Expert Opinion

Silica xerogels as pharmaceutical drug carriers

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This review focuses on silica xerogels obtained by the sol-gel method and their application as drug delivery systems. SiO_2 xerogels are potential biomaterials to be used as matrix materials for the extended and controlled release of different kinds of biologically active agents administered by various routes. The article includes some representative examples that describe the encapsulation of bioactive molecules and model compounds inside a silica matrix produced by the conventional sol-gel method or by ultrasound hydrolysis. The drug release rate from xerogels could be modified by adjusting several parameters, such as the type of precursor, the concentration of the catalyst and drying temperature. *In vitro* and *in vivo* studies have shown the efficacy and biodegradability of these composites. The potential application of silica xerogels as drug carrier systems is critically analyzed and discussed.

Keywords: drug delivery, silica sonogel, silica xerogel, silicon dioxide, sol-gel technique

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1. Introduction

The release of pharmaceutical agents into the systemic circulation and consequently at the site of action to produce an intended pharmacological effect is the ultimate goal of drug delivery. In general, the therapeutic effect depends on the dose, frequency of administration and half-life of the drug. Controlled release focuses on delivering biologically active agents locally over extended periods of time. The site specificity of drug delivery reduces the potential side effects that can be associated with conventional dosage forms [1,2].

The 1950s and 1960s were characterized by great progress in pharmaceutics: biopharmaceutics and pharmacokinetics were developed and, as a result, retarded and controlled drug release became a major focus of attention. In recent years, significant efforts have been devoted to the development of several controlled drug delivery systems, including transdermal, intranasal, ocular and pulmonary drug delivery systems, bioadhesive and implantable systems, polymeric crosslinked carrier matrices, such as hydrogels and supramolecular polymer aggregates, and different types of colloidal drug delivery system. These delivery systems have been widely investigated for the sustained, controlled and targeted delivery of low- or high-molecular-mass drugs and other biologically active agents [1,3-6].

There are several reports that have evaluated the suitability of SiO_2 gels, prepared by the sol-gel process, as biodegradable carrier materials for controlled drug delivery. Several biologically active agents, such as conventional small-sized drug molecules and proteins, have been incorporated into these gels [7-15]. In most of these works, acetic acid, nitric acid, or hydrochloric acid were used as catalysts. In some cases, methanol or ethanol were used as solvents, and polyethylene glycols and sorbitol were used as additives.

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This paper reviews the present state of the art of silica xerogels as drug carriers. We focused particularly on the compilation, comparison and contrast of some of the more recent silica xerogels used for the stabilization and controlled release of drugs, model compounds, proteins and peptides.

2. The sol-gel method

A promising technique for the preparation of controlled delivery systems is the sol-gel procedure, which involves the manufacture of an inorganic matrix through the gelation of a colloidal suspension (sol) at low temperature under mild conditions [12].

The sol-gel technique, using an alkoxysilane as precursor of the silica matrix, has been very useful in the preparation of homogeneous and high purity materials. Silica gels are usually obtained by acid- and/or base-catalyzed hydrolysis and by condensation of alkoxysilanes ($Si(OR)_4$), such as tetramethyl orthosilicate, $Si(OCH_3)_4$, and tetraethyl orthosilicate, $Si(OC_2H_5)_4$, designated as TMOS and TEOS, respectively. These reactions occur in the presence of a common solvent (i.e., ethanol) [11-16]. These materials cause no adverse tissue reactions and degrade in the body to $Si(OH)_4$, which is eliminated through the kidneys in the urine [10]. In fact, amorphous silica particles (in contrast to crystalline silica) are not toxic, and are regularly used as food additives and components of vitamin supplements (as colloidal suspensions) [17].

2.1 Silica xerogels

Wet gels obtained by the sol-gel process frequently have a structure that consists of a continuous solid network embedded in an up to almost 98% volume fraction liquid phase. Drying is a critical step of the sol-gel processing to obtain monolithic dried gels [18,19]. The drying process of silica gels can involve different techniques, by which aerogels, cryogels and xerogels are obtained. The liquid within the pores can be removed above its critical temperature and critical pressure, producing an aerogel; in this case, the gel texture is hardly modified and the gel generally preserves its original dimensions. When the liquid is removed from the pores by freeze-drying, the resulting solid material is called cryogel, which is obtained as a powder [20]. Finally, when conventional drying or ambient drying by solvent evaporation is applied, a xerogel is obtained [21-24]. These different possibilities for drying provide an option to integrate drugs in different ways without altering their integrity. **Figure 1** shows a schematic representation for the obtaining of aerogels, xerogels and cryogels by the conventional method.

Sol-gel derived silica xerogels are considered as promising carrier materials for controlled drug delivery owing to their biodegradability, high drug loading efficiency and, more importantly, their low processing temperature, which allows *in situ* incorporation of drug molecules into the silica matrix [25-27]. The addition of biologically active agents to silica sol may be carried out in the liquid phase, offering the possibility of obtaining a homogeneous distribution of molecules. The substance incorporated into the sol is distributed within the porous silica xerogel network [15]. Also, adsorption of drug molecules on sol-gel processed silica gels may be possible [8,20].

The organically modified metal oxide sols yield homogeneous gels and transparent stable films. Thin composite layers of silica with incorporated bioactive organic compounds can be prepared by mixing oxide sols with dissolved bioactive compounds and coating with a conventional film coating machine. The incorporation of bioactive organic compounds as drugs into metal oxide layers leads to: i) the immobilization of the bioactive agent within the metal oxide matrix, allowing the reaction with smaller diffusible molecules; and ii) the release of the bioactive organic compound from the metal oxide layer into the surrounding phase in a sustained or controlled release mode [28].

Drug release behavior from silica xerogels can be affected to some extent by changing the sol-gel synthesis parameters (i.e., pH, water/alcoxide ratio, temperature, type or concentration of the catalyst, and drying and heating conditions) [29]. These factors are included in **Table 1**.

