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ORIGINAL PAPER

SiO_2–TiO_2 xerogels for tailoring the release of brilliant blue FCF

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Abstract Xerogels consisting of SiO_2 and TiO_2 were explored for controlled release of brilliant blue FCF (BBF). Both SiO_2 and SiO_2–TiO_2 xerogels were prepared by way of sol–gel processing, and the BBF release behavior was compared. SiO_2–TiO_2 xerogels with varying TiO_2 content were also studied and the BBF release behavior was determined for each SiO_2–TiO_2 xerogel. It was found that the release of BBF from SiO_2 xerogels can be increased by the addition of TiO_2 content, and the amount and rate of BBF released from the SiO_2–TiO_2 xerogels can be changed by modifying the amount of TiO_2 included during the preparation of the xerogels, where the SiO_2–TiO_2 xerogels with a higher content of TiO_2 released a higher fraction of BBF in water media when compared to the release from SiO_2–TiO_2 xerogels with lower amounts of TiO_2. The experimental results have to be explained by a combination of porous structure, in situ dissolution–condensation during the BBF elution and the change of surface chemistry of the xerogel network with the addition of TiO_2.

Keywords Sol–gel · BBF release · SiO_2–TiO_2 xerogels · Syneresis

1 Introduction

Controlled drug delivery for administering beneficial agents at specific target areas in the body is one area of interest in biological research [1–6]. There have been studies in the area of controlled drug storage and release utilizing various metallic, ceramic, and biological materials. For example, carbon fiber [7] has been used to adsorb various acidic and basic dyes in order to emulate the function of controlled adsorption of drugs. Double layered hydroxide nanocomposites [3], catalytic self-assembled thin films [8], and ordered structures through assembly of nanoparticles [9] are a few emulated systems for controlled drug release.

For many years, chitosan [10] has been well known as a drug delivery agent and has been studied extensively as a drug carrier for drug distribution and treatment at specific target areas in the body. The advantages of using chitosan include biocompatibility, low toxicity, long systematic retention in the body, and good compatibility with various agents. However, release characteristics are still in question. Controlled release of agents from chitosan-derived carriers is still under investigation for optimum output and more studies are needed for it to exhibit its maximum capacity.

An alternative material that has gained wide attention in the area of biological research is silica which has been widely studied for many applications, including corrosion resistant coatings on metals [11–13], and abrasion resistant coatings on plastics [14]. Silica or silica-based hybrid materials have attracted a lot of attention in biomedical applications [15–18], and has been an ideal candidate for bio-related research due to its biocompatibility [11], and ease of processing for tailoring to specific biological applications requiring precise functionality.

Sol–gel-derived silica xerogel is one type of system explored for controlled drug release. These xerogels are prepared at room temperature, silica-based, amorphous, and they possess a high ultramicroscopic porosity [19–22]. Thus, the drug material in silica sols can be uniformly distributed within the porous silica xerogel networks after

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gelation. Wu et al. [23] showed that silica-based xerogels can release BBF in varying amounts by modifying the composition, processing conditions, and release media. Brilliant blue FCF is one of the two blue colorants certified in the United States for use in drugs, foods, and cosmetics [24], which has a molecular dimension of 1.07 × 1.47 × 1.88 nm [7]. The textural properties of the xerogels, as well as the interactions between BBF and the xerogels, influence the release characteristics in various release media have been demonstrated [23].

To further explore the possibility of altering the drug release characteristics, and porous structure and chemistry of silica-based xerogels, composite xerogels consisting of silica (SiO_2) and titania (TiO_2) are investigated. This paper details the preparation of SiO_2–TiO_2 xerogels for the controlled release of BBF, and compares the BBF release behavior of the SiO_2–TiO_2 composite xerogels to that of the SiO_2 xerogels in an effort to give insight on the potential of developing a composite system with tunable and improved release behavior. The addition of TiO_2 to the SiO_2 xerogel is beneficial in that TiO_2 has also been reported to be biocompatible and has been commercially used by drug companies to coat orally-taken drugs. In addition, the processing of SiO_2 sol in the presence of a TiO_2 precursor leads to a more porous structure by reducing the gelation time through a cross-catalytic effect on the condensation reaction [25–27]. A more porous structure associated with the SiO_2–TiO_2 xerogel is thought to result in improved BBF release.

