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Review

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The applications of Vitamin E TPGS in drug delivery

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ABSTRACT

D-α-tocopheryl polyethylene glycol 1000 succinate (simply TPGS or Vitamin E TPGS) is formed by the esterification of Vitamin E succinate with polyethylene glycol 1000. As novel nonionic surfactant, it exhibits amphipathic properties and can form stable micelles in aqueous vehicles at concentration as low as 0.02wt%. It has been widely investigated for its emulsifying, dispersing, gelling, and solubilizing effects on poorly water-soluble drugs. It can also act as a P-glycoprotein (P-gp) inhibitor and has been served as an excipient for overcoming multidrug resistance (MDR) and for increasing the oral bioavailability of many anticancer drugs. Since TPGS has been approved by FDA as a safe pharmaceutic adjuvant, many TPGS-based drug delivery systems (DDS) have been developed. In this review, we discuss TPGS properties as a P-gp inhibitor, solubilizer/absorption and permeation enhancer in drug delivery and TPGS-related formulations such as nanocrystals, nanosuspensions, tablets/solid dispersions, adjuvant in vaccine systems, nutrition supplement, plasticizer of film, anticancer reagent and so on. This review will greatly impact and bring out new insights in the use of TPGS in DDS.

Keywords

Vitamin E TPGS; P-glycoprotein; Oral bioavailability; Drug delivery systems; Multidrug resistance

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1. Introduction

D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS or Vitamin E TPGS, Fig. 1) is a water-soluble derivative of natural Vitamin E, which is formed by esterification of Vitamin E succinate with polyethylene glycol (PEG) 1000. It has an average molecular weight of 1,513, an amphiphilic structure of lipophilic alkyl tail and hydrophilic polar head with a hydrophilic/lipophilic balance value of 13.2 and a relatively low critical micelle concentration (CMC) of 0.02% w/w. It is a waxy solid (m.p. ~ 37-41^{o}C) and completely dissolves in water (Wu and Hopkins, 1999).

As one of the novel nonionic surfactants, TPGS has been widely used in wetting, emulsification, solubilization, spreading, and detergency (Sadoqi et al, 2009). TPGS displayed significant surface activity and notable effect on the lipid model membrane (Shah and Banerjee, 2011). It can solubilize a variety of both water-soluble and water-insoluble compounds. As the water content increases, TPGS forms lamellar reverse micellar phase, hexagonal phase, and normal micellar phase. TPGS is also miscible with oils, such as soybean oil and medium chain triglyceride, other surfactants, and cosolvents such as propylene and polyethylene glycols. It is stable at pH 4.5-7.5 and less than 10% hydrolysed when kept for 3 months in neutral aqueous buffer. However, it degrades in alkaline environment (Eastman, 2000; Wu and Hopkins, 1999). The stability is still high even at lower pH, 3.4% of TPGS degraded within 8h at pH 1.0 and 37 ^{o}C. The stability of the ester bond between D-α-tocopherol and succinic acid has also been demonstrated (Christiansen et al., 2011b).

The TPGS safety has been reported and the oral LD50 is >7 g/kg for young adult rats of both sexes (Beilman et al., 1988a; Beilman et al., 1988b; Krasavage and Terhaar, 1977; Shepard, 1989; Topping, 1987). In recent years, TPGS has been applied in drug delivery systems (DDSs) since it is an FDA approved pharmaceutically safe adjuvant. On Jan 27 2005, FDA approved Tocosol emulsion formulation of paclitaxel (Sonus Pharmaceuticals, Inc.) for use in the treatment of nonsuperficial urothelial cancer. In the formulation, TPGS is used to create small high-drug loading nanoparticles.

TPGS has been used as an absorption enhancer, emulsifier, solubilizer, additive and permeation enhancer, stabilizer, nutrition supplement, etc (Dintaman and Silverman, 1999; Yu et al., 1999). It can increase the solubility of drugs such as cyclosporines, taxanes, steroids, antibiotics, etc (Constantinides et al., 2002; Fischer et al., 2002; Illum et al., 1997; Liu et al., 2000; Nielsen et al., 2001). TPGS has served as the excipient for overcoming multidrug resistance (MDR) and an inhibitor of P-glycoprotein (P-gp) for increasing the oral bioavailability of anticancer drugs (Collnot et al., 2010; Constantinides et al., 2006; Dintaman and Silverman, 1999; Varma and Panchagnula, 2005). It can increase the cytotoxicity of doxorubicin, vinblastine, paclitaxel and colchicine in the G185 cells by inhibiting P-gp activity (Dintaman and Silverman, 1999). It has exhibited oral absorption enhancement in cyclosporine A, vancomycin hydrochloride and talinolol in animals (Bogman et al., 2005; Boudreaux et al., 1993; Prasad et al., 2003; Sokol et al., 1991). TPGS can also act as an anticancer agent to induce apoptosis and develop a synergistic effect with other anticancer drugs (Mi et al., 2011).

In our previous review (Zhang et al, 2012), we discussed TPGS as a molecular biomaterial for nanomedicine, including TPGS-based prodrug, micelles and liposomes, as a surfactant or additive in fabricating nanoparticles and TPGS-related polymeric nanoparticles for drug delivery. In this

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review, we discuss the original applications of TPGS in DDS and its properties as a P-gp inhibitor (including inhibition mechanisms), solubilizer/absorption enhancer and permeation enhancer. The TPGS formulations are focused on nanocrystals, nanosuspensions, tablets/solid dispersions, adjuvant in vaccine systems, nutrition supplement, plasticizer of film, anticancer reagent and so on. It will have great indication in the use of TPGS in DDS and give an overview of the applications of TPGS in DDS.

2. TPGS properties in drug delivery

The special amphiphilic structure of TPGS, especially the D-α-tocopheryl succinate part, gives it many interesting properties. As a result, TPGS was widely used in DDS (Dintaman and Silverman, 1999; Eastman, 2000; Fischer et al., 2002; Yu et al., 1999).

2.1 P-gp inhibitor and inhibition mechanism

P-gp is an ATP-dependent drug efflux pump, also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1). It is extensively distributed and expressed in the intestinal epithelium, hepatocytes, renal proximal tubular cells, adrenal gland and capillary endothelial cells comprising the blood-brain and blood-testis barrier. It transports a wide variety of substrates across extracellular and intracellular membranes. It can decrease drug accumulation in cells and mediate MDR to cancer cells. Many anticancer drugs such as paclitaxel, etoposide, doxorubicin, vinblastine, etc. are P-gp-substrates. P-gp can affect the drug distribution and bioavailability, limit the drug passage across the blood brain barrier and remove toxic metabolites and xenobiotics from cells into urine, bile and the intestinal lumen (Hoffmeyer and Brinkmann, 2001). Dintaman and Silverman were the first people to investigate the relationship between TPGS and P-gp in 1999. They found out that below its CMC of 0.02 wt%, TPGS could act as an inhibitor of P-gp. This resulted in inhibition of P-gp mediated drug transport and multidrug resistance (Akhtar et al., 2011; Collnot et al., 2006; Lo, 2003). Besides TPGS, other nonionic surfactants such as Tween 80, Pluronic®, Cremophor EL, are also capable of inhibiting P-gp activity. Among them, TPGS was most effective. Rhodamine 123, P-gp-mediated transporter, was inhibited in a concentration-dependent manner for the following surfactants in the order; TPGS > Pluronic PE8100 > Cremophor EL > Pluronic PE6100. These surfactants exhibited a transporter-specific interaction, rather than non-specific membrane permeabilization (Bogman et al., 2003; Hugger et al., 2002; Johnson et al., 2002).

TPGS was found to inhibit the P-gp mediated talinolol transport by Caco-2 model study. In healthy volunteers, TPGS increased AUC (area under concentration) and C_{max} of talinolol by 39% and 100%, respectively after coadministration. This may be attributed to TPGS inhibition of the P-gp activity and resultant increase of talinolol bioavailability (Bogman et al., 2005). TPGS was found to enhance the cytotoxicity of doxorubicin, vinblastine, paclitaxel and colchicine in the human MDR1 cDNA (G185) cells which were 27-135 fold more resistant to these drugs than the parental NIH3T3 cells. However, TPGS did not increase the cytotoxicity of 5-FU (not a P-gp substrate) in the G185 cells (Dintaman and Silverman, 1999; Traber et al., 1986).

The transporter inhibition activity of three nonionic surfactants (TPGS, Tween 80 and Cremophor EL) was investigated on P-gp, the human intestinal peptide transporter, and the monocarboxylic acid transporter in Caco-2 cell monolayers. The role of membrane fluidity and protein kinase C in

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surfactant-induced transporter inhibition was also evaluated. Tween 80 and Cremophor EL were found to significantly increase the apical-to-basolateral (AP-BL) and decrease the basolateral-to-apical (BL-AP) permeability. TPGS exhibited a reduction in the BL-AP permeability of rhodamine 123 in Caco-2 monolayers. Compared to these two surfactants, TPGS rigidized lipid bilayers of cell membrane, and did not inhibit the peptide transporter. Tween 80 inhibited the peptide transporter and only Cremophor EL inhibited the monocarboxylic acid transporter. It seems that TPGS can inhibit the P-gp activity without affecting the membrane fluidity (Rege et al., 2002; Yamagata et al., 2007). P-gp ATPase (P-gp energy source of active transport) inhibition caused by TPGS is the main reason for this (Collnot et al., 2007). Monoclonal CD243 P-gp antibody (UIC2) shift assay results demonstrated that TPGS was neither a substrate nor a competitive inhibitor in P-gp efflux transport. The P-gp ATPase inhibition was due to the allosteric modulation that TPGS binds to the nontransport active binding site and not the Cis(Z)-flupentixol binding site (Collnot et al., 2010; Collnot et al., 2007). The commercially available TPGS1000 is so far the most potential efflux pump inhibitor as studied by Lehr et al. As shown in Fig. 2 and Fig. 3, Collnot et al demonstrated that the PEG length (200-6000) of Vitamin E succinate derivatives can affect the inhibition activity on the efflux pump and the promising TPGS derivatives could be TPGS with PEG 1100-1500 (Collnot et al., 2006).

