Abstract
This review aims to highlight the development of novel vitamin E conjugates for the vectorization of active pharmaceutical ingredients through nanotechnologies. The physico-chemical and biological properties of vitamin E derivatives offer multiple advantages in drug delivery like biocompatibility, improvement of drug solubility and anticancer activity. Nanomedicines have shown high potential in drug delivery since (i) they may offer better drug biopharmaceutical properties such as longer half-life or better bioavailability and (ii) they have shown benefits in cancer therapy by improving anticancer drug therapeutic index. Vitamin E-based nanomedicines were developed to combine the pharmaceutical properties of both vitamin E and nanomedicines for two purposes: (i) to improve water solubility of hydrophobic drugs and (ii) to enhance the therapeutic efficiency of anticancer agents. This review is divided into three parts; the first one describes the biology and the metabolic functions of vitamin E, the second one focuses on the anticancer activity of two vitamin E derivatives: vitamin E succinate (TOS) and vitamin E polyethylene glycol-succinate (TPGS). Finally, in the third part, we discuss vitamin E derivatives based-nanomedicines.

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1. Introduction

1.1. Nanomedicines and drug delivery

The European Science Foundation defines nanomedicines as "nanometer size scale complex systems, consisting of at least two components, one of which being the active ingredient". Although mainstream nanotechnology explores particles between 1 and 200 nm in diameter, the size of individual particles tested for drug delivery of therapeutic and imaging agents may range from 2 to 1000 nm [1]. Nanomedicines can increase efficacy, specificity, tolerability and therapeutic index of corresponding drugs [2]. They must be stable, non-toxic, non-thrombogenic, non-immunogenic, non-inflammatory, biodegradable, avoid uptake by reticuloendothelial system (RES) and should be applicable to various molecules such as small drugs, proteins or nucleic acids [3–7].

Most of the nanomedicines used today are (i) nanoparticles, (ii) polymeric micelles, (iii) liposomes and (iv) self-assembling prodrugs [8].

Nanoparticles include nanocapsules and nanospheres. Nanocapsules are vesicular systems in which a drug is confined to a cavity surrounded by a polymer membrane, whereas nanospheres are matrix systems in which the drug is physically and uniformly dispersed.

Amphiphilic molecules, including amphiphilic polymers, can self-assemble above the critical micellar concentration (CMC) in colloidal dispersions of molecular aggregates of approximately 20 to 100 nm called micelles. The hydrophobic moiety, usually polyethylene glycol (PEG), forms the corona of the micelles whereas the hydrophilic moiety forms their core. In contrast to nanoparticles which display a solid static structure, micelles form a dynamic structure: amphiphilic molecules or copolymers forming the micelles can be exchanged with free unimers. Amphiphilic copolymers provide better kinetic and thermodynamic stability than conventional surfactant. The hydrophobic core of micelles can solubilize poorly soluble drugs and partly protect the drug from the aqueous environment [8].

Liposomes are self-assembled artificial vesicles formed by one or several amphiphilic phospholipid bilayers surrounding an aqueous core domain. Their size can vary from 50 nm to several micrometers. Liposomes are attractive delivery systems due to their ability to isolate drugs from the surrounding environment and to entrap both hydrophilic and hydrophobic drugs [7–9]. Liposomes have been extensively studied but only few formulations have been brought to the market such as Doxil® or Caelix® [9,10]. Other lipid-based nanocarriers have also been investigated [11].

A prodrug is a pharmaceutical agent which is administered in an inactive form and then bioactivated into active metabolites in vivo. The rationale behind a prodrug is usually to improve the pharmacokinetics of a drug [12]. When a drug is conjugated to a polymer or a lipid which forms self-assembling drug–lipid conjugate, the prodrug assembly is considered as a nanomedicine [13,14].

1.2. Nanomedicines for cancer therapy

Cancer is a leading cause of death around the world. The World Health Organization estimates that 84 million people will die of cancer between 2005 and 2015 [8].

The administration of anticancer drugs is one of the most powerful options in cancer treatment. However, chemotherapy triggers the death of fast-dividing cells in both healthy and tumor tissue. It can be harmful for healthy cells of liver, gastro-intestinal tract and bone marrow. Thus the balance between the effectiveness of the drug and a patient’s ability to tolerate the side effects has to be optimized. Nanomedicines can address some of the limitations of traditional chemotherapy due to their ability to selectively target tumor tissue, overcome biological barriers, and respond to the tumor environment to deliver the anticancer drugs [8,15,16].

The first rationale to use nanomedicine for cancer therapy is the preferential delivery of nano-vectorized drugs to solid tumors due to the enhanced permeability and retention (EPR) effect (Fig. 1A) [17]. Tumor vessels surrounding the tumors are leaky due to abnormal baseline membranes and incomplete endothelial linings allowing nanomedicine to reach tumor passively through the leaky vasculature. Hence, EPR effect enables higher local concentration at the tumor site of the drug when carried with a nanovector [7,8,17]. To exploit EPR effect nanocarriers must avoid immune surveillance and circulate for a long period. Three parameters are required to achieve this goal: the size and surface characteristics of the nanoparticle and the immune blindness. To efficiently extravasate from the fenestrations in leaky vasculature, particle diameter should be in a range of 20–300 nm [8]. Nanocarriers should be larger than 10 nm to avoid clearance by first pass renal filtration. The particle charge should be neutral or anionic to evade efficiently the renal elimination. The nanocarriers have to be unseen from the RES, which destroys any foreign material by means of opsonization followed by phagocytosis, through pegylation strategies [7,8]. Efficacy of passive targeting depends mainly on (i) the degree of tumor vascularization and angiogenesis which rely on tumor types and anatomical sites and (ii) the high interstitial fluid pressure and heterogeneous blood flow limiting the uptake and homogeneous distribution of the drug in the tumor [7,8].

Targeting can be improved by grafting ligands at the surface of the nanomedicines, allowing active targeting by binding to the receptors overexpressed by cancer cells or angiogenic endothelial cells (Fig. 1B) [7,8,15].

Nanomedicines can also enhance drug-circulation times, control drug-release kinetics and allow superior dose scheduling [18]. They avoid formulation with toxic excipients that contribute to side effects for many conventional chemotherapeutics like taxanes. Nanomedicines have also the potential to overcome the development of tumor resistance to conventional chemotherapeutics [9,17].

Nanomedicines have potential to deliver more than one therapeutic agent for combination therapy. Theranostic nanomedicines that contain imaging and therapeutic agents have also been developed to enable diagnosis and therapy together with monitoring of therapeutic response.

2. Vitamin E

The potential health benefits and therapeutic uses of vitamin E derivatives have been extensively studied [19,20]. Physico-chemical and biological properties of vitamin E derivatives have also led to the development of a wide range of drug delivery systems [21].

2.1. Vitamin E family

The vitamin E derivatives, also named tocols, belong to the family of tocopherols and tocotrienols (Fig. 2A and B). The basic structure of tocols is a 6-hydroxy-2-methyl-phytylchroman. Eight naturally occurring tocols are known as vitamin E, four tocopherols and four tocotrienols existing in alpha (α), beta (β), gamma (γ), and delta (δ) isomers.

