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Embedding of nifedipine in silica-xerogels by the sol-gel-technique

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Dedicated to Prof. Dr. G. Zessin, Halle (Saale), on the occasion of his 65th birthday

Embedding of the well-known calcium antagonist nifedipine into a silica matrix by sol-gel-technique allows to control its release behavior to a high degree. The liberation rate is increased by the addition of penetration agents such as sorbitol, and is decreased by modification of the silica matrtix with methyl-triethoxysilane or addition of polyethylene glycol 600. It could be shown by differential scanning calorimetry, polarisation microscopy and X-ray diffractometry that nifedipine in silica composites exists in an amorphous state to a large degree until to a concentration of more than 10 wt-%.

1. Introduction

In general, sol-gel-processes mean hydrolysis of metal halogenides or metal-organic substances, e.g. tetraethoxysilane for silica gels. Intermediates of silicon dioxid, polyethoxysilanes or other products of hydrolytic polycondensation, can be used as drug-embedding materials to form a porous silica envelope. Examples in this field where controlled release systems may be applied are consumer products with encapsulated or embedded flavours, vitamins and minerals as well as agrochemicals and biocidal products [1]. Only a few investigations into the embedding of drugs with polycondensates of polyethoxysiloxans isolated [2] and the release of steroids, flavours and biocidal substances [3] from a silica matrix produced by the sol-gel-technique have been published.
The objective of this work was to investigate the influence of sol-gel parameters, matrix modification and the additives polyethylene glycol and sorbitol on the release behavior and release mechanism of drugs. For these model investigations, the calcium antagonist nifedipine was used.

2. Investigations, results and discussion

2.1. Preparation of nifedipine-silica-composites

The procedure for the preparation of such inorganic-organic composites is as follows (Scheme).

Scheme

$$(RO)_4Si \xrightarrow[\text{hydrolysis}]{} (SIO_2)_n \xrightarrow[\text{condensation}]{} (SiO_2)_{kn} \xrightarrow[\text{drying}]{} \text{xerogel}$$

variant A variant B

The bioorganic component is usually added to the silicon- or metal alkoxide before its hydrolysis to the sol (variant A). Nifedipine was added according to variant A as well as variant B (completely hydrolysed sol). The composite structure and the immobilisation behavior of both variants are virtually the same. Differences of nifedipine liberation from both procedures could not be found. This is understandable because embedding actually occurs at the condensation step. From an experimental point of view, variant B offers many advantages, e.g. the ratio of organic to inorganic components can be altered by simple mixing and the composition of the sol can be adapted to take into account the solubility of the drug. Therefore sols can be prepared using aprotic solvents such as acetone or dioxane. This type of sol is then suitable for the embedding of steroids which have low solubility in water and alcohols.
Hydrolysis takes place in acidic surrounding fast but the condensation occurs very slowly. Therefore it is possible to store the sol more than 6 months at room temperature [4]. The silicon- or metal oxid particles in such a sol have

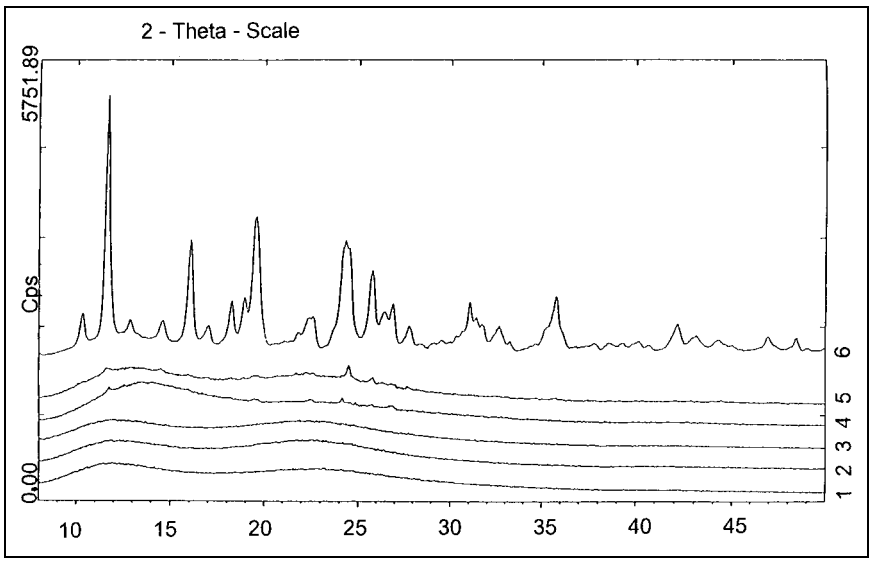


Fig. 1:
X-ray diffraction patterns of silica xerogel unload (1), silica composite with nifedipine 3 wt-% (2), silica composite with nifedipine 10 wt-% (3), silica composite with nifedipine 15 wt-% (4), silica composite with nifedipine 20 wt-% (5), pure nifedipine (6)