2.2 Silica sonogels

The application of ultrasound (sonocatalysis) to xerogel precursors has given rise to new materials, known as sonogels. In 1984, an approach to sol-gel processing avoiding the use of extra solvents (i.e., ethanol) by exposing a TEOS–water mixture to intense ultrasonic irradiation was described [30]. Sonochemistry is an alternative method to promote hydrolysis without using alcoholic solvents, by subjecting the alcoxide–water mixture to the action of high-power ultrasound in presence of the acid catalyst [31,32]. These reactions occur in the small bubbles produced by the cavitation phenomenon [33]. Sonogels have been widely studied by several research groups [19,33-35]. Recently, Ocotlán-Flores and Saniger have reported the synthesis of catalyst-free SiO_2 sonogels prepared by the sonication of a neutral distilled water/TEOS mixture [16]. A schematic representation of the experimental setup for the preparation of these sonogels is shown in **Figure 2**. A mixture of TEOS and distilled water (1:1) was placed in a glass reaction vessel, which was immersed in a water bath under controlled temperature. The total ultrasonic irradiation was 180 min, at a nominal power of 180 W, alternating 5-s irradiation and non-irradiation steps. The ultrasound tip (1.25 cm in diameter) was placed in the initial TEOS/water interface. Twenty-four hours after the end of sonication, the unreacted TEOS (upper phase) was extracted, and the remaining suspension with the sonication products were dropped into a glass container. The sonogels were dried in an oven. **Figure 3** shows the micrographs of samples of SiO_2 sonogels analyzed by scanning electron microscopy (SEM).

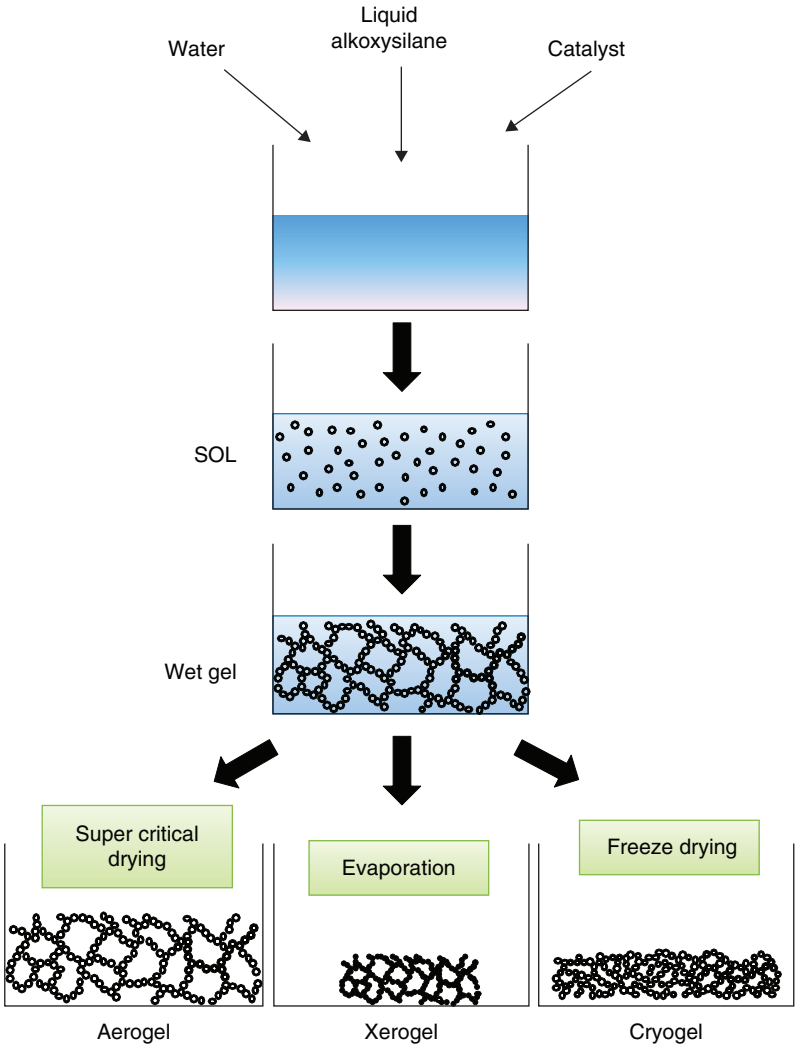

Figure 1. Schematic representation of the obtaining of aerogels, xerogels and cryogels by the conventional method.

3. Pharmaceutical applications of silica xerogels

According to Slowing *et al.* [36], the research groups of Unger, Stucky and Zhao were among the first groups that prepared micrometer-sized mesoporous silica spheres with a narrow size distribution for chromatographic applications. Unger and co-workers suggested the possibility of using sol-gel derived silica xerogels for controlled drug delivery as early as 1983. They developed a variety of methods to incorporate drugs such as ephedrine, codeine, papaverine and reserpine directly into porous silica envelopes with a controlled pore structure. Drug release of non-ionics, neutral salts such as KCl, codeine-HCl or the anionic benzoic acid was very rapid from silica embeddings compared with molecularly entrapped drug bases. Also, this group suggested that silica-embedded drugs could be incorporated into solid dosage forms, such as hard gelatin capsules or tablets [37].

Table 2 lists some typical examples of silica xerogels, and modified silica xerogels obtained by the sol-gel method, precursors, catalyst and drug or model compounds embedded in the xerogels are included. The most representative examples of the applications of silica xerogels and silica sonogels in the pharmaceutical area are included in the following sections. The works were subdivided according to the kind of drug included in the gels.

3.1 Steroids

Sieminska *et al.* [38] prepared a slow-release drug delivery system using a sol-gel glass impregnated with hormones. Four steroids with different numbers of carbonyl and hydroxyl groups were used. Progesterone, estradiol, estrone and hydrocortisone were introduced into the porous glass by immersing sol-gel samples in steroid solutions in benzene, ethanol or dichloromethane. The diffusion coefficients for each steroid inside the pores filled with pure ethanol, 27.5% ethanol–water solution and physiological solution were determined. The authors concluded that diffusion coefficients were determined by several factors, such as the solubility of

Table 1. Sol-gel synthesis parameters.

