Journal of Nanostructure in Chemistry (2021) 11:501–526
https://doi.org/10.1007/s40097-021-00432-7

REVIEW

Metal–polymer-coordinated complexes as potential nanovehicles for drug delivery

Hamed Tabasi[1,2] · Maryam Babaei[1] · Khalil Abnous[1] · Seyed Mohammad Taghdisi[3] · Amir Sh. Saljooghi[4] · Mohammad Ramezani[1,2] · Mona Alibolandi[1,2]

Received: 14 April 2021 / Accepted: 20 July 2021 / Published online: 25 July 2021

Abstract

Hybrid metal–polymer-coordinated complex, as a class of supramolecular coordinated complex, represents a great opportunity for the development of the multipurpose intelligent system of nanomedicine in drug delivery. These structures and their interesting functions are created after the self-assembly process and coordination bond formation between different metal ions and polymers. There is an important difference between metal–organic framework (MOF) and metal–polymer-coordinated complex (MPC). MPCs are convergent structures made of metal and polymeric linkers' combination in 1D, 2D and 3D architectures while MOFs are divergent 3D network structures with metal cores and organic ligands linkers. Until now, many reviews have been published about MOF-based systems while there is no comprehensive review on MPCs. Moreover, the MPCs have exhibited potential nano-chemistry properties to be utilized in nanomedicine applications as smart and multifunction nanovesicles for drug delivery. In this review, the MPC architectures, their synthesis process and their applications in drug delivery are described. The advantages and disadvantages of MPC are summarized. We also categorized smart MPCs for on-demand drug release and intelligent delivery.

✉ Mohammad Ramezani
ramezanim@mums.ac.ir

✉ Mona Alibolandi
alibolandim@mums.ac.ir

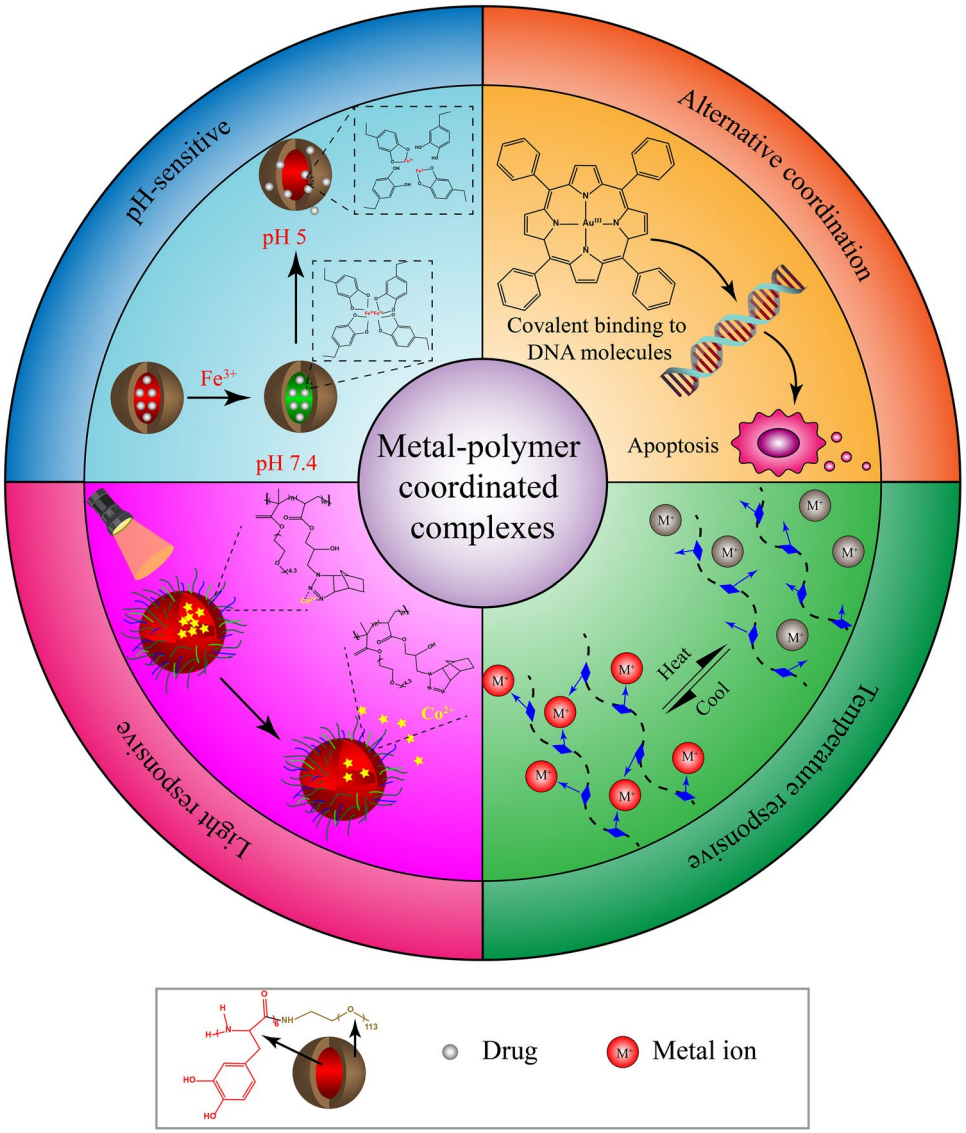
[1] Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

[2] Department of Pharmaceutical Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

[3] Targeted Drug Delivery Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

[4] Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran

Graphic abstract



Keywords Nanomedicine · Drug delivery · Metal–polymer-coordinated complex · Self-assembly · Metallic organic framework

Introduction

In recent years, metal-based hybrid materials have been vigorously studied due to their wide range of applications especially biomedical ones [1]. Various organic/inorganic hybrid nanomaterials can be implemented to fabricate novel platforms in pharmaceutical technology [2]. Metal-based polymers have been utilized for biomedical applications in recent decades [3–5]. However, there are two different hybrid metal-based polymeric materials since they can be produced as either a metal–organic framework (MOF) or metal–polymer-coordinated complex (MPC) depending on the structure and ligand-type circumstances [6, 7]. MOFs are a subclass of MPCs that have a 3D cluster type structure consisting of metal ions and organic ligands of polymers, while MPC has been produced from a separated 1D–3D molecular precursor which contains a self-assembled and coordinated metal center surrounded with polymeric ligands (Fig. 1) [8].

MPC is one of the most useful systems for various biomedical applications including magnetic resonance imaging (MRI) [9, 10], bioseparation [11, 12], and drug delivery

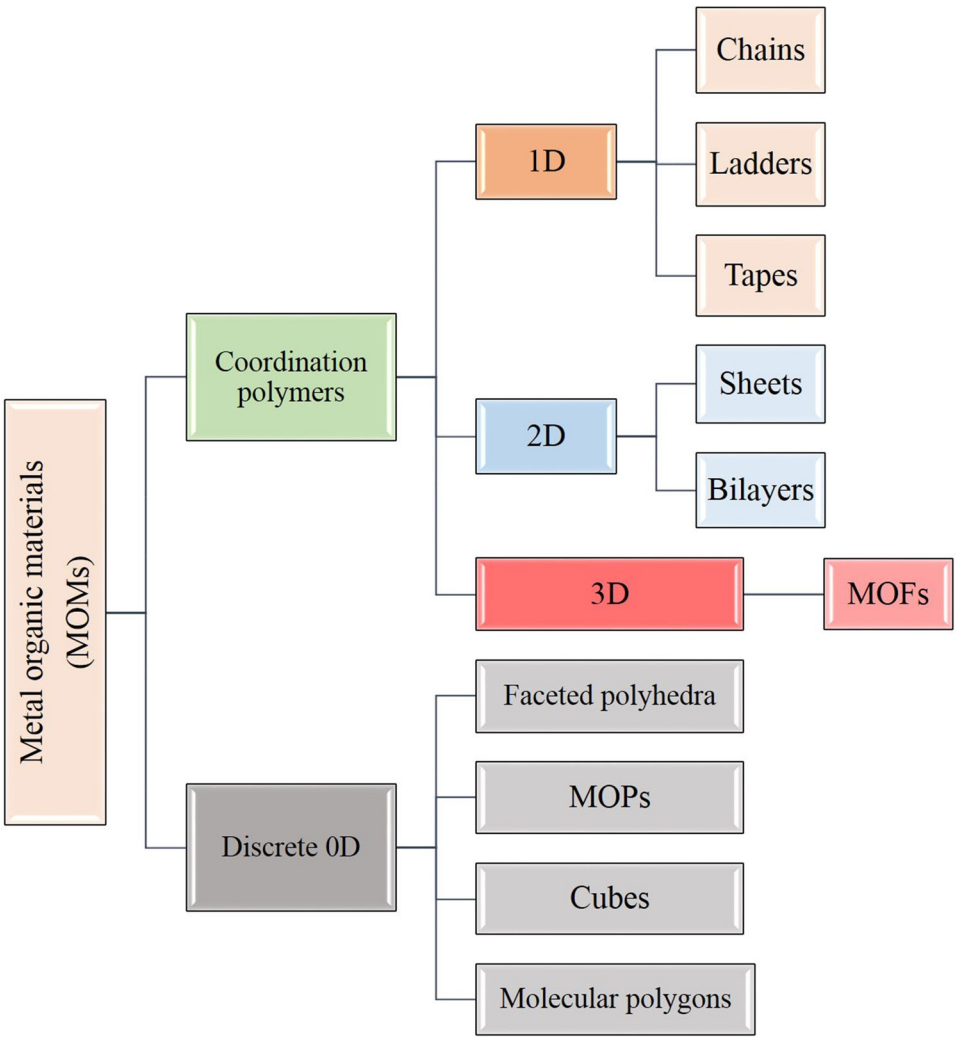


Fig. 1 Metal–organic materials (MOMs) categories

owing to their desirable properties comprising high surface area, biocompatibility, chemical/physical stability, nanoscale dimension and porous structure [13, 14].

MPCs are a favorable class of nanoscale vehicle for drug delivery due to their well-defined architectures, high surface area, tunable porous structures and chemical flexibility toward functionalization. They can deliver therapeutic agents as their building block or via pore encapsulation, surface adsorption and covalent binding.

Metal-based supramolecular coordinated polymers have become increasingly popular as therapeutic agents specially for cancer treatment. However, there are several obstacles to their utilization, such as low stability and high toxicity whereas the MPC could overcome these barriers completely. Moreover, the MPC nanosystem exhibited a high capability of creating a reliable coordinated binding between metal ions and either organic ligands or polymers with safe characteristics to increase stability and provide therapeutics encapsulation potential [15, 16]. On the other hand, the MPC as a functionable system due to the variety of ligands, metal ions and their different interactions in their structures, have the capability to be used for the design of an intelligent system in the field of drugs transportation)Table 1 and Scheme 1).

In comparison with traditional nanocarriers, MPC nanocomplexes have shown fascinating properties owing to their different molecular interactions which could be incorporated into their structures such as covalent, van der Waals, hydrogen bonds or weak electrostatic interactions. The alteration of different coordinations could be considered for producing a variety of smart MPCs' platforms.

Toward drug delivery applications, size of nanocarriers, their loading capacity, safety and toxicity features are important issues that should be considered. In addition, the molecular weight of the organic ligands is another concern which could be addressed though using small and modifiable organic ligands with various chemical structures.

Figure 2a represents metals that have been utilized for the MPC fabrication used in biomedical applications till 2020. Furthermore, Fig. 2b reveals the trend of related publications

Table 1 Smart MPC nanocarriers

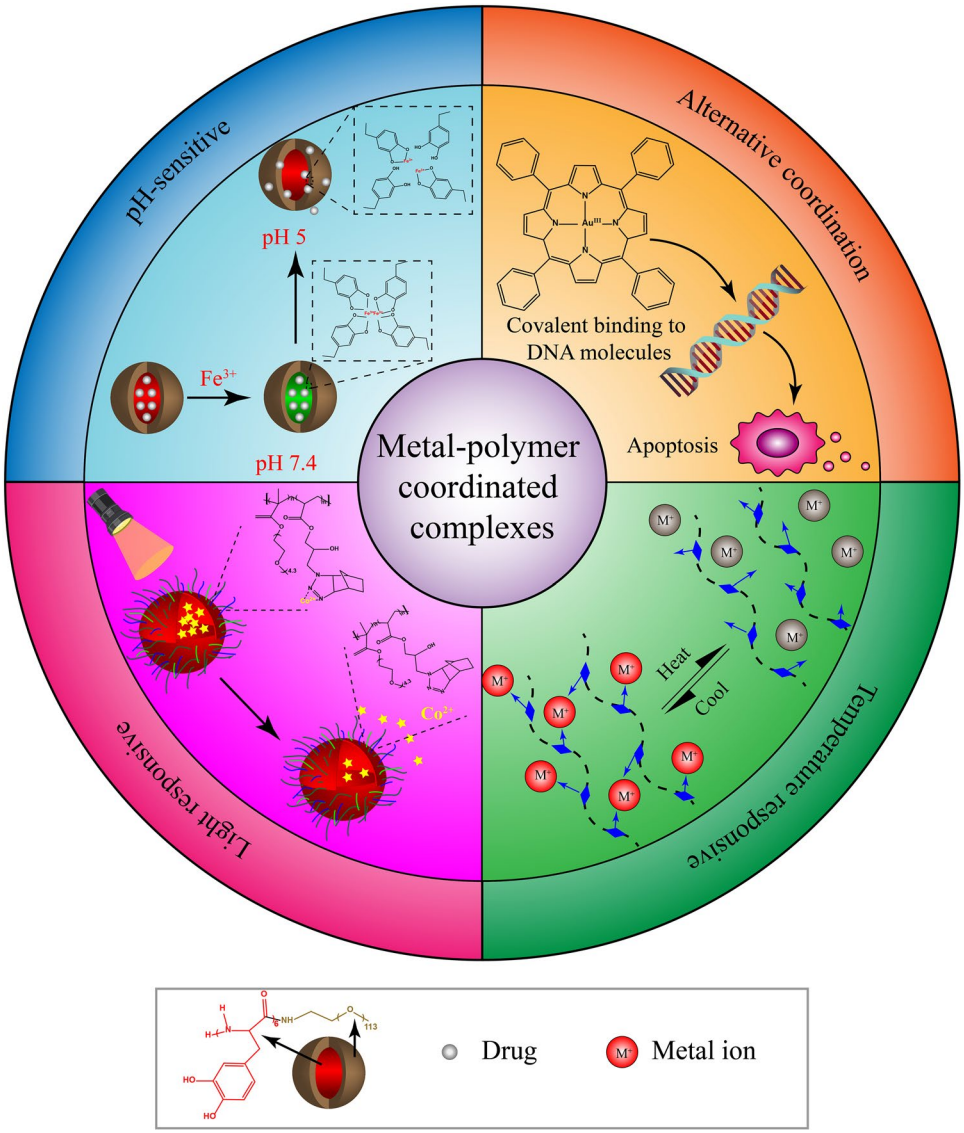
	Nanocarrier	Organic ligands	Therapeutic agent	Cancer cell	Sensitivity	Applications	Refs.
1	(Cu(II))-carboxylate	Citric and hyaluronic acids	Cu–citric acid complex	B16F10	Thermal enzyme	Photothermal therapy	[67]
2	PEI–Cu(II)–phenanthroline	–	Cu (II)	H460	Alternative coordination	Enhanced uptake	[82]
3	PEG–PUSe–PEG	PEG	DOX	–	Alternative coordination	Controlled release	[68]
4	[Au(TPP)]Cl	Porphyrin	Gold (III)	Nasopharyngeal carcinoma	Alternative coordination	Overcome cisplatin resistance	[72, 84, 85]
5	MSN	PEG and iminodiacetic acid	DOX	–	pH and coordination	Long circulation and colloid stability	[86]
6	Polymeric micelles	–	Cisplatin	MDA-MB-435 and MDA-MB-231	pH	Slow release	[87]
7	Al (III)–PNIPAM	GO	Al^{3+}	–	Temperature	Florescent	[88]
8	Pt–OH	Polyphenol–PEG	Cisplatin	HepG2	Alternative coordination	Chemodynamic therapy	[89]
9	Fe–MCCP	Polyethylenimine cyclodextrin	Fe	HEK293	Alternative coordination	Targeted delivery	[40]
10	Fe–TPP–PEG	Porphyrin polycaprolactone–PEG	DOX	HeLa and MCF-7	pH	Chemo-photodynamic therapy	[18]
11	PEG–Zn–PEI	PEG, PEI	MTX	HepG2	Endosomatic activity	Increase cell uptake	[65]
12	Fe–DOX	PEG−dipyridine	DOX	MB49	pH	Drug-loading capability and stability	[90]
13	Fe–DTX	PEG–PDOPA	DTX	–	pH	Self-assembly	[91]
14	ICG–Fe–MTX		MTX	–	pH and laser	Target folate receptors	[9]
15	Porous Cu (II) cage	PEG	5-Fluorouracil	–	Alternative coordination	Water-stable and controlled release	[92]
15	Metal cage	Hexaruthenium carceplex and pyrenyl	Pt and Pd	A2780	Alternative coordination	Block GSH and carbonic anhydrase	[75]
16	Pt (II) cage	Ascorbic acid	Cisplatin	A2780	Alternative coordination	High positive charge	[76]
17	Pd_2L_4 cage	Hydroxymethyl	Cisplatin	A2780	Alternative coordination	Double toxicity	[77]
		BF_4	Cisplatin	–	Alternative coordination	Reversibly disassembled/reassembled	[29]
18	Ru cage	CF_3SO_3	Pyrene	A2780	Alternative coordination	Enhanced cell uptake	[73]

TPP tetraphenylporphyrin, *PUSe* platinum and selenium, *MCCP* metal-coordinated cationic polymer, *DOX* doxorubicin, *MTX* methotrexate, *PDOPA* poly(L-3,4-dihydroxyphenylalanine), *DTX* docetaxel, *ICG* indocyanine green, *GSH* glutathione, *PNIPAM* poly(N-isopropylacrylamide)

in this field from the year 2000–2020 based on a Scopus search.

