Electronic Supporting Information

Building solids inside nano-space: from confined amorphous through confined solvate to confined 'metastable' polymorph

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Contents:

S1. Size and morphology of the MCF and CPG materials.

The size and morphology of the materials were assessed using Scanning Electron Microscopy. As expected the MCF host forms spherical particles with sizes of *ca*. 5 µm while CPG forms large irregular shape particles (Figure S1.1).

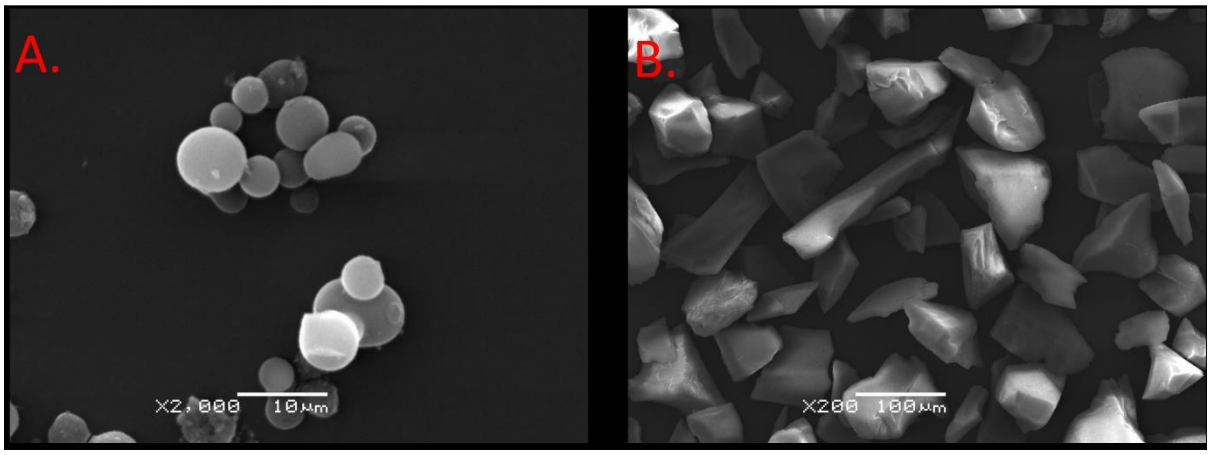

Figure S1.1. SEM images of A. MCF host and B. CPG host.

S2. Optimisation of volume and solvent addition to CPG melt loaded materials

As a standard material we used the CPG porous host due to its previous application in crystallisation studies and commercial availability. To investigate the impact of the solvent on the recrystallisation from an amorphous phase under confinement, we loaded the CPG material with indomethacin at the 85-15, 80-20 and 75-25 host-guest ratios, followed by the addition of three different solvents: methanol, ethanol and acetonitrile. After loading, the materials were dried using a procedure described in the main text. In the first series of experiments the volume of the solvent was adjusted to enable total filling of the pores *i.e*. 1.4 mL/g of the material. The phase composition of the loaded indomethacin was assessed using PXRD. In the cases of using acetonitrile or ethanol as the crystallisation driving solvent, exclusive formation of γ-IMC was observed (Figure S2.1). In the case of using methanol as the crystallisation driving solvent we obtained the metastable IMC form V as confirmed during further studies (Figure S2.2).

In the next step we optimised the volume of methanol required to form a pure crystalline phase of IMC form V. In this experiment, 140 or 560 µl of methanol were added to 200 mg of melt loaded CPG host. These volumes of the solvent were chosen to allow only a partial wetting of the pores (140 µl) and total overloading of the material with the solvent (560 µl). They both lead to the formation of the composites with two phases of indomethacin *i.e*. γ-IMC and IMC form V. Only the host loaded with 20% drug shows a PXRD pattern characteristic exclusively of the IMC form V after addition of 140 µl of methanol (Figure S2.3).

