Pharmaceutical Properties of Paclitaxel and Their Effects on Preparation and Administration

Lawrence A. Trissel, FASHP

Paclitaxel is a mainstay in the treatment of ovarian and breast cancers, and its use in other malignancies is being explored. Although it has great clinical utility, the drug and its formulation components pose a number of challenges to pharmacists and nurses. Paclitaxel is insoluble in water and is formulated in an equal parts mixture of ethanol and Cremophor EL, which disperses the drug in an aqueous medium. At concentrations of 0.3–1.2 mg/ml, paclitaxel is stable for at least 2 days. Additional research identified precipitation as the major limitation to long-term stability and supports the use of an inline filter for all infusions. The formulation vehicle also leaches the plasticizer DEHP from polyvinyl (PVC)-containing solution bags and administration sets. This effect is dependent on the concentration of surfactant, the amount of accessible DEHP, and many other factors. Health care practitioners must educate themselves regarding appropriate non-PVC containers and administration sets for safe and convenient delivery of paclitaxel. The compatibility of this and other drugs in solution is under investigation; currently, amphotericin B, chlorpromazine, hydroxyzine, methylprednisolone sodium succinate, and mitoxantrone have been determined to be physically incompatible with paclitaxel infusions.
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OUTLINE

Paclitaxel has become a mainstay in the treatment of ovarian and breast cancers, and studies are being conducted to investigate other clinical applications of this unusual molecule. Problems exist as a result of its pharmaceutical properties and present a challenge to pharmacists and nurses. Some of the problems that paclitaxel shares with other parenteral drugs are stability in infusion solutions, compatibility with administration equipment, and compatibility and stability with other agents.

Paclitaxel is rarely given alone. Like other antineoplastics, it is almost always part of a complex regimen of infusion solutions; delivery devices composed of various plastics, elastomers, metals, and other materials; pumping devices from complex machines to simple elastomeric pressure devices; and multiple-drug therapy that can consist of as many as 10 agents, such as other antineoplastics, symptomatic and supportive care drugs, and anti-infectives. To facilitate the complicated process of delivering many parenteral drugs with different and intense schedules, multiple-port administration sets, multichannel pumps, and Y and T connectors were developed to provide sufficient access. Since these products are made of many different materials, the opportunity is great for problems

From the Clinical Pharmaceutics and the Pharmaceutical Analysis Laboratory, Division of Pharmacy, University of Texas, M.D. Anderson Cancer Center, Houston, Texas.

Address reprint requests to Lawrence A. Trissel, FASHP, Division of Pharmacy, Box 90, University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030.

with compatibility and stability to occur as drugs come in contact with these materials.

Formulation of Paclitaxel

Paclitaxel is soluble in a variety of organic solvents such as ethanol, methanol, benzene, chloroform, methylene chloride, and others, most of which are unsuitable for human administration. It is insoluble in water and aqueous solutions,[1] a common attribute of many natural products. Because aqueous solutions are the best vehicles for intravenous delivery in terms of ease and tolerability, extraordinary steps were taken to prepare paclitaxel as an aqueous solution.

The drug is formulated in an equal parts mixture of ethanol and Cremophor EL surfactant, a polyoxyethylated derivative of castor oil.[2] Cremophor EL is used in this and other formulations to disperse insoluble drugs in an aqueous medium by forming tiny micellar particles.[3] Consequently, paclitaxel is never in aqueous solution, rather, it is a microdispersion distributed throughout an aqueous medium.

Similar to soapy water, paclitaxel's dispersion appears slightly hazy, which can be observed by shining a light through the dispersion. The haze level is concentration dependent but not linear.[4] Haze increases as the concentrated product is diluted and micellar dispersion forms, achieving maximum haziness at paclitaxel concentrations of 0.3–0.9 mg/ml, which are commonly administered in clinical practice (Figure 1). Turbidity declines as the product becomes more and more diluted to low concentrations. The haze itself is not a concern as long as the particles do not reach clinically relevant size (≥ 10 µm)[5]; many drugs in infusion solutions have an intrinsic haze. Because paclitaxel is not actually in solution, however, precipitation of clinically meaningful size particles eventually occurs; the question is, exactly when this will happen.

