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Pharmacological Effects of Formulation Vehicles

Implications for Cancer Chemotherapy

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Abstract

The non-ionic surfactants Cremophor® EL (CrEL; polyoxyethyleneglycerol triricinoleate 35) and polysorbate 80 (Tween® 80; polyoxyethylene-sorbitan-20-monooleate) are widely used as drug formulation vehicles, including for the taxane anticancer agents paclitaxel and docetaxel. A wealth of recent experimental data has indicated that both solubilisers are biologically and pharmacologically active compounds, and their use as drug formulation vehicles has been implicated in clinically important adverse effects, including acute hypersensitivity reactions and peripheral neuropathy.

CrEL and Tween® 80 have also been demonstrated to influence the disposition of solubilised drugs that are administered intravenously. The overall resulting effect is a highly increased systemic drug exposure and a simultaneously decreased clearance, leading to alteration in the pharmacodynamic characteristics of the solubilised drug. Kinetic experiments revealed that this effect is primarily caused by reduced cellular uptake of the drug from large spherical micellar-like structures with a highly hydrophobic interior, which act as the principal carrier of circulating drug. Within the central blood compartment, this results in a profound

alteration of drug accumulation in erythrocytes, thereby reducing the free drug fraction available for cellular partitioning and influencing drug distribution as well as elimination routes. The existence of CrEL and Tween® 80 in blood as large polar micelles has also raised additional complexities in the case of combination chemotherapy regimens with taxanes, such that the disposition of several coadministered drugs, including anthracyclines and epipodophyllotoxins, is significantly altered. In contrast to the enhancing effects of Tween® 80, addition of CrEL to the formulation of oral drug preparations seems to result in significantly diminished drug uptake and reduced circulating concentrations.

The drawbacks presented by the presence of CrEL or Tween® 80 in drug formulations have instigated extensive research to develop alternative delivery forms. Currently, several strategies are in progress to develop Tween® 80- and CrEL-free formulations of docetaxel and paclitaxel, which are based on pharmaceutical (e.g. albumin nanoparticles, emulsions and liposomes), chemical (e.g. polyglutamates, analogues and prodrugs), or biological (e.g. oral drug administration) strategies. These continued investigations should eventually lead to more rational and selective chemotherapeutic treatment.

Paclitaxel and docetaxel are hydrophobic antineoplastic agents demonstrating significant antitumour activity against a broad spectrum of human malignancies. After the identification of paclitaxel as the active ingredient in crude ethanolic extracts of the bark of the Pacific yew tree, *Taxus brevifolia* L, the development of this drug was suspended for over a decade because of problems in drug formulation.[1] After investigation of a large variety of excipients to enable parenteral administration of paclitaxel, the formulation approach using the polyoxyethylated castor oil derivative, Cremophor® EL[1] (CrEL; polyoxyethyleneglycerol triricinoleate 35), represented the most viable option.[2] Currently, paclitaxel is commercially available as vials containing 30mg of drug dissolved in 5mL of CrEL/dehydrated ethanol USP (1 **:** 1 by volume). CrEL is widely used as a vehicle for the solubilisation of a number of other hydrophobic drugs, including anaesthetics, vitamins, sedatives, photosensitisers, immunosuppressives and (experimental) anticancer drugs (table I). The amount of CrEL per administration of paclitaxel is relatively high, and therefore its toxicological and pharmacological behaviour in the context of chemotherapeutic treatment with paclitaxel is of major importance.[3]

Table I. Examples of clinical drug preparations using Cremophor® EL or Tween® 80

Agent	Therapeutic class	Amount administered (mL)[a]
Cremophor® EL		
Kahalalide F	Antineoplastic	~0.5[b]
Diazepam	Sedative	1.5
Aplidine	Antineoplastic	~1.5[b]
Teniposide	Antineoplastic	1.5
Didemnin B	Antineoplastic	2.0
Cyclosporin	Immunosuppressive	3.5
C8KC	Photosensitiser	5.5
Propofol	Anaesthetic	7.0
Clanfenur	Antineoplastic	10.3
BMS-247550	Antineoplastic	~10[b]
DHA-paclitaxel	Antineoplastic	19.9
Paclitaxel	Antineoplastic	25.8
Tween® 80		
Carzelesin	Antineoplastic	0.1
Docetaxel	Antineoplastic	2.0
Etoposide	Antineoplastic	2.0

a For an average patient with a body surface area of 1.77m^2.

b Investigational agent for which recommended dose has not yet been established.

1 Use of tradenames is for product identification only and does not imply endorsement.

The structurally related taxane docetaxel is prepared by chemical manipulation of 10-deacetyl-baccatin III, an inactive precursor isolated from the needles of the European yew tree, *Taxus baccata* L.[4] Like paclitaxel, it is a potent inhibitor of cell replication by stabilisation of the microtubule cytoskeleton. For clinical use, this slightly less hydrophobic agent is formulated in another polyoxyethylated surfactant, polysorbate 80 (Tween® 80). The clinically used formulation consists of 80mg of docetaxel in 2mL of undiluted Tween® 80. This non-ionic surfactant is also used to solubilise several other anticancer drugs, including etoposide and minor-groove-binding cyclopropylpyrroloindole analogues such as carzelesin (table I).

In recent years, substantial evidence has been generated suggesting that CrEL and Tween® 80 are biologically and pharmacologically active compounds. In this report, we will review the physicochemical and biological properties of both non-ionic surfactants, with a focus on their effects on the disposition characteristics of the carried drugs and that of other agents administered concomitantly.

1. Physicochemical Properties of Surfactants

CrEL is a white to off-white viscous liquid with an approximate molecular weight of 3000Da and a specific gravity of 1.05–1.06. It is produced by the reaction of castor oil with ethylene oxide at a molar ratio of 1 : 35. 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, dihydroxystearic and oleic acids. The non-ionic surfactant produced from castor oil is usually of highly variable composition, with the major component (about 87%) identified as oxyethylated triglycerides of ricinoleic acid (figure 1). As a result of the heterogeneous nature of castor oil and its variable composition, the polyoxyethylated components of CrEL have been poorly characterised. Using fractionation by cyclodextrin-modified micellar electrokinetic capillary chromatography (CD-MEKC) and UV detection, in combination with delayed extraction matrix-assisted laser desorption/ionisation time of flight mass spectrometry (DE-MALDITOF-MS), a more detailed structural

