



Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation

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Abstract

Cremophor EL (CrEL) is a formulation vehicle used for various poorly-water soluble drugs, including the anticancer agent paclitaxel (Taxol). In contrast to earlier reports, CrEL is not an inert vehicle, but exerts a range of biological effects, some of which have important clinical implications. Its use has been associated with severe anaphylactoid hypersensitivity reactions, hyperlipidaemia, abnormal lipoprotein patterns, aggregation of erythrocytes and peripheral neuropathy. The pharmacokinetic behaviour of CrEL is dose-independent, although its clearance is highly influenced by duration of the infusion. This is particularly important since CrEL can affect the disposition of various drugs by changing the unbound drug concentration through micellar encapsulation. In addition, it has been shown that CrEL, as an integral component of paclitaxel chemotherapy, modifies the toxicity profile of certain anticancer agents given concomitantly, by mechanisms other than kinetic interference. A clear understanding of the biological and pharmacological role of CrEL is essential to help oncologists avoid side-effects associated with the use of paclitaxel or other agents using this vehicle. With the present development of various new anticancer agents, it is recommended that alternative formulation approaches should be pursued to allow a better control of the toxicity of the treatment and the pharmacological interactions related to the use of CrEL. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Cremophor EL; Formulation vehicles; Paclitaxel; Pharmacokinetics; Pharmacodynamics

1. Introduction

The choice of a suitable pharmaceutical formulation is an essential step in anticancer drug development. This development starts with the acquisition of a chemical entity from either natural sources or entirely synthetic routes. Subsequently, the compound is screened for cytotoxic activity *in vitro* and *in vivo*. Once the screening process has been completed the compound should be properly pharmaceutically-formulated and produced before entering animal toxicology and pharmacokinetic studies and subsequently human phase I, II and III studies [1,2]. In our opinion, pharmaceutical formulation is a seriously underrated aspect of anticancer drug development.

With only a few exceptions, most new anticancer compounds are initially developed for intravenous (i.v.)

use, despite some drawbacks such as the morbidity associated with gaining i.v. access, risk of i.v. catheter-related infection, thrombosis and extravasation, and patients' preference for oral therapy when equally effective [3]. Important reasons for choosing i.v. use for initial drug development are the fact that usually less gastrointestinal toxicity occurs, there is immediate 100% bioavailability and instantaneous pharmacodynamic effects and there is a possibility to modify the dosing rate or even halt the infusion if necessary. Solubility of the compound is a specific demand for i.v. administration, even for the newer chemotherapeutic agents which are known to be poorly water-soluble. Classical solubility approaches, which will be discussed subsequently, include the use of colloidal systems, pro-drug development or solubilisation techniques.

Colloidal systems such as liposomes, microcapsules, microspheres, nanoparticles or macromolecule complexes may protect the anticancer drug from premature degradation or (chemical) inactivation within the systemic circulation. Prodrugs are inactive derivatives that

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release the active drug following spontaneous degradation or enzymatic reactions. Solubilisation is the process of uptake of drugs through complex formation into for, e.g. oligomers of dextrose and fatty acids, through co-solvent systems (such as ethanol, polyethyleneglycol and glycerol), or through surfactant systems. The surfactant systems consist of either amphoteric compounds (e.g. lecithin or gelatin), ionic surfactants (e.g. sodium palmitate) or non-ionic surfactants (e.g. Tween 80 and Cremophor EL (CrEL)) [4,5]. This review focuses on biological and pharmacological properties of CrEL, which is the formulation vehicle of various hydrophobic drugs, including the anticancer agent paclitaxel.

