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Capsaicin Entrapment in Metal-Organic Framework Material Derived from γ-Cyclodextrin

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Capsaicin, a pungent molecule from red chilli is known for its therapeutic benefits. However, poor aqueous solubility coupled with inherent pungency has limited its applications. We envisaged, encapsulation of capsaicin in biocompatible MOF material derived from γ-cyclodextrin (γ-CD) to overcome solubility and pungency attributes. Encapsulation of capsaicin was accomplished via crystal growth achieved by vapour diffusion of ethanol to synthesis solution consisting of γ-CD, KOH and capsaicin.The accomplished MOF Caps@γ-CDMOF was thoroughly characterized in solid state by powder X-ray diffraction (PXRD), IR, DSC, SEM and in solution by UV, fluorescence, NMR spectroscopic techniques. The encapsulation of capsaicin was found to be slightly higher than 3:1 (γ-CD: capsaicin ratio) in Caps@γ-CDMOF.

File list (3)

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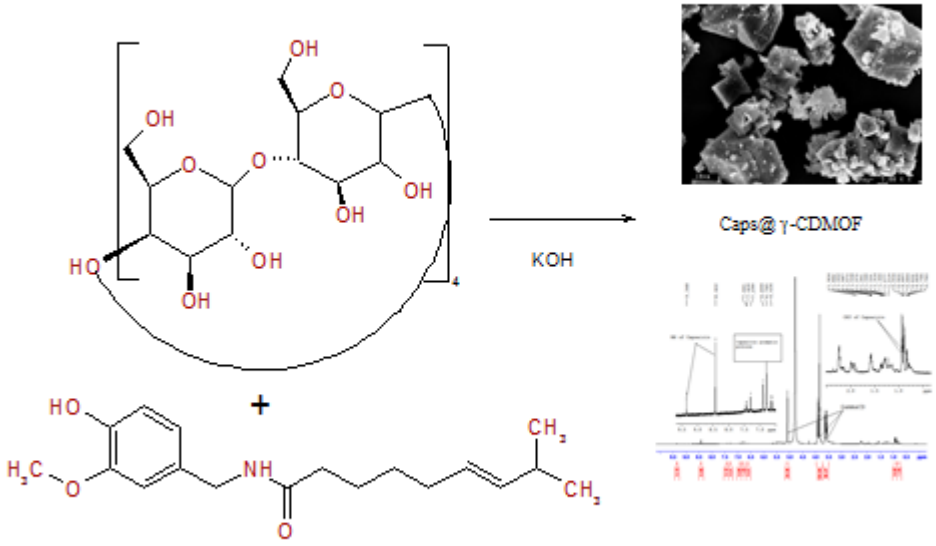
Graphical abstract



Abstract:

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Keywords:

Encapsulation, Capsaicin, Cyclodextrin, MOF, IR, NMR

Introduction

Host guest chemistry of native cyclodextrins has found many practical applications including drug delivery.[1-2] The native cylcodextrins are randomly packed (cage structures) molecules which limits the efficient packing.[3] On the other hand, columnar/channel structure type cyclodextrins due to disadvantages, hardly been employed in drug delivery.[4] A new class of MOF materials derived from cyclodextrins and alkali metals offer superior advantages. The properties including porosity and high surface area and further, ability to control packing by choosing appropriate cyclodextrin and suitable alkali metals has led to many applications of these MOFs.[5-6] Among these emerging materials, γ-CDMOF is a green and biocompatible metal-organic framework (MOF). It is made from self-assembly/crystallization process involving slow diffusion of methanol or grain ethanol to an aqueous solution of γ-CD and KOH. Previously, γ-CDMOF had been prepared accidently in couple of studies [7-8] but never had been recognised. Serendipitous discovery by Stoddart's group established γ-CDMOF's identity and structure with an array of concrete evidences .[5-6] The structure of γ-CDMOF is composed of body centred cube(bcc), wherein each unit of bcc is formed by a cube assembled with six γ-CD molecules (γ-CD tori).[6] Recently, γ-CDMOF has attracted considerable interest due to its striking nanoporous attributes and also for well-established green method of synthesis. In particular, γ-CDMOF has been employed for the applications composed of CO_2 absorption, separation of aromatics and encapsulation of several of pharma molecules .[9-13]

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decent anti-cancer activity.[18] Pungency and poor aqueous solubility of capsaicin limits oral ingestion for many therapeutic applications. Few studies have been carried out on encapsulation of capsaicin employing polymeric matrices and inclusion complexes methodology.[19-22] However, work on the encapsulation of capsaicin using GRAS status green materials with new emerging MOF material derived from γ-CD has not been accomplished. Herein, we disclose synthesis of capsaicin entrapped green and biocompatible MOF material derived from γ-CD and its characterization by an array of spectroscopic techniques including IR and NMR.

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γ-CD ((≥98.0%) was a gift from Wacker Chemie AG India Pvt ltd. Capsaicin (≥95 %) and D_2O (99.9 %) were procured from Sigma-Aldrich India. Ethanol (EtOH) (99.8%) was procured from Merck India. Solvents were used without any purification.

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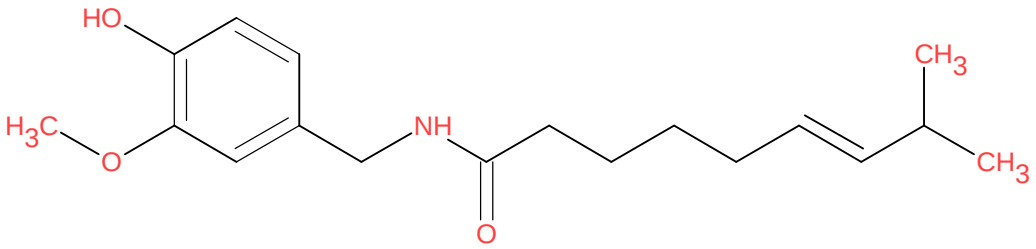


