Review Article

Tocopherols as Versatile Excipients: Mechanistic Insights into their Role in Drug Delivery and Stability

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ABSTRACT

Tocopherols, which are essential components of vitamin E, are strong natural antioxidants that are used extensively in the cosmetic, pharmaceutical, and nutraceutical sectors because of their capacity to improve product stability and stop oxidative degradation. With their distinct physicochemical characteristics, such as amphiphilicity and non-ionic surfactant activity, tocopherols, which come in four main types (alpha, beta, gamma and delta) are perfect as permeability enhancers, emulsifiers, and solubilizers. In addition to providing targeted and sustained delivery systems, they enhance medication solubility, stability, and bioavailability. Tocopheryl polyethylene glycol succinate (TPGS) and other tocopherol derivatives exhibit notable pharmacological properties, making them prospective medicines in the fight against multidrug resistance. Tocopherols serve as stabilizers, penetration enhancers, and anti-aging agents in cosmetics. Tocopherols, which are mostly derived from plant seeds and oils utilizing sophisticated techniques including solvent extraction, ultrasonic-assisted extraction, and supercritical fluid extraction, continue to be crucial for improving drug delivery, lowering oxidative stress, and raising therapeutic efficacy. Although tocopherol has numerous medicinal uses, excessive consumption might have adverse effects such as bleeding risks and cardiovascular issues. This review highlights the multifunctional properties of tocopherols, including their physicochemical and pharmacological properties, antioxidative processes, and structural adaptability, highlighting their critical role in modern industrial and health advancement.

Keywords: Tocopherols, Antioxidants, TPGS, Vitamin E, α-tocopherols, pharmaceutical excipients.

INTRODUCTION

Antioxidant excipients are substances added to pharmaceutical, cosmetic, and food formulations to prevent or delay oxidative degradation, which can affect the stability and efficacy of the active ingredients. Antioxidants have become very relevant over the past few years due to their potentials as prophylactic and curative medicines in many diseases. Free radicals are extremely reactive molecules or chemical species that are unpaired electrons which can result in oxidative stress, which is termed as an imbalance between oxidants and antioxidants in favor of the damage can result, possibly through oxidants [1].

These are the effects of oxidative stress that form the molecular foundation in the pathophysiology of cancer, neurodegenerative diseases, cardiovascular, diabetes and autoimmune disorder [2]. The role of this antioxidant system (Table 1) is to attack the toxic radicals that are formed in the process of oxidative stress [3]. TPGS D-α-tocopheryl polyethylene glycol succinate is a water-soluble polyethylene glycol (PEG) derivative of vitamin E. It finds wide application in different drug delivery systems [4].

The prominent forms of vitamin E are tocopherols; the family of fat soluble phenolic compounds. Vitamin E is a environmentally friendly, very tolerable and low cost molecule. Tocophenol and tocotrienols are known as this generic term comprising two rings of hydrocarbon chain.

Table 1: Antioxidative system

1. Non Enzymatic system	• Ascorbic acid (Vitamin C) • α – tocopherol • Catarenes etc.,
2. Enzymatic system	• Superoxide dismutase (SOD) • Catalase (CAT) • Peroxidase (POX) • Ascorbate peroxidase (APX) • Glutathione reductase (GR) and • Polyphenol Oxidase (PPO) etc..,

The structures resemble each other except that the tocotrienol structure contains two glycosyl moieties on the isoprenoid units. The vitamin E α, β, γ, and δ are referred to as natural vitamin E. proton groups bound to their Benzene rings and the most prevalent and biologically active form is alpha tocopherol (Figure 1) [13].

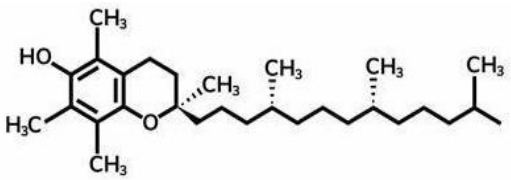

Figure 1: Structure of α–tocopheryl

Every tocopherol comprises of chromanol ring and 16-carbon phytyl chain. With position and number depending, Tocopherols have name anions of methyl

