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Caffeine-loaded gold nanoparticles conjugated with PLA-PEG-PLA copolymer for *in vitro* cytotoxicity and anti-inflammatory activity

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Abstract

The purpose of the study was to develop caffeine-loaded gold nanoparticles (AuNPs) using a poly(lactic acid)-polyethylene glycol-poly(lactic acid) (PLA-PEG-PLA) polymer to enhance the anti-inflammatory activity of caffeine. Caffeine-loaded AuNPs were conjugated to PLA-PEG-PLA copolymer matrix *via* π-back bond between AuNPs and the ester carbonyl group of the polyester. The π-back bonded ester carbonyl oxygen strongly interacted with the caffeine molecule and exhibited enhanced anti-inflammatory activity. The physico-chemical characteristics of the resulting nanoconjugates were evaluated by a series of microscopic, diffraction, and spectroscopic methods. *In vitro* assays indicated increasing membrane stabilization of red blood cells and enhanced inhibition of protein denaturation.

Introduction

Gold nanoparticles (AuNPs) show high potential for application in various fields such as medicine [1], drug delivery [2], cancer treatment [3], sensors [4], antimicrobial activity [5], and catalysis [6], [7] because of their biocompatibility [8] and non-toxicity [9]. Numerous preparative techniques are now available for synthesizing AuNPs [10], [11], [12]. Chemical [13], photochemical, [14] and biosynthetic methods [15] have been reported for the synthesis of AuNPs. Although chemical methods are efficient and convenient, green chemistry approaches have gained attention for the synthesis of AuNPs for their applications in biomedical fields because of their ecofriendly nature [16], [17].

Organic natural products have widely been utilized for the green synthesis of metal NPs [18]. Caffeine belongs to the methylxanthine class of natural products and is chemically related to the bases adenine and guanine of DNA and RNA. Caffeine is widely consumed as a stimulant and acts on the central nervous system. It has a wide natural distribution and is present in phytoproducts such as tea leaves and coffee beans. Numerous previous studies have described the green synthesis of metal NPs using caffeine as a reducing agent. Nadagouda et al. reported the green synthesis of silver and palladium NPs using the extracts of coffee and tea [19], while Sun et al. evaluated the stability of silver NPs synthesized using extracts of tea leaf [20]. Recently, Huang et al. reported the reactivity of various tea extracts for the green synthesis of iron nanoparticles [21]. However, reports on the green synthesis of metal NPs using pure caffeine molecules are limited. Caffeine molecules must be used in pure form to obtain shape-controlled and narrowly distributed metal NPs.

Caffeine has been reported to exhibit several medicinal properties. Jasiewicz et al. reported the anti-oxidant activity of thiol-caffeine derivatives and found that these derivatives were highly potent cytoprotective agents [22]. Chrościńska-Krawczy et al. reported the influence of caffeine on the protective activity of gabapentin and topiramate in a mouse model [23], while Acevedo et al. reported that caffeine stimulates locomotor activity in the mammalian spinal cord *via* an adenosine A1 receptor-dopamine D1 receptor interaction [24]. Recently, caffeine was reported to show good anti-inflammatory activity [25]. However, a suitable delivery vehicle is necessary to enhance the therapeutic effect of caffeine-based nanoconjugates.

The poly(lactic-co-glycolide) (PLGA) and poly(lactic acid)-co-poly ethylene glycol-co-poly(lactic acid) (PLA-PEG-PLA) based block copolymers have widely been used as effective drug carriers because of their biodegradability and biocompatibility [26], [27], [28], [29], [30], [31]. Ishihara et al. suggested that the potential anti-inflammatory activity of betamethasone disodium phosphate-loaded PLA-PEG NPs results from two factors: (i) controlled distribution of the drug in tissues and (ii) controlled release of the drug [32]. The

former controls the stealth property of the NPs achieved through association or dissociation of the PEG moiety, while the latter affects the controlled release of the therapeutic agent. Utilizing these properties of PLA-PEG copolymers, *Leucas aspera* extract-AuNPs-PLA-PEG-PLA and pectin-AuNPs-PLA-PEG-PLA nanoconjugates were recently developed and showed potential *in vitro* anti-inflammatory activities such as inhibition of protein denaturation and membrane stabilization activities [27], [33]. The water-in-oil (W/O) emulsion method is widely employed in the preparation of drug loaded PLGA-PEG-PLGA-based polymer NPs [34]. AuNPs can be conjugated to the carbonyl group *via* the formation of π-back bonding between the filled dπ orbital of Au^0 and unfilled pπ* orbital of the —C═O group [35]. Patnaik et al. found that the zerovalent Au atom formed a π-back bond with the carbonyl group of polycarbonates and suggested that formation of π-back bonding occurs because of back donation of electrons from the filled dπ orbital of Au^0 to the empty pπ* orbital of the carbonyl group [35].

