Journal of Encapsulation and Adsorption Sciences, 2016, 6, 47-55
Published Online June 2016 in SciRes. http://www.scirp.org/journal/jeas
http://dx.doi.org/10.4236/jeas.2016.62005

Sol-Gel Silica Matrix as Reservoir for Controlled Release of Paracetamol: Characterization and Kinetic Analysis

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Received 30 March 2016; accepted 23 May 2016; published 26 May 2016

Abstract

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are usually suitable candidates for the development of drug delivery devices. Sol-gel chemistry represents an easy method to obtain porous silica nanoparticles. Mesoporous silica nanomaterials have been widely used for drug delivery purposes. In this work we synthesized silica based materials using two molar alkoxide:water ratios 1:4 and 1:8, incorporating paracetamol to develop a nano-sized matrix for controlled release purposes. The samples exhibited different values for surface area, porosity, particle size and distinct punctual defects. Infrared and UV-visible spectroscopic studies were carried out to demonstrate the effect of water concentration and the adequate incorporation of paracetamol molecules. Nitrogen adsorption characterization was realized and the estimated BET surface values were from 532 to 825 m^2/g. Kinetic analysis of drug release profiles was performed using the hyperbola model. Transmission electron micrographs showed that all the materials formed aggregates of small particles with size between 10 - 60 nm. Mesoporous SiO_2 materials were proved to be a suitable system for controlled release of paracetamol.

Keywords

Sol-Gel Growth, Nanostructures, Biomaterials, Surface Properties

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How to cite this paper: López, T., Álvarez, M., Ramírez, P., Jardón, G., López, M., Rodriguez, G., Ortiz, I. and Novaro, O. (2016) Sol-Gel Silica Matrix as Reservoir for Controlled Release of Paracetamol: Characterization and Kinetic Analysis. *Journal of Encapsulation and Adsorption Sciences*, **6**, 47-55. http://dx.doi.org/10.4236/jeas.2016.62005

1. Introduction

Oral drug delivery is most preferred route for drugs administration. The absorption of drugs from the gastrointestinal tract relies on two crucial stages: drug solubility and permeability. Intestinal permeability of therapeutic agents is considered as a requirement for oral bioavailability. Hence, assessing and improving drug transportation across intestinal membrane is the key process in drug discovery and development [1] [2].

The consumption of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) causes serious secondary effects in the intestine that is why it is important to design new supplying methods to avoid these serious complications. In order to reach and maintain plasmatic concentrations, an effective dosage control is necessary to avoid significant fluctuations in the plasmatic levels. One of the actual options is controlled drug delivery [3]-[5]. Designing new delivering technologies becomes more important and necessary every day for pharmaceutical research.

A variety of nano biomaterials and many of these nanostructured solids that present great advantages over other conventional pharmaceutical forms, have been developed [6]-[8]. These have the capacity to incorporate, encapsulate, or conjugate a diversity of drugs in order to target specific cells or tissues [9] [10] and to offer tunable and site-specific drug release. Primary goals for research in this field include: more specific drug-targeting and delivery, reduction of secondary effects, increase of therapeutic effect, greater biocompatibility, prolonged times of drug activity and protection to active compounds from degradation [11]-[13].

Sol-gel chemistry represents an easy method to obtain porous silica nanoparticles [14] [15]. Nanomaterials made by the Sol-Gel process have emerged as a hopeful option for the immobilization, stabilization and encapsulation of biological molecules and a great variety of drugs [16]. The materials obtained by this method have particle size between 5 to 40 nm [17]; they are chemically inactive, hydrophilic and easily synthesized, present high biocompatbility with biological tissues and also can be manipulated with the aim of liberating the drug in the specific action site [18] [19].

In this paper we report the preparation of a delivering device for paracetamol, a widely used member of NSAIDs with antipyretic and analgesic properties because of its cyclooxygenase enzyme inhibition (COX). A silica based Paracetamol-SiO_2 material was designed for controlled and sustained drug release purposes. Two different amounts of water were used for the synthesis in order to assess the variations in the properties of the matrix. We obtained nanoparticles that were characterized by FTIR, thermal analysis, N_2 adsorption, and SEM. A kinetic study of the drug releasing was also carried out.