groups on the chromanol ring, tocopherols are referred to as α, β, γ, and δ [14]. Similarly, the increased accumulation of antioxidant enzymes (superoxide dismutase, glutathione peroxidase, catalase, and ascorbate peroxidase) [15] and other antioxidants such as tocopherols and carotenoids are likely to suppress and/or neutralize ROS in desensitization to oxidative stress [16]. The prominent lipid-soluble anti-oxidants in are tocopherols and carotenoids. chloroplast envelope and stroma of thylakoid membrane, where photosynthetic electron transport and light-harvesting takes place. They contribute greatly to photooxidative stress and have an active defense mechanism unlike O_2^- and peroxidation of lipids in thylakoid membranes [17]. Tocopherols play an important role in the postponement of the onset of numerous human degenerative diseases and are commonly used as dietary supplements and cosmetics [18]. Furthermore, tocopherols make sure that proper utilization of food with high quality lipids is achieved namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) to maintain the stocks of essential fatty acids [19]. Presently, the industrial applications use chemically synthesized racemic mixtures of tocopherols that are less active than natural molecules (or) directly extracted from vegetable oils that typically contain lower tocopherol yields [e.g., sunflower (900 $ug \cdot g^{-1}$), olive oil (211 $ug \cdot g^{-1}$) and soybean (1.16 $mg \cdot g^{-1}$) [20-24]. Moreover, the exogenous supply of carbon sources like glucose and ethanol in *Euglena gracilis* have also been found to increase α-tocopherol production [25, 26]. In relation to the pharmacodynamics of tocopherols, a study that has been carried out on human eye has reported that the retinal levels of vitamin E are greater than those of the choroid or vitreous and are related with serum levels of vitamin E [27]. It is established that the vitamin E can only be deposited in its theraupetic concentrations in aqueous humor and lenses through topical application and is concentrated in the retina when taken through the oral or parenteral route [28].

DISCOVERY AND HISTORY

The Vitamin E has been identified as factor X by Evans and Bishop in their research on the dietary factors which are necessary to the reproduction of rats [29]. Sure, who did this and named the substance as such ''vitamin E'' [30]. About the same period, Mattill and Conklin researched the question of whether milk is a perfect or not food, and they reached a conclusion that milk had a substance which prevented reproduction [31]. It is worth noting that the diet used in such experiments was typically rich in lard (10-22%), and Mattill subsequently suggested that animal fats are prone to auto-oxidation [32]. Subsequent expansion of this study indicated that the chemical effect of vitamin E in the prevention of lipid oxidation was possible, and thus it is chemically an antioxidant molecule. Its chemical structure and its biological activity was discovered due to the discovery of the biological activity of vitamin E non-antioxidant and antioxidant activities are recently discussed in details [33, 34, 35].

In 1950, Eastman Kodak Company discovered the innovative polymer by the name Vitamin E TPGS, which was water soluble. Vitamin E deficiency: as a supplement, derive Vitamin E as a natural one. TPGS is prepared through esterifying the natural Vitamin E and PEG 1000. TPGS has been found to exhibit greater aqueous solubility than its parent molecules [36]. The TPGs were observed to be soluble to 20% w/w at 25ºC. A decade after its invention, it was suggested that (1960) TPGS would be a good solubilizing agent in vitamins that were not soluble in water. In the 1970s, the toxicology and the safety profile of TPGS was published and it showed that TPGS is safe to be used [37]. In the 1980s, TPGS was found to have a strong effect in the Vitamin E deficiency treatment in cholestatic children and in zoo animals [38]. Most of the application of TPGS characteristics was reported in the 90s. The enhancement in the absorption through the mouth of cyclosporine and vitamin D was reported in 1996[39]. Furthermore, TPGS was granted as an approved one in 1999 and it was used as a solubilizer and absorption enhancer in the pharmaceutical formulations. Moreover, it is the first FDA-approved in 1999, the amprenavir containing TPGS was reported to be formulated [40]. The percentage of publications and patents of trend is exactly demonstrated by the figures in the past 20 years [41].

SYNONYMS

- Vitamin E
- Alpha – tocopherol
- D-alpha tocopherol
- 5,7,8 – Trimethyltocol [8].

TYPES

These are the group of cpmpounds and a part of Vitamin E. There are 4 types of tocopherols which includes,

- Alpha – tocopherol
- Beta – tocopherol
- Gamma – tocopherol
- Delta - tocopherol [9].

