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Pharmacokinetics, biodistribution, and bioavailability of gossypol-loaded Pluronic® F127 nanoparticles

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ABSTRACT

To enhance the water solubility and improve the bioavailability of gossypol, gossypol-loaded Pluronic® F127 nanoparticles (GLPFNs) for intravenous (i.v.) administration were prepared through thin-film hydration. The morphological characteristics of the GLPFNs were determined by transmission electron microscopy and particle size analysis. Pharmacokinetic and biodistribution studies were performed using Kun Ming (KM) mice by measuring gossypol concentrations in plasma and tissue samples of the mice using ultra-high performance liquid chromatography-electrospray ionization-tandem mass spectrometry (UHPLC- ESI-MS/MS). The GLPFNs exhibited uniform spherical shapes with a dynamic size of 70 ± 2.4 nm. The encapsulation and drug-loading efficiencies of the GLPFNs were 91.2% ± 3.1% and 9.1% ± 0.42%, respectively. The particles further exhibited sustained drug release for about 200 h. The UHPLC-ESI-MS/MS method used in this work for plasma and tissue sample analysis was fully validated. The pharmacokinetics of the GLPFNs was studied after intravenous (i.v.) and intragastric (i.g.) administration to KM mice, and tissue distribution studies of the GLPFNs were performed. The AUC (0–inf) of the GLPFNs exhibited five- and sixfold increases. The clearance of GLPFNs decreased up to 5.6-fold when the gossypol entrapped in GLPFNs was i.g. administered. The absolute bioavailability of GLPFNs, which was 44.32%, increased by threefold compared with that of gossypol alone. The relative bioavailability of the GLPFNs after intravenous (i.v.) and intragastric (i.g.) administration was 192.38% and 560.75%, respectively. The concentration of GLPFNs was higher than that of gossypol, especially in reticuloendothelial cell-containing organs. Thus, the GLPFNs improved the bioavailability of the lipophilic drug gossypol. The gossypol-loaded Pluronic® F127 nanoparticles exhibited high biocompatibility and tunable drug release characteristics for treating cancer.

1. Introduction

Gossypol [1,1′,6,6′,7,7′-hexahydroxy-5,5′-diisopropyl-3,3′-dimethyl-(2,2′- binaphthalene)- 8,8′-dicarboxaldehyde] (Fig. 1), is a yellow polyphenol compound that occurs in various parts of cotton plants, such as seeds, leaves, stems, and roots [1]. Gossypol has received considerable attention because of its unique anti-malignancy characteristic. The drug induces cell apoptosis of tumors through binding with a structural domain of BH3 in BCL-2 family members; this behavior causes apoptosis of tumor cells [2–4]. Modern medical research has proven that in vivo gossypol exhibits high anti-tumor activity in pancreatic cancer [5,6], lymphoma [7,8], head and neck [9], prostate [10–13], cervical [14,15], breast [16,17], and colorectal [18,19]cancers. However, gossypol is not widely used clinically because it is toxic. Moreover, the drug is only soluble in select organic solvents, such as chloroform, ethanol, ether, and acetone. The compound is insoluble in water and low boiling petroleum ether; thus, an injection formulation cannot be prepared for gossypol. Gossypol should therefore be modified to improve its water solubility and the bioavailability, therefore, enhance its therapeutic effects, and convert it into a less toxic form.

Gossypol is difficult to modify chemically. So far over 50 new analogs of gossypol have been synthesized to date. For instance, ApoG2 (apogossypolone), a new derivative of gossypol, exhibits good activity and low toxicity in antitumor studies; however, this compound has not been widely used clinically because of its undesirable side effects, insolubility, and lack of selectivity toward tumor cells.

Nanocarriers have also been used to address problems associated

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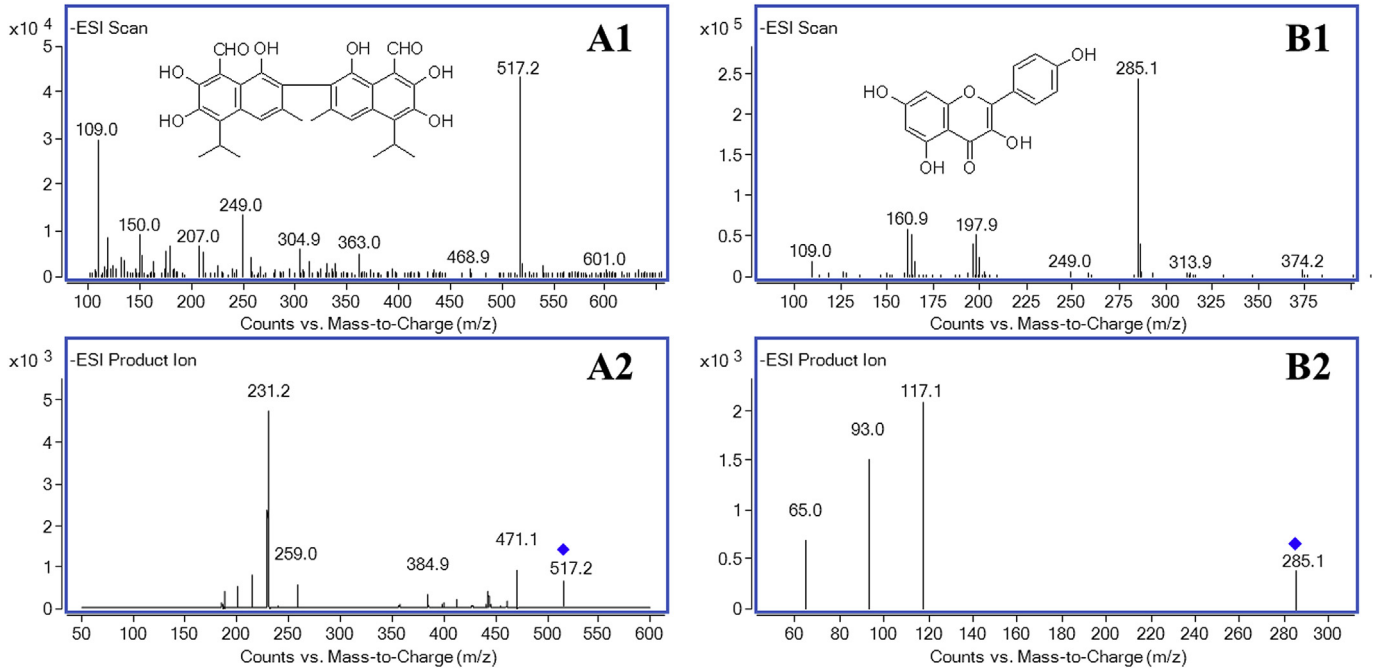

