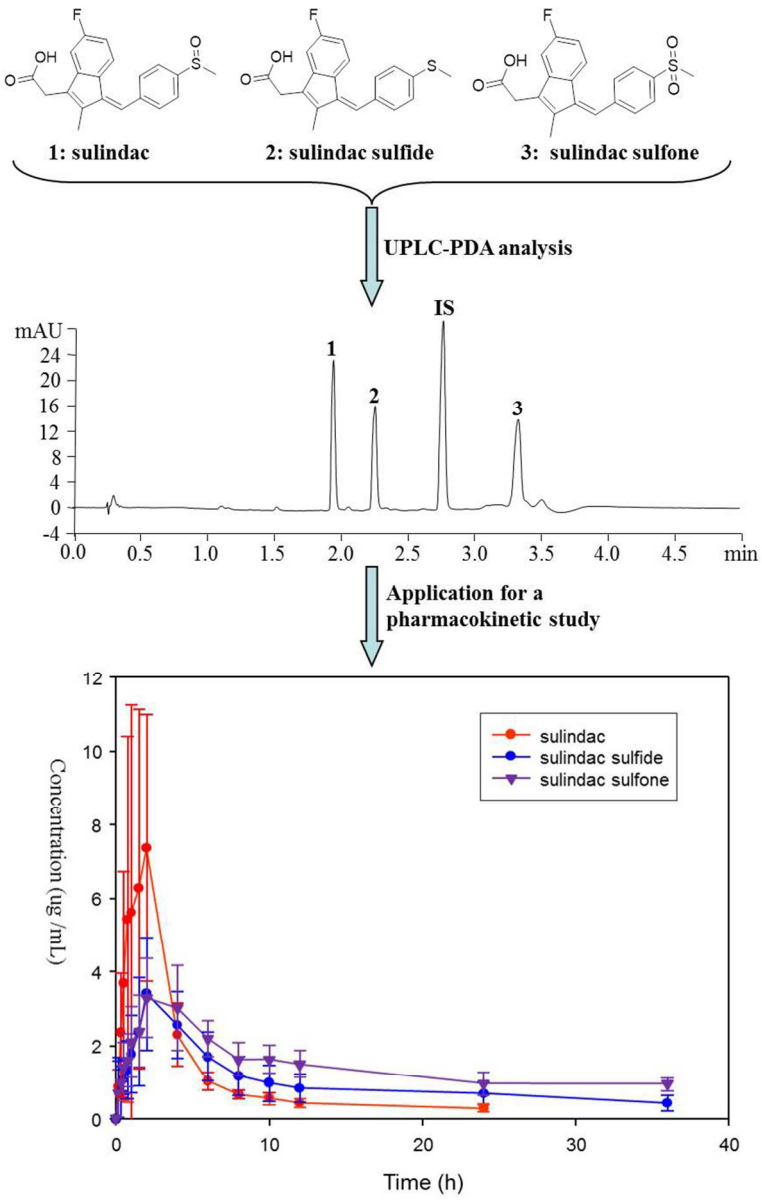

Pharmacokinetic study of Sulindac and its metabolites
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Simultaneous determination of sulindac and its metabolites sulindac sulfide and sulindac sulfone in human plasma by a sensitive UPLC-PDA method for a pharmacokinetic study

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Abstract

A sensitive, rapid and reliable ultra-performance liquid chromatography (UPLC) with Photo-Diode Array (PDA) detection method was developed for simultaneous determination of sulindac and its metabolites sulindac sulfide and sulindac sulfone in human plasma. The analytes were extracted by dichloromethane from human plasma using a liquid-liquid extraction method. The chromatographic separation was performed on Waters Acquity UPLC with a Waters Acquity UPLC BEH C_{18} column (2.1 × 50 mm i.d., 1.7 μm) within 5 minutes. The mobile phase used for gradient elution consisted of ammonium formate buffer (20 mM) containing 1% acetic acid and acetonitrile. The flow rate was maintained at 0.4 ml/min. The monitor wavelength was set at 328 nm for PDA detection. All calibration curves of the analytes showed good linearity within the test ranges. The validated method was successfully applied to a pharmacokinetic study of sulindac, sulindac sulfide and sulindac sulfone in 15 healthy Chinese male subjects with oral administration of sulindac tablets.

