

Metal-Organic Bioactive as New Modification Drug Delivery System

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Abstract: The success of metal materials in their use is very much one of them in medical applications. Metal material is a material that is mostly composed of transition elements and tends to provide high resistance to structures and other properties. The ability of various metal materials has great potential to be applied as drug delivery. Metal-material designs were developed to overcome the problem of poor chemical stability and other advantages as drug delivery. Various methods have been carried out by incorporating metal ions in drugs, or using metal-based materials as direct drug delivery. Studies mention that metal-material-based drug delivery can have its own advantages for the body when degraded and has high resistance in drug storage.

Keywords: Metal-Organic; Bioactive; Drug Delivery.

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1. Introduction

Health science is currently a never-ending focus for the emergence of innovations, in line with various problems in this field. One of the problems that exists is the drug delivery system. A drug delivery system (DDS) is a mechanism for distributing a drug for consumption through the metabolism of a drug. The primary considerations for developing technology for pharmaceutical therapy consist of three main factors, namely creating an effective system (effectiveness), suppressing harmful effects on the system when applied (safety), and making the system well accepted by patients (acceptability) (Martien et al., 2012). Currently, drug delivery technology is increasingly being updated as technology advances. A critical aspect of a drug delivery system is its ability to provide precise control over drug release, both in terms of timing and specific location in the body. The main challenge in the design of drug delivery systems is adjusting the metabolic pathways of drugs that can be consumed orally, transdermally, intramuscularly, or intravenously.

Metal-based materials have considerable potential when applied as new technology in drug delivery systems. Metals such as Cu, Zn, and Fe are essential micronutrients the body needs (Soetan et al., 2010). Metal-material design of drug delivery systems is a rapidly developing field in biomedical science and materials engineering. Metal-based drug delivery systems can efficiently deliver active substances directly to target locations in the body, reducing side effects and increasing therapeutic effectiveness because of the metal's high stability and biocompatibility properties. The main advantages of metallic materials in drug delivery systems include their adaptability to various delivery methods, including targeted delivery and delivery triggered by external stimuli such as heat, light, or magnetic fields. In targeted delivery, the metal will

interact more easily with the receptor, creating a better action target (Winarti, 2013). In addition, the particle size can be controlled with high precision, enabling better penetration into target tissues and cells.

Pharmaceutical formulation technology and drug delivery systems are essential in discovering new pharmaceutical therapies for the public. Physicochemical and molecular considerations, including ion-molecular equilibrium, hydrophilic-lipophilic equilibrium, biopharmaceutical processes, metabolism and biodegradation, drug-receptor affinity, physiological considerations, and biocompatibility of the system, are the main factors that are generally considered when conducting research in this field.

2. Methods

This journal review went through several stages, starting with (1) collecting various references related to organic metals as drug delivery (2) sorting important literature related to the predetermined topic, (3) reviewing the contents of the selected literature to get an overview of the latest developments regarding the use of metal compounds. organic as a drug carried, by analyzing its strengths and weaknesses. The literature review in this article is based on 46 scientific articles, consisting of 1 national proceedings article, 1 accredited national journal article, and 40 articles from leading international journals such as Nature, Science Direct, ACS, MDPI, SciELO, RSC, AACR, PNAS, PMC Europe, ASCO, Karger, Chemical Europe, and Springerlink.

3. Result and Discussion

Metal-based drug delivery designs have developed a lot and become a continuous innovation. We have previously discussed the capabilities and advantages of metal materials in medical applications. Various types of materials that exist include:

3.1 Metal-Organic Frameworks

Metal-organic frameworks (MOFs) or metal-organic frameworks are materials consisting of metal ions or metal oxide clusters with an aromatic or aliphatic bivalent or polyvalent ligand that has carboxylate, phosphonate, sulfonate, imidazolate, amine, or pyridyl functional groups or combinations thereof. as a linker organic compound (Hanif et al., 2018). The metal ion as the center will form a complex by crosslinking reactions with organic ligands to form a framework. The framework formed by this reaction creates unique storage properties, allowing molecules to be trapped within it. The interesting physical and chemical properties of MOFs make

them applicable to drug storage and delivery (Taylor et al., 2010).

MOFs have several advantages when compared with other drug carrier systems, such as liposomes and polymers. These advantages include a structure that can be adjusted according to needs by changing the metal ion and/or organic linker so that it has a certain pore size. The pore size is generally adjusted to the size of the drug to be loaded. In addition, the large surface area of MOFs also provides potential for drug loading. The greater the surface area, size, and number of pores, the greater the possibility of drug encapsulation with greater capacity (Sun et al., 2013).

