Chapter 5

Silica from Rice as New Drug Delivery Systems

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Abstract

The pharmaceutical industry has seen an increased need of carriers or excipients design that allows the controlled release of a drug in the human body. The main role of an excipient is to carry the drug for its administration under therapeutic index. Among the new generation of excipients, the ordered mesoporous silica (MS) presents several advantages, such as excellent biocompatibility, good adsorption capacity, and precise control in the drug delivery. However, the high cost of synthesis of mesoporous silica restricts its use to industrial applications; therefore, a low-cost procedure is necessary for widespread use. Biogenic silica from rice husk (SiO_2-rice) could be a new choice as a drug delivery system. This silica is obtained from an acid leaching of rice husk followed by calcinations processes at low temperatures; these conditions produce silica with good adsorption properties, similar to those of MS. In consequence, the excipient behavior of SiO_2-rice was assessed using folic acid as the model drug, displaying an 18.5% of absorption in the SiO_2-rice pores, while MS absorbed around 19%. The drug release profiles were similar for both the silicas, suggesting that SiO_2-rice could be a low-cost, similar yield excipient for drugs similar to folic acid.

Keywords: mesoporous silica, SiO_2-rice, drug delivery systems, adsorption capacity

1. Introduction

Tablets are solid dose containing an active substance or drug and an excipient. The purpose of the excipient is to provide the optimal concentration of the drug, as well as chemical, physical, and biological stability. **Figure 1a** illustrates the function of excipient in a tablet, which is to catch the drug and allow its release. However, according to **Figure 1b**, the excipient shows an uncontrolled fragmentation causing the release of the drug at differ-

ent speeds (J_1 and J_2), and even part of the drug remains trapped in the tablet, causing the decrease of drug bioavailability [1–3].

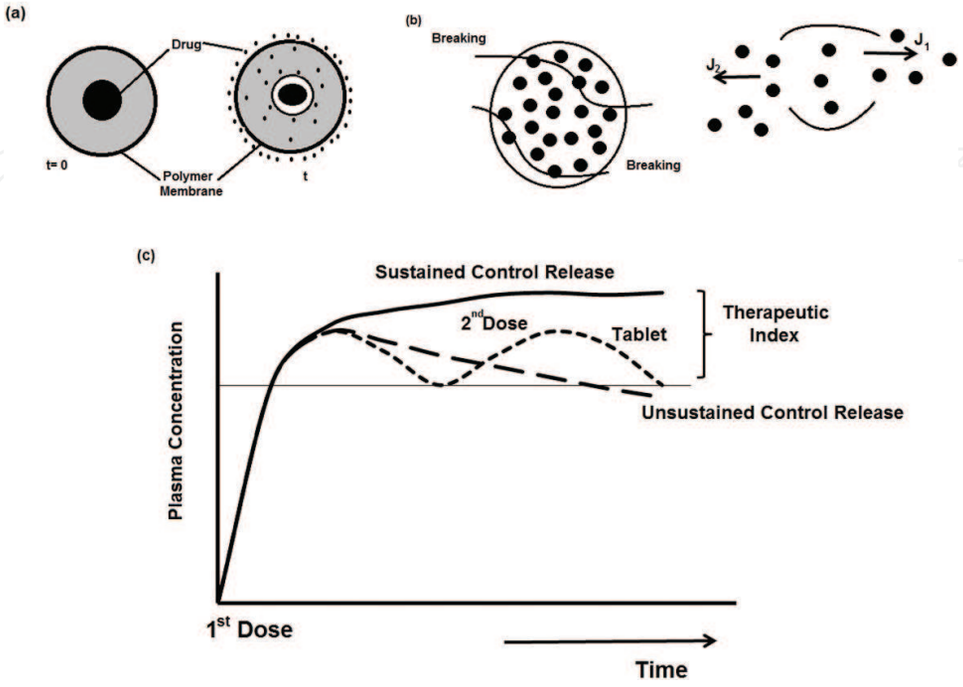

Figure 1. (a) Excipient function. (b) Fragmentation excipient. (c) Release profiles for pharmaceutical formulation.

