International Journal of Pharmaceutics 536 (2018) 146–157

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Development and *in-vitro* characterization of nanoemulsions loaded with paclitaxel/γ-tocotrienol lipid conjugates

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ARTICLE INFO

Keywords:
Nanoemulsion
Paclitaxel
Tocotrienol
PEGylation
Vitamin E TPGS
Drug delivery
Cancer chemotherapy
Nanotechnology

ABSTRACT

Vitamin E TPGS is a tocopherol (α-T) based nonionic surfactant that was used in the formulation of the Tocosol™ paclitaxel nanoemulsion, which was withdrawn from phase III clinical trials. Unlike tocopherols, however, the tocotrienol (T_3) isomers of vitamin E were found to have innate anticancer activity and were shown to potentiate the antitumor activity of paclitaxel. The primary objective of the present study was therefore to develop a paclitaxel nanoemulsions by substituting α-T oil core of Tocosol™ with γ-T_3 in, and vitamin E TPGS with PEGylated γ-T_3 as the shell, and test the nanoemulsions against Bx-PC-3 and PANC-1 pancreatic tumor cells. A secondary objective was to test the activity of paclitaxel when directly conjugated with the γ-T_3 isomer of vitamin E. The synthesis of the conjugates was confirmed by NMR and mass spectroscopy. Developed nanoemulsions were loaded with free or lipid conjugated paclitaxel. Nanoemulsions droplets were < 300 nm with fastest release observed with formulations loaded with free paclitaxel when γ-T_3 was used as the core. Substituting α-T with γ-T_3 was also found to potentiate the anticancer activity of the nanoemulsions. Although marginal increase in activity was observed when nanoemulsions were loaded with free paclitaxel, a significant increase in activity was observed when lipid conjugates were used. The results from this study suggest that the developed paclitaxel nanoemulsions with either γ-T_3, PEGylated γ-T_3, or paclitaxel lipid conjugates may represent a more promising option for paclitaxel delivery in cancer chemotherapy.

1. Introduction

Vitamin E is a term used to represent a family of eight related α, β, γ, and δ tocopherols and tocotrienol isomers, which differ in the degree of methyl substitutions on their chroman moiety and the degree of saturation in their phytyl side chain (Sylvester et al., 2010). While the tocopherols are known for their antioxidant activity (Galli et al., 2016), the tocotrienol isomers were found to display potent anticancer activity, which established a distinction in the health and therapeutic benefits between the tocotrienol and tocopherol isomers of vitamin E (Aggarwal and Nesaretnam, 2012; Sylvester et al., 2010). The poor water solubility of vitamin E isomers, however, limited their clinical use. To overcome this limitation, the α-tocopherol isomer of vitamin E was conjugated to PEG 1000, which is commercially known as D-α-tocopherol polyethylene glycol 1000 succinate or simply vitamin E TPGS or TPGS (Guo et al., 2013). Vitamin E TPGS is currently being used as a pharmaceutical excipient for its solubilization capacity (Guo et al., 2013). During the early 2000s, a tocopherol-based product, known as Tocosol™, was developed as an alternative platform for paclitaxel delivery to reduce the side effects associated with the vehicle used in the commercial Taxol™ formulation (Constantinides et al., 2000). The development of Tocosol™, however, was terminated in phase III clinical trials due to low primary endpoint of overall response rate (ORR, 37% for Tocosol™) when compared to the control arm Taxol® (45%) (Ma and Mumper, 2013).

Tocosol™ paclitaxel was formulated with α-T as the oil core for paclitaxel solubilization and vitamin E TPGS as the primary emulsifier (Constantinides et al., 2000). However, since the tocotrienol isomers of

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https://doi.org/10.1016/j.ijpharm.2017.11.062
Received 18 September 2017; Received in revised form 24 November 2017; Accepted 26 November 2017
Available online 02 December 2017
0378-5173/