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Expert Review

Advances in the Use of Tocols as Drug Delivery Vehicles

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Abstract. There has been increasing interest in recent years in the drug delivery applications of tocols and their derivatives. Their biocompatibility and potential to deliver both poorly soluble and water-soluble drugs make tocols attractive as drug delivery vehicles. This review article will focus primarily on topical, oral, and parenteral drug administration using tocols, although other routes of delivery such as pulmonary and nasal will also be discussed. After an overview of the tocol structures, physicochemical properties with emphasis on their solvent properties, functions, and metabolism, specific case studies will be discussed where tocols have been successfully used in topical, oral, and parenteral drug formulations and marketed drug products. Case studies will be extended to those where tocol-based formulations were administered pulmonarily and nasally. As more clinical data and marketed drug products emerge, the utility and therapeutic value of tocols will certainly increase.

KEY WORDS: bioavailability enhancement; tocol chemistry; drug solubilization; oral; parenteral drug delivery; P-glycoprotein inhibition; tocols; topical.

INTRODUCTION

Tocols and their derivatives, such as esters, are widely used in vitamin supplementation and as antioxidants in the food industry and in many pharmaceutical compositions. However, although in a few cases a potential use in formulating pharmaceutical compositions has been reported, it is only recently that their full potential as drug carriers is being realized (1–3). Their biocompatibility and solvent capacity for poorly soluble drugs make tocols attractive as drug delivery vehicles.

It is the purpose of this review article to present the state-of-the-art in the use of tocols as drug delivery vehicles for topical, oral, and parenteral administration of poorly soluble lipophilic/tocophilic drugs. This review will focus on pharmaceutical applications. There are excellent review articles on the nutraceutical (4) and cosmeceutical applications (5) of tocols. The use of tocol-based vehicles for delivering cosmeceuticals, nutraceuticals, and pharmaceuticals is illustrated by the Venn diagram in Fig. 1. The common area where the three circles intersect represents tocol-based vehicles that are used to deliver these products.

An overview of the chemistry, functions, and metabolism of tocols and their derivatives will be presented first, followed by a discussion on the use of tocols as solvent for poorly soluble compounds/drugs. Among various tocol esters, special emphasis will be given to α-tocopheryl-polyethylene glycol-1000-succinate (TPGS) and its increasing applications in drug solubilization and delivery. Creams, ointments, gels, and liposomes will be discussed under topical drug delivery, softgel formulations incorporating self-emulsifying drug delivery systems (SEDDS) will be addressed under oral delivery, and finally injectable tocol liposomes, emulsions, and nanoparticles will be the subject of parenteral delivery. Aerosolized vitamin E formulations for pulmonary delivery and polymeric microspheres for delivery to the nasal cavity will be discussed in the section dealing with other routes of delivery. Vitamin E represents a family of compounds, consisting of four tocopherols and four tocotrienols, and this will be further discussed in the next section. Case studies will be presented throughout this review article which, at the end, will incorporate some useful conclusions and future perspectives.

CHEMISTRY, FUNCTIONS, AND METABOLISM OF TOCOLS

Chemistry

The term tocols incorporates a family of tocopherols and tocotrienols that are derived from 6-hydroxy-2-methyl-2-phytylchroman, sometimes referred to as "tocol" (Fig. 2). They are oily viscous liquids (m.p. of about 3°C and b.p. of 200–220°C), insoluble in water, heat- and acid-stable, but unstable in the presence of alkali, light, oxygen, and on contact with iron and lead (6,7). Tocols are freely soluble in organic solvents, such as chloroform and acetone, oils, surfactants, and cosolvents, such as ethanol, propylene glycol, and polyethylene glycol. There are eight naturally occurring

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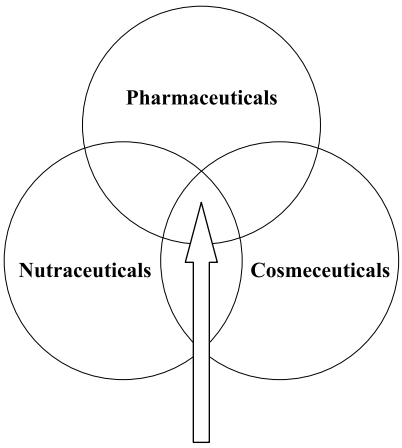

Fig. 1. Tocol-based delivery vehicles for cosmeceuticals, nutraceuticals, and pharmaceuticals. The common area in the Venn diagram represents tocol-based vehicles that are used to deliver these products.

tocols that are known as Vitamin E, four tocopherols and four tocotrienols existing in alpha, beta, gamma, and delta (or α-, β-, γ-, and δ-) isomers. The difference between tocopherols and tocotrienols is in the tail. The tocotrienols have three double bonds in the phytyl tail. The difference between the various isomers is in the head or chroman ring. The head can have additional chemical groups (methyl groups) attached at up to three different locations (Fig. 2). The α-isomer has all three sites filled, β- and γ- have two methyl groups attached, but at different locations, whereas δ- has only one methyl group attached.

Various tocopherol esters are commercially available that include acetate, succinate, tartarate, nicotinate, and polyethylene glycol-1000 succinate (8). Other esters and tocol derivatives have also been reported (9–12). The esterification of tocols provides stability, as tocol esters have been found to be more stable against oxidation than tocopherol. Tocopherol is supplied as oil concentrates of either tocopherol or tocopherol acetate, as dry powders of either tocopherol acetate or tocopherol succinate, and as the water-soluble waxy solid TPGS. These vitamin esters are chemically very stable but *in vivo*, such as within the gastrointestinal tract, ester hydrolysis is considerably fast for vitamin E acetate and slower for vitamin E succinate and TPGS (6,7). Specific rates of vitamin E formation that are dependent on enzymatic activity, pH, and other factors, have not been well investigated.

Functions

Vitamin E has numerous functions, which include antioxidant, anti-inflammatory, antithrombolytic, and other therapeutic effects (6,13–18). Vitamin E protects cell membranes, especially in the lungs and red blood cells, against damage caused by various pollutants, peroxides, and free radicals formed during metabolic processes. Vitamin E works synergistically with other antioxidant nutrients, such as vitamin C, β-carotene, to quench free radicals, peroxides, and other potentially harmful substances. Vitamin E can spare other antioxidants and vice versa, and is vital for nerve and muscle cell function. In regard to its anti-inflammatory effects, vitamin E inhibits the enzyme lipoxygenase, which is responsible for the formation of leukotrienes that cause inflammation (17,18). This can be useful in the treatment of asthma and other inflammatory conditions such as arthritis. At higher doses, vitamin E has been shown to exhibit antithrombolytic activity by increasing the production of prostaglandins (18).

