Biomaterials 33 (2012) 4889–4906

Contents lists available at SciVerse ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Review

Vitamin E TPGS as a molecular biomaterial for drug delivery

Zhiping Zhang [a,b], Songwei Tan [a,b], Si-Shen Feng [c,d,e,*]

[a] Tongji School of Pharmacy, Huazhong University of Science and Technology, Wuhan 430030, PR China
[b] National Engineering Research Center for Nanomedicine, Huazhong University of Science and Technology, Wuhan 430030, PR China
[c] Department of Chemical & Biomolecular Engineering, National University of Singapore, Block E5, 02-11, 4 Engineering Drive 4, Singapore 117576, Singapore
[d] Department of Bioengineering, National University of Singapore, Block E5, 02-11, 4 Engineering Drive 4, Singapore 117576, Singapore
[e] Nanoscience and Nanoengineering Initiative (NUSNNI), National University of Singapore, Block E5, 02-11, 4 Engineering Drive 4, Singapore 117576, Singapore

ARTICLE INFO

Article history:
Received 21 February 2012
Accepted 13 March 2012
Available online 11 April 2012

Keywords:
Cancer nanotechnology
Biodegradable polymers
Liposomes
Micelles
Nanoparticles
Prodrugs

ABSTRACT

D-α-tocopheryl polyethylene glycol succinate (Vitamin E TPGS, or simply TPGS) is a water-soluble derivative of natural Vitamin E, which is formed by esterification of Vitamin E succinate with polyethylene glycol (PEG). As such, it has advantages of PEG and Vitamin E in application of various nanocarriers for drug delivery, including extending the half-life of the drug in plasma and enhancing the cellular uptake of the drug. TPGS has an amphiphilic structure of lipophilic alkyl tail and hydrophilic polar head with a hydrophile/lipophile balance (HLB) value of 13.2 and a relatively low critical micelle concentration (CMC) of 0.02% w/w, which make it to be an ideal molecular biomaterial in developing various drug delivery systems, including prodrugs, micelles, liposomes and nanoparticles, which would be able to realize sustained, controlled and targeted drug delivery as well as to overcome multidrug resistance (MDR) and to promote oral drug delivery as an inhibitor of P-glycoprotein (P-gp). In this review, we briefly discuss its physicochemical and pharmaceutical properties and its wide applications in composition of the various nanocarriers for drug delivery, which we call TPGS-based drug delivery systems.

1. Introduction

D-α-tocopheryl polyethylene glycol succinate (Vitamin E TPGS, or simply TPGS) (as shown in Scheme 1) is a water-soluble derivative of natural Vitamin E, which is formed by esterification of Vitamin E succinate with polyethylene glycol (PEG). As such it has advantages of PEG and Vitamin E in application of various drug delivery device, including extending the half-life of the drug in plasma and enhancing the cellular uptake of the drug. Typically, the molecular weight of TPGS with PEG1000 segment is 1513. TPGS has amphiphilic structure of lipophilic alkyl tail and hydrophilic polar head with a hydrophile-lipophile balance (HLB) value of 13.2 and a critical micelle concentration (CMC) of 0.02% w/w [1]. TPGS safety issue has been investigated in details and it has been reported that the acute oral median lethal dose (LD50), which is defined as the quantity of an agent that will kill 50 percent of the test subjects within a designated period, is >/7 g/kg for young adult rats of both sexes [2]. US FDA has approved TPGS as a safe pharmaceutical adjuvant used in drug formulation.

In recent years TPGS has been intensively applied in developing the various drug delivery systems. TPGS has been used as an absorption enhancer, emulsifier, solublizer, additive, permeation enhancer and stabilizer [3,4]. TPGS has also been served as the excipient for overcoming multidrug resistance (MDR) and inhibitor of P-glycoprotein (P-gp) for increasing the oral bioavailability of anticancer drugs [4–7]. TPGS has also been applied for prodrug design for enhanced chemotherapy [8,9]. Feng's group has been focused in the past decade on various applications of TPGS in nanomedicine, including TPGS-based prodrugs, micelles, liposomes, TPGS-emulsified PLGA nanoparticles and nanoparticles of TPGS-based copolymers, which can significantly enhance the solubility, permeability and stability of the formulated drug and realize sustained, controlled and targeted drug delivery. TPGS has been proved to be an efficient emulsifier for synthesis of nanoparticles of biodegradable polymers, resulting in high drug encapsulation efficiency, high cellular uptake in vitro and high therapeutic effects *in vivo* [10–12]. For example, TPGS may have more than 77 times higher emulsification efficiency compared with the traditional emulsifier polyvinyl alcohol (PVA), *i.e.* to produce the same amount of polymeric nanoparticles by the single emulsion method, the needed TPGS amount can be only 1/77 than that of PVA as the emulsifier used in the process. TPGS-emulsified nanoparticles or TPGS-based nanoparticles have been found to

