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In vitro release of cisplatin from sol–gel processed organically modified silica xerogels

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Abstract SiO_2, SiO_2/PEG and SiO_2/PDMS xerogels were examined as polymeric carriers for the controlled release of cisplatin—an antineoplasmic medicine. Drug/carrier systems were prepared by the sol–gel method. The effect of organic substitution of the silica xerogel matrix and drying conditions on the release of cisplatin was evaluated. Based on the presented results of the study it may be stated that sol–gel method is useful for entrapping a cisplatin in the pores of organically modified silica gels and for releasing cisplatin mainly in the way of diffusion from the pores of the lattice under the in vitro conditions. The use of organic impurities in silica gel increased the release of cisplatin from xerogel (from 62% to 97% within 7 days), and thermal treatment of all xerogels with cisplatin at the temperature of 80 °C resulted in the acceleration of the drug release (2 days) and increase of the released drug (89–98%).

Introduction

The sol–gel process is an efficient method to prepare silica xerogels by the hydrolysis of alkoxysilane precursors (e.g. TEOS—tetraethoxysilan) and by subsequent condensation of the remaining silanols. These reactions lead to obtaining wet, three-dimensional polymers, which after drying produce solid xerogels [1–3]. There are various benefits of these materials: good homogeneity, chemical stability, hardness and porosity. Sol–gel derived silica xerogels are non-toxic and biocompatible in vivo. These materials cause no adverse tissue reactions and degrade in the body to silicic acid, i.e. $Si(OH)_4$, which is eliminated through the kidney [4].

For these properties, the sol–gel synthesized xerogels can be effectively used as biomaterials for the entrapment of medicines in the ambient temperature and for the control their release from these matrices. Such a form of medicine can bring about improved therapeutic activity, protection against degradation, change in pharmacokinetics as well as control of bio-distribution and decrease in toxicity [5–7].

Doping of sol–gel matrices can be generally carried out in two ways: by superficial adsorption (or covalent bonding) or by trapping a molecule in the forming gel [8]. The latter method is particularly interesting, as not many other matrices offer such possibilities. Doping some admixture to a liquid sol and gelating it results in the occludation of a molecule in the formed bonds of Si–O–Si network. A consequence of such initiated immobilisation mechanism is the fact that molecules of variable shapes, sizes and electric charges may be trapped.

Sol–gel techniques can be used to syntesize pure SiO_2 or organically modified silicates by partially replacing TEOS with organic components. In hybrid inorganic-organic materials, organic species are chemically incorporated into an inorganic lattice at molecular level as a result of the hydrolysis and polycondensation reactions occurring in the solution and gel [9–11]. These composite materials are widely used for biomedical application (e.g. bioactive bone-repairing material, implantable or injectable matrix for drugs) [12–14]. By changing the ratio of tetraalkoxide and organic component, the structure and hydrophobicity in the silica gel may be controlled. Presence of these

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compounds influences the size of pores, silica xerogel specific surface area and the rate of release of drugs from such the xerogels.

A cisplatin, an antineoplasmic medicine was used as model drug in this study. Cisplatin is widely prescribed for a variety of tumors (germ-cell, advanced bladder carcinoma, adrenal cortex carcinoma, breast cancer, head and neck carcinoma, lung carcinoma), but its clinical utility is limited by toxicity. Treatment with cisplatin is associated with severe toxic side effects, in particular its nefrotoxicity, myelosuppression, emesis and hearing loss [15]. Local therapy of this drug could give a targeted and long-lasting disease control while decreasing toxicity to several organs [16].

In this study cisplatin was incorporated into the silica, SiO_2/PEG and SiO_2/PDMS xerogels by adding the drug during the sol–gel manufacturing process. Further, the research aimed at the determination of the dynamics of cisplatin release from sol–gel processed silica xerogels to the water phase. The aim of the work was to investigate, how organic impurities in the inorganic lattice and drying conditions influence the release of cisplatin.

