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## DETERMINATION OF A POORLY SOLUBLE DRUG, IBUPROFEN IN RAT PLASMA BY A SIMPLE HPLC ANALYSIS AND ITS APPLICATION IN PHARMACOKINETIC STUDY

A. Nurfazreen<sup>1</sup>, B. E. Tommy Julianto<sup>1</sup> and A. H. Khuriah\*<sup>1, 2</sup>

Department of Pharmaceutics, Faculty of Pharmacy, UiTM, 42300, Bandar Puncak Alam, Selangor <sup>1</sup>,  
Brain and Neurosciences Communities of Research <sup>2</sup>, UiTM, 40450 Shah Alam, Selangor, Malaysia.

### Keywords:

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### Correspondence to Author:

**K. A. Hamid**

Department of Pharmaceutics,  
Faculty of Pharmacy, Universiti  
Teknologi MARA, 42300, Puncak  
Alam, Selangor, Malaysia.

### Email:


khuriah@puncakalam.uitm.edu.my

**ABSTRACT:** In this study, a reversed-phase high performance liquid chromatography (RP-HPLC) method has been developed for the quantification of ibuprofen in rat plasma. The mobile phase consisted of a mixture of acetonitrile and water that was adjusted to pH 2.5 using orthophosphoric acid (70:30). The flow rate was set at 0.5 ml/min and effluent was monitored by using UV detector at a wavelength of 223 nm with retention time of 6.1 min. The chromatographic separation was carried out using a C18 (150 mm × 4.6 mm i.d.) column. The proposed method was validated based on linearity, accuracy and precision. The linearity of ibuprofen was in the range of 0.39-50 µg/ml with mean correlation coefficient of 0.999. The percentage mean recovery was found to be at 99.16%, while the coefficients of variation of within-day and between-day measurements were all found to be less than 5%. The limit of quantification (LOQ) and limit of detection (LOD) of the method were 0.296µg/ml and 0.098µg/ml, respectively. The method was further engaged to identify the pharmacokinetic profiles of ibuprofen nanoemulsion and ibuprofen oil solution after oral administration with AUC value of 6670.10 ± 283.83µg/ml·hr and 3060.32 ± 169.93µg/ml·hr, respectively.

**INTRODUCTION:** Ibuprofen, a phenyl propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) <sup>1</sup>. It is widely used in the treatment of rheumatoid arthritis, osteoarthritis and joint pain <sup>1, 15</sup>. Ibuprofen is available as a white crystalline powder with a molecular weight of 206.27, pKa (COOH) = 4.41 <sup>1, 2</sup>. Ibuprofen inhibits prostaglandin biosynthesis by blocking the enzyme cyclooxygenase, which converts arachidonic acid to prostaglandin <sup>16</sup>. Ibuprofen is practically insoluble in water and has shown incomplete absorption in the GI tract <sup>3, 23</sup>.

Thus, ibuprofen has been formulated into inert lipid vehicles such as microemulsions, nanoemulsions, self-emulsifying formulations and liposomes in order to increase the bioavailability of this poorly soluble drug <sup>4</sup>.

Based on previous studies conducted on various approaches in analysing ibuprofen, high performance liquid chromatography (HPLC) was found to be the most suitable method to determine the concentration of the drug in different types of samples. Recent studies stated that HPLC with UV-Vis detector at a wavelength of 223 nm has successfully determined the concentrations of ibuprofen in nanoemulsion formulations with a retention time of 7.45 min <sup>12</sup>. Meanwhile, another study has developed a method for the analysis of ibuprofen and paracetamol using reversed phase HPLC with UV detector at a wavelength of 230 nm with a retention time of 6.96 and 3.04 min

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respectively<sup>13</sup>. The high sensitivity, accuracy, precision, linearity and stability of HPLC method in the analysis of ibuprofen have made it a widely used method for the determination of ibuprofen concentrations in nanoemulsion formulations.

Nanoemulsion is a heterogeneous system which comprised of oil, surfactant, cosurfactant and an aqueous phase<sup>5, 19</sup>. Developing nanoemulsions as vehicles for carrying active pharmaceutical ingredients is emerging as a promising approach to deliver drug to the targeted site of action<sup>6</sup>. Nanoemulsion with an approximate droplet diameter of about 20-200 nm has the potential to increase the aqueous solubility of poorly water-soluble drugs<sup>5, 30</sup>. They are kinetically stable without any flocculation or coalescence after long-term storage because of the nanometer-sized droplets<sup>9, 20</sup>.

