# Synthesis of ɣ-Cyclodextrin Metal Organic Frameworks and the Encapsulation of Caffeine and Theophylline

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## Abstract

Nanoporous, non-toxic, ɣ-cyclodextrin metal organic frameworks (ɣ-CDMOFs) have potential applications in fields such as drug delivery and organic compound storage. The properties of many methylxanthines (alkaloids such as caffeine and theophylline) could be improved through ɣ-CDMOF encapsulation, yet little research has been performed on the subject. In this study, ɣ-CDMOFs were synthesized in order to 1. Determine if the vapor diffusion synthesis method can produce ɣ-CDMOF crystals that replicate those in literature and 2. Determine if ɣ-CDMOFs are able to encapsulate methylxanthines. The ɣ-CDMOFs were synthesized through vapor diffusion of methanol in a solution of ɣ-cyclodextrin and potassium hydroxide (KOH). The synthesized crystals were activated at 25 °C and 45 °C to remove the residual methanol and water, freeing the nanopores of the crystals. The synthesized and activated crystals were characterized through X-ray diffraction (XRD) and scanning electron microscopy (SEM). Caffeine and theophylline were encapsulated over 24 hours in the ɣ-CDMOFs, which were then analyzed using thermogravimetric analysis (TGA). Characterization results aligned with literature confirming a uniform cubic structure of the crystals with sizes primarily ranging from 1 to 10μm, with a median crystallite size of 2 μm. It was determined that 1. Vapor diffusion is a viable synthesis method for ɣ-CDMOFs and 2. ɣ-CDMOFs are able to encapsulate theophylline, however the data was not conclusive enough to confirm the encapsulation of caffeine.

**Acknowledgments**

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# 1. Introduction

There are several methods for administering drugs, as humans have been using pharmaceutical treatments for centuries [1]. However, over time, doctors have realized traditional administration methods are flawed, leaving a lot of room for improvement. The oral administration of pills as well as the injection of active drugs both lack the ability to effectively control factors such as release rate, targeting of delivery, and the total time of release. This results in consistent and repetitive administration to maintain the desired dosage, while having a large variation in drug release over time. These factors have led to a surge in drug delivery research over the past few decades [2].

With a set goal of delivering the desired amount of drugs to the site of action for the proper duration, scientists and engineers have been developing drug delivery systems (DDS) for over 50 years [3]. While many of the physiochemical barriers have been resolved, biological barriers have presented problems generating well-functioning clinical products. The human body is complicated and unpredictable, thus DDS must be non-toxic and functional in the body throughout the course of drug delivery while avoiding drug precipitation in the bloodstream.

Another problem with drug delivery can be the solubility of the drugs. The Biopharmaceutics Classification System is a model for measuring the permeability and solubility of drugs [4]. Many drugs that are classified as low solubility are flagged and not sent for clinical trials as enhanced formulation techniques would be required [5]. Additionally, many drugs that are already commonly used, such as cefuroxime axetil, require more advanced delivery methods due to their insolubility. This has sparked a lot of interest in cheap and nontoxic methods to increase the solubility of hydrophobic drugs.

*1.1 Nanoporous Materials*

Nanoporous materials are porous frameworks containing cavity sizes that are less than 100 nanometers in size. Recently, it has been found that nanoporous materials can potentially be used for many applications including ion-exchange, drug delivery, and catalysis. Their relevance is due to the materials ability to absorb and coordinate with atoms, ions, and molecules on their interior surface and pore space [6].

Zeolites are a type of nanoporous material that are crystalline solid structures composed of silicon (Si), aluminum (Al), and oxygen (O) which can form over 200 frameworks containing cavities or pores. They can occur naturally, but are often made synthetically. The pores are less than one nanometer in size which can be changed by exchanging the zeolite's interstitial cations. Studies have shown that exchanging $2Na^+$ with a $Ca^{2+}$ will decrease the pore size from .4 nm to .3, while the pore size will increase to .5 nm if $Na^+$ is substituted with $K^+$ [7].

Carbon nanotubes (CNT) are rolled up graphene sheets that form concentric cylinders. CNTs have emerged as a new type of material that has the potential to efficiently locate and transport therapeutic molecules. They are able to be encapsulated with various compounds including bioactive materials and are able to be delivered to organs and cells. Unfortunately, studies have shown that pristine CNT are highly toxic. The health concerns are mainly due to CNT being insoluble in all solvents. An effective methodology for the modification of the CNTs can result in soluble CNTs which can potentially be used for biological applications such as drug delivery. However, further investigation is required, as this research is ongoing and in the early stages of being established for clinical use [8].

*1.2 Metal Organic Frameworks and Cyclodextrins*
Metal organic frameworks (MOFs) are a class of coordination polymers containing nanoscale voids, resulting in a high porosity. Coordination polymers are inorganic polymer structures containing metal cation centers linked by organic ligands. However, most MOFs tested to date are derived from non-renewable petrochemical feedstock and transition metals [9]. One of the roadblocks when preparing MOFs from natural products results from the frequent asymmetry of the building units, which do not typically result in significantly high porosities or stability. The high crystallinity and porosity of MOFs along with controllable and tunable pore structures have led to extensive research of MOFs. However, most organic precursors are expensive, non-renewable, and toxic to humans. Recently a non-toxic, highly stable, and porous MOF has been derived from renewable γ-cyclodextrin [10].