Figure 1. Structure of Capsaicin

Synthesis of Caps@γ-CDMOF

In a round bottom flask, employing γ-CD (324 mg ,0.25 mM) was dissolved in 5 mL of deionised water. Another solution was prepared containing capsaicin (76 mg, 0.25 mM) in 2 mL of EtOH and subsequently both solutions were mixed and stirred at room temperature (30°C) for 2 hrs. Further, KOH (113 mg, 2 mM) was added and stirring was continued for a while by addition of deionised water in an increment of 1mL till transparent solution (approx. 9-10 mL addition) was obtained. Then reaction mixture was concentrated to about 10-11mL by subjecting it vacuum, subsequently it was transferred to glass vial. Further, glass vial was transferred to a beaker filled with ethanol. Then the beaker was closed by watch glass and heated to about 80° C for 5 h and subsequently, this experimental set up was left undisturbed. Crystals appeared in 2-3 days and were collected by washing with ethanol two to three times and later air dried for a day. Anal. Calcd for($K_6C_{162}H_{273}O_{129}N.48H_2O$ (5398.13): C 36.04, H 6.89, N 0.26 (%), found: C 35.76, H 6.82, N 0.233 (%). IR (solid KBr pellet/cm^{-1}): 3374(O-H), 2928(C-H stretch of CH_3 and CH_2), 1648(O-H bending vibrations), 1420(O-H bending vibrations), 1158(O-H bending vibrations), 1518(N-H), 1336 (C-N), 1080(C-O stretch), 1028(C-C stretch), 705(N-H out of plane bend).

Results

Capsaicin entrapped γ-CD MOF (Caps@ γ-CDMOF)

The synthesis of Caps@γ-CDMOF was accomplished relatively faster diffusion of EtOH to aqueous solution containing γ-CD, capsaicin, and KOH as described in the experimental section. The crystals were seen after a period of two to three days. We also made attempts to get Caps@γ-CDMOF via dipping the γ-CDMOF in capsaicin solution. However, reaction was very slow and intractable products were observed as evidenced by ^{1}H NMR spectra.

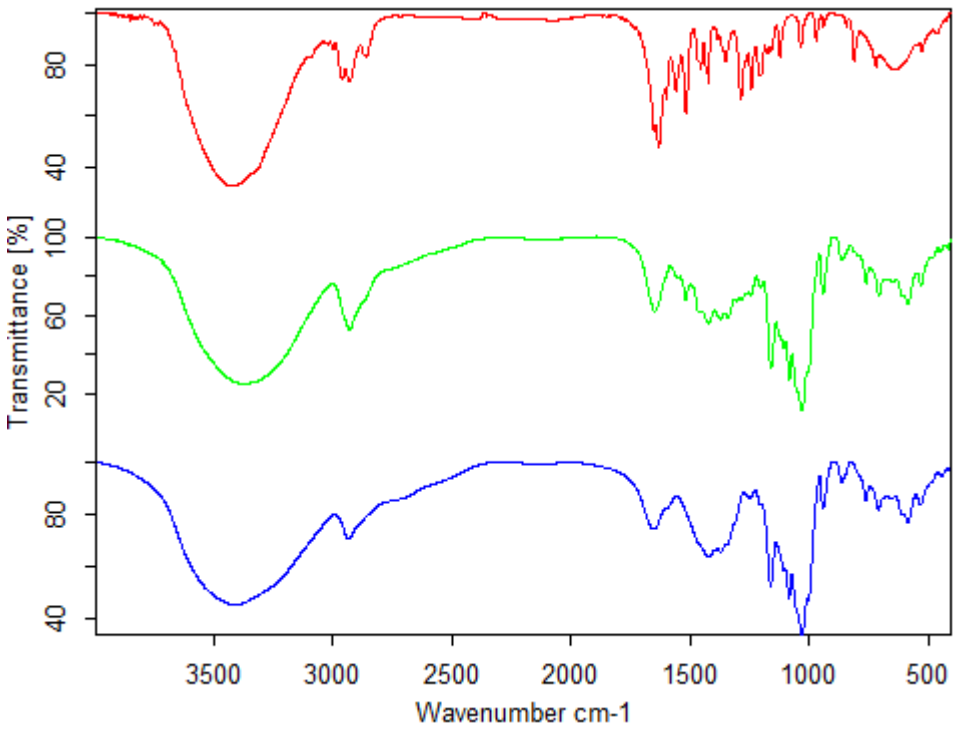


Figure 2:.IR spectra-red-capsaicin, green-Caps@γ-CDMOF and blue-γ-CDMOF

The IR spectra (Figure 2) of Caps@γ-CDMOF revealed several distinctive bands at 3374 cm^{-1} (O-H), 2928 cm^{-1} (C-H stretch of CH_3 and CH_2), 1648 cm^{-1}, 1420 cm^{-1}, 1158 cm^{-1} (O-H bending vibrations), 1080 cm^{-1} (C-O stretch), 1028 cm^{-1} (C-C stretch) confirming the γ-CD motif. The capsaicin encapsulation was confirmed via observation of bands at 1520 cm^{-1} (in-plane bending vibration of NH), 1336 cm^{-1} (C-N), 705 cm^{-1} (N-H out of plane bend) corroborating with encapsulation capsaicin in the γ-CDMOF (Figure 2).

