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# Pharmaceutical Applications of Vitamin E TPGS

*Adnan Mansour Jasim and Mohammed Jasim Jawad*

## Abstract

D-tocopheryl polyethylene glycol succinate (Vitamin E TPGS) has been approved as a safe pharmaceutical adjuvant by FDA, and several drug delivery systems (DDS) based on TPGS have been developed. TPGS properties as a P-gp inhibitor, solubilizer/absorption and permeation enhancer in drug delivery and TPGS-related formulations such as nanocrystals, nanosuspensions, tablets/solid dispersions, vaccine system adjuvant, nutritional supplement, film plasticizer, anticancer reagent, and so on, are discussed in this review. Consequently, TPGS can inhibit ATP-dependent P-glycoprotein activity and act as a potent excipient that promotes the efficiency of delivery and the therapeutic effect of drugs. Inhibition of P-gp occurs through mitochondria-dependent inhibition of the P-gp pump. Many of the latest studies address the use of TPGS for many poorly water-soluble or permeable drugs in the manufacture of nanodrugs or other formulations. In addition, it has been reported that TPGS shows a robust improvement in chylomicron secretion at low concentrations and improves intestinal lymphatic transport, which would also boost the potential of drug absorption. It also indicates that there are still many problems facing clinical translation of TPGS-based nanomedicines, requiring a more deep evaluation of TPGS properties and a future-based delivery method.

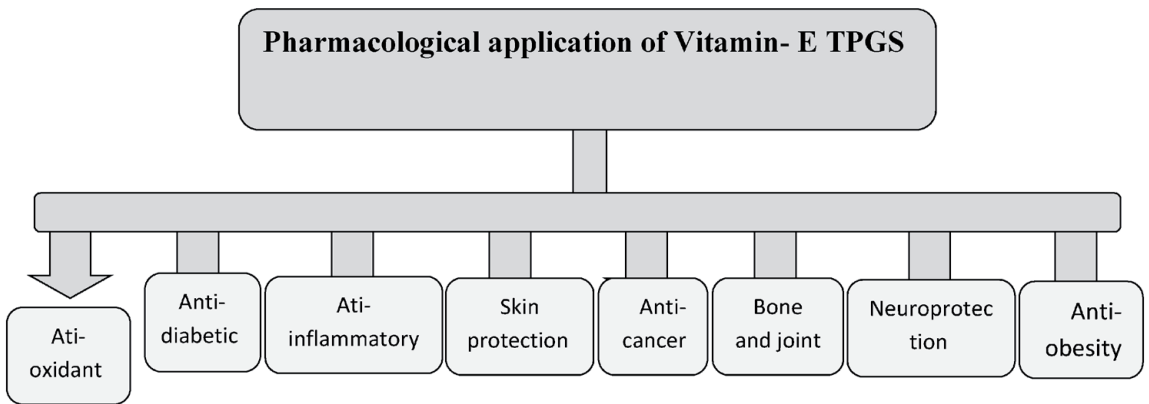
**Keywords:** TPGS, Bioavailability, Cancer cell, Prodrugs, Malaria and Osteoarthritis

## 1. Introduction

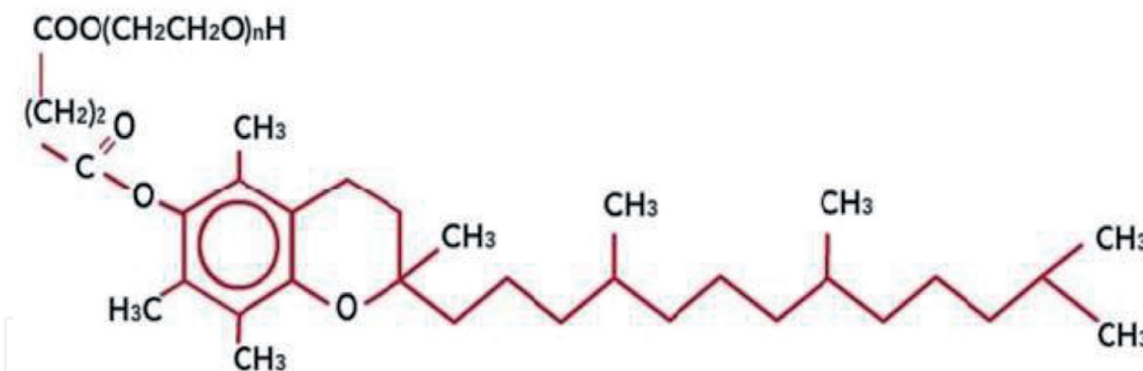
An alternative to PEG, D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS), is an amphiphilic macromolecule, a water-soluble natural vitamin E derivative. It is a powerful nanotechnological emulsifier for biomedical applications. TPGS co-administration can enhance solubility, cellular internalization, inhibit the multi-drug efflux transport mechanism mediated by P-glycoprotein, which increase the oral bioavailability of different anticancer drugs. Vitamin E TPGS is a water-soluble derivative of natural vitamin E derived from vitamin E succinate esterification with polyethylene glycol (PEG) 1000 [1]. Because of its superior water solubility and biocompatibility, PEG is the most widely applied hydrophilic segment. In order for the molecular weight to be higher than the hydrophobic core, the micellar shell is usually chosen to shape the molecule. In micelles, these findings have critical micellar concentrations in the micromolar range, and are often smaller than 100 nm. Vitamin E TPGS is a nonionic surfactant with a molecular weight rate of 1513 g.mol<sup>-1</sup> and a lipophilic alkyl tail and hydrophilic polar head amphiphilic frame that is fully soluble in water. It is constant, range of pH 4.6–7.6 less than 12 percent break down when kept for three months in neutral aqueous buffer. The

Vitamin E TPGS safety has been notified at the oral LD50 is >7 000 mg/kg for adult male rats [2, 3]. In addition, a variety of compounds such as cyclosporines, taxans, hormones and antibiotics, both water-soluble and water-insoluble, can be solubilized by vitamin E TPGS [3]. Vitamin E TPGS could act as a P-gp inhibitor. It has the ability to inhibit the action of P-gp, stronger than other non-ionic surfactants such as Tween 80, Pluronic and Cremophor. It has been used in various formulations/applications, such as producing nano suspensions [4], self-microemulsifying [3], nutrition supplement formulates nanoparticles, dependent prodrug, and strong dispersion/tablet, vaccine system adjuvant [5–8].

Vitamin E TPGS is widely used, with several functions, such as: hydrophobic drug vehicle, to ameliorate ocular permeability and provide ocular retention. TPGS is used as a vitamin E accessory or to treat vitamin E insufficiency in people who are unable to consume lipids due to specific illness [9]. Tocofersolan oral solution has been confirmed by the European Medicines Agency in the treatment of vitamin E deficiency due to digestive malabsorption in pediatric patients, inborn misery or hereditary chronic cholestasis [10]. Tocofersolan is also used as an antioxidant and anti-inflammatory in cosmetics and pharmaceutical products. In different parts of health, especially in neuroprotection, dermal, cardiovascular, and bone health, these crucial benefits of vitamin E are valuable. In nanoformulations involving solid-lipid nanoparticles, nanoemulsions, nanostructured lipid carriers, and polymeric nanoparticles, several TPGS formalizations have recently shown favorable results in improving the efficacy and bioavailability of many drugs [11]. Vitamin E has a prospective ban on metabolic syndrome and cardiovascular diseases (CVDs) [12]. These influences are mediated via inhibition of the HMG-CoA reductase enzyme thus antioxidant, anti-inflammatory activity, and block expression of adhesion molecules. Diabetic rat studies have confirmed that supplementation with TPGS decreases fasting blood glucose, oxidative stress and strengthens the integrity of vascular walls that help to resolve atherosclerotic lesions [13, 14]. Additionally, in dermatology, vitamin E is often used as a protective antioxidant and ultraviolet (UV) radiation that suits photoprotection and retards skin aging through its ability to improve collagen synthesis and avoid collagen dissolution [15, 16]. In addition to adding, TPGS has beneficial anti-cancer properties, such as preventing cancer cell proliferation, prohibiting angiogenesis, altering growth factors, encouraging cell cycle arrest, and inducing apoptosis [17]. The physicochemical and biological properties of TPGS relevant to drug delivery applications are generally described in **Figure 1** as well as, the role of TPGS in enhancing the bioavailability and targetability of anticancer drugs has been highlighted in this review.



