A γ-Cyclodextrin-based Metal–Organic Framework (γ-CD-MOF): A Review of Recent Advances for Drug Delivery Application

Asma Hamedi [1], Anastasia Anceschi [2*], Alessia Patrucco [2], Mahdi Hasanzadeh [3]

[1] Department of Physics, Faculty of Science, Yazd University, P.O. Box 89195-741, Yazd, Iran

[2] CNR-STIIMA, Italian National Research Council, Institute of Intelligent Industrial Technologies and Systems for Advanced Manufacturing, Corso G. Pella 16, 13900, Biella (BI), Italy

[3] Department of Textile Engineering, Yazd University, P.O. Box 89195-741, Yazd, Iran

hamedi.asma66@yahoo.com (A. Hamedi)

m.hasanzadeh@yazd.ac.ir (M. Hasanzadeh)

alessia.patrucco@stiima.cnr.it   (A. Patrucco)

*Correspondence: anastasia.anceschi@stiima.cnr.it (A.A.)

Abstract

The relatively new class of porous material known as metal-organic framework (MOF) exhibits unique features such as high specific surface area, controlled porosity and high chemical stability. Many green synthesis approaches for MOFs have been proposed using biocompatible metal ions and linkers to maximise their use in pharmaceutical fields. The involvement of biomolecules as an organic ligand can act promising because of their biocompatibility. Recently, cyclodextrin metal–organic frameworks (CD-MOFs) represent environmentally friendly and biocompatible characteristics that lead them to biomedical applications. They are regarded as a promising nanocarrier for drug delivery, due to their high specific surface area, high porosity, tunable chemical structure, and easy fabrication. This review focuses on the unique properties of CD-MOF and the recent advances in methods for the synthesis of these porous structures with emphasis on particle size. Then, the state-of-the-art drug delivery systems with various drugs along with the performance of CD-MOFs as efficient drug delivery systems are presented. Particular emphasis is laid on researches investigating the drug delivery potential of γ-CD-MOF.

Keywords: Cyclodextrin; metal-organic framework; synthesis; drug delivery, bioavailability, MOF, drug encapsulation, drug loading.

1. Introduction

Metal-organic frameworks (MOFs) are highly porous crystalline materials comprising organic ligands and metallic ions/clusters. The unique physical and chemical characteristics such as simple synthesis method, large specific surface area, high porosity, controllable pore structure, and functional surface chemistry, have caused considerable attention to these structures [1–5]. MOFs have been considered for diverse potential applications such as adsorption [6–8], gas storage [9], separation [4], catalysis [10], ion exchange [11], water splitting [12, 13], sensing [14] and health care systems [15]. More recently, MOFs have found increasing interest in drug delivery [16, 17]. For instance, Liu et al. [18] investigated the copper-based MOF as a drug carrier to support the sustained pH-responsive release of 5-fluorouracil. In another study, controlled release of anticancer drug-loaded MOF system has been reported [19]. The successful drug release controllability of the pH-responsive loaded drug within MOF has been investigated as well [20].

MOFs are generally synthesized through different approaches, the most common of which is hydrothermal or solvothermal techniques. Several studies have been carried out on synthesizing biocompatible MOFs using non-toxic metal ions such as potassium, calcium, and titanium as well as naturally and biologically occurring compounds such as peptides, carbohydrates, amino acids, cyclic oligosaccharide (cyclodextrins) and their derivatives [21, 22]. Nowadays, for the synthesis of MOFs, iron, zirconium, and zinc are the most employed for the drug delivery systems [1]. Other researchers are focussed on the use of some transition metals for the synthesis of MOFs suitable for drug delivery applications. For instance, Férey and co-workers used the Cr (III) for the synthesis of MOFs, whereas McKinlay et al. employed copper [2 e 3]. Cyclodextrins (CDs) are generally classified into three categories of α-, β-, and γ-CDs consisting of six-, seven-

, and eight-membered sugar rings, respectively. Cyclodextrin-based MOFs (CD-MOFs) are considered environmentally friendly and biocompatible MOFs, attracting most research interest. Generally, one of the primary merits of the MOFs is their variability of both constitutive metals and organic linkers. In particular, the organic linkers perform a main part in the 3D supramolecular. The use of cyclodextrins as ligand is attracting interest due to their intrinsic properties to to stabilize labile guests against oxidation by tailoring the physical properties of guest molecules. Among three types of CDs, γ-CD has been used to prepare biocompatible MOFs due to the presence of -OCCO- binding groups in the primary and secondary faces. These binding groups can be used to form complexes with metal ions, whereas these kinds of structural advantages are not observed in α- and β-CDs . For this reason, the publication tendency revealed an increasing interest in CD-MOF for different applications as shown in Table 1:

Table 1: Number of publications on cyclodextrins MOF (Source: Web of science)

As seen in figure 1, the number of articles grown from 1 article in 2006 to 41 articles in 2019, which increased greatly from 2016. This indicates that the research on CD-MOF is attracting the interest of many researchers in recent years. During the first decade (2006–2016), only 10% of the total articles were published, whereas in the last 3 years from 2017 to 2020, 79% of the total works was published.