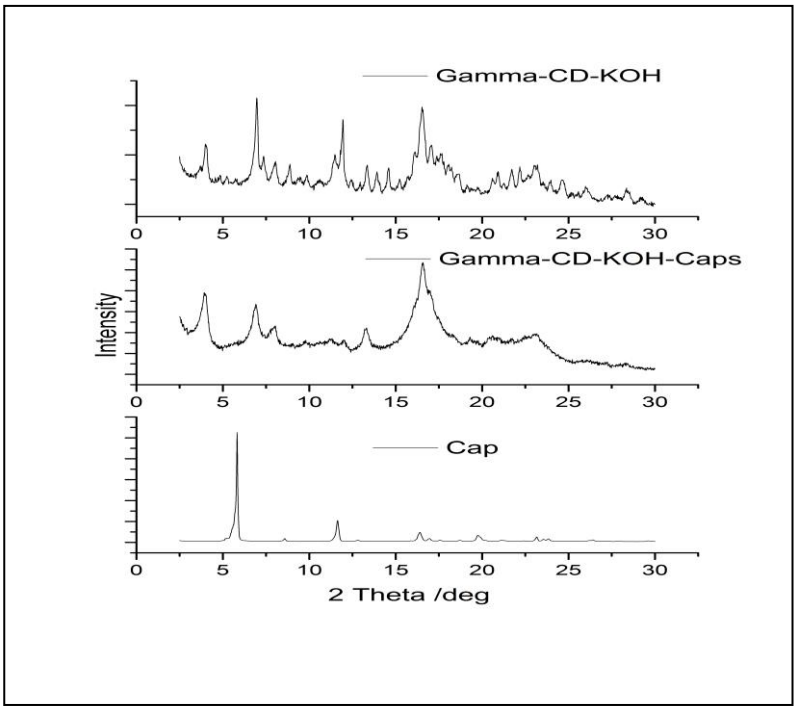


Figure 3:PXRD patterns of capsaicin, γ-CDMOF and Caps@ γ-CDMOF

PXRD data for Caps@ γ-CDMOF clearly indicated the retaining of crystalline nature of the MOF as majority of the reflections (2θ = 6.9, 7.3, 13.3,16.6, 22.4) were similar to PXRD pattern of γ-CDMOF and confirming the encapsulation of capsaicin in the γ-CDMOF (Figure 3). Further, DSC data (Figure 4) revealed the absence of endothermic peak corresponding to melting of capsaicin confirming the encapsulation of capsaicin in the MOF structure. Furthermore, morphology of the crystals of γ-CDMOF by SEM studies (Figure 7) revealed that, they are cubic and are similar to the native γ-CDMOF. The ^{1}H NMR spectra pointed out the encapsulation via observation of well defined peaks due to capsaicin and γ-CD. Specifically, ^{1}H NMR revealed distinct chemical shifts for capsaicin suggesting the two different chemical environments around capsaicin (Figure 8). The encapsulation of capsaicin in γ-CDMOF was also confirmed by fluorescence spectrum (Figure 5) and UV (Figure 6) spectra recorded in H_2O. Fluorescence microscope image revealed the entrapment of capsaicin in γ-CDMOF (Figure 7).