Figure 1c shows the release profile of a tablet. A tablet rapidly releasing the drug and reaching its maximum concentration in short time subsequently loses its biological activity making necessary a second or third dosage to maintain biological activity. However, there are sustained release systems, which release initially the maximum drug concentration and continue to release this amount for sustained periods of time. Commonly, this substances are polymers and hydrogels. **Figure 2** shows the three main mechanisms of drug release through a polymeric matrix [2, 3]:

1. In diffusion from the polymer, the drug is released into the medium through a controlled diffusion process (**Figure 2a**).
2. **Figure 2b** shows a diffusion process through polymer swelling. In this system, the excipient (polymer) undergoes a swelling process due to the adsorption of water or pH change and the structural change of the polymer allows the diffusion of the drug through its structure at a controlled rate.
3. **Figure 2c** shows the polymer erosion and degradation release mechanism. This mechanism requires external factors such as moisture or pH, which will break the layers of the polymer, consequently carrying out a controlled drug release.

Although many substances have been proposed as controlled release systems, these are synthetic chemical substances that could be nonbiocompatible in some cases. Nowadays, new excipients have been proposed, one of them is the ordered MS [4, 5] and biogenic silica obtained from rice husk (SiO_2-rice) [6, 7]. The MS and SiO_2-rice have several chemical

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properties, which provide an excellent biocompatibility that could be employed as a new generation of excipients employed to transport a variety of drugs.

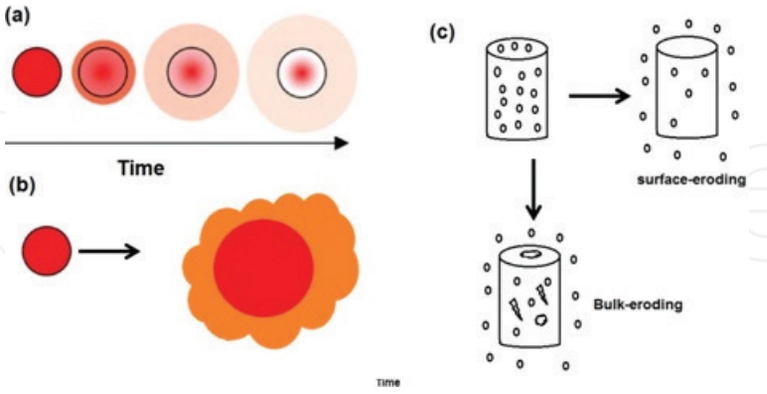

Figure 2. Pharmaco-release mechanism [3].

2. Mesoporous silica as drug delivery

The mesoporous materials are a group of inorganic solids with a system of gaps (pores), which may be arranged to form a hexagonal geometry (**Figure 3**), as well as present disordered pores into the bulk silica. However, in both states the inorganic solid has pore diameters ranging between 2 and 50 nm [8, 9]. **Table 1** shows the classification of porous materials according to the International Union of Pure and Applied Chemistry (IUPAC), which is based in the pore size, therefore, macroporous materials are those whose pore diameters are greater than 50 nm while microporous materials show diameters smaller than 2 nm.

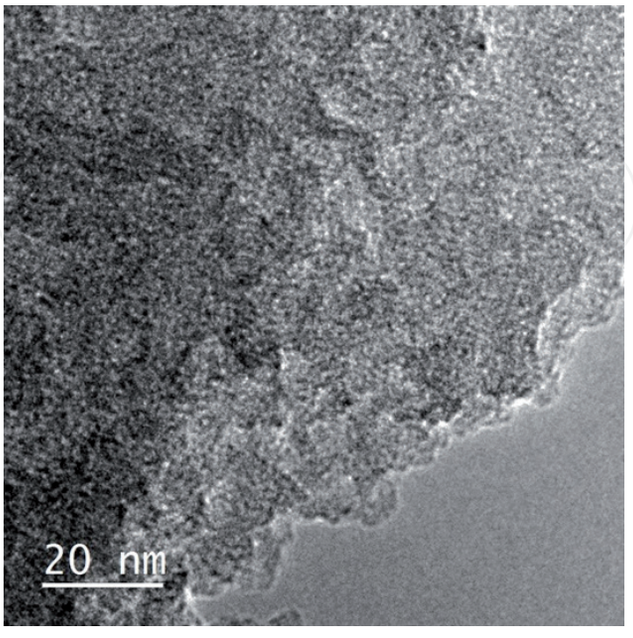

Figure 3. Ordered mesoporous materials structure view by TEM [11].

