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pH DEPENDENT DRUG DELIVERY BASED ON SILICA XEROGEL

*AÉCIO B. P. DE VASCONCELOS, WAGNER E. SILVA, MÔNICA F. BELIAN**

Departamento de Química, Universidade Federal Rural de Pernambuco, 52171-900 Recife, Pernambuco, Brazil.

ABSTRACT

In this work, a matrix based on silica xerogel, synthesized from TEOS, water, ibuprofen (as template) and acetic acid at room temperature, was used for ibuprofen (IBF) incorporation, aiming to create a drug delivery system capable of releasing this compound under a basic pH condition (considering desirable and optimal release in the intestines). The IBF release was checked at different pH values (ranging from 2 to 8), using appropriate buffered solutions. After observing the IBF release performance from the silica xerogel and its dependence on the pH, the same matrix containing IBF was submitted to a novel assay, using only a pH 7 buffered solution as the best way to check the chronological release. This was carried out at 1, 2, 5 and 10 minutes to determine aliquot removal, as well as IBF concentration at each elapsed period.

Keywords: silica xerogel; pH-dependent release; ibuprofen.

1. INTRODUCTION

Silica gel is widely used as a vehicle in pharmaceutical formulae due to its low toxicity and high stability.[1-8] Silica materials may be molded according to the host (drug) desired by the use of catalysts capable of creating a particular morphology and porosity of the silica. According the delivery system and the compound used, different release mechanisms can be applied. The three primary ways by which active agents can be released from this kind of a system are diffusion, degradation, and swelling followed by diffusion. In this work the mechanism applied was swelling followed by diffusion.[3]

After the pharmaceutical compound has been incorporated, the porosity and morphology of the silica is usually sensitive to pH change and temperature; since the guest-host interaction generally is typically a hydrogen bond and van der Walls forces. In the case of silica xerogel, the pH determines a particular series of structural events.[3,5-7]

At a pH below 7, the silica xerogel has the effect of "structural contraction" due to the occurrence of dehydration reactions (formation of siloxane units). This characteristic is advantageous when the drug delivery system (DDS) requires resistance to a low pH, as in the case of oral administration during the passage of the DDS through the stomach. In the case of pH higher than 7, the silica xerogel has the effect of "structural expansion" (here called "swelling" effect) due to the increase of silanol units that force an increase in the porosity and hydrophilicity of the silica.[9-11] In this case, the effect of the drug release must be designed to take into consideration that the best conditions occur when the pH is higher than 7. For example, once the drug has been administered orally, several pH conditions can be tried to see which ones have the best release in the digestive pathway, especially in the intestine.

Ibuprofen (IBF), a common non-steroidal anti-inflammatory pharmaceutical, was used as the model drug due to its molecular size and ability to interact with silanol groups present in the pore walls of the siliceous materials.[12-16]

In other studies, the controlled release tests have been made only with a specific pH of 6.8 (approximate pH of the intestinal region). This limits the application of these materials, given that the gastrointestinal system shows drastic pH fluctuations between the stomach and intestine.[17-21] Tests conducted at pH acids are essential for verifying the material integrity that will affect the delivery of the drug. Another problem is the use of templates or silylants, which can cause high toxicity in the system.[19,21] The textural properties reported in other studies, show high variations in pore volume and increases/decreases in its diameter of the silica matrix[20,21], which results in low interaction of the drug with the host. To resolve these problems, our work involved the synthesis of a homogeneous material (pore volume distribution) using acetic acid as catalyst/template. This material displayed a strong interaction with the guest (ibuprofen) through variation of the pore size according to changes in the pH.

Aiming to produce a silica-based material capable of incorporating ibuprofen and releasing it within a specific pH range; a xerogel matrix was synthesized through the sol-gel process catalyzed by acetic acid (Ac). The silica xerogel was characterized by infrared spectroscopy and thermal analysis (TGA). The pore size and surface area were obtained through use of an adsorption isotherm (BET model).

2. EXPERIMENTAL SECTION

Tetraethyl orthosilicate (TEOS, 98%), Ibuprofen (IBF ≥98%) and acetic acid (Ac, 98%) were obtained from Aldrich and used without further purification. The infrared spectra were obtained with a KBr tablet using a *Fourier* transform IF66 model spectrophotomer in the 4000–400 cm^{-1} range, with a spectral resolution of 4 cm^{-1}. Thermogravimetric curves were obtained using a TGA 50/50H Shimadzu under N_2 atmosphere and a heating rate of 5ºC min^{-1}. To estimate the percentage of ibuprofen release at different pH levels (phosphate buffer) and to check the chronological release at each pH, a calibration curve was constructed according IBF standards and data collected from electronic absorption spectroscopy (UV-VIS). This data acquisition was analyzed using Agilent Model 8453 equipment with a window scan of 280nm at 600nm.

