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Characterization of mesoporous silica used for drug delivery by sorptive interaction – multiple headspace extraction–gas chromatography

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ABSTRACT

A multiple headspace extraction experiment coupled to gas chromatography (MHE-GC) is used for the classification and qualification of different mesoporous silica (MPSi) materials used for drug delivery. In this MHE experiment, a pure liquid solvent probe is fully evaporated in a sealed headspace vial in the presence of the MPSi sample, leading to a gas-solid partitioning that is theoretically described. The obtained results matched with the known characteristics of the studied samples, such as adsorption capacity due to differences in porosity and passivation treatments. Moreover, it proves the effectiveness of a poly dimethyl siloxane (PDMS) coating treatment over a thermal one in reducing the specific interactions of the MPSi. In addition, it evidences the important role of confinement effects when the pore diameter is close to the microporosity range. Finally, a simple experiment for fast screening is proposed by comparison of the results obtained for four different probes used as a mixture.

1. Introduction

Drug delivery systems are specific compounds or devices that help in the assimilation of an active pharmaceutical ingredient (API) by controlling the release rate and release location in the body [1]. Over the last few decades, drug loading systems of different nature have been the focus of intense research activities in the pharmaceutical field. Extensive literature reviews can be found on the topic, where different methods for synthesis of carriers, processing factors and properties are reported, including the use of 3D printing [2,3]. As a result, different materials are commercially available as possible drug delivery systems.

Mesoporous silicas (MPSi) have been largely used and studied for different applications. Thanks to their relatively low cost and low toxicity [4], they have become of great interest, even in highly regulated environments. For example, a large range of MPSi are commercialized for their use in food and pharmaceutical preparations. Moreover, these materials are considered as good candidates for drug delivery systems, helping to overcome the poor aqueous solubility of some APIs [5]. In such cases, the API is loaded on the solid support by means of solvents that are evaporated afterwards [6]. For the final qualification of the medication, the API concentration and release rate, as well as the amount of residual solvents, have to be tested. As manufacturers of MPSi only provide limited information about the properties of their products, a first screening of MPSi to reduce the number of drug delivery candidates for final testing would be useful. Moreover, a batch control technique for MPSi materials before being used in the production would be truly valuable.

Currently, the physico-chemical characterization of such materials mainly relies on the use of adsorption isotherms with nitrogen, argon and carbon dioxide probes to determine most of the physical characteristics of the solids after application of different models that range in complexity depending on the required precision of the results and the nature of the analytes [7]. Other complementary techniques such as inverse gas chromatography (iGC), differential scanning calorimetry (DSC), X-ray diffractometry (XRD) and atomic force (AFM) or scanning and transmitting electron microscopy (SEM and TEM) are proposed [8,9]. None of these methods can lead to a full characterization by itself and all rely on the use of models and approximations. Most characterization methods focus on studying the morphology and even though there has been a great effort to predict the adsorption capacity of the studied materials by these means, only iGC seems to enable more detailed information about the energies involved in the sorptive process. However, even if there have been some attempts to make iGC a more user friendly technique [10,11], is not yet widely spread and it requires some expertise in order to obtain reproducible results. Moreover, the setup and data handling are time consuming and the packing

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of the column may need a considerably large amount of sample, which constitutes a major drawback if intended as batch control or when working with expensive materials. Furthermore, the use of all the aforementioned techniques is somehow limited, due to their cost and absence in most pharmaceutical laboratories.

In this work, the use of multiple headspace extraction coupled to gas chromatography (MHE-GC) is proposed as a simple technique to characterize different types of MPSi, based on their sorption capacity of specific compounds. We call this approach "sorptive interaction–MHE–GC" (SI-MHE-GC).

2. Materials and methods

2.1. Reagents and samples

n-Pentane (analytical grade) and ethanol (absolute) were purchased from Fisher Chemical (Loughborough, UK). n-Hexane (99 +%), methanol (99.8%), 1-propanol (99%) and 1-butanol (p.a.) were from Acros Organics (Geel, Belgium). n-Heptane (extrapure) and n-octane (99 +%) were purchased from Merck (Darmstadt, Germany). n-Decane (> 99%), n-dodecane (GC) and 1-pentanol (> 99%) were from Sigma-Aldrich (St. Louis, MO, USA). 1-Hexanol (98%) was obtained from Janssen Chimica (Beerse, Belgium).

Five different MPSi samples were provided by Grace (Columbia, MD, USA). The surface area was determined by nitrogen adsorption and the particle size and distribution were measured by laser light scattering by Grace. Table 1 lists the main characteristics of three different MPSi samples (type I, II and III). Two post-synthesis treated samples, named type III-PDMS and type III-Heat, were also investigated. Those are modified type III MPSi, coated with poly dimethyl siloxane (PDMS) and thermally treated, respectively.