PHYSICOCHEMICAL PROPERTIES

TPGS is a hydrophilic amphiphilic compound composed of PEG chain in hydrophilic end, and Vitamin E in lipophilic end that portrays nonionic surfactant characteristics. TPGS has an HLB value of 13 [42]. Consequently, TPGS has the property to increase the level of solubility of a lipophilic compound in an aqueous environment by the way of emulsification. PEG 1000 is used in the structural skeleton of its commercial form of TPGS. TPGS appears as a waxy solid material with melting point of 37ºC (Table 2). Viscosity of TPGS reduces as temperature increases [43]. Therefore, the application of TPGS as the promising excipient in the creation and development of pharmaceutical can be utilized formulations. The uptake enhancement characteristics of TPGS were first reported

in 1992, and the enhancing the effect of TPGS on vitamin D was described .

Table 2: Physiochemical properties of α-tocopherol

1.	Chemical formula	$C_{29}H_{50}O_2$
2.	IUPAC name	2-(2-{2-[4-(2,3-dihyroxypropoxy)-3,5,-dimethylphenyl]-2-hydroxyethyl)oxy)ethylhydrogen succinate
3	Solubility	Insoluble in water and soluble in alcohol, ether, acetone, oils
4	Melting point	2.5 to 3.5ºC
5	Molecular weight	430.71 g/mol
6	Taste	Tastelesss
7	Stability	Light sensitive, readily oxidized upon exposure to atmospheric conditions or light
8	Density	0.950 g/cm^3
9	Boiling point	200 to 220ºC
10	Appearance	Yellow brown viscous liquid
11	Storage	Store in a cool place, dry place away from direct sunlight and protected from light

Molar mass : Approximately 530g/ mol

Melting point : Variable, depending on the specific grade and formulation

Appearance : Various Based on the grade,Typically a yellowish to amber liquid or solid.

Solubility : Water soluble, miscible with organic solvents.

Storage: Place in a cool dry place not in the direct sunlight.

Toxicity of tocopherol:

Large doses of alpha tocopherol (2000 IU/day) can trigger the effects of bleeding in those on anticoagulants. via the inhibition of the vitamin K- mediated coagulation cascade. This can also be through vitamin deficient individuals. K deficiency, bleeding ulcers, hereditary bleeding disorders or a history of hemorrhagic stroke in the past.

PHARMACEUTICAL PROPERTIES OF TOCOPHEROL

1. Solubilizer and absorption enhancer

TPGS 1000 is the water-soluble type of Vit-E of TPGS. Although, it is not soluble in its water it can mix with the other oils as well as other surfactants and co-solvents like propylene, polyethylene glycols. TPGS finds application in a host of commercial products including Agenerase®, Nur-ofen®, Wal-profen® and BioResponse-DIM® was used as a solubilizer. The type of nanoformulation absorption enhancer has involved use of TPGS as a solubilizer. Indicatively, Flor *et.al*., have developed novel nelfinavir (NFV) mesylate loaded TPGS1000 to enhance bioavailability and solubility of nelfinavir with succinate micelles. On their part, the 18-fold rise in the NFV was found to be soluble in micelles prepared with TPGS as a solubilizer [44]. In a different study, Romeroa *et.al*., have used TPGS to produce nanoparticles in order to increase the transdermal permeability of cyclosporine. They observed a huge upsurge (6.3-fold) in the permeability of the unaltered cyclosporine [45].

2. Permeation enhancer

Vit-E TPGS is made use of as a permeation enhancer and source of water soluble Vit-E in individual care such as eye drops, nasal sprays or cosmetic care products such as creams and lotions among others that will be applied to the skin. It markets itself in personal care and cosmetic products as being ethanol free, hypoallergenic, non-irritating emulsifier [46].

3. Emulsifier and stabilizer

TPGS has been reported to emulsify and stabilize nanoparticulate system greatly. It has been found to have 67 times the capacity to emulsify in comparison with the conventional polyvinyl alcohol (PVA) emulsifier. Zhao and co-workers prepared vit-E TPGS-emulsified paclitaxel NPs. They found that biocompatibility and emulsification of TPGS was better than other emulsifier such as PVA. Besides, NPs prepared using TPGS as an emulsifier agent had high cargo encapsulation efficiency, stability, improved cellular bioavailability of NPs by cancer cells, and maintained pharmacokinetics sustainability. It was found that sustainable preparedness of the prepared NPs produced therapeutic effect up to 168 h, which was compared to taxol (22 h) with similar dose of 10mg/kg and eventually developed a cargo capacity that was 4 folds that ofTaxol [47].

