RESEARCH ARTICLE

Chrysin Embedded Metal Organic Framework for Anticancer Drug Delivery

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ABSTRACT

Metal-organic frameworks (MOFs) have garnered significant attention in the field of cancer drug delivery owing to their porosity, high drug-loading capacity, and large surface area. In our recent research, we synthesized a redox-responsive MOF using zirconium (Zr) as the metal ion and 4,4-dithiobisbenzoic acid (DTBA) as the organic linker. The synthesis method employed was the hydrothermal method, and it was observed that the MOF synthesized at 400°C had a particle size of less than 200 nm and a zeta potential of +35 mV, indicating its suitability as a carrier for drug delivery. Chrysin, a natural anticancer drug, was used in this study. Glutathione, which is abundantly present in tumor cells, cleaves the disulfide bond in the organic ligand (DTBA), leading to faster drug release. By incorporating chrysin into the synthesized MOF, we observed faster in vitro drug release, with 88 and 89% at pH 7.4 and 5.5, respectively. The synthesis of ZrDTBA MOF opens up new opportunities for its application in drug delivery.

Keywords: Meta organic framework, Chrysin, Redox responsive, Glutathione, Cancer.

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INTRODUCTION

Cancer is a complex and prevailing disease characterized by rapid proliferation of cells beyond the usual confines, causing metastasis. It is a leading health problem nationally and internationally and has been widely studied for better comprehension and management.[1]

Chemotherapy is a commonly utilized treatment for cancer that utilizes cytotoxic medications to target rapidly dividing cancerous cells, thereby impeding their proliferation and dissemination.[2] It can be administered via different pathways, including injections like intravenous oral and proves to be efficacious in managing various types of cancers such as leukemia, lymphoma, breast, and lung cancer. The purpose of chemotherapy may vary, serving as a potential cure, alleviation of symptoms, or as a supplementary measure to augment the effectiveness of alternative treatments like surgery or radiotherapy.[3]

chemotherapy, being the primary therapeutic approach for cancer, exhibits certain limitations that encompass inaccurate dosing based on body surface area, leading to toxicity or reduced efficacy.[4]

It also includes physicochemical barriers like poor drug solubility and biological barriers such as drug efflux transporters, tumor microenvironment, and blood-brain barrier hindrances.[5] The utilization of a novel drug delivery system is currently being implemented in order to address and surpass these inherent limitations.

Novel drug delivery systems (NDDS) offer significant advantages in overcoming the limitations of conventional chemotherapy. NDDS, such as polymeric nanocapsules, nanoparticles, liposomes, and others, enhance therapy efficacy by improving drug solubility, bioavailability, and stability.[6] They also provide targeted drug delivery, reducing toxicity to normal cells and enhancing therapeutic effects. Moreover, NDDS can help overcome multidrug resistance in cancer treatment through various nanoparticle formulations, such as solid lipid nanoparticles and polymeric micelles. Additionally, NDDS can increase patient compliance by reducing dosing frequency and improving treatment duration, ultimately offering a more effective and safer approach to cancer therapy.[7]

Metal-organic frameworks (MOFs) comprise metal ions or clusters linked with organic molecules to form porous structures in one, two, or three dimensions.[8,9] These frameworks are known for their high porosity, large surface areas, and adjustable functionalities, making them suitable for a wide range of uses. MOFs have proven to be effective in storing hydrogen because

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of their strong reversibility and adsorption abilities. Moreover, they are employed in drug delivery, biosensing, and as agents against microbes, releasing metal ions for antibacterial and antifungal purposes.[10] The distinct characteristics of MOFs, including their porous nature and capacity to transport functional substances, underscore their importance in various fields such as catalysis, gas storage, water purification, and new applications in treating microbial infections.[11]

MOFs possess unique properties that make them well-suited for targeted drug delivery. They provide controlled drug release, biocompatibility, and flexibility, all of which improve the efficiency of delivering drugs to specific targets.[12] Compared to other drug delivery systems, MOFs stand out due to their high surface area, low toxicity, and potential for modification. MOFs can be adjusted to release drugs gradually, which in turn enhances the safety and effectiveness of therapy. By incorporating biodegradable linkers and less toxic metal ions, MOFs can be made more sustainable in drug delivery applications while ensuring biocompatibility and controlled drug release.[13] The ability of MOFs to interact with drugs through noncovalent interactions significantly impacts the uptake and release of therapeutics, making them effective carriers for a variety of drugs. Through the regulation of the protein-adhesive surface of MOF nanoparticles, targeted drug delivery systems can be designed to enhance their efficiency in cancer therapy.[14]