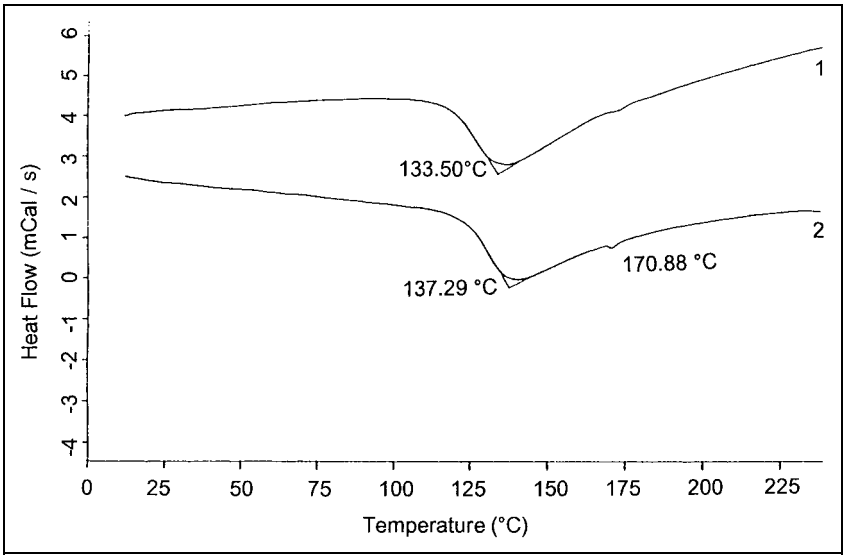


Fig. 2:
Differential scanning calorimetry thermograms of silica xerogel unload (1) and silica composite with nifedipine 10 wt-% (2)

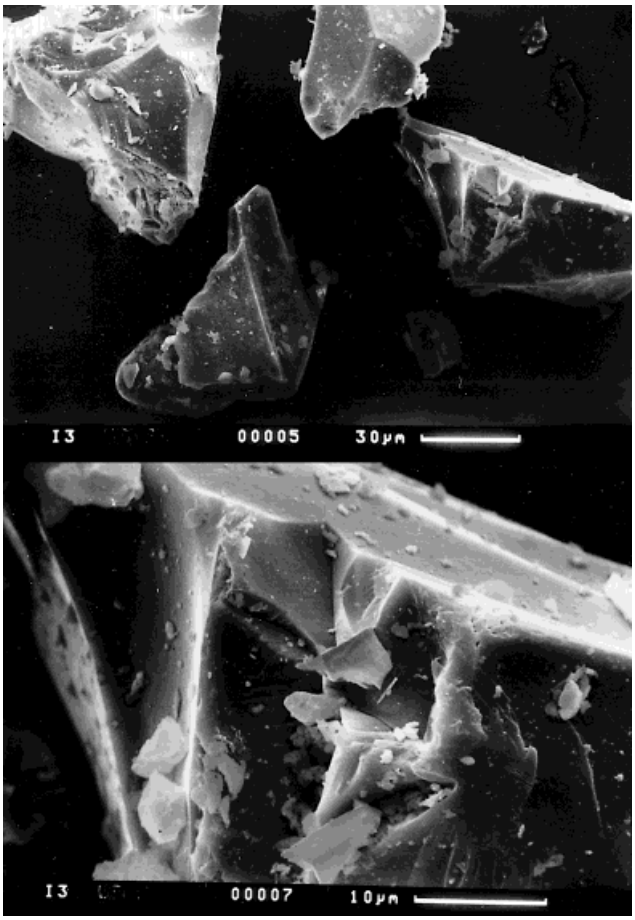


Fig. 3: Scanning electron micrographs of silica composite with nifedipine 10 wt-%

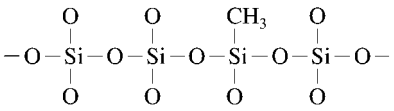
a particle size of about 3 nm [5]. Condensation starts near pH 6 by formation of a gel with net-structure. The rise in temperature is connected with an increase in the rate of condensation and the size of xerogel pores [6]. This is the reason why composites with 10 wt-% nifedipine produced at 25 °C and a gelation time of 30–60 min showed crystalline nifedipine in polarizing microscopy. Nifedipine composites generated at 50 °C with a gelation time of 4 min showed a very high degree of amorphous nifedipine. The clusters are not as closely packed at 50 °C as at 25 °C and the pore surface can bind the drug in an amorphous state more effectively up to a nifedipine concentration of at least 10 wt-%. Composites with more than 10 wt-% nifedipine showed peaks in the x-ray diffractogram according to crystalline substance (Fig. 1). The signals of crystalline nifedipine must also be visible at relatively low concentrations since the mass absorption coefficient of nifedipine is very high in opposite to that of amorphous silica. In such causes the intensity-concentration ratio is superproportional and not linear.