4. Plasticizer

TPGS can be applied as a plasticizer in the production of films out of PLA (Polylactic acid) and HPC (hydroxypropyl cellulose) and so forth. It reduces the change of temperature and bonding force of the films of glass, and increases the flexibility and extension of at flaking point through tensile test. The various TPGS could be utilized to generate implants that would be aimed to transfer localized drugs e.g. a unique structured film created by TPGS. TPGS has been discovered to increase the biocompatibility of the hollow fiber membranes. Polysulfone (Psf) as a blood purification hemodialysis resin [48].

CHEMISTRY OF TOCOPHEROL

Tocopherols are composed of chromanol ring and 15-carbon saturated isoprenoids tail. Alpha tocopherol occurs naturally and as a synthetic.

The natural form consists of a molecule with methyl (-CH 3) groups at the positions of 2, 4 and 8 on the chromanol ring.

The crystalline structure comprises of eight stereoisomers with identical antioxidant properties *in-vitro*. However, four of them are with the methyl ring positioned in the position 2, i.e., synthesized chemically.

Nevertheless, four have the methyl ring on position 2, i.e. the chemically prepared alpha-tocopherol was half as active as the natural counterpart. Supplements contain alpha-tocopherol esters, which are mainly succinate and acetate and are broken down into alpha-tocopherol in the intestine before absorption.

SOURCES OF TOCOPHEROLS

Tocopherol is present almost in all plant seeds, but the best sources of alpha-tocopherol are the seeds of plants, including almonds, sunflower seeds, and hazelnuts. Olive and canola oil is also a good source as well as tomato, avocado and spinach are also good sources. The most common isomer of tocopherol in the American diet is gamma-tocopherol, but there are much lower absorption and utilization and much higher active excretion and metabolism compared to alpha-tocopherol.

Grape seed is also one of the natural sources of vitamin E which contains numerous unsaturated fatty acids, in particular, linoleic acid [5, 6, 7].Grape seed oil is also an effective source of vitamin E since 1922 [10]. It has been discovered with other functions with antioxidant properties, anti-thrombolytic and other effects of therapeutic use with further research [11, 12].

METHOD OF EXTRACTION

Extensive range of procedures has been designed to extract tocols in different food samples (Table 3). The methods of extraction are inclusive of,

- Solvent extraction (soxhlet extraction, direct solvent extraction and saponification),
- Maceration (MAC),
- Matrix solid-phase dispersion (MSPD) extraction,
- Pressurized liquid extraction (PLE), supercritical fluid extraction (SCFE) and
- Ultrasonic-assisted extraction (UAE) [49, 50].

The decision on which process to use in extraction of the tocols released is dependent on the physical and chemical properties of the sample and also on resources and instruments at hand.

Table 3: Tocopherol content in selected plants and their products

S.NO:	Tocopherol Contents	Plant Sources	Alpha-tocopherol
1	Oils	Rice bane, corn and canola	32.30
2	Spices	Paprika & Parsley	29.10 & 8.96
3	Nuts	Pine nuts & Pecans	9.33 & 1.40
4	Seeds	Pumpkin and Squash, Dried flaxseed	2.18 & 3.31
5	Others	Seaweed & Spirulina	5.00 & 5.00

1. Solvent extraction

The most popular technique of extracting tocols in grains and oilseeds and biological tissues is solvent extraction, owing to its lipid-soluble (hydrophobic) property. Saponification in the extraction of tocols in plants samples is commonly carried out using alkaline hydrolysis. This assists in the breakage of carbohydrates and proteins which are normally linked to tocols in plants. There are various types of solvents and solvents blends that have been employed in the extraction of tocols in plant derived materials (Table 4).

The most common procedure used to extract tocols in grain samples, oil and bakery products is extraction using ethanol, followed by hot saponification [51,52]. Extraction of tocols in biological samples (plasma and milk) is performed following deproteinization with ethanol to prevent the action of proteins [53, 54]. Tocols were found to be significantly high in a sample extracted using methanol over chilled acetone and ethanol with saponification. All the extraction steps are carried out in the background of chemical antioxidants (stabilization) and low-light conditions and in an inert atmosphere to prevent the oxidation of tocols pointed out that sample stabilization is vital in vitamin E analysis in raw vegetables [55,56].