2. Paclitaxel formulation

After the identification of paclitaxel as the active ingredient in crude ethanolic extracts of the bark of the Western Yew tree, *Taxus brevifolia*, against several murine tumours [6], the development of the drug was suspended for more than a decade due to problems associated with the solubilisation of the drug. Paclitaxel is insoluble in water (less than 0.03 mg/ml), slightly soluble in octanol, propylene glycol and butanol, soluble in CrEL, ethanol, methanol, chloroform, acetone and ether, and freely soluble in dimethyl acetamide. The formulation approach using 50% CrEL and 50% dehydrated ethanol United States Pharmacopeia (USP) was chosen for further development [7]. The pharmaceutical formulation of paclitaxel (paclitaxel; Bristol-Myers Squibb) contains 30 mg paclitaxel dissolved in 5 ml of this (1:1, v/v) mixture.

The heterogeneous non-ionic surfactant CrEL is a white to off-white viscous liquid with an approximate molecular weight of ~3 kDa and a specific gravity (25°C/25°C) of 1.05–1.06, and it is produced by the reaction of castor oil with ethylene oxide at a molar ratio of 1:35 [4]. Castor oil is a colourless or pale yellow fixed oil obtained from the seeds of *Ricinus communis*, with an extremely high viscosity, and consists mainly of the glycerides of ricinoleic, isoricinoleic, stearic and dihydroxystearic acids. CrEL is usually of highly variable composition, with the major component identified as oxylated triglycerides of ricinoleic acid (i.e. polyoxyethylene glycerol triricinoleate 35) (Fig. 1). Polyvinyl chloride (PVC)-free equipment for CrEL administration is obligatory, since CrEL is known to leach plasticizers from PVC infusion bags and polyethylene-lined tubing sets which can cause severe hepatic toxicity [5].

CrEL is being used as a vehicle for the solubilisation of a wide variety of hydrophobic drugs, including anaesthetics, photosensitisers, sedatives, immunosuppressive agents and (experimental) anticancer drugs (Table 1). The amount of CrEL administered with these drugs averages 5 ml (range, 1.5–10.3 ml), although paclitaxel is an exception as the amount of CrEL is much higher per administration, approximately 26 ml. Therefore, it is important to understand the biological and pharmacological behaviour of CrEL, especially in the formulation of paclitaxel.

3. Biological effects of Cremophor EL (CrEL)

3.1. Anaphylactic hypersensitivity reactions

The most well known biological effect of paclitaxel formulated with CrEL is a clinical acute hypersensitivity reaction, characterised by dyspnoea, flushing, rash, chest pain, tachycardia, hypotension, angio-oedema, and generalised urticaria. Despite premedication, consisting of high-dose corticosteroids, H₁ and H₂ antagonists, minor reactions (flushing and rash) still occur in

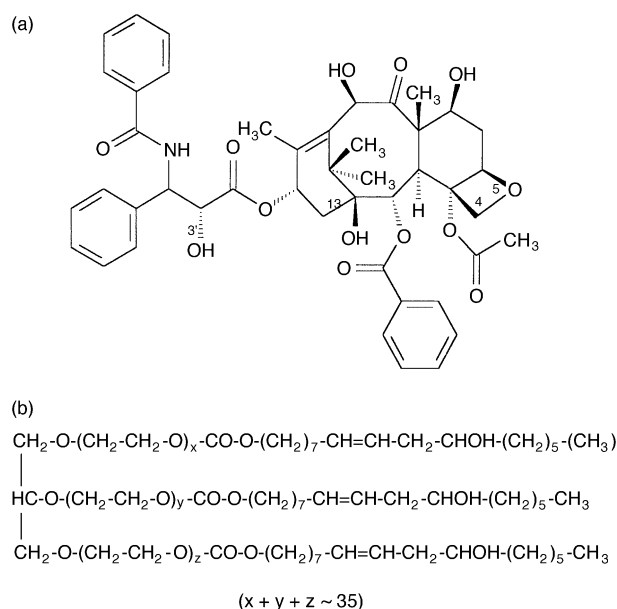


Fig. 1. Chemical structures of paclitaxel (a) of CrEL (polyoxyethyleneglycerol triricinoleate 35) (b).

