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# Using Tocophersolan for Drug Delivery

A natural vitamin E derivative is an innovative excipient.

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**Tocophersolan or d-α-tocopheryl polyethylene glycol succinate (TPGS) was developed 60 years ago as a water-soluble form of vitamin E. Its surfactant properties triggered the interest of drug formulation developers before it steadily moved into the toolbox of pharmaceutical drug-delivery innovators. The author gives an overview of TPGS, including its interesting properties, examples found in the literature, and a brief summary of the regulatory status and marketed formulations.**

Pharmaceutical drug innovation is schematically based either on new entities or new drug solutions. The research activity of the pharmaceutical industry in the past focused on creating novel bioactive molecules, which has produced a huge number of chemical entities. The race to develop new chemical entities (NCE), however, has become more challenging and less successful. The current strategy of pharmaceutical companies has been adjusted and, consequently, a part of the innovation effort has now switched from finding new entities to optimizing drug delivery. Drug release innovation is either focused on improving the efficacy of an existing drug substance (i.e., benefit of a new drug-delivery technology) or re-examining NCE candidates that were previously rejected for being poorly soluble. New delivery technologies will likely be increasingly used for NCEs as soon as the use of these technologies becomes more understood.

The major role of a drug-delivery solution is to ensure the right bioavailability (i.e., the right dose at the right time at the right place), which directly depends on solubility and permeability of the active ingredient. Drug delivery innovation intends to care for the comfort of the patient following the therapy, but drug efficiency is the first target in the benefit-risk balance of a new drug product.

The Biopharmaceutical Classification System (BCS) classifies drug substances based on solubility and permeability. NCEs, despite having interesting activity potential, are increasingly classified as poorly soluble (Class II), with others having low permeability (Class III) or even low permeability and solubility (Class IV). Improving both the solubility and permeability of NCEs is one of most important challenges for drug developers.

d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) offers interesting properties to innovators that can address drug-delivery challenges. This article gives a basic overview of TPGS including properties, applications, and practical information to offer a picture of its interest and of the domains it can serve in pharmaceutical drug delivery innovation.

**History of TPGS**
TPGS (CAS Registry Number 9002-96-4) was invented by Eastman Kodak in 1950. It was developed as a water-soluble form of vitamin E, offering a novel route of vitamin E supplementation. TPGS is a mixed succinate ester of natural vitamin E and polyethyleneglycol 1000, which is prepared in two chemical steps from vitamin E (see **Figure 1**).

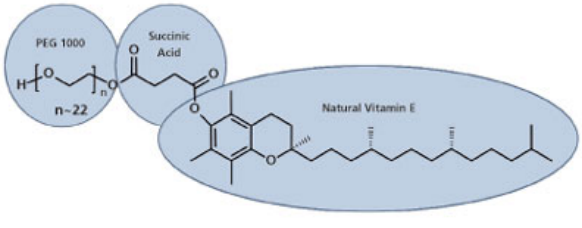


**Figure 1**: Formation of d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) from natural vitamin E and polyethyleneglycol (PEG) 1000.

TPGS is approximately 20% w/w soluble in water at 25 °C. This solubility is high compared to the low water solubility of vitamin E, which is classified as an oil-soluble vitamin. This physical characteristic of TPGS is both the starting point and the core advantage of TPGS-based innovations, especially in the pharmaceutical field.

In 1960, TPGS was suggested as a solubilizing agent for oil-soluble vitamins. Twenty years later, TPGS was used for treatment of vitamin E deficiency and chronic cholestasis (1) as well as vitamin E deficiency in animals (2). Later, its usefulness as a water-soluble antioxidant was established; however, this effect is seen only after water hydrolysis (3). The 1990s marked a major turn for TPGS. The enhancement of cyclosporine and vitamin D absorption was reported in 1996 (4). In 1999, TPGS was accepted as a pharmaceutical solubilizer and absorption enhancer (5); 1999 also marked the first FDA approval for drug using TPGS: amprenavir (Agenerase) (6).

Recently, TPGS has been explored increasingly in pharmaceutical development studies. Over the past 15 years, the number of published articles and patents clearly show this trend (see **Figure 2**).

