Advanced Drug Delivery Reviews 71 (2014) 34–57

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Drug delivery design for intravenous route with integrated physicochemistry, pharmacokinetics and pharmacodynamics: Illustration with the case of taxane therapeutics ☆

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ARTICLE INFO

Article history:
Accepted 24 October 2013
Available online 1 November 2013

Keywords:
Drug delivery systems design
Physicochemistry
Biopharmacy
Pharmacokinetics
Pharmacodynamics
Efficacy
Safety
Taxanes
Classification
Paclitaxel
Docetaxel
Cabazitaxel
Nanoparticles

ABSTRACT

This review is aimed at combining the published data on taxane formulations into a generalized Drug Delivery approach, starting from the physicochemistry and assessing its relationships with the pharmacokinetics, the biodistribution and the pharmacodynamics. Owing to the number and variety of taxane formulation designs, we considered this class of cytotoxic anticancer agents of particular interest to illustrate the concepts attached to this approach. According to the history of taxane development, we propose a classification as (i) "surfactant-based formulations" first generation, (ii) "surfactant-free formulations" second generation and (iii) "modulated pharmacokinetics drug delivery systems" third generation. Since our objective was to make the link between (i) the physicochemistry of the drug and carrier and (ii) the efficacy and safety of the drug in preclinical animal models and (iii) in human, we focused on the drug delivery technologies that were tested in clinic.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Editor's Choice 2014".

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http://dx.doi.org/10.1016/j.addr.2013.10.007

1. Introduction

As the Drug Delivery concepts are becoming more and more widespread as ways to enhance the therapeutic performance of pharmaceutical products, the consideration of the impact of the formulation on the pharmacokinetics and, consequently on the efficacy and safety profiles of a drug, are growing [1–3]. In fact, as far as the intravenous route is concerned, the administration of a drug as a true solution (i.e. when a drug molecule is only interacting with water molecules) is the only situation where Drug Delivery can be considered both theoretically and practically independent of the influence of the formulation. Nevertheless, this situation is more and more rare owing to the poor aqueous solubility of most of the new chemical entities [4,5]. At the same time, when a chemical series has exhibited promising results in a pharmacological model, the design of an enabling formulation aimed at overcoming the poor aqueous solubility of the compounds is the only way forward when the efforts to synthesize soluble derivatives were unsuccessful.

Starting from the basic affinity principle, the pharmacological activity and/or efficacy of a drug is related to its binding constant and its local concentration in the vicinity of the pharmacological target. Thus, a drug exhibiting a lower binding constant but delivered at a significantly higher local concentration is prone to exhibit the same or even higher efficacy than a drug exhibiting a higher affinity but reaching the target at a lower local concentration, due to the dilution process. Since the drug metabolism and elimination are prone to have a significant impact on its distribution (i.e. on the local concentration at the target), these parameters are included in the drug candidate selection criteria, early in the Discovery process, as Absorption, Distribution, Metabolism and Elimination (ADME) package [6]. The impact of other phenomenon, such as the efflux of the drug from the target cell, driven by the Multidrug Drug Resistance (MDR) complex, has led to the addition of this parameter to the drug design.

The general assumption of the Drug Discovery paradigm is that other parameters such as the association of the drug to the components of the enabling formulation has only a minor impact on its biopharmacy and is not significantly different from one drug to another. It is worth mentioning that this assumption is most of the time valid since the drug and the formulation components are quickly dissociated upon dilution in the bloodstream. Nevertheless, in some instances, a particular attention has to be paid to this drug/excipient(s) association to interpret the pharmacokinetic profiles.

The development of the nanotechnologies has shed a new light on the understanding of the physicochemical principles of Drug Delivery and on their impact on the fate of the drug in the body [1]. The notions, of drug/nano-carrier association/dissociation, of interaction of the nano-carriers with the blood components impacting its pharmacokinetics and elimination, and of exchange between the nano-carrier and the natural carriers such as plasma proteins and lipoproteins, are now taken into account on a regular basis by the pharmaceutical scientists for the design of the nano-objects aimed at improving the delivery of the drugs.

In this context, the formulations of taxanes are of particular interest since the biopharmacy of these anti-cancer drugs is closely linked to the formulation. Therefore, the purpose of this article is to review the literature on taxanes formulations in an attempt to outline the relationships between physicochemistry and biopharmacy and to foresee further improvements that could be expected from drug design and drug delivery system design. In order to propose a link between the physicochemistry of the drug carrier and its biopharmaceutical behavior both in preclinic animal models and in human, this article focuses on the drug delivery technologies for which clinical data is available.

1.1. Taxanes

Taxanes form an important class of anticancer agents due to their unique mechanism of action and their wide applications in cancer therapy. Three taxanes i.e., paclitaxel, docetaxel, and cabazitaxel have been approved for human use and commercialized to date for intravenous injection to human.

1.1.1. Paclitaxel

Paclitaxel (Fig. 1a) is a cytotoxic agent that is chemically a complex diterpene having a taxane ring with a four-membered oxetane ring and an ester side chain at position C-13 [7–9]. Paclitaxel binds to β-subunit of tubulin, enhances the polymerization of tubulin to stable microtubules, and also interacts directly with microtubules, stabilizing them against depolymerization by calcium ions [9], thereby leading to the inhibition of the interphase, the mitotic cellular functions, and apoptosis [10,11]. The fact that paclitaxel binds to microtubules macromolecules in the cells in a specific, reversible, and saturable manner, makes this drug unique among chemotherapeutic agents [12]. Paclitaxel has demonstrated activity against ovarian, breast, lung, Kaposi's sarcoma, bladder, prostate, esophageal, head and neck, cervical, and endometrial cancers [13–15].

Paclitaxel was approved by the FDA in 1992 and was commercialized under the trade name Taxol®, a non-aqueous concentrate, designed to be diluted in a suitable parenteral aqueous infusion solution prior to intravenous administration. The composition includes 6 mg paclitaxel dissolved into 527 mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol/mL of concentrate (Bristol-Myers Squibb's package insert for Taxol (paclitaxel) injection, http://packageinserts.bms.com/pi/pi_taxol.pdf). The clinically recommended doses of Taxol® are 135–175 mg/m^2 intravenously administered over a 3 h infusion every 3 weeks. This dose includes also the injection of ~22–29 g Cremphor® EL and ~21–27 mL of alcohol to the patient (see Table 1).

1.1.2. Docetaxel

The pioneering work of Pierre Potier's team using a semi-synthetic pathway based on chemical modification of the 10-deacetylbaccatin III extracted from the needles of the European yew *Taxus baccata* has led to the discovery of docetaxel (Fig. 1b) [16]. Like paclitaxel, docetaxel causes the blockade of G2/M phase of cell cycle of the treated cells [17,18], preventing microtubules depolymerization resulting in an arrest of cell division [19,20]. Docetaxel showed a 1.9-fold higher affinity than paclitaxel for the binding site and, accordingly, induced tubulin polymerization at a 2.1-fold lower critical tubulin concentration [21]. Docetaxel has demonstrated a significant cytotoxic activity in vitro, and a broad spectrum of antitumor activity in preclinical animal models [19,22]. Although docetaxel has shown antitumor activity in paclitaxel-resistant carcinoma in both preclinic [23] and clinical studies [24,25], its potential limitation, as observed for paclitaxel, stands in its resistance observed in preclinical studies [26–29] explained by different mechanisms [30–32], and in clinic [33].

Docetaxel has been commercialized by Sanofi under the brand name Taxotere®, a non-aqueous concentrate, designed to be diluted prior to intravenous infusion with a supplied diluent containing 13% w/w ethanol in water for injection. In this two-vial product, the concentrate

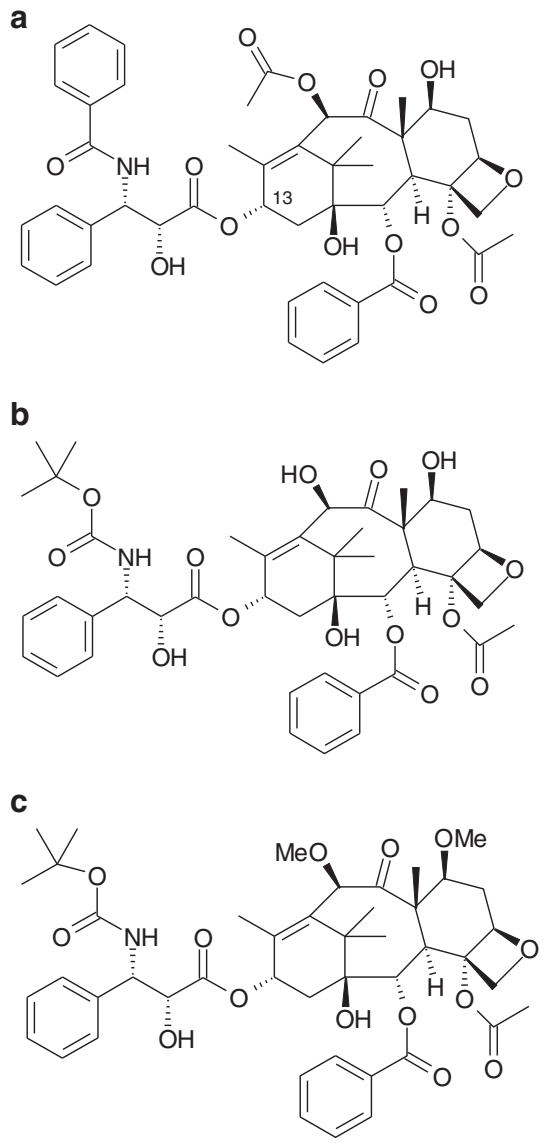

Fig. 1. Chemical structures of the commercialized taxanes a) paclitaxel, b) docetaxel, and c) cabazitaxel.

vial contains docetaxel (anhydrous) dissolved at 40 mg/mL in Polysorbate 80, to be diluted ¼ with the solvent (the second vial), prior to further dilution in infusion solutions. Recently, single vial Taxotere® containing 20 mg docetaxel in 50/50 v/v ratio of Polysorbate 80 to dehydrated alcohol/mL has been introduced for simplified preparation and administration, which required no prior dilution with the diluent and is ready to add to the infusion fluid (http://www.taxotere.com/oncology/dosage_administration/preparation.aspx). Taxotere® has been FDA approved for a variety of indications in oncology [34], for which the clinically recommended doses are 60–100 mg/m^2 administered as a 1 h intravenous infusion every 3 weeks. This dose includes also the injection of ~3–5 g of Polysorbate 80 and ~0.5–0.8 mL of ethanol to the patient (see Table 1).

1.1.3. Cabazitaxel

Cabazitaxel (Fig. 1c) belongs to the next generation of taxanes clinically tested. Cabazitaxel exhibits a poor aqueous solubility, similar to paclitaxel and docetaxel (0.5 μg/mL and 3 μg/mL, respectively) and, in a formulation approach similar to docetaxel, is dissolved in Polysorbate 80, and then diluted with an ethanol-containing solvent prior to intravenous infusion. The key driver of the development of cabazitaxel was its improved activity against preclinical tumor models resistant to chemotherapy including taxanes [35]. Its improved penetration through the blood brain barrier [36] as compared to docetaxel and paclitaxel [37] is noteworthy. Accordingly, cabazitaxel showed a broader spectrum of antitumor activity than docetaxel, including a greater antitumor activity in intracranial glioblastomas [38].

In clinical trials, cabazitaxel (clinically recommended dose: 25 mg/m^2, which includes also 0.65 g of Polysorbate 80 and 0.24 mL of ethanol) (see Table 1) showed improved response rates on taxane-resistant metastatic breast cancer patients [39], and more importantly, a significant efficacy on metastatic prostate cancer patients pre-treated with Taxotere® [40–42]. Cabazitaxel (commercialized under the brand name Jevtana®) has been approved by the FDA, in combination with prednisone, for the treatment of hormone refractory prostate cancer of patients previously treated with docetaxel containing treatment regimen.

2. The three generations of taxanes formulations

The formulations of taxanes for the i.v. route can be classified into 3 generations. The first generation of taxanes formulations is based on the design of solubilizing vehicles containing a surfactant able to form micelles after dilution in an aqueous diluent prone to stabilize supersaturated drug solution and to enable intravenous injection of the poorly

Table 1
List of the surfactant-based taxanes products, their composition, their clinically recommended doses, and the quantity/volumes of excipients used in these products.

Taxane product	Solubility (μg/mL)	Composition	Clinically recommended doses	Qty/vol of excipients injected per dose expressed as mg/m^2
Paclitaxel (Taxol®): Bristol-Myers Squibb	0.5	Per mL of concentrate: Paclitaxel — 6 mg Cremophor EL (purified) — 527 mg (polyoxyethylated castor oil) Alcohol (dehydrated) — 49.7% (v/v) Non-aqueous concentrate for dilution into i.v. fluids	135–175 mg/m^2 as a 3 h i.v. infusion every 3 weeks	Cremphor EL — ~22–29 g Alcohol (dehydrated) — ~21–27 mL
Docetaxel (Taxotere®): Sanofi	3	Per ml of concentrate: Docetaxel (anhydrous) — 40 mg Polysorbate 80–1040 mg Alcohol — ~3.6 mL of 13% w/w in water for injection Concentrate for dilution into i.v. fluids	60–100 mg/m^2 as a 1 h i.v. infusion every 3-week	Polysorbate 80 — ~3–5 g Alcohol — ~0.5–0.8 mL
Cabazitaxel (Jevtana®): Sanofi	8	Per 1.5 ml of concentrate: Cabazitaxel (anhydrous) — 60 mg Polysorbate 80 — 1560 mg Alcohol — ~4.5 mL of 13% w/w in water for injection Concentrate for dilution into i.v. fluids	25 mg/m^2 as a 1 h i.v. infusion every 3 weeks	Polysorbate 80 — 0.65 g Alcohol — 0.24 mL

aqueous soluble taxanes (Fig. 2). These formulations are referred to as surfactant-based formulations. The second generation of taxanes formulations is aimed at overcoming the drawbacks linked to altered pharmacokinetics and toxicological issues associated to surfactant-based vehicles and are referred to as surfactant-free formulations. The third generation of taxanes drug delivery systems is aimed at intentionally modulating the pharmacokinetics of taxanes in an attempt to improve the efficacy/safety profile of the drug.

2.1. First generation of taxanes formulations: surfactant based vehicles

The design of the first generation of taxanes i.v. formulations commercialized was based on a solubilizing vehicle made from a mixture of surfactants such as Cremophor EL (polyoxyethylated castor oil) or Polysorbate 80 (tween 80), and ethanol in significant quantities. The chemical structures of these two surfactants are depicted in Fig. 3.

Cremophor EL [43] (Ph. Eur.) is a synthetic non-ionic surfactant synthesized by reacting 35 mol of ethylene oxide with each mole of (E)-12-hydroxyoctadec-9-enoic acid (castor oil). This surfactant is not a pure single ingredient but a mixture of hydrophobic and hydrophilic constituents. The major component of Cremophor EL is glycerol–polyethylene glycol ricinoleate which, together with fatty acid esters of polyethylene glycol, represents the hydrophobic part of the product. The hydrophilic part consists of polyethylene glycols and ethoxylated glycerol (Cremophor EL BASF Technical leaflet July 1997). Cremophor EL has wide applications as emulsifier for the oral and topical pharmaceuticals, cosmetics, and feedstuffs for veterinary use. This surfactant was first approved for human use by i.v. administration in Taxol®.