	Pore size (nm)
Microporous	<2
Mesoporous	2–50
Macroporous	>50

Table 1. IUPAC mesoporous materials classification.

Meso-porous materials have a pore network that can be disarranged or arranged; the latter is called an ordered mesoporous material whose main characteristic is to have a surface area between the ranges of 300 and 1200 m^2 [9]. According to the absorption capacity and chemical properties of MS, these materials could be used as new adsorption systems at different industrial applications, such as adsorption of pollutants [10, 11], catalyst supports [12], and sustained drug release systems [13–16].

Some drugs like ibuprofen [17], naproxen [18], carbamazepine [19], and fenofibrate [20], among others, have been adsorbed on ordered silica structures, such as MCM-41 and SBA-15. Ordered mesoporous silica can control the drugs kinetic release according to excipients of continuous and controlled release. Actually, biogenic silica such as the silica obtained from husk rice (SiO_2-rice) has been scarcely studied as a drug excipient, due to the limited order in the silica pores which could hinder the drug release [6, 7]. However, the good adsorption properties and the low cost of production may show advantages as a drug excipient.

Salazar-Hernandez and collaborators have performed research of SiO_2-rice as an excipient for folic acid [6]. In these works the high adsorptivity of drugs on the silica, and the drug release profiles at different pH values, were studied. This report will be discussed in this chapter.

3. Silica from rice husk as drug delivery

3.1. Obtained silica from rice husk

Silica is a compound found naturally in plants without playing an essential role for growth or development thereof. Similarly to phosphate ions, the silicate ions can be moved from the ground surface and delivered to the root, stem, and leaves of plants [21]. The role silica plays in plants is circumscribed to mechanical resistance of stems and leaves, and generating resistance to fungal diseases. **Figure 4** shows the mechanism employed by plants to fix the silica. Silicon oxide is transported throughout the plant as silicic acid ($Si(OH)_4$), which is concentrated as gel and depending on water evaporation, the silica is progressively deposited within the intercellular spaces.
Among plants containing a large percentage of silica we find rice husk. It contains between 13 and 29% of the total weight in cellulose and about 24.7% in silica [22–24]. To obtain SiO_2-rice it is necessary to remove all organic matter (cellulose) through prolonged calcinations. A pretreatment with nitric and hydrochloric acid allows the removal of inorganic ions, such as Ca^{2+}, Mg^{2+}, and Fe^{3+}; while the preoxidation of the organic material begins. This procedure favors

the removal of the organic material through calcinations at low temperatures (650°C) [22–24], with the concomitant benefit of avoiding the sintering of silica. **Figure 5** shows the sintering process, which involves the removal of hydroxyl groups distributed on the surface through condensation, causing the collapse of the pores in the material [25]. **Table 2** shows the textural properties observed in SiO_2-rice obtained with nitric/hydrochloric acid treatment and calcinations at different temperatures [6, 22–24].

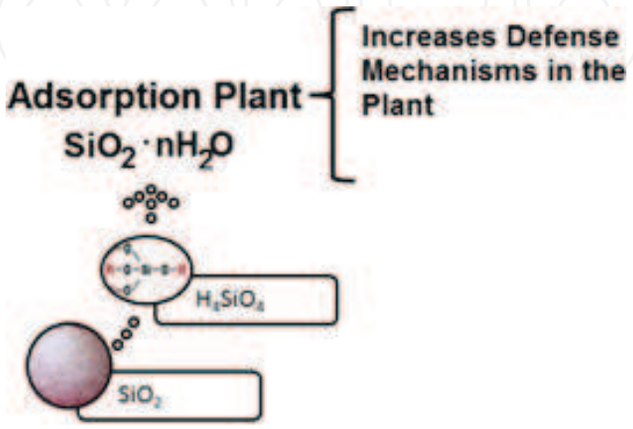

Figure 4. Setting mechanism silica in plants.