* Corresponding author. Department of Chemical & Biomolecular Engineering, National University of Singapore, Block E5, 02-11, 4 Engineering Drive 4, Singapore 117576, Singapore. Tel.: +65 6874 3835; fax: +65 6779 1936.
E-mail address: chefss@nus.edu.sg (S.-S. Feng).

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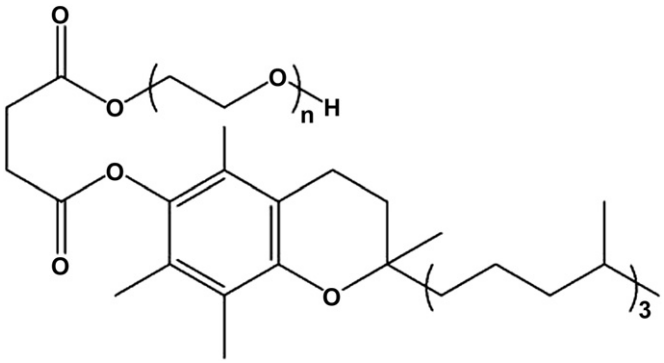
doi:10.1016/j.biomaterials.2012.03.046



Scheme 1. Chemical structure of TPGS.

increase the cell uptake efficiency on Caco-2, HT-29, MCF-7, C6 glioma cells and thus enhance cancer cell cytotoxicity. The TPGS-based nanoparticles have been further found in resulting in a more desired pharmacokinetics of entrapped drug *in vivo*, which could significantly extend the half-life of the formulated drug in the plasma. Feng's group has realized 168 h effective paclitaxel (PTX) chemotherapy by the TPGS-emulsified PLGA nanoparticles formulation in comparison with Taxol® of only 22 h effective chemotherapy at the same 10 mg/kg body weight of rats. Moreover, they have found that 400% higher drug tolerance can be achieved, which could result in 360% AUC as a quantitative measurement of the *in vivo* chemotherapeutical effects. It means that the animal immune system failed to recognize and thus eliminate the nanoparticles. They proved *in vivo* the feasibility of nanomedicine, which had been one of the two major concerns for the newly emerging area nanomedicine as future medicine. They then further confirmed such advantages of nanomedicine that the PLA-TPGS nanoparticle formulation of PTX and docetaxel (DOC) can realize 336 h and 360 h sustained effective chemotherapy respectively in comparison 23 h chemotherapy of Taxotere® at the same 10 mg/kg body weight for rats. Also, a more desirable biodistribution of the drug could be resulted with less drug in kidney, liver, heart and more in blood and lung. Oral delivery and drug delivery across the blood–brain barrier can also be achieved by further development of the nanoparticle technology with enhanced size and size distribution, surface functionalization, and copolymer synthesis [13–15].

In this review, we discuss in details the advantages of the various TPGS-based drug delivery systems such as prodrugs, micelles, liposomes, TPGS-emulsified PLGA nanoparticles and nanoparticles of TPGS copolymers such as PLA-TPGS, TPGS-COOH, PCL-TPGS, and so on.

2. TPGS as prodrug carrier

A prodrug is a pharmaceutical agent which is administered in an inactive form (say conjugated to a polymer) and then bioactivated (say released from the drug-polymer conjugate) into active metabolites *in vivo*. The rationale behind a prodrug is generally to enhance the pharmacokinetics of a drug, *i.e.* to optimize the process of absorption, distribution, metabolism, and excretion (ADME). Prodrugs are usually designed to improve oral bioavailability of the drug with poor absorption from the gastrointestinal tract [16,17]. Among the conjugations discussed, conjugations between biodegradable polymers such as polyethylene glycol (PEG), PLA-PEG, and poly(L-glutamic acid) (PGA) and anticancer drugs such as DOX, PTX, and camptothecin have been intensively investigated [18–24]. Among them, PEG-drug conjugation have been so widely used that resulted in a special term called PEGylation, which means conjugated to PEG [22–24]. Greenwald et al. discussed in details PEG-conjugation application in drug delivery of small molecule anticancer drugs such as PTX as well as biological drugs such as peptides and protein delivery [25,26].

