Paclitaxel-loaded niosomes for intravenous administration: pharmacokinetics and tissue distribution in rats

ZERRİN SEZGİN BAYINDIR
ARZU BEŞİKÇİ
NİLÜFER YÜKSEL

Follow this and additional works at: https://journals.tubitak.gov.tr/medical
Part of the Medical Sciences Commons

Recommended Citation
BAYINDIR, ZERRİN SEZGİN; BEŞİKÇİ, ARZU; and YÜKSEL, NİLÜFER (2015) "Paclitaxel-loaded niosomes for intravenous administration: pharmacokinetics and tissue distribution in rats," *Turkish Journal of Medical Sciences*: Vol. 45: No. 6, Article 33. https://doi.org/10.3906/sag-1408-129
Available at: https://journals.tubitak.gov.tr/medical/vol45/iss6/33

This Article is brought to you for free and open access by TÜBİTAK Academic Journals. It has been accepted for inclusion in Turkish Journal of Medical Sciences by an authorized editor of TÜBİTAK Academic Journals. For more information, please contact academic.publications@tubitak.gov.tr.
Paclitaxel-loaded niosomes for intravenous administration: pharmacokinetics and tissue distribution in rats

Zerrin SEZGİN BAYINDIR1, Arzu BEŞİKCİ2, Nilüfer YÜKSEL1,*

1Department of Pharmaceutical Technology, Faculty of Pharmacy, Ankara University, Tandoğan, Ankara, Turkey
2Department of Pharmacology, Faculty of Pharmacy, Ankara University, Tandoğan, Ankara, Turkey

Background/aim: The purpose of this study was to investigate and compare the pharmacokinetic behavior and tissue distribution of paclitaxel, delivered as commercial preparation Taxol or through Span 40 niosomes, after intravenous injection to rats.

Materials and methods: Paclitaxel-loaded Span 40 niosomes were prepared using the thin-film method. An HPLC method was developed and validated for paclitaxel determination in rat plasma and tissues.

Results: The area under the curve value of the niosome-recipient group (3.22 ± 0.255 µg h/mL) was significantly higher compared to that of the Taxol group (0.725 ± 0.163 µg h/mL). The mean residence time and the elimination half-life of paclitaxel were 1.66 ± 0.133 h and 1.15 ± 0.085 h for Taxol administration, respectively. The elimination half-life (7.63 ± 0.380 h) and the mean residence time (11.0 ± 0.6 h) of paclitaxel were significantly increased, and a pronounced delay was observed in general excretion of paclitaxel from plasma (0.0925 ± 0.00490 h−1) after niosomal administration. The spleen was the main tissue that accumulated paclitaxel from both niosomes and Taxol.

Conclusion: The findings of this study show that niosomal formulation might be a useful drug delivery system for intravenous administration of paclitaxel.

Key words: Niosomes, Span 40, paclitaxel, pharmacokinetics, tissue distribution

1. Introduction
Paclitaxel (PCT) is a chemotherapeutic agent used as a first-line treatment for a wide range of cancers, such as lung, ovarian, breast, prostate, head, and neck cancers, and AIDS-related Kaposi sarcoma. The first commercially available preparation of PCT on the drug market is Taxol. Taxol is a nonaqueous solution of PCT formulated in a 1:1 combination of the solubilizing agent Cremophor EL (polyethoxylated castor oil) and dehydrated ethanol, which is intended for dilution with a suitable parenteral fluid prior to intravenous (i.v.) infusion (1,2). However, the formulation of PCT is still a problem that hinders its use. Severe hypersensitivity reactions, neurotoxicity, and nephrotoxicity are observed after i.v. infusion of PCT and are a result of the Cremophor EL, rather than drug itself. Moreover, upon the contact of the PCT formulation with polyvinyl chloride infusion sets, Cremophor EL causes leaching of the plasticizer diethylhexylphthalate. Another problem with the formulation is the precipitation of PCT after dilution in the infusion solutions (3–5). Additionally, it causes serious side effects after systemic administration due to unspecific biological distribution.