Other forms of vitamin E, such as γ-tocopherol and tocotrienols, exhibit other unique functions. γ-Tocopherol seems to be more potent than α-tocopherol in increasing superoxide dismutase (SOD) activity in plasma and arterial tissues as well as Mn SOD and Cu/Zn SOD protein expression in arterial tissues (19). Although both α-tocopherol and γ-tocopherol increase nitric oxide (NO) production, an important cardiovascular agent, by modulating nitric oxide synthase (NOS) activity, only γ-tocopherol increased NOS protein expression. γ-Tocopherol was also reported to be more effective than α-tocopherol in quenching nitrogen radicals (20). These radicals are the major culprits in several disorders such as, arthritis, multiple sclerosis, and Alzheimer's disease (4,6). A metabolite of γ-tocopherol known as LLU-alpha, seemed to be a natriuretic factor controlling fluid and electrolyte passage through the kidney to the urine. Interestingly, the corresponding metabolite of α-tocopherol was not active (21).

Tocotrienols, particularly γ-tocotrienol, seem to act on 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-

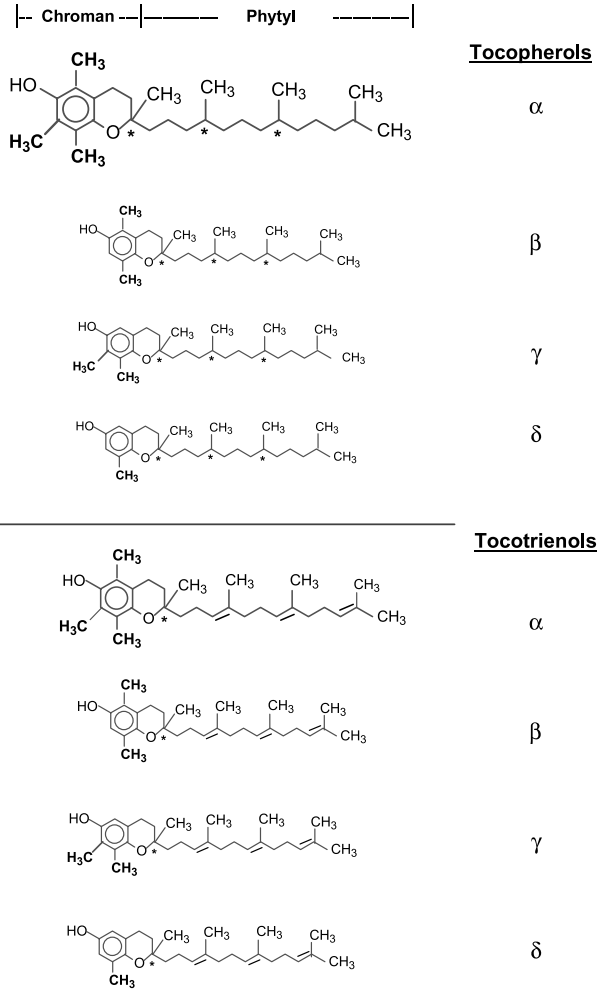

Fig. 2. Chemical structures of tocopherols and tocotrienols. Natural tocols occur as α-, β-, γ-, and δ-tocopherols, and α-, β-, γ-, and δ-tocotrienols (with permission (4)).

CoA), an enzyme involved in cholesterol biosynthesis in the liver (22). Tocotrienols suppress the production of this enzyme, which may result in less cholesterol being manufactured by the liver cells that may in turn result in an overall reduction of plasma cholesterol levels. Laboratory studies indicate that tocotrienols may effect the growth and/or proliferation of some type of cancer cells (23). It was reported that the naturally occurring tocotrienols and RRR-δ-tocopherol induced apoptosis with γ- and δ-tocotrienols being the most effective, whereas α-, β-, and γ-tocopherols had no effect (23). It was also reported that γ-tocotrienol suppressed the growth of rat melanoma cells and more potently the growth of human adenocarcinoma and human leukemic cells (24).

Metabolism

At normal levels of intake, about 20–30% of dietary vitamin E is absorbed. This amount decreases with increased dosage, and vitamin E requirements increase with a diet high in unsaturated fat. In general, the recommended daily intake of vitamin E varies from about 2 to 4 mg kg^{-1} body weight (25). Dietary sources of vitamin E include vegetable oils, particularly wheat germ and soybean oil, sprouted seeds, nuts and grains, green leafy vegetables, egg yolks, and legumes. Vitamin E itself does not form micelles and requires the presence of bile for absorption through micelle formation (1,7,26–28).

Vitamin E is stored in high amounts in the pituitary gland and the adrenals. There does not seem to be a correlation between serum levels and stored vitamin E. Indeed, the storage of vitamin E is limited. The liver briefly stores vitamin E but only in small quantities. Adipose tissue and the adrenal glands also store vitamin E, and in time slowly releases it.

Poor vitamin E absorption (deficiency) can go undetected for a long time. As soon as damage is found, it is largely irreversible particularly in nervous tissue. Other symptoms of vitamin E deficiency include muscular weakness and reproductive failure (6,29). There are several genetic diseases that can lead to the poor absorption of vitamin E. These include, cystic fibrosis, cholestasis, and inflammatory bowel diseases (6,30).

Recent data indicate that a significant portion of ingested vitamin E homologs are metabolized to yield hydrosoluble compounds called carboxyethylhydroxychromans (CEHC), which are excreted through the kidney (31). It has been reported that CEHCs may be biologically active and may also exhibit pharmacological properties (32). The α-tocopherol transport protein (TTP) plays a crucial role in the secretion and incorporation of α-tocopherol into very low-density lipoproteins (VLDL) in the liver and its subsequent transport to the various tissues (33). However, TTP has a low affinity for tocotrienols and does not seem to play a significant role in their mobilization and metabolism in the body. Whether other transfer proteins specific to tocotrienols exist remains unknown at present.

Vitamin E toxicity is generally considered to be very rare and is generally observed at very high doses (>3.2 g kg^{-1} day^{-1}) (6,25). Potential toxicity may include interference with vitamin K metabolism and elevation in blood pressure in certain people with sensitivities to vitamin E. Even upon parenteral (intravenous) administration, vitamin E was found to be well tolerated in humans at doses up to 2.3 g m^{-2} for 9 consecutive days (34).

SOLVENT PROPERTIES OF TOCOLS

Unesterified Tocols

One particular property that makes tocols attractive for drug delivery is their capacity to solubilize a variety of water-insoluble compounds/drugs (1–3,35,36). These compounds are thought to be "tocophilic"—that is, "tocol-loving" in a manner analogous to the term "lipophilic," which means "lipid-loving." This is not to say, however, that all lipophilic compounds are tocophilic, and this has been well demonstrated in the literature (1–3,35,36). Nielsen *et al.* (35) investigated the solubility of several structurally unrelated compounds in tocopherol and sesame oil, and found that the most lipophilic compound, Lu28-179, having a log *P* (octanol/water) of approximately 8, was 10-fold less soluble in tocopherol than in sesame oil (58 *vs.* 550 mg g^{-1}, respectively). It is apparent that other physicochemical and structural factors can affect the solubility of a given compound in tocols.