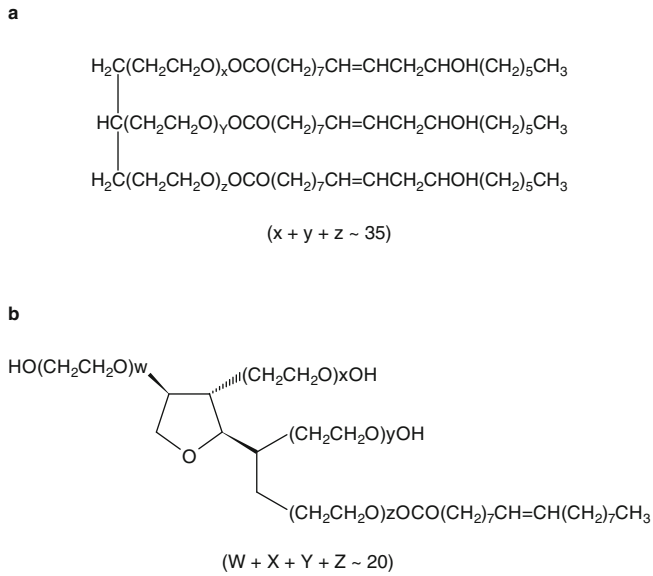

Fig. 1. Chemical structures of the primary constituents of (**a**) Cremophor® EL (polyoxyethyleneglycerol triricinoleate 35) and (**b**) Tween® 80 (polyoxyethylene-20-monooleate).

elucidation and a semiquantitative analysis of CrEL components was achieved recently.[5] These investigations indicated that the elimination of water from ricinoleic acid during the synthesis of CrEL leads to various previously unidentified species, including (glycerol-) polyoxyethylene-$\Delta^{9,11}$-didehydrostearate. It is noteworthy that equipment used for intravenous administration of CrEL should be free of polyvinylchloride, since CrEL is capable of leaching phthalate-type plasticisers from polyvinylchloride infusion bags and polyethylene-lined tubing sets, which can cause severe hepatic toxicity.[6,7]

In contrast to CrEL, Tween® 80 is a relative homogenous and reproducible, amber-coloured, viscous liquid (270–430 centistokes) with a molecular weight of 1309.7Da and a density of 1.064 g/mL. The base chemical name of the major component of Tween® 80 is polyoxyethylene-20-sorbitan monooleate (figure 1), which is structurally similar to the polyethyleneglycols. Like most non-ionic surfactants, CrEL and Tween® 80 are capable of forming micelles in aqueous solution, with critical micellar concentrations of 0.009% (weight/volume) and 0.01% (weight/volume), respectively, in protein-free aqueous solution.[8]

2. Biological Properties of Surfactants

2.1 Acute Hypersensitivity Reactions

The most extensively described biological effect of drugs formulated with CrEL is an acute hypersensitivity reaction characterised by dyspnoea, flushing, rash, chest pain, tachycardia, hypotension, angioedema and generalised urticaria, and this reaction has been attributed to CrEL.[9-12] Nevertheless, allergic reactions to taxanes formulated without CrEL have been reported as well,[13] suggesting that some functionality of the taxane molecule contributes, in part, to the observed effect. Already in the 1970s it was demonstrated that CrEL-containing drug preparations (e.g. rectal diazepam) can cause complement activation.[14,15] The mechanistic basis for this effect has not been fully elucidated, but a number of seminal studies indicate that CrEL-mediated complement activation plays a significant role. It has been postulated that due to binding of naturally occurring anticholesterol antibodies to the hydroxyl-rich surface of CrEL micelles, complement C3 is activated, leading to the clinical signs of hypersensitivity reactions.[16] The CrEL-induced complement activation is clearly concentration dependent, with a minimum CrEL concentration of approximately 2 μL/mL being required, a concentration readily achieved in plasma of cancer patients following standard doses of paclitaxel.[17] This explains why slowing down the infusion rate of paclitaxel formulated with CrEL can alleviate hypersensitivity symptoms, and also explains the need for proper dissolution of CrEL-containing drugs to prevent large variations in CrEL infusion rate leading to unpredictable reactions.[18] A recent investigation into the structure-activity relationships of surfactant-mediated complement activation has shown that several analogues of CrEL have reduced ability to induce complement activation as measured by a decrease in serum concentrations of the SC5b-9 marker (figure 2). Additional clinical studies will be required to evaluate the clinical utility of some of these substitute vehicles for CrEL-containing drugs.

In studies with dogs it was demonstrated that CrEL, mainly its minor free fatty acid constituents such as oleic acid, can cause histamine release.[20] Despite premedication with corticosteroids and histamine H_1 and H_2 blockers, minor reactions (e.g. flushing and rash) still occur in approximately 40% of all patients,[21-24] with major potentially life-threatening reactions observed in 1.5–3% of treated patients.[9]

Oleic acid is also present in Tween® 80, and thus may be a cause of hypersensitivity reactions to docetaxel therapy or other therapies using drugs with Tween® 80 as a solvent. Patients allergic to intravenously administered etoposide tolerated the oral formulation, which is devoid of Tween® 80, very well.[25-28] The early clinical studies with docetaxel revealed an incidence of hypersensitivity reactions ranging from 5–40%, with only a minority of more than grade 2 on the 4-point scale of the National Cancer Institute common toxicity crite-

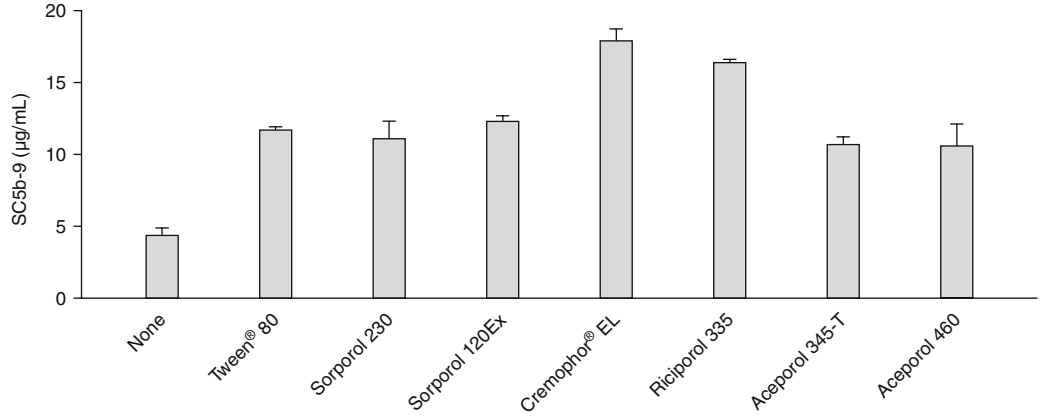

Fig. 2. Vehicle-mediated complement activation in human serum by Cremophor® EL, Tween® 80 and some structurally related analogues. Experiments were based on 50µL human serum incubations (45 minutes at 37°C) in the presence of each respective vehicle at a concentration of 10 µL/mL. The complement activation marker SC5b-9 was measured by enzyme-linked immunoassay. Data are presented as mean values ± SD of triplicate observations and were obtained from Loos et al.[19]

ria.[29-31] Hypersensitivity reactions to docetaxel therapy can be effectively ameliorated by premedication with corticosteroids and antihistamines,[32] consistent with a role of histamine in its aetiology. A comparative evaluation of paclitaxel- and docetaxel-mediated non-haematological toxicities, with the drugs given in an every 21-day schedule, is provided in table II.

