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In vitro release of dexmedetomidine from silica xerogel monoliths: effect of sol-gel synthesis parameters

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Abstract

Dexmedetomidine, an alpha 2-agonist, was incorporated as a hydrochloride salt into silica xerogel in order to evaluate the effect of sol-gel synthesis parameters: pH of the sol, water/alkoxide molar ratio, drug concentration and size of the device on the drug release rate and degradation rate of the matrix. This study showed that diffusion controlled the release of dexmedetomidine from silica xerogel prepared between pH 1 and pH 5. The drug release was, however, slowest near the zero charge of silica xerogel (pH 2–3). The burst of dexmedetomidine, a lipophilic, but in the form of hydrochloride salt water-soluble drug, was increased from the matrix prepared either below or above the isoelectric point. It follows that the optimum pH for preparing a drug delivery device for dexmedetomidine, is near the zero charge of silica xerogel, where the degradation of the matrix was also slowest. In addition to processing pH, the release rate of drugs can be controlled by changing the water/alkoxide molar ratio of the sol.

Keywords: Silica xerogel; Drug delivery; Dexmedetomidine

1. Introduction

Sol-gel derived silica xerogels have been investigated as biodegradable carrier materials for controlled drug delivery (Unger et al., 1983; Nicoll et al., 1997; Böttcher et al., 1998; Kortesuo et al., 1999; Ahola et al., 2000; Kortesuo et al., 2000). Unger and co-workers suggested the possibility of using sol-gel derived silica xerogels for controlled drug delivery as early as 1983. The sol-gel process involves the manufacture of an inorganic matrix through the gelation of a colloidal suspension (sol) at low temperature and in mild conditions that allows the incorporation of sensitive molecules, like proteins and peptides into the gel

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(Nicoll et al., 1997; Santos et al., 1999; Ahola et al., 2001). The drug substance incorporated into the sol is distributed within the porous silica xerogel network. The material causes no adverse tissue reactions and degrades in the body to $Si(OH)_4$, which is eliminated through the kidneys (Kortesuo et al., 2000).

The synthesis parameters that control the drug release from silica xerogel matrix are not, however, widely studied. Compositions, temperature, pH of the sol as well as drying and heating conditions influence the structures and properties of silica xerogels prepared by the hydrolysis and condensation of tetraethoxysilane. Structures and properties depend especially on the water content and the type or the concentration of the catalyst (Ro and Chung, 1991; Curran and Stiegman, 1999). Gelling time is longest near the isoelectric point at pH 2 and rapid gelling occurs in the region of very low pH (< 1) or above the isoelectric point, resulting in more porous structures (Curran and Stiegman, 1999; Meixner and Dyer, 1999). An increase in the water to alkoxide molar ratio correlates with increasing specific surface area, which partly controls the release of incorporated drugs (Tan et al., 1996).

Polymer erosion can be classified as bulk (homogeneous) or surface (heterogeneous) erosion. With an ideal bulk erosion process, material is lost from the entire polymer volume, i.e. the surface to volume ratio of the material defines the erosion rate. The erosion rate depends on the total amount of material and generally decreases as the material is depleted. The length of time the polymer resists can be altered by changes in the chemical composition but not by changes in the material size or shape (Tamada and Langer, 1993). For surface eroding systems, the external surface area and the geometry of the device, i.e. the radius to thickness ratio, have an effect on the rate of degradation of the matrix (Katzhendler et al., 1997; Akbari et al., 1998). As the matrix erodes, the drug release is characterised by zero order kinetics. This is difficult to achieve, however, and often the diffusion of the drug controls the release rate. The release may be an intermediate process between an erosion and a diffusion controlled system (Ritger and Peppas, 1987). Degradation of porous silica xerogel occurs through hydrolysis of the siloxane bonds through the entire network. The hydrolysis rate depends to a great extent on pH and on the amount of OH-groups on the surface (Brinker and Scherer, 1990).

The aim of this study was to evaluate the suitability of silica xerogel as a carrier material for the controlled release of dexmedetomidine, an alpha 2-agonist. This study evaluated the effect of formulation variables, pH of the sol, water/alkoxide molar ratio and drug content as well as the size of the silica xerogel device on the degradation rate of the matrix and dissolution rate of dexmedetomidine.

