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ARTICLE

# Using Hansen solubility parameters to study the encapsulation of caffeine in MOFs

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Hansen solubility parameters (HSP) have found their greatest use in the evaluation of solvent-polymer chemical interactions. Given their great interest in the scientific community, host-guest interactions in metal-organic frameworks (MOFs), with organic and inorganic moieties, could benefit from a HSP approach. In this work we have initiated the application of HSP to the study of caffeine encapsulation in MOFs ZIF-8 and NH2-MIL-88B(Fe). However, the availability of HSP for MOFs is near zero. As a first step to evaluating the potential of HSP for rational design we have made the simplifying assumption that the HSP distance of the caffeine-ligand interaction (i.e. ignoring the metal and the MOF structure) dominates the ability to form a MOF host-guest system. Although much work remains to be done, the first indications are that this approach has much potential.

## Introduction

Encapsulation is a process in which an active material or guest is entrapped within another material or system known also as host, carrier or encapsulant.[1] Although there is strong modern interest in both industry and academia, the concept is not so new. This technique was used in the 50s when capsules containing dyes were incorporated into paper for copying purposes and replaced carbon paper.[2] Besides, the food industry has been using encapsulation for over 60 years as a way to protect the active material from environment degradation.[3] Interest in encapsulation techniques remains high due to the numerous advantages that it provides, among others:

- Thermal enhancement. Encapsulation may enhance the thermal stability of the encapsulated substance, an important effect in some process in which the working temperature is near the degradation temperature of the additive.[4]
- Chemical protection. This aspect is very useful in the food industry, above all in the encapsulation of lipid ingredients, where this method prevents their oxidation and therefore reduces undesirable flavors and odors.[5]
- Controlled release. One important problem of the pharmaceutical industry is how to control the release of medication into the body to maximize its efficacy. Encapsulation provides such controlled release, increasing patient comfort and compliance.[6]
- Compatibility improvement. Nowadays, most drugs used in pharmaceutical industry are poorly water-soluble, which is a problem for the absorption in the body, because first the drug must be dissolved in the gastrointestinal fluids. A solution to this problem is the encapsulation into other material that improves the drug dissolution rate.[7]
- Homogeneous catalyst heterogenization. Host-guest interactions have use in catalysis to heterogenize homogeneous catalysts such as metal complexes that once encapsulated in a porous inorganic matrix (e.g. a zeolite) can be handled as a common solid catalyst.[8]

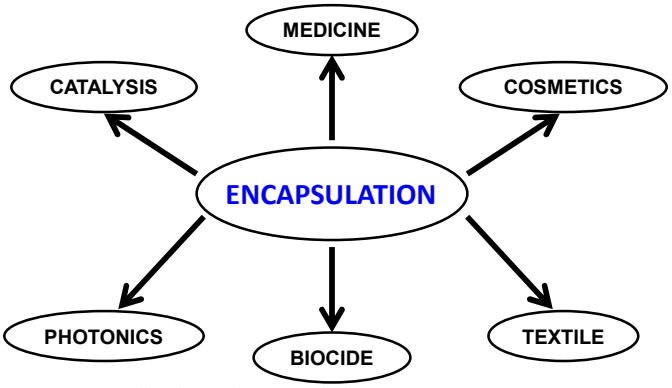


**Figure 1.** Applications of encapsulation.

Porous materials allow the encapsulation of a wide range of chemical compounds thanks to their high specific surface area and tunable micro- or mesoporosity. Some examples of these materials are porous silicas[9] and zeolites.[10] In this context, metal-organic frameworks (MOFs) are a new class of porous materials that combine the properties of organic and inorganic substances,[11] with remarkable features linked to their regular crystallinity and

permanent porosity. MOFs are porous materials formed by the coordination of metal ions or clusters with organic ligands to form 1D, 2D and 3D crystal lattices. These materials are characterized by having large pore volumes and the highest surface areas known to date.[12] Another important characteristic that makes MOFs so attractive is the possibility to modify the chemical functionality and the shape and pore size changing the connectivity of the metal ion or cluster and the nature of the organic ligands.[13]

As said, encapsulation in porous materials applies to a wide range of fields (Figure 1). In catalysis, for example, zeolites have been used as a support for complexes of Co(II), Cu(II) and Zn(II) giving rise to catalysts for the phenol hydroxylation,[14] while cobalt encapsulated into ordered mesoporous silica SBA-15 has been applied to the selective oxidation of cyclohexene.[15] Silica microparticles have been used to encapsulate and control the release of biocides in wood paints.[16] Vitamin E, known for its antioxidants properties, has been encapsulated in zeolite Y in order to obtain special fibers of polyamide.[17] Dyes have been encapsulated into zeolite L searching for artificial photonic antenna systems.[18] Nevertheless, the encapsulation field that nowadays attracts more attention is medicine, where there are a number of reviews that summarize the use of silicas[19] and MOFs[20] for this purpose.

In the case of drug encapsulation, the substance most used as a model molecule is caffeine. The interest in caffeine can be divided into two kinds. The first is related to the chemical field and the other to health. First of all, caffeine is modestly soluble in water (its solubility is comparable to that in acetone but ten times lower than that in aniline), which is very useful during the encapsulation experiment, simplifying the experiments and allowing the use of ecofriendly solvents. The other interesting chemical property of caffeine deals with its amphiphilic nature, which may help the creation of chemical interactions with both organic and inorganic moieties in case of MOFs. Moreover, caffeine is used as an active drug in both cosmetics and pharmaceuticals. Caffeine is a liporeductor,[21] it has positive effects on psychological systems,[22] analgesic properties,[23] etc.

