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Nanostructured biocompatible thermal/electrical stimuli-responsive biopolymer-doped polypyrrole for controlled release of chlorpromazine: Kinetics studies

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ABSTRACT

Biocompatible nanostructured conductive heparin-doped polypyrrole film was fabricated and employed as a high-capacity cation exchanger for programmable release of neuroleptic drug, chlorpromazine (CPZ) with thermally and electrical dual-stimulation. Releasing behavior were studied at different applied potentials and temperatures by in-situ monitoring of UV absorbance measurements. Three mathematical models (Higuchi, Power, and Avrami equation) were employed to investigate kinetics of the release. Based on the obtained results, the Avrami model found to be more comprehensive than two other ones for mathematical description of electro-stimulated release of CPZ. A quantitative relationship between activation energy parameters (E_a, $\Delta G^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$) and release conditions (applied potential and temperature) has been developed and established to predict release rate constants at various applied conditions.

1. Introduction

Controlled delivery of drugs and stimulated release from polymeric systems at a specific site have attracted increasing attention for drug administration in treatment of many diseases in the past few years, due its advantages in enhancing effectiveness of drugs and preventing systemic toxicity (Langer, 1990). A wide range of drug delivery formulations have been prepared (Amidi et al., 2008), with some structures capable of triggering release in response to discrete thermal transitions (Lu et al., 2013), pH (Poon et al., 2011; Yang et al., 2012), light (Han et al., 2013), magnetic (Hu et al., 2008), and electric field (Ge et al., 2012; Zhu et al., 2010). However, precisely controlled drug release from the thin films under mild conditions is still a challenge. A stimulus to control release of therapeutic drugs based on electrical potential could offer unique advantages, because it can easily be controlled by the nature of the stimulation conditions (the current/potential magnitude and frequency) with precise, local, continuous, and reversible features (Graf et al., 2011; Sun et al., 2013). Among the polymers, inherently conducting polymers (ICPs) have electrical and optical properties usually associated with metals, whilst retaining the advantageous mechanical properties and ease of processing at various chemical and electrochemical conditions associated with polymers (Shamaeli and Alizadeh, 2012; Wallace et al., 2009; Manbohi et al., 2014). These smart materials are of considerable interest for a variety of biomedical applications (Guimard et al., 2007; Smela, 2003) including neural interfaces (Abidian et al., 2010; Abidian et al., 2009; Abidian and Martin, 2009; Ludwig et al., 2006), bioelectronics (Berggren and Ritcher, 2007) tissue engineering (Abidian et al., 2012), and drug delivery (Abidian et al., 2006; Pernaut and Reynolds, 2000). Electrochemically controlled drug release based on ICPs are among the most interesting drug delivery systems, as drug incorporated conducting polymers can be easily synthesized on conductive substrates to form different shapes and patterns, and the release can be precisely controlled by applying electrical current or potential stimuli for reversible polymer redox reaction (Svirskis et al., 2010). It has been developed and reported many conducting polymer films in which drugs can be loaded and released in response to electrical stimulus in the past decades (Alizadeh and Shamaeli, 2014; Esrafilzadeh et al., 2013; Li et al., 2012; Miller and Zhou, 1987; Richardson et al., 2009; Shamaeli and Alizadeh, 2013; Svirskis et al., 2010; Wang et al., 2004). The ability to fabricate materials with well-controlled structures on the nanometer length scale is of great interest for controlled drug delivery (Abidian et al., 2006; Gref et al., 1994) and biomedical

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devices (Parthasarathy and Martin, 1994). Previously, a novel technique for encapsulation of drugs into conducting PEDOT nanotubes with well-controlled structures have been developed for electro-stimulated release in a desired precisely controlled way (Abidian et al., 2006). This method can be generally employed for creating low impedance, biologically active polymer coatings, which will facilitate integration of electronically active devices with living tissues. Moreover, these structures can be potentially used in biomedical applications including highly localized stimulation of neurite outgrowth and guidance for neural tissue regeneration, and spatially and temporally controlled drug delivery for ablation of specific cell populations. Drugs and functional molecules could also be loaded into the electrically erodible polymer gel (Kwon et al., 1991) or hydrogels (Ding et al., 2013; Indermun et al., 2014; Niamlang and Sirivat, 2009). The release of drugs can be thus controlled through deswelling or erosion of the gel based on an electrochemical treatment. However, a relatively high voltage and a long-time electrical potential treatment as well as gel fatigue generally limit their applications. Polypyrrole (PPy) is one of the most widely investigated ICPs due to its high conductivity and environmental friendly property and in particular has been shown to be biocompatible and has been proposed for several in vivo applications (Richardson et al., 2009; Wang et al., 2004). During polymerization of PPy, anionic drugs are incorporated in to the polymer to balance out positive charges caused by oxidation. PPy also can be used as a conducting molecularly imprinted polymer (CMIP) for recognative and selective electrochemically loading and release of drugs by the advantage of increased controlling possibility (Shamaeli and Alizadeh, 2013). Incorporation of cationic drugs into conducting polymers has also been reported. PPy films were prepared with large immobilized anions, such as polystyrene sulfonate (PSS) for release of drug cations though electrostatic forces (Miller and Zhou, 1987). It was first reported by Miller and Zhou when PSS used as the primary immobilized dopant to prepare *N*-methylpolypyrrole (Miller and Zhou, 1987). ICP films prepared with various immobilized anions to show different applications as cation binders.

