A Pristine SBA-15 obtained through Fenton-Chemistry based detemplation. Application on the drug adsorption and comparison with various detemplation protocols. §

In this chapter, the effect of the mild detemplation method, based on Fenton chemistry (with and without previous solvent extraction), and calcination was evaluated by the drug uptake capacity of SBA-15 materials. A number of characterization techniques was applied for evaluation and comparison of the materials properties such as TGA, CNH, N₂ physisorption and ²⁹Si NMR. The mild Fenton detemplation method rendered a nearly pristine SBA-15 without structural shrinkage, low residual template, improved surface area, pore volume and silanol concentration. The drug (ibuprofen) adsorption experiments were carried out by solution immersion in powdery form. The mild detemplated samples experienced an enhanced uptake that could be explained by the enhanced total density of silanols, originated from the absence of calcination in the Fenton approaches.

§ This chapter has been published:


Chapter 3

3.1 Introduction

Organized mesoporous materials (OMMs) have found a wide range of applications such as separation, optical, adsorption and heterogeneous catalysts. OMMs are especially known for their regular pore network and high pore volumes with the possibility of combining micro- and mesopores. These materials are synthesized by hydrothermal treatment in the presence of a structure-directing agent, also called template, around which the inorganic framework is formed. The template is usually an organic compound, which determines the pore topology by filling the pore space and maintaining a close geometrical correspondence with the inorganic framework.

The use of mesoporous materials as drug delivery carriers was first introduced by Vallet-Regi et al. Their potential application as drug carriers is due to their biological stability and their well-defined structure, porosity and chemical homogeneity. This represents an advantage compared to many other host materials normally used for drug delivery applications.

In several studies, it has been demonstrated that the inclusion of poorly water-soluble drugs into the pores of a mesoporous silica improves the drug’s solubility rate. When a drug is adsorbed into the pores of the silica material, it is present in the molecular/amorphous state and this form provides faster dissolution rates than the crystalline phase, especially when the solubility is limited by the crystal energy.

A number of aspects related to the host-guest chemistry influences the maximum drug uptake and release. These aspects comprise the nature of the drug (the drug must have certain organic functional groups which allow the formation of hydrogen bonds with the silanol groups of the hosting material), surface’s nature (concentration of silanol groups and surface functionalization), effect of the solvent as well as the silica pore size distribution and pore volume.

SBA-15 is an attractive mesoporous material since it possesses big pore volume, wide pores and relatively low-cost template employed in synthesis. The major problem with SBA-15 as drug carrier is the relatively weak intermolecular hydrogen bonds with the drug, thus the drug uptake is relatively limited despite its large pore volume. Typically 15 wt.% of ibuprofen has been reported, that is relatively low as compared to MCM-41 with uptakes up to 30 wt.%. Surface functionalization can enhance the drug uptake; Song et al. found that ibuprofen uptake can be enhanced significantly after post-synthesis amination, with uptakes of 20-37 wt..% This is due to the stronger host-guest interaction of (NH\(^{3+}\) ... - OOC-) than a hydrogen bond between the silanol group of the silica and the carboxyl group of the ibuprofen. Native and modified SBA-15 have been also successfully applied to the adsorption of heparin,
a highly sulphated linear polysaccharide, that mediates a range of biological and physiological activities such as anticoagulation, vascular regeneration, antiviral activity and release of lipoprotein lipase and hepatic lipase.\textsuperscript{19,20}

The surface properties of the SBA-15 silica can be adjusted by the detemplation method as well. By detemplation it means the step where the organic agent has to be removed from the cavities of the solid in order to develop the porosity after synthesis. The conventional detemplation method is calcination at high temperature in air atmosphere. The high temperatures usually applied, around 550 °C, combined with the steam formed during template removal provoke a partial collapse of the structure with the formation of siloxane bonds at the expense of losing silanols. This means that removing the template at lower temperatures, or chemically without heat, is highly desirable in order to obtain larger pore volumes and a higher density of surface silanols.

In this chapter, the effect of various detemplation methods on the final ibuprofen uptake has been investigated. In particular a method using OH\textsuperscript{+} radicals, which are generated from H\textsubscript{2}O\textsubscript{2} and catalyzed by discrete amounts of Fe cations (Fenton chemistry), were applied. This method has been reported to remove the template of zeolite beta\textsuperscript{21,22} and MCM-41\textsuperscript{23}. It was found that this method enhances the drug uptake of SBA-15 by 50% with respect to the calcined material; the effect is ascribed to the increase of surface area and concentration of silanols.