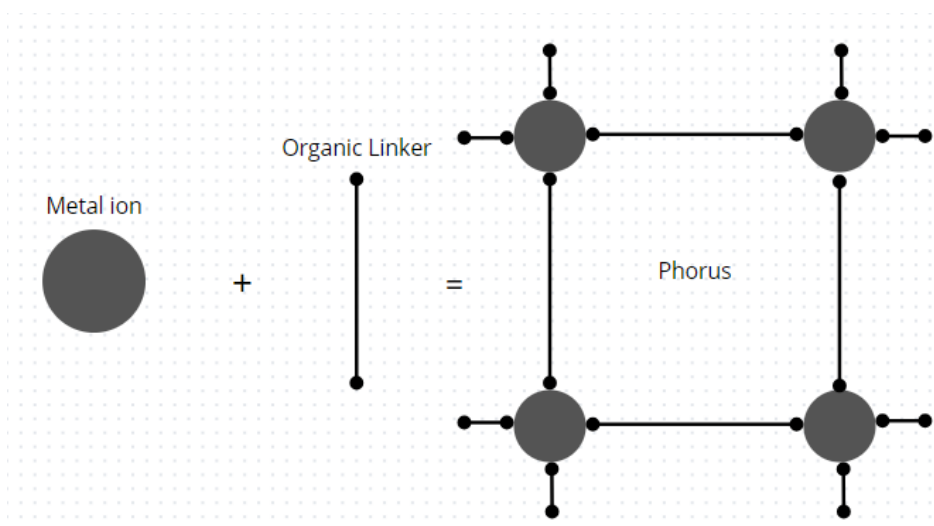


Figure 1. Crosslinking Reaction of MOFs Formation

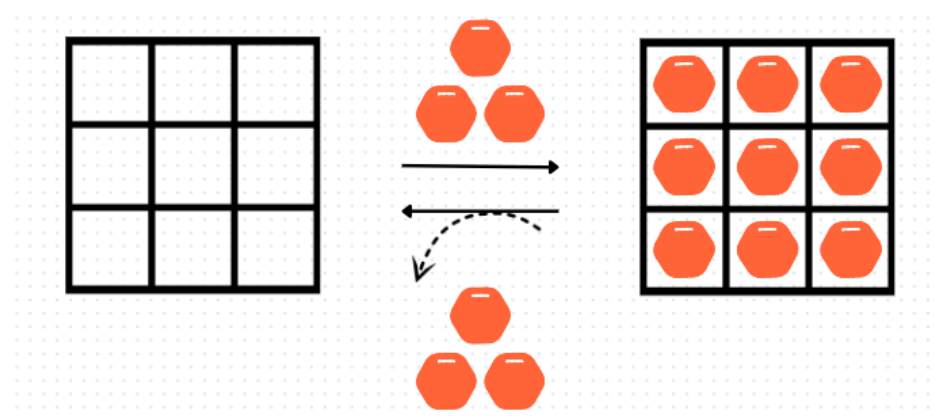


Figure 2. Molecules Loading of MOFs

Another advantage is that the designed MOF framework can produce flexible properties in the MOFs so that they can adapt to their pores to adjust the shape and size of organic molecules. These properties make MOFs that can be used both as drug loading and to control drug release at target areas in the body (Sindoro et al., 2014). Metal ions that have been studied include alkaline earth groups such as calcium (Ca^{2+}), magnesium (Mg^{2+}) (Yang et al., 2012), aluminum (Al^{3+}) (Joaristi et al., 2012), transition metals such as iron (Fe^{3+}) (Horcajada et al., 2006), chromium (Cr^{6+}) (Horcajada et al., 2008), zinc (Zn^{2+}) (Li et al., 1999), copper (Cu^{2+}) (Seo et al., 2009), cobalt (Co^{2+}) (Cho et al., 2012), zirconium (Zr^{4+}) (Abid et al., 2012) and lanthanides such as gadolinium (Gd^{3+}) (Kathryn et al., 2008). Meanwhile, the organic linkers studied are muconic acid, fumaric acid, trimesic acid, terephthalic acid, and terephthalic amino acid (Horcajada et al., 2010).

Ali et al. (2022), in their publication, describe the use of Zn as the central atom, one type of MOF with good potential for drug delivery. Depending on the central atom and organic ligands, various reactions are available in MOFs. The following shows several developments in Zn-Based MOFs in several kinds of literature.

