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Drug release profiles of modified MCM-41 with superparamagnetic behavior correlated with the employed synthesis method

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ABSTRACT

Mesoporous materials with superparamagnetic properties were successfully synthesized by two different methods: direct incorporation (DI) and wet impregnation (WI). The synthetized solids were evaluated as host of drugs for delivery systems and their physicochemical properties were characterized by XRD, ICP, N_2 adsorption-desorption, spectroscopies of UV–Vis DR, FT-IR and their magnetic properties were measured. Indomethacin (IND) was incorporated into the materials and the kinetic of the release profiles was studied by applying the Pepas and Sahlin model. In this sense, materials modified by DI, particularly that with hydrothermal treatment, showed the higher adsorption capacity and slower release rate. This behavior could be associated to the synthesis method used that allowed a high percentage of silanol groups available in the solids surface, which can interact with the IND molecule. This feature coupled with the superparamagnetic behavior; make these materials very interesting for drug delivery systems.

1. Introduction

In recent years, the field of nanotechnology has motivated researchers to develop nanostructured materials for human health care. In this sense, drug-delivery systems with magnetic properties are one of their most promising applications in the field of biomedical, materials science providing advantages over conventional drug therapies [1–4].

Mesoporous silica materials have been researched in order to develop very interesting drug-delivery systems. The literature shows many examples of drug molecules loaded onto mesoporous silica materials [5–7]. Particularly, MCM-41 is one of the most attractive porous materials because it possesses high specific surfaces (>900 m^2/g), tunable pore diameters (2–10 nm), high pore volumes and well organized porosity [8,9]. This huge surface available can lead to higher loading capacity of the drug, thus improving the dose of nanostructures needed as shuttle for the delivery. In addition, the thermal stability, and superior biocompatibility, has made these materials highly desirable in biomedical fields [10–14]. With respect to the biocompatibility, initial *in vitro* studies [15–17] demonstrated remarkable solubility of the mesoporous silica in simulated human plasma and other body fluids as those of the stomach, intestine, lung and/or urinary tract. This property is fundamental due to that the silica is not accumulated in the body; instead it is degraded and the products of its degradation are excreted through the kidneys [18]. In this context, it is pertinent to mention the synthesis of mesoporous composites having magnetic elements embedded in the nanochannels or in the porous framework as an alternative to the release of drugs. In this way, it is expected that, the drug loaded on carrier can be guided by an external magnetic field toward where it should be released, thus preventing its spread throughout the rest of the body.

Meanwhile, the size reduction of magnetic materials below a certain critical value, induces a magnetic transition where ferri-, ferromagnetic and antiferromagnetic nanoparticles become superparamagnetic. Thus, a reduction of the nanoparticles size is searched, due to that the magnetic parameters such as the coercivity can be finely tuned by decreasing the size of them. Moreover, these systems have high magnetic moments under the effect of a magnetic field, but they have not remanent magnetic moment when the external magnetic field is removed. This property is necessary especially *in vivo* experiments due to that the absence of net magnetic moment of the nanoparticles (zero coercivity) after concluding the diagnostic measurement or the therapy will prevent the potential aggregation of the particles that could easily cause the formation of embolisms in the blood vessels.

In this work, we have prepared drug-loaded samples using MCM-41 materials and drug release studies were carried out. Indomethacin

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(IND) is a nonsteroidal anti-inflammatory drug (NSAID) that reduces fever, pain and inflammation. This was chosen as the model drug for the release studies due to its hydrophobic character, similar to that of the substances used in chemotherapy. In fact, some studies have reported the chemo-preventive activity of non-steroidal anti-inflammatory drugs, including IND, against tumor cells [19–21]. Nonetheless, is a growing challenge for the pharmaceutical industry to find new routes to deliver this kind of drugs with hydrophobic character because they are poorly soluble in water and difficult to manage *via* the oral route. On the other hand, there are several mathematical models available in the literature to describe the drug release profile. The nature of the release profile largely depends on the textural properties of the host materials, such as pore diameters, pore volumes, particle morphology and surface modifications.

In this work a detailed study about the performance of superparamagnetic modified MCM-41 in IND-delivery systems has been made. In this way, the intrinsic relationship between their properties derived from synthesis methods and the release mechanism has been studied.

2. Experimental

2.1. Synthesis silica matrix

The MCM-41 type mesoporous molecular sieve was synthesized as previously reported [22].

2.2. Wet impregnation method (WI)

The MCM-41 host, previously calcined for 5 h in oven at 500 °C, was modified with Fe or Co using aqueous solution of several concentrations of the metal precursor. This synthesis method and the characterization of the obtained solids have been reported [23–24]. In this study, the sample corresponding to theoretical Fe loadings of 1 wt.% designated as Fe-WI(0.93) and the sample corresponding to theoretical Co loadings of 2.5 wt.% designated as Co-WI(2.20) have been tested like drug-delivery systems. The value in parentheses corresponds to experimental metal content in wt.%.