Parameter	Effects
Water/alcoxide ratio	Gels prepared with a low amount of water are microporous with linear structure Gels prepared with a greater amount of water produce branched polymers
Type of catalyst	An acidic catalyst leads to the production of small linear polymeric entities A basic catalyst promotes crosslinking and produces branched colloidal particles
Temperature	Increasing drying time and temperature promotes densification of the porous xerogel structure

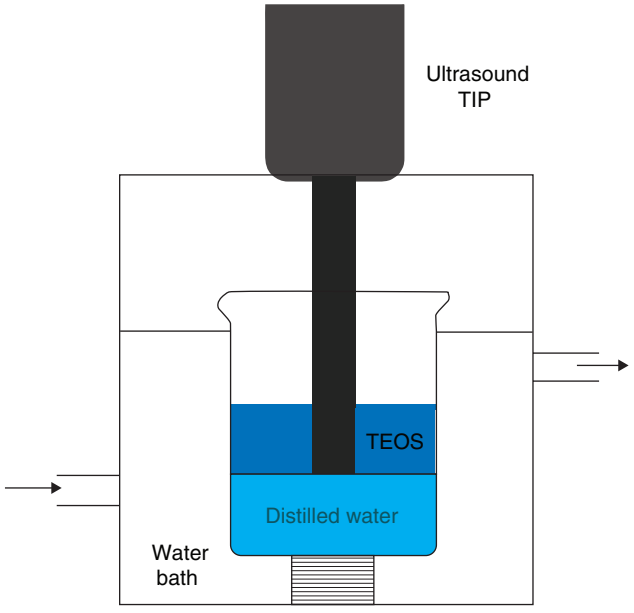

Figure 2. Experimental setup used to prepare the catalyst-free SiO_2 sonogels.

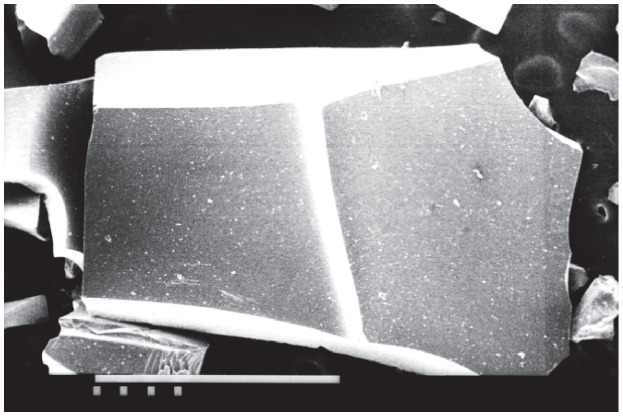

Figure 3. Scanning electron micrograph of SiO_2 sonogel, ×45 (bar = 1 µm).

steroids in the carrier solvent, average pore diameter, molecular mass and size of the drug molecule, the number of hydroxyl and carbonyl groups per steroid molecule, and temperature. Permeability was favored for steroids having fewer hydroxyl and carbonyl groups. Solvents that readily dissolve steroids increase the diffusion rate and, consequently, the amount of material delivered.

3.2 Antibacterials

Thin composite layers of silica with antibacterial benzoic acid were obtained by Böttcher *et al.* [28]. Like other research groups, they noticed that the release rate of the compounds from the metal oxide matrix could be diminished by increasing the methyltriethoxysilane (MTES)/TEOS ratio in the sol-gel procedure. Also, the addition of low molecular soluble additives or high molecular swelling additives (sorbitol and polyethylene glycol 10000, respectively) could improve the diffusion processes within the metal oxide matrix.

3.3 Polypeptides and proteins

As mentioned previously, silica xerogels have been explored as carrier materials for polypeptides. In 1997, Nicoll *et al.* [39] published a study that described the synthesis of a composite bone graft substitute, which consisted in transforming growth factor-β1 (TGF-β1) incorporated into a sol-gel derived silica-based porous glass. The sol-gel procedure was carried out in acidic environments, as TGB-β1 is highly stable under such conditions. The *in vitro* release of TGB-β1 from the xerogels, earlier sterilized by UV radiation, was assayed based on the growth factor's inhibitory effect on the proliferation of Mv1Lu mink lung epithelial cells, a cell line that is arrested by TGB-β1 in the G_1 phase of the cell cycle. The porous structure and the silica network were not appreciably affected by the incorporation of TGB-β1. Sustained release of TGB-β1 over a 7-day period was demonstrated. This work was the first published report in which a silica-based xerogel, obtained by the sol-gel technique, was used to deliver a biologically active growth factor. The implications of this investigation showed the potential of these materials as platforms for the release of drugs such as peptides and proteins.

The sol-gel technique allowed the incorporation of a trypsin inhibitor in silica xerogels. This protein has a similar size to that of growth factors (21 kDa), and for this reason, it was chosen as a model protein [40]. Four different amounts of trypsin inhibitor were incorporated into xerogels. The *in vitro* release studies showed first-order release kinetics for all samples; the data also indicated that the release was dose-dependent.

Roveri *et al.* [41] embedded different molecular mass heparins. After an extensive analysis of gel synthesis parameters, drug release properties and xerogel surface area, the authors concluded that the specific surface area of the matrix, which appeared to be the determinant parameter affecting drug release kinetics, could be modified by varying the catalyst/TEOS molar ratio

Table 2. Typical examples of silica xerogels and modified silica xerogels, obtained by the sol-gel method.

Bioactive agent or model compound	Silica carriers	Precursors	Catalysts and solvents	Drying temperature	Ref.
Vancomycin and bupivacaine	Microspheres and granules	TEOS	0.1 M HCl and NH_4OH	Room temperature	[2]
Nifedipine	Hybrid silica xerogel	TEOS BTSE	Citric acid; ethanol	60°C, 2 days	[5]
Nifedipine	Modified silica matrix	TEOS	0.01 M HCl; ethanol	50°C	[7]
TC	Xerogels	TEOS	HNO_3	40°C for 6 days before sintering at high temperatures	[8]
TC	Xerogels	TEOS	Methanol	40°C until constant weight. Some samples 80 or 120°C	[9]
TC and tritiate toremifene	Xerogel	TEOS	CH_3COOH	40°C, 18 h	[10]
Heparin sodium salt	Xerogels	TEOS	CH_3COOH or NH_4OH	Air-dried	[11]
Dexmedetomidine hydrochloride	Monoliths	TEOS	HCl, CH_3COOH, or HCl and NH_3	40°C until constant weight	[12]
Dexmedetomidine hydrochloride	Alkyl-substituted silica gel (rods and microparticles)	TEOS or TEOS with DMDES, MTES or ETES	HCl	Rods: 40°C until constant weight. Microparticles:mini spray dryer (~ 135°C)	[13]
Bovine serum albumin	Microspheres and monolithic sticks	TEOS	HCl and NaOH for pH adjusting; ethanol	Monoliths: 4 or 40°C. Microspheres: 120 and 135°C	[15]
Gentamicin	Polymer-silica xerogel composite microspheres	TEOS	HNO_3	50°C, 2 days	[25]
Benzoic acid	Composite layers	TEOS	0.01 M HCl solution; ethanol	Air-drying	[28]
Brillant blue FD&C	Doped silica xerogels	TEOS, MTES, VTES, PTES, PhTES	0.010 M HCl; ethanol	Room temperature, 1 day	[29]
Transforming growth factor-β1	Xerogels	TMOS	1 N HCl	37°C	[39]
Trypsin inhibitor	Xerogel	TMOS	0.1 N HCl; ethanol	37°C	[40]
Different molecular mass heparins	Xerogels	TEOS	HCl, methanol and NH_4OH, methanol. Two-step acid-base catalyzed method	Room temperature for 1 week and freeze drying at -40°C	[41]
TC and dexmedetomidine hydrochloride	Microspheres	TEOS	CH_3COOH	Mini spray dryer (~ 134°C)	[42]