Hansen solubility parameters (HSP) have classically been applied to the evaluation of solvent-polymer chemical interactions[24] but also to study barrier properties and chemical resistance of protective clothing,[24] prediction of cytotoxic drug interactions with DNA[25], optimization of the extraction of bioactive compounds from biomass with subcritical water,[26] identification of an alternative, less toxic solvent used in a microencapsulation process,[27] and preparation of stable dispersions of $TiO_2$ and hydroxyapatite nanoparticles in organic solvents,[28] among other prominent examples. Regarding the application of HSP to metal-organic framework (MOF) materials, to the best of our knowledge, there is only a single report dealing with the formation of composites between MOF HKUST-1 (with 5 wt% loading) and poly(L-lactic acid) (PLA).[29] In this case, the solubility distance parameter (see below) between PLA and MOF was found to be 5.9, judged by the authors relatively high, thus explaining the poor affinity between MOF particles and PLA observed by SEM. As suggested by the authors the filler was not able to establish dipolar and hydrogen bonding interactions as happened when the more hydrophilic zeolite NaA was used as filler.[30] Thanks to HSP the basic principle of "like dissolves like", i.e. the qualitative idea behind most of previous examples, realized in numbers easy to handle and compare, as will be shown along the next narrative. Nevertheless, a limitation of HSP application is related to insufficient availability of HSP data for systems of interest (MOFs in particular). Table 1 summarizes the examples of HSP applications described above.

**Table 1**. HSP applications

| Example of application | Reference |
|---|---|
| Evaluation of solvent-polymer interactions | Hansen[24] |
| Study of barrier properties and chemical resistance of protective clothing | Hansen[24] |
| Prediction of cytotoxic drug interactions with DNA | Hansen[25] |
| Extraction of bioactive compounds from biomass with subcritical water | Srinivas et al.[26] |
| Microencapsulation of therapeutic proteins | Bordes et al.[27] |
| Preparation of stable dispersions of inorganic nanoparticles in organic solvents | Wieneke et al.[28] |
| Formation of composites between MOF HKUST-1 and poly(L-lactic acid) | Elangovan et al.[29] |

In this work we propose the application of HSP to evaluate host-guest interactions involving MOFs and different compounds. In particular, the residual solvents and ligands after certain MOF synthesis (those using 2-methylimidazole and $NH_2$-benzenedicarboxylate ligands) and the one-step encapsulation of caffeine into ZIF-8[31] and $NH_2$-MIL-88B(Fe)[4] will be revisited in light of HSP. Finally, Figure 2 shows the structures of MOFs $NH_2$-MIL-88B, ZIF-8 and HKUST-1, whose HSP parameters will be discussed below.

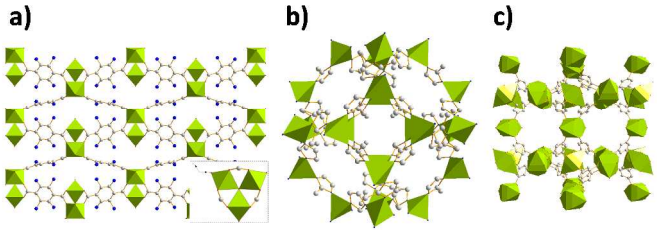


**Figure 2.** (a) Building blocks of $NH_2$-MIL-88B (Fe) with the trimers of $\mu_3$-O-bridged $FeO_6$ octahedra (see inset for detail) in green; (b) building blocks of ZIF-8 with the $ZnN_4$ tetahedra in green; and (c) building blocks of HKUST-1 with dimmers of $CuO_4$. Oxygen, nitrogen and carbon atoms are in red, blue and white, respectively. These structures were made with Diamond 3.2. using the corresponding CIF files.[32-34]

## Application of Hansen solubility parameters to the encapsulation of caffeine

The host-guest interactions established between MOF and solvent or ligand can be of different nature, i.e. dispersion, polar or hydrogen bonds. In case of solvents these interactions can be discussed in terms of the so-called Hansen solubility parameters (HSP).[24] These parameters ($\delta_D$, $\delta_P$ and $\delta_H$ for dispersion or London interaction, polar interaction and hydrogen bonds, respectively) are given in Table 2 for some selected solvents, common in the synthesis and activation of MOFs. However, besides these parameters which account for the possible solvent interactions with MOF, guest molecular dimensions and MOF pore sizes have to be considered, even though they may

not be as important as in the case of rigid materials such as zeolites and other microporous silicates due to the intrinsic flexibility of MOFs revealed as breathing[35] and gate-opening[36] phenomena. In any event, the interaction between two substances 1 (in this case the solvent or the ligand used to synthesize the MOF) and 2 (the MOF itself) can be obtained calculating the parameter Ra[24] with the following equation (1):

$$Ra^2 = 4(\delta_{D1} - \delta_{D2})^2 + (\delta_{P1} - \delta_{P2})^2 + (\delta_{D1} - \delta_{D2})^2 \quad (1)$$

In our case $\delta_{D1}$, $\delta_{P1}$ and $\delta_{H1}$ and $\delta_{D2}$, $\delta_{P2}$ and $\delta_{H2}$ sets of parameters correspond to MOF synthesis solvent, MOF ligand or caffeine (when this molecule is added to the synthesis solution, as shown below), and MOF ligand, respectively. Since HSP are not available for MOFs (with the exception of HKUST-1[29]) we have simplified the approach for the forthcoming discussion by attributing to the ligand the solubility properties of the MOF, or, equivalently, by making the assumption that the solvent/ligand and encapsulant/ligand interactions dominate the encapsulation process. This approach is similar to that established by Hansen when used $\delta_D$, $\delta_P$ and $\delta_H$ of DNA base segments (i.e. guanine, cytosine, adenine and thymine) to estimate affinity between cytotoxic drugs and DNA itself.[25]

