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Correlation between physicochemical properties of doxorubicin-loaded silica/polydimethylsiloxane xerogel and in vitro release of drug

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Abstract

The aim of this study was to prepare organically modified silica xerogels by a two-step acid/base catalyzed sol–gel process that would provide a slow release of an anticancer drug – doxorubicin hydrochloride (DOX). The influence of different amounts of PDMS added on the properties of xerogels intended for the release of the drug and the dissolution of xerogels was investigated. SEM, BET, IR and nitrogen gas adsorption/desorption measurements were performed to characterize the microstructures and chemical properties of xerogels. It is shown that an increase in the proportion of PDMS in the silica network is associated with a decrease in bulk density, specific surface area, total volume of pores and proportion of silanol groups (higher hydrophobicity). These results also revealed the influence of PDMS on the release of doxorubicin hydrochloride and the dissolution behavior of xerogels. An increase in PDMS content results in a decrease in both the rate of drug release and dissolution of xerogels. After the release study, the changes of microstructures and physicochemical properties of these xerogels were also examined.
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Keywords: Doxorubicin hydrochloride; Sol–gel methods; Silica/polydimethylsiloxane xerogels; Drug release

1. Introduction

Silica materials obtained by the sol–gel process are amorphous, inorganic and porous, and have found applications as a coating on implants and medical products [1,2], biocatalyst [2], biosensor [2,3] and matrix for a controlled release of drugs [4–15]. A growing field of interest in silica materials was found in the application for a local drug release at the implanted site. This treatment appears to be a much more interesting alternative, where the goals of drug-releasing systems are to maintain the drug in the desired therapeutic range with just a single dose, localize delivery of the drug to a particular part of the body, reduce the need for follow-up care, preserve drugs that are rapidly destroyed by the body, and to increase patient comfort and/or improve compliance.

The principal advantage of utilized silica materials as an implantable delivery vehicle is that the sol–gel method is non-toxic, uncomplicated, inexpensive, takes place at room temperature (important for thermosensitive drugs), and it does not require the use of pharmaceutically unacceptable solvents. These materials are biocompatible in vivo, cause no adverse tissue reactions and degrade in the body to silicic acid, i.e., $Si(OH)_4$, which is eliminated through the kidneys [8]. Another advantage, namely bioactivity (e.g., materials function like the tissue in which they are implanted) of the sol–gel-derived materials has been widely studied [16–21]. These materials show apatite-forming ability in a simulated body fluid (SBF) and may lead to the bone bonding in vivo circumstances. Therefore, it seems to be a very attractive idea to look for materials that could release a drug in a local and controlled way while showing bioactive properties.

The sol–gel process involves the formation of a colloidal suspension of appropriate compounds (sol) and its gelation

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through hydrolysis followed by polycondensation until a solid network (gel) is formed [22,23]. Bioactive agents can be added during the sol–gel manufacturing process or introduced into gel by adsorbing a drug onto the surface of the gel [4–15]. In the former case, during aggregation of the formed colloidal particles, the drug is incorporated in the lattice of silica gel polymer. Subsequent to further polymerization, aging and drying under atmospheric conditions, the solid sol–gel material called xerogel with encapsulated drug is obtained. In the latter case, a gel of desired porosity is immersed in solution of a drug to be encapsulated [13,14]. This approach is important for labile agents (e.g., biomolecules) to avoid their decomposition under the conditions used for gel production.