### 3.2 Experimental

#### 3.2.1 Synthesis

The SBA-15 mesophase was synthesized according to the procedure followed by Zhao \textit{et al}.\textsuperscript{15,16} The gel composition was: 4.0 g of P-123; 120.0 g of 2.0 M HCl; 30.0 g of H\textsubscript{2}O; 8.5 g of TEOS. The resulting slurry was aged at 105 °C for 24 h and dried at 110 °C overnight.

#### 3.2.2 Detemplation protocols.

Calcination was carried out at 550 °C for 5 h in air. The heating rate to reach this temperature was 1 °C/min. The resulting material was termed CA. Solvent extraction was carried out on the mesophase in absolute ethanol (Aldrich, \textgeq;99.5%) under reflux (78 °C) for 24 h using a ratio of 75 ml/g. The resulting material was dried in a vacuum oven at 110 °C (SE). The Fenton detemplation protocol consisted of the following steps. In a typical experiment, 1.0 g of as-synthesized precursor, or SE material, was mixed with
25 ml of water and 25 mg of iron nitrate, Fe(NO₃)₃·9H₂O (≥98%, Riedel-de Haën). This mixture was placed in an oil bath at 70 °C. Then 50 ml of hydrogen peroxide (commercial grade 30 wt.%, Merck) were added; part of the H₂O₂ (10 ml) is added at the start of the experiment, which gives an initial concentration of 8.6 wt.% H₂O₂. The remaining is added at a rate of 48 ml/h. The reaction took about 7 h. After that, the sample was separated by filtration and dried at 110 °C (denoted by F). A similar protocol was applied to a solvent extracted mesophase (denoted by SE-F).

3.2.3 Drug uptake experiments.

Ibuprofen ((RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid, Sigma Aldrich, ≥98% GC) was dissolved in hexane (33 mg ibuprofen/ml hexane) and the host material was suspended in a ratio of 33 mg SBA-15/mL hexane. The mixture was sealed and stirred for 24 h at room temperature. The ibuprofen-loaded material was then filtered using a glass filter of porosity 3 and dried at 60 °C under vacuum. The amount of adsorbed drug was determined by TGA and UV-Vis as discussed below.

3.2.4 Characterization methods

The template content was quantified by CHN analyses; more details can be found elsewhere. N₂ adsorption at –196.2 °C was performed using an ASAP 2420 gas adsorption analyser; see reference for more details.

The amount of drug loaded into the materials was determined by two different methods: i) Thermogravimetry analysis (TGA) and ii) UV-spectrophotometry. The first method was based on the weight loss of the loaded samples by thermogravimetric analysis (TGA) between 200 and 700 °C in a run using air. The TGA runs were carried out on a Mettler-Toledo analyzer (TGA/SDTA851e) using a flow of synthetic air of 100 mL/min NTP. The temperature was increased from 30 to 700 °C at 10 °C/min. The patterns were corrected using a blank curve, which uses an empty crucible and a similar temperature program. In the UV-spectrophotometry method, the hexane-ibuprofen solution was analyzed in a MultiSpec-1501 (Shimadzu) before and after the loading process; 1 mL of extracted hexane solution was diluted to 50 mL in hexane and measured at 262 nm. The amount of loaded ibuprofen was determined by deducting the concentration of this sample from the initial one (33 mg/mL).

²⁹Si Solid State NMR spectra were measured on a Varian VXR-400S spectrometer using a frequency of 79.44 MHz with the following conditions: spinner of 7-mm zirconium, spinning speed 5 KHz, acquisition time 0.2 s, acquisition delay 20 s, radiofrequency length 3.2 μs, spectral window 30007 Hz. These spectra were referenced to tetramethylsilane (TMS) and the number of scans was 3200. The total Si-OH
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concentration was calculated based on the method reported by Igarashi et al. 26

Small angle X-ray scattering (SAXS) measurements were performed at room temperature using a Bruker NanoStar instrument. 25