Table 1
Examples of surfactant systems using CrEL

Agent	Therapeutic class	Amount administered ^a (ml)
Aplidine	Antineoplastics	~1.5
C8KC	Photosensitisers	5.5
Clanfenur	Antineoplastics	10.3
Cyclosporin A	Immunosuppressives	3.5
Diazepam	Sedatives	1.5
Didemnin B	Antineoplastics	2.0
Paclitaxel	Antineoplastics	25.8
Propofol	Anaesthetics	~7.0
Teniposide	Antineoplastics	1.5

CrEL, Cremophor EL.

^a For an average patient for a single administration of dose.

41–44% of all patients and major, potentially life-threatening, reactions in 1.5–3% [8–10]. Mostly, the hypersensitivity reaction occurs within the first two courses of paclitaxel and can be prevented by reducing the infusion rate. Various (pre)clinical observations, discussed below, point to CrEL as the main contributor to the hypersensitivity reactions:

- (a) Using an elegant series of *in vitro* studies, complement activation by CrEL was found to cause the hypersensitivity reaction associated with paclitaxel chemotherapy [11], as well as reactions seen to other drugs where CrEL was used as a vehicle [12,13]. Recently, it was shown that the CrEL-induced complement activation in human serum was clearly concentration-dependent with a minimum activating CrEL level in the order of 2 µl/ml, a concentration readily achieved clinically in the plasma following standard doses of paclitaxel [14].
- (b) Histamine release in dogs by CrEL was mainly caused by one of its (minor) constituents, oleic acid [15], whereas the cardiac toxicity attributed to paclitaxel, mainly asymptomatic rhythm disturbances, might also be caused by CrEL through a mechanism of histamine release [16].
- (c) Improper mixing of high-dose cyclosporin A infusions caused (non-solubilised) CrEL to sink to the bottom of vials, producing anaphylactoid responses because of highly concentrated CrEL at the initial i.v. bolus [17]. All patients allergic to i.v. cyclosporin A, tolerated the CrEL-free oral formulation [18].
- (d) Finally, the fact that CrEL concentrations are lower with prolonged paclitaxel infusion schemes (see below) may be an explanation for the lower incidence of hypersensitivity reactions with these schemes. Collectively, these findings indicate that CrEL plays a crucial role in the occurrence of hypersensitivity reactions of paclitaxel and other drugs using CrEL as a formulation vehicle.

3.2. Lipoprotein patterns and hyperlipidaemia

Lipoprotein alterations accompanying the administration of miconazole formulated with CrEL were reported as early as 1977 by Bagnarello and colleagues [19]. Later, CrEL was found to alter the buoyant density of high-density lipoproteins (HDL) [20] and shift the electrophoretic and density gradient HDL to low density lipoproteins (LDLs) [21–23]. These authors showed that paclitaxel had a strong affinity for the serum lipoprotein dissociation products, potentially affecting the biodistribution and clearance of the drug. High concentrations of CrEL may also cause hyperlipidaemia, possibly resulting in Rouleaux formation of erythrocytes

and a change in shape of leucocytes in blood smears [24]. This suggests that manual blood-cell count analysis is warranted after the administration of preparations containing CrEL. Whether the observed hyperlipidaemia after CrEL administration increases the risk of vascular accidents is, as yet, unknown.