The release mechanisms of drugs from sol–gel-derived silica materials have not been extensively studied. Some literature reports indicate that the drug release is controlled by simple diffusion through solvent-filled capillary channels while other papers concluded that the release of drug occurs according to a combined process of the diffusion and the erosion process of the matrix [4–15]. Diffusion-controlled release was found for the release of nifedipine, trypsin inhibitor and lidocaine from silica xerogels [4,10,15]. However, the release of toremifene was found diffusion-controlled from crushed particles but conformed to zero-order kinetics from monoliths [5,6]. The zero-order release was found also for drugs with high molecular weight, such as heparin (M_W ~1600) [7]. A diffusion-controlled release of drug seems to be achieved if the drug is released prior to erosion of the silica materials. The diffusion of drug was faster with decreasing device diameter and surface area to volume ratio of the material or with increasing size of open pores in silica materials. In addition to this, the water-soluble drugs and drugs with smaller molecular weight were diffused easier than non-soluble or high-molecular-weight ones. On the other hand, zero-order release of the drug is attained if the drug was released simultaneously with polymers eroding. The erosion rate of silica materials seems to be dependent on the total amount of material and generally decreases as the material is depleted [8]. The rate of silica xerogel erosion in vitro depends on their pore characteristics and on their surface properties. Specifically, the presence of an apatite surface film significantly reduced xerogel erosion resulting also in decrease of drug release [16]. In addition to these, the active agent may also interact with the silica backbone and hence the rate of releasing is controlled by the interactions between drug and polymer. Altogether these studies document that in the design of a more or less diffusion-controlled release system, all aspects, such as chemical properties and molecular size of a drug, the possibilities of interaction between the drug and polymer material, and the size of matrix, have to be taken into consideration. In addition to these, the conditions of gel synthesis, especially pH value and a water/alkoxysilane molar ratio, which affect hydrolysis and condensation reactions, and therefore the texture of silica gel [4–15], also influence the design of less or more diffuse systems. Longer gelation times produce linear silica aggregates and a more condensed microstructure, resulting in the less diffuse system [6]. However, faster gelation leads to the branched structure with a broader distribution of larger pores in silica gels and hence resulting in the opposite effect. The gelation time is longest near the isoelectric point of silica at pH 2, and decreases with increasing pH of the sol [6]. In addition to pH, an increase in the water/silicon alkoxide molar ratio decreases time of gelation and also correlates with increasing specific surface area, which also partly controls the release of drug.

An addition to colloidal tetraethoxysilane-based sols of organic polymers (e.g., polyethylene glycol [4]) or organosilanes (e.g., methyltriethoxysilane, propyltriethoxysilane, [9,15]), most often slows down the rate of drug release compared to non-modified silica gels, which makes them attractive materials for long-term delivery systems. Organic/inorganic gels made by the sol–gel method combine the advantages of both organic and inorganic materials and are expected to possess new properties that individual organic or inorganic materials could not achieve. The inorganic precursors can directly bond to the organic polymers and covalent bonds are formed between them and/or weak-type interactions such as hydrogen bonding or interpenetrating networks may be formed between the organic and inorganic phases.

The objective of previous work was to prepare a doxorubicin hydrochloride-loaded non-modified silica xerogel by the sol–gel method and to examine its stability and drug release [11]. Doxorubicin hydrochloride is a cytotoxic, anthracycline antibiotic used in antimitotic chemotherapy. It was chosen as an active agent due to its common use in the treatment of bone cancer [24]. Presently, the treatment is systematic and, due to the narrow therapeutic index of doxorubicin, a substantial increase in systematic dose to achieve high concentration of the drug at the bone sarcomas is not possible. Currently, doxorubicin is incorporated into physically self-assembled structures (liposomes, micelles) and polymer–drug conjugates [25–28]. Despite enhanced therapeutic effects, low encapsulation efficiency, drug leakiness and low stability of doxorubicin-loaded liposomes or micelles pose serious problems. In the author's previous work it was found that sol–gels synthesized at room temperature can be used successfully for a complete loading with doxorubicin without losses or leaching out and a prolonged drug release was achieved [11]. Furthermore, drug encapsulation significantly delayed doxorubicin degradation kinetics.

The aim of this work was to prepare silica/polydimethylsiloxane xerogels with encapsulated doxorubicin hydrochloride that would provide a slower drug release compared to non-modified silica. Tetraethoxysilane was used as a SiO_2 source. Silanol-terminated PDMS was chosen as an organic, oligomeric component for the synthesis of matrices due to its capability to change hydrophilic properties of the matrix surface, mechanical properties of the matrices and their microstructure [29,30]. In general,

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