This results could be confirmed by means of differential scanning calorimetry. The melting peak of nifedipine at 171 °C can only be proven very weakly and the desorption peak of the solvent in the presence of nifedipine is shifted from 133.5 to 137.3 °C due to the increased sorption (Fig. 2).

After drying and grinding, silica composites form irregularly slate particles with a good flowability. Fig. 3 shows the scanning electron micrographs of silica composites with nifedipine.

2.2. Matrix modification

The silica matrix can be changed by chemical or physical modification. For example the hydrophobicity of the silica matrix can be altered by co-hydrolysis of tetraethoxysilane with triethoxymethylsilane during the sol preparation. The structure of the composite sol can be assumed as following:



This partial substitution results in a successive slowing of the nifedipine liberation from the corresponding composites (Fig. 4).

The composite structure can also be altered physically by the addition of external additives such as sol-soluble low or high moecular weight compounds during composite preparation. Substituting the effective penetrating agent sorbitol at 20 wt-% for silica causes an increase in the cumulative liberation of nifedipine from the silica composite with 10 wt-% nifedipine from 67.6 to 83.0% after 6 h (Fig. 5).

Alternatively, the silica matrix can be modified by the addition of liquid polyethylene glycol (PEG 600). The result-

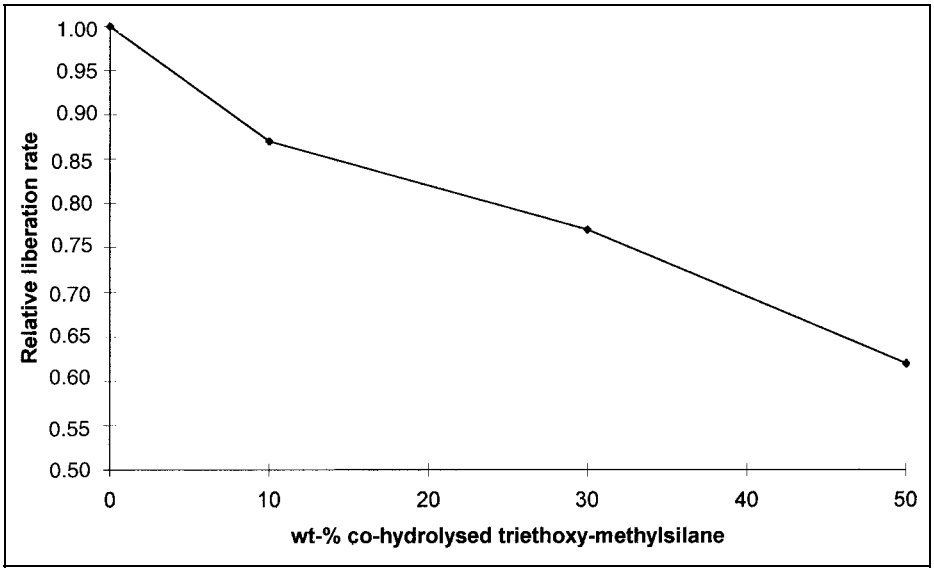


Fig. 4:
Relative liberation rates of nifedipine into water: ethanol (7 : 1) at 25 °C from silica composites (20 wt-% nifedipine) in dependency on the content of co-hydrolysed triethoxy-methylsilane