2. Materials and Methods

2.1. Sample Preparation

Reference-SiO_2 and Paracetamol-SiO_2 samples were synthesized by sol-gel process using tetraethoxysilane (TEOS) (Sigma-Aldrich 98%) as silica precursor. Molar alkoxide:water ratios (R_w) used were 1:4 and 1:8. For the Reference-SiO_2 sample synthesis was as follows, suitable amounts of water and ethanol were mixed into a rounded three neck flask (**Table 1**), then 18.5 mL of TEOS were added dropwise under continuous stirring at room temperature. The obtained sol was left under the same conditions until gel formation. Paracetamol-SiO_2 sample was obtained similarly, but 2.5 mg of paracetamol (Bristol-Myers Squibb) per gram of SiO_2 were mixed with deionized water and added at the beginning of the process. Once the gels were obtained, the samples were dried at room temperature and then grinded for further analysis.

2.2. FTIR Spectroscopy

Infrared absorption spectra of the nanomaterials were obtained on FTIR Affinity-1equipment. A wafer of

Table 1. N_2 adsorption parameters.

Sample	BET surface area (m^2/g)
Reference-SiO_2 1:4	699
Paracetamol-SiO_2 1:4	561
Reference-SiO_2 1:8	532
Paracetamol-SiO_2 1:8	825

potassium bromide (Sigma-Aldrich) for each of the four different samples was prepared for the analysis, the sample (5 wt%) was pressed together with KBr (95 wt%) (2000 ton/in^2).

2.3. Thermal Analysis

Thermograms were carried out using a Simultaneous Thermal Analyzer STA i-1000. Samples were placed in a platinum pan and heated from room temperature to 800˚C at a rate of 10˚C/min in a N_2 atmosphere.

2.4. Transmission Electron Microscopy

Images for the morphology analysis were obtained by means of a high-resolution Transmission Electron Microscope (TEM) JEOL JEM-2100F, operated at 200 kV and equipped with an energy dispersive spectroscopic (EDS) microanalysis system (Oxford). The micrographs were obtained using a Gatan Orius camera.

2.5. Nitrogen Adsorption

Nitrogen adsorption-desorption isotherms were obtained using a Micromeritics Belsorp II, Bell Japan Inc. The Brunauer-Emmett-Teller (BET) method was used to calculate specific surface areas (SBET). Pore volumes and pore size distributions were obtained using BJH method.

2.6. *In Vitro* Paracetamol Release Analysis

A wafer made of each Paracetamol-SiO_2 nanomaterial (1:4 and 1:8 ratios) was placed into a glass containing deionized water (50 - 75 mL). Sampling was performed at different time periods during a total of 200 hours. To assess the amount of drug released, samples were analyzed using ultraviolet spectroscopy (Cary-1 UV-visible, Varian). The increase in main absorption bands reported for paracetamol was monitored in all samples. After measurements, samples were returned to its corresponding glass to maintain a constant volume. A calibration curve was also realized and absorbance spectra were collected. In order to calculate drug concentration, Lambert-Beer law was used. Drug release curves were obtained by plotting cumulative drug concentration versus time. All the determinations were made by triplicate.

2.7. Comparison of Drug Release Profiles

Paracetamol release kinetics from each nanomaterial were analyzed by several mathematical models. Depending on these estimations, suitable mathematical models to describe dissolution profiles were determined. The following plots were made: % of drug released versus time (zero-orderkinetic model); ln dissolution % drug remaining versus time (first-order kinetic model); dissolution % drug released versus square root of time (Higuchi model); cube root of drug % remaining in matrix versus time (Hixson-Crowell cube root law); and dissolution % drug release versus time (hyperbola).