Also, the number of citations is increased as shown in figure 1:

Figure 1: Number of citations related with cyclodextrin MOF publications (source: Web of science)

As reported in figure 1, the citations number of academic papers reflects the academic impact of the papers. For the 143 papers, the maximal value of total citations was 1200 in 2020. The annual total citations were much higher from 2016 to 2020 due to the increase of publications during that period. However, it is predictable that the total citations in recent years would increase further over time.

Interestingly, the 143 articles published covers different area of interest as shown in figure 2:

Figure 2: Area of interest related with cyclodextrin MOF (source: Web of science)

As shown by figure 2, many are the interest fields covered by the cyclodextrins MOFs. This multidisciplinary of CDs MOF is related with the polyvalency of these kinds of materials. Indeed, they found out applications in many fields, such as: adsorption or capture of CO_2, removal of pollutants from aqueous solution and in drug delivery systems [23].

As the CDs can be used as a ligand for the synthesis of MOFs, among three types of CDs, the γ-one has been used for the synthesis of biocompatible MOFs. The internal cavity of CDs provides a suitable accommodation site for guest molecules like drugs, nanoparticles, and gases as briefly shown in figure [24][25].

Figure 3: Host-guest complexes of cyclodextrins

This unique properties of the cyclodextrins can be exploited in MOFs, offering interesting inclusion properties due to the presence of intrinsic cavities in CDs and of the ordinated porous structure of MOFs.

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In this paper, it will be provided a detailed review of the recent developments on relevant literature related to the synthesis of CD-MOFs with particular emphasis on their drug delivery applications. The synthetic approaches as well as their limitations and challenges are described. Finally, the various drug-loaded CD-MOFs currently under investigation for drug delivery are summarized and some of the most recent advances in the field are highlighted.

2. Synthesis of γ-CD-MOF

A typical synthesis process of MOF includes metal ion and organic ligands which form coordination bonds resulting in a highly crystalline structure with extremely high surface area. Generally, in the synthesis of the γ-CD-MOFs, γ-CDs are linked by alkali metal ions, mainly potassium ions, to form a symmetrical structure. An extended 3D structure is formed by the connection of six cubes of γ-CD with four potassium ions and the X-ray analysis reveals that each potassium ion forms eight coordination bonds combining two primary hydroxyl groups, two glycosidic rings and four secondary hydroxyl groups [26].

For the first time, γ-CD-MOF was provided by a vapor diffusion method within 2-7 days [27]. Then, to reduce the formation time and size of the crystals, other techniques such as hydrothermal, modified vapor diffusion, ultrasonic and microwave-assisted syntheses were used.

2.1. Vapor diffusion method

Colorless, cubic, single crystals (200−400 μm) of CD-MOF have been made via a vapor diffusion procedure [27],[28],[29],[30] with a molar ratio of KOH to γ-CD of 1:8 in aqueous solution, subjected by releasing methanol (MeOH) vapor into the solution from 2 to 7 days. The

separated white crystals were washed with MeOH and parched at 50 °C overnight under a vacuum. A schematic representation of the vapor diffusion synthesis is reported in figure 3:

Figure 4: Schematic representation of the vapor diffusion method

In the synthesis of CD-MOF-2 and CD-MOF-3, RbOH and CsOH were used as metal sources, respectively. Their production method was similar to that of CD-MOF-1 [27]. Simultaneous crystallization of K^+ and Li^+ ions with γ-CD was performed by the vapor diffusion method. Although Li^+ ions have somewhat occupied K^+ sites, the framing entirety and convenient porosity of CD-MOF-1 have remained. To achieve the highest possible share of Li^+ ions in the framework, a series of experiments were performed to change the ratio of K^+/Li^+ to γ-CD. The combination of the two metals seems to be effective whereas, the results for CD-MOF-1 including only Li^+ ions produced non-porous materials [31].

Interestingly, the smaller cubic crystals of γ-CD-MOF (5–10 μm) were prepared using an innovative modified vapor diffusion method by adding cetyltrimethylammonium bromide (CTAB) as a surfactant. Also, nanocrystals (200-300 nm) could be obtained by adding both CTAB and methanol during the generation process [32],[33],[34]. The γ-CD-MOF crystal size could be regulated by changing parameters such as the reactant concentrations, temperatures, time, γ-CD ratio to KOH, CTAB concentrations, and solvents [35]. Since CTAB is toxic and carries a venture of sample pollution, it was demonstrated that it is possible to obtain porous cubic crystals using a modified vapor diffusion route without adding any surfactant or emulsifier [36]. Briefly, the γ-CD-MOF cubic crystals (10–15 μm) were prepared by dissolving 1.0 mmol of γ-CD and 8.0 mmol of KOH in 20 mL of deionized water. After filtering, a vessel containing

the product is moved within a Teflon autoclave including methanol, followed by vapor diffusion

of MeOH at 80 °C for 15 h. After cooling the autoclave, the crystals were washed with MeOH

and dried at 40 °C in an oven for 6 h. As a result, increasing the pressure and temperature inside

the autoclave reduced the crystal formation time from 7 days to 15 h and the size of crystals

varies from 200-400 μm to 10–15 μm.

