In Vitro and in Vivo Studies on Plasma-to-Blood Ratio of Paclitaxel in Human, Rabbit and Rat Blood Fractions

Xiang-Rui Liu, a Ke-Chun Wu, a Yue Huang, a Jia-Bei Sun, a Xi-Yu Ke, a Jian-Cheng Wang, a
Wan-Liang Liu, a,b Xuan Zhang, a,b and Qiang Zhang a,b

Department of Pharmaceutics, Peking University; and a State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University; Xueyuan Road 38, Beijing 100083, China.

Received November 17, 2007; accepted March 6, 2008; published online March 10, 2008

Many pharmacokinetic studies of paclitaxel formulations with or without Cremophor (CrEL) have been performed on experimental animals. However, limited studies describe the different pharmacokinetic behaviors of paclitaxel in animals. The different distribution of drug in blood fractions may have great effect on its pharmacokinetic behaviors. Our present study was designed to study the characteristics of paclitaxel distribution in human, rabbit and rat blood, by measuring plasma-to-blood ratio (PBR) of paclitaxel in vitro and in vivo, and analyzing the results of equilibrium dialysis of paclitaxel with erythrocyte, plasma and hemoglobin. It was demonstrated that the paclitaxel PBR values in rat, unlike those in rabbit, are most significantly different from those in human, which may be due to distinct affinity of paclitaxel to blood fractions among different species. The effect of CrEL on increasing paclitaxel plasma concentration and in vitro & in vivo correlation in animal PBR values were observed. The findings in this study are of significance in the evaluation of the newly developed formulations of paclitaxel.

Key words paclitaxel; plasma-to-blood ratio; blood fraction; human; rabbit; rat

Paclitaxel is one of the successful examples of anticancer agents in clinical therapy against a wide variety of tumors.1−3) The commercial formulation of paclitaxel is Taxol® which contains 30 mg of drug dissolved in 5 ml of Cremophor EL (CrEL)/dehydrated ethanol (50:50, v/v).4) As a surfactant, CrEL is also being used as a vehicle for solubilization of a wide range of other hydrophobic drugs (such as cyclosporine A and tocopherol acetate).5) As a matter of fact, many newly-developed formulations of paclitaxel were designed to compare with Taxol® in pharmacokinetics performed on animals, such as rats,6,7) rabbits8) and mice.9)

It has been reported that CrEL profoundly influences the cellular distribution of paclitaxel in human blood leading to changes in the pharmacokinetic behavior.10) However, it is not clear if CrEL produces any influences on paclitaxel pharmacokinetics in animals through the similar mechanism. Moreover, it is unknown if there is any difference in the characteristics of paclitaxel distribution in blood fractions among human and different species of animals.

The pharmacokinetic studies in animals are very crucial in pre-clinical phase. Since the cellular distribution of a drug in different blood fractions may have great effect on the pharmacokinetic behaviors and this effect may be different among human and different species of animals, it seems necessary to investigate the characteristics of drug distribution in blood fractions of human and various animals, simultaneously taking the effect of surfactant into consideration, in order to achieve better pharmacokinetic evaluation.

Using the paclitaxel and CrEL as models for drug and surfactant respectively, the present study was designed to study the characteristics of paclitaxel distribution in human, rabbit and rat blood, by measuring plasma-to-blood ratio (PBR) of paclitaxel in vitro and in vivo, and analyzing the results of equilibrium dialysis of paclitaxel with erythrocyte, plasma and hemoglobin.

MATERIALS AND METHODS

Materials Paclitaxel and docetaxel were obtained from Mei-Lian Co., Ltd. (Chongqing, China). Cremophor EL (CrEL) was purchased from BASF Corporation of Germany (Local Agent in Shanghai, China). Rat hemoglobin and human hemoglobin were from Sigma-Aldrich (Local Agent in Beijing, China). Taxol was commercially available from local hospital of Beijing (Bristol Myers Squibb Co., Princeton, NJ, U.S.A.), and the formulation of Taxol contains 30 mg of paclitaxel in 5 ml of 50% CrEL (v/v) and 50% ethanol (v/v). Paclitaxel DMSO (dimethyl sulfoxide) stock solution (50 μg/ml) was prepared by our laboratory. All other chemicals were of analytical grade or HPLC grade.

