CONTROLLED RELEASE OF *INDOMETHACIN* USING MIL-101(Fe): A PROMISING METAL-ORGANIC FRAMEWORK FOR DRUG DELIVERY

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The use of metal–organic frameworks (MOFs) as drug carriers offers promising potential for controlled drug delivery systems. MIL-101(Fe) is a stable and non-toxic MOF with outstanding pore capacity and wide pore windows that can accommodate and allow entry to a large number of drug molecules. However, it has been hugely underutilized in the development of drug delivery systems. This study investigates the suitability of highly porous MIL-101(Fe) as a carrier for the non-steroidal anti-inflammatory drug *indomethacin*, thereby reducing potential side effects, dosage, and peak plasma concentration, while increasing its half-life. MIL-101(Fe) was synthesized using a modified solvothermal technique to enhance purity, and then loaded with *indomethacin* by suspending 25 mg of the MOF in 25 ml of a 500 mg l^{-1} ethanolic *indomethacin* solution. The drug release behavior was studied by suspending 5 mg of the loaded MOF in phosphate-buffered saline (PBS) at pH 7.4 and hydrochloric acid (HCl) solution at pH 4.0 at 37 ℃ to simulate intestinal and mildly acidic gastric environments, respectively. The MOF structure was confirmed by powder X-ray diffractometry and Fourier Transform Infrared Spectroscopy. A high drug loading capacity of ~27% was observed within 24 hours, with the help of UV-visible spectrophotometry-assisted calculations. The release studies revealed a sustained release profile with no significant initial burst. Release was evaluated using UV-visible spectrophotometry at 317 nm. After 48 hours, ~49.8% of the encapsulated drug was released in PBS, while only ~7.1% was released in HCl, indicating a pH-sensitive release behavior. These findings demonstrate that MIL-101(Fe) is a promising candidate for oral delivery of *indomethacin*, offering slow and targeted release in the intestinal environment while minimizing premature drug release in the stomach and associated side effects. Further research on modifying the MOF structure and implementing post-synthetic modifications may enhance the MOF's affinity to *indomethacin*, thereby increasing its loading capacity and release efficiency. More research is needed to determine whether this MOF can be used as a drug delivery vehicle for additional medications, as well as to minimize MOF degradation under highly acidic conditions within the stomach.

Keywords: controlled release, drug delivery, *Indomethacin*, metal-organic framework, MIL-101(Fe)

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1. INTRODUCTION

Indomethacin is a non-steroidal anti-inflammatory drug that also possesses antipyretic and analgesic properties due to its ability to block prostaglandins. Additionally, it is used to suppress symptoms associated with arthritis and related conditions. It's an extremely potent drug that also causes some adverse side effects, including gastrointestinal (GI) tract-related issues, and kidney and hepatic toxicity. *Indomethacin* is highly bioavailable (~100%) and is readily absorbed in the GI tract, causing high plasma concentrations, and peak plasma concentrations are reached rapidly. Slow-release formulations are designed to mitigate the side effects caused by high plasma concentrations (Lucas, 2016). *Indomethacin* extended-release formulations are currently available, which are polymer-coated particles aimed at slowly dissolving at different rates. But the plasma levels have not shown a significant difference from the conventional formulations after several hours (Lucas, 2016), with these slow-release formulations. Metal-Organic Frameworks (MOFs) are a novel type of material with excellent properties to use as drug delivery vehicles, such as high porosity and high surface area (Vahed et al., 2018). They are much better than polymer-based carriers due to their high capacity, stability, and organized crystal structure. MIL-101(Fe) (MIL = Material of Institut Lavoisier) is such a MOF based on Fe^{3+} ion centers and terephthalic acid linkers with huge pore volume and large pore windows, which can potentially facilitate the accommodation of a large number of different drug molecules. Despite such positive aspects suitable for drug delivery applications, this particular MOF is heavily underutilized in drug delivery applications. This study aims to develop an extended-release formulation for *indomethacin* using this highly porous, non-toxic, and water-stable metal-organic framework to release the drug slowly over 24 hours to minimize peak plasma concentrations, thereby significantly reducing side effects.