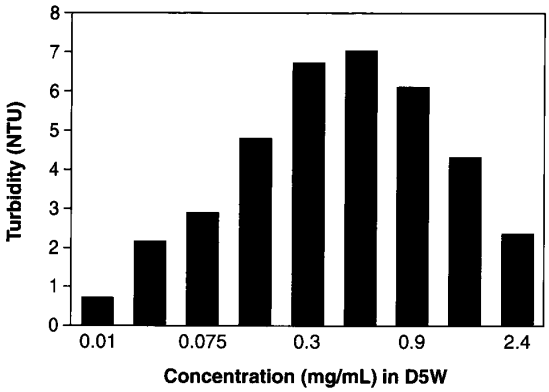

Figure 1. Natural turbidity in paclitaxel admixtures.[4]

Outside influences can affect the rate of precipitation of the paclitaxel dilution. The package insert states that the drug is stable in solution for 27 hours within the standard concentration range of 0.3–1.2 mg/ml.[2] This is usually a safe working time frame for preparing and administering short-term infusions of paclitaxel, which are most commonly prescribed. However, if 24-hour infusions or multiday infusions, which are currently being evaluated, are required, the maximum 27-hour stability limit is approached and possibly exceeded.

Normal time delays in everyday clinical practice often occur before actual drug administration, such as in preparation, storage in the pharmacy until delivery, transit time to the use site, and storage at the use site after delivery. Therefore, the 27-hour stability limit can mean having to prepare two 12-hour doses for each 24-hour period with associated effects on cost and workload. Furthermore, several container changes associated with long infusions of paclitaxel are inconvenient for the patient and potentially increase the risk of microbiologic contamination due to these system breaks. Therefore, longer stability of the drug is desirable, especially when it is to be infused over 24 hours or longer.

Stability in Solutions

In the first report of paclitaxel's stability in infusion solutions beyond 27 hours, the drug was chemically stable for 48 hours.[6] Furthermore, no gross precipitation was reported; however, the formation of subvisual particles was not assessed. The stability limit was not determined because this study ended at 48 hours.

In an attempt to determine a longer stability period, paclitaxel was stored over 31 days.[7] Concentrations of 0.1 and 1 mg/ml, which are most commonly administered, were evaluated in solutions of both 5% dextrose and 0.9% sodium chloride. Samples were stored at 4, 22, and 32°C and evaluated for both chemical and physical stability, including subvisual phenomena. Chemical stability was analyzed by a validated stability-indicating high-performance liquid chromatography (HPLC) assay.[8] Physical

stability was tested using a multistep approach that assessed visual appearance in both normal diffuse light and using a Tyndall beam, changes in turbidity, and the formation of clinically relevant size particulates.[4]

No chemical decomposition of the paclitaxel molecule occurred at any storage temperature in either dextrose or sodium chloride solution at either concentration.[7] Paclitaxel was stable under these conditions until it precipitated; precipitation was identified as the primary stability limitation in infusion solutions. No changes in natural haziness were observed in the test samples. However, microcrystalline precipitation of needlelike crystals formed in some samples after 3 days of storage. Gross white flocculent precipitation was present in several samples within 7–14 days. The HPLC analysis showed that microcrystalline precipitation did not lead to substantial loss of paclitaxel from the solution, indicating that only small amounts of drug were involved. However, when gross precipitation was present, paclitaxel losses of up to 50% were determined by chemical analysis. The precipitate was identified as essentially pure paclitaxel.

