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Influence of synthesis and processing conditions on the release behavior and stability of sol–gel derived silica xerogels embedded with bioactive compounds

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Abstract

The influence of processing parameters and synthetic strategies in the properties of sol–gel derived silica matrices intended for the release of bioactive compounds was investigated. The time-evolution of the matrix properties during its aging at room temperature in the dry and wet forms was investigated by measuring some of its physical and drug retaining properties. The results indicate that long term gel aging in the wet form is fundamental for the obtainment of dry matrices that are stable upon storage, a fundamental requirement for any practical application. In the case of hybrid matrices obtained by replacing part of the tetraethoxysilane precursor with mono-methyl trimethoxysilane, the order of addition of the reaction component is also important in determining the properties of the final dry gel, probably by influencing the polymer structural properties. This parameter acts synergistically with the matrix composition in determining the release properties of xerogels embedded with bioactive compounds.
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1. Introduction

Silica gel obtained by the sol–gel process is an amorphous, highly porous and biocompatible material that has a large number of exploited and potential applications [1–3]. This material is also investigated for its potential use in bio-related applications [2,4–8], among which the controlled release of bioactive compounds [3,9–18]. Silica polymers employed for the sustained delivery of drugs are obtained in a dry (xerogel) and highly porous form from wet gels that form upon hydrolysis and condensation of liquid alkoxysilanes precursors. Each step of xerogel preparation is carried out in mild conditions, compatible with the stability of most bioactive compounds, which therefore can be trapped within the silica network simply by mixing them with the gel precursors while in the "sol" form. The release profile of molecules embedded in sol–gel derived silica polymers depends both on gel structure and porosity and on chemical interactions between gel and embedded molecule. Matrix porosity and internal structure can be varied by changing synthesis parameters [13,15–18] and, for example, the rate of drug release was shown to increase by using high drug loadings, high amounts of water or by increasing the concentration of the alkoxysilane precursors in the sol. In addition, steric and chemical affinity factors are thought to play a key role in the retention properties of organo-functionalized matrices where alkyl residues are introduced in the synthesis by replacing part of the tetra-alkoxysilane precursor with mono-organo functionalized tri-alkoxysilanes. Alkyl residues are thus introduced to increase the drug retention properties of these materials. Indeed, the presence of alkyl residues most commonly slows down the release of embedded organic compounds [9,14,17,19] and this effect is more evident when using long alkyl residues as substituents. On the other hand, the effect

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induced by small alkyl residues appears controversial and, for example, the presence of methyl residues in xerogel formulations was shown to either decrease [9,19], not affect [13] or increase [13,17] the kinetics of drug release. Therefore, it is not possible to explain the effects induced by alkyl residues only in terms of steric hindrance or chemical affinity. Our hypothesis is that the discrepancies on the effect of the methyl group observed in the literature are secondary to structural differences induced by the different synthesis conditions followed by the authors.

This work was meant to evaluate the influence of a combination of gel processing and synthesis parameters on the drug release properties and the stability of xerogels, having in mind that these parameters are closely related to the structural properties of the sol–gel matrices. More precisely, we evaluated the influence of the matrix composition together with the order of addition of the sol components. The effect of the time of wet gel aging before solvent removal was also investigated. Even if all of these parameters are known to affect the structure of sol–gel polymers and the chemical interaction between the matrix and the embedded molecules, their direct impact on the release kinetics of embedded molecules has not yet been described. For this purpose, the drug release properties of gels differently processed were analyzed in parallel with direct and indirect matrix structural characterizations, namely the wet gel mechanical strength and the xerogel surface area. The results obtained provide an insight on the evolution of the wet gel internal structure during the synthesis and room temperature aging processes and demonstrate the importance of monitoring such parameters to obtain matrices that are stable in time and display reproducible and predictable release properties.

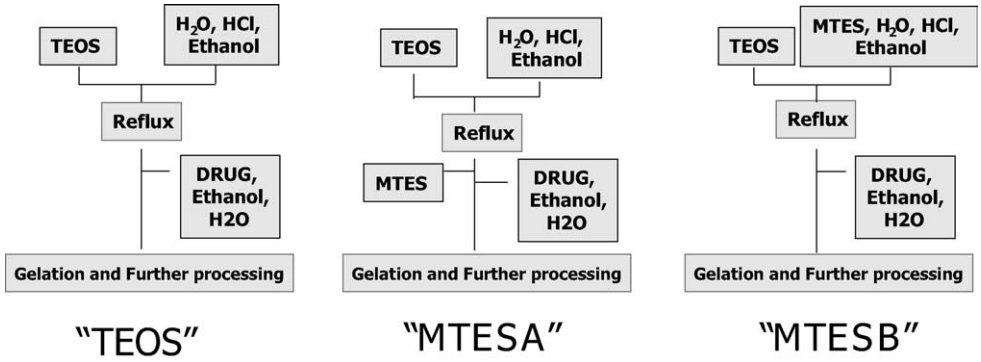
2. Methods

2.1. Materials

Tetraethoxysilane (TEOS) was obtained by Sigma (St. Louis, MI, USA); methyl-triethoxysilane (MTES) was purchased from ABCR Gmbh (Germany). Lidocaine base was of USPh grade and was obtained from Hoechst (Frankfurt, Germany). All other reagents were of analytical grade and were purchased from Sigma.

2.2. Preparation of gels

Gels were synthesized by a two-step acid-base catalyzed method. The initial acid catalyzed hydrolysis of alkoxysilane precursors was carried out by 2 h reflux in abs. ethanol and in the presence of HCl at a H_2O/Si ratio (R) = 2 (Si/HCl/H_2O molar ratios = 1:0.01:2). Two acid-hydrolyzed alkoxysilane "sols" (Sol-T: 100% TEOS or Sol-B: TEOS 80%–MTES 20%) were obtained. The two sols were employed for the synthesis of three different gels which differed either by the matrix composition or by the method of preparation. More precisely (Scheme 1 and Table 1), one matrix was obtained from TEOS only from the Sol-T preparation (*"TEOS"*), while the other two were obtained from a mixture of TEOS [80%] and MTES [20%] either by mixing 0.8 equiv. of TEOS from Sol-T and 0.2 equiv. of MTES from a non pre-hydrolyzed MTES batch ("*MTES-A*"), or by using only Sol-B where TEOS and MTES had been pre-hydrolyzed together ("*MTES-B*"). All gels were cast at room temperature by mixing the initial pre-hydrolyzed sols with the drug lidocaine (dissolved in ethanol), water (final $R = 4$) and, when needed, non-hydrolyzed MTES (Table 1).



Scheme 1. Schematic representation of the synthesis procedure and the order of addition of the reaction components during gel preparation.

Table 1
Reagents used for gel preparation and their amounts

Formulation	*"TEOS"*	*"MTES-A"*	*"MTES-B"*
Type of pre-hydrolysis Sol	Sol-T (TEOS only)	Sol-T (TEOS only)	Sol B (80% TEOS-20% MTES)
ml of Sol	40.6	32.5	40.6
ml of MTES	/	5.4	/
ml of ethanol	47.6	50.4	47.6
ml of stock lidocaine solution (11.72% p/v)	6.8	6.8	6.8
ml of H_2O	4.9	4.9	4.9

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