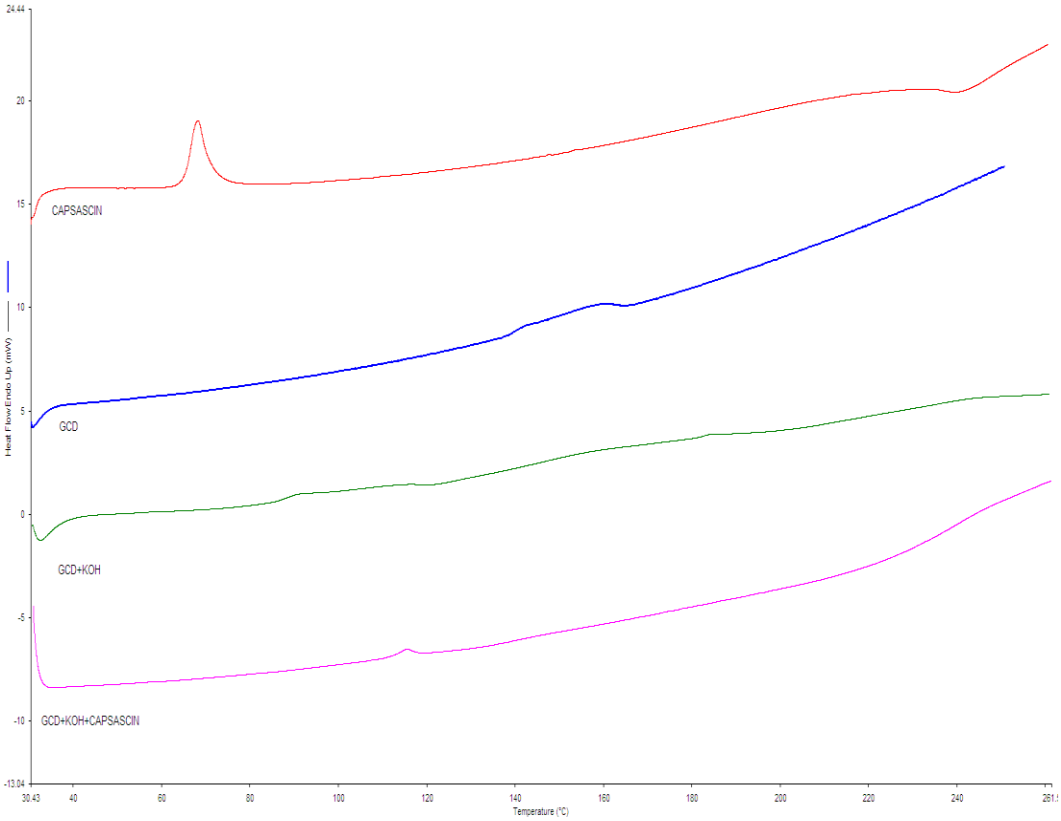


Figure 4: DSC data of Caps@γ-CDMOF

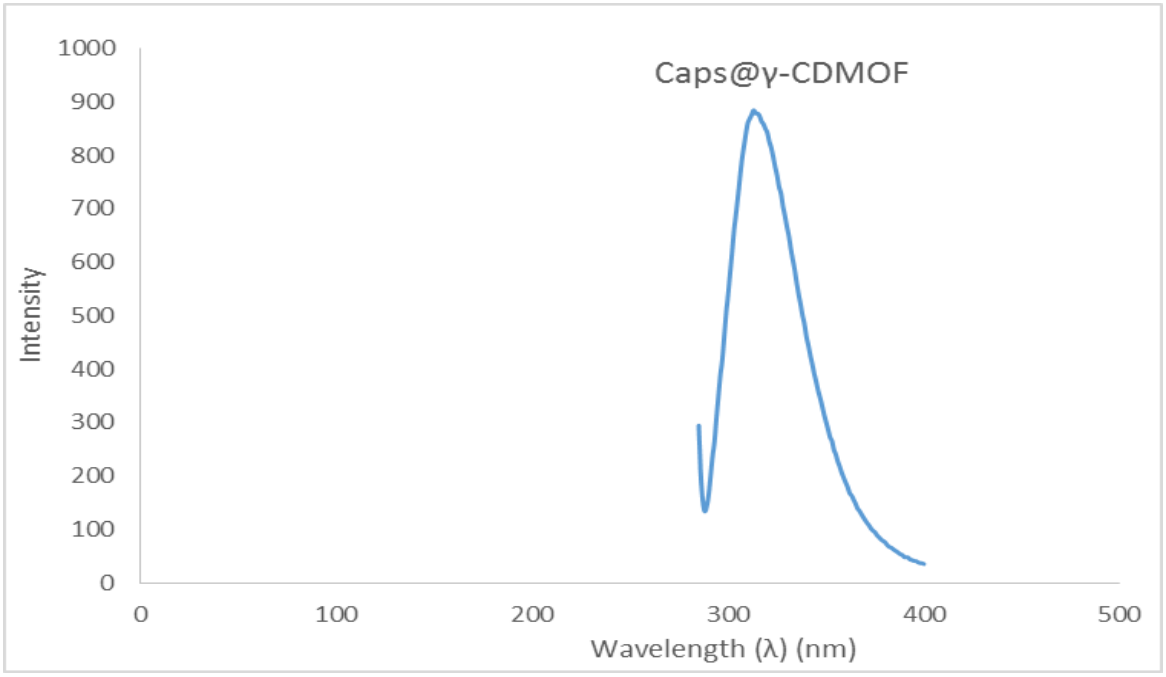


Figure 5: Fluorescence spectrum of Caps@γ-CDMOF

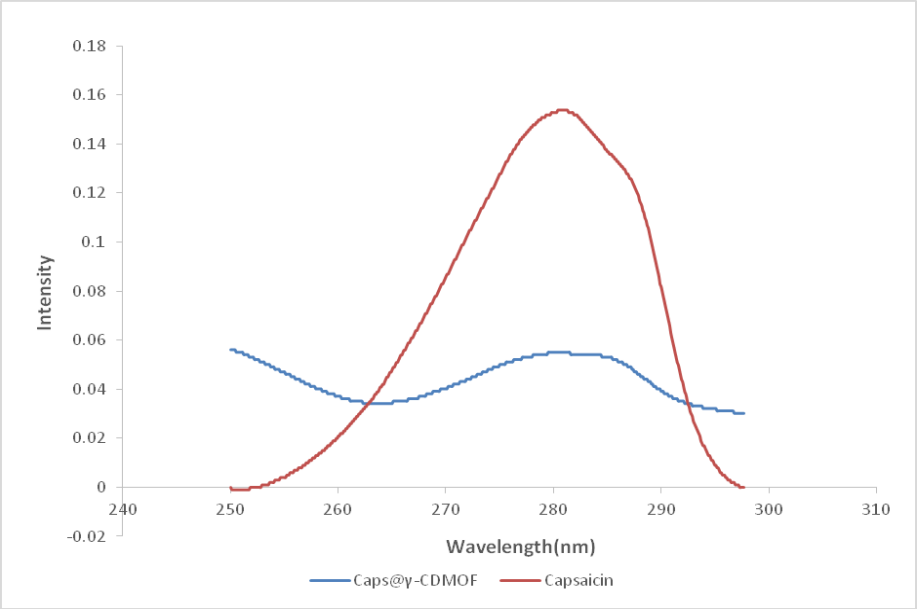
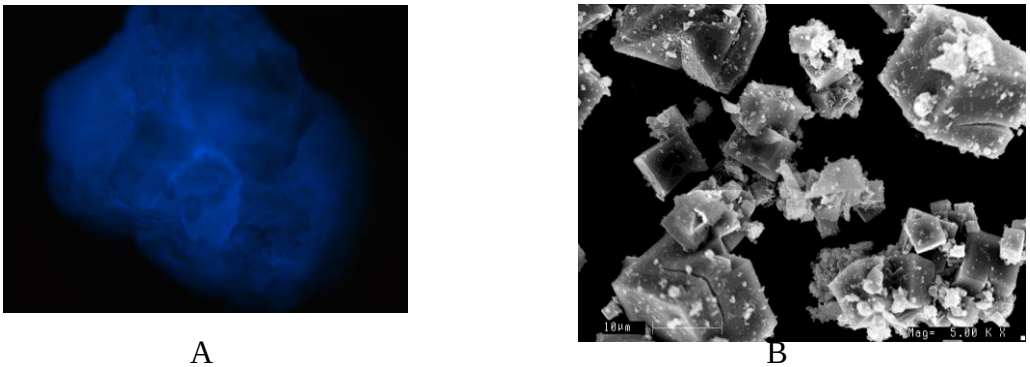


Figure 6: UV spectrum for capsaicin(red) Caps@γ-CDMOF (blue)

Discussion

The material γ-CDMOF is derived from γ-CD having eight glucose units and bears higher symmetry consisting of C_8, C_4 and C_2 axis. The γ-CDMOF structure is characterized by body entered cubic units, wherein each unit is formed by nano cubic unit of $(\gamma\text{-CD})_6$ tori. In turn each $\gamma\text{-CD})_6$ tori is connected by K^+ which is co-ordinated to eight glucopyronosyl units On the other hand, γ-CDMOF is derived from γ-CD having eight glucose units and bears higher symmetry consisting of C_8, C_4 and C_2 axis. γ-CD MOF structure is characterized by body entered cubic units, wherein each unit is formed by nano cubic unit of $(\gamma\text{-CD})_6$ tori. In turn each $\gamma\text{-CD})_6$ tori is connected by K^+ which is co-ordinated to eight glucopyronosyl units along with hydrophilic structural feature. The ^{1}H NMR spectroscopy clearly revealed that (Figure 8) capsaicin is encapsulated in two different chemical environment as evidenced by different chemical shift of methyl and aromatic protons and NH proton.



A B

Figure 7. (A)Fluorescence image of Caps@γ-CDMOF (B) SEM picture of Caps@γ-CDMOF

The usual chemical equivalence of methyl group of capsaicin was lost and two doublets of doublets were observed. The ratio of differently oriented capsaicin was found to be 3:1 as indicated by ^{1}H NMR integration. On the other hand, comparison of NMR integration of anomeric protons of γ-CD and methyl of dominant capsaicin revealed 3:1 ratio for γ-CD:capsaicin. As γ-CDMOF is composed of cubic $(\gamma\text{-CD})_6$ tori, each tori was found to be encapsulated with two capsaicin molecules. Further, we attribute that less prevalent capsaicin is encapsulated in the window channels of 0.78 nm. Because of two different destinations of encapsulation, the total approximate encapsulation ratio of CD to capsaicin was found to be 3:1.33 in Caps@γ-CDMOF.