A coordinated bond (dative, dipolar) involves a two-electron covalent bond in which both electrons come from the same atom. In this regard, coordination of polymers and metal ions forms through hydrogen bonding, ions exchange, van der Waals bonding, π–π interaction, and thermodynamic forces [1, 17]. There are several methods to characterize the MPC nanosystem, such as ^{1}H-NMR spectroscopy, X-ray crystallography, UV and FT-IR spectroscopy which confirm the bonding types, coordinated degree, and structural morphology. ^{1}H-NMR spectroscopy (Fig. 3a) is capable of elucidating the chemical structure of the as-prepared MPC while X-ray crystallography (Fig. 3b) reveals the new structure of an MPC [18, 19].

In this review, we summarized different metal-based coordinated polymers excluding MOFs, with various functions and sensitivity as smart vehicles for therapeutic applications.



Scheme 1. MPC as a functionable system due to the variety of ligands, metal ions and their different interactions in their structures, have the capability to be used for the design of various responsive delivery systems

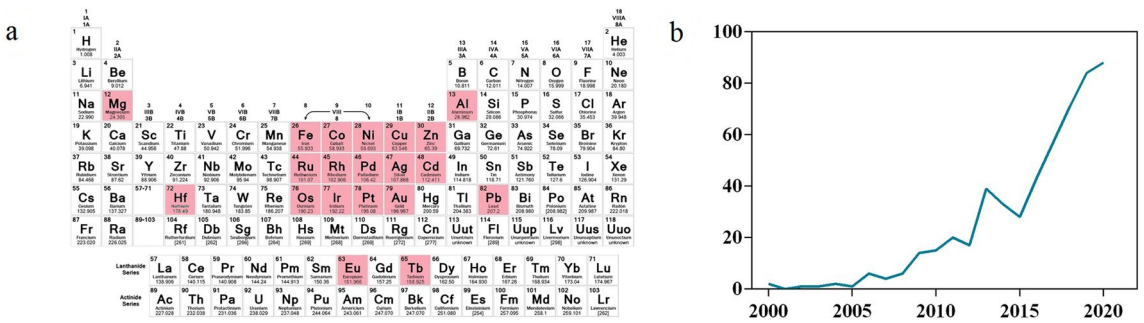


Fig. 2 **a** The periodic table containing metal used in MPC fabrication, extracted from the related articles; **b** chart representing the frequently published articles on MPCs and drug delivery field from the year 2000–2020 based on Scopus search

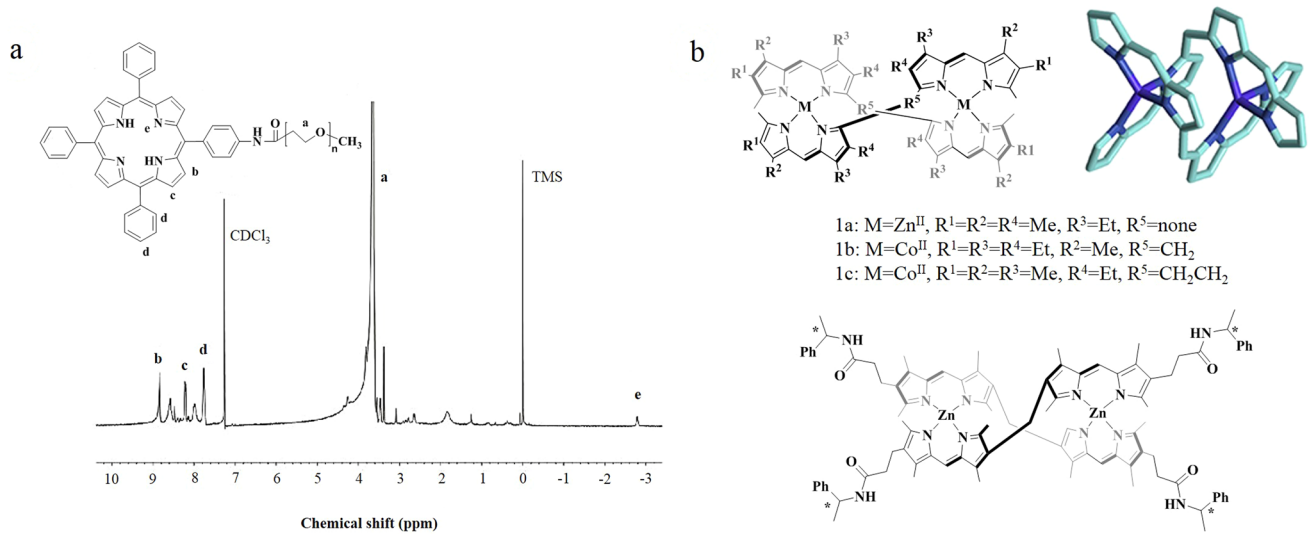


Fig. 3 **a** ^{1}H-NMR spectroscopy of TTP–PEG. Reproduced from [18] with permission from John Wiley and Sons, Copyright © 2018 and **b** X-ray crystallography for double helicate chemical structure. Reproduced from [20] with permission, Copyright © 2018

Synthesis strategies of MPCs

The synthesis of an MPC nanosystem is usually done by exposing a polymer and metallic ion via several techniques such as polymerization [21, 22], solvothermal [23], hydrothermal [24], and precipitation [25].

Polymerization

Driva et al. [22] utilized the polymerization process via adding polystyrene to copper and iron salts at high vacuum to produce a specific metal–polymer complex. Methanol was added dropwise to this solution to adjust the polystyrene/metal ratio and the mixture was stirred for 3 days. The polystyrene/metal ion in methanol was kept for 1 day to precipitate completely followed by the separation of the as-synthesized MPC by filtration. Moreover, in another study, the Fe ions dissolved at high concentration of polymer was used to fabricate a coordination nanocomplex. A micellar-MPC nanosystem has been produced using this method providing a self-healing and reversible drug delivery system in the cytoplasm [26]. A magnesium-based coordination was synthesized via the crystallization method by the Ezzayani research group. They produced the crystalline structure of MPC by diffusing *n*-hexane in CH_2C_2 to prepare the sample for further characterizations [19].

Hydrothermal

Li's and co-workers synthesized Pb-based MPC with five different polymers including $C_{11}H_{10}N_4O_4Pb$, $C_9H_7ClN_4O_2Pb$, $C_9H_7BrN_4O_2Pb$, $C_9H_7IN_4O_2Pb$, and $C_{18}H_{22}N_8O_8Pb$ via hydrothermal technique. The synthesis method was generally done by dissolving five different Pb-salts comprising $Pb(OAc)_2{\cdot}3H_2O$, $PbCl_2$, $PbCl_2$/KBr, PbI_2, and $Pb(NO_3)_2$, into CH_3OH/H_2O mixture. The hydrothermal method was performed by heating of above solutions in a Teflon-lined stainless steel for 72 h [24].

Solvothermal

The solvothermal technique was designated by Liu et al., through dissolving hafnium-salt and bis-(alkylthio) alkene linkers into a mixture of ethanol and dimethylformamide. The polyvinyl pyrrolidone and triethylamine were added to the above solution allowing for hafnium ions reaction with polymer. This mixture was stirred at 120 °C for 1 day to complete the synthesis of the hafnium-based MPC nanocomplex [23].

Precipitation

The precipitation method has been used to synthesize MPC with a high yield. The iron-based MPC, as a nanocarrier, was prepared by 1,4-bis(imidazol-1-ylmethyl)benzene and catechol ligands and was loaded with azidothymidine, as an antiviral drug [25]. They also utilized PVP as a stabilizer and the MPC complex was precipitated after vigorous stirring and reaction completion. The product of MPC complexes with the antiviral drug was reported with 68% yield sing the precipitation method. This high yield was probably obtained owing to the physicochemical interactions between stating materials and ligands.

Supramolecular coordinated complexes (SCCs)

In nanobiotechnology, the structure, morphology, and crystalline shape of the nanoparticle have a pivotal role in the property of the final products. The coordinated supramolecular complexes often constitute a new structure with new functionality (Table 2) which can be evaluated via X-ray crystallography, and nuclear magnetic resonance (NMR) spectroscopy. Different architectures of coordinated nanocomplexes have been synthesized in recent years. Different architectures of coordinated nanocomplexes have been synthesized in recent years. Indeed, MPC as a subclass of SCCs has 1D, 2D, and 3D (Fig. 4a) polyhedral structure containing different bonds in various angles based on the M_xL_y (M: Metal, L: ligand) formula which could produce many nanosystems for biomedical applications due to the possibility of changing the metal ion and polymers within the MPC framework [20, 27, 28]. Figure 4b and c demonstrates that MPC can be produced via two major directions as edge- and face-directed [29, 30]. Fujita et al. reported polyhedral self-assembly of Pd (II) with $M_{12}L_{24}$ and $M_{24}L_{48}$ formula. The fabricated structures and bonding-angles are represented in Fig. 5 [31]. In another study, a self-assembly of Pd (II) nanocage with Pd_2L_4 formula was also reported for drug delivery purposes. They attempted to provide bioconjugation of the model peptide to the prepared nanocage via two approaches: (1) direct conjugation of the peptide onto the surface of nanocage and (2) anchoring of the peptide to the ligand and then self-assembly and formation of the nanocage. Their results demonstrated higher efficiency for the second approach for incorporating targeting ligand into the prepared structure [32].

Several groups have reported self-assembled hierarchical MPC with a cavity structure for drug delivery [10, 33, 34].

The hierarchical assembly is a novel and versatile approach to use primary molecules as a building block for producing complex and nano-architecture structures by assembling these simple molecules.

The metal–polymer coordination has shown great stability in both solution and solid states because of various interactions that can be generated between metal ions and polymers, as coordinated complexes bindings [17, 35]. The successful process of MPC formation needs electron reach atoms such as O, N, and S to form dative bonds. The platinum-metal group (Pt, Pd, Ir, Ru, Rh, and Os) have exhibited well-binding capability with these atoms to produce MPC nanocomplex. In this regard, a review article has summarized and discussed the antimalarial activity of the platinum-group-based coordinated polymers [36].

On the other hand, the supramolecular activity of polymers with active sites is another important factor in forming

Table 2 Different metal–polymer-coordinated supramolecular structures

	Metal	Organic ligand	Coordinated groups	Properties	Refs.
1	Zn (cation)	Sulfonyl-calix[4]arene	(3-4H) $(3\text{-}3H)_2$ $(3\text{-}2H)_2$	–	[46]
2	Mn	Oxalate	H-bonds O•••π-hole	High stability and anticancer	[47]
3	Mg	Porphyrin	H-bond (C–H…N)	Antibacterial	[12, 19]
		Meso-porphyrin	–	Antibacterial	[48]
4	Pb (anion)	Azoles carboxylate	–	–	[24]
5	Cu Fe (anion)	Polystyrene	–	High thermal stability	[22]
6	Ag	Bipyridine	Ag–Ag and bis-urea macrocyclic	–	[52]
		Inosine 5´-monophosphate	–	Antibacterial activity	[11]
7	Cu	Isoconazole	3 new coordination	Antifungal activity	[53]
8	Cd	Pyridinyl triazole carboxylate	12 new coordination	Fluorescent activity	[38]
9	Au	Adenosine	–	Long luminescent activity	[54]
		1,5-Naphthyridine	N-Heterocycle	Antibacterial and antifungal	[55]
10	Ln (Eu^{3+}, Tb^{3+})	Na-alginate/PVA	H-bond	Photoluminescence, cytocompatibility, and antibacterial	[56]
		PVA/AM-Ln $(DPA)_3$	C–C	Long luminescence lifetime, good mechanical properties	[49]

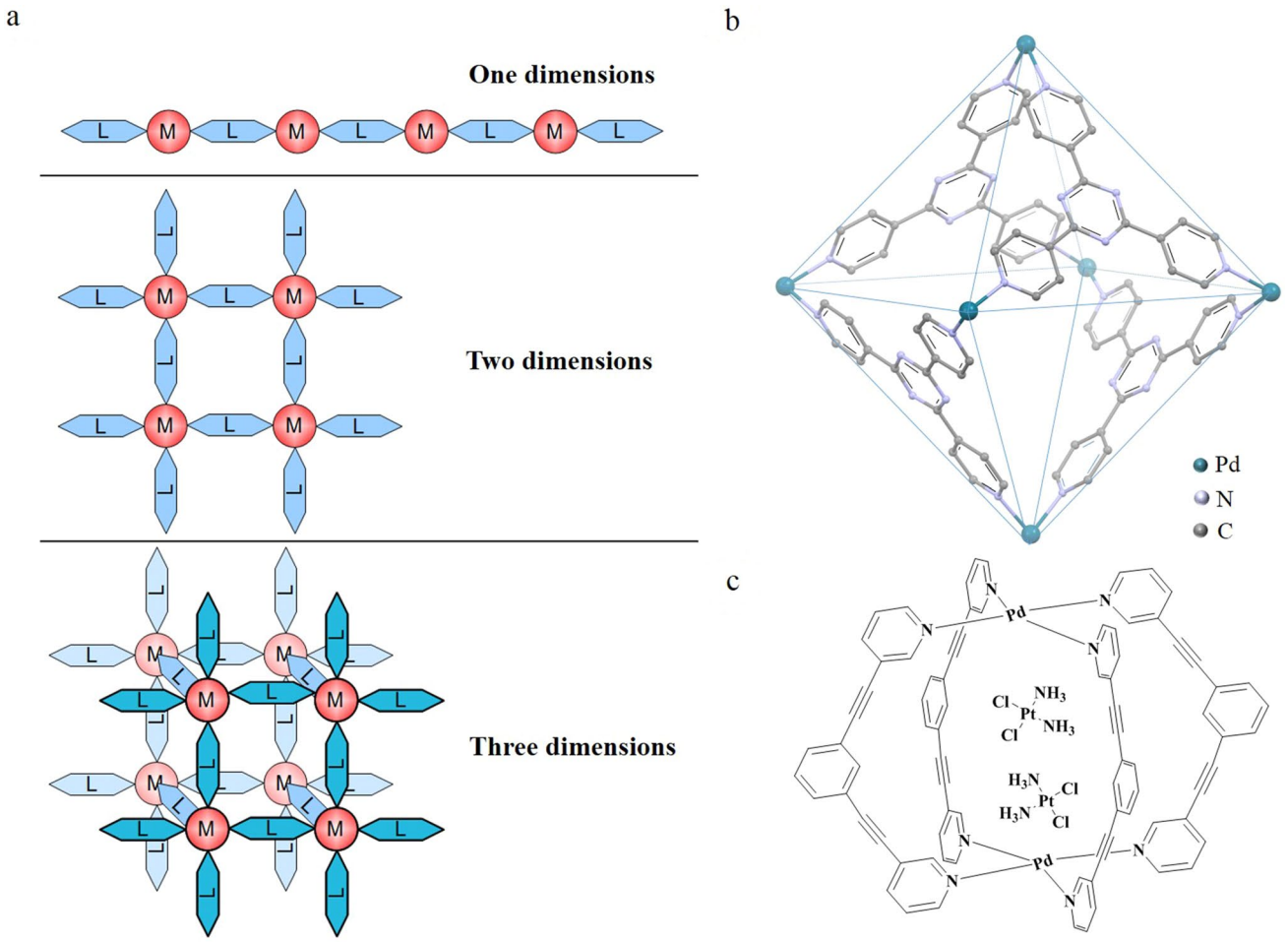


Fig. 4 **a** 1D–3D structure of MPC, **b** face-direction of MPC. Redrawn from [30], and **c** edge-direction of MPC. Reproduced from [29] with permission from Royal Society of Chemistry (Great Britain), Copyright © 2010

a versatile MPC structure. Until now, various polymers have been incorporated into the MPC structures including porphyrin [37], pyridinyl [38], pyrene [39], polyethyleneimine [40], salecan [41–43], pullulan [44], and chitosan [45].

It should be noted that the coordination nanocomplexes can be formed in different architectures and angles. For instance, Hajji and co-workers synthesized a Mg–porphyrin complex as a 1D structure [37]. The Mg^{2+} core bonds to four nitrogen atoms of porphyrin in an axial position (Fig. 6).

In another study, Li et al. [38] designed a series of novel MPC architectures via cadmium(II) and pyridinyl triazole coordination in 12 different ways. They claimed that all 12 forms had fluorescent property due to the electron transition from n to π* orbital.

Numerous types of metal ligands have shown potency to form a nanoscale supramolecular complex. Kniazeva et al. [46] synthesized three zinc-based polymer complexes via nuclear coordination with sulfonyl-calix[4]arene. The obtained results verified the fabrication of a new complex constructed from metal-core coordination with carboxyl and benzyl groups. They introduced four different ligands of (3-4H), $(3\text{-}3H)_2$, $(3\text{-}2H)_2$, and $(3\text{-}2H)_4$ for Zn-coordination in flexible tweezer shape which can be seen in Fig. 7.