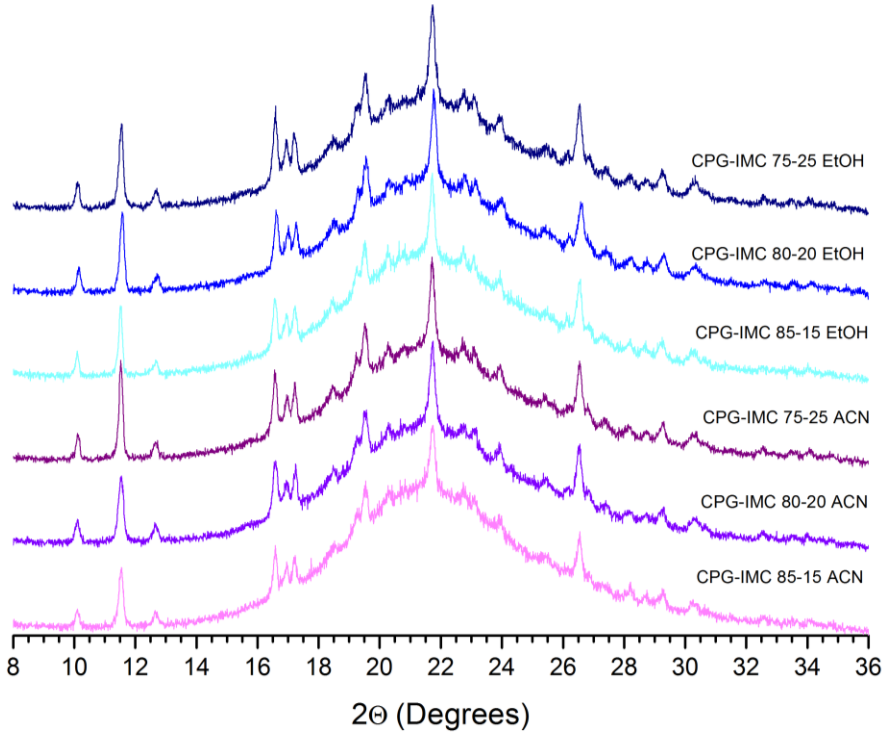

Figure S2.1. PXRD patterns of CPG material loaded with different ratios of indomethacin and subsequently treated with ethanol (EtOH) and acetonitrile (ACN).

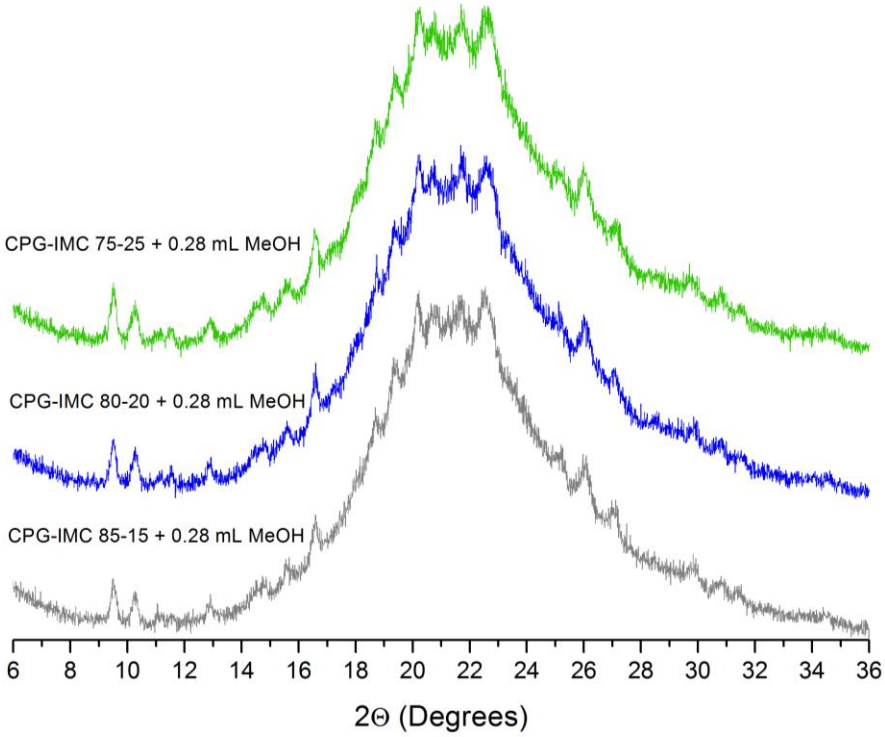

Figure S2.2. PXRD patterns of CPG material loaded with different amounts of indomethacin and subsequently treated with methanol (MeOH).

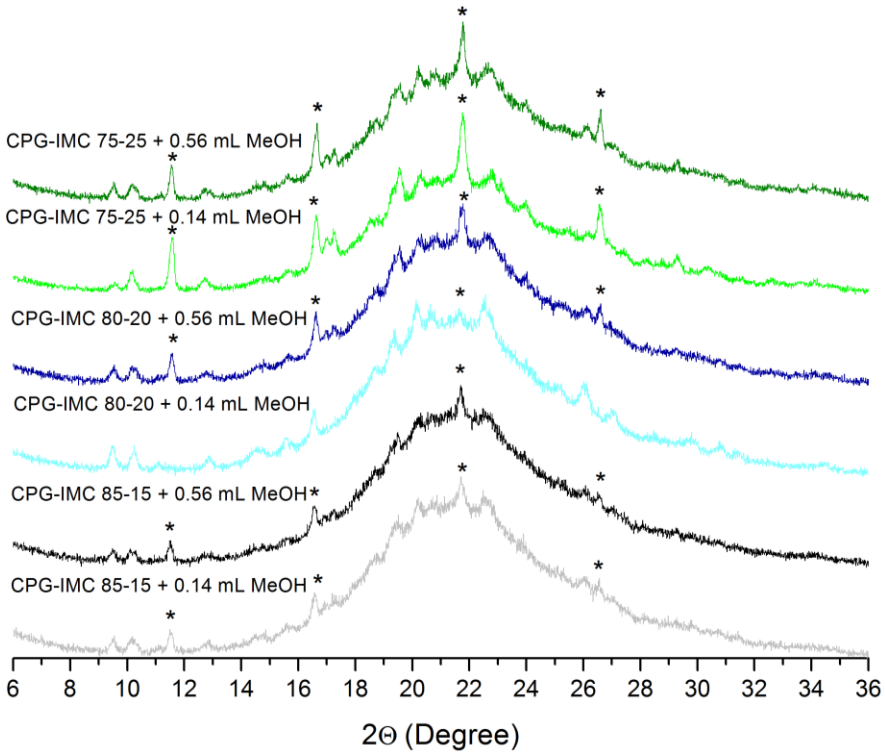

Figure S2.3. PXRD patterns of CPG material loaded with different ratios of indomethacin and subsequently treated with different volumes of methanol (peaks due to γ-IMC are indicated by asterisks).