In order to describe kinetics of controlled release from polymer networks, several mathematical models have commonly been applied (Dash et al., 2010; Siepmanna and Peppas, 2001). Controlled release is mainly described by zero-order and first-order kinetics (Lakkis, 2007). The former expresses as extended release and the latter exhibits an immediate mode (Kytariolos et al., 2010). The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Higuchi (Higuchi, 1963). Initially conceived for planar systems, it was then extended to different geometrics and porous systems (Grassi and Grassi, 2005). This model is based on the hypotheses that (a) initial drug concentration in the matrix is much higher than drug solubility; (b) drug diffusion takes place only in one dimension (edge effect must be negligible); (c) drug particles are much smaller than system thickness; (d) matrix swelling and dissolution are negligible; (e) drug diffusivity is constant; and (f) perfect sink conditions are always attained in the release environment. Accordingly, this model commonly can be used in initial times of release that these conditions exist. Simplified Higuchi model is given by the Eq. (1):

$$\frac{M_t}{M_\infty} = k_H \times t^{1/2} \tag{1}$$

where M_t/M_∞ is the amount of cumulative fraction drug released in time t per unit area A and k_H is the Higuchi rate constant (Arhewoh and Okhamafe, 2004). The data obtained were plotted as cumulative percentage drug release vs. square root of time (Bravo et al., 2002). This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs (Grassi and Grassi, 2005; Arhewoh and Okhamafe, 2004). Another model, there is the semi-empirical one proposed by Korsmeyer that derived a simple relationship (Korsmeyer–Peppas model) which described drug release from a polymeric system. In order to find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer–Peppas model. It is known commonly as Power model (Korsmeyer et al., 1983; Shoaib et al., 2006). It is simply expressed as Eq. (2):

$$\frac{M_t}{M_\infty} = k_p t^{n_p} \tag{2}$$

where M_t/M_∞ is a fraction of drug released at time t, k_p is the Power release rate constant and n_p is the Power release exponent. In this model, the value of n characterizes the release mechanism of drug. To find out the exponent of n, the portion of the release curve where $M_t/M_\infty < 0.6$ should only be used. In order to study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release vs. log time. Release has a diffusion mechanism if $n = 0.5$ and is a zero-order release model if $n = 1$ (Crank, 1975; Hutchison et al., 2000). Avrami's equation is another mathematic model originally used to describe the crystallization mechanism (Avrami, 1940; Lorenzo et al., 2007). It has also been used extensively for description kinetic of encapsulation, and ion exchange release recently (Gao et al., 2013; Machingauta and Hossenlopp 2013; Majoni and Hossenlopp, 2010; Shamaeli and Alizadeh, 2013; Stojakovic et al., 2012). A simple expression of Avrami's equation is described in Eq. (3):

$$\frac{M_t}{M_\infty} = 1 - \exp(-k_A t^{n_A}) \tag{3}$$

where M_t/M_∞ is the fraction of active released at time t, n_A is the Avrami parameter and k is the Avrami release rate constant. Both k_A and n_A express the magnitude of release and are empirically determined. $n = 1$ represents first-order and $n = 0.54$ corresponds to diffusive release kinetics (Lorenzo et al., 2007).

In the present work, we report successful synthesis of a novel nanostructured chlorpromazine (CPZ)-incorporated, heparin (Hep)-doped polypyrrole (PPy–Hep–CPZ) for electrochemically and thermally dual-stimulated release of CPZ (Scheme 1). CPZ, known as an antipsychotic drug, is a major tranquilizer for patients suffering from schizophrenia and other psychoses, particularly during behavioral disturbances (Pickholz et al., 2007). It controls excitement, agitation, and other psychomotor disturbances and reduces the manic phase of manic-depressive conditions. Hep, a bioactive sulphated polyelectrolyte, has been utilized as the biopolymer doping anion (Scheme 1) due to biocompatibility and polyanionic nature; also it can interact with CPZ as cation exchanger. Immobilized Hep within the PPy and on redox switching is unable to exchange out from the polymer due to its bulky and multicharged structure while more mobile cation, CPZ, can move into the polymer and maintain the charges balance. The release kinetics of CPZ from the electrosynthesized PPy–Hep–CPZ have been studied and the relationship of activation parameters with applied potentials have been investigated. Three mathematical models including Higuchi, Power, and Avrami's equations were also employed to analyze the release kinetics and activation energy parameters and their results were compared. A quantitative relationship between activation energy parameters (E_a, $\Delta G^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$) and release conditions (applied potential and temperature) has been proposed and established to predict the drug release. Finally, the relationship was used to derive an equation for expecting the release rate constants.