2.2 Peripheral Neurotoxicity

A well-known adverse effect of agents formulated in CrEL is peripheral neurotoxicity,[35] but it is less well acknowledged that CrEL may play an important causative role. In a study performed with radiolabelled paclitaxel in rats, no detectable paclitaxel could be demonstrated in the peripheral nerve fibres,[36] but electrophysiological studies in patients with neuropathy after treatment with paclitaxel have shown evidence of both axonal degeneration and demyelinisation.[37] In approximately 25% of patients treated with cyclosporin, neurotoxicity is noted.[38] This adverse effect is never induced by oral formulations of cyclosporin, which is consistent with observations that CrEL is not absorbed intact when given orally. Moreover, CrEL plasma concentrations achieved with therapeutic doses of intravenous paclitaxel or cyclosporin have been shown to produce axonal swelling, vesicular degeneration and demyelinisation in rat dorsal root ganglion neurons.[39,40] The precise mechanism of this CrEL-induced neurotoxicity remains unclear, but recent work has indicated that unsaturated fatty acids may cause neurotoxicity, possibly due to the appearance of peroxidation products.[39,40] This suggests that the ethoxylated derivatives of castor oil probably account for most of the neuronal damage in addition to the presence of residual ethylene oxide residues.[41]

A detailed investigation into neurological adverse effects associated with docetaxel chemotherapy was recently performed in a group of 186 patients.[42] Twenty-one patients developed mild to moderate sensory neuropathy on treatment at a wide range of cumulative doses (50–750 mg/m^2) and dose levels (10–115 mg/m^2). Ten of these patients also developed weakness in proximal and distal extremities of varying degree. Nine of the 21 patients had received neurotoxic chemotherapy before, and 16 were treated with docetaxel at a dose level of 100–115 mg/m^2. This suggests that docetaxel produces a mild and predominantly sensory neuropathy in a high proportion of treated patients. This adverse effect appears to be dose-dependent and may be severe and disabling at higher dose levels.[42-44] Corticosteroid comedication does not prevent docetaxel-induced neuropathy.[45]

Table II. Comparative nonhaematological toxicity of paclitaxel and docetaxel[a]

Adverse effect	Incidence (%)	
	paclitaxel (n = 812)	docetaxel (n = 2045)
Hypersensitivity reactions[b]		
All	41	15
Severe (at least grade 3)	2	2
Fluid retention[b,c]		
All	0	64
Severe	0	6.5
Nail changes[d]		
All	2	31
Severe (at least grade 3)	0	2.5
Peripheral neuropathy[e]		
All	60	49
Severe (at least grade 3)	3	4
Skin toxicity[f]		
All	2	48
Severe (at least grade 3)	0	5

a Data represent overall incidence as percentage of patients with solid tumours treated with single-agent regimens containing either paclitaxel formulated in a mixture of Cremophor® EL and ethanol at doses of 135–300 mg/m^2 or docetaxel formulated in Tween® 80 at a dose of 100 mg/m^2, given every 21 days.[33,34]

b All patients received a 3-day dexamethasone premedication (docetaxel, n = 92).

c Characterised by one or more of the following events: poorly tolerated peripheral oedema, generalised oedema, pleural effusion requiring urgent drainage, dyspnoea at rest, cardiac tamponade, or pronounced abdominal distension (due to ascites).

d Mostly changes in pigmentation or discoloration of the nail bed.

e Mostly peripheral sensory (numbness, paraesthesias, loss of proprioception), axonal degeneration and secondary demyelination.

f Primarily involves pressure or trauma sites (e.g. hands, feet and elbows).

Tween® 80 is capable of producing vesicular degeneration. This property depends upon the polyethylene substitutions produced by reaction of the polyol compound with ethylene oxide. However, the incidence of neurotoxicity during treatment with docetaxel is much lower as compared to that of paclitaxel (table II).[46,47] Furthermore, the Tween® 80-containing epipodophyllotoxin etoposide is not known to be neurotoxic. This suggests that the aetiology of taxane-induced neuropathy is different for paclitaxel and docetaxel, with formulation vehicles contributing to the overall picture to a different extent.

2.3 Dyslipidaemia

In the mid-1970s, lipoprotein alterations caused by CrEL were mentioned for the first time.[48] Later, CrEL was found to alter the buoyant density of high-density lipoprotein (HDL) and shift the electrophoretic and density gradient HDL to low-density lipoprotein (LDL).[49-52] These authors demonstrated the strong affinity of paclitaxel for serum lipoprotein degradation products, potentially affecting the pharmacokinetics of the drug by altering protein binding characteristics. High concentrations of CrEL may also cause dyslipidaemia, possibly resulting in rouleaux formation of erythrocytes.[53] Although cyclosporin is known for its atherosclerosis-inducing capacities, it remains unclear if the observed hyperlipidaemia after CrEL administration is contributing to this risk for vascular accidents. *In vivo* studies of the effects of cyclosporin on the de-endothelialised carotid artery of New Zealand White rabbits treated with therapeutic doses of cyclosporin (15 mg/kg/day) or with a vehicle control (CrEL) revealed intimal proliferation in both groups.[54] Mean plasma cholesterol levels were moderately increased in both groups. Although this may have contributed to foam cell formation in the cyclosporin-treated animals, it was not the sole determinant, as foam-cell-rich lesions were not observed in animals receiving only CrEL. In contrast, Tatou et al. observed significant adverse effects of CrEL on endothelial function and vascular muscle on isolated and perfused rat hearts, leading to a reduction of coronary flow and aortic output.[55] The potential clinical implications with respect to these CrEL-related phenomena remain unknown.

2.4 Inhibition of P-Glycoprotein Activity

P-glycoprotein is a drug transporting membrane protein, and its expression is increased in tumour cells having a multidrug resistance phenotype.[56,57] Several *in vitro* studies in the early 1990s observed modulation of the activity of P-glycoprotein by

CrEL.[58-60] Later, similar phenomena were observed for various other non-ionic surfactants, including Tween® 80,[61,62] Solutol HS 15[63] and Triton X-100.[64] However, *in vivo* studies never demonstrated reversal of multidrug resistance by any non-ionic surfactant, including CrEL and Tween® 80.[65-67] The extremely low volume of distribution of CrEL and the rapid degradation of Tween® 80 *in vivo* are the likely explanations for this lack of *in vivo* efficacy (see section 3.2). Indeed, the volume of distribution of CrEL is approximately equal to the volume of the blood compartment, suggesting that concentrations necessary to affect reversal of multidrug resistance *in vitro* are not reached *in vivo* in solid tumours.[68] However, it should be noted that the pharmacokinetic selectivity of CrEL for the central blood and bone marrow compartment can provide an advantage to treatment of haematological malignancies with resistance to chemotherapy caused by elevated P-glycoprotein expression.[69]

2.5 Intrinsic Antitumour Effects

Cell-growth inhibitory properties of CrEL were first observed by Fjällskog et al. in doxorubicin-resistant human breast cancer cell lines,[70,71] and were later confirmed in other malignant cell types.[72,73] The formation of free radicals by peroxidation of polyunsaturated fatty acids and/or a direct perturbing effect on the cell membrane are possible mechanisms responsible for this type of cell growth inhibition.[74-76] Using *in vitro* clonogenic assays, however, it has been demonstrated that CrEL, at clinically achievable concentrations, can antagonise the cytotoxicity of paclitaxel by a cell-cycle block.[77] Several reports also suggest that Tween® 80 has intrinsic antitumour activity in animal models,[78-80] which might be linked to the release of oleic acid, a fatty acid known to interfere with malignant cell proliferation due to formation of peroxides[81] and inhibition of angiogenesis.[82] The exact contribution of Tween® 80 to antitumour activity observed in patients treated with chemotherapeutic drugs formulated in this vehicle substance has not been clarified.