2 Experimental

2.1 Preparation of SiO_2 xerogels

The xerogels consisting of silica (SiO_2) were prepared by way of sol–gel processing, as detailed in Wu et al. [23]. In summary, the sols were prepared by admixing a SiO_2 precursor, tetraethylorthosilicate (TEOS), with ethanol (EtOH), 50 mM BBF solution in deionized water (DI–H_2O), and 0.010 M hydrochloric acid (HCl) solution. The xerogels were then obtained by the addition of ammonia (NH_3) at room temperature to initiate gelation. The final nominal molar ratio of TEOS:EtOH:BBF:DI–H_2O:HCl:NH_3 was $1{:}8{:}8 \times 10^{-4}{:}6{:}8 \times 10^{-5}{:}6 \times 10^{-3}$.

The sols were first allowed to hydrolyze by stirring at room temperature for ~24 h. The pH of each sol was ~3–4. An amount of 1.0 M NH_3 was added to each sol to bring the pH up to ~8, resulting in the gelation of the sols. The gels were then allowed to age for ~12 h at room temperature. Additional drying was required at room temperature for ~72 h, followed by drying at 50 °C for 24 h to obtain the final xerogel products.

2.2 Preparation of SiO_2–TiO_2 xerogels

The composite xerogels consisting of silica (SiO_2) and titania (TiO_2) were also prepared by way of sol–gel processing. The sols were prepared by first mixing a SiO_2 precursor, tetraethylorthosilicate (TEOS), with ethanol (EtOH), deionized water (DI–H_2O), and 0.010 M hydrochloric acid (HCl) solution at 60 °C for ~30 min. A TiO_2 precursor, titanium(IV)isopropoxide (TI), was then added and stirred at 60 °C for an additional 30 min. After the addition of a 50 mM BBF solution in deionized water (DI–H_2O), the sol was stirred at room temperature for ~24 h. The xerogels were then obtained by the addition of ammonia (NH_3) at room temperature to initiate gelation.

The same final nominal molar ratio of TEOS:EtOH:BBF:DI–H_2O:HCl:NH_3 was used, as previously stated. A various amount of TI, was added to the system to obtain three SiO_2–TiO_2 compositions consisting of a) 0.094 mol% TI, b) 0.94 mol% TI, and c) 1.88 mol% TI, in correlation to the amount of TEOS, were prepared. Each sol was allowed to hydrolyze by stirring at room temperature for ~24 h. The pH of each sol was ~3–4. An amount of 1.0 M NH_3 was added to each sol to bring the pH up to ~8, resulting in the gelation of the sols. The gels were then allowed to age for ~12 h at room temperature. Additional drying was required at room temperature for ~72 h, followed by drying at 50 °C for 24 h to obtain the final xerogel products.

It is also important to note that the addition of too much TiO_2 precursor may result in instantaneous precipitation and subsequent gelation with phase separation at room temperature. Therefore, it was found that it was necessary to limit the addition of TI to less than 3 mol%, in correlation to the amount of TEOS.

2.3 Brunauer–Emmett–Teller (BET) analysis

The surface area and pore size of each xerogel were analyzed by obtaining nitrogen adsorption/desorption isotherms at 77 K using a NOVA 4200 surface area analyzer. Each xerogel was degassed for ~24 h at room temperature prior to analysis. The surface area of each xerogel was calculated using the BET isotherm equation, and the pore size of each xerogel was estimated by using the BJH method based on the assumption that the xerogels consisted of cylindrical pores, which is widely used in literatures to calculate the pore size for porous structure though pores in xerogels are highly tortuous and irregular. Both the surface area and the pore size of each xerogel before and after BBF release were obtained for comparison.

2.4 Brilliant blue FCF elution studies

All the SiO_2 and SiO_2–TiO_2 xerogels containing BBF were immersed in an amount of release media, in this case water, to analyze the amount of BBF released in a specified amount of time. Each xerogel was immersed in water with a weight ratio of xerogel to water of 1 to 400. During each release study, each xerogel immersed in water was in constant motion by using a Scienceware spindrive orbital shaker on a stir plate at room temperature.

The BBF release study was performed for a total of 192 h (8 days) with measurements taken every 24 h. The accumulated amount of BBF in water was measured using an Ocean Optics UV–VIS spectrophotometer. The absorption peak obtained from the release of BBF in water every 24 h was compared to the maximum absorption wavelength at $\sim$630 nm for BBF. The fraction of BBF released was calculated by comparing the intensity of the absorption peak obtained at various times to that at maximum intensity for BBF. A more detailed description of the properties of BBF and its release studies in various media can be found in Reference [23].