Animals Male Japanese white rabbits weighing 2.0—2.5 kg and Sprague-Dawley rats weighing 200—250 g were obtained from Experimental Animal Center of Peking University. All care and handling of animals were performed with the approval of Institutional Authority for Laboratory Animal Care of Peking University.

In Vitro Plasma-to-Blood Ratio (PBR) of Paclitaxel

Paclitaxel Solutions Containing CrEL: An aliquot of 20 μl paclitaxel DMSO stock solution was mixed with 30 μl physiological saline (0.9% NaCl, w/v), and then with 0, 1.0, 7.5 or 10.0 μl CrEL, respectively.

PBR of Paclitaxel: Distribution experiment of paclitaxel in blood fraction was performed according to the previous report.10) Briefly, blood specimens were collected from healthy volunteers, rabbits or rats with glass vials containing lyophilized sodium heparin as an anticoagulant and were used within 1 h after collection.

A volume of 950 μl of blood specimens was mixed with the above serial paclitaxel solutions containing CrEL or not, respectively, and the blood mixtures were shaken at a speed of 50 times per minute for 10 min at 37 °C water bath (SHA-C, Jintan Xinyijia Equipment Factory, Jiangsu, China). The final concentrations of CrEL in the blood mixtures were 0.0,
0.10, 0.75, and 1.0% (v/v), respectively, and the final concentration of paclitaxel was 1.0 μg/ml for each.

After shaking, a volume of 300 μl blood mixtures was put in another Eppendorf tube, respectively, and kept at −80 °C for 5 min for causing a complete hemolysis. The remaining parts of the blood mixtures were centrifuged for 5 min at a speed of 3000 g for separating plasma. Paclitaxel in the hemolyzed blood mixtures or in the separated plasma was measured using an HPLC method as below.

**Equilibrium Dialysis** Equilibrium dialysis was performed according to the previous reports. Briefly, erythrocyte suspension and plasma of human, rabbit or rat were prepared with freshly heparinized blood specimens. Erythrocytes were washed twice with 1 ml of ice-cold phosphate buffer (0.01 M potassium phosphate, 0.137 M sodium chloride, 2.7 mM potassium chloride, in the presence of 0.05% (w/v) glucose at pH 7.4) and re-suspended in the same buffer to give the desired hematocrit (0.45). Human or rat hemoglobin was dissolved in phosphate buffer, respectively. The concentration of hemoglobin for each solution was 10 mg/ml. An aliquot of 980 μl erythrocyte suspensions, plasma or hemoglobin solutions was mixed with 20 μl paclitaxel DMSO stock solution, respectively. The final concentration of paclitaxel was 1 μg/ml for each. A volume of 260 μl above erythrocyte suspensions, plasma or hemoglobin solutions was dialyzed against an equal volume of phosphate buffer (receiving apartment) with or without CrEL (0.5%, v/v) for 5 min at a speed of 3000 g for separating plasma. Paclitaxel in the hemolyzed blood mixtures or in the separated plasma was measured using an HPLC method as below.

**In Vivo PBR of Paclitaxel** Animals were allowed free access to standard food and water, maintained on a light/dark cycle under conditions of 25 ± 3 °C and 50% humidity, and acclimatized for 7 d. The animals were fasted for at least 24 h prior to the experiment and were given water freely.

Paclitaxel DMSO solution (1 mg/ml) for i.v. injection contained 35% DMSO, 15% ethanol and 50% physiological saline (v/v/v). Paclitaxel solution was prepared by 30 mg paclitaxel dissolved in 2.5 ml ethanol and 1.25 ml CrEL and then diluted with saline at a paclitaxel concentration of 1 mg/ml. Taxol for i.v. injection was prepared by diluted Taxol with saline at a paclitaxel concentration of 1 mg/ml. The concentration of CrEL in paclitaxel DMSO solution, paclitaxel solution and Taxol were 0, 4.2 and 8.3% (v/v), respectively.

Fifteen male SD rats were randomly assigned to three groups of five rats. Group 1 received an i.v. injection of paclitaxel DMSO solution, Group 2 received an i.v. injection of paclitaxel solution and Group 3 received an i.v. injection of Taxol. All formulations were administrated through the tail vein at the same dose of 5 mg/kg paclitaxel versus the rat body weight. Approximate 0.5 ml of blood was collected from the orbit venous plexus of the rats at 0 (pre-dose), 0.17, 1 and 4 h after administration, respectively. After blood sampling, equivalent volume of physiological saline was injected into the rat through tail vein.