3. Pharmacological Properties of Surfactants

3.1 Analytical Methods

At present, a large variety of analytical procedures are available for clinical pharmacokinetic studies with CrEL and Tween® 80. The first assay developed for measurement of CrEL concentrations in patient material was based on the ability of this vehicle to modulate daunorubicin efflux in multidrug resistant T-cell leukaemia VLB_{100} cells.[83] Alternatively, a more sensitive and reliable method was developed that required sample volumes of only 20μL.[84] This method is based on measurement of ricinoleic acid after base-induced hydrolysis (saponification) of CrEL followed by an acylchloride formation, precolumn derivatisation with naphthylamine, and reversed-phase high-performance liquid chromatography (HPLC) to detect *N*-ricinoleoyl-1-naphthylamine at 280nm. Because of the high costs and the 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 for human plasma samples.[85,86] This method has also been used to measure Tween® 80 concentrations in murine and human plasma.[87] More recently, a potentiometric titration method for CrEL was developed for quantitative analysis in urine and plasma based on coated wire electrode as an end-point indicator with sodium tetraphenylborate at 20°C and pH 10.[88] Each of these methods has its drawbacks and limitations, and the methodological differences between them probably contribute to the variations in measured CrEL concentrations.

In addition to the Coomassie Brilliant Blue G-250 colourimetric dye-binding assay, various other analytical procedures are available for Tween® 80. Initially measurement of the polyoxyethylated portion of the molecule was used for quantification of Tween® 80 concentrations. The so-called polyol moiety is detectable by a wide variety of methods, including a resorcinol-glucose precipitation, a colourimetric method using ammonium cobaltoth-

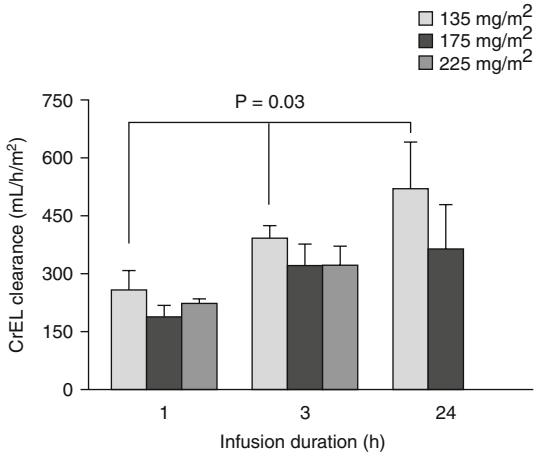

Fig. 3. Effect of infusion duration on the clearance of Cremophor® EL (CrEL). Data are expressed as mean values ± SD and were obtained from patients treated with paclitaxel formulated in CrEL at dose levels of 135 mg/m² (CrEL dose 11.3 mL/m²), 175 mg/m² (CrEL dose 14.6 mL/m²) or 225 mg/m² (CrEL dose 18.8 mL/m²).[17]

iocyanate, turbidimetric or gravimetric procedures, and complex formation with barium phosphomolybdic reagent.[89,90] The ammonium cobaltothiocyanate complexation has also been used in combination with HPLC and UV detection for analysis of Tween® 80 in urine and ascites fluid, using either post-column or on-line complexation.[91-94] A less complex procedure that does not require complexation involves a one-step hydrolysis with sulphuric acid followed by HPLC with UV detection at 210nm.[95] Most recently, Tween® 80 concentration in human plasma samples have been analysed by a liquid chromatographic assay with tandem mass-spectrometric detection, with a 60-fold increased sensitivity as compared with previous published assays.[96]

3.2 Pharmacokinetics

The various analytical methods described above have been used in different pharmacokinetic studies of CrEL, sometimes leading to conflicting results and conclusions. There have been no studies thus far comparing the different analytical methods. Initial pharmacokinetic analyses have indicated that CrEL shows linear pharmacokinetic behaviour.[97] However, with prolongation of infusion duration from 1–3 and 24 hours, CrEL clearance increased from about 160 to 300 and 400 mL/h/m², respectively (figure 3).[17] A recently developed population pharmacokinetic model revealed that the plasma concentration-time data of CrEL were best fitted to a three-compartment model with Michaelis-Menten elimination (table III).[98,99]

It thus appears that CrEL shows schedule-dependent pharmacokinetics, possibly related to saturated elimination due to capacity-limited CrEL metabolism within the systemic circulation. This schedule dependency leads to an increase in systemic exposure, and thus an increase in CrEL-related biological effects, with shortening of the infusion duration. An example of this phenomenon is the apparent increase of allergic reactions in 1-hour versus 3- or 24-hour infusions of paclitaxel,[9,100] as well as increased incidence of peripheral neuropathy with shorter paclitaxel infusions.[101,102] The observed changes in adverse effects as a function of paclitaxel infusion duration will need to be confirmed in larger comparative trials in order to provide recommendations for treating clinicians.

Table III. Population pharmacokinetic parameters of Cremophor® EL following paclitaxel administration[a]

Parameter	Estimate	RSE (%)
V_1 (L)	2.59	7
Q_2 (L/h)	1.44	24
V_2 (L)	1.81	9
Q_3 (L/h)	0.155	22
V_3 (L)	1.61	7
Km (mL/L)	0.122	61
V_{max} (mL/h)	0.193	9
Residual error		
Additional (mL/L)	0.0951	34
Proportional (%)	6.94	8

a Data are from patients treated with paclitaxel formulated in a mixture of Cremophor® EL and ethanol, and were obtained from Van den Bongard et al.[99] Determination of Cremophor® EL in plasma samples was performed by pre-column derivatisation and reversed-phase high-performance liquid chromatography, as described elsewhere.[84]

Km = plasma concentration at half V_{max}; **Q_2, Q_3 =** intercompartmental clearances from the central to the first or second peripheral compartments; **RSE** = relative standard error; **V_{max}** = maximum elimination rate; **V_1, V_2, V_3 =** volumes of the central, first peripheral and second peripheral compartments.