Cyclodextrin metal organic frameworks are nanoporous materials that have sparked the interest of scientists and engineers in numerous fields. Cyclodextrins (CDs) are cyclic oligosaccharides; this family of compounds is made up of sugar molecules arranged in a ring (Figure 1).
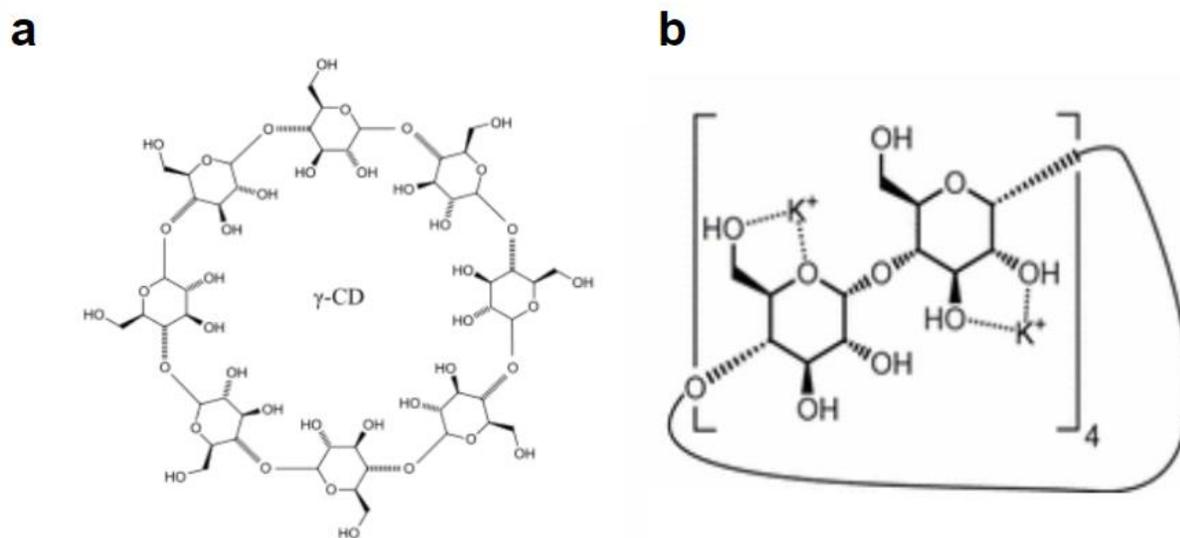


Figure 1. a) Chemical structure of γ-CD [11]; b) Structural formula of CDMOFs, depicting coordination of $K^+$ cations [12]

The most common cyclodextrins are α (six-membered), β (seven-membered), and γ (eight membered) cyclodextrin. The primary hydroxyl groups, on the first face of the compound, have the ability to rotate, but the secondary hydroxyl groups (interior) have rigid, polar chains. The interior torus, while not hydrophobic, is significantly less hydrophilic than the aqueous environment, allowing it to encapsulate hydrophobic compounds. Conversely, the outer face is much more hydrophilic, making cyclodextrins water soluble [13].

The difference in water solubility within the molecule allows for a slew of applications. The ability of cyclodextrins to form a reversible inclusion complex with hydrophobic materials, while maintaining water solubility, drastically increases the solubility of the encapsulated hydrophobic compound [14]. This increases the bioavailability of the compound, the proportion of the drug that has an active effect when exposed to the human body, which is crucial for efficient dosage carrying and release. This amphiphilic nature also paves the way for other industry uses. For example, when quantum dots (nanometer sized semiconductor particles) are synthesized in

organic solvents, they end up with hydrophobic surface ligands but extremely favorable properties for biomedical imaging and detection [15]. Through some processing and exposure to cyclodextrin, hydrophobic quantum dots can become water-soluble and further stabilized [16]. α, β, and γ-CD are all classified as safe by the US FDA, and are used extensively in the food industry for applications ranging from cholesterol removal to the lowering of blood sugar peaks [17],[18].

The different cyclodextrin family members exhibit slight differences in properties, due to the difference in ring size. Properties such as the water solubility and cavity diameter vary greatly between the three members. Table I shows structural results of experimentally synthesized α, β, and γ-CD.

Table I. Structural properties of α, β, and γ-CD [13]

| Property | α-CD | β-CD | γ-CD |
|---|---|---|---|
| Number of glucopyranose units | 6 | 7 | 8 |
| Molecular weight (g/mol) | 972 | 1135 | 1297 |
| Solubility in water at 25°C (%, w/v) | 14.5 | 1.85 | 23.2 |
| Outer diameter (Å) | 14.6 | 15.4 | 17.5 |
| Cavity diameter (Å) | 4.7-5.3 | 6.0-6.5 | 7.5-8.3 |
| Height of torus (Å) | 7.9 | 7.9 | 7.9 |
| Cavity volume (Å) | 174 | 262 | 427 |

Based on the water solubility and cavity volume, γ-CD exhibits the highest potential as it can encapsulate the most material and dissolve in water most easily; the two most important properties for its desired applications.

The benefits of cyclodextrins alone are ample, yet when combined with inorganic compounds such as potassium hydroxide (KOH), cyclodextrin metal organic frameworks (CDMOFs) can form. CDMOFs are highly porous; γ-CDMOF is made up of six γ-CD tori with alternating $K^+$ cation coordination, resulting in three γ-CD cubes. These cubes are also joined by $K^+$ cations coordinated on the secondary face (Figure 2). This coordination results in an extended and highly porous structure [12]
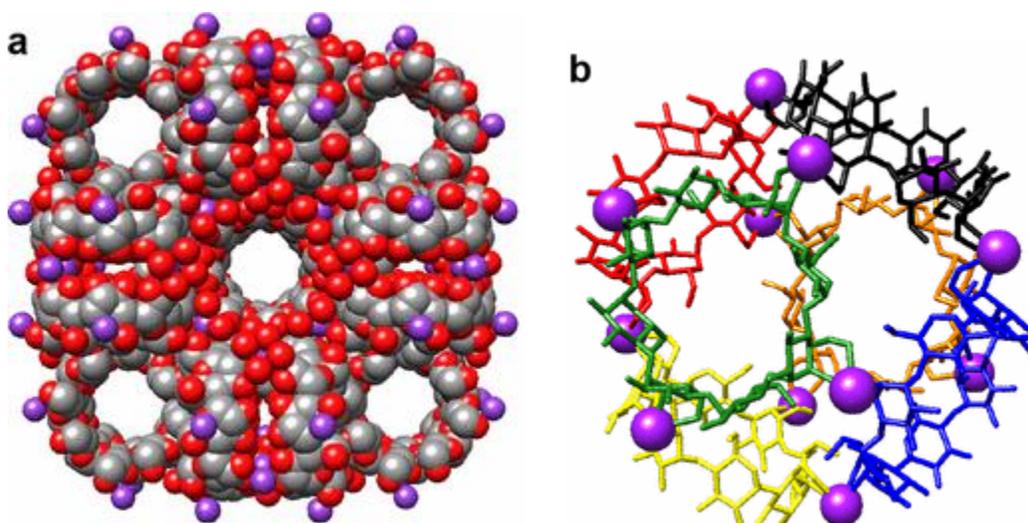