In another attempt, Mn (III)–oxalate supramolecular complex, $\{[Mn_2(\eta^2\text{-}C_2O_4)\ (H_2O)_2Cl_4]\ 2(4\text{-CNpy})\}_n$ (1) (C_2O_4 = oxalate, 4-CNpy = 4-cyanopyridine) was synthesized. This supramolecular complex was fabricated using Mn (III) as center coordinated with two chloride ligands and the oxygen atom of the bridged oxalate. They investigated the complex structures and their existing bonds implementing QTAIM and NCI plot analyses. The obtained results demonstrated interesting O•••π-hole (nitrile) coordinated interactions between nitrile moiety and water molecules providing the stability of the crystalline structures. Among prepared compounds, compound 1 (Fig. 8a) revealed acceptable cytotoxicity against malignant Dalton's lymphoma (DL) cell line, as an anticancer agent in comparison with cisplatin as represented in Fig. 8b [47].

Amiri et al. fabricated a complex between a metal core and a porphyrinic ligand (5,10,15,20-tetrakis(4-bromophenyl)

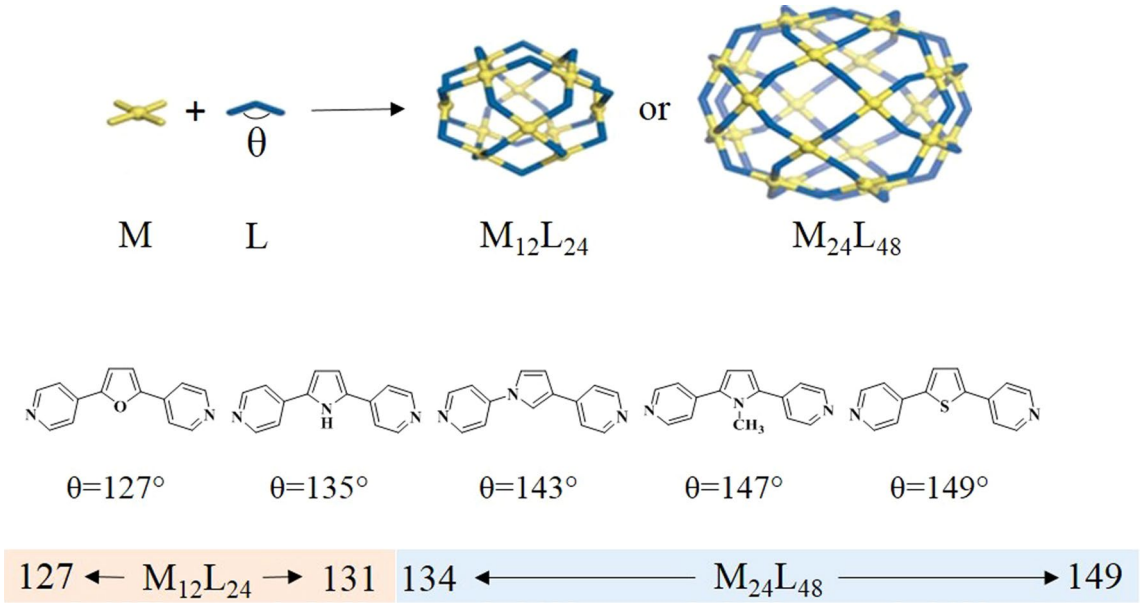


Fig. 5 Pd (II) nanocages with $M_{12}L_{24}$ and $M_{24}L_{48}$ formula and their bond angles. Reproduced from [31] with permission from John Wiley and Sons, Copyright © 2012

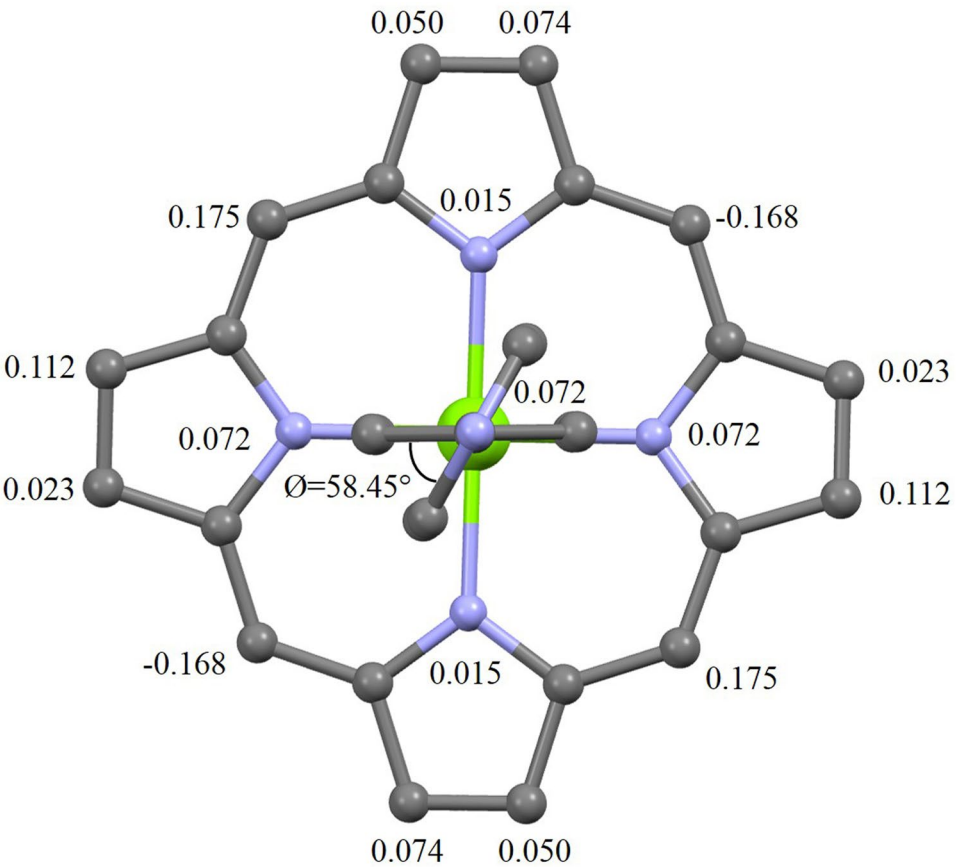


Fig. 6 Mg–porphyrin-coordinated complex. Redrawn from [37]

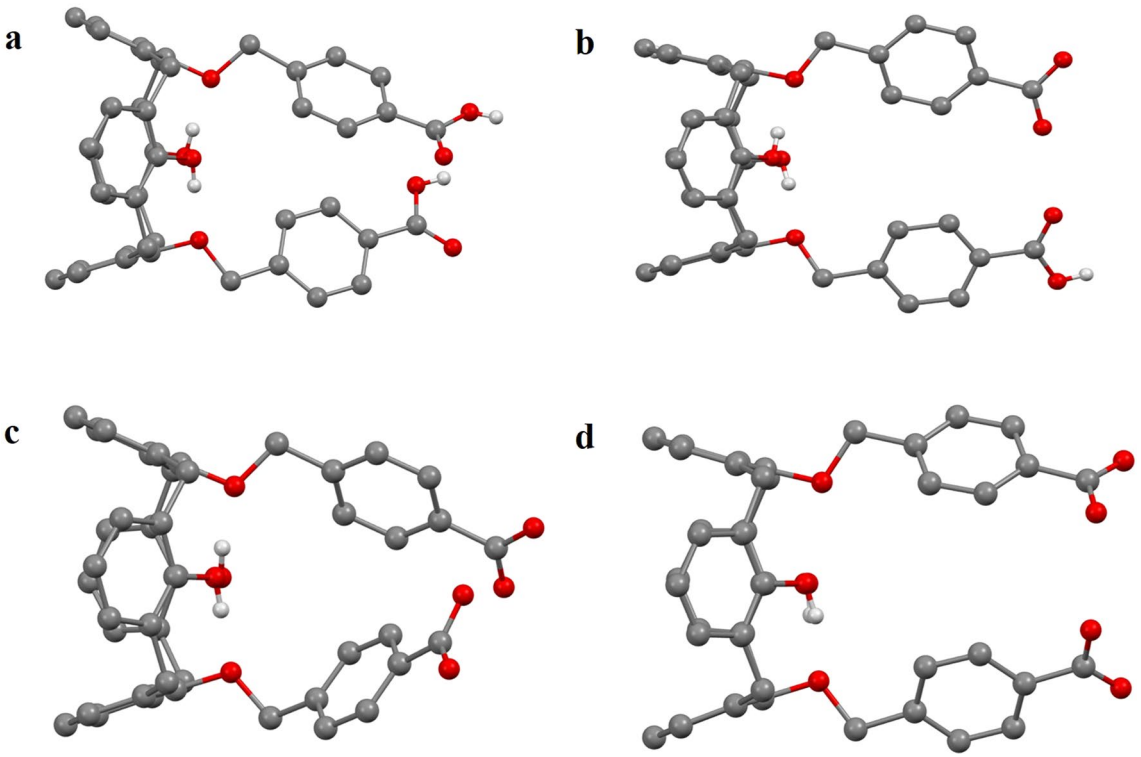


Fig. 7 Zn-coordination in four flexible tweezers shapes bonding with **a** (3-4H), **b** $(3\text{-}3H)_2$, **c** $(3\text{-}2H)_2$, and **d** $(3\text{-}2H)_4$. Reproduced from [46] with permission from Royal Society of Chemistry (Great Britain), Copyright © 2020

porphyrin). They fabricated the complex by coordinating Mg (II) to 5,10,15,20-tetrakis(4-bromophenyl) porphyrin which also bonded to an imidazole ligand (Fig. 9b). The antibacterial efficiency of the Mg-based MPC was characterized on the agar medium at 37 °C for 24 h. The prepared MPC revealed good antibacterial activity against *E. faecalis* after 24 h of incubation at 37 °C [48].

The coordinated polymer via lanthanide ions has provided an extra luminescent activity along with other biological properties [49]. For example, a research group has synthesized Eu-coordinated polymer, Eu–iminodiacetate (IDA), and incorporated it into a hydrophilic temperature-responsive poly(*N, N*-dimethyl acrylamide) matrix. The prepared platform revealed photoluminescent property and multi-stimuli-responsiveness under different stimuli comprising temperature, pH, and metal-ion sonication [50]. Dynamic coordination of the metal–ligand complex (formation and dissociation of Eu–IDA complex) provided reversible sol to gel transition upon aforementioned stimuli which made the hydrogels injectable with switchable ON/OFF luminescence characteristic. The reported supramolecular complex showed great potency for biological sensing applications.

A transition MPC system with the magnetic property was introduced by the Qin research group (Fig. 9a). They synthesized an MPC nanocomplex through coordination of copper ion to polymer ligand named $[Cu(fdc)(dmbpy)(H_2O)]_n$ (**1**) $\{[Ni_2(fdc)_2(bipy)_2(H_2O)_4]\cdot(H_2O)_2\}_n$ (**2**) (fdca = 2,5-furandicarboxylic acid, dmbpy = 3,3′-dimethyl-4,4′-bipyridine, bipy = 4,4′-bipyridine) and investigated its magnetic property [51]. Table 2 represents different coordinations between metal and polymers providing new functionality for MPCs.

Metal–organic frameworks (MOF), as well as coordinated polymers, are nanosystems involving metal ions and organic linkers. MOF is a well-known system for drug delivery having various sensitive ligands with the controlled-release property. However, metal-based coordinate polymers have similar properties as MOFs in addition to their great potential activities due to coordinated supramolecular architecture and hybridized metal–ligands. MOFs can be used as carriers for different drugs while MPCs are capable of interacting with metal-based drugs and polymer to produce remedy properties (Table 2) in addition to their drug delivery capability. Moreover, MOFs with their strong bonding stability may not be well eliminated from the body, thereby inflicting serious problems, whereas MPCs with flexible and changeable bonds, exhibit a more biocompatible and biodegradable feature. Regarding the structure and synthesis method, MOF is a cluster type while MPCs have discrete hierarchical structures. In addition, MOFs can be created from several separated MPCs (Fig. 10).

The self-healing property of the MPCs extends the materials' lifetime and improves their biocompatibility.

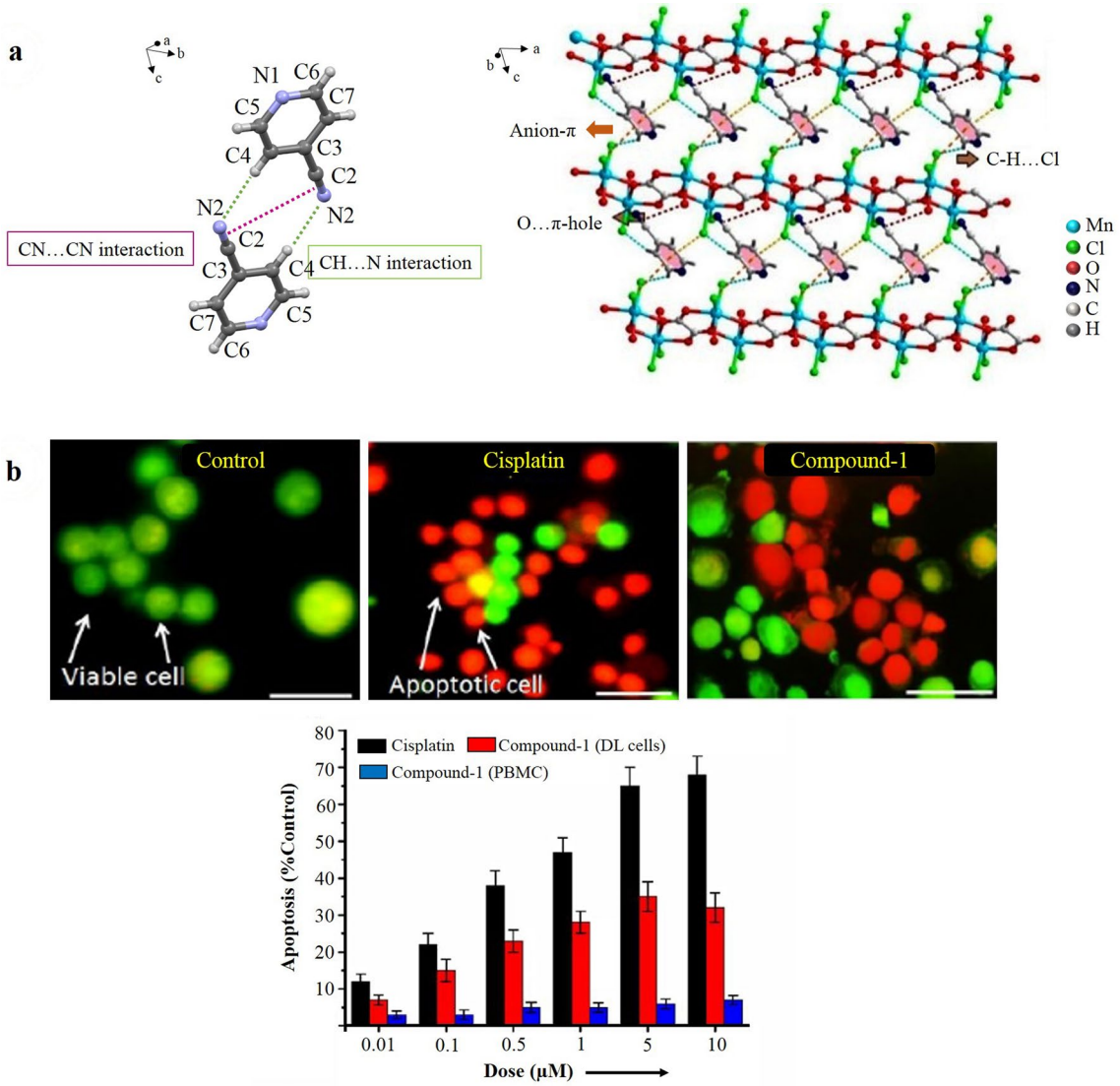


Fig. 8 **a** Schematic representation of Mn (III)–oxalate supramolecular complexes and their interactions, and **b** comparison of cytotoxicity of cisplatin and two prepared MPC reproduced from [47] with permission from Royal Society of Chemistry (Great Britain), Copyright © 2020

A recent study reported desirable self-healing metal–polymer-coordinated complexes consisting of Fe, Zn, and Tb ions (Fig. 11) and diamide pyridine using a low-cost and commercially sound method [58, 59].

Several researchers have evaluated the self-healing property of chitosan in coordination with several metal ions (Fe^{3+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+}, Cr^{3+}) and used these materials as antibacterial agents [45, 60].

The self-assembly of metal–polymer is another approach to design new multifunctional materials with different surface chemistry and easy synthetic method via discrete blocks of SSCs [11, 61–64]. A self-assembly of metal–polymer was designed by Tamaddon et al. with Zn^{2+} ion as the center and PEG and PEI as polymers which are coordinated around the Zn center based on a protonation and deprotonation process (Fig. 12) [65].

Moreover, MPCs oftentimes show florescent property due to the existence of coordinated binding in their structures which provides electron transition ability [66]. In these structures, the coordination between the metal ion and polymer is formed via extra electron of metals in the host-orbital of the polymer thus allowing the release of the generated energy gap by different stimuli including temperature, pH, NIR, and metal-ion sonication.

