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Review

Recent advances in TPGS-based nanoparticles of docetaxel for improved chemotherapy

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ABSTRACT

Docetaxel (DTX) is one of the important antitumor drugs, being used in several common chemotherapies to control leading cancer types. Severe toxicities of the DTX are prominent due to sudden parenteral exposure of desired loading dose to maintain the therapeutic concentration. Field of nanotechnology is leading to resist sudden systemic exposure of DTX with more specific delivery to the site of cancer. Further nanometric size range of the formulation aid for prolonged circulation, thereby extensive exposure results better efficacy. In this article, we extensively reviewed the therapeutic benefit of incorporating D-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS, or simply TPGS) in the nanoparticle (NP) formulation of DTX for improved delivery, tumor control and tolerability. TPGS is well accepted nonionic-ampiphilic polymer which has been identified in the role of emulsifier, stabilizer, penetration enhancer, solubilizer and in protection in micelle. Simultaneously, P-glycoprotein inhibitory activity of TPGS in the multidrug resistant (MDR) cancer cells along with its apoptotic potential are the added advantage of TPGS to be incorporated in nano-chemotherapeutics. Thus, it could be concluded that TPGS based nanoparticulate application is an advanced approach to improve therapeutic efficacy of chemotherapeutic agents by better internalization and sustained retention of the NPs.

Contents

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1. Introduction

Cancer is the leading cause of death in economically developed and undeveloped countries, resulting in 25% of deaths worldwide. Concurrently, incidence of cancer is also increasing worldwide, estimating 14.1million new cases of cancer and 8.2million deaths has been recorded in 2012 (Dubey et al., 2012; Kesharwani et al., 2015; Sharma et al., 2017; Siegel et al., 2015; Zhao et al., 2013a). Chemotherapy, surgical resection and radiotherapy are the major mode to combat this dreadful disease. The process involves application of chemotherapy to reduce the tumor size followed by surgical removal and radiation thereafter (Brannon-Peppas and Blanchette, 2012; Dwivedi et al., 2016; Jain et al., 2014). Thus, chemotherapy plays the vital role to destroy the cancer cells from the body.

DTX (chemical formula, $C_{43}H_{53}NO_{14}$ and molecular weight, 807.9 g/mol) is a semi-synthetic plant alkaloid obtained from the European yew (*Taxus baccata*), taxane group of antitumor agent, used widely in breast, lung, ovarian, prostate, stomach and head and neck cancer (Hendrikx et al., 2016; Oh et al., 2016). Due to its low aqueous solubility (4.93 μg/mL in water), the drug is marketed as a parenteral formulation consist of polysorbate 80 and anhydrous ethanol (Yin et al., 2009). Severe infusion related toxicities such as hypersensitivity reactions, dyspnea, hypoxia, fever upon intravenous administration of Taxotere®, might be due to the presence of high concentration of polysorbate 80 and also the toxicities associated with the drug itself, are the major drawbacks of its clinical use (Li et al., 2010; Saifuddin Sheikh et al., 2015). Therefore, premedication with antihistaminics and corticosteroids become a clinical urge for Taxotere® (Saifuddin Sheikh et al., 2015). However, premedication could not able to overcome the potentially life-threatening reactions approximately in 2% of patients (Ho and Mackey, 2014). Further, extensive metabolism of the drug in liver as well as in cancerous cells by the Cytochrome-P450-3A4 lead to decrease chemotherapeutic efficacy of the drug (Hendrikx et al., 2016). To maintain the sufficient concentration of the chemotherapeutic agent in the systemic circulation over minimum therapeutic level, a higher bolus dose is required considering rapid elimination from the system. Sudden intravenous administration leads to reach a higher concentration in the systemic circulation where the solvent and co-solvent system potentiate unpleasant effects, causing severe toxicities.

