

Enhanced Release of Itraconazole from Ordered Mesoporous SBA-15 Silica Materials

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Materials and Methods

SBA-15 synthesis

SBA-15 materials were synthesized according to procedures described by Zhao *et al.* Briefly, 2.84 g of Triblock copolymer Pluronic P123 (BASF, Antwerp, Belgium) was dissolved in 90 g demineralised water and 60 g of 4 M HCl solution. This mixture was placed in an oil bath at 35 °C and 8 g of tetraethylorthosilane (Acros Organics, Geel, Belgium) was added dropwise while stirring. After 20 hours, the suspension was placed in an oven for hydrothermal treatment during 24 hours at a temperature of 80, 90 and 100 °C which resulted in pore sizes of 6.4 nm, 7.9 nm and 9.0 nm respectively. When no hydrothermal treatment was performed, a pore size of 4.5 nm was obtained. Finally, the powders were washed with demineralised water, dried and calcined at 550 °C for 24 hours under ambient atmosphere to remove the polymer from the pores.

Loading procedure

Loading of SBA-15 was performed by suspending SBA-15 into 10 ml of an itraconazole (Janssen Pharmaceutica, Beerse, Belgium) solution in methylene chloride (4 g/l) and the mixture was rotated for 24 h. Subsequently, the solvent was removed by evaporation and the powder was dried for 48 h at 40 °C under reduced pressure. In this way, drug loadings in the range of 5 to 38.7 wt.-% were prepared.

Nitrogen adsorption and calculations

Nitrogen isotherms were obtained using a Coulter Omnisorp 100 (Coulter electronics inc., Miami, USA) operating in continuous flow mode. The measurements were performed at -196 °C and all samples were pretreated at 150 °C under vacuum prior to analysis. The specific surface area was evaluated using the BET method from nitrogen adsorption data in the relative pressure range from 0.05 to 0.2. The pore volume and the specific surface area of mesopores were assessed using the t-plot method. The mesopore size distributions were computed from the adsorption branches of the isotherms using the Barrett-Joyner-Halenda (BJH) approach.

Differential Scanning Calorimetry

In order to study the physical state of itraconazole in the mesoporous silica matrix, the loaded powders were analyzed using a DSC Q1000 from TA Instruments (TA-Instruments, Brussels, Belgium). The samples were heated from 20 °C to 200 °C at 10 °C/min. Indium was used to calibrate the temperature scale and the enthalpic response. The samples (weight range 10 -13 mg) were analyzed in aluminum sample pans (TA-Instruments, Brussels, Belgium).

FT-IR

In situ FT-IR spectra of powders, compressed to thin films of 3 mg.cm⁻², were recorded on a Nicolet 730 FTIR spectrophotometer under helium flow. Spectra were taken at temperatures ranging from 50 °C to 450 °C after an equilibration at the desired temperature for 30 minutes. The temperature steps raised the temperature by 50 °C with a heating rate of 10 °C.min⁻¹.

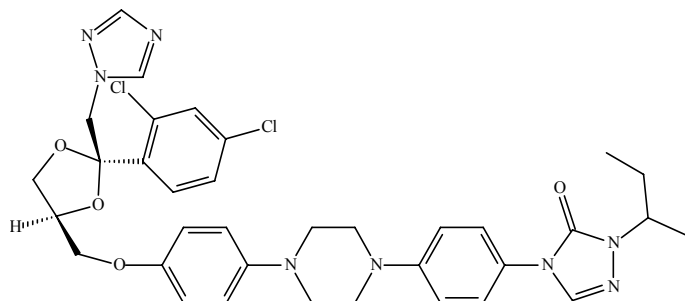
HPLC assay and *in vitro* dissolution

The exact drug content in the loaded mesoporous silica was assayed using an isocratic HPLC method. The HPLC system consisted of a Lachrom[®] L-7100 HPLC pump, an autosampler model L-7200 equipped with a 100 µl loop, a UV detector model L-7420 set at 260 nm, and an Interface D-7000 (Merck, Darmstadt, Germany). UV signals were monitored and peaks were integrated using the D-7000 HSM software. All chromatographic separations were performed at room temperature. The analysis of itraconazole was performed on a RP-18 150 x 4.6mm 5µm Hypersil silica column (Thermo Electron Corporation, Waltham, USA). The mobile phase consisted of acetonitrile/tetrabutyl ammonium hydrogen sulfate 0.01 N (55:45 v/v), and was filtered through a membrane filter (0.45 µm) and degassed by ultrasonication before use. The flow rate amounted to 1.5 ml/min.

In order to study dissolution and release of itraconazole from mesoporous silica materials, the loaded powders were suspended in simulated gastric fluid 0.1 M HCl with 0.5 wt.-% sodium lauryl sulfate (Certa, Braine l'Alleud, Belgium) using a rotary mixer (Labinco, Breda, The Netherlands). SLS was added to install sink conditions. The amount of material in the

release medium was adjusted to have a fixed concentration of drug substance (0.1 mg/ml). This corresponds to approximately 20 % of the saturation solubility of itraconazole in the release medium. At specific time intervals, the concentration of the drug substance in the dissolution medium after filtering through a 0.45 μm membrane, was measured using the HPLC method mentioned above.

Structure of itraconazole



Supplementary results: FT-IR

FT-IR spectra of SBA-15_{4.5} and SBA-15_{7.9} at 200 °C and 400 °C are shown in Figure ESI-1. Infrared absorption in the range 3400-3750 cm^{-1} is attributed to the presence of silanol groups on the surface of the SBA-15 material. Increasing the evacuation temperature dehydrates the surface leaving only free silanol groups covering the SBA-15 surface. This dehydration is manifested by a change of the broad absorption band between 3400-3750 cm^{-1} into a sharp peak at 3750 cm^{-1} (OH) associated with free silanol stretching. Dehydration during a temperature controlled heating gives an indication of the hydrophilicity of the SBA-15 surface. Comparing materials with different pore sizes (SBA-15_{4.5} and SBA-15_{7.9}) confirms the similar surface hydrophilicity of both materials.

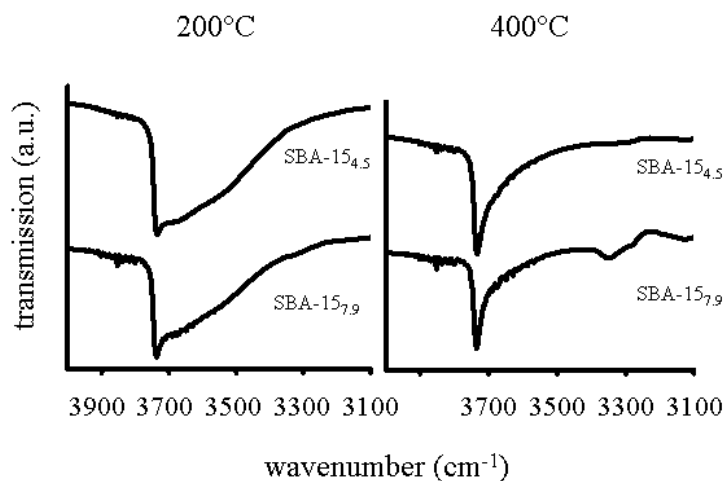


Figure ESI- 1: FT-IR spectra of SBA-15_{4.5} and SBA-15_{7.9} recorded at 200 °C and 400 °C.