3.3. Neurotoxicity

Axonal degeneration and demyelination, one of the principal side-effects of paclitaxel resulting in peripheral neuropathy, is also supposedly a biological effect caused by CrEL. The plasma levels of CrEL achieved after therapeutic doses of paclitaxel and i.v. cyclosporin A (also formulated in CrEL), have been shown to produce axonal swelling, vesicular degeneration and demyelination in rat dorsal ganglion neurones [25]. Interestingly, in rats treated with CrEL-free [³H]-paclitaxel, paclitaxel was not detectable in the peripheral nervous system, indicating that the anticancer drug itself might not be responsible for the observed toxicity [26]. The hypothesis of CrEL-induced neurotoxicity is further supported by the fact that i.v. cyclosporin A causes neurotoxicity in approximately 25% of patients [27], while this side-effect is rarely seen with oral administration. This is also consistent with a previous finding that CrEL is not absorbed when given orally as a result of intestinal degradation [28]. It is also noteworthy that neurological symptoms are 10 times less common after treatment with docetaxel, a semi-synthetic taxane chemically similar to paclitaxel, than with paclitaxel [29]. This could be because unlike paclitaxel, docetaxel is formulated in Tween 80 (i.e. polyoxyethylenesorbitan monooleate), again rendering CrEL as the likely cause of the clinical observations of neuropathy. The neurotoxic properties of CrEL are most likely induced by residual unsaturated fatty acids, possibly due to the appearance of peroxidation products [30]. Therefore, it is suggested that the ethoxylated derivatives of castor oil account for most of the neuronal damage observed [31].

3.4. Reversal of P-glycoprotein activity

In the early 1990s, several groups independently observed that CrEL was able *in vitro* to modulate the activity of P-glycoprotein, a drug-transporting membrane protein that is elevated in tumour cells having a multidrug resistance phenotype [32–35]. More recently, similar phenomena have also been described for various other non-ionic surfactants, including Tween 80 [36], Solutol HS 15 [37] and Triton X-100 [38]. Surprisingly, however, multidrug resistance has never been successfully modified *in vivo* by any non-ionic surfactant, including CrEL [39–41]. A possible explanation for this lack of *in vivo* efficacy is the extremely low volume of distribution of CrEL, approximately equal to the

volume of the blood compartment, suggesting that concentrations necessary to affect reversal of multidrug resistance *in vitro* are probably not attained *in vivo* in (solid) tumours [42]. Recent pharmacokinetic experiments conducted in *mdr1a* P-glycoprotein knockout mice support this lack of efficacy, despite high peak plasma levels of CrEL [28]. In contrast to treatment in solid tumours, the pharmacokinetic selectivity of CrEL for the central blood/bone marrow compartment can be an advantage in the treatment of haematological malignancies, in which the expression of P-glycoprotein is known to be a principal factor contributing to resistance to chemotherapy [43].

3.5. In vitro cytotoxicity

Cytotoxic properties of CrEL in doxorubicin-resistant human breast-cancer cell lines were first reported by Fjällskog and colleagues [44], and confirmed in various human tumour samples [45,46]. It was postulated that formation of free radicals by peroxidation of polyunsaturated fatty acids and/or a direct perturbing effect in the cell membrane causing fluidity and leakage are possible mechanisms contributing to this type of cytotoxicity [47–49]. Using clonogenic assays, however, it has been demonstrated that CrEL can antagonise the cytotoxicity of paclitaxel by blocking the cell-cycle that results in the inhibition of cytokinesis [50]. Thus, although CrEL in itself might have some potential to affect cell survival, the concentrations required to modulate cell growth will also change paclitaxel-mediated (and overall) cytotoxicity. In addition, the pharmacokinetic selectivity of CrEL most likely precludes any vehicle-mediated change in (solid) tumour cell kill *in vivo*.

4. Pharmacokinetics of CrEL

4.1. Analytical methods

In view of the contribution of CrEL to clinically observed effects, and to enable further assessment of the impact of its use on paclitaxel pharmacology, the kinetic behaviour of CrEL has been studied extensively in recent years. For this purpose, a variety of analytical methods have been developed. The first assay developed for the measurement of CrEL concentrations in plasma was based on the ability of CrEL to modulate daunorubicin efflux in multidrug resistant T-cell leukaemia VLB₁₀₀ cells [51]. Later, a more sensitive and reliable method was developed, which required only microvolumes (20 µl) of plasma [52]. This method is based on the measurement of ricinoleic acid after saponification of CrEL followed by precolumn derivatisation and reversed-phase high-performance liquid chromatography.