2. METHODOLOGY

MIL-101(Fe) synthesis was performed using 2.027 g (7.5 mmol) of iron(III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) and 0.415 g (2.5 mmol) of terephthalic acid in a 3:1 ratio to minimize the presence of unreacted terephthalic acid within the MOF pores. The two reactants were dissolved in 25 ml of dimethylformamide (DMF) and autoclaved in a 50 ml Teflon liner for 24 hours at 110 ℃. The

reddish-orange product was washed three times with 10 ml of hot DMF to remove any unreacted terephthalic acid, which was followed by washing with 10 ml of hot ethanol five times to remove DMF. The resulting pale orange MOF was then activated at a full vacuum at 80 ℃ for 1 hour to remove remaining ethanol. Drug loading was performed by immersing 25 mg of the activated MOF in 50 ml of a 500 mg l^{-1} solution of *indomethacin* in absolute ethanol for 24 hours under constant stirring at 600 rpm at room temperature. Loaded MOF was washed quickly with 10 mL of absolute ethanol to remove excess *indomethacin* and dried at 80 ℃ for 1 hour to remove the solvent. Drug release studies were performed by suspending 5 mg of the loaded MOF in phosphate-buffered saline (PBS) at pH 7.4 and in HCl at pH 4.0 media at 37 ℃ over a period of 48 hours under constant stirring at 200 rpm. UV-visible spectroscopy at a wavelength of 317 nm was used for the analysis of drug concentrations during loading and release studies. Powder X-ray diffractometry (PXRD) and Fourier Transform Infrared Spectroscopy (FTIR) were used to confirm the crystal structure of the MOF. All experiments were done in duplicate.

3. RESULTS AND DISCUSSION

3.1 Synthesis and characterization of MIL-101(Fe)

MIL-101(Fe) synthesis was performed using the solvothermal route followed by Hu et al. (2019), with some modifications aimed at increasing its purity by minimizing unreacted terephthalic acid residue within the pores of the MOF. A ratio between Fe^{3+}: terephthalic acid of 3:1 ensures minimal unreacted terephthalic residue, thereby making the activation process easier while resulting in a much cleaner MOF. About half of the autoclave volume was left empty to lower the pressure, to facilitate proper mixing, and to allow enough space for thermal expansion of the reaction mixture. The result was an impressively crystalline product, evidenced by the PXRD and FTIR spectra (Fig. 3.1 and 3.2, respectively). The sharp peaks at 2θ values 8.95, 9.55, and 19.2 of the PXRD spectrum are characteristic of MIL-101(Fe), and match well with the currently reported literature (Hu et al., 2019). The FTIR spectrum shows no broad absorption bands near 3000 $cm^{-1,}$ confirming the absence of free carboxylic acid OH groups, hence the absence of free terephthalic acid within the MOF. It also doesn't show a sharp peak at 1657 cm^{-1}, which corresponds to the C=O group of DMF, hence confirming the absence of DMF within the MOF (Alavijeh and Akhbari, 2020).

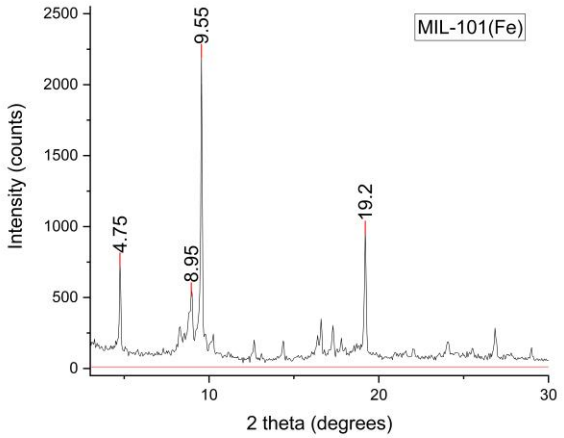

Figure 3.1 The Powder X-Ray Diffractogram of the synthesized MIL-101(Fe)

