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REVIEW

Vitamin E TPGS Used as Emulsifier in the Preparation of Nanoparticulate Systems

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In recent years, nanoparticulate systems have matured from simple devices to multifunctional and more complex systems. They are biodegradable, stable in blood, non-toxic, and non immunogenic construct, capable of delivering drugs in a specific site, thereby improving efficacy. Their capabilities as drug delivery system and the interaction with the biological cells in the target tissue are dependent on their physicochemical properties such as particles size, size distribution, surface charge and morphology. Polymeric nanoparticles are usually produced by two classical methods: nanoprecipitation and emulsion-solvent evaporation technique. In such process, a number of preparation parameters can affect the nature of the nanoparticles as: drug, polymer concentration, temperature, solvent volume, aqueous:organic phase ratio, type and concentration of emulsifier and so forth. One of the most important formulation parameters involves the emulsifier, which is necessary as surfactant stabilizer in the process to form nanoparticles. D-α-tocopheryl polyethylene glycol (PEG) 1000 succinate (TPGS) is a water soluble derivate of natural source vitamin E. It is amphipathic and hydrophilic, exhibiting the characteristics of a typical surface-active agent. This review summarizes recently available information regarding the emulsifying effects of TPGS on the preparation, characterization, *in vitro* release and *in vivo* performance of the nanoparticulate systems, and the advantages of TPGS-drug conjugates.

Keywords: Biodegradable Polymeric Nanoparticles, TPGS-Copolymers, TPGS-Drug Conjugates, Vitamin E TPGS.

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1. INTRODUCTION

Nanomedicine is defined as a nanotechnology medical application which exploits and assimilates recent scientific advances to prevent, diagnose, treat and cure human disease.[1] The continued progress in this field allows us to focus on new drug delivery systems and molecules development to improve illness treatment. The ideal goal for diseases treatment is a high efficient and safety drug transport to the right place at appropiated concentrations for an adequate period of time. Nanoparticulate systems can increase the efficacy and safety of drugs by improving solubility, protecting against metabolism, controlling release and drug targeting.[2] The mingy concentrations of drugs reaching the target tissues and the limited retention time at the cellular level are one of the main factors contributing to treatment failure. These "nano" drug delivery systems seek to concentrate the drug in the site of interest, reducing the relative concentration of the drug in the

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rest of body to improve the medical treatments. Today, commercially available nanotechnology products are an effective alternative drug delivery platform used for the treatment of complex disease.[3] Generally, these products are designed to overcome the problems of drug poor solubility and bioavailability. Nowadays, almost 60% of drugs coming from synthesis are aqueous poorly soluble which led to low oral bioavailability.[4] For example, a water insoluble chemotherapy drug such as paclitaxel (PTX) has been reformulated into albumin nanoparticles (Abraxane®) with a mean particle size of 130 nm.[5] This nanoparticulate system allowed the administration of higher doses of PTX with shorter infusion duration than Taxol® (PTX-solution). For example, the infusion duration is 3 h for Taxol® and only 30 min for Abraxane®. Another encouraging issue was the possibility of overcome solvent-related problems of PTX.[3]

In recent years, nanoparticles (NPs) have matured from simple devices to more complex systems. NPs are defined as solid systems that usually share, as a common feature, a size range from a few nanometers (nm) to several hundred nm.[6] Nanoparticulate systems materials must be biocompatible and biodegradable for their use in the clinic. These biomaterials should be reduce, metabolize and eliminate by the body's natural pathways.[7] The choice of biomaterials with different physicochemical properties (molecular weight, hydrophilic–lipophilic balance and crystallinity) allows the modulation of drug delivery rates. Depending on the method of preparation, it is possible to generate nanocapsules or nanospheres.[8–11] The nanocapsules are vesicular systems in which the drug is adsorbed on the surface of the particle or placed in liquid interior surrounded by the polymeric layer. In contrast, the nanospheres are constituted by a spherical matrix, where the drug can be entrapped within the particle or adsorbed on the surface.[12] A very important point in the nanoparticulate systems is the particle surface. Once in the bloodstream, charged NPs without surface modification can be rapidly opsonized and massively cleared by the fixed macrophages. As a general rule, hydrophobic particles can be opsonized more quickly that hydrophilic particles due the enhanced adsorbability of blood serum proteins on these surfaces.[13] Surface modification of NPs with hydrophilic polymers and/or non-ionic surfactants is the most common way to slow, or even avoid, protein opsonization and to improve the surface properties of the system. These hydrophilic polymers or non-ionic surfactants are adsorbed or grafted in the surface of NPs in order to block electrostatic and hydrophobic interactions that promote opsonization process. This phenomena is denominated PEGylation.[13–14] The polymers and non-ionic surfactants more used in the NPs surface modification include polysaccharides, polyacrylamide, poly(vinyl alcohol), poly(*N*-vinyl-2-pyrrolidone), polyethylene glycol (PEG), and PEG-containing copolymers such as poloxamers, poloxamines, polysorbates, and PEG copolymers.[13] Recently, other polymers such as polyoxazolines, poly(amino acids), polybetaines and polyglycerols have been applied as surface coating agents.[15] One surfactant used recently for surface coating is the