**Figure 1.**  
*Various pharmacological properties of vitamin E.*



**Figure 2.**  
 Chemical structure of vitamin E TPGS. The lipophile to hydrophile equilibrium of the TPGS is an unique amphiphilic structure. Consequently, it is a waxy solid with an air-stable melting point of about 41° C, ranging from yellow to light brown in color. In nature, it is bulky and has a broader surface area, so it is considered the ideal emulsifier and strong solubilizer [19]. The chemical structure of TPGS used in many formulations/ applications shown in **Figure 2**, such as: 1. Improving drug bioavailability, 2. Properties of surfactants which improve the solubilization of drugs poorly water soluble, 3. Stabilizer of amorphous drug forms 4. Inhibiting the efflux of P-glycoprotein which improves drug permeability, 5. Emulsion vehicle, 6. The active ingredient in self-emulsifying formulations, 7. Minimize drug damage to dermal tissues, 8. Carrier for wound care and therapy, 9. Vitamin E water-soluble source, 10. Fabrication nanosuspensions, 11. Self-microemulsifying and solid tablet/dispersion 12. Vaccine device Adjuvant, 13. Boost of nutrition, 14. Nano-particles formulation, 15. Micelles, 16. Liposomes, 17. Based prodrug [20].

## 1.1 Vitamin E TPGS, an amphiphilic polymer

E TPGS is a water-miscible form of vitamin E, which approved by the FDA and commonly used in drug delivery systems as a safe adjuvant. TPGS's biological and physicochemical properties provide several advantages for its drug delivery applications such as high biocompatibility, drug solubility enhancement, drug permeation improvement, and selective antitumor activity [18].

## 1.2 Structure and properties

Vitamin E TPGS (d-alpha-tocopheryl polyethylene glycol 1000 succinate or TPGS) is a water-soluble derivative of natural vitamin E, formed together with polyethylene glycol 1000 by esterification of d-alpha-tocopheryl polyethylene glycol succinate. Furthermore, TPGS is a macromolecule consisting of a lipophilic alkyl tail and a hydrophilic polar head which has amphiphilic properties (see **Figure 2**).

Vitamin E TPGS is an active solubilizer of various compounds that are water-soluble and insoluble in water, such as steroids, antibiotics, cyclosporins, taxanes, etc. [21]. TPGS vitamin E could function as a P-gp inhibitor with a higher capacity than other non-ionic surfactants, such as Tween 80, Pluronics and Cremophor EL, to inhibit P-gp activity [21].

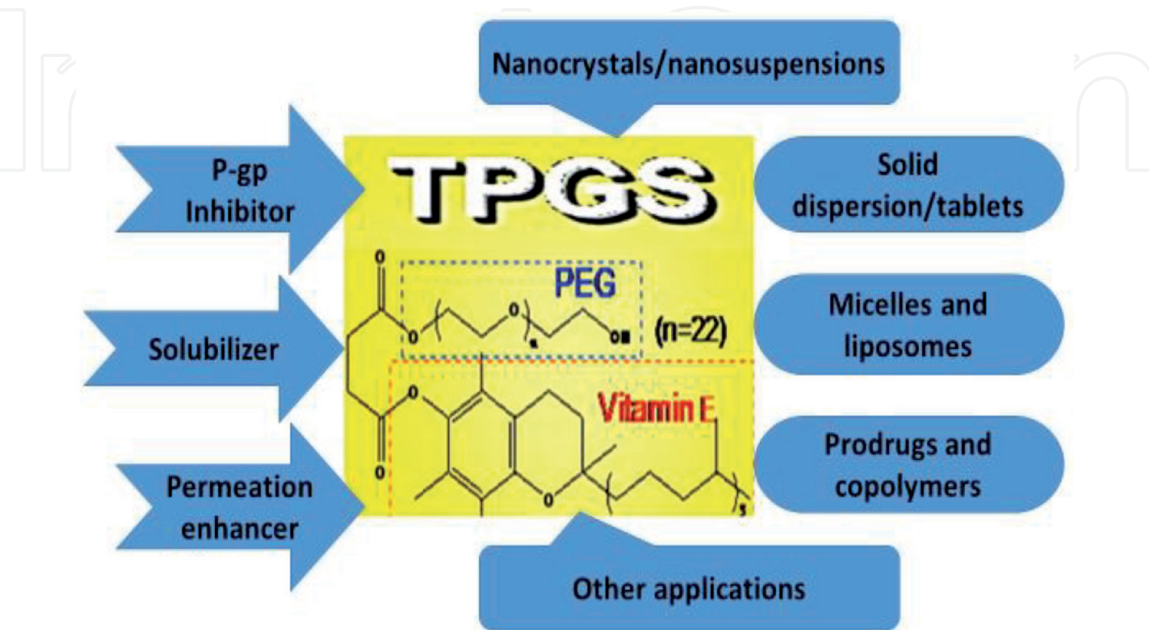
## 2. Absorption/bioavailability enhancer

Several studies indicated that the increased bioavailability was due to micelle formation improving solubility, while others showed that P-glycoprotein (P-gp) inhibition contributes to increased permeability support [22, 23]. Although several instances of TPGS use are poorly water-soluble drugs, there are also examples of the use of TPGS with water-soluble poorly permeable drugs. Many studies have been done to evaluate the mechanism by which TPGS improve bioavailability, many of these suggestions to micelle formation and through enhancing permeability across cell membranes by inhibition of multidrug efflux pump P-gp with regard to oral

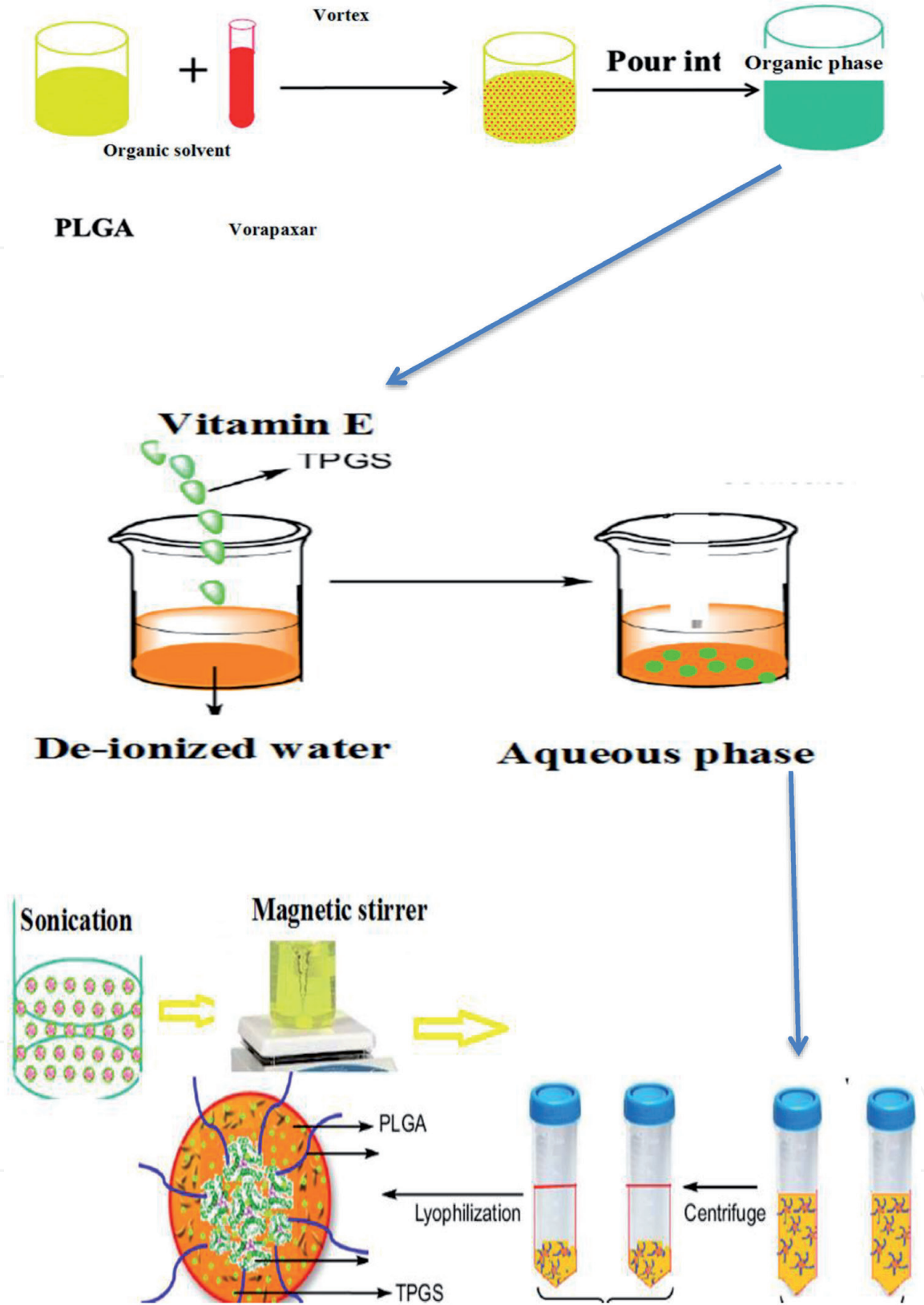
deliveryBy beneficially emulsifying and solubilizing the medication in the finished dosage type and by considering a self-emulsifying drug delivery mechanism in the stomach that may be due to TPGS, TPGS increases the permeability of a drug across cell membranes by inhibiting P-glycoprotein and thus facilitates the absorption of a drug over the intestinal wall and into the cell membranes. Furthermore, TPGS is a more potent P-gp inhibitor than many associated excipients with surfactant properties, such as Pluronic P85 cremophor EL, Tween 80, and PEG 300, **Figure 3**. Yu *et al* [24] The solubility of amprenavir was amended in the existence of vitamin E-TPGS out of micelle solubilization. Vitamin E-TPGS prevent the efflux system and boost the permeability of amprenavir [24]. Chiefly, vitamin E-TPGS promotes the absorption flux of the drug by increasing its solubility and permeability.