Experimental

Obtaining $SiO_{4/2}$ xerogel with cisplatin

Silica gel was prepared by the hydrolysis and polycondensation of tetraethoxysilane (TEOS) with water and hydrochloric acid in a mole ratio of TEOS : H_2O : HCl = 1 :4: 0.6 in ethanol solution, at room temperature [17]. 200 mg PLATIDIAM preparation, containing 10 mg cisplatin, was dissolved in redistilled water and added into the silica solution after 1 h hydrolysis. The beaker content was further mixed for 30 min., upon which it was covered with a parafilm and left for gelation. The final content of cisplatin in the materials was 7.4 mg/g xerogel.

Obtaining SiO_2/PEG and SiO_2/PDMS xerogels with cisplatin

Xerogels were prepared by co-hydrolysis of tetraethoxysilane (TEOS) with polyethylene glycol (M_w = 600)—PEG or poly(dimethylsiloxane)—PDMS (n = 200) with water and hydrochloric acid in a mole ratio of:

TEOS: PEG: H_2O: HCl = 1: 0.0368: 4: 0.6 and

and

TEOS: PDMS: H_2O: HCl = 1: 0.25: 4:0.6

in ethanol solution, at room temperature. In this way xerogels were obtained in which percentage by weight of PEG amounted to: 27.4%, and PDMS : 23.7%. 200 mg Platidiam preparation, containing 10 mg cisplatin, was dissolved in redistilled water and added into the reaction mixture after 1 h hydrolysis. The beaker content was further mixed for 30 min, upon which it was covered with a parafilm and left for gelation. After casting sols, gelation occurred 3 day. All the samples studied were homogeneous and transparent. The final content of cisplatin in the materials was 5.08 mg/g xerogel (SiO_2/ PEG) and 3,07 mg/g xerogel (SiO_2/ PDMS).

The fractions of silica xerogels were heated for 3 h at 40, 80 and 120 °C in order to investigate, how drying conditions influence the release of cisplatin.

Study of in vitro release

The in vitro study of cisplatin release from the different xerogel matrices was detected by means of ultraviolet spectroscopy (Hewlett Packard 8452A UV–VIS spectrophotometer).

A silica gel samples were soaked in 10 mL SBF (simulated body fluid) as the dissolution medium. SBF was prepared by dissolving reagent grade NaCl (136.8 mM), $NaHCO_3$ (4.2 mM), KCl (3.0 mM), K_2HPO_4. $3H_2O$ (1.0 mM), $MgCl_2$. $6H_2O$ (1.5 mM), $CaCl_2$. $2H_2O$ (2.5 mM), Na_2SO_4 (0.5 mM) in redistilled water; the solution was buffered with tris(hydroxymethyl)aminomethane [TRIZMA] and hydrochloride acid at pH 7.40.

The concentration of cisplatin in SBF was measured by taking 8 mL water solution of the examined therapeutic substance released from silica gel into solution, in selected time intervals. The analysis was carried out measuring the absorbance values at the maximum absorbance of cisplatin at a wavelength λ = 301 nm. The experiment was completed when the difference between the subsequent values of the solution absorbance was lesser than 0.01 absorbance units. The measurements of each sample were repeated 3 times.

Degradation of xerogels

Degradation of the matrices in SBF solution was evaluated by the spectrophotometric method based on the reaction of formation of silic-molybdenic blue complex (λ_{max} = 814 nm) for determination of dissolved $Si(OH)_4$ [18, 19].

Results and discussion

Organically modified silica xerogels were used in order to investigate how polymer (PEG or PDMS) concentration influence the release of cisplatin. The release rate of cisplatin from organic-substituted silica xerogels was compared with the release rate from pure silica xerogel.

Study of cisplatin release trapped in xerogels

Cisplatin release profiles from SiO_2, SiO_2/PEG and SiO_2/PDMS xerogels at room temperature are presented in Figs. 1–3. The substance is released 62–97% depending on the gel type. In the case of SiO_2 and SiO_2/PDMS matrices cisplatin release profiles are similar, while PEG modification of matrix increased the release of cisplatin from xerogel. Incorporation of PEG or PDMS into hydrolysis combined with TEOS results in the increase of pore size [20] in comparison with pure $SiO_{4/2}$. Additionally, partial substitution with PEG resulted in a increase in hydrophilicity of the matrix. These factors facilitates water solution penetration inside the silica lattice and accelerates the cisplatin molecules diffusion. Whereas, the observed decrease of cisplatin release from SiO_2/PDMS xerogel may be due to the hydrophobic nature of the CH_3-groups in PDMS, what make difficult cisplatin and water molecules to move. Approximate release time was seven days, with more than half of the trapped cisplatin was released within the first 3 h.