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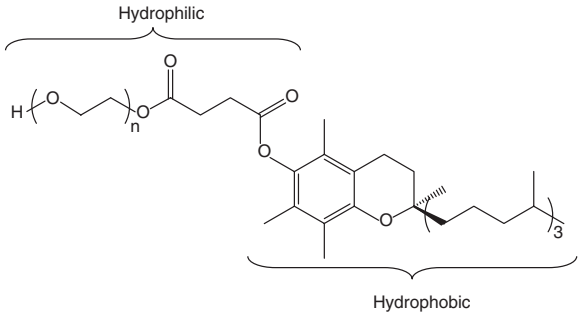
D-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS or TPGS).[16–18] TPGS is a water-soluble derivative of natural source vitamin E and PEG. This molecule results from the esterification of vitamin E succinate with PEG. It contains a lipophilic and a hydrophilic portion (Scheme 1), making it similar to a conventional surface-active agent.[19] Another very important feature is that TPGS can be intact absorbed in the gastrointestinal tracts, and inhibits efflux pumps such as *P*-glycoprotein (*P*-gp). Therefore cytotoxicity of anticancer agents with low oral bioavailability can be enhanced.[16] Also, several authors have also demonstrated the effects of TPGS as an effective oral absorption enhancer for improving bioavailability of several poor absorbed drugs.[20–23]

This review summarizes recently available information regarding the emulsifying effects of TPGS on preparation, characterization, *in vitro* release and *in vivo* performance of nanoparticulate systems, and the advantages of TPGS-drug conjugates.

2. APPLICATIONS AND ADVANTAGES OF TPGS IN NANOPARTICLES FOR DRUG DELIVERY

TPGS is a water-soluble form of the natural Vitamin E (α-tocopherol) which has been approved by the Food and Drug Administration (FDA) as a safe pharmaceutical excipient in drug formulation.[24] TPGS contains 260 mg/g of vitamin E (387 IU/g) and a molecular weight of $\sim$1513 Da. It is a waxy solid which is water miscible in all parts and it presents a HLB value of about 13.2. Also, TPGS is soluble in common excipients used in both preclinical and commercial formulations such as ethanol and PEG400.[25] TPGS melting point is range between 37 and 41 °C.[26] It has been administered satisfactorily for vitamin E deficiency treatment in patients with cystic fibrosis, Crohn's disease, congenital hepatic cholestasis, short bowel and also in premature infants with low birth weight.[27–31] Due to its physicochemical properties it has been used as an oral absorption enhancer to improved oral bioavailability of poorly absorbed drugs such as amprenavir, cyclosporine A and vitamin D.[32–34] In some cases, the bioavailability improvement could be observed at levels below the TPGS CMC value (0.02% w/v at 37 °C).[35–37] Nevertheless, these improvement could be also attributed to the enhanced on drug solubility due to micellar solubilization and/or TPGS capacity to inhibit *P*-gp.[38] Lately, several authors have described that α-tocopheryl succinate (α-TOS) has antineoplastic activity *in vitro* on many cancer cells lines.[39] Also, Youk et al. reported that TPGS was more potent than α-TOS in carcinoma growth inhibition in human lung cells.[40] Additional experiments are still necessary to confirm the potential anticancer activity of TPGS.



Scheme 1. Chemical structure of TPGS.

In recent years, TPGS has been used as an emulsifier for provide stability in the preparation of NPs. Generally, TPGS can be used in a concentration range from 0.015 to 0.06% w/v.[41] Some researchers use concentrations of up to 1% w/v[42] and others up to 5% w/v for the preparation of different NPs.[43] As emulsifier, TPGS was 67 times more effective than polyvinyl alcohol (PVA) in poly-lactic-*co*-glycolic acid (PLGA) NPs preparation by o/w emulsion solvent evaporation method.[41] Further, TPGS could achieve good efficiency of encapsulation (EE) for hydrophobic drugs resulting, in some cases, as high as 100%.[44–45] Additionally, TPGS could be used as a matrix component to improve NPs pharmaceutical properties. To achieve this, an interesting alternative was the synthesis of polymers such as poly-lactic acid (PLA) or poly-ε-caprolactone (PCL) with TPGS to form different copolymers. PTX-loaded PLA-TPGS NPs presented a faster PXT release rate than PTX-loaded PLGA NPs due to the higher hydrophilic character imposed by TPGS.[46] At the cellular level, it has been reported that NPs fabricated with TPGS as emulsifier could have higher cellular uptake efficiency compared to PVA-coated NPs in Caco-2 cells.[47] In Human colon adenocarcinoma cells (HT-29 cells), cellular uptake increased as follows PVA-emulsified PLGA NPs (27%) < TPGS-emulsified PLGA NPs (40%) < PLA-TPGS NPs (53%).[46] These are encouraging results but other experiments should be performed using multiple cell types and *in vivo* models to identify the true benefit.

