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Nutritional effects of folic acid controlled release from mesoporous materials

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Abstract

Folic acid deficiency causes serious disorders in humans and supplementation has numerous health benefits. However, there is initial evidence that suggest a negative impact of an increased exposure to folic with respect to certain developmental and degenerative disorders. In this line, controlled release of folic acid by using mesoporous silica materials, MCM-41, has been studied as an alternative to direct supplementation. For this purpose, various mesoporous solids MCM-41 loaded with folic acid (S1) and functionalized with 3-[2-(2-aminoethylamino)ethylamino]propyl-trimethoxysilane (S2) acting as "gate" have been tested. The results show that at pH 2 a strongly hindered vitamin release is observed, whereas at pH 7.5 a controlled delivery is found. Based on the obtained results of this study, folic acid controlled release could be feasible during a period of 5h using a sensitive to pH gate, and this might reduce traditional fortification negative effects, while nutritional benefits are maintained.

Keywords: Folic acid; control release; mesoporous material; bioavailability; molecular gates.

1. Introduction

Folates are a group of water-soluble vitamins. Their deficiency can cause neural tube defects in developing embryos. To prevent the occurrence of these and other diseases, supplementation of certain foods with this vitamin is required by law in certain countries. However, recent studies suggest that folic

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supplementation could be a double-edged sword, because it could be associated with the incidence of some types of diseases when the excess of folic acid absorbed is directed to alternative metabolic pathways. For example, presently much attention is focused on the role of folic acid fortification in augmenting colon cancer risk. Also earlier in the life cycle, the vitamin may additionally influence insulin resistance [1]. Thus, obtaining systems that allow a reduction of the dose of folic acid while maintaining its vitamin activity is a challenge for current nutritional science.

One alternative to direct fortification, could be the use of encapsulating systems for controlled release based on supramolecular chemistry. This science has recently allowed the design of new hybrid materials showing enhanced functional molecular recognition and functionalities. In this area, one appealing concept is the development of "supramolecular gates". These are nanoscopic systems containing switchable entities that can control at will the state of the gate (closed or open), allowing either the release of the confined guests or the entrance (or access) of molecular species to (or through) certain sites. Gating properties have been reported on surfaces, in membranes, for the design of artificial channels, and recently in mesoporous MCM-41-type siliceous solids. Perhaps one of the most appealing functions is their application in advanced smart delivery systems. For instance, one possible use of pH-controlled gate-like scaffoldings [2,3] could be the development of orally applicable delivery systems designed to have the particular ability to protect the cargo from the acidic conditions of the stomach (acid pH, gate closed) but will release the load at the intestine (basic pH, gate open).

The aim of this study is to evaluate the potential use of folic acid encapsulation in a mesoporous material MCM-41 for controlled release of the vitamin in biologic systems in order to decrease the drawbacks of traditional direct fortification associated to high absorption peaks.

2. Materials and Methods

2.1 Synthesis of MCM-41

The mesoporous MCM-41 support was first synthesized using the so-called "atrane route" in which 4.68 g of CTAB was added at 118°C to a solution of TEAH3 (25.79 g) containing 0.045 mol of a silatrane derivative (11 mL of TEOS). Next, 80 mL of water was slowly added with vigorous stirring at 70 °C. After a few minutes, a white suspension was formed. This mixture was aged at room temperature overnight. The resulting powder was collected by filtration and washed with water and ethanol. Finally, the solid was dried at 70 °C. To prepare the final porous material, the as-synthesized solid was calcined at 550 °C using oxidant atmosphere for 5 h in order to remove the template phase.

2.2 Synthesis of S1

In a typical synthesis, 0.35 g of MCM-41 and 0.07 g (0.066 mmol) of vitamin B9 (folic acid) were suspended in 50 mL of water pH=7.5, inside a round-bottom flask in an inert atmosphere. The mixture was stirred for 24h at room temperature with the aim of achieving maximum loading in the pores of the MCM-41 scaffolding. The loaded solid was isolated by vacuum filtration and dried at room temperature for 36 h. Throughout this time, work is carried out in dark (amber instrumental) and in an inert atmosphere to prevent oxidation of folic acid (see figure 1a).

2.3 Synthesis of S2

The procedure stats as S1, but after 24h of stirring an excess of 3-[2-(2-aminoethylamino)-ethylamino]propyl-trimethoxysilane (4.3 mL, 15.0 mmol) was added. The final mixture was stirred for 5.5 h at room temperature. Finally, the solid (S2) was filtered off, washed with 30 mL of water, and dried at room temperature for 12 h (see figure 1b).

2.4 Solids characterization

XRD, TGA, Fluorescence spectroscopy and UV–visible spectroscopy techniques were employed to characterize the synthesized materials.

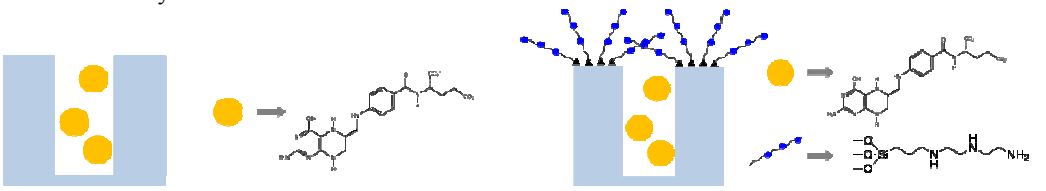

Fig. 1. (a) Design of loaded S1; (b) Desing of loaded S2

2.5 Vitamin release studies

For folic acid release from S1 and S2 a batch system was designed using 10 mg of the study carrier material, which was placed in an amber vial, to which is added a total volume of 25 mL of the delivery solutions (water at pH 2 and pH 7.5) and kept in stirring for different release times studied. At these times, a sample was taken and passed through a nylon filter of 0.45. The delivery of the vitamin from the pore voids to the aqueous solution was monitored via ultraviolet-visible spectroscopy by measuring the absorbance at 280 nm with a spectrophotometer.

