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TEMPLATED AND ACTIVATED CARBONS FOR THE ADSORPTION AND CONTROLLED RELEASE OF DRUGS

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Introduction

The development of a drug delivery system comprises different aspects, being the drug delivery materials one of the most relevant. A variety of drug carriers have been studied in literature[1], polymers, peptides, hydrogels, porous materials. MOFs, silica and carbons are among the porous materials most studied.[1-4] Large pore volume and surface area, tuneable pore size, high stability in aqueous media and excellent biocompatibility made carbon porous materials as a suitable candidate in drug delivery system applications. Carbon-based nanocarriers such as carbon nanotubes, fullerenes and mesoporous carbons have been explore[1,4]

Ibuprofen (2-(4-isobutylphenyl) propionic acid) is one of the medicaments more used since it is a non-steroidal anti-inflammatory and analgesic drug. It is a well-characterized drug, commonly used as a release drug model[1-4].

In this work, we propose porous carbons as a good candidates for drug release systems, due to the properties that make them adequate for this application: large pore volume, high surface area, tailored pore size, mouldable surface chemistry, high stability in aqueous media and excellent biocompatibility[4]. Thus, three different carbons: microporous carbon (SXPlus), carbon with ordered mesoporosity (C.SBA-15), and carbon submicrocapsules with a hollow nucleus and a mesoporous shell (CSC).

Materials and Methods

Carbon materials. SXPlus is a commercial carbon. The C.SBA-15 and CSC carbons were obtained by templating method. A commercial SBA15 (mesostructured, SiO2 99%, Sigma-Aldrich) was used as template of C.SBA-15 carbon. A phenol-formaldehyde resin (Bakelite®PF9934 FL, Hexion Specialty Chemicals Ibérica S.A) was used as carbon precursor for C.SBA15 carbon[6]. The template of the CSCs was a silica home-made sphere with a solid core and a mesoporous shell, whose synthesis was carried out using tetraethoxysilane (TEOS) as silica precursor and hexadecyltrimethoxysilane (C16TMS) as porogenic agent[5]. The carbon precursor was a phenol-formaldehyde resin synthesized inside the template pores[4].

Ibuprofen salt loading. Two loading methods have been used to load ibuprofen salt. Equilibrium method loading: a carbon sample (50 mg) were added to a 35 mL ibuprofen solution of 700 mg/mL until completing 50 mL of final volume with a buffer solution (SBF, pH 7,4, 50 mM). The mixture was kept under stirring at constant temperature (37 ºC) in a thermostatic bath shaker. After the contact time (3 days), the loads carbons were filtered and dried (60ºC, 24h). The residual concentrations of ibuprofen were determined by triplicate using a UV-visible spectrophotometer at a wavelength of 222 nm. The adsorbed amount at equilibrium was calculated through Eq. (1):

$$q\left(\frac{mg}{g}\right) = \frac{(C_0 - C_e)(\frac{mg}{L})}{m_s(g)} \quad (1)$$

being C_0, the initial ibuprofen concentration (g/L), C_e the equilibrium ibuprofen concentration (g/L) m_s the weight of carbons adsorbent (g).
The evaporative method consists of introduce the initial mix of carbon and ibuprofen salt solution in a rotatory evaporator until the total evaporation of the solvent at a temperature, 37ºC and 100 mbar. Samples were extracted from the rotary evaporator and were dried was under oven at 60ºC for 24h.
Ibuprofen salt release. The loaded carbon samples (50 mg) were immersed into buffer solutions (50 mL) thermostatic at 37 ºC and with the pH values adjusted at 1.8 7.4. At given time intervals, 3 mL of solution was removed using a syringe filter and replaced with the same volume of preheated fresh buffer. The concentration of ibuprofen release was measured by triplicate through UV/VIS spectrophotometry at a wavelength of 222 nm. The amount of released ibuprofen salt at time t, calculated through Eq. (2), was expressed as mg:

$$Ibu\ release = V \cdot C_t + \sum v \cdot C_{t-1} \quad (2)$$

being C_t the ibuprofen concentration (mg/L) at time t, the ibuprofen concentration (mg/L) at t-1, V the total volume (L) of the release medium, v the removed volume (L) from the release medium at each interval.

Results and Discussion

Figure 1 shows the N_2 adsorption-desorption isotherm at 77 K of the three carbons and its pore size distribution, where it can be observed that SX-Plus is essentially a microporous carbon with a specific surface area of 846 m^2/g and a mean pore size of 1.2 nm. CSC and C.SBA-15 carbons present nitrogen adsorption in the micro and mesopore range, having a BET surface area of 1125 and 984 m^2/g with a mean pore size of 3.0 and 4.0, respectively. The shape of the C.SBA-15 in the mesopore range is indicative of ordered mesoporous of this sample. TPD analysis (Figure 1c) indicate that the three samples have the same superficial oxygen groups.