3 Results

Figure 1 compares the fraction of BBF released as a function of elution time from the SiO_2–TiO_2 xerogel with 0.094 mol% TiO_2, 0.94, and 1.88 mol% TiO_2 content to that for the SiO_2 xerogel alone. It can be seen that (1) there exists an initial burst release of BBF from all xerogels in the first 24 h. However, the subsequent release of BBF after 24 h was fairly similar, (2) the fraction of BBF released from the SiO_2 xerogel with the addition of TiO_2 significantly increased as compared to that for the SiO_2 xerogel alone, (3) the SiO_2–TiO_2 xerogel consisting of a larger amount of TiO_2 resulted in a higher fraction of BBF released than that for SiO_2–TiO_2 xerogel with lower amount of TiO_2, though the initial concentration of BBF in all the xerogels was the same.

To further illustrate this enhancement of BBF release from the xerogels with the addition of TiO_2, Fig. 2 shows a comparison of the fraction of BBF released from the SiO_2 xerogel and from the SiO_2–TiO_2 xerogels when immersed in water media for 24 h and 192 h (8 days). Without TiO_2 addition, the SiO_2 xerogel released a small fraction of BBF, approximately 7% after 24 h elution in water, and subsequently reached a total fraction of BBF, $\sim$20% after 8 days (192 h) elution. About 80% BBF remains entrapped inside silica xerogel after 8 days elution. With the addition of 0.094 mol% TiO_2, the SiO_2–TiO_2 xerogel released a higher fraction of BBF with a ratio of $\sim$0.32 in the first 24 h, and continued to release a much higher fraction of BBF with a ratio of $\sim$0.59 after 8 days elution. Further increasing the amount of TiO_2 subsequently enhanced the amount of BBF released from the xerogels. Further increasing TiO_2 to 1.88 mol% resulted in the fraction of BBF released after 24 h to $\sim$52%, and 72% in 192 h. This shows that the release behavior, rate and amount, of BBF molecules from the SiO_2 xerogel can be modified by the incorporation of TiO_2 content.

Figure 3 shows the nitrogen sorption isotherms of all the SiO_2 and TiO_2–SiO_2 xerogels before and after BBF release. Table 1 summarizes the corresponding surface area, average pore size, and pore volume of the SiO_2 and SiO_2–TiO_2 xerogels obtained by BET and BJH methods before and after BBF release. The surface area of the SiO_2 xerogel before BBF release was found to be $\sim$36 m^2/g. The

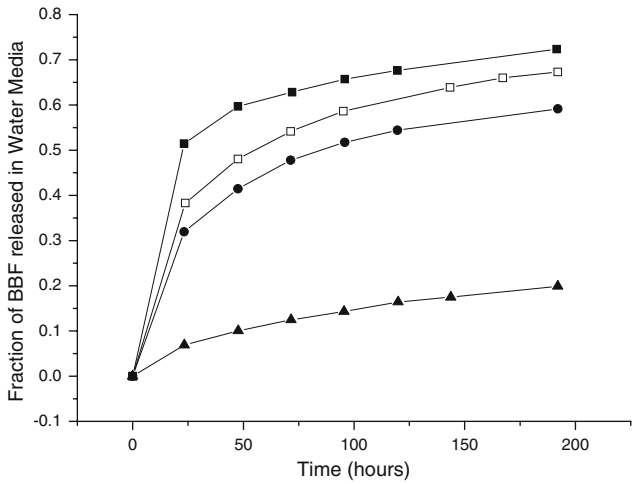

Fig. 1 Plot of the fraction of BBF released from the (▲) SiO_2 xerogel and the SiO_2–TiO_2 xerogels with (●) 0.094 mol% TiO_2, (□) 0.94 mol% TiO_2, and (■) 1.88 mol% TiO_2 into water media as a function of elution time