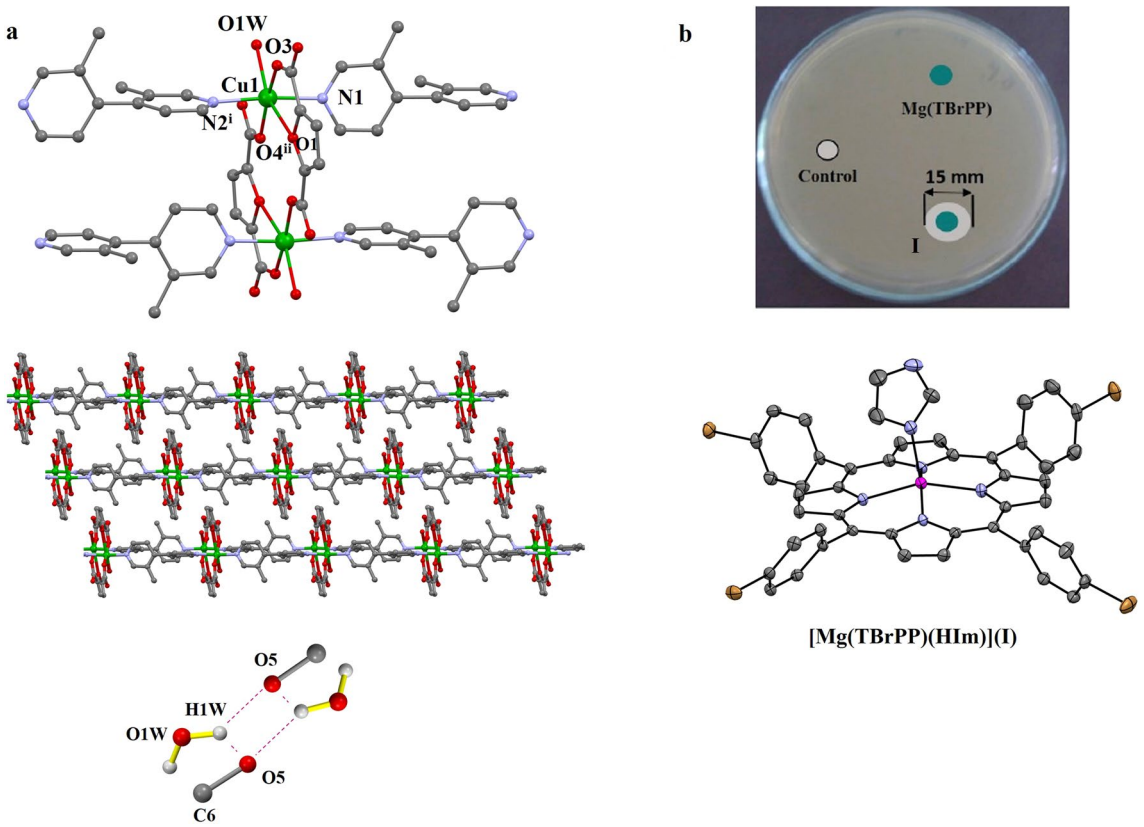


Fig. 9 Schematic representation of **a** Cu and **b** Mg coordination environment with antibacterial activity and their interactions. Redrawn from [48, 51] with permission from Elsevier, Copyright © 2017

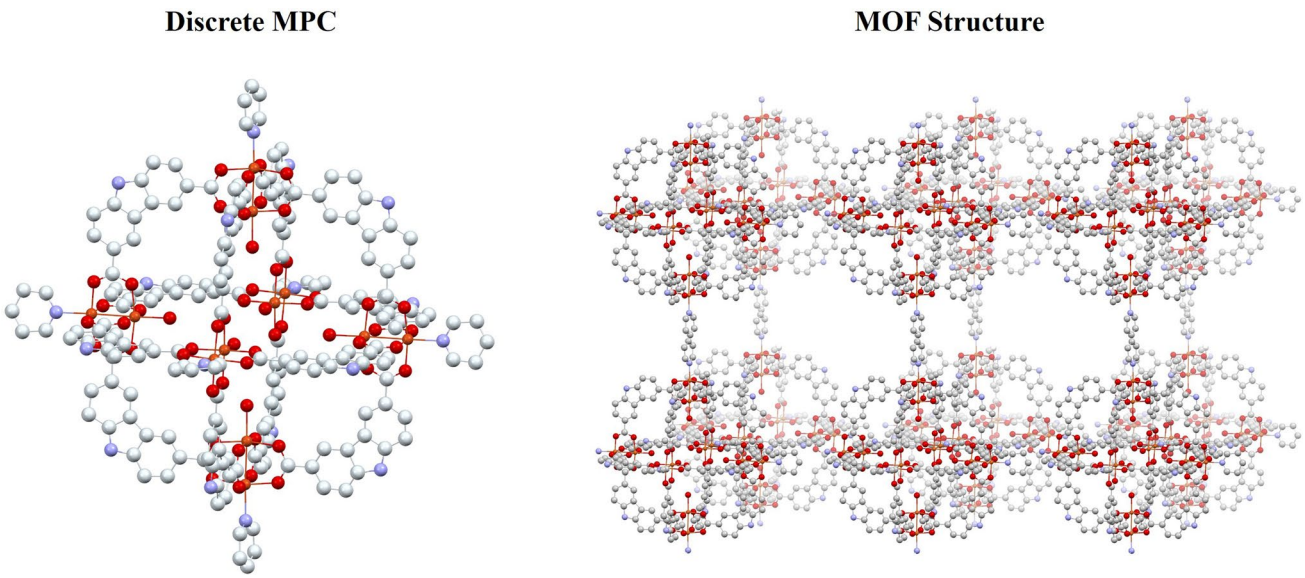


Fig. 10 Structure of a discrete MPC and a MOF which was created from several MPC polyhedral. Reproduced from [57] with permission from American Chemical Society, Copyright © 2012

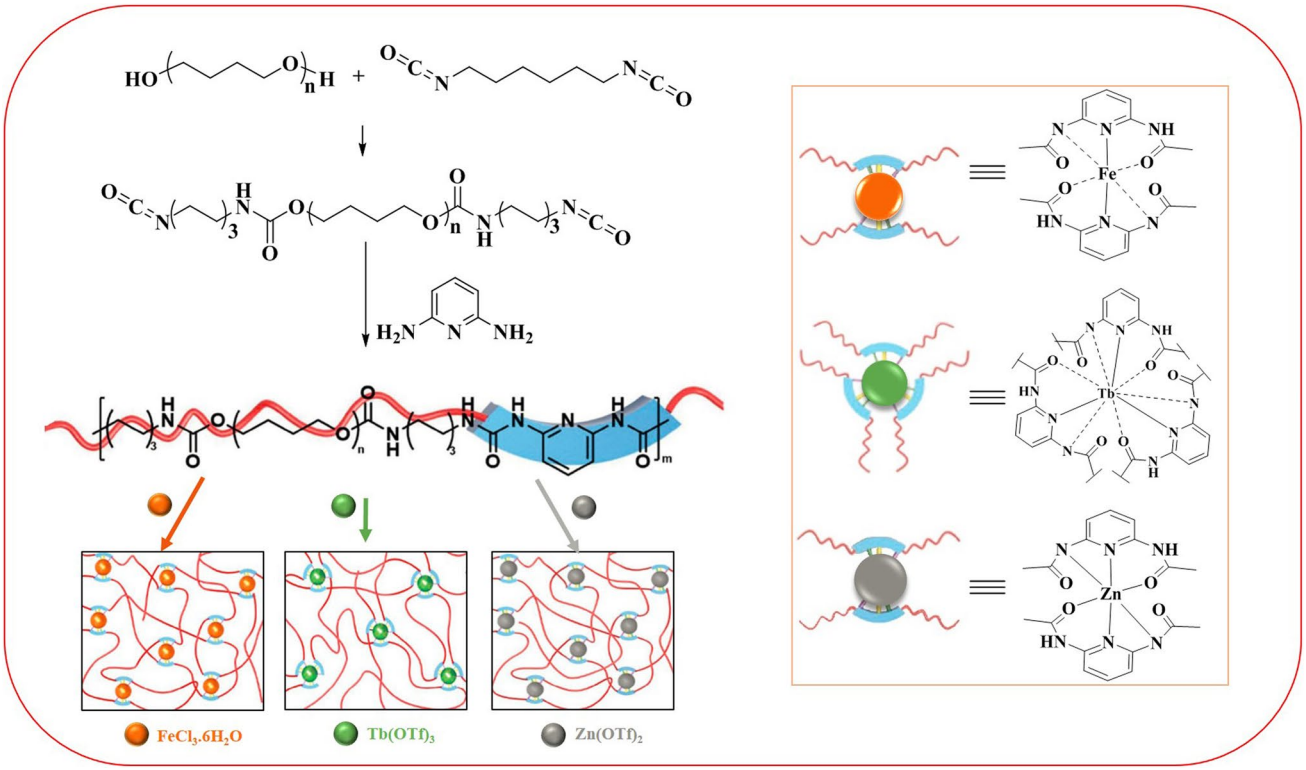


Fig. 11 Schematic self-healing of diamide pyridine with three metal salts. Reproduced from [58] with permission from John Wiley and Sons, Copyright © 2018

Smart metal-based coordinated polymer

In addition to the reservoir role of MPCs, targeted delivery to the site of action and on-demand release of encapsulated drugs is a pivotal issue for the design of a desirable drug delivery system. Responsiveness of the designed platforms is associated with several factors including the desirable treatment strategy and modality, cancerous tissue environment and cargo. The MPCs as a functionable nanocarrier exhibited great capability for the design of a smart drug delivery platform due to their unique properties such as coordination binding, cavity structure, and luminescent characteristics.

MPCs have an inherent smartness due to the host–guest coordination activity in their structures. For example, Zhang et al. synthesized Cu(II)–carboxylate-coordinated complex. The prepared MPCs is consisted of copper ions coordinated with dopamine–hyaluronic acid conjugate and citric acid. In this structure, Cu(II) was coordinated with the carboxyl groups thereby increasing the Cu(II) energy gap and also enhancing the electron transition capability. All these characteristics increase the extinction of the MPC in the near-infrared region used for photothermal therapy (PTT) application. Moreover, the responsiveness of the system in the tumor site, due to the overexpression of hyaluronidase, led to the faster degradation and release of Cu-citric acid complexes demonstrating efficient anticancer activity. The obtained results showed efficient PTT capability of the prepared system with 21.3% tumor growth inhibition [67].

In another study, a coordinated complex was fabricated between platinum as the metallic center and selenium-conjugated polyethylene glycol (PEG) (Fig. 13). The resultant coordinated structure was further loaded with doxorubicin (DOX) and evaluated as a smart system for cancer therapy. This MPC showed an intelligent controlled-release property in the presence of glutathione, because glutathione can coordinate with platinum leading to the destruction of the self-assembled system. This kind of responsiveness is called "alternative coordination" and in the cytoplasm of cancerous cells with high glutathione content, this system could facilitate the release of the cargo at the site of action [68].

In the last decade, metal-based drugs have exhibited potent anticancer activity on different cancers. However, the lack of a safe and effective carrier is an important issue due to their systemic toxicity. The MPC nanosystems provide a great opportunity in the drug delivery technology especially for metal-based drugs owing to the coordination bonding, encapsulating process, and coordination cage host–guest capability. Moreover, several metals such as Co, Cu, and Au have shown therapeutic properties while they do not have enough stability in the biological environment due

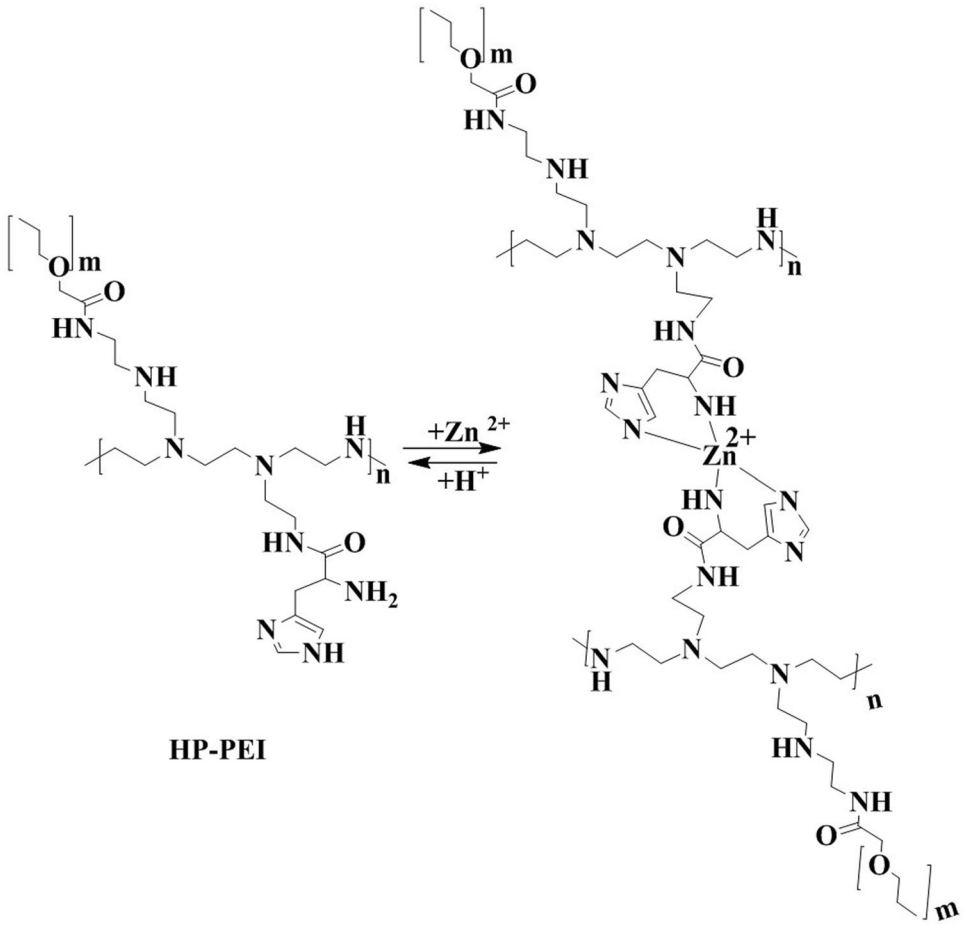


Fig. 12 Self-assembly of PEG–Zn–PEI via a protonation and deprotonation process. Reproduced from [65] with permission from Elsevier, Copyright © 2016

to protein absorption or oxidation. Thus, the formation of metal-coordinated nanocomplex could increase the stability of these metals while enhancing their therapeutic index. Through the complexation of these metal ions with organic ligands and preparation of MPC structures, they could be protected from the harsh biological enzymatic environment. In addition, some prodrugs could be prepared based on the MPC approach using different metal-based anticancer drugs, which are coordinated with different polymers. For this purpose, a metal-based drug interacts with a non-toxic, favorable, and smart polymer which then intelligently transports the metal-based drug to the target cells [69]. For instance, ruthenium was encapsulated via pyrene in a new formula of $[Ru_6\ (p\text{-cymene})_6\ (tpt)_2\ (donq)_3]^{6+}$ ($[1]^{6+}$) (tpt = 2,4,6-tri-(pyridin-4-yl)-1,3,5-triazine; donq = 5,8-dioxydo-1,4-naphthoquinonato) as a metal-cage and host–guest system by Therrien group [39]. This MPC was introduced as a lipophilic and water-soluble system showing high cytotoxicity toward ovarian cancer cells.

Gold (III) have demonstrated high cytotoxicity toward various cancer cells while has low stability and minor solubility/biocompatibility under physiological condition and is almost converted to gold (I) as a cardiotoxic agent [70, 71]. The MPC has addressed this issue. For example, gold (III)-coordinated with porphyrin has been studied as anticancer therapeutics. This MPC system revealed high toxicity toward cancer cells and indicated antitumor activity even 100-fold higher than that of cisplatin [72]. In addition, coordination interactions have shown a potential hydrophobic π–π bonding to create a multifunctional system for co-delivery. Figure 14 illustrates a coordinated carrier-free nano-theranostic system via Fe–PEG conjugate for the methotrexate delivery that could form a π–π bonding with indocyanine green (ICG) as a photosensitizer agent [9]. This metal-coordinated system with a high co-delivery capacity showed favorable stability and prolonged blood circulation. Moreover, the prepared system showed a targeted intelligent drug release in response to either lysosomal acidity or near-infrared 808 nm laser. Due to the presence of Fe (III) in the structure of the system, it has the capability of recognizing cancerous cells thereby providing receptor-mediated endocytosis. This multipurpose system revealed ideal photo-chemotherapy potential with great potency for magnetic resonance/photoacoustic/fluorescence imaging.