2.1 TPGS properties in drug delivery systems

The water-miscible type of vitamin E, TPGS, consists of a hydrophilic chain of PEG connected to the hydrophobic portion of vitamin E. According to a particular amphiphilic structure, it shows wonderful drug delivery capability. Further research has shown that TPGS has great potential for P-gp inhibition and selective anticancer outcomes to resolve MDR tumors [25]. TPGS can be readily conjugated with polymers or therapeutic agents to form TPGS based polymers **Figure 4**. It is possible to further self-assemble the resulting composition into nanoparticles, in order to form nanoformulations, unmodified TPGS can also participate with other active compounds. After cell internalization, in response to the unique intracellular environment (e.g. pH, GSH and ROS), the nanoparticles can be degraded to release the therapeutic agents and TPGS [26]. The drugs can be easily pumped out into the extracellular environment without P-gp inhibition [27]. Dissociated TPGS can bind to mitochondrial respiratory complex II and cause mitochondrial dysfunction, resulting in decreased potential for mitochondrial membranes and increased generation of ROS cell apoptosis with decreased activation a level of P-gp ATP [18]. Besides, to further resolve MDR, TPGS can also inhibit the substrate-induced activity of ATPase. The intracellular concentration of therapeutic drugs can be greatly improved with P-gp inhibition. Meanwhile to enhance cell apoptosis, TPGS can inhibit Bcl-2 and Survivin (**Figure 1**) [28].



**Figure 3.**  
The applications of vitamin E TPGS in drug delivery [20].Polyethyleneglycol (PEG).



**Figure 4.**  
*Nanoprecipitation method for preparing TPGS coated PLGA polymer nanoparticles. PLGA (Polylactic co glycolic acid).*

### 3. TPGS as a surfactant

Poor water solubility and/or poor permeability remain the great snag for maximum activity of therapeutic drugs [3, 29, 30]. In drug delivery, TPGS can be used as a solubilizer, permeation enhancer, diffusion, and emulsifier as well as as

a surface stabilizer. It has been commonly used for many poorly water-soluble or permeable drugs in the manufacture of nanodrugs or other formulations, mainly for class II and IV Biopharmaceutical Classification System (BCS) drugs [31]. In addition, it has been clearly documented that TPGS shows a good boost in low concentration chylomicron secretion and promotes intestinal lymphatic transport [32], which would further improve the drug absorption potential. As a surfactant, TPGS shows a remarkable ability to surpass drug absorption through different biological barriers. For example, TPGS is used to generate repaglinide nanocrystals to increase the saturation solubility of the oral bioavailability reference drug from 15-to 25.7-fold [33]. In addition, TPGS can increase the penetration of drugs in colonic tissue [34]. Importantly, in the production of nanoparticles with small particle size, high drug encapsulation strength, and quick drug release, TPGS may also act as a pore-forming agent [35]. Furthermore, TPGS can be used as an emulsifier or surface stabilizer for drug formulations since the hydrophobic portion can trap hydrophobic drugs and the formulations can be stabilized by the hydrophilic portion.

#### **4. Role of TPGS to control cancer cell**

TPGS acts selectively as an anticancer TPGS by synergistic antitumor action, can induce apoptosis and demonstrate selective cytotoxic activity against in vitro cancer cells that can be combined or loaded with chemotherapeutic drugs to resolve adverse effects and potentiate therapeutic efficiency. The response of cancer cells and normal immortalized breast cells after TPGS therapy is of significant value. Via activating the apoptotic signaling pathways, TPGS can induce G1/S cell cycle arrest in breast cancer cell culture [28]. Jurkat clone E6-1 cells will induce apoptosis on T cell acute lymphocytic leukemia. Apoptosis has been demonstrated by encouraging cell cycle arrest, accelerating nuclear DNA fragmentation, and reducing the possible mitochondrial membrane after treatment with TPGS [36]. The selective processes for TPGS-mediated apoptosis cancer cells are sophisticated and can be described as follows:-

##### **4.1 $\alpha$ -Ractive oxygen species stimulation**

Alpha-tocopheryl succinate (alpha-TOS), through the eradication and suppression of mitochondrial respiratory complex II, would induce cancer cell apoptosis [37]. ROS formation can be activated by the subsidiary electron transfer chain defect. The increase of intracellular ROS, an apoptosis mediator, can induce protein, lipid, and enzyme oxidation and DNA damage that leads to cell destruction [38]. This mechanism is also associated with the selective activity of anticancer, as tumor cells may be more sensitive than healthy cells to ROS. Anti-apoptotic protein downregulation TPGS could inhibit the phosphorylation of protein kinase B and then downregulate Survivin, which represents anti-apoptotic proteins, and Bcl-2, which can induce caspase-3 and caspase-7 potential for programmed cell death dependent on caspase [39]. At the same time, caspase-independent programmed cell death and G1/S phase cell cycle arrest also happened. In general, TPGS also appears to be harmful to malignant cells, such as lung adenocarcinoma and breast cancer, through mitochondria-associated apoptosis and ROS [40], generation [41]. Recently reported that TPGS induces OS apoptosis in acute lymphoblastic leukemia involving a cell death signaling pathway. However, no information is ready to limit whether TPGS might eliminate Neuroblastoma tumor cells [42].

4.2 DNA damage

TPGS can induce both caspase-dependent caspase and -independent DNA damage [43]. The ability of vitamin E to trigger caspase-independent programmed cell death could indeed be effective in prostate cancer chemotherapy as it can block tumor resistance usually associated with the use of classical chemotherapeutic drugs that trigger programmed cell death dependent on caspase [44].

