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Combination of nanoparticles with photothermal effects and phase-change material enhances the non-invasive transdermal delivery of drugs

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ABSTRACT

We describe a promising non-invasive transdermal delivery system comprising block copolymer composite micelles that contained a phase-change material (PCM), photothermal Au nanoparticles (AuNPs), and hydrophobic drugs in the core. To minimize cell toxicity, we developed block copolymer micelles with a poly(ε-caprolactone) (PCL) biodegradable core and a hyperbranched polyglycol (hbPG) shell. The hbPG block formed micelles at a low-molecular-weight fraction of a low-molecular-weight block copolymer. The composite micelles showed excellent biocompatibility with cell viability at high concentrations. Visible light irradiation (λ = 520 nm) of the composite micelles induced the photothermal effects of the AuNPs and melting of the PCM (lauric acid); hence, the drugs were released along with the PCM liquid. The release rate was controlled by the light intensity. Based on *in vitro* and *in vivo* skin penetration studies, the skin permeability of the drug remarkably improved under mild light irradiation (18 J/cm^2) that was much lower than the dose that causes skin damage.

1. Introduction

A transdermal delivery system for the systemic delivery of drugs is of great interest because it avoids the first-pass effects of the liver that can prematurely metabolize drugs [1,2]. In addition, transdermal delivery is noninvasive and can be self-administered [3]. In this system, the skin, which consists of an epidermal layer called the stratum corneum, is the preferred entry route. The stratum corneum provides a protective barrier against the entry of pathogens [4]. Thus, the stratum corneum also restricts the permeation of therapeutic agents into systemic circulation.

One of the major goals in transdermal delivery is the development of an effective method for the permeation of therapeutic agents into the skin. Various methods have been employed to enhance the skin permeation of drugs. These methods include chemical enhancers [5] or physical approaches, such as iontoporesis [6], microneedles [7], and thermal ablation [8]. Although these methods readily permit the effective delivery of drugs, they are limited in controlling the irritation and damage of the skin [9]. Furthermore, these methods often rely on the use of toxic molecules that are damaging to the protective barrier function of the skin that prevents pathogen entry. Therefore, an appropriate transdermal delivery method that can overcome these limitations is critical for enhancing the therapeutic effects *in vivo* without causing side effects.

Mounting evidence has shown that positively charged nanoparticles serve as a platform vehicle for optimizing the efficacy

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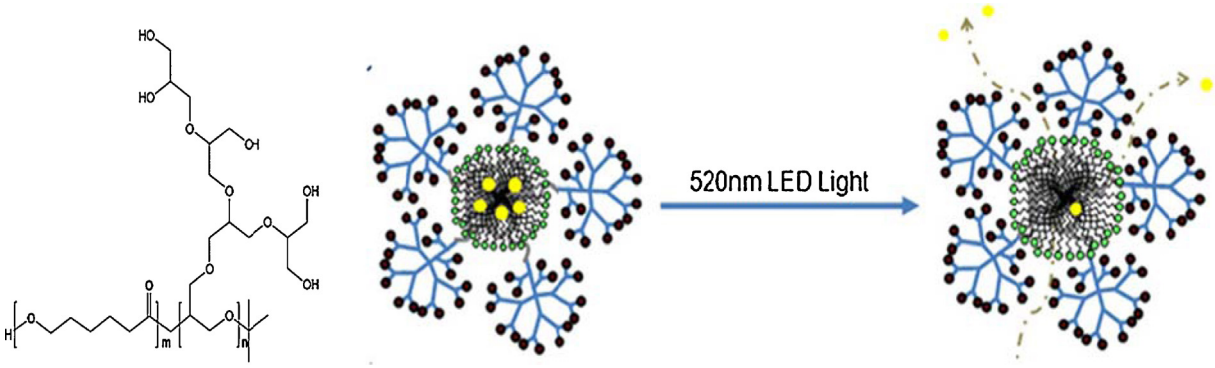

Scheme 1. Molecular structure of poly(ε-caprolactone)-*block*-hyperbranched polyglycerol(PCL-*b*-hbPG) and the schematic illustration of the PCL-*b*-hbPG composite micelle containing the Au nanoparticles (AuNPs), phase changing material (PCM), and indomethacin (IM) as a model drug in the core of the micelle.

of transdermal delivery without side effects [10]. Indeed, various positively charged nanoparticles enhance skin permeation across the stratum corneum [11]. In this strategy, it is critical that the drug carrier is complementary to the biocompatible and biodegradable nanoparticles for effective transdermal delivery. We have already developed biocompatible and biodegradable poly(ε-caprolactone)-*block*-hyperbranched polyglycerol (PCL-*b*-hbPG) micelles for the delivery of hydrophobic drugs [12]. Although considerable improvement has been made in the design and synthesis of micelles, previous studies did not focus on the development of a controllable carrier for transdermal delivery.