Although there is no correlation between lipophilicity and tocophilicity, the elegant work of Illum *et al.* (36) established useful guidelines in predicting tocol solubility of a particular, poorly water-soluble compound/drug. Such prediction can be derived from the solubility of the compound/drug in chlorinated organic solvents and methanol. Drugs with high solubility in chloroform (≥6 mg mL^{-1}, preferably ≥10 mg mL^{-1}) have acceptable solubility in vitamin E (≥1 mg mL^{-1}, ideally ≥10 mg mL^{-1}). On the contrary, if a drug has high solubility in methanol (≥10 mg mL^{-1}), it would have a poor solubility in vitamin E (<1 mg mL^{-1}). A new term, SVE ratio, which is defined as the solubility in chloroform divided by the solubility in methanol (Table I), was introduced by Illum *et al.* for the prediction of drug solubility in vitamin E. A compound with an SVE value of greater than 10 (preferably greater than 100) would have acceptable solubility in vitamin E. Literature aqueous solubility values of intraconazole (37), paclitaxel (2), cyclosporine (38), cholesterol (39), prednisolone (36), and amphotericin B (40) are shown in Table I. No specific value was found on the aqueous solubility of ergosterol; however, it is expected to be similar to that of cholesterol.

Only selected lipophilic drugs are highly soluble in tocopherols and tocotrienols. Furthermore, lipophilic drugs that are charged tend to be adsorbed at the tocol–water interface where they may be subjected to degradation, even while residing in part in the tocol phase. Water-soluble or amphiphilic agents are not readily soluble in tocols. Besides the chemical modification of these drugs to render them more lipophilic, one approach to improve the tocol solubility of charged and amphiphilic drugs is by formation of tocophilic ion pairs (41). Drugs useful for the formation of tocol-soluble ion pairs may be selected on the basis of their amphiphilicity and charge as a function of pH, their octanol/buffer partition coefficient, and/or by their tocol solubility. In the case of multiply charged pharmaceutically active compounds or precursors, at least one charge on the molecule is available for ion pairing. Examples of tocophilic ion pairing

Table I. Solubility of Drugs in Organic Solvents and Vitamin E (Modified from (36))

	Solubility (mg mL^{-1})				SVE[a]	SP[b]
Drug	Water[c]	Methanol	Chloroform	Vitamin E		
Itraconazole	10^{-6}	Insoluble[d]	500	60	>1,000	10.6
Paclitaxel	0.00034–0.030[e]	0.03	6	11	200	11.9
Cyclosporine	0.023	0.71	363	100	520	10.7
Ergosterol	Insoluble[f]	1.5	32	50	25	9.6
Cholesterol	0.002	5	200	150	40	9.6
Prednisolone	0.22	33	5.0	Insoluble	0.02	13.6
Amphotericin	0.1[g]	Soluble[d]	Insoluble	Insoluble	<1	14.4

[a] SVE parameter: ratio of drug solubility in chloroform to that in methanol.
[b] Solubility parameter.
[c] Literature values (see Unesterified Tocols and corresponding references).
[d] Terms not defined in the original references (but do not pose problems for calculating and estimating the SVE).
[e] Solubility is time-dependent and varies from different sources (2).
[f] No specific value was found in the literature, but it is expected to be similar to that of cholesterol.
[g] At pH= 2 (40).

include the combination at neutral pH of a negatively charged vitamin E acetate, succinate, or phosphate with a positively charged drug such as doxorubicin and daunorubicin, camptothecin and analogs, clarithromycin, erythromycin and other macrolide antibiotics, ciprofloxacin and other quinolone antibiotics, amiodarone, and enalapril and other angiotensin-converting enzyme (ACE) inhibitors. Likewise, a positively charged tocol analog such as tocopheramine can be combined with an anionic drug, such as alendronate (41). Thus, tocophilic ion pairing expands the spectrum of drugs than could benefit from the advantages of a tocol formulation.

Tocol Esters: α-Tocopheryl-Polyethyleneglycol-1000-Succinate

Of all the tocol esters reported to date, TPGS is the single most investigated ester with reference to drug solubilization and delivery (8,42). It is a water-soluble form of vitamin E (vitamin E content of 260 mg g^{-1}) with an average molecular weight of about 1,513. It is a waxy solid (m.p. ~37–41°C), and is completely miscible with water [hydrophilic–lipophilic balance (HLB) value of about 13]. It has a specific gravity at 45°C of ~1.06 and its critical micelle concentration (CMC) at 37°C is 0.02%, w/w. At physiological temperature, depending on the water content, it forms various phases in aqueous solutions that can solubilize a variety of compounds, both water-soluble and water-insoluble (8). At low to intermediate water content, it forms liquid crystalline phases, such as lamellar, reverse micellar, and hexagonal phases, whereas conventional micelles (L1 Phase) are formed at high water content (8). All these phases have been investigated for drug solubilization and delivery. In addition to its water miscibility, TPGS is also miscible with oils (such as soybean oil and medium chain triglyceride), other surfactants, and cosolvents such as propylene and polyethylene glycols. In aqueous media, TPGS is stable at pH 4.5–7.5. It is also air-stable but reacts with alkali. The inclusion of cosolvents, particularly propylene glycol, improves the aqueous stability (8). The vendor of TPGS, Eastman Chemical, has on file with the FDA a Type II and Type IV drug master file (DMF nos. 9009 and 12961, respectively) and a USP/NF monograph for TPGS was published in 1998 (42). The name adopted by the USP for TPGS is tocophersolan.

The drug delivery applications of TPGS are numerous and include its use as a carrier for wound care and treatment (8), an oral bioavailability enhancer for poorly absorbed drugs (1,8), and a drug solvent and emulsion vehicle for parenteral administration (3). Each of these applications will be further discussed in the next section. These drug applications for TPGS are supported not only from the scientific and patent literature, but also by marketed drug products such as Agenerase® (GlaxoSmithKline Research Triangle Park, NC, USA) and drug formulations in clinical development, including those of cyclosporine and paclitaxel. Examples of drugs that are soluble in tocols and TPGS include cyclosporines, taxanes, steroids, antibiotics, and other drugs (1–3,35,36,41). Thus, it is not surprising that the patent filing activities on TPGS have increased exponentially in recent years.

DRUG DELIVERY APPLICATIONS OF TOCOLS

Topical: Transdermal and Ocular

The transdermal administration of tocols was developed presumably because of their excellent skin compatibility (43–46). The beneficial use of vitamin E and other tocols continues to be an active area of research in dermatology and cosmetic science. Topical administration has the advantage in that drugs may be administered readily and simply to achieve a systemic or dermal, regional, or localized effect, as required. However, the absorption rate of topically applied drugs is generally much slower than that through the gastrointestinal tract, and achieving therapeutic levels of a particular drug is challenging. Thus, much of the effort in topical drug delivery has been focused on enhancing skin permeation using various approaches, including the use of surfactants and cosolvents (47,48).