Of importance, paclitaxel precipitation was erratic. The microcrystalline precipitation that occurred after 3 days was observed in only a few samples. The gross precipitation that occurred in 14 days in most samples still left some samples with no precipitate at all. There is no doubt that precipitation will occur, but the timing remains highly variable. This uncertainty results from many factors for which there is little control and recognition. For example, the inherent particle burden in aliquots of solutions could be a factor. Higher particle burdens or solutions with somewhat larger (or smaller) particles could seed precipitation. The shape and composition of such particles also may be important. The interior configuration of container surfaces could provide a stimulus for precipitation. It is likely that many other factors remain unknown.

Paclitaxel precipitation leads to obvious issues in drug delivery. Besides precipitation in the container, inline precipitation may occur even when the drug remains in solution in the bag or bottle. According to anecdotal reports,[9, 10] this may occur unpredictably during administration, even within the 27-hour stability period stated in the package insert.[2] Anecdotal reports from our institution's clinic indicate that inline precipitation is sufficiently frequent to be meaningful. It usually occurs just distal to the pumping mechanism of a mechanical pump; furthermore, its frequency is much higher with pumps that use a peristaltic drive to move solutions through the line. In our institution, paclitaxel delivery using a piston-driven pump resulted in only one reported case of inline precipitation. In contrast, use of portable peristaltic pumps for continuous drug delivery increased the number of reports of inline precipitation from our clinics.

It is uncertain how the pumping mechanism affects precipitation, but it can be surmised that the compression and crushing action of a peristaltic pump is more mechanically traumatic to micellar dispersions than a piston pump. In laboratory experiments, we found that high-shear mechanical forces applied to a paclitaxel dispersion can easily generate a precipitate, sometimes in as little as 1 hour after mixing (LA Trissel, unpublished data, 1993). Based on variability in precipitation and to ensure that the precipitate is not delivered to the patient, an inline filter (0.22 µm) is required with all paclitaxel infusions.

Extraction of DEHP Plasticizer from PVC Products

Like other drugs that use a surfactant in their formulation, paclitaxel injection leaches (extracts) the plasticizer diethylhexyl phthalate (DEHP) from polyvinyl chloride (PVC) solution containers, administration sets, and extension sets. Plasticizer extraction does not occur from glass containers or from nonplasticized plastics, such as the polyolefins. Polyethylene, present in Excel and PAB (McGaw) containers, and polypropylene, present in many plastic syringes, have no plasticizers to leach and are suitable for administering paclitaxel. Glass containers may create a problem because the paclitaxel dispersion can wet the air vent of rigid glass bottles and cause leakage.[11] Many other plastic materials may come in contact with solutions, including trioctyl trimellitate (TOTM)-plasticized PVC, ethylene vinyl acetate, Silastic, and polyurethane. The drug's compatibility with these materials has yet to be evaluated.

The surfactant, not the paclitaxel, leaches DEHP.[8] The amount of DEHP leached from PVC materials is dependent on several variables. The concentration of the surfactant, whether Cremophor EL or polysorbate 80, in the solution is crucial, with higher surfactant concentrations resulting in more leached DEHP when all other

Table 1. Extraction of DEHP by Formulation Components at Various Concentrations

Component[a]	Concentration (%)	DEHP Extracted in 24 Hours (µg/ml)
Cremophor EL[b]	5	195
Polysorbate 80[b]	5	179
Polysorbate 80	1	36
Polysorbate 80	5	157
Polysorbate 80	10	227
Polysorbate 80	25	232

[a]Admixed in 50-ml PVC bags of 5% dextrose injection, USP.
[b]Plus ethanol 5%.
From reference 12.