Table 4: Commonly used solvents and solvent mixtures used for the extraction of tocols from various plant-derived samples

Solvent	Samples
Ethanol	Cereal grains, oil, bakery products Panfili et al. (2003)
Hexane	Legumes Kalogeropoulos et al. (2010)
Methanol:hexane (1:1)	Mushrooms Heleno, Barros, Sousa, Martins, and Ferreira (2010)
Isopropanol:chloroform (3:1)	Oil da Costa, Ballus, Teixeira-Filho, and Godoy (2010)
Ethanol : Hexane (4:3)	Tomato Van Meulebroek, Vanhaeeke, De Swaef, Steppe and De Brabander (2012)

Saponification is applied in extraction to eliminate chlorophyll and interfering lipids in leafy specimen. These contaminants disrupt the process of detecting tocols using mass spectrometric (MS) methods. Nevertheless, these impurities do not interfere with the ultraviolet (UV) and fluorescence detection processes [57].

1. Ultrasonic-assisted extraction (UAE)

Ultrasonic-assisted extraction (UAE) is an extraction method applied to oil, protein and bioactives such as carotenoids, polyphenols and gingerol in plant samples. In UAE, ultrasound is applied to perturb the sample matrix that assists in better penetration of the solvent into the cell and enhances mass transfer. The ultrasonic-assisted extraction of a-tocopherol (EL) in oil palm (Elaeis guineensis Jacq) fronds was optimized using RSM (response surface methodology) as well as the CSD (central composite design) [58]. The authors also reported the efficiency of various extraction methods commonly used and the best recovery of tocopherols was reported with UAE doing better than Soxhlet extraction, saponification and maceration.

2. Extraction with matrix solid-phase dispersion (MSPD)

In the extraction with matrix solid-phase dispersion (MSPD), a sample, and an appropriate dispersion sorbent are mixed manually and sampled into a column, which is then sequentially eluted with solvents. MSPD method consumes less solvents (95%), and time (90%) [59]. MSPD is an effective isolation procedure of various classes of substances including pesticides, drugs, pollution, and bioactive compounds [60]. A ratio of 1:50 of sample/eluent solvent (methanol) and sample/dispersion sorbent in the MSPD extraction of tocols in barley grains (alumina) ratios of 1:5 were observed to be optimum.

3. Supercritical fluid extraction (SCFE)

The commonly used process is supercritical (SC) fluid extraction (SCFE), which can be utilized to extract lipids, flavors and bioactive compounds, alcohol in wine and beer, and encapsulate liquids to produce solid products [61]. SCFE is a solvent that utilizes carbon dioxide (CO_2) and can be recovered without harming the substrate and extract. Comparatively, SC-CO_2 extraction was studied to extract a-tocopherol using CO_2 as the solvent against solvent and soxhlet extraction and observed the highest extractability of a-tocopherol with SC-CO_2 extraction. Maximum extractability of a-tocopherol in rice bran was observed in SC-CO_2 extraction method, 48 Mpa pressure, and 55ºC temperature. The author also noted that neither ethanol, nor hexane can extract α-tocopherol at atmospheric pressure, but when using soxhlet extraction, hexane was observed to be superior to ethanol. In this way, the selection of the extraction method and the extraction solvent largely relies on the sample type[62].

4. Pressurized liquid extraction (PLE)

During the process of pressurized liquid extraction (PLE) technique, samples and a mixture of extraction solvents are subjected to high temperature (exceeding their boiling point) and high pressure to increase solubility and mass transfer. PLE is a green chemistry (environmentally friendly) method that aids in the minimization of hazardous organic solvents used in extraction. Nevertheless, PLE is not appropriate with thermolabile compounds and occur in low concentrations. Topcopherols and tocotrienols in cereals have been determined using PLE. Other extraction uses of PLE also include the extraction of a- tocopherols in Brazilian wine industry waste grape seeds [63], cereals [64], fruits and vegetables [65]. Vinas et al (2014) set the PLE of tocopherols as spinach, corn, cranberry, pomegranate and mango-apple juice and also opted the temperature of 50ºC, 1600 psi (110.3 bar) pressure, 3g sample amount, 5 min stationary time, and one extraction cycle at optimum yield of tocopherol.

CHARACTERISTIC FEATURES AND SYNTHESIS

The TPGS is produced by esterifying A-tocopheryl succinate (A-TOS) with PEG1000. The HLB of this amphiphilic agent is favourable, and the compound is useful as a solubilizer, emulsifier [66], penetration and absorption enhancer of hydrophobic drugs. TPGS-formed micelles in an aqueous solution can result in increased medication efficacy against multidrug-resistant (MDR) cells, reduced particle size, and increased solubility [67]. TPGS could also inhibit P-gp expression and alter the activity of efflux pumps, thereby decreasing MDR [68]. Consequently, numerous TPGS-based nano-delivery systems have been examined to overcome P-gp-mediated multidrug resistance [68].