Keywords

Sulindac; Sulindac sulfide; Sulindac sulfone; UPLC; Human plasma

1 Introduction

Sulindac is a non-steroidal anti-inflammatory drug which was approved by FDA in 1978 and has already been used for the treatment of various inflammations more than thirty years [1]. Additionally, many reports have indicated that sulindac had lung tumorigenesis, familial adenomatous polyposis (FAP), colorectal and skin cancer chemopreventive efficacy [2-6]. The pharmacological studies have revealed that sulindac is a pro-drug containing a racemic sulfoxide moiety, which could be transformed to the active sulfide form by the gut flora before absorption [7, 8]. Actually, as a chemopreventive agent in cancer, sulindac has been ascribed to its metabolites, sulindac sulfide and sulindac sulfone [9]. Sulindac sulfide could inhibit the synthesis of prostaglandin due to the COX activity reduction, which could be synthesized by methionine sulfoxide reductase [7, 10]. Sulindac sulfone is also known as exisulind which has been attracting more and more interests on its anticancer effects due to the remarkable efficacy in a colorectal adenoma when administrated with difluoromethylornithine together, although it has been suspended as an independent agent for cancer chemoprevention because of its toxicities [11, 12]. Compared with other non-steroidal anti-inflammatory drug, the pharmacokinetic reports of sulindac formula are relatively limited [10].

A few analytical methods are available for separation and analysis of sulindac as well as simultaneous determination of sulindac and its active metabolites sulindac sulfide and sulindac sulfone [9, 13-15]. Recently, as development as the usage of sulindac, analytical methods such as UV spectrophotometric [16], HPTLC [17], HPLC [18-20], LC–MS

[21-23], electrochemical [24] and high performance capillary electrophoresis [25-27] have been developed and validated for determination of sulindac and its metabolites. Ultra-performance liquid chromatography (UPLC) is devoted to increase separation efficiency with the column packing material of small particle size less than 3 μm. Additionally, small particles strengthen the resolution, sensitivity and peak areas. Compared with HPLC, more eluates could be analyzed and detected in a unit time by UPLC. UPLC method is more often validated at present in pharmacokinetic assessments [28]. However, up to date, no UPLC method has been reported for simultaneous determination of sulindac and its metabolites in human plasma.

In this study, a rapid, sensitive, simple and specific UPLC-PDA method was developed for simultaneous determination of sulindac and its metabolites in human plasma. This method has the advantages of higher sensitivity, shorter run time and less organic solvents consumption. It has been completely validated and successfully applied to a pharmacokinetic study of sulindac tablets in 15 healthy Chinese male subjects with oral administration of this drug.

2 Experimental

2.1 Materials and chemicals

Ammonium formate (purity: 99.5%, batch No.: T20081022) and acetic acid (purity: 99.0%, batch No.: 20080311) were purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, PR China). Sulindac (batch No.: S8139), sulindac sulfide (batch No.: S3131), sulindac sulfone (batch No.: S1438) and indomethacin (batch No.: I7378) were purchased from Sigma-Aldrich (St. Louis, MO, USA). The purity of all

compounds was >98%, which were analyzed by UPLC. The structures of all analytes are shown in Fig.1. The test drug was Zulida (Sulindac Tablets, 100 mg each, batch No.: 060301), which was supplied by Ningbo Team Pharm Co., Ltd (Zhejiang, PR China).

Methanol and Acetonitrile for UPLC were purchased from Merck (Darmstadt, Germany). Deionized water was prepared using a Millipore Milli Q-Plus system (Millipore, Bedford, MA, USA). Blank human plasma was provided by Xiangya Hospital of Central South University (Changsha, PR China).

2.2 Standard and quality control samples preparation

Stock solutions of sulindac (1041.2 μg/mL), sulindac sulfide (2352.0 μg/mL), sulindac sulfone (2088.1 μg/mL) and indometacin (1001.2 μg/mL) were prepared in acetonitrile/water (50/50, *v/v*). All the stock solutions were stored at 4 °C. All analytes were weighed on an electronic analytical balance (AB265-S) from Mettler Toledo (Switzerland).

The samples for standard calibration curves were prepared by spiking the blank plasma with appropriate working solutions of sulindac, sulindac sulfide and sulindac sulfone to yield the corresponding concentrations, respectively (Table 1). Quality control (QC) samples were prepared from blank plasma at concentrations of 104.120, 26.030 and 3.254 μg/mL for sulindac, 117.603, 29.401 and 3.675 μg/mL for sulindac sulfide, and 104.404, 26.101 and 3.263 μg/mL for sulindac sulfone, respectively. All calibration curves and QC samples used to estimate precision and accuracy of the method were prepared from separate stock solutions. The stock solution of internal

standard (IS, Indomethacin) was prepared at a concentration of 1001.2 μg/mL by the same way, which was used as IS working solution for all analyses. All standard calibration curves solutions were stored at –40 °C.