3. Results and Discussion

3.1. FTIR Spectroscopy

Figure 1 and **Figure 2** show the infrared spectra of the materials. In the low energy region, characteristic bands of silica were observed in all the samples, the band located around 477 cm^{-1} corresponds to Si-O-Si vibrations, while the peaks in the interval from 900 to 980 cm^{-1} are typical of the Si-OH bonds (**Figure 1(a)** and **Figure 2(a)**) [20]. The FTIR vibration band of paracetamol located at 3330 cm^{-1} corresponds to N-C-H (**Figure 1(b)** and **Figure 2(b)**). If paracetamol is occluded in the silica sample; some bands appear at the interval from 800 to 1500 cm^{-1}and correspond to symmetric and asymmetric vibrations of C-H and C-N of organic groups. The band at 1251 cm^{-1} corresponds to -H-C-N- vibrations and the bands located at 1600, 1643 and 1655 are attributed to C=O (amide) stretching vibrations (**Figure 1(a)** and **Figure 2(a)**). These bands were higher for 1:8 samples than 1:4 samples. In the high energy region, a broad band accompanied of the other small peaks between 3100 and 3700 cm^{-1} appears in all samples, these bands are formed by stretching vibrations from H-O-H, C-H and N-H bonds [21] [22]. The vibration bands with the higher intensities were exhibited in Paracetamol-SiO_2 1:8 sample (**Figure 2(a)** and **Figure 2(b)**), thus the difference in water concentrations slightly affects the properties of the drug adsorbed in silica matrix.

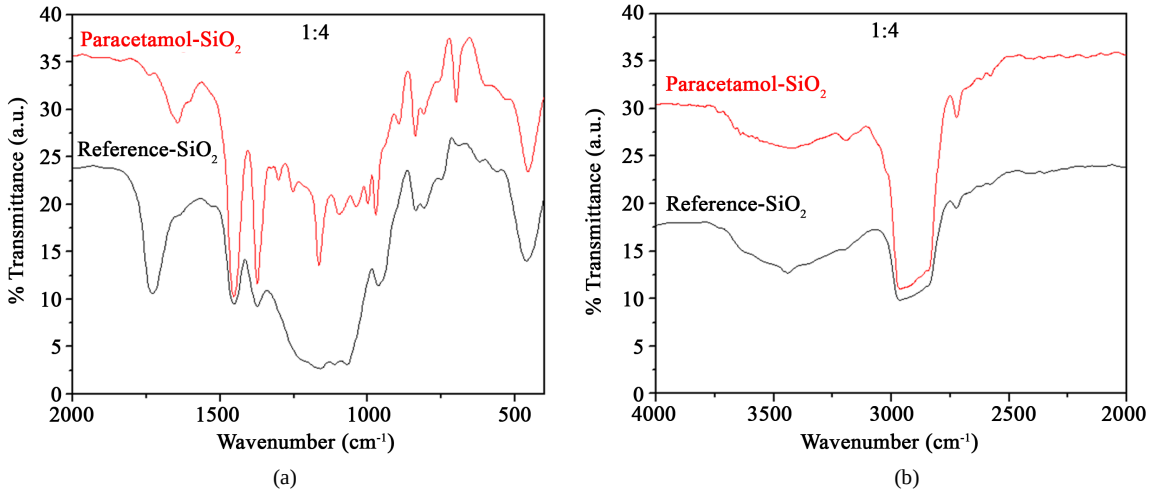


Figure 1. FTIR spectra of Paracetamol-SiO_2 1:4 and Reference-SiO_2 samples (a) low energy region and (b) high energy region.

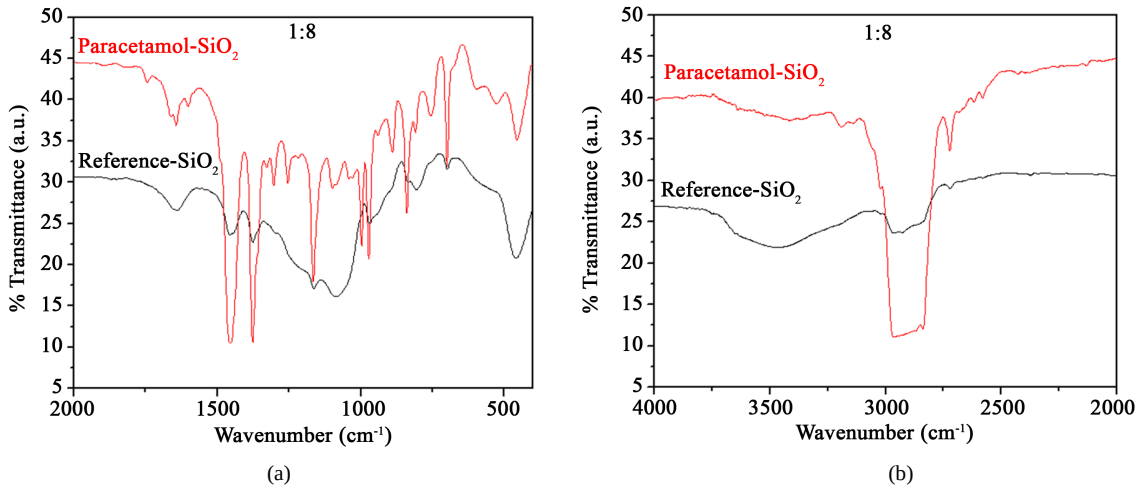


Figure 2. FTIR spectra of Paracetamol-SiO_2 1:8 and Reference-SiO_2 samples (a) low energy region and (b) high energy region.