The commercially available Polysorbate 80 [44] (Ph. Eur.) solution is a chemically diverse mixture of different fatty acid esters, mainly oleic acid [45]. The backbone of Polysorbate 80 is made up of sorbitan ring with polyethylene oxide chains. Polysorbate 80 is prepared by chemical addition of ethylene oxide to sorbitan, followed by partial esterifications with oleic acid. Polysorbate 80 is soluble in a range of polar to non-polar solvents, such as water, ethanol, ethyl acetate and toluene. The hydrocarbon chain of Polysorbate 80 provides the hydrophobicity, whereas ethylene oxide subunits provide the hydrophilicity to this surfactant. The oleic acid containing component forms >58% of the total fatty acid content, while the remaining fatty acids are a mixture of both saturated and unsaturated fatty acids such as myristic, palmitic, palmitoleic, stearic, oleic, linoleic and linolenic acids [46,47]. Polysorbate 80 had been approved for various applications for use in nutritives, creams, ointments, lotions, vaccines, tablets, etc. This surfactant was first approved for human use by i.v. administration in Taxotere®.

Experimental data has indicated that Cremophor EL and Polysorbate 80, irrespective of their drug-solubilizing function owing to their amphiphilic nature and micelle forming property, modify the pharmacokinetics of drug in a concentration-dependent manner [48], induce side-effects and elicit a modest antitumor activity in vitro and in animal models [49–52].

2.1.1. Influence of the surfactant on the pharmacokinetics

The pharmacokinetic behaviors of Cremophor EL and Polysorbate 80 were shown to be significantly different.

Following i.v. injection to cancer patients, Cremophor EL showed a relatively slow clearance and its distribution was found limited to the plasma compartment. After a 3 h i.v. infusion, Cremophor EL displayed long terminal elimination half-life (~84 h) with the persistence of significant concentrations in the blood circulation even after 1 week of injection [53]. Cremophor EL has been shown to display a schedule-dependent pharmacokinetics with an increased systemic exposure [53] at short infusion times associated to pronounced incidence of adverse effects [54,55]. In agreement with its long half-life, short infusion times result in increased circulation concentration of Cremophor EL, possibly due to the saturation of the elimination of Cremophor EL, and surfactant-related side-effects such as peripheral neuropathy. Accordingly, longer infusion times, for instance 24 h, lead to considerably decreased side-effects related to Cremophor EL [54].

It is interesting to note that Cremophor EL was shown to be mostly eliminated by the non-renal and non-hepatobiliary routes [56,57], through a biodegradation into free fatty acids driven by serum carboxylesterase [58], while Polysorbate 80 is rapidly eliminated [59,60] by a hydrolysis catalyzed by carboxylesterase (Fig. 4) [61].

Cremophor EL and Polysorbate 80 were also shown to alter the pharmacokinetics and disposition behaviors of the associated drugs following i.v. injection. More specifically, Cremophor EL has been shown to alter the protein binding characteristics and hepatobiliary secretion, reducing the elimination of the associated drugs. For instance, Cremophor EL has been shown, using re-circulating isolated perfused rat liver, to cause a dose-dependent inhibition of the hepatic elimination of paclitaxel. A nonlinear pharmacokinetics and pharmacodynamics of paclitaxel can be anticipated from the impediment of the processing of the drug by the metabolism and excretion machinery [62]. Polysorbate 80 has also been shown to display a similar effect when used as a vehicle for the formulation of etoposide [63]. Cremophor EL could also modify the binding of lipophilic substances to natural drug carriers such as HDL and LDL [64] as suggested by the alteration of the electrophoretic and density gradient of these lipoproteins [65]. Cremophor EL, but not Polysorbate 80, has

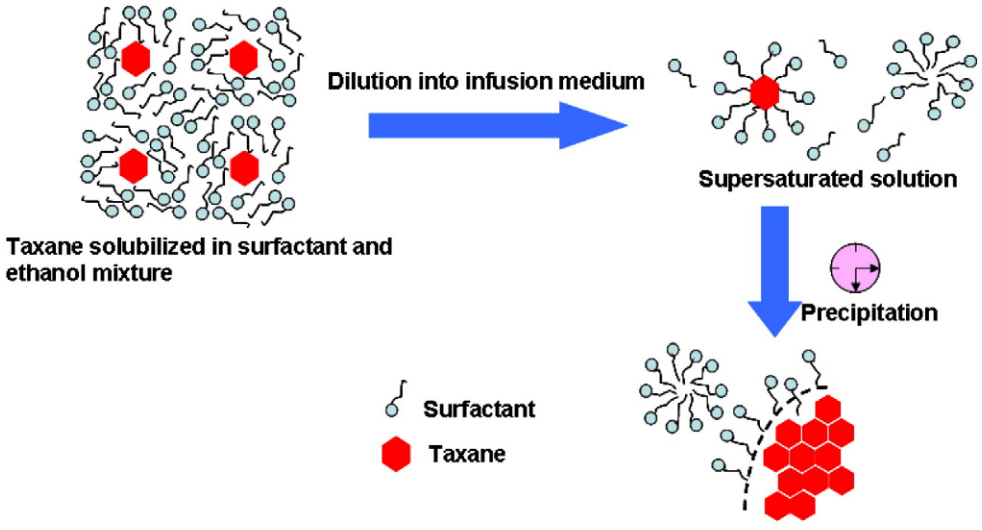

Fig. 2. Mechanistic representation of the surfactant-mediated stabilization of the first-generation taxanes formulations.

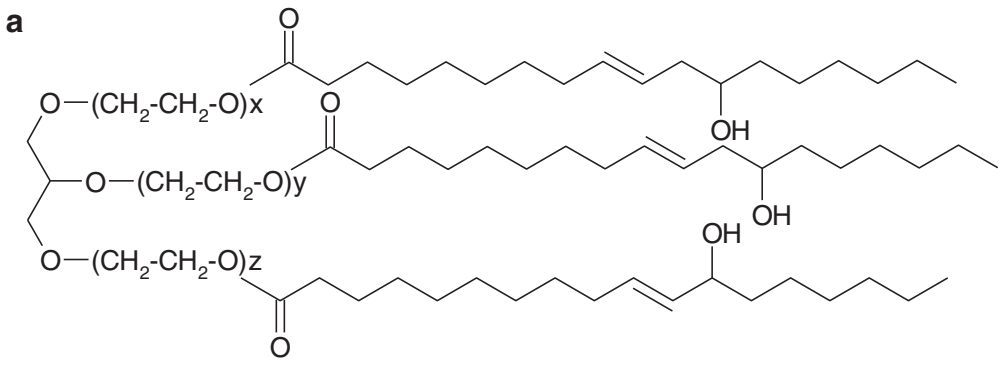

Fig. 3. Chemcial structures of a) Cremophor EL (polyoxyethylene glycerol 35 ricinoleate), and b) Polysorbate 80 (Polysorbate 80, polyoxyethylenesorbitan 20 monooleate).

been shown to cause the dissociation of the native lipoproteins [63,64]. In the absence of Cremophor EL, paclitaxel was shown to be bound to the albumin, HDL and, in small quantity, to LDL. However, in the presence of Cremophor EL, the drug binding pattern was changed significantly such that the drug showed a strong affinity for the lipoprotein dissociation products [66]. While the distribution of the drug to the tumor site could be promoted by the increase of the drug persistence in systemic circulation, the alteration of the drug binding pattern may render difficult the interpretation and anticipation of the pharmacokinetics.

It is worth mentioning that, while the majority of the paclitaxel is distributed in plasma, Cremophor EL in the Taxol® formulation has been shown to decrease the uptake of paclitaxel by erythrocytes in human blood [67] as measured using in vitro partition experiments in blood fractions. In the absence of Cremophor EL, the in vitro equilibrium of paclitaxel (introduced as solution in DMSO:methanol 1:1 v/v) between the whole blood and plasma is reached in 15 min, which denotes the rapidity of the exchange. The addition of Cremophor EL considerably reduced the whole blood:plasma concentration ratio of paclitaxel, in a concentration dependant manner. This inhibition effect was primarily driven by Cremophor EL components such as polyoxyethyleneglycerol triricinoleate along with fatty acid esters of polyethylene glycol formed during polyoxyethylation of castor oil.

Following i.v. injection, Cremophor EL-based paclitaxel has shown a nonlinear exposure of drug and higher than expected plasmatic drug concentrations at increasing doses [68]. For instance, a 3 h infusion of Taxol® at 175 mg/m^2, compared to 135 mg/m^2, has resulted in an 80% higher C_{max} and a 75% higher AUC [69] instead of the expected

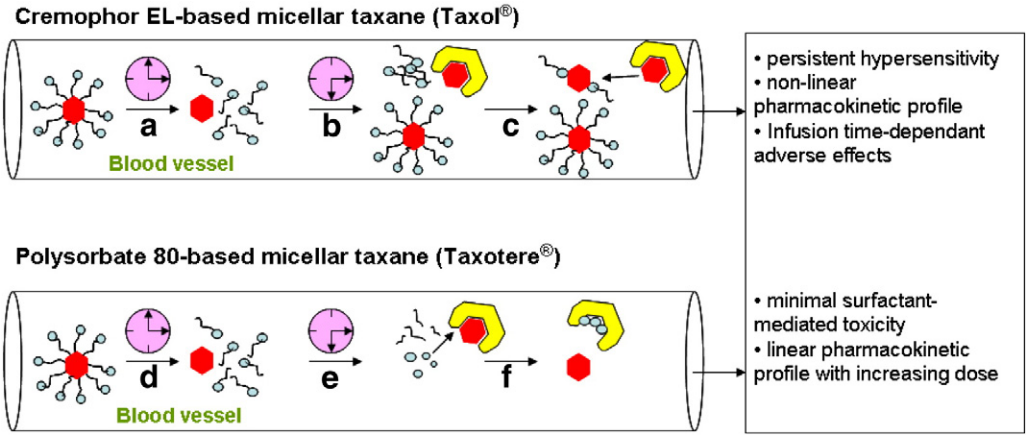

Fig. 4. Mechanistic differences between Cremophor EL- and Polysorbate 80-based taxane formulations. a) Dissociation of Cremophor EL micelles to release the taxane into the blood stream, b) slow degradation of Cremophor EL, resulting in prolonged systemic circulation, c) higher affinity of taxane for Cremophor EL as compared to plasma proteins, leading to a decreased of the unbound drug concentration and also of the albumin bound drug fraction, d) dissociation of Polysorbate 80 micelle to release the taxane into the blood stream, e) rapid degradation of Polysorbate 80 to simple components such as oleic acid, and f) oleic acid-mediated protein-binding displacement of taxane, leading to increased unbound drug concentration. The yellow object in the figure represents albumin or a plasma carrier protein.

~30% increase. This is possibly because of the low volume of distribution of Cremophor EL and higher affinity of paclitaxel for the Cremophor EL micelles than for the plasma proteins. In fact, Cremophor EL was found to be the main carrier of paclitaxel in the vascular compartment and the fraction of paclitaxel not bound to plasma proteins was inversely proportional to the Cremophor EL concentrations [70]. Owing to a significantly higher affinity of paclitaxel for Cremophor EL micelles as compared to its affinity for plasma proteins, the presence of Cremophor EL resulted in a substantial decrease of the fraction of paclitaxel bound to plasma proteins, and especially to albumin. These results [67] have provided some clues to explain the observed non-linear disposition in plasma and brought evidence that the higher than expected plasma concentrations of paclitaxel may be not primarily related to a saturable transport or a saturable tissue binding, and disproportional elimination kinetics, as first suggested [69,71–73]. It is interesting to note that paclitaxel solubilized in Polysorbate 80 or dimethylacetamide, as opposed to the paclitaxel solubilized in Cremophor EL, exhibited a linear exposure versus dose relationship in plasma and tissues, and a linear elimination versus dose pattern [68].

Henningsson and colleagues [74] have proposed a pharmacokinetic model to describe the non-linear pharmacokinetics of paclitaxel based on the pharmacokinetics of total and unbound plasma concentrations, as well as blood concentrations. This model took into account the known compartments of paclitaxel distribution such as encapsulation of paclitaxel in Cremophor EL micelles, binding to erythrocytes, albumin, alpha acid glycoprotein and platelets. From the simulated concentration components in the 24 h infusion of Taxol in patients, because of the lower Cremophor EL concentrations in the systemic compartment, the binding of paclitaxel to plasma proteins and erythrocytes was higher compared to its binding to Cremophor EL. This report has also suggested that the unbound concentration–time profile could be predicted based on total drug and Cremophor EL concentrations in plasma and that the paclitaxel hematologic toxicity established from total drug concentration may not be valid for the vehicles/carriers for paclitaxel other than Cremophor EL. This could have significant clinical implications since if the systemic exposure to unbound drug varies with the infusion time [55], then the pharmacological activity and the safety profile may be dependent upon the infusion schedule.

Polysorbate 80 does not alter to the same extent the fate of docetaxel in the body as denoted by the linear increase of pharmacokinetic parameters (AUC with increasing doses [61]. This property was attributed to the rapid degradation of Polysorbate 80 after i.v. injection [61]. Similar observation of linear pharmacokinetics with dose has been also reported for Jevtana® (the Polysorbate 80/ethanol-based solution of cabazitaxel) [37]. However, it has been reported that Polysorbate 80 decreased the binding of docetaxel to human plasma proteins in vitro by forming complexes [75,76]. Moreover, the addition of Polysorbate 80 at clinically relevant concentrations (up to 5.0 μL/mL) had resulted in a substantial increase in the unbound docetaxel (not bound to Polysorbate 80 and to plasma proteins) (7% in the absence of Polysorbate 80 vs 44% in the presence of Polysorbate 80) in vitro in human plasma samples, and this effect was concentration-dependent leading to changes in the pharmacokinetic behavior of docetaxel, and more precisely the unbound docetaxel (not bound to Polysorbate 80 and to plasma proteins) which exhibit a faster clearance in patients [77]. This increase of unbound docetaxel in the presence of Polysorbate 80 was hypothesized to be the result of oleic acid (a constituent of Polysorbate 80)-mediated protein binding displacement of docetaxel [58,78]. The unbound docetaxel concentration was inversely proportional to the concentration of the natural circulating carrier, the alpha acid glycoprotein (AAG) in plasma, the decrease of total plasma docetaxel clearance being correlated with high plasmatic concentrations of AAG [79]. As cancer patients may show variability in AAG levels, these differences may lead to variability of the pharmacokinetics, which subsequently may induce variability of the activity and toxicity profiles. Accordingly, low AAG levels were correlated to increased severity of neutropenia [80], and therapeutic efficacy [81] of Taxotere®, while high AAG levels were related to a lower efficacy.

As reported for Taxotere®, Jevtana® administered as Polysorbate 80/ethanol solution, showed linear pharmacokinetics between 10 and 25 mg/m^2, when injected as a 1 h i.v. infusion without premedication [37]. The overall plasmatic pharmacokinetics were characterized by a triphasic profile, with a rapid initial phase ($t_{1/2}$ ~ 2.6 min) followed by an intermediate phase ($t_{1/2}$ ~ 1.3 h) and then by a long terminal phase ($t_{1/2}$ ~ 73 h). Jevtana® showed a considerably larger volume of distribution and longer terminal half-life than Taxotere® (~24-fold and ~7-fold, respectively), and a high clearance rate.

2.1.2. Side-effects of taxanes surfactant-based formulations

The potentially more serious taxane formulations- and/or drug-induced adverse events are anaphylactic hypersensitivity reactions, peripheral neuropathy, neutropenia, and stomatitis/mucositis [82,83].

In an attempt to improve the formulation, it appears of primary interest to delineate the side-effects linked to the formulation and those attached to the drug.

2.1.2.1. Acute hypersensitivity reactions. The most characteristic toxicity of taxane therapy is the high incidence of hypersensitivity reactions [84–86].

