Electrochimica Acta 130 (2014) 488–496

Contents lists available at ScienceDirect

Electrochimica Acta

journal homepage: www.elsevier.com/locate/electacta

Electrochemically controlled release of anticancer drug methotrexate using nanostructured polypyrrole modified with cetylpyridinium: Release kinetics investigation

Naader Alizadeh*, Ehsan Shamaeli

Department of Chemistry, Faculty of Sciences, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran

ARTICLE INFO

Article history:
Received 7 January 2014
Received in revised form 11 March 2014
Accepted 12 March 2014
Available online 24 March 2014

Keywords:
Drug delivery
Methotrexate
Electrochemically controlled release
Release kinetics
Conducting polymer

ABSTRACT

A new simple strategy for direct electrochemical incorporation of chemotherapeutic methotrexate (MTX) into conductive polypyrrole (PPy) has been suggested for an electrochemically controlled loading and release system. Electropolymerization of MTX doped polypyrrole yielded poor quality with low efficiency of doping, but a well-doped, nanostructure and increased capacity of drug loading (24.5 mg g^{-1}) has been obtained in the presence of cetylpyridinium (CP) as a modifier. When CP was preloaded onto PPy, the hydrophobic surface of the PPy serves as a backbone to which the hydrophobic chain of the CP can be attached. Electrostatic interaction between cationic CP with anionic MTX and aromatic interaction between pyridinium head of CP with pyrimidine and pyrazine rings of MTX increases drug doping. Then release kinetics were investigated at various applied potentials and temperatures. Kinetics analysis based on Avrami's equation showed that the drug release was controlled and accelerated by increasing temperature and negative potential and sustained by increasing positive potential. At open circuit condition, the release parameter (n) represented a diffusive mechanism and at applying electrochemical potentials, a first-order mode. Activation energy parameters (E_a, $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$) and half-life time ($t_{1/2}$) of drug release are also analyzed as a function of applied potential. The nanostructured polymer films (PPy/CP/MTX) were characterized by several techniques: scanning electron microscopy, Furrier transforms Infrared, UV-vis spectroscopy. Overall, our results demonstrate that the PPy/CP/MTX films, combined with electrical stimulation, permit a programmable release of MTX by altering the interaction strength between the PPy/CP and MTX.

1. Introduction

Chemotherapy is associated with unpleasant side effects many chemotherapeutic drugs are, in themselves, carcinogenic; treatment with these drugs carries a risk of secondary cancer. Many cancer researchers today are therefore committed to producing a new generation of more specific, better-targeted cancer therapies, to improve the quality of life of cancer patients and to minimize the risks of their treatment. There has been considerable interest in drug delivery for enhancing therapeutic efficacy and minimizing systemic side effects [1]. To avoid severe adverse effects, the drug molecules are expected to specifically kill the tumor cells, with only little or no adverse effect on normal tissues or cells. In this study we have focused on methotrexate (MTX, Scheme 1), one of the most studied antitumor chemotherapeutic drugs [2]. It has been widely used since 1948 as an antineoplastic, anti-metabolite drug in cancer and psoriasis treatment. MTX acts as an antagonist of folic acid, which is necessary for DNA synthesis, and has a therapeutic effect on many types of cancer cells that overexpress folate receptors on their surfaces [3]. It is currently widely used as a major chemotherapeutic agent for human malignancies such as acute lymphoblastic leukemia, malignant lymphoma, osteosarcoma, breast cancer and head and neck cancer [4]. Despite its efficacy, the use of MTX is greatly limited due to its toxicity, the systemic use of this drug may provoke any of numerous side effects, including nausea, vomiting, fatigue, headache, dyspnea, leukopenia, thrombocytopenia, anemia, and hepatic toxicity [5].

Today, a wide range of drug delivery formulations such as polymeric implants and microparticles are prepared [6–8], with some structures capable of triggering release in response to discrete thermal transitions [9,10], pH [11,12] or electrical stimuli [13]. Among these polymers, inherently conducting polymers (ICPs)

* Corresponding author. Fax: +98 21 82883455.
E-mail address: alizaden@modares.ac.ir (N. Alizadeh).

http://dx.doi.org/10.1016/j.electacta.2014.03.055
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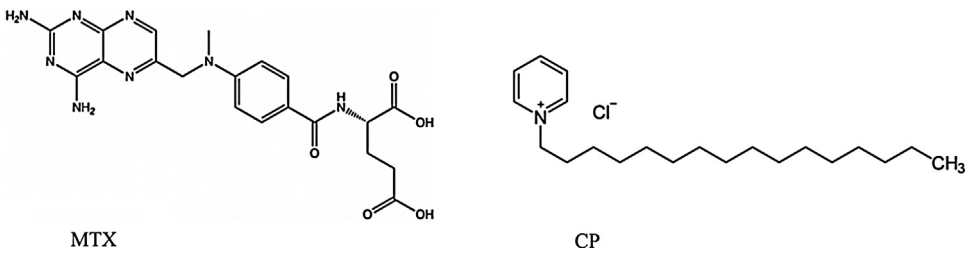

Scheme 1. The chemical structures of MTX and CP molecules.