Tocol esters have been found to be more stable against oxidation than non-ester form of vitamin E. Vitamin E esters are commercially available, including vitamin E acetate, vitamin E succinate (TOS), and vitamin E polyethylene glycol-1000 succinate (TPGS1000) (Fig. 2C and D). In vivo ester hydrolysis speed differs depending on the derivative, i.e. hydrolysis is fast for vitamin E acetate but slower for TOS and TPGS1000 [22].

2.2. Biology of vitamin E

Vitamin E is absorbed in the small intestine by passive diffusion dependent on micellar solubilization with no discrimination between isomers. Pancreatic esterases and bile acids are required for the
micellization of vitamin E as for dietary fat. Then, micelles are taken up by intestinal enterocytes. Vitamin E enters the lymphatic circulation with the triglyceride-rich chylomicra which are secreted into lymphatic system to reach into plasma. At normal level of intake, about 20–30% of dietary vitamin E is absorbed [19,22–24].

Circulating chylomicrons undergo triglyceride lipolysis by lipoprotein lipase (LPL) to form chylomicron remnants. During this process, some tocopherols are transferred to other lipoproteins, like high-density lipoproteins (HDL), and/or taken up by peripheral tissues. Vitamin E is willingly transferred between HDL and other lipoproteins thanks to the phospholipid transfer protein (PLTP) which is also critical for vitamin E intratissular distribution [19]. Next, the chylomicron remnants are taken up by the liver and repackaged with dietary fats into nascent very-low-density lipoproteins (VLDL) for secretion into the plasma. In vivo studies in mice have demonstrated that VLDL are not critical for peripheral tissue distribution of α-tocopherol, suggesting that HDL may be sufficient [19,25,26].

All forms of vitamin E are degraded along the same pathway involving head group and side chain oxidation but with different metabolic rates. The selective accumulation in tissues and the enrichment of plasma of RRR-α-tocopherol are mediated (i) via α-tocopherol transfer protein (α-TTP) binding in the liver and (ii) via regulation of hepatic vitamin E metabolism and excretion [19,24,27].

Vitamin E is metabolized like xenobiotics through (i) the introduction of a functional group via phase 1 enzymes and (ii) the conjugation of the degradation product via phase 2 enzymes [27]. All forms of vitamin E are catabolized by a cytochrome P-450 (CYP)-mediated process, of which CYP3A4 and CYP4F2 are the most likely candidates [27]. α-, β-, γ-, and δ-carboxyethylhydroxynorxochromat (CEHC) are the biologically relevant metabolites. Non-α-tocopherols are more extensively catabolized than α-tocopherol, resulting in much faster turnover of those vitamers [19,24]. Some forms of vitamin E may also induce their own metabolism and affect metabolism of other CYP substrates [27]. α-Tocopherol itself is excreted into bile. Two proteins are involved in this process, Multidrug Resistance 1 (MDR1) and 3 (MDR3) proteins. These ATP-binding cassette (ABC) transporters are known to transport lipophilic compounds to the bile. MDR1 may play a role particularly under conditions of high-dose supplementation. High α-tocopherol doses have been shown to alter the expression of MDR1 which may alter the bioavailability and efficacy of drugs that utilize this transporter [19].

2.3. Metabolic functions of vitamin E

Vitamin E has numerous functions including antioxidant, anti-inflammatory, antithrombolytic, and other therapeutic effects [22,28,
29]. Vitamin E protects cell membranes, especially in the lung and red blood cells, against damage caused by various pollutants, peroxides, and free radicals formed during metabolic process. It works synergistically with other antioxidant nutrients such as vitamin C, beta-carotene to quench free radicals or peroxides, and is vital for nerve and muscle cell function. Vitamin E can spare other antioxidants and vice versa. In regard to its anti-inflammatory effects, vitamin E inhibits the enzyme lipoygenase, responsible of the production of leukotrienes that cause inflammation [22].

Vitamin E is a major lipid-soluble antioxidant which protects lipids and membranes from oxidative damage in vitro and in vivo [27]. Proof of any relevant antioxidant function in vivo is scarce. Most of the clinical trials undertaken to demonstrate a beneficial effect on vitamin E on diseases associated with oxidative stress failed. Nevertheless, almost all vitamin E effects have tentatively been attributed to free radical scavenging [30,31].

When vitamin E was discovered to inhibit cell proliferation and protein kinase C (PKC) activity, it was suggested that this vitamin may act in vivo through ways unrelated to its function as biological antioxidant [24,29,30] (Table 1).

3. Vitamin E and cancer

Therapeutic potential of tocotins has been widely studied. Vitamin E may be beneficial for a variety of disorders including cancer, heart disease and even Alzheimer’s disorder [12,20,23,32–34]. This part will focus on the potential use of the two vitamin E analogs discussed in this review, namely TOS and TPGS, as anti-cancer drugs and anticancer adjuvants.

3.1. Anticancer effect of TOS

Experimental evidence indicated that vitamin E succinate (tocopheryl succinate, TOS) (Fig. 2C) is one of the most effective anti-cancer compounds of the vitamin E family. TOS has been shown to be highly selective for malignant cells whereas it is largely non-toxic to normal cells [35].

At least 50 types of cancer cell lines have shown apoptosis when incubated with TOS, including different origins (human, murine, avian) and tissue types (breast, prostate, lung, stomach, ovary, monocyte, colon, mesothelium) [34]. The effect was dependent upon the TOS concentration, the period of incubation, the tumor cells and the culture conditions [32,36]. For example, half maximal inhibitory concentration (IC_{50}) value was 22 μM for human breast cancer MCF-7 cell lines, 18 μM for human T lymphoma Jurkat cells and 69 μM for human cervical cancer cells after 24 h with TOS [37]. Nevertheless, IC_{50} values of TOS are relatively high in comparison to common anticancer drugs [37,38].

3.1.1. Anticancer mechanisms of TOS

TOS acts on tumors through different mechanisms among which: (i) inhibitory effects on tumor cell proliferation; (ii) induction of apoptosis in tumor cells; and (iii) inhibition of metastasis.

TOS inhibits tumor cell proliferation through (i) inhibition of DNA synthesis, (ii) delay of cell cycle and (iii) control of regulatory proteins for cell cycle [34]. The latest includes the inhibitory effect of TOS through regulating Ras, a oncogene that can lead to continuous proliferation of tumor cells when overly expressed. The Ras down-regulating effect has been shown in several cell lines including human colon cancer (HCT116) and human breast cancer (MDA-MB) cell lines. TOS also regulates transcriptional factors, such as inhibiting the activities of nuclear factor-kappa B (NF-κB) and enhancing these of the activator protein 1 (AP-1), which enable inhibition of cell proliferation [37].

The induction of apoptosis in tumor cells by TOS occurs through regulation of multiple signal pathways: (i) an extrinsic receptor-related pathway and (ii) an intrinsic mitochondrial pathway.