BTSE: bis-1,2-(triethoxysilyl)ethane; DMDES: Dimethyldiethoxysilane; ETES: Ethyltriethoxysilane; MTES: Methyltriethoxysilane; PhTES: Phenyltriethoxysilane; PTES: Propyltriethoxysilane; TC: Toremifene citrate; TEOS: Tetraethyl orthosilicate; TMOS: Tetramethyl orthosilicate; VTES: Vinyltriethoxysilane.

Table 2. Typical examples of silica xerogels and modified silica xerogels, obtained by the sol-gel method (continued).

Bioactive agent or model compound	Silica carriers	Precursors	Catalysts and solvents	Drying temperature	Ref.
TC and tritiate toremifene	Xerogel	TEOS	HNO_3	40°C and sintered for 2 h at 700°C	[43]
Vancomycin	Xerogels	TMOS	1 N HCl	Room temperature to 70% of weight loss	[46,51]
Vancomycin	Xerogels, disks or granules	TMOS	1 N HCl	Room temperature until constant weight	[49,51, 52]
Dexmedetomidine hydrochloride	Fibers	TEOS	HNO_3 or NH_3, ethanol	40°C before cooling and spin drying	[53]
Dexmedetomidine hydrochloride	Microparticles	TEOS		Dried with a mini spray dryer (~ 135°C)	[54]
Lidocaine hydrochloride	Xerogels and surfactant-doped hybrid xerogels	TEOS and co-hydrolysis of TEOS with MTES or PETES	0.01 N HCl, ethanol, 1 M ammonia	Room temperature, 3 days and 50°C, 1 day	[55]
Sodium diclofenac	Nanocapsule-coated xerogel microparticles	TEOS	NaF ethanol	Room temperature, 10 days	[56]
Diclofenac diethylamine	Xerogels	TEOS	HCl, NH_3, ethanol	Room temperature or 3 h at 120°C	[57]
FD&C Yellow 6	Silica sonogels	TEOS	Without catalyst. No organic solvents	25, 40 and 80°C	[62]

BTSE: bis-1,2-(triethoxysilyl)ethane; DMDES: Dimethyldiethoxysilane; ETES: Ethyltriethoxysilane; MTES: Methyltriethoxysilane; PhTES: Phenyltriethoxysilane; PTES: Propyltriethoxysilane; TC: Toremifene citrate; TEOS: Tetraethyl orthosilicate; TMOS: Tetramethyl orthosilicate; VTES: Vinyltriethoxysilane.

used during the matrix synthesis. The heparin release kinetics from xerogels depended on the molecular mass of the heparin embedded; in most cases, data were fitted to the Higuchi diffusion model, but in the case of matrices with lower surface areas loaded with unfractionated heparin, zero-order kinetics was observed.

In another work, Ahola and co-workers [11] proposed the use of silica xerogel matrices with heparin as a local controlled release form at the site of trauma to prevent thrombus formation. The effect of different catalysts (nitric acid and acetic acid) and the moisture content of the matrix as well as of heparin concentration on the heparin release behavior were studied. The nitric acid-catalyzed gel released heparin faster than the corresponding acetic acid-catalyzed gel, and dry gel has a slower release rate than the one containing more moisture. Also, the authors demonstrated that heparin retained ~ 90% of its biological activity.

Viitala *et al.* [15] carried out an exhaustive analysis of the feasibility of incorporating proteins into silica xerogels. Bovine serum albumin was used as protein model, and various pHs were established during the sol-gel procedure to obtain microspheres and monolithic sticks. Several factors involved in the sol-gel process were analyzed in order to control the bioresorption of SiO_2 matrices (monolithic sticks and microspheres). The bovine serum albumin release profiles were linear, and diffusion was not observed because of the large size of proteins.

3.4 Calcium channel blockers

In 1998, Böttcher and co-workers [7] embedded nifedipine into a modified silica matrix using the sol-gel technique. This was one of the first works to perform a detailed analysis of drug release behavior from silica xerogels. Nifedipine is a calcium antagonist used to treat hypertension and angina pectoris. Obviously, the design of new controlled-release forms for this drug is a good alternative for the treatment of these diseases.

The influence of chemical or physical changes to the silica matrix was supported with the results obtained by Böttcher *et al.* [28]. The co-hydrolysis of $Si(OEt)_4$ with $MeSi(OEt)_3$ during sol preparation caused a chemical change in the xerogel and resulted in a decrease of nifedipine release rate. Also, Böttcher *et al.* [7] found that the rate of gel formation had an important influence on the structure and release behavior of xerogels. Higher sol concentrations and gelling temperatures yielded more porous composites with amorphously incorporated drug, which showed a faster drug release rate compared with composites prepared at lower temperatures. In the case of fast gelation at a temperature > 50°C, nifedipine in a crystalline state was detected by differential scanning calorimetry. Nifedipine release rate was inversely proportional to mean grain size. The addition of sorbitol increased the release rate, but the addition of polyethylene glycol 600 retarded nifedipine release from silica composites. In this work, the release rate was assumed to be governed by the relationship between the dissolution and diffusion rates, as the drug slowly dissolves into the permeating fluid phase and diffuses from the xerogel along the solvent-filled capillary channels.

In 2007, Maver and co-workers [5] incorporated a model drug (nifedipine) in hybrid silica xerogels; the study was focused on the determination of the physical state of nifedipine in silica pores and concluded that the solid matrix may contain drug in the amorphous form rather than in the crystalline state. In general, the amorphous form of drugs shows a faster dissolution and a higher solubility when compared with the crystalline form. Drug incorporation into purely TEOS-based silica decreases significantly the release rate; when bis-1,2-(triethoxysilyl)ethane (BTSE) was included, the drug dissolution rate increased.