2.3 Sample preparation

Prior to extraction procedure, all calibration curve, QC and subject frozen samples were thawed and equilibrated at room temperature. 500 μL plasma/subject samples mixed with 100 μL of IS working solution were vortexed for 15 s. After adding 1.0 mL hydrochloric acid (1M) and 1.0 mL dichloromethane, the mixture was vortexed for 10 min and centrifuged at 3000 RPM for 10 min. Then, the subnatant organic layer was separated and evaporated to dryness in a thermostatic control water bath maintained at 40 °C under a slow stream of nitrogen. Subsequently, the residue was redissolved by consisting of 200 μL mobile phase and 200 μL acetonitrile. After brief vortexing, 20 μL samples were injected into the UPLC system.

2.4 UPLC-PDA analysis

The rapid chromatographic separation was performed on a Waters Acquity UPLC system (Milford, MA, USA), which was equipped with a binary solvent manager, a sample manager, a column heater, a photodiode array detector and an in-line filter (2.1 mm, 0.2 μm) and connected to a Waters Empower software. An Acquity UPLC BEH C_{18} column (2.1 × 50 mm i.d., 1.7 μm) was operated for the chemical separation, which was maintained at 40 °C. The monitoring wavelength was set at 328 nm for the detection of sulindac and its metabolites. The mobile phase consisted of solvent A (20 mM ammonium formate with 1% acetic acid) and solvent B (acetonitrile). Gradient

elution with (A) and (B) was : 0 – 0.3 min, 10% B; 0.3 – 1.0 min, 10% – 30% B; 1.0 – 2.7 min, 30% – 60% B; 2.7 – 3.2 min, 60% B; 3.2 – 3.4 min, 60% – 100% B; 3.4 – 5.0 min, 10%B to balance the system. The flow rate was maintained at 0.4 mL/min. The temperature of autosampler was retained at 15 ℃.

2.5 Calibration curves

The prepared samples in ***2.2*** containing three analytes were diluted to appropriate concentrations for the construction of calibration curves. At least six concentrations of the analytes were analyzed in duplicates, and the calibration curves were constructed by plotting plotting the peak area ratios between analytes and internal standard (27.811 μg/mL) versus the concentrations of each compound.

2.6 Lower limits of quantification

The stock solution containing three analytical standards was diluted with blank plasma to a series of appropriate concentrations. After adding appropriate hydrochloric acid (1M) and dichloromethane, the mixture was vortexed for 10 min and centrifuged at 3000 RPM for 10 min. Then, an aliquot of the diluted solutions were injected into UPLC system for analysis. The lower limits of quantification (LLOQ) under the present chromatographic conditions were determined at a signal-to-noise ratio (S/N) of about 10, respectively.

2.7 Precision, accuracy, recovery and stability

System suitability experiment was operated by injecting six consecutive standard mixtures of analytes and IS for each batch during method validation. System performance was confirmed by injecting one prepared blank plasma sample and one

LLOQ sample with IS before each batch analysis. Autosampler carryover was performed by sequentially analyzing extracted blank plasma sample, QC sample, two extracted blank plasma sample, LLOQ sample and extracted blank plasma sample before and after each batch analysis. The method was validated with respect to selectivity, linearity, accuracy, precision, recovery, and stability based on the United States Food and Drug Administration (FDA) bioanalytical method validation guidance.

Selectivity of the method was performed for potential matrix interferences in ten batches of blank human plasma by detection and inspection of interfering peaks in the chromatograms. The plasma samples from human subjects were also ascertained for the selectivity. Additionally, working solutions were dissolved in the mobile phase and injected to check for any possible interference of analytes and IS at the retention time. The chromatographic peaks purity of analytes and IS was calculated according to their UV absorption under the proposed UPLC-PDA conditions.

Calibration curves were prepared and assayed with linear regression. Concentrations of QC samples were calculated using the equation of the calibration curves. The correlation coefficient of calibration curve must be $\geqslant 0.99$ for each analyte. Reinjection reproducibility was also checked by reinjection of extracted samples on an entire analytical run after storage at 4 °C. Intra-day accuracy and precision were evaluated on the same day by analyzing plasma samples repeatedly. The analytical run contained a calibration curve and six replicates of low QC, middle QC and high QC samples. The inter-day precision and accuracy were evaluated by assaying six

replicates of QC samples at the low, middle and high concentrations on three consecutive days. The precision (CV, %) was calculated as the percent error in the calculated mean concentration relative to the nominal concentration. Accuracy was expressed as relative standard deviation (RSD) at each concentration level from the nominal concentration. Usually, the precision and accuracy at each QC level was required to be within 15%.