2.2.   *Hydrothermal method*

A reformed hydrothermal procedure is reported in figure 5 and it was used to reduce the reaction

time and the γ-CD-MOF crystals size [37].

Figure 5: Schematic representation of hydrothermal method

Various parameters such as reagent concentration, γ-CD to KOH molar ratios, solvent nature,

surfactant, temperature and time were investigated for better tailor the γ-CD-MOF crystals size

and the grade of crystallization. Micron (5–10 μm) and nanometer (500–700 nm)-sized CD-MOF

particles were produced by combining KOH and γ-CD in an aqueous solution and adding

methanol at 50 ° C for 6 h [38]. In a similar work, polyethylene glycol 20,000 (PEG 20000) was

used instead of CTAB as a surfactant [39]. The advantage in PEG 20000 is that it is not toxic as

the CTAB and it allows a good and fast formation of crystals. In summary, 64.8 g of γ-CD and

22.4 g of KOH were dissolved in 2000 mL purified water and adding 1200 mL of methanol. The

blend was settled in a water bath at 60 °C to obtain a clear solution. 12.8 g of PEG 20000 was

used for the quick formation of crystalline particles. The suspension was placed in ice water for

12 h. Then, micron cubic crystals (1-5 μm) were centrifuged, washed, and dried for 5 h at 60 ° C [39].

2.3. Microwave Method

The γ-CD-MOFs micron and nanometer crystals were also provided using a rapid and facile technique under microwave irradiation [40]. In the microwave method, PEG 20000 and MeOH were used as size modulators as shown in figure 6.

Figure 6: Schematic representation of microwave method

Surprisingly, 100−300 nm crystals were prepared by blending MeOH with PEG 20000 pending modulation procedure. Concisely, nanometer-sized crystals were prepared by dissolving 325 mg and 112 mg KOH in 10 mL water with the addition of 16 mL of MeOH with 128 mg of PEG 20000. The mixed solution was then heated at 50 °C for 10 min. Then, 256 mg of PEG 20000 was added quickly to crystallize. Nanometer-sized crystals were formed after 1 h, washed with MeOH and EtOH, and dried at 50 °C. The γ-CD-MOF crystals size was optimized by changing several parameters such as reaction time, temperature, the solvent ratio of water to MeOH, and modulators [40].

2.4. Ultrasonic Method

The γ-CD-MOF was also fabricated using the ultrasonic method [41]. Briefly, 112 mg of KOH and 324 mg of γ-CD were added to 10 mL of water with the addition of 6 mL of MeOH. The mixed solution was warmed through ultrasound for 1 h to obtain a clear solution. Then, 128 mg

of PEG 20,000 was added rapidly to form crystals. White crystals were observed after 12 h, washed three times with MeOH, and dried at 50 °C [41]. A schematic representation of the ultrasonic method is reported in figure 7.

Figure 7: Schematic representation of ultrasonic method

Recently, the γ-CD-MOF crystal size (around 500 nm) was successfully adjusted using a combination of solvothermal method and ultrasonic method and finally, the crystals formation time was reduced to 1 h [42]. 3.24 g of γ-CD, 1.12 g of KOH, and 100 mL of deionized water were mixed via ultrasound for 30 min. After filtering, MeOH was added to the solution and heated in an ultrasonic bath until the cloudy liquid became clear. PEG-20000 and MeOH were added to the clear solution and the crystals were formed rapidly and washed by MeOH and EtOH. The crystals were then soaked in dichloromethane for three days, centrifuged, and dried in a vacuum overnight [42].

In all the methods mentioned in Table 2, increasing the temperature and reducing the formation time of the crystals and using surfactants have been resulted in the production of nanoparticles. However, CTAB is toxic and it is suggested that non-toxic and cost-effective surfactants can be used to synthesize γ -CD-MOFs. In the mentioned methods, except for the original vapor diffusion method and the modified vapor diffusion method by Hamedi et al., [36] two or three steps have been used to produce particles. It is recommended to work on a single-step method for the production of nanoparticles.

Table 2: Summary of different synthesis methods of γ-CD-MOFs

In table 3 are reported the advantages and the disadvantages of the proposed synthesis.