Similarly, nine male Japanese white rabbits were equally divided into three groups. Paclitaxel DMSO solution, paclitaxel solution or Taxol were intravenously administered to each rabbit in Group I, II or III via ear brim at a dose of 5 mg/kg paclitaxel, respectively. Approximate 0.5 ml of blood was collected from the ear brim vein at 0 (pre-dose), 0.17, 1 and 4 h after administration, respectively.

An aliquot of 100 μl blood specimens obtained from rats or rabbits were immediately stored at −20 °C. The remaining part of the blood specimens were centrifuged at 3000 g for 5 min for separating plasma. All blood and plasma samples were stored at −20 °C until analysis. The PBR values of paclitaxel in rats or rabbits in vivo were calculated by the concentration of paclitaxel in plasma vs. in blood.

**Measurement of Paclitaxel in Plasma and in Blood** Measurement method of paclitaxel in plasma and blood was modified according to the previous report. Briefly, an aliquot of 100 μl plasma (or blood) samples, and 50 μl docetaxel solution (10 μg/ml, as an internal standard), and 2.5 ml acetonitrile were mixed by a vortex mixer for 30 s. The mixture was centrifuged at 3000 g for 10 min. A volume of 2.0 ml of supernatant was collected, and dried under a gentle nitrogen gas at 50 °C in water bath. The residue was reconstituted using the mobile phase as below, and assayed by Waters HPLC system consisting of a 1525-pump, and a 2487-ultraviolet detector (Waters Co., Inc., Westerville, OH, U.S.A.). Mobile phase was consisted of methanol–water–tetrahydrofuran (70:27.5:2.5, v/v/v), and delivered at a flow rate of 1 ml/min. Chromatographic separation was performed on a Phenomenex ODS2 column (250×4.6 mm, 5 μm, Torrance, CA, U.S.A.). Wavelength was set at 230 nm. The peak areas of paclitaxel (Ap) and docetaxel (Ad) were recorded, and the concentration of paclitaxel was calculated according to the ratio of Ap/Ad. The limit of quantification (LOQ) of the assay was 50 ng/ml, and linearity was obtained for paclitaxel concentrations ranging from 100 to 5000 ng/ml (R²=0.9999). The coefficients of variation of the inter-day and intra-day precision of the quality control samples ranged from 2.6 to 10.4% and accuracy ranged from 95.3 to 101.4%.

**Statistics** Data are presented as the mean ± standard deviation (S.D.). One-way analysis of variance (ANOVA) was used to determine significance among groups, after which post-hoc tests with the Bonferroni correction were used for comparison between individual groups. Statistical significance was established at p < 0.05.

**RESULTS**

**In Vivo Plasma-to-Blood Ratio of Paclitaxel** The in vivo plasma-to-blood ratio (PBR) of paclitaxel in human, rabbit and rat blood samples was depicted in Fig 1. The PBR values of human and rabbit bloods in the absence of CrEL were similar (1.01 in human blood and 0.99 in rabbit blood), however, the PBR value in rat was significantly lower (0.71 in rat blood, p < 0.01). After addition of a lower concentration of CrEL (0.1%) in the blood samples, PBR values of paclitaxel in three groups exhibited the similar pattern (1.19 in human blood, 1.14 in rabbit blood and 0.79 in rat blood) as
Ratio data are expressed as the mean ± standard deviation. Each was repeated for triplicate. *p<0.05; **p<0.01; NS no significant difference.

Table 1 The Distribution of Paclitaxel in Artificial Binary System of the Main Blood Fractions in the Absence or in the Presence of Cremophor (CrEL)

<table>
<thead>
<tr>
<th>Binary system</th>
<th>Buffer (without CrEL): total ratio (%)</th>
<th>Buffer (containing CrEL): total ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffer/human erythrocytes</td>
<td>10.00 ± 0.50</td>
<td>67.15 ± 0.95</td>
</tr>
<tr>
<td>Buffer/human plasma</td>
<td>9.28 ± 0.42</td>
<td>61.52 ± 2.1</td>
</tr>
<tr>
<td>Buffer/rabbit erythrocytes</td>
<td>14.75 ± 0.95</td>
<td>66.09 ± 2.26</td>
</tr>
<tr>
<td>Buffer/rabbit plasma</td>
<td>13.58 ± 0.39</td>
<td>57.31 ± 1.74</td>
</tr>
<tr>
<td>Buffer/rat erythrocytes</td>
<td>7.84 ± 0.20</td>
<td>59.65 ± 0.98</td>
</tr>
<tr>
<td>Buffer/rat plasma</td>
<td>10.27 ± 0.21**</td>
<td>65.63 ± 0.93</td>
</tr>
<tr>
<td>Buffer/human hemoglobin solution</td>
<td>26.76 ± 0.31</td>
<td>95.13 ± 0.64</td>
</tr>
<tr>
<td>Buffer/rat hemoglobin solution</td>
<td>27.85 ± 0.28</td>
<td>95.19 ± 1.02</td>
</tr>
</tbody>
</table>