The extraction recovery and matrix effects were investigated on the extracted samples, working solution samples and post-extraction spiked samples at three QC levels in the same assay. The extraction recovery was calculated by comparing the peak areas of analyts/IS in extracted samples with those in post-extraction spiked samples at corresponding concentrations. The matrix effects were evaluated by comparing the peak areas of the analytes in post-extraction spiked samples with those in working solution samples. This procedure was repeated for six times at each QC levels of sulindac, sulindac sulfide and sulindac sulfone, respectively.

Stability in plasma were evaluated by obtaining the area ratio response (analyte/IS) at three levels of QC plasma samples against freshly prepared comparison standards with six replicates under the experimental condition. The short-term stabilities of analytes were evaluated by analyzing three concentration levels of QC plasma samples after extraction, which were stored for 24 h at room temperature and 6h in auto-sampler after preparation. The long-term stability was examined with three concentration levels of QC plasma samples for each corresponding compound stored for 60 days at −40 °C. Freeze−thaw stability results were determined after freezing at

−40 °C and thawing for three times at room temperature. The stability of analytes and IS working solutions were analyzed at room temperature for 6 h. Stability results were acceptable only when the CV (%) of the measuring data was within 15.0% and the mean accuracy value was not more than ±15.0% of the nominal value.

2.8 Application in pharmacokinetic study

Human plasma was collected from healthy volunteers who participated in pharmacokinetic or pharmacogenetical research in Institute of Clinical Pharmacology, Central South University (CSU, Changsha, China) with permission of the Ethics Committee of Xiangya School of Medicine, CSU. Venous blood samples (5mL) were collected from each subject of 15 male healthy volunteers who received a single 200 mg oral dose of sulindac tablets. Blood samples were collected before dosing (0 h) and at 10 min, 20 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, and 36 h after administration in EDTA(K2)−containing tubes. The plasma was separated by centrifuge at 3000 RPM for 10min. The collected plasma samples were stored at −40 °C until analysis. The pharmacokinetic parameters were calculated by model using Drug And Statistics for Windows (DAS ver1.0) software.

The developed method was used to determine the plasma concentrations of the three compounds. The pharmacokinetic parameters were calculated. Accordingly, the maximum plasma concentration (C_{max}) was directly observed. The elimination rate constant (K) was calculated by linear regression of the terminal points using the semi-log plot of plasma concentration versus time. The half-life of elimination ($T_{1/2}$) was provided according to the formula $T_{1/2} = 0.693/K$. The area under the plasma

concentration–time curve ($AUC_{0–36}$) was calculated using the linear trapezoidal rule. The area under the plasma concentration – time curve to time infinity ($AUC_{0–\infty}$) was obtained from the calculations: $AUC_{0–\infty} = AUC_{0–36} + C_{36}/K$, in which the C_{36} was the pose-dose plasma concentration of analytes at 36 h.

3 Results and discussion

3.1 UPLC analysis and selectivity

The chromatograms indicated that all compounds could be separated independently in 5 min under the chromatographic conditions. In previous study, the targeted ingredients were analyzed to achieve satisfied selectivity in about 6 minutes by HPLC method [18, 19]. Several quantitative assays of sulindac in plasma have been described including HPLC methods coupling with ultraviolet (UV) detection [29-32], fluorescence detection (FLD) [33, 34] and amperometric detection [35-37]. Liquid chromatography based methods are sometimes time and organic solvents consuming. UPLC is a liquid chromatography technique developed recently comparing with conventional HPLC. UPLC systems can assume higher pressures so that sub-2 μm particles columns could be used to get better resolution and sensitivity in a shorter analytical time [38]. Hereby, a UPLC-PDA method was developed to obtain better resolution in a shorter analytical time for simultaneous determination of sulindac, sulindac sulfide and sulindac sulfone in this study. The representative chromatograms were shown in Fig.2, which showed no obvious endogenous peaks at the retention positions of sulindac, sulindac sulfide, sulindac sulfone and IS.