Table 3: Advantages and disadvantages of the different synthetic procedures

A summary of all the methodology for the synthesis of γ-CD-MOF previously described, is reported in figure 8.

Figure 8: Schematic representation of γ-CD-MOF synthesis using a) vapor diffusion, b) hydrothermal, c) ultrasonic, and d) microwave methods.

3. Drug delivery application of γ-CD-MOF

CD-MOFs have been applied in a variety of fields such as CO_2 capture [36], insecticide adsorption and removal [43], sensor [44], and food packaging [45], as briefly described in figure 9.

Figure 9: Summary of some possible application of CD-MOFs

Besides these applications, the unique properties of these materials, such as high porosity and large specific surface area make them suitable for pharmaceutical application and in drug delivery systems. In particular, γ-CDs were successfully used as a ligand to synthesize biocompatible MOF [46]. The biocompatibility of γ-CD-MOF was excellent since cyclodextrin was widely used in drug delivery and proven to be safe [24], [47]. Some preliminary results show the safety profile of γ-CD–MOFs and implemented them in HepG2 (human hepatoma) and

Caco-2 (human epithelial colorectal adenocarcinoma) cells. Moreover, the CD–MOF does not induce any toxicity up to 2000 μg/mL of concentration [29]. The homogenous structure and the nanoscale porosity of γ-CD-MOF effectively improve the drug delivery performances of the material. Indeed, drug molecules containing carboxyl or hydroxyl groups and with suitable size can be loaded into γ-CD-MOF, exploiting electrostatic interaction and hydrogen bonds. Thus, γ-CD-MOF can effectively be used for loading drug molecules and consequently found out the application as a drug delivery system. Some of the pharma applications in which the γ-CD-MOF are effectively tested are reported in figure 10.

Figure 10: γ-CD-MOFs for drug delivery application

Table 4: γ-CD-MOFs for drug delivery application

3.1.   Encapsulation and delivery of Lansoprazole, Fenbufen and Ibuprufen

Lansoprazole (LPZ) is a proton pump inhibitor and is largely employed to reduce gastric acid secretory healing gastric ulcers and reflux esophagitis in treated patients [48]. Anyway, the administration of this drug has many drawbacks mainly due to its instability. Li et al. [33] loaded LPZ in CD-MOF-1 mixing LPZ, γ-CD, and KOH in an aqueous solution. Then, the loaded crystals are washed with ethanol and dried at 50°C overnight. They also tested the CD-MOF-2 that are synthesized like CD-MOF-1, but in this case, the supernatant is transferred in a tube and CTAB is added. After that, the sample is incubated at room temperature for 3 h and washed with ethanol and dried at 50°C overnight. The SEM characterization underlines that all the synthesized CD-MOF show cubic crystals, but the addition of CTAB during the synthesis lead to CD-MOF cubes with regular sizes of around 6 μm.

The LPZ-loaded CD-MOF-2, also, presented the same size ($\sim$ 6 µm) and cubic morphology. The elemental analysis and the HPLC confirm the presence of drug inside the LPZ loaded CD-MOF-1 and LPZ loaded CD-MOF-2. The payload is 21.4 ± 2.3 wt.% and 23.2 ± 2.1 wt.%, respectively, enhancing the excellent affinity of LPZ for CD-MOFs. Interestingly, they, also, found out that the loaded γ-MOF were stable for over two years and the extracted drug showed similar fluorescent spectra of the free one. The stability of the loaded-CD-MOF for over two years allows the use of these materials for being actually applied in drug delivery systems.

CD-MOF-1 was also used for carrying the Fenbufen. Fenbufen is a nonsteroidal anti-inflammatory, analgesic, and antipyretic agent interesting because of its high analgetic efficacy and long duration of action [49]. Liu and co-workers effectively used the γ-CD-MOFs for loading Fenbufen [40]. The synthesis of the γ-CD-MOFs was carried out by microwave irradiation of a water solution of γ-CD, KOH, and methanol. Modifying different processing parameters such as temperature, reaction time, and the ratio between water and methanol, it was possible to modulate the dimension of the γ-CD-MOF crystals. The Fenbufen was loaded into the γ-CD-MOFs by mixing in ethanol the MOFs with 600 mg/mL of Fenbufen solution. Using the HPLC, the adsorption of the drug was estimated and different sized γ-CD-MOF were physically characterized. The specific surface area of the γ-CD-MOF was evaluated using Langmuir model. It was found out the γ-CD-MOF with a size between 100-300 µm shows a high specific surface area of about 751 m^2/g and a rapid and high adsorption capacity for Fenbufen (196 mg/g). The FT-IR also confirmed that Fenbufen is loaded inside the cavities of γ-CD-MOFs rather than adsorbed on the surface of the sample due to the shift or absence of the peak at 1712 cm^{-1} related with the C=O stretching of the free Fenbufen.