a) The concentration of paclitaxel in receiver side was determined by HPLC. After paclitaxel was added in the binary system and incubated for 24h at 37°C. b) Total mean is the concentration of paclitaxel added into the binary system, namely, 1 μg/ml. Ratio data are expressed as the mean ± standard deviation. Each was repeated for triplicates. **p<0.01, data from rat erythrocytes vs data from rat plasma in the absence of CrEL.

Equilibrium Dialysis Table 1 shows the distribution of paclitaxel in artificial binary system of the main blood fractions in the absence or presence of CrEL. As it was demonstrated, without the addition of CrEL, the buffer-to-total ratios of paclitaxel for plasma were close to that for erythrocytes, except of rat group in which the ratios for erythrocytes was significantly lower than those for plasma (p<0.01).

After addition of 0.5% CrEL in the buffer (receptor site), paclitaxel was significantly attracted to the buffer site from the donor site containing erythrocytes, plasma or hemoglobin, resulted in very high buffer-to-total ratios for all groups.

The values obtained from hemoglobin test were much higher than other groups and there was no significant difference in the results of the same test between the human and rat groups.

In Vivo PBR of Paclitaxel in Rabbit and Rat Figure 2 presents the PBR values of paclitaxel at 0.17, 1 or 4 h time points after i.v. administration of paclitaxel DMSO solution (containing 35% DMSO, 15% ethanol and 50% physiological saline, v/v/v, concentration of CrEL 0%, vertical line), Paclitaxel solution (concentration of CrEL 4.2%, horizontal line) or Taxol (concentration of CrEL 8.3%, white) at a dose of 5 mg/kg, respectively.

Data are presented as the mean ± (S.D.) of measurements from 3—5 animals. ***p<0.01; **p<0.05; NS no significant difference.

The Concentration of Paclitaxel in Blood and Plasma Figure 3 shows the concentration of paclitaxel in whole blood and plasma after i.v. administration of paclitaxel with different CrEL levels in rabbits or rats. It is clear that the concentration of paclitaxel in both blood and plasma increased with the enhancement of CrEL concentration and this phenomenon was more evident in the case of plasma. The concentration of paclitaxel in plasma was higher than those in blood when animals were administrated with pacli-
taxel formulations containing CrEL. After i.v. administration of CrEL-free paclitaxel formulation to animals, the concentration of paclitaxel in rabbit plasma was similar with those in whole blood, while that in rat plasma was significantly lower than those in whole blood \( (p<0.01) \).

**Table 2.** The Plasma-to-Blood Ratios (PBR) of Paclitaxel in Rabbits or Rats at 0.17, 1 or 4 h Time Points after an i.v. Administration of Paclitaxel DMSO Solution (Containing 35% DMSO, 15% Ethanol and 50% Physiological Saline, \( v/v/v \)), Paclitaxel Solution (Concentration of CrEL 4.2%) or Taxol (Concentration of CrEL 8.3%) at a Dose of 5 mg/kg, Respectively

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Animal</th>
<th>Concentration of CrEL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.17</td>
<td>Rabbit</td>
<td>0.94±0.02** 1.12±0.12 1.49±0.05</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>0.63±0.04 1.28±0.20 1.40±0.09</td>
</tr>
<tr>
<td>1</td>
<td>Rabbit</td>
<td>0.74±0.01** 0.92±0.05 1.31±0.06</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>0.55±0.09 0.92±0.12 1.28±0.25</td>
</tr>
<tr>
<td>4</td>
<td>Rabbit</td>
<td>0.56±0.03* 0.80±0.07 1.19±0.10**</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>0.39±0.16 0.66±0.14 0.74±0.06</td>
</tr>
</tbody>
</table>

Data are presented as the mean±(S.D.) of measurements from 3—5 animals. **\( p<0.01 \); *\( p<0.05 \), data from PBR values in rabbit vs. data from PBR values in rat.