The extrinsic pathway initiates apoptosis process through extracellular molecular inductive with transmembrane receptor which activates caspase-8. The TOS-regulated apoptosis through extrinsic pathway comprises two main processes: (i) Fas pathway and (ii) transforming growth factor (TGF) pathway. Fas is a death receptor, member of the superfamily of neural growth factor and tumor necrosis factor receptor (NFG/TNF), when stimulated leads to apoptosis. It has been shown that TOS was able to activate Fas/Fas-L pathway through increased expression of Fas receptor and Fas-L protein in breast cancer cells. Hence, TOS transformed breast cancer cells from Fas-tolerant to Fas-sensitive cancer cells [36,39]. TOS can up-regulate TGF genes. TGF is a cytokine binding receptors located in cell membranes associated with inhibition of cell proliferation and induction of epithelial apoptosis. TOS was shown to restore TGF-pathway in human breast cancer cells where the TGF-pathway was non-functional and to increase TGF expression in human gastric tumor cells [35].

TOS primarily induces apoptosis in tumor cells through intrinsic pathway. The intrinsic pathway apoptosis implies dysfunctional mitochondria and is regulated to a certain degree by the extrinsic pathway. The initial triggers in apoptosis induced by TOS are not fully understood. Mechanisms are likely to rely on production by tumor cells of reactive oxygen species (ROS). TOS has been shown to induce ROS in many types of tumor cells. Mitochondria seem to be the site of superoxide generation as well as the target of ROS. The generation of the mitochondrial permeability transition pore may play a central role in TOS induced apoptosis [32,35,39,40].

Some studies have claimed that TOS inhibits angiogenesis. It has been shown that TOS could inhibit the vascular endothelial growth factor (VEGF), a positive control factor for angiogenesis. The regulation of expression by TOS of other proteins implied in the angiogenesis, such as fibroblast growth factor (FGF), NF-κB, Ras and AP-1, may also be involved [34,35]. TOS may also inhibit tumor metastasis by inhibiting matrix metalloproteases-9 (MMP-9) which is an enzyme secreted by tumor to degrade extracellular matrix. TOS may reduce expression of MMP-9 secreted by tumor cells which protect the extracellular matrix [35].

3.1.2. In vivo data on TOS anticancer activity

Exposure to TOS reduced efficiently the incidence of breast, colon, and stomach cancers and melanoma after intraperitoneal (IP) administration (Table 2) [36,39]. Nevertheless, oral administration in rodents was ineffective, suggesting that most TOS may be hydrolyzed by esterases in the intestinal tract before entering in the blood stream [36,39]. Oral administration could be reached by using corresponding other analogs of tocopherol which are not hydrolyzed by esterases [33,39]. Up to

<table>
<thead>
<tr>
<th>Function</th>
<th>Gene products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocopherol uptake</td>
<td>α-TTP</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A, CYP4F2, HMG-CoA reductase, γ-glutamyl cysteine synthase, CRABP-II</td>
</tr>
<tr>
<td>Lipid uptake</td>
<td>SR-BI, CD36, SR-AI/II</td>
</tr>
<tr>
<td>Extracellular proteins</td>
<td>α-Tropomysin, collagen-α1, MMP-1, MMP-19, glycoprotein Ilb</td>
</tr>
<tr>
<td>Cell adhesion</td>
<td>E-selectin, ICAM-1, VCAM-1, integrins</td>
</tr>
<tr>
<td>Cell growth</td>
<td>Connective tissue growth factor</td>
</tr>
<tr>
<td>Extracellular matrix formation/degradation</td>
<td>Collagen α1(1)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>II-2, IL-1, IL-6, TGF-β</td>
</tr>
<tr>
<td>Transcriptional control</td>
<td>PPARγ</td>
</tr>
<tr>
<td>Cell cycle regulation</td>
<td>Cyclins D1 and E, Bcl12-L1, p27, CD95</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>CD95L, Bcl2-L1</td>
</tr>
<tr>
<td>Lipoprotein receptors</td>
<td>CD36, SR-BI, SR-AI/II, LDL receptor</td>
</tr>
<tr>
<td>Other functions</td>
<td>Leptin, tropomysin, a β-secretase</td>
</tr>
</tbody>
</table>
date, no clinical studies have been achieved with TOS alone or in combination with chemotherapy for cancer treatment.

3.2. Anticancer effect of TPGS

TPGS has been shown to inhibit the function of P-glycoprotein (P-gp), also named MDR-1 protein. This well-known transporter is an ATP-dependent drug efflux-pump which can mediate MDR to cancer cells, thus lowering intracellular drug accumulation through transport across extracellular and intracellular membranes. Substrates of P-gp include many anticancer drugs such as paclitaxel (PTX), etoposide, doxorubicin (DOX), and vinblastine. [21,49]. TPGS enhanced DOX, vinblastine and PTX cytotoxicities in MDR-1 resistant cells which were 27–135 fold more resistant than the parental NIH3T3 cells to these drugs [21,50]. The way TPGS acts on P-gp is not fully understood. The transporter inhibition activity of three nonionic surfactants (TPGS, Tween 80 and Cremophor EL) was investigated on P-gp. The role of membrane fluidity and protein kinase C in surfactant-induced transporter inhibition was also investigated. TPGS exhibited a reduction in the basolateral to apical permeability of rhodamine 123 in Caco-2 monolayers. Compared to the two other surfactants, TPGS rigidized lipid bilayers of cell membrane. Hence, TPGS was shown to rigidify cell membranes but this does not appear to be the primary mechanism for inhibition. TPGS property on P-gp could be due to the inhibition of the P-gp ATPase, P-gp energy source of active transport, through its allosteric modulation. TPGS was neither a substrate nor a competitive inhibitor in P-gp efflux transport. TPGS containing a 1 kDa PEG chain exhibits better P-gp inhibition than analogs containing PEG 200 to 6000 whereas the optimal TPGS should have a 1100–1500 PEG chain [51].

It has been reported that TPGS has intrinsic anticancer activities. It was able to inhibit growth of human lung carcinoma cells implanted in nude mice more potently than TOS. TPGS was more potent than TOS to induce ROS generation, apoptosis and growth inhibition, despite similar rate of uptake into cells in vitro. These data are suggesting that PEG conjugation may positively affect the interaction of TOS with membrane lipids thereby leading to more extensive ROS generation [52]. Studies are needed to understand the underlying mechanism(s) of TPGS cancer properties and its activities on other cell lines.

4. Vitamin E-based nanomedicines for anticancer drug delivery

The attractiveness of vitamin E derivatives in drug delivery relies on their biocompatibility, their solvent capacity and the biological

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Table 2
Effects of vitamin E succinate in experimental cancer models (mice).