The silica xerogel samples were submitted to analysis assay using a Micrometrics ASAP 2010 machine comprised of a physical adsorption system that provides the automated data equilibrium of adsorption and desorption. The silica mesoporous samples were degassed for 2 h at 200° C before each test. The specific surface area measurements were based on the Brunauer-Emmett-Teller (BET) [22] methods. The types of and total volume pores were obtained by the Barret-Joyner-Halanda (BJH) [23] method.

2.1 Silica Xerogel

A mixture of 22.33 mL TEOS (1 mol), 25.2 mL of distilled water (14 mol), 0.1316 mL Ac (0.023 mol) and 0.4125g of IBF (0.02 mol) was prepared in a 250 mL volumetric flask. This mixture was kept under magnetic stirring for 24h at room temperature. After formation of the gel, it was dried in a rotary evaporator in a heat bath at 60° C, resulting in the final silica xerogel with IBF incorporated, which looked like a white powder. The IBF-Silica material was decanted, washed 3 times with ethanol, and sequentially dried under vacuum.

2.2 pH dependence of ibuprofen release

For the pH study, different buffer solutions were used ranging from 3 to 8, (pH 3, 4, 5, 6, 7/ citrate-phosphate and pH 8 / phosphate). In a beaker, 10 mg of the IBF-silica matrix and 10mL of buffer in specific pH value desired were added. For all pH values assays, the system was kept under slow stirring for 10, 20 and 30 minutes. After each elapsed time, an aliquot of the supernatant was removed and analyzed by absorption spectroscopy. Then the aliquots were returned to the initial system for the next assay. Perceiving that from 10 minutes, at pH 7, the IBF concentration became constant, a chronological evaluation of IBF release assay was established, since this pH value was determined as the favorable initial condition for checking the total release performance of this material. Using absorption spectroscopy, the same amount of ample and checking was repeated, with IBF aliquot concentrations extracted at 1, 2, 5, and 10 minutes.

3. RESULTS AND DISCUSSION

The silica xerogel, after drying process, showed hygroscopic characteristics when exposed to air (relative humidity = 80%). The water content in the samples

e-mail: mfbelian@gmail.com / monica.freirebelian@ufrpe.br

after 24 and 48 hours of exposure was 12 and 20%, respectively. Isotherm of the sample showed broad capillary condensation at step and a baseline, with desorption coincident with the return of adsorption (Figure 1). This behavior suggests the occurrence of a uniform distribution of mesoporous.

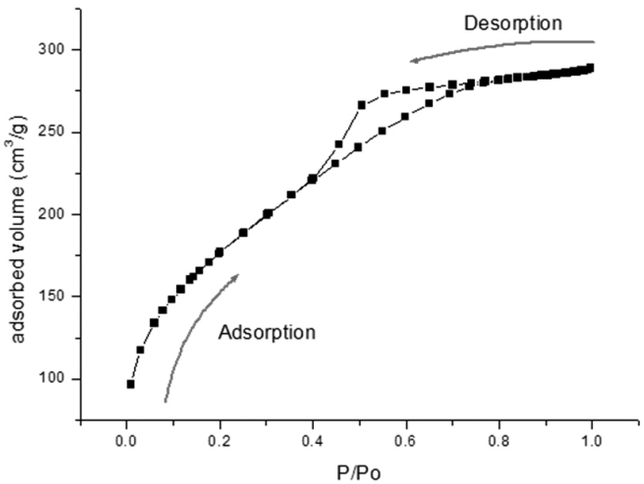

Figure 1. Adsorption isotherm of silica xerogel produced by sol-gel process in the presence of ibuprofen and acetic acid.

Figure 1 shows an adsorption profile, typically of porous adsorbents (range of 15 – 1000 Å), where at higher pressures the slope shows increased uptake of adsorbate as pores filled, and the inflection point occurs near completion of the first monolayer. In the literature, this curve profile is known as isotherm type IV. Another thing that we noticed in the isotherm is the variation in the maximum volume of gas adsorbed. This volume is related to the maximum adsorption capacity of the solid (P/P0 ≈ 1), which is directly linked to the total amount of pores existing in the material [24]. The volume of gas adsorbed by the silica xerogel corroborates with pore volume, as shown in Table 1. Total pore volume is derived from the amount of vapor adsorbed at a relative temperature close to unity (assuming pores are filled with liquid adsorbate). Equation 1 shows the estimate made of the gas volume from the pore volume; where V_{liq} = volume of liquid N_2 in pore, V_{ads} = volume of gas adsorbed, V_m = molar volume of liquid adsorbed, P_a = ambient pressure and T = temperature. The textural properties of the matrix are listed in Table 1.

$$V_{liq} = \frac{P_a V_{ads} V_m}{RT} \qquad \text{(Equation 1)}$$

Table 1. Textural properties of the silica xerogel after thermal treatment.

