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Mesoporous Solid Acid Catalysts: Their Efficiency towards Organic Transformations

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Abstract – The present Paper, entitled "Mesoporous Solid Acid Catalysts :Their Efficiency Towards Organic Transformations", Focuses On The Development Of New Smart Systems For The Controlled Delivery Of Mesoporous Solid Acid For Applications. The first part of the paper shows solid acid encapsulation in polyamine-functionalized Solidporous matrices from a nutritional approach. The first part evaluates not only the influence of the loading method and the type of Solidsupport employed (MCM-41, SBA-15, UVM-7 and Hollow Silica) on the efficiency of folic acid encapsulation, but also the influence of the morphology and porous system on the folic acid delivery profile from different supports. Folic acid release studies from different supports with various pH values have demonstrated that the designed systems are capable of smartly modulating the delivery of the folic acid dependent on the pH of the medium (inhibition of the release at an acidic pH -stomach-, controlled release at a neutral pH -intestine-).

Keywords:- Mesoporous, Solid Acid, Catalysts, Heterogenisation, etc.

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INTRODUCTION

Mesoporous Solid Particles (MSPs) are receiving great attention in the field of oral controlled release due to their capability for improving drug solubility and stability in the gastrointestinal tract, as well as to release the cargo along the time (sustained controlled release) specific places of the gastrointestinal tract (GIT) (targeted controlled release) (Agostini *et al*., 2012; Popat *et al.*, 2012). These reported features that render MSPs unique smart delivery systems are due to their large loading capacity (Coll *et al*., 2011), low toxicity (Suh *et al.*, 2009) and the fact that their surface can be functionalized with molecular/ supramolecular ensembles. This last feature allows the development of gated-MSPs showing "zero delivery", and capability of releasing their cargo on-command in response to specifically designated external stimuli (Mondragón *et al.*, 2014).

Drug delivery/formulation technologies that can improve bioavailability, drug stability and subsequently increase drug effectiveness are much desired in the pharmaceutical sciences. In food technology, encapsulation of bioactive molecules (e.g. vitamins, antioxidants, phytochemicals, etc.) may improve their biological stability, facilitate components handling, mask unpleasant sensorial properties and modulate the bio accessibility of the molecule of interest along the GIT (Pérez-Esteve *et al.*, 2015).

Besides a high loading capacity, controlled release and biocompatibility, the suitability of these MSPs in oral controlled release in *in vivo* applications depend on the chemical stability of the supports though the whole digestive tube. However, it is known that, due to the metastability of MSPs, Solidcan be biodegraded into silicic acids, including monomeric silicic acid and various polysilicic acids with different polymerization degrees, under harsh environments provoking a collapse of the porous structures (He *et al.*, 2009). In this line, Cauda, Schlossbauer & Bein (2010) studied the biodegradation of colloidal mesoporous Solid nanoparticles (50 nm) in simulated body fluid of bare, globally functionalized, and surface poly(ethylene glycol)-coated colloidal mesoporous Solid nanoparticles in simulated body fluid (pH 7.4) for a period of 1 month at 37 °C. After this month, the textural properties of the mesoporous system were lost and pores were blocked because the precipitation of inorganic components from the simulated body solution. Particles stability increased by surface functionalization with poly(ethylene glycol). The degradation behaviour of surfactant-extracted mesoporous Solidin simulated body fluid was also evaluated by He and co-workers (He *et al*., 2010), who proposed a three-stage degradation process comprising a fast bulk degradation on an hour-scale, a silicon concentration decrease stage due to the deposition of calcium/magnesium silicate layer, and a later continuous sustained diffusion over a period of days. The same year, Lin, Abadeer & Haynes (2011), evaluated the stability of small mesoporous Solid nanoparticles (<50 nm) functionalised with poly(ethylene glycol) in H2O,

phosphate buffer solution (PBS) (pH 7.5), and Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum (FBS) (pH ca. 7.5). These particles exhibited long term stability in all these media at both, room and physiological temperature. In a different attempt, El Mourabit *et al.* (2012) studied the stability of mesoporous Solid under acidic conditions. In their work, the loss of textural properties of silicas under acid solutions was observed. However, it was stated that the degradation rate depends of the nature of the acidic media (phosphoric acid have stronger impact than hydrochloric or sulphuric) and also the type of silica.

The surface of the four types of particles was functionalised with *N1*-(3-trimethoxysilylpropyl) diethylenetriamine (N3) according to the procedure described by Pérez-Esteve *et al.* (2014). Concretely, 1 g of the different MSPs were suspended in 40 mL of acetonitrile and an excess of N3 (4.3 mL, 15.0 mol g-1) was then added. Final mixtures were stirred for 5.5 h at room temperature. Finally, the solids were filtered off, washed with 30 mL of deionised water, and dried at room temperature.