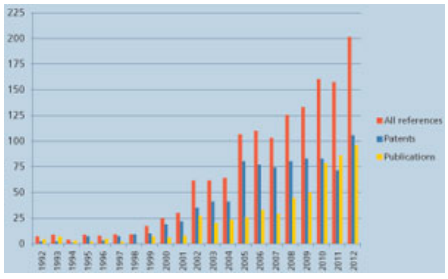


**Figure 2**: References to Tocophersolan (TPGS) in the Chemical Abstracts Service database of the American Chemical Society.

**A non-ionic surfactant**

The TPGS structure shows a hydrophilic head (polyethylene glycol chain) and a lipophilic tail (tocopheryl group) (see **Figure 1**). This amphiphilic skeleton gives TPGS its non-ionic surfactant properties as reflected by the hydrophilic lipohilic balance (HLB) number. The HLB of TPGS is 13, which is within the 0–20 range for non-ionic surfactants. Consequently, it can both act to increase solubility parameters and to allow making emulsions of lipophilic compounds in aqueous systems (7). Other key characteristics of TPGS are given in **Table I.**

**Table I: Tocophersolan (TPGS) surfactant properties.**

| Property | Value |
|---|---|
| Water solubility | 20% w/w at 25 °C |
| Gels in water | four crystalline forms in water mixture at concentration above 20% |
| Hydrophilic lipohilic balance number | 13 |
| Critical micelle concentration | 0.02% w/w at 37 °C |
| Stability in solution at 20 °C | Between pH 4.5 to 7.5 |
| Polyethyleneglycol/propyleneglycol 50/50 mixture | Freely soluble |

**Table I**: Tocophersolan (TPGS) surfactant properties.

Modifying the polyethylene glycol (PEG) chain can modulate the HLB number of the corresponding TPGS. For example, TPGS 200 with a PEG chain of molecular weight of 200 has an HLB number of 9, and TPGS 2000 with a PEG chain of molecular weight of 2000 has an HLB number of 16. TPGS 1000 is the current commercial form; however, TPGS with different chain lengths are available in quantities for research purposes (7).

TPGS solubility is approximately 20% at room temperature. Preparation of such a solution requires a specific procedure to successfully obtain a clear solution. A typical laboratory-scale procedure involves the following:

Melt 20 g of TPGS at 60–65 °C.
Heat 80 mL of water between 60 to 65 °C.
Over 30 min, under moderate stirring, add the melted TPGS to the water while maintaining the temperature of the mixture at 60–65 °C. The stirring must be moderate to avoid formation of foam.
The solubilization is complete after four hours stirring at 60–65 °C.
Cool down the solution to 20–25 °C under stirring to obtain a clear, slightly yellow solution.

TPGS is a waxy solid that melts around 37 °C. These characteristics exclude any crystal or flake forms of bulk product; consequently it is packed as a melted product that solidifies in the drum. Bulk quantities are available up to 100 kg per unit in drums, allowing adequate storage and handling. Bulk product has the capability to resist heat degradation during melting in accordance with cGMP standards (7).

Melted TPGS has a viscosity of 400 cp at 50 °C and 230 cp at 60 °C. Handling is recommended at 60 °C. It has been demonstrated that TPGS is stable enough to resist five heat and cool cycles simulating several melting–emptying operations, which makes it suitable for pharmaceutical drug formulation use.

**A multipurpose tool for drug delivery innovation**

The surfactant property of TPGS is the key driving factor for R&D with this particular excipient in the field of drug delivery. Indeed, TPGS can dramatically increase the concentration of an active substance in an aqueous matrix. The first remarkable achievement is the commercialization of two formulations of an HIV protease inhibitor, amprenavir (Agenerase) (6). TPGS forms micelles with amprenavir and improves solubility in water from 36 $\mu$g/mL to 720 $\mu$g/mL (5). From these results, two formulations have been marketed: a soft gelatin capsule of 50 mg and 150 mg of amprenavir and an oral solution at 15 mg/mL of amprenavir.