On the other hand, the MPC can be synthesized with a cage shape for metal-based drugs to develop a host–guest

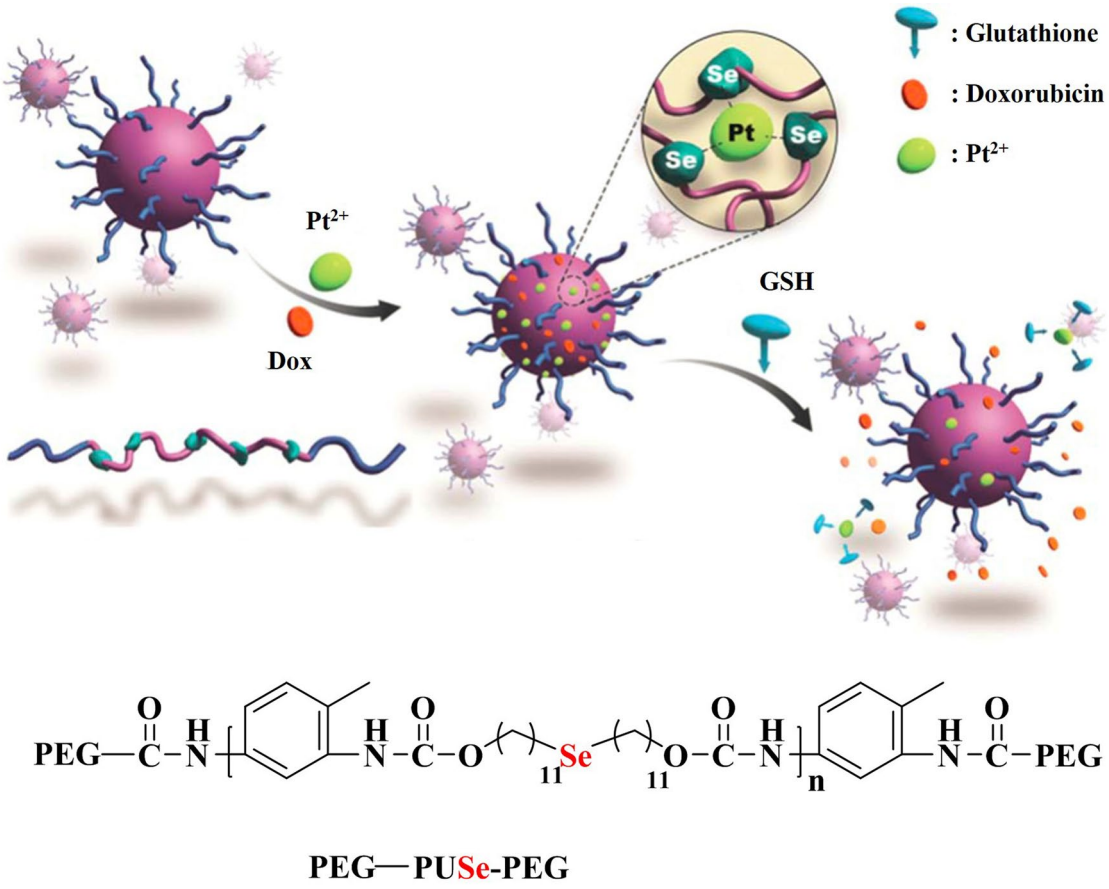


Fig. 13 MPC nanocarrier with coordination responsiveness. Reproduced from [68] with permission from Royal Society of Chemistry (Great Britain) Copyright © 2012

(Fig. 15a) and metal-cage MPC nanosystem [73, 74]. For example, six ruthenium coordination with pyrenyl, produced a smart metal-cage MPC (Fig. 15b) for carrying Pt and Pd to the cancerous cells [75]. The prepared smart MPC showed favorable stability, water solubility and cancer cell targeting capability alongside tumor-enzyme inhibition to overcome drug resistance.

In another study, Lippard et al. [76] encapsulated Pt(IV) via Pt(II) cages as a novel MPC nanocarrier to provide on-demand release of cisplatin in cancer cells. They introduced a new host–guest coordination process for metal-based anticancer drugs. Their results demonstrated that the hexanuclear Pt(II) cage hosting four Pt(IV) prodrug guest molecules, had a size of 3 nm providing the system with a strong positive charge and could efficiently transport the cargo to the cancer cells after reduction reaction to efficiently release its cargo. Casini's research group also designed a potential cytotoxic metal-coordination cage based on the Pd_2L_4 formula [77]. The MPC cage was used for the cisplatin coordination as an anticancer drug to produce metal-cage MPC nanocarrier. Their results showed high cytotoxicity against tumor cells due to the toxicity of both cage and coordinated metal.

There are a lot of therapeutic proteins/monoclonal antibodies for human diseases. However, it should be noted that due to the large size and complex structure of these proteins, their transport to the site of action is a serious challenge in the pharmaceutical industry.

In this regard, several studies have been conducted to produce a versatile nanocarrier for therapeutic proteins among which MPC exhibited acceptable performance. Postupalenko et al. [78] developed an assembly process (Fig. 16) via attachment of o protein onto a polyanionic linear guide (pGi) followed using electrostatic interactions between the pGi-coupled protein and pyridylthiourea-grafted polyethylenimine (pPEI). In addition, Fujita and co-workers produced a large metal-cage MPC via $M_{12}L_{24}$ formula (Fig. 17) for ubiquitinated protein loading [79]. This process was done by self-assembly of the metal-cage MPC around the ubiquitinated protein.

The MPC technology has also been implemented in the field of biosensors for the detection of various antibodies

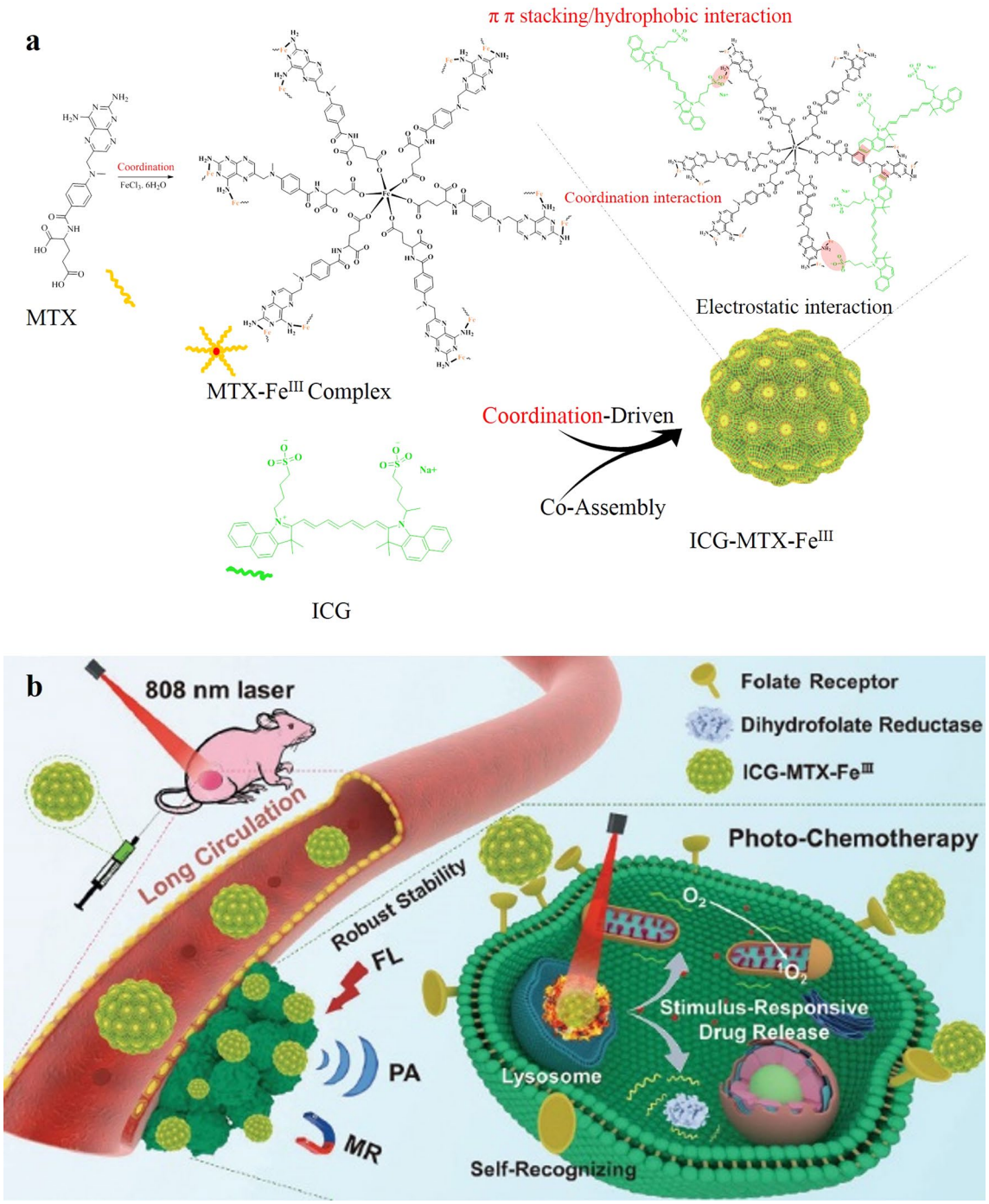


Fig. 14 Schematic representation of **a** coordination and π–π interactions of ICG–Fe–MTX and **b** a prepared MPC nanosystem with targeting and MR responsive ability. Reproduced from [9] with permission from Royal Society of Chemistry (Great Britain) Copyright © 2020

based on competitive-coordinated nanocomplexes. Wang et al. developed a nanosensor in which GO-based poly-heterozygosis pyridine (GO@PHPY) was conjugated for the detection of antibody against AFP. The coordinated Cu(II) to GO@PHPY acts as a signal probe which could detect alpha-fetoprotein (AFP) [80]. Another smart MPC system was designed (Fig. 18) as an immunosensor by Bai and co-workers. They synthesized Au-coordinated poly(glycidyl methacrylate) and conjugated the MPC system to the detection antibody for tumor marker detection via alternative coordination of gold nanoparticles formed between polymer and antibody [81].

In another attempt, polymer–copper(II)–phenanthroline coordination,

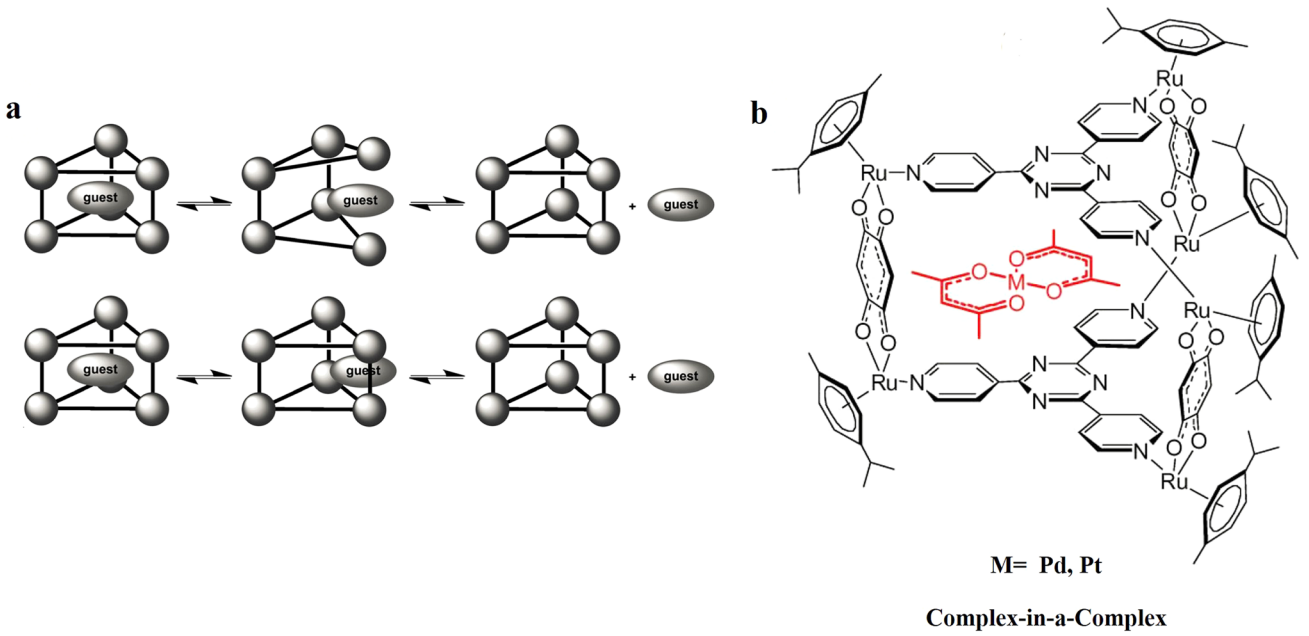


Fig. 15 **a** Reversible host–guest process. Reproduced from [74] with permission from John Wiley and Sons, Copyright © 2011 and **b** metal-cage structure of MPC. Reproduced from [75] with permission from Royal Society of Chemistry (Great Britain), Copyright © 2010

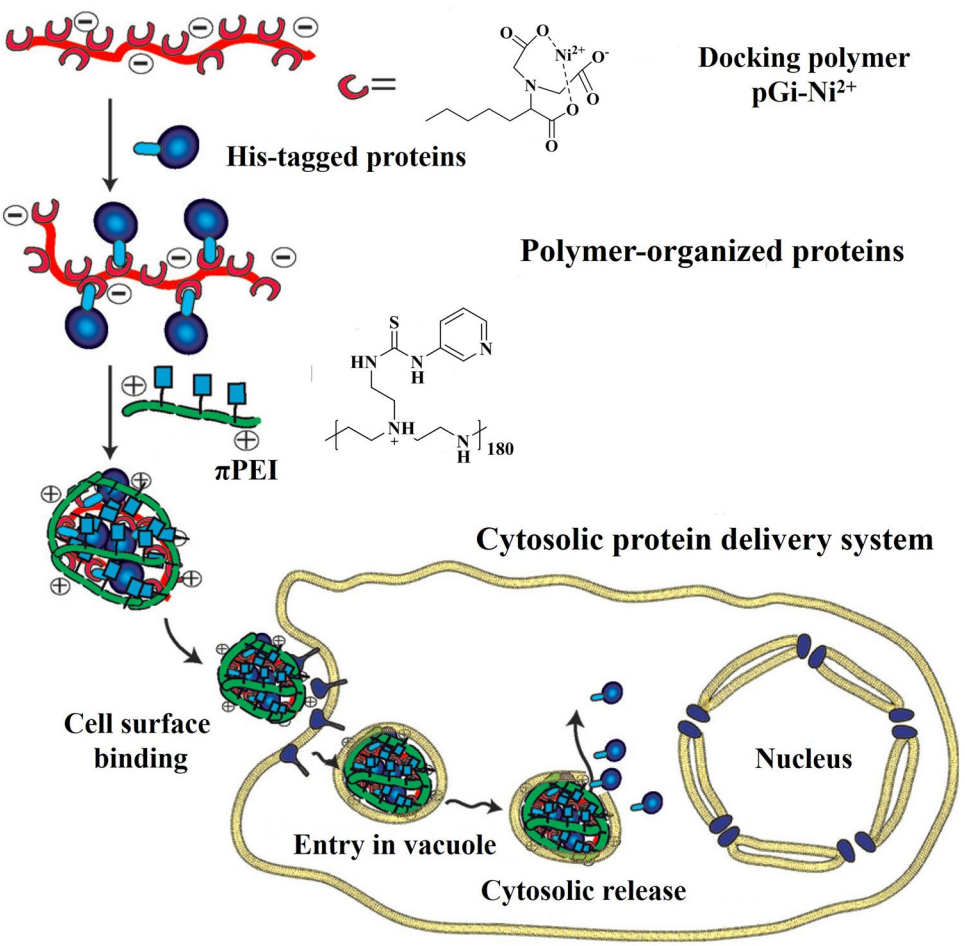


Fig. 16 Protein delivery of polymer-organized protein and its mechanism from conjugation to cell uptake. Reproduced from [78] with permission from John Wiley and Sons, Copyright © 2015

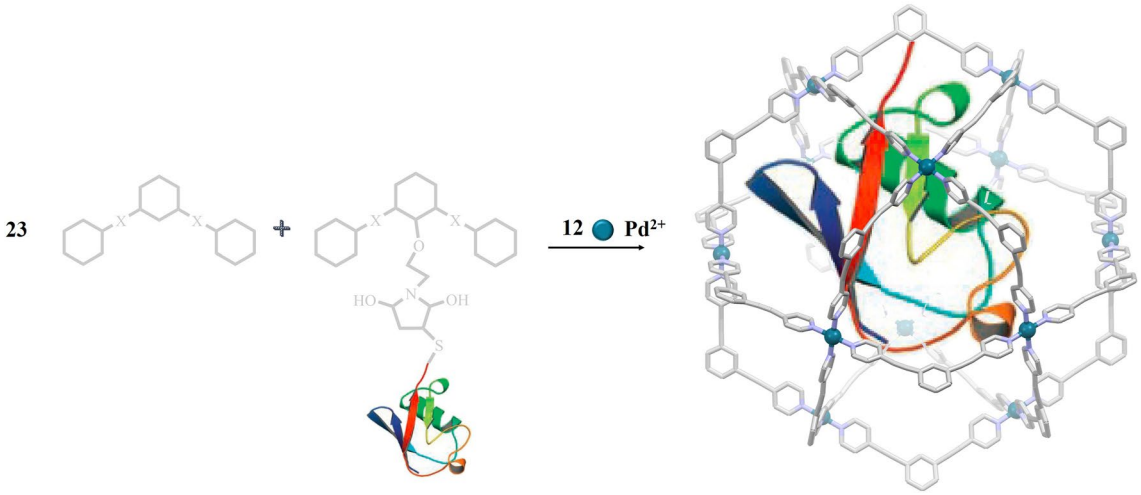


Fig. 17 A large MPC system with 12-Pd^{2+} and 24 linkers for protein delivery. Redrawn from [79]

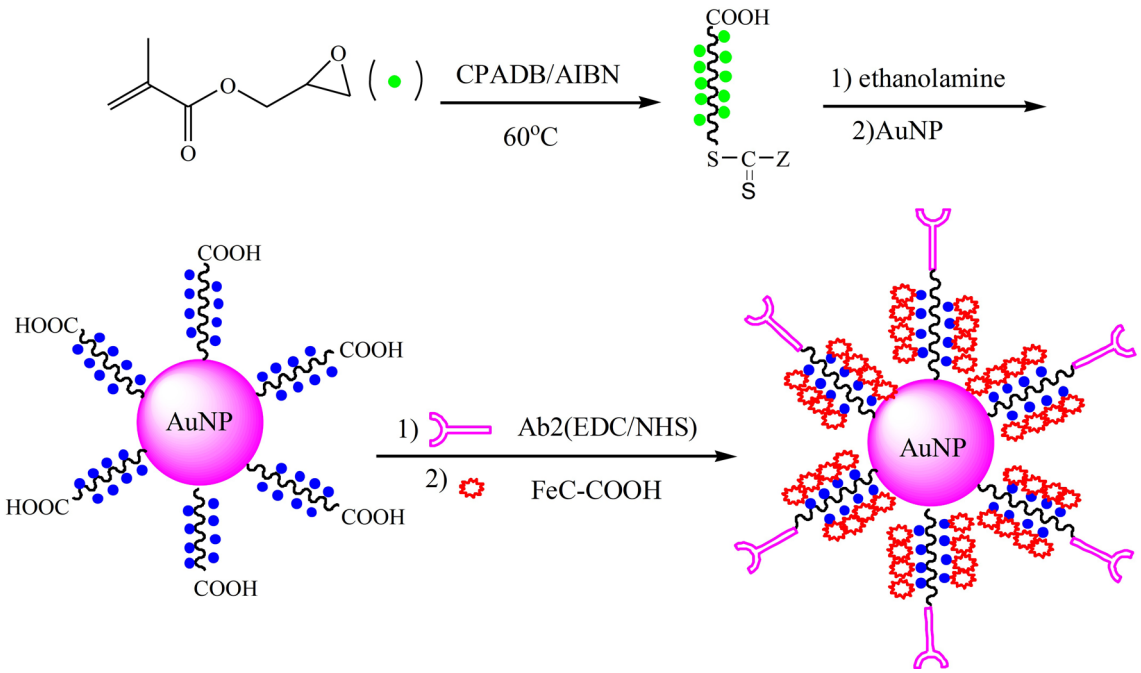


Fig. 18 Schematic representation of the preparation of Au as an MPC nanosystem for immunosensing application. Reproduced from [81] with permission from Elsevier, Copyright © 2016

$[Cu(phen)_2(BPEI)]Cl_2{\cdot}4H_2O$ (phen = 1,10-phenanthroline, BPEI = branched polyethylenimine) was prepared. This positively charged alternative coordination of Cu(II) complex showed high affinity toward DNA thus providing high cellular uptake and anticancer activity. Moreover, the prepared MPC system exhibited efficient antimicrobial activity against fungi, Gram-positive and -negative bacteria compared to the traditional pharmaceutical products such as clotrimazole and ciprofloxacin [82, 83].