**Table 2**. Hansen solubility parameters (HSP) for some common solvents in the synthesis and activation of MOFs, some common ligands, MOF HKUST-1 and caffeine (CAF). THF, DMF, 2MI, BDC, $NH_2$-BDC and BTC correspond to tetrahydrofurane, dimethylformamide, 2-methylimidazole, benzene-1,4-dicarboxylic acid, 2-aminobenzene-1,4-dicarboxylic acid and benzene-1,3,5-tricarboxylic acid, respectively. Distances between materials obtained from Ra calculations with equation (1). In general, HSP values were obtained from literature (solvents, ligands and caffeine from,[37] and HKUST-1 from[29]) with the exception of HSPs for 2MI, BDC, $NH_2$-BDC and BTC, calculated using Y-MB technique with the commercial package Hansen Solubility Parameters in Practice.[38]

| | HSP [$MPa^{0.5}$] | | | Ra | | | | |
|---|---|---|---|---|---|---|---|---|
| | $\delta_D$ | $\delta_P$ | $\delta_H$ | 2MI | BDC | $NH_2$-BDC | BTC | HKUST-1 |
| Chloroform | 17.8 | 3.1 | 5.7 | 8.8 | 9.3 | 13.4 | 13.8 | 8.4 |
| THF | 16.8 | 5.7 | 8.0 | 6.6 | 8.1 | 12.0 | 12.0 | 5.5 |
| Ethanol | 15.8 | 8.8 | 19.4 | 11.6 | 10.8 | 10.4 | 9.3 | 9.7 |
| Methanol | 15.1 | 12.3 | 22.3 | 14.7 | 14.6 | 13.4 | 12.1 | 13.1 |
| DMF | 17.4 | 13.7 | 11.3 | 4.4 | 8.5 | 9.9 | 9.2 | 4.0 |
| Water | 15.1 | 20.4 | 16.5 | 14.0 | 16.9 | 16.4 | 15.2 | 13.2 |
| 2MI | 18.8 | 10.7 | 9.7 | 0 | 5.3 | 8.1 | 8.0 | 2.2 |
| BDC | 20.0 | 7.2 | 12.8 | 5.3 | 0 | 4.2 | 4.7 | 5.4 |
| $NH_2$-BDC | 20.8 | 8.6 | 16.4 | 8.1 | 4.2 | 0 | 1.4 | 8.2 |
| BTC | 20.3 | 9.3 | 17.0 | 8.0 | 2.9 | 1.4 | 0 | 7.9 |
| HKUST-1 | 17.9 | 9.9 | 10.7 | 2.2 | 5.4 | 8.2 | 7.9 | 0 |
| Caffeine | 19.5 | 10.1 | 13.0 | 3.6 | 3.1 | 4.5 | 4.4 | 3.9 |

Table 2 shows HSP for common solvents applied in the synthesis (THF, methanol, DMF, water) and activation (chloroform, methanol) of MOFs. Ligands used for the synthesis of some of the most typical and studied MOFs are also included in this table: 2-methylimidazolate (2MI, for ZIF-8[33]), benzenedicarboxylate (BDC, used for MOF-5,[39] MIL-53,[40] MIL-101,[41] UiO-66,[42] etc.), $NH_2$-benzenedicarboxylate ($NH_2$-BDC, used for $NH_2$-MIL-53,[43] $NH_2$-MIL-101,[44] etc.) and benzenetricarboxylate (BTC, for HKUST-1,[34] MIL-96,[45] etc.). Although "large" HSP distances imply poorer interaction there are no general rules for specifying a minimum Ra for strong interactions. In case of polymer-solvent, Ra values below about 7.5 meet the Flory-Huggins criterion for compatibility[37] which at least gives us a starting scale for looking at MOF Ra values. The relative discrepancy between BTC-HKUST-1 pair (Ra in Table 2 is 7.9), is basically due to the fact that estimated value for the BTC $\delta_H$ (17.0) is higher than expected because most probably all the three OH groups in BTC would not be available for H-bonding, as the experimental HKUST-1 $\delta_H$ (10.7) obtained by Auras et al.[29] suggests.

Table 2 confirms that common ligands are not very soluble in usual solvents; however, chloroform, THF and especially DMF are preferred over small alcohols and water. This is particularly true when, for instance, MIL-53(Al) was synthesized in water and the BDC ligand remained occluded in the MOF microporosity[46] so that the activation of the material was achieved by either calcination at about 330 ºC[46] or DMF extraction at 70 ºC with final drying at 150 ºC.[47] The conclusion is that MIL-53(Al) would prefer the ligand BDC and the activation solvent DMF more than the water used as synthesis solvent.