Factors Affecting on Characteristics of MOF

Factors affecting on structural properties of MOF

- *Particle size*

The particle size of MOFs plays a crucial role in their function as drug delivery systems. Smaller MOFs can provide a controlled and sustained release of drugs, while larger particles may offer enhanced release rates. The ability to tailor the size and surface properties of MOFs allows for improved targeting and treatment of cancer, with the potential for responsive release mechanisms that respond to the unique conditions of the tumor microenvironment.

R. Abazari *et al.* synthesized a metal-organic framework under ultrasound irradiation in which they observed that the Particle size of MOF ranging from micro to nanoscale leads to sustained release of drugs, which is effective for drug delivery systems used in cancer treatment.[15]

Xuechuan Gao *et al.* synthesized a UIO-66-NH2 metal-organic framework in which they illustrated that a smaller particle size (20-200 nm) of synthesized MOF increases the release time of the drug, resulting in improved potentiation of fluorescence imaging.[16]

Porosity

Porosity mainly influences drug loading capacity, release kinetics and stability of metal-organic framework, which are important for controlled drug delivery applications. The porosity of metal-organic frameworks enhances drug delivery by increasing selectivity, adsorption capacity, and diffusion speed, reducing side effects, and improving drug targeting to cancerous sites.[17]

Metal-organic frameworks can hold large amounts of drugs within their structure due to their high porosity. It controls the release rate of drugs and delivers drugs in exact amounts to the target site, improving the efficiency of the drug delivery process.[18]

Shu *et al.* synthesized a persistent luminescent metal-organic framework (PLNPs@MIL-100(Fe)) using the layer-by-layer method. They combined a metal-organic framework with near-infrared glowing nanoparticles to form a dual model that treats cancer by allowing doctors to see where the tumor is and ensuring the medicine is delivered efficiently and effectively, aiming for precise treatment. The author concluded that the porosity of the MIL-100 (Fe) shell in PLNPs at MIL-100 (Fe) enhances drug loading capacity up to 87.1% and enables acid-triggered drug release, facilitating effective drug delivery.[19]

Morphology

The morphology of metal-organic frameworks (MOFs) significantly impacts their effectiveness in drug delivery systems. Various studies have highlighted that the loading of the drug and its effectiveness can be controlled by maintaining the uniformity in the morphology of MOF.[20] The diverse morphologies of MOFs, including spherical, ellipsoidal, cubic, hexagonal, and octahedral shapes, facilitate drug and gene acceptance, making them versatile platforms for drug delivery applications.[21]

Biocompatibility

Biocompatibility is an essential factor in the utilization of MOF for drug delivery. High biocompatibility plays a crucial role in guaranteeing the safety and sustainability of drug delivery systems over prolonged periods. Sustainable MOFs containing biodegradable linkers and non-toxic metal ions have revealed strong results in controlled drug release along with excellent biocompatibility.[22] Additionally, the application of biomolecule-based MOFs, like BioMOFs, shows excellent biocompatibility, absence of toxicity, and high stability, making them potential carriers for drugs.[23] The biocompatible aspect of MOFs critically influences drug efficiency in terms of encapsulation, the control of release kinetics as well as protection from the release of toxic components, hence implicating their drug delivery system efficiency and safety. Furthermore, the expansion of the utilization of MOFs in drug delivery systems derives the importance of biocompatibility in enhancing drug encapsulation and release.[24]

Somayeh *et al.* synthesized two metal-organic frameworks, namely TMU-6(RL1) and TMU-6(RL2), exploring the effect of the pore structure of MOF on drug delivery using characterization like IR, PXRD, XPS, TG. Researchers concluded that the biocompatibility of MOF can be regulated by adjusting the structural properties of MOF, which helps to improve outcomes related to drug delivery.[25]

The efficiency of the metal-organic framework is enhanced on the basis of biodegradability. Biodegradability helps in

drug delivery by offering specific targeting, controlled release, biocompatibility and degradation into non-toxic products.[23]

