Electronic supplementary informations for :

Ionogels as drug delivery system: one-step sol-gel synthesis using imidazolium ibuprofenate ionic liquid

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Experimental section

Chemicals

The following chemicals were purchased and used as received: tetramethoxysilane from Fluka; methyltrimethoxysilane 97% from Alfa Aesar, sodium ibuprofenate from Acros. The ionic liquid 1-butyl-3-methylimidazolium chloride BMImCl has been prepared as described in the literature.[1]

Instrumentation

Infrared spectra were recorded on a Thermo Nicolet Avatar 320-FT-IR spectrometer and Smart Orbit ATR accessory with a diamond crystal with a resolution of 4 cm^{-1}.

The nitrogen adsorption-desorption isotherms at 77 K were measured using a Micrometrics Tristar surface area and porosity analyzer on samples degassed under vacuum at 120 °C for 12 h. The mesopore size distribution was evaluated by the Borekhoff- de Boer (BdB) method applied to the desorption branch of the N_2 adsorption-desorption isotherm.

Powder X-ray diffraction (XRD) patterns were recorded on a Philips X'pert Pro diffractometer, Bragg-Brentano geometry, Cu-Kα wavelength (1.5418 Å, Cu nickel filtered) equipped with X'celerator detector. The measurement parameters are: step-size, 0.016; counting time, 400 s.

Thermogravimetric analysis (TGA) were carried out on a Netzsch STA 409 PC Luxx in alumina crucible under an air flow with a heating rate of 5°C/min up to 850°C followed by an isotherm at 850°C for 30 min.

Measurements of phase-transition temperatures were performed with a Netzsch differential scanning calorimeter model 204F1 Phoenix and the data were evaluated using Netzsch Proteus Thermal Analysis software version 4.8.1. Samples of 10-15 mg were placed in a hermetically sealed aluminum pan; an empty pan was used as reference. Pans were exposed to a N_2 flow atmosphere. The following conditions measurements were applied: 1) heating from room temperature to 150°C at a rate of 10°C/min 2) isotherm at 150°C for 15 min 3) cooling to -120°C at a rate of 10°C/min 4) isotherm at -120°C for 10 min 5) heating to 120°C at a rate of 10°C/min 6) cooling to room temperature at a rate of 10°C/min. The glass transition was determined at the midpoint of a heat-capacity change.

Mass spectrometry analyses (ES^+ and ES^-) were conducted using a Micromass Q-Tof spectrometer.

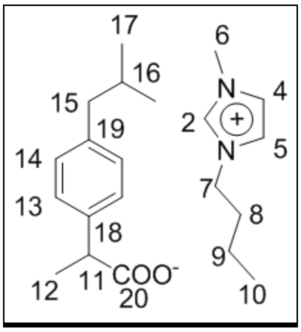
^1H and ^{13}C liquid-state NMR were recorded on a Brucker DRX 400 spectrometer at room temperature. Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks ($CDCl_3$: δ 7.26 ppm ^1H; δ 77.0 ppm ^{13}C). Coupling constants (J) are reported in Hz.

^{29} Si solid-state NMR was performed on ground samples on a Brucker ASX400 using a 3.2 mm probe. Samples were spun at the magic angle using ZrO_2 rotors and the temperature was maintained at 25°C.

Rheological measurements were carried out using an Anton Paar Physica MCR 301 rotational rheometer. All the tests were performed at 25°C using a CP50.1 mobile varying the shearing rate from 0.1 s^{-1} to 1000 s^{-1}.

The density was measured by with 1 mL pycnometer from Micromeritics. The pycnometer was calibrated using acetonitrile and the measure was replicated twice.