<table>
<thead>
<tr>
<th>Inoculated cell line or tumor inducer</th>
<th>Applied dose</th>
<th>Duration of treatment and effect on tumor growth</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA-MB-231 human breast cancer cells</td>
<td>150 mg/kg/day in sesame oil</td>
<td>2 weeks; 80–90% tumor dormancy</td>
<td>[41]</td>
</tr>
<tr>
<td>B16F10 murine melanoma cells</td>
<td>100 mg/kg/day in sesame oil</td>
<td>2 weeks; 80–90% tumor dormancy, inhibition of liver metastasis</td>
<td>[42]</td>
</tr>
<tr>
<td>CT-26 colon cancer cells</td>
<td>100 mg/kg/day in 20% DMSO</td>
<td>2 weeks; 75% inhibition of liver metastases</td>
<td>[43]</td>
</tr>
<tr>
<td>B16F10 murine melanoma cells</td>
<td>150 mg/kg/day in sesame oil</td>
<td>2 weeks; 70% tumor growth inhibition</td>
<td>[44]</td>
</tr>
<tr>
<td>HCT116 human colon cancer cells</td>
<td>100 mg/kg in DMSO every third day</td>
<td>10 days; 75% tumor growth inhibition</td>
<td>[45]</td>
</tr>
<tr>
<td>Human mesothelioma Ist-Mes2 cells</td>
<td>100 mg/kg in DMSO every second day</td>
<td>16 days; &gt;90% tumor growth inhibition</td>
<td>[46]</td>
</tr>
<tr>
<td>Benzol (a)pyrene induced foretomach tumors</td>
<td>20 mg/kg in corn oil twice per week</td>
<td>4 weeks; 85% tumor growth inhibition</td>
<td>[47]</td>
</tr>
<tr>
<td>3 LD122 murine Lewis lung carcinoma cell line</td>
<td>200 mg/kg/day TOS in ethanol or vesiculated TOS</td>
<td>20 days; &gt;70% tumor growth inhibition</td>
<td>[48]</td>
</tr>
</tbody>
</table>

Table 3
Vitamin E-based nanomedicines for anticancer drug delivery.

<table>
<thead>
<tr>
<th>Carrier type</th>
<th>Composition</th>
<th>Drug</th>
<th>Model</th>
<th>Studies</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocopherol</td>
<td>mPEG-PLA-tocopherol</td>
<td>DOX</td>
<td>Breast and uterine cancer</td>
<td>In vitro and in vivo (PK)</td>
<td>[53]</td>
</tr>
<tr>
<td>Polymeric nanoparticles</td>
<td>α-Tocopherol oligochitosan</td>
<td>PTX</td>
<td>Cervical cancer</td>
<td>In vitro and in vivo (efficacy)</td>
<td>[55]</td>
</tr>
<tr>
<td>Micelles</td>
<td>Chitosan/TOS copolymer</td>
<td>PTX</td>
<td>Glioma</td>
<td>In vitro and in vivo (PK)</td>
<td>[56]</td>
</tr>
<tr>
<td>TOS modified pluronic</td>
<td>TPGS cancer coating</td>
<td>DOX and QDs</td>
<td>Breast cancer</td>
<td>In vitro</td>
<td>[60]</td>
</tr>
<tr>
<td>Mixed micelles</td>
<td>Pluronic P407/TPGS</td>
<td>Gambogenic acid</td>
<td>Breast and MDR cancer</td>
<td>In vitro</td>
<td>[57]</td>
</tr>
<tr>
<td>Pluronic P123/TPGS</td>
<td>Quercetin</td>
<td>Breast cancer</td>
<td>In vitro</td>
<td>[58]</td>
<td></td>
</tr>
<tr>
<td>Pluronic P105/TPGS</td>
<td>CPT</td>
<td>Breast cancer</td>
<td>In vitro</td>
<td>[59]</td>
<td></td>
</tr>
<tr>
<td>DSPE-PEG/TPGS</td>
<td>PTX and parthenolide</td>
<td>NSCLC</td>
<td>In vitro</td>
<td>[60]</td>
<td></td>
</tr>
<tr>
<td>Micelles</td>
<td>PLV(2K)</td>
<td>DOX</td>
<td>Breast and MDR cancer</td>
<td>In vitro and in vivo (efficacy)</td>
<td>[61]</td>
</tr>
<tr>
<td>FOL-TPGSroom</td>
<td>DOC</td>
<td>Breast cancer</td>
<td>In vitro</td>
<td>[62]</td>
<td></td>
</tr>
<tr>
<td>Liposomes</td>
<td>TPGS coating</td>
<td>DOX</td>
<td>Glioma</td>
<td>In vitro</td>
<td>[64]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emodin</td>
<td>In vitro and in vivo (PK)</td>
<td>[65]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Topotecan</td>
<td>Breast and melanoma metastatic cancer</td>
<td>In vitro and in vivo (efficacy)</td>
</tr>
<tr>
<td>Complex nanoparticles</td>
<td>Trastuzumab-conjugated TPGS</td>
<td>DOC</td>
<td>Breast cancer</td>
<td>In vitro and in vivo (PK)</td>
<td>[67]</td>
</tr>
<tr>
<td>Nanocrystals</td>
<td>Pluronic PE5-PE/TPGS</td>
<td>PTX and shRNA</td>
<td>Lung and breast cancer</td>
<td>In vitro and in vivo (efficacy)</td>
<td>[68,69]</td>
</tr>
<tr>
<td>Polymeric nanoparticles</td>
<td>TPGS + 4-armed porphyrin-PLA</td>
<td>DOX</td>
<td>Breast cancer</td>
<td>In vitro</td>
<td>[70]</td>
</tr>
<tr>
<td></td>
<td>TPGS + MPEG-SS-PLA</td>
<td>PTX</td>
<td>Lung, breast and uterus cancer</td>
<td>In vitro</td>
<td>[72]</td>
</tr>
<tr>
<td>Polymeric nanoparticles</td>
<td>TPGS + DOX</td>
<td>DOX</td>
<td>Breast cancer</td>
<td>In vitro</td>
<td>[73]</td>
</tr>
<tr>
<td>Polynucleotides</td>
<td>TPGS-Dox</td>
<td>Breast cancer</td>
<td>In vitro</td>
<td>[74]</td>
<td></td>
</tr>
<tr>
<td>Polymeric nanoparticles</td>
<td>TPGS-cisplatin</td>
<td>Cisplatin</td>
<td>Hepatocarcinoma</td>
<td>In vitro</td>
<td>[76]</td>
</tr>
<tr>
<td>Polymeric nanoparticles</td>
<td>TPGS-cisplatin + PLA-TPGS</td>
<td>Cisplatin, DOX and herceptin</td>
<td>Breast cancer</td>
<td>In vitro</td>
<td>[77]</td>
</tr>
</tbody>
</table>

Abbreviation: PK, pharmacokinetics; PTX, paclitaxel; DOX, doxorubicin; PEG-PE, poly(ethylene glycol)-phosphatidyl ethanolamine; PEG-DPPE, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine–N-[amino(polyethylene glycol)]; CPT, camptothecin; PLV(2K) lysine-linked di-tocopherol polyethylene glycol 2000 succinate; DOC, docetaxel; QDs, quantum dots; NSCLC, non-small cell lung cancer; PLA, poly-lactic acid; PLGA, poly (lactic-co-glycolic acid); FOL, folic acid, MDR, Multi Drug Resistance.
properties described previously. This part highlights properties and applications for both TOS and TPGS in anti-cancer drug delivery (Table 3).