Mechanistically, the Cremophor EL has been reported to activate the complement cascade facilitated by the binding of antibodies to the hydroxyl rich surface of Cremophor EL micelles [87]. Moreover, the histamine release following administration of these surfactants has been attributed to the presence of oleic acid [88–91]. Acute hypersensitivity reactions is reported as an adverse event of the i.v. injected Taxol® [92,93,86,94], which are more often observed within the first two injection courses of Taxol® and can be prevented by decreasing the infusion rate. Taxol® administered as a 30-minute or a 45-minute infusion indicated signs of significant hypersensitivity reactions in all patients, even in the presence of standard antiallergenic premedication, which suggests an infusion-time dependence [95]. A non-immunological reaction based on the degranulation of mast cells or basophils has also been observed [86,96] which could be prevented by the pretreatment with antihistamines, H_2-receptor antagonists and corticosteroids [97]. The complement activation was found to be concentration-dependent with a minimum activating Cremophor-EL concentration of ~2 μL/mL, a concentration readily achieved in clinical setting following standard doses of Taxol® injection [98,99]. Moreover, it has been demonstrated that the vehicle Cremophor EL based micelles-mediated complement activation in human serum can be inhibited by soluble complement receptor type 1 and human intravenous immunoglobulin [100], further strengthening the role of complement activation in inducing hypersensitivity reactions. Other postulated reason for complement activation by Cremophor EL-based micelles include a decrease in the electrophoretic mobility of both HDL and LDL by Cremophor EL, resulting in de novo formation of larger molecular size complexes possibly arising from the incorporation of some of the hydrophobic components of Cremophor EL into the lipoproteins [100,101]. The components of Cremophor EL that did not associate with lipoproteins were suggested to form large droplets (up to ~300 nm size) which are capable of activating C3 convertases, presumably as a result of direct C3 binding to the surface-exposed hydroxyl and ethylene oxide residues [99,100]. On the other hand, one of the constituents of Cremophor EL i.e. oleic acid is also suspected to stimulate histamine release responsible for inducing hypersensitivity reactions.

Following i.v. injection, Taxotere®, the Polysorbate 80 based formulation of docetaxel, induces acute hypersensitivity reactions [82,85,102]. Some reports had previously suggested that Polysorbate 80 contains allergens, in particular a new allergen formaldehyde was formed as an oxidative product following exposure to air, that could be responsible for hypersensitivity reactions [103]. However, recent reports have clarified that the hypersensitivity reactions of Taxotere® were not of allergenic origin [104–106]. Oleic acid, one of the constituents of Polysorbate 80, was suspected to be responsible for histamine release and

thus to contribute to hypersensitivity reactions associated to Taxotere® therapy [107]. Overall, the hypersensitivity events rarely form roadblock for Taxotere® treatment [108] and could be managed by oral administration of corticosteroids such as dexamethasone [25]. In parallel, the possible influence of the physicochemical properties of the drug delivery carrier (surfactant micelle in this case) such as size, morphology, surface characteristics, etc. on the complement activation-mediated induction of acute hypersensitivity reactions/pseudoallergic reactions after intravenous injection [109] should be taken into account. Interestingly, as opposed to Taxol® and Taxotere®, Jevtana® did not cause severe hypersensitivity reactions in the absence of premedication, possibly due to the lower concentration of Polysorbate 80 injected with the drug, while it showed an improved tolerance profile compared to the other taxanes.

2.1.2.2. Peripheral neurotoxicity. Both Cremophor EL and Polysorbate 80 injected intravenously at concentrations similar to that present in therapeutically effective concentrations of Taxol® and Taxotere® respectively, were shown to induce peripheral neurotoxicity [97,110–113] in a concentration-dependent manner [111–113]. In preclinical assays, physiologically relevant concentrations of Cremophor EL were shown to cause neurotoxicity, suggesting the link between the exposure to Cremophor-EL and the neurotoxicity [114]. It has been suggested that the ethoxylated derivatives of castor oil in Cremophor EL are responsible for the neuronal damage [115]. Moreover, ^{3}H-paclitaxel solubilized in dimethyl sulfoxide did not accumulate in detectable levels in the peripheral nervous system, suggesting a possible role of Cremophor EL in inducing the neuropathy [116]. In clinical setting, controlling neuropathy is crucial for maintaining the quality of life of patients because it is usually persistent and cumulative after Taxol® treatment [117]. Decreasing the infusion time of Taxol® from 24 h to 3 h or 1 h in clinical studies has significantly increased the AUC of Cremophor EL and decreased the AUC of total and unbound paclitaxel at the same dose level. However, a recent study performed on cancer patients [118] has revealed that an increase in AUC of Cremophor EL had no detectable effect on peripheral neuropathy development, but neuropathy was more linked to the AUCs of total and unbound paclitaxel, thus clarifying that the neuropathy is mainly drug-induced. In this case, optimizing the dosing schedule only may be irrelevant to decrease the neurotoxicity associated with Taxol®, but it should be associated to the modulation of the total and unbound concentrations of paclitaxel.

Peripheral neuropathy is a dose-dependent, cumulative side effect associated with Taxotere® therapy. However, the incidence of neurotoxicity after Taxotere® treatment is much lower as compared to Taxol® treatment [119,120]. In most cases, the symptoms of neuropathy [112,121] disappear following discontinuation of treatment, while in few cases the symptoms persist long after the final dose [122]. Peripheral neuropathy induced by Taxotere® is more commonly minimized by dose reduction [122].

As opposed to Taxol® and Taxotere®, Jevtana® showed limited neurotoxocity at the clinical recommended dose of 20 mg/m^2 in cancer patients [37]. Having said previously that the neurotoxicity in case of Taxol® was primarily drug-induced, the differences in the incidence of neurotoxicity in case of Taxol®, Taxotere® and Jevtana® may possibly be linked to the differences in the injected therapeutic drug doses.

2.1.2.3. Neutropenia. Neutropenia is the most common dose-limiting hematologic toxicity encountered with all the three clinically approved taxanes. Febrile neutropenia is the most clinically relevant and life-threatening condition that requires dose-reduction or delay in treatment schedule [123]. The trend was that the prolonged infusion schedule of Taxol® was associated with a higher incidence of neutropenia, while shorter infusion schedules (1–3 h) were associated with significantly less neutropenia [54]. As described previously, shorter infusion time of Taxol® results in decreased total and unbound paclitaxel due to trapping/re-partitioning of drug into the surfactant micelles [67], while longer infusion time results in increased total and unbound paclitaxel, thus a direct relationship exists between increased exposure (AUC) to the total and unbound paclitaxel concentrations and the incidence of neutropenia after Taxol® treatment [55,124,125].

Hematologic toxicity associated to Taxotere® treatment is myelosuppression and is often the dose-limiting toxicity [123,126]. Similar to Taxol®, the incidence of neutropenia following Taxotere® treatment has been attributed to the total and unbound docetaxel concentration in plasma [80], while the surfactant Polysorbate 80 had no evident role played in this toxicity. Jevtana® has also showed a significant grade 3 or 4 neutropenia at 25 mg/m^2 in phase III study on metastatic castration-resistant prostate cancer patients [40]. Severe neutropenia, if not appropriately managed, could lead to significant mortality [123]. Primary prophylaxis (from the first cycle of treatment) with G-CSF reduces the likelihood that a patient will develop neutropenia [127,128]. To prevent the induction of severe neutropenia in taxane-containing treatment regimens, the prophylactic treatment of patients with bone-marrow colony stimulatory factors such as G-CSF and GM-CSF has become a standard treatment modality [129].

2.1.2.4. Other side-effects. Arthralgia/myalgia are often observed in patients treated with Taxol®, occurring 24–48 h after treatment [82,83] and generally lasting for about 3–5 days. The severity of this side-effect could be reduced by administering oral prednisone after 24 h of completion of chemotherapy with Taxol® [130]. Taxotere®-treated patients may also experience arthralgia/myalgia, however at a lower incidence than observed after Taxol® treatment [131].

On the other hand, treatment with Taxotere®, but not with Taxol® or Jevtana®, led to fluid retention characterized by peripheral edema, ascites and pleural effusions [82,132,37]. The cumulative fluid retention could be dose-limiting in some cases [133], and was found to be closely related to the total administered dose of docetaxel [129]. It was also hypothesized that the fluid retention could be linked to the ability of Polysorbate 80 to alter the membrane fluidity [134]. This side-effect could be reduced by oral administration of dexamethasone during the treatment [25,108].

2.2. Second generation of taxanes formulations: surfactant-free formulations

Avoidance of the inconveniences and the side effects associated to the use of surfactant vehicles of the first generation of taxanes formulations has been the primary goal of the design of the second generation of taxanes formulations while no particular pharmacokinetic and efficacy improvement at equivalent dose was expected.

A wide variety of paclitaxel and docetaxel formulations have been explored. Nevertheless, as mentioned earlier, this article focuses only on those having been tested in clinical trials, namely, methoxy poly(ethylene glycol)–poly(lactic acid) micellar dispersion of paclitaxel (Genexol-PM), poly(vinyl pyrrolidone)-*b*-poly(N-isopropyl acrylamide) micelle of paclitaxel (Nanoxel), tocopherol poly(ethyleneglycol) succinate-based emulsion of paclitaxel (Tocosol® paclitaxel), and nanoemulsion of docetaxel (ANX-514) (see Table 2).

2.2.1. Polymeric micelle formulations

2.2.1.1. Genexol-PM. Block copolymer micelles have gained significant attention in the recent years due to their stability in the blood, their ability to solubilize and transport poorly soluble drugs and their ability to circulate in plasma for a prolonged time. Various drugs have been either physically entrapped into the polymeric micelles or are chemically conjugated [135–137].

Genexol-PM is a diblock copolymeric micelle entrapping paclitaxel. The co-polymer used in Genexol-PM is a ~3750 g/mol amphiphilic diblock monomethoxy poly(ethylene glycol)-block-poly(D,L-lactide) (mPEG–PDLLA) [138]. mPEG–PDLLA copolymers are generally synthesized by ring opening polymerization of D,L-lactide [39–42] in the presence of a catalyst e.g. stannous octoate. These co-polymers

Table 2
Details on the second generation taxane formulations and third generation taxanes delivery systems that have been described in this manuscript.

Taxane formulation/delivery system	Manufacturer	Composition		Dose used in clinic	Adverse effects	Current status
		Drug	Excipient			
Second generation						
Genexol-PM (polymer micelle)	Samyang Pharma	Paclitaxel	Monomethoxy poly(ethylene glycol)-block-poly(D,L-lactide) copolymer Mol wt: ~3750 g/mol	300 mg/m^2 as a 3 h i.v. infusion every 3 weeks	Hypersensitivity reactions, neutropenia, neuropathy, thrombocytopenia	Commercialized
Nanoxel (polymer micelle)	Dabur Pharma	Paclitaxel	Poly(vinyl pyrrolidone)-*b*-poly(N-isopropyl acrylamide) copolymer	220 mg/m^2 as a 1 h i.v. infusion every 3 weeks	n.a.	Commercialized
Tocosol® Paclitaxel emulsion	Sonus Pharma	Paclitaxel	Vitamin E (D,L-α-tocopherol), PEG400, tocopheryl polyethyleneglycol succinate (TPGS), and poloxamer 407	100 mg/m^2 as a i.v. infusion once-a-week	Neutropenia, neuropathy	Discontinued
ANX-514 (emulsion)	Adventrx Pharmaceuticals	Docetaxel	–	75 mg/m^2 as a single dose (for bioequivalence testing)	n.a.	Not bioequivalent
Third generation						
Abraxane® (Nanoparticle)	Abraxis Bioscience (now Celgene Corp.)	Paclitaxel	Human serum albumin	260 mg/m^2 of Abraxane® as a 30 min i.v. infusion every 3 weeks	Hypersensitivity reactions, neutropenia, neuropathy	Commercialized
NK105 (Polymer micelle)	NanoCarrier	Paclitaxel	Poly(ethylene glycol)–poly(aspartic acid) block copolymer Mol wt: ~20,000 g/mol	150 mg/m^2 as a 1 h i.v. infusion every 3 weeks	Neutropenia, leucopenia, lymphopenia, neuropathy	Phase II
BIND-014 (Polymer nanoparticle)	BIND Biosciences	Docetaxel	Poly(lactic acid)–poly(ethylene glycol)–ACUPA	I.v. infusion every 3 weeks	n.a.	Phase I
Opaxio™ (conjugate)	Cell Therapeutics	Paclitaxel	Poly(glutamic acid) Mol wt: 48,000 g/mol	175 mg/m^2 i.v. infusion over 10–30 min every 3 weeks	Neutropenia, anemia, neuropathy, dyspnea, fatigue	Phase III
Taxoprexin® (conjugate)	Luitpold Pharmaceuticals	Paclitaxel	Docosahexaenoic acid, Cremophor EL, ethanol Mol wt: 328 g/mol	1100 mg/m^2 (equivalent to 807 mg/m^2 paclitaxel) as a 2 h i.v. infusion every 3 weeks	Hypersensitivity reactions, neutropenia, neuropathy	Phase III

are amorphous with a T_g (glass transition temperature) between −20 and −50 °C reflecting the influence of the PEG segments [139]. A polymeric micelle is usually made up of several block copolymer molecules, having a densely packed core made of hydrophobic blocks and corona made of hydrophilic blocks, forming an overall spherical core/corona structure of about 20–50 nm diameter. The PEG forming the corona of the micelle is expected to prevent the coating by plasma proteins referred to as opsonins and the subsequent macrophage uptake mediated by the opsonins receptors.

Genexol-PM has been formulated using solid dispersion technique [138], by evaporating the acetonitrile solution of mPEG–PDLLA and paclitaxel mixture, followed by dissolving the resultant transparent gel matrix in water previously heated up to 60 °C. The resultant micellar dispersion can be sterilized by filtration through a 0.22 μm filter, and lyophilized to obtain a dry powder. The paclitaxel loading into Genexol-PM was ~16% w/w of the co-polymer. Such a high drug loading is attributed to the hydrophobic interaction between the poly(lactic acid) block of the co-polymer and paclitaxel. The mPEG–PDLLA micelles have been found to be well tolerated following i.v. injection of ~100 mg/kg in mice and were found to be non-genotoxic and non-mutagenic in in vitro assays [140]. Following i.v. injection into mice, the ^{14}C-labeled copolymeric micelles were found to undergo rapid cleavage into the PDLLA and mPEG portions, followed by rapid elimination in urine. More than 95% of the injected dose of co-polymer micelles was eliminated within 15 h after injection [140]. The ^{14}C-paclitaxel incorporated into mPEG–PDLLA micelles (2 g/mol PLA) underwent a rapid release from the micellar core into the systemic circulation [140], after i.v. injection into mice, suggesting a poor affinity of the drug for the micellar core as compared to the plasma components.

