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PACLITAXEL (TAXOL®) FORMULATION AND PRODRUGS

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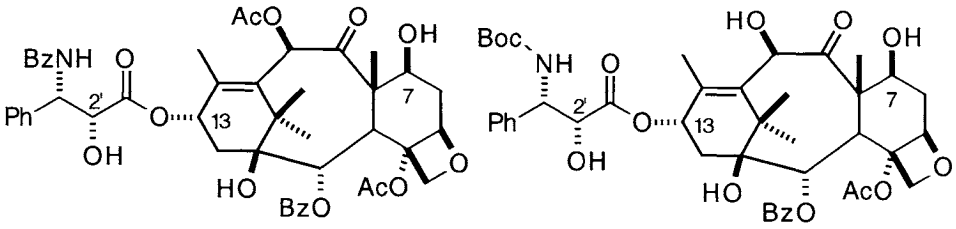
3.1. INTRODUCTION

Paclitaxel (**1.1.1**, Figure 1),[1] a natural diterpene isolated from the bark of *Taxus brevifolia* (Pacific yew) [1] has been heralded as the antitumor agent of the 1990's because of its promising clinical activity against a variety of human solid tumors such as ovary, breast, lung, head and neck, and melanoma [2-4]. Interest in various aspects of this drug has mushroomed due to the clinical significance of its antitumor profile in treating common human cancers [5, 6]. Currently, paclitaxel is an FDA-approved cancer agent in the United States for second-line treatment against *cis*-platinum-refractory ovarian cancer and metastatic breast cancer which is refractory to anthracycline treatment. It has also been approved in other countries for similar indications. On the basis of broader ongoing clinical trials, there is a good likelihood of paclitaxel becoming a first-line chemotherapeutic agent in the very near future [7] .

Within the current arsenal of cancer chemotherapeutics [8], paclitaxel is a unique tubulin-interacting agent. Unlike other clinical antimitotic agents such as the vinca alkaloids [9, 10], which inhibit the microtubule assembly process,

[1] Taxol® is a registered trademark of the Bristol-Myers Squibb corporation. The generic name "paclitaxel" is used throughout this chapter.

paclitaxel promotes tubulin polymerization and stabilizes the resulting microtubules toward depolymerization [11]. This shift in the normal dynamics in the cellular tubulin-microtubule system by paclitaxel is currently widely recognized as its mode of action for cell cytotoxicity. Owing in part to the discovery by Susan Horwitz and coworkers in 1979 [11] of paclitaxel's mechanism of action, the National Cancer Institute (NCI) decided to accelerate the human clinical trials for this drug. Eventual marketing of paclitaxel for oncology clinical use was facilitated by a Cooperative Research and Development Agreement (CRADA) between the NCI and the Bristol Myers Squibb (BMS) Company in 1989 and the subsequent massive efforts by BMS to secure ample clinical supplies of paclitaxel [12].



1.1.1. Paclitaxel (Taxol)

1.1.2. Docetaxel (Taxotere)

Figure 1: Clinically relevant taxanes

In spite of paclitaxel's promising clinical antitumor profile and the ongoing efforts to optimize its utility in multimodality treatment for curative cancer therapy, the drug has presented problems during its intravenous (i.v.) administration to patients [13]. These are formulation-related problems stemming from the use of the excipient Cremophor EL® [14] as a solubilizing detergent for i.v. administration. Interestingly, a close analog of paclitaxel, namely, docetaxel, **1.1.2**(Taxotere®) [15] (Figure 1) which is currently awaiting FDA approval for clinical use, is devoid of such problems. Docetaxel possesses a slightly better aqueous solubility than paclitaxel and is administered as a Tween-80 (polyoxyethylene sorbitan monooleate)/ethanol formulation. Several of paclitaxel's alleged formulation-related patient-care issues, such as hypersensitivity reactions, have been successfully addressed and managed in the clinic [16]. However, the pharmaceutical issues [17] related to Cremophor EL's use still persist during intravenous administration and demand precautions

and adherence to strict pharmacy protocols. The main intent of this chapter is to document and highlight all of the formulation-related issues stemming from the current clinical formulation and briefly discuss possible solutions sought to alleviate or circumvent them. The quest toward the development of a widely acceptable and safe intravenous formulation devoid of Cremophor EL is continuing in several research laboratories and is discussed herein.