Prodrug	Payload	Tumor oodel	Application	Dose	References
TPGS-DOX	DOX	Resistant breast cancer, hepatoma, melanoma,	95-fold lower IC50 in MCF-7/ADR vs. free drug, MCF-7/ADR, B16F10, H22 tumor growth/metastasis inhibition	Dox-TPGS-LPs at concentrations equivalent to 5 µg/ml Dox	[47]
TPGS-DOX	DOX	Glioma, Breast cancer	High cellular uptake and cytotoxicity	5.86 µg mL – 1 of DOX	[48]
TPGS-PTX	PTX	Reluctant ovarian cancer, hepatoma	PTX accumulation in A2780/T, cytotoxicity against A2780 and A2780/T, S180 tumor inhibition	Dox-TPGS-LPs at concentrations equivalent to 5 µg/ml Dox	[47]
TPGS-cisplatin	Cisplatin	Hepatoma	High cell uptake and cytotoxicity, significant neuroprotective effects	At dose 25, 2.5, 0.25, 0.025 g/ mL of cisplatin	[49]
TPGS-cisplatin	Cisplatin, DTX, Herceptn	Breast cancer	Enhanced cytotoxicity against SK-BR-3 cells with overexpression of HER2	Dose at concentrations of 0.5, 0.05 and 0.005 µg/mL	[50]
TPGS-mitoxantrone	5-FU, PTX	Resistant epidermal carcinoma	P-gp, β-tubulin, and p53 protein extracted from KB-8-5 cells, tumor growth inhibition in KB-3-1 and KB-8-5 tumor model	PTX at dose 5 mg/kg)	[51]
TPGS-gemcitabine	Mitoxantrone	Resistant breast cancer	Cell cytotoxicity against MCF7 and MCF7/ADR cells	25 mg/kg	[49]
TPGS-cantharidin	Gemcitabine	Pancreatic cancer	Improved cytotoxicity against pancreatic cancer BxPC-3	At concentration 15.6 mg /ml	[52, 53]

*Doxorubicin (DOX), Paclitaxel (PTX), docetaxel (DTX), 5-fluorouracil (5-FU), lipopolysaccharide (LPS).*

**Table 1.**  
The P-gp inhibition effect of MDR in the drug delivery system is mainly discussed in this section.

### 4.3 TPGS based prodrugs

A prodrug is a drug class with minimal to no therapeutic activity and can be submitted to a set of *in vivo* metabolism to generate parental drugs [45]. It is designed to improve the concentration of pharmacokinetic (PK), pharmaceutical and pharmacodynamic (PD) products, such as boosting drug solubility, safety, bioavailability, permeability, efficiency of treatment and reducing adverse effects. The prodrug can be classified purely into prodrug and precursor prodrug carrier-setup. The carrier-based prodrug, which is synthesized by a temporal connector merely conjugating polymer with the drug, can easily collect itself into nanoformulation as well as provide great potential for clinical recruitment [46]. The data summarized in **Table 1** explain the role of TPGS and prodrug payload on several types of tumor model with their application.

Over one natural system, stimulus-responsive prodrugs based on TPGS can be prepared to recognize optimum cancer therapy [54].

## 5. Effect of TPGS on malaria

Malaria is one of the main worldwide infectious diseases. In 2015 only, 212 million cases of malaria and 430,000 malaria deaths were reported [55]. *Plasmodium falciparum* and *P. vivax* respect the majority of the etiology of malaria and the vast majority of deaths are due to *P. falciparum* malaria [56]. *P. falciparum* infections are most likely to develop into severe symptoms such as intense anemia, difficult respiration and cerebral malaria (CM) among human-adapted Plasmodium spp. infections [57]. Several studies show that alpha-TOS inhibits the mitochondrial complex II in ROS generation, which induces selective apoptosis in several types of malignant cells, although it is mainly non-toxic to healthy cells [44, 58]. In addition, cells that lack the potency of the mitochondrial respiratory chain are resistant to alpha-TOS toxicity. Nevertheless the mechanism for alpha-TOS to remain obscure is selectively effective on cancer cells. The effect of plasmodium parasites that are highly susceptible to oxidative stress is doubtful for alpha-TOS. Alpha-Tocopheryl succinate-inhibits the development of cerebral malaria in mice [59].

TPGS is a suitable candidate for safe new anti-malarial drug, This research has shown that TPGS therapy of malaria, survival rates in mice infected with two parasites have been significantly elevated. Similarly, the severity of Evans blue staining on the brains taken from mice treated with TPGS was lower than the remedy not received by mice. This indicates that TPGS should prohibit the collapse of the BBB and the development of cerebral malaria. These data suggest that the potential candidate for malaria treatment drugs could be vitamin E-TPGS. Higher levels have been found after TPGS administration particularly in mitochondria, plasma membranes, and hepatocyte nuclei [60]. The majority of alpha-TOS in hepatocytes that can hydrolyze the esterified forms of vitamin E which may sooner or later hydrolyzed into alptocopherol [61]. In addition, the amount of alpha-tocopherol is comparatively lower in erythrocytes than in other organs such as the liver, kidney, or heart. Although the amount of TPGS is 10 times greater in well-vascularized normal organs such as the liver and kidney than that found in tumors, Alpha-TOS damages tumor cells but not normal cells, indicating that selective anti-tumor activity of alpha-TOS is not correlated with differences in levels in tissue accumulation [62]. Artemisinin and its derivatives that interact with iron to create free radicals are well known as anti-malarial drugs which reported that have growth inhibitory effects on cancer cells and non-toxicity to normal cells in both *in vitro* and *in vivo* studies. Cancer cells typically contain higher free iron levels than normal cells In the

form of heme molecules, plasmodium parasites often contain a high amount of Fe<sup>2+</sup> [63]. A time-dependent stimulation of mitochondrial hydrogen peroxide development was triggered by the adding of alpha-TOS to cultured cancer cells.

## 6. TPGS based polymers in drug delivery

TPGS-based polymers are extensively used in the drug delivery system, which can enhance the drug's encapsulation efficiency, intracellular cell uptake and therapeutic efficacy in vitro and in vivo [64]. The first synthesized PLA-TPGS drug delivery copolymer which produces significant antitumor efficiency. A set of TPGS-based polymers including poly(lactic-co-glycolic acid) (PLGA)-TPGS, [40] hyaluronic acid (HA)-TPGS, poly(beta-amino ester) (PBAE)-TPGS, polycaprolactone (PCL)-TPGS and chitosan-TPGS have obtained significant benefits and have been synthesized for medical applications [65, 66]. PLGA, a biocompatible polymer, is non-immunogenic and can be metabolized in nature to non-toxic products. PLGA is however, hydrophobic and can be quickly filtered and captured by the reticuloendothelial system in the liver. With the assistance of the TPGS, these shortages could be masterfully prevented. As a polymeric matrix for nanoparticles, the PLGA-TPGS polymer can be used to deliver therapeutic agents that can achieve high drug encapsulation performance, sustained-release action, and improved therapeutic effects [67].

To enhance the pharmacological effects, PLGA-TPGS nanoparticles can be prepared to encapsulate these. Emodin, Tanshinone was loaded through quercetin-loading nanoparticles of PLGA-TPGS, resulting in improved antitumor activity for liver cancer [68, 69]. Gao et al. combined separately loaded heparin sodium and oleanolic acid with PLGA-TPGS nanoparticles indicating synergistic antitumor activity in the HCa-F liver cancer cells [70]. Star-shaped polymer-based drug carriers have lower hydrodynamic radius, minimize solution viscosity, increase drug loading content and increase drug encapsulation performance in comparison to the linear polymers of the same molar mass [71], in comparison to linear PLGA-b-TPGS copolymer-based nanoparticles, doxorubicin-loaded-PLGA-b-TPGS block copolymer nanoparticles present perfect cellular uptake efficiency and sufficient antitumor efficacy. **Table 2** showed that effect of polymers types and drugs loading on tumor model with their application.