Similar to the Fenbufen, the ibuprofen could be successfully loaded inside the CD-MOF-1 [37, 50]. Ibuprofen is one of the widely used nonsteroidal anti-inflammatory and analgesic drugs. It is almost insoluble in water and so for increasing the oral bioavailability uptake, the period of the analgesic and anti-inflammatory effect and for avoiding the production of pure ibuprofen salts, Hartlieb et al. [50] successfully incapsulate ibuprofen into CD-MOF-1. The ibuprofen was loaded into the MOFs using two methods. The first consists in the crystallization of γ-MOF with potassium salts of ibuprofen. In this case, potassium is also the source of metal cations required for the construction of the framework. In the second methodology, the CD-MOF-1 was synthesized using potassium hydroxide in ethanol vapor diffusion of a water solution and the incorporation is made by the absorption of the free-acid form of ibuprofen. After the first synthesis, the presence of the ibuprofen was checked using X-ray diffraction and ^{1}H NMR. The NMR comparison between the integration of the signals attributed to the γ-CD with the signals of the ibuprofen, it was possible to estimate the amount of drug-loaded and it was about 23%. However, the XRD analysis pointed out that the ibuprofen was not located within the framework due to the wide disorder inside the pore structure. On the contrary, in the second approach, the loading of ibuprofen was determined dissolving the crystals in several solvents and analyzed using UV–vis spectroscopy. The amount of ibuprofen absorbed is influenced by the selected solvent. The use of non-polar solvents, such as hexanes and CH_2Cl_2, lead to low absorption of ibuprofen within CD-MOF-1, around 5 wt.%. When ethanol is used, the encapsulation efficiency of ibuprofen is raised to 26 wt.%. The purposed mechanism of loading is related to an anion exchange process. Free acid of ibuprofen is deprotonated by the hydroxyl anions of the CD-MOF-1. The adsorption of Lansoprazole and Ibuprufen depends on the solvent use. A brief

representation of the amount of the two drugs loaded in different solvents is reported in figure 11.

Figure 11: Drug loading percentages (%, w/w) of Ibuprufen (IBU) and Lansoprazole (LPZ) in CD-MOF [37]

Further supporting evidence was that when loading is attempted on CD-MOF-1 prior subjected to an anion exchange with HCl, less than one percent of ibuprofen loading was reached in ethanol. The CD-MOF-1 was also able to be selective in the capture of ibuprofen in a racemic mixture. Enantioselective uptake of ibuprofen was observed within CD-MOF-1 indicating that the MOF could be used to separate enantiomers. Moreover, the CD-MOF-1 was tested in vitro on two cell lines and it resulted to be non-toxic and consequently checked for animal studies. The animal test showed that the maximum concentration of ibuprofen in plasma for the two samples was reached rapidly, between 10-20 min, which is a good value for analgesic drugs. Unexpectedly, it was found out that the physical mixture of γ-CD, ibuprofen, and KOH does not exhibit the same advantages that had been reported for CD-MOF-1, but the pharmacokinetics of ibuprofen across different species are different, and so further studies focused on other animal targets should be carried out.

For improving the performance of CD-MOF-1 as ibuprofen and lansoprazole carrier, Li and co-worker embedded in polymer matrices the γ-CD-MOF. Submicron sizes CD-MOF-1 vesicles were produced.

They are composed of CD-MOFs and polyacrylic acid (PAA), obtained by a solid in oil-in-oil (s/o/o) emulsifying solvent evaporation technique [37]. The encapsulation of ibuprofen and lansoprazole inside CD-MOF-1 was carried out using both an impregnation approach and a co-

crystallization method. The ibuprofen loading capacity of CD-MOF-1/PAA was about 12.7 wt.%, whereas for lansoprazole was 4.5 wt.%. The drug release profiles of ibuprofen and lansoprazole were carried out in vitro under simulated physiological conditions and the reactivity is shown in figure 12.

Figure 12: Schematic representation of drug release

Ibuprofen was slowly released over 48 h, whereas lansoprazole showed a linear release profile during 48 h. By the Grand canonical Monte Carlo (GCMC) simulations of IBU adsorption in CD-MOF, they found out that strong electrostatic interactions were identified between IBU and CD-MOFs on account of the existence of charge-compensating OH^- anions present in CD-MOFs which enhance the adsorbate–adsorbent interactions and induce a slower release. This observation reflects the outstanding dispersion of nanometer-sized drug-CD-MOFs and a homogeneous distribution of drug molecules co-crystallization-loading process is applied. The cellular toxicities of CD-MOF/PAA composite microspheres were assessed using an MTT assay for determining the cell viability values [51]. The obtained results confirmed that the composite of CD-MOF/PAA microspheres improves the cytocompatibility and to be safe for drug delivery.

