Release kinetics from porous xerogels determined by sol-gel synthesis, porous nanostructure and immersion

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Room temperature processed silica sol-gel materials are bioresorbable, biocompatible, controlled release materials. The benefits of porous xerogels for the controlled delivery of drugs have been well documented. However, the relationship among synthesis conditions, nanostructure, and release kinetics has not been addressed in any significant way. This relationship needs to be thoroughly analyzed in order to control release kinetics precisely.

We address this relationship among synthesis, nanostructure and drug release kinetics of xerogels. The effects of sol-gel process parameters such as solvent (for drug introduction), pH of the sol, water to alkoxide molar ratio *R*, and drug payload on xerogel nanostructure and release kinetics were determined.

Using Brunauer–Emmett–Teller (BET) sorption analysis, it is shown that the above mentioned processing parameters affect the nanostructure of xerogels. Varying solvent and pH of the sol produces xerogels with different specific surface areas and pore volumes. Both the specific surface area and pore volume vary linearly with water to alkoxide ratio. The Higuchi rate coefficient as a measure for release kinetics is linearly related with variations of these parameters associated with the nanostructure. It is noteworthy that the porous xerogel appeared non-porous with negligible specific surface area and pore volume when drug was introduced. The release kinetics varied linearly with drug payload. Thus, high drug payload into xerogels results in pore filling, but the pore filling does not affect release kinetics. There are also nanostructural variations, mainly silica restructuring, arising from immersion. Release kinetics can be estimated by drug payload and the nanostructural parameters which vary with sol-gel synthesis. A general equation that takes into consideration the effects of both nanostructure and drug payload on release kinetics is formulated.

Keywords: sol-gel, controlled release, nanostructure, *in vitro*

1. Introduction

Room temperature processed sol-gel silica-based xerogel are bioactive, biodegradable and biocompatible materials [1]. In a typical sol-gel process, silica precursors such as tetramethoxysilane (TMOS) or tetraethoxysilane (TEOS) are subject to a hydrolysis-condensation reaction to form a porous, glassy solid. By virtue of room temperature synthesis and mild processing conditions, therapeutic agents can be incorporated in the porous silica xerogel without experiencing a deleterious change in their biological functionality [2–8].

In general, drugs are added to the liquid sol, and after hydrolysis-condensation, the drugs are homogenously dispersed within the silica xerogel. During the condensation step, silica colloids that form in the sol with a size of about 5 to 10 nm will pack differently and, thereby yield various xerogel structures with porosity ranging from microporous (pore size <1.5 nm) to mesoporous (pore size >1.5 nm) depending on the actual processing conditions [8–10].

When the drug molecule is smaller than the pore size of the xerogel, the molecules that are encapsulated in the xerogel can leach from the porous structure as liquid penetrates the porous matrix, dissolves the drug and diffusion arises. The drug release kinetics is then controlled by the diffusion rate of the molecules from the xerogel.

With the goal to expand the pore size to accommodate larger biological molecules, an acid-base sol-gel process has been introduced. The sol is first hydrolyzed at acidic pH, then the pH is raised to higher values by adding base. Acid-base catalyzed xerogels have a mesoporous structure with an abundance of pores around 3.5 nm [11].

When the size of drug molecules is larger than the size of the pores, the fraction of drug released through diffusion is limited. One can enhance the drug release rate by en-

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hancing a degradational mechanism. Still the silica xerogel degradation rate is slow and mostly dependent on the structure of the silica that forms from the solution. Recent experiment in our laboratory demonstrated that co-hydrolyzing and co-condensing different precursors to synthesize composite xerogels (co-xerogels), degradation rates can be adjusted. As such, the drug release kinetics of large molecules can be increased [12].

For small molecules with high solubility or high diffusion coefficients, burst release occurs even when the xerogel is microporous [13–15]. In order to suppress burst release and achieve suitable release kinetics, xerogels with limited porosity that restricts diffusion have been prepared. By casting the hydrolyzed sol on a large open surface under elevated temperatures, the condensation and drying steps are accelerated. Rapid condensation leads to a weaker structure that collapses during drying at increased temperatures. Thus a xerogel with limited porosity can be obtained. Such xerogels (with limited porosity) can effectively control the release kinetics of small molecules [16].