3.2. Thermal Analysis

Thermograms of all the nanomaterials are shown in **Figure 3(a)** and **Figure 3(b)**. Incorporation of paracetamol into silica sol-gel in both ratios (1:8 and 1:4) causes slight modifications in thermal behavior of SiO_2 being more evident in R_w = 1:4 systems (**Figure 2**); where a difference in total amount of weight loss differs in 3%. At the beginning, Paracetamol-SiO_2 sample lose about 13% from room temperature to 130˚C, while this lost was 13% for SiO_2 alone. This first step is due to residual solvent and adsorbed water. The minimal difference in weight loss may be related to gelation process, since Paracetamol-SiO_2 sample took longer time than SiO_2 leading to complete hydrolysis-condensation reactions. Between 130 and 400˚C both samples showed a loss of 4% for SiO_2 and 6% for Paracetamol-SiO_2. Paracetamol melting (167˚C - 169˚C) and decomposition (326˚C) took place at this temperature range [23] [24]. The oxidative decomposition of the organic chains corresponding to the organic species dispersed in the silica matrix occurred between 250˚C - 320˚C. From the mass losses observed at the range between 250˚C and 280˚C on the three thermogram curves, we noticed that the alkoxide:water ratio used for the synthesis (which determines the nature of the matrix) does not influence significantly. The EG quantity which chemically bounds in the silica network structurally bonded -OH groups, takes place around 450˚C. For the 1:8 ratio materials, thermal behavior was very similar between both samples. The first loss (ca. 14.5%) was recorded around 156˚C for SiO_2 while Paracetamol-SiO_2 sample lost 13.5% at 141˚C. At the

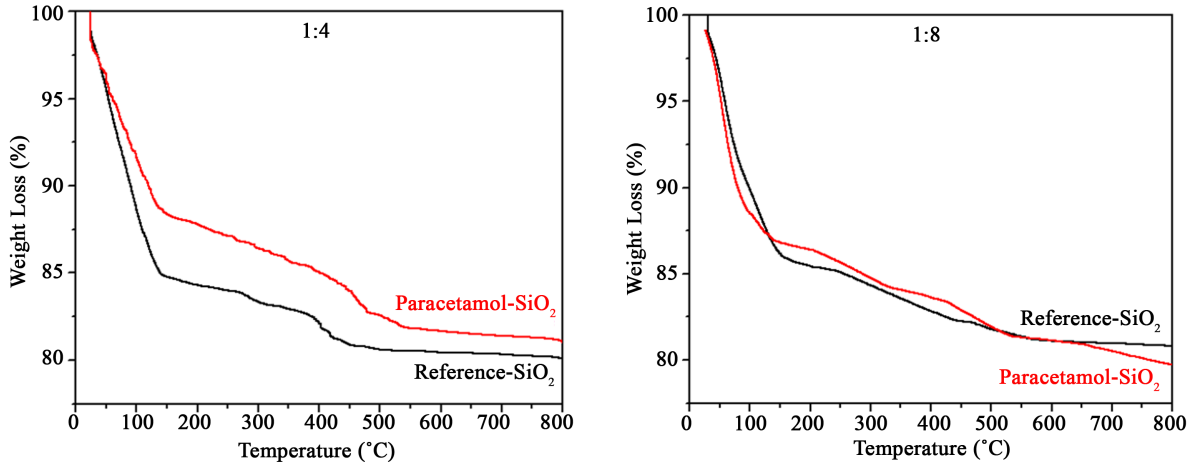


Figure 3. TGA curves of (a) 1:4 and (b) 1:8 samples.

