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Silica xerogel carrier material for controlled release of toremifene citrate

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Abstract

Sol-gel processed silica xerogel was used as a carrier material for toremifene citrate in order to develop an implantable controlled release formulation which could be localised to a desired site providing targeted and long-lasting disease control and resulting in a reduced amount of drug needed. Toremifene citrate, an anti-estrogenic compound, was incorporated into silica xerogel matrixes during polycondensation of organic silicate, tetraethyl ortho silicate (TEOS). The effects of drug amount, drying temperature and polyethylene glycol (PEG) on the release rate of toremifene citrate and degradation of the silica xerogel matrixes were investigated. Addition of PEG (M_w 4600/10 000) decreased the specific surface area of the matrix and lowered the release rate of the drug. Reducing the amount of drug in the matrix also decreased the release rate of toremifene citrate. However, drying temperature did not affect the release rate of silica or toremifene citrate. The release profiles of toremifene citrate were according to zero order kinetics, suggesting that drug release was controlled by erosion of the silica xerogel matrix. These results suggest that the toremifene citrate release rate can be controlled to some extent by adding (PEG) or by varying the amount of drug in the silica xerogel matrix.

Keywords: Sol-gel; Silica xerogel; Controlled release; Polyethylene glycol; Toremifene citrate

1. Introduction

The method of incorporating organic molecules in inorganic oxides through sol-gel process is well documented. These oxide materials can be used as photocatalysts for redox reactions, chemical sensors, filters etc. Growth factor TGF-β1 (Nicoll et al., 1997) as well as several enzymes have been shown to retain their activity in dried silica xerogel matrixes (Yamanaka et al., 1992; Weetal et al., 1993; Heigal-Segal et al., 1995). Conventional drug molecules have also been incorporated into silica gel matrixes (Unger et al., 1983; Ahola et al., 1998).

The sol-gel process involves the manufacture of inorganic matrixes through the formation of a

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colloidal suspension, which is called sol. After gelation a wet gel forms a globally connected solid matrix, which after drying forms the dry gel state, called xerogel. Drug molecules incorporated into the sol state would be located within porous silica xerogel network.

Preparation of silica by the sol-gel process provides several possibilities for preparing various gels. The structure and properties of silica gel prepared by hydrolysis and condensation of tetraethyl ortho silicate (TEOS) is influenced by several factors: water to alkoxide molar ratio, temperature, pH, drying and heating conditions of the mixture (Sakka and Kamiya, 1982; Chen et al., 1986). They depend in particular on the water content and the type of catalyst. Acid catalysed gels consist of chain-like polymers and have narrow pore size distributions (Ro and Chung, 1991). Acid catalysis also produces gels with higher mechanical strength (Scherer, 1989). The specific surface area of xerogel can be affected by material composition, processing temperature during gel formation and drying. The specific surface area of xerogels increases with temperatures up to $\sim$ 300–500°C and decreases with temperatures above that (Ro and Chung, 1991). Ro and Chung (1991) attributed the increase of specific surface area with temperature to the formation of new pores caused by evaporation of physically adsorbed water and oxidation of residual organic groups in gels. The specific surface area and pore size mainly control the release of biologically active molecules (Tan et al., 1996). Addition of water-soluble polymers decreases the surface area and increases the pore size (Sato et al., 1990). According to earlier studies water soluble polymers at concentrations of 5 wt% or more, enhance the release of bioactive molecules (Unger et al., 1983; Böttcher et al., 1997).

Toremifene citrate is an anti-estrogenic compound, that exerts its antitumor action through inhibition of estrogen-mediated growth stimulus (Kallio et al., 1986). Orally administered antiestrogens have been used systemically in the treatment of hormone-dependent breast cancer (Valavaara, 1990). This conventional drug therapy typically involves periodic dosing of a drug substance to maintain the desirable plasma drug level. An implantable drug delivery device could be localised to a desired site providing targeted and long-lasting disease control and reducing the amount of drug needed.