Figure 2. a) Space-filled depiction of solid state extended structure of CDMOFs where grey represents carbon, red represents oxygen, and purple represents potassium; b) Representation of γ-CD with $K^+$ cations (purple) coordinated to primary and secondary faces [12]

This structure results in a high specific surface area which is the total surface area of a material per unit mass or volume that accounts for porosity. Specific surface area is an important property when working with nanoporous materials, as it acts as a method for evaluating adsorption potential and porosity [13]. The structural unity of CDMOFs also promotes cohesion and stability of the molecule. This stability is important so that the CDMOFs do not collapse when exposed to a variety of environments and stresses. The stability, porosity, non-toxicity,

bioavailability, and tailorability of CDMOFs, make them a viable option for use in drug delivery systems.

CDMOFs have a multitude of other benefits and potential applications. Use of CDMOFs have been considered for gas separation techniques. Studies show CDMOFs can facilitate the separation of various mixtures such as ethylbenzene from styrene, terpinenes, haloaromatics, pinenes, and other chiral compounds. Unlike competing amorphous materials such as modified silicas, due to the crystallinity of CDMOFs, the separation behavior can be easily predicted through calculations, and the science behind the separations can be more easily explained [6].

*1.3 Synthesis, Encapsulation, and Analysis*

Different synthesis methods can result in varying particle sizes, size distributions or even morphology, which can affect the material's properties. Various synthesis methods can be used to synthesize MOFs, such as vapor diffusion synthesis of methanol using KOH and microwave-assisted synthesis. Microwave-assisted synthesis is not an ideal method for this project as the microwave alone exceeds the allotted budget and requires additional solvents and materials. Vapor diffusion synthesis is the ideal method due to its accessibility, ease of use, and low cost. The crystals can form in a benign environment using minimal solvents and materials. The vapor diffusion process will take up to a week to complete, but will require minimal hands-on work and materials [19].

For the encapsulation process, γ-CDMOFs will be used to attempt to encapsulate two different methylated xanthines (methylxanthines): theophylline and caffeine. Xanthine is a purine base derived from human body tissues and other organisms [20]. Derivatives of xanthine commonly known as xanthines are a group of alkaloids, naturally occurring compounds containing nitrogen atoms, which are used as stimulants and bronchodilators. Caffeine is the world's most widely used central-nervous system stimulant and can be used to reduce fatigue and enhance physical performance. Caffeine increases the energy metabolism throughout the brain while decreasing cerebral blood flow resulting in a brain hypoperfusion [21]. Theophylline is a drug used to relieve the symptoms of asthma. It relaxes muscles in the airway to open up breathing passages

and decreases the lungs response to irritants [22]. Previous studies have shown that caffeine can be successfully encapsulated in zeolitic imidazolate (ZIF-8) [23].

Focusing on encapsulating more than one compound with similar structures will reduce the risk of failure due to unexpected chemical reactions. Shown below in Figure 3 is the general structure for xanthine and the two different methylxanthines. The only structural difference between the three structures is the change in the R groups attached to the backbone. Shown in Figure 4a is the specific xanthine structure, where all of the R groups are hydrogen atoms; R1 = R2 = R3 = H. In Figure 4b is the structure for caffeine, where the R groups are all methyl groups attached to the xanthine backbone; R1 = R2 = R3 = CH3. The theophylline structure is shown in Figure 4c, where two of the R groups are methyl groups while the third R group is a hydrogen atom; R1 = R2 = CH3, R3 = H.
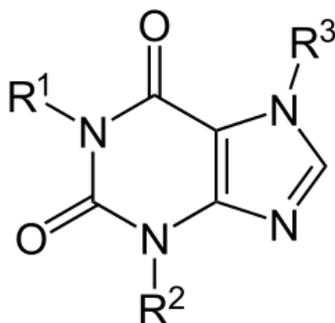
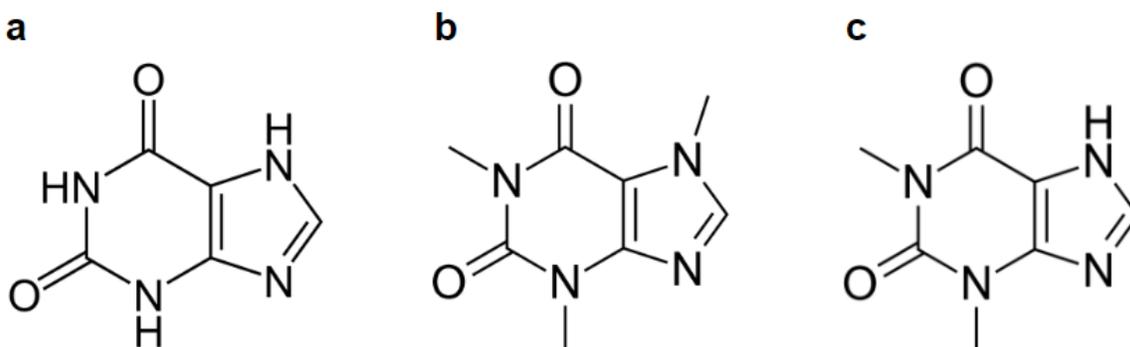Figure 3. The general chemical structure for xanthine and the two methylxanthines [24]

Figure 4. The chemical structure of the xanthine and the two methylxanthines. a) xanthine; b) caffeine; c). theophylline [25],[26],[27]

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There are many ways to investigate and analyze the γ-CDMOFs, but budget and time limitations have resulted in narrowing the analysis down to X-ray diffraction (XRD), thermogravimetric analysis (TGA), and scanning electron microscopy (SEM). XRD will be performed in order to determine the crystal structure and chemical composition of the γ-CDMOFs [28]. After confirming the crystals are γ-CDMOFs, TGA will be performed and SEM images will be taken. The TGA results will be used to determine degradation points of the various components of the γ-CDMOFs in order to determine if encapsulation took place as well as approximate amounts. SEM images will be taken to corroborate the findings from XRD as well as form a better understanding of the microstructure as opposed to just the atomic structure.