2. Materials and methods

2.1. Preparation of dexmedetomidine hydrochloride incorporated silica gels

Silica sols were prepared at room temperature by the hydrolysis and polycondensation of tetraethoxysilane (TEOS, Aldrich) with various water and catalyst contents. Varying amounts of hydrochloric acid or acetic acid were used as acid catalysts (Table 1). Silica sol with pH 5 was prepared by two-phase catalysis with HCl and NH_3. Dexmedetomidine hydrochloride (Orion Corporation, Finland) was dissolved to form a clear hydrolysed sol. The concentration of added dexmedetomidine hydrochloride in silica sol varied between 0.5 and 2.0 wt.%. The silica sol

Table 1
Mole ratios of synthesis precursors in silica sol formulations

pH	TEOS	H_2O	HCl	Dex HCl	CH_3COOH
1	1	14	0.15	0.02	–
2.3	1	14	0.0025	0.02	–
3	1	14	–	0.02	0.023
5[a]	1	14	0.0025	0.02	–
2.3	1	6	0.0025	0.02	–
2.3	1	28	0.0025	0.02	–

[a] The pH of silica sol was 2.3 after hydrolysis. Before dexmedetomidine hydrochloride addition pH was adjusted with 0.1 M ammonia to pH 5.

was cast into Teflon moulds that were tightly closed and kept at 40°C and 40% relative humidity for polycondensation. The silica gels were dried at 40°C and 40% relative humidity to a constant weight to obtain silica xerogel containing incorporated dexmedetomidine hydrochloride.

2.2. Effect of device size on the release rate

In order to examine the effect of device size on the drug release rate, rods of varying diameters (0.95 mm, SD 0.03; 1.4 mm, SD 0.02 and 1.9 mm, SD 0.02) and lengths of 11.5 mm (SD 0.4) were prepared by casting a sol processed at pH 3 containing 1 wt.% dexmedetomidine HCl. In addition, a disc-shaped device with a diameter of 4.6 mm (SD 0.01) and thickness of 1.59 mm (SD 0.07), was prepared. The dimensions of each device were measured using a micrometer screw gauge prior to dissolution studies.

2.3. Drug release and analysis

The dissolution profiles (each data point is the mean of three values) of dexmedetomidine and silica were determined using USP 24 dissolution apparatus II (paddle method, Sotax AT6, Basel, Switzerland and VanKel VK700, USA) at a constant temperature (37°C) with a rotation speed of 50 rpm. Simulated body fluid (SBF, pH 7.4) containing 0.5% (m/v) 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), $K_2HPO_4 \times 3H_2O$ (1.0 mM), $MgCl_2 \times 6H_2O$ (1.5 mM), $CaCl_2 \times 2H_2O$ (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 concentrated hydrochloric acid.

The volume of dissolution medium was 250 ml. At each sample interval, a 2 ml sample was withdrawn from each flask and replaced immediately with an identical volume of fresh medium. The absorbance values of the dissolution samples were measured on a UV–visible spectrophotometer (Hewlett–Packard 845/A, USA) at maximum absorbance of dexmedetomidine HCl (A_{220}). 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).

The following equation was used to evaluate the release kinetics of dexmedetomidine:

$$M_t/M_\infty = kt^n$$

The diffusional exponent (n) of the log (released drug, M_t/M_∞) versus log time plots and release rates (%/$h^{1/2}$) were calculated from the fitted linear regression lines. The 0.5 diffusional exponent in the log–log plot indicates diffusional square root of time dependence, a diffusional exponent between 0.5 and 1.0 which is an anomalous non-Fickian transport and an exponent of 1.0 zero order release kinetics with non-swellable polymers (Ritger and Peppas, 1987). If the penetration rate of medium into the matrix is in the same range as the drug diffusion, the release kinetics is non-Fickian, anomalous.