The terminal half-life of CrEL amounts to approximately 80 hours with reported values ranging between 10 and 140 hours, depending on the sampling time period and the method used for CrEL analysis. Therefore, studies using sparse-sampling strategies with application of the bioassay method may lead to underestimation of the terminal half-life.[103] With the more sensitive colourimetric assay, detectable concentrations of CrEL were demonstrated even 1 week after initial treatment.[68] Despite this relatively long terminal disposition phase of CrEL, long-term weekly administration of paclitaxel does not cause significant accumulation of CrEL although the vehicle is always detectable in pre-dose samples.[104] In all studies, the observed volume of distribution of CrEL was extremely small and almost equal to the volume of the central blood compartment. As outlined, this implies that tissue and tumour delivery of CrEL is insignificant.[68]

Little is known about elimination routes of CrEL. Pharmacokinetic studies in patients with hepatic dysfunction treated with paclitaxel suggested that hepatobiliary elimination of CrEL is not of major importance.[105] Despite its highly hydrophilic nature, the renal elimination of CrEL accounts for less than 0.1% of the administered dose and CrEL pharmacokinetics in a patient with severely impaired renal function were not different from those in historical controls.[106] It is possible that elimination pathways for CrEL are mainly dictated by serum carboxylesterase-induced degradation, leading to the release of free fatty acids such as ricinoleic acid. This metabolic route occurs apparently at a low rate and the involved enzymes may be easily saturated, which explains the peculiar time-dependent nonlinear pharmacokinetics of this vehicle.

The pharmacokinetic behaviour of Tween® 80 is very different from that of CrEL. In animal studies a rapid decline of the concentration was shown after injection (figure 4). Plasma concentrations were below 0.05 μL/mL (i.e. the lower limit of quantification of the analytical method) within 15 minutes after drug administration.[87] Observations in five patients treated with docetaxel as a 1-hour infusion at a dose of 100 mg/m^2 showed peak plasma concentrations of Tween® 80 of 0.16 ± 0.05 μL/mL, consistent with more recent observations.[96,107] *In vitro* experiments have shown that this rapid elimination is caused by a rapid carboxylesterase-mediated hydrolysis in the systemic circulation, cleaving the oleic acid side chain from the molecule.[87] Earlier studies performed in rats and humans with the structurally related surfactants polysorbate 20 and polysorbate 40 have shown similar metabolic pathways, with ester bond cleavage and subsequent oxidation of the fatty acid moiety (reviewed in Van Zuylen et al.[108]).

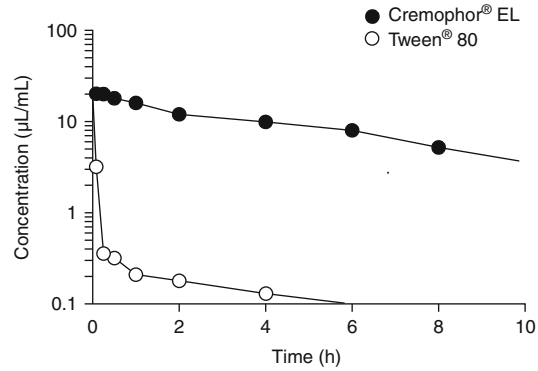

Fig. 4. Comparative plasma concentration-time profiles of Cremophor® EL and Tween® 80 in mice receiving 0.83 mL/kg of each vehicle by bolus injection. Data show mean values of four observations per time point and were obtained from Van Tellingen et al.[87]

4. Modulation of Drug Disposition Patterns

4.1 Intravenous Administration

Various studies have shown that CrEL alters the pharmacokinetic behaviour of many drugs administered intravenously, including cyclosporin, anthracyclines, etoposide, the irinotecan metabolite SN38, the photosensitiser C8KC and paclitaxel (table IV). The most common effect is a substantial increase in the systemic exposure to the studied agent with a concomitantly reduced systemic clearance, as was first described for paclitaxel in a mouse model (figure 5). Various proposed causes of the CrEL-drug interactions have been put forward in recent years,

Table IV. Pharmacokinetic effects of Cremophor® EL and Tween® 80 on intravenously administered drugs

Agent	Species	Pharmacokinetic effect(s)	Reference
Cremophor® EL			
Cyclosporin	Baboon	4.2-fold increased AUC	113
Doxorubicin	Mouse	2-fold increased AUC	114
	Mouse	Increased concentrations in plasma, liver	115
	Mouse	Increased concentrations in heart, liver	116
	Human	1.2-fold increase in AUC	117
Epirubicin	Mouse	Increased concentrations in spleen	118
Etoposide	Rat	4.6-fold increased AUC	111
SN-38	Mouse	2-fold increased AUC	119
C8KC	Mouse	Increased C_{max} and $t_{½\beta}$	120
Oxaliplatin	Rat	1.6-fold increased AUC	121
Paclitaxel	Mouse	7-fold increased AUC	122
	Rat	9-fold increased AUC	109
	Human	2-fold increased AUC	123
Tween® 80			
Doxorubicin	Mouse	Increased concentrations in plasma, spleen	116,124,125
	Human	2-fold reduced AUC	126
Etoposide	Rat	1.2-fold increased AUC	118
Methotrexate	Mouse	Increased uptake in brain	127
Vigabatrin	Rat	Increased GABA in brain	128

AUC = area under the plasma concentration-time curve; **C_{max}** = peak plasma concentration; **GABA** = γ-aminobutyric acid; **$t_{½\beta}$** = half-life of the terminal disposition phase.

including altered protein binding characteristics,[52] altered hepatobiliary secretion,[109] and inhibition of endogenous P-glycoprotein-mediated biliary secretion, thereby reducing elimination of drugs.[110] In the isolated perfused rat liver, CrEL inhibited the hepatic elimination of paclitaxel, preventing the drug from reaching the sites of metabolism and excretion,[109] and the same effect was noted for Tween® 80.[111] However, recent studies indicate that drug-transporting P-glycoproteins are not essential for normal hepatobiliary secretion of paclitaxel,[112] suggesting that this protein does not play a major role.[8]

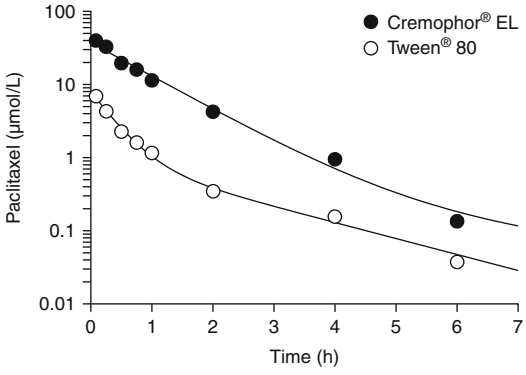

Fig. 5. Effect of Cremophor® EL on the plasma concentration-time profiles of paclitaxel in mice treated at a paclitaxel dose of 10 mg/kg formulated with Cremophor® EL or with Tween® 80. Data were obtained from Sparreboom et al.[122]

In view of the very small volume of distribution of CrEL, it is likely that the pharmacokinetic interaction observed with some drugs takes place within the central blood compartment. This was recently confirmed by *in vitro* experiments demonstrating that encapsulation of the model drug paclitaxel within the hydrophobic interior of CrEL micelles takes place in a concentration-dependent manner, causing changes in cellular partitioning and blood**:**plasma concentration ratios of paclitaxel (table V).[8,19] 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. ~0.01%). Since the 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.[51,52] These findings are consistent with the hypothesis that paclitaxel can be entrapped within micelles, and that these micelles act as the principal carrier of paclitaxel in the systemic circulation.