3.5 Antiestrogens

Many reports have been published about the application of sol-gel processed silica xerogels as a carrier materials for toremifene citrate (TC) [8-10,42-45]. Toremifene citrate is an antiestrogenic compound that exerts its antitumor action through the inhibition of the estrogen-mediated growth stimulus. Antiestrogens have been used in the systemic treatment of hormone-dependent breast cancer [8]. The above-mentioned studies were carried out in order to develop an implantable controlled release formulation that could provide localized drug delivery at the desired site, as well as targeted and long-lasting disease control, reducing the amount of drug required [8,9]. Grains (56 – 200 µm) and disks (7 × 1.3 mm) of silica xerogels, obtained by the sol-gel method, were used for the *in vitro* study of the factors influencing the adsorption and desorption of TC. TEOS, polyethylene glycol 10000, deionized water and HNO_3 were mixed at room temperature; the sol solution was kept at 40°C for polycondensation for 18 h. The aged silica gels were washed and dried at 40°C for 6 days, and finally the silica gels were sintered at elevated temperatures (400, 550, 700, 800, 900 and 1000°C) for 2 h. Materials sintered at 400, 500 and 700°C were impregnated with TC solutions (pH 1.9, 2, 2.5 and 3.5) for 4 h for the grains and 4 days for the disks. The results showed that the adsorption of TC on the surface of silica xerogels was dependent on pH. Adsorption was most effective in the silica xerogel sintered at 700°C, which contained the largest pores and the lowest specific area of the silica xerogel studied. Although the sintering temperature of silica xerogel ranged from 400 to 700°C, it had no significant effect on the TC release rate. Drug release from TC-loaded grains and disks was linear with respect to the square root of time, indicating diffusion-controlled release. The TC release rate from the grains was faster than from the disks. However, short TC release times were detected; 60 – 80% of TC was released from the disks, and 100% of TC was released from grains after 24 h [8]. Taking these results into account, Ahola and co-workers proposed the addition of TC to a porous silica gel network during matrix formation in order to extend the

TC release time [9]. In this case, the silica gels were only dried at 40°C to constant weight. The effects of drug amount, drying temperature and polyethylene glycol (PEG) with a molecular mass of 4600 and 10,000 g/mol on the release rate of TC and on the degradation of the silica xerogel were analyzed. Degradation of the silica xerogel matrix in simulated body fluid (pH = 7.4) containing 0.5 wt% sodiumdodecylsulfate was determined by measuring dissolved $Si(OH)_4$ spectrophotometrically as a molybdenum blue complex at 820 nm. The TC concentration in the matrix did not have any influence on the degradation rate of the silica xerogel matrix; however, the reduction of the amount of TC in the matrix also decreased its release rate. The release profiles of TC corresponded to zero order, and the authors suggested that drug release was controlled by erosion of the silica xerogel matrix. When PEG was added to the xerogels, the TC release rate decreased; similar results were obtained by Böttcher *et al.* for nifedipine [7], but the opposite effect was detected for the release of benzoic acid from silica xerogels [28].

In previous work, Kortesuo and collaborators [43] evaluated the capability of silica xerogel absorbates to deliver TC. *In vitro* and *in vivo* studies were carried out; the distribution of TC in several organs, local tissue reactions, systemic effects and the biodegradability of subcutaneously implanted silica xerogel were evaluated. Toremifene citrate and tritiated toremifene were adsorbed on silica xerogels by the procedure applied by Ahola *et al.* [8]. *In vitro* release studies showed that ~ 60% of the loaded TC was released after 24 h, fitting into the square root of time kinetics. Silica xerogel matrices degrade according to zero-order kinetics. Cleaved silica disks with tritium-labeled toremifene were implanted subcutaneously on the backbone of mice. The disks were excised periodically, and radioactivity was measured. About 40% of tritiated toremifene was released during the first 4 days. After 28 days, the entire drug was released from the matrix and the remaining silica xerogel was ~ 45%. Radioactivity was detected in the liver, lungs, kidney and uterus; maximum levels were detected at 4 days. Sintered silica xerogels did not show any tissue toxicity, although minor local effects were present at the implantation site. It is important to point out that this is one of the first works demonstrating that silica xerogels are biocompatible and biodegradable drug carrier systems.

Taking their earlier studies into account, Kortesuo and co-workers evaluated the *in vitro* and *in vivo* behavior of a TC silica xerogel; in these cases, TC was added before gel drying [10]. As in a previous work [43], tritiate toremifene was included in the subcutaneously implanted silica xerogels. The silica xerogel implant (without TC) did not cause necrosis, although a fibrotic capsule was formed around the implant. Toremifene citrate released from the implant of xerogels with drug caused tissue irritation and necrosis in the close vicinity of the implant. No histological changes were observed in the liver, lymph nodes or kidneys. As expected with these matrices, TC release was retarded. In fact, sustained release of TC for > 6 weeks was detected. Histologically, changes in the uterus caused by TC were detectable. Compared with sintered silica xerogels (700°C) where TC was adsorbed [43], the incorporation of TC into the non-sintered silica xerogel matrix [10] retarded TC dissolution both *in vitro* and *in vivo*. Nevertheless, *in vivo* non-sintered silica xerogel degradation was increased.

In general, it has been shown that several compounds can be incorporated in silica xerogel monoliths and grains [7-10,39,40,43]. However, the inclusion of drugs in silica gel microspheres obtained by the sol-gel method is also possible [42]. It is important to consider that one of the main problems in the preparation of bulk materials is avoiding gel cracking during drying. The production of silica xerogel monoliths without drying control chemical additives such as formamide would take weeks, even months.