An even more interesting conclusion from Table 2 is that caffeine exhibits good interaction with all the four ligands (2MI, BDC, $NH_2$-BDC and BTC, see Figure 3) with Ra values in the 3.1-4.5 range. Furthermore, the caffeine-ligand interaction predictions are better than those corresponding to any solvent-ligand pairs. This is in agreement with the fact that caffeine has been encapsulated in one-step (i.e. adding caffeine directly to the synthesis solution of the MOF) in MOFs ZIF-8[31] and $NH_2$-MIL-88B(Fe)[4] including 2MI and $NH_2$-BDC ligands in their respective formulations. However, even using the same ligand to synthesize both MIL-53(Fe) and UiO-66(Zr) MOFs, the different structure and metal center may give rise to different amounts of encapsulated caffeine depending on the working solvent (multi-step encapsulation, see below):[48] 2.2 and 29.3 wt% for MIL-53(Fe) in water and ethanol, and 22.4 and 2.5 wt% for UiO-66(Zr) in water and ethanol as well. In the case of MIL-53(Fe) the presence of ethanol would lead to a full pore opening form of the MOF favoring caffeine insertion, while in the case of UiO-66(Zr) ethanol could be coordinated to the zirconium unsaturated Lewis sites decreasing the accessibility of caffeine.[48] It is obvious from this discussion that the availability of HSP for MOFs of interest would open a new world of drug-MOF encapsulation not only in one-step but also through the conventional methodology of synthesis-activation-encapsulation (multi-step encapsulation).[49] The comparison of both one-step and multi-step methodologies will be done in a next section.

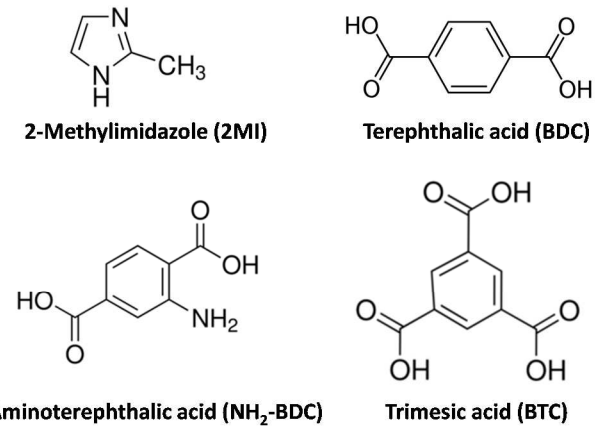


**Figure 3.** Chemical structures of 2-methylimidazole (2MI), benzene-1,4-dicarboxylic acid (BDC), $NH_2$- 2-aminobenzene-1,4-dicarboxylic acid ($NH_2$-BDC) and benzene-1,3,5-tricarboxylic acid (BTC).

A comment must be done to the fact that the HSP of caffeine generally used in the HSP community is that estimated many years ago by Hansen to be [19.5, 10.1, 13.0].[37] The most powerful recent estimation tool using automated functional group contributions within the HSPiP package gives [20.0, 12.7, 8.3].[38] Furthermore, it is fair to point out that HSP theory confidently predicts that caffeine will be insoluble in water; the actual modest solubility in water is variously explained by hydrogen bonding and complex formation.

**Table 3**. Hansen solubility parameters (HSP) for some common polymers and materials, MOF HKUST-1 and caffeine (CAF). Distances from caffeine obtained from Ra calculations with equation (1). HSP values obtained from literature (polymers and caffeine from,[37] PLA and HKUST-1 from[29], and $TiO_2$ and hydroxyapatite from[28])

| | HSP [$MPa^{0.5}$] | | | |
|---|---|---|---|---|
| Materials | $\delta_D$ | $\delta_P$ | $\delta_H$ | Ra |
| Polypropylene (PP) | 18.0 | 0 | 1.0 | 16.0 |
| Polyethylene (PE) | 16.9 | 0.8 | 2.8 | 14.8 |
| Nylon 66 (N66) | 16.0 | 11.0 | 24.0 | 13.1 |
| Teflon (PTFE) | 17.1 | 8.1 | 1.3 | 12.8 |
| Polystyrene (PS) | 22.3 | 5.8 | 4.3 | 11.2 |
| Polyethylene terephthalate (PET) | 18.2 | 6.4 | 6.6 | 7.8 |
| Polylactic acid (PLA) | 18.6 | 9.9 | 6.0 | 7.2 |
| Polysuphone (PSF) | 19.7 | 8.3 | 8.3 | 5.0 |
| Cellulose acetate (CA) | 18.2 | 12.4 | 10.8 | 4.1 |
| HKUST-1 | 17.9 | 9.9 | 10.7 | 3.9 |
| $TiO_2$ | 17.5 | 12.7 | 8.9 | 6.3 |
| Hydroxyapatite | 17.6 | 14.0 | 9.4 | 6.5 |
| Caffeine | 19.5 | 10.1 | 13.0 | 0 |

Indeed, HSP for drugs and MOFs, or in general polymers or porous inorganic materials[17] able to act as capsules, would help to select the best encapsulating material for every drug, rationalizing part of the host-guest practical approach. In fact Table 3 lists a series of polymeric materials, from polypropylene to cellulose acetate which are compared with caffeine. Thus caffeine-polymer distances (Ra values) were calculated and the polymers arranged from highest to lowest values. A quick general behavior can be drawn from the Ra calculations, hydrophobic polymers (PP, PE, N66, PTFE, PS) would not be suitable for caffeine interaction, while hydrophilic polymers (PLA, PSF, CA) could be used as systems in which caffeine would be "dissolved". Moreover, HKUST-1 presents a Ra value (3.9) similar to that of the best polymer CA (4.1). This predicts good caffeine-HKUST-1 interaction and the encapsulation would be in addition enhanced by the microporosity of the MOF (BET surface area of 692 $m^2/g$, pore size of 1 nm[34]). As mentioned above, the availability of HSP for MOFs is almost zero. The same can be stated for traditional materials such as amorphous silica and zeolites.[50] This is why inorganic $TiO_2$ and hydroxyapatite particles, for which data are available,[28] were added, with relatively good result in terms of Ra calculation with caffeine, to Table 3. It is worth emphasizing that different versions of the "same" material are expected to show different HSP values because the measured values will depend strongly on the chemical nature of the surface. For example, the HSP of "silica" will depend on the percentage of Si-OH groups at the surface, on partitioning of additives to the surface and on the porosity and, therefore, the relative amounts of "surface" and "interior". In addition, some of these surface properties may change with particle size suggesting that HSP for nano-sized and micro-sized particles of the same material would present relatively different values. This means that access to high-throughput measurements of the HSP of such systems will be important for progress in this field.