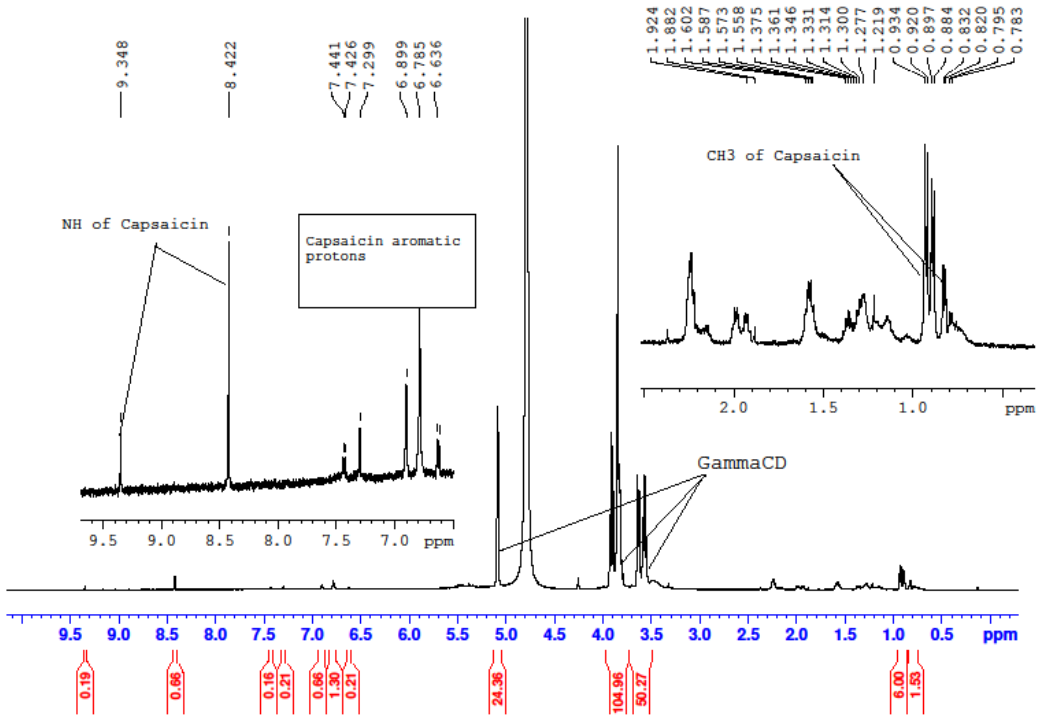


Figure 8. ^{1}HNMR spectrum of Caps@γ-CDMOF

Conclusions

Entrapment of capsaicin in the MOF derived from γ-cyclodextrin is demonstrated by employing an array of solid state and spectroscopic techniques. In particular, NMR has revealed the physical insight on the entrapment in MOF in two chemical environment.

Acknowledgments

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Disclosure Statement

The authors report no conflict of interest.

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307

Dear Editor

Please find our manuscript entitled “ Capsaicin entrapment in metal-organic framework material derived from γ-cyclodextrin ” for publication in preprint platform ChemRxiv.

with best regards,

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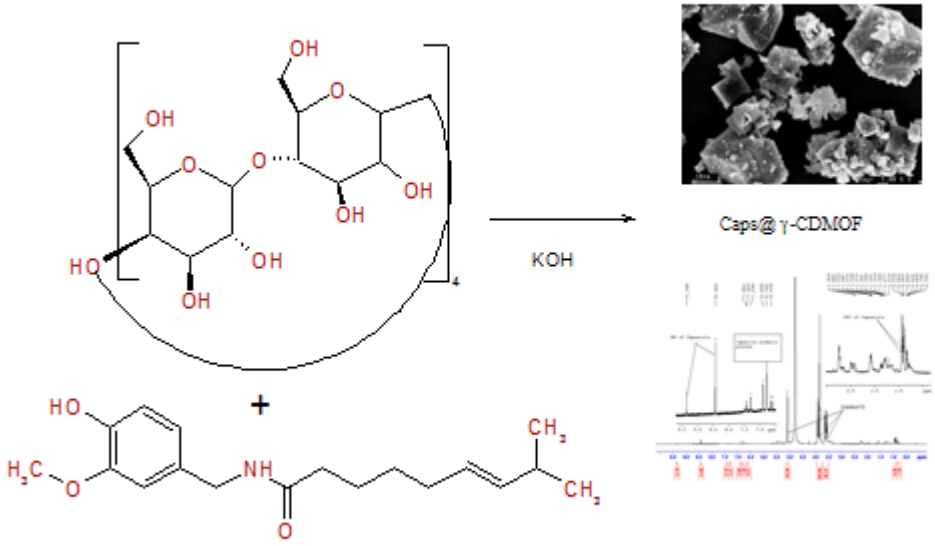

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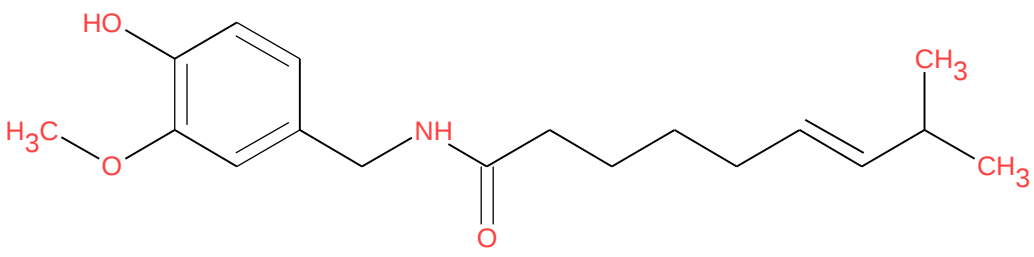


Figure 1. Structure of Capsaicin

Synthesis of Caps@γ-CDMOF

In a round bottom flask, employing γ-CD (324 mg ,0.25 mM) was dissolved in 5 mL of deionised water. Another solution was prepared containing capsaicin (76 mg, 0.25 mM) in 2 mL of EtOH and subsequently both solutions were mixed and stirred at room temperature (30° C) for 2 hrs. Further, KOH (113 mg, 2 mM) was added and stirring was continued for a while by addition of deionised water in an increment of 1mL till transparent solution (approx. 9-10 mL addition) was obtained. Then reaction mixture was concentrated to about 10-11mL by subjecting it vacuum, subsequently it was transferred to glass vial. Further, glass vial was transferred to a beaker filled with ethanol. Then the beaker was closed by watch glass and heated to about 80° C for 5 h and subsequently, this experimental set up was left undisturbed. Crystals appeared in 2-3 days and were collected by washing with ethanol two to three times and later air dried for a day. Anal. Calcd for($K_6C_{162}H_{273}O_{129}N.48H_2O$ (5398.13): C 36.04, H 6.89, N 0.26 (%), found: C 35.76, H 6.82, N 0.233 (%). IR (solid KBr pellet/cm^{-1}): 3374(O-H), 2928(C-H stretch of CH_3 and CH_2), 1648(O-H bending vibrations), 1420(O-H bending vibrations), 1158(O-H bending vibrations), 1518(N-H), 1336 (C-N), 1080(C-O stretch), 1028(C-C stretch), 705(N-H out of plane bend).