Surface area $A_{BET}/m^2.g^{-1}$	Average pore diameter d_p/Å	Pore volume (t-plot) $V_t/10^{-3}$ cm^3/g	*C* constant
643.06	27.65	6.52	90.68

The relative pressure at which adsorption occurs or desorption is possible enables us to calculate the pore size distribution as a function of pore diameter. This method, known as the BJH, is based on the Kelvin equation and was proposed by Barrett, Joyner and Halenda in 1951. The BJH method is used currently in calculating pore diameter distribution. Figure 2 shows the pore size distribution using the BJH method from the desorption data. This result shows that the silica xerogel has a mesoporous distribution conforming to the IUPAC classification.[25,26] The graph confirms that the matrix has a wide distribution of pore diameters between 2 and 190 nm, with unimodal distribution and positive skewness maximum at 27.65 Å (Figure 2). It should be emphasized that the sample, using the t-plot method, showed a microporous volume equal to 6.520 x 10^{-3} cm^3/g. The t-plot method, or statistical thickness method, is a mathematic model whose the mechanism is based on multi-layer formation, in order to calculate a layer "thickness, t" as a function of increasing relative pressure (P/Po). This method is widely used to estimate pore volume in microporous systems.

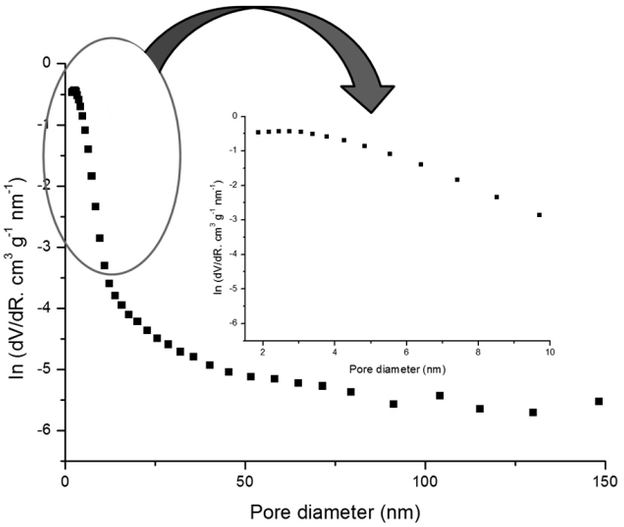

Figure 2. Pore size distribution by the BJH method of silica xerogel.

The ibuprofen, silica xerogel and ibuprofen-silica xerogel were analyzed by thermal analysis (TG), in order to observe possible changes in the decomposition temperatures or on-set temperature of ibuprofen. Figure 3 illustrates the TG curves of the ibuprofen and ibuprofen-silica xerogel. The TG curve of the silica xerogel showed two thermal events, the first event referring to sorbed water molecules at 100 °C and the second at 700 °C related to the silica contraction in the dehydration process, where two silanol type units generate one siloxane unit (not shown in this text).

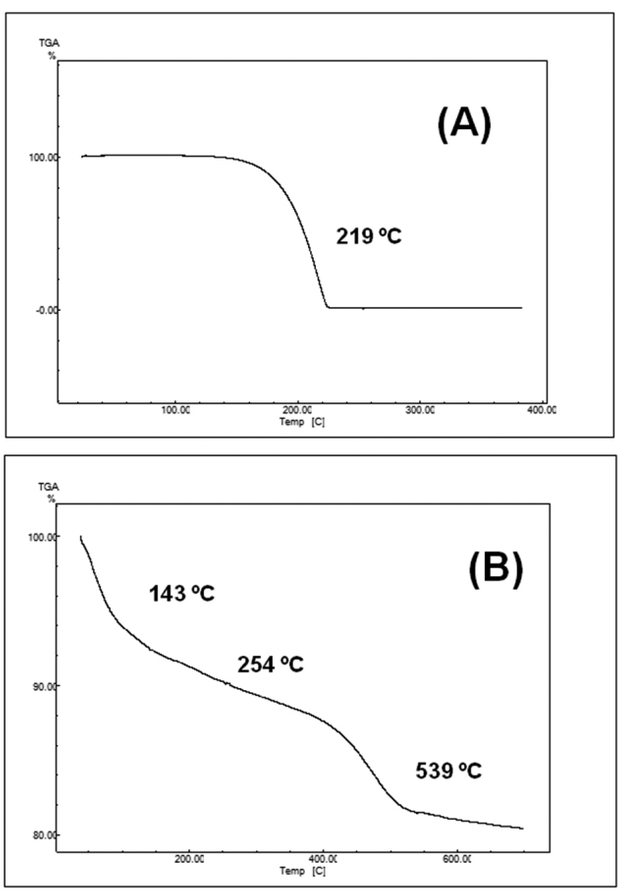

Figure 3. TG curves of the ibuprofen (A) and ibuprofen-silica xerogel (B).