The purpose of this study is to 1. Determine if the vapor diffusion synthesis method can produce γ-CDMOF crystals that replicate those in literature and 2. Determine if γ-CDMOFs are able to encapsulate methylxanthines, using caffeine and theophylline as model compounds.

## 2. Materials and Methodology

### 2.1 Materials

Caffeine powder (1,3,7-Trimethylxanthine, ReagentPlus), Methanol (anhydrous, purity ≥99.9%), theophylline powder (anhydrous, purity ≥99%), desiccant packets (molecular sieves, 0.5g packets), and KOH pellets (ACS reagent, purity ≥85%) were purchased from Sigma-Aldrich Corp (Saint Louis, MO, USA). γ-CD (purity > 99%, food grade) was provided by Ajay Kathuria of California Polytechnic State University (San Luis Obispo, CA, USA).

### 2.2 Overview of Methodology

γ-CDMOFs were synthesized through vapor diffusion of methanol in a solution of γ-CD and KOH. The γ-CDMOFs were activated in a low temperature oven to remove residual methanol and deionized water and open up the pores of the crystals in preparation for encapsulation. SEM and XRD were used to characterize the activated crystals and determine the relationship between the γ-CDMOF crystals and crystals produced in literature. Following characterization, the methylxanthine compounds were encapsulated into the γ-CDMOF crystals and analyzed using TGA to determine if encapsulation took place.

### 2.3 Vapor Diffusion Synthesis

1.30 g of γ-CD and 0.45 g of KOH (1:8 mmol ratio of γ-CD to KOH) were placed into a 50 mL beaker containing 20 mL of deionized water. The mixture was stirred at room temperature for 12 hours. Next, the beaker was placed inside a 500 mL beaker containing 50 mL of methanol. The larger beaker was sealed with parafilm to allow for the diffusion of methanol into the CD/KOH solution. The solution was left for seven days to allow for crystal nucleation and growth. Following growth, the crystals were filtered and soaked in methanol for three days to remove any unlinked K+ from the γ-CDMOF structure.

### 2.4 Activation

The crystals were filtered again, then placed in a beaker to prepare for activation. After, the beaker was placed in an oven at 25°C for 10 hours, then 45°C for 12 hours. Finally, the crystals were stored in a closed container under desiccant to prevent the crystals from absorbing any moisture. Shown in Figure 5 are the synthesis and activation procedures to produce γ-CDMOFs.
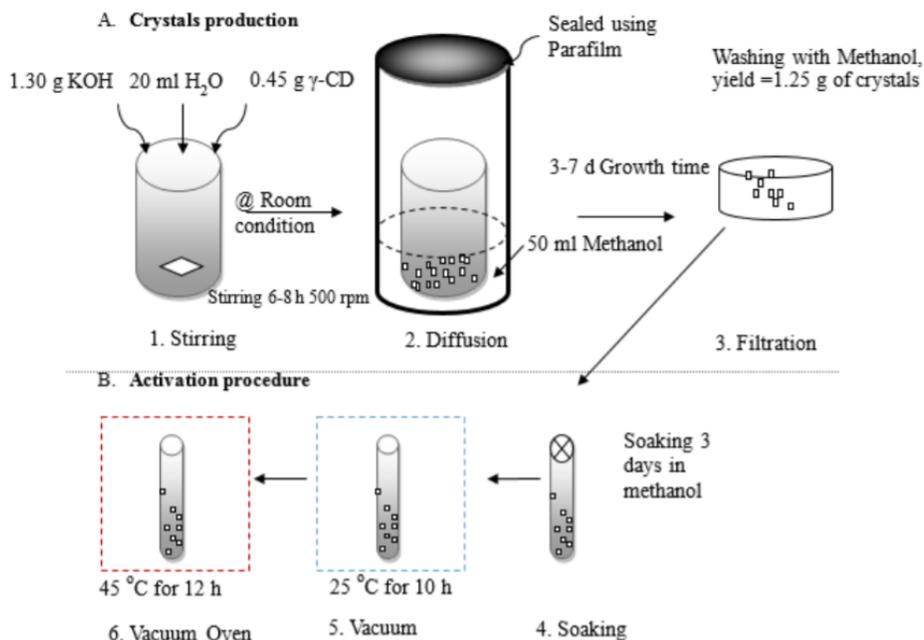
Figure 5. The growth and activation procedure for ɣ-CDMOFs [29]

## 2.5 Encapsulation

Caffeine and theophylline were each dissolved into separate 50 mL beakers containing 20 mL of ethanol; 300 mg and 250 mg, respectively. The solutions were stirred and sonicated until the solutes were fully dissolved. A third beaker containing only 20 mL of ethanol was used as a reference to determine the degradation temperature at which ethanol degrades out of the γ-CDMOFs. After sonication, 100 mg of γ-CDMOF crystals were placed inside each of the three beakers, before the beakers were sealed with parafilm for 24 hours at room temperature. Then, the crystals were filtered out of the solutions and stored in sealed containers until being used for TGA. The encapsulation procedure for the ɣ-CDMOFs are shown in Figure 6 and Figure 7.
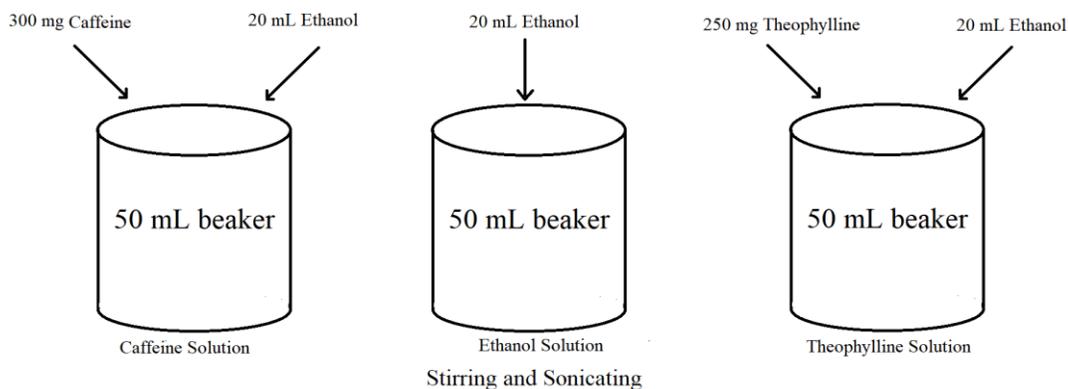
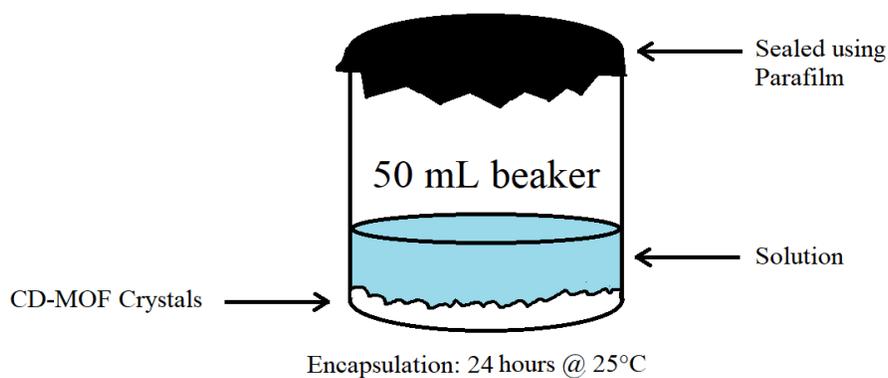Figure 6. Producing the three solutions for the encapsulation procedure for γ-CDMOFs