Two different drugs (TC and dexmedetomidine hydrochloride) were incorporated into sol-gel derived silica gel microspheres obtained by spray drying [42]. The drugs used had different physicochemical properties. *In vitro* release studies for TC and dexmedetomidine hydrochloride showed a dose-dependent burst effect followed by a slower release, which was also proportional to the drug concentration in the range from 3.9 to 15.4 wt%. Dexmedetomidine hydrochloride was released more slowly than TC from the silica gel matrix at drug concentrations < 11.4 wt% and at the same rate as TC when the drug concentration was 11.4 wt% or higher. Other works related to dexmedetomidine hydrochloride are included in the following sections. Also, the combination of silica xerogels with poly(ε-caprolactone-co-D,L-lactide) polymers in order to develop a TC controlled release formulation has been reported [44,45]. In general, the results of one of these studies demonstrate that the *in vitro* release of TC could be adjusted by varying the polymer composition and also the initial drug loading [45]. On the other hand, Rich *et al.* [44] found that the TC release period from poly(ε-caprolactone-co-D,L-lactide) could be adjusted from 3 months to 1 year by varying the initial molecular mass of the copolymer, by incorporating TC in silica xerogel into the composite device, or by changing the device geometry. The combination of silica xerogels with polymers is a subject that deserves further study owing to the fact that such an approach reduces the disadvantages of using these materials individually. Moreover, the probability of building nanometric structures of both materials in conjunction could yield to multifunctional systems.

3.6 Antibiotics

To support the use of xerogels as materials capable of releasing biologically active molecules at bone sites to affect growth, to fight infections, or to control pain, Falaize *et al.* [46] extensively studied the *in vitro* behavior of various xerogels when immersed in typical simulated physiological solutions. Four solutions were used: tris(hydroxymethyl)aminomethane

hydrochloric acid buffer solution plus electrolytes (TE), TE supplemented with 3 vol% H_2O_2, TE with 10 vol% serum and serum [47]. Three xerogel compositions were tested: a silica xerogel, a vancomycin-silica xerogel, and a calcium- and phosphorous-containing silica xerogel. Immersion studies were carried out with and without solution exchange. The results showed that silica xerogels are biodegradable materials that could serve as a scaffold for bone tissue growth. All xerogels studied are capable of forming an apatite surface layer on integral immersion. Supplementary *in vitro* and *in vivo* studies [48] of vancomycin release from silica xerogels were performed.

A time- and load-dependent release of vacomycin over 21 days was found. No 'burst' effect was seen, and a first-order release was observed, suggesting a diffusion-controlled process. The *in vivo* studies were carried out in New Zealand white rabbits; these studies demonstrated that vancomycin silica xerogels were biocompatible and resorbable, and they also demonstrated a gradual resorption of the xerogel granules that was accompanied by extensive bone growth. This research group has carried out several studies in order to demonstrate that silica xerogels are promising controlled release materials for the treatment of bone infections [49-52]. The authors have found that with varying room temperature sol-gel synthesis parameters, such as water/alcoxide molar ratio and vancomycin concentration, the release kinetics of xerogels can be tailored with respect to specific therapeutic goals [52]. For example, in some cases vancomycin release kinetic profiles included a faster first-order initial release and a subsequent steady release of near-zero order. Such a release profile is potentially beneficial for applications that require an immediate postoperative supply of antibiotics and subsequent steady long-term delivery [49]. Also, the tissue response to various xerogels in the subacute implantation phase (up to 4 weeks of implantation) was determined. Silica xerogels implanted either subcutaneously as disks or as granules in the iliac crest of New Zealand white rabbits showed a favorable tissue response [51]. Moreover, considering that the presence of an apatite surface film significantly reduces xerogel degradation [46,50], Ca- and P-free and Ca- and P-containing xerogels with and without apatite surface were used to determine the *in vivo* response. The granules, either with or without Ca and P, gradually resorbed over time. Ca- and P-containing granules with an apatite surface layer showed a slower resorption rate and a more extensive new bone growth than those with no apatite layer. The most favorable tissue response among granules with an apatite surface layer was obtained for vancomycin-loaded granules [51].

To understand the correlations between the drug release behavior and polymer biodegradation at different release stages, Xue and collaborators [25] prepared and analyzed poly(D,L-lactide-co-glycolide)(PLGA)/sol-gel derived silica xerogel composite microspheres. The antibiotic gentamicin was loaded into silica xerogels using an *in situ* method. Single- and double-layered composite microspheres were prepared by encapsulating gentamicin-loaded silica xerogels with biodegradable PLGA polymers, and *in vitro* release studies were carried out. For the single-layered composite microspheres, three drug release stages were observed: a sharp initial burst lasting for 1 day, a slow sustained release lasting for ~ 3 weeks and a fast sustained release stage over a period of another ~ 3 weeks. By applying another layer of polymer encapsulation, the double-layered composite microspheres showed a much reduced initial burst and a long sustained release stage of > 9 weeks. It was clearly observed that the combination of silica and PLGA may offer a new alternative for drug delivery applications.

Recently, Radin and co-workers [2] have reported the synthesis of sol-gel miscrospheres and granules by using a new two-step process: acid-base catalyzed hydrolysis followed by emulsification. The antibiotic vancomycin and the analgesic bupivacaine were incorporated into the sols, where both showed controlled, load-dependent and time-dependent release from the microspheres. The release rates from microspheres were slower in comparison with the granules' release behaviors.

3.7 Anesthetics

Important works analyzing the release behavior of dexmedetomidine hydrochloride from silica xerogel have been published [12,13,53,54]. Dexmedetomidine hydrochloride is an alpha-2-agonist widely used in veterinary anesthesia in several countries. In addition to its sedative effects, the alpha-2-agonist also causes analgesia. However, owing to the short clearance time, dexmedetomidine is rapidly eliminated and the duration of effect is brief. Kortesuo *et al.* [13] observed that when reaction precursor TEOS was partially substituted with tri- or dialkoxysilane, the release of dexmedetomideine and the degradation of the matrix decreased compared with pure TEOS-based gel. The release behavior was influenced by the form of the xerogel (rods or microspheres). Sustained delivery of dexmedetomidine from rods containing 25 mol% dimethyl(diethoxy)silane was obtained for at least 48 h in dogs after subcutaneous implantation. An extensive evaluation of synthesis parameters of the sol-gel processed spray-dried silica gel microparticles on the release rate of this drug was carried out by Kortesuo's research group [54]. They affirmed that one of the most important factors that influence the release rate of dexmedetomidine is the dilution of the sol before spray drying. *In vivo* studies were carried out in dogs; according to bioavailability studies, the dexmedetomidine release from silica gel microparticles was sustained, and the drug serum concentration was still measurable at 48 h after dosing of silica gel microparticles subcutaneously into the dorsal surface of the neck. On the other hand, dexmedetomidine hydrochloride has been incorporated into biodegradable silica fibers [53]. Fibers were characterized thoroughly by Raman spectroscopy, thermogravimetric measurements coupled with mass spectrometry, and scanning electron microscopy. *In vitro* release studies demonstrated that

drug release from sol-gel derived SiO_2 fibers consisted of three steps: an initial burst followed by a diffusion-controlled release behavior, and a step consisting of a slower release rate.