## Solvent and ligand encapsulation as a precedent of one-step encapsulation

During the synthesis of MOFs both solvent and ligand molecules can be converted into guest species in the as-synthesized MOF. This means that it would be possible to make a relation between HSP and the synthesis of MOFs considering the possibility of having as guest in the as made MOF solvent, ligand or other molecule (e.g. caffeine in its one-step encapsulation) present in the synthesis solution. Thus a small Ra between ligand and any other species (e.g. solvent) would be expected to produce a good interaction. This is obviously a simplification that takes into account neither the nature of the metal cluster nor the structure of the MOF (porosity, flexibility, breathing[51]). In any event, after the synthesis certain molecules (solvent, ligand, etc.) may become guest molecules into a MOF, as there is a good interaction between them and appropriate matching between guest molecular size and host porosity.

As shown in Table 4, water (coming from the hydrated zinc salt) and DMF remain encapsulated in the ZIF-8 structure after its synthesis in DMF. In case of water as solvent, ligand (2MI) can remain as well. When the solvent is methanol or a mixture of water and methanol, ZIF-8 is obtained as an activated porous solid. Ra distances for 2MI (as mentioned above, somehow representing ZIF-8) and DMF, methanol and water are 4.4, 14.7 and 14.0 (Table 2), respectively. This is in agreement with the fact that DMF is retained by ZIF-8

after synthesis. The ligand 2MI would remain in the solid when using water and no ethanol as synthesis solvent, this is explained by a better preference of the ligand for the MOF than for water. When caffeine is incorporated into the molar composition it is retained by ZIF-8 better than any other molecule due to the good chemical compatibility between caffeine and 2MI (Ra 3.6, see Table 2).

In contrast to the ZIF-8 synthesis, in the case of $NH_2$-MIL-88B(Fe) (Table 5), a MOF where caffeine was also encapsulated in one-step,[4] there is not a clear relationship between the solvent used in the synthesis and the guest molecule retained by the structure, in general water coming from the hydrated iron salt, and DMF as usual solvent or cosolvent. In terms of HSP, the one step encapsulation of caffeine would be favored given the small Ra between caffeine and the organic ligand $NH_2$-BDC (4.5, see Table 2), explaining the high loading of caffeine in the MOF (38.5%).

**Table 4**. Synthesis of ZIF-8 under different conditions.

| Molar composition | Loading of guest molecules (wt%) | Reference |
|---|---|---|
| $Zn^{2+}$:2MI:DMF= 1:0.91:290 | ($H_2O$, DMF) (28.3) | Park et al.[33] |
| $Zn^{2+}$:2MI:MeOH= 1:8:700 | - | Cravillon et al.[52] |
| $Zn^{2+}$:2MI:$H_2O$= 1:70:1238 | ($H_2O$, 2MI) (11.8) | Pan et al.[53] |
| $Zn^{2+}$:2MI:MeOH:$H_2O$= 0.32:3.84:100:56.7 | - | Liedana et al.[31] |
| $Zn^{2+}$:2MI:MeOH:$H_2O$: CAF= 0.32:3.84:100:56.7:0.31 | Solvent (11), CAF (25) | Liedana et al.[31] |

**Table 5**. Synthesis of $NH_2$-MIL-88B(Fe) under different conditions.

| Molar composition | Loading of guest molecules (wt%) | Reference |
|---|---|---|
| $Fe^{3+}$:$NH_2$-BDC:DMF= 2:1:195 | $H_2O$ (16.8) | Bauer et al.[32] |
| $Fe^{3+}$:$NH_2$-BDC:$H_2O$:AcH: surfactant= 1:0.5:1255:8:0.02 | $H_2O$ (3), surfactant (10) | Pham et al.[54] |
| $Fe^{3+}$:$NH_2$-BDC:DMF= 1:1:282 | (DMF, $NH_2$-BDC) (21.6) | Ma et al.[55] |
| $Fe^{3+}$:$NH_2$-BDC:DMF:$H_2O$= 1:1:52:52 | ($H_2O$, DMF) (15) | Paseta et al.[56] |
| $Fe^{3+}$:$NH_2$-BDC:$H_2O$:CAF= 2:1.5:4167:1.5 | CAF (38.5) | Liedana et al.[4] |

## One-step encapsulation (OSE) versus multi-step encapsulation (MSE)

To encapsulate caffeine or another drug into a porous material there are two possible methodologies. The one-step encapsulation (OSE) corresponds to build the MOF around the guest-molecule which is chosen to encapsulate (Figure 4a). Generally, this experiment consists in putting all reagents and the additive in solvent and stirring and heating for a short time.[31] The other method is the conventional multi-step encapsulation (MSE) (Figure 4b).[49]

At least for caffeine, OSE[4, 31] is superior to the conventional MSE[48,57] which requires: 1) the MOF host synthesis, 2) the subsequent activation of the host, and 3) the encapsulation itself (i.e. the liquid phase adsorption) of the drug to reach at the end a similar value of encapsulated guest. Thus, at least for caffeine, both processes may lead to similar quantitative results.[31] The activation stage is not always an easy process, and a certain amount of solvent may remain in the material affecting its performance. Besides, caffeine was not lost during the procedure and could be recovered as the other compounds used in OSE or MSE methods. In general, MOFs can be prepared in milder conditions than other materials such as zeolites making more likely that expensive and sensitive drugs can survive the encapsulation process.

