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The Pharmacokinetics Evaluation and Bioequivalence of new Docetaxel Injections and Taxotere using Healthy Rats

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Abstract

The docetaxel of sterile freeze-dried powder injections was new developed injections due to overcome some drawbacks of Taxotere. We has been evaluated the pharmacokinetic properties and bioequivalence of the docetaxel of sterile freeze-dried powder injections and Taxotere by highly selective and accurate LC-MS/MS method in healthy rats. The pharmacokinetic parameters and bioequivalence of two injections were obtained by the profession software (DAS, version 2.0). The 90% CIs for the In-transformed ratios of C_{max}: AUC_{0-t} and AUC_{0-8} were 101.3%-104.1%, 99.8%-100.8% and 99.4-100.6%, respectively (all, $p < 0.001$). In this study, we attained the pharmacokinetic parameters of the two injections', meanwhile docetaxel of sterile freeze-dried powder injections appeared to be bioequivalent to Taxotere in healthy rats. The result was beneficially to further study the pharmacokinetics and bioequivalence of the human in the future research.

Keywords: Docetaxel of sterile freeze-dried powder injections; Taxotere; Pharmacokinetics evaluvation; Bioequivalence; LC–MS/MS

Introduction

Docetaxel was a semi-synthetic analogue of paclitaxel, which represented important antineoplastic agents with broad spectra of antitumor activity against various solid tumors including breast, non-small cell lung, head and neck and ovarian carcinomas (Eisenhauer et al., 1998; Pronk et al., 1995; Cortes et al., 1995; Van Oosterom and Schriivers et al., 1995; Piccart et al., 2003; Simon et al., 2003). The structures of docetaxel and paclitaxel are shown in Figure 1. Docetaxel was an antineoplastic agent that acted by disrupting the microtubular net work, thereby blocking cell cycle progression (Rowinsky et al., 1995). Elimination routes of docetaxel were mediated by the cytochrome P450 (CYP) 3A isoforms, notably CYP3A4 and CYP3A5, and the membrane transporter P-glycoprotein (Shou et al., 1998; Bardelmeijer et al., 2002). Docetaxel was the first drug for cancer therapy with the name of Taxotere in France. For clinical use, Taxotere was formulated in the nonionic surfactant polyoxyethylene-20-sorbitan monooleate (polysorbate 80), which was used as the solubilizing agent. In recent years, substantial evidences were generated to show that polysorbate 80 was a biologically and pharmacologically active compound (Ten et al., 2003). It has been also shown that polysorbate 80 has intrinsic antitumor activity, and its use has been implicated in the occurrence of severe anaphylactoid hypersensitivity and cumulative fluid retention associated with docetaxel therapy (Sparreboom et al., 2002). Moreover, it was demonstrated that polysorbate 80 interfered with the normal binding of docetaxel to serum proteins in a concentration-dependent manner and can modulate the pharmacokinetics of docetaxel (Loos et al., 2003). Thus, there was need to develop new docetaxel preparation which can avoid these drawbacks.

Hydroxypropyl-beta-cyclodextrin (HP-β-CD) was a derivative of β-cyclodextrin. It was highly water-soluble at the room temperature and excreted in the urine. Compared with other surfactants, the surface activation and haemolysis activation of HP-β-CD were low. Recently, HP-β-CD was used in the preparation of injection formulations of many drugs, such as Nimodipine(Brewster et al., 1989) (Yoshida et al., 1990), 9α-fluoro-16α-methylprednisolone and aquadiol(Simpkins, 1991), asellacrin and prostaglandin (Chinet al., 1994; Pitha, 1985). So, the China pharmacectic company had been developed the docetaxel of sterile freeze-dried powder injections, which used HP-β-CD as the solubilizing agent to avoid polysorbate 80's drawbacks.