Wu and co-workers analyzed the controlled release of lidocaine hydrochloride from doped silica-based xerogels [55]. This drug is a frequently used local anesthetic in intradermal infiltration, topical anesthesia and peripheral nerve blocks. The design of a long-acting lidocaine hydrochloride form would have clinical importance. The effects of the textural properties of the xerogels and the drug/matrix/dopant interactions on the release rate were determined. The results suggested that the release of lidocaine hydrochloride can be easily controlled by partially substituting TEOS with MTES or propyltriethoxysilane (PTES), and/or by adding Igepal CO 720, a non-ionic surfactant used as dopant agent. The release of lidocaine hydrochloride was suppressed by the addition of the dopant, which was attributed to the hydrophobic interaction between the drug and the surfactant. This work confirmed that drug release can be successfully controlled by manipulating the textural properties and these interactions.

3.8 Analgesic and anti-inflammatory drugs

Da Fonseca and collaborators [56] proposed assembling polymeric Eudragit S100® (Röhm Pharma) nanocapsules at the surface of drug-loaded xerogels in which sodium diclofenac was used as hydrophilic drug model. The *in vitro* release studies showed gastro-resistance and a sustained release of sodium diclofenac.

Silica xerogels containing diclofenac diethylamine were prepared by Czarnobaj and Czarnobaj [57], who demonstrated that the release of diclofenac was highly catalyst-dependent. The effect of two drying temperatures was analyzed as well. Thermal treatment at 120°C reduced the release of diclofenac from xerogels obtained with acid and basic catalyst. In addition, this research group has reported the inclusion of cisplatin into silica xerogels and organically modified silica xerogels [58-60].

3.9 Dyes

Wu and co-workers [29] studied the relationship between brilliant blue FD&C (BBF), a highly water-soluble dye, and xerogel composition. Xerogels were prepared by a two-step sol-gel process. Tetraethoxysilane (TEOS), methyltriethoxysilane (MTES), vinyltriethoxysilane (VTES), propyltriethoxysilane (PTES) and phenyltriethoxysilane (PhTES) were used as precursors, and cetyltrimethylammonium bromide (CTAB), sodium dodecyl sulfate (SDS) and hydroxypropyl cellulose (HPC) were used as dopants. BBF release experiments from the xerogels were performed in three different media (0.0001 M HCl solution, water and 0.001 M NaOH solution). The experimental results showed that the released amount of BBF in basic media was higher than acidic solution and water. Organically modified silica xerogels were used to modify the release behavior. For example, in basic media, the released amount of BBF decreased in the order TEOS > MTES > VTES > PTES > PhTES for both SDS- and HPC-doped xerogels. For the different dopants, the released amount of BBF was in the order SDS > HPC ~ no dopant > CTAB. Similar results had been found previously [61]. This research group attributed the experimental results to the textural properties of the xerogels, to the electrostatic and hydrophobic interactions between BBF and xerogel/matrices/dopants, and to aromatic–aromatic interactions between BBF and PhTES/TEOS xerogels. This work showed that BBF release could be easily controlled by changing the precursors and/or by adding dopants with different charges in order to design new silica materials for controlled drug release.

Ocotlán-Flores and Saniger reported the synthesis of catalyst-free SiO_2 sonogels prepared by the sonication of a neutral distilled water/tetraethyl orthosilicate mixture [16]; subsequently, we evaluated the feasibility of using a catalyst-free SiO_2 sonogel as a pharmaceutical delivery system, incorporating a certified color additive (FD&C Yellow 6 or sunset yellow [SY]) as a model compound for release experiments [62]. The influence of the drying temperature, the amount of SY incorporated into the sonogel and the grain size on release behavior were analyzed as well. The analysis of variance for SY-loaded sonogels dried at 80°C with different SY loads showed no significant differences between the Higuchi's constants (K_H) irrespective of the mean grain size. On the contrary, for SY-loaded sonogels dried at 40°C, differences were found between sonogels loaded with 2.7, 7.7, 12.2 and 18.2% of SY; however, no significant differences were noticed between the mean grain sizes analyzed. **Figure 4** shows the SEM micrographs of samples of SY-loaded sonogels. Considering that the preparation of sonogels by the catalyst-free method allows an easy encapsulation, sonogels may offer an interesting alternative for drug release in the pharmaceutical field.

Up to now, several silica xerogels containing drugs have been investigated; many of them seem to be promising materials for controlled drug delivery to target sites, alternatively to be used as implantable drug delivery systems for long-term disease control. **Table 3** shows the drug releasing behavior and the matrix degradation kinetics of some silica-based xerogels described previously.

4. Expert opinion

Since the publication of the first article proposing the pharmaceutical applications of silica xerogels [37], several issues have been studied extensively by different research groups [5,7,9,15,20,35,40,46,49,54,58,63], including their chemical and physical properties, *in vivo* biocompatibility, microporous structure, drug adsorption or drug entrapment during sol state, interactions with physiological solutions, degradation of silica matrices and potential drug delivery.

Nevertheless, the authors of this review believe that further scientific research is needed to confirm and verify the safety

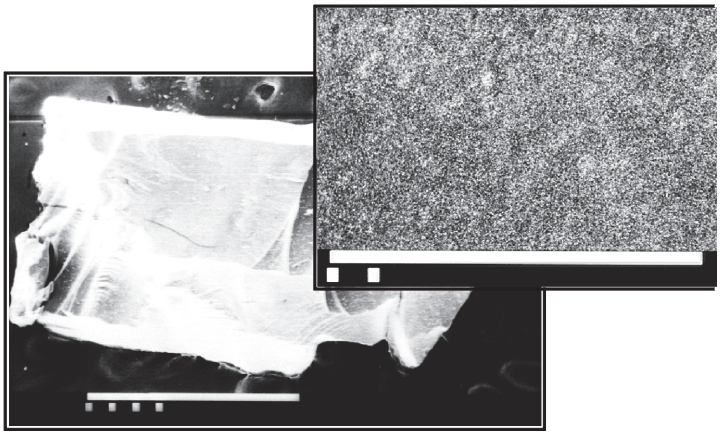

Figure 4. Scanning electron micrographs of sunset yellow-loaded sonogels, × 45 (bar = 1 μm) and × 4500 (bar = 1 μm).