Comparing the TG curves of free ibuprofen and its adsorption in silica xerogel, there was a change in on-set temperature referring to the degradation step of the IBF, with a higher temperature in the case of IBF-silica xerogel (IBF = 219 ºC and IBF-silica = 254 ºC). This behavior suggests that the IBF was in a thermally protected environment, probably occluded in the silica network.

The analytical curve using the ibuprofen standard was obtained in the concentration range of 10^{-4} to 10^{-9} mol L^{-1} (R^2=0.9989). The working parameters to evaluate the IBF release of the silica xerogel were pH and time. Figure 4 shows the results obtained for the parameter pH (A) and time (B), emphasizing the results obtained using 10mg of IBF-xerogel silica dispersed in 10 mL of phosphate buffer - pH = 3, 4, 5, 6, 7 and 8 (time parameters fixed in 10 min). The analysis referring to time of release was 1 to 10 minutes (pH parameters fixed at 7).

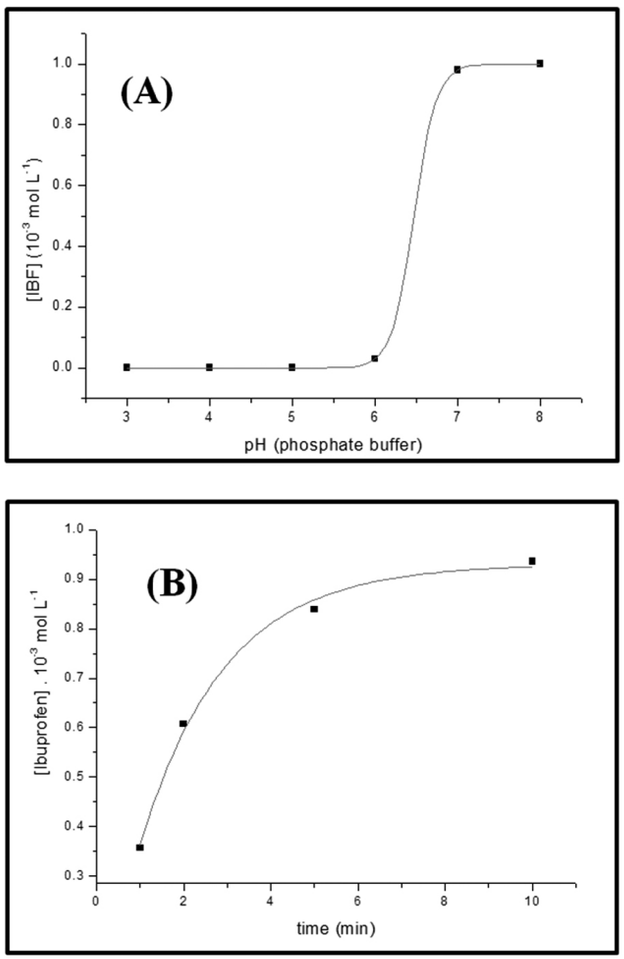

Figure 4. Ibuprofen release profile at different pHs (A) and evaluated as a constant pH 7, with chronological evolution (B).

The behavior of the pH parameter showed a standard sigmoid function with tendency to zero in the case of the acidic medium (pH = 3, 4, 5 and 6) and with maximum values at pH 7 e 8. The parameter studied suggests that the silica xerogel presents an application possibility to pH dependent systems, where the pH for release is basic (ibuprofen in intestinal region - pH>7). In the study of ibuprofen release time it was observed that the release occurs completely in 10 minutes.

4. CONCLUSIONS

The synthesis of the silica xerogel, in the presence of ibuprofen and acetic acid, enabled a material construction with interesting mechanical properties; i.e a porous matrix with pH-dependent contraction-expansion behavior. The use of the IBF template led to the formation of a network with high porosity and adsorption capacity. To make the model work, a similar collection of intermolecular interactions between host and guest in the IBF must be used, since the release rates are directly influenced by the balance of these forces. The properties of contraction and expansion of the network of silica were identified according to a different pH assay. In this case, xerogel had the property of contracting its network at low pH (3, 4, 5, 6) and expanding itself at high pHs, such as 7 and 8.

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