A lot of papers reported to determine the concentration of docetaxel with high-performance liquid chromatography (HPLC) (Ardiet et al., 1999; Rouini et al., 1998; Garg et al., 2000), HPLC-MS (Parise et al., 2003) and HPLC-MS/MS (Wang et al., 2003; Hou et al., 2004; Baker et al., 2004; Mortier et al., 2006; Yu et al., 2008; Li et al., 2009; Jiang et al., 2009; Wu et al., 2009; Huang et al., 2007; Tan et al., 2006; Tong et al., 2003; Paek et al., 2006). And, the solid-phase extraction, liquid–liquid extraction was used to sample precipitate protein. However, the solid-phase extraction involves multi-step purification. The liquid–liquid extraction needs to use high-purity organic solvents

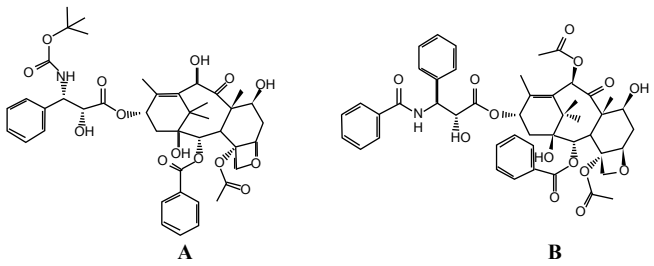

Figure 1: Chemical structures of Docetaxel(a) and Paclitaxel (b).

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and is often also expensive and time-consuming, meanwhile previous studies were reported on the pharmacokinetics of docetaxel that was formulated with other adjuvants. And, literature search did not identify any published data concerning the pharmacokinetic property and bioavailability of the bioequivalence of the docetaxel of freeze-dried powder injections and Taxotere in rats.

In order to appraise the new docetaxel of sterile freeze-dried powder injections, we had to compare with the pharmaceutical parameters and bioequivalence of the docetaxel of sterile freeze-dried powder injections and Taxotere by LC-MS/MS method in healthy rats. In this paper, we described LC-MS/MS method for the determination of the two injections' with a micro-sample volume using one-step protein precipitation. The sample preparation is very simple, fast and low cost. The aim of the present study was attained the pharmacokinetic parameters and was evaluated bioequivalence of the new docetaxel of sterile freeze-dried powder injections and Taxotere in healthy rats.

Experimental

Reagents and materials

Methanol and acetonitrile were high-performance liquid chromatography (HPLC) grade (Merck, Germany), other chemicals and reagents were analytical grade. Docetaxel standard (purity 99.0%) was supplied by Qilu Pharmaceutical Company Limited (Shandong, China). Paclitaxel standard (IS) was obtained from China Drug and Biologic Product Standardization Bureau (Beijing, China). Docetaxel of sterile freeze-dried powder injections was produced by Qilu Pharmaceutical Company Limited (Shandong, China). Taxotere was purchased from Rhône-Poulenc Rarer (Franch).

Instrumentation

Chromatographic separation was performed on an Ultra Fast LC (UFLC) system with a LC-20AD pump and SIL-20A autosampler (Shimazu, Japan). A Gemini (3um, 3.0×75 mm, Phenomenex, USA) column with in-line filter (5um, Phenomenex, USA), maintained at 40°C, was used. The mobile phase was methanol: 2 mmol L^{-1} ammonium acetate (3:1, v/v). The flow rate was set at 0.40 mL min^{-1}. The injection volume was 10 µL. The UFLC system was coupled with an API 3200 (Applied Biosystems, USA) triple quadrupole mass spectrometer equipped with an electrospray ionization (ESI) source and operated in the positive mode. Analyst 1.4 software was used to control all the parameters of UFLC and MS and to collect the data. Quantitation was performed using the multiple reaction monitoring (MRM). The identified precursor→product ion transitions for docetaxel and paclitaxel were *m/z* 830.4→549.3 and *m/z* 854.2→286.2, respectively. Source and compound dependent parameters of docetaxel were optimized as follows: capillary voltage (IS) 5.5 kV, source temperature (TEM) 260°C, collision energy (CE) 38 eV, declustering potential (DP) 65 V, collision cell exit potential (CXP) 8V, entrance potential (EP) 8V, and collision gas (CAD) 10 units. The capillary voltage giving the highest peak area of MRM transition was investigated by changing capillary voltages. Source- and compound-dependent parameters of paclitaxel was optimized as follows: capillary voltage (IS) 5.5 kV, source temperature (TEM) 260°C, collision energy 29.0 eV, DP 42V, EP 7V, and CXP 4V. The capillary voltage giving the highest peak area of MRM transition (*m/z* 854.2→286.2) was determined by varying the capillary voltages. The positive ion ESI mass spectrum and the MS/MS product ion spectrum of these compounds are shown in Figure 2.

