



Chromatographically efficient microspherical composites of molecularly imprinted xerogels deposited inside mesoporous silica



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ABSTRACT

A different approach to the preparation of microspherical particles of molecularly imprinted xerogels (MIX) is presented here. The technique consisted of filling up the pores of spherical, mesoporous, bare silica particles with a pregelification mixture by applying pressure. Upon gelification and drying, thin layers of MIX were deposited on the mesopores. Spherical composites of *S*-naproxen (*S*-NAP) imprints were produced by following this simple strategy. The performance of the imprints was quite satisfactory in terms of recognition ability (ascertained by selectivity against ibuprofen, $\alpha = 4.9$, and an imprinting factor of 13) whereas an outstanding improvement on dynamic features (expressed as column efficiency), as compared to the corresponding bulk format MIX (9 vs. 1.2 theoretical plates/cm), was reached.

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1. Introduction

The process of molecular imprinting aims at the preparation of tailor-made materials exhibiting highly selective binding sites for a molecule of interest (template) [1–4]. Molecularly imprinted xerogels (MIXs) obtained through sol-gel chemistry constitute one possible format for such materials. Typically, MIX particles preparation involves: (i) a pregelification mixture containing the template, organically-modified trialkoxysilanes (ORMOSIL, $R-Si(OR')_3$ or $(OR'_3)Si-R-Si(OR')_3$ where R represents an organic motif with affinity (usually via non-covalent interactions) for the template, tetraalkoxysilanes $(Si(OR')_4)$ as silicate network precursors, basic or acidic aqueous solution and a porogen (usually a short chain aliphatic alcohol); (ii) hydrolysis and condensation of the precursor and ORMOSIL developing a hybrid organic-inorganic network where the template-R motif complexes are trapped upon gelification; (iii) the removal of template leaves a vacant recognition site, with the ability to recognize the shape, the size and the functionality of the template (or structurally related compounds) [4–8]. Typically, the usable MIX particles are obtained in a top-down manner starting from a bulk xerogel by grinding

and sieving to obtain the desired size range. This method has several drawbacks such as being time consuming, requiring intensive labour, low-to-moderate yields, deformation of the binding sites by grinding (loss of selectivity), irregular shape (loss of their flow characteristics in flow-through applications) [9,10]. Alternative, bottom-up schemes that overcome these problems are thus highly desirable. The very scarce literature on the bottom-up synthesis of MIXs reported the use of emulsion methods allowing for the pregelification mixture to disperse into microdroplets to obtain microspherical particles of MIX upon gelification [11–13].

Here we present a different approach to the preparation of microspherical particles of MIX. We used a technique consisting of filling up the pores of spherical, mesoporous, bare silica (see Fig. 1). In this manner, the question of obtaining the microspherical format may be promptly solved due to commercial availability of the silica microspheres (several diameter and pore size ranges available), avoiding the extensive optimization of both emulsion and sol-gel parameters required to achieve satisfactory results [11]. Spherical particles with diameter in the range 45–75 μm and pore size 40 nm were used. The pregelification mixture was introduced inside the pores by applying pressure and followed by removal of the interstitial mixture to avoid surface coverage with MIX. The connectivity between the silica inner-surface and the xerogel was spontaneously obtained by $-Si-OH$ condensation between the forming gel and the previously rehydroxylated silica surface. Upon gelification inside

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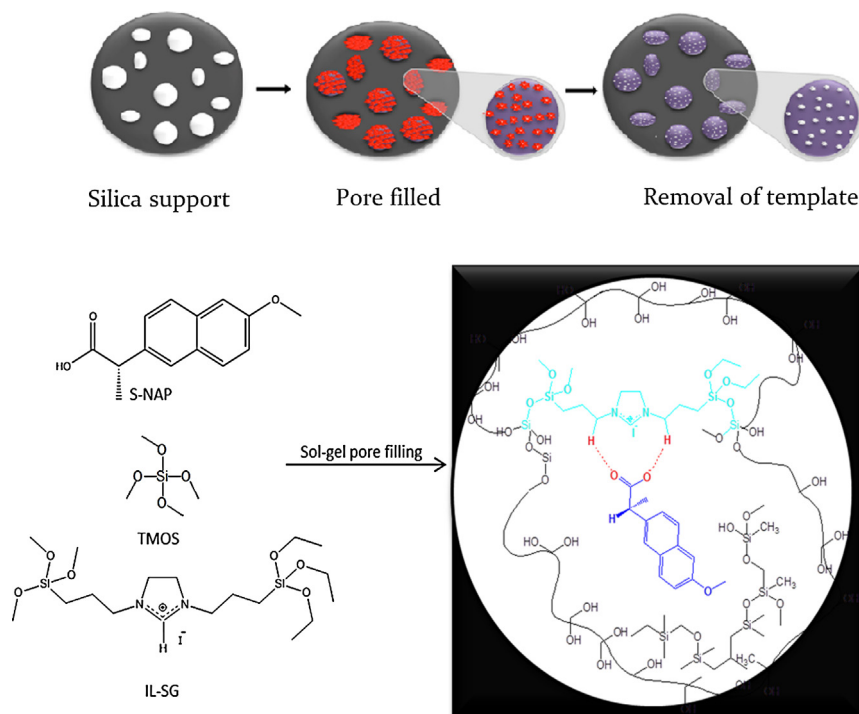