MESOPOROUS SOLID CHARATERIZATION

The characterization of the different mesoporous solids (**S0** and **S1**) was made by powder X-ray diffraction (XRD), transmission electron microscopy (TEM), field emission scanning electron microscopy (FESEM), particle size distribution and zeta potential determinations. XRD was performed on a D8 Advance diffractometer (Bruker, Coventry, UK) using CuKα radiation. TEM images were obtained with a JEM-1010 (JEOL Europe SAS, Croissy-sur-Seine, France). FESEM images were acquired with a Zeiss Ultra 55 (Carl Zeiss NTS GmbH, Oberkochen, Germany) and observed in the secondary electron mode. The particle size distribution was determined using a Malvern Mastersizer 2000 (Malvern Instruments, Malvern, UK). For the measurements, samples were dispersed in distilled water. Data analysis was based on the Mie theory using refractive indices of 1.33 and 1.45 for the dispersant and particle, respectively. An adsorption value of 0.001 was used for all samples. Variation of this adsorption value did not significantly alter the obtained distributions. Measurements were performed in triplicate. A Zetasizer Nano ZS (Malvern Instruments, Malvern, UK) was used to determine the zeta potential (□). Samples were dispersed in distilled water at concentration of 1 mg mL-1. The zeta potential was calculated from the particle mobility values by applying the Smoluchowski model. The measurement was performed at 25°C. Measurements were performed in triplicate. The composition of **S1** was determined by thermogravimetrical analysis (TGA) and 1H NMR. Thermogravimetric analyses were carried out on a TGA/SDTA 851e Mettler Toledo balance, using an oxidant atmosphere (air, 80 mL min-1) with a heating program consisting of a heating ramp of 10 ºC per minute from 393 to 1273 K and an isothermal heating step at this temperature for 30 min. 1H NMR spectra were recorded in at RT using a Bruker AV400 spectrometer after dissolving the sample in NaOD/D2O in the presence of tetraethyl ammonium bromide as internal standard.

MESOPOROUS SOLID PARTICLES SYNTHESIS

Synthesis of micro particulated MCM-41 (**M**) was carried out following the so-called "atrane route", using CTABr as the structure-directing agent and a molar ratio fixed to 7TEAH3: 2TEOS: 0.52CTABr: 0.5NaOH: 180H2O. The procedure consisted in adding CTABr to a solution of TEAH3 and NaOH containing TEOS at 118 °C. After dissolving CTABr in the liquor, water was slowly added with vigorous stirring at 70 °C to form a white suspension. This mixture was aged at room temperature overnight (Bernardos *et al*., 2008).

Nanoparticulate MCM-41 (**N**) was synthesized using the following procedure: NaOH was added to the CTABr solution, followed by adjusting the solution temperature to 95 °C. TEOS was then added dropwise to the surfactant solution. The mixture was allowed to stir for 3 h to give a white precipitate (Bernardos *et al.*, 2010).

UVM-7 (**U**) was synthesised using, once again, the "atrane route". The molar ratio of the reagents in the mother liquor was fixed at 7TEAH3:2TEOS: 0.52CTABr: 180H2O. The TEOS/TEAH3 mixture was heated to 120 °C until no elimination of ethanol was observed. The mixture was cooled to 90 °C and the CTABr was added gradually in small portions, followed by water. The mixture was aged for 24 h (Comes *et al.*, 2009).

The SBA-15 (**S**) sample was synthesized using P123 as the structure-directing agent with the reactant molar ratios: 0.017P123: 1.0TEOS: 6HCl: 196H2O. The preparation was carried mixing an aqueous solution of P123 with HCl solution, and stirring for 2 h, after which the Solid source, TEOS, was added. This final mixture was stirred for a further 20 h (Zhao *et al.*, 1998).

After the synthesis, the different solids were recovered, washed with deionised water, and air-dried at room temperature. The as-synthesized solids were calcined at 550 °C using an oxidant atmosphere for 5 h in order to remove the template phase.

The surface of the four types of particles was functionalised with *N1*-(3-trimethoxysilylpropyl) diethylenetriamine (N3) according to the procedure described by Pérez-Esteve *et al.* (2014). Concretely, 1 g of the different MSPs were

suspended in 40 mL of acetonitrile and an excess of N3 (4.3 mL, 15.0 mol g-1) was then added. Final mixtures were stirred for 5.5 h at room temperature. Finally, the solids were filtered off, washed with 30 mL of deionised water, and dried at room temperature.

SIMULATED DIGESTION PROCEDURE

An *in vitro* digestion model consisting of mouth, gastric and intestinal phases described by Versantvoort *et al.* (2005) was used to simulate the typical chemical composition, pH and residence time periods of each of the three main compartments of the GIT. A schematic representation of the *in vitro* digestion model is presented in **Figure 1**. The pH values of the digestive juices were checked and, if necessary, adjusted to the appropriate interval with NaOH (1 M) or HCl (37% w/w).