An intriguing feature of paclitaxel pharmacokinetics is a distinct dose-dependent pharmacokinetic behaviour, with clearance values decreasing substantially with an increase in drug dose. This effect is particularly evident with 3-hour infusion regimens, and CrEL has been linked to this phenomenon. It has been shown that the percentage of total paclitaxel trapped in micelles increases disproportionally with higher doses of CrEL administered,[8] thereby influencing the unbound drug concentration and making it less available for distribution to tissues, metabolism, and biliary and intestinal secretion. Indeed, the free fraction of paclitaxel is inversely related to CrEL concentrations *in vitro,*[129] and CrEL has also been shown to alter the blood : plasma concentration ratios *in vivo* by reducing drug uptake into red blood cells.[130] Interestingly, when paclitaxel dissolved in another vehicle was administered to mice, no pharmacokinetic nonlinearity in plasma concentration profiles was evident.[122] The concentrations in tissues also increased linearly with increasing dose even when dissolved in CrEL, suggesting linear kinetics for the unbound drug.

Earlier, the nonlinearity in paclitaxel pharmacokinetics had been described by empirical models using both saturable elimination and saturable distribution, where the saturable distribution has been described as saturable transport[131] or saturable binding.[132] A recent study demonstrated that a mechanistic model could be used to describe the nonlinear kinetics of the drug using simultaneous description of total and unbound plasma concentrations, whole blood concentrations and concomitant CrEL concentrations.[133] This pharmacokinetic model has a foundation in the known properties of paclitaxel as determined with micellar trapping of paclitaxel, distribution to red blood cells and binding to serum albumin, α_1-acid glycoprotein and platelets. The results of that study showed that the nonlinear pharmacokinetics are predominantly explained by nonlinear binding to CrEL and that the unbound drug displayed linear pharmacokinetics when administered over a 3-hour period.

The drug fraction not bound to serum proteins or CrEL is a rather small fraction of the total under normal physiological conditions, and at high concentrations, paclitaxel is mainly bound to CrEL. From simulated concentration components in patients treated with 24-hour infusions, it was demonstrated that because CrEL concentrations are rather low, the linear binding to serum proteins and binding to blood cells are of greater importance than the CrEL binding.[133] Because of the schedule-depen-

Table V. Effect of Cremophor® EL (CrEL) and derivatives on the blood:plasma concentration ratio of paclitaxel[a]

Compound added (μg/mL)	Blood : plasma ratio	Change (%)	p[b]
None	1.07 ± 0.004		
CrEL (0.1)	1.09 ± 0.009	+1.83	0.387
CrEL (0.5)	0.990 ± 0.015	−9.35	0.012
CrEL (1)	0.901 ± 0.017	−15.8	0.003
CrEL (5)	0.690 ± 0.005	−35.5	<0.0001
CrEL (10)	0.625 ± 0.008	−41.6	<0.0001
Castor oil (5)	1.23 ± 0.171	+13.0	0.061
CrEL fraction 1 (5)[c]	1.06 ± 0.008	−0.94	0.520
CrEL fraction 2 (5)	0.926 ± 0.018	−13.5	0.043
CrEL fraction 3 (5)	0.763 ± 0.055	−28.7	0.010
CrEL fraction 4 (5)	0.645 ± 0.051	−39.7	0.003
CrEL fraction 5 (5)	0.943 ± 0.039	−11.9	0.103

a Paclitaxel was used at an initial concentration of 1 μg/mL and incubated in whole blood for 15 min at 37°C before fractionation and analysis by high-performance liquid chromatography. Ratio data are presented as mean values ± SD of (at least) triplicate measurements and were obtained from Sparreboom et al.[8]

b Probability of significant difference versus control (unpaired two-sided Student's t test).

c Five CrEL fractions, each with progressively increased hydrophobicity, were isolated as chromatographic peaks, as described elsewhere.[8] The fractionation process was based on reversed-phase high-performance liquid chromatography of crude CrEL. The first fractions mainly contain polyoxyethyleneglycerol and oxyethylated glycerol, and the pharmacologically active fraction 4 contains the micelle-forming component, polyoxyethyleneglycerol triricinoleate along with fatty acid esters of polyethyleneglycerol.

dent clearance of CrEL, this has serious clinical ramifications in that the systemic exposure to unbound paclitaxel will be a function of infusion duration. This was recently confirmed in a randomised comparative clinical trial evaluating drug disposition characteristics following 1- versus 3-hour infusions.[102] The area under the plasma concentration-time curve (AUC) of unbound paclitaxel was 24% ($p = 0.009$) reduced as compared with the 3-hour infusion group (figure 6), despite significantly higher peak concentrations (0.26 ± 0.007 vs 0.15 ± 0.07 μmol/L; $p = 0.0002$). Most importantly, this effect translated into more severe haematological toxicity with the 3-hour schedule of drug administration,[102] suggesting that the various infusion schedules currently employed for paclitaxel administration are not interchangeable or pharmacologically equivalent.

The existence of CrEL in blood as large polar micelles with a highly hydrophobic interior also raises the possibility of interactions occurring with other (poorly water-soluble) drugs. For example, the combination of paclitaxel with anthracycline drugs may result in altered cellular distribution and a concomitantly increased plasma concentration, because

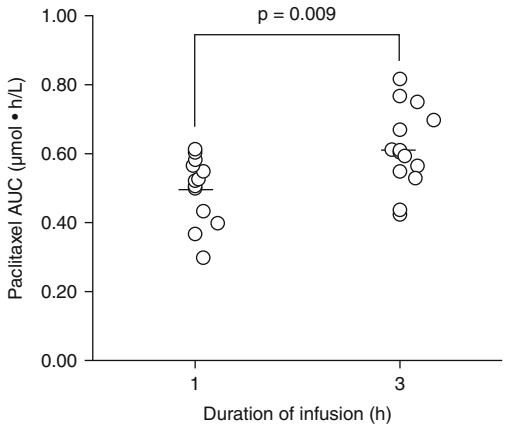

Fig. 6. Effect of infusion duration on systemic exposure (AUC) to unbound paclitaxel. Data were obtained from 29 cancer patients receiving a 1-hour (n = 15; mean ± SD AUC 0.50 ± 0.10 μmol • h/L) or a 3-hour infusion (n = 14; mean ± SD AUC 0.62 ± 0.12 μmol • h/L) and were obtained from Gelderblom et al.[102] Each symbol represents the AUC of an individual patient, and the horizontal lines indicate mean values for each group. **AUC** = area under the concentration-time curve.

