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COMMUNICATION

In Vitro Release Behavior of Toremifene Citrate from Sol-Gel Processed Sintered Silica Xerogels

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ABSTRACT

Factors affecting the adsorption and desorption of toremifene citrate (TC) on sintered silica xerogels were investigated in vitro. TC was attached onto sol-gel processed sintered silica xerogel grains or disks by adsorption. The adsorption of TC on the surface of silica was pH dependent. The results support the conclusion that large pore size results in highest drug adsorption. Adsorption of TC was most effective in xerogels sintered at 700°C and containing the largest pores and lowest specific surface area of the silica xerogels studied in the adsorption tests. The release of TC from the xerogel matrix was linear with respect to the square root of time. The release of TC from the grains was very rapid for the first 5 hr, followed by a slower release. All drug was released from the grains, and 60% to 80% was released from the disks in 24 hr. All drug-silica xerogel formulations showed sustained in vitro release profiles.

INTRODUCTION

Porous silica gels are hydrophilic adsorbents that are recommended as drug carriers in pharmaceuticals owing to their excellent physiological and physicochemical properties (1). The release from physiadsorbates of both porous and colloidal silica has been shown to be fast and dependent on carrier structure and pore size (1), while the release from chemiadsorbates has been shown to be regulated by hydrolysis of Si-O-C bonds (2).

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Sol-gel processed inorganic materials have many advantages over conventional glasses and ceramics, including high purity and homogeneity; low processing temperatures; control of porosity, adsorption, properties and dissolution rates; and excellent biocompatibility (3,4). They are also bioactive, that is, they form bonds with living tissue. Resorption behavior can be controlled with the sintering temperature and the composition of the glass (5,6). Adsorption and desorption of drug molecules on sol-gel processed sintered silica xerogels have been studied earlier (7). In these studies, steroids of different numbers with carbonyl and hydroxyl groups were used as model molecules, and the diffusion rates of model molecules were assessed.

Antiestrogens have been used in the systemic treatment of hormone-dependent breast cancer (8). Local hormone therapy after breast cancer surgery provides targeted and long-lasting disease control. In this study, toremifene citrate (TC), an antiestrogenic compound that exerts its antitumor action through inhibition of estrogen-mediated growth stimulus (9), was used as the model drug. The aim of this study was to investigate the adsorption of TC onto silica xerogel. After adsorption, dissolution studies were conducted in vitro to determine the factors affecting the rate of desorption. It was thought that silica xerogels could be used as a matrix for sustained release.

MATERIALS AND METHODS

Preparation of Silica Xerogel Samples

Pure silica gel was prepared using the sol-gel method published by Nakanishi (10). Tetraethoxysilane (TEOS), polyethyleneglycol (PEG; MW 10,000), deionized water, and nitric acid (HNO_3) were mixed at room temperature in a mole ratio 1.0:0.0024:14.2:0.41. The sol solution was kept at 40°C for polycondensation for 18 hr. The aged silica gels were washed and dried at 40°C for 6 days, then the temperature was increased at 10°C/hr, and the silica gels were sintered at elevated temperatures (400°C, 550°C, 700°C, 800°C, 900°C, and 1000°C) for 2 hr. The materials were ground and sieved to grain size $56 < x < 200$ μm or cut to 7.0 mm × 1.3 mm (SD 0.19) disks.

Physicochemical Properties of Silica Xerogels

Porosity at a diameter range of 6.5 nm to 14 μm was determined by mercury porosimetry (Autoscan 33, Quantachrome Corp., USA). Specific surface area was measured from grain samples using the BET technique based on nitrogen gas adsorption (specific surface area meter Flowsorb 2300II, Micromeritics Instrument Corp., Norcross, GA). Before measurement, the samples were dried in a vacuum for 24 hr at 40°C. Sample density was determined using helium pycnometry (Multipycnometer MVP-1, Quanrachrome Corp., Syosset, NY). Crystal structure was examined using X-ray powder diffraction (Siemens D500, Siemens AG, Karlsruhe, Germany). Infrared spectra were obtained using an IFS66 spectrophotometer to observe the structures of the gel skeletons obtained under the various heat treatment conditions.

Adsorption of Toremifene Citrate on Silica

The TC was dissolved in 5% lactic acid (pH adjusted to 1.9, 2, 2.5, or 3.5 with 1N NaOH) in a concentration of 1 mg/ml. The materials (sintered at 400°C, 550°C, and 700°C) were impregnated with the drug solution, 4 hr for the grains and 4 days for the disks. Before the dissolution test, the disks were cleaved. One-half of them were used in the dissolution test, and the other half for the determination of drug content.