Several advantages of nanoemulsions include smaller droplet size with a larger surface area, increasing dissolution rate and solubility and enhancing mucosal permeability<sup>7, 20</sup>. In nanoemulsions, the oil droplets act as a reservoir for hydrophobic drugs<sup>8, 10</sup>. The most widely used oil molecules are saturated and unsaturated fatty acids, fatty acid esters, soybean oils as well as olive oils<sup>8, 10</sup>.

This study was conducted with the purpose of developing a simple reversed-phase high performance liquid chromatography (RP-HPLC) equipped with a photodiode array detector in order to determine the concentration of ibuprofen in rat plasma. Oral administration was also carried out in this study to identify and compare the pharmacokinetic profiles of ibuprofen nanoemulsion and ibuprofen oil solution respectively.

## MATERIALS AND METHODS:

### Materials

Ibuprofen [2-(4-isobutylphenyl)-propionic acid] was purchased from Sigma-Aldrich (UK). HPLC grade acetonitrile and orthophosphoric acid were obtained from Merck (Darmstadt, Germany). Distilled water was purified prior to use using ELGA Water Purification System R15 supplied with pump and tank (Elga Water System, UK).

Olive oil, glycerol, propyl paraben and methyl paraben were supplied by Zulat Pharmacy (Malaysia). Laurate Sucrose Monoester (SME) (L-1695) was obtained from Ryoto Mitsubishi-Kagaku (Japan). All other chemicals and solvents were of analytical grade.

### Preparation of standard solution

The stock solution of ibuprofen was prepared in acetonitrile at a concentration of 1 mg/ml. Working solutions of ibuprofen with concentrations in the range of 0.39 – 50 µg/ml were obtained by diluting the stock solution with acetonitrile. Serial dilutions were prepared with concentration of 50 µg/ml, 25 µg/ml, 12.50 µg/ml, 6.25 µg/ml, 3.13 µg/ml, 1.56 µg/ml, 0.78 µg/ml and 0.39 µg/ml respectively. Plasma was spiked with ibuprofen by mixing 0.1 ml of ibuprofen stock solution into 0.9 ml of plasma to yield final ibuprofen concentration of 100 µg/ml. The standard solutions (n=6) were prepared with known amount of ibuprofen ranging from 0.39 – 50 µg/ml.

Plasma samples were treated with deproteinizing agent (DA) consisting of acetonitrile: propanol (1:1), at the ratio of 2:1 (DA: sample). The mixture was vortex for 1 min and centrifuged at 10,000 rpm for 10 min at room temperature. A volume of 50 µl of the supernatant was filtered and injected into HPLC system prior to analysis.

### Instrumental and chromatographic conditions

The HPLC analysis was performed using Waters ACQUITY UPLC<sup>®</sup> system (Waters Corp., MS, USA), equipped with a binary solvent delivery system and autosampler. Ibuprofen was detected using Photodiode Array (PDA) detector at 223 nm<sup>18</sup>. The chromatographic separation was carried out using Phenomenex reversed phase C18 column, Jupiter 5 µ C18 with particle size of 5 µm (150 mm x 4.6 mm).

The filtered and degassed mobile phase comprised of a mixture of acetonitrile and water which was adjusted to pH 2.5 with concentrated orthophosphoric acid at a ratio of 70:30<sup>18</sup>. The analysis involved using isocratic elution at a flow rate of 0.5 ml/min. Each wash cycle consisted of 200 µl of strong solvent (90% acetonitrile) and 600 µl of weak solvent (50% acetonitrile).

**Method validation****Linearity**

Six linearity curves were analyzed; each calibration curve consisted of 8 concentrations that were prepared from stock solution over the range of 0.39 – 50µg/ml. Peak area was plotted against concentration and the regression lines were calculated by the least-square method<sup>18</sup>.

**Accuracy and precision**

Accuracy was defined as the closeness of the measured value obtained by the analytical method to the true value<sup>16</sup>. Accuracy could be assessed by calculating the recovery of known amounts of analyte.

In the present study, recovery experiments were performed by spiking known amounts of ibuprofen in blank rat plasma over a range of 0.39 to 50 µg/ml. Samples were prepared at eight concentration levels. For each level, the drug content was determined in triplicates (n=3). The mean accuracy should be within 15% of the true value.