Preparation of calibration standard

Stock solutions of docetaxel and paclitaxel (1 mg mL^{-1}) were prepared in methanol and stored at 4°C. The stock solution of docetaxel was further diluted to give series of standard solutions. Calibration standard of docetaxel (6.25, 12.5, 25, 50, 100, 200, 400, 800, 1600, 2000 ng mL^{-1}) were prepared by spiking appropriate amount of the standard solution in blank plasma. Lowest quality control standards (LQC), median quality control standards (MQC) & highest quality control standards (HQC) were prepared by spiking drup free plasma with docetaxel to give solutions containing 12.5, 800 and 2000 ng mL^{-1}, respectively.

Subjects and methods

Twenty male Wistar rats were obtained from Lanzhou University (Lanzhou, China). They were acclimatized for at least one week before the experiments. They were housed in a temperature-controlled room in a 12 h light–dark cycle and were given food and water ad libitum. Docetaxel of sterile freeze-dried powder injections and Taxotere dissolved in 0.9% sodium

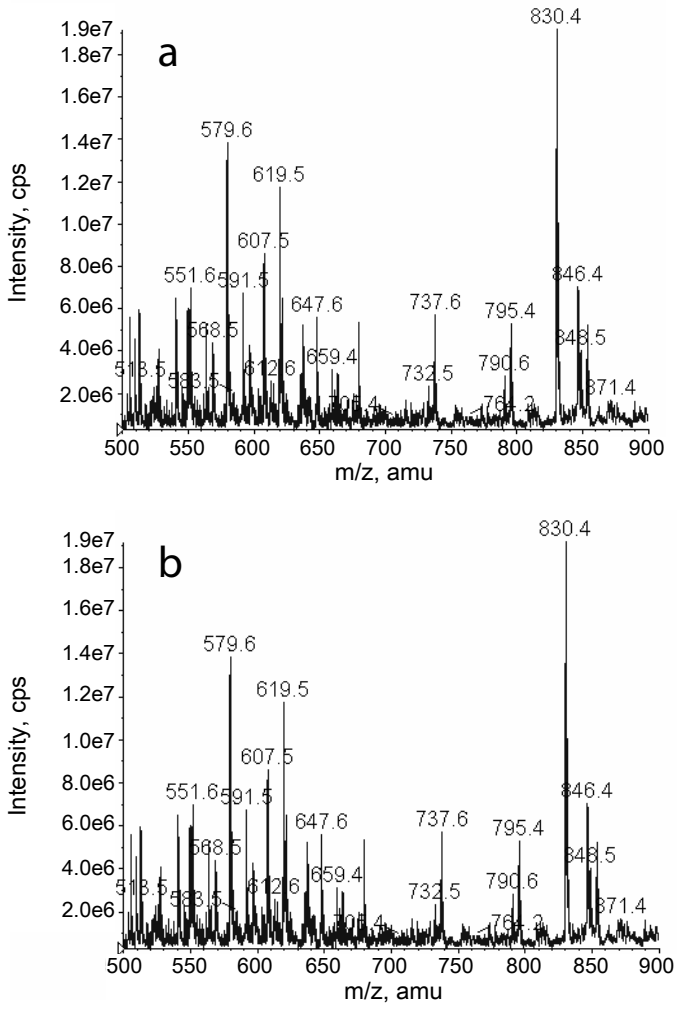

Figure 2: Typical full scan ESI (+) precursor ion mass spectra of Docetaxel (a) and the IS (b).

chloride, then was administered intravenously into the tail vein of the rats at a dose of 2.4 mg per rat, respectively.

Blood samples for the two injections analysis were obtained through a heparin-locked catheter containing 0.2 mL heparin. Blood samples (0.1 mL) were collected into heparinized 0.5 mL microtubes. Samples were obtained 5, 15, 45 min and 1, 1.25, 1.5, 2, 3, 5, 8, 12, 24, 36, 48h after administration. After sampling, the rat plasma was stored at -20 ^{O}C.

Sample preparation

Plasma samples stored at -20^{O}C were allowed to thaw at room temperature. To 50 uL plasma in a 1.5 mL microtube, 300 uL methanol was added, vortex-mixed for 30 s, centrifuged at 12000 r min^{-1} for 5 min. The upper layer (190 uL) was transferred to another microtube, added 10 uL paclitaxel (1.2ug mL^{-1}), vortex-mixed for 30 s, and centrifuged at 12000 r min^{-1} for 5 min. The upper layer was transferred to another clean glass tube and 10 uL was injected into the LC–MS/MS system. A representative LC-MS/MS chromatogram of a plasma sample obtained at 2 h was shown in Figure 3.