The MPC sensitivity

The MPC systems could have characteristic responsiveness to trigger drug release. Most of the smart MPC nanocomplexes have shown flexible bonding and alternative coordination with environmental biomolecules (DNA, cysteine, ascorbic acid, etc.). Furthermore, an MPC nanosystem is able to release its cargo at the site of action

due to the changeability of its structural bonds with biomolecules or loss of coordinated bonds under a specific circumstance (pH, enzyme, temperature, light, and oxide reduction). There are three major sensitive-responsive MPC including alternative coordination, pH-sensitive, and light and temperature-responsive, all of which employ the MPC nanocomplexes as non-toxic and smart vehicles for various anticancer agents.

Alternative coordination

The alternative metal-coordination is a new approach for the fabrication of smart MPC nanosystems. The coordination ability of some metal ions with biomolecules such as DNA, antibodies, cysteine, and ascorbic acid, have adapted them for biomedical applications. The MPC nanosystems have shown the swapping process of the coordinated bonds with various agents based on existing environmental conditions such as pH, temperature, and enzymes. This potential inherent ability of the MPC has triggered the development of a wide range of new MPC nanocomplexes and also introduced them as a multi-responsive vehicle for different therapeutics.

In this regard, copper-based MPC as drugs, have illustrated treatment capability against numerous human diseases comprising neurological disorders, anemia, wound healing, liver cancer prevention and inflammatory diseases. Their therapeutic potency is owing to the versatile alternative coordination between polymeric ligands/metal ions and biomolecules [83].

The gold-porphyrin has become a new MPC nanocomplex because of its alternative coordination activity to overcome Gold(III) instability, insolubility, and toxicity [84, 93]. A research group has shown an alternative-coordination ability of Gold(III) to change the bonding of Gold(III)–porphyrin with DNA of the cancer cells to induce cancer cells apoptosis [94]. This Gold-based MPC demonstrated 100-fold higher HeLa cell killing in comparison with cisplatin while the nanocomplexes had excellent stability in the physiological condition.

Another alternative process revealed high toxicity of as-prepared MPC nanocomplex of Gold(III)–porphyrin on the cancer cell with low toxicity on lung normal cells at about $IC_{50} = 1.2$, and $IC_{50} > 100$ μM, respectively [95]. The as-prepared MPC demonstrated DNA-bonding via the alternative process to inhibit topoisomerase I activity. In addition, this nanocomplex showed Bcl-2 blocking and the MPC exhibited both anticancer and anti-angiogenesis activity. Moreover, several reports have claimed that the Gold(III)–porphyrin exhibited efficient cytotoxicity of 100- to 3000-fold higher than that of platinum-based anticancer drugs [72, 96].

pH-sensitive

pH-sensitive materials were extensively designed for the controlled release of drugs in the tumor microenvironment due to the acidic environment of cancerous tissues [97, 98]. The pH-responsive MPC systems usually lose their coordination bonds in acidic environments [18]. For example, Zhang et al. designed a nanocarrier with mesoporous silica nanoparticles (MSNs) functionalized with polyethylene glycol (PEG)/iminodiacetic acid (IDA) to make coordination nanocomplex with DOX (Fig. 19). Consequently, the MPC/DOX showed controlled release of DOX in the tumor environment due to the acidic condition [86]. The pH-responsiveness of the system was due to the excess of protons in the acidic pH of cancer cell condition (pH: 5) which cause the replacement of the DOX coordination.

A cisplatin-based MPC was synthesized by another research group. In their study, methoxy poly(ethylene oxide)-*b*-poly-(α-carboxylate-ε-caprolactone) (PEO-*b*-PCCL) was synthesized and cisplatin was coordinated with the pendant carboxyl ends on the poly(ε-caprolactone) core. The prepared MPC exhibited slow release of cisplatin in physiological pH while the cisplatin release was significantly accelerated in acidic pH due to loss of coordination bonds between cisplatin and micelle core [87]. The encapsulation efficacy and release profile were studied via ICP-MS (inductively coupled plasma mass spectrometry) analysis and the results illustrated the encapsulation of up to 94% and the cumulative release of about 35% in the acetate buffer solution (pH: 5).

Ren et al. [89] introduced a Pt-based MPC nanosystem as a prodrug via an alternative coordination process. They utilized a polyphenol (epigallocatechin-3-gallate) and phenolic Pt(IV) for this purpose. Their results confirmed a complicated process of conversion of Pt–OH prodrug to cisplatin together with the production of ROS after the alteration of the coordinated bonds involving Pt and Fe^{3+} in an acidic pH environment.

The Fe-based coordinated system was developed as a drug delivery platform due to its enhanced cellular uptake and coordination ability with different drugs. For example, an MPC of Fe^{2+} and doxorubicin was prepared by Ruan and co-workers [90]. This nanosystem was also decorated with PEG–dipyridine to increase physiological stability. Their results indicated high and efficient cellular uptake and co-delivery of doxorubicin and Fe(II), followed by their release due to the acidic pH. Hwang et al., utilized catechol–Fe^{3+} as an MPC nanocomplex for the docetaxel delivery [91]. This nanosystem exhibited pH-sensitivity because of the conversion of catechol–Fe^{3+} from bis to a mono-form complex in the endosomal acidic pH, causing the drug release. The as-synthesized MPC devoted 48% of its surface area to the docetaxel drug while it was able to

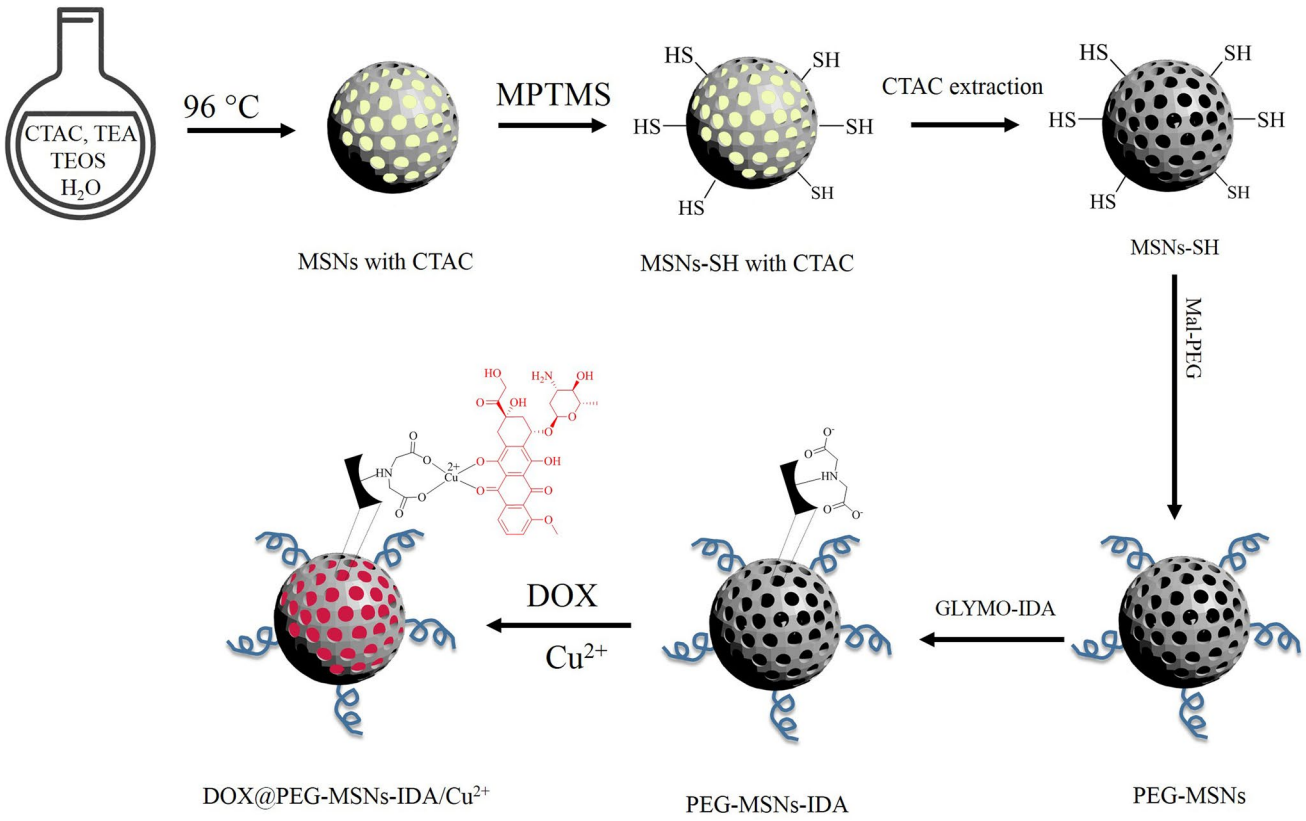


Fig. 19 Preparation of mesoporous silica nanoparticles (MSNs) functionalized with polyethylene glycol (PEG)/iminodiacetic acid (IDA) for fabrication of coordination nanocomplex loaded with DOX. Reproduced from [69] with permission from Elsevier Copyright © 2017

release more than 50% of the encapsulated drug in acidic condition.

Light and temperature responsive

Besides using the metal–polymer system as a nanocarrier, this nanosystem could release its metal ion for treatment purposes. For instance, copper, gold, arsenic, and platinum have been used as remedies [99]. As a result, a novel designated supramolecular system is capable of releasing the metal ions for the treatment of various diseases. Moreover, a controlled-release system can be developed via metal–polymer coordination. Xu et al. [100] synthesized a photo-sensitive metal-based copolymer using Co^{2+} and triazoline-containing amphiphilic polymers. They determined the Co^{2+} release kinetics by exposing the PTA-Co to UV light. The results demonstrated that PTA was converted to micelles in the solution and released the Co^{2+} during the UV exposure (Fig. 20a). Sun and co-workers introduced a light-responsive Cu(II)-based nanocomplex in which tumor temperature was elevated by exposing the nanocomplexes to laser causing weight loss of the tumor (Fig. 20b, c) [67]. They utilized hyaluronic acid as a polymer owing to its coordination ability and abundant carboxylate groups. This MPC nanocomplex was able to release copper ions as a chemotherapeutic agent because of its coordination loss under the infrared wavelength.

On the other hand, the temperature-responsiveness of the smart MPC is a promising property for drug delivery and cancer treatment. Nowadays, photothermal therapy has become an important remedy, especially in the breast cancer treatment. It is important to detect an appropriate metal–polymer interaction with photo/thermo activity to produce a novel MPC nanosystem with thermo-responsiveness. Several polymers have been introduced as promising agents to generate new interactions with metals thereby acting as a thermo-sensitive MPC vehicle that may demonstrate different activities by changing the temperature [101, 102]. For example, aluminum coordinated with brushes type polymers and GO, as a smart MPC, illustrated excellent anticancer and fluorescent potentials (Fig. 21a) together with temperature-sensitive property [88]. In addition, the green fluorescence of the coordination Al^{3+} provided a 2,4,6-trinitrophenol detection for further theranostic applications. This luminescent activity has been produced by the combination charge of the N-isopropyl acrylamide within the polymers because of the temperature-change consequences. Balamurugan et al. produced a luminescent-thermo-sensitive Eu-based MPC with

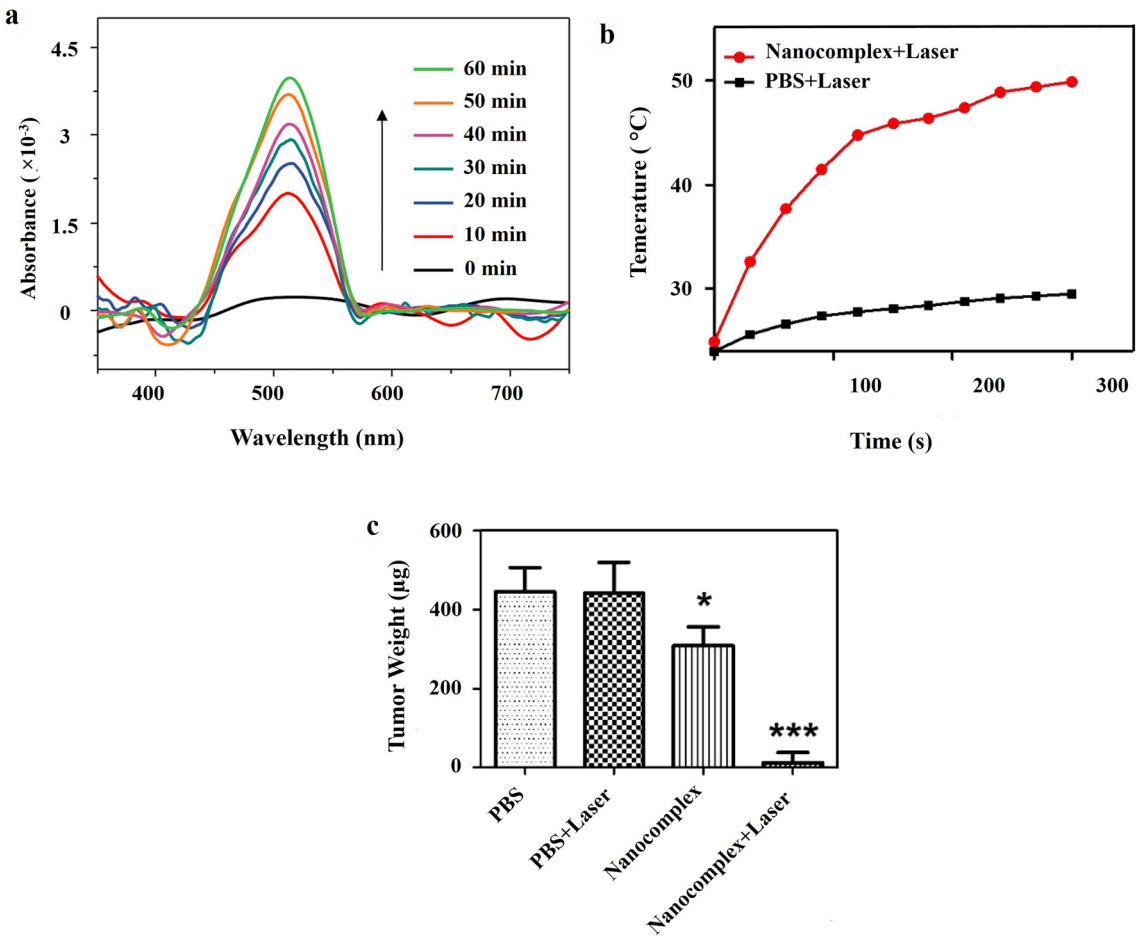


Fig. 20 **a** UV analysis of Co^{2+} release from [100], **b** tumor-temperature elevation, and **c** tumor weight loss after nanocomplex exposure to the laser beam. Reproduced from [67] with permission from Elsevier, Copyright © 2018

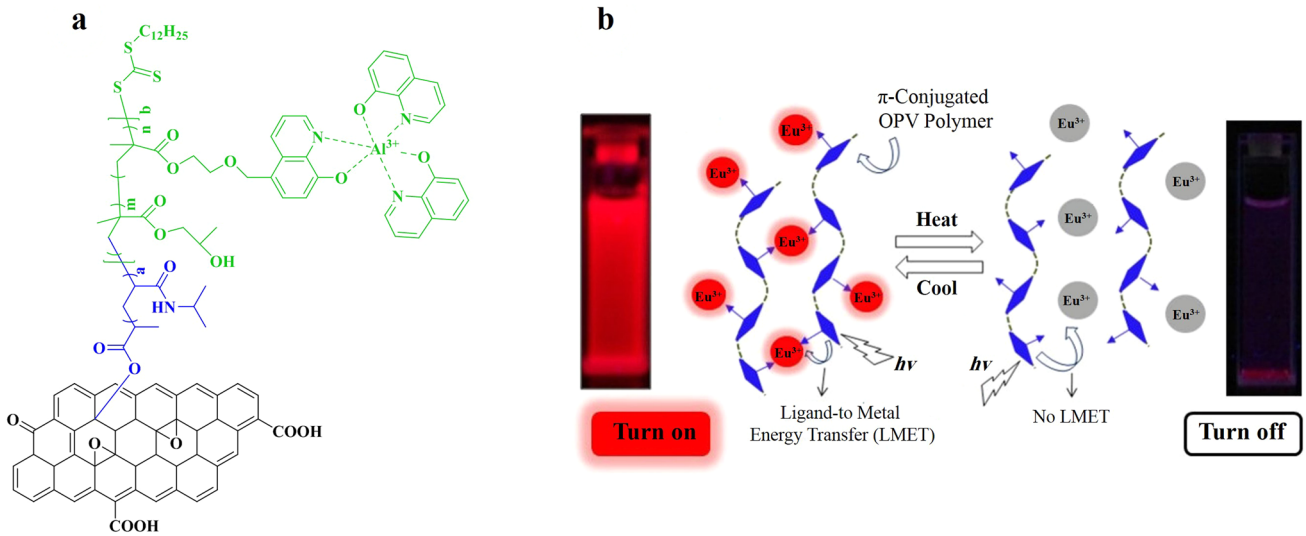


Fig. 21 **a** PL analysis of Al(III)-brushes polymer-GO. Reproduced from [88] with permission from Royal Society of Chemistry (Great Britain), Copyright © 2016 and **b** temperature-responsiveness of Eu-based polymer complex. Reproduced from [103] with permission from Royal Society of Chemistry (Great Britain), Copyright © 2013

π-binding type. This MPC nanocomplex was synthesized via polymerization technique with oligo-phenylenevinylene polymer, and the precipitation was done in the presence of acetonitrile and K_2CO_3 to increase the product yield. Moreover, organic photovoltaics (OPV) polymer chains were added to the synthesized-nanocarrier for thermal study. The results revealed an On/Off ability (Fig. 21b) of the papered MPC nanosystem following the temperature elevation or decrease. The applied temperature, converted the polymer ligand to transfer the energy to the metal center to turn on red-emission of Eu^{3+} ions [103].