Results

Capsaicin entrapped γ-CD MOF (Caps@ γ-CDMOF)

The synthesis of Caps@γ-CDMOF was accomplished relatively faster diffusion of EtOH to aqueous solution containing γ-CD, capsaicin, and KOH as described in the

experimental section. The crystals were seen after a period of two to three days. We also made attempts to get Caps@γ-CDMOF via dipping the γ-CDMOF in capsaicin solution. However, reaction was very slow and intractable products were observed as evidenced by ^{1}H NMR spectra.

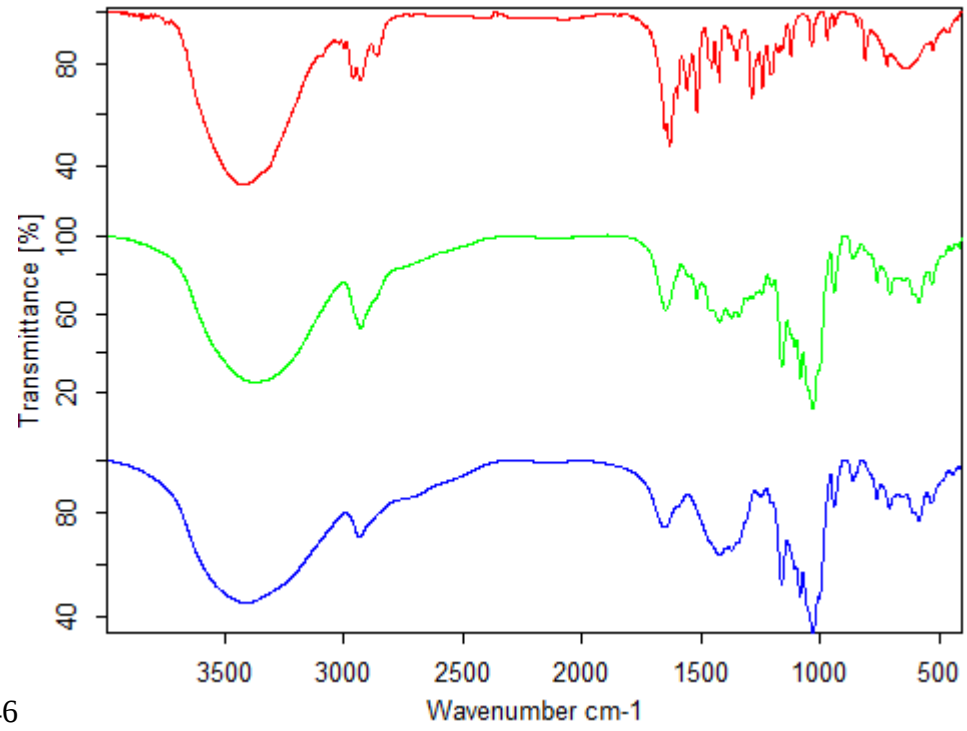


Figure 2:.IR spectra-red-capsaicin, green-Caps@γ-CDMOF and blue-γ-CDMOF

The IR spectra (Figure 2) of Caps@γ-CDMOF revealed several distinctive bands at 3374 cm^{-1} (O-H), 2928 cm^{-1} (C-H stretch of CH_3 and CH_2), 1648 cm^{-1}, 1420 cm^{-1}, 1158 cm^{-1} (O-H bending vibrations), 1080 cm^{-1} (C-O stretch), 1028 cm^{-1} (C-C stretch) confirming the γ-CD motif. The capsaicin encapsulation was confirmed via observation of bands at 1520 cm^{-1} (in [illegible] cm^{-1} (N-H out of plane bend) co[illegible]gure 2).