Meanwhile, precision refers to the reproducibility of multiple measurements of a homogenous sample<sup>16</sup>. Precision could be measured as repeatability (within-day) and intermediate precision (between-day)<sup>16</sup>. Within-day validation included the evaluation of precision and accuracy of six replicates of standard solution which were analysed on the same day. Between-day validation was performed by evaluating the precision and accuracy of same standard solutions on six consecutive days.

The precision and accuracy of all sample concentrations must not exceed 15% of the coefficient of variation (CV %) from the theoretical value<sup>14</sup>.

**Detection and Quantitation Limits**

The limit of detection (LOD) is described as the lowest concentration of the analyte in the sample that can be detected above baseline noise; typically, three times the noise level<sup>16</sup>. Limit of quantification (LOQ) is the lowest concentration of analyte that can be quantitatively determined by a peak height with a signal-to-noise ratio higher than

10<sup>16</sup>. LOD and LOQ were calculated based on the formula recommended by ICH as follow:

$$\text{LOD}=3.3\sigma/S \quad \text{LOQ}=10\sigma/S$$

Where  $\sigma$  is the standard deviation of y-intercepts of regression lines and  $S$  is the slope of the calibration curve.

**Stability**

Three different concentrations of ibuprofen; 50µg/ml, 6.25µg/ml and 0.78µg/ml, were prepared in order to measure the stability of the drug. The stability was evaluated by percentage of recovery according to USFDA<sup>20</sup>. The procedures were developed as follow:

**TABLE 1: STABILITY PARAMETERS**

Stability Parameters
Freshly prepared ibuprofen
Room temperature for 6 hr
Room temperature for 24 hr
Freeze thaw at -20°C for 24 hr
Frozen at -20°C for 30 days

**Pharmacokinetics study**

Male Sprague Dawley rats (weighing from 230 - 250 g) were obtained from Laboratory Animal Facility and Management (LAFAM), UiTM Puncak Alam. The animals were fasted overnight, 16 hr prior to the start of experiment with water ad libitum. All animal experiments were performed in accordance to the guidelines provided by the Committee on Animal Research & Ethics (CARE) of Faculty of Pharmacy, Universiti Teknologi MARA (UiTM) Puncak Alam, Selangor, Malaysia.

For oral administration study, a stainless steel gauge feeding needle was used. The rats were given an oral administration of 30 mg/kg of formulations in a randomized manner<sup>3</sup>. Rats were anesthetized with ketamine to xylazine ratio of 2:1. Blood samples (0.25 ml) were collected from the jugular vein using heparinized syringes at predetermined time intervals of 0, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0 and 6.0 hr. Plasma sample was treated with DA prior to HPLC analysis.

The concentrations of ibuprofen in plasma were identified and the plasma concentration-time profiles of ibuprofen were plotted. Maximum plasma concentration ( $C_{\max}$ ) and time to reach plasma concentration ( $T_{\max}$ ) were determined

directly from plasma concentration-time curves. The area under the curve (AUC) was calculated using the trapezoidal method from zero to the final sampling time (6 hr).

### Preparation of Nanoemulsion Ibuprofen

Nanoemulsion formulation was prepared by D-phase emulsification method<sup>11</sup>. The oil to surfactant ratio used in this study was 4:1. Laurate SME 1695<sup>22</sup> was dissolved in glycerol with gentle agitation at 65°C. Meanwhile, 3% (w/w) ibuprofen was added to olive oil and heated up to 65°C. This is followed by adding the oil phase gradually into the surfactant phase at a similar temperature by gentle stirring. The nanophase gel (NPG) produced was further stored in a glass container at 4°C. Prior to nanoemulsion preparation, 33.3% (w/w) of NPG was introduced into 66.6% (w/w) distilled water and 0.1% propyl paraben and methyl paraben.

## RESULTS AND DISCUSSIONS:

### Ibuprofen chromatogram

Chromatograms obtained for a blank rat plasma and ibuprofen in rat plasma were shown in **Figure 1** and **Figure 2**.