Synthesis of 1-methyl-3-butylimidazolium ibuprofenate BMImIbu



In a round bottom flask, sodium ibuprofen salt (5 g, 21.9 mmol) was dissolved into 30 mL of ethanol. $[C_4mim][Cl]$ (3.81 g, 21.9 mmol) was dissolved into 10 mL of ethanol and added slowly to the previous solution. The resulting mixture was stirred at room temperature for 2 hours. The solution was filtered on Millipore (0.45 μm)and 100 mL of acetone was added leading to the precipitation of NaCl which was further filtered and the solvent was removed under vacuum. The final product was obtained as a yellowish very viscous liquid (7.10 g, 94 %). ^1H NMR (400 MHz, $CDCl_3$) : δ =10.32 (1H, s, H_2) ; 7.24 (2H, d, J = 7.9 Hz, H_{14}) ; 7.10 (2H, d, J = 1.7 Hz, H_5) ; 7.03 (2H, d, J = 1.7 Hz, H_4) ; 6.91 (2H, d, J = 7.9 Hz, H_{13}) ; 4.04 (2H, t, J = 7.3 Hz, H_7) ; 3.74 (3H, s, H_6) ; 3.50 (1H, q, J = 7.1 Hz, H_{11}) ; 2.30 (2H, d, J = 7.1

Hz, H_{15}) ; 1.69 (3H, m, H8, H_{16}) ; 1.36 (3H, d, *J* = 7.1 Hz, H_{12}) ; 1.22 (2H, s, *J* = 7.4 Hz, H_9) ; 0.85 (3H, t, *J* = 4.1 Hz, H_{10}) ; 0.51 (3H, d, *J* = 3.5 Hz, H_{17}). ^{13}C NMR (100.6 MHz, $CDCl_3$) : δ =180.4 (C_{20}) ; 142.7 (C_{18}/C_{19}) ; 139.4 (C_2) ; 138.6 (C_{18}/C_{19}) ; 128.6 (C_{13}/C_{14}) ; 127.4 (C_{13}/C_{14}) ; 122.8 (C_4/C_5); 121.1 (C_4/C_5) ; 49.4 (C_7) ; 49.2 (C_{11}); 45.0 (C_{15}) ; 36.1 (C_6) ; 32.0 (C_8) ; 30.2 (C_{16}); 22.4 (C_{17}) ; 19.7 (C_{12}) ; 19.2 (C_9) ; 13.4 (C_{10}). m/z (ES^+) 139 (M^+, 100). m/z (ES^-) : 205 (M^-, 100) , 411 ($2M^-+H^+$]. νmax/cm^{-1} 3141 and 3060 (νC=C-H imidazolium and phenyl rings), 2949, 2925, 2864 (ν C-H alkyls), 1580 and 1372 (ν COO^-). The density of BMImIbu is 1.057± 0.002 g.cm^{-3} at 25 °C and the viscosity is 2220 cP at 25°C. TGA : $T_{onset5\%}$ = 225 °C, $T_{onset10\%}$ = 237 °C. DSC : Tg = -26 °C

Synthesis of ionogels

Tetramethoxysilane (TMOS) or a mixture of TMOS and methyltrimethoxysilane (MTMOS) (molar ratio TMOS/MTMOS : 50/50 or 75/25) was added to a solution of methanol (0.5 mL) and HCl 0.1 N (100 μL), the resulting solution was stirred overnight at room temperature. In a Teflon vial, BMImIbu was dissolved in 0.5 mL of methanol and the silicon precursor solution was added (molar ratio TMOS or TMOS+MTMOS/ BMImIbu / HCl 0.1N : 1/0.25/0.3 %). After a short stirring, gelation occurred within 5 min or 1 hour depending on the precursor and aging was continued for 15 days.

In vitro release tests

In vitro release tests were performed in a standard pharmaceutical dissolutest USP1 [U.S. Pharmacopeia & National Formulary, 1999.]. 1 L vessels were filled with 0.5 L of intestinal simulated medium (NF18/USP 23 : 13.6 g of KH_2PO_4 in 2.0 L of distilled water, adjusted to pH 7.48 with NaOH 1N). The temperature was set at 37 °C, and the paddle speed at 40 rpm. The ionogels were immersed without any modifications. Samples of 1 mL were taken and replaced by fresh medium.

