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Influence of the Surface Acidity of the Alumina on the Sustained Release of Ketoprofen

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ABSTRACT

This work reports the immobilization of ketoprofen into mesoporous alumina, prepared in different way, to assess their possible applications as a matrix for controlled drug release. The acids' surface properties of the aluminas and their effect on the drug content and release rate were also analyzed. The systems have been characterized by powder X-ray diffractometry, Fourier transformer infrared spectroscopy (FT-IR), N_2 adsorption desorption, transmission electron microscopy, and FT-IR of pyridine adsorption. The results show that the drug is incorporated inside the pores of mesoporous alumina, and the content and release rate depend of surface acidity, when increase the surface acidity decrease the drug content and increase the release rate.

Introduction

The field of porous materials is currently in full expansion owing to the interest in their potential applications as molecular sieves, adsorbents, catalysts, and supports for these and—more recently—as matrices for drug release.[1] For optimum use, the main features sought for these materials are a large surface area, a high pore volume, a narrow pore size distribution, the possibility of controlling pore diameter across a broad size range, high thermal stability, low toxicity, and suitable particle size. The porous solids with the greatest number of applications are zeolites and zeotypes. The main interest in these lies in the possibility of controlling their pore diameters with great precision, and their main drawback is that owing to their microporous nature they do not allow the diffusion of voluminous molecules involved in many processes of interest such as in fine chemistry, pharmaceutical chemistry, and food chemistry. Accordingly, efforts have focused on finding materials with greater pore sizes, in the mesopore range (2-50 nm), for use in processes involving compounds with a greater steric volume.

The first known mesoporous materials were limited to certain amorphous materials (silicas, aluminas, and silica-aluminas) or polymers, but these have a very broad pore size distribution and hence low selectivity in catalysis. Since researchers at Mobil[2,3] synthesized organized mesoporous silica using a surfactant as a template in 1992, much effort has been devoted to synthesizing organized mesoporous oxides, among them alumina, in the same way. However, they are harder to obtain than silica. The first synthesis of organized mesoporous alumina was carried out by Vaudry et al.,[4] using long-chain carboxylic acids as surfactants. Calcination of these materials afforded aluminas with surface areas greater than 700 $m^2\ g^{-1}$. Later, many other preparation methods and reagents were used in the synthesis of these materials.[4-12] In all cases, it was observed that both the synthesis conditions and the thermal treatment used affected the morphology of these materials.[13,14] Moreover, in most cases, the mesoporous alumina obtained showed less organization in comparison with the MCM-41 type silica. Thus, more complete studies are required, above all as regards to the relationship between the synthesis procedure and the surface chemical properties of alumina, since these properties are what determine the interaction of different organic molecules.

The main application of mesoporous alumina has been in catalysis,[12] and there are few studies in which it has been used in controlled drug-delivery systems[15-19] in comparison with organized mesoporous silica, even though α-alumina was the first bioceramic to be used in clinical practice[20,21] owing to its bioinert nature.

Here, we incorporated ketoprofen (KP), a nonsteroid anti-inflammatory agent belonging to the arylpropionic family (Fig. 1), into mesoporous alumina prepared in different ways to assess their possible application as a matrix for controlled drug release. We

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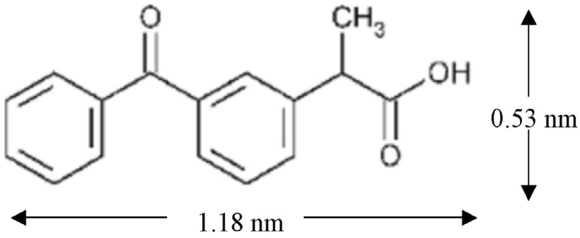

Figure 1. Molecular dimensions of the free ketoprofen, determined with the CS Chem 3D Ultra Pro Programme.

analyzed the acid-base surface properties of the aluminas and their effect on the drug content and release rate. Likewise, we evaluated the pharmacokinetic profile of the different systems prepared by *in vitro* dissolution assays under experimental conditions similar to those of the organism to predict their behavior in the organism as precisely as possible.

Experimental

Materials

Aluminum isopropoxide (IPA), hexadecyltrimethylammonium bromide (CTAB), glucose, sodium dodecylsulfate (SDS), aluminum nitrate ($Al(NO_3)_3.9H_2O$), aluminum sec-butoxide, butanol-2, HNO_3, and HCl, were all of analytical purity and were purchased from Sigma-Aldrich and used without additional purification.

Preparation of the Samples

Four alumina were prepared, using different methods:

M1

A solution of 8 g IPA and 40 g of isopropanol was added to another containing 4.3 g of gel surfactant, CTAB, 5.4 g of distilled water and 7.4 g (6.16 mL) of 37% wt HCl, to achieve a pH $\approx$ 1. The mixture was stirred for 4 h at room temperature (r.t.) (the time during which the hydrolysis of the IPA takes place, causing the solution to turn transparent). Following this, it was heated in a glycerine bath at 80°C under constant stirring to evaporate off the solvent, affording a compact gel. After 2 h the whole solution had gelified. This moment marked the end of the condensation step, achieving a surfactant-aluminum hydroxide mesophase. The surfactant was removed by calcination of the solid in an oven for 5 h at 550°C with a heating ramp of 2°C min^{-1}.