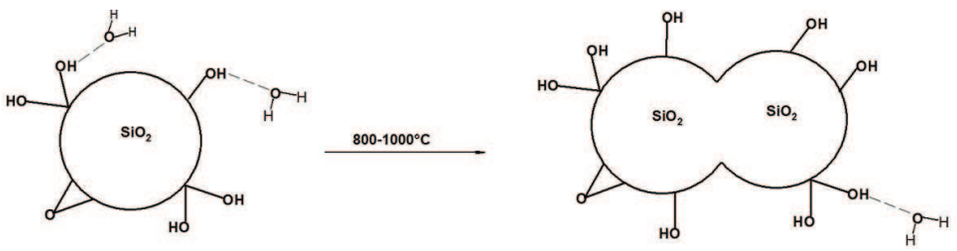

Figure 5. Sintering process of the silica [25].

	Calcination temperature (°C)	Surface area A_{BET} (m^2/g)	Volume pore (cm^3/g)	Size pore, D (nm)
SiO_2-rice	900	94.9	5.37	0.130
SiO_2-rice	500	291.8	4.25	0.320
SiO_2-gel	–	299.0	14.72	1.13

Table 2. Textural properties for SiO_2-rice.

According to **Table 2**, the Area surface calculated by Brunauer, Emmett and Teller Model (BET) surface area of the SiO_2-rice obtained at 500°C is similar to silica gel. The average pore diameter for SiO_2-rice is smaller than those of silica gel; however, this pore size suggests a

similar adsorption capacity to synthetic silicas (SBA-15, MCM-41). When the SiO_2-rice is extracted at high temperatures (900°C), the sintering process causes the elimination of porosity and the consequent loss of any adsorption capacity [6].

The adherence to such conditions (acid pretreatment and calcinations temperatures) is essential in order to control the textural properties and adsorption capacity in the silica. Thus, it is possible to obtain SiO_2-rice with similar adsorption properties than ordered mesoporous silica; opening the possibility to use this biogenic silica as a drug delivery system.

3.2. Silica from rice characterizations

IR analysis for both silicas, SiO_2-rice and MS, is shown in **Figure 6**. Broad signals of Si–O–Si [1027 cm^{-1} (ν_{as}) and 793 cm^{-1} (νs)], water adsorption [3456 cm^{-1} (ν) and 1638 cm^{-1} (δ)], Si–OH groups at 945 cm^{-1} were observed [6, 26]. A signal with smaller intensity at 2934 cm^{-1} was observed, corresponding to C–H of the nonhydrolyzed Si–OC_2H_5 groups on SBA (**Figure 6b**) and the organic material such as cellulose on SiO_2-rice (**Figure 6a**). Silanol groups were present in the MS as a signal at 945 cm^{-1}, while SiO_2-rice shows a shoulder at this wavenumber. These results could suggest a major amount of silanol on the surface of the mesoporous silica. The folic acid adsorption capacity on both silicas will be discussed later.

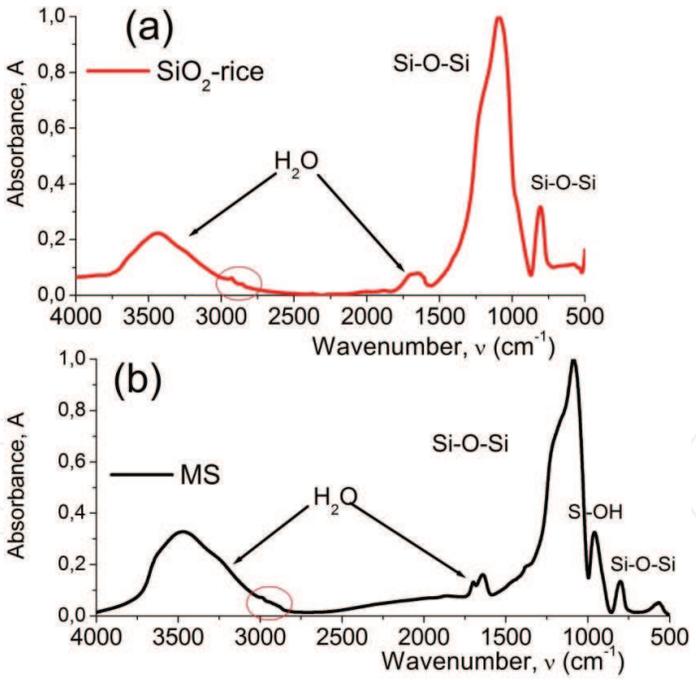

Figure 6. FT-IR analysis of (a) SiO_2-rice and (b) mesoporous silica (MS).