### 6.1 TPGS based formulations to improve drug oral bioavailability

Oral administration is an appealing drug delivery way owing to the simplicity, convenience, high patient compliance, perfect for chronic therapy, and minimize costs for industry and physicians [77]. In addition various inherent challenges, such as reduced permeability through the gastrointestinal tract, low water solubility, enzyme hydrolysis and first-pass elimination, which lead to lower absorption and bioavailability, continue to limit effective drug delivery [78]. P-gp and CYP3A4 substrates are the majority of Class IV biopharmaceutical classification system drugs, resulting in low permeability and existing class metabolism [79]. TPGS-based formulations have several advantages in enhancing the bioavailability of orally administered drugs. In addition, for the sake of a nonionic surfactant, TPGS can improve drug solubility. On the other hand, due to the P-gp inhibition effect, TPGS can enhance drug permeability [72]. Furthermore, the ability to boost drug stability by inhibiting CYP3A4 and CYP2C9-mediated metabolism was confirmed by TPGS [80]. TPGS has shown little inhibition effect on CYP3A activity in other studies [81], which may be linked to dosage [82]. Nanocrystals, nanosuspensions, the

Polymer	Payload	Tumor model	Application	Ref
Chitosan-g-TPGS	DOX	Hepatoma	2.4-fold AUC, 2.0-fold MRT vs. free drug after oral administration	[72]
iRGD-TPGS	PTX	Resistant lung cancer	Significant drug accumulation, downregulation of Survivin expression, and tumor apoptosis	[73]
PLA-PGS, Ce6-TPGS, tLyp-1-TPGS	DOX, Ce6	DOX-resistant breast cancer	In vivo near-infrared imaging of tumor-bearing mice and enhanced antitumor efficiency in MCF-7/ADR	[47, 74]
Transferrin conjugated TPGS	DTX, gold clusters	Breast cancer	In vivo imaging and antitumor efficacy	[75]
4-arm-PEG-TPGS	PTX	Hepatoma	Significant in vivo antitumor effect on S180 sarcoma-bearing mice	[66]
PBAE-g-TPGS	PTX	Resistant breast cancer	Stimuli-responsive release of PTX, targeted drug delivery to tumor, and remarkable MCF-7/ADR tumor inhibition	[66]
PLGA-TPGS	Zontivity	Atherosclerosis atheroma	Reduce the therapeutic dose and remove DNA damage.	[76]

**Table 2.**  
*Inspired by the use of PLA-TPGS copolymer loading antitumer and their effects.*

self-emulsifying/micro emulsifying drug delivery mechanism (SEDDS/SMEDDS), solid dispersions/tablet, solid lipid nanoparticles (SLNs), liposomes and micelles and emulsified TPGS nanoparticles are included in the TPGS formulations.

6.2 TPGS based formulations to improve drug oral bioavailability

Oral administration is an appealing drug delivery way owing to the simplicity, convenience, high patient compliance, perfect for chronic therapy and minimize costs for industry and physicians [83, 84]. Furthermore, there are still different inherent challenges hampering the effective delivery of drugs, such as limited permeability through the gastrointestinal tract, low water solubility, hydrolysis by enzymes and first pass elimination, which lead to lower absorption and bioavailability [85]. In fact, a majority of biopharmaceutics classification system class IV drugs are substrates of P-gp and CYP3A4, result in poor permeability and extensive pre-systemic metabolism [86]. TPGS-based formulations have numerous advantages to improve bioavailability of orally administered drugs. In addition to, as TPGS has ability to increase drug solubility due to a nonionic surfactant. On the other aspect, TPGS can enhance drug permeation due to the P-gp inhibition effect. Furthermore, TPGS has been confirmed with the ability to improve drug stability by inhibiting the CYP3A4 and CYP2C9-mediated metabolism [87]. In other studies, TPGS showed little inhibition effect on CYP3A activity [88, 89], which may be related to the dosage [90]. The TPGS formulations involve nanocrystals, nanosuspensions, self-emulsifying/microemulsifying drug delivery system (SEDDS/SMEDDS), solid dispersions/tablet, solid lipid nanoparticles (SLNs), liposomes and micelles, TPGS emulsified nanoparticles and so on.

Vitamin E (TPGS) is a lipid-soluble organic compound and usually present in the cell membranes. This vitamin has robust antioxidant properties and inhibits the

lipid peroxidation formed by the free hydroxyl and superoxide radicals [91]. This vitamin saves the cell membrane of sperm cells from damages of ROS. In vitro studies have demonstrated that the utilization of vitamin E-TPGS ameliorates the availability, motility and fertilizing capacity of sperm in the egg penetration of animals. Likewise, in vivo research, supplementation of vitamin E was found to be effective in reducing the number and motility of sperms caused by reactive oxygen species (ROS) [92]. The administration of this vitamin during oral route has significant advantages influence on the motility of sperms through the depression synthesis of malondialdehyde (MDA), which is known as the final part of lipid peroxidation [93].

The deficiency of vitamin E may spoil the reproductive organs like harm in the spermatogenesis, testicular dysfunction and seminiferous tubules shrinkage. The utilization of this vitamin boosts the functions of testes in the form of excess in the weight of epididymis and testes. In addition, the antioxidants properties of TPGS, endogenous, antioxidant enzymes like superoxide dismutase (SOD), and glutathione peroxidase are augmented due to the use of this vitamin [94]. This imbalance between the endogenous antioxidants and oxidative stress results in a situation of infertility in males. Antioxidants play an essential role in eliminating these free radicals. Vitamin E is one of the better antioxidants for the sweep of oxidative stress in the male reproductive system. Its use raises functions of the reproductive system and its efficacy. The lack of TPGS results in the declination of germinal epithelium and Leydig cells in seminiferous tubules.

The use of selenium and vitamin E possesses synergistic effects on the male reproductive system. More than 25% of males defeat to output functional sperms for effective insemination [94]. The over production of ROS is the main cause of infertility by damaging the genetic material and enzymes activities of [13]. ROS can be harmful or benefit according to their site as well as level of production [95]. The sperm have the capability to move after the transit stay in epididymis. They demand some physiological processes such as capacitation takes place during the female reproductive tract to fertilize the egg, through this physiological event the sufficient amount of ROS is produced [96]. In the ROS, superoxide is counted as the most harmful agent. The male germ cells are susceptible to ROS due to a higher amount of polyunsaturated fatty acids within the cell membrane and cytoplasm [97].

Vitamin E is considered an essential portion of antioxidants in sperm [38] and acts as a substantial protection to minimize the production of reactive oxygen species [30]. Spermatozoa demand the ROS for natural functions like acrosome functions, capacitation, and incorporation of spermatozoa through the operation of fertilization [43]. But the production of an excess quantity of ROS leads to lipid peroxidation in the membrane of sperm [43, 44]. Vitamin E prevents the production of ROS in the sperm membrane during the various motility processes due to lipid-soluble [43]. In addition to scavenging of ROS, this vitamin has the capacity to conserve the primary reproductive organs and accessory reproductive organs in males. Feeding of vitamin E subsequent metabolism and absorption of vitamin reduction of ROS in blood result in increase in semen quality parameters and testosterone rise in antioxidant enzymes (Superoxide dismutase, glutathione peroxidase). Glutathione peroxidase (GPx) is considered as the significant antioxidant and minimize the amount of lipid peroxidation. This enzyme acts potentiating to vitamin E as an opposite agent for hydrogen peroxide [98].

## 7. Osteoarthritis

Osteoarthritis (OA) of the knee is a major reason of chronic, incompetence in elderly people, the pathogenesis of this disease until now not clear understood [60].

Recent guide demonstrates that oxidative stress, the event wherein oxidant levels overtake those of antioxidative agents, is one of the motives factors of OA [99–101]. ROS including oxidants that are generated under the physiological situation in the human body and controlled by cellular antioxidants, lead to functional and structural damage of cartilage cells. Several report studies of the relationship between oxidative stress and OA have been undertaken. The elevation nitrite, a stable deterioration biochemical marker of the being of nitric oxide, has been confirmed in the plasma and synovial fluid of patients with OA [102]. Vitamin E, a dietary antioxidant capable of augmenting the total cellular antioxidant ability, reportedly has a positive influence on the symptomatic therapy of arthritis [103, 104]. However, there is very little proof from high quality trials that vitamin E modifies oxidative markers and clinical signs in people with knee osteoarthritis [28, 105]. This is the primary randomized controlled trial that converge on the influence of vitamin E in end stage knee OA and entirely estimate clinical symptoms, biochemistry and histology results. We hypothesized that a sustained peroid of vitamin E administration will reduce the oxidative stress, inflammatory process and ameliorate symptoms in patients with end stage knee OA.