3. Results

3.1. Effect of processing pH on the release rate of dexmedetomidine at pH 7.4

Silica xerogel rods (∅ 1.4 mm, SD 0.02) containing 1 wt.% dexmedetomidine HCl in the sol were prepared at varying pH. The release rate of dexmedetomidine was slowest without any large initial burst (6%) from rods prepared at pH 2.3 and fastest with an initial burst about 20% from rods prepared at pH 5 (Fig. 1A). At pH 1, however, the initial burst was accounted for approximately 35%. Dexmedetomidine release conformed to diffusional release kinetics as determined from the slopes of log Q versus log t plots. The diffusional exponent (n), characteristic to the release mechanism, varied between 0.23 (pH 1) and 0.61 (pH 2.3) (Table 2).

Dexmedetomidine was released faster from varying xerogel formulations than the matrix degraded (Fig. 1B). At the end of the dissolution test, about 75% (pH 1) to 85% (pH 2.3) of the

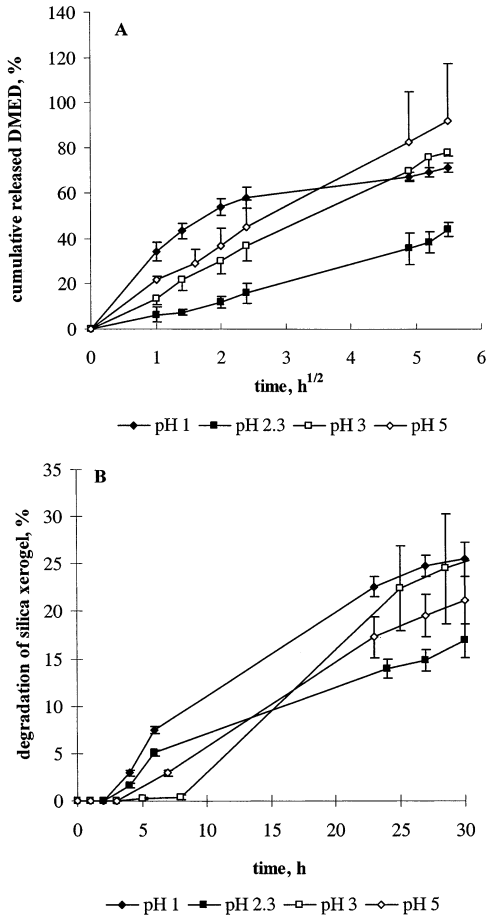

Fig. 1. (A) Release of dexmedetomidine and (B) degradation of the matrix from silica xerogel rods (∅ 1.4 mm) containing 1 wt.% dexmedetomidine HCl in the sol prepared at pH 1, pH 2.3, pH 3 and pH 5 with water/TEOS ratio 14.

matrix still remained, whereas the amount of released dexmedetomidine varied between 50% (pH 2.3) and 80% (pH 1, pH 3 and pH 5).

3.2. Effect of water/TEOS ratio

The effect of water/TEOS molar ratio (r) on the release rate of dexmedetomidine and degradation rate of the matrix was studied at pH 2.3. Decreasing the molar ratio of water to TEOS from $r = 28$ to $r = 6$ also decreased the release rate of dexmedetomidine. (Fig. 2A). Drug release was diffusion controlled from silica xerogels having $r = 14$ ($n = 0.61$) and $r = 28$ ($n = 0.56$, Table 2). From $r = 6$ silica xerogel, the exponential coefficient deviated from the diffusional release mechanism ($n = 0.71$, SD 0.019). The degradation rate of the matrix was 20% faster for rods prepared with water/TEOS ratio 28 than for rods prepared with water/TEOS ratio 6 or 14 (Fig. 2B).

3.3. Effect of dexmedetomidine concentration

The effect of drug concentration was studied at pH 3. As seen in Fig. 3, the release rate of dexmedetomidine from silica xerogel rods with the different loads of dexmedetomidine in the silica sol (0.5, 1, 2 wt.%) was proportional to the drug concentration.