and efficacy of this kind of material, and also to establish their real potential as biodegradable drug delivery materials and to provide adequate evidence for their approval as pharmaceutical systems for humans and animals. It has been documented extensively that these composites have several technological advantages with respect to other drug delivery scaffolds, including the possibility to encapsulate several drugs and highly sensitive molecules, such as proteins and peptides, into the gel, for sustained and controlled release. Perhaps one of the main advantages of these systems is the flexibility of the method and the possibility of modifying the drug release rate by adjusting parameters such as preparation methods (casting or spray-drying), sol composition, type of precursor, precursor ratios, sol pH, catalyst type and concentration, drying conditions, and sol ageing. It is important to point out that several works have shown that silica xerogels are biocompatible and resorbable materials; thus, silica xerogel seems to be a promising carrier material for implantable controlled drug delivery systems. An extra attribute of these materials is the possibility to prepare them by a sonolysis procedure, avoiding the use of organic solvents and acid or base catalysts. Moreover, the sol-gel method allows the preparation of disks or granules that could be administered directly to the patient. One of the most important advantages of the production of silica xerogels by the sol-gel method is that preparative variables can be adjusted in order to incorporate sensitive drugs such as peptides and proteins.

Nevertheless, it is clear that further effort in the field of silica xerogels is necessary in order to develop xerogel composites available in the market that are commercially viable and provide an advantage to patients. The hybrid inorganic–organic systems combining gel materials and some biodegradable polymers offer a new perspective to improve the properties of both materials, as well as the possibility of having new pharmaceutical applications by distinct administration routes. A more futuristic idea is to take advantage of the chemical properties of these materials in order to assembly drug delivery systems to encapsulate biotechnological entities. Xerogels are an interesting option in the nanotechnological build-up of pharmaceutical and medical intelligent devices. Other areas of application involving these technologies are implanting devices, tissue engineering, and nano- and micromedical devices.

Undoubtedly, the use of modified release drug formulations has increased considerably in recent years. This is partly due to the advances in formulation technologies allowing formulations to be designed that provide a better control of drug release at the site of action. However, only a little research has been transformed to commercially available drug delivery systems because of the high costs of research and development scale-up and the length of the procedures needed to secure approval from the regulatory agencies. In the authors' opinion, it is possible that xerogels will be introduced into the market in the near future. The flexibility of the sol-gel method in both the encapsulation and the release of drug molecules represents a significant industrial advantage and opens up an opportunity to scale-up the production of silica xerogels. Highly specialized equipment is not required. Some studies have shown that the sol-gel method used to produce silica xerogels is highly reproducible and efficient for drug incorporation. Although plenty of reports for the transformation of basic investigations into the industrial production of xerogels have been published, we believe that the area of investigation and application of silica xerogels will be strengthened in the coming years.

Finally, it is important to consider that the advent of drug delivery systems may well enhance the future of research-based pharmaceutical companies. Through these systems, products may have an extended patent life and be produced at low cost, and products that have not been commercially available owing to high production costs will now be commercially viable. Thus, the consolidation of silica xerogels as extended and controlled drug delivery systems could be accelerated in the coming years.

Table 3. Drug releasing behavior and matrix degradation kinetics for some silica xerogels.

Drug	Releasing behavior	Matrix degradation kinetics	Ref.
Vancomycin and bupivacaine	The release of both drugs from granules occurs in two stages: a fast release followed by a second stage of slower release (terminal stage). Several models were used to analyze the data: Higuchi, zero order, first order, Hixson and Crowell and Baker-Lonsdale	The dissolution of silica granules and microspheres can be described well by typical first-order dissolution and it was independent of the specific drug that was incorporated	[2]
Toremifene citrate	The release of TC corresponded to zero order and was proportional to the drug concentration between 11.5 and 34.4% w/w		[9]
TC and tritiate toremifene	About 90% of the loaded tritium-labeled toremifene was released after 99 h *in vitro*. The silica xerogel matrix gave sustained release of TC *in vivo* for > 42 days	The amount of silica released after 99 h was equivalent to about 65% weight loss of silica xerogel matrix. Weight loss *in vivo* after 42 days was ~ 75%	[10]
Dexmedetomidine hydrochloride	Dexmedetomidine was released over a prolonged time period from silica xerogels rods. The release rate of the drug from the silica xerogel rods with the different loads of dexmedetomidine in the silica sol (0.5, 1, 2% w/w) was proportional to the drug concentration		[12]
Different molecular mass heparins	The release rate and kinetics profile of heparin from silica xerogels depends on its molecular mass. It was possible to obtain diffusive (fittable with Higuchi model) or zero-order release kinetics		[41]
Vancomycin	The initial release kinetics were first order and were followed by a slower, steady release of near-zero order. The release kinetics and the amount released were load dependent. Good correlation of the released drug versus the square room of time. A linear relationship was observed up to 14 days and up to 21 days for samples containing either 2.2 or 11.1 mg vancomycin/g xerogel. Variations in the water/alcoxysilane ratio affected the release process extensively		[49,52]
Dexmedetomidine hydrochloride	The dexmedetomidine release was diffusion controlled and conformed to the square root of time kinetics from microparticles prepared at pH 1 – pH 5. The amount of drug released after 30 h dissolution varied between about 10% (pH 2.3 and pH 3) and 40% (pH 1)	At the end of the dissolution period, about 99% (pH 2.3 and pH 3) to 80% (pH 5) of the matrix still remained	[54]
Lidocaine hydrochloride	According to the Peppas Power Law model, a diffusion-controlled release was determined for the release of lidocaine	Hybrid gels dissolve more slowly than the pure silica gels. The dissolution of the xerogels was negligible and did not affect drug release	[55]
Diclofenac diethylamine	For the base-catalyzed silica xerogels, 72 – 98% of the drug was released within 5 h. *In vitro* release profile in two steps: an initial diffusion-controlled release followed by a slower release date. For the acid-catalyzed xerogels only 1% was released within 10 days. Data were fitted to the Higuchi model	The *in vitro* degradation of base-catalyzed and acid-catalyzed silica xerogels was 0.7 – 0.8 and 0.2 – 0.4% a month, respectively	[57]

TC: Toremifene citrate.

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