## **8. Conclusions**

In this chapter, we summarized the feature and recent advancements of TPGS in drug delivery and pharmaceutical application. TPGS has been approved by FDA as a secure pharmaceutical adjuvant with top biocompatibility. In addition to TPGS can serve as an effective P-gp inhibitor for overcoming MDR. TPGS oneself can be active as an anticancer agent with selective toxicity to tumor cells. TPGS can be easily combined with nanotechnology to develop nanomedicines, which has been shown as a promising strategy in cancer treatment with increased solubility and stability of therapeutic agents, improved PK/PD, enhanced treatment efficiency, and minimize side effects. Furthermore, the impact of TPGS on the immune system, TPGS can be used as an adjuvant in vaccine development. As to TPGS based formulations, the limitations to realize the precise stimuli-responsive property and deep penetration of nanoformulations in the tumor microenvironment still remain as obstacles for the widespread application of these nanomedicines. However, the production of TPGS nanomedicines is yet on a laboratory scale and the progress in developing novel nanomedicines is comparatively slow, which hinders the effective clinical translation of TPGS based nanomedicines.

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## References

- [1] Cabral, S.C., *SYNTESIS AND CHARACTERIZATION OF CELECOXIB-LOADED NANOMICELLAR TOPICAL FORMULATION ON DIABETIC RETINOPATHY*. 2017, Universidade de Coimbra.
- [2] Almeida, H., et al., *Pluronic® F-127 and Pluronic Lecithin Organogel (PLO): main features and their applications in topical and transdermal administration of drugs*. Journal of Pharmacy & Pharmaceutical Sciences, 2012. **15**(4): p. 592-605.
- [3] Guo, Y., et al., *The applications of Vitamin E TPGS in drug delivery*. European journal of pharmaceutical sciences, 2013. **49**(2): p. 175-186.
- [4] Ghosh, I. and B. Michniak-Kohn, *Influence of critical parameters of nanosuspension formulation on the permeability of a poorly soluble drug through the skin—a case study*. Aaps Pharmscitech, 2013. **14**(3): p. 1108-1117.
- [5] Pandey, P., et al., *From bench to humans: formulation development of a poorly water soluble drug to mitigate food effect*. Aaps Pharmscitech, 2014. **15**(2): p. 407-416.
- [6] Chu, Q., et al., *Liver-targeting Resibufogenin-loaded poly (lactic-co-glycolic acid)-D- $\alpha$ -tocopheryl polyethylene glycol 1000 succinate nanoparticles for liver cancer therapy*. International journal of nanomedicine, 2016. **11**: p. 449.
- [7] Zhang, S., et al., *Liposomal oxymatrine in hepatic fibrosis treatment: formulation, in vitro and in vivo assessment*. Aaps Pharmscitech, 2014. **15**(3): p. 620-629.
- [8] Vadlapudi, A.D., et al., *Aqueous nanomicellar formulation for topical delivery of biotinylated lipid prodrug of acyclovir: formulation development and ocular biocompatibility*. Journal of ocular pharmacology and therapeutics, 2014. **30**(1): p. 49-58.
- [9] Cholkar, K., et al., *Novel nanomicellar formulation approaches for anterior and posterior segment ocular drug delivery*. Recent patents on nanomedicine, 2012. **2**(2): p. 82-95.
- [10] Zaffarin, A.S.M., et al., *Pharmacology and Pharmacokinetics of Vitamin E: Nanoformulations to Enhance Bioavailability*. International journal of nanomedicine, 2020. **15**: p. 9961.
- [11] Alcalá, M., et al., *Vitamin E reduces adipose tissue fibrosis, inflammation, and oxidative stress and improves metabolic profile in obesity*. Obesity, 2015. **23**(8): p. 1598-1606.
- [12] Ahsan, H., et al., *Pharmacological potential of tocotrienols: a review*. Nutrition & metabolism, 2014. **11**(1): p. 1-22.
- [13] Jayusman, P.A., et al., *Effects of palm oil tocotrienol-rich fraction on biochemical and morphological alterations of liver in fenitrothion-treated rats*. Pakistan journal of pharmaceutical sciences, 2014. **27**(6).
- [14] Tang, F., et al., *Vitamin E conditionally inhibits atherosclerosis in ApoE knockout mice by anti-oxidation and regulation of vasculature gene expressions*. Lipids, 2014. **49**(12): p. 1215-1223.
- [15] Kanchi, M.M., et al., *Tocotrienols: the unsaturated sidekick shifting new paradigms in vitamin E therapeutics*. Drug discovery today, 2017. **22**(12): p. 1765-1781.
- [16] Pedrelli, V., M. Lauriola, and P. Pigatto, *Clinical evaluation of*

*photoprotective effect by a topical antioxidants combination (tocopherols and tocotrienols)*. Journal of the European Academy of Dermatology and Venereology, 2012. **26**(11): p. 1449-1453.

[17] Abraham, A., et al., *Vitamin E and its anticancer effects*. Critical reviews in food science and nutrition, 2019. **59**(17): p. 2831-2838.

[18] Yang, C., et al., *Recent advances in the application of vitamin E TPGS for drug delivery*. Theranostics, 2018. **8**(2): p. 464.

[19] Han, F.Y., et al., *Sustained-release ketamine-loaded nanoparticles fabricated by sequential nanoprecipitation*. International Journal of Pharmaceutics, 2020: p. 119291.

[20] Batool, R., et al., *Estimation of phytochemical constituents and in vitro antioxidant potencies of Brachychiton populneus (Schott & Endl.) R. Br*. BMC chemistry, 2019. **13**(1): p. 32.

[21] Neophytou, C.M. and A.I. Constantinou, *Drug delivery innovations for enhancing the anticancer potential of vitamin E isoforms and their derivatives*. BioMed research international, 2015. **2015**.

[22] VANANGAMUDI A., *Targeted delivery of Doxorubicin conjugated to Folic acid and Vitamin E Da-Tocopheryl Polyethylene glycol succinate (TPGS)*. 2009.

[23] Jayah, O.R., *Design, Synthesis, Characterization, and Applications of Novel Fluorescent Lipid Analogs: An Olefin Cross Metathesis Based Approach*. 2020, New Mexico State University.

[24] Yu, L., et al., *Vitamin E-TPGS increases absorption flux of an HIV protease inhibitor by enhancing its solubility and permeability*. 1.

Pharmaceutical research, 1999. **16**(12): p. 1812-1817.

[25] Soni K., *Targeted Delivery of Drug Combinations Via Nanocarriers for Cancer Treatment*. 2017.

[26] Moreira, A.F., D.R. Dias, and I.J. Correia, *Stimuli-responsive mesoporous silica nanoparticles for cancer therapy: A review*. Microporous and Mesoporous Materials, 2016. **236**: p. 141-157.

[27] Cao, A., et al., *Multifunctionalized micelles facilitate intracellular doxorubicin delivery for reversing multidrug resistance of breast cancer*. Molecular pharmaceutics, 2019. **16**(6): p. 2502-2510.

[28] Neophytou, C.M., et al., *D-alpha-tocopheryl polyethylene glycol succinate (TPGS) induces cell cycle arrest and apoptosis selectively in Survivin-overexpressing breast cancer cells*. Biochemical pharmacology, 2014. **89**(1): p. 31-42.

[29] Nozoye, T., *The nicotianamine synthase gene is a useful candidate for improving the nutritional qualities and Fe-deficiency tolerance of various crops*. Frontiers in plant science, 2018. **9**: p. 340.

[30] Hirano, S., et al., *Ketamine nano-delivery based on poly-lactic-co-glycolic acid (PLGA) nanoparticles*. Applied Nanoscience, 2018. **8**(4): p. 655-663.

[31] Zhang, Z., S. Tan, and S.-S. Feng, *Vitamin E TPGS as a molecular biomaterial for drug delivery*. Biomaterials, 2012. **33**(19): p. 4889-4906.

[32] Fan, Z., et al., *A new function of Vitamin E-TPGS in the intestinal lymphatic transport of lipophilic drugs: enhancing the secretion of chylomicrons*. International journal of pharmaceutics, 2013. **445**(1-2): p. 141-147.