Table VI. Clinically relevant drug interactions attributable (partially) to Cremophor® EL

Agents	Pharmacokinetic effect(s)	Reference
Paclitaxel[a]		
Doxorubicin	1.4-fold increased AUC	137
Epirubicin	1.7-fold increased AUC	138
Gemcitabine/ epirubicin	1.7-fold increased epirubicin AUC	139
Irinotecan	1.4-fold increased SN-38 AUC	140
Cyclosporin[a]		
Etoposide	1.8-fold increased AUC	141
Etoposide/ mitoxantrone	1.5-fold increased etoposide AUC	142
Doxorubicin	1.5-fold increased AUC	143
Vinblastine	Increased myelosuppression	144
Valspodar[a]		
Etoposide	1.9-fold increased AUC	145
Doxorubicin	2.0-fold increased AUC	146

a Formulated for clinical use in a Cremophor® EL-containing vehicle, and administered intravenously.

AUC = area under the plasma concentration-time curve.

of incorporation of the anthracycline drug into CrEL micelles.[134] In this respect, several studies have demonstrated significant pharmacokinetic interactions between paclitaxel and/or CrEL and doxorubicin.[110,114,117,135,136] Although not tested explicitly, it is likely that the presence of CrEL in the clinical formulation of certain drugs contributes, at least in part, to various pharmacokinetic interactions described with other agents (table VI).

There are conflicting reports in the literature on the effects of Tween® 80 on the distribution and elimination of drugs administered intravenously (table IV). In mice it was demonstrated that Tween® 80 caused an increase of doxorubicin plasma concentrations by decreasing the plasma volume as a result of the osmotic effect of Tween® 80 on total blood volume.[124,125] However, in patients receiving the same relative amount of Tween® 80 (administered concomitantly with etoposide at a dose of 100 mg/m^2), both the volume of distribution and the clearance of doxorubicin were increased, due to reduced plasma concentrations of doxorubicin in the early phase of the concentration-time profile.[126] In the isolated perfused rat liver, Tween® 80 decreased the clearance and the volume of distribution of etopo-

side,[111] but it increased the renal and biliary excretion of methotrexate.[127] The majority of clinical investigations have shown minimal alteration in the pharmacokinetic profiles of agents when used in combination with drugs formulated in Tween® 80.[135,147,148] This is most likely the result of the rapid degradation of Tween® 80 in plasma by esterases, such that it cannot interfere to any significant extent with the pharmacokinetic behaviour of other agents.

However, recent observations indicate that Tween® 80, at concentrations observed in patients treated with docetaxel, causes a profound and significant alteration of the fraction unbound of docetaxel, which increased by 50% (figure 7).[149] The mechanistic basis for the decreased binding of docetaxel in the presence of Tween® 80, contrary to that observed with CrEL and paclitaxel, is as yet unclear. It is possible, however, that with time Tween® 80 is able to form micellar complexes with proteins, including serum albumin and α_1-acid glycoprotein, so that the binding of docetaxel becomes saturable on single sites.[150] Similar observations have been reported for the binding of several other drugs that bind with high affinity but low capacity to α_1-acid glycoprotein in the presence of structurally-related mixed-micellar systems.[151] Alternatively, the phenomenon might be the result of Tween® 80 metabolism by serum esterases and subsequent oleic acid-mediated protein-binding displacement of docetaxel, causing increases in unbound drug.[152] Regardless of the mechanism underlying this effect, it is consistent with recent observations that, similar to paclitaxel, also in the case of docetaxel nonlinear distribution pathways exist that may be related to the presence of non-ionic surfactants in the clinical formulated product.[153]

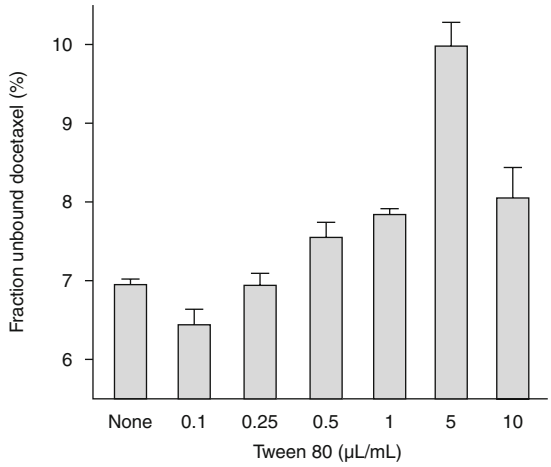

Fig. 7. Extent of docetaxel binding to human plasma *in vitro* expressed as the unbound drug fraction as a function of Tween® 80 concentration. Data are expressed as mean values ± SD of triplicate observations and were obtained from Loos et al.[149]

4.2 Extravascular Routes of Administration

There have been many reports highlighting the ability of Tween® 80 to increase the absorption in *in vitro* systems, animals and humans of numerous agents involving various classes of drug. Typical examples of this phenomenon are provided in table VII. The main overall conclusion from these studies is that Tween® 80 acts as an enhancer of the systemic exposure to orally administered agents by increasing biomembrane permeability,[154,155] as has also been described for intravesical instillation of thiotepa in the presence of Tween® 80 in cancer patients.[156] It has also been proposed that agents like Tween® 80 and CrEL not only support solubilisation, but also may inhibit the activity of P-glycoprotein with oral administration.[157,158] This protein is a membrane-bound drug efflux pump, which is abundantly present in the gastrointestinal tract,[159,160] and mediates direct secretion of substrate drugs into the intestinal lumen, thereby limiting its oral uptake.[112] However, following oral administration, polyoxyethylated surfactants are known to be extensively metabolised in the intestine by pancreatic lipases into the free fatty acid and the polyol moiety, with only less than 3% of the administered dose being excreted into the urine.[108] This makes it unlikely that the modulating effects are predominantly caused by a direct influence on active drug transport by the intact vehicles.

In contrast to the enhancing effects of Tween® 80, addition of CrEL to the formulation of oral drug preparations, in general, seems to result in significantly diminished drug uptake and reduced circulating concentrations (table VII). One of the best stud-

Table VII. Influence of formulation vehicles on oral drug absorption characteristics

Agents	Test system	Effect(s)	Reference
Cremophor® EL			
Acf(N-Mef)NH_2	Caco-2 cells	2.6-fold reduced permeability	157
Digoxin	Human	Decreased lag time	161
Paclitaxel	Human	2.0-fold decreased AUC[a]	162
	Mouse	1.4-fold decreased AUC[b]	163
Saquinavir	Human	5.0-fold increased AUC	164
Phytomenadione	Human (infant)	Decreased PIVKA-II	165
Tween® 80			
Albendazole	Rat	1.9-fold increased AUC	166
Cyclosporin	Rat	33-fold increased bioavailability[c]	167
Danazol	Dog	16-fold increased bioavailability	168
Digoxin	Rat intestine	Increased uptake	158
Griseovulvin	Human	1.5-fold decreased AUC	169
Indomethacin	Rat	1.6-fold increased AUC	170
Itazigrel	Rat	1.5-fold increased absorption	171
Methotrexate	Mouse	2.0-fold increased AUC	127
Tetracycline	Rat intestine	2.7-fold increased absorption	172

a As compared with a Tween® 80 formulation.

b As compared with a formulation containing 7-fold less Cremophor® EL.

c As compared with a nanosphere formulation.