Sol-gel processed silica xerogels have been studied as a carrier material in controlled drug delivery. These studies indicate that silica xerogels are biocompatible and non-toxic materials (Radin et al., 1998; Kortesuo et al., 1999a,b). Earlier studies have shown that these materials degrade controllably, in addition to which incorporated biologically active agents are released in a controlled, time dependent manner (Nicoll et al., 1997; Ahola et al., 1998).

The present study reports trapping of toremifene citrate into a porous silica gel network during matrix formation. The aim of the work is to investigate how changes in silica gel structure influence the degradation of the matrix and further the release of the drug. The effects of water-soluble polyethylene glycol (PEG), toremifene citrate concentration and drying conditions on the release rate of drug are investigated. IR-analysis is performed to verify possible organic residues, which might remain in the matrix.

2. Materials and methods

2.1. Preparation of toremifene citrate incorporated silica gels

Silica gels were prepared by hydrolysis and polycondensation of tetraethyl orthosilicate (TEOS, Aldrich) with distilled water and CH_3COOH (Merck) in 1/14.2/0.5 molar ratio at room temperature. Two types of polyethylene glycol (PEG) (J.T. Baker) were used as additives in ratio 0, 0.00056 (M_w 10 000 g mol^{-1}) or 0.0012 (M_w 4600 g mol^{-1}). The amount of PEG was 1.1 wt%. Toremifene citrate (Orion Corporation, Finland) was added to the clear hydrolysed sol. The concentration of toremifene citrate in silica sol varied between 1.9 and 5.5 wt% corresponding to 11.5–34.4 wt% in the air dried silica xerogel. The silica sol was cast in microtiter plate wells, and kept in an oven at 40°C for hydrolysis, polycondensation and ageing for 18 h. The aged silica gels

were briefly immersed in water to dissolve residual water-soluble organic substances and dried at 40°C to constant weight. A fraction of dried silica xerogels was heated at the rate of 2°C h^{-1} and held isothermally for 2 h at 80 or 120°C. The effect of polyethylene glycol and toremifene citrate concentration on the release rate of toremifene citrate was measured with silica xerogels heated to 120°C.

2.2. IR spectroscopy

An FTIR analysis (Mattson 6030, Galaxy FTIR-series) was done for silica xerogels dried at 120°C, without toremifene citrate, prepared with PEG 4600, PEG 10 000 and without PEG. The FTIR measurements were carried out between 400 and 4000 cm^{-1} using transmission mode and potassium bromide, KBr, as a background material. The KBr pellet of each sample was prepared using $\sim$150 mg of KBr and 1.5 mg of the sol-gel sample. The resolution of the FTIR equipment was 4 cm^{-1}.

2.3. Specific surface area and porosity parameters

These studies were performed from silica xerogels not containing toremifene citrate, prepared with PEG 4600, PEG 10 000 and without PEG. Specific surface area and porosity parameters were measured using the BET technique based on nitrogen gas adsorption (Coulter SA3100, Coulter, Miami, FL, USA). Before measurement, samples were vacuum dried for 20 h at 25°C.

2.4. In vitro dissolution test

The dissolution profiles ($n = 3$) of toremifene citrate and silica were determined using USP XXIII dissolution apparatus II (paddle method, Sotax AT6, Basel, Switzerland) at a constant temperature (37°C). Simulated body fluid (SBF, pH 7.4) containing 0.5 wt% sodiumdodecylsulphate was used as a dissolution medium. SBF was prepared by dissolving reagent grade NaCl (136.8 mM), $NaHCO_3$ (4.2 mM), KCl (3.0 mM), $K_2HPO_4 \cdot 3H_2O$ (1.0 mM), $MgCl_2 \cdot 6H_2O$ (1.5 mM), $CaCl_2 \cdot 2H_2O$ (2.5 mM) and Na_2SO_4 (0.5 mM) in distilled water. The solution was buffered at pH 7.4 with tris(hydroxymethyl)aminomethane (50 mM) and hydrochloric acid.