Natural Anticancer drug

Natural anticancer drugs are therapeutic agents derived from natural sources, such as plants, marine organisms, and microorganisms, which show anti-tumor properties and are used in the treatment of cancer. Selective cytotoxicity, anti-metastatic, anti-mutagenic, anti-angiogenesis, and apoptosis induction are some of the mechanisms through which they show their action.[26] These drugs include a variety of compounds, such as alkaloids, flavonoids, carotenoids, peptides, and anthracyclines, which are known for their anti-tumor activities. Phytochemicals, which are secondary metabolites from plants, have been particularly highlighted for their role in cancer therapy, with some being developed as first-line anticancer drugs.[27] Interestingly, although natural anticancer drugs are praised for their effectiveness and minimal toxicity, challenges such as drug resistance, poor aqueous solubility, and reduced bioavailability have been noted. To overcome these issues, combination therapies with conventional drugs and nanotechnology-based carriers for drug delivery have been explored.[28]

Chrysin

Chrysin is a natural flavonoid extracted from plants and propolis and is known for its pharmacological activities, which include anti-inflammatory, antioxidant, and anticancer properties.[29,30] It has been studied for its potential as an anticancer agent in various cancer cell lines and animal models, demonstrating effects such as inhibition of cell proliferation, induction of apoptosis, and cell cycle arrest. [30-32]

Interestingly, although chrysin alone exhibits anticancer activity, its efficacy can be enhanced through the formation of novel compounds, such as a chrysin-organotin compound (Chry-Sn) with improved anticancer effects.[30] or by creating complexes with metal ions such as gallium (Ga(iii)). These modifications have been shown to increase cytotoxicity against cancer cells and to generate reactive oxygen species (ROS), which contribute to anticancer effects. Additionally, the effects of chrysin on immunological mechanisms, such as enhancing the cytotoxic activity of natural killer (NK) cells, cytotoxic T lymphocytes (CTL), and macrophages, have been observed in melanoma-bearing mice.[32]

MATERIALS AND METHOD

Materials

Zrcl4(metal), 4,4-dithiobisbenzoic acid (organic ligand), GSH, and dimethyl formamide were purchased from Jitendra Scientific, Jalgaon. Chrysin (natural anticancer drug) was purchased from Mehta and Son's chemical company, Sangali.

Methods

Method of Synthesis of ZR (DTBA) MOF

The hydrothermal method was adapted for the synthesis of Zr (DTBA) metal-organic framework (Figure 1). Initially required quantity of metal (Zrcl4) and organic ligand was weighed and transferred to a round bottom flask containing dimethyl formamide (DMF). The above mixture was sonicated for 30 minutes to get a clear solution. After sonication, the mixture was transferred to a Teflon-capped autoclave at 40°C for 15 hours. The resulting mixture was centrifuged at 12000 rpm for 10 minutes and washed with ethanol. Finally, the metal-organic framework obtained was dried in an oven.

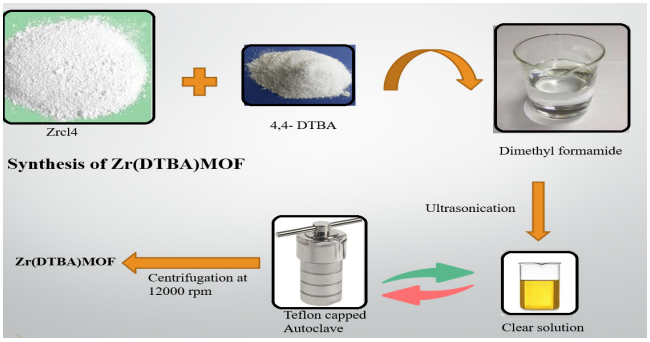

Figure 1: Synthesis of metal-organic framework

Characterisation of ZR (DTBA)MOF

Loading of drug into Zr (DTBA)MOF

For the loading of a drug (Chrysin) into MOF (Zr(DTBA), 0.8 mg/mL of chrysin was added into the beaker containing 10 mL of dimethylformamide. To the above solution, 20 mg of synthesized MOF was added. Allow to stir for 15 minutes. After stirring, the solution was kept overnight and centrifuged to obtain the final product(chrysin@Zr.DTBA). To determine drug loading encapsulation efficiency, drug-loaded MOF was dispersed in the phosphate buffer solution with glutathione (GSH) and absorbance was taken at 290 nm by using a UV-visible spectrophotometer.