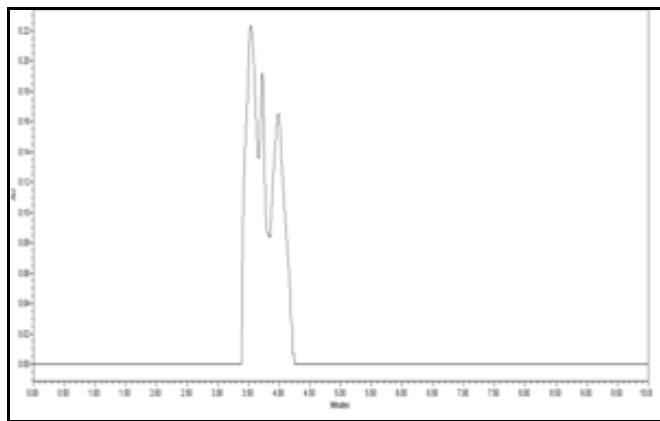


FIGURE 1: CHROMATOGRAM OF BLANK RAT PLASMA

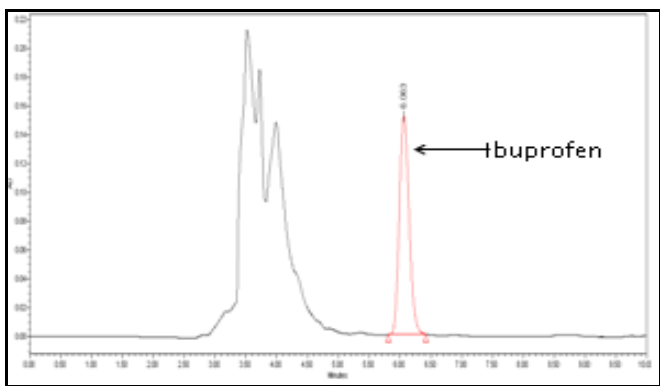


FIGURE 2: CHROMATOGRAM OF RAT PLASMA SPIKED WITH 25 µg/ml IBUPROFEN. IBUPROFEN PEAK WAS ELUTED AT 6.06 MIN.

**Figure 2** showed the chromatogram of ibuprofen (25µg/ml) in rat plasma. From the data, ibuprofen was eluted at 6.06 min in total analysis time of 10 min. Under the optimal chromatogram condition that was developed, ibuprofen peak was well resolved from the neighbouring peaks and displayed excellent peak symmetry and separation efficiency as observed in **Figure 1** and **2**.

Several trials have been conducted to determine the optimum conditions for separation and determination of ibuprofen by selecting the optimum wavelength. The unique chromophoric nature of ibuprofen makes them easily identified in photodiode array absorption spectra at wavelength of 223 nm. It is very important not to have any interference from other ingredients in the formulation since the overlapping peak may affect the actual concentration data.

### Linearity:

The linearity was assessed for standard series of ibuprofen over the range of 0.39 – 50µg/ml. The data was consistent throughout the experiment which allows for a linear coefficient, intercept and slope. The calibration curve exhibited coefficient of correlation,  $R^2$  of 0.999 and y intercept was 3692.8 as shown in **Figure 3**.

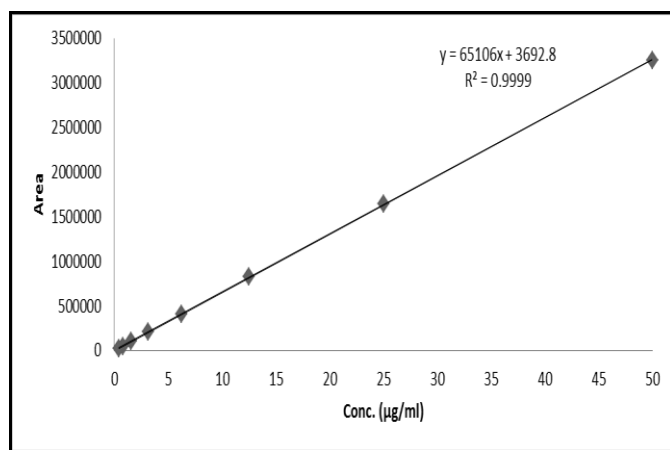


FIGURE 3: STANDARD CALIBRATION CURVE OF IBUPROFEN

### Accuracy and precision

The accuracy of this method was evaluated by the determination of the percentage recovery of ibuprofen in rat plasma for both within-day and between-day variations. The results obtained were summarized in **Table 2** and **Table 3**. According to **Table 2**, the within-day accuracy values ranged



between 99.34 – 100.87% with a mean recovery of 100.13%. Meanwhile, from **Table 3**, it could be observed that the between-day accuracy values ranged between 97.62 – 100.59% with a mean recovery of 99.16%.