TPGS also showed inhibitory effects on cytochrome P450 3A (CYP3A) (Christiansen et al., 2011a; Johnson et al., 2002). It can act as in vitro inhibitor for CYP-mediated metabolism and has the potential for modifying the pharmacokinetics when coadministered with CYP substrates (Christiansen et al., 2011a). However, another study exhibited that TPGS has hardly any direct inhibitory effect on CYP3A but has a significant inhibitory effect on P-gp in rat intestinal mucosa (Mudra and Borchardt, 2010). In vitro cell experiments demonstrated that Cremophor® EL, TPGS and high concentrations of polysorbate 80 could inhibit the efflux transporters, ABCB1 (P-gp) and ABCC2 (MRP2). These two transporters play an essential role in the limitation of oral bioavailability of drugs (Hanke et al., 2010). Thus the oral bioavailability of CYP substrates could be improved by including TPGS in the formulation. However another study showed no significant inhibition of MRP2-mediated efflux in Madin-Darby canine kidney/MRP2 cells from the surfactants (Bogman et al., 2003).

2.2 Solubilizer/Absorption enhancer

Solubilizers/absorption enhancers are functional excipients included in formulations to increase the solubility of a substance or improve the absorption of a pharmacologically active drug. To solubilize water-insoluble drugs for oral and parenteral administration, there are many techniques such as pH adjustment, cosolvents, complexation, microemulsions, self-emulsifying DDSs, micelles, liposomes, and emulsions (Kuentz, 2011; Strickley, 2004). TPGS was found to increase the apparent solubility and stability for some unstable drugs by incorporation into TPGS micelles (di Cagno et al. 2012). TPGS significantly enhanced the aqueous solubility of paclitaxel in a linear relationship when TPGS concentration was higher than 0.1 mg/mL as seen in Fig. 4. The oral bioavailability of paclitaxel was enhanced 4.2-fold and 6.3-fold for [C-14]paclitaxel coadministrated with verapamil (25mg/kg, 19.9% oral bioavailability) and TPGS (50mg/kg, 29.9% oral bioavailability), respectively, compared to Taxol® (4.7% oral bioavailability) as seen in Fig. 5 (Varma and Panchagnula, 2005). TPGS was also used as solubilizer for celecoxib, corticosteroids, capuramycin analogue SQ641 and propofol (Cianetti et al., 2010; Fulzele et al.,

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2006; Momot et al., 2003; Nikonenko et al., 2009; Saidi and Boris, 2001; Varma and Panchagnula, 2005).

TPGS has been shown to increase the absorption flux of a HIV protease inhibitor, amprenavir (Yu et al., 1999), enhance the bioavailability of cyclosporine in human volunteers (Chang et al., 2005) and of colchicine in rats. Colchicine formulation containing TPGS significantly increased the systemic exposures, 2-fold increase of AUC, as compared to the aqueous reference vehicle (Bittner et al., 2002). After oral coadministration with cyclosporine, TPGS (50 mg/kg) increased the C_{max} and $AUC_{0-\infty}$ from 1.3 to 2.9 μg/mL and from 28.5 to 59.7 μg·h/mL, respectively, compared to cyclosporine saline solution. The half-life and MRT were increased by 44% and 24%, respectively (Wacher et al., 2002b). Bordeautx et al (Boudreaux et al., 1993) reported a 2-fold AUC increase when cyclosporine A was co-administered with Liqui E, a glycerol and TPGS. Sokol and Chang et al (Sokol et al., 1991; Chang et al., 1996) also reported a 71% and 61% AUC increase on CsA, respectively. Pan et al (Pan et al., 1996) reported a 32% decrease in CsA daily dosage after coadministration with TPGS and 26% decrease on the CsA cost. This may be attributed to the fact that TPGS can form micelles with improved solubilization of CsA and also interact with P-gp in the intestines. Tocopheryl polypropylene glycol succinate 1000 (TPPG1000), whose structure is similar to TPGS, was also found to enhance the oral bioavailability of raloxifene (Wempe et al., 2009). TPGS enhanced intestinal absorption of hydrophilic macromolecular drug, vancomycin with Labrasolin rats. The C_{max} and AUC_{0-6h} of vancomycin were increased 2.2 and 2.4 times, respectively after the addition of 12.5% of TPGS and 50% Labrasol during formulation (Prasad et al., 2003). It has also been found to significantly enhance the intestinal absorption of Berberine chloride (BBR). At a concentration of 2.5%, TPGS achieved around 2.9 and 1.9-fold improvement on C_{max} and AUC_{0-36} of BBR, respectively after oral administration (Chen et al., 2011).

Although there is a lot of data demonstrating TPGS effects on oral absorption, solubility or permeation enhancement, some studies show contrary results. It has no significant effects on both enterocyte-based metabolism and P-gp efflux of verapamil in excised rat intestine experiment at a concentration of 0.01wt% (Johnson et al., 2002). The inclusion of the TPGS did not result in absorption enhancement of antiviral agent UC-781 in the intestinal perfusion technique (Deferme et al., 2002). It was found to increase the solubility of estradiol through micellar solubilization but it only had an insignificant influence on the skin (Sheu et al., 2003). It did not improve oral bioavailability of R1481 which is a potential agonist for the treatment of overactive bladder and has poor oral bioavailability. R1481 can be metabolically stable due to low intestinal permeability, and P-gp efflux mechanism (Ramsay-Olocco et al., 2004). TPGS can modify the pharmacokinetics of orally administered P-gp substrates without increasing the AUC (Cornaire et al., 2004). It has no effect on oral absorption of sirolimus in rats and no significant effect on P-gp substrates digoxin and celiprolol *in vitro* and *in vivo* (Wacher et al., 2002a). PEG400 accelerated the small intestinal transit but TPGS did not do so when used as a solubility-enhancer in hard gelatin capsules (Schulze et al., 2006). It has no significant effect on the gastrointestinal transit and drug absorption in beagle dogs as the combination of two model drugs, ampicillin (200 mg) and antipyrine (100 mg) with various excipients, PEG 400, propylene glycol, TPGS and Labrasol in capsules (Schulze et al., 2005).

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2.3 Permeation enhancer

Permeation enhancers can be incorporated into formulations to promote their permeation through the skin or intestinal walls. TPGS as an excipient in the formulation of amprenavir, a poorly water-soluble substrate of P-gp, was found to enhance the intraluminal drug concentration and affect the permeability in a concentration-dependent way (Brouwers et al., 2006). TPGS was also found to be a profound enhancer for the penetration flux of minoxidil and its retention in the skin from topical minoxidil formulations of water/alcohol/polyethylene glycol 400 at concentrations higher than 5% (Sheu et al., 2006). The penetration enhancement of estradiol by TPGS was not as significant as ethanol/TPGS cosolvent system (Liou et al., 2009). A microemulsion formulation of temozolomide acid hexyl ester (TMZA-HE) was constructed with oil phase and TPGS as a surfactant. The formulation demonstrated increased solubility and significantly increased permeation. It may be used as a potential formulation for transdermal delivery of TMZA-HE (Suppasansatorn et al., 2007).

TPGS was found to significantly increase the apparent permeability of P-gp substrate, colchicine, without a change in the colonic tissue integrity. TPGS has the potential to enhance drug permeability in colonic tissue (Bittner et al., 2008). It also acted as skin permeation enhancer of diclofenac sodium and temozolomide hexyl ester prodrug by microemulsion systems (Mohammed, 2001; Suppasansatorn et al., 2005). Compared to other systems, for example, Pluronic F-127 and co-solvent, TPGS formulation produced the highest drug permeation rate and the longest crystallization time (Ghosh et al., 2012). TPGS may also alter intestinal permeability, at least *in vitro*, via inhibition of drug transporter function (Yu et al., 1999). However, the permeation enhancement due to P-gp interaction may be depressed by the micelle-association during the inclusion of poorly soluble drugs in micelles. Poorly soluble drugs have a high tendency to nucleate immediately after formulation or even during storage because of thermodynamic challenges. The use of surfactant is indeed effective in reducing drug loss and improving mass balance and also brings about changes in thermodynamic activity (Katneni et al, 2008). This effect was owed to the reduced thermodynamic activity of the drug which is due to micellar association or complexation, and/or the fact that the micelle-bound fraction of drug is not readily permeable. This leads to changes in the free concentration of drug available for transport or diffusion across the membrane (Katneni et al, 2006). The micellar fraction and permeability depression of drug correlated with the surfactant concentration (Fischer et al, 2011a). Other studies have confirmed these results. In the presence of poloxamer 188, the drug permeability was also found to be depressed in a concentration-dependent manner. However, micellar association was one important but not the only factor affecting drug permeability, especially in the case of hydrophilic compounds (Fischer et al, 2011b). Inclusion of poorly soluble drugs in micelles may reduce the drug´s thermodynamic activity and subsequently impair its passive diffusion, which results in a delicate balance between permeation inhibition due to micelle-association and permeation enhancement due to P-gp interaction (Buckley et al., 2011). In paclitaxel formulation with TPGS, paclitaxel exhibited a 26-fold higher BL-AP permeability than AP-BL direction for transport across rat ileum. TPGS exhibited a concentration-dependent increase in AP-BL permeability and decreased BL-AP permeability. At a concentration of 0.1 mg/mL, TPGS demonstrated the maximum efflux inhibition activity. The maximum paclitaxel permeability at 0.1 mg/mL TPGS may be attributed to the interplay of concentration dependent P-gp inhibition and the micellar formation (Varma and Panchagnula, 2005). The similar maximum surfactant concentration for

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poor soluble drugs was also demonstrated in the formulation with polysorbate 80 (Katneni et al, 2006).

3. TPGS formulations

3.1 Fabricating nanocrystals/nanosuspensions

Drug nanocrystals and submicron-sized drug crystals, have recently become a mature drug delivery strategy for oral delivery. The nano-sizes of the particles can increase the drug dissolution rate and improve oral absorption. Surfactants are usually used as stabilizers in this system. TPGS-paclitaxel nanocrystals were fabricated by Liu et al (Liu et al., 2010). TPGS and the drug were dissolved in chloroform and evaporated under nitrogen atmosphere. The film formed was hydrated and sonicated for 10-15 min using a bath sonicator to form nanocrystals. The nanocrystals exhibited moderate uniform particle sizes with the rod width being 40 nm and length around 150 nm and could realize controlled release phenomena for the payload. In P-gp overexpressing cells, NCI/ADR-RES, the TPGS nanocrystals exhibited significant antiproliferation effect compared with other formulations. In xenograft experiment after inoculating NCI/ADR-RES cells in nude mice, only 10 mg/kg of TPGS/drug nanocrystals exhibited obvious tumor regression, as seen in Fig. 6. From the report, TPGS may act as surfactant, stabilizer of the nanocrystals and drug resistance inhibitor to reverse MDR (Liu et al., 2010).