- [33] Gadadare, R., L. Mandpe, and V. Pokharkar, *Ultra rapidly dissolving repaglinide nanosized crystals prepared via bottom-up and top-down approach: influence of food on pharmacokinetics behavior*. AAPS PharmSciTech, 2015. **16**(4): p. 787-799.
- [34] Bittner, B., et al., *Drug-excipient interactions by Vitamin E-TPGS: in vitro studies on inhibition of P-glycoprotein and colonic drug absorption*. Journal of drug delivery science and technology, 2008. **18**(2): p. 145-148.
- [35] Zhu, H., et al., *Co-delivery of chemotherapeutic drugs with vitamin E TPGS by porous PLGA nanoparticles for enhanced chemotherapy against multi-drug resistance*. Biomaterials, 2014. **35**(7): p. 2391-2400.
- [36] Ruiz-Moreno, C., et al., *Vitamin E synthetic derivate—TPGS—selectively induces apoptosis in jurkat t cells via oxidative stress signaling pathways: implications for acute lymphoblastic leukemia*. Apoptosis, 2016. **21**(9): p. 1019-1032.
- [37] Dong, L.-F., et al.,  *$\alpha$ -Tocopheryl succinate induces apoptosis by targeting ubiquinone-binding sites in mitochondrial respiratory complex II*. Oncogene, 2008. **27**(31): p. 4324-4335.
- [38] Su, Z., et al., *ROS-triggered and regenerating anticancer nanosystem: an effective strategy to subdue tumor's multidrug resistance*. Journal of controlled release, 2014. **196**: p. 370-383.
- [39] Nelson, A.E., et al. *A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the US bone and joint initiative*. in *Seminars in arthritis and rheumatism*. 2014. Elsevier.
- [40] Batrakova, E.V., et al., *Effect of pluronic P85 on ATPase activity of drug efflux transporters*. Pharmaceutical research, 2004. **21**(12): p. 2226-2233.
- [41] Cheng, G., et al., *Mitochondria-targeted vitamin E analogs inhibit breast cancer cell energy metabolism and promote cell death*. BMC cancer, 2013. **13**(1): p. 1-14.
- [42] Ruiz-Moreno, C., C. Velez-Pardo, and M. Jimenez-Del-Rio, *Vitamin E D- $\alpha$ -tocopheryl polyethylene glycol succinate (TPGS) provokes cell death in human neuroblastoma SK-N-SH cells via a pro-oxidant signaling mechanism*. Chemical research in toxicology, 2018. **31**(9): p. 945-953.
- [43] Constantinou, C., et al., *Induction of DNA damage and caspase-independent programmed cell death by vitamin E*. Nutrition and cancer, 2012. **64**(1): p. 136-152.
- [44] Bellezza, I., et al.,  *$\alpha$ -Tocopheryl succinate pre-treatment attenuates quinone toxicity in prostate cancer PC3 cells*. Gene, 2014. **539**(1): p. 1-7.
- [45] Rautio, J., et al., *Prodrugs: design and clinical applications*. Nature Reviews Drug Discovery, 2008. **7**(3): p. 255-270.
- [46] Abet, V., et al., *Prodrug approach: An overview of recent cases*. European journal of medicinal chemistry, 2017. **127**: p. 810-827.
- [47] Bao, Y., et al., *A safe, simple and efficient doxorubicin prodrug hybrid micelle for overcoming tumor multidrug resistance and targeting delivery*. Journal of Controlled Release, 2016. **235**: p. 182-194.
- [48] Hou, W., et al., *pH-Sensitive self-assembling nanoparticles for tumor near-infrared fluorescence imaging and chemo-photodynamic combination therapy*. Nanoscale, 2016. **8**(1): p. 104-116.

- [49] Mi, Y., J. Zhao, and S.-S. Feng, *Vitamin E TPGS prodrug micelles for hydrophilic drug delivery with neuroprotective effects*. International journal of pharmaceutics, 2012. **438** (1-2): p. 98-106.
- [50] Mi, Y., J. Zhao, and S.-S. Feng, *Targeted co-delivery of docetaxel, cisplatin and herceptin by vitamin E TPGS-cisplatin prodrug nanoparticles for multimodality treatment of cancer*. Journal of controlled release, 2013. **169**(3): p. 185-192.
- [51] Jampílek, J. and K. Kráľová, *Recent advances in lipid nanocarriers applicable in the fight against cancer*. Nanoarchitectonics in Biomedicine, 2019: p. 219-294.
- [52] Hrabie, J.A. and L.K. Keefer, *Chemistry of the nitric oxide-releasing diazeniumdiolate ("nitrosohydroxylamine") functional group and its oxygen-substituted derivatives*. Chemical reviews, 2002. **102**(4): p. 1135-1154.
- [53] Sheng, S., et al., *Targeting vitamin E TPGS-cantharidin conjugate nanoparticles for colorectal cancer therapy*. RSC Advances, 2015. **5**(66): p. 53846-53856.
- [54] Li, R. and Y. Xie, *Nanodrug delivery systems for targeting the endogenous tumor microenvironment and simultaneously overcoming multidrug resistance properties*. Journal of Controlled Release, 2017. **251**: p. 49-67.
- [55] Alonso, P. and A.M. Noor, *The global fight against malaria is at crossroads*. The Lancet, 2017. **390**(10112): p. 2532-2534.
- [56] Phyto, A.P., et al., *Antimalarial activity of artefenomel (OZ439), a novel synthetic antimalarial endoperoxide, in patients with Plasmodium falciparum and Plasmodium vivax malaria: an open-label phase 2 trial*. The Lancet Infectious Diseases, 2016. **16**(1): p. 61-69.
- [57] Dunst, J., F. Kamena, and K. Matuschewski, *Cytokines and chemokines in cerebral malaria pathogenesis*. Frontiers in cellular and infection microbiology, 2017. **7**: p. 324.
- [58] Yan, B., et al., *Mitochondrially targeted vitamin E succinate efficiently kills breast tumour-initiating cells in a complex II-dependent manner*. BMC cancer, 2015. **15**(1): p. 401.
- [59] Kume, A., et al.,  *$\alpha$ -Tocopheryl succinate-suppressed development of cerebral malaria in mice*. Parasitology research, 2018. **117**(10): p. 3177-3182.
- [60] Tirmenstein, M.A., et al., *Administration of the tris salt of  $\alpha$ -tocopheryl hemisuccinate inactivates CYP2E1, enhances microsomal  $\alpha$ -tocopherol levels and protects against carbon tetrachloride-induced hepatotoxicity*. Free Radical Biology and Medicine, 1999. **26**(7-8): p. 825-835.
- [61] Neuzil, J., et al., *Induction of cancer cell apoptosis by  $\alpha$ -tocopheryl succinate: molecular pathways and structural requirements*. The FASEB Journal, 2001. **15**(2): p. 403-415.
- [62] Weber, T., et al., *Mitochondria play a central role in apoptosis induced by  $\alpha$ -tocopheryl succinate, an agent with antineoplastic activity: comparison with receptor-mediated pro-apoptotic signaling*. Biochemistry, 2003. **42**(14): p. 4277-4291.
- [63] Chen, J., et al., *Multifunctional mesoporous nanoparticles as pH-responsive Fe<sup>2+</sup> reservoirs and artemisinin vehicles for synergistic inhibition of tumor growth*. Biomaterials, 2014. **35**(24): p. 6498-6507.
- [64] Vijayakumar, M.R., M.S. Muthu, and S. Singh, *Copolymers of poly (lactic acid) and D- $\alpha$ -tocopheryl polyethylene glycol 1000 succinate-based nanomedicines: versatile multifunctional platforms for cancer diagnosis and*

therapy. Expert opinion on drug delivery, 2013. **10**(4): p. 529-543.

[65] Zhao, S., et al., *pH-sensitive docetaxel-loaded d- $\alpha$ -tocopheryl polyethylene glycol succinate-poly ( $\beta$ -amino ester) copolymer nanoparticles for overcoming multidrug resistance*. Biomacromolecules, 2013. **14**(8): p. 2636-2646.

[66] Zhang, X.-Y. and Y.-D. Zhang, *Enhanced antiproliferative and apoptosis effect of paclitaxel-loaded polymeric micelles against non-small cell lung cancers*. Tumor Biology, 2015. **36**(7): p. 4949-4959.

[67] Ma, Y., et al., *Nanoparticles of poly (lactide-co-glycolide)-da-tocopheryl polyethylene glycol 1000 succinate random copolymer for cancer treatment*. Nanoscale research letters, 2010. **5**(7): p. 1161-1169.

[68] Zhang, J., et al., *TPGS-g-PLGA/ Pluronic F68 mixed micelles for tanshinone IIA delivery in cancer therapy*. International journal of pharmaceutics, 2014. **476**(1-2): p. 185-198.