Table 2. Extraction of DEHP by Drugs Containing Cremophor EL

Drug	Cremophor EL Concentration (%)	DEHP Extracted in 24 Hours (µg/ml)
Paclitaxel	5	195
Cyclosporine	3.9	102
Miconazole	3	65
Teniposide	1	21

From reference 12.

factors remain equal. Ethanol in the paclitaxel formulation may also contribute to surfactant leaching, but its effect, if any, is minor. Other common organic solvents, such as polyethylene glycol and propylene glycol, appear to have no DEHP-leaching potential.[12]

A study of DEHP leaching by a variety of nonaqueous parenteral agents reported comparable amounts of DEHP leaching by 5% Cremophor EL and 5% polysorbate 80 each in combination with 5% ethanol (Table 1).[12] Over a range of polysorbate 80 concentrations from 1–25%, the amount of DEHP leached from PVC increased with increasing surfactant concentration. This concentration-dependent effect was documented with several surfactant-containing drugs (Table 2). The amount of DEHP leached increased only a small amount when the surfactant concentration was increased from 10% to 25%. This suggests that the amount of DEHP that is accessible also may influence the extent of its leaching.

Typically, flexible PVC bags and tubing contain DEHP equal to approximately 25–30% of total mass to provide adequate flexibility. Pumping segments for peristaltic pumps may contain a higher concentration, and hard PVC connectors may contain none. The concentration of DEHP in PVC, total mass of PVC available, surface area of solution contact, surface configuration, and rate at which plasticizer can migrate from the exterior to the interior of the container or tubing through the plastic matrix may contribute to the maximum amount of DEHP that can be leached from any particular administration setup. Rate of infusion administration, fluid contact time, solution temperature, and administration set bore size also affect DEHP leaching.

The time-concentration pattern of DEHP extraction from PVC varies with concentration. We studied test solutions of paclitaxel injection vehicle corresponding to paclitaxel injection of 0.3 and 1.2 mg/ml delivered in triplicate over 24 hours. At the higher concentration we extracted a large amount of DEHP initially as a spike, with extraction tapering off apparently as accessible DEHP was depleted (Figure 2).[11] In contrast, a relatively constant rate of extraction occurred with 0.3 mg/ml (Figure 3).[11]

These results indicate that frequent changes of administration sets by health care workers because of set incompatibility may actually enhance DEHP leaching and delivery problems by replenishing the DEHP pool. Also, rapid administration of a concentrated dispersion of paclitaxel does not circumvent the need for a non-PVC administration set. Based on our results, the bulk of DEHP delivery would occur in the first 3–4 hours of administration.

Although DEHP is not an acutely toxic substance,[13] there are concerns about potential

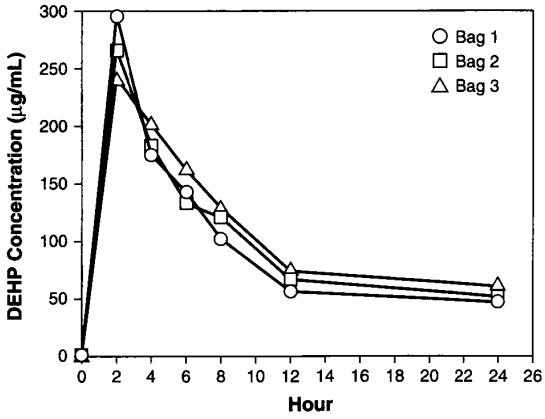

Figure 2. Extraction of DEHP from a standard administration set by the paclitaxel vehicle equivalent to paclitaxel 1.2 mg/ml.[11] Originally published in Trissel LA, XU Q, Kwan J, Martinez JF. Compatibility of paclitaxel injection vehicle with intravenous administration and extension sets. Am J Hosp Pharm 1994;51:2804–10 (c) 1994. American Society of Hospital Pharmacists, Inc. All rights reserved. Reprinted with permission (R9697).

