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Original Article

# Determination of 6258-70, a new semi-synthetic taxane, in rat plasma and tissues: Application to the pharmacokinetics and tissue distribution study ☆

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ABSTRACT

Cancer is the leading cause of death all over the world. Among the chemotherapy drugs, taxanes play an important role in cancer treatment. 6258-70 is a new semi-synthetic taxane which has a broad spectrum of antitumor activity. A fast and reliable high performance liquid chromatography-tandem mass spectrometry (HPLC–MS/MS) method was developed for quantification of 6258-70 in rat plasma and tissues in this paper. After extraction by liquid-liquid extraction method with methyl tert-butyl ether, the samples were separated on a Kinetex $C_{18}$ column (50 mm × 2.1 mm, 2.6 μm, Phenomenex, USA) within 3 min. The method was fully validated with the matrix effect between 87.7% and 99.5% and the recovery ranging from 80.3% to 90.1%. The intra- and inter-day precisions were less than 9.5% and the accuracy ranged from −3.8% to 6.5%. The reliable method was successfully applied to the pharmacokinetics and tissue distribution studies of 6258-70 after intravenous administration in rats. The pharmacokinetic results indicated that the pharmacokinetic behavior of 6258-70 in rats was in accordance with linear features within tested dosage of 1 to 4 mg/kg, and there was no significant difference between the two genders. The tissue distribution study showed that 6258-70 had an effective penetration, spread widely and rapidly and could cross blood-brain barrier. The results of pharmacokinetics and tissue distribution may provide a guide for future study.



## 1. Introduction

The incidence of cancer is increasing, and cancer is becoming the leading cause of death all over the world [1,2]. Plenty of cancer chemotherapy drugs were adopted while taxanes were the most popular and active ones in the last two decades. Taxanes are potent microtubule poisons that promote microtubule to assemble and prevent its depolymerization, which is essential for mitotic function of cancer cell [3–5]. Among these taxanes, paclitaxel and docetaxel are the most widely used drugs as the front-line treatment or combination drugs for the therapy of ovarian cancer, breast cancer, non-small cell lung cancer and cervical cancer [6].

However, the long-term use of taxanes is limited contributed to two major reasons. First, as taxanes have high substrate affinity for multidrug-resistance (MDR) proteins, in particular the ATP-dependent drug efflux pump P-glycoprotein (P-gp), it can lead to MDR reaction. In addition, because of poor solubility of taxanes, Tween 80 and Cromoplor EL need to be used, which can cause hypersensitivity reactions and cumulative fluid retention [7-9]. According to the study of structure-activity relationship, the active compound which is derived from taxanes by modifying C-2, C-10 and C-3′ position shows a great improvement towards MDR and keeps the same activity at the same time [10-12]. These derivative compounds from taxanes include cabazitaxel, larotaxel, and tesetaxel, which are under clinical test [13–16]. Thus, it is very meaningful to modify structure of taxanes in order to obtain new drugs with lower toxicity and higher effect, especially against the drug-resistant human cancer.

6258-70 (Fig. 1A) is a new semi-synthetic taxane derivatived with modification at the C-7, C-10 and C-3′ position from docetaxel (DTX) (Fig. 1B). As one member of taxanes, 6258-70 has the same advantages as other taxanes, including good active and broad spectrum of antitumor activity. In addition, according to the study on structure-activity relationship [10], as phenyl is replaced with isobutenyl at C-3′ position, 6258-70 shows poorer affinity to P-gp compared with docetaxel. These advantages make 6258-70 meaningful for deeper research.

According to ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals [17], preclinical pharmacokinetic study plays an important role in the development of new drugs. The pharmacokinetic parameters in animal species can be used to make critical

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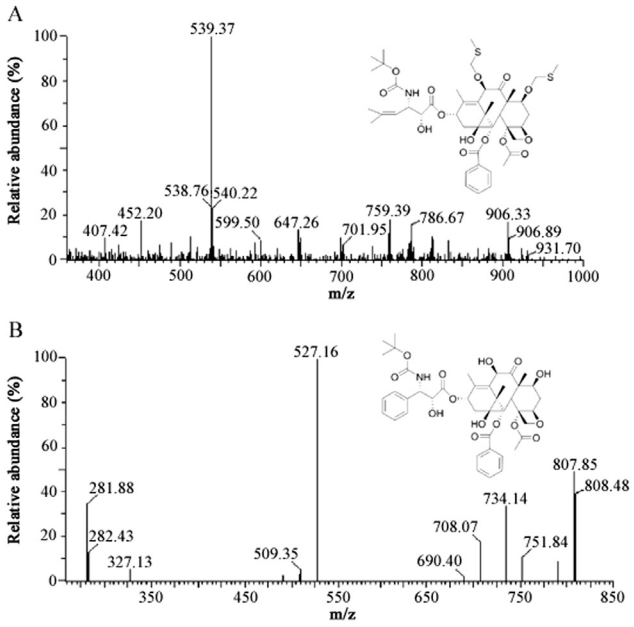


**Fig. 1.** Chemical structures and full scan mass spectra of (A) 6258-70 and (B) docetaxel.

decisions supporting the safety and efficacy of drugs. Selective and reliable analytical methods for the quantitative evaluation of a drug are critical for the conduct of preclinical, biopharmaceutics and clinical pharmacology research. However, as far as we know, there have been no reports on the pharmacokinetics and tissue distribution studies of 6258-70. Thus, a fast and reliable high performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS) bioanalytical method was developed and successfully applied to the quantification of 6258-70 in rat plasma and tissues for the first time in this paper. The pharmacokinetics and tissue distribution properties of 6258-70 after injection were demonstrated and discussed in this work, which will be useful for future studies.