In Vitro Dissolution Test

The dissolution profiles (each data point is the mean of 3 values) of TC and silica from silica xerogel sintered at 400°C, 550°C, or 700°C were studied using USP 22 dissolution apparatus II at 37°C. Simulated body fluid (5) (SBF; pH 7.4) containing 0.5% (m/v) sodiumdodecylsulfate (SDS) was used as a dissolution medium. The volume of dissolution medium was 250 ml, and the total weight of the grain samples was 13.9 ± 1.9 mg. SA/V (surface area/volume) varied between 292 (700°C) and 432 (400°C) cm^{-1} because the surface area was different in the samples sintered at different temperatures. At each sampling interval, 1 ml of sample solution was withdrawn and replaced immediately with an identical volume of fresh medium. Rotation speed was 50 rpm, and the temperature was 37°C.

The absorbance values of the dissolution samples were measured on an ultraviolet-visible (UV-Vis) spectrophotometer (Hewlett Packard 845/A) at the maximum absorbance of TC (A_{278}). The drug content in the silica xerogel grains and disks was determined by dissolving the silica xerogel containing drug in 0.5% SDS/SBF buffer at 37°C. Dissolved silica was measured spectrophotometrically as a siliconmolybdenblue complex at A_{820} (11).

RESULTS AND DISCUSSION

Porosity, Specific Surface Area, Crystal Structure, and Density

Pore volume, pore surface area, and specific surface area decreased with increased sintering temperature (Table 1). At higher sintering temperatures, the mean pore diameter increased, that is, smaller pores disappeared as the sintering temperature increased. Apparent density increased as the heating temperature increased (Table 1) until all the adsorbed water had evaporated (900°C–1000°C). All samples were amorphous, which is typical for gels.

Infrared Spectroscopy

The thermal changes in the structure of silica were investigated by infrared (IR) spectroscopy (Fig. 1). The data show that the small peak in the region 550–600 cm^{-1} results from the skeletal deformation of the fourfold siloxane rings. The cause of the small peak at 960 cm^{-1} is considered to be the vibration of terminal Si-O^- or Si-OH. These peaks disappeared after heating the samples at 700°C. The peak at 800 cm^{-1} and the peak in the region 400–500 cm^{-1}, as well as the strong peak in the region 1050–1100 cm^{-1} are caused by symmetric and asymmetric vibrations of Si-O-Si. These peaks in all samples gradually move to higher wavenumbers with increasing heat-treatment temperature.

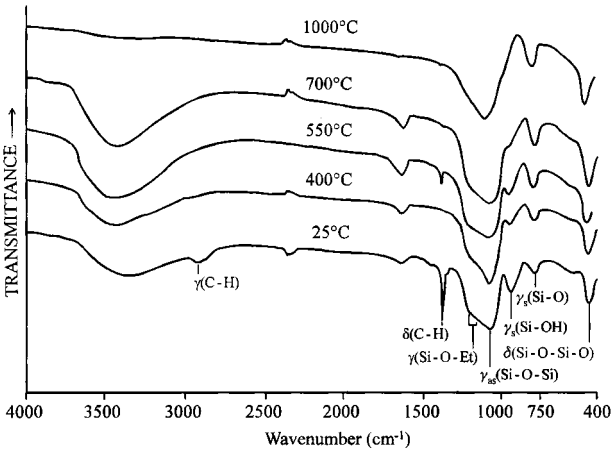

Figure 1. Infrared spectra of silica xerogels.

The presence of adsorbed water is indicated by the adsorption band around 1640 cm^{-1}, which has disappeared at 1000°C. The middle peaks at 2850–2950 cm^{-1} and the peaks at 1300–1500 cm^{-1} are related to the vibration of the C-H bond in organic groups. The strong peak centered at 1100 cm^{-1} is believed to be caused by the vibrations of residual side groups such as Si-OC_2H_5. The vibration peak caused by C-H around 2900 cm^{-1} disappeared at 400°C, but the peak around 1400 cm^{-1} can still be seen at 700°C, and the peak at 1100 cm^{-1} has disap-

Table 1

Physicochemical Parameters of the Silica Xerogels

Heat Treatment Temperature (°C)	Porosity			BET, Specific Surface Area (m^2/g)	Apparent Density (g/cm^3)
	Total Intruded Volume (ml/g)	Total Pore Surface Area (m^2/g)	Mean Pore Diameter (nm)		
Grains					
400	0.80	37.46	84.77	776.66	1.91
550	0.77	34.54	88.77	682.21	2.01
700	0.72	26.00	110.4	525.87	2.16
800	0.74	23.67	125.60	366.17	2.18
900	0.61	16.96	144.50	14.51	2.23
1000	0.58	19.04	121.30	13.22	2.20
Disks					
550	0.64	33.53	76.69	n.d.	2.29
700	0.65	27.75	93.67	n.d.	2.35
900	0.54	21.96	98.20	n.d.	2.38
1000	0.49	28.62	68.56	n.d.	2.31

n.d., no data.