Fig. 1. Strategy for the preparation of imprinted spherical composites (top) and representation of the sol–gel process resulting in imprinted sites (bottom).

the pores and porogen drying, MIX was deposited on the mesopores.

2. Experimental

2.1. Imprinted composite production

Spherical silica (particle size: 45–75 μm ; D_p : 40 nm) was used as a solid support. Activation of the surface was achieved by rehydroxylation. In a 500 mL three necked round bottom flask, 300 mL (115 mL HCl+ 185 mL H₂O) of 17% HCl were poured using a funnel. The round bottom flask was equipped with a condenser and an overhead stirrer. The calcined silica (20 g) was added in small portions while stirring. The flask was placed in an oil-bath (electronic-thermometer; 150 °C; heater: 200 °C) and the suspension was subsequently refluxed for 24 h. The silica was filtered through a glass filter funnel and washed twice with 150 mL aliquots of methanol. Finally, the silica was dried in a vacuum oven at 80 °C for 4 h and at 150 °C for 12 h. The filling of the silica pores was then performed by injecting the polymerization solution (Table 1) into a packed bed of silica beads (1 g) in a glass column, allowing it to enter into the pores at elevated pressure (2–3 bar) and maintaining the conditions for 6 h. After that period of hydrolysis and condensation, when the pressure was released, there was no observable extrusion of liquids, probably because at that stage a highly viscous sol was already formed and covalently attached to the support. In any case, isooctane was thereafter percolated through the column to push out any eventual interstitial polymerization solution remaining (a hydrophobic solvent was chosen so that it could not penetrate the mesopores and disturb the ongoing sol–gel process). Finally, additional condensation and drying was carried out at 60 °C.

The half amount (500 mg) of the dried MIX/NIX was endcapped (NIX stands for the non-imprinted xerogel, the counterparts of MIX, used as reference; see Table 1). In an end-capping process, the composites were treated with an equimolar mixture of chlorotrimethylsilane (23 mmol or 2.5 g) and 1,1,1,3,3,3-hexamethyldisilazane (23 mmol or 3.75 g) at room temperature for

24 h. They were then washed with THF and acetonitrile to remove excess reagents. Finally the materials were washed to remove the target using Soxhlet apparatus with a solution of methanol containing 10% formic acid. Washing was monitored by HPLC and continued until it showed undetectable levels of S-NAP.

2.2. Material characterization

The surface micrographs were acquired using a Hitachi (Tokyo, Japan) H-S4500 FEG microscope in secondary electron mode with an acceleration voltage of 1 kV. The samples were deposited on holders with a carbon foil without gold sputtering. Thermogravimetric analysis was carried out using a TGAQ50 (TA instruments, Eschborn, Germany). The sample (10–15 mg) was placed in a platinum pan, which was suspended in a sensitive balance together with the reference pan. The sample was then heated in a furnace at a heating rate of 200 C/min, under N₂ atmosphere. The surface area and the pore parameters were performed on a Quantachrome Autosorb 6B (Quantachrome Corporation, Boynton Beach, FL) automatic adsorption instrument. Prior to measurements, 100–150 mg of the samples were heated at 40–60 °C under high vacuum (10⁻⁵ Pa) for at least 12 h. The specific surface areas (S) were evaluated using the BET method, the specific pore volumes (V_p) following the Gurvitch method and the average pore diameter (D_p) using the BJH theory applied to the desorption branch of the isotherm.

2.3. Chromatographic evaluation

The materials (~500 mg) were slurry packed into stainless steel columns (50 × 4.6 mm), using MeOH/H₂O 80:20 (v/v) as pushing solvent, and evaluated chromatographically. Pure methanol with 0.05% acetic acid was used as a mobile phase. The flow rate was fixed at 0.5 mL/min. Aliquots (20 μL) of 10 ppm solutions of S-NAP and 30 ppm of IBU prepared in methanol were injected. The elution was monitored by absorbance at 230 nm.

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