The volume of dissolution medium was 250 ml and the weight of the samples was $\sim$45 mg. At each sampling point, a sample of 1 ml was withdrawn from each flask and replaced immediately with an identical volume of medium. The rotation speed was 50 rpm and the temperature 37°C. The absorbance values of the dissolution samples were measured with a UV-visible spectrophotometer (Hewlett Packard 845/A, USA) at the maximum absorbance of toremifene citrate (A_{278}). Degradation of the silica xerogel matrix was determined by measuring dissolved $Si(OH)_4$ spectrophotometrically as a molybdenum blue complex at 820 nm (Koch and Koch-Dedic, 1974).

3. Results

3.1. Effect of toremifene citrate concentration

Fig. 1 presents the release of toremifene citrate from matrixes containing 1.1 wt% of PEG 4600 with the different drug concentrations. When fitted to the zero order model ($r > 0.9863$) the drug release was linear. The release rates from these different matrixes were found to be directly proportional to the drug concentration in the matrix ($r = 0.9996$). The release of silica was also linear ($0.9906 < r < 0.9964$) and the drug concentration did not have an influence on the degradation rate of the silica xerogel matrix (Fig. 2).

3.2. Effect of additives

Polyethylene glycol 4600 decreased the drug release rate from dried (120°C) silica xerogel cylinders containing 22.9 wt% toremifene citrate by 30% when compared with the matrix not containing PEG. The decrease was 40% with PEG 10 000 (Fig. 3). All the profiles were acceptably linear according to zero order release ($r > 0.9758$). The matrix eroded in a linear manner and PEG did not have an influence on the degradation rate of the silica xerogel matrix (Fig. 4).

Polyethylene glycol decreased the specific surface area of silica xerogel samples (Table 1). The effect seems to be greater with PEG 10 000. The addition of PEG 4600 decreased both the pore volume and the surface area of pores and thus decreased the specific surface area. For silica gel

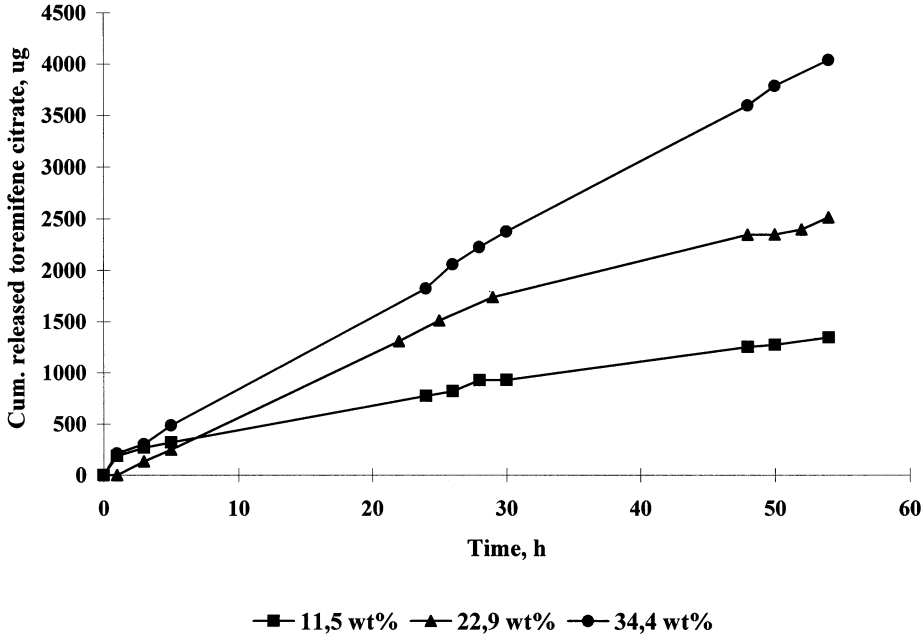

Fig. 1. Cumulative release of toremifene citrate from silica xerogel dried at 120°C with varying drug concentration.

