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Research paper

Effect of coatings and surface modification on porous silicon nanoparticles for delivery of the anticancer drug tamoxifen

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ABSTRACT

Breast cancer is the most common cancer among women and the cancer that causes the most deaths after lung cancer. Tamoxifen has long been used for the treatment of breast cancer in different stages of the disease; however it presents several side effects. The use of delivery systems has been proposed to minimize its side effects, especially hepatotoxicity, and to improve its bioavailability, hence optimizing Tamoxifen therapy. Porous silicon (pSi) nanoparticles present excellent properties for applications in biomedical devices. In this study pSi nanoparticles were fabricated by electrochemical etching of n-type single crystalline Si wafers in order to be used as a carrier for the anticancer drug Tamoxifen. pSi surface was modified by thermal hydrosilylation with undecylenic acid and via coatings such as chitosan, silica-xerogel and a hybrid of these two. The effect of pSi surface modification on the release profile of the drug has been investigated. Tamoxifen completely released within 6 h when loaded into fresh pSi. When the bioactive polymer chitosan was used as a coating the drug release profile was observed to decrease by ~30%. However, silica xerogel coating appeared to have no effect on the release profile. In contrast, when using a mix of chitosan and silica xerogel as a coating the drug release was prolonged from 6 h to a week. In the case of the chemically modified pSi nanoparticles the drug release was prolonged to weeks with minimal to no burst effect. Hence, hydrosilylated pSi nanoparticles have the potential to be used as excellent Tamoxifen controlled release carriers for biomedical application in cancer therapies.

1. Introduction

Tamoxifen ((*Z*)-2-[*p*-(1,2-diphenyl-butenyl) phenoxy]-*N*,*N*-dimethyletylamine) is a class of non-steroidal triphenylethylene used for >20 years as the clinical choice for the antiestrogen treatment of breast cancer. Tamoxifen (TMX) is prescribed during the different stages of the disease, including as a support drug for the recurrence of the cancer, for the prevention in healthy women at high-risk or for early stages of the cancer [1,2] However, TMX presents a few side effects such as thromboembolic events and endometrial cancer due to its proliferative effect on the endometrium. Overall, endometrial pathologies include hyperplasia, polyps, carcinoma and sarcoma [3,4]. Other side effects were reported to be dose dependent including liver cancer, increased blood clotting and ocular side effects, such as retinopathy and corneal opacities [5]. The need to minimize the side effects of TMX has led to its formulation in micro or nanoparticles to increase the oral bioavailability and to deliver the required dose to the tumor location for a longer period.

Several new technologies in clinical development have been used in an attempt to decrease the side effects of TMX and to improve its bioavailability, since due to its administration as a tablet it presents poor solubility. Some researchers have investigated the delivery of TMX loaded in different nanoparticles such as poly (ε-caprolactone) nanoparticles [6], magnetic/poly(L-lactic acid) composite [7], solid lipid nanoparticles [8] and cross-linked with alginate microparticles [9], as well as encapsulated in gelatin and acacia gum microcapsules [10] or in polymeric poly (ε-caprolactone) [11]. Various TMX-carrier systems have been investigated in breast cancer cell lines. TMX-loaded poly (lactic-*co*-glycolic) acid (PLGA) nanoparticles were found to be stable in various simulated media and showed relatively lower cell viability in C127I cells compared to free TMX treated cells. Since TMX-PLGA nanoparticles showed an increased oral bioavailability with reduced hepatotoxicity, they were suggested as a potential oral administration therapy to treat chronic breast cancer [12]. Other preparations efficacy was investigated in human breast cancer cell lines (MCF-7). For example, one consists of a TMX-loaded mixture of two polymers, poly(D,L-lactide-*co*-caprolactone) (PLC) copolymers and poly(D,L-lactide) (PCL) [13] and another was TMX-loaded thiolated alginate-albumin

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nanoparticles [14]. In a recent publication TMX and folic acid were loaded in synthesized PEGylated magnetic nanoparticles and these were used in MCF-7 cell line. Results showed these to selectively target the folate receptors of positive cancer cells [15]. Nevertheless, most of these drug delivery systems present some disadvantages, including poor chemical stability and rapid elimination.

pSi nanoparticles are bound to be a successful device due to their biocompatibility, stability, availability, low cost, small size and the ability to degrade completely in physiological fluids into nontoxic orthosilicic acid ($Si(OH)_4$), which is the natural form of Si found in the body [16]. pSi nanoparticles are already approved for different biomedical applications due to their high specific surface area (200–800 m^2/g), luminescence properties at room temperature, tunable pore size, and porosity [17]. pSi has been applied in different field such as chemical sensors and biosensors, radiotherapy, gas separation, tissue engineering, cell culture and as a potential application for drug delivery [18]. With a mean particle diameter of about 10 to 100 nm they are commonly called silicon nanoparticles (micro, *meso*, and macro) [18]. pSi's unique features allow for different biomolecules to be loaded including drugs. pSi has been used as a drug carrier and investigated in vitro for the loading and release of anticancer drugs such as doxorubicin [19], mitoxantrone dihydrochloride [20], dexamethasone [21], common oral drugs like ibuprofen, antipyrine, griseofulvin, furosemidea, ranitidine [22], and vitamins such as folic acid [18]. On the other hand, little work has been done in vivo with pSi as delivery device. Kilpeläinen et al. used thermally hydrocarbonized mesoporous silicon microparticles as a peptide delivery system in vivo in mice and rat models [23].