3.2. *Encapsulation and delivery of ketoprofen*

The nanoscaled homogenous pores of CD-MOF-1 could effectively be used for aerosolization applications. The particle size of CD-MOF-1 could be planned to modulate some reaction factors during synthesis making them suitable for lung diseases. Pulmonary drug delivery has attracted great interest due to many advantages with respect to intravenous and oral administration. Particularly, pulmonary drug delivery systems can directly carry therapeutic agents to the lungs for local ailments such as respiratory diseases and lung cancer, but also significantly promote the

drug absorption for systematic disease [52]. CD-MOF-1 could be a potential vehicle for the pulmonary drug due to its homogenous nanoscale pore, possibility to tailor the dimensional size, and good biocompatibility. Zhou et al. [53] loaded the drug into CD-MOF by a co-crystallization method during the synthetic process in a single step and denoted as CD-MOF-K-A, CD-MOF-K-B, and CD-MOF-K-C, in which the solutions volume, water bath, temperature, and time were accurately changed and used. These MOFs were applied for pulmonary drug delivery system as shown in figure 13.

Figure 13: Pulmonary drug delivery system action of γ-MOFs

The loaded drug was ketoprofen, which is a nonsteroidal anti-inflammatory drug belonging to the group of substituted 2-phenyl propionic acids. It is scarcely soluble in water and so the purpose is to increase both drug encapsulation stability into the MOFs and its clinical efficacy [54]. During the loading process, some interactions could contribute and promote drug absorption into the cavity of CD-MOF. For instance, hydrogen interaction between the carboxyl groups of ketoprofen and hydroxyl groups of γ-CD and strong electrostatic interactions between ketoprofen and potassium ions could occur leading to ketoprofen loading of 2.77% in CD-MOF-K-A, 2.89% in CD-MOF-K-B, and 2.17% in CD-MOF-K-C, 2.89%. The in vitro drug release profiles of CD-MOF-K-A and ketoprofen were investigated in surrogate lung fluid (SLF) to simulate the lung conditions. The amount of ketoprofen released from CD-MOF-K-A within 2h was 89%. This result can be related to the fact that ketoprofen is a weakly acidic drug with pH-dependent solubility and so the buffer salts improve its dissolution rate and the solubility of ketoprofen. In vitro assessment of drug delivery efficiency of inhalation, particles were tested

using the next-generation pharmaceutical impactor (NGI). It was found out that the deposition rate of CD-MOF-K-A was higher than CD-MOF-K-B and CD-MOF-K-C. The drug deposition rate at pre-separator for CD-MOF-K-B was better than those for CD-MOF-K-A and CD-MOF-K-C. This behavior can be linked a potential particle agglomeration of CD-MOF-K-B. The evaluation of the fine particle fraction (FPF) underlined that the value obtained for CD-MOF-K-A (57.99%) was significantly higher than CD-MOF-K-B (25.14%) and CD-MOF-K-C (11.38%). The FPF values of CD-MOF-K show a correlation with the particle diameters, suggesting that the aerodynamic performance of CD-MOF-K could be improved using different synthesis conditions to tailor the particle size. Furthermore, for pulmonary administration, drugs could enter the blood circulation, and subsequently, the blood compatibility was investigated showing a low value of hemolytic phenomenon. Additionally, the in vivo test confirms the good biocompatibility of the CD-MOF. Indeed, no inflammatory reactions were pointed out by the histological analysis, and the section of the major organ was not damaged, suggesting that the CD-MOF can effectively be used as pulmonary drug delivery carriers.

3.4 Encapsulation and delivery of phytochemicals

Since the CD-MOF-1 can be tailored, many researchers focused their attention on the possibility to use MOFs as a micro-container to improve the stability of guest molecules. In particular, phytochemicals derived from natural food required to be better stabilized in order to improve their health activities.

3.5 Curcumin

The major component of turmeric is curcumin commonly used as a spice and food dye. Recently, it gained attention due to its biological and pharmacological activities. It has been found out to have anti-inflammatory and antioxidant activity, anti-cancerogenic effects and it is also a fluorescent molecule [55]. Curcumin is unstable in neutral and alkaline conditions and so it should be protected. Several approaches have been carried out to protect and deliver it. Moussa and co-workers [56] successfully encapsulated curcumin inside CD-MOF-1.

From the fluorescence spectra of curcumin encapsulated, it was also found out that the interaction between curcumin and γ-cyclodextrin is different from that between curcumin and MOFs. The presence of potassium ions in CD-MOF-1 could promote the interaction and coordination of curcumin with CD-MOFs. Thus, CD-MOF-1 incorporates within the pores the curcumin increasing the stability to a half-life value of about a million hours at pH 11.5. In conclusion, CD-MOFs showed to be a promising system for loading and stabilizing curcumin for many applications.

