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ORIGINAL ARTICLE

Improving the biopharmaceutical attributes of mangiferin using vitamin E-TPGS co-loaded self-assembled phosholipidic nano-mixed micellar systems

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Abstract

The current research work encompasses the development, characterization, and evaluation of self-assembled phospholipidic nano-mixed miceller system (SPNMS) of a poorly soluble BCS Class IV xanthone bioactive, mangiferin (Mgf) functionalized with co-delivery of vitamin E TPGS. Systematic optimization using I-optimal design yielded self-assembled phospholipidic nano-micelles with a particle size of < 60 nm and > 80% of drug release in 15 min. The cytotoxicity and cellular uptake studies performed using MCF-7 and MDA-MB-231 cell lines demonstrated greater kill and faster cellular uptake. The ex vivo intestinal permeability revealed higher lymphatic uptake, while in situ perfusion and in vivo pharmacokinetic studies indicated nearly 6.6- and 3.0-folds augmentation in permeability and bioavailability of Mgf. In a nutshell, vitamin E functionalized SPNMS of Mgf improved the biopharmaceutical performance of Mgf in rats for enhanced anticancer potency.

Keywords Breast cancer · Quality by design (QbD) · Mangiferin · Vitamin E TPGS nanomicelles · Self-assembled phospholipidic nano-mixed miceller system (SPNMS) · Pharmacokinetics · Bioavailability · P-gp efflux · Cellular uptake

Introduction

Mangiferin (Mgf), a naturally produced polyphenol molecule possessing four hydroxyl groups, is an efficient antioxidant for free radical chain termination [1]. Mgf shows potential cytotoxicity effects on cancer cells and may even induce apoptosis by inhibiting and suppressing nuclear factor kappa B (NF-kB) and NF-κB-inducing kinase [2, 3]. Several literature [3, 4] also report Mgf-induced apoptosis, and tumorigenesis through altered gene expression [5–7], especially using Bcl-2 and Bax. Definitive activity of this bioactive phytochemical has also been documented on HL-60 cells programmed cell death, ascribed to suppression of Bcl-xL and XIAP expression and inhibition of the NF-kB pathway [8].

Despite being a very potent antioxidant molecule, Mgf exhibits very low and variable bioavailability (i.e., 1.5 to 5%), owing principally to limited aqueous oral solubility (i.e., 0.1 to 0.3 mg/mL) and poor lipophilicity (i.e., log P of − 0.56), extensive P-gp efflux, high first-pass effect, and considerable metabolism by gut Cytochrome P-450 enzymes [9–14]. By virtue of its low aqueous solubility and lipophilicity, Mgf can be safely regarded as a BCS class IV agent.

Owing to the aforementioned challenges [15], several scientists have attempted to enhance the oral bioavailability of Mgf by formulating its solid dispersions [16], β-cyclodextrin complexes [17, 18], phospholipid complexes [19], and spray-

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