In topical applications, vitamin E has been primarily used as a natural moisturizer. However, other therapeutic uses of topically applied vitamin E include treatment of chronic skin diseases (43), reduction in erythema and swelling (45), and wound healing (44). It is thus not surprising that vitamin E and other tocols are present in many topical drug preparations and cosmetics. Cream formulations of

diclofenac based on vitamin E (49) and creams using vitamin E and its acetate, linoleate, or succinate esters and incorporating hydrocortisone, ketoprofen, and ibuprofen (50) have been reported.

In addition to transdermal administration, vitamin E has been used in ophthalmic delivery although studies in this area have been limited. In one particular study (51), it has been shown in patients who developed postoperative corneal melts (keratolysis) that topical application of diclofenac sodium 0.1% ophthalmic solution incorporating a vitamin E solubilizer (Falcon, Forth Worth, TX, USA) may be associated with aberrant matrix metalloproteinase (MMP) expression in the cornea. Whereas MMP is a normal component of repair, excessive or inappropriate MMP activity is associated with corneal keratolysis (51).

Oral Delivery

The oral administration of drugs is certainly the most preferred route provided that physicochemical and biological barriers to absorption can be successfully overcome (52). With water-insoluble drugs, poor solubility and drug efflux mediated by P-glycoprotein (P-gp) are often the major barriers to achieving good oral bioavailability (52–55). There is an increasing number of reports in the literature on the use of tocols and tocol esters, particularly TPGS, to enhance the oral absorption of several classes of drug molecules (8,53,55). These molecules include cyclosporine (56–60), paclitaxel (60–62), and protease inhibitors (63,68,69).

The oral absorption of cyclosporine is impeded by a number of factors that include poor solubility in aqueous solutions and GI fluids, impaired bile flow, and fat content in the diet. It was first demonstrated by Sokol *et al.* (56) in the clinic using liver transplantation patients that TPGS enhances cyclosporine absorption. Drug absorption enhancement was achieved when TPGS at 65 mg kg^{-1} day^{-1} was coadministered with cyclosporine at doses ranging from 12.5 to 40 mg kg^{-1} day^{-1} compared with 29–136 mg kg^{-1} day^{-1} in the absence of TPGS, thus resulting in approximately 40–70% reduction in cyclosporine daily dose.

Subsequent clinical studies in liver transplantation patients have further confirmed the role of TPGS in enhancing cyclosporine absorption (57–59). For example, a reduction in cyclosporine daily dose and associated costs without any clinical or biochemical evidence of TPGS induced toxicity was reported by Pan *et al.* (57). An increased blood concentration of cyclosporine upon TPGS administration reported by Boudreaux *et al.* (58) was attributed to enhanced drug solubilization through micelle formation. Effects of TPGS on cyclosporine pharmacokinetics with a significant increase in plasma AUC in healthy subjects were reported by Chang *et al.* (59). The improvement in pharmacokinetics was attributed to the effect of TPGS in enhancing drug solubility, as well as inhibiting P-gp and/or intestinal metabolism (54,55).

Another drug with oral absorption limited by P-glycoprotein is paclitaxel, a key chemotherapeutic agent, with other disease indications in clinical development or on the market, such as the recently approved drug-eluting coronary stent (Taxus®, Boston Scientific, Natick, MA, USA). Like cyclosporine, paclitaxel is highly hydrophobic and poorly water-soluble. Improvement of the oral bioavailability of paclitaxel in preclinical and clinical studies using various formulation approaches incorporating P-gp inhibitors, including TPGS, has been the subject of several reports in the literature (60–62,64–67). Yang *et al.* (61) recently reported on the use of a self-microemulsifying drug delivery system (SMEDDS) based on α-tocopherol and TPGS for enhancing the oral bioavailability of paclitaxel in rats (61). In addition to α-tocopherol and TPGS, this SMEDDS incorporated propylene glycol, sodium deoxycholate (DOC-Na), and Cremophor RH40. Although the presence of both TPGS and DOC-Na slightly improved the oral pharmacokinetics and bioavailability of paclitaxel, it was necessary to incorporate other P-gp inhibitors in the formulation, particularly CsA, to obtain therapeutic plasma levels and an acceptable AUC for the drug in rats (Fig. 3). It is evident from the data in Fig. 3 that the AUC/dose values increase upon i.v. administration and decrease upon oral administration either in the absence or presence of CsA. Thus, unlike the P-gp and first-pass extraction of the drug in the liver, which is a saturable process, P-gp and first-pass extraction of paclitaxel in the gut do not reach saturation at the investigated doses of paclitaxel (61).

Enhancement of the oral aborption of paclitaxel with TPGS by affecting drug solubility and permeability *in vitro*, *in situ*, and *in vivo* was recently reported by Varma and Panchagnula (62). As the concentration of TPGS was increased above 0.1 mg mL^{-1}, a linear increase in paclitaxel solubility was observed presumably via micellar solubilization (62), as it has been observed with TPGS and Amprenavir using the reported CMC of TPGS of 0.2 mg mL^{-1} (8,63). Using rat ileum tissue in Ussing chambers, the bidirectional transport of ^{14}C paclitaxel was also monitored in the presence of increasing concentrations of TPGS. The apical-to-basolateral (A→B) permeability of paclitaxel was found to increase in the presence of TPGS, whereas the basolateral-to-apical (B→A) permeability was decreased with maximum effect at 0.1 mg mL^{-1} of TPGS (62). Interestingly, at TPGS concentrations above 0.1 mg mL^{-1}, the A→B permeability was decreased with no change in the B→A permeability, suggesting that monomeric, rather than micellar, TPGS is involved in P-gp inhibition (62).

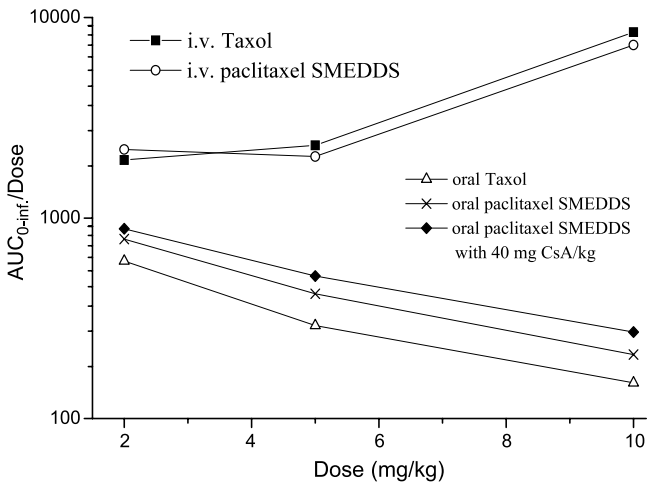

Fig. 3. Relationship between dose-adjusted $AUC_{0\to\infty}$ and administered doses for intravenous and oral administration of paclitaxel SMEDDS and Taxol® with and without cyclosporine (with permission (61)).