There have been studies on several formulation approaches to enhance the solubility of PCT, which is highly hydrophobic; to control its biological distribution; and to avoid and eliminate the problems caused by its formulation. The first outcome of these studies was Abraxane, which was approved by the FDA in 2005. Abraxane is lyophilized powder and contains 800 mg of albumin per 100 mg of paclitaxel. After reconstitution with an isotonic sodium chloride solution before i.v. infusion, the resulting injectable suspension includes PCT-bound albumin nanoparticles that have a size of approximately 130 nm. Paclitaxel passage through the endothelial cells is improved due to albumin, and this was attributed to the gp-60 albumin receptor. The albumin-binding protein SPARC (secreted protein acidic rich in cysteine) leads to the enhanced PCT accumulation in the tumor site. This protein is overexpressed in breast carcinoma cells, and Abraxane is used to treat advanced metastatic breast...
cancer (6,7). Afterwards, a polymeric micelle formulation of PCT, Genexol-PM, and a liposome formulation, Lipusu, were commercialized in Korea and China, respectively. These formulations provide the PCT solubility without using toxic solvents, while they decrease the toxic side effects and improve the drug’s therapeutic efficacy by a better drug distribution (8–11). The phase III clinical trials of a polymeric conjugate of PCT with a water-soluble polymer polyglutamic acid, Opaxio (paclitaxel poliglumex; formerly called Xyotax), is ongoing. The preclinical studies revealed that Opaxio can more effectively target PCT to the tumorous tissue compared to standard PCT. This is explained by the leakage of PCT conjugate through leaky tumor vessels and its entrapment in the tumor site. The proteinic polymer is metabolized inside the tumor cell and then releases PCT (12). Other PCT delivery systems such as solid lipid nanoparticles, nanoparticles of biodegradable polymers, micellar nanocarriers, nanohydrogels, and dendrimers have also been intensively investigated (1,13–19).

In aqueous mediums, nonionic surfactants are known to form niosomes, which are closed, bilayered structures that vary in size from a few hundred nanometers to several micrometers (20). Depending on the preparation technique, niosomes can be in small unilayered or multilayered forms. The hydrophilic head groups of the nonionic surfactants are placed in the outer and inside part of the vesicle, and the hydrophobic groups face each other inside the bilayer (Figure 1). Thus, while the hydrophilic active agents are entrapped inside the vesicle, the hydrophobic agents are entrapped inside the bilayers (21,22). The first niosome formulation was developed in 1975 and was patented as an antiaging cosmetic product by L’Oréal. Afterwards, the studies for the usage of niosomes as drug delivery systems started.

In a previous study, PCT-carrying niosomes were prepared with various surfactant types (Tween 20 and 60; Span 20, 40, and 60; Brij 76, 78, and 72) by using the thin-film technique. The in vitro characterization studies on these formulations revealed the formation of nanosized niosomes with varying surface charges between ~40 and ~53 mV. The Span 20, 40, and 60 and Brij 72 surfactants, which have low hydrophilic-lipophilic balance values, were found to be more appropriate for the entrapment of PCT in niosomes (5). Among these formulations, the niosomes prepared with Span 40 were further evaluated using differential scanning calorimetry and X-ray diffractometry to observe the interaction between PCT and other formulation excipients. The outcomes showed that PCT was in an amorphous form inside the niosomes; the highly lipophilic active agent was loaded inside the bilayer lipid membrane by partition and thus provided slow in vitro PCT release (23).

The purpose of the present work was to investigate the pharmacokinetic behavior and distribution of PCT in the tissues from the PCT-loaded Span 40 niosomes compared to a commercially available i.v. preparation, Taxol, each administered intravenously to rats.

