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Controlled release of acetylsalicylic acid from polythiophene/carrageenan hydrogel via electrical stimulation

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ABSTRACT

Blends between polythiophene (PTh) and a carrageenan hydrogel were fabricated as the matrix for the electric field assisted drug release. The pristine carrageenan and the blend films were prepared by the solution casting using acetylsalicylic acid (ASA) as the anionic model drug and Mg^{2+}, Ca^{2+}, and Ba^{2+} as the crosslinking agents. The ASA was released by the Fickian diffusion mechanism. The diffusion coefficient decreased with increasing crosslinking ratio or decreasing crosslinking ionic radii. The diffusion coefficients were greater with the applied electrical potentials by an order of magnitude relative to those without electric field. Moreover, the diffusion coefficients with PTh as the drug carrier were higher than those without PTh. Thus, the presence of the conductive polymer in the hydrogel blend coupled with applied electric field is shown here to drastically enhance the drug delivery rate.

1. Introduction

Drug delivery through skin, or the transdermal drug delivery, using systemic blood circulation has no drawbacks of oral route such as first pass metabolism and drug degradation by enzymes or pH. Transdermal drug delivery (TDD) provides controlled drug delivery though the skin. A transdermal patch is a medicament adhesive patch which is placed on the skin to deliver a specific dose of medication through the skin and into the blood circulation (Keleb, Sharma, Mosa, & Aljahwi, 2010; Latheeshjal et al., 2011; Shingade et al., 2012). However, there are many drawbacks of TDD such as unsuitable for hydrophilic drug due to lipophilic nature of skin and molecular drug size (Latheeshjal et al., 2011; Zorec, Preat, Miklavcic, & Pavselj, 2012). Iontophoresis is one method to overcome the limitations of TDD by application of low-level electric current (0.5 mA/cm^2 or less) (Dixit, Bali, Baboota, Ahuja, & Ali, 2007; Zorec et al., 2012). It is used to facilitate the movement of drug ions across the membrane and to enhance the skin permeation and the release rate of drugs which have poor absorption or permeation profile through the skin by electrophoresis force (Dixit et al., 2007).

Hydrogel technologies have stimulated development in controlled drug delivery due to their non-toxicity, biocompatibility, and similarity to biological tissues (Langer & Peppas, 2003; Peppas, Wood, & Blanchette, 2004). Hydrogels are water-swollen polymeric materials possessing three-dimensional network structures which are provided by chemical or physical crosslinks (Kim & Peppas, 2003; Peppas et al., 2004). However, the limitations of controlled release by hydrogels are the slow response which limits their ability to deliver the drugs in required period (Lira & Torresi, 2005). The use of an electric field as an external stimulus is a method that has been successfully employed to enhance the amount of drug release and to allow a precise control of release rate from hydrogels (Chien, Lelawong, Siddiqui, Sun, & Shi, 1990). However, the electronic conductivity of a hydrogel is generally low, the current from an electric stimulus cannot readily transmit throughout the structure. Recently, a conductive polymer combined with a hydrogel has attracted attentions as an electroactive hydrogel which is capable of chemical or physical transformations in response to electrical potential. Therefore, conductive polymer/hydrogel blends have been recently investigated for controlled drug release (Tao, Zhao, & Wu, 2005).

Carrageenan, a family of linear water-soluble sulfated polysaccharides extracted from red seaweeds, has the ability to form hydrogels via physical crosslinks with multivalent cations and is extensively used as a gelling agent in food and pharmaceutical industries. Due to its gelling, viscosity building properties, and proven safety, it has been utilized in sustained-release materials and drug delivery applications (Daniel-da-Silva, Ferreira, Gil, & Trindade, 2011; Gupta, Hariharan, Wheatley, & Price, 2001). Picker (1999a,b) studied the release behavior of theophylline

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from kappa-carrageenan. They reported that the release of theophylline depended on kappa-carrageenan concentration, type, concentration of di-valent cations, and drug types. The single carrageenans have been widely used in drug delivery; for example, kappa-carrageenan (Picker, 1999a,b) and lambda-carrageenan (Hariharan, Wheatley, & Price, 1997) were used for the releases of theophylline (Picker, 1999a,b) and tripelennamine HCl (Hariharan et al., 1997), respectively. Moreover, the carrageenan has been modified to be used use in drug delivery in combinations with chitosan (Piyakulawat, Praphairaksit, Chantarasiri, & Muangsin, 2007), agarose (Sjoberg, Persson, & Caram-Lelham, 1999), locust bean gum (Suzuki & Lim, 1994), gellan gum (Rodriguez-Hernandez, 1999), gelatin (Bonferoni et al., 2004), and HPMC (Bonferoni et al., 1998). Although, the carrageenan has been widely used in drug delivery application, its use in combination with a conductive polymer to enhance the drug delivery rate under electrical field has not been reported. Polythiophene (PTh) is an important class of conjugated polymers due to its high thermal stability, processibility, solubility, and excellent electrical conductivity when in a doped state (Stevenson, Moulton, Innis, & Wallace, 2010). PTh results from the polymerization of thiophene which becomes conducting when electrons are added or removed from the conjugated π-orbitals via doping (Lee, Lee, Jung, & Kim, 2008).