### 4.1. Tocopherol and other water-insoluble tocols

#### 4.1.1. Tocopherol and TOS as excipient

Tocols are able to solubilize a variety of hydrophobic drugs. A compound or any of its derivatives that exhibits high affinity/solubility in tocols is characterized as being tocophilic, that is “tocol-loving” in a manner analogous to the term “lipophilic” [22]. However, there is no correlation between lipophilicity and tocophilicity [78].

An interesting method to predict the solubility of drugs in tocol is performed by examining solubility of the compound in chlorinated organic solvents and in methanol. Drugs that are highly soluble in chlorinated solvents (≥ 6 mg/mL, preferably ≥ 10 mg/mL) have acceptable solubility in vitamin E (≥ 1 mg/mL, ideally ≥ 10 mg/mL) whereas molecules that have good solubility in methanol (≥ 10 mg/mL) have low solubility in vitamin E (≤ 1 mg/mL). Thus, a tool named the “solubility in vitamin E parameter” (SVE) was developed to predict solubility of a compound in vitamin E. SVE is defined as the solubility in chloroform divided by the solubility in methanol expressed in mg/mL for both solvents. A SVE of at least 10, preferably greater than 100, would indicate an acceptable solubility in vitamin E [78,79] (Table 4).

Table 4: Solubility of some drugs in organic solvents and vitamin E [22].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Solubility (mg/mL)</th>
<th>SVE</th>
<th>SP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Water</td>
<td>Methanol</td>
<td>Chloroform</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>10≥</td>
<td>Insoluble</td>
<td>500</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>0.0034–0.030≥</td>
<td>0.03</td>
<td>6</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0.023</td>
<td>0.71</td>
<td>363</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>0.22</td>
<td>33</td>
<td>5.0</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>0.1≥</td>
<td>Soluble</td>
<td>Insoluble</td>
</tr>
</tbody>
</table>

Note: a) SVE parameter: ratio of drug solubility in chloroform to that in methanol. b) Solubility parameter. c) Literature values. d) Tocols not defined in the original references. e) Solubility varies from different sources. f) At pH = 2.

Chemical modification of a drug can be achieved for non-tocophilic compounds to ensure high solubility of the modified drug in vitamin E. This strategy was explored by coupling TOS to camptothecin (CPT), 7-ethyl-10-hydroxycamptothecin and other derivatives. After modification, these derivatives can be dissolved in vitamin E and then emulsified in the presence of TPGS, Pluronic 407, and saline to produce a stable nano-emulsion [80].

Despite its well-known ability to solubilize poorly water soluble drugs, TOS is only included in two marketed vitamin deficiency treatments (CoQ10-vitamin E® and SolgarVM-75®). Additionally, to our knowledge, TOS is neither used as excipient in commercial products nor as anticancer delivery system. Nevertheless, TOS was studied as an anticancer agent for cancer prevention such as lung, prostatic or pancreatic cancers [35,36,39].

#### 4.1.2. Tocopherol-based nanomedicines

Vitamin E has been grafted on various polymers to enable drug encapsulation and efficient anticancer drug delivery. A polymeric nanoparticulate drug delivery formulation consisting of the amphiphilic diblock copolymer mPEG-PLA-tocopherol and the sodium salt of poly(lactic-co-mandelic acid) (PLMA-COOH) and incorporating DOX (DOX-PNP) has been developed. Tocopherol moiety was used to increase the stability of the hydrophobic core of the nanoparticles in aqueous medium. The carboxylate end group of the biodegradable polyester allows the formation of ionic complex with DOX. The loading of these 20–25 nm nanoparticles is 0.92%. Compared to free DOX, DOX-PNP exhibited higher cellular uptake into both human breast cancer cell (MCF-7) and human uterine cancer cell (MES-SA) lines, especially into doxorubicin-resistant strains. Upon tail–vein injection, DOX-PNP exhibited 70 times higher bioavailability in rats and showed 2 times higher drug amount in tumor tissue than free DOX [22,53].

Amphiphilic α-tocopherol oligochitosan conjugates were synthesized by conjugating TOS to oligochitosans with various molecular weights. The tocopherol oligochitosan conjugates self-assembled in water to single layered oligomersomes, named TCOsomes, with size depending of the chain lengths of oligochitosans. TCOsomes were used to encapsulate siRNA by taking advantage of the cationic nature of chitosan derivatives. TCOsomes based on oligochitosan size of 4 kDa significantly enhanced the cellular uptake of siRNAs (>98%), and reduced the expression of target protein more effectively when compared with Lipofectamine 2000. The mechanisms by which TCOsomes enhanced the delivery of siRNA need to be studied further. In tumor xenografted mice, the intratumoral administration of siRNA using TCOsomes showed a significant reduction of tumor mass after treatment and prevented the growth of tumor [54]. A similar amphiphilic chitosan/vitamin E succinate copolymer encapsulating PTX was also studied. In vivo efficacy of the polymer encapsulating PTX was higher than Taxol® on U14 cervical cancer cells-bearing mice. The side effects after IV administration were also lower for the polymer encapsulating PTX [55].

TOS-modified pluronic P123 micelles (PF-TOS) were prepared to be used as a vehicle for PTX. Pluronic copolymers have been considered a promising nanocarrier system but have limitations such as low encapsulation efficiency and lack of stability in physiological environment. The rationale for PF-TOS design was based on the expectation that TOS with its lipophilic portion might allow better drug solubilization when conjugated with pluronic P123 [56]. Compared to PF-PTX, PF-TOS-PTX-micelles showed similar uptake and superior cytotoxicity of which might be attributed to the combined effect of enhanced encapsulation efficiency and anti-cancer properties of TOS. The PF-TOS-PTX-micelles had longer systemic circulation time and slower plasma elimination rate than those of PF-PTX-micelles after intravenous administration to mice. This was attributed to the TOS modification, which improved the hydrophobic interactions and the micelles’ stability [56].

Flamel Technologies has developed a polymer, named Medusa, consisting of a poly-L-glutamate backbone with α-tocopherol randomly grafted to some of the glutamate units through hydrolyzable ester bond. This polymer forms a colloidal suspension of nanoparticles due to the self-assembly of the lateral hydrophobic vitamin E groups into hydrophobic nanodomains and the aggregation of the hydrophobic glutamate chains. The polymer is used for subcutaneous slow release formulations of biopharmaceuticals like interferon alpha-2b (IFN-α2b), insulin, interleukin-2 (IL-2), human growth hormone, and glucagon-like peptide-1 analog. Nevertheless, it has never been tested for the encapsulation of an anticancer agent. The controlled release system is obtained by a simple mixing of an aqueous solution of the protein or the peptide with an aqueous solution of the polymer. A clinical trial in patients with hepatitis C has shown that the release of IFN-α2b from Medusa II formulation was extended and that the viral load was lower, in comparison with the IFN commercially available Vitaferon® [81].