3.4. Effect of device size on dexmedetomidine release rate

A model formulation containing 1 wt.% dexmedetomidine HCl in the sol at pH 3 was used in studies investigating the influence of silica xerogel device size on the release rate of drug (Fig. 4A). Rods with diameters of 1.9 mm (77 mm^2), 1.4 mm (54 mm^2) and 0.95 mm (36 mm^2) and a disc with a diameter of 4.6 mm (56 mm^2) were prepared. After the burst, the release rate was proportional to the square root of time and was slightly faster for rods with a diameter of 0.95 and 1.4 mm. The burst release of dexmedetomidine corresponded to about 40% from rods with a diameter of 0.95 mm, whereas it was less than 20% from rods with a diameter of 1.4 and 1.9 mm. From the disc-shaped device the dexmedetomidine release was initially as fast as from the rods. The release rate slowed down, however, and after 30-h dissolution about 54% was released from the discs, whereas about 100% was released from 0.95-mm rods, 80% from 1.4-mm rods and 70% from 1.9-mm rods.

The amount of silica xerogel degraded after 30-h dissolution was lowest (15%, SD 0.8) for a disc-shaped device and highest (28%, SD 4.4) for a rod with a diameter of 0.95 mm (Fig. 4B). Rods with diameters of 1.9 and 1.4 mm as well as discs had a lag phase before the degradation of the silica xerogel matrix began.

4. Discussion

The present study evaluated the effect of sol-gel processing parameters on the delivery of dexmedetomidine and the degradation behaviour of silica xerogel matrix. Varying the processing pH or the water/TEOS ratio and thus affecting the structure of silica xerogel, we could vary the degradation rate of the silica matrix and the release rate of dexmedetomidine.

Dexmedetomidine release was diffusion controlled as calculated from the slopes of the log Q (released drug) versus log t (time) plot at all variations of pH (Ritger and Peppas, 1987). The drug was released when the waterfront penetrated the porous silica xerogel matrix. The drug is a drug solution in the pores of silica xerogel and slowly diffuses from the system along solvent-filled capillary channels. Böttcher and co-workers have earlier shown that the release of nifedipine was diffusion controlled from silica xerogel grains (Böttcher et al., 1998). The release rate of dexmedetomidine was slowest around the zero charge (pH 2–3). At pH 1, where the charge of the silica xerogel is partly positive having the same charge as dexmedetomidine and the pores are larger than at zero charge (Curran and Stiegman, 1999), the burst effect was approximately 35%. Above the isoelectric point (at pH 5), when the pore size again increases, dexmedetomidine was easily diffused out of the matrix. Dexmedetomidine was probably bound to the uncharged SiO_2 at a pH around the zero charge of the matrix by hydrogen bonding (Iler, 1979).

By varying the amount of the catalyst and thus adjusting the pH in the sol-gel process, the structure of the silica xerogel and the degradation rate of the matrix can be changed. The degradation rate of the matrix was slowest when the sol was prepared at the isoelectric point of silica with hydrochloric acid as the catalyst (pH 2.3). Around the point of zero charge, at pH between 2 and 3, the mean micropore diameter reaches a minimum value and silica xerogel has the most condensed structure (Curran and Stiegman, 1999; Meixner and Dyer, 1999). However, the degradation rate of the matrix was enhanced when hydrochloric acid was changed to a weak acid (acetic acid) at pH 3. In acetic acid catalysed silica sol at pH 3, the hydrolysis reaction takes longer than sol catalysed in hydrochloric acid at pH 2.3, although both xerogels are produced near the isoelectric point (Brinker and Scherer, 1990). Thus, polycondensation reaction has proceeded further with strong acid than in the reaction catalysed by a weak acid. The change in structure depending on the type of the catalyst, may result in the increased degradation rate of the matrix prepared at pH 3 as compared to the silica xerogel matrix prepared at pH 2.3 with HCl (Brinker and Scherer, 1990).