2. Materials and methods

2.1. Materials

PCT, cholesterol, and dicetyl phosphate (DCP) were purchased from Sigma-Aldrich (Milwaukee, WI, USA). Docetaxel and Span 40 (sorbitan monopalmitate) were bought from Fluka (Buchs, Switzerland). Acetonitrile, chloroform, methanol, and t-buty methyl ether were
2.2. PCT formulations
Niosomes were prepared using the thin-film method (5). Briefly, Span 40, cholesterol, and DCP were mixed at the molar concentrations of $2.97 \times 10^{-3}$ : $2.97 \times 10^{-3}$ : $2.5 \times 10^{-3}$ in chloroform. PCT solution in acetonitrile (0.234 mM) was added to the obtained organic solution. The organic solvents of the solution were removed by Rotavapor (Buchi 200, Labortechnik AG, Flawil, Switzerland). The thin-film product produced on the inner surface of a round-bottomed flask was hydrated with ultrapure water at 60 °C. After the separation of unentrapped PCT by ultracentrifugation at 150,000 × g for 1.5 h at 4 °C (Beckman Optima XL-100K, Germany), the PCT-loaded niosome pellet was rehydrated in a certain amount of ultrapure water. The obtained niosome suspension was kept in 5 ± 3 °C. The preparation process was performed under aseptic conditions. The particle size and zeta potential of the formulations were determined by dynamic light scattering and laser Doppler anemometric methods, respectively, using a Zetasizer (Malvern Zetasizer nanoZS, Malvern Instruments, UK). The characteristics of the preparations used in the in vivo study are as follows.

2.2.1. Span 40 niosomes
Particle size range and average particle size: 50–300 nm and 133 ± 6 nm
Zeta potential: –65.6 ± 1.2 mV
Fraction of PCT in niosomes: 3.64% (w/w)

2.2.2. Taxol formulation
PCT..........................................................6 mg
Ethanol: Cremophor (1:1 w : w)….q.s….1 mL
After dilution: Particle size range and average particle size: 5.6–24.4 nm and 13.08 ± 0.0415 nm
Zeta potential: –5.90 ± 0.989 mV

2.3. Pharmacokinetic and tissue distribution studies in rats

2.3.1. Animals
The animal studies were approved by the Local Ethics Committee of Ankara University for Animal Experiments (decision number 2007-10-32). Male Wistar rats weighing 200–250 g were used in the studies. The animals were kept in cages under normal conditions and fed with standard diets in the pellet forms. The rats were fasted 24 h before starting the experiments while water was given to them ad libitum.
2.5. Calculation and statistical analysis

PCT formulations were evaluated through the following parameters:

- AUC<sub>0→24h</sub>: Trapezoidal area under the curve of plasma concentration vs. time, from time 0 to last sampling time, 24 h
- C<sub>max</sub>: Maximum plasma concentration
- MRT<sub>0→24h</sub>: Mean residence time
- L<sub>z</sub>: General excretion of drug from plasma
- T<sub>1/2</sub>: Elimination half life
- F<sub>rel</sub>: Relative bioavailability as (AUC<sub>niosome</sub>/AUC<sub>Taxol</sub>) × 100

The pharmacokinetic parameters were calculated by Kinetika ver. 5.0 (Thermo Fisher Scientific, Waltham, MA, USA) using a noncompartmental method. The maximum plasma concentration (C<sub>max</sub>) was directly obtained from plasma concentration-time graphs. The parametric statistical evaluation of the data was performed through one-way variance analysis followed by Tukey multiple comparisons employing SPSS 9.0 for Windows (SPSS Inc., Chicago, IL, USA).