#### 4.1.3. TOS as prodrug nanomedicines

Recently, DOX was conjugated to α-α-tocopherol succinate through an amide bond to form N-doxorubicin-α-α-tocopherol succinate (N-DOX–TOS) (Fig. 3). The prodrug self-assembled in water into 250 nm nanostructures when stabilized with α-α-tocopherol polyethylene glycol 2000 succinate (TPGS2000). Cryo-TEM analysis revealed the formation of nanoparticles with a highly ordered lamellar inner structure. NMR spectra of the N-DOX–TOS nanoparticles indicated that N-DOX–TOS is located in the core of the nanoparticles while PEG
chains and part of the tocopherol are in the corona. High drug loading (34% w/w) and low in vitro drug release were achieved. In vitro biological assessment showed significant anticancer activity and cellular uptake of N-DOX–TOS nanoparticles. In vivo, these nanoparticles showed a greater antitumor efficacy than free DOX [82].

In conclusion, TOS is particularly promising for the tumoral delivery of anticancer drug. Besides the non-toxic and biocompatible characteristics of the vitamin E family, the synergic ability of TOS to act with a chemotherapeutic drug has been demonstrated in vitro and vivo [80]. Hence, TOS-based nanomedicines were designed with (i) high drug loading, (ii) self-assembling properties, (iii) easy manufacture and (iv) size adapted to intravenous injection and to the EPR effect to passively target tumors.

4.2. TPGS

4.2.1. TPGS as excipient

In 1950, Eastman Kodak invented the water soluble vitamin E TPGS. Ten years later, it was suggested that TPGS should be a good solubilizing agent for oil-soluble vitamins without any toxicity. TPGS was firstly used in patients for treating vitamin E deficiency and chronic cholestasis. The TPGS antioxidant properties were further demonstrated as well as its ability to enhance the absorption of cyclosporine and vitamin D. Finally in 2000, TPGS was accepted as a pharmaceutical solubilizer and absorption enhancer for many poorly soluble drugs (Eastman Vitamin E TPGS NF, referred as TPGS).

The tocol ester TPGS_{1000} is a water-soluble form of vitamin E (vitamin E content of 260 mg/g) which can self-assemble in 13 nm micelles. It is a waxy solid (melting point: 37–41 °C) completely miscible with water (hydrophilic–lipophilic balance (HLB) value about 13) and its CMC at 37 °C is 0.02% w/w [22,83]. At physiological temperature, depending on the water content, it forms various phases in aqueous solution that can solubilize a variety of compounds, both water-soluble and water-insoluble. Examples of drugs that are soluble in TPGS include cyclosporine, taxanes, and other drugs. When TPGS concentration is above 20% w/w, it forms high-viscosity liquid crystalline phases. The structure of the TPGS/water phase evolves from globular micellar, to hexagonal then reversed micellar, and finally to the lamellar phase when TPGS concentration is increased [22,83]. In addition to its water miscibility, TPGS is also miscible with oils, other surfactants and cosolvents such as propylene and polyethylene glycols. In aqueous media, TPGS_{1000} is stable at pH 4.5–7.5. It is also air-stable but reacts with alkali [22].

TPGS has been used as an absorption enhancer, emulsifier, solubilizer, additive, permeation enhancer and stabilizer. TPGS has been used as a carrier for wound care treatment, an oral bioavailability enhancer for poorly absorbed drugs, and a drug solvent and emulsion stabilizer for parenteral administration [12,21,22,83,84]. TPGS is included in various commercial products as (i) solubilizer, e.g. Agenerase®, Nurofen®, Wal-profen® and BioResponse-DIM® and (ii) vitamin E supplement, e.g. Ply-vi-sol®, Vidaily® or Liqui-E®. Nevertheless, to our knowledge, only one vitamin E emulsion has been clinically studied for poorly soluble drug delivery. A vitamin E based emulsion named Tocosol® was developed for the parenteral delivery of PTX, a poorly water-soluble anticancer drug which is soluble in tocol. This system employs TPGS and poloxamer 407 as emulsifiers and contains PEG400. Tocosol®-PTX was shown to be better tolerated and more effective than the clinical formulation of PTX, Taxol® (which contains the undesirable Cremophor® EL) using the B16 mouse melanoma model. Tocosol®-PTX has successfully completed Phase I and Phase II clinical investigations [22,85]. Nevertheless, the pivotal phase III study conducted in breast cancer patients failed. The main reason was the lack of advantages in terms of targeting PTX to the cancer cells [86].

TPGS has also served as an excipient for overcoming MDR and inhibitor of P-gp for increasing the oral bioavailability of anticancer drugs. TPGS (IC_{50}: 33 μM) is a more effective P-gp inhibitor than other surfactants like Cremophor® EL (400 μM) but less potent than P-gp inhibitors like cyclosporine (1 μM) or tariquidar (20–50 nM) [71].

Still the permeation improvement due to P-gp interaction may be compromised by the micellization during the inclusion of poorly soluble drugs in micelles. Encapsulation of poorly soluble drugs in micelles may
impair the passive diffusion of drugs which results in a delicate balance between permeation inhibition due to micelle-association and permeation enhancement due to P-gp interaction [21]. TPGS demonstrated the maximum efflux inhibition activity at a concentration of 0.1 mg/mL which may be due to the interplay of concentration dependent P-gp inhibition and the micellar formation. As the concentration of TPGS was increased above 0.1 mg/mL a linear increase in drug solubility was observed, presumably via micellar solubilization [21,22,87,88].

### 4.2.2. TPGS-based nanomedicines

TPGS have been used to develop various nanomedicines including TPGS-based prodrugs, micelles, liposomes, TPGS-emulsified PLGA nanoparticles and nanoparticles of TPGS-based copolymers [12]. These nanomedicines can significantly enhance the solubility, the permeability, and the stability of the formulated drug and achieve sustained, controlled and targeted drug delivery. TPGS is also an efficient emulsifier for the synthesis of nanoparticles of biodegradable polymers, resulting in high drug encapsulation efficiency, high cellular uptake in vitro and high therapeutic effects in vivo. TPGS-emulsified nanoparticles or TPGS-based nanoparticles increase the cell uptake efficiency [12,21].

TPGS-based micelles are used for drug delivery. Nevertheless, TPGS micelles can easily dissociate in the plasma as the CMC of TPGS is relatively high. Therefore, TPGS is often mixed with other materials to form mixed micelles with the ability to increase stability and drug encapsulation. Among these materials, the most studied are poly(ethylene glycol)-phosphatidyl ethanolamine (PEG-PE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amin(polyethylene glycol)] (PEG-DSPE), Poloxamer 407 and PLGA-PEG [21,57-59,89]. For example, mixed micelles made of PEG-PE and TPGS showed a CMC comprised within 10⁻⁶ to 10⁻⁵ M. The solubility of CPT was enhanced at least by 50% compared to that of the PEG-PE micelles due to the increased inner micelle core volume through the vitamin E head. The anticancer efficiency of these mixed micelles was high due to their enhanced CPT solubility, permeability and stability as well as improved cellular uptake. This of these mixed micelles was high due to their enhanced CPT solubility, paclitaxel sensitive and resistant non-small cell lung cancer (NSCL) cell lines. It was shown that efficacy of PTX and parthenolide against both cell lines significantly increased when they were co-administered through mixed micelles [60].

