

# Enhanced release of itraconazole from ordered mesoporous SBA-15 silica materials†

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This *in vitro* study reports on the enhanced release of the hydrophobic drug itraconazole from the ordered mesoporous SBA-15 silica material and on the existence of a critical mesopore diameter for enhancing release.

The majority of new drug candidates emerging from drug discovery programs suffers from poor aqueous solubility and insufficient dissolution which may lead to low oral bioavailability.<sup>1</sup> Developing strategies to overcome this hurdle associated with new innovative drug candidates is one of the great challenges for scientists active in pharmaceutical research.<sup>2</sup> For oral applications, the solid dispersion approach is quite popular but these formulations suffer in most cases from metastability; in addition there is poor understanding of the governing physics.<sup>3</sup> Alternative approaches under investigation include solubilization with emulsion based systems<sup>4</sup> or cyclodextrin complexes<sup>5</sup> and nanosizing of hydrophobic drug crystals to increase the surface area.<sup>6</sup>

Silica materials are non-toxic and are known for their excellent biocompatibility.<sup>7</sup> With the advent of ordered mesoporous silica materials and, especially, MCM-41 in the 1990s,<sup>8,9</sup> new tools to construct drug delivery carriers became available. Several studies dealt with MCM-41 as carrier for controlled drug delivery.<sup>10,11</sup> Originally, the focus of mesoporous silica materials has been on the development of slow release formulations. Release kinetics were evidenced to be controlled by diffusion.<sup>12</sup> In a recent paper dealing with the foam-like mesoporous structure TUD-1, the uptake and fast *in vitro* release of ibuprofen was demonstrated and ascribed to the presence of a three-dimensional mesopore system.<sup>13</sup>

In this paper, we report on the use of SBA-15, an ordered mesoporous material having monodimensional pores,<sup>9</sup> and demonstrate that the presence of a sufficiently wide pore diameter is the key for accelerating the release of the poorly soluble drug itraconazole. The aqueous solubility of itraconazole is estimated at *ca.* 1 ng ml<sup>-1</sup> at neutral pH and *ca.* 4 µg ml<sup>-1</sup> at pH 1.<sup>14</sup> Due to its high lattice energy and extreme hydrophobic character, itraconazole is a good model for low-solubility compounds in order to

evaluate the ability of SBA-15 materials in improving the dissolution properties of this kind of drugs.

Four different SBA-15 materials were synthesized and their porosity characterized using nitrogen adsorption (Table 1). The mesopore width of the materials was varied from 4.5 to 9.0 nm; the pore volume ranged from 0.42 to 0.80 cm<sup>3</sup> g<sup>-1</sup>.

The loading of itraconazole onto SBA-15 was performed using methylene chloride solvent. The physical state of the drug molecules after solvent evaporation was investigated with differential scanning calorimetry. Crystalline itraconazole melts at 168 °C, while glassy itraconazole is characterized by three typical endothermic transitions upon heating: a glass transition at 60 °C and two endothermic transitions due to its liquid-crystalline nature at 75 and 90 °C. The transition at 90 °C is the transition from the chiral nematic mesophase to an isotropic viscous liquid while that at 75 °C is the result of rotational restriction of the molecules.<sup>15</sup> At lower temperature, the material is frozen into a glass. These typical transitions allow to differentiate between the presence of itraconazole particles, either glassy or crystalline, or drug that is molecularly deposited onto the surface of SBA-15. Fig. 1 represents DSC curves of loaded SBA-15 materials with a pore size of 6.4 nm (SBA-15<sub>6.4</sub>) and with an itraconazole loading increasing from 0 to 31.2 wt%. At 24.6 wt% itraconazole loading of SBA-15<sub>6.4</sub>, the absence of bulk phase transitions according to DSC reveals that the itraconazole is molecularly dispersed. One gram of SBA-15<sub>6.4</sub> has a BET surface area of 662 m<sup>2</sup>. The area covered by a molecule of itraconazole is roughly estimated at 2.61 nm<sup>2</sup>. Assuming a monolayer coverage one can predict a monolayer capacity of 22.9 wt% itraconazole onto SBA-15<sub>6.4</sub>. This value is close to the maximum loading of *ca.* 24.6 wt% of molecularly dispersed itraconazole that, according to DSC, could be realized in the SBA-15<sub>6.4</sub> material. At an itraconazole loading of 26.8 wt% and higher, enthalpic responses show the superposition of two endothermic transitions at 60 and 168 °C which characterize the glass transition and melting of bulk phase