3.6 Capsaicin

About phytochemicals derived from natural food, Venkataswamy et al. [57] encapsulated capsaicin inside γ-CD-MOF. Capsaicin is the active principle of hot chili pepper and it seems to be effective in reducing the transmission of painful stimuli from the peripheral nerve fibers to the higher centers. Topical capsaicin can be used as adjuvant therapy in conditions such as post-herpetic neuralgia, diabetic neuropathy, and osteoarthritis, where the pain can be chronic and difficult to treat [58]. The poor aqueous solubility of capsaicin makes it unsuitable for oral ingestion. Venkataswamy loaded capsaicin via crystal growth achieved by vapor diffusion of

ethanol to synthesis solution consisting of γ-CD, KOH, and capsaicin. ^{1}H NMR and FTIR underlined the effective encapsulation of capsaicin inside the MOF.

3.7 Sucralose

Sucralose is another example of an unstable compound. Sucralose is an artificial sweetener relatively new and non-nutritive with a high sweetness without bitter nor metallic taste [59]. As a result of these properties, sucralose is widely used for pharmaceutical applications [60]. Sucralose was initially considered safe, but recently it was pointed out that this molecule could be degraded even at mild temperatures with the generation of polychlorinated aromatic hydrocarbons [61].

Micro and nanoscale CD-MOF-1 can be successfully used as a micro/nano-vehicle and it is also able to protect the sucralose from degradation [62]. Sucralose was loaded into basic CD-MOFs and to neutralized CD-MOFs by incubating CD-MOFs with sucralose solution and different concentrations of sucralose solutions were investigated. The BET surface area of CD-MOF-1 and sucralose loaded-MOF-1 was evaluated. It was found out that the presence of sucralose led to a significant decrease in N_2 uptake proven the interaction between sucralose and the CD-MOFs. Indeed, the sucralose occupies the empty interconnected pores of the MOF framework leaving to a low residual porosity in the MOF samples after the inclusion of sucralose molecules in their pores. Furthermore, the sucralose typically presents a significant weight loss starting at 123 °C. The inclusion complexes showed a shift of the sucralose decomposition to higher temperatures. This result clearly indicated stabilization of the sucralose by the MOF. Using the MOF in nanoscale the degradation temperature was further shifted to a higher temperature, hence the MOFs were able to protect the sucralose prolonging its thermal decomposition. Moreover,

the cubic structure of CD-MOF-1 did not collapse upon sucralose encapsulation, and a proper amount of sucralose can be loaded.

3.8 MOF modification

3.5.1 PEG

Since CD-MOF-1 is susceptible to an aqueous environment, the improvement of the water-stability of CD-MOF-1 for loading drug molecules is gaining attention. Liu et al. [40] synthesized CD-MOFs with microwave irradiation and PEG 20000 was used as the size modulator. The control of size and morphology were obtained and optimized controlling the reaction time, temperature, and solvent ratio during the synthesis process. Fenbufen was selected to investigate the drug loading behavior in micro and nano-MOF. Rapid adsorption over the first h was exhibited with a loading of 196 mg/g. After 2 h the equilibrium was reached. The adsorption kinetics were fitted with a pseudo-second-order kinetic model suggesting that the drug adsorption is mainly associated with chemisorption behavior.

3.5.2 Cholesterol

To develop CD-MOFs with good stabilities in aqueous environments, Singh and co-workers [63] synthesized an effective strategy to graft cholesterol to form a protective hydrophobic layer over the surface of CD-MOFs maintaining an intact outer and inner crystalline structure as shown in figure 14.

Figure 14: Protective hydrophobic layer of cholesterol on γ-MOFs

The chemical reaction was set up for the surface modification of CD-MOFs with cholesterol using a coupling agent and a catalyst at 45 °C in DMF for 24 h. The FT-IR and Raman

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spectroscopies showed a bond between the cholesterol and hydroxyl groups of γ-CDs in CD-MOFs, confirming the grafting. The thermal and HPLC studies allowed to determine the amount of grafting. It was found out that around 3.4 wt.% is grafted with cholesterol. The SEM analysis revealed that cholesterol-modified CD-MOFs have similar morphologies and size distributions to CD-MOFs, showing that the grafting reaction did not affect the supramolecular structures. The cholesterol-modified CD-MOFs were able to retain their porosity, morphology, and crystallinity even after 24 h of water treatment. The cholesterol-modified CD-MOFs were loaded with doxorubicin (DOX) simply by soaking from aqueous solutions, reaching drug adsorption capacities of 60–80 mg/g with a pseudo-second-order kinetic model. Doxorubicin (DOX), an anthracycline and effective anticancer drug, has been widely used in chemotherapy for the treatment of various cancers. The use of DOX has many drawbacks such as intercalation into DNA disrupting gene expression, generation of reactive oxygen species, and inhibition of topoisomerase II, a gyrase important for DNA synthesis and replication and cardiotoxicity [64]. The entrapment of DOX in biocompatible, biodegradable, and safe nanocarrier can prevent its toxicity and target the tumor increasing the therapeutic effect and decreasing side effects of the drug [65]. Indeed, cholesterol-modified CD-MOF particles were able to maintain their crystalline structure after DOX loading and they were administered to study blood clearance compared with free DOX through a pharmacokinetic study. Free DOX was removed from blood circulation faster than the same doses of DOX incorporated in cholesterol-modified CD-MOF.