TPGS acted as surfactant/stabiliser and showed the best results on stability of nanosuspension among 13 different stabilizers from screening study where TPGS concentrations were tested at 25 or 100 wt% of the drug weight (Van Eerdenbrugh et al., 2009b). However, another investigation showed that 10 wt% was good enough to form nanosuspension of itraconazole (Van Eerdenbrugh et al., 2008b). TPGS-stabilized nanosuspensions (25 wt%, relative to the drug weight) were produced by media milling for 9 model drug compounds, cinnarizine, griseofulvin, indomethacin, itraconazole, loviride, mebendazole, naproxen, phenylbutazone and phenytoin (Ghosh et al., 2011; Van Eerdenbrugh et al., 2008a). Curcumin-loaded nanosuspension with TPGS as stabilizer was found to achieve a 3.8-fold and 11.2-fold increase of AUC and MRT respectively, as compared to curcumin solution after intravenous administration (Gao et al., 2010). Rilpivirine nanosuspension was fabricated by using TPGS as a surfactant for long-acting parenteral formulations for prophylactic treatment in HIV. The nanosuspensions were prepared by wet milling (Elan NanoCrystal® technology) in an aqueous carrier with size 200, 400 and 800 nm, respectively. The suspension demonstrated over 6 month stability and homogeneity. 200-nm sized nanosuspensions may act as long-acting injectable formulation (Baert et al., 2009). TPGS was also used as emulsifier for coenzymeQ(10) (CoQ(10)) olive oil emulsion. The plasma concentration and $AUC_{0\text{-}24h}$ of TPGS emulsion were increased up to 7 and 3.7-fold compared with the olive-oil mixed formulation of CoQ10 (Nishimura et al., 2009). Paclitaxel nanoemulsion was fabricated with TPGS in labrasol and exhibited enhanced oral bioavailability, up to 70.2% compared to 10.6% for oral Taxol® (Ke et al., 2005; Khandavilli and Panchagnula, 2007). Iodine-loaded oil-in-water emulsion with 30% lipiodol and 282 mg/mL (9:1 Tween 80: TPGS) was formulated as an interstitial computed tomographic lymphographic agent in a normal rat model. The emulsion exhibited prolonged duration, up to 534.0±481.1 min compared with the duration for iopamidol, 8.2 ±12.3 min (Chung et al., 2010).

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3.2 Fabricating SMEDDS system

TPGS was used as surfactant in fabricating a self-microemulsifying DDS (SMEDDS) to increase the solubility, dissolution rate and oral bioavailability for tacrolimus, anti HIV drug UC781 and penclomedine (De Smidt et al., 2004; Goddeeris and Van den Mooter, 2008). The tacrolimus-loaded particle size was less than 20 nm with the composition of Miglyol 840: TPGS: Transcutol P as 1:7.2:1.8. The formulation exhibited a significant improvement in release characteristics of tacrolimus and achieved 7-fold increase in oral bioavailability compared with homemade solution (Goddeeris et al., 2010; Wang et al., 2011). Wei et al (Wei et al., 2010) prepared SMEDDS composed of medium-chain triglyceride oil and surfactant mixtures of TPGS and Tweens at different ratios. Compared with other surfactant in the composition of SEDDS, TPGS can achieve higher inhibition effect on pancreatic lipase than polysorbate 80, Cremophor EL and sucrose laurate but lower than Cremophor RH40 (Christiansen et al., 2010).

3.3 TPGS in solid dispersion/tablet

TPGS was added in solid dispersions to increase the drug solubility, dissolution rate and also enhance the drug oral bioavailability (Ahn et al., 2011; Moneghini et al., 2010; Schamp et al., 2006). TPGS combined with solutol HS-15 in solid dispersion was found to enhance the solubility and dissolution of nifedipine. It may be attributed to the fact that the micellar formulation can increase the solubility of drug, enhance the separation of drug particle and interaction between polymer and drug, and improve wettability and partial crystalline drug transferred to the amorphous form (Rajebahadur et al., 2006). TPGS-based-capsule was found to increase the oral bioavailability by more than 100%. The AUC was increased 10-fold and dissolution at 30 min was 98% compared to 47% for drug-in-capsule (Vandecruys et al., 2007). Carbamazepine (CBZ) as solid dispersions in polyvinylpyrrolidone (PVP) K30 (Sethia and Squillante, 2004b) or polyethylene glycol (PEG) (Barakat et al., 2009) with either Hf:Gelucire 44/14 or TPGS were prepared by conventional solvent evaporation and supercritical fluid (SCF) processing methods. TPGS was found to increase the dissolution rate up to 10.6-fold compared to neat CBZ. TPGS with 0.1% concentration increased the CBZ permeability and cell cytotoxicity. Solid dispersion with PEG8000 and TPGS increased the AUC up to 2-3-fold compared to neat CBZ after oral administration of 20 mg/kg dosage (Sethia and Squillante, 2004a). TPGS was also added as stabilizer in fabricating itraconazole solid dispersions by co-spray-drying with Aerosil® 200. The oral bioavailability of the drug was significantly enhanced compared to the crystalline drug with around 10-fold AUC increase (Sethia and Squillante, 2002; Van Eerdenbrugh et al., 2009a). Solid dispersions composed of Eudragit E100 and TPGS were found to enhance the dissolution of anti-HIV drug UC 781 (Goddeeris et al., 2008a). Solid dispersions of Hf with TPGS (1:6) and Hf: Gelucire 44/14: TPGS (1:3:3 wt%) increased the oral bioavailability of Hf up to 5 and 7-fold, respectively compared to commercially available tablet (containing 250 mg Hf•HCl, 8.6%) in fasted beagles (Khoo et al., 2000). The aqueous solubility and the dissolution rate of furosemide were rapidly and markedly enhanced from the 1:2 furosemide-TPGS solid dispersion. The solid dispersion changed the crystalline nature and the association of furosemide and TPGS which might occur in the molecular level (Shin and Kim, 2003).

Jin et al (Crowley et al., 2002; Jin and Tatavarti, 2010) investigated the feasibility of forming

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tablets with TPGS by conventional high shear wet granulation. TPGS has a waxy nature and low melting point, around 37 ^{o}C. This may limit its application in solid dosage formulations. Some critical characters such as TPGS levels, binder and extragranular filler were considered during product design. The feasibility of developing monolithic and bilayer coated tablets with up to 10% TPGS was confirmed after optimization studies (Jin and Tatavarti, 2010). TPGS was found to increase the solubility and dissolution effect of carbamazepine (CBZ) tablets in a concentration-dependent manner (Charkoftaki et al., 2011). TPGS levels in tablets can significantly affect the tensile strength, disintegration time and dissolution of the formulation. The fast disintegrating tablets of ternary solid dispersions composed of TPGS and HPMC 2910 or PVPVA 64 have been formulated to improve the dissolution of the anti-HIV drug UC 781 and itraconazole (Goddeeris et al., 2008b; Janssens et al., 2008). TPGS is also used as an additive to improve wettability and dissolution rate of cilostazol and etodolac in capsules (Barakat, 2006; Kim et al., 2010).

3.4 Adjuvant for vaccine system

TPGS was used as an adjuvant for vaccines. It was admixed with antigens at 5wt% and found to significantly increase the levels of the immunoglobulin responses after intranasal administration. The IgG and IgA were increased 5-fold and 100-fold, respectively compared with vaccine formulations without TPGS (Ravichandran et al., 2007). TPGS blended with poly(caprolactone) for nasal immunisation of diphtheria toxoid exhibited enhanced immune response compared with the formulation without TPGS (Somavarapul et al., 2005). The antigen uptake and antibody response was increased by the addition of absorption enhancers to Vibrio anguillarum 02 antigen after oral vaccination (Vervarcke et al., 2004).

3.5 Nutrition supplement

TPGS can act as the alternative formulation of fat-soluble vitamin E (Westergren and Kalikstad, 2011). Water soluble vitamin E formulation Aquanova® (TPGS 100IU and 400mg crystalline vitamin C) was found to increase the oral bioavailability as compared to regular fat-soluble vitamin E formulation (Back et al., 2006). Aqua-E containing TPGS significantly increased the absorption of γ-tocopherol in malabsorbing patients with cystic fibrosis compared with an oil-based formulation (Papas et al., 2007). Oral tocofersolan (TPGS formulation) was more bioavailable than water-miscible Vitamin E formulation in children with chronic cholestasis. Tocofersolan may be an alternative of vitamin E administration to avoid painful intramuscularly injected Vitamin E formulation in chronic cholestasis (Jacquemin et al., 2009). TPGS was also applied as a supplement for traditional post-surgical treatment in cardiac transplant recipients. It was found to prolong the graft survival, decrease rejection and improve the graft fractional shortening. It also prevents the distention in systolic and diastolic lengths in untreated allografts, inhibits nitrosylation in heme protein, decreases the expression of inducible nitric oxide protein by 50%, and inhibits mitogen-stimulated proliferation by both rat and human lymphocytes. These activities are significant and can be exploited in its combination with cyclosporine A therapy. This demonstrates that TPGS has a significant effect in limiting lymphocyte proliferation and activation, extending graft survival and limiting graft rejection and dysfunction (Nguyen et al., 2006). TPGS was used as a vehicle for oral administration of vitamin E and D to prevent or correct deficiency

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states in chronic cholestasis (Argao et al., 1992; Plauth et al., 1997; Socha et al., 1997; Sokol et al., 1993). It is an alternative in correcting vitamin E deficiency in children with chronic cholestasis who are unresponsive to other forms of oral vitamin E. All children exhibited similar response to TPGS with normalization of vitamin E status. Neurological function was improved in 25 patients, stabilized in 27 patients, and worsened in only 2 patients after an average treatment period of 2.5 years. No adverse effects have been reported and thus the dosage of TPGS (20-25 IU/kg/day) appears to be a safe and effective form of vitamin E for reversing or preventing vitamin E deficiency during chronic childhood cholestasis (Sokol et al., 1993). TPGS enhanced vitamin D absorption by micellar structure in eight children (aged 5 months to 19 years) with severe chronic cholestasis. All patients exhibited enhanced absorption of vitamin D3 when coadministrated with 25 mg/kg TPGS. The mean area under the curve for serum vitamin D3 was increased to 403.0±83.1 nmol·h/L compared to 155.6±32.1 ng·h/mL for normal vitamin D3 formulation (Argao et al., 1992). Oral coadministration of TPGS and retinyl palmitate with vitamin A was found to be a good supplement for chronic cholestatic liver disease (Feranchak et al., 2005).

3.6 Anticancer reagent

TPGS was found to possess similar anticancer activity to α-tocopheryl succinate (TOS). It can inhibit the growth of human lung carcinoma cells *in vitro* (Fig. 7) and in nude mice (Fig. 8). TPGS was more effective at inducing apoptosis and the generation of reactive oxygen species compared with TOS (Youk et al., 2005). Recent studies also reported a significant synergistic effect between TPGS2000 and docetaxel as shown from cell cytotoxicity assay in table 1. Up to now, there is no confirmatory data to support its anticancer property (Mi et al., 2011).