Table 1. Data of MOFs with Zn centers

Zn-Based MOF	Bio-MOF-1	Zn-TBDA	[Zn ₂ (1,4-bdc) ₂ (dabco) _n]	Med-MOF-1
Chemical/Empirical Formula	Zn ₈ (Ad) ₄ (BPDC) ₆ O ₂ (NH ₂ (CH ₃) ₂) + 8DMF, 11H ₂ O	[Zn(tbda)] _n	[Zn ₂ (1,4-bdc) ₂ (dabco) _n]	Zn ₃ (curcumin) ₂₇ (DMA) ₃
Organic Linker	Adenatite	4'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3,5-dicarboxylic acid	1,4-diazabicyclo [2,2,2] octane (DBCO)	Curcumin
Drug	Procainamide	Methotrexate	Ibuprofen	Ibuprofen
Loading Degree	0,22 g/g	12,59%	15 wt%	0,24 g/g
Release Rate (Time)	72 h	48 h	288 h	80 h
References	An et al., 2009	Dong et al., 2018	Huong & Thanh, 2016	Su et al., 2015

From Table 1, the various types of linkers used have different delivery capacities from each other. The porosity of the MOF material itself can be engineered depending on the type of constituent. Various types of methods can synthesize zn-based MOFs. The solvothermal method is one type of method most widely used in the synthesis of MOFs (Mid et al., 2023). MOF-5 with Zn metal is one of the MOFs quite often synthesized using the solvothermal method. The biocompatibility properties of MOF-5 make this material have great potential to be used as a drug carrier.

Table 2. Influence of the formation of physical properties of MOFs under various solvothermal conditions

References	Solvent/Catalyst	Temperature (°C)	Times (Hours)	Size/ Pore Volume	Surface area (m ² /g)
Ubaidullah et al., 2020	DMF/TEA	100	20	24.5	638
Rehman et al., 2018	DMF/TEA	120	24	0,48 cm ³ /g	713
Peedikakkal & Aljund, 2021	DMF	100	22	0,383 cm ³ /g	921
Chen et al., 2019	DEF	135	24	0,2918 cm ³ /g	1580.35
Sabouni et al., 2010	DEF	100	20	-	1874
Zhao et al., 2009	DMF	130	2	0,86 cm ³ /g	2304

These results show that the formation of crystals and pores in MOFs depends on synthesis conditions such as temperature and pressure. High temperatures promote the dissolution of metal precursors and organic linkers in solvents, leading to increased reactivity and faster nucleation and growth of MOF crystals (Anim et al., 2023). The solvothermal method is the most practical technique to carry out where MOFs can be synthesized by chemical reactions between organic ligands such as hydrocarbons, which function as carboxylic acids and inorganic salts as a supply of metal ions in polar organic solvents at high temperatures and pressure (Solichah et al., 2022).

3.2 Metal-Micromotor

Micromotor technology has attracted significant attention in various biomedical applications, including drug delivery. Micromotors are micro devices that can move independently in a liquid medium. The use of metal-micromotors as drug delivery offers great potential in improving the efficiency and targeting of treatment compared with conventional methods. The conversion of chemical energy into mechanical energy can create a targeted movement of drugs coated with micromotors (Ye et al., 2024).

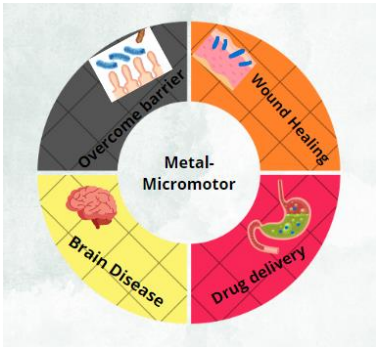


Figure 3. Application of Metal-Micromotor in drug delivery

Metal micromotors are generally made of metallic materials such as gold, silver, or platinum, which have high biocompatibility properties and can be externally controlled via magnetic fields or chemical reactions. One of the main advantages of metal micromotors is their ability to move to specific locations in the body, allowing targeted drug delivery and minimizing side effects on healthy tissue. Wang et al. (2015), in their publication, succeeded in designing a type of Janus-micromotor using gold metal (Au) as the primary material. This metal-micromotor can move with encouragement due to chemical reactions in the body, which then release H₂ as a driving force. Metal-micromotors are made by creating a layer in an Au-SiO₂ precursor solution, which is then dried. Metal-micromotors can be designed to activate drug release only under certain conditions, such as changes in pH or the presence of certain enzymes, providing further control over drug therapy.

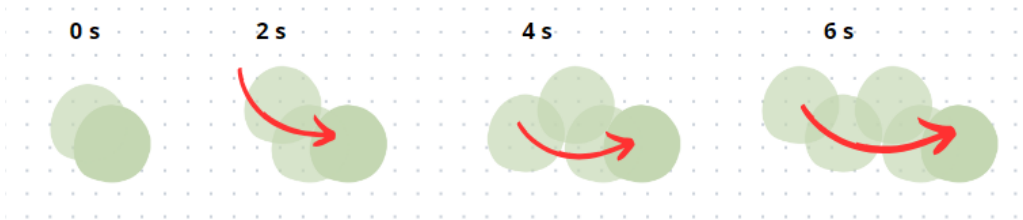


Figure 4. Metal-Micromotor in its delivery

With their biocompatibility properties and unique delivery mechanism, metal micromotors have great potential to become a sound targeted drug delivery system. Cai et al. (2024) is known to have carried out the use of other metals, such as Mg; using the exact mechanism, a micro-sized motor was obtained with a mixture of Mg metal and porous pollen extract coated with targeted drugs. The Mg metal layer creates a boost reaction when it reacts in the stomach, thereby maximizing drug absorption.