The results of the silica thermal analysis are shown in **Figure 7**; the total amount of SiO_2 formed was higher for SiO_2-rice, a value close to 96%, while 76% corresponded to SBA

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(**Figure 7a**). Both silicas appeared around 120°C, represented by an endothermic peak (peak 1 on Differential Temperature Analysis (DTA), **Figure 7b**), corresponding to the complete loss of the water and solvent adsorbed in the structure; however, the intensity of this loss was higher on SBA. On the other hand, the organic material loss was observed for SBA as two exothermic peaks between 240 and 400°C (peaks 2 and 3 on DTA, **Figure 7b**). These reactions could be due to the loss of the remainder pluronic-123 and the unreacted ethoxy groups, Si–OC_2H_5, from TEOS (starting materials for mesoporous silica). Nevertheless, no organic material loss was observed for SiO_2-rice, which is established with the highest ceramic yield observed by the biogenic silica.

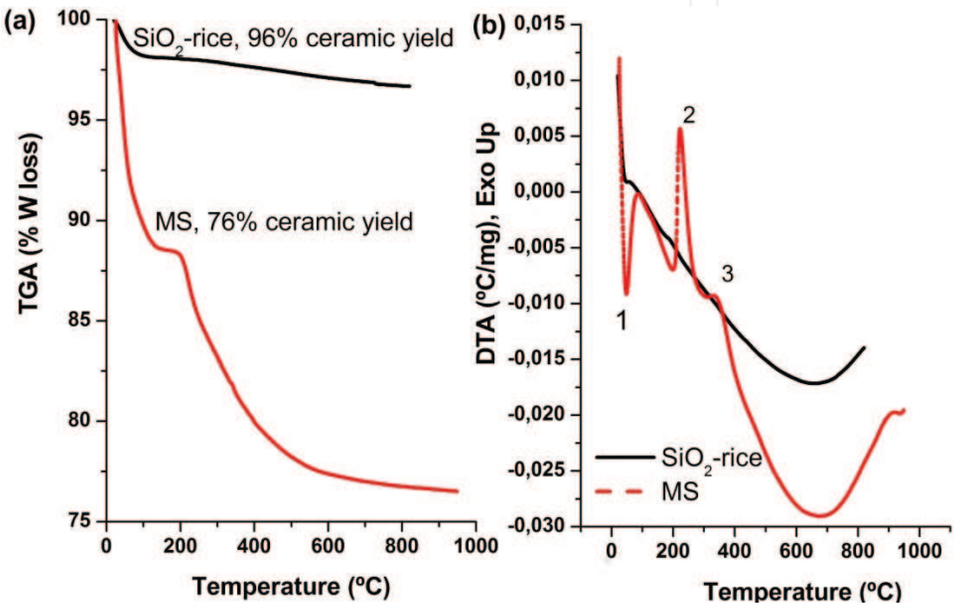

Figure 7. Thermal analysis. (a) TGA and (b) DTA.

3.3. Folic acid load on silica from rice husk

Figure 8a shows the percentage of adsorbed drug, which was calculated from Thermal Gravimetric Analysis (TGA) analysis for the silicas/folic acid adsorbed until 75 min. A large weight loss happened between 200 and 500°C, corresponding to the gradual loss of the organic material (drug adsorbed); the integration from TGA line on this range of temperature corresponding to the amount of drug adsorbed. **Figure 8b** indicates the percentage of drug adsorbed by the silicas at different adsorption times; these results suggest that both silicas have similar adsorption capacities, MS adsorbed 19.3% in weight of folic acid, while SiO_2-rice adsorbed around 18.5%.

Table 3 shows the change on silicas' textural properties after drug adsorption, a major modification on pore volume was observed for MS while the modification in SiO_2-rice was 12% higher. However, SiO_2-rice presented almost two times more modification on BET area in MS.