3.7 TPGS micelles and liposomes

TPGS can formulate micelles for drug or imaging agent delivery with a CMC of 0.02 wt%. TPGS micelles were also used to encapsulate other functional materials like multi-wall or single-wall carbon nanotubes (Xu et al., 2010), as well as C60 fullerenes or iron oxide (Yan et al., 2007). However, the CMC of TPGS is relatively high as mentioned above and TPGS micelles may dissociate in blood. Therefore, TPGS is usually mixed with other materials such as PEG-PE, PEG-DSPE, oleic acid, Pluronic P105, Pluronic P123, PLGA-PEG-FOL and Pluronic F127/poly(butylcyanoacrylate) to form mixed micelles to increase the micelle stability and drug solubilization (Zhang et al., 2012). The addition of TPGS as a surfactant and stabilizer to liposomes or lipid based formulations may bring some advantages to these systems, such as improved cytotoxicity and overcoming MDR (Zhang et al., 2012). TPGS micelles can not only increase the solubility of payload, may also act as antioxidant to increase the stability of entrapped compounds which are prone to oxidation in physiological fluids. On the contrary, the ordinarily used solubilizer of cyclodextrin can not protect the unstable drug from degradation. This may be attributed to the antioxidant property of TPGS micelles (di Cagno et al. 2012).

3.8 TPGS emulsified nanoparticles

TPGS can be used as an emulsifier or an ideal coating molecule in fabricating drug-loaded nanoparticles which can achieve higher drug encapsulation efficiency (up to 100%) and cellular uptake of the nanoparticles, and thus higher therapeutic effects compared with polyvinyl alcohol

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(PVA) emulsified nanoparticles (Feng, 2006). Feng's group showed many impressive results (Zhang et al., 2012). TPGS emulsified nanoparticles displayed a slower release pattern than that of PVA. The content of TPGS as surfactant can be as low as 0.02-0.03wt% and has 67 times higher emulsification effects than PVA. TPGS has been applied as a surfactant in the emulsification of PLGA, PCL, PLA-TPGS, PLGA-PEG and MPEG-SS-PLA NP. The resulted nanoparticles exhibited higher cell cytotoxicity in vitro and lower maximum tolerated drug levels, longer half life, high oral bioavailability and improved therapeutic effects compared with Taxol® *in vivo*.

3.9TPGS based prodrug

Polymer-drug conjugation is one of major strategies to increase drug solubility, permeability and stability and/or circulation time. Three kinds of prodrug based on TPGS have been reported by Feng's group (Zhang et al., 2012). They synthesized TPGS-PTX prodrug, but the *in vitro* experimental results were not presented. The second is TPGS-DOX prodrug, which showed pH dependent release, much higher cellular uptake, higher cell cytotoxicity and lower side effects compared with pristine DOX. The TPGS-cisplatin prodrug also enhanced the chemotherapeutic efficacy of cisplatin against HepG2 cells (Mi et al., 2012).

3.10 TPGS based copolymer

TPGS based copolymers can be easily synthesized by ring opening polymerization. TPGS-PLA, TPGS-PLGA, TPGS–PCL, TPGS-PGA-PCL and TPGS-PLA-PCL were all applied in DDS (Zhang et al., 2012). Among them, TPGA-PLA was mostly reported. Many drugs or functional elements like docetaxel, paclitaxel, doxorubicin, curcumin, supraparamagnetic iron oxide and quantum dots can be encapsulated in TPGS-PLA nanoparticles with high encapsulation efficiency, improved cellular uptake and cell cytotoxicity and long-circulation property (Zhang et al., 2012).

3.11 Other applications

TPGS can act as a plasticizer in film preparation, such as HPC film (Repka and McGinity, 2000) and PLLA films (Repka and McGinity, 2001). It was found to decrease the glass transition temperature and the force of adhesion of the films, as well as the flexibility and elongation at breaking point during tensile testing. TPGS could also promote the drug release rate from paclitaxel-loaded PLLA films, which may be caused by TPGS hydrophilicity and large surface area to volume ratio from PLLA/TPGS films compared with PLLA film (Dong et al., 2008). The special structure of PLLA/TPGS film may make it useful as implant for localized drug delivery or scaffold in tissue engineering.

TPGS was found to enhance the biocompatibility of polysulfone (Psf) hollow fiber membranes (HFMs) for acute and chronic hemodialysis in blood purification. They were prepared by dry wet spinning using 5-20 wt% TPGS as an additive in dope solution and TPGS was successfully entrapped in Psf hollow fiber as confirmed by ATR-FTIR and TGA (Dahe et al., 2011b). TPGS modified Psf HFMs exhibited the most favorable tissue response compared with other HFMs (Dahe et al., 2011a). TPGS can be enzymatically cleaved to deliver the lipophilic antioxidant, vitamin E, to cell membranes. It has been demonstrated to act as antioxidant to partially decrease the cyclosporine A (CsA) mediated reactive oxygen species formation, completely decrease thiobarbituric acid reactive substances formation, prevent the loss of protein-bound sulphydryl

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groups and completely inhibit the CsA cytotoxicity (Wolf et al., 1997). It significantly inhibited SDZ IMM125-mediated cellular Ca^{2+} uptake, a redox-sensitive process in cell culture (Grub et al., 2002). Similar antioxidant activity was also exhibited in the liquid crystalline formulation of quercetin with TPGS (Anstee et al., 2010; Shah and Banerjee, 2011; Vicentini et al., 2007; Yan et al., 2007). Minoxidil solutions supplemented with TPGS in cosolvent systems consisting of water, alcohol, and polyethylene glycol 400 were designed to evaluate the efficacy of promoting hair growth after topical application and the safety in C57BL/6J mice. TPGS was found to increase the proliferation of hair by 0.5% but this effect deteriorated at TPGS concentration above 2% (Chen et al., 2005).

4. Conclusion and Perspective

We have discussed the properties of TPGS as solubilizer, oral absorption/bioavailability enhancer, micellar property as a surfactant, additive or emulsifier, stabilizer in fabricating drug formulations, permeation enhancer and even its anticancer or antioxidant effect. It seems that all the applications of TPGS in drug delivery are based on its amphiphilic structure. The lipophilic structure of vitamin E succinate makes it usable as vitamin E supplement, antioxidant, and anticancer agent. The hydrophilic head of PEG 1000 showed the most P-gp inhibition effects and provided the micellar property for this molecular biomaterial. Until now the most perspective property applied in drug delivery is based on its P-gp inhibition and great surfactant effect on formulations. In further studies, there may be more modifications and related polymers for DDS. The recent TPGS-based copolymer application in drug delivery has exhibited long-circulation and improved oral bioavailability in fabricated nanoparticles. The TPGS-related copolymer, PLA-TPGS, was found to overcome MDR in MCF-7/ADR cells but further investigations may still be required to confirm this. It may be applied in clinical administration of chemotherapeutic agents. Besides this, our group is harnessing the micellar property and P-gp inhibitor effect of TPGS to construct stimuli-responsive prodrug. The prodrug may be cleaved in tumor cells by pH and/or reduced to release conjugated drug and TPGS. It will combine the effects of TPGS in P-gp inhibition and stimuli-responsive drug release.

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Figure legend

Fig. 1. Chemical structure of TPGS

Fig. 2. Rhodamine 123 transport across Caco-2 monolayers in the absence and presence of TPGS analogs possessing different PEG chain lengths; (A) absorptive transport Ap-Bl; (B) secretory transport Bl-Ap; mean±SD, n =18; bars marked with * are significantly different from negative control. (P <0.05) and ** are very significantly different (P <0.001) (Collnot et al., 2006). Reproduced with permission.

Fig. 3. Influence of vitamin E, vitamin E succinate and PEG 1000 on rhodamine 123 transport across Caco-2 monolayers; mean±SD, n =9; bars marked with ** are very significantly different from control (P <0.001) (Collnot et al., 2006). Reproduced with permission.

Fig. 4. TPGS concentration-dependent solubility of paclitaxel. Inset shows total solubility of paclitaxel vs micellar concentration of TPGS. Each bar represents mean±S.D. (n = 3) of equilibrium solubility at 48 h (Varma and Panchagnula, 2005). Reproduced with permission.

Fig. 5. Plasma concentration–time profile of [14C] paclitaxel in rats after (a) intravenous administration (2 mg/kg); (b) after oral administration (25 mg/mL) of [14C]paclitaxel alone and in combination with verapamil or TPGS. Data points represent mean and error bars show S.E.M. (n = 4). $*P < 0.05$ and $**P < 0.01$, significantly different when compared to oral paclitaxel alone. $\#P < 0.05$ and $\#\#P < 0.01$, significantly different when compared to oral paclitaxel in combination with verapamil (Pcl, [14C]paclitaxel; Ver, verapamil) (Varma and Panchagnula, 2005). Reproduced with permission.

Fig. 6. TPGS/paclitaxel nanocrystals formulated. Transmission electron microscope images of PTX formulations, tumor growth inhibition effect of PTX/TPGS nanocrystals, Taxol and TPGS alone in the NCI/ADR-RES xenograft model. Solid arrows indicate the days of intravenous administration and the structure of TPGS and paclitaxel (Liu et al., 2010). Reproduced with permission.

Fig. 7. TPGS more effectively inhibited the growth of H460 and A549 lung carcinoma cell lines in comparison with TOS. (A) Dose–growth curve for H460 and A549 cells after treatment with TOS (●) or TPGS (○). (B) The effect of TOS, TPGS, PEG 1000, and both TOS and PEG 1000 on the growth of H460 cells. Cells were seeded at a density of $4x10^3$/well in 96-well plates and, starting 24 h later, were incubated for 48 h with varying doses of TOS, TPGS, PEG 1000 or both TOS and PEG 1000 and their growth and viability of cells were determined by MTT assay. Results are expressed as percentage growth (mean±S.D. of triplicate wells) relative to untreated cells (Youk et al., 2005). Reproduced with permission.

Fig. 8. TPGS suppressed the growth of human A549 lung cancer cells implanted in nude mice.

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Nude mice were subcutaneously injected with A549 cells, tumors were allowed to reach approximately 50 mm^3, and the treatment was initiated. The asterisks denote significant differences between tumor volume of TPGS versus vehicle-treated mice ($p<0.05$) (n =6, 6 and 8 for TOS, TPGS and vehicle treatment group, respectively) (Youk et al., 2005). Reproduced with permission.