In addition to polymerisation pH, water/TEOS ratio (r) also affected the release rate of dexmedetomidine. The release rate was decreased and the release kinetics deviated from the diffusion controlled process ($n > 0.5$), when the water/TEOS ratio of silica sol was lowered to $r = 6$. Diffusion of drug solution from the matrix was restricted, possibly due to the more condensed

Table 2
Release of dexmedetomidine from silica xerogel rods containing 1 wt.% of drug in the sol prepared at various pH with water/alkoxide ratio 14 (r) or with water/alkoxide ratio 6 and 28 at pH 2.3 ($n = 3$)

Formulation	n[a] (SD)	Release rate%/$h^{1/2}$ (SD)	Correlation coefficient
pH 1; $r = 14$	0.23 (0.03)	6.98 (0.45)	0.930
pH 2.3; $r = 14$	0.61 (0.11)	8.49 (1.36)	0.987
pH 3; $r = 14$	0.53 (0.06)	14.70 (0.36)	0.997
pH 5; $r = 14$	0.43 (0.06)	16.03 (5.34)	0.986
pH 2.3; $r = 6$	0.71 (0.02)	6.21 (0.62)	0.993
pH 2.3; $r = 28$	0.56 (0.04)	11.92 (0.94)	0.996

[a] n is the diffusional coefficient determined from the slope of the log Q vs log t plot.

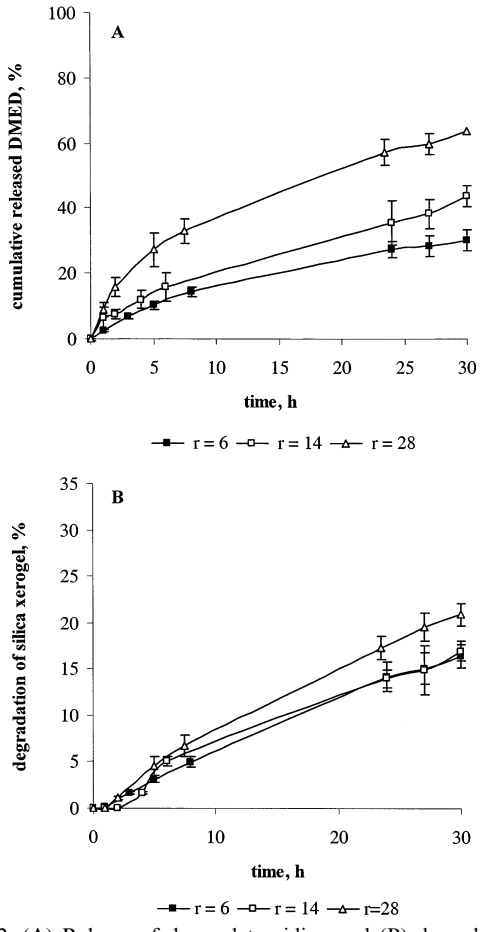

Fig. 2. (A) Release of dexmedetomidine and (B) degradation of matrix from silica xerogel rods (∅ 1.4 mm) containing 1 wt.% dexmedetomidine HCl in the sol prepared at pH 2.3 with water/TEOS ratios $r = 6$, $r = 14$, $r = 28$.

structure of the silica xerogel. The microstructure of xerogels is dependent on the water/TEOS ratio (r) during sol synthesis (Meixner and Dyer, 1999). At low values of r, close to the hydrolytic stoichiometric value of $r = 4$, gelation occurs readily and the structure of xerogel shows no mesoporosity or microporosity.

The release of dexmedetomidine was governed by diffusion and simultaneous degradation of the matrix. When the release is diffusion controlled, it is anticipated that the release is faster with decreasing device diameter and SA/V (surface area to volume ratio of the material) defines the diffusion rate (Tamada and Langer, 1993; Lemmouchi and Schacht, 1997). This was also shown in this study, because the release rate was somewhat faster from rods with a diameter of 0.95 and 1.4 mm. From the disc-shaped device, the dexmedetomidine released, after the burst, at the same rate as from the rod with a diameter of 1.9 mm. Both devices had the same SA/V ratio. In addition, about 40% was released in an hour from a rod with a diameter of 0.95 mm suggesting that the device is possibly too small for controlled drug delivery.