For most studies on xerogels as controlled release materials, conventional, acid-catalyzed, room-temperature processing has been used [17, 18]. For these xerogels, the release kinetics can be regulated by adjusting sol conditions, such as the pH of the sol and the water to alkoxide molar ratios [19]. The conditions of the sol affect the intermediate capillary pressures of the gel during the drying step, which govern the nanostructure of xerogel. When the sol is prepared at a pH close to the isoelectric point of the silica colloids, the silica colloids easily form a densely packed structure and silica xerogels have a condensed structure with small pore size and limited pore volume. With increasing water to alkoxide molar ratio, pore volume and surface area of the xerogels increase without a concomitant change of their pore size. Such variations of the nanostructure of the silica xerogel, in turn affect the release kinetics of incorporated drug molecules [20].

To achieve therapeutic goals, the need exists to incorporate large quantities of drugs. With a low drug payload, the porous structure is not affected by the volume of molecules in the pores [7]. However, it is conceivable that at higher drug payloads, the xerogel structure will be altered. It is likely that drug molecules may reduce the pore size by depositing on the pore wall [21], shrink the pore volume by fully filling the pore, or even expand the pore size by interfering with the xerogel condensation during drying. These structural change caused by the drug molecules will inevitably modify its release kinetics.

Taken together, there exists a strong need to establish sol-gel synthesis–nanostructure–release kinetics properties for porous sol-gel controlled release materials. Thus, in this study, the relationships among sol-gel processing parameters, xerogel nanostructure with high drug payload (up to 20 wt %) and drug release kinetics were determined. The nanostructural changes caused by immersion and the effect on drug release kinetics were also investigated. Synthesis parameters were varied to obtain silica xerogels with different nanostructures and actual drug release kinetics. The drug molecule bupivacaine, a commonly used analgesic, was used in the experiments. Nitrogen adsorption-desorption isotherms (BET analysis) were recorded to determine the porous nanostructure.

2. Materials and methods

The composition and nomenclature of the sol-gels prepared are summarized in Table 1.

Table 1. The nomenclature of all xerogels synthesized.

Sample name	BP payload, mg/g silica	Acid catalyst	BP Solvent	TEOS : water : BP solvent molar ratio
R6	0	HCl	/	1 : 6
R10	0	HCl	/	1 : 10
R15	0	HCl	/	1 : 15
R10-M	0	HCl	Methanol	1 : 10 : 4.0
R10-E	0	HCl	Ethanol	1 : 10 : 5.0
R6-AA	0	Acetic acid	/	1 : 6
R6-50AA-M	50	Acetic acid	Methanol	1 : 6 : 1.1
R6-50-M	50	HCl	Methanol	1 : 6 : 1.1
R6-100-M	100	HCl	Methanol	1 : 6 : 2.2
R6-200-M	200	HCl	Methanol	1 : 6 : 4.4
R10-100-M	100	HCl	Methanol	1 : 10 : 2.2
R10-150-M	175	HCl	Methanol	1 : 10 : 4.0
R10-150-E	175	HCl	Ethanol	1 : 10 : 5.0
R10-150-R	175	HCl	Water	1 : 10 : 6.5
R15-100-M	100	HCl	Methanol	1 : 15 : 2.7

2.1. Preparation of silica xerogels with different solvents

Bupivacaine containing silica xerogel was prepared at room temperature via a one-step acid-catalyzed sol-gel process [17]. Briefly, tetraethoxysilane (TEOS, Sigma-Aldrich, St. Louis, MO), deionized water and hydrochloride acid (HCl, Thermo Fisher Scientific, Waltham, MA) were mixed and stirred to form an acid-catalyzed sol. The molar ratio of hydrochloride acid (HCl) catalyzed sol was [TEOS : water : HCl] = 1 : 10 : 0.007. With the goal of determining the effect of solvent as one of the properties affecting nanostructure and release kinetics, several solvents including methanol, ethanol and water were used. Bupivacaine (Spectrum Chemicals, Gardena, CA) was dissolved either in methanol, ethanol or water first and the bupivacaine solution was added to the HCl catalyzed sol. The solubility of bupivacaine varies with the solvent used, but we prepared the xerogels of the same bupivacaine payload. We prepared stable bupivacaine solutions at 70, 40 and 40 mg/ml in methanol, ethanol and water respectively. Each time a bupivacaine payload of 17.5 % of dry silica weight was selected. Sols without bupivacaine, but with the same amount of methanol, ethanol or water were also prepared. Upon mixing, the sols were cast into cylindrical polystyrene vials. The vials were sealed and the sols were allowed to gel and age at 37 °C. Subsequently, the vials were opened, and the gels were allowed to dry in an oven at 37 °C until the gel weight became constant. The dried xerogel discs were then crushed to granules with a size in the range 52–210 μm.