So far, the caffeine OSE has been applied to MOFs ZIF-8[31] and $NH_2$-MIL-88B(Fe).[4] The one-step encapsulation of caffeine in ZIF-8 produced high guest loading, i.e. ca. 28 wt% in only 2 h at 25 ºC, when the multi-step methodology required at least 3 days working at 80 ºC to achieve similar encapsulated amount. In the case of $NH_2$-MIL-88B(Fe) the caffeine loading was 38.5 wt%. It is worth mentioning that the absence of caffeine from the synthesis solution led to a different framework ($NH_2$-MIL-53(Fe)). Thus caffeine played the role of a structure directing agent or template. In both cases, controlled release of caffeine in both water and PBS (phosphate-buffered saline) was achieved.[4, 31]

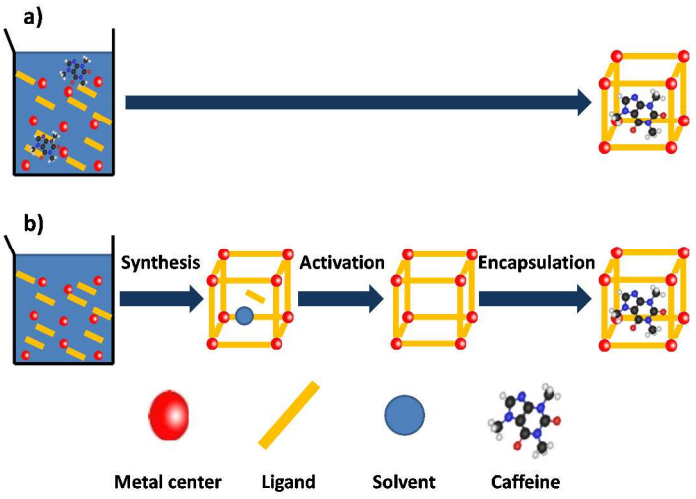


**Figure 4**. Encapsulation of caffeine in MOFs: a) one-step encapsulation (OSE); b) multi-step encapsulation (MSE).

Although there are potentially thousands of drugs to be encapsulated, the interest for caffeine is not only related to its properties but to its role as model substance[57] (as ibuprofen[58] is often studied by many other researchers) used several times to evaluate different materials and strategies.

Table 6 summarizes the advantages and disadvantages of the two encapsulation strategies. OSE is simpler than MSE, not requiring of activation, since caffeine would be favored in the synthesis conditions over solvents and ligands. Of course a low guest chemical stability may limit the applicability of OSE but most MOFs are prepared in milder conditions or their synthesis routes can be adapted by searching for low temperature reactions in presence of environmentally friendly solvents. In both strategies of encapsulation excess reactants would be reused giving rise to a simple and scalable process. From the point of view of the industrial operation, it would

be more difficult to scale up three different stages than a single one. In any event, it is expected that HSP can facilitate a more rational optimization approach than the trial and error system. First, HSP can be used to find a solvent (or solvent blend) with similar solubility properties (a solvent like DMF is unusably toxic in the context of drug delivery). Second, there will be a balance between solvents that are too good (they will preferentially be encapsulated in the MOF) and those that are too bad (insufficient solubility to allow the process to take place). There is an interesting parallel with the use of HSP in the development of low molecular weight organo-gelators (MOGS) which similarly must be in a narrow optimal zone.[59] Another field of possible application of HSP would be related to the development of mixed matrix membranes (MMMs),[60] in which a porous filler (e.g. silica, zeolite, MOF, etc.) is dispersed into a membrane polymer to enhance the membrane performance in terms of permeability and separation selectivity. In these MMMs the filler-polymer interaction is of paramount importance to achieve homogeneous filler dispersion and enhanced performance. The availability of HSP for fillers and polymers of interest would be of practical interest to obtain optimum MMMs.

**Table 6**. Main differences between one-step (OSE) and multi-step encapsulation (MSE)

| Methodology | Advantages | Disadvantages |
|---|---|---|
| OSE | Simplicity<br>No need of activation<br>Template effect | Synthesis conditions limited to guest stability<br>Optimization for every guest |
| MSE | Middle conditions for encapsulation | Complexity: synthesis-activation-encapsulation |

As mentioned above, the caffeine-ligand interaction predictions in terms of HPS were better than those corresponding to any solvent-ligand pairs. This points to the fact that during the one-step encapsulation process of caffeine this molecule can be favored over solvent molecules even though these are smaller.

## Conclusion

Even though for the same ligand the MOF texture, structure and composition (different metal) affect drug encapsulation in MOFs, Hansen solubility parameters (HSP) appear as a new tool which may help to predict the best encapsulating material and solvent system for a target drug, helping to convert the traditional trial and error approach into a rational one to be applied to a wider library of possible hosts and guests.

The availability of HSP for MOFs is almost zero, so it is important to measure values for common MOFs, preferably by using high-throughput techniques that will make such measurements scalable.

In case of having HSP for MOFs their especial features (breathing and pore opening maximum flexibility effects; richness of isostructures, i.e. phases having different chemical composition but the same crystallographic structure), predictions should be carefully considered in combination with existing drug encapsulation experimental results.

In the particular case of the one-step encapsulation of caffeine, the caffeine-ligand interaction predictions in terms of HPS were better than those corresponding to any solvent-ligand pairs. This is in agreement with the fact than caffeine is favored over solvent molecules, even though these are smaller, and is efficiently encapsulated.