Because of the high costs, and time consuming nature of both assays a new method, based on a selective binding of CrEL to the Coomassie brilliant blue G-250 dye in protein-free extracts, was developed [53,54]. Most recently, an electrochemical detection method was developed [55]. Large-scale pharmacokinetic studies have only recently been possible with the development of these newer methods.

4.2. CrEL Disposition

Clinical pharmacokinetic studies with CrEL following 3-h paclitaxel infusions indicate a dose-independent behaviour with a terminal disposition half-life of approximately 80 h, with a large range depending on the method used for measurement [56,57]. Interestingly, with prolongation of the duration of infusion from 1 to 3 and to 24 h, the CrEL clearance increased from approximately 160 to 300 to 400 ml/h/m², respectively [14] (Fig. 2). It thus appears that CrEL shows a linear and dose-independent, but schedule-dependent pharmacokinetic behaviour, possibly related to the saturation of serum esterase-mediated metabolic degradation. This schedule dependency leads to an increase in systemic exposure, and thus an increase in the possible CrEL-related biological (side-)effects with a shortening of the infusion duration. An example of this phenomenon is the higher risk of allergic reactions in the 1-h versus 3-h or 24-h infusions of paclitaxel.

As mentioned earlier, the volume of distribution of CrEL is extremely low, implying that the tissue (and tumour) delivery of CrEL is probably insignificant. This is in line with observations that CrEL levels in normal and tumour tissue were not detectable in mice [58].

Not much is known about the elimination routes of CrEL. CrEL may be largely degraded in the blood compartment by serum carboxylesterase-induced degradation, similar to that described for Tween 80 [59], causing a gradual release of the ricinoleic acid residues

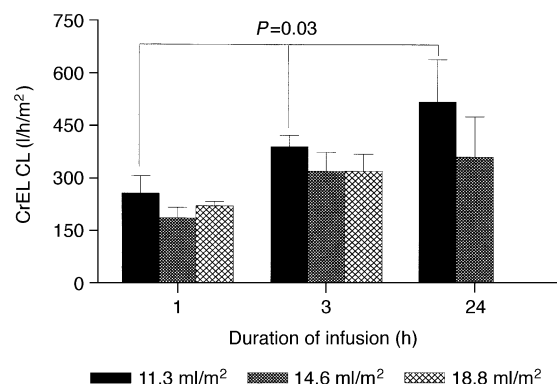


Fig. 2. Schedule-dependency for CrEL clearance (CL) as a function of the duration of infusion in cancer patients treated with paclitaxel at dose of 135 (CrEL: 11.3 ml/m²), 175 (CrEL: 14.6 ml/m²) and 225 (CrEL: 18.8 ml/m²) mg/m² [14].

attached to the triglyceride structure. It has been shown that hepatobiliary elimination of CrEL is a minor elimination pathway [60]. In addition, the urinary excretion of CrEL accounted for less than 0.1% of the administered dose, in spite of its relatively hydrophilic nature [61].