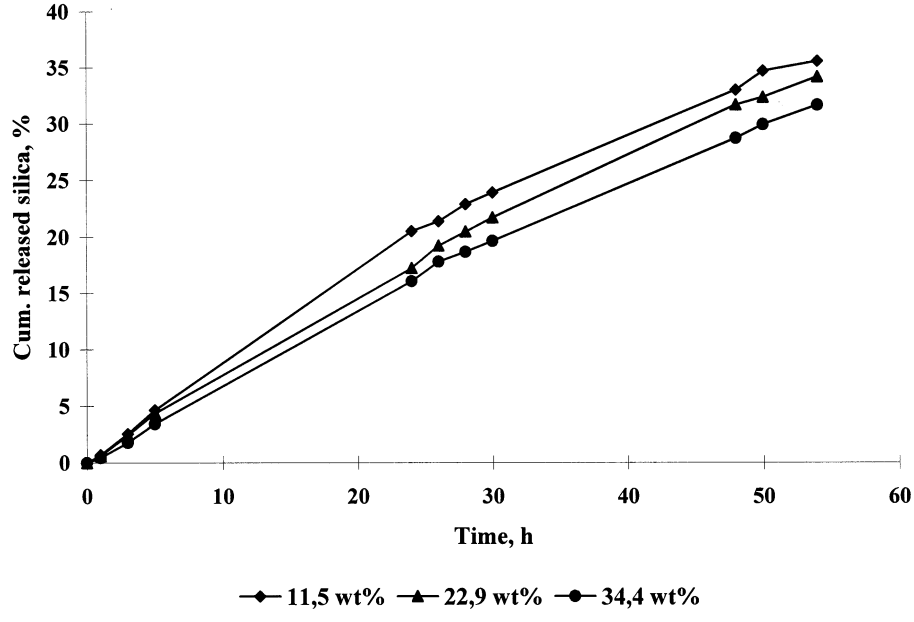

Fig. 2. Degradation of silica xerogel matrix dried at 120°C with varying drug concentration.

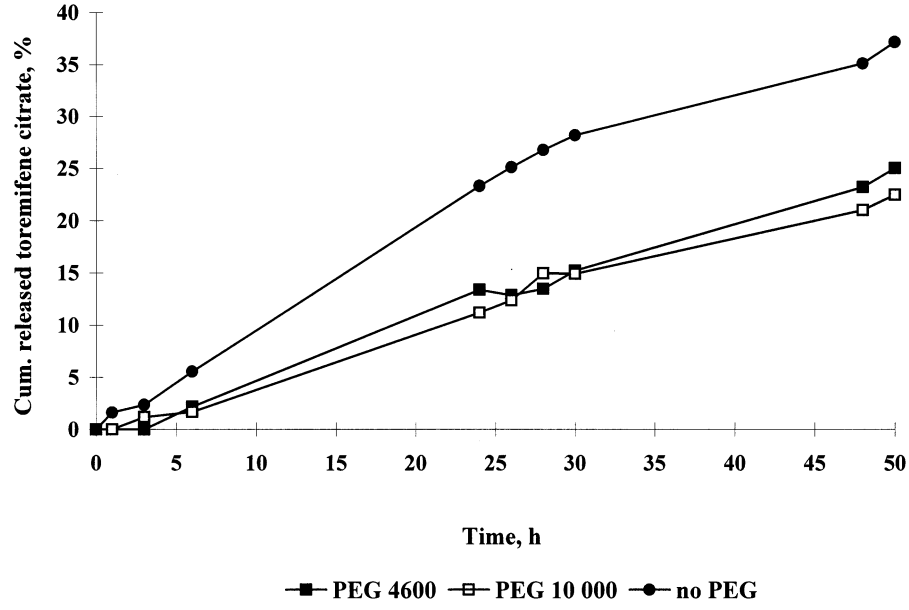

Fig. 3. Cumulative release of toremifene citrate from silica xerogel dried at 120°C as a function of molecular weight of added polyethylene glycol.