Enzyme responsive

The enzymatic environment of the cancer cells offers a potential to produce prodrug and safe nanocarriers. There is a complicated system of cytoplasm due to the presence of various enzymes such as phosphatase, protease, glycosidase, cholinesterase, gelatinase, deoxyribonuclease, etc. which have a pivotal role in the cell cycle but can also be utilized as an enzyme-responsive for drug delivery system [104–106]. The enzymatic system has provided several possible binding mechanisms with polymer as the electrostatic, non-covalent, and dynamic covalent bond that can influence coordinated covalency bonds of MPC to trigger drug release under a controlled condition [107]. Novio et al. [25], for example, produced an iron-based MPC as a prodrug for HIV treatment via enzyme-responsive, controlled release of azidothymidine. This prodrug designated based on losing coordination bonds of catechol via hydrolysis, catalyzed by the enzymatic activity. The HPLC and ICP analyses revealed the drug loading content and the iron-bonded percentage of 25 and 5.5%, respectively. This formula of MPC exhibited 50-fold higher cellular uptake in comparison with that of free azidothymidine.

A cholinesterase-responsiveness of MPC has been introduced by Guan and co-workers [108]. They synthesized a host–guest system as a prodrug with sulfate-β-cyclodextrin polymer and chlorambucil as an anticancer drug. The results exhibited a cleavage ability of cholinesterase in the presence of the as-prepared MPC. The drug can be cleaved through this enzymatic environment due to the ester binding of chlorambucil (choline-modified). The HPLC analysis confirmed the ability of the enzymatic environment to disassemble the as-synthesized MPC to release the chlorambucil up to 100%.

Another benefit of the MPC nanocomplexes is that the metal ion can be delivered to the enzymatic environment as an inhibitor, in a safe and non-toxic condition [109]. Meggers et al. [110] designated six models of ruthenium-based MPC as P-kinase inhibitors. Their results confirmed the high selective properties for six models of P-kinase (FLT4, PIM1, PAK1, MLCK, DAPK1, and GSK3R). The ruthenium centers of the MPC illustrated a competitive-coordinated binding to the P-kinase binding-sites in the glycine-rich environment.

The theranostic applicability of the MPC nanocomplexes is another advantage which can be employed in the enzyme-responsiveness situation. Nivorozhkin et al. introduced this application in a two-step process to detect cancer cells based on the tumor-HSA rich condition. First, they designated Ga-based MPC nanocomplexes in which Ga-ions were released and converted to Ga-DTPA supramolecular by the HSA-binding rich of cancer cells. Then, the magnetization-enhancement of this process can be detected by MRI which produced a theranostic ability of the Ga-based MPC [106].

Oxidoreductase responsive

GSH of the cytoplasm has shown a promising approach to produce reliable MPC as a smart nanocarrier. The GSH environment causes electron transition and loss of coordination bond for the release of metal ion center. Several studies have demonstrated successful redox-responsive MPC with different metal centers as Fe, Cu, Zn, and Ca [26, 111–114]. For example, Courtois et al. [111] produced a stable colloidal 1D discrete MPC with terpyridine–Zn^{2+} while losing its coordination binding through the GSH environment. In another work, the copper-based MPC illustrated cancer cell targeting alongside GSH-responsiveness [112]. As shown in Fig. 22**,** the tumor cells were targeted by hyaluronic acid followed by the 6-mercaptopurine release after the MPC disassembly owing to the loss of coordinated bonds in the GSH environment.

An oxidoreductase-responsiveness was introduced by Yan et al. via a new micellar-MPC nanosystem. They utilized Fe^{2+} and Fe^{3+} as a metallic center and "1,11-bis(2,6-dicarboxypyridin-4yloxy)-3,6,9-trioxaundecane (L2EO4)" as polymer. Their results illustrated that the produced Fe(II)–L2EO4 and Fe(III)–L2EO4 had a reversible and redox switchable activity under an MRI field because of the superparamagnetic properties of the ferrous ions [26].

Conclusion and future perspective

The MPC is becoming increasingly popular in a wide range of bio-applications especially drug delivery technology due to the safety of the nanocomplexes of various metals as a smart vehicle. This smart nanosystem could be responsive to different environmental conditions such as temperature, pH, NIR wavelength, oxidoreduction and alternative coordination. The changeable coordination binding exhibited great potential for producing the safest smart nanocarriers for toxic and unstable metal-based drugs, in addition to their new functions such as antibacterial (Gram positive and

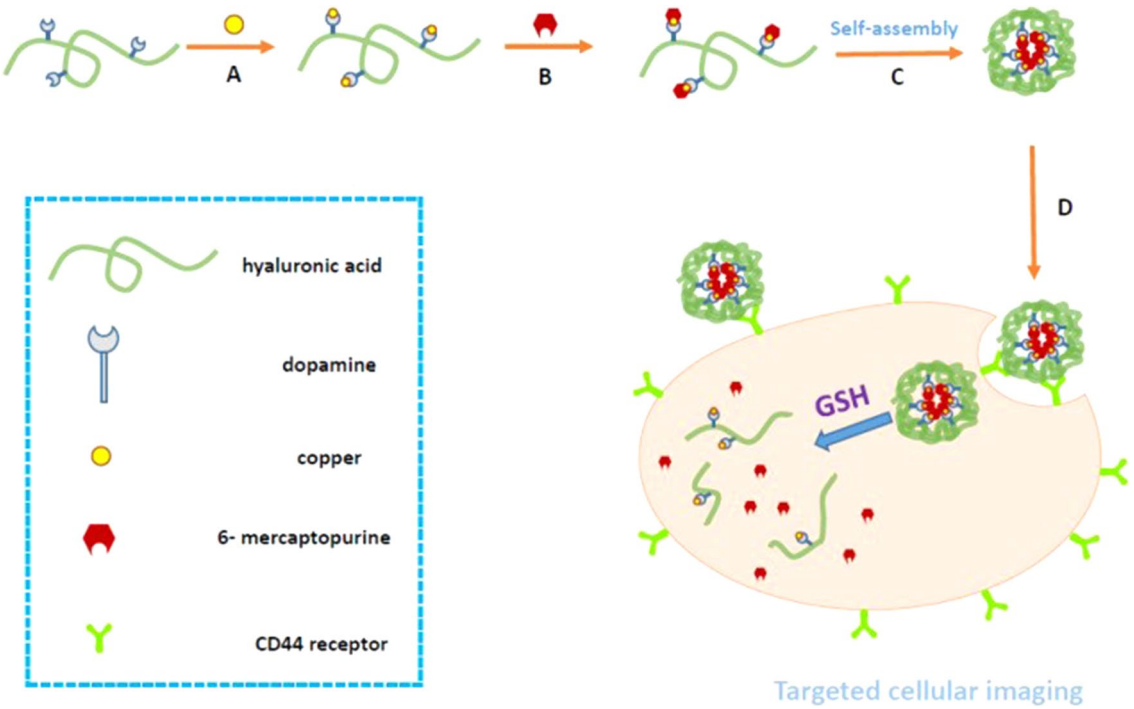


Fig. 22 Schematic representation of copper-based MPC as a GSH-responsive from [112] with permission from MDPI, Copyright © 2020

negative), antimicrobial, and antifungal. As a result, a smart nanocarrier with these new functions would be a potential nanosystem for cancer treatment with negligible or no toxicity and side effects. On the other hand, several properties of the MPC (in comparison to MOFs), have enabled the construction of a completely practical nano-biosystem with various features including self-assembly, self-healing, self-fluorescent, biocompatible, and biodegradable. The self-healing property of MPC, for instance, has introduced the MPC as a long-life smart nanocarrier whereas the high luminescent feature produced a vehicle with a fluorescent linker.

MPC has shown their distinctive advantages in drug delivery, and different smart release patterns have been reported. In this regard, numerous MPCs have demonstrated promising properties in terms of safety, non-toxicity, controlled drug release pattern and stability which could be suggested as candidates for translational research.

Regarding MPC as a nanocarrier, low bonding/loading capacity is an important barrier that should be improved in future works. In addition, the high molecular weight of polymers is a major limitation that should be addressed to start a new research in this field. One of the important issues regarding the implementation of MPC is the possible toxicity of metals centers and their corresponding organic ligands. It should be noted that the metal toxicity of some metal-based drugs such as cisplatin, is acceptable as an anticancer agent. However, it is pivotal to fabricate the MPC structures based on non-toxic transition metals comprising Fe, Zn, Ti and Ca. Previously it was demonstrated that the daily uptake of certain transition metals at the tolerable dosage is safe with no adverse effects. In this regard, the safety of organic ligand is another important factor toward MPC design and fabrication which should be seriously considered. Thus, it was suggested either to use "Generally Recognized As Safe" (GRAS) additives such as citric acid, acetic acid which are permitted in food within the European Union or to follow the Food and Drug Administration (FDA) Inactive Ingredient Guide (IIG).

Administration routes should also be considered in the road to MPCs development for the pharmaceutical industry. Sterilization is another pivotal concern for the administration of these materials in the clinic, and thus, it is necessary to provide a resistant platform to high-temperature steam and irradiation or harsh conditions. Future investigations on MPCs should address the long-term stability of these systems (long shelf time) under ordinary conditions and their compatibility with excipients for pharmaceutical manufacturing.

While the highlights of MPCs as carrier and therapeutics have been the topic of many original research articles, to date no product in clinic or on-going clinical trials for them exist. We hope this review could attract researchers' attention to this field to facilitate the clinical translation of this type of platform.

Acknowledgements The authors are grateful for the Mashhad University of Medical Sciences (980838).

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Wei, Z., et al.: Metals in polymers: hybridization enables new functions. J. Mater. Chem. **8**(45), 15956–15980 (2020)
2. Clarke, M.J.: Ruthenium metallopharmaceuticals. Coord. Chem. Rev. **236**(1–2), 209–233 (2003)
3. Zhang, D., Peng, F., Liu, X.: Protection of magnesium alloys: from physical barrier coating to smart self-healing coating. J. Alloys Compd. **853**, 157010 (2021)
4. Callari, M., et al.: Polymers with platinum drugs and other macromolecular metal complexes for cancer treatment. Prog. Polym. Sci. **39**(9), 1614–1643 (2014)
5. Cai, H., et al.: A nanostrategy for efficient imaging-guided antitumor therapy through a stimuli-responsive branched polymeric prodrug. Adv. Sci. (Weinh). **7**(6), 1903243 (2020)
6. Batten, S.R., et al.: Coordination polymers, metal–organic frameworks and the need for terminology guidelines. CrystEngComm **14**(9), 3001 (2012)
7. Biradha, K., Ramanan, A., Vittal, J.J.: Coordination polymers versus metal−organic frameworks. Cryst. Growth Des. **9**(7), 2969–2970 (2009)
8. Casini, A., Woods, B., Wenzel, M.: The promise of self-assembled 3D supramolecular coordination complexes for biomedical applications. Inorg. Chem. **56**(24), 14715–14729 (2017)
9. Tu, L., et al.: Self-recognizing and stimulus-responsive carrier-free metal-coordinated nanotheranostics for magnetic resonance/photoacoustic/fluorescence imaging-guided synergistic photochemotherapy. J Mater Chem B. **8**(26), 5667–5681 (2020)
10. Zhou, P., et al.: Supramolecular self-assembly of nucleotide–metal coordination complexes: from simple molecules to nanomaterials. Coord. Chem. Rev. **292**, 107–143 (2015)
11. Thakur, N., et al.: Multifunctional inosine monophosphate coordinated metal-organic hydrogel: multistimuli responsiveness, self-healing properties, and separation of water from organic solvents. ACS Sustain Chem Eng. **6**(7), 8659–8671 (2018)
12. Ezzayani, K., et al.: Building-up novel coordination polymer with magnesium porphyrin: Synthesis, molecular structure, photophysical properties and spectroscopic characterization. Potential application as antibacterial agent. Inorganica Chim. Acta. **514**, 119960 (2021)
13. Wang, Z., et al.: Organelle-specific triggered release of immunostimulatory oligonucleotides from intrinsically coordinated DNA–metal–organic frameworks with soluble exoskeleton. J. Am. Chem. Soc. **139**(44), 15784–15791 (2017)
14. Jańczewski, D., et al.: Organometallic polymeric carriers for redox triggered release of molecular payloads. J. Mater. Chem. **22**(13), 6429 (2012)
15. Duangjai, A., et al.: Combination cytotoxicity of backbone degradable HPMA copolymer gemcitabine and platinum conjugates toward human ovarian carcinoma cells. Eur. J. Pharm. Biopharm. **87**(1), 187–196 (2014)
16. Cai, H., et al.: Cathepsin B-responsive and gadolinium-labeled branched glycopolymer-PTX conjugate-derived nanotheranostics for cancer treatment. Acta. Pharm. Sin. B. **11**(2), 544–559 (2021)
17. Anderegg, G., et al.: Critical evaluation of stability constants of metal complexes of complexones for biomedical and environmental applications* (IUPAC Technical Report). Pure Appl. Chem. **77**(8), 1445–1495 (2005)
18. Wang, J., et al.: Acid-triggered synergistic chemo-photodynamic therapy systems based on metal-coordinated supramolecular interaction. J Biomed Mater Res A. **106**(11), 2955–2962 (2018)
19. Ezzayani, K., et al.: Complex of hexamethylenetetramine with magnesium-tetraphenylporphyrin: synthesis, structure, spectroscopic characterizations and electrochemical properties. J. Mol. Struct. **1137**, 412–418 (2017)
20. Matsuoka, R., Nabeshima, T.: Functional supramolecular architectures of dipyrrin complexes. Front Chem. **6**, 349 (2018)
21. MacLachlan, M.J., et al.: Shaped ceramics with tunable magnetic properties from metal-containing polymers. Science **287**(5457), 1460–1463 (2000)
22. Driva, P., et al.: Complexes of end-functionalized polystyrenes carrying amine end-group with transition metals: association effects in organic solvents. Biointerface Res. Appl. Chem. **10**(1), 4764–4773 (2020)
23. Liu, J., et al.: Light-controlled drug release from singlet-oxygen sensitive nanoscale coordination polymers enabling cancer combination therapy. Biomaterials **146**, 40–48 (2017)
24. Li, B., et al.: Five lead(II) coordinated polymers assembled from asymmetric azoles carboxylate ligands: Synthesis, structures and fluorescence properties. Inorganica Chim. Acta. **514**, 120035 (2021)
25. Solorzano, R., et al.: Versatile iron-catechol-based nanoscale coordination polymers with antiretroviral ligand functionalization and their use as efficient carriers in HIV/AIDS therapy. Biomater Sci. **7**(1), 178–186 (2018)
26. Yan, Y., et al.: Redox responsive molecular assemblies based on metallic coordination polymers. Soft Matter **6**(14), 3244 (2010)
27. Ovsyannikov, A., et al.: Coordination polymers based on calixarene derivatives: structures and properties. Coord. Chem. Rev. **352**, 151–186 (2017)
28. Cook, T.R., Stang, P.J.: Coordination-driven supramolecular macromolecules via the directional bonding approach, In Hierarchical macromolecular structures: 60 years after the Staudinger Nobel Prize I. Advances in Polymer Science, vol. 261, pp. 229–248. Springer, Cham (2013)
29. Lewis, J.E.M., et al.: Stimuli-responsive Pd2L4metallosupramolecular cages: towards targeted cisplatin drug delivery. Chem. Sci. **3**(3), 778–784 (2012)
30. Yoshizawa, M., Tamura, M., Fujita, M.: Diels-alder in aqueous molecular hosts: unusual regioselectivity and efficient catalysis. Science **312**(5771), 251–254 (2006)
31. Bunzen, J., et al.: Self-assembly of M24L48 polyhedra based on empirical prediction. Angew. Chem. Int. Ed. **51**(13), 3161–3163 (2012)
32. Han, J., et al.: Bioconjugation strategies to couple supramolecular exo-functionalized palladium cages to peptides for biomedical applications. Chem. Commun. (Camb) **53**(8), 1405–1408 (2017)
33. Lee, Y.H., He, L., Chan, Y.T.: Stimuli-responsive supramolecular gels constructed by hierarchical self-assembly based on metal-ligand coordination and host–guest recognition. Macromol. Rapid Commun. **39**(22), e1800465 (2018)
34. Datta, S., Saha, M.L., Stang, P.J.: Hierarchical assemblies of supramolecular coordination complexes. Acc. Chem. Res. **51**(9), 2047–2063 (2018)
35. Wei, Z., et al.: Metals in polymers: hybridization enables new functions. J. Mater. Chem. C. **8**(45), 15956–15980 (2020)
36. Mbaba, M., Golding, T.M., Smith, G.S.: Recent advances in the biological investigation of organometallic platinum-group metal