Table 3. Unacceptable Extraction of DEHP from Administration Sets by the Paclitaxel Vehicle

Administration Set (manufacturer, model)	Equivalent Paclitaxel Concentration (mg/ml)	DEHP Concentration in Effluent (µg/ml)[a]
Vented nitroglycerin set (Baxter, 2C7552S)	0.3	6.3 ± 0.5
	1.2	68.5 ± 3.0
Vented basic solution set (Baxter, 1C8355S)	0.3	7.4 ± 0.4
	1.2	82.1 ± 12.0
Horizon-pump vented nitroglycerin i.v. set (McGaw, V7450-original)	0.3	8.5 ± 0.2
	1.2	81.6 ± 2.8
Horizon-pump vented nitroglycerin i.v. set (McGaw, V7450-new)	0.3	7.2 ± 0.2
	1.2	62.6 ± 3.5
Intelligent-pump vented nitroglycerin i.v. set (McGaw, V7150)	0.3	6.8 ± 0.7
	1.2	58.5 ± 1.7

[a]Mean ± SD (n=6).
Note: No paclitaxel was present. Diluent tested equivalent to 0.3 and 1.2 mg/µl.
From reference 11.

exposure. In humans, prolonged exposure to DEHP leached into blood products was not associated with specific toxicities.[14] However, in animals, changes in hepatocellular structure and liver function and development of hepatocellular carcinoma occurred with DEHP exposure.[15–17] Teratogenicity and cardiotoxicity were reported with DEHP and its metabolite, mono-(2-ethylhexyl)-phthalate, respectively.[18, 19] Consequently, knowingly delivering such an extraneous material when it could be easily avoided by careful selection of drug-delivery equipment is both undesirable and unprofessional.

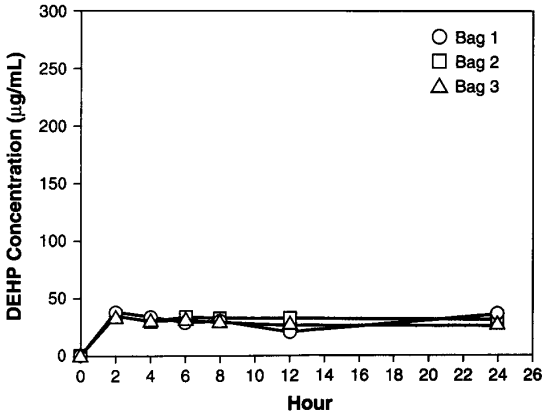

Figure 3. Extraction of DEHP from a standard administration set by the paclitaxel vehicle equivalent to paclitaxel 0.3 mg/ml.[11] Originally published in Trissel LA, XU Q, Kwan J, Martinez JF. Compatibility of paclitaxel injection vehicle with intravenous administration and extension sets. Am J Hosp Pharm 1994;51:2804–10 (c) 1994. American Society of Hospital Pharmacists, Inc. All rights reserved. Reprinted with permission (R9697).

At this time, there are no definitive acceptable amounts of DEHP that can be infused with paclitaxel or any other drug solutions. For research purposes, we established benchmarks for DEHP[11] based on the acceptability of certain types of administration sets by the Food and Drug Administration as listed in the paclitaxel package insert. The use of conventional PVC sets to administer paclitaxel injection is not recommended. Thus, an unacceptable amount of DEHP was approximately 100 µg/ml or more because that was the amount leached from a 24-hour infusion through those sets.[11]

The paclitaxel package insert specifies the use of IVEX-2 filter sets (Abbott) to prevent precipitate administration.[2] These sets are made with about 20 cm of PVC tubing. Approximately 20 µg/ml of DEHP was leached during a 24-hour infusion of paclitaxel 1.2 mg/ml through the IVEX-2 set and IVEX-HP. Therefore, leached DEHP levels exceeding approximately 20 µg/ml at maximum paclitaxel concentrations were considered unacceptable; lower amounts were considered acceptable, but they can be avoided through careful selection of administration sets.

Using these benchmarks, we studied 50 administration and extension sets.[11] Although the study was not comprehensive, it offers pharmacists and nurses an information base on which to make selection decisions. Twenty-six administration sets that were represented by their manufacturers as potentially compatible with paclitaxel and 24 extension sets were evaluated for the amount of DEHP leached by paclitaxel concentrations of 0.3 and 1.2 mg/ml. The paclitaxel infusions were run over 24 hours in triplicate for each set, and the effluent was

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