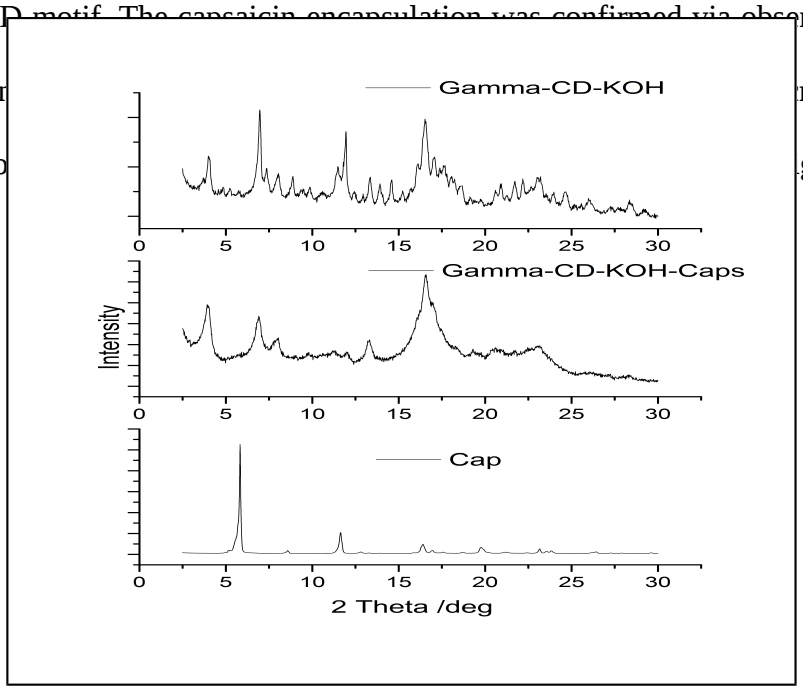
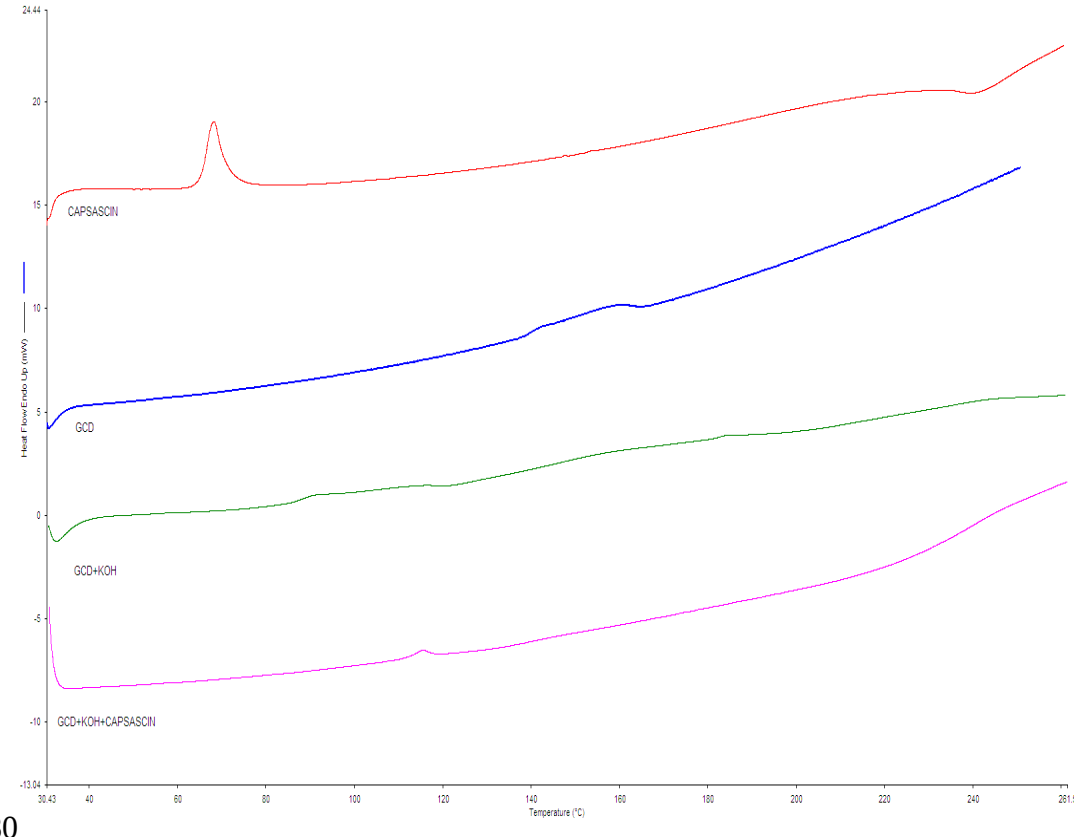


Figure 3:PXRD patterns of capsaicin, γ-CDMOF and Caps@ γ-CDMOF

PXRD data for Caps@ γ-CDMOF clearly indicated the retaining of crystalline nature of the MOF as majority of the reflections (2θ = 6.9, 7.3, 13.3,16.6, 22.4) were similar to PXRD pattern of γ-CDMOF and confirming the encapsulation of capsaicin in the γ-CDMOF (Figure 3). Further, DSC data (Figure 4) revealed the absence of endothermic peak corresponding to melting of capsaicin confirming the encapsulation of capsaicin in the MOF structure. Furthermore, morphology of the crystals of γ-CDMOF by SEM studies (Figure 7) revealed that, they are cubic and are similar to the native γ-CDMOF. The ^{1}H NMR spectra pointed out the encapsulation via observation of well defined peaks due to capsaicin and γ-CD. Specifically, ^{1}H NMR revealed distinct chemical shifts for capsaicin suggesting the two different chemical environments around capsaicin (Figure 8). The encapsulation of capsaicin in γ-CDMOF was also confirmed by fluorescence spectrum (Figure 5) and UV (Figure 6) spectra recorded in H_2O. Fluorescence microscope image revealed the entrapment of capsaicin in γ-CDMOF (Figure 7).



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181Figure 4: DSC data of Caps@γ-CDMOF

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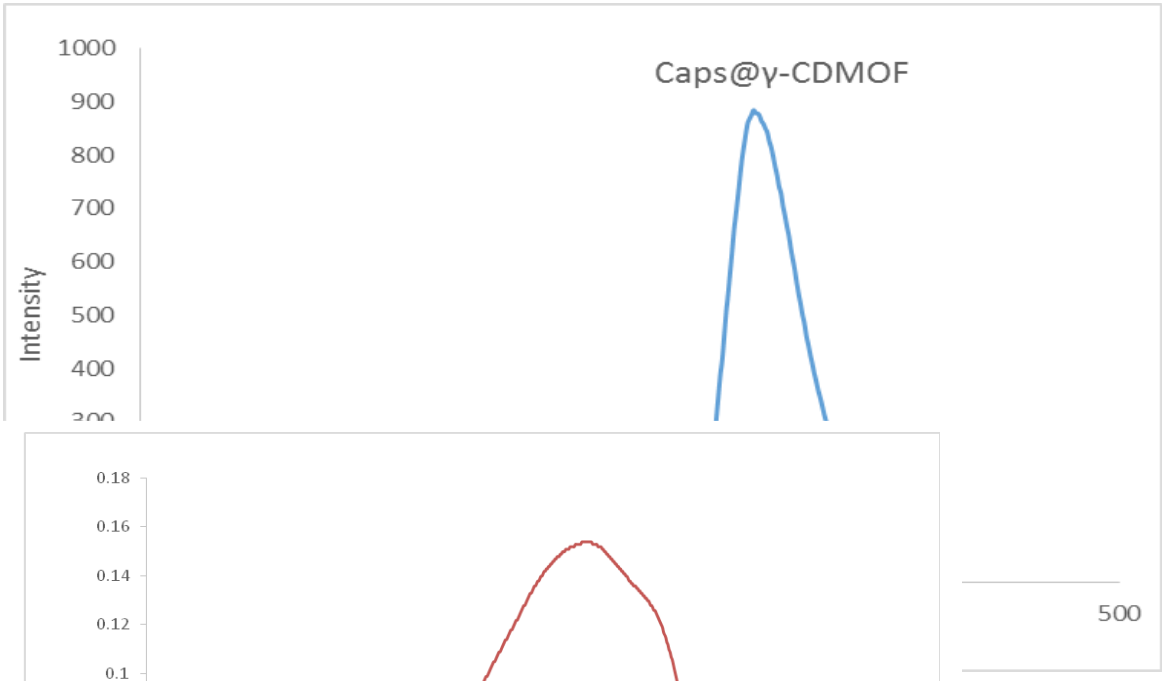