**Table 1**
Calibration curves of 6258-70 in rat plasma and tissue homogenate.

| Samples | Slope $\times 10^{-2}$ | Intercept $\times 10^{-2}$ | $R$ | Linear ranges (ng/mL) |
|---|---|---|---|---|
| Plasma | 1.24 | 0.87 | 0.999 | 4–4000 |
| Liver | 1.18 | 0.43 | 0.997 | 4–4000 |
| Heart | 1.08 | 0.52 | 0.998 | 4–4000 |
| Spleen | 0.72 | 3.94 | 0.997 | 4–4000 |
| Lung | 0.93 | 5.11 | 0.993 | 4–4000 |
| Kidney | 0.98 | 3.93 | 0.994 | 4–4000 |
| Intestine | 1.19 | 1.94 | 0.992 | 4–4000 |
| Stomach | 1.07 | 3.51 | 0.996 | 4–4000 |
| Muscle | 1.11 | 0.60 | 0.997 | 4–4000 |
| Bladder | 1.05 | 2.34 | 0.998 | 4–4000 |
| Brain | 0.92 | 4.52 | 0.999 | 4–4000 |
| Fat | 1.66 | 0.84 | 0.999 | 4–4000 |
| Pancreas | 1.23 | 0.76 | 0.996 | 4–4000 |
| Testicle | 0.83 | 1.51 | 0.997 | 4–4000 |
| Uterus | 0.86 | 0.42 | 0.997 | 4–4000 |

## 2. Experimental

### 2.1. Chemical reagents and animals

6258-70 (purity $>98.0\%$), docetaxel (DTX, purity $>98\%$) (IS) and 6258-70 injection were supplied by Professor Xing Tang from Shenyang Pharmaceutical University. Acetonitrile, methanol and ammonium acetate of HPLC grade were purchased from Fisher Scientific (Fair Lawn, NJ, USA). Distilled water was provided by Wahaha Co., Ltd. (Hangzhou, China) and used throughout the study. Other chemical reagents were of analytical grade.

Sprague-Dawley (SD) rats (mean weight $220 \pm 10$ g) were

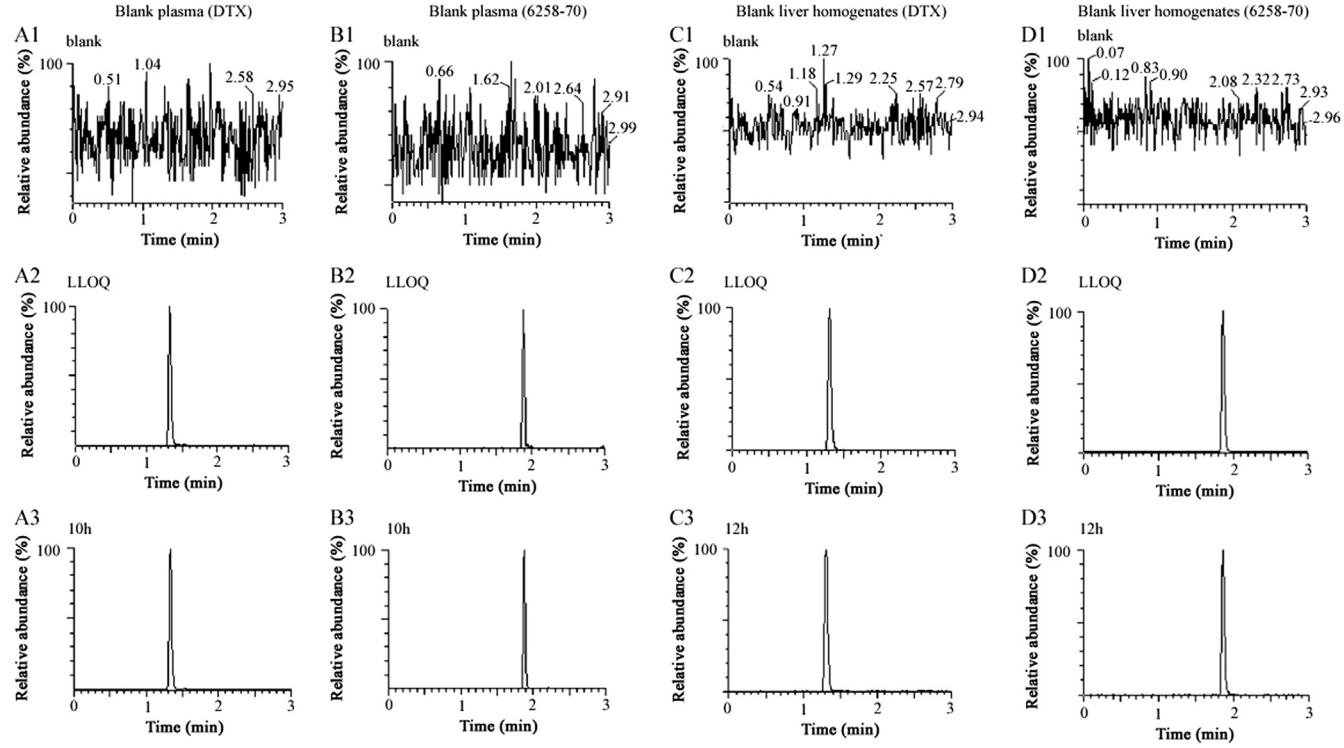


**Fig. 2.** MRM chromatograms of blank rat matrix (plasma or liver homogenate), blank rat matrix spiked with 6258-70 and IS, and rat plasma sample at 10 h or liver homogenate at 12 h.