156˚C - 246˚C range SiO_2 showed a minimal loss of 0.6% that did not occurred in the 1:4 SiO_2 sample, this may be explained because of the difference in water content. The following event occurred from 246˚C to 442˚C with a loss of 3% and the last one is observed between 468˚C and 553˚C with a loss of almost 1%. Thermal behavior of paracetamol-SiO_2 1:8 sample showed a small difference compared to 1:4 samples. Since the first one registered a two-step mass loss between 141˚C and 530˚C with a lower loss. Both losses, 203˚C - 329˚C and 329˚C - 424˚C were around 2%. It is well known that increased values of water promote silicon ratio hydrolysis leading to minimum alkoxide residuals, with increased gelation rates [25] [26].

3.3. Transmission Electron Microscopy

Transmission electron micrographs from Paracetamol-SiO_2 1:4 are shown in **Figure 4**. From the TEM images, aggregates of particles with estimated size of 10 - 60 nm were observed.

3.4. Nitrogen Adsorption

N_2 isotherms and BET surface areas for both samples and its references were obtained (**Figure 5(a)** and **Figure 5(b)**). We observed that both 1:4 and 1:8 samples were classified as type IV isotherms according to IUPAC classification [27] the adsorption is very similar up to P/P_0 = 0.4. All the samples presented an H2 hysteresis loop typical of materials with pores in the form of ink, characteristic of the majority of inorganic oxides. The most striking features of type IV isotherm are the hysteresis loops and the plateaus at high P/P_0, the isotherms of this type are produced by adsorbents for which capillary condensation occurs in the mesopore range, such as many silica gels, the majority of inorganic oxides some other metals [28] [29]. The surface areas obtained from the BET analysis of the isotherms are summarized in **Table 1**, this parameter did not considerably vary between the samples.

The idea of varying the water concentration is to have a different specific surface area and mean pore diameter, in **Table 1** we can observe that Paracetamol-SiO_2:water 1:4 has an specific surface area of 561 m^2/g, while Paracetamol-SiO_2:water 1:8 considerably increases to 825.

3.5. *In Vitro* Paracetamol Release Analysis

Figure 6 and **Figure 7** show paracetamol release curves the reservoirs monitored over a period of 0 - 3 and 0 - 200 hours, the amount of released drug was 50% and 60% respectively in both samples (1:4 and 1:8). The main purpose of paracetamol addition at the beginning of the synthesis with different amounts of water is to bond paracetamol to the silica network avoiding the degradation of the drug, allowing the formation of a gel with the drug bonded by means of Van der Waals interactions to the silica complex. In this way we ensure that paracetamol, which remains at the surface, will be released during the first hour, and the drug that remains at the internal surface will be slowly released in latter times (**Figure 7(a)** and **Figure 7(b)** and **Figure 8**).