1. Chemical modification of TPGS

TPGS is typically a 1513 g/mol molecular weight with a critical micelle concentration (CMC) of 0.02 percent weight-wise, and HLB of 13.2 [70]. TPGS can also be functionalized with chemical groups to make their properties adaptable to allow required functional groups to be deployed to bind ligands across nanomedicine surfaces. Many studies utilized TPGS-COOH to prepare COOH functionalized nanomedicines that can be post-conjugated to receptor-specific monoclonal antibodies, including cetuximab to target EGFR and bevacizumab to target VEGF [71]. Viswanadh *et.al*., in a study prepared TPGS-SH through reaction.

TPGS-COH 4-aminothiophenol + carbodiimide crosslinkers (EDC/NHS). Redox-sensitive nanoparticles were synthesized using prepared TPGSSH [72]. Li *et al*. in a different study prepared TPGS-NH_2 by reacting with triethylamine in the presence of p-toluenesulfonyl chloride (activator of primary alcohol). TPGS-NH_2 was subsequently conjugated with folic acid in the presence of EDC/NHS to yield TPGS Folic acid [73].

APPILICATIONS

1. TPGS as a P-gp Modulator with Anticancer Property

TPGS anticancer activity has been reported both as a single agent and together with conventional chemotherapies (Figure 2). Comparison of TPGS and a-TOS revealed that the latter was more efficient in the growth suppression. TPGS can influence apoptosis in H460 cells strongly, which could be explained by the high

efficiency of its ability to form reactive oxygen species (ROS) and, thus, induce apoptosis. PEG conjugation mediates the effect of TPGS anticancer action. TPGS was also discovered to produce higher levels of ROS, cause greater apoptosis (cell death), and reduce growth than TOS [74]. Mechanism analysis indicated that TPGS suppresses AKT phosphorylation that ultimately results in the downregulation of anti-apoptotic proteins such as Survivin and Bcl-2 and finally leads to the occurrence of apoptosis [51].Besides exhibiting an anticancer effect, TPGS causes AKT phosphorylation to be inhibited, which consequently downregulates the anti-apoptotic proteins like Survivin and Bcl-2 and ultimately induces apoptosis (Figure 1)[75]. It also possesses the supplementary benefit of inhibiting P-gp efflux, which renders it a more useful treatment of cancer [76].

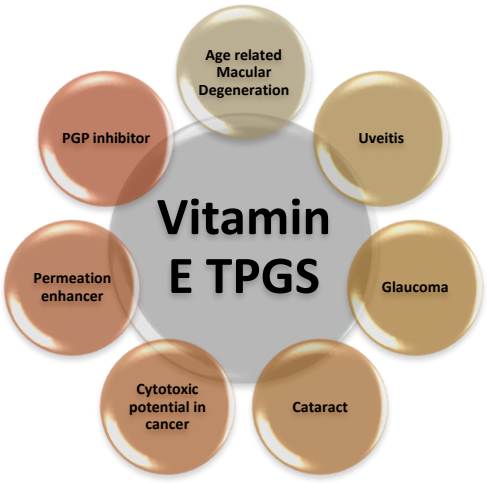

Figure 2: Applications of Vitamin E TPGS

2. TPGS formulations to enhance drug oral bioavailability

Oral route is an attractive route of drug delivery due to the ease, convenience, high compliance by patients, appropriateness in chronic therapy and low physician and industry costs [77, 78]. Nevertheless, various intrinsic issues, including low water solubility, low permeability rate across the gastrointestinal tract, poor stability to enzymes and hydrolysis effect result in poor absorption and bioavailability [79]. Indeed, most of the BCS class IV drugs are P-gp and CYP3A4 (CYP3A4) substrates, thus showing low permeability and broad pre-systemic metabolism [80]. TPGS-based preparations possess numerous strengths to enhance the bioavailability of drugs that are administered orally. On the one hand, TPGS is a nonionic surfactant and can enhance solubility of drugs. Conversely, TPGS has the potential to increase the permeation of the drug because of the inhibitory effect on P-gp [81]. Moreover, TPGS has been shown to be able to enhance drug stability and suppress the CYP3A4 and CYP2C9 metabolism [82]. Elsewhere, TPGS did not exhibit much inhibition on the activity of CYP3A which could be associated with the dosage [83, 84, 85]. The TPGS Phase-gating systems include nanocrystals, nanosupensions, self-emulsifying/ microemulsifying drug delivery system (SEDDS/SMEDDS), solid dispersions/tablet, solid lipid nanoparticles (SLNs), liposomes and micelles, TPGS emulsified nanoparticles and others. It is generally accepted that nanocrystals and nanosupensions are effective formulations to enhance the low solubility, dissolution and bioavailability of hydrophobic drugs. Andrographolide nanocrystals may be prepared with the help of TPGS as a stabilizer (Figure 3).