Figure 2. Procedure for the extraction of PCT from blood and tissue samples after i.v. administration of niosome dispersion and Taxol to the rats.
3. Results

3.1. Quantitative analysis of PCT in biological samples and method validation

The HPLC method was described in our previous studies (5,24). The method was fully validated and used for the determination of PCT in blood and tissue samples after i.v. administration to the rats. In HPLC methods, accuracy and precision can often be improved by using an internal standard. An internal standard compensates for the potential changes in the sample size or concentration originating from instrumental variations by correcting fluctuations in detector response (27). Docetaxel (DCT) was used as an internal standard in this study. Samples were prepared by spiking the rat plasma with known concentrations of PCT and DCT and then extracting the drug according to the procedure given in Figure 2. The retention times were 11.5 min for PCT and 9.91 min for DCT (Figure 3). The calibration curve obtained by plotting the peak area ratio of PCT to DCT versus PCT concentrations became linear over the range of 0.04–0.60 µg/mL with the determination coefficient (r²) of 0.9905. The limits of quantification and detection were 16.18 × 10⁻³ µg/mL and 5.34 × 10⁻³ µg/mL, respectively.

The accuracy of a method describes the proximity of mean test results to the true concentrations, while precision describes the proximity of each measurement result obtained from the procedure, which is repeatedly applied to the biological samples. The accuracy and precision by repeatability were indicated by performing 6 measurements on each of 3 different concentrations of PCT (low: 0.1 µg/mL, medium: 0.2 µg/mL, and high: 0.5 µg/mL), prepared by spiking the solutions into the rat plasma and calculating the concentrations by the calibration curve of the drug. Furthermore, the precision was also determined using intermediate precision. The intermediate precision is established depending on the variations, such as different days and analysts, to see the effects of random events on the precision of the analytical procedure (25). Three different concentrations of PCT (low, medium, and high) in rat plasma were prepared, and each of them was measured 6 times by HPLC on different days (1st, 2nd, and 3rd days) by the same analyst. Relative standard deviations of these determinations were quite low at the level of 2%, showing adherence to the FDA guideline (26). Blank samples of rat plasma and tissues as a biological matrix and the solvents that were used in the analytical method were handled the same as in the extraction procedure in Figure 2 and analyzed by HPLC. The peaks from the blank samples did not interfere with those of the samples containing PCT and DCT, demonstrating the selectivity of the analytical method.

3.2. Pharmacokinetic and tissue distribution studies

Figure 4 shows the measured plasma concentrations of PCT versus time after i.v. administration of the niosome formulation and of the commercially available i.v. preparation, Taxol, given to the rats in a single dose of 2.5 mg/kg. The plasma concentrations of PCT obtained within the first 2 h after drug administration were similar in both administration groups, as seen in the inset of Figure 4. Then a fast decline in PCT plasma concentration occurred in the rats administered Taxol, with the final PCT measurement occurring after 6 h. On the other hand, the PCT plasma curve of the rats administered PCT-loaded Span 40 niosomes formed a plateau at an almost steady-state concentration starting at 2 h and lasting until 24 h.

The pharmacokinetic parameters calculated from the plasma concentrations vs. time curves are given in the Table. The maximum plasma concentrations (C_max values) were 0.754 ± 0.123 µg/mL and 0.872 ± 0.187 µg/mL for Taxol and the niosomes, respectively. The difference between the C_max values was not statistically significant (P > 0.05). The value of area under the curve, AUC₀–₂₄, was 0.725 ± 0.163 µg h/mL in the group that received Taxol. When this value is compared to the AUC₀–₂₄ value of the group that received niosomes (3.22 ± 0.255 µg h/mL), the niosomes were found to be significantly more effective for enhancing the bioavailability of PCT (P < 0.001). In the rat group that received Taxol, the mean residence time (MRT) and the elimination half-life (T₁/₂) of PCT were estimated as 1.66 ± 0.133 h and 1.15 ± 0.085 h, respectively. The MRT and T₁/₂ values of PCT were 11.0 ± 0.6 h and 7.63 ± 0.380 h, respectively, in the rat group that received niosomes. There were statistically significant differences between these values (P < 0.001).