A second illustration is Paclitaxel, a non-polar molecule with an extremely low solubility of 1.34 $\mu$g/mL in water at 37 °C. When using a TPGS concentration of 5 mg/mL, Paclitaxel solubility is increased by approximately 38-fold to 50 $\mu$g/mL (8). These two examples demonstrate that TPGS improves the solubility of poorly soluble drugs in commercial formulations by taking advantage of its surfactant properties. The application of TPGS, however, is not limited to only basic solubility enhancement. The following examples draw a general picture of the numerous applications for innovative delivery solution based on TPGS. They are classified according to a recent detailed review on TPGS developments (9). Summarized here are the main applications along with one corresponding literature example:

- TPGS-based micelles: Surfactant properties of TPGS 1000 and 400 compared to other non-ionic sufactants (Triton-X 100 and Triton-X 165) have been reported (10).
- TPGS as a pro-drug carrier: Targeted chemotherapy using doxorubicin (DOX) conjugated with TPGS and folic acid has been studied showing improved performances compared to DOX (11).
- TPGS-based liposomes: TPGS has been successfully explored for a coated liposome drug-delivery system for docetaxel (12). Increased encapsulation efficiency as well as higher cellular uptake and efficacy have been obtained with the use of TPGS.
- TPGS-emulsified nanoparticles: TPGS drug-encapsulation efficiency has been compared with the traditional chemical emulsifier polyvinlyalcohol. TPGS improves the encapsulation efficiency by 100% (13).
- TPGS as an additive for nanoparticle formulation: TPGS can confer stability of a fluoroquinolone antibiotic lipid-polymer hybrid nanoparticles based on biodegradable poly (lactic-co-glycolic acid) (PLGA) and phosphatidylcholine (14).
- TPGS biodegradable copolymers with polylactic acid (PLA): PLA-TPGS copolymers have been shown to be potential candidates for drug delivery, which can be developed to deliver anticancer compounds such as paclitaxel, docetaxel, doxorubicin, protein bovine serum albumin, as well as imaging reagent quantum and iron nanoparticles. TPGS-PLA offers higher encapsulation efficiency compared with commonly used PLGA (9).
- TPGS as an additive for nanoparticle formulation: In peptide-loaded PLGA microparticles, the use of 5% and 10% of TPGS reduces the burst release and the lag-phase time (15).
- Biodegradable PLA-TPGS copolymers in drug delivery: The first copolymer PLGA-TPGS nanoparticles (PLGA-TPGS NP) were prepared in 2006 (16) and have been the starting point of several studies for drug-delivery systems based on PLGA-TPGS NP for various families of APIs, such as small molecules or proteins (9).

These examples show that TPGS is currently widely investigated as a tool to design efficient drug-delivery solutions. Moreover, the examples highlight some interesting properties of TPGS over a simple solubility enhancer.

**An absorption or permeation enhancer**

In 1992, absorption enhancement properties of TPGS were first registered and the enhancing effect of TPGS was described for vitamin D in chronic cholestatic liver disease of infancy and childhood (17). In 1999, the increased absorption of an anti-HIV protease inhibitor was suggested as a consequence of the drug's solubility and permeability increase (6). Inhibition of the P-glycoprotein (P-gp) efflux pump by TPGS with various PEG chain lengths was investigated using Caco-2 cell monolayers (18). PEG 1000 chain was shown to be the near optimal chain length. The P-gp efflux pump inhibition mechanism of TPGS has been published, but is debated by the scientific community. The inhibition effect, however, is not debated (19).

More recently, several studies have emphasized the permeation or absorption-enhancing properties of TPGS as follows:

- The addition of TPGS in folate conjugated PLGA-PEG NP with DOX loading was found to increase the cellular uptake of DOX. A higher degree of DNA damage and apotosis and thus higher cytotoxicity on drug-resistant cancer cells were observed. TPGS may act as a P-gp efflux pump inhibitor and can strengthen the therapeutic effect of the micelles (20).
- The enhancement of corneal permeation of riboflavin-5'-phosphate through TPGS has been established, opening the door to promising approaches in corneal trans-epithelial crosslinking treatment. Moreover, due to its tocopherol moiety, TPGS exerts a protective effect on biological membranes against free-radical damage (21).
- The preparation and evaluation of dermal delivery systems of griseofulvin containing TPGS as a penetration enhancer has suggested that TPGS and ethanol synergistically enhanced the drug permeation and drug retention in the skin (22).
- Berberine bioavailability enhancement by TPGS has been studied on intestinal absorption in rats; TPGS was a good absorption enhancer capable of enhancing intestinal absorption (23).

Based on these published results, TPGS can be considered more than a simple surfactant. Indeed, these examples lead to the conclusion that TPGS can improve drug efficiency at the cellular level.

**Dosage form and route of administration**

TPGS can be used in all classical routes of administration. Numerous publications and patents refer to the use of TPGS in formulations for oral, inhalational, parenteral, topical, and suppository administration.