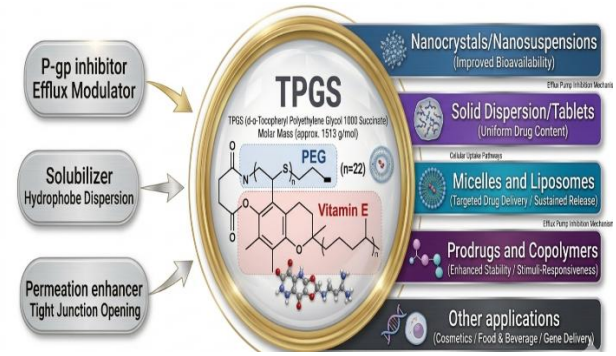

Figure 3: Applications of TPGS with Pharmaceutical properties

EVALUATION

1. Assay (95.0% - 105.0%)

Method: High- performance liquid chromatography or UV-visible spectroscopy.

Procedure: To top up high performance liquid chromatography, prepare a known amount of tocopherol in the right solvent (eg., ethanol or methanol) and inject into the chromatograph and determine the peak area of tocopherol. In ultraviolet-visible, scan the sample at a wavelength of 280-320 nm and compare the absorbance with a standard tocopherol solution.

2. pH (4.5 -7.0)

Method: pH meter

Procedure: Dissolve a small portion of tocopherol in distilled water (in case it is in the liquid state, use a dilute solution). Standard buffers are used to test the pH meter. Take the pH reading and insert pH probe in the solution.

3. Loss on drying (<_0.5%)

Method: Oven drying

Procedure: Weigh a clean, dry, container and record the weight. Wet weight Add a known weight of tocopherol sample and rewet. Put the sample in a drying oven at 105^0C and dry it 2-4 hours. Dry and weigh the sample after drying it in a desiccator. Calculate:

Loss on drying= loss on weight/initial weight x 100.

4. Ultraviolet spectroscopy

Method: ultraviolet- vis spectrophotometry.

Procedure: Dissolve tocopherol in a solvent. Put the solution into a quartz cuvette. A scan between 250-350nm is then performed to monitor typical absorption peaks

(around 290nm), and compare it with the standard values to determine the quality.

5. **Infrared spectroscopy**

Method: Fourier transform infrared spectroscopy.

Procedure: Place the sample in pellet form (Kbr) and put a small sample directly onto the fourier transform infrared sample holder and scan the fourier transform infrared between the ranges of 4000-400cm-1. Compensate the obtained sppectrum with a reference or standard tocopherol spectrum to validate the functional groups.

STORAGE

- Cool, dry place
- Away from direct sunlight
- Temperature range:2-8^{0}C(36-46^{0}F)
- Humidity regulation:Less than 60% relative humidity.

PACKAGING

- Airtight Containers (Eg., Glass or plastic bottles)
- Light-resistant dark-colored containers.
- Oxygen has to be beaten out with nitrogen or argon.
- Drying powder or silica gel to prevent moisture.
- Tamper-evident closures or child- resistant closures [88].

SIDE EFFECTS OF α-TOCOPHEROL

- Stomach cramps
- Blood thinning
- Allergic reaction (hives,itching, skin rashes)
- Blurred vision
- Increased risk of bleeding
- peeling of treated skin
- stevens-johnson syndrome
- thrombophlebitis
- Apnea (pause in breathing)
- Neurotoxicity

These findings prompted the authors of the HOPE-TOO trial to extend the HOPE study to 7 years where they did not find any differences in cancer incidences or deaths, but major cardiovascular event rates were higher in the atocopherol group (50 percent) [89].The GISSI-Preventione Investigators, in their turn, measured the development of congestive heart failure (CHF) in their patients but did not find any differences in cancer incidences or deaths [90]. Intervention involving the administration of 500 mgRR-a-tocopherol/day 1 of diabetes type 2 patients during 6 weeks compared to the anticipated outcome raised systolic and diastolic blood pressure significantly [91].