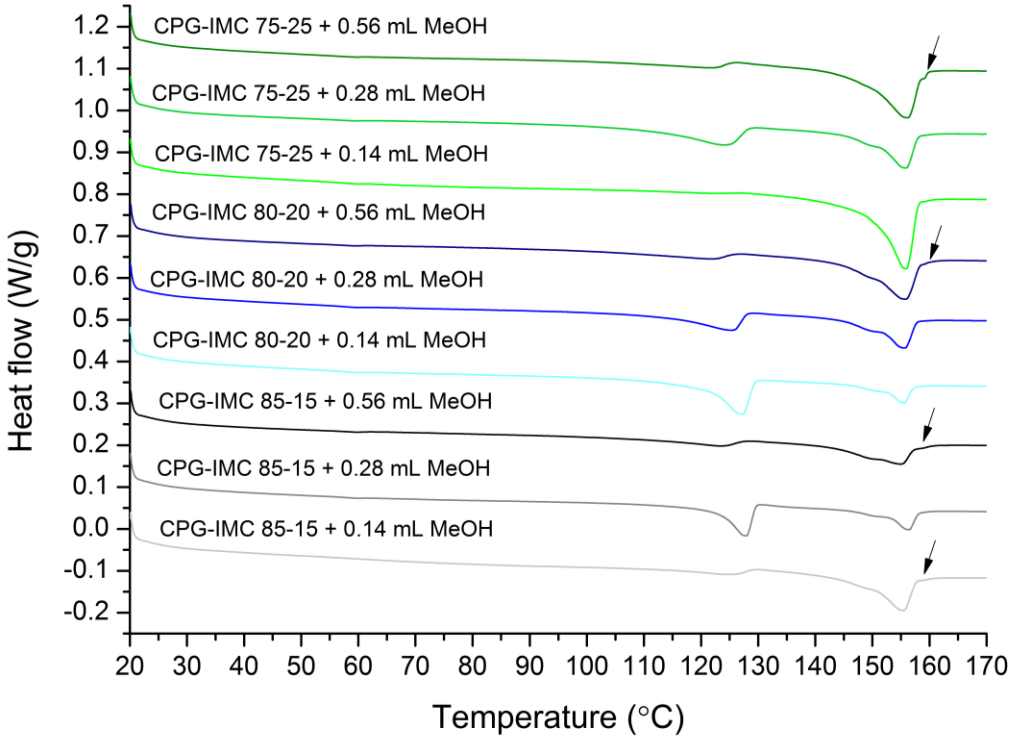

Figure S2.4. DSC thermograms of CPG material loaded with different ratios of indomethacin and subsequently treated with different volumes of methanol. The arrows indicate melting of bulk IMC outside the pores.

S3. Structural transformations of IMC loaded into the CPG material using the melting method after addition of methanol.

Indomethacin loaded into CPG host is amorphous as confirmed with solid state NMR, PXRD and DSC. The addition of methanol leads to the formation of confined IMC methanol solvate. Subsequent drying of the loaded mesoporous composites leads to the desolvation of the confined IMC solvate and its transition into IMC form V as confirmed by solid-state NMR (Figure S3.1).

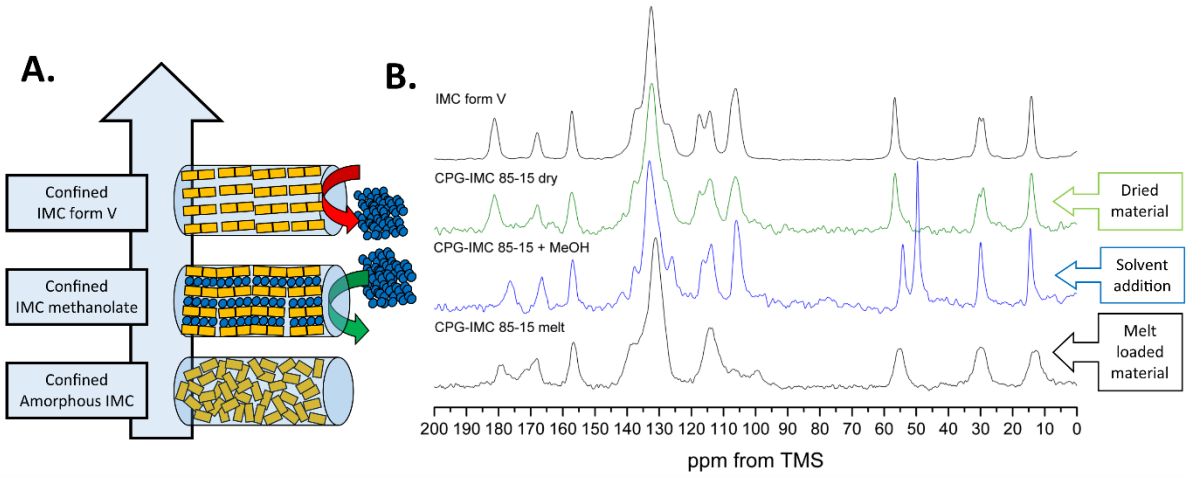

Figure S3.1. A. Graphical summary of the structural transformations of confined IMC under addition of methanol and subsequent drying. B. ^{1}H-^{13}C CP/MAS NMR spectra of confined IMC inside the CPG material after (from the bottom) melt loading, addition of methanol, drying and comparison with IMC form V (spectra acquired at 300 MHz and spinning speed of 10 kHz).