Longer PEG chain derivatives have been synthesized in an attempt to improve the stability of TPGS based micelles. A study has shown that TPGS₁₀₀₀ with PEG chain of 2 kDa, had a lower CMC (0.022 mg/mL) than TPGS₂₀₀₀ (0.2 mg/mL), which improved the micelle stability and docetaxel (DOC) encapsulation. The cellular uptake and cytotoxicity of TPGS₂₀₀₀ loaded with DOC by MCF-7 cancer cells in vitro were enhanced compared with Taxotere®. Moreover, a synergistic effect between TPGS₂₀₀₀ and DOC from cytotoxicity assay was also shown. Thus, the design of drug delivery systems where the carrier material can also have therapeutic effects, which either modulate the side effects or promote a synergistic interaction with the formulated drug could be a promising approach in cancer therapy. Mixed micelles composed of TPGS₂₀₀₀ and a new derivative, TPGS₁₃₅₀-folic acid (TPGS₁₃₅₀-FOL), were also developed to target folate-receptor rich tumors [12,62].

Another way to improve the TPGS-based micelle stability was achieved by synthesizing a star-shape copolymer of lysine-linked di-TPGS₂₀₀₀ (PLV2K) (Fig. 4A). The system formed micelles with a CMC as low as 1.14 μg/mL. In DOX-resistant cells, MCF-7/Adr, the cytotoxicity was significantly enhanced with PLV2K micelles loaded with DOX (PLV2K-DOX) compared to DOX. The promotion of cellular cytotoxicity and cellular uptake to overcome MDR by PLV2K-DOX micelles in P-gp over-expressing MCF-7/Adr cell was proposed to rely on: (i) enhanced solubility and high encapsulation efficiency of DOX in PLV2K micelles, (ii) uptake of PLV2K-DOX micelles in MCF-7/Adr cells by endocytosis, escaping the efflux induced by P-gp and overcoming the MDR, (iii) the endocytotic pathway of PLV2K-DOX micelles which is caveolin-independent, avoiding degradation under lysosomal conditions, and (iv) the intracellularly released PLV2K could inhibit P-gp transporter ATPase activity, increasing the DOX cellular accumulation of DOX in the resistant cells (Fig. 4B). In vivo, PLV2K-DOX enhanced the antitumor activity and reduced the cytotoxicity compared with free DOX. DOX encapsulated in PLV2K was more effective in inhibiting tumor than TPGS-DOX, which may be due to the lower CMC, better stability and prolonged circulation time of PLV2K-loaded micelles [61].

TPGS has been used as surfactant and/or constituent in liposomal formulations since it may provide advantages for the sustained and controlled drug release. TPGS-based liposomes have been used to deliver anticancer agents like DOC, DOX and topotecan [63-66].

Recently, TPGS coated theranostic liposomes containing both DOX and quantum dots (QDs) were developed for combined cancer imaging and therapy. The TPGS coating of the liposomes allowed long-circulation effects, enhanced cellular uptake, and conjugation with
folic acid for active targeting effect. A significantly higher cellular uptake and cytotoxicity was demonstrated for the folate receptor targeted liposomes compared to non-targeting liposomes [63]. Other targeted TPGS-based liposomes have been developed successfully like trastuzumab-conjugated TPGS-based liposomes for the delivery of DOX for Human Epidermal Growth Factor Receptor 2 (HER-2) overexpressing breast cancer treatment. In vivo, IV administration of trastuzumab-conjugated liposomes showed longer half-life, 1.9 and 10 times more than PEG-coated liposomes and PTX respectively, demonstrating their greater potential for sustained and targeted chemotherapy in the treatment of HER-2 overexpressing breast cancer [67].

A new delivery system, Pluronic 85-PEI/TPGS complex nanoparticle conveying survivin shRNA (shSur) and PTX (PTPNs) for reversing drug resistance was designed and developed. shSur was used to down-regulate survivin gene expression since survivin protein is up-regulated in the most of malignant tumors but rarely in normal differentiated tissues. The 150 nm nanoparticles were shown to be more effective than free PTX in vitro in resistant (A549/T) and non-resistant (A549) human lung cancer cells. In vivo studies of PTPNs and PTX (Taxol®) on nude mice bearing A549/T showed a better efficacy of the PTPN formulation. Thus, the co-delivery of PTX and shSur by PTPNs could be a powerful approach to improve the therapeutic effect of PTX in resistant lung cancer [68].

Pluronic 85-PEI/TPGS complex nanoparticles were also used for the co-delivery of both shRNA and PTX to inhibit both metastasis and tumor growth. Twist is a transcription factor which plays a major role in metastasis of breast cancer. The complex was studied on metastatic 4T1 breast cancer cell line and its pulmonary metastasis mice model. Prolonged circulation and increased accumulation of PTX and shTwDr in lung and tumor were demonstrated. The in vivo antitumor efficacy showed that PTPNs could inhibit the in situ tumor growth effectively and completely restrict the pulmonary metastasis in pulmonary metastatic mice model whereas Taxol® did not [69].

Drug nanocrystals require surfactant as stabilizers [70,90]. TPGS has been used to develop TPGS–PTX nanocrystals to overcome multidrug resistance in cancer [21,70]. PTX formulations were characterized by crystals with a rod width being 40 nm and length being around 150 nm. The TPGS–PTX nanocrystals showed a significant antiproliferation effect compared with Taxol® when tested in P-g-p overexpressed cells (NCI/ADR-RES). Beyond its surfactant properties which are crucial for the nanocrystal stability, TPGS could act as a P-gp inhibitor to reverse MDR in cancer cells [21,70].

Drug-loaded nanoparticles emulsified with TPGS can achieve higher drug encapsulation efficiency (up to 100%) and cellular uptake, and thus higher therapeutic effects compared with polyvinyl alcohol (PVA) emulsified nanoparticles. TPGS (0.02–0.03%) can have 67 times higher emulsification effects than PVA in the PLGA nanoparticles. TPGS has been used as surfactant for the fabrication of PLGA, PCL, PLA–TPGS and PLGA–PEG nanoparticles. TPGS coated nanoparticles can also take advantage of its P-gp inhibition properties, especially in MDR cancer cells like MCF-7/ADR [71]. The main limitation to these nanoparticles is their low loading efficiency i.e. 2.4% in TPGS-emulsified PLGA [91] and 2.6% in MPEG–PLA [72] nanoparticles. Higher rates could be reached with TPGS-emulsified NPs made of a new redox-sensitive polymer, namely poly(ethylene glycol)-b-poly(lactic acid) (MPEG–SS-PLA), for which the loading efficiency was 9.1%. This stimuli-responsive polymer was prepared to carry PTX. It can release the drug as triggered and mediated by intracellular stimuli, here glutathione (GSH) which reduces disulfide bonds in the cytoplasm [71].