AUC = area under the plasma concentration-time curve; **PIVKA-II** = des-gamma-carboxyprothrombin.

ied examples is the influence of CrEL on the oral absorption of paclitaxel. Oral administration of this drug is an attractive alternative for the currently used intravenous regimen, because it is convenient and practical for patients and it may circumvent systemic exposure to CrEL, which is known to be not absorbed intact after oral administration.[173,174] A study of paclitaxel formulated in Tween® 80 resulted in a significant increase in the peak concentration and AUC of paclitaxel in comparison with the CrEL formulations.[162,163] Fecal elimination data revealed a decrease in excretion of unchanged paclitaxel for the Tween® 80 formulation compared with the CrEL formulations, suggesting that entrapment of paclitaxel in CrEL micelles is an important factor limiting the absorption of orally administered paclitaxel from the intestinal lumen. Obviously, this has significant clinical ramifications in that oral paclitaxel shows very distinct apparent saturable absorption kinetics with no further increase of the AUC with a given increase in dose (figure 8).[175-178] Similar dose-dependence was not observed with oral administration of docetaxel formulated in Tween® 80,[179] suggesting that the effect is CrEL specific, and that other formulations should be developed in order to increase the usefulness of oral paclitaxel administration.

Entrapment of drug in CrEL micelles has also been demonstrated for several agents delivered intraperitoneally (e.g. O^6-benzylguanine in mice[180]

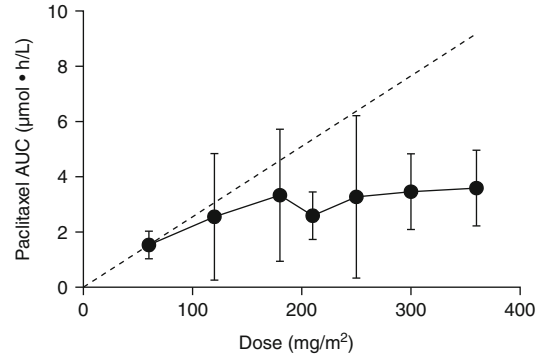

Fig. 8. Effect of oral drug dose on the systemic exposure to paclitaxel in cancer patients. Data are expressed as mean values ± SD and were obtained from Malingre et al.[175] The broken line indicates the hypothetical dose-proportional increase in the area under the plasma concentration-time curve (AUC).

Table VIII. Influence of Cremophor® EL (CrEL) on the pharmacokinetics of intraperitoneal paclitaxel[a]

Parameter	With CrEL	Without CrEL	p[b]
C_{max} (μmol/L)	0.14 ± 0.08	0.26 ± 0.07	0.062
AUC (μmol • h/L)	5.04 ± 1.92	7.55 ± 3.38	0.044
F (%)	31.4 ± 5.18	98.8 ± 16.6	0.005

a Data were obtained from four cancer patients treated in a randomised cross-over setting with paclitaxel administered at a dose of 125 mg/m^2 in the presence and absence of CrEL, and represent mean values ± SD; from Gelderblom et al.[123]

b Probability of significant difference versus control (two-sided test for matched pairs).

AUC = area under the plasma concentration-time curve; **C_{max}** = peak plasma concentration; **F** = bioavailability.

and paclitaxel in cancer patients[123]) or intravesically (e.g. paclitaxel in dogs[181]). The major goal of intraperitoneal therapeutic strategies is to expose tumours within the peritoneal cavity to higher concentrations of antineoplastic agents for longer periods of time than can be achieved by systemic drug administration.[182,183] Treatment with paclitaxel given intraperitoneally is attractive in patients with ovarian carcinoma, since paclitaxel has proven single-agent activity in this disease.[184] With this route of drug administration, the presence of CrEL as an integral component of the clinical formulation may actually be advantageous as it prolongs exposure to the tumour cells and reduces transport across the peritoneal/blood barrier (table VIII).

5. Conclusion

Numerous investigations have studied the role of pharmaceutical vehicles such as CrEL and Tween® 80 in the pharmacological behaviour of the formulated drugs. These investigations have yielded fundamental insight into modes of action, pharmacokinetic profiles and considerations of dosage and scheduling. Indeed, the administration of CrEL and Tween® 80 to patients presents a number of serious concerns, including unpredictable intrinsic adverse effects such as acute hypersensitivity reaction and peripheral neuropathy. Furthermore, these substances modulate the disposition profiles of

Table IX. Examples of alternative approaches to development of taxane drugs

Strategy	Example(s)	Stage	Reference
Pharmaceutical			
Co-solvents	HSA-paclitaxel[a]	Preclinical (*in vivo*)	188
Emulsions	S8184	Clinical (phase I)	189
	LDE-paclitaxel[b]	Preclinical (*in vivo*)	190
Liposomes	Liposome-encapsulated paclitaxel	Clinical (phase I)	191
Cyclodextrins	PTX-CYD	Preclinical (*in vivo*)	192
Nanoparticles	ABI-007	Clinical (phase II)	187,193
Microspheres	Paclimer	Preclinical (*in vivo*)	194
Chemical			
Analogues	BMS-184476	Clinical (phase II)	195
	BMS-275183 (oral)	Clinical (phase I)	196
	IDN5109/BAY59-8862 (oral)	Clinical (phase I)	197
	RPR 109881A	Clinical (phase II)	198
Prodrugs	DHA-paclitaxel[c]	Clinical (phase II)	199,200
	PNU-166945[d]	Discontinued	201
	CT-2103[e]	Clinical (phase I)	202
Biological			
Oral administration	Paclitaxel + cyclosporin	Clinical (phase II)	203

a Poly(ethylene glycol)-human serum albumin-paclitaxel conjugate.

b Cholesterol-rich emulsion that binds to low-density lipoprotein receptors.

c Docosohexaenoic acid-paclitaxel.

d Water-soluble polymeric conjugate of paclitaxel.

e Polyglutamated paclitaxel.

various drugs using them as vehicles, and of other compounds administered concomitantly, by alteration of the blood distribution resulting from entrapment of the compound in circulating micelles.

The drawbacks presented by the presence of CrEL or Tween® 80 in drug formulations have instigated extensive research to develop alternative delivery forms, and currently, several strategies are in progress to develop formulations of the anticancer agents docetaxel and paclitaxel that are free from Tween® 80 and CrEL, respectively.[185] A recent dose-finding study with a new submicronic Tween® 80-free dispersion formulation of docetaxel suggested a lower incidence and severity of haematological and non-haematological toxicity (fluid retention) at equimolar doses compared with the current formulation of docetaxel with Tween® 80.[186] Likewise, the absence of CrEL in a novel formulation of paclitaxel (ABI-007) permitted drug administration without the premedication routinely used for the prevention of hypersensitivity reactions, as well as increases in the maximum tolerable dose as compared with paclitaxel formulated in CrEL.[187] A summary of various approaches currently pursued to eliminate non-ionic surfactants from taxane formulations is provided in table IX. Continued investigations into the role of pharmaceutical vehicles in taxane-related drugs should eventually lead to a more rational and selective chemotherapeutic treatment with these agents.

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