![Figure 3](image-url)
Table. Pharmacokinetic parameters of PCT calculated from Taxol solution and PCT-loaded Span 40 niosomes after i.v. administration in rats at a single dose of 2.5 mg/kg.

<table>
<thead>
<tr>
<th>N</th>
<th>Cmax (µg/mL)</th>
<th>AUC_{0–24} (µg h/mL)</th>
<th>MRT_{24} (h)</th>
<th>T_{1/2} (h)</th>
<th>Lz (h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxol</td>
<td>Niosome</td>
<td>Taxol</td>
<td>Niosome</td>
<td>Taxol</td>
<td>Niosome</td>
</tr>
<tr>
<td>1</td>
<td>0.618</td>
<td>1.32</td>
<td>0.729</td>
<td>3.22</td>
<td>2.11</td>
</tr>
<tr>
<td>2</td>
<td>0.552</td>
<td>0.429</td>
<td>0.331</td>
<td>2.83</td>
<td>1.19</td>
</tr>
<tr>
<td>3</td>
<td>1.20</td>
<td>0.479</td>
<td>1.48</td>
<td>2.69</td>
<td>1.72</td>
</tr>
<tr>
<td>4</td>
<td>0.871</td>
<td>0.573</td>
<td>0.569</td>
<td>3.93</td>
<td>1.91</td>
</tr>
<tr>
<td>5</td>
<td>0.362</td>
<td>1.51</td>
<td>0.723</td>
<td>2.61</td>
<td>1.57</td>
</tr>
<tr>
<td>6</td>
<td>0.919</td>
<td>0.923</td>
<td>0.519</td>
<td>4.02</td>
<td>1.46</td>
</tr>
<tr>
<td>Mean</td>
<td>0.754</td>
<td>0.872</td>
<td>0.725</td>
<td>3.22</td>
<td>1.66</td>
</tr>
<tr>
<td>SE</td>
<td>0.123</td>
<td>0.187</td>
<td>0.163</td>
<td>0.255</td>
<td>0.133</td>
</tr>
</tbody>
</table>

95% Confidence interval

| LL: Lower limit; UL: Upper limit; SE: Standard error. *: P < 0.001. |
from plasma, the L value, determined from the Taxol-administered group was found to be significantly higher (0.624 ± 0.0532 h⁻¹) than the value determined from the niosome-administered group (0.0925 ± 0.00490 h⁻¹) (P < 0.001).

The tissue distribution of PCT in the liver, intestines, kidneys, heart, lungs, and spleen after i.v. administration of Taxol and Span 40 niosomes to the rats at 24 h is shown in Figure 5. The concentrations of PCT in the Taxol group seem to be higher in all tissues in comparison to the niosome group, and the values calculated for liver (P < 0.05), heart (P < 0.05), and kidneys (P < 0.10) were statistically significantly different. The accumulation of PCT was substantially high in the spleen compared to the other tissues after both niosome and Taxol administration.

4. Discussion
Liposomes have been widely studied as drug delivery systems in the vesicular system, and there are currently numerous liposome preparations on drug market (28). However, some hurdles have been faced in regard to the pharmaceutical development of these systems. These obstacles include the poor quality of the phospholipids used for the preparation of liposomes, their expensiveness, chemical stability problems such as hydrolysis and oxidation that lead to too-short shelf life, and scale-up problems. Due to these issues, niosomes have been presented as an alternative system (21,29).

Niosomes behave similarly to liposomes in vivo. Besides the general advantages of drug delivery systems, they have distinct advantages such as control of shape, size, composition, and fluidity when required; biodegradability, biocompatibility, and nonimmunogenicity to the body; targeting drugs to various organs; sustained drug release; entrapment of both hydrophilic and hydrophobic drugs; easy handling and storage conditions; suitability for industrial manufacture due to relatively low cost of materials; and sterilization by membrane filtration, autoclaving, and gamma irradiation (21,30).