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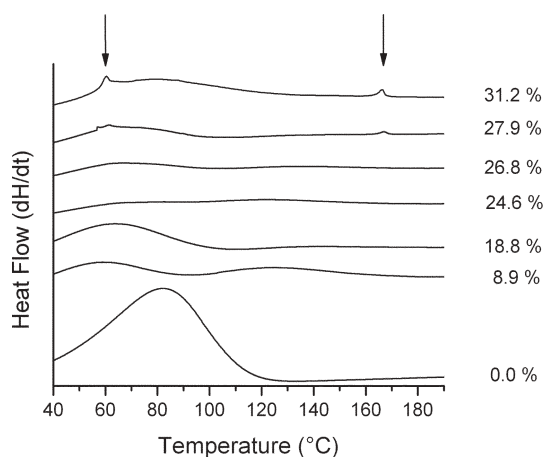
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**Table 1** Texture of SBA-15 materials determined with nitrogen adsorption

Material	w/nm	S/m <sup>2</sup> g <sup>-1</sup>	S <sub>p</sub> /m <sup>2</sup> g <sup>-1</sup>	V <sub>t</sub> /cm <sup>3</sup> g <sup>-1</sup>
SBA-15 <sub>4.5</sub>	4.5	506	321	0.42
SBA-15 <sub>6.4</sub>	6.4	662	483	0.63
SBA-15 <sub>7.9</sub>	7.9	661	461	0.77
SBA-15 <sub>9.0</sub>	9.0	662	404	0.80

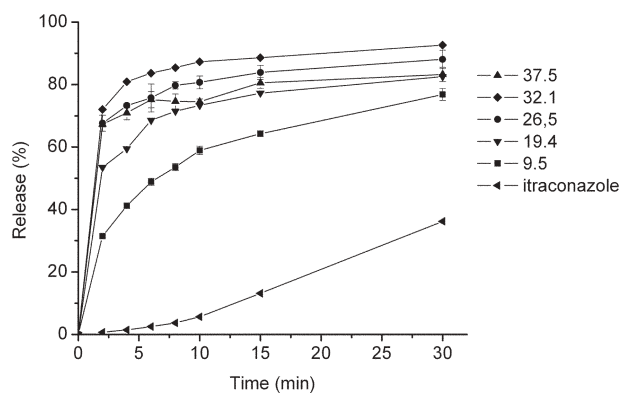
<sup>a</sup> w (nm): pore width, S (m<sup>2</sup> g<sup>-1</sup>): BET surface area, S<sub>p</sub> (m<sup>2</sup> g<sup>-1</sup>): mesopore surface area determined from t-plot analysis, V<sub>t</sub> (cm<sup>3</sup> g<sup>-1</sup>): total pore volume determined from t-plot analysis.



**Fig. 1** Differential scanning calorimetry analysis of SBA-15<sub>6.4</sub> loaded with different amounts of itraconazole (wt%), arrows indicate  $T_g$  of glassy itraconazole and  $T_m$  of crystalline itraconazole.

itraconazole, respectively. The capacity of SBA-15<sub>6.4</sub> to incorporate molecularly dispersed itraconazole appears to be exceeded above 24.6 wt%. The existence of a critical loading was observed for the other SBA-15 materials too. Each DSC curve of SBA-15 loaded with itraconazole is also characterized by one or two broad endothermic transitions which represent the desorption of physically adsorbed water. With increasing loading of itraconazole onto SBA-15<sub>6.4</sub>, this endothermic desorption of water tends to shift to lower temperatures indicating that the adsorption of itraconazole renders the surfaces less hydrophilic. Unloaded SBA-15 exhibits an endothermic maximum of its water desorption around 85 °C, while loaded materials are characterized by an endothermic response around 65 °C.

The *in vitro* release performance of itraconazole loaded SBA-15 materials was assessed using simulated gastric fluid at pH 1.2. All release experiments showed good reproducibility. The release behaviour of itraconazole from SBA-15<sub>7.9</sub> is illustrated for different loadings in Fig. 2 and compared to the dissolution of crystalline itraconazole. After 30 min, SBA-15<sub>7.9</sub> released at least 70% of its initial drug content for every loading. At this time, crystalline itraconazole was only 36% dissolved. The percentage release after 5 min is *ca.* 40% at 9.5 wt% itraconazole loading. It

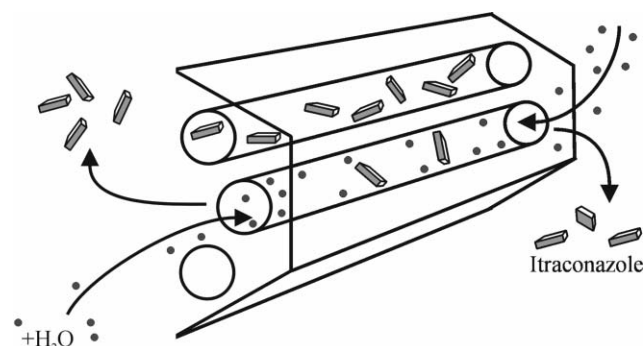


**Fig. 2** Release profiles from SBA-15<sub>7.9</sub> with different loadings of itraconazole (wt%) and comparison with dissolution of crystalline itraconazole.