Drying effect

Drying of silica xerogel at 40, 80 and 120 °C shows a significant effect on the release of cisplatin (Figs. 1–4).

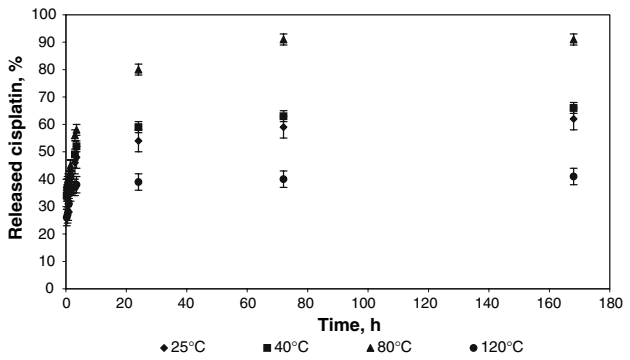

Fig. 1 Release of cisplatin from silica (SiO_2) xerogel dried at room temperature, 40, 80 and 120 °C

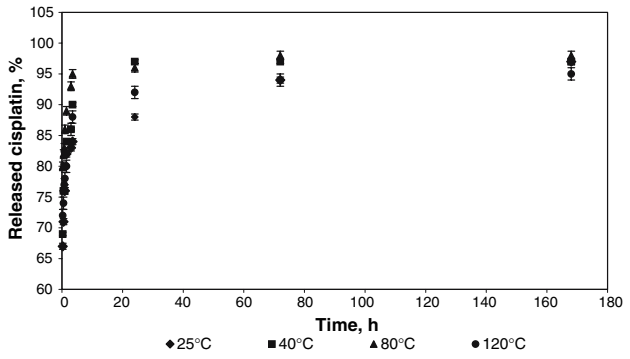

Fig. 2 Release of cisplatin from SiO_2/PEG xerogel dried at room temperature, 40, 80 and 120 °C

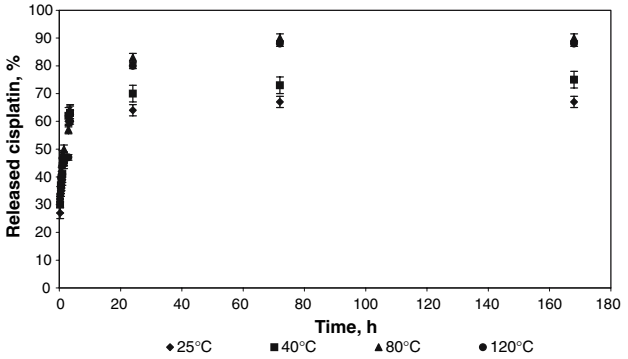

Fig. 3 Release of cisplatin from SiO_2/PDMS xerogel dried at room temperature, 40, 80 and 120 °C

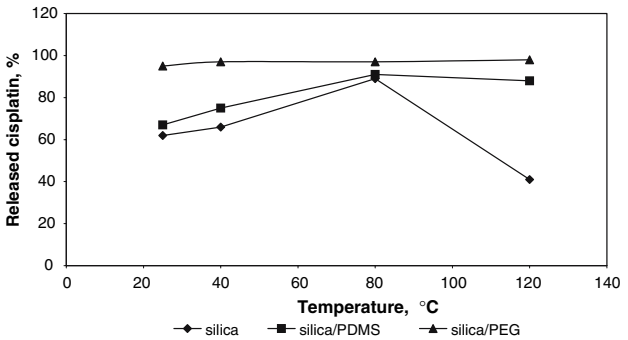

Fig. 4 Changes in release rate of cisplatin entrapped in SiO_2, SiO_2/PEG and SiO_2/PDMS xerogels after thermal treatment at various temperatures

The temperature has an influence on modifications the structure of the matrix. Physically adsorbed water is removed at 115 °C [21] and silanol groups are condensed.