S4. BET surface area of the CPG host after loading

The BET surface area of the loaded CPG hosts decreases when compared with the pure CPG material (Table S4.1.). However interpretation of the BET surface results is not straightforward for large-pore materials formulated as complex composite.

Table S4.1. BET surface are of CPG composites loaded with IMC

Composite	S_{BET} (m^2/g)	Composite	S_{BET} (m^2/g)
CPG	50.426		
CPG-IMC 85-15	30.436	CPG-IMC 85-15 + 0.28 mL MeOH	38.44
CPG-IMC 80-20	33.326	CPG-IMC 80-20 + 0.28 mL MeOH	22.39
CPG-IMC 75-25	33.688	CPG-IMC 75-25 + 0.28 mL MeOH	35.29
CPG-IMC 70-30	15.449	CPG-IMC 70-30 + 0.28 mL MeOH	29.11
CPG-IMC 50-50	N/A*	CPG-IMC 50-50 + 0.28 mL MeOH	3.26

* Adsorption below acceptable limits for BET calculations

S5. Structural and thermal transitions of indomethacin loaded into MCF and CPG composites using the melting method.

PXRD patterns of indomethacin loaded into CPG and MCF hosts using the melting method show no peaks characteristic of the crystalline drug (Figure S5.1 and Figure S5.2).

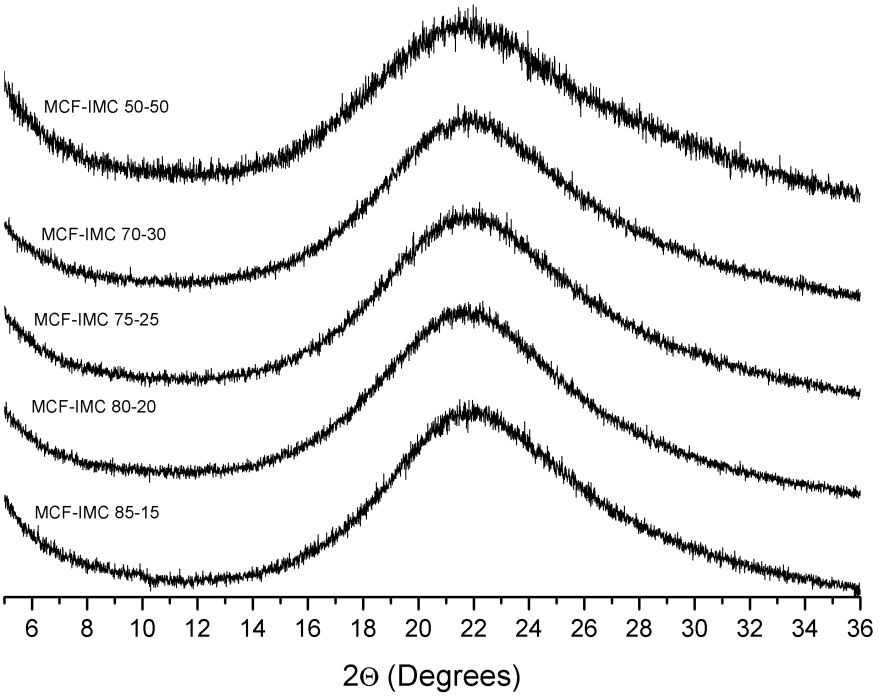

Figure S5.1. P XRD patterns of MCF material loaded with molten IMC at different host-guest ratios.