3. BIODEGRADABLE POLYMERS USED IN NANOPARTICULATES SYSTEMS USING TPGS AS EMULSIFIER/STABILIZER

Nanoparticulates systems can be prepared from preformed polymers or from a monomer during its polymerization by several methods.[48] The most commonly-applied strategy for polymeric NPs production relies on premade polymers.[49] Because of the non toxic properties and biocompatibility of the degradation products, it is better to use biodegradable polymers. These can be from a natural or a synthetic origin. Natural biodegradable polymers are based on its low cost, its biocompatibility and its solubility in aqueous medium. Despite these advantages, they have a limited use due to the variability in its composition and molecular weight between batches. On the other

hand, synthetic biodegradable polymers have a high reproducibility between batches. This allows controlling and predicting the degradation kinetics of these polymers.[50] The synthetic biodegradable polymers more studied and used for NPs preparation, using TPGS as surfactant, are PLA[51] and PLGA.[45, 47, 52–54] PLA and PLGA belong to polyesters aliphatic family which was initially developed by the pharmaceutical industry for use as degradable surgical sutures.[55] Other polyester commonly used is poly-ε-caprolactone (PCL) which is less expensive than PLA and PLGA.[56] This family has gained popularity, mainly because of their noteworthy properties in terms of biocompatibility, biodegradability, and by its approval for use in human by the FDA.[57] This is relevant for the pharmaceutical industry because, FDA-approved pharmaceutical excipients appear as a better alternative for the development of pharmaceutical products than other new copolymers under evaluation which need long and expensive biocompatibility assays.

Particularly, these NPs are usually produced by two classical methods: nanoprecipitation and emulsion-solvent evaporation technique. In both techniques, NPs are formed by the precipitation of polymer in a TPGS-containing aqueous phase followed by solvent evaporation. In the nanoprecipitation, the polymer and drug are dissolved in an organic solvent miscible with water (e.g., acetone) and then mixed into an aqueous phase with TPGS. After the addition of the organic phase, the diffusion of the solvent into the aqueous phase will cause the polymer to precipitate, and drug-loaded NPs, will be form. In the emulsion-solvent evaporation method, the polymer and drug are dissolved in a non water-miscible solvent (e.g., dichloromethane, ethyl acetate) and mixed into an aqueous phase with TPGS forming an oil-in-water emulsion. This dispersion is formed upon mixing by sonication or high speed homogenization of the two phases and particles form upon solvent evaporation. The emulsion-solvent evaporation method is used to encapsulate either hydrophobic or hydrophilic drugs.[41] If the drug is hydrophilic, the technique should be modified to form a water-in-oil-in-water (w/o/w) emulsion. TPGS plays a key role to improve the characteristics of the NPs (size, surface morphology, drug loading and drug release).[57–60]

3.1. PLA and PLGA NPs Emulsified/ Stabilized with TPGS

Several approaches have been proposed for the preparation of PLA and PLGA NPs (Table I). PLGA NPs are frequently used for the encapsulation of various anticancer drugs such as PTX. It is an antineoplastic agent (mitotic inhibitor) with poor water solubility and effective for various cancer especially ovarian and breast cancer. The commercial formulation (Taxol®) is formulated with high Cremophor EL concentrations, which has been associated with severe side effects.[61] Mu et al. reported that optimizing the formulation parameters, drug EE could be as high as 100% for PTX-loaded PLGA NPs with TPGS as emulsifier agent.[41] Also, under the same fabrication condition, the required amount of TPGS was 67 times lower than the required amount of PVA to achieve the same emulsifying effects. This point is very important because it would need only a small amount of surfactant to produce NPs. For example 1% w/v of PVA would be equivalent to 0.015% w/v of TPGS. Other study has demonstrated that, PLA and PLGA NPs prepared with a TPGS concentration between 0.02–0.03% w/v showed the best nanoparticle yield. Also different NPs formulations fabricated with two PLGA types (75:25 and 50:50) and 0.03% w/v of TPGS, as emulsifier, showed EE between 49 and 84%. These NPs presented a hydrodynamic diameter ranged between 370–655 nm. Under SEM and AFM observation, all particles had a fine spherical shape. As to the *in vitro* release assays, an initial release burst was prominent during the first day ($\geq 15\%$). Then, the release gradually decreases and remains constant even after 1 month.[41] Win and Feng evaluated this type of NPs on *in vitro* assays with HT-29 cells. PTX loaded-PLGA NPs showed higher toxicity than the commercial formulation.[52] *In vitro* cytotoxicity studies in C6 glioma cells revealed that PTX-loaded PLGA NPs ($IC_{50} = 9.6\ \mu g/ml$) showed 3.40 times greater cytotoxicity than PTX solution ($IC_{50} = 32.7\ \mu g/ml$) in 48 h culture at 37 °C. In addition, the mortality was almost despicable for the blank PLGA NPs.[62] More over, Feng's group evaluated PTX-loaded PLGA NPs for oral chemotherapy. These NPs presented spherical shape of 200–300 nm diameters with an EE of 80.9%. NPs *In vivo* evaluation achieved more than 10 times higher oral bioavailability than Taxol®, which result 9.74-fold higher therapeutic effect and 12.56-fold longer sustainable therapeutic time than Taxol®.[63] In case of I.V. route, NPs produced a significant increase in the half life of PTX in an *in vivo* s.c. C6 cells xenograft model. Moreover, a single administration of NPs achieved a sustained therapeutic effect for 7 days, while PTX solution effect remained only for 22.2 hours. In addition, these NPs administered via intratumoral were 1.5 times more effective than Taxol® to suppress tumor growth.[63] Also, PTX-loaded TPGS-emulsified PLGA NPs administered I.V. increased the AUC (area-under-the-curve) by a factor of 4.9 compared to Taxol®.[52]

Due to complications presented by the I.V. route, the oral route is a very good alternative for ambulatory cancer patient's therapy. For this reason, the deeply investigation of the oral administration of the traditionally I.V.-administered anticancer drugs represent a real challenge.[64] Caco-2 cell line (colon adenocarcinoma) can be used to *in vitro* simulate the gastrointestinal barrier and to evaluate cellular uptake of oral anticancer drugs. Win and Feng prepared PVA-emulsified and TPGS-emulsified coumarine-6-labelled PLGA NPs to evaluate uptake cellular. Images of confocal laser scanning microscopy (CLSM)

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Table I. Examples of NPs prepared with biodegradable polymers using TPGS as emulsifier/stabilizer.