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934 **Table legend**

935 **Table 1.** IC_{50} of docetaxel formulated in Taxotere®, TPGS2k micelles and FA-TPGS2k micelles
936 after 24, 48, 72 h incubation with MCF-7 breast cancer cells at 37 ^{o}C (Mi et al., 2011).
937 Reproduced with permission.
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939 **Table 2.** TPGS applications as solubilizer, permeation enhancer, vitamin E alternative, oral
940 absorption enhancer and so on in drug delivery system
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Figure(1)

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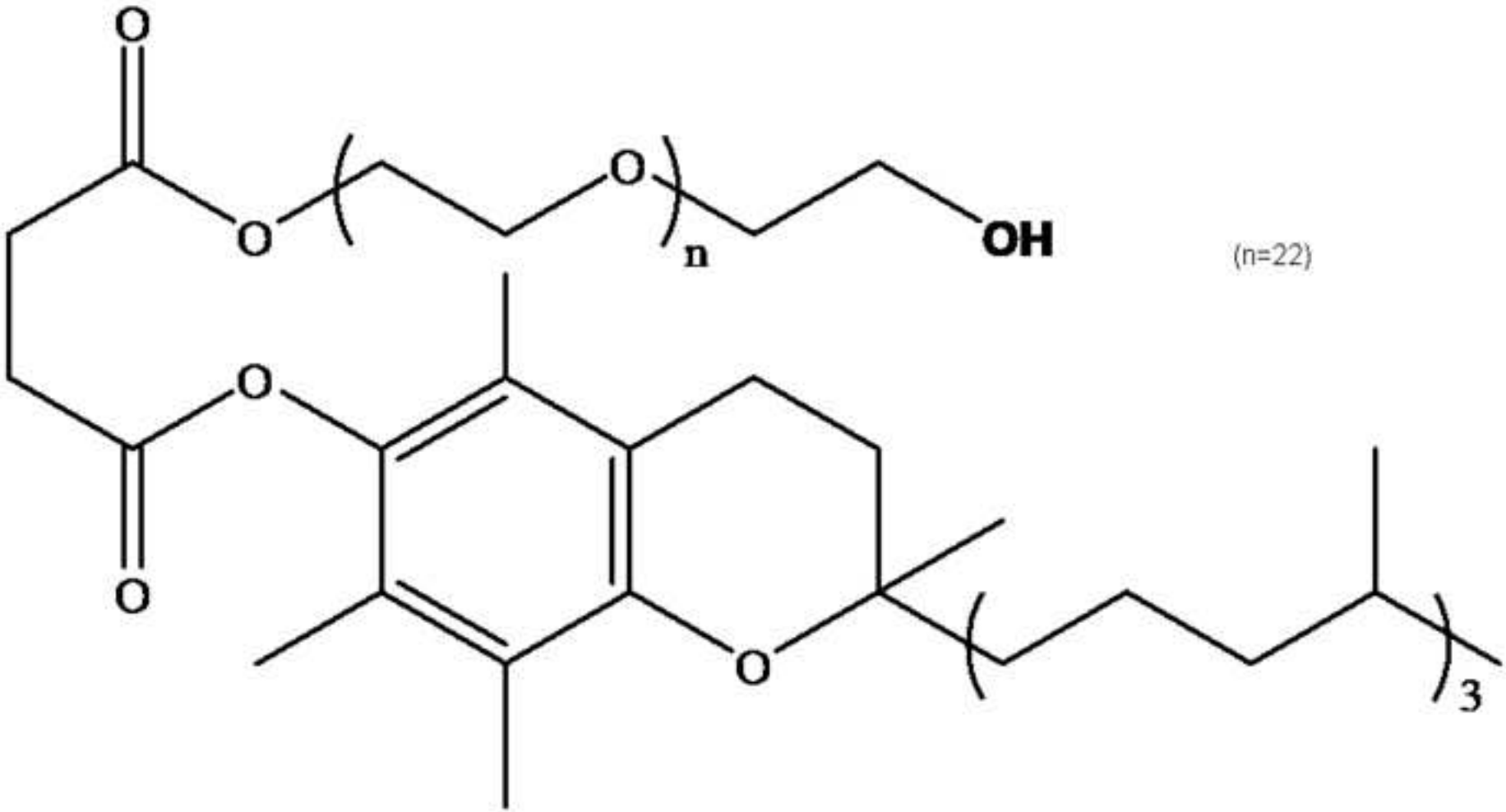

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Figure(2)

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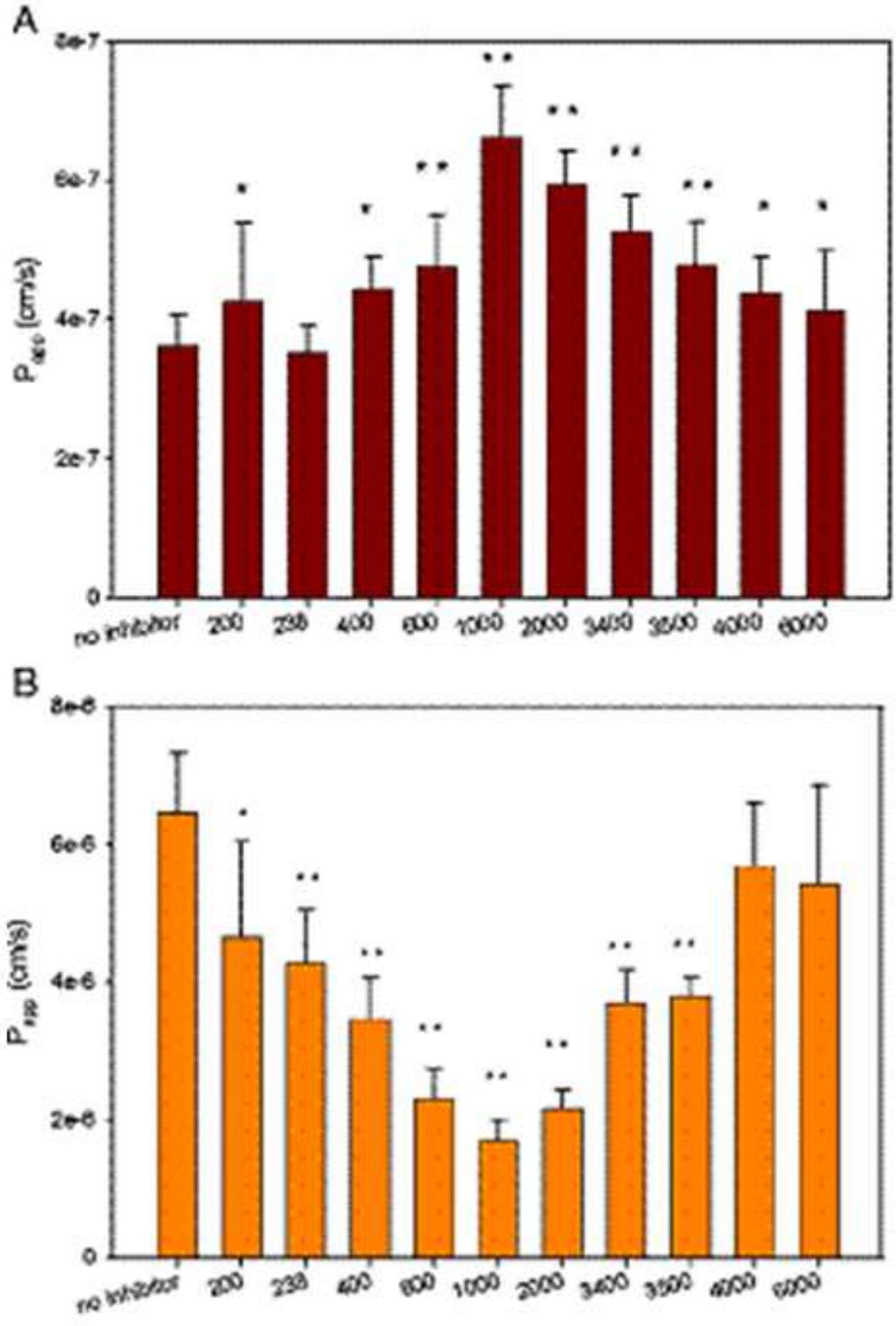

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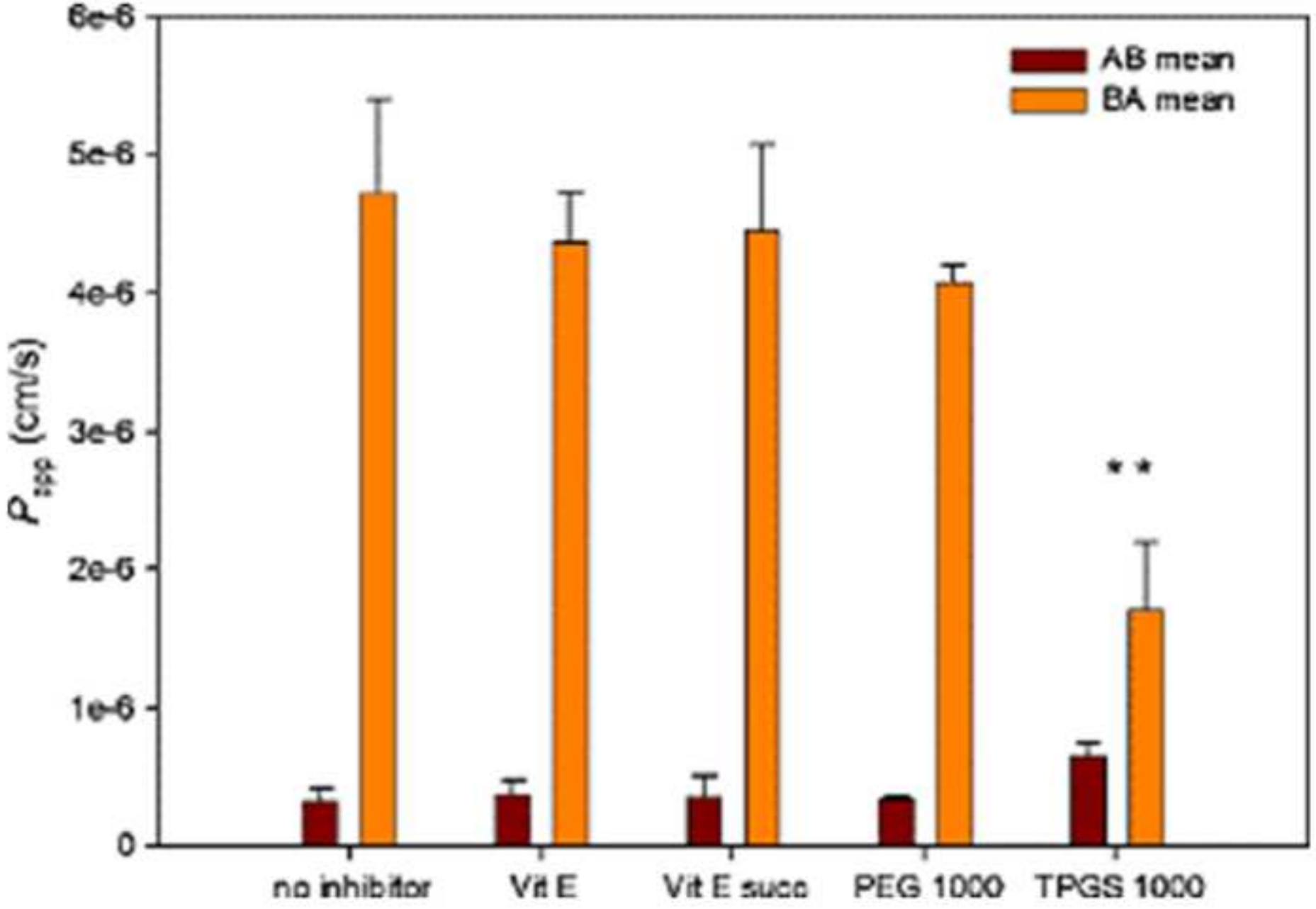