**DISCUSSION**

A great deal of studies now has associated with evaluating the systemic exposure of paclitaxel in animals. However, the difference of paclitaxel distribution in blood fractions, as well as such difference between human and animals was unclear. Our study was designed to explore these questions in the absence or presence of CrEL in vitro and in vivo.

In the in vitro experiments, similar PBR values of paclitaxel in human and rabbit were observed in the absence of CrEL. Interestingly, PBR values of paclitaxel in rat were evidently lower than those in other two groups. Similarly, the differences in PBR values between human and rat in the presence of CrEL were of significance. We also found similar PBR values of paclitaxel among mouse, dog, rabbit and human, significantly different with that of rat, in the absence or presence of CrEL (data not shown). Recently, Yokogawa et al. evaluated the PBR values of paclitaxel after i.v. or i.p. administration of Taxol or Taxotere (docetaxel commercial product) to rats, in order to investigate the influence of CrEL or Polysorbate-80. This paper did not compare the PBR values in different kinds of animals.

Since the paclitaxel distribution pattern in rabbit group was very similar with that of humans’ and the pattern in rat...
group was most significantly different from that of humans’ *in vitro*, the rats and rabbits were included in the following study for further exploring the different PBR of paclitaxel *in vivo*.

Our *in vivo* study also found that the PBR of paclitaxel in rabbit was comparable to that in human and the PBR in rat was significantly different with that in human.14) This finding based on both *in vitro* and *in vivo* PBR is important for choosing the right animal in the pharmacokinetic investigation of paclitaxel formulations.

The pharmacokinetic behaviors and parameters both in plasma and blood were reported in evaluating paclitaxel formulations. Recently, Gelderblom et al. reported that the measurement of unbound paclitaxel concentrations is a particularly useful index for the pharmacological effect of paclitaxel.15) The difference of paclitaxel concentration in plasma and blood was observed in our *in vitro* and *in vivo* results, indicating that the instinct distributing capability of paclitaxel in blood fractions might potentially alter the pharmacokinetic behaviors and parameters of paclitaxel.

It was indicated in our studies that the PBR values of paclitaxel all increased with the adding of CrEL. This fact is in accordance with previous published data in humans.10) Some *in vitro* studies in human blood have demonstrated that the CrEL micelles could lead to increase the distribution of paclitaxel in plasma and the PBR values of paclitaxel10,16) due to paclitaxel being encapsulated into the CrEL micelles and these micelles mainly exist in water phase of the plasma.

In our *in vivo* experiments, the PBR values in animal after administration of paclitaxel formulations decreased with time. The possible reason for PBR value decreasing was the elimination of unbound paclitaxel from plasma water phase and little supplementation of paclitaxel released from erythrocytes. As we know, most drugs are bound to some extent to plasma proteins and/or partitioned into erythrocytes. The carriage effect of red cell would play an important role of potential barrier, which acts as a shield against drug release and elimination.17,18) The bound, partitioned and unbound drug fractions in blood coexist and equilibria are maintained between the unbound and bound species. In contrast to the unbound drug molecules, the bound or partitioned molecules are not immediately available for elimination.19) Therefore, along with unbound paclitaxel elimination, plasma paclitaxel concentration reduced fast than that in blood, leading to decreased PBR values. In the presence of CrEL, the decreasing tendency of PBR values is also noted. Although the terminal half-life of CrEL amounts to approximately 80 h reported in clinical pharmacokinetic studies,20,21) CrEL can be slowly eliminated. The PBR values would also decrease along with CrEL elimination.

Erythrocytes have by far the largest cell volume and surface area when compared to other cellular components of the blood. The relationship of erythrocytes partitioning with PK parameters (Cl and Vd) is extremely important as the drug is usually measured in plasma and not in whole blood. It would be worthwhile to consider erythrocytes as a separate compartment while modeling concentration time data for high erythrocytes partitioning drugs.22) Several previous studies have found evidence that drug binding to erythrocytes can act as a barrier to hepatic elimination. Additionally, the importance of the erythrocyte uptake of drugs and the influence of drug–drug combination on their erythrocyte–plasma partition ratios has also been recognized.23–26) It was reported that erythrocytes formed secondary transport system for paclitaxel in whole blood (CrEL micelles act as the principal carrier of paclitaxel in the systemic circulation).10) According to the rationale mentioned above, higher partition of paclitaxel binding to erythrocytes, meaning lower PBR values, would induce the reduction of free paclitaxel in plasma water phase in the absence of CrEL. Hence, the AUC or Cmax of paclitaxel in whole blood would increase compared to those in plasma, meanwhile the clearance or distribution volume of paclitaxel would decrease. However, few studies focused on the effect of PBR values on the pharmacokinetics of drugs. So, the effect of PBR on paclitaxel pharmacokinetics in different animal species in whole blood or plasma should be investigated in the future.