2.2. Preparation of silica xerogels at different pH

In a next set of experiments, the hydrolysis of tetraethoxysilane was catalyzed using either hydrochloride acid (HCl) or acetic acid (AA) at molar ratios of [TEOS : HCl] = 1 : 0.007 or [TEOS : AA] = 1 : 0.16 respectively. The pH of the HCl and acetic acid catalyzed sols were 2.2 and 3.3 respectively. Bupivacaine was dissolved in methanol and the bupivacaine methanol solution was added to the acid-catalyzed sol. As indicated in Table 1, the bupivacaine payload in the final silica xerogel was 5 % of silica weight. The dried xerogel discs were crushed into granules with a size in the range 20–105 μm.

2.3. Preparation of silica xerogels at different water to TEOS ratios

A next set of experiments was performed to study water to TEOS ratios *R*, in the range of 6 to 15. Hydrochloride acid (HCl) was used to hydrolyze the tetraethoxysilane with molar ratios of [TEOS : HCl] = 1 : 0.007. Bupivacaine was dissolved in methanol first, and the bupivacaine methanol solution was added to the acid-catalyzed sol. The bupivacaine payload in the final silica xerogel was 10 % of silica weight. The dried xerogel discs were crushed into granules with a size in the range 20–105 μm.

2.4. Preparation of silica xerogels at different bupivacaine payloads

Experiments were also performed to study the variation of drug payload. After tetraethoxysilane hydrolyzation with HCl, the bupivacaine methanol solution was added. The bupivacaine payload in the final silica xerogel varied between 5 and 20 % of silica weight. After condensation and drying at 37 °C, the dried xerogel discs were then crushed into granules with a size in the range 20–105 μm.

2.5. In vitro release study

25 mg of bupivacaine-loaded xerogel granules were immersed in 5 ml of phosphate buffered saline (PBS, pH = 7.4, Gibco®, Carlsbad, CA) (5 mg/ml) and the solutions were exchanged daily. Three samples were run in parallel. The release study was conducted at 37 °C and the vials were shaken on a shaker table rotating at 150 rpm for five days. The concentration of released bupivacaine was measured using a UV-visible spectrophotometer (Ultraspec Plus, Pharmacia LKP, Piscataway, NJ) at 265 nm. Bupivacaine standard PBS solutions were prepared with concentrations ranging from 2 to 250 mg/ml for calibration.

2.6. Surface area, pore size and pore volume of xerogels

BET gas (N_2) sorption analysis (Autosorb-1, Quantachrome, Boynton Beach, FL) was used to determine the specific surface area, pore size and pore volume of xerogels. Before nitrogen adsorption-desorption isotherms were obtained, the samples were outgassed at 50 °C for 20 hours. The specific surface areas and pore size of xerogels were evaluated using the Brunauer–Emmett–Teller (BET) and Barrett–Joyner–Halenda (BJH) method respectively [22].

3. Results

Both the R10-150-E and R10-150-R have shown significant fast initial releases (Fig. 1), more than 60 % bupivacaine was released within the first 24 hours. Conversely, the R10-150-M showed a less prominent initial fast release with only 45 % over the same period.

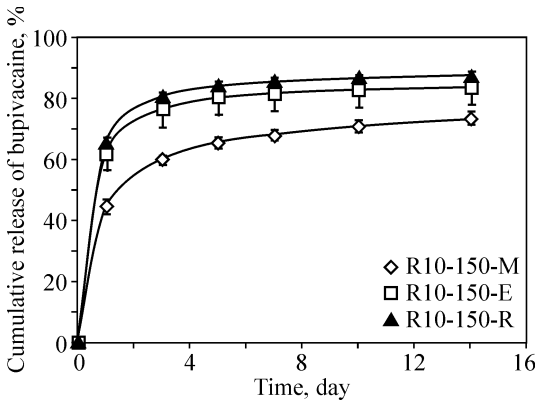

Fig. 1. The effect of solvent used on release kinetics.