[69] Liu, H., et al., *A promising emodin-loaded poly (lactic-co-glycolic acid)-d- $\alpha$ -tocopheryl polyethylene glycol 1000 succinate nanoparticles for liver cancer therapy*. Pharmaceutical research, 2016. **33**(1): p. 217-236.

[70] Gao, M., et al., *Oleanolic acid-loaded PLGA-TPGS nanoparticles combined with heparin sodium-loaded PLGA-TPGS nanoparticles for enhancing chemotherapy to liver cancer*. Life sciences, 2016. **165**: p. 63-74.

[71] Maglio, G., et al., *Synthesis and Characterization of Star-Shaped Diblock Poly ( $\epsilon$ -caprolactone)/Poly (ethylene oxide) Copolymers*. Macromolecular rapid communications, 2004. **25**(12): p. 1139-1144.

[72] Guo, Y., et al., *Chitosan-g-TPGS nanoparticles for anticancer drug delivery*

*and overcoming multidrug resistance*. Molecular pharmaceutics, 2014. **11**(1): p. 59-70.

[73] Wu, Y., et al., *D- $\alpha$ -tocopherol polyethylene glycol succinate-based derivative nanoparticles as a novel carrier for paclitaxel delivery*. International journal of nanomedicine, 2015. **10**: p. 5219.

[74] Jiang, D., et al., *Actively targeting D- $\alpha$ -tocopheryl polyethylene glycol 1000 succinate-poly (lactic acid) nanoparticles as vesicles for chemo-photodynamic combination therapy of doxorubicin-resistant breast cancer*. Nanoscale, 2016. **8**(5): p. 3100-3118.

[75] Muthu, M.S., et al., *Theranostic vitamin E TPGS micelles of transferrin conjugation for targeted co-delivery of docetaxel and ultra bright gold nanoclusters*. Biomaterials, 2015. **39**: p. 234-248.

[76] Jasim, A.M., H.F. Hasan, and M.J. Awady, *Preparation of Vorapaxar loaded with Vitamin E TPGS and PVA emulsified PLGA nanoparticles In vitro studies*. Research Journal of Pharmacy and Technology, 2019. **12**(9): p. 4503-4510.

[77] Xu, W., P. Ling, and T. Zhang, *Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs*. Journal of drug delivery, 2013. **2013**.

[78] Morales, J.O., et al., *Challenges and future prospects for the delivery of biologics: oral mucosal, pulmonary, and transdermal routes*. The AAPS journal, 2017. **19**(3): p. 652-668.

[79] Ghadi, R. and N. Dand, *BCS class IV drugs: Highly notorious candidates for formulation development*. Journal of Controlled Release, 2017. **248**: p. 71-95.

[80] Christiansen, A., et al., *Effects of non-ionic surfactants on cytochrome P450-mediated metabolism in vitro*

European Journal of Pharmaceutics and Biopharmaceutics, 2011. **78**(1): p. 166-172.

[81] Mudra, D.R. and R.T. Borchardt, *Absorption barriers in the rat intestinal mucosa. 3: Effects of polyethoxylated solubilizing agents on drug permeation and metabolism.* Journal of pharmaceutical sciences, 2010. **99**(2): p. 1016-1027.

[82] Vasconcelos, T., S. Marques, and B. Sarmiento, *The biopharmaceutical classification system of excipients.* Therapeutic Delivery, 2017. **8**(2): p. 65-78.

[83] XU, Wei; LING, Peixue; ZHANG, Tianmin. Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs. Journal of drug delivery, 2013, 2013.

[84] DE PORTU, Simona, et al. Cost analysis of capecitabine vs 5-fluorouracil-based treatment for metastatic colorectal cancer patients. *Journal of Chemotherapy*, 2010, 22.2: 125-128.

[85] Morales JO, Fathe KR, Brunaugh A, Ferrati S, Li S, Montenegro-Nicolini M. et al. Challenges and future prospects for the delivery of biologics: oral Mucosal, pulmonary, and transdermal routes. *AAPS J.* 2017;19:652-668

[86] Ghadi R, Dand N. BCS class IV drugs: highly notorious candidates for formulation development. *J Control Release.* 2017;248:71-95

[87] Christiansen A, Backensfeld T, Denner K, Weitschies W. Effects of non-ionic surfactants on cytochrome P450-mediated metabolism in vitro. *Eur J Pharm Biopharm.* 2011;78:166-167

[88] Mudra DR, Borchardt RT. Absorption barriers in the rat intestinal mucosa. 3: effects of polyethoxylated

solubilizing agents on drug permeation and metabolism. *J Pharm Sci.* 2010;99:1016-1027

[89] Johnson BM, Charman WN, Porter CJ. An in vitro examination of the impact of polyethylene glycol 400, Pluronic P85, and vitamin E d-alpha-tocopheryl polyethylene glycol 1000 succinate on P-glycoprotein efflux and enterocyte-based metabolism in excised rat intestine. *AAPS PharmSci.* 2002;4:193-205

[90] Vasconcelos T, Marques S, Sarmiento B. The biopharmaceutical classification system of excipients. *Ther Deliv.* 2017;8:65-78

[91] Keskes-Ammar, L., et al., *Sperm oxidative stress and the effect of an oral vitamin E and selenium supplement on semen quality in infertile men.* Archives of andrology, 2003. **49**(2): p. 83-94.

[92] Ahsan, U., et al., *Role of selenium in male reproduction—A review.* Animal reproduction science, 2014. **146**(1-2): p. 55-62.

[93] Zubair, M., *Effects of dietary vitamin E on male reproductive system.* Asian Pacific Journal of Reproduction, 2017. **6**(4): p. 145.

[94] Wang, S., et al., *Beneficial effects of vitamin E in sperm functions in the rat after spinal cord injury.* Journal of andrology, 2007. **28**(2): p. 334-341.

[95] Agarwal, A. and R.A. Saleh, *Role of oxidants in male infertility: rationale, significance, and treatment.* Urologic Clinics of North America, 2002. **29**(4): p. 817-828.

[96] Makker, K., A. Agarwal, and R. Sharma, *Oxidative stress & male infertility.* Indian Journal of Medical Research, 2009. **129**(4): p. 357.

[97] Alvarez, J.G. and B.T. Storey, *Differential incorporation of fatty acids*

*into and peroxidative loss of fatty acids from phospholipids of human spermatozoa. Molecular reproduction and development*, 1995. **42**(3): p. 334-346.

[98] Rahman, H., M. Qureshi, and R. Khan, *Influence of Dietary Zinc on Semen Traits and Seminal Plasma Antioxidant Enzymes and Trace Minerals of B eetal Bucks. Reproduction in Domestic Animals*, 2014. **49**(6): p. 1004-1007.

[99] Wieland, H.A., et al., *Osteoarthritis—an untreatable disease?* Nature reviews Drug discovery, 2005. **4**(4): p. 331-344.

[100] Sarban, S., et al., *Plasma total antioxidant capacity, lipid peroxidation, and erythrocyte antioxidant enzyme activities in patients with rheumatoid arthritis and osteoarthritis. Clinical biochemistry*, 2005. **38**(11): p. 981-986.

[101] Suantawee, T., et al., *Oxidative stress, vitamin e, and antioxidant capacity in knee osteoarthritis. Journal of clinical and diagnostic research: JCDR*, 2013. **7**(9): p. 1855.

[102] Karan, A., et al., *Synovial fluid nitric oxide levels in patients with knee osteoarthritis. Clinical rheumatology*, 2003. **22**(6): p. 397-399.

[103] Bhattacharya, I., R. Saxena, and V. Gupta, *Efficacy of vitamin E in knee osteoarthritis management of North Indian geriatric population. Therapeutic advances in musculoskeletal disease*, 2012. **4**(1): p. 11-19.

[104] Vasanthi, B., J. Komathi, and K. Arun, *Therapeutic effect of vitamin E in patients with primary osteoarthritis. Int J Recent Adv Pharm Res*, 2012. **2**: p. 46-50.

[105] Zheng, L., et al., *Nicotianamine, a novel enhancer of rice iron bioavailability to humans. PLoS One*, 2010. **5**(4): p. e10190.