On the other hand, the precision of this method was assessed based on the repeatability of ibuprofen formulation for both within-day and between-day variations. The precision is described as the percentage coefficient of variation (CV%). From **Table 2**, the within-day values ranged from 1.51 – 4.16% while the between-day precision values ranged from 1.41 – 4.30% as stated in **Table 3**. Furthermore, the accuracy and precision of all sample concentrations were less than 10%. Hence, the method is proven precise and accurate because the results obtained met the criteria stated by USFDA guidelines for accuracy and precision<sup>14</sup>.

**TABLE 2: WITHIN-DAY RESULTS EXPRESSED IN MEAN ± STANDARD DEVIATION (S.D.), PRECISION IN COEFFICIENT OF VARIATION (CV, %) AND ACCURACY (% RECOVERY). EACH DATA REPRESENTS A SET OF TRIPLICATES.**

Within-day			
Concentration (µg/ml)	Mean ± S.D. (µg/ml)	Precision (CV %)	Accuracy (% Recovery)
50.00	49.87 ± 0.75	1.51	99.75
25.00	24.96 ± 0.80	3.19	99.83
12.50	12.59 ± 0.43	3.45	100.74
6.25	6.30 ± 0.23	3.57	100.84
3.13	3.15 ± 0.10	3.28	100.87
1.56	1.56 ± 0.06	3.67	99.79
0.78	0.78 ± 0.02	2.21	99.88
0.39	0.39 ± 0.02	4.16	99.34

**TABLE 3: BETWEEN-DAY RESULTS EXPRESSED IN MEAN ± STANDARD DEVIATION (S.D.), PRECISION IN COEFFICIENT OF VARIATION (CV, %) AND ACCURACY (% RECOVERY). EACH DATA REPRESENTS A SET OF TRIPLICATES.**

Between-day			
Concentration (µg/ml)	Mean ± S.D. (µg/ml)	Precision (CV %)	Accuracy (% Recovery)
50.00	49.78 ± 0.70	1.41	99.56
25.00	24.42 ± 0.67	2.73	97.69
12.50	12.57 ± 0.32	2.56	100.59
6.25	6.10 ± 0.20	3.32	97.62
3.13	3.13 ± 0.10	3.21	100.10
1.56	1.56 ± 0.06	3.75	99.97
0.78	0.77 ± 0.03	4.30	98.74
0.39	0.39 ± 0.01	3.09	99.04

### Sensitivity

Eight different concentrations of ibuprofen standard solution were analyzed to calculate the limit of detection (LOD) and limit of quantitation (LOQ). The detection limit for ibuprofen was found

to be 0.098µg/ml while quantitation limit was 0.296µg/ml.

### Stability

The stability of ibuprofen in rat plasma was determined by comparing the freshly prepared ibuprofen in rat plasma and samples with several predetermined conditions. The data obtained for stability studies was shown in **Table 4**. The stability percentage ratios ranged from 98.24% to 100.48%. The differences in recovery value between control and samples were within the acceptable range.

**TABLE 4: STABILITY DATA RESULTS ARE EXPRESSED AS THE MEAN RECOVERY (%) ± STANDARD DEVIATION (S.D.) WITH SAMPLE CONCENTRATIONS OF 50 µg/ml, 6.25 µg/ml and 0.78 µg/ml. SAMPLES WERE ASSIGNED INTO PREDETERMINED CONDITIONS. EACH DATA REPRESENTS A SET OF TRIPLICATES.**

Recovery (%) ± S.D.			
Concentration (µg/ml)	50	6.25	0.78
(a) Freshly prepared ibuprofen	100.42 ± 0.27	100.48 ± 0.37	99.03 ± 0.27
(b) Room temperature for 6 hr	100.20 ± 0.26	100.17 ± 0.28	98.72 ± 0.63
(c) Room temperature for 24 hr	100.14 ± 0.09	100.28 ± 0.39	98.41 ± 1.01
(d) Freeze thaw at -20°C for 24 hr	99.59 ± 0.34	99.93 ± 0.15	98.36 ± 0.32
(e) Frozen at -20°C for 30 days	99.55 ± 0.32	99.86 ± 0.12	98.24 ± 0.93

### Pharmacokinetic profiles

The developed method was successfully applied for the determination of pharmacokinetic profile of ibuprofen oil solution and nanoemulsion in rats after oral administration.

