REVIEW ARTICLE

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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.

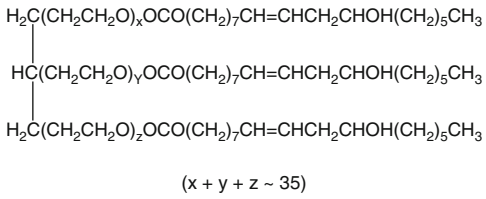
The structurally related taxane docetaxel is prepared by chemical manipulation of 10-deacetyl-baccatin III, an inactive precursor isolated from the needles of the European yew tree, *Taxus baccata* L.[4] Like paclitaxel, it is a potent inhibitor of cell replication by stabilisation of the microtubule 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

a



b

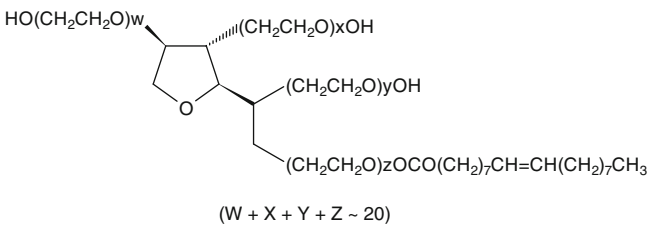


Fig. 1. Chemical structures of the primary constituents of (**a**) Cremophor® EL (polyoxyethyleneglycerol triricinoleate 35) and (**b**) Tween® 80 (polyoxyethylene-20-monooleate).

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-

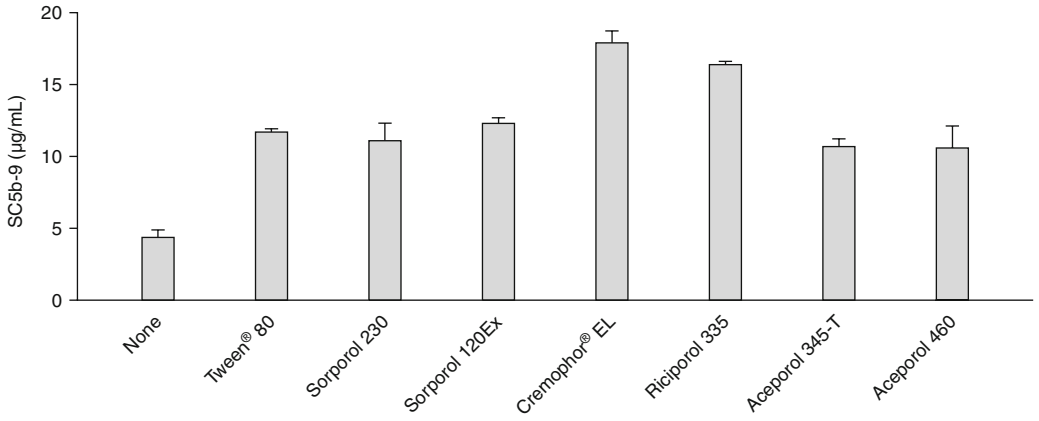


Fig. 2. Vehicle-mediated complement activation in human serum by Cremophor® EL, Tween® 80 and some structurally related analogues. Experiments were based on 50µL human serum incubations (45 minutes at 37°C) in the presence of each respective vehicle at a concentration of 10 µL/mL. The complement activation 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]

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