In preclinical studies, Genexol-PM has showed a 3-fold higher maximum tolerable dose (MTD) (60 mg/kg versus 20 mg/kg for Taxol® formulation, injected on days 1, 5 and 9 after i.v. injection to nude mice [138]. In a comparative pharmacokinetic study, following i.v. injection at the MTDs in mice, the Genexol-PM showed a lower AUC and higher clearance and volume of distribution as compared to Taxol®. These results are consistent with the slow biodistribution of paclitaxel sequestered by Cremophor EL micelles resulting in low clearance and low volume of distribution from the one hand, and the quick release followed by rapid tissue distribution observed with Genexol-PM, on the other hand. This was further evidenced from the significantly higher tumor concentrations of Genexol-PM as compared to Taxol® at MTDs in tumor bearing mice [138]. Moreover, Genexol-PM has shown a significantly greater antitumor activity as compared to Taxol®, and also showed complete tumor regression in various human ovarian and breast cancer xenograft mice models, indicating a preclinical pharmacokinetic and efficacy advantage over Taxol® formulation [138]. In a phase I study conducted in cancer patients, the MTD of Genexol-PM administered as a 3 h i.v. infusion every 3 weeks without premedication was found to be 390 mg/m^2 which is 2.3 times higher than the dose recommended for Taxol® [141]. Therefore, Genexol-PM could be injected at dose 123% higher than Taxol®. No hypersensitivity reactions were observed with Genexol-PM, despite the absence of premedication, as opposed to Taxol®. Genexol-PM induced grade 3 neutropenia at and above 230 mg/m^2 dose, while grade 4 neutropenia appeared at the 390 mg/m^2 dose. Neuropathy, myalgia and neutropenia were the dose-limiting toxicities of Genexol-PM. Clinical pharmacokinetic analysis revealed that Genexol-PM exhibited a biphasic decline in plasma concentration over time, while the AUC and C_{max} of total paclitaxel showed a roughly proportional increase with increasing dose. Dose proportional increase in AUC and C_{max} with increasing dose of Genexol-PM injected in a weekly schedule has been also reported [142]. The terminal half-life of paclitaxel administered as Genexol-PM was ~12 h which is significantly lower than that of paclitaxel administered as Taxol® (~20 h), both at doses 175 mg/m^2 by 3 h i.v. infusion [141], consistent with the expected effects of mPEG–PDLLA and Cremophor EL micelles on paclitaxel elimination.

In a multicentric phase II study conducted in advanced non-small cell lung cancer patients, Genexol-PM injected as 3 h i.v. infusion in the 230–300 mg/m^2 dose range in combination with cisplatin 60 mg/m^2 as a 3-week cycle, as first-line therapy, resulted in a significant anticancer activity, with an overall response rate of 37.7%, median time to progression of 5.8 months, and median survival period of 21.7 months. These clinical efficacy results are significantly better than those reported previously in a phase III trial with Taxol® and cisplatin combination (26% overall response rate, median time to progression of 4.1 months and median survival period 8.1 months, for Taxol® at 175 mg/m^2 and cisplatin at 80 mg/m^2, as a 3 h infusion, as 3-week cycle) in NSCLC patients [143]. In another phase II trial conducted in metastatic breast cancer patients, Genexol-PM at 300 mg/m^2 was injected alone as a 3 h i.v. infusion every 3 weeks without premedication [144]. Significant efficacy was reported with 58.5% overall response rate and 9 months median time to progression of the disease. In both the above trials, ~10–13% of patients experienced hypersensitivity reactions. Thrombocytopenia was observed in some patients while neutropenia and neuropathy were the major taxane-mediated toxicities.

In a recent phase II study in pancreatic cancer patients, Genexol-PM as a single arm at 300 mg/m^2 injected as a 3 h infusion every 3 weeks has showed efficacy comparable to that reported previously for gemcitabine in a phase III trial [145,146], at least in terms of median overall survival (6.2 months) but with a lower overall response rate (6.2% for Genexol-PM vs. 12.4% for gemcitabine) [147].

After receiving US IND approval in Feb 2002, Genexol-PM is being marketed in Korea since Feb. 2007 for the treatment of metastatic or recurrent breast cancer, and locally advanced or metastatic non-small cell lung cancer as first-line therapy. A phase IV study of Genexol-PM is currently underway on taxane pretreated recurrent breast cancer patients (clinical trial identifier: NCT00912639), while other clinical trials of Genexol-PM with drug combinations are ongoing (http://www.clinicaltrial.gov/ct2/results?term=Genexol-PM).

2.2.1.2. Nanoxel. Nanoxel is another micellar formulation (80–100 nm mean diameter) of paclitaxel obtained by physical encapsulation of paclitaxel into a diblock copolymer poly(vinyl pyrrolidone)-*b*-poly(N-isopropyl acrylamide) (PVP-*b*-PNIPAAM) [148]. Poly(N-isopropyl acrylamide) block confers pH-sensitivity to the copolymer such that, in acidic conditions, this block undergoes degradation leading to destabilization of the micellar structure resulting in subsequent release of the encapsulated paclitaxel. Nanoxel injected as a 1 h i.v. infusion every 3 weeks without premedication has showed linear pharmacokinetics over the dose range tested in cancer patients. Despite the absence of premedication, no hypersensitivity reactions were observed [149]. No information on preclinical or phase I pharmacokinetic parameters and safety profile were found by the authors for this product. The phase II study on metastatic breast cancer patients revealed a comparable efficacy but an improved safety profile as compared to Taxol® [149]. These results had prompted the approval of Nanoxel in India in 2006 for the treatment of metastatic breast cancer, ovarian cancer, non-small cell lung cancer and AIDS related Kaposis's sarcoma, and has been commercialized by Dabur Pharma in India in January 2007. The recommended dose for Nanoxel for the approved indications is 220 mg/m^2 as a 1 h i.v. infusion every 3-weeks. Recently, a multicentric, open label, non-randomized phase I study (clinical trial identifier: NCT00915369) on Nanoxel has been initiated in advanced breast cancer patients to study the pharmacokinetics at the four dose levels (220, 260, 310 and 375 mg/m^2), and to identify a dose higher than 220 mg/m^2 that could demonstrate better efficacy and manageable toxicity.

2.2.2. Emulsions

2.2.2.1. Tocosol® paclitaxel emulsion. Tocols are a family that includes tocopherols, tocotrienols and their derivatives, exhibiting good solubilizing property for lipophilic substances [150]. Among the various tocopherols, vitamin E has been widely used to manufacture emulsions for i.v. injection, especially for dietary supplementation [151,152]. The term 'Tocosol®' has emerged from the use of a 'tocol' (vitamin E) as a principal ingredient, for the development of pharmaceutical emulsion of paclitaxel. Tocosol® paclitaxel was the first tocol-based emulsion formulation that had reached clinical trials. Tocosol® paclitaxel emulsion primarily contained vitamin E (D,L-α-tocopherol) as the oily phase, PEG400 as a co-solvent, tocopheryl polyethyleneglycol succinate (TPGS) and poloxamer 407 as surfactants aimed at stabilizing the emulsion droplets [153]. The emulsion formulation was prepared mixing the oil phase containing drug with PEG400, and emulsifying the resulting solution into an aqueous phase under vigorous mixing at 45 °C to obtain a crude emulsion. The crude emulsion was then further processed by high pressure homogenization to obtain a mean droplet size of ~60 nm in which the diameter of 99% droplets were less than 150 nm. The emulsion was then sterilized by filtration through a 0.2 μm filter. The droplets size of the emulsion formulation remained essentially the same up to a 3 L scale. A paclitaxel concentration of ~8–10 mg/mL (0.8–1.0%) has been achieved in this emulsion which is higher than paclitaxel concentration in the Taxol® formulation. The optimized Tocosol® paclitaxel formulation (QW8184) was shown to be physically stable (estimated from droplets size evolution) and chemically stable after 9–12 months storage at 4 °C and 25 °C.

In preclinical studies, Tocosol® paclitaxel has shown an improved tolerability as compared to Taxol®, with a MTD of 70 mg/kg versus 20 mg/kg for Taxol®. The emulsion vehicle did not show any signs of toxicity at the equivalent volume of drug formulation. Moreover, Tocosol® paclitaxel showed a considerably higher tumor growth inhibition and improved antitumor activity as compared to Taxol®, in subcutaneously grafted B16 melanoma mice model at MTDs or even at concentrations lower than MTD. Tocosol® paclitaxel has also shown an improved activity as compared to Taxol® in a HCT-15 tumor mice model overexpressing P-glycoprotein [154]. A preclinical pharmacokinetic study in tumor bearing mice revealed that Tocosol® paclitaxel exhibited an increased tumor accumulation as compared to Taxol® (1.5-times higher C_{max} and 2.2-times higher AUC in tumors), when injected at equivalent doses (10 mg/kg), although the plasma concentrations of both formulations were similar [155]. Overall, the main features of Tocosol® paclitaxel emulsion were high drug loading, improved tolerability and enhanced efficacy. These features have prompted the move of this formulation to clinical trials.

Tocosol® paclitaxel injected as a 15 min i.v. infusion without premedication in cancer patients in a phase I study revealed a 20-times higher C_{max} and 4-times higher mean AUC as compared to previously reported pharmacokinetic parameters for Taxol® injected as a 3 h i.v. infusion [155]. The Tocosol® paclitaxel has also shown proportinal increase in C_{max} and AUC with increasing doses (in the 25–225 mg/m^2 range tested). Interestingly, in another clinical trial comparing Tocosol® paclitaxel as a 15 min infusion vs Taxol® as a 3 h infusion at equal doses (175 mg/m^2) in patients with solid tumors, 67% and 108% higher unbound (not bound to formulation and to plasma proteins) and total paclitaxel exposure, respectively, were observed for Tocosol® paclitaxel comparatively to Taxol®, while both formulations led to a comparable terminal half-life [156,157]. In a dose escalation phase I study, Tocosol® paclitaxel could be administered up to 225 mg/m^2 every 3 weeks.

Tocosol® paclitaxel was administered at 80, 100 or 120 mg/m^2 in weekly schedules in phase IIa studies (see review by [154]). Objective responses were seen in patients with ovarian (16%), colorectal (6%), NSCLC (22%), bladder (17%) cancers, and in platinum-resistant ovarian cancer (31%) [158,159]. Neutropenia was the major hematologic toxicity observed in all clinical studies, and neuropathy (not severe grade-4 type) was the non-hematological toxicity observed (see review by Wang [160]). No toxicity related to vitamin E or other excipients was noted [158]. After these phase IIa and IIb results, Sonus pharmaceuticals had initiated a pivotal 2-arm phase III trial [161], comparing Tocosol® paclitaxel to Taxol® in metastatic breast cancer patients on a weekly dosing schedule in September 2005. However, this phase III trial did not succeed in

meeting the primary end point of non-inferiority on objective response rate (ORR) when compared to the Taxol® control arm. The results showed an objective response rate of 37% with Tocosol® paclitaxel versus 45% with Taxol® ($p = 0.085$). Tocosol® paclitaxel arm showed a significantly higher neutropenia and febrile neutropenia than the Taxol® arm, while no statistically significant differences in neuropathy were observed between the two arms. Such higher toxicity observed with Tocosol® paclitaxel, has been explained using compartment modeling based on population pharmacokinetic methodology [162]. The model predicted the existence of drug loaded nanodroplets of Tocosol® paclitaxel in plasma suggesting prolonged drug release described by a paclitaxel solubility-limited process, and that the drug release was saturable. Afraction of the emulsion dose (~9.8%) was predicted to enter directly into the deep peripheral compartment. The release of the dose fraction into the deep peripheral compartment increases the unbound AUC in this compartment and may have contributed to the difference in toxicity, as compared to Taxol® [162]. The above described clinical results have led to the discontinuation of the phase III study (OncoGeneX website).

2.2.2.2. Docetaxel emulsion (ANX-514). ANX-514 is an intravenously injectable lyophilized nanoemulsion formulation containing docetaxel, developed by Adventrx pharmaceuticals. This PS80/ethanol-free formulation was aimed at reducing the severity and/or incidence of hypersensitivity reactions associated with Taxotere® treatment. The objective of the preclinical and clinical studies was to demonstrate the safety and pharmacokinetic bioequivalence of ANX-514 as compared to Taxotere®. The preclinical bioequivalence studies conducted in beagle dogs (at 1 mg/kg dose) revealed, a) bioequivalent pharmacokinetics of ANX-514 as compared to Taxotere® and b) no hypersensitivity reactions including changes in histamine levels and blood pressure, as opposed to Taxotere®, possibly due to the absence of Polysorbate 80 which is not well tolerated in dog [163]. When tested on MDA-MB-435 human breast, H22 hepatoma and S180 murine sarcoma tumor models at equivalent doses (10 mg/kg multiple doses), ANX-514 exhibited similar antitumor activity as compared to Taxotere® [164].

In humans, a comparable overall safety profile has been reported with ANX-514 as compared to Taxotere®, at a single dose of 75 mg/m^2. Recently, the pharmacokinetic equivalence of ANX-514 as compared to Taxotere® was assessed in terms of C_{max} and AUC in an open-label, randomized, crossover phase I study in patients with advanced cancer potentially sensitive to docetaxel (http://clinicaltrials.gov/ct2/show/NCT00664170). In this study of 168 h observation period, ANX-514 showed increased plasma levels of docetaxel up to 10 min after completion of the infusion, which was considered not up to the benchmark regulatory standards for bioequivalence, whereas in the later time points, pharmaceutical equivalence with Taxotere® was observed. However, if such pharmacokinetic differences in the initial time points have clinically relevant influence on the safety and efficacy of ANX-514 is not known.

2.3. Third generation taxanes drug delivery systems

The prime objective of the 3rd generation of taxane drug delivery systems is to intentionally modulate the pharmacokinetics of taxanes by a better controlled or sustained drug release after intravenous administration, and/or an improved delivery of the drug in the tumor, either a) by a non-covalent association of the taxane to the carrier, or b) by chemical linkage of taxane with the drug carrier (prodrug approach). The term "drug delivery system" appears to be more appropriate than "formulation" here since "formulation" is restricted to non-covalent association. Out of a large variety of carrier-mediated prodrugs designed for taxanes, only three prodrugs of paclitaxel/docetaxel have reached the clinical testing stage [165–171]. Also, since our purpose is to outline the link between the physicochemistry and the preclinical and clinical biopharmacy data, this review is restricted to these two prodrugs in addition to the non-covalent association cases of Abraxane®, NK105, and BIND-014 (see Table 2).

2.3.1. Non-covalent approach

2.3.1.1. Albumin-bound paclitaxel nanoparticle (Abraxane®). Abraxane® (currently commercialized by Abraxis Biosciences) is a formulation of paclitaxel associated to human serum albumin (HSA) nanoparticle of ~ 130 nm mean size prepared by high pressure homogenization [172]. Abraxane® is commercially available as a sterile lyophilized powder, at a paclitaxel:HSA ratio of 1:9 w/w, for reconstitution in 0.9% sodium chloride solution for injection prior to intravenous infusion. Abraxane® has taken advantage of the carrier properties of albumin based on the non-covalent and reversible binding to paclitaxel. The claimed benefits of Abraxane® over Taxol® include a) reduced infusion time (30 min vs. 3 h for Taxol), b) low necessity of premedication, as opposed to Taxol®, attributed to the lower incidence or absence of hypersensitivity reactions, c) improved efficacy linked to the ability to deliver a 49% higher dose of paclitaxel than Taxol, without compromising safety. Abraxane® is indicated for the treatment of breast cancer after the failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy (prior therapy should have included an anthracycline unless clinically contraindicated).