3.2 LLOQ and linearity

The mean regression equations, test ranges, correlation coefficients and LLOQs were shown in Table 2. The six calibration curves were linear over the test concentration range for each analyte, respectively. The accuracy and precision (CV) for the calibration curve standards covered from 99.1 to 100.7% and 1.98 to 4.79% for sulindac, 98.9 to 101.6% and 2.45 to 3.78% for sulindac sulfide and 98.5 to 103.2% and 3.25 to 5.18% for sulindac sulfone, respectively. The precision (RSD) and accuracy (RE) of LLOQ were less than 3.7% and within ±7.8%, respectively. The experimental data indicated that the investigated compounds had appropriate correlations between their concentrations and peak areas within the test ranges. The mean correlation coefficient for all the standard curve were at least 0.99. The results showed a higher sensitivity for sulindac, sulindac sulfide and sulindac sulfone in the developed method, which could be used to measure the trace concentration of the mentioned analytes in human plasma.

3.3 Inter- and intra-batch precision and accuracy

The overall intra- and inter-day precision (RSDs) and accuracy (extraction recovery) for sulindac, sulindac sulfide and sulindac sulfone were listed in Table 3. The intra- and inter-day precisions were within 4.92 – 11.06% at each QC level of these analytes. The established method had good accuracy with overall recovery from 94.92% to 109.16% of the analytes. These results indicated that the developed method was precise and accurate.

3.4 Extraction recovery

The extraction recoveries of sulindac, sulindac sulfide and sulindac sulfone from

human plasma were conducted on Low, Middle and High concentrations of sulindac and its metabolites. The results were provided in Table 4. The matrix effects were calculated to be acceptable within 85.7–102.3% for analytes and 101.5 ± 3.6% for IS. The results indicated that the method had good accuracy with extraction recovery.

3.5 Stability

Table 5 summarized the freeze and thaw, short-term and long-term stability data of sulincac, sulindac sulfide and sulindac sulfone. All the results showed good stability within these tests so that there were no stability related problems for the routine analysis of samples in pharmacokinetic studies. For the stability of working solutions, the result showed the working solutions were stable within testing time.

3.6 Clinical applications

The developed method was successfully applied to a pharmacokinetic study of sulindac tablets. Fifteen healthy male subjects (Age: 20.5 ± 3.1 years; Height: 175.5 ± 8.6 cm; Weight: 65.5 ± 5.5 kg.) were enrolled in the study according to the clinical protocol. All the healthy subjects signed informed consent after the assessments of physical examination, electrocardiogram, medical history and standard laboratory test results including blood cell, urinalysis and biochemical profile.

A randomized, one-period and single-dose protocol was adopted. The validated method above was successfully applied to a pharmacokinetic study of sulindac tablets. The plasma concentrations of sulindac, sulindac sulfide and sulindac sulfone were determined for 36 h after oral administration of 200 mg sulindac tablets. A representative chromatogram of the plasma sample was plotted in Fig. 2 (C), which

was collected at 2 h from a subject after oral administration with sulindac tablets. The mean concentration time curve of sulindac, sulindac sulfide and sulindac sulfone were shown in Fig.3. Kinetic parameters of the test tablets were listed in Table 6.

3.7 Comparison with reported methods

The advantages of this method include good sensitivity, high extraction efficiency, less organic solvents consumption and short run time. The developed method is more sensitive and faster than other procedures for determination of sulindac and its metabolites. In 1987, a HPLC-UV method had been reported to determine the analytes in more than 10 min with narrow test ranges from 0.6 to 20.0 μg/mL [39]. Recently, a fast HPLC was established to quantify these compounds within 6 minutes (r.t.: sulindac ~2.1 minutes, sulphide ~2.7 minutes and sulphone ~5.4 minutes) with the LLOQs at 0.506 μg/mL for sulindac, 0.128 and 0.224 μg/mL for sulindac sulfide and sulindac sulfone, respectively [18]. However, we found the LLOQs at 0.062 μg/mL for sulindac, 0.080 and 0.031 μg/mL for sulindac sulfide and sulindac sulfone by UPLC method, respectively (Table 2). Additionally, a capillary electrophoresis method was also employed to analyze the three ingredients within 18 min as the chromatographic rum time. Moreover, the chromatograms showed that the chromatographic peaks did not have good symmetry due to weak resolution of the analytes [27].

4 Conclusions

A UPLC-PDA method was first developed for simultaneous determination of sulindac, sulindac sulfide and sulindac sulfone in human plasma. The method was fully

validated by following FDA guidelines. The proposed method has a good sensitivity for all the analytes in different biological matrices. The short run time of 5.0 min per sample renders the method useful in high-throughput bio-analysis. The matrix interference is absent on the evidence of the precision values for the slopes of calibration curves from different plasma sources. This method has adequate accuracy and stability for analyzing samples in pharmacokinetic studies of sulindac tablets.