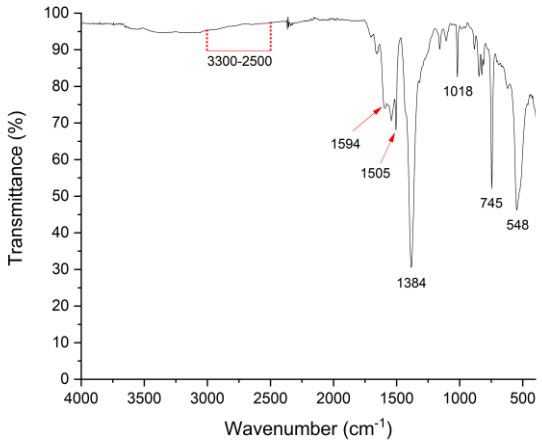

Figure 3.2 The FTIR spectrum of the synthesized MIL-101(Fe)

3.2 Loading of *indomethacin* into MIL-101(Fe)

UV-visible spectroscopy showed a decrease in the initial *indomethacin* concentration (500 mg l^{-1}) of the loading solution (50 ml), confirming the drug absorption into the 25 mg of the MOF used, but with a decreasing rate over time. As per the results, the ideal loading time was established to be 24 hours, as the absorption after that was negligible. A calibration curve of *indomethacin* in absolute ethanol was used to find the mass of the drug encapsulated after 24 hours. Calculations revealed that 6.86 mg of the drug was absorbed into the MOF, accounting for a drug loading capacity of 0.274 mg mg^{-1} MOF, and a loading efficiency of 27.45% w/w in trial 1, and 6.95 mg of the drug was absorbed into the MOF, accounting for a drug loading capacity of 0.278 mg mg^{-1}

MOF, and a loading efficiency of 27.80% w/w in trial 2.

Figure 3.3 UV-visible spectra of *indomethacin* in the loading solution at different time intervals

3.3 Drug-release studies

Release tests conducted over a 48-hour period demonstrated a slow and progressive release of *indomethacin* from the 5 mg of the *indomethacin*-loaded MOF into the 25 ml of the PBS solution. No significant burst release was observed during two different, simultaneously conducted trials. A mass of 0.74 mg of the drug was released into PBS over the 48 hours, accounting for a release efficiency of 49.83%, according to the calculations done with the aid of a calibration curve of *indomethacin* in PBS.

Figure 3.4 Comparison of release profiles of *indomethacin* in HCl and PBS

Drug release into the HCl solution was significantly weak, with only a very small amount being released, showing the pH-sensitive release capability of the MOF. After 48 hours, only a mass of 0.11 mg of the drug was detected in the release medium, accounting for just 7.13% of the loaded drug. Being an acid itself, *indomethacin* did not show much affinity for the HCl solution but would rather stay within the MOF pores. Although the MOF is stable under slightly acidic conditions (down to pH 4.0), highly acidic conditions will degrade the MOF, thereby releasing more of the drug within acidic environments, like the stomach.

CONCLUSIONS/RECOMMENDATIONS

According to the obtained results and calculations, it can be concluded that MIL-101(Fe) is a suitable candidate to be used as a carrier for *indomethacin*, for both good loading capacity and controlled (extended and pH-sensitive) release capabilities. It shows an *indomethacin* loading capacity of 0.276 mg mg^{-1} MOF on average, which corresponds to a loading efficiency of 27.63% on average. It does not show a surge release within the intestinal conditions while showing an excellent ~49% release efficiency. Furthermore, the release of the drug from the MOF into a mildly acidic environment is minimal, so that release within the stomach under post-prandial conditions will be minimal.

The MOF is stable in slightly acidic, neutral, and slightly basic pH conditions but will degrade in highly acidic conditions. Hence, under fasting conditions, since the stomach acidity is very high, the MOF will degrade and release much more of the drug than was observed in the experiment. Therefore, this formulation will be better taken after or with a meal or a while after having antacid tablets. Further work on post-synthetic modifications to coat the MOF particles with an acidic polymer may ensure that premature release is avoided. Also, the loading capacity may be further improved by tweaking the structure of the MOF by using different functional groups on the terephthalic linker.

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