peared at 1000°C. As a result, many breaking points in the Si-O-Si network disappear, and the network becomes more condensed, as indicated by the gradual shift of Si-O-Si stretching IR peaks toward higher wavenumbers. These results would indicate that the gels become more stable at elevated temperatures, as has been reported earlier (6).

Adsorption of Toremifene Citrate on the Silica Xerogel Surface

The adsorption of TC on the surface of silica xerogel was dependent on pH. Adsorption was lowest at pH 2, which is the isoelectric point of silica gel (12). At pH 3.5, the surface area of the silica xerogel is negatively charged, and the adsorption of TC is increased. Adsorption was not determined at higher pH levels than pH 3.5 because the solubility of TC decreases with increasing pH. TC, which is positively charged at pH 3.5 (pK_a = 8), is probably attached to the surfaces of negatively charged O^- groups by electrostatic interaction (5). Large surface area and pore size provide the optimum conditions for drug adsorption (7). Adsorption was most effective in the silica xerogel sintered at 700°C, which contained the largest pores and lowest specific area of the silica xerogels studied. The concentration of TC was 303.5 μg/m^2 on silica xerogel grains sintered at 700°C and 193.8 μg/m^2 on silica xerogel sintered at 400°C. In addition, the content of OH^- groups may affect the adsorption of ionic drugs. According to their physical and chemical characterization, silica xerogels sintered above 700°C are not suitable matrices for drug adsorption owing to their low surface area and the number of their OH groups. The concentration of TC in the disks was a function of their thickness; the concentration was smaller in thick disks than in thinner ones, indicating that TC was adsorbed only on the surface of the disks and not throughout.

Toremifene Citrate Release from Drug-Loaded Silica Xerogel Grains and Disks

Drug release from drug-loaded grains and disks was linear with respect to square root of time, indicating diffusion-controlled release (Fig. 2, $.945 < r < .989$). The rate of drug release from the grains was faster than from the disks. The lower drug content and smaller surface area of the disks of course may affect the release rate. After 24 hr, 100% of TC had been released from the grains and 60% to 80% from the disks. The initial release from the grains was rapid; about 20–30% of the total amount was released in 1 hr. The release of silica from the silica xerogels was linear ($.982 < r < .998$). No difference was seen in the rate of drug or silica release between the silica xerogels sintered at different temperatures, suggesting that the physical changes in the materials are not great enough at temperatures ranging from 400°C to 700°C to alter their physical characteristics and release behavior. Earlier studies have shown that specific surface area and OH^- group concentration on the surface of the silica xerogel decrease and also the resorption of the silica xerogel decreases with increasing temperature (5,6). However, in our case, the difference in the specific surface area of the silica xerogels sintered at 400°C to 700°C was not sufficient.

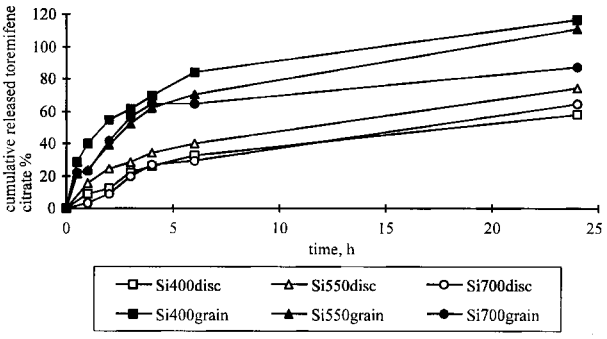

Figure 2. Dissolution profiles (n = 3) of toremifene citrate (adsorbed at pH 3.5) from drug-loaded silica xerogel grains and disks.

CONCLUSION

The adsorption of TC on the surface of silica xerogel was pH dependent, and it was most effective in xerogels containing the largest pores. The sintering temperature of silica xerogel had no significant effect on the release rate of drug molecule. TC was released in a sustained manner under in vitro conditions. However, because of the quite short release times (<24 hr), sintered silica xerogels may not be a suitable matrix for long-term sustained release of TC. The possibility to decrease the release rate by incorporating the drug substitute directly into the nonsintered silica gel during gelation will be examined in the next in vitro study.

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