**Figure 4** showed the pharmacokinetic profiles of ibuprofen after oral administration in rats. The concentration of ibuprofen in rat plasma after oral administration of the two dosage forms increased rapidly within one hour before being eliminated. The maximum ibuprofen concentration in plasma ( $T_{max}$ ) of both dosage forms was recorded at 1.0 hr. The incorporation of ibuprofen in nanoemulsion dosage form has significantly increased the absorption of ibuprofen through gastrointestinal tract (GIT) as compared to the ibuprofen oil solution.

**Table 5** showed the pharmacokinetic parameters ( $C_{max}$ ,  $T_{max}$ , AUC and  $T_{1/2}$ ) of ibuprofen after oral administration. The AUC value and half-life of

ibuprofen nanoemulsion were  $6670.10 \pm 283.83$   $\mu\text{g/ml}\cdot\text{hr}$  and  $2.02 \pm 0.28$  hr, respectively whereas the AUC value and half-life of ibuprofen oil solution were  $3060.32 \pm 169.93$   $\mu\text{g/ml}\cdot\text{hr}$  and  $1.87 \pm 0.41$  hr.

The AUC value of ibuprofen nanoemulsion was statistically significant ( $p < 0.05$ ) compared to the ibuprofen oil solution. The AUC increased 2.2-fold after the oral administration of ibuprofen nanoemulsion. These results confirmed that the absorption of ibuprofen formulated as nanoemulsion enhanced the oral absorption in rats compared to ibuprofen oil solution.

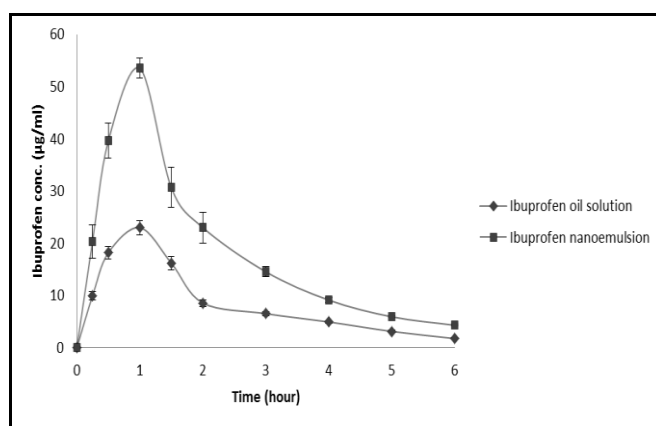


FIGURE 4: PLASMA CONCENTRATION OF IBUPROFEN VERSUS TIME FOLLOWING ORAL ADMINISTRATION OF IBUPROFEN (30 mg/kg) IN RATS. THE RESULTS ARE EXPRESSED AS THE MEAN  $\pm$  S.D. OF AT LEAST 5 EXPERIMENTS.

TABLE 5: PHARMACOKINETIC PARAMETERS OF IBUPROFEN (30mg/kg) FOLLOWING ORAL ADMINISTRATION IN RATS.

	$C_{\max}$ ( $\mu\text{g/ml}$ )	$T_{\max}$ (hr)	$T_{1/2}$ (hr)	$AUC_{0-6h}$ ( $\mu\text{g/ml}\cdot\text{hr}$ )
Ibuprofen oil solution	$23.02 \pm 1.36$	1.00	$1.87 \pm 0.41$	$3060.32 \pm 169.93$
Ibuprofen nanoemulsion	$53.50 \pm 1.93$	1.00	$2.02 \pm 0.28$	$6670.10 \pm 283.83^*$

Results are expressed as the mean  $\pm$  S.D. of 5 experiments. \* $P < 0.05$ , N.S. no significant difference, compared to control.

**CONCLUSION:** In summary, high performance liquid chromatography (HPLC) method has been successfully developed and validated for the determination of ibuprofen concentration in rat plasma. This method is found to be highly specific, accurate and precise and is suitable for routine analysis of ibuprofen in plasma. Additionally, this method was successfully applied in a pharmacokinetic study of ibuprofen oil solution and ibuprofen nanoemulsion after oral administration. The oral bioavailability of ibuprofen nanoemulsion was 2.2-fold higher than that of the ibuprofen oil solution.

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