From a pharmacokinetic perspective, Abraxane® has shown particular advantages over Taxol®. In a comparative randomized crossover pharmacokinetic study conducted in human patients with solid tumors, Abraxane® administered at a 260 mg/m^2 single-dose as a 30 min i.v. infusion has resulted in a 3.8-fold higher C_{max} for paclitaxel as compared to a 175 mg/m^2 single-dose of Taxol® injected as a 3 h i.v. infusion [173]. The overall total paclitaxel exposure was comparable for both treatments due to the increased clearance of paclitaxel after Abraxane® injection, despite a higher C_{max} observed initially, compared to that of paclitaxel after Taxol® injection. Additionally, the mean unbound paclitaxel fraction was ~ 2.7-fold higher after Abraxane® administration as compared to Taxol® [173]. In a phase I clinical study, the C_{max} and AUC showed a dose proportional increase over the 135–300 mg/m^2 dose range, but a trend toward non-linearity was observed at 375 mg/m^2 (the highest dose level tested) after a 30 min i.v. infusion of Abraxane® [174–176]. In this study, the MTD of Abraxane was determined to be 300 mg/m^2 on a 3-week cycle compared to 175 mg/m^2 for Taxol®. Neutropenia and peripheral neuropathy were the taxane-related toxicities observed with abraxane although less frequent than that observed with Taxol®. Overall, this phase I study concluded that Abraxane® could be administered with a shorter infusion time (prone to be more comfortable for the patient) with a favorable toxicity profile without the risk of hypersensitivity reactions thus eliminating the need of premedication. In another comparative clinical pharmacokinetic study, Abraxane® 260 mg/m^2 injected as a 30 min i.v. infusion was compared to Taxol® 175 mg/m^2 as a 3 h i.v. infusion on a 3-week cycle. Abraxane® showed a 6.5-fold higher C_{max} as compared to Taxol®, while both the formulations exhibited comparable half-lives (21.6 h for Abraxane® and 20.5 h for Taxol®) [177]. The mean paclitaxel AUC values were also similar for both formulations, while the clearance and volume of distribution were significantly higher for Abraxane® as compared to Taxol® (21.13 vs 14.76 L/h/m^2, and 663.8 vs 433.4 L/m^2). These differences between Taxol® and Abraxane® could be attributed to the previously described plasma sequestration effect of Cremophor EL that contribute to the decreased peripheral distribution of paclitaxel and hence reduced accessibility to the tissues, as opposed to Abraxane®. Administration of Abraxane® in a once-a-week schedule for 3-weeks has also revealed proportional increase in AUCs with doses (80–200 mg/m^2 tested). The mean plasma half-life ranged from 15 to 18 h, and the clearance ranged from 22 to 30 L/h/m^2 (except for 200 mg/m^2 dose with the clearance value of 18 L/h/m^2). The observed relatively large volume of distribution of paclitaxel exceeded total body water, indicating that Abraxane® was extensively distributed and/or bound to tissue and extravascular proteins [178].

In a multicentric phase II study conducted on breast cancer patients, Abraxane® injected at 300 mg/m^2 as a 30 min i.v. infusion every

3-weeks without premedication resulted in significant antitumor activity with 48% overall response rates, while median time to progression was 26.6 weeks and median survival was 63.6 weeks. No hypersensitivity reactions were observed despite the absence of premedication, but typical taxane-related toxicities were observed such as grade 4 neutropenia (in 24% patients), grade 3 sensory neuropathy (in 11% patients), and grade 4 febrile neutropenia (in 5% patients) [179].

The better efficacy and favorable toxicity profile of Abraxane® as compared to Taxol® has been demonstrated in a comparative phase III trial conducted on breast cancer patients [180,181]. In this trial comparing the administration of 260 mg/m^2 of Abraxane® without premedication to 175 mg/m^2 of Taxol® with premedication, as 3-week cycles, Abraxane® demonstrated a significantly higher response rates compared to Taxol® (33% vs 19%, respectively) and a significantly longer time to tumor progression (23.0 weeks vs 16.9 weeks, respectively). On the other hand, the administration of Abraxane® resulted in significantly lower incidence of grade 4 neutropenia as compared to Taxol® (9% vs 22%, respectively), while grade 3 sensory neuropathy was more common after Abraxane® than after Taxol® treatment (10% vs 2%, respectively). The favorable results of this phase III study, especially better efficacy and safety as compared to Taxol®, have led to the approval of Abraxane® by the FDA for metastatic breast cancer treatment in January 2005, and by the Therapeutic Product Directorate of Health Canada in June 2006 for metastatic breast cancer, including use as a first-line agent [182].

Apart from the pharmacokinetic advantage over Taxol®, the primary contributing factor, other advantages have been claimed for Abraxane® such as: a) endothelial transcytosis of paclitaxel through glycoprotein 60 kDa (gp60) receptor and b) enhanced tumor deposition of paclitaxel mediated by binding of albumin to SPARC (Secreted Protein Acid and Rich in Cysteine). Endothelial transcytosis of paclitaxel is thought to be facilitated by albumin binding to the cell surface gp60 receptor (albondin) that in turn binds to an intracellular protein caveolin-1 resulting in the formation of caveolae (invagination of cell membrane to form transcytotic vesicles) (see review by Hawkins et al. [183]). This has been demonstrated in vitro using radiolabeled paclitaxel. The endothelial binding and transcytosis of paclitaxel were markedly higher for Abraxane® as compared to Taxol®, while the transcytosis was inhibited by the methyl β-cyclodextrin, a known inhibitor of endothelial gp60 receptor/caveolar transport [184]. According to this claimed advantage, as opposed to Cremophor EL which inhibits the binding of paclitaxel to endothelial cells and albumin, the human serum albumin plays a role in Abraxane® formulation, at least in part, enhancing the tumor delivery of the administered paclitaxel. According to the second claimed advantage, Abraxane® enhances the tumor transport and accumulation of paclitaxel by binding of albumin to a 43 kDa SPARC, an extracellular matrix glycoprotein overexpressed in a variety of cancers [185–187], described as playing an important role in tumor progression and metastasis [188]. SPARC, induced by hypoxia and acidity, can be produced by both cancer cells and the reactive stromal cells, and was found to be highly expressed in the tumor–stroma interface of the invading tumors [189]. The pancreatic cancer cells that generally overexpress SPARC, especially in the stroma described as forming a tough barrier over the pancreatic cancer cells limit the drug penetration. Abraxane® has been shown to cause stromal collapse (collapse of the stromal structure), to increase the tumor accumulation and is thought to enhance the efficacy of the co-administered gemcitabine [190]. The median time to progression-free survival (PFS) for the combination of Abraxane® and gemcitabine increased by 2 months as compared to Gemcitabine alone (7.9 months vs 5.9 months). Moreover, the median progression-free survival increased from 4.8 months for SPARC-negative patients to 6.2 months for SPARC-positive patients [191,192], further supporting the possible role of albumin in increasing the antitumor activity of abraxane through SPARC-binding. Nevertheless, further molecular and cellular evidences would be of interest to confirm SPARC expression as a predictive biomarker. Overall, Abraxane® has shown efficient activity in a variety of cancer patients, alone or as combination therapy, including pancreatic [193,194], head and neck [187], previously-treated metastatic esophageal cancers, non-small cells lung cancer, small cells lung cancer [195,196] and breast cancer [180,197].

In summary, the superior efficacy of Abraxane® over Taxol® was attributed, apart from the ability to inject 49% higher dose of paclitaxel, to the following reasons; a) improved pharmacokinetic profile including an increased unbound drug concentration, high volume of distribution and relatively rapid clearance as compared to Cremophor EL-based Taxol® formulation, and b) binding of the albumin to the albumin receptors at the cell surface and subsequent initiation of transcytosis of nanoparticle-bound and unbound paclitaxel across the endothelial cell into the interstitial space, and enhanced accumulation into the tumors potentially mediated by binding of albumin to SPARC, generally overexpressed on a variety of tumors. Although further evidences are worthy of consideration for the definite contribution of gp60 and SPARC proteins in improvement of Abraxane® activity, the enhanced efficacy of paclitaxel administered as Abraxane® are, in the authors opinion, primarily related to the improved pharmacokinetic profile in turn linked to the higher injectable dose of paclitaxel over the Cremophor EL-based formulation Taxol®.

Abraxane® (paclitaxel albumin-bound nanoparticles) has also shown a superior efficacy over the subsequent taxane Taxotere® (Polysorbate 80-based docetaxel formulation). In a comparative phase III clinical trial conducted on previously untreated breast cancer patients, Abraxane® i.v. infused at 100 mg/m^2 weekly or 150 mg/m^2 weekly was compared to a Taxotere® 100 mg/m^2 3-week schedule [198]. Interestingly, 150 mg/m^2 weekly Abraxane® demonstrated significantly longer progression-free survival (PFS) that Taxotere® (median, 12.9 months vs 7.5 months, respectively). Grade 4 neutropenia occurrence was more frequent in Taxotere®-treated patients (in 75% patients) as compared to Abraxane®-treated patients (in <10% patients). However, the occurrence of peripheral neuropathy was similar for both treatments. The results of this phase III clinical trial suggests that formulation related biopharmaceutical properties could be a key factor in taxanes ranking.

Although the superiority of Abraxane® over Taxol® in clinic was attributed to the various probable mechanisms described above, the physicochemistry differences between Abraxane® and Taxol®, and its translation into pharmacokinetic differences of these two formulations cannot be fully elucidated from a literature review. Some of the physicochemical aspects would be worthy of clarification such as i) the release rate of paclitaxel from the albumin nanoparticles and the factors influencing drug release, ii) the association of paclitaxel to the albumin nanoparticles delivered to the tumor, and iii) the binding of paclitaxel to the albumin nanoparticles as compared to circulating albumin and the potential competition between the endogenous and exogenous albumin carrier. A better insight into the physicochemistry of Abraxane® and its relation to the pharmacokinetics would be prone to further improve the understanding of this drug delivery system and to allow, from a physicochemical perspective, comparison with other drug carriers.

2.3.1.2. NK105. NK105 is a paclitaxel loaded poly(ethylene glycol)–poly(aspartic acid) block copolymer micelle formulation. The poly(aspartic acid) block in the copolymer was substituted by the 4-phenyl-1-butanol by an esterification process in order to increase the hydrophobicity of the block and potentially increase the affinity of the hydrophobic drug toward this block [199]. NK105 has been manufactured by a self-association process to obtain micelles of ~85 nm mean diameter (size range 20–430 nm). In this micellar formulation, paclitaxel concentrates in the hydrophobic modified poly(aspartate) block that forms the micelle core while the hydrophilic PEG constitutes the outer shell of the micelle. This nano-assembly is comparable to that of Genexol-PM micelle. The PEG moiety of the micelle is accounted for conferring stealth property to the micelle thereby minimizing the recognition of the carrier by the Mononuclear Phagocytic System (MPS) following i.v. injection leading to the long circulating property of the micelles.

PEGylated polymeric nano-carriers have been described as exhibiting prolonged circulation time due to the delayed capture by the reticulo-endothelial system [200,201]. The molecular weight of NK105 is ~20,000 g/mol including a PEG block of 12,000 g/mol and a modified polyaspartate block of 8000 g/mol. The drug product is a freeze dried formulation with noticeably high paclitaxel loading of ~23% w/w [199,202,203].

In preclinical studies, the i.v. injected NK105 showed a significantly higher C_{max} and AUC (~15-fold and ~65-fold, respectively) as compared to Taxol® at equivalent doses. NK105 has also exhibited a 4–6 times longer terminal half-life, a very low steady state volume of distribution (100-fold lower than the volume of distribution observed for Taxol®) and a lower clearance, consistent with the prolonged residence of this micellar formulation in the systemic circulation. Owing to its pharmacokinetic property, NK105 showed a markedly higher and prolonged tumor accumulation in vivo in colon-26 tumor bearing mice. The C_{max} and AUC of NK105 in tumors were 3- and 25-times higher, respectively, as compared to Taxol®. As a result, NK105 demonstrated a significantly improved antitumor activity as compared to Taxol®, and comparable activity at a 4-fold lower equivalent dose of Taxol® on subcutaneously grafted HT-29 colon tumors in mice. Moreover, lower neuropathy inducing potential was demonstrated for NK105, as compared to Taxol®, in preclinical models. The improved drug delivery performance of NK105 as compared to Taxol® may be due to various reasons such as a) better stability of the micelles upon dilution in the blood, b) long circulating property of micelles attributed to the PEG block, c) sustained paclitaxel release from the micelle in vivo possibly due to the higher affinity of drug for the carrier and d) increased tumor accumulation favored by the enhanced permeability and retention (EPR) effect which facilitates passive accumulation of long circulating micelles in the tumor.

In a phase I study carried out in patients with refractory solid tumors, the MTD of NK105 was found to be 180 mg/m^2, while the recommended dose for phase II was 150 mg/m^2 as a 1 h i.v. infusion every 3 weeks without premedication [204]. In this study, NK105 showed a proportional increase in C_{max} and AUC with dose in the 10 to 180 mg/m^2 tested range. Consistent with the data obtained in preclinical studies, NK105 injected as 150 mg/m^2 dose showed a 15-fold higher AUC as compared to Taxol® injected at 210 mg/m^2 (the standard dose in Japan) indicating that the distribution of the micelles is mostly restricted to the vascular compartment. In addition, the volume of distribution and clearance were considerably lower than those reported for Taxol®. The pharmacokinetic parameters of NK105 differ from those reported for Abraxane® and Genexol-PM, since NK105 formulation exhibited a lower volume of distribution and clearance. Although the recommended dose of NK105 is lower than that of Taxol®, a significantly higher AUC is expected to result in improved efficacy of NK105. Neutropenia was the dose-limiting toxicity in this Phase I study, while neuropathy was of grade-2 type and other non-hematological toxicities of grade-1. Only one of the 19 patients treated with 180 mg/m^2 (MTD) showed grade-2 hypersensitivity reaction.

In summary, NK105 demonstrated improved pharmacokinetics profile as compared to Taxol®, and favorable toxicity profile in this phase I trial. These encouraging phase I results have prompted move into the phase II study for this formulation [205]. In phase II study carried out on patients suffering from advanced or recurrent gastric cancer after failure of first-line chemotherapy, NK105 injected as 150 mg/m^2 every 3 weeks resulted in overall response rate (ORR) of 25%, median progression-free survival (PFS) was 3 months, and median overall survival (OS) was ~14.4 months, suggesting modest activity of this formulation [206]. The major toxicities were grade 3–4 neutropenia (in 64.9% patients), leucopenia (in 17.5% patients), and lymphopenia (in 8.8% patients) [207].

2.3.1.3. BIND-014. BIND-014 is a docetaxel-loaded nanoparticle formulation made of poly(lactic acid)–poly(ethylene glycol)–ACUPA. ACUPA (*S*,*S*-2-[3-[5-amino-1-carboxypentyl]-ureido]-pentanedioic acid) is a small molecule targeting ligand for the prostate-specific membrane antigen (PSMA) expressed on the prostate cancer cells and in the non-prostate solid tumor neovasculature [208]. BIND-014 is composed of copolymer made of $PLA_{16\ kDa}$ and $PEG_{5\ kDa}$ and PLA16–PEG5–ACUPA (97.5% PLA–PEG and 2.5% PLA–PEG–ACUPA of the polymer mass), prepared as nanoparticles having size of ~100 nm, and a 10% w/w docetaxel loading.

Optimization of nanoparticles composition was achieved by formulating a combinatorial library of several nanoparticle compositions having different physicochemical characteristics, such as, polymer composition and molecular weight, nanoparticles size and surface characteristics, targeting ligand density, etc., obtained using nanoprecipitation method [208]. In the in vitro drug release studies (carried out using dialysis tube method with PBS containing 2.5% betacyclodextrin as release medium), the docetaxel-loaded nanoparticles (DTNPs) with different composition showed a different drug release kinetic. The 50% of the docetaxel release from DTNPs varied from 6 h to 45 h depending on the nanoparticles copolymer composition. Such differences in release kinetics were also correlated with the in vivo plasma concentrations of these nanoparticles, in which the nanoparticles with slow in vitro docetaxel release showed slower docetaxel clearance in vivo after single dose i.v. injection to rats. When compared to the commercial docetaxel formulation (made of Polysorbate 80 and ethanol), at equivalent doses, the BIND-014 showed a 670-fold higher total docetaxel AUC, 844-fold lower clearance, and 684-folds lower volume of distribution, suggesting the prolonged systemic circulation of the nanoparticles formulation. The nanoparticles formulation (^{14}C-labeled) also showed lower level of distribution to liver and bone marrow relative to plasma, while the distribution to spleen was higher than in plasma especially at 12 and 24 h post-injection [208].