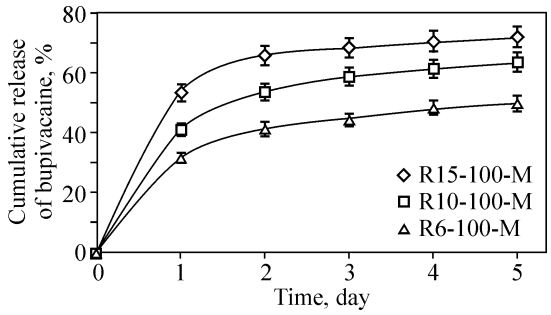

Fig. 2. The effect of molar ratio of water to tetraethoxysilane *R* on release kinetics.

Figure 2 shows that bupivacaine was continually released from silica xerogel granules for 5 days. The data demonstrated the release rate is associated with *R*. R15-100-M xerogel showed a 57% release for the first day, higher than the 42 and 25 % of R10-100-M and R6-100-M xerogels respectively.

As shown in Fig. 3, the percentage drug released within the first day increased as drug payload increased. The amount released over the first day was 23, 32 and 43 % for the R6-50, R6-100 and R6-200 silica xerogel granules respectively.

For sols catalyzed at different pH values, the acetic acid catalyzed xerogel demonstrated a much faster release (>60 %) within the first day than xerogels catalyzed with HCl (Fig. 4).

The results of BET sorption analysis of xerogels without BP are listed in Table 2. Both specific surface area and pore volume of xerogels decreased when methanol was introduced compared with xerogels synthesized using ethanol or water as drug solvent. Conversely, increasing water to TEOS ratio led to higher specific surface area and pore volume. The surface area (540.4 m^2/g) and pore volume (0.294 cm^3/g) of acetic acid catalyzed xerogel (R6-AA) were much higher than those of HCl catalyzed xerogels (R6).

N_2 adsorption-desorption isotherms results (Table 3) indicate that when bupivacaine was introduced, the as-prepared xerogels appeared to be nonporous with negligible

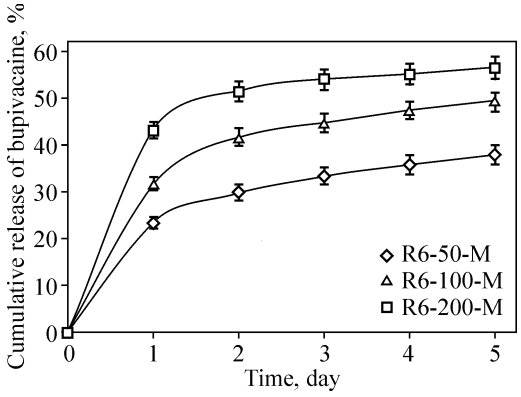

Fig. 3. The effect of drug payload on release kinetics.

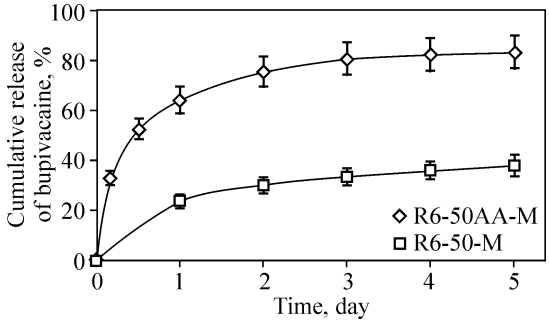

Fig. 4. The effect of acid catalyst on release kinetics.

specific surface area (0.1–16.0 m^2/g) and pore volume (0.005–0.015 cm^3/g). However, after 24 hours of immersion, these apparently non-porous bupivacaine containing xerogels became porous as their specific surface area and pore volume increased considerably. For example, the specific surface area and pore volume of R6-100-M increased more than 10 times to 173.6 m^2/g and 0.094 cm^3/g after 24 hours immersion.

4. Discussion

In a previous study, it was shown that drug release from acid-catalyzed, room-temperature processed silica xerogels included two stages: a fast release followed by the second stage of slower release [17]. The first stage is controlled by a diffusional release mechanism and showed an excellent fit with the Higuchi model [17, 23], which can be expressed as:

$$\frac{M_t}{M_\infty} = kt^{0.5},$$

where M_t/M_∞ is the fractional drug release at time *t*, and *k* is the Higuchi rate coefficient which depends on the structural and geometrical characteristics.

Considering diffusion controlled drug release, water penetration and drug diffusion are largely determined by the nanostructure of the silica xerogel such as porosity. Hence the Higuchi rate coefficient *k* should have a strong correlation with the nanostructure of xerogel. Smaller channels and fewer channels in the xerogel will reduce the value of *k*.