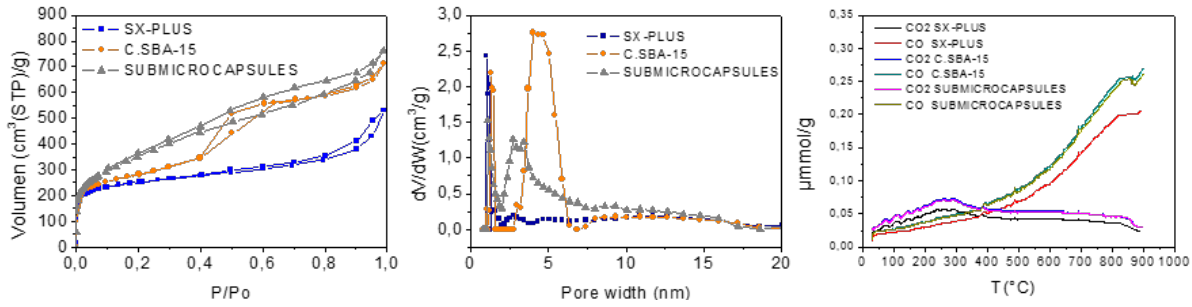

Figure 1. a) N2 adsorption-desorption isotherm at 77 K and b) pore width distribution and c) Temperature programmed desorption of carbon samples

The ibuprofen adsorption in aqueous medium at 37 ºC and pH 7.3 was studied and the adsorption isotherms for the materials calculated. The isotherm of SXPlus and CSC carbons present a high equilibrium mass adsorbed for a low values of ibuprofen in the medium, although the equilibrium plot for C.SBA-15 has a less pronounced increase. This difference can be associated with the ordered pores of this material.

The kinetics curves of ibuprofen release at 7.4 and pH 1.8 are obtained for the two loadings methods, equilibrium and evaporative loading for a NaIBU loading of 250 mg/g. The three carbons showed a kinetic curve with an initial step of fast release of NaIBU (first 50 min) and a slow release step until reach a plateau. In the case of the equilibrium loading samples, the (**Figure 2**) CSC and SX-Plus showed a similar kinetic curves for pH 7.4, reaching percentages of NaIBU release of 50%, the C.SBA-15 kinetic was slower with a maximum release percentage of 34%. This difference can be a consequence of the ordered mesoporous of this carbon. At pH 1.8 the release behaviour of NaIBU change, with a decrease of the maximum release percentage, being this decrease less pronounced in the case of the CSC carbon. Thus, it is clear that the ibuprofen salt release is strongly dependent on the pH, due to the interactions between the ibuprofen molecules and the surface groups of the carbons. At pH 7.4, the ibuprofen is predominant deprotonated (pK_a=4.85), and the carbon surface are close to the pH slurry (5.9, 6.9 and 7.2 for CSC, SX-Plus and C.SBA-15, respectively), which can favour the easy release of NaIBU. In the case of use the evaporative method, the kinetic curves showed a similar trend that the equilibrium one, although with a smaller percentage release reached (21-29%). The evaporative method allows to load a higher mass of NaIBU in carbon samples (**Figure 2c**), reaching the maximum values of 486, 633 and 1000 mg NaIBU/g. The spherical morphology of carbon capsules with the hollow nucleus allow to reach a higher quantity of NaIBU loaded in the carbon material. The NaIBU release of the maximum loaded CSC was also the highest in a pH 7.4, although no release was detected at pH 1.8.

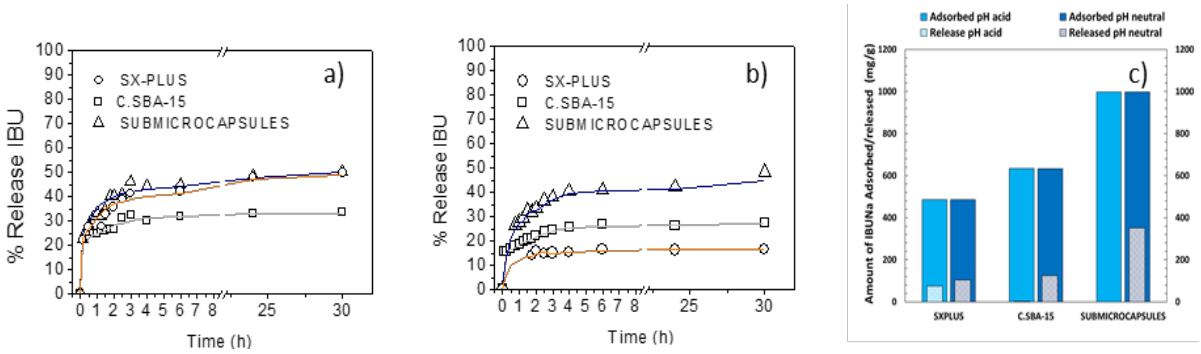

Figure 2. Ibuprofen release profile for the drug equilibrium loaded SX-PLUS, C.SBA-15 and capsules (250 mg IBU/g) at 37 °C a) pH 7.4. b) pH 1.8 c) maximum amount of IBU loaded in each material and the corresponding IBU release.

Conclusions

Three carbons with similar specific surface area and different porous structures and morphology are compared in the adsorption of NaIBU and release. The kinetic release of NaIBU from the three carbons is very fast during the first 50 minutes. The carbon capsules showed the highest release percentages for both loading methods, equilibrium and evaporative. The influence of pH on kinetic release, for samples with 250 mg/g of NaIBU loaded, was less pronounced in the case of carbon

capsules. The pH influence on NaIBU release was less pronounced in the case of carbon capsules. The carbon capsules morphology allow to load a higher amount of NaIBU by evaporative method.

Acknowledgment

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