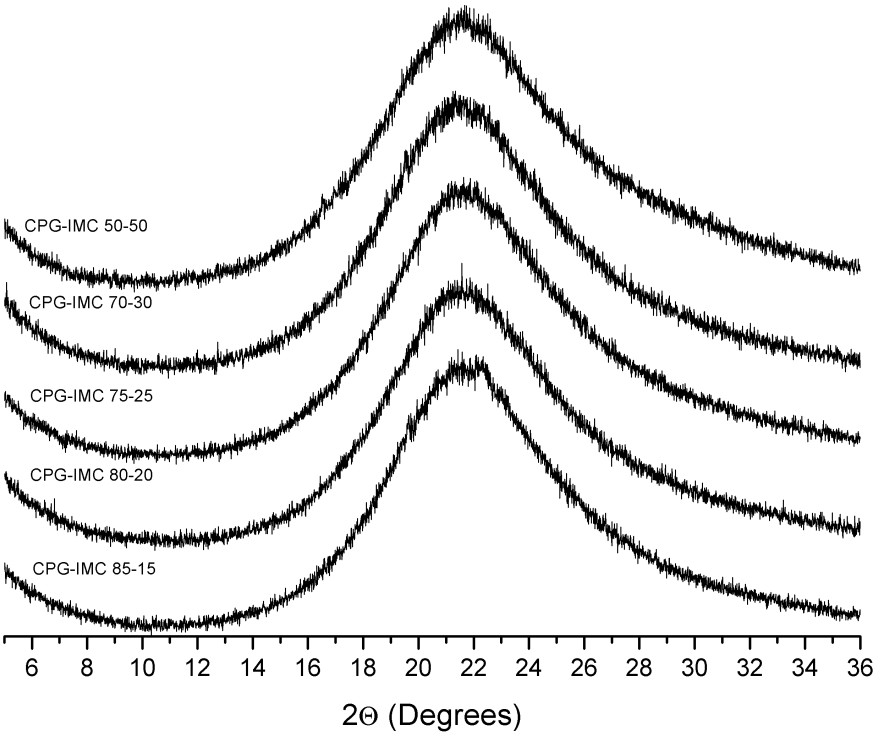

Figure S5.2. PXRD patterns of CPG material loaded with molten IMC at different host-guest ratios.

The confinement of indomethacin inside the MCF host prevents the thermally induced recrystallisation into either α- or γ-polymorph, which is characteristic for bulk amorphous IMC (Figure S5.3).

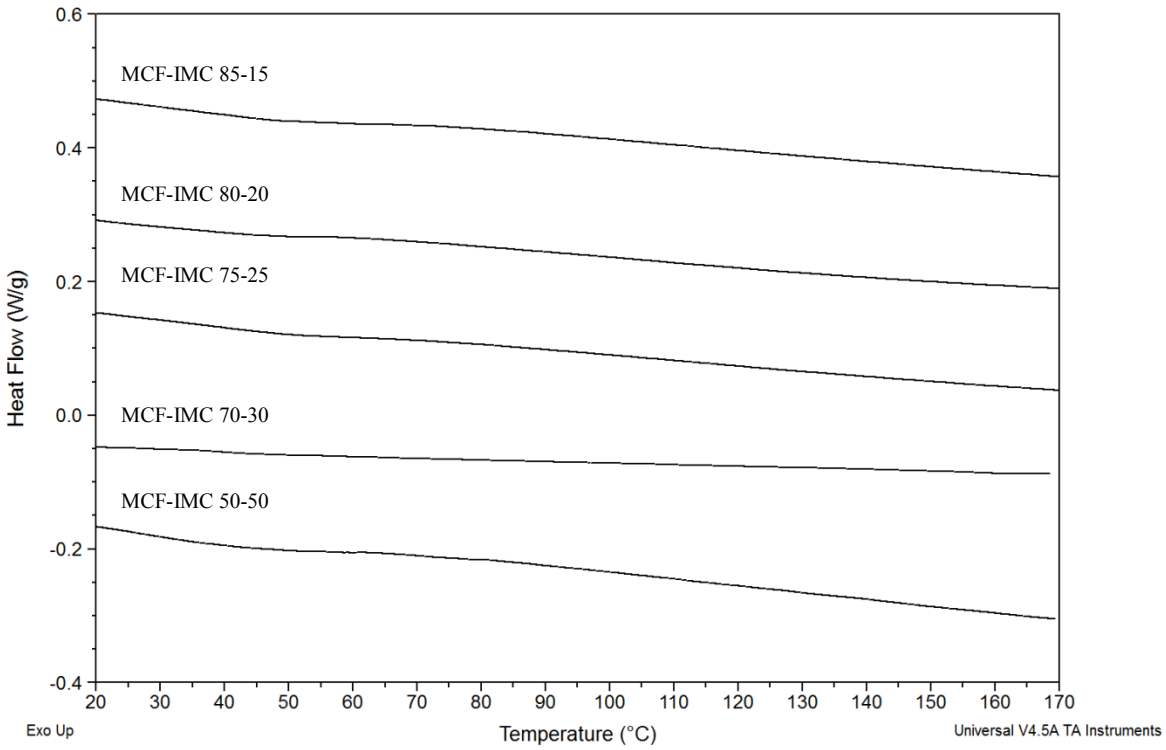

Figure S5.3. DSC thermograms of MCF host loaded with IMC from the melt with different host:drug ratios.

S6. Deposition of indomethacin outside the pores of MCF and CPG composites at high drug loadings (30 and 50%) after methanol addition.

As shown in the main text (Figure 9) the CPG host loaded with high drug contents of 30 and 50 wt. % shows thermally driven recrystallisation of IMC loaded outside the pores as confirmed by observation of the bulk melting temperature of both IMC polymorphs (α- and γ-).