Results and Discussion

Selection of IS and mass spectrometry

Paclitaxel was adopted because of its similarity of retention time, ionization and recovery. It was found that the positive ion signals were stronger than the negative ion signals of docetaxel and paclitaxel. Therefore, positive ion mode was chosen. In the precursor ion full scan spectra, the most abundant ions was the quasi-molecular ion $[M+Na]^+$ with *m/z* 830.4 for docetaxel and $[M+H]^+$ with *m/z* 854.2 for Paclitaxel. In the product ion scan spectra, the most prominent product ions were *m/z* 549.3 for docetaxel and *m/z* 286.2 for the Paclitaxel. Therefore, the transition ions of *m/z* 830.4→549.3 for docetaxel and *m/z* 854.2→286.2 for the Paclitaxel were used.

Calibration and method validation

The method exhibited excellent linear response over the selected concentration range of from 6.25 to 2000ng mL^{-1} by weighted ($1/x^2$) least-squares linear regression analysis. The mean standard curve was typically described by the equation: y = 0.00353x - 0.00213, r = 0.9993, where y corresponds to the peak area ratio of docetaxel to the paclitaxel and x refers to the concentration of docetaxel added to plasma. Results of five representative standard curves for LC–MS/MS determination of docetaxel were given in Table 1.

Data for intra-day and inter-day precision and accuracy of the method were presented in Table 2. The intra-day accuracy of the method for docetaxel ranged from 99.00% to 99.68%, while the intra-day precision ranged from 1.01% to 2.93%. The inter-day accuracy of the method ranged from 99.50% to 100.40%, while the inter-day precision ranged from 1.18% to 2.20%. The results revealed good precision and accuracy.

Table 3 summarized the results of the short-term stability, long-term stability and freeze and thaw stability of docetaxel in rat plasma. The data showed that docetaxel was stable under the conditions tested.