3.2. PHARMACEUTICAL DEVELOPMENT SUMMARY

Paclitaxel's early pharmaceutical development history [12, 18, 19] is mainly confined to the NCI laboratories, since it was through a joint NCI-USDA (United States Department of Agriculture) initiative in the early 1960's to screen plant material for novel cytotoxic agents that paclitaxel was first discovered. The isolation and identification of this agent were accomplished in 1966 at the NCI contract laboratories of the Research Triangle Institute, North Carolina, by M. Wani and M. Wall, approximately four years after the initial collection of *Taxus Brevifolia* plant material [18]. The isolation of pure paclitaxel was facilitated through a bioassay-guided fractionation protocol following *in vitro* cytotoxicity in KB cells and *in vivo* antitumor activity against murine tumor models such as leukemia P1534 and carcinosarcoma Walker 256. During the next few years, the preclinical antitumor profile of paclitaxel in several of the NCI's murine hematological tumor models, namely leukemias L1210, P388, and P1354, was established. Also, activity against the Walker 256 sarcoma model was demonstrated. These efficacy evaluations were carried out in mice by administering paclitaxel as a suspension in the peritoneal (i.p.) cavity against i.p.-implanted tumors. Due to the extremely hydrophobic character of paclitaxel [20], it was difficult to obtain a purely water-based formulation for i.v. or i.p. administration. Consequently, the vehicles employed for i.p. administration included steroidal suspensions, vegetable oils (peanut, sesame, olive), normal saline and carbomethoxy cellulose (CMC). It was not until 1974 that the first evidence of paclitaxel's efficacy in an i.p./i.p. murine solid tumor, B16 melanoma, was obtained. Until this time, paclitaxel was considered an unexciting cytotoxic agent with solubility problems and *in vivo* efficacy confined mainly to i.p./i.p. localized tumor models. Consequently, there was little enthusiasm in pushing this drug further toward human clinical trials. However, by 1980 several new findings had made paclitaxel a prime candidate for human clinical trials. In

1978, after the introduction of human tumor xenograft models to the NCI screening program, paclitaxel was shown for the first time to possess distal tumor efficacy against the LX-1 lung, the MX-1 breast, and the CX-1 colon xenografts [18]. In all these tumor models the drug was administered subcutaneously to the human tumor implanted in the sub-renal capsule (kidney) of mice. More importantly, the excitement and interest about this drug was heightened in 1979 when a report by S.Horwitz and coworkers [11] disclosed that paclitaxel acted *via* a novel tubulin-interacting mechanism. Unfortunately, at this juncture a suitable formulation for intravenous administration of the drug was lacking and remained to be developed. At the outset [21], it was determined at the NCI that paclitaxel was totally devoid of any activity when administered orally to mice up to a dosage of 160 mg/Kg.

3.2.1. Early Formulation Studies

Since 1978, a major effort at the NCI was directed at developing an intravenous formulation for paclitaxel in order to initiate human clinical studies. Paclitaxel's extremely low water solubility (< 0.01mg/ml), coupled with the absence of a suitable chemical functionality (amine or carboxylic acid) for salt formation, led to the evaluation of cosolvents and excipients as the first strategy for developing an i.v. formulation. Much of this effort is described in detail in a recent report [21]. The approximate solubility of paclitaxel in aqueous vehicles and certain organic solvents are reported in Table 1.

Table 1: Solubility of Paclitaxel in Various Solvents[a]

Solvent	Solubility (mg/ml)
Methylene Chloride	> 19
Ethanol	*ca.* 39
75% Propylene glycol	<1.4
75% Polyethylene glycol 400 (PEG 400)	31
35% PEG 400	0.03
Soybean oil	0.3
Triacetin	75

(a) adapted from ref. 21.

Paclitaxel has substantial solubility in organic solvents such as ethanol and methylene chloride. Highly concentrated (millimolar) paclitaxel solutions in some of these solvents were attainable. However, diluting paclitaxel solutions of water-miscible solvents (such as ethanol) with water presented problems of precipitation. The solubility of paclitaxel in lipids such as soybean oil (intralipid) was also not quite adequate for formulation considerations.

The two intravenous formulations which received in-depth evaluation at the NCI were those involving cosolvent PEG(polyethylene glycol) 400 (75%) and surfactant Cremophor EL® [19, 21]. The 75% PEG 400 solution in water containing 16 mg/ml paclitaxel was found to be chemically stable by HPLC analysis and free of particulate material for up to 14 days at 25°C. However, upon dilution for infusion, precipitation (cloudiness) was discernible. Formulation with solubilizing surfactant Cremophor EL® (5%) in ethanol (5%) and 0.9% saline under equilibrium conditions gave a solution with paclitaxel concentration of about 0.1 mg/ml. With this formulation, concentrations greater than 0.6 mg/ml were achievable by dilution of a 6 mg/ml solution of paclitaxel in 1:1 Cremophor EL:EtOH. Fortunately, this solution had adequate physical and chemical stability over periods as long as 24 h; >96% of drug was found in solution over this time period. Thus, the Cremophor formulation provided some assurance against the possibility of drug precipitating during the infusion period. Also, this formulation was the best on an efficacy basis, since paclitaxel administered i.p. as an aqueous suspension containing Cremophor EL® was found to be more efficacious against an i.p.-implanted B16 melanoma tumor than paclitaxel administered i.p. in PEG 400. Due to all these considerations, in 1980 the Cremophor formulation was selected for clinical trials. The current clinical dosage form of paclitaxel consists of a 5ml size vial containing 30 mg of paclitaxel, 2.64 g of Cremophor EL® and 49.7% EtOH (1:1 v/v). This concentrated solution required further dilution with injectable fluids such as 5% dextrose, 0.9% sodium chloride, and 5% dextrose in Ringers solution. The intact vial shelf-life is estimated to be 5 years under refrigeration [21].

3.2.2. Formulation Issues

With the launching of paclitaxel into clinical trials, several pharmaceutical and patient-care issues surfaced at the very outset. These apparently stemmed from the use of Cremophor EL® as an excipient in the intravenous formulation. Cremophor EL® is a chemically and physiologically

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