In a separate experiment (62), ^{14}C paclitaxel was dissolved in cremophor/ethanol (1:1) and, upon dilution with saline, was administered perorally to anesthetized rats with and without the coadministration of TPGS (50 mg kg^{-1}) or Verapamil (25 mg kg^{-1}). Both the C_{max} and AUC of paclitaxel were increased in the presence of TPGS or Verapamil with the effect of TPGS on both parameters being higher. A 6.3-fold *vs.* 4.2-fold increase in apparent bioavailability was observed with TPGS and Verapamil, respectively (62). It is not clear, however, whether TPGS enhances the oral biovailability of paclitaxel by improving drug dissolution through micellar solubilization, as suggested by the authors and/or by other mechanisms. Interestingly, P-gp inhibition *in vitro* is diminished in the presence of TPGS micelles (8,62,63).

TPGS was also shown to improve the bioavailability of amprenavir, a protease inhibitor marketed as Agenerase® by GSK (63). A soft gelatin formulation using a SEDDS and incorporating TPGS, PEG 400, and propylene glycol was used to increase the bioavailability of amprenavir. TPGS was found to have various effects: (1) improved the solubility (S) and thus dissolution of amprenavir through micellar solubilization, and (2) enhanced the permeability (P_{eff}) of amprenavir across the gut wall, presumably through drug efflux inhibition. Hence, TPGS enhanced the overall absorption flux ($J = P_{eff}S$) of the drug (Fig. 4) by increasing its solubility and intestinal permeability (63). The softgel formulation containing 20% TPGS produced 69 ± 8% absolute bioavailability in beagle dogs at a drug dose of 25 mg kg^{-1}. Increasing TPGS from 20 to 50% in the formulation improved the absolute bioavailability to 80 ± 16% (63). A good correlation was found between the *in vivo* absorption data and the *in vitro* Caco-2 permeability measurements.

The poorly soluble HIV protease inhibitor, saquinavir, marketed as Fortovase® by Roche (Nutley, NJ, USA), has been solubilized by a mixture of vitamin E and medium-chain mono- and diglycerides in softgels incorporating 200 mg of the drug (68,69). The oral bioavailability of saquinavir increased by approximately 3-fold in this formulation compared to the solid dosage form Invarase® (68). The reported oral bioavailability of saquinavir in Invarase® is variable

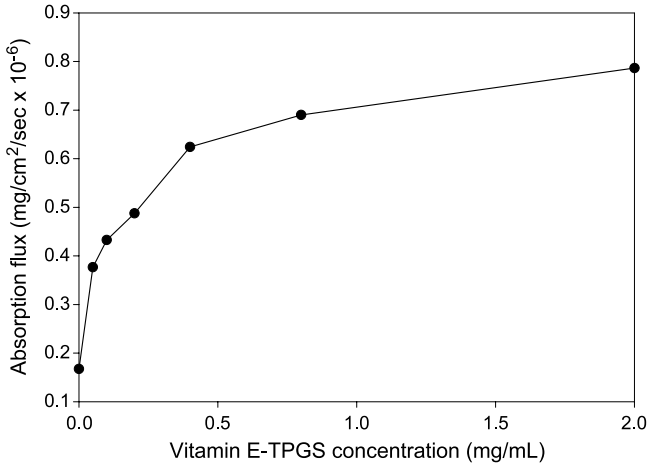

Fig. 4. Amprenavir absorption flux as a function of α-tocopheryl-polyethylene glycol-1000-succinate (TPGS) concentration. At low TPGS concentrations, absorption flux increases rapidly with increase in TPGS; above 0.5 mg mL^{-1} vitamin E TPGS, the rate of increase levels off (with permission (63)).

(1–9%), averaged at about 4%, suggesting that the drug bioavailability from the Fortovase® formulation (which has not been reported), is about 15% (69).

TPGS has also been used in oral formulations of R1481 a BCS Class 3 compound (70), having high solubility and low permeability (71), and in the development of microemulsion systems for the oral delivery of protein drugs (72). R1481 is a subtype-selective muscarinic receptor antagonist. It is a water-soluble viscous semisolid drug substance with poor oral bioavailability due to a low intestinal permeability and P-gp efflux (70). It has been formulated as an oral solution in orange juice and in soft gelatin capsules (SGC), incorporating medium-chain mono-/diglycerides (Capmul MCM) with and without TPGS. The oral bioavailability of R1481 in micropigs ($n = 2$) was found to increase in the order of Capmul MCM+ TPGS, SGC (44.4%) >solution (33.3%) >Capmul MCM, SGC (24.6%), however, with high intersubject variability (70). When tested in healthy male and female volunteers, all three formulations produced similar plasma concentrations *vs.* time profiles without significant differences in the calculated pharmacokinetic parameters (70). It was thus concluded that the systemic exposure of R1481 in humans was not improved by the addition of TPGS. Potential differences in the intestinal P-gp between the micropig and human may explain, at least in part, the lack of an effect by TPGS in improving the oral bioavailability of R1481. Even in the micropig model, the observed high intersubject variability does not indicate any significant effect of TPGS on R1481, presumably because it is a water-soluble molecule.

In an effort to develop microemulsion systems incorporating TPGS and other excipients useful for the oral delivery of protein drugs, detailed phase diagrams were constructed and reported (72). These pseudo-ternary phase diagrams were composed of Captex 300 oil, water, and incorporating TPGS as the primary surfactant, polysorbates (Tween 20, 40, 60, and 80) as secondary surfactants, and PEG 400 and 600, and polyols (ethanediol, 1,2-propanediol, 1,3-propanediol, 1,3-butanediol, 1,4-butanediol, and glycerin) as cosurfactants. Stable and transparent microemulsion and gel regions were identified in the quaternary systems composed of water/Captex 300/TPGS/Tweens, PEGs, and polyols (72). The presence of polyols as cosurfactants was found to be essential in the formation of stable microemulsions. As the relative concentration of polyols increased, the maximum amount of solubilized oil decreased and inclusion of TPGS is critical to the oil solubilization by polyols. It was reported by the authors that application of these microemulsion systems for peptide delivery is currently under investigation. As mentioned earlier with R1481, however, it is not clear what effect, if any, TPGS has on the oral bioavailability enhancement of water-soluble drugs/peptides besides its general use as a hydrophilic surfactant in lipid-based formulations of these molecules.

Parenteral Delivery

A Lesson from Early Formulations of Parenteral Vitamin E

An intravenous form of vitamin E was first clinically used in the early 1980s in low-birth-weight and premature infants for the treatment of the retrolental fibroplasias, a cause of blindness observed among premature infants. The

commercial formulation, E-ferol, contained 25 mg mL^{-1} of DL-(α)-tocopherol, polysorbate 80 at 90 mg mL^{-1}, and polysorbate 20 at 10 mg mL^{-1} in the form of an aqueous dispersion. This formulation was usually diluted in an appropriate intravenous solution prior to administration and a dose between 25 and 50 mg was usually used, which was not generally prescribed on body weight (73). As vitamin E has been safely used orally for such a long time, this particular intravenous formulation was developed and marketed without detailed safety tests. Unfortunately, severe adverse effects, including hepatomegaly and renal failure, were observed among infants exposed to E-ferol, and it was later confirmed that many of the deaths during that period of time were attributable to the use of E-ferol (74). Although it could be argued that vitamin E caused the toxic effects, available evidence suggests that the observed toxicity was more likely due to the excipient polysorbate 80 (75). The incident with E-ferol clearly demonstrates the need to carefully select excipients/emulsifiers in vitamin E emulsions that are intended for parenteral administration.