3. Results and Discussion

3.1 Characterization of solids

Fig.2 shows powder X-ray patterns of the solids MCM-41 as-synthesized, MCM-41 calcined and S1 and S2. PXRD of siliceous MCM-41 as-synthesized shows four low-angle reflections typical of a hexagonal array that can be indexed as (100), (110), (200), and (210) Bragg peaks with an a0 cell parameter of 45.6 Å (d100 spacing of 39.5 Å). A significant shift of the (100) reflexion in the XRD powder of the MCM-41 calcined sample is clearly demonstrated in the curve b, corresponding to an approximate cell contraction related to condensation of silanols during the calcination step. Fig. 2 also shows curve that corresponds to S1 and S2. For these solids the reflections (110) and (200) are lost, most likely related to a reduction of contrast due to the filling of the pore voids with the vitamin (see figure3).

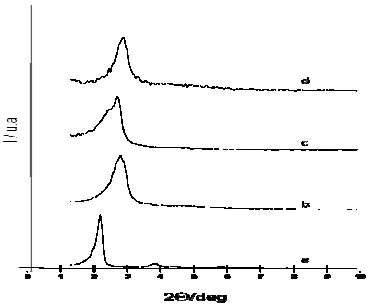

Fig. 2. Powder X-ray patterns of the solids (a) MCM-41 as-synthesized, (b) MCM-41calcined, and the final solids containing the vitamin B9 (folic acid) (c) S1 and (d) S2

3.2 Release from S1

In the study of S1, folic acid release was intended under different conditions; i.e. pH 2 and pH 7.5. Folic acid has low solubility at acidic pH, so as shown in Figure 3 it was not possible to release more than 15% of the load after 400 minutes when the delivery is done in water at pH 2. When release is performed in an aqueous medium at pH 7.5, folic acid molecules are in the form of salt, increasing the solubility. In this molecular configuration, 80% of the cargo is released for the first 15 minutes and a 100% release is achieved after 400 minutes.

Consequently, we can say that folic acid encapsulation in MCM-41 material, is a technique which accounts for regulating the release of folic acid as a function of pH. With this behavior, if folic acid were introduced to human body through digestive system in the form of S1, folic acid molecules would not be delivered during passage through the stomach and will be released at the entrance of the intestine, where pH increases due to the presence of bile salts.

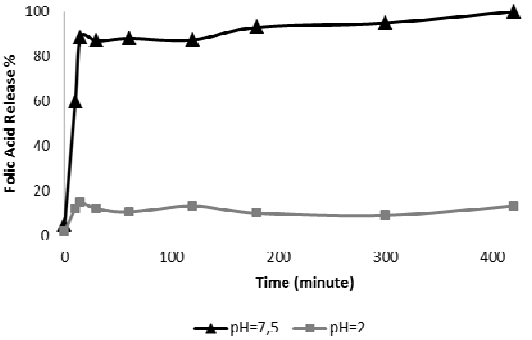

Fig. 3. Release profiles of folic acid from the pores of solid S1 at pH 2 and pH 7.5

3.3 Release from S2

The effect of polyamines as molecular gates was studied in S2 release assays, using two aqueous solutions (pH 2 and pH 7.5). Figure 4 shows how at pH 2 there is negligible release. However there are noticeable differences from the delivery of S2 when compared with S1.

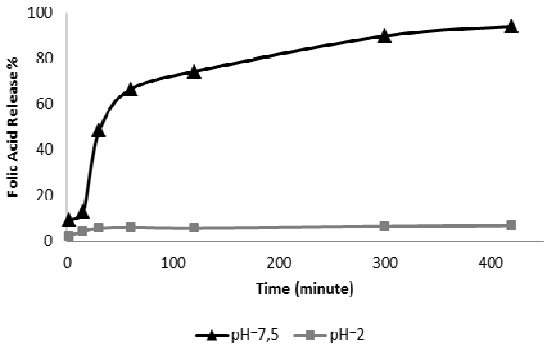

Fig. 4. Release profiles of folic acid from the pores of solid S2 at pH 2 and pH 7.5

The first difference is that S2 shows a stronger hindrance of vitamin release at pH 2, because the effect of low solubility is added to the steric hindrance at the exit of the pores imposed by the anchored polyamine derivative. The second difference is that at pH 7.5, at which the delivery from S1 is very quick, when using solid S2 a more sustained delivery was observed. This behavior shows that the use of polyamines as pH-responsive gate-like allows folic acid controlled release for long times (up to 7 hours). Thus, not only folic acid protection during passage through the stomach can be achieved, but also progressive release systems.

4. Conclusion

Administration of encapsulated folic acid can be achieved by using mesoporous materials MCM-41. This system protects the vitamin from the external environment during passage through the stomach, being able to release in the intestine. This effect can only be achieved through encapsulation due to the low solubility of folic acid in acid pH, or by using molecular gates.

When controlled release over time is needed, it is necessary to use molecular gates, being able to secure a progressive release of folic acid along the digestion period, using a pH gate-like. Once this in vitro behavior has been described, "in vivo" studies should be done in order to relate the controlled release with an improved bioavailability of the vitamin.

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