M2

IPA 4.2 g and 3.6 g of glucose (used as template) were dissolved in 54 mL of twice-distilled water and the resulting solution was stirred at r.t. for 2 h. Then, a solution of 10% wt HNO_3 was added dropwise until a pH of 5 was attained. After a resting period of 5 h, the mixture was heated in air to 100°C to remove the water and other volatile compounds. The resulting solid was calcined at 600°C for 6 h at a heating rate of 1°C min^{-1} to remove the template.

M3

In this method, SDS, an anionic surfactant, was used as template and $Al(NO_3)_3.9H_2O$ was used as the source of aluminum; 20.8 g of $Al(NO_3)_3.9H_2O$, 4.0 g of SDS, and 16.6 g of urea were dissolved in 60 mL of twice-distilled water. The resulting solution was kept stirred for 1 h at r.t., after which it was subjected for 48 h to hydrothermal treatment at 100°C in a digestion pump. The resulting solid was collected by filtration, washed with twice-distilled water, dried in an oven at 100°C for 24 h, and finally calcined in air at 540°C for 3 h at a heating rate of 1°C min^{-1}.

M4

The surfactant used in this method was the same as that used in the preparation of sample M1; 4.4 g of the cationic surfactant CTAB was added to a solution containing 10 g de aluminum sec-butoxide (8 mL) and 40 g of butanol-2 (49.7 mL). Then, a solution of 1.4 g of H_2O in 5.0 g of butanol-2 (6.2 mL) was slowly added to the mixture and this was stirred. The solution gradually evolved to a gel and was then subjected to hydrothermal treatment at 100°C for 5 h. Finally, the solid sample was calcined at 500°C in an oven at a heating rate of 1°C min^{-1}.

Incorporation of the KP to the different matrices was accomplished via the impregnation method. A solution of nonsteroidal anti-inflammatory drugs (NSAID) formed by 1 g of KP and 20 mL of butanol-2 was added to 1 g of matrix alumina (previously heated at 120°C under vacuum to remove the H_2O adsorbed inside the pores, since alumina is easily hydrated in contact with the atmosphere). The mixture was kept under stirring conditions for 7 days. The solid obtained was separated by filtration, rinsed with butanol-2, and centrifuge to remove the nonadsorbed drug molecule. The loaded materials were dried at 100°C (boiling temperature of butanol-2) in an oven to remove the solvent. The samples obtained were designated "MXKP," where X = 1, 2, 3, and 4, depending on the matrix impregnated.

Characterization Techniques

The amount of KP loaded in the different samples was monitored by 2 techniques: (1) carbon analysis in a CHNS 932 Leco Model and (2) UV-vis spectroscopy (Perkin Elmer Lambda 35 spectrophotometer) after treating the samples in basic media (NaOH 0.1 M, pH 10), by applying the Lambert-Beer equation from the calibration line drawn at pH = 10 for a wavelength of 260 nm.

Powder X-ray diffraction diagrams, from 10° to 70°, were collected on a Siemens D-500 using CuKα radiation (λ = 1.5405 Å) and quartz as an external standard. In the case of low angle, 0.5°-10°, were collected in a Philips X'Pert PRO MPD (λ = 1.5406 Å) scanning rate of 0.3°/min and step = 0.0167°.

Fourier transform infrared spectra (FT-IR) were collected in a Perkin-Elmer BX FT-IR instrument in the wavenumber region from 4000 to 350 cm^{-1}, using the KBr pellet technique; 100 scans were averaged to improve the signal-to-noise ratio, at a nominal resolution of 4 cm^{-1}.

Transmission electron micrographs (TEM) were registered in a Zeiss-902 equipped with a digital camera; the samples were prepared on a coppered grid after evaporating a drop of dispersed sample in water.

The textural properties were studied from the N_2 adsorption-desorption isotherms, recorded at −196°C in a Gemini instrument from Micromeritics. The samples were previously outgassed at 120°C for 2 h.

Surface acidity was studied through FT-IR spectroscopic monitoring of pyridine (Py) adsorption in a Perkin-Elmer Spectrum BX coupled to a high-vacuum Pyrex system. Self-supported disks were used, outgassed *in situ* in a special cell (built in Pyrex with CaF_2 windows) at 400°C for 2 h before Py adsorption. Twenty scans were taken to improve the signal-to-noise ratio at a nominal resolution of 2 cm^{-1}. The gas was admitted to the IR cell at r.t. After 15 min of equilibration, the gas phase was removed by outgassing at different temperatures (from r.t. to 400°C), and the spectrum was recorded.