The nanoparticles formulation was found well tolerated up to 2000 mg/kg (12,000 mg/m^2) in rat following single dose i.v. injection, with no abnormal clinical observations, blood chemistry parameters and body weight changes. Following i.v. treatment to PSMA-expressing human prostate tumor (LNCaP)-bearing mice, BIND-014 exhibited a statistically significant, although not remarkable, antitumor efficacy as compared to the non-targeted nanoparticles (without ACUPA), while the efficacy was similar to that of the non-targeted nanoparticles when tested on PSMA non-expressing tumors such as breast (MX-1) and non-small cell lung cancer (NCI-H460) xenograft bearing mice. The antitumor efficacy of the BIND-014 and non-targeted nanoparticle formulations was found remarkably higher only in the MX-1 tumor bearing mice [208]. The tumor distribution data (in LNCaP tumor bearing mice) revealed that the concentration of deocetaxel administered as BIND-014 was ~7-fold higher vs commercial docetaxel formulation at 12 h post-injection, but at 2 h post-injection the docetaxel concentration in tumor for these two formulations was not very different, suggesting the accumulation of the nanoparticle formulation with time in the tumor.

BIND-014 showed a consistent plasma pharmacokinetic profile across the three different species, such as, tumor-bearing mice, healthy rats and cynomolgus monkeys. In addition, in these species, the BIND-014 showed dose proportional increase of C_{max} and AUC for the tested dose range.

In the recently initiated phase I clinical study (NCT01300533) on patients with different solid tumor types [208], the BIND-014 injected as i.v. infusion showed higher plasmatic concentrations than that of commercial docetaxel formulation indicating the prolonged systemic circulation, and also a dose proportional pharmacokinetics at the doses ranging from 3.5 mg/m^2 to 75 mg/m^2. Moreover, very interestingly, the BIND-014 administered as i.v. infusion once every 3 weeks showed early signs of efficacy in a couple of patients, starting from doses 5-times lower (docetaxel equivalent) than that of the commercial docetaxel formulation, suggesting the clinical benefit of the nanoparticle approach.

2.3.2. Covalent approach

2.3.2.1. Opaxio™ (paclitaxel–poly(glutamic acid)). Opaxio™ is a peptide polymer conjugate of paclitaxel synthesized by covalent coupling of

poly(glutamic acid), a biodegradable polymer, onto the 2′-OH function of paclitaxel via an ester linkage (Fig. 5a). In Opaxio™, paclitaxel is chemically bound to poly(L-glutamic acid) at a ratio of ~37% w/w, which is equivalent to about one paclitaxel molecule per 11 glutamic acid residues, while the median molecular weight of this polymer is 48,000 g/mol. Opaxio™ was produced as a neutral form with all the carboxylic acid functions of the polymer protonated [209]. In a mild acidic solution (at approx. pH 6.0), complete ionization of Opaxio™ leads to solubilization. Supplied as a freeze-dried product, Opaxio™ is reconstituted as an injectable clear solution for intravenous administration.

After i.v. administration of ^{3}H-paclitaxel coupled to the polymer at equivalent dose of ^{3}H-paclitaxel as Taxol® formulation in mice bearing ovarian carcinoma subcutaneous tumors, Opaxio™ showed, as compared to Taxol®, a 11 times longer half-life [210], an ~101 times higher AUC and a 5-times higher tumor accumulation [211]. The plasma terminal elimination half-life of Opaxio™ was ~1.7-fold higher than paclitaxel administered as Taxol® (60.1 h vs 34.6 h, respectively), and the low volume of distribution suggested the large confinement of the Opaxio™ to the systemic circulation, and partly to the extracellular body fluids. The concentration of free paclitaxel measured as percent of total taxanes in tumors after Opaxio™ treatment increased considerably with time from 4% to 17% over 144 h, suggesting the contribution of prolonged circulation of prodrug on its progressive accumulation in the tumors. The potential pathways of antitumor activity of Opaxio™ was proposed to be the necrosis of the tumor tissue along with mild apoptotic induction, while the antitumor activity of Taxol® was based on significant apoptosis induction [210]. At the cellular level, Opaxio™ penetrates cells by an endocytosis process, while the release of the active paclitaxel moiety from Opaxio™ could be either by enzymatic hydrolysis in tumor interstitial space, or intracellularly by cathepsin-mediated proteolytic digestion of the polymer backbone [212,213]. After i.v. injection, Opaxio™ showed significant distribution to the macrophage-rich organs like liver and spleen followed by the slow release of the free paclitaxel and its metabolites [214], suggesting a preferential uptake by the phagocytic system. This was further confirmed by the in vitro experiments which revealed the recovery of significant concentrations of the prodrug metabolites such as monoglutamyl- and diglutamyl-paclitaxel in cells with phagocytic activity, as compared to cancer cells [212]. In preclinical studies, the MTD of a single-dose i.v. injection of Opaxio™ was found to be ~120–160 mg/kg equivalent of paclitaxel in mice, which is approximately twice the MTD of Taxol® (80 mg/kg after single dose i.v. injection, reported by Mathew et al. [215]). Opaxio™ has shown a significantly greater antitumor activity as compared to Taxol® against Oca-1 murine ovarian carcinoma, and also against 13762F rodent breast tumors in vivo (the MTD in rats was 60 mg/kg equivalent of paclitaxel) [210].

In human, Opaxio™ showed a biphasic decline of plasma concentration followed by a prolonged distribution phase and a slow terminal phase with drug detected in plasma up to 3 weeks at 200 mg/m^2 dose [216,217]. The release of free paclitaxel was slow and progressive and its plasma concentration declined in a biexponential manner in parallel to the Opaxio™ concentrations, suggesting that the disposition of free paclitaxel may be limited by the conjugate cleavage rate [217]. Various Phase I studies were carried out on Opaxio™ either as a single agent or in combination with platins at different dosing schedules [218–222]. Opaxio™ as a single agent injected as a 30 min i.v. infusion in weekly, 2-weekly or 3-weekly schedules without premedication, led to MTDs of 70 mg/m^2, 177 mg/m^2, and 233 mg/m^2, respectively. Opaxio™ exhibited a long plasma half-life of 185 h in the phase I study [222] (while the AUC of free paclitaxel was ~1–2% of the AUC of the conjugate) and a low volume of distribution, consistent with the observations in preclinical studies [223], suggesting that the prodrug is quite stable in blood and gradually releases the paclitaxel. Therefore, despite the considerably shorter infusion time, as compared to Taxol®, the peak plasma concentrations of free paclitaxel released from Opaxio™ were significantly lower than that observed after 3 h infusion of Taxol®, at similar

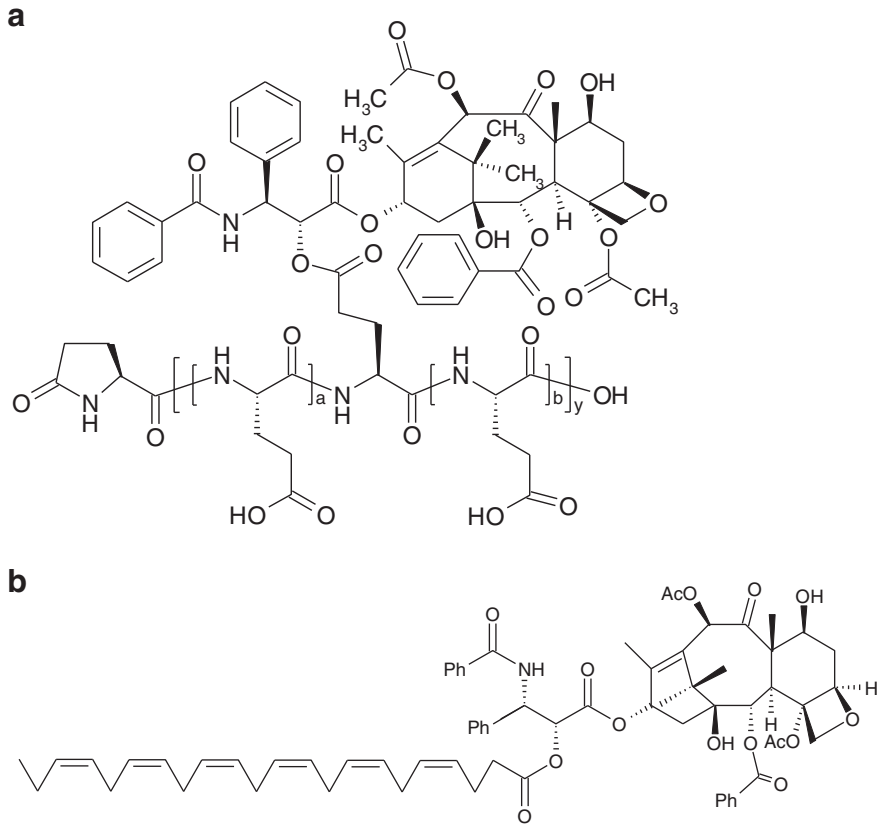

Fig. 5. Chemical structures of a) polyglutamic acid–paclitaxel (Opaxio™), and b) docosahexaenoic acid–paclitaxel (Taxoprexin®).

dose levels. However, because the terminal half-life of free paclitaxel released from Opaxio™ is longer than that for Taxol®, the AUC of free paclitaxel released from Opaxio™ became comparable to that of Taxol® [224,225]. Neutropenia and neuropathy were the dose-limiting toxicities of Opaxio™, with no notable alopecia as opposed to Taxol® [223,226,227]. Alopecia has been considered as the most traumatic and distressing side-effect of cancer chemotherapy [228], which was attributed to the deposition of anticancer drugs in the hair follicles [229]. Negligible or absence of alopecia after Opaxio™ treatment may possibly be due to its reduced concentration in the scalp follicles, since the alopecia associated with Taxol treatment was linked to the accumulation of paclitaxel in the scalp [230]. Absence of alopecia may offer certain optimism to the patients for the use of Opaxio™ over Taxol, since alopecia has been reported to be severe and irreversible in some patients treated with paclitaxel [231]. As neurotoxicity was observed at doses higher than 175 mg/m^2, this dose was proposed for phase II evaluation.

In phase II studies carried out on patients with different tumor types, mostly at a dose of 175 mg/m^2 infused over 10–30 min without premedication, Opaxio™ was reasonably well tolerated with dose-limiting toxicity similar to that of taxanes, such as neutropenia and neuropathy, and has also demonstrated a therapeutic activity comparable to that of other single agents in the respective cancer types. However, the overall hematological toxicity especially grade 3 and grade 4 neutropenia of Opaxio™ administered at 175 mg/m^2 as a 10 min i.v. infusion once every 3 weeks was relatively low compared to that of Taxol®. In some studies, especially those carried out on metastatic breast cancer patients, severe hypersensitivity reactions occurred after Opaxio™ treatment [232]. The observed hypersensitivity was uncommon in other studies, and thus was linked to the potential hormonal differences in patients. Overall, the convenient administration (shorter infusion time) and the favorable toxicity profile of Opaxio™ in Phase II studies has prompted its further evaluation in STELLAR (Selected Targeted Efficacy in Lung Cancer to Lower Adverse Reactions) Phase III trials on NSCLC patients. STELLAR 3 and STELLAR 4 trials included Opaxio™ as first-line treatment, while STELLAR 2 included Opaxio™ as second line treatment [233–235]. Opaxio™ (175 mg/m^2 or 210 mg/m^2 as 10–20 min infusion) was compared as a single agent with docetaxel (75 mg/m^2 as 1 h infusion) in STELLAR 2 trial. Opaxio™ (210 mg/m^2 as 10 min infusion every 3 weeks) combined to carboplatin was compared to Taxol® (225 mg/m^2 as 3 h infusion every 3 weeks) combined to carboplatin in STELLAR 3 trial, while Opaxio™ (175 mg/m^2 every 3 weeks) was compared as a single agent with gemcitabine or vinorelbine in STELLAR 4 trial. In all these trials, Opaxio™ showed an efficacy comparable to that of the control arms, while in STELLAR 4 trial, a trend towards improved survival of Opaxio™-treated women of less than 55 years age compared with the women of control arms of gemcitabine or vinorelbine was observed. This was attributed to the differences in hormone levels in premenopausal and postmenopausal women. In all of these phase III trials, Opaxio™ was associated with considerably lower hematological toxicity as compared to the other standard single agents tested like gemcitabine, vinorelbine or docetaxel. Especially, comparatively to docetaxel (75 mg/m^2), Opaxio™ showed a significantly lower neutropenia, grade 3 or 4 neutropenia, febrile neutropenia and anemia. The neurotoxicity caused by Opaxio™ was found to be dose-dependent with a considerably higher neuropathy especially grade-3 type was evident at 210 mg/m^2 as compared to 175 mg/m^2. This result suggests that a slow accumulation of Opaxio™ may occur in the peripheral nerves (also linked to the longer terminal half-life of Opaxio™) [225]. Overall, the phase III trials have revealed a favorable and better toxicity profile with comparable efficacy to that of the standard agents for lung cancer, and also a better efficacy in premenopausal women possibly attributed to the high estrogen levels. The preclinical rationale for this observation was that the estrogen levels regulate the expression of the lysosomal enzyme cathepsin B, a major metabolizing enzyme of poly(L-glutamic acid) backbone in Opaxio™, and that higher estrogen levels in premenopausal women probably have resulted in increased antitumor activity of Opaxio™ [236]. In order to confirm the influence of estradiol levels on Opaxio™ efficacy, a clinical trial has been initiated to compare Opaxio™ combined to carboplatin to Taxol® combined to carboplatin in women with NSCLC, who have estradiol levels >30 pg/mL (clinical trial identifier: NCT00576225). In parallel, a phase III trial is ongoing, with the primary objective to verify if carboplatin addition to Opaxio™ could improve the overall survival of the patients compared to those who are treated with Taxol® combined to carboplatin (clinical trial identifier: NCT00551733).

2.3.2.2. Taxoprexin® — docosahexaenoic acid–paclitaxel (DHA–paclitaxel). Taxoprexin® is a fatty acid conjugate of paclitaxel synthesized by covalent coupling of DHA (docosahexaenoic acid) onto the 2′-OH function of paclitaxel molecule (Fig. 5b). DHA is an omega-3, C_{22} natural polyunsaturated fatty acid having six cis double bonds. DHA is a constituent of cell membrane, found in human milk, and classified as a nutritional additive by the FDA. It is generally believed that the fatty acids are required for tumor growth and hence are rapidly taken up by tumors from systemic circulation [237–239]. Accordingly, DHA is rapidly taken up by the cells and incorporated into the membrane phospholipids [238]. DHA was also shown to display anticancer activity on various tumors in vitro and in vivo. The mechanism of such activity was found to be apoptosis induction [240,241].