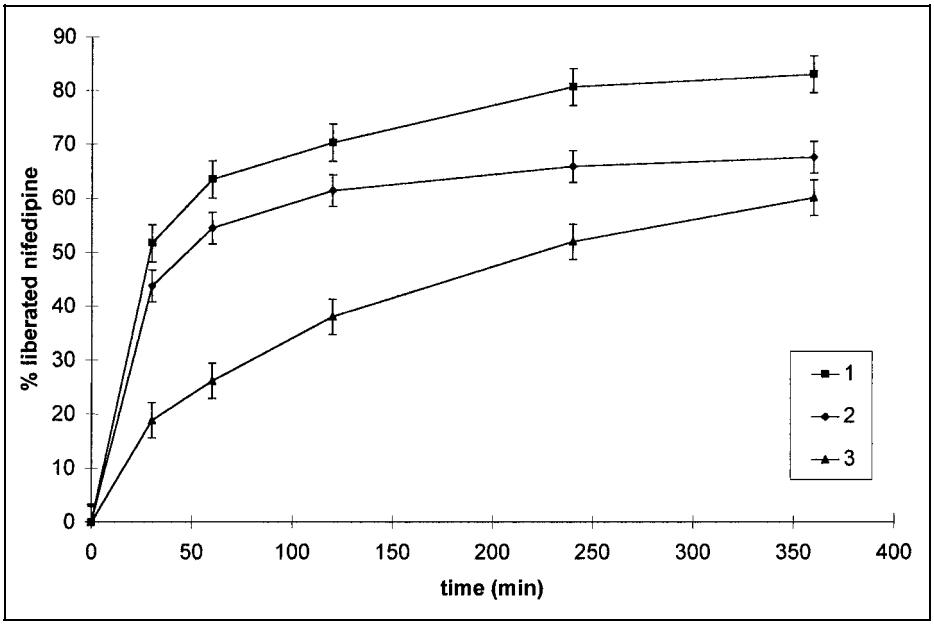


Fig. 5:
Drug release profiles of silica-nifedipine composites (10 wt-% nifedipine) with 20 wt-% sorbitol (1), without additives (2), with 18 wt-% polyethylene glycol (3), confidence intervals for n = 6, 95% probability (Student's distribution)

ing nifedipine-silica-PEG composite (18 wt-% PEG 600) forms also dry, stable, pale yellow granules but exhibits a surprising liberation behavior. Fig. 6 shows that the liberation from this composites is retarded in comparison to that from the pure silica composite.

It can be assumed that there is an interaction between the liquid polyethylene glycol and the silica matrix due to the formation of hydrogen bridges. Complex formation between silicon dioxid sols and high molecular weight polyethylene glycol (molecular weight about 100,000), which can give rise to a phase separation, was described by Nakamisha et al. [7]. It has been proved that the liberation of nifedipine from silica composites produced by the sol-gel-technique can be controlled to a high degree. Advantages of the sol-gel-technique for the embedding of drugs could be:

- the technique is very simple and offers "soft conditions"
- the oxid matrix is cheep, inert and untoxic
- the liberation behavior of the drug is controlled by the porosity of the matrix and the properties of the additives.

3. Experimental

3.1. Materials

Tetraethoxysilane, triethoxymethylsilane (Nünchritz, Germany), nifedipine (Arzneimittelwerk Dresden GmbH, Dresden, Germany), polyethylene glycol (Merck-Schuchardt, Hohenbrunn, Germany) were used. All other materials and solvents were of analytical grade. The experiments were carried out under conditions of protection from light since nifedipine is photosensitive in nature.

3.2. Preparation of nifedipine-silica composites

Nifedipine (2.33 g) was dissolved in 500 ml sol (prepared by mixing 100 ml tetraethoxysilane, 400 ml ethanol and 200 ml 0.01 n HCl under stirring for 20 h at room temperature). In order to modify the matrix an aliquot of tetraethoxysilane was substituted by triethoxymethylsilane. After neutralisation with ammonia at 50 °C (0.25 ml 1 wt-% ammonia-solution per 10 ml sol) a pale yellow transparent homogeneous gel was formed within a few minutes. The light-sensitive gel was dried at 50 °C in a light-protected oven until the weight was constant (23.3 g).

3.3. Release investigations

The composite substance was ground and classified by sieving (sieve tower RETSCH AS 200 basic, Retsch GmbH; Haen, Germany) 10 min with an amplitude of 45 μm. The liberation rates of nifedipine into water from the sieve fraction 180–250 μm of silica-nifedipine composite (or silica-nifedi-

pine sorbitol-, silica nifedipine PEG 600 composites) were determined by soaking samples (all with an absolute content of 5 mg nifedipine in one litre of water under standard condition of 37 °C, 50 rotations per min in a light-protected paddle device (Erweka DT 6, Erweka GmbH, Heusenstamm, Germany). The resulting solutions were analysed by HPLC (HPLC V 2200, Bischoff GmbH, Leonberg, Germany, column RP 18, solvent methanol/water (80/20), UV detector at 238 nm). The deviations between two measurements were smaller than 5%.

3.4. X-ray powder diffraction

Diffraction patterns of the samples were obtained by scanning at 2 °/min through the 2θ angle on a diffractometer using Cu−K α radiation. Only sieved fractions smaller than 45 µm of the samples were used. The investigations were carried out at the X-ray laboratory of the University of Leipzig.

3.5. Differential scanning calorimetry

The investigations were carried out with a differential scanning calorimeter (Polymer Laboratories, Surrey, UK). The heating rate was 10 °C/min. Standard aluminium sample pans were used. The samples (13–17 mg) were weighed into an empty pan; the pans were then crimped using a standard sample pan crimper press.

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