Polymer	Preparation method	Drug	Size (nm)	PDI	EE%	Comments	Ref.
PLGA (50:50)	Emulsion-solvent evaporation	PTX	~685	0.005	100	In comparison with PVA, the TPGS could significantly improve the encapsulation efficiency of the drug in the NPs.	[46]
PLGA (50:50); (75:25) and PLA	Emulsion-solvent evaporation	PTX	~515; ~272 and ~589 for each polymer	0.005; 0.245 and 0.326	~53; ~50 and ~43	NPs of nanometer size with narrow distribution can be obtained.	[41]
PLGA (50:50)	Emulsion-solvent evaporation	PTX	~236	0.012	~66	The AUC for 48 h for TPGS emulsified PLGA NPs of PTX were found 4.9 times larger than that for the Taxol®.	[52]
PLGA (50:50)	Emulsion-solvent evaporation	PTX	~288	0.028	~93	TPGS-emulsified NPs have great advantages versus PVA-emulsified NPs for local delivery of antiproliferative drugs.	[54]
PLGA (50:50)	Emulsion-solvent evaporation	Atorvastatin calcium	~140	0.150	~35	NPs presented better efficacy and safety parameters that marketed formulation.	[69]
PLGA	Emulsion-solvent evaporation	PTX	200–300	N.D.	~81	NPs achieved more than 10 times higher oral bioavailability than Taxol®, which resulted 9.74-fold higher therapeutic effect than Taxol®.	[63]
PLGA	Emulsion-solvent evaporation	Iron oxides	~280	0.120	N.D.	NPs were tested *in vivo* using xenograft mice. They are able to reach the tumor by EPR as shown by magnetic resonance imaging.	[123]
PLGA (50:50)	Nanoprecipitation Emulsion-solvent evaporation	Meloxicam	~220 1st population: 68–82; 2nd population: 367–475	0.109 0.449–0.651	N.D. 50–58	NPs produced with TPGS showed bimodal size distribution. An increase in sonication time leads to an increase in the production of smaller particles with narrower size distribution.	[44]

Notes: *Abbreviations*: PLGA, poly-lactic-*co*-glycolic acid; PTX, paclitaxel; PVA, polyvinyl alcohol; TPGS, D-α-tocopheryl polyethylene glycol (PEG) 1000 succinate; AUC, area under curve; N.D., not data.

clearly showed that the particles were internalized in the cells and that surface modification of PLGA NPs with vitamin E TPGS improved the cellular uptake (1.4 fold).[47] More recently, Zhao and Feng evaluated TPGS-emulsified PTX-PLGA NPs for oral chemotherapy. The NPs developed showed an oral bioavailability 10 times greater than Taxol® in rats.[63]

With other therapeutic purpose, PTX has been used in treatment of coronary in-stent restenosis with PTX-coated balloon catheters.[65] Considering this application, Feng et al. encapsulated PTX in PLGA NPs using PVA or TPGS as emulsifier agent. These NPs were tested for the treatment and prevention of restenosis in coronary artery smooth muscle cells (CASMCs) and in an animal model (rabbit). *In vitro* study showed that PVA and TPGS-emulsified NPs presented higher antiproliferative effects than Taxol® (3.66 and 5.15 times, respectively). Furthermore, TPGS-emulsified NPs ($IC_{50} = 160$ ng/ml) was 47% more effective than Taxol® ($IC_{50} = 748$ ng/ml) and 1.3% more effective than PVA-emulsified PLGA NPs ($IC_{50} = 204$ ng/ml). *In vivo* model of restenosis was used only to observe the uptake of fluorescent NPs.[54]

Not only PXT but also a variety of therapeutic agents with different aqueous solubility could be encapsulated in PLGA NPs using TPGS as emulsifier. For example, rifampicin and estradiol valerate were chosen as model of hydrophilic and hydrophobic drugs, respectively. TPGS was a good emulsifier in terms of loading efficiency with estradiol (insoluble) and not so good for rifampicin, a slightly water-soluble molecule.[53] Other drug with low solubility and membrane permeability is amphotericin B (AmB). It is an antifungal and antileishmanial drug with negligible absorption when it is orally administered. Therapy with conventional dosage form of AmB (Fungizone®) involves I.V. administration over long periods of times according to disease.[66] However, its therapeutic effect is limited due to several drug-related side effects as renal toxicity.[67] The existence of an effective and safe AmB oral formulation would have great impact in the clinical field. AmB-loaded PLGA NPs of ~ 170 nm were prepared by nanoprecipitation method employing TPGS as stabilizer. These NPs were administered I.V. in rats to determine the potential nephrotoxicity. The animals treated with Fungizone® presented a significant increase in blood urea nitrogen and plasma creatinine levels compared to control; while AmB-loaded PLGA NPs showed lower levels demonstrating greater safety. Also, the relative bioavailability of AmB was $\sim 800\%$ for the NPs ($AUC_{0-inf} = 7939$ ng · h/ml) as compared to Fungizone® ($AUC_{0-inf} = 1001$ ng · h/ml).[68] These NPs offer a valuable possibility of treating systemic fungal infection and leishmaniasis by oral route. Similarly, NPs prepared with PLGA and TPGS as emulsifier were used to encapsulate statins by emulsion evaporation method.[69] Statins are a class of drugs used to decrease blood cholesterol levels achieving important benefits for the large populations of individuals at high risk for coronary disease.[70] Statins have rare but severe adverse effects, particularly muscle aches or muscle weakness with increase in creatine phosphokinasa (CPK). This muscle weakness is named "Myophaty." The myotoxicity of the statins varies as follows: atorvastatin > (pravastatin = simvastatin = lovastatin) > fluvastatin.[71] Meena et al. prepared atorvastatin-loaded PLGA NPs using TPGS as stabilizer demonstrating equal effectiveness in comparison to Lipicure® (commercial formulation), at a 66%-reduced dose in treating the hyperlipidemia. Also, NPs showed non negligible myotoxicity in comparison to the marketed formulation.[69] Once more, TPGS-emulsified NPs showed significant improvement compared with commercially available formulations.