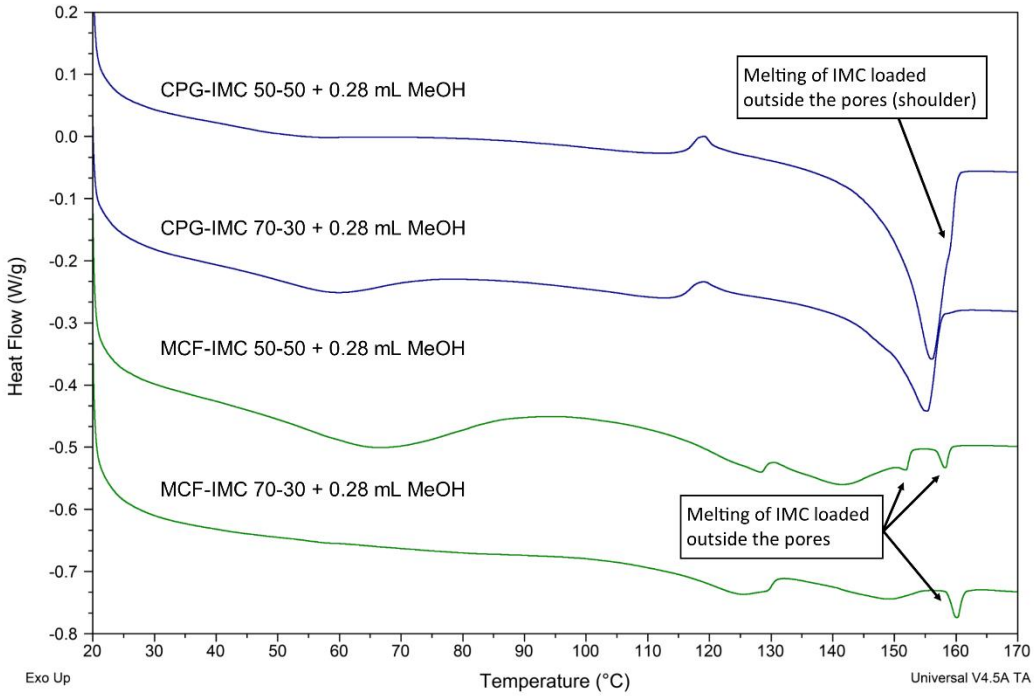

Figure S6.1. DSC thermograms of MCF and CPG hosts loaded with IMC from the melt at concentrations of 30 and 50 wt. % after the addition of methanol.

When IMC was loaded from the melt into the MCF host no signs of drug loaded outside the pores could be detected using DSC, PXRD and solid state NMR. However, addition of methanol into the MCF host loaded from the melt at high concentrations (30 and 50 wt. %) leads to the deposition of the drug outside the pores as shown by the DSC results (Figure S6.1.). This may be related to the dissolution of the drug loaded close to the pore entrance and its further diffusion outside the pores. Similar findings regarding ibuprophen confined within MCM-41 were recently published by Skorupska *et al.* [1]

Solvent driven recrystallisation of the IMC loaded within MCF and CPG hosts at high IMC concentrations leads to a mixture of phases which are loaded inside and outside the pores. Presence of either α-, γ- and form V IMC was detected using PXRD and solid state NMR (Figure S6.2. and S6.3), however, due to the complex thermal transitions it is difficult to state unequivocally which phase is formed due to the confinement or is loaded outside the pores. Further investigation of concomitant crystallisation of non-confined systems is beyond the scope of the manuscript.

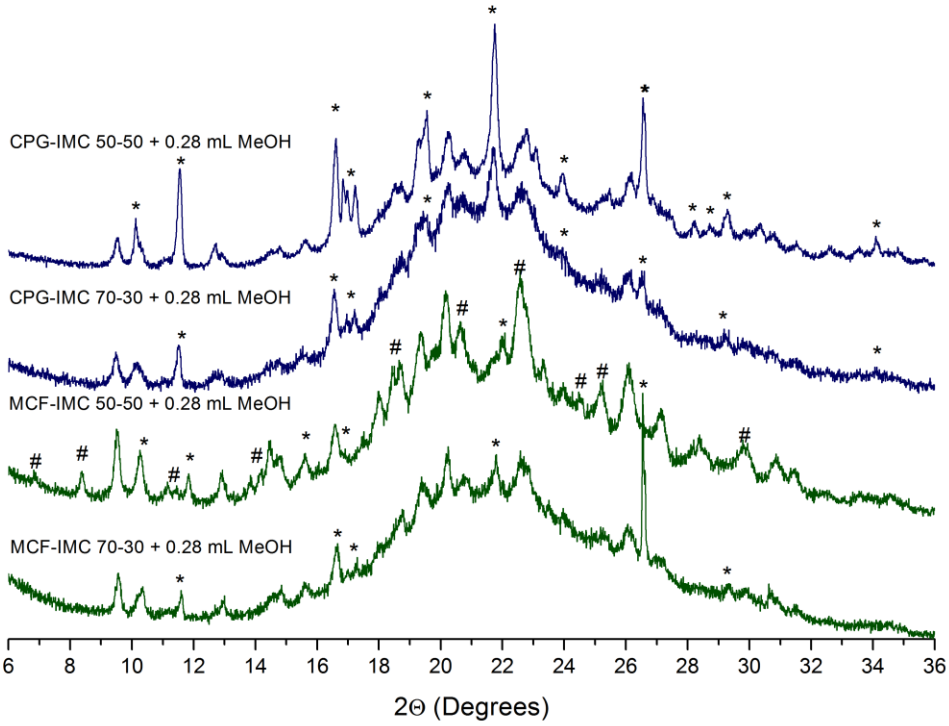

Figure S6.2. PXRD patterns of IMC loaded into MCF and CPG host from the melt at concentrations of 30 and 50 wt. % after addition of methanol (peaks showing the presence of γ-IMC are labelled with asterisks whereas peaks showing α-IMC are labelled with hash marks).