(Ir, Ru, Rh, Os, Pd, Pt) complexes as antimalarial agents. Molecules **25**(22), 5276 (2020)
37. Amiri, N., et al.: Synthesis, molecular structure, photophysical properties and spectroscopic characterization of new 1D-magnesium(II) porphyrin-based coordination polymer. Res. Chem. Intermed. **44**(9), 5583–5595 (2018)
38. Li, J., et al.: Twelve cadmium(II) coordination frameworks with asymmetric pyridinyl triazole carboxylate: syntheses, structures, and fluorescence properties. Cryst. Growth Des. **19**(7), 3785–3806 (2019)
39. Pitto-Barry, A., et al.: Encapsulation of pyrene-functionalized poly(benzyl ether) dendrons into a water-soluble organometallic cage. Chem Asian J. **6**(6), 1595–1603 (2011)
40. Mao, J., et al.: A zipped-up tunable metal coordinated cationic polymer for nanomedicine. J Mater Chem B. **8**(7), 1350–1358 (2020)
41. Qi, X., et al.: Cationic Salecan-based hydrogels for release of 5-fluorouracil. RSC Adv. **7**(24), 14337–14347 (2017)
42. Qi, X., et al.: Development of novel hydrogels based on Salecan and poly(N-isopropylacrylamide-co-methacrylic acid) for controlled doxorubicin release. RSC Adv. **6**(74), 69869–69881 (2016)
43. Wei, W., et al.: Smart macroporous salecan/poly(N, N-diethylacrylamide) semi-IPN hydrogel for anti-inflammatory drug delivery. ACS Biomater. Sci. Eng. **2**(8), 1386–1394 (2016)
44. Su, T., et al.: Facile fabrication of functional hydrogels consisting of pullulan and polydopamine fibers for drug delivery. Int. J. Biol. Macromol. **163**, 366–374 (2020)
45. Yan, K., et al.: A multifunctional metal-biopolymer coordinated double network hydrogel combined with multi-stimulus responsiveness, self-healing, shape memory and antibacterial properties. Biomater Sci. **8**(11), 3193–3201 (2020)
46. Kniazeva, M.V., et al.: Nuclearity control in calix[4]arene-based zinc(ii) coordination complexes. CrystEngComm **22**(44), 7693–7703 (2020)
47. Dutta, D., et al.: Oxalato bridged coordination polymer of manganese(iii) involving unconventional O···π-hole(nitrile) and antiparallel nitrile···nitrile contacts: antiproliferative evaluation and theoretical studies. New J. Chem. **44**(46), 20021–20038 (2020)
48. Amiri, N., et al.: Synthesis, crystal structure and spectroscopic characterizations of porphyrin-based Mg(II) complexes—potential application as antibacterial agent. Tetrahedron **73**(50), 7011–7016 (2017)
49. Li, Q.-F., et al.: Lanthanide-based hydrogels with adjustable luminescent properties synthesized by thiol-Michael addition. Dyes Pigm. **174**, 108091 (2020)
50. Weng, G., Thanneeru, S., He, J.: Dynamic coordination of Eu–Iminodiacetate to control fluorochromic response of polymer hydrogels to multistimuli. Adv Mater. **30**(11), 1706526 (2018)
51. Ma, D., et al.: Synthesis, characterization, and magnetic properties of two transition metal coordination polymers based on 2,5-furandicarboxylic acid and N-donor ligands. Inorg Organomet Polym Mater. **26**(5), 1053–1060 (2016)
52. Dawn, S., et al.: A trinuclear silver coordination polymer from a bipyridine bis-urea macrocyclic ligand and silver triflate. Inorg. Chem. Commun. **15**, 88–92 (2012)
53. Dulcevscaia, G.M., et al.: New copper(II) complexes with isoconazole: Synthesis, structures and biological properties. Polyhedron **52**, 106–114 (2013)
54. Lopez, A., Liu, J.: Light-activated metal-coordinated supramolecular complexes with charge-directed self-assembly. J. Phys. Chem. C. **117**(7), 3653–3661 (2013)
55. Đurić, S., et al.: New polynuclear 1,5-naphthyridine-silver(I) complexes as potential antimicrobial agents: the key role of the nature of donor coordinated to the metal center. J. Inorg. Biochem. **203**, 110872 (2020)
56. Hu, C., et al.: Dual-physical cross-linked tough and photoluminescent hydrogels with good biocompatibility and antibacterial activity. Macromol. Rapid. Commun. **38**(10), 1600788 (2017)
57. Cook, T.R., Zheng, Y.R., Stang, P.J.: Metal-organic frameworks and self-assembled supramolecular coordination complexes: comparing and contrasting the design, synthesis, and functionality of metal-organic materials. Chem. Rev. **113**(1), 734–777 (2013)
58. Wang, Z., et al.: A facile strategy for self-healing polyurethanes containing multiple metal–ligand bonds. Macromol Rapid Commun. **39**(6), e1700678 (2018)
59. Wei, Z., et al.: Adaptable Eu-containing polymeric films with dynamic control of mechanical properties in response to moisture. Soft Matter **16**(9), 2276–2284 (2020)
60. Liu, W., et al.: C-coordinated O-carboxymethyl chitosan metal complexes: Synthesis, characterization and antifungal efficacy. Int. J. Biol. Macromol. **106**, 68–77 (2018)
61. Nie, Z., et al.: Self-assembly of metal-polymer analogues of amphiphilic triblock copolymers. Nat. Mater. **6**(8), 609–614 (2007)
62. Gao, B., Rozin, M.J., Tao, A.R.: Plasmonic nanocomposites: Polymer-guided strategies for assembling metal nanoparticles. Nanoscale **5**(13), 5677–5691 (2013)
63. Tandon, S.S., et al.: Self-assembly of antiferromagnetically-coupled copper(II) supramolecular architectures with diverse structural complexities. Molecules **25**(23), 5549 (2020)
64. Carnes, M.E., Collins, M.S., Johnson, D.W.: Transmetalation of self-assembled, supramolecular complexes. Chem. Soc. Rev. **43**(6), 1825–1834 (2014)
65. Abolmaali, S.S., et al.: Chemically crosslinked nanogels of PEGylated poly ethyleneimine (l-histidine substituted) synthesized via metal ion coordinated self-assembly for delivery of methotrexate: Cytocompatibility, cellular delivery and antitumor activity in resistant cells. Mater. Sci. Eng. C. **62**, 897–907 (2016)
66. Li, J., Li, J.: A luminescent porous metal–organic framework with Lewis basic pyridyl sites as a fluorescent chemosensor for TNP detection. Inorg. Chem. Commun. **89**, 51–54 (2018)
67. Zhang, C., et al.: A multifunctional ternary Cu(II)-carboxylate coordination polymeric nanocomplex for cancer thermochemotherapy. Int. J. Pharm. **549**(1–2), 1–12 (2018)
68. Cao, W., et al.: Coordination-responsive selenium-containing polymer micelles for controlled drug release. Chem. Sci. **3**(12), 3403 (2012)
69. Beck, J.B., Rowan, S.J.: Multistimuli, multiresponsive metallosupramolecular polymers. J. Am. Chem. Soc. **125**(46), 13922–13923 (2003)
70. Hoke, G.D., et al.: In vivo and in vitro cardiotoxicity of a gold-containing antineoplastic drug candidate in the rabbit. Toxicol. Appl. Pharmacol. **100**(2), 293–306 (1989)
71. Tiekink, E.R.T.: Gold derivatives for the treatment of cancer. Crit. Rev. Oncol./ Hematol. **42**(3), 225–248 (2002)
72. To, Y.F., et al.: Gold(III) porphyrin complex is more potent than cisplatin in inhibiting growth of nasopharyngeal carcinoma in vitro and in vivo. Int J Cancer. **124**(8), 1971–1979 (2009)
73. Zava, O., et al.: Evidence for drug release from a metalla-cage delivery vector following cellular internalisation. Chem. **16**(5), 1428–1431 (2010)
74. Barry, N.P., et al.: Excellent correlation between drug release and portal size in metalla-cage drug-delivery systems. J. Chem. **17**(35), 9669–9677 (2011)
75. Mattsson, J., et al.: Drug delivery of lipophilic pyrenyl derivatives by encapsulation in a water soluble metalla-cage. Dalton Trans. **39**(35), 8248–8255 (2010)

76. Zheng, Y.R., et al.: Encapsulation of Pt(IV) prodrugs within a Pt(II) cage for drug delivery. Chem Sci. **6**(2), 1189–1193 (2015)
77. Schmidt, A., et al.: Evaluation of new palladium cages as potential delivery systems for the anticancer drug cisplatin. Chem. **22**(7), 2253–2256 (2016)
78. Postupalenko, V., et al.: Protein delivery system containing a nickel-immobilized polymer for multimerization of affinity-purified his-tagged proteins enhances cytosolic transfer. Angew. Chem. Int. Ed Engl. **54**(36), 10583–10586 (2015)
79. Fujita, D., et al.: Protein encapsulation within synthetic molecular hosts. Nat. Commun. **3**, 1093 (2012)
80. Wang, N., et al.: Facile fabrication of a controlled polymer brush-type functional nanoprobe for highly sensitive determination of alpha fetoprotein. Anal Methods. **12**(36), 4438–4446 (2020)
81. Wang, Y., et al.: Synthesis of PGMA/AuNPs amplification platform for the facile detection of tumor markers. Mater. Chem. Phys. **183**, 534–541 (2016)
82. Kumar, R.S., et al.: DNA binding and biological studies of some novel water-soluble polymer-copper(II)-phenanthroline complexes. Eur. J. Med. Chem. **43**(10), 2082–2091 (2008)
83. Badea, M., Uivarosi, V., Olar, R.: Improvement in the pharmacological profile of copper biological active complexes by their incorporation into organic or inorganic matrix. Molecules **25**(24), 5830 (2020)
84. Lum, C.T., et al.: A gold(III) porphyrin complex as an anti-cancer candidate to inhibit growth of cancer-stem cells. Chem. Commun (Camb) **49**(39), 4364–4366 (2013)
85. Zhang, J.-J., et al.: Organogold(III) supramolecular polymers for anticancer treatment. Angew. Chem. Int. Ed. **51**(20), 4882–4886 (2012)
86. Zhang, Q., et al.: A surface-grafted ligand functionalization strategy for coordinate binding of doxorubicin at surface of PEGylated mesoporous silica nanoparticles: toward pH-responsive drug delivery. Colloids Surf B Biointerfaces. **149**, 138–145 (2017)
87. Shahin, M., Safaei-Nikouei, N., Lavasanifar, A.: Polymeric micelles for pH-responsive delivery of cisplatin. J Drug Target. **22**(7), 629–637 (2014)
88. Song, Y., et al.: Temperature responsive polymer brushes grafted from graphene oxide: an efficient fluorescent sensing platform for 2,4,6-trinitrophenol. J. Mater. Chem C. **4**(29), 7083–7092 (2016)
89. Ren, Z., et al.: A metal-polyphenol-coordinated nanomedicine for synergistic cascade cancer chemotherapy and chemodynamic therapy. Adv Mater. **32**(6), e1906024 (2020)
90. Ruan, L., et al.: Doxorubicin-metal coordinated micellar nanoparticles for intracellular codelivery and chemo/chemodynamic therapy in vitro. ACS Appl. Bio Mater. **2**(11), 4703–4707 (2019)
91. Hwang, G.H., et al.: pH-responsive robust polymer micelles with metal–ligand coordinated core cross-links. Chem. Commun. (Camb) **50**(33), 4351–4353 (2014)
92. Zhao, D., et al.: Surface functionalization of porous coordination nanocages via click chemistry and their application in drug delivery. Adv Mater. **23**(1), 90–93 (2011)
93. Sun, R.W.-Y., Che, C.-M.: The anti-cancer properties of gold(III) compounds with dianionic porphyrin and tetradentate ligands. Coord. Chem. Rev. **253**(11–12), 1682–1691 (2009)
94. Che, C.-M., et al.: Gold(iii) porphyrins as a new class of anticancer drugs: cytotoxicity, DNA binding and induction of apoptosis in human cervix epitheloid cancer. Chem Comm **14**, 1718 (2003)
95. Sun, R.W., et al.: Stable anticancer gold(III)-porphyrin complexes: effects of porphyrin structure. Chem. **16**(10), 3097–3113 (2010)
96. Chow, K.H., et al.: A gold(III) porphyrin complex with antitumor properties targets the Wnt/beta-catenin pathway. Cancer. Res. **70**(1), 329–337 (2010)
97. Tabasi, H., et al.: pH-responsive and CD44-targeting by Fe3O4/MSNs-NH2 nanocarriers for Oxaliplatin loading and colon cancer treatment. Inorg. Chem. Commun. **125**, 108430 (2021)
98. Pan, D., et al.: PEGylated dendritic diaminocyclohexyl-platinum (II) conjugates as pH-responsive drug delivery vehicles with enhanced tumor accumulation and antitumor efficacy. Biomaterials **35**(38), 10080–10092 (2014)
99. Fricker, S.P.: Metal based drugs: from serendipity to design. Dalton Trans **43**, 4903–4917 (2007)
100. Xu, X., et al.: Photo-controlled release of metal ions using triazoline-containing amphiphilic copolymers. Polym. Chem. **10**(26), 3585–3596 (2019)
101. Ding, H., et al.: Synthesis and characterization of temperature-responsive copolymer of PELGA modified poly(N-isopropylacrylamide). Polymer **47**(5), 1575–1583 (2006)
102. Parikh, S.J., et al.: Evaluating glutamate and aspartate binding mechanisms to rutile (α-TiO2) via ATR-FTIR spectroscopy and quantum chemical calculations. Langmuir **27**(5), 1778–1787 (2011)
103. Balamurugan, A., Reddy, M.L.P., Jayakannan, M.: π-Conjugated polymer–Eu3+complexes: versatile luminescent molecular probes for temperature sensing. J. Mater. Chem. A. **1**(6), 2256–2266 (2013)
104. Ding, Y., Kang, Y., Zhang, X.: Enzyme-responsive polymer assemblies constructed through covalent synthesis and supramolecular strategy. Chem. Commun. (Camb) **51**(6), 996–1003 (2015)
105. Chandrawati, R.: Enzyme-responsive polymer hydrogels for therapeutic delivery. Exp. Biol. Med. (Maywood) **241**(9), 972–979 (2016)
106. Nivorozhkin, A.L., et al.: Enzyme-activated Gd(3+) magnetic resonance imaging contrast agents with a prominent receptor-induced magnetization enhancement. Angew. Chem. Int. Ed. Engl. **40**(15), 2903–2906 (2001)
107. Garcia, F., et al.: Multi-responsive coordination polymers utilising metal-stabilised, dynamic covalent imine bonds. Chem. Commun. (Camb) **52**(58), 9059–9062 (2016)
108. Guan, X., et al.: Enzyme-responsive sulfatocyclodextrin/prodrug supramolecular assembly for controlled release of anti-cancer drug chlorambucil. Chem. Commun. (Camb) **55**(7), 953–956 (2019)
109. Villemin, E., et al.: Polymer encapsulation of ruthenium complexes for biological and medicinal applications. Nat. Rev. Chem. **3**(4), 261–282 (2019)
110. Feng, L., et al.: Structurally sophisticated octahedral metal complexes as highly selective protein kinase inhibitors. J. Am. Chem. Soc. **133**(15), 5976–5986 (2011)
111. Courtois, J., et al.: Redox-responsive colloidal particles based on coordination polymers incorporating viologen units. Inorg. Chem. **59**(9), 6100–6109 (2020)
112. Tao, B., Yin, Z.: Redox-responsive coordination polymers of dopamine-modified hyaluronic acid with copper and 6-mercaptopurine for targeted drug delivery and improvement of anticancer activity against cancer cells. Polymers (Basel). **12**(5), 1132 (2020)
113. Abdul-Hassan, W.S., et al.: Redox-triggered folding of self-assembled coordination polymers incorporating viologen units. Chem. **24**(49), 12961–12969 (2018)
114. Shen, S., et al.: Renal-clearable ultrasmall coordination polymer nanodots for chelator-free (64)Cu-labeling and imaging-guided enhanced radiotherapy of cancer. ACS Nano **11**(9), 9103–9111 (2017)