3.2. Nanoparticles Prepared with TPGS-Copolymers

The synthesis of biodegradable copolymers based upon TPGS as a matrix component has great potential for the manufacture of polymeric NPs (Table II). Thus, we can prevent desorption of TPGS from the NPs surface.[60] Moreover, NPs surface modifications with TPGS also provide a platform for conjugation of ligands, and prevent the opsonization.[72–73] Recently, the properties combination of both, polymers and TPGS, have been explored in order to synthesized different copolymers such as PLA-TPGS,[74–75] PLGA-TPGS,[76–78] PCL-TPGS,[79] PCL-PLA-TPGS[80] and PCL-PGA-TPGS.[81] Some authors have used these copolymers for NPs preparation. For example NPs fabricated of PLA-TPGS copolymer were prepared by modified solvent extraction technique with and without TPGS as emulsifier. In both cases, PTX-loaded PLA-TPGS NPs of ~ 300 nm showed higher EE and achieve a faster drug release than PLGA NPs.[82] Furthermore, the PLA-TPGS NPs showed higher cellular uptake compared to traditional PLGA NPs in HT-29 cells. The IC_{50} of PTX-loaded PLA-TPGS NPs was decreased 14 fold for HT-29 and 2 fold for Caco-2 cells after 48 hours incubation in comparison to PTX solution. I.V. administration of PTX-loaded PLA-TPGS NPs in rats revealed 1.6-fold larger AUC values and enhanced the plasma residence times of drugs compared to commercial formulation.[83]

NPs containing TPGS have been proposed to provide an innovate solution for oral chemotherapy. Feng et al. prepared PLA-TPGS NPs incorporating montmorillotine (PLA-TPGS/MMT NPs) a potent detoxifier for oral delivery of chemotherapeutic agent as docetaxel (DTX). The *in vitro* activity of DTX-loaded PLA-TPGS NPs could be enhanced by combining it with MMT. *In vitro* studies in MCF-7 cells, DTX formulated in PLA-TPGS ($IC_{50} = 5.11$ μg/ml) and PLA-TPGS/MTT ($IC_{50} = 3.68$ μg/ml) were ~ 2 and ~ 3-fold more effective than the Taxotere® (DTX solution) ($IC_{50} = 11.3$ μg/ml) after 24 h treatment, respectively. Moreover, *in vivo* experiments with

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Table II. Examples of NPs prepared with TPGS-copolymers.

Copolymer	Preparation method	Drug	Size (nm)	PDI	EE%	Comments	Ref.
PLA-TPGS	Emulsion-solvent evaporation	PTX	~300	>0.20	62–92	PLA-TPGS copolymer can greatly increase the drug encapsulation efficiency and achieve much faster drug release than the PLGA nanoparticles to meet the therapeutic needs.	[74]
PLA-TPGS	Emulsion-solvent evaporation	PTX	~300	0.20–0.30	60–90	The novel PLA-TPGS NP formulation of paclitaxel also showed significant advantages in achieving larger cytotoxicity and smaller IC_{50} over the Taxol®.	[46]
PLA-TPGS	Doble emulsion-solvent evaporation	BSA	260–360	0.21–0.34	44–75	PLA-TPGS NPs have advantages over the PLGA NPs: smaller size, more uniform size distribution, higher EE, and desired release profile and more importantly, protect the activity of the formulated proteins.	[85]
PLA-TPGS:TPGS-COOH	Emulsion-solvent evaporation	PTX	310–330	0.14–0.32	~51	PLA-TPGS copolymer is employed as matrix and the TPGS-COOH copolymer is used to facilitate folate decoration for targeting the cancer cells rich of the folate receptors on their surface. NPs have great advantages versus the pristine drug and the folate-decoration can significantly promote targeted delivery of the drug to the corresponding cancer cells.	[98]
PLA-TPGS	Emulsion-solvent evaporation	QDs	~200	~0.15	46	QDs were encapsulated in the interior of the polymeric matrix. These NPs can be used for molecular imaging for detection of diseases at their earliest stage.	[73]
PLA-TPGS:TPGS-COOH	Emulsion-solvent evaporation	QDs	~280	0.16–0.20	~45	QDs-loaded PLA-TPGS/TPGS-COOH NPs showed lower *in vitro* cytotoxicity compared to free QDs.	[72]
PLA-TPGS	Nanoprecipitation	DTX	228–245	~0.27	~60	IC_{50} data showed that the Tf adsorbed PLA-TPGS NPs of DTX could be 23.4%, 16.9% and 229% more efficient than the PLGA NPs, the PLA-TPGS NPs and Taxotere® after 24 h treatment, respectively	[94]
PLA-TPGS	Emulsion-solvent evaporation	DOX	~130	0.06	98	PLA-TPGS NPs showed the inhibition of *P*-gp activity and improvement in intracellular accumulation and nuclear localization of DOX.	[121]
PLGA-TPGS	Emulsion-solvent evaporation	DTX	207–290	0.32–0.49	59–99	DTX-loaded PLGA-TPGS NPs could achieve much faster drug release in comparison with PLGA NPs. Also, PLGA-TPGS NPs were biocompatible, and DTX-loaded PLGA-TPGS NPs had significant cytotoxicity against Hela cells.	[77]
PCL-PLA-TPGS	Emulsion-solvent evaporation	DTX	~200	>0.20	54	DTX-loaded PCL-PLA-TPGS NPs presented advantages over Taxotere® in terms of cytotoxicity against HeLa cells.	[80]
PLA-TPGS:TPGS-COOH	Nanoprecipitation	DTX	160–240	0.09–0.20	N.D.	Adjusting the PLA-TPGS:TPGS-COOH blend ratio could controlled the targeting effects in HER2 positive breast cancer cells.	[102]