Figure 7. The γ-CDMOF crystals were soaked in the solutions for 24 hours at room temperature

## 2.6 Characterization

A FEI Quanta 200 scanning electron microscope was used to analyze the structure of the γ-CDMOF crystals. The γ-CDMOF crystal samples were prepared by mounting the crystals onto conductive carbon tape then sputter depositing a layer of gold onto the sample's surface using a Cressington 108 Auto Sputter Coater.

The degradation temperature of the γ-CDMOF samples was determined using a Mettler Toledo Thermogravimetric Analyzer. The samples were heated at a rate of 10℃/min using a temperature range from 25-500℃.

A Siemens Diffractometer D5000 was used to analyze the crystalline characteristics of the ɣ-CDMOF crystals by XRD operating with CuKα radiation ($\lambda = 0.154$ nm) at 40 kV and 40 mA. Scans were taken from 2° to 15° using a scan step of 0.05°.

## 3. Results and Discussion

*3.1 Scanning Electron Microscopy*

Images of the as-activated γ-CDMOF crystals are shown in Figure 8. At low magnifications (Figure 8a), the crystals did not show a symmetrical structure and sizes varied significantly. Upon further magnification (Figure 8b) however, smaller crystals were seen with a consistent cubic shape. This is because the crystals seen at low magnification were made up of thousands of smaller cubic crystals less than a few microns wide. These small crystals appeared to have similar shapes and sizes to crystals synthesized in past literature [13].
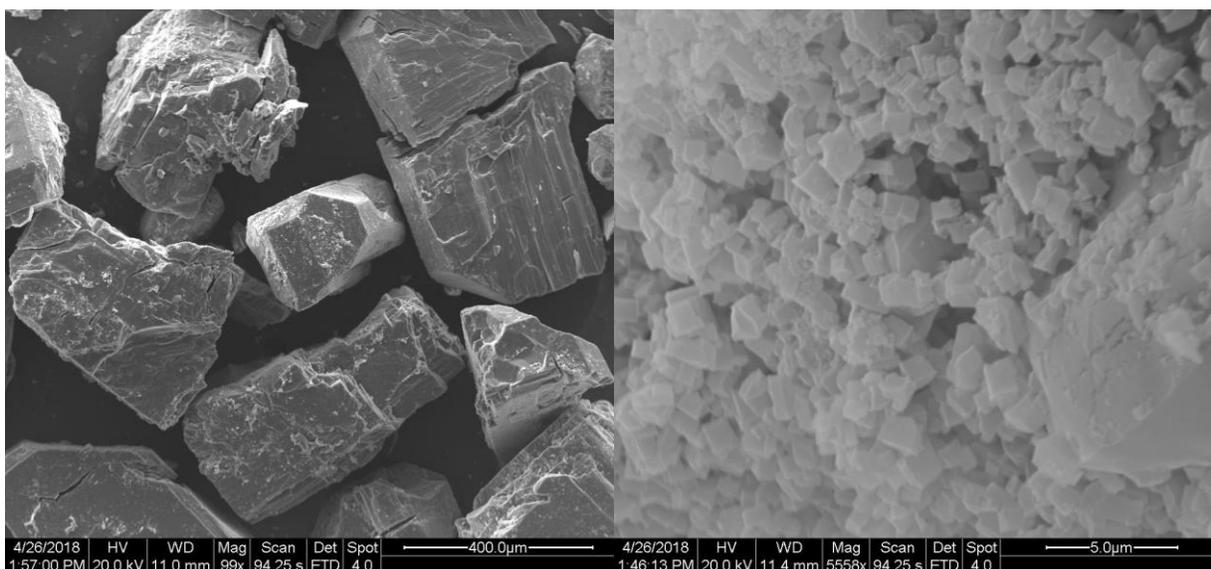


Figure 8. a) 99x magnification; b) 5558x magnification of one of the larger crystals seen on the left