In vitro drug release

In-vitro drug release study was carried out by taking 1-mg of chrysin-loaded MOF in 4 ml phosphate buffer having different pH values (pH 7.4 and 5.5) containing 1 to 10 mM GSH. Temperature maintained at 37°C. About 1-mL of the medium was removed (Which was replaced by fresh phosphate buffer) and the amount of chrysin released was determined by UV-visible spectrophotometer at 290 nm.

Particle size

Particle size was measured by using an instrument zetasizer (Malvern- serial no: MAL1051945).

Zeta potential

Zeta potential was carried out using the instrument zeta sizer which measured as serial no: MAL1051945.

RESULT AND DISCUSSION

In-vitro drug release

In chrysin@zrMOF, the organic ligand used is 4,4-dithibisbenzoic acid, in which a disulphide bond is present. Cellular cytoplasm of cancerous cells contains abundant

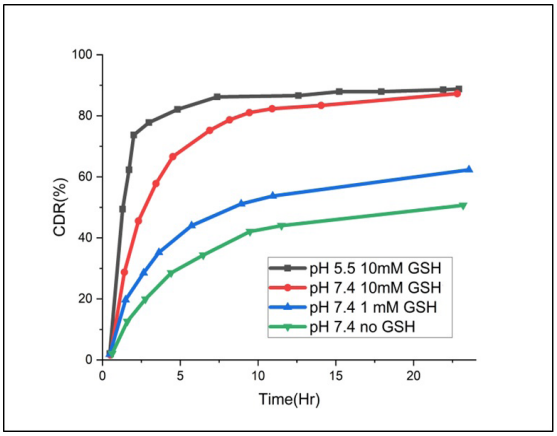

Figure 2: Cumulative drug release in PBS with and without GSH

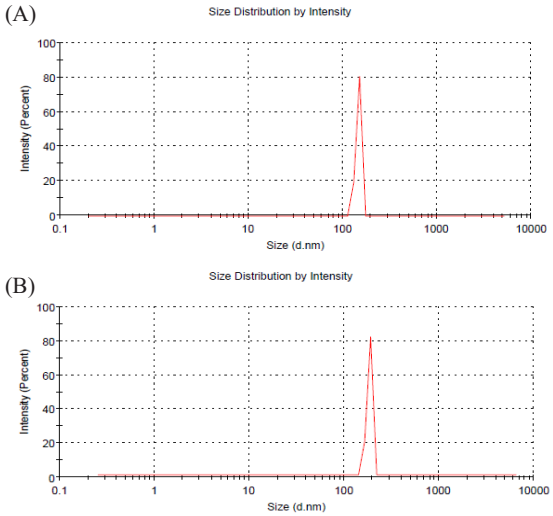

Figure 3: (A) Particle size of MOF; (B): Particle size of chrysin loaded MOF

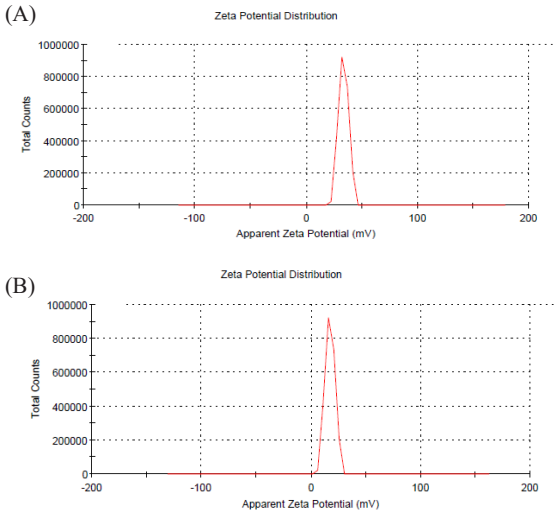

Figure 4: (A) Zeta potential of MOF; (B) Zeta potential of chrysin-loaded MOF

amounts of glutathione (GSH) ranging from 2 to 10 Mm. Once drug-loaded MOF enters into the cancerous cell through cellular endocytosis, GHS present in the cancerous cell helps to break the disulfide bond of the linker, which results in the accelerated release of drug to the target site

In Figure 2 cumulative drug release at different Ph with and without glutathione is shown. Cumulative drug release (after 20 hours) in phosphate buffer of pH 7.4 with a GSH concentration 10 Mm is 88%, decreasing the concentration of GSH (1-mM) in phosphate buffer of pH 7.4, cumulative drug release is also decreased which is 59%. It was observed that the release of chrysin in the phosphate buffer of pH 7.4 with no GSH was 42%. It is considered that pH of tumor tissue is more acidic than the normal tissue and blood. In acidic pH5.5 with 10 Mm GSH concentration, the release of chrysin is found to be 89%. From the graph, it is concluded that the amount of GSH in phosphate buffer affects the release of a drug.