In the work, polythiophene (PTh)/carrageenan as a conductive polymer/hydrogel blend was prepared as the drug carrier/matrix for the electrically controlled drug release of acetylsalicylic, a model drug

The release mechanism was investigated in terms of crosslinking agent type (Mg^{2+}, Ca^{2+}, and Ba^{2+}), crosslinking ratio, and applied electric field at various electrical potentials. The release mechanism and the drug diffusional constants of the pristine carrageenan and PTh/carragenan blends are compared with other biomaterial hydrogels and their conductive polymer blends.

2. Experimental

2.1. Materials

κ-Carrageenan (Thai Food and Chemicals Co., Ltd.) was used as the polymer matrix. Acetylsalicylic acid, ASA, (Sigma Aldrich) was used as the model drug and dopant. Barium chloride, calcium chloride, and magnesium chloride (Ajax chemicals) were used as the crosslinking agents. 2-(N-morpholino) ethanesulfonic acid, MES, (Sigma Aldrich) was used as the buffer solution. Thiophene (Sigma Aldrich) and iron (III) chloride, $FeCl_3$ (Ajax Chemicals) were used as the monomer and the oxidant for the polymerization of polythiophene (PTh), respectively. Methanol (AR grade, RCI Labscan), chloroform (AR grade, RCI Labscan), hydrogen peroxide, H_2O_2 (AR grade, RCI Labscan), and distilled water were used as solvents.

2.2. Preparation of acetylsalicylic acid-loaded carrageenan (ASA-CAR) hydrogels

Carrageenan powder was dissolved in distilled water under stirring at 60 °C to prepare a carrageenan solution at concentration of 1.3% w/v. Then, 2.5 wt% (based on the weight of carrageenan) of acetylsalicylic acid (ASA) was added into the carrageenan solution under a constant stirring. The salt solution ($CaCl_2$, $MgCl_2$, and $BaCl_2$) of a crosslinker was added into the carrageenan solution at various crosslinking ratios (mole ratio of a crosslinker and the ester sulfated group monomer) of 0.4, 0.6, 1.0, 1.4, 2.0, and 3.0. The mixture solution was cast onto a mold (8 cm diameter) at room temperature. The sample thickness obtained was 0.32 mm.

2.3. Synthesis of polythiophene (PTh)

PTh was synthesized via the Fe^{3+}-catalyzed oxidative polymerization according to the method of Sugimoto et al. (1986). Thiophene (1 mol) was dispersed into chloroform (50 mL) at constant stirring for 45 min. $FeCl_3$ (5 mol) in 30 mL chloroform was added to the monomeric solution. The polymerization was allowed to proceed for 24 h with stirring at room temperature. The collected sample was washed with methanol in order to remove the excess $FeCl_3$ and then, the sample was dried at 80 °C for 24 h.

2.4. Preparation of acetylsalicylic acid-doped polythiophene (ASA-doped PTh)

The ASA-doped PTh was prepared by the acid-assisted redox doping reaction according to the method of Sanden (1997). 1 g of PTh was stirred with 100 mL of ASA solution and 50 mL H_2O_2 for 24 h. ASA-doped PTh particles were filtered and vacuum dried for 24 h.

2.5. Preparation of acetylsalicylic acid-doped polythiophene/carrageenan (ASA-PTh/CAR) blend films

The ASA-doped PTh (0.1 g) was dispersed into the carrageenan solution (1.3%w/v), and the mixture was stirred for 30 min at 30 °C. The mixture was then cast on the mold (8 cm diameter) and dried at 30 °C. The sample thickness obtained was 0.32 mm.

2.6. Polythiophene characterizations

The FTIR spectrometer (Thermo Nicolet, Nexus 670) was used to identify the functional groups of the synthesized PTh and doped PTh using KBr as a background material. The ATR-FTIR spectrometer was used to investigate interactions between the drug and the matrices of the drug-loaded carrageenan and drug-PTh loaded carrageenan hydrogel; the interaction was observed and identified from the shifts in the functional groups. The FTIR was carried out in the transmission mode with 64 scans between 4000 and 400 cm^{-1} at a resolution of 4 cm^{-1}.

2.7. Carrageenan hydrogel characterizations

The morphology of the carrageenan hydrogels was examined using a scanning electron microscope (SEM, Hitachi, S4800). After the hydrogel was immersed in distilled water at 37 °C for 3 days, it was rapidly frozen in liquid nitrogen at −40 °C for 24 h, and lyophilized at −50 °C for 24 h in a freeze-dryer (LABCONCO, Freezone 2.5). The sample was scanned at a 120× magnification.

The carrageenan hydrogel swelling was investigated to determine the degree of swelling in the MES buffer solution at 37 °C for 2 days, using Eq. (1) (Peppas & Wright, 1998).

$$\text{Degree of swelling } (\%) = \frac{M - M_d}{M_d} \times 100 \quad (1)$$

where M is the weight of the sample after immersing in the buffer solution, M_d is the weight of the sample after immersing in the buffer solution in its dry state, and M is the initial weight of the sample in its dry state.

In order to correlate the release behavior of the loaded drug to the physical characteristics of the carrageenan hydrogels, experiments were carried out to determine the molecular weight between crosslinks, $\bar{M}_c$, and the mesh size, ξ. A sample of the carrageenan hydrogel was cut (area of 4 cm^2 and thickness of 0.32 mm), then immediately placed in distilled water at 37 °C. For 5 days, it was allowed to swell to equilibrium, and then weighed in air and heptane. Finally, the sample was dried at 25 °C in a vacuum oven for 5