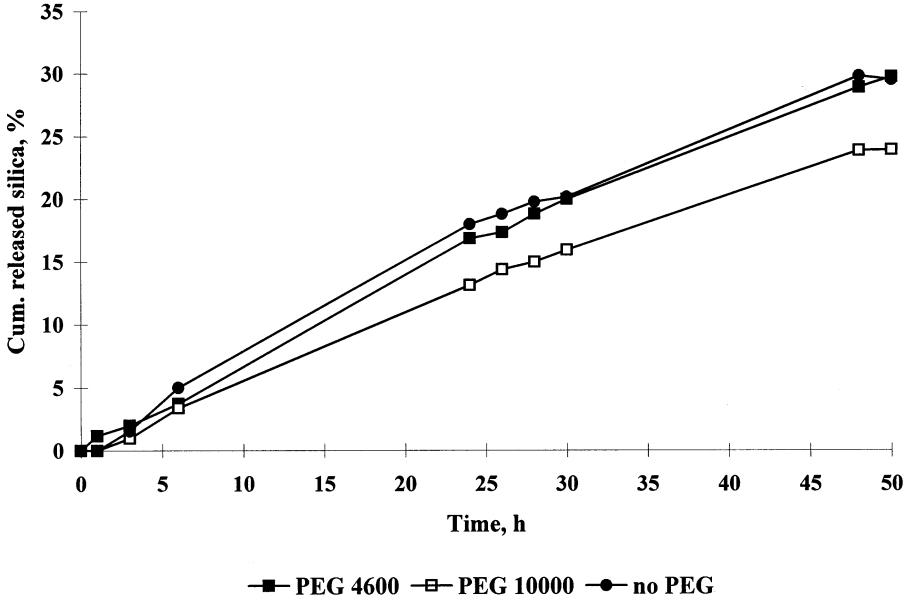

Fig. 4. Degradation of silica xerogel matrix dried at 120°C as a function of molecular weight of added polyethylene glycol.

PEG 10 000 the porosity analysis was not applicable because the pore volume was too small to be measured accurately with this technique.

3.3. Effect of drying

Drying of silica xerogel (containing 1.1 wt% PEG 4600 and 22.9 wt% toremifene citrate) at 40, 80 or 120°C did not show any significant effect on the release rate of toremifene citrate or on the degradation rate of the matrix (Figs. 5 and 6). Drug release rate ranged from 0.53 to 0.56% h^{-1} and degradation rate from 0.61 to 0.67% h^{-1}.

3.4. IR spectroscopy

The results of the FTIR studies are shown in Fig. 7. The peaks at 1250–990, 797 and 454 cm^{-1} are caused by the symmetric and asymmetric stretching vibrations of Si–O–Si and a bending Si–O–Si mode, respectively. The absorption band at 952 cm^{-1} is related to the vibration of Si–OH bonding. The presence of absorbed water in all studied silica xerogels is indicated by the OH-bands at 3800–3000 and 1632 cm^{-1}. An additional peak at 1717 cm^{-1} is observed as polyethylene glycol is used for the sample preparation. This is considered to be the C = O bonding vibration.

Table 1
Porosity parameters and specific surface area of the silica xerogels[a]

Sample	Volume of pores <100 nm (ml g^{-1})	Surface area of micropores (m^2 g^{-1})	Volume of micropores (ml g^{-1})	Specific surface area (m^2 g^{-1})
No PEG	0.2355	289.00	0.1275	491
PEG 4600	0.1613	141.04	0.06112	309
PEG 10 000	ND	ND	ND	144

[a] ND, not determined.