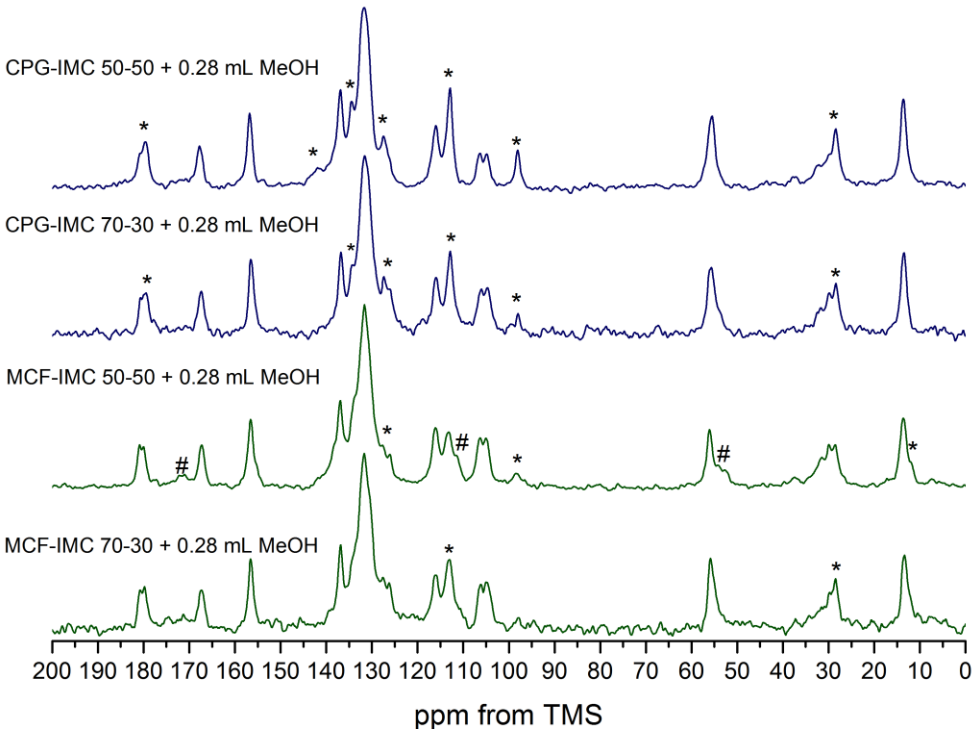

Figure S6.3. ^{1}H-^{13}C CP-MAS solid-state NMR spectra of MCF and CPG hosts loaded with molten IMC at concentrations of 30 and 50 wt. % after addition of methanol (peaks showing the presence of γ-IMC are labelled with asterisks whereas peaks showing α-IMC are labelled with hash marks).

S7. Impact of the volume of the loading solution on the deposition of the drug on the external surface of the material.

To investigate the impact of the volume of the loading solution added to the material on the final composition of the loaded hosts, we used the CPG host and loaded it with the volume equal to *ca*. 0.5 and 0.75 times the total pore volume. As described in the main text, the host loaded with the lower volume of the IMC solution shows only small traces of the drug loaded outside the pores.

In the case of CPG composites loaded with a higher volume of the loading solution, PXRD traces show the presence of more than one IMC phase, as shown on the CPG 250 mg/mL MeOH example below (Figure S7.1).

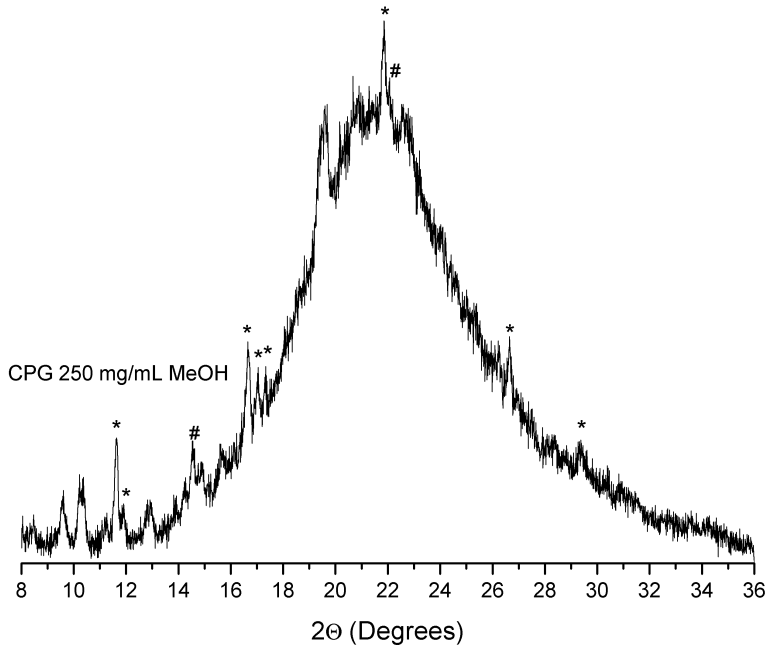

Figure S7.1. PXRD pattern of the CPG material loaded with IMC using the IW method and the higher volume of loading solution. Asterisks and hash marks indicate peaks of the γ- and α-forms, respectively.