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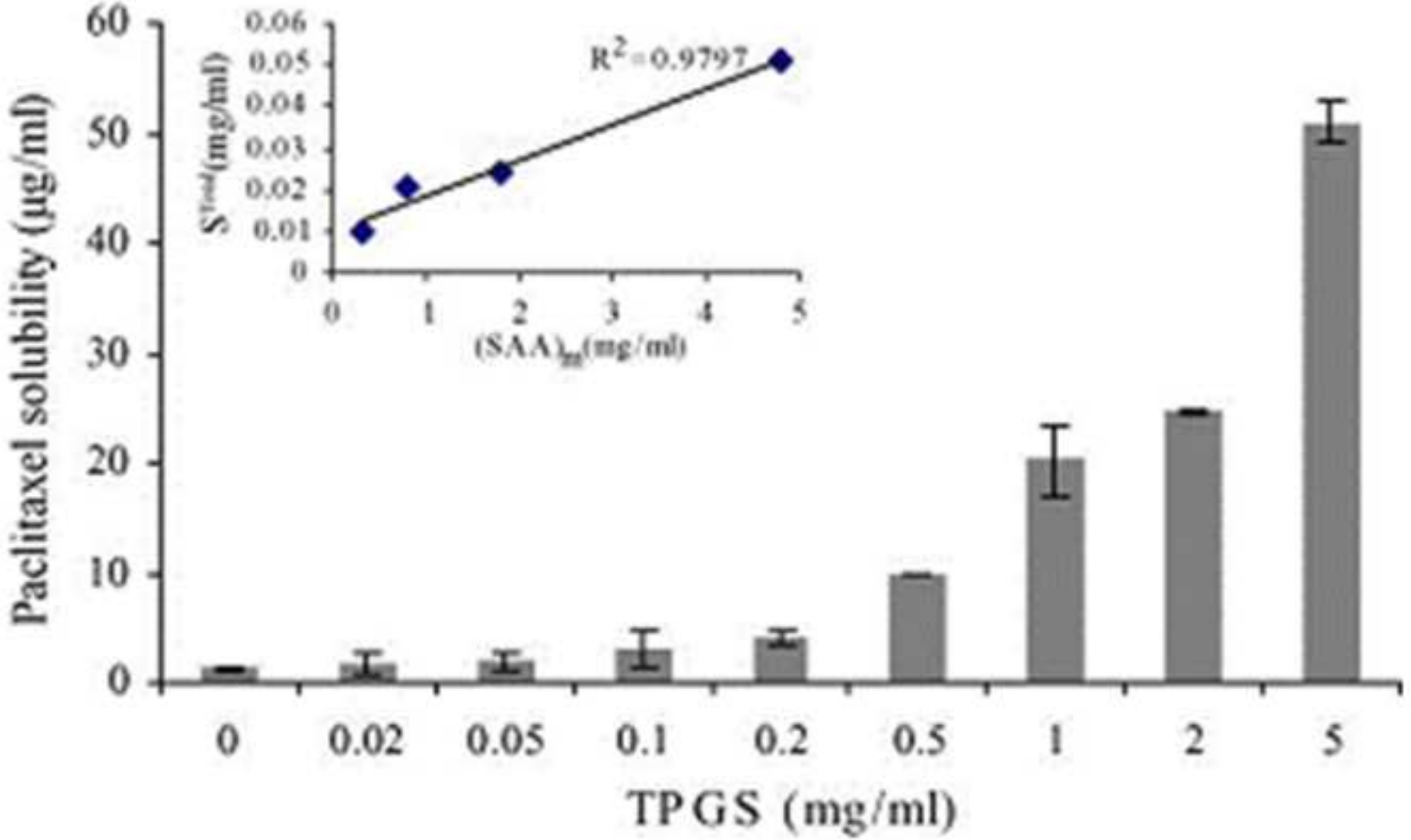

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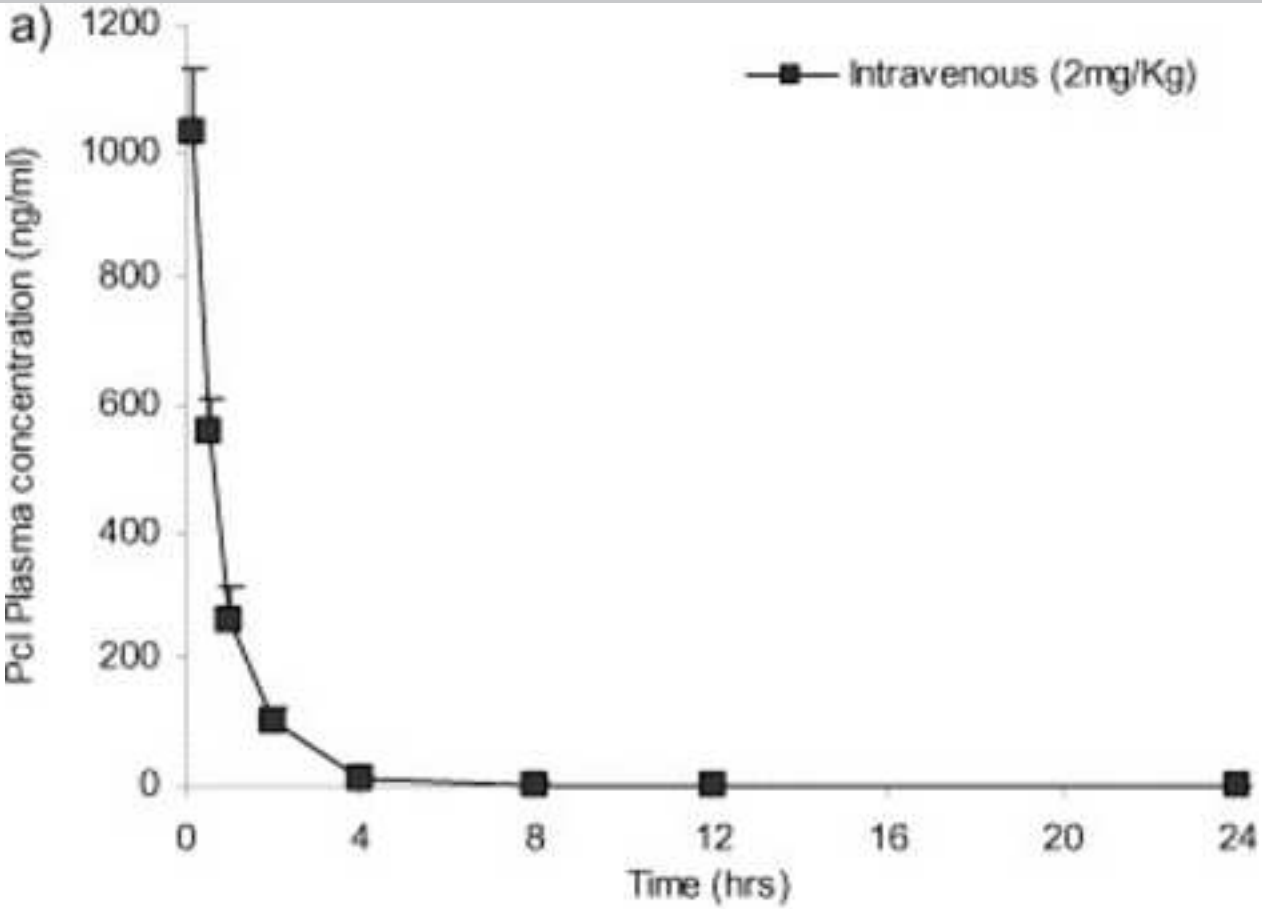