2.3. Direct incorporation method (DI)

The iron-containing MCM-41 type mesoporous materials were prepared by a direct hydrothermal method using cetyltrimethylammonium bromide (CTAB) as template, tetraethoxysilane (TEOS) as silicon source and ferric nitrate ($Fe(NO_3)_3 \cdot 9H_2O$) as metal precursor. The pH of the reaction mixture was adjusted to 12 by adding a 2 M sodium hydroxide (NaOH) aqueous solution. The catalysts were synthesized from a gel of molar composition: Si/Fe = 20; OH/Si = 0.5; CTAB/Si = 0.12; H_2O/Si = 132. In a typical synthesis, CTAB were dissolved in a NaOH solution in water under agitation at 40 °C. Then, TEOS and the metal source were added to this solution at 25 °C and the stirring was maintain for 4 h and then 3 h at 70 °C. Finally, this gel was filtered, washed with distilled water and dried at 60 °C overnight or treated hydrothermally under autogeneous pressure using a Teflon-lined stainless-steel autoclave, kept in an oven at 100 °C for 1 day. Again, the hydrothermally treated final solid were filtered, washed with distilled water until pH ~ 7 and dried at 60 °C overnight. The template was removed from the samples by heating (2 °C/min) under N_2 flow (45 mL/min) at 500 °C for 6 h and then calcinated at 500 °C for 6 h under dry air flow (45 mL/min). These samples were designated as Fe-DI(6.27) and Fe-DI(6.27)HT where the metal content in wt.% is indicated in brackets, "DI" indicates that the direct method was used and "HT" indicates that an hydrothermal treatment was applied.

2.4. Drug incorporation

Loading of Indomethacin within support was done by immersing the solid (0.150 g) into a highly concentrated ethanol solution of IND (0.450 g in 3 mL), which was mixed under stirring for 24 h in a thermostated bath at 68 °C. After the loading, the suspension was filtered and the resulting solid was dried in an oven at 36 °C. After incorporating IND in supports, samples were renamed as: Fe/WI(0.93)/IND, Co/WI(2.20)/IND, Fe-DI(6.27)/IND, Fe-DI(6.27)HT/IND and MCM-41/IND.

Finally, the loaded drug in the support was determined by extraction in ethanol of this, from a known amount of support-IND at 36 °C under stirring for 3 h. The extracted drug was measured by UV–Vis spectroscopy using the corresponding calibration curve obtained at $\lambda = 320$ nm (wavelength where IND has its maximum absorption). The amount of drug incorporated on the support is expressed in wt.% with respect to the loaded sample.

2.5. Drug release experiments

Drug release studies were performed in the dissolution apparatus Hanson Research SR6 serie II baskets type. The baskets rotation speed was 50 rpm and the vessels were kept in a thermostatically controlled circulation water bath at 37.0 ± 0.5 °C. The used dissolution media consisted of simulated body fluid [25] (SBF) at pH 7.4 ± 0.05, taking in mind a possible drug supply route *via* blood. A liter of this solution contained reagents added in amounts and order indicated as follow: 1) NaCl (8.036 g), 2) $NaHCO_3$ (0.325 g), 3) KCl (0.225 g), 4) K_2HPO_4 $3H_2O$ (0.230 g), 5) $MgCl_2$ $6H_2O$ (0,311 g), 6) 1 M HCl (40 mL), 7) $CaCl_2$ (0,293 g), 8) Na_2SO_4 (0,072 g), 9) 2-Amino-2-hydroxymethyl-1,3-propanediol (TRIS) (6063 g) and about 0,8 mL of HCl 1 M. The release studies were done by adding a known amount of IND in 750 mL of medium under sink conditions. Samples of 7 mL were withdrawn at predetermined intervals, followed by replenishment after each withdrawal with the same volume of fresh medium equilibrated at 37.0 ± 0.5 °C. Samples were appropriately filtered (filter type: 0.45 μm, Milipore 13 mm) and analyzed by UV absorption using a spectrophotometer Jasco 7800 at $\lambda = 320$ nm. The released drug amount at each time was expressed as a fraction of the total amount of IND. Drug release was monitored for 8 h; IND concentration was reported as an average of three determinations.

2.6. Characterization

X-ray diffraction patterns (XRD) were recorded in a Philips PW 3830 diffractometer with Cu Kα radiation ($\lambda = 1.5418$ Å) in the range of 2θ from 1.5° to 7° and from 20° to 80°. The specific surface, the pore size distribution, and the total pore volume were determined from N_2 adsorption-desorption isotherms obtained at −196 °C using a Micromeritics ASAP 2010. The surface was determined by the Brunauer-Emmet-Teller (BET) method in the pressure range of P/P_0: 0.01–0.21, while the pore sizes were determined by the NLDFT (Non-Local Density Functional) method [26]. The Fe content was measured by inductively coupled plasma optical emission spectroscopy (ICP) using a VISTA-MPX CCD Simultaneus ICP-OES-VARIAN. FT-IR spectral measurements were performed on a Jasco FT-IR 5300 spectrometer equipped with a DTGS detector. A self-supporting wafer for each sample (~20 mg and 13 mm of diameter) was prepared, placed in a thermostatized cell with CaF_2 windows connected to a vacuum line, and evacuated for 8 h at 400 °C in order to remove water adsorbed. The background spectrum was recorded first after cooling the sample to room temperature. UV–Vis diffuse reflectance (UV–Vis DR) spectra in absorbance mode were recorded using a Jasco V 650 spectrometer with an integrating sphere, in the wavelength range of 200–900 nm. TEM images were obtained in a JEOL Model JEM-1200 EXII System, working voltage: 120 kV. A small drop of the dispersion (sample in