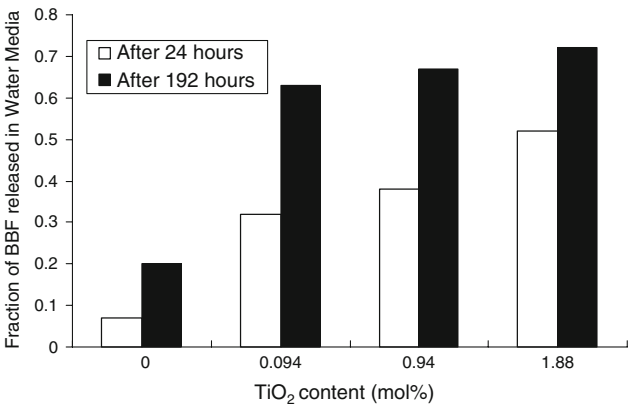

Fig. 2 Comparison of the fraction of BBF released from the SiO_2 xerogel and from the SiO_2–TiO_2 xerogels with 0.094, 0.94, and 1.88 mol% TiO_2 content after immersion into water media (□) for 24 h (1 day), and (■) for 192 h (8 days)

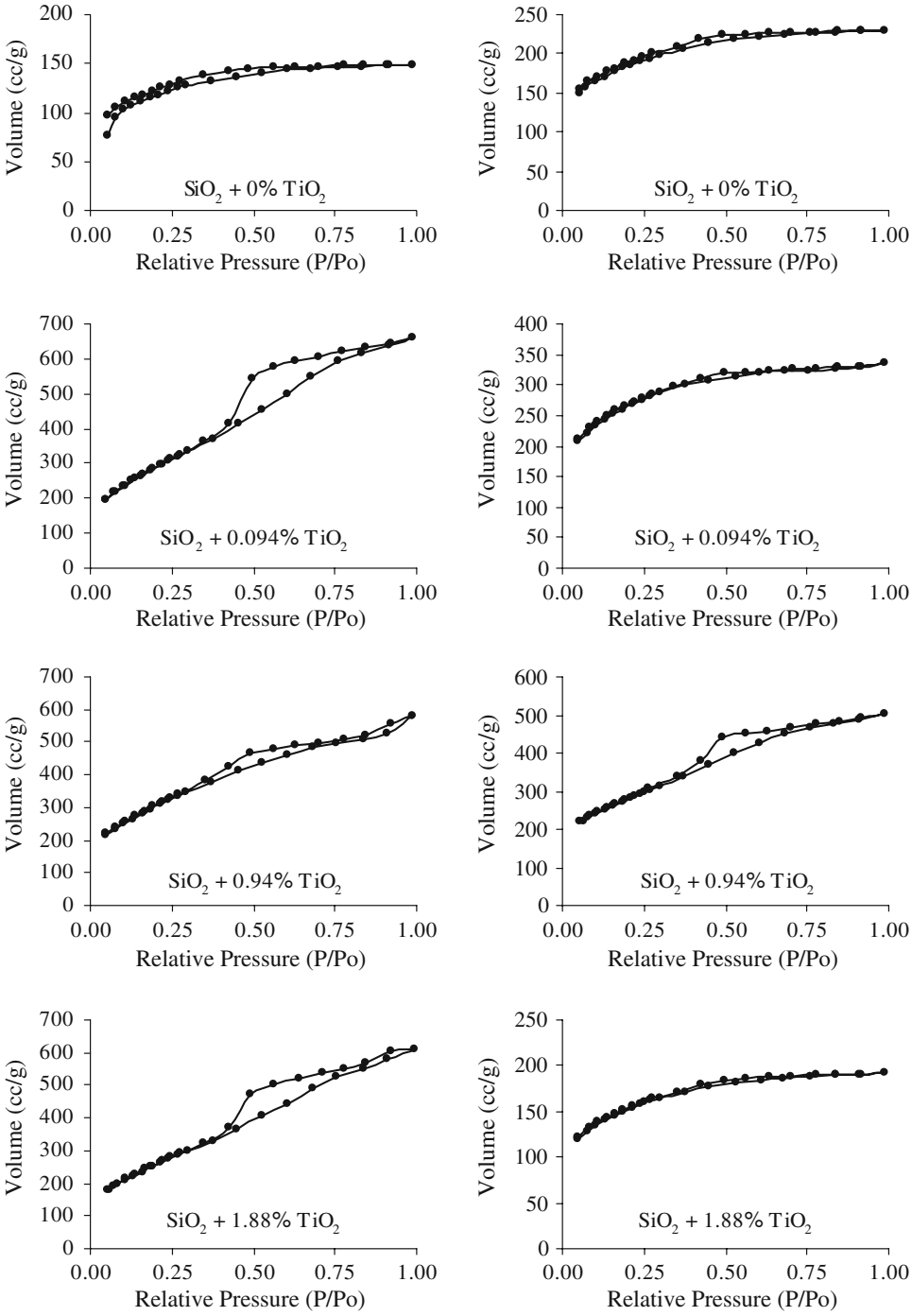

Fig. 3 Nitrogen sorption isotherms of all the SiO_2 and SiO_2–TiO_2 xerogels studied in the present study: *left column*, before BBF release and *right column*: after 192 h BBF release