3.3 Results and discussion

SAXS analysis of the SBA-15 mesophase reveals a hexagonally packed cylindrical morphology characterized by a distance between the cylinders of 12.4 nm (Fig. 1, Table 1). Thermogravimetric analysis shows that the precursor requires temperatures of 450-550 °C to burn-off the surfactant with a weight loss of 47 wt.% (Fig. S-1); this corresponds to a carbon content of 29.7 wt.% (Table 1). Calcination of the precursor gives rise to a structural shrinkage of 10% as can be seen in the reduction of the $a_0$ from 12.4 to 11.1 nm (Table 1). This effect can be visualized in the SAXS pattern with a shift towards higher angles (Fig. 1). The precursor was subjected to ethanol extraction to reduce the amount of template, which was found to be 5.7 wt.% based on carbon (Table 1) after the extraction. Calcination of the solvent extracted material produced a similar shrinkage as the directly calcined material; this is consistent with a previous study on solvent extraction of SBA-15 mesophases. 27

<table>
<thead>
<tr>
<th>Sample</th>
<th>$C$ (wt.%)</th>
<th>$a_0$ (nm)</th>
<th>Shrinkage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor</td>
<td>29.7</td>
<td>12.4</td>
<td>0</td>
</tr>
<tr>
<td>SE</td>
<td>5.7</td>
<td>12.4</td>
<td>0</td>
</tr>
<tr>
<td>CA</td>
<td>0.1</td>
<td>11.1</td>
<td>10</td>
</tr>
<tr>
<td>F</td>
<td>0.4</td>
<td>12.4</td>
<td>0</td>
</tr>
<tr>
<td>SE-F</td>
<td>0.2</td>
<td>12.4</td>
<td>0</td>
</tr>
</tbody>
</table>

The Fenton detemplation protocol was applied to the precursor and solvent extracted precursor (SE), the latter has an 81% reduction of the template content with an absolute value of 5.7 wt.%. After the Fenton treatment, the template was almost eliminated from the solid; the carbon content (Table 1) was significantly reduced with a final carbon level of 0.4 wt.% (when starting with the precursor) and 0.2 wt.% (starting with SE). This implies that the Fenton detemplation efficiency is about 92 and 96 %, considering the background carbon level of the calcined material (0.1 wt.%).
Characterization by SAXS reveals that the position of the 100 reflection, as well as secondary ones, for both detemplated materials (F and SE-F) coincide with the precursor (Fig. 1); indicating the lack of shrinkage during the oxidation of the precursor (Fig. 1); indicating the lack of shrinkage upon oxidation/drying steps. The structural ordering is confirmed by TEM. Visualization of the F material shows a regular and well-ordered structure, comparable to that of the calcined sample (cf. Figs. 2a and 2b).

Table 2. Summary of the textural, Si-OH concentrations and drug loading properties.

<table>
<thead>
<tr>
<th></th>
<th>$S / m^2g^{-1}$</th>
<th>$V / cm^3g^{-1}$</th>
<th>$PS_{BJH}$ (nm)$^a$</th>
<th>$%e$</th>
<th>$%/nm^2$</th>
<th>mmolg$^{-1}$</th>
<th>UV-vis $^d$</th>
<th>TGA $^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>720</td>
<td>164 (556)</td>
<td>0.96</td>
<td>0.07</td>
<td>6.3 (4.8)</td>
<td>30</td>
<td>4.2</td>
<td>5.00</td>
</tr>
<tr>
<td>F</td>
<td>909</td>
<td>285 (624)</td>
<td>1.33</td>
<td>0.13</td>
<td>7.2 (5.2)</td>
<td>44</td>
<td>4.9</td>
<td>7.33 (47)</td>
</tr>
<tr>
<td>SE-F</td>
<td>944</td>
<td>272 (672)</td>
<td>1.29</td>
<td>0.12</td>
<td>7.1 (5.3)</td>
<td>47</td>
<td>5.0</td>
<td>7.83 (57)</td>
</tr>
</tbody>
</table>