Advantages of TPGS can be utilized to overcome the high hydrophobicity of poly(lactic acid) polymers and their slow degradation. The synthesis of TPGS based copolymers is easily done by ring opening polymerization such as TPGS–PLA, TPGS–PLGA, TPGS–PCL, TPGS–PGA–PCL or TPGS–PLA–PCL [14]. TPGS has been used for triggering nanoparticles for faster drug release by improving the biodegradability of PLA/PLGA. The nanoparticles formed by PLA–TPGS polymers have been shown to get a higher drug encapsulation efficiency, cellular uptake and cytotoxicity on cancer cells in comparison with the classic PLGA nanoparticles [14,21,92]. The nanoparticle formulation relies on several classic methods like nanoprecipitation, solvent extraction/evaporation method, dialysis method and double emulsion method [21]. PLA–TPGS copolymers have been used for the delivery of DOX, PTX, DOX, curcumin, superparamagnetic iron oxides (SPIONs) and QDs. PLA–TPGS were even used for the co-delivery of SPIONs and QDs to develop a multimodal imaging system for concurrent imaging of the magnetic resonance imaging and the fluorescence imaging [12,14].

Modification of the surface of these nanoparticles was achieved to target specific membrane receptors such as trastuzumab for DOX delivery in HER-2 overexpressed cancer cells and folic acid for DOX delivery in folate-receptor rich tumors [12,14,73,74]. Transferrin (TI)-conjugated nanoparticles of PLA–TPGS loaded with DOX were studied for the targeted therapy across blood–brain-barrier [14].

PLA–TPGS nanoparticles loaded with DOX could also inhibit the P-gp activity which increased intracellular drug accumulation in MCF-7/ADR cells. It was proposed that PLA–TPGS nanoparticles loaded with DOX improved drug efficacy through the combination effect of P-gp inhibition and increase of drug entering into nucleus of drug-resistant MCF/ADR cells [12].

4.2.3. TPGS as a prodrug carrier

TPGS has been applied for prodrug design for enhanced chemotherapy since it may induce apoptosis and develop a synergistic effect with other anticancer drugs [62].

To reduce side effects from DOX, evade drug resistance and enhance its therapeutic efficiency, DOX was conjugated to TPGS. The prodrug demonstrated higher cellular uptake and better efficiency in MCF7 breast cancer cells and glioma C6 cells compared with the parent drug. The pharmacokinetic parameters such as half-life of the prodrug were improved in comparison with free DOX [12,75].

TPGS–DOX–folic acid (FOL) conjugate (TPGS–DOX–FOL) for targeted chemotherapy was synthesized and compared with TPGS–DOX conjugate and DOX. Targeting conjugate TPGS–DOX–FOL was 45-fold more effective than DOX in cytotoxicity on MCF-7 cells, while TPGS–DOX conjugate was only 1.19-fold effective than DOX. The half-life of TPGS–DOX and TPGS–DOX–FOL were extended from 2.69 h (DOX) to 10.2 h and 10.5 h, respectively. Conjugates also significantly decreased the drug distribution in gastric, intestine, and heart suggesting that TPGS conjugates, especially TPGS–DOX–FOL, could reduce side effects of the drug [12,73].

TPGS prodrug micelle strategy was developed for hydrophilic drug formulation with cisplatin as a drug model. The TPGS–cisplatin prodrug micelles show good potential to deliver the hydrophilic cisplatin with a low CMC, a drug load of 4.95% w/w and a controlled release. TPGS-cisplatin micelles showed higher uptake efficiency and better anticancer effects than the original cisplatin for HepG2 cancer cells, which may be due to the advantages of nanomedicine and the anti-cancer effect of TPGS [76].

TPGS–cisplatin prodrug was further used for the targeted delivery of cisplatin, DOC and hereceptin (HTCP) for multimodality treatment of breast cancer with HER-2 overexpression (Fig. 5). Co-polymers PLA–TPGS and TPGS–COOH were added to stabilize the nanoparticles and facilitate HTCP binding. The targeting effects of HTCP nanoparticles were demonstrated on several cell lines in vitro with high and low HER-2 overexpressions [77].

In conclusion, TPGS properties (solubilizer, surfactant, emulsifier, stabilizer, permeation enhancer as well as anticancer or antioxidant effect) have been discussed and illustrated. Majority of applications of TPGS rely on its amphiphilic structure. The lipophilic structure of TPGS explains its antioxidant and its anticancer activity. The hydrophilic part is responsible of the P-gp inhibition and provides the micellar property. Until now, TPGS-based nanomedicines exploit the P-gp inhibition and the surfactant effect of TPGS on formulations [21]. The anticancer
or antioxidant efficacy of TPGS included in nanomedicines remains unclear. Anyway, TPGS-based nanomedicines provide sufficient preclinical data to suggest that they should be applied in clinical administration of chemotherapeutic agents in the future.

5. Conclusions and perspectives

In conclusion we have described the functions of vitamin E and its anticancer activity to better understand the rationale of designing vitamin E derivatives-based nanomedicines for anticancer drug delivery. According to the literature, two vitamin E derivatives (vitamin E succinate (TOS) and vitamin E polyethylene glycol-succinate (TPGS)) have been highlighted as promising anticancer agents [50,92].

TOS or TPGS-based nanomedicines were widely developed to combine the pharmaceutical properties of both vitamin E and nanomedicine for two purposes: (i) they improve water solubility of hydrophobic drugs and (ii) they enhance the therapeutic efficiency of anticancer agents.

More particularly, TOS presents various advantageous properties for anticancer drug delivery: (i) non-toxic and biocompatibility, (ii) anticancer activity (inhibition of tumor proliferation and apoptosis), (iii) solubilizer and emulsifier of poorly water soluble drugs (nevertheless, the use of a stabilizer is mandatory), (iv) TOS is currently under clinical investigation in lung, prostate and pancreas cancer prevention, but this property is not exploited in TOS-based nanomedicines, and (v) TOS-based nanomedicines present (a) high drug loading, (b) self-assembling properties, (c) easy manufacture and (d) size adapted to intravenous injection and to the EPR effect to passively target tumors.

TPGS is also suitable for anticancer drug delivery: (i) non-toxic and biocompatibility, (ii) FDA approval as a safe pharmacetical adjuvant, (iii) anticancer activity, TPGS acts a P-gp inhibitor and has been used as an excitant for overcoming MDR, (iv) solubilizer, emulsifier and stabilizer, and (v) TPGS-based nanomedicines present (a) high drug encapsulation efficiency, (b) high cellular uptake in vitro and (c) high therapeutic effects in vivo due to their adapted size to intravenous injection and to the EPR effect.

In this review many examples of proof of concept of the potential benefit to use vitamin E derivatives-based nanomedicines in the treatment of cancer have been described both in vitro and when available in vivo. These examples clearly illustrate the promise of these vitamin E derivatives-based nanomedicines for novel anticancer treatments in the future.

References