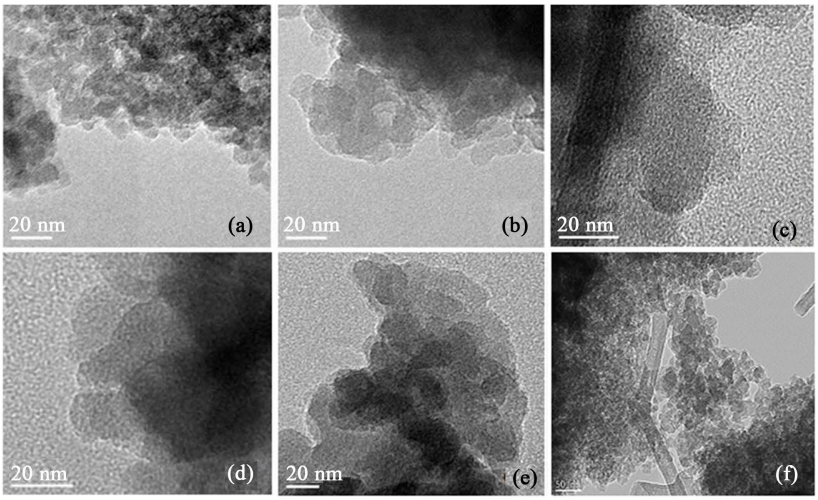
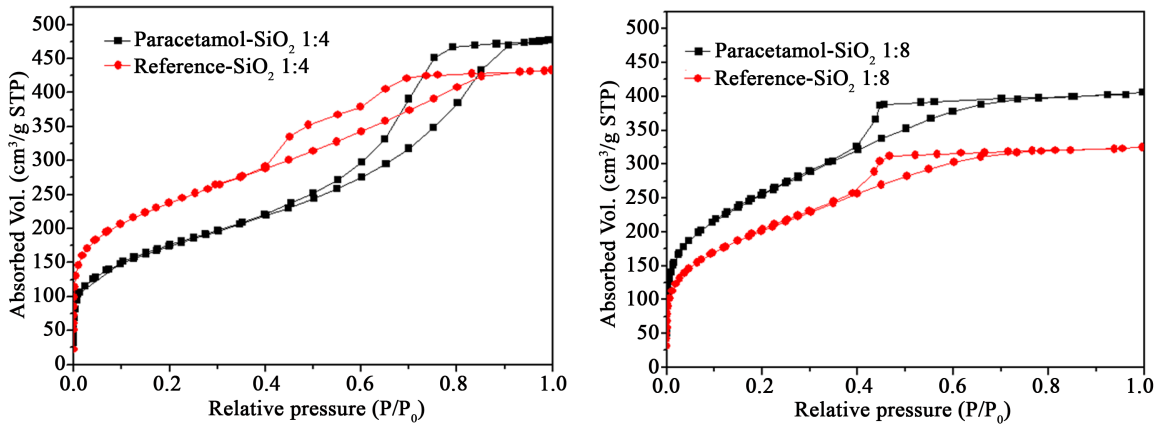
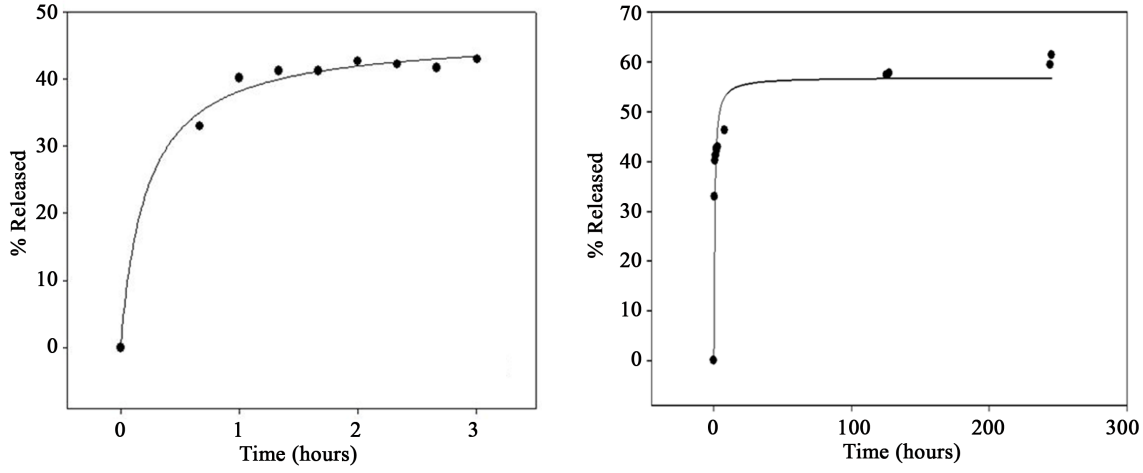


Figure 4. TEM images from Paracetamol-SiO_2 1:4 samples (from (a) to (e) the magnification is 20 nm and (f) shows a magnification of 50 nm).



(a) (b)

Figure 5. Nitrogen adsorption isotherms of (a) 1:4 and (b) 1:8 samples.



(a) (b)

Figure 6. Release profiles of Paracetamol-SiO_2 1:8 from 0 to 3 hours (left) and from 0 to 200 hours (right).