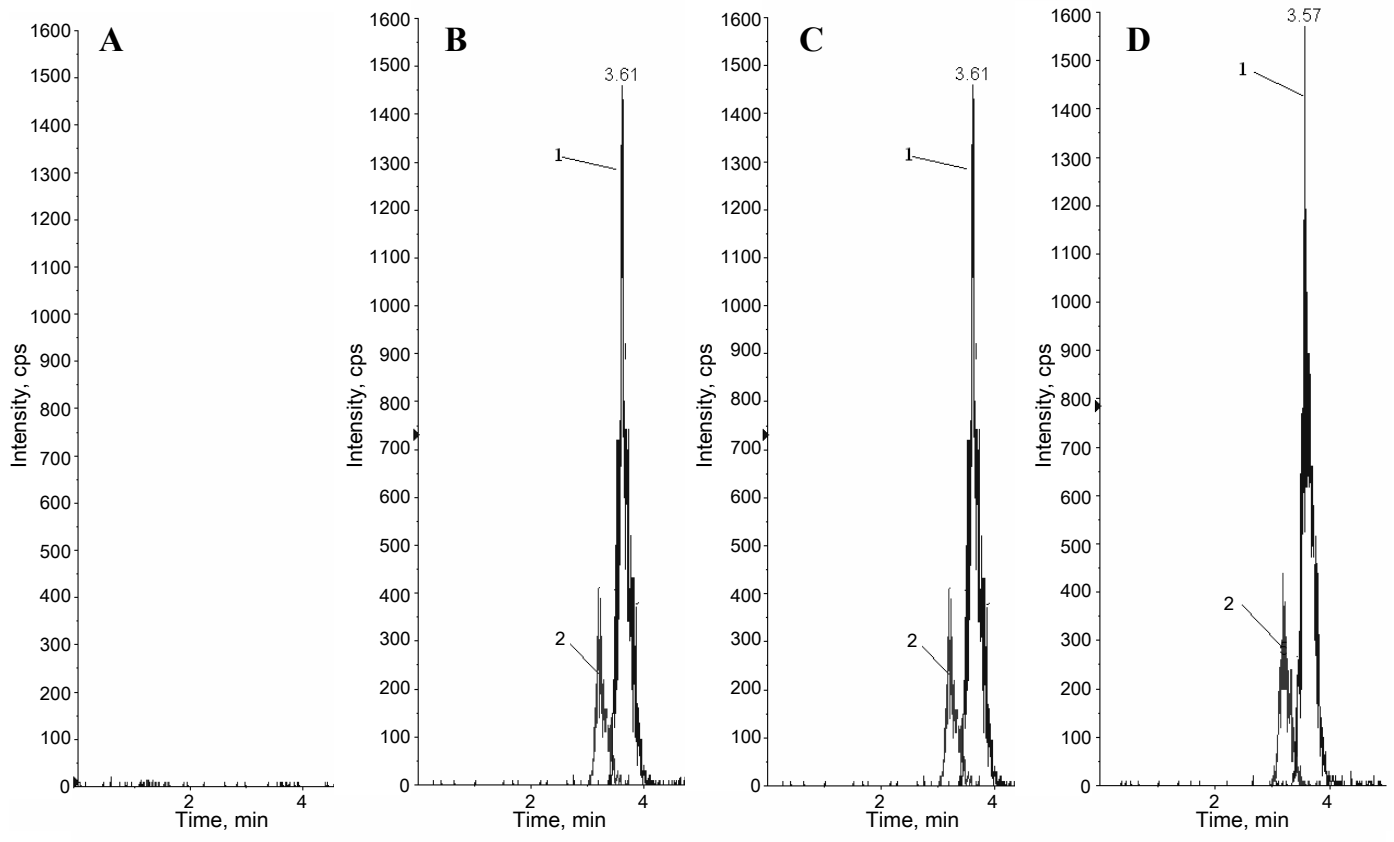

Figure 3: Chromatogram of the blank plasma (a), docetaxel (1ug mL^{-1}) spiked with IS (b), plasma control sample of docetaxel (1ug mL^{-1}) spiked with IS (c) and rat plasma control sample of Docetaxel (1ug mL^{-1}) spiked with IS (d). 1- Docetaxel; 2-Paclitaxel.

Nominal concentration (ng mL^{-1})	Mean ±S.D (n = 5)	RSD (%)	Accuracy (%)
6.25	6.24±0.23	3.75	100.04
12.5	12.44±0.46	3.67	99.34
25	25.22±0.75	2.96	101.08
50	51.26±1.17	2.28	102.62
100	97.90±2.71	2.77	97.90
200	200.04±6.65	3.32	100.36
400	392.60±14.67	3.74	98.26
800	795.00±21.80	2.74	99.54
1600	1602.00±58.91	3.68	100.04
2000	2028.00±19.24	0.95	101.04

Table 1: Precision and accuracy of calibration samples of docetaxel in rat plasma.

Nominal Concentration(ng/ml^{-1})	Mean ± S.D.	RSD (%)	Accuracy (%)
Intra-day variation (n=5)			
12.5	12.46±0.24	1.93	99.68
800	792.40±0.27	1.01	99.05
1600	1584.00±0.27	2.39	99.00
Inter-day variation (n=5)			
12.5	12.55±0.27	2.20	100.40
800	796.00±9.43	1.18	99.50
1600	1592.67±25.00	1.57	99.50

Table 2: Intra- and inter-day precision of determination of docetaxel in rat plasma.

Pharmacokinetic properties

Pharmacokinetic parameters of docetaxel new formulation and Taxotere were calculated from the total drug plasma concentration curve against the time after administration for each rat using DAS software (version 2.0). The mean concentration-time profiles of the two injections' were shown in Figure 4. C_{max} and T_{max} were obtained directly from the plasma concentration-time curves of docetaxel (A) and Taxotere (B). Comparing to the $AUC_{0\to48}$ of the docetaxel of sterile freeze-dried powder injections was 11977.564 ng mL^{-1} h^{-1}, the $AUC_{0\to48}$ of Taxotere was 11599.145 ng mL^{-1} h^{-1}, which marked increases. Both the terminal half-life ($t_{1/2}$) of the docetaxel of sterile freeze-dried powder injections and Taxotere were 11.644 h and 14.305 h, respectively. The maximum peak of the docetaxel of sterile freeze-dried powder injections was achieved at the time of 1.5 h. The maximum peak of Taxotere was achieved at the time of 3.0 h. The results showed that the pharmacokinetic parameters of the docetaxel of sterile freeze-dried powder injections were similar to Taxotere in rats (Table 4).