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Figure legends

Fig.1. Chemical structures of all the investigated compounds and internal standard (IS).

Fig.2. Chromatograms of (A) blank plasma spiked with sulindac (0.814 μg/mL)**, sulindac sulfide** (0.919 μg/mL)**, sulindac sulfone** (0.816 μg/mL) **and internal standard** (2.781 μg/mL) **for the calculation of LLOQs; (B) blank plasma spiked with sulindac** (26.030 μg/mL)**, sulindac sulfide** (29.401 μg/mL)**, sulindac sulfone** (26.101 μg/mL) **and internal standard** (27.811 μg/mL)**; (C) 2h samples after oral administration of 200 mg sulindac tablets at the concentration of 6.850, 5.881 and 3.262 μg/mL for sulindac, sulindac sulfide, sulindac sulfone, respectively, with internal standard (5.562 μg/mL).**

The retention times of sulindac, sulindac sulfide, sulindac sulfone and internal standard were 1.96, 2.25, 3.36 and 2.78 min, respectively. **1**. sulindac; **2**. sulindac sulfide; **3**. internal standard; **4**. sulindac sulfone.

Fig.3. The mean plasma concentration-time profiles of sulindac, sulindac sulfide and sulindac sulfone in human after oral administration of 200 mg sulindac tablets (n=15).

Table 1. The solution concentrations of samples for standard calibration curves (μg/mL).

No.	Sulindac		Sulindac sulfide		Sulindac sulfone	
	WS [a]	SCCS [b]	WS	SCCS	WS	SCCS
S1	2.716	0.814	3.063	0.919	2.719	0.816
S2	5.423	1.627	6.126	1.838	5.438	1.632
S3	10.847	3.254	12.251	3.675	10.876	3.263
S4	21.693	6.508	24.501	7.370	21.751	6.526
S5	43.383	13.015	49.001	14.700	43.502	13.051
S6	87.667	26.030	98.003	29.401	87.004	26.101
S7	175.333	52.600	196.005	58.801	174.007	52.202
S8	347.067	104.120	392.010	117.603	348.013	104.404

[a] WS: working solution. [b] SCCS: standard calibration curves solution.

Table 2. The calibration curves, linear ranges and LLOQs of Sulindac and its metabolites.

Analytes	Regression equation	r^2	Test range (μg/mL)	LLOQ (μg/mL)
Sulindac	Y = (0.119±0.0052)X−(0.00247±0.00092)	0.9963	0.814−104.120	0.062
Sulindac sulfide	Y = (0.0913±0.0033)X+(0.0118±0.0097)	0.9972	0.919−117.603	0.080
Sulindac sulfone	Y = (0.108±0.0068)X+(0.00899±0.0023)	0.9928	0.816−104.404	0.031

Table 3. Precision and accuracy for the determination of sulindac, sulindac sulfide and sulindac sulfone in human plasma.

Compounds	Conc. added (CA, μg/mL)[a]	Intra-day (n = 6)			Inter-batch (n = 30)		
		Mean conc. measured (MCM, μg/mL) ±SD[b]	Accuracy (%)[c]	CV (RSD, %)[d]	Mean conc. measured (MCM, μg/mL)	Accuracy (%)[b]	CV (RSD, %)[c]
Sulindac	3.254	3.411±0.331	109.16	6.36	3.380±0.760	103.92	6.70
	26.030	26.212±2.210	106.70	8.03	25.921±3.241	99.56	9.63
	104.120	105.570±7.712	95.49	5.26	105.462±6.433	101.29	5.40
Sulindac sulfide	3.675	3.402±0.251	104.43	7.60	3.491±0.520	94.92	8.80
	29.401	28.741±3.322	111.87	10.50	29.512±4.272	100.37	11.06
	117.603	116.263±9.793	115.99	7.96	113.221±8.893	96.28	6.25
Sulindac sulfone	3.263	3.232±0.121	103.21	5.20	3.250±0.661	99.64	5.42
	26.101	26.601±3.220	108.31	11.57	25.761±0.984	98.69	10.69
	104.404	104.742±10.241	104.50	4.92	104.862±4.241	100.44	5.79

[a] conc. is the abbreviation of concentration.
[b] SD: standard deviation.
[c] Accuracy (%) = (MCM / CA)×100.
[d] CV, coefficient of variation (%) = SD/MCM.

