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Encapsulation of poorly water-soluble drugs into organic nanotubes for improving drug dissolution

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ABSTRACT

Hydrocortisone (HC), a poorly water-soluble drug, was encapsulated within organic nanotubes (ONTs), which were formed via the self-assembly of *N*-{12-[(2-α,β-D-glucopyranosyl) carbamoyl]dodecanyl}-glycylglycylglycine acid. The stability of the ONTs was evaluated in ten organic solvents, of differing polarities, by field emission transmission electron microscopy. The ONTs maintained their stable tubular structure in the highly polar solvents, such as ethanol and acetone. Furthermore, solution-state ^{1}H-NMR spectroscopy confirmed that they were practically insoluble in acetone at 25 °C (0.015 mg/mL). HC-loaded ONTs were prepared by solvent evaporation using acetone. A sample with a 3/7 weight ratio of HC/ONT was analyzed by powder X-ray diffraction, which confirmed the presence of a halo pattern and the absence of any crystalline HC peak. HC peak broadening, observed by solid-state ^{13}C-NMR measurements of the evaporated sample, indicated the presence of HC crystals. These results indicated that HC was successfully encapsulated in ONT as an amorphous state. Improvements of the HC dissolution rate were clearly observed in aqueous media at both pH 1.2 and 6.8, probably due to HC amorphization in the ONTs. Phenytoin, another poorly water-soluble drug, also showed significant dissolution improvement upon ONT encapsulation. Therefore, ONTs can serve as an alternative pharmaceutical excipient to enhance the bioavailability of poorly water-soluble drugs.

1. Introduction

Various pharmaceutical formulations incorporate excipients such as cyclodextrin (Brewster and Loftsson, 2007; Carrier et al., 2007), surfactant (Pongpeerapat et al., 2006; Wanawongthai et al., 2009), and water-soluble polymers (Kojima et al., 2012) to improve the solubility of poorly water-soluble drugs (Yamamoto et al., 2011). Mesoporous materials have also been employed for the preparation of solid dispersions, in which drugs can be distributed into host materials. Zeolite (Braschi et al., 2010), silica xerogel (Braschi et al., 2010), calcium carbonate (Wang et al., 2006), and folded mesoporous porous silica (Nishiwaki et al., 2009) are also known as host materials for small-molecule incorporation owing to their mesoporous structure. Drug incorporation into the pores of the host is typically achieved by evaporation, supercritical fluid, or sealed-heating methods. Drug amorphization by incorporation into mesoporous materials resulted in enhanced dissolution characteristics and improved pharmacokinetics (Wang et al., 2009). However, mesoporous materials, such as those including metallic nuclei like Si and Al, cannot be readily used as pharmaceutical excipients owing to their unfavorable toxicological properties (Di Pasqua et al., 2008).

Organic nanotubes (ONTs) are hollow cylindrical nanomaterials composed of monomeric units containing both hydrophilic and hydrophobic functionalities. The unique structures of these amphiphilic molecules drive their self-assembly in aqueous media (Masuda and Shimizu, 2004; Shimizu et al., 2005). Processes for the large-scale synthesis of amphiphiles from natural materials, such as fatty acids and glucoses, and an efficient method to induce their self-assembly into ONTs were recently disclosed (Asakawa et al., 2008). The resulting ONTs showed no toxicity in acute oral toxicity tests using rat models. Furthermore, biodegradation tests

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using environmental microorganisms revealed negligible influence of ONTs on the environment. As expected, these desirable properties have garnered considerable interest into the design and development of novel ONTs as next-generation biomaterials in various fields, especially in pharmaceutical and medical sciences.

ONTs can encapsulate larger guest molecules than conventional organic host materials such as cyclodextrins can, owing to their much larger pore size (ranging from several nanometers to 100 nm). Encapsulation is typically achieved by the simple incubation of the host and guest materials in aqueous media. Indeed, the encapsulation of proteins (Kameta et al., 2008) and DNA (Ding et al., 2011; Meilander et al., 2003) has been achieved via this method. The process is driven by the combination of capillary action and electrostatic attraction. Ding et al. and Wakasugi et al. recently reported the loading of doxorubicin, an amphipathic anticancer drug, into ONTs (Ding et al., 2012a; Wakasugi et al., 2011). In this study, pH changes were utilized to affect the release of doxorubicin from the ONTs. The frequency of reports describing the loading of water-soluble drugs into ONTs is also increasing. Although the application of ONTs to encase amphipathic and water-soluble substrates is known, an efficient and reliable method for the loading of poorly water-soluble drugs into ONTs has not yet been reported. Drug encapsulation in inorganic porous materials using organic solvents has been rather successful (Nishiwaki et al., 2009); however, it is not universally applicable to ONTs because their structure is not stable in certain organic solvents.