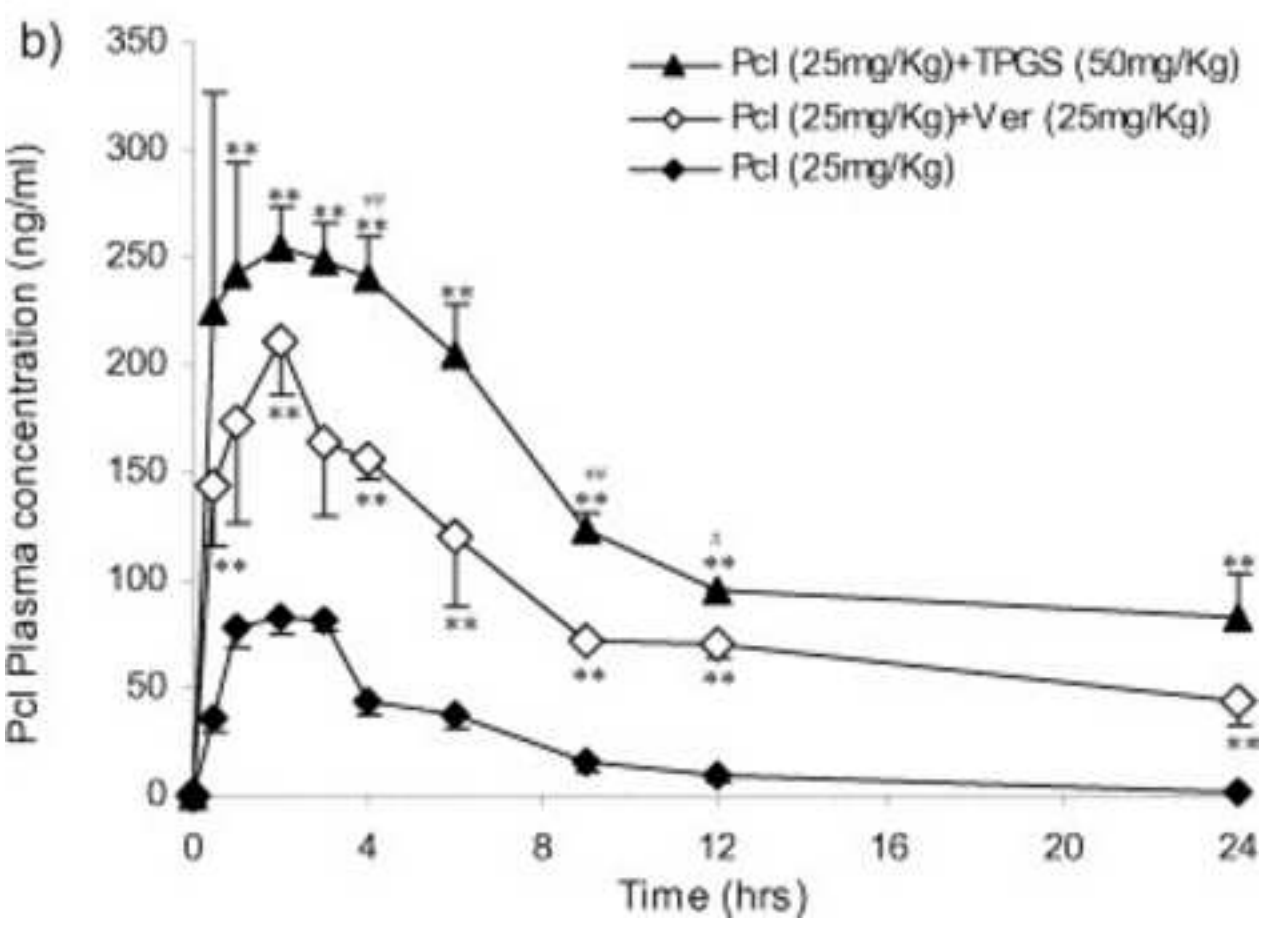

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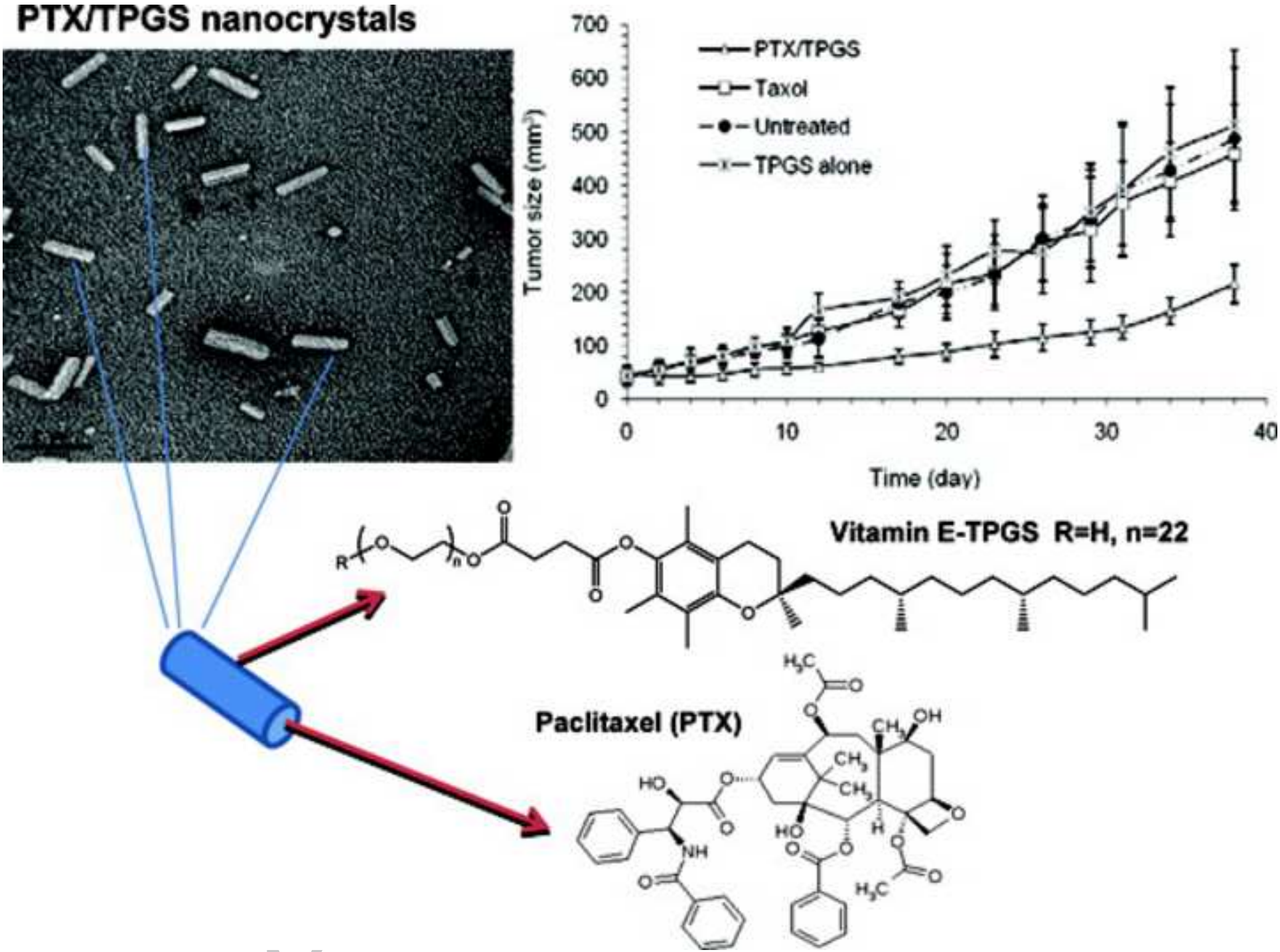

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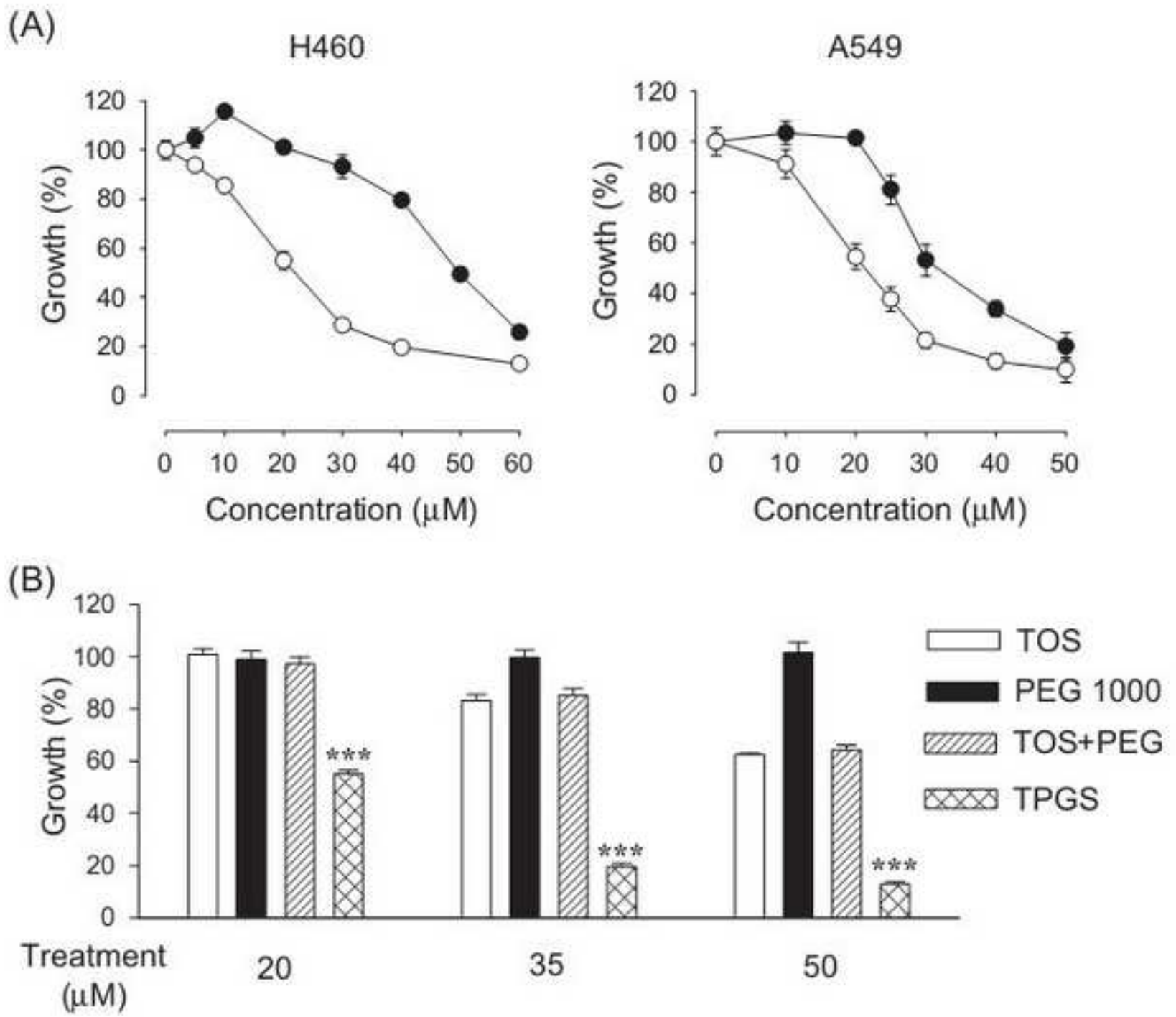