Table 2. BET results for silica xerogels without BP prepared using different solvents.

Sample name	Specific surface area, m^2/g	Average pore size, nm	Pore volume, cm^3/g
R10	386.6	2.2	0.21
R10-M	297.3	2.3	0.17
R10-E	359.2	2.2	0.20
R15	495.2	2.2	0.27
R6	280.3	2.2	0.16
R6-AA	540.4	2.2	0.29

Table 3. Specific surface area, average pore size and pore volume of xerogels before and after immersion in PBS for 24 hours.

Sample name	Specific surface area, m^2/g		Average pore size, nm		Pore volume, cm^3/g	
	Before	After	Before	After	Before	After
R6	280.6	377.0	2.2	2.2	0.158	0.209
R6-50-M	16.0	131.3	n/a	2.2	0.015	0.073
R6-100-M	12.0	173.6	n/a	2.2	0.008	0.094
R6-200-M	0.8	466.8	n/a	2.1	0.002	0.249

With the goal to correlate the Higuchi rate coefficient to nanostructure, the nanostructural parameters of the xerogel were determined with BET sorption analysis, namely, specific surface area, pore volume and pore size were derived from the isotherm. The data suggest that the bupivacaine solvent has a strong effect on the nanostructure of the xerogel. During drying, the capillary forces cause collapse of the gel network made of silica colloid, causing a reduction in specific surface area and pore volume. A stronger gel structure that can withstand capillary forces during drying produces the xerogels with higher pore volume. In this study, the specific surface area and pore volume of the xerogels decreased when methanol was added, suggesting a weaker gel structure. Using ethanol as the bupivacaine solvent did not alter the strength of the gel structure in comparison with water as the solvent.

It has been reported previously that alcohols with longer chains can promote higher specific surface area and porosity, possibly due to a stronger gel structure [24]. Excessive water diluted the silica colloidal particles in the gel, created a larger void space, and left a greater amount of pores after drying. As the result of their differences in nanostructure (smaller pore volume and specific surface area for R10-M than R10 and R10-E), the R10-150-M showed a less prominent initial fast release than both the R10-150-E and R10-150-R (Fig. 1), both of which shared similar release profiles. Thus, it follows that methanol is the better solvent to introduce bupivacaine into xerogel, and achieve sustained release.

The pH can also be varied to adjust the nanoporosity of xerogel. When sol is prepared at the isoelectric point, the silica colloids aggregate easily due to a less repulsive electrical force. As a result, the silica xerogel has a more condensed structure. Above the isoelectric point, the xerogel has a more porous structure. Previously, it was shown that the isoelectric point for acid-catalyzed sol is pH 2.2 [25]. The results of BET sorption analysis (Table 2) confirm that silica xerogel catalyzed at pH 2.2 with HCl (R6) had a smaller surface area and pore volume compared with xerogel catalyzed at pH 3.3 with acetic acid (R6-AA). Along with the nanostructural differences, the R6-50AA-M showed a much faster initial release (>70 % released within first 24 hours) than R6-50-M (Fig. 4).

The water to TEOS ratio can also affect the xerogel nanostructure. Previous studies showed that the pore volume of xerogels increased with higher water to TMOS ratio [7]. The results of the present study confirmed and expand on these previous findings. Herein, the specific surface area and pore volume varied linearly with the water to TEOS ratio in the range of 6 to 15 (Fig. 5).

The silica colloid condensation (silica network formation) can be disturbed as more drug is "squeezed" into the pore space. The apparent nonporous nanostructure (Table 3) suggests that the pores were filled with bupivacaine. Similar results were also reported for mesoporous silica (MCM 41): its specific surface area and pore volume decreased as more drug was packed into its pores [21, 26]. Despite the BET based determination of non-porosity, the drug release experiments revealed a markedly faster release associated with a higher drug payload (Fig. 3). Plotting the drug payload with initial Higuchi rate coefficient (0–24 h), a linear relationship is clearly observed (Fig. 6).

Considering that the drug payloads (in xerogels containing drug) and specific surface areas (of xerogels containing no drug but otherwise synthesized using the same conditions) are independent as they were determined from two different sets of xerogels, these data lead to the following mathematical expression for the Higuchi release rate coefficient:

$$k = a_0 S + a_1 D + a_2, \quad (1)$$

where k is the Higuchi rate coefficient ($\times 10^2$, $h^{-1/2}$), D is the drug load of the xerogel (mg drug/g silica), and S is the specific surface area of the xerogel without drug (m^2/g) (specific surface area of drug unloaded xerogel with otherwise the same synthesis conditions), a_0, a_1 and a_2 are constants.