Ibuprofen releases were quantified by HPLC (LC-2010 AHT, Shimadzu) on a C18 Prontosil 120 Å, 5 μm (250x4.6 mm) column, mobile phase CH_3CN/0.5% acetic acid (65:35), with a flow rate of 1.2 mL/min, UV detector wavelength at 264 nm.

Experimental data have been plotted with Korsmeyer-Peppas models that described pure Fickian diffusion has usually observed in silica mesoporous materials. Nevertheless, the R^2 coefficient did not exceed 0.985, implying much complex release mechanism.

The best fit was obtained with Eq. 1 ($R^2 = 0.999$), that describes the relationship between the total drug amount released (Q) vs time (t):

$$Q = \sum_{i=1}^{n} Q_n(1 - e^{-K_n t}) \text{ (Eq 1)}$$

n is the number of release mechanisms, Qn (%) is the amount of drug released at equilibrium and K_n (h^{-1}) is the drug release rate parameter. K_n depends on the material surface that governs the drug mass transfer as previously described in pure and organo-modified mesoporous silica .[2]

Lin et al. proposed a model with the mathematical expression:

$$Q = Q_e[1 - e^{-K_L.a.t}] \text{ (Eq 2)}$$

where *Q* (%) is the amount of drug in dissolution medium in time *t*, Q_e (%) is the amount of drug released in the interface liquid at the equilibrium, $K_L.a$ is the volumic mass transfer coefficient, and $a = S/V$ (*S* is the silica surface at which is applied the mass transfer process and *V* the volume of dissolution medium).

According to the first Fick law, Eq 2 could be written as:[3]

$$Q = Q_e[1 - e^{-Kt}] \qquad \text{(Eq 3)}$$

With $K = D/h$ where *D* is the drug diffusion coefficient in the interfacial liquid layer with thickness *h*.

Eq. 1 is the sum of two terms with the Eq 3 form.