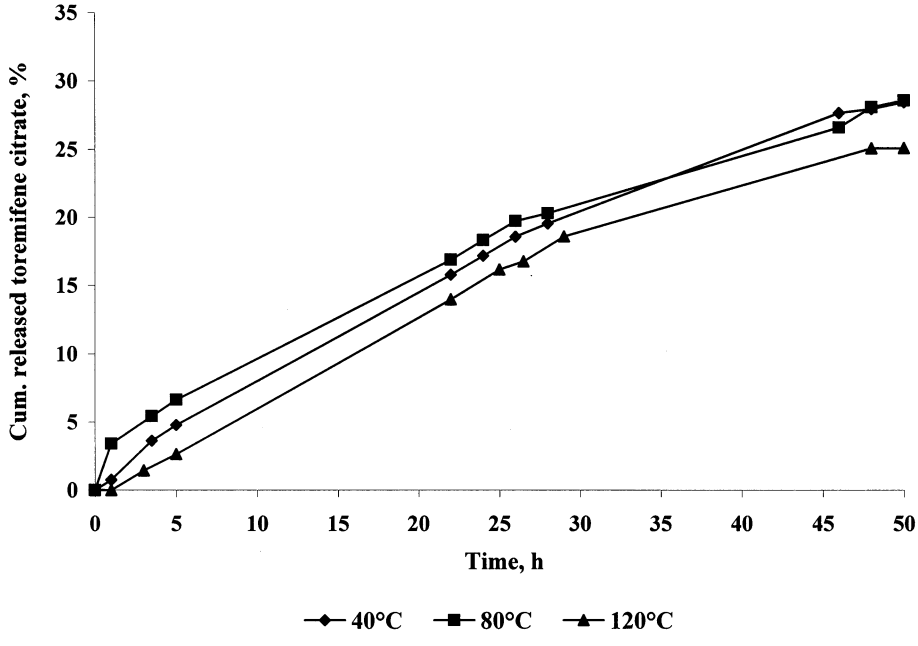

Fig. 5. Cumulative release of toremifene citrate from silica xerogel dried at 40, 80 and 120°C.

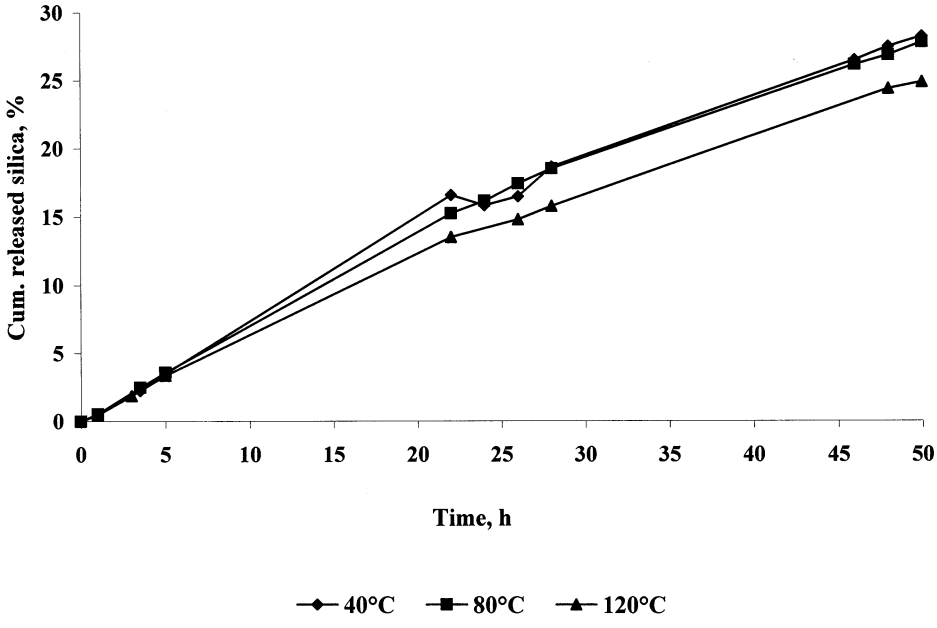

Fig. 6. Degradation of silica xerogel matrix dried at 40, 80 and 120°C.

4. Discussion

The release of toremifene citrate corresponded to zero order and was proportional to the drug concentration between 11.5 and 34.4 wt%. The drying temperature used has no significant effect on the release of toremifene citrate or the silica xerogel matrix confirming that the temperature was not high enough to change the structure of the matrix. Iler (1979) has demonstrated that physically adsorbed water is removed at 115°C but silanol groups start to condense and generate water extensively approximately at 170°C or above.