Using the experimental data, D, k and S can be calculated. D and k were achieved from the release experiments with drug loaded xerogels (R6-50-M, R6-100-M, R6-200-M, R10-100-M, R15-100-M and R6-50AA-M) and S from the xerogels containing no drug but otherwise synthesized

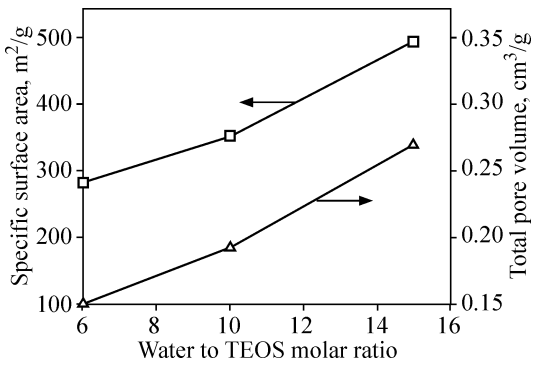

Fig. 5. The effect of water to TEOS ratio on the nanostructure of xerogels without bupivacaine (R6, R10 and R15).

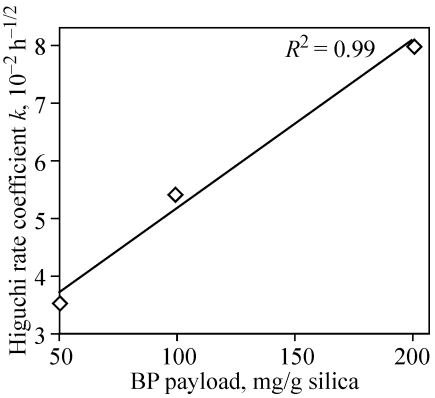

Fig. 6. The effect of bupivacaine payload on the Higuchi rate coefficient during the first 24 hour release (R6-50-M, R6-100-M, R6-200-M).

using the same conditions (R6, R10, R15 and R6-AA) were determined. The fitting was conducted with MATLAB's curve fitting function toolbox (cftool). Equation (2) expresses the result:

$$k = 0.0368S + 0.0296D - 7.893 \quad (2)$$

with $R^2 = 0.9245$.

The high R^2 value indicates a close fit. Given that this equation only accounts for effects of specific surface area and drug payload but not for other properties of the matrix material, it is logical to suggest that other controlled release systems (such as e.g. mesoporous silica) which rely on a diffusional release mechanism could also be described by Eq. (1). There is a caveat in applying Eq. (1) though. The coupling effect between the *D* and *S* is not considered (i.e. $k = a_0S + a_1D + a_2SD + a_3$). It is worthwhile to investigate such effect in the future.

The equation above considers only the initial condition of material. During the immersion, the silica xerogel degraded and the nanostructure of xerogel changed as the result of the degradation. A recent study in our laboratory revealed pore expansion resulting from xerogel restructuring after immersing in PBS [11]. The BET sorption analysis in this study revealed a changed structure as the surface area and pore volume of R6 xerogel increased after immersed in PBS for 24 hours. The changed nanostructure of the xerogel then influences the release kinetics at later stages of release, as is shown in Table 4.

Table 4. Higuchi rate coefficient *k* of drug release determined using the simplified Higuchi square root of time model for the 0–24 h and 24–48 h time space of release.

Sample name	k, $\times 10^{-2}$ h$^{-1/2}$	
	0–24 h	24–48 h
R6-50-M	3.57	3.87
R6-100-M	5.42	3.55
R6-200-M	8.02	4.26
R10-100-M	8.42	4.34
R15-100-M	11.00	5.93
R6-50AA-M	13.06	5.26

5. Conclusion

In this study, the sol-gel synthesis parameters such as solvent of bupivacaine, pH of sol, water to alkoxide molar ratio, and drug payload were varied to tailor release kinetics through the changes in nanostructural properties of silica xerogel. The relationship among the synthesis parameters, xerogel nanostructure and release kinetics (as expressed with the Higuchi rate coefficient) was identified. A general equation that considers the effects of both nanostructure and drug payload on release kinetic is proposed, and can be used to design controlled delivery systems consisting of silica xerogels.

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