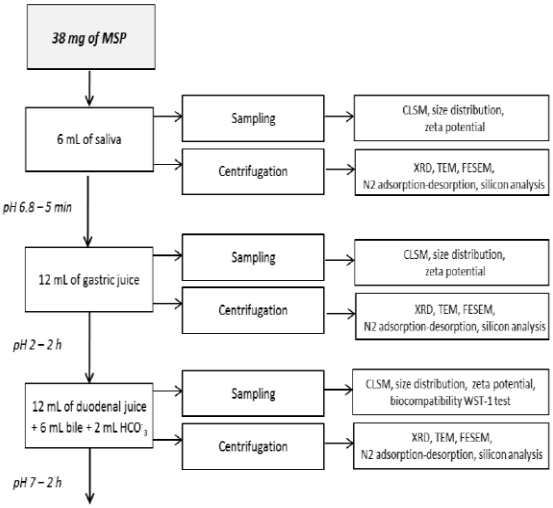

Figure 1. *Schematic representation of the in vitro digestion process. The in vitro digestion model describes a three-step procedure simulating the digestive processes in mouth, stomach and small intestine. In each compartment, the matrix is incubated at 37 °C for a time relevant for the compartment. The digestion is initiated by addition of artificial saliva to the material. Subsequently, gastric juices and intestinal fluids are added to simulate the digestive processes in stomach and small intestine, respectively.*

RESULTS

In results, it is stated that all the studied MSPs are altered as a consequence of the *in vitro* digestion process. However, the degradation degree depends on the type and size of the particles. In this context, El Mourabit *et al.* (2012) studied the structure alteration of several porous Soliddiffering in particle size, particle shape, pore-size distribution, specific surface area, pore volume and average of pore diameter caused by immersion in acid solutions and found that the degradation of the supports was not obviously influenced by textural properties of the particles. Nevertheless, in our study, it seems to be clear that particle size and wall thickness seem to be the characteristics that condition the degradation.

In order to correlate the impact of each of the phases of the digestion with the steps of the particle's degradation, a further experiment was done. For this detailed experiment MCM-41 nanoparticles were selected given that it was the most affected support by the whole digestion process. For this purpose, **N** was put in contact with water over 4 h. In parallel, a typical *in vitro* digestion process (4 h) was performed. After each of these steps, samples were washed and observed with TEM.

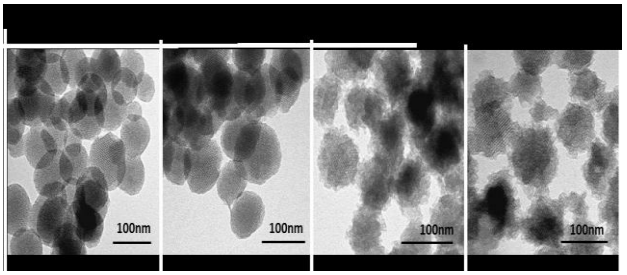

Figure 2 shows TEM micrographs of **N** after 4 h in contact with water (a) and after each of the phases of the *in vitro* digestion process: buccal (b), gastric (c) and intestinal (d). As observed, particle size (ca. 100 nm) did not vary during the digestion suggesting that particle structure remains unaltered after the whole digestion process. Moreover, surface and porosity of MCM-41 remained unchanged after 4 h in water, meaning that particles do not collapse easily in water solution. Particles are also intact after the 5 min of contact with simulated saliva. However, particles change dramatically their conformation after the 2 h of gastric phase. Concretely, after this digestion step, particles lose their clearly spherical shape and ordered porous conformation and become irregular shaped spheres with disordered porosity. Little differences among particles observed after gastric and after both, gastric and intestinal phases are shown. Therefore, it is thought that once the digestive solution is neutralized by the addition of intestinal juices, the degradation process is stopped.

CONCLUSION

The present work demonstrates the effect of an *in vitro* digestion process on the stability of bare and amine-functionalized mesoporous Solidparticles. Results showed that bare SBA-15 and MCM-41 microparticles were very stable against degradation. However, supports based on nanoparticles (i.e. MCM-41 nanoparticulated and UVM-7) exhibited an evident degradation of its structure characterized by a loss of pore order and surface attack. In the degradation process, only ca. 5% of the silicon present in the sample was dissolved in the digestion fluids, confirming that the degradation process is not

caused by the loss of matter, but in the chemical transformation of the SiO2 in other silicic phases. This degradation was avoided by the functionalization of the external surface of the particles with *N*1-(3-trimethoxysilylpropyl) diethylen etriamine. These findings evidence the importance of particle size and surface modification on the degradation behaviour during an *in vitro* digestion process. In addition, despite the formation of free silicon during the different phases of the digestion, neither the digested particles nor the biodegradation products show any toxicity to HCT116, HEPG2 HK2 and HeLa cells. In accordance to these results, the utilization of mesoporous Solidmicro particles, and over all, amine-functionalized mesoporous Solidmicro particles in the design of oral delivery systems guarantees the chemical stability of the supports through the whole digestive tube.

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