The surface area and the pore volume decreased in matrixes in the presence of PEG. The effect on the specific surface area seems to be stronger with PEG 10 000. Earlier studies have reported that the addition of PEG increases the average particle size in the silica sols and decreases the specific surface area of xerogels. PEG affects formation of colloidal silica particles during polycondensation by forming hydrogen bonds with residual silanol groups in the silica network. Silica may thus form bigger particles than without PEG and this relaxes internal tension in silica network (Vong et al., 1997; Jokinen et al., 1998). The effect of water-soluble polymers on the release rate of drug substances has been studied earlier. Böttcher et al. (1997) described the controlled release of benzoic acid from silica gel layers containing different amounts of water-soluble polymers. The release was controlled by addition of soluble agents at

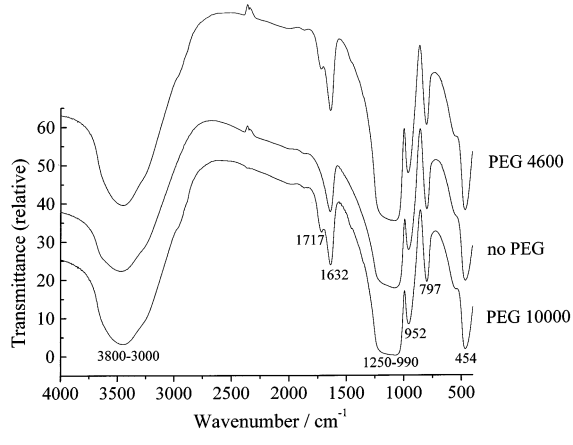

Fig. 7. IR spectra of plain silica xerogels dried at 120°C without PEG, containing 1.1 wt% PEG 4600 or PEG 10 000.

the concentration of 19 wt% or more. High molecular swelling additives, i.e. polyethylene glycol, improved diffusion and release of benzoic acid. It was suggested that by varying the type and concentration of added penetration agent it is possible to control the release behaviour of bioactive components. In the present study polyethylene glycol (1.1 wt%) clearly decreased the release rate of toremifene citrate from dried (120°C) silica xerogel containing 22.9 wt% toremifene citrate. We assume that the small amount of PEG probably relaxes the silica network by forming larger silica capsule particles. The drug dissolved in silica sol is also encapsulated inside these larger particles and the release rate is decreased. If the concentration of PEG is high, 19 wt% or more, network formation during polycondensation is severely disturbed resulting in increased dissolution of incorporated bioactive molecules.

In this study silica xerogels have been studied as an implantable delivery material. Therefore, the verifaction of the possible impurities in the matrix is important. These organic impurities can remain in the matrix because of the processing conditions or incomplete chemical reactions. However, the IR-spectroscopy analysis showed that the characteristic peaks of residues of organic side groups ($-CH_2$, $-CH_3$) were not visible after drying at 120°C when the silica xerogels were prepared using high water content ($TEOS:H_2O = 1:14.2$). Due to method sensitivity there may be less than 1% of these residues present. Sensitive chromatographic methods are needed to identify and quantify these residues. The IR absorption bands due to C–H bonding vibrations would appear at $\sim 2800–2900$ and $1400–1500\ cm^{-1}$ if organic compounds are present in the silica xerogel matrix (Ro and Chung 1991). This has been observed for silica xerogels made using low water content ($TEOS:H_2O = 1:2/4$). Ro and Chung (1991) have shown that organic residues still present after heating at 100°C do not appear after heating at 300°C.

In conclusion, silica xerogels produced via sol-gel process dissolve in a controlled manner simultaneously with the drug and hence can be used as a controlled release carrier for toremifene citrate. Drug release may be controlled by the addition of polyethylene glycol, which decreases the surface area of silica xerogel, as well as by varying the amount of drug in the matrix.

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