INCOMPATIBILITIES

- Warfarin - strengthen anti coagulant effects, which increases the risk of bleeding.
- Doxorubicin - oxidative stress prevention in cancer therapy.
- Cyclosporin - can change the metabolism of cytochrome p450 enzyme.
- Benzodiazepine - increase the effects of CNS depressants on sedation such as benzodiazepine.
- Orlistat - inhibition of fat absorption raised the vitamin E absorption.
- The level of good cholsterol can be reduced by Niacin - intract with vitamin E and other anti oxidant.
- Selumetinib - raise the risk of bleeding [92].

PRECAUTIONS AND WARNINGS

Oral: Vitamin E is probably harmless to the majority of individuals at doses lower than 1000mg per day which is equivalent of 1100 IU of synthetic vitamin E (all-rac-alpha-tocopherol) or 1500 IU of natural vitamin E (RRR-alpha-tocopherol). The chances of side effects are more with the increased doses. Side effects may include bleeding, fatigue, nausea and headache. Vitamin E is potentially not safe when consumed in exceeding doses bigger than 1000 mg each day. Inhalation: Vitamin E inhalation is potentially considered as dangerous . Varying products that contain vitamin E acetate, when using e-cigarettes and other products, have also been associated with severe lung damage in individuals[86].

Breast-feeding: Vitamin E probably does not harm when consumed orally as the recommended dose. The highest level of recommended vitamin E during breast-feeding is 800mg in patients between the age group of 14-18 years and 1000mg in patients who are above the age of 18 years. Vitamin E may be considered toxic when administered more than the maximum recommended dosage.

Children: In children, Vitamin E consumption is considered safe when properly administered through oral route.. However, children are not supposed to take vitamin E in amounts above the maximums per day. These are 300 IU of children under the age of 1-3 years, 450 IU of children under the age of 4-8 years, 900 IU of children under the age of 9-13 years, and 1200 IU of children under the age of 14-18 years.

Diabetes: Vitamin E intake may raise the risk of heart failure among diabetic peoples. Diabetics must not take more than 400 IU of vitamin E/day [87].

FUNCTIONS OF TOCOPHEROL

1. Based on pharmaceutical

- Solubilizer -increase the solubility of water insoluble drug (0.01 -10%), in water.
- Injectable formula - solubilizer and stabilizer (0.01% -2%)
- Sustained/targeted delivery system (0.5% - 3%) Controlled drug release.

2. Based on nutraceutical

- Vitamin E supplement - enhances absorption and bioavailability (100 -400 mg)per day anti oxidant, prevents oxidative degradation of drug (0.01% - 2%).

3. Based on cosmetics

- Dermal lotions and creams - Enhanced penetration (1%)
- Anti-aging formulation - antioxidant damage (0.5% -3%)

PATENTS

1. Patent 1: Invention - process of synthesizing alpha tocopherol with recombinant micro organisms.

Inventor - seung-hwan lee

Year of grant - 2011

Year of expiry - 2031

2. Patent 2: Invention - process of manufacturing alpha tocopherol with the help of a genetically modified yeast.

Inventor - hiroshi shimizu

Year of grant - 2015

Year of expiry - 2035

3. Patent 3: Invention - fungus recombinant process of making alpha tocopherol.

Inventor - hiroshi shimizu

Year of grant - 2020

Year of expiry - 2040

4. Patent 4: Invention - tocopherol based pharmaceutical composition to cure the oxidative stress related diseases.

Inventor- Dr.John Smith (university of california)

Year of grant - 2018

Year of expiry - 2038

CONCLUSION

Tocopherols are a multifunctional and highly useful group of excipients with a high contribution in the pharmaceutical, cosmetic and nutraceutical care. Their good antioxidant effect with a distinct physicochemical characteristic like amphiphilicity and non-ionic surfactant activity allows them to increase drug solubility, stability, and permeability as well as bioavailability. The variety of tocopherols and their derivatives, TPGS, in particular, even expands their functionality by providing a level of drug delivery solution and even an opportunity to overcome multidrug resistance. There is also their efficacy as stabilizers and anti-aging agents and this highlights their significance in cosmetic preparations. In as much as these have benefits, dosage must be taken carefully because there are side effects that are likely to come about when it is consumed in excess. Altogether, tocopherols remain an important part of the enhancement of therapeutic and product efficacy, which makes them indispensable in the contemporary formulation science and healthcare development.

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