Table 1 Summary of the surface area, average pore size, and pore volume of the SiO_2 xerogel and of the SiO_2–TiO_2 xerogels with varing TiO_2 contents before and after BBF release

TiO_2 content (mol%)	Before BBF release			After BBF release		
	Surface area (m^2/g)	Average pore (nm) size	Pore volume (cc/g)	Surface area (m^2/g)	Average pore size (nm)	Pore volume (cc/g)
0.000	35.75	2.16	0.03	62.99	3.32	0.05
0.094	158.1	3.34	0.13	72.76	2.54	0.07
0.940	156.7	3.33	0.12	135.7	2.17	0.10
1.880	95.24	3.33	0.12	56.07	2.18	0.04

surface area varied slightly in SiO_2–TiO_2 xerogels with 0.094 mol% and 0.94 mol% TiO_2 content, and was found to be ~158 and ~157 m^2/g, respectively. However, the SiO_2–TiO_2 xerogel with 1.88 mol% TiO_2 content had a much lower surface area of ~95 m^2/g. The average pore size and pore volume increased appreciably with increased amount of TiO_2 introduced to the xerogels. The significant increase in both pore size and pore volume accompanied with a reduction of surface area could be attributed to the cross-catalytic effect when the titanium isopropoxide was admixed with TEOS during the sol–gel processing [25–27]. It is well known that such cross-catalysis results in a much faster hydrolysis and condensation reactions, leading to much open gel network and consequently more porous xerogels [26]. After BBF release, the surface area, the average pore size, and the pore volume of the SiO_2 xerogel increased to ~63 m^2/g, ~3.3 nm, and ~0.06 cc/g, respectively, which are expected as the result of BBF removal from the pores. However, it has been found that all surface area, pore size and pore volume of SiO_2–TiO_2 xerogels decreased appreciably after the removal of BBF by 8 days immersing in water. Although the exact mechanism for such a collapse of porous structure in TiO_2 containing xerogels is not known, the seemingly unexpected reduction of pore size, pore volume, and specific surface area after the release of BBF from the porous SiO_2–TiO_2 xerogels could be attributed to the surface dissolution–condensation and relaxation during xerogel aging similar to syneresis, when the sample was immersed in water for an extended period of time [26]. Strong syneresis in titania xerogels during aging has been well reported in literature [28–30].

4 Discussion

From the above results, it is evident that the addition of TiO_2 to the SiO_2 xerogel network resulted in (1) more open porous structure with large pores and pore volume, (2) an increased amount of BBF released into water media with a higher release rate, and (3) a higher content of TiO_2 in the SiO_2 xerogel would result in a higher amount of BBF released. These experimental results will be explained in term of the change of textural properties by the addition of TiO_2.

Although more open porous structure of xerogels with the addition of TiO_2 is a well documented phenomenon [25–27], as explained by cross-catalytic effect [26], the observed different BBF release can not be directly and only attributed to the change of the porous structure. More rapid release of BBF released from the SiO_2–TiO_2 xerogel can be attributed to the larger pores and high pore volume of the SiO_2–TiO_2 xerogel as compared to the SiO_2 xerogel. The xerogel with larger pore size and large pore volume would allow an easier release of BBF entrapped within the pores, resulting in an increase in BBF released during the elution tests. In addition, comparison of nitrogen sorption isotherms of SiO_2 and SiO_2–TiO_2 xerogels prior to BBF release illustrated in Fig. 3, it is evident that the addition of TiO_2 into the silica xerogel network not only resulted in much high pore volume and large pore size, but also led to much broader size distribution as indicated in a continuous increase in the amount of nitrogen adsorbed as the partial pressure increases. A broader size distribution with large pores would also favor the release and transport of BBF from the porous xerogels during the elusion experiments.