4.3. Effects of CrEL on drug disposition

Various studies have shown that CrEL alters the pharmacokinetics of many drugs including cyclosporin A, etoposide, doxorubicin, a number of photosensitisers (e.g. C8KC) and paclitaxel. Initially, the effect of CrEL on the disposition of paclitaxel was studied in mice that received the drug by i.v. injection at doses of 2, 10 and 20 mg/kg in the presence of various amounts of CrEL [58] (Fig. 3). The paclitaxel clearance of 2.4 l/h/kg at the lowest dose level was reduced to 0.33 and 0.15 l/h/kg at the 10 and 20 mg/kg dose levels. It was also shown that the area under the concentration time curve (AUC) of paclitaxel is higher when it is formulated in CrEL compared with formulation in Tween 80, suggesting that CrEL is responsible for the non-linearity of paclitaxel disposition. Despite the fact that much higher plasma levels of paclitaxel are reached when given in the CrEL-containing formulation, the tissue levels of paclitaxel were essentially similar with all tested preparations, indicating that the profound influence of CrEL is only taking place in the central blood compartment. In subsequent years, numerous causes of this apparent non-linear pharmacokinetic behaviour were proposed. It has been suggested that CrEL might interfere with P-glycoprotein-mediated biliary secretion, thereby reducing paclitaxel elimination [62]. In the isolated perfused rat liver, CrEL inhibited the hepatic elimination of paclitaxel, primarily preventing the drug from reaching the sites of metabolism and excretion [63]. However, recent studies indicate that drug-transporting P-glycoproteins are not essential *per se* for normal hepatobiliary secretion of paclitaxel [28,64] and that, as discussed, the dis-

position of CrEL itself limits the potential to modulate P-glycoprotein activity *in vivo* [42].

More recently, it has been proposed that the effect of CrEL on paclitaxel pharmacokinetics is associated with encapsulation of the drug within CrEL micelles, causing (concentration-dependent) changes in cellular partitioning and blood:plasma concentration ratios of paclitaxel [64] (Fig. 4). It was shown that the affinity of paclitaxel was (in decreasing order) CrEL > plasma > human serum albumin, with CrEL present above the critical micellar concentration (i.e. $\sim 0.01\%$). Since this effect was also observed in the absence of plasma proteins, it could not have been caused by altered protein binding or by an increased affinity of paclitaxel for protein dissociation products that are produced by the action of CrEL on native lipoproteins [22]. These findings are consistent with the hypothesis that paclitaxel can be entrapped within micelles (composed primarily of polyethyleneglycerol triricinoleate) and that these micelles act as the principal carrier of paclitaxel in the systemic circulation. The percentage of total paclitaxel trapped in micelles increases disproportionately with higher doses of CrEL administered.

The hypothesis that the non-linear pharmacokinetics of paclitaxel is related to time-varying CrEL concentrations was recently confirmed in a group of cancer patients all receiving increasing doses of 135, 175 and 225 mg/m² [65]. Again, the plasma clearance of paclitaxel turned out to be dose-dependent with the slowest clearance at the highest dose level (Fig. 5). In line with the *in vitro* data, the non-linear disposition of paclitaxel in the plasma appeared to be an artifact caused by dose-related levels of CrEL in blood [65]. Therefore, the non-micellar bound or unbound fraction of paclitaxel in plasma might be a better pharmacokinetic parameter to predict toxicity and to guide dosing of paclitaxel, since it is generally acknowledged that the unbound fraction of a drug is capable of diffusing across biological barriers and interacting with essential structures in (tumour) tissues [66].

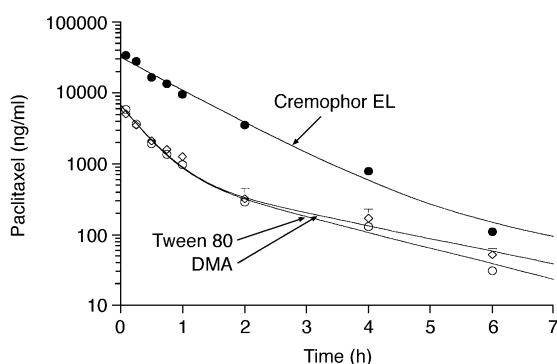


Fig. 3. Effect of the formulation vehicle (CrEL, Tween 80 or dimethylacetamide (DMA)) on paclitaxel concentration in female FVB mice receiving paclitaxel at a dose of 10 mg/kg [58].