Finally, beyond the classical HSP applications (mainly dealing with solvent-polymer chemical interactions) and besides the new use of HSP proposed here for caffeine encapsulation in MOFs, HSP could help the development of different systems in which the interaction of relatively heterogeneous materials to be combined (as is the case of low molecular weight organo-gelators and mixed matrix membranes) would have to be taken into account. In the context of this paper, HSP could as well help to predict the release in the body of the drugs encapsulated in a certain porous material. In any event HSP parameters for the possible involved substances would need to become available.

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## Notes and references

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1 A. Madene, M. Jacquot, J. Scher and S. Desobry, *Int. J. Food Sci. Technol.,* 2006, **41**, 1-21.

2 E. Campos, J. Branquinho, A. S. Carreira, A. Carvalho, P. Coimbra, P. Ferreira and M. H. Gil, *Eur. Polym. J.,* 2013, **49**, 2005-2021.

3 J. Juan-Alcaniz, J. Gascon and F. Kapteijn, *J. Mater. Chem.,* 2012, **22**, 10102-10118.

4 N. Liédana, P. Lozano, A. Galve, C. Téllez and J. Coronas, *J. Mater. Chem. B,* 2014, **2**, 1144-1151.

5 A. Lopez-Rubio, R. Gavara and J. A. Lagaron, *Trends Food Sci. Technol.,* 2006, **17**, 567-575.

6 P. Srikanth, N. Raju, S. W. Raja and S. B. Raj, *Int. J. Adv. Pham.,* 2013, **3**, 51-58.

7 K. Moribe, T. Makishima, K. Higashi, N. Liu, W. Limwikrant, W. Ding, M. Masuda, T. Shimizu and K. Yamamoto, *Int. J. Pharm.,* 2014, **469**, 190-196.

8 G. Li, L. Chen, J. Bao, T. Li and F. Mei, *Appl. Catal. A: Gen.,* 2008, **346**, 134-139.

9 N. Liédana, E. Marín, C. Téllez and J. Coronas, *Chem. Eng. J.,* 2013, **223**, 714-721.

10 J. Muñoz-Pallares, A. Corma, J. Primo, E. Primo-Yufera, *J. Agric. Food. Chem.,* 2001, **49**, 4801-4807.

11 R. J. Kuppler, D. J. Timmons, Q. Fang, J. Li, T. A. Makal, M. D. Young, D. Yuan, D. Zhao, W. Zhuang and H. Zhou, *Coord. Chem. Rev.,* 2009, **253**, 3042-3066.