Concerning the advantages of the niosomal drug delivery systems, our objective was to develop an alternative formulation that could overcome the poor aqueous solubility of PCT and avoid the use of Cremophor EL, which causes serious adverse effects in the clinical application of Taxol. Different classes of nonionic surfactants have been used for the preparation of niosomes. The diversity of the surfactants offers a chance to design the niosomes to meet our expectations. The selection of the surfactants highly depends on the in vitro performance and qualities of the niosomes, such as drug-loading efficiency, particle size, and drug release (5,23,24). In this report, PCT-loaded niosomes were prepared with the most appropriate surfactant, Span 40, that we had previously determined with in vitro studies. The pharmacokinetic parameters and tissue distribution of PCT upon i.v. administration were investigated by comparing these values with Taxol administration.

The HPLC method, which was used to measure PCT in plasma and tissue samples, was validated. The linearity range covered the studied concentrations, and PCT was separated from the endogenous components without any interference (Figure 3). Figure 4 shows the mean plasma concentrations of PCT against time, measured after i.v. administration of niosomes and Taxol. The early time points on the graph show that the decrease in PCT concentration was fast for both preparations initially, and at later time points the decrease slowed down for the niosomes. The first part of the graph covers the distribution phase of the PCT from the plasma to the tissues, which also includes elimination. After attaining steady-state concentrations between plasma and tissue, PCT concentrations decrease only by elimination. Upon oral administration of the same niosome formulation, a similar plasma concentration–time profile was obtained following the PCT absorption stage (24).

![Figure 5. Tissue distribution of PCT after i.v. administration of Taxol and Span 40 niosomes at 24 h (*: P < 0.05; **: P < 0.1).](image-url)
Pharmacokinetic parameters of PCT from the niosome formulation were significantly better than the results from the Taxol group (Table). The AUC value of PCT from the group administered niosomes was 4.44 times higher compared to the group administered Taxol. The MRT value of PCT is 11 h, and it was 6.6 times higher than that of Taxol. Similarly, the PCT elimination half-life $t_{1/2}$ value after the niosome application was 6.6 times higher than the half-life of Taxol. Therefore, the coefficient of general excretion of the drug was 6.7 times lower than in the Taxol group.

The long blood-circulation time of the niosomes was related to the small particle size of the niosomes, which was $133 \pm 6$ nm. On the other hand, the size of the micelles formed upon dilution of Taxol with water was $13.08 \pm 0.0415$ nm. The literature data show that nanoparticles with small sizes (40–300 nm or 200 nm) have the ability to escape from the reticuloendothelial system and thus exhibit a slower clearance rate (31). The importance of particle size is very well known for sustained drug release and targeted delivery of drugs. Tumor cells display leaky blood vessels and poor lymphatic drainage. While unattached drugs may distribute nonspecifically into the body, nanocarriers can accumulate specifically into the tumor tissue through the enhanced permeability effect of the tumor vasculature (32,33). The prolonged circulation time and the small particle size of PCT-loaded Span 40 niosomes demonstrated the potential of niosomes for the passive targeting of cancer cells. This situation can be further elucidated with in vivo experiments on tumor-bearing animals. The long blood-residence time also demonstrated the niosome stability. The stability of a nanocarrier is important for its eventual accumulation in the tumor tissue (31). Similar pharmacokinetic behavior was observed upon i.v. administration of PCT-loaded pegylated polymeric micelles as another nanoparticulate drug-delivery system. The investigators compared the results with a commercially injectable PCT product and observed higher AUC, longer systemic circulation times, and slower plasma elimination rates upon administration of micellar formulation. Therefore, they suggested the usage of polymeric micelles due to their long-circulating property.