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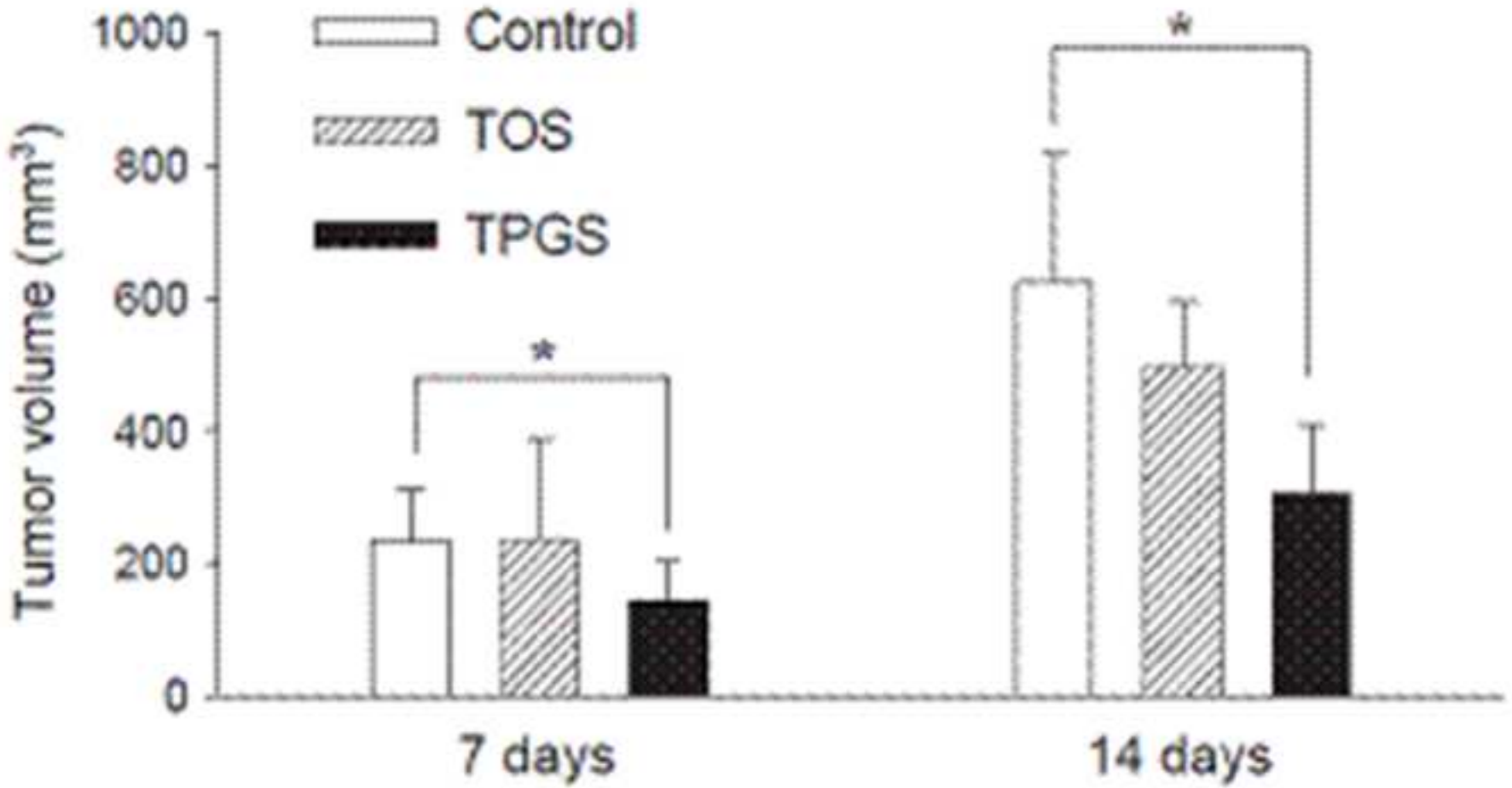

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Table 1. IC_{50} of docetaxel formulated in Taxotere®, TPGS2k micelles and FA TPGS2k micelles after 24, 48, 72 h incubation with MCF-7 breast cancer cells at 37 °C (Mi et al., 2011). Reproduced with permission.

Incubation time (h)	IC50 (μg/ml)			
	Taxotere®	Micelles without DXL [a]	Micelles with DXL	FA Micelles with DXL
24	103.4	1.350	0.526	0.178
48	1.28	1.530	0.251	0.152
72	0.148	7.58	0.233	0.114

[a] the value represents the concentration of docetaxel, that is equivalent to the concentration of $TPGS_{2k}$ for 50% viability.

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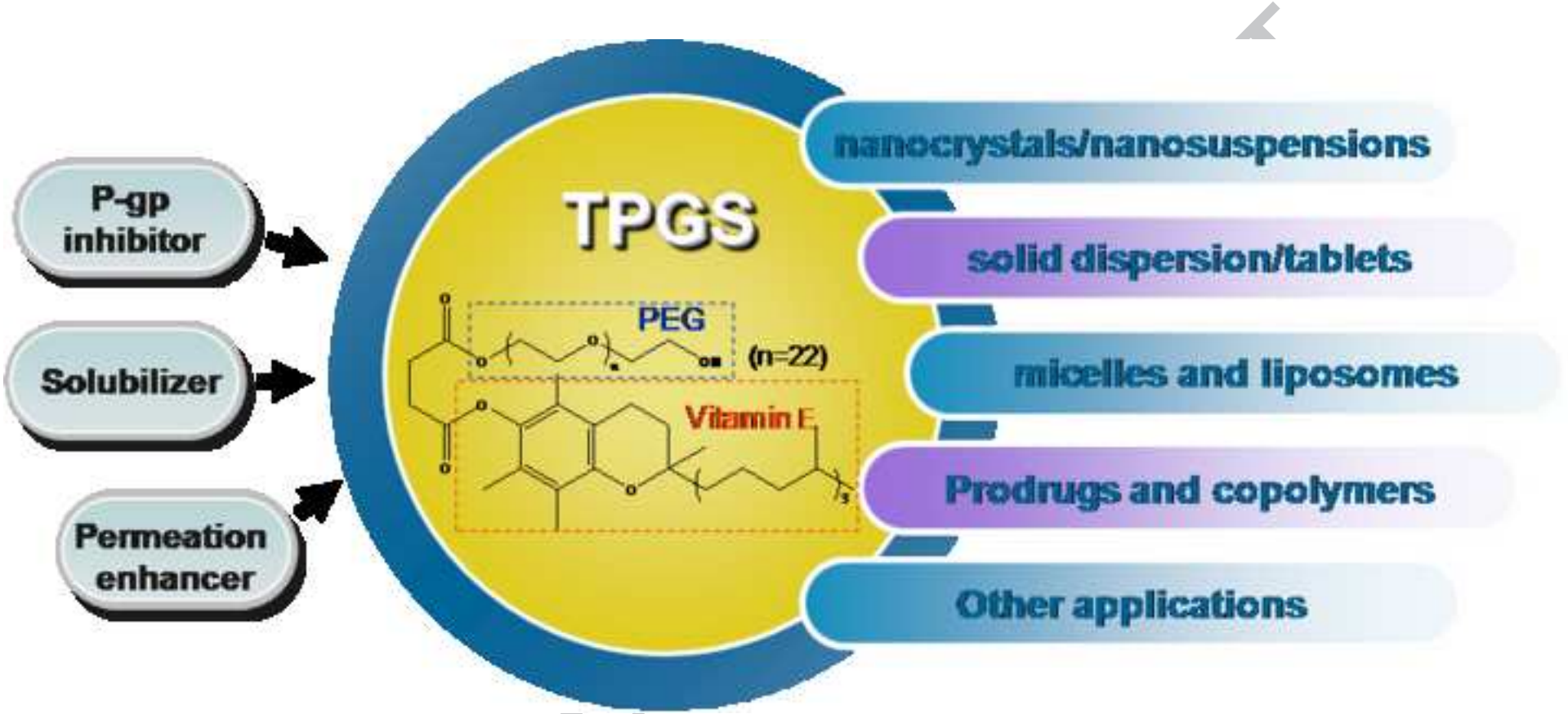
Table2 TPGS application as solubilizer, permeation enhancer, vitamin E alternative, oral absorption enhancer and so on in drug delivery system

Formulation	Drug model	Purpose	Significant effects
Tablet	Carbamazepine/ UC781	Dissolution effect	Increase the solubility, wettability and dissolution property (Kim et al., 2010).
Capsule/ Dissolution	Ampicillin/Antipyrine Verapamil	Oral absorption	No effect on small intestine transit (Schulze et al., 2006), gastrointestinal transit (Schulze et al., 2005), oral bioavailability R1481 and sirolimus (Wacher et al., 2002).
Solid dispersion	Itraconazole/UC781 Nifedipine/halofantrine	Oral bioavailability	Enhance the AUC of drug around 2-5 fold in rat and dog TPGS/Labrasol/GL44/14 (Ahn et al., 2011).
Nanosuspension	Curcumin/Itraconzole Loviride	Oral absorption Stabiliser	9-fold of AUC and 5-fold of C-max in TPGS nanosuspension compared to the coarse suspension after oral administration (Baert et al., 2009; Ghosh et al., 2011).
Surfactant/ Micelle structure Nanocrystal SEDDS SMEDDS	Paclitaxel/Cyclosporine Epirubicin/Raloxifene Verapamil/Quercetin Amprenavir/Talinolol Colchicine/Vancomycin	P-gp inhibition mechanism/ Solubility enhancer/ Oral absorption enhancer	P-gp inhibition from Caco-2 monolayer model; influence of ATPase activity without membrane fluidity changement (Rege et al., 2002); inhibitor for CYP-mediated metabolism (Christiansen et al., 2011); Inhibitor of P-gp and MRP2 (Hanke et al., 2010); increased AUC and C_{max} after coadministration; 6-fold increase on the oral bioavailability of paclitaxel after coadministrated with 50 mg/kg TPGS (Varma and Panchagnula, 2005).
Anticancer	TOGS/TPGS	Anticancer mechanism	Inhibit human lung carcinoma cells in nude mice and cell culture (Youk et al., 2005).
Adjuvant	vaccine	Adjuvant	5-fold of IgG and 100-fold of IgA improved (Ravichandran et al., 2007).
Alternative/ Nutrition	Vitamin E Vitamin D/A	Oral absorption	In cholestasis and thoracic duct-cannulated rats; Vitamin D and E deficiency patients and children (Feranchak et al., 2005; Jacquemin et al., 2009).
Surfactant Additive	Estradiol/Colchicine	Permeation enhancer	Delivery of drug through skin and skin permeation enhancers (Mohammed, 2001); HP-β-CD/HPMC/TPGS 1000 microparticle (Sethia and Squillante, 2004a).
Surfactant/ Antioxidant		Absorption for lung injuries therapy Pan-capase inhibition	Reduce the oxidative stress and partially decrease the cyclosporine A mediated reactive oxygen species formation (Grub et al., 2002; Wolf et al., 1997).
Film/TPGS	paclitaxel	Additive/Plasticizer	The elongation at break was 7-20 fold for TPGS 5-15% in PLLA film (Dong et al., 2008).


P-gp inhibitor
Solubilizer
Permeation enhancer
TPGS
PEG
(n=22)
Vitamin E
nanocrystals/nanosuspensions
solid dispersion/tablets
micelles and liposomes
Prodrugs and copolymers
Other applications

ACCEPTED