Suitable Emulsifier Systems for Tocols

The widely used vegetable oil emulsions for parenteral nutrition are usually stabilized by lecithins, HLB = 9.2–9.5 (76), and excellent stability has been observed (77). However, stable tocopherol emulsions could not be prepared if lecithins were the only emulsifiers used (2,78). The reason for this observation could be that vitamin E is more polar than vegetable oil because of the existence of a hydroxyl group on the aromatic ring and such polarity may result in higher solubility of lecithin in the vitamin E phase with the result that it becomes less available at the tocol/water interphase. Therefore, a hydrophilic coemulsifier with higher HLB value would be more likely to create a stabilized interface. Among the emulsifiers evaluated by Han *et al.* (78) for this purpose were poloxamer 188 (a nonionic polymeric PEO–PPO–PEO surfactant, HLB = 29), polysorbate 80 (HLB = 15), potassium oleate (HLB = 19), and sodium deoxycholate (HLB = 24); the last one had the best emulsifying properties and was more suitable for the emulsification of vitamin E.

There has been great interest in using pegylated phospholipids for various drug delivery applications (79,80). The polyethylene glycol derivatives of phospholipids (PEGylated phospholipids) are also potentially good emulsifiers for tocols. A more hydrophilic PEO polymer chain is added to the phospholipid structure, and as a result, the pegylated phospholipids are more hydrophilic than conventional phospholipids and can provide better stabilization of micellar, liposomal, and emulsion formulations. A pegylated phospholipid, PEG5000PE, has been used in a vitamin E emulsion as a steric stabilizer for increased stability in plasma and this will be discussed in the next section.

TPGS with an HLB value of 13 (8,81) is another good candidate for stabilizing tocol emulsions. The tocol moiety of the TPGS will naturally have strong tendency to associate with tocol phase, whereas the polyethylene glycol moiety will remain highly associated with the aqueous phase. It is unique as an emulsifier for tocol emulsions in that TPGS itself is a tocol derivative and it has been successfully used in a tocol emulsion by Constantinides *et al.* (3,82) for the intravascular delivery of paclitaxel. These studies will be reported below under the applications of vitamin E in parenteral drug delivery.

Stability in plasma is an important requirement for i.v. emulsions as flocculated droplets may result in lung embolism. It was found that tocol emulsions stabilized by sodium deoxycholate/lecithins flocculated strongly when mixed with mouse, rat, and sheep plasma and serum, whereas soya oil emulsions with the same emulsifiers did not (78). It was hypothesized that this effect was caused by the adsorption of plasma proteins onto the tocol droplets (opsonization). Indeed, the steric stabilization of tocol emulsions with the PEO containing emulsifiers poloxamer 188 or PEG5000PE proved to be effective in the stabilization of tocol emulsions in plasma. Fig. 5 (2,78) shows the stability of emulsions containing 2% PEG5000PE as compared to that without PEG5000PE after incubation in plasma and serum at 37°C for 24 h. The pegylated phospholipid containing emulsion (mean diameter, ca. 200 nm) did not show any change in droplet size, whereas the emulsion without this emulsifier showed significant increase in droplet size in all media tested (1,000–6,500 nm). The PEO chains that are present in PEG5000PE and poloxamer 188 are proven to have protein-rejecting effects (83) and could therefore stabilize emulsions in plasma.

Any emulsifier containing PEO chains could potentially be used as steric stabilizer for tocol emulsions. It has been reported that polymers with longer PEO chains provide better protein-rejecting effects (84), and an emulsifier with a long PEO chain should be selected wherever possible. TPGS contains PEO chains, and consequently emulsion formulations incorporating TPGS, such as those developed by Constantinides *et al.* (82), are sterically stabilized to a significant degree.

Applications of Vitamin E in Parenteral Drug Delivery

Tocol emulsions are potentially useful for the delivery of any drug that is poorly soluble in water but soluble in tocol such as the chemotherapeutic agent paclitaxel (2,3,82). As discussed earlier, however, not all poorly soluble drugs are necessarily soluble in a tocol, although drugs with poor triglyceride oil solubility can exhibit good solubility in a tocol oil. Thus, tocol emulsions can be used with poorly soluble

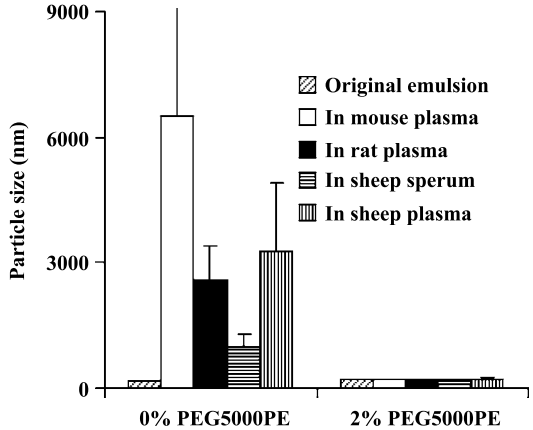

Fig. 5. Stability of vitamin E emulsions containing 2% PEG5000PE in plasma and serum after 24 h incubation at 37°C (78).

drugs where triglyceride emulsions are not an option. Importantly, steric stabilization of the emulsion with PEO containing emulsifiers was proven to be crucial to achieve stability in plasma. Constantinides *et al.* (82) developed a filter-sterilizable vitamin E emulsion for paclitaxel (TOCOSOL®-paclitaxel). This system employed TPGS and poloxamer 407 as the emulsifiers and contained PEG400. TOCOSOL®-paclitaxel was shown to be better tolerated and more efficacious than the current clinical formulation of paclitaxel Taxol® (which contains the undesirable Cremophor EL) using the B16 mouse melanoma model. B16 melanoma is a fast-growing solid murine tumor and has been commonly used in early screening of different anticancer agents (3,82,85). Fig. 6 presents tumor growth regression for the dosing regimen administered every 3 days for a total of 5 times (q3dx5). TOCOSOL®-paclitaxel was evaluated at different doses and compared to the reference Taxol® formulation at its maximum tolerated dose (MTD) of 20 mg kg^{-1}. It is clear from these data that TOCOSOL®-paclitaxel was more efficacious than Taxol® in a dose-dependent manner.