Our study about the influence of some commonly used excipients showed that CrEL has the unique effect on the PBR of paclitaxel, while Poloxamer 188, polyvinyl-pyrrolidone, castor oil, hydroxypropyl-β-cyclodextrin, polyethylene glycol 6000, lecithin and cholesterol did not affect the distribution of paclitaxel (data not shown).

It is well known that lots of CrEL-free paclitaxel formulations have been evaluated by comparing systemic exposure of paclitaxel in plasma with Taxol which containing CrEL. Results of the current studies showed that the concentrations of paclitaxel in plasma after given a CrEL containing formulation were much higher than those given CrEL-free formulation, suggesting the obvious effect of CrEL on the enhancement of paclitaxel plasma distribution, not only in human, but also in rabbits and rats. However, few animal pharmacokinetic studies noticed this fact. Therefore it seems necessary to take the addition of CrEL into consideration when evaluating the paclitaxel formulations.

Equilibrium dialysis was performed to elucidate the possible mechanism of different PBR values among different species animals. The ratios of buffer-to-total values of paclitaxel in plasma over those in erythrocytes were nearly 1.0 in human and rabbit (1.08 for human and 1.09 for rabbit), however, those in rat was only 0.77. These results were similar with the PBR of paclitaxel *in vitro* in the absence of CrEL (1.01 in human, 0.99 in rabbit and 0.71 in rat), revealing that the different affinity of paclitaxel with erythrocytes or plasma for different species may be a major reason for the distinction in PBR values. As for hemoglobin, the only protein in erythrocytes, the binding of paclitaxel to this protein in rat is not evidently different from that in human, suggesting this factor may contribute less to the diversity.

In addition, it was reported that more than 90% paclitaxel in plasma binds rapidly and extensively to plasma proteins.27) In the meanwhile, paclitaxel also binds extensively to erythrocyte. Therefore, PBR values would mainly reflect the competitive binding ability of paclitaxel between plasma protein and erythrocyte. The buffer-to-total ratio in rabbit plasma (without CrEL) was higher than that in rat plasma or in human plasma, showing weaker affinity of paclitaxel with rabbit plasma protein than that in rat or human. Similar situation was also observed in the buffer-to-total ratio of rabbit erythrocyte (without CrEL), suggesting that the binding of paclitaxel to rabbit erythrocyte is also weaker than that in rat or human. It was believed that the difference in buffer/total
ratio came from the variance of binding ability of paclitaxel with plasma protein or erythrocyte among different species.

It was observed that there was a good in vitro & in vivo correlation (IVIVC) in terms of PBR values in animals. The PBR values in rabbits both in vitro and in vivo after treatment of paclitaxel formulations with or without CrEL (0, 4.2 or 8.3%) were higher than those in rats. The in vivo PBR values in both animals at the first time point (0.17 h) were nearly equal with those in vitro in the absence of CrEL. The good IVIVC results may guarantee the significance of the simple in vitro test.

CONCLUSION

In conclusion, PBR values of paclitaxel in rats are most significantly different from those in humans. The difference in PBR values between human and rat may be due to the fact that the distribution of paclitaxel in rat blood fractions was different with that in humans’. Therefore, the differences in PBR values of paclitaxel among different species should be taken into consideration when the newly developed formulations of paclitaxel are evaluated. In addition, the addition of CrEL in the formulation has increased the distribution of paclitaxel in plasma for all the species studied. Finally, there was an in vitro & in vivo correlation (IVIVC) in terms of animal PBR determination. The present study has offered important information for the pharmacokinetic evaluation of paclitaxel formulations.

Acknowledgment This work was supported by High Technology Project of Ministry of Science and Technology of China (Grant No.: 2004AA2Z3072) and the National Natural Science Foundation of China (30430760).

REFERENCES AND NOTES

3) Horwitz S. B., Ann. Oncol., 5 (Suppl. 6), S3—S6 (1994).