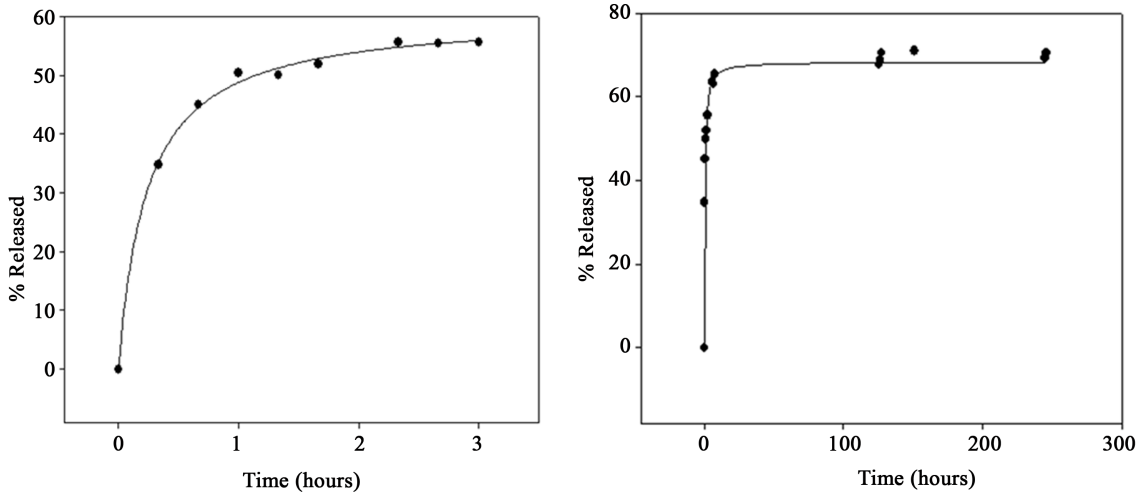


Figure 7. Release profiles of Paracetamol-SiO_2 1:4 from 0 to 3 hours (left) and from 0 to 200 hours (right).

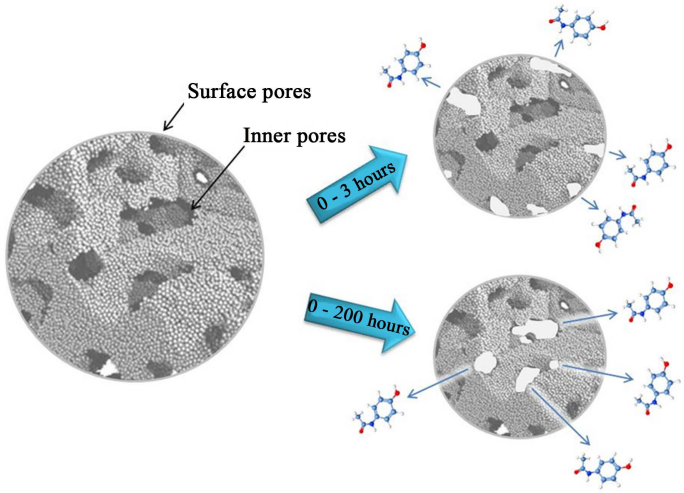


Figure 8. Graphical representation of the mechanism of paracetamol released from Paracetamol-SiO_2 materials.

The amount of drug released from SiO_2 1:4 reservoir correspond to 60% and 80% at time periods of 0 - 3 (**Figure 6(a)**) and 0 - 200 hours respectively (**Figure 7(b)**). A slower release rate is observed in 1:8 nanomaterial (**Figure 7(a)** and **Figure 7(b)**) with respect to 1:4, this could be explained because of the higher BET area showed by paracetamol 1:8 sample since it is encapsulated in a network with major stability in the extent that is released. After first 3 hours both reservoirs followed a sustained type profile determined largely by stoichiometric ratio of the silica matrix and particle size [30] [31]. Hyperbola t was the model that best fit for all *in vitro* release profiles of paracetamol, with lineal correlation coefficients of $R^2 = 0.9$ for both nanomaterials.

4. Conclusion

Paracetamol-SiO_2 materials were prepared by the variation of the water:alkoxide ratio and studied as drug release systems. Paracetamol molecules were successfully hosted into the silica network, maintaining its original structure, when prepared by the sol-gel method varying the water ratio during the hydrolysis of TEOS. Only slight differences between 1:4 and 1:8 samples were observed and did not generate significant variations in the release profiles. From the Paracetamol-SiO_2 adsorption results, it can be concluded that the drug loading ability is closely related with the specific area and pore dimensions of each material. The *in vitro* paracetamol release kinetics indicate the existence of two different release steps, a fast release during the first hours and from then

on a fixed sustained rate of release. Therefore mesoporous SiO_2 materials are a suitable matrix to allocate paracetamol molecules and subsequently deliver the drug in a controlled-sustained way.

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