To further analyze the crystals optically, the SEM was used to measure crystal sizes. Figure 9 shows a histogram of 152 crystals that were randomly chosen to be measured. The synthesized crystals ranged from 1 µm to 11 µm and the median crystal size was found to be 2 µm. In work done by Li et al, both micron sized crystals (1-10 µm) and nano-sized crystals (< 1 µm) were synthesized with similar processing conditions and appearance to those synthesized in this work [30]. Kar Yan et al synthesized cubic crystals averaging 3 µm in width [10]. The crystals synthesized in this study have similar appearance, structure, and sizes to those made in past literature, providing some evidence that the vapor diffusion process employed in this work is suitable for the formation of γ-CDMOFs.
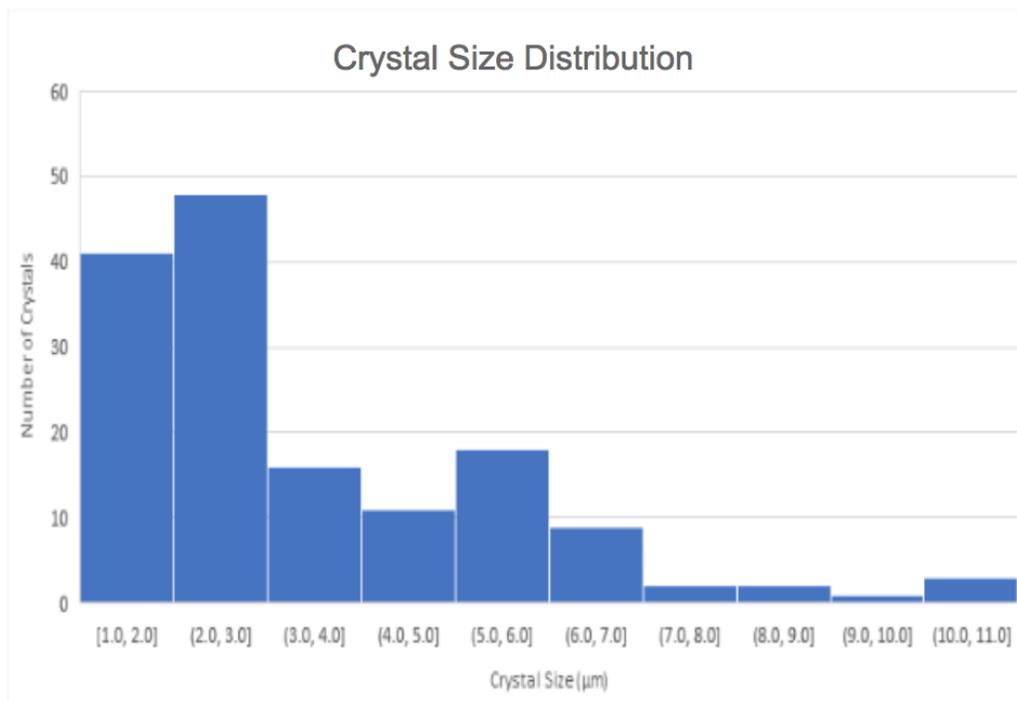
Figure 9. Histogram depicting the size of 152 randomly chosen crystals, resulting in a median crystal size of 2 µm

*3.2 X-Ray Diffraction*

Figure 10 shows the XRD diffractogram produced from the as-activated crystals. Three distinct peaks are seen, the first at 3°, the second at 5°, and the third at 7°. The peaks were determined to correspond to the 110, 200, and 211 crystallographic planes respectively. Diffractograms with similar peak angles are found throughout past literature. Intensities between batches can vary significantly due to factors such as the size of the crystal face or instrumentation differences, so only the peak angles were compared with past literature. γ-CDMOFs synthesized by Al-Ghamdi et al as well as Kar Yan et al had peaks at approximately the same angles, though different intensities [10, 13].

Bragg's Law was used to determine the d-spacing of the synthesized crystals. The d-spacing, or interplanar spacing, corresponds to the distance between planes of atoms that give rise to diffraction peaks. The d-spacing of the 110 plane was found to be 2.9 nm, somewhat larger than most in past literature. For example, Al Ghamdi et al calculated a d-spacing of 2.1 nm at that plane. The variance in d-spacings could be due to the different crystal face sizes and

instrumentation accuracy. It could also be due to differences in the residual moisture or volatile content of the crystals, which could slightly change the crystal structure or orientation.
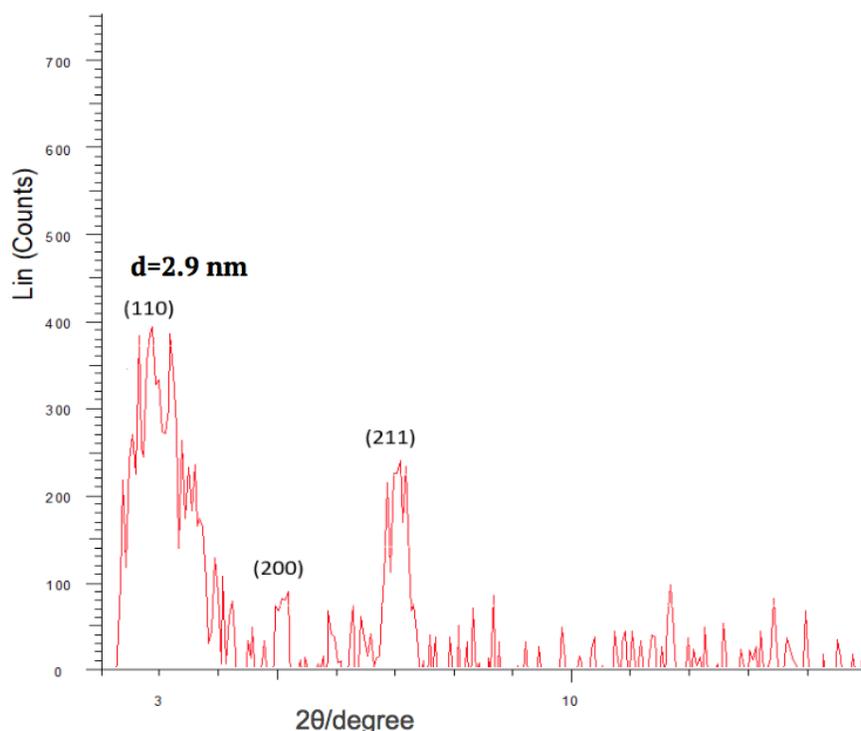


Figure 10. XRD diffractogram of the as-activated γ-CDMOFs showing three distinct peaks associated with different crystal planes

## 3.3 Thermogravimetric Analysis

The thermograms of the as-activated γ-CDMOF, pure compounds, and encapsulated γ-CDMOFs are shown in Figures 11-13. The as-activated sample (included as a reference on all thermograms) showed two drops of interest. The first, prior to 125°C, was associated with the expulsion of residuals such as water and methanol, and equated to about 8% of the mass. The second drop, with a peak mass loss at 185°C, was associated with the organic component of the γ-CDMOF. The leftover material that slowly diminished after this second drop was the inorganic potassium that required greater temperatures to fully degrade.