Research efforts since last three decades brought several developments of alternative delivery carriers for this chemotherapeutic agent to retain the cytotoxic agent in the circulation, controlled release in the blood, and more site specific delivery, with less effect to the normal cells (Herbst and Khuri, 2003; Liu et al., 2010; Zhao et al., 2013b; Zhu et al., 2014). Thus, improvement of quality of life and life expectancy could be achievable by targeted delivery of the chemotherapeutic agent with limited release in the circulation. Now-a-days nanotechnology platform has been proved to be a promising delivery system for chemotherapeutic agents and other drugs to improve therapeutic effect. Nanocarriers helps to incorporate lipophilic and hydrophilic drugs into the nano-environment to promote the release in a controlled manner within the systemic circulation, more targeted delivery, prolonged circulatory behaviour and pronounced safety (Chall et al., 2015; Choudhury et al., 2017, 2016; Gorain et al., 2016, 2014). On the other hand, nanocarriers, in the 20–200 nm size range, circulate longer in the circulation by escaping from phagocytic elimination of reticulo endothelial system (RES). Based on the properties of the nanocarriers, various characterization parameters are optimized by using sophisticated and modern instruments (Choudhury et al., 2014b; Dou et al., 2014; Gorain et al., 2013; Li et al., 2016a; Muthu et al., 2011). Hanging on the researcher's interest to deliver chemotherapeutic agents to the site of action for site specific treatment and to minimize the toxic effects, TPGS has been introduced in the nanocarriers for the interesting outcomes in pharmaceutical formulations; such as enhancement of solubility, inhibition of efflux pump P-Glycoprotein, and established antitumor action. There are very few articles available in the literature focusing on TPGS based nanocarriers of DTX for the improvement of chemotherapy, with the extensive role of TPGS in the improvement of formulation and penetration aspects *via* development of novel targeted/non-targeted nanocarriers, and clinical overview. In this article, we extensively reviewed the role of TPGS in various nano-approaches in the enhancement of the delivery system through augmentation of pharmacokinetic and pharmacodymic profile of the entrapped chemotherapeutic agent, DTX, to facilitate disease cure. This study has also incorporated the positive and negative aspects of several clinical studies on the TPGS loaded DTX nano-delivery system in the treatment of sensitive as well as MDR cancers. The readers will be benefitted with the expert's explanations on various roles of TPGS in the improvement of DTX therapy to the cancer patients, which may help them to direct their research towards serendipitous avenue in chemotherapy. Connecting section of the article will reveal the role of TPGS as an effective component in nanotechnology for the treatment of cancer.

2. TPGS as effective component of nanocarrier

In recent years, there had been a great deal of attention in the potential use of natural products in the delivery of chemotherapeutic agents (Gaonkar et al., 2017). Due to complementary nature, these components are well accepted by the formulation scientists all over the world. Among these products, TPGS is getting pronounced attention in drug delivery system as emulsifier, stabilizer, penetration enhancer, solubilizer and also in protection of micelle (Guo et al., 2013). TPGS is a derivative of natural vitamin E (Vit-E) and polyethylene glycol 1000 (PEG-1000) having ampiphilic nature (Cao and Feng, 2008). Studies suggested that TPGS helps in the enhancement of drug encapsulation in the nanoparticulate delivery, improved cellular uptake, enhanced therapeutic efficacy, improved oral bioavailability with prolongation of circulation time (Dong et al., 2016; Guo et al., 2013; Sun et al., 2014). Additionally, TPGS has become a key ingredient to inhibit P-glycoprotein (P-gp) efflux in MDR tumor (Dintaman and Silverman, 1999).

2.1. Background of vitamin E and TPGS

Vitamin E (Vit-E) is an essential micronutrient, crucial for maintenance of cellular anti-oxidation reaction. It guards the cell membrane of erythrocytes and lung cell from free radical invectives. Additionally it also exhibits ant-inflammatory activity *via* inhibiting protein lipoxygenase (Constantinides et al., 2006; Grammas et al., 2004). Vit-E is a lipid soluble compound having eight isoforms categorized into tocopherols (TOS) and tocotrienols in which α-TOS find copiously in human tissue and plasma.