One major obstacle for the use of nanoparticles in vivo is the rapid clearance from the body. Therefore, there is an imperative demand for engineering new targeting nanodelivery systems possessing improved stability in human plasma and capable of efficiently and safely delivering therapeutic agents to the targeted tumor tissues [24,25]. To achieve efficient in vivo targeting of cells with high specificity, it is ideal for particles to exhibit blood circulation times of at least 12 h [26]. Park et. al (2009) reported the fabrication of porous silicon nanoparticles with a half-life (i.e., the time it takes for dissolved silicon content to reach 50% of the initial content) of approximately 10 min, which is too short for in vivo usages [27]. Different methods have been proposed to increase the half-life. Thermal oxidization and thermal hydrocarbonization are the two most conventional physical approaches that have been applied to improve pSi stability.

pSi degradation in physiological fluids is associated with the erosion of the pores and its porosity. Then, biodegradation can be controlled through the fabrication of the material. Surface modification has been extensively studied since it plays an important role during degradation of pSi in vivo and in vitro. Hence, different methods have been used to increase pSi stability following electrochemical etching. These consist of modification by oxidation, hydrosilylation and grafting, which improve the ability of pSi as a controlled and localized drug delivery as reviewed extensively by Anglin et al. [17,18]. Drug release can be further controlled with the use of coating materials such as chitosan and silica xerogel. These offer a flexible and biocompatible platform for designing coatings that protect surfaces from infection [28]. Chitosan performance as a biocompatible, bioabsorbent, biodegradable and non-toxic material with immunological activity (due to a large number of amine groups) has been reported to enhance the absorption efficiency [29,30]. Silica xerogel has been used as a coating material for metallic implants such as titanium [31,32]. Meanwhile, silica xerogel biocompatibility, non-toxicity and degradability have led to the exploration of this material as a carrier for controlled drug delivery in in vivo and in vitro studies [33,34].

In this work, we have studied the effect of surface coatings and surface modification of pSi nanoparticles on the drug release. TMX was chosen as a drug model due to its relatively poor aqueous solubility. Hence, pSi nanoparticles were used as the drug delivery candidate.

2. Materials and methods

All chemicals such as hydrofluoric acid 49%, ethanol alcohol (99.8%), ammonium hydroxide 28%, undecylenic acid (≥95%), hydrochloric acid (AR, 35–37%), hydrogen peroxide (30 wt% in H_2O), sodium hydroxide, acetic acid (≥99.7%), chitosan (low molecular weight), tetraethylorthosilicate (TEOS ≥99.0%) and phosphate buffer saline (PBS, pH = 7.4) were purchased from Sigma Aldrich (Malaysia). The n-type Si wafers were purchased from Siltronix SAS (Archamps, France) and the anticancer drug TMX from DNA Bioscience Malaysia.

2.1. Preparation and characterization of pSi nanoparticles

pSi samples were fabricated from (n-type) silicon wafers with a resistivity of 0.008–0.018 Ω cm, orientation (100) and a thickness of 500 ± 25 μm. The silicon wafers were first cleaned by a standard cleaning procedure to eliminate organic, ionic and heavy metal contamination and to remove the protective thin oxide layer. Electrochemical etching of the silicon wafers was carried out in a Teflon cell containing an electrolyte solution of (1:4) hydrofluoric acid 49% and ethanol (99.8%). A current density of 20 mA/cm^2 was applied for 30 min and following the etching procedure the porous layer was separated from the substrate by increasing the current density to 250 mA/cm^2. This pSi film was placed in an ultrasonic bath containing ethanol, sonicated for 10 min and converted into microparticles. pSi films before and after modification and loading with TMX were characterized by Field Emission Scanning Electron Microscopy (FE-SEM), Energy Dispersive Spectroscopy (EDX) and Field Transmission Infrared (FTIR) spectroscopy to determine the morphology, element analysis and chemical bonds, respectively. Nitrogen adsorption-desorption isotherm measurements were carried out to determine the specific surface area of the pSi nanoparticles. Prior to the adsorption experiment, the samples were degassed in situ at 130 °C for 1 h. The specific surface area was determined using the Brunauer-Emmett-Teller (BET) model. X-ray diffraction analysis (XRD) and UV-spectrometer were used to monitor TMX release.

2.2. Loading TMX in pSi nanoparticles

The drug loading solution consisted of 2.69×10^{-2} M TMX in ethanol. The particles were soaked in drug solution for 3 h and constantly stirred to allow homogeneity. The solvent was allowed to evaporate and the particles were briefly washed with ethanol to remove any excess drug remaining on the surface that had not infiltrated the pores. The drug loading efficacy was calculated as per equation below (Eq. (1)).

$$\text{DRUG LOADING}(\%) = \frac{\text{WT TMX} - \text{pSi}}{\text{WT pSi}} \times 100 \quad (1)$$

where,

WT TMX-pSi weight of TMX-loaded pSi
WT pSi weight of pSi only

2.3. Hydrosilylation of pSi nanoparticles

Following the etching procedure the pSi nanoparticles are typically unstable in aqueous solution, a fact attributable to the oxidation of the reactive surface hydrides. Hence, hydrosilylation was used to enhance their stability. The freshly prepared pSi nanoparticles were then placed in a 10 ml Pyrex beaker and 1 ml of undecylenic acid (≥95%) was added. This solution was heated in a commercial consumer microwave oven at full power (800 watts) during 5 min and the particles were then rinsed with ethanol to remove any excess undecylenic acid [35].