Silica xerogel is very porous and degrades by hydrolysis of the siloxane bonds on the surface through the matrix, when water penetrates the microporous structure resulting in mass loss of the silica device (Brinker and Scherer, 1990). The cumulative release of $Si(OH)_4$ was monitored over the release period in order to approximate the life time of the devices with different geometry. The degradation rate of silica xerogel seems to be dependent on the total amount of the material, meaning that the SA/V ratio (surface area to volume ratio of the device) defines the erosion rate. A study of the effect of the size on the degradation on poly(DL-lactic acid) showed that large devices degrade much faster than smaller ones, but the erosion time is the same (Tamada and Langer, 1993; Grizzi et al., 1995). With an erosion controlled system, larger devices exhibit

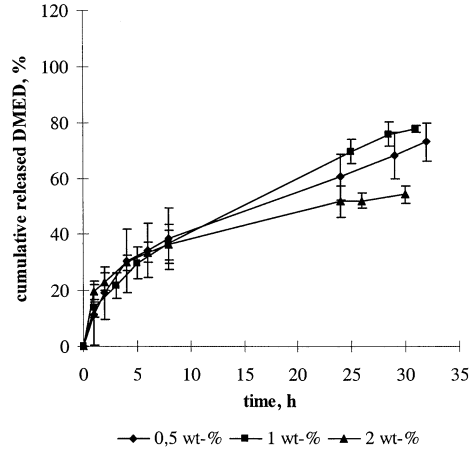

Fig. 3. Release of dexmedetomidine from silica xerogel rods (∅ 1.4 mm) prepared at pH 3 with water/TEOS ratio 14 and containing 0.5, 1 and 2 wt.% dexmedetomidine HCl in the sol.

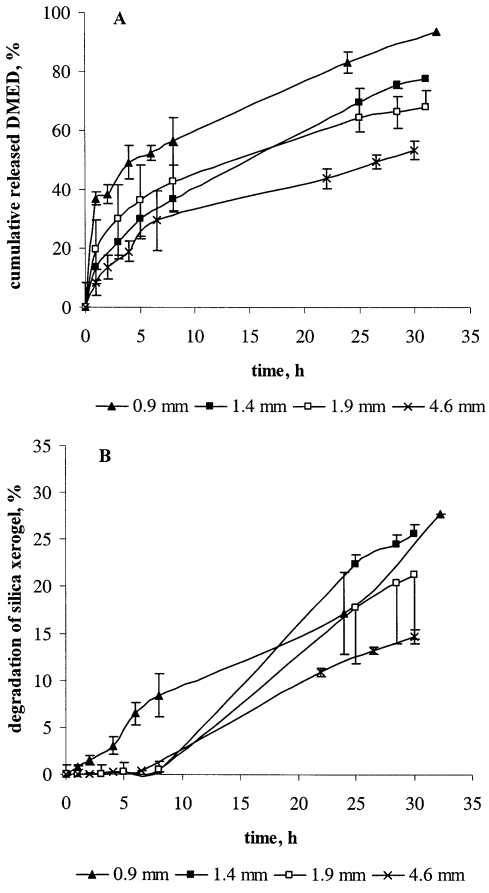

Fig. 4. (A) Release of dexmedetomidine and (B) degradation of matrix from silica xerogel devices prepared at pH 3 with water/TEOS ratio 14 containing 1 wt.% dexmedetomidine HCl in the sol. Rods with a length of 11.5 mm and diameters of 0.95 mm (36 mm^2), 1.4 mm (54 mm^2) and 1.9 mm (77 mm^2) or disc with a diameter of 4.6 mm and thickness of 1.5 mm (56 mm^2).

longer periods of erosion, although the erosion rate is constant (Tamada and Langer, 1993; Akbari et al., 1998).

5. Conclusions

The present study showed that dexmedetomidine was released over a prolonged time period from silica xerogel rods. The release rate of dexmedetomidine was proportional to the drug concentration between 0.5 and 2 wt.% in the sol. The release rate of dexmedetomidine can be controlled by varying the processing pH and water/alkoxide ratio during sol-gel processing. In addition, the size of the silica xerogel influenced the release rate of the drug. The release of dexmedetomidine from porous silica xerogel was chiefly governed by diffusion and simultaneous degradation of the silica xerogel matrix.

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