have electrical, magnetic 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 [13]. ICPs can be used as versatile molecular recognition systems for various doping anions by doping–dedoping process [14,15]. Electrochemically controlled drug release based on ICPs are among the most interesting drug delivery systems, as drugs 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 [16]. The polymer redox reaction involves charging and discharging of the polymer and is also accompanied by the movement of hydrated ions in and out of the bulk. Utilizing this feature, many conductive polymer films have been developed and reported in which drugs can be loaded and released in response to electrical stimulus since the 1980s [16–34]. Electrically stimulated drug delivery systems have the advantage of tuning the release profile by the nature of the stimulation conditions (the current/potential magnitude and frequency) employed [19] consequently, electrical stimulation to effect localized and controlled release of therapeutic drugs is becoming an attractive option in the treatment of acute disease or chronic illness [22]. Polypyrrole (PPy) is one of the most widely investigated ICPs due to its high conductivity and environmentally friendly properties and in particular has been shown to be biocompatible and has been proposed for several in vivo applications [24,28,30]. Recently, dexamethasone (an anti-inflammatory drug), penicillin and streptomycin (antibiotics) and ciprofloxacin have been incorporated into polypyrrole (PPy) [19,20,28] whilst dexamethasone has also been incorporated into poly(3,4-ethylenedioxythiophene) (PEDOT) and released using electrical stimulation [23]. Also the intercalation of positively charged drugs into polypyrrole films and their release have previously been studied using the electrochemical quartz crystal nanobalance enabling direct monitoring of the species ingress/egress [33,34].

Kinetically, release of guests in pharmaceutical has been studied extensively; mechanisms and methods for controlled release are reviewed [35]. Controlled release is mainly described by zero-order and first-order kinetics [36]. The former expresses as extended release and the latter exhibits an immediate mode [37]. Various mathematical models have been commonly applied to describe kinetics of controlled release. The Power Law is a release kinetics model commonly used in pharmaceutical research [38]. It is simply expressed as Eq. (1):

$$X = kt^n \tag{1}$$

where, k is the release rate constant and n is the diffusive release mechanism parameter; X is the release fraction of accumulated active at time t.

Release has a diffusion mechanism if n = 0.5. The Power Law is a zero-order release model if n = 1 [39]. Avrami's equation is another mathematic model that originally used to describe the crystallization mechanism [40]. It has also been used extensively for release kinetics description.[27,41–46] A simple expression of Avrami's equation is described in Eq. (2) [47]:

$$X = 1 - \exp(-kt^n) \tag{2}$$

where, X is the fraction of active species released at time t, n is the Avrami parameter or release mechanism and k is the release rate constant. Both k and n express the magnitude of release are empirically determined [37]. $n = 1$ represents first-order kinetics and $n = 0.54$ corresponds to diffusive release [48]. Half-life ($t_{½}$) release that indicates the time it takes for 50% of the accumulated actives to release, if X value is 0.5, $t_{1/2}$ can be calculated by Eq. (3).

$$t_{1/2} = \exp(-(\ln k + \ln(0.5))/n) \tag{3}$$

Based on the Taylor expansion Eq. (2), for X tends to zero (when $t \to 0$, $k \to 0$ and/or $n \to 0$), 1-exp(-kt^n) tends towards kt^n. It means that, fractions of released drug calculated by using Avrami and Power equations are the same values at the first times of release (limit of this time is dependent to magnitude of rate constants and/or n values). When time and/or k tend to infinite it is expected that X tends towards 1 that is obtained by Avrami equation whereas for Power equation X tends towards infinite that is not reliable. So at long times, the semi-empirical Avrami model gave better fitting data (k or n) for release studies than the Power model. In other words, rate constant and n, Avrami equation tends to Power equation at lower times. So considering these two models for release characteristics, we proposed that at low temperatures and OCP condition, release data can be fitting well with both of these models for first times of release. At higher applied potential and temperature Avrami model gave a better fitting than the Power model at long times (when X tends to 1). Therefore, we used Avrami as a more comprehensive prediction model.

In the present study, we proposed a novel strategy for the electropolymerization of MTX-doped conductive PPy film that has been suggested for a variety of applications, especially for an electrochemically controlled release system. Electropolymerization of MTX doped polypyrrole yielded poor quality with low efficiency of drug doping, but a well-doped, nanostructure and increased capacity of drug loading has been obtained in the presence of cetylpyridinium (CP), as a cationic surfactant, in solution. CP is used in some types of mouth washes, toothpastes, lozenges, throat sprays, breath sprays, and nasal sprays. It has been shown to be effective in preventing dental plaque and reducing gingivitis [49]. Its safety and efficacy have been evaluated extensively and proven based on cytotoxicity data collected from many animal studies [50–53]. With intravenous infusion as the delivery mechanism, the LD_{50} of cetylpyridinium chloride has been measured at 36 mg/kg in rabbits [54]. These findings warrant further investigation of clinical performance, safety, and possible clinical applications [52]. Besides its common use as antimicrobial preservative in various pharmaceutical formulations, cationic surfactants have also been employed as solubilizer in drug formulations [55,56] and drug release testing [57–60], dissolution rate controlling agents [61]. CP as a cationic surfactant, in which is composed of a hydrophilic positively charged pyridinium head group and a hydrophobic tail act as a modifier that