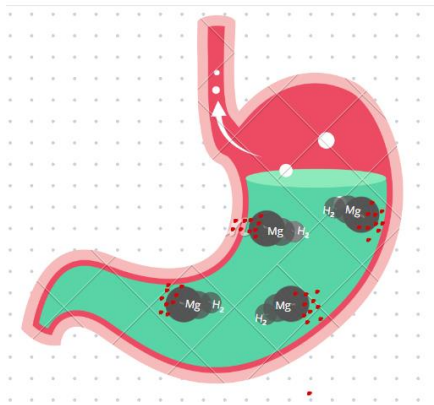


Figure 5. Metal-micromotor delivery mechanism

3.3 Metal-Nanoparticles

The study of drug delivery via nanoparticles is currently quite popular. This is because of the efficiency resulting from the application. Metal nanoparticles are a type of nano-sized material from 1 to 100 nm (Martien et al., 2012). The ability of nanoparticles in drug delivery design has been widely demonstrated in various types of delivery, both oral (Martien et al., 2006), intravenous (Li et al., 2009), pulmonary (Tonnis et al., 2012), and transdermal (Ravichandran, 2009).

In delivery, metal nanoparticles can be applied in various forms, such as coating or direct delivery. Nano-sized particles facilitate direct delivery because penetration can easily penetrate different barriers in biological systems. Such Ag-based nanoparticles in anti-cancer therapeutic applications are currently entirely developed. Ag nanoparticles can stimulate the production of reactive oxygen to destroy mitochondria in cancer cells (Chandrakala et al., 2022). Various studies related to the effectiveness of nanoparticles in cancer therapy can be seen in Table 3. The size and properties of metal nanoparticles make this material very good for use as a drug delivery agent. The size and properties of metal nanoparticles make this material very good for use as a drug delivery agent.

Table 3. Studies related to AgNPs in cancer therapy

Material NPs	Cell activities	References
PVP-coated AgNPs	Acute myeloid leukemia (AML) cells	Deeb et al., 2015
AgNPs	Human liver (HepG2) cells	Sahu et al., 2014
AgPCA	HCT116 colorectal cells	Rozalen et al., 2020
AgNPs-MTX	Lung cancer cell line (A-549)	Thapa et al., 2017
(MTX-GO/AgNPs)	Anti-cancer pharmacological activity	Palai et al., 2019
IMAB-AgNPs	Cytotoxicity in MCF-7 cells	Yuan et al., 2017
AgNPs	Cytotoxic effect to MCF-7 breast cancer	Chung et al., 2016

In their fabrication, metal-nanoparticles can be designed or synthesized using various methods, whether physical, chemical or biological methods. These various methods certainly have their own advantages and disadvantages.

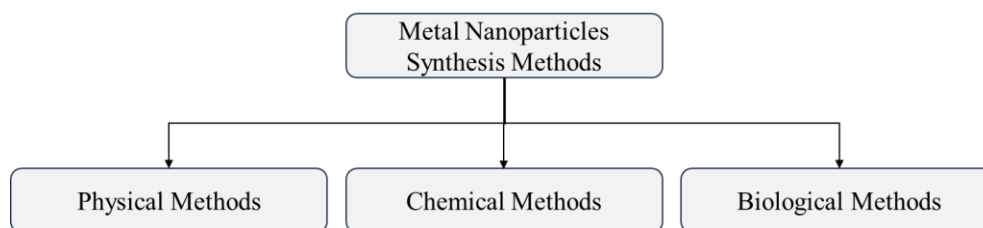


Figure 6. Scheme of metal-nanoparticle synthesis method

Physical methods are methods that are used by relying on external variables such as temperature, pressure, and others to produce nanomaterials. The chemical method is a method for synthesizing nanoparticles with various types of chemical reactions, while the biological method is a method for synthesizing nanoparticles with biological aspects (Bagheri et al., 2023). Whether with any design, metal nanoparticles are an innovation that has superior potential in drug delivery. Studies on metal-nanoparticle design are still developing today.

4. Conclusions

The design of metal-based materials in drug delivery applications has high potential as a promising future innovation. This is due to the nature and effectiveness offered by its use. Apart from that, the use of metal-based materials in medical applications has the advantage of being a good micronutrient if in sufficient doses.

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