Thermal treatment of all xerogels with cisplatin at the temperatures of 40, 80 and drying SiO_2/PEG and SiO_2/PDMS xerogels at the temperature of 120 °C resulted in the acceleration of the drug release and increase of the released drug amount to 89–98% (at 80 °C) within two (2) days. This is due to the removal of considerable amounts of solvents from the pores, which facilitated the drug diffusion from the matrix.

Drying of pure silica xerogel with cisplatin at 120 °C clearly decreased the release rate of drug (40%). This is due to the shrinkage and the closing in part of the small pores of SiO_2 during too high thermal treatment of matrix.

Study of the degradation of the organomodified silica xerogel matrix

Partial substitution of TEOS with PEG or PDMS affected the degradation behaviour of the silica xerogel matrix in vitro (Fig. 5). The degradation of the matrix was linear and the degradation rate increased with an increasing

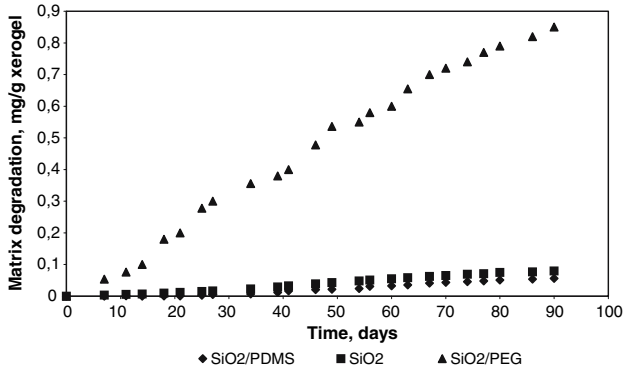

Fig. 5 Degradation of SiO_2, SiO_2/PEG and SiO_2/PDMS xerogels

hydrophilic character of the matrix. In the case of SiO_2/PDMS matrix the degradation rate was slowest (0.05 mg/g xerogel within 3 months), in comparison with SiO_2 (0.08 mg/g xerogel) and SiO_2/PEG (0.85 mg/g xerogel).

Experimental results suggest that the release of cisplatin from silica xerogel matrices is a combination of diffusion, erosion of the matrix and swelling of the matrix.

The degradation of xerogels is negligible in this study and have a weak effect on the drug release.

Matrix swelling occurs in the organic hydrogels. In the hybrid silica xerogels used in this study, there are organic groups incorporated into the silica network (SiO_2/PEG xerogels) or the organic groups exist only as end groups (CH_3-groups in SiO_2/PDMS xerogel). Thus, in case of SiO_2/PEG xerogels the swelling of matrix is the important factor of the drug release. In case of SiO_2/PEG xerogels, the water solution freely penetrated the pores of matrices causing its swelling, whereas release of medicine occurred without any obstacles.

The release of cisplatin is also diffusion controlled from the pores of the xerogels. It was observed that the cisplatin was released in the two stages. During the initial 3 h the cisplatin was released quickly and than slower, in a controlled manner during the rest of the experimental period. During the first hours of release, the release proceed mainly by dissolution and diffusion of cisplatin in the superficial layers of xerogels. Therefore, the cisplatin was released quickly at first. Thereafter, a slower drug release accurs. Within the inner part of xerogels, three-dimensional network of silica effectively immobilized cisplatin molecules, making it difficult for the medicine, due to steric reason, to pass to the water phase.

Conclusions

We have been developing the sol–gel processed binary polymeric matrices: SiO_2/PEG and SiO_2/PDMS containing cisplatin to control release of drug from these xerogels.

Based on the accomplished results of the study it may be stated that the sol–gel method is a useful for trapping a medicine like cisplatin in the pores of organically modified silica gels and produces repeatable results regarding cisplatin release from the pores of the lattice under the in vitro conditions.

From 100% SiO_2 and SiO_2/PDMS monoliths the release was comparable and occurred mainly by diffusion. In the case of SiO_2/PEG xerogels the release was more rapid and occurred by diffusion and swelling of matrix.

In vitro release studies of cisplatin revealed a similar release profile of two stages, which was explained as the drud release from the surface and from the pore channels in the innert part of the xerogels, respectively. The total time of releasing was 7 days at room temperature.

The thermal treatment of all xerogels with cisplatin at the temperature of 80 °C resulted in the acceleration of the drug release (2 days) and increase of the released drug (89–98%).

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