Although the initial amount of BBF introduced to the xerogels during the sol preparation was kept the same, a larger fraction of BBF released from SiO_2–TiO_2 xerogels has been found than that from silica xerogels. In addition, the fraction of BBF released from SiO_2–TiO_2 xerogels increased with the increasing amount of TiO_2 incorporated into the xerogel network. After 192 h elution in water, less than 20% BBF was released from the porous silica xerogels, while approaching 80% BBF was released from SiO_2–TiO_2 xerogels with the addition of 1.88% Ti. The exact reason for such a significant difference in the amount of BBF released from porous xerogels is not known yet. However, the relatively smaller pores, pore volume and more uniform porous structure with narrow size distribution in SiO_2 xerogels may lead to partial entrapment of some BBF molecules, though the size of BBF molecules, $1.07 \times 1.47 \times 1.88$ nm [7], is smaller than the pore diameter, 2.16 nm before and 3.32 nm after 192 h elution testing, in silica xerogels. Considering the tortuous nature of the pores in xerogels, there likely exist some apertures or bottlenecks smaller than the size of BBF molecules. There exists, however, at least another possible mechanism for such a significant difference in the amount of BBF released, particularly considering the pore size of SiO_2–TiO_2 xerogels lies in the same range: ~3.3 nm before and ~2.3 nm after BBF elution, very comparable to that of SiO_2 xerogels. Broader size distribution and larger pore volume would certainly allow more BBF molecules diffuse out of the porous network of SiO_2–TiO_2 xerogels. However, porous structure alone would not be able to explain the increased amount of BBF released from SiO_2–TiO_2 xerogels with an increased amount of TiO_2, though the porous structure did not show the same trend of change.

A higher fraction of BBF released from TiO_2–SiO_2 xerogels may also be associated with the shrinkage (syneresis) of porous structure during the water elution. Xerogels exhibit significant syneresis when the constituent of a xerogel has a relatively higher solubility and relatively fast dissolution–condensation rate. Under the BBF elution tests in water, TiO_2–SiO_2 xerogels underwent appreciable

change of porous structure; a reduced pore size, a shrinking pore volume and a lowered specific surface area, suggesting a syneresis-type process occurred. Dissolution–condensation of TiO_2 during water elution may very well promote the release of BBF molecules.

Yet another possible explanation is the interaction between the BBF molecules and xerogel network. During the sol–gel preparation, BBF molecules are homogeneously admixed in the sol and uniformly dispersed in the porous xerogel. It is likely that the BBF molecules are adsorbed onto the inner surface of the porous xerogels. The introduction of titania into silica xerogel network would modify the surface chemistry of inner pores of the xerogels. Such a change of surface chemistry would definitely affect the interaction between the BBF molecules and the surface of xerogels. The incorporation of titanium ions into the SiO_2 xerogels makes the BBF more readily to be released, resulting in a higher fraction of BBF release.

It is not clear at the moment which mechanism is predominant. However, it is very likely that all three mechanisms contributed to the enhancement in both the released amount and the release kinetics. Further experiments are obviously required to verify the explanations for further development of porous xerogels for efficient drug release with desired amount and rate.

5 Conclusions

The release rate and amount of BBF from SiO_2 xerogels can be increased significantly by the incorporation of TiO_2 to the xerogel networks due to the increased pore volume, larger pore size with broader size distribution, and possibly modified surface chemistry. The admixing of titanium alkoxide exhibited cross-catalytic effects, resulting in much faster hydrolysis and condensation reactions, consequently leading to the formation of more porous structure. The higher fraction of BBF released with a high release rate from the SiO_2–TiO_2 xerogels during the entire stage of release, as compared to the fraction of BBF released from the SiO_2 xerogel, could be due to the larger pore size, broader size distribution, and higher pore volume in the SiO_2–TiO_2 xerogels. It has also demonstrated that the silica xerogels experienced little or no syneresis during the release of BBF when immersed in water; however, there was a significant reduction of pore size, pore volume, and specific surface area in SiO_2–TiO_2 xerogels as a result of syneresis during the release of BBF in water media. The dissolution–condensation process associated with syneresis may contribute to the enhanced rate and amount of BBF release from SiO_2–TiO_2 xerogels. This work demonstrated that a controlled drug release could be obtained by manipulating porous structure and chemistry of hosting matrix.

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