Table 4. The extraction recovery of sulindac, sulindac sulfide and sulindac sulfone in human plasma at different QC levels (n = 6).

Compounds	Recoveries (%)		
	Low conc.[a]	Middle conc.	High conc.
Sulindac	78.9±4.5	75.4±5.2	77.8±5.5
Sulindac sulfide	72.8±2.9	77.4±2.5	76.6±3.1
Sulindac sulfone	68.0±6.8	65.8±3.3	67.5±4.5
IS		75.5 ±3.5	

[a] conc. is the abbreviation of concentration.

Table 5. Stability of sulindac, sulindac sulfide and sulindac sulfone in human plasma at different QC levels (n = 6).

Analytes	Conc. added (CA, μg/mL)[a]	Short-term (24h, room temperature)		Long-term (60 days, -40 °C)		Freeze-thaw (three cycles, -40 °C)	
		Mean conc. measured (MCM, μg/mL)±SD[b]	Deviation (%)[c]	Mean conc. measured (MCM, μg/mL)±SD	Deviation (%)	Mean conc. measured (MCM, μg/mL)±SD	Deviation (%)
Sulindac	3.254	3.428±0.232	5.3	3.382±0.450	3.9	3.278±0.340	0.74
	26.030	26.139±1.051	0.4	25.732±2.281	-1.1	25.209±3.451	-3.2
	104.120	107.618±3.541	3.4	104.626±3.771	0.5	106.291±1.282	2.1
Sulindac sulfide	3.675	3.571±0.460	-2.8	3.631±0.640	1.2	3.632±0.253	-1.2
	29.401	30.988±1.210	5.4	28.278±1.432	-3.8	29.772±3.050	1.3
	117.603	114.235±9.642	-2.9	110.402±0.892	-6.1	114.592±9.233	-2.6
Sulindac sulfone	3.263	3.390±0.260	3.9	3.383±0.321	3.7	3.342±0.061	2.4
	26.101	26.832±4.231	2.8	26.302±1.522	0.8	27.452±0.783	5.2
	104.404	106.402±5.780	1.9	107.449±2.911	2.9	106.855±2.052	2.3

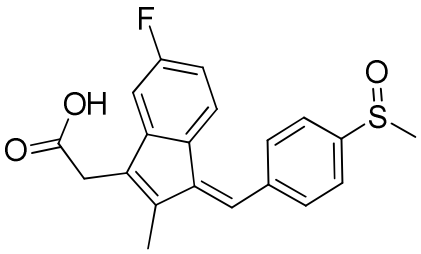
[a] conc. is the abbreviation of concentration.
[b] SD: standard deviation.
[c] Deviation (%) = (MCM/CA × 100) − 100.

Table 6. Pharmacokinetic parameters of healthy volunteers after oral administration of sulindac tablets (mean±SD, n = 15).

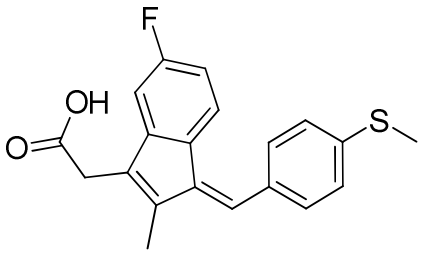
Parameters	Sulindac	Sulindac sulfide	Sulindac sulfone
$T_{1/2}$ (h)	6.61±1.69	13.55±8.72	14.81±1.01
T_{max} (h)	1.65±0.48	1.90±1.36	2.10±1.01
C_{max} (μg/mL)	7.44±3.48	3.58±1.49	3.56±1.01
AUC_{0-tn} (ng·h/mL)	34.40±8.29	41.54±18.04	57.35±15.81
$AUC_{0-\infty}$ (ng·h/mL)	64.46±27.60	82.87±43.23	150.76±57.63
$MRT_{0-\infty}$ (h)	47.55±33.27	74.91±33.32	66.53±19.27

$T_{1/2}$: half-life of elimination; T_{max}: time of maximum plasma concentration; C_{max}: maximum plasma concentration; AUC: area under the plasma concentration vs time curve; MRT: mean residence time.