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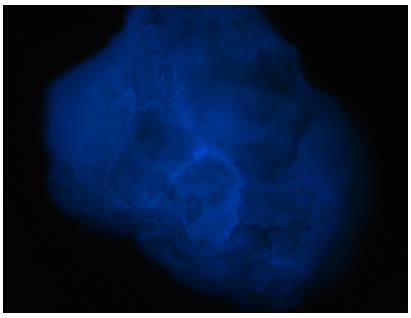
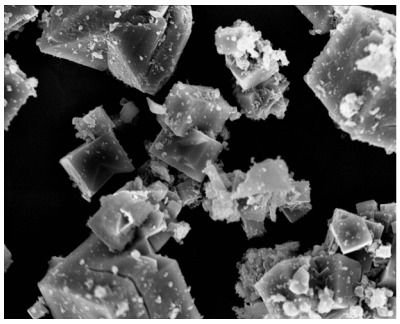
Figure 6: UV spectrum for capsaicin(red) Caps@γ-CDMOF (blue)

Discussion

The material γ-CDMOF is derived from γ-CD having eight glucose units and bears higher symmetry consisting of C_8, C_4 and C_2 axis. The γ-CDMOF structure is characterized by body entered cubic units, wherein each unit is formed by nano cubic unit of $(\gamma\text{-CD})_6$ tori. In turn each $\gamma\text{-CD})_6$ tori is connected by K^+ which is co-ordinated to eight glucopyronosyl units On the other hand, γ-CDMOF is derived from γ-CD having eight glucose units and bears higher symmetry consisting of C_8, C_4 and C_2 axis. γ-CD MOF structure is characterized by body entered cubic units, wherein each unit is formed by nano cubic unit of $(\gamma\text{-CD})_6$ tori. In turn each $\gamma\text{-CD})_6$ tori is connected by K^+ which is co-ordinated to eight glucopyronosyl units along with hydrophilic structural feature. The ^{1}H NMR spectroscopy clearly revealed that (Figure 8) capsaicin is encapsulated in two different chemical environment as evidenced by different chemical shift of methyl and aromatic protons and NH proton.





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225Figure 7. (A)Fluorescence image of Caps@γ-CDMOF (B) SEM picture of Caps@γ-
226CDMOF

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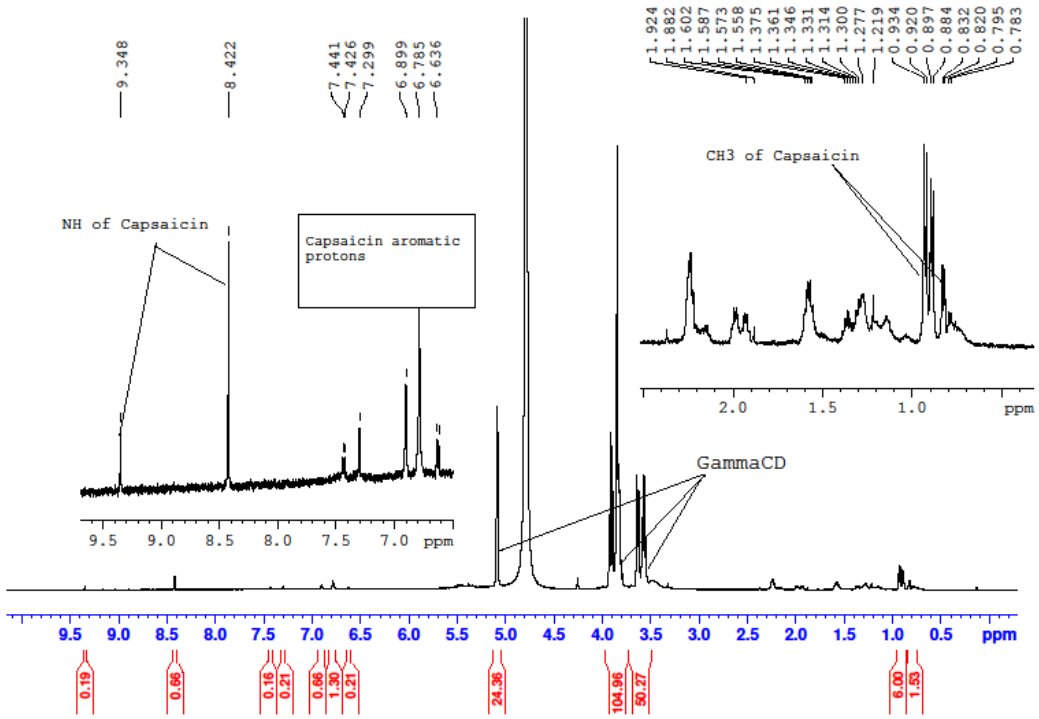
228The usual chemical equivalence of methyl group of capsaicin was lost and two doublets of
229doublets were observed. The ratio of differently oriented capsaicin was found to be 3:1 as
230indicated by ^{1}H NMR integration. On the other hand, comparison of NMR integration of
231anomeric protons of γ-CD and methyl of dominant capsaicin revealed 3:1 ratio for γ-
232CD:capsaicin. As γ-CDMOF is composed of cubic $(\gamma\text{-CD})_6$ tori, each tori was found to be
233encapsulated with two capsaicin molecules. Further, we attribute that less prevalent capsaicin
234is encapsulated in the window channels of 0.78 nm. Because of two different destinations of
235encapsulation, the total approximate encapsulation ratio of CD to capsaicin was found to be
2363:1.33 in Caps@γ-CDMOF.



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238Figure 8. [1]HNMR spectrum of Caps@γ-CDMOF

239**Conclusions**

240 Entrapment of capsaicin in the MOF derived from γ-cyclodextrin is demonstrated by 241employing an array of solid state and spectroscopic techniques. In particular, NMR has 242revealed the physical insight on the entrapment in MOF in two chemical environment.

243**Acknowledgments**

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247**Disclosure Statement**

248 The authors report no conflict of interest.

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307