12 J. L. C. Rowsell and O. M. Yaghi, *Angew. Chem.-Int. Ed.,* 2005, **44**, 4670-4679.
13 G. Férey, *Chem Soc. Rew.,* 2008, **37**, 191-214.
14 B. P. Nethravathi, K. R. Reddy and K. N. Mahendra, *J. Porous Mater.,* 2014, **21**, 285-291.
15 S. S. Reddy, B. D. Raju, A. H. Padmasri, P. K. S. Prakash and K. S. Rama Rao, *Catal. Today,* 2009, **141**, 61-65.
16 G. Sørensen, A. L. Nielsen, M. M. Pedersen, S. Poulsen, H. Nissen, M. Poulsen and S. D. Nygaard, *Prog. Org. Coat.,* 2010, **68**, 299-306.
17 E. Pérez, L. Martín, C. Rubio, J. S. Urieta, E. Piera, M. A. Caballero, C. Téllez and J. Coronas, *Ind. Eng. Chem. Res.,* 2010, **49**, 8495-8500.
18 D. Brühwiler and G. Calzaferri, *Microporous Mesoporous Mater.,* 2004, **72**, 1-23.
19 C. Barbé, J. Bartlett, L. Kong, K. Finnie, H. Q. Lin, M. Larkin, S. Calleja, A. Bush and G. Calleja, *Adv. Mater.,* 2004, **16**, 1959-1966.
20 P. Horcajada, C. Serre, M. Vallet-Regi, M. Sebban, F. Taulelle and G. Ferey, *Angew. Chem.-Int. Ed.,* 2006, **45**, 5974-5978.
21 D. Hexsel, C. Orlandi and D. Zechmeister do Prado, *Dermatol. Surg.,* 2005, **31**, 866-872.
22 M. J. Glade, *Nutrition,* 2010, **26**, 932-938.
23 K. Hagen, K. Thoresen, L. J. Stovner and J. Zwart, *J. Headache Pain,* 2009, **10**, 153-159.
24 C. M. Hansen, *Prog. Org. Coat.,* 2004, **51**, 77-84.
25 C. M. Hansen, *Eur. Polym. J.,* 2008, **44**, 2741-2748.
26 K. Srinivas, J. W. King, J. K. Monrad, L. R. Howard and C. M. Hansen, *J. Food Sci.,* 2009, **74**, E342-E354.
27 C. Bordes, V. Fréville, E. Ruffin, P. Marote, J. Y. Gauvrit, S. Briançon and P. Lantéri, *Int. J. Pharm.,* 2010, **383**, 236-243.
28 J. U. Wieneke, B. Kommob, O. Gaer, I. Prykhodko and M. Ulbricht, *Ind. Eng. Chem. Res.,* 2012, **51**, 327-334.
29 D. Elangovan, U. Nidoni, I. E. Yuzay, S. E. M. Selke and R. Auras, *Ind. Eng. Chem. Res.,* 2011, **50**, 11136-11142.
30 I. E. Yuzay, R. Auras and S. Selke, *J. Appl. Polym. Sci.,* 2010, **115**, 2262-2270.
31 N. Liédana, A. Galve, C. Rubio, C. Téllez and J. Coronas, *ACS Appl. Mater. Interfaces,* 2012, **4**, 5016-5021.
32 S. Bauer, C. Serre, T. Devic, P. Horcajada, J. Marrot, G. Férey and N. Stock, *Inorg. Chem.,* 2008, **47**, 7568-7576.
33 K. S. Park, Z. Ni, A. P. Cote, J. Y. Choi, R. D. Huang, F. J. Uribe-Romo, H. K. Chae, M. O'Keeffe and O. M. Yaghi, *P. Ntl. Acad. Sci. USA,* 2006, **103**, 10186-10191.
34 S. S. Chui, S. M. Lo, J. P. H. Charmant, A. G. Orpen and I. D. Williams, *Science,* 1999, **283**, 1148-1150.
35 B. Seoane, S. Sorribas, A. Mayoral, C. Tellez and J. Coronas, *Microporous Mesoporous Mater.*, 2014, DOI: 10.1016/j.micromeso.2014.10.016.
36 S. A. Moggach, T. D. Bennett and A. K. Cheetham, *Angew. Chem.-Int. Ed.,* 2009, **48**, 7087-7089.
37 C. M. Hansen, *Hansen solubility parameters: a user's handbook*, CRC Press, Boca Raton, 2nd edn., 2007.
38 S. J. Abbott, C. J. Hansen and H. Yamamoto, http://www.hansen-solubility.com, accessed September 2014.
39 H. Li, M. Eddaoudi, M. O'Keeffe and O. M. Yaghi, *Nature,* 1999, **402**, 276-279.
40 C. Serre, F. Millange, C. Thouvenot, M. Nogues, G. Marsolier, D. Louer and G. Ferey, *J. Am. Chem. Soc.,* 2002, **124**, 13519-13526.
41 G. Ferey, C. Mellot-Draznieks, C. Serre, F. Millange, J. Dutour, S. Surble and I. Margiolaki, *Science,* 2005, **309**, 2040-2042.
42 J. H. Cavka, S. Jakobsen, U. Olsbye, N. Guillou, C. Lamberti, S. Bordiga and K. P. Lillerud, *J. Am. Chem. Soc.,* 2008, **130**, 13850-13851.
43 B. Arstad, H. Fjellvåg, K. O. Kongshaug, O. Swang and R. Blom, *Adsorption,* 2008, **14**, 755-762.
44 M. Hartmann and M. Fischer, *Microporous Mesoporous Mater.,* 2012, **164**, 38-43.
45 C. Volkringer and T. Loiseau, *Mater. Res. Bull.,* 2006, **41**, 948-954.
46 T. Loiseau, C. Serre, C. Huguenard, G. Fink, F. Taulelle, M. Henry, T. Bataille and G. Férey, *Chem. A Eur. J.,* 2004, **10**, 1373-1382.
47 E. Haque, N. A. Khan, J. E. Lee and S. H. Jhung, *Chem. A Eur. J.,* 2009, **15**, 11730-11736.
48 D. Cunha, M. Ben Yahia, S. Hall, S. R. Miller, H. Chevreau, E. Elkaïm, G. Maurin, P. Horcajada and C. Serre, *Chem. Mater.,* 2013, **25**, 2767-2776.
49 P. Horcajada, T. Chalati, C. Serre, B. Gillet, C. Sebrie, T. Baati, J. F. Eubank, D. Heurtaux, P. Clayette, C. Kreuz, J. Chang, Y. K. Hwang, V. Marsaud, P. Bories, L. Cynober, S. Gil, G. Ferey, P. Couvreur and R. Gref, *Nat. Mater.,* 2010, **9**, 172-178.
50 J. Coronas, *Chem. Eng. J.,* 2010, **156**, 236-242.
51 G. Ferey and C. Serre, *Chem. Soc. Rev.,* 2009, **38**, 1380-1399.
52 J. Cravillon, S. Munzer, S. J. Lohmeier, A. Feldhoff, K. Huber and M. Wiebcke, *Chem. Mater.,* 2009, **21**, 1410-1412.
53 Y. Pan, Y. Liu, G. Zeng, L. Zhao and Z. Lai, *Chem. Commun.,* 2011, **47**, 2071-2073.
54 M. Pham, G. Vuong, A. Vu and T. Do, *Langmuir,* 2011, **27**, 15261-15267.
55 M. Ma, H. Noei, B. Mienert, J. Niesel, E. Bill, M. Muhler, R. A. Fischer, Y. Wang, U. Schatzschneider and N. Metzler-Nolte, *Chem. A Eur. J.,* 2013, **19**, 6785-6790.
56 L. Paseta, B. Seoane, D. Julve, V. Sebastián, C. Téllez and J. Coronas, *ACS Appl. Mater. Interfaces,* 2013, **5**, 9405-9410.
57 C. Gaudin, D. Cunha, E. Ivanoff, P. Horcajada, G. Chevé, A. Yasri, O. Loget, C. Serre and G. Maurin, *Microporous Mesoporous Mater.,* 2012, **157**, 124-130.
58 P. Horcajada, C. Serre, G. Maurin, N. A. Ramsahye, F. Balas, M. Vallet-Regi, M. Sebban, F. Taulelle and G. Férey, *J. Am. Chem. Soc.,* 2008, 130, 6774-6780.
59 Y. Lan, M. G. Corradini, X. Liu, T. E. May, F. Borondics, R. G. Weiss and M. A. Rogers, *Langmuir,* 2014, (DOI:10.1021/la5008389).
60 H. B. T. Jeazet, C. Staudt and C. Janiak, *Dalton Trans.,* 2012, 41, 14003-14027.