A limited number of publications deal with dosage forms that include TPGS. In addition to liquid formulations, tablet and capsule formulations can benefit from TPGS' improvement of solubility of poorly soluble drugs (24). Other publications highlight TPGS' ability to be used in hot-melt extrusion (HME) processes as well as in wet-

granulated formulations.

In the field of bioadhesive topical films produced by HME technology, it has been shown that the incorporation of TPGS in hydroxypropylcellulose (HPC) films provides better wetting of the film and doubles the adhesive strengths when compared to HPC/PEG films (25). Thermal stability of polyethylene oxide (PEO) sustained-release tablets of chlorpheniramine maleate prepared by HME has been studied. TPGS dispersed at the molecular level in the hot-melt extruded tablets has been found to be a suitable stabilizer of PEO during the process (26).

TPGS in conventional, high-shear wet-granulation formulation processes has been assessed. The feasibility of monolithic and bilayer coated tablets formulation has been demonstrated by a case study (27).

**Regulatory status and TPGS approval**
TPGS is listed under the name Tocofersolan as an inactive ingredient by FDA. The *United States Pharmacopeia/National Formulary* (*USP/NF*) has published a monograph for vitamin E polyethylene glycol succinate since 1998 (28). Although TPGS is not considered an active ingredient, one active Type II Drug Master File owned by ISOCHEM is published at FDA. Eastman, the originator of this product, has a self-affirmed generally recognized as safe (GRAS) status, and this statement has never been challenged by FDA.

Since 1999, TPGS has been approved for several specialty products (see **Table II**). Four drugs containing TPGS in their formulations have been authorized for US and European markets since then. TPGS is also the active ingredient in Vedrop as a source of supplemental vitamin E.

**Table II: Approved drug formulations using Tocophersolan (TPGS).**

| | | | | Approval date | | | |
|---|---|---|---|---|---|---|---|
| Active substance | Tradename | Company | Form | ANSM | FDA | EMEA | MHRA |
| Ibuprofen | Ibuprofen | Banner Pharmacaps | softgel capsule | / | 24/03/2009 | / | 10/06/2008 |
| Tripanavir | Aptivus | Boehringer Ingelheim | solution | 23/06/2009 | 23/06/2008 | 25/10/2005 | / |
| Amprenavir | Agenerase | GSK and Vertex license | solution | 20/10/2000 | 15/04/1999 discontinued | 20/10/2000 Withdrawn for commercial Reasons on 29/10/2010 | / |
| Tocofersolan (TPGS) | Vedrop | Orphan-Europe | solution | 24/07/2009 | / | 24/07/2009 | / |

**Table II**: Approved drug formulations using Tocophersolan (TPGS).

**The future of TPGS**
TPGS is now clearly established as a solid option for drug delivery innovation as a result of its non-ionic surfactant characteristics; its solubilizing, emulsifying, and stabilizing properties; and even its permeation- and absorption-enhancement effects. A first wave of drug products based on TPGS solubilization improvement started in the 2000s. In parallel, the steady increase in patent filing and scientific publication activity reflects the attractiveness of TPGS. Today, TPGS is used in a large number of Phase I, II, or III clinical trials. Will there be a second wave of launched drugs in the coming years, in which TPGS plays a key role in drug efficacy? Based on the previous statements, the answer would be likely, but it remains to be seen what the future brings.

Recalling the beginnings of TPGS as a water-soluble form of vitamin E, this excipient was poised to serve the pharmaceutical market but also the nutrition and food industries. Can TPGS also play a role in nutritional supplements as it has for pharmaceuticals? Considering patents filed during recent years on fatty acids in nutritional formulation using TPGS, the answer is potentially, yes (29–32).

**Conclusion**
Tocophersolan, otherwise known as vitamin E TPGS, is an “old molecule” with a long history. However, the strong demand of innovation in pharmaceutical drug delivery is offering it a greater life. The patent and scientific publication activity regarding TPGS in addition to its track records in marketed products allows the scientific community to think about a promising future for this multifaceted molecule. In addition, it is readily available for the pharmaceutical market in large quantities at a high quality standard. TPGS can also be used in other fields of application, such as nutrition, food, or even cosmetics. Indeed, these markets need innovative solutions as well and they could possibly benefit from TPGS’s unique properties. TPGS has almost 50 years of history, and it makes sense to think of using it in new commercial applications in the coming decade.

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