The purpose of this study was to develop naturally obtained caffeine-loaded AuNPs-PLA-PEG-PLA (caffeine-AuNPs-PLA-PEG-PLA) nanoconjugates to use as anti-inflammatory agents. Caffeine has been isolated from coffee beans and used as a reducing and stabilizing agent in the green synthesis of AuNPs. Caffeine-AuNPs were attached to the PLA-PEG-PLA polymer matrix by W/O emulsification and solvent evaporation techniques. The physico-chemical properties of the synthesized caffeine-AuNPs-PLA-PEG-PLA nanoconjugates were characterized by UV–vis absorption spectroscopy, X-ray photoelectron spectroscopy (XPS), transmission electron microscopy (TEM), X-ray diffraction (XRD), selected area electron diffraction (SAED), and energy dispersive spectroscopy (EDS) analyses. Finally, the *in vitro* cytotoxicity, inhibition of protein denaturation, and membrane stabilization activities of the developed nanoconjugates were investigated to demonstrate the potential of caffeine-AuNPs-PLA-PEG-PLA nanoconjugates as a drug carrier platform.

Section snippets

Chemicals

Ethyl acetate, hexane, anhydrous sodium sulfate, anhydrous sodium carbonate, green tea leaves, sulfuric acid, hydrochloric acid, and sodium hydroxide were from Merck Chemicals Pvt., Ltd. (Kenilworth, NJ, USA). $HAuCl_4 \cdot 3H_2O$ was from Sigma Aldrich (St. Louis, MO, USA). These reagents were used without further purification.

Isolation of caffeine from coffee beans by solvent extraction method

Coffee beans (10 g) were refluxed in double-distilled water containing 2 g of sodium carbonate for 3 h with a reflux condenser. A few porcelain bits were added to the reaction

Characterization of nanoconjugates

The green synthesis of AuNPs using caffeine molecules and the preparation of caffeine-AuNPs-PLA-PEG-PLA nanoconjugates are shown in Scheme 1. In the first step, caffeine acted as a reducing agent and stabilizing agent in the green synthesis of AuNPs. In the second step, the AuNPs and excess caffeine molecules were conjugated with the PLA-PEG-PLA polymer matrix *via* the formation of a synergic π-bond. Because AuNPs are transition metals with a zero-oxidation state, they can easily form π-back

Conclusions

Caffeine has been isolated from coffee bean extract and successfully used as a reducing agent in the green synthesis of AuNPs. Caffeine-AuNPs were attached to a PLA-PEG-PLA amphiphilic copolymer matrix by W/O emulsification and solvent evaporation. UV–vis absorption spectral analysis confirmed the SPR signal of AuNPs at 527 nm. TEM analysis confirmed that the AuNPs were 8–15 nm in diameter and the conjugation of AuNPs on PLA-PEG-PLA nanoconjugates. Powder XRD analysis was used to determine the

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> …Nanohybrid materials, including dendrimers, solid-lipid nanoparticles, nanospheres, polymeric nanoparticles [12], hybrid nanorods [13], and metallic nanoparticles [14–16], have become a rapidly growing area of scientific research and have been used in various applications in engineering, biomedical, and drug delivery systems to overcome these limitations of various drugs [2,17]. Among the broad diversity of metallic nanoparticles, gold nanoparticles (AuNPs) have recently emerged as a promising drug delivery system for the efficient delivery and release of chemotherapeutic drugs in diverse cell types [18,19]. AuNPs have greater advantages than other metallic nanoparticles when used as potential nanocarriers for drug delivery because they contain an inert material, are not cytotoxic, exhibit high biocompatibility, and possess unique physical, chemical, thermal and mechanical properties [20,21]….

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