Due to poor aqueous solubility exhibited by DHA–paclitaxel, it was solubilized using 10% Cremophor EL + 10% ethanol + 80% normal saline. Thus, Taxoprexin® formulation contains ~81% less Cremophor EL than that of Taxol® on a molar basis. When tested for microtubule assembly in solution, DHA–paclitaxel was inactive in vitro. However, it induced the formation of microtubule bundles in cell culture indicating that the prodrug is inactive per se, and needs to be hydrolyzed to release the active paclitaxel moiety. In vitro, DHA–paclitaxel demonstrated >99.6% binding to human plasma proteins in a concentration-independent manner as compared to 86% protein binding for paclitaxel administered as Taxol®. The high protein binding was attributed to the influence of DHA, because fatty acids have been reported to show extensive protein binding [242]. The drug was essentially bound with a high affinity to human serum albumin and alpha acid glycoprotein. During preclinical assessment, DHA–paclitaxel showed a considerably greater tolerance as compared to Taxol® in mice. The MTD after i.v. daily injection for 5 days was 120 mg/kg for Taxoprexin® (equivalent to 88 mg/kg paclitaxel) as compared to 20 mg/kg for Taxol®. When injected at the MTD or at a dose 50% lower than the MTD, Taxoprexin® showed a significant improvement in tumor inhibition and antitumor activity in M109 murine lung tumor bearing mice model and in HT-29 colon carcinoma xenograft model, as compared to Taxol® formulation injected at the MTD [243]. The significant improvement of the antitumor activity of Taxoprexin® was attributed to its more favorable pharmacokinetic profile (lower Cmax and higher AUC) as compared to Taxol®. When injected at equimolar dose or at the MTD in mice, Taxoprexin® showed long circulation in blood followed by a sustained release of paclitaxel, leading to a significantly higher AUC as compared to Taxol®. Taxoprexin® has also shown progressive and longer accumulation duration into tumors. The mean tumoral AUC of paclitaxel released from Taxoprexin® was ~5.8-fold higher, as compared to Taxol®, suggesting that this prodrug leads to an improved delivery to tumors. Overall, the observed significant efficacy and improved tolerance of Taxoprexin® was attributed to the sustained release of the drug in plasma associated to a prolonged accumulation in the tumors and the maintenance of the concentration of the active paclitaxel moiety above the tumor growth inhibition concentration for a longer time.

In clinical pharmacokinetic study, Taxoprexin® was tested in a 200–1100 mg/m^2 dose range (equivalent to 147–807 mg/m^2 paclitaxel) injected as a 2 h i.v. infusion (using inline filters). At the low doses (200 and 400 mg/m^2) plasma concentrations were not measurable after the completion of infusion, while at the high doses, the unbound DHA–paclitaxel exhibited a linear pharmacokinetics. The majority of

DHA–paclitaxel was found to be confined to plasma with a negligible distribution into blood cells fraction, while the drug showed extensive binding to the plasma proteins (especially albumin and α_1-acid glycoprotein), consistent with the in vitro results. The paclitaxel released from Taxoprexin® was found to decline in parallel to Taxoprexin®, suggesting that its elimination is conjugate cleavage rate limited. The unbound paclitaxel plasma concentration (not bound to formulation and plasma proteins) after Taxoprexin® injection was dose-dependent, potentially due to the binding of DHA–paclitaxel to plasma proteins [244]. In a Phase I study carried out on patients with advanced refractory solid tumors in the 200–1100 mg/m^2 dose range (equivalent to 147–807 mg/m^2 paclitaxel), injected as a 2 h i.v. infusion every 3 weeks with premedication, DHA–paclitaxel showed a dose proportional increase in AUC [245]. However, the exposure to paclitaxel released from Taxoprexin® increased disproportionately with increasing dose level of Taxoprexin®, while the exposure was lower for a prolonged time. Taxoprexin® injection led to significant paclitaxel plasma concentrations (>0.01 μM) up to 6–7 days, considerably sustained as compared to Taxol®, suggesting that Taxoprexin® is confined principally to the systemic circulation. In summary, Taxoprexin® injected as 1100 mg/m^2/2 h (the recommended dose for phase II, equivalent to 807 mg/m^2/2 h paclitaxel), showed a considerably higher half-life (7-fold), lower volume of distribution (52-fold) and lower clearance (290-fold), while the paclitaxel released from DHA–paclitaxel showed a 5.3-fold longer half-life, 8 to 10-fold lower C_{max}, and comparable AUC, as compared to paclitaxel administered as Taxol® (injected as 135 mg/m^2/3 h). More interestingly, the toxicity profile of Taxoprexin® was different from the previously observed toxicity profile of Taxol®. Taxoprexin® did not cause noticeable neuropathy, arthralgia, myalgia, while the neutropenia was the dose-limiting toxicity. Similar results were obtained in another Phase I trial with Taxoprexin® injected weekly for 3 out of 4 weeks instead of once every 3-week [246]. Taxoprexin® could be injected at least up to 600 mg/m^2 in this weekly schedule with grade-3 hyperbilirubinemia and grade-1 sensory neuropathy, occurring at the highest dose level [246]. Overall, the phase I results of Taxoprexin® revealed a higher injectable dose, a prolonged exposure of paclitaxel, and a more favorable toxicity profile, as compared to Taxol®. These phase I results have prompted phase II study on esophageal metastatic adenocarcinoma patients treated with Taxoprexin® 1100 mg/m^2 (equivalent to 807 mg/m^2 paclitaxel) as a 2 h i.v. infusion every 3-weeks. Taxoprexin® showed a modest activity, not superior to the previously reported activity of Taxol® or Taxotere® [247]. Taxoprexin® showed an objective response rate of 9.4% (as compared to 4–23% and 5–29% with Taxol® and Taxotere®, respectively [248], a median overall survival of 8.7 months and a median time to tumor progression of 2.8 months. Grade 3 to 4 neutropenia and febrile neutropenia were observed in many patients, but severe neuropathy was evident in patients treated with Taxoprexin®. Overall, the phase II results of Taxoprexin® on esophageal adenocarcinoma patients did not demonstrate superiority over Taxol® and Taxotere®. Another phase II trial conducted on NSCLC patients has revealed a median survival of 8.1 months, comparable to standard platinum-based combination chemotherapy. In other phase II studies conducted on hormone refractory prostate cancer patients, and pancreatic cancer patients, Taxoprexin® showed results comparable with those observed previously with other chemotherapeutic agents such as gemcitabine [249,250]. The efficacy of Taxoprexin® as a first-line therapy for metastatic melanoma evaluated in a phase II study in melanoma patients treated in a 500 mg/m^2/week (equivalent to 367 mg/m^2/week paclitaxel) for 5 weeks in 6-week cycle by a 1 h infusion did not exceed the efficacy seen with other single-agent chemotherapies such as dacarbazine [251]. The median survival time was 14.8 months. Less frequent and lesser degree of neuropathy and alopecia was observed with DHA–paclitaxel treatment as compared to that previously reported for Taxol® treatment, while the frequency of grade 3 or 4 neutropenia was lower in this study compared with that of once every 3-week schedule. Various other phase II clinical trials are ongoing using Taxoprexin® as a single agent, in patients with metastatic colorectal carcinoma (NCT00024401), locally advanced, metastatic, or unresectable kidney cancer (NCT00024388), metastatic pancreatic cancer (NCT00024375), and metastatic prostate cancer not responding to hormone therapy (NCT00024414), and a phase III trial on patients with metastatic malignant melanoma (NCT00087776).

2.4. Drug design and drug delivery system design perspective

Taxanes are of particular interest owing to the continuous efforts put to further improve the efficacy and safety profiles of these high medical service drugs. The variety of drug delivery approaches explored, especially for paclitaxel, allows the comparison of designs in a wide spectrum. As described in this review, interesting findings in Discovery and promising preclinical data may not always translate into the expected improvements in clinical proof of concept studies. Therefore, there is a need to better identify the key physicochemical and biopharmaceutical parameters, to understand their inter-relationships and to develop models to extrapolate the animal data to human. From this view point, we restricted this review to Drug Delivery approaches of taxanes that are already assessed in clinic, even though other interesting approaches, currently at the preclinical stage, are prone to bring an added value to oncology.

The primary goal of the first generation of taxanes formulations was to allow the solubilization and injection of the drug, with minimum side-effects related to the solubilizing agent, and a satisfactory reproducibility of the pharmacokinetic parameters. However, as illustrated with Taxol®, a Cremophor EL-based formulation, the delayed dissociation of the drug from the surfactant micelles is prone to alter the drug pharmacokinetics and in turn the efficacy and safety. Thus, when the solubilizing agent present in the formulation acts as a drug carrier after injection, a deviation from the behavior of the free drug in solution is anticipated and, as a consequence, carrier mediated alteration of the pharmacokinetics is likely. This in turn may complicate the extrapolation of the animal data to human and/or the anticipation of the consequences of the modification of parameters such as the infusion time. In addition, the use of surfactants as solubilizing agents, such as cremophor EL and Polysorbate 80, at high concentrations may result in hypersensitivity reactions [133], limiting the injectable dose of the drug which may impact the efficacy of the treatment. The intensity of hypersensitivity reactions may depend upon the injected surfactant concentration/dose. Compared to Taxol®, the concentrations of surfactant per injected dose in case of Taxotere® and Jevtana® are ~6.25-fold and ~38-fold lower, respectively, whereas the surfactant concentration per injected dose of Jevtana® is ~6.2-fold lower, as compared to Taxotere® (see Table 1). Consequently, the lowest injected surfactant quantity per dose in the case of Jevtana®, as compared to Taxol® and Taxotere®, may be related to the very minimal/absence of hypersensitivity in the patients treated with this product.

The side-effects associated to surfactant-based formulations has motivated the design of surfactant-free vehicles compatible with intravenous injection, referred to as the second generation of taxanes formulations. Even though the primary objective was to design a bioequivalent surfactant-free formulation to prevent the hypersensitivity reactions, a different kinetic of the drug release from the carrier after injection may be associated to an unintended modification of the pharmacokinetics and biodistribution, and to a deviation from bioequivalence as observed with docetaxel emulsion (ANX-514). In fact, since the expected role of the second generation formulations is primarily aimed at enabling the intravenous injection of the drug, a quick (i.e. close to immediate) dissociation of the taxane from the solubilizing agent after intravenous injection would be the best option to avoid the variability associated to biopharmaceutical parameters in the release behavior. In this context, a quick release of the drug from the surfactant micelles of the first generation formulations, taken as reference, would have favored the transition to a surfactant free formulation. However, as described earlier, the drug is

not instantaneously dissociated from the micelles after administration of Taxol® and, to a lesser extent, from Taxotere®. According to physicochemical principles, after the i.v. administration of a formulation, the instantaneous dilution into the bloodstream leads to a displacement of the drug/carrier binding equilibrium. When dissociated from the carrier, the drug can bind to the natural circulating carriers such as the plasma proteins and the lipoproteins. As a consequence, a comparable taxane-to-carrier association and release kinetic is needed to design a bioequivalent formulation.

It is generally accepted that only the free drug fraction (i.e. the fraction not bound to the formulation carrier and natural carriers such as blood components) accounts for the pharmacological activity and/or toxicity of the injected drug [252] (see Fig. 6). The variation of the free fraction may also alter the clearance, considering that the drug is metabolized and eliminated in a molecular state (i.e. unbound). Therefore, even if a surfactant free formulation may lead to very minimal/absence of hypersensitivity, a quicker increase of free fraction in the blood is prone to modify the efficacy/safety profile. The more rapid release of paclitaxel from Genexol-PM, as compared to Taxol® micelles, was associated with a higher clearance which is translated into lower AUC at equivalent dose (see Table 3). At the same time, a higher C_{max}, a better accessibility to the tissue and an increased drug concentration in tumor in animal model was observed with Genexol-PM micelles. The absence of hypersensitivity reaction with Genexol-PM supports the role played by Cremophor-EL in the appearance of this side-effect with Taxol®. At the same time, considering that paclitaxel is quickly released from Genexol-PM, neuropathy, myalgia and neutropenia, the dose limiting toxicities of Genexol-PM, may be attributed to the drug itself. It is interesting to note that the quicker release of paclitaxel did not prevent the increase of the injectable dose with Genexol-PM, as compared to Taxol®, probably compensated by a quicker elimination [141].

Nanoxel may exhibit properties comparable to Taxol® but physicochemical and preclinical data are missing to establish correlations. In the case of Abraxane, physicochemical data are missing to assess the impact of the association of the drug to the carrier on the tolerance improvement. The increased unbound concentration and the higher clearance suggest that paclitaxel is released quickly after administration of Abraxane, as compared to Taxol®. Therefore, even though the exposure to total paclitaxel is comparable for Abraxane and Taxol, a potentially higher plasma concentration of the free drug for a shorter period may be beneficial to decrease the incidence of neutropenia. The dissociation of the drug from the carrier may also lead to an increase of the volume of distribution and, as a consequence, to a better concentration of the drug available to diffuse into the tumor. Alternatively, a higher volume of distribution of the albumin nanoparticles as compared to the Cremophor EL micelles may also explain the higher volume of distribution observed with Abraxane®, as compared to Taxol®.

Finally, if the taxane release from the surfactant-free formulation carrier is quicker than the dissociation of the drug from the surfactant micelles, then this difference in behavior should be taken into account and controlled to manage the efficacy/safety.

Another point worthy of consideration is the sustained association of a fraction of the drug to the carrier (i.e. an incomplete release) which may trigger the progressive accumulation of the drug in a compartment undesirable from a safety standpoint, as observed in the case of Tocosol® Paclitaxel emulsion [162]. An accumulation (even of a small fraction of dose) of the carrier-associated drug may result in significant toxicity, especially after repeated injections. Therefore, a particular attention should be paid to the design of the carrier (i) toward its ability to completely release the drug (including through a destabilization/degradation process) and (ii) toward its distribution/accumulation in specific tissues. In fact, if part of the carrier distributes to tissues other than the tumor, it is preferable that the carrier reaches these compartments unloaded, to avoid undesired accumulation of the drug. The quick degradation of the carrier after administration is prone to decrease the fraction of unreleased drug. In this perspective, the quick degradation of the PS 80 [61] and the mPEG–PDLLA copolymer used in Genexol-PM [140] may appear as an advantage. Provided that the carrier exhibits a satisfactory safety profile, the quick release also facilitates the extrapolation of animal data to human since (i) the biodistribution of the carrier is expected to be less critical in terms of efficacy/safety and (ii) the systemic sustained delivery can be more easily compared to an infusion.

Finally, the release kinetic of the drug from the carrier versus the kinetic of the carrier distribution in the organs and how it compares in preclinical models and in human are worthy of consideration when designing a second generation formulation of taxanes. The safety profile of the carrier itself is another key aspect of the formulation design. A high drug loading appears as an advantage since a low amount of carrier is administered to deliver a given dose. Nevertheless, low drug loading

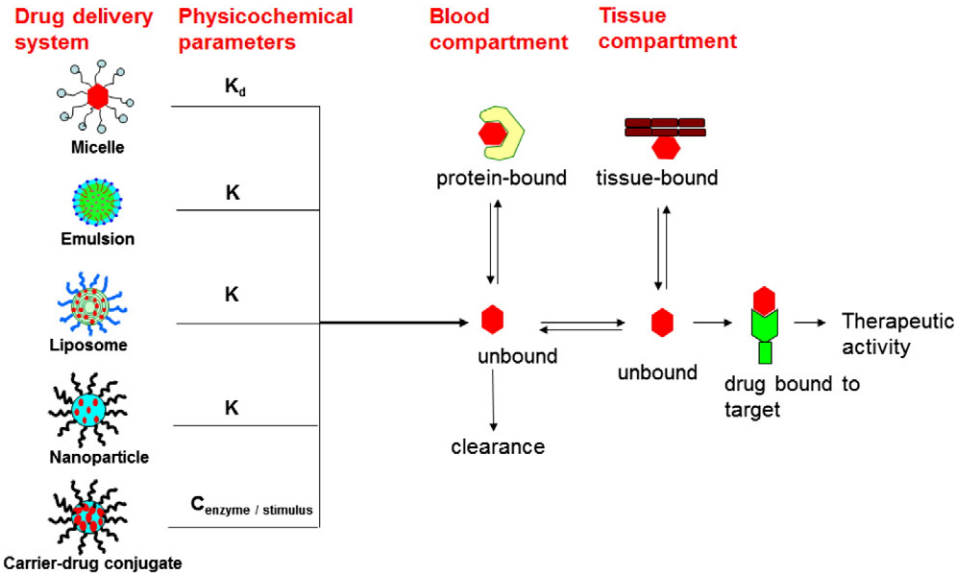

Fig. 6. Parameters controlling the drug release from the carrier after intravenous administration of different drug delivery systems. The drug release from the carrier is controlled by specific rate constants, which inturn influence the unbound drug concentration in the systemic compartment. Note: The size of the different drug carriers shown below may be different ranging from few nanometers to few hundreds of nanometers. K: partition coefficient, K_d: dissociation constant, $C_{enzyme/stimulus}$: enzyme/stimulus concentration.