Pure theophylline and pure caffeine were tested to obtain degradation points for each (Figure 11). Both had smooth thermograms with a single distinct drop. Theophylline exhibited a peak

mass loss at 200°C while caffeine exhibited one at 191°C. They both degraded completely, due to being fully organic compounds with high purity. The degradation points acquired were used as a reference when analyzing the encapsulated frameworks.
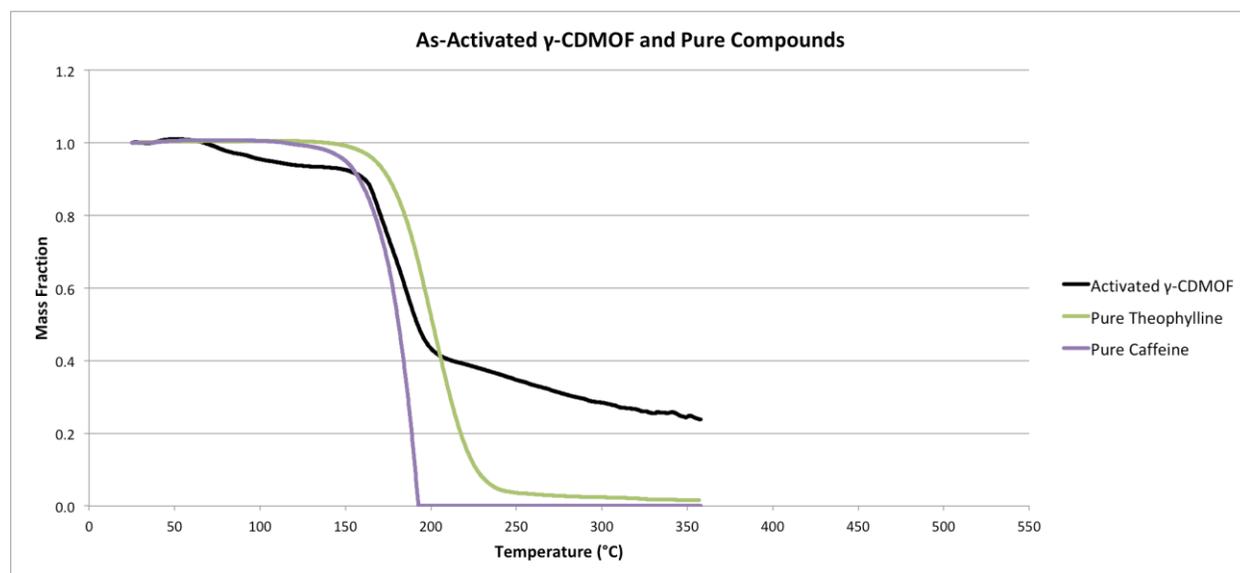


Figure 11. Thermograms of the as-activated γ-CDMOF, pure theophylline, and pure caffeine

The thermogram of the theophylline-encapsulated γ-CDMOF provided encouraging results (Figure 12). As shown in the as-activated sample, there was an initial drop (~8%) due to residuals. However, the next drop was larger than the as-activated sample and had two distinct slopes, as illustrated in the derivation curves. These two slopes correspond to two different degradation points. The first, peaking at 184°C, is associated with the organic component of the γ-CDMOF and aligns with the degradation temperature seen in the as-activated sample. The second, peaking at 205°C, is associated with theophylline degradation and aligns with the degradation temperature seen in the pure theophylline sample. The location of the peaks in mass loss provide some evidence that theophylline was encapsulated, while the remaining inorganic material after degradation provides further evidence. Despite having the same amount of residuals, the theophylline encapsulated sample lost 16% more mass than the as activated sample over the course of degradation. This is likely because the encapsulated sample had a higher percentage of organic material that could degrade due to the presence of theophylline. The location of the degradation peaks as well as the total amount of degradation both help to confirm that theophylline was encapsulated in the γ-CDMOF sample.
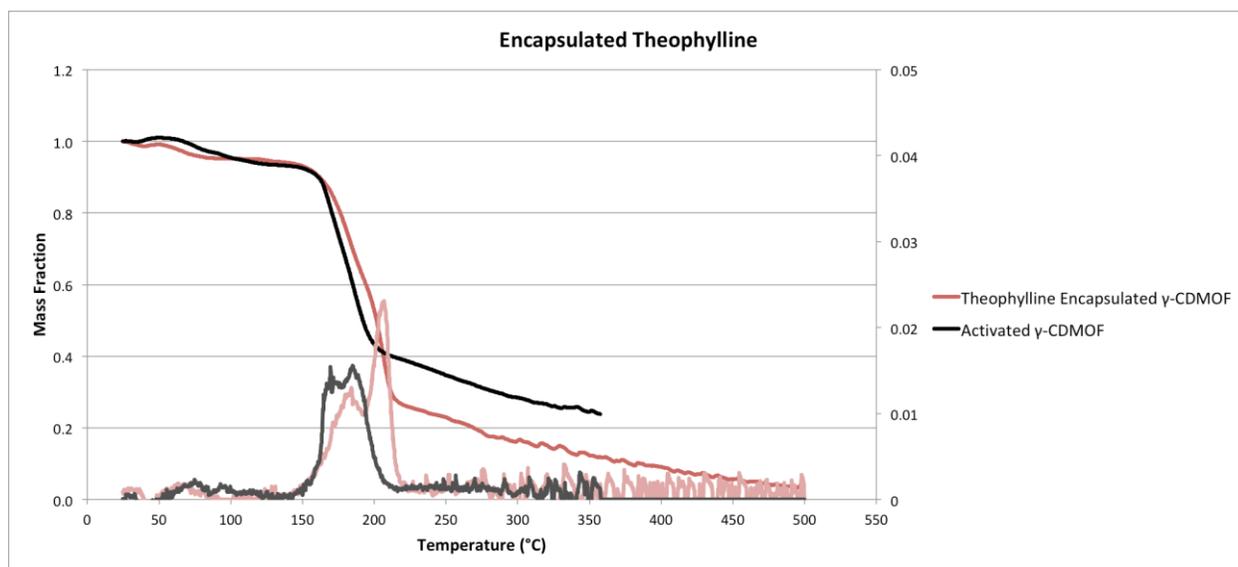
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Figure 12. Thermograms with derivation curves of the theophylline-encapsulated sample and the as-activated sample

The thermogram of the caffeine-encapsulated sample is shown in Figure 13. Once again, a drop due to residuals can be seen, yet it is much larger than observed in the previous samples (17% compared to 8%). This 9% difference in residual content is likely due to ethanol adsorption during the encapsulation procedure, however, the theophylline encapsulated sample did not show any sign of ethanol adsorption despite undergoing the same conditions. It is possible that caffeine exhibits a lower affinity for adsorption to the γ-CDMOF than theophylline and ethanol, but further testing and analysis would be required to find out.