2.1. TPGS-DOX conjugate

Doxorubicin (DOX), an anthracyclinic antibiotic, is a DNA interacting drug for treatment of various cancers especially breast, ovarian, prostate, brain, cervix and lung cancers. Clinical application of DOX was limited by its short half-life in the plasma and severe gastrointestinal and cardiovascular toxicity. The drug resistance also limits its intracellular level. To reduce side effect from DOX, evade drug resistance and enhance its therapeutic efficiency, DOX was conjugated to TPGS in Cao et al. studies (Scheme 2) [8]. In vitro drug release from the conjugate was studied to show pH dependent favor with no burst release. After 10 days, there were around 52.3%, 43.6% and 12.6% DOX released after incubating conjugate at pH 3.0, 5.0 and 7.4, respectively. DOX conjugate exhibited higher cellular uptake of 1.7-, 1.3-, 1.2-, 1.2- fold for the MCF-7 cells and 5.4-, 5.9-, 1.3-, 1.1-fold for the glioma C6 cells after 0.5, 1.5, 4, 6 h culture, respectively ($p < 0.05$), compared with the pristine DOX. The prodrug demonstrated 31.8, 69.6, 84.1% more effective with MCF-7 breast cancer cells and 43.9, 87.7, 42.2% more effective with C6 glioma cells than the parent drug after 24, 48, 72 h culture, respectively based on IC_{50} value. After *i.v.* administrated DOX pristine formulation or the prodrug at 5 mg/kg dose in rats, the $t_{1/2}$ and MRT were increased from 2.53 h and 2.86 h to 9.65 h, 10.9 h, respectively as seen in Fig. 1. The $AUC_{0-\infty}$ was also significantly increased from 288 ng-h/ml for DOX to 6812 ng-h/ml for the prodrug. Biodistribution also exhibited the lower side effects of the conjugate compared with the DOX. The AUC value from heart, gastric, and intestine was decreased from 307, 313, and 246 μg-h/g tissue for the DOX to 155, 114.3 and 86.7 μg-h/g tissue, respectively. It seems that the TPGS-DOX prodrug demonstrated higher therapeutic efficiency and lower side effects compared with the pristine drug.

Anbharasi V et al. further developed a TPGS-DOX-folic acid (FOL) conjugate (TPGS-DOX-FOL) for targeted chemotherapy and compared it with TPGS-DOX conjugate and pristine DOX [9]. Targeting conjugate TPGS-DOX-FOL can be 45.0-fold effective than DOX in cytotoxicity on MCF-7 cells judged by the IC_{50} results, while TPGS-DOX conjugate was only 1.19-fold effective than DOX. The half-life ($t_{1/2}$) of TPGS–DOX and TPGS–DOX–FOL were extended from 2.69 h (DOX) to 10.2 h and 10.5 h, respectively. The AUC values of TPGS-DOX and TPGS-DOX-FOL were 19.2 and 14.5 times than the DOX, respectively. Conjugates also significantly decreased the drug distribution in gastric, intestine, and especially in heart. Indeed, TPGS conjugate, especially TPGS-DOX-FOL can deduce the gastrointestinal side effect of the drug [9].

2.2. TPGS-paclitaxel conjugate

PTX is one of the best anticancer drug, which processes excellent therapeutic effects against various cancers such as breast and ovarian cancers. However, due to its extremely low solubility (<0.03 mg/L in water), its clinical administration formulation (Taxol®) has to use an adjuvant called Cremophor EL, which causes severe side effects including hyperaction, nephatoxocity, cardiotoxicity and neurotoxicity. In order to deal with this problem, various strategies were employed in seeking alternative formulation. Lee et al. presented a prodrug, formulated by conjugation of PTX with TPGS [27]. The conjugate was expected to improve the cellular uptake and further increase the cancer cell cytotoxicity. Unfortunately, no further in vitro or *in vivo* data were published yet.