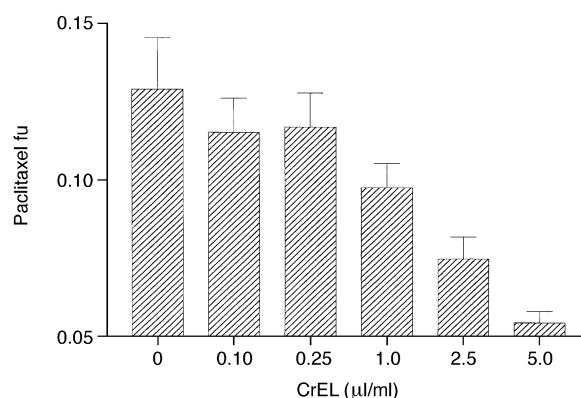


Fig. 4. Effect of the CrEL concentration on the fraction of unbound paclitaxel (fu) in human plasma [56].

4.4. Effects of CrEL on anticancer drug pharmacodynamics

Besides its effect on (anticancer) drug disposition, the use of CrEL has also been associated with alterations in the pharmacodynamic outcome of a number of drugs co-administered with paclitaxel. For example, clinical combination chemotherapy studies with paclitaxel and cisplatin revealed important sequence-dependent differences in toxicity, with less myelotoxicity when the taxane was given before cisplatin, that could not be linked to consistent changes in pharmacokinetics [67,68]. Interestingly, no toxicity- or pharmacokinetic-sequence interaction was seen in the combination of carboplatin and paclitaxel [69]. One of the mechanisms underlying these clinically important interactions appears to be related to a selective inhibition of cisplatin accumulation in peripheral blood and bone marrow cells by CrEL, without affecting antitumour activity [70–72] (Fig. 6). In addition, it has been demonstrated that CrEL markedly reduced the level of serum haematopoietic inhibitory activity, which resulted in a decrease in femoral bone marrow cellularity and an upregulation of B and T cells, as well as a transiently elevated incidence of both primitive and committed haematopoietic progenitor cells within several hours after injection [73]. Taken together, these findings suggest that the unusual clinical observations noted with cisplatin-paclitaxel combination therapy are due to a (myelo)protective interaction with cisplatin by CrEL. Since CrEL doses of up to 30 ml/m² as a 3-h infusion can be safely administered [74], it is anticipated that an improvement in the therapeutic window for cisplatin could be obtained by re-formulation of this agent with CrEL. This concept is currently under further investigation (data not shown).

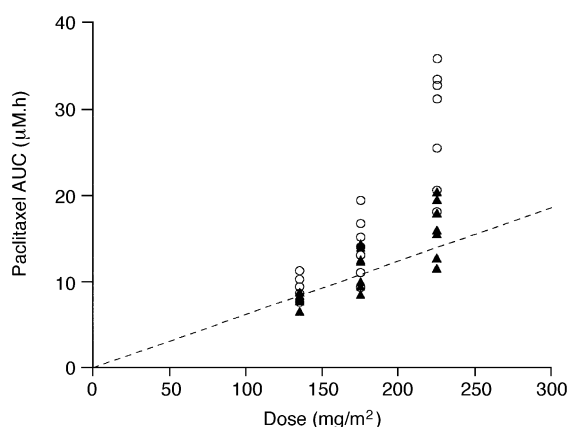


Fig. 5. Effect of dose on paclitaxel plasma (circles) and whole blood area under the concentration curve (AUC) (triangles) in cancer patients treated with paclitaxel at three different dose levels [65]. Please note that the higher the AUC, the slower the clearance of a drug.

In contrast to the potential benefits obtained from the use of CrEL in the case of cisplatin chemotherapy, combination studies conducted with the combination of paclitaxel and doxorubicin have shown that CrEL can be linked to clinically important kinetic and dynamic interactions that greatly impact upon the overall toxicity profiles. Two independent studies have shown profound decreases in doxorubicin clearance, particularly when paclitaxel was given prior to the anthracycline [62,75], resulting in substantially worse mucositis and haematological toxicity. Therefore, it is advised to administer doxorubicin first in this combination. In addition, it is expected that even minor modifications in the duration of the infusion or dose may lead to unpredictable pharmacodynamic consequences. Similar interactions with CrEL have also been described for etoposide, epirubicin and the irinotecan metabolite SN-38 [76]. Clearly, the magnitude of these interactions depend largely on the combination drug involved, the paclitaxel and CrEL dose administered, and the duration of infusion administration sequence used for the combined agents.