Notes: *Abbreviations*: PLA, poly-lactic acid; TPGS, D-α-tocopheryl polyethylene glycol (PEG) 1000 succinate; PTX, paclitaxel; BSA, bovine serum albumin; PLGA, poly-lactic-*co*-glycolic acid; PVA, polyvinyl alcohol; QDs, Organic Quantum Dots; DTX, docetaxel; DOX, doxorubicin; PCL, poly-ε-caprolactone; N.D., not data.

rats showed that the oral administration of NPs achieved ~20 times longer half life of DTX. Additionally, the oral bioavailability of DTX could be increased to 91.3% by the PLA-TPGS formulation compared to 3.6% for Taxotere®.[84] PLA-TPGS NPs also can be used for delivery and protection of peptides and protein. Lee et al. showed that modulating the ratio weight content of PLA:TPGS could affect the burst release characteristic from the albumin (BSA)-loading PLA-TPGS NPs. Unfortunately, the EE decreased from 75.6% to 44.3% when the TPGS's content in the copolymers was increased from 3.4% to 12%.[85] Another novel approach was the synthesis of PLGA-TPGS for the delivery of anticancer drugs. PLGA-TPGS NPs encapsulating DTX showed a significant anti-proliferative activity *in vitro* against HeLa cells. This activity is positively correlated to greater cellular uptake and little toxicity of the drug-free PLGA-TPGS NPs.[86] In other study, Ma et al. developed a formulation based on PCL-PLA-TPGS random copolymer for NPs formulation of DTX. The IC_{50} value for DTX incorporated into PCL-PLA-TPGS NPs toward HeLa cells was determined to be 4.6 μg/ml versus 28.1 μg/ml for Taxotere®, after 72 h. In addition, the cummulative drug release was 12.2% for PCL-PLA-TPGS NPs after 72 h.[87] An interesting strategy for increase retention time at the cell surface is modify the surface charge of NPs. Chen and co-workers prepared PLGA-TPGS NPs with a cationic surfactant didodecyldimethylammonium bromide (DMAB) to change the surface charge of NPs. Zeta potential values confirmed that surface modification with DMAB changed the PLGA-TPGS NPs from a negative to a positive surface charge. DMAB-modified PLGA-TPGS NPs (+32 mV) have significantly higher level of the cellular uptake than that of DMAB-modified PLGA NPs (−29 mV) and unmodified PLGA-TPGS NPs (−22 mV).[88] All studies demonstrate that TPGS-copolymers are very promising for the preparation of novel nanocarriers for drug delivery, but more assays are necessary to ensure biodegradability and biocompatibility.

4. TPGS IN NANOPARTICLES-BASED TARGETED DRUG DELIVERY

Generally, tumor cells express many molecules on their surface at levels higher than normal cells. For example, the transferrin receptor (TfR1) is ubiquitously expressed in normal human tissue but it is overexpressed on surface of many malignant cells. This high expression, its ability to internalize by endocytosis, and the necessity of iron for cancer cell proliferation make this receptor a widely accessible portal for entry of drugs into solid tumor.[6] Recent studies involve the coupling of transferrin (Tf), antibodies against TfR or peptides to the NPs surface.[89–91] Thus, Zheng and co-workers prepared hybrid NPs composed of PLGA, phosphatidylcholine (PC) and TPGS, with and without Tf, for targeted delivery of an aromatase inhibitor (7α-APTDAD).[92] TPGS was used as stabilizer because hybrid NPs exhibit high drug loading but little stability in saline solutions. This inconvenient could be improved by adding TPGS[93] which provides steric stabilization of NPs due to the hydrophilic PEG chain. 7α-APTDAD is a potent irreversible aromatase inhibitor with activity in many cell lines including human mammary carcinoma MCF-7 cells and choriocarcinoma JAr cells.[94] None of the formulations studied showed significant cytotoxicity at 24 h against breast cancer cell line (SKBR-3 cells). Therefore, the drug and the NPs were essentially non-toxic to SKBR-3 cells. On the other hand, Tf-PLGA NPs were visualized into endosomal vesicles indicating receptor-mediated endocytosis by CLSM. Finally, aromatase inhibition by the drug-loaded Tf-NPs in SKBR-3 cells was more effective than that by the non-targeted NPs.[83] The presence of Tf improves the efficiency and specificity of drug delivery systems. In other study, DTX-loaded PLA-TPGS NPs were prepared by nanoprecipitation and Tf was adsorbed on NPs surface (DTX-PLA-TPGS/Tf). Different formulations were evaluated *in vitro* with C6 glioma cells. IC_{50} data showed that DTX-PLA-TPGS/Tf NPs could be 23.4%, 16.9% and 229% more efficient than DTX-PLGA NPs, DTX-PLA-TPGS NPs and Taxotere® after 24 h treatment, respectively. Also, the confocal images of C6 glioma cell line with 6-coumarin loaded NPs formulations showed that the intracellular uptake of PLA-TPGS/Tf NPs was significantly enhanced compared with PLA-TPGS NPs.[95]