Nanoparticles can be functionalized with a specific targeting agent in order to improve the deformability of drugs, which may be a factor that affects skin permeation. Indeed, drugs with high deformability have a significantly higher drug flux than those with low deformability [13]. Therefore, deformable drugs in nanoparticles can overcome the limitations and enhance the strengths of transdermal delivery. Herein, the purpose of this study was to investigate a transdermal delivery system that uses PCL-*b*-hbPG micelles. Therefore, we incorporated hydrophobic drugs together with phase-change material (PCM) in order to enhance drug deformability and Au nanoparticles (AuNPs) for heat generation in the core of the PCL-*b*-hbPG micelles (Scheme 1). The physicochemical properties of micelles containing AuNPs and PCM were examined with a size distribution analysis and transmission electron microscopy (TEM) imaging. The toxicity of the nanocarriers used for the transdermal delivery was measured with a Hen's egg test on the chorioallantoic membrane (HET-CAM) test. In addition, the efficacy of the transdermal delivery was visualized *in vitro* and *in vivo* with a fluorescent imaging system.

2. Experimental procedures

2.1. Materials

PCL-*b*-hbPG (M_w = 5000) was synthesized according to our previous study [12]. The monomer composition of caprolactone and glycerol was 50/50. The AuNPs were synthesized according to a previous study [14]. Indomethacin (99%, IM), lauric acid (98%), toluene (99.8%), oleylamine (98%), hydrogen tetrachloroaurate (99.9%), ethanol (99.8%), nile red (98%, NR) dye, dimethylsulfate (99%, DMSO), sodium lauryl sulfate (99%, SLS), L-α-phosphatidyl choline (99%, PC), cholesterol (99%, Ch) and physiological saline were purchased from Sigma-Aldrich Co. LLC (St. Louis, MO, USA).

2.1.1. Preparation of the PCL-b-hbPG micelles encapsulating IM, PC/Ch/IM liposome, and SLS 1% micelles solubilizing IM

IM (0.1 g) and PCL-*b*-hbPG (1 g) were dissolved in 50 mL of ethanol. The ethanol solution was poured into 100 mL of deionized (DI) water during vigorous mechanical stirring. Then, the ethanol in the mixture was removed on a rotary evaporator. After 1 h at 40 °C, the PCL-*b*-hbPG micelles encapsulating IM were filtered through a polyvinylidene fluoride (PVDF) membrane filter (0.45-μm pores) and washed with fresh water thrice to remove the residual ethanol. To prepare the IM-containing SLS micelles, SLS (1 g) was dissolved in the ethanol solution mentioned above, and the same procedures were applied. To prepare the IM/PC/Ch liposomes, IM (0.1 g), PC (1 g), and Ch (0.25 g) were dissolved in 50 mL of ethanol. The ethanol solution was poured into 100 mL of DI water with vigorous mechanical stirring. To prepare liposome with narrow size distribution, the liposomes were passed through a high-pressure homogenizer thrice at 1000 bars. After 1 h at 40 °C, the PCL-*b*-hbPG micelles encapsulating IM and SLS were filtered through a PVDF membrane filter (0.45-μm pores) and washed with fresh water 3 times to remove the residual ethanol.

2.1.2. Preparation of the PCL-b-hbPG composite micelles encapsulating IM, AuNPs, lauric acid (the PCM), and NR

AuNPs (2 mg), lauric acid (20 mg), IM (0.2 g), and PCL-*b*-hbPG (2 g) were dissolved in 50 mL of ethanol. The ethanol solution was poured into 50 mL of DI water during vigorous mechanical stirring. The ethanol in the mixture solution was then removed on a rotary evaporator. After 1 h at 40 °C, the PCL-*b*-hbPG composite micelles encapsulating IM, AuNPs, and lauric acid (the PCM) were filtered through a PVDF membrane filter (0.45-μm pores) and washed with fresh water 3 times to remove the residual ethanol. To prepare the NR-containing PCL-*b*-hbPG composite micelles, a small amount of NR (1 mg) was dissolved in the ethanol solution mentioned above, and the same procedures were applied.

2.2. Characterization

TEM (JEM-2100, JEOL Ltd., Tokyo, Japan) and atomic force microscopy (AFM, Dimension 3100, Digital Instrument Co., Ltd., Bangkasor, Northaburi, Thailand) studies were performed to investigate the morphology of the AuNPs/PCM/PCL-*b*-hbPG composite micelles. The size of the micelles was measured by dynamic light scattering (DLS, Nano ZS, Malvern Instruments Ltd., Worcestershire, UK). Differential scanning calorimetry (DSC, DSC Q1000, TA Instruments, New Castle, DE, USA) was used to record thermograms of lauric acid (5–10 mg), which was sampled separately in a hermetic pan. The pan was heated from 25 °C to 80 °C with a heating rate of 1 °C/min under a N_2 gas flow (50 mL/min). After the first run, the sample was cooled to 25 °C with a cooling rate of 1 °C/min, and the sample was heated again with a heating rate of 1 °C/min to 80 °C (second scan). In addition, DSC thermograms of the AuNPs/IM/PCM/PCL-*b*-hbPG micelles were recorded after the