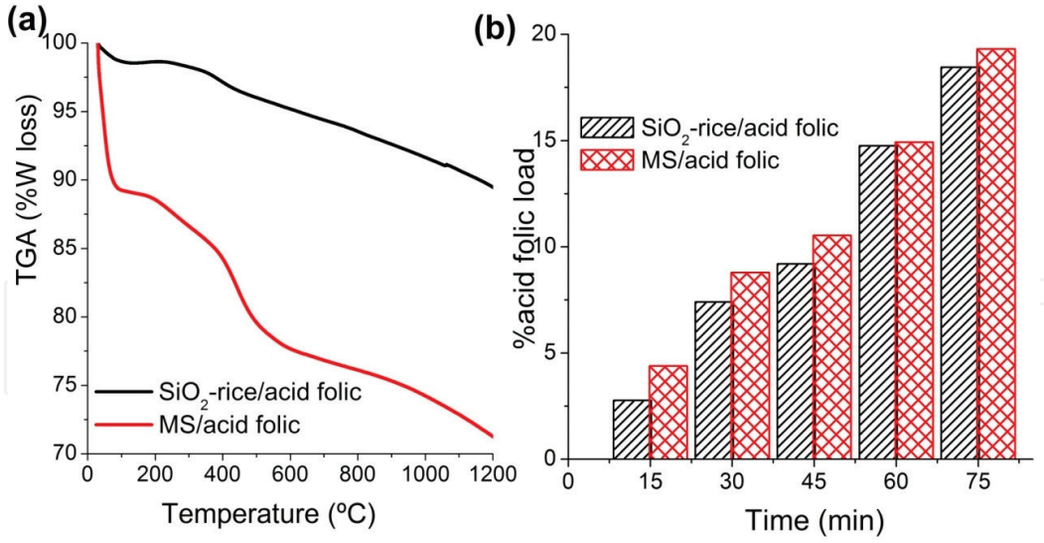

Figure 8. Folic acid adsorption on silica. (a) TGA analysis and (b) adsorption at different time.

	A_{BET} (m^2/g^{-1})			V_{pore} (cm^3/g^{-1})		
	Before adsorption	**After adsorption**	**% change**	**Before adsorption**	**After adsorption**	**% change**
SiO_2-rice	286.17	145.31	49.2(−)	0.3183	0.2531	20.5(−)
MS	600.04	461.37	23.1(−)	0.5922	0.4021	32.1(−)

Table 3. Silica textural properties before and after of the folic acid adsorption.

3.4. Folic acid releases using therapeutic concentration

Folic acid is a vitamin administered orally with a daily dose for adults of 400 μg. Then, the release profile of 400 μg of folic acid adsorbed on silicas was compared to a similar process with a commercial tablet and the same drug dosage (**Figure 9**). The obtained results indicated that the MS and biogenic silica allow a similar drug release profile as a commercial tablet. In gastric condition, pH 3, silicas and commercial tablet desorbed around 3% of the drug, reaching desorption equilibrium at 30 min (**Figure 9a**). However, desorption equilibrium was not observed at pH 5.5 and pH 7 for silicas and commercial excipient. At pH 5.5, around 90% of the drug was released by silica systems, while a commercial tablet desorbed around 80% (**Figure 9b**). **Figure 9c**, with a drug release profile at pH 7, shows an 80% release of folic acid for the commercial tablet and the biogenic silica, while MS shows only a 72% release.

These results suggest an important effect of pH on the desorption process of folic acid, an acid pH most probably increase attractive interactions between the silica surface and the drug. According to **Figure 10**, an acid pH could lead to a positive polarization of the silica surface due to the silanol groups' protonation, and a negative polarization of folic acid due to the deprotonation of acid groups. Therefore, a strong electrostatic attractive force will be generated, delaying the release process where the attractive interaction would decrease concur-

rently to a pH reduction in the system. On the other hand, a high amount of silanols on the MS surface were identified by FT-IR. This result suggests a strong interaction between this silica and the drug, because more silanols are able to interact with folic acid (**Figure 10**). However, the release profile indicated a similar desorption behavior for both silicas, which may be due to some molecules of folic acid being trapped in the pore and did not show interaction with the MS surface. These results make us think that drug size may affect the desorption process.