One of the major limitations of cancer therapy is the nonspecific systemic distribution of anticancer agents, which can lead to severe side effects in sensitive healthy tissues. Therefore, tissue distribution studies on the vital organs were conducted (16,34). Figure 5 shows tissue distribution of PCT after i.v. administration of Taxol and PCT-loaded niosomes at the end of 24 h. In the Taxol-administered rat group, PCT was distributed widely to all of the examined tissues, although it could not be detected in plasma beyond 6 h after administration. However, PCT-loaded Span 40 niosomes clearly altered the tissue distribution of PCT in rats. The accumulated amounts of PCT in the liver, kidneys, and heart were significantly reduced in the niosome-administered group. This result emphasized the selective tissue distribution of the niosomes. Additionally, lower accumulation of PCT in the heart and kidneys might be an important piece of evidence in terms of the prevention of cardiotoxicity and nephrotoxicity observed during chemotherapy. The spleen accumulations of the drug were higher than in the other tissues in both PCT formulations. This result reveals that PCT is filtered by the spleen during the circulation in the blood and suggests the potential usage of niosomes for specific drug delivery to the spleen.

There are several studies in which niosomes were evaluated as drug carrier systems for anticancer agents such as hydroxycamptothecin (HCPT), doxorubicin, methotrexate, 5-fluorouracil, cisplatin, and pentoxifylline (35–44). The results obtained in the present study agree well with those of the previous studies. The pharmacokinetics and tissue distribution of anticancer agent HCPT-loaded Span 60 niosomes, pegylated niosomes, and an active targeting agent, transferrin-bound pegylated niosomes, were investigated following their i.v. administration in tumor-bearing mice in a model compared with a plain drug solution. In the group given the HCPT solution, the HCPT was removed very rapidly from the blood circulation. The plasma levels of HCPT for the Span 60 niosomes remained high for the longest time, followed by pegylated niosomes and, finally, transferrin-pegylated niosomes. The tissue distribution of HCPT from the niosome preparations showed the highest concentration in the spleen and tumor tissues. The liver, lungs, kidneys, heart, and brain were in the same rank for niosomes; the lowest accumulation values were observed for the HCPT solution (36). In another study, doxorubicin as a polymeric conjugate was entrapped in niosomes prepared with hexadecyl diglycerol ether surfactant and polyethylene glycol compound Solulan C24. The plasma clearance of the polymeric conjugate-loaded niosomes with a mean size of 420 nm was rapid, and the niosomes were uptaken mainly by the liver and spleen of the reticuloendothelial system. The rapid plasma clearance was different in the present study, and this might be ascribed to the different composition and larger particle size of the niosomes. However, the sustained release of the free drug in the liver by the niosomes proposes the usefulness of niosome-containing prodrugs in the treatment of liver-related diseases (37).

In this study, PCT-loaded Span 40 niosomes with a mean size of 133 nm were prepared by thin-film method. A simple, sensitive HPLC method was developed and
validated for the determination of PCT from Span 40 niosomes in rat plasma and tissues. The niosomes increased the AUC value of PCT by 4.44-fold compared to the commercial preparation of PCT, Taxol. Likewise, when this result was compared with the previous results obtained upon oral administration of the niosomes, there was an 8.09 times improvement in AUC values (24). The prolonged detection of PCT in plasma revealed the slow release of the drug from niosomes. According to the tissue distribution study, niosomes were removed from the blood by the spleen and the amounts of PCT from niosomes in the liver, kidneys, and heart were significantly lower than those obtained from Taxol. These results provide strong support for the targeting of niosomes to tumor tissues and the reduction of side effects to healthy tissues. Further evaluations of niosomes in tumor-bearing mice have been planned and will be beneficial for the demonstration of passive tumor targeting ability of PCT-loaded niosomes.

Acknowledgments
The authors wish to thank Dr Nilüfer Vural (Ankara University, Faculty of Engineering, Department of Chemical Engineering) for helping with HPLC analysis. This study was supported by the Scientific and Technological Research Council of Turkey (TÜBİTAK) under grant 107S248.

References