Bioequivalence

As proposed by the US FDA to assess the bioequivalence between the two formulations, 90% CIs of the geometric means

Nominal Concentration (ng mL^{-1})	**12.5(ng mL^{-1})**	**Found (Mean ± S.D.) 800(ng mL^{-1})**	**1600(ng mL^{-1})**
Short-term stability (7h, room temperature)	12.62 ± 0.26	806.00 ± 8.43	1610.10± 0.62
Long-term stability (36h, −20°C)	12.44±0.30	798.20 ± 7.69	1602.00±14.83
Freeze and thaw stability (3 cycles, −20°C)	12.58±0.29	792.60± 10.11	1592.00±16.43

Table 3: Stability data of docetaxel in rat plasma.

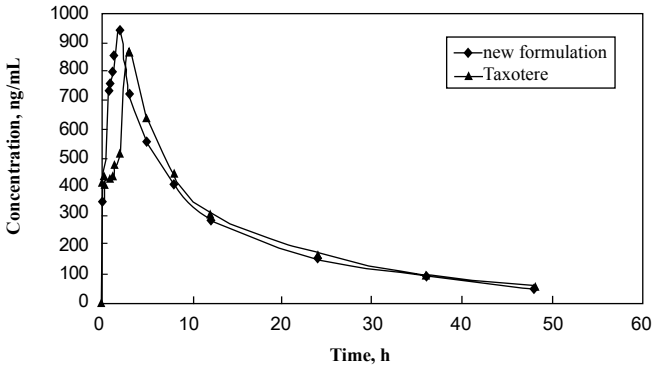

Figure 4: Plasma concentration-time profile of Docetaxel (sterile freeze-dried powder) (A) and Texotere (B) in rats after intravenous administration at the dose of 8.0mg kg^{-1}.

of the individual test/reference (T/R) ratios for these three variables were obtained. The formulations were to be considered bioequivalent if the logarithm-normal (In)-transformed ratios of C_{max} and AUC were within the predetermined range of 80% to 125%. Table 5 shows the 90% CIs obtained for the pharmacokinetic parameters after log-transformation of the data. None of the differences between the test and reference formulations were significant (C_{max}: 1.013-1.041, $AUC_{0\text{-}t}$: 0.998-1.008 and $AUC_{0\sim8}$: 0.994-1.006), and all fell within the predetermined, regulatory 90% CI range for bioequivalence (0.80-1.25) for the T/R ratio.

Conclusions

The validated LC–MS/MS method was successfully used to quantify docetaxel concentration for the bioequivalence and the pharmacokinetic parameters of the new docetaxel of freeze-dried powder injections and Taxotere in rat plasma. In these healthy rats, results from pharmacokinetic property analysis suggested that the test (the docetaxel of sterile freeze-dried powder

Parameter	$AUC_{0\to36}$ ng·mL^{-1}·h^{-1})	$AUC_{0\to\infty}$ (ng·mL^{-1}·h^{-1})	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng·mL^{-1})	CL_Z	$MRT_{0\to36}$ (h)	$MRT_{0\to\infty}$ (h)
Docetaxel (test)	11977.564	12698.001	11.644	1.500	1051.014	0.021	12.921	15.813
Taxoter(reference)	11599.145	12691.495	14.305	3.000	868.35	0.012	13.89	18.633

Table 4: Main pharmacokinetic parameters of Docetaxel (sterile freeze-dried powder) (test) and Taxotere (reference) (Mean ± S.D, n = 10).

P for Exceeding the Limits of Acceptance for Bioavailability					
PK Property	Ratio Test*: Reference#	90% CI	<80%	>125%	Power
C_{max}	121.54	101.3%-104.1%	<0.001	<0.001	0.99
$AUC_{0\to36}$	103.14	99.8%-100.8%	<0.001	<0.001	0.99
$AUC_{0\to\infty}$	100.09	99.4%-100.6%	<0.001	<0.001	0.99

*Manufactured by Qilu Pharmaceutical Company Limited, Shandong, People's Republic of China
Taxotere

Table 5: Comparison of pharmacokinetic (PK) properties between two formulations of docetaxel in rat.

injections) and reference (Taxotere) injections' were bioequivalent. This developed method will be used for the later pharmacokinetics study of the docetaxel of freeze-dried powder injections in humans.

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