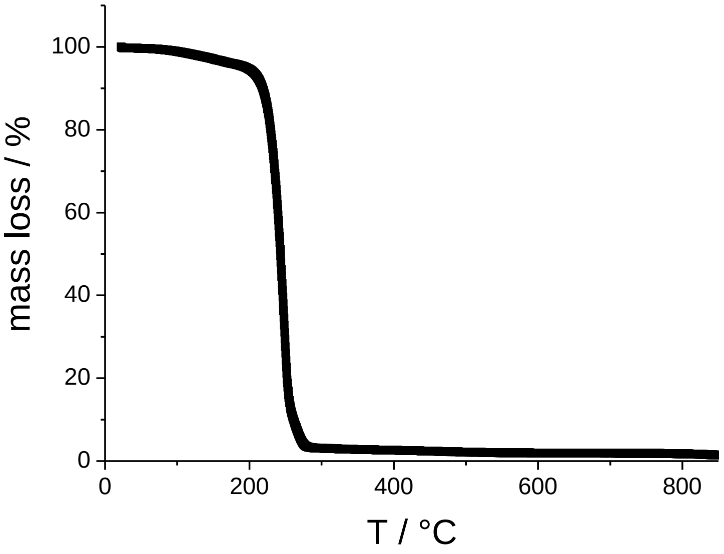


Fig S1 TGA of BMImIbu

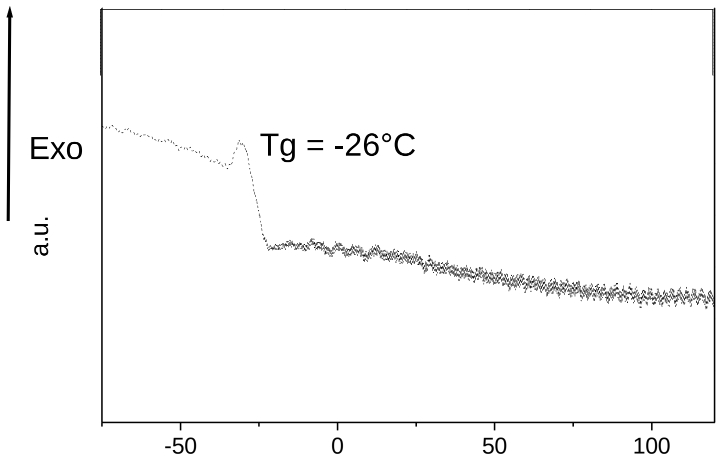


Fig S2 DSC of BMImIbu

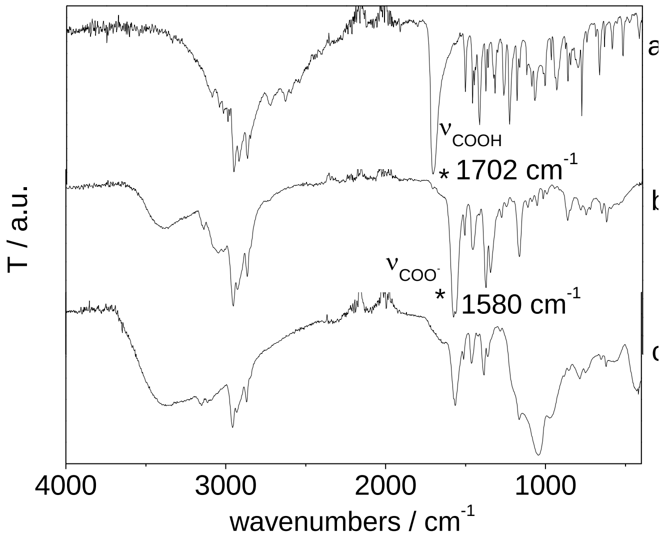


Fig. S3 FTIR spectra of (a) ibuprofen crystals, (b) BMIMIbu, (c) ionogel **1**

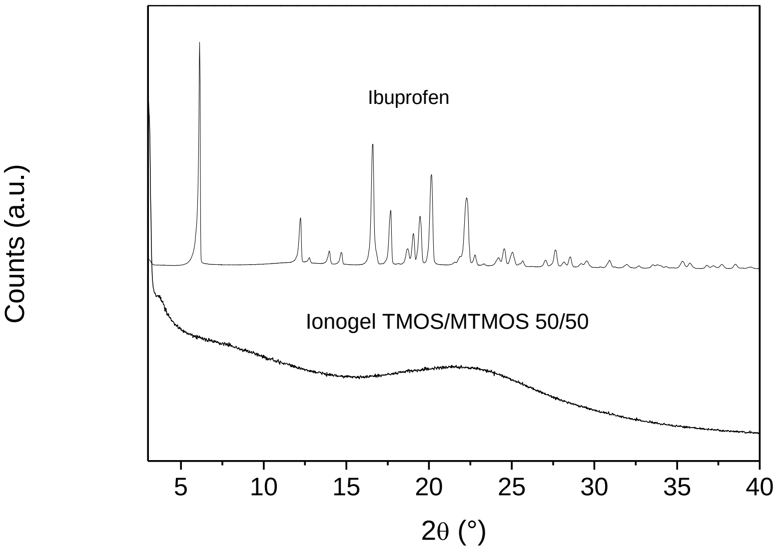


Fig. S4 X-Ray diffraction of ibuprofen crystals and ionogel **3** TMOS/MTMOS 50/50