5. Conclusions and future perspectives

Recent investigations have revealed that CrEL, a widely used formulation vehicle, is a biologically and pharmacologically active ingredient of various commercially available drugs. For example, when used in paclitaxel administrations, an exceptionally large amount of CrEL is inevitably co-administered with the i.v. infusions, causing important biological events that can lead to serious acute hypersensitivity reactions and neurological toxicity, depending on the dose and duration of infusion. In addition, the substantial effects of

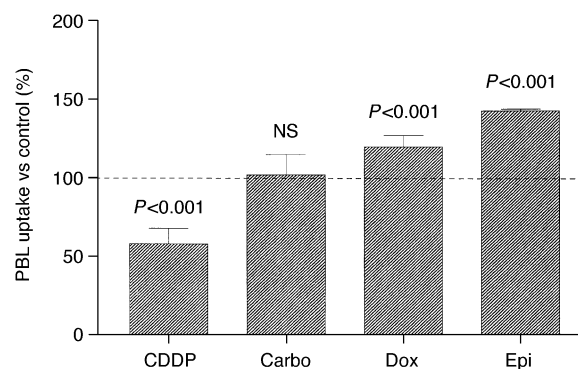


Fig. 6. Influence of CrEL on anticancer drug pharmacodynamics. Bars indicate the amount of drug accumulated in peripheral blood leucocytes (PBL) (expressed as percentage relative to a 100% control) for 2-h incubations with cisplatin (CDDP), carboplatin (Carbo), doxorubicin (dox), and epirubicin (Epi) ([70], data not shown). NS, non significant.

CrEL on the disposition of other co-administered drugs (e.g. anthracyclines) with a narrow therapeutic window in poly-chemotherapeutic regimens also can be potentially hazardous to the patient. In contrast, the *in vitro* and *in vivo* observations of myeloprotective effects related to the use of CrEL in combination with some agents, such as cisplatin, might be used to re-formulate such agents with CrEL in order to achieve an optimisation of their therapeutic window.

In view of the inherent problems associated with the use of CrEL, it can be anticipated that there may be a therapeutic advantage from using paclitaxel formulations in which CrEL is absent. Such new formulation approaches should clearly be pursued to allow a better control of the systemic (CrEL-mediated) toxicity and pharmacokinetic interactions observed with numerous agents given in combination with the taxane. Obviously, alternative paclitaxel formulations should allow the drug to be delivered at adequate doses, and the preparation should be stable for several hours to allow handling in the clinical setting. Currently, a large variety of new (CrEL-free) formulation vehicles for paclitaxel are in (pre)clinical development, including co-solvent systems (Tween 80/ethanol/Pluronic L64), water-soluble polymers (e.g. polyethylene glycols), emulsions (e.g. triacetin), liposomes, cyclodextrines, nanocapsules and microspheres (reviewed in Ref. [76]). Although one of these preparations might eventually replace the current paclitaxel formulation, for the coming years we will have to cope with the drawbacks of CrEL in the clinical setting. It is also important to keep in mind that CrEL is widely used not only by oncologists, but also by anaesthetists and in transplantation medicine, and that few physicians are aware of the biological and pharmacological activity of the compound. It is thus essential to find other ways to solubilise the drugs formulated in CrEL but also, in some cases, to explore the potential positive effects of this castor oil derivative. It is of note that a proper understanding of all the biological effects of the formulation would presumably have avoided the major delays in development of paclitaxel as an anticancer agent. This underscores the importance of the choice of vehicle in drug development in general.

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