3.5.3 Diphenyl carbonate

Singh et al. also studied the possibility to obtained well-organized γ-CDs in cross-linking with diphenyl carbonate by a facile single-step chemical reaction [66]. The different cross-linking degrees were synthesized and studied. SEM analysis revealed the perfect cubic shapes of this particle ranging in nano and micrometer sizes. The adsorption of doxorubicin within micro- and nano-cubes was found to be significantly higher (60–80 mg/g) and the adsorption capacity increased with the cross-linking reaction time.

3.5.4 Fullerene

In order to improve the water stability of γ-CD-MOF, Li et al. synthesized a composite with fullerene. Fullerene (C60) had attracted interest in biomedicine and so it was incorporated in the matrix of a γ-CD-MOF through a facile co-incubation process. In this procedure, the C60 with a diameter size of 0.7 nm was accessed into the open pores of a γ-CD-MOF and partially trapped within γ-CD ligands, forming a γ-CD-MOF/C60 composite [67].

The Raman analysis reveals the formation of γ-CD/C60 inclusion complexes within γ-CD-MOF/C60 composites. The N_2 gas adsorption shows a moderate decrease in the surface area of γ-CD-MOF/C60 (from 1226 m^2/g to 1126 m^2/g) due to the contributions of non-porous C60 to the mass of the composite. The XRD measurements on γ-CD-MOFs before and after C60 incorporation confirmed that the crystalline structure of MOFs is not affected by the inclusion of C60. The water-stability of γ-CD-MOFs before and after C60 incorporation was evaluated showing that γ-CD-MOF/C60 crystals retain their shape in water solution for over 24 h and through SEM observations, no changes in MOF morphology were found out. The DOX was successfully loaded inside this kind of MOF and the content of DOX was found about 6.5 wt.%

using the NMR measurement. These results allowed γ-CD-MOF/C60 to be exploited as potential drug delivery vehicles.

3.5.5 Potassium benzoate

Al-Gahmdi and co-workers synthesized two different γ-CDs using potassium hydroxide and potassium benzoate as sources of K^+ ion named CD-MOF-a and CD-MOF-b, respectively by using the vapor diffusion crystallization process at room temperature [68]. The N_2 isotherms of CD-MOF-an and CD-MOF-b samples were used for investigating the potential drug delivery system. Type-I isotherms were observed for both the CD-MOFs, but CD-MOF-a has a larger surface area than CD-MOF-b. This difference can be attributed to the presence of the benzoate as counter-anions in the pores of CD-MOF-b. SEM analysis revealed that the morphology, size, and shape of a crystal were influenced by the source of metal ions. CD-MOF-b had a larger size may be due to lower nucleation rate and slower crystal growth. The presence of benzoate counter-anions has a great influence on crystal growth. Both CD-MOF-an and CD-MOF-b were evaluated for the encapsulation of acetaldehyde. Acetaldehyde is a natural antifungal, but it is water-soluble and volatile and so it requires to be stabilized. The acetaldehyde was successfully loaded in CD-MOF-b with good release kinetics. To quantify the amount of acetaldehyde encapsulated, TGA was used. Around 4% of acetaldehyde loaded was found out. The strong quadrupole-quadrupole interactions between acetaldehyde and electron-rich aromatic ring of benzoate counter-anion still entrap in the MOF structure could promote the successful encapsulation of acetaldehyde in the γ-CD-MOF-b. The acetaldehyde released from 1 g of CD-MOF-b is 53 µg after 5 h and 30 µg after 24 h.

4. Conclusion

This review reports the recent progress in the synthesis of γ-CD-MOFs. The γ-MOFs can be prepared and tuned using various metal ions and water stabilized using different compounds such as C60 and diphenyl carbonate. Several synthetic approaches are also presented. Vapor diffusion is one of the most commonly used procedures due to its tunable performances and well-assessed method. This technique required time, from 2 to 7 days, and so for reducing the reaction time a reformed hydrothermal or ultrasonic method can be successfully applied. Furthermore, the unique properties of γ-CD-MOFs make them suitable for being used in drug delivery systems. In this review several drugs delivered are presented, from natural as capsaicin to synthetic and widely diffuse such as ketoprofen and ibuprofen. The γ-CD-MOFs can protect and deliver the drug to the organ target enhancing the properties of the selected molecules.

Declaration of interest:

The authors report no declarations of interest

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