Following residual loss, the rate of mass loss in the caffeine encapsulated sample rose slowly, having a small peak at 144°C before peaking once more at 190°C. The peak in mass loss at 144°C is unidentifiable and does not relate to any expected degradation point. The peak at 190°C comes where expected for caffeine expulsion (expected at 191°C), but a prior peak accounting for the organic component of the γ-CDMOF (expected at 185°C) is absent. Due to the missing peak and the closeness in degradation points of the organic component of the γ-CDMOF and the caffeine, the peak at 190°C could be a result of the degradation of either. For this reason, the peak locations of the thermogram do not provide clear evidence that caffeine was encapsulated. At first glance, the difference in inorganic material left at the end appears to show the presence

of caffeine but most of this difference can be explained by the extra residuals. Upon subtracting the difference in residual loss between the as-activated and the caffeine encapsulated samples, the caffeine encapsulated sample only lost 2% more mass over the course of degradation, which could be explained by sample variance. The high residual content, mass loss at unexpected temperatures, and missing degradation peaks make the data too inconclusive to state that caffeine was encapsulated.
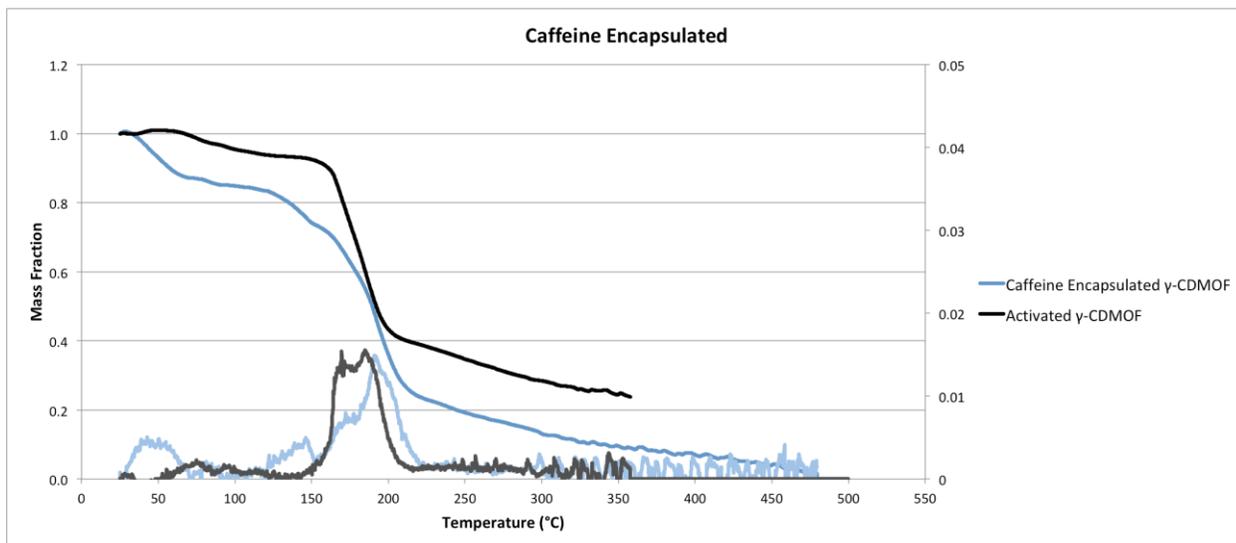


Figure 13. Thermograms with derivation curves of the caffeine encapsulated sample and the as-activated sample

## 4. Conclusions

1. Vapor diffusion is a viable synthesis method for ɣ-CDMOFs. SEM and XRD characterization confirmed that the synthesized crystals held similar shapes, sizes, and crystal structures to those from literature.

2. ɣ-CDMOFs are able to encapsulate theophylline, yet the data was not conclusive enough to confirm the encapsulation of caffeine.

## 5. Recommendations and Future Work

The work conducted in this study was a preliminary investigation on the encapsulation of methylxanthines in γ-CDMOFs. Problems arose that would need to be addressed before industry use. First, the activation process needs to be improved. As shown in the TGA curves, there was residual solvents encapsulated into the γ-CDMOFs. Even small amounts of residual solvents such as methanol or ethanol would make the γ-CDMOFs unusable for drug delivery. Activating under vacuum or increasing the activation time could help expel the unwanted residuals and allow for the γ-CDMOFs to be completely biocompatible.

Another way to reduce the effect of the solvents would be to use organic compounds in liquid form. The anhydrous forms of the caffeine and theophylline required the use of ethanol in order for successful encapsulation, which resulted in inconclusive evidence for γ-CDMOF encapsulation of caffeine. Compounds in liquid form would allow for the encapsulation into γ-CDMOFs without the need for ethanol.

Lastly, to be viable for use in industry, the γ-CDMOFs will need to encapsulate a higher amount of the organic compounds. In previous work, ZIF-8, a zeolitic MOF, was shown to encapsulate up to 28 wt% caffeine [23]. Based on the TGA thermograms, assuming no variance between the as-activated and theophylline encapsulated samples, only 14 wt% theophylline was encapsulated in this study. However, if residual adsorption could be mitigated, a higher organic compound concentration could be encapsulated. Thanks to their non-toxicity and low cost, better encapsulation yields could make γ-CDMOFs more desirable than most nanoporous materials for biomedical applications.

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