The blood brain barrier (BBB) presents important obstacles in the treatment of brain tumors because it regulates the internal environment of the brain selecting the passage of desired molecules from the blood to the brain parenchyma. The presence of TfR in the luminal membrane of capillary endothelium of the BBB suggests that this mechanism could be exploited to solve the problems of brain drug administration.[96] For example, Gang and Feng investigated the biodistribution of 6-coumarin loaded NPs in rats. The concentration of 6-coumarin in the brain tissue from the PLA-TPGS/Tf was higher than the PLA-TPGS NPs. PLA-TPGS NPs presented lower concentration in the brain than PLA-TPGS/Tf, but higher than PLGA NPs; this is probably due to the TPGS inhibitory function in the *P*-gp efflux transporters present in the BBB.[86]

Other strategy for tumor targeting, involves folate-modified nanocarriers because folate receptor is frequently overexpressed in many malignant cells.[97] Zhang et al. synthesized TPGS-folate (TPGS-FOL) to decorate NPs prepared with doxorubicin (DOX) conjugated to PLGA-TPGS (DOX-PLGA-TPGS). TPGS-FOL was blended with DOX-PLGA-TPGS at various ratios to control the targeting process. In the cellular uptake assay, the NPs prepared with a ratio 1:1 TPGS-FOL:DOX-PLGA-TPGS showed an increase of 1.3 fold for MCF-7 and 1.2 fold for C6 glioma cells after 6 hours cell culture compared to NPs prepared without TPGS-FOL. The MCF-7 and C6 cell viability

was decreased from 50.8% and 49.6% for NPs without TPGS-FOL to 8.2% and 30.6% for TPGS-FOL:DOX-PLGA-TPGS (1:1) NPs, respectively, after incubation for 24 hours.[98] The NPs with TPGS-FOL presented better *in vitro* cytotoxicity probably due to targeting effects of FOL in the cancer cells with overexpression of the FOL receptors. Similarly, PTX-loaded FOL decorated NPs (FOL-PTX-NPs) were prepared with blends of two copolymers PLA-TPGS and TPGS-carboxylic acid terminated (TPGS-COOH), which facilitated the conjugation of ligands such as folate. *In vitro* studies with MCF-7 and C6 cells demonstrated that FOL-PTX-NPs were more effective in decrease the cell viability than non-targeted NPs and Taxol®.[99] More recently, TPGS-FOL and PTX conjugated to monomethoxy-poly-(ethylene glycol)-*b*-poly-(lactide) (mPEG-PLA-PTX) were used to prepare NPs with various molar ratios of both copolymers. *In vitro* assays demonstrated that the cytotoxicity of PTX-loaded NPs to C6 and Hella cells were improved by folate component.[100] A similar strategy was used to combine Herceptin® (a FDA approved monoclonal antibody named trastuzumab) to the surface of NPs composed of PLA-TPGS and TPGS-COOH for targeting delivery of DOX to breast cancer cells overexpressing the human epidermal growth factor receptor 2 (HER2 receptor).[101] Zhao and co-workers found than adjusting the PLA-TPGS:TPGS-COOH blend ratio could controlled the targeting effects in HER2 positive breast cancer cells of two ways: controlling the surface density of TPGS-COOH, and adjusting the feeding concentration of herceptin in the conjugation process. This fact had a direct impact on cellular uptake and cytotoxicity.[102] All these *in vitro* studies shows a high selectivity of the NPs decorated with ligands, however, *in vivo* experiments are needed to confirm a real effect at the site of action.