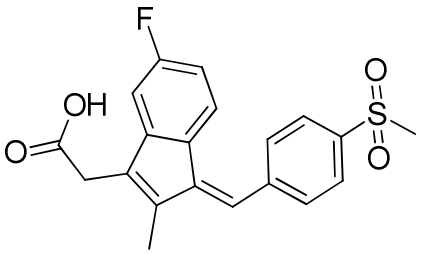
Figure 1



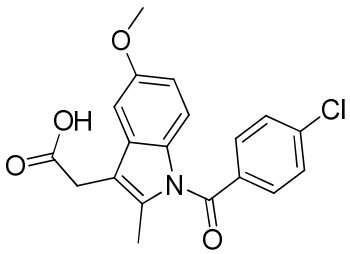
A: sulindac



B: sulindac sulfide



C: sulindac sulfone



D: indometacin (IS)

Figure 2

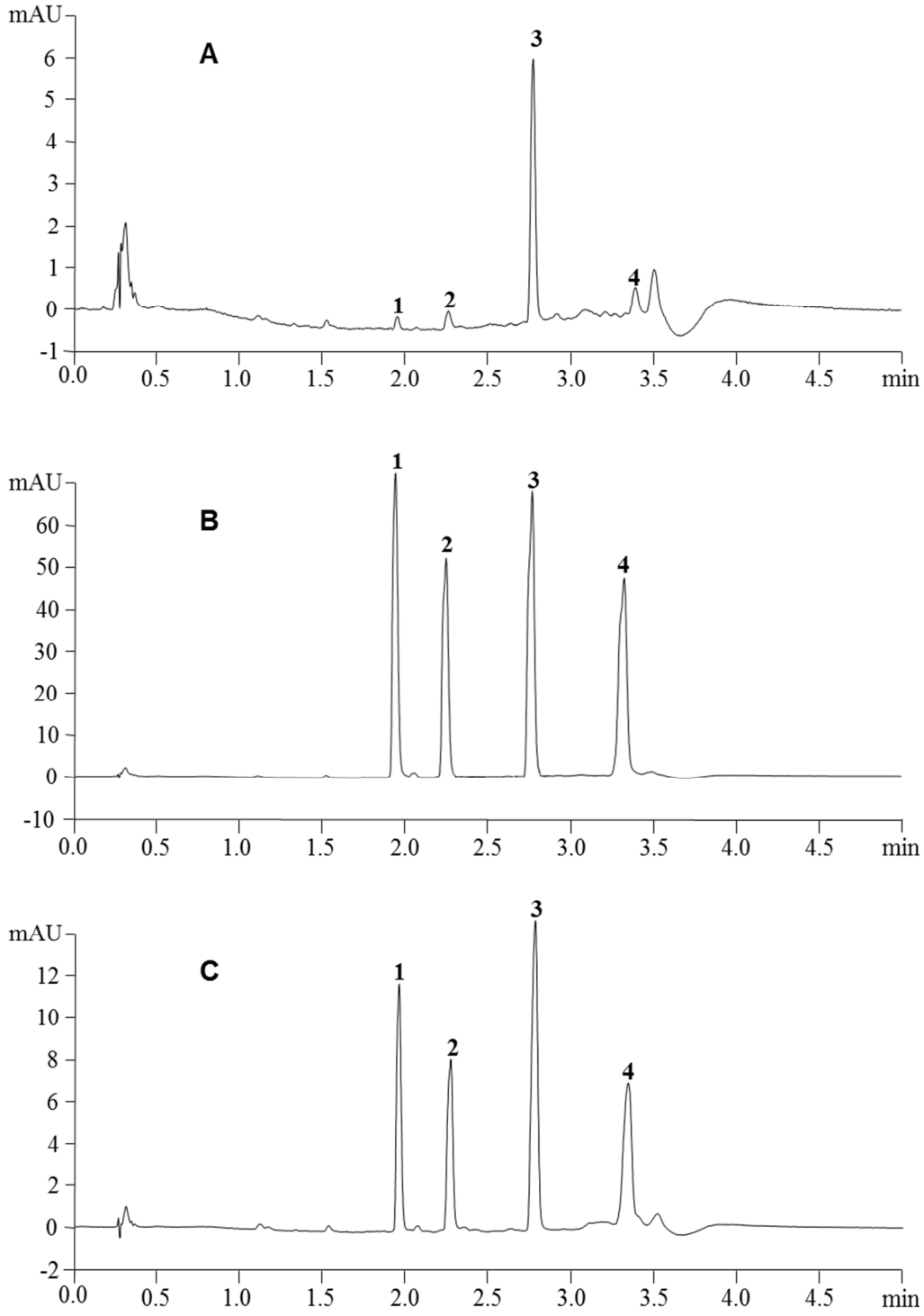


Figure 3