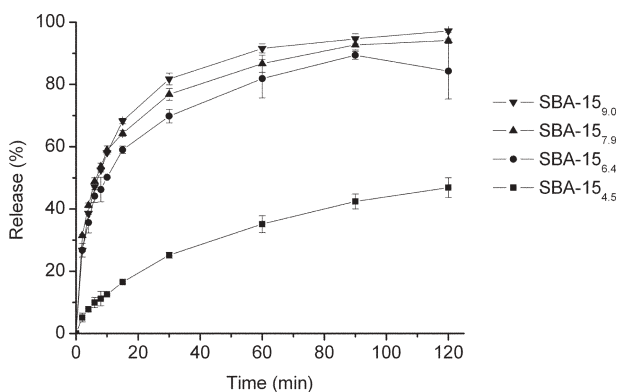
increases to *ca.* 60% at 19.4 wt% loading, *ca.* 70% at 26.5 wt% loading and *ca.* 80% at 32.1 wt% loading. At the highest itraconazole loading of 37.5 wt%, the release after 5 min is 70%. The increase of the percentage release with the loading up to the optimum suggests that the SBA-15 surface presents a minor fraction of strong adsorption sites for itraconazole, but that the majority of sites are weaker and show a preference for water adsorption. Increasing the loading beyond the optimum of *ca.* 31.2 wt% leads to a decreased release rate due to the presence of crystalline and amorphous regions of itraconazole and itraconazole intermolecular hydrophobic interactions.

A dependence of percentage release on drug loading was observed for each investigated SBA-15 carrier. In this respect, SBA-15 behaves differently from organic polymer based solid dispersions, for which the dissolution rate decreases with increasing drug-to-polymer ratio. SBA-15 materials as carriers combine high drug loadings with fast *in vitro* release kinetics. Rapid release kinetics from SBA-15 are tentatively explained in terms of a displacement desorption of itraconazole by the influx of water. Adsorbed itraconazole molecules will be effectively desorbed from the surface by competitive adsorption with water molecules because of the hydrophilicity of the silica pore walls (Scheme 1).

To investigate the influence of the pore size on the enhanced release behaviour of itraconazole, SBA-15 materials with different pore widths (Table 1) were loaded with approximately 10 wt% drug and their *in vitro* release performances compared. Prior DSC analysis had shown no endothermic transitions characteristic for bulk properties of itraconazole, evidencing the molecularly dispersed state of adsorbed molecules in all cases. FT-IR spectra (ESI†) in the hydroxyl stretching region of SBA-15 materials with a different pore size are very similar, showing that SBA-15 materials with different pore size have similar surface hydrophilic properties. Release curves (Fig. 3) reveal that enlarging the pore size from 4.5 to 6.4 nm drastically enhances the release of itraconazole. A further increase in pore size to 7.9 and 9.0 nm results only in a minor further improvement. These data suggest the occurrence of molecular diffusion barriers in pores measuring 4.5 nm and the existence of a critical pore size which discriminates between facile diffusion and sterically hindered diffusion of itraconazole through the pores of SBA-15. These findings show that itraconazole release from SBA-15 materials can be tuned by varying the pore size of the material. In previous drug release studies from ordered mesoporous silica materials, the pore width



**Scheme 1** Enhanced release of itraconazole from SBA-15 resulting from the rapid influx and competitive adsorption of water.



**Fig. 3** Release profiles of itraconazole from SBA-15 materials with different pore sizes (nm). Each release experiment was performed in triplicate.

was less than 5 nm which might have been sub-optimal for obtaining fast release.<sup>10–13,16</sup>

In conclusion, DSC analysis revealed the existence of a molecular dispersion of itraconazole in SBA-15 silica material up to a certain loading. Loaded SBA-15 materials with pore sizes from 6.4 to 9.0 nm show the strongest enhancement of the release of itraconazole when compared to the dissolution of crystalline itraconazole itself. Breaking up the intermolecular itraconazole interactions of the crystal structure by separating the drug molecules onto the SBA-15 silica surface is the key to circumvent slow dissolution kinetics. When the carrier pore size is decreased to 4.5 nm, the release of itraconazole is significantly slower. There exists a minimal pore size at which the release kinetics of bulky hydrophobic itraconazole molecules are maximized.

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‡ Estimated with Chemskech<sup>®</sup> software after 3D optimization. See ESI† for the chemical structure of itraconazole.

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