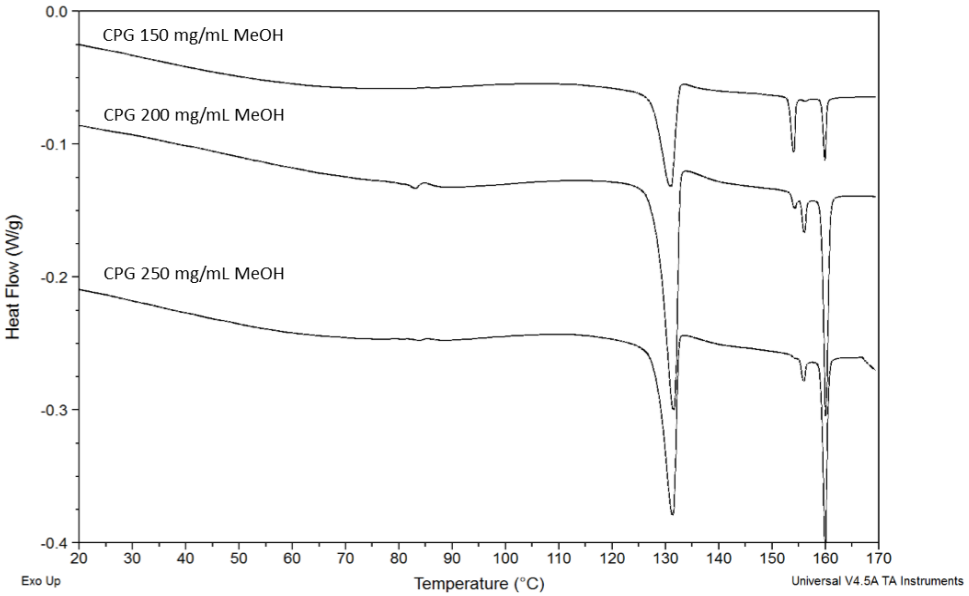

Figure S7.2. DSC thermograms of the CPG host loaded with IMC using the IW method with the higher volume (0.75 mL/g) of loading solution.

Table S7.1. Thermal parameters of CPG hosts loaded using the IW method from methanol with 0.75 mL/g volume of loading solution.

Host-guest composite	Melting onset (°C)	Melting peak (°C)
CPG 150 mg/mL MeOH,	127.3	131.0
	153.1	154.1
	159.3	159.9
CPG 200 mg/mL MeOH	128.1	131.6
	153.6	154.2
	155.4	156.0
	159.3	160.0
CPG 250 mg/mL MeOH	128.1	131.6
	159.2	155.9
	155.2	160.1

DSC analysis of the CPG composites loaded using the IW method with the larger volume of the loading solution demonstrates melting peaks of all three IMC polymorphs. The melting peak of form V shows broadening and a decrease of the melting onset temperature in comparison to the bulk phase (Table S7.1.). Furthermore, additional thermal events are observed: first, at *ca*. 85°C prior to the melting of form V (desolvation of the methanol solvate), followed by a second small exotherm (recrystallization, Figure S7.2.).

S8. Nitrogen adsorption-desorption isotherms of MCF material loading using incipient wetness method.

Nitrogen adsorption-desorption isotherms show decrease of total pores volume of loaded materials. Composite loaded with highest concentration of IMC in methanol (250 mg/mL) shows higher pore volume than host loaded with 200 mg/mL indicating possible loading of IMC outside the pores of the silica scaffold.

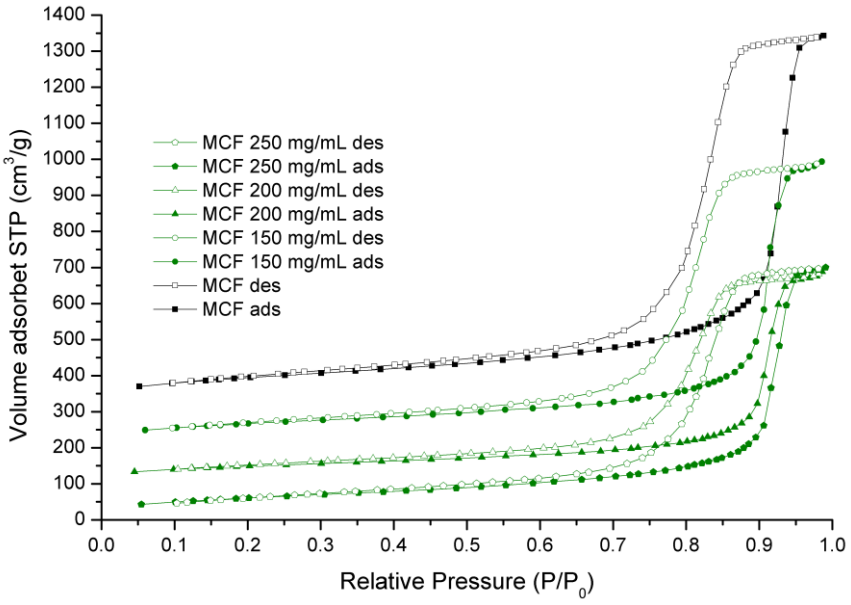

Figure S8.1. Nitrogen adsorption-desorption isotherms of MCF host loaded with IMC using incipient wetness method from methanol at different concentrations of loading solution. The isotherms are offset by 100 cm^3/g.

Reference

1. E. Skorupska, A. Jeziorna, P. Paluch and M. J. Potrzebowski, *Molecular pharmaceutics*, 2014, 11, 1512-1519.