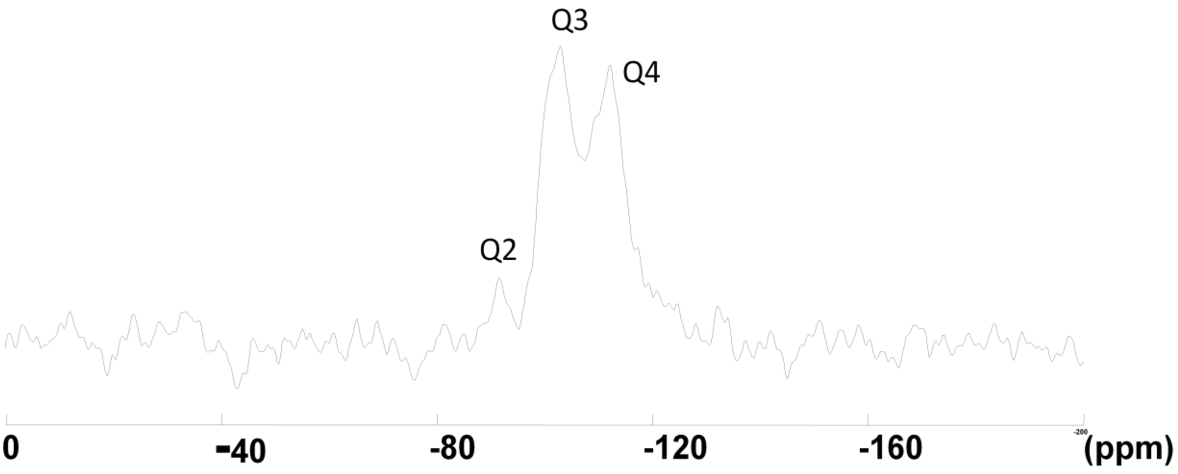


Fig.S5 ^{29}Si NMR Ionogel **1** TMOS

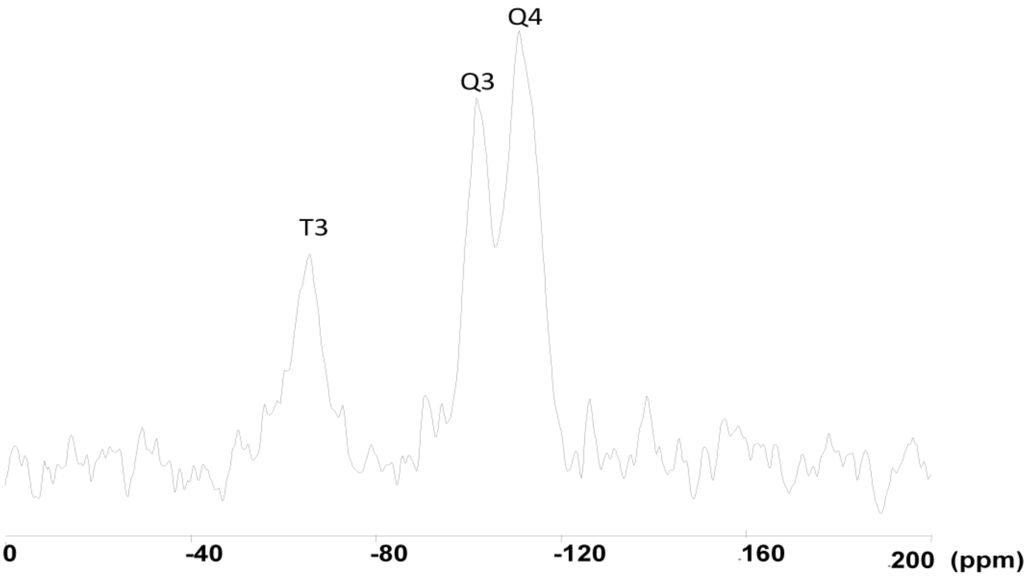


Fig.S6 ^{29}Si NMR Ionogel **2** TMOS/MTMOS 75/25

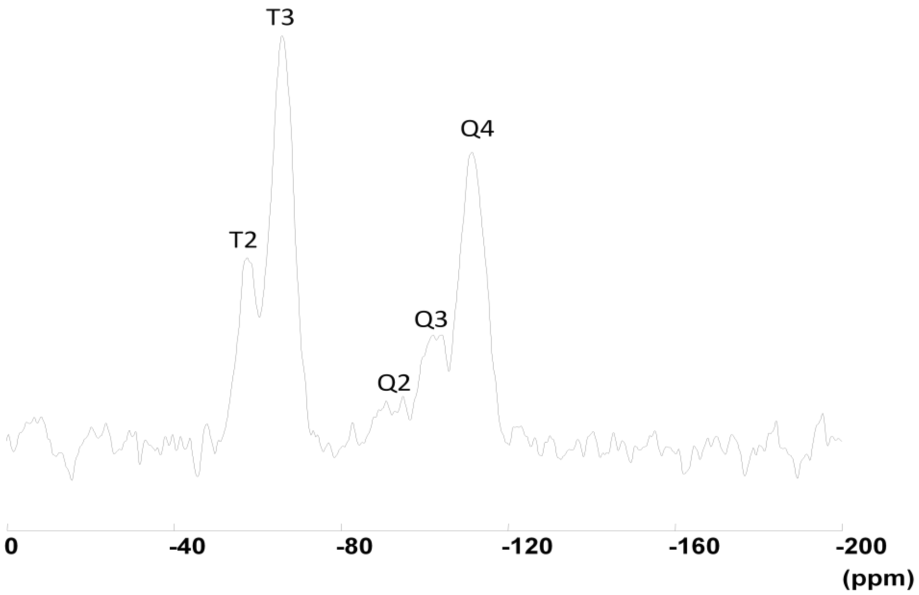


Fig.S7 ^{29}Si NMR Ionogel **3** TMOS/MTMOS 50/50

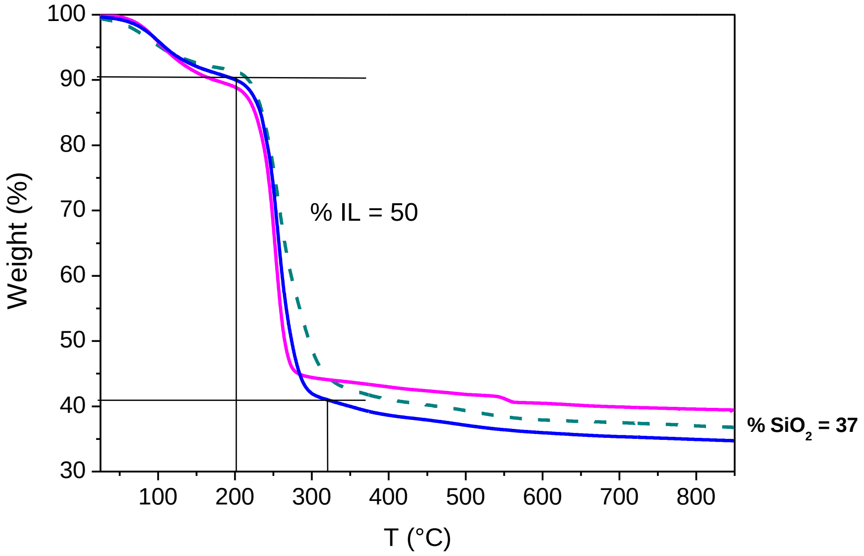


Fig. S8 TGA of ionogels **1** (--), **2** (**--**) and **3**(**--**)

Determination of IBU content :

According to TGA analysis, the weight pourcent of BMImIbu for ionogel **2** is 50 %and the final residual mass corresponded to the % of SiO_2, which means that 50 g of BMImIbu are confined in 37 g of SiO_2.

The pourcentage of BMImIbu can be calculated like this : %BMImIbu / % SiO_2 residual

In the case of ionogel **2** : BMImIbu (g / g SiO_2) = 50/37
= 1.35

Considering M(IBuIm) = 344 $g.mol^{-1}$ and M(IBU) = 205 $g.mol^{-1}$

$$\textbf{IBU (g / g SiO}_\mathbf{2}\textbf{)} = (1.35/344)*205 = 0.8$$

Table S1 Surface properties of the ionogels after calcinations at 850°C

TMOS	MTMOS	$S_{BET}(m^2/g)$	Vp (cm^3/g)	D (nm)
100	0	151	0.238	5.2
75	25	257	0.225	4.4
50	50	447	0.564	8.0

1. P. Bonhote, A.-P. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Graetzel, *Inorg. Chem.*, 1996, **35**, 1168-1178.
2. C. X. Lin, S. Z. Qiao, C. Z. Yu, S. Ismadji and G. Q. Lu, *Microporous Mesoporous Mater.*, 2009, **117**, 213-219.
3. P. Costa, J. Manuel and S. Lobo, *European Journal of Pharmaceutical Sciences*, 2001, **13**, 123-133.