Particle size

In Figure 3(a) ZrMOF synthesized at 40°C showed a particle size of 127 nm, which is suitable for drug delivery. In Figure 3(b), the particle size after the incorporation of chrysin was found to be 175 nm. It was concluded that, after the incorporation of drug into the metal-organic framework, the particle size was increased, but it was still below 200 nm, which is considered satisfactory for drug delivery.

Zeta potential

The zeta potential of Zr (DTBA)MOF was obtained as +35 mV (Figure 4 (a)) and the zeta potential of chrysin-loaded Zr (DTBA)MOF is +15mv (Figure 4 (b)). It was also seen there was a decrease in the zeta potential of the drug-loaded metal-organic framework after the drug incorporation. The high value of zeta potential is favorable for drug delivery.

X-ray diffraction

Based on the findings discussed above, it can be inferred that the broad diffraction peak observed for Zr@MOF at approximately 3°C indicates the amorphous nature of MOF (Figure 5). Furthermore, the diffraction peak of Zr@MOF was maintained even after drug loading, with no chrysin peaks, thereby confirming the structural stability of Zr@MOF.

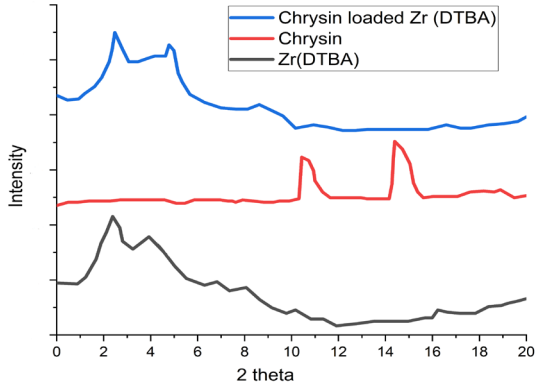

Figure 5: X-ray diffraction of chrysin, MOF, drug-loaded MOF

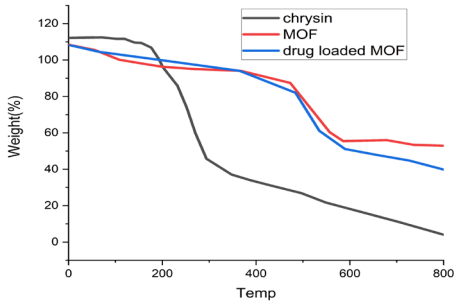

Figure 6: TGA of chrysin, MOF, chrysin loaded MOF

Thermogravimetric analysis

The graph depicts that the thermal decomposition of Zr@MOF and chrysin-loaded Zr@MOF commences at temperatures above 400°C, while both experience significant weight loss at approximately 550°C. Conversely, the degradation of free chrysin begins at 210°C. This finding indicates that the thermal stability of chrysin is enhanced when incorporated within the Zr@MOF structure (Figure 6).

CONCLUSION

In the present study, a chrysin-loaded zirconium-based metal-organic framework was synthesized by using hydrothermal synthesis, which proved to be a convenient method. Chrysin, a natural anticancer drug, due to its hydrophobicity is not preferred in drug delivery. However, the current research work concluded that the hydrophobicity is overcome by loading chrysin into a porous metal-organic framework; chrysin release from the metal-organic framework was found to be 89% after 20 hours. Organic linkers used in the synthesis of metal-organic framework helped to release more drugs at the target site due to the present disulfide linkage in it, which is cleaved by glutathione present in a tumor cell. MOF displayed a particle size of 175 nm, a zeta potential of + 15 mV, a diffraction peak at 3°C and thermal stability at 550^0C. The above result depicted that Zr (DTBA)MOF presents promising opportunities for controlled drug release in cancer therapies.

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