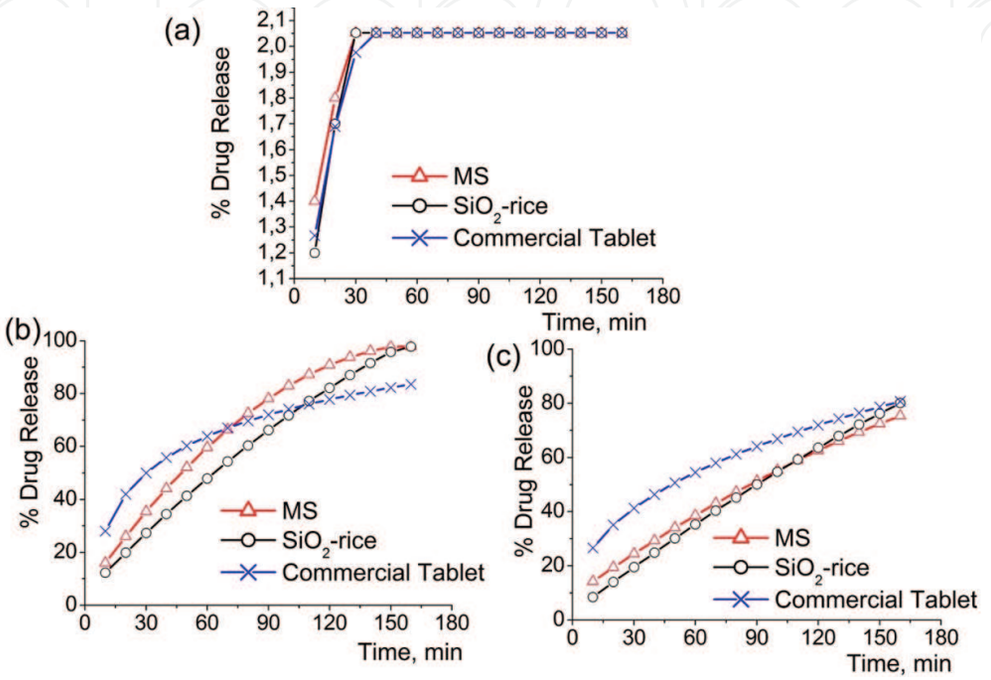

Figure 9. Folic acid release profile for 400 μg of drugs adsorbed.

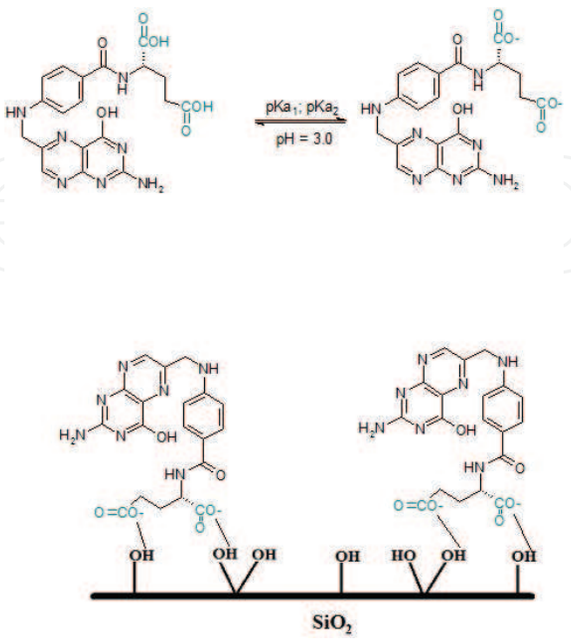

Figure 10. The pH effect on folic acid desorption process.

4. Conclusion

Biogenic silica, SiO_2-rice, presented a similar adsorption-desorption behavior to mesoporous silica. This silica adsorbed around 18% of the drug, while the MS adsorbed 19% of it; also, similar drugs release profile was observed for both silicas at different pH studies. The results obtained suggest that the size of the drug affects the adsorption/desorption process of folic acid on both silicas. On the other hand, pH shows an important effect on the drug desorption process, evidenced by the studied folic acid model. An acid pH could increase the attractive interaction between the surface silica and the drug, delaying the release of the folic acid, thus, pH 5.5 and 7 (pH for duodena after and before eating) would be the optimal condition for desorption of this drug. Additionally, the drug release profile observed for 400 μg adsorbed on silicas allow us to suggest that biogenic silica could be an excellent drug delivery system for folic acid and probably for other drugs. This silica, in comparison with MS, has a low-cost obtaining process.

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