5. TPGS-DRUG CONJUGATES

Polymer-drug conjugates are platforms therapeutics for drug delivery composed of a polymer covalently bound to a drug trough a linker, generally biodegradable. Many polymer-drug conjugates are in different stages of clinical studies or have entered into routine clinical use in oncology.[103] DOX is an anthracycline antibiotic used in the treatment of a wide range of cancers, unfortunately its clinical application is limited because of severe side effects, including cardiotoxicity, myelosupresion, and neprotoxicity.[104] To minimize the adverse effects of DOX, it has been chemically conjugated to TPGS, changing significantly the intracellular and tissue biodistribution of pristine DOX.[105] This DOX-TPGS conjugated has shown higher cytotoxicity *in vitro* against MCF-7 and C6 cells at low drug concentration. The IC_{50} of DOX-TPGS conjugated in comparison to free DOX was 84.1% more effective for MCF-7 and 42.2% more effective for C6 cells after 72 hours culture.[106] Also, DOX-TPGS conjugate has been chemically conjugated to folate-hydrazide (FOL-DOX-TPGS) in an effort to deliver DOX directly to cancer cell that overexpressing high levels of folate receptor. The IC_{50} of FOL-DOX-TPGS, DOX-TPGS and free DOX were 0.59, 22.8 and 27.9 μM, respectively. Therefore, the IC_{50} of FOL-DOX-TPGS in comparison to free DOX was reduced by 45 fold for MCF-7 cells.[97] The pharmacokinetics of DOX-TPGS and FOL-DOX-TPGS were evaluated in rats. The half life of DOX in plasma was 10.2, 10.5, and 2.69 hours by DOX-TPGS, FOL-DOX-TPGS and pristine DOX, respectively. Therefore, the conjugates delay the blood clearance and have similar biodistribution.[97–98] More importantly, both conjugates decreased the heart accumulation of DOX. The AUC was increased by more than $\sim$15 times.[97] The previously results show that polymer-drug conjugates are a viable strategy for formulation of drug delivery systems. Importantly, the inhibitory effect of *P*-gp motivates the search of TPGS-drug conjugates to solve problems associated with drug's pharmacokinetic. However, these conjugates have the drug chemically conjugated to the polymer and therefore they are new chemical entities.

6. INHIBITION OF EFFLUX TRANSPORTER FOR TPGS

P-gp is a class of multi-drug resistance (MDR) protein that it is present on the cell membrane and cause the efflux of drugs reducing its efficacy. Naturally, these ATP dependent transporter proteins are expressed in a wide range of normal tissues to minimize the exposure to potentially toxic xenobiotics.[107] *P*-gp is extensively distributed and expressed normally in the intestinal epithelium, liver, kidney, placenta, adrenal gland and capillary endothelial cells comprising the BBB and blood-testis barrier.[108] Also, it is overexpressed in cancer cells and is responsible for one of the MDR mechanisms most extensively studied in this kind of cells. The MDR is a major clinical problem to the success of cancer therapy.[109] Approximately 50% of marketed drugs have lately been identified to be *P*-gp substrates, inhibitors or inducers.[110] *P*-gp inhibitors have been developed and co-administrated with chemotherapeutic agents (e.g., verapamil, cyclosporine A), however, the efficacy of these inhibitors was largely compromised by pharmacokinetic interactions and increased side effects.[111] Several excipients used in marketed formulations (e.g., PEG400, TPGS, polysorbate 80, Solutol HS 15, Labrasol, Cremophor EL and different poloxamers) are potential candidate to enhance drug absorption. They were identified as more or less potent *P*-gp inhibitors.[112–114] Wempe and co-workers investigated the potential of novel TPGS analogs using Caco2 permeability model.[115] *In vitro* results showed that TPGS concentration of 30 μM ($< 0.005\%$ w/v) reduced rhodamine 123

(*P*-gp substrate) efflux by 33% compared to cyclosporine (*P*-gp inhibitor) that show a complete efflux inhibition. *In vivo* studies confirmed TPGS ability to inhibit *P*-gp mediated efflux, resulting in significant improvement of PTX bioavailability in rats and increased oral talinolol and cyclosporine bioavailability in humans.[116–118] Most recent studies revealed that modulation of ATPase activity correlated with inhibitory potential for *P*-gp mediated efflux. Therefore, TPGS modulates *P*-gp efflux transport via *P*-gp-ATPase inhibition.[119–120] Furthermore, TPGS inhibitory potential may be increased or decreased by a modification of the PEG chain length. Collnot and coworkers synthesized TPGS analogues (TPGS 200-6000) finding that TPGS 1000 was the most potent inhibitor of rhodamine 123 transport in Caco-2 monolayers.[121] Li et al. prepared DOX-loaded PLA-TPGS NPs and founded that the activity of *P*-glycoprotein in drug-resistant breast cancer MCF-7/ADR cells was decreased after incubation with these NPs.[122] NPs prepared with TPGS could exhibit inhibitory effect on *P*-gp to enhance drugs bioavailability. Certainly, the potential function of TPGS as an inhibitor of efflux pump makes it a suitable choice for the NPs manufacture.

7. CONCLUSIONS

The present work has reviewed the use of TPGS as emulsifier in the preparation of NPs. TPGS has many advantages over conventional surfactants. This can increase the solubility, permeability and bioavailability of many drugs which are difficult to deliver orally. Also, TPGS can modulate *P*-gp efflux transport and improve the bioavailability of various drugs. In recent years, TPGS has been used as a very good emulsifier for produce NPs. As stated, TPGS is more effective as emulsifier than traditional PVA, present better performance in emulsification and drug encapsulation efficiency. Due to its structure, TPGS can be used in the replacement of PEG to coat the NPs surface and enhance cellular uptake, *in vitro* cancer cell cytotoxicity, and more desirable *in vivo* pharmacokinetics. The applications of TPGS in nanomedicine are numerous, therefore will be necessary more research about on the pharmacokinetics, biodistribution, and safety of these drug delivery systems. Finally, the largest number of publications is in cancer. This opens the possibility to work in other diseases exploiting this information.

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REVIEW