- \(a\). Pore size derived from the BJH model. Value in parenthesis is the wall thickness calculated as \(a_0 - BJH\) pore size.
- \(b\). Micropore area is calculated from the \(t\)-plot method. The value in parenthesis is the external surface area calculated as \(S_{BET} - \text{micropore area}\).
- \(c\). Si-OH calculated as \((2Q_2+Q_3)/(Q_2+Q_3+Q_4)\) \(^{26}\). Patterns are given in Fig. S-2, S-3 and S-4.
- \(d\). Value in parenthesis is the relative increase, compared to the calcined counterpart.
- \(e\). Patterns are given in Fig. S-5, S-6 and S-7.
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The porosity of these materials was evaluated by N₂ physisorption and compared to the calcined counterpart. The isotherms were always of type IV with H1 hysteresis (Fig. 3) representing solids with cylindrical pore geometry with relatively high pore size uniformity and facile pore connectivity \(^{28}\); the isotherms of the Fenton-detemplated materials (F and SE-F) show higher adsorbed volumes in the complete p/p₀ range than the calcined counterpart, which at a first sight means that the micropore volume, total surface area and total pore volume are higher. The derived textural parameters are compiled in Table 2.

Figure 2. TEM images of the a) CA and b) SE-F materials. Inset: intensity profile.
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The surface area and pore volume for the mild detemplated materials are significantly higher than the calcined counterpart. In terms of the surface area, the SE-F is slightly more porous than the F; with an increase of 31 and 26 %, compared to the calcined material. The increase of the surface area is mostly ascribed to the micropore contribution, with 65-73% increase, with respect to the calcined counterpart, while the mesoporous surface area increases to a lesser extent (12-20%). Such an increase in the micropore area can be attributed to the lack of shrinkage that produces thicker walls which contain a larger fraction of void space. It is noted that the residual carbon (0.2 and 0.4 wt.%, SE-F and F) does not have an effect on the textural properties of the Fenton-derived materials; showing higher parameters than the calcined material. The calcined material has a lower pore size (0.8 nm difference) and wall thickness (0.5 nm) compared to the SE-F. This is due to the significant shrinkage occurring upon calcination, which affects to both the void space and inorganic framework.

The concentration of total silanols was determined by $^{29}$Si NMR, showing remarkable values for the mild detemplated samples (Table 2), of 44 and 47%, compared to 30% for the calcined. In terms of density, the calcined possesses 4.2 groups/nm$^2$ while it increases to 4.9-5.0 groups/nm$^2$ for the Fenton-derived materials. Thus the surface is highly hydroxylated; though the absolute values must be considered with care. It has been demonstrated that NMR derived Si-OH concentration often gives slightly overestimated values due to the fact that NMR provides information from the bulk and not for the accessible groups.$^{29}$

![Figure 3. N$_2$ physisorption isotherms at -192.6 °C for various materials (CA, F and SE-F).](image)
The adsorption capacity of the Fenton-derived materials was studied in the uptake of ibuprofen and compared to the calcined counter parts; note that the SE material is hydrophobic and its ibuprofen adsorption capacity would become limited (thus it was omitted from the study). The adsorption experiments were carried out by immersion in powdery form in an ibuprofen-based hexane solution, and the drug uptake was determined by two methods, TGA and UV-Vis. The TGA based uptakes were always higher than the UV-Vis (Table 2), though the relative increase trends are comparable. It is supposed that the TGA gives an overestimation due to the overlapping weight loss in the TGA patterns from the Si-OH dehydroxylation; a contribution that can be significant since the total silanols concentration was in the range of 30-47% (Table 2). A proof in favour of the UV-Vis is that the uptake for the calcined material coincide to that reported by Song et al. Thus, the UV-Vis seems to be giving reliable absolute values, and these values were taken for further comparison. The adsorption capacity of the mild-detemplated materials was superior with 19.7 and 22 wt.%, which represents a relative increase of 35 and 51% higher than the directly calcined sample. The enhancement is yet lower compared to the ammino functionalized SBA-15, which reported absolute uptakes as high as 37 wt.% or calcined MCM-41 with 34 wt.% but comparable to TUD-1 with 20 wt.. In the presented data, the increased uptake found for the Fenton-derived materials can be explained by total number of OH (OH/g, see Table 1); this parameter shows increased values that are consistent with the relative increase in the ibuprofen uptakes.

### 3.4 Conclusions

A mild detemplation method, based on Fenton chemistry, has been applied to a SBA-15 mesophase, with and without solvent extraction. Evaluation of the materials properties reveals no shrinkage, low residual template, enhanced textural features (especially microporosity) and a larger fraction of total silanols. These materials adsorb more ibuprofen than a calcination-derived material, and the effect is ascribed to the enhanced total silanols due to the lack of calcination of the Fenton-derived samples.
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References


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