Table 3
MTD and pharmacokinetic parameters of taxanes formulations.

Taxane	Generation		Drug delivery principle	MTD in preclin. models	MTD in human	Dose for PK in human (mg/m^2)	$t_{1/2}$ (h)	AUC (h*μg/mL)	Vss (L)	Cl (L/h/m^2)	Reference
Paclitaxel	1st surfactant-based	Physicochemical approach	Taxol® — solubilization based on Cremophor EL/ethanol micelle formulation	20 mg/kg injected on 0, 4 and 8 days in mice	175 mg/m^2 as a 3 h infusion every 3-weeks	175	21.0	20.82	n.a.	8.9	Gardner et al. [173]
	2nd surfactant-free		Genexol-PM — solubilization based on mPEG–PDLLA copolymer micelle formulation	60 mg/kg injected on 0, 4 and 8 days in mice	390 mg/m^2 as a 3 h infusion every 3-weeks	300	11.4	11.58	n.a.	29.3	Kim et al. [141]
			NanoXel — solubilization based on PVP-*b*-PNIPAAM copolymer micelle formulation	n.a.							
			Tocosol® paclitaxel emulsion — solubilization in an oily phase dispersed as an emulsion	70 mg/kg in mice	120 mg/m^2 as a 15 min infusion every week	n.a.					
	3rd targeting		Abraxane® — drug physically bound to albumin	n.a.	300 mg/m^2 as a 0.5 h infusion every 3-weeks	260	20	20.32	n.a.	13.2	Gardner et al. [173], Ibrahim et al. [174]
			NK105 — drug carrier based on polyaspartic acid–PEG micelle	n.a.	180 mg/m^2/h infusion every 3-weeks	150	10.6	370	n.a.	0.41	Hamaguchi et al. [204]
			BIND-014 — drug carrier based on polylactic acid–PEG–ACUPA nanoparticle	n.a.	n.a.	3.5–75 reported	n.a.	n.a.	n.a.	n.a.	Hrkach et al. [208]
		Chemical approach	Opaxio™ — covalent coupling of drug to polyglutamic acid	120–160 mg/kg equivalent of paclitaxel after single dose vs 80 mg/kg for Taxol® in mice	70 mg/m^2 as a 10 min infusion every week	70 Conjugated form	15.7	455	1.41	0.16	Mita et al. [221]
						Unconjugated form	16.6	3.15			
					233 mg/m^2 as a 10–20 min infusion every 3 weeks	233 Conjugated taxane	120	1583	6.2	0.28	Boddy et al., [264]
						Unconjugated taxane	10.6	27.8	n.a.	n.a.	
			Taxoprexin® — covalent coupling of drug to docosahexaenoic acid	120 mg/kg vs 20 mg/kg of Taxol®, everyday for 5 days in mice	1100 mg/m^2 as a 2 h infusion every 3-weeks	1100	α-17 β-112	21.0	7.5	0.055	Wolff et al., [245]
Docetaxel	1st surfactant-based		Taxotere® — solubilization based on Polysorbate 80/ethanol micelle formulation	n.a.	115 mg/m^2 as a 2 h infusion every 3 weeks	100	18.5	5.93	95	17	Extra et al., [265]
Cabazitaxel	1st surfactant-based		Jevtana® — solubilization based on Polysorbate 80/ethanol micelle formulation	n.a.	25 mg/m^2 as a 1 h infusion every 3-weeks	25	81.9	1.04	1.99	25	Mita et al. [221]

MTD: maximum tolerable dose, PK: pharmacokinetics, $t_{1/2}$: half-life, AUC: area under the curve, Vss: volume of distribution (steady state), Cl: clearance, n.a.: not available, PEG: poly(ethylene glycol), mPEG–PDLLA: methoxy poly(ethylene glycol)–poly(lactic acid), PVP-*b*-PNIPAAM: poly(vinyl pyrrolidone)–poly(N-isopropyl acrylamide).

does not preclude drug delivery application if the carrier exhibits a satisfactory safety profile, which enables the injection of high amounts of the formulation carrier and associated high drug doses.

Another important aspect from a safety standpoint is the immune stimulation property of the nanosized carrier. It is worth mentioning that, due to their high surface area, nano-objects such as micelles, liposomes or nanoparticles may strongly interact with the blood components such as the complement [109,253–256] and the coagulation systems [257] leading to adverse effects such as acute hypersensitivity and pseudoallergic reactions and formation of thrombi [258] impacting the safety. Therefore, a particular attention should be paid to these nano-objects associated safety aspects in preclinical and clinical studies.

The fraction of drug reaching the tumor cells and further the targeted tubulin primarily depends on the systemic free drug concentration, and on the ability of the concentration gradient to promote the diffusion of the compound into the tumor tissue and the tumor cells. Expulsion from the tumor cells linked to the affinity of the drug for the P-glycoprotein [259] is another keypoint to consider for anticipating the availability of the drug at the target site (Fig. 7). Finally, the binding of the taxane to the targeted tubulin, driven by a binding equilibrium based on the affinity and the local concentration, is revealed by its ex-vivo and in vivo cytotoxicity [260]. As mentioned before, the low binding constant of a drug may be compensated by its higher local concentration when the drug is better delivered. Since, a key requisite to observe the therapeutic efficacy of taxanes is to reach a sufficient drug concentration at the targeted tubulin site [261,262], the third generation drug delivery systems having the potential to achieve this, could be of high therapeutic value.

The drug carrier design needs to be considered from a different perspective for the third generation of taxanes drug delivery systems since the drug should stay associated to the carrier, to be preferentially delivered and released in the tumor. Two kinds of strategies have been explored to achieve this goal: (i) the physicochemistry based drug delivery concept consisting of a non-covalent association of the drug to a nano-assembled carrier such as a polymeric micelle, a liposome or a polymeric nanoparticle and (ii) the chemistry based drug delivery concept consisting of a covalent coupling of the drug to a non-active carrier moiety to result in a soluble or nano-assembled conjugate.

In both the non-covalent and covalent approaches, the prolonged systemic circulation of the drug carrier is prone to increase the chances of the drug to be infused and, when a passive or active targeting strategy is operated, accumulate into the tumor tissue. The long circulating properties are an asset especially when the timescale of release of the drug from the carrier is long as compared to the timescale of elimination and/or capture by the liver and spleen macrophages. Prolongation of the systemic circulation of the nano-carriers could be achieved by covering the surface with hydrophilic polymers such as PEG (stealth effect) [200,201]. From an anatomical and physiological point of view, the vascularization of the tumor and the associated Enhanced Permeability and Retention (EPR) effect [263] have also been taken into consideration to explain the distribution of the drug delivery carrier in the vicinity of the cancer cells. In addition to the long circulating property, surface coupling of a homing device onto the nanocarriers can be considered as a way to increase, in addition to the EPR effect, the probability of retention in the targeted organ/tumor. Finally, all the above distribution factors are combined and it is often difficult, as of today, to delineate their interplay.

It is interesting to note that, inversely, the association of the drug to the carrier may prevent the distribution to an undesired compartment as was observed with Opaxio™ which minimizes the paclitaxel concentration in the scalp follicles.

In practice, it can be anticipated that a partial early release of the drug from the third generation carriers make them share some features of the second generation, in particular when non-covalent approach is considered. In the case of Abraxane®, the pharmacokinetic parameters indicate a rapid release of paclitaxel (higher C_{max} and clearance as compared to Taxol®) (see Table 3) [173] suggesting that, following i.v. injection, paclitaxel dissociates rapidly from the albumin-based carrier. According to the definitions of the taxanes formulations generations proposed here, this falls into the situation of the second generation formulations. However, the efficacy of Abraxane, in addition to the alteration of pharmacokinetic profile, was attributed to its enhanced tumor tissue accumulation preceded by enhanced endothelial trancytosis, facilitated by albumin binding to SPARC and gp60 proteins, respectively [184,187]. In this context, Abraxane can also be considered as a third generation carrier.

A precise control over the release kinetic of the drug from the carrier after i.v. injection is the basis of the design of a second or third generation carrier or the combination of both. If a tissue/tumor-specific drug accumulation is expected, the drug should be associated to the carrier till the moment the carrier reaches the target tissue. At the same time, if efficacy and neutropenia are better compromised with higher plasma concentration of free drug during a shorter period, as described with Genexol-PM, then long circulation of residual drug may be unfavorable, from a safety standpoint.

In the non covalent approach, the drug release from the nanocarrier is driven by its partition coefficient (K) between nanocarrier and the biological milieu. If the drug is partitioned between the carrier and the blood, we can anticipate that the higher is the partition in favor of the carrier, the higher is the dilution needed to displace the partition

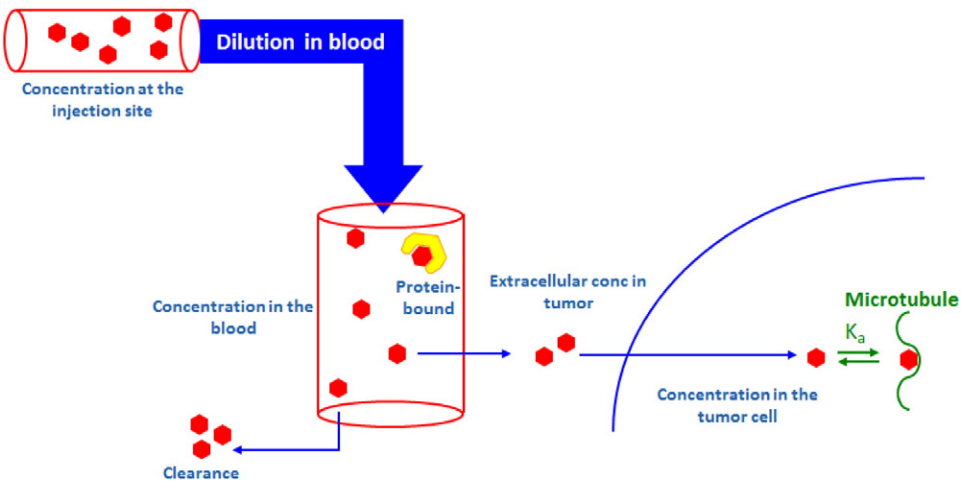

Fig. 7. Depiction of the factors influencing the taxanes accumulation at the target tubulin site. K_a — association constant.

equilibrium and the longer the drug will be associated to the carrier. This potentially results in increased half-life of the encapsulated drug and reduced volume of distribution and clearance, as observed in the case of NK105 polymeric micelle formulation. In this context, appropriate mathematical models are missing to integrate the physicochemical (partition, release kinetic) and the pharmacokinetic parameters (dilution in the blood, distribution), to anticipate the evolution of the free and carrier associated drug fractions. These models would be of particular interest to anticipate from the dilution conditions of the drug/carrier in the blood and the release kinetic in animal how the behavior of the drug delivery systems can be extrapolated to human. These models would also help to outline the key attributes of the carrier/drug which should be preserved when the manufacturing process is scaled-up and to anticipate their impact on the performances of the formulation.

For the above reasons, the chemical synthesis of a drug conjugate in which the drug is covalently coupled to a carrier appears as a more predictable way to associate the drug to the carrier than non-covalent binding. However, from the development standpoint, this approach results in a new chemical entity (NCE) that requires full development program particularly from the efficacy and safety evaluation. In the case of paclitaxel, the carrier–drug conjugates have been synthesized by coupling the carrier at the 2′-OH function of taxane moiety, which is the functional group that binds to tubulin, resulting generally in an inactive prodrug necessitating hydrolysis for showing activity, as described at least for Taxoprexin® [243]. This may contribute to high MTD of the conjugate, and may in turn facilitate the injectability of higher doses of taxane, as observed for Taxoprexin® (see Table 3). The inactive conjugate needs activation in the body by release of taxane exposing the 2′-OH function responsible for tubulin binding. The longer systemic circulation timescale of the conjugate in addition to sustained drug release, as reported in the case of Opaxio™ and Taxoprexin®, minimizes the V_d and maintain sustained plasma unbound taxane concentration (taxane not bound to plasma proteins and to formulation). Longer systemic confinement of the conjugate may also potentially result in progressive tumoral accumulation, thereby augmenting the drug availability to tumor. At the same time, as described in the non covalent approach, long circulation of residual drug may be unfavorable to minimize neutropenia.

The release rate of taxane from the conjugate and the site of conjugate cleavage are the critical parameters that define the efficacy and safety of the conjugate. Rapid conjugate cleavage in the systemic compartment may lead to the situation of the second generation formulation. An ideal situation would be that the release of taxane from the conjugate occurs specifically in the tumor compartment once the conjugate accumulates, and that the tumor accumulated fraction should still carry taxane.

Overall, from the quality management standpoint, the immediate release case (drug delivery systems intended for immediate release of the drug) and the altered pharmacokinetics case (drug delivery systems intended to exhibit the altered pharmacokinetics) are very different, and thus the distinction between these two cases should be appropriately considered. For the immediate release case, since the expected benefit is the quick drug release to mimic the pharmacokinetics of a solution, the standard tests/tools used for modeling and monitoring of the pharmacokinetics and safety may serve because the efficacy and safety are related to the plasma pharmacokinetics and the distribution of the drug-free delivery carrier to the different organs. However, for the altered pharmacokinetics case, especially if the drug accumulation and the release is intended specifically in the pathological tissues, e.g. in tumors exhibiting EPR effect, it is the distribution to the pathological tissue and drug release kinetic within this tissue that determines the efficacy, while the safety is related not only to the plasma pharmacokinetics but also to the distribution of the drug delivery system to the undesired compartments in the body and subsequent drug release within these compartments. Hence, for the altered pharmacokinetics case, the aspects such as the variability linked to the human biology, the injected dose-distribution relationship (the distribution ratio to the desired tissue and undesired tissues) and the drug release kinetic, and the associated impact of these on the efficacy and safety of the drug delivery system are critical and therefore should be anticipated, modeled, and monitored, using appropriate tools to ensure the translation of the drug delivery concept to clinic.

3. Conclusion

The integration of physicochemistry and biopharmacy concepts and tools are prone to make the taxanes delivery safer and more efficient. As described in this review, the role of the solubilizing agent/carrier and the dissociation kinetics of the drug following i.v. injection may have important implications on the biopharmacy of the drug (pharmacokinetics, pharmacodynamics, safety). Moreover, the aspect of immune stimulation by the carrier, owing to its physicochemical status especially size and surface properties in terms of plasma proteins activation may have significant implications on the nano-objects safety and should be anticipated during preclinical studies. Of the three generations of taxanes drug delivery systems, the third generation has considerable potential in achieving the optimal efficacy and safety. More specifically the covalent approach may provide the possibility of achieving tunable and desired drug release profile and tumor-specific drug release using linker chemistry. Finally, the development of specific models to make the links between the physicochemistry of the drug delivery system, the preclinical data and their extrapolation to human are prone to facilitate the smooth translation of drug delivery concepts from the bench to the bedside.

Acknowledgments

The authors wish to thank Sanofi colleagues especially Pierre Wils, Maria-Teresa Peracchia, Patricia Rortais, Eric Didier, Patricia Vrignaud, and Dorothee Semiond for their comments which helped in improving the manuscript.

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