Table II summarizes the overall results of the efficacy study on a q3dx5 schedule including mean survival times, median tumor weights, and log cell kills (LCKs) for each group and treatment schedule. The various values in Table III are calculated by using median values from the treatment and control groups and although survival within a group can be represented as mean ± SD, using the median group value in the calculations results in one number. By all end points of efficacy (85), TOCOSOL®-paclitaxel exhibited superior antitumor activity in mice at doses that included or well exceeded the MTD of Taxol®, but which were well tolerated. Log cell kill values of 1.8 and 3.0 were observed with TOCOSOL®-paclitaxel at 20 and 40 mg kg^{-1} doses, respectively, as compared to a value of 0.5 obtained with Taxol® at 20 mg kg^{-1}. TOCOSOL®-paclitaxel has successfully completed Phase I and Phase II clinical investigations (3) and a Phase III study is being initiated.

An intravenous tocopherol emulsion for the delivery of amiodarone has been investigated in an effort to replace the current clinical formulation Cordarone®, which contains 2% polysorbate 80. It was shown to be better tolerated in mice and to reduce venous irritation in rabbits (Kessler *et al.*, unpublished data, 2002).

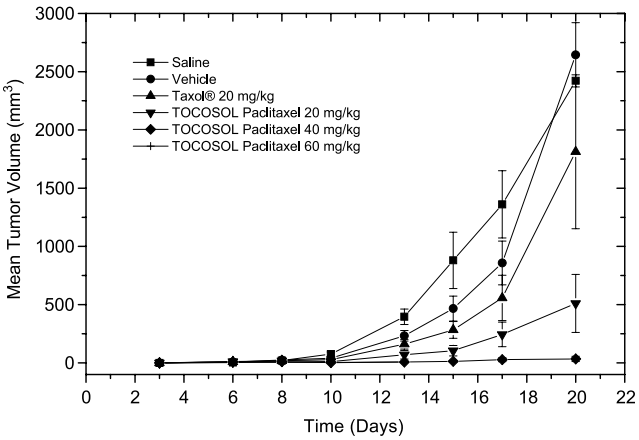

Fig. 6. Comparative tumor growth of B16 Melanoma-bearing mice. The data points for the 60 mg kg^{-1} TOCOSOL®-paclitaxel group are overlaid on the data points of the 40 mg kg^{-1} dose for this group (values shown are mean ± SEM (3,82)).

Wang *et al.* (86) have studied the antitumor effects and pharmacokinetics of an injectable aclacinomycin-containing vitamin E emulsion incorporating pegylated lipid and cholesterol. They reported that it had a lower acute toxicity and greater potential antitumor effects than the free aclacinomycin. They also studied a microemulsion composed of PEG lipid, oleic acid, vitamin E, and cholesterol as a delivery system for vincristine. Again, the emulsion formulation was more effective in terms of anticancer effect and had a lower toxicity than the free drug (87).

Oil-in-water emulsion compositions based on a tocopherol (or a tocopherol derivative) as the disperse phase have been described in a patent granted to Dumex (88). The emulsion is intended for use with compounds that are sparingly soluble in water. Interestingly, the emulsifying agent has been restricted to vitamin E TPGS. The emulsion is claimed to be suitable for intranasal, buccal, vaginal, or rectal application, or for administration via the oral cavity. The emulsion could also be used parenterally. The examples provided were mainly for the so-called "nose drop" systems with drugs such as diazepam, cinnarizine, and budesonide. Some limited studies in rabbits were also reported. However, more data are needed to support the use of tocol emulsions in these areas.

In addition to its use in parenteral emulsions, α-tocopherol in an esterified form has also been used in pH-sensitive liposomes, which are stable at neutral pH but become unstable and leaky when the pH is changed to an acidic value. These liposomes have been studied as cytoplasmic delivery carrier systems. When the liposomes are entrapped in the acidic medium of the endosome, the first step of the endocytotic process is to eliminate foreign particles from the body, then the liposomes become unstable and will release the drug into the cytoplasm. However, liposomes made from pH-sensitive materials, such as palmitoylhomocysteine or mixtures of phosphatidylethanolamine (PE) and oleic acid or cholesteryl hemisuccinate, were not sensitive enough to achieve the desired results (89). Better sensitivity could be achieved by using the tocopherol derivative, α-tocopherol hemisuccinate (THS), either alone or in combination with phosphatidylethanolamine (90). The permeability of the liposomes made from THS alone increased dramatically (from well below 10% to over 90% for the release of carboxyfluorescein) from pH 6 to 5. The change in permeability was correlated with the change in light scattering intensity, which is an indication of aggregation or fusion of the liposomes. The pH sensitivity has been attributed to the pK_a of the carboxylic group of the tocopherol hemisuccinate. The increased sensitivity, as compared to the materials mentioned above, was probably the result of the bulky hydrophobic group being adjacent to the hydrophilic part of THS molecule as compared to the nontocopherol esters. Similar sensitivity was observed with liposomes composed of THS/PE. Incorporation of cholesterol into the THS/PE increased the stability of the liposomes at neutral pH without compromising the pH sensitivity.

Micellar solubilization using the tocol derivative TPGS has been employed to improve the solubility of estradiol (91). The solubility increased consistently with an increase in

Table II. Antitumor Activity of TOCOSOL®-Paclitaxel *vs.* Taxol® Against B16 Melanoma on a q3dx5 Schedule (3,82)

Group (8 mice/group)	Dose (mg kg^{-1})	% T / C[a], day 20	%TGI[b], day 20	T − C[c] (days)	LCK[d]
Vehicle	N/A	93	3	3	N/A
Taxol®	20	77	23	3	0.5
TOCOSOL®-paclitaxel	20	11	89	10	1.8
TOCOSOL®-paclitaxel	40	0	100	17	3.0

[a] % Treated / Control (T / C) = (median tumor weight of treated / median tumor weight of control) × 100.
[b] % Tumor growth inhibition (TGI) = 100 − (% T / C).
[c] T − C = Tumor Growth Delay Value is the median time for the treatment group (T) and control (C) to reach a predetermined size (>750 mg).
[d] Log cell kill (LCK) = (T − C value) / (3.32 × tumor doubling time).

TPGS concentration, with or without the presence of alcohol. In another study, TPGS has been shown to increase the solubility of cyclosporin A (92) most likely by micellar solubilization as discussed above.

Apart from serving as a vehicle for other therapeutic drugs, vitamin E itself has important pharmacological functions as discussed earlier in this review article. In the case of parenteral administration, for example, vitamin E succinate was shown to decrease lung cancer tumor growth in mice via intraperitoneal injection of its solution in polyethylene glycol and dimethysulfoxide (7 and 93%, respectively) (93). Interestingly, it was recently reported that TPGS, which is a pegylated vitamin E succinate, inhibited the growth of human lung carcinoma cells implanted in nude mice, and in an *in vitro* cell culture system, more potently than vitamin E succinate (94). As cell uptake of both molecules followed similar kinetics, the enhanced efficacy of TPGS was attributed to its increased ability to induce apoptosis (94). Although these early results look promising, more work is needed using multiple cell types and tumor models to rigorously demonstrate the enhanced antitumor activity of TPGS and identify the underlying mechanism(s).