2.2. Apparatus and operational conditions

All experiments were carried out on a Clarus 480 gas chromatograph equipped with a flame ionization detector (FID) and coupled to a Turbo Matrix 40 headspace auto-sampler (Perkin Elmer, Waltham, MA, USA). All GC data were collected and processed using TotalChrom™ Software (Perkin Elmer). The GC system was equipped with an AT-Aquawax™ column of 30 m × 0.53 mm × 0.5 µm (Grace, Columbia, MD, USA) and operated in split mode with a split flow of 20 mL/min. The injection port was kept at 210 °C and the detector at 220 °C.

As in a normal MHE experiment, a first extraction from the gas phase is carried out and injected into the GC after the first equilibrium has been established. Although the accuracy of the results increases when more extractions are performed, the instrument allows up to nine extractions only (9 injections per vial). Indeed, at some point, the depletion in concentration leads to a non-detectable signal and for many probes, nine injections are the maximum. The GC system was operated either in thermostatic mode at 100 °C for analysis of the pure solvent probes or using a temperature program (40 °C during 2.5 min, then rise at 20 °C/min to 120 °C and hold for 8.5 min) allowing a short analysis time without affecting repeatability when analysing the solvent mixture probe. All HS parameters are summarized in Table 2.

Table 1
Mesoporous silica samples. Main characteristics and given names.

MPSi type	Particle size (µm)	Pore diameter (nm)	Specific surface area (m^2/g)
I	5–7	2–3	600–700
II	25–45	6–7	500
III	40–63	25	300

Table 2
Used HS-sampler parameters.

HS parameter	Set value
Carrier gas pressure	140 kPa
Needle withdrawal time	0.2 min
Pressurization time	3 min
Equilibration time	25 min
Equilibration temperature	190 °C
Needle temperature	200 °C
Transfer line temperature	200 °C
Injection time	0.04 min

2.3. Preparation of solutions and sample vials

All solvents listed in the reagents section were first used as single pure probes to prove that the method can lead to rational results and then four solvents (n-pentane, n-heptane, 1-butanol and 1-hexanol) were mixed in equal proportions and used as a mixture probe.

Only a gas-solid interphase was considered, thus avoiding additional phenomena from the liquid-solid interaction and simplifying the system. Indeed, if a liquid-solid interface would be present from the beginning of the experiment, strong bonding of the liquid phase to the solid could occur [12] and the energy and time needed to achieve the equilibrium condition would be increased and eventually become unachievable. In practice, a small amount (20.0 ± 0.5 mg) of the MPSi sample was placed into a regular headspace vial (Perkin Elmer, Waltham, MA, USA) with a nominal volume of 20 mL. Then, 2 µL of a pure solvent or 8 µL of the solvent mixture (the probe) was loaded in a smaller HPLC/CE vial of 32 × 11.6 mm (Clean Pack, VWR, Leuven, Belgium) that was placed uncapped inside the larger headspace vial. This way, issues related to the direct contact of the liquid probe with the MPSi were avoided and the solvents could fully evaporate and interact in the gas phase with the MPSi before the first extraction. Next, the large vial was capped with a PTFE/silicon septum and aluminium crimp cap (Perkin Elmer). Finally, it was thermostatted in the autosampler oven for a duration that was long enough to guarantee full evaporation and reach an equilibrium between the solid and the gas phase (see Section 3.2 for chosen temperature and time).

2.4. Principle of the method

The variation of the concentration of the species of interest over the extraction steps is described as an exponential decay (Eq. (1)) for all MHE-GC experiments [13]:

$$C_i = C_0 \bullet e^{-q(i-1)} \quad (1)$$

Where C_i is the measured concentration at a certain extraction step i and C_0 is the initial sample concentration. Parameter q describes the decay and it will be characteristic for each sample and analyte. Since the concentration is directly proportional to the measured peak area (A), q can be calculated as the slope of a semi logarithmic plot of A vs. i (MHE plot).

Kolb and Ettre introduced a parameter Q that relates q to the ratio of two consecutive peak areas and they proved its relation to the partition kinetics by considering the mass balance of a liquid-gas system [13,14]. The proposed gas-solid system in this work can be regarded in an analogous way and even an expression can be derived that allows to estimate the partition coefficient of the investigated process from the evaluation of the slope of the MHE plot:

$$Q = \frac{K \bullet K^{\varnothing} \bullet \mathscr{A}/V_G + \rho}{K \bullet K^{\varnothing} \bullet \mathscr{A}/V_G + 1} \quad (2)$$

Where V_G is the volume of the gas phase (approximately the nominal headspace vial volume) and $\mathscr{A} = s \bullet w$, where , s and w are the surface area of the solid sample, its specific surface area (determined by