Herein, we report the application of self-assembled ONTs derived from the amphiphilic *N*-{12-[(2-α,β-D-glucopyranosyl) carbamoyl]dodecanyl}-glycylglycylglycine acid (Fig. 1a) for the encapsulation of the hydrophobic drugs, hydrocortisone (HC) and phenytoin (PHE). This amphiphile possesses terminal glucose- and triglycine-headgroups to facilitate self-assembly. The resulting ONTs consist of a single monolayer lined with polyglycine-II-type hydrogen-bond networks among the triglycine moieties (Kameta et al., 2007). Therefore, the ONTs have orthogonal inner and outer surfaces adorned with polar carboxylic acid group and neutral glycosyl moieties, respectively. These ONTs demonstrate favorable dispersion properties in water owing to the presence of a cylindrically arranged monolayer membrane structure with the hydrophilic hydroxyl groups facing the solvent. Various solvents were examined in order to identify solvents in which the tubular structure of the ONTs is maintained. This study identified acetone as the optimal solvent for the encapsulation of poorly water-soluble drugs via solvent evaporation. The encapsulation of HC was confirmed by powder X-ray diffraction (PXRD) and solid-state ^{13}C-NMR spectroscopy. Finally, the dissolution behavior of HC from the ONTs in an aqueous medium, was evaluated.

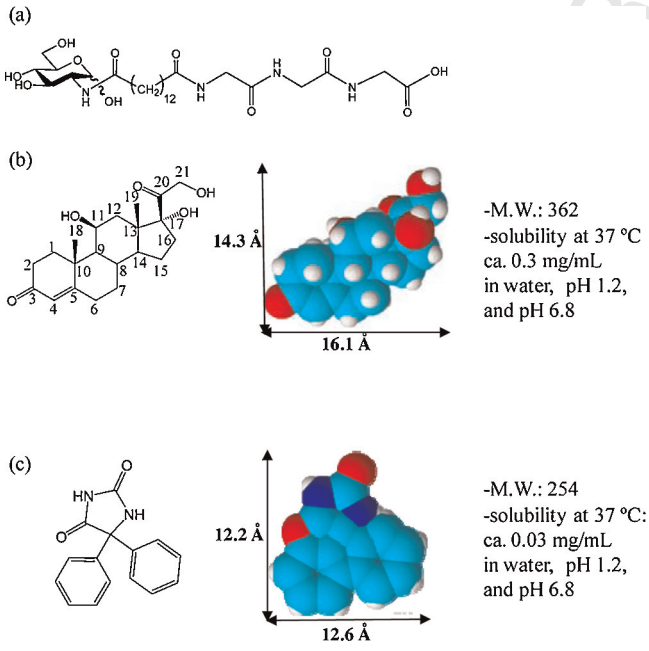

Fig. 1. Molecular structure of (a) *N*-{12-[(2-α,β-D-glucopyranosyl)carbamoyl] dodecanyl}-glycylglycylglycine acid, (b) hydrocortisone (HC), and (c) phenytoin (PHE).

2. Materials and methods

2.1. Materials

The amphiphilic molecule, (*N*-{12-[(2-α,β-D-glucopyranosyl) carbamoyl]dodecanyl}-glycylglycylglycine acid), containing glucose and triglycine groups at both ends, was synthesized as reported by Ding et al. (Ding et al., 2012b). Reagent grade HC and PHE were purchased from Wako Pure Chemical Industries, Ltd. (Kyoto, Japan) and Nacalai Tesque, Inc. (Tokyo, Japan), respectively. The chemical structures of both HC and PHE are shown in Fig. 1.

2.2. ONT assembly

The amphiphile was first pulverized by mortar and pestle. The resulting material was dispersed in distilled water at a concentration of 1.0 mg/mL via sonication. The resulting suspension was then refluxed at 100 °C for 10 min. At this point, the amphiphile was completely dissolved and the solution was homogenous. Next, the ONTs were precipitated by slowly cooling the solution to room

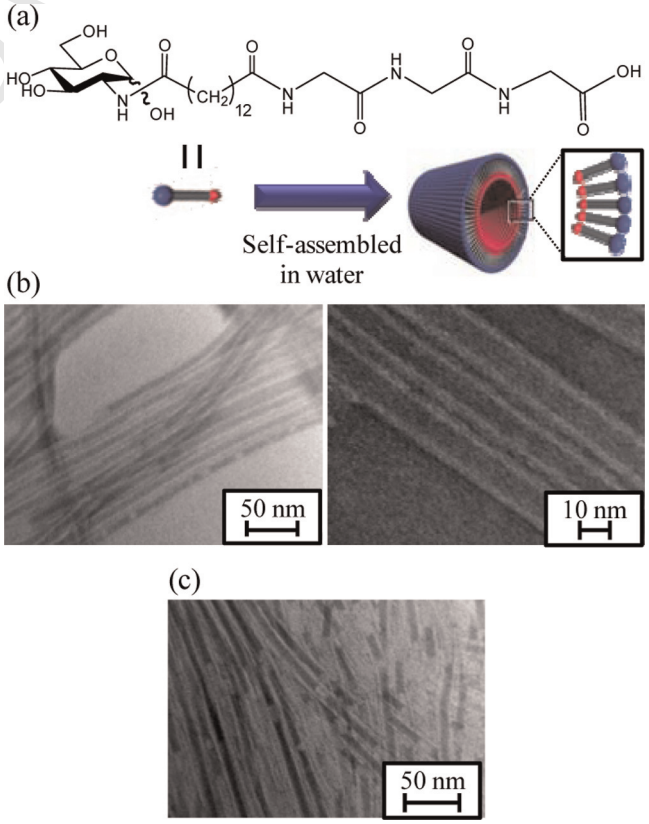

Fig. 2. Organic nanotubes (ONTs). (a) A schematic illustration of the molecular packing of ONTs resulting from the self-assembly of the amphiphile in water. TEM images of ONT (b) negatively stained with phosphotungstate and (c) treated with acetone.

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