A clinical study on 68 patients has shown that intravenously administered vitamin E (in vegetable oil emulsions) may have beneficial effects by reducing the impact of ischemia and reperfusion (IR) injury in liver surgery (95). IR is usually involved in liver surgery and may lead to oxidative stress and cell damage. The intravenous administration of a pharmacological dose of vitamin E (3 × 600 IU = 3 × 540 mg before surgery) seems to be a safe and efficient method to increase vitamin E plasma concentrations and could therefore be beneficial in preventing cell damage due to the free radical-based oxidation.

A polymeric nanoparticle consisting of the amphiphilic diblock copolymer of mPEG-PLA-Toco and PLMA-COONa and incorporating doxorubicin (Dox-PNP) has recently been developed (12). Up to 95% of doxorubicin can be entrapped in these nanoparticles (loading of 0.92%, w/w) having a mean diameter of 20–25 nm and a narrow size distribution. Compared to free doxorubicin (free-Dox), Dox-PNP exhibited higher cellular uptake into both human breast cancer cell line (MCF-7) and human uterine cancer cell (MES-SA), especially into doxorubicin-resistant strains (12). Upon tail-vein injection in rats and tumor-bearing mice, the pharmacokinetics and tumor distribution of free-Dox and Dox-PNP were compared. It was found that Dox-PNP exhibited ~70 times higher bioavailability in rats and showed 2 times higher bioavailability in tumor tissue in mice than free doxorubicin (12).

Table III. Drug Delivery Applications of Tocols

Route of Administration	Form of Tocol/Lipid Vehicle	Drug	Ref.
Oral	TPGS/SEDDS	Cyclosporine	(56–60)
	Vitamin E/SEDDS	Cyclosporine, Taxoid	(60)
	Vitamin E, TPGS/SMEDDS	Paclitaxel	(61)
	TPGS/Cremophor EL:ethanol:saline	Paclitaxel	(62)
	TPGS/SEDDS	Amprenavir	(63)
	Vitamin E/oily solution with medium-chain mono-/diglycerides	Saquinavir	(68,69)
	TPGS/oily solution with medium-chain mono-/diglycerides	R1481, a subtype selective muscarinic receptor antagonist	(70)
Parenteral	α-Tocopherol, TPGS/microemulsion	Paclitaxel	(3,82)
	α-Tocopherol, TPGS/microemulsion	Amiodarone	(3, unpublished data)
	Vitamin E/emulsion	Paclitaxel	(78)
	Vitamin E/emulsion	Aclacinomycin	(86)
	α-Tocopherol/microemulsion	Vincristine	(87)
	α-Tocopherol/liposome	Contraceptive vaccines	(96)
Topical	α-Tocopherol/gel, cream	Diclofenac	(49)
	Tocopherol, acetate, nitotinate or succinate esters/cream	Hydrocortisone, ketoprofen, ibuprofen and other	(50)
	TPGS/gel	wound healing	(8)
Nasal, rectal/vaginal	α-Tocopherol/emulsion	Diazepam, cinnarizine, miconazole	(88)
Nasal	TPGS/PCL microspheres	Diphtheria toxoid	(99)

Liposomes incorporating γ-inulin and vitamin E as a combination adjuvant system has been reported for the development of contraceptive vaccines (96). The adjuvant potential of this system was evaluated in mice using contraceptive vaccines with sperm protein extracts or a synthetic HE2 peptide and its performance was compared to that of Freud's adjuvant. The toxicity of the adjuvant systems was determined by histopathology and by monitoring the treated animals for signs of pain or distress (96). It was observed that with sperm protein extracts, the combination adjuvant system was better than Freund's adjuvant, because it elicited good antibody titers without any toxicity. However, using the HE2 peptide as antigen, the combination adjuvant system was found to be less effective than the Freund's adjuvant, although the elicited anti-HE2 antibodies were shown to be highly specific and to recognize native structures in sperm (96). At the investigated doses, the combination adjuvant system was reported to be nontoxic and nonpyrogenic (96). Thus, it will be interesting to see how this combination adjuvant system behaves in humans using a variety of antigens and adjuvant doses.

Other Routes of Delivery: Pulmonary and Nasal

Aerosolized vitamin E (0.3–3 μm) has been prepared by supercritical fluid aerosolization and has been shown to be effective in increasing lung tissue vitamin E levels and in decreasing interleukin-1 induced lung damage in rats when directly administered to the lungs (97). The level of vitamin E in the lung increased more than 100% in 10 min, which is significantly faster than the increase observed after oral or i.v. administration.

Liposomal vitamin E has also been shown to protect the lung against paraquat-induced damage when instilled intratracheally into the lungs of rats (98). Reactive oxygen species are known to play a key role in the development of acute lung injury and the mechanism of protection by vitamin E was again due to its antioxidation effects.

The possible use of tocol emulsions for the delivery of challenging drugs to the nose and other mucosal sites has been discussed above. In reference to nasal delivery, the use of TPGS as an adjuvant for the nasally administered diphtheria toxoid has been reported (99). The vaccine was loaded into poly(caprolactone) microspheres (PCL) with and without the inclusion of TPGS, and the incorporation of TPGS into the PCL microparticles did not compromise diphtheria toxin loading. Control PCL microspheres without TPGS and microspheres incorporating TPGS (PCL-TPGS) were administered nasally to anesthetized BALB/c mice, and their ability to elicit IgG response was monitored and compared. A 10-μg dose of diphtheria toxoid per mouse ($n = 5$) in the aforementioned microspheres was administered on day 1, followed by a 5 μg boost on day 28 (99). Immune responses measured after 15 and 45 days were significantly higher with PCL-TPGS microspheres than with PCL alone (99). The potential of TPGS to serve as adjuvant for other vaccines in a variety of drug delivery systems need to be established, however, prior to its general acceptance as a vaccine adjuvant.

The drug delivery applications of tocols discussed in this review article are summarized in Table III. Although the list represents major drug delivery applications of tocols, there may be other applications reported in the scientific and patent literature that are not included in this list. It does nevertheless emphasize the diversity and versatility in the use of tocols as drug delivery vehicles.

CONCLUSIONS

Outside of their well-established nutraceutical and cosmeceutical applications, tocols are becoming attractive delivery vehicles for poorly soluble drugs, particularly in reference to oral and parenteral administration. Advantages of tocols include high solubilization capacity and compatibility with other pharmaceutical excipients and solvents, reduced toxicity, improved efficacy, and oral bioavailability. The drug delivery potential and therapeutic benefits of tocols for a particular drug can be realized through its clinical progression. In the future design of tocol-based formulations, the pharmacological effects of tocols and the intended medical indications of the drugs should be considered along with the physicochemical properties of the formulations. A broad experience with tocol formulations using multiple drug types and doses, patient populations, and disease indications will most likely increase the therapeutic value and utility of these drug delivery systems.

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