Fig. 1. The chemical structure, parent and daughter ion scan spectra of gossypol (A1,A2) and kaempferol (B1,B2).

with the use of gossypol. This approach enables several gossypol molecules to be loaded into a nanocarrier that can be easily dispersed in water even at high concentrations. The nanocarriers exhibit sustained release or target specific tissues; thus, the anti-tumor effect of gossypol in vivo is enhanced, and its toxicity is decreases. Although some studies on gossypol and its anti–tumor effects and mechanism have been reported, few studies on gossypol nanocarriers are available. Cho H et al., reported that gossypol PEG-PCl polymers improve the bioavailability and toxicity of gossypol; however, the drug encapsulation efficiency of the polymers is < 5% [20]. Moreover, the polymers exhibit wide-size distributions, which limits their absorption in vivo [20]. Zhai G et al., prepared gossypol liposomes to improve the toxicity of the drug *in vitro* [21]. The liposomes produced, however, are unstable in solution and feature low drug loading; thus, an in vivo study of these liposomes has not been published [21]. To date, no studies on the pharmacokinetics, biodistribution, and bioavailability of gossypol nanocarriers have been reported. A suitable nanocarrier for encapsulating gossypol with high drug loading and uniform size should be developed; moreover, studies on the pharmacokinetics and biodistribution of this compound should be performed to address challenges associated with the application of gossypol.

Amphiphilic polymers, which are important drug-carrier materials, are macromolecular polymers possessing both hydrophilic and hydrophobic segments. The polymers can form polymeric micelles with a core-shell structure; moreover, they can achieve drug encapsulation self-assembly in solution [22,23]. Amphiphilic polymer micelles exhibit advantages as drug delivery carriers. These polymers have a hydrophobic core that acts as a reservoir for insoluble drugs with high loading capacity and enable controlled release of drugs. The polymers also present nanostructures with small particle size, which facilitates accumulation of vehicles in tumor tissues. Accumulation occurs because of enhanced permeability and retention (ERP) effects; thus, passive targeting may be achieved. The hydrophilic shell of the polymers enables longer drug circulation times; active targeting is realized when the polymer is modified with suitable targeting groups [24,25].

Pluronics® are amphiphilic synthetic polymers composed of hydrophilic poly (ethylene oxide) (PEO) and hydrophobic poly(propylene oxide) (PPO) blocks. The blocks are arranged in a triblock structure: PEO-PPO-PEO [26,27]. Pluronic® is safe to use, some varieties of this polymer have been approved by the FDA for use as excipients in intravenous (i.v.) and non-i.v. formulations in the pharmaceutical field; this polymer is also widely used as a drug carrier [28]. Pluronics® improves the solubility and bioavailability of lipophilic molecules as drug delivery carriers when a drug is incorporated into the hydrophobic cores of the micelles [29,30], especially as excipients in injection formulations, because of its excellent compatibility with blood [31]. Sahu A et al., prepared a nano-formulation based on Pluronic® F127 to improve the solubility of lipophilic phytochemical curcumin; encapsulation efficiency, drug release, and cytotoxicity of drug-loaded micelles *in vitro* were investigated in this study, but in vivo studies were not performed [32]. Zhang W et al. prepared paclitaxel-loaded Pluronic® P123/F127 mixed micelles and investigated their in *vitro* and in *vivo* characteristics; results showed that mixed micelles improve the solubility and bioavailability of paclitaxel [33]. Based on the results obtained in previous studies, we chose Pluronic® F127 as a drug carrier to prepare gossypol-loaded Pluronic® F127 nanoparticles (GLPFNs) with improved solubility and bioavailability.

The current study investigated the pharmacokinetics, biodistribution, and bioavailability of GLPFNs. Pluronic® F127 was used as the gossypol carrier intended for i.v. administration. The GLPFNs, which represent a new formulation developed to improve the solubility of gossypol, were prepared by thin-film hydration. The GLPFNs exhibited uniform particle size, high drug-loading capacity, and excellent stability. A simple, specific, sensitive, and accurate ultra-high performance liquid chromatography-electrospray ionization-tandem mass spectrometry (UHPLC- ESI-MS/MS) method was established and applied to allow pharmacokinetic, biodistribution, and bioavailability studies of the GLPFNs. The concentrations of the GLPFNs in mice plasma and tissues after i.v. and intragastric (i.g.) administration were determined. The results of this study showed that the proposed formulation approach improves the bioavailability and therapeutic efficacy of poorly soluble lipophilic drugs, such as gossypol.

2. Materials and method

2.1. Materials

Gossypol (purity > 99.0%) and kaempferol (IS, purity > 99.0%)